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Hydrolysis of cyclic phosphoramides. Evidence for *syn* lone pair catalysis †

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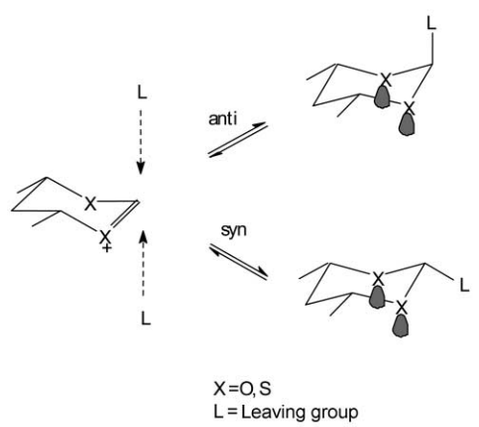
Hydrolysis between 1.5 < pH < 4 of five and six membered cyclic phosphoramides has been followed by UV and ^{31}PNMR spectroscopy. The observed rates fit the equation: $k_{obs} = k_{H_2O}[H^+]/([H^+] + Ka) + k'_{H_2O}$, where k_{H_2O} and k'_{H_2O} are the pseudo first-order rate constants of water attack on the protonated phosphoramide and its unprotonated form, respectively, and *K*a is the phosphoramide acidity equilibrium constant. Although, faster hydrolysis rates on the five membered ring are expected due to the energy released in going from a strained cyclic to a "strained free" trigonal-bipyramidal-pentacoordinated intermediate, with one of the cyclic nitrogens occupying the apical position, these compounds react slightly faster (k_{H_2O} values) but slower regarding the k'_{H_2O} values than the six membered analogs. The balance in reactivity is attributed to the additional stability obtained in the six membered cyclic compounds by a *syn* orientation of the two lone pairs of the cyclic nitrogen to the water attack. This stabilization does not exist in the five membered phospholidines since the water attack is perpendicular to the electron pairs of the cyclic nitrogen. In agreement with the incoming water orientation, the product ratios from the hydrolysis show that in the five membered rings the main product is the one produced by endocyclic cleavage; meanwhile, in the six membered cyclic phospholines the kinetic product is the one produced by exocyclic cleavage. The *syn* orientation of two electron pairs on nitrogen stabilizes the transition state of water approach to the phosphoramides by *ca*. 3 kcal mol^{-1} when compared to the orthogonal attack.

Introduction

The stereoelectronic control theory (SCT)

The stereoelectronic control theory[1] (SCT) claims that there is preferential cleavage when two electron pairs are antiperiplanar to the leaving group, and SCT has received intense investigation on several systems. At the aldehyde oxidation level interesting models based on restricted-conformation flexibility have been used[2] as evidence for SCT. However, against SCT, the principle of least nuclear motion has emerged[3] to explain the relative reactivity in pyranoside systems. Acyl oxidation hydrolysis of cyclic-orthoesters[1,4] and amidines,[5] are some of the classical studies that have been carried out. The reactivity or kinetic-product ratios have been presented as evidence in favour of SCT. The conclusion that one can reach after a general revision[6] is that the SCT effect where it does exist, is weak. A similar conclusion is reached when attempts are made to extrapolate the hypothesis to systems where phosphorus is involved. Although some evidence in favor of the hypothesis has been presented,[7] there is also doubt of its application.[6] The latter conclusion is also supported by theoretical calculations.[8]

In general, the hypothesis is based on a stabilization introduced by the n–σ* orbital interaction at the transition state. Qualitatively, its application to phosphorus looks more promising than to carbon based on two facts: phosphorus is slightly less electronegative than carbon and the apical bonds (from which heteroatoms leave or arrive) in the pentacoordinated intermediate, are elongated relative to the equatorial bonds or its equivalent carbon bonds. These two properties make the σ* orbital involved more stable and therefore improves its interaction with the n orbital. If the electron donor capacity of the n orbital is also improved (for instance n(N) instead of n(O)) then we may observe an effective SCT effect. There is also a third important point when considering phosphorus as compared with carbon. Due to the involvement of the 3d orbitals, the attack or departure from phosphorus could be oriented orthogonal to the plane formed by the n(X) electrons and the P–X bond. Therefore, a *syn* or *anti*-periplanar orientation may be compared to an orthogonal one, in the latter there is no possibility for overlap between the n orbital and the leaving or incoming group σ* orbital. This provides a good model to compare and quantify the SCT effect. The last point is quite important since antiperiplanar stabilization has been found to be relatively small in cyclic orthoesters,[9] thioesters[10] and in cyclic amidines[5] since the competing path is a *syn* orientation that is also recognized[11] as a stabilizing one. In fact, it has been found[9,10] that the *anti* orientation is equally or slightly more stabilizing than the *syn* one (see Scheme 1).



Scheme 1 Orientation of an incoming group L to yield *anti* or *syn* products. Since the carbon is sp^2 hybridized, the axial electron pair on X, at the transition state is either *syn* or *anti* oriented to L. Both interactions are stabilizing and there is no significant difference between k_{anti} and k_{syn}.

