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Intramolecular ring rearrangements in the mass spectrometric fragmentation of 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters under electrospray ionization conditions

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Abstract

The mass spectrometric fragmentation of 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters has been investigated under positive ion electrospray ionization conditions. All protonated title compounds predominantly eliminate a phosphite monoester via a four-membered ring hydrogen rearrangement to yield protonated *N*-ethoxycarbonyl arylmethylimines, which could further undergo four-, six-, or eight-membered ring rearrangements to produce mainly *N*-substituted/unsubstituted arylmethylimine ions by loss of carbon dioxide, ethene, and cyanic acid alone or together. It is interesting to note that the protonation of 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters should be occurred in their arene rings.

Keywords: 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters; Electrospray ionization; Mass spectrometry; Ring rearrangement

1. Introduction

1-Aminoalkylphosphonic acids are important phosphorus analogues of amino acids. Their esters and depsidipeptides have been widely used as enzyme inhibitors [1,2] and haptens for the production of catalytic antibodies with esterase or amidase activity [3,4] because they are considered either as transition-state analogues [1,2] or as nonhydrolyzable phosphate surrogates [5]. The *N*-protected 1-aminoalkylphosphonates are also building blocks for the synthesis of phosphonopeptides and depsiphosphonopeptides [6]. Many synthetic methods for the preparation of 1-aminoalkylphosphonic monoesters and *N*-protected 1-aminoalkylphosphonates have been reported till now [7–12].

The mass spectrometries of 1-[*N*-benzyloxycarbonyl(Cbz) amino]arylmethylphosphonic diesters have been investigated under the electron impact ionization (EI) conditions [13] and the electrospray ionization (ESI) conditions [14]. In our previous paper, we reported that protonated dimethyl and diethyl 1-(*N*-Cbz-amino)arylmethylphosphonic diesters favorably undergo a six-membered ring benzyl rearrangement to produce benzylphosphonate ions [14]. Very recently we found that protonated methyl and ethyl 1-(*N*-Cbz-amino)arylmethylphosphonic monoesters favorably undergo a series of four-membered ring hydrogen, benzyl, and benzyloxycarbonyl rearrangements to produce diverse nitrogen-containing fragment ions [15]. Herein, we present the mass spectrometric behavior of methyl, ethyl, and phenyl 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters under the ESI conditions and found they showed apparently different fragmentation mechanisms from the corresponding 1-(*N*-Cbz-amino)arylmethylphosphonic monoesters under the same conditions.

2. Experimental

Methyl, ethyl, and phenyl 1-(*N*-ethoxycarbonylamino) arylmethylphosphonic monoesters **1**–**9** (Scheme 1) were prepared by the method described in the literature [12]. The mass spectra were acquired using a Bruker ESQUIRE∼LC^{TM} ESI ion trap spectrometer equipped with a gas nebulizer probe, capable of analyzing ions up to *m*/*z* 6000. The experiments were oper-

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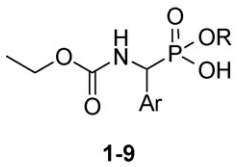


1-9

1. Ar = Ph, R = Me
2. Ar = Ph, R = Et
3. Ar = Ph, R = Ph
4. Ar = 4-ClPh, R = Me
5. Ar = 4-ClPh, R = Et
6. Ar = 4-ClPh, R = Ph
7. Ar = 4-MeOPh, R = Me
8. Ar = 4-MeOPh, R = Et
9. Ar = 4-MeOPh, R = Ph

Scheme 1. Structures of 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters **1**–**9**.

ated in the positive mode as follows: nitrogen was used as a drying gas with flow rate 4 L/min; nebulizer pressure 7 psi; capillary voltage 4 kV; heated capillary temperature 300 °C. The samples dissolved in methanol were ionized by electrospray ionization and continuously infused into the ESI chamber at a flow rate of 4 μL/min by a Cole-Parmer 74900 syringe pump (Cole-Parmer Instrument Company). The scan range of the ions is *m*/*z* values from 50 to 400 and cutoff mass 50 was used during ion accumulation. Precursor ions of interest were isolated and collided with helium to obtain collisionally activated dissociation (CAD) spectra (MS^n) spectra. The fragmentation amplitude values are 0.5–1.0 V and the fragmentation time is 40 ms.

