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Charge-tagged *N*-heterocyclic carbenes (NHC): Direct transfer from ionic liquid solutions and long-lived nature in the gas phase

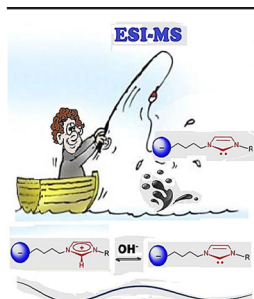
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Abstract. Negatively charge-tagged *N*-heterocyclic carbenes have been formed in solution via deprotonation of imidazolium ions bearing acid side groups and transferred to the gas phase via ESI(-)-MS. The structure of the putative and apparently stable gaseous carbenes formed in such conditions were then probed via reactions with carbon dioxide using a triple quadrupole mass spectrometer particularly optimized for ion/molecule reactions of ESI-generated ions. Complete conversion to imidazolium carboxylates was achieved, which seems to demonstrate the efficiency of the transfer, the gas-phase stability, and the long-lived nature of these unprecedented charge-tagged carbenes and their predominance in the ionic population. Comprehensive studies on the intrinsic reactivity of *N*-heterocyclic carbenes with

silent charge tags are therefore possible.

Keywords: *N*-heterocyclic carbenes, ionic liquids, ion/molecule reactions

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Introduction

Carbenes are key reaction intermediates and are involved in many pivotal reactions in chemistry [1–3]. Due to their elusive nature, however, such highly reactive hypovalent species were for a long time inaccessible to experimental observation. *N*-heterocyclic carbenes (NHC) such as **1** (Scheme 1), which are also stabilized by resonance with the adjacent *N*

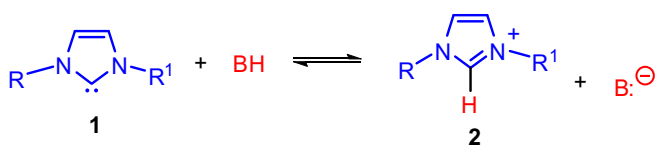
atoms, were the first stable “bottable” carbenes to be isolated and fully characterized [4], and soon after their availability, NHC became major players in several areas in chemistry such as in catalysis [5–7], and as ligands for organometallic complexes [8–10].

NHC also play a major role in chemistry in their protonated forms, that is, as imidazolium ions (**2**, Scheme 1). Such species are vastly used, for instance, as a major class of cations in ionic liquids (IL) [11]. NHC function, however, as strong bases; hence the acid-base equilibrium of Scheme 1 is strongly delocalized in favor of the imidazolium ions, and the relative low acidity of the C2-H hydrogens in **2** leads to pK_a in the range of 21–23 [12]. Free NHC, despite this disfavored equilibrium and controversy, are believed to influence the properties and reactivity of IL [13], in pure or protic solutions of imidazolium IL [14]. The presence of such species has been evidenced in reactions involving bases such as in Baylis-

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Scheme 1.

Hillman reactions [15, 16] or in the solubilization of CO₂ in 1,3-dialkylimidazolium acetate IL [17]. NHC have also been suggested as possible key species involved in IL distillation [18], and evidence has been presented for their role in stabilizing metal complex derivatives and metal nanoparticles or acting as catalysts for reactions performed in such “non-innocent” IL [19–21].

Mass spectrometry (MS) is inherently blind to neutrals [22] and therefore has had a limited role in studying the intrinsic chemistry of carbenes. Gas-phase MS experiments have therefore employed mainly ionized carbenes [23, 24] or performed indirectly via neutralization-reionization MS (NRMS) experiments [25, 26]. Using the elegant strategy of “silent” charge tags [27], which are properly placed in remote or as electronically possible isolated parts of the molecular backbone to eliminate or minimize influence in reactivity, and with the arrival of electrospray ionization (ESI) [28], charge-tagged NHC have, however, been formed in solution and “fished” out [29, 30] directly to the gas-phase environment for MS measurements and for intrinsic reactivity investigations [31].

