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Dissociation of a protonated secondary amine in the gas phase via an ion–neutral complex

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Dedicated to Jean Futrell, doughty pioneer of gas phase ion chemistry.

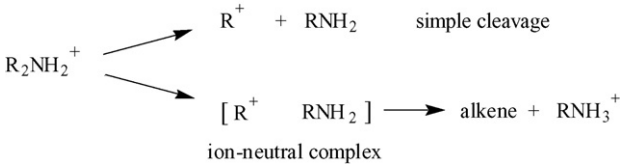
Abstract

Collisionally activated dissociation of conjugate acid ions of neopentyl isopropylamine (**1**) gives loss of a neutral C_5H_{10} molecule, MH^+–C_5H_{10}, as the predominant decomposition peak (≥70% of the total fragment ion abundance). Quantitative evaluation of the relative peak intensities from protonated **1** and its deuterated analogues permits an assessment of the contribution of hydrogen transfer from the CH_3 of the neopentyl group (γ-position) relative to the CH_2 (α-position), as well as the corresponding kinetic isotope effects. The ratio of γ-transfer to α-transfer from the neopentyl group is on the order of 5:1, implying that loss of 2-methyl-1-butene is preferred over loss of 2-methyl-2-butene, despite the fact that the latter C_5H_{10} isomer is >6 kJ mol^{-1} more stable than the former. An alternative interpretation of the γ-/α-transfer ratio would suppose that all 11 hydrogens in the neopentyl group randomize prior to dissociation. Measured differences between α- and γ-isotope effects argue against hydrogen randomization: the k_H/k_D for proton transfer from CH_2 versus CD_2 has a value close to unity, while the deuterium isotope effect for transfer from CH_3 versus CD_3 exhibits $k_H/k_D = 1.6$. Experimental results support a mechanism in which bond fission forms a [*tert*-amyl cation isopropylamine] ion–neutral complex, which then decomposes via proton transfer from the charged to the neutral partner.

Keywords: Isotope effect; Wagner–Meerwein rearrangement; MS/MS; Collisional activation; Ion trap; Alkene expulsion; Elimination

Mass spectrometrists have traditionally divided unimolecular ion decompositions into two general categories: simple cleavages versus rearrangements [1]. Rearrangements produce fragments that have atoms bonded to one another, which were not originally connected in the parent neutral. Rearrangement mechanisms may be further subdivided into two mechanistic classes: those in which bond-breaking precedes the formation of new bonds [2,3] versus those in which bond making comes before (or is concerted with) bond breaking. Fragmentations are known that are composites of both types of mechanism.

For acyclic parent ions, rearrangements initiated by bond breaking typically pass through ion–neutral complexes, in which two fragments are held together by electrostatic forces for a long enough duration that they can react further [4,5]. The motivation for the present investigation was to explore whether an ion–neutral complex intervenes in the collisionally activated dissociation of an amine conjugate acid ion, as Eq. (1) represents schematically. The experiments examine the decomposition of a protonated secondary amine to a protonated primary amine via alkene loss.



(1)

In the mechanism drawn in Eq. (1), bond fission leads to two competing outcomes: either simple cleavage to yield an alkyl cation (R^+, which may have a rearranged structure different from the alkyl group in the parent ion) or formation of an ion–neutral complex. Proton transfer from the alkyl cation to the neutral amine within the complex then produces a neutral alkene plus an ammonium ion. Despite many published studies of gaseous alkylammonium dissociations [6–10], experimental tests of such a pathway have been limited.

