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RESEARCH ARTICLE

Mass Spectrometry Studies of the Retro-Cycloaddition Reaction of Pyrrolidino and 2-Pyrazolinofullerene Derivatives Under Negative ESI Conditions

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Abstract

Substituted pyrrolidino- and 3-alkyl-2-pyrazolinofullerenes ionize under ESI and MALDI mass spectrometry conditions and negative mode of detection undergoing mass spectral fragmentations, which can be easily correlated with the reported results for the thermal and electrochemical retro-cycloaddition reactions of these compounds. 2-Pyrazolinofullerenes lead directly to a [60] fullerene product ion formed through a retro-cycloaddition process regardless of the substituents attached at the carbon and nitrogen atoms of the heterocyclic ring. These results are different from whose reported for the thermal and electrochemical processes. In contrast, pyrrolidinofullerenes undergo different fragmentative reactions depending upon the substituents (hydrogen, alkyl, or acyl) attached at the nitrogen atom of the heterocyclic ring leading eventually to the pristine C_{60} in the last step of the fragmentation pathway.

Key words: ESI, Retrocycloaddition reaction, Pyrazolinofullerenes, Pyrrolidinofullerenes

Introduction

Just 25 years after the discovery of fullerenes [1], there is still an unabated interest in their chemistry and applications [2–5]. In particular, these carbon allotropes have shown appealing applications in different fields such as materials science and medicinal chemistry [6, 7]. On the other hand, in the last two decades, the mass spectrometry capabilities have been dramatically enhanced by the development of laser desorption ionization (LDI) and electrospray ionization (ESI) techniques, both able to ionize nonvolatile molecules [8]. Since the discovery of fullerenes, mass spectrometry has been a useful analytical technique to determine the gas-phase chemistry of fullerenes and also to characterize the huge number of fullerenes that has been prepared thus far [9]. Moreover, very recently, fullerenes have found applications in mass spectrometry. Thus, a C_{60}-based primary ion beam system has been developed for TOF-SIMS analysis of organic materials [10]. Primary ion sources from Ga^+, Au^+, and Au_3^+ have been used for TOF-SIMS analysis of different size of fullerenes [11].

Dedicated to Professor Antonio García Martínez on the occasion of his retirement

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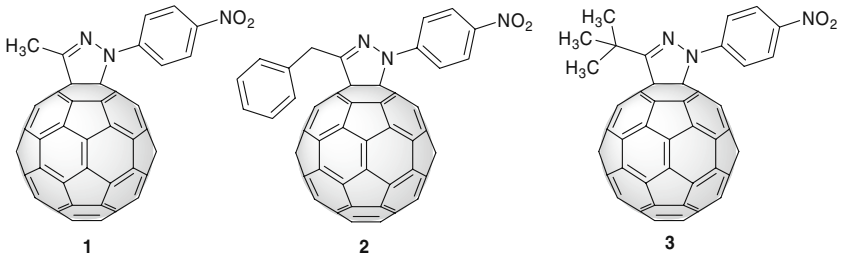


Chart **1**. 3-Alkyl-2-substiuted pyrazolinofullerenes investigated

Moreover, derivatized fullerenes covalently bound to silica particles has been used as thin layer for LDI mass spectrometry analysis of low-mass range molecules [12], and to serve as polydisperse analyte whose mass spectra give an accurate measurement of the molecular mass distribution [13]. Although the spectrometric fragments formed in the oxidation reactions of some fluorinated fullerenes have been observed under EI conditions [14], fullerenes and their functionalized derivatives are mainly analyzed under LDI and ESI conditions. The electrochemical properties of fullerene derivatives permit the analysis of these molecules under ESI conditions and sometimes the formation of odd-electron molecular ions [15, 16].

The Diels-Alder reaction of suitably functionalized *ortho*-quinodimethanes (*o*-QDMs) as highly reactive dienes and C_{60} and C_{70} as dienophiles affords the preparation of a variety of homo- [17] and heterocyclic fused fullerenes [18–21]. Because C_{60} acts as an electron poor olefin, the cycloaddition reaction with azomethine ylides leads to the formation of pyrrolidinofullerenes [22, 23] while the dipolar cycloaddition of nitrile imines affords the corresponding pyrazolinofullerenes [24]. During the course of our investigations on the homo- and heterocyclic fullerene cycloadducts, we have observed that the molecular odd-electron ions generated under ESI conditions and negative mode of detection from substituted isoxazolinofullerenes [25] undergo under CID conditions a retro-cycloaddition reaction forming as base peak the corresponding pristine [60]- and [70]fullerene ions at *m/z* 720 and 840, respectively. In contrast, the corresponding protonated molecules $[M+H]^+$ obtained in positive mode of detection behave differently forming in the first step of the fragmentation an epoxide

