Mass Spectrometric Behaviour of Phosphorus-containing Heterocycles and Ring-chain Tautomerism of some 1,3-*O,N*-heterocycles

PhD Thesis

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CONTENTS

ABBREVIATIONS AND SYMBOLS

Ar	aryl
Bu	butyl
CI	chemical ionization
EI	electron ionization
Et	ethyl
K	[ring]/[chain]
$M^{+\bullet}$	molecular ion
Me	methyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propy
RA	relative abundance
rDA	retro Diels-Alder
THF	tetrahydrofuran
V^a	Meyer parameter
δ	chemical shift (ppm)
ρ	reaction constant
σ^+	Hammett-Brown parameter

PUBLICATIONS

Papers related to the thesis

I.   **Márta Juhász**, Olli Martiskainen, Zita Zalán, Ferenc Fülöp, Kalevi Pihlaja,
      Electron ionization mass spectra of phosphorus-containing heterocycles. I.
      1,4,4a,5,6,7,8,8a-Octahydro-2*H*-3,1,2-benzoxazaphosphinine 2-oxides,
      Rapid Commun. Mass Spectrom. **2006**, *20*, 433-437.

II.   Olli Martiskainen, **Márta Juhász**, Zita Zalán, Ferenc Fülöp, Kalevi Pihlaja,
      Electron ionization mass spectra of phosphorus-containing heterocycles. II.
      1,2,3,4,4a,5,6,7,8,8a-Decahydro-1,3,2-benzodiazaphosphinine 2-oxides,
      Rapid Commun. Mass Spectrom. **2006**, *20*, 1621-1627.

III. **Márta Juhász**, Zita Zalán, Ferenc Fülöp, Kalevi Pihlaja,
      Electron ionization mass spectra of phosphorus-containing heterocycles. III.
      1,3,4,2-Oxadiazaphosphinane 2-oxides,
      Rapid Commun. Mass Spectrom. **2006**, *20*, 3595-3604.

IV.   **Márta Juhász**, László Lázár, Ferenc Fülöp,
      Substituent effects in the ring-chain tautomerism of 4-alkyl-2-aryl substituted
      oxazolidines and tetrahydro-1,3-oxazines,
      J. Heterocycl. Chem. **2007**, *44*, 1465-1473.

V.   **Márta Juhász**, Ferenc Fülöp, Kalevi Pihlaja,
      Substituent effects on the gas-phase ring-chain tautomerism of 3,4,5,6-tetrahydro-2*H*-
      1,3-oxazines,
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VI.   Kalevi Pihlaja, **Márta Juhász**, Henri Kivelä, Ferenc Fülöp
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VII. **Juhász Márta**, Ovcharenko Vladimir, Zalán Zita, Pihlaja Kalevi, Fülöp Ferenc,
      Néhány *O,N,P*-heterociklus fő fragmentációs útvonalainak tömegspektrometriás
      vizsgálata,
      MKE Vegyészkonferencia
      Hajdúszoboszló, 2005. június 28-30., Abstr.: P-37.

VIII. **Márta Juhász**, Zita Zalán, Ferenc Fülöp, Kalevi Pihlaja,
      Mass spectrometric behaviour of 1,3,4,2-oxadiazaphosphinane 2-oxides under electron
      ionization,
      24th Informal Meeting on Mass Spectrometry
      Ustron, 14-18 May, 2006, Abstr.: MoPo08.

IX.   Olli Martiskainen, **Márta Juhász**, Zita Zalán, Ferenc Fülöp, Kalevi Pihlaja,
      Electron ionization mass spectra of phosphorus-containing heterocycles.
      1,2,3,4,4a,5,6,7,8,8a-decahydro-1,3,2-benzodiazaphosphinine 2-oxides,
      24th Informal Meeting on Mass Spectrometry
   Ustron, 14-18 May, 2006, Abstr.: MoPo18.

X.   **Márta Juhász**, Olli Martiskainen, Zita Zalán, Ferenc Fülöp, Kalevi Pihlaja,
Effects of *N*- and *P*-substitutions on the fragmentations of some *P*-containing heterocycles under EI,
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Prague, 27 August-1 September, 2006, Abstr.: TuP-112.

XI.   **Márta Juhász**, László Lázár, Ferenc Fülöp, Kalevi Pihlaja,
Ring-chain tautomerism in 4-alkyl-2-aryl-1,3-oxazolidines,
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XII.   **Juhász Márta**, Lázár László, Fülöp Ferenc,
Szubsztituenshatások vizsgálata 4-alkil-2-aril-1,3-*O,N*-heterociklusok gyűrű-lánc tautomériájában,
MKE Centenáriumi Vegyészkonferencia
Sopron, 2007. május 29-június 1., Abstr.: SZ-P-26.

1. INTRODUCTION AND AIMS

Compounds possessing an oxazaphosphorinane ring system are very important pharmacological building blocks of matrix metalloproteinase-inhibitors and alkylating anti-cancer drugs, *e.g.* cyclophosphamide, *N,N*-bis(2-chloroethyl)-2*H*-1,3,2-oxazaphosphinan-2-amine-2-oxide (**1**), iphosphamide, *N*,3-bis(2-chloroethyl)-2*H*-1,3,2-oxazaphosphinan-2-amine-2-oxide (**2**), and trophosphamide, *N*,3-bis(2,2-dichloroethyl)-2*H*-1,3,2-oxazaphosphinan-2-amine-2-oxide (**3**). Such compounds exhibit pesticidal and antimicrobial activities. Diastereomeric 1,3,2-dioxaphosphorinanes and oxazaphosphorinanes with an $N(CH_2CH_2Cl)_2$ group on the *P* atom display similar, moderate activities against lymphocytic leukaemia P388 cells in mice.[1]

$$\textbf{1} \qquad \textbf{2} \qquad \textbf{3}$$
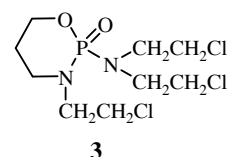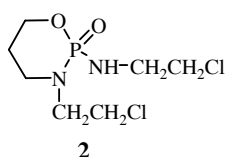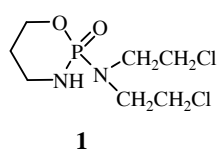
The syntheses, bioactivities and conformational analyses[2a–i,3] of various monocyclic 1,2,3-oxazaphosphorinane derivatives and 1,3,2-diheterophosphorinanes have already been studied, and bicyclic analogues of **1** with *N* at bridgehead position 3 have been synthetized for medical purposes.[4] Because of their fundamental importance (bioactive and synthetic), we have studied the fragmentations of a few saturated 3,1,2-benzoxazaphosphinine-2-oxides (**4–17**),[1] their *N*-analogue 1,3,2-benzodiazaphosphinine-2-oxides (**18–34**)[II] and various condensed 1,3,4,2-oxadiazaphosphinane derivatives (**35–42**)[III] under electron ionization (EI) at 70 eV, to elucidate the roles of various substituents on the ring *N* and *P* atoms, of the *cis-trans*-annelated isomers, and of the *P* stereochemistry on the fragmentations of the diastereomeric pairs.

$$\textbf{4-17} \qquad \textbf{18-34} \qquad \textbf{35-39}$$
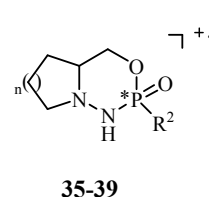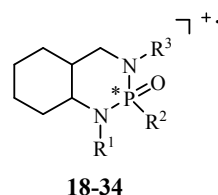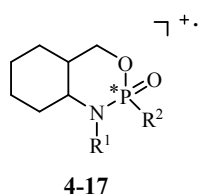
cis and *trans*; R^1 = H, Me, CH_2Ph; R^2 = Ph, OPh, $N(CH_2CH_2Cl)_2$; R^3 = H, Me; *n* = 1,2

$$\textbf{40} \qquad \textbf{41} \qquad \textbf{42}$$

cis and *trans*; R^2 = Ph
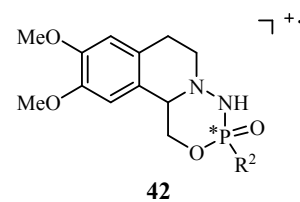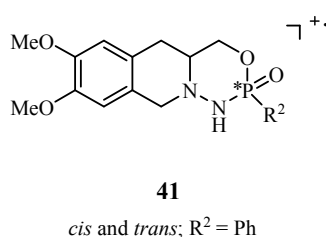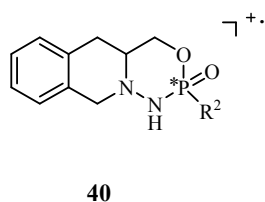
The reversible intramolecular addition of an OH group to a C=N double bond to form a cyclic structure is a well-known phenomenon among *N*-unsubstituted 1,3-*O,N*-heterocycles.[5] This ring-chain tautomeric process influences the reactivity and therefore the synthetic applicability of these compounds.[6] The electronic effects of 2-aryl groups on the ring-chain tautomerism in solution have been thoroughly investigated,[7–14] but much less attention has been paid to them in the gas phase.[15–18] We set out to study the ring-chain equilibria in the gas phase for several simple five- and six-membered 1,3-*O,N*-heterocyclic compounds[V,VI] since EI mass spectrometry (MS) can be used for this purpose by observing the ratio of the relative abundances {*RA*s(%)} of ions associated with one or the other tautomeric form. Another aim was to inspect the effects of 4-alkyl and 4/5-Ph substituents (besides the 2-aryl groups) on the equilibria in $CDCl_3$ solution[IV] and to compare them with those in the gas phase.

(Literature references are given as superscripts with Arabic numerals and the references to the publications related to my research as superscripts with Roman numerals.)

2. LITERATURE

2.1. P-containing organic compounds

In the following, the common features of *P*-containing organic compounds under EI have been collected and the pharmacological importance of a few compounds is described, together with a brief discussion of the synthesis of compounds **4–42** investigated in my work.

2.1.1. Synthesis of the P-containing compounds studied

The cyclization of *cis*- and *trans*-2-(hydroxymethyl)cyclohexylamines and of *cis*- and *trans*-2-(aminoethyl)cyclohexylamines with phenylphosphonic dichloride, phenyl dichlorophosphate and/or bis(2-chloroethyl)phosphoramidic dichloride at ambient temperatures yields saturated 3,1,2-benzoxazaphosphinane-2-oxides (**4–17**) and 1,3,2-benzodiazaphosphinane-2-oxides (**18–34**), respectively.

1,3,4,2-Oxadiazaphosphinane derivatives (**35–42**) were prepared by the cyclization of suitable hydrazino alcohols with phenylphosphonic dichloride, phenyl dichlorophosphate and/or bis(2-chloroethyl)phosphoramidic dichloride at room temperature in tetrahydrofuran (THF) in the presence of Et_3N. In most cases, two *P*-2 epimers differing in the relative configuration of the *P* atom (**a**(*R**) and **b**(*S**)) were formed; they were separated by column chromatography.[19–22]

### *2.1.2. MS studies of compounds containing a P atom*

Many (previous) MS studies of organophosphorus compounds have been focused primarily on data obtained on neutral compounds investigated by means of EI and chemical ionization (CI).[23a–g] However, the EI spectra give more structural information about the compounds studied than the CI spectra. MS behaviour of organic esters of *P* oxyacids were also reported.[24,25]

Within organophosphates, the degree of rearrangement and atomic migrations have been investigated; the fragmentations that occur with extensive H-migrations under EI for various alkyl esters of phosphinic,[25–28] phosphonic[25,29,30] and phosphoric acids[24,31,32] are well known. H-migration phenomena were orignally observed by McLafferty[24] in Et_3PO_4. Harless[27] studied a series of dialkyl (di-Me, di-Et, di-*n*-Pr, di-*i*-Pr, diallyl and di-*n*-Bu) phosphites and observed the cleavage of the alkyl chains and a very high degree of H-transfer from the alkyl group to the *P* part of the molecule. Ions formed by one or two H-transfers from the substituent and by simple bond cleavages were found also for trialkyl phosphites.

Within trialkyl phosphates (except for Me_3PO_4), loss of one of the alkyl groups from the molecular ion ($M^{+\bullet}$) initiated the fragmentation and was accompanied by a transfer of two H atoms to the *P*-containing part. A consecutive loss of two alkyl groups as neutral olefins was also observed. Jakobsen *et al.*[33] observed that the molecular ions of compounds possessing a 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane ring lost the C_5H_7 radical, which involved three H-transfers in a two-step fragmentation process. Murai and Kainosho[34] grouped the fragments generated from compounds containing a dioxaphosphorinane ring into three classes: fragments with *P*; those with a Ph group; and those consisting of parts of the alkyl group. The ejections of C_5H_7 and C_5H_8 from the dioxaphosphorinane part, involving the transfer of two or three H atoms to the *P*-containing moiety, was also observed in this type of compounds. The ions generated in this way were very abundant. Extensive rearrangements of the molecular ions with accompanying Ph-migration were also significant, as observed for Et_2PhPO_4.[29]

Ejection of hydrocarbon fragments by McLafferty rearrangements with simple and multiple H-transfers are typical for 1,3,2-dioxaphosphorinanes[35,36] and for substituted tetrahydro-1,3,2-oxazaphosphorinane-2-oxides.[37] Multiple H-transfers from the cyclic alkyl residues and simple bond fissions are also characteristic for 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanes (**43**–**52**), as described by Francis *et al.*[38]
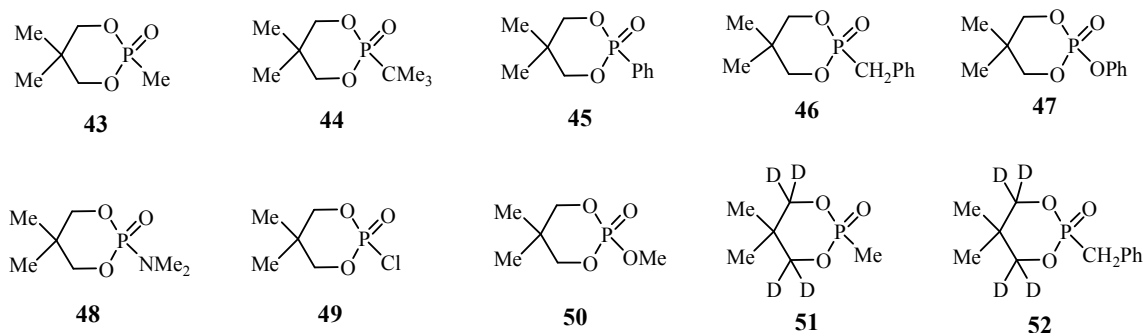
The relative abundances of ions formed via H-transfers and the consequent loss of hydrocarbon fragments (such as $C_4H_5^{\bullet}$, C_4H_6 and $C_4H_7^{\bullet}$) are influenced by the heteroatom attached to the *P* and also by the substituents connected to the exocyclic *N* in the case of the compounds studied by Zielinska and Stec,[35] a Ph substituent on the exocyclic *N* increasing the abundance of these ions, and alkyl groups decreasing it. The electronegativity of substituents influences the extent of the loss of hydrocarbon fragments (due to variation in the localization of the initial charge) and also the stability of the particular fragments under given conditions.[33,37]

