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PAPER

Charge-tagged *N*-heterocyclic carbenes†‡

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The interception, formation and characterization of the first stable, long lived charge-tagged *N*-heterocyclic carbenes of the general type 4^{x+} (x = 1–3) and analogues is reported. *Via* ESI(+)-MS of solutions of bromine salts of doubly, triply and quadruply charged imidazolium ion IL ($3 \cdot Br_n$, n = 2–4), the isolated 4^{x+} as well as charged aggregates $[3 \cdot Br_{(n-x)}]^{x+}$ likely to be participating in the $[3 \cdot Br_{(n-x)}]^{x+} \rightleftharpoons 4^{x+} + HBr$ solution equilibrium could be transferred and characterized in the gas phase. Mimicking the solution equilibrium, the gaseous $[3 \cdot Br_{(n-x)}]^{x+}$ were found to dissociate nearly exclusively *via* HBr loss during thermal activation *via* collisions to form gaseous 4^{x+}, which were found to add to acrolein and acetone.

Introduction

Carbenes,[1] due to their high reactivity, hypo-valent carbon and exotic electronic structures with low-lying singlet and triplet states, have long fascinated theoretical and experimental chemists. These highly reactive and transient species add to alkenes, insert to C–H bonds, and react with heteroatoms to yield ylides, and many reactions have also been found or designed to involve carbenes as intermediates. But due to their elusive nature, carbenes were for a long time inaccessible to experimental observation. Fortunately, however, owing to crossed resonance with the two vicinal ring nitrogens, long-lived *N*-heterocyclic carbenes such as those of the imidazolidene type **1** (Scheme 1) were discovered and isolated as the first stable carbenes.[2] *N*-heterocyclic carbenes have then been used as efficient catalysts,[3] as ligands for transition metals,[4] to stabilize highly reactive species,[5] to activate small molecules,[6] and as key reactants for catalytic organometallic transformations[7] and many key organic reactions.[8]

Mass spectrometry is inherently blind to neutrals[9] hence simple carbenes have been investigated *via* gas phase MS experiments mainly in ionized forms[10] such as $Cl_2C^{+\cdot}$ or $ClHC^{-\cdot}$ or indirectly *via* neutralization-reionization MS (NRMS) experiments.[11] To cure this blindness, an elegant MS strategy has been elaborated using charge tags and applied to handle gaseous radicals with distant charge sites.[12] With the arrival of electrospray ionization (ESI),[13] charge tags have also been used in solution to allow the favourable "fishing"[14] of charge-tagged molecules directly from solution into the isolated gas phase environment for MS measurements and intrinsic reactivity investigations.[15]

Composed of organic cations and inorganic complex anions, room temperature ionic liquids (ILs) have attracted great attention in many fields such as synthesis, catalysis, electro-chemistry, nanomaterials, processes of extraction and separation, and as a new class of materials and solvents for green chemistry.[16] ILs based on singly charged 1,3-dialkylimidazolium ions 2^+ (Scheme 1) have been one of the most thoroughly studied classes of such salts. Recently, multiply charged imidazolium ions of the general formula 3^{n+} (Scheme 1, Table 1) have also been prepared.[17] We have then applied ESI(+)-MS to transfer from solution directly to the gas phase such multiply charged cations so as to use them as precursors of gaseous charge-tagged (di)-radicals.[18]

