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The Gibbs constant and pH solubility profiles

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A well known property of solubility profiles of weak acids and bases as a function of pH is the presence of a specific pH at which the solubility has a maximum value (Chowhan et al., 1978; Streng et al., 1984). The pH at this point is referred to as $\mathrm{p}H_{\max}$ (Figs. 1 and 2). Recently (Avdeef et al., 1998), a suggestion was made to name this pH the Gibbs $\mathrm{p}K_\mathrm{a}$ since it is related to the equilibrium properties of the weak acid or weak base with the symbol $\mathrm{p}K_\mathrm{a}^{(\mathrm{s})}$. This is a conditional constant because it is dependent upon the concentrations of the counter ions to the charged weak acid or weak base species. The following equation was shown to hold when the counter ion concentration is constant:

$$\mathrm{p}K_\mathrm{a}^{(\mathrm{s})} - \mathrm{p}K_\mathrm{a} = \mathrm{p}S_0 - \mathrm{p}S_\mathrm{i}$$

where S_0 is the solubility of the uncharged species (intrinsic solubility) and S_i is the solubility of the charged species. A similar relationship holds for octanol–water partition analysis.

When the counter ion concentration is changing, the value for $\mathrm{p}H_{\max}$ has been shown to be dependent upon the anion concentration for a weak acid and the cation concentration for a weak base (Streng et al., 1984). Although $\mathrm{p}H_{\max}$ is not a constant, a relationship can be derived which relates $\mathrm{p}H_{\max}$ to another constant which, in accordance with the earlier suggestion, will be designated the Gibbs constant (K_G^A and K_G^B). Depending on the type of compound, weak acid or weak base, the equations are different and therefore there is the superscript A or B.

1. Weak acid

For the equilibria:

$$\mathrm{HA} \leftrightarrow \mathrm{H}^+ + \mathrm{A}^-$$

The equilibrium constant is given by:

$$K_\mathrm{a} = \frac{\{\mathrm{H}^+\}\{\mathrm{A}^-\}}{\{\mathrm{HA}\}} \tag{1}$$

In Eq. (1) {} represents the activity of the indicated species. For a saturated solution containing excess material, the solid material in equilibrium with the solution at any pH other than $\mathrm{p}H_{\max}$ will be either the free acid or the salt. At $\mathrm{p}H_{\max}$ the system is invariant and therefore there is an infinite number of concentration ratios for the free acid and salt in the solid phase. As a consequence of this, the system is described by both the intrinsic solubility of the free acid and the solubility product for the salt formation of the weak acid (Eq. (2)).

$$K_\mathrm{sp} = \{\mathrm{M}^+\}\{\mathrm{A}^-\} \tag{2}$$

In Eq. (2), $\{\mathrm{M}^+\}$ is the counterion of the weak acid anion. Substituting $K_\mathrm{sp}/\{\mathrm{M}^+\}$ and the intrinsic solubility of the weak acid, $\{\mathrm{HA}\}_\mathrm{s}$, into Eq. (1):

$$K_\mathrm{a} = \frac{\{\mathrm{H}^+\}_{\max} K_\mathrm{sp}}{\{\mathrm{M}^+\}\{\mathrm{HA}\}_\mathrm{s}} \tag{3}$$

Rearranging and taking logarithms:

$$\log K_\mathrm{G}^\mathrm{A} \equiv \log K_\mathrm{a} + \log\{\mathrm{HA}\}_\mathrm{s} - \log K_\mathrm{sp} = \log \frac{\{\mathrm{H}^+\}_{\max}}{\{\mathrm{M}^+\}} \tag{4}$$

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Eq. (4) defines the Gibbs constant for a weak acid, K_G^A. According to this equation there will be an increase in hydrogen ion concentration of maximum solubility with an increase in cation concentration. Multiplying Eq. (4) through by -1:

$$pK_G^A = pK_a + p\{HA\}_s - pK_{sp} = -\log\frac{\{H^+\}_{max}}{\{M^+\}} \tag{5}$$

As can be seen in Eqs. (4) and (5), the Gibbs constant for a weak acid is a combination of three constants and is therefore also a constant. Therefore, if the Gibbs constant and cation concentration are known, pH_{max} can be determined.

