Intramolecular Single and Double Hydrogen Migrations in the Mass Spectra of Substituted Tetrahydro-1,3,2-oxazaphosphorin-2-oxides†

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The mass spectral fragmentation of substituted tetrahydro-1,3,2-oxazaphosphorin-2-oxides occurs by the cleavage of ring bonds. The ions due to simple cleavage, single and double hydrogen migration, seem to be triggered by C—O bond cleavage of the oxazaphosphorin ring. The variations in the relative abundance of ions arising due to similar fragmentation modes have been found to depend on the nature of the substituent and the stability of the particular fragment. The single hydrogen transfer process is supported by metastable ion and shift techniques.

INTRODUCTION

The mass spectrometry of biologically active organophosphorus heterocyclic systems such as 1,3,2-dioxaphosphorinanes and 1,3,2-oxazaphosphorinanes is a subject of current interest.[1-5] A variety of substituted diastereoisomeric 1,3,2-dioxaphosphorinanes have been examined by the deuterium labelling, high resolution and metastable scan techniques. Single and multiple hydrogen migrations are reported in these compounds.[1,5] Relatively little information on the electron impact induced fragmentation of substituted 1,3,2-oxazaphosphorinanes is available.[6,7] The relative abundance of molecular ions is reported to be very small, about 1% in the electron impact process.[6] The mass spectrometry of the phosphorus-containing antitumour drugs, cyclophosphamides, and their metabolic products, having a 1,3,2-oxazaphosphorinane cyclic skeleton, has received much attention by the field desorption technique due to the thermal instability of these compounds. The present work reports the electron impact fragmentations observed in a variety of substituted 1,3,2-oxazaphosphorinanes (**1–14**). The mass spectra of these compounds are of importance because of the little information on this cyclic skeleton.[6,7] These compounds are also likely to be biologically active and are being screened against standard P-388 lymphocytic leukaemia.

RESULTS AND DISCUSSION

The present 3,6-diphenyl-substituted tetrahydro-1,3,2-oxazaphosphorin-2-oxides (compounds **1–12**) and 3-phenyl-5,6-tetramethylenetetrahydro-1,3,2-oxazaphosphorin-2-oxides (**13, 14**) are unusual in having different heteroatoms and phenyl rings in close proximity. The electron impact process could lead to molecular ions with charge or radical site localized at either the two phenyl rings, ether oxygen, doubly bonded phosphoryl oxygen or the nitrogen atom and which could then direct further fragmentations. Since there is a wide variation in the nature of the substituents attached at the 2,3,6-positions of the ring, a wide variation in the relative intensities of ions arising due to similar fragmentations is observed.

The molecular ions are significant in all spectra (Table 1). When chlorine in the 2-position in compounds **2**, **3** and **5** is substituted by the aziridino group, the resulting compounds **8**, **9** and **10** exhibit greater molecular ion abundance. This may be due to the lowering of the ionization energy of the molecules by the electron-donating aziridino group relative to chlorine, which increases the fraction of non-decomposing molecular ions formed under electron ionization. The stability of the exocyclic P—N bond to the electron impact process in the spectra of oxazaphosphorines has been pointed out by Edmundson[7] and may contribute to the greater molecular ion abundance in **8–10**.

In the mass spectra of organophosphorus heterocycles, C—O bond cleavage with or without hydrogen migration is common.[2,7-9] The mass spectra of 1,3,2-dioxaphosphorinanes[3,4] reveal the loss of the hydrocarbon fragment C_mH_n, the charge being carried by the $[M-C_mH_n]^+$ ion and/or the complementary ion $[C_mH_n]^+$. The mass spectra of substituted tetrahydro-1,3,2-oxazaphosphorinane-2-oxides reveal this type of fragmentation.