In imidazolium ions, the ring hydrogens are acidic, mostly particular the C2–H with relatively high pK_a values (21–23) roughly intermediate between the acidities of acetone (pK_a = 19.3) and ethyl acetate (pK_a = 25.6).[19] Depending on the nature of the anion, the C2–H easily exchanges with deuterium from D_2O.[20] This H/D exchange is believed to be promoted by the basic anion/solvent and to occur *via* *N*-heterocyclic carbenes, but
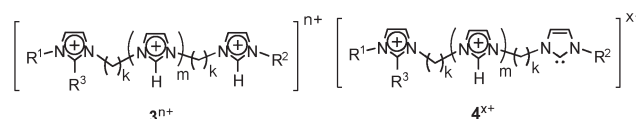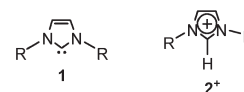
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† Dedicated to Dr Hilkka I. Kenttämaa for her pioneering work on gas phase charge-tagged radicals.
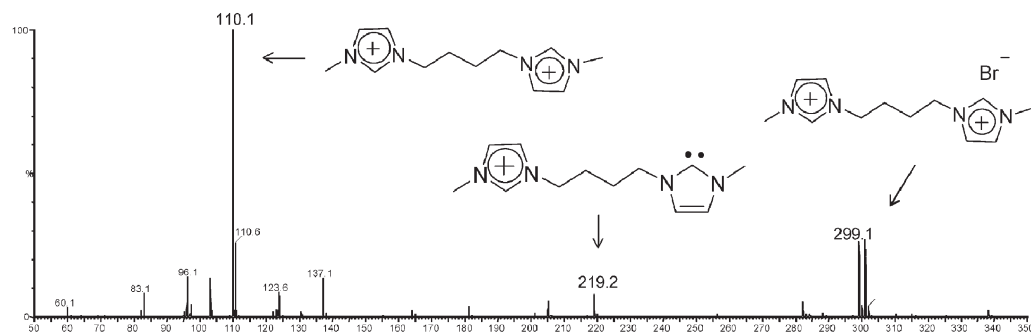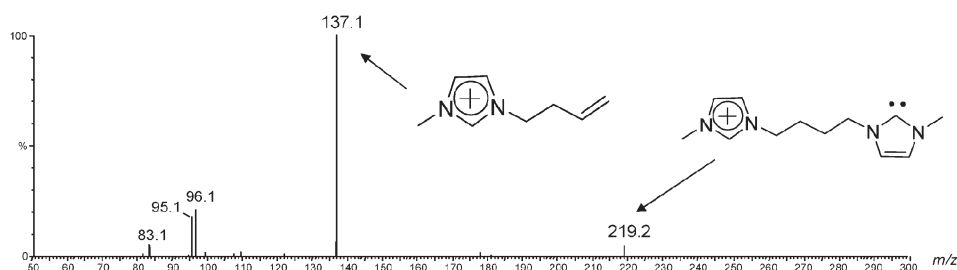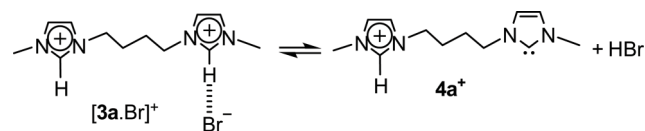‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ra00024a

Scheme 1

Table 1 Structural details of the multiply charged imidazolim ions 3^{n+} and m/z of their charged aggregates

3	R^1	R^2	R^3	m	k	n	$[3a.Br_{(n-x)}]^{x+}$	m/z
3a	Me	Me	H	0	4	2	$[3a.Br]^+$	299
3b	Me	Me	H	0	3	2	$[3b.Br]^+$	285
3c	Me	Me	H	0	2	2	$[3c.Br]^+$	271
3d	Me	Me	Me	0	2	2	$[3d.Br]^+$	285
3e	Me	Bu^n	H	0	2	2	$[3e.Br]^+$	313
3f	Me	$(CH_2)_2OMe$	H	0	3	2	$[3f.Br]^+$	315
3g	Me	Me	H	1	2	3	$[3g.Br]^{2+}$	183
3h	Me	Me	H	1	2	3	$[3h.Br_2]^+$	445
3i[a]	Me	Me	H	2	2	4	$[3i.Br_2]^{2+}$	284
3j[a]	Me	Me	H	2	2	4	$[3j.Br]^{3+}$	163

[a] For 3i and 3j, a -$(CH_2)_4$- bridge connects the two central imidazolium rings. For $m = 0$ there is only one -$(CH_2)_k$- bridge connecting the imidazolium rings.

such transient intermediates have never been directly observed.[21] N-heterocyclic carbenes are also invoked to stabilize metal complexes of ILs and metal nanoparticle based catalysts.[22]

