

Collisional activation of protonated C-halogenopyrazoles

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Abstract

Collisional activation of protonated 3-halogenopyrazoles (X–Pz, X = Cl, Br and I) in the high or low translational energy regime induced an intense loss of X giving $C_3H_4N_2^+$ radical cations whose structure depends on the nature of the halogen. Protonated 3-I–Pz generated thus ionized pyrazole **a**, whereas protonated 3-Cl–Pz was a precursor of an isomeric species ascribed to a dehydropyrazolium distonic structure **b**. A mixture of $C_3H_4N_2^+$ ions was formed in protonated 3-Br–Pz. B3LYP/6-31++G(d,p) computations confirmed a regioselective N_2 -protonation, and a low energy content of the distonic ions **b** or **c** (50 kJ mol⁻¹ above **a** and lying in deep energy wells). Two competitive C–H and C–X bond cleavages were invoked to explain the contrasting behaviour of various protonated X–Pz under dehalogenation conditions. © 2001 Elsevier Science B.V. All rights reserved.

1. Introduction

The generation and thermochemistry of ionized carbenes in the gas phase of a mass spectrometer has recently been reviewed [1]. Among these interesting radical cations, heterocyclic carbenes have been thoroughly studied in recent publications. For instance, the gas phase stability of the hydrogen shift isomers of pyridine [2,3], imidazole [4], thiazole [5], pyrimidine [6] pyrazine [7], *s*-triazole [8]... was convincingly demonstrated by collisional activation experiments. Ion–molecule reactions in a hybrid mass spectrometer have also

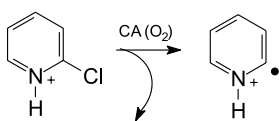
definitively demonstrated the unusual connectivity of these ions [9].

Most of these ions were prepared by dissociative electron ionization, but, in some cases, collisional dehalogenation of protonated compounds has afforded distonic ions with a very high efficiency. Dechlorination of protonated 2-chloropyridine to generate the α -ylide ion of pyridine, by collisions, worked well, provided that oxygen was used as the collision gas (cf. Scheme 1) [10].

We report here the behaviour of protonated halogenopyrazoles in collisional activation mass spectrometry. The aim of the study was twofold. First we focused on the preparation of new carbene (ylid) ions derived from pyrazoles making use of tandem mass spectrometric methodologies in a hybrid mass spectrometer of sector–quadrupole–sector configuration [11,12]. Second, we set out to determine useful quantitative parameters of

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Scheme 1.

X-pyrazoles and to rationalize their contrasting behaviour in collisional activation experiments.

2. Mass spectrometric experiments

The spectra were recorded on a large-scale tandem mass spectrometer (Micromass AutoSpec 6F, Manchester) combining six sectors of $c_1E_1B_1c_2E_2qc_4E_3B_2c_5E_4$ geometry (E_i stands for electric sector, B_i for magnetic sector, q for a quadrupole collision cell and c_i for collision cell). General conditions were reported elsewhere [11].

The installation of a radiofrequency-only quadrupole collision cell (Qcell) inside the instrument between E_2 and E_3 has also been reported [12]. This modification allows the study of associative ion–molecule reactions and the study of collisional activation of decelerated ions (ca. 20–30 eV kinetic energy). Briefly, the experiments utilizing the quadrupole consist of the selection of a beam of fast ions (8 keV) with the three first sectors ($E_1B_1E_2$) and the deceleration of these ions to approximately 20–30 eV. The interaction between the ions and the reagent gas is thereafter realized in the Qcell and, after reacceleration at 8 keV, all the ions generated in the quadrupole are separated and mass measured by scanning the field of the second magnet (Fig. 1b). The high-energy CA spectra of mass-selected ions generated in the Qcell can be recorded by a scanning of the field E_4 after selection of the ions of interest with E_3 and B_2 (Fig. 2).

