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Reactivity of Electron Impact Ionized Large-ring Cycloalkylamines. Loss of C_nH_{2n+1}· Alkyl Radicals from Long-chain Aliphatic Compounds with a Terminal Enamine or Ester Function (Lipids)

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Large-ring cycloalkylamines rearrange after electron impact ionization into long-chain enamines. A general mechanism is proposed for their fragmentation, and a parallel is established with the fragmentation of long-chain esters (lipids). It is shown that the parent ions rearrange into a series of interconverting branched onium ions from which alkyl radicals are lost. The mechanism of the interconversion is discussed.

INTRODUCTION

The electron impact ionization (EI)-induced fragmentation of long-chain aliphatic compounds with a terminal functional group such as lipids (esters)[1] results essentially from the loss of homologous alkyl radicals, C_nH_{2n+1}·, as shown by a series of peaks 14 u apart (CH_2) in both their standard spectra and mass-analysed ion kinetic energy (MIKE) spectra. Moreover, it has long been observed that some of these peaks, separated by 56 u (4 CH_2) are relatively more intense and seem to indicate the favoured participation of six-membered ring transition states in rearrangements involving the hydrocarbon chain.[2]

More recently,[3] we have shown that ionized large-ring cycloalkylamines rearrange readily after ring opening into ionized long-chain enamines whose reactivity, besides the loss of ammonia, shows great similarities with that of long-chain esters, in particular the same loss of homologous alkyl radicals with the same 'C_4 periodicity,' and we have proposed a new and general mechanism for the fragmentation of long-chain aliphatic compounds with a terminal functional group. This paper reports a more detailed examination of this mechanism and an interpretation of the 'C_4 periodicity' by a study of a series of differently substituted cycloalkylamines (Table 1) (the loss of ammonia will be treated elsewhere).

EXPERIMENTAL

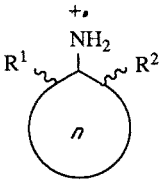
The cycloalkylamines **1–11** (Table 1) were prepared by reduction of the corresponding ketone oximes with lithium aluminium hydride in refluxing tetrahydrofuran. The cycloalkanones were prepared according to the classical method of Stork *et al.*[4]

The standard EI mass spectra were measured with an MS 50 instrument (Kratos, Manchester, UK) located at ICSN, Gif sur Yvette, France. MIKE spectra were measured with a reversed-geometry ZAB-2F instrument (VG Analytical, Manchester, UK) located at Ecole Polytechnique, Palaiseau, France. The electron energy was 70 eV, the trap current 100 μA and the acceleration voltage 8 kV. The source temperature was 180–220 °C. Samples were introduced directly into the ion source.

RESULTS AND DISCUSSION

Cyclohexadecylamine (**1**), for example, fragments after EI essentially by losing homologous alkyl radicals C_nH_{2n+1}·. (Table 2). The conjugated immonium ion at m/z 56 dominates in the ion source[3] whereas it is very

Table 1. Substituted cycloalkylamines studied



n = number of C atoms in the ring

Compound	n	R^1	R^2
1	16	H	H
2	6	H	$C_{10}H_{21}$
3	10	H	C_6H_{13}
4	6	C_4H_9	C_6H_{13}
5	6	C_8H_{17}	C_2H_5
6	6	C_5H_{11}	C_5H_{11}
7	12	H	C_6H_{13}
8	12	H	$C_{12}H_{25}$
9	6	$C_{10}H_{21}$	$C_{10}H_{21}$
10	6	$C_{12}H_{25}$	$C_{12}H_{25}$
11	6	C_6H_{13}	$C_{12}H_{25}$

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Table 2. Relative intensities of the most important peaks in the MIKE spectra as a percentage of the total ion current of fragment ions

Compound	$-NH_3$	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294	308	322	336	350	364	378	392	406
					m/z																					
					C_6																					
							C_{10}																			
1	23	1	1	2	7	6	10	7	10	7	9	4														
2	31	1	1	2	6	4	8	6	10	7	10	4														
3	18	2	3	3	10	7	10	7	10	7	8	3														
4	10	1	3	3	8	5	12	7	13	7	11	5														
5	9	1	5	3	7	6	14	8	14	6	7	4														
6	5	1	1	1	5	23	8	4	9	21	5	2														
					C_6																					
								C_{10}																		
7	18	1	1	3	8	4	4	5	14	6	5	5	8	4												
					C_6																					
								C_{18}																		
									C_{10}																	
										C_{14}																
8	15	0.5	1	1	5	2	2	3	6	4	5	4	5	4	6	3	3	4	8	2						
11	3	0.5	1	1	2	2	8	3	5	4	11	4	8	3	5	3	7	2	1	1						
9	4	2	2	1	1	3	8	3	2	4	13	3	2	3	11	3	2	2	4	1	1	1				
10	4		0.5	1	2	1	0.7	2	7	2	2	3	13	3	2	3	11	2	1	2	4	1	0.7	0.8	2	0.9

scarce in the field-free region (FFR) (see Fig. 4) where other radical losses are important.

In the MIKE spectrum of the tetradeuterated derivative of **1** (Fig. 1), three important features may be noted.

