ORGANIC MASS SPECTROMETRY, VOL. 26, 1097–1108 (1991)

Alkene Loss from Metastable Methyleneimmonium Ions: Unusual Inverse Secondary Isotope Effect in Ion–Neutral Complex Intermediate Fragmentations

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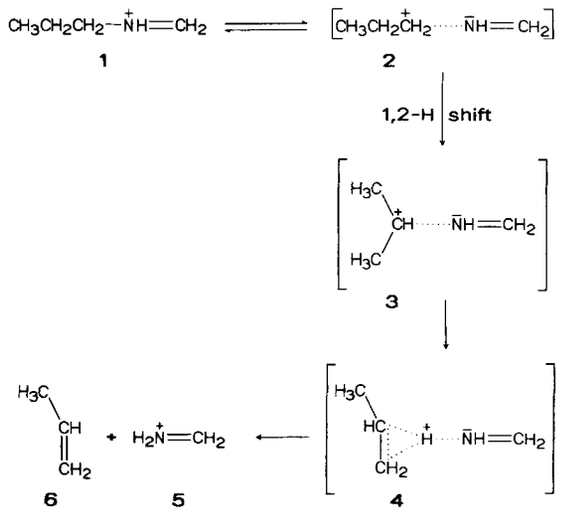
The mechanism of propene elimination from metastable methyleneimmonium ions is discussed. The first field-free region fragmentations of complete sets of isotopically labelled methyleneimmonium ions ($H_2C{=}\overset{+}{N}HR^1R^2$: $R^1 = R^2 = n\text{-}C_3H_7$; $R^1 = R^2 = i\text{-}C_3H_7$; $R^1 = n\text{-}C_3H_7$; $R^2 = C_2H_5$; $R^1 = n\text{-}C_3H_7$; $R^2 = CH_3$; $R^1 = n\text{-}C_3H_7$; $R^2 = H$) were used to support the mechanism presented. The relative amounts of H/D transferred are quantitatively correlated to two distinct mathematical concepts which allow information to be deduced about influences on reaction pathways that cannot be measured directly. Propene loss from the ions examined proceeds via ion–neutral complex intermediates. For the di-*n*-propyl species rate-determining and H/D distribution-determining steps are clearly distinct. Whereas the former corresponds to a 1,2-hydride shift in a 1-propyl cation coordinated to an imine moiety, the latter is equivalent to a proton transfer to the imine occurring from the 2-propyl cation generated by the previous step. For the diisopropyl-substituted ions which directly form the 2-propyl cation-containing complex, the rate-determining hydride shift vanishes. The 2-propyl cation-containing complex can decompose directly or via an intermediate proton-bridged complex. Competition of these routes is not excluded by the experimental results. Assuming a 2:1:3 distribution, a preference for the α- and β-methylene of the initial *n*-propyl chain as the source of the hydrogen transferred is detected for *n*-propylimmonium ions containing a second alkyl chain R^2. This preference shows a clear dependence on the steric influence of R^2. During the transfer step isotopic substitution is found to affect the H/D distribution strongly. For the alternative route of McLafferty rearrangement leading to C_2H_4 loss, specific γ-H transfer is observed.

INTRODUCTION

The existence of ion–neutral complexes as intermediates in unimolecular reactions of isolated organic ions has been demonstrated in a considerable number of papers during the last decade.[1] For the loss of ethene from *N*-ethylmethyleneimmonium ions, Bowen *et al.*[2] proposed ion–neutral complex intermediates in the fragmentation of immonium ions for the first time. Soon after, the elimination of propene (**6**) from metastable *N*-propylmethyleneimmonium ions (**1**), was interpreted in terms of a mechanism involving ion–neutral complexes (**2**, **3**, **4**), consisting of a propyl cation and methyleneimine (Scheme 1).[3]

Further investigations[4–6] revealed that this type of alkene loss, named 'onium reaction' neither involves competing transition states of different ring size, leading all to the same products,[7] nor proceeds via a single four-membered ring transition state of a concerted reaction[8] as assumed in earlier studies. The name 'onium reaction' characterizes the type of reaction, not the mechanism because this reaction is also widespread among other onium ions (oxonium, sulphonium, phosphonium). The onium reaction results in elimination of an alkene having the same number of carbon atoms as R^1, and therefore it occurs if R^1 is C_nH_{2n+1}, $n \geqslant 2$. A second process proceeds with the expulsion of an alkene, having one less carbon than R^1, e.g. the elimination of C_2H_4 from *N*-*n*-propylmethyleneimmonium ions. Evidence was presented which shows that this reaction (related to the McLafferty rearrangement) is best explained using a two-step



Scheme 1

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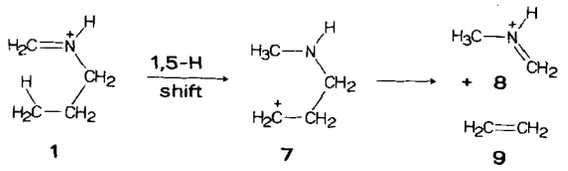
Received 15 May 1991
Revised manuscript received 30 July 1991
Accepted 9 August 1991



Scheme 2

mechanism as represented in Scheme 2.[9] After a 1,5-hydride shift leading to a primary carbocation, the alkene is expelled.

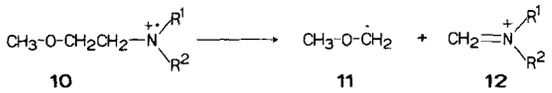
Bowen[3] discussed the unimolecular reactions of isomeric propylmethyleneimmonium ions (**1**) mainly in terms of a potential energy approach. Isotope effects were assumed to be slight and just of the magnitude to rationalize the difference between the values measured and the distribution postulated.

In order to probe the mechanism more deeply, we report and discuss here the decompositions of deuterium-labelled analogues of *n*-propyl- and isopropyl-substituted methyleneimmonium ions.

RESULTS AND DISCUSSION

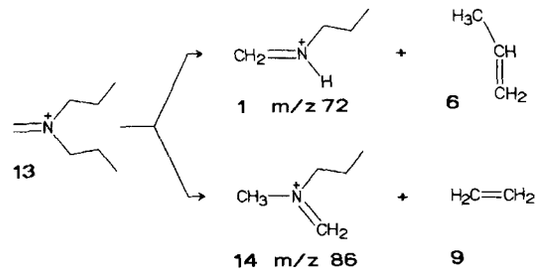
All di-*n*-propylmethyleneimmonium ions were generated directly in the ion source by α-cleavage from deuterium-labelled *N*-(2-methoxy-ethyl)-di-*n*-propylamines (Scheme 3). The di-*n*-propylmethyleneimmonium ions examined are summarized in Fig. 1.

