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Bifunctional Even-electron Ions

V.[†] Fragmentation Behaviour of Aliphatic Hydroxonium Ions Containing an Additional Cyano Group

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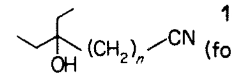
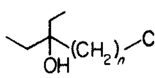
The fragmentation behaviour of a series of bifunctional hydroxonium ions $C_2H_5-C(=\overset{+}{O}H)-(CH_2)_n-CN$ ($n = 0$–6), a_n, has been investigated by electron impact mass spectrometry. The type of interaction-induced reactions depend strongly on the chain distance between the oxonium and the cyano moiety, but the initial step in all cases is proton transfer from the hydroxy to the cyano group. The following selective primary fragmentations have been found: loss of $C{=}NH$ (HCN) from a_0, loss of $CH_2{=}C{=}NH$ from a_1, loss of HNCO from a_2–a_4, loss of $CH_3-CH{=}C{=}O$ from a_4–a_6, and loss of CO from a_3. In addition, loss of NH_3 and H_2O, respectively, are observed as general fragmentations, except for the lowest homologues (a_0 and a_1). Mechanistic pathways of the selective reactions have been deduced with the aid of metastable ion spectra, high resolution, deuterium labelling and comparison of metastable ion spectra with those of independently generated ions.

INTRODUCTION

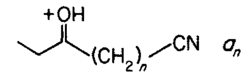
The interaction between a hydroxonium moiety and an additional functional group, for example Cl, OCH_3, and $COOCH_3$, within the bifunctional even-electron ions *b* and *c* leads to the elimination of HCl and CH_3OH, respectively, as a general and main primary fragmentation,[1,2] whilst ordinary reactions of hydroxonium ions are not observable or strongly suppressed. This obviously energetically most favourable reaction is preceded by proton transfer from the oxygen of the charge centre to the second functional group. Probably, this is the general type of primary fragmentation of a hydroxonium ion containing an additional substituent with a singly bonded heteroatom, since it is also found for NH_2, $OCOCH_3$, and Br as the second functional group leading to loss of NH_3, CH_3COOH, and HBr, respectively (unpublished results).



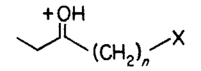
1a - 1g (for n = 0 - 6) ;



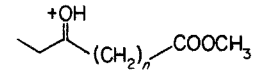
2 (R = H, alkyl)



a_n (n = 0-6)



b_n (X = Cl, OCH_3; n = 1-6)



c_n (n = 0-5)

It is of interest in this respect to find out how a corresponding bifunctional hydroxonium ion behaves when it has no singly bonded heteroatom as part of the second functional group and, therefore, cannot undergo this type of elimination.

Two of the common substituents, namely $-C(R){=}O$ and $-C{\equiv}N$, meet this requirement. Of these, the cyano group was chosen mainly for preparative reasons. The precursor compounds **2** could not be obtained in the open-chain form for $n = 2$ and $n = 3$, in which case cyclization to a five- and a six-membered ring, respectively, takes place.

The cyano group by itself is interesting in two respects. (i) the $C{\equiv}NH^+$ group, which is expected to be formed by proton transfer from the $C{=}OH^+$ moiety to the cyano group of *a*, is analogous to the $C{\equiv}O^+$ group, which plays a role as an inherent moiety after CH_3OH loss from *c* and which has a strong influence on the further fate of these ions.[2] (ii) The more electropositive nitrogen compared to oxygen may have consequences concerning the directions of the succeeding fragmentations. As will be shown, both the analogies of these two

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units and the differences due to the nitrogen are clearly recognizable.

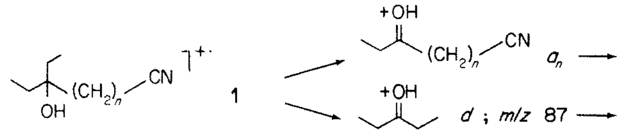
The methodology of this study is based on the previously described one[1] but is extended by additional proof of the relations between the parent and daughter ions by metastable ion (MI) spectra (daughters and parents) and of the elemental composition of the relevant ions by high-resolution measurements in each case. Where necessary, D-labelling studies have been performed and ions of proposed structures have been independently generated.

As before, the main emphasis of this study is on the elucidation of interaction-induced reaction pathways, whereas rigorous proof of ion structures is not intended. Nevertheless, the proposed ion structures probably are correct in most cases.

To our knowledge, no related investigations directed to the interaction of an oxonium moiety with a cyano group have been undertaken. Electron impact (EI) studies on other bifunctional aliphatic oxonium ions not cited later in this paper are noted in Ref. 3.