3. Results and discussion

The characteristic product ions formed upon CAD of the protonated compounds **1**–**9** under ESI conditions were observed and are compiled in Table 1. The proposed fragmentation mechanisms of the compounds, as suggested by observations from CAD spectra, are presented in Schemes 2 and 3. The mass spectrum and CAD product ion sprctra of compound **1** were selected as representatives and are shown in Fig. 1.

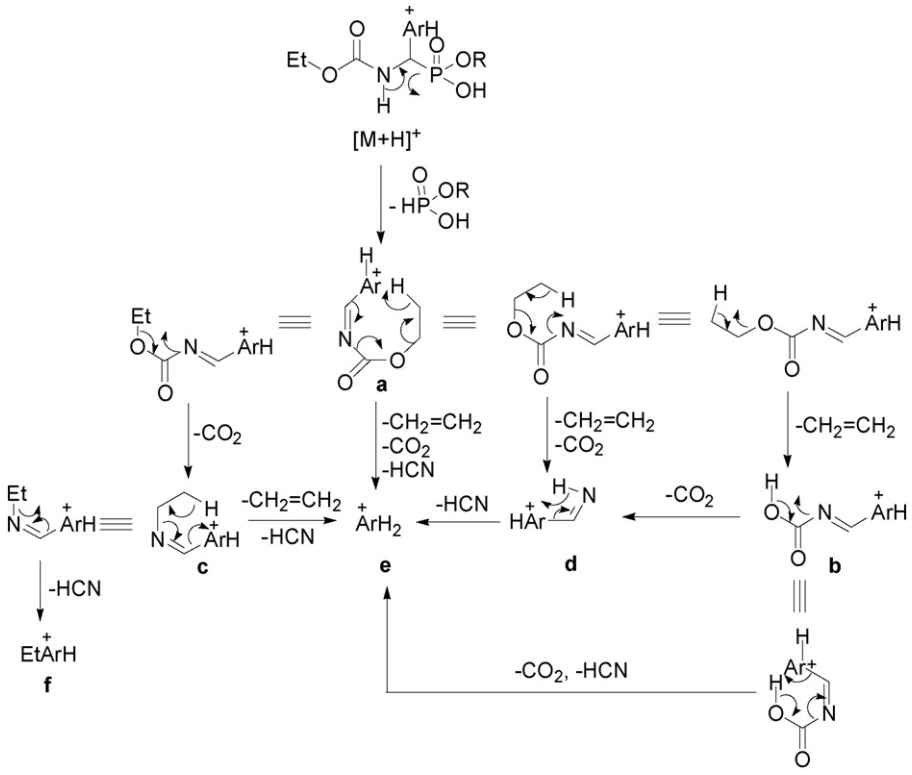
All title compounds **1**–**9** showed similar fragmentation pathways under positive ion ESI conditions (Scheme 2). The arene-protonated molecular ions $[M+H]^+$ could undergo a four-membered ring hydrogen rearrangement to lose a molecule of phosphite monoester to yield protonated *N*-ethoxycarbonyl arylimine ions (**a**), which could further undergo four-membered ring hydrogen or ethyl rearrangements to produce protonated *N*-arylmethylidene carbamic acid ions (**b**) and protonated *N*-ethyl arylimine ions (**c**) by loss of ethylene or carbon dioxide, respectively. The ions (**a**) could also undergo a six-membered ring hydrogen rearrangement to produce protonated arylimine ions (**d**) by loss of ethylene plus carbon dioxide simultaneously. It is interesting to observe that the ions **a** could also undergo eight-membered ring hydrogen rearrangement to yield protonated arene ions (**e**) by loss of ethylene, carbon dioxide, and cyanic acid together, which could also be generated from ions **b**, **c**, and **d** via six- or four-membered hydrogen ring rearrangements and loss of ethylene plus cyanic acid, carbon dioxide plus cyanic acid, or cyanic acid, respectively. The ions **b** could further undergo a four-membered ring hydrogen rearrangement to give rise to the ions **d** by loss of carbon dioxide. The ions **c** could further undergo ethyl rearrangement to yield protonated ethylarene ions (**f**) by loss of cyanic acid.

