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International Journal of Mass Spectrometry 236 (2004) 1–9
International Journal of Mass Spectrometry
www.elsevier.com/locate/ijms

Reactions of ionised pyridazine, aminopyrazine and aminopyridine and their isomeric α-distonic ions

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Received 25 March 2004; accepted 26 April 2004

Dedicated on the occasion of his retirement to Professor Dudley Williams in recognition of his outstanding contribution to the theory and practice of organic mass spectrometry.

Available online 17 July 2004

Abstract

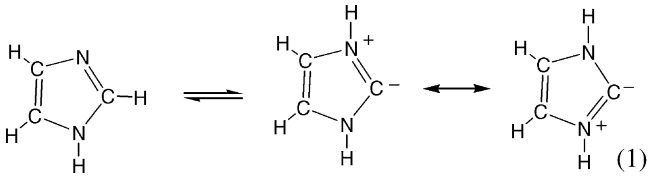
The reactions of ionised pyridazine, aminopyrazine and aminopyridine and the corresponding α-distonic ions are examined by a combination of tandem mass spectrometric techniques, including analysis of metastable ion (MI), collision induced dissociation and neutralisation–reionisation mass spectra (NRMS). Further insight into the relative stability and energy barriers towards tautomerism of each ionised heterocycle with its α-distonic isomer is obtained by computational methods. In all these systems, both the conventional radical-cation and the α-distonic tautomer are stable species which exist in discrete energy wells, with a significant barrier towards their interconversion. Although each α-distonic ion is sufficiently stable to survive neutralisation–reionisation, the conventional ionised heterocycle is more stable in each case. The possibility of investigating proton-transport catalysis in the tautomerism of these ionic systems is discussed.

Keywords: Pyridazine; Aminopyrazine; Aminopyridine; Radical-cation; Distonic ion; Ylid; CBS-QB3 calculations; Neutralisation–reionisation

1. Introduction

Heterocyclic compounds, particularly those with two nitrogen atoms in one ring, are of ubiquitous importance in organic chemistry, biology and medicine [1]. Moreover, many diazine and diazole derivatives have pharmacological activity [2,3]. Consequently, experimental and theoretical studies of these heterocyclic systems have proliferated in recent years [4–8].

An important facet of the chemistry of diazoles, especially imidazole derivatives, is the existence of comparatively stable ylid tautomers, in which the positive charge is delocalised without disrupting the aromatic sextet, as illustrated for imidazole in Eq. 1. Such ylids may play a part in the biological activity of imidazole and related heterocycles by facilitating acid/base catalysis and/or nucleophilic catalysis.


(1)

The structure and reactivity of such α-distonic ions, which are formally ionised ylids, and their conventional isomers may be conveniently studied by mass spectrometry. In particular, the tautomerism of these distonic and conventional isomers may be investigated. Combined experimental and computational studies of ionised heterocycles including pyridine [9,10], pyrazine [11], pyrimidine [12], imidazole [13], pyrazole [14] and thiazole [15] indicate that both the conventional radical-cations and the corresponding distonic ions generally are stable. Moreover, there is usually a significant energy barrier towards the interconversion of the conventional and distonic tautomers. In favourable cases, these barriers may be reduced by interaction of one tautomer with a base (or acid) which removes (or adds) a proton from one

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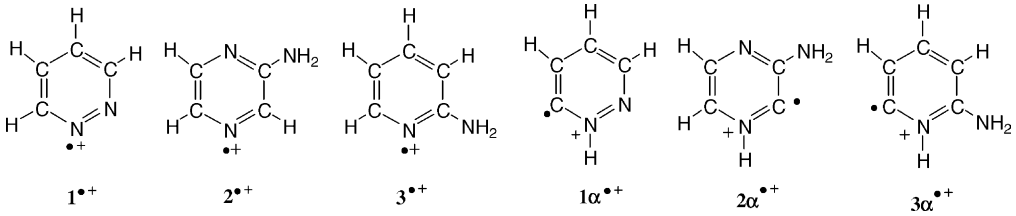
doi:10.1016/j.ijms.2004.04.017

site in a collision complex. Addition (or removal) of a proton from another position then forms the other tautomer. This proton transfer catalysis [16,17] is analogous to the base (or acid) catalysis that is familiar in solution chemistry.

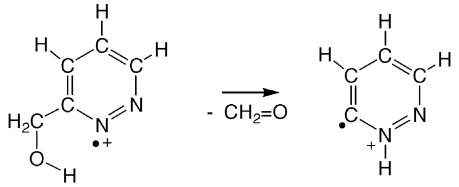
The tautomerism of ionised pyridine with its α-distonic ion has been shown to be subject to proton-transport catalysis [10]. The possibility that this form of catalysis may occur in other ionised heterocyclic systems is worthy of investigation, not least because the biological activity of certain heterocycles probably reflects their ability to undergo protonation and/or deprotonation under physiological conditions [1]. Moreover, the intermediacy of ylids in some of these proton transfer steps may be crucial. Ionised pyridazine, whose dissociation chemistry has been studied in considerable detail [18], was thought worthy of investigation because it is the only diazine system that has not yet been subject to detailed scrutiny in this context. In addition, the effect of an amino substituent in the ring on the relative stability of the conventional and distonic isomers was considered worthy of study, not least because many heterocycles found in nature contain one or more amino groups. The possibility that isomerisation of the conventional radical-cations to their distonic tautomers might be facilitated by proton-transport catalysis was particularly attractive.

