

Determination of the Distribution Constant of a Compound Reacting with One of the Phases

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A formula has been deduced for calculation of the distribution constant of a compound which reacts with one of the phases according to a first order reaction. The application of the formula is illustrated by the distribution of 2-methoxy-ethyl nicotinate between xylene and water. Another formula has been deduced in the case of association of the compound in one phase in addition to its decomposition in the other.

The distribution constant of a compound which reacts with one of the phases can be accurately determined if the concentrations of the solute are determined in each phase. Distribution constants, however, are generally evaluated from determinations of the concentration of the solute in one phase, the concentration in the other being obtained as a difference. In the case of reaction between the compound and one of the phases the total amount of compound is reduced, and an erroneous concentration in the unanalysed phase is obtained. Hence the error of the distribution constant will be considerable. In this investigation it has been found that the distribution constant of a compound can also be calculated from measurements of its reaction rate in the phase in question.

Let us consider the concentrations in the two phases of a compound distributed between an organic solvent and water, when the compound hydrolyses in the aqueous phase according to a first order reaction.

The following symbols will be used:

- []_{aq} or []_{org} = concentrations in aqueous and organic phases, respectively;
- α = slope of the line, when $\log [A]_{aq}$ is plotted against t ;
- A = unhydrolysed compound;
- A₂ = double molecule of A;
- D = optical density;
- k = reaction rate constant of A in water;
- k_{ass} = association constant of A in organic phase;
- k_d = distribution constant of A between organic and aqueous phase;

P = one of the hydrolysis products;
 t = time;
 v = phase volume.

Assuming that at a given moment the concentration of the hydrolysis product is

$$[P]_{\text{aq}} = \int_0^t k \cdot [A]_{\text{aq}} dt \quad (1)$$

Then the total amount of the compound and its hydrolysis product is

$$v_{\text{org}}[A]_{\text{org}} + v_{\text{aq}}[A]_{\text{aq}} + v_{\text{aq}}[P]_{\text{aq}} = \text{const.} \quad (2)$$

Further the distribution constant is

$$k_d = \frac{[A]_{\text{org}}}{[A]_{\text{aq}}}$$

On differentiating eqn. (2) we obtain

$$v_{\text{org}}d[A]_{\text{org}} + v_{\text{aq}}d[A]_{\text{aq}} + v_{\text{aq}}d[P]_{\text{aq}} = 0 \quad (4)$$

and on substitution of $d[P]_{\text{aq}}$ which according to eqn. (1) is

$$d[P]_{\text{aq}} = k \cdot [A]_{\text{aq}} dt \quad (5)$$

in eqn. (4), we get

$$\frac{v_{\text{org}}}{v_{\text{aq}}} \cdot \frac{d[A]_{\text{org}}}{dt} + \frac{d[A]_{\text{aq}}}{dt} = -k \cdot [A]_{\text{aq}} \quad (6)$$

From eqn. (3) we obtain on differentiating with respect to time

$$\frac{d[A]_{\text{org}}}{dt} = k_d \frac{d[A]_{\text{aq}}}{dt} \quad (7)$$

On introduction of this expression into eqn. (6) we get

$$\frac{d[A]_{\text{aq}}}{dt} \left(\frac{v_{\text{org}}}{v_{\text{aq}}} k_d + 1 \right) = -k \cdot [A]_{\text{aq}} \quad (8)$$

When this equation is integrated, we obtain

$$\frac{k \cdot t}{\frac{v_{\text{org}}}{v_{\text{aq}}} k_d + 1} = \ln \frac{[A]_{\text{aq}}^0}{[A]_{\text{aq}}} \quad (9)$$

where $[A]_{\text{aq}}^0$ is the concentration of A in the aqueous phase at distribution equilibrium, at which time no hydrolysis is assumed to have occurred.

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

$$|\alpha| = \frac{0.4343 \cdot k}{\frac{v_{\text{org}}}{v_{\text{aq}}} k_d + 1} \quad (10a)$$

or

$$k_d = \frac{v_{\text{aq}}}{v_{\text{org}}} \left(\frac{0.4343 \cdot k}{|\alpha|} - 1 \right) \quad (10b)$$

If the compound is associated to some extent into double molecules in the organic phase, a straight line would not be obtained. On the assumption that such an association occurs, the distribution constant can be calculated from eqn. (11) which can be deduced analogously to eqn. (9).

