The Thiazole Ylide: A Frequently Invoked Intermediate Is a Stable Species in the Gas Phase

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Abstract: The 1,2-hydrogen shift isomers of neutral (singlet and triplet) thiazole (**1**) and its radical cation have been investigated by a combination of mass spectrometric experiments and hybrid density functional theory calculations. The latter were used to probe the structures and stabilities of selected C_3H_3NS and $C_3H_3NS^{\bullet+}$ isomers and transition state structures. Although 3*H*-thiazole-2-ylidene (**2**) is less stable than **1**, by 31.5 kcal mol^{-1}, it is expected to be capable of independent existence, since the 1,2-hydrogen shift from carbon to nitrogen involves a very large energy barrier of 72.4 kcal mol^{-1}. The other 1,2-hydrogen shift reaction from C(2) leads not to the expected cyclic 1*H*-thiazole-2-ylidene structure (**3**), which is apparently unstable, but rather to the ring-opened species HSCH=CHNC (**4**), which is 34.5 kcal mol^{-1} higher in energy than **1**. The barrier in this case is lower but still large (54.9 kcal mol^{-1}). The triplet ground states of **1**, **2** and **4** are considerably destabilised (69.5, 63.2 and 58.7 kcal mol^{-1}) relative to their singlet states. Interestingly, in addition to $\mathbf{2}^{\bullet+}$ and $\mathbf{4}^{\bullet+}$, the cyclic radical cation $\mathbf{3}^{\bullet+}$ is predicted to be stable although it is substantially higher in energy than ionised thiazole $\mathbf{1}^{\bullet+}$ (by 53.9 kcal mol^{-1}), whereas $\mathbf{2}^{\bullet+}$ and $\mathbf{4}^{\bullet+}$ are much closer in energy (only 10.2 and 27.0 kcal mol^{-1} higher, respectively). Dissuading $\mathbf{2}^{\bullet+}$ and $\mathbf{3}^{\bullet+}$ from isomerising to $\mathbf{1}^{\bullet+}$ are energy barriers of 52.6 and 15.3 kcal mol^{-1}, respectively. Experimentally, dissociative ionisation of 2-acetylthiazole enabled the generation of $\mathbf{2}^{\bullet+}$, which could be differentiated from $\mathbf{1}^{\bullet+}$ by collisional activation mass spectrometry. Reduction of the ylide ion $\mathbf{2}^{\bullet+}$ in neutralisation–reionisation mass spectrometry experiments yielded the corresponding neutral molecule **2**. This direct observation of a thiazolium ylide provides support for postulates of such species as discrete intermediates in a variety of biochemical transformations.

Keywords
carbenes · density functional calculations · mass spectrometry · thiamin · ylides

Introduction

Thiamin (Vitamin B_1) is a coenzyme that is essential to several biochemical processes.[1] The decarboxylation of pyruvic acid to acetaldehyde exemplifies its involvement in the catalytic cycles of many carbon–carbon bond forming and breaking reactions.[2] The enzymatic activity has been suggested to stem from the relatively easy deprotonation of the thiazolium ring to form an active, thiazolium ylide intermediate. Breslow's fundamental studies[3] on model systems laid foundations for this current understanding of thiamin action. Despite a considerable body of other supportive experimental work,[1, 4–9] including the recent synthesis and characterisation of a few metallocarbene complexes,[10–12] the direct observation of free thiazolium-2-ylides remains elusive. In contrast, closely related five-membered ring heterocycles of the imidazole-2-ylidene family proved to be isolable compounds,[13, 14] although the parent species itself was only recently generated and characterised as a gaseous molecule.[15] More highly substituted members of this class have been probed spectroscopically in the gas phase.[16] Among related heterocycles, oxazole-2-ylidene has similarly been observed[17] in neutralisation–reionisation mass spectrometry (NRMS)[18] experiments.