In this work, we have selected the halogenopyrazoles shown in Scheme 2 as precursors. The synthesis of compounds 1–4 have been described in previous publications [13–16] whereas the compounds 5, 6, 10 and 11 were commercially available (Aldrich) and used without further purification. The *N*-methylated compounds 7–9 were

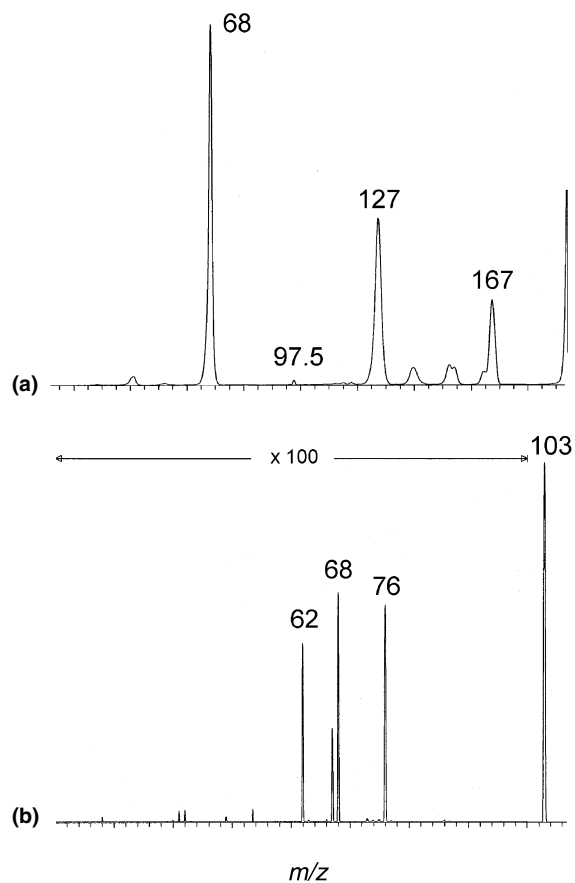


Fig. 1. High-energy CA spectrum of protonated 3-iodopyrazole $3H^+$ using helium as the collision gas (a) and low-energy CA spectrum using argon as the collision gas (b).

prepared by direct methylation of 4–6 in alkaline media.

3. Results and discussion

3.1. Preparation of the $C_3H_4N_2^+$ radical cations

Chemical ionization of the halogenated pyrazoles 1–6 using either methane or ammonia as the reagent gas affords with high yields the corresponding protonated molecules $1H^+$ – $6H^+$. Although the proton affinities of these reagent gases are very different from each other, namely $PA(CH_4) = 551 \text{ kJ mol}^{-1}$ and $PA(NH_3) = 854 \text{ kJ}$

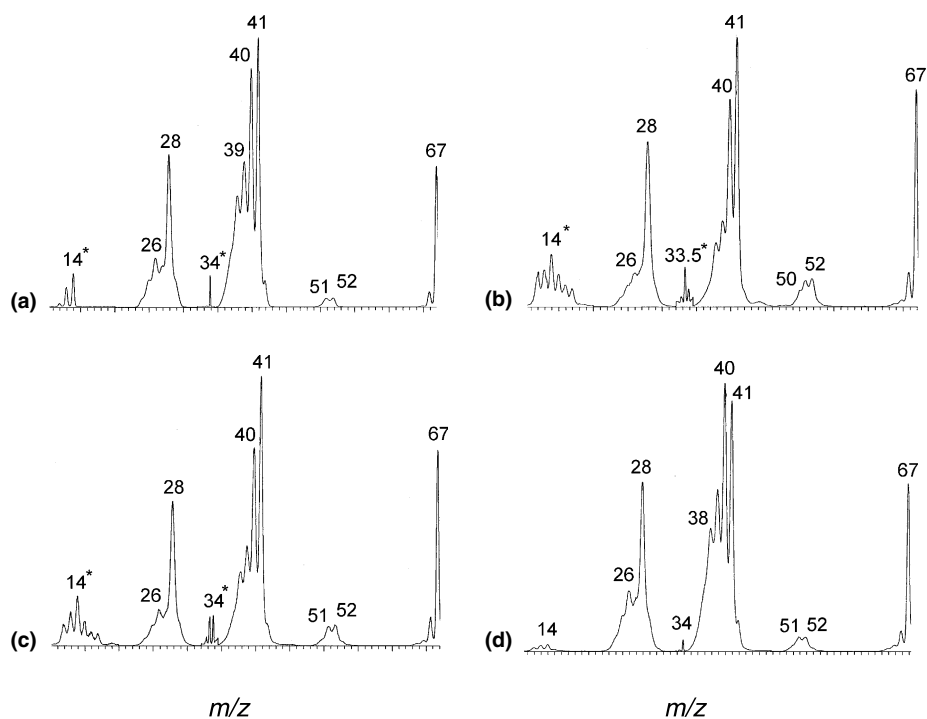
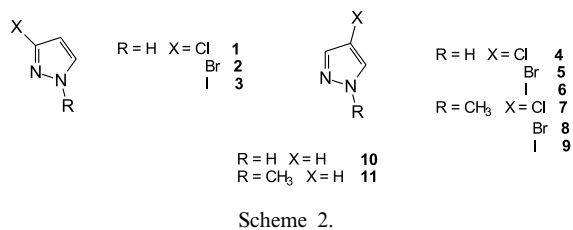


