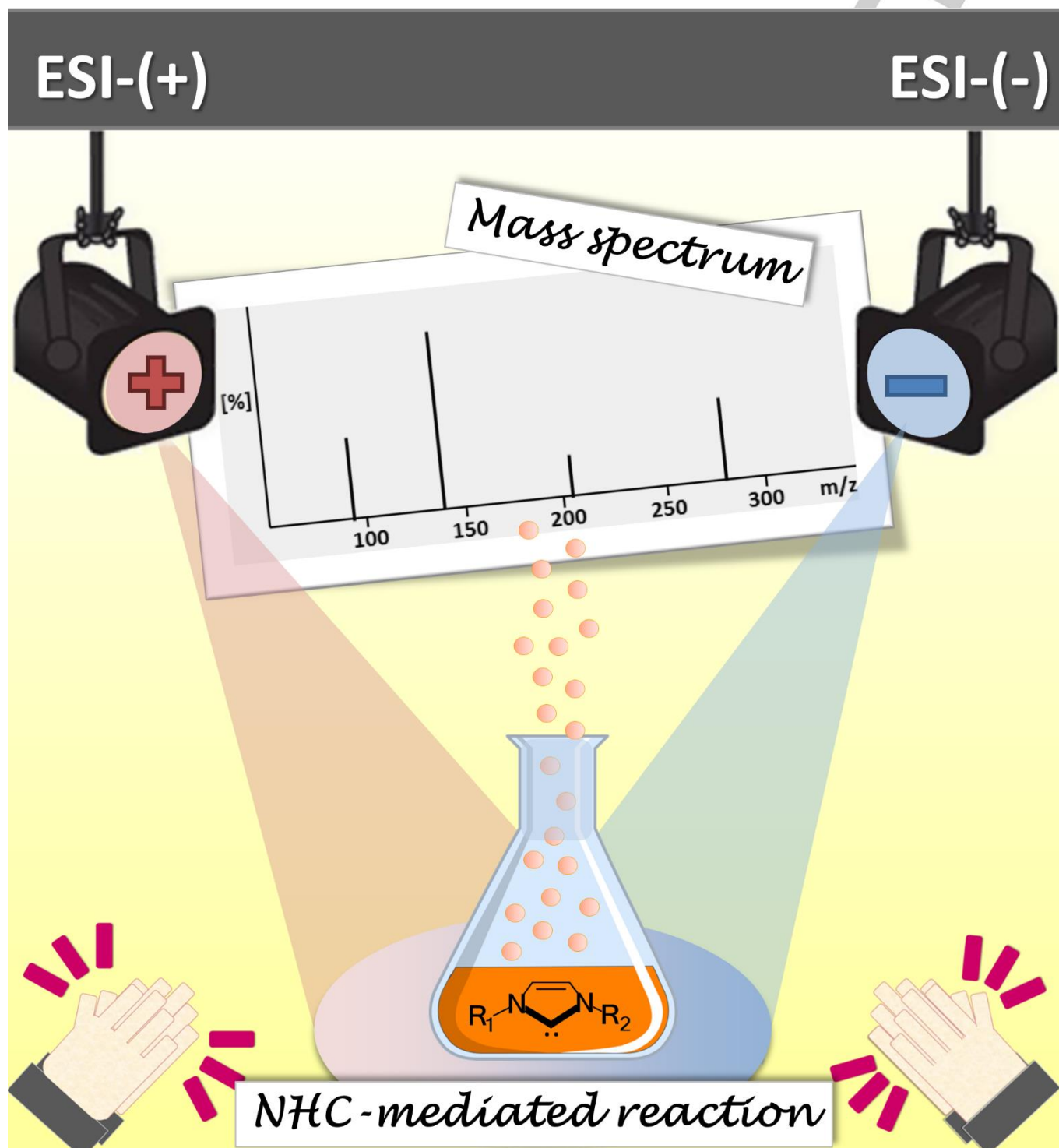**MINIREVIEW**

Charge-Tagged *N*-Heterocyclic Carbenes (NHCs): Revealing the Hidden Side of NHC-Catalysed Reactions through Electrospray Ionization Mass Spectrometry

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Abstract: *N*-heterocyclic carbenes (NHCs) are key intermediates in a variety of chemical reactions. Owing to their transient nature, the interception and characterization of these reactive species have always been challenging. Similarly, the study of reaction mechanisms in which carbenes act as catalysts is still an active research field. This review describes the contribution of electrospray ionization mass spectrometry (ESI-MS) to the detection of charge-tagged NHCs resulting from the insertion of an ionic group into the molecular scaffold. The use of different mass spectrometric techniques, combined with the charge-tagging strategy, allowed to clarify the involvement of NHCs in archetypal reactions and to study their intrinsic chemistry.

1. Introduction

N-heterocyclic carbenes (NHCs) are electron-rich species which act as bases or nucleophiles in a great variety of chemical reactions.[1] In their protonated forms, NHCs represent a major class of organic cations typically found in room-temperature ionic liquids (RT-ILs).[2] The resonance stabilization of the aromatic ring increases the bond strength towards the counter anion, thus conferring excellent thermal stability and ignorable vapour pressure to ILs.[3] In recent years, the insertion of functional groups into the cation or anion also allowed to finely design "*task-specific*" ionic liquids favouring their customized use as green-solvents and catalysts in different processes.[4]

Owing to their increased commercial availability and eco-friendly properties, ILs are still predominantly employed as stable and handling precursors of transient NHCs arising from chemical or electrochemical deprotonation (Scheme 1A).[5] In the case of imidazolylidenes, the reaction involves the C2-H bond of the cation (see the inset in Scheme 1), the most acidic among the ring hydrogen atoms, having a pK$_a$ value in the range of 21-23, intermediate between those of acetone (pK$_a$ = 19.3) and ethyl acetate (pK$_a$ = 25.6).[6] The C2-H bond can also be activated by transition-metal nanoparticles (e.g. [Ir(0)]$_n$) forming *carbene-ligand-stabilized* nanoclusters detected in elegant H/D labelling experiments performed by NMR[7] and in X-ray photoelectron spectroscopic analysis.[8]

Regarding the 1,2,4-triazolium cations, the corresponding carbenes are typically generated by the elimination of methanol from a 5-methoxytriazole intermediate, according to the reaction in Scheme 1B.[9]

Notwithstanding the elusive nature of the NHCs, Arduengo *et al.* were the first to synthesize and isolate an air-stable crystalline carbene,[10] the 1,3-di-1-adamantyl-imidazol-2-ylidene, obtained

by the chemical deprotonation of 1,3-di-1-adamantylimidazolium chloride ionic liquid.
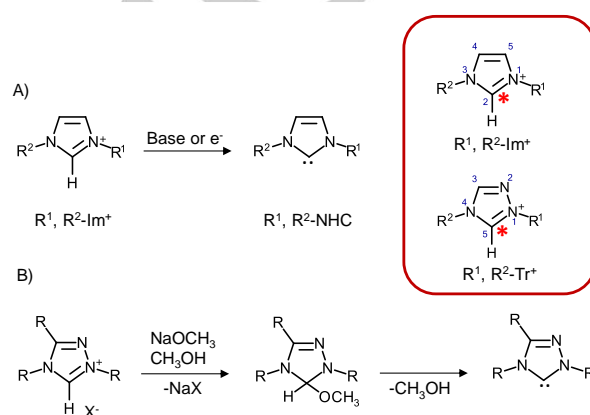
Scheme 1. A) Chemical or electrochemical formation of imidazole-2-ylidenes from 1,3 dialkyl-imidazolium cations; B) formation of triazol-5-ylidenes from 1,2,4-triazolium-based ionic liquids (R = Phenyl, X⁻ = ClO₄⁻), adapted from Ref. [9]. In the inset the imidazolium and triazolium cations are numbered and the C2-H and C5-H acidic hydrogen atoms are marked with an asterisk.

This species was structurally characterized by X-ray crystallography as a monomeric unit, whereas less bulky *N*-substituents than the adamantyl ones induced dimerization processes, deeply investigated in the condensed phase.[11]

According to their nucleophilic activity, the NHCs catalyse the *Umpolung* reaction, a chemical modification consisting in the polarity inversion of a functional group.[12] The ability of the NHCs to trigger the *Umpolung* is related to their chemical properties, showing a cyanide-like behaviour. The carbene can act as an electron donor and as an electron acceptor due to the simultaneous presence in its structure of a sp^2 lone pair and an empty p-orbital. Many synthetic procedures take advantage of these chemical features, the most known of which involves the reaction between the NHC and an aldehyde, giving rise to the "Breslow" intermediate (Scheme 2). This intermediate is characterized by a nucleophilic carbonyl carbon atom, resulting from a proton transfer with consequent polarity inversion.[13] This type of mechanism has been invoked in important processes, such as the benzoin condensation[14] and Stetter reaction,[15] both of which have been recently extended with oxidative protocols for the synthesis of different organic compounds, such as aldehydes, acids, and amides.[16]

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Another intriguing application of the nucleophilic NHCs concerns the possibility of catching and storing atmospheric greenhouse gases.[17]

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Anna Troiani received her master's degree in Pharmaceutical Chemistry and Technology in 1992 and a PhD in Pharmaceutical Sciences at Sapienza University of Rome in 1997, where she joined Prof. Giulia de Petris group as a research assistant in 2002. She is currently Associate Professor and her main research interests cover different aspects of ionic and neutral chemistry in the gas phase, investigated with mass spectrometric techniques.
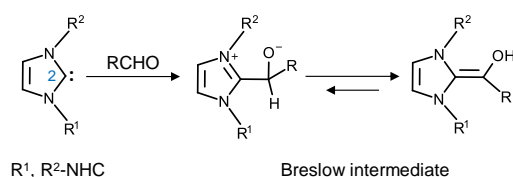
Scheme 2. Formation of the Breslow intermediate from the reaction between a dialkyl-*N*-heterocyclic carbene (R[1], R[2]-NHC) and a generic aldehyde (RCHO).