Table 1
Product ions observed in CAD product ion spectra of title compounds **1**–**9**

Compounds	Precursor ions *m*/*z* (ion)	Fragment ions *m*/*z* (ion)
1	274 ($[M+H]^+$)	178 (**a**)
	178 (**a**)	150 (**b**), 134 (**c**), 106 (**d**), 79 (**e**)
	150 (**b**)	106 (**d**), 79 (**e**)
	134 (**c**)	107 (**f**), 79 (**e**)
	106 (**d**)	79 (**e**)
2	288 ($[M+H]^+$)	178 (**a**)
	178 (**a**)	150 (**b**), 134 (**c**), 106 (**d**), 79 (**e**)
	150 (**b**)	106 (**d**), 79 (**e**)
	134 (**c**)	107 (**f**), 79 (**e**)
	106 (**d**)	79 (**e**)
3	336 ($[M+H]^+$)	178 (**a**)
	178 (**a**)	150 (**b**), 134 (**c**), 106 (**d**), 79 (**e**)
	150 (**b**)	106 (**d**), 79 (**e**)
	134 (**c**)	107 (**f**), 79 (**e**)
	106 (**d**)	79 (**e**)
4	308 ($[M+H]^+$)	212 (**a**)
	212 (**a**)	184 (**b**), 168 (**c**), 140 (**d**), 113 (**e**)
	184 (**b**)	140 (**d**), 113 (**e**)
	168 (**c**)	141 (**f**)
	140 (**d**)	113 (**e**)
5	322 ($[M+H]^+$)	212 (**a**)
	212 (**a**)	184 (**b**), 168 (**c**), 140 (**d**), 113 (**e**)
	184 (**b**)	140 (**d**), 113 (**e**)
	168 (**c**)	141 (**f**)
	140 (**d**)	113 (**e**)
6	370 ($[M+H]^+$)	212 (**a**)
	212 (**a**)	184 (**b**), 168 (**c**), 140 (**d**), 113 (**e**)
	184 (**b**)	140 (**d**), 113 (**e**)
	168 (**c**)	141 (**f**)
	140 (**d**)	113 (**e**)
7	304 ($[M+H]^+$)	208 (**a**), 215 (**g**)
	208 (**a**)	180 (**b**), 164 (**c**), 136 (**d**), 109 (**e**)
	180 (**b**)	136 (**d**), 109 (**e**)
	164 (**c**)	137 (**f**)
	136 (**d**)	109 (**e**)
8	318 ($[M+H]^+$)	208 (**a**), 229 (**g**)
	208 (**a**)	180 (**b**), 164 (**c**), 136 (**d**), 109 (**e**)
	180 (**b**)	136 (**d**), 109 (**e**)
	164 (**c**)	137 (**f**)
	136 (**d**)	109 (**e**)
9	366 ($[M+H]^+$)	208 (**a**), 277 (**g**)
	208 (**a**)	180 (**b**), 164 (**c**), 136 (**d**), 109 (**e**)
	180 (**b**)	136 (**d**), 109 (**e**)
	164 (**c**)	137 (**f**)
	136 (**d**)	109 (**e**)

Besides general fragmentation, the protonated molecular ions $[M+H]^+$ of compounds **7**–**9**, in which the aryl group is *para*-methoxyphenyl, could also elinminate a molecule of ethyl carbamate to yield (*para*-methoxyphenyl)methylphosphonate ions (**g**) probably because they could tautomerize to the ions **g′**, in which all of the atoms are in the stable octet structure (Scheme 3).

Ring rearrangement is a general fragmentation pathway in mass spectrometry and has often been observed in mass spec-



Scheme 2. Proposed fragmentation mechanisms of protonated 1-[*N*-ethoxycarbonylamino]arylmethylphosphonic monoesters **1**–**9**.

