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Collision induced dissociation of alpha hydroxy acids: Evidence of an ion-neutral complex intermediate

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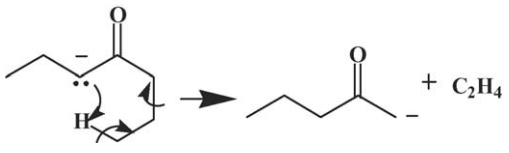
Abstract

Alpha hydroxy acids typically dissociate in tandem mass spectrometric experiments to produce product ions representing a neutral loss of 46 Da (CH_2O_2) in negative ion mode. Although it is widely accepted that the carboxylate group is lost in the dissociation process, the origin of the remaining two hydrogens is unclear. The current study utilizes an alpha hydroxy acid chemical library and deuterium labeling experiments to identify the origin of the two hydrogens lost during dissociation. Secondly, this study investigates the lower *m/z* region of the CID spectrum, a region previously unexplored, to aid in characterizing the dissociation mechanism. Further experiments testing the energy requirements and time parameters of the dissociation also are consistent with criteria previously defined for ion-neutral complex formation. In addition to describing the mechanism for the loss of CH_2O_2, we have conducted experiments that demonstrate the important chemical features of molecules that can prevent alpha hydroxy acids from undergoing the loss of 46 Da. By understanding the chemical composition of the 46 Da loss, the dissociation mechanism responsible for the loss, and the factors that hinder this mechanistic pathway, chemical information about alpha hydroxy acids can be obtained from their CID data.

Keywords: Ion-neutral complex; Alpha-hydroxy acid; Dissociation mechanism; Isotopic labelling; Triple quadrupole

1. Introduction

With the diversity of ionization sources now available for generating negative ions in the gas phase, including fast atom bombardment (FAB), chemical ionization (CI), and electrospray ionization (ESI), mass spectrometry is increasingly utilized for investigations probing the fundamentals of negative ion unimolecular dissociations. These studies are important because structural information about classes of ions that dissociate in a similar fashion can be obtained by understanding the mechanistic pathways leading to the observed losses in a mass spectrum [1–5]. For example, propyl ketones dissociate by a mechanism involving a γ hydrogen transfer followed by loss of a neutral ethene molecule [4–8].



Through an understanding of this mechanism, the observed neutral loss of an alkene from a precursor ion with unknown structure in negative ion mode can signify the presence of a propyl ketone with a γ hydrogen [4–8]. This example is just one instance where understanding the mechanisms involved in producing the observed neutral losses can be utilized to determine structural features of the parent compound.

One of the goals of our research is to extend these types of studies to other biologically significant functional groups. Fatty acids are a biologically important class of compounds, and because of their importance, studies analyzing their fragmentation patterns in MS/MS experiments have become more prevalent [9–16]. For example, alpha hydroxy acids (AHA) are associated with brain mylination [17–21] and are utilized to identify bacterial strains [16,22,23]. Previous research has shown that AHAs can be distinguished from other carboxylic acids by the different neutral losses observed in MS/MS experiments. Typically, carboxylic acid compounds subjected to collision induced dissociation (CID) in negative ion mode yield product ions representing the neutral loss of 44 Da (CO_2) [5,6,24]. Conversely, AHAs exhibit neutral losses of 46 Da, generally accepted to be a loss of CH_2O_2 [14,15]. A mechanism accounting for this loss has

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been proposed to involve two steps: (1) initial heterolytic cleavage and loss of CO_2, followed by (2) homolytic cleavage and loss of H_2 [15]. Although it is agreed that the neutral loss of 46 Da involves the carboxylate moiety, the origin of the additional H_2 loss is proposed to come from various sites in the molecule [15]. Because the exact location of the additional two hydrogens is unclear, valuable information that can aid in characterizing the structure of unknown fatty acids is lost.

