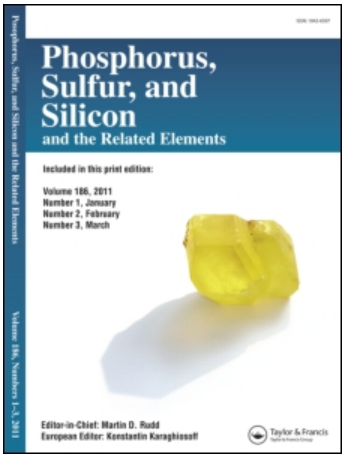

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ACID-CATALYZED HYDROLYSIS OF N-PHENYL PHOSPHORIC AMIDES. KINETIC IMPLICATION OF THE REACTION VIA THE O-PROTONATED INTERMEDIATE

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Rates of the acid-catalyzed hydrolysis of N-phenyl dimethylphosphoramidate, 2-(phenylamino)-2-oxo-1,3,2-dioxaphospholan and 2-ethoxy-2-oxo-3-phenyl-1,3,2-oxazaphospholan, as well as of the corresponding non-cyclic monoester amidates were determined. In cyclic substrates the endocyclic P—O bond is hydrolyzed first, indicating the initial *O*-protonation of the phosphoroamidate function.

The remarkable solvolytic lability of the P—N bond demonstrated by *N*-phosphoryl derivatives under acidic conditions is explained in terms of the mechanism involving the preequilibrium protonation at nitrogen, followed by the $S_N2(P)$ type displacement (Eq. 1).[1]

$$X_2P(O)NR_2 \overset{H^+}{\rightleftharpoons} X_2P(O)NHR_2^+ \xrightarrow{SOH} X_2P(O)OS + R_2NH + H^+ \qquad (1)$$

The *N*-protonation leading to the reactive intermediate with an excellent leaving group present explains the high reactivity of *N*-alkyl phosphinamidates,[2] and was postulated by Hudson *et al.*[3] to occur even in the alkaline media, to account for the observed P—N fission in cyclic phosphoramidates. However, for the *N*-aryl derivatives the basicity of nitrogen should be significantly lower than that of the *N*-alkyl compound, hence the participation of the phosphoryl oxygen protonated form of a conjugate acid in the solvolysis of the former system cannot be excluded. Structure-reactivity correlations in the acid-catalysed hydrolysis of phosphinanilides indicated the *N*-protonated form as a reactive intermediate, but the predominant *O*-protonation was expected for these substrates.[4]

The direct displacement of an amine from the *N*-protonated substrate (Eq. 1) can be tested kinetically by comparing reactivities of the cyclic and noncyclic derivatives. According to Westheimer's theory[5] the P—N cleavage should be subject to steric acceleration in compounds with the P and N atoms incorporated into a five-membered ring, since in the rate-determining TS (or intermediate) the positively charged nitrogen can occupy the apical position, suitable for the departure step.[6] Such an acceleration was indeed demonstrated in the acidic cleavage of *N*-alkyl 1,3,2-oxazaphospholanes.[7]

We wish to report that we have now measured rates of the acid-catalyzed hydrolysis of three phosphoric anilides: *N*-phenyl dimethylphosphoramidate **(1)**, 2-(phenyl-

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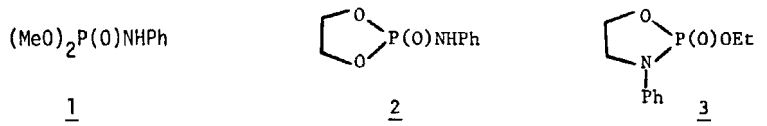
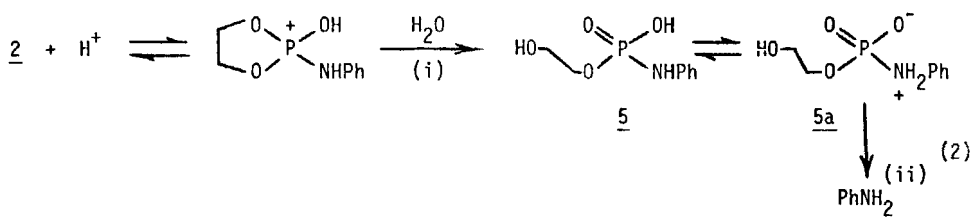
amino)-2-oxo-1,3,2-dioxaphospholan **(2)**, and 2-ethoxy-2-oxo-3-phenyl-1,3,2-oxazaphospholan **(3)**.