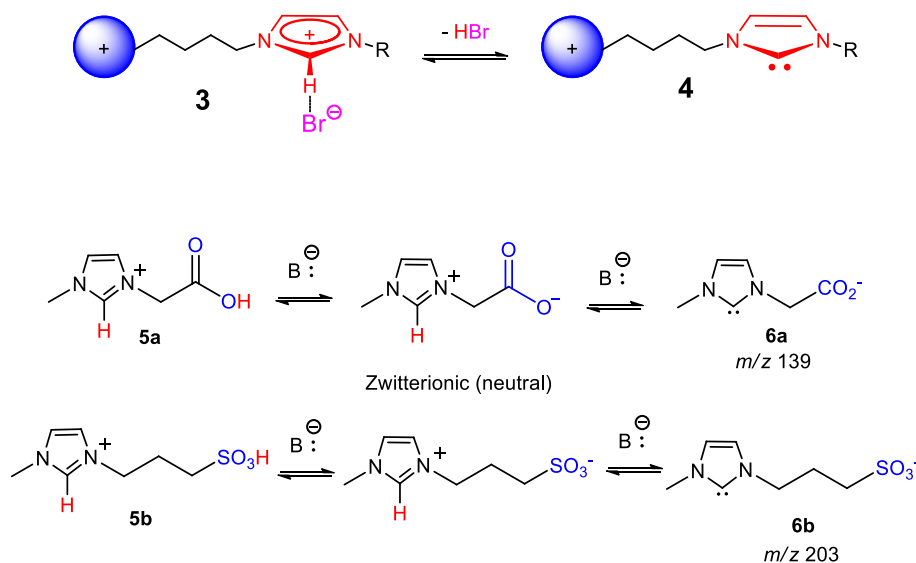
Recently, using the charge tag strategy, a series of stable, positively charge tagged NHC (**4**) involved in the **3** = **4** equilibrium (Scheme 2) has been apparently fished out via ESI(+)-MS from the solution to the gas phase [32]. More recently, we also reported on the extension of the family of charged carbenes via ESI(–)-MS fishing of negatively charge-tagged NHC **6a,b** (Scheme 3) formed in solution via

deprotonation of the imidazolium ions **5a,b** bearing acid side groups (Scheme 2) [33].

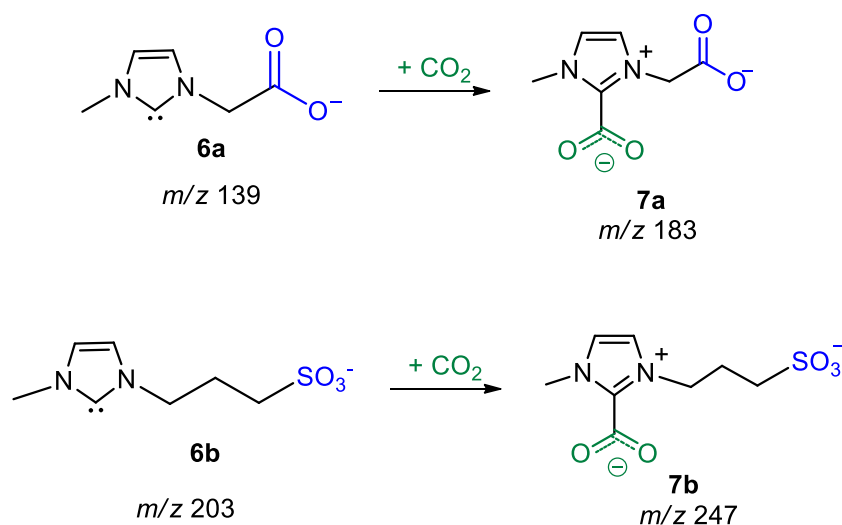
To probe the sampling of stable gas-phase species directly from IL solutions, the structures of these charge-tagged NHC were investigated via CID in ESI-MS/MS experiments. NHC in IL solutions are also known to add CO₂ to form imidazolium carboxylates [34]; hence, ion/molecule reactions of the gaseous **5a,b** with CO₂ were performed. In parallel with the solution chemistry [34], CO₂ addition was indeed observed forming the negatively charge-tagged imidazolium carboxylates **7a,b** (Scheme 3). Yields were, however, quite low; hence, their long-lived nature and the actual contribution of free carbenes in the total ion populations was questionable. In addition, due to MS/MS limitation of the QTOF instrumentation used, the structures of the charge-tagged imidazolium carboxylates **7a,b** could not be properly probed via further CID of the isolated products.

Therefore, to more accurately probe the actual ionic population and the sampling directly from IL solutions to the gas-phase environment of a mass spectrometer, of free and long-lived charge-tagged NHC that would allow studies of the intrinsic gas-phase reactivity of NHC, we have employed a modified triple-quadrupole mass spectrometer optimized for maximum yields of ion/molecule reactions of ESI-generated ions (Figure 1) [35, 36].

