The Henderson–Hasselbalch Equation: Its History and Limitations

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The Henderson–Hasselbalch equation plays a pivotal role in teaching acid–base equilibrium and therefore receives considerable attention in general, analytical, and biochemistry courses. Buffer problems, titration curves, and a host of related phenomena, including the extent of ionization and electrical charge on a polypeptide, can be discussed with relative ease using this equation or its non-logarithmic form. As is often the case, however, for a subject that has moved from one generation of textbooks to the next for much of the century, certain subtleties of the Henderson–Hasselbalch equation have become lost and the distinction between exact and approximate results has blurred. This article presents a critical evaluation of the reliability of the Henderson–Hasselbalch equation and comments on its history, including the development of the pH scale.

Henderson Equation

We will discuss the limitations of the Henderson–Hasselbalch equation focusing on the titration curve of a weak acid with a strong base. Over much of the titration range, the calculation of pH relies on the Henderson–Hasselbalch equation,

$$\mathrm{pH} = \mathrm{p}K_a + \log\frac{[\mathrm{A}^-]}{[\mathrm{HA}]} \qquad (1)$$

where K_a is the dissociation constant of the weak acid, $\mathrm{p}K_a = -\log K_a$, and [HA] and [$A^-$] are the molarities of the weak acid and its conjugate base. The Henderson–Hasselbalch equation is, of course, the mass action expression cast in logarithmic format, and many students of chemistry have wondered if the thought of taking the logarithm of both sides of an expression should warrant immortalization of these two scientists.

Lawrence Joseph Henderson (1878–1942), a native of Massachusetts, spent most of his professional life at Harvard where he received an M.D. in 1902. He devoted much of his early career to the study of blood and its respiratory function (*1*). It was known at the time that blood resists changes in acidity and basicity, but the relationship between the composition of a buffer, its buffering capacity, and the hydrogen ion concentration had not yet been appreciated. In 1908, one year before the word "puffer" in German was first introduced into chemical lexicon, Henderson published two papers in the *American Journal of Physiology* and in them put forward a simple formula linking [H^+] and the composition of a buffer (*2, 3*):

$$[\mathrm{H}^+] = K_a\frac{[\mathrm{acid}]}{[\mathrm{salt}]} \qquad (2)$$

Using indicators, he also demonstrated that near neutrality the buffering capacity peaked when K_a approached 10^{-7}.

One might view eq 2 as a trivial rearrangement of the dissociation quotient of a weak acid. In the context of early 20th century chemistry, however, Henderson's formula represented a giant step toward understanding buffer behavior. Although the concept of equilibrium had made its appearance in the literature through the works of several 19th century scientists[1] and the law of mass action had been formulated in 1864 by two Norwegian brothers-in-law, Peter Waage (1833–1900) and Cato Maximillian Guldberg (1836–1902), the nature of electrolytes remained fuzzy around the turn of the century (*4*). Principles of equilibrium as applied to ionic compounds were far from being expressed in the succinct fashion of a general chemistry text and it fell to a medical doctor to recognize the simple relationship between a weak acid, its salt, and the hydrogen ion concentration.

The law of mass action articulated by Guldberg and Waage remained dormant for more than a decade until Wilhelm Ostwald recognized its significance in 1877. Ostwald demonstrated its validity as he set forth his "dilution law" through a study of more than 250 weak acids. The dilution law, which can be regarded as the Ostwald's version of the mass action expression for weak acids, stated that

$$\alpha^2/\mathrm{M}(1-\alpha) = \text{a constant}$$

where α is the fraction of ionization and M is the molarity of the acid. While the dilution law held "excellently for all slightly ionized electrolytes, it fell way off the mark for highly ionized electrolytes"(*5*). The latter did not even approximately follow Ostwald's expression and this brought the validity of the mass action law into question in relation to fully ionized substances. Thus, set against what was known about electrolytes around the turn of the century, Henderson's equation, in our view, represents a significant advance in understanding acid–base behavior.