† Electronic supplementary information (ESI) available: *K*obs values at various pH values. See http://www.rsc.org/suppdata/ob/b3/b300916e/

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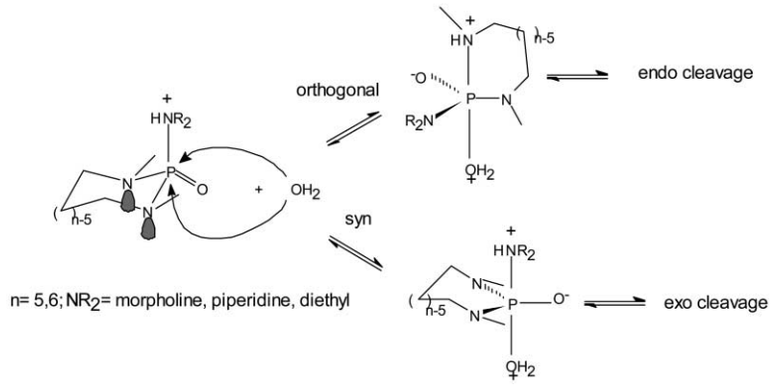


Scheme 2 Water orientation at the phosphorus attack in the five ($n = 5$) and six ($n = 6$) membered phosphoramides. For $n = 5$ the attack is orthogonal oriented to the electron pairs on the cyclic nitrogen meanwhile, it is *syn* oriented for $n = 6$. In agreement with the water orientation, for $n = 5$ only *endo* cleavage is detected in the products and mainly *exo* cleavage kinetic product is observed for $n = 6$.

Orientation of the water attack

We propose that in the phosphoramides studied in this work, the acid catalyzed water attack occurs on the conjugated acid form of the reactant. Preliminary[12] molecular mechanics optimizations MM^+ and semiempirical PM3 methods, performed on the phosphoramides acid forms, show that the α conformer is more stable than the corresponding β one. These calculations also show that the five membered phosphoramides are less stable than the six membered conformers. Five membered destabilization is quite well documented[13] for the case of cyclic phosphate esters and is based on the five membered ring strain. This strain is released when one of the phospholidine nitrogens is oriented apical (longer bond) in the trigonal bipyramidal pentacoordinated intermediate (TBP). Therefore, in the five membered ring phosphoramides the water attack must occur orthogonal to the ring nitrogen electron pairs in order to accomplish ring release. In the case of the six membered ring phosphoramides, there is no strain to release but an extra stabilization to gain (*via* SCT) at the transition state, if the water attack occurs *syn* to the cyclic nitrogen electron pairs (Scheme 2). A strong piece of evidence for this water attack orientation, is the fact that in the case of the five membered phosphoramides only endocyclic cleavage hydrolysis product is obtained. Meanwhile, in the case of the six membered ring phosphoramides only exocyclic cleavage kinetic hydrolysis product is observed.

Experimental

Materials

The following compounds were used without further purification: phosphorus oxychloride (Aldrich), ethylphosphonic dichloride (Aldrich), phenylphosphonic dichloride (Aldrich), *N*,*N*′-dimethylethylenediamine (Aldrich), *N*,*N*′-dimethyl-1,3 propanediamine, morpholine (Aldrich), piperidine (Merck), diethylamine (Merck), benzene (Merck), triethylamine (Riedel-de Haen) and chloroacetic acid (Merck).

Synthesis

The general procedure[14] used to synthesize the phosphoramides studied in this work was as follows:

A solution of 10 mmol of the corresponding secondary amine and 10 mmol of triethylamine in 25 ml of dry benzene were added while stirring to a solution of 10 mmol of phosphorus oxychloride in 25 ml of dry benzene. The mixture was kept at room temperature while stirring during two hours and filtered to separate the triethylamine hydrochloride. To the resultant liquid, a solution of 10 mmol of *N*,*N*′-dimethylethylenediamine (or *N*,*N*′-dimethyl-1,3 propanediamine) and 20 mmol of triethylamine in 25 ml of dry benzene were added. The mixture was filtered again to separate the triethylamine hydrochloride and the solvent was evaporated under reduced pressure. The residual was purified using column chromatography packed with Al_2O_3. Chloroform was used as eluent. A colorless liquid that decomposes when heating was finally found. The phospholidines (five membered ring phosphoramides) or phospholines (six membered ring phosphoramides) were characterized using GCMS (Shimadzu GC-17A with a QP-5000 detector), ^{1}H NMR and ^{31}P NMR (Bruker 300 MHz). The yield and the corresponding signals were as follows:

1,3-Dimethyl-2-morpholinyl-1,3,2-diazaphospholidine-2-oxide (M5). Yield: 80–90%. Mass Spectrum: *m*/*z* (rel. intensity %): 219[$M^{\bullet+}$](8), 133(100), 86(49), 44(91), 42(63). ^{1}H NMR($CDCl_3$): δ: 2.55 (6H, d, $J = 9.60$ Hz), 3.10 (8H, m), 3.57 (4H, t, $J = 3.96$ Hz). ^{31}P NMR: ($CDCl_3$) δ 22.71.

1,3-Dimethyl-2-morpholinyl-1,3,2-diazaphospholine-2-oxide (M6). Yield: 31%. Mass Spectrum: *m*/*z* (rel. intensity %): 233 [$M^{\bullet+}$](11), 147(100), 86(23), 44(63), 42(83). ^{1}H NMR($CDCl_3$): δ: 1.75 (2H, m), 2.49 (6H, d, $J = 10.55$ Hz), 3.03 (8H, m), 3.56 (4H, m). ^{31}P NMR: δ 19.93.

1,3-Dimethyl-2-piperidinyl-1,3,2-diazaphospholidine-2-oxide (P5). Yield: 80–90%. Mass Spectrum: *m*/*z* (rel. intensity %): 217[$M^{\bullet+}$](5), 133(20), 84(100), 44(37), 42(29). ^{1}H NMR($CDCl_3$): δ: 1.45 (6H, m), 2.48 (6H, d, $J = 9.80$ Hz), 3.02 (8H, m). ^{31}P NMR ($CDCl_3$): δ 23.46.

