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Intramolecular four-membered ring rearrangements of 1-(*N*-benzyloxycarbonylamino)arylmethylphosphonate monoesters under electrospray ionization conditions

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Abstract

The mass spectrometric behavior of 1-[*N*-benzyloxycarbonyl(Cbz)amino]arylmethylphosphonate monoesters was studied under positive ion electrospray ionization (ESI) conditions. The most interesting feature is that all title compounds predominantly undergo four-membered ring rearrangements to yield mainly nitrogen-containing fragment ions by loss of a carbon dioxide, phosphite, carbon dioxide plus phosphite, or benzyloxycarbonylphosphonate monoester. The fragmentation is obviously different from the corresponding 1-(*N*-Cbz-amino)arylmethylphosphonate diesters, which show a tendency to undergo an intramolecular six-membered ring benzyl rearrangement.

Keywords: 1-(*N*-Cbz-amino)arylmethylphosphonate monoesters; Electrospray ionization; Four-membered ring rearrangements

1. Introduction

Phosphonate esters are an important class of phosphorus analogues of amino esters and peptides, which have been widely applied 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]. Many synthetic methods for the preparation of 1-aminoalkylphosphonate esters have been reported till now [6–11].

The mass spectrometries of aminoalkylphosphonic acids have been studied either by derivatization [12–14] or by chemical ionization (CI) [15]. The mass spectrometries of 1-(*N*-Cbz-amino)alkylphosphonate diesters have been investigated either under the electron impact ionization conditions (EI) by Yuan et al. [16] and under the electrospray ionization conditions in conjunction with tandem mass spectrometry (ESI-MS^n) by us [17]. Previously, we found that dimethyl and diethyl 1-(*N*-Cbz-amino)arylmethylphosphonates favorably undergo a six-membered ring benzyl rearrangement to produce benzylphosphonate ions besides the eliminations of ether, benzyl alcohol, phosphite and an ether plus benzyl alcohol from molecular ions under ESI conditions [17]. We investigated the mass spectrometric behavior of methyl and ethyl 1-(*N*-Cbz-amino)arylmethylphosphonate monoesters and found they showed remarkably different fragmentation patterns from the corresponding diesters under ESI conditions. Herein, we present the ESI-MS^n fragmentation of 1-(*N*-Cbz-amino)arylmethylphosphonate monoesters (Scheme 1).

2. Experimental

Methyl and ethyl 1-(*N*-Cbz-amino)arylmethylphosphonates **1**–**6** were prepared by the method described in the literature [18]. 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 operated 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

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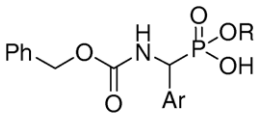


1-6

1. Ar = Ph, R = Me
2. Ar = Ph, R = Et
3. Ar = *p*-ClPh, R = Me
4. Ar = *p*-ClPh, R = Et
5. Ar = *p*-MeOPh, R = Me
6. Ar = *p*-MeOPh, R = Et

Scheme 1. Structures of 1-(*N*-Cbz-amino)arylmethylphosphonate monoesters **1**–**6**.

74900 syringe pump (Cole-Parmer Instrument Company). The scan range of the ions is *m*/*z* values from 50–500 and cutoff mass 50 was used during ion accumulation. The ions of the mass-to-charge ratio (*m*/*z*) of interest were isolated and fragmented through the collision with helium to obtained 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 fragment ions observed in the tandem mass spectra of the title compounds are listed in Table 1. The fragmentation patterns of the title compounds are presented in Scheme 2. Compound **5** was selected as a representative sample. Its ESI and tandem ESI spectra were shown in Fig. 1.