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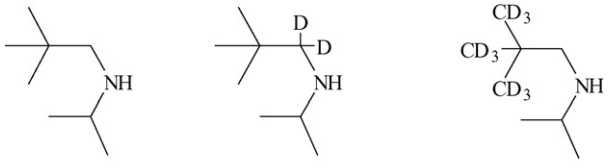
Metastable ion decompositions of *n*-propylammonium ion ($CH_3CH_2CH_2NH_3^+$) and its deuterated analogues exhibit hydrogen transfer from all the carbon positions to nitrogen when it expels propene to give ammonium ion (NH_4^+) [11]. The relative proportions are consistent with prior isomerization of the *n*-propyl to isopropyl, as intermediacy of an ion–neutral complex would predict. The data, however, do not explicitly rule out a dyotropic rearrangement (simultaneous interchange of the C–N bond with a vicinal C–H bond) of *n*-propylammonium to isopropylammonium. In principle, such a rearrangement could occur without necessarily passing through an ion–neutral complex. Even if the rearrangement pathway is assumed to proceed via an intermediate [iPr^+ NH_3] ion–neutral complex, the reported data do not tell whether the complex subsequently collapses to reform a C–N covalent bond in the course of dissociation.



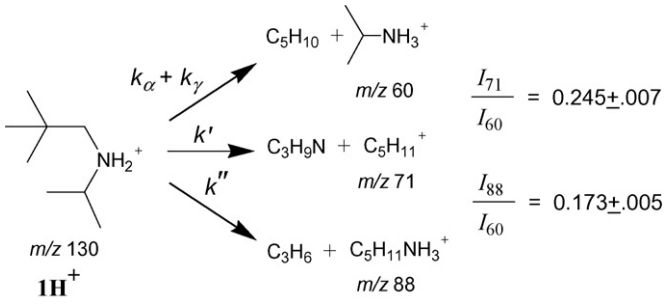
1 **2** **3**

This paper describes decomposition of a protonated secondary amine having two different alkyl groups attached to the nitrogen. The major pathway operates through a [R^+ NH_2R'] complex ($R \neq R'$), in which proton transfer subsequently takes place without reforming covalent bonds. The evidence consists of the collisionally activated dissociation (CAD) patterns of the conjugate acid ions of neopentyl isopropylamine (**1**) and its deuterated analogues **2** and **3**. Since the neopentyl group contains no hydrogens β to the nitrogen, alkene elimination cannot occur via a 4-center cyclic transition state. The neopentyl group isomerizes to a *tert*-amyl structure. Isotopic distributions of the fragment ions argue against a dyotropic rearrangement and support the general mechanism illustrated in Eq. (1).

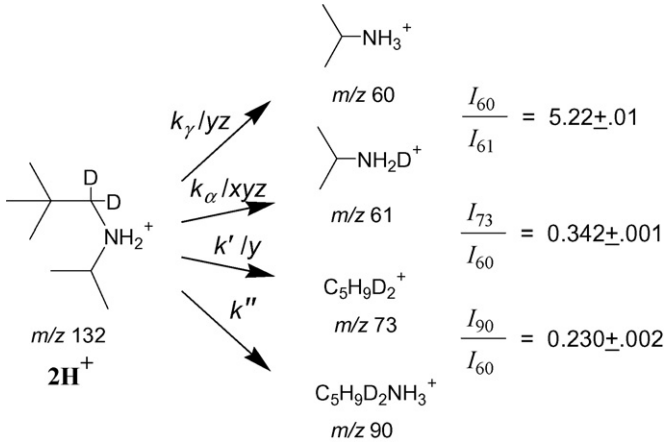
1. Experimental

Neopentyl isopropylamine (**1**) was prepared by reducing *N*-isopropylpivalamide with lithium aluminum hydride in refluxing THF. Dideuterated analogue **2** was prepared in the same fashion, using lithium aluminum deuteride instead. Nonadeuterated analogue **3** was synthesized by lithium aluminum hydride reduction of *N*-isopropylpivalamide-d_9, which, in turn, had been prepared from pivalic acid-d_9 [12]. Products were characterized by HPLC/MS on an orthogonal quadrupole/time-of-flight (QTof) instrument (QTof Ultra, Micromass Ltd., Altrincham, UK).