The capture of carbon or sulphur dioxide, through the attack of the carbenic atom to the electrophilic carbon or sulphur atoms, leads to covalent adducts that can then release the gaseous moiety in a controlled manner.[18]

Despite the mechanisms of the described NHC-mediated reactions being commonly accepted, some debates remain about the identity of the intermediates involved in the process. The reason is that carbenes are usually inaccessible in the condensed phase owing to the reactive divalent carbon atom with a low valence shell,[19] likewise the Breslow intermediate remained elusive until 2012.[20]

The thermal stability of the Arduengo's carbene represents an exception due to the steric hindrance of the adamantyl *N*-substituents and the crossed resonance between the two vicinal ring nitrogen atoms.[9] In this regard, the effects of the aromatic/non-aromatic character on the thermodynamic properties of imidazole-2-ylidenes were theoretically investigated in a sophisticated study by Schwarz *et al.*[21]

Although many efforts were spent improving the high-speed capability of the spectroscopic techniques,[22] their scarce selectivity still prevents the characterization of transient intermediates, especially in the case of multi-stage processes,

such as cascade or radical chain reactions.[23] A promising approach to circumvent these issues is to study the reactions involving carbenes by mass spectrometric techniques boasting high sensitivity, selectivity and speed essential to isolate and characterize short-lived intermediates.[23-26]

In the past decades, electron ionization mass spectrometry (EI-MS) was predominantly used to study the gas-phase chemistry of the *N*-heterocyclic carbenes.[27] To this end, an appropriate precursor, such as an imidazolium-based ionic liquid, was vaporized under vacuum and energetically ionized by electron impact.[27c] The non-thermal ions thus obtained, readily dissociated into the corresponding carbenic radical cations that were prone to be investigated by ion-molecule reactions (IMR)[28] and neutralization-reionization experiments.[29] However, the high-energy electron impact ionization process produces an extensive fragmentation of the parent ion, and in addition is also not representative of the solution conditions, in which the NHC-catalysed reactions occur.

At the end of the '80s, the advent of soft ionization methods, in particular the electrospray ionization (ESI) technique,[30] allowed to gently volatilize charged species present in solution, paving the way, inter alia, to track the progress of chemical reactions under thermal conditions. In this respect, Eberlin *et al.*[31] exploited the ESI speed and sensitivity to efficiently "fish" the ionic reactants, intermediates, and products of a reaction from the condensed phase.[32] Accordingly, the ESI-MS technique can be used to reveal mechanistic details of catalytic reactions by intercepting transient and highly reactive intermediates, which, once transferred in the gas-phase environment, can be isolated and interrogated to assess their inherent structure and reactivity. In this way, the elementary steps of a complex process can be highlighted, for example by collision-induced dissociation (CID) or by ion-molecule reactions.[24a] The main advantage of a gas-phase approach is indeed the possibility to investigate ions in the isolated state, excluding any possible interference of the solvent molecules and counterions in the reaction.[24] In addition, the experimental results collected in the gas phase can be directly compared to the theoretical data.[25]

Chemical investigation of NHCs by ESI-MS requires their ionization, for example by forming electrostatic adducts with metal ions that confer a stable positive charge.[33] Such an approach was either used to follow the time-progress of reactions, in which metal-NHCs play the role of organo-catalysts, or to study their intrinsic properties.[34] Otherwise, intermediates that are in equilibrium with their protonated forms can be fished from the solution and analysed.[35] Accordingly, electrospray ionization mass spectrometry was used for the first time in 2007 to study the conjugate *Umpolung* reaction between an α,β-unsaturated aldehyde and a carbene catalyst.[36]

Despite the relevance of these approaches in the detection of intrinsic neutral species, only metal-catalysed processes and reactions involving protonated substrates/products can be studied. Therefore, the use of a charge tag represents a useful strategy consisting in the derivatization of the reactive species with a charged group, which makes reagents, intermediates and products detectable by mass spectrometry.[37]

In this review we summarized the main results obtained by the application of this intriguing strategy to study the *N*-heterocyclic carbene chemistry with different types of mass spectrometric approaches. The review covers the last twenty years, without the intent of being exhaustive, focusing on the following topics:

i.   selection of positive and negative charge-tagged *N*-heterocyclic carbenes,

ii. detection and characterization of tagged NHCs by electrospray ionization mass spectrometry,

iii. mechanistic investigations of selected carbene-mediated reactions (NHC dimerization, CO_2 catch-and-release, benzoin condensation, Stetter reaction and Breslow oxidative processes).

2. Charge tags

2.1.   Positive

Positive charge-tagged *N*-heterocyclic carbenes were mainly obtained from a particular class of ionic salts known as dicationic ionic liquids (DILs). DILs are composed of two imidazolium, triazolium, or thiazolium cations coordinated with two anions and separated by a rigid or flexible spacer.[38] Hence, the possibility of structural modification is greater than in the case of monocationic ionic liquids. Accordingly, cations and anions of the DILs can be opportunely selected, as well as the structure and the length of the linker (Figure 1A).
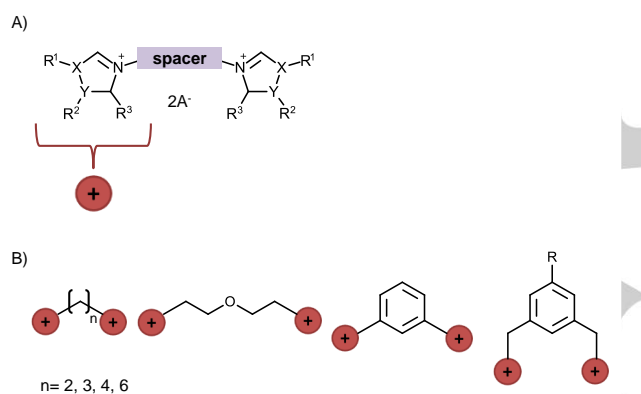

Figure 1. A) Positive charge-tagged imidazolium (X = N, Y = C), thiazolium (X = S, Y = C) and triazolium (X = Y = N) ionic liquids as precursors of *N*-heterocyclic carbenes. A⁻ = anion, typically bromide; B) common chemical structures of the spacers used to divide the two cationic units in DILs.

The nature of the linker (aliphatic, xylyl, aromatic) can influence the reactivity of the corresponding dicarbenes, obtained by deprotonation of both heterocyclic cation moieties. For example, dicarbenes from xylyl dications are less stable than the aliphatic ones due to a debenzylation reaction.[39]
Concerning the mass spectrometric studies of positive NHCs (Table 1), DILs have the remarkable advantage of being intrinsically charge-tagged, as one heterocyclic cation represents the positive tag, and the other is the precursor of the active carbene.
A strong base can be used to deprotonate the cation unit, although in most cases DILs were synthesized as bromide salts so that the bromide anion can abstract the more acidic of the two hydrogen atoms. The deprotonation the C2-H moiety of an imidazolium cation, through the basic counterion, occurs in the so-called "*non-innocent*" ionic liquids, in which low concentrations of NHC are intrinsically present.[40] The anions (A⁻) with high basicity promote the proton transfer forming the carbene

derivative and HA, which can interact with a hydrogen bond or dissociate depending on the experimental conditions. Under the low-pressure environment of a mass spectrometer, the equilibrium between the hydrogen-bonded moieties and the neutrals typically favours the carbene dissociation from the HA counterpart and consequently, the positive NHC can be fished from the solution (Scheme 3).[27c]

Table 1. Charge-tagged *N*-heterocyclic carbenes studied by different electrospray ionization mass spectrometric (ESI-MS) techniques.

NHC scaffold	Charge tag	MS technique	Ref.
Imidazolydene	Imidazolium (+)	ESI-MS	[45]
		CID MSⁿ[a]	[46]
		CID MS	[52]
		IM-MS[b]	[61]
		RM-MS[c]	[74, 75]
	-COOH (-); -CH₂SO₃H (-)	CID MS	[54]
		IMR-MS[d]	[43]
Triazolydene	Triazolium (+)	CID MS	[50]
		RM-MS	[75]
Thiazolydene	Thiazolium (+)	RM-MS	[75]
	-N(CH₃)₃ (+)	IRMPD[e]	[41]
	-CH₂SO₃H (-)	RM-MS	[44]
		IMR-MS	[69]
Imidazolylidene	Imidazolinium (+)	RM-MS	[75]

[a] CID: collision-induced dissociation; [b] IM: Ion Mobility; [c] RM: Reaction Monitoring; [d] IMR; Ion-Molecule Reaction; [e] IRMPD: Infra-Red Multiphoton Dissociation).
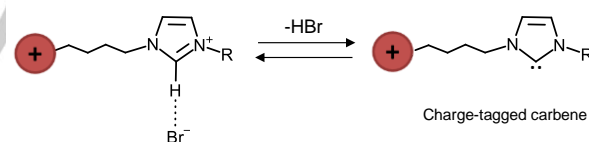
Scheme 3. Proton abstraction by bromide and formation of positive charge-tagged carbenes.