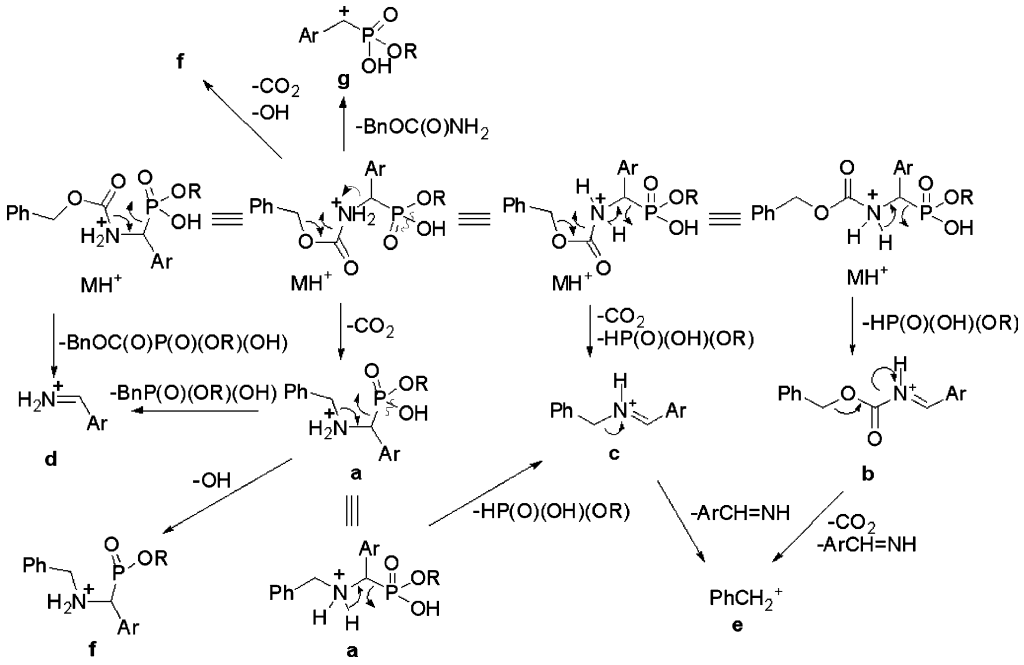
All title compounds **1**–**6** show similar fragmentation pathways under positive ion ESI conditions (Scheme 2). The nitrogen-protonated molecular ions $[M + H]^+$ could undergo a four-membered ring rearrangement to lose a molecule of carbon dioxide to yield 1-(*N*-benzylamino)arylmethylphosphonate monoester ions **(a)**, which could further undergo a four-membered ring rearrangement to produce protonated aryliminium ions **(d)** by loss of benzylphosphonate monoesters. The ions **(d)** could also be yielded directly form the protonated molecular ions $[M + H]^+$ via a four-membered ring rearrangement by loss of Cbz-phosphonate monoester. The nitrogen-protonated ions **(a)** could also undergo a four-membered ring rearrangement to eliminate phosphite monoester to form *N*-benzyl aryliminium ions **(c)**, which could also be formed directly from the molecular ions $[M + H]^+$ via two four-membered ring rearrangements simultaneously by loss of a carbon dioxide plus phosphite monoester together. The protonated molecular ions $[M + H]^+$ could undergo a four-membered ring rearrangement to eliminate a phosphite monoester to give rise to *N*-Cbz aryliminium ions **(b)**. Both ions **(b)** and **(c)** could undergo an *i*-cleavage to generate benzyl carbocation **(e)**.

For compounds **5** and **6**, in which aryl group is *para*-methoxyphenyl, their molecular ions $[M + H]^+$ could yield protonated 1-(*N*-benzylamino)arylmethylphosphinate ions **(f)** by loss of a carbon dioxide plus hydroxy group, which could also be formed via the ions **(a)** by loss of a hydroxy group. Their molecular ions $[M + H]^+$ could also undergo an *i*-cleavage to eliminate a molecule of benzyl carbamate to give rise to arylmethylphosphonate monoester ions **(g)**.

