Solvolysis of Organic Phosphates. VIII. γ-Elimination in the Spontaneous Hydrolysis of 2-Chloro-3-pyridylmethyl Phosphate[1]

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2-Chloro-3-pyridylmethyl phosphate was hydrolyzed in aqueous media. All runs were carried out in a pH range 1—3 where the reactive species are essentially of neutral and monoanion forms. The main reaction product was 3-hydroxymethyl-2-pyridone, the reaction following an apparent first-order kinetics with respect to both pyridone formation and liberation of inorganic phosphate. The hydrolytic elimination of the 2-chlorine atom was catalyzed to a great extent by the phosphate group. The dephosphorylation was effected by the presence of the 2-chlorine atom as well. The hydrolysis of the neutral phosphate species, which is in general inert to hydrolysis, was much accelerated in the present hydrolysis. A plausible mechanism was presented in terms of the concerted elimination of both 2-chlorine atom and phosphate moiety by their mutual catalytic participation. Besides the main reaction process, a normal hydrolysis affording 2-chloro-3-pyridylmethanol was also detected to proceed to a minor extent.

In a series of studies on the hydrolysis of organic phosphates, we have shown some distinct types of neighboring group participation in dephosphorylation processes. Both pyridinium and quinolinium groups were observed to play an intramolecular general acid catalysis in the hydrolysis of 2-pyridylalkyl phosphates[2,3] and 8-quinolyl phosphate,[4] respectively, in their zwitterion forms. A neighboring hydroxyl group acted as a remarkable acid catalyst in the hydrolysis of 3-hydroxy-2-pyridylmethyl phosphate.[5]

The phosphate group occasionally provides a proximity effect on the elimination of another functional group in the molecule. The hydrolytic elimination of β-chlorine in 2,2,2-trichloroethanol was almost inhibited by the presence of a phosphate group, as apparent in the solvolysis study of 2,2,2-trichloroethyl phosphate.[6] This study on the hydrolysis mechanism of 2-chloro-3-pyridylmethyl phosphate provides another type of proximity effect caused by the participation of both γ-chlorine atom and phosphate. These groups located mutually in the neighboring space showed marked catalytic effects in their hydrolytic elimination.

Experimental

Materials. Details of synthesis and purification procedures for 2-chloro-3-pyridylmethyl phosphate are described elsewhere.[7] UV (in 0.02 M-perchloric acid at room temperature): 266 nm (ε 3100) and 273 nm (ε 2800). NMR (0.71 M in DMSO-d_6, TMS as internal reference): δ 5.03 (2H, d, $J_{CH_2-^{31}P}$=8.0 Hz, $-C\underline{H}_2-$), 6.61 (2H, s, $-O\underline{H}$), 7.54 (1H, q, J_{4-5}=7.5 Hz and J_{5-6}=5.0 Hz, H-5), 8.02 (1H, q, J_{4-6}=2.0 Hz, H-4), and 8.46 (1H, q, H-6).

2-Chloro-3-pyridylmethanol was prepared by LAH reduction of methyl 2-chloronicotinate.[7] UV (in 0.02 M-perchloric acid at room temperature): 266 nm (ε 4700) and 273 nm (ε 4400). NMR (0.40 M in DMSO, TMS as internal reference): δ 4.57 (2H, d, J_{CH_2-OH}=4.5 Hz, $-C\underline{H}_2-$), 5.49 (1H, t, $-O\underline{H}$), 7.43 (1H, q, J_{4-5}=7.5 Hz and J_{5-6}= 4.5 Hz, H-5), 7.95 (1H, q, J_{4-6}=2.0 Hz, H-4), and 8.19 (1H, broad d, H-6).

3-Hydroxymethyl-2-pyridone was synthesized through diazotization of 2-amino-3-hydroxymethylpyridine followed by hydrolysis.[7] UV (in 0.02 M-perchloric acid at room temperature): 228 nm (ε 5300) and 297 nm (ε 5140). IR (0.2 M in 0.1 M-deuteroperchloric acid): 1640 cm^{-1} (C=O). NMR (0.40 M in DMSO, TMS as internal reference): δ 4.28 (2H, broad s, $-C\underline{H}_2-$), 4.91 (1H, broad s, $-O\underline{H}$), 6.17 (1H, t, $J_{4-5}=J_{5-6}$=6.5 Hz, H-5), 7.22 (1H, broad q, J_{4-6}= 1.5 Hz, H-4), and 7.38 (1H, broad d, H-6).

