

Determination of Rate Constants of Hydrolysis by a Distribution Technique and its Application to *iso*Propoxy-methyl-phosphoryl Chloride

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An improved formula¹ for the determination of the distribution constant of a compound reacting with one of the phases according to a first order reaction is given. Based on this formula a method for the study of rapid hydrolyses is described. The application of the method is illustrated by the determination of the rate of the hydrolysis of *isopropoxy-methyl-phosphoryl chloride*, and its relationship to that of the corresponding fluorine derivative (Sarin) is discussed.

In an earlier paper¹ the author has deduced the following formula for the calculation of the distribution constant of a compound which reacts with one of the phases according to a first order or a pseudo-first order reaction:

$$\ln [A]_{\text{aq}} = - \frac{k \cdot t}{\frac{v_{\text{org}}}{v_{\text{aq}}} k_d + 1} + C \quad (1)$$

where $[A]_{\text{aq}}$ = concentration of unhydrolysed compound in the aqueous phase;

C = integration constant;

k = reaction rate constant of A in water;

k_d = distribution constant of A between organic and aqueous phase;

t = time;

v = phase volume.

By plotting $\log [A]_{\text{aq}}$ against t a straight line is obtained the slope of which, α , is

$$|\alpha| = \frac{0.4343 k}{\frac{v_{\text{org}}}{v_{\text{aq}}} k_d + 1} \quad (2)$$

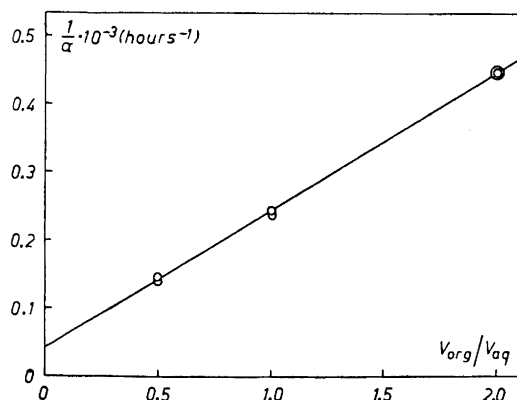


Fig. 1. The reciprocal of the rate of the hydrolysis of 2-methoxy-ethyl nicotinate at various ratios of xylene and water.

The application of the formula was illustrated by the determination of the distribution constant of the ester 2-methoxy-ethyl nicotinate between xylene and water. The rate constant of the hydrolysis was determined in a separate experiment. However, both the rate constant and the distribution constant can be determined simultaneously from a series of experiments where the ratios of the phase volumes are varied. If eqn. (2) is rearranged to

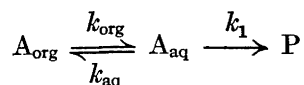
$$\frac{1}{|\alpha|} = \frac{k_d}{0.4343 k} \cdot \frac{v_{\text{org}}}{v_{\text{aq}}} + \frac{1}{0.4343 k} \quad (3)$$

it appears that a straight line is obtained when $1/|\alpha|$ is plotted against $v_{\text{org}}/v_{\text{aq}}$. The rate constant, k , is thus obtained from the intercept of the ordinate and the distribution constant, k_d , from the slope of the line. This is illustrated in Fig. 1 by the example given in the previous paper¹. As shown in Table 1, k and k_d determined in this way agree well with earlier results.

Table 1. The rate constant of the hydrolysis of 2-methoxy-ethyl nicotinate and its distribution constant between xylene and water.

	According to	
	eqn. (3)	previous paper ¹
k hours ⁻¹	5.36×10^{-2}	5.07×10^{-2}
k_d	4.67	4.28

The problem can also be considered as a consecutive reaction *i.e.*:



where P is a hydrolysis product. If this system is treated according to the improved steady-state approximation given by McDaniel and Smoot², and $k_{\text{aq}}/k_{\text{org}} = k_d$, then

$$\ln [A]_{\text{aq}} = - \frac{k_1 \cdot t}{\frac{v_{\text{org}}}{v_{\text{aq}}} \left(k_d + \frac{k_1}{k_{\text{org}}} \right) + 1} + C \quad (4)$$

If $k_{\text{org}} \gg k_1$ which is the case in slow reactions, eqn. (4) is reduced to eqn. (1). In rapid reactions none of the constants can be neglected and we get, analogously to eqn. (3)

$$\frac{1}{|a|} = \frac{1}{0.4343} \left(\frac{k_d}{k_1} + \frac{1}{k_{\text{org}}} \right) \cdot \frac{v_{\text{org}}}{v_{\text{aq}}} + \frac{1}{0.4343 k_1} \quad (5)$$

Obviously from this equation, k_1 can be determined, by plotting $1/|a|$ against $v_{\text{org}}/v_{\text{aq}}$; k_d , however, cannot be determined, because it is not possible to estimate k_{org} .

The distribution technique is particularly suitable for studies of rapid hydrolysis. The diminished rate due to the inert phase added permits measurements of reactions which in aqueous solutions run too fast for accurate determinations. The technique was therefore used in the determination of the rate constant of the hydrolysis of *isopropoxy-methyl-phosphoryl chloride*. The study of this hydrolysis forms part of an investigation of the influence of the substituents on the rate of hydrolysis of Sarin analogues³. *Isopropoxy-methyl-phosphoryl chloride* is assumed to hydrolyse according to a first-order reaction when the pH is maintained constant, and eqn. (5) is thus valid.

