

Determination of the Dissociation Constant of a Weak Acid Using a Dissolution Rate Method

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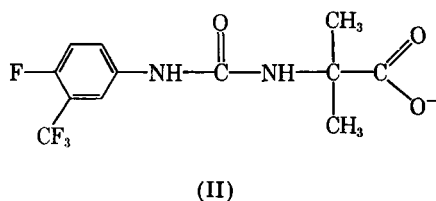
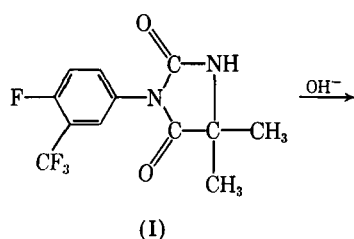
Abstract □ Based on theories of diffusion-controlled mass transport for dissolution processes of weak acids in aqueous alkaline media, a method for the determination of the dissociation constant of a weak monoprotic acid is described. The method includes measurements of the initial dissolution rate as a function of pH, using the rotating-disk technique, and determination of the intrinsic solubility. The method was applied to determine the apparent dissociation constant ($\mu = 0.1$) of 5,5-dimethyl-3-($\alpha,\alpha,\alpha,4$ -tetrafluoro-*m*-tolyl)hydantoin, a new schistosomicide. For comparison, a spectrophotometric method for the pK_a determination was developed. Due to rapid hydrolysis of the compound in the pH range required for the determination of the pK_a , the development of the latter method turned out to be complicated and tedious. The results of both methods were in good agreement. For compounds with unfavorable properties for titrimetric or spectrophotometric determination of the pK_a value, the dissolution rate method can be a useful alternative.

Keyphrases □ Dissociation constant determinations—use of a dissolution rate method, weak acids, 5,5-dimethyl-3-($\alpha,\alpha,\alpha,4$ -tetrafluoro-*m*-tolyl)hydantoin □ Dissolution rate method—determination of dissociation constants, weak acids, 5,5-dimethyl-3-($\alpha,\alpha,\alpha,4$ -tetrafluoro-*m*-tolyl)hydantoin

The determination of the dissociation constant of weakly acidic or basic drugs is normally a routine matter, using one of the established techniques (1–3). However, in some cases the compound may have unfavorable properties which makes such a routine determination difficult. Such is the case when the compound undergoes a fast chemical reaction in the medium required for the measurements.

From the dissolution rate model of weak acids in alkaline media (4), and the theories of the influence of irreversible reactions on the dissolution of a solid (5), it could be expected that dissolution behavior could form the basis for a method to determine the dissociation constant of a weak acid undergoing fast degradation in the pH range around the pK_a value.

This study utilized, 5,5-dimethyl-3-($\alpha,\alpha,\alpha,4$ -tetrafluoro-*m*-tolyl)hydantoin (I), a new schistosomicide (6).



The hydantoin derivative (I) is expected to be a weak acid.

The compound is stable in the acidic and neutral pH range, but undergoes a fast hydrolysis in aqueous alkaline media forming the hydantoic acid (II).

For the determination of the dissociation constant of the acid (I), two methods have been compared: the method based on the dissolution rate and a spectrometric method.

THEORETICAL

Determination of pK_a by Spectroscopy—The determination of the dissociation constant by spectroscopy is possible if un-ionized and ionized species of the molecule yield different spectra in UV-visible range (1–3). Measuring the absorbance at a particular wavelength, the K_a for acids can be obtained from the equation:

$$K_a = \frac{\epsilon_M - \epsilon}{\epsilon - \epsilon_1} [H^+] \quad (\text{Eq. 1})$$

where ϵ_M and ϵ_1 are molar absorptivities for the un-ionized and ionized species, and ϵ is the molar absorptivity at $[H^+]$. In cases where ϵ_1 is not directly obtainable, Maroni (7) has proposed a method, based on the rearrangement of Eq. 1:

$$\epsilon = \epsilon_1 - \frac{(\epsilon - \epsilon_M)[H^+]}{K_a} \quad (\text{Eq. 2})$$

Plotting a series of ϵ values against $(\epsilon - \epsilon_M)[H^+]$ gives a straight line and K_a can be calculated from the slope. If the compound undergoes a rapid reaction, it will be impossible to measure the ϵ -values directly. However, if the reaction is of first order, the ϵ -values may be obtained from measurements of the absorbance as a function of time, using the Guggenheim method (8).