Concerning the spacer, a variety of linkers have been used in the structural and reactivity characterization of positive charge-tagged carbenes (Figure 1B), whereas in some cases cyclic compounds of the cyclophane type were employed as carbene precursors (see references in Table 1).
On the other hand, an example of monocationic ionic liquid precursor was reported by Schäfer *et al.* in a study in which 3,4-Dimethyl-5-[2-(trimethylammonio)ethyl]-1,3-thiazolium diiodide was synthesized to generate the corresponding positive-charged thiazolin-2-ylidene.[41]

2.2. Negative

Negative charge-tagged ionic liquids represent the precursors of the corresponding anionic *N*-heterocyclic carbenes. Studies exploiting the negative charge-tagging strategy in the investigation of NHC reactivity (Table 1) are generally limited,

reflecting the less explored chemistry of the anions in the gas phase. The scarce attention paid to the negative polarity is either due to the ionization processes that produce a minor abundance of negative ions, compared to the positive ones, or to less reactivity often encountered with anions, although exceptions to this general trend exist.[42]

Negative NHCs were formed from imidazolium or thiazolium ionic liquids bearing an easily deprotonable site on the cation, such as a carboxylic or sulfonic acidic group (Figure 2).

The formation of negatively charged NHCs occurs through a double deprotonation performed in solution by a strong base, such as potassium tert-butoxide (KOtBu), triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The first deprotonation, involving the acidic tag (carboxylic or sulfonic acid), generates a zwitterionic neutral intermediate, undetectable by mass spectrometry. The second deprotonation at the C2-H moiety leads to the formation of free negatively charged NHCs, which are prone to be fished out from the solution and investigated in the gas phase.
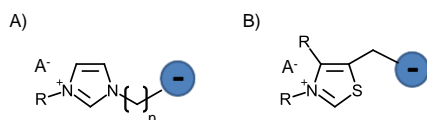
Figure 2. Negative charge-tagged A) carboxylate/sulfonate imidazolium and B) sulfonate thiazolium-based ionic liquids as precursors of N-heterocyclic carbenes. Negative tags: -COO⁻, -SO₃⁻; R = methyl; n = 1-4; A⁻ = anion, typically chloride.

In addition to the NHCs derived from the precursors reported in Figure 2, Rodrigues et al.[43] extended the study to negative charge-tagged DILs to verify the possible formation of stable negative dicarbenes in the gas phase.

Since the charge tags should be "silent" to minimize their interferences in reactivity, the acidic group is set away from the active centre through an alkyl chain. Nevertheless, the folding of this chain to reach the carbene site, forming a "closed" structure that could affect the NHC reactivity, is only possible if five- or six-membered rings are formed. However, calculations at the B3LYP-6-31G (d,p) level of theory[43] demonstrated that this interaction is very weak, amounting to only 5 kcal mol⁻¹ for the carboxylate-charged derivatives, without therefore affecting the reactivity of carbenes. Zeng et al. evaluated the influence of the sulfonate charge tag on the catalytic activity of the thiazolium carbene.[44] According to their calculations, the sulfonate group renders the carbene centre more basic when compared to its neutral counterpart. This difference, however, disappears when the effects of solvation and the water dielectric field were considered. Overall, N-heterocyclic carbenes, labelled with negatively charged tags, maintain their catalytic efficiency in solution.

3. ESI-MS detection and characterization of charge-tagged N-heterocyclic carbenes

The first study on the observation of N-heterocyclic carbenes by electrospray ionization mass spectrometry dates back to 2000.[45] Alcalde et al. analysed a series of dicationic imidazolium prototypes, having M•2X (M stands for the dicationic moiety and

X for the anion) as general formula, to verify if they were precursors of imidazolylidenes in the gas phase. Therefore, macrocyclic and open-chain dications bearing imidazolium units were synthesized (Figure 3A) and their potential in generating NHCs was related to the chemical framework of each compound. Positive ESI mass spectra of these species consist of three main ionic signals, as reported in Figure 3B for the representative compound **1a·2Cl**: the doubly charged ion [M]²⁺ at m/z 171 and two singly charged ions, [M•Cl]⁺ and [M-H]⁺ at m/z 377 and m/z 341, respectively, the intensity of which strictly depends on the experimental conditions. The doubly charged ion [M]²⁺ is the most intense species (base peak) when soft conditions are used by setting low cone voltage values (up to 50 V). Interestingly, the [M-H]⁺ ion, compatible with an imidazolylidene ion as a result of the loss of two counter anions and a proton, becomes the base peak using harsher conditions, by increasing the cone voltage from 50 V to 80 V.
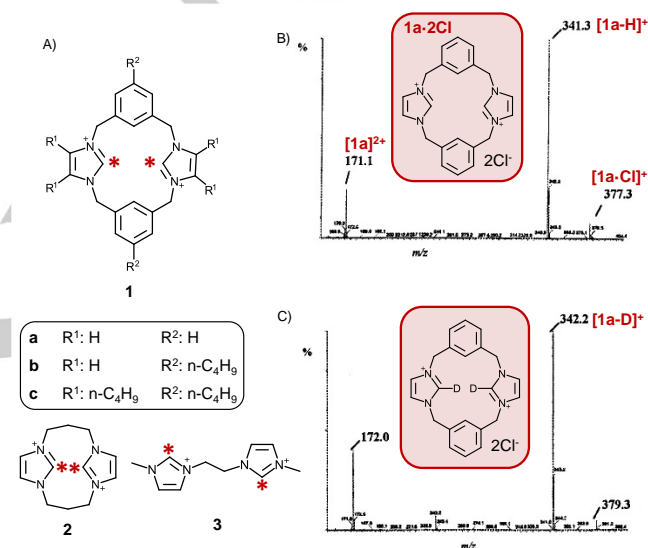
Figure 3. A) Dicationic imidazolium ionic liquids synthesized by Alcalde et al. as precursors of NHCs for MS studies (the deprotonable carbon atoms are marked with an asterisk). Typical ESI(+) mass spectra of B) the compounds **1a·2Cl** and C) the corresponding deuterated species. Reproduced and adapted from Ref. [45] with permission from Wiley-VCH.

The ESI mass spectrometric detection of the singly charged imidazolylidene ion [M-H]⁺ was confirmed by dissolving the parent compound **1a·2Cl** in D₂O. The [M-H]⁺ base peak shifted of 1 m/z unit to m/z 342, corresponding to the singly charged [M-D]⁺ ion (Figure 3C). This result agrees with the presence of only two labile hydrogen atoms in **1a·2Cl**, presumably the imidazolium acidic hydrogens at positions 23 and 25. Hence, the [M-D]⁺ species is obtained from the dissociation of two counter anions and further fission of one C-D bond. The same experimental approach was also applied in the investigation of the other dicationic compounds, reported in Figure 3A (compounds **2** and **3**), demonstrating that the relative ionic signal intensity of the positive carbene [M-H]⁺ strictly depends on the chemical framework of the parent species. For example, **2·2Br** and the open-chain **3·2Br** still produce the three characteristic peaks described above. However, the singly charged ions [M-H]⁺ and [M-D]⁺ prevail at low cone voltage (50 V). To elucidate the origin of the positive NHCs ([M-H]⁺) observed by Alcalde et al.[45], a deeper investigation by the same research

group on imidazolium-based macrocyclic and open-chain dications was performed by ion trap mass spectrometry (IT MS).[46] This technique allows subsequent cycles (n) of isolation and fragmentation (MS[n]) of a selected precursor ion.[47] It was demonstrated that the imidazolylidene species [M-H][+] arises from [M•X][+], by the loss of neutral HX, rather than from deprotonation of [M][2+]. The formation of similar carbene ions [M-H][+] was also observed in the electrospray mass spectra of analogous dicationic protophanes and heterophanes.[48] The negative ion electrospray of the above mentioned macrocyclic and open-chain dications[45] revealed the formation of non-covalent aggregates as a consequence of the hydrogen bonds between the imidazolium dications and the halide counterions. These intermolecular interactions are known to play a significant role in generating the NHCs in the gas phase. A further approach involved the use of a transition metal halide in the anion scaffold. Accordingly, Kuhn *et al.* synthesized a nickel-containing dicationic ionic liquid, in which the [NiCl$_4$][2-] anion considerably increased the collisionally induced formation of the carbenes, due to the additional stabilization of the metal species.[49]

In 2003, Lyapchenko *et al.* studied the *N*-heterocyclic carbenes deriving from a series of 1,2,4-triazolium perchlorates (Figure 4) by electrospray ionization and liquid secondary ion mass spectrometry (LSI-MS).[50]
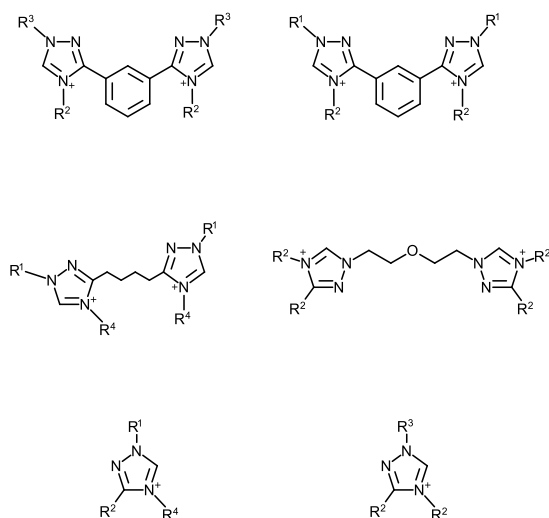

Figure 4. Triazolium cations investigated by Lyapchenko *et al.* (R^1 = adamantyl, R^2 = phenyl; R^3 = benzyl, R^4 = 4-bromophenyl). Adapted from Ref. [50] with permission from Elsevier.

