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REARRANGEMENT AND HYDROGEN ABSTRACTION REACTIONS OF AMINE CATION RADICALS;

A GAS-PHASE ANALOGY TO THE HOFMANN-LÖFFLER-FREYTAG REACTION

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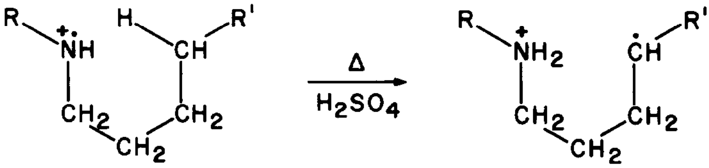
ABSTRACT: Low-energy molecular ions of gas-phase primary and secondary aliphatic amines undergo reciprocal NH/CH exchange of hydrogen atoms prior to fragmentation on the microsecond time-scale; the subsequent decomposition reactions are significantly different from those observed in the mass spectrometer ion source.

It is well known that the cation radicals of many simple aliphatic compounds may fragment in the gas-phase after transfer of a remote hydrogen atom to the functional group. The loss in the mass spectrometer of H_2O from aliphatic alcohols and of HX from alkyl halides are examples of this. However, it has been generally accepted that gas-phase amine cation radicals do not exhibit similar behavior. This is perhaps surprising, since the $\rangle NH^{+\cdot}$ group of aliphatic amine cation radicals is known to react in solution by intramolecular abstraction of hydrogen atoms in the synthetically useful Hofmann-Löffler-Freytag reaction, where abstraction occurs with a high degree of positional specificity in a six-membered cyclic transition state.[2]

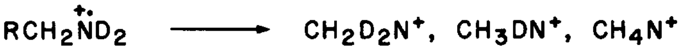


The mass spectrometry, in particular the ion-source processes, of aliphatic amines has been thoroughly studied.[3] It is well known that α-cleavage is the predominant decomposition reaction of the molecular ions; rearrangements occur infrequently and are of little importance, and in particular the hydrogen atoms of the amino group of small aliphatic amines have been reported to remain structurally distinct through the primary and many secondary fragmentation reactions.[4,5] However, an examination of the reactions that occur microseconds after ionization for low-energy simple primary or secondary amine cation radicals - that is, the reactions of metastable amine molecular ions in the field-free regions of the mass spectrometer - has now shown that the $-NH_2^{+\cdot}$ or $\rangle NH^{+\cdot}$ groups do in fact participate in extensive intramolecular hydrogen exchange reactions with remote CH groups.

Furthermore, the important slow reactions of these ions are β-cleavage and/or skeletal rearrangement processes, rather than simple fission of the α C-C bond.

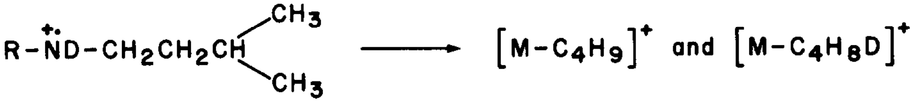
The following examples[6] illustrate these points:

(i) The amino group of primary and secondary alkylamines with chains of four or more carbon atoms takes part in extensive hydrogen exchange reactions prior to fragmentation: where butylamine gives m/z 30 ions, the N,N-d_2 derivative produces m/z 30 (34%), 31 (54%), and 32 (12%); 4-methylpentylamine-N,N-d_2 loses NH_3 (37%), NH_2D (49%), and NHD_2 (14%); the m/z 44 ion (see below) of octylamine becomes m/z 44 (41%), 45 (49%), and 46 (10%) for the N,N-d_2 derivative.

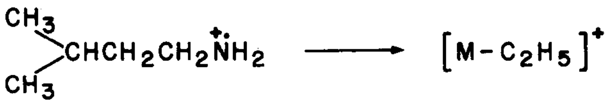


$$RCH_2\overset{+\bullet}{N}D_2 \longrightarrow CH_2D_2N^+,\ CH_3DN^+,\ CH_4N^+$$

(ii) The exchange reactions in primary and secondary amines may involve several methylene groups along the chain; n-octylamine-N,N-d_2 loses (inter alia, see below) $C_3H_7^\bullet$ and $C_3H_6D^\bullet$; diisopentylamine loses $C_4H_9^\bullet$, the N-d derivative $C_4H_9^\bullet$ and $C_4H_8D^\bullet$ in a 1.6:1 ratio.[8] By contrast, there is nothing to suggest that the hydrogen atoms of tertiary alkylamines lose their positional identity.