Determination of pK_a by Dissolution Rate—Based on the film theory of Nernst (9) for heterogeneous reactions, Higuchi *et al.* (4) have formulated a model for dissolution of a weak acid in a basic medium. This model postulates that the dissolution rate is controlled by a rapid, reversible chemical reaction and simultaneous diffusion of all important species taking part in the processes that occur within a boundary layer. It is assumed in this model that the diffusion layer for all solute species is equal. A schematic diagram of the Higuchi model is presented in Fig. 1, where HA is the acid, B^- is the incoming base and h is the thickness of the diffusion layer. Under sink condition, $[HA]_h$ and $[A^-]_h$ will effectively be zero.

The general equation, based on this model for the initial dissolution rate or flux J as a function of the bulk concentration of the incoming base, is relatively complicated (4). If the base happens to be the hydroxide ion, the equation will be simpler (10):

$$J = \frac{D_{HA}[HA]_0}{h} + \frac{(D_{OH})^2 [OH^-]_h}{h} \left(\frac{D_A[HA]_0 K_a / K_w}{(D_{OH})^2 + D_A D_{OH} [HA]_0 K_a / K_w} \right) \quad (\text{Eq. 3})$$

where D_S is the diffusion coefficient of species S in the system, $[HA]_0$ is the intrinsic solubility, *i.e.*, the solubility of the undissociated species, and K_a and K_w are dissociation constants of the acid and water, respectively.

If we assume that $D_A = D_{HA}$ and substitute $K_w/[H^+]_h$ for $[OH^-]_h$, and J_0 for $D_{HA}[HA]_0/h$, rearrangement of Eq. 3 gives:

$$J = J_0 + \frac{J_0 D_{OH} K_a}{[H^+]_h (D_{OH} + D_{HA} [HA]_0 K_a / K_w)} \quad (\text{Eq. 4})$$

Plotting a series of values of the flux against the corresponding reciprocal values of $[H^+]_h$ gives the slope:

$$a = \frac{J_0 D_{OH} K_a}{D_{OH} + D_{HA} [HA]_0 K_a / K_w} \quad (\text{Eq. 5})$$

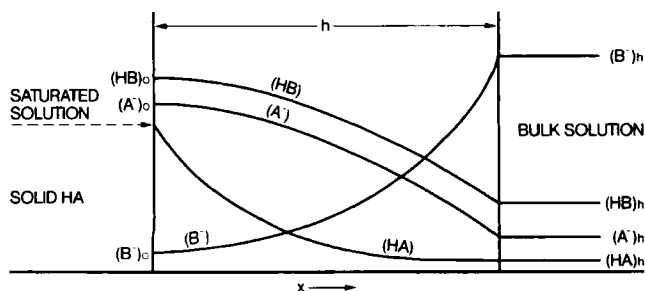


Figure 1—Schematic diagram of the model of Higuchi et al. (4) for the dissolution of an acid, HA, into a reactive medium containing base B⁻.

and by rearrangement:

$$K_a = \frac{aD_{OH}K_w}{J_0D_{OH}K_w - aD_{HA}[HA]_0} \quad (\text{Eq. 6})$$

Studies of the dissolution rate can be performed with the rotating-disk technique, where the flux as a function of hydrodynamic conditions has been studied very extensively by Levich (11). For the rotating disk, the mass flux is given as:

$$J = 0.62D^{2/3}\nu^{-1/6}\omega^{1/2}[HA]_0 \quad (\text{Eq. 7})$$

where ν is the kinematic viscosity and ω is the angular velocity of rotation.

The corresponding diffusion boundary layer may be written as:

$$h = 1.612 D^{1/3}\nu^{1/6}\omega^{-1/2} \quad (\text{Eq. 8})$$

Higuchi et al. (5) have studied the influence of an irreversible reaction on the dissolution rate of a compound undergoing a rapid hydrolytic reaction simultaneously with the dissolution. It was found that the influence depends on the diffusion time t_D , which is the average lifetime for an element to travel through the diffusion layer, and on the reaction rate of the irreversible reaction.

The diffusion time was expressed as:

$$t_D = \frac{h^2}{2D} \quad (\text{Eq. 9})$$

EXPERIMENTAL

Materials—5,5-Dimethyl-3-($\alpha,\alpha,\alpha,4$ -tetrafluoro-*m*-tolyl)hydantoin was of purity >99.8%. All other chemicals were of analytical grade.