The mechanism presented herein is based on new findings in the product ion spectrum. Tandem mass spectrometric experiments inclusive of the low *m/z* region of the spectrum, an area not previously investigated, are presented. By probing this region, a new product ion is observed that suggests an additional dissociation mechanism, not previously outlined, may be occurring. An AHA chemical library and deuterium labeling experiments were utilized to identify the two hydrogens involved in the dissociation. The mechanistic pathway proposed is a two-step process involving the formation of an ion-neutral complex. The product ion formed upon dissociation is a resonance stabilized enolate ion. In addition to providing the structural features involved in the neutral loss of 46 Da, this study discusses other structural features that can prevent this dissociation, such as additional hydrogen bonding groups. These results, and an understanding of the mechanism, help identify the presence and absence of specific structural features necessary for the neutral loss of 46 Da and aid in structural characterization of unknown compounds.

2. Methods

2.1. Alpha hydroxy acid preparation

All AHAs and reagents were obtained from Sigma–Aldrich (St. Louis, MO). Reagents were used without further purification. AHAs were dissolved in a 0.5% solution of concentrated aqueous ammonia in HPLC grade methanol. If the compound was not readily soluble in the ammonia/methanol solution, it was dissolved in a 2:1 HPLC grade water/methanol solution. All solutions were then diluted with the 0.5% concentrated aqueous ammonia/methanol solvent to approximately 0.1 mM. Deuterium labeling experiments were performed by dissolving the alpha hydroxy acids in a 2:1 D_2O/MeOD solution. The compounds were then diluted to 0.1mM with MeOD.

2.2. Mass spectrometry

2.2.1. Ion trap MS data

Sample solutions were introduced into the mass spectrometer via a syringe pump at a flow rate of 10 μL/min. All samples were analyzed on an LCQ Advantage, a quadrupole ion trap mass spectrometer (Thermo Finnigan, San Jose, CA). Tuning was performed to produce optimal signal intensity and data for alpha hydroxy acids were acquired in negative ion mode. A spray voltage of 3.5–4.0 kV and a capillary temperature of 200 °C were utilized. For all the data shown herein, identical ion activation conditions were used. Specifically, the precursor ion isolation width was 5 Da. Each precursor ion was activated for 30 ms with 30% normalized collision energy (as defined by the Xcalibur 1.3 software), and a q_z value of 0.25 was used. One exception to the above experimental conditions is the product ion spectra shown in Fig. 4A and B. These samples were analyzed using an isolation width of 1 Da.

2.2.2. Triple quadrupole MS data

Samples were introduced into a Quattro Ultima electrospray ionization (ESI) source (Waters Corp., Milford, MA) via a syringe pump at a flow rate of 10–20 μL/min. The capillary voltage was set at 2.80 kV and the cone voltage at 45 V. The source and desolvation temperatures were 80 and 150 °C, respectively. Tandem mass spectrometry (MS/MS) experiments were conducted using a collision energy (Elab) of 16 eV with an argon target gas density range of 1.83e−3 to 1.92e−3 mTorr. Beam attenuation was greater than 50%.

3. Results and discussion

3.1. Fragmentation trends for alpha hydroxy acids

3.1.1. Chemical library experimental findings

AHAs analyzed in negative ion mode on a quadrupole ion trap mass spectrometer *commonly* produce neutral losses of 46 Da under the CID conditions described above. The molecular formula responsible for the loss is CH_2O_2, which is accounted for by the carboxylate group (44 Da) and two additional hydrogens [14,15]. The two hydrogens involved in the 46 Da loss are determined experimentally herein.

Fig. 1 shows structures of the molecules analyzed in this study. The chemical library is divided into four groups, and Table 1 lists these compounds and the relative abundance of the product ion produced through the neutral loss of 46 Da.