According to the *n*-propyl groups of **13**, both, the cleavage of the N—C(α) bond, resulting in propene loss (onium reaction) and ethene loss (McLafferty rearrangement), leading to ions **1** and **14**, respectively, are observed in metastable dissociation (Scheme 4). The metastable ion (MI) spectrum of ion **13γ-*d*$_3$** (*m/z* 117) is shown in Fig. 2. The peaks at *m/z* 87 and 89 are due to ethene loss from the deuterium-labelled and the unlabelled propyl group, respectively. Note that there is



a) $R^1 = R^2 = n\text{-}C_3H_7$
b) $R^1 = R^2 = i\text{-}C_3H_7$
c) $R^1 = n\text{-}C_3H_7$, $R^2 = C_2H_5$
d) $R^1 = n\text{-}C_3H_7$, $R^2 = CH_3$
e) $R^1 = n\text{-}C_3H_7$, $R^2 = H$

Scheme 3



Scheme 4

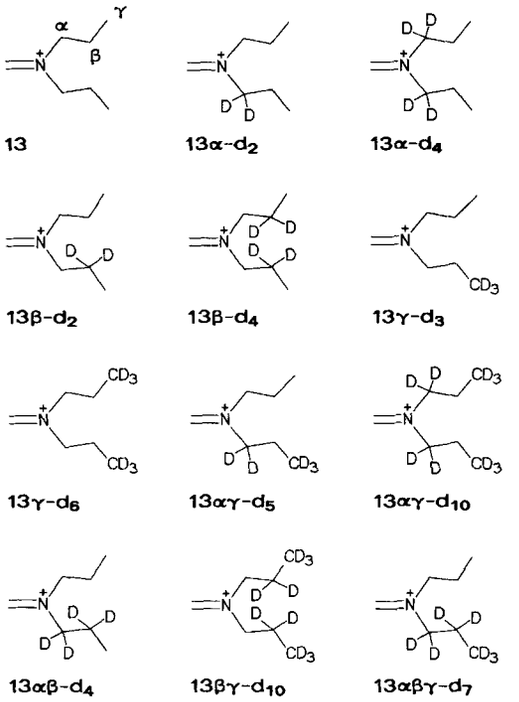


Figure 1. Di-*n*-propylmethyleneimmonium ions examined.

no α- or β-H transfer from the labelled propyl group which would lead to another peak at *m/z* 86. Instead, absolute γ-specificity, i.e. specificity for D-transfer from the γ-position, is observed. This specificity of the McLafferty rearrangement has been proved throughout the ions examined. Consequently, diisopropylmethyleneimmonium ions (**15**) exclusively show propene loss by onium reaction.

In contrast to the McLafferty rearrangement, the onium reaction is accompanied by transfer of protons originating from all positions of the propyl group. The relative abundances of $C_3H_{6-n}D_n$ expelled from di-*n*-propylmethyleneimmonium ions are given in Table 1. From the relative intensities of the metastable peaks, the ratio of H/D transferred can be calculated:

$$\frac{H}{D} = \frac{[m_1^+ - C_3H_{6-(n+1)}D_{n+1}]}{[m_1^+ - C_3H_{6-n}D_n]} \qquad (1)$$

For example **13γ-*d*$_3$** eliminates $C_3H_3D_3$ if α- or β-H is transferred and $C_3H_4D_2$ if γ-D is transferred from the labelled propyl chain, yielding *m/z* 72 and 73, respectively (Fig. 2). Thus, from Table 1, H/D = [72]/[73] = 31.4/15.4 = 2.04. As far as ions labelled symmetrically in both propyl groups are concerned (**13α-*d*$_4$**, **13β-*d*$_4$**, **13γ-*d*$_6$**, **13αγ-*d*$_{10}$** and **13βγ-*d*$_{10}$**), within experimental error the same H/D ratios as for the unsymmetrically labelled ions, i.e. having deuteriums in only one group (**13α-*d*$_2$**, **13β-*d*$_2$**, **13γ-*d*$_3$**, **13αγ-*d*$_5$**, **13βγ-*d*$_5$** and **13αβγ-*d*$_7$**) have been detected (Table 1).

Rate-determining step of propene loss

For unsymmetrically labelled ions the relative abundances of the competing propene losses from the

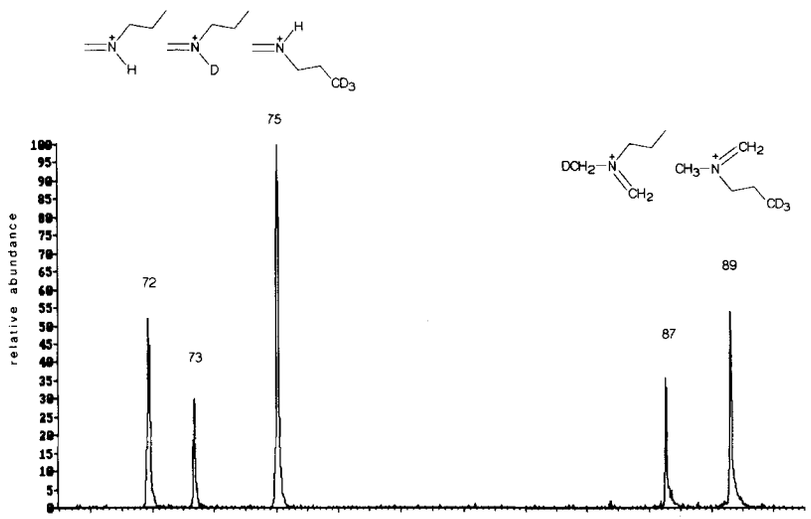


Figure 2. MI spectrum of **13γ-d_3** (70 eV, *B/E* linked scan). Ion current normalized to the most intense peak in the spectrum. Peaks and ion structures on the left correspond to onium reaction, peaks and ion structures on the right to the McLafferty-analogous fragmentation.

unlabelled and the labelled group, respectively, (Table 1) can be used to calculate the ratio r as defined by the equation

$$r = \frac{[m_1^+ - C_3H_6]}{[m_1^+ - C_3H_{6-n}D_n] + [m_1^+ - C_3H_{6-(n+1)}D_{n+1}]} \quad (2)$$

Again for **13γ-d_3**, Eqn (2) gives $r = 53.2/(15.4 + 31.4) = 1.13$ (70 eV MI). The ratio r provides valuable information on the rate-determining step of the onium reaction because it offers the possibility of determining intramolecular isotope effects. As can be seen from Table 1, immonium ions labelled in the β-position exhibit the largest ratios r, i.e. a deuterium located at the β-position of the propyl group undoubtedly causes the most significant retardation of the onium reaction.

Lowering the ionization energy from 70 to 15 eV leads to a decrease in r. At 15 eV the ratios r corresponding to ions with a deuterium label in the β-position range from 1.42 to 1.45 and still exceed those of the ions without any β-label (cf. Table 1). Hence the assumption that the β-hydrogens are involved in the rate-determining step of propene loss[3] has become proof. It is obvious that r corresponds to some isotope effect on this step. It may be concluded that the 1,2-hydride shift (Scheme 1) is the step of the reaction which is affected by the observed isotope effect. This isotope effect will be called the total isotope effect I_t and therefore $I_t = r$.

Table 1. Relative abundances for propene loss from di-*n*-propylmethyleneimmonium ions examined at 70 and 15 eV by *B/E* linked scan

		Propene loss (%)[b]								
Ion structure	(eV)	C_3H_6	C_3H_5D	$C_3H_4D_2$	$C_3H_3D_3$	$C_3H_2D_4$	C_3HD_5	C_3D_6	H/D[c]	r[d]
13α-d_2	70	57.8	11.6	30.6					2.64 ± 0.15	1.37 ± 0.10
	15	51.2	14.3	34.5					2.41 ± 0.21	1.05 ± 0.04
13α-d_4	70		28.2	71.8					2.55 ± 0.16	
13β-d_2	70	65.5	3.9	30.6					7.85 ± 0.85	1.90 ± 0.10
	15	58.9	5.3	35.8					6.75 ± 0.90	1.43 ± 0.09
13β-d_4	70		12.5	87.5					7.00 ± 0.88	
13γ-d_3	70	53.2		15.4	31.4				2.04 ● 0.12	1.13 ± 0.05
	15	52.1		15.1	32.8				2.17 ± 0.13	1.09 ± 0.06
13γ-d_6	70			32.2	67.8				2.10 ± 0.12	
13αγ-d_5	70	61.4				31.0	7.6		0.25 ± 0.03	1.59 ± 0.11
	15	53				37.5	9.5		0.25 ± 0.03	1.13 ± 0.10
13αγ-d_{10}	70					82.3	17.7		0.22 ± 0.02	
13αβ-d_4	70	68.2			15.7	16.1			1.03 ± 0.08	2.15 ± 0.20
	15	58.7			20.9	20.4			0.98 ± 0.09	1.42 ± 0.10
13βγ-d_{10}	70					60.9	39.1		0.64 ± 0.04	
	15					62.5	37.5		0.60 ± 0.05	
13αβγ-d_7	70	66.2						33.8		1.96 ± 0.10
	15	59.2						40.8		1.45 ± 0.13

[a] For ion structures, see Fig. 1.
[b] Relative abundances are normalized to the sum of the ion current corresponding to the onium reaction.
[c] H/D ratios as calculated from Eqn (1).
[d] Ratio r as calculated from Eqn (2). The errors quoted correspond to one standard deviation.