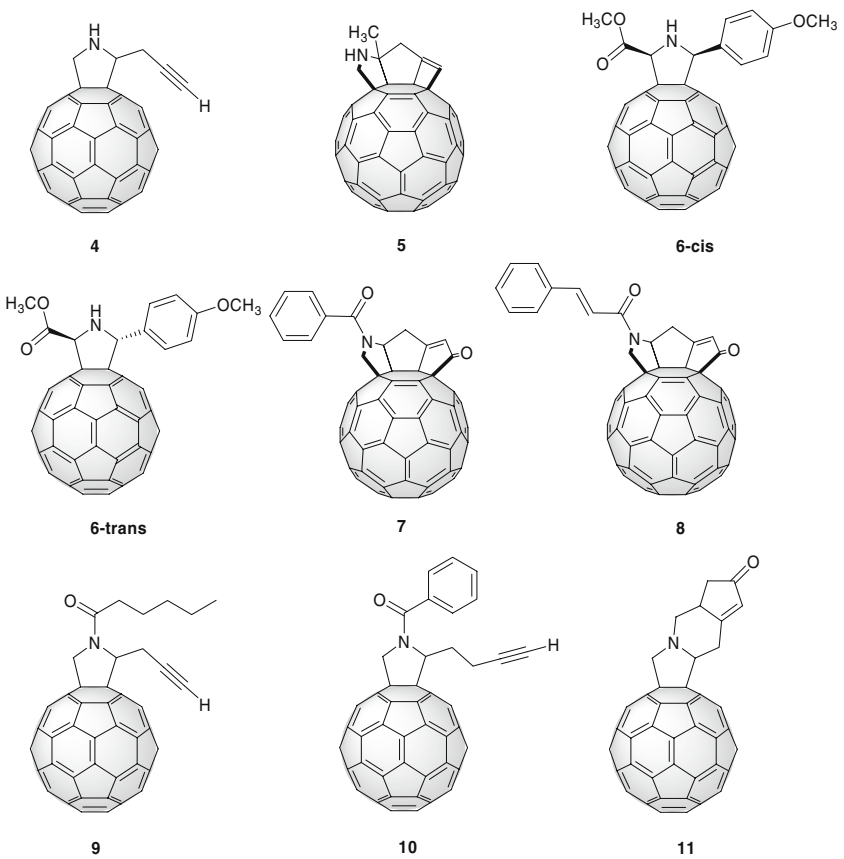


Chart **2**. Pyrrolidinofullerenes investigated

Table 1. Negative ESI-MS/MS spectra of 3-alkyl-2-substituted pyrazolinofullerenes **1–3**

Compound	Molecular ion	Fragment ions (*m/z*)
1	897.1 (M^{-})	720.0
2	973.8 (M^{-})	720.0
3	938.9 (M^{-})	720.0

fullerene, which finally affords the corresponding $[C_{60}H]^{+}$. On the other hand, the retro-Diels-Alder reaction (RDA) is a well-known process, which can be generated in a mass spectrometer [26–28], and is one of the most investigated spectrometric process in the fullerene chemistry [29–31]. A RDA process is observed when substituted tetrahydroquinazolinofullerenes undergo a fragmentation forming as the only product ion the [60]fullerene [32]. It is interesting to note that in the case of the *bis*(methylsulfonyl)tetrahydroquinazolinofullerenes, these compounds extrude consecutively two sulfur dioxide molecules before undergoing the usual RDA process leading to the C_{60} ion [33].

We report herein that the isolated molecular ions generated from substituted 2-pyrazolinofullerenes (**1-3**) under ESI conditions undergo by CID-induced fragmentation a retro-cycloaddition reaction forming the [60]fullerene ion. In contrast, the substituted pyrrolidinofullerenes (**4-11**) fragment differently depending on the substituent (hydrogen, alkyl, or acyl) attached at the nitrogen atom. Although eventually the last step of the fragmentation pathway frequently leads to the formation of C_{60} ion, different plausible mechanisms are proposed to explain the obtained results.

Materials and Methods

Compounds Investigated

3-Alkyl-2-substituted pyrazolinofullerenes (**1-3**) (Chart 1) were prepared according to the previously reported synthetic methods [34, 35]. Purity and identity were assessed and confirmed by spectroscopic methods.

Pyrrolidinofullerenes (**4-11**) (Chart 2) were synthetized following reported methods [36–38] and the purity and structure were checked using standard spectroscopic protocols.

Mass Spectrometry

Electrospray ionization (ESI) mass spectra were recorded in positive and negative mode of detection using an Esquire-LC (Bruker Daltonics, Bremen, Germany) ion-trap spectrometer, a FTMS Bruker Apex Q IV (4.7 T) spectrometer, and a Qstar pulsar i (Applied Biosystems, Carlsbad, CA, USA) with a hybrid quadrupole-time of flight (QTOF) detector. The direct injection of samples was achieved using a syringe pump (Cole Palmer, Vernon Hills, IL, USA) through a short length of PEEK tubing of 254 μm i.d. (Upchurch, Scientific, Oak Harbor, WA, USA) with a flow rate of 3 μL min^{-1}. To prepare the samples, fullerene derivatives were dissolved in dichloromethane/toluene (1:1, vol/vol) and methanol (with 1% ammonium hydroxide or