Acid Dissociation Constants. The acid dissociation constants of the phosphate were obtained by the usual potentiometric titration.[2] The values found for pK_{H_2A} and pK_{HA} were 1.8 and 6.3 at 80 °C, and 2.17 and 5.97 at 25 °C, respectively, an ionic strength being maintained at 0.10 with potassium nitrate. The neutralization equivalence was 106.68 and 108.90 (calcd. 111.77) at 80 and 25 °C, respectively. The values of acid dissociation constants at elevated temperature were not sufficiently reproducible, especially for pK_{H_2A}. This was most likely caused by a trace hydrolysis of the phosphate during the course of titration to give off hydrochloric acid.

Product Analyses. The chromatographic solvent used was a mixture of *n*-propanol, concentrated aqueous ammonia, and water (6 : 3 : 1 by vol.). An acid molybdate spray reagent[8] was used for detection of phosphorus-containing spots. Paper chromatography and tlc were carried out with Toyo Roshi No. 50 filter paper and Tokyo Kasei spot film (silica gel), respectively, in combination with the above solvent and developing reagent. The R_f-values found for inorganic phosphate and 2-chloro-3-pyridylmethyl phosphate were $\approx$0.0 and 0.34, respectively, by paper chromatography, and 0.0 and 0.45 by tlc.

(i) A 2.02×10^{-3} M aqueous solution of 2-chrolo-3-pyridylmethyl phosphate was hydrolyzed in a sealed pyrex tube for 10.5 hr at 90 °C and pH 1.0 with an ionic strength of 0.10 ($HClO_4$). At the end the conversion was 30.0%, calculated from the determination of liberated inorganic phosphate. UV spectrum of the resulting hydrolyzate indicated the formation of 2-chloro-3-pyridylmethanol and 3-hydroxymethyl-2-pyridone (Fig. 1). No other organic phosphorus compounds besides the starting phosphate were

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[1] Contribution No. 278 from this Department.

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[3] Y. Murakami, J. Sunamoto, and N. Kanamoto, This Bulletin, **46**, 871 (1973).

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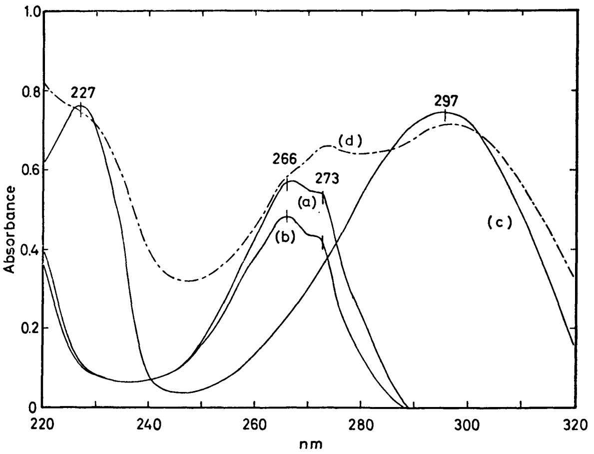


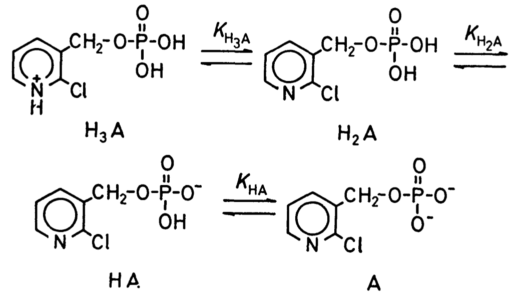
Fig. 1. Ultraviolet absorption spectra in 0.02 M-perchloric acid: (a) 2-chloro-3-pyridylmethyl phosphate, 1.58×10^{-4} M; (b) 2-chloro-3-pyridylmethanol, 1.26×10^{-4} M; (c) 3-hydroxymethyl-2-pyridone, 1.44×10^{-4} M; (d) the hydrolyzate of 2-chloro-3-pyridylmethyl phosphate, the initial phosphate solution of 0.103 M was treated at 90 °C and $-\log[H^+]=1.0$ for 23 hr and diluted 5/3 times for measurement.