Solutions containing 10 μM amine in water were infused into standard electrospray sources. Resultant ions were then isolated, collisionally activated, and mass analyzed in separate experiments on two different instruments, an LTQ Linear Ion Trap Mass Spectrometer (Thermo Electron Corp., West Palm Beach, FL) and the QTof. Relative fragment ion intensities were the same in both mass spectrometers. The error bars for the LTQ



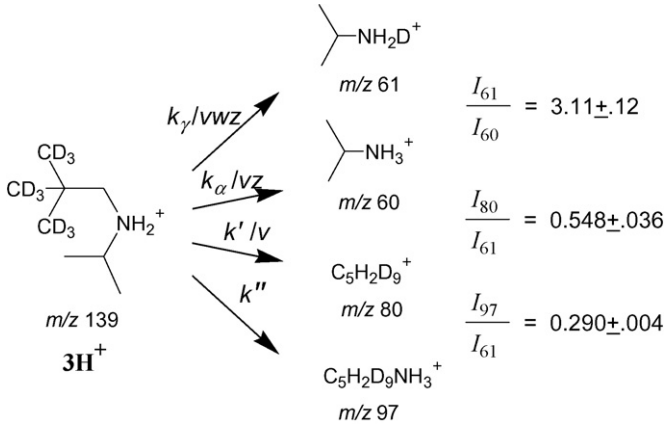
Scheme 1.



Scheme 2.

data were much smaller, and only those data are reported here in Schemes 1–3.

Source and ion transmission settings on the LTQ were optimized to maximize observation of protonated amines. Once isolated, ions were resonantly excited with a normalized collision energy setting of 30%, conditions under which undissociated parent ion represented only 8–12% of the total ionization. The collision gas was helium, maintained at a pressure of 0.1 Pa in the ion trap. Spectra obtained were averaged over 100 consecutive scans. Fragment ion intensities for each compound were measured on three separate occasions, and the reported ratios of peak intensities include 95% confidence limits, indicated as ±



Scheme 3.

