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Modeling acid dissociation constant of analytes in binary solvents at various temperatures using Jouyban–Acree model

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Abstract

A mathematical equation, namely Jouyban–Acree model, for calculating apparent acid dissociation constants (pK_a) in hydro-organic mixtures with respect to the concentration of organic solvent and temperature is proposed. The correlation ability of the model is evaluated by employing pK_a values of 17 different acids in water–cosolvent systems. The results show that the model is able to correlate the pK_a values with an overall average percentage differences (APD) of $1.71 \pm 1.86\%$. In order to test the prediction capability of the model, nine experimental pK_a values from each data set have been employed to train the model, then the pK_a values at other solvent compositions and temperatures were predicted and the overall APD obtained is $2.10 \pm 2.42\%$. The applicability of the extended form of Jouyban–Acree model on pK_a data of analytes in ternary solvent mixtures is also shown.

Keywords: Cosolvency; Acid dissociation constant; Hydro-organic mixtures; Different temperatures; Jouyban–Acree model

1. Introduction

During the lead optimization phase of drug discovery studies, where a large number of molecules are biologically evaluated in parallel, the determination of physico-chemical properties is essential to ensure adequate characterization and quality of developed candidates [1]. The knowledge of acid dissociation constants of these new chemical entities is of fundamental importance in order to provide information for scientists working on chromatographic separations (retention times and selectivity dependence of mobile phase pH) [2], capillary electrophoresis separations (migration times or mobilities of the ionic species over a range of pH values) [2], pharmaceutical drug discovery and development [3], chemical reactivity (selection of conditions for synthesis by considering the effects of pH on reaction products and properties of postulated intermediates), salt formation, purification process [1] and pharmaceutical formulation development [1].

Experimental measurements of pK_a values are expensive, difficult, time consuming and limited by purity of compounds (almost all experimental methods except capillary electrophoresis) [3], low analyte solubility (in potentiometry), the range of pH (in high performance liquid chromatography), spectral similarities (in spectrometric methods), and stability of analytes (e.g. chemical reactions intermediates). The most important limitation is that before synthesis of a compound, its pK_a value cannot be estimated experimentally.

Although water is the most common solvent in chemical/pharmaceutical applications, organic solvents are used as a cosolvent in order to adjust separation selectivity and modify solubility, stability, pK_a and other characteristics of the analytes. Temperature plays a significant role in most of the chromatographic and electrophoretic methods and it is recognized as the most relevant parameter in gas chromatography. Many separation scientists have traditionally

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disregarded temperature effects in liquid chromatography whereas elevated temperature is a usual controlling variable in reversed phase liquid chromatography. Today publications stated the reasons for fearing of such methods and now temperature in combination with pH and cosolvent addition are introduced as variables to adjust selectivity towards acidic and basic compounds e.g. see Refs. [4–6].

Since the pK_a value of many compounds is determined commonly at 25 °C, prediction of pK_a at different temperatures (e.g. body temperature 37 °C) would be very useful tool for biological and biomedical applications. Using mixed solvents in the analytical/pharmaceutical areas is a common method to optimize solubility and/or separation efficiency. However, the number of solvent compositions and temperature combinations is quite large and it is difficult to determine all possible combinations by experiments. Thus, a good alternative is to use computational methods. The aim of this work is to present a mathematical treatment of pK_a values as a function of solvent composition and temperature. The accuracy of the proposed model is assessed by using available pK_a values in mixed solvents at various temperatures collected from the literature.

2. Theoretical treatment

A dissociation reaction of a monoprotic acid (HA) in a solvent can be represented as:

$$\mathrm{HA} \leftrightarrow \mathrm{H^+} + \mathrm{A^-}, \quad K_a = \frac{a_{\mathrm{H^+}} \cdot a_{\mathrm{A^-}}}{a_{\mathrm{HA}}}$$

where a is the activity of the chemical species. The logarithm of K_a expressed as:

$$2.303RT \log K_a = \mu_{\mathrm{H^+}} + \mu_{\mathrm{A^-}} - \mu_{\mathrm{HA}} \tag{1}$$

where μ denotes chemical potential of the species.

The chemical potential in aqueous cosolvent mixtures can be expressed as the mole fractions of the cosolvents:

$$\mu^{\mathrm{m}}_{\mathrm{H^+}} = X^{\mathrm{c}}\mu^{\mathrm{c}}_{\mathrm{H^+}} + X^{\mathrm{w}}\mu^{\mathrm{w}}_{\mathrm{H^+}} + A_0 X^{\mathrm{c}}X^{\mathrm{w}} + A_1 X^{\mathrm{c}}X^{\mathrm{w}}(X^{\mathrm{c}} - X^{\mathrm{w}}) \tag{2}$$

$$\mu^{\mathrm{m}}_{\mathrm{A^-}} = X^{\mathrm{c}}\mu^{\mathrm{c}}_{\mathrm{A^-}} + X^{\mathrm{w}}\mu^{\mathrm{w}}_{\mathrm{A^-}} + B_0 X^{\mathrm{c}}X^{\mathrm{w}} + B_1 X^{\mathrm{c}}X^{\mathrm{w}}(X^{\mathrm{c}} - X^{\mathrm{w}}) \tag{3}$$

$$\mu^{\mathrm{m}}_{\mathrm{HA}} = X^{\mathrm{c}}\mu^{\mathrm{c}}_{\mathrm{HA}} + X^{\mathrm{w}}\mu^{\mathrm{w}}_{\mathrm{HA}} + C_0 X^{\mathrm{c}}X^{\mathrm{w}} + C_1 X^{\mathrm{c}}X^{\mathrm{w}}(X^{\mathrm{c}} - X^{\mathrm{w}}) \tag{4}$$

where superscripts m, c and w denote mixed solvent, pure cosolvent and pure water, respectively, X is the mole fraction of the solvents, and A, B and C the solute–solvent and solvent–solvent interaction terms. These terms represent the two body and three body interactions in the solution [7].