Fig. 2. CA (nitrogen collision gas) spectra of the $C_3H_4N_2^+$ radical cations generated by collisional dehalogenation (argon collision gas) of protonated 3-halogenopyrazoles **1–3H**⁺ (b–d) and by electron ionization of pyrazole **10** (a).



mol⁻¹ [17], the CA spectra listed in Table 1 of the **1H**⁺–**6H**⁺ ions are found to be similar suggesting that, in our experimental conditions, a single protonation site is involved, ascribed to the dicoordinated nitrogen of the pyrazole ring [18]. However, an increasing abundance of the ions corresponding to the loss of the halogen atom is noticed in all the Cl (CH₄) experiments and this modification of the CA spectra parallels an intensity decrease for the loss of a hydrogen atom. The reason for these changes will be discussed below on the basis of theoretical considerations.

Let us first consider the CA spectra recorded with helium as the collision gas in the high translational energy regime. Loss of a halogen atom X[•] was consistently observed for all the protonated halogenopyrazoles but the resulting yields are strongly dependent on the nature of the halogen atoms (see Table 1 and Fig. 1a). While iodine is, as expected, most readily expelled, other reaction channels become more competitive for the brominated and chlorinated ions.

In the low kinetic energy regime, the loss of atomic chlorine from **1H**⁺ is also observed, but does not constitute the major fragmentation (Table 1 and Fig. 1b). With the notable exception for the peak at *m/z* 62 ascribed to the formation of protonated cyanogen chloride, ClCNH⁺, the attribution of the other peaks to a N₂-protonated species is not straightforward. The CA spectra are dramatically simplified if chlorine is replaced by bromine or iodine whatever the position (3 or 4) on the pyrazole ring. In these cases, the loss of the

Table 1

Most intense peaks in the high-energy CA spectra of the protonated *C*-halogenopyrazoles **1–6H**⁺ using helium as the collision gas (8 keV kinetic energy of the ions) and low-energy CA spectra using argon as the collision gas (20–30 eV kinetic energy of the ions)

