*ADMET & DMPK 3(4) (2015) 359-362; doi: **10.5599/admet.3.4.209***

ADMET

Open Access : ISSN : 1848-7718

http://www.pub.iapchem.org/ojs/index.php/admet/index

Note

Application of the Henderson-Hasselbalch equation to solubility determination: NSC-639829 Case Study

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Received: August 11, 2015; Revised: October 04, 2015; Published: December 30, 2015

A number of publications which challenge the applicability of the Henderson-Hasselbalch equation to saturated solutions have appeared in the last few years (Avdeef [1-3], Butcher *et al.* [4], and Volgyi *et al.* [5]). In the most recent of these, Butcher *et al.* [4] suggested "the Henderson-Hasselbalch equation may not always be an accurate predictor of the pH dependence of solubility." They claimed that the p*K*a of 4.70 determined by Jain *et al.* [6] for NSC-639829 is incorrect and that the value of 3.76, which they obtained by extrapolation of spectrophotometrically determined p*K*a values in 22, 30, and 41 percent methanol-water solutions, is the correct value. We believe that 4.70 is the correct value and that there are several serious flaws in their analysis. These are described below.

Prediction

Schonherr *et al.* [7] calculated and measured the solubilities of 34 active pharmaceuticals. They found that all solubility-pH profiles showed the expected shape and appearance, which are in good agreement with the values calculated using the Henderson-Hasselbalch equation.

It is clear from the observed data in Figure 1 that a pKa 4.70, (as reported by Jain *et al.* [6]), for NSC-639829 gives good estimates of the observed solubilities and that a p*K*a of 3.76 (as proposed by Butcher et al. [4]) will give solubility predictions that are nearly an order of magnitude less than the observed values. In order to justify their p*K*a value Butcher *et al.* have to postulate the existence of a mixed charge dimer (or higher order oligomers) using weighted, nonlinear regression which is then iterated. There is no way to calculate the solubility of NSC-639829 as a function of pH without using the value of 4.70**.** The postulation of a logK_2 of 7.8, so that the logarithmic factor in Equation A7 (from ref. [4]) is 0.94, only serves to bring the p*K*a 3.76 up to 4.70, which is identical to value of Jain et al. [6].

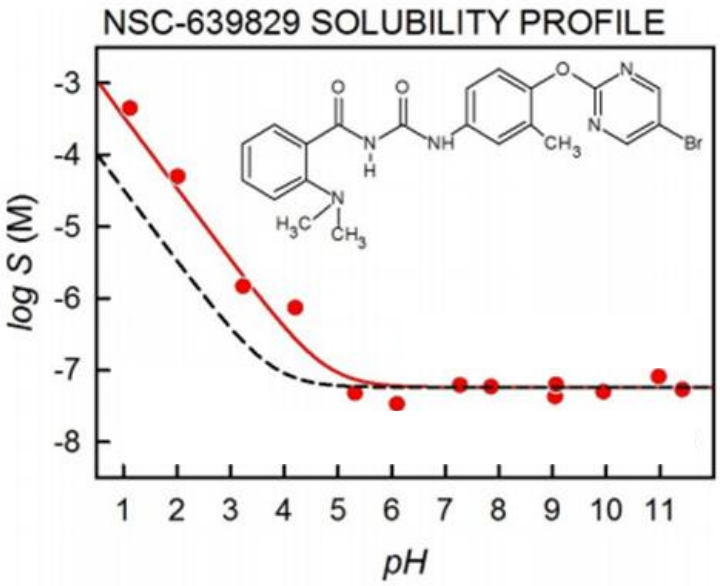

Figure 1. Solubility-pH profile for NSC-639829. **(a)** Points and solid curve from Jain et al. [6]. **(b)** The dashed curve from Butcher et al. [4].

Extrapolation

The p*K*a value proposed by Butcher *et al.* [4] was obtained by extrapolation. While extrapolation is a valuable tool, it must be used with caution. The use of data from 22 - 41 % methanol to obtain the value in 0 % methanol represents a long extrapolation (roughly 100 % on the basis of methanol concentration or roughly 50 % on the basis of reciprocal dielectric constant). Since self-association of NSC-639829 is minimal in methanol and dilute aqueous solution, the predicted p*K*a or Butcher et al. [4] is likely that of the monomeric species.

pKa of monomer and associated forms

The p*K*a of any compound is profoundly affected by its environment. The p*K*a of a compound at infinite dilution, or even at a low concentration, is different from its value in an aggregate, whether the aggregate is a dimer, a micelle, or something in between. Therefore, even if the p*K*a of the monomer is 3.74, it is of no value for calculating the total drug concentration in a saturated solution. As stated by Burns et al. “The pKa … is an aggregation dependent value. Therefore, a concentration-appropriate pKa must be applied when interpreting the results of experiments ….” [8]. It is noteworthy that Avdeef et al. [9] indicate that the observed p*K*a of a dimer often differs from that of the monomer.