Spectrophotometric Method—A 1-ml portion of $1.7 \times 10^{-2} M$ of the acid (I) in ethanol was added to 50 ml of 0.1 N NaCl or solutions of sodium hydroxide adjusted to an ionic strength of 0.1 with sodium chloride and stirred at 25.0°. The solutions were injected into a 1-cm cell of a UV-visible spectrophotometer¹, thermostated at $25.0 \pm 0.1^\circ$, and the change of absorbance with time was measured at 254 nm. The pH of the solutions was measured at 25° using a combination pH microelectrode² with low alkaline error and a pH meter³.

Dissolution Rate Method—The dissolution rates were determined using the rotating disk technique, with an apparatus similar to that described by Wood et al. (12). A disk (1.6 cm in diameter) of the compound was compressed at 3×10^3 kg for 3 min in a hydraulic press. The disk assembly was rotated by a variable-speed synchronous motor that was calibrated by a tachometer. The dissolution rates were determined at $25.0 \pm 0.1^\circ$ using a constant temperature water bath.

Solubility—The solubility of I was determined by shaking an excess of the compound in 0.1 N NaCl solution at 25.0° in a water bath for 24 hr, during which time equilibrium solubility was reached. After equilibration the solution was filtrated through a membrane filter (0.45 μ m). The filtrate was diluted appropriately with water, and the assay was made spectrophotometrically at 270 nm ($\epsilon = 858$).

Diffusion Coefficient and Boundary Layer Thickness—The dissolution rate measurements were performed using the rotating disk in 500 ml of 0.1 N NaCl at 25.0° with rotation speeds varying from 50 to 299 rpm. At each rotation speed the dissolution rate was determined after a rotation period of 20 min. A 1-ml solution of 1 N NaOH was added to 10.0 ml

Table I—Experimental Data of the Spectrophotometric Method for the Determination of the Apparent pK_a at 25°^a

pH	$t_{1/2}$, min	$\epsilon_{254 \text{ nm}}$	pK_a^b
7.40		542	
11.77	9.50	787	12.12
11.89	8.21	835	12.12
11.93	7.85	861	12.10
11.99	7.43	891	12.09
12.05	6.81	915	12.10
12.11	6.41	947	12.10
12.17	6.00	950	12.14
12.28	5.56	1006	12.13
12.35	5.17	1051	12.09
12.48	4.77	1098	12.10
12.57	4.58	1131	12.10
			Average 12.11 (± 0.03)

^a $\mu = 0.1$. ^b The individual values were calculated from Eq. 1, where $\epsilon_M = 542$ and $\epsilon_1 = 1332$. ϵ_1 was obtained from Eq. 2.

of the sample, and the solutions were kept at 25° for 1 hr. The solutions were diluted appropriately with 0.1 N sodium hydroxide and measured by UV spectrophotometry at 239 nm ($\epsilon = 16180$).

Dissolution-pH Profile—The determination of the dissolution rate as a function of pH was performed with the same compressed disk for the whole pH profile, and the test solution was not renewed. However the different pH values were obtained by successive additions of 0.1 N NaOH solution to the test solution, and the dissolution was determined after each change of pH. Corrections for added volumes of 0.1 N NaOH and the samples withdrawn were considered.

The dissolution-pH profile was determined with a rotation speed of 100 rpm. The starting medium was 500 ml of 0.1 N NaCl. The disk was initially stirred in the medium for about 15 min, and the pH was then adjusted to a higher predetermined value by adding 0.1 N NaOH. A sample was withdrawn after equilibrating for 5 min and again after 20 min. The pH was then adjusted to the next higher pH value, and the procedure for sampling was repeated. The procedure was repeated until samples from a representative number of pH values had been collected. The assay of the samples was performed in the same way as described for determination of diffusion coefficient.