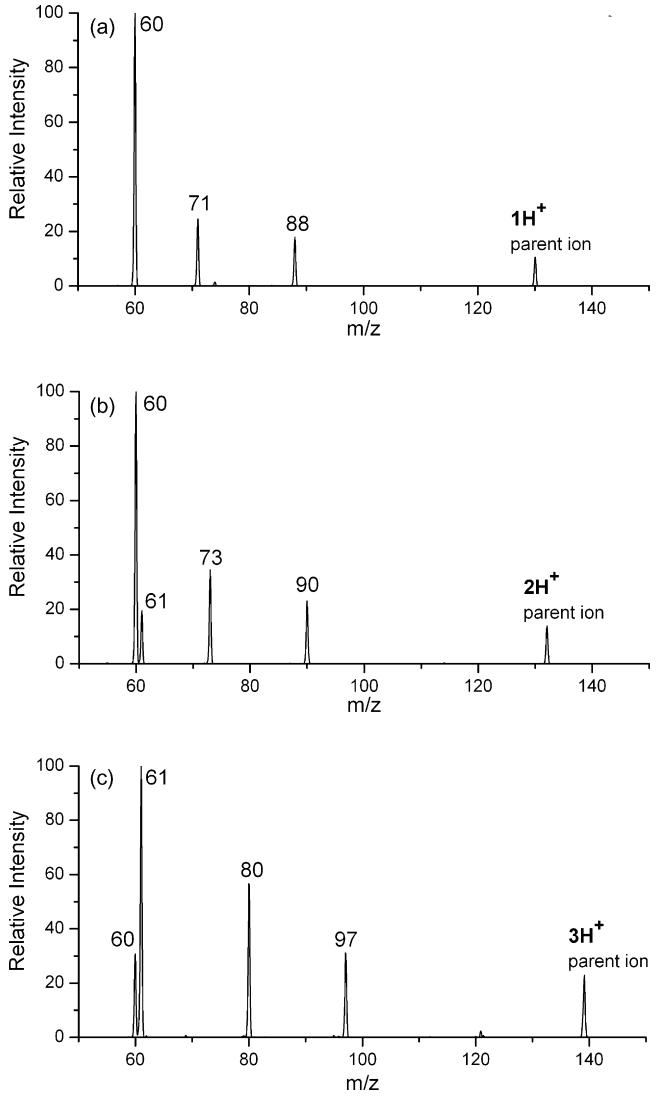


Fig. 1. Linear ion trap MS/MS spectra for collisionally activated dissociation of conjugate acid ions of neopentyl isopropylamine and its isotopic analogues: (a) undeuterated ion **1H$^+$**; (b), dideuterated ion **2H$^+$**, and (c), nonadeuterated ion **3H$^+$**.

values. In order to ascertain that excitation conditions were the same for different isotopic variants, *m/z* 130 and *m/z* 139 ions from a mixture of **1** and **3** were isolated and dissociated under identical conditions and found to give fragment ion ratios within experimental error of the ratios from separate samples.

2. Results

Protonated **1** (**1H$^+$**) exhibits only three fragment ions upon collisionally activated dissocation (CAD). In order of decreasing *m/z* the observed fragments correspond to propene loss (*m/z* 88), simple cleavage to give $C_5H_{11}^+$ (*m/z* 71), and loss of C_5H_{10} (*m/z* 60). The last of these, expulsion of a pentene isomer, represents the most intense peak in the CAD. Fig. 1 reproduces the CAD MS/MS spectra of **1H$^+$** and its deuterated analogues **2H$^+$** and **3H$^+$**.

Scheme 1 summarizes the identities of the dissociation products from **1H$^+$** and the intensity ratios of the fragment ions, I_{71}/I_{60} and I_{88}/I_{60}. The two pathways drawn schematically in Eq. (1), where the most stable carbocation R^+ forms, compete to yield the most abundant fragments, Simple cleavage to expel neutral isopropylamine gives *m/z* 71. As will be discussed below, the corresponding ion–neutral complex produces *m/z* 60 along with a mixture of C_5H_{10} alkenes that corresponds to the two 2-methylbutene isomers. Relative phenomenological rate constants can be extracted from the experimental data by considering the fragment ion intensity ratios from **1H$^+$** and its deuterated analogues. Scheme 2 summarizes the fragment ions observed for the conjugate acid ion of the dideuterated analogue **2**.

Deuteration of the neopentyl group leads to formation of two isotopic variants of the lightest CAD fragment. No interchange of deuterium takes place between the neopentyl and the isopropyl group or the NH hydrogens. Deuteron transfer from the α-position of the neopentyl group of **2H$^+$** gives monodeuterated isopropylammonium ion, *m/z* 61, while proton transfer from the γ-position gives *m/z* 60. If isotope effects be neglected, the intensity ratio of the unlabeled *m/z* 60 fragment peak to the *m/z* 61 fragment peak, 5.22, would correspond to the ratio of rate constants k_γ/k_α. Isotope effects, however, cannot be ignored.

In the competition between transfer from position α versus position γ of the neopentyl group, the combined primary and secondary isotope effects k_H/k_D for transfer from CD_2 in the α-position (represented as *x*) must be considered. Also, in the competition between simple cleavage and other decompositions, a secondary isotope effect k_{CH_2}/k_{CD_2} (represented as *y*) needs to be taken into account. If an ion–neutral complex intervenes, the bond fission that forms this intermediate is also subject to a secondary isotope effect, which is scaled by a factor *z* relative to the secondary isotope effect for simple cleavage. As will be summarized below, the measured isotope effects *x, y*, and *yz* are all found to have values within experimental error of unity.