Table 1
The relative abundances of $[M - H - 46]^-$ product ions for compounds in Fig. 1

	Compound	$[M - H - 46]^-$ (% rel. ab.)
A		
1	2-Hydroxy-3-methybutyric acid	100
2	Sodium-2-hydroxybutyrate	45
3	2-Hydroxycaproic acid	100
4	2-Hydroxyisocaproic acid	100
5	(*R*)-(+)-Hexahydromandelic acid	15
6	(*S*)-(+)-Hexahydromandelic acid	15
B		
7	2-Hydroxy-2-methylbutyric acid	40
8	alpha-Hydroxyisobutyric acid	30
9	2-Ethyl-2-hydroxybutyric acid	100
10	DL-Atrolactic acid hemihydrate	90
C		
11	(*S*)-(−)-2-Hydroxy-3,3-Dimethylbutyricacid	3
12	(*R*)-(−)-Mandelic acid	0
13	Benzilic acid	0
D		
14	D-Gluconic acid	0
15	(1*R*,3*R*,4*R*,5*R*)-(−)-Quinic acid	0
16	Chlorogenic acid	0
17	Glucaric acid	0

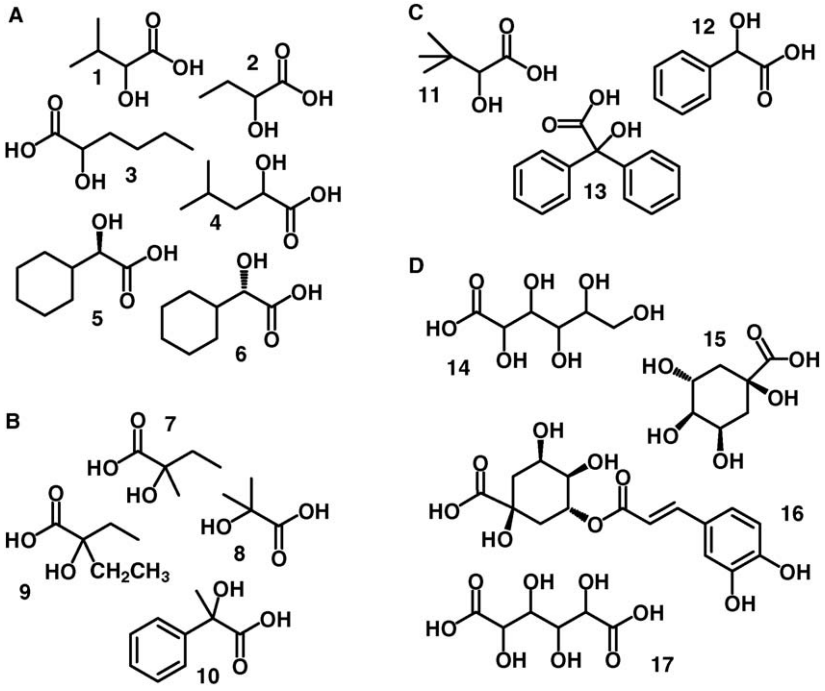


Fig. 1. Library of alpha hydroxyl acids analyzed in negative ion mode. Compounds are divided according to structural features. (A) Compounds have both alpha and beta hydrogens; (B) compounds with beta hydrogens present but no alpha hydrogens; (C) compounds with alpha hydrogens but not beta hydrogens; (D) compounds with alpha hydrogens, beta hydrogens, and additional hydrogen bonding groups.

The alpha hydroxy acids in Groups 1A and 1B consistently exhibit neutral losses of 46 Da with moderate to high relative abundances (15–100%). All of these structures contain beta hydrogens. Group 1A compounds contain both alpha and beta hydrogens and group 1B compounds have beta hydrogens but no alpha hydrogens. Representative spectra of groups 1A and 1B compounds are shown in Fig. 2A and B. 2-Hydroxyisocaproic acid (**4**) ($[M-H]^-$, *m/z* 131) produces a product ion peak at *m/z* 85, under the applied CID conditions. Similarly, the dissociation of the carboxylate anion of 2-hydroxy-2-methylbutyric acid (**7**), a compound with no alpha hydrogens, produces a product ion representing the same neutral loss of 46 Da (*m/z* 71). Through comparison of 1A and 1B compounds, it appears that the loss of 46 Da does not depend on the presence of alpha hydrogens.