The first step in the fragmentation process seems to be the cleavage of the C—O bond, generating the ring-opened intermediate $[M_1]^{+\cdot}$ followed by simple cleavage of the C(4)—C(5) bond. Cleavage of this bond (β-cleavage) should be favoured by localization of charge either on the C(6) aryl ring or on the endocyclic nitrogen atom of the ring. One would expect the relative abundance of these two simple cleavage product ions, viz. styryl ion (*a*) or phenylimine ion (*b*) (Scheme 1), to vary depending on the nature of the substituent. The *p*-nitro group on the styryl moiety *a*

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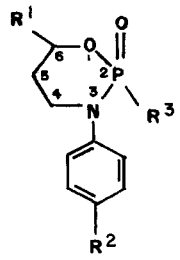
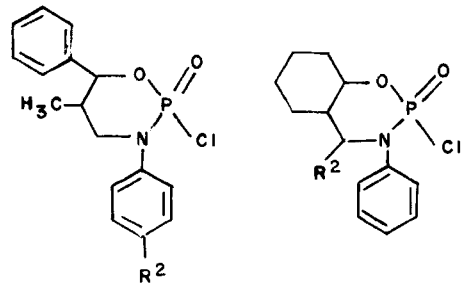


	R^1	R^2	R^3	m.p. (°C)		R^1	R^2	R^3	m.p. (°C)
1	C_6H_5	H	Cl	124	6	2-Naphthyl	CH_3	Cl	142
2	C_6H_5	Cl	Cl	148	7	p-ClC_6H_4	CH	Cl	154
3	C_6H_5	OCH_3	Cl	139	8	C_6H_5	Cl		110
4	C_6H_5	CH_3	Cl	141	9	C_6H_5	OCH_3		88
5	p-$NO_2C_6H_4$	CH_3	Cl	182	10	p-$NO_2C_6H_4$	CH_3		191