(i) The peaks now appear as multiplets representing ions with different label contents from d_0 to d_4 and in each multiplet the most intense peaks are those corresponding to d_1- or d_3-labelled ions. This indicates that the main decomposition pathway involves rearranged parent ions in which the four deuterium atoms are now differently arranged: one D atom has become isolated and the three others stay together. This is readily explained after the initial α-cleavage by the specific rearrangement og a D atom on the terminal carbon (Scheme 1).[5] d_3-Labelled alkyl radicals are lost from the end of the chain, whereas d_1-labelled alkyl radicals are lost from the part of the chain close to the functional group.

(ii) A general symmetry is observed in the MIKE spectra of all homologues.[3] On both sides of the axis drawn in Fig. 1 the peaks (except loss of ammonia) are roughly comparable in their intensities so that each peak representing a d_1-labelled ion on one side corresponds to a 'symmetrical' peak representing a d_3-labelled ion on the other side.

These observations indicate the intermediacy of 'key' ions, ionized branched enamines, resulting formally from the transfer of the terminal aminocarbene unit on different radical sites in the chain by the mechanism shown in Scheme 1, from which d_1- or d_3-labelled radicals may be lost with about equal probabilities.[3] A crucial step in this mechanism is the reaction of the radical in distonic ions,[6] with the immonium ion leading to recyclization.[7] All carbon atoms in the chain may act more or less as branching carbons in isomeric ionized enamines and the proportion of each enamine in the general decomposition may be appreciated from the relative abundance of its daughter fragment ions.

(iii) The most important branching carbons are C(6) and C(10). This four-carbon difference between prominent peaks (C_4 periodicity) is a common feature of the spectra of all the cycloalkylamines studied (Table 2) and seems to indicate the favoured intermediacy of six-membered ring transition states in rearrangements along the chain.

The MIKE spectra of the isomers **1**, **2** and **3** are very similar. This indicates that they rearrange after ring opening into the same long-chain terminal enamine. In the same way, **7** and **8** also rearrange into long-chain enamines with 18 and 24 carbons, respectively. Metastable parent ions of **3**, **7** and **8** suffer essentially the initial

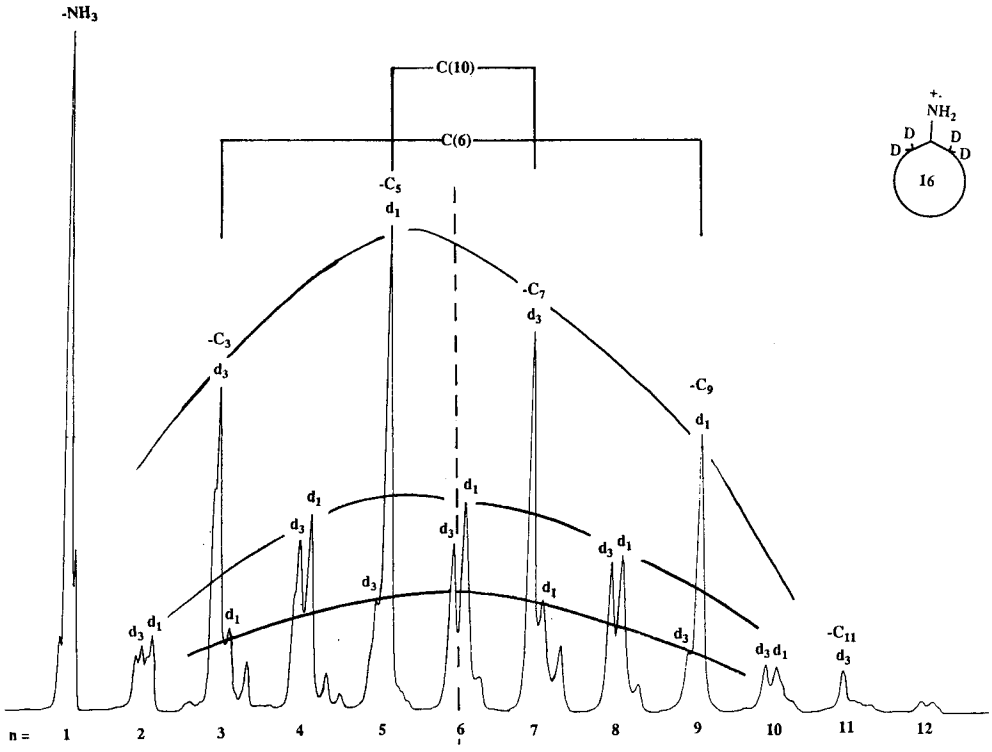
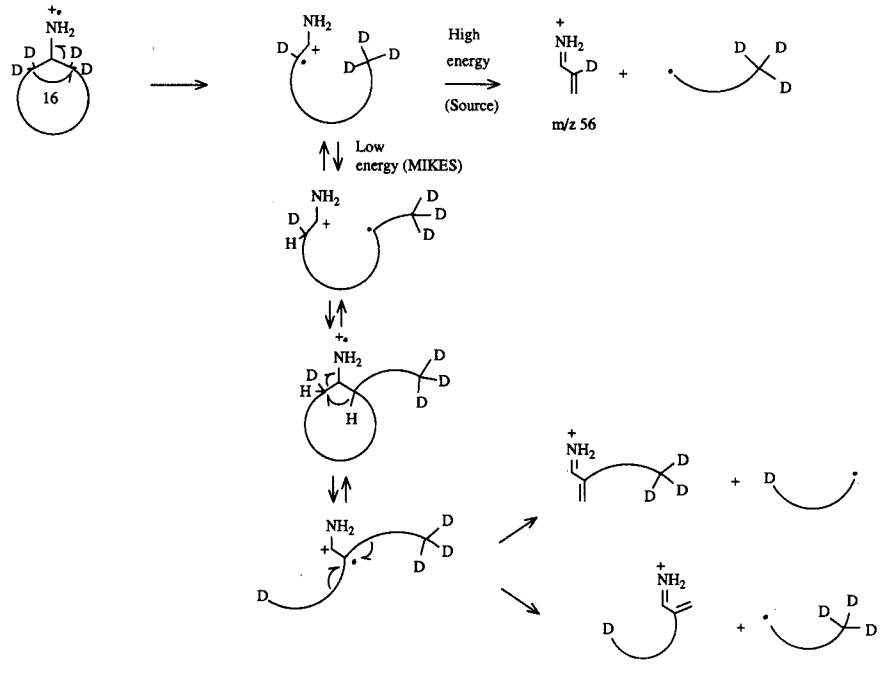


