Electron Ionization Induced Fragmentation of Macrocyclic Amines $C_nH_{2n-1}NH_2$: Evidence for the Rearrangement of Aminocarbene Radical Cations and a Comparison with Long-Chain Esters

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A general mechanism is proposed for the fragmentation of macrocyclic amines under electron ionization (EI). The mechanism involves their rearrangement into long-chain enamines followed by the transfer of the aminocarbene radical cation $[CHNH_2]^{+\cdot}$ through large-ring transition states. A similar mechanism could be applied also to the EI-induced fragmentation of long-chain esters with the transfer of the methoxyhydroxycarbene $[C(OH)(OCH_3)]^{+\cdot}$ radical cation. *(J Am Soc Mass Spectrom 1990, 1, 238–248)*

After ionization of amines in the gas phase, the charge is generally stabilized by the heteroatom as an ammonium or immonium distonic ion [1] by a rearrangement or α-cleavage. The radical induces bond cleavages and bond formations that may result, after a more or less complicated pathway, in the dissociation of the parent ion. So the unimolecular dissociation of ionized amines results essentially from the radical reactivity [1].

Only small-ring alicyclic amines have been considered so far—amines that either are monocyclic [2–5] or participate in polycyclic structures such as steroidal amines.

In this paper we describe the fragmentation under electron ionization (EI) of macrocyclic amines C_nH_{2n-1}—$NH_2^{+\cdot}$ with different ring sizes and with n extending from 7 to 16.

This study was instructive with respect to not only the reactivity of amines under EI but, more generally, the reactivity of long-chain aliphatic compounds with different functional groups like esters.

Experimental

The cyclic amines were obtained by standard procedures from the corresponding commercial cyclic ketones (lithium aluminium hydride reduction of the corresponding oximes in tetrahydrofuran). d_1-C(1)-Cyclohexadecylamine was prepared by reduction of the cyclohexadecanone oxime with lithium aluminium deuteride. The tetradeuterated derivatives were prepared by the same procedure following exchange with deuterium of the enolizable hydrogens of the ketones (MeOD, D_2O, Na).

The amines studied are transformed more or less rapidly into carbonates by simply standing in the atmosphere. The carbonates are crystalline, are less volatile and more easily handled than free amines, and liberate the bases spontaneously under the conditions of introduction of the samples in the ion source. The direct introduction probe was used without heating; the source temperature was 150 °C.

The EI mass spectra were measured with an MS 50 instrument (ICSN, Gif sur Yvette). Mass-analyzed ion kinetic energy (MIKE) spectra were measured with a ZAB 2F instrument (Ecole Polytechnique). The electron energy was 70 eV, the trap current 100 μA, and the acceleration voltage 8 kV.

Results and Discussion

The 70-eV EI mass spectra of macrocyclic amines show a base peak at *m/z* 56 and other minor peaks representing homologous ions resulting from the cleavage of all the other C—C bonds of the ring. Some of these fragmentations appear more favored than others, however, like the loss of 43 mass units and the production of an ion of *m/z* 112 (Figure 1; see also Figure 14).

In the MIKE spectra, the peak at *m/z* 56 is absent, the other peaks becoming relatively more important (Figure 2). An additional M−17 peak representing the loss of ammonia is also present but will not be discussed here.

The α cleavage of amines is well known as a facile process [6] that leads to a distonic ion in which the re-

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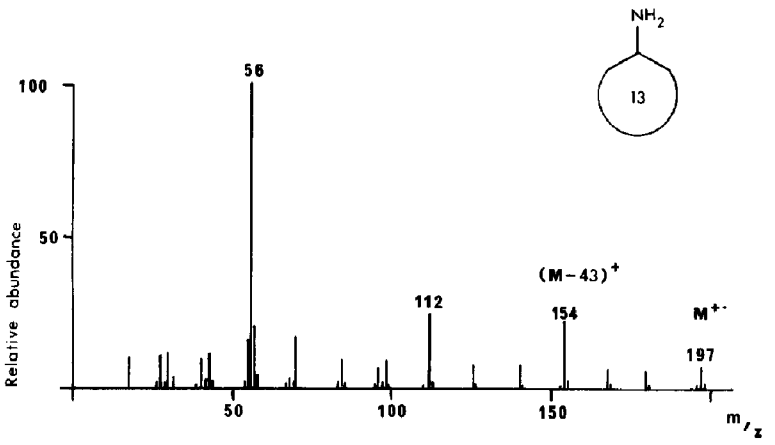


Figure 1. 70-eV EI mass spectrum of cyclotridecylamine.

arrangement of a hydrogen from C(2) usually follows, leading to a radical ion **a**. Ion **a** is nothing else than an ionized enamine (Scheme I), commonly formed in the fragmentation of cyclic amines after ring opening.

Ions **a** of high energy decompose by C(3)—C(4) cleavage, leading to the fragment ion *m/z* 56. Low-energy ions **a**, instead, suffer radical-induced rearrangements; the radical is displaced along the chain where it may induce C—C bond cleavages. Displacement of the radical and C—C bond cleavages are competing reactions.

To shed some light on these low-energy decompositions, we have examined the fragmentation of the d_1-C(1)-cyclohexadecylamine (n = 16) and also the d_4-C(2)C(n) derivatives of all the compounds studied.

The presence of one D atom on C(1) adds 1 mass unit to all the fragment ions formed (70 eV EI and MIKE spectra). This shows definitely that all these ions contain C(1) attached to the amine function.

