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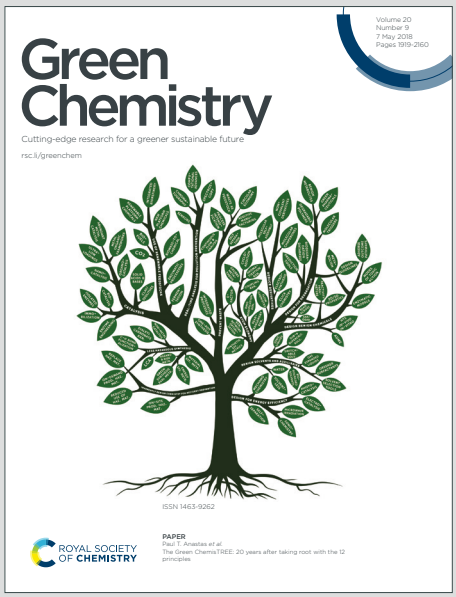
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Stability of ionic liquids in Brønsted-basic media

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Abstract

Ionic liquids are generally recognized as highly stable compounds with high thermal decomposition temperatures and wide electrochemical windows. While the former claim has been the subject of recent scrutiny and controversy, comparatively little attention has been paid to another important aspect of ionic liquid applicability: their chemical stability. Brønsted bases constitute an important class of reagents to which ionic liquids are generally sensitive. Due to the positive charge of cations and the resultant polarization of methylene and methine protons in their structure, many ionic liquid cations tend to be weakly acidic and susceptible to either deprotonation or base-induced fragmentation. As a result, several common classes of ionic liquids are incompatible with Brønsted-basic reagents. This is unfortunate due to the wide scope of possible applications of strong Brønsted bases, in fields such as synthesis, catalysis and separations. Nevertheless, several authors have investigated the design of ionic liquids with improved resistance to Brønsted-basic reagents, and numerous reports exist on the stability of the common classes of cations in basic media. This review discusses the existing literature on the alkaline decomposition of ionic liquids.

Keywords: *alkaline decomposition; base-stability; ionic liquids; isotope exchange; organic cations*

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Introduction

The 21st century has thus far brought forth a number of trends in the field of chemistry. In particular, new methods and materials have been developed to enhance the safety and environmental aspects of chemical processes. One of the most notable of these is the use of ionic liquids as alternative solvents. Depending on the author, ionic liquids are generally defined either as 'solvents consisting entirely of ions'[1,2] or 'salts with melting points below 100 °C',[3–5]. Since the publication of a number of seminal papers by renowned authors such as Seddon,[1,5] Wilkes[4] and Welton,[6] research interest in these reputedly green solvents has increased dramatically. This reputation has arisen as non-volatility and non-flammability are more or less common properties among ionic liquids. These properties emerge from the fact that Coulombic attraction between ions results in a very low vapor pressure for most ionic liquids, such that evaporation can be considered negligible at room temperature.[5–7] Ionic liquids also feature intrinsic electrical conductivity and wide electrochemical windows, making them ideal for electrochemical applications.[8,9] Furthermore, ionic liquids are highly modular in nature, which facilitates rational design of the solvent properties. This modular nature, in principle, allows tailoring an ionic liquid to a specific application. Ionic liquids have, therefore, been termed '*designer solvents*'.[10] An ionic liquid can be viewed as the combination of a cation and an anion, allowing chemists to 'pick and choose' from a library of ions known to impart certain properties to the solvent. Realistically, the cation should itself be viewed as a modular unit, consisting of a core structure bearing the positive charge, a number of side chains of variable constitution and, if required, a functional group. By combining different cationic cores, side chains and anions, one can tune a wide range of properties such as melting point, viscosity, density, surface tension, conductivity and solvation properties.

Ionic liquids are generally hailed as highly stable compounds. Most ionic liquids feature wide electrochemical windows and high thermal decomposition temperatures.[8,9,11] The latter claim

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has been scrutinized in the more recent literature, as long-term experiments have demonstrated slow decomposition at temperatures well below the reported decomposition temperature, and some ionic liquids may even decompose violently at modest temperatures.[12–15] Another aspect of ionic liquid stability that is rarely highlighted is their chemical stability, although a number of reviews have been published on this subject.[16–19] These reviews generally focus on imidazolium ionic liquids, in particular on the issue of carbene formation. The stability of ionic liquids towards Brønsted bases deserves particular attention. Some of the most versatile chemical transformations involve the use of Brønsted basic reagents: aldol condensations and related enolate chemistry, Wittig reactions, Suzuki and Heck coupling reactions, Grignard reactions and other coupling reactions involving organometallic species. In the field of extractive separations, alkaline or basic media are often used to improve selectivity, while in electrochemistry, bases are often used either as water scavengers or to modify electrode potentials. As will be elaborated upon in this review, ionic liquids are highly sensitive to Brønsted bases as a result of the positive charge of the organic cation. Nevertheless, many published applications of ionic liquids make use of Brønsted-basic reagents, often leading to unwanted interference from the ionic liquid and decomposition of the solvent. In many cases, authors fail to report on these shortcomings.

The mechanism, rate and extent of the decomposition reaction are dependent on the type of cation, the strength and steric demands of the base, the reaction medium and, to a lesser extent, the anion. The stability of ionic liquids towards attack by Brønsted bases is mainly governed by the nature of the cation, as Brønsted bases, being nucleophiles, have a natural tendency to attack the ionic liquid cation. Hence, we elected to organize our discussion of the base-stability of ionic liquids on the basis of the nature of the cation. The following classes of ionic liquids will be included in the discussion: imidazolium, quaternary ammonium, cyclic ammonium, quaternary phosphonium, pyridinium, sulfonium, and 1,2,3-triazolium. The structures of these

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cations are shown in Fig. 1. Evidently, the discussion is limited to aprotic ionic liquids. Protic ionic liquids, which are ionic liquids derived from an acid and an organic base, decompose immediately upon treatment with base by deprotonation of the cation.[20]

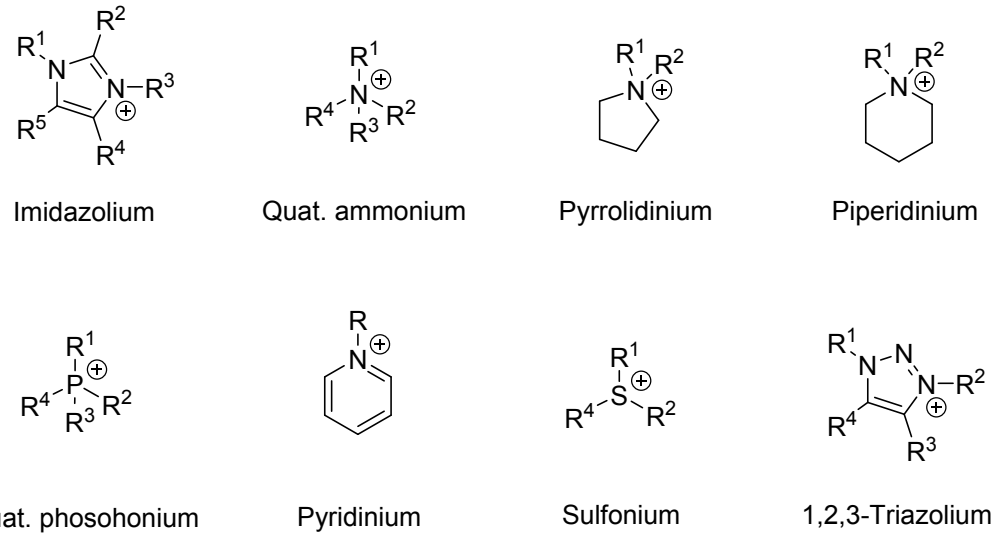


Fig. 1: General structures of the cations included in this discussion.

Imidazolium ionic liquids

Deprotonation and carbene formation

Unfortunately, the most common class of ionic liquids, 1,3-dialkylimidazolium ionic liquids, is also one of the least stable in the presence of Brønsted bases. The proton in the 2-position of these cations is significantly acidic due to a combination of the inductive effects of the flanking nitrogen atoms, the positive charge of the ring, resonance stabilization of negative charge on the C2-carbon, and a high s-character of the lone pair orbital in the conjugate base (Fig. 1).[21,22] The negative charge is delocalized to both nitrogen atoms to a near-equal extent, reducing the double bond character of the C–N bonds. Note that the lengthening of the C–N bonds as a result of this decreased double bond character results in a smaller N–C–N bond angle, which in turn requires the lone pair orbital to acquire a stronger s-character.[22] Hence, mesomeric effects and

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lone pair orbital characteristics work synergistically in stabilizing the conjugate base form. Similar effects affect other cations with N–C=N motifs in their structure, such as imidazolinium and 1,2,4-triazolium cations.[23]

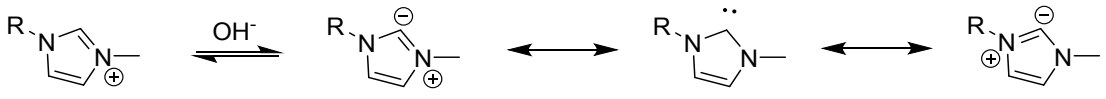


Fig. 2: Deprotonation of an imidazolium cation to yield a neutral species with partial carbenic and partial ylidic character.

A pK_a of about 23 has been observed for 1-ethyl-3-methylimidazolium chloride in water.[23] Values of bis(trifluoromethylsulfonyl)imide (bistriflimide) ionic liquids in DMSO are slightly lower, generally around 20.[24] There is little dependency of the acidity on either the length of the alkyl side chain or the anion of the ionic liquid in solution, but *tert*-butyl groups were observed to reduce the acidity somewhat.[23,24] The latter observation is consistent with the high electron-donating power of tertiary alkyl groups, which acts to stabilize the positively charged acidic species.[23] Steric hindrance between the voluminous lone pair and the bulky *tert*-butyl group may also be of significance in causing this effect. In neat ionic liquids, a stronger dependence of the acidity of imidazolium ionic liquids on the nature of the anion has been suggested (*vide infra*).[25] The conjugate base resulting from the acid-base reaction (Fig. 1) is an *N*-heterocyclic carbene, a class of stable carbene ligands used extensively in organometallic chemistry.[26]

The pK_a values quoted above may at first appear negligibly high, but the sensitivity to bases was found to be greatly increased under solvent-free conditions for 1-butyl-3-methylimidazolium bistriflimide by Lapis *et al*.[27] When dissolved in ethanol, the ionic liquid was virtually unaffected by the addition of cesium carbonate. Under neat conditions, however, a very strong attenuation of the C2-signal was observed using ^{13}C NMR spectroscopy. This was attributed to the deprotonation of the C2-carbon, which shifts downfield nearly 100 ppm upon

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acquiring a carbenic character due to a strong paramagnetic chemical shift contribution. This is similar to what is observed to a lesser extent upon heating of dialkylimidazolium acetate ionic liquids (*vide infra*). The attenuation of the signal corresponded to near complete deprotonation, despite the weakly basic nature of the carbonate anion. The nature of the solvent is important in determining the reactivity of the C2-position of imidazolium salts. Computational and experimental work performed by the groups of Nyulászi and Maschmeyer have shown that an aqueous solvent protects the C2-position by solvation of strong bases, allowing the imidazolium hydroxide ion pair to exist without the occurrence of C2 deprotonation or other decomposition reactions.[28,29] Nevertheless, the C2-proton is noninnocent even under aqueous conditions, as evidenced by the work of Olafson *et al*.[30] In a borate buffer with a pD of 8.92, the half-life for isotope exchange at the C2-position is 4.5 min. While this does not necessarily imply the presence of a significant equilibrium concentration the conjugate base of the cation, it does signify the labile and reactive nature of the acidic proton. The issue of C2 deprotonation is discussed extensively by Chowdhury *et al.* in their 2007 review article.[19]

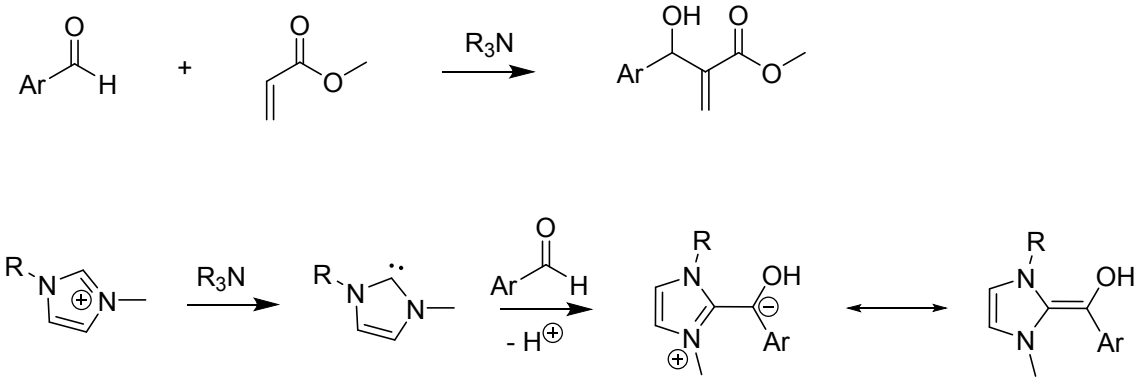


Fig. 3: Involvement of imidazolium ionic liquid reaction media in the Baylis-Hilman reaction.[31]

The main result of the deprotonation of imidazolium ionic liquids is the loss of the ionic nature of the solvent, which forms the basis for many of the perceived benefits and possible applications of ionic liquids. The carbon skeleton of the cation is not initially lost, but a reactive

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carbene is formed. The anion of the ionic liquid may act as the attacking base itself.[28] This is exemplified by 1-butyl-3-methylimidazolium hydroxide, which decomposes very rapidly in the dry state and cannot be isolated due to the deprotonation of the cation by the hydroxide anion. A 'wet carbene' is formed as a result.[28] The most problematic aspect to the formation of carbenes is their reactivity towards other compounds. For instance, imidazolium-derived carbenes have been observed to add to aldehydes, which hampers the use of imidazolium ionic liquids as reaction media in the Baylis–Hillman reaction (Fig. 3).[31] This results in low yields at high substrate conversion. When one attempts to recycle the ionic liquid using a different set of starting materials, mixed Baylis–Hillman-type reaction products are observed, resulting from the reaction of the aldehyde reactant with the imidazolium-aldehyde adduct formed in the previous reaction cycle. This occurs regardless of the weak basicity of the tertiary amines used as catalysts. Wittig–Horner-type reactions, which also involve aldehydes and Brønsted bases (Fig. 4), are also poor-yielding when performed in dialkylimidazolium ionic liquids, likely due to the formation of similar adducts.[31,32] Tseng and coworkers also demonstrated the nucleophilicity of imidazolium carbenes when they performed nucleophilic aromatic substitutions in 1-butyl-3-methylimidazolium ionic liquids. The desired reaction involved the attack of a secondary amine on 1-fluoro-2-nitrobenzene, catalyzed by a tertiary amine. Unfortunately, deprotonation and subsequent nucleophilic attack of the solvent was competitive with that of the secondary amine, leading to the formation of a solvent-substrate adduct as side product.[33] A final example shows that, even in the absence of catalytic amounts of Brønsted base, the reactivity of the C2-position towards aldehydes is significant. Imidazolium ionic liquids with hydrogen-bonding anions have been hailed as solvents for cellulose.[34] This has in fact become one of the most notable examples of the promise of ionic liquids as versatile solvents. However, Ebner *et al.* demonstrated that imidazolium ionic liquids are not innocent solvents for cellulose, as the cation slowly forms an adduct with the reducing ends of cellulose

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over time.[35] The structure of this adduct is similar to that shown in Fig. 3. The adduct was observed to form in the absence of base, but catalytic amounts of triethylamine increased the rate of its formation. More recently, the group of Welton demonstrated that, when ionic liquids with the slightly basic acetate ionic liquid are used, this adduct became the first intermediate in a catalytic cycle which ultimately leads to the decomposition of the glucose units in the cellulose chain.[36]

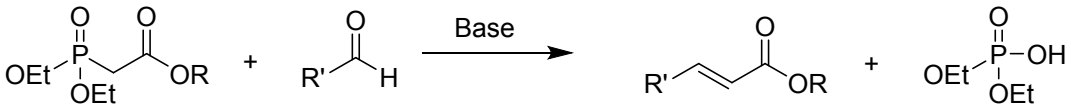


Fig. 4: Wittig-Horner reaction.

Similarly, caution should be taken when dialkylimidazolium ionic liquids are used as solvents for Brønsted bases in tandem with transition metals, as the resulting carbenes may bind to the metals as *N*-heterocyclic carbene ligands. This can lead to the degradation of homogeneous catalysts by ligand substitution. In Heck reactions, palladacyclic catalysts are observed to underperform in imidazolium ionic liquids compared to other ionic liquids, likely as a result of carbenes bonding to the palladium centers.[37,38] Phosphinopalladium catalysts can efficiently catalyze the Sonogashira reaction in imidazolium tetrafluoroborate ionic liquids for a single cycle, but in subsequent cycles the yield of the reaction drops markedly, which may either result from catalyst leaching or carbene-induced decomposition.[39,40] In other cases, the palladium catalyst does not decompose due to ligand substitution, but protonation of the ligand by the imidazolium cation simply causes the complex to dissociate and the central metal atom to precipitate.[38] Sometimes, however, the catalyst may become more active after ligand substitution, in which case the lability of the ionic liquid may be an advantage.[41,42] Wellens *et al.* described an example of base-induced interaction between imidazolium ionic liquids and metal centers in a more metallurgical context. The authors found that a variety of 1,3-

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dialkylimidazolium ionic liquids with chloride, thiocyanate, acetate, and dicyanamide anions were capable of dissolving basic metal oxides. The driving force is provided by deprotonation of the imidazolium cations by the oxide and the subsequent coordination of the resultant carbenes to the metal ions. Nickel(II), copper(II), zinc(II) and silver(I) oxide all dissolved in the ionic liquids according to reactions described by Eqn. 1 and 2:

$$Ag_2O + 3\,[Hc_nmim][X] \rightarrow [Ag(c_nmim)_2][X] + [Hc_nmim][AgX_2] + H_2O \quad (1)$$

$$ZnO + 2\,[Hc_nmim][X] \rightarrow [Zn(c_nmim)_2X_2] + H_2O \quad (2)$$

in which Hc_nmim denotes the 1-alkyl-3-methylimidazolium cation with *n* carbon atoms in the alkyl chain. The reaction did not occur for bistriflimide ionic liquids, possible due to the lack of coordinating ability of the anion.