1,3-Dimethyl-2-piperidinyl-1,3,2-diazaphospholine-2-oxide (P6). Yield: 59%. Mass Spectrum: *m*/*z* (rel. intensity %): 231[$M^{\bullet+}$](18), 147(40), 84(100), 44(58), 42(73). ^{1}H NMR-($CDCl_3$): δ:1.50 (6H, m), 1.82 (2H, m), 2.63 (10H, m), 2.92(4H, m). ^{31}P NMR ($CDCl_3$): δ 20.63.

1,3-Dimethyl-2-diethylamino-1,3,2-diazaphospholidine-2-oxide (D5). Yield 80–90%. Mass Spectrum: *m*/*z* (rel. intensity %): 205[$M^{\bullet+}$](8), 190(7), 133(98), 72(100), 44(63), 42(55). ^{1}H NMR($CDCl_3$): δ: 1.06 (6H, t, $J = 7.20$ Hz), 2.51 (6H, d, $J = 9.80$ Hz), 3.05 (8H, m). ^{31}P NMR($CDCl_3$): δ: 28.13.

1,3-Dimethyl-2-diethylamino-1,3,2-diazaphospholine-2-oxide (D6). Yield: 32%. Mass Spectrum: *m*/*z* (rel. intensity %): 219[$M^{\bullet+}$](15), 147(100), 72(63), 44(68), 42(82). ^{1}H NMR($CDCl_3$): δ: 1.14 (6H, m), 1.46 (2H, m), 2.59 (6H, m), 2.97 (8H, m). ^{31}P NMR($CDCl_3$): δ: 22.14.

1,3-Dimethyl-2-hydroxy-1,3,2-diazaphospholidine-2-oxide potassium salt (O5). A solution of 0.88 g (1.06 mL, 10 mmol) of *N*,*N*′-dimethylethylenediamine and 2.02 g (2.78 mL, 20 mmol) of triethylamine in 25 ml of dry benzene were added while stirring over a solution of 1.53 g (0.93 mL, 10 mmol) of

phosphorus oxychloride in 25 ml of dry benzene. The reaction mixture was kept at room temperature during two hours while stirring. The liquid was filtered and 2 g (35 mmol) of KOH was added to the liquid while stirring vigorously. After two hours the mixture was extracted with water. The water phase was evaporated under reduced pressure and the solid was suspended in methanol and filtered. The obtained yield is 70%. ^{1}H NMR(D_2O): δ: 2.31 (6H, d, J = 10.50 Hz), 2.81 (4H, d, J = 11.10 Hz). ^{31}P NMR(D_2O/H_2O): δ: 27.86.

1,3-Dimethyl-2-ethyl-1,3,2-diazaphospholidine-2-oxide (E5) and 1,3-dimethyl-2-ethyl-1,3,2-diazaphospholine-2-oxide (E6). According to the general reported[15] procedure, a solution of 1.47 g (1.07 ml, 10 mmol) of ethylphosphonic dichloride in 25 ml of dry benzene were added while stirring to a solution of 10 mmol of *N*,*N*′-dimethylethylenediamine (for **E5**) or *N*,*N*′-dimethyl-1,3-propanediamine (for **E6**) and 2.02 g (0.78 ml, 20 mmol) of triethylamine in 25 ml of dry benzene. The reaction mixture was maintained at room temperature during two hours while stirring. The solid was filtered and the solvent evaporated under reduced pressure. The residual was purified using a column packed with Al_2O_3 and chloroform as eluent. **E5**: Mass Spectrum: *m*/*z* (rel intensity %): 162[$M^{\bullet+}$](22), 134(25), 133(76), 90(98), 44(100), 42(55). ^{1}H NMR($CDCl_3$) δ: 0.84 (3H, dt, J_{HH} = 7.53 Hz, J_{PH} = 19.87 Hz), 1.76 (2H, dq, J_{HH} = 7.26 Hz, J_{PH} = 16.17 Hz), 2.45 (6H, d, J = 9.90 Hz), 2.00 (4H, m). ^{31}P NMR($CDCl_3$): δ: 41.22. **E6**: Yield 83%. *m*/*z* (rel intensity %): 176[$M^{\bullet+}$](15), 147(100), 70(30), 44(69), 42(70). ^{1}H NMR-($CDCl_3$): δ: 0.96 (3H, m), 1.66 (2H, m), 1.70 (2H, m), 2.58 (6H, d), 2.95 (4H, m). ^{31}P NMR($CDCl_3$): δ: 36.65.

1,3-Dimethyl-2-phenyl-1,3,2-diazaphospholidine-2-oxide (Ph5) and 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholine-2-oxide (Ph6). 5 mmol of phenylphosphonic dichloride, were dissolved in 50 ml of dry benzene. This solution was slowly added over a 5 mmol solution of *N*,*N*′-dimethyl-1,3-propanediamine (**Ph6**) or 5 mmol of *N*,*N*′-dimethylethanediamine (**Ph5**) in 10 mmol of triethylamine. After the addition, the reaction was kept stirring for 45 min. The reaction mixture was filtered to separate the triethyl ammonium chloride. To the filtered solution, 20 g of alumina were added and the mixture was kept on stirring for 5 h. The last mixture was filtered and the solution was evaporated on reduced pressure to eliminate benzene. A final yellow liquid was obtained. This liquid was purified using a column packed with alumina and dry chloroform was used as eluent. Compounds were characterized by means of mass spectrometry and NMR (^{31}P and ^{1}H). **Ph5:** Yield 87%. *m*/*z* (rel intensity %): 210[$M^{\bullet+}$](20), 133(40), 77(23), 42(100). ^{1}H NMR($CDCl_3$): δ: 2.56 (6H, m), 4.27 (4H, m), 7.46 (5H, m). ^{31}P NMR($CDCl_3$): δ: 26.80. **Ph6:** Yield 90%. *m*/*z* (rel intensity %): 224[$M^{\bullet+}$](8), 147(19), 77(12), 44(50), 42(100). ^{1}H NMR($CDCl_3$): δ: 1.98 (2H, m), 2.42 (6H, d, J = 14.3 Hz), 3.08 (4H, m), 7.36 (3H, m), 7.65 (2H, m). ^{31}P NMR($CDCl_3$): δ: 32.55.