The following ions were studied:



$\mathbf{1}^{\bullet+}$ $\mathbf{2}^{\bullet+}$ $\mathbf{3}^{\bullet+}$ $\mathbf{1}\alpha^{\bullet+}$ $\mathbf{2}\alpha^{\bullet+}$ $\mathbf{3}\alpha^{\bullet+}$

The formation of each of the conventional radical-cations, $\mathbf{1}^{\bullet+}$, $\mathbf{2}^{\bullet+}$ and $\mathbf{3}^{\bullet+}$, was readily accomplished by ionisation of the parent heterocycles, **1**, **2** and **3**, respectively. The corresponding α-distonic ions, $\mathbf{1}\alpha^{\bullet+}$, $\mathbf{2}\alpha^{\bullet+}$ and $\mathbf{3}\alpha^{\bullet+}$, were not accessible by ionisation of the corresponding ylids, **1**α, **2**α and **3**α, but they were obtained unambiguously by dissociative ionisation of appropriate derivatives of **1**, **2** and **3**, as illustrated in Eqs. 2–4.



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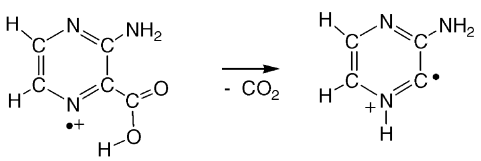

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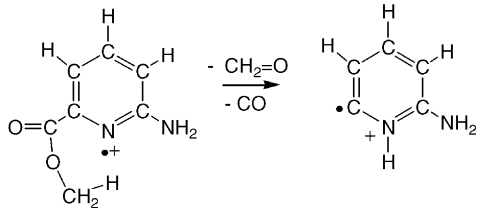


(4)

3-Hydroxymethylpyridazine (Eq. 2), pyridazine-3-carboxylic acid and its methyl ester were suitable precursors for $\mathbf{1}\alpha^{\bullet+}$. 3-Aminopyrazine-2-carboxylic acid (Eq. 3) was a suitable precursor for $\mathbf{2}\alpha^{\bullet+}$, whereas both methyl 2-aminopyridine-6-carboxylate (Eq. 4) and methyl 2-acetamidopyridine-6-carboxylate were suitable precursors for $\mathbf{3}\alpha^{\bullet+}$.

2. Experimental and theoretical methods

2.1. Mass spectrometry

Tandem mass spectrometric experiments were performed on the VG Analytical ZAB-R mass spectrometer. Details of the geometry of this three-sector (BEE) instrument have been published [19]. Metastable ion (MI) spectra were recorded for ions dissociating in the second field free region (2ffr); collision-induced dissociation (CID) spectra were recorded using oxygen as the collision gas in the 2ffr or 3ffr (third field free region). Unless otherwise stated, the accelerating voltage for these experiments was 8 kV. CID spectra of reference ions having a translational energy close to that of the product ions resulting from earlier dissociations (MI or CID) in the 2ffr were also obtained in the 3ffr. Neutralisation–reionisation mass spectra (NRMS) were recorded using *N*,*N*-dimethylaniline as the electron donor and oxygen gas for reionisation. The CID spectra of "survivor" ions in the NRMS were obtained by subjecting ions that survived neutralisation and reionisation to further collision in the third field free region. All spectra were recorded by means of a small PC-based data system developed by Mommers Technologies Inc. (Ottawa). The quoted data were typically compiled from 2 to 5 individual scans.

Apart from pyridazine, which was admitted via a quartz probe fitted with a glass bulb, all samples were introduced into the instrument via a direct insertion probe with a tube

into which the sample was packed. The pressure, as indicated by a remote ionisation gauge, was typically 10^{-7}–10^{-6} Torr during electron ionisation.

2.2. Precursor molecules

Pyridazine, 2-aminopyrazine, 3-aminopyrazine-2-carboxylic acid, 2-aminopyridine and 6-methyl-2-aminopyridine were obtained from Aldrich. The routes by which the other required heterocycles were synthesised are summarised in Scheme 1 [20–27].

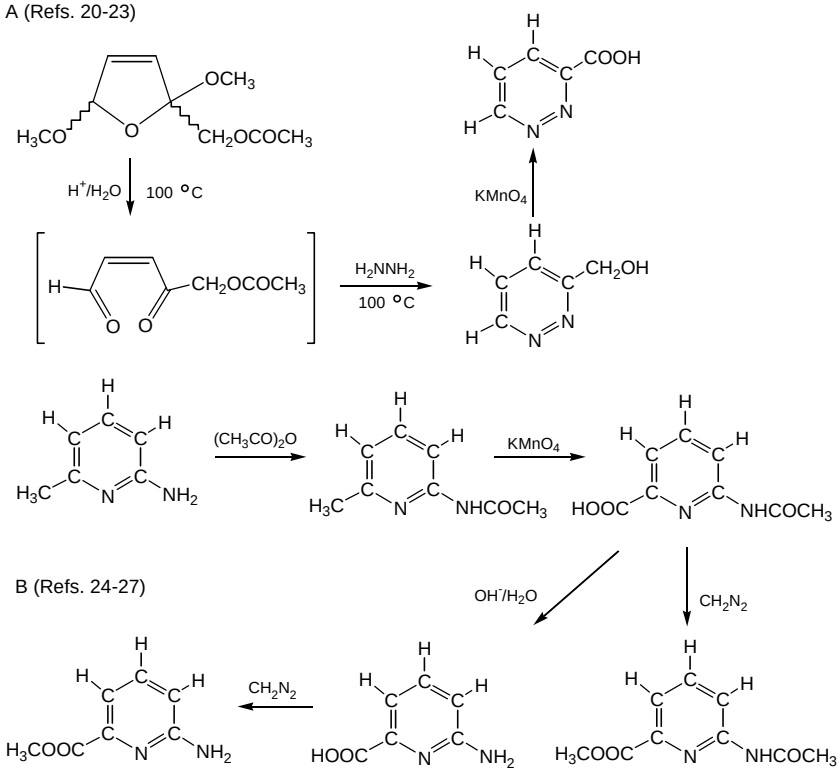
The experimental procedures are illustrated by the following detailed description of the preparation of pyridazine-3-carboxylic acid via 3-hydroxymethylpyridazine.