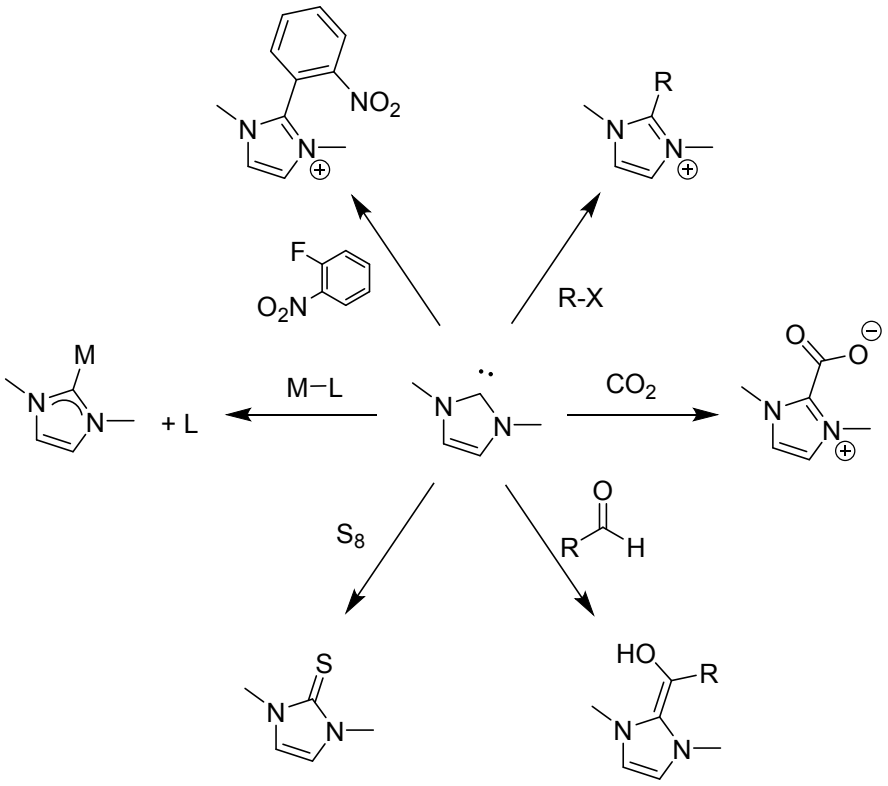


Fig. 5: Notable examples of reactions of imidazolium-derived carbenes with electrophiles.[31-36,49]

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Methylation of the 2-position has been explored in an attempt to render the imidazolium cation more compatible with bases. While this does decrease the acidity of the cation, the C2-methyl protons still retain a significant degree of acidity due to mesomeric stabilization of the conjugate base, leaving the proton vulnerable to isotope exchange (Fig. 6). The half-life for the isotope exchange of methyl protons in 1-butyl-2,3-dimethylimidazolium chloride in D_2O, catalyzed by 0.2 mol L^{-1} trimethylamine, is about 12 days at room temperature. With potassium hydroxide catalysis, this reduces to 5.5 hours.[43] A further demonstration of the acidity of these protons is the reaction of 1-butyl-4-hydroxymethyl-3-methylimidazolium iodide with iodomethane in the presence of sodium hydride (Fig. 7).[43] One may expect the acidity of the C2-proton to allow this position to be methylated by iodomethane after deprotonation. However, the methylated product is not detected. Rather, the 2-ethyl derivative is obtained, as a result of the 2-methyl derivative reacting with a second equivalent of iodomethane, after deprotonation of the 2-methyl derivative. Deprotonated C2-methyl imidazolium cations are also known to react with CO_2 (Fig. 8) and to bind to transition metal ions.[44,45]

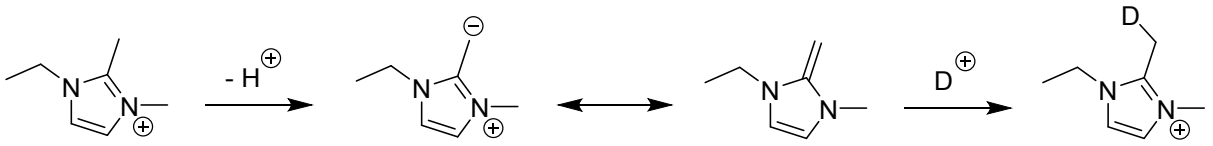


Fig. 6: Deprotonation and deuteration of a C2-methylated imidazolium cation.

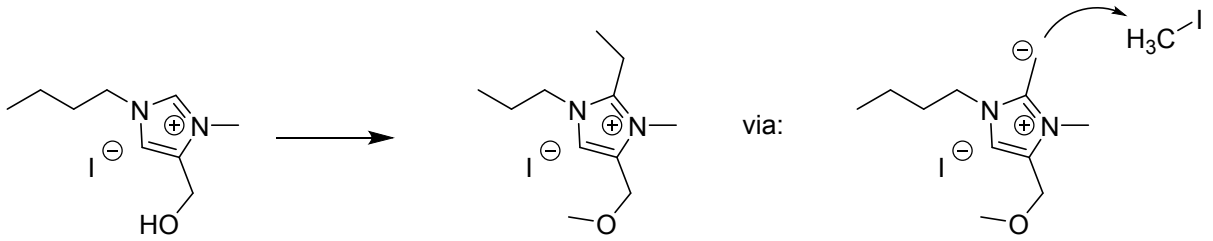


Fig. 7: Double methylation of an imidazolium salt resulting from the acidity of 2-alkyl substituents.[43]

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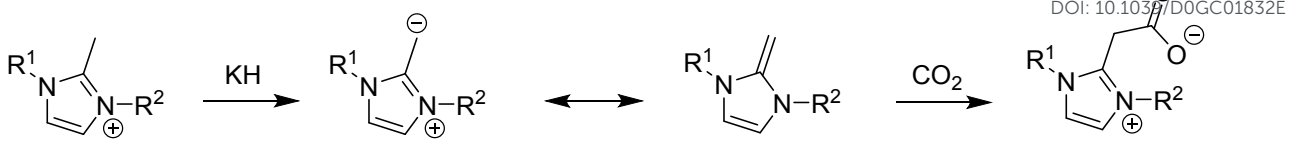


Fig. 8: Reaction of 1,3-dialkyl-2-methylimidazolium cations with CO2 under basic conditions.[45]

Handy reported that 1-butyl-2-isopropyl-3-methylimidazolium bistriflimide is remarkably resistant to deprotonation at the branching carbon of the isopropyl group, such that it can be used as a solvent for Grignard reactions (but not for reactions involving organolithium reagents).[46] The author hypothesizes that conjugation of the lone pair is only possible if the isopropyl group lies in the plane of the ring, such that the *p*-orbital occupied by the lone pair is parallel to those participating in the ring conjugation. Computational results indicate that this conformation is disfavored for the cation, resulting in a decrease of its acidity.[46,47] Maton *et al.* drew similar conclusions from their investigation of peralkylated imidazolium ionic liquids, containing alkyl substituents on all carbon and nitrogen atoms.[48] Isotope exchange could be easily suppressed by substituting the C2-position with an isopropyl group, and bromobenzene could be lithiated using *n*-butyllithium and subsequently coupled to benzaldehyde (Fig. 9).

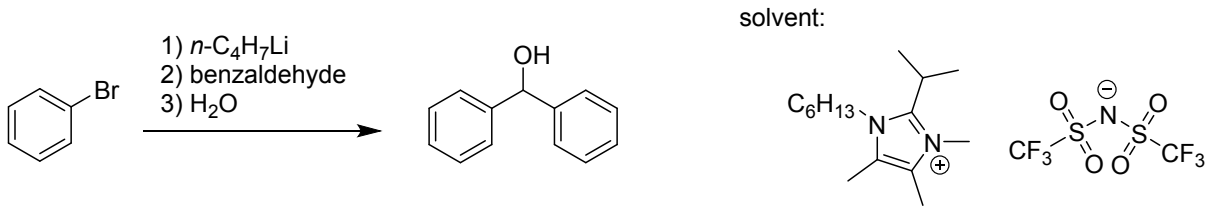


Fig. 9: Lithiation of bromobenzene and coupling to benzaldehyde in a peralkylated ionic liquid as described by Maton and coworkers.[48]

The C4 and C5-positions of imidazolium salts are also susceptible to deprotonation, but their lability is lower than that of the C2-proton.[49] Nevertheless, full deuteration can be achieved in D_2O within about 12 hours in the presence of 0.26 mol L^{-1} cesium hydroxide at 60 °C. This

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study was performed on 1-butyl-3-methylimidazolium tetrafluoroborate. The C5-proton adjacent to the butyl substituent, was found to exchange more rapidly than the C4-proton adjacent to the methyl group by a factor of 1.3. The bistriflimide salt, dissolved in methanol-*d*, exhibited a similar trend in relative labilities of the protons, but the exchange was more rapid by a factor of 10. As with the C2-proton, the acidity is higher in organic solvents than in water.

Deprotonation at sites other than the C2-position may also lead to unexpected side reactions. Tommasi and Sorrentino reported the formation of C4 and C5-carboxylated imidazolium cations after treatment of 1-butyl-3-methylimidazolium chloride with sodium carbonate in *N,N*-dimethylformamide at elevated temperatures and high CO_2 pressures (50 bar).[50] This is analogous to the carboxylation of the C2-position shown in Fig. 5. Hugar *et al.* hypothesized that protons peripheral to the ring nitrogen atoms are also susceptible to exchange in protic deuterated solvents, and that this could lead to rearrangements that ultimately lead to decomposition of the cation.[51] The authors reason that side chain deprotonation may be the progenitor to a number of unidentified decomposition products in alkali-treated imidazolium samples that do not correspond to any of the other known pathways of decomposition.

Ring opening

The C2-position is not only susceptible to deprotonation, but also to nucleophilic attack.[47,51,52] Urahata and Ribeiro reported a combined partial positive charge of approximately 0.6 for the methine group in the 2-position on the basis of a Mulliken population analysis of 1,3-dialkylimidazolium structures computed at the MP2 level of theory.[53] This result elucidates the preference of basic nucleophiles to interact with this site of the cation. Lin *et al.* studied the alkaline decomposition of a variety of derivatives of 1-ethyl-3-methylimidazolium bromide, wherein the C2-position is substituted with either hydrogen, methyl, isopropyl and phenyl.[47] At

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1 mol L^{-1} potassium hydroxide, only the 2-H derivative exhibited any decomposition, even at elevated temperatures. The decomposition product was a ring-opened compound formed after nucleophilic attack of hydroxide anion to the C2-position. This process is shown in Fig. 10. The other derivatives underwent similar reactions at higher concentrations of base (2 mol L^{-1} for the isopropyl and phenyl derivatives and 6 mol L^{-1} for the methyl derivative). Myles and coworkers demonstrated that weakly basic nucleophiles such as methanol may also attack this position, but did not observe any further degradation of the ring structure.[54] Yang and coworkers found that, in the presence of 1 mol L^{-1} sodium hydroxide, nucleophilic attack by methanol can lead to ring opening.[55]

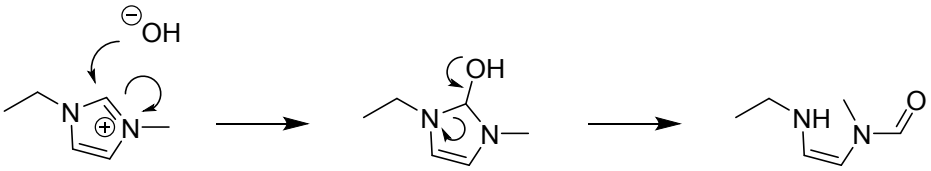


Fig. 10: Ring-opening of imidazolium cations under alkaline conditions.[47]

Ring opening reactions are influenced by steric and electronic factors. Several authors have examined the influence of substitution on the activation barriers and rates of these reactions by both computational and experimental means.[47,51,56–58] Computational studies indicate that the rate-limiting step is not the initial addition of the hydroxide anion, but the opening of the intermediate adduct.[56,57] Nevertheless, some authors have related the alkaline stability of imidazolium cations to the energy of the LUMO. Lin *et al.* determined that the 2-phenyl salts are more sensitive to nucleophilic attack by hydroxide ions than 2-alkyl derivatives and attributed this to a lower LUMO energy as a result of conjugation.[47] The unsubstituted cations exhibited the lowest stability. The authors varied the substituent at the C2-position observed the degree of ring opening to increase in the order of methyl < isopropyl < phenyl. Their computationally obtained LUMO energies accorded well with this sequence. However, the

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results obtained by Hugar *et al.* showed an opposite trend: a higher stability of the 2-phenyl cation with respect to the 2-methyl cation as a result of steric hindrance.[51] In this particular instance, the use of different solvents (Water by Lin and methanol by Hugar) may have caused the discrepancy. Dong *et al.* also argue in favor of using the LUMO energy as a means to predict the alkaline stability of imidazolium cations, on the basis computational studies of a variety of 1,2,3-trialkylimidazolium salts, which were compared with experimental results obtained by Gu *et al*.[58,59] They found that, in general, cations with long, α-branched alkyl substituents on the nitrogen positions have higher LUMO energies due to hyperconjugation, and that they also tend to exhibit higher alkaline stability. However, many examples deviated from this relationship, indicating that other factors also come into play, including steric effects and factors that stabilize the transition state of the ring opening step. Considering that the second step is rate-determining, the role of the LUMO energy should thus lie in determining the equilibrium concentration of the intermediate adduct.

Methylation of the C4 and C5-positions also inhibits ring opening reactions.[51,55,56,60] This has been explained in terms of the electron-donating effect of the methyl substitutents.[56,60] Hugar *et al.* found that, when these positions are substituted with electron-withdrawing phenyl groups instead, the degree of ring opening increased, but the salts remained more stable than their unsubstituted analogs.[51] Similar to what Lin *et al.* observed when substituting the 2-position of imidazolium salts, the lack of substitution results in the lowest stability, regardless of electronic effects, suggesting the involvement of either steric factors or intermediate deprotonation.[47,51]

Dealkylation

Yang and coworkers observed yet another mechanism by which imidazolium salts decompose, which entails the removal of a side chain, resulting in the formation of a neutral imidazole (Fig.

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11).[55] This mechanism was secondary to ring opening in methanol. Hugar *et al.* argue that a S_N2 attack at the α-position is responsible for the observed formation of imidazoles. This conclusion is supported by their observations that (1) no alkene products are observed in the reaction mixture, even in sealed vessels; (2) *N*-methyl and *N*-benzyl groups are also susceptible to removal; and (3) *N*-ethyl groups are less sensitive to removal than *N*-methyl groups. S_N2 reactions or deprotonations at the *N*-substituents are not usually the main decomposition pathways of imidazolium salts, but Hugar *et al*. report that they become dominant when ring opening is greatly suppressed, at least when sensitive methyl or benzyl groups are present at these positions.[51] The benzyl group was determined to be cleaved to a greater extent than the methyl group by integration of the product resonances in proton NMR. Dealkylation reactions can also be promoted by substitution of the side chains with electron-withdrawing groups in the β-position, including nitrile groups or other cationic entities. In this case, the process occurs *via* a β-elimination, yielding an alkene derived from the side chain in addition to the imidazole (Fig. 12). These reactions readily occur at room temperature upon treatment with dilute aqueous alkali.[61,62]

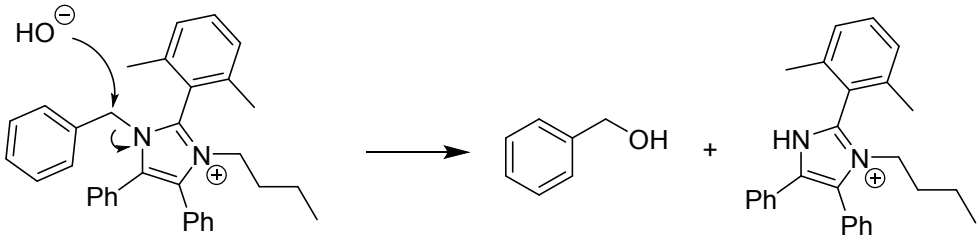


Fig. 11: S_N2 attack of hydroxide at the α-carbon of an imidazolium cation, yielding an alcohol and an imidazole.[51]

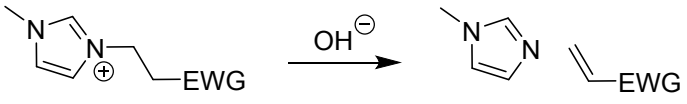


Fig. 12: β-Elimination of electron-poor side chains from imidazolium cations.[61,62]

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Imidazolium cations with high base stability

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The extensive study by Hugar *et al.* concluded that extremely base-stable imidazolium cations could be obtained by tethering a 2,6-dimethylphenyl group to the C2-position. This sterically demanding group prevents nucleophilic attack at the C2-position, and its conformation nearly perpendicular to the imidazolium ring prevents electron delocalization.[51,56] In combination with the substitution of the C4 and C5-positions with either methyl or phenyl groups, C2-addition and concomitant ring opening becomes negligible. To prevent dealkylation reactions from occurring at the *N*-substituents, longer alkyl groups such as butyl should be attached at these positions. The resulting cation (Fig. 13) can be heated to 80 °C in methanolic potassium hydroxide (5 mol L^{-1} for 30 days with less than 1 percent decomposition as a result.[51] One should take into account that ionic liquids based on these cations are most likely to have high viscosities and melting points due to the inclusion of an aromatic substituent. Maton *et al.* prepared imidazolium ionic liquids with dicyanamide and bistriflimide anions which offer a compromise between base-stability and physical properties.[48] The salts were substituted with isopropyl at the C2-position and hexyl at the N1-position, and were methylated on all other positions. This rendered them more viscous than less substituted derivatives, but resistant to decomposition and isotope exchange by organolithium reagents at 0 °C. Unfortunately, the ionic liquids could not be fully recovered after contacting with 1 mol L^{-1} aqueous sodium hydroxide at elevated temperatures for 24 hours.

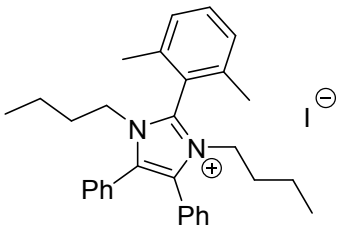


Fig. 13: Highly base-stable imidazolium salt described by Hugar et al.[51]

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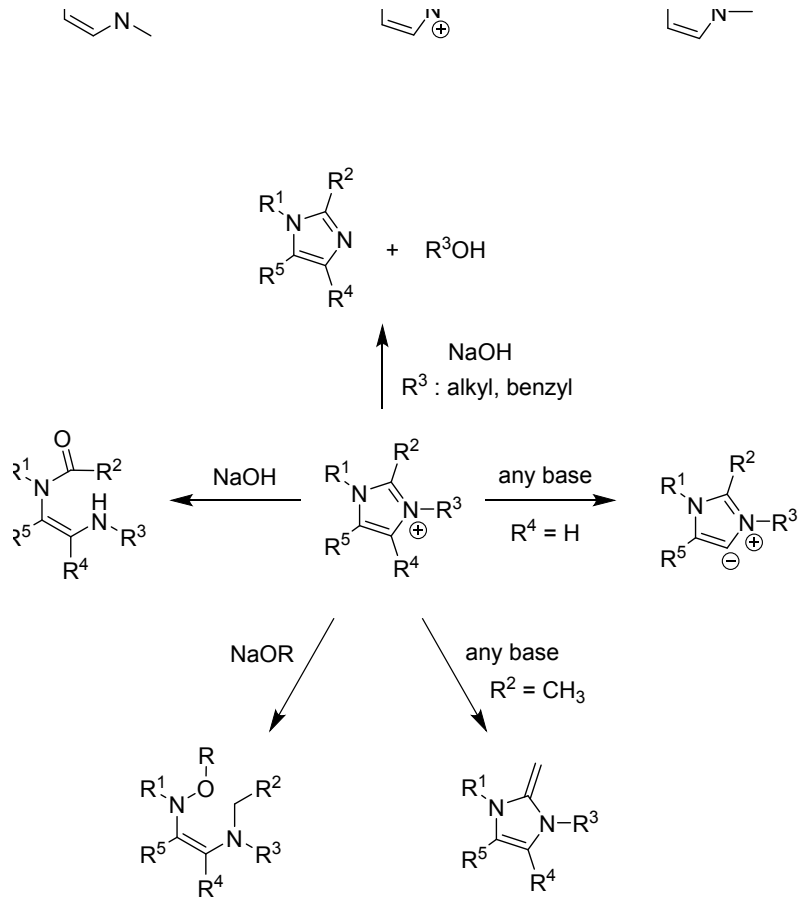


Fig. 14: Decomposition pathways of imidazolium cations in basic media.

The chemistry of imidazolium salts in basic media is thus rich and highly dependent on both the nature of the substituents on the cation and the nature of the Brønsted-basic species. Imidazolium salts unsubstituted at the C2, C4 and C5 positions are sensitive to deprotonation. Substituents placed at the N1, C2 or N3 positions remain sensitive to deprotonation, especially by strong bases. Compact bases, such as hydroxide or methoxide, may induce ring opening by addition to the C2-position, which can be prevented by substitution of the ring with electron donating groups and by adding steric bulk to the C2-position. Cleavage of the *N*-substituents remains a possibility for groups prone to nucleophilic substitution. Organometallic reagents,

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while highly basic, are not observed to induce either ring opening or side chain cleavage and imidazolium salts are thus more resistant to these reagents than to hydroxide bases.

Readily available 1,3-dialkylimidazolium ionic liquids are poor choices for applications requiring any sort of Brønsted basic reagents. Even weak bases can deprotonate the C2-position to a significant extent, forming reactive carbenes which react with a wide array of electrophiles to undergo addition and substitution reactions. Peralkylated imidazolium ionic liquids offer far superior stability in basic media, but ring opening remains an issue in the presence of hydroxide and alkoxide bases, at least for ionic liquids with substituents resulting in good physical properties. The resulting enaminones and hydroxylamines are not inert and may act as potential interferents in synthesis. The 2-position should be substituted with either an isopropyl group or a phenyl group to prevent deprotonation at this site, although this is detrimental to the physical properties of the ionic liquids. Grignard and organolithium compounds can be used in such peralkylated imidazolium ionic liquids without issue.