Since these latter types of species are biochemically less significant than the thiazole ylides, it is important to address this deficit. Herein we describe the successful identification of the parent 3*H*-thiazole-2-ylidene (**2**) using the technique of NRMS. Although not identical to the suggested active form of thiamin, this structure is the simplest model compound for the vitamin. While extensive computational studies have been carried out on

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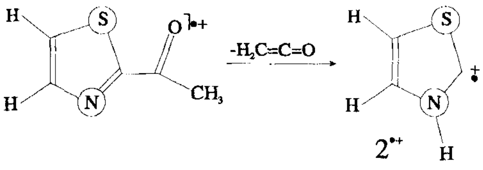
imidazole-2-ylidene[14,19,20] much less information is available for the thiazole ylides;[20–24] this has prompted us to use quantum chemical calculations of the hybrid density functional theory[25] type to investigate aspects of the C_3H_3NS potential energy surface relevant to the characterisation of thiazole-2-ylidenes and their radical cations.[26] It should be mentioned that the issue of "aromaticity"[27] in five-membered ring heterocycles has long attracted attention.[28] Aromatic stabilisation energies determined by means of ab initio calculations incorporating perturbation theory (MP2)[20,21] apparently indicated that **2** is less stabilised than imidazole-2-ylidene, and the exact extent of its aromatic stabilisation has continued to be a subject of controversy.[14,19] Given the difficulties inherent to establishing unambiguously the exact extent of aromatic stabilisation in **2**, notwithstanding recent calculated magnetic susceptibility anisotropy data,[21] we confine ourselves to a comparison of its structural features and energies relative to its isomers.

Results and Discussion

Generation of $\mathbf{2}^{\cdot+}$ might be accomplished analogously to previous "gas-phase syntheses" of carbene radical cations[17,18] by dissociative electron ionisation (EI) of an appropriately substituted thiazole, such as the readily available acetyl-2-thiazole (Scheme 1), which has a sizeable $C_3H_3NS^{\cdot+}$ peak at *m/z* 85 in its EI mass spectrum.



Scheme 1. Gas-phase synthesis of of $\mathbf{2}^{\cdot+}$.

The proper identification of neutral species by NRMS requires that one can confidently establish the parent-ion structure. Details of neutralisation–reionisation (NR) mass spectrum acquisition[29] and other tandem mass spectrometric experiments[30] used to generate and characterise C_3H_3NS ions and neutrals are given in the Experimental Section.

The collisional activation (CA) mass spectrum of the *m/z* 85 ions obtained according to Scheme 1 was compared to that of thiazole radical cations ($\mathbf{1}^{\cdot+}$), which are produced simply by 70 eV EI of thiazole (Figure 1).[31] The *m/z* 85 ions generated from the two precursors give rise to reasonably similar spectra, except for two crucial differences. First, only the *m/z* 85 ions that are expected to have the ylide ion structure produce a peak at *m/z* 73 ($C_2H_3NS^{\cdot+}$), which formally corresponds to the extrusion of the ylidic carbon atom from the ring. Secondly, the peak at *m/z* 59 ($HNCS^{\cdot+}$) provides definite evidence for a structure that can readily lose acetylene, that is, $\mathbf{2}^{\cdot+}$.[32] Ion $\mathbf{3}^{\cdot+}$, although energetically disfavoured compared to $\mathbf{2}^{\cdot+}$ (see Table 1), could also provide *m/z* 59 ions ($HSCN^{\cdot+}$ or $C_2H_3S^+$).[33] However, an MS/MS/MS experiment[30] confirmed the identity of the ions as $HNCS^{\cdot+}$.[34] Ring cleavage in $\mathbf{1}^{\cdot+}$ would lead to the ion $N{=}CH{-}S^{\cdot+}$, which is undoubtedly of higher energy, and this process is therefore not observed. Furthermore, the near absence of the *m/z* 59 peak in the CID mass spectrum of $\mathbf{1}^{\cdot+}$ effectively rules out the possibility that isomerisation to ionised thiazole by a 1,2-H shift occurs to a significant extent prior to dissociation. Perhaps not surprisingly, an analogous situation is observed for the imidazole/imidazole-2-ylidene radical cation system, where the two isomers with otherwise similar CID mass spectra are clearly distinguished on the basis of the acetylene elimination reaction.[15] Depending upon thermochemical considerations, it may be that this is a generic differentiating feature for simple five-membered ring heterocyclic molecular ions and their ionic 2-ylide isomers. We hasten to add that such a generalisation clearly has limits, as demonstrated by the challenge of identifying the pyridine-2-ylide ion, which is a six-membered ring heterocycle.[35]