In contrast, compounds in Group 1C have product ions representing the neutral loss of 46 Da that are significantly less abundant or absent in the MS/MS data. Fig. 2C is a CID spectrum of mandelic acid (**12**), a compound in group 1C. The product ion representing the neutral of 46 Da (*m/z* 105) is absent. Group 1C compounds do not have beta hydrogens. From these experimental findings, one can conclude that beta hydrogens are instrumental in the neutral loss of 46 Da. When beta hydrogens are absent, the loss of 46 Da is also absent.

In addition, Group 1D compounds have beta hydrogens, but these structures have additional hydrogen bonding functional groups present in their structure. Fig. 2D shows D-gluconic acid (**14**), the compound's structure, and the resulting MS/MS data. A product ion peak at *m/z* 149 that would indicate the neutral loss of 46 Da, is absent. The presence of three additional hydroxyl groups can have numerous effects prohibiting the neutral loss and are discussed in more detail below.

To summarize the experimental results from the chemical library in Fig. 1, the MS/MS spectra of alpha hydroxy acids commonly show neutral losses of 46 Da. The deprotonated carboxylate group accounts for 44 Da of the 46 Da that comprise the loss. Furthermore, as demonstrated by compounds in Fig. 1C, a beta hydrogen is participating in the dissociation process. When beta hydrogens are absent, the neutral loss of 46 Da is not appreciably observed. In addition, hydrogen bonding groups (Fig. 1D) also interfere with the dissociation mechanism.

3.1.2. Deuterium labeling experiments

Deuterium labeling experiments were performed to determine whether or not the hydroxy hydrogen is lost in the dissociation. Fig. 3 is a spectrum of 2-OD isocaproic acid (**4**) obtained under the deuterium labeling conditions described above. The only exchangeable proton present on the molecule is the hydroxy hydrogen. The spectrum shows the deuterated and non-deuterated form of the parent ion at *m/z* 132 and 131, respectively. After application of the CID conditions, only a single product ion is detected, at *m/z* 85. This single peak indicates that the deuterium present on the alpha hydroxy group is lost during the fragmentation process. Based on all the data demonstrated to this point, the loss of CH_2O_2 shown for alpha hydroxy acids, in negative ion mode, is the loss of the deprotonated carboxylate group, a beta hydrogen, and the alpha hydroxy hydrogen.

3.2. Proposed mechanism for the loss of 46 Da

Scheme 1 demonstrates the proposed mechanism for the neutral loss of 46 Da observed for the AHAs used in this study.

