Spectrophotometry

The determination of ionization constants by UV or visible spectrophotometry may be particularly useful for insoluble compounds (Albert and Serjeant 1984). For many insoluble compounds, a solution with a concentration as low as 10^{-6} M may still give an analytically useful chromophore. The method depends upon the direct determination of the ratio of molecular species (neutral molecule) to ionized species in a series of non-absorbing buffer solutions. A wavelength, typically called the *analytical wavelength*, is chosen at which the greatest difference between the absorbances of the two species is observed (Albert and Serjeant 1984).

For acids, Equation 4.31 is used if A_I is greater than A_M, whereas Equation 4.32 is used if the reverse is the case.

$$pK_a = pH + \log\frac{A_I - A}{A - A_M} \tag{4.31}$$

$$pK_a = pH + \log\frac{A - A_I}{A_M - A} \tag{4.32}$$

where A_I and A_M are the absorbances of the ionized species and the neutral species, respectively. A is the observed absorbance at any particular pH.

For bases, Equation 4.33 is used if A_I is greater than A_M, and Equation 4.34 if the reverse is the case.

$$pK_a = pH + \log\frac{A - A_M}{A_I - A} \tag{4.33}$$

$$pK_a = pH + \log\frac{A_M - A}{A - A_I} \tag{4.34}$$

Potentiometric Titration

Potentiometric titration is a commonly used technique for pK_a determination (Albert and Serjeant 1984, Takacs-Novak et al. 1997, Glomme et al. 2005). The PCA101 chemical analyzer, developed and manufactured by Sirius Analytical Instruments Ltd., is the first commercial instrument designed specifically to determine ionization constants (Avdeef 1993).

To use the potentiometric titration method, the compound typically must have a solubility of at least 5×10^{-4} M. For insoluble compounds, a mixed solvent approach can be used (Avdeef 1993). Methanol is the most commonly used co-solvent for this purpose and its effect on pK_a has been studied extensively. Experimentally, several pK_a measurements need to be performed in mixed solvent solutions having various methanol-water proportions. The aqueous pK_a is deduced by extrapolation of the apparent pK_a values to zero methanol. Other co-solvents that can be used for this purpose and that are supported by the PCA101 include ethanol, ethylene glycol, DMSO, and 1,4-dioxane. Keep in mind that different co-solvents will have different effects on the pK_as and these effects are also different for acids and bases. Plots of apparent pK_a versus weight percent organic solvent (typically 0%–60%) show either a *hockey-stick* shape, or a *bow* shape, but rarely a straight line.

pK_a Prediction

Despite all the methods available for pK_a measurement, there are cases where the compounds are too insoluble or too unstable to measure. In the case of polyacids and bases, assigning experimental pK_a values to particular sites might be challenging. In some cases, only an estimation of a pK_a value is needed, such as in the early discovery stages. For these reasons, a method for a quick pK_a estimation may be very useful.

There are excellent reviews available for pK_a prediction (Fraczkiewicz 2006, Wan and Ulander 2006, Cruciani et al. 2009, Dearden 2012). A unique predictive algorithm has been established