1 2 3

According to the mechanism of hydrolysis presented by Eq. 1, reactivity of **(1)** and **(2)** should be similar† and much lower than that of **(3)**, for which the endocyclic location of the nitrogen should give rise to the steric acceleration effect. Contrary to this prediction, both phospholan systems **(2)** and **(3)** react with similar rates, while the acyclic substrate **(1)** is *ca* 10^3 times less reactive (Table 1). In addition, the absorbance vs. time plot for hydrolysis of **(2)** shows the initial increase, followed by the usual decrease to the value characteristic of the released anilinium ion (Figure 1).

We attribute this behavior to the initial fast ring opening reaction via the P—O bond cleavage of the *O*-protonated **(2)** yielding the phosphoramidic acid derivative **(5)** which can then release aniline via its zwitterionic form **(5a)** (Eq. 2).



(2)

We believe that the increase of the absorbance (Figure 1) corresponds to the ring opening step (i), also strongly acid-catalyzed. For the hydrolysis of **(2)** at pH 1.1 and pH 3.0, A_{max} is reached in less than 2 min and after *ca* 3h, respectively. At pH = 2 the rate constant for the P—O bond cleavage (formation of **5**) calculated

TABLE 1

Pseudo first-order rate constants for the hydrolysis of the P—N bond in phosphoramidates at 25°C.[a]

	$10^4 \times k_{obs}$, s^{-1} Substrate					
pH	**1**	**2**[b]	**3**	**4**[c]	**5**[d]	**6**[d]
1.1	0.020	23.5	21.0	1.66	15.4	62.0
2.0	0.0017	1.03	4.1	0.46	1.06	18.8
3.0	—	0.115	0.525	—	0.122	1.8
4.0	—	0.014	—	—	0.017	—

[a] Aq. HCl; $c_{substrate} = 10^{-4}$ M.
[b] Calculated from the right-side section of the *A* vs. time plot.
[c] Tetramethylammonium salt.
[d] Sodium salt.

† For the *N*-tert-butyl analogues of **(1)** and **(2)** the ratio of the P—N bond solvolysis rates in anh. TFA is *ca* 0.5.[8] For *N,N*-dimethyl derivatives the rates ratio with respect to trichloroacetic acid is *ca* 1.6.[7]

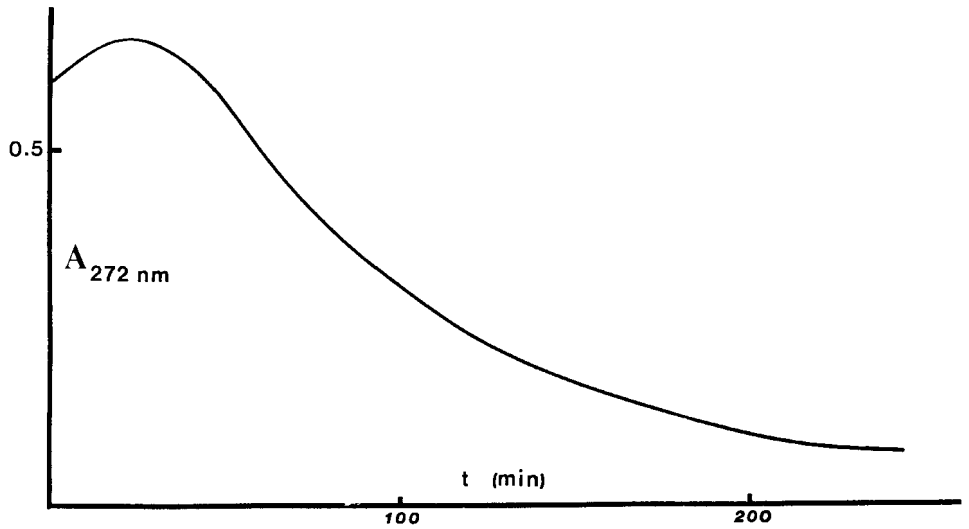
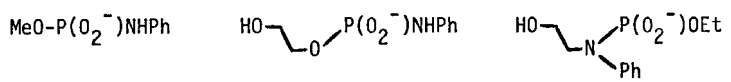


FIGURE 1 Hydrolysis of **(2)** at pH 2, 25°C.

