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Michael Hippler and George D. Metcalfe

USING ACTIVITIES TO CORRECT THE HENDERSON-HASSELBALCH EQUATION

KEYWORDS

Physical Chemistry, Analytical and Bioanalytical Chemistry, Chemical Education Research, Acids/Bases, pH, Titrations

ABSTRACT

The Henderson-Hasselbalch equation is central in chemistry teaching and has many practical applications. The equation, however, has many inherent approximations which limit its application. Here, we focus on one particular approximation, the use of concentrations instead of activities. We show that this can be easily corrected for in a modification which extends the useful range of the equation to moderately strong electrolytes ($I < 0.5$). Without this correction, the calculated pH of a typical phosphate buffer is too high by up to 0.4. The correction can be easily automated in a spreadsheet and is straightforward to implement into the chemistry and biochemistry teaching and laboratory curriculum. It introduces students to the concept of activities in thermodynamic equilibrium, and to the Debye-Hückel equation. It further emphasizes the importance of using activities instead of concentrations when the ionic strength exceeds 0.005 M, in contrast to the approach found in textbooks where activities are introduced, but then ignored 'for the sake of simplicity', even in example calculations where the use of concentrations is clearly not appropriate. In this contribution we intend also to stimulate discussions about how to teach chemical equilibria, Brønsted-Lowry acid-base reactions and titrations, buffer solutions, the concept of activity and the concept and definition of pH.

INTRODUCTION

The Henderson-Hasselbalch equation (HH),

$$\text{pH} = \text{p}K_{\text{a}} + \lg \{c(\text{A}^-)/c(\text{HA})\} \quad (1)$$

is central in the chemistry curriculum with many practical applications in general and analytical chemistry, biochemistry and electrochemistry (lg is \log_{10} , all other quantities are de-

finied below). The history and some of the inherent approximations of HH have been discussed in the chemical educational literature before.^[1-5] In our research lab we routinely prepare phosphate-buffered growth media in which we culture bacteria (*E. coli*) and analyse their metabolites, using a variety of analytical techniques including liquid-phase Raman spectroscopy.^[6-8] In comparing pH measured by electrodes and pH calculated by HH, we found large discrepancies of the order of 0.4 around pH = 7. This led us to review the approximate nature of HH and explore ways how to correct it to make it more accurate. It appears to us that there are 3 main problems with the Henderson-Hasselbalch equation: **(a)** the concentrations of the weak acid and its corresponding base, $c(\text{HA})$ and $c(\text{A}^-)$, respectively, are often taken as the *analytical concentrations*, that is the amount weighed in and added to the solutions, but not the *actual concentrations* which adjust according to the thermodynamic equilibrium of the ionization of the acid, the ionization of water and mass and charge balances. This effect is well understood and appreciated, and correction procedures are detailed in the literature (see, e.g., refs [2,5,9]). Because we work close to pH = 7, this is not the problem with our phosphate buffers, and we measure actual concentrations by spectroscopy regardless. **(b)** Deriving HH from thermodynamic equilibrium, it is clear that activities and not concentrations should be used. This is widely appreciated *in principle*, but then waived away 'for the sake of simplicity' as if it was not really relevant *in practice* in most general-chemistry textbooks. It turned out that this was the problem with our phosphate buffer calculations and we will focus on that in the following. And finally **(c)**, of course, there is the 'elephant in the room', what is pH anyway?^[10-15]

In this contribution, our aim is to show how to extend and apply HH correctly in many practical situations and the theory behind it, and how to implement it into the chemistry curriculum. We also wish to stimulate discussions among chemical educators about how to teach chemical equilibria, Brønsted-Lowry acid-base reactions and titrations, buffer solutions, the concept of activity and the concept and definition of pH.

THEORY

The ionization of a weak, monoprotic Brønsted-Lowry acid in water as solvent,



is described by the thermodynamic equilibrium constant K_{a} .^[16]