The pH Scale and the Henderson–Hasselbalch Equation

One year after Henderson's papers, the Danish biochemist Søren Sørensen (1868–1939) suggested the removal of the awkward negative exponent in the [H^+] expression and created the pH scale (*6*). (In the same paper Sørensen introduced the word buffer.) The scale found immediate acceptance among biochemical researchers, who had been intrigued by the ability of living organisms to buffer against excessive acidity or alkalinity. It did not become familiar to chemists, however, until Leonor Michaelis (1875–1949) published a book on hydrogen ion concentration, entitled *Die Wasserstoffionenkonzentration*, in 1914. Michaelis emigrated to the United States in 1926, Arnold Beckman developed his portable pH meter in 1935, and soon after Sørensen's pH scale became a prominent feature of the general chemistry curriculum (*7, 8*).

In 1916, K. A. Hasselbalch from the University of Copenhagen merged Henderson's buffer formula with

Sørensen's pH scale and wrote an expression now known as the Henderson–Hasselbalch equation (*9*). Hasselbalch had earlier done significant work on infant respiration, but it was the simple idea of casting the Henderson equation in logarithmic format that immortalized his and Henderson's names in the annals of chemistry.[2]

Few students of chemistry today realize that it was the physiologists and medical scientists working with biological fluids who pushed the subject of buffers and pH into mainstream chemistry. Henderson realized the limitations of his equation when [HA] and [A^-] were interpreted as the *initial* molarities—that is, prior to dissociation or hydrolysis—and probably neither he nor Hasselbalch expected that their equation would become a prominent feature of general chemistry instruction. As the scope of its application expanded, however, the approximate nature of the Henderson–Hasselbalch equation faded out of curriculum. None of the textbooks of general or biochemistry chemistry we recently examined offered a quantitative discussion of the reliability of pH calculations from eq 1 or its non-logarithmic form.

As we will show, the discrepancy between the exact and approximate calculations, even at moderate concentrations and pH values not far from the pK_a, can be as much as 50% (when $K_a = 10^{-3}$ and the acid and base are 0.01 M), and many buffer problems solved through Henderson–Hasselbalch equation—with the usual interpretation of [HA] and [A^-] as the initial molarities—do not warrant an answer with more than a single significant digit. Buffer problems that carry two or more significant figures are often fictional exercises in general chemistry.

Approximate and Exact Calculations of Hydrogen Ion Concentration

Returning our attention to titration curves, we note that three kinds of calculations are involved in deriving the approximate pH during a titration. At the beginning, before the addition of any base, [H^+] is calculated as in any aqueous solution of a weak acid. At the equivalence point, when the number of moles of base added equals the number of moles of acid started with, the problem is one of hydrolysis, and the pH is calculated the same way as in a solution of A^-, the conjugate base of the acid titrated. Between the starting and the end points, the titration mixture is regarded as a buffer and [H^+] is determined from the Henderson–Hasselbalch equation in which [acid] and [base] are interpreted as the molarities that would have been present had there been no dissociation or hydrolysis.

An exact calculation of [H^+] in a buffer, however, must take into account the dissociation of HA, the hydrolysis of A^-, and the ionization of water. A set of four independent equations must be satisfied:

$$[H^+][OH^-] = 10^{-14}$$

$$[H^+] = K_a[HA]/[A^-]$$

$$[HA] + [A^-] = (n_A + n_B)/V$$

$$[H^+] + n_B/V = [A^-] + [OH^-]$$

In these equations n_A and n_B are the number of moles of acid and its salt used in making the buffer and V is the volume of the buffer. The first and the second equations are the mass action law applied to the ionization of water and the dissociation of the acid. The third equation comes from mass balance; the sum of V[HA] and V[A^-] must clearly equal to the number of moles of acid and base dissolved. The fourth equation reflects charge balance, n_B/V being the molarity of Na^+, if sodium salt of the acid or sodium hydroxide is used

