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Charge-remote fragmentation of fatty acid molecular anions: examination by using resonance electron capture mass spectrometry

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Abstract

The fragmentation pathways observed for fatty acid odd-electron molecular anions formed by resonance electron capture at 1.2 and 7.2 eV are markedly different and appear to be determined by the electronic state of the precursor ion. The molecular anions formed by resonance electron capture at 7.2 eV yield $[M - H]^-$ species having lost a hydrogen from the aliphatic chain and show charge-remote fragmentation. Variation of the electron energy within the borders of the resonance yielding precursor ions in different electronic states results in different product ion profiles. At the maximum of the resonance and higher energies mainly ions corresponding to the combined loss of a hydrogen and alkanes are detected, whereas at the lower energies of the resonance alkyl losses are also observed. Experiments performed at 1.2 eV revealed that variation of the energy alone within the borders of the resonance does not induce charge-remote fragmentation reactions. Examination of D_2-labeled fatty acids shows that the probability for loss of a hydrogen in the aliphatic chain depends on its position, the order being C(3) > C(4) > C(2) > C(9). These results support a previous proposal that $[M - H]^-$ ions are produced by an interaction between the excited functional group and the aliphatic chain with subsequent elimination of a hydrogen atom. Comparison of the spectra of 9,9-D_2 $C_{16:0}$, 1-OD, 9,9-D_2 $C_{16:0}$ and unlabeled $C_{16:0}$ acids shows that only one ion in the spectrum of unlabeled $C_{16:0}$ acid is affected by D_2 labeling of a methylene group. On the basis of deuterium labeling results a mechanistic proposal is presented for the formation of charge-remote fragment ions under resonance electron capture conditions. It is proposed that resonance electron capture of free fatty acids at 7.2 eV leads to a doubly excited M** species which is partially deactivated by loss of a hydrogen from the aliphatic chain. Subsequently, the $[M - H]^-$ ions formed can fragment further in a concerted manner by loss of an alkyl radical and a hydrogen radical which can either originate from the carboxyl group or from the chain. (Int J Mass Spectrom 198 (2000) 23–32) © 2000 Elsevier Science B.V.

Keywords: Charge-remote fragmentation; Collision-induced dissociation; Electron capture; Excited states; Fatty acids

1. Introduction

Fatty acids are basic components of cell membrane lipids and were among the first biomolecules to be studied by mass spectrometry by using electron ionization in the 1960s. Despite the fact that their structures are relatively simple the mechanism of fragmentation of their even-electron molecular ion species produced with the more recently developed soft ionization techniques [i.e. fast atom bombardment (FAB) and electrospray ionization] is still unclarified. Most fragmentation reactions are either rad-

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ical-site or charge-site initiated. A different class of fragmentation reactions that have been found under high-energy collisional activation in closed-shell ions such as fatty acid carboxylate anions and have been termed "charge-remote fragmentations" (CRFs) were first described by Gross and co-workers (for a review, see [1]). The approach of structural determinations based on charge-remote fragmentation has been applied successfully to a large variety of biomolecules and other organic molecules (for reviews, see [1,2]).

The CRF phenomenon has been addressed by examining fatty acids and functionalized alka(e)nes because these compounds have sufficiently simple structures on the one hand and give characteristic CRF product ion spectra on the other. In the first investigations of CRFs, it was reported that the product ion spectra of deprotonated saturated fatty acids contain terminally unsaturated product ions corresponding to charge-remote formal losses of elements of *n*-alkanes [C_nH_{2n+2}; $n > 1$] [3]. For the description of these losses a concerted electrocyclic 1,4-elimination of molecular hydrogen was suggested [4], that operates at different positions all along the alkyl chain, rationalizes the formation of the homologous series of terminally unsaturated ions, but did not explain all observed experimental results. Especially, in the case of unsaturated fatty acids the 1,4-H_2-elimination mechanism does not explain the observed product ion profile, i.e. the enhanced formation of ions involving cleavage of allylic and homoallylic bonds. In addition to the 1,4-H_2-elimination mechanism, alternative mechanisms that CRF is initiated by homolytic C–C cleavage have also been proposed to explain the formation of the homologous series of terminally unsaturated product ions [5–9]. Further support for a homolytic mechanism was later obtained which demonstrated that CRF processes occur by a multistep radical mechanism involving C–H cleavage as a product-determining step [10]. However, the impetus for C–H and C–C cleavage at positions remote from the charge remains unclear till now. In the case of high-energy collision induced dissociation (CID) of alkali-cationized fatty acid esters [11] and *n*-alkyltriphenylphosphonium cations [12] the involvement of an excited state of the functional part of the precursor ion was suggested but not proven. The role of the charged functional group in CRF processes was considered by Wysocki et al. [13] who established that the internal energy required to observe CRF is compound dependent. The charged functional group was shown to be essential for CRF in a study of three-substituted adamantane carboxylate anions where the carboxylate function could sterically not approach the alkyl chain and CRF reactions corresponding to *n*-alkane losses were not observed [14]. CRF was also found to occur under resonance electron capture conditions [15]; more specifically, saturated fatty acids yield deprotonated molecules in two energy regions, i.e. at 1.2 and 7.2 eV, where those formed by electron capture at 7.2 eV exhibit CRF behavior. These results indicate that an electronically excited species of the molecules triggers CRF reactions and suggest that CRF results from deactivation of an electronically excited state and corresponds to a nonergodic process.

