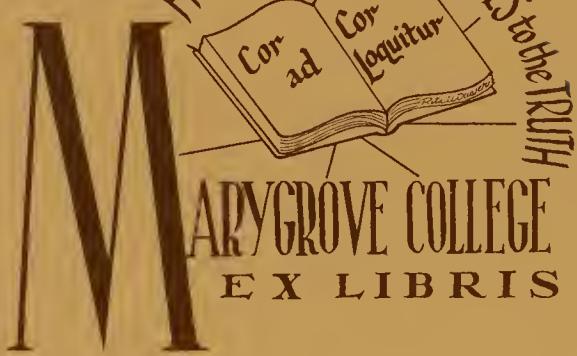


# HOW TO UNDERSTAND ACID-BASE

A Quantitative Acid-Base Primer  
for Biology and Medicine

Peter A. Stewart

ELSEVIER NEW YORK











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Peter A. Stewart

Brown University  
Providence, Rhode Island



**ELSEVIER • NEW YORK  
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## PREFACE

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The approach to understanding hydrogen ion behavior that is presented in this book has been developing ever since, as an undergraduate chemistry major, I first confronted the confusion surrounding biological uses of the terms “pH” and “buffer.” The derivations and discussions always seemed so circular and frustrating. No general answer was ever given to the question “What is it that determines hydrogen ion concentration in a solution?” and that surely is the first question! When, about 1973, I finally worked out the astonishingly simple answer to that question, computers had arrived, and it suddenly became easy to use the answer in satisfactorily practical ways. Continuing feedback since then, from colleagues and from graduated students who are now practicing physicians, research scientists, and teachers, has reinforced my conviction that doing it right is much easier than it looks, and that understanding is more powerful than memorized formulas. A result of that conviction is that this book is most rewarding when studied and thought through, rather than just read.

Because this approach is so different from the classical and historical one, I have tried to keep them separate, and to start fresh and uncluttered by the limitations of pre-computer science. Despite many urgings, I have therefore largely omitted references to the historical development of “acid–base” in biology and medicine. I have also assumed that anyone who reads this book will have some useful acquaintance with general chemistry, biology, and mammalian physiology, so that references to particular textbooks are not needed when kidneys, lungs, osmolarity, and so forth are mentioned. For both these reasons, almost no references to the literature are presented. The development of the subject is sufficiently self-contained that detailed references should not be needed at this stage.

When they do become necessary, readers can supply their own from the enormous relevant literature.

It should also be clear from the beginning that there is nothing sacred, guaranteed, or absolute about the numerical values used here. In my own perusal of the literature, I have been amazed at the range of values quoted as "true" or "correct" or "best." From that range, I have assembled some idiosyncratically weighted averages to use here. If you don't like any of them, please use your own favorite values. Precise numerical values, even if they were meaningful, are not the point of this story. The results we get, and the principles involved, are illustrated by the many computer-plotted curves throughout the book. Adjusting their scales to fit "better" or "preferred" parameter values is easily accomplished, and will not affect the arguments or conclusions.

So many friends, critics, and fellow students of all sorts have contributed to the development of this book that it would be impossible to acknowledge them all. It is also difficult to rank their contributions. Sometimes pages of detailed criticisms, sometimes just a few casual words or just the right question were needed to unlock a long-standing problem. I am extremely grateful to all who have thus contributed. None of them, of course, bears any responsibility for the remaining defects. Special thanks must go to the following who have provided crucial help of many sorts: V. Fencl, G. Filly, R. E. Forster, P. M. Galletti, J. Gamble, L. Homer, D. Jackson, N. Kindig, A. Portela, B. Reeves, and B. T. Stewart. Paul Palatt and Wayne Thornburg, both now deceased, provided continuing stimulation and encouragement, each in his special way. They are sorely missed.

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# INTRODUCTION

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Acid–base chemistry is an important topic in biology, biochemistry, physiology, and clinical medicine, a topic that should be thoroughly understood by everyone in these fields. Despite this importance, the topic is usually approached in a piecemeal, qualitative, and confusing way, so that misunderstanding and disagreement seem to be much more common than the kind of useful quantitative understanding that is needed. The reason is partly that acid–base chemistry, like many topics in biology and medicine, can only be simplified down to a certain minimum level before serious errors and misinterpretations result. This minimum level is the elementary physical chemistry of aqueous solutions containing ions. Its major message is that we can only make sense of acid–base behavior of body fluids by taking into account how all the ions, not just hydrogen ions, participate in that behavior; hydrogen ions in body fluids cannot be understood as independent entities. Treating that elementary chemistry quantitatively, as we shall do in this book, not only enables us to understand hydrogen ion behavior clearly, it also relates that behavior to fluid and electrolyte balance in the whole organism in a direct and coherent way. Mastering the elementary chemistry is therefore well worth the minor effort involved.

We present the minimum necessary physical and chemical principles in Chapter 2. The rest of the book will then demonstrate their relevance and power by explaining the apparent complexities of acid–base phenomena in simple but thorough and quantitative terms. The treatment will progress from the simplest system, pure water, in Chapter 3, through

progressively more complex solutions and body fluids in succeeding chapters, to the final, surprisingly simple treatment of whole-body acid–base balance in Chapter 9.

Modern chemistry, even at the elementary level needed to understand hydrogen ion behavior, is largely understood in quantitative, and therefore mathematical, terms. Until recently, that mathematics has been avoided in acid–base chemistry for the sensible reason that it was not very much help before computers became available. Hydrogen ion concentration, the focus of acid–base chemistry, depends on severable variables, and the quantitative description of its behavior requires many simultaneous equations. Explicit analytical solutions for such sets of equations, when they can be written at all, are not usually regarded as useful because they are so unwieldy for practical calculations. Computers, including hand-held programmable calculators, have completely changed this situation; numerical values for the solutions to such equations are now easily and rapidly obtained by computer-implemented techniques of numerical analysis. As a result, computers have revolutionized our ability to analyze, understand, and predict the acid–base behavior of body fluids, or any solutions of biological or medical interest. This book is both an exposition, and an exploitation for its practical usefulness, of that revolution.

The treatment of acid–base chemistry and biology in this book is necessarily not at all like the treatments in current textbooks and research journals. References to previous literature are therefore sparse. There are so many differences in detail between the quantitative analytical treatment presented here and the conventional qualitative treatments that comparisons with even a few of the classical descriptions would have greatly increased the size of this book. It seemed more valuable in this introductory account to concentrate on the basic principles, and their important quantitative consequences, leaving to the reader the task of comparison and translation.

The nonmathematically oriented reader may ask at this point, how much of this new quantitative understanding of acid–base can be achieved without actually working through all the tedious details of the mathematics and the computer programs? The answer supplied by this book is that the minimum level of mathematical sophistication required is only that needed to appreciate what the relevant equations mean, why they must be true, and how they are related to each other. How they are to be solved can then be treated as an incidental technical problem. Most of the mathematical details therefore appear in appendices to the appropriate chapters rather than in the main text. They are there for those who want them, but for those who do not, they will not interrupt the flow of the main arguments. What we want to know is what the mathematics tells us about the behavior of all the variables in body fluids, especially hydrogen ion concentration, once we have specified the quantitative constraints on that

behavior that the laws of physics and chemistry require. Once calculated by the computer, that behavior is readily understood from computer-generated graphs and tables of values. These provide qualitative as well as quantitative pictures of the acid-base behavior of each solution.

In summary, this book presents a nontraditional treatment of acid-base behavior in body fluids. Its purpose is to help the reader work through the elementary physical chemistry of ionic solutions to the synthesis of a clear, quantitative, and practical understanding of how and why hydrogen ion concentration behaves as it does in those solutions and in the whole organism.

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## CHAPTER ONE

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# BODY FLUIDS

---

### 1.1. INTRODUCTION

The treatment in the following pages will focus on acid–base behavior in the fluids of the human body, but it should be clear that the method and the results are easily extended to any and all biological situations in which acid–base phenomena are important. The properties of human body fluids are of obvious clinical importance, and therefore provide a highly motivating as well as specific and concrete referent for our analyses.

The human body is normally about 60% water. In a standard 70-kg male adult, therefore, there must be about 42 liters of aqueous solutions whose acid–base properties we need to understand. That means understanding why the hydrogen ion concentration has the values it does in these fluids and how and why it changes as it does. We shall begin to do that in the next chapter. First, in this chapter we present a summary picture of those 42 liters of solutions.

The body is not, of course, simply a 42-liter tank. It is organized into organs, tissues, and cells, so that there are many different little solutions, and we might expect each of them to have its own peculiar acid–base behavior. Fortunately, we find that they may be lumped together conveniently into a surprisingly small number of representative solutions, so that a satisfactory analysis of body-fluid acid–base behavior is indeed practical. Two obvious major subdivisions of the 42 liters are the intracellular solution, about 25 liters, and the extracellular solution, about 17 liters.

In the body, solutions are separated from one another by membranes, and the properties of these membranes can also be expected to affect acid-base behavior by controlling the kinds of interactions that can occur between the solutions that they separate. We shall therefore first develop the theory and techniques needed to understand the behavior of solutions in isolation (Chapters 2 through 7) before turning to the complications introduced by these membranes (Chapter 8). We shall then be well prepared to understand acid-base phenomena in the whole body, so-called "acid-base balance," and its regulation by the lungs and kidneys (Chapter 9).

## 1.2. INTRACELLULAR SOLUTIONS

Though intracellular solutions form the largest aggregate fluid compartment in the body, they occur as at least  $10^{14}$  tiny separate individual solutions, one inside each cell. Because different cell types are chemically different, there is no reason to expect their internal solutions to be identical. In fact, we know that they are not. Fortunately, they all share a few common differences from extracellular solutions, and it is really on this basis that we justify lumping them all together as intracellular fluid. Intracellular solutions are always high in potassium and magnesium ions and low in sodium and chloride; extracellular solutions are just the reverse. Intracellular solutions contain high concentrations of organic acids; extracellular solutions almost never do.

We shall therefore find it useful to discuss an idealized intracellular fluid whose chemical composition is our best estimate of what we would have if we could put all  $10^{14}$  of those tiny drops of real intracellular fluids together. We shall use ICF as the symbol for this fluid. In view of its ideal or virtual nature, numerical values for its composition must always be understood to be representative rather than strictly factual, except in those rare cases in which specific chemical measurements have somehow been made. To keep this representative quality of ICF always in sight, we shall refer to it frequently as "standard" ICF.

## 1.3. INTERSTITIAL SOLUTIONS (TISSUE FLUIDS)

Extracellular fluids may be subdivided into interstitial solutions or tissue fluids, blood plasma, and "others." We shall devote a brief section here to each one. The largest by far (13.5 liters) is the interstitial fluid that bathes most of the cells in the body and constitutes the "internal environment" whose regulation by several organs of the body gives rise to the physiologists' concept of homeostasis. Its major chemical features are

low potassium and magnesium ion concentrations, high sodium and chloride concentrations, and very low or negligible concentrations of proteins or other organic acids.

Like intracellular fluid, interstitial fluid occurs in innumerable tiny pockets of solution in the interstices of all body tissues. These are mostly in the form of very thin layers, on the order of 1  $\mu$  thick or less, and virtually impossible to sample for chemical analysis. Each one is somewhat different from its neighbors, although probably not as different as the corresponding intracellular samples would be. What we mean by interstitial fluid is the whole 13.5 liters of solution we would have if we could somehow instantaneously remove all those little pockets from the tissues, mix them together, and store them at 37°C under appropriate partial pressures of oxygen and carbon dioxide. It is therefore an ideal or virtual fluid also. We shall use the symbol ISF for it and refer to it often as "standard" ISF to remind us that it too is representative rather than "real."

A special subset of ISF is the lymphatic fluid, or lymph. Physiologically, lymph can be thought of as the overflow fluid from the tissues, en route back to the bloodstream by way of the lymphatic vessels. It arises because reabsorption of fluid at the venous ends of capillaries seldom precisely balances filtration out at the arterial ends, and also because of leakage of protein out of the capillaries. These proteins, along with the excess fluid, are constantly removed from the tissues and returned to the circulating blood plasma as lymph. Because lymph is in vessels, it is possible to sample it, so that measurements of lymph composition are often cited as approximations of the composition of ISF. In most cases, they are all that we have, but they may be rather poor approximations.

#### 1.4. BLOOD PLASMA

The third largest fluid entity in the body is blood plasma. It is a single fluid, confined to the interior of the cardiovascular system, so it is not such an idealized or "lumped" fluid as ISF and ICF. It is certainly the most frequently analyzed fluid in all of biology and medicine, because samples are so easy to obtain by simple venipuncture.

Plasma volume is about 4% of body weight, or 3 liters. Seventy percent of it, about 2 liters, is normally contained in the veins. It circulates rapidly throughout the body and is in effective diffusion equilibrium with the ISF for most solutes except macromolecules. Plasma therefore differs in composition from ISF mainly in its protein content, and this difference has some acid-base consequences.

In the body, plasma has a large content of suspended red blood cells, normally 40 to 45% of the total blood volume. The presence of these suspended cells has to be taken into account when analyzing the behavior

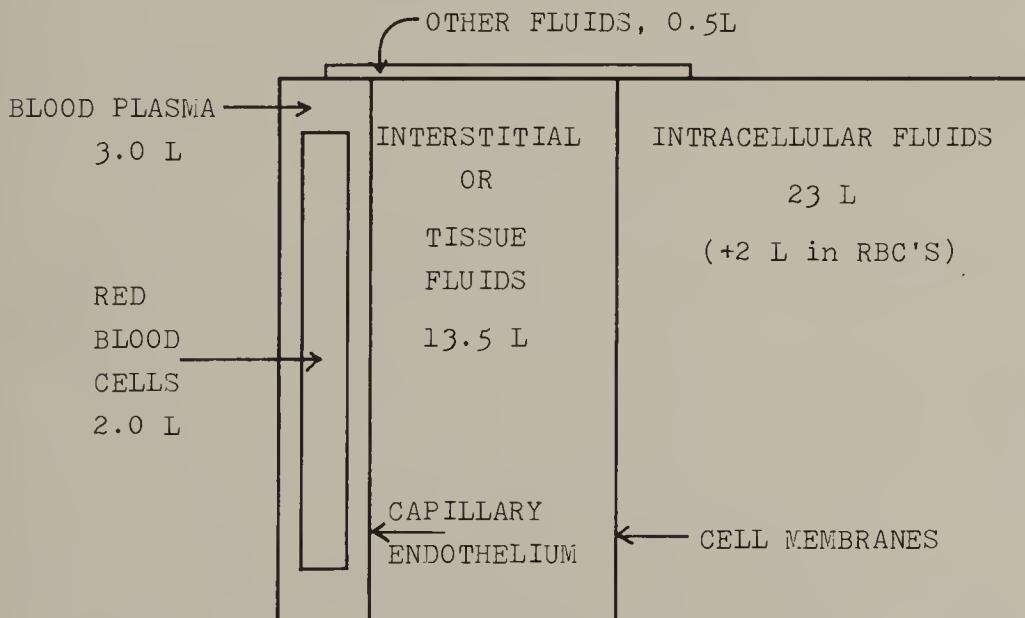
of plasma, and complicates that analysis somewhat. We shall therefore analyze blood plasma twice, first in isolation, without blood cells, in Chapter 7, and then, with its normal complement of red blood cells, as whole blood, in Chapter 8. It is useful, in this context, to think of blood plasma as the interstitial fluid of a very special (liquid) tissue, namely, whole blood.

### 1.5. OTHER BODY FLUIDS

This category includes a variety of small volumes of special, usually rather small and localized, solutions such as aqueous humor, synovial and bursal fluids, bile, saliva, and many others. These are sometimes referred to as "transcellular" fluids. Each one is extremely important in its own local situation, but they are not of much quantitative significance for whole-body acid-base behavior because they only total about 0.5 liter on the average.

Two of these special fluids, however, are of acid-base importance, gastric "acid" and pancreatic secretion. Gastric acid can be as much as 0.1N HCl, and pancreatic "juice" contains high concentrations of sodium but almost no chloride. We shall examine in Chapters 4 and 6 how such solutions can be produced from (alkaline) blood plasma and how they

**Figure 1.1.** Diagrammatic representation of major body fluid volumes and relationships in a standard 70-kg human body.



$$\begin{aligned}\text{TOTAL BODY WATER} &= 23 + 13.5 + 3.0 + 2.0 + 0.5 \text{ L} \\ &= 42 \text{ L}\end{aligned}$$

interact in the duodenum. Otherwise, we shall generally ignore the “other” body fluids.

### 1.6. SUMMARY

The volumes, membranes separating, and topological relationships between the major body fluids just discussed are summarized diagrammatically in Fig. 1.1. All these solutions are generally considered to be in osmotic equilibrium because all the membranes are freely permeable to water. Body-fluid osmolarity is normally maintained by the hypothalamus–pituitary–kidney team at a value close to 0.285 osmole/liter.

The solutions involved in major body fluids are (70 kg man):

1. Intracellular Fluid (ICF)

25 liters      The sum of all the solutions inside all the cells of the body.

2. Interstitial Fluid (ISF)

13.5 liters      The sum of all the little pockets of tissue fluid in the interstices between cells throughout the body.

3. Blood Plasma

3 liters      The interstitial fluid of blood.

4. Other Fluids

0.5 liter

Total Body Water = 42 liters = 25 + 13.5 + 3 + 0.5 liters.

---

## CHAPTER TWO

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# GOALS, DEFINITIONS, AND BASIC PRINCIPLES

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### 2.1. RATIONALE AND GOALS

Hydrogen ion concentration in body fluids is extremely low, on the order of one ten-millionth to one hundred-millionth of an equivalent per liter. Why are we so interested in the behavior of such a rare species? One reason is that as protons, hydrogen ions are very small, and therefore have a very high charge density. This in turn results in very large electric field gradients in their neighborhoods. They may therefore have important effects on other molecules in the solution around them, even at very low concentrations. In particular, hydrogen bonds are important in the determination of macromolecular structure and configuration, and their strengths should be particularly sensitive to local hydrogen ion concentrations. Partly for these reasons, enzyme activities are often significantly dependent on local hydrogen ion concentration.

Changes in hydrogen ion concentration may also have important effects on biochemical reaction rates simply because hydrogen ions are involved in so many biochemical reactions. This multiple involvement also contributes to the complexities of understanding the dynamics of hydrogen ion concentration changes. In particular, hydrogen ions can be formed from water or can be destroyed by the formation of water. Because water is by orders of magnitude the most concentrated substance in living systems (55.3M), it provides an effectively inexhaustible source, or unfillable sink, for hydrogen ions as well as for hydroxyl ions. These two ions therefore behave quite differently from other kinds of ions that do not have such resources available to them.

Clinically, hydrogen ion concentration, ( $[H^+]$ ), in body fluids is important as a useful indicator of several different kinds of pathology.  $[H^+]$  is most easily measured in blood, via a small venipuncture sample and a pH meter. The  $[H^+]$  of a mixed venous blood sample is usually near  $4.5 \times 10^{-8}$  Eq/liter (pH 7.35), while arterial blood  $[H^+]$  is near  $4.0 \times 10^{-8}$  Eq/liter (pH 7.40). Values above about  $1.2 \times 10^{-7}$  Eq/liter (pH 6.9) or below about  $1.6 \times 10^{-8}$  Eq/liter (pH 7.8) indicate life-threatening situations and demand immediate intervention. Between these limits, wide variations can occur, sometimes very rapidly. It is important to understand how such variations arise, how blood  $[H^+]$  is related to  $[H^+]$  in other body fluids, and how the body may be helped to restore normal conditions.

The general goal of this book is quantitative explanation and understanding of hydrogen ion concentration and its changes in any biological solution. Quantitative understanding requires precise knowledge of the significant variables in the system and the physically necessary quantitative relationships between them. Our specific goal may therefore be stated in these terms:

In any given solution, under any specified conditions, we want to establish the quantitative relationships between hydrogen ion concentration in that solution and all the other variables in the solution that determine that hydrogen ion concentration. We shall then be able to understand, and explain, the value of the hydrogen ion concentration in terms of those determining variables.

Armed with this quantitative understanding, we shall be able to answer precisely and confidently any questions about how and why the hydrogen ion concentration changes as it does, and to design rational and effective therapy, on a quantitative basis, for situations involving abnormal  $[H^+]$  values (acid-base disorders).

To achieve this goal, we must first spend some time and effort to make sure that we agree on definitions and then, in the rest of this chapter, formulate clearly the basic physical and chemical principles that will be our major tools for analysis and quantitative understanding of hydrogen ion behavior in body fluids.

## 2.2. DEFINITIONS: NEUTRAL, ACIDIC, ALKALINE, ACID, BASE

The concept of an acid or a base has a long folk history, but a rather short scientific history, and emotional arguments have often centered on the meanings of these words. For the purposes of this book, we shall adopt the very simple but practical and useful definitions given below. They are very close to current common usage in biology and medicine, and they

will serve very well our goal of understanding quantitatively how biological acid–base systems behave.

**Definition:** A solution is said to be acid–base neutral if its hydrogen ion concentration is equal to its hydroxyl ion concentration.

Acid–base neutrality is a very special, rarely achieved condition. It must be carefully distinguished from electrical neutrality, a very different, and completely general, requirement that all solutions must satisfy (Section 2.4).

**Definition:** A solution is said to be acidic, or acid, if its hydrogen ion concentration is greater than its hydroxyl ion concentration.

**Definition:** A solution is said to be alkaline, or basic, if its hydrogen ion concentration is less than its hydroxyl ion concentration.

Hydrogen ion concentration, by itself, is clearly not a reliable measure of acidity, alkalinity, or neutrality, nor is its negative logarithm, pH. In pure water, for example, hydrogen and hydroxyl ion concentrations are always equal, so pure water is always acid–base neutral, but its hydrogen ion concentration varies significantly with temperature, from  $3.4 \times 10^{-8}$  Eq/liter (pH 7.5) at 0 C to  $8.8 \times 10^{-7}$  Eq/liter (pH 6.1) at 100 C. The common textbook statement that neutrality is at pH 7.0, corresponding to hydrogen ion concentration of  $1.0 \times 10^{-7}$  Eq/liter, is only true in pure water at 25 C. In particular, it is not true at body temperature, 37 C, for which the pH of pure water is 6.8.

**Definition:** A substance is an acid if, when added to a solution, it brings about an increase in the hydrogen ion concentration of the solution, all other independent variables in the solution remaining constant.

**Definition:** A substance is a base if, when added to a solution, it brings about a decrease in the hydrogen ion concentration of the solution, all other independent variables in the solution remaining constant.

Acids achieve their effect either by dissociating in solution to yield an anion plus a hydrogen ion or by associating with a hydroxyl ion and thereby increasing the dissociation of water. Bases act either by dissociation to form a cation plus a hydroxyl ion or by associating with a hydrogen ion. In all cases, water dissociation equilibrium (Chapter 3) readjusts, with the final result specified in the definition.

These definitions may appear old-fashioned and very simpleminded, particularly to the advanced student of physical chemistry. It is much

more fashionable to follow Bronsted and define an acid as a proton donor and a base as a proton accepter. That terminology is useful in many non-biological situations, but in complex solutions and living organisms, the definitions given here are much more useful. Unfortunately, the proton-donor/proton-accepter terminology has encouraged an identification of “acid” with “hydrogen ion,” which is very misleading. It leads to the common, and confusing, assumption that the only significant aspect of “adding acid” to a solution is adding hydrogen ions, or that adding hydrogen ions is equivalent to “adding acid,” which it is not, as we shall see in Chapter 4. This misidentification of “acid” with “hydrogen ion” underlies much of the deep-rooted confusion about cause–effect relationships in acid–base chemistry. It also suggests that hydrogen ion concentration must be an independent variable in solutions, whereas in fact hydrogen ion concentration is always a dependent variable. It also hinders us from calling carbon dioxide an acid, whereas in fact carbon dioxide functions as by far the most important single weak acid in living systems and their environments.

Fortunately, such labels are not so important as the information and understanding behind them. What matters in biology and medicine is what happens to the hydrogen ion concentration of important solutions, such as blood plasma, ISF, and ICF, and why. Whether or not we call  $\text{Na}^+$  a base, or carbon dioxide an acid, is not nearly as important as whether we can explain quantitatively the effects on any solution of adding  $\text{Na}^+$  or  $\text{CO}_2$ . What enables us to do that is not terminology but calculations based on sound physical and chemical principles. To achieve our goal, we need to develop the rules by which such calculations can be carried out. The results will then provide us with the kind of quantitative understanding of hydrogen ion behavior that is essential in biology and medicine.

### 2.3. DEFINITIONS: IONS, NONELECTROLYTES, STRONG AND WEAK ELECTROLYTES

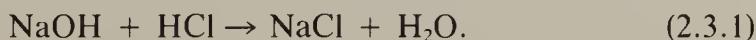
Many substances, when dissolved in water, dissociate into charged particles called ions. For these substances, therefore, the process of going into solution in water is more than a simple physical process; it is a chemical process in which the chemical identity of the molecular species changes. Substances that dissociate to form ions are called electrolytes, and it is convenient to subdivide them into two classes, strong and weak. Substances that do not dissociate in this way are called nonelectrolytes, and they are of very little interest in acid–base chemistry, except insofar as they affect water concentration (osmolarity) or alter the value of parameters such as dissociation constants.

Because a major feature of ions is their charge, it is customary to express their concentration in terms of moles of charge rather than moles of atoms. One equivalent of an ion is that amount that contains, if it is negatively charged, or is missing, if it is positively charged, one mole of electrons ( $6 \times 10^{23}$ ). For univalent ions, concentration in equivalents per liter is the same as concentration in moles per liter. For an  $n$ -valent ion, concentration in equivalents per liter is just  $n$  times the concentration in moles per liter. A solution that has a concentration of  $y$  equivalents per liter of any ion is said to be “ $y$  normal” in that ion, abbreviated  $yN$ . For example,  $0.01M\ K_2SO_4$  is  $0.02N$  in  $K^+$  because there are  $2K^+$  per mole, and  $0.02N$  in  $SO_4^{2-}$  because  $SO_4^{2-}$  is bivalent. We shall use the conventional symbols  $[X]$  from here on to represent the concentration of  $X$  in equivalents per liter, which is also the concentration of charge carried by  $X$ , in moles of electrons (+ or -) per liter.

### 2.3a. Strong Electrolytes

Strong electrolytes are always completely dissociated in solution, so that the parent substance disappears when dissolved in water. Solutions of strong electrolytes contain only the ions derived from the parent substances, none of the undissociated parent molecules. There are, for example, no  $NaCl$  molecules in a solution of common salt, just sodium ions,  $Na^+$ , and chloride ions,  $Cl^-$ , (and water and  $H^+$  and  $OH^-$ ).

An important, and frequently overlooked, consequence of this aspect of strong electrolyte solutions is that it prohibits us from writing some ordinary and otherwise legitimate-looking chemical reaction schemes. For example, when we mix a solution of hydrogen chloride,  $HCl$ , in water, called hydrochloric acid, with a solution of sodium hydroxide,  $NaOH$ , the temptation is to write this reaction to represent the mixing process:



In fact, the “ $NaOH$ ” solution is a solution containing  $Na^+$ ,  $OH^-$ , and  $H^+$  ions, but no  $NaOH$ , and the “ $HCl$ ” solution contains  $Cl^-$ ,  $OH^-$ , and  $H^+$  ions, but no  $HCl$ . After mixing, we have a solution that contains  $Na^+$ ,  $Cl^-$ ,  $OH^-$ , and  $H^+$  ions, but no  $NaCl$ . The only chemical reaction that has occurred is the readjustment of the equilibrium for water dissociation:



The  $Na^+$  and  $Cl^-$  have not taken part in any reactions, and no  $NaCl$  is formed; (2.3.1) is simply incorrect.

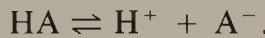
It is difficult not to be misled by the sloppy conventional terminology that persistently invokes such nonexistent entities in solution as “sodium chloride” or “sodium bicarbonate,” but it is essential to be clear about

their strictly imaginary status. Ideally, we should refer to a solution of NaOH added to water as an “ $\text{Na}^+ + \text{OH}^- + \text{H}^+$  solution” rather than as an “NaOH solution.” It is often useful to compromise by referring to an “NaOH” solution, or a “KCl” solution, to keep these facts always before us without losing the obvious convenience of the conventional name without quotes.

Ions such as  $\text{Na}^+$  or  $\text{Cl}^-$  that are derived from strong electrolytes are usefully called strong ions, to remind us of their special status. The most common strong ions in biological solutions are  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ ,  $\text{Mg}^{2+}$ ,  $\text{SO}_4^{2-}$ ,  $\text{Ca}^{2+}$ , and a few organic acid anions, notably lactate<sup>-</sup>. Lactate<sup>-</sup> ion functions as a strong acid anion because of the large dissociation constant of lactic acid (Section 2.3b).

### 2.3b. Weak Electrolytes

Weak electrolytes are substances that only partially dissociate when dissolved in water, so that molecules of the parent substance as well as the products of dissociation all exist together in solution. Taking a weak acid, HA, as our prototype weak electrolyte, we can write this reaction:



Equilibrium requires that the rate of dissociation equal the rate of recombination and leads to this quantitative requirement on the concentrations of the three molecular species:

$$[\text{H}^+] \times [\text{A}^-] = K_A \times [\text{HA}]. \quad (2.3.2)$$

The equilibrium constant,  $K_A$ , is usually called the dissociation constant. Its unit in this case must be equivalents per liter.

The equilibrium constant is exponentially related to the standard free energy change per mole for the reaction, so that much of the analysis presented in the following chapters could also be expressed in terms of free energies rather than equilibrium constants. Thorough and useful quantitative analyses of body-fluid chemistry have been carried out using free energies and have led to clinically useful computer programs [1, 2].

It is important to understand just what Equation (2.3.2) does and does not say. What it says is that no matter what else may be happening, the numerical values of the concentrations of  $\text{H}^+$ ,  $\text{A}^-$ , and HA at equilibrium must satisfy this equation. By itself, it does not say what any of those values must be; it does not determine any of them. It merely expresses one of the requirements that they must satisfy. What determines the actual values of those concentrations is the fact that they must each satisfy a number of such requirements simultaneously and independently.

Dissociation reactions proceed very rapidly, and equilibrium is achieved with half times on the order of microseconds or less. We are therefore

justified in always assuming equilibrium status for such reactions in biological solutions. Carbon dioxide presents some interesting complications in this context, but they are usually taken care of by the enzyme carbonic anhydrase.

A quantity sometimes used to describe the status of a dissociation equilibrium is the degree of dissociation, symbol  $\alpha$ , defined as the concentration of one of the product ions divided by the total concentration of the weak electrolyte present:

$$\alpha_A = \frac{[A^-]}{[A^-] + [HA]} = \frac{[A^-]}{[A_{TOT}]} \quad (2.3.3)$$

Here  $[A_{TOT}] = [A^-] + [HA]$  is the total concentration of "A" present in the two forms, HA and  $A^-$ . Because by definition there are no other reactions in the solution involving  $A^-$  or HA, there can be no change in  $[A_{TOT}]$  except by mass transfer of either HA or  $A^-$  into or out of the solution.  $[A_{TOT}]$ , in other words, can only be changed from outside the solution, so it is an externally controlled, or independent, variable. More on this in Section 2.5 and Chapter 5.

The degree of dissociation may be expressed either as a percentage or as a decimal fraction. Thus, if conditions are such that  $[A^-] = [HA]$ , then  $\alpha_A = 0.5$  or 50%, and the weak acid is 50% dissociated. Under some conditions, for example, an excess of strong base cations such as  $Na^+$  in the solution, a weak acid may be essentially all in the dissociated form, so  $\alpha_A$  approaches 1.0. How does HA now differ from a strong acid? The answer lies in its response to a change in the conditions. If "HCl" were added to the solution just described, then as  $[Cl^-]$  increased,  $A^-$  would convert to HA,  $\alpha_A$  would decrease and would approach zero as soon as  $[Cl^-]$  exceeded  $[Na^+]$ . Similar changes would not be observed in  $[Na^+]$ ;  $Na^+$  would remain as  $Na^+$  regardless of  $[Cl^-]$  or  $[A^-]$ . Strong electrolytes remain completely dissociated. Weak electrolytes change their degree of dissociation depending on conditions, even though they can be completely dissociated under some conditions. This difference is profoundly important in understanding the acid-base behavior of biological solutions.

This strong-weak distinction that is so useful in acid-base chemistry should not be confused with the ordinary-language use of the same words to refer to concentrations, often to hydrogen ion concentrations. In acid-base chemistry, strong and weak always refer to whether a substance is one or the other kind of electrolyte, and cannot be used as adjectives for solutions. Dilute and concentrated refer to solutions. Thus we could have a dilute or a concentrated solution of a strong or a weak acid. Unfortunately, in ordinary speech, a strong salt solution means a concentrated one, and a weak acid solution means one in which the hy-

hydrogen ion concentration is low, for whatever reason, and regardless of whether the acid in question is strong or weak!

It should also be clear that chemically, the strong-weak classification does not reflect the existence of two distinct categories of substances in nature, but rather a spectrum of dissociation constant values. For biological purposes, any substance whose dissociation constant is larger than about  $10^{-4}$  Eq/liter will function as a strong electrolyte in biological solutions, and anything with a dissociation constant smaller than about  $10^{-12}$  Eq/liter is effectively a nonelectrolyte. Anything in between these limits is a weak electrolyte.

#### 2.4. GENERAL PRINCIPLE: ELECTRICAL NEUTRALITY

In any macroscopic sample of any aqueous solution, the sum of all the positively charged ion concentrations always equals the sum of all the negatively charged ion concentrations. An aqueous solution is always electrically neutral.

“Macroscopic” in this statement means “large enough that concentration can be meaningfully defined.” Conceptual, theoretical, and practical problems arise in this context inside cells where very small compartments are often described, such as mitochondria, presynaptic vesicles, etc.

This requirement, that solutions be electrically neutral, is not only important conceptually in understanding why they behave as they do, it is also useful in the quantitative analysis, because it provides a link between the concentrations of the nonreacting strong ions and the equilibrating weak ones. Its physical basis is Coulomb’s law, which specifies the very large electrical forces that come into play whenever charge imbalance occurs. An excellent discussion of this topic for the reader who wishes a more detailed treatment may be found in Guggenheim [3].

A most important consequence of this principle is that it is not possible to add a single species of ion to a solution all by itself. Some other species of opposite charge must always be added at the same time, and its amount and identity must be incorporated into calculations of the final result of such additions. Adding  $\text{Na}^+$  as “ $\text{NaOH}$ ” has a very different effect on a solution from adding the same amount of  $\text{Na}^+$  as “ $\text{NaCl}$ ,” for example. It is surprisingly easy to overlook this requirement when attention is focused on a single ion species, particularly when examining membrane transport processes.

The strength of the electrical neutrality requirement may be dramatized by the following calculation. Imagine a small sphere of solution, 1 mm in radius, containing  $1.0 \times 10^{-7}$  Eq/liter excess positive ions over negative ions. The volume of the sphere is  $4.2 \times 10^{-6}$  liters, so that it contains

a net positive charge of  $4.2 \times 10^{-6} \times 10^{-7} = 4.2 \times 10^{-13}$  Eq. One equivalent = 96,500 coul, so the charge on the sphere is  $4.2 \times 10^{-13} \times 96,500 = 4.0 \times 10^{-8}$  coul. Coulomb's law in electrostatics says that the potential on a sphere of radius  $r$  (meters) carrying a charge  $Q$  (coulombs) is  $Q/1.1 \times 10^{-10} r$  (volts). Substituting the above values for  $r$  and  $Q$ , we get 400,000 V, almost half a million! The chemically insignificant concentration difference of  $10^{-7}$  Eq/liter produces an enormous electrical effect. Because ions in solution are free to move about, they will of course redistribute themselves very rapidly in response to such electrical forces, so that electrical neutrality is maintained to an extremely high level of precision at all times.

## 2.5. GENERAL PRINCIPLE: CONSERVATION OF MASS

The amount of each component substance in any aqueous solution remains constant unless:

**Condition 1.** That substance is added to or removed from the solution from the outside.

or

**Condition 2.** That substance is generated or destroyed by chemical reactions within the solution.

This is such a basic, simple, commonsense, obvious idea that it may seem pedantic to mention it. It turns out to be extremely important to understand that in discussing hydrogen ions, condition 2, not condition 1, is the important one. Much of the confusion and conceptual difficulties in classical acid-base theory arise from the mistaken idea that only condition 1 applies to hydrogen ions.

When only condition 1 applies, as is almost always the case for strong ions, only very simple additive bookkeeping on the separate molecular species is needed to explain and understand concentration changes. If we add  $x$  Eq of  $\text{Na}^+$  to 1 liter of solution, then  $[\text{Na}^+]$  increases by  $x$  Eq/liter.

On the other hand, when chemical reactions such as dissociation and recombination can occur, so that condition 2 applies, then we have much more complicated bookkeeping to do. For example, if we add  $x$  Eq of HA to 1 liter of solution, the concentration of HA will not go up by  $x$  Eq/liter. Some of the added HA will dissociate to  $\text{A}^-$  and  $\text{H}^+$ , but the extent to which this will happen depends on several other quantities in the solution, not just on  $x$ . We cannot even expect that  $[\text{H}^+]$  will increase by the amount of this dissociation, even though that produces hydrogen ions. How to calculate just how much  $[\text{H}^+]$  will change in such circumstances is what this book is all about. At this stage, the important point is that we cannot take for granted that reacting substances such as HA or  $\text{H}^+$  will behave

additively in solutions even though nonreacting substances such as  $\text{Na}^+$  or  $\text{K}^+$  do.

Another application of conservation of mass that we have already used is the definition of  $[\text{A}_{\text{TOT}}]$  in Section 2.3b. Even though both  $\text{HA}$  and  $\text{A}^-$  are reacting species, the fact that their sum is independent of those reactions means that  $[\text{A}_{\text{TOT}}]$  only has to satisfy condition 1 above. For a weak base,  $\text{BOH}$ , that dissociates to  $\text{B}^+$  and  $\text{OH}^-$ , we may similarly define the total quantity of "B,"  $[\text{B}_{\text{TOT}}]$ , =  $[\text{B}^+] + [\text{BOH}]$ .

## 2.6. OSMOTIC COEFFICIENTS, ACTIVITIES, AND CONCENTRATIONS

We have characterized strong electrolytes as completely dissociated, so that we should expect their colligative properties to be appropriate integer multiples of those of nonelectrolytes at the same molar concentrations. In fact, they are usually less than integer multiples, and this is sometimes erroneously interpreted to indicate fractional dissociation. For example, because the molar freezing point depression coefficient for water is 1.86°/mole/liter,  $\text{NaCl}$  or  $\text{KCl}$  dissolved in water should give solutions with freezing point depressions of  $2 \times 1.86 = 3.72^\circ/\text{mole/liter}$ . The observed freezing point of 0.1M "NaCl" solution is  $-0.316^\circ\text{C}$ . The ratio of measured to expected freezing point depression, 0.85 in this case, is called the osmotic coefficient. What it means is that the  $\text{Na}^+$  and  $\text{Cl}^-$  ions do not change the thermodynamic activity of the water as much as the same concentration of uncharged molecules does. It does not mean that  $\text{NaCl}$  molecules are present, nor does it tell us what the effective concentrations of  $\text{Na}^+$  and  $\text{Cl}^-$  are in the solution.

Measured departures from "ideal" behavior such as this have led to the concept of thermodynamic activity, or effective concentration, and strictly speaking whenever we discuss equilibria we should use activities rather than concentrations. Equilibrium states by definition are determined by activities of reactants rather than by concentrations. It is customary to minimize the distinction between them, especially in introductory treatments such as this book attempts to be, and we shall keep to that convention. Fortunately, strong ions, which are the ones in highest concentrations in biological fluids, do not generally participate to any significant extent in any chemical equilibria. Nonetheless, the distinction between measured concentration and activity or effective concentration is always lurking in the background. It should be carefully examined whenever disparities arise between simple theory and the results of measurements. For most of the analyses in this book, we shall assume that the distinction is not important and use the symbols [ ] to mean either concentration or activity, whichever is appropriate, always in equivalents/per liter unless otherwise indicated.

One place in which the distinction between activity and concentration is customarily made explicit is in the specification of dissociation constants. When the constant is written with a prime, as  $K'_A$ , that conventionally indicates that the value has been obtained under experimental conditions in which concentrations have been measured. Its value can then be expected to change with concentrations of reactants, because activities are generally nonlinear functions of concentrations. When the dissociation constant is specified without the prime, as  $K_A$ , the implication is that activities rather than concentrations should be used, and then its value can be expected to be constant over a range of concentrations. Fortunately, these distinctions are seldom important in body fluids because of the relatively small changes in concentrations of weak electrolytes that they generally experience.

## 2.7. CHAPTER SUMMARY

1. The goal of this approach to acid–base chemistry is to establish the quantitative relationships that determine  $[H^+]$  in any solution.
2. Solutions are defined to be acid if  $[H^+] > [OH^-]$ , alkaline if  $[H^+] < [OH^-]$ , and neutral if  $[H^+] = [OH^-]$ .
3. A substance is called an acid if it raises the  $[H^+]$  when added to a solution and a base if it lowers  $[H^+]$ .
4. Strong electrolytes are completely dissociated in solution. Weak electrolytes are partly dissociated and obey a dissociation equilibrium. *Nonelectrolytes do not dissociate into ions in solution.*
5. Molecules of salts do not exist in solution.
6. Solutions must be electrically neutral.
7. Conservation of mass applies in two different ways.
8. Distinctions between activities and concentrations of ions may be important in some situations, but will be largely ignored in this elementary treatment.

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## CHAPTER THREE

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# THE SIMPLEST ACID-BASE SYSTEM: PURE WATER

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### 3.1. INTRODUCTION

“Acid–base” means “what happens to hydrogen ions in aqueous solutions,” so that the first acid–base system we must understand, and the simplest, is water itself. Pure liquid water is a substance with anomalous physical properties and a complex statistical structure still not completely understood. Many of its peculiar properties are crucial for life, and it is by far the major component of all living systems [1–3]. Its three most interesting properties for acid–base chemistry are its large dielectric constant, its very small dissociation constant, and its very high concentration.

The large dielectric constant means that substances whose molecules contain strongly ionic bonds will dissociate to some extent when they dissolve in water to yield solutions containing ions. Substances that produce hydrogen or hydroxyl ions in this way will be particularly interesting for our purposes.

Water itself dissociates into hydrogen and hydroxyl ions. At 37 C, the dissociation constant is  $4.3 \times 10^{-16}$  Eq/liters, so that water is a nonelectrolyte by the definition of the preceding chapter. It is a special case, however, and the biological importance of this minuscule dissociation constant is out of all proportion to its small magnitude.

The concentration of water is about 55.3M at 37 C. This is almost 400 times the concentration of the next most concentrated substances in body fluids, sodium ions at 0.14M extracellularly and potassium ions at 0.15M

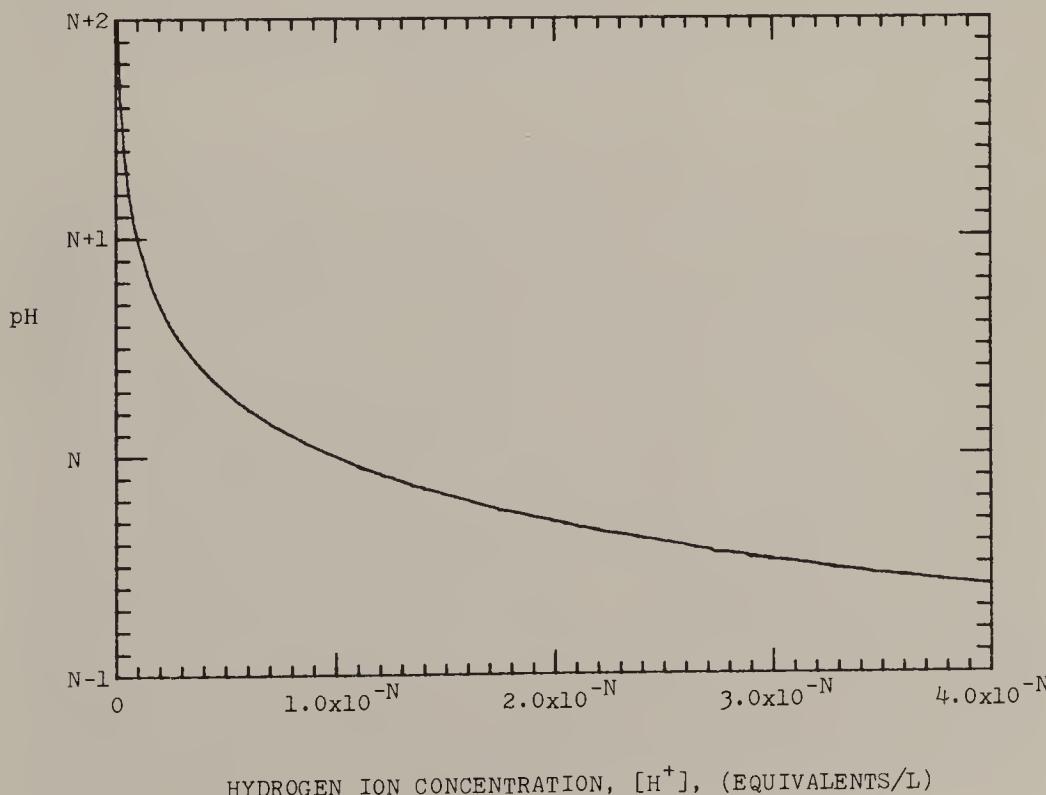
intracellularly. Hydrogen ions in body fluids are a thousand million times less concentrated than water. These comparisons can be very useful in simplifying our analytical tasks later on.

In Section 2.2 we pointed out that the hydrogen ion concentration of pure water changes with temperature, and yet pure water is always acid–base neutral. Our goal for this chapter is to arrive at a clear quantitative understanding of why that is so, in terms of the definitions and basic principles presented in the previous chapter.

### 3.2. THE MEANING OF $[\text{H}^+]$ AND $[\text{OH}^-]$

Strictly speaking, it is almost meaningless to talk of a hydrogen ion, meaning a free proton, as having an independent existence in liquid water. Protons react easily and rapidly with water molecules, and also surround themselves with layers of electrically attracted water molecules, so that only a careful quantum statistical analysis would provide a precise description of just what we mean when we say “hydrogen ion.” Nonetheless, at the macroscopic chemical level that is appropriate for quantitative

**Figure 3.1.** The general form of the pH– $[\text{H}^+]$  relationship, Equations (3.3.1).  $N$  is any integer, but in practice  $N$  is restricted to the range from –1 to +14. See Figure 3.2 also.



understanding of acid-base behavior, we need a way to represent the average effects of whatever all the individual protons may be doing. The symbol  $H^+$  and the words “hydrogen ion” should be understood in just this sense, as a kind of metaphor for what must be a very complex situation at the molecular level. Similar comments apply to “ $OH^-$ ” and “hydroxyl ion.” Some writers use the symbol  $H_3O^+$  and speak of the hydronium ion, as if this were a more accurate representation. What should be written is  $\{H:(H_2O)_n\}^+$  if we want our symbol to remind us of the proton’s attraction for water molecules. Both these larger symbols are typographically inconvenient compared to  $H^+$ , so we shall continue to use  $H^+$ . It should be recognized as a symbol for a metaphor, which ignores considerable molecular complexity, but is useful to represent the relevant chemical behavior of one product of water dissociation. Many of the remarkably emotional arguments in the acid-base literature seem to stem from failure to recognize this metaphorical status of  $H^+$  and  $OH^-$ .

### 3.3. pH

For a variety of historical reasons, it is conventional to express hydrogen ion concentration in two very different ways, either directly as  $[H^+]$  or indirectly as pH. The relationship between them can be written in three different-looking but mathematically equivalent forms:

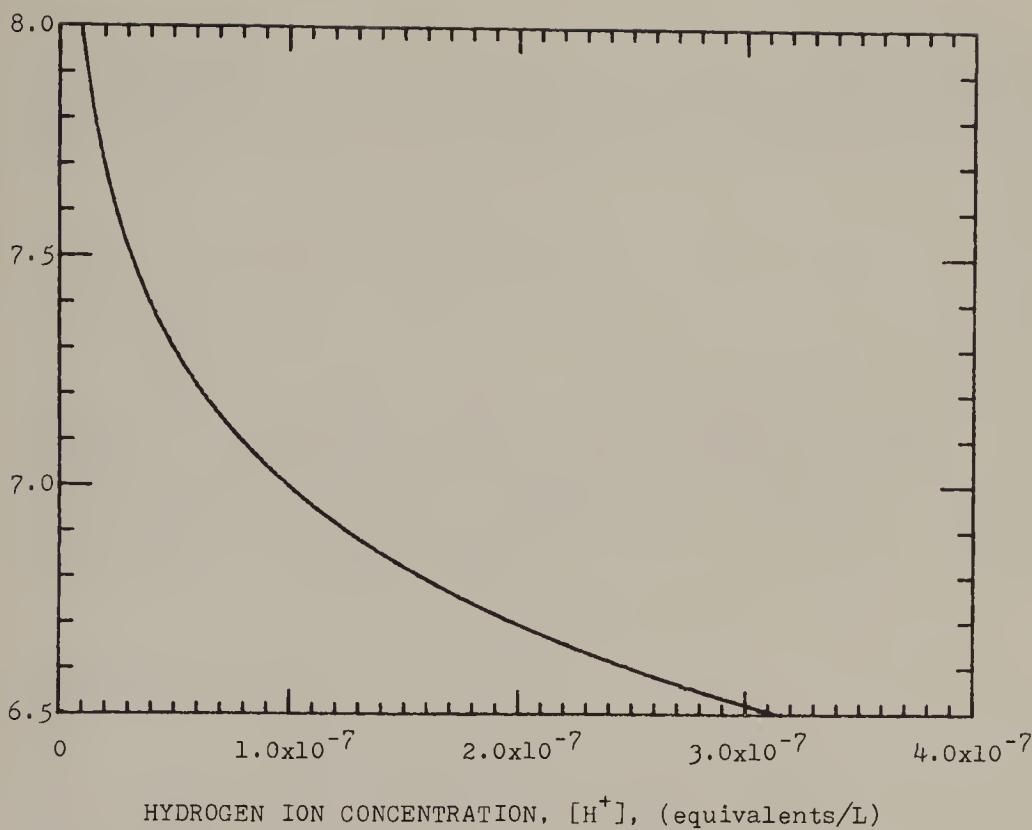
$$pH = \log_{10} \left\{ \frac{1}{[H^+]} \right\}$$

$$pH = -\log_{10} \{ [H^+] \} \quad (3.3.1)$$

$$[H^+] = 10^{-pH}$$

A generalized display of these relationships is shown in Figure 3.1, while Figure 3.2 covers the specific range of physiological interest, from pH 6.5 to pH 8. This figure may be useful for actual numerical conversion from pH to  $[H^+]$  or from  $[H^+]$  to pH.

The relationship between  $[H^+]$  and pH has several important characteristics that can cause unnecessary confusion if not understood clearly. The first is that the numerical value of the logarithm goes from minus infinity through zero to plus infinity as its argument goes from zero through one to plus infinity. As  $[H^+]$  increases from 0 to 1.0 Eq/liter, therefore, the pH decreases from plus infinity to 0. Any volume of solution that contains no  $H^+$  has  $pH = +\infty$ ! pH continues to decrease from 0 toward minus infinity as  $[H^+]$  increases above 1.0 Eq/liter. It is very difficult to get  $[H^+]$  in aqueous solutions below about  $10^{-15}$  or above about 15 Eq/liter, so that the practical limits on the pH scale are –1.2 and 15. The common textbook statement that the pH scale goes from 0 to 14 has no basis in chemical reality, but merely reflects the arbitrary appearance



**Figure 3.2.** pH versus  $[H^+]$  over the physiological range from 6.5 to 8.0. This curve may be used as a graphical "calculator" to convert from one scale to the other in either direction.

of most pH meter scales. Ordinary concentrated hydrochloric acid has a pH of about -1.1.

Because pH is a logarithmic reflection of  $[H^+]$ , it should permit easy graphical visualization of a wide range of  $[H^+]$  values. Unfortunately, it does it backwards; pH goes down as  $[H^+]$  goes up. A direct logarithmic scale would be much less confusing in this respect, except that its values would be mostly negative, and therefore would presumably seem less "real."

A related problem with pH is that the effective concentration of  $H^+$  is 4 to 7 orders of magnitude less than that of most other ions with which we are concerned in biological solutions.  $H^+$  is, in this sense, very much a "trace substance" in body fluids. It is not intuitively obvious how we should think about its chemical behavior in qualitative terms. By disguising this very small magnitude of  $[H^+]$ , the pH notation obscures many qualitative aspects of the chemical relationships that are involved in acid-base behavior and distorts the apparent quantitative significance of  $[H^+]$ .

The equilibrium states of chemical reactions in which  $\text{H}^+$  is involved are determined by the effective concentrations of the reacting substances, so that  $[\text{H}^+]$  is what we must think about and deal with if we wish to analyze quantitatively and understand systems of such reactions. From this viewpoint, pH is a very strange and confusing doubly nonlinear transformation of  $[\text{H}^+]$ . Starting with the variable that is significant in acid-base reactions,  $[\text{H}^+]$ , you must first take its reciprocal, which is a nonlinear process, and then take the logarithm of the result, a second nonlinear process. As a result, it is very difficult to think about what must be happening quantitatively to  $[\text{H}^+]$  when pH values are cited.

One pragmatic justification for using pH might be that we have “pH meters” that measure pH “directly.” The physical fact is that a pH meter measures an electrical potential difference that is, under carefully controlled circumstances, a logarithmic function of  $[\text{H}^+]$ . Interpreting this potential difference in terms of pH rather than  $[\text{H}^+]$  is simply a matter of putting a linear, rather than exponential, scale on the voltmeter.

The supposed “units” of pH may also cause confusion. It should be clear that pH is a dimensionless number; pH values are simply dimensionless numbers and should be treated as such. A reflection of the widespread confusion that exists about the physical meaning of pH is the frequency with which pH is incorrectly referred to in concentration units, or even as “pH concentration”! In fact, the quantity whose logarithm gives us pH is a volume per equivalent, just the inverse of concentration. pH could be correctly seen as a logarithmic measure of the volume required to contain 1 Eq of  $\text{H}^+$ . In blood plasma at pH 7.4, that volume is 25 million liters!

Finally, pH suffers from a serious drawback because of the nonlinearity of the logarithmic function. The logarithm of the sum of several numbers is not equal to the sum of their logarithms. The important electrical neutrality requirement for ionic solutions is necessarily expressed in terms of the algebraic sum of all ion concentrations, so that pH cannot be used in it,  $[\text{H}^+]$  must be. The equation that sets that sum equal to zero is always essential in the quantitative analysis of any solution’s acid-base behavior.

Although the historical reasons for the introduction of pH may be understandable, its continued use is difficult to justify. It adds much more to confusion about how  $[\text{H}^+]$  behaves than to understanding. In this book we shall use linear  $[\text{H}^+]$  scales, direct logarithmic scales, and pH in plotting graphs to show acid-base behavior. The reader may decide which are the most informative.

### 3.4. WATER DISSOCIATION EQUILIBRIUM: THE WATER ION PRODUCT, $K'_w$

As already indicated, water dissociation can be described by this chemical reaction scheme:



This is a very fast reaction in either direction, and complete equilibrium may always be assumed in biological situations. The quantitative requirement on the three component substances at equilibrium is

$$[\text{H}^+] \times [\text{OH}^-] = K_w \times [\text{H}_2\text{O}]. \quad (3.4.1)$$

The water dissociation constant,  $K_w$ , is highly temperature dependent and very small. Its value is  $1.8 \times 10^{-16}$  Eq/liter at 25 C and  $4.3 \times 10^{-16}$  Eq/liter at 37 C.

Equation (3.4.1) can be simplified by recognizing that in most biological situations,  $[\text{H}^+]$  and  $[\text{OH}^-]$  are well below  $10^{-6}$  Eq/liter, while  $[\text{H}_2\text{O}]$  is over 55 Eq/liter. What this means is that the dissociation process has no significant effect on the water concentration.  $[\text{H}_2\text{O}]$  can therefore be considered constant and combined with  $K_w$  into a new constant,  $K'_w$ , called the ion product for water:

$$K'_w = K_w \times [\text{H}_2\text{O}].$$

Therefore, from (3.4.1),

$$[\text{H}^+] \times [\text{OH}^-] = K'_w. \quad (3.4.2)$$

Because  $[\text{H}_2\text{O}]$  is affected by dissolved solutes, and because  $K_w$  changes with temperature, the value of  $K'_w$  will also change with both these variables. The value of  $K'_w$  also depends on the ionic strength of the solution in question and on the presence of specific ions. The most useful source of numerical values for  $K'_w$  is the classic book by Harned and Owen [4]. In pure water at 25 C,  $K'_w = 1.0 \times 10^{-14}$  (Eq/liter)<sup>2</sup>; at 37 C,  $2.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>.

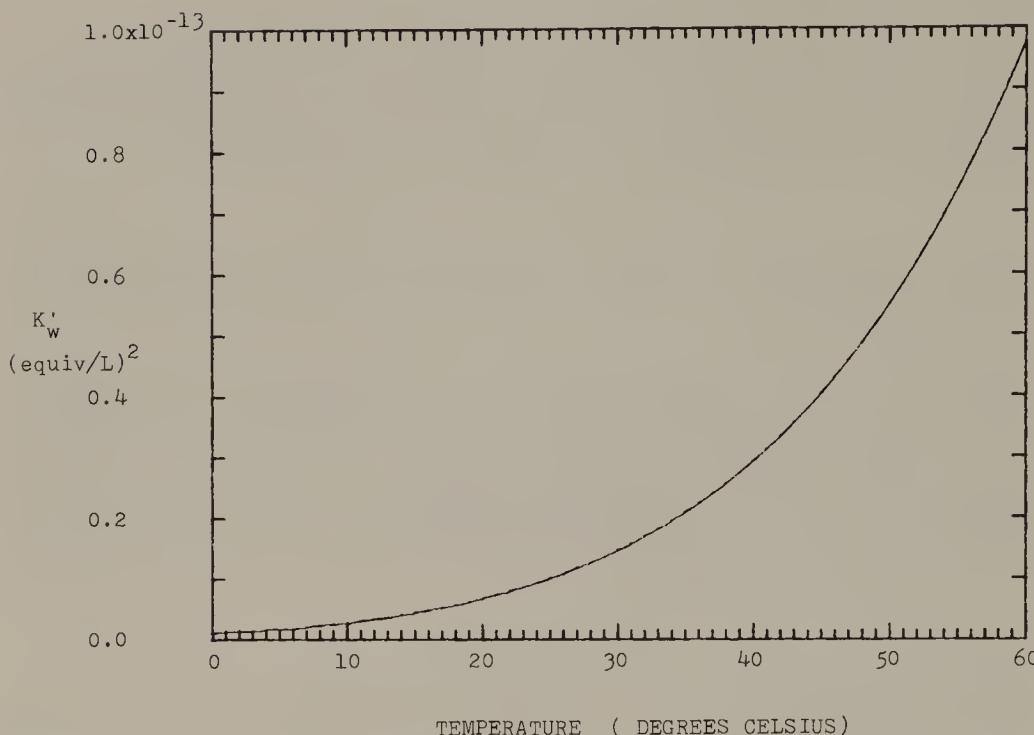
Figure 3.3 presents empirical data from Harned and Owen to show the variation of  $K'_w$  with temperature in pure water. The following formula fits this curve to better than 1% and is useful in calculations, although it has no theoretical significance:

$$K'_w = 8.754 \times 10^{-10} \times \exp \left\{ \frac{-1.01 \times 10^6}{T^2} \right\},$$

where  $T$  is in degrees Kelvin. In solutions, different values of  $K'_w$  apply. The value used in calculations must always be that appropriate to the solution in question.

### 3.5. ACID-BASE ANALYSIS OF PURE WATER

Equation (3.4.2) expresses in approximate (but good to about 1 part in 1 billion!) form the dissociation equilibrium for water and provides us with one quantitative relationship between  $[\text{H}^+]$  and  $[\text{OH}^-]$ . In order to be able to predict the values of these two quantities, we must have another



**Figure 3.3.** The variation with temperature of the water ion product,  $K'_w$ , in pure water. Data from Harned and Owen [4].

quantitative relationship between them. It is provided by the physical requirement of electrical neutrality. Because  $\text{H}^+$  and  $\text{OH}^-$  are the only ions present, we must have

$$[\text{H}^+] - [\text{OH}^-] = 0. \quad (3.5.1)$$

Now we have two independent equations in the two unknowns,  $[\text{H}^+]$  and  $[\text{OH}^-]$ , so we can solve for them. In this case, the algebra is trivial, but the procedure is the same one we shall use again and again in the more complicated cases that arise in the following chapters. From Equation (3.5.1), we can substitute  $[\text{H}^+]$  for  $[\text{OH}^-]$  in (3.4.2) and write

$$[\text{H}^+] \times [\text{H}^+] = K'_w \text{ or } [\text{H}^+] = \sqrt{K'_w}. \quad (3.5.2)$$

Alternatively, we may use (3.5.1) to substitute  $[\text{OH}^-]$  for  $[\text{H}^+]$  and write

$$[\text{OH}^-] \times [\text{OH}^-] = K'_w \text{ or } [\text{OH}^-] = \sqrt{K'_w}. \quad (3.5.3)$$

Equations (3.5.2) and (3.5.3) tell the whole story of the acid-base properties of pure water. Pure water must always be acid-base neutral because  $[\text{H}^+]$  always equals  $[\text{OH}^-]$ . Because  $K'_w$  is a strong function of temperature, however, the neutral value of  $[\text{H}^+]$  and  $[\text{OH}^-]$  must be also. Figure 3.4 shows how  $[\text{H}^+]$ ,  $[\text{OH}^-]$ , and pH vary with temperature in pure water over the same temperature range as in Figure 3.3. With this figure, which is just a graphical presentation of what Equations (3.5.2) and (3.5.3) say,

we have achieved our goal of understanding the values of  $[H^+]$  and  $[OH^-]$  in pure water.

### 3.6. UPDATED DEFINITIONS: NEUTRAL, ACIDIC, AND BASIC SOLUTIONS

In Section 2.2 solutions were defined as neutral, acidic, or basic in terms of the size of  $[H^+]$  compared to  $[OH^-]$ . Equations (3.5.2) and (3.5.3) provide a less relative basis for these definitions by tying them to the parameter  $K_w'$ .

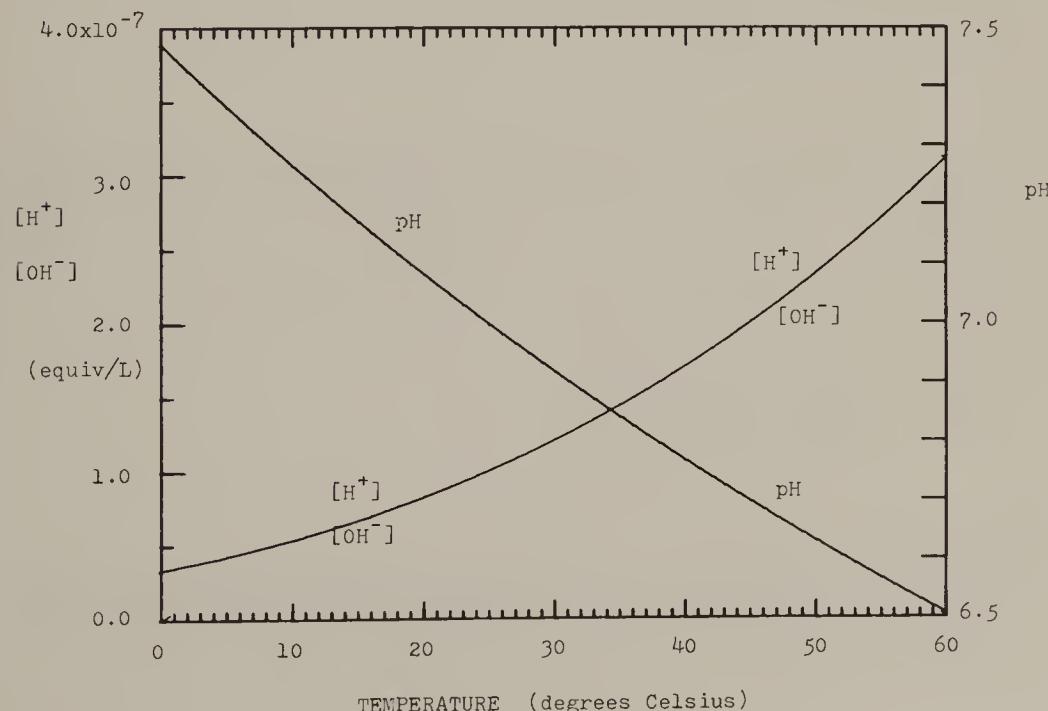
**Definition.** A solution is acid–base neutral if its  $[H^+] = \sqrt{K_w'}$ . Its  $[OH^-]$  will then also =  $\sqrt{K_w'}$ .