2.2.1. 3-Hydroxymethylpyridazine

A cold solution of concentrated sulphuric acid (3.9 g, 40 mmol) in distilled water (80 mL) was cautiously added to 2,5-dimethoxy-2,5-dihydrofurfuryl acetate (20.2 g, 100 mmol, obtained from furfuryl alcohol by acetylation followed by oxidation with bromine in methanol [20,21]) in a 500 mL round-bottomed flask equipped with a reflux condenser. After refluxing for 1 min, the resultant brown solution was rapidly cooled in ice-water. Hydrazine hydrate (10 mL, 200 mmol) was added and the mixture was refluxed for 20 min. [Caution: unless the mixture is thoroughly chilled before the hydrazine hydrate is added, the reaction may become uncontrollably violent.] After cooling to room temperature, the black residue was saturated with potassium carbonate (80 g) and the product was extracted with ethyl acetate (10 portions of 100 mL). The combined extracts were dried with potassium carbonate (140 g), filtered and evaporated at reduced pressure to leave an amber residue, which was distilled at reduced pressure to give 3-hydroxymethypyridazine as a yellow oil (6.3 g, 57%; bp 120–1 °C @ 0.03 mmHg; lit bp 150 °C @ 1 mmHg), which easily solidified, even in an air condenser. Recrystallisation from toluene/ethyl acetate gave almost colourless crystals (mp 63–65 °C; lit mp 66 °C [21]).

2.2.2. Pyridazine-3-carboxylic acid

Finely powdered potassium permanganate (4.5 g, 28 mmol) was added in small portions (ca. 0.5 g) at intervals of 10 min to a mechanically stirred solution of 3-hydroxymethypyridazine (2.1 g, 19 mmol) in distilled water (100 mL) at 65 °C in a 500 mL three-necked round-bottomed flask equipped with a condenser and thermometer. Stirring was continued for 30 min after the last portion of oxidant had been added. The brown manganese dioxide was filtered off and the colourless filtrate was concentrated (to ca. 20 mL) by evaporation at reduced pressure from a warm water bath. After acidification with concentrated hydrochloric acid to pH 2, the solution was allowed to stand for 1 h, whereupon pyridazine-3-carboxylic acid (2.31 g, 98%; mp 198–199 °C, lit mp 201 °C, dec [21]) separated as a white solid that was collected by filtration.



Scheme 1.

Table 1
CBS-QB3 computational results for the pyridazine (**1**), aminopyrazine (**2**), and 2-aminopyridine (**3**) systems of ions and neutrals[a]

Structure	$E_{B3LYP/CBSB7}$	ZPVE	$E_{CBS\text{-}QB3(0\,K)}$	ΔH_f (298 K)	Exp.[c]	E_{rel}
1$^{\bullet+}$	−264.04083	47.3	−263.51456	271	266	0
1α$^{\bullet+}$[b]	−264.01654	47.7	−263.49011	287		15
1b$^{\bullet+}$[b]	−264.00473	43.5	−263.48980	288		17
TS **1**$^{\bullet+}$ → **1**α$^{\bullet+}$	−263.96095	44.2	−263.39314	348		76
TS **1**α$^{\bullet+}$ → **1b**$^{\bullet+}$[b]	−263.97473	43.9	−263.45977	306		35
1	−264.35173	47.1	−263.84063	67	66.5	
1α	−264.29742	47.5	−263.78433	102		
1b	Ring closes					
2$^{\bullet+}$[b]	−319.46270	57.1	−318.84714	239		0
2α$^{\bullet+}$[b]	−319.43564	58.2	−318.80947	262		23
TS **2**$^{\bullet+}$ → **2**α$^{\bullet+}$[d]	−319.34989	53.9				71
2	−319.76550	57.4	−319.15775	43		0
2α	−319.70341	57.7	−319.09503	83		39
3$^{\bullet+}$[b]	−303.44268	65.4	−302.82185	215	213	0
3α$^{\bullet+}$[b]	−303.41097	65.4	−302.78265	236		20
TS **3**$^{\bullet+}$ → **3**α$^{\bullet+}$[b]	−303.31926	61.1	−302.70178	291		76
3	−303.73090	65.4	−303.11919	29	28	0
3α	−303.65324	65.0	−303.04206	78		49
TS **3** → **3**α	−303.58870	61.0	−302.98248	115		86

[a] $E_{B3LYP/CBSB7}$ and $E_{CBS\text{-}QB3(0\,K)}$ in Hartrees, all other components, including the ZPVE scaled by 0.99, in kcal mol^{-1}.
[b] Spin contamination occurs in the CBS-QB3 calculation above the value of 0.825.
[c] From Ref. [32].
[d] E_{rel} calculated from the B3LYP/CBSB7 energies.

2.3. Computational methods

Structures and energies of ions, neutral species, connecting transition states and products were probed by the standard CBS-QB3 model chemistry [28] as implemented in Gaussian 98, Revision 11.3 [29]. This model chemistry is a hybrid empirical correction-pair correlation energy extrapolation scheme, which uses the B3LYP density functional method with the 6-311G(2d,d,p) basis set (denoted as B3LYP/CBSB7 in Table 1) for geometry optimisation. Frequency calculations gave the correct number of negative eigenvalues for all minima and transition states; the connections of the transition states were checked by geometry optimisations and frequency calculations. Table 1 lists the energies and enthalpies of formation (ΔH_f) at 298 K for the principal ions and neutrals. For some of the ions the amount of spin contamination was fairly high so that the derived enthalpies may be slightly overestimated [30]. The complete set of computational results including optimised geometries of the structures is available from the authors on request.