detected by means of paper and thin layer chromatographic techniques. (ii) A 0.103 M 2-chloro-3-pyridylmethyl phosphate solution in 0.1 M-deuteroperchloric acid was placed in a sealed Pyrex tube and allowed to stand for 23 hr at 90 °C. White precipitates formed were removed by filtration and the filtrate was subjected to IR measurement. The absorption band attributable to the carbonyl stretching mode was weak but observable at 1640 cm^{-1}. The white precipitates formed was identified as 3-hydroxymethyl-2-pyridone by tlc with the use of UV light for detection, R_f 0.65. A 0.196 M solution of 2-chloro-3-pyridylmethanol in 0.1 M-deuteroperchloric acid was treated under the same conditions. However, significant transformation of this alcohol was not detected by any analytical method. (iii) 2-Chloro-3-pyridylmethyl phosphate (47.32 mg) was dissolved in DMSO-d_6 (0.30 ml) containing 10 μl of deuterium oxide, placed in a sealed Pyrex tube and kept at 95 °C for 21 hr. The reaction was followed by NMR with TMS as an internal reference. A doublet signal of the methylene protons in the starting phosphate gradually decreased, whereas a singlet signal assignable to the methylene protons of 2-chloro-3-pyridylmethanol increased in intensity. Another signal due to the methylene protons appeared at 4.28 ppm and increased markedly in intensity with the progress of reaction. This signal was assigned to the methylene protons in 3-hydroxymethyl-2-pyridone with the aid of an authentic sample. No other methylene signal of a doublet nature was detected throughout the reaction. After 4 hr of the reaction period, a white crystalline mass (the pyridone) started to precipitate. The yield of the pyridone was approximately 90% at the end of the reaction.

Kinetic Procedures. The experimental and analytical procedures were essentially the same as those employed for the hydrolysis studies of 2-pyrdidylalkyl phosphates at higher temperature.[3] All runs were carried out in aqueous media at 90.0±0.1 °C with an ionic strength of 0.10 ($HClO_4$–$NaClO_4$) over the $-\log[H^+]$ range 1.0—3.0, where the phosphate exists in three forms, cation, neutral, and monoanion. The pH-deviation did not exceed ±0.02 during the course of reaction. The hydrolytic decomposition of the phosphate was followed by determination of the liberated inorganic phosphate.[2-5] The formation of 3-hydroxymethyl-2-pyridone was measured spectrophotometrically at 297 nm.

Results and Discussion

Acid Dissociation Process. The second acid dissociation constant found for the present phosphate ($pK_{H_2A}\approx2$) was comparatively smaller than those for the other pyridylalkyl phosphates (pK_{H_2A} 4-5).[2-6] Brown and McDaniel obtained spectrophotometrically the pK_a-values of chloropyridines in aqueous system at 25 °C; 0.72 for the 2-isomer and 2.84 for the 3-isomer.[9] The pK_a-values for dissociation of a pyridinium proton in pyridine[10] and 3-pyridylmethyl phosphate[11] are 5.45 and 4.86 at 25 °C, respectively. The phosphorylated hydroxymethyl group apparently tends to act as an electron-withdrawing substituent to some extent. Thus, the pK_a-value for dissociation of a pyridinium proton in the present phosphate should be less than that for 2-chloropyridine. The most plausible acid dissociation process is presented in Scheme 1. An intramolecular hydrogen bonding of the phosphate moiety with the chlorine atom may cause the trapping of the phosphate proton, and consequently the pK_{H_2A}-value may become a little larger than that of ordinary alkyl phosphates.



Scheme 1.

Reaction Mechanisms. We may conclude from product analyses that 2-chloro-3-pyridylmethyl phosphate undergoes hydrolytic decomposition to afford 3-hydroxymethyl-2-pyridone as the major product

TABLE 1. APPARENT FIRST-ORDER RATE CONSTANTS FOR THE SPONTANEOUS HYDROLYSIS OF 2-CHLORO-3-PYRIDYLMETHYL PHOSPHATE; OBTAINED FROM THE ANALYSIS OF INORGANIC PHOSPHATE AT 90.0±0.1°C AND $\mu=0.10$

$-\log[H^+]$	$10^5\times k_{P_i}$, sec^{-1}	$-\log[H^+]$	$10^5\times k_{P_i}$, sec^{-1}
1.01	0.85	1.92	0.72
1.14	0.83	2.15	0.68
1.83	0.73	2.26	0.59
1.91	0.70	2.82	0.57