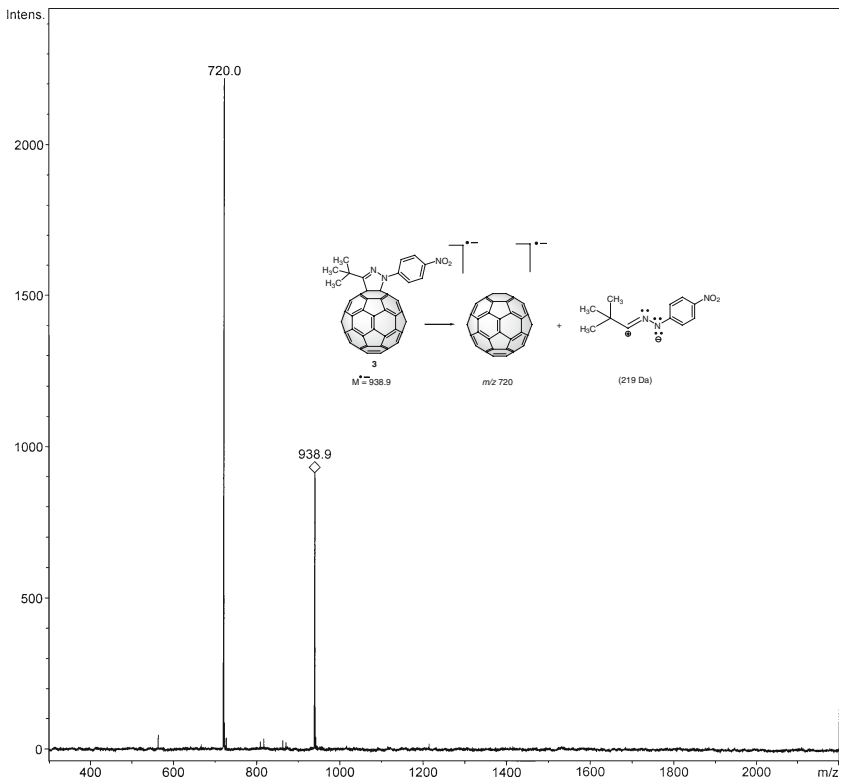


Figure 1. Negative ion ESI-MS/MS of Compound **3**

Table 2. ESI- and MALDI-MS/MS spectra of pyrrolidinofullerenes **4–6**

Compound	Molecular ion	Fragment ions (*m/z*)
4	801 ($M^{-\cdot}$)	720
5	815 ($M^{-\cdot}$)	786, 720
5	816 $[M + H]^+$	787
6-*cis*	927 ($M^{-\cdot}$)	720
6-*trans*	927 ($M^{-\cdot}$)	720

0.1% formic acid) was added in order to produce the ionization of samples. In the positive mode and negative mode, the conditions were: capillary voltage 3 kV, nebulizing gas pressure 10 psi, drying gas flow 4 $L min^{-1}$, drying gas temperature 350 °C (Esquire-LC and Apex Q IV) and capillary voltage 4,2-5,5 kV, nebulizing gas pressure 10–30 psi, curtain gas pressure 20 psi (Qstar pulsar i). MS^n spectra were carried out using collision induced dissociation (CID) with helium after isolation of the appropriate precursor ions using a fragmentation voltage amplitude of 0.60 V and a fragmentation time of 40 ms, fragmentation delay 0 µs and fragmentation width of 10.00 *m/z* (Esquire and Apex Q IV), collision voltage of 11 V, source accumulation of 0.5 s and TOF of 2.4 ms (Apex Q IV) and a collision energy of 80–65 eV using nitrogen as collision gas (Qstar pulsar i). MALDI mass spectra were recorded in a Ultraflex III (Bruker Daltonics, Bremen, Germany) using reflectron mode and *trans*-2-[3-4(*tert*-butylphenyl)-2-methyl-2-propenylidene]malonitrile (DCTB) as matrix (positive and negative mode). Polyethylene glycol (PEG) and C_{60} were used as internal standards for the HRMS analysis.

Results and Discussion

3-Alkyl-2-substituted pyrazolinofullerenes (**1-3**) exhibit under ESI conditions and negative mode of detection the formation of odd-electron molecular ions (Table 1).

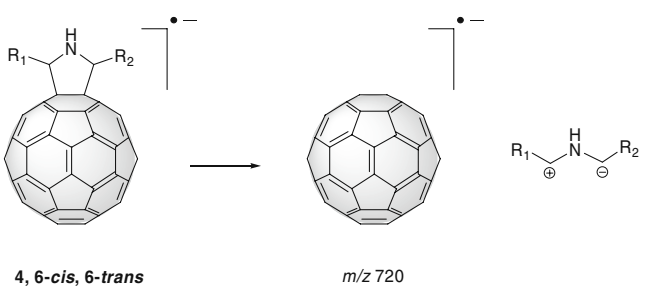
The isolation and subsequent fragmentation of these ions by CID with helium reveal the formation of a single ion at *m/z* 720.0, which corresponds to a $C_{60}^{-\cdot}$. This process indicates that Compounds **1–3** easily undergo a retro-cycloaddition process with loss of a 1,3-dipole such as the corresponding nitrile imine. The MS^2 spectrum of Compound **3** is collected in Figure 1 showing the molecular ion at *m/z* 938.9 and the fullerene radical ion at *m/z* 720.0 together with the proposed mechanism for this elimination. Although there are different proposed structural possibilities to describe the nitrile imine, we use the 1,3-dipolar structure because recent investigations demonstrate that the nitrile imine is the major structure involved in the 1,3-dipolar cycloaddition reactions [39]. No differences were found for the alkyl substituents attached at the C3 position of the heterocyclic ring. The MS^2 spectra of Compounds **1** and **2** are included in the supplementary material (Figures S1 and S2).

In agreement with the results obtained by mass spectrometry, 3-alkyl-2-arylpyrazolinofullerenes undergo an efficient retro-cycloaddition process when they are refluxed in *ortho*-dichlorobenzene (*o*-DCB) for 48 h in the presence of a strong dipolarophile such as maleic anhydride [24]. The presence in the thermal reaction of a metal salt in which metal cation possesses Lewis acid property (copper triflate) activates the retro-cycloaddition process increasing the obtained yields. The cycloreversion reaction of these compounds seems to take place efficiently only when charged species, induced either by Lewis acid metals or ESI conditions, are involved. In contrast, diaryl substituted 2-pyrazolinofullerenes are thermally stable compounds and the retro-cycloaddition process does not take place even under microwave irradiation [24, 40].