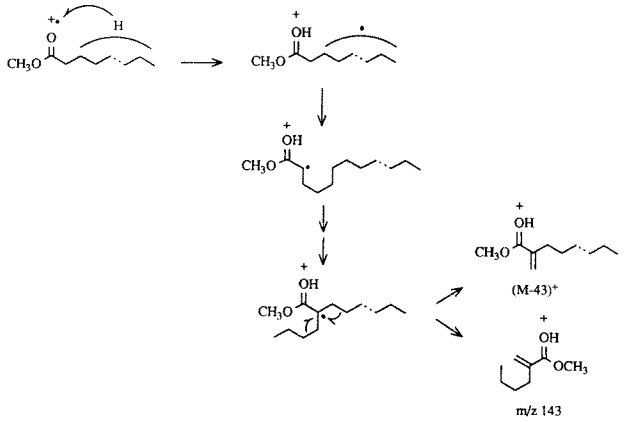
Figure 1. MIKE spectrum of tetradeuterated cyclohexadecylamine (**1**).

cleavage of the more substituted C(α)—C bond leading to the terminal enamine, whereas for more excited ions, fragmenting in the source, the cleavage of the less substituted C(α)—C bond is also observed, leading to the important fragment ions from the resulting branched enamines at C(10) (**3**) or C(12) (**7** and **8**). In all these spectra the same symmetry is observed as well as the same C_4 periodicity of prominent peaks.

In the case of esters the same mechanism applies, initiated by an intramolecular protonation of the functional group and rearrangement into a stable enol structure (Scheme 2), and the same symmetry and C_4 periodicity are observed. Abundant ions $[M - 43]^+$ (loss of C_3H_7) and *m/z* 143 are complementary (symmetrical) and show the important role of C(6) as a branching carbon in the process. In the mass range between them, two symmetric series of peaks are present, some of them more prominent, deriving from enol structures whose



Scheme 1



Scheme 2

branched C atoms are regularly C_4 units apart. For example, in the spectrum of methyl octacosanoate (Fig. 2), prominent peaks correspond to each other symmetrically at *m/z* 395, 339 and 283 on one side and *m/z* 143, 199 and 255 on the other. In the case of methyl nonadecanoate (Fig. 3), prominent peaks at *m/z* 269 and 213 are symmetric with prominent peaks at *m/z* 143 and 199 respectively.

Two hypothesis may be proposed *a priori* in order to explain the C_4 periodicity.

(i) Some particular conformations of the carbon chain of the ionized terminal enamine in the gas phase may be favoured, corresponding to relatively more stable mono- or polycyclohexyl structures (Scheme 3). Conformations presumed to be preferential may be drawn with successively six-, ten- or fourteen-membered rings and lead after the displacement of the radical to C(6), C(10), C(14), respectively, and ring closure with C(1), etc., to relatively more abundant enamines with C(6), C(10), C(14), etc., as branching carbons. This hypothesis was suggested in a previous paper[3] as a possibility in accordance with the model of Meyerson and Leitch[8]