| | Gas | 102 | 76 | 75 | 68 | 67 | 62 | 51.5 | 41 | 40 | 28 |
|------|-----------------|-----|-----|------|-----|----|------|------|----|----|----|
| 3-Cl | He | 100 | 84 | 11 | 8 | 31 | 17 | 5 | 14 | 21 | 13 |
| | Ar | <1 | 100 | – | 44 | 15 | 48 | – | 4 | <1 | <1 |
| 4-Cl | He ^a | 86 | 100 | 52 | 12 | 10 | 4 | 5 | 9 | 10 | 22 |
| | Ar | 5 | 100 | – | 33 | 18 | – | – | – | – | – |
| | Gas | 120 | 119 | 106 | 92 | 79 | 73.5 | 68 | 67 | 41 | 40 |
| 3-Br | He | 93 | 32 | 23 | – | 10 | 5 | 100 | 36 | 30 | 26 |
| | Ar | 15 | – | – | – | – | – | 100 | – | – | – |
| 4-Br | He | 100 | 52 | 4 | 13 | 2 | <1 | 74 | 7 | 13 | 9 |
| | Ar | 20 | – | – | – | – | – | 100 | – | – | – |
| | Gas | 167 | 127 | 97.5 | 68 | 67 | | | | | |
| 3-I | He | 23 | 44 | – | 100 | 9 | | | | | |
| | Ar | – | – | – | 100 | – | | | | | |
| 4-I | He | 23 | 44 | – | 100 | 9 | | | | | |
| | Ar | – | – | – | 100 | – | | | | | |

^a Peaks also detected at *m/z* 49 (15%) and 48 (17%).

halogen atom is by far the most prominent process.

3.2. Experimental characterization of the C₃H₄N₂^{•+} radical cations

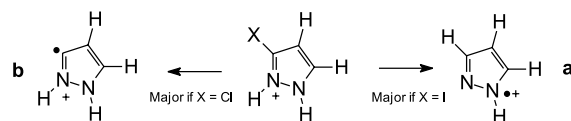
Given the fact that the protonated halogenopyrazoles undergo efficient dehalogenation within the quadrupole collision cell, the consecutive characterization of the C₃H₄N₂^{•+} radical cations can be performed on 8 keV ions, and more importantly without loss of resolution and sensitivity which was a drawback of the classical MS/MS/MS methodology. The CA spectra of the C₃H₄N₂^{•+} radical cations generated by the protonation–dehalogenation sequence are compared in Fig. 2 to the CA spectrum of the molecular ions of pyrazole. Surprisingly, the spectra of the ions produced from all three halogenated compounds are found to be only slightly different, the major differences being seen in the *m/z* 12–17 and *m/z* 32–35 (doubly charged ions) regions. In fact, the CA spectrum of the ions generated from 3-iodopyrazole is quite similar to that of ionized pyrazole itself and peaks at *m/z* 33.5, 17–15 are gradually increasing in intensity when iodine is replaced by bromine or chlorine. It seems thus reasonable to propose that isomeric C₃H₄N₂^{•+} radical cations are produced in

the dehalogenation reactions, a peculiar situation as, at first sight, all these reactions can be considered as simple cleavage reactions.

The loss of a chlorine atom generates a C₃H₄N₂^{•+} species likely to be the ylid (carbenic) ions **b** shown in Scheme 3, but this cannot experimentally be demonstrated as telltale peaks are *not* detected in the CA spectra.

A similar trend was equally observed in the protonated 4-halogenopyrazole series. Deiodination of **6H**⁺ produces mainly ionized pyrazole, while peaks corresponding to an isomeric species are again appearing for the debromination products of **5H**⁺ and the dechlorination products of **4H**⁺. The differences in the CA were found nevertheless less meaningful than for the 3-substituted compounds.

Nitrogen methylation of the 4-halogenopyrazoles was readily achieved in basic media. Given the position of the halogen atom, only one isomer was obtained in these experiments. The CA spectra of



Scheme 3.

Table 2

CA (nitrogen collision gas) spectra of the $C_4H_6N_2^+$ radical cations generated by collisional dehalogenation (argon collision gas) of protonated 1-methyl-4-halogenopyrazoles **7–9H⁺** and by electron ionization of 1-methylpyrazole **11**