It is very interesting to note that 1-(*N*-Cbz-amino) alkylphosphonate diesters are favorably protonated or formed sodium adducts at their oxygen atoms of phosphonate moiety

Table 1
Fragment ions observed in the tandem mass spectra of compounds **1**–**6**

Compound	Precursor ions, *m*/*z* (ion)	Fragment ions, *m*/*z* (ion, relative intensity percentage)
1	336 ($[M + H]^+$)	292 (**a**, 20), 240 (**b**, 23), 196 (**c**, 100), 106 (**d**, 27)
	292 (**a**)	196 (**c**, 24), 106 (**d**, 100)
	240 (**b**)	196 (**c**, 100), 91 (**e**, 19)
	196 (**c**)	91 (**e**, 100)
2	350 ($[M + H]^+$)	306 (**a**, 21), 240 (**b**, 18), 196 (**c**, 100), 106 (**d**, 30)
	306 (**a**)	196 (**c**, 38), 106 (**d**, 100)
	240 (**b**)	196 (**c**, 100), 91 (**e**, 13)
	196 (**c**)	91 (**e**, 100)
3	370 ($[M + H]^+$)	326 (**a**, 22), 274 (**b**, 16), 230 (**c**, 100), 140(**d**, 48)
	326 (**a**)	230 (**c**, 51), 140 (**d**, 100)
	274 (**b**)	230 (**c**, 100), 91 (**e**, 11)
	230 (**c**)	91 (**e**, 100)
4	384 ($[M + H]^+$)	340 (**a**, 34), 274 (**b**, 13), 230 (**c**, 100), 140(**d**, 57)
	340 (**a**)	230 (**c**, 40), 140 (**d**, 100)
	274 (**b**)	230 (**c**, 100), 91 (**e**, 54)
	230 (**c**)	91 (**e**, 100)
5	366 ($[M + H]^+$)	322 (**a**, 5), 270 (**b**, 53), 226 (**c**, 14), 136 (**d**, 6), 305 (**f**, 48), 215 (**g**, 100)
	322 (**a**)	226 (**c**, 74), 136 (**d**, 42), 305 (**f**, 100)
	270 (**c**)	226 (**c**, 100), 91 (**e**, 6)
	226 (**b**)	91 (**e**, 100)
6	380 ($[M + H]^+$)	336 (**a**, 4), 270 (**b**, 28), 226 (**c**, 8), 136 (**d**, 6), 319 (**f**, 39), 229 (**g**, 100)
	336 (**a**)	226 (**c**, 62), 136 (**d**, 67), 319 (**f**, 100)
	270 (**b**)	226 (**c**, 100), 91 (**e**, 6)
	226 (**c**)	91 (**e**, 100)



Scheme 2. Fragmentation observed in the ESI tandem mass spectra of compounds **1**–**6**.