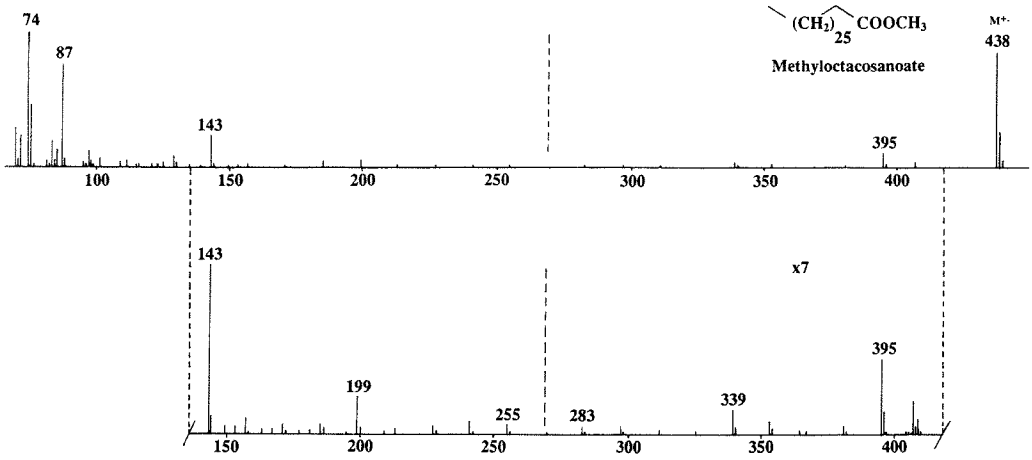


Figure 2. Standard mass spectrum of methyl octacosanoate.

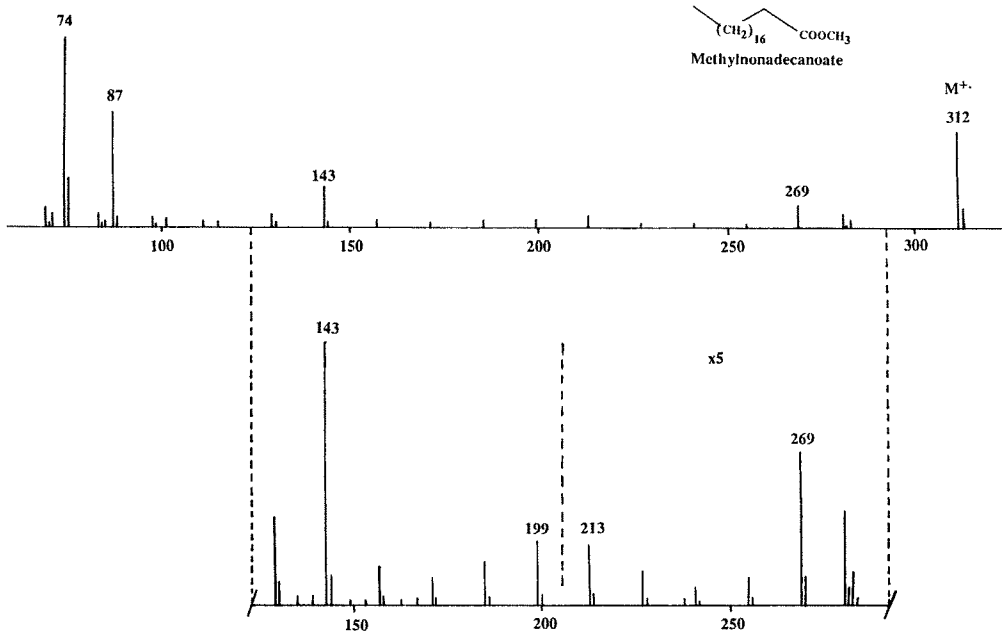
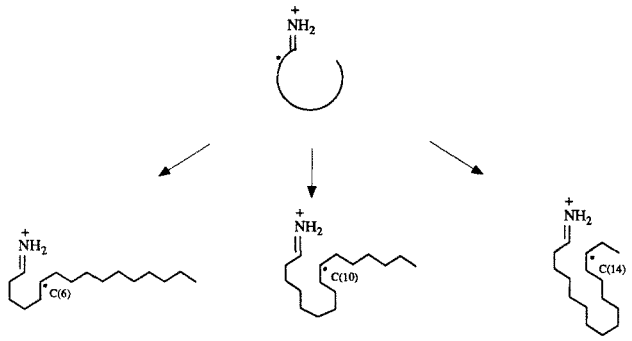


Figure 3. Standard mass spectrum of methyl nonadecanoate.

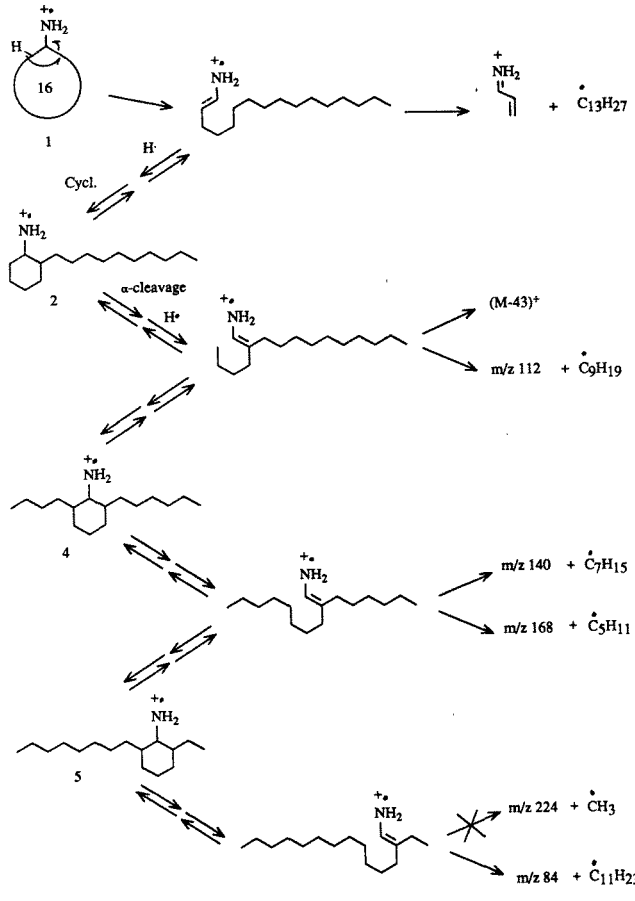


Scheme 3

accounting for 'the tendency of flexible molecules to coil back on themselves' and stabilize by 'internal solvation.'

