Summary of PhD Thesis

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

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A. Introduction and aims

Compounds possessing an oxazaphosphorinane ring system are very important pharmacological building blocks of matrix metalloproteinase-inhibitors and alkylating anti-cancer drugs.

Because of their fundamental importance (bioactive and synthetic), we set out to elucidate the effects of various substituents on the ring nitrogen and phosphorus atoms, *cis-trans* isomerism and the phosphorus stereochemistry on the fragmentations of the diastereomeric pairs under 70 eV ionization for a few saturated 3,1,2-benzoxazaphosphinine-2-oxides (**1**–**14**), their nitrogen analogue 1,3,2-benzodiaza-phosphinine-2-oxides (**15**–**31**) and various condensed 1,3,4,2-oxadiazaphosphinane derivatives (**32**–**39**).

The structures of numerous five- and six-membered, *N*-unsubstituted, 1,3-*X*,*N*-heterocycles (X = O, S and NR) can be characterized by the ring-chain tautomeric equilibria of the 1,3-*X*,*N*-heterocycles and the corresponding Schiff bases. This ring-chain tautomeric process influences the reactivity and therefore the synthetic applicability of these compounds.

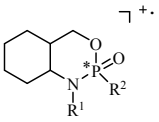
The electronic effects of 2-aryl substituents were studied most thoroughly in solution. A linear correlation was found between the log *K* values of the equilibria (*K* = [ring]/[chain]) and the Hammett-Brown parameters σ^+ of the different substituents X on the 2-aryl group (Eq. 1):

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

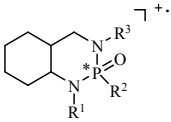
As relatively little attention has been paid to the gas-phase tautomeric equilibiria, it was important to investigate the electronic effects of 2-aryl substituents on the tautomeric equilibria for a few five- and six-membered 1,3-*O*,*N*-heterocyclic compounds. Electron ionization (EI) mass spectrometry can be used for this purpose by observing the ratio of the relative abundances of fragment ions associated with one or the other tautomeric form. A further aim was to inspect the effects of 4-alkyl or 4-phenyl substituents on the ring-chain tautomeric equilibria.

B. Results

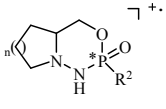
1. The derivatives of *cis*- and *trans* cyclopentane- or cyclohexane-fused 3,1,2-benzoxazaphosphinane- (**1**–**14**) and 1,3,2-benzodiazaphosphinane- (**15**–**31**) and 1,3,4,2-oxadiazaphosphinane-2-oxides (**32–39**) (Figure 1) gave rise to similar EI mass spectra, because the isomers underwent fast ring cleavage reactions, during which the differences in stereochemistry were lost.



1-14

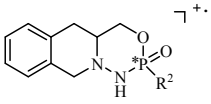


15-31



32-36

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



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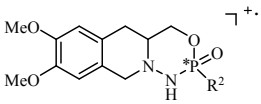

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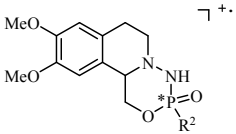
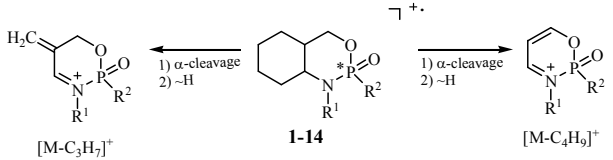