For the esters of phosphonic acid, the fragment ion obtained by ejection of the hydrocarbon part from the phosphorinane ring can be stabilized by the resonance effect caused by the even electrons and the charge. Due to the possibility of additional resonance structures in the case of Ph and OPh derivatives, this ion is stabilized and provides the base peak of the spectra. This proves that the aromatic moieties can carry and stabilize the charge.[24,25] However, in the compounds studied by Francis *et al.*[38] mentioned above (**43–52**), there are too many heteroatoms close to each other and they have different electronic characters, so the location of charge in $M^{+\bullet}$ is not so evident, the initial ionization occurring on the ring *O*, on the phosphoryl *O* or on the exocyclic substituents attached to the *P* (*e.g.* Ph or NMe$_2$).[38,39]

Bafus *et al.*[31] showed that in Me$_3$PO$_4$ or Et$_3$PO$_4$ the initial charge is located on one of the ester *O* atoms or on the substituent (CH$_2$Ph, Ph or OPh) connected to the *P* atom, as the lowest ionization potential was detected for these (CH$_2$Ph, Ph or OPh) groups.[40]

In the case of **1** and two compounds related to **1** (**53,54**), Kenttämaa[41a–c] established that the gas-phase behaviour depends more on the exocyclic substituent and also, but less, on the ring size. For **1** and **53**, $M^{+\bullet}$ is of low abundance, since N(CH$_2$CH$_2$Cl)$_2$ groups can be easily ejected from the *P* because of the weak exocyclic P-N bond. Further bond fissions can readily occur within these groups. The NMe$_2$ increases the stability of the $M^{+\bullet}$ of **54**, and consequently the cleavages do not occur at the exocyclic P-N bond or within the NMe$_2$ group, but within the five-membered ring, producing radical cation fragments.

53   **54**
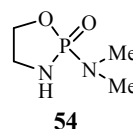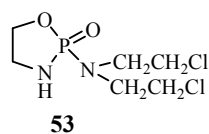
Fission of the bond between the *P* and the exocyclic substituent and also bond cleavages within the exocyclic group are marked for the 5,5-dimethylperhydro-1,3,2-oxazaphosphorine 2-oxides and 2-sulphides and for their 3-Me derivatives. The cleavage of P-N bonds in N-substituted benzodiazaphosphole-2-oxides, together with two H-transfers, led to the corresponding *o*-phenylenediamine fragment as a common feature for all compounds containing a benzodiazaphosphole heterocyclic ring.[42,43] Fission of the P-O bond with H-transfer to the phosphoryl *O* also occurred.[44] However, the exocyclic P-N bond in the 2-aminodioxaphosphorinanes is resistant to EI. The Cl substituent is ejected, while the [M–PhO]$^+$ and [M–PhOH]$^{+\bullet}$ fragment ions are missing from the compounds with an OPh susbtituent, which is quite unusual behaviour.[45] The stability of the exocyclic P-N bond in

substituted 1,3,2-oxazaphosphorinane-2-oxides with an aziridino group on the *P* atom (**55–57**) was reported by Kulkarni *et al.*[37]

55

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57

R = Ph, *p*-NO$_2$Ph
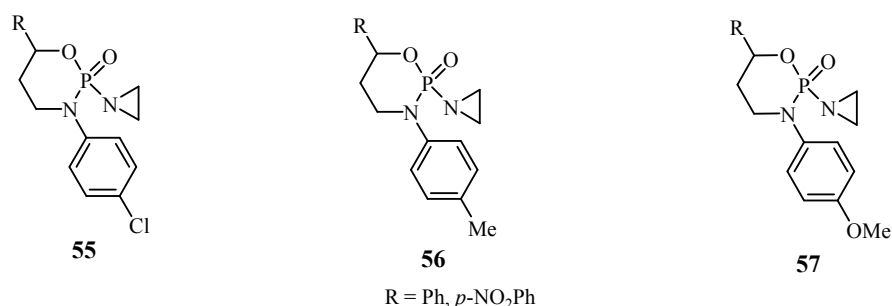
If the ring *O* in the above 1,3-dioxa-2-phospha(V)cyclohexanes or related ring systems is replaced by NH or NCH$_3$, the stability of the heteroring increases and the fragment ions [M–PhO]$^+$ and [M–PhOH]$^{+\bullet}$ also appear for the OPh derivatives.[46] Neither the perhydro-1,3,2-oxazaphosphorinanes nor dioxaphosphorinanes with an OPh substituent on the *P* and with an *O* in the ring give the fragment ions [M–PhO]$^+$ and [M–PhOH]$^{+\bullet}$. Some loss of PhO$^\bullet$ and of PhOH takes place in *O,O*-diphenyl phosphoramidates[47] and in the *α,ω*-bis(diphenoxyphosphinylamino)alkanes,[48] with the abundance increasing with the length of the carbon chains in the latter case. Reddy and Rao[49] reported that the molecular ions of 2-aryl-substituted octahydro-1*H*-1,3,2-benzodiazaphosphole 2-oxides decompose through four main routes, with cleavage of the P-O and P-N bonds (Scheme 1).

$[M-R^1R^2C_6H_3O]^+$

$[M-C_6H_{12}N_2OP]^+$

$[M-R^1R^2C_6H_3O_2P]^+$

$[M-C_6H_{12}N_2]^+$

R^1 = H; R^2 = 2-, 3-, 4-Me, 4-Cl; R^{1}R^2 = 3,4-, 3,5-, 2,5-Me$_2$
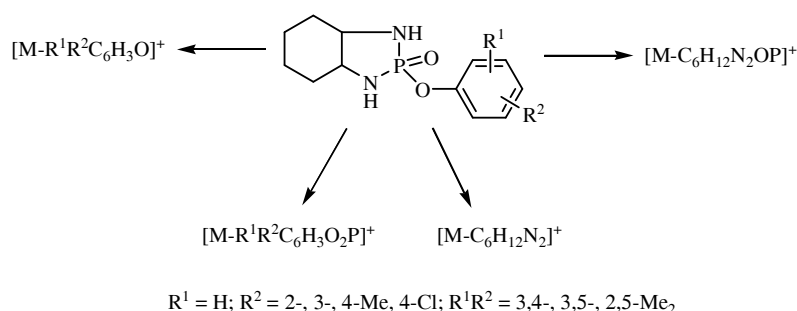
Scheme 1

P-containing moieties were ejected from many 5- and 6-membered *P*-heterocycles possessing a tertiary phosphine oxide or phosphinic ester function, as described by Keglevich *et al.*[50]

The most abundant product ion from **1** is created by the ejection of N(CH$_2$CH$_2$Cl)$_2$ via N-P bond cleavage, but the bond ruptures within the exocyclic group generating HCl and CH$_2$Cl$^\bullet$ ejections with both sequential and competing pathways and the rearrangement including one H-transfer are also typical processes.[51]

Cleavage of the central C-O bond led to the loss of phosphoramide mustard and provided the base peak for 4-OH-**1**. For the hydroperoxy derivative of **2**, *i.e.* 4-OOH-**2**, the loss of $CH_2Cl^{\bullet}$ and $Cl^{\bullet}$ was favoured, similarly as in 4-keto-**2**. Molecular ions were of low abundance, as in the substituted 1,3,2-oxazaphosphorinanes.[52a,b]

2.1.3. Stereochemical aspects

Many authors have shown that the diastereomer pairs behave similarly under EI and follow similar fragmentation routes, *i.e.* they do not exhibit stereospecific fragmentation.[53a–d] However, they often differ from each other with respect to the *RA*s of the corresponding peaks, due to the different internal energies of the isomeric ions.[53b] Molecular ions of organophosphorus compounds isomerize to thermodynamically more stable structures after ionization in the mass spectrometer.[54,55]

The fragmentation pathways can be modified by the size of the *P*-containing ring besides the various substituents on the *P*. In the case of cyclic organophopshorus compounds, the different substituents attached to the *N* atom not only modify the *RA*s of the characteristic ions, but also lead to specific fragment ions through P-N bond cleavage and charge retention on the moiety including the *N* atom. This confirms the sterically controlled fragmentations between the *cis* and *trans* isomers of cyclic organophosphorus compounds.[35] Different isomeric structures of the parent molecules cause differences in the rates of the individual fragmentation reactions, as was found for derivatives of **1** by Mruzek and Shaw.[51] The similarity of the EI mass spectra of the different isomeric alkyl and chloroalkyl phosphates was described by Thruston *et al.*[56]

Zielinska and Stec[35] observed that the *RA*s were different not only for $M^{+\bullet}$, but also for other fragment ions of 4-methyl-1,3,2-dioxaphosphorinanes, typically in the spectra recorded at low electron energy.

2.1.4. Applications and biological effects

Nitrogen mustard alkylating agents, from the oxazaphosphorine group (*e.g.* **1**–**3**) are used in cancerchemotherapy. Most of the novel *P* heterocycles (*e.g.* **58**–**60**) with an exocyclic P-C bond possess marked antifungal (*e.g.* on *Aspergillus niger* and *Helminthosphorium oryzae*) and antibacterial activities (*e.g.* on *Staphylococcus aureus* and *Escherichia coli*).
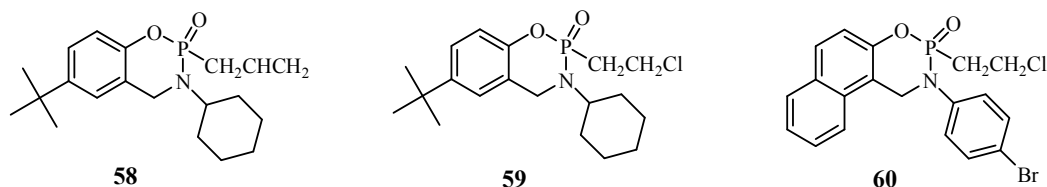
Racemic *N,N*-bis(2-chloroethyl)-2*H*-1,3,2-oxazaphosphinan-2-amine-2-oxide has become the most widely used drug among all alkylating agents since its introduction into cancer chemotherapy in 1958. Phosphonates are significant inhibitors of gene expression in mammalian cells[57a] and also act as antibiotics.[57b] They are used as insecticides,[57b] herbicides,[57b,c] fungicides[57b,d] and plant growth regulators[57c] and as agents for the treatment of bone disorders.[57d] Tris(1,3-dichloro-2-propyl)phosphate displays mutagenic activity.

2.2. Ring-chain tautomerism in 1,3-*O,N*-heterocycles

Since the ring-chain tautomerism of 1,3-*X,N*-heterocycles in solution has been widely reviewed,[6,58] the following discussion will be limited mainly to solution data on 1,3-*O,N*-heterocycles with certain substituents. As for the gas phase, not many literature reports are available concerning solutions, but the examples of ring-chain tautomerism here relate mainly to the 1,3-*O,N*-heterocycles.

2.2.1. Ring-chain tautomerism in the gas phase

Substituents with different electronic characters affect the fragmentations of compounds in the gas phase, and Hammett-type correlations can be found between the abundance of a given ion and substituent parameters (*e.g.* the Hammett-Brown parameter σ^+); this can indicate, for example, the presence of the well-known process, ring-chain tautomerism. Only a few 1,3-*O,N*-heterocycles with substituents with different electronic characters have been investigated in the gas phase previously, in order to inspect their ring-chain tautomerism. The present aim was to extend this treatment to derivatives with aryl and alkyl groups in different positions. For comparison, the same compounds were studied in CDCl$_3$ solutions by nuclear magnetic resonance (NMR).

There are fragment ions which can indicate the presence of ring-chain tautomeric equilibria for 1,3-*O,N*-heterocycles. However, it is difficult to carry out quantitation since many factors (*e.g.* ionization energy, appearance energy, distribution of internal energies, frequency factors, stability of the ions formed, the possibility of competing and consecutive pathways, *etc.*)[60] play roles and can contribute to variation of the *RA*(%) of a given fragment ion associated with one or the other tautomeric form and to obtain good linear correlations for

the tautomeric equilibia *vs.* σ^+. The first paper dealing with the gas-phase ring-chain tautomerism of 4,4-dimethyl-2-phenyl-1,3-oxazolidine and a few of its aryl-substituted derivatives (**61**) was published by Rennekamp *et al.*[60] It showed that the fragment ions [M–C$_6$H$_4$X]$^+$, [M–H]$^+$ and [M–CH$_2$O]$^+$ were related to the ring-closed form, while [M–CH$_2$OH]$^+$ and [M–OH]$^+$ arose from the open-chain tautomer. The tautomerism resembled that observed in non-polar solvents, *i.e.* electron-withdrawing substituents on the Ph ring favoured the ring form, whereas electron-donating ones favoured the open-chain form.