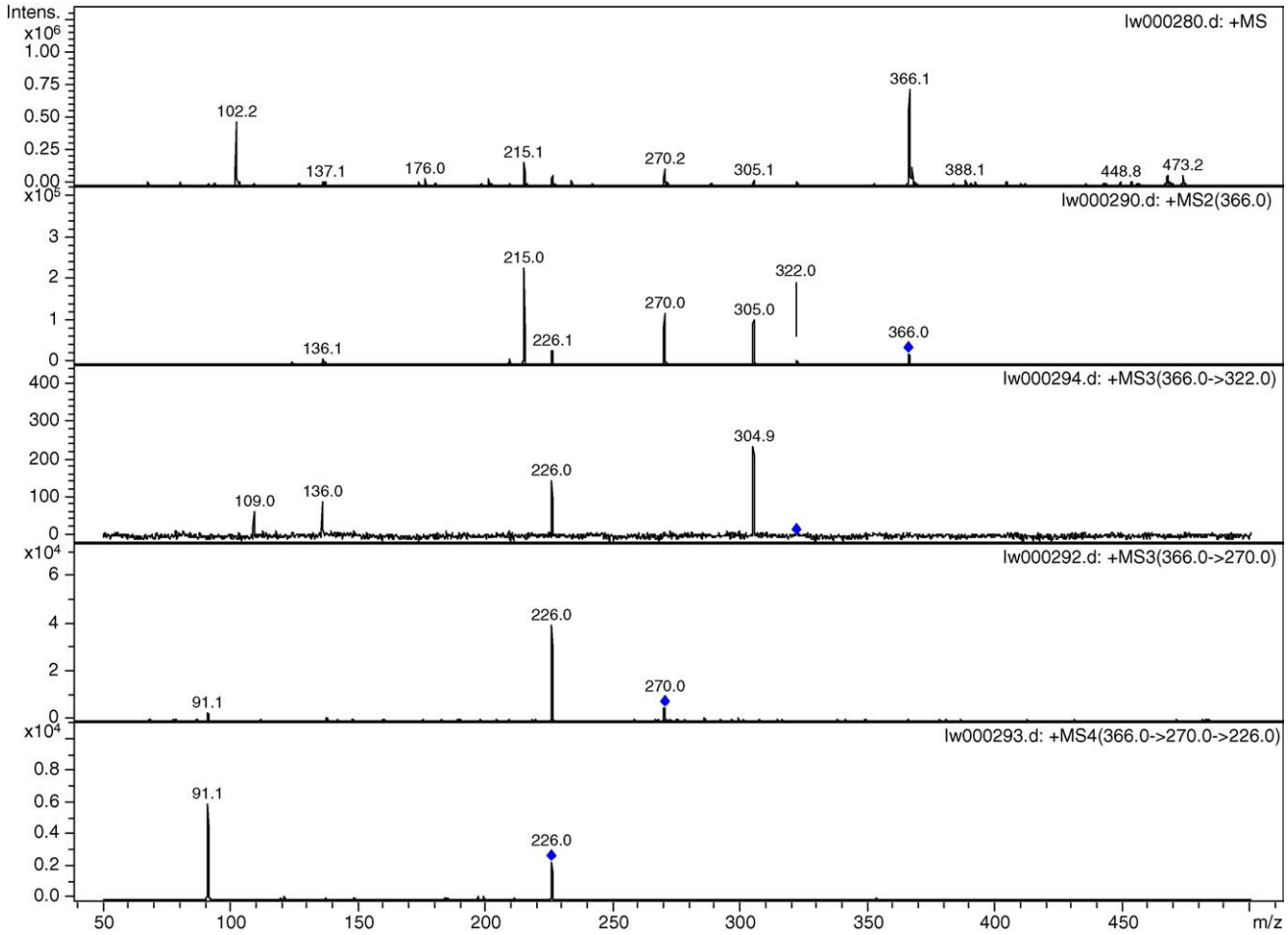


Fig. 1. The ESI mass spectrum and tandem mass spectra of protonated methyl 1-(*N*-Cbz-amino)(4-methoxyphenyl)methylphosphonate monoester (**5**) under positive ion ESI conditions.

to produce mainly phosphorus-containing fragment ions [17], while 1-(*N*-Cbz-amino)alkylphosphonate monoesters are favorably protonated at their nitrogen atom to generate mainly nitrogen-containing fragment ions. The difference is rationalized that phosphonate monoesters contain a free phosphonic hydroxy group, which could form intramolecular hydrogen bonds with either P=O or P–OR groups. Thus, the oxygen atoms in phosphonate moiety could not be further protonated.

Another major diffenent between *N*-Cbz protected aminoalkylphosphonate monoesters and diesters is that diesters preferentially eliminate benzyl alcohol, phosphite, ether, ether plus benzyl alcohol and could also undergo a six-membered ring benzyl rearrangement to yield benzylphosphonate ions under ESI-MS conditions [17], while the corresponding monoesters favorably undergo various four-membered ring hydrogen, or benzyl, or benzyloxycarbonyl rearrangements to produce diverse nitrogen-containing fragment ions. Four-membered ring rearrangement is a general fragmentation pathway in mass spectrometry and has also been observed in mass spectrometric investigation recently [19–24].

4. Conclusions

In conclusion, the ESI-MS fragmentation pathways of 1-(*N*-benzyloxycarbonylamino)arylmethylphosphonate monoesters were rationalized and supported by tandem mass spectrometry. These compounds predominantly undergo four-membered ring rearrangements to yield diverse nitrogen-containing fragment ions, while the corresponding 1-(*N*-benzyloxycarbonylamino)arylmethylphosphonate diesters are prefer to give rise to phosphorus-containing fragment ions and show a tendency to undergo an intramolecular six-membered ring benzyl rearrangement. A reasonable explanation of the difference is that phosphonate monoesters contain a free phosphonic hydroxy group, which could form intramolecular hydrogen bonds with the oxygen atom of either P=O or P–OR groups. Thus, the oxygen atoms in phosphonate monoesters moiety could not be protonated.

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