**Definition.** A solution is said to be acid, or acidic, if its  $[H^+]$  is greater than  $\sqrt{K_w'}$ . From (3.4.2), its  $[OH^-]$  will then be less than  $\sqrt{K_w'}$ .

**Definition.** A solution is said to be alkaline, or basic, if its  $[H^+]$  is less than  $\sqrt{K_w'}$ . From (3.4.2), its  $[OH^-]$  will then be greater than  $\sqrt{K_w'}$ .

It follows from the definition of acid–base neutral that “neutrality”

**Figure 3.4.** The variation of  $[H^+]$ ,  $[OH^-]$ , and pH with temperature in pure water. Right-hand scale for pH, left-hand scale for  $[H^+]$  and  $[OH^-]$ , which are always equal.



occurs at a different  $[H^+]$ , or pH, for each solution, because the value of  $K'_w$  is specific for each solution. For example, in blood plasma at body temperature,  $K'_w = 4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>, so that acid-base neutral means  $[H^+] = 2.1 \times 10^{-7}$  Eq/liter, pH 6.7. "Standard" arterial blood plasma has  $[H^+] = 4 \times 10^{-8}$  Eq/liter, pH 7.4, so that it is an alkaline fluid, with  $[OH^-] = 28 \times [H^+]$ .

Textbooks often cite the formula

$$pH + pOH = 14.$$

This formula is obtained by taking logarithms of both sides of Equation (3.4.2) and using the obvious analogy to pH for both pOH and  $pK'_w$ . It should therefore be written as

$$pH + pOH = pK'_w.$$

We can then see that the value of 14 for the right-hand side only applies when  $K'_w = 1.0 \times 10^{-14}$  (Eq/liter)<sup>2</sup>, which is for pure water at 25 C. In blood plasma,  $pK'_w = 13.4$  at 37 C. Once again, it is essential to use the value of  $K'_w$  appropriate to the solution and the conditions under analysis.

### 3.7. SUMMARY

1. The acid-base properties of pure water are very simple and are fully described quantitatively by

$$[H^+] = \sqrt{K'_w} \quad (3.5.2)$$

$$[OH^-] = \sqrt{K'_w}. \quad (3.5.3)$$

2. Water dissociation equilibrium requires that in aqueous solutions,  $[H^+]$  and  $[OH^-]$  must always satisfy

$$[H^+] \times [OH^-] = K'_w. \quad (3.4.2)$$

The value of  $K'_w$  used must always be that appropriate to the solution in question.  $K'_w$  changes with temperature, concentration, ionic strength, and the presence of specific substances. In body fluids at 37 C,  $K'_w = 4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>.

3. Neutral, acidic, and basic solutions are defined with reference to the value of  $\sqrt{K'_w}$ :

Neutral:  $[H^+] = \sqrt{K'_w} = [OH^-]$

Acidic:  $[H^+] > \sqrt{K'_w} > [OH^-]$

Basic:  $[H^+] < \sqrt{K'_w} < [OH^-]$ .

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## CHAPTER FOUR

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# STRONG IONS AND THE STRONG ION DIFFERENCE

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### 4.1. INTRODUCTION

The hydrogen ion concentration of any solution turns out to depend to a large extent on the concentrations of strong ions that it contains. The next step in our progressive analysis of biological solutions and their acid–base behavior is therefore to understand thoroughly the properties of solutions containing only strong ions. Fortunately, such solutions are simple to analyze. Because strong electrolytes are completely dissociated, the only equilibrium we have to keep track of is that for water dissociation. As a result, the quantitative description of strong ion solutions is only slightly more complicated than that for pure water.

If they did not contain CO<sub>2</sub>, sea water and interstitial fluid would provide two biologically important examples of such strong ion solutions. Their CO<sub>2</sub> content complicates their behavior, however, so we shall not analyze them until Chapter 6. In the meantime, the relatively simple analysis of this chapter will provide an essential basis for that more complex one and, indeed, make it possible.

### 4.2. ANALYSIS OF STRONG IONS IN WATER

Consider first a simple solution made up by adding specified amounts of NaOH and HCl to water so that it contains only Na<sup>+</sup>, Cl<sup>-</sup>, OH<sup>-</sup>, and H<sup>+</sup>. [Na<sup>+</sup>] and [Cl<sup>-</sup>] are known quantities. Given them, how can we predict [H<sup>+</sup>] and [OH<sup>-</sup>]?

This is a typical physics problem. We have two unknowns,  $[H^+]$  and  $[OH^-]$ , so that we must be able to write two, but not more than two, simultaneously valid but independent quantitative relationships between them. Chapters 2 and 3 provide them immediately.

First, the constraint of electrical neutrality requires that

$$[Na^+] - [Cl^-] + [H^+] - [OH^-] = 0. \quad (4.2.1)$$

Second, water dissociation equilibrium requires that

$$[H^+] \times [OH^-] = K_w'. \quad (4.2.2)$$

We have our two equations in two unknowns and can solve them easily by the same procedure we used in Chapter 3.

If we use (4.2.2) to substitute  $K_w'/[H^+]$  for  $[OH^-]$  in (4.2.1) and clear of fractions, the result is

$$[H^+]^2 + ([Na^+] - [Cl^-]) \times [H^+] - K_w' = 0. \quad (4.2.3)$$

Alternatively, we may substitute  $K_w'/[OH^-]$  for  $[H^+]$  and get

$$[OH^-]^2 - ([Na^+] - [Cl^-]) \times [OH^-] - K_w' = 0. \quad (4.2.4)$$

Such quadratic equations may be solved by the standard formula:

$$\text{If } AX^2 + BX + C = 0, \text{ then } X = \sqrt{(B/2A)^2 - C} - (B/2A).$$

Applying this formula to (4.2.3) and (4.2.4) gives us

$$[H^+] = \sqrt{K_w' + ([Na^+] - [Cl^-])^2/4} - ([Na^+] - [Cl^-])/2 \quad (4.2.5)$$

$$[OH^-] = \sqrt{K_w' + ([Na^+] - [Cl^-])^2/4} + ([Na^+] - [Cl^-])/2. \quad (4.2.6)$$

Equations (4.2.5) and (4.2.6) solve the problem! Given any values for  $[Na^+]$  and  $[Cl^-]$  in an "NaCl" solution, we can calculate the values that  $[H^+]$  and  $[OH^-]$  must have from these equations.

These equations tell us that we have also solved the more general problem. The strong ion concentrations enter all these equations only in terms of the difference between the total strong cation and total strong anion concentrations. Thus, in this simple solution, if we were to increase both  $[Na^+]$  and  $[Cl^-]$  by the same amount, so that their difference was unchanged, (4.2.5) and (4.2.6) tell us that  $[H^+]$  and  $[OH^-]$  would also be unchanged. That would correspond to adding "neutral salt," NaCl, to the solution. (For simplicity, we ignore for the moment any effects that the increased osmolarity might have on the value of  $K_w'$ .) It follows that if we were to add other strong ions, such as  $K^+$ ,  $Mg^{2+}$ ,  $SO_4^{2-}$ , etc, the only change in the above equations would be that the term  $([Na^+]$

$- [\text{Cl}^-]$ ), wherever it occurs would be expanded to

$$([\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] - [\text{Cl}^-] - [\text{SO}_4^{2-}] \cdots \text{etc}).$$

Equations (4.2.5) and (4.2.6) appropriately expanded enable us to predict the  $[\text{H}^+]$  and  $[\text{OH}^-]$  values for any solution containing only strong ions.

Physically, this surprising simplicity results from the fact that because strong ions are not involved in any chemical reactions in the solution, all that matters is the sign of their electrical charge and how much of it there is. The expression  $([\text{Na}^+] - [\text{Cl}^-])$  can therefore be seen as a measure of the net positive electrical charge in the solution due to the presence of the strong ions  $\text{Na}^+$  and  $\text{Cl}^-$ . Electrical neutrality requires that charge to be counterbalanced by the net negative electrical charge supplied by  $[\text{OH}^-] - [\text{H}^+]$ . That is just what Equation (4.2.1) says. Equations (4.2.5) and (4.2.6) then tell us how this requirement must be met so that water dissociation equilibrium is also satisfied, given any specific values for  $[\text{Na}^+]$  and  $[\text{Cl}^-]$  (and  $K_w'$ ). The specific identity of the strong ions does not enter the argument; it is the net amount of strong ion positive electrical charge that determines (Equation (4.2.1) appropriately expanded) how large the  $[\text{OH}^-] - [\text{H}^+]$  difference must be.

### 4.3. THE STRONG ION DIFFERENCE, [SID]

The long string of symbols expressing the net strong ion positive charge when many different species of strong ions are present in a solution is cumbersome to write out repeatedly. It is both typographically and conceptually convenient to call it the *strong ion difference*, [SID].

**Definition.** The *strong ion difference*, [SID], in any solution is defined as (the sum of all the strong base cation concentrations) minus (the sum of all the strong acid anion concentrations), all expressed in equivalents per liter.

$$[\text{SID}] = (\Sigma[\text{strong base cations}]) - (\Sigma[\text{strong acid anions}]). \quad (4.3.1)$$

Our system-defining equations for solutions of strong electrolytes may then be rewritten more compactly in terms of [SID] thus:

$$[\text{SID}] - [\text{OH}^-] + [\text{H}^+] = 0 \quad (4.3.2)$$

$$[\text{H}^+] \times [\text{OH}^-] = K_w'. \quad (4.3.3)$$

The algebraic solutions to these are, from the previous section,

$$[\text{H}^+] = \sqrt{\dot{K_w'} + ([\text{SID}]/2)^2} - ([\text{SID}]/2) \quad (4.3.4)$$

$$[\text{OH}^-] = \sqrt{K_w' + ([\text{SID}]/2)^2} + ([\text{SID}]/2). \quad (4.3.5)$$

In a formal sense, our goal has been reached. Equations (4.3.1), (4.3.4), and (4.3.5) solve the problem. Given the strong ion composition of any solution that contains only strong electrolytes, we can at once calculate the  $[H^+]$  and  $[OH^-]$  of that solution from these equations. This dry statement of the mathematical result does not go very far to convey the powerful generality and understanding implicit in these equations. To do that, we need to examine what these equations say from a number of different perspectives. We shall then have a more thorough basis for the more complicated analyses required when solutions also contain weak electrolytes, as well as  $CO_2$ .

Clearly, negative values for individual ion concentrations have no physical meaning, but the value of [SID] may be negative, zero, or positive, depending on whether strong acid anions or strong base cations or neither are in excess. The acid-base behavior of solutions is surprisingly different in these three situations, and it is essential to understand those differences. We shall examine them in detail in the next few sections.

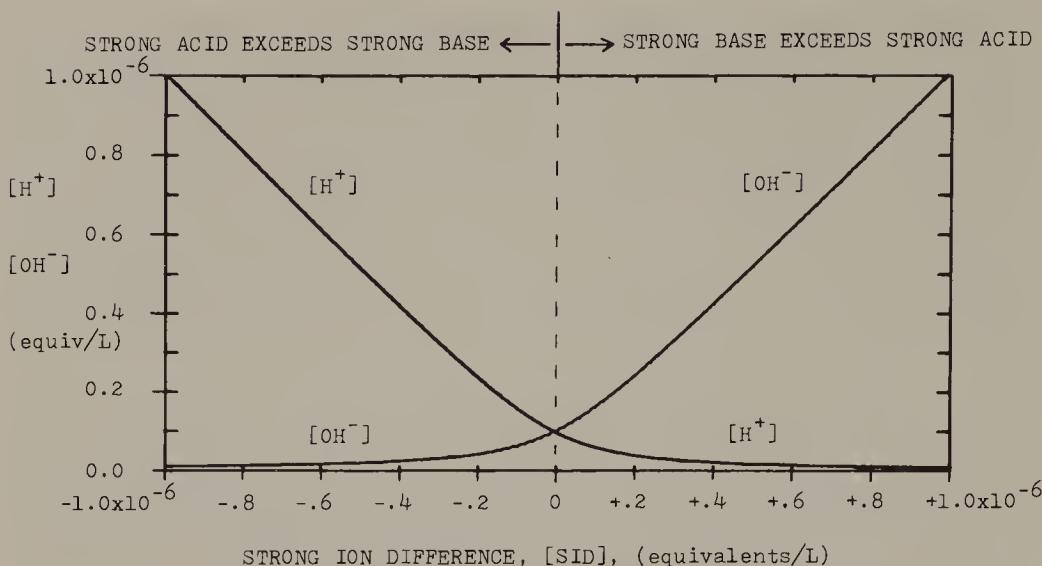
In biological solutions, [SID] is almost always positive. In mammalian body fluids, it is on the order of +40 mEq/liter (0.04 Eq/liter). In extracellular fluids,  $Na^+$  and  $Cl^-$  are the major strong ions present, and [SID] is normally close to ( $[Na^+]$  –  $[Cl^-]$ ). Intracellularly,  $K^+$  and  $Mg^{2+}$  are the major strong ions,  $[Cl^-]$  is usually small, and [SID] is approximately ( $[K^+]$  +  $[Mg^{2+}]$ ).

Until the [SID] notation becomes familiar, it may help the reader to replace [SID] by ( $[Na^+]$  –  $[Cl^-]$ ) in thinking about the meaning of equations and graphs or whenever [SID] appears in the following discussion.

#### 4.4. SMALL [SID] VALUES: "NEUTRAL SALT SOLUTIONS"

The solutions for Equations (4.3.4) and (4.3.5) for values of [SID] ranging from  $-10^{-6}$  to  $+10^{-6}$  Eq/liter are displayed in Figure 4.1. "small" for [SID] means "values close to  $\sqrt{K_w'}$ ". This follows from the form of the expression inside the square root in Equations (4.3.4) and (4.3.5). Whenever  $([SID]/2)^2$  is much larger than  $K_w'$ , then the value of  $\sqrt{K_w' + ([SID]/2)^2}$  is very close to  $[SID]/2$ .  $K_w'$  is on the order of  $10^{-14}$  (Eq/liter)<sup>2</sup>, so  $\sqrt{K_w'}$  is on the order of  $10^{-7}$  Eq/liter, and small [SID] means less than about  $10^{-6}$  Eq/liter. [SID] in body fluids, by comparison, is generally larger than 0.02 Eq/liter.

When [SID] is small by this criterion, and is negative (left half of Figure 4.1),  $[H^+]$  is always larger than  $[OH^-]$ , which is hardly a surprise, because negative [SID] means strong acid exceeds strong base. What is surprising at first is the difference between the  $[H^+]$  and the  $[OH^-]$  curves.  $[H^+]$  varies linearly with [SID] once the magnitude of [SID] is above about  $10^{-7}$  Eq/liter, whereas  $[OH^-]$  varies in a curvilinear fashion, and appears to asymptote toward zero as [SID] becomes increasingly negative.



**Figure 4.1.**  $[H^+]$  and  $[OH^-]$  versus [SID] in solutions of strong ions with [SID] values smaller than  $10^{-6}$  Eq/liter.  $K'_w = 10^{-14}$  (Eq/liter)<sup>2</sup>, so that when [SID] = 0,  $[H^+] = [OH^-] = \sqrt{K'_w} = 10^{-7}$  Eq/liter. These curves describe the acid–base behavior of any solution containing only strong ions, over this [SID] range.

When [SID] is exactly zero, a true neutral “salt solution,” then we should find  $[H^+] = [OH^-] = \sqrt{K'_w}$ , and this is indeed the case. The  $[H^+]$  and  $[OH^-]$  curves intersect just at [SID] = 0.

When [SID] is positive, corresponding to a small excess of strong base over strong acid, then  $[H^+]$  and  $[OH^-]$  play opposite roles to those described above. Now  $[OH^-]$  varies linearly with [SID] once [SID] is larger than about  $10^{-7}$  Eq/liter, whereas  $[H^+]$  varies nonlinearly, and approaches zero as [SID] increases. Whenever [SID] is positive,  $[OH^-]$  is larger than  $[H^+]$ , as expected.

Figure 4.1 demonstrates all these points, but it may be helpful to look at some specific numerical values. It is also informative to plot the results of these calculations on Figure 4.1. Consider first a dilute “NaCl” solution with an initial [SID] value of  $-1.0 \times 10^{-7}$  Eq/liter. This value means that  $[Cl^-]$  is  $10^{-7}$  Eq/liter larger than  $[Na^+]$ . Assuming 25 C, so that  $K'_w = 1.0 \times 10^{-14}$  (Eq/liter)<sup>2</sup>, we can use Equations (4.3.4) and (4.3.5) to calculate the values in the first row of the table below. What happens if we now add  $1.0 \times 10^{-7}$  Eq/liter of HCl to this solution? [SID] increases (negatively) to  $-2.0 \times 10^{-7}$  Eq/liter, and the other values change as indicated in the table. These results should be examined carefully to see how they differ from intuitive expectations. No  $OH^-$  was added or removed, but  $[OH^-]$  decreased by 34%.  $10^{-7}$  Eq/liter of  $H^+$  was added, but  $[H^+]$  only increased by  $7.9 \times 10^{-8}$  Eq/liter.

	[SID]	[H <sup>+</sup> ]	pH	[OH <sup>-</sup> ]
Original solution	$-1.0 \times 10^{-7}$	$1.6 \times 10^{-7}$	6.79	$6.2 \times 10^{-8}$
Amount added	$-1.0 \times 10^{-7}$	$1.0 \times 10^{-7}$	—	0
Final value	$-2.0 \times 10^{-7}$	$2.4 \times 10^{-7}$	6.62	$4.1 \times 10^{-8}$
Change	$-1.0 \times 10^{-7}$	$+7.9 \times 10^{-8}$	-0.18	$-2.1 \times 10^{-8}$

All amounts in equivalents, concentrations in equivalents per liter.

As a second example, on the other side of [SID] = 0, imagine adding the same amount of HCl to a dilute "NaCl" solution in which [SID] is initially  $+2.0 \times 10^{-7}$  Eq/liter. In this case, as the following table indicates, [OH<sup>-</sup>] falls by 54%, although we still have not added or removed any OH<sup>-</sup>, while [H<sup>+</sup>] rises by only 47% of the amount of H<sup>+</sup> added.

	[SID]	[H <sup>+</sup> ]	pH	[OH <sup>-</sup> ]
Original solution	$+2.0 \times 10^{-7}$	$4.0 \times 10^{-8}$	7.38	$2.4 \times 10^{-7}$
Amount added	$-1.0 \times 10^{-7}$	$1.0 \times 10^{-7}$	—	0
Final value	$+1.0 \times 10^{-7}$	$6.2 \times 10^{-8}$	7.05	$1.6 \times 10^{-7}$
Change	$-1.0 \times 10^{-7}$	$+2.1 \times 10^{-8}$	-0.33	$-7.9 \times 10^{-8}$

All amounts in equivalents, concentrations in equivalent per liter.

In neither of these examples does the change in [H<sup>+</sup>] bear a simple, obvious relationship to the amount of H<sup>+</sup> added. Even more striking, [OH<sup>-</sup>] changes by comparable amounts, even though no OH<sup>-</sup> was added or removed. If we had added NaOH instead of HCl, the opposite would have occurred; [OH<sup>-</sup>] would have increased and [H<sup>+</sup>] would have decreased, even though no H<sup>+</sup> was transferred into or out of the solution. The only safe guides to predicting and understanding what happens to [H<sup>+</sup>] and [OH<sup>-</sup>] in these situations are Equations (4.3.4) and (4.3.5) or the curves of Figure 4.1. There is, however, one useful general rule from all this: whenever [SID] changes in the negative direction (more strong acid or less strong base), then [H<sup>+</sup>] increases and [OH<sup>-</sup>] decreases. Whenever [SID] changes in the more positive direction, [OH<sup>-</sup>] increases and [H<sup>+</sup>] decreases. It is also noteworthy that when [SID] is positive, the change in [H<sup>+</sup>] is always much less than the change in [SID]. In order to be useful, this general rule must be supplemented by numerical calculations, as was done above.

Equations (4.3.4) and (4.3.5) have an extraordinarily important consequence that has been implicit in the above discussion but must be thoroughly understood. That is, because the value of [SID] determines the values of [H<sup>+</sup>] and [OH<sup>-</sup>] in these solutions, *observation of a change in [H<sup>+</sup>] can only mean that [SID] has changed*. Measured [H<sup>+</sup>] changes can tell us nothing about whether there has been any transfer of H<sup>+</sup> into or out of the solution; they only tell us that strong ions have been added or removed so as to change [SID].

#### 4.5. [SID] NEGATIVE AND LARGER THAN $10^{-6}$ EQ/LITER

When the excess of strong acid anions over strong base cations is larger than about  $10^{-6}$  Eq/liter, Equation (4.3.4) simplifies to

$$[\text{H}^+] = -[\text{SID}]. \quad (4.5.1)$$

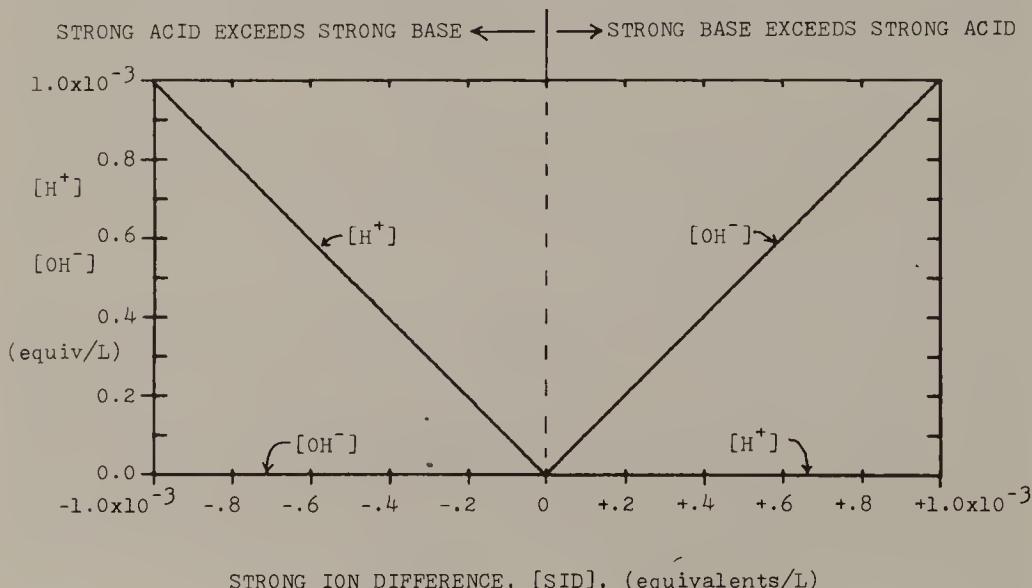
Equation (4.3.5) becomes useless under these circumstances and merely tells us that  $[\text{OH}^-]$  is close to zero. Equation (4.3.3) along with (4.5.1) above is more helpful and results in

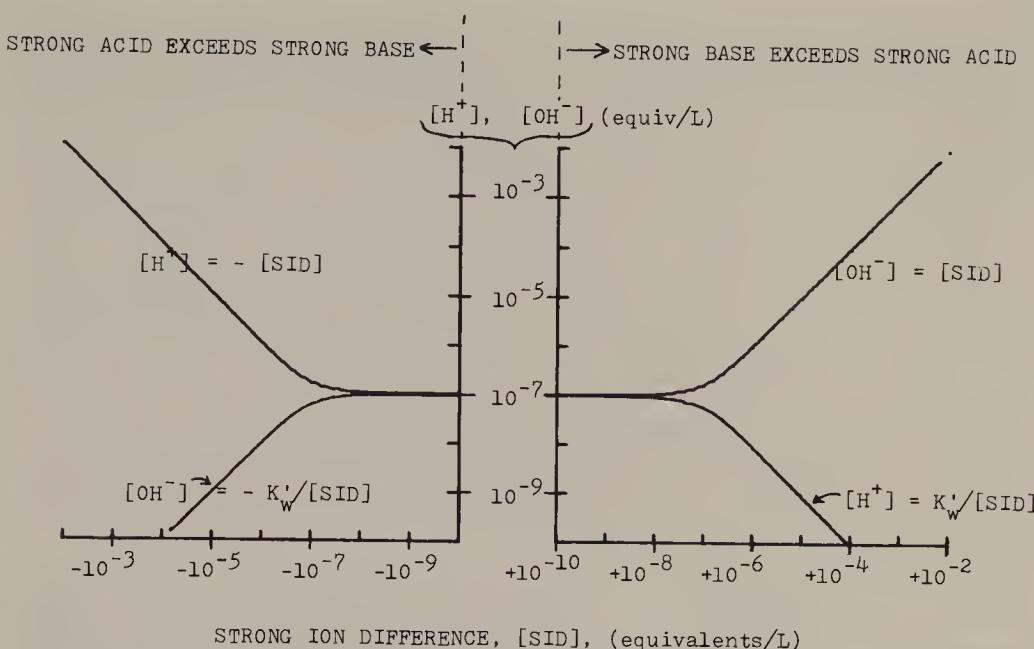
$$[\text{OH}^-] = K'_w / -[\text{SID}]. \quad (4.5.2)$$

Equations (4.5.1) and (4.5.2) tell us how  $[\text{H}^+]$  and  $[\text{OH}^-]$  behave in strong acid solutions, which means solutions with more strong acid anions than strong base cations, so that [SID] is negative. Such solutions are rare in biological systems.

The behavior predicted by these two equations is simple, but difficult to visualize graphically on linear scales. Figure 4.2 shows this in its left half, where  $[\text{H}^+]$  follows a  $45^\circ$  straight line, and  $[\text{OH}^-]$  is too small to be seen. The log-log plots of Figure 4.3 are more useful. The left half of this figure shows directly that  $[\text{H}^+]$  is equal to the magnitude of [SID] while  $[\text{OH}^-]$  is inversely proportional to [SID]. It also shows that as [SID]

**Figure 4.2.**  $[\text{H}^+]$  and  $[\text{OH}^-]$  versus [SID] in strong ion solutions with [SID] values up to  $10^{-3}$  Eq/liter. Compare with Figure 4.1, which may be seen as an enlargement of the region close to [SID] = 0. The most important feature of this figure is its clear demonstration that changes in  $[\text{H}^+]$  are not equal to changes in [SID] when [SID] is positive.  $K'_w = 1.0 \times 10^{-14}$  (Eq/liter)<sup>2</sup>.





**Figure 4.3.** Log-log plots of  $[H^+]$  and  $[OH^-]$  versus [SID] in solutions containing only strong ions (plus  $[H^+]$  and  $[OH^-]$ ) over a wide [SID] range. The straight lines when [SID] is larger than  $10^{-7}$  Eq/liter reflect the approximations that  $[OH^-] = [SID]$  and  $[H^+] = K'_w/[SID]$ . For negative [SID] values, they reflect  $[H^+] = -[SID]$  and  $[OH^-] = K'_w/-[SID]$ .  $K'_w = 1.0 \times 10^{-14}$  (Eq/liter)<sup>2</sup>.

becomes very small,  $[H^+]$  and  $[OH^-]$  both approach the neutral value of  $\sqrt{K'_w}$ . It is also noteworthy from Equation (4.5.1) that under these conditions of excess strong acid,  $[H^+]$  is independent of  $K'_w$ , but  $[OH^-]$  depends directly on  $K'_w$ .

#### 4.6. [SID] POSITIVE AND LARGER THAN $10^{-6}$ EQ/LITER

When [SID] is positive and larger than  $10^{-6}$  Eq/liter, corresponding to a significant excess of strong base cations over strong acid anions in the solution, Equation (4.3.5) simplifies to

$$[OH^-] = [SID]. \quad (4.6.1)$$

Under these circumstances,  $[H^+]$  is very small and given by a combination of (4.6.1) and (4.3.3):

$$[H^+] = K'_w/[SID]. \quad (4.6.2)$$

The right-hand halves of Figures 4.2 and 4.3 depict what these equations say.  $[OH^-]$  varies directly with [SID], while  $[H^+]$  is very small and varies inversely with [SID]. As [SID] approaches zero from positive values, both  $[H^+]$  and  $[OH^-]$  approach  $\sqrt{K'_w}$ , as they must.  $[H^+]$  depends directly on  $K'_w$ ,  $[OH^-]$  does not.

A useful view of the value of Equations (4.6.1), (4.6.2), (4.5.1), and (4.5.2) is provided by the following simple example. Imagine that we have 750 ml of a  $1.0 \times 10^{-3}$ N “NaOH” solution and that we add 250 ml of a  $1.0 \times 10^{-3}$ N “HCl” solution. We should like our equations to tell us the  $[H^+]$ ,  $[OH^-]$ , and pH values in all three of these solutions. To compare results with the examples above and with Figures 4.1 through 4.4, we assume  $K'_w = 1.0 \times 10^{-14}$  (Eq/liter)<sup>2</sup> throughout. The original “NaOH” solution contains  $Na^+$  but no  $Cl^-$ , so its  $[SID] = [Na^+]$ . Similarly the added “HCl” solution has  $Cl^-$  but no  $Na^+$ , and its  $[SID] = -[Cl^-]$ . The final 1 liter of mixed solution contains  $0.75 \times 10^{-3}$  Eq of  $Na^+$  and  $0.25 \times 10^{-3}$  Eq of  $Cl^-$  so that its  $[SID]$  value is  $+0.50 \times 10^{-3}$  Eq/liter. Applying the appropriate equations, we can therefore easily fill in the following quantitative description of the solutions before and after mixing:

Substance or quantity	Amount in original “NaOH” solution (Eq)	Amount in added “HCl” solution (Eq)	Total amount added to mixture (Eq)	Concentration in final mixture (Eq/liter)
$Na^+$	$7.5 \times 10^{-4}$	0	$7.5 \times 10^{-4}$	$7.5 \times 10^{-4}$
$Cl^-$	0	$2.5 \times 10^{-4}$	$2.5 \times 10^{-4}$	$2.5 \times 10^{-4}$
$[SID]$	—	—	—	$+5.0 \times 10^{-4}$
$H^+$	$7.5 \times 10^{-12}$	$2.5 \times 10^{-4}$	$2.5 \times 10^{-4}$	$2.0 \times 10^{-11}$
$OH^-$	$7.5 \times 10^{-4}$	$2.5 \times 10^{-12}$	$7.5 \times 10^{-4}$	$5.0 \times 10^{-4}$
pH	11.0	3.0	—	10.7

$$(K'_w = 1.0 \times 10^{-14} \text{ (Eq/liter)}^2).$$

This example is deceptively simple once Equations (4.6.1) and (4.6.2) have been established. It clearly shows that neither the change in  $[H^+]$  (from  $1.0 \times 10^{-11}$  in the original NaOH solution to  $2.0 \times 10^{-11}$  in the final mixture, a change of  $1.0 \times 10^{-11}$  Eq/liter) nor the final value of  $[H^+]$  bears any obvious simple relationship to the amount of  $H^+$  added,  $2.5 \times 10^{-4}$  Eq, under these conditions of positive  $[SID]$  values in both the initial and final solutions.

Finally, it should be noted that under these conditions of positive  $[SID]$ , the value of  $[H^+]$  depends directly on the value of  $K'_w$ , as Equation (4.6.2) shows, so it is essential to use the appropriate value for  $K'_w$  in such calculations.

#### 4.7. pH CURVES, TITRATION, AND NEUTRALIZATION

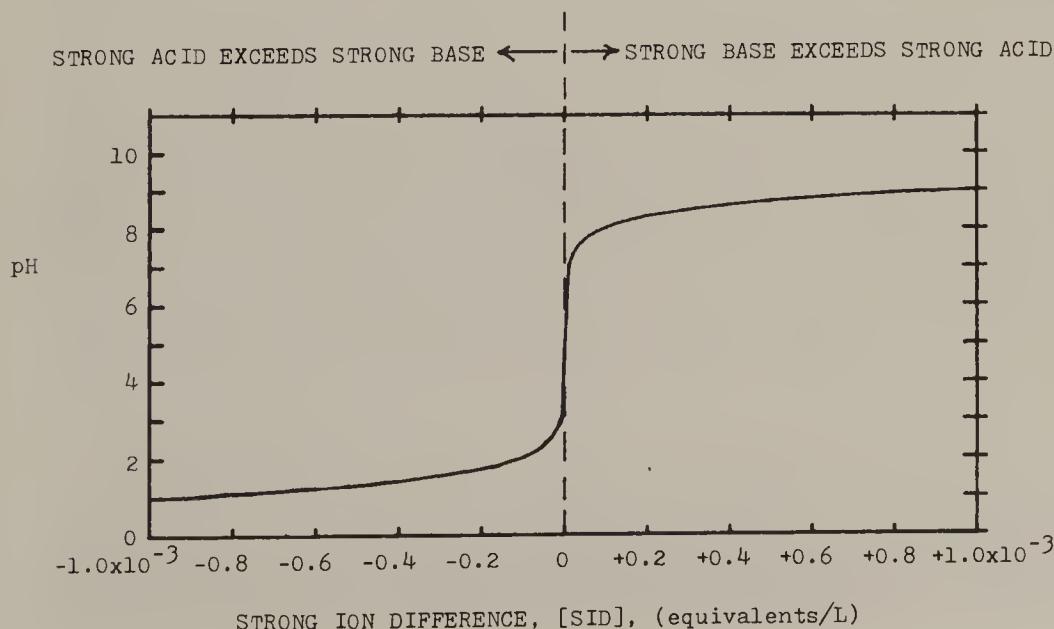
The pH transformation of the  $[H^+]$  versus  $[SID]$  curve in Figure 4.2 is displayed in Figure 4.4 and should be familiar as what is usually called a “titration” curve. It is often presented as resulting from the addition of successive small amounts of base, such as ‘NaOH’, to a strong acid

solution, in which case the curve is traced from the left side toward the center, or as the result of addition of acid to a strong base solution, in which case the curve is traced from the right side toward the center. When titration is "complete," all the acid has been "neutralized" by added base, or vice versa, the solution has  $[SID] = 0$ , and  $pH = pK'_w/2$ , at the center point of the curve. This corresponds to the  $[SID] = 0$ ,  $[H^+] = [OH^-] = \sqrt{K'_w}$  point in Figure 4.1.

This "pH titration" curve is very useful in practice because the large and relatively abrupt pH change that occurs near the neutral point is easily detected experimentally with considerable precision. It should be clear from the graph that the amount of strong acid or base that must be added to a solution to bring it to that neutral point is a direct measure of the  $[SID]$  value in the original solution. Titration is therefore an important analytical technique for measuring the  $[SID]$  in solutions of strong ions. It is so easy to carry out that it is also often performed on more complex solutions such as urine or blood plasma. Its interpretation under these conditions is much more complicated, as we shall see in the next chapter. It is still a direct measure of how much  $[SID]$  has to be changed to get the solution to a specified  $[H^+]$ , but its significance in terms of the original acid-base status of the original solution can only be understood if that solution's composition is accurately known.

The differences between the  $[H^+]$  versus  $[SID]$  curves of Figures 4.1,

**Figure 4.4.** Titration curve for strong ion solutions with  $K'_w = 1.0 \times 10^{-14}$  (Eq/liter)<sup>2</sup>. pH plotted against  $[SID]$  over the same  $[SID]$  range as in Figure 4.2. This pH curve is the transform of the  $[H^+]$  curve in Figure 4.2, by means of equations (3.3.1).



4.2, and 4.3 and the pH versus [SID] curve in Figure 4.4 are curious. The rapid pH change in the neighborhood of  $[SID] = 0$  has no counterpart in the  $[H^+]$  curves; it is a mathematical artifact resulting from the particular properties of the doubly nonlinear  $[H^+]$  to pH transformation. The symmetry about  $[SID] = 0$  of the pH curve is also very misleading, as is the form of the pH curve when  $[SID]$  is negative. That part of the pH curve suggests that as  $[SID]$  becomes more and more negative, changes in  $[H^+]$  become smaller, whereas in fact, as Figure 4.2 clearly shows,  $[H^+]$  continues to equal  $-[SID]$  throughout this range, so that changes in  $[H^+]$  always equal changes in  $[SID]$ . You would never guess that from the left portion of the pH curve. Overall, though it is familiar, it seems clear that the pH curve is conceptually mysterious and misleading. It adds nothing to our understanding of  $[H^+]$  behavior as a function of  $[SID]$ . The log-log plots of Figure 4.3, on the other hand, are much more easily interpreted and tell the whole story at a glance.

The process of reducing  $[SID]$  to zero is also called “neutralizing.” The excess acid or base in the solution is said to be neutralized by the added strong base or acid. What this means is that the electrical charges on the added strong ions of appropriate sign cancel the original excess charge of opposite sign, so that the added  $H^+$  (or  $OH^-$ ) can combine with the  $OH^-$  (or  $H^+$ ) originally present to form water. “Neutralization” really means “forming water from  $H^+$  and  $OH^-$  as a result of reducing the size of  $[SID]$  to zero.” What is “neutralized” is the excess electrical charge on strong ions, which is just what  $[SID]$  measures. The acid-base neutrality condition, that  $[H^+] = [OH^-] = \sqrt{K_w}$ , can only be met if there is no other net ionic charge in the solution. When only strong ions are present, that is what  $[SID] = 0$  means.

#### 4.8. INTERSTITIAL FLUID

The acid–base behavior of interstitial fluid (ISF) *in vivo* depends strongly on its  $CO_2$  content as well as on its  $[SID]$ , as we shall see in Chapter 6. ISF can still provide an interesting example for this stage of our analysis if we nonetheless remove the  $CO_2$  from it. A sample of ISF with all the  $CO_2$  removed is a very alkaline solution, in which the major constituents by far,  $Na^+$  and  $Cl^-$ , are set at quite different concentrations. Its  $[H^+]$  is  $1.4 \times 10^{-12}$  Eq/liter, pH 11.9. Its detailed composition is listed in Table 4.1.

The results of titrating 1 liter of this solution by adding successive aliquots of HCl are also listed in Table 4.1. Because the initial  $[SID]$  value is 0.031 Eq/liter, we have made the first HCl addition 0.011 simply to bring  $[SID]$  to a round number, 0.02 Eq/liter. Successive additions are all 0.01 Eq of HCl. As expected, the  $[H^+]$  and pH values in this table lie on curves similar to those in Figures 4.3 and 4.4, but not identical to them

TABLE 4.1. Titration of CO<sub>2</sub>-Free Tissue Fluid

HCl added (Eq)	[SID]	[H <sup>+</sup> ]	[OH <sup>-</sup> ]	pH
none	0.031	$1.42 \times 10^{-12}$	0.031	11.9
0.011	0.020	$2.20 \times 10^{-12}$	0.02	11.7
0.010	0.010	$4.40 \times 10^{-12}$	0.01	11.4
0.010	0.00	$2.10 \times 10^{-7}$	$2.10 \times 10^{-7}$	6.68
0.010	-0.010	0.010	$4.40 \times 10^{-12}$	2.00
0.010	-0.020	0.020	$2.20 \times 10^{-12}$	1.70

All concentrations in Eq/liter.

Composition: [Na<sup>+</sup>], 0.137; [Cl<sup>-</sup>], 0.111; [OH<sup>-</sup>], 0.031; [K<sup>+</sup>], 0.003; [Mg<sup>2+</sup>], 0.002; [Ca<sup>2+</sup>], 0.001; [SO<sub>4</sub><sup>2-</sup>], 0.001; [H<sup>+</sup>],  $1.42 \times 10^{-12}$ . ( $K_w' = 4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>).

because ISF has a different  $K_w'$  value than was used for those figures.

Initially, [SID] is large and positive, so that [OH<sup>-</sup>] = [SID] = 0.031 Eq/liter and [H<sup>+</sup>] =  $K_w'/[SID] = 1.42 \times 10^{-12}$  Eq/liter. These values are listed in the first row of Table 4.1, labeled "none" for no HCl addition.

Adding the first 0.011 Eq/liter of HCl has the effect of lowering [SID] to + .020 Eq/liter, so [OH<sup>-</sup>] also falls to this value. [H<sup>+</sup>] rises by a minuscule amount.

The second HCl aliquot of 0.01 Eq/liter lowers [SID] to + 0.01 Eq/liter, which is still large and positive, so [OH<sup>-</sup>] becomes 0.01 Eq/liter, and [H<sup>+</sup>] again rises by a minuscule amount.

The third HCl addition reduces [SID] to zero and tells us, if we had not known it originally, that [SID] in the original sample was + 0.031 Eq/liter. [OH<sup>-</sup>] falls, and [H<sup>+</sup>] rises, to the acid-base neutral value of  $\sqrt{K_w'}$ , or  $2.1 \times 10^{-7}$  Eq/liter (pH 6.68, not 7.0!).

The fourth and fifth HCl additions carry us well beyond acid-base neutrality into the negative [SID] region, so that now [H<sup>+</sup>] = - [SID], and [OH<sup>-</sup>] is minuscule. [H<sup>+</sup>] increases by 0.01 Eq/liter with each HCl addition.

This table also provides an example of the strange behavior of the [H<sup>+</sup>] to pH transform. Compare the changes between the second and third rows, and the fifth and sixth rows. In both cases, [SID] falls by 0.01 Eq/liter, but in the first case [H<sup>+</sup>] rises by  $2.2 \times 10^{-12}$  Eq/liter, while in the second it rises by 0.01 Eq/liter, almost  $5 \times 10^9$  times greater. Despite this enormous difference in the [H<sup>+</sup>] changes, the pH change is the same in the two cases, namely, 0.3!

#### 4.9. GAMBLEGRAMS

A convenient terminology often used clinically refers to the [SID] not as a "difference" but as a "gap." Often there is an implication of a gap in our knowledge of the identity of at least some of the ions involved in

making up this “gap,” as we shall see in the next chapter. We may think of the physical fact that a positive [SID] value represents an electrical imbalance or charge “gap” that must be filled by excess OH<sup>-</sup> ions in a solution such as our CO<sub>2</sub>-free ISF, because OH<sup>-</sup> is the only negatively charged weak electrolyte ion present. In succeeding chapters we shall see that when other weak electrolytes are present, how this strong ion “gap” is filled becomes more complicated.

A clever way to visualize this gap, as well as to keep track of the ionic composition of a solution, was introduced in 1939 by a pediatrician, Dr J. L. Gamble. His diagrams are now universally called “gamblegrams.” Figure 4.5 is an example and shows the gamblegram for the CO<sub>2</sub>-free ISF of Table 4.1.

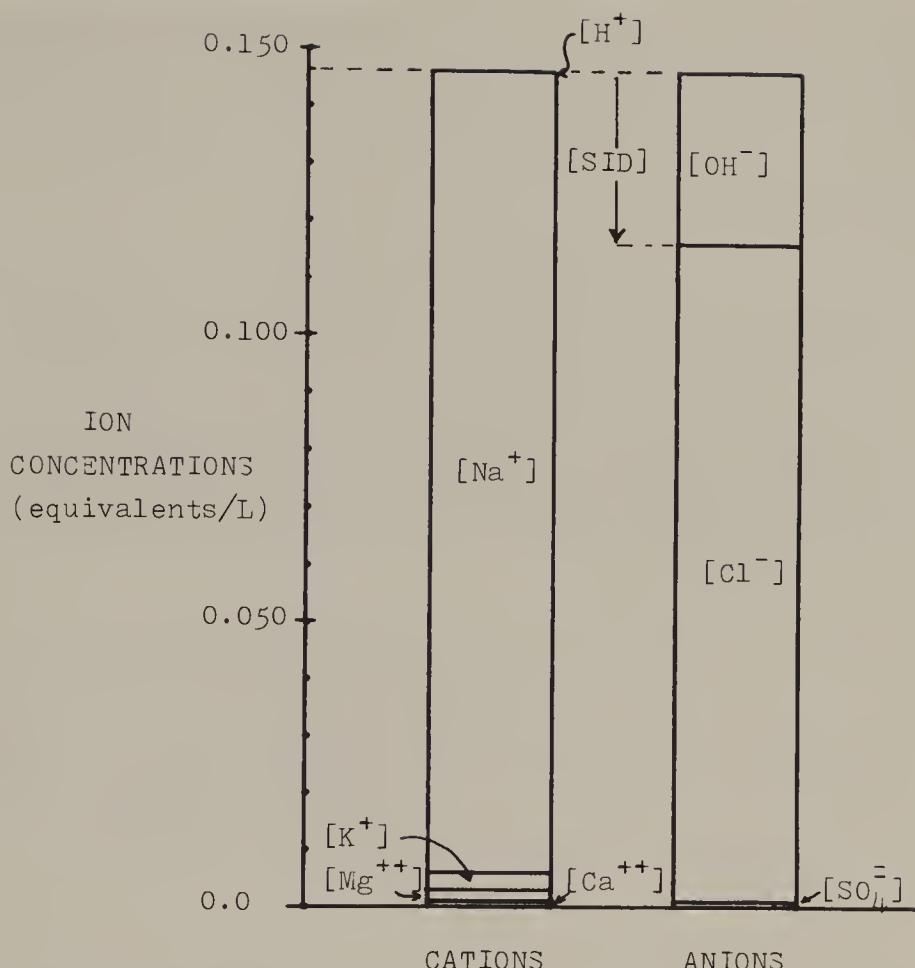
A gamblegram consists of a pair of vertical bars, one for cations, the other for anions. The heights of the bars are proportional to the total concentrations of the positive and negative ions, so they must be equal (electrical neutrality). A proportional section of each bar is allocated to each individual ion species.

A gamblegram makes clear that there are no “salts” in ionic solutions. To ask whether a particular Na<sup>+</sup> is matched to a particular Cl<sup>-</sup> or OH<sup>-</sup> is meaningless, because their arrangement in the diagram is completely arbitrary. There simply is no NaCl in a gamblegram.

Gamblegrams are always helpful in understanding the acid–base behavior of solutions, and the reader is urged to draw them frequently. After a little practice, you will feel able to do them in your head. Do Not! It is remarkably easy to forget important components or not realize that you have left something out. Drawing the diagram carefully is excellent insurance against this and will thoroughly repay the small time and effort it requires.

#### 4.10. STOMACH ACID

The solution secreted by the gastric mucosa was mentioned in Chapter 1 as being very acid, as high as 0.1N “HCl,” which means [H<sup>+</sup>] = 1.0 × 10<sup>-1</sup> Eq/liter, pH 1.0. This remarkable fluid is manufactured by the oxyntic cells from the tissue fluid surrounding them, which in turn is derived from the plasma circulating through it. The analysis in this chapter permits us to understand the net result very clearly and simply. These cells take their tissue fluid, with a normal [SID] value in the neighborhood of 0.03 Eq/liter, and change it to a solution in the stomach with a [SID] value of 0.1 Eq/liter. The only strong ion present in the gastric secretion in significant concentration is Cl<sup>-</sup>, so what these cells accomplish is transport of Cl<sup>-</sup>, but not Na<sup>+</sup> or any other strong ion, from ISF to the secreted fluid. ISF is constantly renewed by the circulating plasma, so in effect the Cl<sup>-</sup> has been transported from plasma to stomach lumen. The cellular



**Figure 4.5.** Gamblegram for the solution described in Table 4.1,  $CO_2$ -free interstitial fluid. See Table 4.1 for numerical values.

and molecular mechanisms by which this result is achieved are not yet understood. Some weak ions must accompany the  $Cl^-$ , but these can be  $OH^-$  moving in the opposite direction,  $H^+$  moving in the same direction,  $HCO_3^-$  moving in the opposite direction, or any combination. There is no way to distinguish experimentally between  $H^+$  and  $OH^-$  movements, but more important, it does not matter. What matters is that no strong cations be allowed to accompany the  $Cl^-$ . This is probably the only solution in the body that can be understood so simply. For all the others, we must also take into account changes in carbon dioxide or other weak acids, as well as strong ions.

The essential role of  $[SID]$  in determining  $[H^+]$ , developed in this chapter, thus simplifies very much the problem of analyzing the mechanisms of stomach acid secretion. Clearly, the question is not how is  $H^+$  secreted, nor how much  $H^+$  is secreted. It is not even possible to tell whether  $H^+$

is secreted; exchanging  $\text{OH}^-$  for  $\text{Cl}^-$  is indistinguishable from secreting both  $\text{Cl}^-$  and  $\text{H}^+$ . The effect in either case is a transfer of  $\text{Cl}^-$  that alters [SID], and it is [SID] that determines  $[\text{H}^+]$ , as we have seen. The question is very simply, how do the oxytic cells secrete  $\text{Cl}^-$ ? Secreting  $\text{H}^+$ , by itself, cannot result in an acid solution; no change in [SID] means no change in  $[\text{H}^+]$ .

The other half of the question is, what happens to the ISF from which the  $\text{Cl}^-$  has been removed? Its [SID] should rise, and it should become more alkaline. It does, but only slightly, for the physiological reason that it is constantly perfused by the circulating blood plasma, so that its  $[\text{Na}^+]$  and  $[\text{Cl}^-]$ , and therefore [SID] and  $[\text{H}^+]$ , are maintained close to normal. Nonetheless, the plasma leaving the stomach has had some of its  $\text{Cl}^-$  removed by the activity of the oxytic cells, so that its [SID] is slightly above normal. The change is observable and has been referred to classically as “the alkaline tide.”

On entering the duodenum, the acid secretion from the stomach is “neutralized” by pancreatic juice. This secretion is relatively low in  $\text{Cl}^-$ , so that its [SID] is high, and it should therefore be very alkaline. It would be if  $\text{CO}_2$  were not present, as we shall see in Chapters 6 and 7. Because of its high [SID] value, when pancreatic juice mixes with the gastric acid a solution results with normal [SID] and therefore normal  $[\text{H}^+]$ . In conventional terminology, the  $\text{Cl}^-$  in the gastric juice neutralizes the  $\text{Na}^+$  in pancreatic juice.

#### 4.11. CHAPTER SUMMARY

1. Strong ions, derived from strong electrolytes, are always completely dissociated in biological solutions. They do not participate in chemical reactions in those solutions. Therefore, all that matters is their charge. Their effect on  $[\text{H}^+]$  and  $[\text{OH}^-]$  in solution is entirely dependent on the net strong ion positive charge, called here the strong ion difference, [SID].
2. In solutions containing only strong ions plus  $\text{H}^+$  and  $\text{OH}^-$ ,  $[\text{H}^+]$  and  $[\text{OH}^-]$  are completely determined by the value of [SID] and the water ion product,  $K'_w$ , by Equations (4.3.4) and (4.3.5). To a very good approximation, when [SID] is negative (excess strong acid),  $[\text{H}^+] = -[\text{SID}]$  and  $[\text{OH}^-] = K'_w / -[\text{SID}]$ . Under these (biologically very unusual) conditions, adding  $\text{H}^+$  as part of a strong acid results in an increase of  $[\text{H}^+]$  just equal to the amount of  $\text{H}^+$  added. In most biological solutions, [SID] is positive, and under these conditions  $[\text{H}^+]$  is very small and changes only very slightly with changes in [SID].
3. The pH versus [SID] or titration curve is a confusing and misleading representation of how  $[\text{H}^+]$  changes with [SID].
4. Because  $[\text{H}^+]$  in strong ion solutions is determined only by [SID] and  $K'_w$ ,  $[\text{H}^+]$  can only be changed in such solutions by changing [SID], if  $K'_w$  is con-

stant.  $[H^+]$  changes cannot be understood, or explained, in terms of adding  $H^+$ . Observed changes in  $[H^+]$  can only be interpreted to mean that strong ion composition of the solution has changed, not that  $H^+$  ions have been added or removed.

5. The acid–base behavior of  $CO_2$ -free interstitial fluid can be explained quantitatively in terms of its [SID] values, because it contains no significant concentrations of weak acids or bases (Table 4.1).
6. Gamblegrams provide a useful way to visualize ion concentrations and the significance of electrical neutrality.
7. The formation of stomach acid requires net movement of the strong ion  $Cl^-$  from blood plasma to stomach lumen so as to produce a large negative [SID] value in the lumen. Some weak ion must also move, but  $H^+$  secretion or transport is not required and by itself could not acidify the luminal fluid.

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## CHAPTER FIVE

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# WEAK ELECTROLYTES AND BUFFERS

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### 5.1. INTRODUCTION

Weak electrolytes affect the acid–base behavior of aqueous solutions in more complicated ways than strong ions do because they introduce additional equilibria involving  $\text{H}^+$  or  $\text{OH}^-$ . In body fluids, weak electrolytes are usually weak acids, so we shall emphasize them in this chapter. Fortunately, the analysis that produced such illuminating results in the previous chapters works equally well here, although the mathematical complexity is much greater. As promised, most of that complexity will be relegated to the Appendix of this chapter.

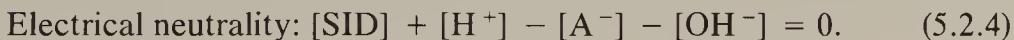
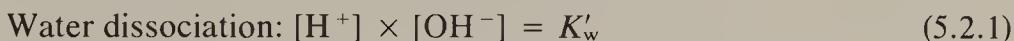
One result of the additional equilibria in weak electrolyte solutions is that the analysis produces very large amounts of detailed information. Rather than the three graphs that were all we needed to display the total range of acid–base behavior in a strong electrolyte solution in the previous chapter, many dozens of such graphs would be needed here to tell the complete story. We are therefore forced to select only those aspects of weak electrolyte solution behavior that are most pertinent for understanding biologically important solutions. Nothing is lost by this, however, because the procedure we must use to arrive at this small subset is all that is needed to generate the complete story also, whenever that is desired. The acid–base behavior of any weak electrolyte solution can be understood in detail by the procedures developed in this chapter.

We therefore begin by analyzing the behavior of a solution containing

a single weak acid, HA, as well as strong ions. Such a solution can be viewed as the result of simply adding HA to the strong ion solutions analyzed in the previous chapter. Its analysis will lead us into the need for computers, as well as the concept of buffering, and will provide the basis for quantitative analysis of real-life solutions that also contain CO<sub>2</sub> (Chapters 6 and 7).

## 5.2. WEAK ACID SOLUTIONS: THE EQUATIONS

In addition to strong ions, water, H<sup>+</sup>, and OH<sup>-</sup>, a weak acid solution contains the molecular species HA and A<sup>-</sup>. The strong ions are represented by their electrical resultant, specified by the value of [SID], as in Chapter 4. Water concentration is high, as always, and assumed constant; its value is included in the value of K<sub>w</sub> for the solution. What we know about HA and A<sup>-</sup> is that they must satisfy the two requirements of dissociation equilibrium and conservation of mass for "A." These requirements plus water dissociation equilibrium and electrical neutrality permit us, or better, require us to write the following four simultaneously valid, independent quantitative relationships between the four unknown, dependent variables, [H<sup>+</sup>], [OH<sup>-</sup>], [A<sup>-</sup>], and [HA], and the two externally controlled, independent variables, [SID] and [A<sub>TOT</sub>].



Because we have four unknowns and four equations, we can solve for the unknowns by the same systematic substituting procedure we used in Chapters 3 and 4. The result, presented in the Appendix, is a set of four cubic equations. Classically, which in this case means "before computers," the quantitative analysis of acid-base phenomena came to a paralyzed halt at this point! Getting values for [H<sup>+</sup>] from its cubic equation, given values for [SID], [A<sub>TOT</sub>], K<sub>A</sub>, and K<sub>w</sub>, although possible in principle, was so long and tedious a process as to be impractical. The whole process of quantitative analysis leading up to those cubic equations was therefore generally discarded as useless also.

Fortunately, the development of computers and programmable calculators has completely changed this situation. It is now just as easy to solve such equations as it is to solve a simple quadratic. The computer does all the work, and the numerical techniques work just as well with the even more complicated fourth- and higher-order equations that result when we turn our attention to solutions like blood plasma. The general procedure is presented in the Appendix to this chapter. From a practical point of

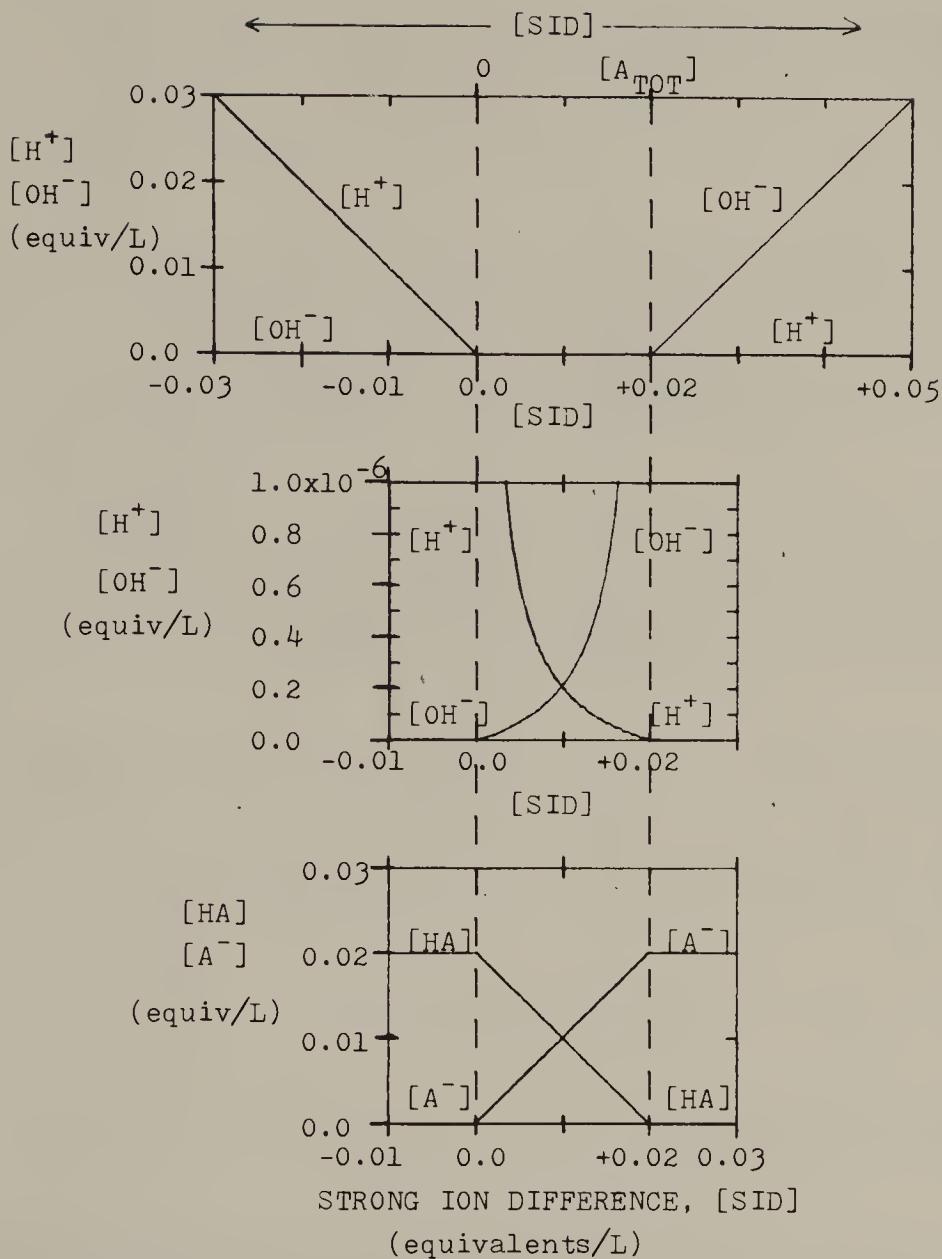
view, the Appendix may be viewed as the analog for this weak acid solution of the one-line formula for solving a quadratic equation that we used in Chapter 4 to go from Equation (4.2.3) to (4.2.5).

This new fact, that computers make practical the numerical solution of previously useless equation sets, changes profoundly our ability to understand acid-base phenomena in living systems. It permits the thorough quantitative approach that is the rationale for this book and that distinguishes this analysis from conventional treatments of the subject. Throughout the rest of this book, we shall assume that computer implementation of these general techniques is always available, so that if we can write the appropriate equations, we can get numerical answers from them.

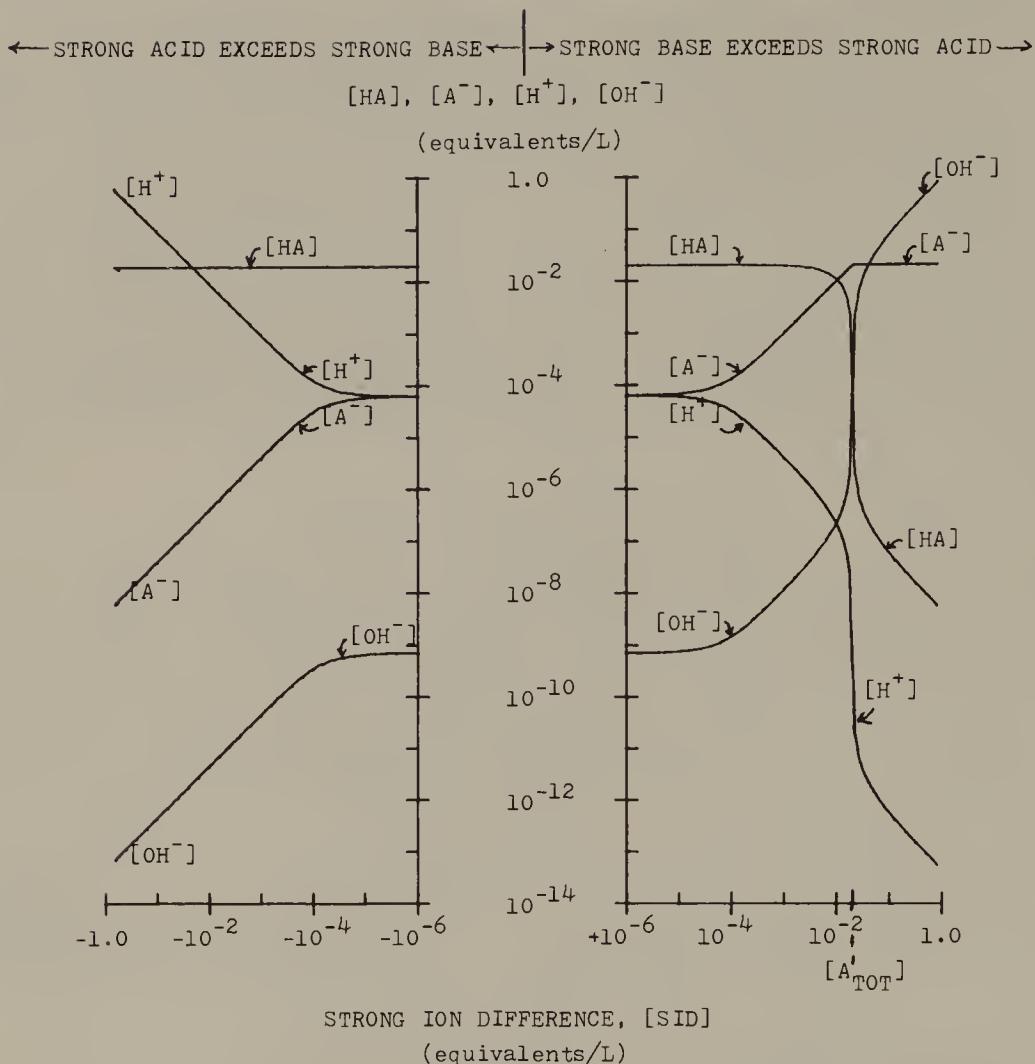
### 5.3. ACID-BASE BEHAVIOR OF WEAK ACID SOLUTIONS

The computer-implemented numerical solutions to the four equations describing a weak acid plus strong ions in water present us with a large amount of information to digest. Fortunately, one of the independent variables, namely, the total amount of weak acid present,  $[A_{TOT}]$ , is usually rather well regulated in living systems, for reasons not directly related to acid-base considerations. We may therefore restrict our attention, at least initially, to variations in the dependent variables resulting only from changes in the other independent variable,  $[SID]$ . That behavior is presented in Figures 5.1, 5.2, and 5.3. They will repay careful study, including comparison with their counterparts in the previous chapter. The following points are especially important.