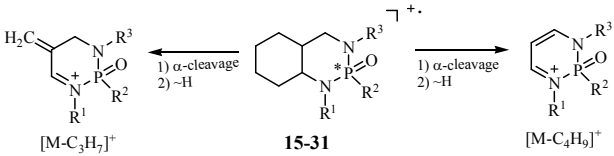
39

cis and *trans*; R^2 = Ph

Figure 1

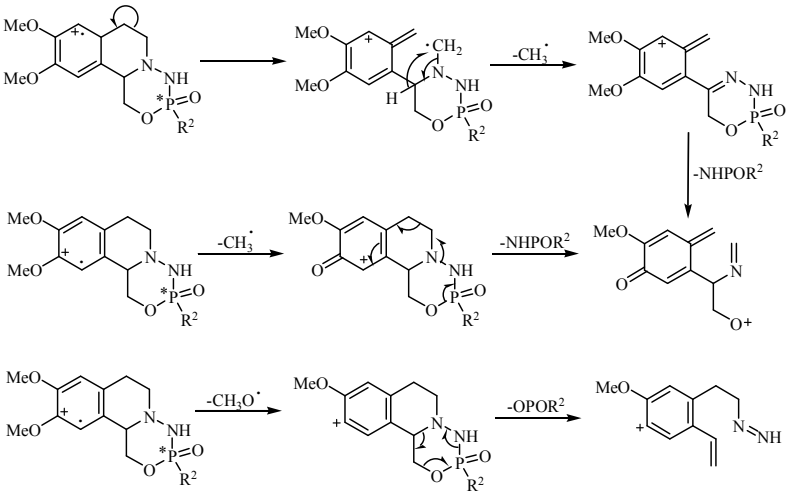
2. The ready ejection of various alkyl radicals was typical for compounds **1**–**14** and **15**–**31**. The formations of fragment ions $[M–C_3H_7]^+$ and $[M–C_4H_9]^+$ accompanied by H-transfers were favoured (Scheme 1).



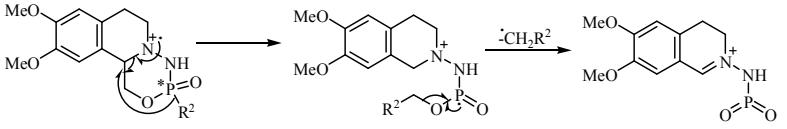


Scheme 1

3. Due to the factors stabilizing the positive charge, various fragmentation pathways of $M^{+\bullet}$ (the molecular ion) were observed for the oxadiaza compounds (**32**–**39**), *e.g.* fragmentations initiated from the aromatic moities (Scheme 2a) and fragmentations occurring after the migration of R^2 (Scheme 2b).

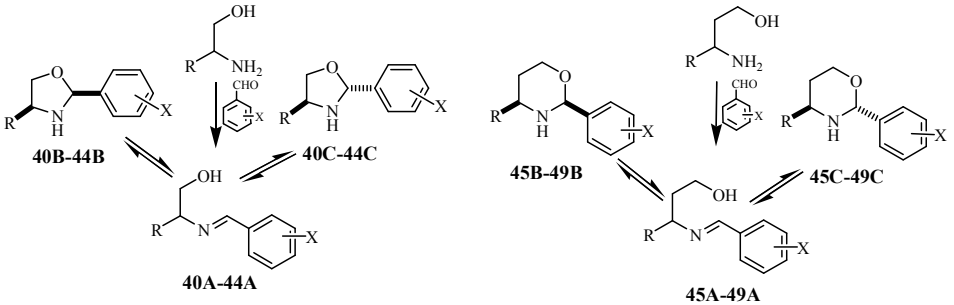


Scheme 2a



Scheme 2b

4. Compounds **40**–**49**, prepared by the condensation of the appropriate aminoalcohols with aromatic aldehydes, exhibited three-component tautomeric equilibria (open-chain (**A**) and cyclic *cis*(**B**) and *trans*(**C**)) (Scheme 3) in deuterochloroform, and two-component tautomeric equilibria involving open-chain(**A**) and ring forms(**B**+**C**) in the gas phase, when both the *cis* ring form and the *trans* ring form gave the same fragment ions.



Scheme 3

5. Each equilibrium could be characterized by the Hammett equation (Eq. 1). Besides the steric effect (V^a, the Meyer parameter) of the 4-alkyl substituent, the different electronic (inductive and resonance) properties of the 2-aryl groups also influenced the tautomeric equilibria of the oxazolidines, which could be described by Hansch-type equations (Eqs 2 and 3):

$$\log K = k + \rho^R V^a + \rho^X \sigma^{+X} \qquad \text{Eq. 2}$$

$$\log K = k + \rho^R V^a + \rho_F{}^X \sigma_F{}^X + \rho_R{}^X \sigma_R{}^X \qquad \text{Eq. 3}$$

Through multiple linear regression analysis of Eqs 2 and 3, we determined the free term (k) and the coefficients of the independent variables (V^a, $\sigma_F{}^X$ and $\sigma_R{}^X$), which are given in Table 1.

Table 1. Multiple linear regression analysis of the equilibrium constant log K_B for the *cis* ⇌ open-chain and log K_C for the *trans* ⇌ open-chain equilibria for compounds **40**–**43** and **45**–**48** according to Eq. 3

Equilibrium	k	ρ^R	$\rho_F{}^X$	$\rho_R{}^X$	r
40–43B ⇌ 40–43A	-1.532	0.189	0.386	1.114	0.974
40–43C ⇌ 40–43A	-1.748	0.190	0.567	1.384	0.983
45–48B ⇌ 45–48A	0.422	[a]	0.735	1.607	0.966
45–48C ⇌ 45–48A	-0.938	[a]	0.930	1.590	0.976

[a] Insignificant results.

