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Determination of overlapping pK_a values from solubility data *

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Summary

A method will be derived which allows for the calculation of both the pK_a values and the limiting solubility of bifunctional acids and bases, respectively, from their solubilities as a function of the pH of the medium. In deriving the algorithms special interest has been paid to the numerical stability of the equations to avoid serious rounding errors.

Introduction

In an earlier paper (Zimmermann, 1983) a method was presented which allowed for the calculation of both the pK_a value and the solubility of the neutral molecular form of a substance from its solubility as a function of the pH of the medium. By means of a slight modification this method can also be applied to determine pK_a values of bifunctional acids or bases.

Theory

Acids

The dissociation of a bifunctional acid can be described as follows:

$$H_2A \overset{K_{1a}}{\rightleftharpoons} H^+ + HA^- \qquad (1a)$$

$$HA^- \overset{K_{2a}}{\rightleftharpoons} H^+ + A^{2-} \qquad (1b)$$

The dissociation constants K_{1a} and K_{2a} are defined by:

$$K_{1a} = \frac{[H^+][HA^-]}{[H_2A]} \qquad (2a)$$

$$K_{2a} = \frac{[H^+][A^{2-}]}{[HA^-]} \qquad (2b)$$

In a solution of a bifunctional acid the following

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* This paper is dedicated to the distinguished Prof. Dr. Claus Führer on his 60th birthday.

[a] Upon request listings of a FORTRAN program for performing these calculations will be supplied.

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species can be found:

H_2A, HA^- and A^{2-}.

Therefore the solubility S_i of the acid at a given pH can be expressed as:

$$S_i = [H_2A] + [HA^-]_i + [A^{2-}]_i \tag{3}$$

From Eqn. 2b we obtain:

$$[A^{2-}]_i = K_{2a}\frac{[HA^-]_i}{[H^+]_i} \tag{4}$$

Inserting this expression into Eqn. 3 we obtain:

$$S_i = [H_2A] + [HA^-]_i\left\{1 + \frac{K_{2a}}{[H^+]_i}\right\} \tag{5}$$

The concentration $[HA^-]$ is given by Eqn. 2a:

$$[HA^-]_i = \frac{K_{1a}\,[H_2A]}{[H^+]_i}$$

By insertion into Eqn. 5 we obtain:

$$S_i = [H_2A]\left\{1 + \frac{K_{1a}}{[H^+]_i} + \frac{K_{1a}K_{2a}}{[H^+]_i^2}\right\}$$

In saturated solutions $[H_2A]$ corresponds to the limiting solubility S_0 of the neutral molecule.

$$S_i = S_0\left\{1 + \frac{K_{1a}}{[H^+]_i} + \frac{K_{1a}K_{2a}}{[H^+]_i^2}\right\} \tag{6}$$

S_i and $[H^+]_i$ can be determined experimentally. Considering that $S_0 = [H_2A]$, K_{1a} and K_{2a} are constants we can define new constants:

$$\begin{aligned} m &= [H_2A] \\ a_1 &= [H_2A]\cdot K_{1a} \\ a_2 &= [H_2A]\cdot K_{1a}\cdot K_{2a} \\ x_i &= 1/[H^+]_i \end{aligned} \tag{7}$$

So we obtain the simple equation

$$S_i = m + a_1x_i + a_2x_i^2 \tag{8}$$

Bases

The dissociation of a difunctional base can be described as follows:

$$BH_2^{2+} \overset{K_{1a}}{\rightleftharpoons} BH^+ + H^+$$

$$BH^+ \overset{K_{2a}}{\rightleftharpoons} B + H^+$$

The expressions corresponding to the Eqns. 2 are given by:

$$K_{1a} = \frac{[BH^+][H^+]}{[BH_2^{2+}]} \tag{9a}$$

$$K_{2a} = \frac{[B][BH^+]}{[BH_2^{2+}]} \tag{9b}$$

In a solution of a difunctional base we can identify the following species:

$[B]$, $[BH^+]$, $[BH_2^{2+}]$

Therefore the counterpart to Eqn. 5 is given by:

$$S_i = [B] + [BH^+]_i + [BH_2^{2+}]_i \tag{10}$$

Considering that

$$[BH_2^{2+}]_i = \frac{[H^+]_i[BH^+]_i}{K_{1a}} \tag{11}$$

TABLE 1

MEANING OF THE PARAMETERS OF EQN. 8

Parameter	Acids	Bases
m	$[H_2A]$	$[B]$
a_1	$[H_2A]\cdot K_{1a}$	$[B]/K_{2a}$
a_2	$[H_2A]\cdot K_{1a}\cdot K_{2a}$	$[B]/K_{1a}\cdot K_{2a}$
x_i	$1/[H^+]_i$	$[H^+]_i$

$$[BH^+]_i = \frac{[B][H^+]_i}{K_{2a}} \tag{12}$$

we obtain:

$$S_i = [B]\left\{1 + \frac{[H^+]_i}{K_{1a}} + \frac{[H^+]_i^2}{K_{2a} \cdot K_{2a}}\right\} \tag{13}$$

In saturated solutions [B] corresponds to the limiting solubility S_0 of the neutral molecule. Considering that $S_0 = [B]$, K_{1a} and K_{2a} are constants we can define new constants

$$\begin{aligned} m &= [B] \\ a_1 &= \frac{[B]}{K_{2a}} \\ a_2 &= \frac{[B]}{K_{1a}K_{2a}} \\ x_i &= [H^+]_i \end{aligned} \tag{14}$$

By insertion of these constants into Eqn. 13 we obtain an expression corresponding to Eqn. 8.

Determination of the coefficients m, a_1, a_2

From a set of solubility figures as a function of the pH we can determine the unknown parameters m, a_1, a_2 by means of a least-squares procedure.

As shown in the appendix, S_0, K_{1a} and K_{2a} can be calculated from the expressions:

$$S_0 = m$$

for acids:

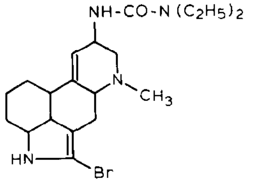
$$K_{1a} = \frac{a_1}{m} \qquad pK_{1a} = -\log\left(\frac{a_1}{m}\right)$$

$$K_{2a} = \frac{a_2}{K_{1a}} \qquad pK_{2a} = -\log\left(\frac{a_2 \cdot m}{a_1}\right)$$

for bases:

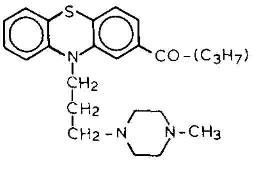
$$K_{2a} = \frac{a_1}{m} \qquad pK_{2a} = -\log\left(\frac{a_1}{m}\right)$$

$$K_{1a} = \frac{a_2}{K_{2a}} \qquad pK_{1a} = -\log\left(\frac{a_2 m}{a_1}\right)$$



Bromerguride

Fig. 1.



Butaperazine

Fig. 2.

Materials and Methods

The solubilities of Bromerguride [3-(2-brom-9,10-didehydro-6-methyl-8α-ergonyl)-1,1-diethyl-urea] were determined at room temperature (25 °C). The buffers used were made by mixing different amounts of 1/15 M solutions of KH_2PO_4

TABLE 2

pK_a VALUES AND SOLUBILITY OF BUTAPERAZINE

pH	Solubility		Difference (Calc. – Expt.)	Error (%)
	Expt.	Calc.		
6.0	283.4	283.4	0.00	0.00
6.4	113.8	113.4	−0.01	−0.01
6.6	72.5	72.5	0.01	0.02
6.8	46.5	46.5	−0.00	−0.01
7.0	30.1	30.1	−0.01	−0.04
7.2	19.7	19.7	0.04	0.21
7.4	13.2	13.2	0.02	0.12
7.6	9.1	9.1	−0.00	−0.03
7.8	6.5	6.5	−0.00	−0.00
8.0	4.9	4.9	−0.04	−0.80

Mean square deviation: 0.02.
Limiting solubility: $S_0 = 2.06$ mg/100 ml.
$pK_{2a} = 3.62$.
$pK_{1a} = 8.13$.