| | <i>m/z</i> | | | | | | | | | | | | | | |
|-----------------------|------------|----|----|-----|----|----|----|----|----|----|----|-----|----|----|----|
| | 66 | 65 | 55 | 54 | 53 | 52 | 42 | 41 | 40 | 39 | 38 | 28 | 27 | 26 | 15 |
| 7H⁺ | 22 | 32 | 81 | 81 | 61 | 92 | 66 | 37 | 51 | 60 | 65 | 100 | 60 | 48 | 14 |
| 8H⁺ | 14 | 19 | 70 | 100 | 47 | 77 | 60 | 32 | 56 | 55 | 49 | 95 | 77 | 51 | 7 |
| 9H⁺ | – | 14 | 45 | 100 | 43 | 68 | 64 | 26 | 44 | 52 | 52 | 91 | 61 | 61 | 14 |
| 11 | – | 9 | 51 | 100 | 44 | 67 | 60 | 24 | 40 | 49 | 51 | 93 | 60 | 63 | 13 |

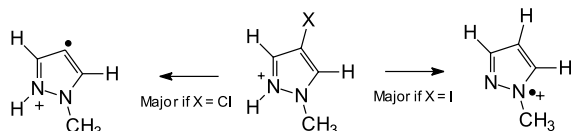
Losses of hydrogen(s) are not included.

the ions resulting from the protonation (methane CI)–dehalogenation sequence are collected in Table 2 together with the CA spectrum of the molecular ions of 1-methylpyrazole. It is clear from these spectra that the iodinated ion **9H⁺** furnishes mainly, if not exclusively, the conventional 1-methylpyrazole **11⁺** radical cation.

Some very significant differences appear in the CA spectrum of the $C_3H_4N_2^+$ radical cations generated by collisional dehalogenation of protonated 1-methyl-4-chloropyrazoles (**7H⁺**) and 1-methyl-4-bromopyrazoles (**8H⁺**) and by electron ionization of 1-methylpyrazole pointing out again the appearance of a new isomeric species again ascribed, if ring opening does not occur, to a distonic species as shown in Scheme 4. It is worth noting that an increased intensity of the loss of 15 Da was also detected in the CA spectrum of the $[M + H - NO_2]^+$ ion of 1-methyl-4-nitropyrazole [19].

3.3. Quantum chemical calculations

Ab initio calculations with the GAUSSIAN 98 series of programs [20] have been employed to derive some useful quantitative parameters for interpreting the experimental results. Geometries of the considered structures were optimized using density functional theory [21] with its popular hybrid functional B3LYP [22,23] in conjunction



Scheme 4.

with the 6-31G(d,p) basis set. The zero-point vibrational energies (ZPE) were estimated at this level. Geometries were then reoptimized making use of the larger 6-311++G(d,p) basis set including diffuse functions. Throughout this section, the relative energies mentioned were derived from, unless otherwise noted, (U)B3LYP/6-311++G(d,p) + ZPE calculations.

First of all, we have considered the proton affinities (PAs) of the parent pyrazole and various C-halogenopyrazoles at all five possible nitrogen and carbon protonation sites of the five-membered ring. The calculated results are recorded in Table 3. For pyrazole itself, the PA values point out that the dicoordinated nitrogen N_2 is by far the most basic center of pyrazole, in line with the information provided in [24,25]. The calculated PAs at N_2 for pyrazole itself (892 kJ mol⁻¹) and 4-chloropyrazole (867 kJ mol⁻¹) are in agreement with the experimental data presented in [26,27]. Halogen substitutions at positions C_3 , C_4 , C_5 do not, as expected, significantly modify the regioselectivity of the protonation.

The PAs of halogenopyrazoles at the nitrogen N_2 site are gradually reduced when going from iodo- (having the largest) to bromo-, chloro-, and to fluoro-pyrazoles (having the smallest). They are, however, still larger than those of other sites. Moreover, it is noted that the preferential ordering of the remaining sites turns out to be dependent on the position of halogen substitution. In other words, the PA has the largest value when the halogen is attached to the C_5 position, followed by the C_3 - and finally the C_4 -substitutions. Thus, in the chemical ionization experiments described above, regioselective protonation occurs at the doubly bonded nitrogen N_2 and that the obser-