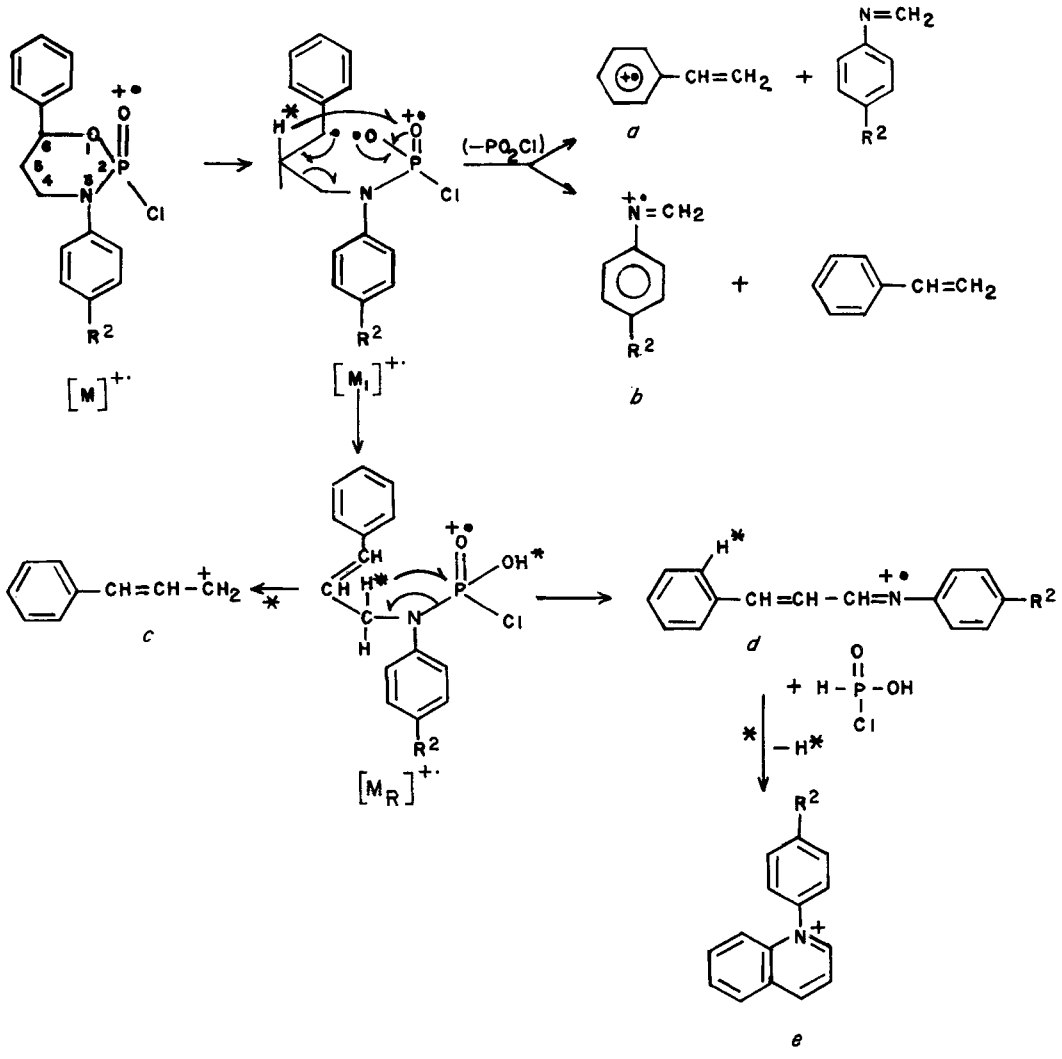
11 R^2=H, mp 168 °C 13 R^2=H, mp 130 °C

12 R^2=CH_3, mp 152 °C 14 R^2=C_6H_5, mp 166 °C

or the *p*-methoxy substituent on the phenylimine ion *b* should reduce the abundance of ion *a* relative to the complementary ion *b*, and this is observed in compounds **5**, **10**, **3** and **9** (Table 1). This simple cleavage process is competing with single and double hydrogen migration processes. Localization of charge on the doubly bonded phosphoryl oxygen atom or on the ether oxygen atom in the ring-opened intermediate $[M_1]^{+\cdot}$ is followed by hydrogen transfer from the C(5) methylene via a six-membered transition state. Cleavage of the C—N bond in the rearranged ion results in the formation of a strong peak at *m/z* 117 in the mass spectra of compounds **1**, **2**, **3**, **4** and **9**. This McLafferty-type hydrogen transfer is supported by the metastable peak. The driving force for this fragmentation process, resulting in the charge being carried by the hydrocarbon fragment, seems to be the stability of the phenylallyl ion *c*. In the mass spectra of

Table 1. Relative abundances of some characteristic ions in the mass spectra of tetrahydro-1,3,2-oxazaphosphorin-2-oxides

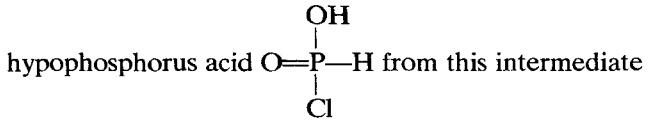
Compound no.	$[M]^{+\cdot}$ *m/z* (rel.ab.,%)	Styrene ion (*a*) *m/z* (rel.ab.,%)	Phenylimine ion (*b*) *m/z* (rel.ab.,%)	Phenylallyl ion (*c*) *m/z* (rel.ab.,%)	Schiff base ion (*d*) *m/z* (rel.ab.,%)	Quinoline-type ion (*e*), $[d-H]^+$ *m/z* (rel.ab.,%)
1	307(30)	104(32)	105(30)	117(100)	207(9)	206(18)
2	341(23)	104(19)	139(25)	117(100)	241(4)	240(7)
3	337(23)	104(13)	135(20)	117(100)	237(3)	236(2)
4	321(21)	104(11)	119(18)	117(100)	221(4)	220(7)
5	366(73)	149(6)	119(57)	162(11)	266(6)	265(9)
6	371(18)	154(67)	119(15)	167(100)	271(11)	270(11)
7	355(21)	118(16)	119(25)	151(100)	255(4)	254(8)
8	348(75)	104(42)	139(75)	117(100)	241(5)	240(17)
9	344(84)	104(17)	135(78)	117(100)	237(5)	236(8)
10	373(100)	149(1)	119(93)	162(10)	266(6)	265(9)
11	321(33)	118(64)	105(38)	131(100)	221(7)	220(20)
12	335(55)	118(62)	119(37)	131(100)	235(4)	234(11)



Scheme 1

compounds **5** and **10** containing a *p*-nitro substituent the relative abundance of this *p*-nitrophenylallyl ion *c* is small due to further fragmentaion by loss of NO_2. In the mass spectra of compounds **11** and **12** viz. 3,6-diaryl-5-methyltetrahydro-1,3,2-oxazaphosphorin-2-oxide, the phenylallyl ion *c* is shifted to *m/z* 131 (100%) due to the methyl substituent at the C(5) position.