RESULTS AND DISCUSSION

Spectrophotometric Method—The molar absorptivity of the non-ionized species ϵ_M could be obtained directly from the measurement of the absorbance in the 0.1 N NaCl solution in which the compound is stable. In the pH range of 11.79–12.57, the absorbance at time zero had to be calculated from the absorbance-time curve. Preliminary studies have shown, that the hydrolysis of I to the corresponding hydantoic acid, as would be expected, is of first order. The Guggenheim method (8) could, therefore, be applied for the calculation of the ϵ values from the initial part of the absorbance-time curves. From these curves kinetic data of the hydrolytic reaction could also be obtained by the Guggenheim method. A reliable value for ϵ_1 could not be found; therefore, K_a was calculated according to Eq. 2. This gave a slope -1.282×10^{12} ($r = 0.991$) corresponding to $K_a = 7.803 \times 10^{-13}$ or $pK_a = 12.11$.

The development of this spectrophotometric method turned out to be very tedious. Because of the fast hydrolytic reaction, it was difficult to find an optimal analytical wavelength.

Dissolution Rate Method—The intrinsic solubility $[HA]_0$ of I in 0.1 N NaCl was found to be $1.44 \times 10^{-3} M$. Rearranging Eq. 7, an expression for the diffusion coefficient can be found:

$$D_{HA} = \left(\frac{J\nu^{1/6}\omega^{-1/2}}{0.62[HA]_0} \right)^{3/2} = 4.8 \times 10^{-6} \text{ cm}^2/\text{sec} \quad (\text{Eq. 10})$$

where $J\omega^{-1/2}$ determined from the slope of the linear plot J against $\omega^{1/2}$ ($r = 0.996$) was found to be 5.60×10^{-10} moles/cm²/sec^{1/2}; $\nu = 8.93 \times 10^{-3}$ Stokes is the kinematic viscosity of water at 25° (13).

From the investigations of Higuchi et al. (5) on the influence of irreversible chemical reactions on dissolution rate of a solid, it was found that for a diffusion time $t = 3$ sec, a half-life of the irreversible reaction greater than the order of 10 sec would have no influence on the dissolution rate. A rotation speed of 100 rpm of the rotating disk gives, according to Eq. 8, a diffusion layer thickness $h = 3.8 \times 10^{-3}$ cm. The diffusion time for (I) under this hydrodynamic condition will be $t_D = 1.5$ sec.

From the kinetic data given in Table I, it is obvious that by using the

¹ Uvikon, model 820, Kontron, Zürich, Switzerland.

² EA 125, Metrohm, Herisau, Switzerland.

³ Model E 603, Metrohm, Herisau, Switzerland.

rotating disk at 100 rpm the dissolution rate will not be affected by the hydrolytic reaction in the pH range of 11.8–12.6. These hydrodynamic conditions were, therefore, used for the present pH profile study. Plotting the values of the flux J (see Table II) against the reciprocal values of the bulk hydrogen ion concentration $[H^+]_h$ a linear relationship was found. Using the least-squares method gave the slope $\alpha = 7.530 \times 10^{-20}$ with the intercept $J_0 = 1.071 \times 10^{-7}$ moles/cm²/min and a coefficient of correlation $r = 0.995$. Using these data, the experimental values of D_{HA} and $[HA]_0$ and assuming the diffusion coefficient of hydroxide ion in water D_{OH} to be 2.42×10^{-5} cm²/sec (from Ref. 4), the dissociation constant was obtained from Eq. 6: $K_a = 7.178 \times 10^{-13}$ or $pK_a = 12.14$.

Equation 3 is based on the diffusion layer theory of Nernst. However, several aspects of the Nernst model have been criticized (11, 14). One drawback of the model is the erroneous assumption that the diffusion layer thickness is equal for all diffusing species under the same hydrodynamic conditions. For the rotating disk, the diffusion layer thickness of a diffusing species depends on the diffusion coefficient according to Eq. 8 (11). As D_{OH} is about 5 times greater than D_{HA} , the concentration of hydroxide ion at h_{HA} , $[OH^-]_h$ will be somewhat lower than the hydroxide ion concentration of the bulk solution $[OH^-]_{bulk}$. This could have a significant influence on the value for K_a , calculated from Eq. 6. An evaluation of $[OH^-]_h$ can be made by the following considerations.