Table 1. Titration of 100 mL of 0.10 M Weak Acids with 0.10 M NaOH

NaOH/ mL	[H^+] Calcd[a]	pK_a of Acid 3	5	7	9	11
10	Eq 3	5.3×10^{-3}	**8.9×10^{-5}**	**9.0×10^{-7}**	**9.0×10^{-9}**	**9.1×10^{-11}**
	Eq 2	9.0×10^{-3}	**9.0×10^{-5}**	**9.0×10^{-7}**	**9.0×10^{-9}**	**9.0×10^{-11}**
	% Error	69	**1**	**0**	**0**	**–1**
20	Eq 3	3.2×10^{-3}	**4.0×10^{-5}**	**4.0×10^{-7}**	**4.0×10^{-9}**	**4.1×10^{-11}**
	Eq 2	4.0×10^{-3}	**4.0×10^{-5}**	**4.0×10^{-7}**	**4.0×10^{-9}**	**4.0×10^{-11}**
	% Error	25	**0**	**0**	**0**	**–2**
50	Eq 3	9.4×10^{-4}	**1.0×10^{-5}**	**1.0×10^{-7}**	**1.0×10^{-9}**	1.1×10^{-11}
	Eq 2	1.0×10^{-3}	**1.0×10^{-5}**	**1.0×10^{-7}**	**1.0×10^{-9}**	1.0×10^{-11}
	% Error	6	**0**	**0**	**0**	-6
80	Eq 3	**2.4×10^{-4}**	**2.5×10^{-6}**	**2.5×10^{-8}**	**2.5×10^{-10}**	3.4×10^{-12}
	Eq 2	**2.5×10^{-4}**	**2.5×10^{-6}**	**2.5×10^{-8}**	**2.5×10^{-10}**	2.5×10^{-12}
	% Error	**3**	**0**	**0**	**0**	-26
90	Eq 3	**1.1×10^{-4}**	**1.1×10^{-6}**	**1.1×10^{-8}**	**1.1×10^{-10}**	2.3×10^{-12}
	Eq 2	**1.1×10^{-4}**	**1.1×10^{-6}**	**1.1×10^{-8}**	**1.1×10^{-10}**	1.1×10^{-12}
	% Error	**2**	**0**	**0**	**–2**	-51

[a]Equation 3 yields exact values; eq 2 gives approximate values. The % error is defined as $100\times([H^+]_{approx} - [H^+]_{exact})/[H^+]_{exact}$; a negative value indicates that $[H^+]_{approx}$ is smaller than the exact value. The % error may be nonzero even though exact and approximate concentrations are the same to two significant figures as given in the table.

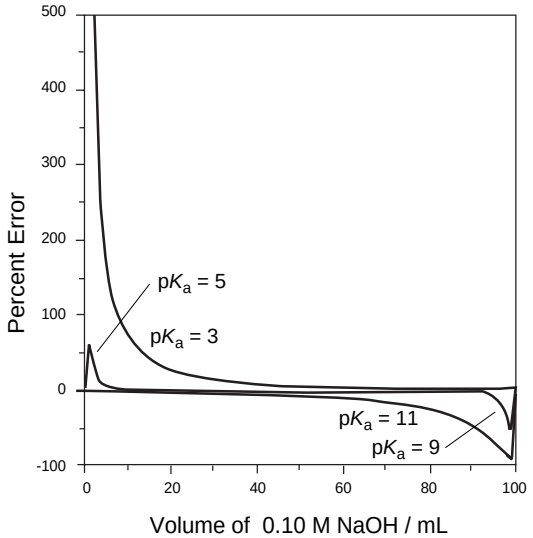

Figure 1. Percent error in approximate [H^+] as a function of base volume during titration of 100 mL of 0.10 M acid. Sodium hydroxide concentration is the same as acid concentration. pK_a of the acid is indicated near the curve corresponding to it. For pK_a = 9 at the beginning, and for pK_a = 5 near the end of titration, the deviation between approximate and exact [H^+] is too small to be seen in the figure. For pK_a = 7, the percent error is too small to be seen over the entire range of titration.

in making the buffer. Rearrangement of these equations yields the expression

$$[H^+] = K_a\{M_A - [H^+] + [OH^-]\}/\{M_B + [H^+] - [OH^-]\} \quad (3)$$

where M_A and M_B stand for n_A/V and n_B/V, and $[OH^-]$ is $10^{-14}/[H^+]$. The sole unknown in this expression is $[H^+]$ and it can be solved by iterative techniques using spreadsheet software.[3]