1. The curves for  $[HA]$  and  $[A^-]$  in Figure 5.1 are surprisingly linear and symmetrical about the midpoint of the  $[SID]$  range from zero to  $[SID] = [A_{TOT}]$ . (The degree of dissociation,  $\alpha$ , follows a curve just like that for  $[A^-]$ , because  $\alpha$  is directly proportional to  $[A^-]$  when  $[A_{TOT}]$  is constant.)
2. That midpoint, at which  $[SID] = [A_{TOT}]/2$ , can be seen from the equations to be the point at which  $[HA] = [A^-] = [SID] = [A_{TOT}]/2$ ,  $\alpha = 0.5$  or 50%,  $[H^+] = K_A$ ,  $[OH^-] = K'_w/K_A$  and  $pH = pK_A$ . Detailed analysis of the equations shows that these equalities are valid only so long as  $K_A$  is within an order of magnitude or so of  $\sqrt{K'_w}$ , ie, in the neighborhood of  $10^{-7}$  Eq/liter.
3. Over the  $[SID]$  range from zero to  $[A_{TOT}]$ ,  $[H^+]$  is much larger, and changes more rapidly with  $[SID]$ , than was the case in strong ion solutions at these same  $[SID]$  values. The  $[H^+]$  and  $[OH^-]$  curves are no longer symmetrical about the neutral point,  $[H^+] = [OH^-]$ , and that point no longer occurs at  $[SID] = 0$ . The presence of the weak acid requires that some excess strong base cations be present



**Figure 5.1.**  $[H^+]$ ,  $[OH^-]$ ,  $[HA]$ , and  $[A^-]$  versus [SID] for a weak acid solution.  $[A_{TOT}] = 0.02$  Eq/liter and  $K_A = 2 \times 10^{-7}$  Eq/liter. The  $K'_w$  value for plasma is used,  $4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>, at 37 C. The vertical scale in the middle graph has been expanded in order to show how  $[OH^-]$  and  $[H^+]$  behave over the  $[SID] = 0$  to  $[SID] = [A_{TOT}]$  range, indicated by the vertical dashed lines. The horizontal scales for [SID] are the same, and in register, for all three graphs.



**Figure 5.2.** Log-log plots of  $[H^+]$ ,  $[OH^-]$ ,  $[HA]$ , and  $[A^-]$  versus  $[SID]$  for the same solution as Figure 5.1.

when  $[H^+]$  and  $[OH^-]$  are equal. Conventional terminology would say that some strong base is required to “neutralize” the weak acid. That suggests that  $[H^+] = [OH^-]$  should occur at  $[SID] = [A_{TOT}]$ , which Figure 5.1 shows is far from the truth. The situation is best understood by recognizing that the  $[SID]$  value at which neutrality occurs depends on the specific forms of both the  $[H^+]$  and the  $[OH^-]$  curves, which means it is a property of the whole system. Any change in  $[A_{TOT}]$ ,  $K_A$ , or  $K'_w$  will change it.

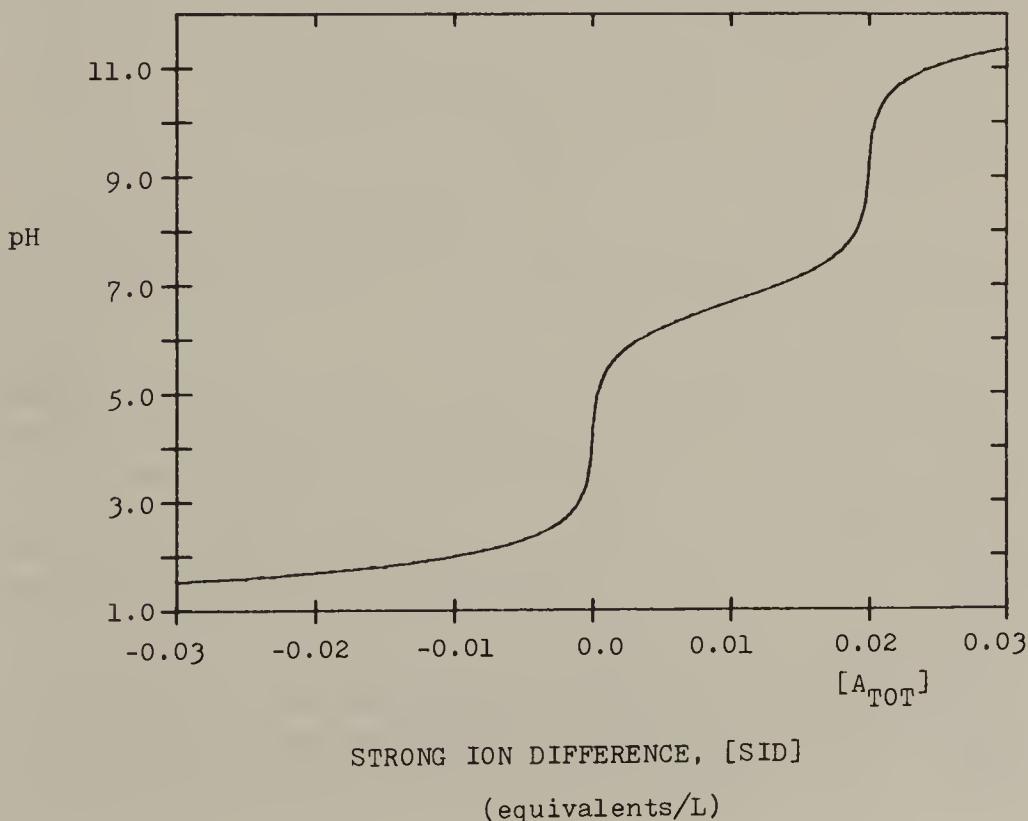
4. Outside the zero to  $[A_{TOT}]$  range for  $[SID]$ ,  $[H^+]$  and  $[OH^-]$  behave very much as they do in strong ion solutions without weak acid. When  $[SID]$  is negative,  $[H^+] = -[SID]$  and  $[OH^-] = -K'_w/[SID]$ , just as before. When  $[SID]$  is positive and above  $[A_{TOT}]$ ,

$[\text{OH}^-] = ([\text{SID}] - [\text{A}_{\text{TOT}}])$ ,  $[\text{H}^+] = K_w' / ([\text{SID}] - [\text{A}_{\text{TOT}}])$ , and the system behaves just like a strong ion only solution with the origin of the  $[\text{SID}]$  axis displaced to  $[\text{A}_{\text{TOT}}]$ . These properties are reflected in the  $[\text{H}^+]$  and  $[\text{OH}^-]$  curves at the top of Figure 5.1 as well as at the ends of Figure 5.2.

The curves of Figure 5.1 and 5.2 present the quantitative relationships between the four internal or dependent variables,  $[\text{A}^-]$ ,  $[\text{HA}]$ ,  $[\text{OH}^-]$ , and  $[\text{H}^+]$ , and the single independent variable,  $[\text{SID}]$ , when the other independent variable,  $[\text{A}_{\text{TOT}}]$ , is constant, and the system is in equilibrium, satisfying Equations (5.2.1) through (5.2.4). We should also like to understand qualitatively what processes lead to these equilibrium results, and how they interact.

Suppose that in the solution described by these two figures, we begin with a  $[\text{SID}]$  value of +0.01 Eq/liter and then raise  $[\text{SID}]$  by adding 0.001 Eq/liter of KOH. The immediate result is to increase the excess strong ion positive charge by 0.001 Eq/liter so that the net amount of weak electrolytes ions bearing negative charge must also increase by 0.001 Eq/liter.

Figure 5.3. The pH versus  $[\text{SID}]$  curve for the  $[\text{H}^+]$  values in Figure 5.1.



The only weak anions available are  $\text{OH}^-$  and  $\text{A}^-$ , and we have added 0.001 Eq/liter of  $\text{OH}^-$  along with the  $\text{K}^+$ , so why does anything have to happen? Why does  $[\text{OH}^-]$  not just go up by 0.001 Eq/liter and everything else stay the same as it was? What actually happens, as the curves show, is that  $[\text{OH}^-]$  hardly changes at all! It increases by less than  $10^{-6}$  Eq/liter, and  $[\text{H}^+]$  goes down by an even smaller amount. What goes up by almost exactly 0.001 Eq/liter is  $[\text{A}^-]$ .

The reason for these changes is that the added  $\text{OH}^-$ , although it could in principle serve to balance the added excess positive charge on the  $\text{K}^+$ , also has the effect of driving the water-forming reaction in the direction of more water and lowered  $[\text{H}^+]$ . The effect of the lowered  $[\text{H}^+]$ , in turn, is to drive the  $\text{HA}$  dissociation reaction in the direction of increased dissociation, thereby forming more  $\text{A}^-$ . The overall effect of the two processes interacting, therefore, is to replace  $\text{OH}^-$  by  $\text{A}^-$ . The added  $\text{OH}^-$  is converted into water, but more  $\text{HA}$  dissociates, so that proper  $[\text{H}^+]$  and charge balance are restored. Now the question becomes, why do  $[\text{H}^+]$  and  $[\text{OH}^-]$  change at all? Why does  $\text{A}^-$  not replace  $\text{OH}^-$  completely and leave  $[\text{H}^+]$  and  $[\text{OH}^-]$  just as they were? The answer lies partly in the relative magnitudes of the water and the weak acid dissociation constants and partly in the fact that this is a system, so that all four of the physical requirements on it must always be satisfied, not just electrical neutrality.  $\text{A}^-$  largely replaces  $\text{OH}^-$  because  $K_A$  is so much larger than  $K'_w$  (water is a very weak electrolyte), but it cannot do so completely because when all the reactions have settled down to equilibrium again,  $[\text{H}^+]$ ,  $[\text{OH}^-]$ , and  $[\text{A}^-]$  not only have to satisfy Equation (5.2.4) for electrical neutrality, they also have to satisfy the other three equations. The end result is that  $[\text{OH}^-]$  is a little higher than it was,  $[\text{H}^+]$  is a little lower,  $[\text{A}^-]$  is almost 0.001 Eq/liter higher, and  $[\text{HA}]$  is almost 0.001 Eq/liter lower. Within the zero to  $[\text{A}_{\text{TOT}}]$  range of  $[\text{SID}]$ , there is no simpler way to understand what is happening. The key point is that the water reactions are just as important as the weak acid ones. Neither one alone can explain what happens.

Outside the zero to  $[\text{A}_{\text{TOT}}]$  range, there are two very different regions, just as there were before we added weak acid. When  $[\text{SID}]$  is negative, it must be balanced by positively charged weak electrolyte ions, and  $\text{H}^+$  is the only one available, so  $[\text{H}^+] = -[\text{SID}]$ . When  $[\text{SID}]$  is positive and larger than  $[\text{A}_{\text{TOT}}]$ , it must be balanced by negatively charged weak electrolyte ions.  $\text{A}^-$  and  $\text{OH}^-$  are both available, but  $[\text{A}^-]$  cannot exceed  $[\text{A}_{\text{TOT}}]$ , so  $\text{OH}^-$  has to fill the gap still remaining. That is why  $[\text{OH}^-] = ([\text{SID}] - [\text{A}_{\text{TOT}}])$  in this region.

As long as  $[\text{SID}]$  is well within the interesting range from  $[\text{SID}] = 0$  to  $[\text{SID}] = [\text{A}_{\text{TOT}}]$  in a single weak acid solution such as this and  $K_A$  is within an order of magnitude of  $\sqrt{K'_w}$ , the following formulas may be

easily derived from Equations (5.2.1) through (5.2.4) and are often useful:

$$[A^-] \cong [SID]$$

$$[HA] \cong [A_{TOT}] - [SID]$$

$$[H^+] \cong K_A \times \left\{ \frac{[A_{TOT}]}{[SID]} - 1 \right\}$$

$$pH \cong pK_A - \log_{10} \left\{ \frac{[A_{TOT}]}{[SID]} - 1 \right\}$$

$$[OH^-] = K'_w/[H^+].$$

Except for the last one, these formulas are only valid in a single weak acid solution and only useful if  $K_A$ ,  $[A_{TOT}]$ , and  $[SID]$  are known. They may be rearranged as desired if other pairs of variables than  $[A_{TOT}]$  and  $[SID]$  have been measured, but only if  $[SID]$  is known to be within the range specified can they give usable numbers.

Most biological solutions, and all body fluids except acid gastric juice, have large positive  $[SID]$  values, well above  $[A_{TOT}]$  for any weak acid present, but their acid–base behavior is very different from that of Figures 5.1, 5.2, and 5.3 because they also contain carbon dioxide. We shall see in the next two chapters why that makes so much difference. From the analysis so far, the message is that whenever CO<sub>2</sub> is not present and the total amount of weak acid is constant, then what determines the  $[H^+]$  (or pH) is the resultant of the strong ion concentrations, expressed as the  $[SID]$ , and how it compares with  $[A_{TOT}]$ .

#### 5.4. BLOOD PLASMA WITHOUT CO<sub>2</sub>

CO<sub>2</sub> is a major determinant of the  $[H^+]$  in blood plasma *in vivo*, as we shall see in Chapter 7, but an isolated plasma sample without its CO<sub>2</sub> can still provide an interesting example of a weak acid solution such as that analyzed in the previous section. The composition of such a plasma sample is listed in Table 5.1 and may be compared with the CO<sub>2</sub>-free interstitial fluid sample described in Table 4.1 of the previous chapter. The  $[A_{TOT}]$ ,  $K_A$ , and  $K'_w$  values in Table 5.1 have been used in the calculations that produced Figures 5.1, 5.2, and 5.3, so that Table 5.1 may be viewed as a set of selected points from those figures. By analogy with Table 4.1, it may also be read as listing the results of titrating 1 liter of the plasma sample with HCl. The major difference between the results in the two tables is that  $[H^+]$  for corresponding (positive)  $[SID]$  values is larger in Table 5.1 than in Table 4.1.

The first row of Table 5.1, labeled “none,” shows that the original

TABLE 5.1. Titration of CO<sub>2</sub>-Free Blood Plasma

"HCl" Added (Eq)	[Cl <sup>-</sup> ]	[SID]	[H <sup>+</sup> ]	[OH <sup>-</sup> ]	pH
none	0.107	0.042	$2.0 \times 10^{-12}$	0.022	11.7
0.01	0.117	0.032	$3.7 \times 10^{-12}$	0.012	11.4
0.012	0.129	0.020	$6.6 \times 10^{-10}$	$6.6 \times 10^{-5}$	9.18
0.01	0.139	0.010	$2.0 \times 10^{-7}$	$2.2 \times 10^{-7}$	6.70
0.01	0.149	0.000	$6.3 \times 10^{-5}$	$7.0 \times 10^{-10}$	4.20
0.01	0.159	-0.01	0.010	$4.4 \times 10^{-12}$	2.00
0.01	0.169	-0.02	0.020	$2.2 \times 10^{-12}$	1.70

All concentrations in Eq/liter.

Initial Composition: [Na<sup>+</sup>], 0.143; [K<sup>+</sup>], 0.004; [Mg<sup>2+</sup>], 0.002; [Ca<sup>2+</sup>], 0.001; [Cl<sup>-</sup>], 0.107; [SO<sub>4</sub><sup>2-</sup>], 0.001; [SID], 0.042; [OH<sup>-</sup>], 0.022; [H<sup>+</sup>],  $2.0 \times 10^{-12}$ ; [A<sub>TOT</sub>], 0.020; [A<sup>-</sup>], 0.020; [HA],  $2 \times 10^{-7}$ ;  $\alpha = 100\%$ .

Parameter values: 37 C,  $K'_w = 4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>;  
 $K_A = 2.0 \times 10^{-7}$  Eq/liter.

[SID] value in plasma is +0.042 Eq/liter, well above [A<sub>TOT</sub>]. We therefore have [OH<sup>-</sup>] = [SID] - [A<sub>TOT</sub>] = 0.022 Eq/liter and [H<sup>+</sup>] =  $K'_w/0.022 = 2.0 \times 10^{-12}$  Eq/liter, pH 11.7. [OH<sup>-</sup>]/[H<sup>+</sup>] is above  $10^{10}$ , so this is an extremely alkaline solution. The weak acid is effectively completely dissociated at this [SID] value; [A<sup>-</sup>] = 0.02, [HA] =  $2.0 \times 10^{-7}$  Eq/liter.

Adding 0.01 Eq of HCl reduces [SID] to +0.032 Eq/liter, row 2, but this is still much larger than [A<sub>TOT</sub>], so [OH<sup>-</sup>] falls by 0.01 Eq/liter, [H<sup>+</sup>] rises by  $1.7 \times 10^{-12}$  Eq/liter, while [A<sup>-</sup>] and [HA] do not change significantly.

Adding 0.012 Eq of HCl brings us to the [SID] = [A<sub>TOT</sub>] point. The changes in [HA] and [A<sup>-</sup>] are still insignificant, and the change in [H<sup>+</sup>] is still minuscule,  $6.6 \times 10^{-10}$  Eq/liter. [OH<sup>-</sup>] falls by slightly less than 0.012 to  $6.6 \times 10^{-5}$  Eq/liter.

The next addition of 0.01 Eq of HCl puts [SID] just at the midpoint of the zero to [A<sub>TOT</sub>] region, at [SID] = 0.01 Eq/liter. Now [A<sup>-</sup>] = [HA] = [SID] = [A<sub>TOT</sub>]/2 = 0.01 Eq/liter. [H<sup>+</sup>] =  $K_A = 2.0 \times 10^{-7}$  Eq/liter, [OH<sup>-</sup>] =  $K'_w/K_A = 2.2 \times 10^{-7}$  Eq/liter, and pH = pK<sub>A</sub> = 6.66. For this system, because K<sub>A</sub> is very close to  $\sqrt{K'_w}$ , this point is very close to the acid-base neutral point, at which [H<sup>+</sup>] = [OH<sup>-</sup>] =  $2.1 \times 10^{-7}$  Eq/liter, pH 6.68.

One more HCl addition puts [SID] at zero. This is well on the acid side of neutrality, due to the weak acid. [H<sup>+</sup>] is now much larger than [OH<sup>-</sup>], although both are still very small. [HA] is very close to [A<sub>TOT</sub>], at 0.0199 Eq/liter, and [A<sup>-</sup>] is the same as [H<sup>+</sup>] at  $6.3 \times 10^{-5}$  Eq/liter.

Further additions of HCl make [SID] more and more negative, so [H<sup>+</sup>] and [OH<sup>-</sup>] behave just as they did in Table 4.1. [H<sup>+</sup>] is just - [SID], [HA] is equal to [A<sub>TOT</sub>], almost, while [OH<sup>-</sup>] and [A<sup>-</sup>] are extremely small.

A more precise analysis of this solution would show that there are in fact many weak acids, not just one, each at a low concentration. All the  $K_A$ 's and small  $[A_{TOT}]$ 's could be included in a more precise set of calculations, but the net result, after an enormous amount of computer work and time, would not be significantly different from these representative results using single  $K_A$  and  $[A_{TOT}]$  values.

## 5.5. BUFFERS, BUFFERING, AND BUFFER STRENGTHS

“To buff” is defined in the dictionary as “to lessen the shock of,” and a “buffer” is “that which buffs.” In acid–base chemistry, a weak acid such as the HA we have been analyzing in this chapter is often referred to as a buffer. The essentially universal reliance on pH values, instead of  $[H^+]$ , has very much confused the quantitative aspects of buffering in weak acid solutions and has led to a misplaced emphasis on their supposed ability to “resist” changes in  $[H^+]$ . The quantitative analysis serves to clarify this situation very much and suggests some important restrictions on how we should think about “buffering.”

In solutions of strong ions only, considered in the previous chapter,  $[H^+]$  is determined only by the value of [SID] in such a way that whenever [SID] is positive,  $[H^+]$  is very small, and changes in  $[H^+]$  are a minute fraction of the changes in [SID] that bring them about. (See Figures 4.1, 4.2, and 4.3.) In a solution containing a weak acid in addition to strong ions, the value of  $[H^+]$  is determined by two variables, [SID] and  $[A_{TOT}]$ , as we have just seen. If we continue to consider only situations in which  $[A_{TOT}]$  does not change, then changes in the value of  $[H^+]$  can only result from changes in [SID] in these weak acid solutions also. Figures 5.1 and 5.2 show clearly that  $[H^+]$  changes in response to [SID] changes are still very small, so long as [SID] is positive, but that over the [SID] range from zero to  $[A_{TOT}]$ ,  $[H^+]$  is much larger and changes much more for a given [SID] change than it does over the same [SID] range when no weak acid is present. Direct comparison of the log–log  $[H^+]$  versus [SID] curves with and without weak acid in Figure 5.4 clearly demonstrates this fact. Our quantitative analysis, in other words, shows that the presence of a weak acid “buffer” actually causes  $[H^+]$  to change more rapidly with changes in [SID] than when no weak acid is present.

In terms of pH, the same conclusion can be reached by comparing the pH, or titration curves of Figure 5.5. At every [SID] value between zero and  $[A_{TOT}]$ , the pH curve without weak acid is flatter than when weak acid is present.

Nonetheless, the presence of the weak acid does make an important difference. It changes the  $[H^+]$  or pH value of the solution at any [SID] value to a more acid condition. It thus alters the  $[H^+]$  or pH range that the solution experiences in response to a given range of [SID] values, so

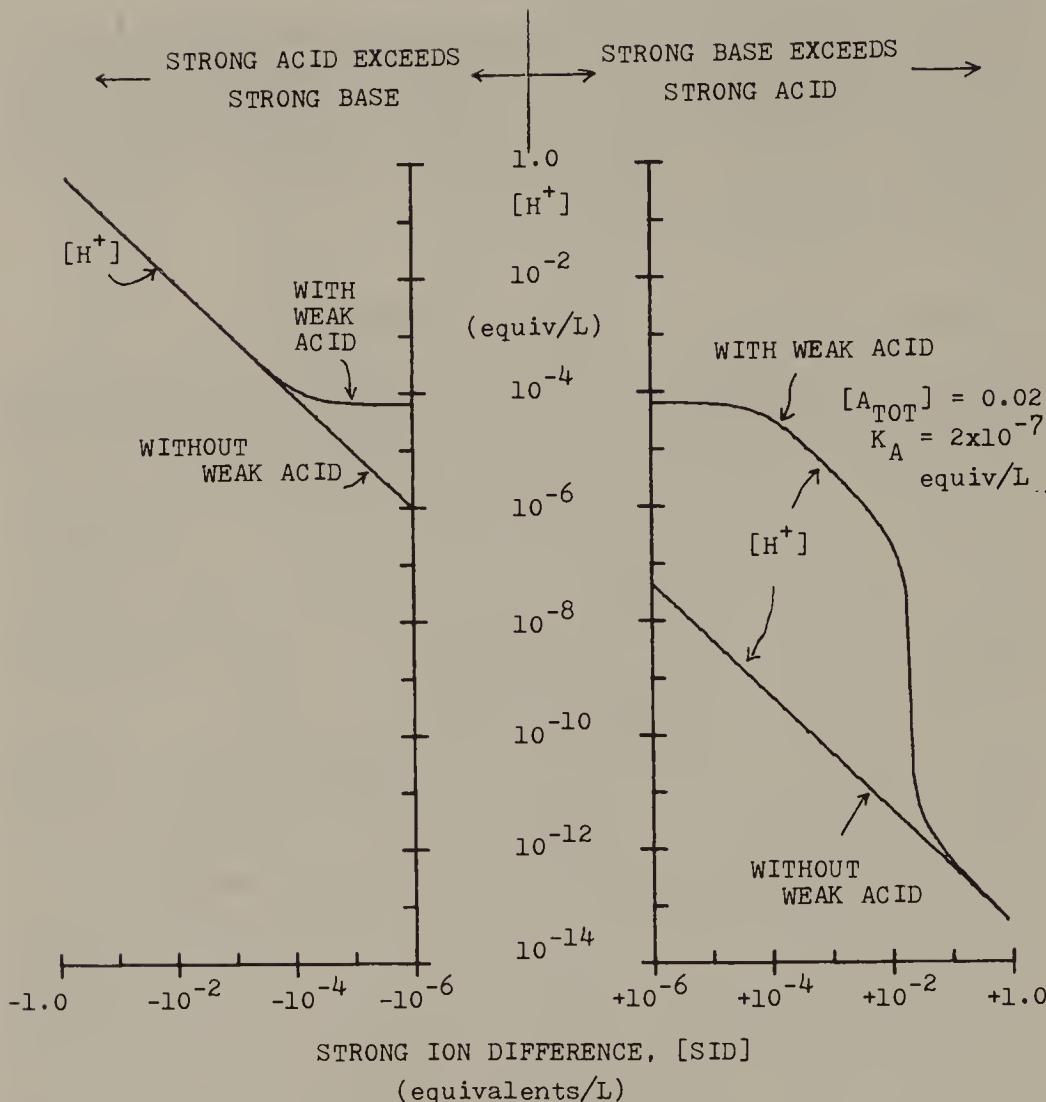


Figure 5.4. Log-log plots of  $[H^+]$  versus [SID] for two solutions, one with no weak acid, the other the same as in Figures 5.1 and 5.2.

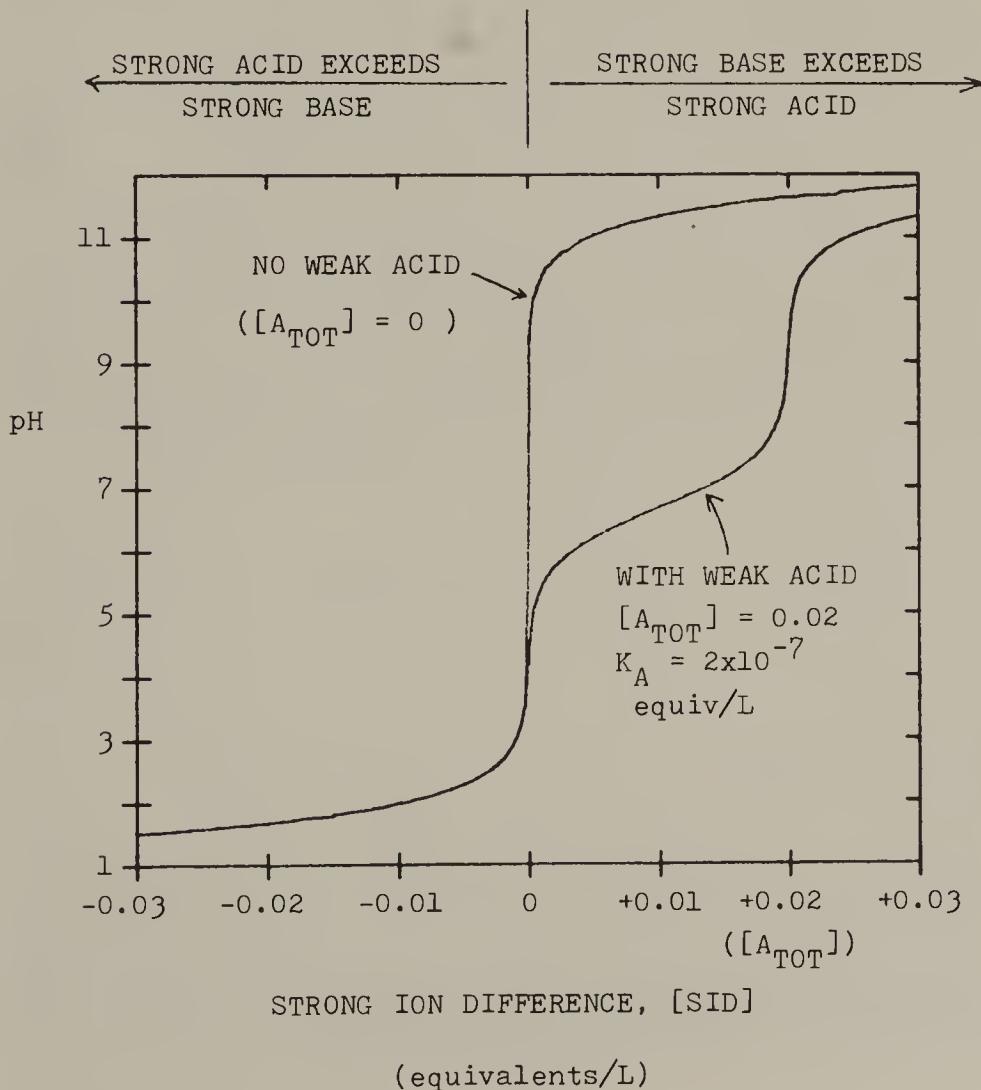
long as [SID] is positive. If, as is customary, we concentrate on the [SID] range in the neighborhood of the  $[SID] = [A_{TOT}]/2$  point, we can go further and say that the effect of the weak acid is to put  $[H^+]$  in the neighborhood of  $K_A$ , or pH in the neighborhood of  $pK_a$ . Without the weak acid,  $[H^+]$  in this neighborhood is simply  $K_w/[SID]$ , a very small value. pH is therefore large, on the order of 11 or 12. What the weak acid "buffer" does, this analysis tells us, is change the point around which  $[H^+]$  changes, for a given range of [SID] values. It does not decrease the amount of  $[H^+]$  change; in fact it increases it. A weak acid "buffer" is therefore not an  $[H^+]$  or pH "regulator" but rather an  $[H^+]$  or pH "setter." It "resists"  $[H^+]$  or pH changes much less effectively than the same solution without any weak acid.

Quantitatively, the ability of a solution to "resist" changes in  $[H^+]$  or pH in response to [SID] changes is indicated by the slope of the  $[H^+]$ , or pH, versus [SID] curve. The steeper the curve, the greater the  $[H^+]$ , or pH, change in response to a [SID] change, and therefore the "weaker" the buffering action. The reciprocal of this slope serves as a measure of buffer "strength," because the flatter the curve, the larger it will be. We therefore define the following "buffer strengths":

$[H^+]$  buffer strength = the reciprocal of the slope of the  $[H^+]$  versus [SID] curve for a solution.

pH buffer strength = the reciprocal of the slope of the pH versus [SID] curve for a solution.

Figure 5.5. pH versus [SID] for the same two solutions as in Figure 5.4.



$[H^+]$  buffer strength is a dimensionless number because it represents the number of equivalents per liter or ions per liter, of strong ions that must be added to or removed from a solution in order to change  $[H^+]$  by 1 Eq/liter or ion/liter. pH buffer strength, because it is the number of equivalents per liter of [SID] change needed to bring about a pH change of 1, and pH is dimensionless, has the dimensions of [SID], equivalents per liter.

As indicated in the Appendix, the formulas for these two quantities, given below, can be derived by straightforward application of elementary calculus to the equations for  $[H^+]$  as a function of [SID] and  $[A_{TOT}]$ .

1. For positive [SID] values in solutions of strong ions only:

$$[H^+] \text{ buffer strength} = - [SID]^2 / K_w' \quad (5.5.1)$$

$$\text{pH buffer strength} = 2.3 \times [SID] \text{ Eq/liter.} \quad (5.5.2)$$

2. For solutions containing a weak acid, HA, at a total concentration of  $[A_{TOT}]$ , under the condition that [SID] is positive and very close to  $[A_{TOT}]/2$ :

$$[H^+] \text{ buffer strength} = - [SID]/2K_A \quad (5.5.3)$$

$$\text{pH buffer strength} = 1.2 \times [SID] \text{ Eq/liter.} \quad (5.5.4)$$

As an example, to indicate the magnitude of the numbers involved as well as to verify that adding a weak acid reduces the buffer strength of a solution, consider the  $\text{CO}_2$ -free plasma solution of Table 5.1. Its  $[A_{TOT}]$  is 0.02 Eq/liter, so we need to calculate under (1) above the buffer strength values for a strong ion only solution with [SID] = 0.01 Eq/liter and compare them with the results under (2) for a solution with the same [SID] value and  $K_A = 2.0 \times 10^{-7}$  Eq/liter. The results are as follows:

Solution	$[H^+] \text{ buffer strength}$	pH buffer strength
no weak acid $[SID] = 0.01 \text{ Eq/liter}$	$-2.3 \times 10^9$	0.023 Eq/liter
weak acid $[A_{TOT}] = 0.02$ $[SID] = 0.01$ $K_A = 2.0 \times 10^{-7} \text{ Eq/liter}$	$-2.5 \times 10^4$	0.012 Eq/liter

What these numbers, along with the curves that they represent, tell us conceptually is that when [SID] is positive and equal to 0.01 Eq/liter and no weak acid is present, then a large number of strong ions (2.3 billion) must be moved into or out of the solution in order to change  $[H^+]$  by just 1  $H^+$ . The reason for this is that  $[\text{OH}^-]$  is also changing, almost exactly in proportion to [SID] (45° straight lines in Figures 4.2 and 4.3, so that

$[H^+]$  has to change only enough to keep the ion product constant, Equation (5.2.1).

When a weak acid is also present, at  $[A_{TOT}] = 0.02$ , so that  $[SID]$  at 0.01 Eq/liter is just  $[A_{TOT}]/2$ , then changes in  $[SID]$  cause changes in  $[A^-]$  as well as in  $[OH^-]$ , and  $[H^+]$  must readjust to satisfy two equilibria rather than just one. The corresponding changes in  $[H^+]$  are therefore much larger. It now takes only (!) 25,000 strong ions to change  $[H^+]$  by 1  $H^+$ . This interpretation of the  $[H^+]$  buffer strength as a measure of the number of  $K^+$  or  $Na^+$  or  $Cl^-$  ions per unit volume that must be moved into or out of a solution in order to change the  $[H^+]$  of that solution by just 1  $H^+$  ion is very useful.

These considerations are also helpful in reminding us that  $[H^+]$  buffer strength is a dimensionless number, because it is the ratio of equivalents per liter to equivalents per liter, or ions per liter to ions per liter. pH buffer strength, on the other hand, has the dimensions of  $[SID]$  or  $[A_{TOT}]$ , namely, equivalents per liter, because pH is a dimensionless number.

Two additional aspects of buffering may cause confusion if not understood in the context of all four of the quantitative relationships that define a weak acid solution, Equations (5.2.1) through (5.2.4). The first, often implicit in qualitative discussions of buffering, is the abstract comparison between how much  $H^+$  has been added to the solution and how much  $[H^+]$  changes. If  $[H^+]$  changes by less than the amount of  $H^+$  added per unit volume, it may be suggested that the solution has somehow “resisted” the added  $H^+$ . As already pointed out, this reasoning ignores the central fact that  $H^+$  is involved in reactions, such as water dissociation and recombination, so that we cannot expect it to behave like strong ions that are not involved in any reactions. There is no a priori reason to expect the change in  $[H^+]$  to bear any simple relationship to the amount of  $H^+$  added. Unfortunately, when strong acid is added to a strong acid solution, then  $[H^+]$  behaves just as if  $H^+$  were a strong ion. The change in  $[H^+]$  is just equal to the change in  $[SID]$ , which in turn is just equal to the added  $H^+$ . Careless extrapolation from this special situation to solutions with positive  $[SID]$  values, in which  $[H^+]$  behaves very differently, is responsible for much confusion in the acid–base literature. It is worth emphasizing that even in this very simple case of strong acids and negative  $[SID]$  values,  $[H^+]$  changes still cannot be understood in terms of  $H^+$ . When  $[SID]$  is increased, for example, by adding strong base instead of strong acid, no  $H^+$  is removed, in fact a minute amount is added, but  $[H^+]$  still falls. How much and why  $[H^+]$  falls can only be understood by taking into account all the variables and relationships in the solution, not by looking only at  $H^+$ .

The second important confusion about buffering arises from failure to recognize that all four equations (5.2.1) through (5.2.4) must be satisfied. Every one of them is essential.  $[H^+]$  is determined by  $[A_{TOT}]$ ,  $K_A$ ,  $K'_w$ ,

and [SID], not because of any single one of those four equations, but because they must all be satisfied simultaneously. The cause-effect relationships between the independent variables,  $[A_{TOT}]$  and [SID], and the dependent ones,  $[HA]$ ,  $[A^-]$ ,  $[OH^-]$ , and  $[H^+]$ , hidden away in the cubic equations in the Appendix, and represented by the curves in Figures 5.1 and 5.2, cannot be derived from any one of the four system-defining equations, but only from all four of them. Equation (5.2.2) is often erroneously singled out for attention as most important and interpreted to show how  $[H^+]$  "depends on" the ratio of  $[HA]$  to  $[A^-]$ . Since all three of these quantities are dependent variables determined by  $[A_{TOT}]$  and [SID], they cannot depend on each other in any meaningful physical sense. Equation (5.2.2) can, of course, be rearranged in several ways that are all equivalent mathematically:

$$\begin{aligned}[H^+] &= K_A \times [HA]/[A^-] \\ K_A &= [H^+] \times [A^-]/[HA] \\ [A^-] &= K_A \times [HA]/[H^+] \\ [HA] &= [H^+] \times [A^-]/K_A.\end{aligned}$$

They cannot all be telling us how one of the variables depends on the other two. Which one is "correct"? They all are! The problem lies in understanding clearly what this equation means physically rather than mathematically. What it tells us is not a single cause-effect relationship, but rather one of the physical constraints on these three variables that is imposed by the requirement of equilibrium. Any of the above forms of Equation (5.2.2) may obviously be used for calculating one of the three variables if the other two are known, but a calculation is not the same as a physical cause-effect relationship. Equation (5.2.2) must be satisfied at equilibrium, but that is not what determines the value of  $[H^+]$  nor  $[HA]$  nor  $[A^-]$ . Those three quantities are determined, in this solution, only by [SID] and  $[A_{TOT}]$ . They cannot, and do not, determine each other.

In view of the very different behavior of weak base "buffers," analyzed in the next section, it is interesting to see what happens to  $[OH^-]$  in the weak acid buffers of this section. Comparison of the  $[OH^-]$  curves in Figures 4.2 and 4.3 with those in Figures 5.1 and 5.2 makes it clear that the change in  $[OH^-]$  over the [SID] region around  $[SID] = [A_{TOT}]/2$  is much less than it is when no weak acid is present. If we were to calculate the slopes, and their reciprocals, by strictly analogous procedures to those we used for the  $[H^+]$  and pH buffer strengths above, we should find that the  $[OH^-]$  curves are indeed flatter when weak acid is present. Qualitatively, we could say that a weak acid "buffers"  $[OH^-]$ , but not  $[H^+]$ , much better than water alone can do.

In summary, any solution with a positive [SID] value "buffers" in the usually implied sense that when  $H^+$  is added, the change in  $[H^+]$  is less

than the amount of  $\text{H}^+$  added per unit volume. This property follows from the dissociation equilibrium for water. A weak acid added to such a solution reduces its buffer strength, but changes the  $[\text{H}^+]$  value around which it appears to buffer.

## 5.6. WEAK BASE SOLUTIONS

A weak base,  $\text{BOH}$ , partially dissociates in solution to the ions  $\text{B}^+$  and  $\text{OH}^-$ . A solution containing strong ions plus a weak base at a total concentration  $[\text{B}_{\text{TOT}}]$  must obey, at equilibrium, the following four equations, comparable to those specified for a weak acid solution in Section 5.2.

$$\text{Water dissociation equilibrium: } [\text{H}^+] \times [\text{OH}^-] = K'_w \quad (5.6.1)$$

$$\begin{aligned} \text{Weak base dissociation equilibrium: } & [\text{B}^+] \times [\text{OH}^-] = \\ & K_B \times [\text{BOH}] \end{aligned} \quad (5.6.2)$$

$$\text{Conservation of weak base: } [\text{B}^+] + [\text{BOH}] = [\text{B}_{\text{TOT}}] \quad (5.6.3)$$

$$\text{Electrical neutrality: } [\text{SID}] + [\text{B}^+] + [\text{H}^+] - [\text{OH}^-] = 0. \quad (5.6.4)$$

As before, we have four simultaneous independent equations and four unknown quantities,  $[\text{BOH}]$ ,  $[\text{B}^+]$ ,  $[\text{OH}^-]$ , and  $[\text{H}^+]$ , so we can in principle solve for the four unknowns. The same kinds of mathematical problems arise as with a weak acid, and the same numerical techniques are needed as outlined in the Appendix to this chapter. The results are presented in Figures 5.6, 5.7, and 5.8, which should be carefully compared with the previous five figures as well as with those in Chapter 4. Values used for these calculations were chosen to facilitate this comparison, namely,  $[\text{B}_{\text{TOT}}] = 0.02$ ,  $K_B = 2.2 \times 10^{-7}$  Eq/liter,  $K'_w = 4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>.

These figures show that the effect of the added weak base is primarily over the  $[\text{SID}]$  range from zero to  $-[\text{B}_{\text{TOT}}]$ . At the midpoint of this range,  $-[\text{SID}] = [\text{B}_{\text{TOT}}]/2 = [\text{BOH}] = [\text{B}^+]$ ,  $[\text{OH}^-] = K_B$  and  $[\text{H}^+] = K'_w/K_B$ . Unlike the weak acid solution, this weak base solution is an effective  $[\text{H}^+]$  buffer at this point; the  $[\text{H}^+]$  versus  $[\text{SID}]$  curve is much flatter at this  $[\text{SID}]$  value ( $-0.01$  Eq/liter) in Figure 5.6 than in Figure 4.2. Slope calculations show that the following formulas apply at this point.

1. Strong ions only, for negative  $[\text{SID}]$  values:

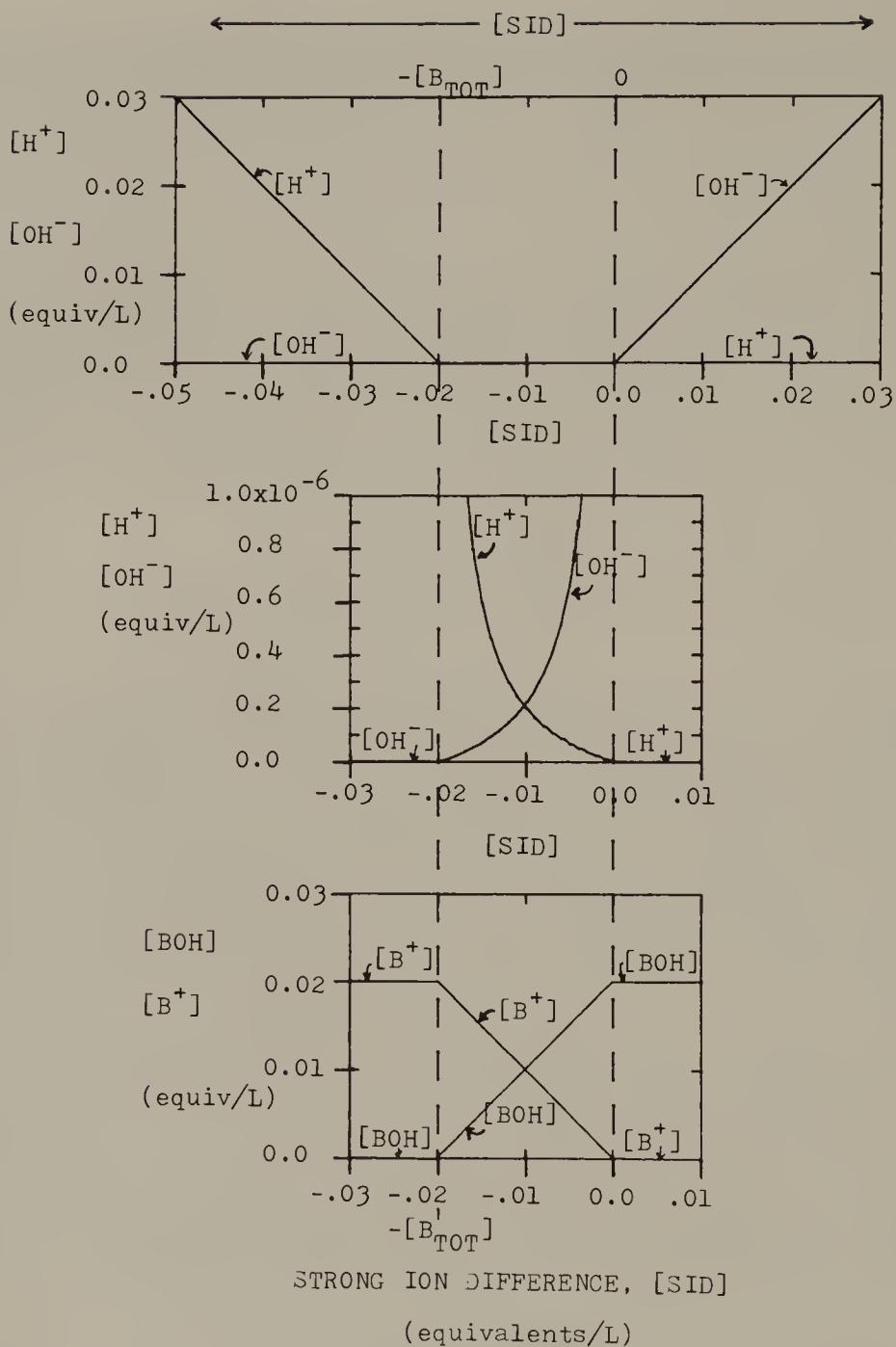
$$[\text{H}^+] \text{ buffer strength} = -1.0 \quad (5.6.5)$$

$$\text{pH buffer strength} = -2.3 \times [\text{SID}] \text{ Eq/liter.} \quad (5.6.6)$$

2. Solution of a single weak base,  $\text{BOH}$ , at  $[\text{SID}] = -[\text{B}_{\text{TOT}}]/2$ :

$$[\text{H}^+] \text{ buffer strength} = [\text{SID}] \times K_B/(2 \times K'_w) \quad (5.6.7)$$

$$\text{pH buffer strength} = -1.2 \times [\text{SID}] \text{ Eq/liter.} \quad (5.6.8)$$

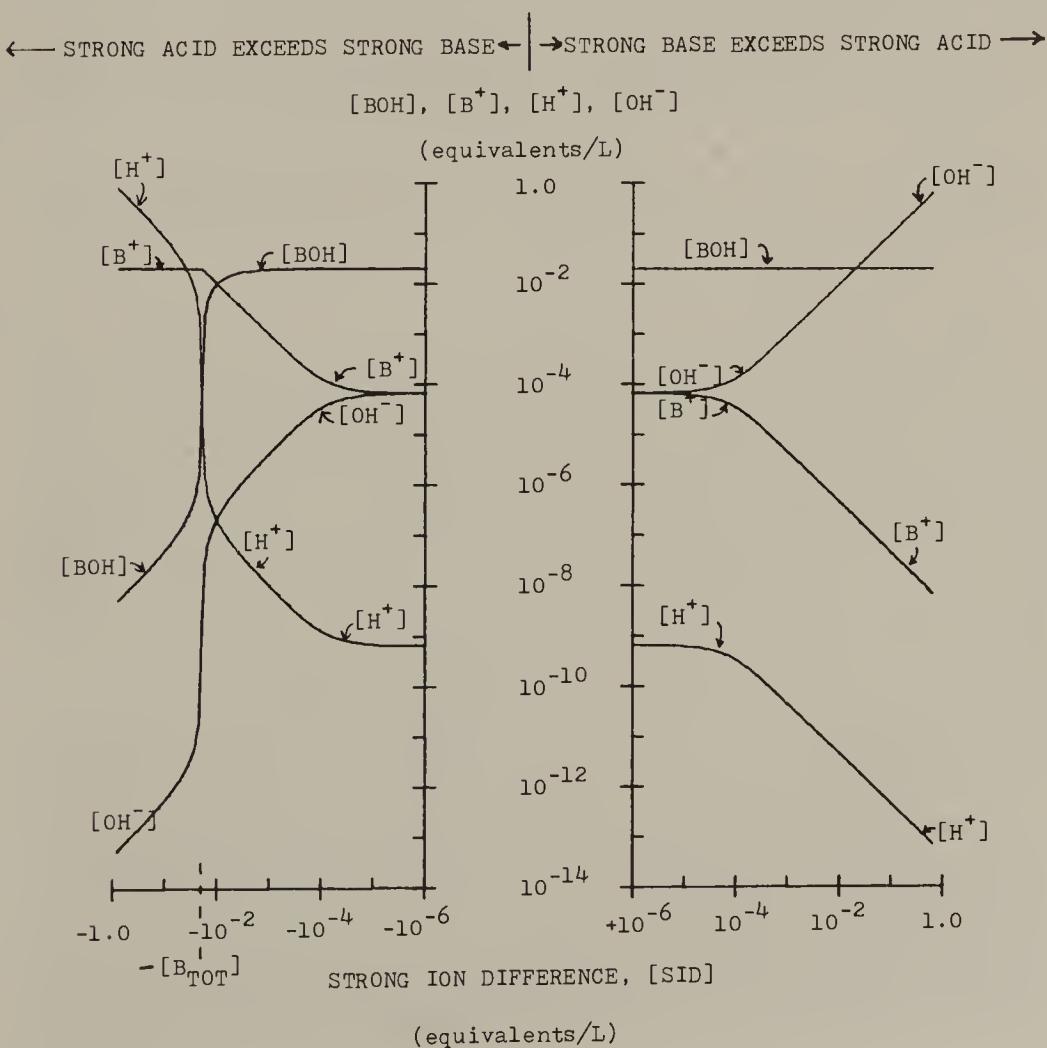


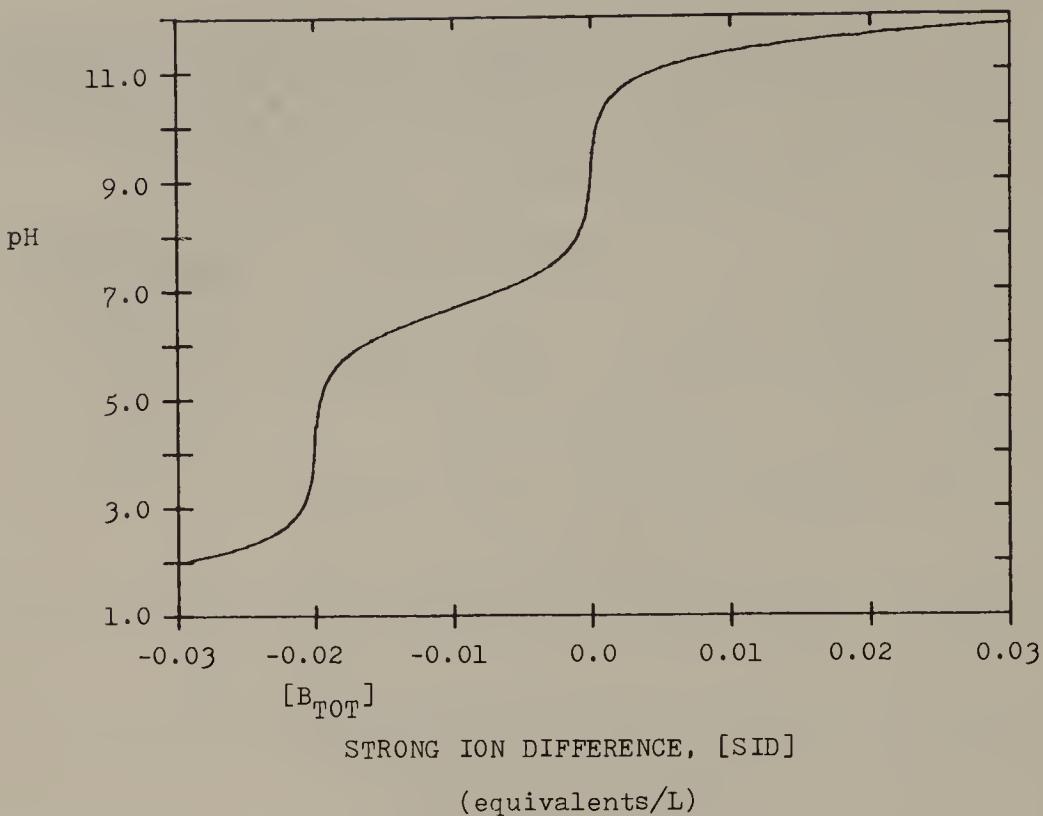
**Figure 5.6.**  $[H^+]$ ,  $[OH^-]$ ,  $[BOH]$ , and  $[B^+]$  versus [SID] for a single weak base solution with  $K_B = 2.2 \times 10^{-7}$  and  $[B_{TOT}] = 0.02$  Eq/liter.  $K'_w = 4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>. Enlarged vertical scale in the middle graph to show how  $[H^+]$  and  $[OH^-]$  vary with [SID] over a range from,  $-[B_{TOT}]$  to 0. Compare with Figure 5.1.

The numbers resulting from application of these formulas to our  $[B_{TOT}] = 0.02$  Eq/liter solution are presented in the table below. Most striking is the very large difference between the  $[H^+]$  buffer strength values in this solution and the weak acid solution just considered, compared with the identity of the pH buffer strengths in the two cases.

Solution	$[H^+]$ buffer strength	pH buffer strength
no weak base		
$[SID] = -0.01$ Eq/liter	-1.0	0.023 Eq/liter
weak base		
$[B_{TOT}] = 0.02$		
$[SID] = -0.01$	$-2.5 \times 10^4$	0.012 Eq/liter
$K_B = 2.2 \times 10^{-7}$ Eq/liter		

Figure 5.7. Log-log plots for the same solution as Figure 5.6. Compare with Figure 5.2.





**Figure 5.8.** The pH versus [SID] curve for the solution of Figure 5.6. Compare with Figures 5.3 and 5.5.

The difference in the  $[H^+]$  buffer strengths is just opposite to what it was in the weak acid case. Here, the weak base solution is a better  $[H^+]$  buffer by a factor of 25,000, whereas in the weak acid case, the solution without weak acid was a better  $[H^+]$  buffer by a factor of almost 100,000. The pH buffer strength entries here are identical to those in the weak acid case, despite the large differences in  $[H^+]$  behavior. This leads to the apparently contradictory conclusions that although it is 25,000 times better as an  $[H^+]$  buffer, the weak base solution is only half as good a pH buffer as the strong acid solution without weak base.

In the single weak acid case, we found that “[ $OH^-$ ] buffering” was much better than in a strong ion only solution at the same [SID] value. In this case, a single weak base solution, the opposite is true. This solution is a better  $[H^+]$  buffer but a worse  $[OH^-]$  buffer than a strong ion only solution at the same (negative) [SID] value. So far as pH buffering is concerned, both weak electrolyte solutions are worse pH buffers than a strong ion only solution.

The concentration of the weak electrolyte clearly affects a solution’s buffer strength, but as  $[A_{TOT}]$  or  $[B_{TOT}]$  becomes larger, so does the mag-

nitude of [SID] at the  $[SID] = [A_{TOT}]/2$  or  $-[SID] = [B_{TOT}]/2$  point. The  $[H^+]$ ,  $[OH^-]$ , and pH versus [SID] curves all become flatter at this point, however, so that buffer strengths all increase with increasing  $[A_{TOT}]$  or  $[B_{TOT}]$ . The formulas for buffer strengths given in this and the preceding section all show this effect clearly when  $[A_{TOT}]/2$  or  $[B_{TOT}]/2$  are substituted appropriately for [SID]:

1. Weak acid solution at  $[SID] = [A_{TOT}]/2$ :

$$[H^+] \text{ buffer strength} = -[A_{TOT}]/4K_A$$

$$\text{pH buffer strength} = 0.6 [A_{TOT}] \text{ (Eq/liter).}$$

2. Weak base solution at  $-[SID] = [B_{TOT}]/2$ :

$$[H^+] \text{ buffer strength} = -[B_{TOT}] \times K_B/4K'_w$$

$$\text{pH buffer strength} = 0.6 [B_{TOT}] \text{ (Eq/liter).}$$

Because of this dependence on  $[A_{TOT}]$  and  $[B_{TOT}]$ , pH buffer strength is sometimes divided by  $[A_{TOT}]$  or  $[B_{TOT}]$  and called simply "buffer strength," or "molar buffer strength." From the above formulas, this quantity is simply 0.6 (0.576 to three significant figures) and dimensionless, although it may be described as 0.6 Eq/liter [SID] change needed to produce a pH change of 1.0 in a weak acid or weak base solution at a concentration of 1.0 Eq/liter.

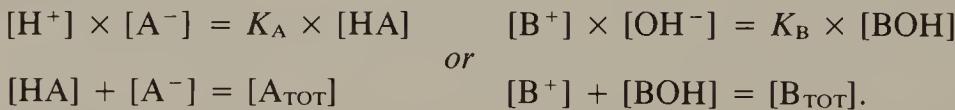
Another feature of weak acid and weak base solutions follows from this analysis. In a weak acid solution with [SID] set to  $[A_{TOT}]/2$ ,  $[H^+] = K_A$  and  $\text{pH} = pK_A$ . In a weak base solution with  $-[SID]$  set to  $[B_{TOT}]/2$ ,  $[H^+] = K'_w/K_B$  and  $\text{pH} = pK'_w - pK_B$ . We can therefore use either a weak acid solution at  $[SID] = [A_{TOT}]/2$  or a weak base solution at  $[SID] = -[B_{TOT}]/2$  to make a "buffer" solution at any desired  $[H^+]$  value simply by choosing a substance with the appropriate  $K_A$  or  $K_B$  value. Once [SID] is set to the midpoint value of  $[A_{TOT}]/2$  or  $-[B_{TOT}]/2$ , then it is not whether the weak electrolyte is an acid or a base that determines the  $[H^+]$  value of the solution but the numerical value of the dissociation constant compared to  $\sqrt{K'_w}$ . The conventional terminology may confuse this issue by suggesting that it should be weak acids that buffer strong bases and weak bases that buffer strong acids. It should be clear from the preceding discussion that the "buffer" is the whole solution, not just the weak electrolyte, and the role of water is at least as important as that of any other component. In fact, "buffering" is a property of the whole system, and it is misleading to attribute it to any single component.

A frequently used terminology to refer to the [SID] value is "buffer base." The idea behind this term is that the net excess strong base, which is just the [SID] when [SID] is positive, specifies how much electrical space is available for weak acid (and therefore, supposedly, "buffer") anions. The difficulty with this terminology is that it ignores the impor-

tance of both the water and the strong ions and suggests that it is the weak electrolyte that does the buffering. A more accurate term that is often used clinically is “base excess” or “base deficit.” It refers to the departure of [SID] from its normal value. The term “anion gap” is also often used. We defer more detailed discussion of these terms until the effects of CO<sub>2</sub> have been analyzed in Chapters 6 and 7.

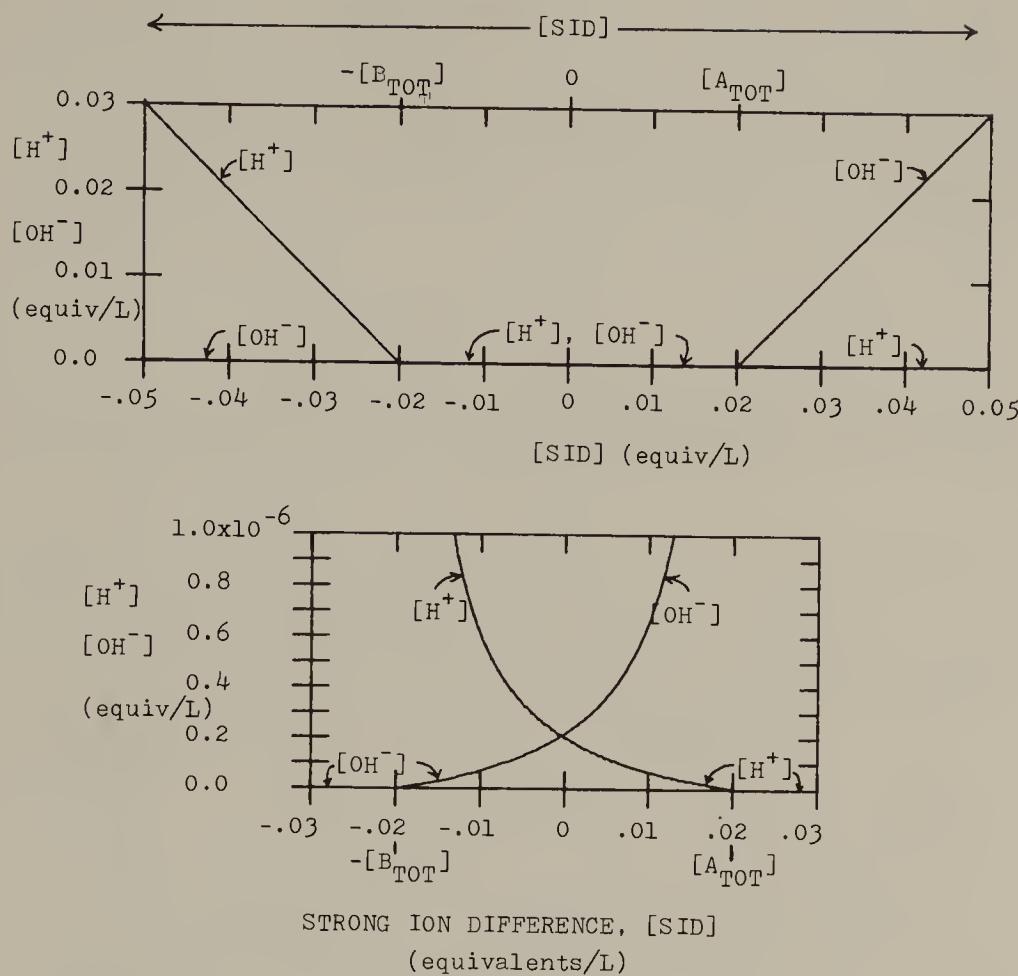
### 5.7. MIXTURES OF WEAK ACIDS AND WEAK BASES

In principle, nothing new needs to be added to our analytical procedure in order to understand quantitatively a solution containing both a weak acid and a weak base, or in fact any number of each. This is another point at which the potential wealth of detail mentioned at the beginning of the chapter appears, because each particular case requires its own specific equations, with its own set of [A<sub>TOT</sub>], K<sub>A</sub>, [B<sub>TOT</sub>], and K<sub>B</sub> values, and its own particular graphs. Many pages could be spent exploring the large universe of all such systems and their acid–base properties. It will suffice to point out here that each weak electrolyte adds two additional internal or dependent variables, its [HA] and [A<sup>-</sup>] or [BOH] and [B<sup>+</sup>], one additional externally determined or independent variable, [A<sub>TOT</sub>] or [B<sub>TOT</sub>], one additional parameter, K<sub>A</sub> or K<sub>B</sub>, and two necessary additional equations, either



The additional ionic species, either A<sup>-</sup> or B<sup>+</sup>, must also be included in the electrical neutrality equation, which therefore becomes correspondingly longer. So far as the calculating procedure introduced in the Appendix to Section 5.2 is concerned, this increased complexity is easily handled, and the procedure will always give us numbers and graphs as desired.