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$$K_a = a(\text{H}^+) a(\text{A}^-) / a(\text{HA}), \quad (3)$$

with $a(\text{H}^+)$, for example, being the (dimensionless) activity of H^+ , that is concentration c divided by the standard concentration c° ($1 \text{ mol L}^{-1} = 1 \text{ M}$) multiplied by the activity coefficient γ which depends on the charge z of the species and the composition of the solution, in particular on the ionic strength $I = \frac{1}{2} \sum (z_i^2 c_i / c^\circ)$. (aq) denotes that water is the solvent, and H^+ , for example, is a hydrated proton.^[16] In electrochemistry, molalities (moles of solute per mass of solvent) are often used instead of concentrations; similar, equivalent equations and definitions then apply. We prefer concentrations, however, because this is what is measured by spectroscopy. Taking the \lg of Equ. (3), identifying $\text{p}K_a = -\lg K_a$ and $\text{pH} = -\lg a(\text{H}^+)$ and rearranging, Equ. (4) is obtained,

$$\text{pH} = \text{p}K_a + \lg \{a(\text{A}^-)/a(\text{HA})\} = \text{p}K_a + \lg \{c(\text{A}^-)/c(\text{HA})\} + \lg \{\gamma(\text{A}^-)/\gamma(\text{HA})\} \quad (4)$$

Approximating activities with actual concentrations, and actual concentrations by 'analytical' concentrations, this is essentially the Henderson-Hasselbalch equation. More complicated expressions are derived for polyprotic acids, but if the different ionization constants are sufficiently separated, the reactions can be approximated by step-wise single ionization reactions. This applies to phosphoric acid with $\text{p}K_{a,1} = 2.14$, $\text{p}K_{a,2} = 7.20$ and $\text{p}K_{a,3} = 12.34$ at 25°C .^[17]

Activities are defined thermodynamically by the change of the chemical potential with concentration. Debye-Hückel have derived approximate expressions for highly diluted electrolytes ($I \ll 0.1$), based on ions interacting by electrostatic forces with surrounding ions ('ion atmosphere'), depending on the concentration of ions *via* I and their distance of closest approach α (also called ion size parameter, in Å units),

$$\lg \gamma_i = -0.51 z_i^2 \sqrt{I} / (1 + 0.33 \alpha_i \sqrt{I}), \quad (5)$$

where 0.51 and 0.33 are constants for water as solvent at 25°C .^[5, 14, 18, 19] Davies modified and extended this expression semi-empirically to higher I (up to ≈ 0.5).^[5, 14, 19, 20]

$$\lg \gamma_i = -0.51 z_i^2 \{ \sqrt{I} / (1 + \sqrt{I}) - 0.3 I \} \quad (6)$$

Note that both eqs and related expressions are of the form

$$\lg \gamma_i = -A(I) z_i^2, \quad (7)$$

where the factor A depends on the ionic strength I and on ion and water properties.

Here, a short comment on pH is in order. pH was originally defined by Sørensen in 1909 in terms of the H^+ concentration.^[10] In general, concentrations are always well defined and in principle measurable, for example by spectroscopy *via* the Beer-Lambert law. In the thermodynamic equilibrium constant expression, however, activities are used, and an electrochemical H_2 electrode as part of a pH meter senses activities *via* the Nernst equation. It seems thus logical and sensible that our current definition of pH is $-\lg(a(\text{H}^+))$ (see IUPAC, and refs [10-

15]). There are, however, two fundamental problems associated with this: first, activities depend on the composition, *i.e.*, the concentration and the interaction of all ions in the solution; it is a *combined* property of the thermodynamic equilibrium. The concept of a *single* ion activity, specific, separated and assigned to a single ion, is therefore ill-defined and debatable. Second, pH meters have 2 electrodes, the $a(\text{H}^+)$ sensitive electrode (standard H_2/Pt electrode, or more commonly a glass electrode), and a reference, usually an internal Ag/AgCl electrode. Both electrodes are usually connected *via* a salt bridge/junction which introduces additional voltages that are not negligible and depend on ion concentrations. It is thus problematic to define experimental procedures to measure pH absolutely. These practical difficulties are somewhat alleviated by defining certain standard (buffer) solutions, assign a pH value to them and calibrate the response of a pH meter with them.

DISCUSSION

As an example, in a phosphate buffer around $\text{pH} = 7$, the relevant acid ionization reaction is



with $\text{p}K_{a,2} = 7.20$ at 25°C .^[17] In equilibrium, there is $x \text{ M}$ of HPO_4^{2-} and $y \text{ M}$ of H_2PO_4^- . The pH of this buffer is given by Equ. (4). After adding $z \text{ M}$ of a strong acid which completely dissociates into H^+ , essentially all $z \text{ M}$ of its H^+ will react with HPO_4^{2-} to form H_2PO_4^- (full conversion) in order to keep the equilibrium in (8), thus converting $x \rightarrow x-z$; $y \rightarrow y+z$. Similarly, if $z \text{ M}$ of a strong base was added, $z \text{ M}$ of OH^- are created which would react almost completely with H_2PO_4^- to form HPO_4^{2-} and water, converting $x \rightarrow x+z$; $y \rightarrow y-z$. In principle, the combination of thermodynamic equilibrium of the ionization of the acid, the ionization of water, mass and charge balance, and further equilibria of the polyprotic acid have to be taken into account, but under our conditions, where the buffer capacity is not 'overpowered', full conversion is an accurate enough approximation. Due to the logarithm in Equ. (4), the pH value of the solution will not change much by the changing composition x and y , hence the buffering effect.