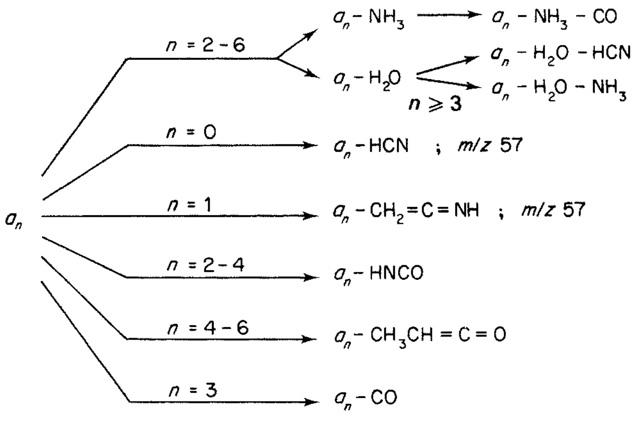
RESULTS AND DISCUSSION

The homologous series **1** ($n = 0$–6) has been used as the precursors for the bifunctional ions a_n. To obtain the EI mass spectra of a_n, compounds **1** have been measured at 20 eV and at low source temperature (~80 °C). Under these conditions the fragmentations of **1** (as for the other bifunctional tertiary alcohols) are dominated by the α-fissions at the hydroxy group),[1,2] leading to the ions a_n and d and their subsequent fragment ions. The MI spectra have been recorded and the high-resolution measurements performed at normal 70 eV conditions. Where elemental compositions of ions or of neutrals are given, these have been established by high resolution.



Mass spectra of the bifunctional ions *a* (general)

The 20 eV mass spectra of a_0–a_6 have been obtained as described elsewhere[1] and are summarized in Fig. 1. The ion abundances are given as fractions of the total ion abundance of the respective spectrum.† Abundances of such daughter ions which are not presented in this diagram are added to the abundances of the corresponding parent ions. In addition, the scheme of the main fragmentations of ions a_n, derived from appropriate metastable ion transitions of the 20 eV spectra and confirmed by MI spectra (70 eV) of the ions in question, is presented in Scheme 1. The neutrals losts are taken from the discussion of the fragmentation pathways below.



Scheme 1

The spectral comparison of a with other bifunctional hydroxonium ions[1,2] shows that the overall decomposition of a is moderate but depends on the chain length separating the functional groups, the maximum of decomposition being for $n = 4$, 5. On the other hand, both Fig. 1 and Scheme 1 reveal that the fragmentation modes are strongly dependent on the chain distance of the functional groups. Thus, the interaction between the cyano group and the hydroxonium moiety seems to be very effective and specific, and the comparably low overall decomposition of a reflects only that the early stages of the reactions are rearrangements to relatively stable ions rather than fragmentations. Since loss of HCN from a is not found except for a_0, this is expected for reactions involving a substituent like CN with a triply bonded heteroatom. One mode (or type) of rearrangement is cyclization, as can be directly deduced from the loss of HNCO from a_2–a_4.

As for the other bifunctional hydroxonium ions so far investigated, the ordinary fragmentations of hydroxonium ions play no role, except for the loss of H_2O which partly may not be interaction-triggered.

Discussion of the fragmentation pathways of *a*

From the earlier investigations it is expected that the primary reaction preceding most of the fragmentations is proton transfer from the $\overset{+}{\text{C}}{=}\text{OH}$ unit to the nitrogen of the CN group, leading to a_n'. Cyclization of a_n^0 via attack of the carbon of the original charge centre by the free electron pair of the nitrogen is only conceivable for long-chain distances because of the rod-like structure of the $-\text{C}{\equiv}\text{N}$ unit (Scheme 2).

Although the fragmentations of *O*-deuterated a_1–a_6 (a_1-OD, a_6-OD) showed that the deuterium is not fully retained with the nitrogen, these labelling experiments are in line with the primary formation of a', and the interpretations of the specific reaction pathways are suggestive of this formation (see Schemes 3–7).

The nitrilium unit $\text{C}{\equiv}\overset{+}{\text{N}}\text{H}$ is analogous to the $\text{C}{\equiv}\overset{+}{\text{O}}$ unit. Therefore, attention is given to the analogies and differences with respect to the implications on the fragmentation modes of ions a' and e, the latter playing a role as intermediate in the fragmentations of c.

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† By this representation the relative abundances of a_n are a direct measure of the proportion of undecomposed a_n, and high relative abundances of daughter ions of a_n indicate that these ions are stable and preferentially formed.