3. Results and discussion

3.1. Pyridazine system

The MI spectra, Fig. 1, of ionised pyridazine, **1**$^{\bullet+}$, and its α-distonic tautomer, **2**α$^{\bullet+}$, are quite distinct: the former eliminates only N_2, whereas the latter loses only HCN or perhaps, though less likely, its higher energy isomer HNC. Regardless of this nuance, it is clear that **1**$^{\bullet+}$ and **1**α$^{\bullet+}$ are discrete species, which do not tautomerise before dissociation. This conclusion is supported by the distinctive CID and NRMS spectra of **1**$^{\bullet+}$ and **1**α$^{\bullet+}$.

Besides the tendency of **1**$^{\bullet+}$ and **1**α$^{\bullet+}$, to lose N_2 and HCN, respectively, several pertinent differences are found in the CID spectra. Thus, loss of H$^{\bullet}$ is important for **1**α$^{\bullet+}$, but negligible for **1**$^{\bullet+}$. Similarly, the signal at *m/z* 40 arising by charge-stripping to give $C_4H_4N_2^{2+}$ is significant for **1**α$^{\bullet+}$ but not **1**$^{\bullet+}$. This increased ease of charge-stripping is typical in the CID spectra of distonic ions. Finally, the ratio of the intensities of the peaks at *m/z* 26 and 28 decreases from almost 4 for **1**$^{\bullet+}$ to 0.6 for **1**α$^{\bullet+}$.

Parallel, though less pronounced, trends are found in the NRMS. In addition, both **1**$^{\bullet+}$ and **1**α$^{\bullet+}$ show strong "survivor" signals at *m/z* 80, corresponding to species that have survived neutralisation and reionisation. The intense signal in the latter case is especially significant because it establishes that the neutral $C_4H_4N_2$ species formed by neutralisation of **1**α$^{\bullet+}$ is sufficiently stable to survive for at least several microseconds. The close similarity of the CID spectra of survivor ions at *m/z* 80 in the NRMS of **1**α$^{\bullet+}$ and ions of this structure transmitted to the 3ffr without undergoing neutralisation and reionisation are consistent with the interpretation that the $C_4H_4N_2$ species is the ylid **1**α. Theory supports this view: **1**α is calculated to be a stable species. In contrast, the neutral counterpart of **1b**$^{\bullet+}$, which, as shown in Scheme 2, is accessible from