This work reports on the interception, formation and characterization of the first stable, long lived charge-tagged N-heterocyclic carbenes of the general type 4^{x+} (Scheme 1) and analogues *via* ESI(+)-MS of solutions of $3.Br_n$ (Table 1). In solution, imidazolium ions are stabilized by intermolecular interactions with solvents and counter ions forming a large supramolecular network, which is preserved to some extent during ESI transfer to the gas phase and MS analysis.[23] When methanolic solutions of IL salts $3a–j.Br_n$ were subjected to ESI(+), as Fig. 1 exemplifies for $3a.Br_2$ (and Fig. S1‡ for $3f.Br_2$), we found that this gentle ionization technique was able to transfer to the gas phase, together with the free doubly charged imidazolium ion $3a^{2+}$ of m/z 110, the unique singly charged supramolecular species $[3a.Br]^+$ detected mainly as its pair of ^{79}Br and ^{81}Br isotopologue ions of m/z 299 and 301.
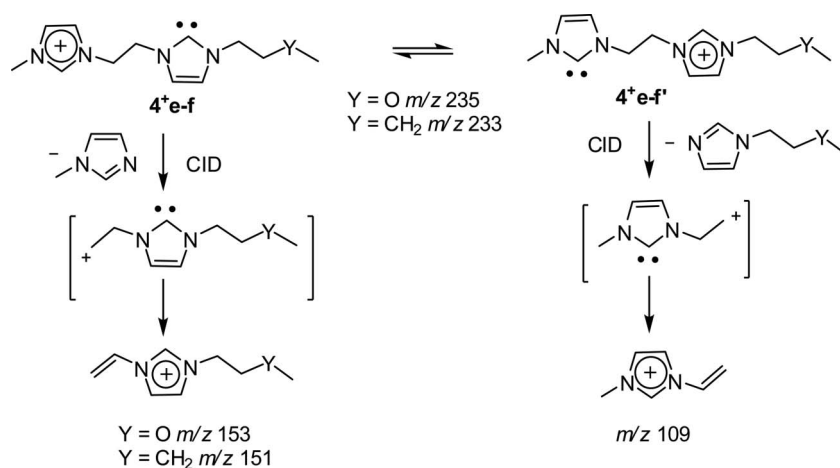
Scheme 2

Yet more interestingly, another unique ion of m/z 219 was observed in Fig. 1, most likely the gaseous charge-tagged carbene $4a^+$ (Scheme 2). Therefore, it is likely that both $[3a.Br]^+$ and $4a^+$ were "fished" by ESI(+) from the $[3a.Br]^+ \rightleftharpoons 4a^+ + HBr$ solution equilibrium in which Br^- abstracts the most acidic C2–H hydrogen. Such abstraction was also used in solution by Arduengo[2] to form the first neutral N-heterocyclic carbene.

To confirm the charge-tagged carbene structures of these new species, ESI(+)-MS/MS experiments were performed, in which 4^{x+} as well as their counterparts $[3.Br_{(n-x)}]^{x+}$ were isolated and subjected to CID. Fig. 2 illustrates such spectra for $4a^+$, Fig. S2 for $[3a.Br]^+$ whereas Fig. S3 compares those for $4a^+$, $4b^+$ and $4c^+$.‡
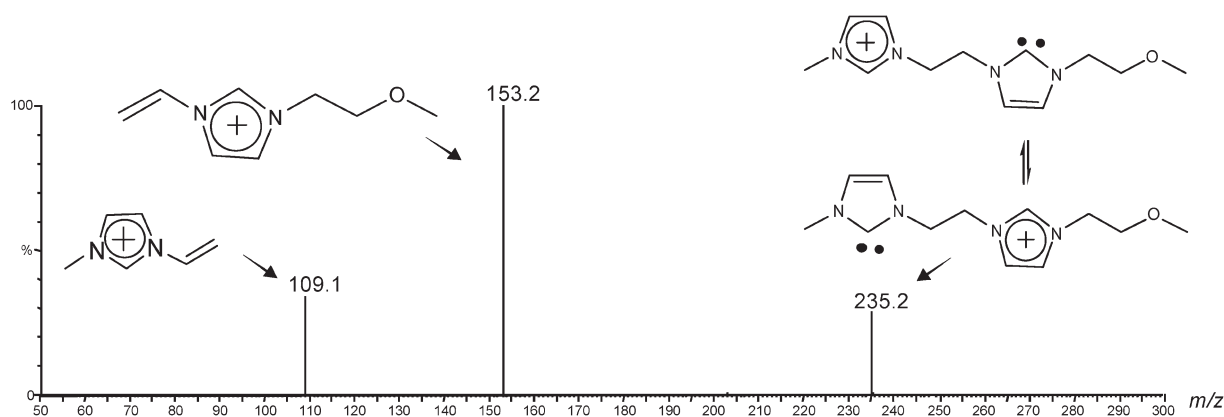
The dissociation chemistry observed for 4^+ corroborates the charge-tagged carbene structures while revealing interesting intramolecular proton transfer equilibrium. The major dissociation channel of 4^+ involves the loss of the neutral 1-methyl-imidazol of 82 Da *via* straightforward charge-induced dissociation that forms, after fast proton shift, the vinyl methyl imidazolium ion of m/z 109 (Scheme 3).