Ammonium, piperidinium and pyrrolidinium ionic liquids

Substitution and elimination

The Hofmann elimination and nucleophilic substitution comprise the two dominant pathways of decomposition for ammonium cations in aqueous alkali.[63–65] The former is generally dominant for tetraalkylammonium cations (Fig. 15a).[64] The Hofmann elimination is a concerted β-elimination (E2), which implies that a proton located on the β-carbon is abstracted with concurrent elimination of the trialkylamine leaving group.[56,63,66] An amine and an alkene are thus formed as reaction products. Generally, this reaction proceeds starting from an *anti*-periplanar conformation, as do most bimolecular elimination reactions. This is due to steric considerations and favorable interaction between the bonding orbital of the C–H bond and the

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antibonding orbital of the C–N bond in the formation of the new π-bond.[64] Nevertheless, *syn*-elimination can occur as well. Examples hereof include intramolecular or unimolecular eliminations (*vide infra*) and the decomposition of long-chain, secondary ammonium salts in which steric hindrance prevents the formation of a more stable, *trans*-alkene *via* an *anti*-attack.[67–71]. However, the absence of β-protons in an anti-position does influence the reactivity of ammonium salts to a certain extent.[63] In addition, the Hofmann elimination is highly sensitive to steric hindrance, and hindered ammonium cations react significantly less rapidly.[66,72] Furthermore, the least hindered alkene is generally formed as the major product, a trend referred to as the Hofmann rule.[73,74] It has also been argued that the Hofmann rule and the sensitivity to substitution results from electronic rather than steric effects: the acidity of the β-protons decrease with increasing substitution.[67,74] In either case, the ethyl group is by far the most reactive.[63,75] When Hofmann elimination is impossible or highly disfavored, substitution becomes the principal pathway of decomposition.[64] Nucleophilic substitution of a quaternary ammonium cation proceeds *via* a S_N2 pathway at the α-carbon (Fig. 15b) and is thus also a concerted reaction with high sensitivity to steric hindrance. This implies a slight increase in the reaction barrier with increasing chain length, a finding confirmed by computational results.[64]

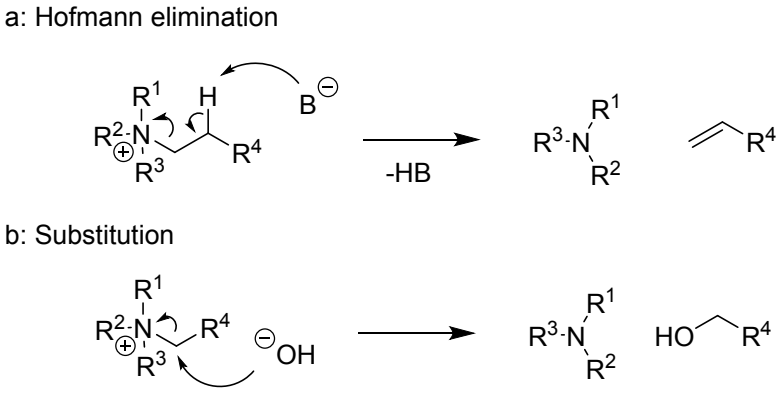


Fig. 15: Principal pathways of alkaline decomposition of ammonium cations: Hofmann elimination (a, above) and bimolecular substitution (b, below).

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Rearrangement reactions

The acidity of the β-hydrogen atoms is limited, but that of the α-hydrogen atoms is considerable.[66] The energy barrier for deprotonation is very low, and hence the reaction is highly reversible, albeit unfavorable.[64] Isotope exchange can readily be observed under alkaline aqueous conditions which decompose the cation.[64–66,76] The loss of an α-proton can trigger one of two rearrangement reactions, the first of which is the Stevens rearrangement.[77] This reaction entails the [1,2]-migration of one of the nitrogen substituents to the deprotonated α-site, yielding a neutral, α-branched amine. The reaction proceeds with retention of configuration, which excludes a concerted mechanism on the basis of orbital symmetry requirements (a concerted mechanism requires rearward attack and would hence result in inversion of the configuration).[78–81] This leaves an ionic and radical pathway as possible mechanisms, although either requires a recombination rapid enough to prevent diffusion of the components after dissociation in order to achieve retention of configuration.[79] Recent computational evidence strongly favors a mechanism occurring *via* a radical couple intermediate, with radical dissociation as rate-determining step (Fig. 16a).[81] Nevertheless, the anionic stability of the substituents strongly influences the rate of reaction, as the reaction is initially triggered by the loss of a substituent α-proton.[77] Hence, tetraalkylammonium ionic liquids are inherently less prone to this pathway of decomposition compared to benzyl or allyl-substituted salts. This does not preclude this pathway from being dominant for fully saturated derivatives: it has, for instance, been observed to occur more readily than β-elimination when *N,N*-dimethylpyrrolidine-derived ylides are heated.[82] These ylides are stable at room temperature, but decompose into a mixture of products when heated. Wittig and Burger hypothesized that the negative charge resides on the more acidic methyl substituents and ascribed the dominance of the Stevens rearrangement to the steric constraints precluding efficient β-elimination by a

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methyl-centered nucleophile.[82] The expected Hofmann product dominates when the salt is treated with potassium amide in liquid ammonia.[82]

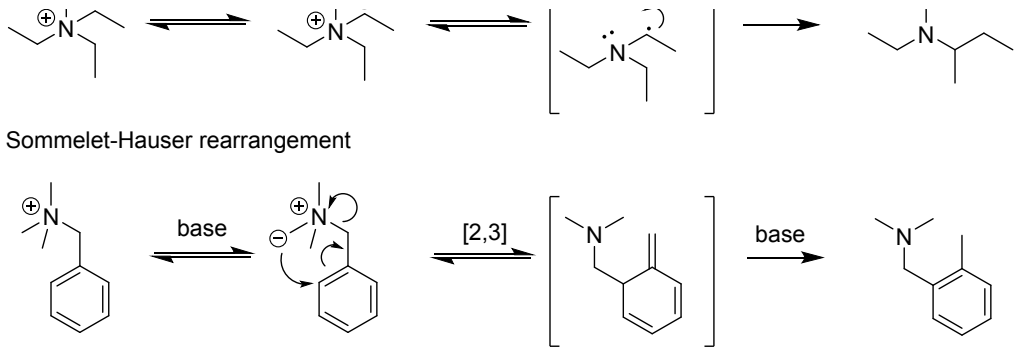


Fig. 16: Stevens rearrangement (a, above) and Sommelet-Hauser rearrangement (b, below) of ammonium salts. Methyl and ethyl substituents are shown for visual clarity.

Benzylic ammonium salts are subject to a related, competing reaction known as the Sommelet-Hauser rearrangement. The reaction cannot occur in salts lacking a benzylic substituent and involves a [2,3]-sigmatropic rearrangement followed by a tautomerization/rearomatization (Fig. 16b).[77] The intermediate before tautomerization is isolable, confirming the reaction mechanism.[83] The Sommelet-Hauser rearrangement is reported to dominate under protic conditions and at higher temperatures.[81,84] However, these results assume the presence of an *N*-methyl substituent in addition to the *N*-benzyl substituent. Steric constraints prevent the rearomatization step from occurring if the progenitor ylid was centered on an alkyl chain other than methyl.[85,86] In the presence of an excess of (weak) base, rearomatization is once again possible for such compounds, allowing both rearrangement pathways to occur competitively.[86]

A variation of the Hofmann elimination is also competitive with the Stevens rearrangement. This reaction is a rearrangement of an ammonium ylid to an unsaturated amine (Fig. 17). Isotope labeling studies have shown the actual mechanism to be an intramolecular, concerted

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syn-elimination via a cyclic transition state, caused by the attack of an ylidic α-carbon at the β-position of an adjacent chain.[68] This has been observed under pyrolytic conditions of quaternary ammonium hydroxides, when steric constraints prevent intramolecular *anti*-elimination.[68,69] This process also appears to be the standard mechanism of elimination under the influence of organolithium bases.[70,71] It has been hypothesized that some cases of *cis*-elimination are in fact intramolecular reactions, in which the first step is the removal of the acidic proton, followed by the dissociation of the ylidic chain to an alkene via a $E_{1C}B$ mechanism. This differs from the aforementioned intramolecular pathway in that the ylide is initially located on the chain that forms the alkene, rather than one of the adjacent chains that is incorporated in the amine after reaction.[68]

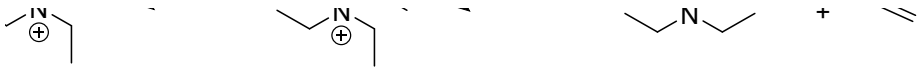


Fig. 17: Intramolecular Hoffman elimination with ylidic intermediate.[68,69]

Alkaline stability tetraalkylammonium cations

Landini *et al.* investigated the decomposition products of several ammonium cations in chlorobenzene solutions contacted with aqueous sodium hydroxide.[87] While the research was conducted in the context of phase-transfer catalysis, the cations included in the study were all relevant to the field of ionic liquids in that they contained at least three long-chain alkyl groups. It should be noted that transfer of hydroxide into the organic phase is strongly influenced by the nature of the anion (*vide infra*) and the hydrophobicity of the solvent. No products related to either rearrangement pathway were detected. The authors concluded that long-chain

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tetraalkylammonium ionic liquids quantitatively decompose to tertiary amines and alkenes *via* the Hofmann pathway. Benzylic cations with longer alkyl also yield smaller amounts (<25%) of S_N2-products (trialkylamine, dibenzyl ether). For methyltrioctylammonium, the principal cation in Aliquat® 336, methyl-centered S_N2 was the main pathway of decomposition, leading to the formation of trioctylamine, although the Hofmann pathway still represented about 20% of the observed decomposition. Mohanty and Bae assayed the decomposition products of a range of trialkylbenzylammonium cations under homogeneous aqueous conditions and found no evidence of either Stevens or Sommelet-Hauser rearrangement products, in spite of the fact that several of the investigated compounds are archetypical substrates for this reaction. The authors mainly found benzyl alcohol or derivatives thereof (resulting from substitution), or Hofmann elimination products if the side chains were particularly sensitive hereto (isopropyl). Long *et al.* and Marino and Kreuer also report only substitution and elimination products under aqueous alkaline conditions.[63,64] The rearrangement pathways are thus unlikely to be significant in the decomposition of ionic liquids by aqueous sodium hydroxide, although they may be of significance under anhydrous conditions in the presence of strong bases.[85,86]

Landini and coworkers found little dependence of the length of the long alkyl chains on the stability of the cation.[87] Under the phase-transfer conditions investigated, decomposition of the chlorides salts occurred with half-lives of 18–35 hours at 25 °C in contact with 50 wt% sodium hydroxide. Conversely, Marino and Kreuer observed a strong dependence of the decomposition half-life on the alkyl chain length in alkyltrimethylammonium cations under homogeneous conditions.[63] The authors observed that shorter chains, from methyl to hexyl, are highly resistant to alkaline attack. The exception in this series is ethyl, which is highly susceptible to Hofmann elimination due to a lack of steric inhibition. Further extension of the chain length results in a gradual decline of the stability of the cation. Marino and Kreuer assume this to result from micelle formation, which decreases the degree of cation-anion dissociation, hereby increasing

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the local hydroxide concentration. This effect should hence not occur for more symmetric ammonium cations. Landini *et al.* reported that methyltrioctylammonium exhibited a stability similar to other tetraalkylammonium cations, in spite of the difference in decomposition pathway.[87] On the other hand, Marino and Kreuer found a decrease in stability in the order tetramethylammonium > butyltrimethylammonium > tetrabutylammonium.[63] It thus appears that methyl chains are indeed more resistant to attack than longer chains, but that the substitution of only one chain by methyl has a limited effect on the alkaline stability. Both groups observed that the stability of benzylic cations was somewhat lower than that of tetraalkylammonium cations.

Branching of the side chains can have a profound effect on the stability of ammonium cations. In general, branching at the α-position of side chains does little to improve the alkaline stability of the salts, as Hofmann elimination is the main pathway of decomposition for hydrocarbon chains longer than methyl and this occurs at the β-carbon. In fact, the number of acidic β-protons increases with α-branching, and the incipient double bond in the transition state is stabilized by hyperconjugation to any α-alkyl substituent.[88] This leads to faster Hofmann-type eliminations from α-branched salts than from linear salts. For example, Mohanty and Bae found that the benzylbis(isopropyl)methylammonium exhibited far more rapid decomposition in alkaline solutions than the *n*-propyl analog.[89] An exception are cyclic substituents, such as cyclohexyl. While they are α-branched, the *anti*-periplanar Hofmann transition state introduces excessive ring strain in the substituent and is therefore highly unfavorable.[89] Cyclohexyl groups are particularly unreactive as the ammonium moiety preferentially acquires an equatorial position in the cyclohexyl rings, in which case there is no β-proton in an *anti*-periplanar position.[90] Additionally, S_N2-type substitution is also slow due to the secondary nature of the α-carbon. Hence, these substituents are more resistant to alkaline attack than their linear analogs.[89]

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By contrast, introducing branching at the β-position is a very effective method to improve the base-stability of ammonium cations. This was demonstrated by Lethesh *et al.,* who synthesized a range of ionic liquids based on the bis(2-ethylhexyl)dimethylammonium cation (Fig. 18).[72] The chloride salt, when subjected to 50 wt% sodium hydroxide under phase transfer conditions in 1,2-dichloroethane, showed no evidence of decomposition after 120 hours, even at 80 °C. Conversely, Landini found that tetrahexylammonium chloride had a half-life of 0.4 hours at 60 °C under similar conditions.[87] The ionic liquids were all, unfortunately, quite viscous (> 1450 cP). Follow-up studies by Damilano and coworkers on similar ionic liquids revealed a further increase in the base-stability for longer chain lengths.[91] The authors noted that some (20 mol%) decomposition of the shorter-chain (2-butyloctyl) cation occurred when the chloride salt was added directly to 20 wt% sodium hydroxide at 55 °C for 24 hours. These conditions are milder than those employed by Lethesh *et al.*, but the absence of the organic solvent allows more sodium hydroxide to diffuse into the ionic liquid phase. In methanolic sodium hydroxide, decomposition occurred for all β-branched ionic liquids.

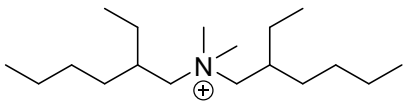


Fig. 18: Structure of the bis(2-ethylhexyl)dimethylammonium cation, an ammonium cation with high alkaline stability.[72]

The resistance of β-branched cations to Hofmann elimination can be attributed to the steric hindrance at the β-site.[72] It has also been hypothesized that the electron-donating effect of the alkyl substituents on the β-site assists in reducing the acidity of the β-protons.[90] Interestingly, Lethesh *et al.* found no evidence of S_N2-type substitution either, to which methyl substituents are generally sensitive. Crowding around the ammonium center may prevent hydroxide anions from effectively attacking the α-position, a fact also reflected by the harsh alkylating conditions

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required by the authors to convert the amine to its quaternary form (dimethyl sulfate, 80 °C, 48 hours). In spite of the high stability of this 2-ethylhexyl derivative, experimental and computational results obtained by the group of Pivovar suggest that the isobutyl group, while also featuring a branched β-carbon, is insufficiently hindered to effectively prevent Hofmann elimination.[64] In fact, the authors predicted somewhat higher sensitivity to elimination due to strain in the cation that is relieved by elimination.

One may assume that full substitution of the β-carbon would further stabilize the ammonium center by preventing Hofmann elimination entirely and by further shielding the α-positions. However, Mohanty and Bae found that the trimethyl(neopentyl)ammonium cation actually decomposed more rapidly than the trimethylpropylammonium cation.[89] The authors attributed this to the possible occurrence of pathways such as the Stevens rearrangement in such compounds. Unfortunately, the decomposition products were not identified. This cation was also included in the computational study by the group of Pivovar, and their results also indicated that it was unlikely for substitution to be responsible for the rapid decomposition of this cation, as the barrier for reaction at the *N*-methyl groups was similar to that of other ammonium cations, while attack at the neopentyl group was highly unfavorable.[64]

Cyclic ammonium cations

Pyrrolidinium and piperidinium ionic liquids are often considered separate cationic classes, but chemically these cations are cyclic ammonium salts. This is reflected in their chemistry in alkaline media, as they share the same pathways of decomposition in Brønsted-basic media with other ammonium salts, i.e. Hofmann elimination and S_N2 substitution. However, the cyclic nature of the cations has profound implications concerning the rate of these reactions.

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The rate of Hofmann elimination is greatly diminished in piperidinium and pyrrolidinium rings due to stereo-electronic factors related to ring geometry. Pyrrolidinium rings, in their lowest-energy conformation, contain no protons *anti*-periplanar to the ammonium center, while this configuration strongly favors Hofmann elimination (Fig. 19).[63] The ring must thus be distorted from its most stable conformation for the elimination to occur. Piperidinium rings, on the other hand, contain protons *anti*-periplanar to the ammonium center in the strain-free chair configuration.[63] Quite unexpectedly, Hofmann elimination is strongly inhibited in piperidinium rings as well. Marino and Kreuer hypothesize that the transition state geometry is responsible for the slow observed reaction rate.[63] While the substrate geometry is optimal to initiate elimination, the ring distorts as the reaction progresses. As a result, ring strain increases, and eclipsed and transannular interactions of the ring hydrogen atoms grow stronger (Fig. 20a). However, the geometry of the transition state remains cyclic, and therefore the increased strain cannot be relieved. The transition state is thus highly energetic, which increases the required activation barrier for Hofmann elimination. In either case, the reduced free rotation of cyclic systems also reduces the statistical likelihood of elimination.[90] Von Braun and Jewers and McKenna found that the both ring systems are approximately equally sensitive to Hofmann elimination.[90,92] Jewers and McKenna argue that the lack of an *anti*-periplanar proton in pyrrolidinium cations is offset by the higher ring strain before reaction.[90]

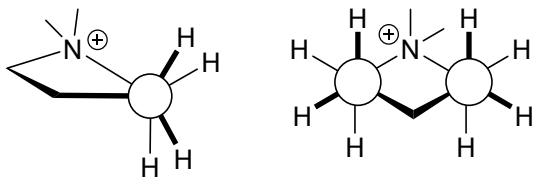


Fig. 19: Lowest-energy conformations of pyrrolidinium (left) and piperidinium (right) showing the geometry of ß-hydrogen atoms relative to the ammonium center.[63]

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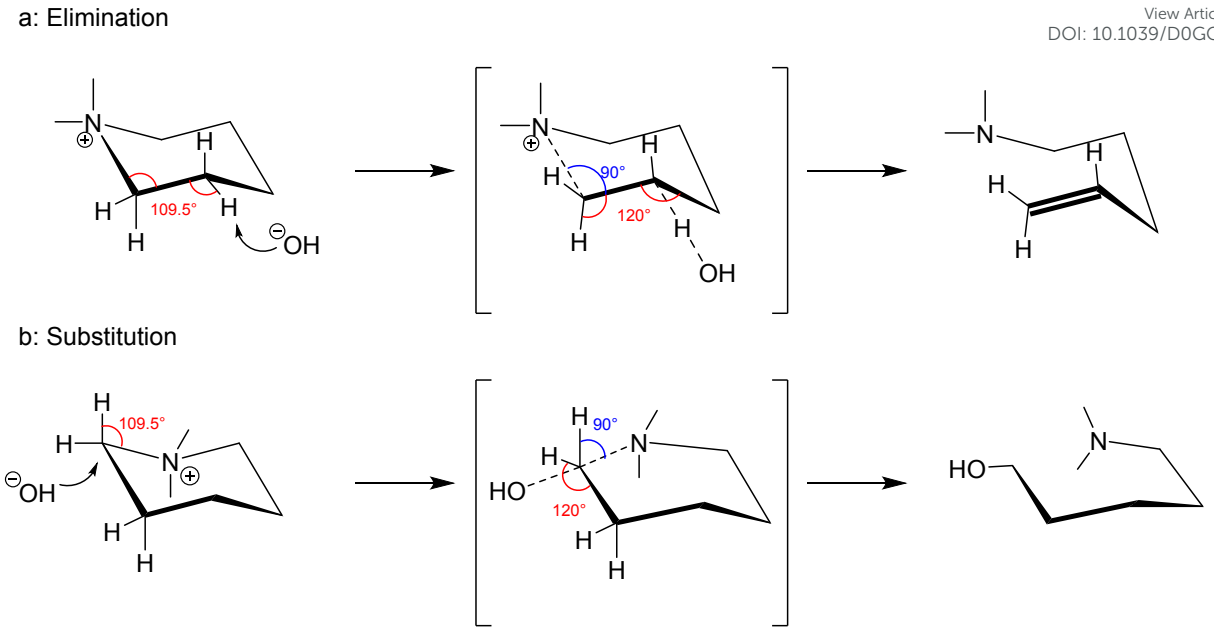


Fig. 20: Reaction pathways of Hofmann elimination (a, above) and S_N2 (b, below) showing the distortion of the cyclic transition states, respectively due to a change of hybridization from sp^3 to sp^2 and due to configuration inversion.[63]