(ii) The first six-membered ring H transfer in the initial ionized enamine displaces the radical to C(6), and the following ring closure leads to a 2-alkyl-substituted cyclohexylamine. The latter rearranges into the first branched enamine which may either decompose into $[M-43]^+$ or m/z 112 fragment ions (Scheme 4), or rearrange further successively into a series of 2,6-alkyl-substituted cyclohexylamines and branched enamines interconverting into each other. The loss of alkyl radicals from the enamines occurs competitively with the rearrangement process (Scheme 4).

Briefly, the question is whether the aminocarbene group rearranges on any radical site of the chain directly through transition states of corresponding ring sizes (some of them being preferential as shown in Scheme 3), or whether it rearranges through 2,6-alkyl-branched cyclohexyl structures interconverting along the hydrocarbon chain, as shown in Scheme 4.



Scheme 4

A series of arguments support the second hypothesis.

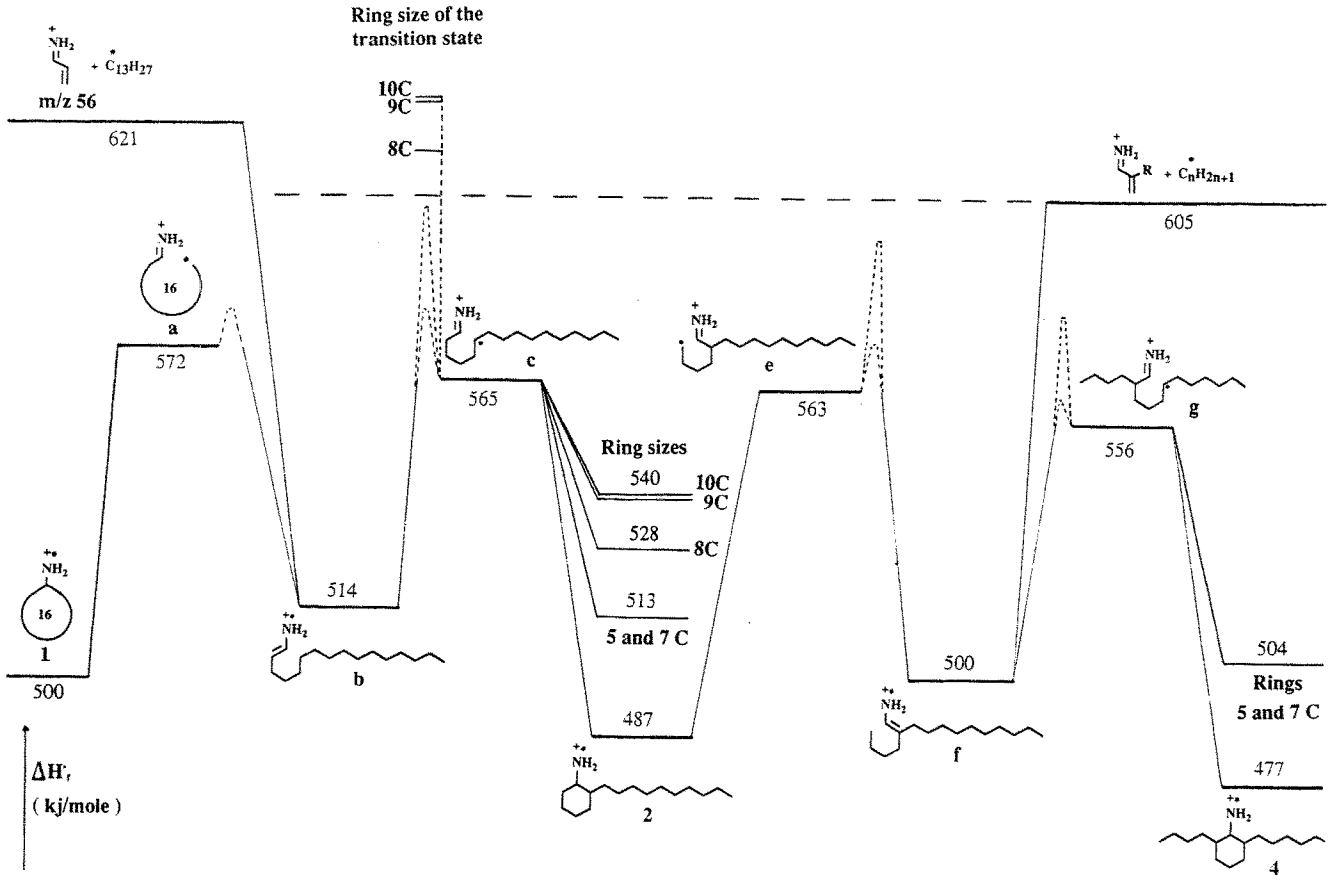
(i) Thermochemical estimations (cf. Appendix) lead to the potential energy profile shown in Scheme 5 for the case of cyclohexadecylamine.