A feature of high-energy CID is that the appearance of product ion spectra is independent of the internal energy of the precursor ion [16,17]. This characteristic, however, does not hold for high-energy CID spectra of fatty acid carboxylate ions and functionalized alkanes. It was first reported by Wysocki and Ross [6] that the CRF product ion profile is dependent on the internal energy of the precursor ion. These workers showed that the method to prepare ions prior to collisional activation affects the overall fragmentation pattern detected following collisional activation. Fast-atom bombardment (FAB)-generated trimethyloctadecyl-ammonium ions, for example, give rise to formal losses of elements of *n*-alkanes, whereas the same collisionally cooled precursor ions not only yield products formed by losses of *n*-alkanes but also by losses of alkyl radicals. The effect of lower internal energy was confirmed by comparing the high-energy CID of FAB-produced precursor ions (alkali-cationized fatty acids and deprotonated sulphated and sulphonated lipids) with those produced by electrospray ionization (ESI) [18,19]. It was found that ESI-produced precursor ions give rise to both

n-alkane and alkyl losses, while the FAB-produced ions mainly undergo elimination of elements of *n*-alkanes.

In the present work we have examined deuterium labeled fatty acids using resonance electron capture (REC) ionization in an effort to obtain more insight into the CRF phenomenon. Compared to high-energy CID of FAB- or ESI-generated precursor ions the use of REC as an ionization technique to investigate charge-remote fragmentation has the advantage that the internal energy of the precursor ion giving rise to charge-remote fragmentation is well defined as it is determined by the resonance energy. In addition, the internal energy of the precursor ion may be varied to some extent within the limits of the resonance so that the CRF product ion profile can also be evaluated as a function of the internal energy of the precursor ion. This approach of using a method alternative to collision-induced dissociation has been followed in previous studies aimed at investigating fundamental processes in the ion dissociation chemistry of polyatomic ions [20,21]. In these studies, sample molecules were first ionized by electrons at threshold energies, and, subsequently, the ions generated were excited by electrons with variable energies (but lower than the ionization energy). The spectra obtained by this electron impact excitation method were shown to be analogous to those obtained by CID.

It is worth noting that the low-energy CID and metastable-ion spectra of fatty acid methyl ester odd-electron molecular ions ($M^{+\cdot}$) are very similar to high-energy CID spectra of closed-shell precursor ions (i.e. carboxylate fatty acid anions and alkalicationized fatty acids) [22,23]. The product ions of fatty acid methyl ester molecular ions can be rationalized by simple bond cleavages but detailed investigation using deuterium and carbon-13 labeled isotopomers demonstrated that the formation of the product ions is more complex than originally thought [23]. Complex radical site-induced rearrangements were found to occur and ions with the same *m/z* value were formed by different pathways (i.e. have different structures) dependent on the internal energy of the precursor ion.

2. Experiment

Materials: 2,2-D_2-, 3,3-D_2-, 9,9-D_2-, and fully labeled D_{31}-palmitic acids were purchased from CDN Isotopes (Point Claire, Canada). The D_2 contents were 99% for the D_2-labeled palmitic acids and 98% for the fully labeled D_{31}-palmitic acid. 4,4-D_2-heptadecanoic acid (D_2 content: 97%) was synthesized in our laboratory and was available from a previous study [24]. 1-OD palmitic acid was prepared by exchange with D_2O (D_1-content $> 70\%$).

Mass spectrometry: the resonance electron capture mass spectra were obtained on a VG70SEQ (Micromass, Manchester, UK) instrument modified for operation in the REC mode. To implement the REC mode on this instrument the circuit of the filament power supply was changed; namely, the filament current was not set automatically in accordance with the electron trap (EI mode) or emission current (CI mode) but was adjusted manually using a potentiometer insulated from the high voltage. This configuration enabled us to operate at electron energies of about 0 eV and a total emission current up to 50 μA without filament breakage. Electron energies (the energies of resonances) were set manually by a second ten-turn potentiometer. To obtain spectra at low energy resonances, a 1.5 V battery was installed in the electron energy circuit which allowed to shift the electron energy distribution. The fatty acids were introduced through the direct inlet system. The instrumental conditions were as follows: accelerating voltage, 8 kV; emission current, 5 μA; analyzer pressure (1–4) $\times 10^{-6}$ Torr; ion chamber temperature, 180 °C.