As reported by Alcalde *et al.* in the case of positive imidazolylidenes,[45] the [M-H][+] ionic species, corresponding to the charged triazolylidenes, were generated from [M•X][+] (X = ClO$_4$[-]) by the loss of HClO$_4$.

Regardless of the chemical identity of the aromatic ring (imidazolium vs triazolium), the loss of a proton from [M][2+] was not observed. Instead, this doubly charged species fragmented by the elimination of N1 substituent, following a simple heterolytic bond cleavage as a result of a charge separation process.

The decomposition of ionic triazolium carbenes was also elucidated by collision-induced dissociation (CID) experiments and is reported in Scheme 4 for the ionic species at *m/z* 545. The

cleavage of N1-N2 bond leads to the product ion at *m/z* 337, confirming the carbenic nature of the parent species.
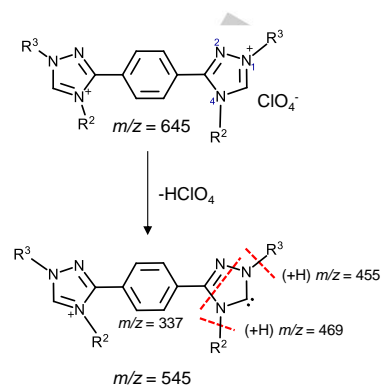
Scheme 4. Formation and decomposition of 1,2,4-triazolium carbene at *m/z* 545. Adapted from Ref. [50] with permission from Elsevier.

The breaking of the triazole ring is a characteristic reaction of the NHCs and occurs spontaneously when the N-N bond is situated at the α position to the carbene centre.[51] Moreover, the N1-N2 cleavage is not a fragmentation channel in the decomposition of the ionic non-carbenic species [M][2+]. The loss of N1 and N4 substituents, respectively, leads to the ionic species at *m/z* 455 and 469. These dissociations proceed through a hydrogen transfer probably from the eliminated alkyl chain to the reactive carbene centre. This is further evidence of the carbenic identity of the ion at *m/z* 545. Accordingly, the hydrogen transfer is not reported in the loss of N1 substituent from the [M][2+] parent species. In addition, the N4 alkyl chain elimination is not even a fragmentation channel of this ion.[50]

Likewise, the fragmentation loss of the *N*-alkyl substituents from the heterocyclic moiety of the imidazole-based precursors was used by Corilo *et al.* to confirm the carbene identity of the ionic species, obtained by a series of multiply charged imidazolium cations.[52] The major dissociation channel of the symmetrically substituted charge-tagged carbene consists in a proton transfer leading to the vinyl methyl imidazolium ion at *m/z* 109, resulting from the loss of a neutral 1-methyl-imidazole (Scheme 5A).

Such a structurally diagnostic rearrangement was confirmed by dissociating the asymmetric charge-tagged carbenes which undergo two dissociation routes, following an alternative N1 or N3 proton transfer, as shown in Scheme 5B. These results agree with the previous experiments performed by Lyapchenko on triazolium carbenes.[50] Calculations at the B3LYP/6-31G+(d,p) level of theory were also carried out to optimize gaseous structures of the analysed NHCs, highlighting that the acidic hydrogen of the imidazolium moiety is involved in the intramolecular H-bonding with the heterocyclic asymmetric carbene centres. Small differences in the intrinsic acidity (ca. 0.2-1.0 kcal mol^{-1}) of the two possible C2-H carbenes were also found.

Interestingly, in the same work, Corilo *et al.* also observed doubly and triply charged aggregates that provide prompt access to several new multiply charged mono and dicarbenes, by dissociation through HBr loss (Figure 5).[52] The thermal activation, in which the bromide anion acts as a base, mimics the solution equilibrium indicating that, when imidazolium-based ionic liquids are employed in the reaction, a small amount of *N*-heterocyclic

carbenes is formed.[40] Therefore, NHCs in imidazolium ILs are present, and their involvement in the reaction should always be

A)

B)

Y = O m/z = 235
Y = CH$_2$ m/z = 237

Y = O m/z = 153
Y = CH$_2$ m/z = 151

m/z = 109
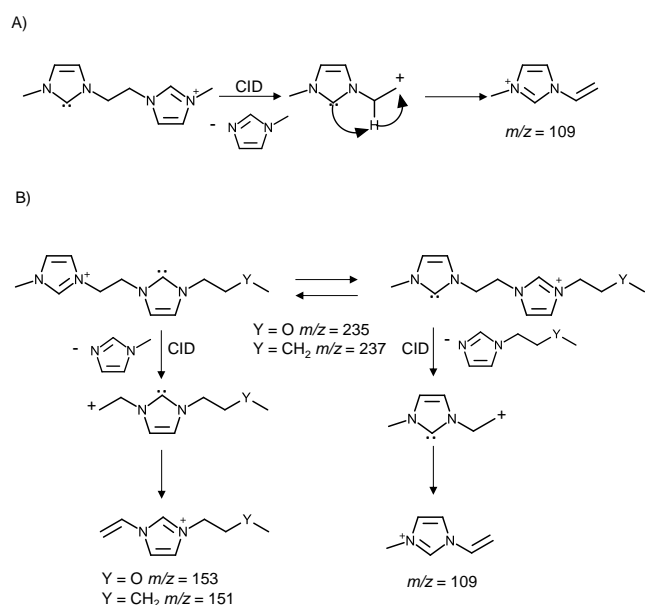
Scheme 5. Characteristic fragmentation pathway of A) symmetrically and B) asymmetrically substituted positive charge-tagged NHCs. Adapted from Ref. [52] with permission from The Royal Society of Chemistry.

evaluated in the light of the anion basicity. Similarly, the acid-base properties of the ions can affect the distillation mechanism of ionic liquids, that can reach the vapour phase as ion pairs or free neutrals, NHC and H-anion. Accordingly, Diniz et al. applied the tagging strategy to study the carbene role in the distillation process, demonstrating that both the cation and anion nature can affect the process.[53] In particular, anions from Lewis acids ([InCl$_4$]$^-$), that commonly prevent the acid-base reactions responsible for the NHC formation in solution, favoured the distillation of ionic liquids as ion pairs, by preserving the cation-anion interaction. As far as the influence of the cation is concerned, the same authors suggested that a dicationic moiety could react with the [InCl$_4$]$^-$ anion, allowing the ionic liquid to distillate as a bidentate NHC complex.[53]

Turning to the negative ion mode, Lalli et al. succeeded for the first time in 2012 in the isolation of N-heterocyclic carbenes bearing negative charge tags.[54] In this case, deprotonation of imidazolium parent cation does not occur through the intervention of the basic counter anion, as in the positive ion mode, but by adding an excess of a strong base (KOtBu). This approach results in an ESI(-) spectrum that displays predominant ions corresponding to the intact negative charge-tagged NHCs. The interception of negative NHCs was confirmed by CID experiments that revealed the diagnostic fragmentation of a carbene-like structure (Scheme 6).

