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SOLVOLYSIS OF ORGANIC PHOSPHATES. VII. SPONTANEOUS HYDROLYSIS OF 2,2,2-TRICHLOROETHYL PHOSPHATE[1)]

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The spontaneous hydrolysis of 2,2,2-trichloroethyl phosphate was investigated at 90°C in aqueous media with an ionic strength of 0.10 (KNO_3) over pH 3-5. The reaction followed apparent first-order kinetics with respect to the phosphate species. Trichloroethanol once produced during the reaction was further hydrolyzed with the liberation of hydrochloric acid. However, the liberation of hydrochloric acid has never been detected unless the phosphate was hydrolyzed. No significant participation of the neighboring β-chlorine atom was observed in the phosphate hydrolysis.

In order to establish a structure-reactivity relationship for the hydrolyses of alkyl phosphates in their monoanion forms, we have extensively studied the hydrolyses of various organic orthophosphates, including especially pyridylalkyl phosphates, from mechanistic and kinetic view points.[2~5)] For further contribution to this series of work, we investigated in this work the hydrolysis of 2,2,2-trichloroethyl phosphate[6)] in aqueous media to examine a participation of neighboring β-chlorine atom in the hydrolysis. Meanwhile, it has been demonstrated that trichloroethyl phosphate acted as a hypnotic, where the phosphate was rapidly hydrolyzed by phosphatase in the body affording trichloroethanol, one of the most effective and safe hypnotics.[7,8)] From the present investigation, therefore, one may also obtain a useful information about its pharmacological properties.

When trichloroethyl phosphate (2×10^{-3}M) was hydrolyzed in aqueous media at 90°C and pH 3 for 5hr, hydrochloric acid was certainly liberated along with inorganic phosphate. The former was detected by the precipitation of silver chloride with aqueous silver nitrate solution and by the pH-depression during the course of run, while the latter was determined by development of the molybdenum blue according to the Allen's method. When the reaction was carried out under similar condition at 71°C for 4hr, however, the liberation of neither inorganic phosphate nor hydrochloric acid was detected. On the other hand, trichloroethanol being in contact with water underwent relatively rapid formation of hydrochloric acid even at room temperature. Above two reactions were then carried out in both deuterium oxide and d_6-DMSO containing a small amount of deuterium oxide, and followed by nmr measurements. In the hydrolysis of trichloroethyl phosphate (0.2M in D_2O) at 90°C for 23hr, only two distinct methylene signals were observed. One of them was attributable to the methylene protons of the unreacted phosphate, appearing at 1.33 ppm (TMAC, internal standard) as an doublet due to coupling with ^{31}P. The other was due to those of the produced alcohol, being observed at 1.03 ppm as a singlet signal. The latter signal was entirely identical with that of the reaction product of trichloroethanol with water or deuterium oxide. No other proton peaks such as an olefin- or aldehyde-proton were observed under the present conditions. Therefore, it seems most reasonable to assume that the liberation of hydrochloric acid occurred upon hydrolysis of trichloroethanol which was the hydrolyzate of trichloroethyl phosphate. As a result, the formation of hydrochloric acid never proceeds prior to the primary hydrolysis of trichloroethyl phosphate. Although we have no conclusive evidence for the structure of an alcohol produced in the final reaction step, the nmr suggests the formation of 2,2-dichloroethyleneglycol.

On the basis of the preceding results, the kinetic study on the hydrolysis of 2,2,2-trichloroethyl phosphate was carried out at 90°C in aqueous media with an ionic strength of 0.10 over the $-\log[H^+]$ range from 3.0 to 5.0, where the major fraction of the phosphate was in the monoanion form. The procedures for kinetic measurements and calculations of kinetic parameters were the same as those described previously.[2~5] The results are listed in Table 1. The first-order specific rate constant for the monoanion hydrolysis (k_{HA}) and the second acid dissociation constant of the phosphate (pK_{HA}) are 2.18×10^{-5} sec^{-1} and 5.95 at 90°C, respectively, both being calculated by the dynamic method as described previously.[3~5] Meanwhile, the pK_{HA}-value obtained by potentiometric titration at