A significant correlation was found between the Meyer parameter (which characterizes the steric effect of the 4-alkyl substituent) and the tautomeric equilibria for the oxazolidines, *i.e.* increasing bulk of the 4-alkyl group favoured the ring-closed tautomers, but the Meyer parameter did not indicate a significant effect for the corresponding 1,3-oxazines.

The opposite tendency was observed for the parameters σ_F^X and σ_R^X, *i.e.* the parameters describing the inductive and resonance effects of different aryl substituents influenced the equilibria more markedly for the tetrahydro-1,3-oxazines than for the oxazolidines.

6. For the oxazolidine derivatives, two equilibrium constants were defined. One of them was calculated with the relative abundances of the ring-related fragment ion $[M–CH_2O]^{+\bullet}$ and of the open-chain-related $[M–CH_2OH]^+$. To describe the equilibrium closer, besides these two fragment ions, further fragment ions were also considered. For the corresponding 1,3-oxazine derivatives, the tautomeric equilibria could be described with the latter approach only.

7. For the oxazines and oxazolidines, better correlations were achieved by excluding the strong electron donor-substituted derivatives from the regression analysis (Tables 2a), due to some factor which probably makes the molecular ions of these derivatives favour the open-chain forms in the final gas-phase equilibria.

Table 2a. Linear regression analysis data for 4-*t*-Bu-2-aryl-substituted oxazolidines (**43**) and 4-*t*-Bu-2-aryl-substituted 3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**48**) in gas phase

	Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a] (f)	Correlation coefficient (r)
70 eV	**43**(**B**+**C**) ⇌ **43A**	6[b,c]	0.69(±0.06)	-1.40(±0.03)	0.987
	48(**B**+**C**) ⇌ **48A**	6[b]	0.54(±0.12)	1.60(±0.06)	0.908
14 eV	**43**(**B**+**C**) ⇌ **43A**	6[b,c]	0.45(±0.10)	-1.45(±0.05)	0.914
	48(**B**+**C**) ⇌ **48A**	6[b]	0.33(±0.02)	1.79(±0.01)	0.996

[a] Standard errors in parentheses. [b] *p*-NMe_2 derivatives excluded. [c]Calculated via $\log K_1 = \log([M–CH_2O]^{+\bullet})/([M–CH_2OH]^+) = \log [\mathbf{B}+\mathbf{C}]/[\mathbf{A}]$

As shown in Tables 2a and b, better correlations were achieved for each case in deuterochloroform than in the gas phase for the corresponding equilibria.

Table 2b. Linear regression analysis data for 4-*t*-Bu-2-aryl-substituted oxazolidines (**43**) and 4-*t*-Bu-2-aryl-substituted 3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**48**) in solution

	Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a] (f)	Correlation coefficient (r)
$CDCl_3$	**43B** ⇌ **43A**	7	0.46(±0.01)	-0.13(±0.01)	0.996
	43C ⇌ **43A**	7	0.54(±0.01)	-0.30(±0.01)	0.996
	43(**B**+**C**) ⇌ **43A**	7	0.49(±0.01)	0.10(±0.01)	0.999
	48B ⇌ **48A**	7	0.65(±0.04)	0.63(±0.03)	0.992
	48C ⇌ **48A**	7	0.80(±0.04)	-0.97(±0.03)	0.994
	48(**B**+**C**) ⇌ **48A**	7	0.65(±0.03)	0.64(±0.03)	0.993

[a] Standard errors in parentheses.

C. Publications

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. i.f.: 2.680

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. 2.680

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. 2.680

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. 0.776

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
Rapid Commun. Mass Spectrom. **2007**, *21*, 3701-3710. 2.680

VI. Kalevi Pihlaja, **Márta Juhász**, Henri Kivelä, Ferenc Fülöp
Substituent effects on the ring-chain tautomerism of some 1,3-oxazolidine derivatives
Rapid Commun. Mass Spectrom. accepted for publication. 2.680

D. Conference lectures

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, Poland, 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, Poland, 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
17th International Mass Spectrometry Conference,
Prague, Czech Republic, 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
25th Informal Meeting on Mass Spectrometry
Nyíregyháza-Sóstó, 6-10 May, 2007, Abstr.: TuPo19.

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.