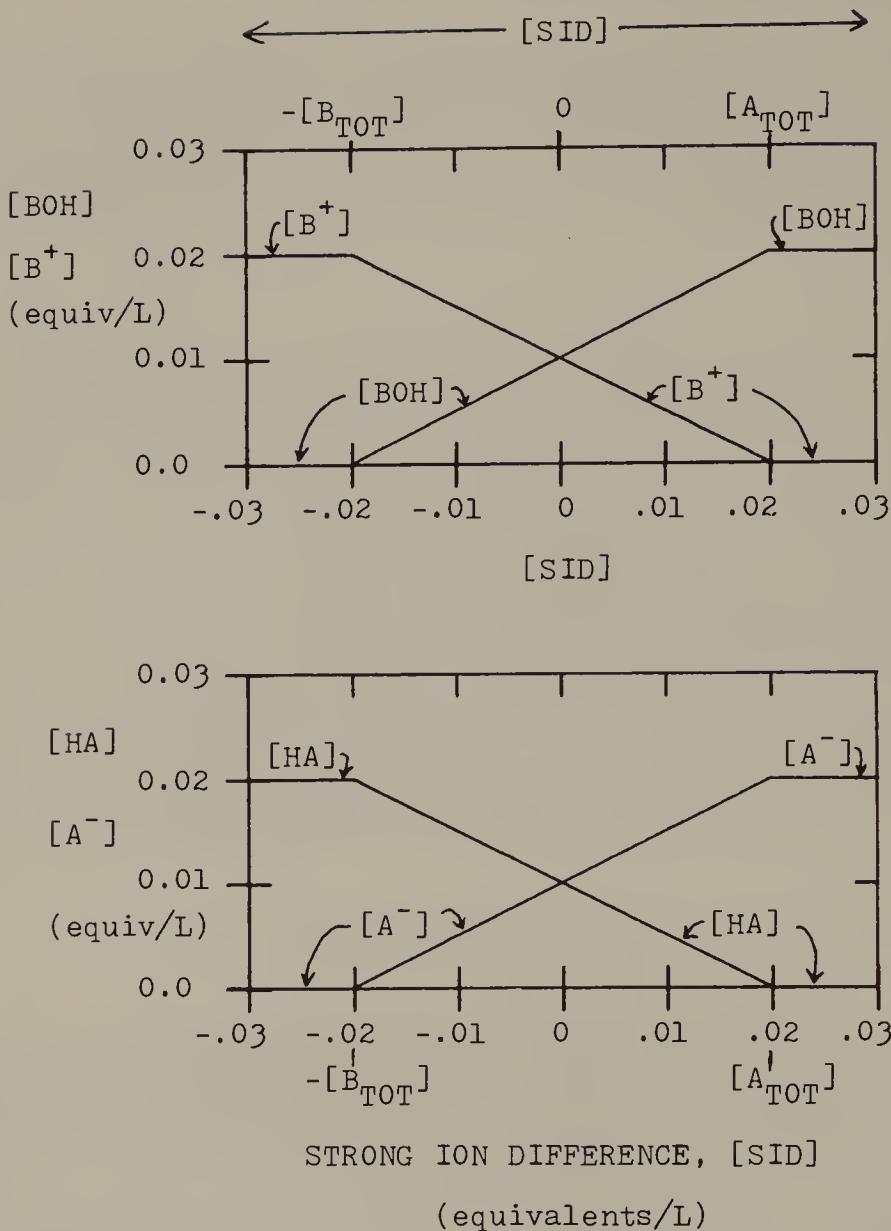
The results of such calculations for a rather simple mixture, a single weak acid and a single weak base, with the same [A<sub>TOT</sub>], [B<sub>TOT</sub>], K<sub>A</sub>, K<sub>B</sub>, and K<sub>w</sub>' values as used in the three previous sections, are presented in Figures 5.9, 5.10, 5.11, and 5.12. These figures should be carefully compared with their counterparts above to appreciate that the acid–base behavior of this mixture is not in any sense the sum of the behaviors of the separate weak acid and weak base solutions. The presence of each weak electrolyte profoundly affects the behavior of the other. The effect of HA is no longer restricted to positive [SID] values, nor is that of BOH restricted to negative [SID]; both weak electrolytes are involved over the



**Figure 5.9.**  $[H^+]$  and  $[OH^-]$  versus [SID] for a solution containing both the weak acid of Figure 5.1 and the weak base of Figure 5.6. The vertical scale in the lower half of the figure has been expanded to show how  $[H^+]$  and  $[OH^-]$  behave over the [SID] range from  $-[B_{TOT}]$  to  $+[A_{TOT}]$ . The horizontal scales for [SID] are the same, and in register, for both graphs.

full [SID] range from  $-[B_{TOT}]$  to  $+[A_{TOT}]$ . As a result, the special properties of the  $[SID] = [A_{TOT}]/2$  and  $[SID] = -[B_{TOT}]/2$  points are no longer present.

Such mixtures are much too complicated to think about qualitatively. We can only answer questions about their behavior by being able to calculate it. That is why the quantitative approach is essential. It permits us to understand such systems by calculating and plotting their behavior. In this particular case, that behavior seems rather simple, but it should be recognized that this is a very special case in that we have chosen  $[A_{TOT}] = [B_{TOT}]$  and  $K_B = K'_w/K_A$ . These special values account, among other things, for the symmetry of the curves in Figures 5.9 through 5.11 about



**Figure 5.10.**  $[BOH]$ ,  $[B^+]$ ,  $[HA]$ , and  $[A^-]$  versus  $[SID]$  for the same solution as in Figure 5.9. Compare with Figures 5.1 and 5.6.

the  $[SID] = 0$  point, and may be somewhat misleading. The general case can be as complex as you wish to make it!

### 5.8. GAMBLEGRAMS

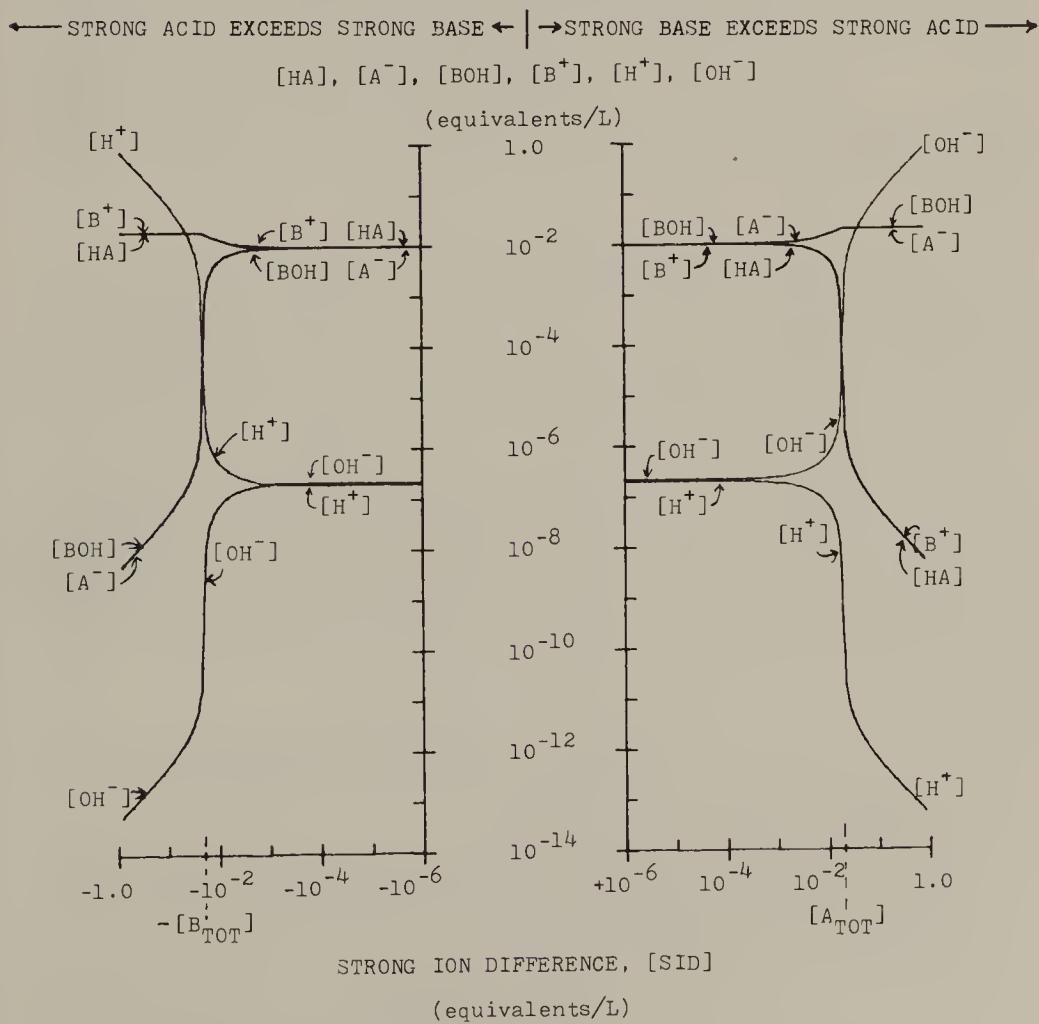
The properties of these various weak electrolyte solutions may also be looked at in terms of gamblegrams. A very wide variety of them could be drawn for a wide range of  $[SID]$  values in each solution considered so

far. The reader is urged to draw lots of them as an informative exercise. As illustrations, we present four of them for the interesting points  $[SID] = [A_{TOT}]/2$  in the weak acid solution and in the mixture, and  $[SID] = -[B_{TOT}]/2$  in the weak base solution and in the mixture. These are shown in Figure 5.13. They should provide a useful review of all the preceding analysis and discussion and should be easily understood on the basis of that analysis.

## 5.9. SALTS

Salts may be defined as substances that dissociate in aqueous solution to pairs of ions other than  $H^+$  or  $OH^-$ . These ions may be strong or weak, so that there are four cases to consider.

**Figure 5.11.** Log-log plots of all six dependent variables versus [SID] for the solution of Figure 5.9. Compare with Figures 5.2, 5.4, and 5.7.



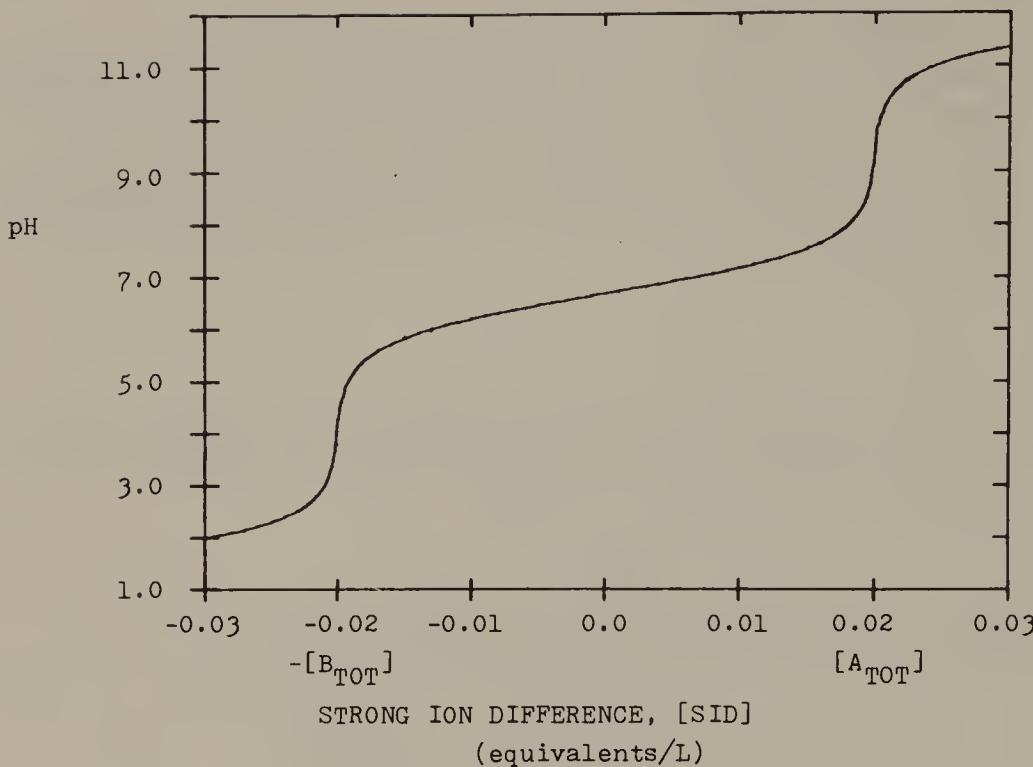


Figure 5.12. pH versus [SID] for the solution in Figure 5.9. Compare with Figures 5.3, 5.5, and 5.8.

1. If both ions are strong, then the solution is described quantitatively by the results in Chapter 4, with  $[SID] = 0$ . It will be acid–base neutral. Such solutions in fact are usually called “neutral salt solutions” even though, as already emphasized, they do not contain any “salt” per se, but only ions. Obvious examples are NaCl or KCl dissolved in water.
2. If the cation is strong, but the anion weak, then the solution is indistinguishable from a weak acid solution with  $[SID] = [A_{TOT}]$ . The analysis of Section 5.2 and 5.3 applies and shows that such a solution must be alkaline, with  $[H^+]$  less than  $[OH^-]$ . In this case, the cubic equation for  $[H^+]$  reduces to

$$[H^+] = \sqrt{K_w' \times K_A / [A_{TOT}]} \quad (5.9.1)$$

This means that as the salt concentration increases,  $[H^+]$  decreases, the solution becomes more alkaline.

3. If the cation is weak and the anion strong, then we have  $-[SID] = [B_{TOT}]$  and the analysis of Section 5.6 applies. In this case, the equation for  $[H^+]$  becomes

$$[H^+] = \sqrt{K_w' \times [B_{TOT}] / K_B} \quad (5.9.2)$$

This solution becomes more acidic as more salt is added.

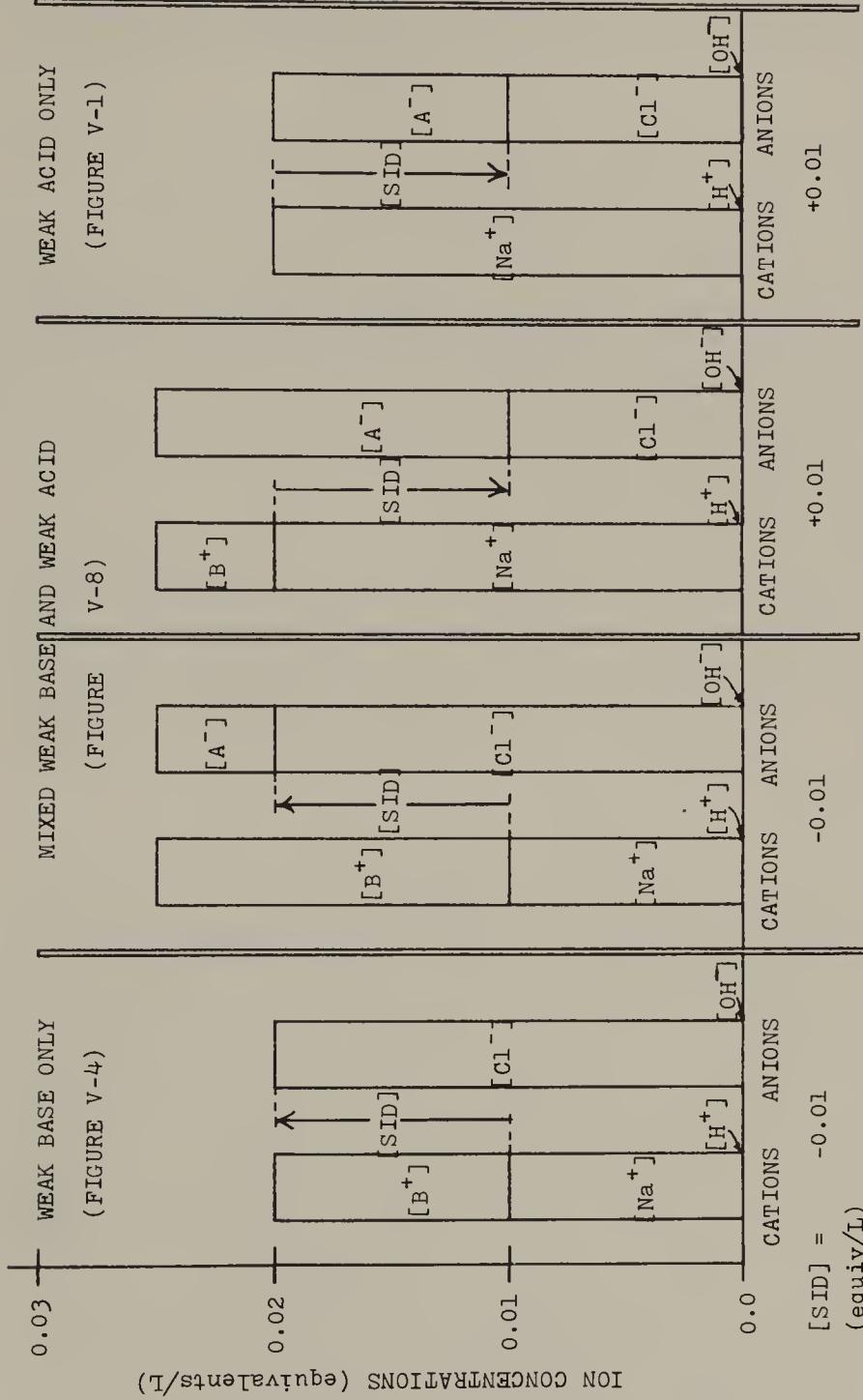


Figure 5.13. Gamblegrams for selected specific [SID] values in the solutions of Figures 5.1, 5.6, and 5.9. In order to simplify the figure, only  $Na^+$  and  $Cl^-$  have been used to achieve desired [SID] values. In all cases,  $[H^+]$  and  $[OH^-]$  are too small to be seen on this vertical scale.

4. If both cation and anion are weak, then  $[SID] = 0$  because there are no strong ions present, and the equation for  $[H^+]$  becomes

$$[H^+] = \sqrt{K_w' \times K_A/K_B}. \quad (5.9.3)$$

This tells us that whether the solution is acidic, basic, or neutral depends only on the ratio of the dissociation constants.

We assume throughout that the salt itself is completely dissociated in solution. If that is not the case, then we must add another equilibrium expression to our list of equations and another variable, the concentration of undissociated salt. There is no problem in doing this, and our numerical techniques will continue to provide any desired calculations for such a system. It is usually the case, however, that such salts are completely dissociated, and the only equilibria we must account for are the water, weak acid, or weak base dissociations.

In summary, salts of weak acids or weak bases, when dissolved in water, do not result in acid–base neutral solutions. Salts of strong bases and weak acids have alkaline solutions, salts of strong acids and weak bases have acidic solutions, and salts of weak bases and weak acids may have either, depending on the values of the two dissociation constants.

## 5.10. INDICATORS

If the two forms of a weak electrolyte have different colors in solution, then the color of their solution will change as  $[SID]$ , and therefore  $[A^-]/[HA]$  or  $[B^+]/[BOH]$ , changes. Because  $[H^+]$  also changes with  $[SID]$ , and there is a necessary correlation between these ratios and  $[H^+]$ , because of Equation (5.2.2) or (5.6.2), the color of such a solution is an indicator of its  $[H^+]$ . Theoretically, it should not matter how many other electrolytes are present; they cannot alter the validity of those equations. In practice, however, the presence of specific substances, as well as changes in total ionic content, may affect the value of  $K_A$  or  $K_B$  for an indicator substance, and corrections may have to be made for such effects. A solution with an indicator added is a mixture and should be analyzed in the terms of Section 5.7, but usually indicator substances are intensely colored, so that they need to be present at only very small  $[A_{TOT}]$  or  $[B_{TOT}]$  values. Their effects on the other weak electrolytes, and specifically on the  $[H^+]$  of the solution, can therefore usually be ignored.

A wide variety of such intensely colored substances is available, with dissociation constants covering the whole useful range of  $[H^+]$ . They may be used in lieu of pH meters for approximate measurements and are often called “pH indicators.” Historically, their use preceded by many years the glass-electrode electronic amplifier pH meter. “pH papers” are commercially available, impregnated with a series of selected indicator dyes.

The  $[H^+]$  (pH) of an unknown solution may be estimated by moistening a small strip of the paper with it and comparing the color obtained to a reference chart.

Such indicator substances may also be used to estimate  $[H^+]$  in otherwise inaccessible solutions, such as inside cells, provided  $K_A$  or  $K_B$  can be assumed to be known in such solutions. The results have generally been controversial, however, and the indirect procedure described in the following section is preferred.

Indicators have also contributed to the widespread misunderstanding of the meaning of Equations (5.2.2) and (5.6.2), relating  $[H^+]$  to  $[HA]/[A^-]$  or to  $[B^+]/[BOH]$ . The first paragraph of this section might be misinterpreted to indicate that if the indicator is sufficiently dilute, then the other electrolytes in the solution determine  $[H^+]$ , and  $[H^+]$  in turn determines  $[HA]/[A^-]$  for the indicator. It is very important to understand that this is not the case. It is the value of  $[SID]$  that determines the values of  $[H^+]$ ,  $[OH^-]$ , and the  $[A^-]$  and  $[HA]$ 's for all the weak acids in the solution, given fixed values for all the  $[A_{TOT}]$ 's. As already discussed, the equilibrium requirement for HA dissociation, Equation (5.2.2), tells us how these resulting values must be related, but it does not tell us how they are determined physically. The color of the indicator therefore tells us what the  $[H^+]$  is, but it does not determine the  $[H^+]$ , nor does the  $[H^+]$  determine it. They are both determined by the value of  $[SID]$ .

### 5.11. INDIRECT $[H^+]$ MEASUREMENT WITH WEAK ACID OR BASE

If the undissociated form of weak acid or weak base is lipid soluble, it can be expected to permeate most cell membranes easily, even though the ionized form will probably be impermeable. At equilibrium, if the substance is not actively metabolized or otherwise processed by the cell, the concentration of the undissociated molecule should be the same inside and outside the cell. If the dissociation constant can be assumed to be the same in both solutions, this equality of  $[HA]$  or  $[BOH]$  makes it possible to estimate  $[H^+]$  inside the cell on the basis of relatively simple concentration measurements.

To demonstrate the argument, suppose that we have a known volume of cells suspended in a known volume of solution, and a weak acid, HA, which is not metabolized by the cells, has a known  $K_A$  and enters the cells easily in the form HA. We add a known total amount,  $[A_{TOT}]_A$ , of HA to the cell suspension, mix, and wait for equilibrium. We then analyze an aliquot of the external solution for its concentration of HA plus  $A^-$ ,  $[A_{TOT}]_e$ , and its  $[H^+]_e$ . From these two values, the known  $K_A$  value, and Equations (5.2.2) and (5.2.3), we can calculate  $[HA]_e$  and  $[A^-]_e$  in the external solution. We also analyze an aliquot of the cells for their total content of HA +  $A^-$ , call it  $[A_{TOT}]_i$ . Assuming that  $[HA]_i = [HA]_e$ , we

now know  $[A_{TOT}]_i$  and  $[HA]_i$ , so we can calculate  $[A^-]_i$  from Equation (5.2.3) and then  $[H^+]_i$  from (5.2.2). Alternatively, because we know  $[A_{TOT}]_A$  and have measured  $[A_{TOT}]_e$ , we can calculate  $[A_{TOT}]_i$  instead of measuring it, assuming none of the originally added HA has been lost.

A weak base would obviously work just as well, with appropriate substitution of variables and equations. Ideally, the substance used should be easily measured at very low concentrations, so that radioactively labeled weak acids or bases are attractive candidates. A variety of substances is used by different laboratories, and the results obtained generally indicate that intracellular  $[H^+]$  is somewhat higher than extracellular, but that different cells can be very different.

## 5.12. TITRATION OF WEAK ELECTROLYTE SOLUTIONS

In Section 4.7 the process of titration was described as a systematic change in the [SID] of a solution brought about by adding small amounts of strong acid or strong base, while measuring  $[H^+]$  (pH), until acid–base neutrality is achieved. In a solution containing only strong ions, this procedure yields a measure of the original [SID] value in the solution. Neutrality is easily identified by virtue of the large and rapid pH change near that point on the pH versus [SID] curve.

As Figure 5.3 indicates, there are three interesting points on the pH versus [SID] curve for a weak acid solution, not just one. The first is at  $[SID] = [A_{TOT}]$ , where the pH (but not the  $[H^+]!$ ) goes through a relatively large and abrupt change as [SID] passes through it. Another is at  $[SID] = 0$ , where the same thing happens. Here also, there is nothing in the  $[H^+]$  curve to correspond to the pH behavior. The third point is at  $[SID] = [A_{TOT}]/2$ , where, as we have seen in Section 5.3,  $pH = pK_A$  or  $[H^+] = K_A$ . Neither the  $[H^+]$  nor the pH curve has any remarkable feature at this point. It is simply halfway from zero to  $[A_{TOT}]$  on the [SID] axis. Because the first two of these three points may be easily identified on the pH versus [SID] curve, and the third is just halfway between them, this curve permits us to estimate the values of  $[A_{TOT}]$ ,  $K_A$ , and the original [SID] value in the solution if these were not known. All of this only applies, it must be noted, when only a single weak acid is present. Figure 5.6 shows that corresponding information about a single weak base can be obtained from the pH titration curve of its solution.

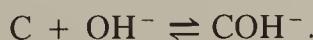
In the solution containing more than one weak electrolyte, on the other hand, the pH curve provides very little information. Large and abrupt pH changes can no longer be counted on to show up at the  $[SID] = [A_{TOT}]$  or  $[SID] = 0$  points, and there is no way to identify  $K_A$ 's or  $K_B$ 's. Titration of such a mixed solution to neutrality ( $pH = pK_w'/2$ ) may provide a very approximate measure of the original [SID] in the solution if it is assumed that [SID] at neutrality is reasonably close to  $[SID] = 0$ , but that may

be a very rough estimate in some cases. The term “titratable acidity” is often used in this context. It is usually defined as the amount of strong base that must be added to the solution in order to bring the pH to some arbitrary value, often that of standard arterial plasma, pH 7.40. It is then interpreted as if it were a measure of the amount of  $H^+$  present in the original solution. This completely erroneous interpretation seems to have arisen historically from the equally erroneous notion that  $H^+$  is a strong ion like  $K^+$ . “Titratable acidity” is a measure of how much [SID] had to be changed to bring pH to the value 7.40, but in a complex solution such as urine, it is not a measure of anything else unless the detailed composition of the solution is known, in which case the information it supplies is superfluous. The presence of  $CO_2$  in the solution changes the situation significantly, however, and we shall consider titratable acidity again in Chapter 9.

### 5.13. ADD-ON WEAK ACIDS AND WEAK BASES AND THEIR SALTS

Instead of dissociating to form an anion plus  $H^+$  or a cation plus  $OH^-$ , an uncharged molecule can become an ion by binding an  $H^+$  or an  $OH^-$ . A well-known example is the ammonia molecule,  $NH_3$ , which dissolves readily in water and then combines with  $H^+$  to form the ammonium ion,  $NH_4^+$ . A substance that binds  $H^+$  in this way will lower  $[H^+]$  in the solution, and therefore functions as a base. A substance that binds  $OH^-$  functions as an acid, because it raises  $[H^+]$ . It is convenient to refer to such substances as “add-on” acids or bases.

The quantitative analysis of solutions containing such substances follows exactly the same process already applied in this chapter. The only complication is the definition of equilibrium constants. For an add-on weak acid, C, the equilibrium reactions are

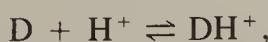


If we write the quantitative requirements for this equilibrium in this form:

$$[C] \times [OH^-] = (K'_w/K_C) \times [COH^-], \quad (5.13.1)$$

then the quantity  $K_C$  behaves just like  $K_A$  for a dissociating weak acid. The larger the value of  $K_C$ , the stronger the add-on weak acid, and the larger  $[H^+]$  is for a given  $[C_{TOT}]$  and [SID]. All the discussion of dissociating weak acid solution properties in Section 5.3 applies to a solution of C plus  $COH^-$ , and Figures 5.1, 5.2, and 5.3 show the behavior of such a solution, with [C] in place of [HA] and  $[COH^-]$  in place of  $[A^-]$ .

For an add-on weak base, the equilibrium reactions are



and the equilibrium constraint may be written

$$[D] \times [H^+] = (K_w/K_D) \times [DH^+]. \quad (5.13.2)$$

$K_D$  defined by this equation functions just like  $K_B$  for a dissociating weak base in Equation (5.6.2). This system's total acid–base behavior is just like that shown in Figures 5.6, 5.7, and 5.8, with  $[D]$  in place of  $[BOH]$  and  $[DH^+]$  in place of  $[B^+]$ .

Many of the weak acids and bases in body fluids are proteins, and their weak properties are mainly due to their amino side groups, which function in solution as add-on bases.

Our notion of a salt must be extended by these add-on types of acids and bases, because only their ionic forms can become salts. For example, if HCl is added to a solution of an add-on weak base, D, to the point that  $-[SID] = [D_{TOT}]$ , and the solution is then evaporated to dryness, crystals of the substance  $DH^+Cl^-$  may be obtained. Such “salts” are usually called “hydrochlorides” rather than just chlorides, to emphasize that they require both  $H^+$  and  $Cl^-$  in order to exist.

A significant low-molecular-weight add-on weak base in some body fluids is ammonia,  $NH_3$ . It is a gas that dissolves in water and then combines with  $H^+$  to form the cation  $NH_4^+$ , called the ammonium ion. The name forces comparison with sodium and potassium ions, but it is essential to realize that they are strong ions whereas  $NH_4^+$  is a weak cation. Historically,  $NH_4^+$  was supposed to be formed by dissociation of the hypothetical weak base  $NH_4OH$ , formed by the combination of  $NH_3$  with water. No evidence has been presented that such a substance exists in aqueous solution.  $NH_4^+$  is formed instead by the combination of an  $H^+$  with a dissolved  $NH_3$  molecule:



$NH_3$  is therefore an add-on weak base. Figures 5.6, 5.7, and 5.8 therefore describe qualitatively the acid–base behavior of its solutions at constant  $[N_{TOT}] = [NH_3] + [NH_4^+]$ . For a precise quantitative description, these figures must be redrawn using the appropriate value for  $K_B$ , as well as  $[N_{TOT}]$ .

#### 5.14. OTHER VARIABLES

$[SID]$  has been treated as if it were the only independent variable in this chapter; we have assumed throughout that  $[A_{TOT}]$  or  $[B_{TOT}]$  were held constant, and only  $[SID]$  was allowed to vary. The practical justification for this treatment is that significant changes in  $[SID]$  do frequently occur in body fluids, but weak electrolyte concentrations generally change very little. The  $[SID]$  value of circulating plasma is continually modified by the actions of the gastrointestinal tract and the kidneys, and may change sig-

nificantly over periods of hours. The [SID] of ISF may be altered locally by the action of individual cells that may ‘pump’  $\text{Na}^+$  or  $\text{K}^+$  or  $\text{Cl}^-$ , or produce lactate $^-$ . (Lactate $^-$  functions as a strong ion in body fluids because the  $K_A$  for lactic acid is very large, on the order of  $5 \times 10^{-4}$  Eq/liter.)

Weak electrolytes in body fluids are mainly proteins, and their concentrations normally vary by small amounts, and very slowly, except in traumatic situations such as severe burns or hemorrhage. Nonprotein weak electrolytes are generally present at  $[A_{\text{TOT}}]$  values on the order of 1 mM, and their effects on body-fluid acid–base behavior are negligible compared to those of carbon dioxide, as we shall see in Chapter 7. In addition, appropriate slope calculations show that equivalent changes in  $[\text{H}^+]$  require twice the change in  $[A_{\text{TOT}}]$  as in [SID].

Temperature, osmolarity, and ionic strength should also be mentioned as “other variables,” because changes in any of them will alter the values of the dependent variables in weak electrolyte solutions. Fortunately, body fluids function, and are usually analyzed at 37°C, so temperature changes are not normally important. Body fluid osmolarity is very tightly regulated by the hypothalamus–posterior pituitary–kidney system and can also be conveniently assumed to be constant, as can ionic strength. Whenever changes in any of these quantities do become significant, their effects are easily incorporated into the quantitative calculations used here. Generally, this must be done in terms of empirical relationships rather than simple theory. Because our goal here is basic quantitative understanding, we shall continue to assume that changes in all these other variables can be ignored.

### 5.15. SUMMARY

1. Weak electrolytes introduce additional equilibria involving  $\text{H}^+$  and  $\text{OH}^-$  in solution and therefore require more complicated mathematical analysis. Computer-implemented numerical solutions are needed to get results from the relevant equations (See Appendix).
2. In a single weak acid solution, there are four dependent variables,  $[\text{HA}]$ ,  $[\text{A}^-]$ ,  $[\text{H}^+]$ , and  $[\text{OH}^-]$ , whose values are determined physically by two independent variables, [SID] and the total quantity of weak acid present,  $[A_{\text{TOT}}]$  ( $= [\text{HA}] + [\text{A}^-]$ ), and the parameters  $K_w'$  and  $K_A$ . The quantitative relationships are displayed in Figures 5.1, 5.2, and 5.3.
3. Buffering refers to the rate of change of  $[\text{H}^+]$  with change in [SID].  $[\text{H}^+]$  buffer strength is the reciprocal of the slope of the  $[\text{H}^+]$  versus [SID] curve; pH buffer strength is the reciprocal of the slope of the pH versus [SID] curve.
4. For [SID] values between zero and  $[A_{\text{TOT}}]$  in a single weak acid solution, the presence of the weak acid reduces the buffer strength, but changes the

$[H^+]$  value. At  $[SID] = [A_{TOT}]/2$ ,  $[H^+] = K_A$ ,  $pH = pK_A$ ,  $[HA] = [A^-] = [SID] = [A_{TOT}]/2$ ,  $[H^+]$  buffer strength =  $-[A_{TOT}]/4K_A$ , and pH buffer strength = 0.6  $[A_{TOT}]$  Eq/liter.

5. In a single weak base solution, the four dependent variables,  $[BOH]$ ,  $[B^+]$ ,  $[OH^-]$ , and  $[H^+]$ , are determined physically by the two independent variables,  $[SID]$  and  $[B_{TOT}] (= [BOH] + [B^+])$ , and the parameters  $K'_w$  and  $K_B$ , as shown in Figures 5.6, 5.7, and 5.8.
6. In a single weak base solution at  $[SID] = -[B_{TOT}]/2$ ,  $[OH^-] = K_B$ ,  $[H^+] = K'_w/K_B$ ,  $[BOH] = [B^+] = -[SID] = [B_{TOT}]/2$ ,  $[H^+]$  buffer strength =  $-[B_{TOT}] \times K_B/4K'_w$ , pH buffer strength = 0.6  $[B_{TOT}]$  Eq/liter.
7. Mixtures of weak electrolytes have very complicated acid–base behavior. A special case is shown in Figures 5.9, 5.10, 5.11, and 5.12.
8. The acid–base properties of salts in solution depend directly on the dissociation constants of the acids and bases from which they are formed.
9. Indicator substances are useful and indicate the value of  $[H^+]$  because although  $[HA]$ ,  $[A^-]$ , and  $[H^+]$  are each physically determined by the value of  $[SID]$ , they must also satisfy the equilibrium relationships that  $[H^+] = K_A \times [HA]/[A^-]$ .
10. Titration of a weak electrolyte solution may provide useful information only if a single weak electrolyte (and no  $CO_2$ ) is present.
11. Neutral molecules may also function as weak acids or bases by associating with an  $OH^-$  or  $H^+$  ion, rather than by dissociating.
12. Other independent variables, such as temperature and osmolarity, are theoretically important, but may be treated as constants for body fluids because they are normally well regulated in the body.

## APPENDIX

### 5A.1. HOW TO FIND VALUES FOR $[H^+]$ , $[OH^-]$ , $[HA]$ , AND $[A^-]$ FROM EQUATIONS (5.2.1), (5.2.2), 5.2.3), AND (5.2.4)

The first step is to “separate variables.” To do this, we eliminate  $[OH^-]$  and  $[A^-]$  from Equation (5.2.4) in favor of  $[H^+]$  by using the other three equations. Thus, from (5.2.1),  $[OH^-] = K'_w/[H^+]$ . From (5.2.3),  $[HA] = [A_{TOT}] - [A^-]$ . If we substitute this expression for  $[HA]$  into (5.2.2) and rearrange, we get

$$[A^-] = K_A \times [A_{TOT}]/(K_A + [H^+]).$$

Substituting these expressions for  $[A^-]$  and  $[OH^-]$  in (5.2.4), we get

$$[SID] + [H^+] - K'_w/[H^+] - K_A \times [A_{TOT}]/(K_A + [H^+]) = 0. \quad (5A.1.1)$$

This can be cleared of fractions and written in polynomial form as

$$\begin{aligned} [H^+]^3 + \{K_A + [SID]\} \times [H^+]^2 + \{K_A \times ([SID] \\ - [A_{TOT}]) - K'_w\} \times [H^+] - K_A \times K'_w = 0. \end{aligned} \quad (5A.1.2)$$

Equations (5A.1.1) or (5A.1.2) may be written, and conveniently thought about, as  $F([H^+]) = 0$ .

It is merely a matter of tedious algebra to show by similar substitutions and rearrangements that a similar equation can be written for each of the other three dependent variables. Given values for [SID],  $[A_{TOT}]$ ,  $K_A$ , and  $K'_w$ , we should "in principle" now be able to calculate values for the four dependent variables from these equations, just as we did from the quadratic equations for  $[H^+]$  and  $[OH^-]$  in Chapter 4. As already mentioned, that process is so long and tedious as to be impractical, but several computer-implemented numerical methods for getting all that tedious calculation done by machine are available, and these make it possible to get the information from these equations just as easily as from the quadratics of Chapter 4.

## 5A.2. ITERATIVE NUMERICAL METHOD FOR SOLVING (5A.1.1)

Inspection of (5A.1.1) shows that it is a monotonic function of  $[H^+]$ , over the physiologically interesting range for  $[H^+]$ , and also that if a guessed value for the solution,  $[H_g^+]$ , is substituted for  $[H^+]$ , then if  $[H_g^+]$  is larger than the correct value,  $F([H_g^+])$  will be larger than zero, or positive, whereas if  $[H_g^+]$  is too small,  $F([H_g^+])$  will be negative. We can therefore tell from the sign of  $F([H_g^+])$  which way to correct our guess. Also, the closer  $[H_g^+]$  is to the correct value, the closer  $F([H_g^+])$  is to zero. All we need is a systematic way of revising our initial guess in the light of these properties of  $F([H_g^+])$  in order to arrive at a value for  $[H_g^+]$  that is as close as we please to the correct value.

Such a systematic process is the following. Let us set a value, to be called HI, that is larger than any possible correct value of  $[H^+]$ . For our purposes, this could be 1.0, as  $[H^+]$  is never this large in physiologically meaningful situations. Also set a value, called LO, that is smaller than any possible  $[H^+]$ . The value of  $K'_w$  is a useful such value. Now set our initial guess for  $[H_g^+]$  to the value  $\sqrt{HI \times LO}$ .

Now calculate the value of  $F([H_g^+])$ . We have two questions to ask. First, is it acceptably close to zero? If so, the value of  $[H_g^+]$  we have is acceptably close to the correct value. If  $F([H_g^+])$  is too large, the second question is, is it positive or negative? If it is positive,  $[H_g^+]$  is too large, so we reduce the value of HI to the current value of  $[H_g^+]$  and go back to calculate a new value for  $[H_g^+]$  from  $\sqrt{HI \times LO}$ . If  $F([H_g^+])$  is negative,  $[H_g^+]$  is too small, so we raise LO to the current value of  $[H_g^+]$  and use the new LO and old HI to calculate a new  $[H_g^+]$ . By this procedure, successive values of HI and LO will come closer and closer to each other and to the correct value of  $[H^+]$ , and the value of  $[H_g^+]$  will rapidly converge also to that value.

The meaning of "acceptably close to zero" in the first question above has to be defined at the beginning of the procedure by setting a value, which we call CRIT (for "criterion") in our computer programs for this procedure. CRIT is usually  $10^{-6}$ .

The advantage to this procedure is that it works very well for all the more complex forms of  $F([H^+])$  that arise in the following chapters. All we have to do is to add the necessary terms to Equation (5.A.1) for each of the added weak ions, expressed as functions of  $[H^+]$ , which they can always be. Its major dis-

advantage is that it takes about 15 to 20 cycles of repetition to satisfy a CRIT of  $10^{-6}$ . Other related methods are faster for this chapter, but tend to be significantly more complicated, and slower, for subsequent chapters. This procedure also has the advantage of being rather simple to understand and to program in any computer language or on a programmable calculator. Figure 5A.1 summarizes the procedure in the form of a flow chart, from which it is a simple matter to write such a program. Once it has been written and debugged, such a program provides us with the effective equivalent of the quadratic formula solutions we used in Chapter 4, Equations (4.3.4) and (4.3.5). By systematically increasing [SID] in small steps over a desired range and calculating  $[H^+]$  for each [SID] value, graphs may also be plotted by computer if the necessary hardware is available. All the graphs in this book were plotted in this way, using a Hewlett-Packard 9810A desk-top programmable calculator and 9861A plotter.

### 5A.3. HOW TO CALCULATE $[OH^-]$ , $[HA]$ , AND $[A^-]$ ONCE $[H^+]$ IS KNOWN

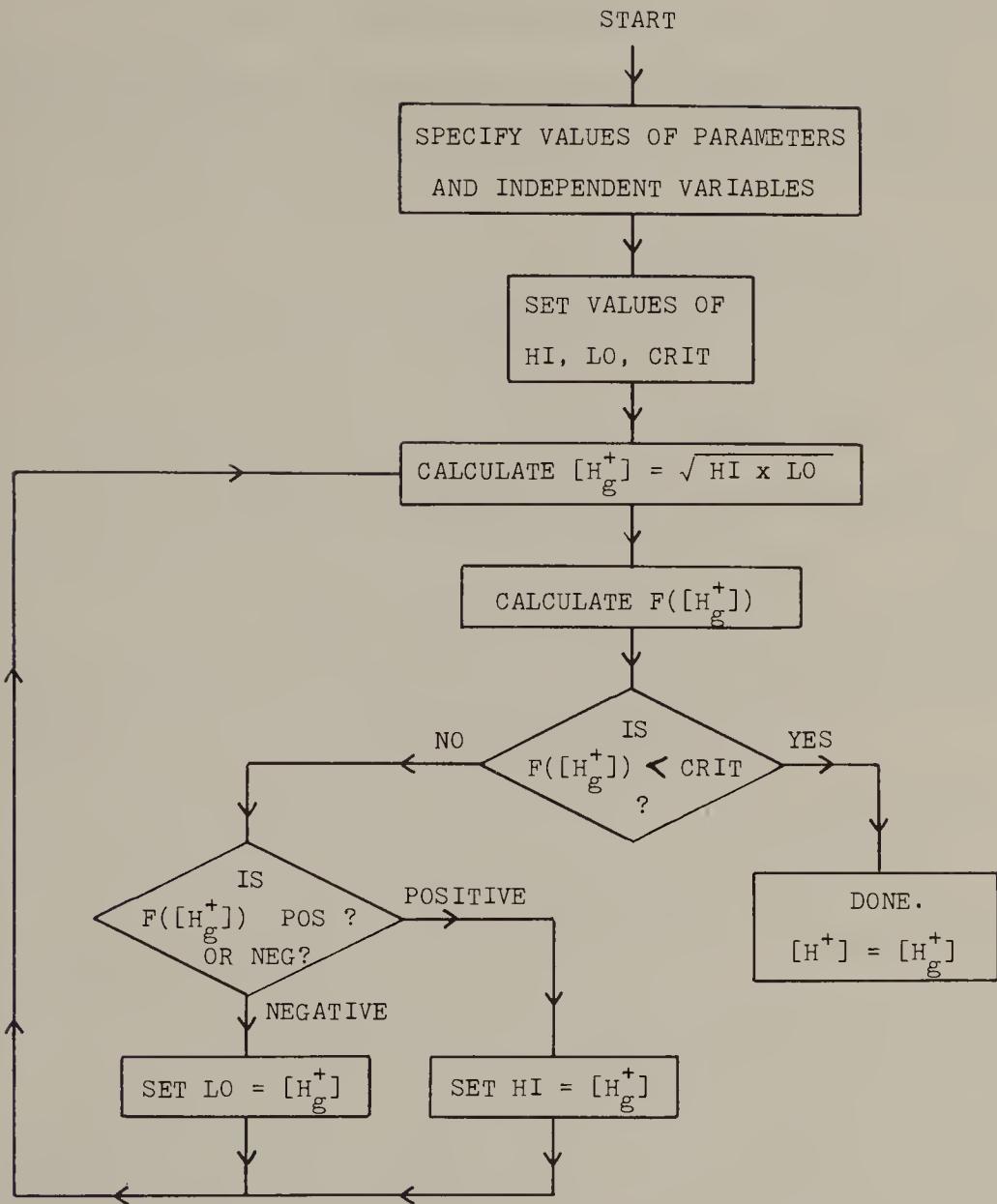
Theoretically, we could find the other three dependent variables' values by the same procedure, but we can save an enormous amount of calculating time by noticing that in order to get to Equation (5.A.1), we have already expressed them in terms of  $[H^+]$ . Once we have a value for  $[H^+]$ , therefore, it is much more efficient to use those expressions to calculate values of  $[OH^-]$ ,  $[HA]$ , and  $[A^-]$ . To summarize, they are

$$[OH^-] = K_w/[H^+] \quad [A^-] = K_A \times [A_{TOT}]/(K_A + [H^+]) \\ [HA] = [A_{TOT}] - [A^-].$$

The most important aspect of these equations is that they are simple rearrangements of the original system-defining equations and not new expressions designed to tell us how, for example,  $[OH^-]$  depends on  $[H^+]$ . It does not, for both  $[OH^-]$  and  $[H^+]$  are dependent variables. Single equations can always be used to calculate a value of one quantity when all the others are known, but understanding which variables depend on which, in physical terms, requires the whole set of simultaneous equations, not just one of them. It is essential to keep this basic distinction between mathematical and physical dependence clearly in mind when using these equations.

### 5A.4.A COMPUTER PROGRAM FOR THIS PROCEDURE

Although the reader who has reached this point is very likely to be able to write her/his own program, the following is presented as an example, in FORTRAN, to help the beginner to get started. This program will simply print out the values of all the independent variables and parameters listed in the initial DATA statements, followed by the values of the dependent variables corresponding to them. It can easily be expanded to print out a table of values for a series of [SID] or  $[A_{TOT}]$  or  $K_A$  values, or any desired combination.



**Figure 5A.1.** Flow chart for numerical procedure to solve  $[H^+]$  equations. Diamond-shaped boxes indicate decisions; rectangular boxes calculations or other procedures.  $F([H_g^+]) = 0$ , is the equation to be solved for  $[H^+]$ . See text of 5A.2 for details.

## FORTRAN PROGRAM

```

C THIS PROGRAM SOLVES EQUATION (5A.1.1) FOR THE VALUES
C OF [SID], [ATOT], KA, AND KW LISTED IN THE DATA STATE-
MENTS
C
C      DATA AKW,ATOT,AKA/4.4E-14,0.020,2.0E-7/
C      DATA SID/0.010/
C      DATA HI,HLO/1.0,4.4E-14/
C
C      SET UP HEADING FOR PRINTOUT
C
C      WRITE(6,400)
C
C      CALCULATE VALUE OF H+ FROM HI AND LO
C
C      10      H = SQRT(HI*HLO)
C
C      CALCULATE OH- AND A- AND THEN F(H +)
C
C      OH = AKW/H
C      A = AKA*ATOT/(AKA + H)
C      FH = SID + H - OH - A
C
C      TEST TO SEE IF FH IS SMALL ENOUGH, IF SO, GO TO PRINT OUT.
C      IF(ABS(FH).LE.1.0E-6) GO TO 50
C
C      IF NOT, TEST IF FH IS POS. OR NEG. AND ACT ACCORDINGLY.
C
C      IF(FH)40,50,60
C
C      FOR NEG. FH, CHANGE HLO.
C
C      40      HLO = H
C              GO TO 10
C
C      FOR POS. FH, CHANGE HI.
C
C      60      HI = H
C              GO TO 10
C
C      PRINT OUT ALL VALUES, AFTER FIRST CALCULATING PH AND
C      HA.
C
C      50      PH = - ALOG10(H)
C              HA = ATOT - A

```

```

        WRITE(6,401)AKW,AKA,ATOT,SID,H,PH,OH,A,HA
        STOP
400      FORMAT(25X,'SINGLE WEAK ACID SOLUTION',/,4X,
     A 'KW',8X,'KA',7X,'ATOT',6X,'SID',8X,'H+',8X,
     B 'PH',8X,'OH',8X,'A-',8X,'HA')
401      FORMAT(9E10.3)
        END

```

Similar programs can be written easily for hand-held programmable calculators by working from the flowchart in Figure 5A.1.

## 5A.5. SLOPES AND BUFFER STRENGTHS: STRONG IONS ONLY

### 5A.5.1 Slope of $[H^+]$ Versus $[SID]$ Curve and $[H^+]$ Buffer Strength

In this case,  $[H^+]$  is determined by Equation (4.2.3):

$$[H^+]^2 + [SID] \times [H^+] - K'_w = 0. \quad (5A.5.1)$$

The slope of this curve is just the derivative,  $d[H^+]/d[SID]$ , which is easily found by taking the derivative of each term with respect to  $[SID]$  and solving the result for  $d[H^+]/[SID]$ :

$$2[H^+] \times d[H^+]/d[SID] + [SID] \times d[H^+]/d[SID] + [H^+] - 0 = 0, \quad (5A.5.2)$$

so that

$$d[H^+]/d[SID] = \frac{-[H^+]}{(2[H^+] + [SID])}. \quad (5A.5.3)$$

The  $[H^+]$  buffer strength is simply the reciprocal of this:

$$\begin{aligned} \text{[H}^+\text{] buffer strength}_{\text{strong ions only}} &= \frac{-(2[H^+] + [SID])}{[H^+]}. \end{aligned} \quad (5A.5.4)$$

When  $[SID]$  is negative and larger in magnitude than  $10^{-7}$  Eq/liter, we know from Chapter 4 that  $[H^+] = -[SID]$ , so that (5A.5.4) =  $-1$ , corresponding to the  $45^\circ$  straight line on the left of Figure 4.2.

When  $[SID]$  is positive, the algebra becomes much more tedious, because now we must use Equation (4.3.4):

$$[H^+] = \sqrt{K'_w + ([SID]/2)^2} - ([SID]/2).$$

Substituting this expression into (5A.5.4) and simplifying gives

$$\begin{aligned} \text{[H}^+\text{] buffer strength}_{\text{[SID] positive}} &= \frac{-([SID]^2/2 + [SID] \times \sqrt{K'_w + ([SID]/2)^2} + 2K'_w)}{K'_w}. \end{aligned}$$

Because we are only interested in situations for which  $[SID]^2$  is orders of magnitude larger than  $K'_w$ , we may neglect  $K'_w$  wherever it occurs additively in the

numerator of this expression. The result is

$$\frac{[\text{H}^+] \text{ buffer strength}}{\begin{array}{l} \text{strong ions only} \\ \text{positive [SID] only} \end{array}} \equiv \frac{-[\text{SID}]^2}{K'_w}. \quad (5A.5.5)$$

### 5A.5.2. pH Buffer Strength

We know from calculus that

$$d\{\log_{10}(y)\}/dx = \frac{1}{\log_e 10} \times \frac{1}{y} \times \frac{dy}{dx}.$$

Because  $\text{pH} = -\log_{10}([\text{H}^+])$ , this means that

$$d\text{pH}/d[\text{SID}] = \frac{-1}{2.30} \times \frac{1}{[\text{H}^+]} \times \frac{d[\text{H}^+]}{d[\text{SID}]} \quad (5A.5.6)$$

Substituting from (5A.5.4) for  $d[\text{H}^+]/d[\text{SID}]$ , taking the reciprocal, and rearranging yield:

$$\frac{\text{pH buffer strength}}{\text{strong ions only}} = 2.3 \times |[\text{SID}]|. \quad (5A.5.7)$$

This remarkably simple result applies whether [SID] is positive or negative.

## 5A.6. SLOPES AND BUFFER STRENGTHS: SINGLE WEAK ACID

### 5A.6.1. $[\text{H}^+]$ Buffer Strength

In this case, the  $[\text{H}^+] - [\text{SID}]$  relationship is Equation (5A.1.2). Assuming  $[\text{A}_{\text{TOT}}]$  constant, we differentiate each term of this equation with respect to [SID] and solve the result for  $d[\text{H}^+]/d[\text{SID}]$ . Eventually, this yields

$$\frac{d[\text{H}^+]}{d[\text{SID}]} = \frac{-([\text{H}^+]^2 + K_A \times [\text{H}^+])}{3[\text{H}^+]^2 + 2[\text{H}^+] \times (K_A + [\text{SID}]) + K_A \times ([\text{SID}] - [\text{A}_{\text{TOT}}]) - K'_w}.$$

The general expression for the  $[\text{H}^+]$  buffer strength is simply the reciprocal of this expression, and this may be used to calculate numerical values for the  $[\text{H}^+]$  buffer strength for any desired values of [SID],  $[\text{A}_{\text{TOT}}]$ , and  $K_A$ . Conventionally, the most interesting point is that for which  $[\text{SID}] = [\text{A}_{\text{TOT}}]/2$ . As we have seen, so long as  $K_A$  is not too far from  $\sqrt{K'_w}$ , then  $[\text{H}^+] = K_A$  at this point, and the above expression simplifies to

$$d[\text{H}^+]/d[\text{SID}] = -1/\{5/2 + [\text{A}_{\text{TOT}}]/4K_A - K'_w/2K_A^2\}.$$

So long as  $[\text{A}_{\text{TOT}}]$  is on the order of milliequivalents per liter or larger, the first and last terms in the denominator are negligible compared to the second. Dropping

them and taking the reciprocal, we have

$$\begin{aligned} \text{[H}^+\text{] buffer strength} \\ \text{single weak acid only} &\cong \frac{-[\text{A}_{\text{TOT}}]}{4K_A} \\ \text{at [SID]} &= [\text{A}_{\text{TOT}}]/2 \end{aligned} \quad (5\text{A}.6.1)$$

### 5A.6.2. pH Buffer Strength

Using the above general expression for  $d[\text{H}^+]/d[\text{SID}]$  in Equation (5A.5.6), we can calculate  $d\text{pH}/d[\text{SID}]$  and hence pH buffer strength for any desired [SID] and  $[\text{A}_{\text{TOT}}]$  values. At the special point  $[\text{SID}] = [\text{A}_{\text{TOT}}]/2$ , this results in

$$\begin{aligned} \text{pH buffer strength} \\ \text{single weak acid} &\cong \log_e 10 \times [\text{A}_{\text{TOT}}]/4 = 0.576[\text{A}_{\text{TOT}}] \\ \text{at [SID]} &= [\text{A}_{\text{TOT}}]/2 \end{aligned} \quad (5\text{A}.6.2)$$

### 5A.7. SLOPES AND BUFFER STRENGTHS: SINGLE WEAK BASE

The procedure here is identical to that followed in Section 5A.2 above except that the  $[\text{H}^+]$ -[SID] relationship in this case is the analogous equation to (5A.1.2) obtained by combining Equations (5.6.1) through (5.6.4), namely:

$$\begin{aligned} [\text{H}^+]^3 + ([\text{SID}] + [\text{B}_{\text{TOT}}] + K'_w/K_B) \times [\text{H}^+]^2 + (K'_w/K_B) \\ \times ([\text{SID}] - K_B) \times [\text{H}^+] - K'^2_w/K_B = 0. \end{aligned} \quad (5\text{A}.7.1)$$

The results are those listed in Section 5.6.

### 5A.8. FORMULAS

- When  $[\text{SID}] = [\text{A}_{\text{TOT}}]/2$ , then  $[\text{H}^+]$  and  $[\text{OH}^-]$  are both several orders of magnitude smaller than [SID] or  $[\text{A}^-]$ , and the electrical neutrality equation, (5.2.4), can be written as  $[\text{A}^-] = [\text{SID}]$ , so that  $[\text{HA}] (= [\text{A}_{\text{TOT}}] - [\text{A}^-])$  also = [SID], and equation (5.2.2) then becomes

$$\begin{aligned} [\text{H}^+] &= K_A \times \{([\text{A}_{\text{TOT}}] - [\text{SID}])/[\text{SID}]\} \\ &= K_A \times \{([\text{A}_{\text{TOT}}]/[\text{SID}]) - 1\}. \end{aligned}$$

At  $[\text{SID}] = [\text{A}_{\text{TOT}}]/2$  exactly, this becomes just  $[\text{H}^+] = K_A$ . Taking the reciprocal of both sides and then taking logarithms yield

$$\text{pH} = \text{p}K_A - \log_{10} \{([\text{A}_{\text{TOT}}]/[\text{SID}]) - 1\}.$$

Warning: these results require that only one weak acid, and no  $\text{CO}_2$ , is present, and that *both*  $[\text{H}^+]$  and  $[\text{OH}^-]$  are negligibly small compared to [SID] and  $[\text{A}^-]$ .

- In a solution containing only the salt “ $\text{Na}^+\text{A}^-$ ”,  $[\text{SID}] = [\text{A}_{\text{TOT}}]$ , and  $K_A$  is generally orders of magnitude smaller than  $[\text{A}_{\text{TOT}}]$ . Equation (5A.1.2) can

therefore be reduced to

$$[\text{H}^+]^3 + [\text{A}_{\text{TOT}}] \times [\text{H}^+]^2 - K'_w \times [\text{H}^+] - K_A \times K'_w = 0.$$

$[\text{H}^+]$  is always much less than  $K_A$  when  $[\text{SID}] = [\text{A}_{\text{TOT}}]$ , so that the first and third terms are negligible, and this becomes

$$[\text{A}_{\text{TOT}}] \times [\text{H}^+]^2 = K_A \times K'_w, \quad \text{or} \quad [\text{H}^+] = \sqrt{K_A \times K'_w / [\text{A}_{\text{TOT}}]}.$$

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## CHAPTER SIX

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# STRONG IONS PLUS CARBON DIOXIDE (ISOLATED, INTACT INTERSTITIAL FLUID)

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### 6.1. INTRODUCTION

Carbon dioxide,  $\text{CO}_2$ , is the major end product of body metabolism. Each adult produces, on the average, about 360 liters, or 1.5 pounds or 14 moles of  $\text{CO}_2$ , each 24 hours.  $\text{CO}_2$  is a gas under physiological temperatures and pressures and is moderately soluble in water. It also reacts with water chemically, so that its solution behaves much like a weak acid solution.  $\text{CO}_2$  is therefore an important substance in body-fluid acid-base chemistry, equally as important as the strong ions.

Normally, the body is an open system for  $\text{CO}_2$ , and the circulatory and respiratory systems function so that  $\text{CO}_2$  is eliminated from the lungs as fast as it is produced in the tissues. Its concentration in body fluids therefore usually remains within fairly narrow limits, but can change rapidly within those limits. Such changes are important in body-fluid acid-base behavior.

Adding  $\text{CO}_2$  to a solution of strong ions with a negative [SID] value turns out to have no significant effect on  $[\text{H}^+]$ , as the subsequent analysis will show. When [SID] is positive, however, adding  $\text{CO}_2$  raises  $[\text{H}^+]$  dramatically. Our major goal for this chapter is to understand these effects in quantitative terms. We shall then be ready to understand thoroughly the acid-base behavior of isolated interstitial fluid with its in vivo  $\text{CO}_2$  content intact.

Before applying our usual analytical procedures to  $\text{CO}_2$  solutions, how-

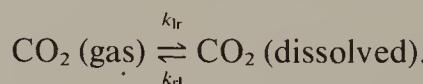
ever, we must first look carefully at two features of such solutions that distinguish them from solutions of nonvolatile weak acids or bases, such as those we analyzed in Chapter 5. One of these is the concept of partial pressure as a convenient measure of concentration (Section 6.2). The other is the series of physical and chemical processes that occurs when  $\text{CO}_2$  is equilibrated with water (Section 6.3). More detailed treatments may be found in [1, 2].

## 6.2. PARTIAL PRESSURE IN SOLUTIONS

Introducing gaseous substances into solutions requires another look at the concept of effective concentration or chemical availability. From the gas law,  $P = nRT/V$ , we know that the hydrostatic pressure in a gas sample is proportional to the concentration,  $n/V$ . In terms of the kinetic-molecular picture of matter, this pressure represents an equilibrium between the effective collision frequency of gas molecules against the walls of the container, or "escaping tendency," and the restraining effect of those walls. Pressure can be thought of as a number that tells us the rate at which the gas molecules would leave the region in question if the walls were suddenly removed. It is thus a measure of molecular "availability" or "activity," just as concentration is.

In the mixture of gases, the molecules of each chemical species bounce around independently, so that a corresponding fraction of the total pressure can be attributed to each substance present in the mixture, on the basis of its fractional concentration. Furthermore, because the molecules do move independently, that part of the total pressure must be just the pressure that the substance would exert if it alone occupied the available volume. It therefore follows that in a gas sample the sum of all these partial pressures due to the individual chemical species must equal the total pressure. More important, each partial pressure is a measure of the effective concentration of that particular gaseous substance in the mixture, and is therefore the appropriate variable to use whenever reactions involving these gaseous substances are analyzed. The rate at which a gaseous substance reacts, physically or chemically, depends on its partial pressure.

In the case of  $\text{CO}_2$ , we are interested only in the very simple physical reaction of dissolving in water:



From the preceding discussion, we can say that the left to right reaction proceeds at a rate proportional to the partial pressure of  $\text{CO}_2$  in the gas phase, which we symbolize for convenience as  $P_{\text{C}}(\text{g})$ . The right to left reaction, by the law of mass action, should proceed at a rate proportional

to the concentration of dissolved CO<sub>2</sub> molecules, [CO<sub>2</sub>(dissolved)]. At equilibrium, these two rates must be equal:

$$k_{lr} \times P_C(g) = k_{rl} \times [\text{CO}_2(\text{dissolved})].$$

Rearranging and combining rate constants, we can write this as

$$[\text{CO}_2(\text{dissolved})] = S_C \times P_C(g). \quad (6.2.1)$$

This equation says that the concentration of dissolved CO<sub>2</sub> is directly proportional to the CO<sub>2</sub> partial pressure in the gas phase with which the solution is in equilibrium. The proportionality constant,  $S_C$ , is called the gas solubility coefficient, or the Henry's Law constant, for Equation (6.2.1) is often referred to as Henry's Law.

These solubility coefficients are highly substance specific and temperature dependent, decreasing rapidly with increasing temperature. Their values also depend on the presence of specific other substances in the solution, often in unpredictable ways. At 37 °C in most body fluids, a useful value for  $S_C$  is  $3.0 \times 10^{-5}$  Eq/liter per mm Hg or  $2.3 \times 10^{-7}$  Eq/liter per Pascal.

Except for blood plasma while it is traversing the pulmonary capillaries, body fluids are not even in contact with, let alone in equilibrium with, a gas phase, but they nonetheless contain dissolved CO<sub>2</sub>. It is therefore very convenient to express that CO<sub>2</sub> concentration in terms of an equivalent, but hypothetical, partial pressure value, defined by using Equation (6.2.1) backwards, thus:

**Definition:** *The partial pressure of a gas in a solution* is the value that  $P$  must have in Equation (6.2.1) given the value of the dissolved gas concentration in that solution.  $P$  is therefore the partial pressure of the gas that would be in equilibrium with that dissolved gas concentration if the solution were in contact with a gas phase.

This extended definition of partial pressure in solution is simply a convenient alternative to the concentration of dissolved gas. The partial pressure difference between two solutions for a particular gas therefore indicates which way, and how fast, dissolved gas molecules will diffuse between the two solutions. Inside cells, CO<sub>2</sub> is constantly being manufactured, so that  $P_C$  is higher there than in the interstitial fluid. Dissolved CO<sub>2</sub> therefore diffuses out of cells into ISF. It then diffuses from tissue fluid into blood plasma for the same reason and is carried away to the lungs, where it diffuses into alveolar gas.

In the gas, the partial pressures must always add up to the total ambient pressure on the gas, but partial pressures in solutions are under no such constraint. In body fluids, the sum of the partial pressures of all the dissolved gaseous substances is usually significantly less than atmospheric

pressure. This fact has important consequences for the absorption of gas bubbles from blood and tissues.

Because the body is an open system for  $\text{CO}_2$ ,  $P_C$  in body fluids is set by the balance between metabolism and respiration.  $P_C$  is therefore an independent variable for these fluids; its value is imposed on them by overall body functions. Each body fluid, as a solution, can therefore only react to its  $P_C$  value; it cannot control it or change it. The end result, as we shall see clearly in the next few sections, is that  $P_C$  and [SID] are the primary determinants of  $[\text{H}^+]$ , and therefore of acid-base behavior, in all body fluids.

In a closed system, on the other hand, total  $\text{CO}_2$  content is the independent variable, and  $P_C$  becomes a dependent variable defined by Equation (6.2.1). Over short times or under conditions of inadequate circulation, local tissue regions may become temporarily closed systems for  $\text{CO}_2$ . A slightly more complex quantitative analysis is then needed to keep track of their detailed  $\text{CO}_2$  and  $[\text{H}^+]$  behavior than we shall present here for open systems [3].