Finally, the formation of negative charge-tagged dicarbenes was reported by Rodrigues et al. through the MS analysis of a doubly charged diimidazolium ion, bearing two carboxylic acid groups (Scheme 7).[43]
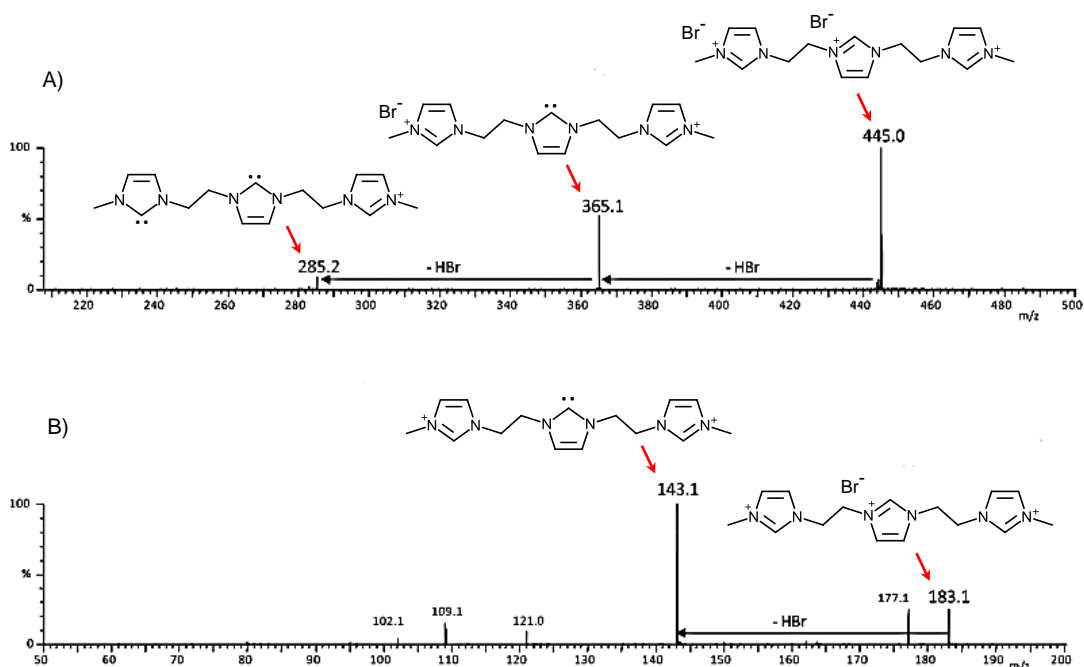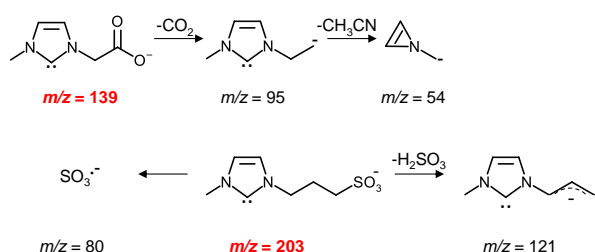

Figure 5. ESI(+)-MS/MS of A) singly charged ion at m/z 445 leading to the charge-tagged N-heterocyclic dicarbene at m/z 285 by two consecutive HBr losses and B) doubly charged ion at m/z 183 leading to the monocarbene at m/z 143 by HBr loss. Reproduced and adapted from Ref. [52] with permission from The Royal Society of Chemistry.

Scheme 6. Proposed pathways of collision-induced dissociation for the gaseous negative charge-tagged NHCs at m/z 139 and 203 synthesized by Lalli *et al.* Reproduced and adapted from Ref. [54] with permission from The Royal Society of Chemistry.
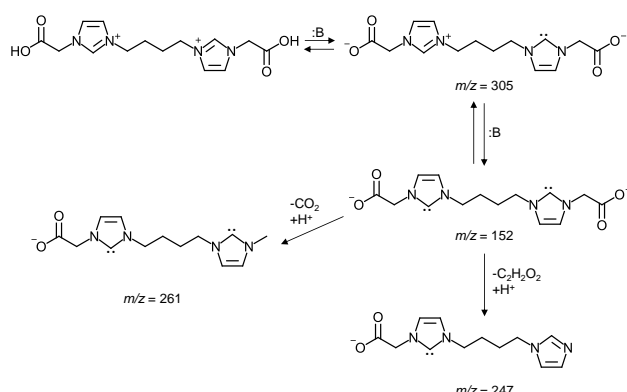

Scheme 7. Formation pathway of the singly charged monocarbene at m/z 305 and doubly charged dicarbene at m/z 152. Decomposition products at m/z 261 and 247 arising from ion at m/z 152 are also reported. Reproduced and adapted from Ref. [43] with permission from the American Chemical Society.

The singly charged monocarbene at m/z 305 and the doubly charged dicarbene at m/z 152 were generated by a single and double deprotonation of the diimidazolium precursor, respectively. Two other charge-tagged carbenes at m/z 261 and m/z 247 were also detected, probably formed from the decomposition of the ions at m/z 152, occurring in solution. ESI is a soft ionization technique that does not form ions, rather transfers those already present in solution directly in the gas phase.[31,43]

4. NHC-mediated dimerization

Owing to their high basicity,[55] *N*-heterocyclic carbenes are supposed to behave as strong hydrogen-bond acceptors, able to interact with the corresponding azolium salts, by forming **C••HC⁺** dimeric aggregates, in which **C** is used here to indicate the *N*-heterocyclic carbene, for the sake of clarity.[56] Accordingly, a hydrogen-bonded **CHC⁺** dimer was first characterized in solution by Arduengo[57] and recently investigated by theoretical calculations.[58] Since the hydrogen bond is quite strong, these thermodynamically stable complexes[27a] can influence the reactivity of the NHCs, especially when the corresponding ionic liquids are used in large amounts as reaction medium. For instance, NHC-catalysed C-C coupling reactions leading to γ-butyrolactones showed lower rates and selectivity when performed in ionic liquid, rather than in tetrahydrofuran.[59]

Alternatively, the nucleophilic NHC can attack the azolium salt forming a covalent **CCH⁺** intermediate, referred to as the precursor of a neutral C=C dimer, reported for the first time by Wanzlick and Schikora.[11] The occurrence of these covalent species in solution was independently verified in two different works by Alder[11c,d] and Chen[60], describing the mechanism postulated for the dimerization process (Scheme 8).
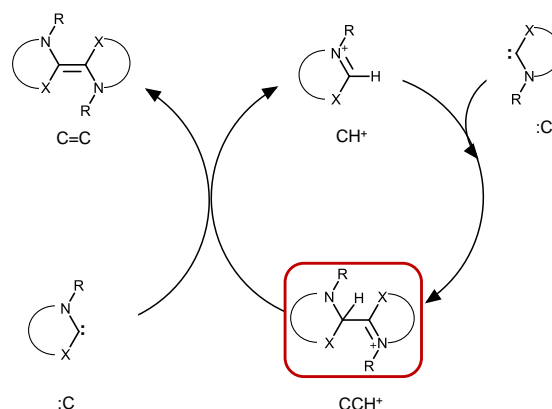
Scheme 8. Mechanism of the azolium-catalyzed NHC dimerization, R = methyl, ethyl, *iso*-propyl or *tert*-butyl, X = N-R;[11c,d] S .[60] Adapted from Ref. [61] with permission from Wiley-VCH.

Many factors, such as the identity of the *N*-substituents, the aromaticity of the heterocyclic ring and the solvent or counterion effects may influence the outcome (**CHC⁺** versus **CCH⁺** formation) of the NHC-azolium interaction. Since **CHC⁺** and **CCH⁺** are isobaric species, Paul *et al.* investigated the dimerization process by using travelling wave ion mobility mass spectrometry (TW IMS).[61] This method exploits the different mobility of charged molecules, sharing the same m/z ratio, through a cell filled with a counter-flowing buffer gas (helium or nitrogen). The application of an electric field between the entrance and the exit of the chamber propels the ions with a velocity that depends on their compactness, and from which a parameter strictly related to the shape of the ions (Collision Cross Section, CCS) can be derived.[62]
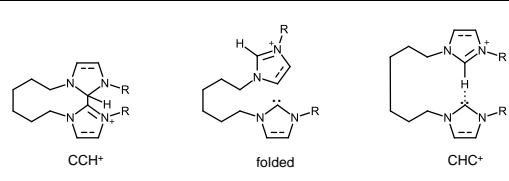
Accordingly, Paul *et al.* synthesized four bis-azolium dicationic ionic liquids and analysed the intramolecular interactions between the NHC moiety (**C**), obtained under ESI conditions by the loss of one proton, and the azolium cationic head (**CH⁺**). The formation of **CHC⁺** or **CCH⁺** ions was thus correlated to the aromaticity/non-aromaticity of the carbene moieties and the steric hindrance of the *N*-substituents. Table 2 reports the experimental and theoretical collision cross sections (CCS_m and CCS_t, respectively) for the covalent **CCH⁺** and the hydrogen-bonded **CHC⁺** dimers, along with those of a folded conformer. The latter is formed as a transient species in the gas-phase folding from an extended structure to the compact **CHC⁺** or **CCH⁺** conformers.

The aromatic species are both characterized in the gas phase by only one structure, as confirmed by the presence of only one drift-time peak (Table 2). This points to the formation of the covalent C-C bond dimer **CCH⁺**, as suggested by the agreement between the measured CCSs and the theoretical values calculated for the corresponding structures. However, Boltzmann-weighted (Bw) calculations[61] showed that the concomitant presence of the two conformers could not be excluded since the CCS_t values of the

CHC+ and the **CCH+** isomers (R=Dipp) are too similar, regardless of the level of theory employed. The hydrogen-bonded conformer, however, resulted to be ca. 34 kJ mol^{-1} more stable than the covalent dimer.

Table 2. Experimental (CCS$_m$) and theoretical (CCS$_t$) collision cross sections for the covalent (**CCH+**), folded, and hydrogen bonded (**CHC+**) dimers investigated by ion mobility mass spectrometry. Adapted from Ref. [61] with permission from Wiley-VCH

	CCS$_m$[a]	CCS$_t$[a]		
		CCH+	**folded**	**CHC+**
Aromatic				
R= Me	156	153	161	161
R=Dipp	229	230 (226)[b]	225	227 (229)[b]
Non-aromatic				
R= Me	156; 161	155	165	162
R=Dipp	226; 238	224	233	234

[a] CCS: Collision Cross Section (Å^2); [b] Boltzmann-weighted calculations; Me: methyl, Dipp: 2,6-diisopropylphenyl.