3. Results and discussion

In order to facilitate the following discussion we will first re-present and summarize results obtained in previous experiments [15,25]. Free fatty acids capture electrons in two different energy regions with an energy difference of approximately 6 eV so that these compounds provide a suitable model system for evaluating the energy requirements of charge-remote fragmentation. Fig. 1 illustrates the REC mass spectra

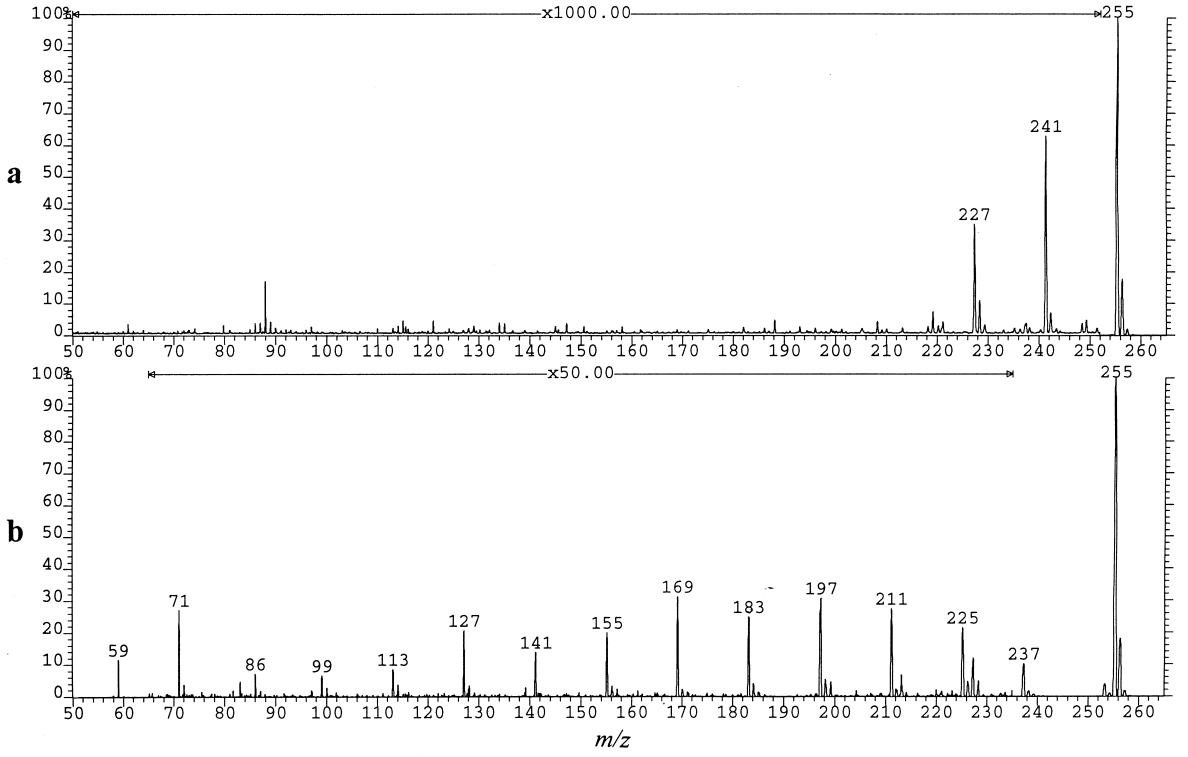


Fig. 1. REC mass spectrum of palmitic acid at (a) low energy (1.2 eV) and (b) high energy (7.2 eV) resonances.

of palmitic acid obtained at the middle of the low (E_{max} = 1.2 eV) and high (E_{max} = 7.2 eV) resonance regions, respectively. The mass spectrum obtained at the low resonance [Fig. 1(a)] is devoid of CRF ions and in addition to deprotonated palmitic acid at *m/z* 255 shows ions at *m/z* 227 and 241 corresponding to deprotonated myristic acid ($C_{14:0}$) and pentadecanoic acid ($C_{15:0}$), respectively, which are present as minor impurities in the sample (<0.1%). Spectra recorded at electron energies lower and higher than the E_{max} (not shown) yielding precursor ions with a different internal energy content revealed the same features, i.e. did not show CRF ions. The mass spectrum obtained at the high resonance of 7.2 eV [Fig. 1(b)] clearly shows a homologous series of CRF ions corresponding to the combined loss of a hydrogen atom and formal losses of elements of *n*-alkanes (C_nH_{2n+2}; $n > 1$). In addition, ions at *m/z* 237 and 253 which can be explained by loss of water and molecular hydrogen respectively from $[M - H]^-$ ions are also observed.