Herein, we report on an ion/molecule investigation of the ability of direct transfer from IL solutions to form the desirable charge-tagged carbenes, **6**, their actual proportion in the ionic population, as well as their stability in the gas phase. Due to the possibility of performing either ion/molecule reactions or CID in both the transfer hexapole (H0) and in the hexapole collision cell (H2), the triple quadrupole mass spectrometer used is also capable of pseudo-MS³ scans [37]; hence, the structure of the putative CO₂ addition products **7** were also investigated via CID.



Scheme 2.



Scheme 3.

Experimental

Sample solutions in methanol were introduced into the ESI source using an infusion pump (Cole Parmer, 74900 series) at a flow rate of $400\ \mu\text{L}\ \text{h}^{-1}$. Triple-quadrupole experiments were recorded using a homemade modified Quattro II mass spectrometer (Micromass, Manchester, UK) equipped with a Z-spray source. The ESI capillary voltage was maintained at 3.0 kV, and the cone voltage was varied from $-15\ \text{V}$ to $-25\ \text{V}$. Nitrogen was used as the desolvation and nebulization gas. The source and desolvation temperatures were kept at $100\ ^\circ\text{C}$. For ESI(-)MS/MS ion/molecule experiments, CO_2 was introduced into the H0 collision cell to a final pressure of 3×10^{-3} mbar. The MS/MS data were collected by selecting the desired precursor ion with Q1 and by scanning Q3. For the pseudo- MS_3 scans, CO_2 was added at H0 at a pressure of ca. 10^{-3} mbar and collision energy of ca. 3 eV, whereas Ar at a pressure of 3×10^{-3} mbar was added at H2 at collision energy of ca 10 eV.

Results and Discussion

The charge-tagged carbenes were formed, as already mentioned, by the double deprotonation of **5a,b**

(Scheme 2), but an additional precursor, a doubly charged di-imidazolium ion bearing two acid carbon chains (**5c**), was also used (Scheme 4) to test for the possible solution formation, transfer, and gas-phase stability of the charge-tagged dicarbene **6c2** via **6c1**. A base (KOtBu) was therefore added to $100\ \mu\text{M}$ methanolic solutions of the chloride salts of **5a-c**, and the ESI(-)MS (Figure 2) of such solutions indeed displayed predominant ions of $m/z\ 139$ (**6a**) and $m/z\ 203$ (**6b**) corresponding to the free negatively charge-tagged NHC.

Full deprotonation in solution and ESI(-) fishing of the doubly charged di-imidazolium ion with two acid sites **5c** generated, although to a quite minor extent, the expected singly charged monocarbene **6c1** of $m/z\ 305$ and the doubly charged dicarbene **6c2** of $m/z\ 152$ (Scheme 4, Figure 2c). Two other charge-tagged carbenes, **6c3** of $m/z\ 261$ and **6c4** of $m/z\ 152$, were also detected, probably from solution decomposition/protonation of **6c2**, which could explain the low abundance of **6c2**. ESI [38] is known to be an ionization technique that actually does not form ions, but transfers those already present in solution directly to the gas phase; hence, **5a-c** were most likely directly fished to the gas phase via electrostatic ion ejection [39, 40] from the IL solution.