The positive mode of detection does not afford molecular ions with the adequate intensity to be isolated. In contrast, it is reported that the LSIMS/MS spectra of substituted thiazolidinofullerenes (which present also two heteroatoms in the fused heterocyclic moiety) in positive mode of detection show a strong peak at *m/z* 720, which indicate a retro-cycloaddition reaction. In this case, with comparable intensity to $[C_{60}]^+$, a fragment at *m/z* 752 corresponding to $[C_{60}S]^+$ was also found [41]. Similar results are found in the ESI-MS/MS spectra in positive mode from fullerene fused to heterocyclic rings containing oxygen atoms such as isoxazolinofullerenes (also two heteroatoms in the heterocyclic moiety), which fragment leading to a fragment $[C_{60}O+H]^+$ [25]. In contrast, an analogous fragment $[C_{60}NH+H]^+$ is not observed in the MS/MS mass spectra of nitrogen containing heterocyclic fullerenes. The mass spectrometric behavior of pyrazolinofullerenes could be used as a rapid and efficient tool in order to predict the viability of the retro-cycloaddition process under thermal conditions.

On the other hand, pyrrolidinofullerenes that have only one heteroatom in the heterocyclic moiety afford very different results. Thus, Compounds (**4–6**) with a NH group ionize under ESI and MALDI conditions and negative mode of detection affording odd-electron molecular ions. Even-electron ions from protonated molecules are found using ESI conditions and positive mode of detection (Table 2).

The data collected in Table 2 indicate that *N*-unsubstituted pyrrolidinofullerenes **4** and **6** undergo only a retro-cycloaddition reaction which affords as main fragment the C_{60} ion (Figures S3–S7). The direct elimination of the



4, 6-*cis*, 6-*trans* *m/z* 720

Scheme **1.** Compounds **4** and **6** undergo a direct cycloreversion process

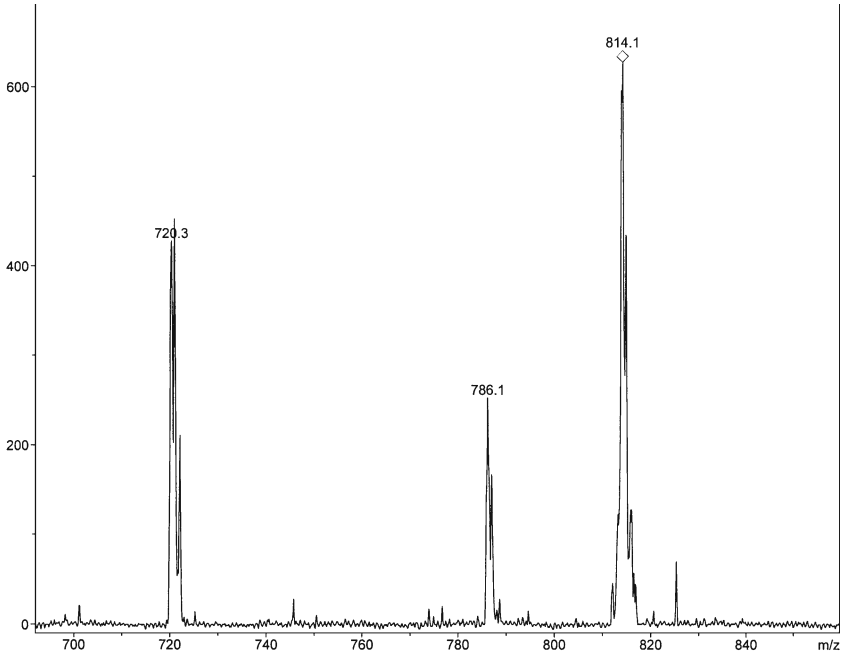


Figure 2. Negative ion spectrum ESI-MS/MS of Compound **5**

corresponding 1,3-dipole explains the formation of the fullerene ion product (Scheme 1). No differences were found between the fragmentation products of Compounds **6-*cis*** and **6-*trans*** indicating that the stereochemistry of the substituents attached at the pyrrolidine ring does not affect the retro-cycloaddition reaction.

Compound **5** ($M^{\cdot -}$ = 815, Figure S8) undergoes a retro-cycloaddition process forming the corresponding fullerene product ion at *m/z* 720 and a new different fragmentation pattern affording a product ion **12** at *m/z* 786 (Δm = 29) (Figure 2).

This process is also observed in the positive mode in which **5** forms the corresponding $[M + H]^+$ at *m/z* = 816, and

