pH and the Henderson–Hasselbalch Equation

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The two foundations of analysis of acid-base equilibria in solution are the (1) law of mass action and (2) the concept of acidification as protonation, achieved by dissociation of a proton donor. Transfers of protons by proton donors to the conjugate bases of other buffer pairs are treated as reversible reactions subject to quantitative analysis by the Henderson-Hasselbalch equation, a deduction from the mass law; this type of kinetic analysis has enabled us for nearly a century to relate theoretically the changes of the acidic intensity of dilute solutions to a quantity of acid or base added or subtracted. The contemporary form of the Henderson-Hasselbalch equation:

$$pH = pK' + \log \{base\}/\{acid\} \qquad (1)$$

has rested for a half-century upon a method of relating concentrations theoretically to activities by taking into account the effect of interionic attraction on the buffer ratios [1].

It is difficult to overrate the importance to the development of acid-base physiology and medicine of the theoretic relation obtaining between pH and the position of equilibrium of every buffer pair in dilute aqueous solution. Even so routine a procedure as the evaluation of the buffer strength of a mixture of (undetermined) nonvolatile buffers in solution (as in estimating urinary titratable acidity) rests entirely upon our confidence in the reliability and generality of equation 1. A disquieting phenomenon of our day has been the initiation and continuation of controversies in the clinical literature which have had the effect of weakening the confidence of physicians and medical students in the authority of equation 1.

The equation has been assailed from two opposite and irreconcilable quarters, rather as orthodox Christianity was menaced, in its troubled youth, by the opposite heresies of the Ebionites and the Docetes. Some investigators [2-6] recommend expressing acidic intensity as "$\{H^+\}$" (meaning the concentration of the hydronium ion $[H_3O^+]$ and its hydrates); pH was originally represented in this camp as a mischievous novelty frivolously introduced some two generations ago by "Hasslebalch" [2] (it was introduced by Sørensen), the

usage having been perpetuated for two generations by inertia or deference to outmoded authority [4]. And on the other hand—sometimes, astonishingly enough, by some of the selfsame investigators [4]—we hear that inasmuch as the absolute concentration of the hydronium ion cannot be derived theoretically from the pH measurements now routinely used to determine acidic intensity, kinetic analysis of acid-base equilibria according to equation 1 is invalid [4,7], Sørensen's definition of pH is long since outmoded [7], and editors who publish estimates of $\{H_3O^+\}$ derived from pH measurements are derelict in their duties [7].

The campaign against pH, now 12 years old, has reached what one must hope to be high-water mark in a call for foundation of an organization of those dedicated to the elimination of the unit from the teaching of chemistry in colleges and medical schools [6]. Current antagonism to pH appears to be based primarily on the conviction that it is possible, by expressing acidic intensity as $\{H_3O^+\}$, to spare the student and physician a confrontation with logarithms [3-6].

Unfortunately, however, no understanding of physiologic acid-base chemistry is adequate which hopes to begin and end with contemplation of $\{H_3O^+\}$. In weak electrolyte solutions the very small quantity present seldom interests us intrinsically as a concentration [1]. The fundamental importance of acidic intensity in physiology derives rather from the fact that when pH is altered the concentrations of every conjugate base and acid of every weak electrolyte change owing to shifts of the ratios of every buffer pair. The significance of the uniformly symmetrical curves obtained when the proportions of conjugate bases are plotted against pH has been discussed elsewhere [8]; it is the esthetic expression of the fundamental fact that differences of pH between different solutions, not differences of $\{H_3O^+\}$, exactly and uniformly express the thermodynamic relationships (including the voltage generated when they are connected by suitable paired electrodes) obtaining between any pair of weak electrolyte solutions in respect to their differing acidic intensity [8,9].