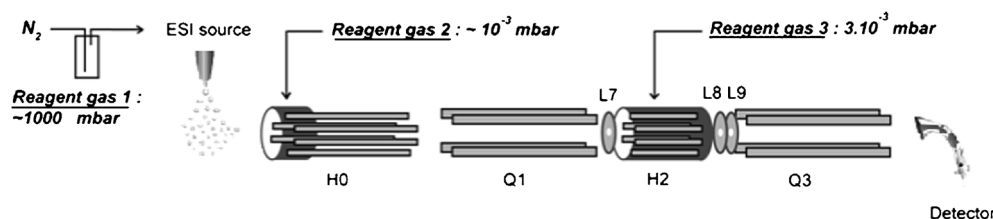
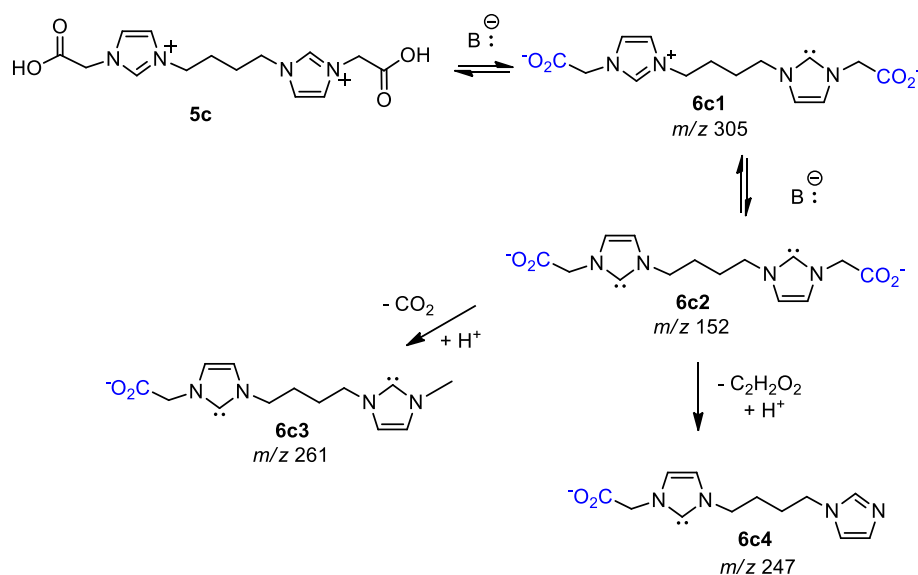


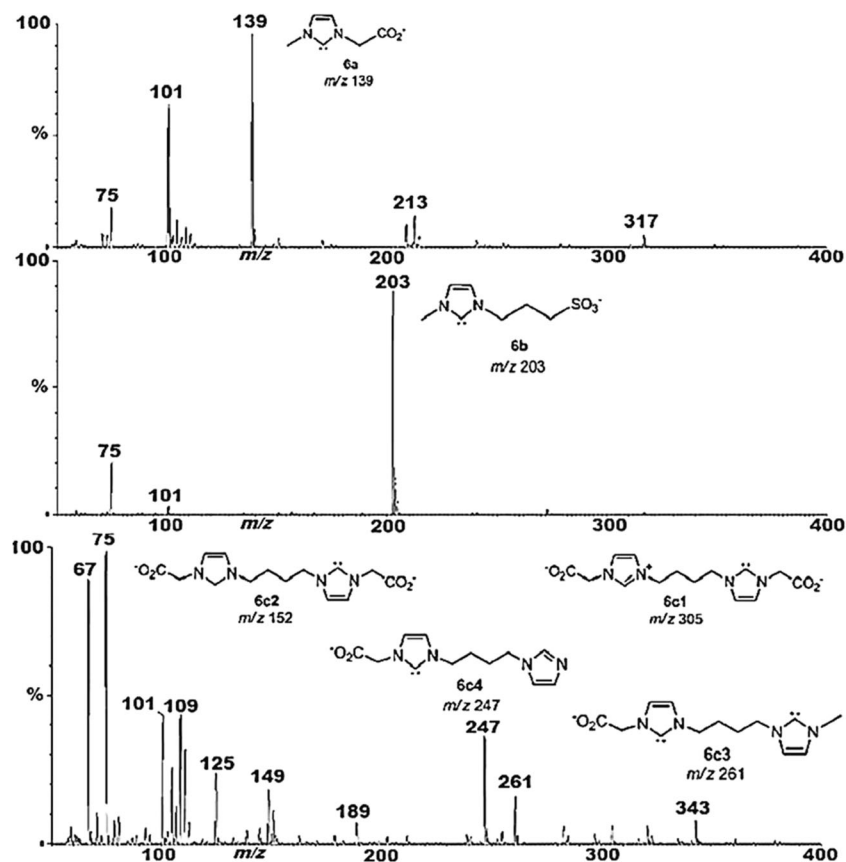
Figure 1. Schematic of the modified triple quadrupole mass spectrometer used to perform the ESI(-)MS/MS experiments in this work. Note that either ion/molecule reactions or CID can be efficiently performed in this instrument at H0 and H2 at pressures of about 10^{-3} mbar, or even at the ESI source, at variable collision energies. The transfer H0 was turned into a collision/reaction cell via encapsulation turning using a 5 cm long Teflon tubing; hence, the pressure could be increased to ca. 10^{-3} mbar



Scheme 4.