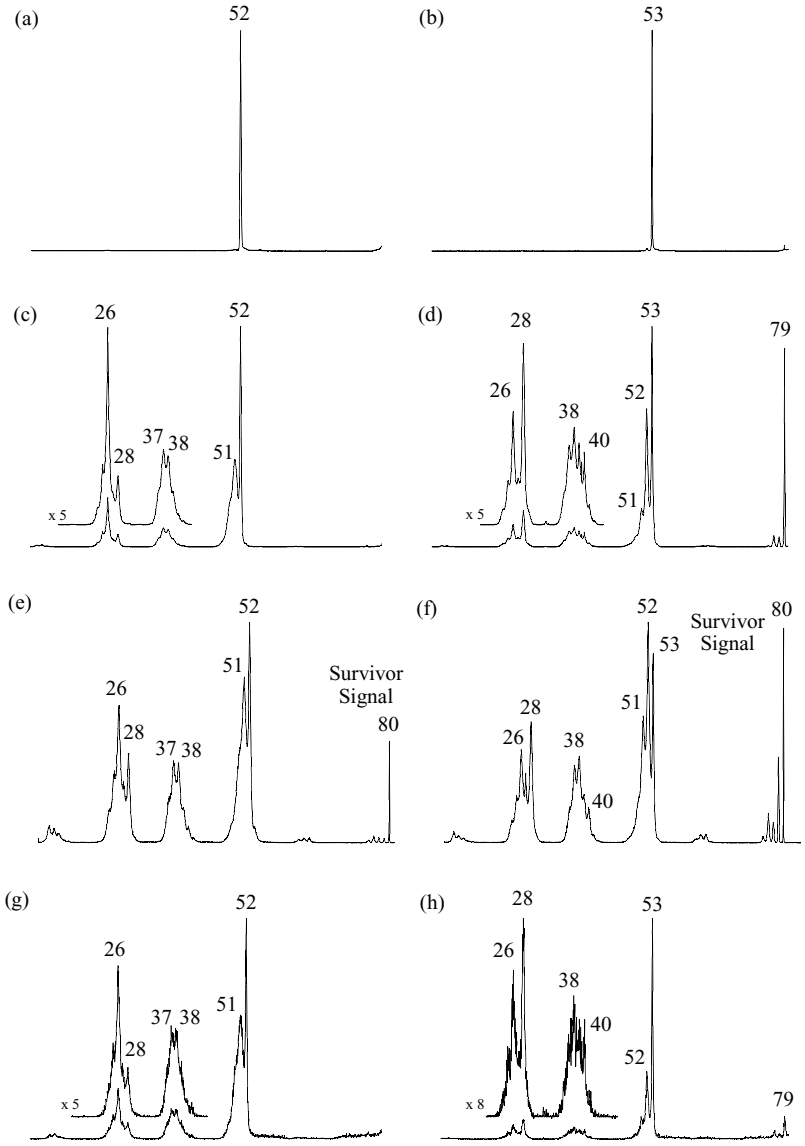


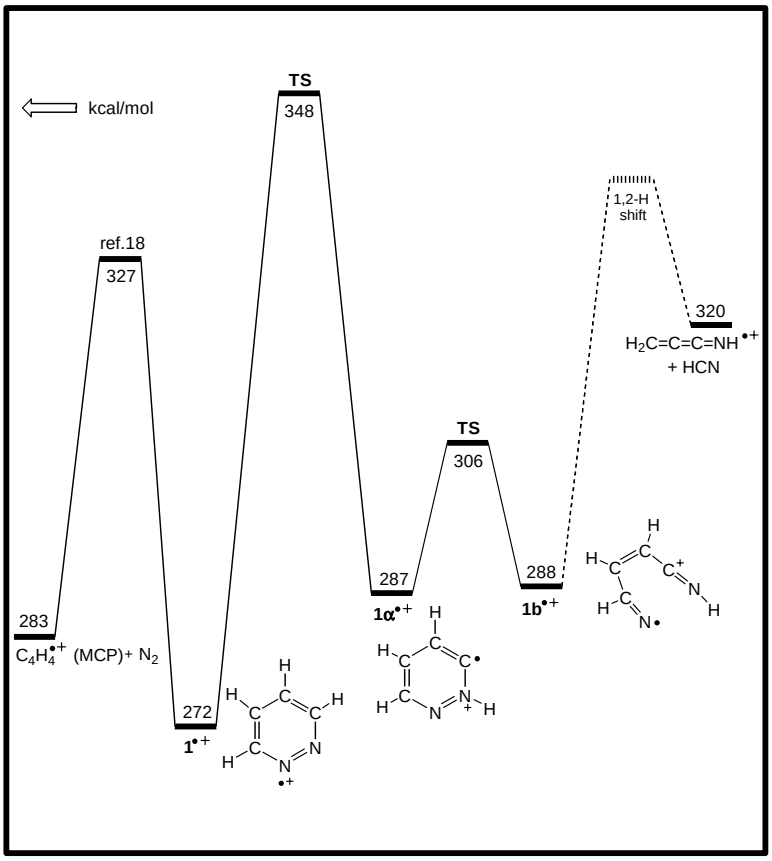
Fig. 1. MI spectra of (a) pyridazine ion $\mathbf{1}^{\bullet+}$ and (b) pyridazine-3-ylidene $\mathbf{1}\alpha^{\bullet+}$; CID spectra of (c) $\mathbf{1}^{\bullet+}$ and (d) $\mathbf{1}\alpha^{\bullet+}$; NR spectra of (e) $\mathbf{1}^{\bullet+}$ and (f) $\mathbf{1}\alpha^{\bullet+}$; NR/CID spectra of (g) $\mathbf{1}^{\bullet+}$ and (h) $\mathbf{1}\alpha^{\bullet+}$.

$\mathbf{1}\alpha^{\bullet+}$, is not a minimum structure. All attempts to calculate $HN{=}C^{+}CH{=}CHCH{=}N^{-}$, **1**b, failed: the geometry invariably optimised to a cyclic structure. Thus, experiment and theory lead to the conclusion that the ylid **1**α is stable.

The chemistry of $\mathbf{1}^{\bullet+}$ and $\mathbf{1}\alpha^{\bullet+}$ is summarised by the energy diagram of Scheme 2. These tautomers react in characteristically different ways and may be readily distinguished by MI, CID or NMRS. The conventional species, $\mathbf{1}^{\bullet+}$, has an appreciably lower heat of formation than the distonic tautomer, $\mathbf{1}\alpha^{\bullet+}$, but both isomers and their neutral counterparts are stable.

The thermochemical energy requirement for the dissociation $1^{\bullet+} \rightarrow C_4H_4{}^{\bullet+} + N_2$ is only modest: 12 kcal mol^{-1} for the formation of ionised methylene cyclopropene (MCP), the most stable $C_4H_4{}^{\bullet+}$ isomer [31,32]. However, the earlier detailed study utilising PEPICO [18] has established that the energy required to induce N_2 elimination is much higher, 55 kcal mol^{-1}. At this energy, several other $C_4H_4{}^{\bullet+}$ isomers, including ionised cyclobutene and the acyclic ions $CH_2{=}C{=}C{=}CH_2{}^{\bullet+}$ or $CH_2{=}CH{-}C{\equiv}CH^{\bullet+}$ are accessible. Unfortunately, CID experiments cannot be used to probe the structure of isomeric $C_4H_4{}^{\bullet+}$ ions [33], so the mechanism of this dissociation cannot be established. Regardless of the structure of the $C_4H_4{}^{\bullet+}$ product ion, however, the energy required to promote N_2 loss from $\mathbf{1}^{\bullet+}$ is still significantly lower than that needed to surmount the large energy barrier (76 kcal mol^{-1}) calculated for the 1,2-H shift from nitrogen to carbon that would effect tautomerism of $\mathbf{1}^{\bullet+}$ to $\mathbf{1}\alpha^{\bullet+}$.