In the MIKE spectra of C(2)C(n)-tetradeuterated compounds (n = 7–16), (Figures 3–10), the largest peaks correspond to d_1- or d_3-labeled ions (marked with filled and open circles, respectively, in the figures). They are accompanied by smaller satellite peaks representing ions with different label content (d_0, d_2, and d_4). This clearly indicates that the parent ions decompose preferentially by losing either d_3- or d_1-labeled alkyl radicals, respectively. Therefore, it seems reasonable to postulate that the d_3-labeled neutral fragments originate from the terminal part of the chain of

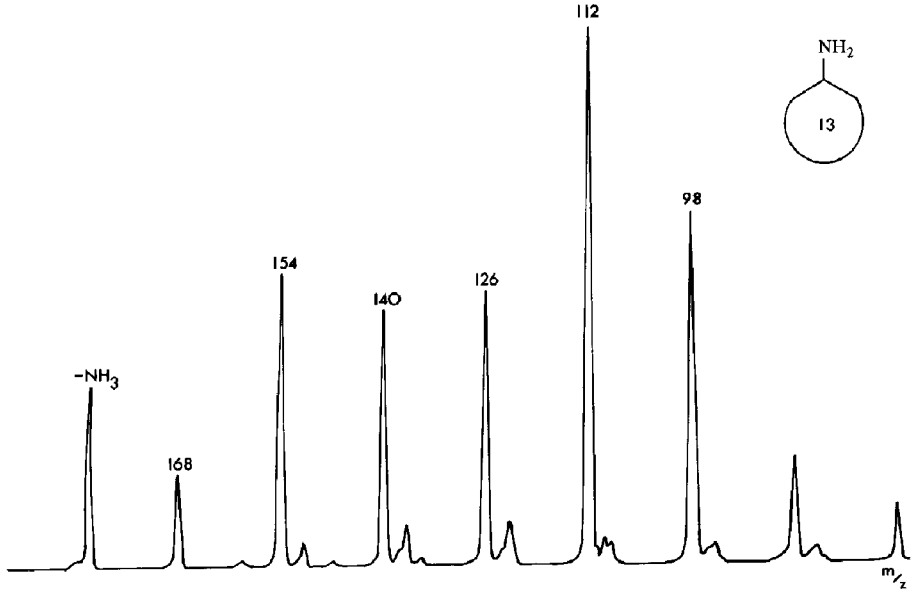
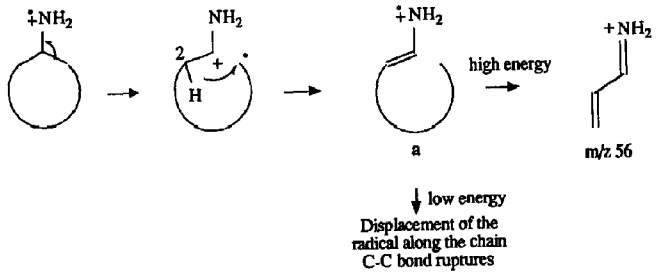


Figure 2. MIKE spectrum of cyclotridecylamine.



Scheme I

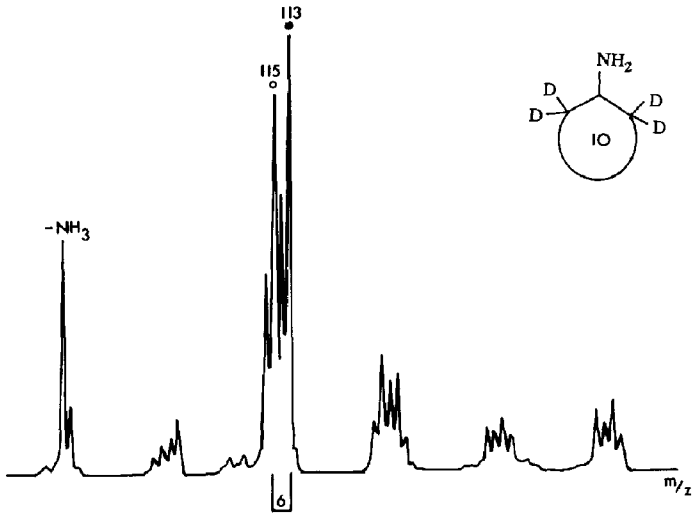


Figure 3. MIKE spectrum of d_4-C(2)C(10) cyclodecylamine (● and ○ labels are for d_1 and d_3, respectively, in Figures 3–10.)

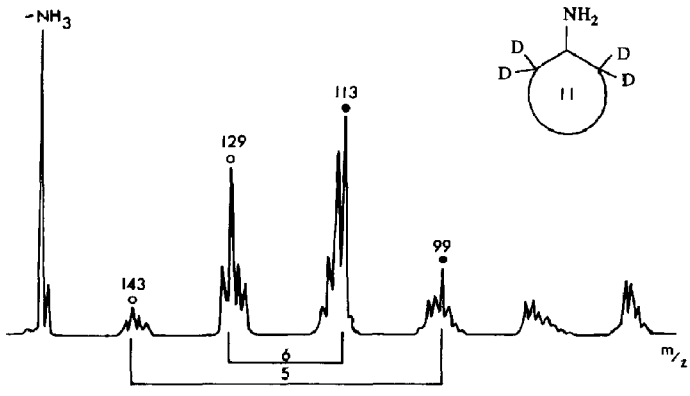


Figure 4. MIKE spectrum of d_4-C(2)C(11) cycloundecylamine.