Kinetics

The hydrolysis kinetics at different pHs were run using chloroacetic–chloroacetate as a buffer. Use of phosphate buffer at pH *ca*. 3, resulted in formation of byproducts that incorporate the buffer to phosphorus.

Each pH was adjusted using a total chloroacetic concentration of 2.0 M. Kinetics were monitored at 24 ± 0.2 °C using ^{31}P NMR (300 MHz Bruker). In a typical run, 125 μL of a solution of 0.25 M phosphoramide or phosphonamide in water was transferred to a NMR tube of 5 mm. To the tube, 500 μl of buffer solution were added and spectra were taken in an interval of 8–60 min (depending on the phosphoramide) using 16 scan/spectrum. A small amount of NaH_2PO_4 was added to the reaction mixture as internal reference. Kinetics were followed by observing the disappearance of the phosphoramide signal. A typical kinetic is shown in Fig. 1 for compound **P5**. The rates constants were directly obtained from a plot of $\ln(I_t - I_{inf.})$ *vs.* time; where I is the ratio (phosphoramide/$H_2P0_4^-$) of ^{31}P NMR signal integrals. Alternatively, kinetics were also followed by UV, using diode array HP instrument following the disappearance of the absorption band at 230–240 nm. Comparison between the rate constants obtained by NMR and UV show a good agreement (*ca*. 5% deviation) between both methods. To test for general acid catalysis the pH was fixed at 3.2 and the [buffer] was varied in an interval from 1.6 to 2.4 M. General acid catalysis was not detected. For the proton inventory,[16] rates of hydrolysis of **M5** were measured at pH = 3.2, using the ^{31}P NMR technique described above. The D_2O fractions used were: 0, 0.1 and 1. The rates as a function of the D_2O fraction (n) show a flat plot in agreement with the equation: $kn = k_H(1 - n + n\phi_{OH})(1 - n + n\phi_{OH}) / (1 - n + n\phi_{OH})$,[2] where ϕ_{OH} = fractionation factor of OH = 1, in agreement with the mechanism shown in Scheme 4.

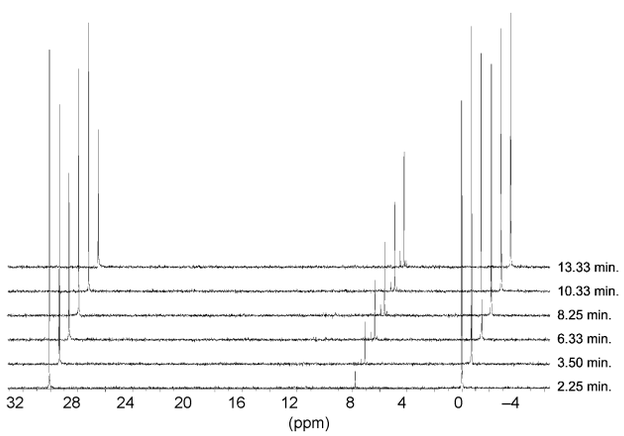


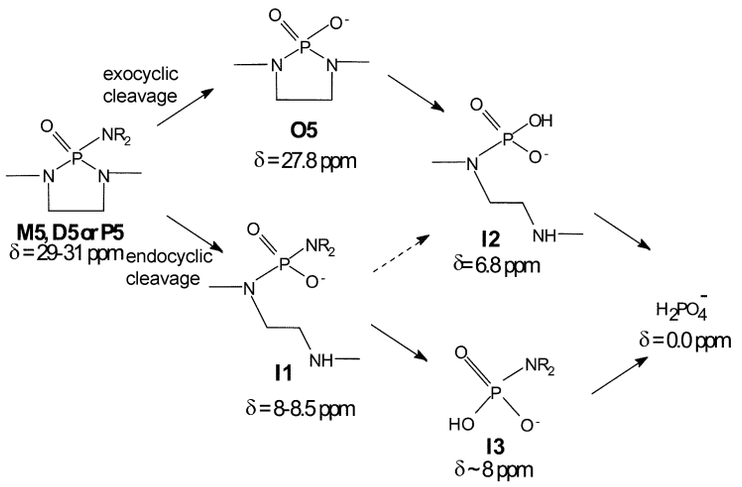
Fig. 1 ^{31}P NMR spectra for the hydrolysis (pH = 3.0) of **P5** at different times. The signals at 30, 8.0, 7.9 and 0.0 ppm correspond to: **P5**, **I1, I3** and H_3PO_4, respectively (see Scheme 3). For the kinetics, the ratio of the signal integrations at 30 ppm and 0 ppm, were used to make the plot: $\ln(I_t - I_{inf})$ *vs.* t.