from the first section of the curve is *ca* $2.3 \times 10^{-3}s^{-1}$. After extrapolating to common acidity (log k_{OBS} vs. pH for **(2)** gives straight line with the slope = 1.09; r = 0.992), this value can be compared with the rate of the hydrolysis of the phospholan ring in ethylene phosphate **(7)**.[9] The relative reactivity of the ring in **(2)** and **(7)** is *ca* 20, well in agreement with the expected difference in basicity of these two substrates.†

The P—N bond in **(5)** is expected to be much more reactive than in the neutral diester **(2)**,[1] and the intermediacy of the zwitterions of the type of **(5a)** in hydrolysis of phosphoramidate monoanions has been well established.[13] Rate constants obtained for **(3)** can be explained by the analogous sequence of reactions as in Eq. 2, involving the initial fast cleavage of the endocyclic P—O bond. For the acyclic substrate **(1)** no enhanced reactivity of the ester functions is expected; we have demonstrated (^{1}H NMR) that the ester groups in **(1)** are stable over a period necessary to bring at least 85% of the P—N cleavage. Since the P—N fission via the zwitterion intermediate is in this case not possible, hydrolysis of **(1)** is much slower and follows the "normal" mechanism represented by Eq. 1.

In order to support the conclusion about the initial cleavage of the endocyclic P—O bond in **(2)** and **(3)** (requiring the *O*-protonation of a substrate), followed by the P—N bond fission, we have synthesized salts of the corresponding acidic amidoesters **(4)**, **(5)**, **(6)**, and measured rates of the amide bond hydrolysis in these substrates (Table 1).



4 5 6

† ΔpK_a of phosphinic *N*-alkylamides and esters is *ca* 2.[10] ΔpK_a of *N*-phenyl[11] and *N*-ethyl[12] acetamides is *ca* −0.7; to a first approximation the ΔpK_a for **(2)** and **(7)** should be about 1.3, i.e. k_{rel} about 20.

As expected, reactivity of the amide function in the ring-opened compound **(5)** and its precursor **(2)** is practically identical (av. k_{rel} **(2/5)** = 1.06 ± 0.30), indicating that **(5)** is indeed formed as intermediate in the hydrolysis of **(2)**. The intermediacy of **(5)** is also supported by the UV spectrophotometric properties of the substrates. ϵ_{max} value for the Na salt of **(5)** is indeed greater than ϵ_{max} for **(2)** (at 272–274 nm ϵ_{max} values are 780 and 660, respectively), which explains the initial increase in the absorbance during the hydrolysis of **(2)**.

For substrate **(3)** it was not possible to separate steps (i) and (ii) (Eq. 2) (no initial increase of absorbance); therefore the spectrophotometrically monitored P—N cleavage is delayed (relative to the hydrolysis of **6**) by the ring-opening step. However, the fact that the cyclic compound is slightly *less* reactive than the ring-opened one (av. k_{rel} **(3/6)** = 0.28 ± 0.06) gives the evidence against the mechanism involving direct displacement of the *N*-protonated substrate.

On the other hand, substrate **(4)**, which can react via the mechanism involving zwitterionic species, is more reactive than its noncyclic, neutral precursor by a factor of *ca* 100, similar to that reported for the analogous pair of substrates.[1]

EXPERIMENTAL

Substrates. Anilides **(1)** and **(2)** were prepared from aniline and the corresponding phosphorochloridate in ether and purified by crystallization. **(1)**, mp 83–85°C (from pet. ether). Anal. Calc. for $C_8H_{12}NO_3P$: C, 47.76; H, 6.01; N, 6.96. Found: C, 47.75; H, 5.95; N, 6.9%. **(2)**, mp 108–110°C (from benzene-pet. ether). Anal. Calc. for $C_8H_{10}NO_3P$: C, 48.25; H, 5.06; N, 7.03. Found: C, 48.50; H, 5.10; N, 7.05%. **(3)** was prepared from 2-phenylaminoethanol, ethyl phosphorodichloridate and triethyl amine (two equivalents) in benzene at 40–60°C. After filtering off the triethylammonium chloride the benzene solution was washed with water, dried and evaporated. The remaining dark oily product was purified by column chromatography (silica gel 40, chloroform-acetone, 4:1), yielding the colorless oil, chromatographically pure (TLC). Anal. Calc. for $C_{10}H_{14}NO_3P$: C, 52.86; H, 6.21; N, 6.17. Found: C, 52.05; H, 6.05; N, 6.10%. ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, $J_{H,H}$ = 7.5 Hz, CH_3); 3.64 – 3.90 (2H, m, CH_2N); 4.13 (2H, quint., $J_{H,H}$ = 7.5 Hz; $J_{H,P}$ = 7.0 Hz, CH_2O exocyclic); 4.24 – 4.60 (2H, m, CH_2O endocyclic); 6.86 – 7.40 (5H, m, C_6H_5).