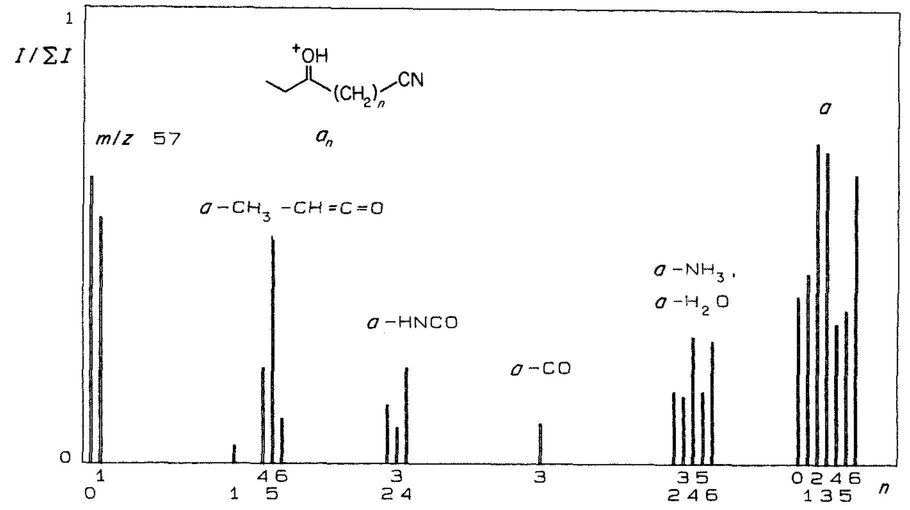
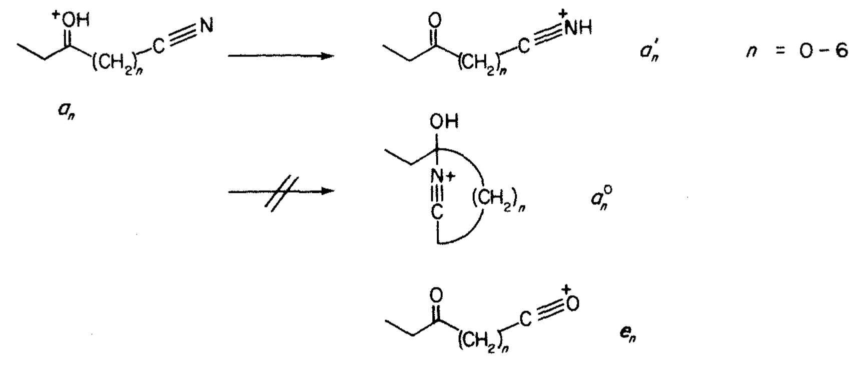


Figure 1. Schematic mass spectra at 20 eV of ions a_n.



Scheme 2

Loss of water and loss of ammonia

Except for the lowest homologues a_0 and a_1, these reactions are ubiquitous for a. The abundances of $a - H_2O$ and $a - NH_3$, given together in Fig. 1, include the ion abundances from the subsequent reactions indicated below and show that losses of H_2O or NH_3 are fairly effective reaction channels of the overall decompositions of a. The loss of NH_3 decreases from a_2 to a_6, the reverse being valid for the loss of H_2O. From a_2-OD 90% of the label is lost with NH_3. The corresponding value from a_4-OD is ~50%. Although three hydrogens must migrate to the nitrogen prior to the loss of NH_3 and, therefore, the possibility of reversible hydrogen-exchange must be taken into account, the loss of the label is rather high. This indicates proton transfer from the oxygen to the nitrogen as one of the preceding reactions and a rather high reluctance of the nitrogen in the intermediate species to reversibly exchange hydrogen with the carbon atoms.

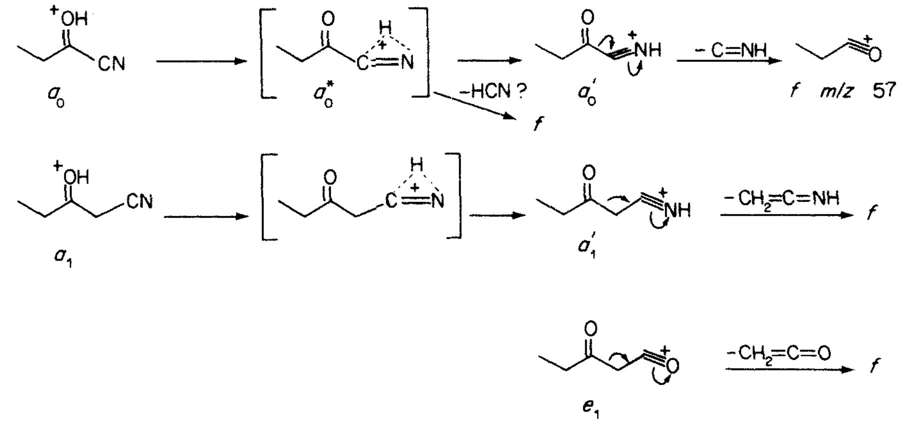
The elimination of NH_3 must be the result of a complex process, and since the competitive H_2O loss hampers the pursuit of the reaction pathway for NH_3 loss, a detailed investigation of both fragmentations was not undertaken. Certainly there are cross-overs in the pathways of these reactions (especially proton transfers between N and O at different stages).