$$k \cdot t = \left(\frac{v_{\text{org}}}{v_{\text{aq}}} k_d + 1 \right) \ln \frac{[A]_{\text{aq}}^0}{[A]_{\text{aq}}} + 4k_{\text{ass}} \cdot k_d^2 \frac{v_{\text{org}}}{v_{\text{aq}}} ([A]_{\text{aq}}^0 - [A]_{\text{aq}}) \quad (11)$$

where $k_{\text{ass}} = \frac{[A_2]_{\text{org}}}{[A]_{\text{org}}^2}$

EXPERIMENTAL

The application of the method is illustrated by determination of the distribution constant of 2-methoxy-ethyl nicotinate between xylene and a buffer solution at pH 9.15. At this pH the nicotinic ester may be regarded as completely unionized. The two phases are nearly insoluble in each other. Hydrolysis of the ester proceeds as a first order reaction, when the pH remains constant. In order to verify the result obtained with this method the distribution constant was also determined in the conventional manner from the concentrations of the ester in the aqueous phase before and after shaking to equilibrium. The hydrolysis of this compound is negligible during the time required for this experiment.

Materials. 2-Methoxy-ethyl nicotinate: To 17.7 g (0.10 mole) of the hydrochloride of nicotinyll chloride, prepared from nicotinic acid and thionyl chloride¹, was gradually added 22.8 g (0.30 mole) of 2-methoxy-ethanol. The reaction mixture was refluxed for two hours in a water bath. After cooling, the mixture was neutralized with a saturated solution of potassium carbonate and extracted three times with ether. After drying of the ether extract overnight the ether was evaporated, and the ester was distilled under reduced pressure; b.p. 80–83°/0.20–0.25 mm Hg. A solid, colourless product was obtained which was recrystallized from acetone. Yield 11.0 g (61 %). (Found: C 59.5; H 6.0, Calc. for C₉H₁₁O₂N: C 59.7; H 6.1.)

Buffer solution: A borax buffer solution with pH 9.15 was used. It was standardized at 25°C against 0.05 M solution of potassium hydrogen *o*-phthalate, pH 4.01², with a Radiometer pH-meter, type 3.

Xylene: Reagent grade; b.p. 139–140°; $n_D^{20} = 1.4957$.

Procedure I. All experiments were carried out in a thermostat at 25°C. Each series of experiments consisted of 6–8 samples with the same concentration. The 2-methoxy-

Table 1. The distribution constant of 2-methoxy-ethyl nicotinate calculated from the hydrolysis rate of the ester. $[A]_{\text{org}}$ denotes the original ester concentration in xylene.

$v_{\text{org}}/v_{\text{aq}}$	$[A]_{\text{org}}$ mmole/l	$\alpha \times 10^3$ hours ⁻¹	k_d
1:2	8.73	7.16	4.15
	6.57	6.90	4.38
1:1	8.01	4.11	4.35
	5.75	4.20	4.24
2:1	8.26	2.24	4.42
	5.45	2.25	4.39

Mean value 4.32 ± 0.10

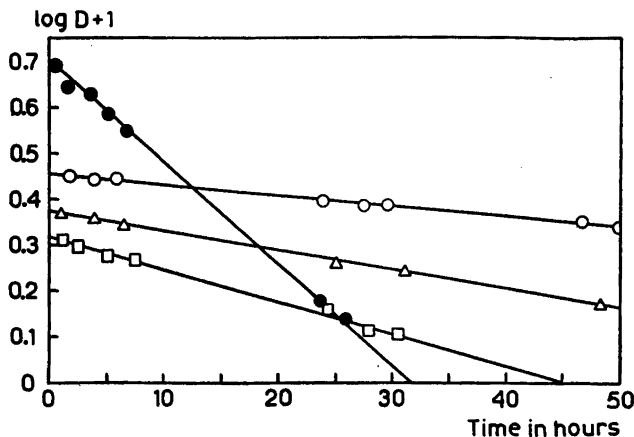


Fig. 1. Hydrolysis of 2-methoxy-ethyl nicotinate in buffer solution (●) and in mixtures of xylene - buffer solution $v_{org}/v_{aq} = 1:2$ (□), $v_{org}/v_{aq} = 1:1$ (△) and $v_{org}/v_{aq} = 2:1$ (○).