A series of norephedrine and norpseudoephedrine derivatives (**62**) proved to be ideal for investigation of the tautomerism in the gas phase by means of MS.[16–18]


61
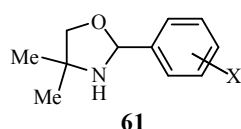
X = *m*-NO$_2$, *m*-Cl, *p*-Cl, *m*-OMe, H, *p*-Me, *p*-OMe, *p*-NMe$_2$

62
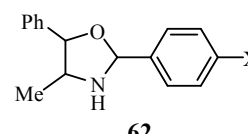
X = NO$_2$, CN, Cl, H, Me, OMe, NMe$_2$

The ratios of the *RA*s(%) of [M–C$_7$H$_6$O]$^{+\bullet}$ and [M–C$_7$H$_7$O]$^+$ are illustrative of the ring-chain tautomeric equilibirium. These two fragment ions are formed by α-cleavage with respect to the ionized *N* atom. The amount of the open-chain form increases with increasing temperature and ionization energy, while that of the ring form decreases. The ring form is somewhat more favourable for the norephedrine and norpseudoephedrine derivatives than for 4,4-dimethyl-2-aryl-1,3-oxazolidines.[12,60]

For monocyclic perhydro-1,3-oxazines (**63–65**), the formation of [M–H]$^+$, [M–CH$_2$O]$^{+\bullet}$, [M–C$_2$H$_4$O]$^{+\bullet}$, [M–C$_6$H$_4$X]$^+$ and C$_7$H$_6$X$^+$ is related to the ring form. The loss of the radical C$_6$H$_4$X was less preferred than the loss of alkyl groups from the alkyl-substituted derivatives.[15] [M–CH$_3$O]$^+$ and [M–C$_2$H$_5$O]$^+$ can arise from the ions [M–H]$^+$ or directly from the open-chain tautomer. Compound **65** cannot attain an open-chain form. Electron-withdrawing substituents increase the amount of the ring form, while electron-donating substituents display an opposite effect. The amount of the open-chain form increases slightly with increasing source temperature.


63
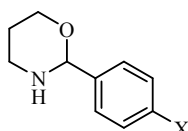
X = NO$_2$, Cl, H, Me, OMe, NMe$_2$

64

65
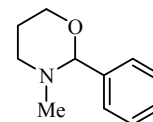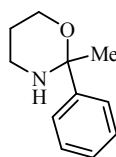
In the 2-phenyl-2-methyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**64**), the ions $[M–CH_3O]^+$ and $[M–C_2H_5O]^+$ related to the open-chain form predominate. In the case of electron-donating substituents, ionization occurred on the Ph group and the ion $C_7H_6O^+$ was formed. Electron-withdrawing substituents preferred the charge location on the ring *N* and the ion $C_7H_7N^{+\bullet}$ was formed. Both $C_7H_6O^+$ and $C_7H_7N^{+\bullet}$ are related to the ring tautomer; only a few ions of low abundance (*e.g.* $[M–CH_3O]^+$) representing the open-chain form were present. In solution too[8] the ring form was more abundant than the open-chain form.[18]

The presence of ring and chain forms of 2-aryl-substituted octahydro-1,3- and -3,1-benzoxazines (**66** and **67**) was indicated by the corresponding fragment ions, *i.e.* $C_8H_7NX^+$ (formed directly through α-cleavage with respect to the ionized azomethine *N* atom) and $C_7H_6NX^{+\bullet}$ (obtained after H-transfer), respectively. Further, the compounds with electron-withdrawing substituents produced the ions $C_7H_4OX^+$, $[M–OH]^{+\bullet}$, $C_8H_8NX^{+\bullet}$ and $C_7H_7NX^+$ by α-cleavage; they were also more abundant for the *trans*-annelated compounds in the gas phase. $[M–CH_2O]^{+\bullet}$, $C_7H_7NX^+$, $C_7H_5OX^{+\bullet}$ and $C_7H_6X^+$ were generated from the ring form, but only $C_7H_6NX^{+\bullet}$ and $[M–CH_2OH]^+$ from the open-chain form. Electron-donating substituents on the 2-aryl group shift the equilibria toward the open-chain form[61] as was the case in solution.

66   **67**

X = *p*-NO$_2$, *m*-NO$_2$, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe$_2$
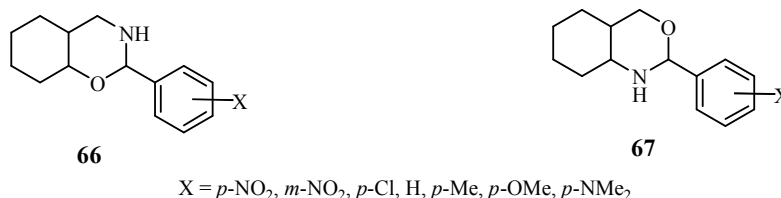
Oxazolidines derived from 2-aminoethanol and *p*-substituted acetophenones gave $[M–CH_3O]^+$ from the open-chain tautomer, but $[M–Ph]^+$ and $[M–CH_3]^+$ cannot be adequately related to the ring forms. Although the ring-chain equilibria could not be characterized with Hammett-type equation, it showed that the open-chain form predominates as in solution.[17] Likewise, for heteroaryl-substituted octahydro-1,3- and -3,1-benzoxazines, determination of the exact positions of the equilibria was not possible because of the numerous decompositions of the fragment ions, generally in low abundance.[62]
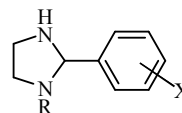
For the alkyl-substituted oxazolidine derivatives (**68**), $[M–CH_2O]^{+\bullet}$ was related to the ring form and $[M–CH_3O]^+$ to the open-chain form.

For these compounds, the open-chain form was more abundant under higher electron energy,[63] as was the case for the 1-*N*- and 2-aryl-substituted imidazolidines (**69–73**).
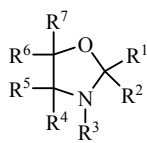
68

R^1 = H, Me, Et, *n*-Pr, Ph; R^2 = H, Me, Et, *i*-Pr, *n*-Bu, Ph;
R^3 = H, Me, Et; R^4 = R^5 = R^6 = H, Me; R^7 = H

69: R = Me; **70**: R = Et; **71**: R = *n*-Pr; **72**: R = *i*-Pr; **73**: R = Ph
X = *m*-NO_2, *p*-NO_2, *p*-Br, H, *p*-Me, *p*-OMe, *p*-NMe_2

With increasing size of the alkyl substituent, the ring form became less abundant, similarly as in solution, but exceptionally the more electron-withdrawing groups preferred their open-chain tautomers, in contrast with the situation in solution[64] and with the results obtained for other heterocycles in the gas phase.

For aminodiol and aminoalcohol derivatives (**74** and **75**), as in solution,[65] electron-withdrawing substituents shifted the equilibria toward the ring forms, the proportions of which were always higher in the gas phase[66] than in solution.[65]
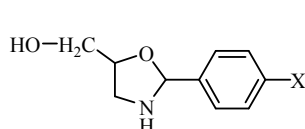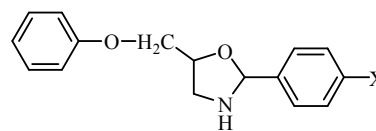
74   **75**

X = NO_2, CN, Br, Cl, H, Me, OMe, NMe_2

2.2.2. Ring-chain tautomerism in solution

Molecular refraction, IR and UV spectroscopic methods were used earlier to study the tautomeric equilibria, but they did not provide very quantitative results.[67a,b,68a–g] For solutions, NMR spectroscopy is a suitable tool that can permit very precise determination of the tautomeric equilibria, which depend on the temperature and the solvent.[11,12,69–71]

McDonagh and Smith[70] established a linear correlation between the log K and σ values for 2-substituted 3,4-dihydro-2*H*-1,3-benzoxazines. Later, Paukstelis *et al.*[12,71] found a better correlation between the log K and Hammett-Brown σ^+ values for 2-aryl-substituted oxazolidines (**76**). Alva Astudillo *et al.*[14] reported that 3,4,5,6-tetrahydro-2*H*-1,3-oxazines and oxazolidines in the solid state gave exclusively the open-chain form, while in $CDCl_3$ the ring form predominated.

For 2-aryl-oxazolidines (**76**) and 4,4-dimethyl-substituted derivatives (**77**), the ring-chain tautomeric equilibria obey the Hammett-type equation. Substitution with a 2-Me group did not greatly affect the ring-chain equilibria since the slopes for the 2-Me-substituted oxazolidine derivatives (**78**) and oxazine derivatives (**79**) are close to those for the corresponding 2-aryl derivatives (**76**), although the 2-Me increased the amounts of the ring tautomers.[7]
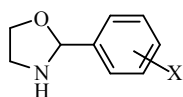
76   **77**   *n* = **78**: 1; **79**: 2

X = *p*-NO$_2$, *m*-NO$_2$, *m*-Cl, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe$_2$ X = NO$_2$, Br, H, Me, OMe
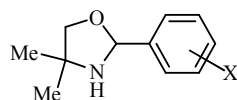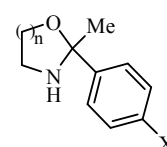
When double substituent effects in 3,4,5,6-tetrahydro-*2H-1*,3-oxazines were investigated, it was established that the aryl substituents at positions 4 and 6 increase the contribution of the ring form; the effect is less pronounced for 6-substituted derivatives (**80**) than for 4-substituted ones (**81**).[9]

80

X = H, Me, OMe

81
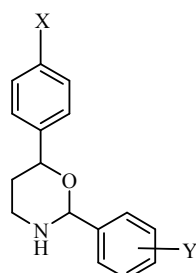
X = *m*-Cl, *p*-Cl, H, *p*-Me, *p*-OMe

Y = *p*-NO$_2$, *m*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe$_2$
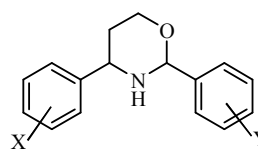
Double substituent effects were first described quantitatively by a Hansch-type equation for the regioisomeric naphthoxazines, *i.e.* for 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**82**) and 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines (**83**), where the field, but not the resonance effects significantly influenced the equilibria.[72]
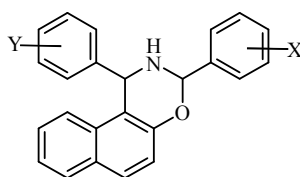
82

X = *p*-NO$_2$, *m*-Br, *p*-Br, *p*-Cl, H, *p*-Me, *p*-OMe

Y = *p*-NO$_2$, *m*-NO$_2$, *m*-Br, *p*-Cl, *p*-F, *p*-Me, *p*-OMe
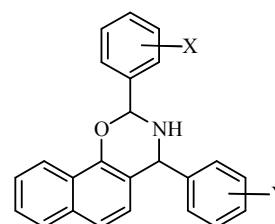
83

Y = *m*-NO$_2$, *m*-Br, *p*-Br, *p*-Cl, H, *p*-Me, *p*-OMe
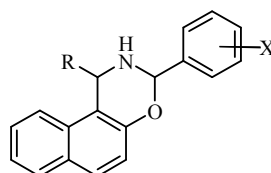
84: R = Me; **85**: R = Et; **86**: R = Pr; **87**: R = *i*-Pr; **88**: R = *t*-Bu

X = *p*-NO$_2$, *m*-Cl, p-Br, p-Cl, H, *p*-Me, *p*-OMe

This Hansch-type equation was applied to the 1-alkyl-3-aryl-substituted naphthoxazines (**84–88**) for a quantitative study of the effects of alkyl substituents besides the aryl effect on the three-component equilibria present in CDCl$_3$ solution. The bulkier the alkyl substituents, the more they shifted the equilibria towards the open-chain form and caused different degrees of stabilization in the *cis* and *trans* ring forms.[73]

In the case of 2,4-diarylnaphth[2,1-*e*][1,3]oxazines, the electron-withdrawing substituent X on the 2-Ph group increased the amount of the ring tautomer both inductively and by resonance. Electron-withdrawing substituents on the 4-Ph group have an analogous inductive influence on the ring-chain tautomeric equilibria of the *trans* isomers.[72] The ring-chain ratios were influenced not only by the substituent X, but also by the *N* substituents of the imidazolidine ring in the case of *N*-phenyl-2-aryl-substituted imidazolidines (**89–93**). The amounts of the ring forms increased in the following sequence: *i*-Pr < Ph < *n*-Pr ≈ Et < Me of the *N* substituents.[74] The *N* substituents also affected the ring-chain ratio in the case of 3-substituted-2-aryldecahydroquinazolines (**94–96**), *i.e* compounds with a small substituent (Me) provide exclusively the ring form, while compounds with larger substituents (*i*-Pr or Ph) exist in three-component tautomeric equilibria.[75]

89: R = Me; **90**: R = Et; **91**: R = *n*-Pr; **92**: R = *i*-Pr; **93**: R = Ph
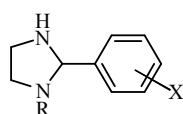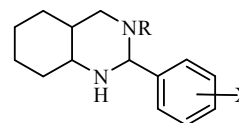X = *p*-NO$_2$, *p*-CN, *m*-Br, *p*-Br, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe$_2$

94: R = Me; **95**: R = *i*-Pr; **96**: R = Ph
X = *p*-NO$_2$, *m*-Br, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe$_2$

More complex ring-chain tautomeric equilibria, involving more than three tautomeric forms, were established for the ring-chain tautomerism of Schiff bases containing 1,2- and 1,3-amino alcohol moieties,[76] also in the case of *cis*- and *trans*-aminocyclohexanediols condensed with aromatic aldehydes,[77] for compounds derived from (1*S*,2*S*)- and (1*R**,2*S**)-2-amino-1-phenyl-1,3-propanediols[78] and for those of (1*S*,2*S*)-2-amino-1-phenyl- and -(*p*-nitrophenyl)-1,3-propanediols condensed with terephthalaldehyde.[79] Besides the 1,3-*O*,*N*-heterocycles discussed above, a number of other 1,3-*X*,*N*-heterocycles (X = N*H*, N*R* and S) have been studied with regard to their tautomerism in solution.[5,67b,74,75,80–85]

2.2.3. *Applications and biological effects*

Oxazolidines derived from ephedrine and pseudoephedrine (with aromatic aldehydes) are used as chiral derivatizing agents,[86] and resolving agents.[87] 3,4,5,6-Tetrahydro-2*H*-1,3-oxazine possesses herbicidal activity,[88] and its substituted derivatives can be used as bronchial

dilators,[89] blood-pressure elevators,[88] insecticides[89] and fungicides.[90] Many *N*-substituted 3,4,5,6-tetrahydro-2*H*-1,3-oxazines have anti-inflammatory,[91] bactericidal,[92] herbicidal[93] or spasmolytic activity.[91] Many of the fused ring 1,3-oxazine derivatives also exhibit pharmacological properties.[94–96]

The ring-chain tautomerism was utilized to determinie σ^+ for 2-, 3- and 4-pyridyl, 2- and 3-furyl, 3-thienyl and 2-pyrrolyl substituents in oxazolidine, 1,3-oxazine and 3,1-oxazine derivatives in the gas phase[17] and in solution.[10,97] σ^+ was also calculated for heteroaryl-substituted Ph groups of three sets of oxazolidines and 1,3-oxazines in CDCl$_3$. For oxazolidines derived from norephedrine and norpseudoephedrine, the σ^+ values were additionally determined in the gas phase.[98]

3. RESULTS AND DISCUSSION

3.1. EI mass spectra of P-heterocycles

3.1.1. 3,1,2-Benzoxazaphosphinane-2-oxides and 1,3,2-benzodiazaphosphinane-2-oxides

The mass spectra of the diastereomers were so similar that no qualitative difference was observed between the *cis*- and *trans*-annelated isomers, and the fragmentations occurred with the same or very similar mechanisms, *i.e.* most of the fragment ions were generated by initial ionization on some of the heteroatoms (*O*, *N* or *P*) in the heterocyclic ring[37] or on the Ph, OPh or $N(CH_2CH_2Cl)_2$ substituents on the *P* atom. Some *cis*- and *trans*-annelated isomers and/or *P*-2 epimers could be differentiated through the different internal energies of isomeric molecular ions.[53a–d,99]

More abundant molecular ion peaks are present in the spectra of compounds with a Ph or OPh on the *P* atom as compared with the $N(CH_2CH_2Cl)_2$-substituted ones. The stability of the molecular ions decreased in the sequence Ph > OPh > $N(CH_2CH_2Cl)_2$ for **4–17** and **18–34**, and further decreased with the increasing size of R^1 (H > Me > CH_2Ph) for **4–17** (Table 1).