The ions $a - NH_3$ and $a - H_2O$ eliminate CO and HCN (C=NH), respectively, leading to ions of the general formula $[C_mH_{2m-3}]^+$, but for the latter ions losses of the homologous neutrals C_2H_3N (probably $CH_2{=}C{=}NH$) and C_3H_5N (probably $CH_2{=}CH{-}CH{=}NH$) are also found with increasing number of n of the CH_2 chain. C=NH and $CH_2{=}C{=}NH$ correspond to C=O and $CH_2{=}C{=}O$, these neutrals being lost in the course of some degradations of c.

The ions $a - H_2O$ additionally eliminate NH_3 ($n \geq 3$). A loss of five hydrogens with the heteroatoms from a with only one hydrogen attached to the oxygen is amazing and implies formation of the poly-unsaturated ions $[C_mH_{2m-7}]^+$.

Loss of HCN (C=NH) and loss of $CH_2{=}C{=}NH$

Only a_0, the lowest possible homologue ($n = 0$), exhibits the loss of HCN, forming the carbonyl ion $C_2H_5CO^+$ (f) in high abundance (Fig. 1). No other fragmentation is observed. A firm explanation of why only a_0 can eliminate HCN cannot be given, but the reaction pathway can be easily rationalized assuming through-bond interaction, typical of bifunctional even-electron ions with the functionalities in close vicinity (Scheme 3). Unfortunately, the analogous ion e_0 is not



Scheme 3

formed from c_0[2] so that a comparison could not be made. It is expected, however, that e_0 eliminates CO quite readily.

Correspondingly, the loss of $CH_2{=}C{=}NH$ is only found for a_1, again forming f is high abundance. From a_1-OD this fragmentation results in >90% loss of the label, which indicates that a proton transfer from the oxygen precedes fragmentation. An analogous, thoroughly studied elimination (loss of $CH_2{=}C{=}O$ under formation of f) takes place for e_1 and is not found for the other homologues of e.[1] This relation and the observation that bifunctional even-electron ions containing a $C{\equiv}O^+$ unit show CO loss for a certain homologue and $CH_2{=}C{=}O$ loss for the next higher one[4] leads to the assumption that the neutrals lost from a_0 and a_1 are $C{=}NH$ and $CH_2{=}C{=}NH$, respectively (Scheme 3). However, the loss of HCN from a_0 via the tentatively proposed ion a_0* as the reactive species could also be envisioned.

Loss of HN=C=O

This reaction is only found for a small range of ions, namely a_2 to a_4, within the homologous series, and in the final stage of this pathway the heteroatoms of both functional groups are lost. Both these findings indicate that there is a cyclization step prior to loss of HNCO. Five- to seven-membered rings are most favoured in unimolecular cyclizations. Therefore, the intermediates are expected to be five-membered for a_2 and seven-membered for a_4. Furthermore, the highest abundances of undecomposed ions a are found for a_2 and a_3, the ions with the highest probability for cyclization. From this it is concluded that the greatest proportion of these ions are stable cyclic species. The ion a_4 is expected to cyclize less and to decompose more readily. This can also be inferred from the experimental findings, namely the relatively low abundance of undecomposed a_4, the rather high abundance of a_4 – HNCO (i_4) and the similarly high abundances of fragment ions of a_4 arising from reactions other than HNCO loss (Fig. 1, Scheme 1).

Finally, the reaction behaviour of a_2–a_4 turned out to parallel the reaction behaviour of c.[2] Where, according to the underlying mechanism, formation of five- and six-membered rings, respectively, is possible, these latter ions readily react to form the cyclic ions j by the elimination of CH_3OH, and in this case the ions j are formed in high relative abundances, typical of this kind of ion (high probability of formation and high stability).†

The summary of the results, and of the above arguments, lead to the reaction steps for cyclization depicted in Scheme 4. Also, this mechanism follows from the basic assumption that the initial reaction of bifunctional hydroxonium ions is proton transfer from the oxygen of the $C{=}OH^+$ unit to the second functional group.

Although these cyclizations starting from a and c show the analogies for ions containing a CO and a CN unit, respectively, the reaction behaviour of the open-chain ions a' and j' as well as that of the cyclic ions a'' and j is remarkably different. This is ascribed to the more electropositive character of nitrogen compared to oxygen. In competition for the positive charge of these ions the nitrogen prevails. Thus, cyclization of a' to form g via $C{=}NH$ expulsion obviously is not possible, whereas j' can cyclize to g via CO elimination.

The inability of a' to react to g prevents a'' from decomposing via ring opening to a', this reaction mode being the favoured fragmentation route of j. Instead, a_3 reacts by the observed HNCO loss. The pathway leading to this loss can be described by the mechanism shown in Scheme 4.