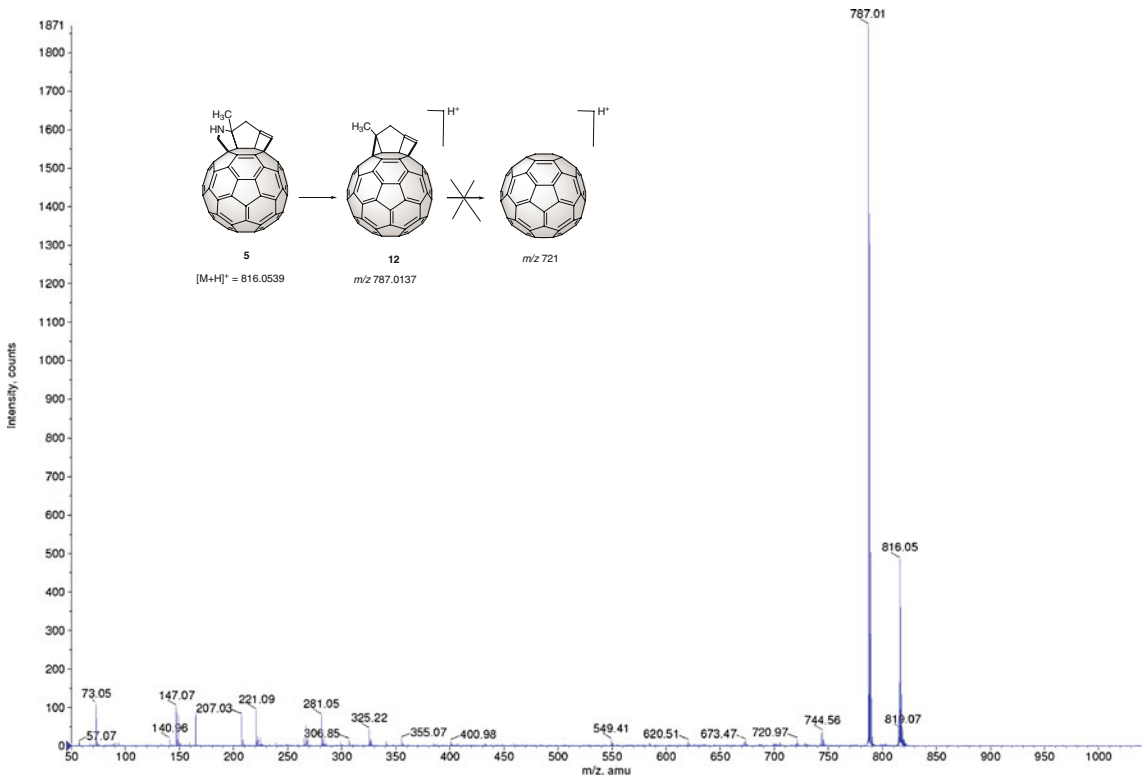
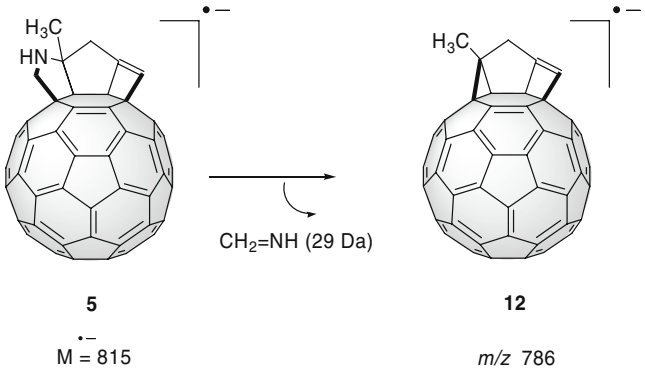


Figure 3. Positive ion spectrum of ESI-MS/MS of Compound **5**



Scheme **2**. Compound **5** eliminates methanimine

undergoes an elimination affording a product ion at *m/z* 787. The loss of a molecule of methanimine (CH_2 = NH, 29 Da) from the pyrrolidine ring could account for these results (Figure 3). A similar fragmentation has also been observed in the positive ESI-MS/MS spectra of *N*-methylpyrrolidinofullerenes bearing an arylpiperazine unit [42] or a 1,4-dihydropyridine group at the C2 position [43]. In both reported cases and due to the presence of a methyl group attached at the nitrogen atom of the pyrrolidine ring, the fragmentation leads to the elimination of *N*-methylmethanimine (43 Da). This fragmentation, which involves the loss of the nitrogen atom of the pyrrolidine ring, yields probably to the formation of a product ion (**12**) whose structure presents a cyclopropane ring (Scheme 2). These facts indicate that another fragmentation possibility involving the formation of an aziridinofullerene using the nitrogen atom of the pyrrolidine ring is not plausible. The cyclopropane addend on the fullerene sphere is well-known as the Bingel synthesis of fullerene derivatives [44]. These compounds have proven good thermal and chemical stability and do not undergo further retro-cycloaddition reactions [45]. Substituted methanofullerenes evolve forming the C_{60} ion under fragmentation conditions [42, 43]. The isolation of product ion **12** and the subsequent fragmentation using different CID conditions does not afford the fullerene ion indicating a high stability of **12** either in the positive mode or the negative mode of detection (Figures 3 and 4).

These results indicate that the detected fullerene ion at *m/z* 720 in the negative fragmentation reaction of **5** is formed directly from the molecular ion through a retro-cycloaddition process involving the elimination of the corresponding 1,3-dipole. The different spectrometric behavior observed in these *N*-H pyrrolidino derivatives can be explained assuming that the substitution at the C2 position on the pyrrolidine ring plays an important role. Thus, Compounds **4** and **6** only undergo a direct retro-cycloaddition reaction, while **5** fragments in a different pathway due to the extended rings fused to the fullerene sphere which avoid partially the elimination of a suitable 1,3-dipole and, in consequence, a loss of methanimine takes place forming the intermediate fragment **12**. The reported data on the thermal retro-cycloaddition process for Compound **6** indicate that the process takes place easily even in the absence of a dipolarophile [46]. The stabilization in the eliminated azomethine ylide, specially produced by the electron-withdrawing character of the methoxycarbonyl group on the C2 position of the pyrrolidine ring (Compound **6**), accelerates the thermal reaction. The results obtained from the electrochemical reactions of pyrrolidinofullerenes indicate that these compounds are unstable towards electro-