The CID spectrum (not shown) of the $C_3H_3N^{\bullet+}$ species produced by elimination of HCN from metastable $\mathbf{1}\alpha^{\bullet+}$ is closely similar to that of $CH_2{=}C{=}C{=}NH^{\bullet+}$ determined in earlier investigations of ionised pyrimidine and its distonic



Scheme 2. Potential energy diagram derived from the CBS-QB3 (298 K) calculations of ionised pyridazine and its isomers.

isomers [12]. Not only is this ionised imine calculated to be the most stable isomer of $C_3H_3N^{\bullet+}$, but it may be readily formed if loss of HCN occurs by ring opening of $\mathbf{1}\alpha^{\bullet+}$, with an associated 1,2-H shift. In this case, it is probable that fission of the N–N bond in $\mathbf{1}\alpha^{\bullet+}$ gives the acyclic distonic ion, $\mathbf{1}b^{\bullet+}$, which is only marginally higher in energy than $\mathbf{1}\alpha^{\bullet+}$. The calculated barrier to this ring opening (19 kcal mol^{-1}) is comparatively small and substantially less than the corresponding barrier (61 kcal mol^{-1}) for tautomerism to $\mathbf{1}^{\bullet+}$. The energy of the transition state for the 1,2-H shift that must accompany loss of HCN from $\mathbf{1}\alpha^{\bullet+}$ was not calculated, but it must be lower than that for tautomerism to $\mathbf{1}^{\bullet+}$. It is interesting that the ionised acyclic ylid, $\mathbf{1b}^{\bullet+}$, which is of comparable energy to $\mathbf{1}\alpha^{\bullet+}$, exists in a discrete energy well; in contrast, the corresponding acyclic neutral ylid, **1b**, is not a minimum on the $C_4H_4N_2$ potential energy surface.

The discovery that $\mathbf{1}\alpha^{\bullet+}$ is less stable than $\mathbf{1}^{\bullet+}$ means that attempts to investigate whether this tautomerism is subject to proton-transport catalysis are unlikely to be fruitful: $\mathbf{1}^{\bullet+}$ would not be expected to isomerise to $\mathbf{1}\alpha^{\bullet+}$; and it is not possible to generate $\mathbf{1}\alpha^{\bullet+}$ directly so as to study its rearrangement to $\mathbf{1}^{\bullet+}$.

In an attempt to find ionised heterocycles that are less stable than their α-distonic tautomers, the effects of amino substitution on selected azine systems were investigated.

3.2. Aminopyrazine system

As shown in the previous section, the dissociation characteristics of $\mathbf{1}^{\bullet+}$ and its α-distonic isomer $\mathbf{1}\alpha^{\bullet+}$ are very different. This clear distinction is exceptional: the radical cations of related heterocyclic molecules, such as pyrazine, pyrimidine, pyridine, imidazole and pyrazole [9–14] all yield CID mass spectra which are similar, although not identical, to their α-distonic counterparts. The usual similarity does not reflect relatively low barriers towards tautomerism: theory predicts that internal energies in the range of 50–70 kcal mol^{-1} are required to cause isomerisation. Rather, it arises because the most facile dissociation of both isomers is loss of the same neutral species (often HCN) at energies close to or even above that needed to induce tautomerism. For example, the energy barrier for rearrangement of ionised pyridine to its α-distonic tautomer is 57 kcal mol^{-1}, but even more energy (95 kcal mol^{-1} [9]) is required to promote loss of HCN, which occurs from both tautomers. In such circumstances, the CID spectra of the isomers tend to be similar, though not identical: the spectra often contain minor, but structure characteristic peaks, resulting from fast dissociations at high internal energies [10,12,13].

Ionised 2-aminopyrazine, $\mathbf{2}^{\bullet+}$, and its α-distonic isomer, $\mathbf{2}\alpha^{\bullet+}$, whose CID spectra are presented in Fig. 2a–f, also

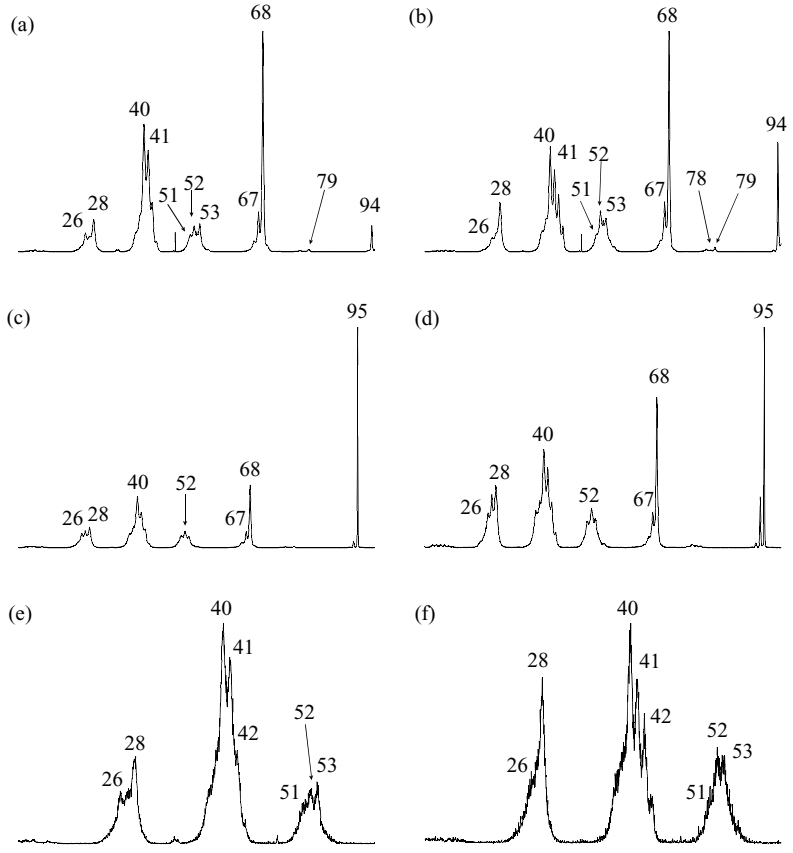


Fig. 2. CID spectra of (a) 2-aminopyrazine ion $\mathbf{2}^{\bullet+}$ and (b) 2-aminopyrazine-3-ylidene $\mathbf{2}\alpha^{\bullet+}$; NR spectra of (c) $\mathbf{2}^{\bullet+}$ and (d) $\mathbf{2}\alpha^{\bullet+}$; partial NR/CID spectra of (e) $\mathbf{2}^{\bullet+}$ and (f) $\mathbf{2}\alpha^{\bullet+}$.