The expression for exact $[H^+]$ does not differentiate between starting, intermediate, and end points of the titration and can be used to generate the entire exact titration curve. We calculated the approximate and the exact $[H^+]$ values from eqs 2 and 3 and tabulated them along with the percentage errors in the approximate values in Tables 1–3 for the titration of five weak acids with NaOH. In all cases the volume of the acid is 100 mL and concentration of the base equals that of the acid. In Table 1, the acids are 0.100 M, their pK_a values range from 3 to 11 in steps of 2, and the volume of NaOH added is selected as 10, 20, 50, 80 and 90 mL. In Tables 2 and 3, the acid concentrations are 1.00×10^{-2} and 1.00×10^{-3} M; the rest of the format remains the same as in Table 1. The regions in which the approximate $[H^+]$ is within 5% of the exact value are in boldface print.[4] The percentage error values in these tables are also displayed in Figures 1–3 for the entire range of NaOH addition from 0 to 100 mL.

Table 2. Titration of 100 mL of 0.010 M Weak Acids with 0.010 M NaOH

NaOH/ mL	$[H^+]$ Calcd[a]	pK_a of Acid 3	5	7	9	11
10	Eq 3	2.1×10^{-3}	8.2×10^{-5}	**9.0×10^{-7}**	**9.0×10^{-9}**	1.0×10^{-10}
	Eq 2	9.0×10^{-3}	9.0×10^{-5}	**9.0×10^{-7}**	**9.0×10^{-9}**	9.0×10^{-11}
	% Error	337	10	**0**	**0**	-12
20	Eq 3	1.6×10^{-3}	**3.9×10^{-5}**	**4.0×10^{-7}**	**4.0×10^{-9}**	4.7×10^{-11}
	Eq 2	4.0×10^{-3}	**4.0×10^{-5}**	**4.0×10^{-7}**	**4.0×10^{-9}**	4.0×10^{-11}
	% Error	154	**3**	**0**	**0**	-15
50	Eq 3	6.7×10^{-4}	**9.9×10^{-6}**	**1.0×10^{-7}**	**1.0×10^{-9}**	1.5×10^{-11}
	Eq 2	1.0×10^{-3}	**1.0×10^{-5}**	**1.0×10^{-7}**	**1.0×10^{-9}**	1.0×10^{-11}
	% Error	50	**1**	**0**	**–1**	-33
80	Eq 3	2.0×10^{-4}	**2.5×10^{-6}**	**2.5×10^{-8}**	**2.6×10^{-10}**	7.7×10^{-12}
	Eq 2	2.5×10^{-4}	**2.5×10^{-6}**	**2.5×10^{-8}**	**2.5×10^{-10}**	2.5×10^{-12}
	% Error	27	**0**	**0**	**–4**	-67
90	Eq 3	9.0×10^{-5}	**1.1×10^{-6}**	**1.1×10^{-8}**	1.3×10^{-10}	6.5×10^{-12}
	Eq 2	1.1×10^{-4}	**1.1×10^{-6}**	**1.1×10^{-8}**	1.1×10^{-10}	1.1×10^{-12}
	% Error	23	**0**	**0**	-14	-83

[a]See the footnote for Table 1.

Table 3. Titration of 100 mL of 0.0010 M Weak Acids with 0.0010 M NaOH

NaOH/ mL	$[H^+]$ Calcd[a]	pK_a of Acid 3	5	7	9	11
10	Eq 3	5.1×10^{-4}	5.3×10^{-5}	**8.9×10^{-7}**	**9.1×10^{-9}**	2.1×10^{-10}
	Eq 2	9.0×10^{-3}	9.0×10^{-5}	**9.0×10^{-7}**	**9.0×10^{-9}**	9.0×10^{-11}
	% Error	1662	69	**1**	**–1**	-56
20	Eq 3	4.2×10^{-4}	3.2×10^{-5}	**4.0×10^{-7}**	**4.1×10^{-9}**	1.1×10^{-10}
	Eq 2	4.0×10^{-3}	4.0×10^{-5}	**4.0×10^{-7}**	**4.0×10^{-9}**	4.0×10^{-11}
	% Error	852	25	**0**	**–2**	-62
50	Eq 3	2.2×10^{-4}	9.4×10^{-6}	**1.0×10^{-7}**	1.1×10^{-9}	4.6×10^{-11}
	Eq 2	1.0×10^{-3}	1.0×10^{-5}	**1.0×10^{-7}**	1.0×10^{-9}	1.0×10^{-11}
	% Error	365	6	**0**	-6	-79
80	Eq 3	7.3×10^{-5}	**2.4×10^{-6}**	**2.5×10^{-8}**	3.4×10^{-10}	3.2×10^{-11}
	Eq 2	2.5×10^{-4}	**2.5×10^{-6}**	**2.5×10^{-8}**	2.5×10^{-10}	2.5×10^{-12}
	% Error	242	**3**	**0**	-26	-92
90	Eq 3	3.5×10^{-5}	**1.1×10^{-6}**	**1.1×10^{-8}**	2.3×10^{-10}	2.9×10^{-11}
	Eq 2	1.1×10^{-4}	**1.1×10^{-6}**	**1.1×10^{-8}**	1.1×10^{-10}	1.1×10^{-12}
	% Error	218	**2**	**–2**	-51	-96