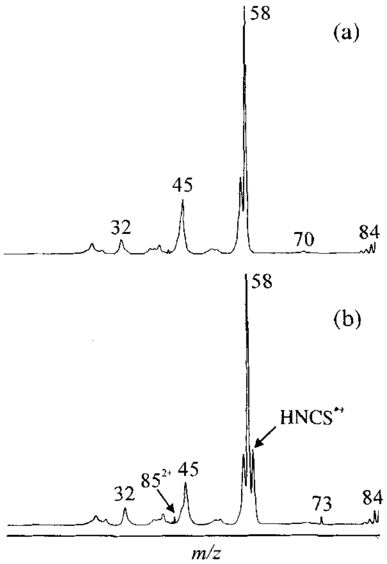


Figure 1. CA mass spectrum of the *m/z* 85 ions generated from a) ionised thiazole and b) ionised 2-acetylthiazole.

Encouraged by the indications that the dissociative ionisation of 2-acetylthiazole produces *m/z* 85 radical cations of structure $\mathbf{2}^{\cdot+}$, we employed neutralisation–reionisation mass spectrometry (NRMS)[18] to attempt to generate and characterise the neutral ylide **2**. Ideally, near vertical electron transfer to the ion should yield the desired neutral. However, the internal energy content of the neutral produced in this way will depend on the Franck–Condon overlap between the ion and neutral. If the energy barrier to isomerisation in the neutral molecules is less than the minimum bond dissociation energy, then rearrangement of excited neutral molecules is possible and may occur. In such a case, subsequent reionisation would lead to a mixture of ions and, as a result, to NR mass spectra that do not match the corresponding CA mass spectra.

The neutralisation–reionisation (NR) mass spectra of the two ions $\mathbf{1}^{\cdot+}$ and $\mathbf{2}^{\cdot+}$ (Figure 2) are quite

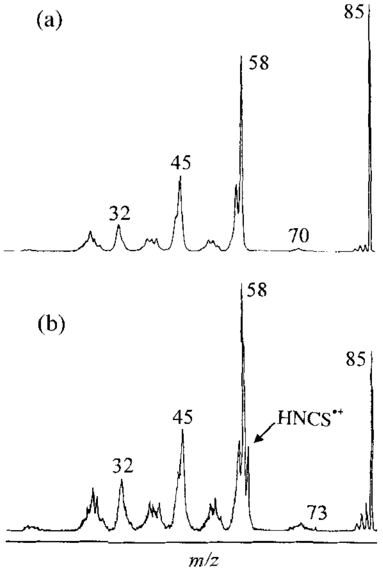


Figure 2. NR mass spectrum of the *m/z* 85 ions generated from a) ionised thiazole and b) ionised 2-acetylthiazole.