Usually, isotope effects increase with decreasing internal energy of the reacting species, since the differences in zero-point energy will be more important for reactions occurring near the threshold.[10a, c] Moreover, only the lowest critical energy processes give rise to metastable peaks and thus isotope effects are frequently encountered in metastable ion studies.[11] Therefore, a high-energy process competing with the low-energy loss of propene seems not to explain the observed variation of I_t. This assumption is supported by the fact that the characteristic distribution of H/D in the daughter ions is not affected by changing the ionization energy.

The unusual change of r may be explained by subsequent alkene eliminations[10a] at 70 eV from **1** that is formed by propene loss from **13**. Isotope effects on these subsequent decompositions cause the population of the unlabelled ion **1** to deplete more rapidly than that of its labelled isotopomer.

It should be mentioned that the results obtained by B/E = constant linked scan are comparable to other investigations made using mass-analysed ion kinetic energy spectrometry (MIKES). This was ensured by comparison of the ratios r measured from **13-d_7**. At 70 eV the linked scan yielded $r = 1.96$ whereas MIKES yielded $r = 1.92$, i.e. isotope effects on kinetic energy release accompanying propene loss do not influence the measurements by B/E = constant linked scan. As a consequence of the explanation for the variation of I_t given above, I_t will be overestimated from 70 eV measurements. At 15 eV, the secondary fragmentations mentioned are negligible and the results obtained from MI spectra are no longer distorted by subsequent decompositions. Therefore, the mechanistic discussion will only be based on the I_t values derived from the 15 eV spectra.

Any effect rising from isotopic substitution will be called an isotope effect. Isotope effects as detected by mass spectrometry are isotope effects upon relative abundances A of ions.[10a] They give a direct measure of kinetic hydrogen isotope effects k_H/k_D only if the dependences on the internal energy E of the rate constants $k_H(E)$ and $k_D(E)$ are equal, i.e. $k_H(E)/k_D(E)$ = constant. Especially for low-energy metastable species $A_H/A_D \approx k_H/k_D$ is a valid approximation. An isotope effect is said to be primary if the isotopic bond itself is broken or formed and secondary if it is caused by influences of isotopic substitution at any other position.[10a–c] Secondary isotope effects are usually given as isotope effect per D atom.[12]

The overall I_t observed should consist of a primary kinetic isotope effect I_{tprim} that belongs directly to the hydride shift and of contributions from secondary isotope effects; I_{tprim} is directly obtained from the ratio r as measured for **13β-d_2** ($r = 1.42$). In the strict sense, α-, β- and γ-positions could exhibit different secondary isotope effects; however, their difference should be negligible. Assuming one common secondary isotope effect I_{tsec} for the three positions, I_{tsec} may be calculated from the ions unlabelled in the β-position using the equation

$$I_{tsec} = \sqrt[n_D]{I_t} \qquad (3)$$

where I_{tsec} = isotope effect per deuterium and n_D = number of deuteriums contained in the propyl group. For $I_{tsec} = 1.025$, the calculated I_t fits the experimental I_t most satisfactorily (Table 2). Thus, I_t has been resolved into $I_{tprim} = 1.4$ and $I_{tsec} = 1.025$.

Table 2. Comparison of experimental and calculated total isotope effect I_t (Eqn (3))

Ion structure[a]	I_t Experimental	I_t Calculated from Eqn 3
13α-d_2	1.05	1.05
13γ-d_3	1.09	1.08
13αγ-d_5	1.13	1.13

[a] For ion structures, see Fig. 1.

Mathematical deconvolution of the H/D distribution-determining step

The H/D ratios listed in Table 1 can be used to determine the contribution to the proton transfer of each position along the propyl group. It should be mentioned that in contrast to r these H/D ratios do not change within experimental error on lowering the ionization energy from 70 to 15 eV.

It is apparent from the results that a fragmentation pathway passing through a four-membered cyclic transition state of a concerted[8] or even stepwise reaction can be excluded because 100% β-specificity should be found in this case.

The observed H/D ratios are not consistent with the statistical ratios for H/D transfer from the original α-, β- or γ-position of the leaving propyl moiety. Both complete scrambling prior to fragmentation and random selection of positional origin of the proton transferred demand a distribution of 2:2:3 = 0.286:0.286:0.429 (CH_2—CH_2—CH_3). Table 3 supports the experimental values and the ratios expected from different mechanistic assumptions and from the resulting mathematical descriptions. The results of Levsen and McLafferty[13] are important arguments against scrambling of any kind. They found a high stability of seven immonium ion structures with respect to scrambling. A tendency for hydrogen and skeletal isomerizations was not detected. Further evidence for immonium ion stability was presented by Ucella *et al.*,[14] who observed exclusively the loss of C_2H_4 from $CH_3CH_2NH{=}CD_2$. Our results with Et(Pr)$\dot{N}$H=CD_2 (**17-d_2**, m/z 102; cf. Fig. 7) reveal that exclusively C_3H_6 is lost by an onium reac-

Table 3. Experimental H/D ratios calculated from different mechanistic assumptions

Ion structure[a]	H/D ratios Experimental	Calculated Statistical (2:2:3)	Statistical (2:1:3)	From Eqns (8a–f)	From Eqns (12a–f)
13α-d_2	2.57	2.50	2.00	2.74	2.74
13β-d_2	7.20	2.50	5.00	7.22	7.18
13γ-d_3	2.11	1.33	1.00	1.95	1.96
13αγ-d_5	0.24	0.40	0.20	0.25	0.26
13αβ-d_4	1.00	0.75	1.00	0.94	0.94
13βγ-d_{10}	0.62	0.40	0.50	0.67	0.67

[a] For ion structures, see Fig. 1.

tion to yield m/z 60. Involvement of the double-bonded methylene can therefore be excluded.

We shall adopt these results as basic assumptions for the discussion of the H/D distribution-determining step of the onium reaction. Only the leaving propyl group (R^1) and the nitrogen connected to it participate directly in the expulsion of propene. Other substituents (R^2) will only exhibit steric effects or they will influence the behaviour of the whole immonium ion, for example, by offering competing fragmentation pathways.

If the mechanism postulated by Bowen[3] (Scheme 1) is correct, a H/D distribution of $2:1:3 = \alpha:\beta:\gamma$ is expected for the proton transfer from the methyl groups of the 2-propyl cation which was previously generated by 1,2-hydride shift from the *n*-propyl precursor. Indeed, the distribution resembles more 2:1:3 than 2:2:3, but coincidence is not achieved (Table 3).