The operation of such characteristic, structurally diagnostic dissociation (Scheme 3) was corroborated when dissociating the asymmetrically substituted charge-tagged carbenes $4e^+$ (Fig. S4‡) and $4f^+$ (Fig. 3).

Dissociation of $4d^+$ (Fig. S5‡) was also revealing, as for the intrinsic acidity of imidazolium ions, since two dissociation routes were also observed (Scheme 4). These independent dissociations indicate fast intramolecular proton exchange likely

Fig. 1 ESI(+)-MS of a methanolic solution of $3a.Br_2$.

Fig. 2 ESI(+)-MS/MS of the charge-tagged carbene $4a^+$ of m/z 219.

Scheme 3

Fig. 3 ESI(+)-MS/MS of the asymmetrically substituted charge-tagged carbene **4f⁺** of m/z 235.

involving the C2–H and C2–Me hydrogens. This intrinsic equilibrium, observed in the gas phase but also likely to occur in solution, further confirms that C2–H by C2-R replacement does not limit the acidity of imidazolium ions.[24] Theoretical calculations at the Beck3LYP/6-31G+(d,p) level for the optimized gaseous structures of these new charge-tagged carbenes 4^{x+} reveal a stable and interesting gaseous structure in which the C2–H is involved in intramolecular H-bonding with the heterocyclic carbene center (Fig. 4).

Calculations also indicate very small differences in intrinsic acidity (for instance 0.2–1.0 kcal mol⁻¹ for **4f⁺**, Fig. S6‡) for the two possible C2–H in the asymmetrically substituted charge-tagged