Substitution is also influenced very strongly by the cyclic nature of pyrrolidinium and piperidinium cations. Both rings are less susceptible to S_N2 reactions than acyclic ammonium systems, as a result of transition state geometry. The S_N2 transition state coordination geometry of the α-carbon is trigonal bipyramidal, while the entire system remains cyclic (Fig. 19b). Similar to the Hofmann transition state, bond strain and transannular interactions increase strongly in the S_N2 transition state, which increases the activation barrier and inhibits reaction.[63] Bond strain is lower in the piperidinium system than in pyrrolidinium system, and hence one may expect the activation barrier to be correspondingly greater in the piperidinium system.[90] Indeed, the piperidinium system is far less sensitive to S_N2 ring opening than the pyrrolidinium system, and the difference in reactivity of the two cation types is greater than for Hofmann elimination.[63,90,92]

Several authors report that pyrrolidinium and piperidinium cations are superior in their alkaline stability compared to other common classes of cations used in ionic liquids.[59,93] For instance,

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Meek and Elabd report no decomposition of butylmethylpyrrolidinium after 168 hours of contact with nearly 10 mol L^{-1} sodium hydroxide at 30 °C, or 4 mol L^{-1} at 80 °C.[93] Similarly, Olsson reported no decomposition of a dimethylpiperidinium salt after 336 hours of contact with a 2 mol L^{-1} sodium hydroxide solution at 120 °C.[94] Conversely, Gu *et al*. report that even the most stable dialkylpyrrolidinium cations exhibit about 2–3 wt% of decomposition in 1 mol L^{-1} sodium hydroxide in 3/1 methanol/water at 80 °C after 168 hours.[95] Many examples exist of polycationic polymers containing piperidinium and pyrrolidinium cations, but these examples are left out of this comparison as the inclusion of cations in a polymer backbone may drastically affect the stability of the cation.[93,94] Marino and Kreuer, in their systematic study, concluded that dimethylpyrrolidinium and dimethylpiperidinium respectively had half-lives about one third longer and shorter than tetramethylammonium in hot, concentrated alkali, which casts doubts on the purported extreme base-stability of the dialkyl cyclic ammonium cations.[63] Both Marino and Kreuer and Chu *et al.* reported that the decomposition mechanisms for piperidinium salts exclusively involve the alkyl groups in aqueous solutions, rather than the ring structure.[63,96]

In other solvent media, this preference may disappear. Illuminati and Lillocci investigated the stability of dimethylpyrrolidinium, dimethylpiperidinium and open-chain ammonium cations in methanolic sodium methoxide and reported that pyrrolidinium cations are particularly sensitive to ring-opening substitution as a result of ring strain, while piperidinium cations mainly decompose *via* demethylation.[97] In addition, they found pyrrolidinium cations to be slightly less stable than an open-chain analog and piperininium cations to be slightly more stable than the open-chain cation.[98] For both cations, elimination and ring-based substitution occurred to a certain extent. The α-methyl analogs of these cyclic cations underwent Hofmann elimination very readily as ring strain factors are less pertinent in the E2 transition states of these cations.[99] At room temperature, dialkylpyrrolidinium salts appear fairly compatible with

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alkoxides, as evidenced by the long-term stability at room temperature of butylmethylpyrrolidinium isopropoxide/bistriflimide mixtures at ambient temperatures (up to 8 months).[100] Pyrolysis of cyclic ammonium hydroxides or treatment of these cations with ammoniacal potassium amide mostly yields unsaturated decomposition products. Under these conditions, the share of substitution reduces even further, and elimination becomes the only substantial mechanism of decomposition.[82,101]

Taking into account the stability of the ring structures in aqueous solutions, Marino and Kreuer designed a pair of highly stable, *spiro*-fused ammonium salts, which do not contain linear alkyl groups.[63] These compounds, shown in Fig. 21 are termed 5-azonia-spiro[4.4]nonane and 6-azonia-spiro[5.5]undecane and can respectively be seen as *N-spiro*-fused bis(pyrrolidinium) and bis(piperidinium) cations. The alkaline stability of the former is rather disappointing, as the ring in pyrrolidinium salts remains sensitive to S_N2 attack, but the bis(piperidinium) cation exhibits exceptional alkaline stability, and has a half-life about twice that of tetramethylammonium under identical conditions. Decomposition occurs exclusively *via* S_N2 substitution in aqueous solutions.[63] Pyrolysis of the corresponding hydroxide salts occurs *via* a combination of substitution and elimination.[90] The group of Jannasch also observed excellent alkaline stability for cations derived from the bis(piperidinium) cation, with no decomposition occurring after 1800 hours in 1 mol L^{-1} sodium deuteroxide at 120 °C.[102]

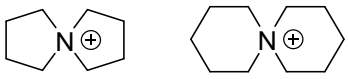


Fig. 21: Structures of 5-azonia-spiro[4.4]nonane (left) and 6-azonia-spiro[5.5]undecane (right).

Decomposition pathway

As mentioned above, rearrangements that are triggered by α-deprotonation are uncommon for ammonium, pyrrolidinium and piperidinium salts in aqueous media, except in cases where the

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α-position is particularly acidic due to the inclusion of electron-withdrawing groups.[77] Pine concluded that this can be extended to polar solvents in general and that weaker bases tend to give more substitution and elimination products.[77] The requisite factor for the occurrence of rearrangement pathways appears to be for the ylidic form to be sufficiently long-lived and abundant. Many examples illustrate these tendencies. Thomson and Stevens observed that dibenzyldimethylammonium chloride cleanly decomposed by methyl-centered substitution when heated in methanolic sodium methoxide or pentanolic sodium pentoxide, yielding dibenzylmethylamine and the corresponding ethers.[103] This is striking as the substrate in these reactions is quite prone to rearrangement processes. When the possibility of reprotonation of the α-position was suppressed, the rearrangement pathways became dominant: the authors obtained a roughly 50/50 mixture of substitution and Stevens rearrangement products when the same substrate was fused with sodium methoxide.[103] When the fusion was carried out with sodium amide, substitution became insignificant. Wittig and Burger reported that dimethylpyrrolidinium iodide decomposes into the Hofmann product when treated with potassium amide in liquid ammonia.[82] The thermal decomposition of the methyl-centered ylide derived from this salt by treatment with butyllithium gave a strikingly different result. The authors also found that under these solvent free-conditions, the Stevens rearrangement product could be detected (*N*-ethylpyrrolidine), in addition to the elimination product (*N,N*-dimethylaminobutene) and *N*-methylpyrrolidine, a likely substitution product (Fig. 22). Dimethylpiperidinium iodide behaved similarly. Several other authors have reported the occurrence of rearrangement pathways after treating various cyclic or benzylic ammonium cations with organolithium compounds in aprotic ethereal or hydrocarbon solvents.[104–107]

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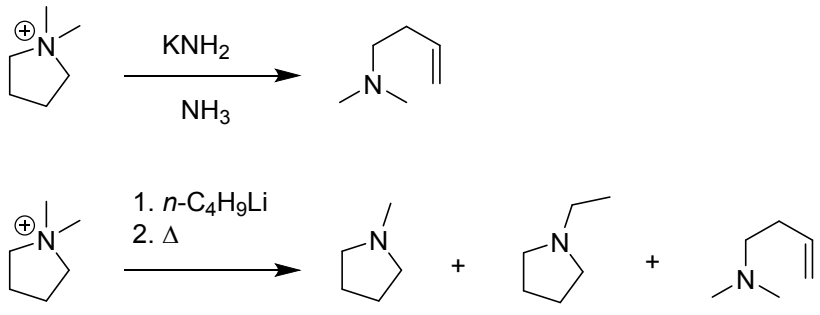


Fig. 22: Dependence of the decomposition products of dimethylpyrrolidinium iodide on the nature of the base.[82]

The tendency of extended alkyl groups to eliminate from ammonium salts is strong and this process remains the major pathway of decomposition for aliphatic ammonium salts, even in less polar and strongly basic media. Fully aliphatic ammonium cations treated with alkyllithium reagents decompose *via* elimination through an ylide intermediate.[70,71] The same holds true for the pyrolysis of basic ammonium salts. Ingold and Patel reported that the hydroxides, ethoxides and methoxides of ethyltrimethylammonium and isobutyltrimethylammonium all decomposed upon heating *via* a combination of substitution and elimination, with the latter dominating.[108] Other authors obtained similar results.[71,109] Nevertheless, salts containing linear, acyclic alkyl chains may undergo rearrangement-type decomposition, even in polar solvents, if particularly α-acidic substituents are also present.[110,111] An illustrative example is the reaction of ammoniacal sodium amide with ammonium cations containing both a benzyl group and extended alkyl chains (ethyl, propyl, butyl, isobutyl and isopentyl). Under these conditions, all cations exhibited a certain propensity to elimination, but rearrangements remained dominant due to the acidity of the benzyl group.[112] The inclusion of two alkyl chains (ethyl and isobutyl) in benzylic ammonium cations caused elimination to become dominant, with rearrangement pathways representing only 2% of the decomposition by ammoniacal sodium amide.[112]

Cyclic ammonium cations, while aliphatic, undergo eliminations less readily and this is observed upon treatment with organolithium bases. As discussed above, the methyl-centered

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ylide derived from dimethylpyrrolidinium undergoes rearrangement more readily than elimination.[82] Methylbenzylpiperidinium iodide also decomposes *via* a combination of rearrangement pathways when treated with ammoniacal sodium amide.[113] By contrast, the analogous morpholinium salt decomposes by elimination under similar conditions, due to the higher flexibility of the ring and the activation of the β-protons by the adjacent oxygen atom (Fig. 23).[114]

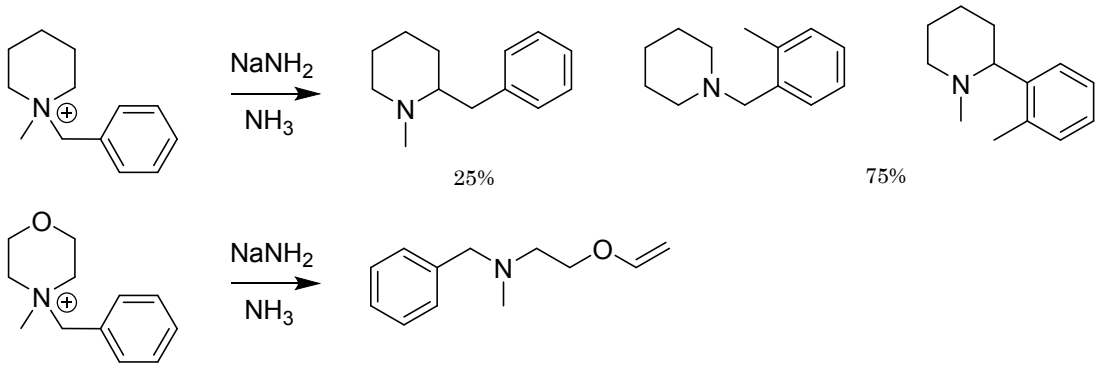


Fig. 23: Decomposition of 6-membered heterocyclic ammonium salts by ammoniacal sodium amide.[114]

Simple tetraalkylammonium ionic liquids offer a good compromise between cost, physical properties and base stability. At ambient temperatures and on shorter time scales, most tetraalkylammonium salts will largely retain their structure in contact with moderately strong bases. Incorporating β-branched alkyl chains is an effective means to improve the base-stability of these ionic liquids, but even β-branched ammonium salts may show decomposition at elevated temperatures when contacted with strongly alkaline solutions. Moreover, this substitution comes at the cost of increased viscosity. Cyclic ammonium salts (piperidinium, pyrrolidinium) have been hailed by some authors as candidates for extremely base-stable ionic liquids, but in practice, their stability is only marginally superior to that of other ammonium salts. All ammonium salts are poorly compatible with alcoholic solutions of alkoxides, amide bases and organolithium reagents.

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The amines and alkenes formed as decomposition products may potentially interfere with organic reactions conducted in ammonium ionic liquids. For instance, amines may conceivably compete with other nucleophiles to form unwanted addition and substitution products. Alkenes may enter coupling reactions such as the Heck coupling, should ammonium ionic liquids be chosen as solvents for this reaction requiring stoichiometric amounts of base.

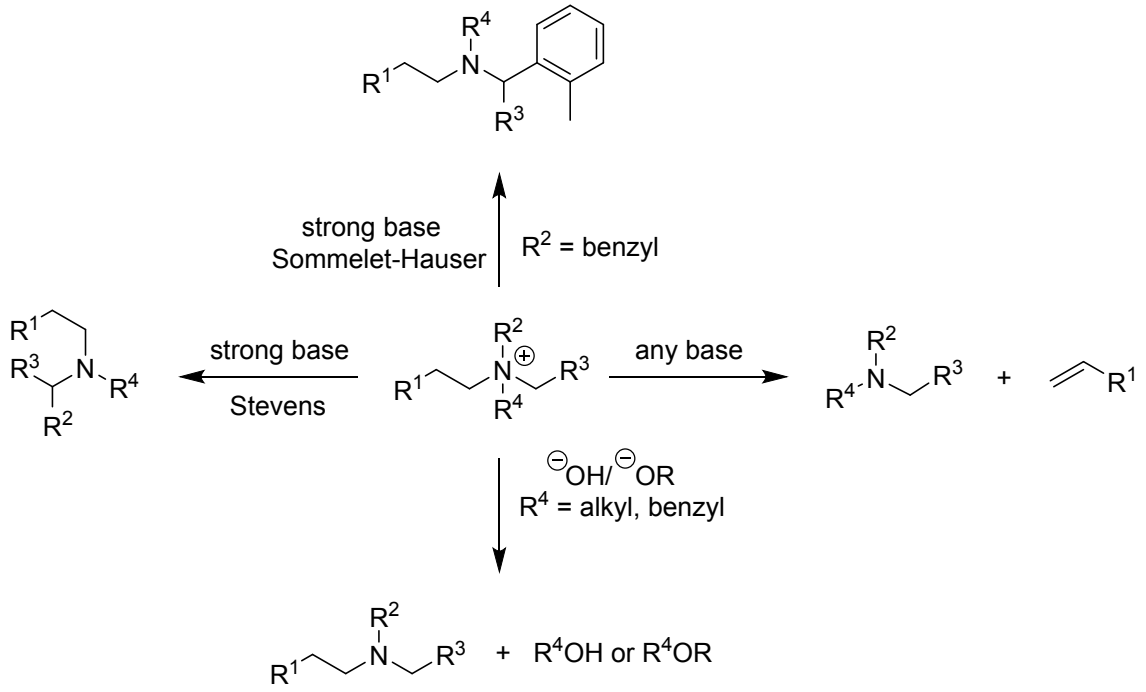


Fig. 24: Decomposition pathways of quaternary ammonium salts in basic media.

Phosphonium ionic liquids

Alkaline hydrolysis

Phosphonium salts are a more recent class of ionic liquids which exhibit higher thermal stabilities and lower viscosities than analogous ammonium salts.[115] Unfortunately, this class of cations has been known for some time to be poorly compatible with alkaline conditions, due to the tendency of phosphonium salts to convert to phosphine oxides.[116] In fact, they are less stable with respect to alkaline attack than the corresponding ammonium salts.[87] Fenton and Ingold

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investigated the mechanism of phosphonium cation decomposition as early as 1929.[117] They found that, in addition to a phosphine oxide, an alkane was produced during the reaction. By analyzing the product mixtures obtained by heating asymmetric phosphonium hydroxides, the authors obtained the following order of lability: benzyl > phenyl > methyl > 2-phenylethyl > ethyl ≈ higher alkyl. This sequence corresponds well with the stability of the corresponding carbanions, leading the authors to postulate a mechanism in which the hydroxide anion first attacks the phosphorus center, the hydroxide proton is then lost, and a carbanionic alkyl (or aryl) group is finally expelled and protonated to yield an alkane. However, it is very likely that the incipient carbanion is protonated concertedly with its formation.[118] The reaction proceeds as shown in Fig. 25. Two molecules of sodium hydroxide are involved in the process: one is required for adduct formation, the other to deprotonate the adduct. The existence of the intermediate adduct was recently confirmed.[118] Siegel found that this reaction is second order in hydroxide for nearly all substituents, meaning that the rate determining step is the expulsion of the carbanion.[116]

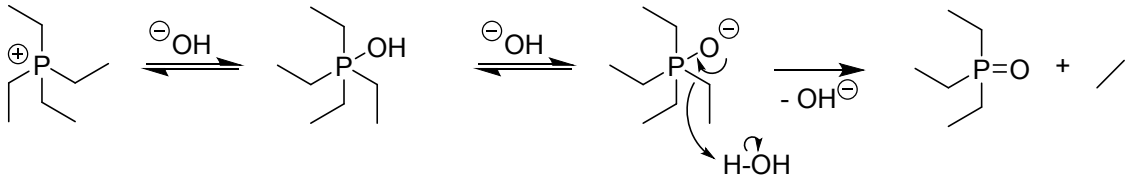


Fig. 25: Mechanism of hydroxide-induced phosphonium salt decomposition as proposed by Fenton and Ingold.[117]

Protons peripheral to phosphonium centers exchange at rates many orders of magnitude greater than those adjacent to ammonium centers, due to resonance stabilization of the conjugate base (phosphorus ylide formation).[119–121] At room temperature, the exchange process takes several days, but at moderately elevated temperatures (50–70 °C) this occurs within a few hours in 0.1 mol L^{-1} to 1 mol L^{-1} deuteroxide solutions.[120,121] In spite of the structural similarity of

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phosphonium and ammonium ionic liquids, Hofmann elimination is not a significant pathway of decomposition for phosphonium salts in aqueous alkali. This is due to the lower electronegativity of phosphorus and the resulting lower acidity of the β-protons.[117] However, Fenton and Ingold reported that Hofmann elimination may occur for phosphonium salts with electron-withdrawing groups placed at the β-carbons of the substituents.[117] When compared to quaternary ammonium ionic liquids, phosphonium ionic liquids are significantly less base-stable.[87] Landini and coworkers found that tetrabutylphosphnium chloride dissolved in chlorobenzene had a half-life of about 2 min in contact with 50 wt% sodium hydroxide solution at room temperature. This contrasts starkly with the 18 hour half-life of the corresponding ammonium salt (tatrabutylammonium chloride). Lengthening of the substituents did little to increase the stability of the chloride salts, as the half-life of tributyl(hexadecyl)phosphonium chloride was identical under the same conditions. Phosphonium bromides were found to be slightly more stable, and at elevated temperatures, the long-chain bromide was more stable than the short-chain bromide by a factor of about four.

Zhang *et al.* used knowledge on the mechanism of phosphonium salt hydrolysis to rationally design a highly base-stable phosphonium cation by crowding the quaternary center with groups with poor anionic stability and a high electron-donating potential: methyltris(2,4,6-trimethylphenyl)phosphonium (Fig. 26).[122] Hence, both the initial formation of the hydroxide-phosphonium adduct and the heterolysis of the phosphorus-carbon bond are suppressed. Unfortunately, the aromatic nature of the substituents resulted in the salts to be solids.

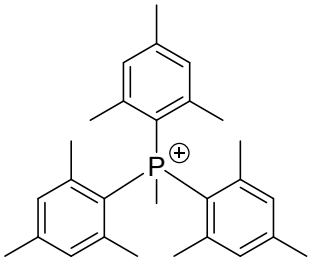


Fig. 26: Highly base-stable phosphonium cation designed by Zhang et al.[122]

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Cristau *et al.* found that the nature of the solvent greatly influenced the decomposition rate, and solvents of intermediate polarity were found to promote decomposition under phase transfer conditions.[123] Homogeneous systems in which sodium hydroxide and the phosphonium salt resided in the same phase resulted in the fastest decomposition. Khalil and Aksnes found that the enthalpy of activation increases strongly with solvent polarity and attributed this to increased solvation of the phosphonium and hydroxide ions in polar solvents.[124–126] However, these studies were conducted on the tetraphenylphosphonium cation. Phosphonium ionic liquid are generally tetraalkylphosphonium salts, which raises the question whether this conclusion can be extended to non-aromatic phosphonium salts. This is not the case, as the group of Waite observed a drastic increase in the sensitivity of the alkaline hydrolysis rate to the solvent polarity with the number of phenyl substituents.[127] The authors determined the third-order rate constants of hydrolysis in alkaline methanol/water mixtures (50 °C) and alkaline tetrahydrofuran/water mixtures (40 °C). In all cases, the latter solvent system caused more rapid hydrolysis of the salt, but the ratio of the third-order rate constants decreased progressively from 770 to 1.5 over the range from tetraphenylphosphonium iodide to tetrabutylphosphonium iodide. The authors rationalized their results by invoking the electron-donating properties of alkyl substituents. Alkyl groups reduce the magnitude of the positive charge on the phosphorus atom and hence the degree of solvation in highly polar solvents. Changing solvents will thus have greater effect on arylphosphonium salts than alkylphosphonium salts.