Different isotope effects exert themselves in the decomposition of the protonated γ-d_9 amine **3H$^+$**. The combined primary and secondary isotope effects on proton transfer from a CD_3 in position γ of the neopentyl group is represented as $k_H/k_D = w$, and the secondary isotope effect on simple cleavage is represented as *v*. The same factor, *z*, is applied to this secondary isotope effect in scaling the bond fission that forms the ion–neutral complex relative to the simple cleavage.

3. Discussion

Examination of hydrogen transfer from neopentyl groups in radical cations served as a major piece of evidence, which demonstrated the intermediacy of ion–neutral complexes in unimolecular ion dissociations [12]. In that previous work, k_γ/k_α was assessed simply by multiplying two product ratios and taking the square root, because there were no competing reactions to serve as reference. In the present case, this estimate would correspond to $[(5.22)(3.11)]^{1/2} = 4.03 \pm .16$ (and the corresponding average deuterium isotope effect to $[(5.22)/(3.11)]^{1/2} = 1.30 \pm .05$, which agrees with previous values [12]), but here the fit to data can be improved. Propene

expulsion provides a reference reaction that is assumed to operate without an isotope effect.

Conditions under which unimolecular ion fragmentations can be treated using first-order kinetics have been discussed elsewhere [13]. Thermal activation of an ion in a linear trap takes place by means of many collisions, each of which changes the internal energy of the ion by a small increment. Such a regime looks very much like the Lindemann–Hinshelwood activation scheme [14] (unlike the regime of a single, highly energetic collision).

The lifetime of an ion–neutral complex, once formed, is much briefer than the interval between successive collisions. Where it has been possible to assess their duration, available evidence suggests that ion–neutral complexes from unimolecular dissociations live on the order of nanoseconds or less [2–5]. On this basis, the analysis in terms of competing first-order reactions represented by Schemes 1–3 appears justified.

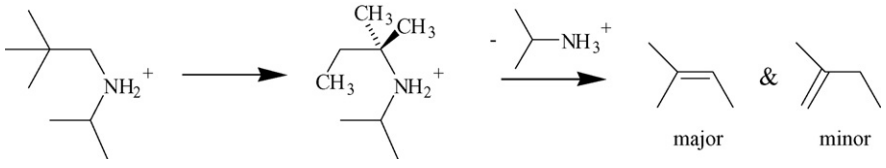
Taking advantage of the reactions that compete with formation of ion–neutral complexes, the following interpretation of Schemes 2 and 3 yields a more accurate phenomenological k_γ/k_α ratio: the I_{80}/I_{60} ratio from $\mathbf{3H}^+$ is equal to the product of I_{61}/I_{60} times I_{80}/I_{61}, which gives the value of $z(k'/k_\gamma)(k_\gamma/k_\alpha)$. The I_{73}/I_{60} ratio from $\mathbf{2H}^+$ gives $z(k'/k_\gamma)$. Dividing the I_{80}/I_{60} ratio from $\mathbf{3H}^+$ by the I_{73}/I_{60} ratio from $\mathbf{2H}^+$ gives $k_\gamma/k_\alpha = 4.98 \pm 0.38$. That k_γ/k_α value differs significantly (but not enormously) from the estimate made in the first paragraph of this section. Table 1 summarizes the relative rate constants extracted from Schemes 1–3.

Three features stand out from this data summary. First, the k_γ/k_α ratio is much larger than 1. If the dissociation had proceeded simply by isomerization of the neopentylammonium ion to a *tert*-amylammonium ion, as symbolized by Eq. (2), a very different outcome would have been obtained. RRKM calculations [15] predict that direct dissociation of ammonium ions should favor the thermodynamically more stable alkene. In that case, 2-methyl-2-butene (the product of hydrogen transfer from the α position) should have predominated, giving, contrary to fact, $k_\gamma/k_\alpha < 1$.