The rearrangement of **1** into the terminal enamine *b* is about thermoneutral after the endothermic ring opening by α-cleavage (*a*). Then, an endothermic H transfer in *b* leads to *c* followed by exothermic ring closure to the alkyl-branched cyclohexylamine **2**. The stability of possible isomers of **2** with rings of different sizes may be evaluated by taking into account the corresponding increments due to ring strain[9,10] cyclopentyl and cycloheptyl isomers are less stable than cyclohexyl isomers by 26 kJ mol^{-1}, cyclooctyl, cyclononyl and cyclodecyl isomers being still higher in energy by 41, 52 and 53 kJ mol^{-1}, respectively. It is reasonable to assume that these differences in the heats of formation of cyclic isomers should be 'felt' also in the H transfers in *b* since they have the same transition-state ring sizes. Although it is not possible to know the exact energy levels of these transition states, one may consider, nevertheless, that the same ordering according to ring sizes is conserved.

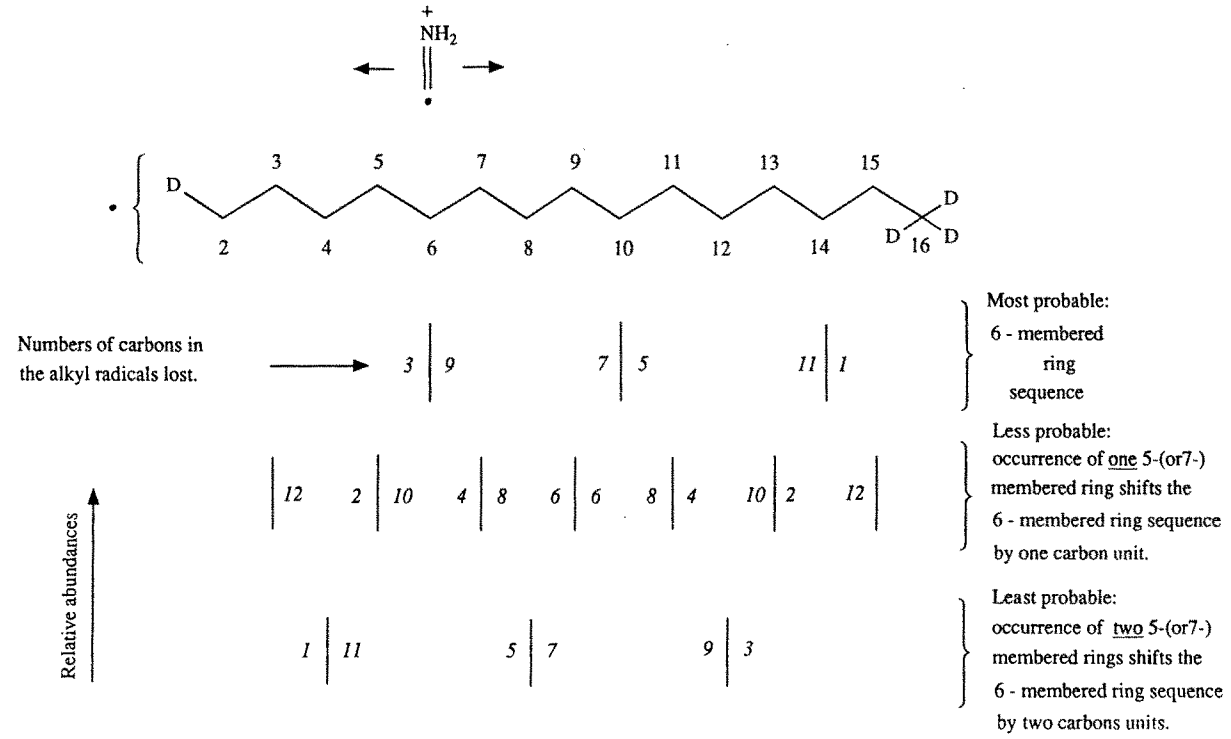
Obviously, this order of stabilities does not fit with the observed preference for C(10) as branching carbon (Table 2) and contradicts the first hypothesis.

Considering the heat of formation of the products (605 kJ mol^{-1}) and the fact that m/z 56 ions are not observed in the MIKE spectrum (621 kJ mol^{-1}), one may presume that six-membered and, to a lesser extent, five- and/or seven-membered ring transition states may operate, but that larger ring transition states cannot compete significantly at these energies. Under these conditions the original parent ions, rearrange into branched ring structures which are essentially six-membered and possibly also five- and seven-membered in minor proportions. The heats of formation of all the other intermediates *e*, *f*, etc., are found below the enthalpy of the products, 605 kJ mol^{-1}, as probably also are the transition states leading to them.