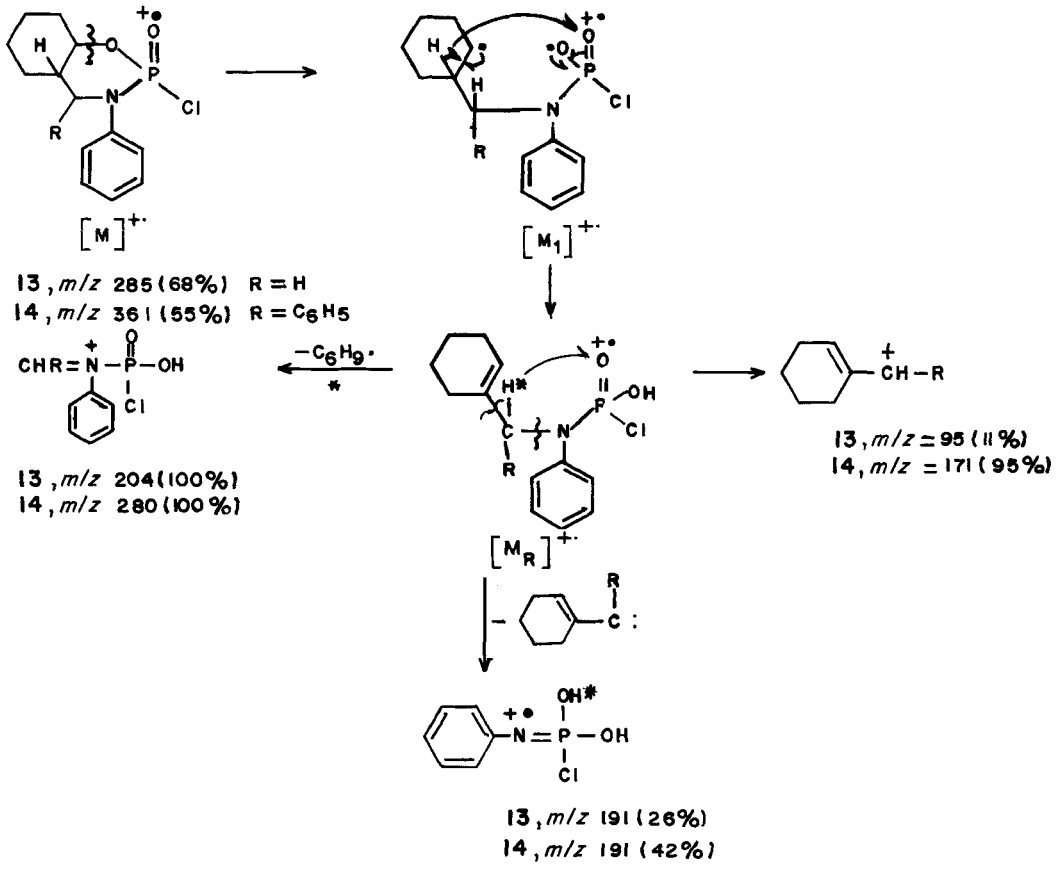
The fragmentation process initiated by McLafferty-type hydrogen transfer from the C(5) methylene to the phosphoryl oxygen atom is followed by a second hydrogen migration from the C(4) methylene to the phosphorus atom. Elimination of monochloro-



hypophosphorus acid from this intermediate

ion results in strongly conjugated α,β-unsaturated Schiff base ion *d*. The Schiff base ion *d* then eliminates a hydrogen atom from the *ortho* positions of the phenyl ring by substitution–elimination reactions. The metastable-supported hydrogen atom loss resulting in cyclization of the α,β-unsaturated Schiff base ion to quinoline-type ion *e* has been discussed earlier in cycloreversion reactions of substituted 3,4-dihydro-1,3,2-oxazaphosphorin-2-oxides.[11] It may be pointed out that similar quinoline-type structures have been assigned to $[M-H]^+$ ions in the spectra of α,β-unsaturated oximes.[12]

The mass spectra of 2-chloro-3-phenyl-5,6-tetramethylenetetrahydro-1,3,2-oxazaphosphorin-2-oxide (**13**) and an analogous 2-chloro-3,4-diphenyl-5,6-tetramethylenetetrahydro-1,3,2-oxazaphosphorin-2-oxide (**14**) show similar fragmentation behaviour. In these compounds formation of the phenylallyl type of ion is not possible. The base peak is at *m/z* 204 for **13** and *m/z* 280 for **14**. The origin of these ions is supported by the metastable peak. A reasonable speculation is that C—O bond cleavage in the molecular ion is followed by single hydrogen migration from the C(5) methylene to the phosphoryl oxygen resulting in the formation of the intermediate ion $[M_R]^{+\cdot}$ (Scheme 2). Loss of cyclohexenyl radical $C_6H_9^{\cdot}$ from this ion and stabilization of the charge by phosphorus-containing fragments explains the mechanism of formation of these ions. Also cleavage of the C—N bond from this McLafferty rearrangement process results in the formation of carbonium ions at *m/z* 95 and *m/z* 171 in the spectra of **13** and **14**, respectively. Similarly strong peaks at *m/z* 191 in the spectra of these compounds could be ascribed to C—N bond cleavage accompanied by a second hydrogen migration from