EXPERIMENTAL

Materials: *Isopropoxy-methyl-phosphoryl chloride* was synthesized by reacting methyl-phosphoryl dichloride⁴ with *isopropanol*, and was freshly distilled before use. B.p. 51°C/4 mm Hg; n_D^{25} 1.4275; d_4^{25} 1.140.

Chloroform: E. Merck; anal. reagent.

Procedure: The rate of the hydrolysis of *isopropoxy-methyl-phosphoryl chloride* during the distribution between chloroform and a 0.100 M solution of potassium chloride was studied at pH 7.00 and 25.0°C. The pH was maintained constant by means of an automatic recording titrator⁵ which was standardized before each run against a 0.05 M solution of potassium hydrogen *o*-phthalate (pH 4.01). A constant temperature, circulating water bath maintained the jacketed reaction vessel at $\pm 0.1^\circ\text{C}$ or better.

A 0.80 mM stock solution of the compound in dry chloroform was prepared. Experiments were performed with four different ratios of the volumes of chloroform solution to aqueous solution as shown in Table 2. The total volume of each sample was 40 ml.

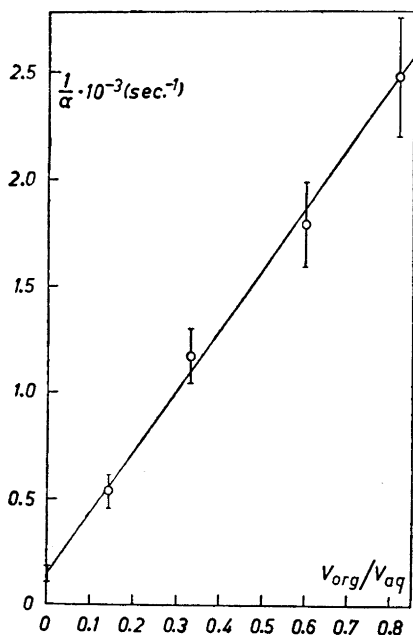


Fig. 2. The reciprocal of the rate of the hydrolysis of *isopropoxy-methyl-phosphoryl chloride* at various ratios of chloroform and water.

Table 2. Ratio of the volumes of chloroform solution to aqueous solution.

$v_{\text{org}} / v_{\text{aq}}$	5 : 35	10 : 30	15 : 25	18 : 22
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The aqueous solution was in advance adjusted to the desired pH. The addition of pure chloroform to the aqueous solution has no influence upon pH. Each set of experiment was repeated five times. Some difficulties arose in getting a suitable speed of the magnetic stirrer. Too rapid stirring caused great fluctuations of pH during the run owing to chloroform splashing over the electrodes and shielding them. On the other hand slow stirring did not permit equilibrium to be attained. With a few exceptions the variations of pH during the runs were ± 0.1 or less. The products formed in the hydrolysis, hydrochloric acid and *isopropoxy-methyl-hydroxy-phosphine oxide*, are assumed to be completely soluble in the aqueous phase at the actual pH. The curves obtained were treated according to Guggenheim⁶. Straight lines were obtained the slopes of which were calculated. The straight lines indicate that no appreciable association did occur in the chloroform phase¹.

RESULTS AND DISCUSSION

When $1/|\alpha|$ is plotted against $v_{\text{org}}/v_{\text{aq}}$ for the hydrolysis of *isopropoxy-methyl-phosphoryl chloride* in various ratios of chloroform and water at pH 7.00 a straight line is obtained as shown in Fig. 2. The equation of the line was calculated by the method of least squares with weighted values (9:5:2:1). The intercept of the ordinate of the line was found to be $(0.151 \pm$

$0.041) \times 10^3$ which corresponds to a rate constant of the hydrolysis of $(1.5 \pm 0.4) \times 10^{-2} \text{ sec.}^{-1}$.

If it is assumed that the rate of the hydrolysis of isopropoxy-methylphosphoryl chloride is proportional only to the hydroxyl ion concentration as is valid for Sarin ³, the bimolecular rate constant, k_2 , would be $1.2 \times 10^5 \text{ l mole}^{-1} \text{ sec.}^{-1}$, *i.e.* 5×10^3 times greater than that of the fluorine derivative (Sarin). Because of the greater electronegativity of fluorine which makes the phosphorus atom more electron deficient and positive, the formation of the P-OH bond is facilitated more in the fluorine than in the chlorine compound. By using Pauling's values of electronegativity of P, Cl and F a rough calculation according to Hannay and Smyth ⁷ shows that the P-F and P-Cl bonds are 43 and 17 % ionic, respectively. If the difference in the ionic character of the bonds is the rate determining factor, one would expect that the fluorine compound would hydrolyse more rapidly than the chlorine compound. The considerably greater hydrolytic stability of the fluorine derivative may, however, be ascribed principally to the higher bond energy of the P-F bond, 120 kcal/mole, in comparison with that of the P-Cl bond, 80 kcal/mole ⁸.

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