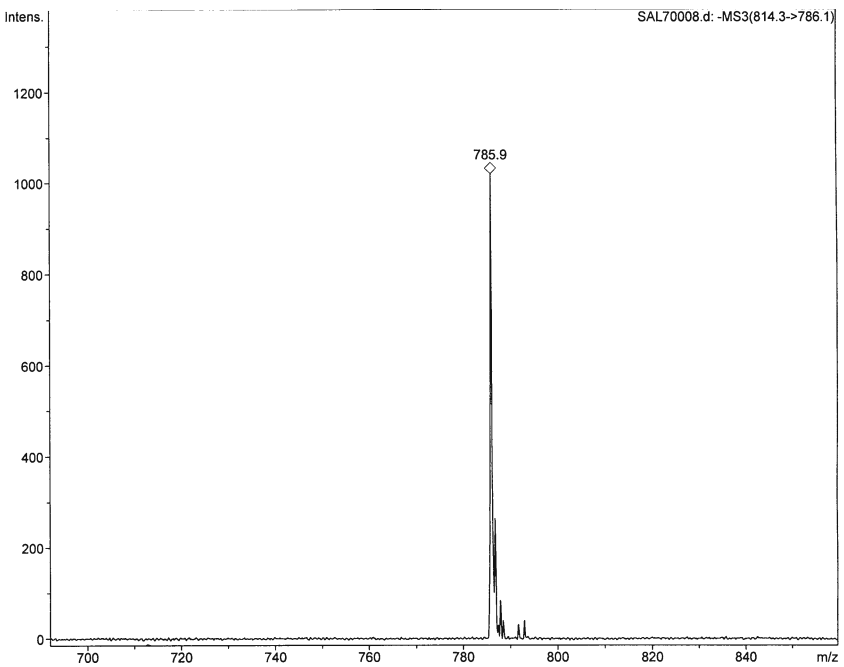


Figure 4. Negative ion spectrum of ESI-MS/MS of product ion **12**

Table 3. ESI-MS/MS spectra of fulleropyrrolidines **7**–**11**

Compound	Molecular ion	Fragment ions (*m/z*)
7	933 ($M^{\bullet-}$)	905, 799, 771, 720
8	959 ($M^{\bullet-}$)	–
9	899 ($M^{\bullet-}$)	801, 772, 761, 720
10	919 ($M^{\bullet-}$)	786, 720
11	869 ($M^{\bullet-}$)	720

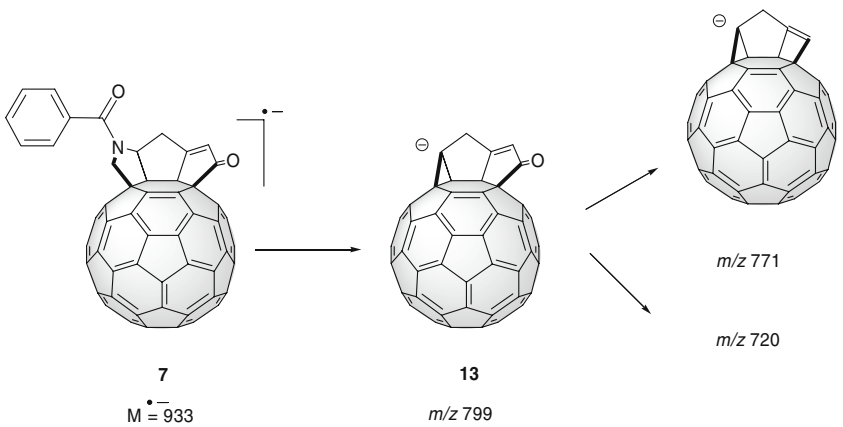
chemical oxidation undergoing easily a retro-cycloaddition process [47]. We can conclude that the retro-cycloaddition reaction in *N*-H pyrrolidinofullerenes takes place either by thermal or oxidative reactions or under spectrometric conditions, affording similar results. However, derivatives with several cycles fused on the fullerene sphere seem to follow a different fragmentation pathway.

N-Acyl and *N*-alkylpyrrolidinofullerenes (**7–11**) ionize under negative ESI and MALDI conditions affording odd-electron molecular ions. The positive mode of detection only produces peaks from protonated molecules of very low intensity and in consequence not adequate for further fragmentation studies. In Table 3 are collected the molecular peaks and the observed fragment ions under CID conditions.

The *N*-benzoyl fulleropyrrolidine **7** (Figure S9) that presents a tricyclic structure fused to the fullerene sphere affords similar results to those obtained for **5**. The direct retro-cycloaddition is not observed, probably due to the impossibility to eliminate a stable 1,3-dipole (azomethine ylide). However, an important fragment ion at *m/z* 799 (**13**) (Scheme 3 and Figure 5) is observed whose formation can be attributed to the loss of a *N*-methylbenzamide radical (134 Da). The subsequent isolation and fragmentation of **13** produces a CO extrusion (*m/z* 771) and the corresponding retro-cycloaddition reaction to form fullerene (Figure 6).