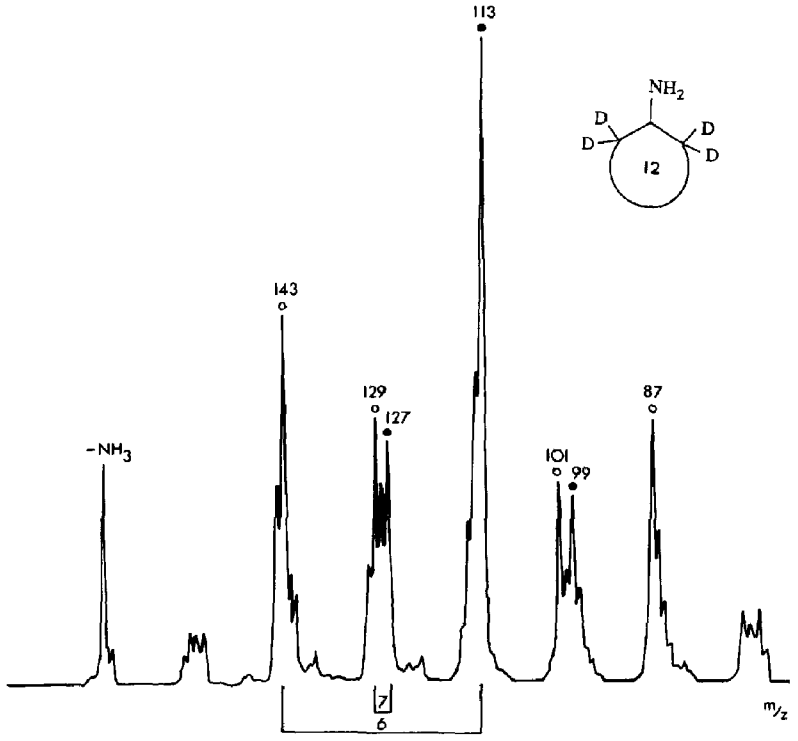


Figure 5. MIKE spectrum of d_4-C(2)C(12) cyclododecylamine.

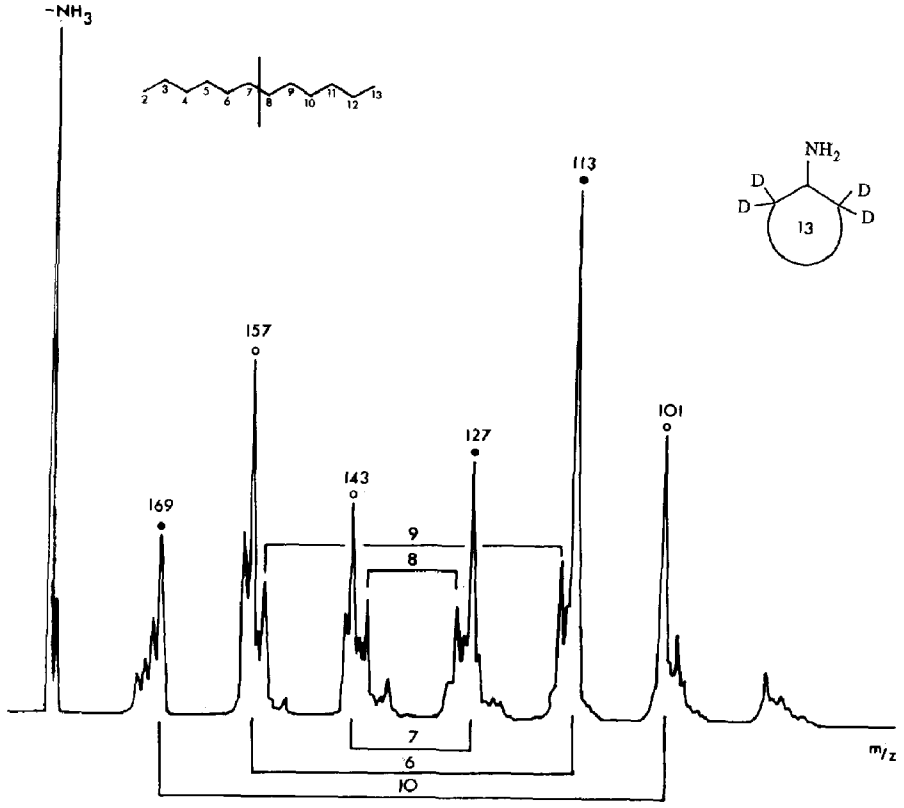


Figure 6. MIKE spectrum of d_4-C(2)C(13) cyclotridecylamine.

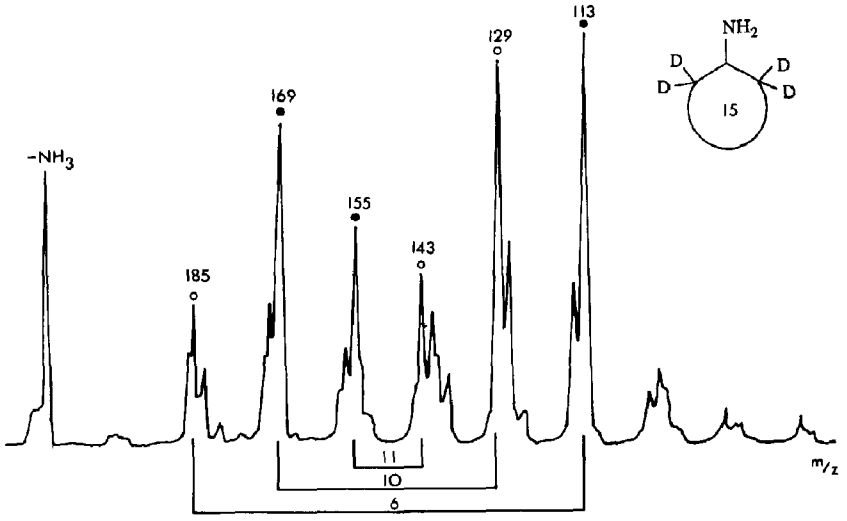


Figure 7. MIKE spectrum of d_4-C(2)C(15) cyclopentadecylamine.