As mentioned, the “silent” charge should be placed in remote or as electronically possible isolated parts of the ion backbone to minimize influence in reactivity, but the charges of **6** are added via alkyl chains, which are not rigid, and therefore cannot be assumed to be in principle isolated, at least spatially, from the carbene site and could still affect reactivity. Calculations at the Beck3LYP-6-31G(d,p) level

have been carried out, therefore, to investigate for instance whether “intramolecular” interactions would be favored for **6a** and **6b** such as in **6a'** or if indeed the charge site would tend to stay far away from the carbene center, such as in **6a'**. Indeed, calculations for all ions employing an exhaustive conformational survey demonstrated that structures such as **6a''** may play a role particularly if five- or six-membered

Figure 2. ESI(-)MS of 100 μ M methanolic solutions of the chloride salts of **5a-c** after addition of KOtBu

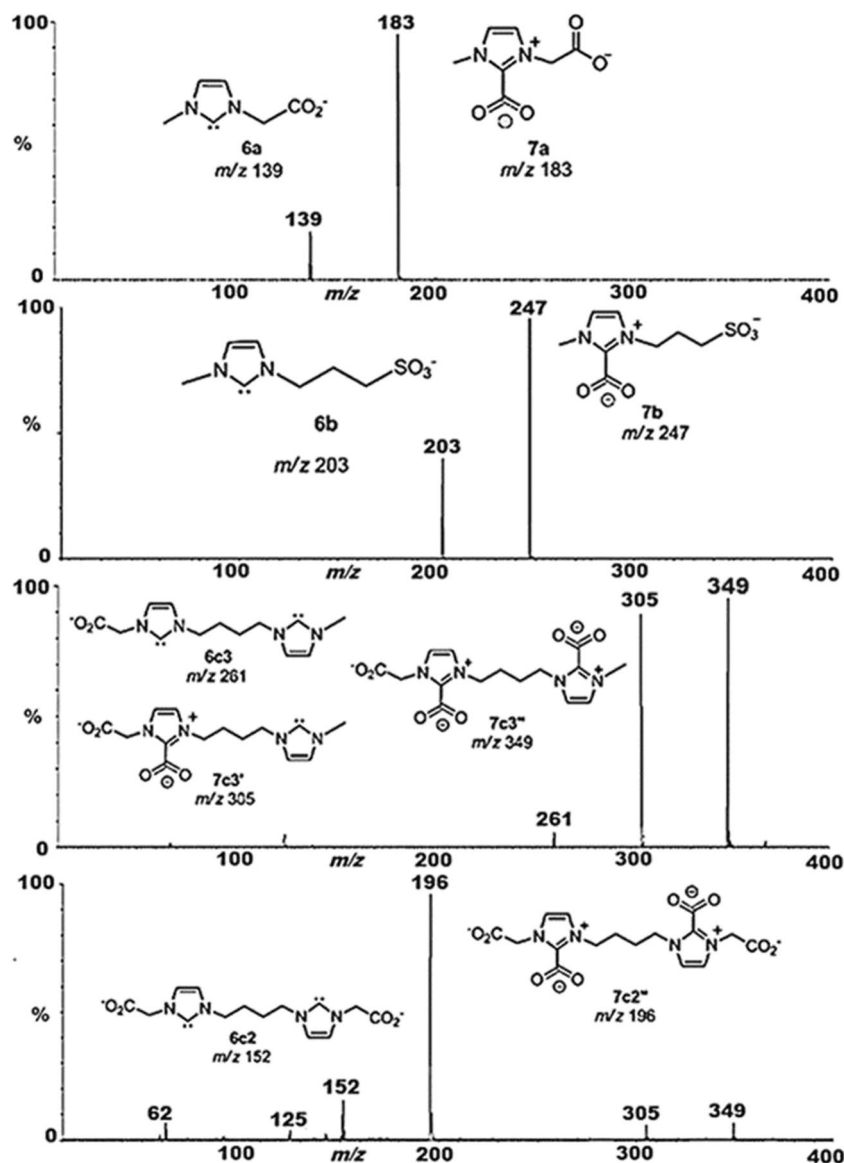
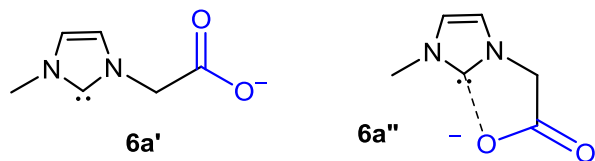


Figure 3. ESI(-)-MS/MS for ion/molecule reactions of the charge-tagged NHC **6a-c** with CO_2