carbenes. Interestingly, despite considerable intramolecular charge repulsion expected for such small species, ESI(+) was also able to transfer to the gas phase intact doubly and triply charged supramolecular aggregates such as $[\mathbf{3g,i}.Br_2]^{2+}$ and $[\mathbf{3j}.Br]^{3+}$ (Table 1). Dissociation by HBr loss (Fig. 5) of these unique species seems to provide prompt access to several new multiply charged mono- and di-carbenes. The di-carbenes could undergo fast intramolecular coupling and this possibility is still to be fully scrutinized but their similar dissociation chemistry (Fig. S7‡) to that observed for the charge-tagged mono-carbenes seems to indicate that the N-heterocyclic carbene centers are preserved.
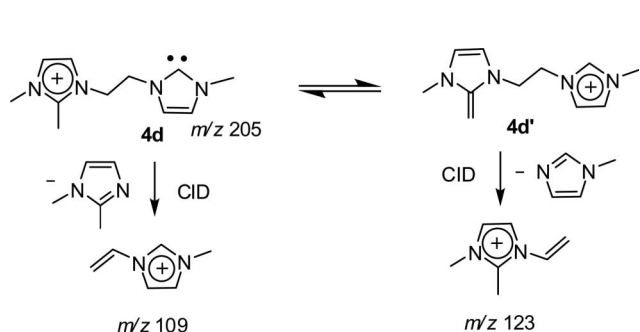
Scheme 4
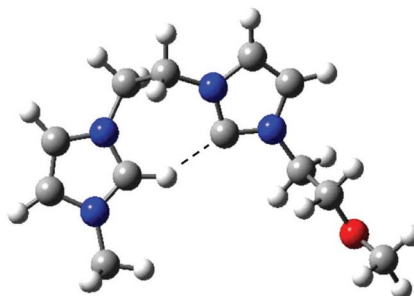
Fig. 4 Beck3LYP/6-31G+(d,p) optimized structure of the charge-tagged carbene **4f⁺**.
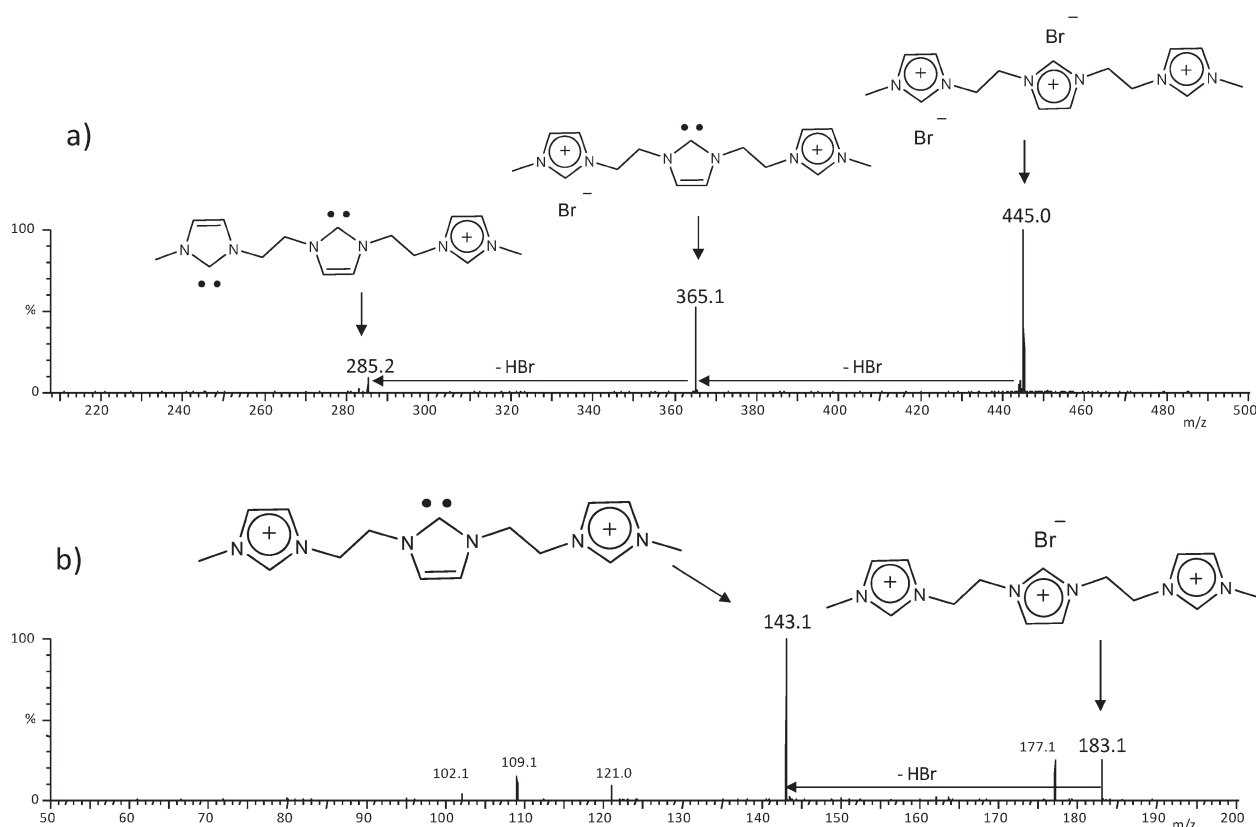
Fig. 5 ESI(+)-MS/MS of a) [3h.Br$_2$]$^+$ of m/z 445 which forms by HBr loss the charge-tagged N-heterocyclic dicarbene **4h**$^+$ of m/z 285 and b) [3g.Br]$^{2+}$ of m/z 183 which forms the doubly charged N-heterocyclic monocarbene **4g**$^{2+}$ of m/z 143. Note that the structures shown are likely to be in equilibrium with isomers via intramolecular Br$^-$ or C2–H exchanges.

Fig. S7 shows the ESI(+)-MS/MS for the dissociation of the doubly charged dicarbene **4h**$^+$ and the triply charged monocarbene **4j**$^{3+}$, which again corroborate their proposed and unprecedented structures.‡

The same major dissociation routes observed for the singly charged carbenes **4**$^+$ was also observed for the doubly (**4**$^{2+}$) and triply charged carbenes (**4**$^{3+}$) as Fig. 6 exemplifies for **4g**$^{2+}$. C-N cleavage of **4g**$^{2+}$ forms a singly charged imidazolium ion of m/z 109 but the counterpart neutral imidazole remains charge-tagged

and is consequently detected by MS as the fragment ion of m/z 177 (Scheme S1‡).