[a]See the footnote for Table 1.

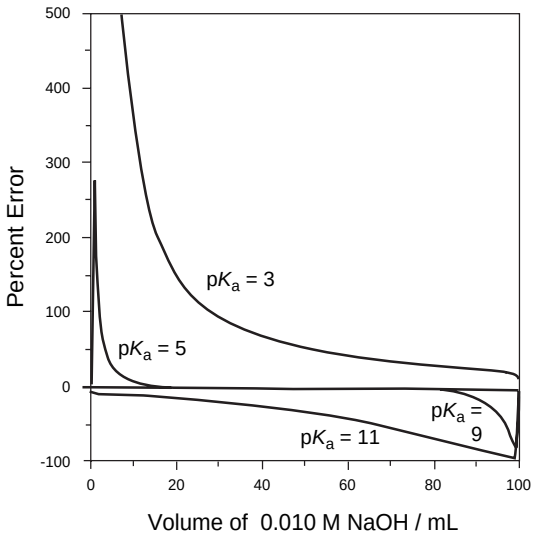

Figure 2. Percent error in approximate $[H^+]$ as a function of base volume during titration of 100 mL of 0.010 M acid. Sodium hydroxide concentration is the same as acid concentration. pK_a of the acid is indicated near the curve corresponding to it. For pK_a = 9 at the beginning, and for pK_a = 5 near the end of titration, the deviation between approximate and exact $[H^+]$ is too small to be seen in the figure. For pK_a = 7, the percent error is too small to be seen over the entire range of titration.

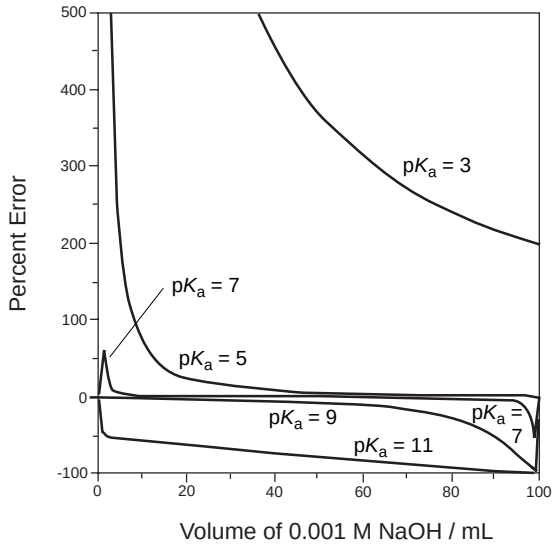

Figure 3. Percent error in approximate $[H^+]$ as a function of base volume during titration of 100 mL of 0.0010 M acid. See legend to Figure 1 for other details, but here the difference between approximate and exact $[H^+]$ near the beginning and end of the titration emerges for pK_a = 7. The smaller negative deviations may seem curious until one considers the definition: % error = $100\times\{[H^+]_{approx} - [H^+]_{exact}\}/[H^+]_{exact}$. If $[H^+]_{approx}$ is smaller than the exact value, the percentage error cannot exceed -100%. No such mathematical restriction, of course, is imposed when $[H^+]_{approx} > [H^+]_{exact}$.

