Determination of pK_a values from solubility data

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Summary

At constant ionic strength the pH-dependent solubility of an ionogenic compound can be calculated by means of a method described by Krebs and Speakman (Krebs, Speakman, 1945) if the pK_a value of the substance and the solubility of the neutral molecular form are known. In the following we derive a method which allows 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.

Introduction

Only dissolved drugs can be absorbed. Therefore, the solubility of a drug is an extremely important parameter in planning the development of tablets. The solubility of ionogenic compounds, however, is very much dependent on the pH value of the media.

As Krebs and Speakman (1945) already demonstrated, at a constant ionic strength the solubility of an ionogenic substance can be calculated from the pH dependence of the solubility if the pK_a value of the substance and the solubility of the neutral molecular species — the limiting solubility — are known (Albert and Serjeant, 1971).

Determination of the limiting solubility is — especially with sparingly soluble substances — extremely difficult and subject to many errors. In practice, these factors very much limit application of the Krebs-Speakman method.

In the following, it will be shown that at constant ionic strength both the pK_a value and the limiting solubility of a substance can be calculated only from its solubility as a function of the pH of the medium.

Theory

Following Krebs and Speakman (1945), the solubility S of a substance at a given pH is due to the solubility of its ionized form and the limiting solubility of the neutral molecule:

$$S = [HA] + [A^-] \quad \text{for acids} \tag{1a}$$

or

$$S = [B] + [BH^+] \quad \text{for bases} \tag{1b}$$

From the definition of the ionization constant, K_a,

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

$$K_a = \frac{[B][H^+]}{[BH^+]}$$

it follows that

$$S = [HA] + \frac{K_a \cdot [HA]}{[H^+]} = [HA] \cdot \left(1 + \frac{K_a}{[H^+]}\right) \tag{2a}$$

$$S = [B] + \frac{[B][H^+]}{K_a} = [B] \cdot \left(1 + \frac{[H^+]}{K_a}\right) \tag{2b}$$

Whereas in Eqns. 2 the concentration of hydrogen ions is experimentally given, the solubility S of the substance can be determined. As can easily be seen, Eqns. 2 show the straight-line form

$$y = mx + a \tag{3}$$

with $y = S =$ solubility of the substance. The meaning of the other parameters is given in Table 1.

TABLE 1

MEANING OF THE PARAMETERS OF EQN. 3

Parameter	Acids	Bases
m	$K \cdot [HA]$	$[B]/K_a$
x	$1/[H^+]$	$[H^+]$
a	$[H_a]$	$[B]$

By means of the least-squares method the parameters of Eqn. 3, the slope m and the intercept a can be calculated from the following set, the solubility S_i of the substance at the concentration of hydrogen ion $[H^+]_i$, which is experimentally known.

As shown in the appendix, the intercept a and the slope m are given by

$$a = \bar{S} - m\bar{x} \tag{4}$$

and

$$m = \frac{\sum\limits_{i=1}^{n} S_i x_i - \frac{1}{n} \sum\limits_{i=1}^{n} S_i \sum\limits_{i=1}^{n} x_i}{\sum\limits_{i=1}^{n} x_i^2 - \sum\limits_{i=1}^{n} x_i \sum\limits_{i=1}^{n} x_i}$$

or

$$m = \frac{\sum\limits_{i=1}^{n} (S_i - \bar{S})(x_i - \bar{x})}{\sum\limits_{i=1}^{n} (x_i - \bar{x})^2} \tag{5}$$

where $\bar{S}$, $\bar{x}$ are the average values of S_i or x_i. Hence the solubility of the neutral molecule, the limiting solubility, is given by the intercept m, Eqn. 4, whereas the pK_a value is given by

$$pK_a = -\log\frac{m}{[HA]} = -\log\frac{m}{a} \tag{6a}$$

$$= \log a - \log m \qquad \text{for acids}$$

or

$$pK_a = -\log\frac{[B]}{m} = -\log\frac{a}{m} \tag{6b}$$

$$= \log m - \log a \qquad \text{for bases}$$

Materials and methods

The solubilities of LHM[1] and pyrazolic acid were determined at a temperature of 37°C. The buffers used were made by mixing different amounts of 1/15 M solutions

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[1] Lisuride hydrogen maleate.

of KH_2PO_4 and $Na_2HPO_4 \cdot 2H_2O$, respectively. The solubilities at the different pH values were determined from the concentrations of the substances in the supernatant liquid. The concentration of pyrazolic acid was measured by direct photometry, whereas the concentration of LHM was measured by means of a HPLC procedure.