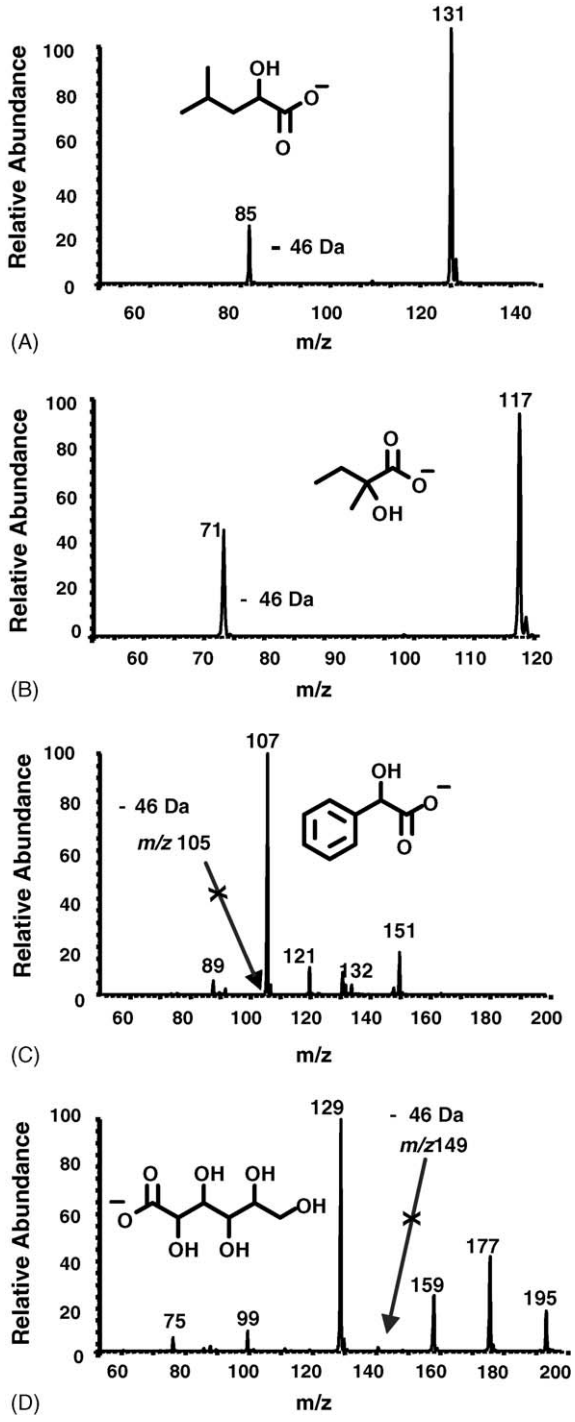


Fig. 2. Alpha hydroxy acids analyzed under the CID conditions described. Product ion peaks representing the neutral loss of 46 Da are indicated. (A) 2-Hydroxyisocaproic acid (**4**), a group A compound; (B) 2-hydroxy-2-methylbutyric acid (**7**), a group B compound; (C) mandelic acid (**12**), a group C compound; (D) D-gluconic acid (**14**), a group D compound.

For the compounds in the chemical library shown in Fig. 1, the mechanism accounts for the three important aspects of the observed dissociation processes, including the loss of the carboxylate group, the loss of the alpha hydroxy hydrogen, and the loss of a beta hydrogen. These losses occur by a two-step, heterolytic mechanism involving the formation of an intermediate

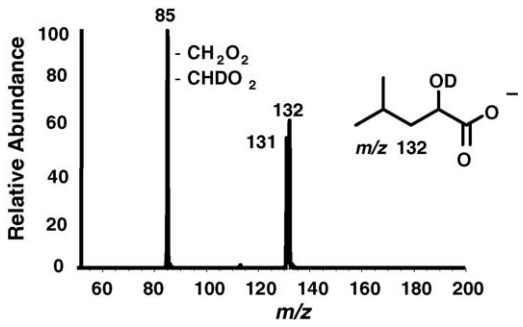


Fig. 3. Product ion spectrum of deuterium labeled 2-hydroxyisocaproic acid (**4**). Precursor ion peaks at *m/z* 132 and 131 represent deuterated and non-deuterated forms. Single product ion at *m/z* 85 indicates deuterium is lost during dissociation.

ion-neutral complex. Support for this mechanism is provided below.

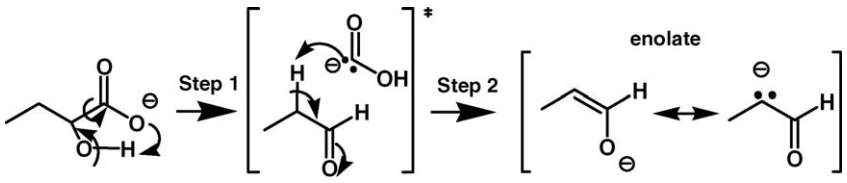
3.2.1. Abstraction of the hydroxy hydrogen

Prior to fragmentation, AHAs are preferably deprotonated at the carboxylate group [5,6,25], with intramolecular solvation stabilizing the carboxylate anion [26–30]. Intramolecular solvation involves hydrogen bonding with other functional groups present in the molecule [26–28] and/or unconventional hydrogen bonding with aliphatic beta and gamma hydrogens [29,30]. One of the hydrogen atoms confirmed to be lost (i.e., either the beta hydrogen or the hydroxy group hydrogen) must be abstracted by the carboxylate group to form an intermediate negative ion of 45 Da (Scheme 1), and is likely to be the hydrogen interacting more strongly with the carboxylate moiety. The maximum stabilizing effect produced through intramolecular solvation occurs when the distance between the carboxylate and the stabilizing group is at a minimum and the polarizability of the interacting group is high [29,30]. It is therefore reasonable to conclude that the hydroxy hydrogen interaction would be more favorable versus unconventional hydrogen bonding with the beta hydrogen, and abstraction of this hydrogen by the carboxylate group would be more favorable.