The resonance energy of 1.2 and 7.2 eV corresponds to the internal energy of the fragmenting molecular anion ($M^{-\cdot}$) formed upon resonance electron capture. It is worth reminding that previous experiments established that for resonance electron capture of free fatty acids at 1.2 eV the hydrogen atom lost originates from the carboxyl function and at 7.2 eV from positions in the alkyl chain [25]. The finding that at different resonance energies markedly different dissociation pathways are followed which involve the cleavage of a carboxylic O–H or an aliphatic C–H bond points to a nonstatistical dissociation character of molecular negative ions formed. A similar observation on fragmentation from an isolated electronic state was made in a study on the fragmentation of perfluoropropylene molecular ions in electronically and vibrationally excited states [26]. If the resonance

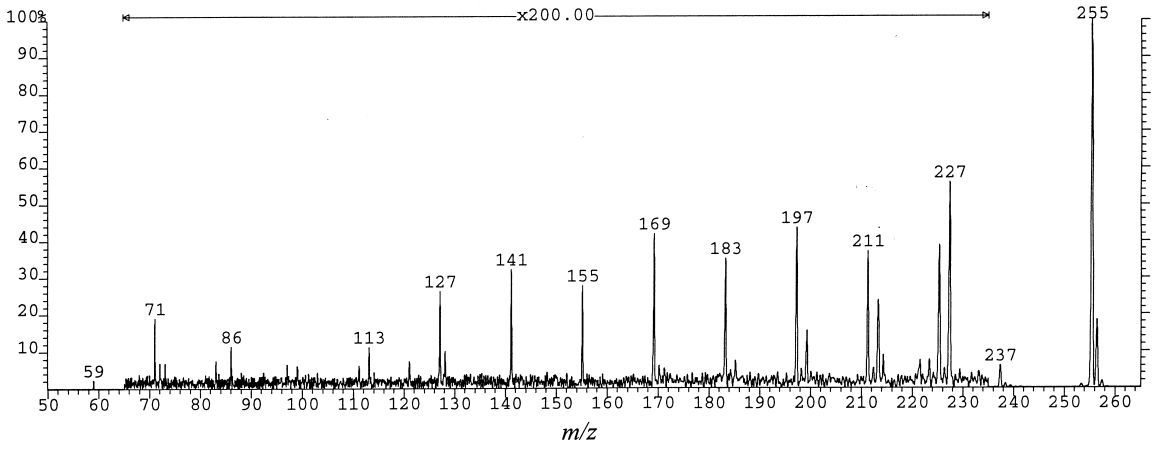


Fig. 2. REC mass spectrum of palmitic acid at an electron energy slightly below the E_{max} of 7.2 eV.

energy of 7.2 eV (or 161 kcal/mol) is randomized over the whole fatty acid molecule the energy gained by individual C–C and C–H bonds becomes negligible. Thus, the conclusion can be drawn that charge-remote fragmentation observed at a resonance energy of 7.2 eV in free fatty acids is a nonergodic process. In this context, it is relevant mentioning that the electron capture dissociation of gaseous multiply charged proteins involving cleavage of peptide N–C bonds and S–S bonds has been found to be a nonergodic process releasing an energetic hydrogen atom [27,28].

Fig. 2 shows the REC mass spectrum of palmitic acid recorded at an electron energy slightly below the E_{max} of 7.2 eV. Compared to the spectrum obtained at the E_{max} [Fig. 1(b)] the spectrum recorded at this lower electron energy reveals larger relative abundances for ions at *m/z* 185, 199, 213, and 227 corresponding to loss of alkyl radicals from the molecular anion ($M^{-\cdot}$) containing a lower internal energy. Alternatively, these ions may be explained by combined loss of a hydrogen atom and elements of *n*-alkenes. Charge-remote loss of alkyl radicals has been reported for *n*-alkyltrimethylammonium cations which were generated by fast atom bombardment and contained a low internal energy and which were subsequently subjected to high-energy collision-induced dissociation [6]. The observation made in the present study that charge-remote loss of alkyl radicals occurs at an electron energy below the E_{max} is thus consistent with previous results obtained by Wysocki and Ross [6] revealing that charge-remote loss of alkyl radicals is a lower energy process than the charge-remote loss of elements of *n*-alkanes. Examination of the spectrum obtained at the E_{max} of 7.2 eV [Fig. 1(b)] shows that the ions corresponding to losses of alkyl radicals are also present but with much lower relative abundances. The spectrum recorded at an electron energy slightly higher than the E_{max} was virtually similar to that obtained at the E_{max} (not shown).