One method to treat the data from labelling studies is to calculate the isotope effect and the contribution of a certain position to the sum of transfer from complementary labelled pairs of ions.[15,16] We can combine three such pairs from the ions prepared and examined: (i) **13α-d_2/13βγ-d_{10}**, (ii) **13β-d_2/13αγ-d_5** and (iii) **13γ-d_3/13αβ-d_4**. Let the partition of the position labelled in the first ion be x, then the partition of the positions labelled in the second ion becomes $1 - x$. Let any occurring isotope effect be expressed by I, then the expression for the metastable ratio of the first ion is given by

$$\left(\frac{H}{D}\right)_1 = \frac{I(1-x)}{x} \tag{4}$$

and that of the complementary second ion by

$$\left(\frac{H}{D}\right)_2 = \frac{Ix}{(1-x)} \tag{5}$$

Solution of the simultaneous equations gives values for x and I:

$$I = \left(\left(\frac{H}{D}\right)_1\left(\frac{H}{D}\right)_2\right)^{1/2} \tag{6}$$

$$x = \frac{1}{1 + \left(\left(\frac{H}{D}\right)_1 \Big/ \left(\frac{H}{D}\right)_2\right)^{1/2}} \tag{7}$$

For a single pair of ions there will always be a solution of the equations. For the pairs mentioned above we obtain (i) $I = 1.25$, $x_\alpha = 0.331$, (ii) $I = 1.31$, $x_\beta = 0.154$ and (iii) $I = 1.45$, $x_\gamma = 0.407$. It is striking that each pair yields an isotope effect of its own and it is even more suspicious that the sum $x_\alpha + x_\beta + x_\gamma$ is 0.892 rather than 1.00. Consequently, a solution is required not only for pairs of complementary labelled ions but for the system of all combinations of labelling in its entirety.

This can be achieved by constructing a general equation to describe the H/D ratios. Let the partition of any unlabelled position i of the propyl group be x_{Hi} and the partition of any labelled position j be x_{Dj}. The ratio H/D is then equal to the sum of all x_{Hi} divided by the sum of all x_{Dj}. Usually H will react faster than D. Therefore, all positions without a deuterium label will have this advantage over the labelled positions. In order to distinguish the isotope effects of the rate-determining step (I_{tprim} and I_{tsec}) from those of this H/D distribution-determining step, we denote them I_d and I_{dsec}. I_d refers to the primary hydrogen isotope effect that accompanies bond fission of the proton which is to be transferred from one of the propyl carbons to the nitrogen. I_{dsec} is introduced to compensate for any secondary isotope effects during the transfer step. Thus, we obtain the general equation

$$\frac{H}{D} = \frac{I_d\, I_{dsec}{}^{nD} \sum_i^i x_{Hi}}{\sum_j x_{Dj}} \tag{8}$$

Application to the six combinations of labelling available explicitly leads to

$$\textbf{13α-}d_2: \quad \frac{H}{D} = \frac{I_d\, I_{dsec}{}^{nD}(x_\beta + x_\gamma)}{x_\alpha} = 2.57 \tag{8a}$$

$$\textbf{13β-}d_2: \quad \frac{H}{D} = \frac{I_d\, I_{dsec}{}^{nD}(x_\alpha + x_\gamma)}{x_\beta} = 7.20 \tag{8b}$$

$$\textbf{13γ-}d_3: \quad \frac{H}{D} = \frac{I_d\, I_{dsec}{}^{nD}(x_\alpha + x_\beta)}{x_\gamma} = 2.11 \tag{8c}$$

$$\textbf{13αγ-}d_5: \quad \frac{H}{D} = \frac{I_d\, I_{dsec}{}^{nD} x_\beta}{(x_\alpha + x_\gamma)} = 0.24 \tag{8d}$$

$$\textbf{13αβ-}d_4: \quad \frac{H}{D} = \frac{I_d\, I_{dsec}{}^{nD} x_\gamma}{(x_\alpha + x_\beta)} = 1.00 \tag{8e}$$

$$\textbf{13βγ-}d_{10}: \quad \frac{H}{D} = \frac{I_d\, I_{dsec}{}^{nD} x_\alpha}{(x_\beta + x_\gamma)} = 0.62 \tag{8f}$$

In addition, the equation

$$x_\alpha + x_\beta + x_\gamma = 1.00 \tag{9}$$

will be needed. A solution for the simultaneous Eqns (8a–f) and (9) is easiest found by a numerical method because there will be no exact solution. Every H/D ratio bears some percentage error and instead of one solution there is a small region of best coincidence of calculation and experiment. The degree of coincidence might be measured using a factor of correlation C defined as the ratio of calculated to experimental H/D with $C = 1.00$ as best fit. A BASIC program was run on a microcomputer to do this fuzzy work and a correlation of $C = 1.07$ was obtained as an optimum, thus reflecting the order of experimental error (cf. Table 3). At this correlation we obtain $x_\alpha = 0.382$, $x_\beta = 0.190$, $x_\gamma = 0.428$, $I_d = 2.28$ and $I_{dsec} = 0.86$. The order of magnitude of $I_{dsec} = 0.86$ per D atom is most astonishing because this would represent an unusually large inverse secondary isotope effect.

At this stage of reasoning we should remember that Eqn (8) does not imply any conception of a mechanism, but merely represents a well working mathematical description of experimental H/D ratios. It offers values for the contribution of each position along the alkyl chain to the reaction, and yields isotope effects that cannot be measured directly but only mathematically

deconvoluted from experimental H/D ratios because the proton transfer lies after the rate-determining step.

The approach of using seven simultaneous equations to describe the experiment should be easily applied to the mechanistic model of Bowen.[3] They assume the hydrogen to be transferred solely from the methyl groups of the 2-propyl cation. According to the geometry of complex **3** and its origin by hydride shift from **2** an appropriate general equation can be set up as follows: the relative partitions are determined by the number of H atoms (n_H) of D atoms (n_D) present in each position. For C(α), there are two hydrogens (deuteriums) present and their identity is not affected during isomerization. Exactly one of the two hydrogens (deuteriums) at C(β) is transferred during the hydride shift to C(α), thus being one half of the two atoms attached to C(β). The hydrogens (deuteriums) at C(γ) are not involved until the transfer step begins. As the resulting general equation to describe the H/D distribution for the transfer step according to the mechanistic proposal of Bowen and Williams, we obtain

$$\frac{H}{D} = \frac{I_d(n_{H\alpha} + 0.5n_{H\beta} + n_{H\gamma})}{(n_{D\alpha} + 0.5n_{D\beta} + n_{D\gamma})} \qquad (10)$$

where I_d represents a primary hydrogen isotope effect for the bond fission of the proton which is actually transferred. If, for example, C(α) bears the label, Eqn (10) becomes

$$\frac{H}{D} = \frac{I_d(1 + 3)}{2} = 2I_d = 2.57 \qquad (10a)$$

However, it is not possible to correlate the equations derived from Eqn (10) with experiment. Instead a preference seems to exist for H/D transfer originating from the methyl being formed at C(α) and thus a preference for the β-position too. In order to correct Eqn (10) for the preference detected, a preference factor p has been introduced:[17,18]

$$\frac{H}{D} = \frac{I_d(pn_{H\alpha} + 0.5pn_{H\beta} + n_{H\gamma})}{(pn_{D\alpha} + 0.5pn_{D\beta} + n_{D\gamma})} \qquad (11)$$

Repeating the numerical evaluation for the equations derived from Eqn (11), it turns out that all ions labelled in just one position yield good correlations whereas those labelled in two positions do not. It is evident that the degree of labelling influences the H/D distribution. Again, I_{dsec} is introduced to compensate for any secondary isotope effects influencing the proton transfer from the 2-propyl cation to the nitrogen:

$$\frac{H}{D} = \frac{I_d I_{dsec}^{nD}(pn_{H\alpha} + 0.5pn_{H\beta} + n_{H\gamma})}{(pn_{D\alpha} + 0.5pn_{D\beta} + n_{D\gamma})} \qquad (12)$$

Explicitly, Eqn (12) yields

13α-d_2: $$\frac{H}{D} = \frac{I_d I_{dsec}^{nD}(3 + p)}{2p} = 2.57 \qquad (12a)$$