Carbenes, in the singlet state, can react either as electrophiles or as nucleophiles depending on the nature of the counter reactant.[25] With carbonyl compounds, carbenes readily acts as nucleophiles adding to the carbonyl carbon.[25a] To test the usefulness of such unique long lived, gaseous charge-tagged **4**$^{x+}$ species in assessing the intrinsic gas phase reactivity of N-heterocyclic carbenes, **4g**$^{2+}$ of m/z 143 was reacted with
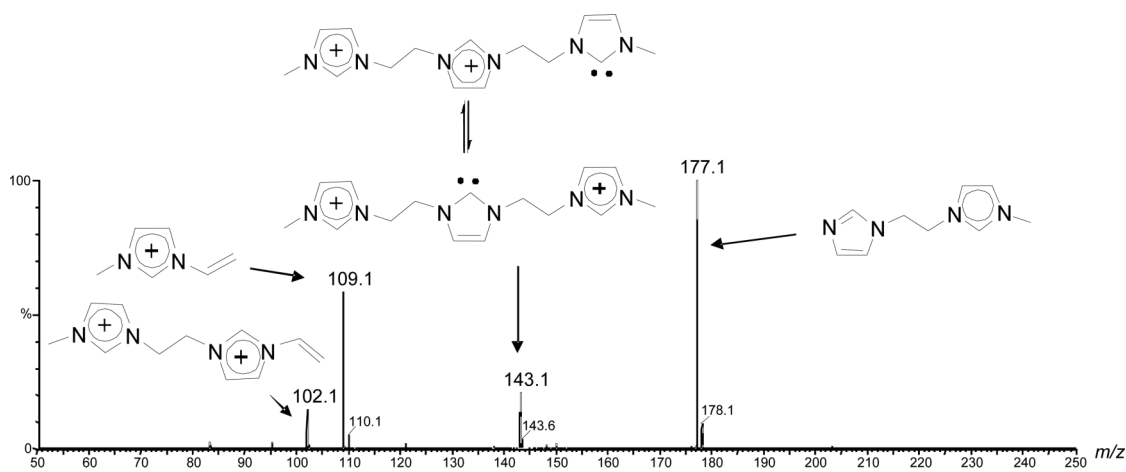
Fig. 6 ESI(+)-MS/MS of the charge-tagged N-heterocyclic carbene **4g**$^{2+}$ of m/z 143.
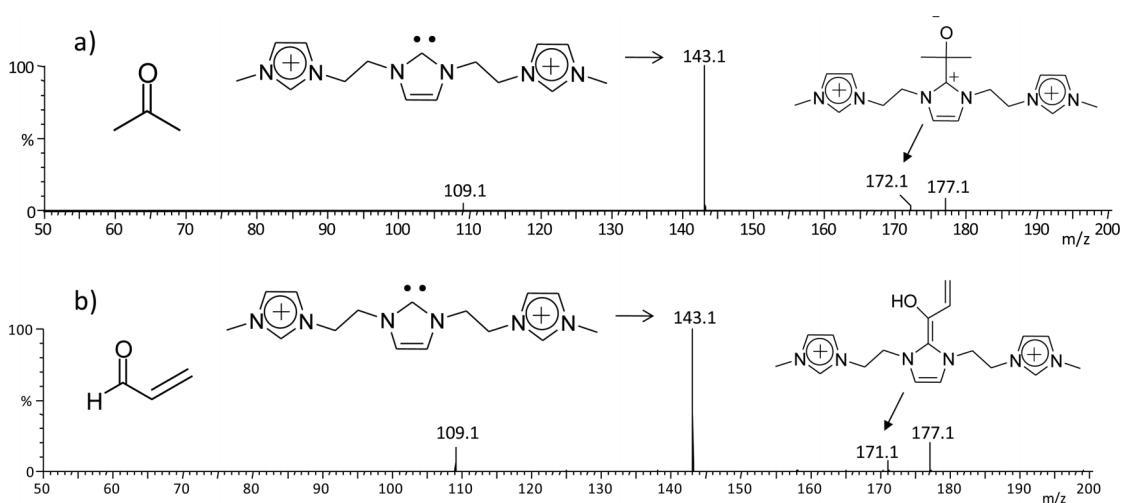
Fig. 7 ESI(+)-MS/MS for ion/molecule reactions of the charge tagged *N*-heterocyclic carbene $4g^{2+}$ of *m/z* 143 with a) acetone and b) acrolein.

acrolein and acetone (Fig. 7). Although the cell conditions in the mass spectrometer used are not optimized for ion/molecule reactions, addition products with acrolein (*m/z* 172) and acetone (*m/z* 171) were indeed detected together with CID fragments of $4g^{2+}$ (Fig. 6).