Several experimental results from deuterium labelled a_4 support this mechanism. (i) From a_4-OD only ~20% of the label is lost with the neutral, suggesting that there is reversible proton exchange after ring opening to a'''. (ii) From a_4-7D_2 40% of DNCO is lost, indicating proton transfer from C(7) to the nitrogen.

These results can be interpreted in terms of a reversible proton transfer involving five hydrogens. Proton transfer within a_4''' is expected to take place between the nitrogen and the olefinic moiety comprising C(6) and C(7). If the hydrogen positions at N and C(7) were only involved, 66% loss of DNCO from a_4-7D_2, and correspondingly 33% loss from a_4-OD is expected, but proton transfer from C(6) may occur after a 1,2-H

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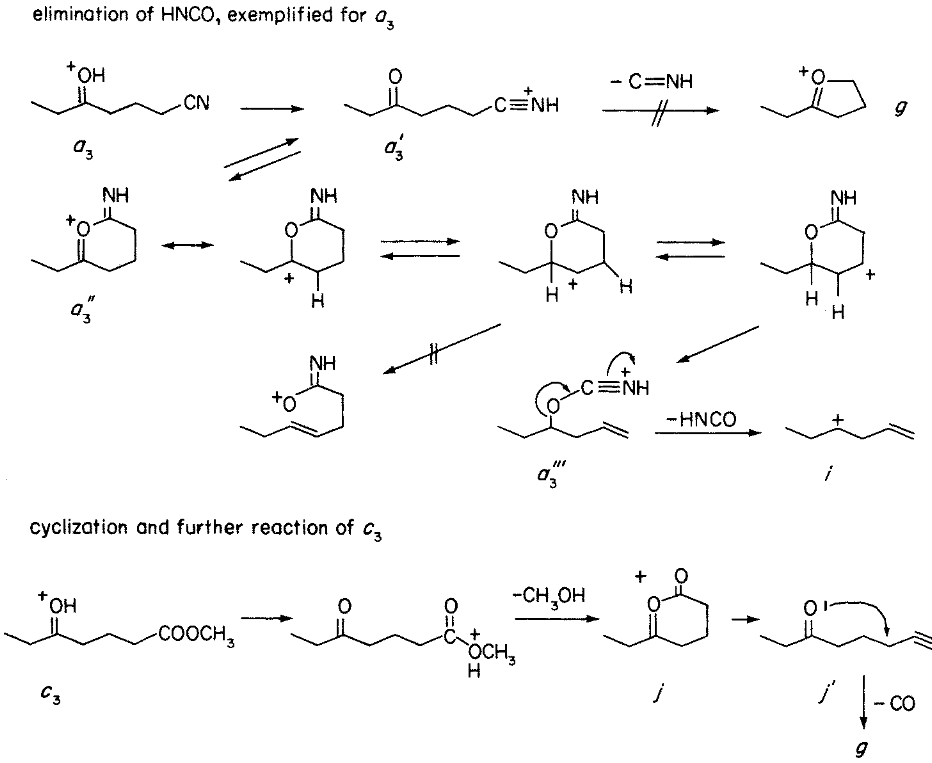
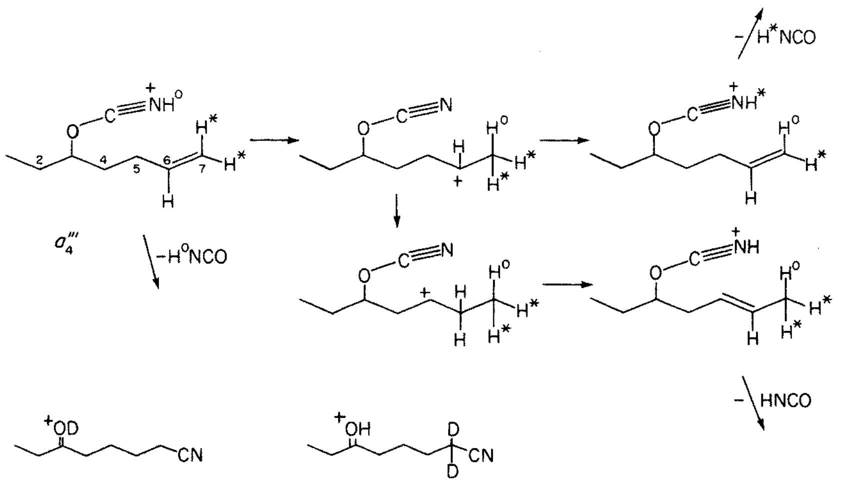
† By this representation the relative abundances of a_n are a direct measure of the proportion of undecomposed a_n, and high relative abundances of daughter ion's of a_n indicate that these ions are stable and preferentially formed.



Scheme 4



Scheme 5

shift. Scheme 5 serves to show how HNCO loss from a_4 may involve H loss from N, C(6) and C(7); it does not represent the mechanism of the reversible proton transfers.