Table 1. *RA*s(%) of $M^{+\bullet}$ and a few primary fragment ions for several oxaza derivatives.

Comp.	R^1	R^2	Configuration	Annelation	$M^{+\bullet}$	$[M–H]^+$	$[M–R^2]^+$
10a	H	OPh	2*R**,4a*S**,8a*R**	*cis*	88	6	18
10b	H	OPh	2*S**,4a*S**,8a*R**	*cis*	83	6	18
11a	H	OPh	2*R**,4a*S**,8a*S**	*trans*	87	7	23
11b	H	OPh	2*S**,4a*S**,8a*S**	*trans*	83	7	19
12a	Me	OPh	2*R**,4a*S**,8a*R**	*cis*	53	2	4
12b	Me	OPh	2*S**,4a*S**,8a*R**	*cis*	49	1	4
13a	Me	OPh	2*R**,4a*S**,8a*S**	*trans*	48	2	4
13b	Me	OPh	2*S**,4a*S**,8a*S**	*trans*	52	2	4
14a	CH_2Ph	OPh	2*R**,4a*S**,8a*R**	*cis*	58	1	2
14b	CH_2Ph	OPh	2*S**,4a*S**,8a*R**	*cis*	42	0.6	2
15a	CH_2Ph	OPh	2*R**,4a*S**,8a*S**	*trans*	37	1	2
15b	CH_2Ph	OPh	2*S**,4a*S**,8a*S**	*trans*	33	1	2

For the diaza analogues in which R^2 = Ph and R^1 = H, the base peak was given by $M^{+\bullet}$, which was more abundant than for those with R^1 = Me and R^2 = OPh or $N(CH_2CH_2Cl)_2$, where the opposite situation prevailed, *i.e.* R^1 = Me increased the abundance of $M^{+\bullet}$ over that for R^1 = H. Substituent R^3 did not have an evident effect on the *RA*(%) of $M^{+\bullet}$.

The ions $[M-H]^+$ were more abundant (*RA* 6–9%) when R^1 = H than when R^1 = Me or CH_2Ph (*RA* 1–2%), independently of the nature of R^2 on *P* within the oxaza set. However, the *RA* of $[M-H]^+$ within the diaza analogues depended mainly on R^2, as it decreased as R^2 increased in size. From an inspection of the effects of R^1 (H or Me) in the compounds with R^2 = Ph or OPh, it was established that $[M-H]^+$ behaves in the same way as $M^{+\bullet}$. R^3 also had a clear effect here, since for the compounds with R^2 = Ph and R^1 = H $[M-H]^+$ was less abundant for R^3 = H than for R^3 = Me, while for the compounds with R^2 = OPh and R^1 = H $[M-H]^+$ was more abundant than for R^1 = Me.

The compounds can be divided into different categories on the basis of the *RA*s of the ions produced on the loss of different hydrocarbon fragments. Hydrocarbon ejections with or without H-transfers are characteristic for many *P*-containing compounds, as reported earlier.[33,34,38]

Four different groups can be formed with regard to the type of hydrocarbons lost. The first group, involving compounds with R^1 = H, is mainly characterized by the loss of of some alkenes (C_3H_6, C_4H_6 and C_5H_8). Fewer alkyl radicals (C_4H_7, C_4H_9 and C_7H_9) were ejected from the compounds belonging in the second group, where R^1 = Me.

The members of the third group (R^1 = CH_2Ph, and R^2 = Ph or OPh) produced only very abundant tropylium ion ($C_7H_7^+$) (*RA* 51–100%), since the CH_2Ph group (as an electron-withdrawing substituent) increases the electrophilic activity of the *N* atom, and the ions formed through the loss of hydrocarbon fragments were missing. The complementary $[M-C_7H_7]^+$ was also present in each spectrum in the third group (*RA* 7–33%). Loss of the fragment C_7H_{11} was similarly common within this group.

For 3,1,2-benzoxazaphosphinine 2-oxides, both electron-donating (Me) and electron-withdrawing (CH_2Ph) substituents decreased the proportions of the ions $[M-R^2PO_2H]^{+\bullet}$, $R^2PO_2H^{+\bullet}$ and $R^2H^{+\bullet}$ formed by ring cleavage in the heterocyclic part of the molecule as compared with the *N*-unsubstituted one (and also those of $[M-C_3H_7]^+$ and $[M-R]^+$), while they increased the amount of $[M-C_7H_{11}]^+$.

The cyclophosphamide derivatives (R^1 = H and R^2 = $N(CH_2CH_2Cl)_2$) constitute their own group. As mentioned above, these compounds are rather unstable under EI, as revealed by the low abundance of $M^{+\bullet}$, while bond cleavages between *P* and the exocyclic substituent and within the latter were marked instead of hydrocarbon ejection.

Most of the neutral species lost were formed in *α*-cleavage reactions initiated at the ring *N*, together with more or less extensive H-transfers (or without any H-transfer), as for the corresponding 1,4,4a,5,6,7,8,8a-octahydro-2*H*-3,1,2-benzoxazaphosphinine 2-oxides,

although the latter lost only alkyl radicals and alkenes when R^2 = Ph or OPh. *N*-containing radicals or neutrals were likewise lost by some $M^{+\bullet}$ of these diaza compounds (**1–6**, when R^1 = R^3 = H or Me, and R^2 = Ph) (Scheme 2).
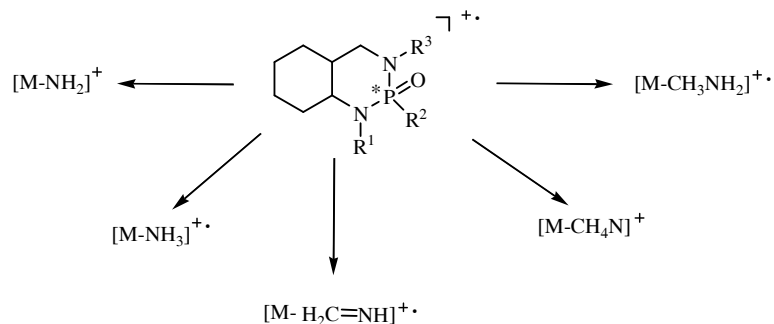
Scheme 2. Some small *N*-containing fragments from the diaza compounds (R^1 = H or Me, and R^2 = Ph).

The primary ejections of hydrocarbon fragments for derivatives with R^1 = Me within the 3,1,2-oxaza and 1,3,2-diaza compounds, *e.g.* the ions $[M–C_3H_6]^{+\bullet}$, $[M–C_4H_8]^{+\bullet}$, $[M–C_6H_9]^+$, $[M–C_6H_{11}]^+$ and $[M–C_7H_9]^+$ and the *N*-containing fragment ions (*e.g.* $[M–NH_2]^+$, $[M–NH_3]^{+\bullet}$ and $[M–CH_2=NH]^{+\bullet}$), were not as abundant as for the unsubstituted (R^1 = H) derivatives, and only a few fragment ions were more abundant in the former, *e.g.* $[M–CH_3]^+$, $[M–C_5H_{11}]^+$, $[M–C_6H_{12}]^{+\bullet}$ and $[M–CH_4N]^+$. The influence of R^3 was reflected in the abundance of the above-mentioned fragment ions: when R^3 = Me, the ions $[M–CH_3]^+$, $[M–C_5H_{11}]^+$, $[M–C_6H_{11}]^+$ $[M–C_7H_{11}]^+$, $[M–NH_3]^{+\bullet}$ and $[M–CH_4N]^+$ were more abundant than for the *N*-unsubstituted ones, while $[M–C_3H_6]^{+\bullet}$, $[M–C_4H_8]^{+\bullet}$, $[M–C_6H_{12}]^{+\bullet}$, $[M–C_7H_9]^+$ and $[M–CH_2=NH]^{+\bullet}$ were less abundant than for the compounds with R^3 = H.

The 3,1,2-*O,N,P* compounds all produced a very abundant ion $[M–C_3H_7]^+$ (Scheme 3), which was the base peak when R^1 = H or Me, but less abundant when R^1 = CH$_2$Ph. Besides this strongly resonance-stabilized structure, there was another fragment ion (stabilized again by conjugation), likewise created by α-cleavage, followed by an H-transfer: $[M–C_4H_9]^+$, which was more significant for 1,3,2-*N,N,P* than for 3,1,2-*O,N,P* derivatives. In the oxaza and diaza derivatives with *cis* annelation, the steric interactions assist the C8–C8a bond cleavage and a parallel H-transfer leading to $C_3H_7^{\bullet}$ ejection. In the *trans* isomer, these steric interactions are missing and hence the ring does not open so easily. While these two ions were totally absent from the spectra of the oxaza derivatives containing an N(CH$_2$CH$_2$Cl)$_2$ group, and also from those of the diaza compounds in which R^1 = H, R^2 = N(CH$_2$CH$_2$Cl)$_2$ and R^3 = H or Me, they were present in the diaza series for those *P*-2 epimers where R^1 = Me, R^2 =

N(CH$_2$CH$_2$Cl)$_2$, and R^3 = H, probably because the directing influence of the R^1 = Me substituent allows the formation of the fragment ions [M–C$_3$H$_7$]$^+$ (*RA* 10–13%) and [M–C$_4$H$_9$]$^+$ (*RA* 13–16%).
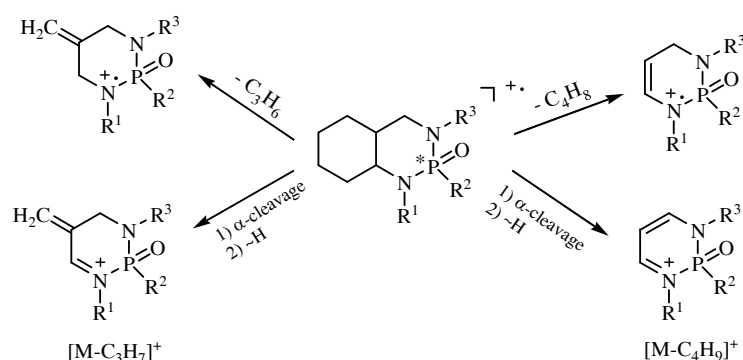
Scheme 3. Possible mechanism of C$_m$H$_n$ loss from the cycloalkane-condensed 1,3,2-benzodiazaphosphinanes (**18–34**) (Note: the same cleavages were also observed in the 3,1,2-benzoxaza derivatives (**4–17**), but [M–C$_4$H$_9$]$^+$ was minor.)

Table 2. *RA*s(%) of M$^{+\bullet}$ and a few primary fragment ions for several diaza derivatives.

Comp.	R^1	R^2	R^3	M$^{+\bullet}$	[M–H]$^+$	[M–R^2]$^+$	[M–C$_3$H$_7$]$^+$	[M–C$_4$H$_9$]$^+$
18a	H	Ph	H	100	10	5	58	44
18b	H	Ph	H	100	10	4.5	58	44
20a	H	Ph	Me	100	18.5	4	31	31
20b	H	Ph	Me	100	19	4	33	36
22a	Me	Ph	H	76	8	2	100	56
22b	Me	Ph	H	78	8	3	100	56.5
24a	H	OPh	H	53.5	3	100	21	13
24b	H	OPh	H	50	3	100	21	13
26a	H	OPh	Me	40	2	100	4	5
26b	H	OPh	Me	34	3	100	4	5
28a	Me	OPh	H	80	6	62	100	34
28b	Me	OPh	H	79	5	55	100	33.5

All compounds in Table 2 are *cis*-annelated and the relative configurations of the annelation carbons are *R**, while that of *P* is *R**(**a**) or *S**(**b**).

A further common primary fragmentation was the ejection of R^2. For the diaza derivatives, the base peak was in most cases [M–OPh]$^+$ or [M–N(CH$_2$CH$_2$Cl)$_2$]$^+$, but [M–Ph]$^+$ was relatively weak for the Ph-substituted compounds and was missing for the oxaza derivatives, which shows that the bond between *P* and *C* is stronger than that between *P* and the heteroatom (*O* or *N*) (Table 2). Complementary ions [R^2]$^+$ were also present in the EI spectra. For the oxadiazaphosphinane 2-oxides (**35–39**), [M–Ph]$^+$ was weak, but [M–

N(CH$_2$CH$_2$Cl)$_2$]$^+$ provided the base peak; it was totally absent from the spectra of the derivatives containing fused aromatic rings (**40–42**).