Dicationic phosphonium salts (meaning compounds containing two quaternary phosphonium centers) have been the subject of separate studies concerning their decomposition in alkaline media. These compounds are of interest as the derived ionic liquids feature high ion concentrations and improved thermal stabilities.[128] Wittig found that the two phosphonium centers do not always react independently.[129] Brophy and Gallagher later confirmed these findings.[130] Independent decomposition of the two centers would yield two equivalents of

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phosphine oxide (or a bis(phosphine oxide)) and one or two equivalents of alkane, and this behavior is indeed observed for methylene-bridged and trimethylene-linked phosphonium dications.[130,131] Ethylene-bridged phosphonium dications, however, yielded one equivalent of phosphine oxide and one equivalent of phosphine, with the loss of one equivalent of ethylene gas being inferred.[130] This behavior was studied extensively by Brophy and Gallagher, who proposed a mechanism involving concerted formation of the phosphine oxide and elimination of the phosphine from an *anti*-periplanar transition state (Fig. 27a).[130] Vinylene-bridged compounds react analogously to form acetylene in addition to a phosphine oxide and a phosphine. In benzylic salts, this reaction competes with the formation of a bis(phosphine oxide), *i.e.* independent decomposition of the phosphonium centers, due to the lability of benzylic groups with respect to elimination from phosphonium salts. Most interesting is the fact that fully aliphatic phosphonium cations, *i.e.* those most relevant to the field of ionic liquids, undergo this reaction less readily and produce substoichiometric amounts of the phosphine oxide, while relatively large amounts of phosphine are found in addition to a hydroxyethylphosphonium salt. This suggest competing β-elimination, which is facilitated by the poor stability of alkyl anions and the polarization of the β-protons by the adjacent phosphonium center in the linker group. The mechanism of this competing reaction is given in Fig. 27b.

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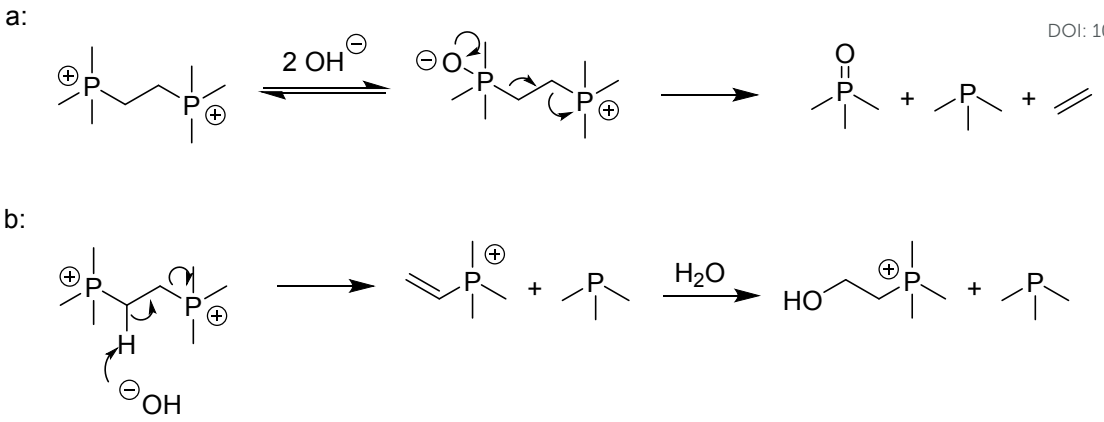


Fig. 27: Two pathways of decomposition of ethylene-bridged aliphatic bis(phosphonium) salts, and their mechanisms as proposed by Brophy and Gallagher: concerted fragmentation (a, above) and β-elimination (b, below).[130] Methyl substituents are shown for visual clarity.

Organometallic, hydride and alkoxide bases

While the sensitivity of phosphonium ionic liquids to alkaline hydrolysis is high, Grignard reagents can be stored in some phosphonium ionic liquids for extended periods of time.[119] The prerequisite hereto is the presence of groups which coordinate the magnesium ion of the Grignard reagent. This was the conclusion of Ramnial *et al.*, who performed their experiments in trihexyl(tetradecyl)phosphonium ionic liquids (Cyphos® IL101).[119] In the absence of coordinating groups, the Grignard reagent readily attacks the phosphonium cation, causing its decomposition. These groups can either be supplied by a cosolvent (e.g. tetrahydrofuran), by the ionic liquid anion (e.g. carboxylates, *vide infra*) or even by the ionic liquid cation itself. The group of Kawatsura reported that Grignard reagents could be stored without cosolvent in an ether-functionalized ionic liquid, tributyl(methoxyethyl)phosphonium bistriflimide (Fig. 28).[132] Adding benzaldehyde to the resulting solution and quenching with water afforded the expected secondary alcohol. Conversely, the authors could not synthesize Grignard reagents *in situ*, a finding later corroborated by Ford *et al.* using a similar ionic liquid incorporating octyl rather than butyl chains.[133] Addition of diethyl ether allowed the *in situ* generation of Grignard reagents by Ford *et al*.

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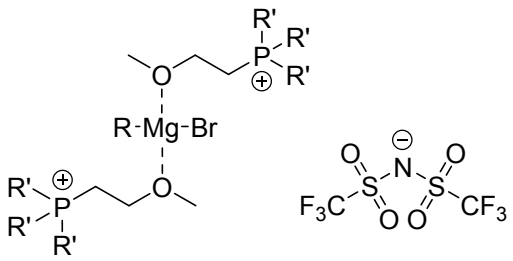


Fig. 28: Coordination of ether-functionalized phosphonium cations to Grignard reagents as observed by Kawatsura et al.[132]

In the absence of coordinating groups, the Grignard reagent readily attacks the phosphonium cation, causing its decomposition.[119] This occurs, for instance, in phosphonium chloride, dicyanamide or bistriflimide ionic liquids. In the latter two ionic liquids, decomposition occurs even in the presence of tetrahydrofuran. The decomposition products identified by Ramnial and coworkers included those of the Hofmann elimination (hexene and the corresponding phosphine), although the authors hypothesize that electron transfer leads to the formation of these products.

Other organometallic reagents behave similarly to Grignard reagents in that they tend to decompose tetraalkylphosphonium salts into a phosphine and an alkene. Ramnial *et al.* reported that *n*-butyllithium could not be stabilized in Cyphos® IL101-derived ionic liquids, regardless of the ionic liquid anion or the presence of tetrahydrofuran, and that the aforementioned products were identified. Coffman and Marvel also reported the formation of an alkane (derived from the base), triethylphosphine and an alkali metal iodide when tetraethylphosphonium iodide was treated with either butyllithium or sodium tritylate.[134]. The decomposition mechanism thus appears to be a Hofmann-type E2 elimination (Fig. 29). Organozinc compounds do not attack phosphonium cations at ambient temperatures. At elevated temperatures (150 °C), Staudinger and Meyer observed the formation of triethylphosphine, zinc iodide and an alkane when treating tetraethylphosphonium iodide salts with diethylzinc.[135]

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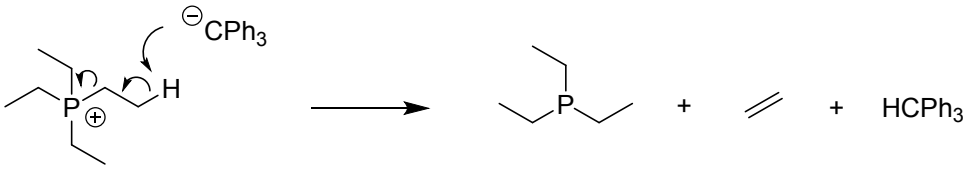


Fig. 29: Decomposition of phosphonium salts by organometallic bases as observed by Coffman and Marvel.[134]

Hydride bases (generally supplied as $LiAlH_4$ in the literature) are relatively compact and can therefore attack at the phosphorus center itself, analogously to hydroxide bases. After initial attack at the phosphorus center, a neutral, pentavalent phosphorane is formed, which decomposes to lose an alkane (Fig. 30).[136] As observed for alkaline hydrolysis of phosphonium salts, benzyl and phenyl groups leave preferentially over alkyl groups, reflecting the order of anionic stability.[137,138] Conversely, Gough and Trippett noted an exception to this rule, as isopropyltriphenylphosphonium iodide yielded triphenylphosphine after treatment with $LiAlH_4$.[138] The steric constraints imparted by the phenyl and secondary alkyl groups may prevent the hydride from accessing the central phosphorus atom and thereby forcing a mechanism similar to that adopted by carbon-centered Brønsted bases (Fig. 31).[136] Brophy and Gallagher reported that ethylene and vinylene-bridged bis(phosphonium) salts treated with sodium hydride once again exhibited a concerted decomposition of both phosphonium centers to yield two phosphines, a proton and ethylene or acetylene gas.[136] The mechanism most likely proceeds according to that shown in Fig. 30, which is analogous to that observed for the alkaline hydrolysis of similar salts.

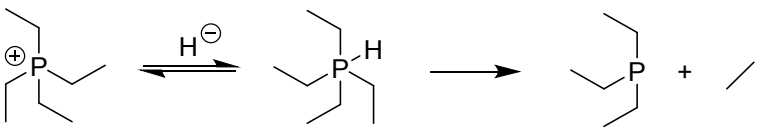


Fig. 30: Reduction of phosphonium salts by hydride bases.[136]

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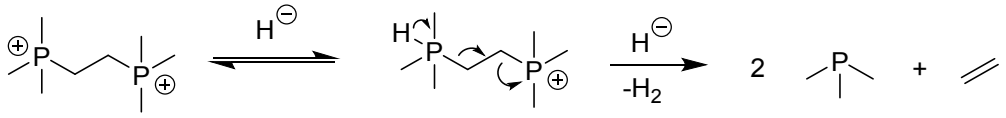


Fig. 31: Reduction of ethylene-bridged bis(phosphonium salts) according to Brophy and Gallagher.[136] Methyl substituents are shown for visual clarity.

Ramnial *et al.* also reported that phosphonium ionic liquids are resistant to deprotonation by sodium borohydride and *N*-heterocyclic carbenes derived from imidazolium salts.[119,139,140] The authors argue that the resistance of phosphonium ionic liquids to deprotonation is grounded in the steric hindrance provided by the long alkyl chains surrounding the center of charge. In support of this hypothesis, the authors note that methyltriphenylphosphonium and ethyltriphenylphosphonium salts, which have more readily accessible α-protons, can be deprotonated by Grignard reagents when dissolved in a long-chain phosphonium ionic liquid. The conjugate base, a neutral phosphorane with an ylidic character (Ph_3P=CHR), is a Wittig reagent and can subsequently be reacted with carbonyl compounds to yield olefins.[119]

Grayson and Keough investigated the reactivity of phosphonium salts with respect to alkoxides and concluded that only benzylic phosphonium salts decomposed under the action of such bases.[141] The authors propose that, in contrast to hydroxide bases, alkoxide bases do not form a stable adduct with the phosphonium salt and the attack is concomitant with the expulsion of a carbanion as leaving group. Hence, only benzylic groups are reactive, as other groups are insufficiently stable as carbanions. Indeed, the authors observed no attack of alkoxides to butyltriphenylphosphonium bromide and tetraethylphosphonium bromide under similar conditions. However, these salts remain subject to decomposition if impurities of water are present in the reaction mixture. After attack of the alkoxide and expulsion of the benzyl anion, an alkoxyphosphonium salt is formed, which further solvolyzes to form a phosphine oxide and

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an ether (Fig. 32). Trials by Parisek *et al.* with optically active salts supported the S_N2-type mechanism proposed by Grayson and Keough.[142]

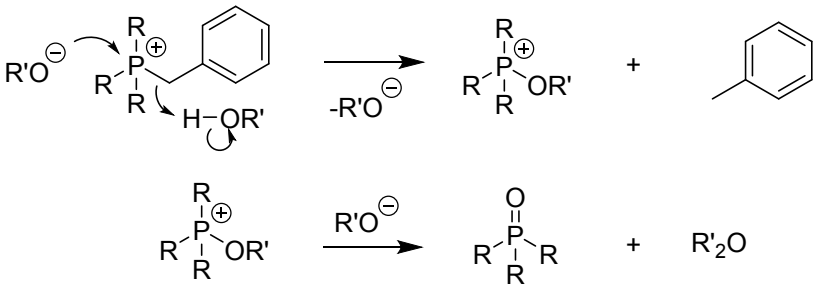


Fig. 32: Decomposition of benzylic phosphonium salts under the influence of alkoxides as observed by Grayson and Keough.[141]

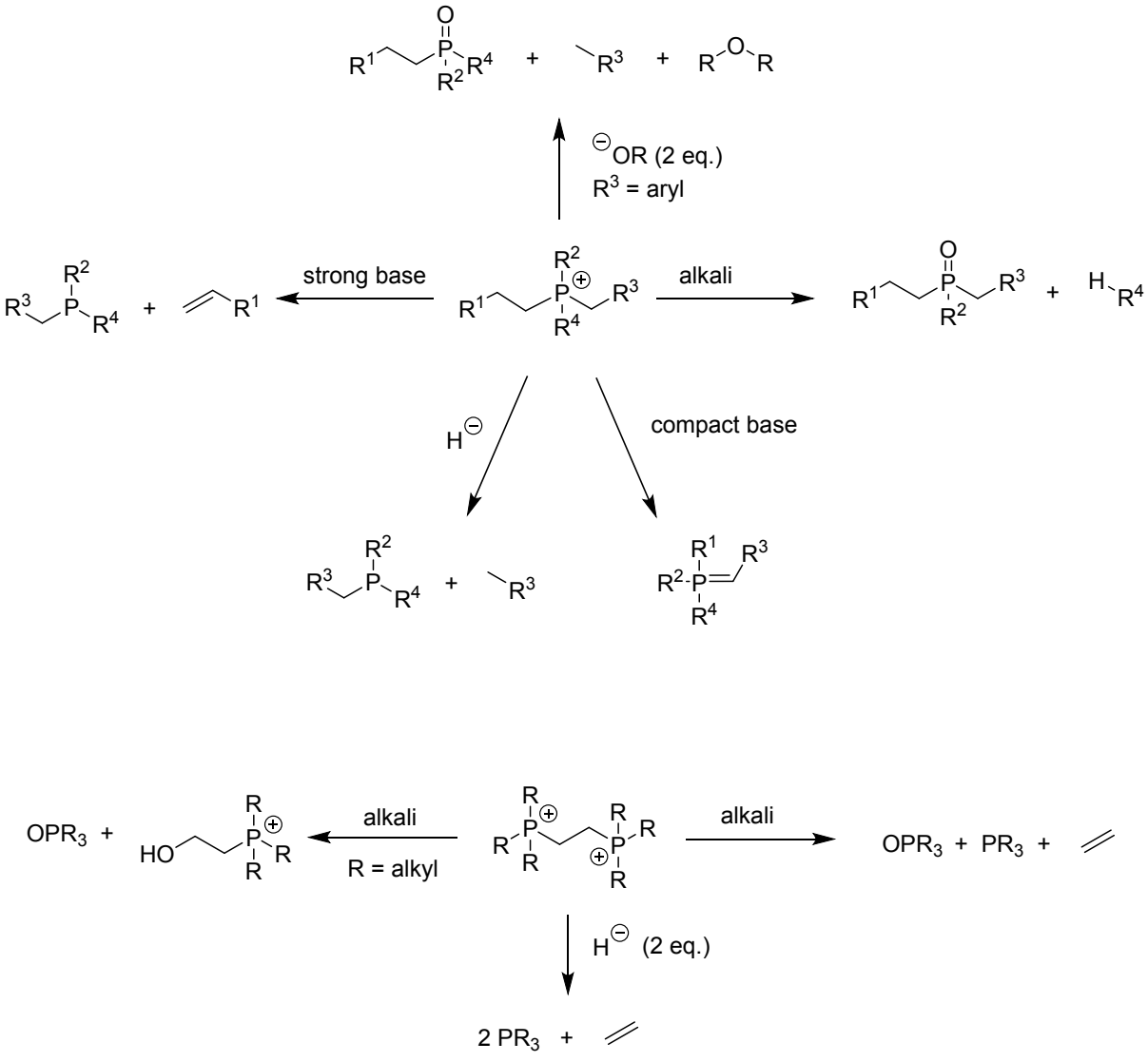


Fig. 33: Decomposition pathways of phosphonium salts in basic media

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Phosphonium ionic liquids are very poorly compatible with hydroxide bases, and generally incompatible with organometallic reagents. Grignard reagents can be used in certain phosphonium ionic liquids, if groups are incorporated which are capable of coordinating to the magnesium center, or if cosolvents are added containing coordinating groups. If these conditions are not met, phosphonium ionic liquids decompose to an alkene and a phosphine, as they do in contact with organolithium reagents. Phosphonium ionic liquids are also readily reduced by most hydride bases (but not sodium borohydride). Conversely, it may be possible to use alkoxide bases in tetraalkylphosphonium ionic liquids, as only benzylic phosphonium salts have been observed to react with alkoxides.

Phosphine oxides and alkanes formed as decomposition products are largely inert and are not expected to interfere with processes being conducted in the ionic liquid very often. Phosphine oxides are, however, strongly coordinating with respect to metals, and may destroy transition metal catalysts or interfere with solvent extraction of metal ions. Phosphines and alkenes formed as decomposition products may potentially interfere with organic reactions conducted in phosphonium ionic liquids. For instance, phosphines may conceivably compete with other nucleophiles to form unwanted addition and substitution products. Alkenes may enter coupling reactions such as the Heck coupling, should ammonium ionic liquids be chosen as solvents for this reaction requiring stoichiometric amounts of base.

Other cations

Pyridinium ionic liquids

A number of other cations have been investigated in the context of ionic liquids, albeit to a lesser extent. Of these, pyridinium cations are one of the more common types. The stability of these cations in aqueous alkali is limited. *Ortho*-unsubstituted pyridinium cations generally

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exhibit stabilities intermediate between 2-unsubstituted and 2-methylated imidazolium cations.[89,143] Hnát *et al.* report the stability as being intermediate between ammonium and phosphonium cations.[144] The mechanism consists of two steps: (1) *ortho*-addition of the hydroxide anion to the pyridinium ring and (2) oxidation to form an *N*-substituted 2-pyridone (Fig. 34).[144,145] Since the attack does not involve the *N*-substituent, alkylpyridinium and benzylpyridinium decomposition rates are similar.[75,144,146] Conversely, electronic substituent effects do influence the susceptibility of the aromatic ring to nucleophilic attack.[147] This is evidenced by the hydrolysis of cyanopyridinium salts to 4-pyridones at pH of only 12.[148] On the other hand, the *ortho*-methylated *N*-benzyl-2-methylpyridinium is are somewhat more resistant to decomposition than its 2-unsubstituted congener and tends to decompose by S_N2 rather than nucleophilic addition.[89] The methyl protons in 2-methylpyridinium (2-picolinium) salts are somewhat acidic, and the cation can be quantitatively deprotonated under the influence of strong bases such as potassium hydride.[44] The 2-position of pyridinium salts is also acidic and subject to proton-deuterium exchange. The half-life for exchange at a pH of 10 is about 2 hours at 75 °C for both benzyl and alkylpyridinium cations.[149]

Other strong bases also attack pyridinium cations at the 2-position. It has been well established that the hydride anion (supplied by sodium borohydride) reduces pyridinium cations to dihydropyridines. In the absence of directing groups, this attack occurs at the 2-position (Fig. 34). A 1966 review by Lyle and Anderson covers the influence of ring and nitrogen substituent effects on the reduction process.[150] Organolithium reagents and Grignard reagents add to the 2-position in pyridinium cations in an analogous manner to yield 2-alkyl or 2-aryl-1,2-dihydropyridines.[151–153] Nevertheless, Law *et al.* have described the synthesis and use of Grignard reagents in pyridinium ionic liquids.[154] An additional coordinating ligand (pyridine) was required to stabilize the Grignard reagent in solution and obtain the desired Grignard reaction products. Without the ligand, secondary alkyl iodides and pinacol coupling products

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were observed. Ford *et al.* circumvented this problem by using an ether-functionalized pyridinium ionic liquid, a strategy similar to that adopted by the group of Kawatsura when using phosphonium ionic liquids as solvents for Grignard reagents.[132,133] However, the authors noted a limited recovery of the ionic liquid after reaction (approx. 80%) and the formation of other side products (primary alcohols). Side product formation decreased in the presence of diethyl ether. The authors concluded that the most likely mechanism involved addition of the Grignard reagent to the pyridinium cation and subsequent reduction of the aldehyde to the primary alcohol by the formed dihydropyridine. This suggests that the ether moiety incorporated in the cation did not sufficiently stabilize the Grignard reagent for the desired Grignard reaction to occur selectively. Law *et al.* did not study the structural integrity of the cation after reaction.[154] However, considering the elevated temperatures used during reaction and the numerous previous reports of facile Grignard reagent addition to pyridinium salts, this issue deserves attention in future work.