2. Weak base

For the equilibria:

$$HB^+ \leftrightarrow H^+ + B$$

The equilibrium constant is given by:

$$K_a = \frac{\{H^+\}\{B\}}{\{HB^+\}} \tag{6}$$

Similar to the weak acid derivation, $K_{sp}/\{X^-\}$, $\{X^-\}$ is the counterion for the weak acid cation, and the intrinsic solubility of the free base can be substituted into Eq. (6)

$$K_a = \frac{\{H^+\}_{max}\{B\}_s}{\frac{K_{sp}}{\{X^-\}}} = \frac{\{H^+\}_{max}\{B\}_s\{X^-\}}{K_{sp}} \tag{7}$$

Rearranging Eq. (7) and taking logarithms:

$$\log K_G^B \equiv \log K_a - \log\{B\}_s + \log K_{sp}$$
$$= \log(\{H^+\}_{max}\{X^-\}) \tag{8}$$

Eq. (8) defines the Gibbs constant for a weak base, K_G^B. According to this equation there will be a decrease in the hydrogen ion concentration of maximum solubility with an increase in anion concentration. Multiplying Eq. (8) through by -1:

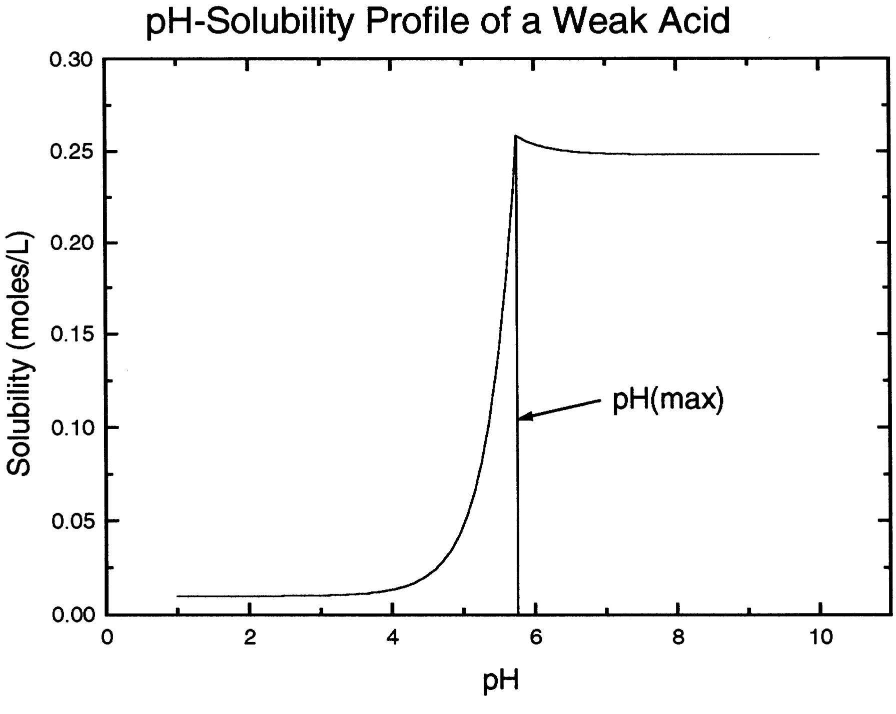

Fig. 1.