13β-d_2: $$\frac{H}{D} = \frac{I_d I_{dsec}^{nD}(2p + 3)}{p} = 7.20 \qquad (12b)$$

13γ-d_3: $$\frac{H}{D} = \frac{I_d I_{dsec}^{nD} \times 3p}{3} = 2.11 \qquad (12c)$$

13αγ-d_5: $$\frac{H}{D} = \frac{I_d I_{dsec}^{nD} p}{3 + 2p} = 0.24 \qquad (12d)$$

13αβ-d_4: $$\frac{H}{D} = \frac{I_d I_{dsec}^{nD} \times 3}{3p} = 1.00 \qquad (12e)$$

13βγ-d_{10}: $$\frac{H}{D} = \frac{I_d I_{dsec}^{nD} \times 2p}{3 + p} = 0.62 \qquad (12f)$$

As can be seen from Table 3, the results from Eqns (12a–f) are most reasonably correlated ($C = 1.07$) with the experiment for $I_d = 2.28$, $I_{dsec} = 0.86$ and $p = 1.34$. Further, a comparison of the values obtained from Eqns (8a–f) with those obtained from Eqns (12a–f) shows that they are extraordinarily similar (Table 3) and exactly yield the same I_d and I_{dsec}. The preference factor is also directly reflected by the x_i computed from Eqns (8a–f). Instead of the ideal values $x_\alpha : x_\beta : x_\gamma = 0.333 : 0.166 : 0.500 = 2 : 1 : 3$, a distribution of $0.382 : 0.190 : 0.428$ has been evaluated for an unlabelled ion, i.e. an ion that is not distribution-distorted by isotope effects. The ratio $(x_\alpha + x_\beta) : x_\gamma = 0.572 : 0.428 = 1.34$ directly yields p.

Thus, we have two independent mathematical descriptions of different origin leading to correlations of equal quality. Both provide the same values for the primary isotope effect I_d and the secondary isotope effect I_{dsec} by which the rate of the transfer step is influenced. While the approach using Eqns (8a–f) and (9) yields the contributions to H transfer from the respective positions, Eqns (12a–f) give an insight into mechanistic details. The most surprising result from these calculations is the unusual value of the secondary isotope effect $I_{dsec} = 0.86$ per deuterium. Figure 3 clearly shows the straightforward dependence of correlation C and I_{dsec} while the preference factor p is kept constant.

Diisopropylmethyleneimmonium ions

The positional dependence of the total isotope effect I_t lead us to conclude that an isomerization by 1,2-hydride shift takes place and that this step is rate determining as far as *n*-propyl species are concerned. During this step

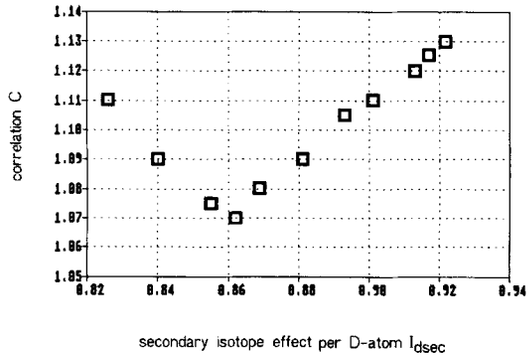


Figure 3. Dependence of correlation C on secondary isotope effect per deuterium atom I_{dsec} for the di-*n*-propyl ions (**13**). The BASIC program used allowed the isotope effect on the distribution-determining step I_d and preference factor p to adjust freely during each run at fixed I_{dsec}. Whereas I_d varied on variation of I_{dsec}, p remained constant at 1.34 throughout the interval shown.

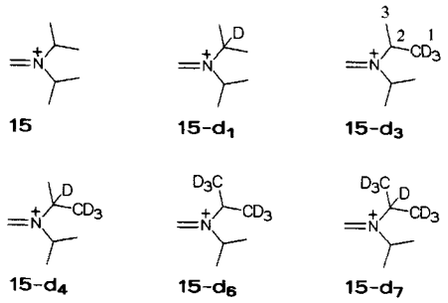


Figure 4. Diisopropylmethyleneimmonium ions examined.

the original 1-propyl cation formed by N—C(α) bond rupture rearranges to a 2-propyl cation. Diisopropylmethyleneimmonium ions should allow us to verify this assumption because they will directly dissociate into imine and the coordinated 2-propyl cation without rearrangement.

The diisopropylmethyleneimmonium ions examined are summarized in Fig. 4 and the results from 15 eV MI spectra are shown in Table 4. The specific loss of C_3HD_5 from **15-d_6** demonstrates that the hydrogen is specifically transferred from the methyls of the isopropyl groups, i.e. there is no isomerization within the isopropyl prior to proton transfer.

The ratio $r = 1.00$ (Eqn (2)) for the losses of C_3H_6 and C_3DH_5 from **15-d_1** indicates that the fission of the C—N bond is not influenced by an isotope effect. This finding is confirmed by the fact that the pairs **15-d_3**, **15-d_4** and **15-d_6**, **15-d_7** show common values of the ratio r. Again, the deuterium at C(2) of the isopropyl has no remarkable influence on the rate constant of propene loss.

The H/D ratios for propene loss from the labelled isopropyl group of **15-d_3** and **15-d_4** (Eqn (1)) are found to be H/D ≈ 1.6, i.e. H transfer from CH_3 is 1.6 times faster than D transfer from CD_3. If both methyls are labelled as in **15-d_6** and **15-d_7**, the ratio $r \approx 1.6$ is obtained (Eqn (2)), i.e. loss of propene from an unlabelled isopropyl occurs 1.6 times faster than from an isopropyl-d_6 (-d_7). Both of these values directly reflect the influence of isotopic substitution on the proton transfer step because interferences with preceding steps can be excluded. Therefore, one can infer that the H/D ratio of **15-d_3** and **15-d_4** and the ratio r of **15-d_6** and **15-d_7** correspond to the isotope effect on the H/D distribution-determing step I_d. The ratio r also allows us to calculate I_d for ions **15-d_3** and **15-d_4**; $r = 6I_d/(3I_d + 3)$. In this way, one obtains $I_d = 1.63$ (**15-d_3**) and $I_d = 1.53$ (**15-d_4**). For the onium reaction of diisopropylmethyleneimmonium ions $I_d = 1.6$ must be assumed, preferring the H transfer from CH_3 over D transfer from CD_3. In contrast to di-*n*-propylmethyleneimmonium ions, proton transfer has become the rate-determining step of propene loss because the preceding rearrangement has vanished.

We may now adapt the mathematical concepts to ions **15-d_3** and **15-d_4** in order to put them to the test. Equation (8) is simplified to

$$\frac{H}{D} = \frac{I_d I_{dsec}{}^{nD} x_3}{x_1} \tag{13}$$

where x_1 denotes the contribution of the labelled position and Eqn (12) becomes

$$\frac{H}{D} = \frac{I_d I_{dsec}{}^{nD}(n_{H1} + n_{H3})}{(n_{D1} + n_{D3})} \tag{14}$$

The I_d calculated from Eqn (13) ($I_d = 1.62$, $I_{dsec} = 1.00$) and from Eqn (14) ($I_d = 1.62$, $I_{dsec} = 100$) equate the I_d as obtained above directly from the H/D ratios measured.

These results are proof for the irreversible isomerization of the coordinated propyl cation by 1,2-hydride shift and for the rate-determining character of this process for the onium reaction of *n*-propyl-substituted immonium ions.