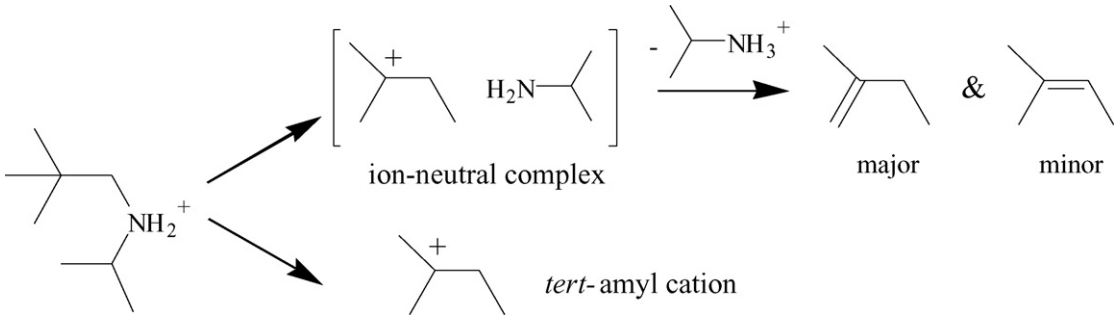
Table 1
Ratios of phenomenological first-order rate constants and kinetic isotope effects extracted from the experimental data summarized in Schemes 1–3, with 95% confidence intervals indicated by ± values

Symbol	Definition	Value
k_γ/k_α	Proton transfer from neopentyl CH_3 vs. CH_2 in $\mathbf{1H}^+$	4.98 ± .38
k'/k_γ	Simple cleavage vs. proton transfer from CH_3 in $\mathbf{1H}^+$	0.294 ± .024
k''/k_γ	Propene expulsion vs. proton transfer from CH_3 in $\mathbf{1H}^+$	0.208 ± .017
x	Isotope effect k_H/k_D on proton transfer from CH_2 vs. CD_2	1.0 ± .08
y	CH_2 secondary isotope effect for simple cleavage	0.95 ± .11
z	Scaling factor for secondary isotope effects (see text)	1.16 ± .10
w	Isotope effect k_H/k_D on proton transfer from CH_3 vs. CD_3	1.60 ± .14
v	CH_3 secondary isotope effect for simple cleavage	0.75 ± .11

The phenomenological rate constants agree more closely with Eq. (3), which exemplifies a pathway in which an ion–neutral complex, once formed, undergoes a proton transfer from the *tert*-amyl cation to the neutral amine. The neopentyl group of the precursor ion rearranges its skeleton to give a *tert*-amyl cation, a reaction that has been known for more than a century. It represents one of the simplest examples of a Wagner–Meerwein rearrangement. The experimental k_γ/k_α ratio, 4.98, has a value greater than the 2-methyl-1-butene:2-methyl-2-butene ratio inferred for the deprotonation of free, gaseous *tert*-amyl cation, 2.5 ± 1 [16], but it does not lie far from the simple ratio of γ to α hydrogens, 9:2. Does the observed k_γ/k_α ratio reflect complete scrambling of all hydrogens (a process that has been observed by NMR to have an activation barrier on the order of 90 kJ mol^{-1} for the free *tert*-amyl cation in solution [17])?



(2)



(3)

The second striking feature of the tabulated data is the difference between the two isotope effects represented by x and w in Table 1, which addresses the question of whether the neopentyl hydrogens randomize completely. The measured isotope effects argue against hydrogen scrambling. If hydrogens did randomize, k_γ/k_α would not correspond to the 2-methyl-1-butene:2-methyl-2-butene ratio and the net isotope effects for α and γ transfer in Table 1 should have been identical. However, the isotope effect for transfer from the α-position (x) does not differ significantly from unity, while the isotope effect for transfer from the γ-position has a value of $w = 1.6$. Hence, it is likely that hydrogen does not transpose between positions α and γ and that k_γ/k_α does indeed reflect the 2-methyl-1-butene:2-methyl-2-butene ratio from the unimolecular decomposition of **1H**$^+$.