^{31}P NMR signals assignments

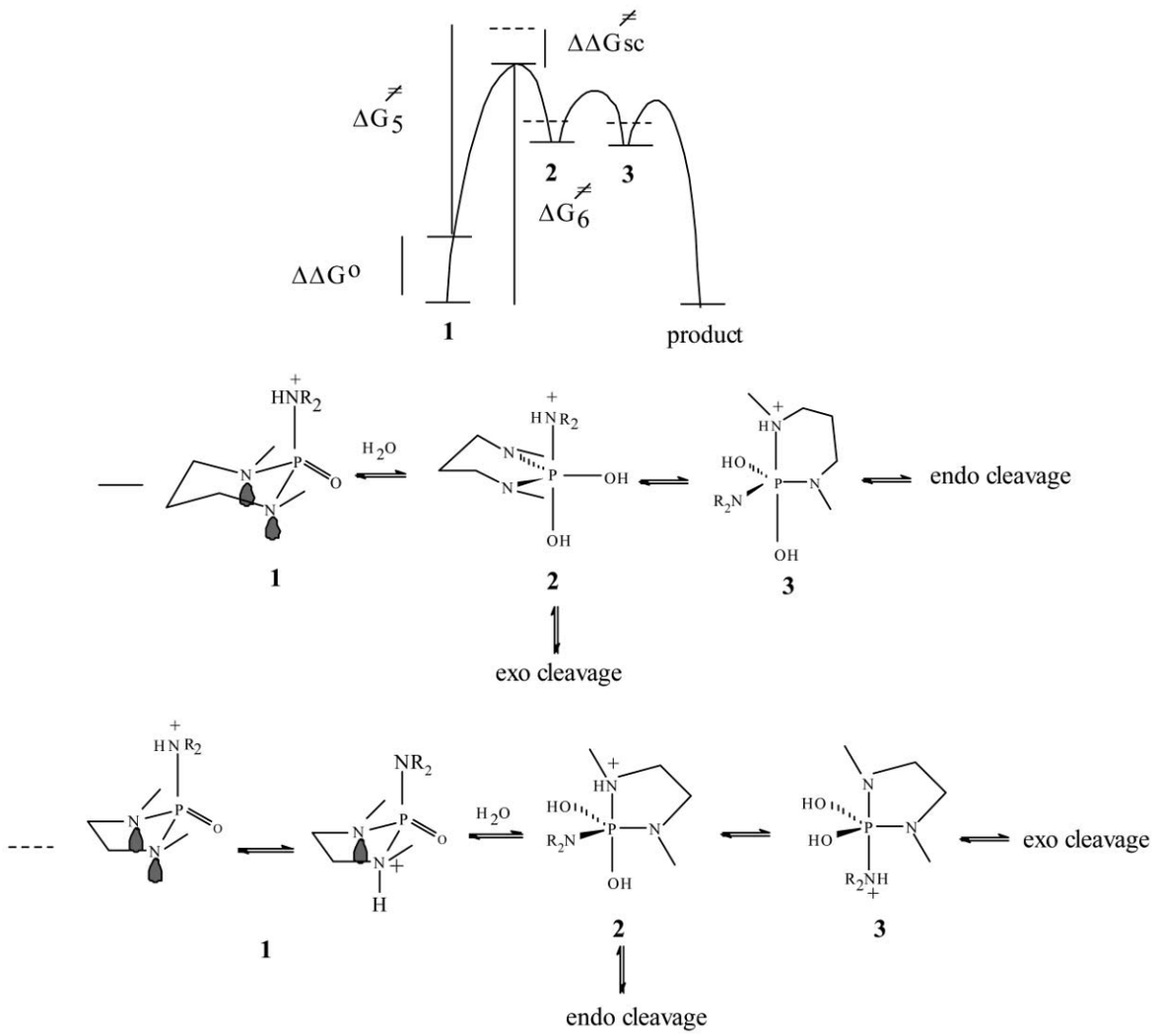
In all cases $H_2PO_4^-$ was used as chemical shift reference at δ = 0.0 ppm.

1,3-Dimethyl-2-hydroxy-1,3,2-diazaphospholidine-2-oxide potassium salt (O5). As expected the hydrolysis of compound **O5** produces signals at 6.8 ppm and 0 ppm, corresponding to aminoamide-phosphoric acid and to phosphoric acid, respectively. The reaction at pH < 4 is very fast and the signal of **O5** cannot be detected after 1 min when the first ^{31}P spectrum is taken. However, the signal at 6.8 ppm can be followed. This signal also disappears rapidly with a $t_{1/2}$ *ca*. 3 min at pH = 3. It is important to recognize that the signal at 6.8 ppm is important for evaluating products ratio in the hydrolysis of the phosphoramides of this work since its intensity measures the amount of exocyclic cleavage (see Scheme 3, *exo* path).

M5, P5 and D5. The ^{31}P NMR signals corresponding to the hydrolysis of the phospholidines **M5, P5** and **D5** are summarized in Scheme 3. Only for compound **M5** exocyclic cleavage is observed (signal at 6.8 ppm). The exocyclic product is compound **O5**. However, its hydrolysis is fast and its ^{31}P NMR signal is not directly observed. What is observed is the signal at 6.8 ppm corresponding to the intermediate **I2** in Scheme 3, that is, the aminoamide-phosphoric acid. As shown in the scheme, the latter compound can also be produced from the endocyclic hydrolysis product intermediate **I1**, the aminoamide phosphoamide. However we have discarded this possibility based on the fact[17] that the endocyclic first intermediate **I1** cleaves further to **I3** faster than its cleavage to **I2**. Therefore, if **I2**



Scheme 3 Hydrolysis products paths and ^{31}P NMR chemical shift for the five membered ring phospholidines.



Scheme 4 Energy diagram and hydrolysis mechanism for the six membered (—) and five membered (- - -) phosphoramides.

is observed, it is formed exclusively *via* exocyclic cleavage. However, according to the experimental results, its formation is also limited compared with the endocyclic cleavage, even though the leaving ability of the morpholine (p*K*a = 8.6[18]) is favored compared to the endocyclic amine departure (p*K*a = 9.9)[18] corresponding to the second p*K*a of *N*,*N*-dimethylethylenediamine.

M6, P6. The hydrolysis products for these two compounds were also followed with time. The signal (^{31}P NMR) corresponding to the intermediate obtained from exocyclic cleavage (equivalent to **I2** in Scheme 3) appears at 7.2 ppm. Meanwhile, the ones corresponding to the equivalent to **I1** intermediate (endocyclic cleavage in Scheme 3) appear at 8.67 ppm (**M6**) and 9.64 ppm (**P6**).