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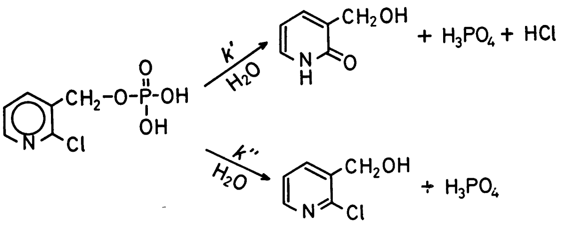
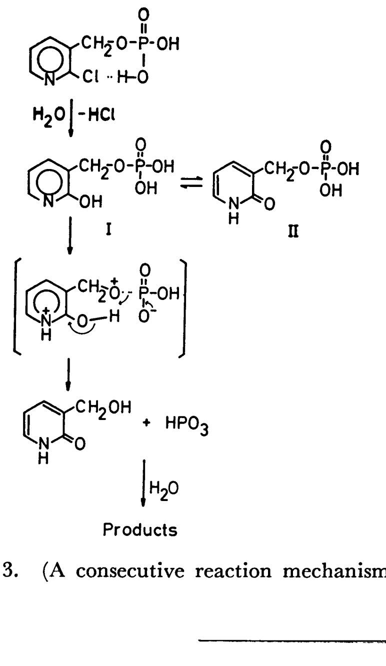
along with a small amount of 2-chloro-3-pyridylmethanol. The apparent first-order rate constants obtained from analysis of the liberated inorganic phosphate are listed in Table 1. A good first-order kinetics was also established for the pyridone formation. The rate constants obtained by both methods were almost comparable: for example, $k_{\mathrm{P}_i}=1.02\times10^{-5}$ sec^{-1} for the liberation of inorganic phosphate and $k'=0.93\times10^{-5}$ sec^{-1} for the formation of the pyridone at 90.7±0.1 °C and $-\log[\mathrm{H}^+]=1.0$ with an ionic strength of 0.10 ($\mathrm{HClO_4}$). The difference between these two rate constants is significant since the presence of a small amount of 2-chloro-3-pyridylmethanol, the normal hydrolysis product, was no doubt detected by NMR. Thus, the whole reaction scheme consists of two competitive reactions as shown in Scheme 2. One may provide two possible mechanisms for the pyridone formation process; consecutive (Scheme 3) and concerted bimolecular (Scheme 4). Although other organic phosphates besides the starting one could not be detected in the course of hydrolysis reaction, we would not completely eliminate the possible formation of 2-hydroxy-3-pyridylmethyl phosphate (I or its keto-isomer, 1,2-dihydro-2-oxo-3-pyridylmethyl phosphate, II) as a labile intermediate in the pathway to the pyridone formation.

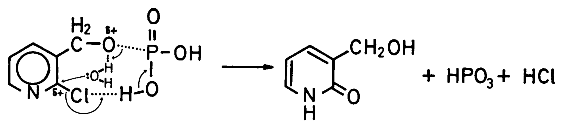
The neighboring acidic phosphate moiety seems to promote the elimination of the γ-chlorine atom through the intramolecular Cl···H···O hydrogen bonding. Examination by the Dreiding-type model (Fig. 2) shows that the chlorine atom and the phosphate hydroxyl group can be favorably oriented in space to form a linear hydrogen bonding with the preferential orbital direction.



Scheme 2.



Scheme 3. (A consecutive reaction mechanism).



Scheme 4. (A concerted bimolecular mechanism).

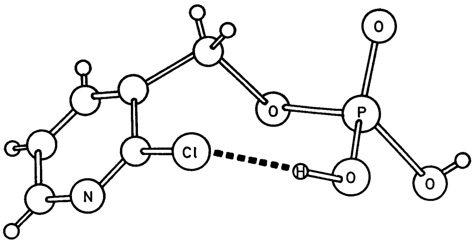


Fig. 2. Stereoview of the molecular configuration and the geometry for intramolecular hydrogen bonding between the chlorine atom and the phosphate moiety in 2-chloro-3-pyridylmethyl dihydrogen phosphate.

Using pK_a-values evaluated at 80 °C for each ionic species of the present phosphate[12] and the observed rate constants listed in Table 1, we calculated the apparent specific rate constants for the hydrolysis according to the usual computation procedures;[2-5] $k_{\mathrm{H_2A}}=1.0\times10^{-5}$ and $k_{\mathrm{HA}}=0.5\times10^{-5}$ sec^{-1} at 90 °C. It is well-known that the neutral alkyl dihydrogen phosphates are in general very inert to hydrolysis.[13,14] The hydrolysis rate constants for the neutral species of methyl and ethyl phosphates, for example, are 0.5×10^{-6}[13] and 0.7×10^{-6} sec^{-1}[14] at 100 °C, respectively. The hydrolysis reaction of the present neutral phosphate species, mainly giving rise to pyridone formation, was apparently much accelerated relative to the hydrolysis of those alkyl phosphates. The profound rate enhancement for the neutral phosphate hydrolysis can not be explained only by the usual electronic effect brought about by the 2-chloropyridyl group, but can be attributed to direct participation of the chlorine atom at the dephosphorylation site.

In conclusion, 2-chloro-3-pyridylmethyl phosphate was hydrolyzed primarily to afford the pyridone by the mutual participation of the chlorine atom and the phosphate group (Scheme 4).

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12) The p$K_{\mathrm{H_3A}}$-value for dissociation of the pyridinium proton was estimated to be 0.7 in reference to the value for 2-chloropyridine.[9] Care was taken to minimize the possible error in each specific rate constant caused by this estimation.

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