Immonium ions with $R^1 = n\text{-}C_3H_7$, $R^2 = H$, CH_3, C_2H_5

Immonium ions with $R^1 = n\text{-}C_3H_7$, $R^2 = H$ (**1**), $R^2 = CH_3$ (**16**) or $R^2 = C_2H_5$ (**17**) exclusively exhibit propene loss via onium reaction from the propyl. Figures 5, 6 and 7 show the ions examined. They allow the influence of R^2 on the onium reaction to be studied in order to achieve a deeper insight into where the preference factor arises and what the nature of the unusual I_{dsec} calculated for di-*n*-propyl ions is. The rate-determining 1,2-hydride shift still takes place but it will not be detected because these ions offer no internal standard as the unlabelled propyl of the di-*n*-propyl ions does. In other words, ions **1**, **16** and **17** will provide more information on the H/D distribution-determining step.

In the case of **17**, competing ethene losses from the propyl group via McLafferty rearrangement and from the ethyl group by onium reaction might be possible,

Table 4. Relative abundances for propene loss from diisopropylmethyleneimmonium ions examined at 15 eV by *B/E* linked scan

	Propene loss (%)[b]								
Ion structure[a]	C_3H_6	C_3H_5D	$C_3H_4D_2$	$C_3H_3D_3$	$C_3H_2D_4$	C_3HD_5	C_3D_6	H/D[c]	r[d]
15-d_1	50.0	50.0							1.00 ± 0.04
15-d_3	55.4		17.4	27.2				1.57 ± 0.06	1.24 ± 0.07
15-d_4	54.7			17.2	28.1			1.64 ± 0.07	1.21 ± 0.09
15-d_6	60.2					39.8			1.51 ± 0.11
15-d_7	62.1						37.9		1.64 ± 0.12

[a] For ion structures, see Fig. 4.
[b] Relative abundances are normalized to the sum of the ion current corresponding to the onium reaction.
[c] H/D ratios as calculated from Eqn (1).
[d] Ratio r as calculated from Eqn (2). The errors quoted correspond to one standard deviation.

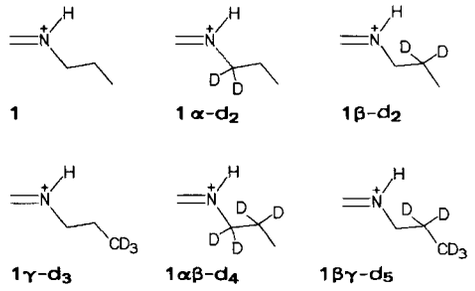


Figure 5. *n*-Propylmethyleneimmonium ions examined.

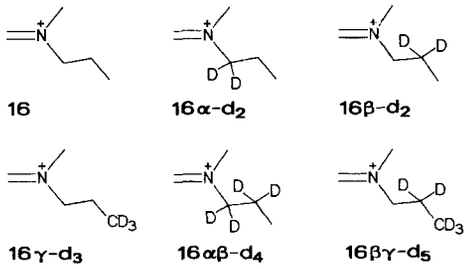


Figure 6. Methyl-*n*-propylimmonium ions examined.

but the labelling study shows that ≥99% of ethene loss arise from the propyl group.

For ion **1** and its isotopomers the results from 15 eV MI spectra are shown in Table 5. Ion **1α-d_2** has already been examined by Bowen,[3] who found 29% D and 71% H transfer; these values are confirmed by our results (27.9% D and 72.1% H transfer). The ions of the structural types **1**, **16** and **17** offer a good test for the applicability of the mathematical treatment and the reliability of the model on the whole. Table 5 summarizes the MI spectra and Table 6 compares the calculations according to Eqns 8 and 12. In each case, Eqns (8) and (12)

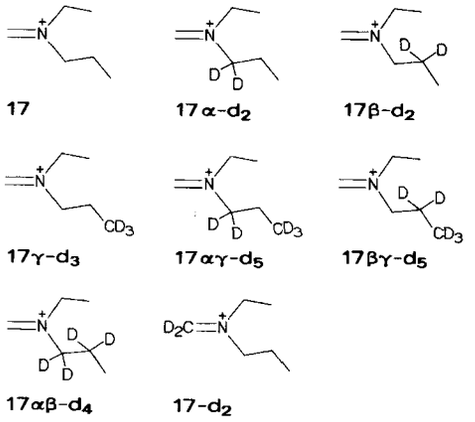


Figure 7. Ethyl-*n*-propylimmonium ions examined.

yield consistent values for the isotope effects of the proton transfer step I_d and I_{dsec}. Whereas from Eqn (8) the relative contributions from the respective positions are obtained, Eqn (12) gives a measure of the preference factor *p*.

As can be seen for ion **1**, the distribution 2:1:3 is perfectly realized and hence the preference factor $p = 1.00$. The primary hydrogen isotope effect on bond cleavage of the leaving proton is obtained as $I_d = 1.23$ and $I_{dsec} = 1.00$. Our results confirm Bowen's and our treatment is verified by this coincidence in the case of **1**.

The influence of R^2 on the onium reaction can be seen from the plots of I_d, I_{dsec} and *p* versus the structural type (Fig. 8). Within the homologous series of immonium ions (R^2 = Pr, Et, Me, H), a clear tendency to smaller I_d and *p* and to I_{dsec} approaching 1.00 can be seen on going from propyl to lower homologues.

The change in the values of I_d can be rationalized by comparing the number of vibrational degrees of freedom,[19,20] $N_v = 3N - 6$, of an ion with the I_d

Table 5. Relative abundances for propene loss from *n*-propylmethyleneimmonium ions (1), methyl-*n*-propylmethyleneimmonium ions (16) and ethyl-*n*-propylmethyleneimmonium ions (17) examined at 15 eV by *B/E* linked scan

	Propene loss (%)[b]						
Ion structure[a]	C_3H_6	C_3H_5D	$C_3H_4D_2$	$C_3H_3D_3$	$C_3H_2D_4$	C_3HD_5	H/D[c]
1α-d_2		27.9	72.1				2.58 ± 0.12
1β-d_2		14.8	85.2				5.75 ± 0.21
1γ-d_3			46.7	53.3			1.14 ± 0.09
1αβ-d_4				43.3	56.7		1.31 ± 0.10
1βγ-d_5					60.6	39.4	0.65 ± 0.03
16α-d_2		24.7	75.3				3.05 ± 0.23
16β-d_2		13.8	86.2				6.25 ± 0.35
16γ-d_3			35.0	65.0			1.86 ± 0.10
16αβ-d_4				40.3	59.7		1.48 ± 0.09
16βγ-d_5					54.9	45.1	0.82 ± 0.03
17α-d_2		25.6	74.4				2.91 ± 0.19
17β-d_2		14.1	85.9				6.08 ± 0.36
17γ-d_3			32.5	67.5			2.08 ± 0.13
17αβ-d_4				43.5	56.5		1.30 ± 0.06
17αγ-d_5					75.5	24.5	0.33 ± 0.02
17βγ-d_5					62.9	37.1	0.59 ± 0.04
17-d_2	100						—

[a] For ion structures, see Figs 5, 6 and 7.
[b] Relative abundances are normalized to the sum of the ion current corresponding to the onium reaction.
[c] H/D ratios as calculated from Eqn (1). The errors quoted correspond to one standard deviation.

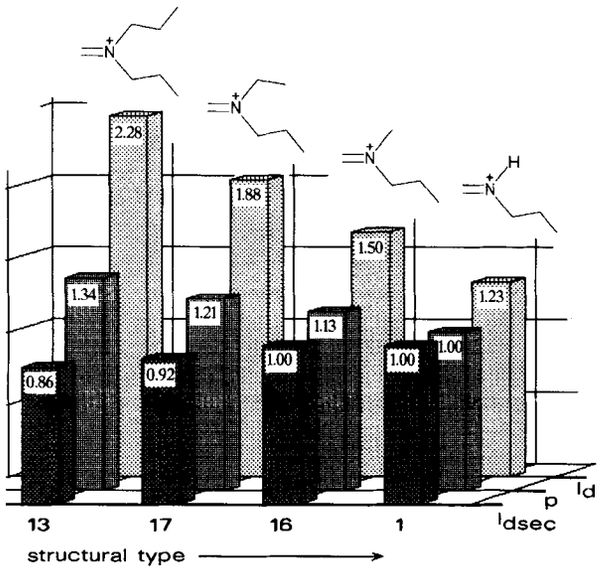


Figure 8. Plot of primary hydrogen isotope effect on distribution-determining step I_d, corresponding secondary isotope effect I_{dsec} and preference factor p as calculated from Eqns (12a–f) versus the n-propyl ions examined.