Results and discussion

Product ratio

The acid hydrolysis of **O5**, is quite fast ($t_{½}$ *ca.* 1 min) and it produces only two signals at 6.8 ppm and 0 ppm in the ^{31}P

NMR. These signals correspond to the intermediate **I2** of Scheme 3 and phosphoric acid, respectively. Therefore, **I2** corresponds to the *exo* cyclic product of cleavage. In the hydrolysis of **P5** and **D5**, the signal at *ca*. 6.8 ppm is not detected and a signal at 8–8.2 ppm is observed. We conclude, that for these two compounds only endocyclic cleavage occurs. In the case of **M5**, the signal at 6.8 is observed, but a plot of *exo*/*endo* intensity *vs*. time shows an intercept of 0.03. According to Scheme 3, compound **I2** (with ^{31}P NMR signal at 6.8 ppm) may be produced from **I1**, however we have discarded[17] this possibility. Therefore, the kinetic product for **M5** is also the *endo* product (*endo*/*exo* *ca*. 97%). With these results we can conclude that the hydrolysis of the phospholidines (five membered phosphoramides) produces exclusively endocyclic cleavage kinetic products.

The hydrolysis of the six membered compounds (phospholines) produce ^{31}PNMR signals that resemble the five membered ones shown in Scheme 3. However, for these compounds the kinetic product is the *exo* one instead of the *endo*. As shown in Fig. 2, a plot of *endo*/*exo* intensity *vs*. time for compound **P6** gives an intercept < 0. The results for **M6** are similar to the **P6** ones. However, for **M6** some kinetic *endo* product is detected. This result is unexpected since the p*K*a (8.6[18]) of the exocyclic amine morpholine is quite low when compared to p*K*a (10.7)[18] the first p*K*a of the amine *N*,*N*′-dimethyl-1,3 propanediamine that cleaves *via* endocyclic rupture. Therefore, for **M6**, from consideration of the leaving ability, more exocyclic product as compared to **P6** (with a p*K*a = 11.1 for the *exo* group) is expected. Since the result is the opposite, it is quite probable that the protonation of the amine instead of its leaving ability is what makes the difference. Protonation occurs on the more basic amine (endocyclic nitrogen) and the equilibrium is shifted toward positioning the endocyclic nitrogen in the apical position *via* phosphorus pseudorotation (see Scheme 4) that is promoted based on the apicophilicity[19] that favors the protonated groups at apical position.

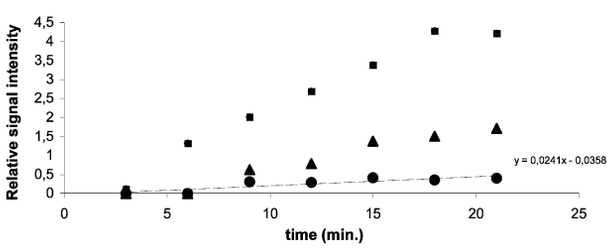


Fig. 2 Relative ^{31}PNMR integration signals *vs*. time for: *exo* product (squares), *endo* product (triangles) and [*endo*]/[*exo*] (circles joined with straight line) for compound **P6** hydrolysis.

From the product ratio measurements *vs*. time it is concluded that in the five membered phospholidines the hydrolysis kinetic product is *endo* and for the six membered phospholines it is *exo*. This provides strong evidence for the water molecule orientation proposal and *syn* orientation catalysis as the main factors controlling the process.

k_{obs} *vs*. pH profile

In Fig. 3, the log k_{obs} *vs*. pH profiles for the hydrolysis of **M5** and **M6** (phosphoramides) are shown. In Fig. 4, the hydrolysis profiles for **Ph5** and **Ph6** (phosphonamides) are also depicted. The solid lines correspond to the best fit to the equation:

$$k_{obs} = k_{H_2O}[H^+]/([H^+] + Ka) + k_{OH^-}K_w/K_a \qquad (1)$$

Where, k_{H_2O}, corresponds to the pseudo first order rate constant for water attack on the conjugated acid of the phosphoramides (or phosphonamides), *K*a is the phosphoramide

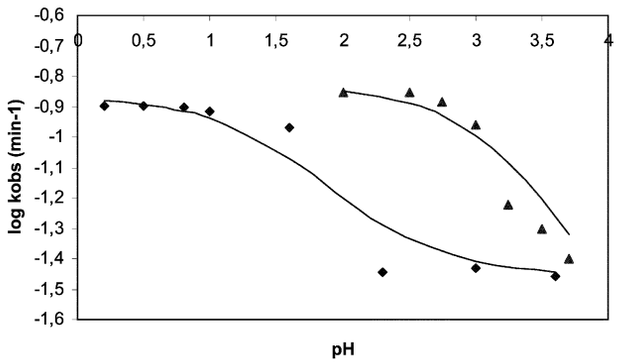


Fig. 3 log k_{obs} *vs*. pH plot for the phosphoramides **M5** (right) and **M6** (left). The solid lines correspond to the best fitting of the experimental points (average k_{obs} values with a uncertainty ≤ 5%) to equation 1. The k'_{H_2O} (high pH leveling) value for **M5** is less reliable than the one for **M6** since it was obtained from extrapolation of the best fitting value.