similar to the corresponding CA mass spectra and both exhibit survivor signals at *m/z* 85. The observation of recovery peaks is consistent with the computational predictions (see below), provided that the ions generated from 2-acetylthiazole are $\mathbf{2}^{\cdot+}$ as opposed to $\mathbf{3}^{\cdot+}$, since the latter are not expected to yield stable species upon neutralisation. More importantly, the distinguishing peaks at *m/z* 59 and 73 again appear only in the spectrum assigned to $\mathbf{2}^{\cdot+}$. Because of the absence of unique peaks for the thiazole structure itself, we cannot say with absolute certainty whether or not the ion $\mathbf{1}^{\cdot+}$ is also generated from 2-acetylthiazole. However, the *m/z* 85 ions from 2-acetylthiazole were analysed after NR by CA[35] (spectrum not shown) and they again showed a substantial *m/z* 59 peak; we therefore conclude that the majority of the ions have the structure $\mathbf{2}^{\cdot+}$. It is thus clear that thiazole-2-ylidene (**2**) is formed by one-electron reduction of $\mathbf{2}^{\cdot+}$ in the gas phase and that **2** does not readily isomerise to the neutral thiazole structure **1**.

The search for stationary points corresponding to the thiazole isomers **1**–**3**, their radical cations and the connecting transition structures of the 1,2-hydrogen shifts was conducted on a 6-processor SGI-POWER-Challenge computer using the Gaussian94 program package.[36] Analytical frequency calculations confirmed the assignment of stable or transition structures based on the correct number of eigenvalues of the Hessian matrix, 0 or 1, respectively. The geometric parameters and energies of the structures were obtained with the 6-31G** basis set by using the standard hybrid density functional theory option (HF/DFT) designated Becke3LYP.[37] Relative energies were corrected for nonscaled zero-point vibrational energy (ZPE) contributions. The energy data and $<S^2>$ expectation values of the open shell systems are collected in Table 1. The latter show that the Becke3LYP wave functions do not suffer appreciably from spin contamination.[38] Table 2 contains the geometric details for the structures shown in Figure 3.

Table 1. Calculated energies [a] for selected C_3H_3NS neutrals [b], radical cations and transition structures.
a) Neutrals.

	B3LYP/6-31G*$_S$	ZPVE$_S$	ΔE_{T-S}	ZPVE$_T$	$<S^2>_T$	E_{rel}
1	−569.051841	34.7	69.5	31.9	2.000	0
2	−569.001609	34.7	63.2	33.1	2.007	31.5
4	−568.991753	31.5				34.5
TS1–2	−568.930103	30.7	58.7	29.9	2.021	72.4
TS1–4	−568.957245	30.2				54.9

b) Ions.

	B3LYP/6-31G**	ZPVE	$<S^2>$	IE$_a$	E_{rel}
$\mathbf{1}^{\cdot+}$	−568.718007	33.6	0.750	9.04	0
$\mathbf{2}^{\cdot+}$	−568.703864	34.9	0.750	8.11	10.2
$\mathbf{3}^{\cdot+}$	−568.629387	31.9	0.750		53.9
$\mathbf{4}^{\cdot+}$	−568.671657	31.5	0.750	8.71	27.0
TS$\mathbf{1}^{\cdot+}$–$\mathbf{2}^{\cdot+}$	−568.613426	30.8	0.758	8.62	62.8
TS$\mathbf{1}^{\cdot+}$–$\mathbf{3}^{\cdot+}$	−568.602495	30.3	0.759	9.66	69.2

[a] Total energies are in hartree; zero-point vibrational energies (ZPVE), triplet–singlet gap energies (ΔE_{T-S}) and relative energies of singlet species (E_{rel}) in kcal mol^{-1}; ionisation energies (IE$_a$) in eV. [b] Subscript S and T are used to indicate values for singlet- and triplet-state neutral species.