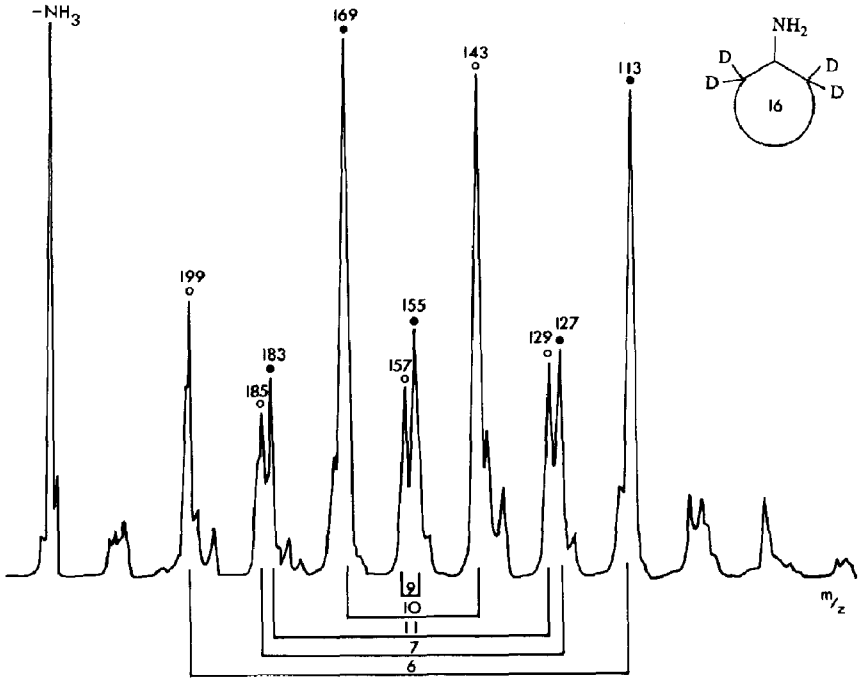


Figure 8. MIKE spectrum of d_4-C(2)C(16) cyclohexadecylamine.

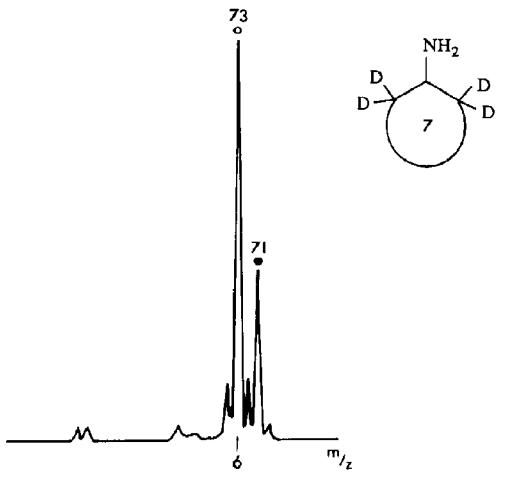


Figure 9. MIKE spectrum of d_4-C(2)C(7) cycloheptylamine.

ion **a** (Scheme II), whereas the d_1-labeled neutral fragments contain C(2) and therefore result from the "expulsion" of an alkyl radical from the central part of the chain with rearrangement of the $[C(1)HNH_2]^{+\cdot}$ unit.

This clear-cut dichotomy of the dominant fragment ions between monodeuterated and three-deuterated species, confirms also, incidentally, that, for ions of low internal energy, the H transfer from C(2) to C(n) is probably the most rapid reaction after the initial ring opening, leading to a terminal CD_3 group (ion **a** in Scheme III).

The rearrangement of the $[CHNH_2]^{+\cdot}$ group can be understood only as induced by the radical on different sites in the chain and leading to intermediate ions **d** as shown in Scheme III.

For ion **a**, the transfer of a hydrogen from the chain to C(2) leads to a distonic ion **b**. If the carbon chain of the latter adopt an adequate conformation (see later), the rearrangement of the $[CHNH_2]^{+\cdot}$ unit may occur, leading to ion **c**, which, in turn, may be readily transformed into the more stable ion **d** by further hydrogen transfer. The ion **d** is an isomer of the parent ion whose structure is such that it may lose an alkyl radical from either side of the branching carbon, resulting in "complementary" ions **e** or **f**, d_1- or d_3-labeled, respectively (Figures 3–10).

Such a radical cation rearrangement is not unprecedented if one considers the analogy between aminocarbene $[CHNH_2]^{+\cdot}$ and hydroxycarbene radical cations. The latter were shown several times to rearrange during reactions in the gas phase [7]. For example, the 1,2-migration of the $[C(OH)_2]^{+\cdot}$ radical cation occurs in the dissociation of carboxylic acids [8–12], and the 1,2-migration of the $[C(OH)(OCH_3)]^{+\cdot}$ radical cation in the case of esters [13]. Our results show that analogue aminocarbene radical cations are also prone to rearrange and do so through large-ring transition states as well.

Several arguments that corroborate this hypothesis are set forth in the following paragraphs.

The most obvious feature of the MIKE spectra of the largest ring compounds (Figures 3–8) is a certain symmetry in their general profile. As already mentioned, the dominant dissociations into either d_1- or d_3-labeled fragment ions indicate that the major part of the dissociating parent ions contains one D at C(2) and three D at C(n) as shown by Scheme III. However, H–D randomization competes with these dissociations, leading to a small fraction of parent ions with a different distribution of the label and therefore, possibly, to differently labeled fragment ions (d_0, d_2, and d_4) represented by smaller peaks in the spectra. Consequently, the spectra appear as a series of "multiplets," each of them representing the same fragment ion with different label contents from d_0 to d_4 and resulting from the loss of isomer alkyl radicals from both ends of the C(2)–C(n) carbon chain (Scheme III).