### 6.3. CARBON DIOXIDE REACTIONS IN WATER

The first reaction is the one discussed in the previous section, namely,  $\text{CO}_2$  dissolving in water to become dissolved  $\text{CO}_2$ . Its quantitative description at equilibrium is Henry's Law, Equation (6.2.1).

Dissolved  $\text{CO}_2$  molecules can be removed from solution by two further reactions, each with the same end result, the formation of bicarbonate ions.  $\text{CO}_2$  can combine with water molecules like a classical anhydride, to form carbonic acid,  $\text{H}_2\text{CO}_3$ . This molecule can then dissociate to form  $\text{H}^+$  and  $\text{HCO}_3^-$  ions.  $\text{CO}_2$  can also combine with  $\text{OH}^-$  ions, like an add-on weak acid, to form  $\text{HCO}_3^-$  directly.

For the first reaction, equilibrium requires that

$$[\text{CO}_2(\text{dissolved})] \times [\text{H}_2\text{O}] = K \times [\text{H}_2\text{CO}_3],$$

where  $K$  is the equilibrium constant. We may treat  $[\text{H}_2\text{O}]$  as a constant, however, as we did in Chapter 3, and we may substitute for  $[\text{CO}_2(\text{dissolved})]$  from Equation (6.2.1). If we then combine all the constants into one,  $K_H$ , and rearrange, the equilibrium requirement becomes, finally,

$$[\text{H}_2\text{CO}_3] = K_H \times P_C. \quad (6.3.1)$$

This expression looks just like Henry's Law, but  $\text{H}_2\text{CO}_3$  is not a gas and  $K_H$  is not a solubility constant.  $K_H$  in body fluids at 37°C is  $9 \times 10^{-8}$  Eq/liter, so that Equations (6.2.1) and (6.3.1) tell us that  $[\text{CO}_2(\text{dissolved})]$  is usually on the order of several hundred times larger than  $[\text{H}_2\text{CO}_3]$ . It is therefore common practice to neglect  $[\text{H}_2\text{CO}_3]$ . Unfortunately this straightforward and simple step is often made unnecessarily confusing in

textbooks by a statement to the effect that dissolved CO<sub>2</sub> includes H<sub>2</sub>CO<sub>3</sub>, as well as CO<sub>2</sub>(dissolved).

For the dissociation of H<sub>2</sub>CO<sub>3</sub>, equilibrium requires

$$[\text{H}^+] \times [\text{HCO}_3^-] = K \times [\text{H}_2\text{CO}_3].$$

In this equation, we may substitute from (6.3.1) for [H<sub>2</sub>CO<sub>3</sub>] and combine constants again, to arrive at

$$[\text{H}^+] \times [\text{HCO}_3^-] = K_C \times P_C. \quad (6.3.2)$$

K<sub>C</sub> in body fluids at 37°C is  $2.6 \times 10^{-11}$  (Eq/liter)<sup>2</sup>/mm Hg.

Equilibrium for the formation of HCO<sub>3</sub><sup>-</sup> by combination of CO<sub>2</sub> and OH<sup>-</sup> requires us to write

$$[\text{CO}_2(\text{dissolved})] \times [\text{OH}^-] = K \times [\text{HCO}_3^-].$$

In this expression, we may substitute for [CO<sub>2</sub>(dissolved)] from Equation (6.2.1) and for [OH<sup>-</sup>] from the ion product expression for water, once more combine constants, and we end up with

$$[\text{H}^+] \times [\text{HCO}_3^-] = K_C \times P_C. \quad (6.3.2)$$

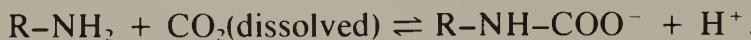
The reaction of CO<sub>2</sub> with either water or OH<sup>-</sup> is very slow. Half time for equilibrium is on the order of 30 seconds at body temperature, compared to equilibrium half times on the order of microseconds or less for most electrolyte dissociations. The assumption that equilibrium always exists therefore may not always be true for these CO<sub>2</sub> reactions in body fluids. Fortunately, in most physiological situations where problems would arise from this, an active enzyme, carbonic anhydrase, is usually present and reduces the equilibration half time to the order of microseconds. This enzyme is not present everywhere, however, and the dynamics of CO<sub>2</sub>-H<sub>2</sub>O interactions must be carefully examined in some cases. For the purposes of understanding isolated body fluids, we shall ignore this problem for the present and assume either that carbonic anhydrase is always present or that we can wait long enough so that these CO<sub>2</sub> reactions have equilibrated. Given this assumption, Equation (6.3.2) is the quantitative description of equilibrium for the first phase of CO<sub>2</sub>-H<sub>2</sub>O interactions.

The second phase is the dissociation of HCO<sub>3</sub><sup>-</sup> to H<sup>+</sup> and CO<sub>3</sub><sup>2-</sup>, the carbonate ion. This is a typical dissociation, with fast equilibrium. At equilibrium, we must have

$$[\text{H}^+] \times [\text{CO}_3^{2-}] = K_3 \times [\text{HCO}_3^-]. \quad (6.3.3)$$

In body fluids at 37°C, K<sub>3</sub> =  $6 \times 10^{-11}$  Eq/liter. It is important to remember that because CO<sub>3</sub><sup>2-</sup> is a bivalent ion, its concentration in equivalents per liter is just twice its molar concentration.

$\text{CO}_2$  is also removed from solution to a small extent when proteins are present, by direct combination with amino side groups to form carbamino compounds. Although this reaction plays a role in the transport of  $\text{CO}_2$  by whole blood, the effective concentration of available  $-\text{NH}_2$  groups is so low in most body fluids that it is of very little acid-base significance. The reaction can be represented by this reaction scheme:



Because there is very little protein in ISF, we shall ignore this reaction in the rest of this chapter.

All these  $\text{CO}_2$  reactions are reversible, and this reversibility has two interesting consequences. The first is that if the partial pressure of  $\text{CO}_2$  is zero in the gas above a solution containing any  $\text{CO}_2(\text{dissolved})$ ,  $\text{H}_2\text{CO}_3$ ,  $\text{HCO}_3^-$ , or  $\text{CO}_3^{2-}$  molecules, all the reactions will be driven to the left, and all these species will disappear. Limestone rocks, coral reefs, mollusk shells, and similar  $\text{CaCO}_3$ -based solid structures are stable in sea water only because  $P_c$  in the atmosphere, and therefore in the ocean, is not zero, but about 0.3 mm Hg, or 40 Pa. Bubbling  $\text{CO}_2$ -free gas through a solution of "NaHCO<sub>3</sub>" or "Na<sub>2</sub>CO<sub>3</sub>" will drive off all the  $\text{CO}_2$  and convert it to a solution of "NaOH," ie,  $\text{Na}^+$  plus  $\text{H}^+$  plus  $\text{OH}^-$ .

The second consequence of reversibility is a practical measurement that for many years was the only available way for estimating  $P_c$  in body fluids. It follows from the quantitative relationships presented in the next section that making [SID] negative in a  $\text{CO}_2$ -containing solution will drive all the  $\text{CO}_2$  out of  $\text{HCO}_3^-$  and  $\text{CO}_3^{2-}$  and into  $\text{H}_2\text{CO}_3$  and  $\text{CO}_2(\text{dissolved})$ . These forms, in turn, can be converted to  $\text{CO}_2(\text{gas})$  by placing the solution sample in an evacuated container and collecting the  $\text{CO}_2$  that appears. The amount of  $\text{CO}_2$  thus collected is a measure of the "CO<sub>2</sub> content," or "total CO<sub>2</sub>," in the original solution. Under physiological conditions in blood plasma, most of the  $\text{CO}_2$  is in the form of  $\text{HCO}_3^-$ , so that [total CO<sub>2</sub>] is an approximate measure of  $[\text{HCO}_3^-]$ , which is very difficult to measure directly. [Total CO<sub>2</sub>] became popular because there was no other practical way to measure  $[\text{HCO}_3^-]$  quickly in plasma samples, and there was no convenient way to measure  $P_c$ . Given the pH, or  $[\text{H}^+]$ , of a plasma sample and its  $[\text{HCO}_3^-]$ , however, its  $P_c$  could be calculated easily from Equation (6.3.2). Now that  $P_c$  and  $[\text{H}^+]$  (pH) can be easily and quickly measured by commercially available specific electrode meters, the value of  $[\text{HCO}_3^-]$ , if needed, can be much more easily, and just about as accurately, calculated from Equation (6.3.2).

In all extracellular fluids, [total CO<sub>2</sub>] is much larger than [CO<sub>2</sub>(dissolved)]. In interstitial fluid with [SID] = 0.031 Eq/liter and  $P_c$  = 50 mm Hg, for example, [CO<sub>2</sub>(dissolved)] is 0.0015 Eq/liter, while [total CO<sub>2</sub>] is 0.033 Eq/liter, 22 times larger. It is important not to confuse these two quantities, as some textbooks do. [Total CO<sub>2</sub>] does not obey Henry's Law,

but is determined by the value of [SID] much more than by  $P_C$ , whereas [CO<sub>2</sub>(dissolved)] depends only on  $P_C$  and is independent of [SID].

In summary, CO<sub>2</sub> in water gives rise to two neutral molecules and two ions. [CO<sub>2</sub>(dissolved)] and [H<sub>2</sub>CO<sub>3</sub>] are simply proportional to  $P_C$  and independent of [SID]. [HCO<sub>3</sub><sup>-</sup>] and [CO<sub>3</sub><sup>2-</sup>], on the other hand, are determined by both [SID] and  $P_C$ .

#### 6.4. QUANTITATIVE BEHAVIOR OF STRONG IONS PLUS CO<sub>2</sub>

When we add CO<sub>2</sub> to the strong ion solutions whose behavior we analyzed in Chapter 4, we add the four molecular species discussed in the preceding section. Such a solution therefore contains H<sub>2</sub>O, strong ions, CO<sub>2</sub>(dissolved), H<sub>2</sub>CO<sub>3</sub>, HCO<sub>3</sub><sup>-</sup>, CO<sub>3</sub><sup>2-</sup>, OH<sup>-</sup>, and H<sup>+</sup>. The first four have been taken care of by our previous discussion;  $K'_w$  represents water dissociation equilibrium, [SID] incorporates the effects of all strong ions present, and [H<sub>2</sub>CO<sub>3</sub>] and [CO<sub>2</sub>(dissolved)] are proportional to  $P_C$ . [HCO<sub>3</sub><sup>-</sup>], [CO<sub>3</sub><sup>2-</sup>], [OH<sup>-</sup>], and [H<sup>+</sup>] are the internal, dependent variables in this solution, and in order to understand its acid-base behavior, we must be able to calculate their values from the values of the two independent variables, [SID] and  $P_C$ .

Four simultaneous, independent equations are needed, and we already have three of them:

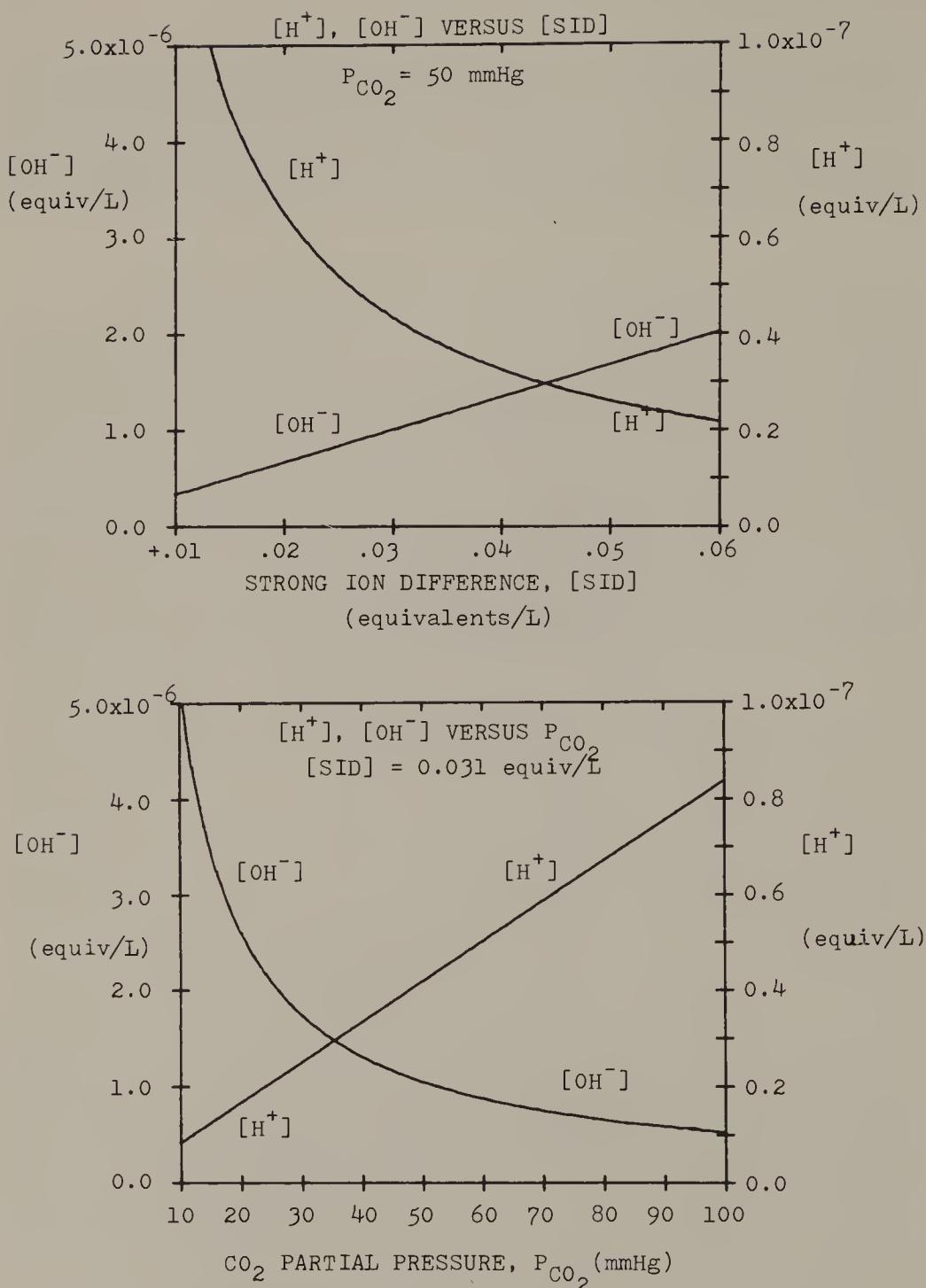


The fourth equation is, of course, that for electrical neutrality:

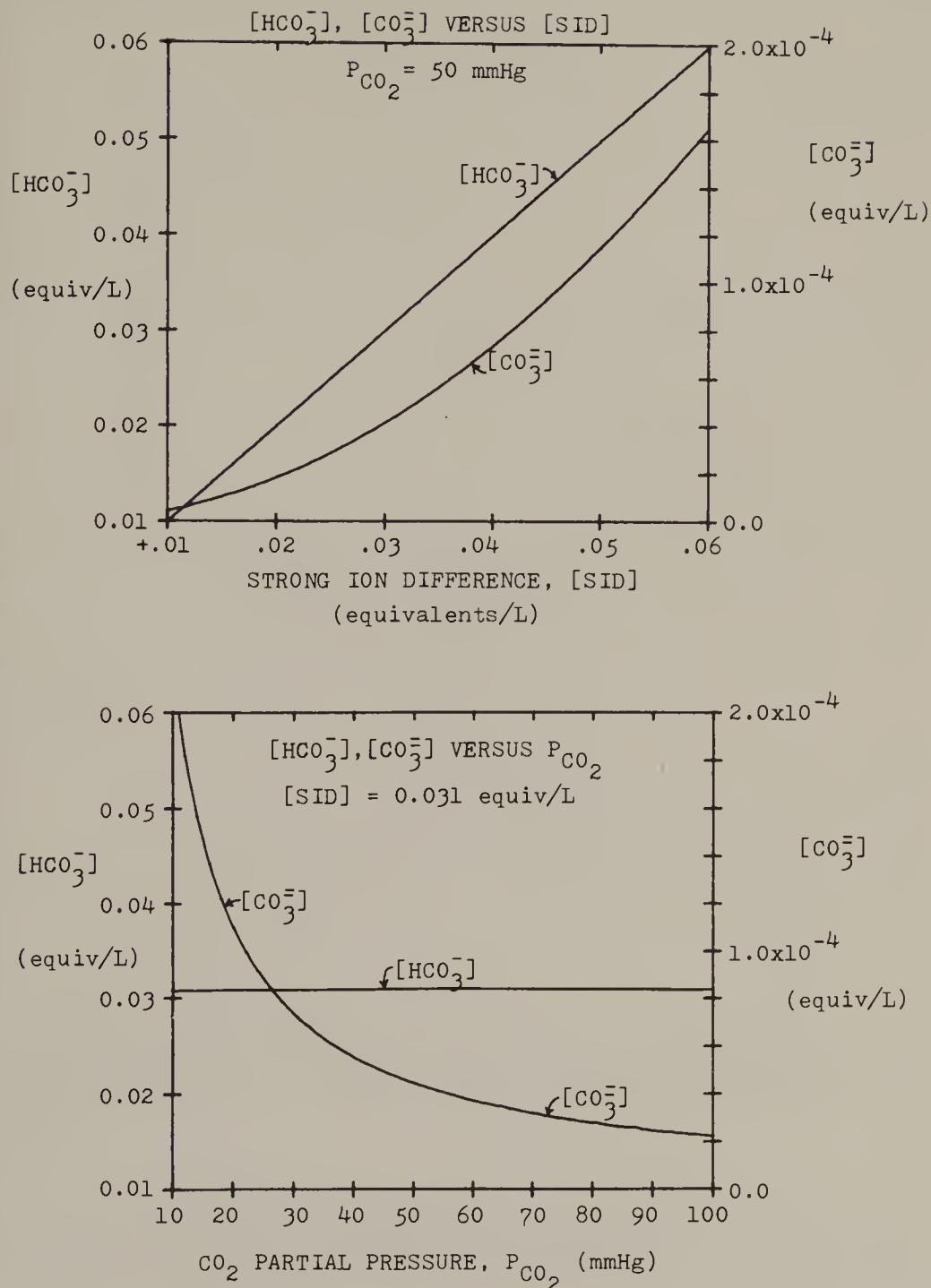
$$[\text{SID}] + [\text{H}^+] - [\text{OH}^-] - [\text{HCO}_3^-] - [\text{CO}_3^{2-}] = 0. \quad (6.4.4)$$

As we have done in each previous case, we can combine and rearrange these equations into four different ones, one for each of the dependent variables, and then solve them by the numerical method presented in the Appendix of Chapter 5. The procedure is essentially the same as in Chapter 5, and is outlined briefly in the Appendix of this chapter. We shall proceed on the assumption that this procedure has been carried through, so that appropriate calculations of all desired variable values are available as needed.

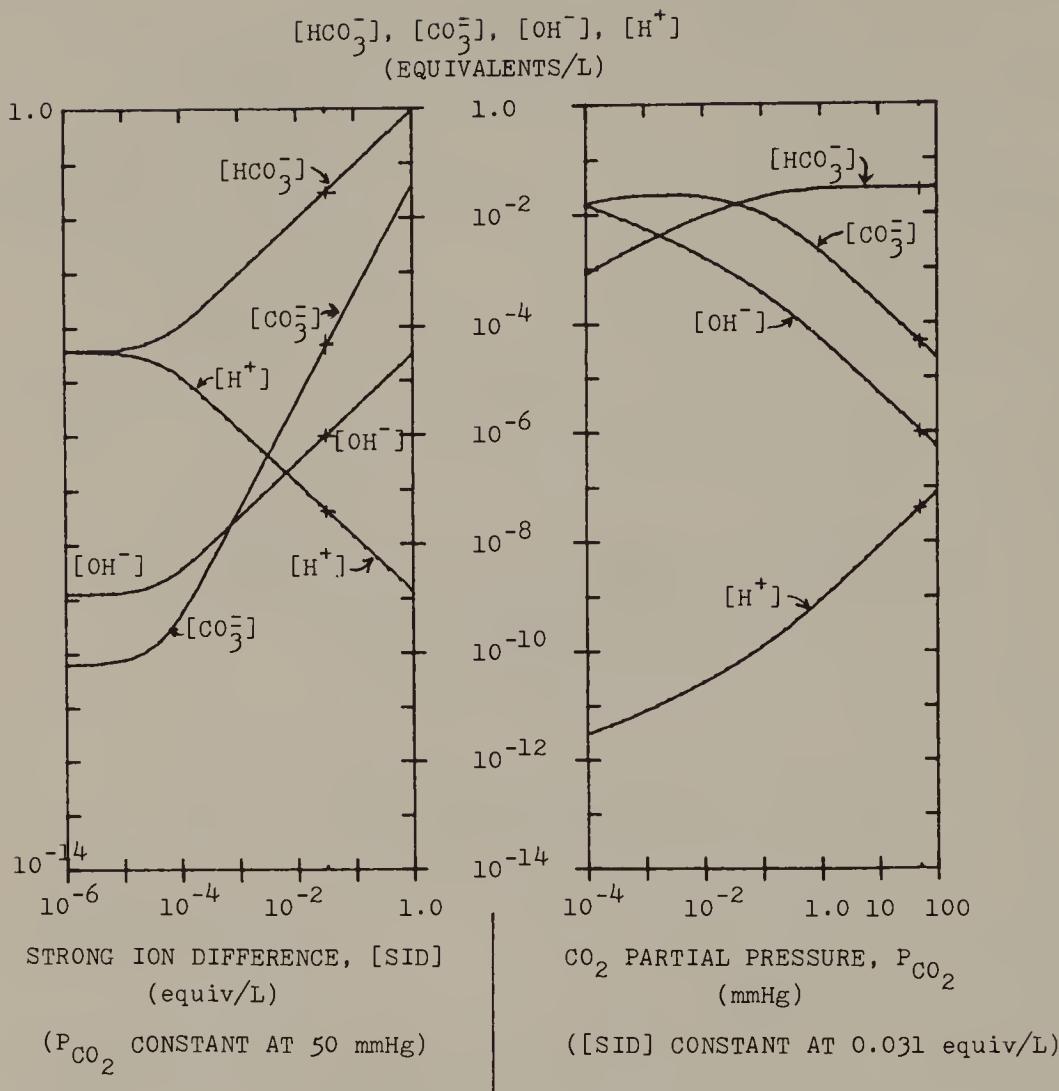
Selected results from such calculations provide the graphs of Figures 6.1 through 6.5, which display the ionic behavior of solutions containing only strong ions and CO<sub>2</sub> under the conditions of positive [SID] values. For convenience in later sections, we have used parameter values in these calculations appropriate to standard interstitial fluid, as noted in the caption to Figure 6.1. As pointed out in Chapter 4, ISF is essentially a solution



**Figure 6.1.**  $[H^+]$  and  $[OH^-]$  plotted against  $[SID]$  with  $P_{CO_2}$  constant at 50 mm Hg (top) and plotted against  $P_{CO_2}$  with  $[SID]$  constant at +0.031 Eq/liter (bottom), for standard ISF. Parameter values used in all calculations are listed in Table 6.1 (page 101). Left-hand vertical scale in each case is that for  $[OH^-]$  and is  $50 \times$  the right-hand scale for  $[H^+]$ .



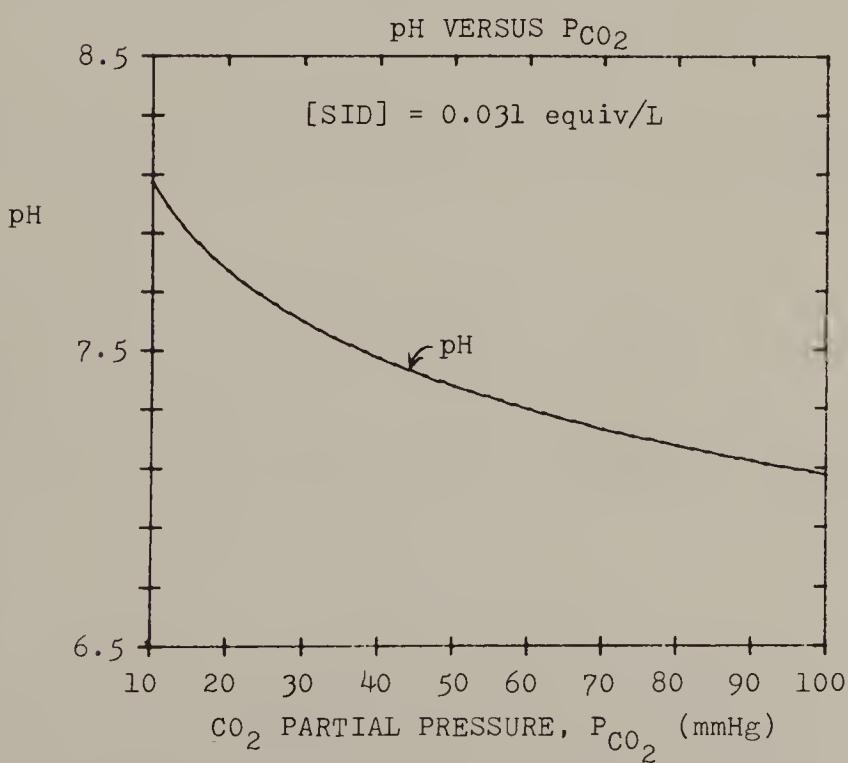
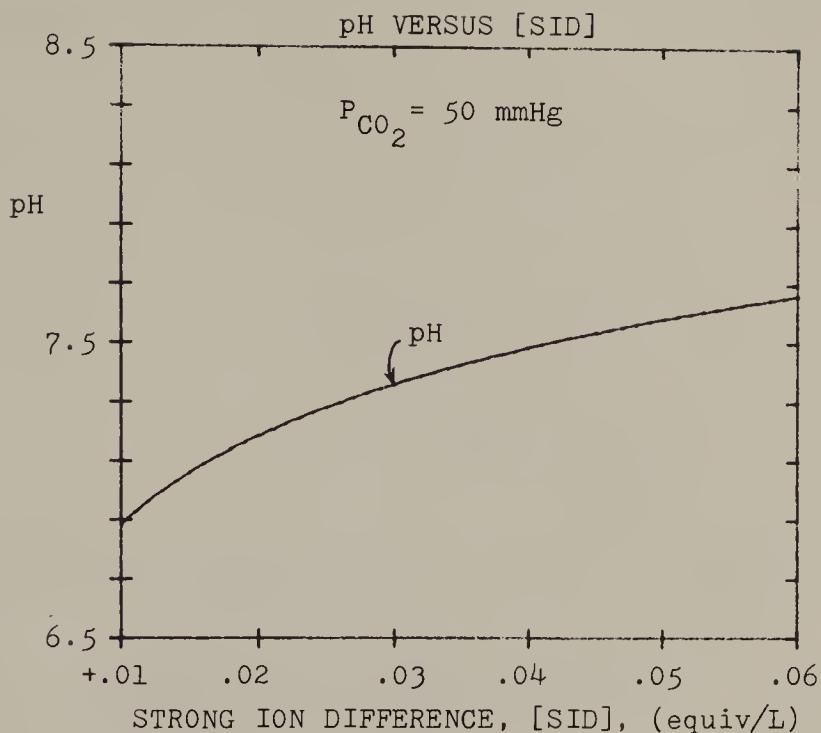
**Figure 6.2.**  $[HCO_3^-]$  and  $[CO_3^{2-}]$  plotted against [SID] with  $P_{CO_2}$  constant (top) and against  $P_{CO_2}$  with [SID] constant (bottom), over the same ranges as in Figure 6.1. Left-hand vertical scales for  $[HCO_3^-]$  do not begin at zero, and are  $250 \times$  right-hand vertical scales for  $[CO_3^{2-}]$ , which do begin at zero. Same parameter values used as in Figure 6.1.



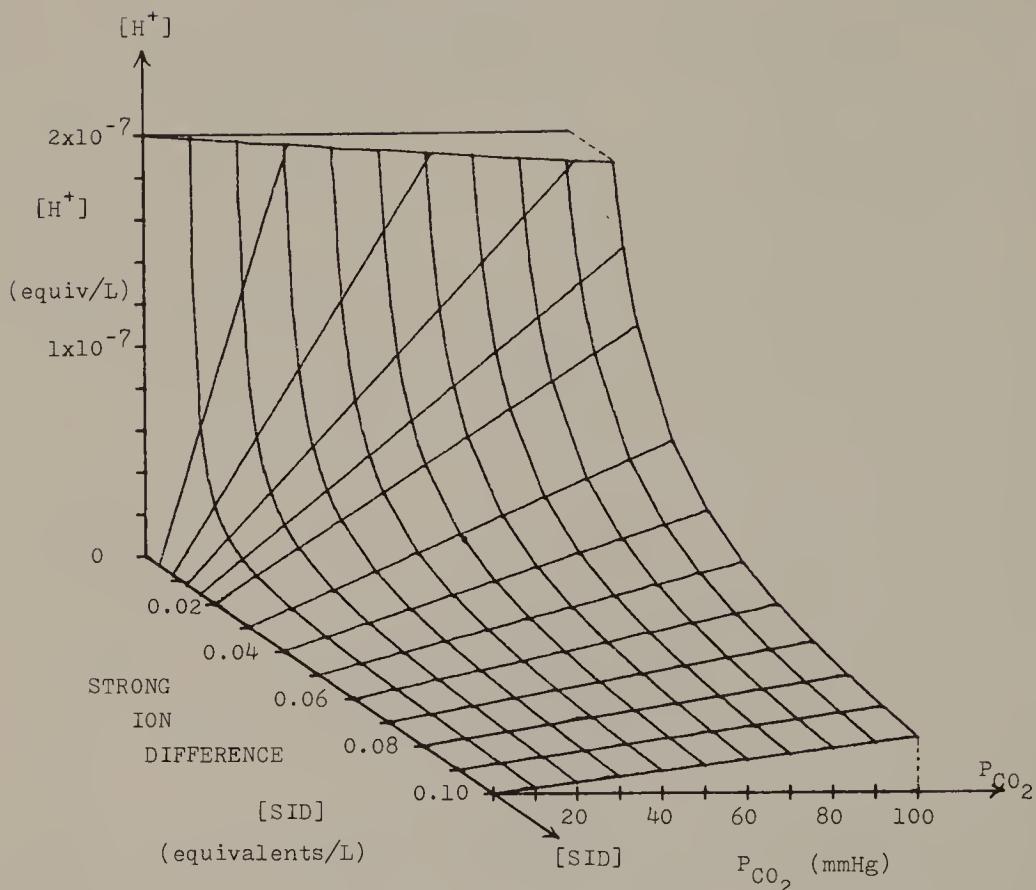
**Figure 6.3.** Log-log plots of all four dependent variables in ISF,  $[\text{HCO}_3^-]$ ,  $[\text{CO}_3^{2-}]$ ,  $[\text{OH}^-]$ , and  $[\text{H}^+]$ , versus [SID] on the left, with  $P_{\text{CO}_2}$  constant at 50 mm Hg, and versus  $P_{\text{CO}_2}$  on the right, with [SID] constant at +0.031 Eq/liter. Same parameter values used as in Figure 6.1.

of strong ions plus  $\text{CO}_2$ , so it is reasonable to label these graphs "Interstitial Fluid," as we have done. The [SID] value for standard ISF was listed in Chapter 4 as 0.031 Eq/liter. Here we must add the standard  $P_{\text{C}}$  value of 50 mm Hg.

Because the two independent variables in this system, [SID] and  $P_{\text{C}}$ , can, and do, both change at the same time and independently, it may be desirable to have three-dimensional plots of the surfaces that represent how the dependent variables vary with [SID] and  $P_{\text{C}}$  simultaneously. A perspective view of that surface for  $[\text{H}^+]$  is presented in Figure 6.5. It is difficult to read numerical values from such a graph, but the three-



**Figure 6.4.** pH versus [SID] (top) and versus  $P_{CO_2}$  (bottom). Same conditions and parameter values as in Figure 6.1.



**Figure 6.5.** A perspective view of the three-dimensional surface representing  $[H^+]$  as determined by [SID] and  $P_{CO_2}$ . The scales and ranges on the axes are comparable to those in Figure 6.1. Same parameter values as in Figure 6.1.

dimensional view is helpful in grasping some of the qualitative aspects of this solution's behavior.

A very large amount of information is presented in all these graphs, and many of their important aspects are not immediately obvious. Considerable time and thought are needed to absorb their significance. For the understanding of interstitial fluid, the following specific points should be clearly seen.

#### 6.4a. $[H^+]$ and $[OH^-]$ Behavior (Figures 6.1 and 6.3)

When [SID] is positive,  $[H^+]$  decreases nonlinearly with increasing [SID], as it did in Chapter 4, and increases linearly with  $P_C$ . Within a wide range near physiological conditions, the exact equation for  $[H^+]$  in terms of [SID] and  $P_C$  can be shown to reduce to the following very convenient

formula that is accurate to better than 1%:

$$[\text{H}^+] = K_C \times P_C / [\text{SID}] \quad (6.4.5)$$

The standard value for  $K_C$  in this equation yields

$$[\text{H}^+] = 2.6 \times 10^{-11} \times P_C / [\text{SID}] \text{ Eq/liter.} \quad (6.4.6)$$

We can now take logs and change signs so as to write this result in terms of pH as

$$\text{pH} = 10.6 + \log_{10} \left\{ \frac{[\text{SID}]}{P_C} \right\} (\text{Eq/liter}) \quad (6.4.7)$$

with [SID] in equivalents per liter and  $P_C$  in millimeters of mercury. If [SID] is specified in milliequivalents per liter, this becomes

$$\text{pH} = 7.6 + \log_{10} \left\{ \frac{[\text{SID}]}{P_C} \right\} (\text{mEq/liter}). \quad (6.4.8)$$

Any of these formulas may be used to calculate any one of the three variables involved if the other two have been measured, and they are very useful for this purpose. They are also important conceptually, because they show that  $[\text{H}^+]$  in this solution is determined only by  $P_C$  and [SID]. Any observed change in  $[\text{H}^+]$  can only be interpreted to mean that either  $P_C$  or [SID] (or both) has changed. As always, changes in  $[\text{H}^+]$  cannot tell us how much, if any, H<sup>+</sup> has been moved into or out of the system.

For positive [SID] values, [OH<sup>-</sup>] is always larger than [H<sup>+</sup>] and behaves qualitatively in the opposite way to [H<sup>+</sup>], as Figures 6.1 and 6.3 show. The effect of the added CO<sub>2</sub> is to decrease [OH<sup>-</sup>], for it is no longer the only weak anion present, so that some, in fact most, of the excess strong ion positive charge measured by [SID] can be balanced by [CO<sub>3</sub><sup>2-</sup>] and [HCO<sub>3</sub><sup>-</sup>].

When [SID] is negative, there is an excess of negative strong ion charge, and positive weak ions are needed. H<sup>+</sup> is still the only one available, so under these conditions, all three of the weak anions, OH<sup>-</sup>, CO<sub>3</sub><sup>2-</sup>, and HCO<sub>3</sub><sup>-</sup>, can exist only at extremely low concentrations (see Table 6.1), and the solution looks very much like the strong ion only solution of Chapter 4, with  $[\text{H}^+] = -[\text{SID}]$ . It is easy to show that in this case,  $[\text{HCO}_3^-] = -K_C \times P_C / [\text{SID}]$ ,  $[\text{CO}_3^{2-}] = K_3 \times K_C \times P_C / [\text{SID}]^2$  and  $[\text{OH}^-] = -K_w / [\text{SID}]$ . In other words, [OH<sup>-</sup>], [HCO<sub>3</sub><sup>-</sup>], and [CO<sub>3</sub><sup>2-</sup>] are all extremely small when [SID] is negative and they can generally be neglected.

### 6.4b. $[\text{HCO}_3^-]$ Behavior (Figures 6.2 and 6.3)

$[\text{HCO}_3^-]$  is by orders of magnitude the largest of the four dependent variables under positive [SID] conditions, so that the electrical neutrality condition for this case can be written very accurately as

$$[\text{HCO}_3^-] = [\text{SID}]. \quad (6.4.9)$$

This is a useful equation and simplifies life very much, but unfortunately it carries some confusion with it. It may tend to blur the essential distinction between the independent variable status of [SID], whose value is imposed on the solution by the strong ion composition, and the dependent variable status of  $[\text{HCO}_3^-]$ , whose value is the result of adjustment of the  $\text{CO}_2$ -water reaction equilibria in response to the value of [SID]. They are very close to equal numerically, but very different physically; [SID] determines  $[\text{HCO}_3^-]$ , but not vice versa. Conceptually, we must always return to the whole set of four equations for the system, (6.4.1) through (6.4.4), in order to understand what is happening.

Another puzzling feature of Equation (6.4.9) is that it says that  $[\text{HCO}_3^-]$  is independent of  $P_{\text{C}}$ . This is clearly counterintuitive, but Figure 6.2 shows it to be true. A deeper view is provided by Figure 6.3, which shows that  $[\text{HCO}_3^-]$  does indeed vary with  $P_{\text{C}}$ , but only when  $P_{\text{C}}$  is very small, well below any physiological value. For all biological purposes,  $[\text{HCO}_3^-]$  in ISF is indeed independent of  $P_{\text{C}}$  and just equal to [SID]. This conclusion means that if [SID] is constant, but  $P_{\text{C}}$  changes,  $[\text{CO}_3^{2-}]$ ,  $[\text{OH}^-]$ , and  $[\text{H}^+]$  will all change, but  $[\text{HCO}_3^-]$  will not.  $[\text{HCO}_3^-]$  is therefore not a very useful quantity in the analysis or understanding of interstitial fluids.

### 6.4c. $[\text{CO}_3^{2-}]$ Behavior: Figures 6.2 and 6.3

$[\text{CO}_3^{2-}]$  is generally ignored in biomedical acid-base analyses, but its behavior is interesting and important. It is even more counterintuitive than  $[\text{HCO}_3^-]$ ;  $[\text{CO}_3^{2-}]$  decreases with increasing  $P_{\text{C}}$ ! It increases more rapidly with [SID] than  $[\text{HCO}_3^-]$  does;  $[\text{CO}_3^{2-}]$  goes up with  $[\text{SID}]^2$ , as the straight line in Figure 6.3 indicates. Over the physiological range, the numerical value of  $[\text{CO}_3^{2-}]$  is always much less than that of  $[\text{HCO}_3^-]$ , usually about 1/50th, but it is always at least 30 times larger than  $[\text{OH}^-]$  and 1000 to 2000 times larger than  $[\text{H}^+]$ . The pH notation makes it very easy to overlook the fact that  $[\text{CO}_3^{2-}]$  is more than three orders of magnitude larger than  $[\text{H}^+]$ . The log-log plots in Figure 6.3 help to put this behavior in context.

The most important role of  $[\text{CO}_3^{2-}]$  in body fluids that results from the fact that its value goes up with decreasing  $P_{\text{C}}$  is probably in  $\text{Ca}^{2+}$  homeostasis. The solubility product for  $\text{CaCO}_3$  is approximately  $10^{-8}$  (Eq/

liter)<sup>2</sup>, so that if  $[CO_3^{2-}]$  rises above  $10^{-5}$  Eq/liter,  $[Ca^{2+}]$  should fall below 1 mEq/liter. An example is hyperventilation, which lowers  $P_C$ , thereby raising  $[CO_3^{2-}]$ , and thus lowering  $[Ca^{2+}]$ . Moderately decreased  $[Ca^{2+}]$ , in turn, increases excitability in many tissues and gives rise to the classical symptoms of hyperventilation, such as muscle spasms.

#### 6.4D. SUMMARY

The ionic properties of this solution when [SID] is positive and  $P_C$  is larger than 0.1 mm Hg may be summarized in the following statements to supplement Figures 6.1 through 6.5.

1. Apart from strong ions, the major ion present is  $HCO_3^-$ .  $[HCO_3^-]$  in this solution plays the role that  $[OH^-]$  played in Chapter 4. Its value is effectively equal to [SID] and independent of  $P_C$ .
2.  $CO_3^{2-}$  is present at about 1/500th the concentration of  $HCO_3^-$ . Its concentration decreases rapidly with increasing  $P_C$  and increases with [SID]<sup>2</sup>.
3.  $[OH^-]$  is usually about 1/30th of  $[CO_3^{2-}]$  and 1/10<sup>4</sup>th  $[HCO_3^-]$ . It increases directly with [SID] and decreases with increasing  $P_C$ .
4.  $[H^+]$  is always the smallest ionic quantity. It is usually about 1/30th of  $[OH^-]$  and 1/10<sup>6</sup>th of  $[HCO_3^-]$ . It decreases with increasing [SID] and increases with increasing  $P_C$ .

#### 6.5. TITRATION OF ISOLATED STANDARD INTERSTITIAL FLUID

In Chapter 4, Table 4.1 presented the results of titrating a sample of  $CO_2$ -free interstitial fluid. Those results were quantitatively explained in terms of the properties of strong ion solutions. Table 6.1 similarly lists the results of titrating a sample of ISF with its normal  $CO_2$  content, indicated by its

TABLE 6.1. Titration of Intact, Isolated Interstitial Fluid ( $P_{CO_2} = 50$  mm Hg)

HCl added	[SID]	$[HCO_3^-]$	$[CO_3^{2-}]$	$[OH^-]$	$[H^+]$	pH
none	+ 0.031	0.031	$4.5 \times 10^{-5}$	$1.1 \times 10^{-6}$	$4.2 \times 10^{-8}$	7.38
0.011	+ 0.020	0.020	$1.8 \times 10^{-5}$	$6.8 \times 10^{-7}$	$6.5 \times 10^{-8}$	7.19
0.010	+ 0.010	0.010	$4.6 \times 10^{-6}$	$3.4 \times 10^{-7}$	$1.3 \times 10^{-7}$	6.89
0.010	0	$3.6 \times 10^{-5}$	$6.0 \times 10^{-11}$	$1.2 \times 10^{-9}$	$3.6 \times 10^{-5}$	4.44
0.010	- 0.010	$1.3 \times 10^{-7}$	$7.8 \times 10^{-16}$	$4.4 \times 10^{-12}$	0.010	2.0
0.010	- 0.020	$6.5 \times 10^{-8}$	$2.0 \times 10^{-16}$	$2.2 \times 10^{-12}$	0.020	1.7

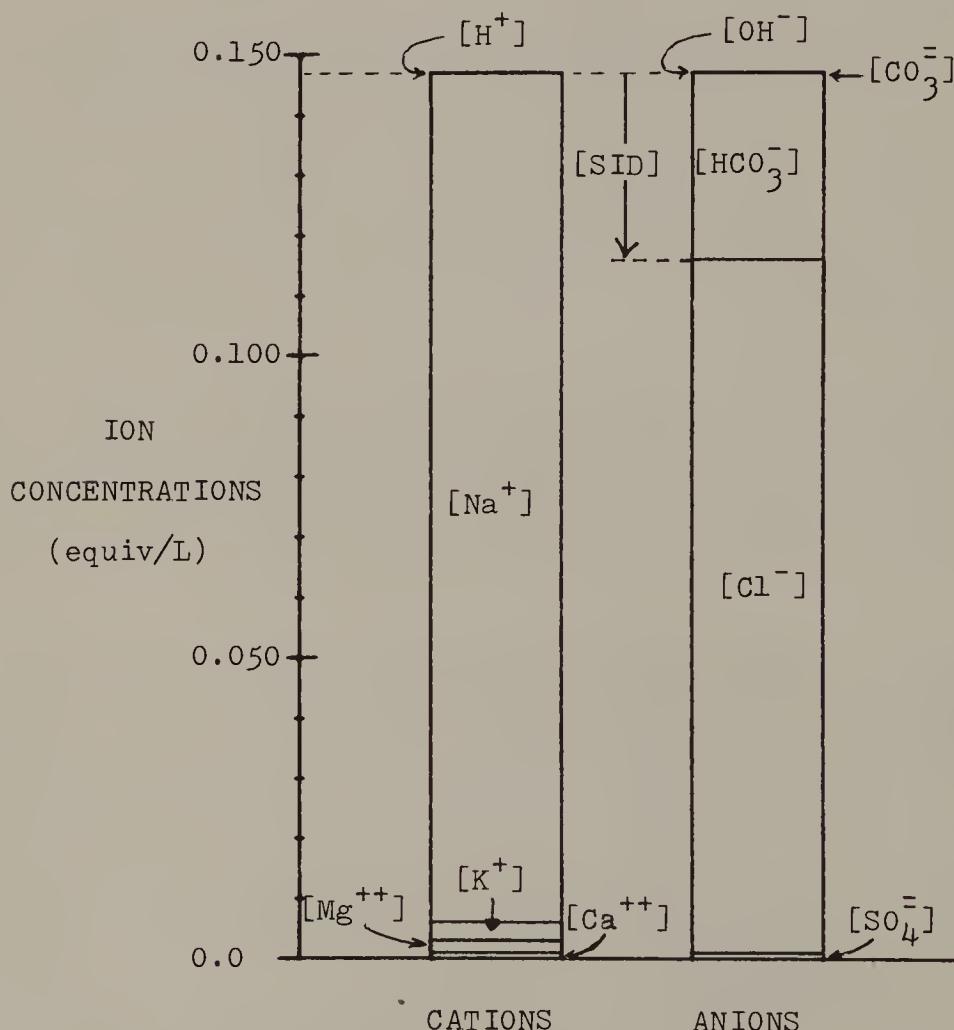
All concentrations in Eq/liter.

Composition:  $[Na^+]$ , 0.137;  $[Cl^-]$ , 0.111;  $[HCO_3^-]$ , 0.031;  $[K^+]$ , 0.003;  $[Mg^{2+}]$ , 0.002;  $[CO_2(\text{dissolved})]$ , 0.0015;  $[Ca^{2+}]$ , 0.001;  $[SO_4^{2-}]$ , 0.001;  $[CO_3^{2-}]$ ,  $4.5 \times 10^{-5}$ ;  $[OH^-]$ ,  $1.1 \times 10^{-6}$ ;  $[H^+]$ ,  $4.2 \times 10^{-8}$

Parameters:  $K_w$ ,  $4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>;  $K_C$ ,  $2.6 \times 10^{-11}$  (Eq/liter)<sup>2</sup>/mm Hg;  $K_3$ ,  $6 \times 10^{-11}$  Eq/liter;  $S_C$ ,  $3 \times 10^{-5}$  (Eq/liter)/mm Hg; 37 C

$P_C = 50$  mm Hg value. These results may be equally well understood in quantitative detail on the basis of the analysis in the previous section. The reader is urged to carry out the appropriate detailed interpretation of Table 6.1 on the basis of Figures 6.1 through 6.5. There should be no mysteries in the numbers in this table. Formulas given in the previous section may be needed to reproduce values off the scales of the figures.

For convenience of reference, we have included in Table 6.1 the parameter values used to characterize standard ISF, as well as its detailed ionic composition under standard conditions of  $[SID] = +0.031$  Eq/liter and  $P_C = 50$  mm Hg. The gamblegram for these conditions is presented in Figure 6.6. Comparison with the gamblegram without  $\text{CO}_2$ , Figure 4.5, illuminates the role of  $\text{HCO}_3^-$  in this solution.



**Figure 6.6.** Gamblegram for standard ISF with  $[SID] = +0.031$  Eq/liter and  $P_{\text{CO}_2} = 50$  mm Hg. Values for  $[\text{CO}_3^{=}]$ ,  $[\text{OH}^-]$  and  $[\text{H}^+]$  are smaller than line thickness on the vertical scale. Comparison with Figure 4.5 indicates that  $[\text{HCO}_3^-]$  in this solution has replaced  $[\text{OH}^-]$  in the strong ions only solution of Chapter 4.

## 6.6. BUFFERING AND BUFFER STRENGTHS

From the cubic equation for  $[H^+]$  as a function of [SID] and  $P_C$  presented in the Appendix of this chapter, it is a straightforward task to find the formulas for the  $[H^+]$  buffer strength and the pH buffer strength in this solution. Details are outlined in Appendix 6A.1. The results are

$$\left. \begin{array}{l} [H^+] \text{ buffer strength} \\ \text{strong ions plus CO}_2 \\ [SID] \text{ positive} \\ P_C \text{ above } 0.1 \text{ mm Hg} \end{array} \right\} = \frac{-[SID]^2}{K_C \times P_C} \text{ (strong ions per H}^+)\text{}$$

(= -7.4 × 10<sup>5</sup> for standard ISF)

$$\left. \begin{array}{l} \text{pH buffer strength} \\ \text{strong ions plus CO}_2 \\ [SID] \text{ positive} \\ P_C \text{ above } 0.1 \text{ mm Hg} \end{array} \right\} = 2.3 \times [SID] \text{ Eq/liter}$$

(= 0.07 Eq/liter for standard ISF).

As expected, the  $[H^+]$  buffer strength depends on  $P_C$  as well as on [SID], just as  $[H^+]$  itself does. The fact that the pH buffer strength is not dependent on  $P_C$  is surprising. It suggests an insensitivity to changes in  $P_C$  that the  $[H^+]$  curves do not indicate.

These buffer strengths should be compared with those presented in Chapter 5, to clarify what the buffering effects of the added CO<sub>2</sub> are. The necessary formulas for ISF without CO<sub>2</sub> were presented in Section 5.5, along with those for a weak acid buffer. The pH buffer strength is the same, with and without CO<sub>2</sub>, but the  $[H^+]$  buffer strength formula when CO<sub>2</sub> is not present uses  $K'_w$  in place of  $K_C \times P_C$ . It therefore yields values that are larger by the ratio of these two quantities, roughly 10<sup>4</sup>. In other words, standard ISF with  $P_C = 50$  mm Hg has an  $[H^+]$  buffer strength less than 10<sup>-4</sup> times that of the same solution without CO<sub>2</sub>. Adding the CO<sub>2</sub> reduces the  $[H^+]$  buffer strength by a factor of 10<sup>4</sup>; it does not alter the pH buffer strength.

There is, however, a very large difference in the  $[H^+]$  values in the two solutions. At [SID] = 0.031 Eq/liter, with no CO<sub>2</sub>,  $[H^+] = 1.4 \times 10^{-12}$  Eq/liter, pH 11.9; with  $P_C = 50$  mm Hg,  $[H^+] = 4.2 \times 10^{-8}$  Eq/liter, pH 7.38.

Another interesting comparison can be made with the weak acid solution of Chapter 5. If we use [SID] = 0.031 Eq/liter as the  $[A_{TOT}] / 2$  point and the same  $K_A$  as used in Chapter 5,  $2.0 \times 10^{-7}$  Eq/liter, we find the  $[H^+]$  buffer strength value for the weak acid solution is  $-2 \times 10^5$ , slightly more than one-quarter the value for ISF with CO<sub>2</sub> at this [SID] value. The pH buffer strength for the weak acid solution is 0.037 Eq/liter, close to one-half the value for the ISF solution. CO<sub>2</sub> apparently conveys greater buffering power on a solution than this weak acid, but neither of them yields as high a value for  $[H^+]$  buffer strength as the strong ion only solution.

**TABLE 6.2.** Interstitial Fluid: Comparison of [SID] and  $P_C$  Effects on  $[H^+]$ , pH, and  $[HCO_3^-]$ 

Conditions	[SID]	$P_C$ (mm Hg)	$[H^+]$	% change in $[H^+]$	pH	% change in pH	$[HCO_3^-]$	% change in $[HCO_3^-]$
standard	0.031	50.0	$4.17 \times 10^{-8}$	—	7.38	—	0.031	—
[SID] 5% above standard	0.0326	50.0	$3.97 \times 10^{-8}$	-4.8	7.40	+0.3	0.0325	+5.0
[SID] 5% below standard	0.0295	50.0	$4.39 \times 10^{-8}$	+5.2	7.36	-0.3	0.0294	-5.0
$P_C$ 5% above standard	0.031	52.5	$4.38 \times 10^{-8}$	+5.0	7.36	-0.3	0.031	0.0
$P_C$ 5% below standard	0.031	47.5	$3.96 \times 10^{-8}$	-5.0	7.40	+0.3	0.031	0.0
[SID] 5% above	0.0326	52.5	$4.17 \times 10^{-8}$	0.0	7.38	0.0	0.0325	+5.0
$P_C$ 5% above	0.0295	47.5	$4.17 \times 10^{-8}$	0.0	7.38	0.0	0.0294	-5.0
$P_C$ 5% below								

All concentrations in Eq/liter.

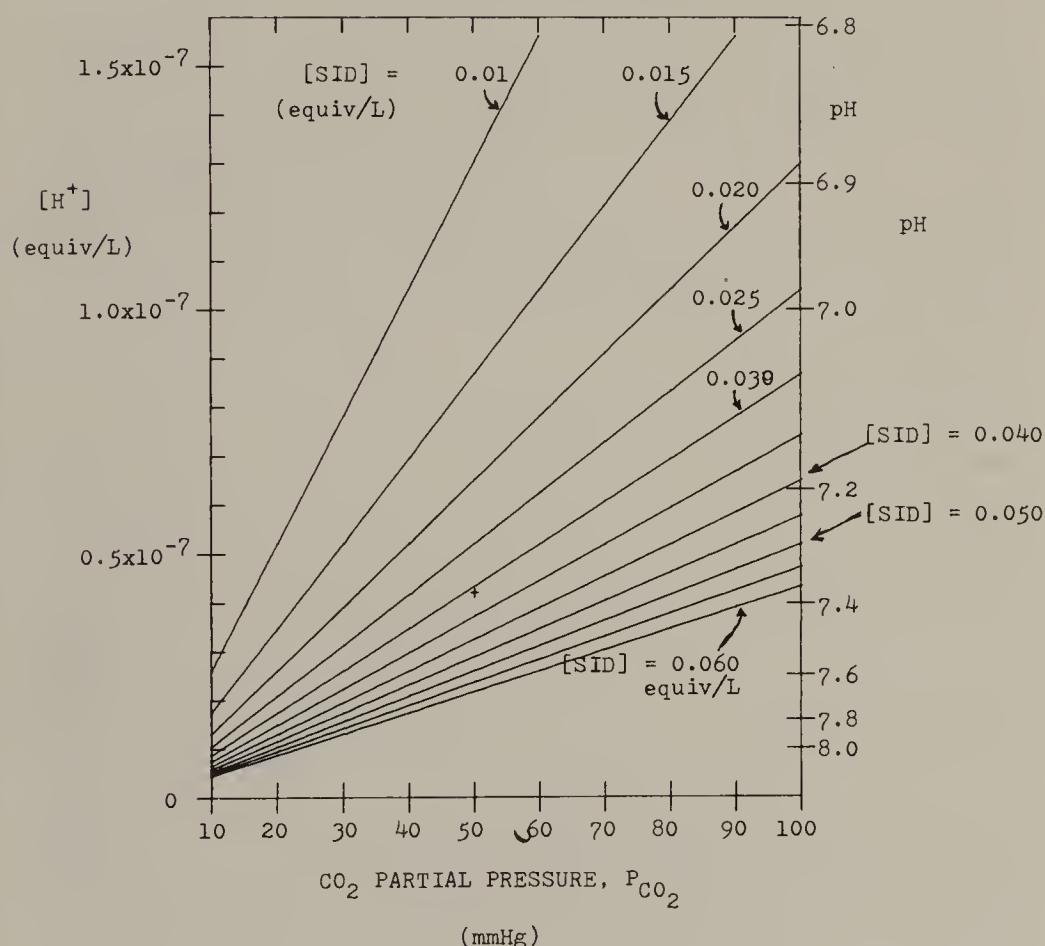
Finally, because  $[H^+]$  and pH also change with changes in  $P_C$ , it would be theoretically desirable to evaluate analogous buffer strengths from the slopes of the  $[H^+]$  and pH versus  $P_C$  curves. This can be done easily enough, but the difficulty arises that [SID] and  $P_C$  are different kinds of quantities and have very different units. Comparing the values of derivatives with respect to each of them is therefore difficult. It is not clear how we should compare a change of 1 mm Hg in  $P_C$  with a change of 1 Eq/liter in [SID]. There are several ways of getting around this problem, but the easiest is simply to calculate the response to the same, small, relative change in each of them. This has been done for standard ISF, in Table 6.2 by calculating the changes in a number of variables that result when either  $P_C$  or [SID] or both change by 5% from their standard values. The results indicate that this solution is very nearly equally well buffered against changes in [SID] or  $P_C$ ; a 5% change in either one results in roughly a 5% change in  $[H^+]$  and a 0.3% change in pH.

The last two rows in Table 6.2 also demonstrate how a change in either one of these independent variables may compensate for, or cancel, the effect of a similar change in the other, so far as a single dependent variable is concerned,  $[H^+]$  in this case. Raising or lowering both [SID] and  $P_C$  by 5% results in no change in  $[H^+]$ . In either case,  $[HCO_3^-]$  is changed by 5%, so the compensation only works for  $[H^+]$ , not for  $[HCO_3^-]$ .

### 6.7. THE $[H^+]$ — $P_{CO_2}$ GRAPH

The wide range of quantitative information in the three-dimensional plot of Figure 4.5, as already noted, is not very accessible from that figure. A much more useful display of this information is the set of  $[H^+]$  versus  $P_C$  curves in Figure 6.7. Each curve in this figure has been plotted for a specific constant [SID] value, as indicated on the figure. This graph may be seen, therefore, as a succession of slices through the surface of Figure 6.5, taken perpendicular to the [SID] axis. In principle, everything we can know about the  $[H^+]$  behavior of isolated interstitial fluid is presented in this figure.

Its usefulness arises mainly from the practical fact that  $[H^+]$  (from pH meter readings) and  $P_C$  are so easy to measure with presently available



**Figure 6.7.**  $[H^+]$  plotted against  $P_{CO_2}$  for a series of constant [SID] values. The right-hand vertical scale is the pH conversion of the left-hand  $[H^+]$  scale, so that either  $[H^+]$  or pH may be used to locate points on this graph. The value of [SID] in the sample may then be estimated from the position of the point with respect to the  $[SID] = \text{constant}$  lines. The “+” at  $P_{CO_2} = 50$  mm Hg and  $[H^+] = 4.2 \times 10^{-8}$  Eq/liter is the standard point for ISF.

instruments, even on minute samples, down to a few microliters. Given those data, we can, by locating them on this graph, immediately evaluate [SID] in the sample and, from what has been said earlier in this chapter, calculate  $[OH^-]$ ,  $[CO_3^{2-}]$ , and  $[HCO_3^-]$ , if we have any need for these latter quantities. The position of the  $[H^+]-P_C$  point on this graph completely characterizes the acid-base status of the sample in question.

For example, if measurement on an ISF sample yields  $P_C = 70$  mm Hg, pH 7.00, then  $[H^+] = 1.0 \times 10^{-7}$  Eq/liter, and the corresponding point on Figure 6.7 is in the position where we should expect the  $[SID] = 0.018$  Eq/liter line to be if it had been drawn in. We can therefore assign that value to [SID] in that sample. As  $[HCO_3^-] = [SID]$  in these solutions, 0.018 Eq/liter must also be the value of  $[HCO_3^-]$  in the sample.  $[OH^-]$  and  $[CO_3^{2-}]$  can easily be calculated from the equations in Section 6.4 to be  $4.4 \times 10^{-7}$  and  $1.1 \times 10^{-5}$  Eq/liter, respectively.

Conceptually, this graph may also be seen to dramatize the essentially simple overall nature of the  $[H^+]$  behavior of this solution.  $[H^+]$  depends on  $P_C$  and on [SID], and only on them, and Figure 6.7 shows that dependence. Any change in  $[H^+]$  can only result from a change in  $P_C$  or [SID], or both, just as in Chapter 4,  $[H^+]$  could only change if [SID] changed. A change in  $[H^+]$  cannot be interpreted to indicate that  $H^+$  has been added to or removed from this solution by its environment, but only that strong ions or  $CO_2$  have been. All we have to look at in order to understand what happens to  $[H^+]$  is what happens to strong ions, and what happens to  $P_C$ . Whether or not  $H^+$  is transferred between the solution and its environment is not relevant to what happens to  $[H^+]$ .

Another conceptually important feature of Figure 6.7 is that it clearly shows that  $[H^+]$  does not depend on  $[HCO_3^-]$ . The usual qualitative discussions of this subject are very unclear on this point and make it seem much more complicated than it is by suggesting that  $[H^+]$  depends on  $[HCO_3^-]$  some times, whereas  $[HCO_3^-]$  seems to depend on  $[H^+]$  at other times. As briefly mentioned in Section 6.3,  $[HCO_3^-]$  was very important historically because its value could be calculated from the measured value of total  $CO_2$ , and if  $[H^+]$  was also known,  $P_C$  could then be calculated. Now that we can measure  $P_C$  directly,  $[HCO_3^-]$  is no longer interesting, or even relevant, so far as the equilibrium behavior of  $[H^+]$  is concerned. This statement may be the most startling result of the above quantitative analysis from the historical viewpoint. Figure 6.7 indicates its validity by not mentioning  $[HCO_3^-]$  while providing a complete description of  $[H^+]$  behavior.

It is of course true that the values of  $[H^+]$  and  $[HCO_3^-]$  can be calculated from each other when appropriate by using Equation (6.4.2). That does not mean that either one physically determines the other. As we saw in Section 6.4, it takes all four of the equations describing this system to

determine the value of  $[H^+]$ , or  $[HCO_3^-]$ , or to put it more accurately, to establish just how the value of  $[H^+]$ , or  $[HCO_3^-]$ , is determined by the values of the independent variables in the system,  $P_C$  and [SID].

Sea water, like ISF, contains no significant concentrations of weak electrolytes, but does contain high concentrations of strong ions, mostly  $Na^+$ ,  $Mg^{2+}$ , and  $Cl^-$ . Its [SID] is approximately +0.002 Eq/liter. Sea water is in equilibrium with the atmosphere for  $CO_2$ , so its  $P_C = 0.3$  mm Hg. These two values tell us that at 25 C, using  $K'_w = 1.7 \times 10^{-14}$  (Eq/liter)<sup>2</sup>, sea water must have  $[HCO_3^-] = 0.002$  Eq/liter,  $[CO_3^{2-}] = 3 \times 10^{-5}$  Eq/liter,  $[OH^-] = 4 \times 10^{-6}$  Eq/liter, and  $[H^+] = 4 \times 10^{-9}$  Eq/liter, pH 8.4. These values change significantly with both temperature and pressure.

## 6.8. SUMMARY

1. Carbon dioxide dissolves in, and then reacts with, water to produce four different molecules,  $CO_2$ (dissolved),  $H_2CO_3$ ,  $HCO_3^-$ , and  $CO_3^{2-}$ .  $[CO_2\text{(dissolved)}]$  and  $[H_2CO_3]$  are directly proportional to  $P_{CO_2}$  and do not depend on the [SID] in the solution.
2.  $[HCO_3^-]$ ,  $[CO_3^{2-}]$ ,  $[OH^-]$ , and  $[H^+]$  in a solution containing only strong ions and  $CO_2$  are determined by the values of the two independent variables in the solution, [SID] and  $P_{CO_2}$ . Isolated interstitial fluid is such a solution (Figures 6.1 through 6.7).
3. For physiological conditions, which means positive [SID] and  $P_{CO_2}$  above 0.1 mm Hg,  $[H^+] = K_C \times P_C/[SID]$  is a useful, very close approximation to the exact equation that is cubic in  $[H^+]$  (Figures 6.1, 6.3, and 6.5).
4. For physiological conditions,  $[HCO_3^-]$  in ISF is independent of  $P_{CO_2}$  and approximately equal to [SID] (Figure 6.2).
5.  $[CO_3^{2-}]$  decreases with increasing  $P_{CO_2}$  over the physiological range and increases with [SID]<sup>2</sup> (Figures 6.2 and 6.3).
6. The  $[H^+]$  buffer strength of ISF is  $10^{-4}$  times that of the same solution without  $CO_2$ , but the pH buffer strength is the same as the  $CO_2$ -free solution. A comparable weak acid solution has a lower  $[H^+]$  buffer strength and pH buffer strength than ISF.
7. ISF is buffered to the same extent against changes in [SID] and in  $P_{CO_2}$ , in the sense that the same small percentage change in either of these two independent variables brings about the same percentage change in  $[H^+]$ . The actual value of the  $[H^+]$  change is extremely small, on the order of one-millionth of the change in [SID] that causes it (Table 6.2).
8. The  $[H^+]-P_{CO_2}$  plot is a useful summary of the  $[H^+]$  behavior of isolated ISF. It can be used to evaluate [SID] if  $[H^+]$  (or pH) and  $P_{CO_2}$  are known. It also demonstrates that  $[H^+]$  is not determined by  $[HCO_3^-]$ .