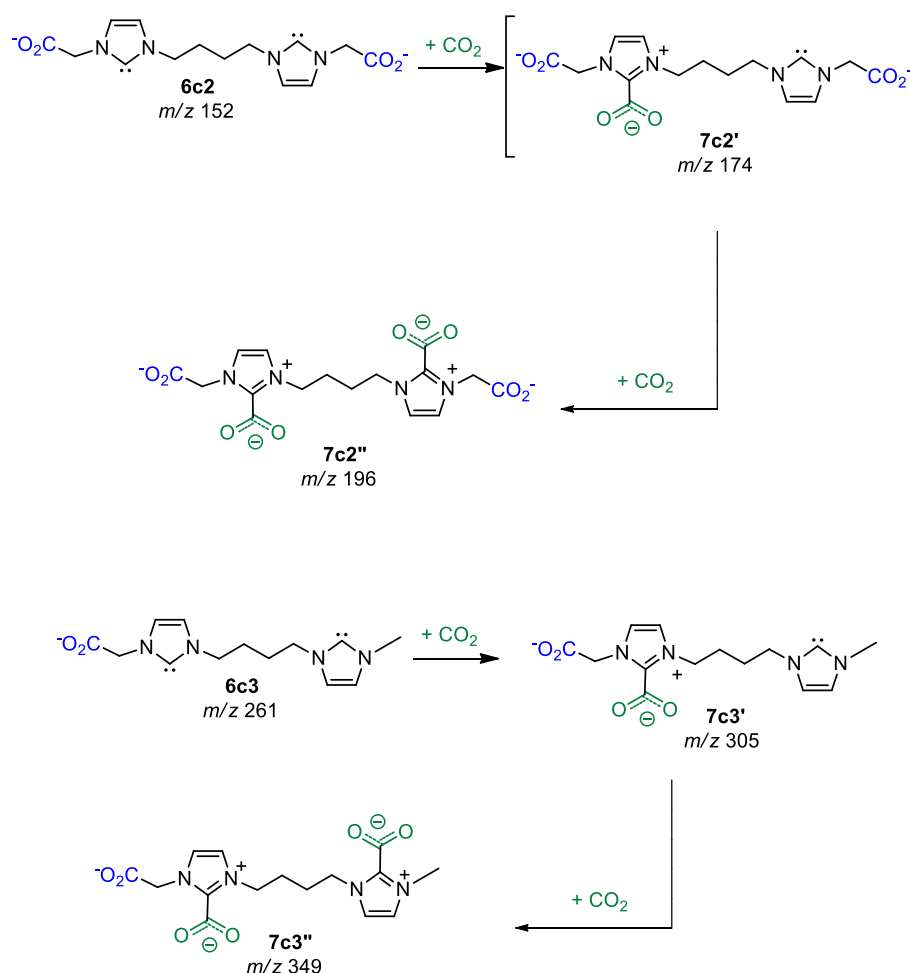
rings are formed, but such interactions were calculated to be very weak (ca. 5 kcal/mol or less) and, hence, to have no significant effect on the reactivity of the charge-tagged carbenes.



Next, each gaseous negatively charge-tagged mono-NHC **6a-b** and the double-NHC **6c2** and **6c3** were selected by Q1 and reacted with CO_2 in the H2 chamber at near zero energy collisions. Under optimized ion/molecule conditions, practically full conversion to imidazolium carboxylates products were attained (Figure 3). Note for the double-NHC **6c3** of m/z 261, the favorable tandem double addition of CO_2 forms the mono

and double imidazolium carboxylate derivatives of m/z 305 and 349 (Scheme 5), whereas the doubly charged di-NHC **6c2** was promptly reactive by double CO_2 addition (+22 m/z units per addition) and the double-imidazolium carboxylate ion **7c2''** of m/z 196 was always observed as the prominent product regardless of the CO_2 pressure. The mono-NHC ions **6c1** and **6c4** also displayed prompt reactivity towards CO_2 addition (spectra not shown).

Note that the spectra of Figure 3 show partial conversion to products but when increasing the CO_2 pressure, total conversion to the CO_2 addition products **7** was always attained. This full conversion demonstrates that indeed the great majority of the gaseous ionic population, if not the entire population, is indeed composed of the free, stable, and long-lived gaseous charge-tagged NHC **6** bearing negative charge tags.



Scheme 5.