Compounds **6–9**, with R^1 = Me or CH$_2$Ph and R^2 = Ph, and compounds **16** and **17** with R^1 = H and R^2 = N(CH$_2$CH$_2$Cl)$_2$, did not produce [R^{2}H]$^+$ (**16** and **17** gave a peak at *m/z* 94, but this was the ^{37}Cl isotopic equivalent of C$_3$H$_7$^{35}Cl$^{+\bullet}$ at *m/z* 92). For **4** and **5a/b**, R^{2}H$^+$ (*m/z* 94) was formed through an H-transfer, obviously from N*H* to P=O, with a consequent O*H*-transfer to Ph, producing the ion PhOH$^{+\bullet}$ from the 3,1,2-benzoxazaphosphinines. Compounds **18–23** (1,3,2-benzodiazaphosphorinanes) gave a moderate, and compounds **24–30** a very weak ion [R^{2}H]$^{+\bullet}$, whereas compounds **31–34** did not provide it at all, due to the predominant loss of R^2 (instead of the R^{2}H$^+$ ejection), as mentioned above.

In the latter compounds (**31–34**), the more favourable R^2 fission is again the reason for the absence of the ion R^{2}PONHR$^{1(3)+\bullet}$. However, this was a common primary fragment ion generated by P–N(1)R^1 and C(4)–N(3)R^3 or P–N(3)R^3 and C(8a)–N(1)R^1 bond cleavages with a concomitant H-transfer in compounds **18–30** and it was most abundant for those derivatives where R^1 = R^3 = H and R^2 = Ph. The complementary ions were of rather low abundance, especially for **30a+b**, which have no N*H* in the ring.

The significance of direct α-cleavage reactions is reflected in immediate stereochemical effects. In the diaza derivatives, for instance, the ion [M–C$_7$H$_9$]$^+$ formed directly from M$^{+\bullet}$, requiring three H-transfers to the heterocyclic ring, was more abundant for the *cis*- than for the *trans*-annelated isomer in R^2 = Ph derivatives. For the 3,1,2-*O,N,P* analogues, the change in the *RA*(%) of this ion was not so evident, and for the 1,3,4,2-oxadiazaphosphinanes, it was not present at all. [M–C$_3$H$_7$]$^+$, also produced through direct α-cleavage, was more abundant for the *cis*- than for the *trans*-annelated isomer in the 3,1,2-*O,N,P* series, and more abundant or equally stable in the 1,3,2-*N,P,N* series. [M–C$_4$H$_9$]$^+$ was more abundant for the *cis*-annelated isomers when R^2 = Ph, but less abundant when R^2 = OPh, as compared with the *trans*-fused isomers.

Both [M–CH$_2$Cl]$^+$ and [M–HCl–CH$_2$Cl]$^+$ were much more abundant for the diaza than for the oxaza set, while [M–HCl]$^{+\bullet}$ was moderately abundant for the diaza compounds, but was missing from the oxaza analogues. For the cyclohexane-condensed 1,3,2-benzodiaza-phosphinine 2-oxides (**18–34**), [M–HCl]$^{+\bullet}$ was more abundant for the *cis*- than for the *trans*-annelated compounds when R^2 = N(CH$_2$CH$_2$Cl)$_2$ and R^1 = R^3 = H. In the *cis*-fused isomers, [M–HCl]$^{+\bullet}$ was more abundant for the 2*R** than for the 2*S** configuration.

3.1.2. Condensed 1,3,4,2-oxadiazaphosphinane-2-oxide derivatives

The low aromaticity and low electron affinity of 3,1,2-benzoxazaphosphinine 2-oxides (**4–17**) and 1,3,2-benzodiazaphosphinine 2-oxides (**18–34**) led to extensive hydrogen loss. The higher aromaticity of 1,3,4,2-oxadiazaphosphinane 2-oxides (**40–42**) meant a lower loss of H and less abundant $[M–H]^+$; moreover, the relative loss of odd-electron fragments was low, which ensured rather abundant $M^{+\bullet}$ for these aromatic compounds, except where $R^2 =$ $N(CH_2CH_2Cl)_2$ (**39a,b**) and **40b** (the only derivative in this set with a *cis*-annelated saturated ring where Ph is connected to the *P*) due to the increased spatial strain in the neighbourhood of the hetero rings, which led to readier loss of H and ejections of other fragments in the latter compounds.

Not only the substituent R^2 on the *P* atom, but also the ring size influenced the *RA*s of the fragment ions. Isomeric differentiation was simple on the basis of the mass spectra of *cis* and *trans* cyclopentane- or cyclohexane-fused pyrimidinediones. However, the stability of $M^{+\bullet}$ did not depend on the ring size, *i.e.* it gave the base peak for the *cis* and *trans* cycloalkane-fused compounds when $R^2 = OPh$ (**36** and **38**), whereas with $R^2 = Ph$, more abundant molecular ions were obtained for the cyclopentane- (**35a,b**) than for the cyclohexane-fused derivatives (**37a,b**).

A number of fragment ions, $[M–C_4H_8]^{+\bullet}$ and R^{2+}, $[M–R^2PONH]^{+\bullet}$, $R^2PONH_2^+$ (or $R^2PO_2^+$), $[M–R^2PO_2H]^{+\bullet}$, $R^2PO_2H^{+\bullet}$, and the ions at *m/z* 81 ($C_5H_7N^+$) and *m/z* 64 ($PO_2H^{+\bullet}$), were more abundant for compounds with $n = 1$ (**35** and **36**) than for those with $n = 2$ (**37** and **38**), indicating that the former can decompose faster and produce more abundant primary fragment ions. In general, relatively few fragments ($[M–C_6H_8N]^+$ and $[M–R^2PO_2NH_2CH_2]^+$, *m/z* 95 and 83) were more abundant for compounds with $n = 2$ than for those with $n = 1$. Similarly, the *m/z* 82 ion was more stable for compounds with $n = 1$. The *RA*s of $[M–R^2]^+$ and $R^2H^{+\bullet}$ increased in the sequence of side-chain flexibility: Ph < OPh < $N(CH_2CH_2Cl)_2$.

Many ions were observed for 1,3,4,2-oxadiazaphosphinane 2-oxides with $R^2 = Ph$ or OPh (**35–38**), generated in the same way as those for the corresponding 3,1,2-benzoxaza- (**4–17**) and 1,3,2-benzodiazaphosphinine 2-oxides (**18–34**), *e.g.* $[M–R^2]^+$, $[M–R^2H]^{+\bullet}$, $[M–HCl]^+$, $[M–CH_2Cl–HCl]^+$ (the latter two were found for the $N(CH_2CH_2Cl)_2$ derivatives **39**) and $[M–C_4H_8]^{+\bullet}$.

The ion $R^2PO_2H^{+\bullet}$ for **40–42**, formed via an H-transfer, was more abundant than its counter ion $[M–R^2PO_2H]^{+\bullet}$, which was also present for the oxaza compounds, and even giving the base peak for **35b**.

Fragment ions containing an N atom ($R^2PONH^{+\bullet}$ and $C_4H_8N^+$) and fragment ions obtained by the loss of N-containing fragments ([M–NH$_2$]$^+$, [M–NH$_3$]$^{+\bullet}$, [M–CH$_3$NH$_2$]$^{+\bullet}$ and [M–R^{2}PONH$_2$]$^+$ for **35–42** were also observed as common features for diaza derivatives.

Compounds **35–42** can also be classified into three groups on the basis of a few fragment ions, as was the case with **1–17** and **18–34**. The first group consists of the compounds where R^2 = Ph or OPh (**35–38**), which produced fragment ions at both low and high *m/z* values. The second group consists of compounds **40–42** which did not give fragment ions with small *m/z* values, and only moderate amounts of those with higher *m/z* values (*e.g.* [M–R^2]$^+$, [M–R^{2}H]$^{+\bullet}$ and R^{2}PONH$^{+\bullet}$). The ionization also took place on the aromatic part of these isoquinoline derivatives (Scheme 4).
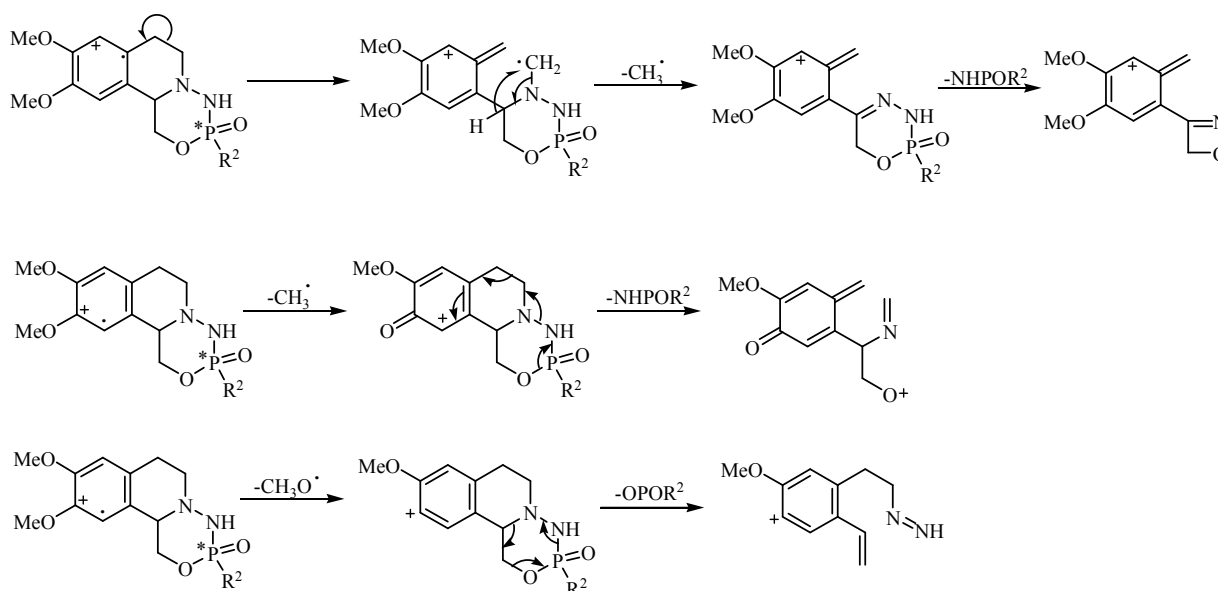
Scheme 4. Fragmentations initiated from the aromatic moieties. (The fragmentations in Schemes **4–8** are illustrated only for compound **42** for which R^2 = Ph.)

The compounds with R^2 = N(CH$_2$CH$_2$Cl)$_2$ (**39**) comprising the third group behaved like the oxaza and diaza derivatives. A further two groups could be defined as regards the site of the initial ionization. It was stated earlier that the charge or radical site can be localized mainly on the aromatic part or on one of the heteroatoms present in the ring,[37] as demonstrated by our model compounds. The charge localization on the aromatic moiety (Scheme 4) was found only in derivatives **40–42**, which produced the primary ions [M–CH$_3$]$^+$ and [M–CH$_3$O]$^{+101}$ before further decomposition.
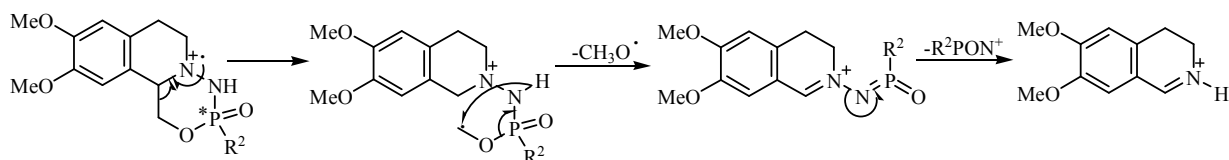
Scheme 5. $M^{+\bullet}$ lost $CH_3O^\bullet$ via an H-transfer or in a concerted reaction via an H-ejection from N*H*, accompanied by a formal retro Diels-Alder (rDA) reaction.

Most of the new fragment ions were obtained by ionization initiated at the bridgehead *N* atom (Schemes 5–8) since *N* has a higher electron-donating ability than that of *O*. Compounds **40–42** decompose effectively, giving rise to several *N*-containing hydrocarbon fragment ions. Most of these *N*-containing fragment ions were favoured by the cyclopentane-fused compounds, probably because of the higher strain in the fused five- than the fused six-membered aliphatic ring, but this was not reflected in the abundance of $M^{+\bullet}$ discussed above.
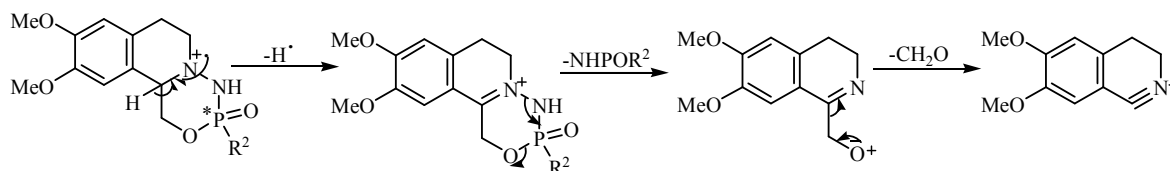
Scheme 6. Further fragmentations taking place through the bridgehead *N* atom initiated by the loss of H accompanied by bond-cleavages. The final step was a CH_2O ejection.
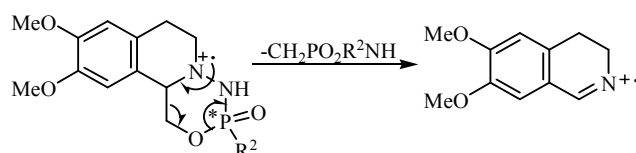
Scheme 7. For oxadiaza compounds, $CH_2PO_2R^2NH$ ejection yielded quite stable fragment ions (*RA* 9–51%), except when $R^2 = N(CH_2CH_2Cl)_2$.
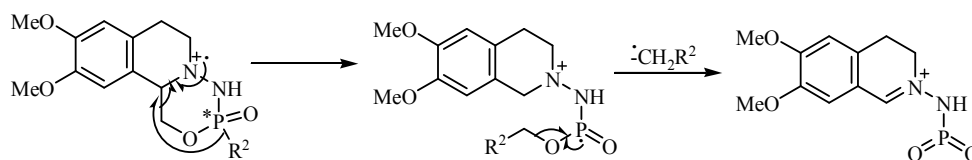
Scheme 8. Fragmentations also occurred after the migration of substituent $R^{2(100)}$.