Applications

By a simple transformation of Eqn. 2 one obtains Eqns. 7, originally used by Krebs and Speakman.

$$pK_a = pH_i - \log\left\{ \frac{S_i}{[HA]} - 1 \right\} \text{ for acids} \tag{7a}$$

or

$$pK_a = pH_i + \log\left\{ \frac{S_i}{[B]} - 1 \right\} \text{ for bases} \tag{7b}$$

For this procedure of determining the pK_a value it is necessary to know the limiting solubility. The determination of this value is rather laborious. Firstly it is determined at a pH at which it is suspected that the neutral molecule will predominate. Secondly, two further determinations are made 0.5 pH unit above and below the formerly used value. If, as a necessary condition, the 3 solubility figures agree within the range of experimental error, the average is accepted as the limiting solubility.
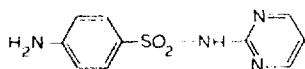
Sulphadiazine
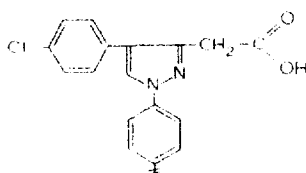
Pyrazolic acid
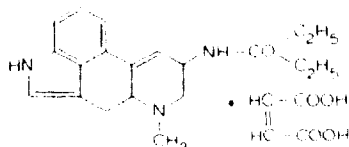
Lisuride hydrogen maleate

TABLE 2

EXPERIMENTAL AND CALCULATED DATA FOR SULPHADIAZINE

pH	Solubility (mg/100 ml)		Difference (calc. − expt.)	Error (%)
	Expt. [a]	Calc.		
6.01	8.50	8.16	0.342	4.19
6.35	11.10	10.88	0.219	2.01
6.82	19.40	20.67	1.270	6.15
7.23	43.50	43.92	0.421	0.96
7 56	86.00	87.23	1.228	1.41
7.67	114.00	1^1.68	3.319	3.00
8.00	229.00	229.96	0.959	0.42

Coefficient of correlation: $r = 1.0$. Limiting solubility (calc.) 5.86 (mg/100 ml). pK_a value (calc.): 6.42.
[a] The solubility values are taken from Krebs and Speakman (1945).

Sulphadiazine

Krebs and Speakman published the determination of the pK_a values of sulpha-diazine. The limiting solubility determined by an extrapolation procedure was 6.16 mg/100 ml. The experimental data used by them are summarized in Table 2. The pK_a value determined by this method is given by $pK_a = 6.45 \pm 0.04$. Sulphadiazine is an amphoteric substance. Krebs and Speakman determined a pK_b value of 11.9. The calculation using the method described above give the following figures: $pK_a = 6.42$, limiting solubility 5.86 mg/100 ml and $pK_b = 12.07$. This pK_b value is in agreement with the pK_b value determined by Bell and Roblin (Krebs and

TABLE 3

EXPERIMENTAL AND CALCULATED DATA FOR PYRAZOLIC ACID

pH	Solubility (mg/100 ml)		Difference (calc. − expt.)	Error (%)
	Expt.	Calc.		
5.00	4.00	7.08	3.08 *	43.5 *
5.50	11.00	11.83	0.83	7.05
6.00	25.00	26.86	1.86	6.92
6.20	39.00	39.71	0.71	1.79
6.50	82.00	74.37	7.63	10.26
6.80	146.00	143.53	2.47	1.72
7.00	221.00	224.62	3.62	1.61

Limiting solubility (calc.): 4.89 (mg/100 ml). pK_a value (calc): 5.35. Coefficient of correlation: $r = 0.999$.
* This large difference (error) can be explained by the formation of insoluble complexes between pyrazolic acid and bivalent ions from the glass vessels. This complex formation always impairs the exact determination of solubility at low concentrations of pyrazolic acid.

TABLE 4

EXPERIMENTAL AND CALCULATED DATA FOR LHM

pH	Solubility (mg/100 ml)		Difference (calc. − expt.)	Error (%)
	Expt.	Calc.		
8.3	2.05	2.24	0.194	8.64
7.9	2.25	2.51	0.264	10.51
7.5	2.97	3.19	0.223	6.99
7.0	5.84	5.63	0.207	3.68
6.75	7.86	8.41	0.550	6.54
6.40	15.64	16.27	0.629	3.86
6.20	26.14	24.58	1.564	6.36
5.80	59.20	58.61	0.589	1.00
5.50	114.39	114.89	0.500	0.44

Limiting solubility (calc.): 2.06 (mg/100 ml). pK_a value (calc.): 7.24. Coefficient of correlation: $r = 1.00$.

Speakman, 1945). The difference between the experimentally determined and the calculated limiting solubilities is given by 0.33 mg/100 ml only. The calculated figures are also summarized in Table 2.