Table 1. Spontaneous hydrolysis of 2,2,2-trichloroethyl phosphate at 90.0±0.1°C and μ=0.10 (KNO_3)

$-\mathrm{Log}[H^+]$	3.01	3.92	3.95	4.92	4.95
$10^5 \times k_{obs}$, sec^{-1}	2.18	2.23	2.20	2.11	2.04

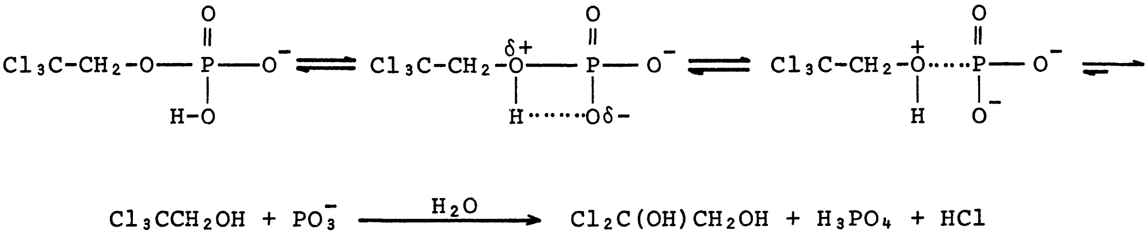
80°C and μ=0.10 (KNO_3) is 6.14. If one consider the temperature dependency of this dissociation constant the agreement between both pK_{HA}-values seems to be satisfactory.

In the LFER studies independently investigated by us, a linear relationship (1) has been established for the hydrolysis of alkyl phosphate monoanions at 90°C by employing the second acid dissociation constant of the phosphate moiety (at 80°-90°C) as a structural parameter.

$$\log k_{HA} \text{ (at 90°C, sec}^{-1}\text{)} = 2.87 - 1.27pK_{HA} \text{ (at 80°-90°C)} \qquad (1)$$

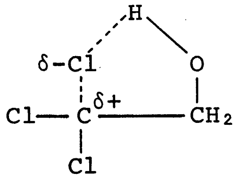
Application of the above equation to the hydrolysis of 2,2,2-trichloroethyl phosphate leads to provide a predicted value of $\log k_{HA}$ -4.69: the pK_{HA} employed in this calculation is 5.95. The experimental $\log k_{HA}$ value was -4.66. A good agreement between predicted and experimental values suggests that no unusual electronic or steric effect are operational in the hydrolysis of 2,2,2-trichloroethyl phosphate monoanion.

As a result, the most plausible mechanistic process is illustrated in Scheme 1, where the pre-equilibrium protonation from the phosphate moiety to the ester oxygen atom takes place, followed by the unimolecular P-O bond cleavage.



Scheme 1

An early work of Heine and his co-workers suggested that no cyclic intermediate participated in the hydrolyses of ethylene and trimethylene chlorohydrins on the basis of activation entropy values, and that a S_N2 mechanism with water accounted for the hydrolysis reaction.[9] If this is the case in the hydrolysis of trichloroethanol, the replacement of the alcohol group of trichloroethanol by a phosphate moiety would increase the hydrolysis rate due to the electron-withdrawing effect of the phosphate group. Contrary to what would be expected, the rate of hydrolysis of the present phosphate decreased markedly compared to that of trichloroethanol. This fact suggests that the hydroxyl group would participate in the formation of the transition state through the cyclic intermediate I in the hydrolysis of trichloroethanol. Such a proximity effect seems to accelerate the reaction rate.



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6) 2,2,2-Trichloroethyl phosphate: mp 112-113°C. Found: C, 10.54; H, 1.93%. Calcd for $C_2H_4O_4PCl_3$: C, 10.47; H, 1.76%. IR (KBr disk): ν_{OH}, 3400 and 3000-2700cm^{-1}; $\nu_{P=O}$, 1250 and 1120cm^{-1}; $\nu_{P-O-C(alk)}$, 1040, 960, and 945cm^{-1}; ν_{C-Cl}, 775 and 715cm^{-1}.

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