Comparison of the REC spectra obtained at low and high resonance energy [Fig. 1(a) and (b)] reveals that only at a high resonance energy of 7.2 eV CRF is observed and that the process is also affected by the internal energy content of the precursor ions. Since CRF is not observed in the resonance energy region centered at 1.2 eV the conclusion can be drawn that (1) variation of the internal energy alone is not sufficient to induce CRF reactions, and, that (2) CRF is triggered by the electron configuration of the excited molecular anion species formed upon REC at 7.2 eV. In this regard, it is worth mentioning that in the case of CRF of alkali-cationized fatty acid esters [11] and *n*-alkyltriphenylphosphonium cations [12] which is observed at high-energy CID arguments have been presented for the involvement of an excited functional group in CRF reactions. It has been re-

ported that high-energy CID of FAB- and ESI-produced precursor ions (alkali-cationized and deprotonated fatty acids) show different product ion profiles [18,19]; ESI-produced precursor ions give rise to both *n*-alkane and alkyl losses, whereas the FAB-produced precursors mainly undergo elimination of elements of *n*-alkanes. In light of the REC MS observations made in the present study on palmitic acid by altering the electron energy in a resonance energy region the different appearance of high-energy CID spectra of FAB- and ESI-generated precursor ions can be rationalized in terms of a different initial vibrational energy content of the precursor ions prior to collisional activation involving an electronic excitation of the functional group to different electronically excited states.

The loss of a hydrogen atom from different positions of the alkyl chain is a key feature of REC spectra of free fatty acids recorded at 7.2 eV. In previous experiments it was demonstrated that at 7.2 eV $[M - H]^-$ and CRF ions are only detected for fatty acids with a carbon length greater than 7 [25]. In addition, it was also found that $[M - H]^-$ and CRF ions are not formed in the case of three-substituted fatty acids (3-hydroxy and 3-keto) and their methyl esters [15,25]. These findings led to the proposal that $[M - H]^-$ ions are produced by an interaction between the excited functional group and the aliphatic chain with subsequent elimination of a hydrogen atom. In the present study experiments were performed using specifically D_2-labeled fatty acids with the aim to determine the relative probabilities for the elimination of a hydrogen atom from different positions along the alkyl chain. The experiments show that the highest yield of D-atom elimination (i.e. $[M - D]^-/[M - H]^-$ ratio) at the electron energy corresponding to a maximum yield of $[M - H]^-$ ions is observed for the C(3) position (16%) while smaller yields are found for the C(4) and C(2) positions (10% and 6%, respectively) and the lowest one is observed for the C(9) position (4%). These results point to a participation of the carbonyl group in the hydrogen elimination process because the highest losses are found for five to six member cycles. If one assumes that the elimination of a hydrogen atom at the other positions is approximately the same as for the C(9) position (i.e. not higher than 4%) the total calculated amount of hydrogen loss adds up to approximately 75%. The remaining 25% can be explained by isotope effects or hydrogen elimination from the carboxyl function. The latter possibility has to be taken into account despite the fact that elimination of a deuterium atom is not observed in the case of 1-OD acids probably because of different bond strengths of O–H and O–D bonds. Examination of palmitic acid fully deuterium labeled in the alkyl chain ($D_{31}C_{16:0}$) confirmed that a hydrogen atom is lost from the carboxyl function and showed that the $[M - H]^-$ peak is approximately 15% of the $[M - D]^-$ peak at the electron energy corresponding to the maximum of the second resonance. Thus, at the second resonance the $[M - H]^-$ ion population also contains carboxylate anions.

A next series of experiments were aimed at evaluating the effect of electron energy on the formation of $[M - H]^-$ ions observed at REC conditions. To this end, deuterium labeled fatty acids were investigated at different electron energies within the borders of the second resonance and the molecular ion regions examined. These data reveal that the maximum yield of $[M - D]^-$ ions depends on the position of the deuterium atom, the highest energy being required for the elimination of a carboxylic deuterium atom. With regard to the elimination of deuterium atoms from the alkyl chain, the highest energy is needed for loss from the C(2) position, while the lowest is required for loss from the remote C(9) position. These results thus explain the large width of the second resonance for $[M - H]^-$ ion formation. As the fragmentation of the different $[M - H]^-$ ions is governed by the position of the created radical site the appearance of REC spectra will be dependent on the applied electron energy. Fig. 3 illustrates the REC spectra for $D_{31}C_{16:0}$ acid at E_{max} and electron energies lower and higher than the E_{max}. The spectra reveal that their appearance is dependent on the internal energy of the precursor ions. Two series of CRF ions can be discerned in the spectrum obtained at E_{max}: one series corresponding to C_nD_{2n+2} losses from $[M - D]^-$ precursor ions and a second series corresponding to $C_nD_{2n+1}H$ losses from carboxylate anions $[M - H]^-$. As ex-