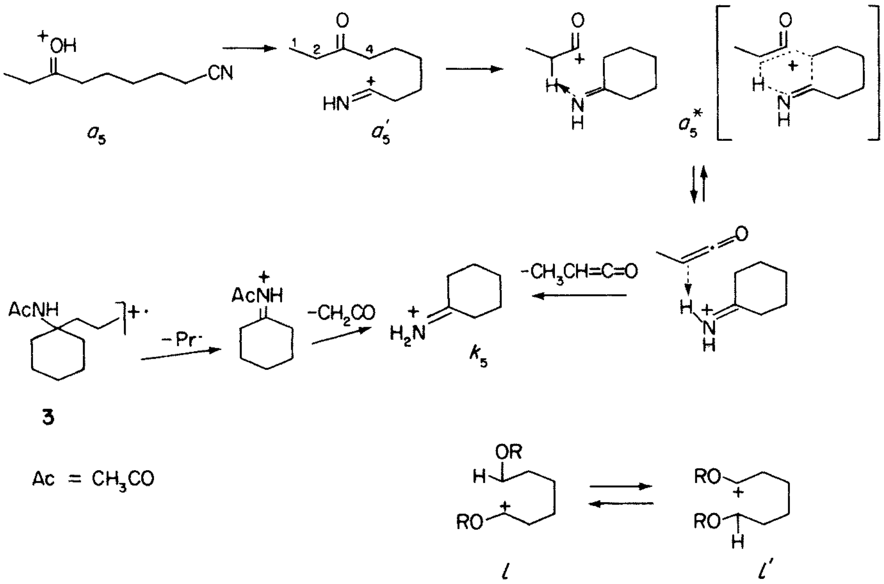
Loss of $CH_3—CH=C=O$

This elimination has been observed for a_1 and for a_4–a_6. It is obvious from Fig. 1 that the reactions from a_1 and from a_4–a_6, respectively, proceed via different mechanisms, as will be further substantiated in the following discussion.

Only the interesting reaction starting from a_4–a_6 is discussed here. For these ions it is easily shown that the methyl ketene lost contains the carbon atoms of the ethyl group. For example, $CH_3CH_2CH_2—C(=OH^+)—CH_2CH_2CH_2CH_2CN$, an ion homologous to a_4 in which the ethyl group is replaced by a propyl group, eliminates $CH_3CH_2—CH=C=O$ instead of $CH_3—CH=C=O$.

As for the case of HNCO loss, the reaction is restricted to the range of three homologues (a_4–a_6) within series a (the strong decrease of the abundances of $a - CH_3CHCO$ from a_5 to a_6 suggests that the next homologue a_7 will not undergo this loss). This again points to a reaction pathway involving the formation of, at least, intermediate cyclic ions. Moreover, the resulting ions are very stable according to their missing subsequent fragmentations in the 20 eV spectra. The high relative abundance of $a_5 - CH_3CHCO$ and the lack of further fragmentations strongly suggests a cyclic immonium structure for all these ions[5] (five-membered from a_4, seven-membered from a_6. The argument also holds for $a_4 - CH_3CHCO$, but note that a_4 exhibits an HNCO loss as a competing cyclization).

Taking this into account, the general ideas concerning the fragmentation behaviour of bifunctional oxonium ions leads to *k* as the resulting ion via the pathway depicted in Scheme 6.



Scheme 6

This will be briefly discussed. After the initial proton transfer from the OH group to the nitrogen (formation of *a'*) the favourable sterical conditions lead to the attack of C(4), neighbouring the CO group, by the carbon site of the charge centre. This process corresponds to the frequently observed ω-hydride transfer within bifunctional even-electron ions (compare, for example pseudoisomerization of l^6 in Scheme 6). For ions containing a keto-carbonyl unit, no activated hydrogen is available for hydride transfer but only C(2) and C(4) are activated for migration as an anion through withdrawal of the electrons from the respective C—CO bond. Of these C(4) is highly preferred in this reaction because of the sterical requirements of step $a' \rightarrow a^*$. In the conventional view, attack of the nitrogen site of the charge centre is not possible on mechanistical grounds; the nitrogen in the resonance form $C{\equiv}NH^+$ has a closed electron shell. This also results from the experimental findings; cyclization by attack of the nitrogen at the activated C(4) would lead to six- to eight-membered rings starting from a_4–a_6, which is not favourable for intramolecular cyclizations.