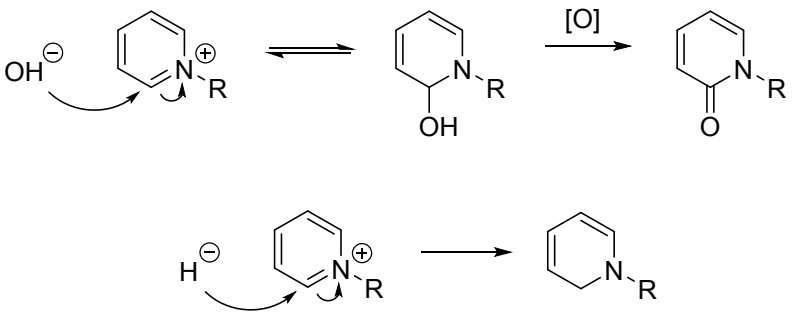


Fig. 34: Addition of hydroxide or hydride anions to pyridinium cations to yield 2-pyridines or 1,2-dihydropyridines.[144,145,150]

Sulfonium ionic liquids

A small body of literature exists investigating the use of sulfonium ionic liquids, and some examples are commercially available. The reactivity of these salts in alkaline media is substantially higher than that of ammonium salts, but the decomposition mechanisms are

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analogous. Under the influence of hydroxide or alkoxide bases in water or alcohols, they mainly undergo Hofmann elimination and substitution.[74,155] Compared to ammonium salts, the share of the substitution mechanism is generally higher, which has been attributed to the combined effects of the lower β-acidity of sulfonium salts and weaker C–S bond.[74] Sulfides are less basic than amines and hence better leaving groups. As a result, sulfonium salts decompose significantly more rapidly than ammonium salts.[74,88] The Hofmann rule is followed for eliminations, but the elimination rate of sulfonium salts is far less dependent on the degree of substitution than that of ammonium salts, making sulfonium salts more difficult to stabilize.[74] This has been explained both in terms of the reduced steric demands of the disubstituted sulfonium group and the nature of the transition state. The latter explanation invokes the higher leaving group ability of the sulfide leaving group, which results in a mechanism that is shifted more towards an E1-type, wherein the acidity of the β-protons if of lesser importance.[74] Due to the high similarity of sulfonium and ammonium Hofmann eliminations, patterns observed for ammonium salts concerning reactivity as a function of branching remain pertinent for sulfonium salts.[74,88] Highly hindered (branched) dimethylsulfonium salts yield only small amounts of Hofmann product and decompose nearly exclusively *via* substitution.[74,155] By contrast, substitution is insignificant when the β-protons are benzylic.[156] Evidence for ylide formation and subsequent intramolecular elimination has also been found in sulfonium systems treated with organometalics.[157] Five-membered cyclic sulfonium salts treated with such bases (thiolanium salts) may fragment to ethylene and an alkyl vinyl sulfide *via* a cycloreversion (Fig. 36).[158] Sulfonium analogs also exist for both the Stevens and Sommelet-Hauser rearrangements.[80,159,160] In some cases, the high α-acidity of sulfonium cations appears to promote the Sommelet-Hauser rearrangement over substitution even in aqueous media.[160] Exchange rates of these protons are roughly two orders of magnitude higher than phosphonium α-protons, making them highly labile.[121]

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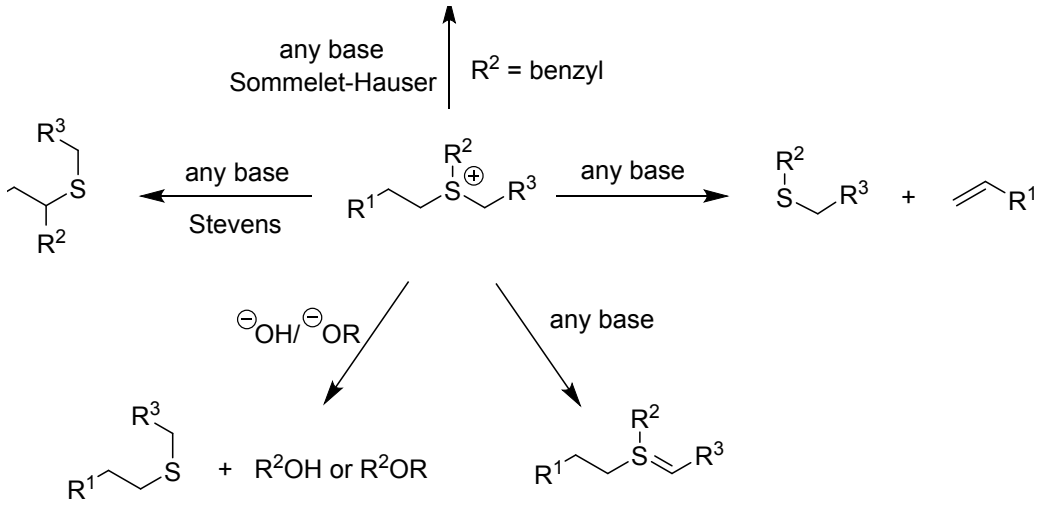


Fig. 35: Reactions of acyclic sulfonium salts in basic media.

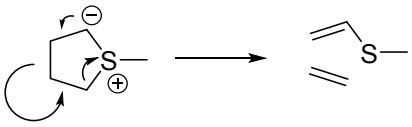


Fig. 36: Cycloreversion of a deprotonated thiolanium cation.[158]

1,2,3-Triazolium ionic liquids

1,2,3-Triazolium ionic liquids constitute a more recent class that has found application as a more base-stable alternative to imidazolium ionic liquids. They lack the labile proton on the C2-carbon, and only the C4 and C5 protons remain as potential sites for deprotonation. Carbene formation is hence far more difficult, and impossible for peralkylated 1,2,3-triazolium cations.[161,162] About 5% of exchange is observed after seven days in 0.1 mol L^{-1} sodium hydroxide in methanol/water at room temperature.[163] This is not the case for the isomeric 1,2,4-triazolium ionic liquids, which undergo carbene formation in a fashion similar to imidazolium salts. A certain propensity towards isotope exchange remains for the α-protons of the C4- and

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C5-substituents, indicating that these are the most acidic positions of 1,2,3-triazolium cations.[163,164] The rate of exchange of these protons requires far harsher conditions, however, than the exchange of 2-methyl protons in 2-methylimidazomium ionic liquids.[43,164] The polarization of the 2-position in 1,2,3-triazolium cations should also be reduced as compared to that in imidazolium ionic liquids, as positions 1, 2 and 3 are all occupied by nitrogen atoms with equal electronegativity. This is expected to make 1,2,3-triazolium cations less susceptible to base-induced ring opening. Furthermore, the incipient N–OH bond is considerable weaker than the C–OH bond, making the addition step more likely to reverse and destabilizing the transition state.[165]

Raiguel et al. investigated the stability of a number of alkylated 1,2,3-triazolium ionic liquids with respect to Brønsted bases.[164,166] The stability was greatly compromised if the cation was not alkylated at all ring positions. The authors found that the decomposition mechanism of 1,2,3-triazolium ionic liquids is variable and depends on the substitution of the cation, the nature of the base and the polarity of the medium. Two major pathways could be very distinctly identified from the pattern of decomposition pathways. The first is a Hofmann-type β-elimination, yielding an alkene and a neutral, 1,2,3-triazole (Fig. 37a). This pathway was found to occur very rapidly for cations with ethyl and isopropyl substituents on the nitrogen positions. The ethyl and isopropyl chains were selectively cleaved from the cations over 2-ethylhexyl side chains. The Hofmann pathway was also identified for 4-ethyl-1,3-bis(2-ethylhexyl)-5-methyltriazolium nitrate (Fig. 367a, **1**) upon contact with concentrated sodium hydroxide solution. Conversely, the analogous bistriflimide ionic liquid (Fig. 37b, **2**) yielded 2-ethylhexanol and 4-ethyl-1-(2-ethylhexyl)-5-methyltriazole (Fig. 37b, **3**). The isomeric triazole, resulting from the cleavage of the side chain peripheral to the ethyl substituent, was not detected. Interestingly, the unbranched 4-ethyl-1,3-dihexyl-5-methyltriazolium bistiflimide (Fig. 37c, **4**) exhibited higher base-stability than the branched compound **3**. The exact nature of

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the mechanism could not be determined, but isotope exchange studies revealed that the most acidic group was the methyl group in the 5-position of the cation, exhibiting about 50% isotope exchange in both **3** and **4** after 3 hours in 40 wt% sodium deuteroxide (60 °C). This indicates the possible involvement of a methyl-centered ylide in the decomposition process, which would also explain the regioselectivity of the decomposition. A bistriflimide ionic liquid with isobutyl substituents on both nitrogen positions was also investigated, but its alkaline decomposition yielded unidentified products that could not be ascribed to either pathway. The authors postulated that the hydroxide anion may directly attack the cationic ring of this ionic liquid.

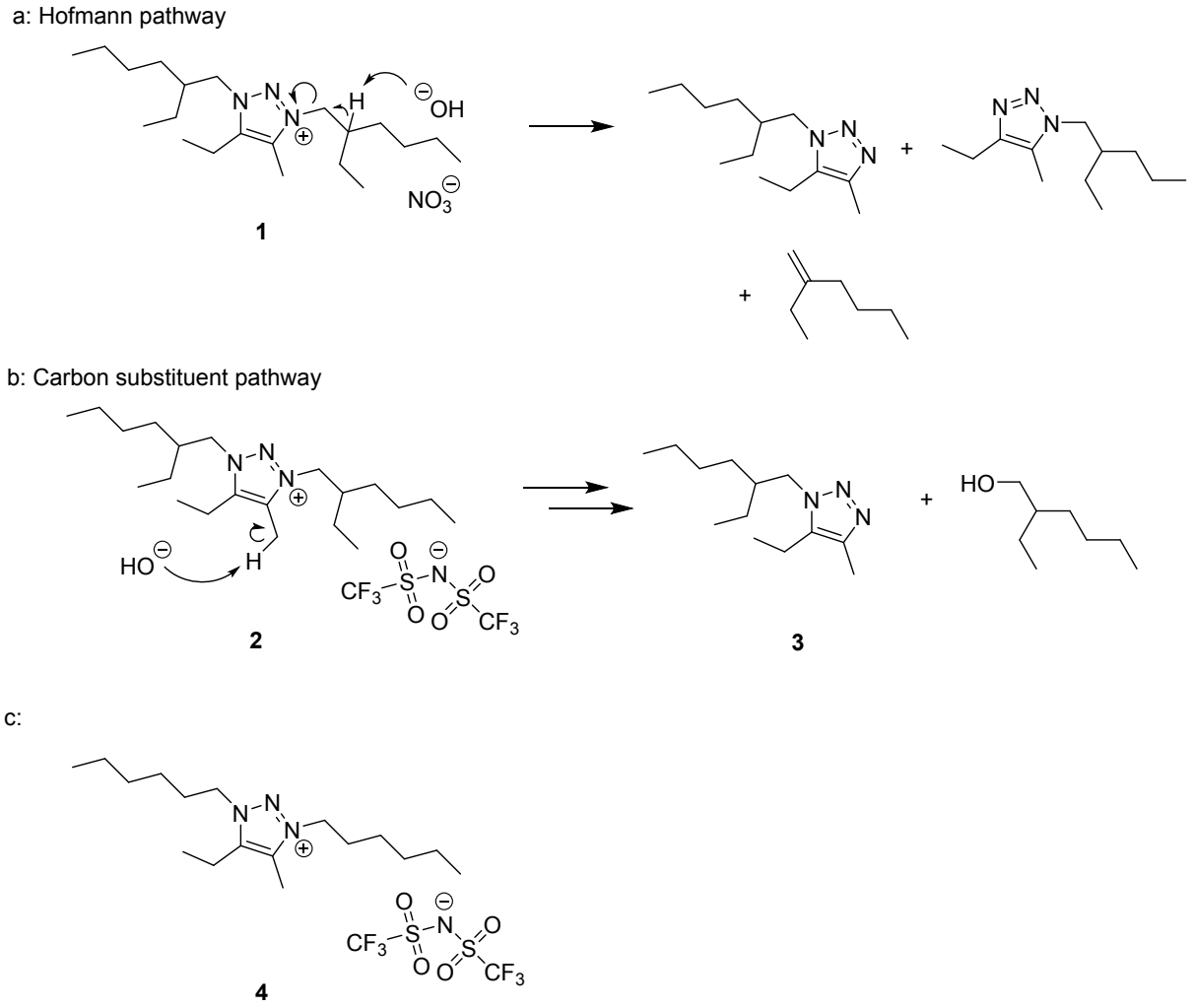


Fig. 37: (a) Decomposition of a hydrophilic 1,2,3-triazolium ionic liquid via a Hofmann elimination. (b) Decomposition of a hydrophobic 1,2,3-triazolium ionic liquid to yield a triazole and an alcohol. (c) Example of an 1,2,3-triazolium ionic liquid with high base-stability.[164]

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Raiguel *et al.* also investigated the degree of decomposition of the aforementioned cations under a number of strongly basic conditions.[164] The authors found that **4** exhibited no decomposition after contact with 50 wt% sodium hydroxide at 60 °C for 24 hours under phase-transfer conditions. On the other hand, compounds **1** and **2** were less stable under these conditions and exhibited 5 and 3 mol% decomposition, respectively. Similarly, the unbranched **4** showed 2 mol% decomposition after contact with ethylmagnesium bromide in THF (1 mol L^{-1}), while this increased to 7 mol% for the branched **2**. The Grignard reagent was decomposed by the nitrate anion in compound **1**. Both compounds **3** and **4** were rapidly decomposed by *n*-butyllithium, but remarkably the isobutyl-functionalized ionic liquid was quite stable with respect to this reagent. Compounds with isopropyl and ethyl substituents on the nitrogen positions were far less stable, to the extent that *N*-ethyl cations slowly decomposed in aqueous solutions with a pH of 13 upon heating.[166]

The stability of 1,2,3-triazolium ionic liquids towards bases has been exploited by a number of authors. Among the first examples hereof was the use of 1,3-dialkyltriazolium ionic liquids by Jeong and Ryu in the amine-catalyzed Baylis-Hillman reaction.[167] As noted by Aggarwal and coworkers, 1,3-dialkylimidazolium ionic liquids are unsuitable media for this reaction, as imidazolium-derived carbenes are formed, which bind to the aldehyde substrate (*vide supra*, Fig. 3). By contrast, Jeong and Ryu experienced no such issues. The authors concluded that 1,2,3-triazolium ionic liquids behave as stable and recyclable solvents in the process and proposed the use of 1,2,3-triazolium ionic liquids as base-stable alternatives for 1,3-dialkylimidazolium ionic liquids. High yields of up to 96% were obtained for the Baylis-Hillman adduct of 4-chlorobenzaldehyde and methyl acrylate. [167] Under identical conditions, the analogous imidazolium ionic liquid yielded only 67% of the desired product. Similar findings were obtained by Fall *et al.* and by Mendoza-Espinosa *et al*.[168,169] Srivastava demonstrated the usefulness of a wide range of 1,3,4-trisubstituted 1,2,3-triazolium ionic

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liquids as solvents for the asymmetric, proline-catalyzed crossed aldol condensation of acetone and 4-nitrobenzaldehyde. The ionic liquids outperformed conventional solvents in terms of yield and enantiomeric excess.[170] Raiguel and coworkers demonstrated that the Grignard reaction could be performed in 1,2,3-triazolium ionic liquids, but found that the Grignard reagent was active only in the presence of an ethereal cosolvent, similar to what Law *et al.* observed in pyridinium ionic liquids.[154,164] 1,2,3-Triazolium ionic liquids have also been applied as diluents and extractants for the solvent extraction of metal ions.[166,171,172]

Pyridinium and sulfonium ionic liquids are readily decomposed by nearly all forms of Brønsted bases, forming strongly reducing dihydropyridines and nucleophilic sulfides, respectively. but 1,2,3-triazolium ionic liquids show promise as potential solvents for applications requiring hydroxide bases. While even peralkylated imidazolium ionic liquids exhibit ring opening in contact with hydroxide solutions, certain 1,2,3-triazolium ionic liquids show no decomposition upon heating in contact with 50 wt% sodium hydroxide solution. Unfortunately, stability towards organometallic reagents is poorer, and these ionic liquids are entirely incompatible with organolithium compounds. For these applications, peralkylated imidazolium ionic liquids are preferable.

Anion-related effects

While the cation is the entity generally attacked by Brønsted bases, the anion may significantly influence the stability of a particular cation either by stabilizing the cation, by stabilizing the attacking base or by influencing the transfer of reactive species into the ionic liquid. Stabilization of the cation can be conferred by the interactions of anions with the acidic protons in ionic liquids. An example hereof was presented by Choi *et al.*, who investigated an electron transfer process catalyzed by the acidic C2-protons in imidazolium ionic liquids diluted in dichloromethane.[25] They found that the catalytic ability, resulting from the acidity of the cation,

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decreased in the series $SbF_6^- > PF_6^- > Tf_2N^- \approx BF_4^- >> Cl^-$. This reflects the coordinating ability of the anions to the C2-proton and the resulting suppression of the acidity. The effect of the anion on the acidity of imidazolium salts diminishes greatly upon dilution in more polar solvents due to the solvation of the constituent ions.[23,24,173] Chu *et al.* found a very minimal influence of the nature of the anion on the pK_a of the cation in DMSO, on the order of 0.1 units.[24] The order of acidity was the same as that found by Choi and coworkers. Similarly, Adam and coworkers found consistently higher acidities for the cations of protic nitrate ionic liquids than for the corresponding acetates in acetonitrile and DMSO, but the effect vanished in the highly polar methanol.[173] Interestingly, this order appears to reverse for acid/base couples dissolved in neat ionic liquids.[174–176] Acids dissolved in ionic liquids become stronger as the coordinating ability of the anion increased. The authors of these studies reason that strongly coordinating anions are needed to solvate the protons released by the acidic species. Unfortunately, there appear to be no studies investigating the acidity of ionic liquid cations themselves in neat ionic liquids.

The anion can also stabilize the attacking base, either directly or indirectly. Direct stabilization of the basic species has been observed by Ramnial *et al.* in phosphonium carboxylate ionic liquids treated with Grignard reagents. While trihexyl(tetradecyl)phosphonium bistriflimide, chloride and dicyanamide rapidly underwent Hofmann-type elimination under the influence of ether-free ethylmagnesium bromide, the decanoate ionic liquid was resistant to attack by the Grignard reagent.[119] A computational study indicated that the binding of a carboxylate ligand to magnesium is highly exothermic, which led the authors to conclude that the decanoate anion stabilizes organomagesium species in solution in a fashion similar to diethyl ether.