Conclusions

The first stable charge tagged *N*-heterocyclic carbenes 4^{x+} (*x* = 1–3) as well as $[3.Br_{(n-x)}]^{x+}$ aggregates have been "fished", likely from the $[3.Br_{(n-x)}]^{x+} \rightleftharpoons 4^{x+}$ + HBr solution equilibrium, and fully characterized in the gas phase. Analogous neutral carbenes for singly charged ILs have long been hypothesized to form from imidazolium ions in solution *via* C2–H abstraction by counter anions or bases, and the present finding supports this hypothesis. The dissociation of the $[3.Br_{(n-x)}]^{x+}$ aggregates (in which Br^- works as the base) *via* thermal activation during collisions has also been found to mimic the solution equilibrium and to form gaseous 4^{x+} by HBr loss. The fishing directly from solution to the gas phase, isolation, and investigation of gas phase chemistry of long-lived charge-tagged *N*-heterocyclic carbenes is likely to provide insight into the intrinsic (solvent and counter ion free) reactivity of these key but elusive intermediates and their roles in IL solution chemistry, catalysis and metal coordination. The interception of 4^{x+} and the dominance of HBr loss (C2–H abstraction by Br^-) for gaseous $[3.Br_{(n-x)}]^{x+}$ also indicates that, when imidazolium based ionic liquids are employed in solutions, even under relatively "neutral" conditions, the relatively stable *N*-heterocyclic carbenes are most likely to be formed with either detrimental or beneficial results. The presence of *N*-heterocyclic carbenes in imidazolium IL solutions is therefore most probably inevitable; hence, their participation should always be considered in processes performed in imidazolium IL or using ILs as reactants or catalysts.

Experimental section

The imidazolium salts were prepared according to the procedures described in the literature.[17–18] ESI mass and tandem mass spectra in the positive ion mode were acquired using a Waters Micromass (Manchester, UK) QTOF instrument with ESI-QTOF configuration having 5000 mass resolution and less than 50 ppm mass accuracy in the TOF mass analyzer. The following typical operating conditions were used: 3 kV capillary voltage, 40 V cone voltage, and desolvation gas temperature of 100 °C. ESI-MS/MS analyses were performed using 15–30 eV collision-induced dissociation (CID) of mass-selected ions with argon. Selection was generally performed by Q1 using a unitary *m/z* window, and collisions were performed in the rf-only hexapole collision cell, followed by mass analysis of product ions by the high resolution orthogonal-reflectron TOF analyzer. Reactions were performed by mass selection of the ion of interest and through low-energy (about 3 eV) collisions in the rf-only hexapole collision cell.

Note added after first publication

This article replaces the version published on 18th July 2011, which contained errors in Schemes 2–4 and Fig. 6 and 7.

References

1 (*a*) W. Kirmse, *Carbene Chemistry*, Academic Press, New York, 1971; (*b*) R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719; (*c*) H. W. Wanzlick, *Angew. Chem.*, 1962, **74**, 129.
2 A. J. Arduengo, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361.
3 N. Marion, S. Diez-Gonzalez and I. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988.
4 (*a*) W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1291; (*b*) O. Navarro, R. A. Kelly and S. P. Nolan, *J. Am. Chem. Soc.*, 2003, **125**, 16194.
5 (*a*) O. Back, M. A. Celik, G. Frenking, M. Melaimi, B. Donnadieu and G. Bertrand, *J. Am. Chem. Soc.*, 2010, **132**, 10262; (*b*) O. Back, B. Donnadieu, P. Parameswaran, G. Frenking and G. Bertrand, *Nat. Chem.*, 2010, **2**, 369.
6 O. Back, G. Kuchenbeiser, B. Donnadieu and G. Bertrand, *Angew. Chem., Int. Ed.*, 2009, **48**, 5530.