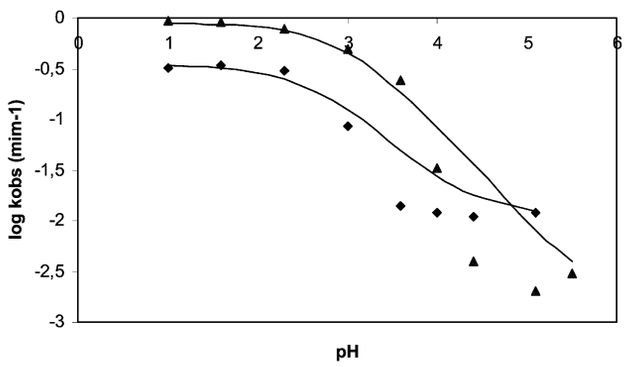


Fig. 4 log k_{obs} *vs*. pH plot for the phosphonamides **Ph5** (top) and **Ph6** (bottom). The solid lines correspond to the best fit of the experimental points (average k_{obs} values with an uncertainty ≤ 5%) to equation 1.

(or phosphonamide) equilibrium acidity constant and k_{OH^-} the second order rate constant of hydroxy attack to the phosphoramide (or phosphonamide) conjugated acid. The second term of the equation is kinetically equivalent to k'_{H_2O}, where this pseudo-first order rate constant corresponds to the water attack on the conjugated base of the phosphoramide (or phosphonamide).

From the described best fit, rate constants and K_a values were obtained. These values are shown in Table 1. In Table 1, the pK_a values titrimetrically obtained are also shown. As shown in Table 1, the titrimetric and kinetic pK_a are in good agreement. It is worth noting that for the phospholines (six membered phosphoramides) the p*K*a values are *ca*. 1–1.5 p*K*a lower than the five membered ones (phospholidines). We attributed this difference to the steric destabilization induced by the axial cation water solvation that switches the acid equilibrium toward its conjugated base in the six membered cycle. The $\Delta\Delta G°$ from this extra destabilization (compared to the five membered analog acidity) is *ca*. 1.7 kcal mol^{-1}.

The k_{H_2O} and k'_{H_2O} ($k_{OH^-}K_w/K_a$) are shown in Table 1 and in Table 2, the $\Delta G_5^{\#} - \Delta G_6^{\#}$ are also shown. These values are negative for water attack on the conjugated acid of the phosphoramides studied (first row of values). However, for the case of water attack on the conjugated base of the phosphoramides, the $\Delta G_5^{\#} - \Delta G_6^{\#}$ values are positive (second row of values), meaning that there is an extra stabilization in the six membered compounds that more than balances the destabilization induced by the ring strain of the five membered cycle. At this point it is important to emphasize that the values (positive or negative) of $\Delta G_5^{\#} - \Delta G_6^{\#}$ are small meaning that there is a small difference in reactivity between the 5- and 6-membered ring systems. When the Table 2 third row values are multiplied by the corresponding K_a and divided by K_w

Table 1 Rate and equilibrium constants obtained experimentally by best fit of the experimental points according to equation: $k_{obs} = k_{H_2O}[H^+]/([H^+] + K_a) + k_{OH^-}K_w/K_a$ (or k'_{H_2O}). The experimental (titrimetrically obtained) pK_a values for the phosphoramides and the corresponding values for the *exo* cyclic amines, are also shown

$n = 5$ five membered $n = 6$ six membered	D	P	M	Ph	E	05
k_{H_2O} (min^{-1}) ± 10%						
$n = 5$	0.030	0.17	0.15	0.90	0.20	> 2.3
$n = 6$	0.050	0.08	0.10	0.34	0.10	
$k_{OH^-}K_w/K_a$ (min^{-1}) ± 5%						
$n = 5$	0.003	0.015	0.020	0.002	0.10	0.1
$n = 6$	0.017	0.050	0.035	0.011	0.07	
k_{OH^-} (min^{-1} M^{-1})						
$n = 5$	3.8×10^8	4.7×10^{10}	2.0×10^9	2.0×10^8	2.0×10^{10}	1×10^{11}
$n = 6$	1.1×10^{11}	2.5×10^{11}	8.7×10^{10}	2.0×10^9	7.0×10^9	
pK_a (kinetic)						
$n = 5$	2.9	2.5	3.0	3.0	2.7	2.0
$n = 6$	1.2	1.3	1.6	2.7	3.0	
ΔΔ$G°$ pK_a	(2.3)	(1.6)	(1.9)			
pK_a (titrimetric)						
$n = 5$	3.2	3.3	3.2	3.0	—	—
$n = 6$	1.4	1.9	1.9	2.7	3.3	
pK_a (*exo* group, as free amine)	10.5	11.1	8.6	—	—	—

Table 2 Kinetic energy barriers difference ($\Delta G^{\#}_5 - \Delta G^{\#}_6$), thermodynamic internal energy difference ($\Delta\Delta G°$ (5–6)) and *syn* stereoelectronic control energy barrier ($\Delta\Delta G^{\#}_{SCT}$) for the water attack on the phosphoramide protonated form $\Delta\Delta G^{\#}$ (k_{H_2O}), for the water attack on the unprotonated phoshoramide $\Delta\Delta G^{\#}$ (k'_{H_2O}) and for the OH^- attack on the protonated phosphoramide $\Delta\Delta G^{\#}$ (k_{OH^-})

kcal mol^{-1}	D	P	M	Ph	E
$\Delta G^{\#}_5 - \Delta G^{\#}_6$ (k_{H_2O}), 25 °C	0.30	−0.45	−0.24	−0.57	−0.41
$\Delta G^{\#}_5 - \Delta G^{\#}_6$ (k'_{H_2O}), 25 °C	1.03	0.71	0.33	1.01	−0.21
$\Delta G^{\#}_5 - \Delta G^{\#}_6$ (k_{OH^-}, 25 °C)	3.34	2.35	2.24	1.41	−0.62
$\Delta\Delta G°$ (5–6) MM+ − PM3					
Protonated	6.5	4.1	5.8	4.4	3.8
Non-protonated	2.8	2.3	1.7	1.2	3.0
$\Delta\Delta G^{\#}_{SCT}$ (k_{H_2O})	6.8 (4.2)[a]	3.6 (2.0)	5.5 (3.6)[a]	3.8	3.4
$\Delta\Delta G^{\#}_{SCT}$ (k'_{H_2O})	3.8	3.0	2.0	2.2	2.8
$\Delta\Delta G^{\#}_{SCT}$ (k_{OH^-})	9.8	6.4	8.0	5.8	3.2