Both the substituents and the stereochemistry influenced the decompositions of isomeric compounds. Within the angular compounds (**42**), the *trans*-annelated isomer provided more stable fragments (and $M^{+\bullet}$) than the *cis*. Further, within the linear compounds (**40**), the *trans*-annelated isomer provides more stable fragments (and $M^{+\bullet}$) than the *cis*. In the

cyclohexane-fused derivatives, the rate of the rDA decomposition was higher for the *cis*-fused than for the *trans*-fused isomer. As the annelation H and the Ph (*i.e* R^2) substituent on the *P* atom are situated further away from each other, the strain energy between them is lower in the *trans* than in the *cis* isomer, which leads to higher stability for the former.

The great differences in the *RA*s of $[M-R^2PONH]^{+\bullet}$, $[M-R^2PONH_2]^+$, $[M-R^2PO_2H]^{+\bullet}$ and $R^2PO_2H^{+\bullet}$ for compounds **35–42** and of many minor ions (*e.g. m/z* 98 and 95) can be utilized in isomer differentiation. The ions $[M-PhPONH]^{+\bullet}$ and $[M-PO_2H]^{+\bullet}$ in the spectra of **35** and **37** (with *n* =1 or 2) and the ions $[M-PhPONH]^{+\bullet}$ and $[M-PO_2H]^{+\bullet}$ for **41a** and **42**, were more stable for the **a** than for the **b** isomers. Moreover, $[M-R^2PONH_2]^+$ and $[M-R^2PO_2H]^{+\bullet}$ for **35–42** were more abundant for the **a** than for the **b** epimers, with the exceptions of **38a** and **38b**. The differences in *RA* between the isomeric structures (*P*-2 epimers) were greater for compounds with R^2 = Ph or $N(CH_2CH_2Cl)_2$ than for those with R^2 = PhO, at least as concerns the *RA*s of the latter two fragments.

$M^{+\bullet}$, $[R^2]^+$, $R^2H^{+\bullet}$, $R^2PO_2H^{+\bullet}$, $[M-R^2PO_2NH_2]^{+\bullet}$ and $R^2PO_2H_2^+$ (the latter ion, typical for *N*-substituted benzodiazaphosphole-2-oxides[48]) were formed through P-N bond fission accompanied by a double H-transfer for **35–42**. The abundance of $[M-R^2PO_2NH_2]^{+\bullet}$ was higher for **40a** than for **40b**. For **42**, the **a** and **b** epimers could be distinguished via the abundances of $[M-H]^+$ and the ions at *m/z* 343, 329, 296 ($[M-PO_2H]^+$), 221 ($[M-R^2PONH]^{+\bullet}$) and 220 ($[M-R^2PONH_2]^+$). $[M-R^2PONH]^{+\bullet}$, $[M-PO_2H]^{+\bullet}$ $[M-R^2PONH_2]^+$ and $[M-R^2PO_2H]^{+\bullet}$ were more abundant for the **a** than for the **b** epimers in the spectra of **35** and **37** with *n* = 1 or 2 and R^2 = Ph, and in those of **41a** and **42**.

3.2. Ring-chain tautomerism in 4-alkyl-2-aryl-substituted oxazolidines and tetrahydro--1,3-oxazines

The condensation products of 2-aminoethanols (**97–104**) or 3-aminopropanols (**118–122**) (bearing an alkyl or Ph substituent on the *C* adjacent to the *N*) with substituted benzaldehydes (obtained in the synthetic process described earlier[IV]) exist as tautomeric mixtures of the *cis* (**B**) and *trans* (**C**) five- or six-membered 1,3-*O,N*-heterocycles and the corresponding imines (**A**) (**105–110** and **123–126**) both in the gas phase and in solution. A few acetophenone derivatives were also synthetized (**111b,d,f** and **112b,d,f**)[101] to prove that the loss of H or CH_3 from position 2 is characteristic for the ring tautomer in the gas phase (Schemes 9a and b).
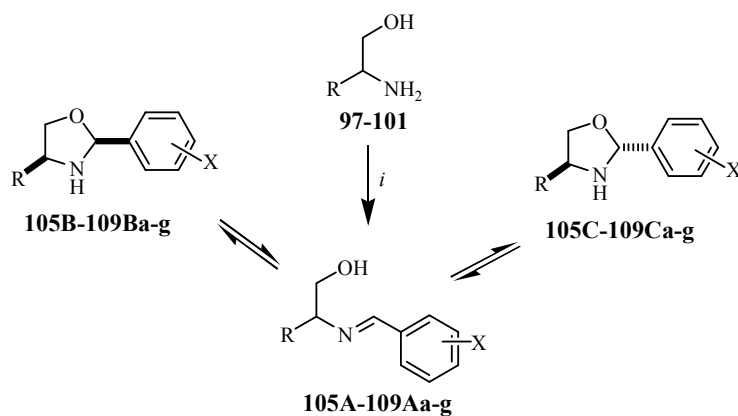
97, 105: R = Me; **98, 106**: R = Et; **99, 107**: R = *i*-Pr; **100, 108**: R = *t*-Bu; **101, 109**: R = Ph;
a: X = *p*-NO$_2$; **b**: *m*-Br; **c**: *p*-Cl; **d**: H; **e**: *p*-Me; **f**: *p*-OMe; **g**: *p*-NMe$_2$
Reagents and conditions: (*i*) XC$_6$H$_4$CHO, MeOH, r.t., 1 h, 65-100%
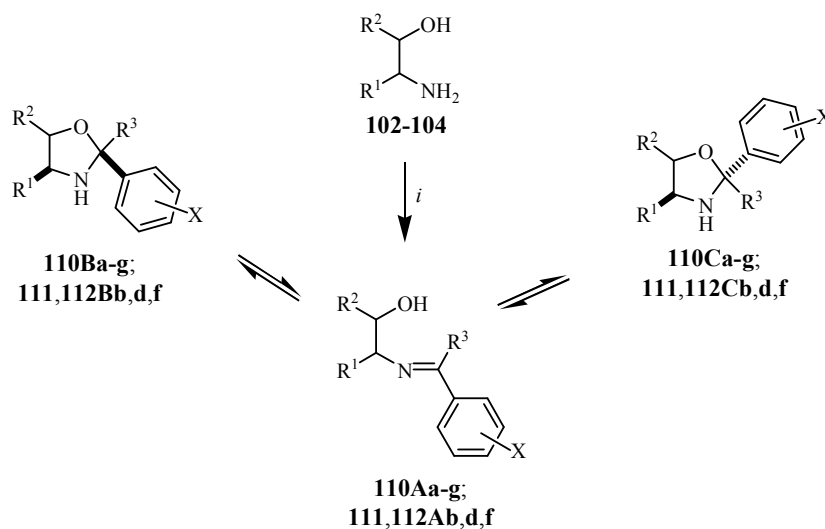
102, 110: R^1 = H, R^2 = Ph, R^3 = H; **103, 111**: R^1 = Me, R^2 = H, R^3 = Me; **104, 112**: R^1 = H, R^2 = Me, R^3 = Me;
a: X = *p*-NO$_2$; **b**: *m*-Br; **c**: *p*-Cl; **d**: H; **e**: *p*-Me; **f**: *p*-OMe; **g**: *p*-NMe$_2$
Reagents and conditions: (*i*) XC$_6$H$_4$CR^{3}O, MeOH, r.t., 1 h, 65-100%; XC$_6$H$_4$CR^{3}O, C$_6$H$_5$CH$_3$, 140 °C, 16 h

Scheme 9a. Synthetic routes to oxazolidines (**105–112**) (*cis* (**B**) is the major ring form for **105–109**, and the minor ring form for compounds **110–112**).
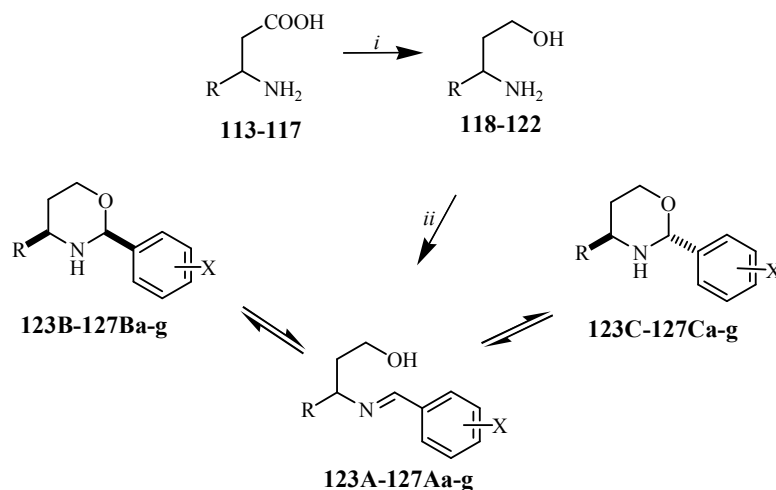
113, 118, 123: R = Me; **114, 119, 124**: R = Et; **115, 120, 125**: R = *i*-Pr; **116, 121, 126**: R = *t*-Bu; **117, 122, 127**: R = Ph
a: X = *p*-NO$_2$; **b**: *m*-Br; **c**: *p*-Cl; **d**: H; **e**: *p*-Me; **f**: *p*-OMe; **g**: *p*-NMe$_2$
Reagents and conditions: (*i*) LiAlH$_4$, THF, reflux, 8 h, 68-81%; (*ii*) XC$_6$H$_4$CHO, MeOH, r.t., 1 h, 61-100%

Scheme 9b. Synthetic routes to 3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**123–127**) (*cis* (**B**) is the major ring form for **123–127**).

The ring-chain tautomeric equilibria can be described by linear Hammett-type correlations based on Eq. 1:

$$\log K = \rho \sigma^+ + f \tag{Eq. 1}$$

where log K = log ([ring]/[chain]), σ^+ is the Hammett-Brown substituent constant for substituents X on the 2-Ph group, ρ is the slope, which reflects the sensitivity of the reaction to the electronic effects of substituent X, and f is the intercept, which reflects, for example, steric effects.

The electron-withdrawing effect of the aryl substituent (*p*-NO$_2$, *m*-Br, *p*-Cl, H, *p*-Me, *p*-OMe and *p*-NMe$_2$) shifts the equilibrium towards the ring form at both 14 and 70 eV in the gas phase and also in solution, except for the acetophenone derivatives. In gas phase, each equilibrium constant was calculated by the ratios of the sum of the *RA*s of the ring-related fragment ions and of the open-chain related fragment ions. The fragment ions relating to the ring tautomers (**B**+**C**) are [M–H]$^+$ (loss of *H* occurs mainly from C-2[18] and [M–R^3]$^+$ for compounds **112**), [M–R]$^+$, [M–Ar]$^+$ (formed through a simple α-cleavage initiated by the ring *N* atom), [M–CH$_2$O]$^{+\bullet}$ for compounds **105–109**, **123–127** and the corresponding [M–CHR^{2}O]$^{+\bullet}$ for compounds **110–112** and also [M–C$_2$H$_4$O]$^{+\bullet}$ (produced by two bond cleavages)[18] for compounds **123–127**. For **127a** (*p*-NO$_2$-substituted compound), [M–C$_8$H$_8$]$^+$ and [M–C$_2$H$_4$O–HNO$_2$]$^+$ also originated from the ring form and were added to the above mentioned ring-related fragment ions in the calculations of the ring-chain equilibria; some of

compounds **127a–d** additionally furnished small amounts of $[M–C_2H_5]^+$ from the ring tautomers. $[M–CH_2OH]^+$ for compounds **105–109** and **123–127**, the corresponding $[M–CHR^2OH]^+$ for compounds **110–112**, and $[M–C_2H_4OH]^+$ (also formed by *α*-cleavage from the azomethine *N* atom) and $C_8H_9O^+$ (*m/z* 121 for the *p*-OMe derivatives) for the open-chain Schiff bases were taken to represent the [ring]/[chain] equilibria (Scheme 10, Tables 3a and b and 4).
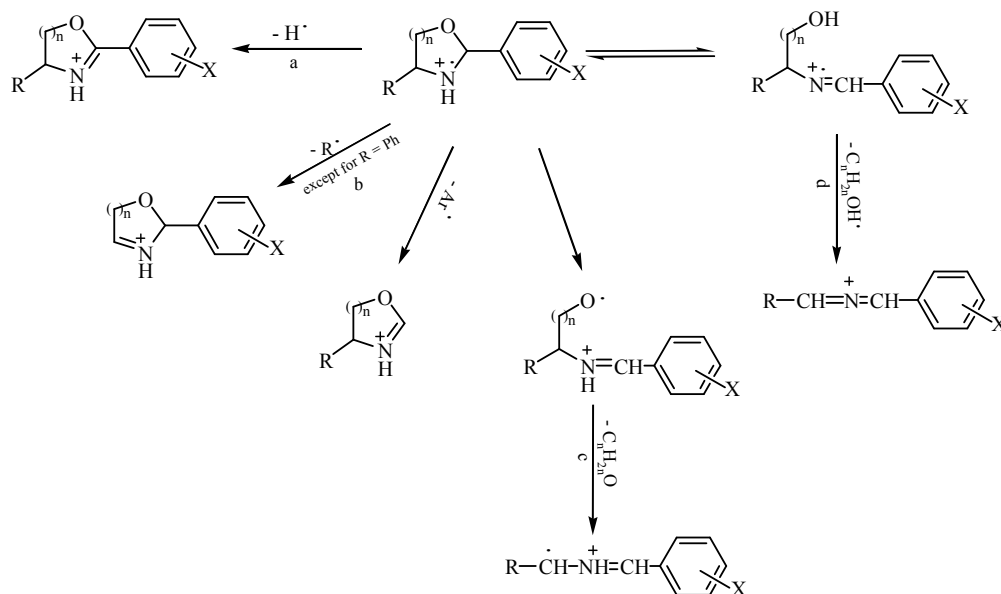
Scheme 10. Characteristic main fragmentation routes for the ring and open-chain forms of **105–109** and **123–127** (*n* = 1 or 2; for R, X see Scheme 9).
[a] Corresponds to $R^{3\bullet}$ loss for **110–112**. [b] Corresponds to $R^{1\bullet}$ loss for **110–112**. [c] Corresponds to CHR^2O loss for **110–112**. [d] Corresponds to $CHR^2OH^\bullet$ loss for **110–112**.