Pyrazolic acid

The solubility figures of pyrazolic acid as a function of the pH at a temperature of 37°C are summarized in Table 3. The limiting solubility is calculated as 4.89 mg/100 ml. The calculated pK_a value is given by $pK_a = 5.35$. The correlation coefficient is given by $r = 0.999$.

Lisuride hydrogen maleate (LHM)

LHM is a polyfunctional base. Apparently, the pK_a values of the different functional groups are so far separated that only one pK_a value can be calculated from the solubility data, as given in Table 4.

The calculated limiting solubility of the neutral molecule and the pK_a value are given by 2.06 mg/100 ml and $pK_a = 7.24$, respectively. The correlation coefficient reaches its maximum value $r = 1.0$, meaning that in the pH range from 5.5 to 8.3 we can measure the ionization process of only one functional group.

Discussion

The Krebs-Speakman equation allows calculation of the solubility of a substance as a function of the pH if the pK_a of this substance and the limiting solubility of the neutral molecule are known. Starting from this equation, we derived a procedure which allows calculation of the pK_a value of a substance and the limiting solubility of its neutral molecule.

Experimental determination of low solubilities and hence of the limiting solubility of a neutral molecule is rather laborious and subject to many errors. When calculating the solubilities according to the Krebs-Speakman equation, these errors are propagated. Thus especially the figures for high solubilities are extremely imprecise.

For, to calculate as exactly as possible pK_a values and solubility data by means of the procedure derived above, one should use only such data as can be determined precisely especially as the determination of these values needs a minimum of time.

Strictly speaking, the correlation coefficient has no meaning in this procedure as the underlying equations give a correct description of the physical situation. Thus its value always should be $r = 1.0$. Deviations from this maximum value are a measure of the reliability of the experimental data. If we apply the procedure derived above to the evaluation of solubility data of polyfunctional substances, a significant deviation of the correlation coefficient from its maximum value shows that the pK_a values of the different groups are not sufficiently separated as to be determined as single values.

A generalization of the procedure derived above, which also will allow determination of less separated pK_a values of polyfunctional substances, will be given in another report.

Appendix

As shown above, the solubility data S_i at pH_i follow a linear relationship. i.e. they approximate to a straight line

$$y_i = mx_i + a$$

The approximation criterion is given by

$$\sum_{i=1}^{n} (S_i - y_i)^2 = \sum_{i=1}^{n} (S_i - mx_i - a)^2 \overset{!}{=} 0 \tag{A1}$$

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

$$\frac{\partial}{\partial a} \sum_{i=1}^{n} (S_i - mx_i - a)^2 = 0 \tag{A2a}$$

$$\frac{\partial}{\partial m} \sum_{i=1}^{n} (S_i - mx_i - a)^2 = 0 \tag{A2b}$$

From the equations (A2) it follows that

$$\sum_{i=1}^{n} (a + mx_i - S_i) = 0$$

$$na + m\sum_{i=1}^{n} x_i = \sum_{i=1}^{n} S_i \qquad (A3a)$$

By analogy we have

$$\sum_{i=1}^{n} \left(mx_i^2 + ax_i - S_i x_i\right) = 0$$

$$m\sum_{i=1}^{n} x_i^2 + a\sum_{i=1}^{n} x_i = \sum_{i=1}^{n} S_i x_i \qquad (A3b)$$

Considering that $\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$ and $\bar{S} = \frac{1}{n}\sum_{i=1}^{n} S_i$ we have from Eqn. A3a

$$a = \bar{S} - m\bar{x} \qquad (A4)$$

By insertion of Eqn. A4 into Eqn. A3b it follows that:

$$m = \frac{\sum_{i=1}^{n} S_i x_i - \frac{1}{n}\sum_{i=1}^{n} S_i \sum_{i=1}^{n} x_i}{\sum_{i=1}^{n} x_i^2 - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} x_i}$$

or

$$m = \frac{\sum_{i=1}^{n} (S_i - \bar{S})(x_i - \bar{x})}{\sum_{i=1}^{n} (x_i - \bar{x})^2}$$

Thus the solubility of the neutral molecular form is given by the intercept a whereas the value of pK_a is given by:

$$pK_a = -\log\frac{m}{[HA]} = -\log\frac{m}{a} \text{ for acids}$$

or

$$pK_a = -\log\frac{[B]}{m} = \log\frac{m}{a} \text{ for bases}$$

The correlation coefficient is given by Draper and Smith (1981), and Dunn and

Clark (1974):

$$\gamma = \frac{\sum\limits_{i=1}^{n}(x_i - \bar{x})(S_i - \bar{S})}{\sqrt{\sum\limits_{i=1}^{n}(x_i - \bar{x})^2 \sum\limits_{i=1}^{n}(S_i - \bar{S})^2}}$$

The meaning of x is given in Table I.

Acknowledgements

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