Summation of Eqs. (2)–(4) yields:

$$\begin{aligned}\mu^{\mathrm{m}}_{\mathrm{H^+}} + \mu^{\mathrm{m}}_{\mathrm{A^-}} - \mu^{\mathrm{m}}_{\mathrm{HA}} &= X^{\mathrm{c}}(\mu^{\mathrm{c}}_{\mathrm{H^+}} + \mu^{\mathrm{c}}_{\mathrm{A^-}} - \mu^{\mathrm{c}}_{\mathrm{HA}}) + X^{\mathrm{w}}(\mu^{\mathrm{w}}_{\mathrm{H^+}} + \mu^{w}_{\mathrm{A^-}} - \mu^{\mathrm{w}}_{\mathrm{HA}}) \\ &\quad + (A_0 + B_0 - C_0)X^{\mathrm{c}}X^{\mathrm{w}} \\ &\quad + (A_1 + B_1 - C_1)X^{\mathrm{c}}X^{\mathrm{w}}(X^{\mathrm{c}} - X^{\mathrm{w}})\end{aligned} \tag{5}$$

Replacing the corresponding equals from Eq. (1) into Eq. (5) with appropriate rearrangements give:

$$\begin{aligned}2.303R \log K_a^{\mathrm{m},T} &= X^{\mathrm{c}}(2.303R \log K_a^{\mathrm{c},T}) + X^{\mathrm{w}}(2.303R \log K_a^{\mathrm{w},T}) \\ &\quad + (A_0 + B_0 - C_0)\frac{X^{\mathrm{c}}X^{\mathrm{w}}}{T} \\ &\quad + (A_1 + B_1 - C_1)\frac{X^{\mathrm{c}}X^{\mathrm{w}}(X^{\mathrm{c}} - X^{\mathrm{w}})}{T}\end{aligned} \tag{6}$$

Since $(A_0 + B_0 - C_0)$, $(A_1 + B_1 - C_1)$ and $2.303R$ are constant values and p$K_a = -\log K_a$, it is possible to simplify Eq. (6) as:

$$\mathrm{p}K_a^{\mathrm{m},T} = X^{\mathrm{c}}\,\mathrm{p}K_a^{\mathrm{c},T} + X^{\mathrm{w}}\mathrm{p}K_a^{\mathrm{w},T} + W_0\frac{X^{\mathrm{c}}X^{\mathrm{w}}}{T} + W_1\frac{X^{\mathrm{c}}X^{\mathrm{w}}(X^{\mathrm{c}} - X^{\mathrm{w}})}{T} \tag{7}$$

where $W_0 = (A_0 + B_0 - C_0)/2.303R$ and $W_1 = (A_1 + B_1 - C_1)/2.303R$. It is obvious that one can use the volume /weight fractions of the solvents instead of the mole fractions [7] and rewrite Eq. (7) as:

$$\mathrm{p}K_a^{\mathrm{m},T} = f^{\mathrm{c}}\,\mathrm{p}K_a^{\mathrm{c},T} + f^{\mathrm{w}}\,\mathrm{p}K_a^{\mathrm{w},T} + K_0\frac{f^{\mathrm{c}}f^{\mathrm{w}}}{T} + K_1\frac{f^{\mathrm{c}}f^{\mathrm{w}}(f^{\mathrm{c}} - f^{\mathrm{w}})}{T} \tag{8}$$

where K_0 and K_1 are the curve-fitting parameters. The numerical values of K_0 and K_1 can be computed by fitting the experimental values of $(\mathrm{p}K_a^{\mathrm{m},T} - f^{\mathrm{c}}\,\mathrm{p}K_a^{\mathrm{c},T} - f^{\mathrm{w}}\,\mathrm{p}K_a^{\mathrm{w},T})$ against $\frac{f^{\mathrm{c}}f^{\mathrm{w}}}{T}$ and $\frac{f^{\mathrm{c}}f^{\mathrm{w}}(f^{\mathrm{c}} - f^{\mathrm{w}})}{T}$ by using a no intercept least square analysis.

The general form of the proposed equation can be expressed as:

$$\mathrm{p}K_a^{\mathrm{m},T} = f^{\mathrm{c}}\,\mathrm{p}K_a^{\mathrm{c},T} + f^{\mathrm{w}}\,\mathrm{p}K_a^{\mathrm{w},T} + f^{\mathrm{c}}f^{\mathrm{w}}\sum_{q=0}^{n}\frac{K_q(f^{\mathrm{c}} - f^{\mathrm{w}})^q}{T} \tag{9}$$

The model could possess as many curve-fitting parameters as needed for accurate representation of experimental data. However, it is preferred to employ the lowest number of curve-fitting parameters, since it requires minimum number of experimental data in model training process. In some cases, the numerical values of pK_a^{c} are not available. If so, it is pos-