When the fragmentation reaction of **7** was investigated using a Q-TOF detector, a new fragment ion at *m/z* 905 was detected (Figure S10). The formation of this ion can be attributed to the loss of a CO molecule (28 Da). Because pyrrolidinofullerene **7** presents two carbonyl groups in its structure, it is not possible to determine unequivocally the origin of this elimination. Surprisingly, Compound **8** with a similar structure but with a double bond attached at the carbonyl group of the amide moiety does not undergo neither the CO extrusion nor the retro-cycloaddition process (Figures S11 and S12). It is important to note that the thermal retro-cycloaddition reactions of *N*-acylpyrrolidinofullerenes do not take place even in the presence of strong dipolarophiles and copper triflate [46]. Theoretical calculations have shown that the benzoyl substituent destabilizes the azomethine ylide, thus preventing the reaction. On the other hand, the mass spectrometry of these compounds indicates that the retro-cycloaddition takes place only if a previous CO elimination occurs. The CO extrusion forms a *N*-alkyl derivative which can undergo a further retro-cycloaddition either under thermal [36] or under mass spectrometry conditions. The difference of thermal reactivity between *N*-acyl and *N*-alkylpyrrolidinofullerenes is so remarkable that they could find synthetic usefulness in the selective preservation of *N*-benzoyl derivatives in the presence of *N*-alkylpyrrolidines, provided that benzoylation of these rings is a reversible reaction [47]. The cycloreversion of *N*-alkylpyrrolidinofullerenes is easily achieved not only by heating but also under microwave irradiation or using ionic liquid phases in quantitative yield [48].

Compounds **9** and **10,** which cannot undergo retro-cycloaddition thermal reaction [46], behave differently under mass spectrometry conditions, presenting a very important cycloreversion process. However, this process does not take place directly from the molecular ion, being necessary a previous elimination of the acyl group in order to form an appropriate pyrrolidine derivative for the cycloreversion process. Thus, the isolated molecular ion from **9** at *m/z* 899 (Figures S13 and 14) eliminates the 1-hexanoyl group as neutral ketene leading to a fragment at *m/z* 801, whose structure (Compound **4**) is able to undergo a new elimination in order to form the corresponding the fullerene ion through a cycloreversion process. Another observed fragmentation is the



Scheme **3**. Fragmentation pathway of Compound **7**

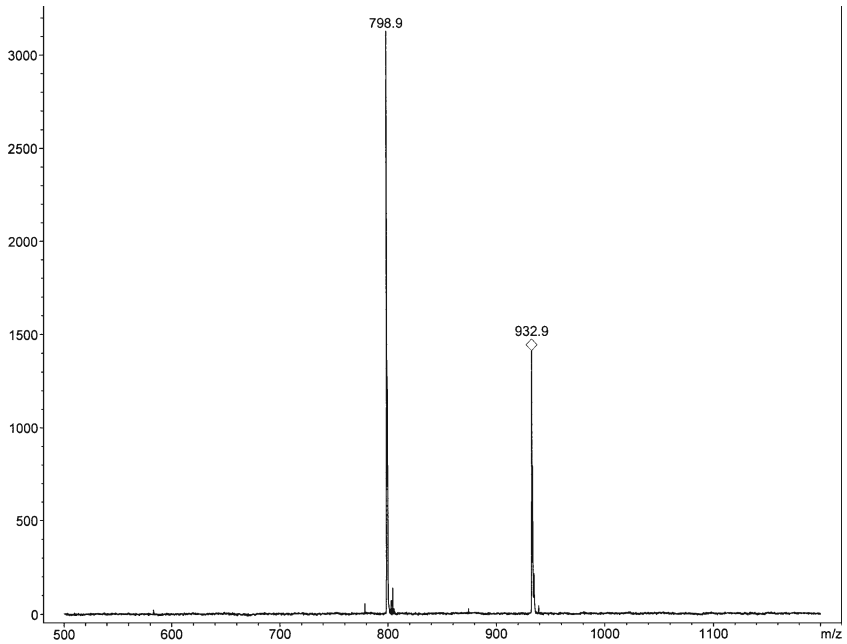


Figure 5. Negative ion spectrum of ESI-MS/MS of Compound **7**

elimination of a substituted methanimine, affording the corresponding methanofullerene (**14**) that undergoes a further retro-cycloaddition reaction (Scheme 4 and Figure S15).

Similarly, the benzoylpyrrolidine **10** ($M^{\cdot-}$ = 919) (Figures S16 and S17) eliminates *N*-benzoylmethanimine (133 Da) affording a fragment at *m/z* 786 with the postulated methanofullerene structure (**15**). A subsequent retro-cycloaddition from **15** or through a previous loss of the alkynyl chain (*m/z* 734) leads to the formation of fullerene (Scheme 5 and Figure S18). In contrast, the *N*-alkylpyrrolidine **11** (Figures S19 and S20) undergoes a direct cycloreversion process. These results are in total agreement with the reported data on the thermal retro-cycloaddition reactions of substituted fulleropyrrolidines [46].