Looking at the spectra (Figures 3–8), we see immediately that the profiles of the multiplets correspond to one another more or less like mirror images. This shows indeed that each couple of symmetric multiplets

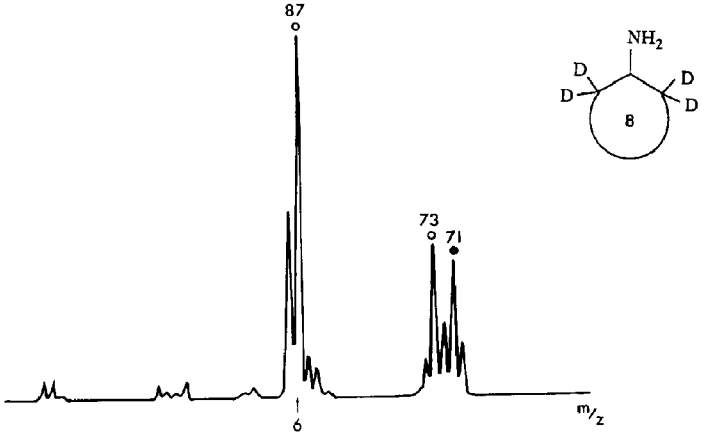
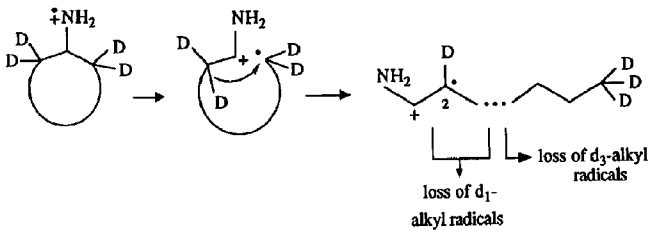


Figure 10. MIKE spectrum of d_4-C(2)C(8) cyclooctylamine.



Scheme II

represents complementary fragment ions **e** and **f** deriving from key ions **d** whose branching carbons are located at symmetric positions equally distant from the center of the C(2)–C(n) carbon chains. The "symmetry" in the profiles of the multiplets results, of course, from the fact that the abundances of ions **e** and **f** deriving from the same parent ion **d** are roughly similar because the probabilities for ions **d** of losing either alkyl radical are not very different except for the loss of a methyl radical, which is always very weak or absent.

The 70-eV EI mass spectra of the d_4-labeled amines also deserve some comment because they show the contribution of parent ions of higher internal energy. They also display multiplets for homologous fragment ions, but large and often dominant peaks are now those that represent d_2-labeled fragment ions (Figure 11).

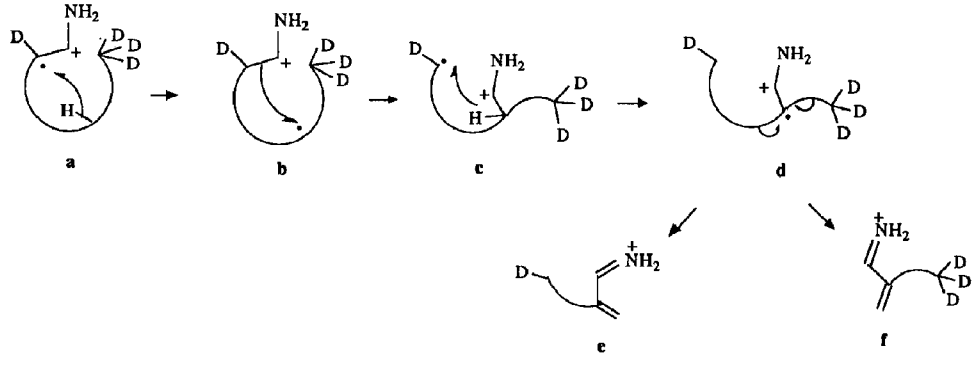
In particular, important [M−45], [M−44], and [M−43] peaks represent d_2-, d_3-, and d_4-labeled fragment ions, respectively, in the order of decreasing abundance. The MIKE spectra of $[M-44]^{+\cdot}$ and $[M-43]^{+\cdot}$ ions show a very abundant ion at m/z 70(71) characteristic of the structure of ions **e** (see later), whereas the MIKE spectrum of the $[M-45]^{+\cdot}$ ions does not and appears different. Obviously, the d_2-labeled fragment ions, on the one hand, and the d_1- and d_3-labeled fragment ions, on the other hand, originate from high- and low-energy parent ions, respectively, through different mechanisms.

This striking difference between MIKE and 70-eV mass spectra may be interpreted as follows: As the internal energy accumulates in the dissociating C—C bond (α-cleavage), it may reach a level at which the separation of ion and radical is not completed but does allow the thermodynamically favored transfer of a D atom from C(2) to the radical at C(n), leading finally to d_1- and d_3-labeled fragments by the mechanism described above. Instead, when more internal energy is present in the reaction coordinate, ion and radical separate more readily and the direct transfer of a D atom from C(2) to C(n) becomes less probable. In this case, the rearrangement of other hydrogens of the carbon chain to the radical takes over, leading to ions **b** (Scheme III) with two D atoms at C(2) and two D atoms at C(n), which decompose essentially into d_2-labeled fragments by different pathways.

As a consequence, the interesting dichotomy described above between d_1- and d_3-labeled fragments is hidden in 70-eV EI mass spectra and shows up only in the decomposition of low-energy ions.

The above rearrangement of a hydrogen from C(2) to C(n) in low-energy cyclic amines has also been described [14] in the fragmentation of low-energy linear aliphatic amines, which lose an alkane molecule in competition with the loss of an alkyl radical.