(iii) Amines with branched primary alkyl groups undergo skeletal rearrangements prior to fragmentation; e.g., the predominant reaction of isopentylamine (3-methylbutylamine) is loss of $C_2H_5^\bullet$ (the amino hydrogens are retained in the charge-retaining moiety in this reaction); secondary amines with an N-isopentyl group likewise lose $C_2H_5^\bullet$.



(iv) For primary n-alkylamines, α-cleavage is an important fragmentation pathway only when the chain is less than four carbon atoms long; in most cases, the major reaction corresponds formally to β-cleavage (for n-octylamine, more than 80% of the fragmenting molecular ions react to give m/z 44, $C_2H_6N^+$, only about 1% give $CH_2NH_2^+$; in addition, minor signals are observed for loss of C_1-C_5 alkyl radicals). Similarly, with secondary di-n-alkylamines β-cleavage outweighs α-cleavage for chains of four carbon atoms or more. Tertiary amines, however, react nearly exclusively by α-cleavage.

$$RCH_2CH_2\overset{+\bullet}{N}H_2 \longrightarrow C_2H_6N^+$$

There are strong indications that the hydrogen exchange reactions are initiated by specific abstraction by the $-NH_2^{+\bullet}$ of an alkyl hydrogen atom four carbons removed: firstly, amines with shorter carbon chains show no or very little exchange; furthermore, for 3-methylbutylamine-*N*,*N*-d_2, deuterium may be incorporated into the methyl groups, while the methyls of 4-methylpentylamine-*N*,*N*-d_2 are not involved (about equal loss of $CH_3^\bullet$ and $CH_2D^\bullet$ from the former, only $CH_3^\bullet$ loss from the latter); finally, loss of NH_3 from the molecular ion is for most primary amines a minor process, but it becomes the most important fragmentation pathway when the δ hydrogen is tertiary, as in 4-methylpentylamine. The similarity and apparent site-specificity of the initial steps of the slow (on the mass spectrometer time scale) intramolecular reactions of amine cation radicals in the gas-phase and in solution suggests that the Hofmann-Löffler-Freytag reaction is another condensed-phase reaction that has a mass spectrometric counterpart; this provides experimental confirmation of the suggestion[9] that this reaction may be seen as bridging mass spectrometry and free radical chemistry.[10]

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References and Notes:

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5. Abstraction or exchange reactions have been observed for amines with benzylic hydrogen atoms and for aliphatic diamines; see D.A. Lightner, F.W. Sunderman, L. Hurtado and E. Thommen, *Org. Mass Spectrom.*, **3**, 1325 (1970); H. Schwarz, C. Wesdemiotis, B. Hess and K. Levsen, *Org. Mass Spectrom.*, **10**, 595 (1975); F. Mayerl and H. Hesse, *Helv. Chim. Acta*, **59**, 127 (1976); P.-A. Blanc, G.A. Singy and A. Buchs, *Org. Mass Spectrom.*, **11**, 995 (1976).

6. The reactions were examined by mass analyzed ion kinetic energy (MIKE) spectrometry performed on an unusually large mass spectrometer (ref. 7) built in this department; in this instrument, the magnetic analyzer precedes the electric analyzer. The decompositions observed take place in a 2.7 m long field free region between the analyzers.

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8. Exchange reactions of this nature clearly invalidate mechanistic conclusions drawn from the ratio of labeled to unlabeled radical lost in competing α-cleavage reactions of deuterium labeled secondary amines; see J.F. Wendelboe and S. Hammerum, *Adv. Mass Spectrom.*, **8** (1980), in press.

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10. Also the α-cleavage reaction of amines has a condensed-phase counterpart. 2-Phenylethylamine cation radicals have been shown to fragment in solution by fission of the C_α-C_β bond; see F. Minisci and R. Galli, *Tetrahedron Letters*, *1966*, 2531 and J.R.L. Smith, R.O.C. Norman and A.G. Rowley, *J.C.S. Perkin I*, *1972*, 228.

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