TABLE 3

pK_a VALUES AND SOLUBILITY OF BROMERGURIDE

pH	Solubility		Difference (Calc. – Expt.)	Error (%)
	Expt.	Calc.		
3.6	250.28	277.74	27.46	10.9
3.6	278.28	277.74	–0.54	–0.2
3.6	305.25	277.74	–27.51	–9.0
3.81	143.18	153.12	9.94	6.9
3.81	159.50	153.12	–6.38	–4.0
3.81	153.41	153.12	–0.29	–0.2
4.40	41.56	40.30	–1.26	–3.04
4.40	43.88	40.30	–3.58	–8.16
4.40	40.08	40.30	0.22	0.54
4.60	30.61	28.72	–1.89	–6.17
4.60	29.86	28.72	–1.14	–3.82
4.60	29.47	28.72	–0.75	–2.54
4.80	23.40	21.74	–1.66	–7.07
4.80	20.88	21.74	0.86	4.14
5.00	17.25	17.47	0.22	1.30
5.00	15.11	17.47	2.36	15.65
5.00	16.14	17.47	1.33	8.27
5.18	13.74	15.04	1.30	9.49
5.18	13.45	15.04	1.59	11.85
5.22	14.44	14.63	0.19	1.32

Mean square deviation: 8.96.
Limiting solubility: $S_0 = 10.41$ μg/ml.
$pK_{2a} = 3.33$.
$pK_{1a} = 4.82$.

and $Na_2HPO_4 \cdot 2\ H_2O$, respectively. The solubilities at different pH values were determined from concentrations of the substance in the supernatant liquid. The concentrations of Bromerguride were measured by means of a HPLC procedure.

Applications

(a) Butaperazine

pK_a values and solubility figures of Butaperazine have been published by Kala et al. (1980). Using these figures we obtain the data summarized in Table 2. Limiting solubility $S_0 = 2.06$ mg/100 ml; $pK_{1a} = 3.62$; $pK_{2a} = 8.13$. These figures are in good agreement with the data reported by Kala et al. They found $pK_{2a} = 3.58$; $pK_{1a} = 8.14$ and $S_0 = 2.03$ mg/100 ml.

(b) Bromerguride

The solubility figures of Bromerguride as a function of the pH at 25°C are summarized in Table 3. The limiting solubility is calculated as 10.41 μg/ml. The calculated pK_a values are $pK_{2a} = 3.33$ and $pK_1 = 4.82$.

Discussion

The procedure derived in this report allows calculation of overlapping pK_a values of bifunctional acids and bases, respectively.

If the pK_a values of bifunctional acids or bases are sufficiently separated ($\Delta pK_a \geqq 3$), the earlier reported method (Zimmermann, 1983) can be applied. With overlapping pK_a values ($\Delta pK_a < 3$) numerical problems may arise due to ill-conditioning of the system of linear equations. Therefore special interest has been paid to the numerical handling of the regression problem.

Appendix

As shown in Eqn. 8, the solubility data S_i at pH_i follow a linear model of second order, i.e. they approximate to a parabola.

$$y_i = m + a_1x_i + a_2x_i^2 \tag{A1}$$

The approximation criterion is given by:

$$\sum_{i=1}^{n} (S_i - y_i)^2 = \sum \left(S_i - m - a_1x_i - a_2x_i^2\right)^2 \overset{!}{=} \text{Min.} \tag{A2}$$

This condition is fulfilled if all the partial derivatives of the right side of Eqn. A1 with respect to m, a_1 and a_2, respectively, are set equal to zero. Thus we have three equations to determine the values of m, a_1 and a_2.

$$\frac{\partial}{\partial m_1} \sum (\ldots)^2 =$$

$$-2\sum \left(y_i - m - a_1x_i - a_2x_i^2\right) = 0$$

$$\frac{\partial}{\partial a_1} \sum (\ldots)^2 =$$

$$-2\sum x_i\left(y_i - m - a_1 x_i - a_2 x_i^2\right) = 0$$

$$\frac{\partial}{\partial a_2}\sum(\ldots)^2 =$$

$$-2\sum x_i^2\left(y_i - m - a_1 x_i - a_2 x_i^2\right) = 0$$

By means of simple rearrangements we obtain the following set of linear equations

$$\sum m + a_1\sum x_i + a_2\Sigma x_i^2 = \Sigma y_i$$

$$m\sum x_i + a_1\sum x_i^2 + a_2\sum x_i^3 = \sum x_i y_i$$

$$m\sum x_i^2 + a_1\sum x_i^3 + a_2\sum x_i^4 = \sum x_i^2 y_i$$

Or in matrix notation:

$$\begin{bmatrix} n & \sum x_i & \sum x_i^2 \\ \sum x_i & \sum x_i^2 & \sum x_i^3 \\ \sum x_i^2 & \sum x_i^3 & \sum x_i^4 \end{bmatrix} \cdot \begin{bmatrix} m \\ a_1 \\ a_2 \end{bmatrix} = \begin{bmatrix} \sum y_i \\ \sum x_i y_i \\ \sum x_i^2 y_i \end{bmatrix} \tag{A3}$$