3.2.2. Formation of ion-neutral complex

Ion-neutral complexes are characterized by many defining criteria [31–40]. Four criteria that directly apply to this study are outlined below [31–40]:

(1) Ion-neutral mediated reactions are the lowest energy processes and will occur at lower energies than the dissociation of the complex.
(2) Ion-neutral complexes can form when the timeframe of the experiment is long. In addition, this relatively long timeframe allows reactions, such as hydrogen transfers, to occur.
(3) As internal energy increases, dissociation of the ion-neutral complex will be observed.
(4) Alternative mechanisms to account for the observed losses would require multiple bond formations, multiple bond breaking events, or concerted reactions with high-energy conformations.



Scheme 1. Proposed mechanism for the neutral loss of 46 Da involving the carboxylate group, a beta hydrogen, and the alpha hydroxy hydrogen. The two-step, heterolytic process involves a formic acid/aldehyde complex intermediate. The ion then proceeds to abstract an acidic hydrogen from the aldehyde to form the final resonance stabilized enolate.

When the above criteria, which outline the energy requirements and time parameters associated with ion-neutral complexes, are considered in the context of this study, it leads to the conclusion that an ion-neutral complex intermediate is formed. Each of the criteria describing ion-neutral complex formation is discussed below.

The product ion spectrum of 2-hydroxybutyrate (**2**) in Fig. 4A is evidence supporting the formation of a formic acid/aldehyde complex because of the formation of a very small, but reproducible peak at *m*/*z* 45. The only possible composition that accounts for this product ion in negative ion mode is $[HCO_2]^-$. If this corresponds to the dissociation of the ion-neutral complex, then the deuterated form of this compound analyzed under identical conditions should produce a negative ion at *m*/*z* 46. The MS/MS experiment on the deuterated form of compound (**2**) is shown in Fig. 4B. The product ion at *m*/*z* 46 results from abstraction of the deuterium from the alcohol group and formation of the formic acid anion.

The peak at *m*/*z* 45 (*m*/*z* 46 for the deuterated complex) is in very low relative abundance. Attempts to increase the relative abundance of this ion through increases in collision energy on the quadrupole ion trap were unsuccessful. This result verifies that the energy required to dissociate the complex into its individual components is higher than the subsequent process of acidic hydrogen abstraction. This is criterion 1 above. Reactions between the formic acid anion–aldehyde complex, such as hydrogen transfers, occur at a much lower energy than dissociation of the complex [31–40]. Therefore, the neutral loss of 46 Da occurs readily and the relative abundance for *m*/*z* 45 remains low.

The same experiments performed on the quadrupole ion trap with compound (**2**) were performed on a triple quadrupole mass spectrometer, with the expectation that the triple quadrupole would deposit more energy into the precursor ion and separate the ion-neutral complex into its individual components more readily [41]. Furthermore, the microsecond activation time using the triple quadrupole mass spectrometer (versus the millisecond activation time using the ion trap) would prevent formation of the ion-neutral complex and result in an increase in abundance for *m*/*z* 45. This would verify that criteria 2 and 3 above are satisfied. As shown in Fig. 4C and D, the product ion spectra have an increased relative abundance by about a factor of 10 for *m*/*z* 45 (*m*/*z* 46 for the deuterated form).