The hydrophilicity of the anion has a strongly adverse effect on the stability of ionic liquids under phase transfer conditions.[87,123,177] When an ionic liquid is contacted with an aqueous phase containing a dissolved salt, an anion-exchange equilibrium is instated. The higher the

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hydration enthalpy of the anion in the ionic liquid (corresponding to anion polarity), the more readily it is exchanged for anions in the aqueous phase.[178] Due to the high hydration enthalpy of the hydroxide anion, its exchange for ionic liquid anions is unfavorable, but a permanent equilibrium concentration of hydroxide is extracted to the ionic liquid phase by this anion exchange mechanism. The higher the polarity of the ionic liquid anion, the higher the equilibrium concentration of hydroxide and, hence, the faster the rate of decomposition.[87,123,177] The magnitude of this effect is considerable: Landini and coworkers list a number of examples in their work, including the highly illustrative example of tributylhexadecylphosphonium ions in chlorobenzene. This solution was brought into contact with 50 wt% aqueous sodium hydroxide at 25 °C.[87] Half-lives were recorded as being 0.03 and 2 hours for the chloride and bromide salts, respectively, while the iodide salt exhibited only 8% decomposition after three days. The presence of the anion exchange equilibrium also implies that the decomposition of the ionic liquid can be mitigated by the addition of a source of ionic liquid anions in the aqueous phase.[87] This results from the reversal of the anion exchange equilibrium by the high aqueous concentration of ionic liquid anions. The work of Landini *et al.* also illustrates this effect: when the aforementioned organic cation solutions were contacted with aqueous solutions that contained approx. 0.1 mol L^{-1} of either sodium chloride, bromide or iodide, the half-lives of the chloride and bromide system increased to 0.8 and 220 hours (as opposed to 0.03 and 2 hours), respectively, while the iodide salt exhibited no detectable decomposition after 6 days.[87]

Brønsted basic ionic liquids

A number of authors have incorporated Brønsted basic moieties into the structure of the ionic liquid, in particular amines. Amines are most commonly tethered to the cation and often proposed as catalytically active solvents for aldol-type reactions.[179–183] Chiral, cyclic amines

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were found to be especially effective for asymmetric synthesis.[184–188] Tethering basic catalysts to the cation structure prevents leaching of the catalyst upon extraction of the product from the ionic liquid during workup, while retaining the activity and selectivity of homogeneous catalysts.[189] These ionic liquids have also been used as stoichiometric bases, which are regenerated after completion of the reaction. An example is the use of amine-functionalized ionic liquids for Heck reactions.[179] They are also capable of sequestering CO_2 by means of carbamate formation.[190,191] Amino acid-based ionic liquids incorporate an amino functionality in the anionic unit of the ionic liquid, providing a stronger Brønsted basic site than the sulfonate or carboxylate group bearing the negative charge. As with other amino-functionalized ionic liquids, they are often employed as chemisorbants for CO_2. They have also been applied as solvents for biopolymers.[192-195] While the amino groups are more strongly basic than the carboxylate groups, they do not appear to significantly impact the stability of the ionic liquid, as decomposition temperatures for imidazolium carboxylate and aminocarboxylate ionic liquids are similar.[196,197] However, it cannot be excluded that the ionic liquid is at least partially converted to its carbenic form, especially at elevated temperatures. This, in fact, seems likely as carbenes are known to form transiently in imidazolium acetate ionic liquids under certain conditions.[198–200]

While these structures may be stable at room temperature, the reactions are often carried out at elevated temperatures, either due to deliberate external heating or due to the liberation of reaction heat. The thermal stability of the ionic liquids is drastically reduced by the presence of the amino group, in particular for the less nucleophilic anions. Paun and coworkers found that tetraalkylammonium cations tethered to amine groups can show significant decomposition after just one reaction cycle of less than one hour at 65 °C.[180] Luo *et al.* demonstrated that β-amino-functionalized 1,3-dialkylimidazolium ionic liquids showed relatively low decomposition temperatures (200-300 °C), with little dependence on the anion (bromide, tetrafluoroborate or

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hexafluoroplatinate).[201] Nevertheless, Xue *et al.* determined that the halides in this class decompose via anion-initiated S_N2.[202] Liu and coworkers observed that thermal decomposition occurred nearly exclusively via *a* unimolecular subsitution mechanism for 1-aminoethyl-3-methylimidazolium tetrafluoroborate ionic liquid, where the attack was carried out by fluoride.[203] The amino group serves only to polarize the side chains, thereby increasing the reactivity of the ionic liquid. Forsyth *et al.* have noted that the basicity of a particular group depends on the length of the linker chain between the cation center and the basic moiety.[179] This can be related to the electron-withdrawing inductive effect of the positive charge, which destabilizes proximal protonated sites bearing a second positive charge. The amino group thus becomes more basic and less likely to affect the stability of the ionic liquid as it is located further away from the cationic center.

Conjugate bases of weak acids may be used as anions in ionic liquids, conferring Brønsted basicity to the resulting ionic liquids. A frequently encountered example is 1-butyl-3-methylimidazolium hydroxide, purported to be a strongly basic ionic liquid to be used as a recyclable basic catalyst. As discussed above, this ionic liquid is inherently unstable as the hydroxide anion will readily deprotonate the cation to yield a carbene and water.[28] The ionic form may exist in aqueous solutions, due to stabilization of the anion by solvation. For similar reasons, quaternary ammonium and phosphonium salts are always supplied as aqueous solutions, but are still frequently contaminated with decomposition products.[204]

Using the appropriate cation, very strongly basic anions can be incorporated in ionic liquid structures. The pyrrolidinium isopropoxide/bistriflimide binary ionic liquids discussed above exemplify this class of ionic liquids.[100] The authors observed no decomposition after storage at room temperature for up to 8 months. The ionic liquids proved suitable as solvents for the aldol and Knoevenagel condensations. The alkoxide anion has a similar Hamett basicity to sodium hydroxide and methoxide when diluted in methanol. The basicity of the anion in the neat ionic

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liquid was not assessed, but it cannot be excluded that the basicity of the anion further increases in the absence of stabilizing influence of the protic methanol solvent. The authors hypothesized that the high viscosity of the ionic liquid is key to its stability, by reducing the mobility of the basic species and hence preventing nucleophilic attack. Due to the unique decomposition pathways of quaternary phosphonium ionic liquids (*vide supra*), strongly basic but sterically hindered can be successfully incorporated in such ionic liquids. This includes imidazolate, tetrazolate and phenolate anions, and several other conjugate bases of azoles.[205,206]The pK_a values for the conjugate acids of these bases are between 10 and 20 in DMSO. These bases are sterically incapable of attacking the phosphonium center directly, but insufficiently basic to induce Hofmann elimination at ambient temperatures. These ionic liquids are efficient chemisorbants for CO_2.[207,208]

1,3-Dialkylimidazolium cations can interact even with weakly basic anions. Maton and coworkers investigated dynamic equilibria of 1-ethyl-3-methylimidazolium hydrogen carbonate in the solid phase and in various solvents, and observed the formation of a zwitterionic carboxylate species in chloroform (Fig. 30).[209] In methanolic and aqueous solutions, the formation of the carboxylate was suppressed due to solvolysis of the CO_2 adduct. In the solid state, the inner salt form was not detected either. The combination of the carbene and carbonic acid were never present in detectable amounts, despite being an obvious intermediate in the equilibrium. In dialkylimidazolium acetate ionic liquids, carbenes can exist at elevated temperatures or in the presence of glass or metal surfaces, as evidenced by changes in NMR spectra and theoretical calculations.[198–200] In the bulk ionic liquid phase, carbene formation is insignificant at ambient temperatures.[198]

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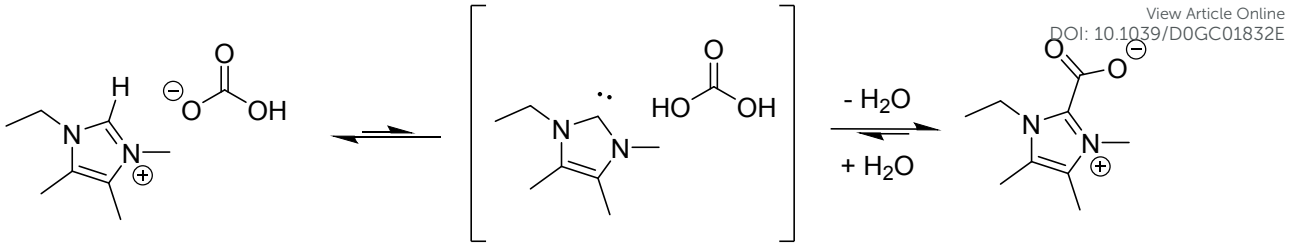


Fig. 30: Equilibrium between 1-ethyl-3-methylimidazolium hydrogen carbonate and the corresponding zwitterionic carboxylate.

Conclusion

The stability of ionic liquids towards Brønsted bases is determined by the nature of the cationic core, the substituents, the anion, the solvent properties of the medium and the attacking base. The influence of the anion is fairly small and is limited to stabilizing the attacking base and the cation, or by determining the degree to which bases dissolve into the ionic liquid. Attack of the base nearly always occurs at the cation, implying that the nature of the cation and its substitution are paramount in determining the base-stability of ionic liquids. In general, quaternary ammonium cations (including cyclic derivatives) and 1,2,3-triazolium cations are relatively stable towards alkaline attack, while imidazolium, phosphonium, sulfonium and pyridinium cations are more labile. The degree of substitution and the nature of the substituents is equally influential, but the requirements for good stability differ depending on the nature of the cation. Ammonium cations are likely to decompose *via* substitution at the α-carbon or elimination at the β-carbon. Hence, these cations can be stabilized by substitution with β-branched alkyl substituents or by incorporating the cationic center in a six-membered ring. Similar patterns of substitution can stabilize sulfonium salts, albeit to a lesser extent. The structurally analogous quaternary phosphonium cations usually decompose by direct attack of the base at the phosphorus atom, followed by the expulsion of a substituent bearing a partial negative charge. As a result, the order of base-stability of the substituents is the inverse of the order of anionic

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stability. Imidazolium cations are prone to deprotonation of the ring positions and to ring-opening resulting from addition of the base to the imidazolium core. Full substitution with sterically hindered, electron-donating substituents can prevent such reactions. Elimination and substitution of the nitrogen substituents usually occur only if other reaction paths are strongly impeded, and are often not observed for highly substituted cations. 1,2,3-Triazolium ionic liquids should be fully alkylated and bear branched *N*-substituents for stability in wet conditions, or linear *N*-substituents for stability under dry conditions. Pyridinium cations are highly susceptible to addition reactions. Substitution of the ortho-position redirects the attacking base to the *N*-subtituent.

The nature of the base and the medium are important as the various decomposition mechanisms have different steric and solvation requirements. Steric considerations appear to be relevant for imidazolium and phosphonium cations, wich are generally attacked at the ring and phosphorus center, respectively. Hence, bulky organometallic bases may be less reactive towards the cations than expected, although other pathways of decomposition may become relevant due to the very strong basicity of these reagents. In general, base-induced decomposition is strongly promoted in apolar solvents, as basic species are poorly stabilized in such media. An exception to this rule of thumb can be found under phase-transfer conditions, where the transfer of aqueous bases to the organic phase should also be taken into account.

The information discussed in this review can largely be condensed into the following rules of thumb. 1,3-Dialkylimidazolium, sulfonium and pyridinium ionic liquids should always be avoided if Brønsted basic conditions are required. 1,2,3-Triazolium ionic liquids offer excellent resistance to solutions of hydroxide bases. Decomposition of peralkylated imidazolium ionic liquids is also slow under these conditions, but an isopropyl or aryl group must occupy the 2-position, which detrimentally affects physical properties. Peralkylated imidazolium ionic liquids are, however, the best choice for oranometalic bases, including organolithium reagents.

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These imidazolium salts appear to be the only ionic liquids to be resistant to highly reactive organolithium compounds. Ammonium ionic liquids offer moderate base stability and may be the optimal choice for use at ambient temperatures and low base concentrations, due to their low cost. Phosphonium ionic liquids are generally poorly compatible with bases, but may be promising solvents for alkoxide bases and Grignard reagents, although the latter requires the presence of coordinating groups, either incorporated in the ionic liquids structure or in the form of a cosolvent.

Table 1: Stability of ionic liquids in the presence of various bases. --: Rapid decomposition occurs. -: Significant decomposition occurs over extended periods of time, depending on substitution and reaction conditions. =/-: Slow decomposition may occur depending on substitution and reaction conditions. +: No or very limited decomposition.

	Alkali	Alkoxide	Hydride	Amides	Grignard	Organo-lithium
Dialkylimidazolium	--	--	--	--	--	--
Peralkylated imidazolium	+-	+-	n.a.	n.a.	+	+
Open-chain ammonium	-	-	n.a.	--	--	--
Cyclic ammonium	+-	-	n.a.	--	--	--
Phosphonium	--	+[a]	--	n.a.	+-[b]	--
Pyridinium	--	--	--	--	--	--
Sulfonium	--	--	--	--	--	--
1,2,3-Triazolium	+	n.a.	n.a.	n.a.	+-	--

[a]Benzylic salts are reactive towards alkoxides. [b]Carboxylate salts are inert towards Grignard reagents.

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Conflict of interest

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There are no conflicts to declare.

References

1 K. R. Seddon, *Nat. Mater.*, 2003, **2**, 363-365.

2 B. Kirchner, O. Hollóczki, J. N. C. Lopes and A. A. H. Pádua, *Wiley Interdiscip. Rev. Comput. Mol. Sci.*, 2015, **5**, 202–214.

3 M. Smiglak, W. Mathew Reichert, J. D. Holbrey, J. S. Wilkes, L. Sun, J. S. Thrasher, K. Kirichenko, S. Singh, A. R. Katritzky and R. D. Rogers, *Chem. Commun.*, 2006, 2554–2556.

4 J. S. Wilkes, *Green Chem.*, 2002, **4**, 73–80.

5 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792–793.

6 T. Welton, *Chem. Rev.*, 1999, 99, 2071–2084.

7 J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667–3692.

8 A. M. O'Mahony, D. S. Silvester, L. Aldous, C. Hardacre and R. G. Compton, *J. Chem. Eng. Data*, 2008, **53**, 2884–2891.

9 H. Liu, Y. Liu and J. Li, *Phys. Chem. Chem. Phys.*, 2010, **12**, 1685–1697.

10 M. Freemantle, *Chem. Eng. News*, 1998, **76**, 32–37.

11 C. Maton, N. D. Vos and C. V. Stevens, *Chem. Soc. Rev.*, 2013, **42**, 5963–5977.

12 S. Wellens, B. Thijs and K. Binnemans, *Green Chem.*, 2013, **15**, 3484–3485.

13 M. Kosmulski, J. Gustafsson and J. B. Rosenholm, *Thermochim. Acta*, 2004, **412**, 47–53.

14 R. E. Del Sesto, T. M. McCleskey, C. Macomber, K. C. Ott, A. T. Koppisch, G. A. Baker and A. K. Burrell, *Thermochim. Acta*, 2009, **491**, 118–120.

15 A. Seeberger, A.-K. Andresen and A. Jess, *Phys. Chem. Chem. Phys.*, 2009, **11**, 9375–9381.

16 B. Wang, L. Qin, T. Mu, Z. Xue and G. Gao, *Chem. Rev.*, 2017, **117**, 7113–7131.

17 J. Dupont and J. Spencer, *Angew. Chem. Int. Ed.*, 2004, **43**, 5296–5297.

18 S. Sowmiah, V. Srinivasadesikan, M.-C. Tseng and Y.-H. Chu, *Molecules*, 2009, **14**, 3780–3813.

19 S. Chowdhury, R. S. Mohan and J. L. Scott, *Tetrahedron*, 2007, **63**, 2363–2389.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

20 T. L. Greaves and C. J. Drummond, *Chem. Rev.*, 2008, **108**, 206–237.

21 A. J. Arduengo, J. R. Goerlich and W. J. Marshall, *J. Am. Chem. Soc.*, 1995, **117**, 11027–11028.

22 D. A. Dixon and A. J. Arduengo, *J. Phys. Chem.*, 1991, **95**, 4180–4182.

23 E. M. Higgins, J. A. Sherwood, A. G. Lindsay, J. Armstrong, R. S. Massey, R. W. Alder and A. C. O'Donoghue, *Chem. Commun.*, 2011, **47**, 1559–1561.

24 Y. Chu, H. Deng and J.-P. Cheng, *J. Org. Chem.*, 2007, **72**, 7790–7793.

25 D. S. Choi, D. H. Kim, U. S. Shin, R. R. Deshmukh, S. Lee and C. E. Song, *Chem. Commun.*, **2007**, 3467–3469.

26 M. J. Panzner, C. A. Tessier and W. J. Youngs, in *The Chemistry of Pincer Compounds*, eds. D. Morales-Morales and C. M. Jensen, Elsevier Science B.V., Amsterdam, 2007, pp. 139–150.

27 A. A. M. Lapis, L. F. de Oliveira, B. A. D. Neto and J. Dupont, *ChemSusChem*, 2008, **1**, 759–762.

28 A. K. L. Yuen, A. F. Masters and T. Maschmeyer, *Catal. Today*, 2013, **200**, 9–16.

29 O. Hollóczki, P. Terleczky, D. Szieberth, G. Mourgas, D. Gudat and L. Nyulászi, *J. Am. Chem. Soc.*, 2011, **133**, 780–789.

30 R. A. Olafson, W. R. Thompson and J. S. Michelman, *J. Am. Chem. Soc*, 1964, **86**, 1865–1866.

31 V. K. Aggarwal, I. Emme and A. Mereu, *Chem. Commun.*, 2002, 1612–1613.

32 T. Kitazume and G. Tanaka, *J. Fluor. Chem.*, 2000, **106**, 211–215.

33 M.-C. Tseng, Y.-M. Liang and Y.-H. Chu, *Tetrahedron Lett.*, 2005, **46**, 6131–6136.

34 A. Pinkert, K. N. Marsh, S. Pang and M. P. Staiger, *Chem. Rev.*, 2009, **109**, 6712–6728.

35 G. Ebner, S. Schiehser, A. Potthast and T. Rosenau, *Tetrahedron Lett.*, 2008, **49**, 7322–7324.

36 M. T. Clough, K. Geyer, P. A. Hunt, S. Son, U. Vagt and T. Welton, *Green Chem.*, 2015, **17**, 231–243.

37 V. P. W. Böhm and W. A. Herrmann, *Chem. Eur. J.*, 2000, **6**, 1017–1025.

38 A. Corma, H. García and A. Leyva, *Tetrahedron*, 2005, **61**, 9848–9854.

39 T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato and I. Ryu, *Org. Lett.*, 2002, **4**, 1691–1694.

40 I. Kmentová, B. Gotov, V. Gajda and Š. Toma, *Monatsh. Chem.*, 2003, **134**, 545–549.

41 L. Xu, W. Chen and J. Xiao, *Organometallics*, 2000, **19**, 1123–1127.

42 X. Yang, Z. Fei, T. J. Geldbach, A. D. Phillips, C. G. Hartinger, Y. Li and P. J. Dyson, *Organometallics*, 2008, **27**, 3971–3977.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

43 S. T. Handy and M. Okello, *J. Org. Chem.*, 2005, **70**, 1915–1918.

44 A. Fürstner, M. Alcarazo, R. Goddard and C. W. Lehmann, *Angew. Chem. Int. Ed.*, 2008, **47**, 3210–3214.

45 Y.-B. Wang, Y.-M. Wang, W.-Z. Zhang and X.-B. Lu, *J. Am. Chem. Soc.*, 2013, **135**, 11996–12003.

46 S. T. Handy, *J. Org. Chem.*, 2006, **71**, 4659–4662.

47 B. Lin, H. Dong, Y. Li, Z. Si, F. Gu and F. Yan, *Chem. Mater.*, 2013, **25**, 1858–1867.

48 C. Maton, N. D. Vos, B. I. Roman, E. Vanecht, N. R. Brooks, K. Binnemans, S. Schaltin, J. Fransaer and C. V. Stevens, *ChemPhysChem*, 2012, **13**, 3146–3157.

49 R. Giernoth and D. Bankmann, *Tetrahedron Lett.*, 2006, **47**, 4293–4296.

50 I. Tommasi and F. Sorrentino, *Tetrahedron Lett.*, 2006, **47**, 6453–6456.

51 K. M. Hugar, H. A. Kostalik and G. W. Coates, *J. Am. Chem. Soc.*, 2015, **137**, 8730–8737.

52 Y. Ye and Y. A. Elabd, *Macromolecules*, 2011, **44**, 8494–8503.

53 S. M. Urahata and M. C. C. Ribeiro, *J. Chem. Phys.*, 2004, **120**, 1855–1863.

54 L. Myles, R. G. Gore, N. Gathergood and S. J. Connon, *Green Chem.*, 2013, **15**, 2740–2746.

55 Y. Yang, J. Wang, J. Zheng, S. Li and S. Zhang, *J. Membrane Sci.*, 2014, **467**, 48–55.

56 H. Long and B. Pivovar, *J. Phys. Chem. C*, 2014, **118**, 9880–9888.

57 W. Wang, S. Wang, X. Xie, Y. lv and V. Ramani, *Int. J. Hydrog. Energy*, 2014, **39**, 14355–14361.

58 H. Dong, F. Gu, M. Li, B. Lin, Z. Si, T. Hou, F. Yan, S.-T. Lee and Y. Li, *ChemPhysChem*, 2014, 15, 3006–3014.

59 F. Gu, H. Dong, Y. Li, Z. Si and F. Yan, *Macromolecules*, 2014, **47**, 208–216.

60 J. Wang, S. Gu, R. B. Kaspar, B. Zhang and Y. Yan, *ChemSusChem*, 2013, **6**, 2079–2082.

61 S. Kumar, D. Jaller, B. Patel, J. M. LaLonde, J. B. DuHadaway, W. P. Malachowski, G. C. Prendergast and A. J. Muller, *J. Med. Chem.*, 2008, **51**, 4968–4977.