[a] Corrected for axial solvation destabilization (see text)

$$\Delta\Delta G^{\#} = \Delta G^{\#}_5 - \Delta G^{\#}_6 + \Delta\Delta G°$$

($K_w = 1 \times 10^{-14}$ M^2), the second order rate constant for OH^- nucleophilic attack on the protonated phospholidine are obtained.

Proposed mechanism and stereoelectronic control effect (SCT)

In Scheme 4, the energy diagram for the hydrolysis of the five and six membered phosphoramides is shown. The proposed mechanism is also depicted. For the case of the six membered ring phosphoramides (solid line in the energy diagram) the water attack occurs *syn* oriented to the in-ring electron pairs. This *syn* orientation causes a stabilization of the transition state that decreases significantly the reaction $\Delta G^{\#}$ values. Once the pentacoordinated intermediate is formed *exo* cleavage proceeds to yield *exo* product. The intermediate may also pseudorotate to orient one of the phospholine nitrogens to an apical position allowing *endo* cleavage to occur. If phosphorus pseudorotation is slow compared to the **TBP** intermediate cleavage, only kinetic *exo* cleavage product is expected. Only *exo* cleavage will be observed (even if pseudorotation is fast) if for instance, the intermediate **3** of Scheme 4 is too unstable when compared to intermediate **2**. For the five membered phospholidines, proton transfer to one of the phospholidine nitrogens might occur before the water attack (see also dash lines in the energy diagram) that is oriented orthogonal to the in-ring electron pairs to form the **TBP** intermediate that cleaves to yield ***endo*** cleavage hydrolysis product. However, through pseudorotation the intermediate may locate the *exo* group in apical position to yield *exo* cleavage product. As deduced from the energy diagram of Scheme 4, the **SCT** energy contribution can be estimated from the relation: $\Delta\Delta G^{\#}_{SCT} = \Delta G5^{\#} - \Delta G6^{\#} + \Delta\Delta G°$. In Table 2 the values of $\Delta\Delta G^{\#}_{SCT}$ have been obtained from the experimental $\Delta G5^{\#} - \Delta G6^{\#}$ data and from $\Delta\Delta G°$ semiempirical PM3 calculations performed on mechanical MM^+ optimized conformations of the protonated and unprotonated five *vs.* six membered phosphoramides. The first observation worth mentioning, is that the $\Delta\Delta G^{\#}_{SCT}$ values for the mechanism of OH^- attack on the protonated phosphoramides (last row on Table 2) are the highest values obtained. However, lower $\Delta\Delta G^{\#}_{SCT}$ values are expected for this diffusion controlled reaction since it should be less selective. Therefore, this inconsistency in $\Delta\Delta G^{\#}_{SCT}$ allows us to discard this mechanism as the reason for the second leveling observed in the k_{obs} *vs.* pH profile and to propose a kinetically equivalent one that consists of water attack on the unprotonated phosphoramides.

The $\Delta\Delta G^{\#}$ values for the mechanism of water attack on the protonated phospholidine are also high compared to the corresponding attack of the unprotonated phosphoramides. However, these values must be corrected for the destabilization factor (Table 1, four row of data) observed in the reduction of p*K*a for the six membered ring as compared to the five membered ones that is due to axial solvation. This extra destabilization of the six membered ring protonated phosphoramide is not taken into account in the gas phase calculations. This destabilization energy of the protonated six membered ring is 1.5–1.9 kcal mol^{-1} (see Table 1). When the $\Delta\Delta G^{\#}_{SCT}$ data are corrected with these values the obtained **SCT** stabilizations are close to the ones corresponding to the water

attack on the unprotonated phosphoramides. As shown in Table 2, these values are in the range of 2.0–3.8 kcal mol^{-1}. It is also important to note that there is no difference between the $\Delta\Delta G^{\#}_{SCT}$ obtained for the phosphoramides **D**,**P** and **M** and the phosphonamides **Ph** and **E**. This means that the exocyclic electron pair on nitrogen of the phosphoramides does not play an important role on the **SCT** stabilization. As shown in Scheme 4, in the intermediate **2** formed by water attack on the six membered phospholidines there are two electron pairs from nitrogen oriented *syn* to the water molecule and a third electron pair on OH that may be also oriented *syn* to the water. In the case of the intermediate **2** from the five membered ring phospholidine, there is one electron pair on the *exo* amine that may be oriented *syn* to the water and one electron pair on OH that also may be oriented *syn*. Since there is no difference in $\Delta\Delta G^{\#}_{SCT}$ between phosphoramides and phosphonamides, the *exo* amino group in equatorial position of the five membered ring does not contribute to the stabilization of its intermediate **2**, because substitution of the amino for ethyl or phenyl does not influence the estimated $\Delta\Delta G^{\#}_{SCT}$. This is probably due to the entropic destabilization induced by the loss of two of the three bond rotation modes. Finally, we must conclude that the values estimated in this work of *ca*. 3 kcal mol^{-1} correspond to the stabilization of two electron pairs on nitrogen *syn* oriented to an incoming water *vs*. none (the OH electron pair effect is cancelled since it is present in the five and six membered phospholidines) in the formation of HO–P bond.

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