The product ion at *m*/*z* 45 in Fig. 4B indicates that an additional mechanism or dissociation step is occurring. Comparison of Fig. 4B and D indicates that the mechanism for forma-

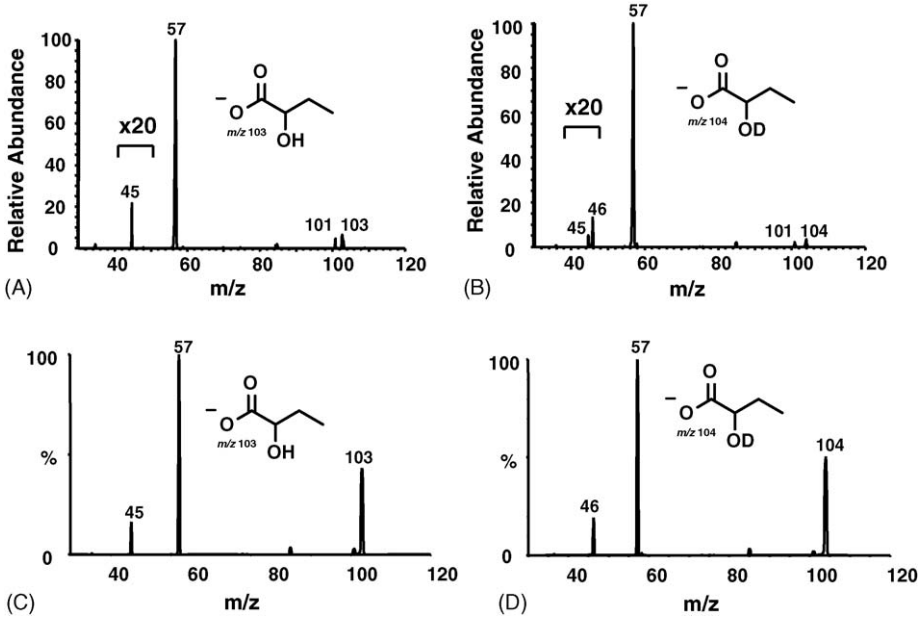


Fig. 4. Product ion spectra of compound (**2**): (A) non-deuterated form and (B) deuterated form analyzed on a quadrupole ion trap mass spectrometer; (C) non-deuterated and (D) deuterated form analyzed on a triple quadrupole mass spectrometer. Spectra confirm the presence of *m*/*z* 45 (*m*/*z* 46) supporting the formation of a formic acid anion.

tion of *m/z* 45 is more favorable in the ion trap because this peak is absent in Fig. 4D. Intramolecular hydrogen scrambling prior to dissociation and scrambling via hydrogen–deuterium exchange within ion-neutral complexes are dependent on internal energy and time [42–44]. It is reasonable to conclude that scrambling may be occurring in the ion trap because the precursor ion is subjected to low energy conditions and ion lifetimes are relatively long, conditions that are favorable for scrambling.

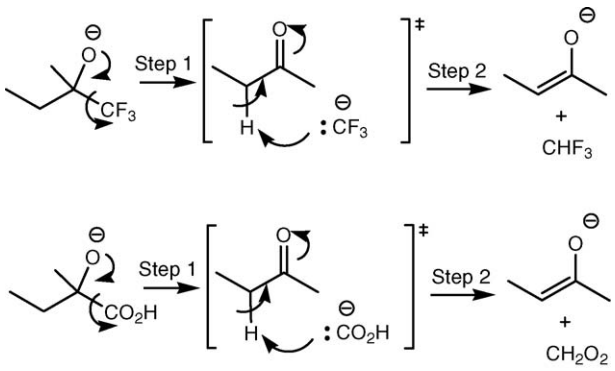
In addition to supporting the hypothesis that CH_2O_2 is lost via an ion-neutral complex, confirmation of a peak at *m/z* 45 (*m/z* 46) also rules out the other high-energy mechanisms that could explain a loss of CH_2O_2. Specifically, loss of $H_2O + CO$, the loss of $CO_2 + H_2$, or the concerted loss of dihydroxycarbene, $C(OH)_2$, would not result in a product ion at *m/z* 45. These potential alternative losses also require multiple intramolecular interactions resulting in high energy transition states, multiple bond dissociations, and multiple bond formations (criterion 4 above) [31–40].