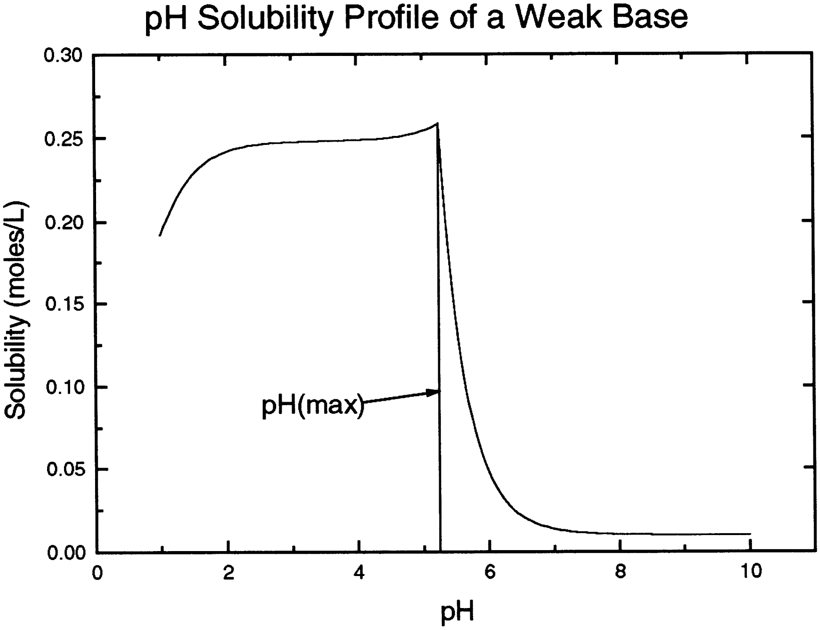

Fig. 2.

$$
\begin{aligned}
pK_G^B &= pK_a + \log\{B\}_s + pK_{sp} \\
&= -\log(\{H^+\}_{max}\{X^-\}) \qquad (9)
\end{aligned}
$$

As can be seen in Eqs. (8) and (9) the Gibbs constant for a weak base is a combination of three constants and is therefore also a constant. Therefore, if the Gibbs constant and anion concentration are known, pH_{max} can be determined.

Two additional useful equations can be obtained.

For a weak acid, it is not always possible to know the cation concentration since it forms the precipitated salt with the weak acid. As previously described (Streng et al. 1984), a substitution can be made for the cation concentration in Eq. (3) using the charge balance equation, where [] represent concentrations:

$$
[H] + [M] = [OH] + [A] + [X] \qquad (10)
$$

Substituting into Eq. (4) for the cation concentration and inserting the Gibbs constant the following equation can be obtained.

$$
\{H\}_{max} = \frac{[X] + \left([X]^2 + 4\left(\frac{1}{K_G^A y_M} + \frac{1}{y_H}\right)\left(\frac{K_w}{y_{OH}} + \frac{K_a\{HA\}_s}{y_A}\right)\right)^{1/2}}{2\left(\frac{1}{K_G^A y_M} + \frac{1}{y_H}\right)} \qquad (11)
$$

In Eq. (11), y_i is the activity coefficient of species i.

Similar substitutions can be made for a weak base using the charge balance equation:

$$
[H] + [M] + [HB] = [OH] + [X] \qquad (12)
$$

Substituting into Eq. (8) for the anion concentration and inserting the Gibbs constant the following equation can be obtained.

$$
\{H\}_{max} = \frac{-[M] + \left([M]^2 + 4\left(\frac{\{B\}_s}{K_a y_{HB}} + \frac{1}{y_H}\right)\left(\frac{K_w}{y_{OH}} + \frac{K_G^B}{y_X}\right)\right)^{1/2}}{2\left(\frac{\{B\}_s}{K_a y_{HB}} + \frac{1}{y_H}\right)} \qquad (13)
$$

From Eqs. (11) and (13), it can be seen that there is a constant, designated the Gibbs constant, which can be used to determine the pH of maximum solubility for a weak acid or weak base. These equations are similar to those previously described (Streng et al., 1984).

References

Avdeef, A., 1998. pH-metric solubility. 1. Solubility–pH profiles from Bjerrum plots. Gibbs buffer and pK_a in the solid state. Pharm. Pharmacol. Commun. 4, 165–178.

Chowhan, Z.T., 1978. pH–solubility profiles of organic carboxylic acids and their salts. J. Pharm. Sci. 67, 1257–1260.

Streng, W.H., Hsi, S.K., Helms, P.E., Tan, H.G.H., 1984. General treatment of pH–solubility profiles of weak acids and bases and the effects of different acids on the solubility of a weak base. J. Pharm. Sci. 73, 1679–1684.