Equally inescapable is the essentially exponential change of the buffer ion concentration of a volatile buffer system as pH is altered while the concentration of dissolved gas is stabilized at a relatively low value. Understanding this relationship, and the reason for it, is a prerequisite to understanding the physiologic function of the carbon dioxide (CO_2) buffer system [1], the dominant buffer of extracellular fluid, and one of the two dominant urinary buffers. I have further argued elsewhere [10] that evolutionary selection of blood

pH 7.4 in mammals becomes intelligible when this relationship in blood plasma, and the unique fitness of CO_2 for buffering the body fluids, are remarked. And the function of the other principal urinary buffer system, ammonia, is wholly analogous to the urinary CO_2-HCO_3 system: its effectiveness is based upon exploitation of the same physiochemical features of open systems with high ion to gas ratios and stabilized gas concentration [1]. It is an illusion to suppose that any real understanding of physiologic acid-base regulation is possible without a thorough understanding of the various elementary exponential relationships expressed by equation 1.

One keeps hoping and believing that, like the approximately contemporaneous American intervention in Vietnam, the campaign against pH will soon be consigned forever to the inexorable sentence of history; but unfortunately disengagement is still being retarded by last-ditch defenses of $\{H_3O^+\}$ [11] which evade the real issues as sedulously as did their predecessors [1, pp 38,39].

Attacks from the opposite quarter on the theoretic basis of equation 1 issue from the undeniable facts that certain theoretic and practical difficulties render impossible an exact and general derivation of $\{H_3O^+\}$ from the activity of H_3O^+, and of the latter from pH [4,7]. Of this onslaught it may at least be said that it is not based on faulty scholarship and pedagogic wishful thinking. Physicians and physiologists should indeed keep in mind (1) that published values for $\{H_3O^+\}$ are based on a convention according to which the activity coefficient of $\{H_3O^+\}$ is assigned an arbitrary value of unity, the concentration of hydronium ion being taken equal to its activity; (2) that minor readjustments in the relation between measured pH and calculated $\{H_3O^+\}$ in extracellular fluid and urine might be necessitated by advances in potentiometric technic or by international convention; and (3) that there is no uniform *general* chemical relation between pH and the activity of H_3O^+ [12].

Acid-base physiology has until recently been concerned principally with extracellular fluid and urine, solutions which approach ideality closely enough so that changes of their pH can be related theoretically to changes of buffer ratios with a degree of precision altogether exceptional in biology. As far as such solutions are concerned, uncertainty as to the proper relation of the pH scale to H_3O^+ activity cannot bring into question the derivation of equation 1 from the mass law, any more than our understanding of · atomic structure is invalidated by Heisenberg's uncertainty principle. It is in potentiometry, not in the enduring insights

of Arrhenius, van't Hoff, Ostwald and Sørensen, that we are obliged to accept shortcomings [1]. We are entirely justified in continuing to treat pH for purposes of kinetic theory as $\log (1/\{H_3O^+\})$, while fully recognizing the propriety and indeed the necessity of a purely operational definition of pH among those concerned with potentiometric methodology [12]. Students of acid-base equilibria in compartments of cell water are not so fortunate; the specters of structured water, high ionic strength and limited accessibility of discrete compartments cry aloud for continuing healthy skepticism about published estimations of (mean) cell pH insofar as they are offered as anything more than phenomenological entities [1].

It is ironic that a recent communication [7] which does not shrink from offering an estimate derived from pH of the absolute statistical concentration of "hydrogen ions" (i.e., H_3O^+) in a very small hypothetical compartment of cell water should simultaneously enjoin editors from publishing any values of $\{H_3O^+\}$ derived from pH. The superiority of pH over $\{H_3O^+\}$ as the expression of

the acidic intensity of extracellular fluid and urine rests, not essentially upon the operational primacy of pH measurements, but rather upon more cogent grounds alluded to herein and amplified elsewhere [1,8,9,13].

In conclusion, one must deprecate the protracted intrusion into journals directed at practicing physicians of ill founded jousting against use of the Henderson-Hasselbalch equation in medicine; and one can only deplore such influence as this literature may have exerted in increasing the resistance of medical students and house officers to the necessary chore—never, as I recollect, especially welcome—of mastering enough physical chemistry to handle clinical acid-base disorders with informed skill. It seems appropriate to inquire whether undesirable educational by-products of this protracted controversy could not have been avoided. Might not timely, critical, and comprehensive review, conducted under the auspices of scientific societies concerned with the field, have resolved the issues entirely outside the pages of journals directed toward the practicing physician?

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