After formation of the ion-neutral complex, step 2 of the mechanism involves abstraction of a hydrogen from the C2 position of the neutral aldehyde and formation of a resonance stabilized enolate ion. This is one of the most common complex mediated processes associated with the formation of an ion-neutral complex: a single hydrogen transfer (SHT) [33–40]. In many cases, a hydrogen adjacent to the site of bond cleavage is transferred in the ion-neutral complex [36]. In this study, this is the beta hydrogen in the initial structure. Through hydrogen transfer, the negative charge residing on the aldehyde structure can be resonance stabilized.

The mechanism involving the ion-neutral complex, Scheme 1, can also be used to explain why some AHAs did not undergo the loss of CH_2O_2. The loss is not observed because additional hydrogen bonding groups in the parent compound would prevent the formation of the ion-neutral complex. Group D compounds in Fig. 1 do not undergo the loss of CH_2O_2. Specifically, as shown in Fig. 2D, compound (**14**) has a beta hydroxy group involved in hydrogen bonding to the carbonyl oxygen of the carboxylic acid group. The additional interaction increases the activation energy for formation of the ion-neutral complex, making other dissociation pathways more favorable (*m/z* 149, which corresponds to loss of CH_2O_2, is not observed). Hydrogen bonding also affects other chemical processes necessary for dissociation. For example, hydrogen bonding may also alter the gas-phase conformation of these compounds making transition state geometries unattainable. In addition, hydrogen bonding can cause steric hindrances resulting in dissociation pathways that are more favorable than the loss of 46 Da.

3.2.3. Alkoxide fragmentation

The mechanism describing the loss of CH_2O_2 for AHAs resembles previous works by Brauman and co-workers on dissociation of gas phase alkoxide ions analyzed in negative ion mode [45–48]. In this work, deprotonated tertiary alcohols were subjected to CID and produced various product ions representing the neutral loss of alkyl groups attached to the central carbon. Scheme 2 demonstrates the mechanism. Deuterium isotope effects suggest that the mechanism is a two-step, heterolytic process involving an ion-neutral complex. It was further established that oxide anions have trends in leaving group propensities (CF_3 > Ph > H > ethyl > methyl) [44–48].



Scheme 2. (A) The two-step dissociation mechanism for a tertiary alkoxide anion as proposed by Brauman and co-workers [45–48]. (B) The two-step dissociation mechanism proposed for AHAs.

The formic acid anion formation in the complex and the subsequent single hydrogen transfer reaction in the current study are identical to the trifluoroalkoxide dissociation observed in previous studies. The formic acid anion described in this study can be estimated to have a similar leaving group propensity as CF_3. The electronegativity of the oxygen atoms in the formic acid anion can stabilize the anion through inductive effects, similar to the fluorine atoms of CF_3. In addition, the C2 hydrogen transfer, that is required to form the resonance stabilized enolate anion in the alkoxide fragmentation mechanism, is highly exothermic. Formation of the enolate anion in AHA acid dissociation is also expected to be favorable.

4. Conclusion

The neutral loss of 46 Da observed in the negative ion mode mass spectrometric dissociation of alpha hydroxy acids involves the carboxylate group, the hydroxy hydrogen, and a beta hydrogen. Intramolecular solvation promotes the transfer of the hydroxy hydrogen to the carboxylic acid moiety. Dissociation occurs by a two-step heterolytic mechanism involving an ion-neutral complex. Observation of the product ion at *m/z* 45 confirms the formation of a formic acid anion, the ion in the ion-neutral complex. The inability to increase the relative abundance of this peak is typical behavior for ion-neutral complexes because subsequent processes are energetically more favorable than dissociation of the complex. Step two of the dissociation mechanism involves abstraction of an acidic C2 hydrogen from the neutral aldehyde resulting in a resonance stabilized enolate ion. Understanding the mechanism of AHA dissociation, the specific atoms involved in the dissociation, and the structural features that may interfere with the neutral loss of 46 Da will aid in characterizing structure of unknown fatty acids analyzed by mass spectrometry in negative ion mode.

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