The most abundant ions in the cases of cyclic amines with n = 7–13 (Figures 3–6, 9, and 10) result from the fragmentation of ion **d** with C(6) as branching carbon. This preference may be explained in the following way: Key ions **d** derive from a series of consecutive rearrangements whose critical energies are governed by the ring size of their transition state. Indeed, C(6)



Scheme III

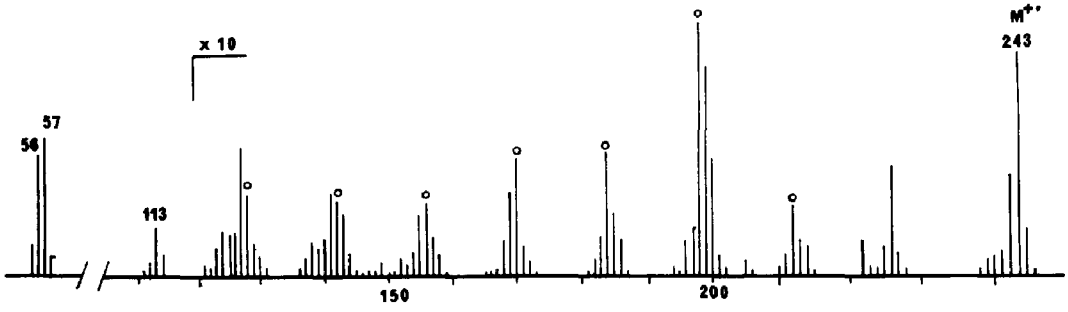


Figure 11. 70-eV EI mass spectrum of d_4-C(2)C(16) cyclohexadecylamine. (O labels indicate d_2-containing fragment ions.)

is the best site for participating in the process, since in that case all successive rearrangements involve six-membered ring intermediates (Scheme IV). This ring size probably allows a relatively more stable "chair" conformation of the coiling alkyl chain during the rearrangements.

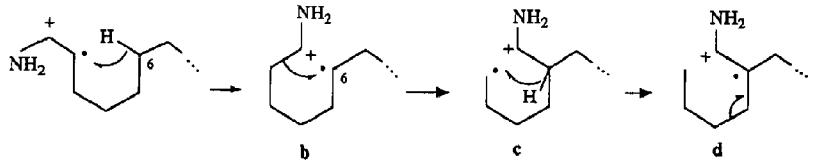
In the cases of cyclopentadecylamines (n = 15) and cyclohexadecylamines (n = 16) (Figures 7 and 8), the formation of 10-membered ring intermediates (double chair) appears to be favored (Scheme V). All other possible ring intermediates (seven-membered, five-membered, etc.) play a less important role.

It may be noticed, incidentally, that the H-D randomization mentioned above appears relatively more important when competing with more difficult processes. Peaks representing d_3- and d_1-labeled ions deriving from favored rearrangements on C(6) or C(10) are much more prominent than those deriving from less favored ones.

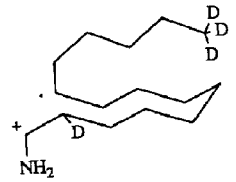
The MIKE spectra of corresponding ions **e** and **f** are very similar. For example, the MIKE spectrum of ion **f** $[M - 44]^+$, resulting from the expulsion of a d_1-propyl radical (Figure 12) from d_4-C(2)C(16)-cyclohexadecylamine, displays a large peak at m/z 70. The MIKE spectrum (Figure 13) of the complementary ion **e**, m/z 113, shows the same peak, m/z 70, partially shifted to m/z 71, probably because of prior H–D exchanges in the parent ion. Ions of m/z 70(71) may be produced by a six-membered ring H rearrangement with loss of an olefin (Scheme VI). This shows a similarity in the structures of ions **e** and **f** deriving from a common ion **d** by loss of homologous neutral radicals. One may also conclude from these two spectra that the D atom of ion **e** is more prone to randomize than the three D atoms of ion **f** because the latter dissociates only into unlabeled m/z 70 ions. This may confirm that the location of the three Ds in ion **f** is the less reactive terminal methyl group.

Cyclic amines with smaller rings present, of course, a more limited number of possibilities. In the case of cyclooctylamine (Figure 10), the complementary ion for the loss of the d_1-propyl radical (which gives the ion of m/z 87) would result from the loss of a d_3-methyl radical and is not observed. Two peaks of equal size appear at m/z 71 and 73. They derive from rearrangement of the aminocarbene radical cation on C(3) or C(7) with about equal probabilities. This possibly indicates the intermediacy of a common ion structure involving these two symmetric sites.

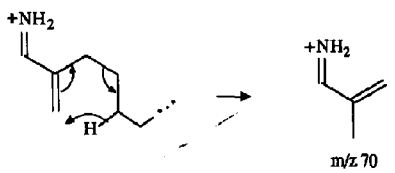
In the case of cycloheptylamine (Figure 9), the rearrangement on C(6) is also dominant (loss of the d_1-propyl radical). Here again one observes, although to