We have prepared phosphate buffer solutions by dissolving 50 mM (x) monobasic and 50 mM (y) dibasic anhydrous potassium phosphate salts (Sigma Aldrich). Known concentrations of HCl or NaOH were added as necessary; we define an independent variable, the $\text{H}^+_{\text{index}}$ in mM, that is positive if HCl is added (*e.g.*, $+z \text{ mM}$), and negative if NaOH is added (*e.g.*, $-z \text{ mM}$). The concentrations x and y then readjust as described above. pH measurements were made using a Mettler Toledo SevenMulti pH meter (glass electrode with internal Ag/AgCl reference). Fig. 1 shows pH measured with the pH meter, and pH calculated with the Henderson-Hasselbalch Equ. (1) and the actual concentrations of the phosphate anions. The difference is striking, calculated pH is consistently 0.4 too high. In practical formulations of buffer solutions, it is usually recommended that after adding the required amount of buffer salts according to the HH equation, the pH should then be adjusted with HCl or NaOH to get the target pH, presumably because of this

discrepancy between calculated and desired pH. In fact, most astute buffer preparers dispense with the HH equation entirely, simply adding the requisite amount of acid (or corresponding base) and titrate to the target pH with NaOH (or HCl). It is not difficult, however, to do the necessary corrections to convert concentrations to activities; this will provide much more accurate calculated pH values of a buffer solution or in a titration (Fig. 1).

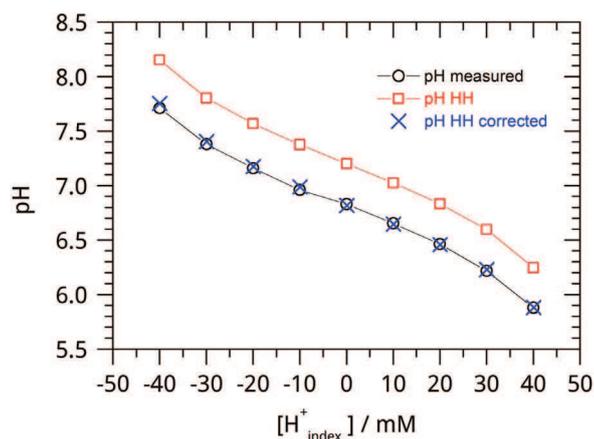


Fig 1. Phosphate buffer solution containing 50 mM K_2HPO_4 and 50 mM KH_2PO_4 . Positive H^+ index: z mM HCl added. Negative H^+ index: -z mM NaOH added. pH HH: pH calculated with the HH equation using concentrations; pH HH corrected: pH calculated with the modified HH equation using activities with Davies activity coefficients.

Combining Eqs (4) and (7) gives a modified/corrected Henderson-Hasselbalch equation including actual concentrations and activities,

$$pH = pK_a + \lg\{c(A^-)/c(HA)\} - A(I) \{(z^2(A^-) - z^2(HA))\} \quad (9)$$

For a (monoprotic) acid where A^- is singly charged and HA neutral, the last correction term is just $-A(I)$. Applying Equ. (9) to the phosphate buffer, however, $z^2(HPO_4^{2-}) = 4$ and $z^2(H_2PO_4^-) = 1$, so

$$pH = 7.20 + \lg\{c(HPO_4^{2-})/c(H_2PO_4^-)\} - 3A(I) \quad (10)$$

is obtained with a correction term $-3A(I)$. Depending on the ionic strength I , this correction can become quite considerable. Unfortunately, there are many examples in the literature, including text books, where the HH equation is used with concentrations instead of activities at an ionic strength that is too high to justify this approximation, for example when calculating the ratio of phosphate anions under physiological conditions (blood), or when calculating the buffer composition to target a certain pH.^[5] To illustrate the extent of the error and its dependence on ionic strength, we can use Davies's expression Equation (6) for $A(I)$ to show that at 25 °C, the $3A(I)$ correction factor for phosphate buffer around pH 7 rises dramatically as ionic strength increases (from 0 to 0.1 M), and asymptotically approaches 0.41 for $I > 0.15$ M (see Fig 2).