In short-hand notation:

$$X \cdot A = Y \tag{A4}$$

The coefficients m, a_1 and a_2, respectively, are then given by:

$$A = X^{-1} \cdot Y$$

As can be proved the matrix X is ill-conditioned, this means the numbers calculated by this procedure are wrong due to rounding errors.

To circumvent this problem Eqn. Al is written as suggested by Späth (1973) as:

$$y_i = \tilde{m} + \tilde{a}_1(x_i + \gamma) + \tilde{a}_2\left(x_i^2 + \alpha x_i + \beta\right) \tag{A5}$$

The coefficients m, a_1 and a_2, respectively, are determined by means of the procedure outlined above. We then obtain the following set of equations:

$$\tilde{m} + \tilde{a}_1\sum(x_i + \gamma) + \tilde{a}_2\sum\left(x_i^2 + \alpha x_i + \beta\right) = \sum y_i$$

$$\tilde{m}\sum(x_i + \gamma) + \tilde{a}_1\sum(x_i + \gamma)^2 + \tilde{a}_2\sum(x_i + \gamma) \times \left(x_i^2 + \alpha x_i + \beta\right) = \sum(x_i + \gamma)y_i \tag{A6}$$

$$\tilde{m}\sum\left(x_i^2 + \alpha x_i + \beta\right) + \tilde{a}_1\sum(x_i + \gamma)\left(x_i^2 + \alpha x_i + \beta\right) + \tilde{a}_2\sum\left(x_i^2 + \alpha x_i + \beta\right)^2 = \sum\left(x_i^2 + \alpha x_i + \beta\right)y_i$$

The set of coefficients is determined in such a way that the matrix of coefficients in the above system of equations becomes a diagonal matrix.

$$\sum(x_i + \gamma) = 0$$

$$\sum(x_i + \gamma)\left(x_i^2 + \alpha x_i + \beta\right) = 0$$

$$\sum\left(x_i^2 + \alpha x_i + \beta\right) = 0$$

Thus we obtain:

$$\gamma = -\frac{1}{n}\sum x_i = -\bar{x}$$

$$a = \frac{\sum x_i^2(x_i - \bar{x})}{\sum x_i(x_i - \bar{x})}$$

$$\beta = \alpha \cdot \gamma - \sum x_i^2$$

The denominator in the expression, α, disappears only if all the x_i are the same [a]. By insertion of α, β and γ into the equations A5 we obtain

$$\tilde{m} = \frac{1}{n}\sum y_i = \bar{y}$$

$$\tilde{a}_1 = \frac{\sum(x_i + \gamma)y_i}{\sum(x_i + \gamma)^2}$$

$$\tilde{a}_2 = \frac{\sum\left(x_i^2 + \alpha x_i + \beta\right)y_i}{\sum\left(x_i^2 + \alpha x_i + \beta\right)^2}$$

Inserting $\tilde{m}$, $\tilde{a}_1$, $\tilde{a}_2$, α, β and γ respectively into Eqn. A5 we obtain the following expressions for the coefficients of Eqn. A1:

$$m = \tilde{a}_2\beta + \tilde{a}_1\gamma + \tilde{m}$$

$$a_1 = \tilde{a}_2\alpha + \tilde{a}_1$$

$$a_2 = \tilde{a}_2$$

References

Zimmermann I., Determination of pK_a values from solubility data. Int. J. Pharm., 13 (1983) 57–65.

Kala H., Wendorff D. and Moldenhauer H., Untersuchungen zur Löslichkeit und dem Verteilungsverhalten von Butaperazindibimaleinat. Pharmazie, 35 (1980) 306–310.

Späth H., Algorithmen für lineare Ausgleichsmodelle, R. Oldenbourg-Verlag, München, 1973.