## APPENDIX

6A.1. EQUATION FOR  $[H^+]$ 

Following the same procedure as in previous chapters, we separate variables by using (6.4.1), (6.4.2), and (6.4.3) to express  $[OH^-]$ ,  $[HCO_3^-]$  and  $[CO_3^{2-}]$  in terms of  $[H^+]$ :

$$\text{From (6.4.1)} \quad [OH^-] = K'_w/[H^+] \quad (6A.1.1)$$

$$\text{From (6.4.2)} \quad [HCO_3^-] = K_C \times P_C/[H^+] \quad (6A.1.2)$$

$$\text{From (6.4.3)} \quad [CO_3^{2-}] = K_3 \times K_C \times P_C/[H^+]^2. \quad (6A.1.3)$$

Substituting these into (6.4.4) gives us

$$\begin{aligned} [SID] + [H^+] - K'_w/[H^+] - K_C \times P_C/[H^+] \\ - K_3 \times K_C \times P_C/[H^+]^2 = 0. \end{aligned} \quad (6A.1.4)$$

Clearing of fractions by multiplying through by  $[H^+]^2$  and rearranging gives

$$\begin{aligned} [H^+]^3 + [SID] \times [H^+]^2 - (K_C \times P_C + K'_w) \\ \times [H^+] - K_3 \times K_C \times P_C = 0. \end{aligned} \quad (6A.1.5)$$

Either of these two forms becomes the  $F([H^+])$  for use in the iterative numerical procedure described in the Appendix of Chapter 5 and permits us to evaluate  $[H^+]$  for this system just as we did in that chapter. Equations (6A.1.1), (6A.1.2), and (6A.1.3) can then be used to calculate values for the three other dependent variables.

6A.2. SLOPES AND BUFFER STRENGTHS FOR STRONG IONS PLUS CO<sub>2</sub>

The equation this time is (6A.1.5). Taking derivatives with respect to [SID] of each term and rearranging, we find

$$d[H^+]/d[SID] = \frac{-[H^+]^2}{\{3[H^+]^2 + 2[H^+] \times [SID] - (K_C \times P_C + K'_w)\}}.$$

We may substitute  $[H^+] = K_C \times P_C/[SID]$  because we are only interested in the physiological range, and drop  $K'_w$  because it is at most  $10^{-4}$  times  $K_C \times P_C$ . These substitutions simplify our derivative to

$$d[H^+]/d[SID] = -K_C \times P_C/[SID]^2.$$

As before, the  $[H^+]$  buffer strength for this solution is just the reciprocal of this expression:

$$\left. \begin{array}{l} [H^+] \text{ buffer strength} \\ \text{strong ions plus CO}_2 \\ [\text{SID}] \text{ positive} \\ P_C \text{ above } 0.1 \text{ mm Hg} \end{array} \right\} = -[SID]^2/K_C \times P_C. \quad (6A.2.1)$$

At  $[SID] = 0.031$  Eq/liter and  $P_C = 50$  mm Hg, this is 740,000 strong ions/ $H^+$ .

For the pH buffer strength, we again use Equation (5A.5.6) in the Appendix of Chapter 5 to go from  $d[H^+]/d[SID]$  to  $d\text{pH}/d[SID]$ . The result is:

$$\left. \begin{array}{l} \text{pH buffer strength} \\ \text{strong ions plus CO}_2 \\ [\text{SID}] \text{ positive,} \\ P_C \text{ above } 0.1 \text{ mm Hg} \end{array} \right\} = 2.3 \times [\text{SID}] \text{ Eq/liter.} \quad (6A.2.2)$$

It is surprising that this pH buffer strength is independent of  $P_C$ .

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## CHAPTER SEVEN

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# **STRONG IONS PLUS CARBON DIOXIDE PLUS WEAK ACID ISOLATED BLOOD PLASMA AND ISOLATED INTRACELLULAR FLUID**

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### **7.1. INTRODUCTION**

We have so far analyzed the quantitative behavior of  $[H^+]$  in water, in strong ion solutions, in solutions containing strong ions plus weak acid, and in solutions containing strong ions plus  $CO_2$ . As pointed out in Chapter 5, blood plasma is essentially a solution containing strong ions plus weak acid plus  $CO_2$ , so that the next logical step is to examine  $[H^+]$  behavior in such a solution, and that is our task in this chapter. We shall thereby complete our analysis of the acid-base properties of all major body fluids presented in Chapter 1.

Blood plasma will be considered first because it is the body fluid for which the most and best analytical data are available. Intracellular fluids also contain strong ions, weak acids, and  $CO_2$ , so that they have similar, but not identical,  $[H^+]$  behaviors. The intracellular fluid of red blood cells, designated RBC-ICF for convenience, is the best known and can be described quantitatively with the same level of confidence as plasma. Intracellular fluids of other tissue cells are not uniform in composition and differ significantly from RBC-ICF. We shall therefore also examine the properties of a generalized representative intracellular fluid and refer to it as ICF.

Preparation of isolated blood plasma involves separating it from RBCs; it is therefore referred to clinically as separated plasma. We shall use the terms "separated" and "isolated" interchangeably.

A solution containing strong ions plus  $CO_2$  plus weak acid may be seen as the result of adding  $CO_2$  to the solution analyzed in Chapter 5, or of

adding weak acid to the solution analyzed in Chapter 6. In both cases, the comparisons are informative and sometimes surprising. The reader is urged to cross-compare corresponding graphs between these three chapters frequently. Generally speaking, it turns out that the  $\text{CO}_2$  is much more important than the weak acid.

Isolated blood plasma contains strong ions,  $\text{CO}_2$  and its products, many small organic molecules, and many proteins. The proteins serve a number of different roles. They are involved in immunological responses, they transport lipids, hormones, and other substances, they increase the osmolar concentration of plasma above that of ISF, and they function as weak acids. For our purposes in this chapter, only the last function is of interest. It is likely that there are in excess of 5,000 different molecular species of protein in plasma, each one at a rather low concentration and each one showing a whole range of  $K_A$  values, due to its own specific set of amino acid side chains. Many of the small organic molecules in the plasma also function as weak acids, notably organic phosphates. To carry through a careful quantitative specification of all the  $[A_{\text{TOT}}]$  and  $K_A$  values that this complex assembly contains would therefore be a hopelessly intricate and time-consuming task, if in fact it could even be accomplished. Fortunately, it can be shown that the end result of such a complete analysis, if it were practical, would be an  $[\text{H}^+]$  behavior indistinguishable for any useful purpose from that obtained in the next section by lumping all these weak acids into one and letting a single  $[A_{\text{TOT}}]$  and  $K_A$  value represent them. For the purposes of this analysis and understanding, we shall accept this simplified ideal solution as an adequate model for real isolated blood plasma. Comparable remarks apply to our model RBC-ICF and ICF. Fortunately, the quantitative differences between these models and the real world are generally well within the accuracy and meaning of available clinical measurements.

## 7.2. QUANTITATIVE ANALYSIS OF ISOLATED BLOOD PLASMA: STRONG IONS PLUS WEAK ACID PLUS $\text{CO}_2$

The components of this solution are, in decreasing order of concentration, water, strong ions,  $\text{HCO}_3^-$ ,  $\text{A}^-$ ,  $\text{HA}$ ,  $\text{CO}_2(\text{dissolved})$ ,  $\text{CO}_3^{2-}$ ,  $\text{H}_2\text{CO}_3$ ,  $\text{OH}^-$ , and  $\text{H}^+$ . The independent variables are the  $[\text{SID}]$ , the  $\text{CO}_2$  partial pressure,  $P_C$ , and the total amount of weak acid present,  $[A_{\text{TOT}}]$ . There are four parameters that must be specified,  $K'_w$ ,  $K_A$ ,  $K_C$ , and  $K_3$ , as defined in previous chapters. There are eight dependent variables, two of which we shall largely ignore,  $[\text{CO}_2(\text{dissolved})]$  and  $[\text{H}_2\text{CO}_3]$ , because their values are simply proportional to  $P_C$  and unaffected by  $[\text{SID}]$  or  $[A_{\text{TOT}}]$  (unless the latter alter the solubility of  $\text{CO}_2$ !) and easily found whenever wanted from Equations (6.2.1) and (6.3.1).

For the other six dependent variables,  $[\text{HCO}_3^-]$ ,  $[\text{A}^-]$ ,  $[\text{HA}]$ ,  $[\text{CO}_3^{2-}]$ ,  $[\text{OH}^-]$ , and  $[\text{H}^+]$ , we need six equations. Given the procedure of the last three chapters, they almost write themselves.

Water dissociation:

$$[\text{H}^+] \times [\text{OH}^-] = K_w \quad (7.2.1)$$

Weak acid dissociation:

$$[\text{H}^+] \times [\text{A}^-] = K_A \times [\text{HA}] \quad (7.2.2)$$

Weak acid conservation:

$$[\text{HA}] + [\text{A}^-] = [\text{A}_{\text{TOT}}] \quad (7.2.3)$$

$\text{HCO}_3^-$  formation:

$$[\text{H}^+] \times [\text{HCO}_3^-] = K_C \times P_C \quad (7.2.4)$$

$\text{CO}_3^{2-}$  formation:

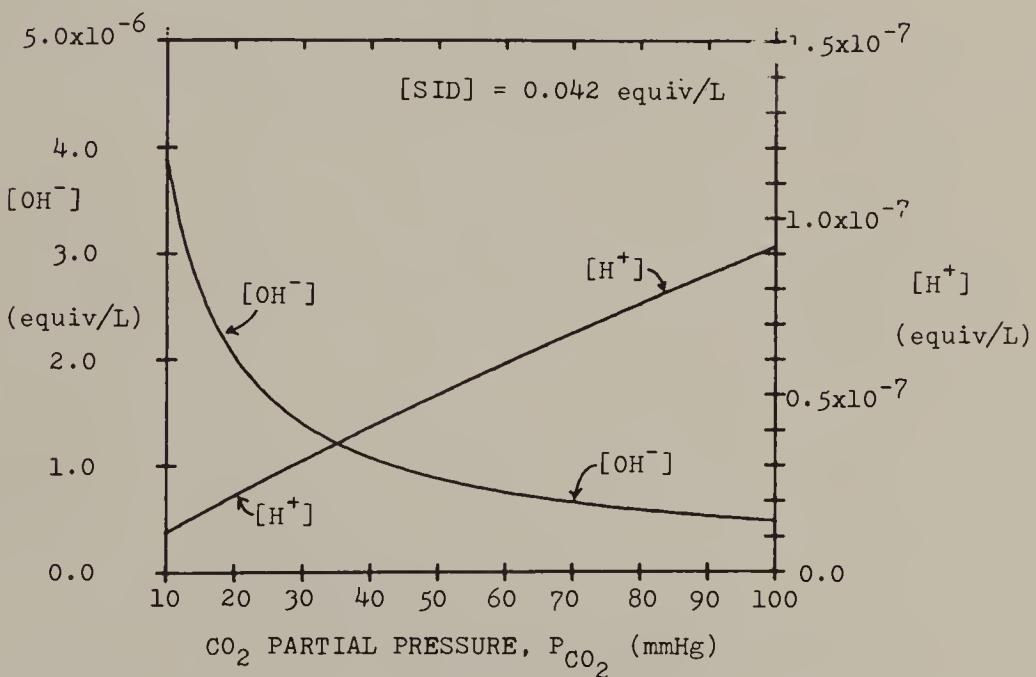
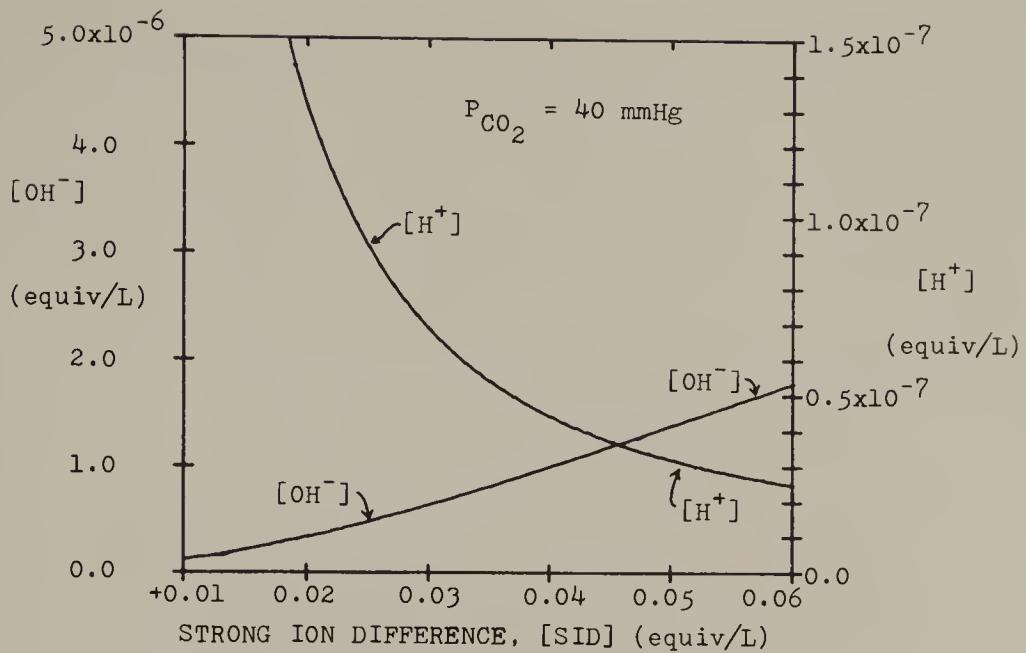
$$[\text{H}^+] \times [\text{CO}_3^{2-}] = K_3 \times [\text{HCO}_3^-] \quad (7.2.5)$$

Electrical Neutrality:

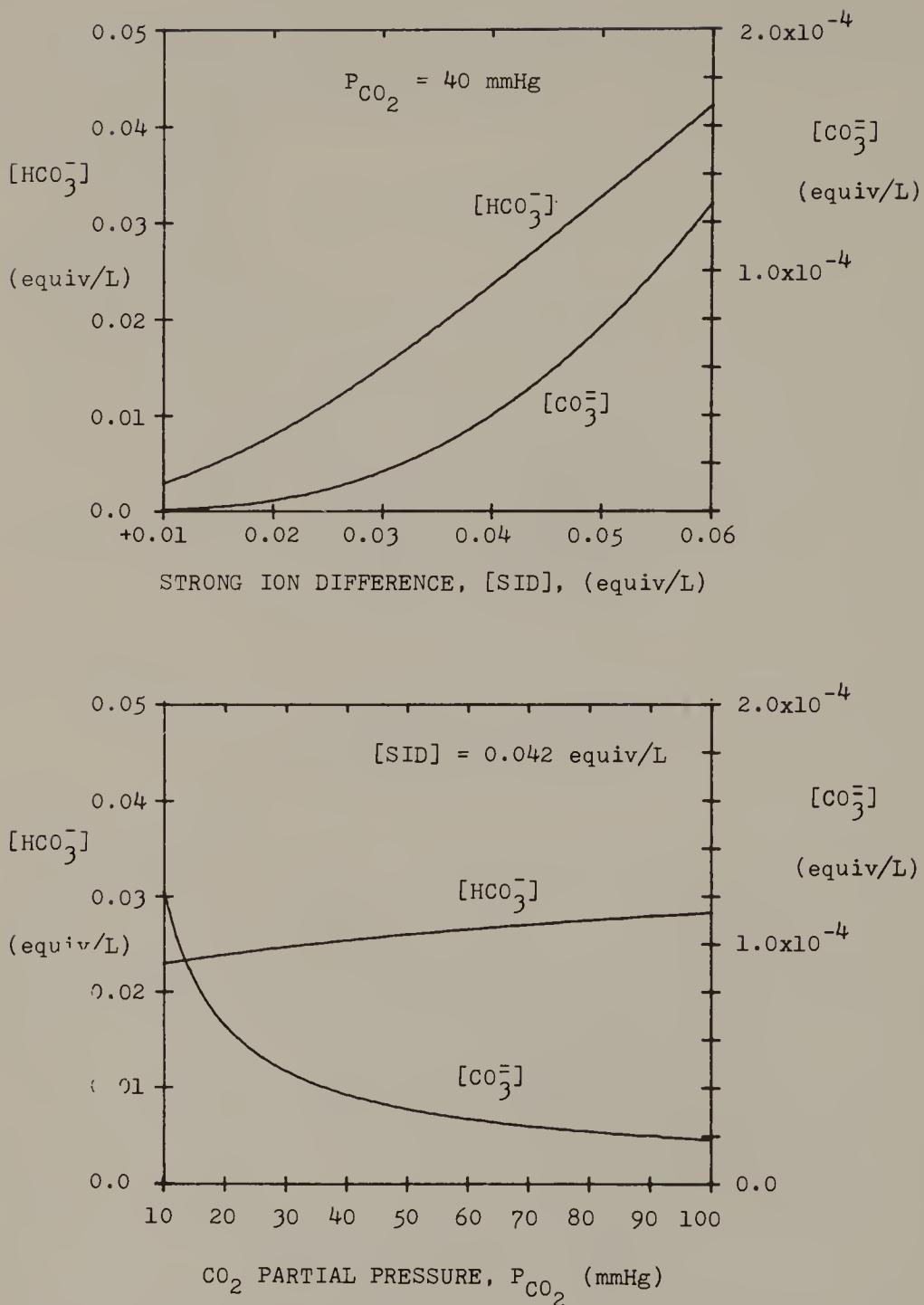
$$[\text{SID}] + [\text{H}^+] - [\text{HCO}_3^-] - [\text{A}^-] - [\text{CO}_3^{2-}] - [\text{OH}^-] = 0. \quad (7.2.6)$$

This formidable array of equations may be combined and rearranged, just as in previous chapters, into a single equation for  $[\text{H}^+]$  in terms of  $[\text{SID}]$ ,  $P_C$ ,  $[\text{A}_{\text{TOT}}]$ , and the parameters. This time the equation is a fourth-order polynomial, as detailed in the Appendix of this chapter, but our computer-implemented solution process handles this easily and enables us to calculate  $[\text{H}^+]$  as well as all the other dependent variables, as desired. Selected results are displayed in Figures 7.1 through 7.6.

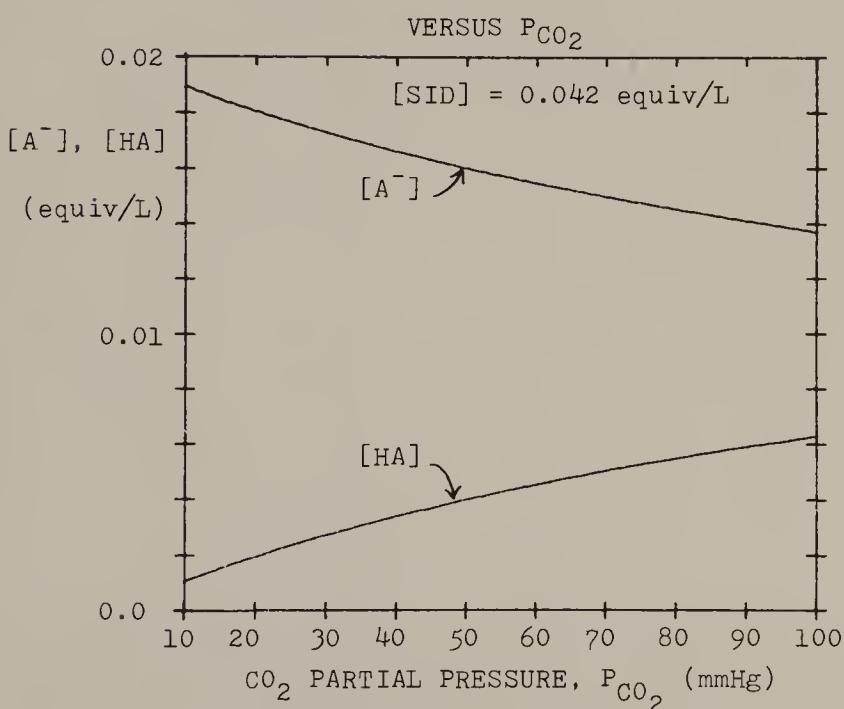
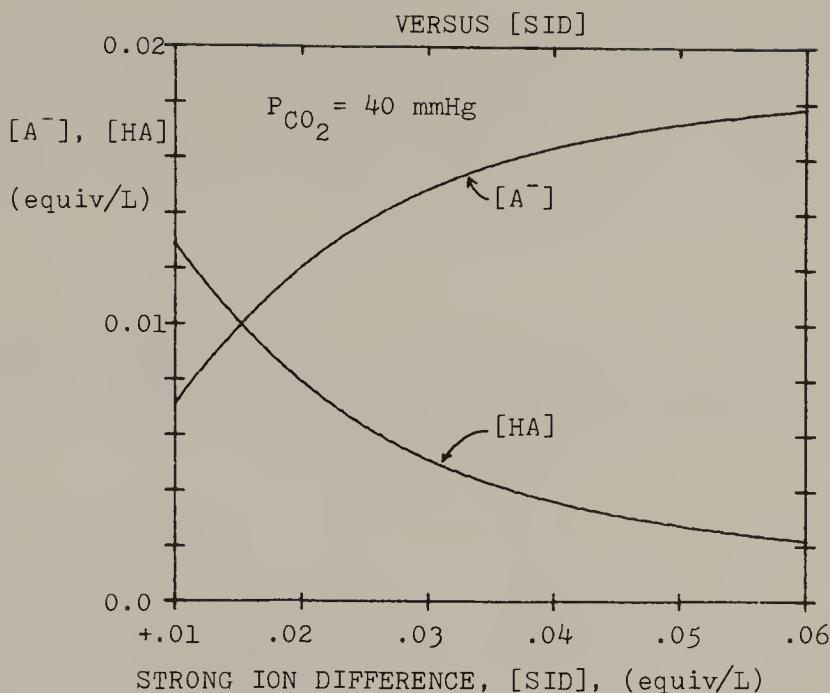
Because we now have three independent variables, we should need a four-dimensional plot to show the complete dependence of  $[\text{H}^+]$  on those three variables. Fortunately, it is very rare for  $[\text{A}_{\text{TOT}}]$  to change significantly under physiological conditions, so that it is reasonable, and very convenient, to hold  $[\text{A}_{\text{TOT}}]$  constant. We can now treat the solution graphically just as we did the simpler ISF solution in the previous chapter. Figures 7.1, 7.2, 7.4, 7.5, and 7.6 may therefore be compared directly with their counterparts in Chapter 6. Figure 7.3 displays the behavior of  $[\text{A}^-]$  and  $[\text{HA}]$  as  $[\text{SID}]$  and  $P_C$  vary over the physiological range, and may be compared with its counterpart in Chapter 5, Figure 5.1.



**Figure 7.1.**  $[\text{H}^+]$  and  $[\text{OH}^-]$  for isolated standard blood plasma plotted against [SID] in the upper graph and against  $P_{\text{CO}_2}$  in the lower.  $[\text{A}_{\text{TOT}}]$  values are constant at 0.02 Eq/liter. Left-hand scales are for  $[\text{OH}^-]$ , right-hand for  $[\text{H}^+]$ . Parameter values used are listed in Table 7.4 and apply to all of the following figures for plasma.



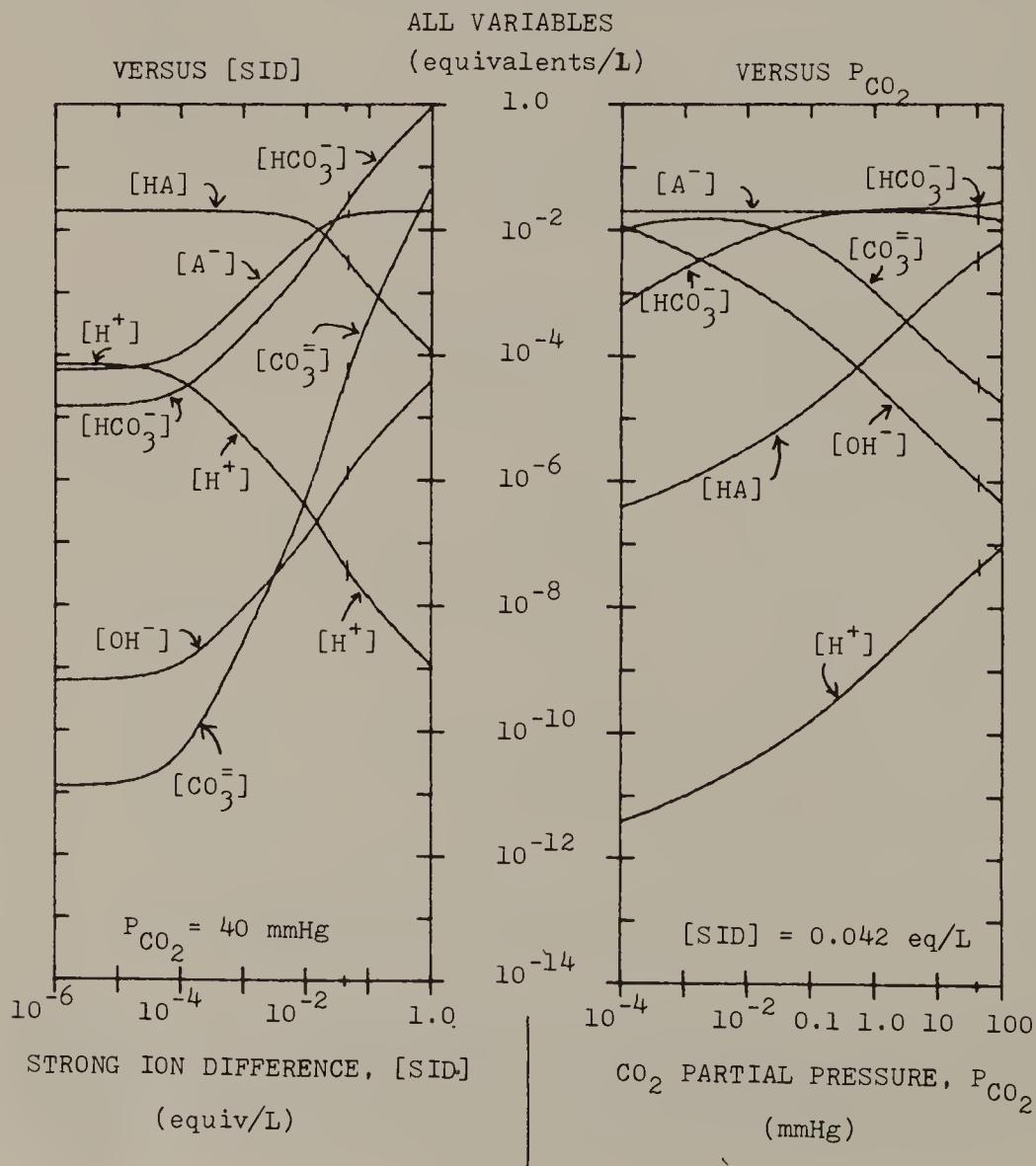
**Figure 7.2.**  $[HCO_3^-]$  and  $[CO_3^{2-}]$  plotted against [SID] and  $P_{CO_2}$ , as indicated, for isolated plasma.  $[A_{TOT}]$  values are constant at 0.02 Eq/liter. Left-hand scales for  $[HCO_3^-]$ , right-hand for  $[CO_3^{2-}]$ . Horizontal scales are the same as in Figure 7.1.

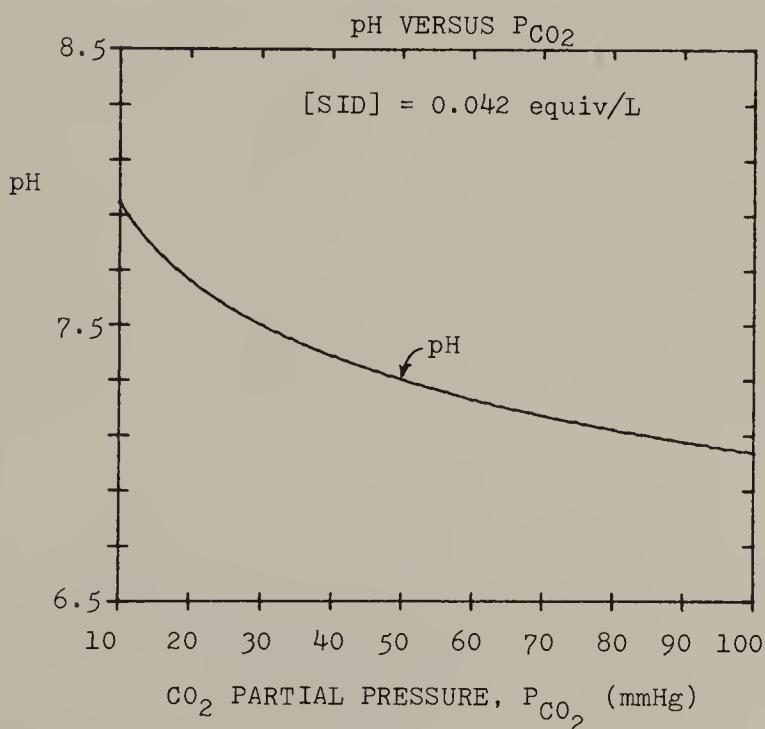
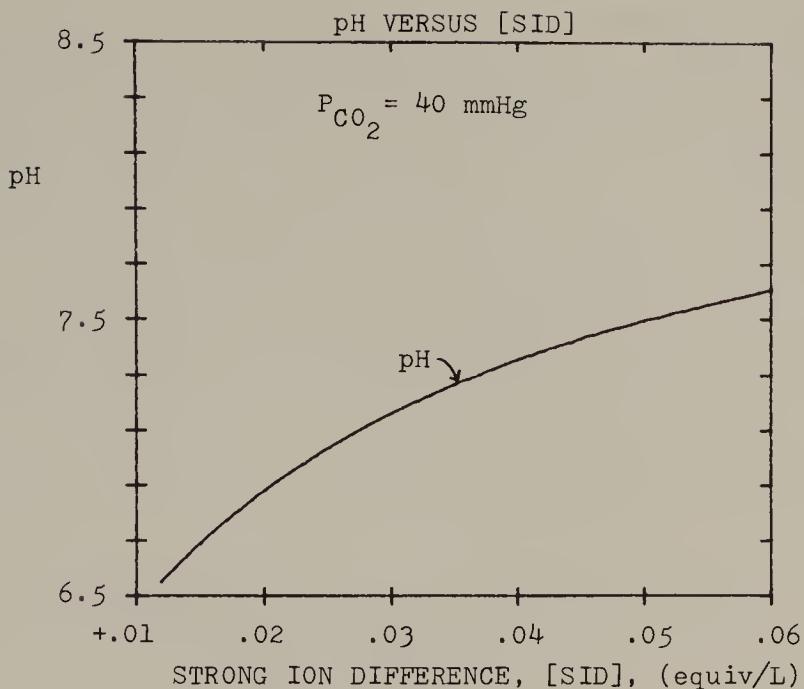


**Figure 7.3.**  $[A^-]$  and  $[HA]$  plotted against [SID] and  $P_{CO_2}$ , as indicated, for isolated plasma.  $[A_{TOT}]$  values are constant at 0.02 Eq/liter. Horizontal scales are the same as in Figures 7.1 and 7.2.

Once again we are faced with an enormous amount of information, and the significance of all these graphs takes some time to digest. Furthermore, such a small number of graphs cannot display the complete range of behavior of this solution. The major items to understand as a basis for explaining plasma's role in whole-body acid-base behavior are therefore summarized in the following subsections.

**Figure 7.4.** Log-log plots of all six dependent variables in plasma, against [SID] in the left-hand graph, and against  $P_{CO_2}$  in the right-hand graph.  $[A_{TOT}]$  values are constant at 0.02 Eq/liter. Compare with Figure 6.3.



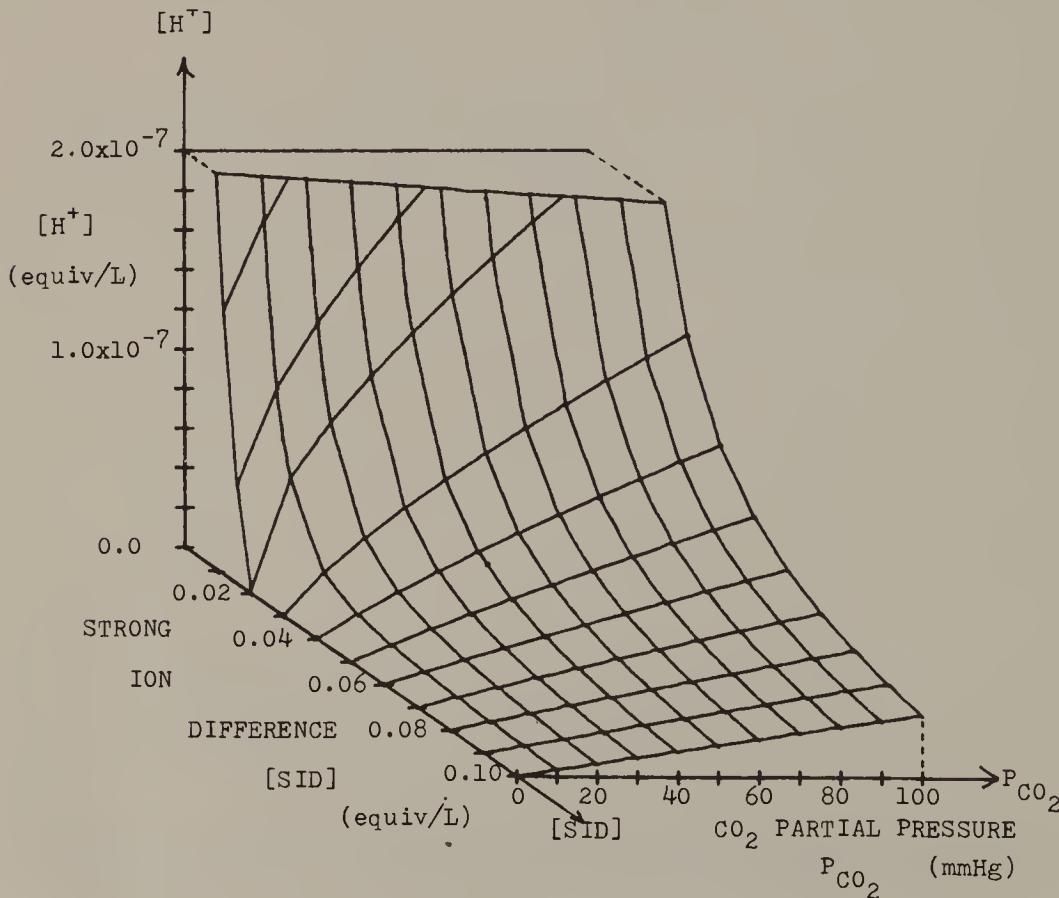


**Figure 7.5.** pH for isolated plasma plotted against [SID] and  $P_{CO_2}$ .  $[A_{TOT}]$  values are constant at 0.02 Eq/liter. Compare with Figure 7.1.

### 7.2a. $[H^+]$ and $[OH^-]$ Behavior (Figures 7.1, 7.4, and 7.6)

In general,  $[H^+]$  decreases nonlinearly with increasing positive [SID] and increases with increasing  $P_{CO_2}$ .  $[H^+]$  is slightly larger in this solution at given [SID] and  $P_{CO_2}$  values than it is in ISF where no weak acid is present.  $[OH^-]$  rises with increasing positive [SID], but nonlinearly, and falls nonlinearly with increasing  $P_{CO_2}$ . The log-log plots of Figure 7.4 emphasize the nonlinearity of all these relationships. Figure 7.6 shows a projection of the  $[H^+]$ -[SID]- $P_{CO_2}$  surface and provides the same sort of qualitative picture as Figure 6.5 did for ISF. The major conclusions from all these graphs are that  $[H^+]$  is still the smallest component in this solution under physiological conditions and that increasing [SID] or decreasing  $P_{CO_2}$  lowers  $[H^+]$  whereas decreasing [SID] or increasing  $P_{CO_2}$  raises  $[H^+]$ .

**Figure 7.6.** Perspective view of  $[H^+]$ -[SID]- $P_{CO_2}$  surface for isolated plasma. Compare with Figure 7.1, which can be seen as two perpendicular slices through this surface.



Not shown on these figures is the response to negative [SID] values. As might be expected from the results in Chapters 5 and 6,  $[H^+]$  in this solution when [SID] is negative behaves as if neither the  $CO_2$  nor the weak acid were present.  $[H^+]$  is just equal to  $-[SID]$  as it was in Chapter 4, and all the weak anions are present in very small concentrations only.

The pH curves corresponding to these  $[H^+]$  curves are displayed in Figure 7.5. As expected from the nonlinearity of the  $[H^+]$  to pH transform, pH rises nonlinearly with [SID] and falls nonlinearly with  $P_C$ . These curves may also be of interest in the context of the pH buffer strength values of this solution, to be discussed in Section 7.3.

### 7.2b. $[HCO_3^-]$ and $[CO_3^{2-}]$ Behavior (Figures 7.2 and 7.4)

$[HCO_3^-]$  in this solution increases with increasing positive [SID], but nonlinearly. The electrical neutrality equation in this system can be very closely approximated by

$$[SID] = [HCO_3^-] + [A^-] \quad (7.2.7)$$

because  $[HCO_3^-]$  and  $[A^-]$  are orders of magnitude larger than the concentrations of the other three weak ions. Both  $[HCO_3^-]$  and  $[A^-]$  change with [SID], and via different relationships, so there is no reason to expect one to depend linearly on [SID]. For this reason, this equation is not of much practical use. In particular, it tells us nothing at all about  $[H^+]$ , because  $[H^+]$  has to be ignored to write this equation.

$[HCO_3^-]$  in this solution does depend on  $P_C$ ; it increases with increasing  $P_C$ , although not very rapidly. This behavior may be qualitatively seen from Equation (7.2.7) above, for  $[A^-]$  also depends on  $P_C$ , and we are keeping [SID] constant when we vary  $P_C$  in these figures.

$[CO_3^{2-}]$  decreases with increasing  $P_C$  very much as it did in ISF and increases with increasing [SID]. Its value is significantly smaller in this solution than in ISF, however.

### 7.2c. $[A^-]$ and $[HA]$ Behavior (Figures 7.3 and 7.4)

The behavior of  $[A^-]$  and  $[HA]$  in this solution is no longer linear with [SID] over the zero to  $[A_{TOT}]$  range, as it was in Chapter 5. In fact, neither the  $[SID] = [A_{TOT}]$  nor the  $[SID] = [A_{TOT}]/2$  points have any special significance in this solution.  $[A^-]$  increases nonlinearly with [SID], appearing to asymptote toward a value of  $[A_{TOT}]$  at very large [SID], whereas  $[HA]$  decreases correspondingly.

With increasing  $P_C$ ,  $[A^-]$  falls and  $[HA]$  rises, but not very dramatically. Both quantities are clearly more sensitive to changes in [SID] than in  $P_C$ .

Although these curves are not very interesting from the point of view of understanding  $[H^+]$  behavior in this isolated solution, their counterparts for intracellular fluid may be very interesting, because these curves represent changes in the effective charge on protein molecules, and such changes may, in turn, alter the enzymatic, or other, function of those molecules. What is important to understand from the analysis of this chapter is that these changes are dependent on, and physically caused by, changes in  $[SID]$  and  $P_C$ , just as changes in  $[H^+]$  are, but it is not, from this analysis and the reactions it is based on, changes in  $[H^+]$  that determine changes in  $[A^-]$ , or vice versa.

#### 7.2d. Gamblegram (Figure 7.7)

The gamblegram for isolated plasma under standard conditions is shown in Figure 7.7. Comparison with Figure 6.6 indicates that  $[HCO_3^-]$  now shares with  $[A^-]$  the electrical "space" or "gap" represented by the  $[SID]$  value and that all the other weak ions are present at very low concentrations, as usual.

### 7.3. BUFFERING AND BUFFER STRENGTHS IN ISOLATED PLASMA

Although it is still in principle possible to derive formulas for  $[H^+]$  buffer strength and pH buffer strength for isolated plasma by applying simple calculus to the fourth-order polynomial equation for  $[H^+]$  derived in the Appendix, it is much easier simply to calculate the changes in  $[H^+]$  and pH in response to small changes in  $[SID]$  or  $P_C$  or both, as we did in Table 6.2. This is even more informative than calculating buffer strengths because what we are really interested in is how much  $[H^+]$  changes in response to specific, finite changes in  $[SID]$  and  $P_C$  such as occur clinically. Buffer strengths per se are simply a means to that end.

The results of a series of such calculations are presented in Table 7.1. The following conclusions may be drawn from those results.

Despite its additional weak acid component, this solution is no better a buffer than ISF. Its  $[H^+]$  buffer strength calculated from Table 7.1 at  $[SID] = 0.042$  Eq/liter and  $P_C = 40$  mm Hg is  $-7 \times 10^5$  strong ions/ $H^+$ . Its pH buffer strength is 0.07 Eq/liter. For the ISF solution of Chapter 6, with no weak acid, but with  $[SID] = +0.031$  Eq/liter and  $P_C = 50$  mm Hg, the corresponding values are identical. At  $[SID] = +0.042$  Eq/liter and  $P_C = 40$  mm Hg, on the other hand, ISF  $[H^+]$  buffer strength is  $-1.7 \times 10^6$  strong ions/ $H^+$ , and pH buffer strength is 0.1 Eq/liter. From these values, as well as from the curves in this and the preceding two chapters, we may conclude that the presence of the weak acid in plasma decreases, rather than augments, the buffering ability of plasma.

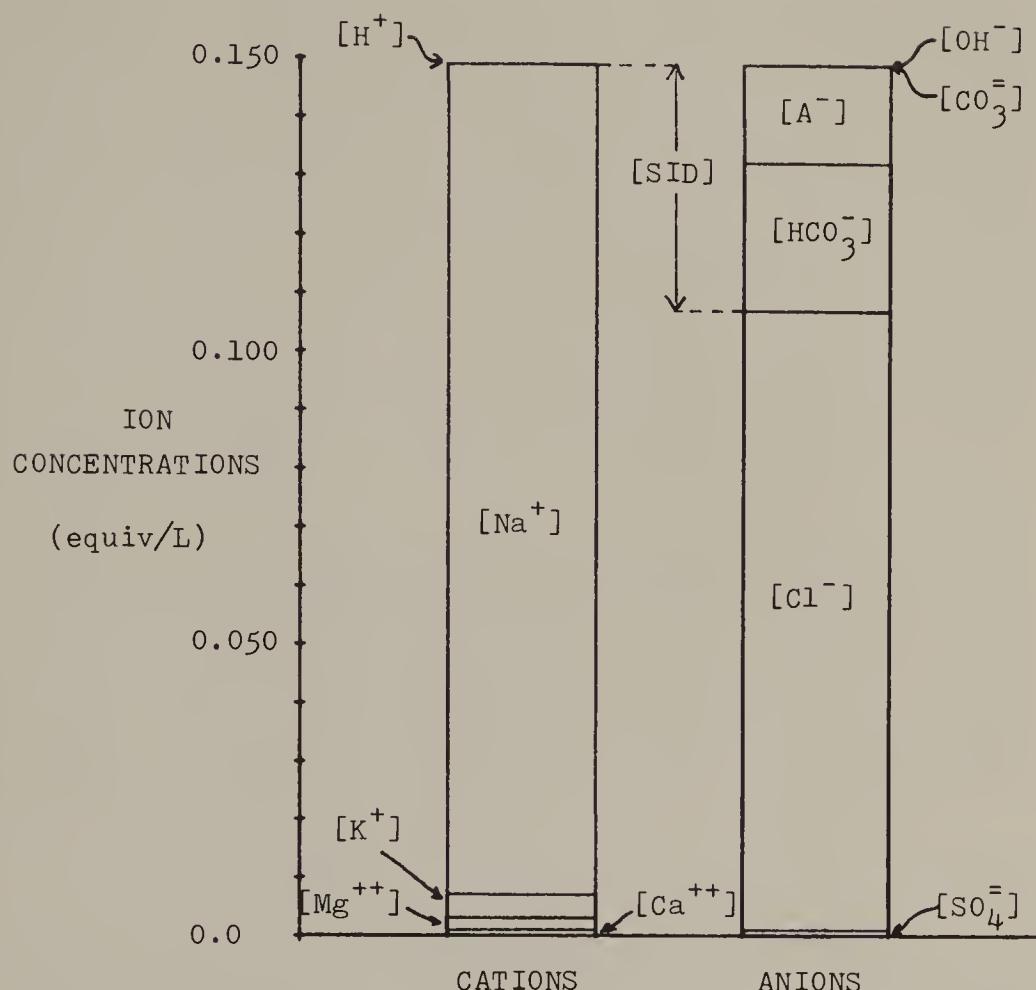


Figure 7.7. Gamblegram for isolated plasma at  $P_{CO_2} = 40$  mm Hg and  $[SID] = 0.042$  Eq/liter,  $[A_{TOT}] = 0.02$  Eq/liter.

This result of the quantitative analysis is just the reverse of conventional treatments of plasma, in which significant buffering contributions are generally attributed to the weak acid (protein) component. Although the conventional approach seems qualitatively reasonable, it overlooks two important features of ionic solutions that the quantitative treatment forces us to take into account. The first is the size of  $[SID]$  relative to  $[A_{TOT}]$ . As we saw in Chapter 5, the conventional treatment of a weak acid solution as a "buffer" only applies when  $[SID]$  is very close to  $[A_{TOT}]/2$ . In plasma,  $[SID]$  is more than four times larger than  $[A_{TOT}]/2$ , so we should not expect any buffering in the conventional sense.

The second, and more fundamental, point is that the properties of mixtures are seldom simply the sum of properties of their components. In fact, the properties of complex systems, such as the solution analyzed in this and the previous sections, are often quite contrary to qualitative

TABLE 7.1. Isolated Plasma: Responses to Small Changes in [SID] and  $P_{CO_2}$ 

[SID] (mEq/liter)	% change	$P_{CO_2}$ (mm Hg)	% change	Independent variables				Dependent variables			
				[H <sup>+</sup> ] (Eq/liter)	% change	pH	% change	[HCl <sub>3</sub> <sup>-</sup> ] (mEq/liter)	% change		
42.0	—	40.0	—	4.07 × 10 <sup>-8</sup>	—	7.39	—	25.3	—		
44.1	+5.0	40.0	—	3.79 × 10 <sup>-8</sup>	-7.0	7.42	+0.4	27.2	+7.5		
39.9	-5.0	40.0	—	4.40 × 10 <sup>-8</sup>	+8.0	7.36	-0.4	23.5	-7.1		
42.0	—	42.0	+5.0	4.25 × 10 <sup>-8</sup>	+4.5	7.37	-0.3	25.5	+0.8		
42.0	—	38.0	-5.0	3.89 × 10 <sup>-8</sup>	-4.5	7.41	+0.3	25.2	-0.4		
44.1	+5.0	42.0	+5.0	3.96 × 10 <sup>-8</sup>	-2.8	7.40	+0.1	27.4	+8.3		
39.9	-5.0	38.0	-5.0	4.20 × 10 <sup>-8</sup>	+3.2	7.38	-0.2	23.3	-7.9		
44.1	+5.0	43.3	+8.3	4.07 × 10 <sup>-8</sup>	—	7.39	—	27.4	+8.3		
39.9	-5.0	36.7	-8.3	4.07 × 10 <sup>-8</sup>	—	7.39	—	23.2	-8.3		

Composition (standard values):  $[Na^+] = 0.143$ ;  $[Cl^-] = 0.107$ ;  $[HCO_3^-] = 0.0253$ ;  $[A^-] = 0.017$ ;  $[K^+] = 0.004$ ;  $[HA] = 0.003$ ;  $[Mg^{2+}] = 0.002$ ;  $[Ca^{2+}] = 0.001$ ;  $[SO_4^{2-}] = 0.001$ ;  $[CO_3^{2-}] = 3.7 \times 10^{-5}$ ;  $[OH^-] = 1.1 \times 10^{-6}$ ;  $[H^+] = 4.07 \times 10^{-8}$ ; all in Eq/liter.  $P_{CO_2} = 40$  mm Hg;  $[CO_2(dsvd)] = 0.012$ ;  $[Ar_{tot}] = 0.020$ ; all in Eq/liter.

Parameters:  $K'_v = 4.4 \times 10^{-14}$  (Eq/liter)<sup>2</sup>;  $K_A = 2.0 \times 10^{-7}$  Eq/liter;  $K_3 = 6.0 \times 10^{-11}$  Eq/liter;  $K_C = 2.58 \times 10^{-11}$  (Eq/liter)<sup>2</sup>/mm Hg.

predictions. In this case, to explain and understand the properties of this solution we must include the information embodied in all six of the quantitative relationships between its components, Equations (7.2.1) through (7.2.6). Equations (7.2.2), dealing with  $[H^+]$  and  $[A^-]$ , and (7.2.4), dealing with  $[H^+]$  and  $[HCO_3^-]$ , are not enough and cannot tell the story. When we include all six equations, we get the results displayed in the figures, and those results tell us that, quite contrary to what we expected after putting Chapters 5 and 6 together in our heads, adding a weak acid to a  $CO_2$ -containing solution actually decreases the buffering ability of that solution rather than increases it. It is important to remember also that we are dealing here only with isolated plasma, although a similar problem arises when we analyze the behavior of whole blood in Chapter 8.

The apparently paradoxical nature of this result may be somewhat diminished by recalling that in Chapter 5 we concluded from the quantitative analysis of buffer strengths that adding a weak acid to a simple strong ion solution decreased rather than increased its buffer strength. In Chapter 6, also, adding  $CO_2$  to a simple strong ion solution decreased its buffer strength. On this basis, it is not quite so surprising that adding a weak acid diminishes the buffering ability of a  $CO_2$ -containing solution, but to understand how it does, and by how much, we have to have the quantitative analysis of the previous section.

Isolated plasma is more sensitive to changes in [SID] than to changes in  $P_C$ . This can be seen most clearly in the last two rows of Table 7.1, which show that an 8.3% change in  $P_C$  is required to compensate for a 5% change in [SID] and keep  $[H^+]$  unchanged from its standard value. Isolated ISF, in Chapter 6, turned out to be equally sensitive to [SID] or  $P_C$  changes.

The use of relative changes, expressed as percentages, in Table 7.1 is a convenient way of comparing [SID] and  $P_C$  effects, but it should not obscure the enormous differences in actual magnitude between [SID] changes and  $[H^+]$  changes. The generally large numerical values of the  $[H^+]$  buffer strengths also may serve to keep this distinction in view, but it is useful to review the numbers involved. For example, a 5% change in [SID] means a change of 2.1 mEq/liter in strong ion concentration, most likely  $[Na^+]$  or  $[Cl^-]$ . The result in isolated plasma is an  $[H^+]$  change of only 3 nEq/liter, so the [SID] change is roughly a million times larger. At the same time, the change in  $[HCO_3^-]$  is only slightly less than the strong ion change, namely, 1.9 mEq/liter, and also about a million times larger than the  $[H^+]$  change. Similarly, a 2 mm Hg change in  $P_C$  results in a 2 nEq/liter change in  $[H^+]$ , but a 0.2 mEq/liter change in  $[HCO_3^-]$ , more than 100,000 times the  $[H^+]$  change.

A little further exploration of the numbers involved in this solution shows that the actual changes in  $[OH^-]$  are generally about 30 times,

changes in  $[CO_3^{2-}]$  several thousand times, and changes in  $[A^-]$  several hundred thousand times larger than the changes in  $[H^+]$ .

For all the above analyses, we have kept  $[A_{TOT}]$  in this solution constant at 0.02 Eq/liter. We may also ask how sensitive  $[H^+]$  is to changes in this third independent variable. The necessary calculations are easily carried through and lead to the results summarized in Table 7.2. Isolated plasma is not as sensitive to changes in  $[A_{TOT}]$  as it is to changes in  $[SID]$  or  $P_{CO_2}$ . Calculations such as those required for Tables 7.1 and 7.2 show that in this solution a 1% change from standard conditions in  $[H^+]$  requires a 0.7% change in  $[SID]$ , or a 1.1% change in  $P_{CO_2}$ , or a 1.7% change in  $[A_{TOT}]$ .

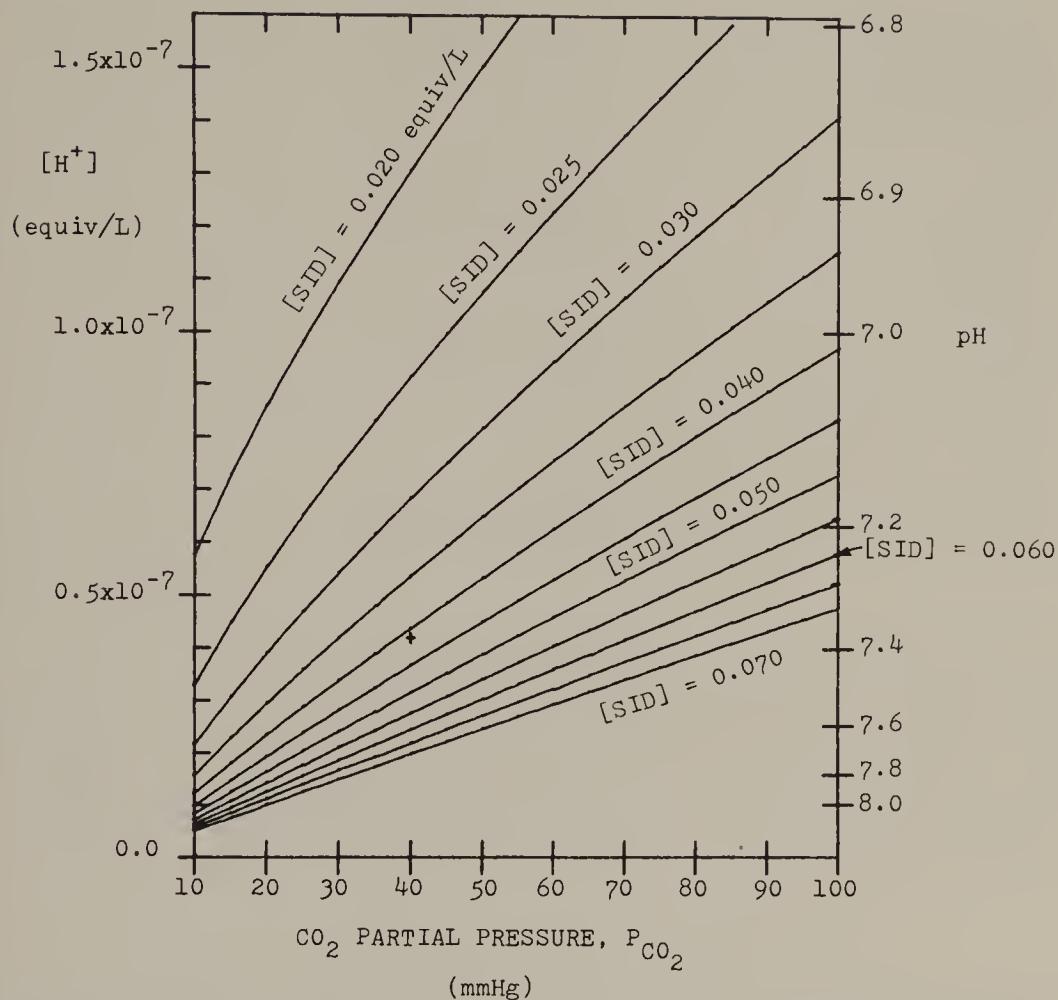
#### 7.4. THE $[H^+]-P_{CO_2}$ GRAPH FOR ISOLATED PLASMA

In Chapter 6, the  $[H^+]-P_{CO_2}$  diagram, Figure 6.7, was presented as a useful means of encompassing all the  $[H^+]$  behavior of isolated ISF. In the same spirit, Figure 7.8 presents the corresponding curves for isolated plasma over a range of  $[SID]$  values. Comparison of the two figures shows again that their  $[H^+]$  behaviors, although similar, are significantly different in detail. For a given  $[SID]$  value,  $[H^+]$  is larger and more sensitive to  $P_{CO_2}$ , in plasma than in interstitial fluid.

As pointed out frequently, measurements of  $P_C$  and pH are very often carried out on blood plasma. From Figure 7.8 we may use those data to evaluate  $[SID]$  and thereby gain a clear picture of the acid-base status of the sample and of the patient from whom it came. We shall therefore return to this diagram later, in the context of interpreting clinical measurements. For the present, it may be viewed as a kind of graphical computer, enabling us to find the value of any one of  $[H^+]$ ,  $[SID]$ , or  $P_C$  whenever the other two are known.

A similar diagram to Figure 7.8 is sometimes presented in conventional acid-base discussions, but with lines of constant  $[HCO_3^-]$  instead of constant  $[SID]$ . This presumably stems from the common misunderstanding of the roles of both  $[HCO_3^-]$  and  $[H^+]$  as dependent variables. Because  $[HCO_3^-]$  is a dependent variable, we could easily plot  $[HCO_3^-]$  versus  $P_{CO_2}$  curves for a variety of  $[SID]$  values in a figure analogous to Figure 7.8. It would be of no practical use, however, for we have no convenient analytical procedure for determining  $[HCO_3^-]$  in plasma samples. More important conceptually, it is not clear why information about  $[HCO_3^-]$  would be useful if  $[H^+]$ ,  $P_C$ , and  $[SID]$  were already known, as they would have to be evaluated  $[HCO_3^-]!$  Involving  $[HCO_3^-]$  in discussions of  $[H^+]$  behavior can only add confusion, for they are both dependent variables. Neither one is explained by, nor caused by, the other; they are both dependent on the values of  $[SID]$ ,  $P_{CO_2}$ , and  $[A_{TOT}]$ .

In many clinical situations, plasma pH is known, but plasma  $P_{CO_2}$  is



**Figure 7.8.**  $[H^+]$ - $P_{CO_2}$  diagram for isolated plasma. For each curve,  $[SID]$  is constant, at the value indicated.  $[A_{TOT}]$  values are constant at 0.02 Eq/liter. The + indicates the standard value of Figure 7.7, at which  $[H^+] = 4.1 \times 10^{-8}$  Eq/liter, pH 7.39.

not. Total  $CO_2$  content of plasma is usually measured instead of  $P_{CO_2}$ .  $[HCO_3^-]$  may be calculated approximately from total  $CO_2$ , and Equation (7.2.4) may then be used to calculate  $P_{CO_2}$  equally approximately. This chain of calculations should not be permitted to confuse the physical cause-effect relationships; the fact that the  $P_{CO_2}$  value can be calculated from the  $[HCO_3^-]$  and the  $[H^+]$  values does not mean that  $[HCO_3^-]$  determines  $P_{CO_2}$ .

## 7.5. INTRACELLULAR FLUID OF RED BLOOD CELLS

Red blood cells (RBC) are highly specialized cells, but they have great experimental merit because they are easy to isolate and analyze. Their physiology and composition have therefore been extensively studied.

TABLE 7.2. Isolated Plasma: Sensitivity to  $[A_{TOT}]$  Changes

Independent				Dependent			
$[A_{TOT}]$ Eq/liter	$\% \text{ change}$	$[H^+]$ Eq/liter	Change Eq/liter	pH	$\% \text{ change}$	$[A^-]$ Eq/liter	$\% \text{ change}$
0.020	—	$4.07 \times 10^{-8}$	—	7.39	—	0.0166	—
0.021	+ 5.0%	$4.19 \times 10^{-8}$	$+ 1.2 \times 10^{-9}$	7.38	- 0.2%	0.0174	+ 4.5%
0.019	- 5.0%	$3.96 \times 10^{-8}$	$- 1.2 \times 10^{-9}$	7.40	+ 0.2%	0.0159	- 4.6%
						0.0253	—
						0.0246	- 2.9%
						0.0261	+ 3.0%

(SID) = 0.042 Eq/liter and  $P_{CO_2} = 40 \text{ mm Hg}$  throughout.

(Change in  $[A_{TOT}]$ ) / (change in  $[H^+]$ ) = +8.3  $\times 10^5$  (molecules/ion).

Because we are mainly concerned at this point with  $[H^+]$  behavior in an intracellular fluid, the intracellular fluid of isolated RBCs provides a most convenient model to examine. The results may easily be extended to other cell types whenever desired simply by substituting appropriate values for the parameters and the independent variables.

The intracellular fluid of RBCs contains  $CO_2$  and its derivatives, strong ions at markedly different concentrations than in plasma, and weak acids consisting mostly of the protein hemoglobin, but including significant and variable amounts of diphosphoglyceric acid (DPG). We begin by lumping all the weak acids into a single idealized HA, present at a normal  $[A_{TOT}]$  value of 0.060 Eq/liter, three times larger than in plasma. In order to account for established  $[H^+]$  values, it is also necessary to use a different value for  $K_C$  from that in plasma, namely,  $2.4 \times 10^{-11}$  (Eq/liter)<sup>2</sup>/mm Hg. This difference most likely follows from an effect of the high protein concentration on the  $CO_2$  solubility, for the latter is incorporated in  $K_C$ .

Given this  $[A_{TOT}]$  value and the parameter values, the same equations apply to this solution as to plasma, so we can at once plot all the usual graphs and calculate the effects on  $[H^+]$  of small changes in [SID],  $P_C$ , and  $[A_{TOT}]$  just as we have done for plasma in the previous sections. The results are displayed in Figures 7.9 through 7.15 and in Table 7.3. As usual, there is a large amount of information in these graphs and tables, but the following special features are important to understand.

### 7.5a. $[H^+]$ Behavior (Figures 7.9, 7.12, and 7.13)

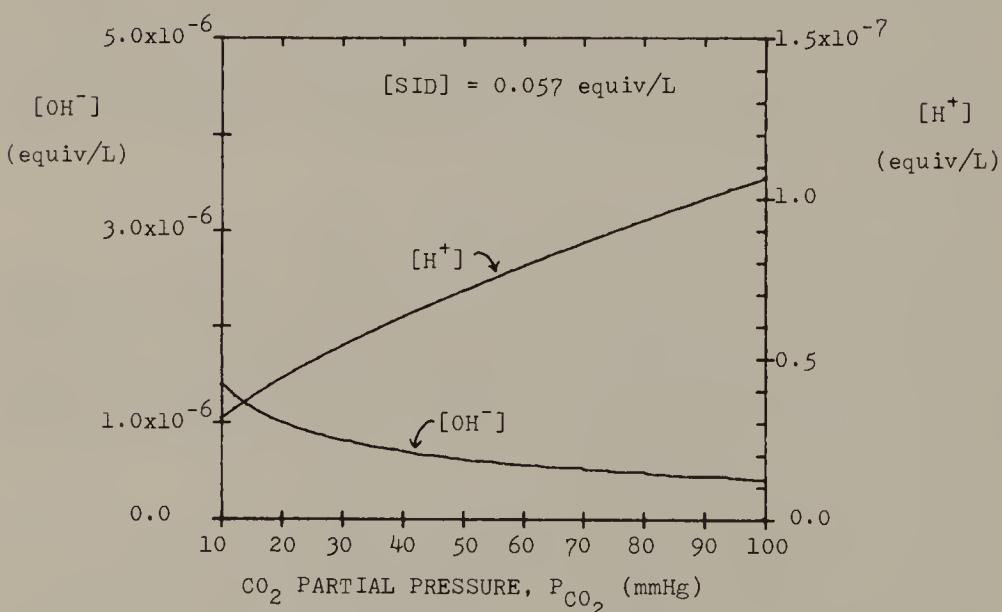
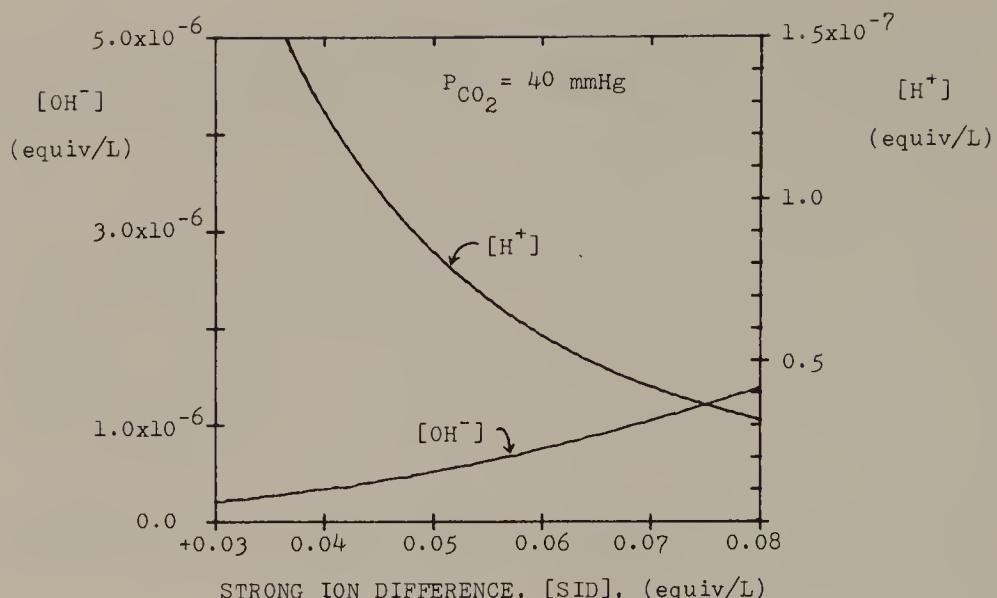
Comparison of Figure 7.9 with 7.1 shows that  $[H^+]$  is both larger and less well regulated in RBC-ICF than in plasma. It also varies much more nonlinearly with  $P_C$ . The general directions of  $[H^+]$  response are the same in the two solutions, however, as we might expect from the fact that they obey the same equations.  $[H^+]$  decreases with increasing [SID] and increases with increasing  $P_C$ .