The triple quadrupole instrument used herein (Figure 1) is also capable of pseudo MS^3 experiments in which ion/molecule reactions can be performed in H0 and CID with argon in H2. Since there is no selection prior to H0, the entire ion population generated by ESI was directed to H0 and subjected to reactions with CO_2 . Selection was possible, however, for each individual

product ion; hence, each of the charge-tagged imidazolium carboxylates **7a-c** was selected by Q1 and submitted to CID with argon in H2. The resulting pseudo- MS^3 spectra collected by Q2 showed, in all cases, major dissociation of **7a-c** by CO_2 loss, as exemplified for **7c2''** in Figure 4. However, as expected from the relative stability of the fragment ions, CO_2 is more likely

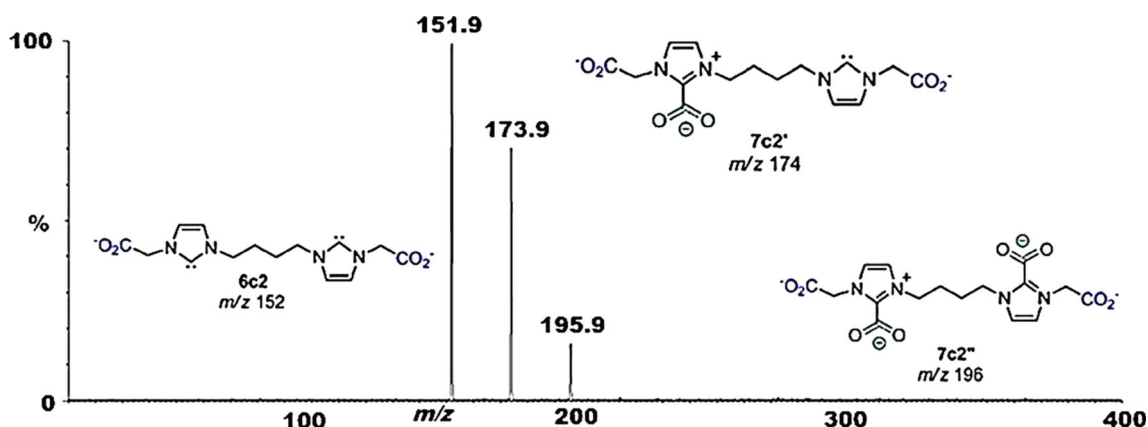


Figure 4. “Pseudo”- MS^3 for CIF of the product ion **7c2''** of m/z 196 formed by double addition of CO_2 to the doubly charged double-NHC **6c2**. Note the sequential loss of CO_2 , which corresponds to a doubly charged ion to the loss of 22 m/z units

lost from the imidazolium carboxylate ring (green CO₂) compared with the carboxylate charge sites (blue CO₂). The substantial resistance towards dissociation requiring moderate Ar pressures at 10 eV collision energy further points to the covalently bonded nature of **7a-c**.

Theoretical calculations were also performed to shed some light on the reactivity of such species. Gas-phase proton affinity (PA) and gas-phase basicity (GB) at 298 K, which are defined as the enthalpy change and free energy change, respectively, during the protonation processes in gas-phase are calculated as follows:

$$\text{PA} = H_{\text{gas}}^{\circ}(\text{A}^{-}) + H_{\text{gas}}^{\circ}(\text{H}^{+}) - H_{\text{gas}}^{\circ}(\text{AH}) \quad (1)$$

and

$$\text{GB} = G_{\text{gas}}^{\circ}(\text{A}^{-}) + G_{\text{gas}}^{\circ}(\text{H}^{+}) - G_{\text{gas}}^{\circ}(\text{AH}). \quad (2)$$

The standard gas-phase enthalpy (H_{gas}°) and free energy (G_{gas}°) of each species (HA and A⁻) were calculated with the highly accurate CBS-QB3 level of theory [41]. This state-of-the-art method is a multilevel model chemistry that combines the results of several electronic structure calculations and empirical terms to predict molecular energies to around 1 kcal/mol accuracy when compared against gas-phase deprotonation reactions in the National Institute of Technology (NIST) database [42, 43]. Under the standard state conditions, the values of the enthalpy and entropy of the gas-phase proton are $H_{\text{gas}}^{\circ}(\text{H}^{+}) = 1.48$ kcal/mol and $S_{\text{gas}}^{\circ}(\text{H}^{+}) = 26.02$ kcal/mol, respectively, and lead to a $G_{\text{gas}}^{\circ}(\text{H}^{+}) = H(\text{H}^{+}) - TS_{\text{gas}}^{\circ}(\text{H}^{+}) = -6.28$ kcal/mol according to Sackur-Tetrode equation.