62 A. R. Katritzky, G. R. Khan and C. M. Marson, *J. Heterocycl. Chem.*, 1987, **24**, 641–644.

63 M. G. Marino and K. D. Kreuer, *ChemSusChem*, 2015, **8**, 513–523.

64 H. Long, K. Kim and B. S. Pivovar, *J. Phys. Chem. C*, 2012, **116**, 9419–9426.

65 S. Chempath, B. R. Einsla, L. R. Pratt, C. S. Macomber, J. M. Boncella, J. A. Rau and B. S. Pivovar, *J. Phys. Chem. C*, 2008, **112**, 3179–3182.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

66 V. J. Shiner and M. L. Smith, *J. Am. Chem. Soc.*, 1958, **80**, 4095–4098.

67 W. H. Saunders and D. S. Bailey, *J. Am. Chem. Soc.*, 1970, **92**, 6904–6910.

68 A. C. Cope and A. S. Mehta, *J. Am. Chem. Soc.*, 1963, **85**, 1949–1952.

69 A. C. Cope, G. A. Berchtold and D. L. Ross, *J. Am. Chem. Soc.*, 1961, **83**, 3859–3861.

70 G. Wittig and R. Polster, *Justus Liebigs Ann. Chem.*, 1958, **612**, 102–108.

71 A. C. Cope, N. A. LeBel, P. T. Moore and W. R. Moore, *J. Am. Chem. Soc.*, 1961, *83*, 3861–3865.

72 K. C. Lethesh, W. Dehaen and K. Binnemans, *RSC Adv.*, 2013, **4**, 4472–4477.

73 J. F. Bunnett, *Angew. Chem. Int. Ed. Engl.*, 1962, *1*, 225–235.

74 D. V. Banthorpe, E. D. Hughes and C. Ingold, *J. Chem. Soc.*, 1960, 4054.

75 T. Sata, M. Tsujimoto, T. Yamaguchi and K. Matsusaki, *J. Membr. Sci.*, 1996, **112**, 161–170.

76 W. K. Musker and R. R. Stevens, *J. Am. Chem. Soc.*, 1968, **90**, 3515–3521.

77 S. H. Pine in *Organic Reactions*, ed. Bill Dauben, John Wiley & Sons, Hoboken, NJ, 1970, vol. 18, pp. 403–464.

78 J. H. Brewster and M. W. Kline, *J. Am. Chem. Soc.*, 1952, **74**, 5179–5182.

79 R. K. Hill and T.-H. Chan, *J. Am. Chem. Soc.*, 1966, **88**, 866–867.

80 J. E. Baldwin and R. E. Hackler, *J. Am. Chem. Soc.*, 1969, **91**, 3646–3647.

81 G. Ghigo, S. Cagnina, A. Maranzana and G. Tonachini, *J. Org. Chem.*, 2010, **75**, 3608–3617.

82 G. Wittig and T. F. Burger, *Justus Liebigs Ann. Chem.*, 1960, **632**, 85–103.

83 S. H. Pine and B. L. Sanchez, *Tetrahedron Lett.*, 1969, **10**, 1319–1320.

84 J. B. Sweeney, *Chem. Soc. Rev.*, 2009, **38**, 1027–1038.

85 S. Okazaki, N. Shirai and Y. Sato, *J. Org. Chem.*, 1990, **55**, 334–337.

86 T. Tanaka, N. Shirai, J. Sugimori and Y. Sato, *J. Org. Chem.*, 1992, **57**, 5034–5036.

87 D. Landini, A. Maia and A. Rampoldi, *J. Org. Chem.*, 1986, **51**, 3187–3191.

88 C. J. M. Stirling, in *Organic Chemistry of Sulfur*, ed. S. Oae, Springer US, Boston, MA, 1977, pp. 473–525.

89 A. D. Mohanty and C. Bae, *J. Mat. Chem. A*, 2014, **2**, 17314–17320.

90 K. Jewers and J. McKenna, *J. Chem. Soc.*, 1958, 2209–2217.

91 G. Damilano, K. Binnemans and W. Dehaen, *Org. Biomol. Chem.,* 2019, **17**, 9778–9791.

92 J. von Braun, *Ber. Dtsch. Chem. Ges.*, 1916, **49**, 2629–2642.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

93 K. M. Meek and Y. A. Elabd, *Macromolecules*, 2015, **48**, 7071–7084.
94 J. S. Olsson, T. H. Pham and P. Jannasch, *Adv. Funct. Mater.*, 2018, **28**, 1702758.
95 F. Gu, H. Dong, Y. Li, Z. Sun and F. Yan, *Macromolecules*, 2014, 47, 6740–6747.
96 X. Chu, Y. Shi, L. Liu, Y. Huang and N. Li, *J. Mater. Chem. A*, 2019, **7**, 7717–7727.
97 G. Illuminati and C. Lillocci, *J. Org. Chem.*, 1977, **42**, 2201–2203.
98 G. Cerichelli, G. Illuminati and C. Lillocci, *J. Org. Chem.*, 1980, **45**, 3952–3957.
99 G. Cospito, G. Illuminati, C. Lillocci and H. Petride, *J. Org. Chem.*, 1981, **46**, 2944–2947.
100 P. McNeice, A. C. Marr, P. C. Marr, M. J. Earle and K. R. Seddon, *ACS Sustain. Chem. Eng.*, 2018, **6**, 13676–13680.
101 H. Booth, A. H. Bostock, N. C. Franklin, D. Vaughan Griffiths and J. H. Little, *J. Chem. Soc. Perkin Transa. 2*, 1978, 899–907.
102 T. H. Pham, J. S. Olsson and P. Jannasch, *J. Am. Chem. Soc.*, 2017, **139**, 2888–2891.
103 T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 1932–1940.
104 G. Wittig, R. Mangold and G. Felletschin, *Justus Liebigs Ann. Chem.*, 1948, **560**, 116–127.
105 K. P. Klein, D. N. Van Eenam and C. R. Hauser, *J. Org. Chem.*, 1967, **32**, 1155–1160.
106 S. H. Pine, J. Cheney, B. Catto and J. D. Petersen, *J. Org. Chem.*, 1974, **39**, 130–133.
107 A. R. Lepley and R. H. Becker, *Tetrahedron*, 1965, **21**, 2365–2373.
108 C. K. Ingold and C. S. Patel, *J. Chem. Soc.*, 1933, 68–69.
109 F. Weygand, H. Daniel and H. Simon, *Chem. Ber.*, 1958, **91**, 1691–1706.
110 W. R. Brasen and C. R. Hauser, *Org. Synth.*, 1954, **34**, 61.
111 W. H. Puterbaugh and C. R. Hauser, *J. Am. Chem. Soc.*, 1964, **86**, 1105–1107.
112 F. N. Jones and C. R. Hauser, *J. Org. Chem.*, 1962, **27**, 1542–1547.
113 L. P. A. Fery and L. van Hove, *Bull. Soc. Chim. Belg.*, 1959, **68**, 65–84.
114 L. P. A. Fery and L. van Hove, *Bull. Soc. Chim. Belg*, 1960, **69**, 79–94.
115 K. Tsunashima and M. Sugiya, *Electrochem. Commun.*, 2007, **9**, 2353–2358.
116 B. Siegel, *J. Am. Chem. Soc.*, 1979, **101**, 2265–2268.
117 G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 1929, 2342–2357.
118 P. A. Byrne, Y. Ortin and D. G. Gilheany, *Chem. Commun.*, 2015, **51**, 1147–1150.
119 T. Ramnial, S. A. Taylor, M. L. Bender, B. Gorodetsky, P. T. K. Lee, D. A. Dickie, B. M. McCollum, C. C. Pye, C. J. Walsby and J. A. C. Clyburne, *J. Org. Chem.*, 2008, **73**, 801–812.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

120 M.-C. Tseng, H.-C. Kan and Y.-H. Chu, *Tetrahedron Lett.*, 2007, **48**, 9085–9089.

121 W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 1955, **77**, 521–526.

122 B. Zhang, R. B. Kaspar, S. Gu, J. Wang, Z. Zhuang and Y. Yan, *ChemSusChem*, 2016, **9**, 2374–2379.

123 H. J. Cristau, A. Long and H. Christol, *Tetrahedron Lett.*, 1979, **20**, 349–352.

124 F. Y. Khalil, G. Aksnes, R. Friman, U. Rudén and W. Nimmich, *Acta Chem. Scand.*, 1973, **27**, 3832–3838.

125 F. Y. Khalil and G. Aksnes, *Z. Phys. Chem.*, 2011, **97**, 179–188.

126 F. Y. Khalil and G. Aksnes, *Can. J. Chem.*, 1978, **56**, 1933–1939.

127 J. Graham Dawber, J. C. Tebby and A. A. C. Waite, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1923–1925.

128 H. Shirota, T. Mandai, H. Fukazawa and T. Kato, *J. Chem. Eng. Data*, 2011, **56**, 2453–2459.

129 G. Wittig, H. Eggers and P. Duffner, *Justus Liebigs Annalen der Chemie*, 1958, **619**, 10–27.

130 J. J. Brophy and M. J. Gallagher, *Aust. J. Chem.*, 1969, **22**, 1385–1398.

131 A. M. Aguiar, H. J. Aguiar and T. G. Archibald, *Tetrahedron Lett.*, 1966, **7**, 3187–3192.

132 T. Itoh, K. Kude, S. Hayase and M. Kawatsura, *Tetrahedron Lett.*, 2007, **48**, 7774–7777.

133 L. Ford, F. Atefi, R. D. Singer and P. J. Scammells, *Eur. J. Org. Chem.*, 2011, **2011**, 942–950.

134 D. D. Coffman and C. S. Marvel, *J. Am. Chem. Soc.*, 1929, **51**, 3496–3501.

135 H. Staudinger and J. Meyer, *Helvetica Chimica Acta*, 1919, **2**, 612–618.

136 J. J. Brophy and M. J. Gallagher, *Aust. J. Chem.*, 1969, **22**, 1399–1404.

137 W. J. Bailey and S. A. Buckler, *J. Am. Chem. Soc.*, 1957, **79**, 3567–3569.

138 S. T. D. Gough and T. R. of A. H. with L. A. H. Trippett, *J. Chem. Soc.*, 1961, 4263–4264.

139 T. Ramnial, D. D. Ino and J. A. C. Clyburne, *Chem. Commun.*, 2005, 325–327.

140 B. Gorodetsky, T. Ramnial, N. R. Branda and J. A. C. Clyburne, *Chem. Commun.*, 2004, 1972–1973.

141 M. Grayson and P. T. Keough, *J. Am. Chem. Soc.*, 1960, **82**, 3919–3924.

142 C. B. Parisek, W. E. McEwen and C. A. Vander Werf, *J. Am. Chem. Soc.*, 1960, **82**, 5503–5504.

143 Z. Sun, J. Pan, J. Guo and F. Yan, *Adv. Sci.*, 2018, **5**, 1800065.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

144 J. Hnát, M. Paidar, J. Schauer, J. Žitka and K. Bouzek, *J. Appl. Electrochem.*, 2011, **41**, 1043.

145 B. Bauer, H. Strathmann and F. Effenberger, *Desalination*, 1990, **79**, 125–144.

146 K. Emmanuel, B. Erigene, C. Cheng, A. N. Mondal, M. M. Hossain, M. I. Khan, N. U. Afsar, L. Ge, L. Wu and T. Xu, *Sep. Purif. Technol.*, 2016, **167**, 108–116.

147 A. G. Anderson and G. Berkelhammer, *J. Org. Chem.*, 1958, **23**, 1109–1112.

148 M. J. Politi and H. Chaimovich, *J. Phys. Org. Chem.*, 1991, **4**, 207–216.

149 J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.*, 1970, **92**, 7547–7552.

150 R. E. Lyle and P. S. Anderson, in *Advances in Heterocyclic Chemistry*, eds. A.R. Katritzky, A.J. Boulton, Elsevier, Amsterdam, 1966, vol. 6, pp. 45–93.

151 R. Grashey and R. Huisgen, *Chem. Ber.*, 1959, **92**, 2641–2645.

152 R. Grewe and A. Mondon, *Chem. Ber.*, 1948, **81**, 279–286.

153 O. Schnider and A. Grüssner, *Helv. Chim. Acta*, 1949, **32**, 821–828.

154 M. C. Law, K.-Y. Wong and T. H. Chan, *Chem. Commun.*, 2006, 2457–2459.

155 I. N. Feit, F. Schadt, J. Lubinkowski and W. H. Saunders, *J. Am. Chem. Soc.*, 1971, **93**, 6606–6609.

156 W. H. Saunders and R. A. Williams, *J. Am. Chem. Soc.*, 1957, **79**, 3712–3716.

157 V. Franzen and C. Mertz, *Chem. Ber.*, 1960, **93**, 2819–2824.

158 F. Weygand and H. Daniel, *Chem. Ber.*, 1961, **94**, 3145–3146.

159 T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 1932, 69.

160 G. E. Hilbert and L. A. Pinck, *J. Am. Chem. Soc.*, 1938, **60**, 494–494.

161 P. Mathew, A. Neels and M. Albrecht, *J. Am. Chem. Soc.*, 2008, **130**, 13534–13535.

162 S. Sanghi, E. Willett, C. Versek, M. Tuominen and E. B. Coughlin, *RSC Adv.*, 2012, **2**, 848–853.

163 M.-C. Tseng, H.-T. Cheng, M.-J. Shen and Y.-H. Chu, *Org. Lett.*, 2011, **13**, 4434–4437.

164 S. Raiguel, J. Thomas, K. Binnemans and W. Dehaen, *Eur. J. Org. Chem.*, 2018, **2018**, 4850–4856.

165 R. D. Harrison, H. Ellis, H. D. B. Jenkins and N.-C. C. Trust, Book of data, Nuffield Advanced Science, London, Rev. ed., 1984.

166 S. Raiguel, D. Depuydt, T. Vander Hoogerstraete, J. Thomas, W. Dehaen and K. Binnemans, *Dalton Trans.*, 2017, **46**, 5269–5278.

167 Y. Jeong and J.-S. Ryu, *J. Org. Chem.*, 2010, **75**, 4183–4191.

168 A. Fall, I. Seck, O. Diouf, M. Gaye, M. Seck, G. Gómez and Y. Fall, *Tetrahedron Lett.*, 2015, **56**, 5128–5131.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

169 D. Mendoza-Espinosa, R. González-Olvera, C. Osornio, G. E. Negrón-Silva and R. Santillan, *New J. Chem.*, 2015, **39**, 1587–1591.

170 V. Srivastava, *Asymm. Organocatal.*, 2012, **1**, 2–7.

171 S. Raiguel, W. Dehaen and K. Binnemans, *Green Chem.*, 2019, **21**, 3948–3960.

172 S. Raiguel, W. Dehaen and K. Binnemans, *Dalton Trans.*, 2020, **49**, 3532–3544.

173 C. Adam, M. V. Bravo and P. M. E. Mancini, *Tetrahedron Lett.*, 2014, **55**, 148–150.

174 R. Barhdadi, M. Troupel, C. Comminges, M. Laurent and A. Doherty, *J. Phys. Chem. B*, 2012, **116**, 277–282.

175 D. Millán, M. Rojas, J. G. Santos, J. Morales, M. Isaacs, C. Diaz and P. Pavez, *J. Phys. Chem. B*, 2014, **118**, 4412–4418.

176 H. Deng, X. Li, Y. Chu, J. He and J.-P. Cheng, *J. Org. Chem.*, 2012, **77**, 7291–7298.

177 D. Landini, A. Maia and F. Montanari, *Isr. J. Chem.*, 1985, **26**, 263–269.

178 D. Dupont, D. Depuydt and K. Binnemans, *J. Phys. Chem. B*, 2015, **119**, 6747–6757.

179 S. A. Forsyth, U. Fröhlich, P. Goodrich, H. Q. N. Gunaratne, C. Hardacre, A. McKeown and K. R. Seddon, *New J. Chem.*, 2010, **34**, 723–731.

180 C. Paun, J. Barklie, P. Goodrich, H. Q. N. Gunaratne, A. McKeown, V. I. Pârvulescu and C. Hardacre, *J. Mol. Catal. A: Chem.*, 2007, **269**, 64–71.

181 Y. Cai, Y. Peng and G. Song, *Catal Lett*, 2006, **109**, 61–64.

182 Y. Peng and G. Song, *Catal. Commun.*, 2007, **8**, 111–114.

183 Z.-Z. Yang, L.-N. He, X.-Y. Dou and S. Chanfreau, *Tetrahedron Lett.*, 2010, **51**, 2931–2934.

184 O. V. Maltsev, A. S. Kucherenko, A. L. Chimishkyan and S. G. Zlotin, *Tetrahedron: Asymmetry*, 2010, **21**, 2659–2670.

185 S. S. Khan, J. Shah and J. Liebscher, *Tetrahedron*, 2010, **66**, 5082–5088.

186 S. S. Khan, J. Shah and J. Liebscher, *Tetrahedron*, 2011, **67**, 1812–1820.

187 Z. Yacob, J. Shah, J. Leistner and J. Liebscher, *Synlett*, 2008, **2008**, 2342–2344.

188 J. Shah, S. S. Khan, H. Blumenthal and J. Liebscher, *Synthesis*, 2009, **2009**, 3975–3982.

189 Z. Yacob and J. Liebscher, in *Chemistry of 1,2,3-triazoles*, eds. W. Dehaen and V. A. Bakulev, Springer International Publishing, Cham, 2015, pp. 167–210.

190 L. M. Galán Sánchez, G. W. Meindersma and A. B. de Haan, *Chem. Eng. Res. De.*, 2007, **85**, 31–39.

191 L. M. Galán Sánchez, G. W. Meindersma and A. B. de Haan, *Chem. Eng. J.*, 2011, **166**, 1104–1115.

Green Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0GC01832E

192 Y.-Y. Jiang, G.-N. Wang, Z. Zhou, Y.-T. Wu, J. Geng and Z.-B. Zhang, *Chem. Commun.*, 2008, 505–507.

193 B. E. Gurkan, J. C. de la Fuente, E. M. Mindrup, L. E. Ficke, B. F. Goodrich, E. A. Price, W. F. Schneider and J. F. Brennecke, *J. Am. Chem. Soc.*, 2010, **132**, 2116–2117.

194 P. Yan, Z. Xu, C. Zhang, X. Liu, W. Xu and Z. C. Zhang, *Green Chem.*, 2015, **17**, 4913–4920.

195 X.-D. Hou, N. Li and M.-H. Zong, *Biotechnol. Bioeng.*, 2013, **110**, 1895–1902.

198 S. Gehrke, W. Reckien, I. Palazzo, T. Welton and O. Hollóczki, *Eur. J. Org. Chem.*, 2019, **2019**, 504–511.

199 A. Filippov, O. N. Antzutkin and F. U. Shah, *Phys. Chem. Chem. Phys.*, 2019, **21**, 22531–22538.

200 N. M. A. N. Daud, E. Bakis, J. P. Hallett, C. C. Weber and T. Welton, *Chem. Commun.*, 2017, **53**, 11154–11156.

201 M. T. Clough, K. Geyer, P. A. Hunt, J. Mertes and T. Welton, *Phys. Chem. Chem. Phys.*, 2013, **15**, 20480–20495.

202 N. Muhammad, Z. B. Man, M. A. Bustam, M. I. A. Mutalib, C. D. Wilfred and S. Rafiq, *J. Chem. Eng. Data*, 2011, **56**, 3157–3162.

203 S.-P. Luo, D.-Q. Xu, H.-D. Yue, L.-P. Wang, W.-L. Yang and Z.-Y. Xu, *Tetrahedron: Asymmetry*, 2006, **17**, 2028–2033.

204 Z. Xue, Y. Zhang, X.-q. Zhou, Y. Cao, T. Mu, Thermochim. Acta, 2014, **578**, 59-67.

205 S. Liu, Y. Chen, Y. Shi, H. Sun, Z. Zhou and T. Mu, *J. of Mol. Liq.*, 2015, **206**, 95–102.

206 M. E. Bos, in *Encyclopedia of Reagents for Organic Synthesis*, ed. P. L. Fuchs, John Wiley & Sons, Hoboken, 2001.

207 L. Moura, L. C. Brown, M. Blesic and J. D. Holbrey, *ChemPhysChem*, 2017, **18**, 3384–3389.

208 C. Wang, X. Luo, H. Luo, D. Jiang, H. Li and S. Dai, *Angewandte Chemie*, 2011, **123**, 5020–5024.

209 C. Wang, H. Luo, D. Jiang, H. Li and S. Dai, *Angewandte Chemie*, 2010, **122**, 6114–6117.

210 C. Maton, K. V. Hecke and C. V. Stevens, *New J. Chem.*, 2014, **39**, 461–468.

Green Chemistry Accepted Manuscript