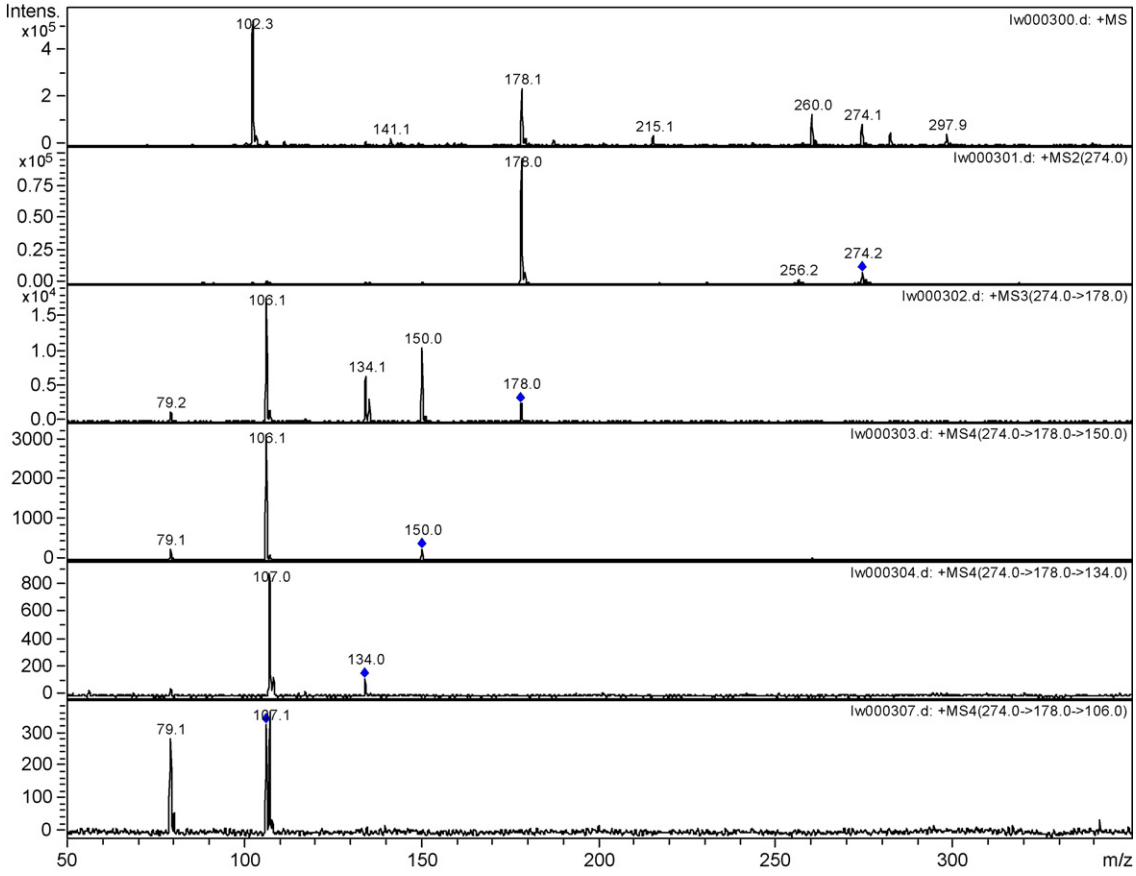
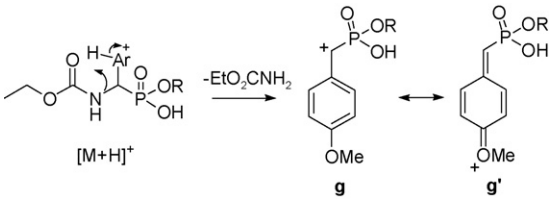


Fig. 1. ESI mass spectrum and product ion spectra of protonated methyl 1-(*N*-ethyloxycarbonylamino)phenylmethylphosphonic monoester (**1**) under ESI conditions.