Scheme IV



Scheme V



Scheme VI

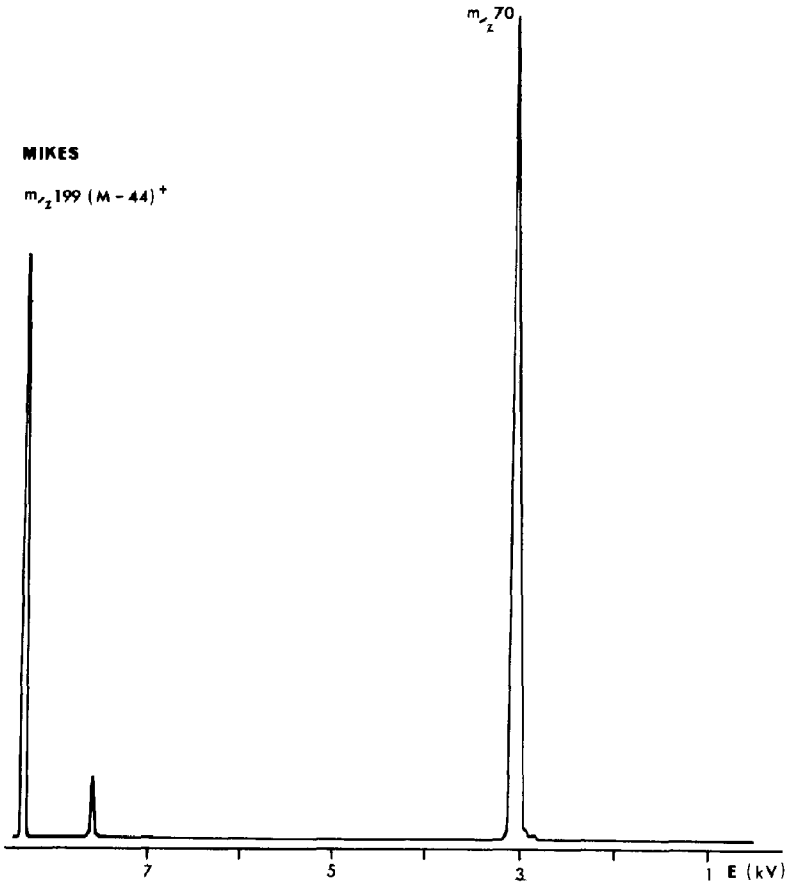


Figure 12. MIKE spectrum of the d_3 f ion $[M - 44]^+$ from d_4-C(2)C(16) cyclohexadecylamine.

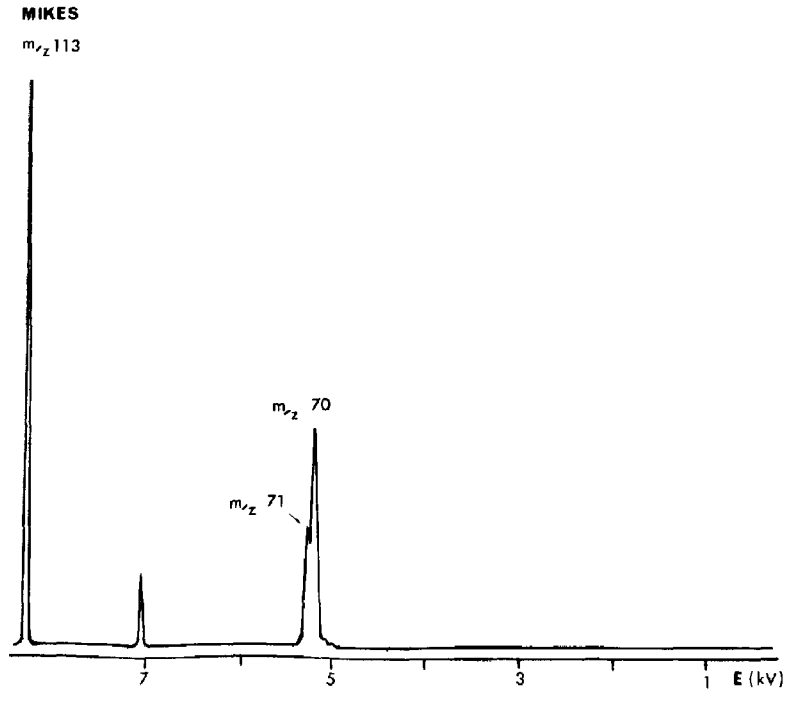


Figure 13. MIKE spectrum of the d_1 e ion (m/z 113) from d_4-C(2)C(16) cyclohexadecylamine.

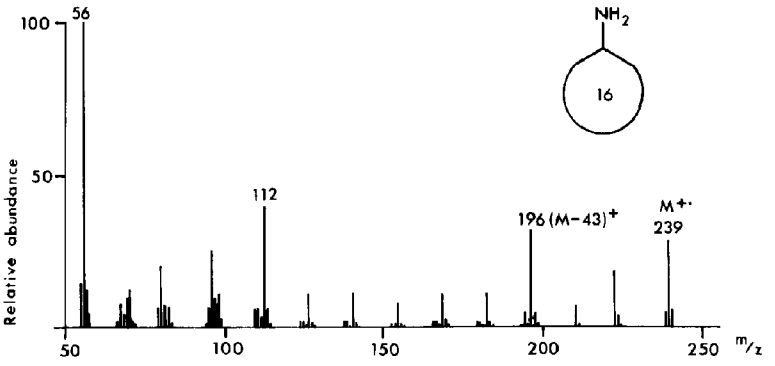


Figure 14. 70-eV EI mass spectrum of cyclohexadecylamine.

a lesser extent, the loss of the d_3-propyl radical resulting from rearrangement of the aminocarbene radical cation on C(3).

In the case of d_4-C(2)C(10)-cyclodecylamine (Figure 3), large peaks of about equal height are observed at *m/z* 113 and 115. In this case, the ion **d** with C(6) as branching carbon has a perfectly symmetric structure and loses either propyl radical (d_3 or d_1) with equal probabilities.

It is noteworthy that, in the fragmentation of the largest macrocyclic amines (or long-chain enamines) of low energy, 10-membered ring intermediates are preferred (Figures 7 and 8). In the 70-eV mass spectra, on the other hand, six-membered ring intermediates play the major role to give the *m/z* 112 ion and the $[M-43]^{+\cdot}$ (Figure 14). These observations are in accord with the model proposed by Meyerson and Leitch [15] many years ago, accounting for the "tendency of flexible molecules to coil back on themselves." The 10- membered (and possibly 14-membered and larger) ring intermediates are probably better stabilized by a more extended "internal solvation" [15]. On the other hand, the entropy factor is probably more favorable in the case of six-membered ring intermediates, which play a major role in the reactivity of ions with more internal energy.