seem to fit into this category. The calculations (Table 1) indicate that $\mathbf{2}^{\bullet+}$ and $\mathbf{2}\alpha^{\bullet+}$ are distinct species existing in discrete energy wells. Thus, $\mathbf{2}^{\bullet+}$ is calculated to be more stable than $\mathbf{2}\alpha^{\bullet+}$ by 23 kcal mol^{-1}, but the barrier towards tautomerism to $\mathbf{2}\alpha^{\bullet+}$ is quite high, 71 kcal mol^{-1}. Nevertheless, the energy required to induce the common [H,C,N] loss which dominates the CID mass spectra of $\mathbf{2}^{\bullet+}$ and $\mathbf{2}\alpha^{\bullet+}$ may well be close to that needed to promote tautomerism. Indeed, the CID spectra $\mathbf{2}^{\bullet+}$ and $\mathbf{2}\alpha^{\bullet+}$ are superficially similar but some diagnostic differences may be discerned: the RIs of the signals at *m*/*z* 94 as well as 42 and 43 are higher in the spectrum of $\mathbf{2}\alpha^{\bullet+}$; the ratio of the RIs of *m*/*z* 26 ($C_2H_2^{\bullet+}$) and 28 ($HCNH^+$) is 0.3 and 0.6 in the spectra of $\mathbf{2}^{\bullet+}$ and $\mathbf{2}\alpha^{\bullet+}$, respectively; the ratio the RIs of *m*/*z* 51 and 52 is greater in the spectrum of $\mathbf{2}^{\bullet+}$; and a weak signal at *m*/*z* 78 (perhaps arising by loss of NH_3) appears only in the spectrum of $\mathbf{2}\alpha^{\bullet+}$.

The NRMS spectra of $\mathbf{2}^{\bullet+}$ or $\mathbf{2}\alpha^{\bullet+}$ also show characteristic differences, especially the more intense signal at *m*/*z* 94 arising by loss of $H^{\bullet}$ from $\mathbf{2}\alpha^{\bullet+}$, and similar trends to those found in the CID spectra for the RIs of the peaks at *m*/*z* 26 and 28. Each spectrum also contains a strong survivor signal at *m*/*z* 95, thus indicating that **2** and **2**α (or, possibly, some isomer to which **2**α readily isomerises) are stable species. Confirmation that the stable neutral species is actually **2**α is provided by the CID spectrum of the survivor ions in the NRMS of $\mathbf{2}\alpha^{\bullet+}$. This spectrum closely resembles the relevant portion of the 3ffr CID spectrum of $\mathbf{2}\alpha^{\bullet+}$ which has not been subjected to neutralisation and reionisation. Moreover, the CID spectrum of the survivor signal in the NRMS of $\mathbf{2}^{\bullet+}$ is closely similar to the CID spectrum of $\mathbf{2}^{\bullet+}$, but shows the usual characteristic differences from that of $\mathbf{2}\alpha^{\bullet+}$. Consequently, it is also clear that **2**α produced by neutralisation of $\mathbf{2}\alpha^{\bullet+}$ does not collapse to **2**, even though calculations, see Table 1, indicate that it is 39 kcal mol^{-1} less stable than its conventional tautomer.

In summary, both $\mathbf{2}^{\bullet+}$ or $\mathbf{2}\alpha^{\bullet+}$ are stable radical-cations, existing in discrete energy wells. Furthermore, the neutral ylid, **2**α, also is stable and does not readily rearrange to its more stable conventional tautomer, **2**. Unfortunately, however, the greater stability of the conventional radical-cation is not conducive to studying the possibility of proton-transport catalysis in this system.

3.3. 2-Aminopyridine system

The MI spectra of ionised 2-aminopyridine, $\mathbf{3}^{\bullet+}$, and its α-distonic isomer, $\mathbf{3}\alpha^{\bullet+}$, are dominated by a peak at *m*/*z* 67, corresponding to loss of [H,C,N].

It has been proposed [34] that a mixture of ionised pyrrole and its tautomer, ionised 2-pyrroline, is formed by loss of [H,C,N] from metastable ionised $\mathbf{3}^{\bullet+}$. In addition, it has