In imidazolium ions, all ring-H as well as C α -H are considerably acidic. Based on Scheme 2, the values of PA and GB (Supplementary Material) could be obtained for **5a** and **5b**. The comparison of such PA and GB indeed demonstrate that the charged tagged carbenes **6** would be formed as the most likely double deprotonation products from **5** (Scheme 2). These calculated values also proven to be in accordance with those for non-functionalized imidazolium cations [44] using this state-of-the-art level of theory, which is indeed the most appropriate for the prediction of such thermodynamic parameters in both gas phase and solutions.

Also, to confirm CO₂ addition to C2, Fukui functions [45] were employed to determine the reactivity sites of **7** at the mp2/6-311+G(2d,2p) level. This function, denoted as $f(r)$, is defined as the derivative of the electron density, $\rho(r)$, with respect to the total number of electrons of the system, N , under a constant external potential, $v(r)$:

$$f(\vec{r}) = \left[\frac{\partial \rho(\vec{r})}{\partial N} \right]_{v(\vec{r})} \quad (3)$$

Due to the discontinuity of the first derivative in Equation (3) with respect to the number of electrons N , the following three functions can be defined in a finite difference approximation:

$$f^{+}(\vec{r}) = \rho(\vec{r})_{N+1} - \rho(\vec{r})_N \quad (4a)$$

$$f^{-}(\vec{r}) = \rho(\vec{r})_N - \rho(\vec{r})_{N-1} \quad (4b)$$

$$f^0(\vec{r}) = \frac{1}{2} \left[\rho(\vec{r})_{N+1} - \rho(\vec{r})_{N-1} \right] \quad (4c)$$

where $\rho(r)_{N+1}$, $\rho(r)_N$ and $\rho(r)_{N-1}$ are the electronic densities of the system with $N + 1$, N , and $N - 1$ electrons, respectively, all with the ground state geometry of the N electron system. Equations 3a-c are used to determine most likely sites for nucleophilic, electrophilic, and free radical attacks, respectively [46]. The finite difference formulation is frequently used in combination with the condensed Fukui function. The condensed Fukui functions can also be employed to determine the reactivity of each atom in the molecule. The corresponding condensed functions are given by

$$f_k^{+} = q_k(N) - q_k(N + 1) \quad (\text{for nucleophilic attack}) \quad (3a)$$

$$f_k^{-} = q_k(N - 1) - q_k(N) \quad (\text{for electrophilic attack}) \quad (3b)$$

$$f_k^0 = [q_k(N + 1) - q_k(N - 1)]/2 \quad (\text{for radical attack}) \quad (3c)$$

where $q_k(N + 1)$, $q_k(N)$ and $q_k(N - 1)$ are the partial charges at atom k on the anion, neutral, and cations species, respectively. We calculated partial charges of each atom using charges from electrostatic potentials using a grid (CHELPG)-based method [47]. The calculations were carried out using the Gaussian 09 program [48] as well as homemade codes to perform subsequent analysis.

For **6a** (Scheme 2 and also see in the Supporting Information), an f^+ value of 1.222 was calculated at C2, which was much higher than those for the oxygen atoms of the carboxylate (0.059 and 0.070), indicating that indeed C2 (Scheme 3) is the most likely site for CO₂ addition.

Conclusions

Free and long-lived charge-tagged NHC carbenes such as **6** can indeed be directly fished from IL solutions of IL **5** to the gas-phase environment of a mass spectrometer. The ion/molecule reactions and CID experiments performed in a modified triple-quadrupole mass spectrometer also allowed us to probe the structures of the charge-tagged imidazolium carboxylates **7a,b** formed in reactions with CO₂, and that ionic population of **6** could be quantitatively converted into the imidazolium carboxylates **7**. Therefore, **6** was efficiently transferred to the gas phase and the gaseous ions are long-lived and predominate in the ionic population. The calculations also corroborate the formation of **6** from **5** via double deprotonation as well as predominant CO₂ addition to the C2 site of **6**. An efficient methodology to form charge tagged carbenes is therefore available and should allow for comprehensive and unprecedented studies of the intrinsic gas-phase reactivity of these pivotal chemical species.

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