From Eqs (9) and (10), it is obvious that there are in principle two possibilities to correct the Henderson-Hasselbalch equation: (i) combine the correction term with the pK_a constant to define a new pK_a' which is valid for a given ionic strength.^[15] This has the advantage that it still looks like the original HH and

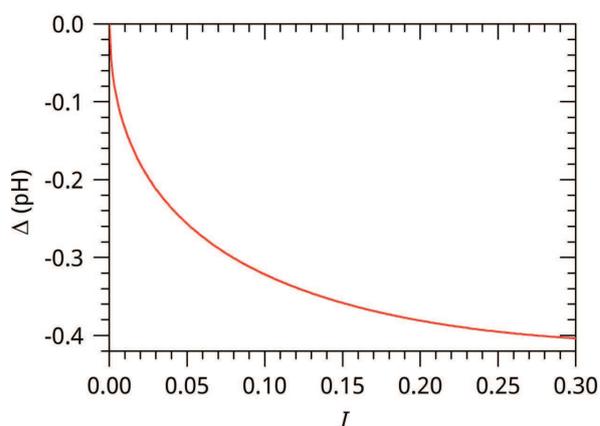


Fig 2. Davies's $3A(I)$ correction to the pH for different ionic strength I .

allows the use of concentrations. The disadvantage is, however, that it replaces a constant pK_a with a non-constant pK_a' . Under physiological conditions ($I \approx 0.16$), e.g., $pK_{a,2}$ of phosphoric acid in a phosphate buffer changes from 7.20 to $pK_{a,2}' \approx 6.8$.^[15] This procedure may seem pragmatic, but it is confusing and illogical in our opinion. (ii) The preferred procedure is using Eqs (9) and (10), i.e., with the thermodynamic equilibrium constant and concentrations corrected to activities.

Under our conditions, ionic strengths I with all ionic species including counterions are between 0.16 and 0.28. The Davies equation (6) then gives $3A(I)$ between 0.32 and 0.41. Finally the corrected calculated pH values as shown in Fig. 1 are obtained with an excellent agreement between calculated and measured pH. This correction procedure can be easily implemented and automated in a spreadsheet and is straightforward to implement into the chemistry and biochemistry teaching and laboratory curriculum. Having an accurate expression linking the pH of a solution to the concentration of an acid and its corresponding base has at least two important practical applications in research and teaching laboratories: Measuring the pH (*ex situ*) allows the calculation of concentrations (chemical analysis). Alternatively, measuring actual concentrations by spectroscopy allows the calculation of the pH of a solution *without* taking samples (*in situ*). In a forthcoming research publication we will demonstrate this approach by reporting the pH change of a phosphate-buffered growth medium during anaerobic fermentation of microbes, measured *in situ* by Raman spectroscopy.^[8]

CONCLUSIONS

The Henderson-Hasselbalch equation is central in chemistry teaching and has many practical applications. At a first glance, the equation seems to be just the 'mass-action law cast in logarithmic form', which would imply that it is exact, at least in principle; this is not true, however, and the equation has many inherent approximations which limit its application. Here, we have focused on one particular approximation, the use of concentrations instead of activities. We have shown that this can be easily corrected for in a modification which extends the useful range of the equation to moderately strong electrolytes (I

< 0.5). Without this correction, the calculated pH of a typical phosphate buffer is too high by up to 0.4. The correction can be easily implemented and automated in a spreadsheet and is straightforward to implement into the chemistry and biochemistry teaching and laboratory curriculum. It introduces students to the concept of activities in thermodynamic equilibrium, and to the Debye-Hückel equation, and it further emphasizes the importance of using activities instead of concentrations when the ionic strength exceeds 0.005 M. This is in contrast to the approach found in textbooks where activities are introduced, but then ignored 'for the sake of simplicity', even in example calculations where concentrations are clearly not appropriate. Our approach has many relevant applications in research and teaching laboratories, including in chemical analysis (measuring pH to calculate concentrations) and to determine the pH *in situ* by spectroscopy. We hope that this article may also stimulate discussions about how to teach chemical equilibria, Brønsted-Lowry acid-base reactions and titrations, buffer solutions, the concept of activity and finally the concept and definition of pH.

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