As shown in Figure 2, many physical properties change with increasing concentration, especially if there is self-association [10]. In fact, Yalkowsky and Zografi [11] showed that the p*K*a of the carboxyl group of the decylcarnitine zwitterion (Figure 3) is constant and independent of concentration below the critical micelle concentration (CMC), begins to increase at the CMC and asymptotes the micellar value at higher concentrations. The micellar p*K*a is lower because the positive charge resulting from the partially neutralized acid of the micelle repels the hydronium ion. This phenomena has been reported for a number of other systems, including: alkylamine oxides by Tokiwa and Ohki [12], aliphatic bases by Matulis and Bloomfield [13], carboxylic acids by Kanicky and Shah [14], and resveratrol by Lopez-Nicolas and Garcia-Carmona [15]. It is also responsible for the sharp increase in solubility of prostaglandin observed by Roseman and Yalkowsky [16].

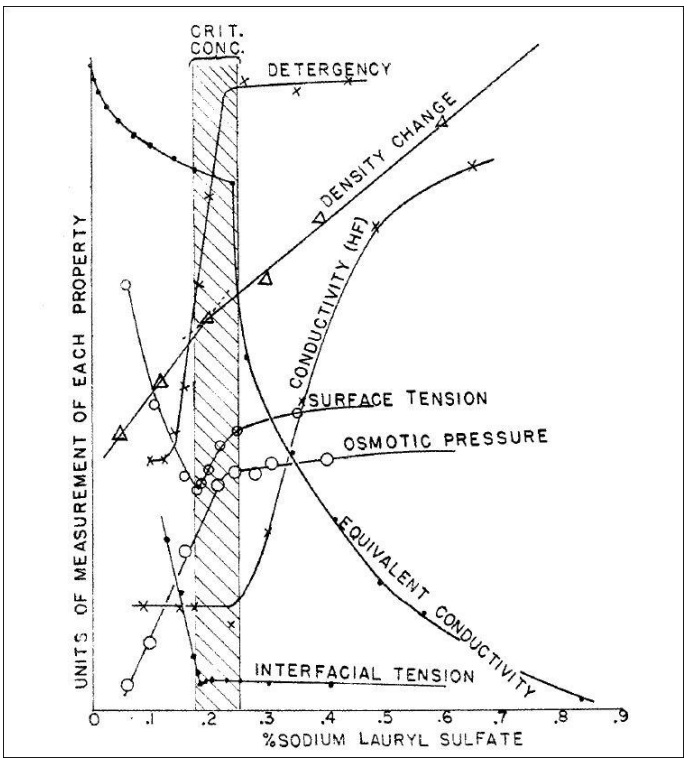

Figure 2. Physical property curves for sodium lauryl sulfate from Preston [10].

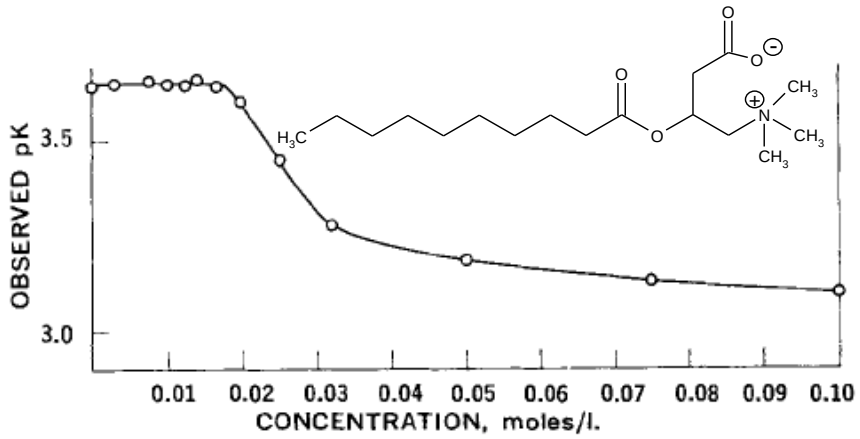

Figure 3. p*K*a vs. concentration of decylcarnitine from Yalkowsky and Zografi [11].

Conclusions

The Henderson-Hasselbalch equation, as used by Jain *et al.* [6] is an accurate predictor of the pH dependence of solubility, provided that the correct p*K*a is used. The monomer and the aggregated forms of any compound can, and often do, have different values for many physical properties, including p*K*a values. The p*K*a of the monomer should be used for calculations involving dilute solutions, where association is minimal, and p*K*a of the form that exists at saturation should be used for solubility studies, including the study of the solubility of NSC-639829.

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