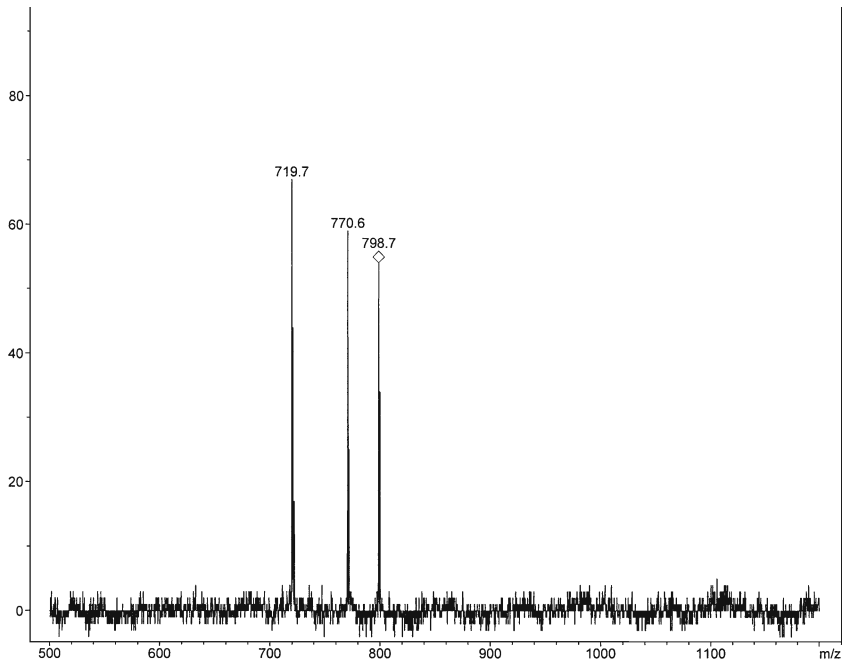
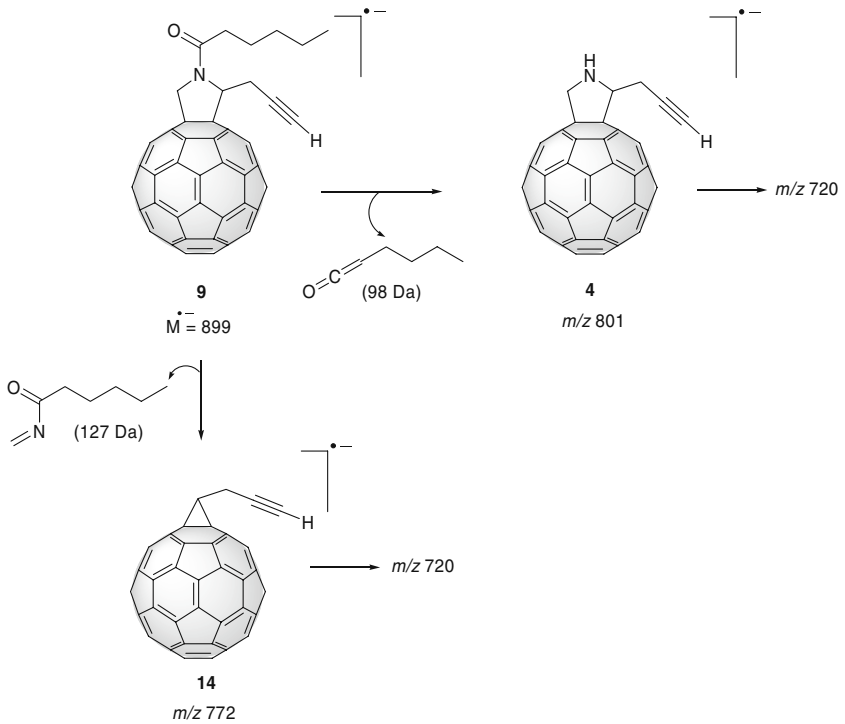


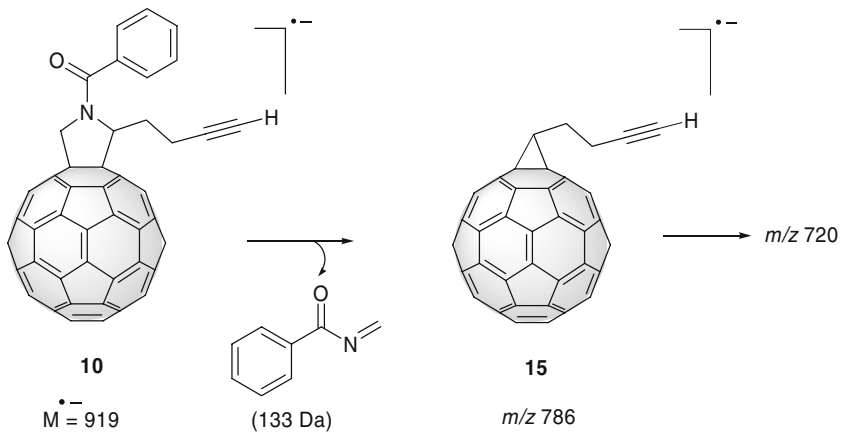
Figure 6. Negative ion spectrum of ESI-MS/MS of fragment ion **13**



Scheme **4.** Fragmentation pathways of Compound **9**

Conclusions

C-Alkyl-*N*-aryl-2-pyrazolinofullerenes undergo a retro-cycloaddition reaction under mass spectrometry conditions affording the corresponding fullerene fragment ion. This cycloreversion takes place as well when these compounds are heated in presence of a dipolarophile with a metal acid Lewis. Pyrrolidinofullerenes behave under mass spectrometry conditions depending on the substituent attached at the nitrogen atom of the pyrrolidine ring. Thus, unsusbtituted NH and *N*-alkyl pyrrolidines undergo a cycloreversion leading to the formation of fullerene. Similar results were obtained in the thermal retro-cycloaddition reactions of these compounds. In contrast, *N*-acylpyrrolidines whose thermal treatment do not afford retro-cycloaddition reaction, undergo the cycloreversion under mass spectrometry conditions. This process requires the previous elimination of the acyl group or a CO extrusion, thus affording *N*-alkyl pyrrolidinofullerenes, which eventually afford the fullerene as result of a retro-cycloaddition process. The mass spectrometry study of these compounds can be used for a better understanding of the structural requirements for the retro-cycloaddition reactions in the pyrazolino- and pyrrolidinofullerene derivatives.



Scheme **5**. Fragmentation pathways of Compound **10**

Acknowledgments

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