$[OH^-]$  is correspondingly smaller in RBC-ICF than in plasma and much less sensitive to  $P_C$ .

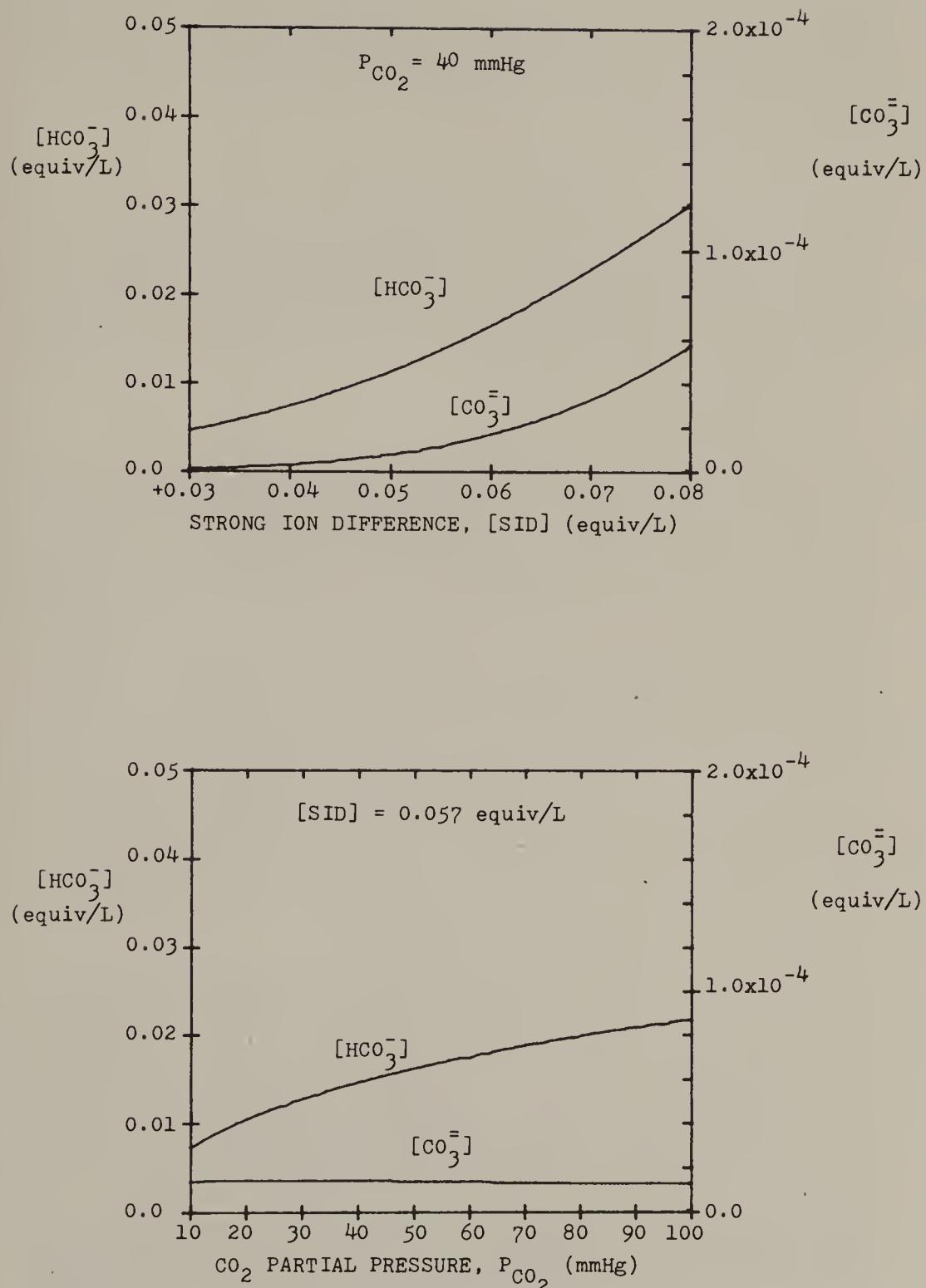
There are corresponding differences in the pH curves; pH is generally lower in RBC-ICF than in plasma. Its variation with [SID] (Figure 7.13) is almost linear.

### 7.5b. $[HCO_3^-]$ and $[CO_3^{2-}]$ Behavior (Figures 7.10 and 7.12)

There are striking differences between plasma and RBC-ICF so far as these quantities are concerned, especially when the difference between the [SID] scales in Figures 7.2 and 7.10 is recognized. Despite the much larger [SID] value,  $[HCO_3^-]$  is much lower in RBC-ICF than in plasma,



**Figure 7.9.**  $[\text{H}^+]$  and  $[\text{OH}^-]$  for isolated standard RBC-ICF plotted against [SID] and  $P_{\text{CO}_2}$  as in Figure 7.1 for plasma. Parameter values used are listed in Table 7.3 and apply to all of the following figures for RBC-ICF. [SID] scale is different from Figure 7.1.  $[\text{A}_{\text{TOT}}]$  values are constant at 0.060 Eq/liter.



**Figure 7.10.**  $[HCO_3^-]$  and  $[CO_3^{2-}]$  plotted against  $[SID]$  and  $P_{CO_2}$ , as indicated, for RBC-ICF.  $[A_{TOT}]$  values are constant at 0.060 Eq/liter. Horizontal scales are the same as in Figure 7.9.

and  $[A^-]$  is much larger.  $[HCO_3^-]$  is more strongly dependent on  $P_C$  in RBC-ICF than in plasma, but  $[CO_3^{2-}]$  has almost lost its “counterintuitive” negative dependence on  $P_C$ ; Figure 7.10 suggests that  $[CO_3^{2-}]$  is almost independent of  $P_C$  in RBC-ICF.

### 7.5c. $[HA]$ and $[A^-]$ (Figures 7.11 and 7.12)

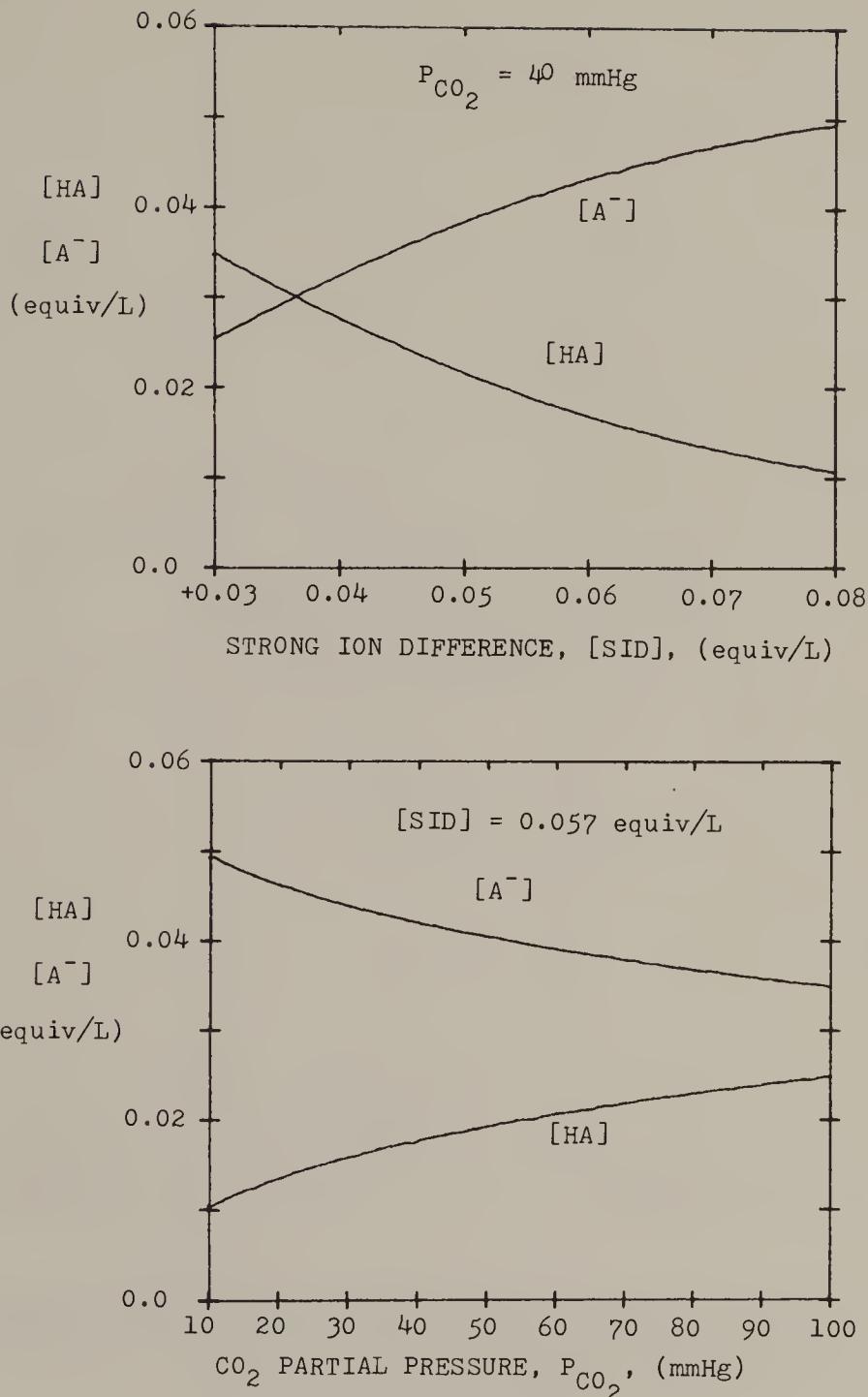
Perhaps the most striking feature of Figure 7.11 is the similarity of the form of the  $[HA]$  and  $[A^-]$  versus  $[SID]$  curves to those in Figure 7.3, despite the large differences in both the horizontal and vertical scales. By themselves, these curves tell us very little about the  $[H^+]$  behavior or the properties of either solution.

### 7.5d. Gamblegram (Figure 7.14)

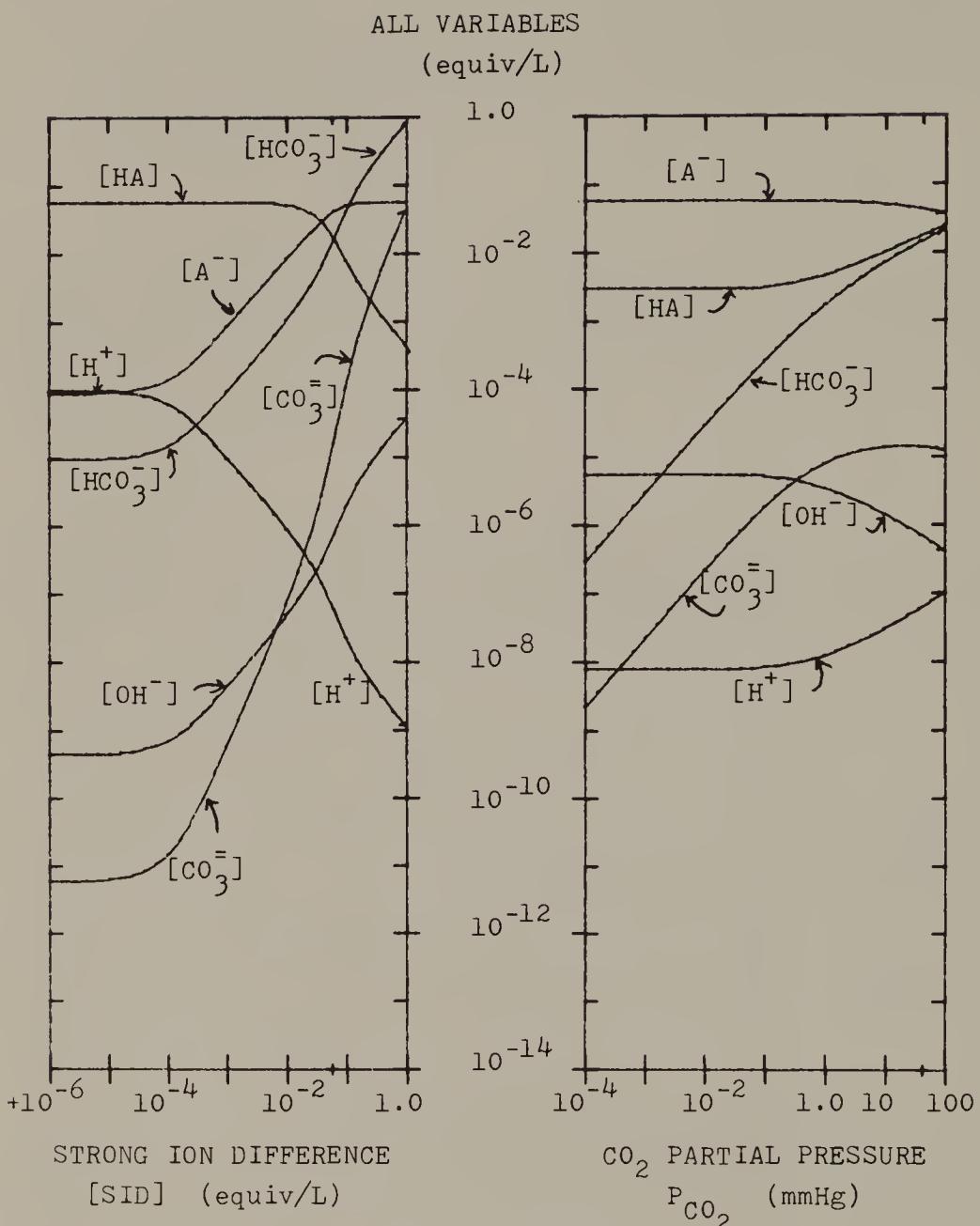
Drawn on the same vertical scale as Figure 7.7 for plasma, the gamblegram for RBC-ICF clearly reflects the lower total ionic content of RBC-ICF compared to plasma, the large difference in cation composition, and the much larger  $[SID]$  value. It is still the case that only  $HCO_3^-$  and  $A^-$  among the dependent variable ions occur in any significant concentration compared to the strong ions.

The relatively large box on the anion side labeled “[ $SO_4^{2-}$ ] etc.” reflects the complication that some of the low-molecular-weight organic acids in this solution have sufficiently large  $K_A$  values to be counted as strong acids for our purposes. Lactic acid is the most commonly invoked; it may also occur in significant concentrations in plasma and ISF as well as in RBC-ICF. The total concentration of such strong organic acid anions in RBC-ICF is normally large enough to bring the effective  $[SID]$  value down to 0.057 Eq/liter from the value of 0.067 Eq/liter we should calculate if only the  $Cl^-$  were counted as a strong anion.

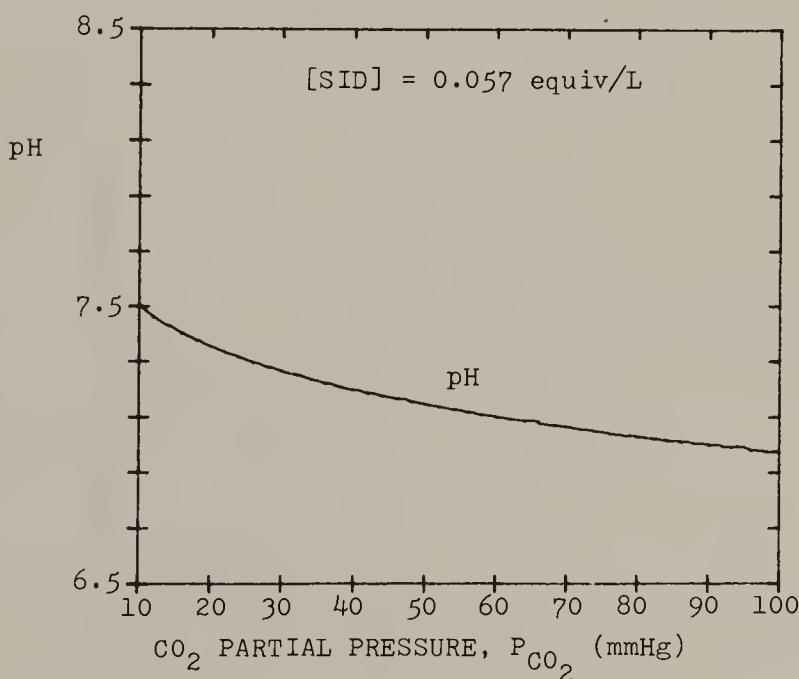
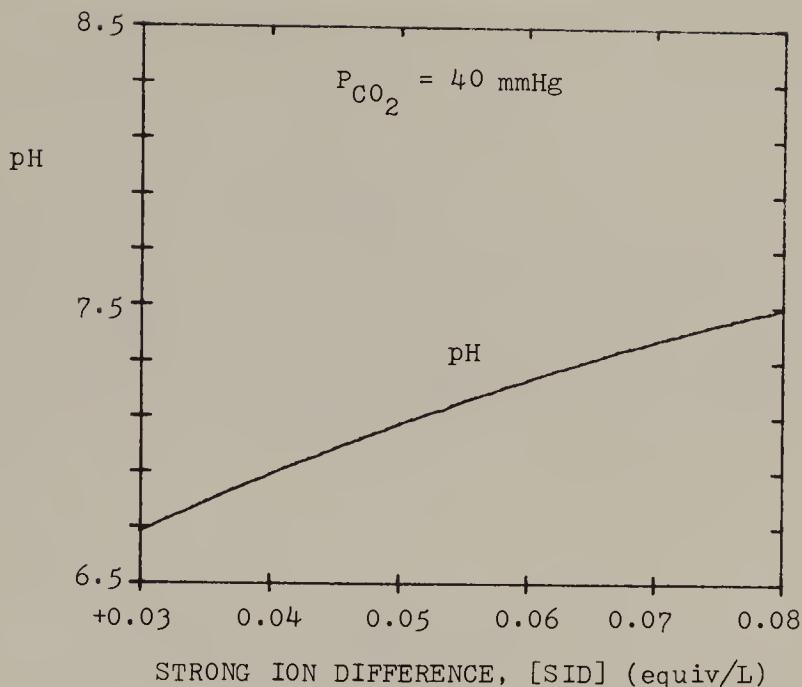
It should be realized in this context, and we reemphasize it here, that all numerical values used in these analyses are intended to be representative; they may not fit precisely any individual set of data from any particular real-life sample. One reason for this is that many of the quantities for which we have adopted “standard” values are in fact different in different real samples,  $[A_{TOT}]$  for example. Another reason is that some of the parameter values, notably  $K'_w$  and  $K_3$ , have not yet been accurately evaluated experimentally in all of these fluids. The “standard” values adopted here should be accepted in this spirit. They are generally well within reasonable limits of what most workers in the field describe as normal, but they should not be regarded as dogmatically fixed or authoritatively established. Fortunately, the differences between the properties of the major body fluids are much larger than can be accounted for by the uncertainties in any of these standard values.



**Figure 7.11.**  $[A^-]$  and  $[HA]$  plotted against [SID] and  $P_{CO_2}$  for RBC-ICF.  $[A_{TOT}]$  values are constant at 0.060 Eq/liter. Same horizontal scales as Figures 7.9 and 7.10.



**Figure 7.12.** Log-log plots of all six dependent variables in RBC-ICF, against [SID] in left-hand graph and against  $P_{CO_2}$  in right-hand graph.  $[A_{TOT}]$  values are constant at 0.060 Eq/liter. Compare with Figure 7.4.



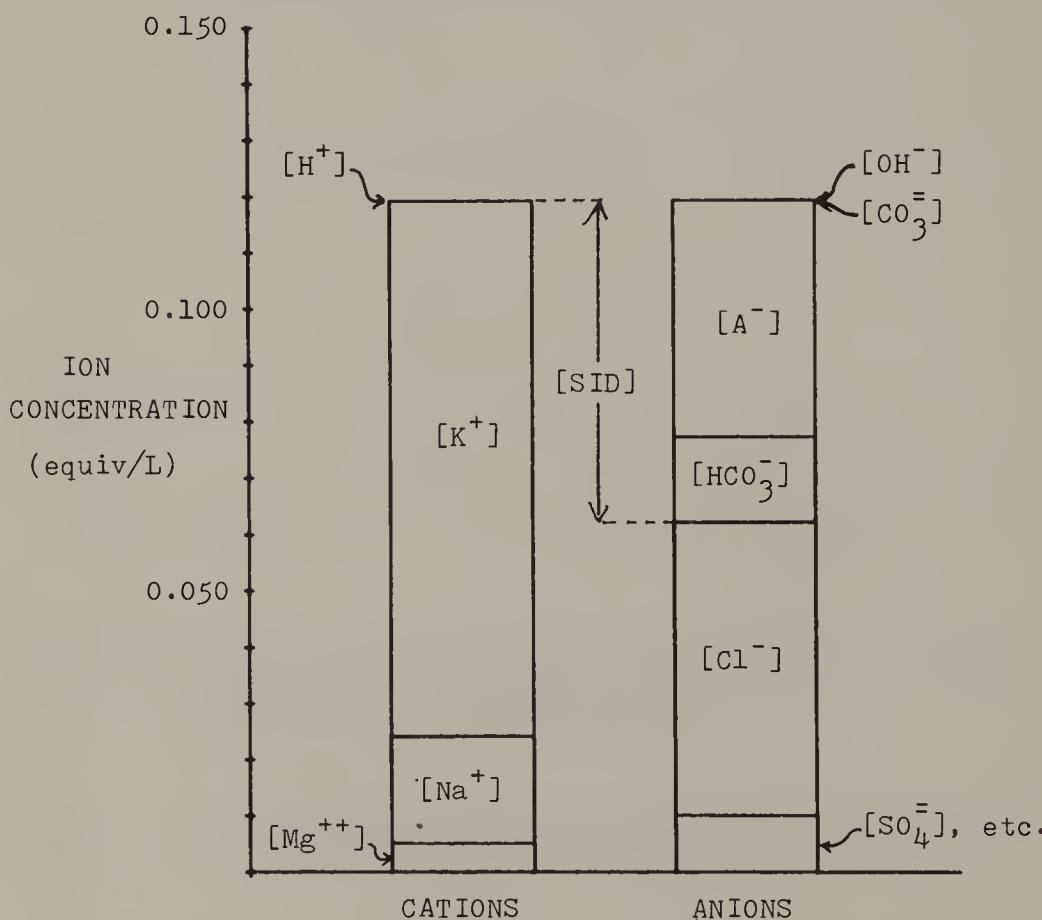
**Figure 7.13.** pH for RBC-ICF plotted against [SID] and P<sub>CO<sub>2</sub></sub>. [A<sub>TOT</sub>] values are constant at 0.060 Eq/liter. Compare with Figures 7.9 and 7.5.

### 7.6. THE $[H^+]$ - $P_{CO_2}$ DIAGRAM FOR RBC-ICF (FIGURE 7.15)

As in the other solutions, if it is reasonable to assume that  $[A_{TOT}]$  is indeed constant, then the  $[H^+]$ - $P_C$  diagram of Figure 7.15 describes in a useful way the  $[H^+]$  behavior of RBC intracellular fluid and may be used to follow changes in the acid-base status of that fluid. The major differences between this diagram and the corresponding ones for isolated plasma, Figure 7.8, and for isolated ISF, Figure 6.7, are the larger [SID] values in this case and the slightly greater curvature of the constant [SID] curves.

These diagrams will all be very useful when we examine the interactions between these body fluids in the following chapters, because whenever strong ions move between any two of these solutions so as to change the [SID] values, changes in  $[H^+]$  must result. These  $[H^+]$  changes can be

**Figure 7.14.** Gamblegram for RBC-ICF at  $[SID] = 0.057$  Eq/liter,  $P_{CO_2} = 40$  mm Hg, and  $[A_{TOT}] = 0.06$  Eq/liter. Compare with Figure 7.7.



followed and understood most easily on the basis of the appropriate curves in these figures.

### 7.7. OTHER INTRACELLULAR FLUIDS: STANDARD ICF

Although no other intracellular fluid has been as thoroughly analyzed chemically as RBC-ICF, it is well established that the cytoplasmic fluid of most body cells is high in  $K^+$ , on the order of 0.155 Eq/liter, and low, but variable, in  $Mg^{2+}$ ,  $Na^+$ , and  $Cl^-$ .  $[Ca^{2+}]$  is about the same as  $[H^+]$  in most cells in which it has been measured, on the order of  $10^{-7}$  Eq/liter.  $[SID]$  values in most cells are therefore very large compared to those

**Figure 7.15.**  $[H^+]$ - $P_{CO_2}$  diagram for RBC-ICF. The + indicates the standard value of Figure 7.14, at which  $[H^+] = 6.4 \times 10^{-8}$  Eq/liter, pH 7.2. Compare with Figure 7.8 and 7.7.

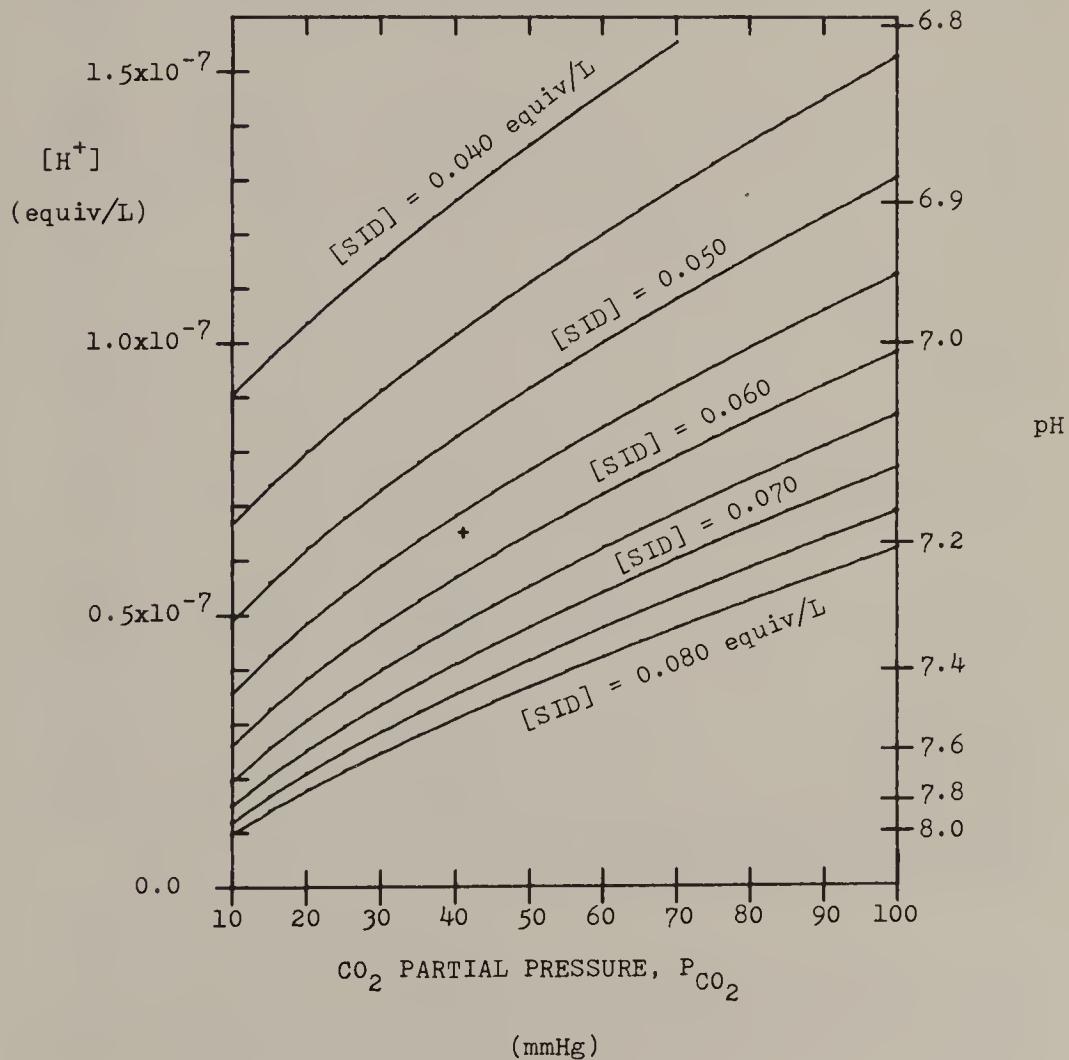


TABLE 7.3. Summary Listing of Body Fluid Values

Quantity	Solution			
	Interstitial fluid	Blood plasma	RBC-ICF	General ICF
[Na <sup>+</sup> ]	0.137	0.143	0.019	0.010
[K <sup>+</sup> ]	0.003	0.004	0.095	0.155
[Mg <sup>2+</sup> ]	0.002	0.002	0.005	0.010
[Ca <sup>2+</sup> ]	0.001	0.001	—	—
[Cl <sup>-</sup> ]	0.111	0.107	0.052	0.010
Other strong anions	0.001	0.001	0.010	0.035
[SID]	0.031	0.042	0.057	0.130
[A <sub>TOT</sub> ]	—	0.020	0.060	0.200
P <sub>CO<sub>2</sub></sub>	50	40	40	50
K <sub>A</sub>	—	2.0 × 10 <sup>-7</sup>	1.5 × 10 <sup>-7</sup>	1.5 × 10 <sup>-7</sup>
K <sub>C</sub>	2.58 × 10 <sup>-11</sup>	2.58 × 10 <sup>-11</sup>	2.40 × 10 <sup>-11</sup>	2.40 × 10 <sup>-11</sup>
K <sub>3</sub>	6.0 × 10 <sup>-11</sup>			
K' <sub>w</sub>	4.4 × 10 <sup>-14</sup>			
[HCO <sub>3</sub> <sup>-</sup> ]	0.031	0.025	0.0150	0.0116
[A <sup>-</sup> ]	—	0.0166	0.0420	0.118
[HA]	—	0.0034	0.0180	0.0820
[CO <sub>3</sub> <sup>2-</sup> ]	4.5 × 10 <sup>-5</sup>	3.7 × 10 <sup>-5</sup>	1.4 × 10 <sup>-5</sup>	6.7 × 10 <sup>-6</sup>
[OH <sup>-</sup> ]	1.1 × 10 <sup>-6</sup>	1.1 × 10 <sup>-6</sup>	6.9 × 10 <sup>-7</sup>	4.3 × 10 <sup>-7</sup>
[H <sup>+</sup> ]	4.2 × 10 <sup>-8</sup>	4.1 × 10 <sup>-8</sup>	6.4 × 10 <sup>-8</sup>	1.0 × 10 <sup>-7</sup>
pH	7.4	7.4	7.2	7.0
Δ[SID]/Δ[H <sup>+</sup> ]	-7.5 × 10 <sup>5</sup>	-6.9 × 10 <sup>5</sup>	-4.3 × 10 <sup>5</sup>	-5.8 × 10 <sup>5</sup>
ΔP <sub>CO<sub>2</sub></sub> /Δ[H <sup>+</sup> ]	+1.2 × 10 <sup>9</sup>	+1.1 × 10 <sup>9</sup>	+1.1 × 10 <sup>9</sup>	+2.5 × 10 <sup>9</sup>
Δ[A <sub>TOT</sub> ]/Δ[H <sup>+</sup> ]	—	+8.3 × 10 <sup>5</sup>	+6.1 × 10 <sup>5</sup>	+9.8 × 10 <sup>5</sup>
% Δ[SID]/% Δ[H <sup>+</sup> ]	-1.0	-0.67	-0.48	-0.46
% ΔP <sub>CO<sub>2</sub></sub> /% Δ[H <sup>+</sup> ]	+1.0	+1.1	+1.8	+5.2
% Δ[A <sub>TOT</sub> ]/% Δ[H <sup>+</sup> ]	—	+1.7	+0.66	+0.51
Δ[SID]/ΔpH	+0.078	+0.065	+0.064	+0.14
ΔP <sub>CO<sub>2</sub></sub> /ΔpH	-120	-100	-170	-600
Δ[A <sub>TOT</sub> ]/ΔpH	—	-0.078	-0.091	-0.23
% Δ[SID]/% ΔpH	+19	+11	+8.0	+7.4
% ΔP <sub>CO<sub>2</sub></sub> /% ΔpH	-17	-19	-30	-83
% Δ[A <sub>TOT</sub> ]/% ΔpH	—	-29	-11	-8.1

Units are Eq/liter, mm Hg, or appropriate combinations.  
See listing of buffer strengths, page 140, for units.

in ISF, plasma, and RBCs, somewhere between 0.10 and 0.15 Eq/liter. Different cell types also have different, and on occasion rapidly varying, amounts of organic acids, some strong, such as lactic, but most weak, such as proteins and organic phosphates. The strong organic acids contribute to the effective [SID] value. The weak acids cover a much wider range of  $K_A$  values than in RBCs, where the major protein by far is hemoglobin.

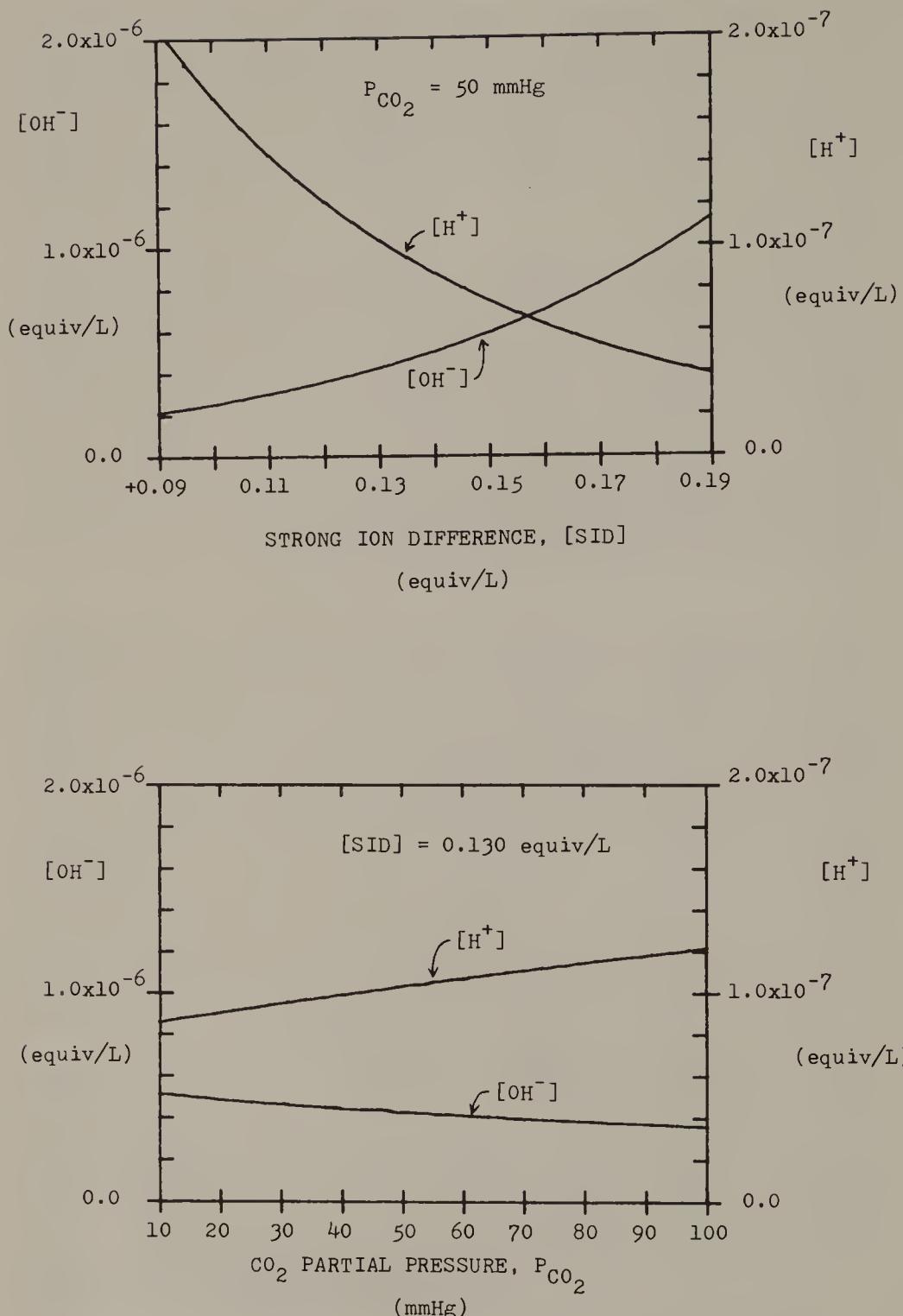
Despite its quantitative importance as the largest fluid type in the body, intracellular fluid clearly cannot be described quantitatively with nearly the same degree of confidence in standard numerical values as we have expressed for ISF, plasma, and RBC-ICF. Nonetheless, if we continue to lump all of the many weak acids into a single representative [HA], as we have done in the previous cases, we can again apply the same principles, equations, and solution procedures to the resulting, somewhat more hypothetical, standard or model ICF. The results will provide an approximate quantitative picture of ICF  $[H^+]$  behavior and allow us to see how it differs from those other solutions with which it interacts in the body.

The numerical values used here for the parameters and the standard values of [SID],  $P_C$ , and  $[A_{TOT}]$ , which serve to define our standard ICF, are listed in Table 7.3 at the end of this chapter along with those for the other three solutions. We take  $[A_{TOT}]$  as 0.20 Eq/liter,  $K_A$  the same as in RBCs, at  $1.5 \times 10^{-7}$  Eq/liter, and  $P_C$  the same as in ISF, at 50 mm Hg. [SID] is somewhat arbitrarily set at 0.130 Eq/liter. Fortunately, as the graphs and the numerical values at the bottom of Table 7.3 indicate,  $[H^+]$  in this solution is not very sensitive to small changes in these standard values.

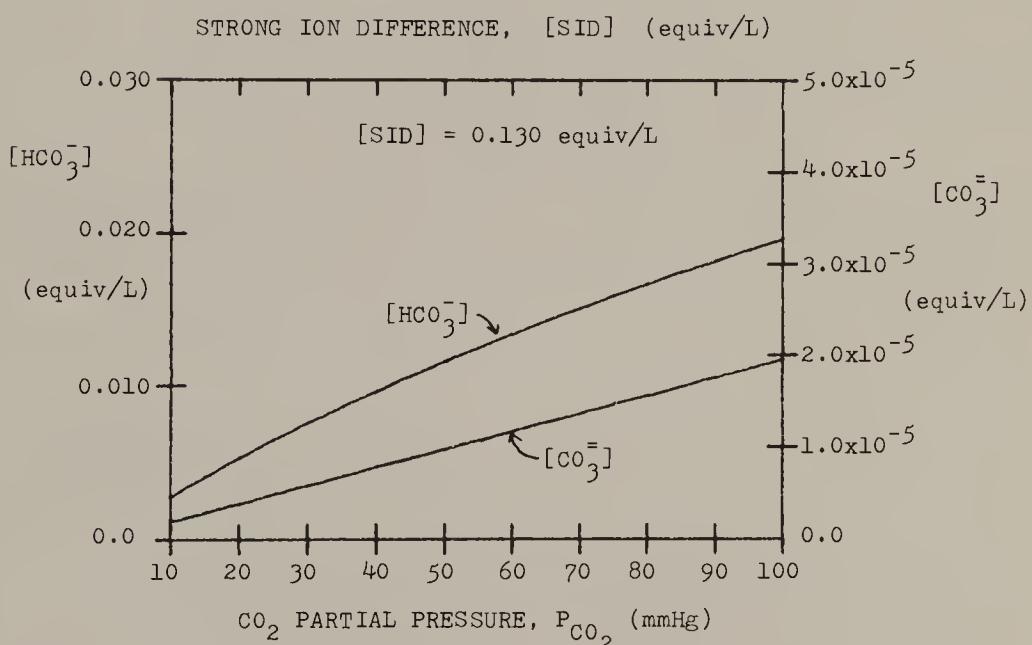
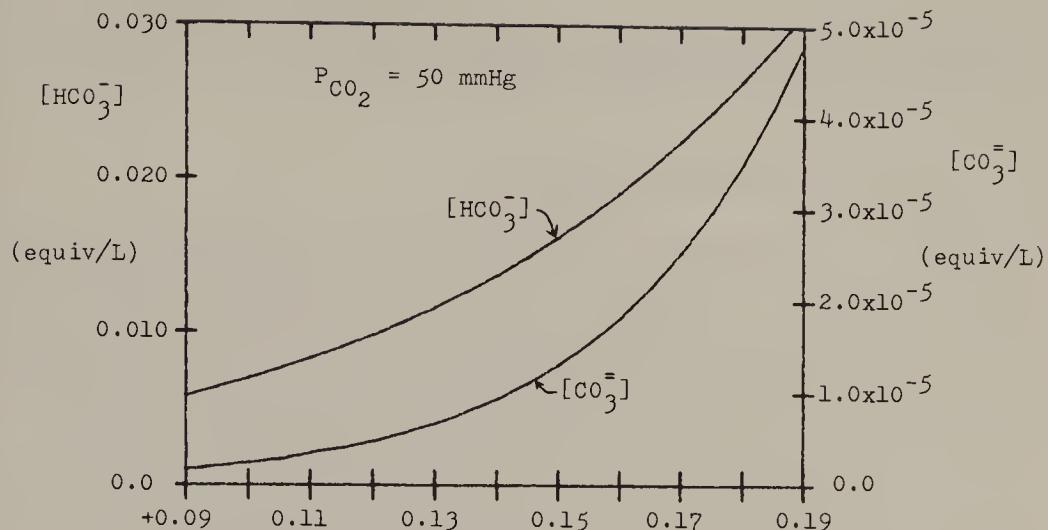
Given these assumptions, our standard ICF is a solution just like plasma or RBC-ICF in that it contains strong ions,  $CO_2$ , and weak acid. Equations (7.2.1) through (7.2.6) therefore apply and can be solved as before for the six dependent variables. Solution results are displayed in the graphs of Figures 7.16, 7.17, 7.18, and 7.19 and in Table 7.3.

By this stage, after examining all the previous graphs in this and the preceding chapter, the reader should find few surprises in these figures, particularly if the very large numerical values of  $[A_{TOT}]$  and [SID] are kept in mind. Although many detailed comparisons may be made and will be illuminating, the most striking aspect of the figures is the much greater stability of this solution toward changes in  $P_C$ . Its  $[H^+]$  buffer strength toward [SID] changes, on the other hand, is slightly less than that of either ISF or plasma. Numerous other comparisons of this sort can be made from the figures and Table 7.3.

Finally, the  $[H^+]-P_C$  diagram for this solution is presented in Figure 7.20, for comparison with those of the other three body fluids and for reference in the following chapters. Its general features are similar to those of Figure 7.15 for RBC-ICF, but there are important specific



**Figure 7.16.**  $[H^+]$  and  $[OH^-]$  for isolated idealized intracellular fluid, plotted against [SID] and  $P_{CO_2}$  as in Figure 7.1 for plasma and Figure 7.9 for RBC-ICF.  $[A_{TOT}]$  values are constant at 0.20 Eq/liter. Parameter values used are listed in Table 7.3 and apply to all of the following graphs for ICF. The [SID] scale is different from that in Figures 7.1 and 7.9.



**Figure 7.17.**  $[HCO_3^-]$  and  $[CO_3^{2-}]$  plotted against [SID] and  $P_{CO_2}$ , as indicated, for ICF.  $[A_{TOT}]$  values are constant at 0.02 Eq/liter. Horizontal scales are the same as in Figure 7.16.

differences in numerical values, particularly of [SID]. As was true for the other fluids, this diagram summarizes the whole  $[H^+]$  story for standard ICF provided  $[A_{TOT}]$  does indeed remain constant.

### 7.8. GENERALIZED BUFFER STRENGTHS

In Chapter 5, we defined  $[H^+]$  buffer strength as the reciprocal of the slope of the  $[H^+]$  versus [SID] curve and saw that its numerical value measures the number of strong ions that must be added to, or removed from, 1 liter of a solution in order to change its  $[H^+]$  by 1  $H^+$ . The larger this quantity is, the less  $[H^+]$  will change in response to a given change in [SID], so the better buffered the solution is against [SID] changes.

In the more complex solutions analyzed in this chapter, we have found it more practical to evaluate the  $[H^+]$  buffer strength by calculating the change in  $[H^+]$  resulting from a small [SID] change and taking their ratio, rather than deriving a formula by the techniques of calculus. If we let the symbol  $\Delta$  stand for a small change, we may then rewrite our definition for  $[H^+]$  buffer strength in these terms:

$$[H^+] \text{ buffer strength} \approx \Delta[\text{SID}]/\Delta[H^+] \text{ (strong ions/H<sup>+</sup>)}$$

Similarly, the pH buffer strength becomes

$$\text{pH buffer strength} \approx \Delta[\text{SID}]/\Delta\text{pH} \text{ (Eq/liter)}$$

We have established that  $[H^+]$  is determined by  $P_C$  and by  $[A_{TOT}]$  as well as by [SID], so that it makes sense to extend our definition of buffer strength, and our concept of buffering, to include these other independent variables.

The obvious way to do this is by the following generalizations of the above definitions:

$$[H^+] \text{ buffer strength against [SID]} \approx \Delta[\text{SID}]/\Delta[H^+] \text{ (strong ions/H<sup>+</sup>)}$$

$$[H^+] \text{ buffer strength against } P_C \approx \Delta P_C/\Delta[H^+] \text{ (mm Hg/Eq/liter)}$$

$$[H^+] \text{ buffer strength against HA} \approx \Delta[A_{TOT}]/\Delta[H^+] \text{ (Eq/Eq)}$$

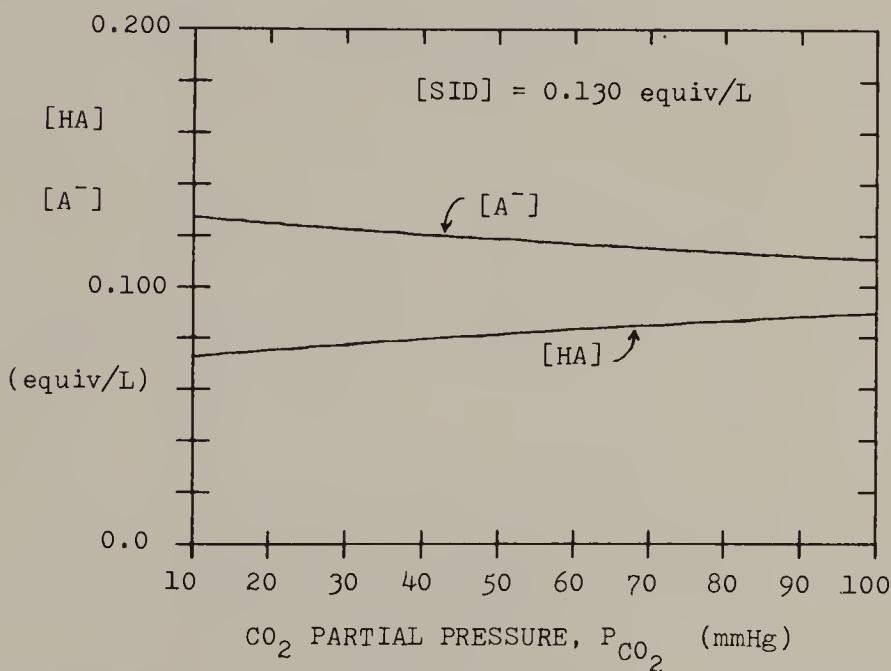
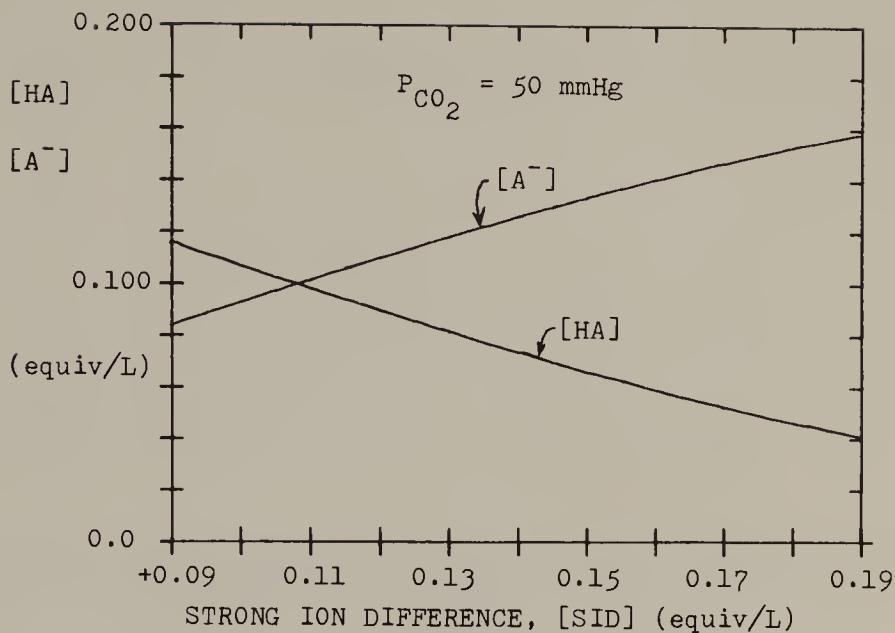
$$\text{pH buffer strength against [SID]} \approx \Delta[\text{SID}]/\Delta\text{pH} \text{ (Eq/liter)}$$

$$\text{pH buffer strength against } P_C \approx \Delta P_C/\Delta\text{pH} \text{ (mm Hg)}$$

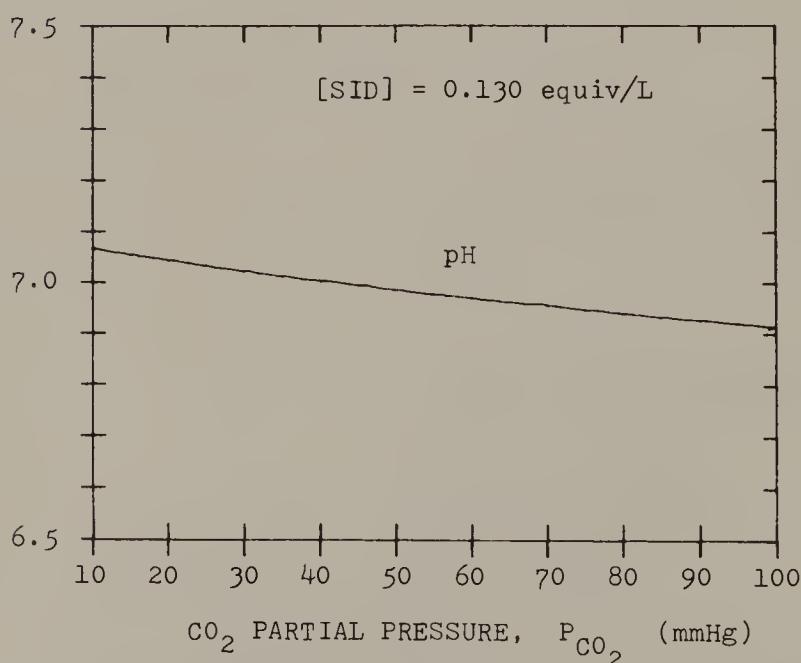
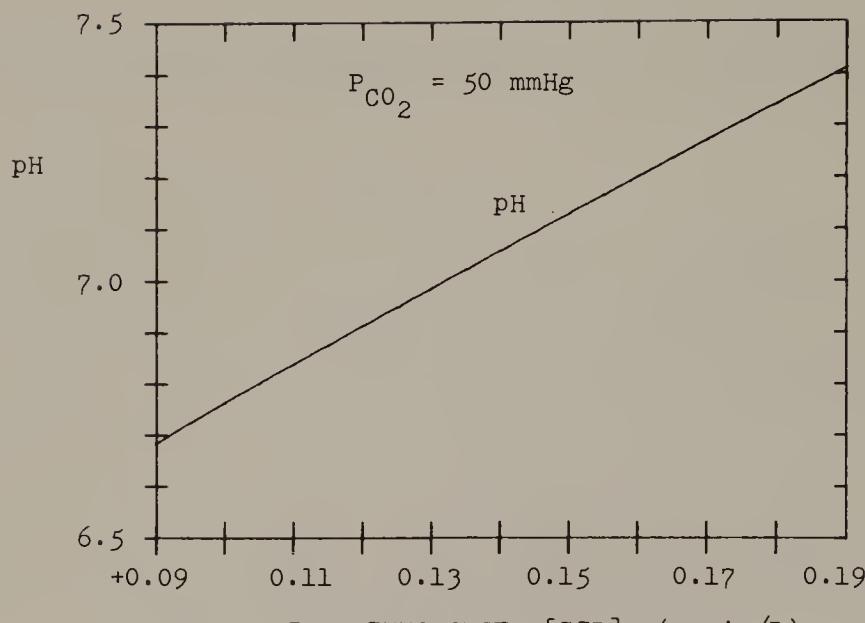
$$\text{pH buffer strength against HA} \approx \Delta[A_{TOT}]/\Delta\text{pH} \text{ (Eq/liter).}$$

Numerical values for each of these quantities, for each of the four major body fluids at their standard values, are listed in Table 7.3 to facilitate comparisons between solutions and between variables.

We have also confronted in this chapter the problem that it is difficult to compare the effectiveness of different independent variables when their units are different. We dealt with this problem in Table 7.1 by comparing relative changes, in  $[H^+]$  and pH as well as in the independent variables,



**Figure 7.18.**  $[A^-]$  and  $[HA]$  plotted against  $[SID]$  and  $P_{CO_2}$ , as indicated, for ICF.  $[A_{TOT}]$  values are constant at 0.20 Eq/liter. Same horizontal scales as Figures 7.16 and 7.17.



**Figure 7.19.** pH for ICF plotted against [SID] and  $P_{CO_2}$ .  $[A_{TOT}]$  values are constant at 0.20 Eq/liter. Compare with Figures 7.1, 7.13, and 7.16.

expressed as percentage departure from the standard value. This approach provides an interesting basis of comparison for some purposes. It suggests another whole set of generalized buffer strength definitions in terms of percentage changes, namely, the following:

$$\% [H^+] \text{ buffer strength against } [SID] \approx \% \Delta[SID]/\% \Delta[H^+]$$

$$\% [H^+] \text{ buffer strength against } P_C \approx \% \Delta P_C/\% \Delta[H^+]$$

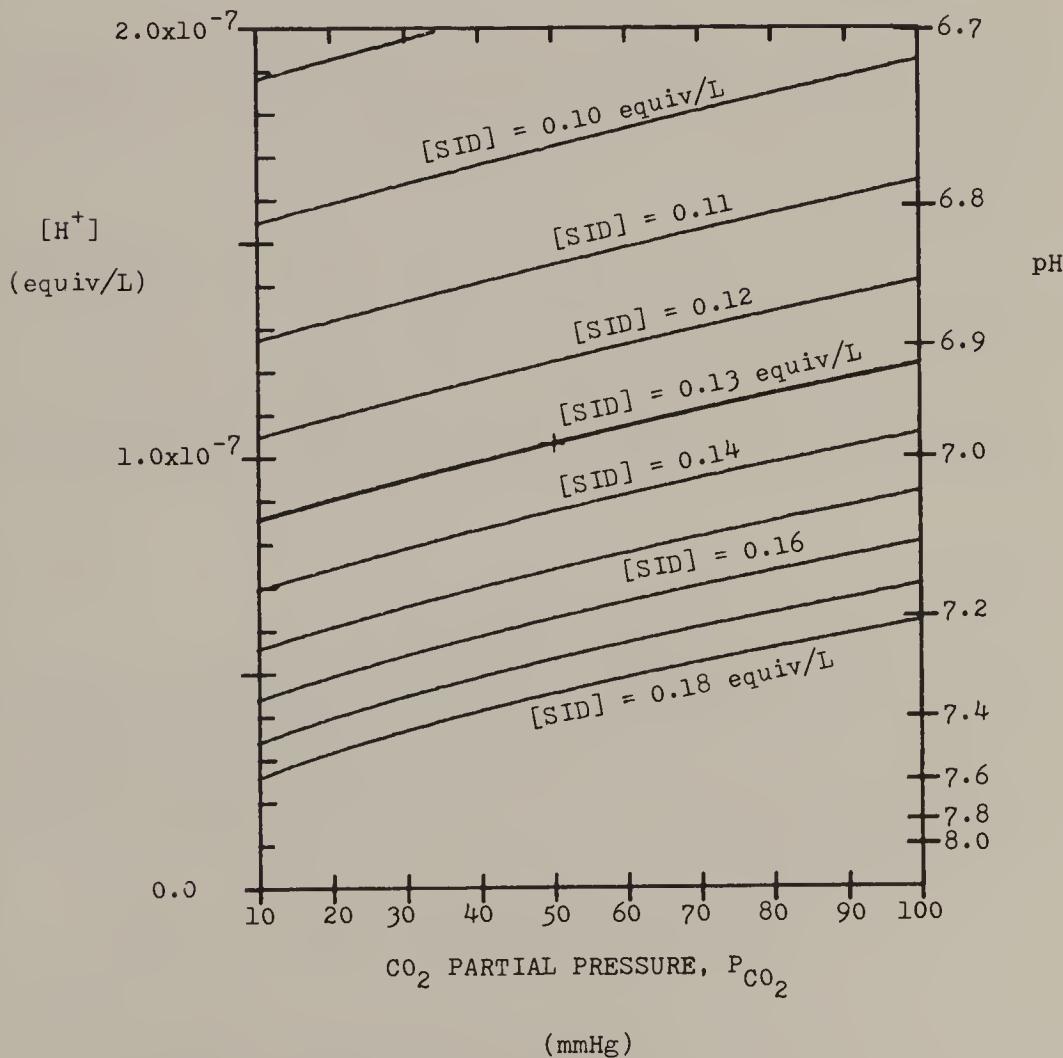
$$\% [H^+] \text{ buffer strength against HA} \approx \% \Delta[A_{TOT}]/\% \Delta[H^+]$$

$$\% \text{ pH buffer strength against } [SID] \approx \% \Delta[SID]/\% \Delta \text{pH}$$

$$\% \text{ pH buffer strength against } P_C \approx \% \Delta P_C/\% \Delta \text{pH}$$

$$\% \text{ pH buffer strength against HA} \approx \% \Delta[A_{TOT}]/\% \Delta \text{pH}.$$

**Figure 7.20.**  $[H^+]$ - $P_{CO_2}$  diagram for ICF. The + indicates the standard point listed in Table 7.3.  $[A_{TOT}]$  values are constant at 0.20 Eq/liter. Compare with Figures 7.8, 7.15, and 6.7.



All these quantities are dimensionless numbers because they are each the ratio of two percentage values, and this may make them somewhat easier to comprehend. Their values are also listed in Table 7.3.

Every one of these 12 quantities has its use, but it is essential not to confuse them with each other, and only to compare appropriate ones between solutions. In general, it is always the case that the larger the value of any given buffer strength, the smaller the  $[H^+]$  or pH change for a given small change in the relevant independent variable. Beyond that, one must be on guard against apparently paradoxical results, such as those already pointed out in Chapter 5 when differences in pH buffer strength were seen to be in an opposite direction from those of  $[H^+]$  buffer strength in some circumstances, but not in others. It is always dangerous to draw conclusions about  $[H^+]$  behavior from information about pH behavior. Specific calculations of numerical values provide the only sure way to avoid confusion.

## 7.9. SUMMARY

We have now completed our analysis of the  $[H^+]$  behavior of isolated body fluids and have established the quantitative basis we need in order to understand and explain what happens to  $[H^+]$  in each of these fluids when they interact, through membranes, in the intact body. That understanding will be our goal for the remaining chapters.

In preparation for them, and as a comparative summary of the results of these first seven chapters, Table 7.3 presents the ionic composition, independent variables, parameter values, dependent variables, and buffer strengths for the four isolated body fluids, ISF, plasma, RBC-ICF, and general ICF. It should be seen as a complement to the four  $[H^+]-P_C$  diagrams, Figures 6.7, 7.8, 7.15 and 7.20, which provide a broader view of the  $[H^+]$  (and pH) behavior of each solution, always assuming constant  $[A_{TOT}]$ . We shall find both sources of information essential in our analysis of body fluid interactions in the following chapters.

## APPENDIX

### THE $[H^+]$ EQUATION FOR ISOLATED PLASMA

We already know from Chapter 6 that Equations (7.2.4) and (7.2.5) can be rearranged to express  $[HCO_3^-]$  and  $[CO_3^{2-}]$  in terms of  $[H^+]$ . From Chapter 5, Equations (7.2.2) and (7.2.3) can be combined and rearranged to express  $[A^-]$  in terms of  $[H^+]$ . Equation (7.2.1) is easily rearranged to express  $[OH^-]$  in terms of  $[H^+]$ . We may therefore substitute all these rearrangements into the electrical neutrality equation, (7.2.6), with this result:

$$[SID] + [H^+] - \frac{K_C \times P_C}{[H^+]} - \frac{K_A \times [A_{TOT}]}{(K_A + [H^+])} - \frac{K_3 \times K_C \times P_C}{[H^+]^2} - \frac{K'_w}{[H^+]} = 0. \quad (7A.1.1)$$

This is now an equation containing only  $[H^+]$  as a dependent variable, and is the

$F([H^+])$  we must use in the iterative numerical procedure presented in Chapter 5, in order to find the value of  $[H^+]$ , in this solution. Although this equation is in a useful form for these calculations, it may also be cleared of fractions and rewritten as the following quartic in  $[H^+]$ :

$$\begin{aligned} [H^+]^4 + \{K_A + [SID]\} [H^+]^3 + \{K_A ([SID] - [A_{TOT}]) - (K_C \\ \times P_C + K'_w)\} [H^+]^2 - \{K_A (K_C \times P_C + K'_w) + K_3 \times K_C \\ \times P_C\} [H^+] - K_A \times K_3 \times K_C \times P_C = 0. \quad (7A.1.2) \end{aligned}$$

As before, once  $[H^+]$  has been evaluated from (7A.1.1), values for the five other dependent variables can be calculated from the expressions used in constructing (7A.1.1).

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## CHAPTER EIGHT

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# INTERACTIONS BETWEEN BODY FLUIDS

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### 8.1. INTRODUCTION

Our progressive analysis of  $[H^+]$  behavior in body fluids now comes to an astonishingly simple climax. It tells us that acid–base interactions between body fluids occur almost entirely in terms of strong ions. Under most circumstances, the only way body fluids can interact through membranes, so as to cause  $[H^+]$  changes, is via [SID] changes.