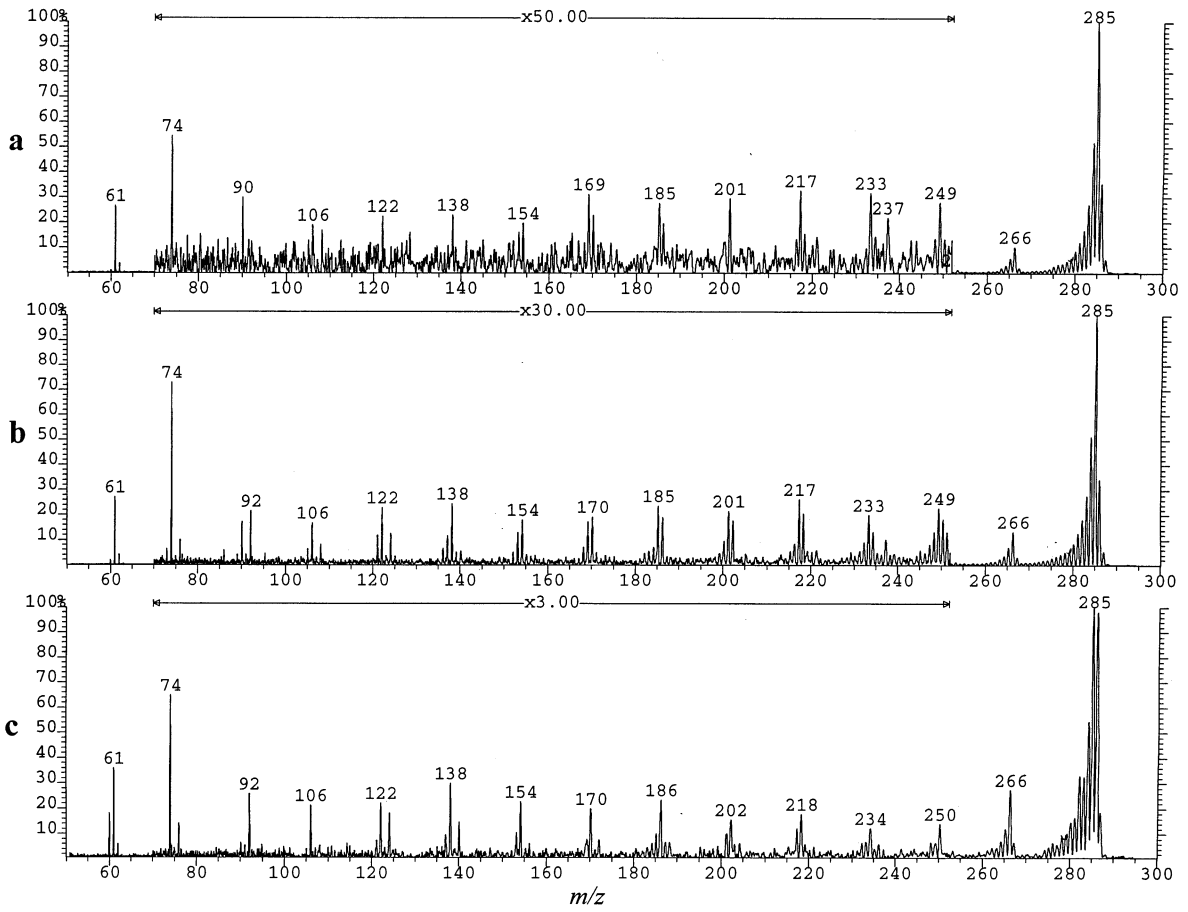


Fig. 3. REC mass spectra of $D_{31}C_{16:0}$ acid recorded at the lower (a), middle (b), and higher (c) energy of the resonance centered at 7.2 eV.

pected, the latter ion series becomes more predominant at the higher electron energy. Furthermore, it is worth noting that at this higher electron energy the ion at *m/z* 61 is accompanied by an ion one unit lower consistent with the loss of a carboxylic hydrogen.

A following series of experiments were performed to obtain information on the composition of CRF ions. To this aim, REC spectra were recorded for 9,9-D_2 $C_{16:0}$ and 1-OD, 9,9-D_2 $C_{16:0}$ acids at an electron energy corresponding to the E_{max} (7.2 eV) (Fig. 4).

Comparison of the spectrum obtained for 9,9-D_2 $C_{16:0}$ acid [Fig. 4(a)] with that of the unlabeled $C_{16:0}$ acid [Fig. 1(b)] reveals that only one ion in the spectrum is affected by D_2 labeling at position C(9). The marked effect of D_2 labeling of a methylene group on the CRF product ion profile can be reconciled with previous results indicating that C–H cleavage is a key step in the CRF phenomenon [10]. The other peaks of the homologous series of CRF ions do not show evidence for deuterium/hydrogen scrambling in the alkyl chain which points to a concerted, synchronous process. Instead of one peak at *m/z* 169 in the spectrum of the unlabeled $C_{16:0}$ acid [Fig. 1(b)] three peaks at *m/z* 169, 170, and 171 are detected in the spectrum of 9,9-D_2 $C_{16:0}$ acid [Fig. 4(a)], indicating that in the CRF process two, one, as well as no deuterium atoms from the C(9) position can be lost. The spectrum of 1-OD, 9,9-D_2 $C_{16:0}$ acid [Fig. 4(b)] demonstrates that the peaks at *m/z* 170 and 171 are not shifted revealing that the carboxylic deuterium is