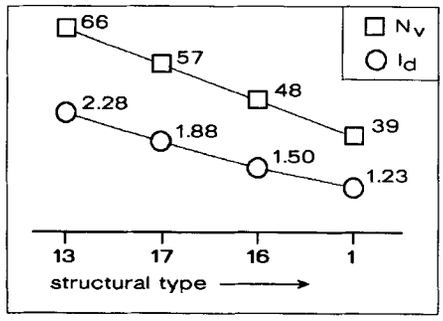


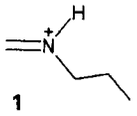
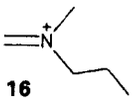
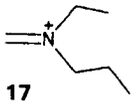
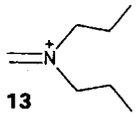
Figure 9. Plots of (○) primary hydrogen isotope effect on distribution-determining step I_d as calculated from Eqns (12a–f) and of (□) the number of vibrational degrees of freedom $N_v = 3N - 6$ of the corresponding immonium ions versus the n-propyl ions examined. The ordinates are of different scales.

exhibited. Figure 9 shows the decrease in I_d with decreasing N_v. If the amount of internal energy E of any of the immonium ions is assumed to be nearly the same as a result of the equal excitation during ionization[21] of the corresponding precursor amine and from equal enthalpy $\Delta_r H$ of the preceding α-cleavage, then it will be randomized over more vibrational degrees of freedom the higher is the number N of atoms. Thus, vibrational excitation will be higher the lower is N_v over which E is randomized.

As already explained, the first step in the onium reaction is due to the formation of an ion–neutral complex containing a 2-propyl cation. The 2-propyl cation is generated by irreversibly rearranging the original n-propyl group via a 1,2-hydride shift. This process is rate determining. Whether a complex such as **18** is long-lived enough or not to equilibrate with the initial immonium ion **13** may not be derived directly from the experimental results (Scheme 5). We assume that the necessary weakening of the C—N bond does not correspond to a minimum on the potential surface but rather to a slight plateau on the reactions way up to the transition state **19** of the isomerization to the electrostatically bound 2-propyl cation in **20**.

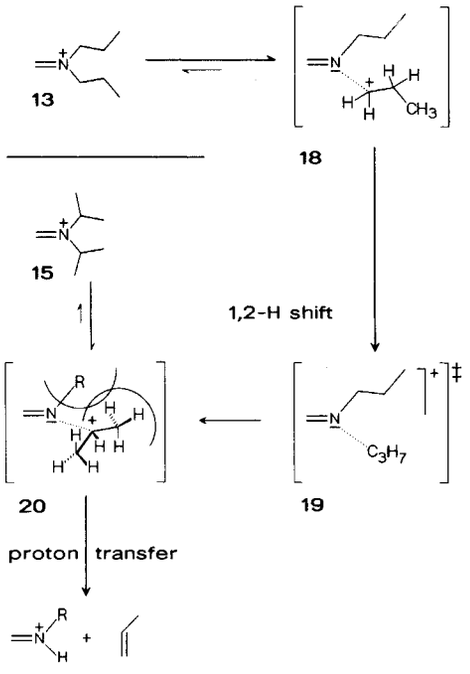
If the hydrogen in **1** is replaced by an alkyl (**16**, **17**, **13**), the 2-propyl cation contained in complex **20** should exhibit neither high rotational symmetry towards the imaginary N—C(β) axis nor the possibility of unrestricted rotation around this axis. Instead, as can be derived from the preference factor p, some restriction must be effective. The observed restriction can be explained by steric hindrance causing a rotational

Table 6. Summary of the results from the mathematical deconvolution procedures[a]

Ion	Calculated from Eqn No.	I_d	I_{dsec}	p	x_α	x_β	x_γ
 **1**	(8)	1.22	1.00	—	0.333	0.167	0.500
	(12)	1.23	1.00	1.00	—	—	—
 **16**	(8)	1.59	1.00	—	0.333	0.196	0.471
	(12)	1.50	1.00	1.13	—	—	—
 **17**	(8)	1.94	0.92	—	0.340	0.210	0.450
	(12)	1.88	0.92	1.21	—	—	—
 **13**	(8)	2.28	0.86	—	0.382	0.190	0.428
	(12)	2.28	0.86	1.34	—	—	—

[a] I_d = primary hydrogen isotope effect on distribution-determining step; I_{dsec} = corresponding secondary isotope effect; p = preference factor. The x_i refer to the relative contributions of the positions along the n-propyl group.

barrier that increases as the size of R^2 increases (Table 6). This barrier is visualized by the circles drawn in Scheme 5. If the dissociation into the products proceeds irreversibly and exhibits a relatively small critical energy, the rate constant is close to the order of rotational frequency. This is why a preference for the original α- and β-positions, which have stil retained their initial orientation towards the nitrogen lone pair, is detected. If complex **20** is directly formed from the diisopropyl ion **15**, high symmetry towards the N—C axis must be assumed because neither a preference factor nor a secondary isotope effect have been found.



Scheme 5

The inverse secondary isotope effect I_{dsec} opposes the primary effect, i.e. it compensates for the lower reaction rate by offering an advantage of deuterium over hydrogen. Normally, inverse secondary hydrogen isotope effects have been observed only for the fragmentation of highly excited ions.[12]

As far as ions **13**, **16** or **17** are concerned, the advantage mentioned is caused by a shifted centre of mass of the 2-propyl cation. On comparing an unlabelled propyl and a propyl labelled in the α-position, we find the centre of mass shifted from an axis through C(β) to somewhere between C(α) and C(β), thus forcing C(γ) to an outer position. Now the labelled position compensates for its lower rate constant by having the better orientation towards the lone pair of the imine-nitrogen. Therefore, the inverse secondary isotope effect I_{dsec} in the distribution-determining step of propene loss arises from the influence of labelling on the relative orientation of the reactands in **20**. This is supported by the fact that $I_{dsec} < 1.00$ only for R^2 = Et or Pr has been detected.

Redman and Morton[22] proposed for the gas-phase deprotonation of 1-methylcyclopentyl cations by amines a locked-rotor critical configuration of the acid with respect to the base. We may adopt this model of bimolecular gas-phase reactions for the onium reaction also. As a difference, the reactands do not meet by random collisions because they develop close together by a unimolecular step from a common precursor ion. The situation found in complex **20** might be called pseudo-bimolecular. The acid (2-propyl cation) transfers its proton to the base (corresponding alkylmethyleneimine) only if the correct configuration is attained. This corresponds to an entropic bottleneck as described by Redman and Morton[22] and McAdoo.[1b]

A competition of direct dissociation of **20** into the products with a pathway passing through a hydrogen-bridged intermediate[3] can be considered, but we found no experimental evidence for such a complex.

CONCLUSION

The onium reaction as exhibited by the metastable immonium ions examined proceeds via at least one ion–neutral complex intermediate that consists of a 2-propyl cation coordinated to an alkylmethyleneimine. This intermediate is formed during the rate-determining step by scission of the N—C(α) bond and subsequent 1,2-hydride shift. Isopropyl-substituted immonium ions do not undergo such a rearrangement. It cannot be decided unambiguously whether the ion–neutral pair formed while the N—C(α) bond collapses to yield the imine and an incipient 1-propyl cation may be called an ion–neutral complex, or whether its lifetime makes it more resemble an early transition state. When the former complex dissociates, propene and a new immonium ion are formed as final products of this distribution-determining step.