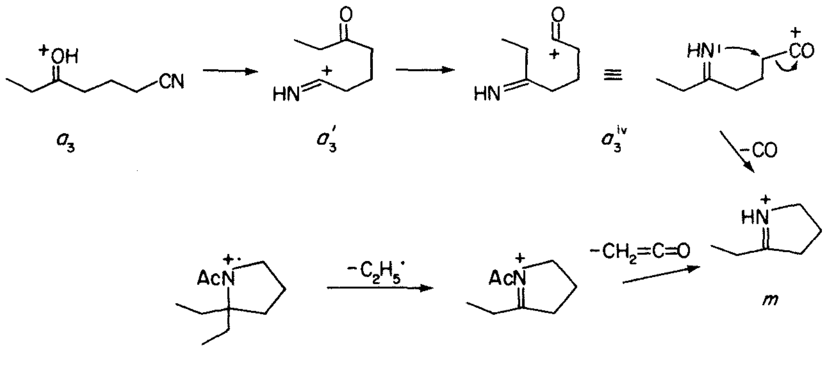
It cannot be decided, whether the reaction $a \rightarrow k$ proceeds stepwise via the depicted ion–molecule complex or by a concerted ring closure and proton transfer via the alternatively presented transition state. However, a relatively long-living loose complex seems to be involved in the course of the reaction. This can be inferred from the labelling results of the *O*-deuterated ions (a_4-OD–a_6-OD). The label is only retained with *k* to a portion of ~80%, indicating a partial exchange of the deuterium with hydrogens of the ethyl group.

The ion k_5 (*m*/*z* 98), generated from a_5, shows in its mass-analysed ion kinetic energy (MIKE) spectrum a weak peak for loss of NH_3 (*m*/*z* 81) of narrow Gaussian shape, and a very faint broader peak for loss of 42 u (*m*/*z* 56). The independently generated authentic ion (see Scheme 6) exhibits the same features in its MIKE spectrum. This result supports the suggestion that the ion formed from a_5 by loss of $CH_3CH{=}C{=}O$ has the structure *k*.

Loss of CO

The loss of CO is only found for a_3. At first glance, this reaction appears very strange, especially because it is restricted to only one homologue of series *a*. All control experiments, metastable ion spectra of a_3 (daughter ions, first field-free region (1st FFR) and MIKE (2nd FFR)), and of $a_3 - CO$ (parent ions, 1st FFR), confirmed the findings. The search for a convincing explanation revealed a very close connection between the loss of methylketene from a_4–a_6 and this CO loss. As pointed out in the discussion of the elimination of $CH_3{-}CH{=}C{=}O$, there are two carbon sites, C(2) and C(4), suited for migration as an anion. Considering C(2) as the favourite site within a_3' for the attack of the carbon of the charge centre provides the key for a very probable mechanism by applying the approved reaction principles used before. This mechanism is outlined in Scheme 7.

The initial stages $a_3 \rightarrow a_3' \rightarrow a_3^{iv}$ correspond to the steps $a_5 \rightarrow a_5' \rightarrow a_5^*$ (see Scheme 6). It is evident that the sterical conditions favour the reactive conformation of a_3' shown in Scheme 7 and explain why, in contrast to a_4–a_6, C(2) is the preferred reaction site. However, the process corresponding to cyclization via the ion–molecule complex a_5^* leads to ethyl anion migration



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Scheme 7

and formation of the rearranged ion a_3^{iv}. Subsequent proton migration, which for a_5 finally leads to k_5 and $CH_3CH{=}C{=}O$, could only generate another isomer of a_3. However, the sterical conditions again are very favourable for a reaction leading to the very stable immonium ion *m* and CO. A large kinetic energy release for this process can be concluded from the corresponding broad dish-shaped peak in the MIKE spectrum of a_3.

Finally, the MI spectra of $a_3 - CO$ (*m*/*z* 98) and of independently generated authentic *m* (Scheme 7) have been compared. Although for $a_3 - CO$ these spectra are rather poor because of the low abundance of this ion, in both cases the spectra consist of peaks from daughter ions at *m*/*z* 81, 70, 69, 57 and 56 with the ion at *m*/*z* 81 having the highest abundance. Thus, these results are in line with the proposed structure *m* for $a_3 - CO$.

Whilst a_2 could also form an isomer a_2^{iv} (structurally corresponding to a_3^{iv}) via a five-membered transition state, CO loss form this ion is not favourable any more (formation of a four-membered cyclic ion). Therefore, it is understandable that HNCO elimination via the five-membered a_2'' (see correspondingly for a_3'' in Scheme 4) prevails for a_2, whereas for a_3 both reactions are competing.

The CO loss from a_3 is an example of the (expected) displacement of C=O by C=NH, corresponding to the displacement of C=O by C=O (Scheme 4). Displacement of C=NH by C=O, however, is not observed.