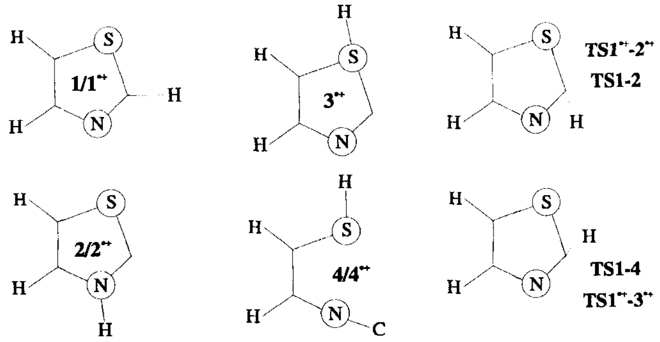


Figure 3. Optimised Becke3LYP/6-31G** geometries of selected C_3H_3NS molecules, radical cations and their connecting transition structures (see also Table 2 for details of geometries). Torsion angles for nonplanar species are as follows: $\mathbf{1}_T$: C-N-C(2)-H, 232.6°; C-S-C(2)-H, 165.8°; S-C(2)-N-C, 12.8°; C(2)-S-C-C, 11.2°; C-C-N-C(2), 4.0°. $\mathbf{2}_T$: C-C-N-C(2), 21.8°; C-N-C(2)-S, 21.8°; C-C-N-H, 127.5°. $\mathbf{3}^{\cdot+}$: C-C-S-H, 98.6°. **TS**$\mathbf{1}_S$–$\mathbf{2}_S$: H-C(2)-N-C, 101.5°. **TS**$\mathbf{1}_T$–$\mathbf{2}_T$: H-C(2)-N-C, 128.5°.

According to the Becke3LYP calculations thiazole (**1**) ($^1A'$) is planar, with C–S bonds of almost equal length (1.737 and 1.731 Å) and a typical C=C double bond. This result is remarkably close to the structure of **1** determined by microwave spectroscopy.[39] In its triplet state **1** is nonplanar. As well as having an out-of-plane hydrogen atom, the ring skeleton exhibits some torsion (≈10°), and by comparison with the singlet-state struc-

Table 2. Optimized Becke3LYP geometries (angles/°, bond lengths/Å) for selected C_3H_3NS neutrals [a], radical cations and transition structures.

	S-C(2)-N	C(2)-N-C	N-C-C	C-C-S	C(2)-X-H [c]	S–C(2)	C(2)–N	N–C	C=C	C–S	X–H [c]
$\mathbf{1}_{expt.}$ [b]	115.2	110.1	115.8	109.6	121.3	1.713	1.304	1.372	1.367	1.713	
$\mathbf{1}_S$	115.2	110.4	116.1	109.8	121.5	1.750	1.300	1.377	1.365	1.733	1.083
$\mathbf{1}_T$	112.4	110.5	114.8	115.6	130.1	1.848	1.406	1.294	1.452	1.746	1.088
$\mathbf{1}^{\cdot+}$	114.8	110.9	115.1	111.5	120.5	1.820	1.308	1.339	1.450	1.672	1.086
$\mathbf{2}_S$	103.6	120.9	111.3	108.5	118.2	1.742	1.312	1.399	1.349	1.755	1.013
$\mathbf{2}_T$	113.5	108.3	114.9	113.0	118.8	1.780	1.390	1.401	1.348	1.778	1.022
$\mathbf{2}^{\cdot+}$	115.5	112.6	111.5	111.8	123.5	1.682	1.352	1.398	1.356	1.755	1.019
$\mathbf{3}^{\cdot+}$	110.6	117.0	113.4	110.7	94.1	1.834	1.216	1.419	1.306	1.803	1.368
$\mathbf{4}_S$	95.8	175.6	122.9	123.8	162.0	3.806	1.201	1.355	1.398	1.696	1.353
$\mathbf{4}^{\cdot+}$	95.6	179.3	122.9	122.0	164.2	3.788	1.183	1.374	1.342	1.762	1.346
TS$\mathbf{1}_S$–$\mathbf{2}_S$	116.0	110.8	112.5	113.2	60.0	1.731	1.324	1.385	1.377	1.737	1.308
TS$\mathbf{1}_T$–$\mathbf{2}_T$	115.3	105.6	118.2	113.4	60.2	1.784	1.431	1.392	1.357	1.786	1.339
TS$\mathbf{1}^{\cdot+}$–$\mathbf{2}^{\cdot+}$	108.3	115.3	113.3	112.7	60.7	1.768	1.372	1.397	1.362	1.740	1.316
TS$\mathbf{1}_S$–$\mathbf{4}_S$	93.6	130.1	114.9	116.5	23.3	2.650	1.196	1.392	1.366	1.714	1.979
TS$\mathbf{1}^{\cdot+}$–$\mathbf{3}^{\cdot+}$	110.4	116.9	114.0	116.8	49.4	1.885	1.245	1.371	1.373	1.740	1.529