We have shown that isotope effects on both rate-determining and distribution-determining steps are far from negligible. Isotope effects complicate the interpretation of labelling data by yielding results that are at first sight curious, but their existence offers a reliable guide to a reaction's critical steps.

For a multi-stage reaction as represented by the onium reaction of dialkylimmonium ions, the evaluation of isotope effects and H/D distributions was only possible from a complete set of isotopically labelled ions. Several types of information on the reaction pathway, the rate-determining step, intermediates and the contribution to H transfer of each of the positions involved can exclusively be obtained by application of this method.

For ion–neutral complex intermediate fragmentations, the common practice of evaluating the relative contributions of a labelled position by taking the experimental H/D ratio as the final result can be misleading because isotope effects of unknown size are neglected. Also, a single pair of complementary labelled ions will yield only a coarse survey of the mechanism of interest.

EXPERIMENTAL

The metastable dissociations were examined on a Varian MAT 311A double-focusing mass spectrometer

of reversed geometry. All immonium ions under investigation were generated directly in the ion source by α-cleavage of appropriate precursors. Ionization was done using electrons having a nominal energy of 70 and 15 eV, respectively. The source pressure was 2×10^{-6}–7×10^{-6} Torr (1 Torr = 133.3 Pa). The accelerating voltage was 3 kV.

The first field-free region dissociations were examined by means of the B/E = constant scan. The linked scan was achieved using an MSP-Friedli model 8103 linked scan unit. Typically 15–20 scans were acquired to ensure reliable abundance ratios which were calculated from the peak areas. Data acquisition and peak areas were obtained with a Teknivent Vector/one data system. The erors quoted correspond to one standard deviation.

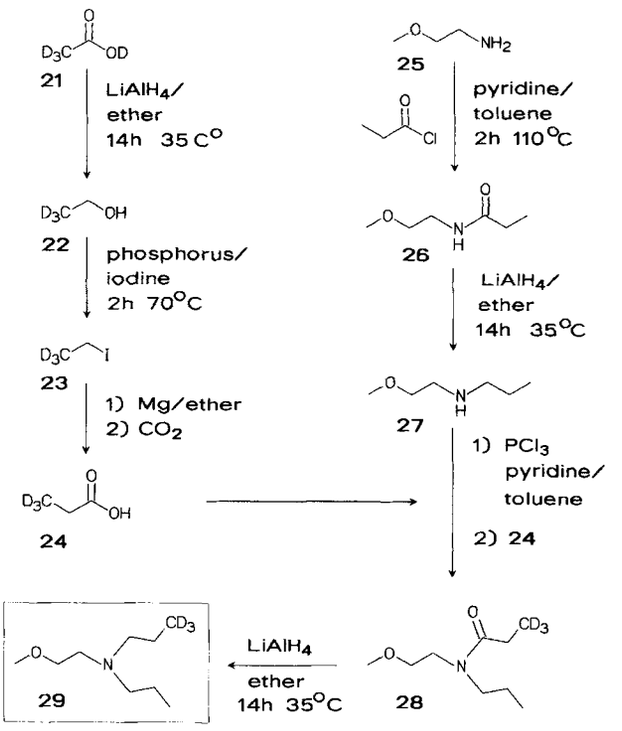
N-(2-Methoxyethyl)di-*n*-propylamine and its specifically labelled isotopomers were prepared starting from 2-methoxyethylamine (**25**) by reaction with appropriately labelled propionic acid (cf. Scheme 6). As described by Grimmel *et al.*,[23] amides were prepared conveniently from amines and carboxylic acids using PCl_3 in toluene. The secondary amides were reduced by $LiAlH_4$ or $LiAlD_4$, yielding the α-unlabelled or α-labelled amines, respectively. Repetition of these steps led to tertiary amide and amine. The method of Einhorn and Hollandt[24] was used to prepare the unlabelled secondary *N*-(2-methoxyethyl)-propylamine as a precursor for the synthesis of the unsymmetrically labelled compounds.

Propionic acid-3,3,3-d_3 (**24**) was synthesized according to a method published by Duffield *et al.*[25] by reducing acetic acid-d_4 (**21**) with $LiAlH_4$–diethyl ether, halogenation of the resulting ethanol-d_3 (**22**) to yield the iodide **23** and finally by Grignard reaction to yield the acid **24**. Propionic acid-2,2,-d_2 was obtained by reduction of acetic acid with $LiAlD_4$ and subsequent treatment as just described or by three times repeated H/D exchange using D_2O–NaOD and sodium propionate.[26] Propionic acid-2,2,3,3,3-d_5 was prepared starting from ethanol-d_6.

Scheme 6 illustrates the concept described above for the preparation of an unsymmetrically labelled precursor (**29**). Any of the tertiary amines may be synthesized by an appropriate combination of the single steps.

2-(Methoxyethyl)-*N*-propylamine and its labelled isotopomers were obtained as intermediates during the preparation of the tertiary amines as described above. *N*-Methyl-(2-methoxy)-acetamide was prepared from 2-methoxyacetic acid chloride and methylamine hydrochloride in toluene.[27] The amide was then reduced with $LiAlH_4$. The labelled tertiary amines were prepared analogously to the di-*n*-propyl-substituted amines by reaction of 2-(methoxyethyl)methylamine with the appropriate propionic acid[23] and subsequent reduction of the amides. 2-Methoxyethylamine was converted into *N*-(2-methoxyethyl)acetamide,[24] reduced with $LiAlH_4$ and then used to prepare the *N*-(2-methoxyethyl)-*N*-ethylpropylamines using the technique described above.

Propylamine and methoxyacetic acid chloride were reacted to yield the amide[24] which then yielded *N*-propyl(2-methoxy)ethyl-1,1-d_2-amine by reduction with



Scheme 6

$LiAlD_4$. This was then used to prepare the precursor of **17-d_2**. *N*-Isopropyl(2-methoxy)acetamide was prepared from 2-methoxyacetic acid chloride and 2.4 equiv. of isopropylamine in 1,2-dichloroethane.[28] $LiAlH_4$ reduction yielded *N*-(2-methoxyethyl)isopropylamine. The labelled isopropyl group was introduced by reaction of the secondary amine for 24 h with the corresponding isopropyl mesylates using a slight excess of 2,2,6,6-tetramethylpiperidine as the base. The amines were purified by preparative liquid chromatography on an alumina column using dichloromethane as eluent. The mesylates were obtained from the labelled isopropanols using methanesulphonic acid chloride in pyridine–diethyl ether.[29]

Isopropanol-2-d_1 was prepared by $LiAlD_4$ reduction of acetone, isopropanol-1,1,1,3,3,3-d_6 by $LiAlH_4$ reduction of acetone-d_6, isopropanol-1,1,1,2,3,3,3-d_7 by $LiAlD_4$ reduction of acetone-d_6, isopropanol-1,1,1-d_3 by reaction of CD_3MgI with excess of acetaldehyde and isopropanol-1,1,1,2-d_4 by $Na_2Cr_2O_7$ oxidation of isopropanol-1,1,1-d_3 to yield acetone-1,1,1-d_3 and subsequent $LiAlD_4$ reduction.

Purity and labelling were confirmed by thin-layer chromatography,[30] electron impact mass spectra and 300 MHz ^1H and 75 MHz ^{13}C NMR spectrometry.

Acknowledgement

Financial support by the Fonds der Chemischen Industrie, Frankfurt am Main, is gratefully acknowledged.

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