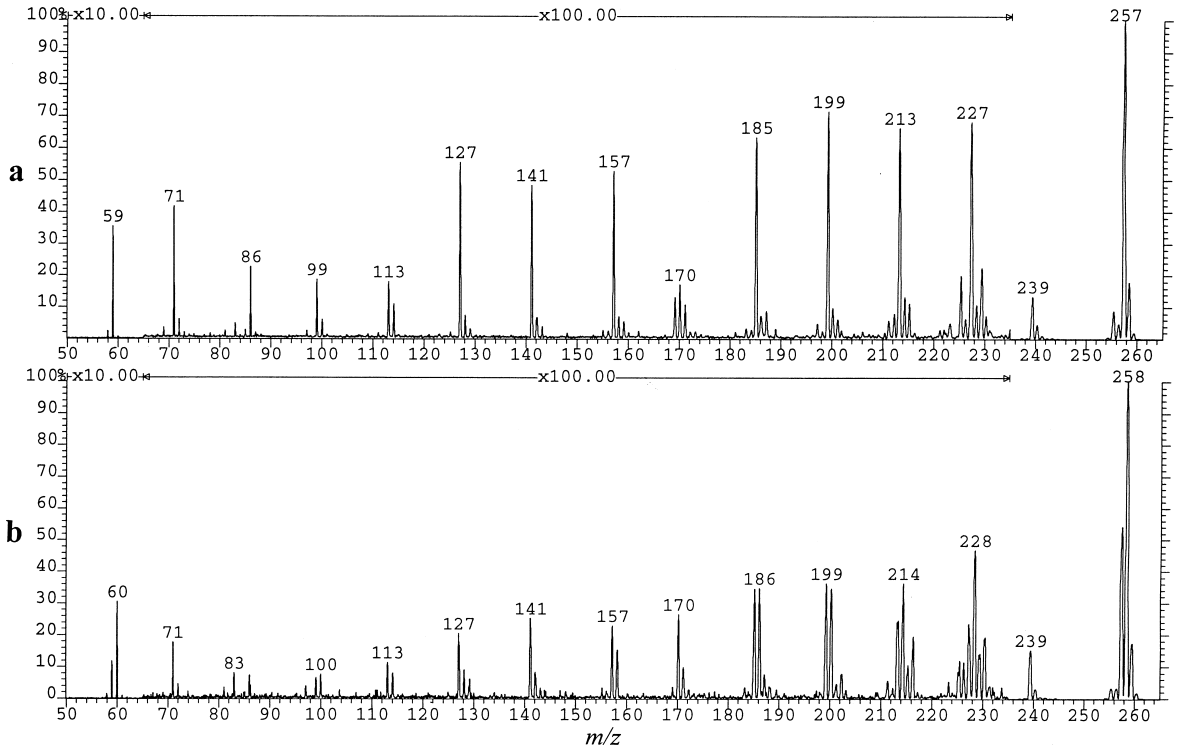
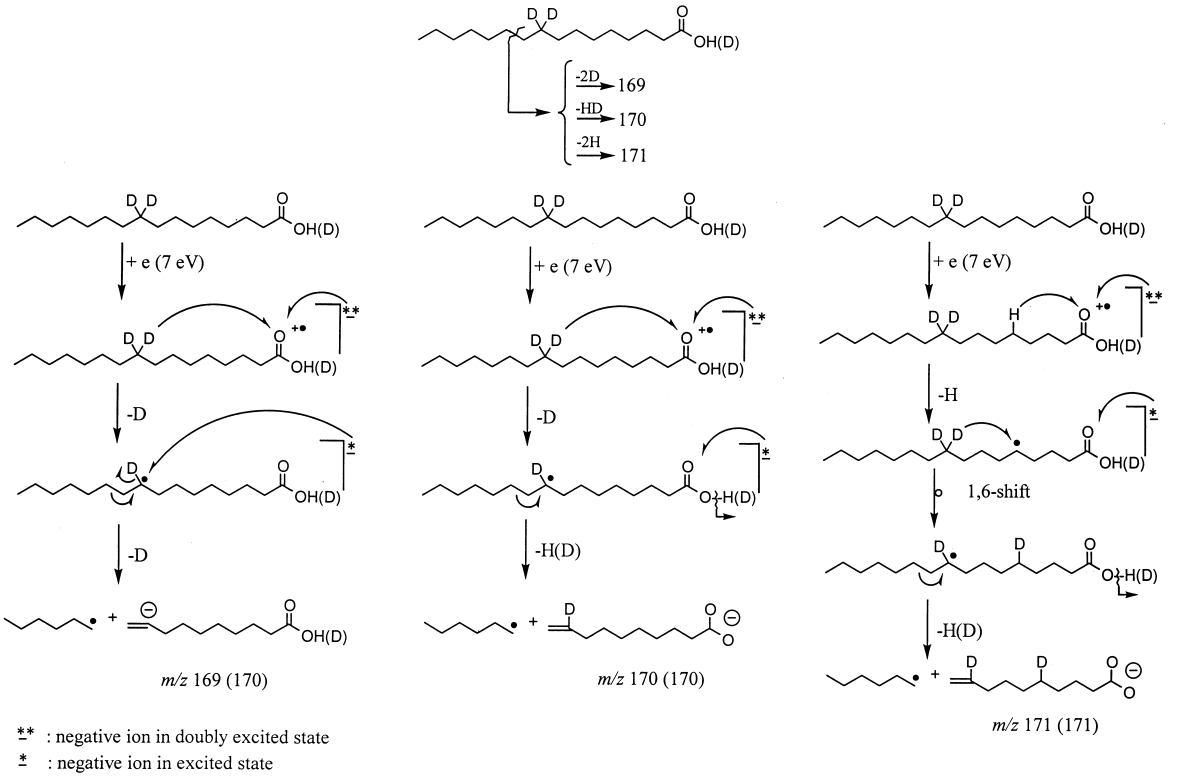