(4) was prepared from **(1)** *by incubating the acetone solution of* **(1)** *with an excess of trimethylamine* for 24 hours at room temp. Crystalline hygroscopic product was filtered off, washed with acetone and dried. Mp 212–216°C. ^{1}H NMR (D_2O): δ 3.19 (12H, s, NMe_4^+); 3.54 (3H, d, $J_{H,P}$ = 11.5 Hz, OCH_3); 6.86 – 7.42 (5H, m, C_6H_5). **(5)** was prepared from **(2)** by incubating the aqueous-dioxane solution of **(2)** with one equivalent of NaOH for 36 hours at room temp. Solvent was removed under reduced pressure and the remaining solid was dried in vacuum over phosphorus pentoxide. Mp 215–217°C. Anal. Calc. for $C_8H_{11}NO_4PNa$: C, 40.17; H, 4.64; N, 5.86. Found: C, 38.55; H, 4.60; N, 5.30%. ^{1}H NMR (D_2O): δ 3.64 (2H, t, $J_{H,H}$ = 5.0 Hz, CH_2OD); 3.80 – 4.00 (2H, m, CH_2OP); 6.84 – 7.41 (5H, m, C_6H_5). **(6)** was prepared from **(3)** in the identical manner as substrate **(5)** from **(2)**. Mp 220–225°C. ^{1}H NMR (D_2O): δ 1.20 (3H, t, $J_{H,H}$ = 7.0 Hz, CH_3); 3.58 – 3.73 (4H, overlapping t and m, NCH_2CH_2O); 3.89 (2H, quint., $J_{H,H} \approx J_{H,P}$ = 7.0 Hz, CH_2 of Et group); 7.08 – 7.31 (5H, m, C_6H_5).

Products determination. P—N cleavage: *ca.* 5×10^{-4} M solutions of substrates **(1)–(6)** were prepared in aqueous hydrochloric acid of pH 1.1, 2.0, 3.0 and 4.0. UV spectra of these solutions were recorded in the range of 220–300 nm, until no further change in a spectrum was observed. The final spectra (corresponding to the complete hydrolysis) were in each case identical with the UV spectrum of solutions containing the same concentration of aniline (for substrates **1, 2, 4, 5**) or N-methyl aniline (for substrates **3** and **6**) in the same medium. P—O cleavage: *ca* 5% solutions of substrates **(1)–(3)** in aqueous hydrochloric acid-acetone-d_6 mixture (1:1) were prepared; the acidity of these solutions was similar to that of solutions used in kinetic measurements. The ^{1}H NMR spectra of these solutions were recorded over periods of time comparable with those of the kinetic runs. The signals of the methyl ester groups of **(1)** (d, $J_{H,P}$ ≈ 11.5 Hz) remained unchanged for up to 300 h, and no signals corresponding to methanol were observed. For cyclic substrates **(2)** and **(3)** signals of the ring methylene groups were replaced fast by signals corresponding to the non-cyclic compounds **(5)** and **(6)**.

Rate measurements. 3.0 ml of aqueous hydrochloric acid of a required pH contained in a 10-mm silica cuvette was maintained at 25.0 (±0.2)°C in a Beckman UV 5260 spectrophotometer with constant temperature water circulating through the sample cell compartment. A solution of the amide in meth-

anol (0.05 ml) was added to give a reaction mixture having substrate's concentration *ca* 5×10^{-4} M. After thorough mixing the decrease in the absorbance with time was continuously monitored at 272–274 nm for a period $\geq 4 \times t_{1/2}$. The value of A_∞ was taken as the absorbance of the reaction mixture after a period $>8 \times t_{1/2}$; this was usually not significantly greater than zero. Plots of ln $(A_t - A_\infty)$ vs. time gave straight lines ($r > 0.999$), from the slopes of which the values of rate constants were taken. Each value of k_{OBS} in the Table is the average of two determinations (reproducible to within ±5%).

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