(ii) This conclusion is corroborated by the MIKE spectra of tetradeuterated derivatives. Taking cyclohexadecylamine as an example, any alkyl radical lost may be d_1- or d_3-labelled depending on which side of the chain it comes from by fragmentation of the corresponding branched enamine. Scheme 6 represents schematically the alkyl chain with one D atom at one end and three D atoms at the other end with the rearranging aminocarbene unit. All branched enamine ions are generated to some extent since all homologous fragment ions are observed (except $[M-CH_3]^+$, which is very scarce or absent owing to its high heat of formation). We can list the fragment ions deriving from all intermediate branched enamines in order of their probabilities of occurrence depending on the relative energies of the cyclic intermediates involved. The most favoured ring intermediates (cyclohexyl) from the initial long-chain parent enamine lead to enamines branched at C(6), C(10) and C(14). The corresponding d_1- and d_3-labelled fragment ions (first row) are in fact the most abundant (Fig. 1). If the six-membered ring intermediacy were the only



Scheme 5



Scheme 6. Number of carbons n in the allyl radicals C_nH_{2n+1} lost. For example, the first enamine branched at C(6) loses either a d_1-labelled radical with three carbon units, or a d_3-labelled radical with nine carbon units, leading to d_3- and d_1-labelled fragment ions, respectively.

possibility, these fragment ions would be observed to the exclusion of all others. However, during this six-membered ring sequence, *one* five- or seven-membered ring closure may incidentally occur, although with a lower probability. After such an event the facile six-membered ring sequence continues again but is now shifted by one C atom and therefore involving in turn C(3), C(5), C(7), C(9), C(11), C(13) and C(15). The fragment ions derived (second row) should be of lower abundance, as observed (Fig. 1). Finally, in order for the remaining C(4), C(8) and C(12) to be involved, the six-membered ring sequence must be shifted by two C atoms. This requires the occurrence of *two* five- or seven-membered ring closures in the sequence. This, of course, takes place with a still lower probability and the resulting fragment ions (third row) should be the least abundant, as they actually are (Fig. 1).

Hence the relative peak intensities in the MIKE spectra of the tetradeuterated compounds reflect exactly the probabilities of occurrence of the corresponding fragment ions which may be expected from this model (second hypothesis).

(iii) Another interesting feature is observed in all the MIKE spectra: as indicated by the curves in Fig. 1, the peaks at both ends of the spectrum are less intense than those in the middle (except for the loss of ammonia). This also corroborates hypothesis (ii): if the aminocarbene unit could rearrange, at random, directly from any position to any other position in the chain, the abundances of the resulting fragments should be similar, and therefore the intensity of the corresponding peaks should not depend on their position in the spectrum. Instead, if the aminocarbene unit is bound to proceed along the chain through small ring structures succeeding one another from neighbour to neighbour, the structures with the ring near either ends of the chain should be statistically disfavoured. Consequently, the peak intensities of the corresponding fragments should be smaller, as observed.

(iv) Finally, isomers of cyclohexadecylamine (**1**), considered, according to the second hypothesis, to be most important in their participation in the spectrum, i.e. belonging to the original six-membered ring sequence, have been synthesized (**2**, **4** and **5**). Their MIKE spectra are all very similar (Fig. 4) (except for the loss of ammonia) (Table 1), confirming that all of them are interconverting, i.e. leading in the FFR of the instrument to approximately the same mixture of isomers. In contrast, the spectrum of the isomer bis(2,5-*n*-pentylcyclohexyl)amine (**6**), for example, which does not belong to the six-membered ring sequence above, displays a very different spectrum with major peaks at *m/z* 126 and 182 resulting from the fragmentation of the original structure.

The similarity of the MIKE spectra of the C_{16} isomers belonging to the six-membered ring sequence (**2**, **4** and **5**) also results from the fact that the hydrocarbon chain is relatively short. This offers the possibility for only a small number of interconverting structures. Obviously, higher homologues are more sensitive to the kinetic aspect of the process. The most probable six-membered ring sequence of **8** (C_{24}) contains up to five possible isomeric structures along the chain (branching carbons C(10), C(14), C(18) and C(22)). The fourth is identical with **11** (disregarding stereochemistry) (Scheme 7). The MIKE spectra of **8** and **11** (Table 2) are different, which shows that these structures have insufficient time to equilibrate; the dominant branching carbons