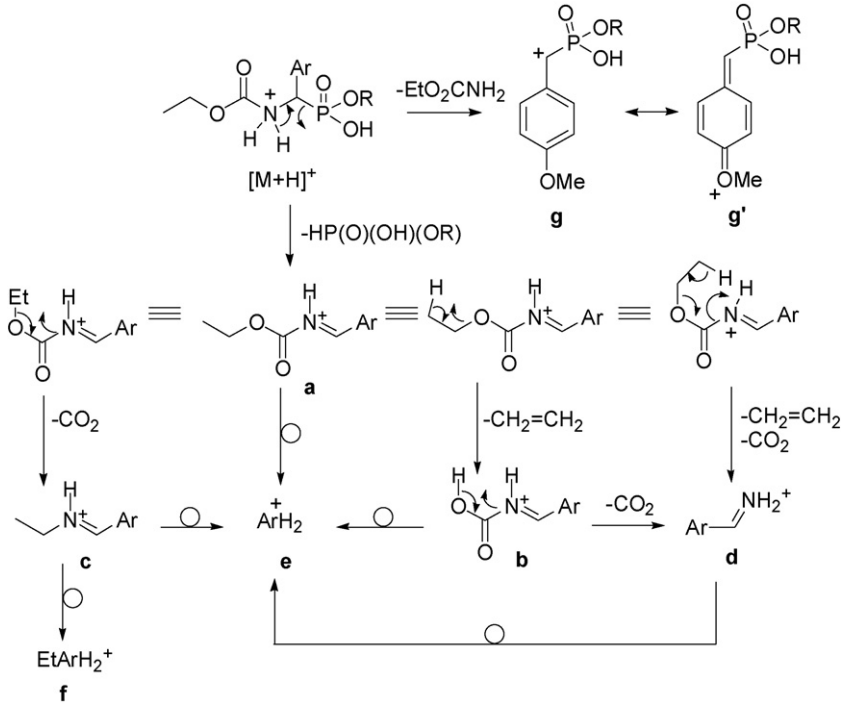
Scheme 3. Proposed ions **g** fragmentation mechanisms of protonated compounds **7–9**.

trometric investigation for Cbz-protected amino acids recently [14–17]. For instance, the deprotonated *N*-Cbz protected substituted taurines favorably undergo a four-membered ring rearrangement to eliminate a molecule of benzyl alcohol under negative ion ESI conditions [17]. The protonated 1-(*N*-Cbz-amino)arylmethylphosphonic diesters preferentially undergo four-membered ring rearrangements to eliminate benzyl alcohol, phosphite, ether, and ether plus benzyl alcohol and could also undergo a six-membered ring benzyl rearrangement to yield benzylphosphonate ions under ESI–MS conditions [14]. However, their corresponding monoesters, methyl and ethyl 1-(*N*-Cbz-amino)arylmethylphosphonates favorably undergo various four-membered ring rearrangements to produce diverse nitrogen-containing fragment ions from *N*-protonated molecular ions directly [15].

In the present study, however, the remarkable difference is that the protonation of 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters should be occurred at the aromatic ring, so that the formation of most of the fragment ions could be explained by reasonable cleavage patterns. If only the nitrogen atom of 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters is protonated, the fragment ions **e** yielded from ions **a**, **c** and **d**, and the fragment ions **f** generated from **a** are difficult to be given a equitable mechanism, since the loss of molecule of HCN is impossible in the nitrogen protonated structures (see Scheme 4). Thus, if the proton is not only absolutely affined in the arene ring moiety, it must be existed in both nitrogen atom and arene ring of the title compounds.

4. Conclusions

The various *N*-protection groups of the 1-subsititued aminoarylmethylphosphonic monoesters caused apparent dissimilar ESI mass spectrometric fragment patterns. The major mass spectrometric fragmentation difference between 1-(*N*-ethoxycarbonylamino)arylmethylphosphonic monoesters with their corresponding 1-(*N*-Cbz-lamino)arylmethylphosphonic monoesters, is that the former compounds could be protonated predominantly at their arene ring moieties, while the latter compounds could be protonated mainly on their nitrogen atoms. The protonated title compounds predominantly undergo a four-membered hydrogen ring rearrangement to yield protonated *N*-ethoxycarbonyl arylmethylimine ions, which could further undergo different four- to eight-membered ring rearrangements to give rise to several types of protonated arylimine ions and protonated arene ions.



Scheme 4. Proposed fragmentation mechanisms of nitrogen protonated 1-[*N*-ethoxycarbonylamino]arylmethylphosphonic monoesters **1–9**.

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