Discussion

Figures 1 through 3 reveal that for acids whose pK_a is not far from 7, the difference between exact and approximate [H$^+$] is vanishingly small over most of the titration range. The Henderson–Hasselbalch equation is eminently suited to calculate the pH of buffers made with acids whose pK_a lies in the range of about 5 to 9, so long as the composition of the buffer is not highly skewed in favor of one or the other component. For an acid with a pK_a of 7, the approximate and exact [H$^+$] remain within a percentage point of each other over almost the entire titration range—from 3 mL of NaOH until 95 mL for the titration of 100 mL of 0.01 M acid.

The Henderson–Hasselbalch equation, however, becomes unreliable for calculating [H$^+$] when the dissociation constant of the acid departs from 10^{-7} by more than two orders of magnitude. When K_a is 10^{-3}, for example, even in buffers made with equal number of moles of acid and base (i.e., at the midpoint of a titration), the approximate [H$^+$] differs from the exact value by as much as 365% in dilute solutions. Thus for acids such as HNO_2, HF, HCOOH, $BrCH_2COOH$, $ClCH_2COOH$, and lactic acid, whose K_a's are around or above 10^{-4}, the Henderson–Hasselbalch equation is not appropriate to derive the titration curves. Buffers made with very weak acids ($K_a < 10^{-10}$) do not lend themselves to approximate calculations either; the dissociation of the acid and the hydrolysis of the base must be considered in such solutions and the [H$^+$] must be calculated from eq 3.

Approximate calculations break down near the beginning and the end of a titration where the relative concentrations of the acid and base differ substantially. For example, in the titration of 100 mL of an acid with $K_a = 10^{-3}$ and M = 0.01, the approximate [H$^+$] after the addition of 5 mL of NaOH is 1.9×10^{-2} M. The exact [H$^+$], however, is 2.36×10^{-3} M—ca. one-eighth of the approximate value. The limitation of the Henderson–Hasselbalch equation at the extremities of a titration is seen in Figures 1–3. When $K_a = 10^{-3}$ and M = 0.001, the approximate [H$^+$] after the addition of 10 mL of NaOH is off the exact value by 1662%. At 5 mL of NaOH, the discrepancy climbs to 3280%.

A final comparison of the exact and approximate pH values is displayed in Figure 4 for an acid with an initial concentration of 0.01 M. Once again we see that when pK_a is not far from 7 the exact and approximate values match very well except in the immediate neighborhood of the starting and the end points. The rather flat appearance of the curve near the beginning for acids with a small pK_a (<4) or near the end for acids with a pK_a of 10 or larger, does not reveal itself in approximate treatments and is seldom brought out in general chemistry classes.

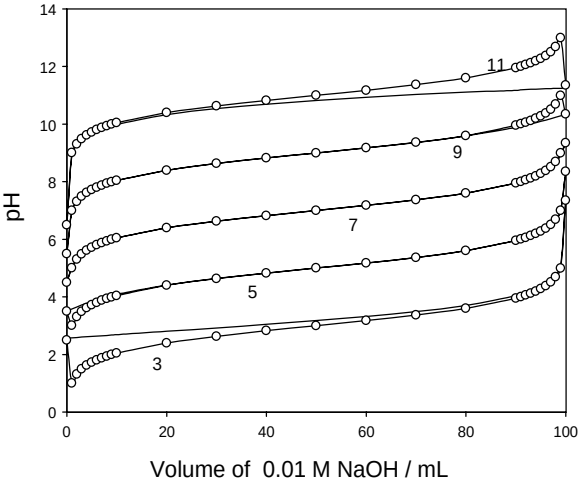

Figure 4. Approximate and exact pH as a function of base volume during titration of 100 mL of 0.010 M acid. Base concentration is also 0.010 M. pK_a of the acid is identified near the curve corresponding to it. Circles are the approximate values; continuous solid curves without circles represent the exact pH. Note the flatness of the exact pH curves near the beginning of titration for acids with smaller pK_a values, and near the end for acids with larger pK_a values.