Preference for the thermodynamically less stable alkene results from a combination of statistical and steric effects, which has ample precedent. Neutral product studies have measured isomer distributions from bimolecular deprotonations of gaseous tertiary carbocations by tertiary amines [15,16,18,19]. When the amine is small (e.g. trimethylamine) the ratio of alkene isomers simply reflects the ratio of acidic methyl hydrogens to acidic methylene hydrogens. In the case of the *tert*-amyl cation (Eq. (3)), that ratio is 6:2 (or 3:1).

As the amine becomes bulkier (e.g. triethylamine) the preference for deprotonating the methyl increases. This is taken to reflect the greater steric accessibility of CH_3 relative to CH_2. By analogy to the bimolecular reaction, deprotonation of *tert*-amyl cation by isopropylamine within an ion–neutral complex would be expected to yield a >3:1 ratio of 2-methyl-1-butene:2-methyl-2-butene, in agreement with the experimental value of k_γ/k_α.

The third striking feature of the results summarized in Table 1 is the magnitude of the secondary isotope effect v. This inverse isotope effect means that deuterating the methyl groups increases the rate with which methyl migration occurs to isomerize the neopentyl to produce free *tert*-amyl cation. The corresponding isotope effect on the isomerization to form *tert*-amyl cation in an ion–neutral complex has the value vz, which corresponds to a secondary isotope effect $k_H/k_D = 0.87 \pm 0.15$. That value is to be compared with the isotope effects reported in the solvolysis of neopentyl tosylates [20], where deuterating the non-migrating methyl groups exerts an inverse isotope effect, which opposes the normal isotope effect from deuterating the itinerant methyl. The position of the transition state for the gas phase dissociation in Eq. (3) should be different from that of the transition state for solvolysis; hence, the balance between the normal isotope effect of the migrating methyl and the inverse effect of the other two CD_3 groups should be perturbed. That is to say, an inverse secondary isotope effect is not inconsistent with previously reported data from solution.

As a final comment, the competition represented by Eq. (1) warrants consideration as a general mechanism for elimination from protonated gaseous amines. Naively, one might expect that the corresponding simple cleavage ought to accompany every alkene expulsion. Why, then, is isopropyl cation (m/z 43) not seen in competition with propene loss (m/z 88) in Scheme 1?

Thermochemical considerations play a role here. The 300 K enthalpy difference between the two most abundant pathways in Scheme 1 – elimination to give 2-methyl-1-butene versus simple cleavage to give m/z 71 – is $\Delta\Delta H = 108\ \mathrm{kJ\ mol^{-1}}$ (the proton affinity difference between isopropylamine and 2-methyl-1-butene [21]) in favor of the former reaction. By contrast, the enthalpy difference between propene expulsion and simple cleavage to give isopropyl cation is $\Delta\Delta H = 177\ \mathrm{kJ\ mol^{-1}}$ (the proton affinity difference between neopentylamine and propene [21]). This large difference in endothermicities renders the simple cleavage to give $C_3H_7^+$ energetically inaccessible under the collisionally activated dissociation conditions used in the present experiments.

4. Conclusions

The eight measured fragment ion abundance ratios from CAD of the three conjugate acid ions **1H**$^+$–**3H**$^+$ permit an assessment of relative proportions of hydrogen transfer from the α and γ positions of the neopentyl group as well as five deuterium isotope effects. Transfer from the γ position greatly predominates over all other pathways. Isotope effects indicate that this preponderance does not result from hydrogen randomization but instead reflects that expulsion of 2-methyl-1-butene is preferred by nearly a factor of 5 over expulsion of the thermodynamically more stable 2-methyl-2-butene.

Preference for loss of the thermodynamically less favored alkene contradicts expectation based on elimination from a covalently bound parent ion (Eq. (2)), but is consistent with previous reports for deprotonation of *tert*-amyl cation by amines [15,16]. On that basis, the ion–neutral complex mechanism (Eq. (3)) passes yet another test of validity.

Acknowledgments

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