Table 3a. *RA*s(%) of primary fragment ions generated from the ring forms (**B+C**) at 70 eV at constant source temperature (443 K) for compounds **105a–g**.

	70 eV				
Comp.	$[M–H]^+$	$[M–R]^+$	$[M–Ar]^+$	$[M–CH_2O]^{+\bullet}$	$\Sigma_{\text{ring (RA\%)}}$
105a	16.1	1.7	11.7	8.8	38.3
105b	22.2	1.4	18.7	7.4	49.7
105c	9.7	0.7	3.5	5.6	19.5
105d	9.3	0.5	4.5	2.05	16.35
105e	4.7	0.7	1.4	1.0	7.8
105f	5.5	0.5	0.75	1.3	8.05
105g	2.5	1.0	0.7	2.9	7.1

Table 3b. *RA*s(%) of primary fragment ions generated from the ring forms (**B+C**) at 14 eV at constant source temperature (443 K) for compounds **105a–g**.

Comp.	[M–H]$^+$	[M–R]$^+$	[M–Ar]$^+$	[M–CH$_2$O]$^{+\bullet}$	$\Sigma_{ring\,(RA\%)}$
105a	7.9	0.8	5.1	5.0	18.8
105b	7.0	0.8	16.2	7.0	31.0
105c	9.9	0.55	2.9	2.7	16.05
105d	8.3	0.3	3.8	1.7	14.1
105e	5.8	0.75	1.5	0.9	8.95
105f	5.45	0.5	0.55	1.5	8.0
105g	1.9	0.8	0.1	4.8	7.6

*(column header spanning: **14 eV**)*

Table 4. *RA*s(%) of primary fragment ions generated from the open-chain form (**A**) at 70 eV and 14 eV at constant source temperature (443 K) for compounds **105a–g**.

Comp.	[M–CH$_2$OH]$^+$ 70 eV	14 eV
105a	99.8	99.75
105b	196.9	196.8
105c	140.5	131.4
105d	99.9	99.9
105e	99.9	99.95
105f[a]	99.95	99.85
105g	99.9	99.9

[a] Total *RA*% for these chain forms = 104.35% (contains C$_8$H$_9$O$^+$, *RA* = 4.4%) at 70 eV and 102.05% (contains C$_8$H$_9$O$^+$, *RA* = 2.2%) at 14 eV. Total *RA*s(%) of some ions are more than 100% due to the fact that they contain both $^{35/37}$Cl and $^{79/81}$Br counterparts.

For the oxazolidine derivatives, two equilibrium constants K_1 and K_2 (Eqs 2 and 3a) were calculated, while for the oxazine derivatives only one was calculated ($K_2^{'}$, Eq. 3b) since Eq. 2 led to a very poor or even non-existent correlation for the oxazines.

$$\log K_1 = \log \frac{[M-CH_2O]^{+\bullet}}{[M-CH_2OH]^+} = \log \frac{[\mathbf{B+C}]}{[\mathbf{A}]} \tag{Eq. 2}$$

$$\log K_2 = \log \frac{[M-CH_2O]^{+\bullet} + [M-H]^+ + [M-R]^+ + [M-Ar]^+}{[M-CH_2OH]^+} \tag{Eq. 3a}$$

$$\log K_2^{'} = \log \frac{[M-CH_2O]^{+\bullet} + [M-C_2H_4O]^{+\bullet} + [M-H]^+ + [M-R]^+ + [M-Ar]^+}{[M-CH_2OH]^+ + [M-C_2H_4OH]^+} \tag{Eq. 3b}$$

For **110**, $[M–CH_2O]^{+\bullet}$ and $[M–CH_2OH]^{+}$ in Eqs 2 and 3a are replaced by $[M–PhCHO]^{+\bullet}$ and $[M–PhCHOH]^{+}$, respectively. For **111**, $[M–H]^{+}$ and $[M–R]^{+}$ in Eq. 3a are both replaced by $[M–CH_3]^{+}$. For **112**, $[M–H]^{+}$ in Eq. 3a is replaced by $[M–CH_3]^{+}$, and $[M–CH_2O]^{+\bullet}$ and $[M–CH_2OH]^{+}$ in Eqs 2 and 3a are replaced by $[M–CH_3CHO]^{+\bullet}$ and $[M–CH_3CHOH]^{+}$, respectively. Excluding a few derivatives better correlations were achieved, namely **127g** and **130g** for the oxazines and (**106–110**)**g** for oxazolidines both at 70 and 14 eV and as to oxazolidines also for **106f** at 70 eV and **106f** and **109f** at 14 eV, probably due to some factor which makes the molecular ions to favour the open-chain forms in the final gas-phase equilibria (Tables 5a,b).

Table 5a. Log K_2 values for **105**–**109** and log $K_2^{'}$ values for **123**–**127** at 70 eV.

Comp.	log K_2					log $K_2^{'}$				
	105	**106**	**107**	**108**	**109**	**123**	**124**	**125**	**126**	**127**
	Me	Et	*i*-Pr	*t*-Bu	Ph	Me	Et	*i*-Pr	*t*-Bu	Ph
a	−0.42	−0.48	0.05	0.79	−0.39	0.63	0.80	1.22	1.93	0.26
b	−0.60	−0.56	−0.04	0.60	−0.78	0.47	0.56	1.05	1.76	0.26
c	−0.86	−0.70	−0.12	0.52	−0.92	0.39	0.47	0.97	1.70	0.10
d	−0.79	−0.70	−0.14	0.45	−0.97	0.36	0.46	0.95	1.72	0.10
e	−1.11	−0.86	−0.30	0.34	−1.11	0.28	0.38	0.88	1.60	0.06
f	−1.11[a]	−1.00	−0.45	0.17	−1.24	0.18	0.25	0.66	0.99	−0.01
g	−1.15[a]	−0.91[a]	−0.24[a]	0.50[a]	−0.79[a]	−0.16	0.18	0.85[a]	1.59[a]	−0.36

[a] These values were omitted from the calculations.

Table 5b. Log K_2 values for **105**–**109** and log $K_2^{'}$ values for **123**–**127** at 14 eV.

Comp.	log K_2					log $K_2^{'}$				
	105	**106**	**107**	**108**	**109**	**123**	**124**	**125**	**126**	**127**
	Me	Et	*i*-Pr	*t*-Bu	Ph	Me	Et	*i*-Pr	*t*-Bu	Ph
a	−0.73	−0.57	0.06	0.59	−0.56	1.29	1.07	1.47	2.05	0.41
b	−0.80	−0.54	−0.09	0.55	−0.72	1.14	1.09	1.14	1.92	0.34
c	−0.91	−0.74	−0.19	0.41	−0.89	0.94	0.93	1.06	1.83	0.28
d	−0.85	−0.71	−0.14	0.41	−0.91	1.04	1.05	1.02	1.78	0.34
e	−1.05	−0.87	−0.35	0.35	−1.07	1.00	0.96	0.97	1.71	0.25
f	−1.11	−0.96	−0.41	0.31[a]	−1.18	0.81	0.83	0.83	1.52	0.18
g	−1.12[a]	−0.92[a]	−0.24[a]	0.55[a]	−1.30[a]	0.21	0.53	1.20[a]	1.80[a]	−0.24

[a] These values were omitted from the calculations.

Better correlations were obtained in CDCl$_3$ solution than in the gas phase; the slopes were positive both in solution and in the gas phase, indicating that electron-withdrawing substituents favour the ring tautomers (Table 6), except for the acetophenone derivatives in the gas phase.

Table 6. Linear regression analysis data for 4-*t*-Bu-2-aryl-substituted oxazolidines (**108**) and 4-*t*-Bu-2-aryl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**126**).

	Equilibrium	No. of points	Slope^a (ρ)	Intercept^a (f)	Correlation coefficient (r)
70 eV	**108(B+C)** ⇌ **108A**	6^{b,c}	0.69(±0.06)	−1.40(±0.03)	0.987
	108(B+C) ⇌ **108A**	6^{b,d}	0.39(±0.01)	0.46(±0.01)	0.997
	126(B+C) ⇌ **126A**	6^b	0.54(±0.12)	1.60(±0.06)	0.908
14 eV	**108(B+C)** ⇌ **108A**	6^{b,c}	0.45(±0.10)	−1.45(±0.05)	0.914
	108(B+C) ⇌ **108A**	6^{b,d}	0.19(±0.03)	0.43(±0.01)	0.956
	126(B+C) ⇌ **126A**	6^b	0.33(±0.02)	1.79(±0.01)	0.996
CDCl$_3$	**108B** ⇌ **108A**	7	0.46(±0.01)	−0.13(±0.01)	0.996
	108C ⇌ **108A**	7	0.54(±0.01)	−0.30(±0.01)	0.996
	108(B+C) ⇌ **108A**	7	0.49(±0.01)	0.10(±0.01)	0.999
	126B ⇌ **126A**	7	0.65(±0.04)	0.63(±0.03)	0.992
	126C ⇌ **126A**	7	0.80(±0.04)	−0.97(±0.03)	0.994
	126(B+C) ⇌ **126A**	7	0.65(±0.03)	0.64(±0.03)	0.993

^{a}Standard errors in parentheses. ^{b}*p*-NMe$_2$ derivatives excluded. ^{c}Calculated via Eq. 2. ^{d}Calculated via Eq. 3a.

Common fragmentations were initiated from the ionized *N* atom by α-cleavage with or without H-transfers. Fewer fragments were present in the spectra of the *i*-Pr and *t*-Bu sets and this situation also prevailed at 14 eV relative to that at 70 eV.

The fragment ions [M–H]$^+$, [M–R]$^+$, [M–Ar]$^+$, [M–CH$_2$O]$^{+\bullet}$ and [M–C$_2$H$_4$O]$^{+\bullet}$ were more abundant for the 1,3-oxazine derivatives with R = Me, Et or Ph (**123**, **124**, **127**) than for the corresponding oxazolidines (**105**, **106** and **109**), but less abundant for the oxazines with R^1 = *i*-Pr or *t*-Bu than for the corresponding oxazolidines; and [M–CH$_2$OH]$^+$ was less abundant for the 1,3-oxazines (with R^1 = Me–Ph) than for the oxazolidines at both 70 and 14 eV. For the 1,3-oxazines, M$^{+\bullet}$ was less abundant than [M–H]$^+$, except for the compounds with X = *p*-NMe$_2$ (**123**–**127**)**g** and for **127a** (R = Ph and X = *p*-NO$_2$). The same was true for the oxazolidine derivatives, *i.e.* for the *p*-NMe$_2$ compounds (**105**–**109**)**g**, and for a few *p*-OMe derivatives (**105f**, **106f** and **108f**) M$^{+\bullet}$ was more abundant than [M–H]$^+$. In general, the *RA*s of

$[M–H]^+$, $[M–Ar]^+$, $[M–CH_2O]^{+\bullet}$, $[M–C_2H_4O]^{+\bullet}$, $[M–CH_2OH]^+$ and $[M–C_2H_4OH]^+$ for the ring and open-chain forms decreased from R = Me to t-Bu, and increased for Ph for both oxazolidines and 1,3-oxazines. However, the abundance of $[M–R]^+$ increased from R = Me to t-Bu, and it even gave the base peak for the 4-i-Pr and 4-t-Bu series, but for R = Ph it was not present.

For the oxazolidines, better correlations were obtained with the log K_2 *vs* σ^+ regression, except for compounds **109** and **110** at 70 eV and for compounds **105**, **108** (calculated with five data points) and **109** at 14 eV, but clearly better correlations were obtained in solution. Increasing bulk of the 4-alkyl group increased the contributions of the cyclic tautomers (as was the case in solution). For the 1,3-oxazine derivatives, log $K_2{}'$ increased from Me to t-Bu, and for Ph it decreased similarly to the log K_2 values for the oxazolidines. The log $K_2{}'$ values were the smallest for the R = Me set, and increased from Et to Ph at 70 and 14 eV. This type of behaviour of the equilibrium constants was not observed for the 1,3-oxazines in solution. The different trends in the influences of the 4-alkyl substituents in the ring-chain equilibria of the homologous 1,3-O,N-heterocycles may be due to the different conformations of the oxazolidine and 1,3-oxazine rings, which influence the stereoelectronic effects of alkyl and aryl substituents on the equilibria of the oxazolidines (**105–108**).[75,102] For compounds with R = Et or t-Bu at 70 eV, and for those with R = Et, i-Pr or Ph at 14 eV, better correlations were obtained for the oxazolidines than for the 1,3-oxazines, and for the compounds with R = Me, the correlation coefficients were similar when log K_2 *vs* σ^+ was compered with the corresponding log $K_2{}'$ *vs* σ^+ correlation.

Especially for the 1,3-oxazine derivatives, better correlations were observed in solution than in the gas phase. The oxazolidine derivatives gave slightly better correlations than the oxazines. Higher electron energy usually favours the open-chain form (*i.e.* opening of the ring form).[16,18,64] This was also the case with the 1,3-oxazine derivatives (**123–127**),[V] as indicated by the smaller log $K_2{}'$ values at 70 eV as compared with those at 14 eV. In the oxazolidines, however, the situation is not equivocal: for most derivatives within the sets of from R = Me to t-Bu, the lower ionization energy favours the open-chain forms, while for R (**109**) or R^2 = Ph (**110**) and for acetophenone derivatives (**111**, **112**), the lower ionization energy favours the formation of the ring forms, based on the log K_1 *vs* σ^+ and also the log K_2 *vs* σ^+ correlations. This proves the decisive role of Ph substitution.