ethyl nicotinate was dissolved in xylene; in this way a smaller amount of the compound came into contact with water, before equilibrium was attained, than if the compound was dissolved in buffer solution. The buffer solution was added at zero time. The mixtures were shaken mechanically in sealed ampoules which were withdrawn from the thermostat at annotated times. After separation and filtration, the concentration of unhydrolysed ester in the aqueous phase was determined colorimetrically with the method reported by Hestrin³. The colour intensities of the samples were measured in a 10 mm cell at 5 200 Å with a Beckmann B Spectrophotometer. In the different series both the concentration of ester and the ratio of the volumes of xylene to buffer solution were varied as shown in Table 1. The total volume of each sample was 30 ml. Preliminary mutual saturation of the immiscible layers was unnecessary, since it was found to have no effect on the distribution constant. The pH of the solutions was determined at the beginning and end of hydrolysis, and was found to remain constant within 0.01 pH unit. Because Beer's law was obeyed, the logarithm of the optical density rather than that of the concentration of unhydrolysed ester was plotted against time. This is illustrated in Fig. 1. From the slope of the line obtained the distribution constant was calculated by means of eqn. (10b).

The rate constant of hydrolysis of the ester in buffer solution alone was determined colorimetrically as described above and calculated from the first order equation

$$k = \frac{1}{t} \ln \frac{D^0}{D} \quad (12)$$

Table 2. The rate constant for the hydrolysis of 2-methoxy-ethyl nicotinate.

[A] _{aq} mmole/l	$k \times 10^2$ hours ⁻¹
2.96	5.10
3.39	5.02
3.71	5.09

Mean value 5.07×10^{-2}

Table 3. The distribution constant of 2-methoxy-ethyl nicotinate calculated from the concentrations of the ester in both phases. $[A]_{aq}$ denotes the original ester concentration in the buffer solution.

v_{org}/v_{aq}	$[A]_{aq}$ mmole/l	D'	D	k_d
1:2	10.39	1.712	0.545	4.28
	5.33	0.884	0.273	4.48
	5.08	0.862	0.270	4.39
1:1	11.27	1.798	0.337	4.33
	7.53	1.316	0.253	4.20
	5.67	0.962	0.182	4.28
2:1	11.50	1.830	0.193	4.24
	6.17	1.070	0.114	4.19
	5.33	0.884	0.096	4.10

Mean value 4.28 ± 0.11

where D^0 and D are the optical densities at zero time and t time, respectively. The values obtained are given in Table 2.

Procedure II. Buffer solutions in which the ester was dissolved, were shaken with xylene for about 5 minutes. The concentration of ester and the ratio of the volumes were varied as in the previous experiment. The concentration of ester in the aqueous phase before and after shaking was determined colorimetrically as described in procedure I. The unshaken buffer solutions had to be diluted four times before they were analysed. The values of the optical density, D' , given in Table 3 have been converted for this dilution. Mixtures shaken for 3, 6, 9, and 12 minutes showed that equilibrium was already attained after 3 minutes. As Beer's law proved to be valid, the distribution constant was calculated from

$$k_d = \frac{[A]_{org}}{[A]_{aq}} = \frac{v_{aq}}{v_{org}} \cdot \frac{D' - D}{D} \quad (13)$$

where D' and D are the optical densities before and after shaking, respectively.

RESULTS AND DISCUSSION

From Tables 1 and 3 it will be seen that the distribution constant calculated from kinetic data is in close agreement with that obtained from analysis of the aqueous phase before and after shaking, and that the precision of the two methods is approximately the same. When the logarithm of the optical density is plotted against time (Fig. 1), straight lines are obtained, indicating that no appreciable association occurs in the xylene phase. Further confirmation of this is that the distribution constant is independent of concentration.

The kinetic method is of course more time-consuming than the other, but it is far more reliable. Eqn. (9) is, however, not exactly valid, because no account has been taken of the distribution rate of the solute. The internal controlling factor in this process is the rate of solute diffusion across the interfacial stationary films⁴, but the thicknesses and surfaces of the interfacial films vary considerably with the experimental conditions. The rate of distribution will consequently be very difficult to determine. However, since equi-

librium is generally attained very rapidly⁵, the method can be applied in all cases where the reaction rate is relatively low, or where the concentration of the solute in the indifferent phase is high compared to that of the reacting phase. The assumption made in eqn. (9) concerning $[A]_{\text{aq}}^0$, on the other hand, does not influence the accuracy, because zero time can just as well be taken as the moment when equilibrium is attained.

The method described may also be used in the study of rapid reactions, for the reaction rate can be reduced appreciably by adding a suitable solvent which must be immiscible with the reacting phase and readily dissolve the solute. One must consider that errors may arise from neglecting the rate of distribution and, in this case, from $[A]_{\text{aq}}^0$ too, if this value is used for determination of the distribution constant.

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