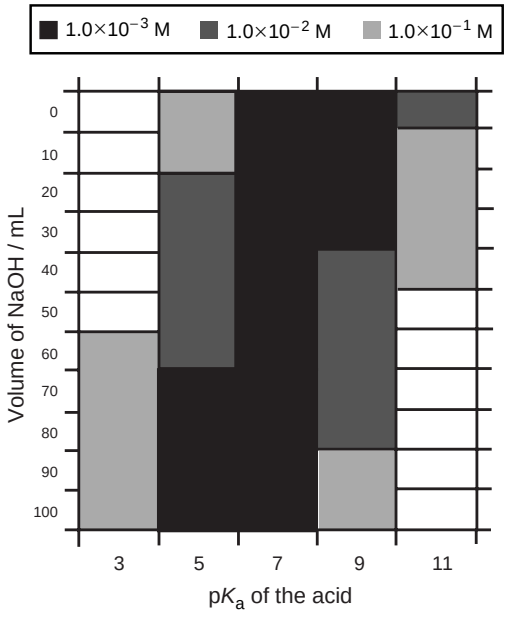

Figure 5. Domains of reliability of approximate [H$^+$] calculations. In shaded regions approximate calculations are within 5% of the exact [H$^+$]. Light gray is for 0.10 M acid titrated with 0.10 M NaOH, medium gray is for 0.010 M, and black is for 0.0010 M. The lighter shaded areas also extend into darker regions. The volume of NaOH changes in increments of 10 mL and the pK_a in units of 2. Thus, in the left column the 6th rectangle from the top corresponds to the addition of 50 mL of NaOH to 100 mL of acid whose pK_a is 3. Since the rectangle is unshaded, the approximate [H$^+$] is off by more than 5% at all three concentrations.

Conclusions

The boundaries of the regions beyond which exact and approximate [H$^+$] differ by more than 5% are shown in Figure 5. Approximate [H$^+$] calculations with more than a single significant figure are not warranted outside of these regions. For acids with a pK_a close to 7, approximate calculations remain very close to exact values over nearly the entire titration range even in dilute systems (see the region shaded black in Fig. 5).

With powerful and friendly computational tools now within reach of all students one might wonder if there is any need for the approximate methods in calculating pH. Hydrogen ion concentration can be calculated exactly from eq 3 for any acid–base mixture at any dilution without omitting dissociation of the acid, hydrolysis of the base, or the ionization of water. But there is a downside to exact calculations. Although eq 3 provides an excellent opportunity for computer assignments, it does not present a clear picture of what is happening in a solution. From a pedagogical point it may be advantageous to emphasize that the acid and its conjugate base to a first approximation can be assumed to remain intact and that the pH can be calculated from the simple mass action expression or the Henderson–Hasselbalch equation. The dissociation of the acid and the hydrolysis of the base are then introduced as corrections that are significant in dilute systems. It is further stressed that these corrections gain additional prominence when the K_a of the acid differs substantially from 10^{-7} (by at least two orders of magnitude). In such cases eq 3 must be used for reliable hydrogen ion calculations.

It has been said about quantum mechanics that the more accurate the calculations the less prone they are to easy visualization. The same may hold true in pH calculations: the more exact the method the less susceptible it may be to pictorial comprehension.

Notes

1. Among the scientists who contributed to the understanding of equilibrium are Heinrich Rose (1795–1864), Nikolai Beketov (1827–1911), Marcellin Berthelot (1827–1907), Leon Pean de Saint-Gilles (1832–1862), William Esson (1839–1916), Jacobus Henricus van't Hoff (1852–1911), Wilhelm Ostwald (1853–1932), and Hermann Walther Nernst (1864–1941). For more details see ref *4.*

2. The idea of writing the mass action expression in logarithmic format appears to have first occurred to the Danish chemist Niels Bjerrum (1879–1958). Hasselbalch in his 1916 paper states that in writing the mass action expression in logarithmic format he is following an "unpublished work by Bjerrum". It is interesting to note that in Denmark the Henderson–Hasselbalch equation is often known as the Bjerrum equation. Another curious fact is the absence of any reference to Henderson in Hasselbalch's paper.

3. We will be happy to send a copy of the spreadsheet program designed for use in the general chemistry course.

4. Concentrations above 0.1 M are not considered to avoid the involvement of activities.

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