Concerning the saturated compounds, the profiles of the arrival times show a two-peak distribution, providing evidence for the simultaneous presence of both **CCH+** and **CHC+** isomers, as confirmed by the comparison of the experimental and theoretical CCS values (Table 2).

The prevalence of the covalent dimer **CCH+** was observed under soft ionization conditions, whereas harsher conditions favoured the hydrogen-bonded aggregate **CHC+**. The non-aromatic **CCH+** ions acquire sufficient energy, increasing the cone voltage, to isomerize to the **CHC+** species by overcoming an inter-conversion barrier, calculated to be ca. 83-85 kJ mol^{-1}, thus allowing the formation of both isomers.

More generally, the possible formation of covalently bonded species should always be taken into account when dealing with DILs, as this process may reduce the availability of the carbene catalyst in solution, negatively affecting the reaction outcome.

5. NHC-mediated CO$_2$ catch and release

Carbenes can react either as electrophiles or nucleophiles depending on the nature of the reactant. With carbonyl compounds, for example, carbenes behave as nucleophiles adding to the carbonyl group. Accordingly, NHCs in ionic liquid solutions are known to react with carbon dioxide forming imidazolium-carboxylates, representing potential storing systems to reduce CO$_2$ concentration in the atmosphere.[63] The covalent nature of the so-formed C-C bond identifies the phenomenon as a "chemical" absorption, increasing the capture capability of the ionic liquids that typically solubilize this gas through a "physical" process.[64] Chemical adsorption is also prominent with aprotic

heterocyclic anion (AHA) ILs, in which the basicity of the anionic moiety derived from weak nitrogen acids (e.g. imidazolate from imidazole) is crucial to specifically tune the properties of ILs for carbon dioxide capture.[65]

The possibility to assess the intrinsic reactivity of charge-tagged carbenes was verified by gas-phase ion-molecule reaction experiments. For instance, mass-selected positive charge-tagged NHCs react as nucleophiles adding to the carbonyl group of acrolein or acetone in the collision cell of the mass spectrometer.[52]

Following this approach, Lalli *et al.* probed the NHC reactivity towards CO$_2$ by using carboxylate-tagged NHCs. These ionic species reacted with CO$_2$ in the gas phase forming negatively charged imidazolium dicarboxylates, in agreement with the solution chemistry.[54] However, the scarce reaction yields were attributed to the presence of kinetic barriers or to the absence of C2 carbene in the ionic population. To tackle this issue, Rodrigues *et al.* employed a modified triple-quadrupole mass spectrometer that was optimized for maximum yields of ion-molecule reactions.[43] Accordingly, the transfer line of the instrument, placed between the ion source and the first quadrupole, was turned into a collision/reaction cell, via encapsulation with a 5 cm long Teflon tubing, in order to increase the pressure of the neutral reagent (CO$_2$) to ca. 10^{-3} mbar. Under these conditions, the ion-molecule reaction between negative charge-tagged NHCs and CO$_2$ led to an almost complete conversion resulting in imidazolium carboxylate products (Figure 6), demonstrating that most of the gaseous ionic population is composed of long-lived NHCs.
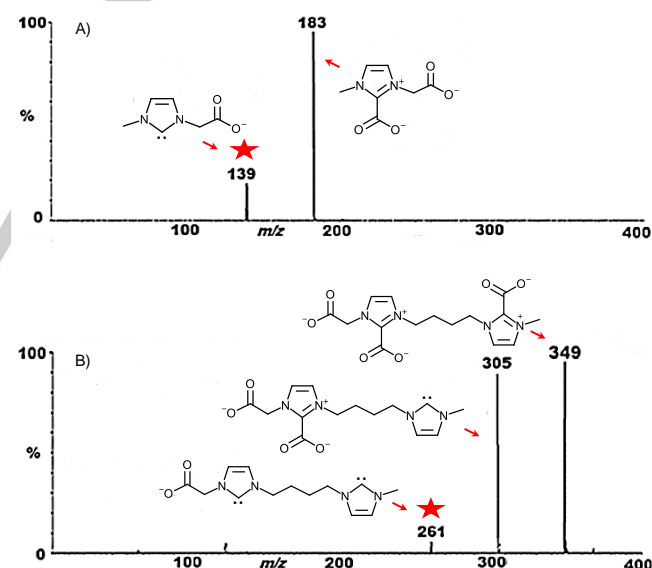

Figure 6. ESI(-)-MS/MS of the ion-molecule reactions between the carboxylic acid-tagged carbene at *m/z* 139 A) or dicarbene at *m/z* 261 B) and CO$_2$ (the reactant ions are marked with a star). Reproduced and adapted from Ref. [43] with permission from the American Chemical Society.

The major fragmentation channel of the so-formed imidazolium carboxylates was the dissociation of a CO$_2$ moiety which, owing to the stability of the fragment ions, was lost from the imidazolium carboxylate ring, and not from the carboxylate charge tag.

Calculations at CBS-QB3 level of theory were also performed to elucidate the gas-phase carbene reactivity. From the predicted

values of proton affinity (PA) and gas-phase basicity (GB), all the ring-H and Cα-H resulted acidic. Accordingly, the so-called abnormal carbenes (carbene at C4 or C5 carbon atoms) are commonly reported, as well as the corresponding imidazolium 4- and imidazolium 5-carboxylates.[66] Nevertheless, calculations carried out by Rodrigues et al.[43] using the condensed Fukui functions at the MP2/6-311+G (2d,2p) level of theory demonstrated that the C2 is the most reactive site for the CO_2 addition.

6. NHC-mediated *Umpolung*

As described in the Introduction, *N*-heterocyclic carbenes are known to catalyse two important condensation processes: the benzoinic and the Stetter reactions,[14,15] consisting in an aldehyde-aldehyde dimerization and a condensation between an aldehyde and an enone, respectively. In both cases, the *Umpolung* is invoked to explain the reaction mechanism.

Concerning the benzoin condensation, two mechanisms are commonly accepted. The first one, known as the "Breslow" mechanism, requires the NHC attack to the aldehyde and the subsequent proton transfer, leading to the formation of the enolic Breslow intermediate (Scheme 9A).[13] The second one, proposed by Lemal, is known as the "dimer" mechanism and assumes the formation of a NHC dimer as the key intermediate (Scheme 9B).[67] To establish which of the two mechanisms is the more feasible in solution, Zeng et al. tracked the progress of a thiazolylidene-catalyzed benzoin condensation using electrospray ionization-mass spectrometry (ESI-MS).[44] To this end, a thiazolium-based ionic liquid with a sulfonate tag was synthesized and dissolved in methanol in the presence of benzaldehyde and triethylamine, the latter used to deprotonate the thiazolylidene precursor forming the carbene catalyst.
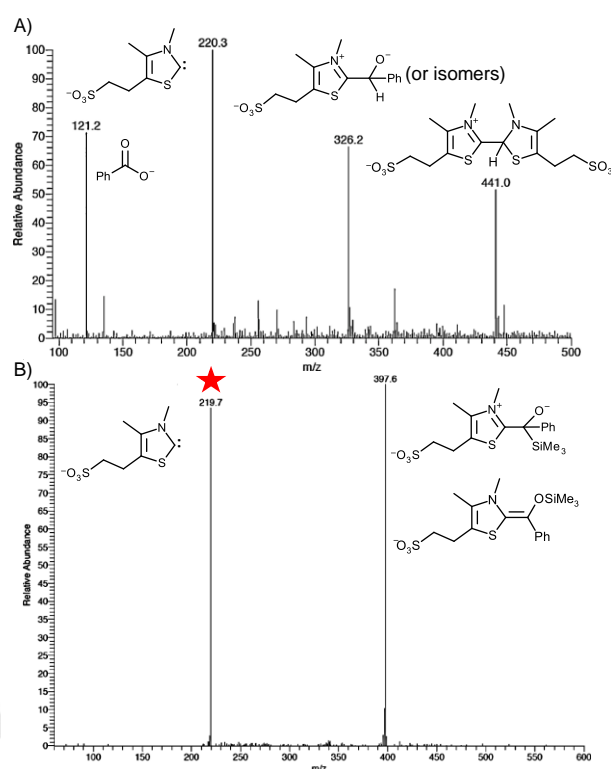