Fig. 4. REC mass spectra of (a) 9,9-D_2 palmitic acid and (b) 1-OD, 9,9-D_2 palmitic acid recorded at high energy resonance (7.2 eV).

eliminated in both cases. The total abundance of ions at *m/z* 169, 170, and 171 in the spectrum of 9,9-D_2 $C_{16:0}$ acid [Fig. 4(a)] is low in comparison with neighboring ions at *m/z* 157 and 185, and is likely due to an isotope effect previously reported for cognate compounds [12]. The ions at *m/z* 170 and 171 can be explained by mechanisms analogous to the ones proposed in an earlier study on the CRF behavior of *n*-alkyltriphenylphosphonium cations observed at high-energy CID [12]. Although the ion at *m/z* 170 can be rationalized by loss of a deuterium atom from the C(9) position followed by the concerted loss of an alkyl radical and a carboxylic hydrogen, the ion at *m/z* 171 one mass unit higher can be interpreted by loss of a hydrogen atom from a position between C(2) and C(8) [unknown but C(5) position is probably most preferable] in the chain and rearrangement of a deuterium atom prior to the concerted loss of an alkyl radical and a carboxylic hydrogen. A mechanistic proposal for the formation of CRF ions under resonance electron capture conditions is presented in Scheme 1.

Interaction of high energy electrons with the fatty acid molecule results in an electronic excitation of the carboxylic function accompanied by electron capture (preferably by an electronically excited Feshbach resonance although an electronically excited shape resonance cannot be excluded) yielding a doubly excited odd-electron molecular negative ion state M^{**}. This M^{**} species is partially deactivated by elimination of a hydrogen radical from different positions in the chain giving rise to $[M - H]^-$ ions which are relatively stable and are as such detected in the REC spectrum. Subsequently, these $[M - H]^-$ ions fragment further in a concerted manner by loss of an alkyl radical ($R^{\cdot}$) and a hydrogen radical which can either originate from the carboxyl group or from the chain. Further examination of CRF product ions using



Scheme 1. Mechanistic proposal for the formation of CRF ions under resonance electron capture conditions.

CID and tandem mass spectrometry should enable us to support the proposed structures and is currently in progress in our laboratory.

4. Conclusions

Resonance electron capture at 7.2 eV of free fatty acids is a high energy process that can release a hydrogen from the aliphatic chain giving rise to $[M - H]^-$ ions. These $[M - H]^-$ ions fragment further in a concerted manner by the combined loss of an alkyl radical and a hydrogen radical which can either originate from the carboxylic group or from the aliphatic chain. Variation of the energy within the borders of the resonances at 1.2 and 7.2 eV giving rise to precursor ions with a different internal energy content showed that charge-remote fragmentation reactions are affected by it at 7.2 eV. More specifically, at energies lower than the E_{max} ions corresponding to alkyl losses are also observed.

The appearance of REC spectra of free fatty acids at 7.2 eV is strikingly similar to that observed for fatty acid carboxylate anions generated by fast atom bombardment under high-energy CID conditions [18,19]. Different mechanisms have been proposed to rationalize the formation of charge-remote fragment ions corresponding to formal losses of alkanes or alkyl radicals under high-energy CID conditions for fatty acid carboxylate anions and functionalized alkanes [4,6,10,11]. Taking into account the results obtained in the present and previous studies [15,25] on the REC behavior of free fatty acids it appears very likely that under high-energy CID conditions the charge-remote fragmentations observed are induced by an excited functional group. Furthermore, the different product ion profiles observed for precursor ions gen-

erated by fast atom bombardment and electrospray ionization [18,19] (i.e. alkyl losses are more pronounced in the case of ESI) can be explained in terms of a different vibrational energy content of the precursor ions prior to collisional activation involving an electronical excitation of the functional group to different electronic states.

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