[a] Subscript S and T are used to indicate values for singlet- and triplet-state species. [b] Compare ref. [39]. [c] X = C(2) for structures **1**, X = N for structures **2** and **TS1–2**, and X = S for structures $\mathbf{3}^{\cdot+}$, **4**, **TS1**–$\mathbf{3}^{\cdot+}$ and **TS1–4**.

ture all the bonds except C(4)–N are longer with the S-C(2)-N angle narrowing slightly to accommodate the change. The triplet–singlet gap is large, 69.5 kcal mol^{-1} including zero-point vibrational energy contributions. Ionisation of **1** yields a planar C_s structure with bond lengths and angles intermediate between neutral thiazole in its singlet and triplet states. According to the DFT calculations the separation of **1** from $\mathbf{1}^{\cdot+}$ is smaller than the experimentally determined ionisation energy for thiazole (9.51 eV).[40] The difference is somewhat smaller for imidazole,[15,41] and for the imidazole carbene[14a,19f] theory and experiment concur.

Like **1**, the ylide **2** ($^1A'$) is also planar; its C=C bond is shorter and its C–N bond is a little longer; the C–S distances are about the same. In contrast to Sauer's structure for **2** derived by using a method based on a single determinant,[20] the Becke3LYP-derived structure (Figure 3) has longer (by at least 0.02 Å) C–S bonds and shorter C(2)–N and C=C bonds (by 0.043 and 0.01 Å, respectively), although the S-C(2)-N angle is virtually the same. On going to the triplet state of **2** the S-C(2)-N angle widens noticeably from 103.6 to 113.5° and the two adjacent heteroatom–carbon bonds lengthen. Upon ionisation, further widening of the S-C(2)-N angle to 115.5° occurs, but while the associated C–N bond becomes slightly longer in $\mathbf{2}^{\cdot+}$, the C(2)–S bond actually shortens to 1.682 Å and the other C–N and C–S bonds remain essentially unchanged. The geometry changes relative to singlet **2** are consistent with substantial localization of the HOMO at C(2). Energetically, reduction of the ions favours the formation of singlet **2** in the NRMS experiments, although, especially considering the similarity of the S-C(2)-N angles in $\mathbf{2}^{\cdot+}$ and triplet **2**, the possibility of some endothermic neutralization to the latter cannot be ruled out on the basis of geometric differences.

The transition structure **TS1–2** possesses features one expects for a 1,2-hydrogen shift and has a typical frequency ($\approx$2000 cm^{-1}) for this type of process.[42] The energy required to surmount the barrier is 72.4 kcal mol^{-1} coming from **1**. Similarly, $\mathbf{TS\,1^{\cdot+}-2^{\cdot+}}$, the corresponding structure for the ions, lies 62.8 kcal mol^{-1} above $\mathbf{1}^{\cdot+}$.