Figure 7. A) Mass spectrum of the reaction mixture (sulfonate-tagged thiazolium, benzaldehyde and triethylamine) after 5 minutes. Reproduced and adapted from Ref. [44] with permission from Elsevier; B) Mass spectrum of the ion-molecule reaction between the isolated sulfonate-tagged thiazolium carbene, marked with a star, and benzoyltrimethylsilane. Reproduced and adapted from Ref. [69] with permission from the American Chemical Society.
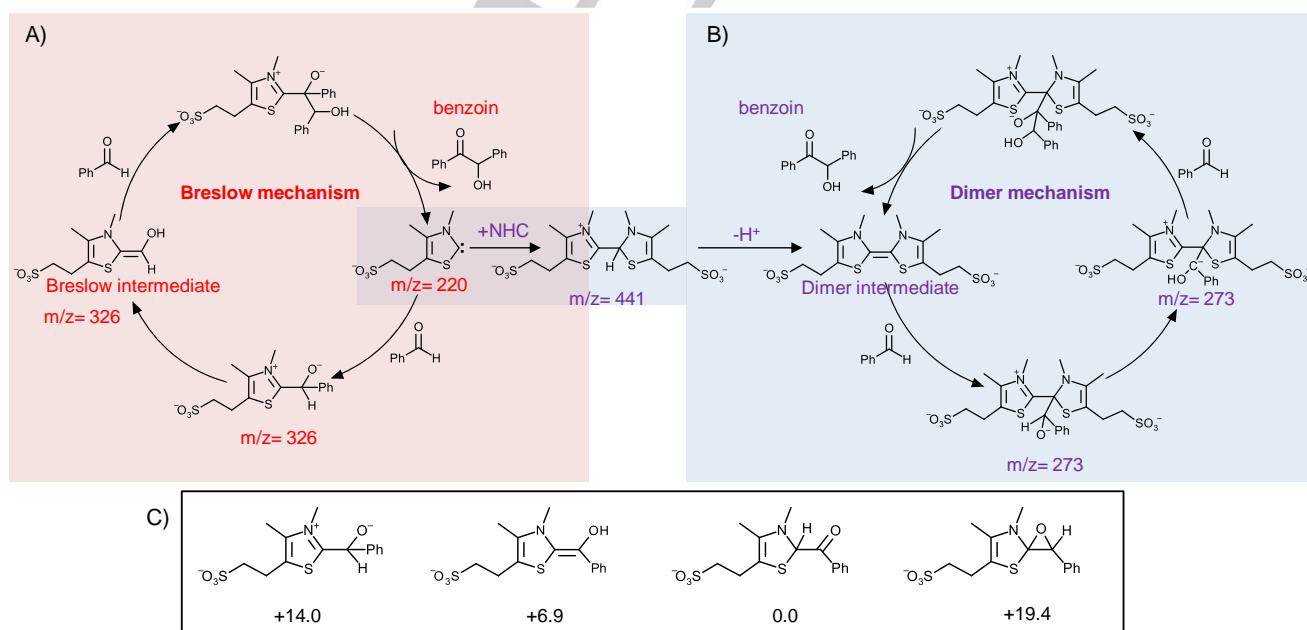
Scheme 9. A) Breslow and B) dimer mechanism for the benzoinic condensation; C) Relative stability for the possible structures of the ionic species at *m/z* 326 (ΔH at 298 K in kcal mol^{-1} B3LYP/6-31+G(d)). Adapted from Ref. [44] with permission from Elsevier.

The mass spectrum of the reaction after 5 minutes, displayed in Figure 7A, shows the ions at *m/z* 220 and 326 that were attributed to the negative charge-tagged NHC and to the first intermediate adduct, respectively, formed upon addition of the thiaozolylidene catalyst to benzaldehyde. The subsequent step of the reaction is the formation of the Breslow intermediate following a proton transfer, as shown in the Scheme 9A.

Since the thiazolylidene-benzaldehyde adduct and the Breslow intermediate both have a *m/z* ratio of 326, theoretical calculations by the same authors established that the ketonic structure is the most stable, among the four possible isomers found (Scheme 9C). However, the formation of the Breslow intermediate was not excluded, due to very small energy differences between their enol- and keto-tautomers (+6.9 vs.0.0 kcal mol^{-1}). Hence, the presence of the ionic species at *m/z* 326 was considered diagnostic for the occurrence of the Breslow mechanism in solution. Interestingly, the isolation of a stable ketonic intermediate was reported in previous studies on the benzoin condensation[68] and recently Schäfer *et al.* described the first gas-phase characterization of charge-tagged Breslow intermediates by Infra-Red Multiphoton Dissociation (IRMPD) spectroscopy.[41] The infrared irradiation of three different *N*-heterocylic carbene-derived aldehyde adducts led to the unambiguous evidence that thiazolin-2-ylidenes and 1,2,4,-triazolin-5-ylidenes form stable keto-tautomers, whereas classic enol Breslow intermediates arise from imidazolidin-2-ylidenes.

Concerning the dimer mechanism (Scheme 9B), the singly charged thiazolylidene-thiazolium dimer at *m/z* 441 was not catalytically active. The absence in the reaction mixture of the key intermediate at *m/z* 273, which should result from the addition of a benzaldehyde to the dimer, excludes the occurrence of this pathway.

To study the intrinsic carbene reactivity in the benzoinic and Stetter reactions, Tian *et al.* reported the first study of the *Umpolung* reaction of *N*-heterocyclic carbenes with carbonyl compounds in the gas phase, by using ion-molecule reactions.[69] Thus, the negative sulfonate-tagged carbene at *m/z* 220, previously described,[44] was electrosprayed and isolated in an ion trap mass spectrometer that was in-house modified to allow the introduction of the neutral substrates. In the presence of benzaldehyde, as neutral reagent, no signal corresponding to the addition or Breslow intermediates was observed. The formation of the Breslow intermediate from oxyanion adduct requires a proton shift, that in solution is rapidly mediated by the solvent or by the *N*-alkyl group of the thiazolium catalyst (Scheme 9A). In the gas phase however, a direct intramolecular 1,2-proton shift is thermodynamically unfavourable, having an energetic barrier of 39 kcal mol^{-1}.[69] On the contrary, when the silyl analogue of benzaldeyde (the benzoyltrimethylsilane) was employed as neutral reagent, the sila-Breslow intermediate at *m/z* 398 was detected (Figure 7b), following an intramolecular 1,2-silyl shift, a low-energy process with an energetic barrier of only 0.4 kcal mol^{-1}, known as Brook rearrangement.

Passing to the Stetter reaction, the ionic species at *m/z* 398 thus formed, was isolated and reacted by ion-molecule reaction with the methyl vinyl ketone and, alternatively, with acrolein, without observing any appreciable reactivity. According to the mechanism proposed by Scheidt[70] for the sila-Stetter process (Scheme 10), the sila-Breslow intermediate undergoes a desilylation reaction before the enone addition, regenerating the classic Breslow intermediate.
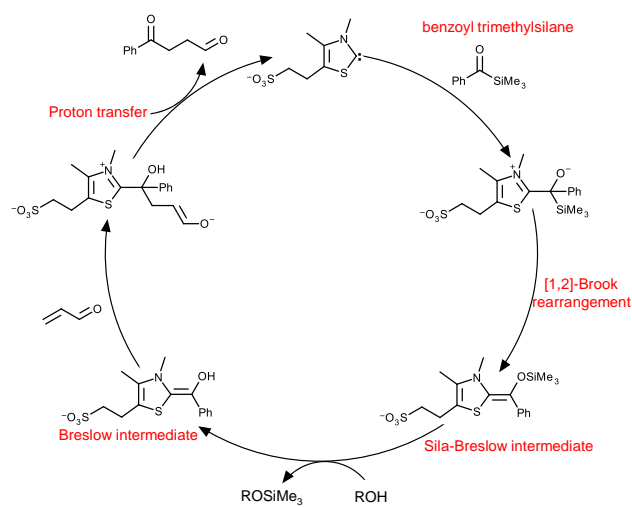

Scheme 10. The Scheidt mechanism for the sila-Stetter reaction. Adapted from Ref. [70] with permission from the American Chemical Society.

Theoretical calculations, performed by *Tian et al.*,[69] predicted that the non-silylated Breslow intermediate has a barrier for enone addition 13 kcal mol^{-1} lower than that of the sila-Breslow intermediate. This evidence supports the Scheidt's hypothesis postulating the occurrence of a desilylation for the reaction progress.

The Breslow oxidative reactions for the synthesis of different classes of compounds, such as acids and esters, have also been studied.[16] The oxidation of the Breslow intermediate usually occurs in the presence of inorganic or organic oxidants. When dioxygen is used as the oxidant, the reaction can follow two alternative pathways, the oxigenative and the oxidative paths, leading to different products.[71]

As shown in Scheme 11A for generic NHCs, the complex **I**, formed as a product of single-electron-transfer (SET) from the Breslow intermediate to O$_2$, can alternatively evolve into the isobaric intermediates **IIA** or **IIB**. The intermediate **IIA** converts into the species **IIIA** by adding a second aldehyde molecule, according to a Baeyer-Villiger-like oxidation process[72], which leads to the formation of two acid molecules (**oxigenative path A**). On the contrary, the intermediate **IIB** rearranges into the acylic cation **IIIB**, with the liberation of the hydroperoxy anion (**oxidative path B**). The electrophilic acylazolium ion **IIIB** can easily react with a nucleophile, such as an alcohol, leading to the formation of an ester molecule.[73] Bortolini *et al.*[74] demonstrated that the reaction outcome switches from ester (**oxygenative path**) to acid (**oxidative path**) when *ortho*- or *para*-substituted benzaldehydes are used. For instance, the ratio between methyl ester/carboxylic acid changes from 5:47 by using *o*-bromo-benzaldehyde to 89:11 in the presence of *p*-bromo-benzaldehyde, hinting at a strict correlation with the position of the substituent on the aldehydic aromatic ring. The present hypothesis was verified by mass spectrometric investigations and supported by theoretical calculations.[75] *N*-methylated 1,1'-(hexan-1,6-diyl) azolinium salts of the heterocyclic scaffolds imidazole, imidazoline, triazole and thiazole (Scheme 11B) were synthesized and used as carbene precursors, with the second ring acting as the positive tag. Their reactivity was probed towards *o*-bromo-benzaldehyde and *p*-mo-benzaldehyde under aerobic conditions. Reaction mixtures were