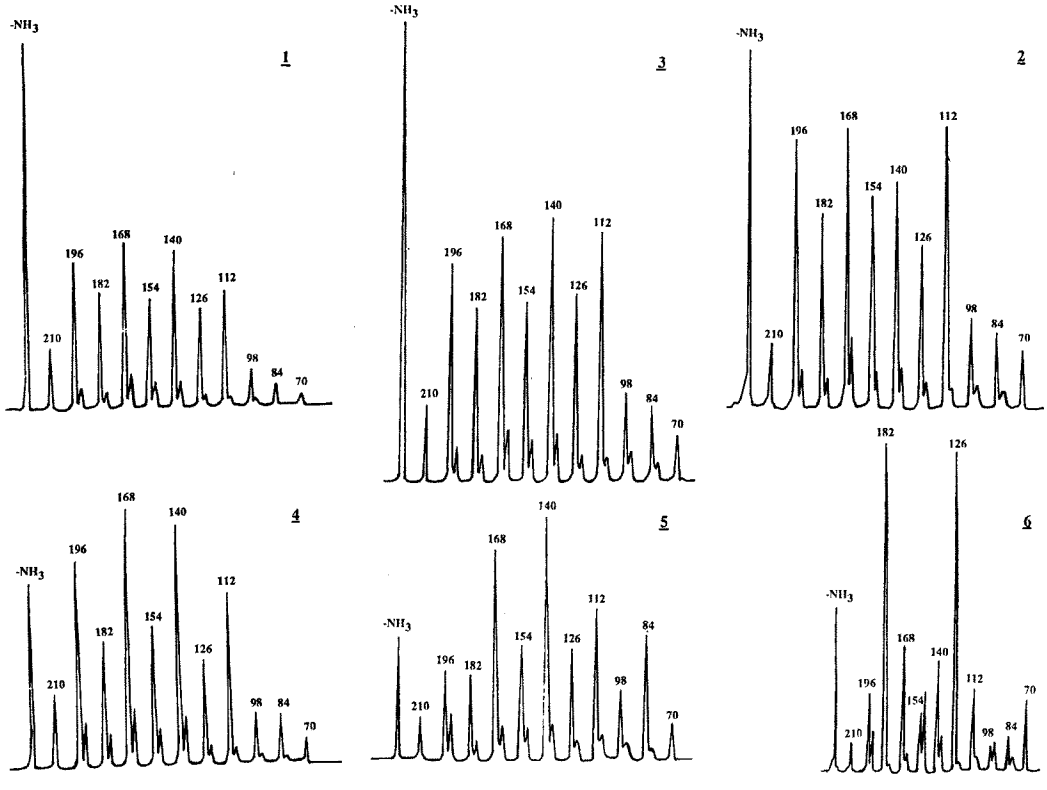
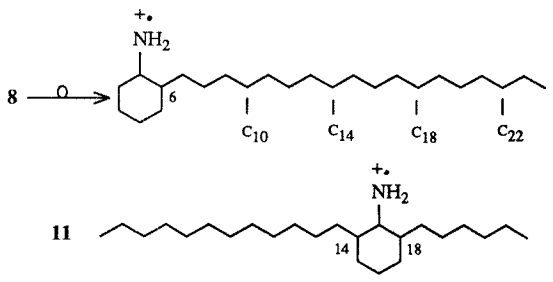


Figure 4. MIKE spectra of isomers **1**–**6**.



Scheme 7

are C(6), C(10) and C(14) for **8** whereas they are C(14), C(18) and C(10) for **11**.

In the same way, the loss of alkyl radicals from cyclohexylamines **9** and **10** with two *n*-alkyl chains with ten and twelve carbons, respectively, shows clearly the C_4 periodicity resulting from the rearrangement of the cyclohexyl ring along the chains, and decreasing peak intensities, symmetrically from the original positions.

CONCLUSION

The EI-induced fragmentation of large-ring cycloalkylamines and long-chain enamines of low energy is essentially the loss of homologous alkyl radicals.[11] The molecular ions arriving in the FFR after a few microseconds lifetime have rearranged into a mixture of interconverting isomeric alkyl-substituted cyclohexylamines and alkyl-branched enamines (Scheme 4). The loss of alkyl radicals occurs from enamines in competition with further rearrangement of the latter. The C_4 periodicity observed in the loss of alkyl radicals derives from the dominant (energetically favoured) formation of six-membered rings in the process.

This general mechanism applies also to long-chain compounds with different terminal functional groups, such as esters. In this case the initial intramolecular protonation of the functional group leads to a distonic onium ion in which the displacement of the radical is the most facile process. The enol (non-distonic) in which the radical is conjugated with the onium ion is particularly stable. The radical may be displaced on different sites of the hydrocarbon chain by H transfers, and may react with the onium ion leading to cyclic (mainly cyclohexyl) structures. Then, ring opening and H transfer lead to branched enol structures which may either lose one of two alkyl radicals with comparable probabilities or rearrange further competitively. The preferred formation of intermediate cyclohexyl structures explains the observed predominance of certain peaks C_4 units apart in the spectra.

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APPENDIX

Heats of formation of the ionic parent, intermediates and products may be estimated from ΔH_f° of lower homologues corrected for alkyl substitution by addition of suitable increments.[9] Ionized cycloalkylamines, from cyclohexyllamine $\Delta H_f^\circ = -105$ kJ mol^{-1}, [12]$IE = 8.37$ eV,[13] plus corrections for ring strain.[9,10] Ionized enamines, from $CH_3CH{=}CHNH_2^{+\bullet}$, $\Delta H_f^\circ = 781$ kJ mol^{-1}.[14] Distonic immonium ions, from $CH_3CH_2CH{=}NH_2^+$, $\Delta H_f^\circ = 636$ kJ mol^{-1},[12] and *BDE* D(C—H) = 422 (primary) and 415 kJ mol^{-1} (secondary).[12] Heats of formation of products are estimated from $CH_2{=}C(CH_3)CH{=}NH_2^+$, $\Delta H_f^\circ = 691$ kJ mol^{-1},[14] and C_7H_{15}, $\Delta H_f^\circ = 15$ kJ mol^{-1}.[12]