Table 3

Proton affinities (at 0 K, kJ mol⁻¹) of various sites of pyrazole and halogenopyrazoles in different positions^a

| Compounds | Nitrogen 1 | Nitrogen 2 | Carbon 3 | Carbon 4 | Carbon 5 |
|-----------|----------------|------------|----------|----------|----------|
| Pyrazole | 748 | 892 | 758 | 797 | 763 |
| 3-fluoro | – | 855 | 678 | – | – |
| 3-chloro | 736 | 869 | 701 | 787 | 738 |
| 3-bromo | 741 | 875 | 720 | 791 | 742 |
| 3-iodo | 749 | 884 | 751 | 799 | 751 |
| 4-fluoro | – | 862 | – | – | – |
| 4-chloro | 733 | 867 | 751 | 748 | 764 |
| 4-bromo | 736 | 870 | 754 | 765 | 768 |
| 4-iodo | – ^b | 876 | – | – | – |
| 5-fluoro | – | 870 | – | – | – |
| 5-chloro | 735 | 876 | 739 | 795 | 717 |
| 5-bromo | 740 | 879 | 744 | 800 | 732 |
| 5-iodo | – | 887 | – | – | – |

^a At the B3LYP/6-311++G(d,p)+ZPE level of density functional theory.^b Not calculated.

vation of pyrazole radical cation formation in the MS/MS experiments is not ascribed to ring-carbon protonation.

Although the effect of substituents on the basicity of pyrazoles (N₂ protonation) has been discussed in detail [18, and references therein], other protonated cations exist and these also deserve mentioning. Due to the small number of points, at most four, only monoparametric equations could be tested. The substitution effects can be obtained from Table 3 by simply subtracting the value of the halogenopyrazole from that of pyrazole itself. We will note these effects as X_{nm}, *n* being the position of the substituent and *m* that of protonation. The most correlated parameter is Taft's σ_I [28] which signifies:

$$X_{52} = (26 \pm 2) - (131 \pm 3)\sigma_I, \quad (1)$$

4 points, $r^2 = 0.999$,

$$X_{33} = (216 \pm 19) - (571 \pm 42)\sigma_I, \quad (2)$$

4 points, $r^2 = 0.989$,

$$X_{34} = (97 \pm 6) - (146 \pm 13)\sigma_I, \quad (3)$$

3 points, $r^2 = 0.992$,

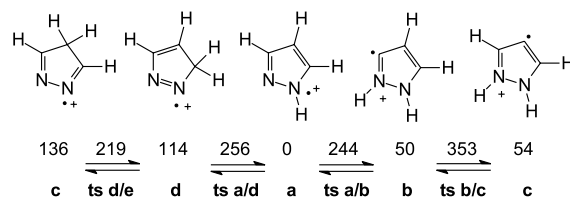
$$X_{35} = (50 \pm 4) - (160 \pm 10)\sigma_I, \quad (4)$$

3 points, $r^2 = 0.996$.

The slope of these equations reflects the sensitivity of the proton affinity (in kJ mol⁻¹) to the inductive effect of the halogen. Note that it is very

large for X₃₃, that is, when the substituent is on the position where the protonation takes place (the same happens for X₄₄ and X₅₅, but only two values were available). In most cases, a halogen substituent decreases the basicity of pyrazole, the only exceptions being X₃₄ and X₅₄, i.e., when the halogen is at positions 3 or 5 and the cation has the proton at C4.

Relative energies of pyrazole radical cation and its isomers together with those of the 1,2-H shift transition structures connecting them are given in Scheme 5 (values given in kJ mol⁻¹). The conventional ion **a** appears to be the most stable, but the distonic **b** and **c** are also found to be remarkably stable, lying only 50 and 54 kJ mol⁻¹, respectively, above **a**. Conversely, the energy barriers for their inter-conversion are rather large amounting to 244 and 353 kJ mol⁻¹ for the transition structures for 1,2-H shifts **a/b** and **b/c** (note that in neutral pyrazole the 1,2-H migration between both nitrogen atoms has a calculated barrier



Scheme 5.

of 200–215 kJ mol⁻¹ [29,30]). These results indicate that distonic species **b** and **c** should be stabilized and detectable species in the gas phase cells of a mass spectrometer. The other ion isomers **d** and **e** are markedly less stable and, lie about 114 and 136 kJ mol⁻¹ above **a**, respectively. They are unlikely to be involved in the CA spectra.