7 V. Lavallo, A. El-Batta, G. Bertrand and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2011, **50**, 268.
8 (*a*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534; (*b*) R. Singh, R. M. Kissling, M. A. Letellier and S. P. Nolan, *J. Org. Chem.*, 2004, **69**, 209; (*c*) D. Enders and U. Kallfass, *Angew. Chem., Int. Ed.*, 2002, **41**, 1743; (*d*) M. S. Kerr, J. R. de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298; (*e*) V. Nair, V. Sreekumar, S. Bindu and E. Suresh, *Org. Lett.*, 2005, **7**, 2297; (*f*) H. Rigby and Z. Q. Wang, *Org. Lett.*, 2002, **4**, 4289.
9 F. Coelho and M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2011, **50**, 5261.
10 (*a*) R. R. Julian, J. A. May, B. M. Stoltz and J. L. Beauchamp, *Int. J. Mass Spectrom.*, 2003, **228**, 851; (*b*) S. M. Villano, N. Eyet, W. C. Lineberger and V. M. Bierbaum, *J. Am. Chem. Soc.*, 2008, **130**, 7214.
11 (*a*) F. A. Wiedmann, J. N. Cai and C. Wesdemiotis, *Rapid Commun. Mass Spectrom.*, 1994, **8**, 804; (*b*) F. Turecek in Transient intermediates of chemical reactions by neutralization-reionization mass spectrometry, *Topics in Current Chemistry*, 2003, vol. **225**, p. 77, Springer-Verlab, Berlin.; (*c*) D. J. Lavorato, T. K. Dargel, W. Koch, G. A. McGibbon, H. Schwarz and J. K. Terlouw, *Int. J. Mass Spectrom.*, 2001, **210–211**, 43.
12 K. G. Stirk and H. I. Kenttamaa, *J. Am. Chem. Soc.*, 1991, **113**, 5880.
13 J. B. Fenn, M. Mann, C. K. Meng, S. F. Wong and C. M. Whitehouse, *Science*, 1989, **246**, 64.
14 (*a*) C. Hinderling, C. Adlhart and P. Chen, *Angew. Chem., Int. Ed.*, 1998, **37**, 2685; (*b*) C. Adlhart and P. Chen, *Helv. Chim. Acta*, 2000, **83**, 2192; (*c*) L. S. Santos, C. H. Pavam, W. P. Almeida, F. Coelho and M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2004, **43**, 4330; (*d*) A. Sabino, A. Machado, C. Correia and M. Eberlin, *Angew. Chem., Int. Ed.*, 2004, **43**, 2514.
15 (*a*) M. A. Schade, J. E. Feckenstem, P. Knochel and K. Koszinowski, *J. Org. Chem.*, 2010, **75**, 6848; (*b*) P. Chen, *Angew. Chem., Int. Ed.*, 2003, **42**, 2832.
16 (*a*) J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667; (*b*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773.
17 (*a*) J. L. Anderson, R. F. Ding, A. Ellern and D. W. Armstrong, *J. Am. Chem. Soc.*, 2005, **127**, 593; (*b*) G. N. Sheldrake and D. Schleck, *Green Chem.*, 2007, **9**, 1044; (*c*) X. Han and D. W. Armstrong, *Org. Lett.*, 2005, **7**, 4205.
18 F. M. Nachtigall, Y. E. Corilo, C. C. Cassol, G. Ebeling, N. H. Morgon, J. Dupont and M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2008, **47**, 151.
19 T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas and K. Toth, *J. Am. Chem. Soc.*, 2004, **126**, 4366.
20 (*a*) R. Giernoth and D. Bankmann, *Eur. J. Org. Chem.*, 2008, 2881; (*b*) J. D. Scholten and J. Dupont, *Organometallics*, 2008, **27**, 4439.
21 J. Dupont and J. Spencer, *Angew. Chem., Int. Ed.*, 2004, **43**, 5296.
22 (*a*) L. S. Ott, M. L. Cline, M. Deetlefs, K. R. Seddon and R. G. Finke, *J. Am. Chem. Soc.*, 2005, **127**, 5758; (*b*) J. Dupont and J. D. Scholten, *Chem. Soc. Rev.*, 2010, **39**, 1780.
23 (*a*) F. C. Gozzo, L. S. Santos, R. Augusti, C. S. Consorti, J. Dupont and M. N. Eberlin, *Chem.–Eur. J.*, 2004, **10**, 6187; (*b*) B. A. D. Neto, L. S. Santos, F. M. Nachtigall, M. N. Eberlin and J. Dupont, *Angew. Chem., Int. Ed.*, 2006, **45**, 7251.
24 J. D. Scholten, G. Ebeling and J. Dupont, *Dalton Trans.*, 2007, 5554.
25 (*a*) O. Illa, H. Gornitzka, V. Branchadell, A. Baceiredo, G. Bertrand and R. M. Ortuno, *Eur. J. Org. Chem.*, 2003, 3147; (*b*) K. A. Williams and C. W. Bielawski, *Chem. Commun.*, 2010, **46**, 5166.