Analogy with Long-Chain Esters

Because the fragmentation of macrocyclic amines under EI occurs, as shown above, essentially after ring opening into ionized long-chain enamines, it may be compared with the fragmentation of other long-chain compounds with a different functionality, like esters.

The 70-eV mass spectra of long-chain esters are well known [16, 17], with two large peaks at *m/z* 74 and 87 and many minor peaks representing homologous fragment ions resulting from cleavage of all C—C bonds of the chain (Scheme VII). Some of these fragment ions, here again, are relatively more abundant, like $[M-43]^+$ and the *m/z* 143 ion. All these peaks remain important in the MIKE spectra except ions of *m/z* 74 and 87

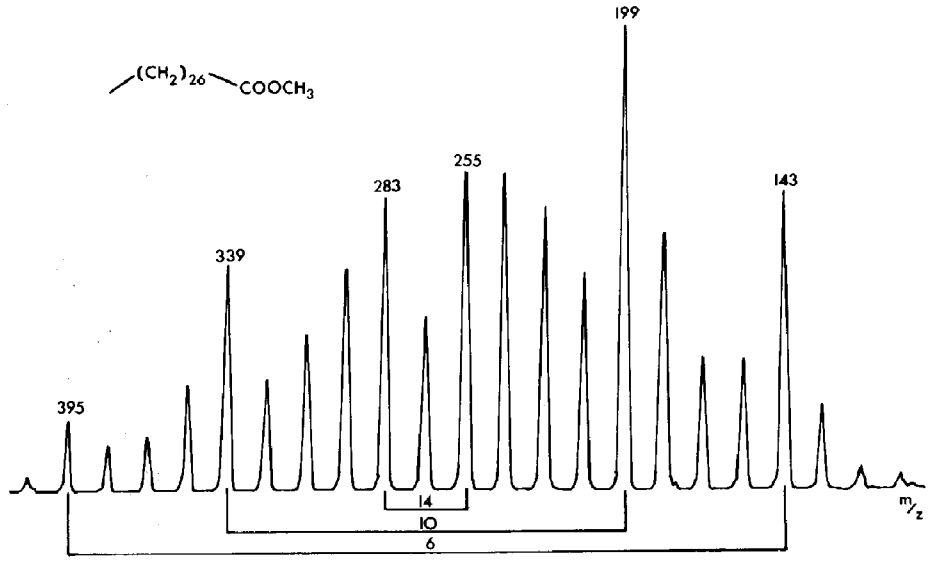
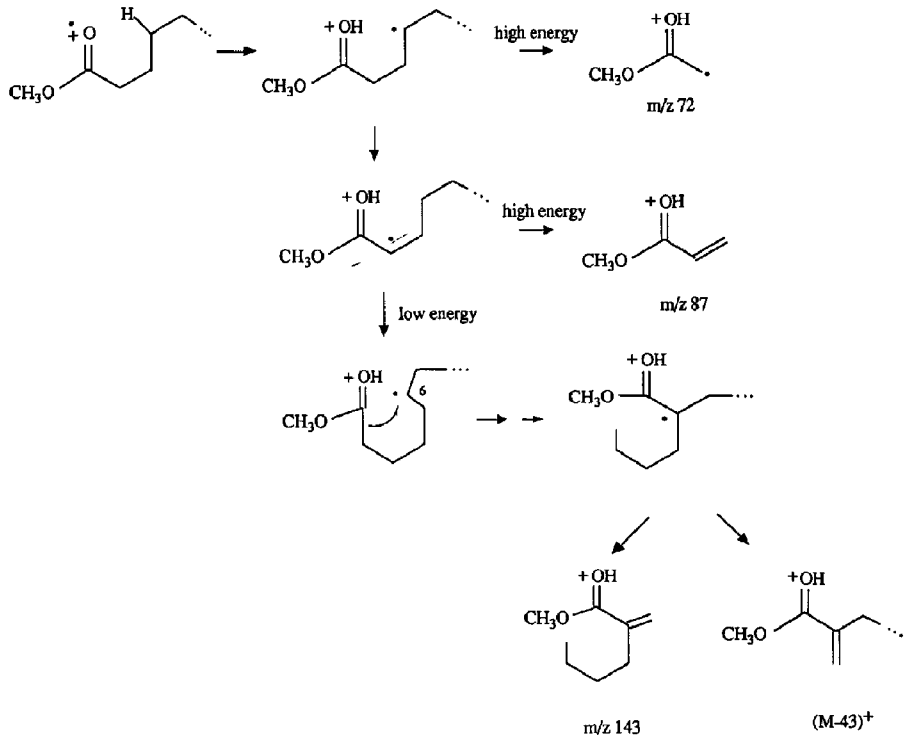


Figure 15. MIKE spectrum of methyloctacosanoate.



Scheme VII

(Figure 15). It has already been shown [16] that the $[M-43]^+$ ion results from the expulsion of the propyl radical C(2)–C(4), and a different interpretation was proposed for this fragmentation [18].

We suggest, however, that the general fragmentation mechanism discussed above could be applied to long-chain esters with rearrangement of the methoxy-hydroxy carbene radical cation $[C(OH)(OCH_3)]^{+\cdot}$ (Scheme VII). As noted before, the 1-2 transfer of this group has already been reported in the literature [7, 13]. In the case of long-chain esters, it seems to occur through large-ring transition states as well, some ring sizes being more favored than others. This may be illustrated by the MIKE spectrum of methyl octacosanoate (Figure 15), where some prominent peaks could represent fragment ions deriving from the same precursor ions **d** with branching carbons C(6), C(10), or C(14).

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