Scheme 2

the C(4) methylene to the oxygen and resulting in the loss of cyclohexenyl-substituted carbene (Scheme 2). No metastable peak is observed for this process. Reported[10] eliminations of vinylidene diradical and methylcarbenes in the double hydrogen migrations in the spectra of phosphates supports the above fragmentation mechanism.

CONCLUSION

The present 1,3,2-oxazaphosphorin-2-oxide system examined is likely to exist in different conformations and configurations due to the presence of a variety of substituents at the 2,3,4- and 5,6-positions.[13] The basic cleavages of the 1,3,2-oxazaphosphorinane ring system under electron impact remain unaltered. It is, therefore, concluded that the fragmentation is triggered after initial C—O bond cleavage following the loss of conformational and configurational rigidity of the molecule.

EXPERIMENTAL

All mass spectra were recorded on an AEI MS30 mass spectrometer at 70 eV. The probe was kept at room temperature and all the samples were volatilized by heating the source at 60–120 °C.

In a typical experiment phosphorus oxychloride (1.0 g, 0.007 mol) was added dropwise to an ice-cold mixture of 1-phenyl-4-phenylamino-1-propanol (1.135 g, 0.005 mol) and triethylamine (3.5 g) in methylene chloride (20 cm^3) and stirred for 16 hours. Column chromatography of the reaction mixture afforded 2-chloro-3,6-diphenyltetrahydro-1,3,2-oxazaphosphorin-2-oxide (**1**) (1.15 g, 67% yield). The 2-substituted aziridino compounds (**8–10**) were prepared by treating equimolar quantities of aziridine and compounds **2–4** in dry dichloromethane for 15 minutes. Dichloromethane was removed under vacuum. The solids separated were crystallized from alcohol (yields 90%). Details of the preparation of the compounds used for the mass spectral studies in the present paper will be published separately.

REFERENCES

1. G. W. Francis, K. Jiessem, A. Dale and T. Gramstad, *Acta. Chem. Scand.* **30B**, 31 (1976).
2. A. Murari and M. Kainosho, *Org. Mass. Spectrom.* **11**, 175 (1976).
3. B. Zielinska and W. J. Stec, *Org. Mass. Spectrom.* **13**, 65 (1978).
4. W. J. Stec, B. Zielinska and B. Van de Graef, *Org. Mass. Spectrom.* **15**, 105 (1980).

5. Z. J. Lesnikowski, W. J. Stec and B. Zielinska, *Org. Mass. Spectrom.* **15,** 454 (1980).
6. (a) H. R. Schulten, *Biomed. Mass Spectrom.* **1,** 223 (1974). (b) H. R. Schulten, *Int. J. Mass Spectrom. Ion Phys.* **32,** 97 (1979).
7. R. S. Edmundson, *Org. Mass Spectrom.* **17,** 558 (1982).
8. H. Kentnttamaa and J. Engvist, *Org. Mass Spectrom.* **15,** 520 (1980).
9. M. Eto, *Organophosphorus Pesticides: Organic and Biological Chemistry,* pp. 113–121, CRC Press, Cleveland, Ohio (1979).
10. S. Meyerson, E. S. Kuhn, F. Ramirez, J. F. Merecek and H. Okazaki, *J. Am. Chem. Soc.* **102,** 2398 (1980).
11. V. N. Gogte, P. S. Kulkarni, A. S. Modak and B. D. Tilak, *Org. Mass Spectrom.* **16,** 515 (1981).
12. R. K. M. R. Kallury, A. C. Loudon and A. Maccoll, *Org. Mass Spectrom.* **13,** 218 (1978).
13. (a) S. Chandrasekaran and W. G. Bentrude, *Tetrahedron Lett.* **21,** 4671 (1980). (b) D. G. Gorenstein, R. Rowell and J. Findlay, *J. Am. Chem. Soc.* **102,** 5077 (1980).

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