In order to get some insights into the experimental observations, we constructed a portion of the potential energy surface of N₂-protonated-3-halogenopyrazole (**P1**) related to the C–X bond cleavages. The results are summarized in Fig. 3. Interestingly, for each protonated form, two different channels for the halogen loss were identified, namely, a simple cleavage of the C–X bond of **P1**, a process which could be considered as a continuously endothermic fragmentation giving the distonic isomer **b**, and a pseudo-simple cleavage in which the dissociation of the C–X bond is preceded by a 1,2-hydrogen shift converting **P1** to C₃-protonated-3-halogenopyrazole (**P2**). The latter channel finally produces pyrazole radical cation **a**. It thus turns out to be clear that although the protonation takes place at the nitrogen N₂ site, the radical cations produced upon collision activation

could be both ions **a** and **b**. The ratio **a/b** is dependent on the internal energies of the sampled ions, i.e. on the nature of the leaving halogen. The product distribution for such a situation clearly needs to be evaluated using an RRKM type of treatment of the rate constants $k_i(E)$ which goes beyond the scope of the present study. It is confirmed that the C–I cleavage is the most facile process (cf. Fig. 3).

Finally, the adiabatic ionization energies (IE) of the parent pyrazole and its hydrogen-shift isomers were also theoretically estimated. The calculated IE of pyrazole (9.23 eV) compares well with the experimental value of 9.25 eV [17]. The IE of the carbene associated with ion **b** is significantly lower, IE = 7.67 eV, and it becomes even lower for the allene form associated with ion **c**, IE = 7.0 eV.

4. Concluding remarks

By using a combination of molecular orbital calculations and tandem mass spectrometry methods, it was shown that 3(5)-halogenopyrazoles and 4-halogenopyrazoles suffer regioselective protonation on the dicoordinated nitrogen in chemical ionization conditions. Collisional dehalogenation of the protonated halogenopyrazoles was shown to produce conventional pyrazole radical cations or distonic cyclic isomers depending on the nature of the halogen atoms via competitive C–X bond cleavages: a continuously endothermic C–X bond cleavage and a pseudo-simple cleavage where the dissociation of the C–X bond followed a hydrogen rearrangement reaction. Distonic (cyclic) isomers of ionized pyrazole were found theoretically less stable than ionized pyrazole itself but by only ca. 50 kJ mol⁻¹.

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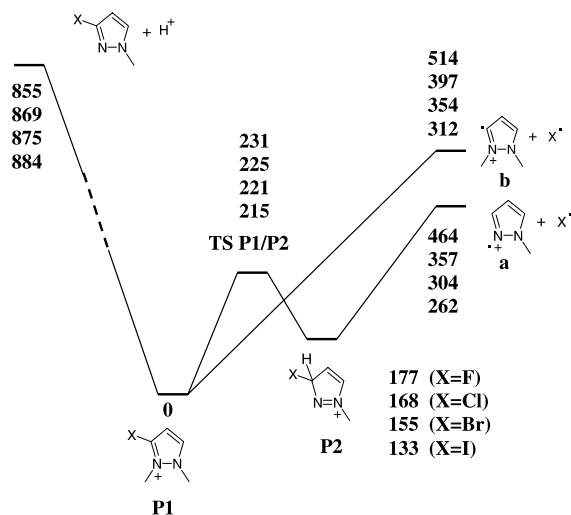


Fig. 3. Potential energy surface related to the dehalogenation of N₂-protonated 3-halogenopyrazoles. Values given in kJ mol⁻¹ obtained from B3LYP/6-311++G(d,p)+ZPE calculations. The entries are X = F (upper), X = Cl, X = Br and X = I (lower).

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