From Eq. 8 and the numerical values of D_{HA} and D_{OH} a ratio N can be calculated:

$$N = \frac{h_{HA}}{h_{OH}} = \left(\frac{D_{HA}}{D_{OH}}\right)^{1/3} = 0.58 \quad (\text{Eq. 11})$$

To calculate the hydrogen ion concentration at the solid–liquid interface $[H^+]_0$ of the Higuchi model, Mooney *et al.* (15) have derived the equation:

$$-D_H[H^+]_0^2 + [H^+]_0(D_H[H^+]_h - D_{OH}[OH^-]_h) + K_w(D_{OH} + D_A[HA]_0K_a/K_w) = 0 \quad (\text{Eq. 12})$$

If $[H^+]_0$ and $[H^+]_h \ll [OH^-]_h$, and also assuming $D_{HA} = D_A$ and considering that $[OH^-]_0[H^+]_0 = K_w$, a rearrangement of Eq. 12 gives:

$$[OH^-]_0 = \frac{D_{OH}[OH^-]_h K_w}{D_{OH}K_w + K_a D_{HA}[HA]_0} \quad (\text{Eq. 13})$$

Defining the ratio R as:

$$R = \frac{[OH^-]_h - [OH^-]_0}{[OH^-]_{bulk} - [OH^-]_0} \quad (\text{Eq. 14})$$

and substituting Eq. 13 into Eq. 14, the following relationship between $[OH^-]_h$ and $[OH^-]_{bulk}$ is found:

$$[OH^-]_h = \frac{D_{OH}K_w + K_a D_{HA}[HA]_0}{D_{OH}K_w + K_a D_{HA}[HA]_0/R} [OH^-]_{bulk} \quad (\text{Eq. 15})$$

From investigations with the rotating-disk electrode, Levich (11) has derived the mathematical formula of the concentration gradient curve for a diffusing element in the diffusion layer of the rotating disk. Using this formula, the ratio R can be calculated for the value at a relative distance N from the solid–liquid interface:

$$R = \frac{\int_0^N e^{-u^3} du}{\int_0^\infty e^{-u^3} du} \quad (\text{Eq. 16})$$

For a value of $N = 0.58$, R was found to be 0.82. For this value of R Eq. 15 gives:

$$[OH^-]_h = 0.996 [OH^-]_{bulk}$$

It is obvious that a factor of 0.996 will have no significant influence on the K_a value calculated on the basis of Eq. 4. For cases where the product $K_a [HA]_0$ is appreciably larger, a small influence may, however, be expected.

From Eq. 6 it can be estimated that the relative low value of the product $K_a [HA]_0$ also means that very high accuracy of the value for D_{OH} and D_{HA} is not required in the present case, and a simple calculation of D_{HA} using the square root method (16), for instance, may replace the experimental method used here. Equation 3 is valid only if $[OH^-]_0$ and $[OH^-]_h$ are essentially higher than $[H^+]_0$ and $[H^+]_h$. Otherwise the complete formula for the Higuchi model (4) has to be used.

The good agreement between the results of the spectrophotometric and the dissolution rate methods for determination of pK_a , shows that the theoretical approach used here may give a sound basis for the determination of the dissociation constant from the dissolution behavior.

Table II—Experimental Data of the Dissolution Method for the Determination of the Apparent pK_a at 25°^a

pH	J , moles/cm ² /min $\times 10^7$	pK_a^b
11.81	1.605	12.10
11.91	1.713	12.12
12.02	1.826	12.16
12.12	2.123	12.12
12.18	2.159	12.17
12.25	2.382	12.15
12.33	2.576	12.17
12.41	3.004	12.14
12.49	3.483	12.13
		Average 12.14 (± 0.04)

^a $\mu = 0.1$. ^b The individual values were obtained from Eq. 4, where $J_0 = 1.071 \times 10^{-7}$ moles/cm²/min.

Using the technique described here, the dissolution rate method can be applied advantageously for compounds with unfavorable properties for determination by a titrimetric or a spectrophotometric method.

In analogy to the approach used in the Higuchi model for pK_a determinations of weak acids, it may be expected that it can also be used for determinations of the pK_a values of weak bases by using, for instance, hydrochloric acid solutions as the reaction media. The dissociation constant may also be obtained from dissolution rates in buffer solutions. Simplified models for dissolution behavior in these media have been proposed (17, 18), assuming the pH of the solid–liquid interface to be equal to the pH of the bulk solution. However, as has been shown by Mooney *et al.* (19) this is generally not the case and may give erroneous results. The use of the extension of the Higuchi model for dissolution behavior in buffer solutions, as has been proposed by Mooney *et al.* (19) may, however, form a suitable basis for the determination of pK_a values in such media.

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