CONCLUSIONS

The interaction of the hydroxonium moiety with the cyano group leads to a variety of primary reactions which strongly depend on the chain length separating the functional groups and which are unprecedented by the behaviour of other analogous bifunctional ions. In contrast to these ions, so far investigated, the second functional group is not lost in part or as a whole by simple displacement. This is certainly due to two factors: (i) the nitrogen is bound by a triple bond, and (ii) the nitrogen is very potent in stabilizing the positive charge in its vicinity and, thus, is less prone to be lost as a neutral as, for example, oxygen or chlorine. The difference with respect to this latter property is clearly seen from the fate of the $C{\equiv}O^+$ unit and the $C{\equiv}NH^+$ unit, contained in ions generated from *c* and *a*, respectively. While the $-CO^+$ unit is expelled as CO by the central functional group originating from the hydroxonium unit in *c*, the $-CNH^+$ unit formed from *a* triggers reactions which leave the nitrogen as an immonium ion (loss of $CH_3{-}CH{=}C{=}O$ and of CO, respectively) or which lead to loss of N together with the O from the central functional group (loss of HNCO). The fact that these reactions of *a* are so selective allows a good insight into the factors and conditions which govern such differences in reactivity.

EXPERIMENTAL

The normal mass spectra were obtained at an electron energy of 20 eV (nominal) and at 80 °C source temperature using a Varian MAT CH 5 mass spectrometer. The undeuterated samples were introduced by direct insertion according to the special procedure described in Ref. 1. The spectra of the deuterated samples were recorded via gas chromatography/mass spectrometry (GC/MS) from slow gas chromatographic runs using a packed SE-30 column. For *O*-deuteration of the samples the column had been saturated with D_2O before every sample introduction of **1** following the procedure described in Ref. 2.

The high-resolution mass measurements (resolution ~10000) were performed and the metastable ion spectra (daughter ions, first field-free region (1st FFR), B/E = constant) and second field-free region (DADI/mass-analysed ion kinetic energy spectrometry; B = constant) and parent ions, 1st FFR (B^2/E = constant)) were measured at 70 eV and at 150–250 °C source temperature using a Finnigan MAT 8222 instrument. The samples were introduced as noted above.

Preparation of compounds 1

1a: $Et_2{-}CO \xrightarrow[H_2SO_4]{NaCN} Et_2{-}C(OH){-}CN$ (**1a**) Ref. 7

$$\mathbf{1b}\text{: } Cl-CH_2-COOEt \xrightarrow[\text{Ether}]{\text{EtMgBr}}$$

$$Et_2-C(OH)-CH_2Cl \xrightarrow[\text{NMP}]{\text{NaCN}}$$

$$Et_2-C(OH)-CH_2CN\ (\mathbf{1b})$$

$$\mathbf{1c}\text{–}\mathbf{1g}\text{: } Et_2-C(OH)-(CH_2)_{2-6}OH \xrightarrow[\text{pyridine}]{p\text{-TsCl}}$$

$$Et_2-C(OH)-(CH_2)_{2-6}-OTs \xrightarrow[\text{NMP}]{\text{NaCN}}$$

$$Et_2-C(OH)-(CH_2)_{2-6}CN\ (\mathbf{1c}\text{–}\mathbf{1g})$$

Preparation of compounds 3 and 4 (precursors for the reference ions k_5 and m)

$$\mathbf{3}\text{: } (CH_2)_5-C(OH)-C_3H_7 \xrightarrow[\text{AcOH, }H_2SO_4]{CH_3CN}$$

$$(CH_2)_5-C(NHAc)-C_3H_7 \quad (\mathbf{3})$$

(Ritter reaction)[8]

$$\mathbf{4}\text{: } Et_2-C(OH)-(CH_2)_3-OH \xrightarrow[\text{AcOH, }H_2SO_4]{CH_3CN}$$

$$Et_2-C(NHAc)-(CH_2)_3-OAc \xrightarrow[CH_3OH]{OH^-}$$

$$Et_2-C(NHAc)-(CH_2)_3-OH \xrightarrow[\text{pyridine, 0°C}]{p\text{-TsCl}}$$

$$Et_2-C(NHAc)-(CH_2)_3-OTs \xrightarrow[\text{80°C, 3h}]{\Delta}$$

$$Et_2-C-(CH_2)_3-NAc \quad (\mathbf{4})$$

(intramolecular displacement of OTs by NAc)

Compounds **1** and **4** were purified by distillation *in vacuo*, **1b**–**1g** were further purified by preparative gas chromatography (SE-30, 100 °C (**1b**)–180 °C (**1g**)). Compound **3** was purified by sublimation (90 °C/1 Torr) and successive recrystallization from cyclohexane (m.p. 83–84 °C).

Preparation of the deuterated compounds 1

1-OD: see above. Deuterium content (evaluated after GC/MS introduction) was 80–90%

$$\mathbf{1e}\text{-}7D_2 \text{ (precursor for } a_4\text{-}7D_2\text{): } \mathbf{1e} \xrightarrow[\text{60°C, 5h}]{\text{NaH, }CH_3OD}$$

$$\xrightarrow{H^+} Et_2-C(OH)-(CH_2)_3-CD_2-CN \quad (\mathbf{1e}\text{-}7D_2).$$

Deuterium content (evaluated by mass spectrometry) was 50 ± 1%.

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