According to our calculations there is a stable radical cation $\mathbf{3}^{\cdot+}$ that has a cyclic structure, but curiously there seems to be no corresponding neutral molecule; optimisation attempts led instead to spontaneous ring opening and eventually to structure **4**. The ionised counterpart of the latter ($\mathbf{4}^{\cdot+}$) is also lower in energy than the cyclic ion $\mathbf{3}^{\cdot+}$ by 27 kcal mol^{-1}. The deprotonated counterpart of **4** has been proposed to rationalise reactions of thiazole with bases in both solution[43] and gas-phase chemistry.[44]

The transition structures **TS1–4** and $\mathbf{TS\,1^{\cdot+}-3^{\cdot+}}$ determined for 1,2-hydrogen shifts from C(2) to the sulfur atom should lie high enough in energy (20.4 and 15.3 kcal mol^{-1} relative to **4** and $\mathbf{3}^{\cdot+}$) for the stable isomers to be observable under appropriate conditions.

If the heat of formation of thiazole and also its ionisation energy were well established it should be possible to evaluate $\Delta H_f(\mathbf{2})$ and $\Delta H_f(\mathbf{2}^{\cdot+})$ from the computed energy differences between the various species. However, the Lias compendium[32] indicates that $\Delta H_f(\mathbf{1}) = 37 \pm 2$ kcal mol^{-1} is an estimated value. If we rely on this estimate together with our calculated difference between **1** and **2**, it puts $\Delta H_f(\mathbf{2})$ at 68.5 kcal mol^{-1}. Using the calculated energy difference between ylide **2** and its radical cation, we estimate $\Delta H_f(\mathbf{1}^{\cdot+})$ to be 256 kcal mol^{-1} with an uncertainty of several kcal mol^{-1}. The energy difference between the two neutrals can be combined with $\Delta H_f(C_3H_4NS^+) = 187$ kcal mol^{-1}, from the experimental proton affinity of thiazole (PA(**1**) = 216.5 kcal mol^{-1}).[45] However, we note that the value PA(**2**) = 247 kcal mol^{-1} thus obtained is quite different from the 254.7 kcal mol^{-1} predicted by Sauer's calculations.[20] Further calculations and experiments are necessary, and underway, to alleviate this discrepancy.

Conclusion

The stability of the gaseous thiazole ylide **2**, a model compound of Vitamin B_1, provides support of mechanisms of thiamin action involving ylidic intermediates. The high barriers to isomerisation indicated by the computational and experimental results point to the possibility of directly observing **2** in the condensed phase under appropriate conditions, for example, by low-temperature matrix isolation.

Experimental Procedure

The tandem mass spectrometry experiments were performed at McMaster University on the VG Analytical ZAB-R. This BE_1E_2 (B = magnet, E = electric sector) instrument and the details of the neutralization–reionization mass spectrum acquisition have been previously described [29].

The ions of interest (e.g., *m/z* 85 in the case of $C_3H_3NS^{\cdot+}$) are mass-selected by B and subsequently (in a small gas cell located between B and E_1) subjected to collision with *N,N*-dimethylaniline. This results in neutralisation of a fraction of the ions generated in a 10 kV source by fast electron transfer. After exiting the cell any remaining ions are deflected away by a positively charged electrode, so that only a beam of fast-moving neutral species enters a second gas cell, whereupon they are (dissociatively) reionised by collisions with oyxgen molecules. The resulting ions are analysed by scanning E_1. If instead the reionised species are selectively transmitted at a fixed E_1 setting and helium gas is introduced in a third cell located between E_1 and E_2, an NR/CID mass spectrum characteristic of the reionised neutrals can be obtained by scanning the latter sector. Comparative CID experiments are performed analogously, but with the deflector electrode switched off. Spectra were recorded with a PC-based data system (Mommers Technologies, Ottawa, Canada).

The compounds were purchased from commercial sources and used without further purification. Samples were introduced to the mass spectrometer either through an all-glass heated inlet system equipped with a leak valve or through a direct insertion-type probe having a glass bore and reservoir. At indicated pressures (monitored by a remote ionisation gauge) of typically 10^{-6} Torr, ions were formed by electron ionisation (70 eV) with the source temperature at 150 °C.

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