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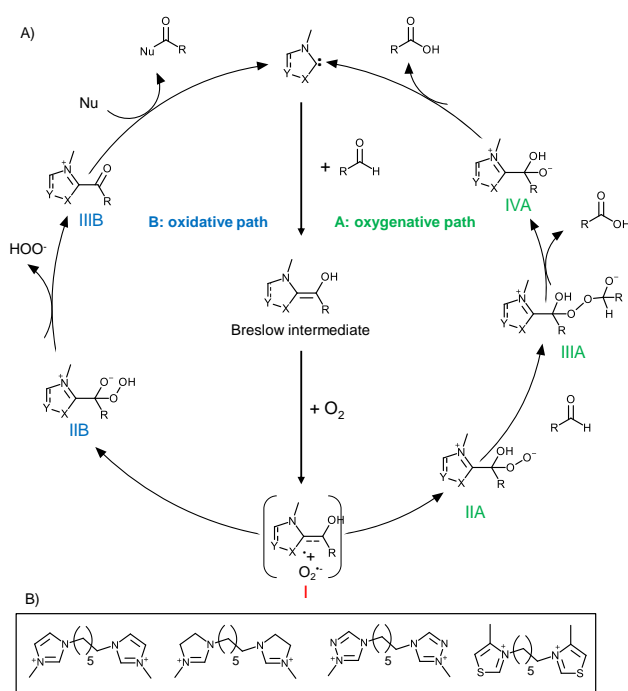
Scheme 11. A) Mechanisms of the oxygenative (**A**) and oxidative (**B**) paths proposed for the NHC-catalysed aerobic oxidation of aldehydes (Imidazole = Y: CH, X: N; Imidazoline = Y: CH₂, X: N; Triazole = Y: N; X: N; Thiazole = Y: CH; X: S); B) Structures of the *N*-methylated 1,1'-(hexane-1,6-dyl) azolium salts synthesized by Bortolini *et al.* as charge-tagged carbene precursors. Adapted from Ref. [75] with permission from the American Chemical Society.

analysed by ESI-MS to intercept and characterize the intermediates of the process. The acylazionium cation **IIIB,** representing the key intermediate of the oxidative path, is typically detected by using *p*-bromo-benzaldehyde, whereas the oxo-Breslow **IVA**, characteristic of oxygenative path, is predominantly intercepted by using *o*-bromo-benzaldehyde. The catalyst activity is in the order imidazole> triazole> thiazole> imidazoline derivatives. The imidazoline carbene does not positively affect the reaction outcome and its scarce catalytic action has made the isolation of the Breslow intermediate possible. This intermediate resulted barely reactive when the C4-C5 bond on the imidazolium scaffold is saturated.[20] In the CID spectrum of the ionic species attributed to the Breslow intermediate the main fragmentation path consists in the cleavage of the imidazolinium ring, hinting at a covalent bond between the catalyst and the aldehyde. Moreover, the back dissociation to carbene and *o*-bromo-benzaldehyde, typical of a loosely bonded adduct, is only a minor fragmentation channel. The fate of the Breslow intermediate was investigated by theoretical calculations, as shown in the energy profile reported in Figure 8A.[75]

The reaction between the catalyst and *ortho*-substituted benzaldehyde is favoured with imidazole and triazole derivatives (**Im** and **Th**), whereas a stable Breslow intermediate is formed by an exothermic process from the imidazoline one (**Imi**). **IIA** and **IIB** triplet and singlet states have been considered, since the symmetry of the ³O₂ can easily be broken, as a result of third body processes. When *p*-bromo-benzaldehyde (Figure 8B) was used, O₂ attacks on C1 atom, and the subsequent proton transfer from the OH group leads to an hydroperoxidic structure. Remarkably,
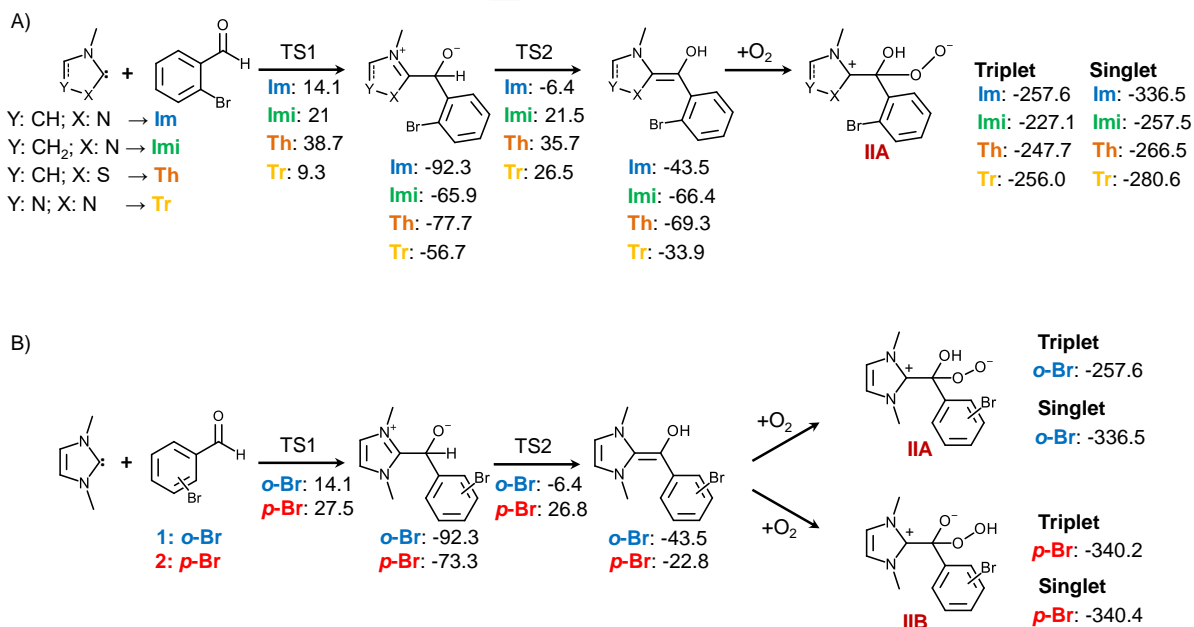
Figure 8. A) Energetics for the reactions of the imidazolium- (**Im**), imidazolinium- (**Imi**), thiazolium- (**Th**) and triazolium-derived (**Tr**) carbenes towards *o*-bromo benzaldehyde and B) for the reactions between the imidazolylidene and *ortho*- or *para*- substituted benzaldehyde. Chemical structures of the intermediates are reported, and the energies are expressed in kJ mol⁻¹. Adapted from Ref. [75] with permission from the American Chemical Society.

the position of the substituent on the aldehyde aromatic ring controls the chemical fate of the Breslow intermediate in the oxidation reaction.

7. Summary and Outlook

N-heterocyclic carbenes are extensively used in organic synthesis as efficient catalysts, however their neutral nature has long made them invisible to the mass spectrometry detection.

In the present review, we described the mass spectrometric studies aimed at the characterization of the NHCs, by using the charge-tagging strategy. Mass spectrometry is a widespread technique employed to elucidate reaction mechanisms and intrinsic properties of transient species.

NHCs derivatised with suitable positive and negative tags were intercepted by electrospray ionization mass spectrometry and isolated in the gas phase to probe their unimolecular and bimolecular reactivity, by CID experiments and ion-molecule reactions, respectively. In addition, chemical transformations in which NHCs play the role of catalysts were analysed by monitoring the time-progress of the reactions, to obtain a clear mechanistic picture of the processes under investigation.

These approaches have the merit to directly connect the gas-phase and solution chemistry, representing a bridge between these two only apparently incompatible environments. At the same time, the studies here reported lay the foundation for a deep investigation of the ion-molecule reactions between charge-tagged carbenic species and environmental contaminants, such as SO_2, COS and CS_2. The research in this field could actively contribute to design commercial devices for the storage of toxic gases, as in the case of PH_3 and BF_3, stocked into standard gas cylinders, through a chemical complexation process by suitable ILs.[76]

Recent advances also include the coupling of mass spectrometry with ion-mobility techniques and IR optical spectroscopy, allowing one to provide structural information unavailable from conventional tandem mass spectrometry methodologies[77]. Examples are the structural characterization of charge-tagged Breslow intermediates and their keto tautomers[41] and the disclosure of hydrogen tunnelling rearrangement at noncryogenic temperatures, responsible for the isomerization of hydroxycarbenes to their respective aldehydes through a 1,2-hydrogen shift reaction.[78]

Although these technical implementations could promote, inter alia, the unambiguous discrimination between very similar ionic structures, the present review aimed at demonstrating how a gas-phase approach by using mass spectrometry contributes to solve common issues of the catalysis and solution chemistry.

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Charge-tagging strategy has been successfully applied to investigate the chemistry of *N*-heterocyclic carbenes (NHCs) in the gas phase. These neutral species, intrinsically invisible to mass spectrometry, become detectable by the insertion of a positive- or negative-charged group into the molecular scaffold, allowing their isolation from the reaction mixture and mechanistic elucidation of archetypal NHC-catalysed processes.