In CDCl$_3$ at 300 K, three-component tautomeric mixtures of the diastereomeric five- or six-membered 1,3-O,N-heterocyclic ring forms and the corrresponding imines exist, since it is possible to detect the *cis* (**B**) and *trans* (**C**) ring forms separately through their distinct ^{1}H-

NMR signals, and good linear correlations were obtained for both ring forms *vs* the Hammett-Brown σ^+ parameters of substituent X of the 2-Ph group (Fig. 1a,b).
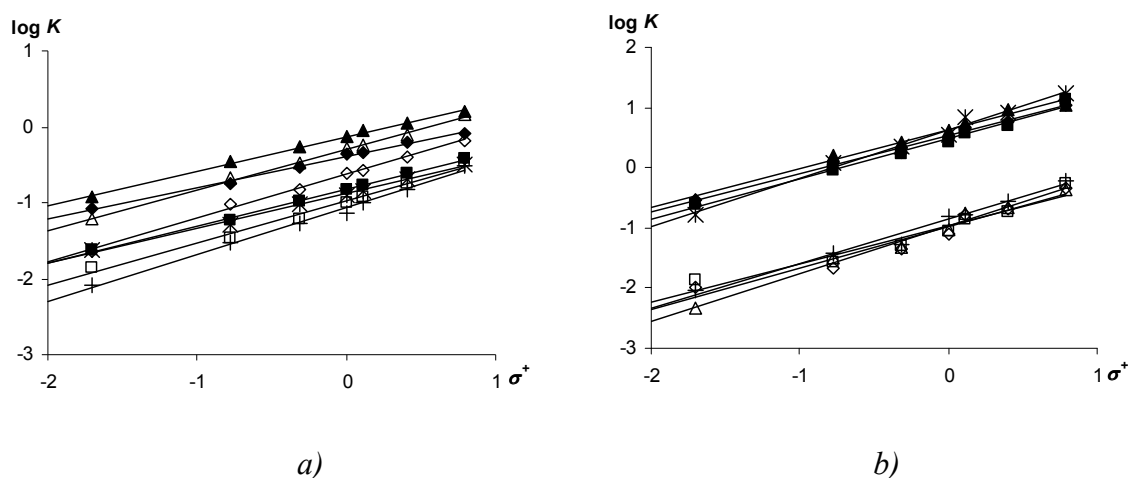
Figure 1.
a) Plots of log K_B or log K_C (CDCl$_3$, 300 K) for **105B** (⊁), **105C** (+), **106B** (■), **106C** (□), **107B** (♦), **107C** (◊), **108B** (▲) and **108C** (Δ) *vs* Hammett-Brown parameter σ^+.
b) Plots of log K_B or log K_C (CDCl$_3$, 300 K) for **123B** (⊁), **123C** (+), **124B** (■), **124C** (□), **125B** (♦), **125C** (◊), **126B** (▲) and **126C** (Δ) *vs* Hammett-Brown parameter σ^+.

In solution, electron-withdrawing substituents X favour the ring form due to the polarity of the C=N moiety[103] (Table7), and often similarly in the gas phase.[14–18,61]

Table 7. Proportions (%) of the ring-closed tautomeric forms (**B** and **C**) in tautomeric equilibria for compounds **105**, **108**, **123** and **126** (CDCl$_3$, 300 K).

| Compd. | | **105** | | **108** | | **123** | | **126** | |
| | R (V^a) | Me (2.84) | | *t*-Bu (7.16) | | Me (2.84) | | *t*-Bu (7.16) | |
	X (σ^+)	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**
a	*p*-NO$_2$ (0.79)	19.9	18.5	39.5	35.7	91.5	3.2	88.4	3.5
b	*m*-Br (0.405)	15.1	11.1	39.1	26.4	86.7	2.9	88.4	2.1
c	*p*-Cl (0.114)	11.7	7.9	36.1	23.0	85.4	2.1	82.1	2.6
d	H (0)	10.3	6.1	33.5	22.6	75.0	3.4	79.4	1.8
e	*p*-Me (−0.311)	8.2	4.7	29.1	17.6	67.9	1.3	71.7	1.3
f	*p*-OMe (−0.778)	4.7	2.8	22.6	13.5	57.1	1.7	60.7	1.2
g	*p*-NMe$_2$ (−1.7)	2.3	0.8	10.0	5.1	14.0	0.7	22.9	0.4

The bulkier the 4-alkyl group, the more stable the cyclic tautomer of oxazolidines **105–108**, but this behaviour was not found for the corresponding 1,3-oxazines. The different behaviour can be rationalized in terms of the different conformations of the oxazolidine and

1,3-oxazine rings, which influence the stereoelectronic effects of alkyl and aryl substituents[73,102] on the equilibria of oxazolidines **105–108**. The stability differences between the *cis* (**B**) and *trans* (**C**) isomers of the 2,4-disubstituted cyclic forms can be characterized by the differences in their substituent effect parameters (Δc_S, calculated as the differences between the intercepts for the given compounds **105–108** or **123–126** and those for the parent 2-aryloxazolidine[104] or 2-aryltetrahydro-1,3-oxazine[8]), which are smaller (Δc_S: 0.15–0.24) for the epimeric oxazolidines (**B** and **C**) than for the homologous epimeric 1,3-oxazines (Δc_S: 1.45–1.60).

The double substituent dependence of log K_B and log K_C for the ring-chain equilibria in **105–108** and in **123–126** were studied with a Hansch-type equation (Eq. 4):

$$\log K = k + \rho^R P^R + \rho^X \sigma^{+X} \qquad \text{(Eq. 4)}$$

The best correlation was achieved with the Meyer parameter V^a (the volume of the portion of the substituent that is within 0.3 nm of the reaction centre)[105] for the equilibria of oxazolidines (**105–108**), while for the equilibria of 1,3-oxazines (**123–126**), none of the four different alkyl substituent parameters, *i.e.* V^a, v (derived from the van der Waals radii),[106] E_s (calculated from the hydrolysis and aminolysis of esters)[105] and G (describing the shape in terms of the ratio of the surface area substituent to its volume)[105] applied, resulted in a significant ρ^R value (Table 8).

Table 8. Multiple linear regression analysis of log K_B and log K_C for **105–108** and **123–126** according to Eq. 4 ($P^R = V^a$).

Equilibrium	k	ρ^R	ρ^X	r
105–108B $\rightleftharpoons$ **105–108A**	−1.500	0.189	0.453	0.982
105–108C $\rightleftharpoons$ **105–108A**	−1.681	0.188	0.573	0.989
123–126B $\rightleftharpoons$ **123–126A**	0.510	[a]	0.689	0.984
123–126C $\rightleftharpoons$ **123–126A**	−0.801	[a]	0.712	0.978

[a] Insignificant (level of significance 0.05).

The increasing proportion of the cyclic forms **B** and **C** correlates with the increasing bulk of the alkyl substituents to nearly the same extent ($\Delta \rho^R$:<0.02) for the equilibria (**105–108**)**B** $\rightleftharpoons$ (**105–108**)**A** and (**105–108**)**C** $\rightleftharpoons$ (**105–108**)**A**, due to the similar hyperconjugative (anomeric) effects occurring in the cyclic *C*-2 epimeric forms.[81,101]

With another Hansch-type equation (Eq. 5), we established that both the inductive (σ_F^X) and the resonance effects (σ_R^X) of the aryl group had a more marked influence on the equilibria in the 1,3-oxazines than on those in the oxazolidines.

$$\log K = k + \rho^R V^a + \rho_F^X \sigma_F^X + \rho_R^X \sigma_R^X \qquad \text{(Eq. 5)}$$

While both ρ_F^X and ρ_R^X were considerably different for the equilibria (**105–108**)B ⇌ (**105–108**)A and (**105–108**)C ⇌ (**105–108**)A, ρ_R^X was less sensitive to the relative configuration of the cyclic tautomer in the 1,3-oxazines (Table 9).

Table 9. Multiple linear regression analysis[a] of log K_B and log K_C for **105–108** and **119–122** according to Eq. 5.

Equilibrium	k	ρ^R	ρ_F^X	ρ_R^X	r
105–108B ⇌ 105–108A	−1.532	0.189	0.386	1.114	0.974
105–108C ⇌ 105–108A	−1.748	0.190	0.567	1.384	0.983
123–126B ⇌ 123–126A	0.422	[b]	0.735	1.607	0.966
123–126C ⇌ 123–126A	−0.938	[b]	0.930	1.590	0.976

[a] X = *m*-Br derivatives (**b**) were omitted from the calculations. [b] Insignificant (level of signifycance 0.05).

For the ephedrine (**110a–g**) and acetophenone derivatives (**111b,d,f**; **112b,d,f**), the value of ρ was again positive, *i.e.* the electron-withdrawing property of substituent X on the 2-Ph ring favours the ring-closed tautomer.

3.3. Methods

Details of the syntheses, physical and analytical data on the new compounds described in the thesis, and descriptions of the mass spectrometric and NMR spectroscopic analyses of the compounds and of the tautomeric equilibria can be found in the experimental sections of the enclosed publications.

4. SUMMARY

My PhD studies related to the fragmentation of *P*-containing heterocycles. The effects of the *P* configurations and *cis-trans* isomerism on the fragmentations were not significant, but those of the different substituents were. The ring-chain tautomeric equilibria of the prepared oxazolidine and oxazine derivatives were sensitive to the electronic and/or steric effects of the substituents. The main findings are as follows:

I. The derivatives of *cis*- and *trans*-cyclopentane- or cyclohexane-fused 3,1,2-benzoxazaphosphinane- (**4–17**) and 1,3,2-benzodiazaphosphinane- (**18–34**) and 1,3,4,2-oxadiazaphosphinane-2-oxides (**35–42**) gave rise to the same fragment ions and, in spite of small differences, the abundances of these were so similar that isomeric differentiation of oxaza (**4–17**) and diaza derivatives (**18–34**) in general was not possible. These compounds presumably undergo rapid bond cleavage and hence the mass spectra do not reveal the stereoisomeric differences. In contrast with the stereochemisty of the ring fusion, the nature of the *N*- and *P*-substitutions exerted marked effects on the fragmentation patterns. For the diaza compounds (**18–34**), the *trans*-annelated isomer was in general always more resistant to EI than the *cis* isomer, as concluded from the more abundant ions $M^{+\bullet}$ for the *trans*-annelated compounds.

II. The ions $M^{+\bullet}$ are relatively abundant except for compounds with the $N(CH_2CH_2Cl)_2$ substituent on the *P*. The abundances of the ions $M^{+\bullet}$ and $[M–H]^+$ were not significantly influenced by either the size of the ring *N* substituent or the diastereomeric configuration. For the 1,3,4,2-oxadiaza derivatives (**35–42**), the bulkier ring *N* substituent (H < Me < CH_2Ph) destabilized $M^{+\bullet}$ due to both steric and electronic factors. The *RA*% of $M^{+\bullet}$ also decreased in the following fusion sequence: cyclopentane > cyclohexane > benzo.

III. The *P* compounds studied exhibit different conformations and configurations, but the fact that the main fragmentation pathways under EI are similar confirms that they proceed in such a way that the differences in conformational and configurational rigidity between the diastereomers is lost. The major fragments were formed through decompositions initiated at the ring *N*. Due to the different factors stabilizing the positive charge, various pathways of $M^{+\bullet}$ fragmentation (*e.g.* initiated from the aromatic ring) were observed for the oxadiaza compounds (**35–42**). Replacement of Ph or OPh substituents by $N(CH_2CH_2Cl)_2$ also opened up new fragmentation channels and made $M^{+\bullet}$ almost non-existent. Extensive H-transfer to the heterocyclic part of the molecules was also observed.

IV. Facile ejection of various alkyl radicals is typical for compounds **4–17** and **18–34**. The loss of $C_3H_7^•$ is most favourable. The ion $[M–C_3H_7]^+$ is more abundant for the *cis*-fused compounds where $R^1 = CH_2Ph$ and $R^2 = OPh$ as compared with the *trans*-fused ones, and also more abundant for the *P(R*)*-2 epimers than for the *P(S*)*-2 epimers, due to stereoelectronic and steric effects which provide different internal energies for the isomers (and hence different stabilities) and different decomposition rates for a certain fragment ion. As concerns **35–42**, common fragments are more abundant for the *cis*- than for the *trans*-fused isomers (of pyrrolo-condensed derivatives) when *n* = 1, due to the steric interactions caused by the proximate groups and the ring strain, which is more favourable for the ring cleavage in the *cis* isomer, resulting in an enhanced abundance of the common fragment ions. The opposite effect appears when *n* = 2 (pyrido-condensed derivatives), due to the decreased steric interactions and ring strain.

V. Compounds (**105–112**, **123–127**), prepared by condensing suitable aminoalcohols with aromatic aldehydes exhibit the same tautomeric forms in the gas phase and in solution. In solution, we could simply and accurately determine the ring-chain tautomeric equilibria and also establish the separate contributions of the *cis* and *trans* epimers of the ring form, which was not possible in the gas phase since both ring forms gave the same ions.

VI. The ring-chain tautomeric equilibria are sensitive to electronic and also to steric effects in solution, which could be characterized by Hammett-type and Hansch-type equations. For the gas-phase equilibria, it appears that especially the ions $M^{+•}$ of *p*-NMe_2-substituted derivatives may attain the open-chain form and in these cases the equlibria did not fit into the Hammett-type correlations. Electron-withdrawing substituents on the 2-Ph substituent preferred the ring forms both in the gas phase and in solution.

VII. Ph substitution at C-5 had a decisive effect in compounds **110a–g**, since excellent correlations were observed even for the ring-chain equilibria calculated based on only two fragment ions, $[M–PhCHO]^{+•}$ and $[M–PhCHOH]^+$. Not only the steric, but also the electronic properties of the Ph group play a role as regards the state of equilibrium. The stability differences between the *cis* and *trans* epimers are more pronounced for the *P*-2 epimers of 3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**123–126**) than for those of the oxazolidines (**105–108**). The inductive and resonance effects of the aryl group influenced the equilibria of the former (**123–126**) more than those of the latter (**105–108**).

5. ACKNOWLEDGEMENTS

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