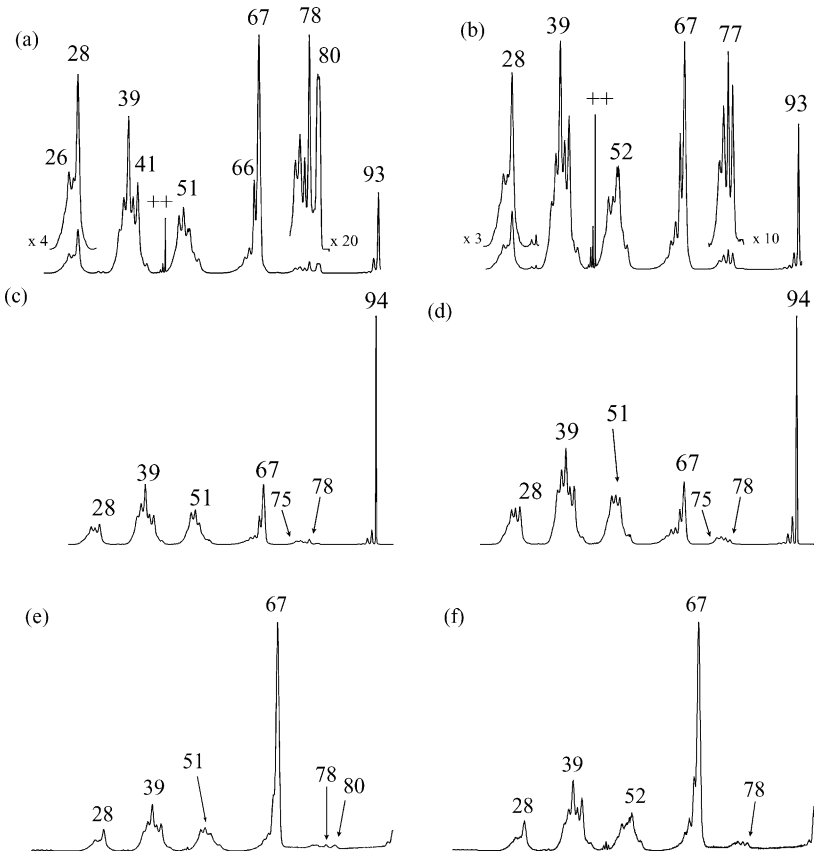


Fig. 3. CID spectra of (a) 2-aminopyridine ion $\mathbf{3}^{\bullet+}$ and (b) 2-aminopyridine-6-ylidene ion $\mathbf{3}\alpha^{\bullet+}$; NR spectra of (c) $\mathbf{3}^{\bullet+}$ and (d) $\mathbf{3}\alpha^{\bullet+}$; NR/CID spectra of (e) $\mathbf{3}^{\bullet+}$ and (f) $\mathbf{3}\alpha^{\bullet+}$.

been shown [35] that the internal energy needed to promote this reaction is ca. 70 kcal mol^{-1} and that the neutral species lost is largely HNC. The calculations, see Table 1, indicate that about the same amount of energy is required to cause tautomerism of $\mathbf{3}^{\bullet+}$ to $\mathbf{3}\alpha^{\bullet+}$.

Thus, it is not surprising that the CID mass spectra of $\mathbf{3}^{\bullet+}$ and $\mathbf{3}\alpha^{\bullet+}$ (Fig. 3a and b) are similar and have a common base peak at *m*/*z* 67. However, the spectra also show characteristic differences. The ratio of the RIs of *m*/*z* 51 and 52 is greater in the spectrum of $\mathbf{3}\alpha^{\bullet+}$; in addition, the somewhat weak cluster of peaks at higher *m*/*z* is dominated by *m*/*z* 78 and 77, respectively, in the spectra of $\mathbf{3}^{\bullet+}$ and $\mathbf{3}\alpha^{\bullet+}$. Moreover, only the spectrum of $\mathbf{3}^{\bullet+}$ contains a significant diagnostic peak at *m*/*z* 80, produced by loss of N$^{\bullet}$. This reaction is only observed in CID mass spectra obtained with oxygen as the collision gas [36]. Finally, the signals at *m*/*z* 47 and 46.5, corresponding to $C_5H_6N_2^{++}$ and $C_5H_5N_2^{\bullet++}$, respectively, are much more intense in the spectrum of $\mathbf{3}\alpha^{\bullet+}$.

The NRMS of $\mathbf{3}^{\bullet+}$ and $\mathbf{3}\alpha^{\bullet+}$ (Fig. 3c and d) also show distinctive differences, several of which follow the same trends as are observed in the CID spectra. Moreover, the presence of a very intense survivor signal in each spectrum establishes that the species formed by neutralisation of $\mathbf{3}^{\bullet+}$ and $\mathbf{3}\alpha^{\bullet+}$ are stable. In addition, the CID spectra of these survivor signals are similar to those of $\mathbf{3}^{\bullet+}$ and $\mathbf{3}\alpha^{\bullet+}$ recorded in the 3ffr (Fig. 3e and f). Consequently, neutralisation of $\mathbf{3}\alpha^{\bullet+}$ evidently produces $\mathbf{3}\alpha$, which is subsequently reionised to the original α-distonic ion.

Computational evidence (Table 1) supports this interpretation: $\mathbf{3}$ is calculated to be 49 kcal mol^{-1} more stable than $\mathbf{3}\alpha$, but both species lie in deep energy wells with a barrier of 86 kcal mol^{-1} for tautomerism of $\mathbf{3}^{\bullet+}$ to $\mathbf{3}\alpha^{\bullet+}$. It is perhaps surprising that the barrier towards isomerisation of $\mathbf{3}$ to $\mathbf{3}\alpha$ is even larger than that for the analogous tautomerism of the radical-cations. Unfortunately, the lower heat of formation of the conventional species, $\mathbf{3}^{\bullet+}$, precludes attempts to study proton-transport catalysis of its tautomerism to $\mathbf{3}\alpha^{\bullet+}$.

4. Conclusions

Ionised pyridazine, 2-aminopyrazine, 2-aminopyridine and at least one of their α-distonic tautomers are all stable species in the gas-phase, though the α-distonic isomer of ionised pyridazine may undergo fairly facile rearrangement to an acyclic species. The conventional ionised heterocycles and their distonic tautomers may be distinguished on the basis of their collision-induced dissociation and neutralisation–reionisation mass spectra. The neutral ylids produced by neutralisation of the distonic tautomers are also

stable, with sizeable energy barriers towards rearrangement to the ordinary heterocycles. In each heterocyclic system, the conventional ionised species is more stable than its distonic tautomer. This order of stability precludes investigation of the proton-transport catalysed isomerisation of these ionised heterocyclic species. Computational evidence reinforces and refines the conclusions about the structure and stability of the ionised heterocycles, their distonic tautomers and the corresponding ylids.

Acknowledgements

J.K.T. thanks the natural Sciences and Engineering Research Council of Canada (NSERC) for continuing financial support.

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