This important conclusion follows from several physiological facts as well as from the quantitative analyses in the previous chapters. That analysis has made clear that in each of the body fluids,  $[H^+]$  is determined by [SID],  $P_C$ , and  $[A_{TOT}]$ . In order for body fluids to interact, they must somehow alter each other's [SID], or  $P_C$ , or  $[A_{TOT}]$ . There is no other way to change  $[H^+]$ . One physiological fact is that the weak acids, which we have lumped into the representative  $[A_{TOT}]$  for each fluid, are mostly impermeable proteins that do not move from one fluid to another to any extent. Even the lower-molecular-weight weak acids generally stay within their own compartments. Physiologically, in other words,  $[A_{TOT}]$  values seldom change significantly. Body fluids do not normally interact by weak acid movements between them. Membrane transport systems for weak acids do exist throughout the body, especially in the kidneys and the intestine, but their operations are more specifically directed. Under most circumstances, they do not bring about numerically significant changes in the total weak acid concentrations of the major body fluids.

That leaves  $P_C$  and [SID]. The second important physiological fact is that  $CO_2$ , being a small, nonpolar molecule, is both water and lipid soluble,

and therefore highly permeable to all membranes in the body.  $\text{CO}_2$  simply diffuses down whatever  $P_{\text{C}}$  gradient it finds itself in, and ignores membranes.  $P_{\text{C}}$  gradients arise from interactions between metabolism in cells, which produces  $\text{CO}_2$ , and the combination of diffusion and perfusion that eventually gets that  $\text{CO}_2$  out of the body in the expired alveolar gas. Membranes can do little to affect these  $\text{CO}_2$  movements or  $P_{\text{C}}$  gradients directly, so that  $P_{\text{C}}$  values throughout the body have to be thought of as imposed on body fluids by metabolism, diffusion, circulation, and respiration, rather than as quantities to be changed by interactions across membranes. Changes in  $P_{\text{C}}$  do occur, and they will necessarily cause changes in  $[\text{H}^+]$  that must be accounted for, but they are not significantly affected by membranes.

We are left with [SID] change as the only available mechanism by which body fluids can affect each other's  $[\text{H}^+]$  values. We can therefore conclude that  $[\text{H}^+]$  changes in body fluid interactions must mainly result from strong ion exchanges between those fluids bringing about [SID] changes. It follows from the nature of [SID] that such [SID] changes must be in opposite directions in the two interacting solutions.

This simple description of body fluid interactions is completely different from the conventional one, which focuses on  $\text{H}^+$  and  $\text{HCO}_3^-$  to explain  $[\text{H}^+]$  changes. Unfortunately,  $[\text{H}^+]$  and  $[\text{HCO}_3^-]$  are always dependent variables, so that changes in their values cannot be understood in terms of, nor affected by,  $\text{H}^+$  and  $\text{HCO}_3^-$  movements between solutions. This is such a central concept in acid-base chemistry that it is essential to see why it is true in mechanistic terms.

Consider, therefore, the simple idealized situation presented in Figure 8.1. Two identical samples of ISF, A and B, are separated by a membrane that we initially assume to be impermeable to everything except  $\text{CO}_2$ .  $P_{\text{C}}$  is therefore always the same in both solutions and is assumed fixed at 50 mm Hg. Initially, the concentrations of all ions are those listed in Table 7.3. The values for [SID] and all four weak ions are listed in the first part of Figure 8.1, labeled "INITIAL STATE." We now carry out three separate experiments.

In the first experiment, we somehow arrange to transport 0.001 Eq of  $\text{Na}^+$  from the 1 liter in A to that in B, and ask what happens as a result. The first step in arriving at an answer is to recognize that we cannot move only one kind of ion, because of the very powerful electrical neutrality constraint. Either a negative ion must accompany the  $\text{Na}^+$  or a positive ion must move in the opposite direction.  $\text{Cl}^-$  cannot be used because then [SID] would not change in A or B.  $\text{HCO}_3^-$  is present at the highest concentration of any weak ion, by two orders of magnitude, so it is reasonable to assume that 1  $\text{HCO}_3^-$  accompanies each  $\text{Na}^+$  in the first experiment.

INITIAL STATE  
 STANDARD ISF  
 IN A AND B

A	B
0.031	0.031
0.031	0.031
$4.5 \times 10^{-5}$	$4.5 \times 10^{-5}$
$1.06 \times 10^{-6}$	$1.06 \times 10^{-6}$
$4.2 \times 10^{-8}$	$4.2 \times 10^{-8}$
7.38	7.38

EXPERIMENT No. 1  
 0.001 eq/L  $\text{Na}^+$  AND  $\text{HCO}_3^-$   
 MOVED FROM A TO B

A	B
0.030	0.032
0.030	0.032
$4.2 \times 10^{-5}$	$4.8 \times 10^{-5}$
$1.02 \times 10^{-6}$	$1.09 \times 10^{-6}$
$4.3 \times 10^{-8}$	$4.0 \times 10^{-8}$
pH	7.37
	7.39

(ALL CONCENTRATIONS IN EQUIVALENTS/L)

$$P_{\text{CO}_2} = 50 \text{ mmHg} \text{ THROUGHOUT}$$

EXPERIMENT No. 2  
 0.001 eq/L  $\text{Na}^+$  AND  $\text{OH}^-$   
 MOVED FROM A TO B

A	B
0.030	0.032
0.030	0.032
$4.2 \times 10^{-5}$	$4.8 \times 10^{-5}$
$1.02 \times 10^{-6}$	$1.09 \times 10^{-6}$
$4.3 \times 10^{-8}$	$4.0 \times 10^{-8}$
7.37	7.39

EXPERIMENT No. 3  
 0.001 eq/L  $\text{H}^+$  AND  $\text{HCO}_3^-$   
 MOVED FROM A TO B

A	B
0.031	0.031
0.031	0.031
$4.5 \times 10^{-5}$	$4.5 \times 10^{-5}$
$1.06 \times 10^{-6}$	$1.06 \times 10^{-6}$
$4.2 \times 10^{-8}$	$4.2 \times 10^{-8}$
pH	7.38
	7.38

**Figure 8.1.** Tabular display of the results of three different transport experiments described in the text. A and B are each 1 liter of ISF, separated by a membrane assumed for convenience to be freely permeable to  $\text{CO}_2$  but impermeable to everything else. Numerical values in each horizontal row are identified by the symbols in the vertical columns down the center of the figure.

In A, the loss of  $\text{Na}^+$  means that [SID] decreases to 0.030 Eq/liter. All dependent ion concentrations therefore readjust, as indicated by the values under A in the figure for Experiment 1. In B, [SID] increases to 0.032 Eq/liter so that the other ion concentrations also readjust, as shown. On each side, the change in  $[\text{HCO}_3^-]$  is just equal to the change in [SID], and to the amount of  $\text{HCO}_3^-$  transported, but all other dependent variables have also changed, even though  $\text{HCO}_3^-$  was the only dependent variable ion transported.

To understand how this can be, we must look at the processes that must reequilibrate when the  $\text{Na}^+$  and  $\text{HCO}_3^-$  leave A and arrive in B.  $[\text{HCO}_3^-]$  is lowered in A by the departure of  $\text{HCO}_3^-$ , so that  $\text{CO}_2$  (dissolved) +  $\text{OH}^- \rightleftharpoons \text{HCO}_3^-$  will shift to the right, lowering  $[\text{OH}^-]$  and  $[\text{CO}_2(\text{dissolved})]$ .  $\text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{OH}^-$  will therefore shift to the right, generating more  $\text{OH}^-$  and  $\text{H}^+$  and raising  $[\text{H}^+]$ .  $\text{HCO}_3^- \rightleftharpoons \text{H}^+ + \text{CO}_3^{2-}$  will shift to the left, lowering  $[\text{CO}_3^{2-}]$  and generating more  $\text{HCO}_3^-$ . All these interlocking reactions must finally settle down in a state that satisfies their equilibrium conditions and electrical neutrality, specified by Equations (6.4.1) through (6.4.4). The same processes are involved in B, but they all go in the reverse direction. The final results are just those listed in Figure 8.1 under Experiment No. 1.

A nonionic result of the  $\text{HCO}_3^-$  transport is that  $[\text{CO}_2(\text{dissolved})]$  initially falls in A and rises in B. The membrane permeability to  $\text{CO}_2$  ensures that  $\text{CO}_2$  will then diffuse back from B to A as needed, until  $P_{\text{C}}$  is again 50 mm Hg everywhere. In this experiment, the total amount of  $\text{CO}_2$  diffusing is small.

In Experiment No. 2, 0.001 Eq/liter of  $\text{Na}^+$  is again moved from A to B, but this time  $\text{OH}^-$  is assumed to be the accompanying ion rather than  $\text{HCO}_3^-$ . As the figure shows, the result is indistinguishable from that in Experiment No. 1  $[\text{HCO}_3^-]$  goes down in A and up in B, even though we have transported no  $\text{HCO}_3^-$ , while  $[\text{OH}^-]$  changes by only  $7 \times 10^{-8}$  Eq/liter, although 0.001 Eq/liter of  $\text{OH}^-$  was transported.

In this case,  $[\text{OH}^-]$  is lowered in A by the removal of  $\text{OH}^-$  ions, so that water dissociation increases, raising  $[\text{H}^+]$ .  $\text{HCO}_3^- \rightleftharpoons \text{CO}_2(\text{dissolved}) + \text{OH}^-$  also shifts to the right, increasing  $[\text{CO}_2(\text{dissolved})]$  and lowering  $[\text{HCO}_3^-]$ .  $\text{HCO}_3^- \rightleftharpoons \text{CO}_3^{2-} + \text{OH}^-$  will therefore shift to the left, lowering  $[\text{CO}_3^{2-}]$ . The raised  $[\text{CO}_2(\text{dissolved})]$  will ensure that  $\text{CO}_2$  diffuses from A to B, where  $[\text{CO}_2(\text{dissolved})]$  is falling due to all of these reactions proceeding in opposite directions. Finally, everything must settle down on both sides of the membrane, as shown in the figure.

In these two experiments, identical results have been obtained by the transport of  $\text{OH}^-$  in one case and  $\text{HCO}_3^-$  in the other. Their common feature is the fact that  $\text{Na}^+$  was transported in both cases, so that [SID] was changed. The dependent variable ions are essentially irrelevant. Fur-

thermore, it is apparent that we cannot tell, from the change in  $[HCO_3^-]$ , whether or not  $HCO_3^-$  ions were transported, just as we cannot tell from the change in any of the dependent variables that those ions were transported. All we can tell from the fact that  $[HCO_3^-]$  or  $[H^+]$  changed while  $P_C$  did not is that  $[SID]$  must have changed, so that strong ions must have been transported between the two solutions. It makes no difference what weak ion accompanies the strong ion; the changes in weak ion concentrations are determined only by the change in  $[SID]$ .

It is important also to be clear about what happens to the  $CO_2$  in these experiments. In both cases,  $[HCO_3^-]$  goes down in A and up in B, so 0.001 Eq/liter of  $CO_2$  have to move from A to B to permit reequilibration at 50 mm Hg everywhere. In Experiment No. 1 the  $CO_2$  moves through the membrane as  $HCO_3^-$  ions go from A to B. In Experiment No. 2 it moves as  $CO_2$  directly, because the reequilibrium of  $HCO_3^- \rightleftharpoons OH^- + CO_2(\text{dissolved})$  raises  $[CO_2(\text{dissolved})]$  in A, thereby raising  $P_C$  temporarily, and correspondingly lowers it in B. This movement of  $CO_2$  is essential to reequilibration, but it does not have to occur as  $HCO_3^-$  transport. In the real world, in fact, where we can only measure changes in strong ion concentrations and  $[H^+]$  (and  $P_C$ ), we have no way of knowing which of the available weak ions has been transported, nor how the  $CO_2$  has moved, when a change in  $[HCO_3^-]$  is found.

Finally, in the third experiment shown in Figure 8.1, we suppose that no strong ions are transported, but that 0.001 Eq/liter of  $H^+$  is somehow moved through the membrane from A to B. Now what happens, particularly to  $[H^+]$ ?  $[SID]$  cannot change if no strong ions move, so the final state must be the same as the initial one, despite the transport of all that  $H^+$ . In other words, nothing can happen to  $[H^+]$  as a result of  $H^+$  transport. As before, some negative ion must accompany the  $H^+$ , either  $HCO_3^-$ ,  $CO_3^{2-}$ , or  $OH^-$ .  $Cl^-$  will not, because it would change  $[SID]$ . Again,  $HCO_3^-$  is the most likely candidate because of its high concentration, so we suppose that an  $HCO_3^-$  accompanies each  $H^+$  from A to B.

The  $H^+$  leaving A will decrease  $[H^+]$  there, so that  $H_2O \rightleftharpoons H^+ + OH^-$  will move to the right, raising  $[OH^-]$ . The  $HCO_3^-$  leaving A will decrease  $[HCO_3^-]$ , on the other hand, so that  $CO_2(\text{dissolved}) + OH^- \rightleftharpoons HCO_3^-$  will move to the right, lowering  $[OH^-]$  and  $[CO_2(\text{dissolved})]$ . The lowered  $[CO_2(\text{dissolved})]$  will result in  $CO_2$  diffusing from B to A, particularly because  $[CO_2(\text{dissolved})]$  is rising in B by the reverse reactions due to the arrival of  $HCO_3^-$ . When all of these interlocking processes have again equilibrated, and Equations (6.4.1) through (6.4.4) have been satisfied,  $[SID]$  and  $P_C$  will be unchanged, and therefore all the dependent variables must have been restored to their initial values. The only effect of the  $H^+$  and  $HCO_3^-$  transport has been the movement of 0.001 Eq/liter of  $CO_2$  from A to B as  $HCO_3^-$  and from B to A as  $CO_2(\text{dissolved})$ . No change in strong

ions means no change in  $[HCO_3^-]$ ,  $[CO_3^{2-}]$ ,  $[OH^-]$ , or  $[H^+]$ , regardless of whether any of those weak ions have been transported through the membrane.

In all three experiments, the assumed impermeability of the membrane to everything but  $CO_2$  is merely a simplifying convenience to keep the transported ions in place once they have been transported. Making the membrane permeable to everything except the strong ions would have resulted in exactly the same conclusions.

Those conclusions are so important, so simple, so different from conventional wisdom, and so central to the understanding of acid-base interactions between body fluids, that it may be useful to state them once more in formal terms.

1. Given the assumptions that  $[A_{TOT}]$  stays constant and that  $P_C$  is not affected by membranes because they are so  $CO_2$  permeable, it then follows that body fluids can only interact across membranes by exchanging strong ions so as to alter their  $[SID]$  values.
2. Only  $[SID]$  changes can bring about changes in  $[H^+]$ ,  $[HCO_3^-]$ , or any other dependent variable, assuming constant  $P_C$  and  $[A_{TOT}]$ .
3. Transport of weak ions, or dependent variable ions, such as  $H^+$ ,  $HCO_3^-$ , and  $OH^-$ , across membranes separating body fluids cannot result in changes of  $[H^+]$ ,  $[HCO_3^-]$ , etc, unless these ions are accompanied by strong ions, and then it is the effect of the strong ions on  $[SID]$  that determines the  $[H^+]$ ,  $[HCO_3^-]$ , etc, not the transport of the  $H^+$  etc. Dependent ion transport is essentially irrelevant to the determination of  $[H^+]$ ,  $[HCO_3^-]$ , etc.

We may now examine the nature of the three pairwise interactions between body fluids indicated by the summary diagram of Figure 1.1 in Chapter 1. The simplest one is that between plasma and ISF across the capillary endothelium, so we begin there in the next section.

## 8.2. ACID-BASE INTERACTIONS BETWEEN ISF AND PLASMA: CAPILLARIES

Capillary endothelium in most tissues is effectively impermeable to plasma proteins and relatively freely permeable to the other ions and small molecules in plasma and ISF. Small amounts of protein do leak out of capillaries, but normally only slowly. Our assumption that ISF contains no protein, and therefore no weak acid, is not precisely true, but it is an excellent approximation under normal conditions. Another physiological fact is that there is usually a higher hydrostatic pressure in the plasma inside the capillary than in the ISF outside it. ISF is often described as an ultrafiltrate of plasma on the basis of these facts, but that is a more complicated description than it may at first appear to be.

If we compare the electrical neutrality equations for ISF, (6.4.4), and for plasma, (7.2.6), we find that the only difference is the presence of  $[A^-]$  in the plasma equation but not in the ISF one. This difference suggests, because the  $A^-$  is impermeable and the strong ions are permeable, that  $Cl^-$  might be likely to move out of plasma to ISF, and  $Na^+$  might move in. The difference in their concentrations, which is most of [SID], might be somewhat higher in plasma than in ISF as a result. Table 7.3 shows that this is the case. Standard plasma [SID] at 0.042 Eq/liter is 35% larger than standard ISF [SID] at 0.031 Eq/liter. We should like to understand why this value is 35%.

To do so, we must invoke some thermodynamic constraints on this system. First is the requirement that at equilibrium in such a system as this, plasma and ISF separated by the capillary membrane, the chemical potential of any permeable substance must be the same in both solutions. This requirement must be satisfied whether the substance is present as actual molecules (e.g.,  $CO_2$ (dissolved)) or only potentially present because its component ions are present (e.g.,  $NaCl$ ). Chemical potentials depend logarithmically on concentrations. For an electrolyte such as  $NaCl$ , assuming ideal behavior, we can show that the chemical potential is proportional to the logarithm of the product of the constituent ion concentrations. Equality of chemical potentials for  $NaCl$  can therefore be expressed by

$$[Na^+]_{\text{plasma}} \times [Cl^-]_{\text{plasma}} = [Na^+]_{\text{ISF}} \times [Cl^-]_{\text{ISF}}$$

or

$$\frac{[Na^+]_{\text{plasma}}}{[Na^+]_{\text{ISF}}} = \frac{[Cl^-]_{\text{ISF}}}{[Cl^-]_{\text{plasma}}} = r_D. \quad (8.2.1)$$

$r_D$  is called the Donnan ratio, and this kind of simple membrane equilibrium is usually called a Donnan equilibrium [1]. From the values in Table 7.3,  $r_D$  for plasma/ISF  $Na^+$  and  $Cl^-$  is 1.04.

The hydrostatic pressure difference across the capillary membrane is also necessary for equilibrium, because it affects the chemical potentials, primarily of water, and counteracts the osmotic effect of the plasma proteins. The pressure difference, the total amount of impermeable protein, and the amounts of  $Na^+$ ,  $Cl^-$ , etc, along with the  $P_C$  value, together determine the relative volumes of ISF and plasma and the concentrations of all the ions. A complete set of equations for this combined system can be written, and they may be solved by the same techniques used in earlier chapters [2]. Twenty-six equations and ten independent variables are required, so it seems inappropriate to reproduce the analysis here, even in an appendix. The results are exactly those in Table 7.3, however, so that we may say the 35% difference in [SID] values is understood in quantitative physical and chemical terms. A system consisting of standard

plasma in contact with standard ISF through a capillary membrane, with a hydrostatic pressure difference of 30 to 35 mm Hg across the membrane, will be in equilibrium, with values close to those in Table 7.3.

There must also be a steady flow of  $\text{CO}_2$  through the membrane from ISF to plasma, due to the  $P_{\text{C}}$  difference. In the body, this  $\text{CO}_2$  is removed by circulation and respiration, so that plasma with the composition listed in Table 7.3 is constantly being brought to the capillary membrane, and altered (venous) plasma, with a higher  $P_{\text{C}}$ , constantly being removed. Quantitatively, this is the major ISF-plasma interaction, but strong ion interactions are also important and need to be examined carefully.

A primary factor in strong ion interactions is the relative volume of ISF compared to plasma; at 13.5 liters it is 4.5 times larger than plasma at 3 liters. Together, they constitute the extracellular fluid, or ECF, at 16.5 liters. The most important strong ion interaction between them is the simple dilution by the ISF of any strong ions added to the plasma, or of the effect of strong ion removal from the plasma. Any strong ions added to the plasma will be rapidly distributed throughout the whole ECF and will only cause about one-fifth as much change in plasma [SID] as would have occurred if they had stayed in the plasma. The resulting plasma  $[\text{H}^+]$  changes will also be smaller than expected, so that it may appear as if the ISF is somehow "buffering" the plasma. Conversely, any attempt to manipulate plasma  $[\text{H}^+]$  deliberately by injecting strong ions (usually in the form of  $\text{Na}^+$  in " $\text{NaHCO}_3$ " solution) must take into account the whole ECF volume and not just the plasma.

As a specific example, consider the effects of adding 0.0165 Eq of HCl to the 3 liters of plasma in our model of plasma plus ISF. If complete mixing in the plasma alone is assumed to occur before any of the added  $\text{Cl}^-$  can diffuse into the ISF, then the immediate effect will be to decrease plasma [SID] by  $0.0165/3 = 0.0055$  to 0.0365 Eq/liter. Plasma  $[\text{H}^+]$  will therefore rise to  $5.04 \times 10^{-8}$  Eq/liter, pH 7.30. After one circulation time, we may assume that the added  $\text{Cl}^-$  will have equilibrated throughout the ISF as well, so that the decrease in [SID] in both plasma and ISF will only be  $0.0165/16.5 = 0.001$  Eq/liter. Plasma [SID] therefore ends up at 0.041 Eq/liter, so that plasma  $[\text{H}^+]$  is  $4.22 \times 10^{-8}$  Eq/liter, pH 7.37, much closer to the standard value of  $4.07 \times 10^{-8}$  Eq/liter, pH 7.39. If we only look at plasma samples, and if we do not take our first sample until after the added  $\text{Cl}^-$  has distributed throughout the ECF, then it will appear that the plasma is somehow "buffered" by being in contact with the ISF. Its  $[\text{H}^+]$  only goes up by  $1.5 \times 10^{-9}$  Eq/liter, instead of the  $9.7 \times 10^{-9}$  Eq/liter we expect in response to an [SID] change of 0.0055 Eq/liter. If we measure  $[\text{H}^+]$  (pH), but not [SID], in our plasma sample, we do not automatically know that [SID] has only changed by 0.001, not 0.0055 Eq/liter. That is why the  $[\text{H}^+]-P_{\text{CO}_2}$  diagram (Figure 7.8) is so important. Placing our  $[\text{H}^+]$  of  $4.22 \times 10^{-8}$  Eq/liter at  $P_{\text{C}} = 40$  mm Hg on that diagram tells us immediately that [SID] is not 0.0365 but 0.041 Eq/liter,

and explains the small change in  $[H^+]$ . It is not due to "buffering" in the usual sense; it is simply due to dilution of the added  $Cl^-$  by the ISF.

The importance of the dilution factor also reminds us that we must not conclude from the [SID] value of 0.041 Eq/liter in the plasma that only 0.003 Eq of  $Cl^-$  have to be removed. The whole 0.0165 Eq of  $Cl^-$  originally added must be removed in order to restore [SID] to normal in the ECF. The plasma is only one-fifth of that ECF.

Strong ions are often added to ISF in the form of lactate<sup>-</sup>, usually by inadequately oxygenated cells. ISF [SID] therefore falls. In this case, the relatively small volume of plasma is not of comparable help to the ISF. As the lactate is distributed to the plasma from the ISF, plasma [SID] also falls, and  $[H^+]$  rises, even if  $P_C$  is kept constant at 40 mm Hg. Once more, Figure 7.8 will tell us what is happening. Because lactate is a metabolic product, this condition in the plasma is called metabolic acidosis. It is normally also corrected metabolically, by restoration of adequate oxygen supplies to the tissues, whereupon lactate is taken up from the ISF and further metabolized. [SID] therefore rises back to normal in the ISF, and hence in plasma.

The interactions between plasma and ISF may be summarized in the following statements.

1.  $CO_2$  flows from cells to ISF to plasma. Arterial plasma  $P_C$  is normally kept close to 40 mm Hg by circulation and respiration.
2. Plasma is one-fifth and ISF four-fifths of the ECF volume. The capillary membranes that separate plasma from ISF are permeable to strong ions, so that any departures from normal strong ion concentrations in either fluid are rapidly distributed between them. Observed changes in plasma [SID] must be understood in terms of [SID] changes in the whole ECF.
3.  $[H^+]$ , (pH), and  $P_{CO_2}$  measurements on plasma samples can be used with Figure 7.8 to evaluate plasma [SID], and thereby to monitor ECF [SID] changes. Plasma [SID] cannot change unless ECF [SID] changes, and vice versa.
4. Because of the distribution of strong ions throughout the whole ECF, even when added directly to plasma, plasma  $[H^+]$  changes in response to added strong ions are much less *in vivo* than in isolated plasma samples. This is not "buffering" in the usual sense, nor dilution of hydrogen ions, but the simple consequence of that strong ion distribution from plasma to ISF.

### 8.3. CELL MEMBRANES: ISF-ICF INTERACTIONS

Intracellular and interstitial fluids are by far the two largest body fluid compartments. The situation between them resembles that between plasma and ISF chemically, in that ICF contains large amounts of protein,

and therefore has a high  $[A_{TOT}]$  value, while ISF has essentially none. The similarity ends there, however. There is nothing in this pairwise interaction to compare with the rapid circulation of plasma through the capillaries. Both ISF and ICF have to depend mainly on diffusion and random local movements for the even distribution of substances moving between them. The cell membranes that separate them are largely impermeable, except to  $\text{CO}_2$  and water, and have many special abilities to transport ions. As Table 7.3 clearly shows, [SID] is very large in ICF, as is  $[A_{TOT}]$ . The high  $[A_{TOT}]$  is mostly impermeable proteins, as in plasma, so it can have no effect on the  $[\text{H}^+]$  of ISF. The high [SID] is mainly  $[\text{K}^+]$  and reflects the virtual exclusion of strong acid anions from the ICF. So long as the  $\text{K}^+$  stays inside the cells, it also cannot in any way affect [SID] or  $[\text{H}^+]$  in ISF. As a result, the net effect of ICF-ISF interactions on ISF or plasma  $[\text{H}^+]$  turns out to be small.

ICF is the source of  $\text{CO}_2$  in the body, so that  $\text{CO}_2$  constantly flows across the cell membranes from ICF to ISF. This interaction is important insofar as it determines the ISF, and then the plasma,  $P_c$  value, which in turn determines  $[\text{H}^+]$  in those fluids, but this is generally a one-way flow, rather than an interaction, and is not directly affected by the cell membranes per se.

Production of lactate ions by tissue cells under conditions of low  $P_{O_2}$  is quantitatively the most important ionic interaction between ICF and ISF. It results in a lower [SID], and therefore higher  $[\text{H}^+]$ , in ISF and in plasma.

Another important ionic interaction between ICF and ISF involves strong ion active transport mechanisms through cell membranes. Most cells seem to respond to changed  $[\text{H}^+]$  in their local ISF by moving small amounts of  $\text{K}^+$ ,  $\text{Na}^+$ , and  $\text{Cl}^-$  in or out, so as to alter ISF [SID] in the appropriate direction to change  $[\text{H}^+]$  back toward normal. Plasma [SID] will also be affected, so that plasma  $[\text{H}^+]$  will be closer to normal than predicted from the original plasma [SID] change. This effect is often termed "tissue buffering," or "cellular buffering," but it is clearly not "buffering" in the usual weak acid sense of the word. It is a limited mechanism, because ICF is only about 40% larger than ISF, and necessarily temporary, because cells have no external source or sink for strong ions other than ISF. It may also be hazardous physiologically, for raised ISF  $[\text{K}^+]$  may disrupt a wide variety of electrophysiological mechanisms. It does occur, however, and it is important to understand it as a strong ion mechanism between ICF and ISF. Conventionally, the effect of the extra  $\text{K}^+$  on ISF [SID], and therefore on ISF  $[\text{H}^+]$ , is usually discussed in terms of the cells taking in an  $\text{H}^+$  for each  $\text{K}^+$  extruded, thereby lowering ISF  $[\text{H}^+]$ . The added intracellular  $\text{H}^+$  is then supposed to be "buffered" by the large  $[A_{TOT}]$ . It should be clear that this qualitative description is only attractive because it is qualitative. Quantitatively, it

is nonsense. There is no one for one trade-off between strong ion concentration and  $[H^+]$  in aqueous solutions with positive [SID] values. As the [SID]- $[H^+]$  buffer strength values in Table 7.3 indicate, it takes hundreds of thousands of  $K^+$  to produce a change of 1  $H^+$  in  $[H^+]$ . There is also no way that removing those  $H^+$  will change the  $[H^+]$  value. Finally, changing the [SID] will cause the  $[H^+]$  to change as it does independently of whether  $H^+$  is removed from the solution. It may be removed, or  $OH^-$  may be added, or  $HCO_3^-$  may be added, as we saw in Section 8.1. All that matters is what the strong ions do, so far as  $[H^+]$  is concerned.

In pathological conditions, notably diabetes mellitus, cells may produce significant amounts of other strong acids, and their effects on ISF will be just like those of lactate $^-$ , namely, to lower [SID] and raise  $[H^+]$ . Plasma [SID] will also fall, and  $[H^+]$  rise, so this condition is referred to as diabetic acidosis. The abnormally low [SID] may be treated temporarily by injecting  $Na^+$  in appropriate amounts, usually as “ $NaHCO_3$ ” solution, but it is essential to realize that this is treating the symptom, not the disease. Effective therapy requires control of the underlying pathology, which is endocrine, not ionic.

In summary, the two major ionic interactions between ICF and ISF are these:

1. Occasional release of lactate $^-$  ions into ISF when cells become hypoxic. This lowers [SID] in ISF and in plasma, and therefore raises  $[H^+]$  in both fluids. [SID] changes as large as 15 to 20 mEq/liter may result from this process.
2. Movement of strong ions between tissue cells and ISF in response to changes in ISF  $[H^+]$ . The result is to restore ISF [SID] and therefore  $[H^+]$  toward normal, but the effect is generally small compared to that of the kidneys.

#### 8.4. WHOLE BLOOD: THE PLASMA-RBC-ICF INTERACTION

Whole blood is both a liquid and a tissue. It is a tissue because it consists of cells, the RBCs, and their interstitial fluid, the plasma. It is therefore a two-compartment system, not a solution in the sense that all the other body “fluids” are. The fact that blood is liquid makes it very easy to overlook its heterogeneity and to think of it as if it were a solution. Blood is not a solution and does not have a [SID] or an  $[H^+]$  value or a pH, despite the ease with which a whole blood sample can be placed in a pH meter. What the meter reads is the pH of the plasma in the blood sample. We may not ask about the  $[H^+]$  behavior of whole blood. Rather, we must ask, how do plasma and RBC-ICF interact through the RBC membrane, and how does that interaction affect the  $[H^+]$  behavior of plasma? Plasma in contact with RBCs, which is to say plasma in whole blood, is often

called "true plasma" to distinguish it from the isolated (false?) plasma we analyzed in Chapter 7.

RBCs differ from most other cells in two important respects. First, they are highly specialized for the transport of oxygen and  $\text{CO}_2$  by virtue of their size, shape, and high hemoglobin content. Second, they have been studied and analyzed in enormous detail, so that a great deal is known about them, only some of which is useful in understanding their effects on the  $[\text{H}^+]$  behavior of plasma. The hemoglobin content has several important consequences for the properties of RBC-ICF, as we saw in Chapter 7. It represents an  $[A_{\text{TOT}}]$  value three times that of plasma. As in the other interactions, however, this is not interesting so long as all of these weak acids stay in their own fluids. There is no way hemoglobin in RBC-ICF can directly affect  $[\text{H}^+]$  in plasma, for it is not a part of plasma  $[A_{\text{TOT}}]$ . It must, of course, affect the  $[\text{H}^+]$  of RBC-ICF. Hemoglobin can also bind  $\text{CO}_2$ , as carbamate, and when it does so, its  $K_A$  changes. Its  $K_A$  also changes when it binds  $\text{O}_2$ . Its affinity for  $\text{CO}_2$  changes when it binds  $\text{O}_2$ , and vice versa. It also reacts with DPG, diphosphoglyceric acid, and that interaction affects all these others. The role of hemoglobin inside the RBC is therefore obviously complex. None of that matters to the plasma unless it somehow alters the  $[\text{SID}]$  or the  $P_c$  of plasma. RBCs are small—about  $2 \times 7 \mu$ —so that  $P_c$  in RBC-ICF must be identical to that in plasma except during brief transients when blood goes through capillaries. In any blood sample,  $P_c$  is necessarily uniform.

As always, we are left with strong ion interactions as the only means by which RBC-ICF can interact with plasma, or vice versa. Those interactions are constrained here, just as they are in the ISF-ICF case, by the special properties of the RBC membrane, which does not permit strong ions in general to distribute freely throughout the blood volume. Even if it did, the effects would not be large, because RBC-ICF volume is only 40 to 45% of blood volume, or 70 to 80% of plasma volume, compared to ISF volume, which is 450% of plasma volume. In whole blood, when plasma  $[\text{SID}]$  changes, or when  $P_c$  changes, RBCs are able to move  $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{K}^+$  between plasma and RBC-ICF in a way that slightly reduces the amount of  $[\text{SID}]$  change in the plasma, and therefore reduces the  $[\text{H}^+]$  change in the plasma. These changes are the result of the specific strong ion active transport mechanisms in the RBC membrane, as well as the presence in the RBC of impermeable protein, and they have been explained quantitatively [2]. What matters here is that they occur and that their effect on plasma is to reduce the magnitude of  $[\text{SID}]$  changes in response to addition or removal of strong ions. They are therefore usually described in terms of buffering effects, and in fact it is conventional to ascribe the "buffering" to the hemoglobin in the RBC. When the strong ions are taken into account,  $\text{Cl}^-$  is usually the only one mentioned, and the phenomenon is then referred to as "the chloride shift," the shift being

from plasma into RBC when plasma [SID] goes down or  $P_C$  goes up, and from RBC to plasma in the opposite cases. The fact that  $\text{Na}^+$  and  $\text{K}^+$  also move in this situation is often ignored, presumably because the  $\text{Cl}^-$  movement is generally supposed to result from  $\text{HCO}_3^-$  movement. Because  $[\text{HCO}_3^-]$  is a dependent variable and  $[\text{Cl}^-]$  is an independent one, it is difficult to understand how such a process could alter  $[\text{Cl}^-]$ .

In any event, strong ion interactions between plasma and RBC-ICF do occur and have the effect of slightly improving the apparent "buffering" of plasma. Quantitatively, they are not nearly so important in the body as the plasma-ISF-ICF interactions, but they are talked about more because blood samples are so much easier to obtain than ISF samples. They are also important in understanding the relatively small ionic changes that occur in plasma when it is transformed from venous to arterial during passage through the lung capillaries, or from arterial to venous during passage through tissue capillaries. Despite their popularity in textbooks, these processes have very little quantitative significance for whole-body acid-base balance.

### 8.5. KIDNEY TUBULES: PLASMA-URINE INTERACTIONS

In a functional sense, the kidney tubule may be thought of as a stretched out capillary, in which the tubular filtrate may be thought of as similar to ISF, while the urine is what is left over after that filtrate has been mostly reabsorbed by the length of the tubule. From the point of view of plasma  $[\text{H}^+]$  behavior, the interesting question is, what can the kidneys do between filtrate and plasma that will affect the acid-base status, which means the [SID],  $P_C$ , and  $[\text{A}_{\text{TOT}}]$ , of the plasma? Once again, for most practical purposes, the answer involves strong ions. The tubule returns  $\text{Na}^+$  and  $\text{Cl}^-$  and other strong ions to the plasma in such a way as to maintain their normal concentrations, and therefore the normal plasma [SID] of 0.042 Eq/liter. How the tubule cells know to do this is not known completely, although parts of the picture have been clarified. For our present purposes, it is convenient to regard the tubules as a device that removes water, strong ions, and small molecules from the plasma at a remarkably high rate, about 20% per minute, and returns most of them to the plasma, retaining in the urine just the right amounts so that over a period of a few minutes for water, and several hours for strong ions, imposed changes in plasma concentrations are corrected. The remarkable feature of this system is that the very high blood flow rate enables it to achieve significant changes in plasma composition by relatively small amounts moved over long periods of time. This feature is important to understand because of the confusion between urine content and plasma concentration. Phosphate, for example, exists in plasma at a low concentration, on the order of 0.001 Eq/liter, and is not a significant com-

ponent of plasma  $[A_{TOT}]$ . Large quantities of phosphate are incorporated in food, however, and must be eliminated. The tubule systematically retains phosphate in the filtrate under these conditions, only returning to the plasma enough to keep the plasma concentration at the proper value. The rest accumulates in the urine, where it is completely irrelevant to plasma  $[H^+]$ .

Another important source of confusion about kidney tubule function is  $NH_4^+$ . This ion exists at extremely low concentrations in plasma, but is manufactured in tubule cells by deamination of amino acids, notably glutamic acid. It is often stated that the tubule cells are thereby "removing  $H^+$  from the body," for the  $NH_3$  resulting from the deamination must capture an  $H^+$  to become  $NH_4^+$ . This description completely ignores the dependent status of  $[H^+]$  and is thoroughly misleading. Every water molecule that leaves the body carries an  $H^+$  with it in just the same sense, which is no sense at all. Whether the urine is alkaline, neutral, or acid, and why, makes no difference at all to the  $[H^+]$  of plasma. What determines the  $[H^+]$  of plasma is its  $[SID]$ , its  $P_C$ , and its  $[A_{TOT}]$  and only to the extent that kidney tubule cells affect one or more of these independent variables can they affect plasma  $[H^+]$ . They do affect plasma  $[SID]$ , by altering the relative amounts of  $Na^+$ ,  $K^+$ , and  $Cl^-$  that they return to the plasma from the filtrate, as already pointed out, and this is the only significant acid-base interaction across the tubule. We shall return to this most important kidney-plasma interaction in the context of whole-body acid-base balance in the next chapter.

## 8.6. SUMMARY AND CONCLUSIONS

The concept of simple pairs of interactions between body fluids is convenient intellectually, but is clearly an extreme simplification. In the living body, all of these interactions occur simultaneously, so that the real situation is dynamic and complicated. Two important features of the body fluid system are useful in keeping this complexity manageable and can serve as an important focus for the conclusions of this chapter.

The central physiological feature of body fluid interactions is the very rapid circulation of blood plasma throughout all body tissues, and its consequent roles as a meeting ground and final common pathway for those interactions.  $CO_2$  and strong ions from tissue cells may enter the ISF, but they move very rapidly into the plasma in the tissue capillaries. They are then taken to the lungs and kidneys for appropriate processing. The result is rapid and effective interaction between ICF, ISF, lungs, and kidneys, which permits these organs to regulate the  $P_C$  and the  $[SID]$ , and therefore the  $[H^+]$ , of all of these body fluids, not just the plasma.

The relative volumes of body fluids are equally important in understanding their dynamic interactions. Because strong ions can move freely between plasma (3 liters) and ISF (13.5 liters), for example, the circulating plasma is "mechanically" buffered by the ISF. Plasma  $[SID]$  changes require much larger amounts of strong

ions to be added or removed than the 3-liter plasma volume would indicate. In the other direction, the small RBC volume of only 2 liters means that RBC-ICF can only contribute significantly to plasma [SID] changes, and therefore to  $[H^+]$  behavior, when blood is isolated from the ISF, for example, in venous or arterial pools or in the biochemistry laboratory. Also in the other direction, any attempts by the kidneys to regulate plasma [SID] require processing much larger amounts of  $Na^+$  and  $Cl^-$  than would be the case if only the plasma were involved.

All of these features of body fluid interactions contribute to whole-body acid-base balance, which we are now ready to look at quantitatively in the next chapter.

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## CHAPTER NINE

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# WHOLE-BODY ACID-BASE BALANCE

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### 9.1. INTRODUCTION

Precisely what is meant by “acid–base balance” is often far from clear and may be quite different in different practical situations. In light of the analysis and conclusions from the preceding eight chapters, we adopt the following as a useful working definition:

“Acid–base balance,” or “whole-body acid–base balance,” refers to the set of mechanisms by which the parts of the body, notably the lungs, kidneys, and gastrointestinal tract, control the composition of the circulating blood plasma, so as to keep its  $[H^+]$  generally within the range from  $2 \times 10^{-8}$  to  $1 \times 10^{-7}$  Eq/liter, or pH 7.7 to 7.0.

Our purpose in this chapter is to clarify those mechanisms and their interactions.

Clinically, the central question is, “How must we interpret measured changes in circulating plasma  $[H^+]$  values in terms of the ionic effects of lungs, kidneys, and GI tract and interactions with other body fluids?” Understanding acid–base balance means having clear answers to this question, and the quantitative analysis of the preceding chapters supplies them.

As a basis for looking at these answers, Figure 9.1 adds to the diagram

of body fluid compartments in Figure 1.1 the highlights of what we now know about the ionic composition in each of those fluids. The appropriate  $[H^+]-P_C$  diagram in Chapter 7 presents the  $[H^+]$  behavior for each of them in isolation. The lungs, kidneys, and GI tract have also been added in Figure 9.1 to suggest their roles in regulating plasma  $[H^+]$ . We must now examine those roles carefully.

## 9.2. THE LUNGS

In the lung capillaries,  $CO_2$  in circulating plasma equilibrates with  $CO_2$  in alveolar gas.  $P_C$  in the alveoli is therefore determined by the balance between this equilibration and the effects of periodic exchange with ambient air that we call breathing, or alveolar ventilation. The result under normal conditions is an alveolar, and a circulating plasma,  $P_C$  value close to 40 mm Hg. Practically speaking, end-tidal gas is very close to alveolar gas in its  $P_C$  value, so that arterial  $P_C$  may be easily and noninvasively estimated simply by measuring  $P_C$  in end-tidal expired air.

Changes in alveolar ventilation can occur rapidly (in seconds) and result in equally rapid changes in alveolar and arterial plasma  $P_C$ . Effects on plasma  $[H^+]$  are equally rapid. They may be predicted and understood from the  $[H^+]-P_C$  diagram for plasma that is reproduced in Figure 9.2. Superimposed on the  $[H^+]$  versus  $P_C$  curves in this figure are four areas representing data from a large number of patients with acid-base disorders resulting from changes in  $P_C$  [1, 2]. The areas labeled "ACUTE" are for patients with short-duration  $P_C$  abnormalities. As expected, the area for increased  $P_C$ , and therefore increased  $[H^+]$ , acute respiratory acidosis, lies parallel to the lines of constant [SID]. When  $P_C$  falls, there appears to be some change in [SID]; the area for acute respiratory alkalosis is not quite parallel to the  $[SID] = \text{constant}$  lines, but tends to slope toward regions of decreased [SID] as  $P_C$  decreases. Some of this [SID] change may be due to strong ion shifts between plasma and RBC-ICF, discussed in Chapter 8, and some must be due to small readjustments of the Donnan distributions across the capillary membranes between plasma and ISF, but it is not obvious why the effects are so much greater when  $P_C$  falls. In any case, the [SID] effects are small, and it is reasonably correct to think of acute respiratory changes as reflecting simply the effect on plasma  $[H^+]$  of above or below normal  $P_C$ .

Circulating plasma is the final common pathway by which  $CO_2$  moves from inside cells to alveolar gas, as Figure 9.1 indicates. Any change in plasma  $P_C$  must alter diffusion flow rates from ISF to plasma and quickly result in a corresponding change in ISF  $P_C$ . The altered ISF  $P_C$  must similarly alter diffusion from ICF to ISF and thereby change ICF  $P_C$ . As the  $[H^+]-P_C$  diagram for each of these fluids tells us, these  $P_C$  changes must cause  $[H^+]$  changes. In other words, any change in alveolar  $P_C$ , and

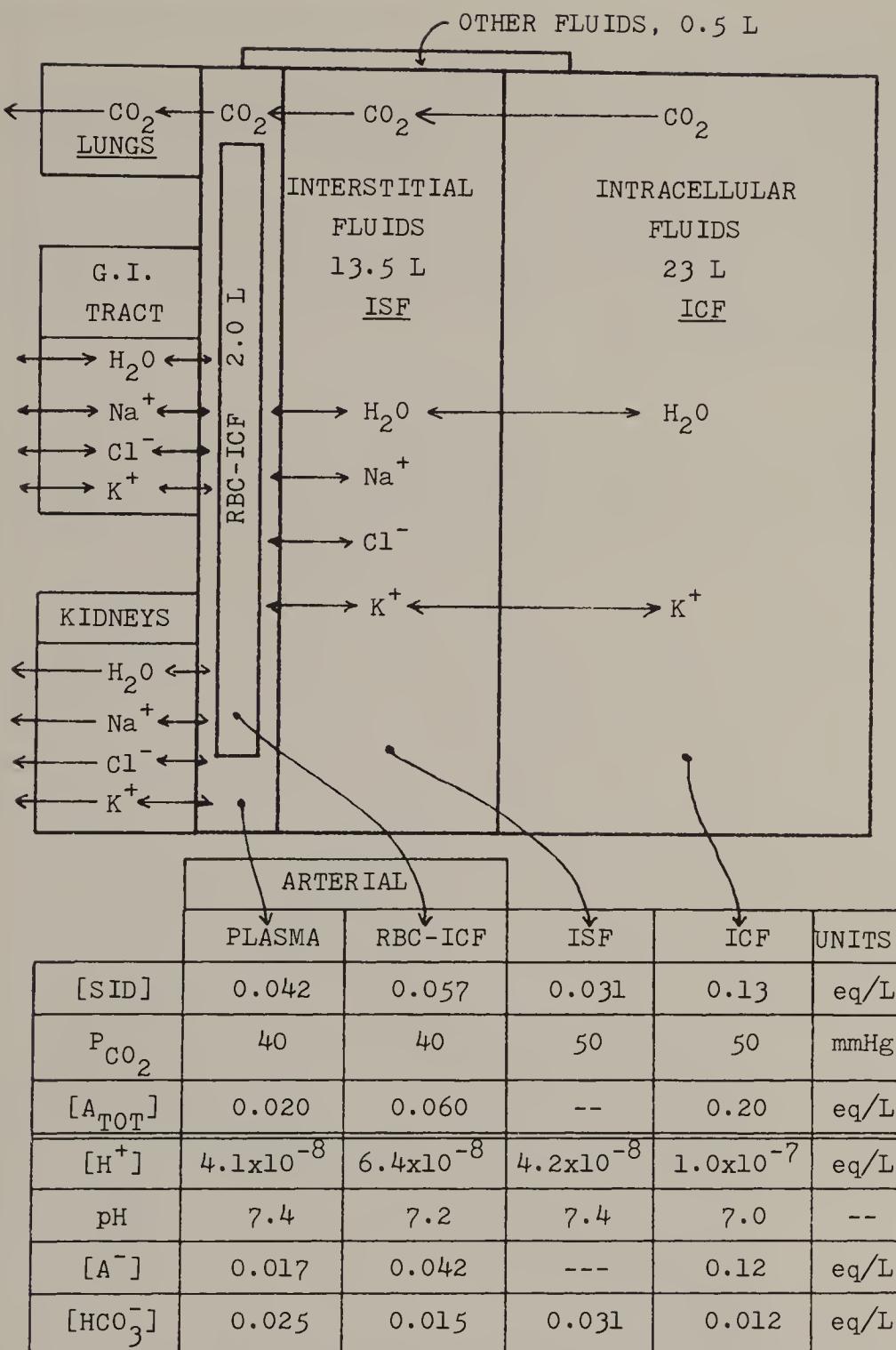
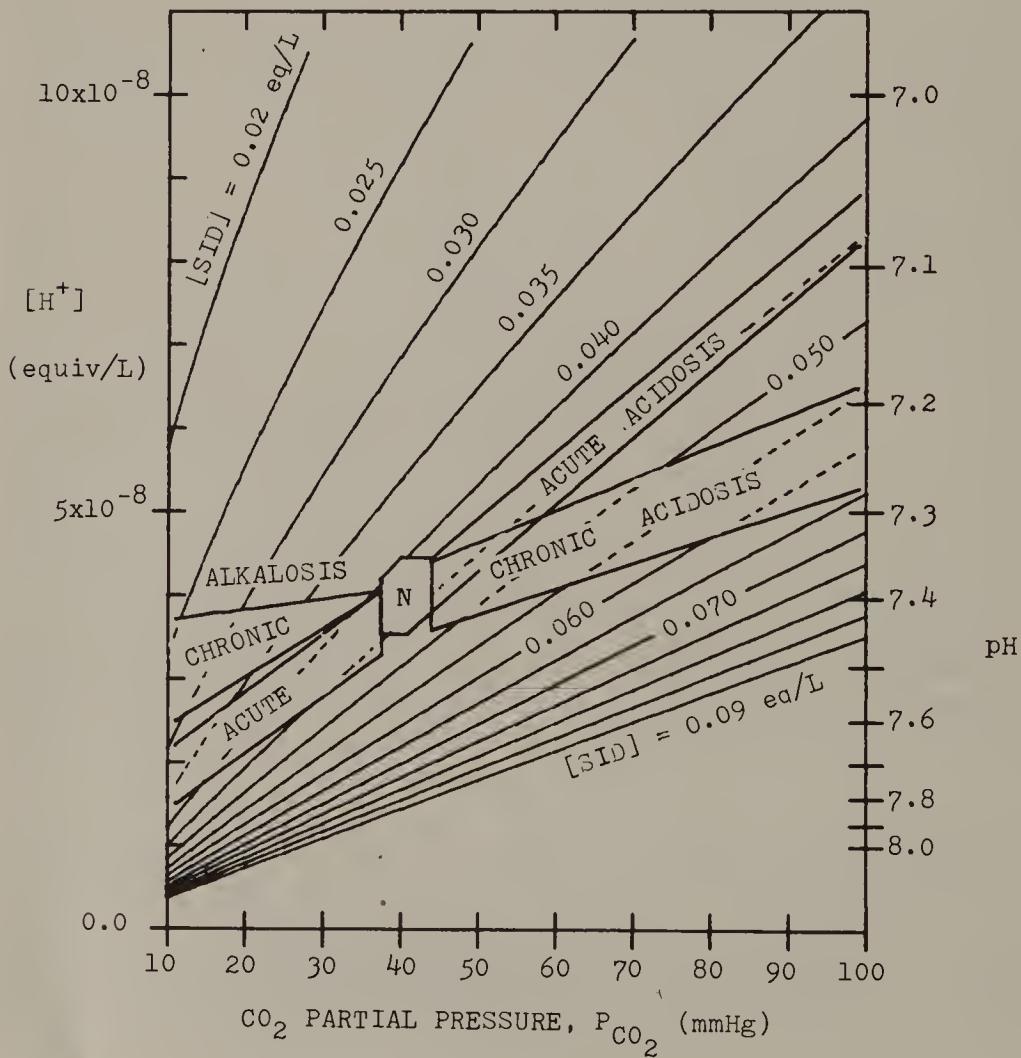


Figure 9.1. An expansion of the body-fluid diagram in Figure 1.1 to include the major ionic data relevant to acid-base behavior of body fluids.

therefore in circulating plasma  $P_C$ , results in changes in all body fluid  $[H^+]$  values, not just in that of plasma.

Normal breathing frequencies are 4 or 5 per minute, so that  $P_C$  may change in seconds or minutes. If an abnormal  $P_C$  value is maintained for many minutes or for hours or days, additional mechanisms come into play, and the condition is called "chronic respiratory acidosis" or "chronic respiratory alkalosis." The areas corresponding to these states are also shown on Figure 9.2. They indicate much larger [SID] changes than in the "ACUTE" cases, and we must turn to the role of the kidneys to explain those changes.

**Figure 9.2** The  $[H^+]-P_{CO_2}$  diagram for plasma, with superimposed areas to indicate normal values (N) and common ranges of values for patients with acute or chronic  $P_{CO_2}$  abnormalities, labeled acidosis and alkalosis. Modified from [1].



### 9.3. THE KIDNEYS

Circulating plasma perfuses the kidneys at an average rate of about 600 ml/min. Filtration in the glomeruli produces 120 ml/min of protein- and RBC-free filtrate from that plasma. This filtrate is processed by reabsorbing and secreting mechanisms in the tubule cells as it proceeds along the tubules toward the ureters. Almost all of the filtrate is reabsorbed and returned to the plasma; only about 1 ml/min ends up as urine to be eliminated from the body. This very small urine volume—less than 0.2% of the perfusing plasma—has important implications for the time course of kidney effects on plasma acid–base status. It tells us that the kidneys can only change strong ion concentrations in the plasma by a very small amount each minute, and therefore must take many minutes to produce any significant change in plasma [SID]. When we add to this the plasma–ISF interaction that requires that the kidneys deal with the strong ion content of the whole ECF, not just the plasma, it becomes clear that kidney effects on plasma  $[H^+]$  via [SID] changes must be slow compared to lung effects via  $P_C$  changes.

The small urine volume has another important acid–base consequence that is very widely misunderstood. The kidneys eliminate a wide variety of low-molecular-weight “waste” substances in the urine, and some of these have acid–base properties that are important in the urine because these substances become relatively concentrated there. They are unimportant in acid–base balance, however, because they all occur at such low concentrations in circulating plasma. Two important examples are phosphate ions and ammonia. Phosphate in plasma occurs as  $HPO_4^{2-}$  and  $H_2PO_4^-$  at concentrations usually below 0.001 Eq/liter. They constitute such a small part of plasma  $[A_{TOT}]$  that they are completely negligible, particularly because the effects of  $[A_{TOT}]$  on plasma acid–base behavior are so small compared to those of  $CO_2$ . The concentration of  $NH_3$ , or its add-on cation,  $NH_4^+$ , is well below  $10^{-6}$  Eq/liter normally, so it also has no effect on plasma  $[H^+]$ . Both  $NH_4^+$  and phosphate ions are accumulated in the urine, however, and have important effects on urine  $[H^+]$ . Phosphate contributes significantly to  $[A_{TOT}]$ , and  $NH_4^+$  to  $[B_{TOT}]$ , in the urine. Their presence there has no effect on the [SID],  $P_C$ , or  $[A_{TOT}]$  of plasma, and therefore cannot have any effect on plasma  $[H^+]$ . It is essential to realize this distinction clearly.

Strong ion processing by the kidneys is important because every  $Cl^-$  filtered but not reabsorbed means a corresponding increase in plasma [SID], and every  $Na^+$  or  $K^+$  not reabsorbed means a decrease in plasma [SID]. The kidney–volume receptors–aldosterone ECF volume regulating system has the net effect of using plasma, or ECF,  $[Na^+]$  as the determining variable for ECF volume. The kidneys must therefore balance net  $Cl^-$  excretion against net  $Na^+$  excretion in order to regulate plasma [SID] effectively, while still regulating ECF volume. The mechanisms and path-

ways by which this  $[Cl^-] - [Na^+] - [SID]$  balance is achieved are not yet fully understood. The end result may be summarized very simply, however. If the circulating plasma arriving at the kidneys has an above normal  $[H^+]$  value, the kidneys will react by reabsorbing less  $Cl^-$ , thereby slowly raising plasma  $[SID]$ , increasing  $Cl^-$  excretion, and lowering urine  $[SID]$ . Conversely, if plasma  $[H^+]$  is below normal,  $Cl^-$  reabsorption will be increased, plasma  $[SID]$  decreased, and urine  $[SID]$  increased. Because of the primary role of plasma  $[Na^+]$  in ECF volume regulation, manipulation of  $Cl^-$  reabsorption is the only mechanism the kidney has for affecting plasma  $[SID]$  and thereby plasma  $[H^+]$ . In lactic acidosis, when plasma  $[SID]$  is below normal because of excess lactate $^-$ , the kidney may also work to restore  $[SID]$  to normal by filtering and not reabsorbing lactate $^-$  as well as  $Cl^-$ , but that is a special case. Usually, the only strong anion it has to work with is  $Cl^-$ .

A crude indicator of the strong ion content in the urine is the quantity called "titratable acidity." It is crude because, as pointed out in Chapter 5, the significance of a measured  $[H^+]$  change in a titration can only be clearly understood if the precise composition of the solution is known, and this is seldom the case for urine. Its clinical use seems to be based on the conventional but unfortunately false notion that  $[H^+]$  behaves in the same way when  $[SID]$  is positive as when it is negative. For all body fluids, when  $[SID]$  is negative, it is the case that adding 1  $H^+$ /liter (along with a strong ion, of course!) will raise  $[H^+]$  by 1 ion/liter. Adding 1  $Na^+$  or  $K^+$  (along with an  $OH^-$  or an  $HCO_3^-$ )/liter will lower  $[H^+]$  by 1 ion/liter. In no body fluid other than stomach juice is  $[SID]$  ever negative, so these statements should be dismissed as true but mostly irrelevant. When  $[SID]$  is positive, such one for one bookkeeping is not applicable to  $H^+$ , and trying to apply it is simply wrong. All the value of titratable acidity in the urine can tell us is roughly how much more ( $Cl^- + SO_4^{2-} +$  lactate $^-$ ) the kidneys have excreted than ( $Na^+ + K^+ + Ca^{2+} + Mg^{2+}$ ) since the last urine collection.

We have seen in the preceding section that one cause of abnormal plasma  $[H^+]$  is abnormal  $P_C$ , and that when this state is maintained, the kidneys react to it by appropriately, but slowly, changing plasma  $[SID]$ . The areas for chronic respiratory acidosis and alkalosis in Figure 9.2 show the significant extent of this real compensation; plasma  $[H^+]$  may be restored very nearly to normal by the  $[SID]$  change, whether the sustained  $P_C$  level is above or below normal.

The acid-base balance situation in conditions of abnormal  $P_C$  can be understood in quantitative terms and described very simply: when an abnormal  $P_C$  value is maintained, the kidneys respond by changing  $[SID]$  so as to bring plasma  $[H^+]$  back toward normal. Unfortunately, the universal terminology for any change in plasma  $[H^+]$  that is not caused by a  $P_C$  change is "metabolic." The conventional description of the  $[SID]$ -compensated chronic respiratory abnormalities therefore is "chronic res-

piratory acidosis with accompanying metabolic alkalosis" and "chronic respiratory alkalosis with accompanying metabolic acidosis." This terminology seems inappropriate for two reasons. First is the use of the word "metabolic" to refer to strong ion effects. One reason strong ions are so important in understanding acid-base balance is that they are not involved in chemical reactions, so that their electrical charges are always present and have to be taken into account. That is just what [SID] does. If there is anything strong ions are *not*, it is "metabolic." Historically, the terminology arose because of lactate<sup>-</sup>, which is a metabolically active substance as well as a strong ion. It is therefore useful, as we shall see below, to distinguish between the contributions to [SID] of inorganic ions, which are clearly not metabolic, and of lactate<sup>-</sup>, as well as the keto-acids of diabetic ketoacidosis, which clearly are. The blanket term "metabolic" for all [SID] changes is not helpful.

The second problem with the conventional terminology is the ambiguity of "acidosis" and "alkalosis." Do they mean plasma  $[H^+]$  above or below neutral, as they "should," do they mean plasma  $[H^+]$  above or below normal, as they often seem to, or do they mean plasma  $[H^+]$  potentially above or below normal if other factors were not present, as they seem to in the description "chronic respiratory acidosis with accompanying metabolic alkalosis"? Acid-base neutrality for plasma is  $[H^+] = 2.1 \times 10^{-7}$  Eq/liter, pH 6.7. Plasma is always highly alkaline, therefore, even under conditions of extreme "acidosis," so the first possible meaning is not applicable. The second meaning is often used in situations when only the  $[H^+]$  (pH) is known. If it is below normal, the patient has "alkalosis," if above, "acidosis." Once we learn more about the acid-base status, however, we are likely to shift to the third meaning. In chronic respiratory acidosis, the patient has acidosis in the sense that plasma  $[H^+]$  is above normal, and this is due to the increased  $P_C$ .  $[H^+]$  is not as high as it would be if [SID] were normal, however, so that downward shift of  $[H^+]$  due to the increased [SID] value is described as an "alkalosis," even though  $[H^+]$  is still above normal. This confusing ambiguity stems from the historical assignment of an independent role to  $[H^+]$ . Once the dependent role of  $[H^+]$  is recognized, the appropriate terminology becomes obvious and explanatory. Fortunately, translation is easy once the difficulty has been recognized and the mechanisms understood.

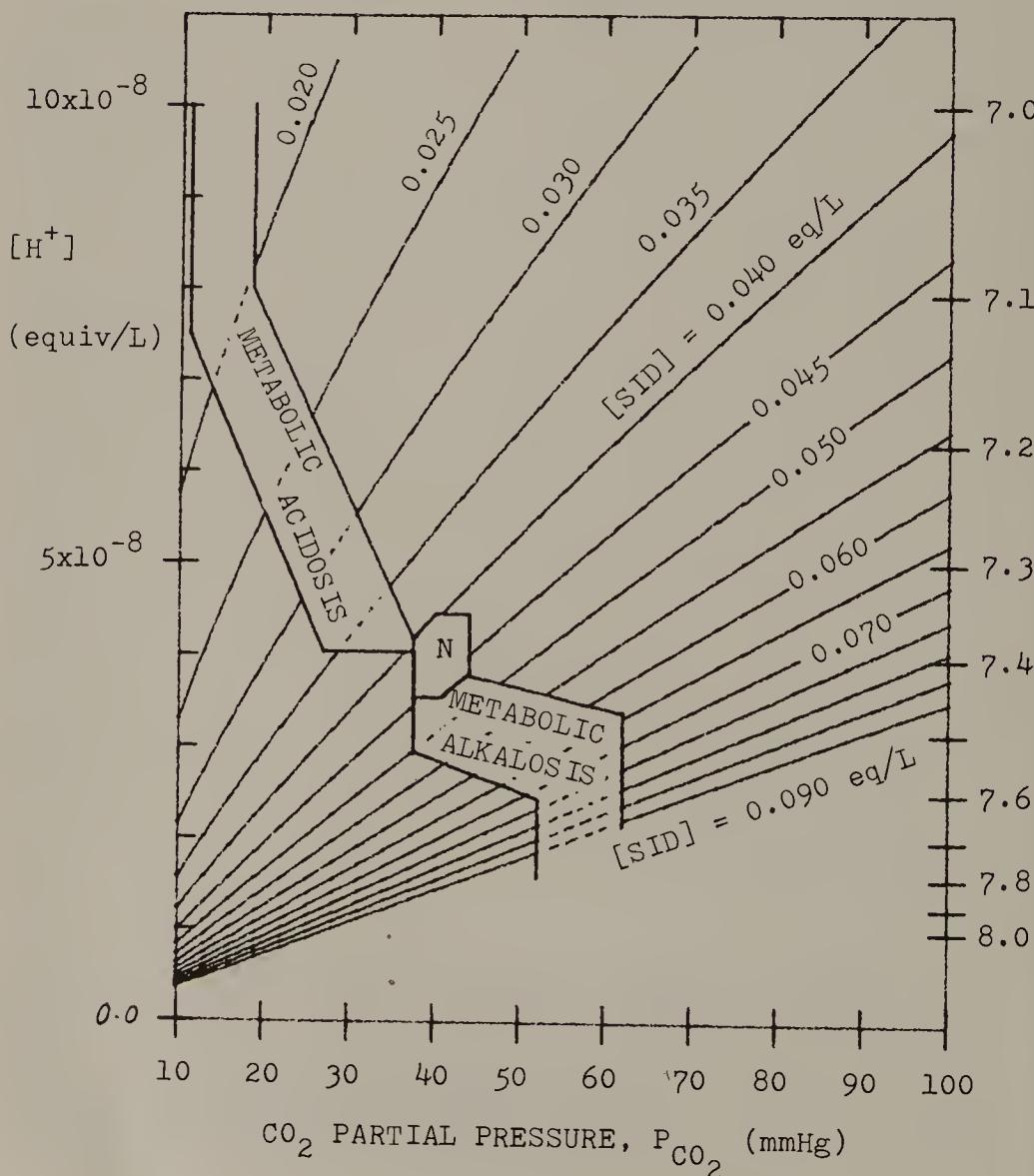
The four abnormal areas in Figure 9.2 should be described by the following translated terms:

Acute respiratory acidosis	= $P_C$ up briefly, so plasma $[H^+]$ up.
Acute respiratory alkalosis	= $P_C$ down briefly, so $[H^+]$ down.
Chronic respiratory acidosis	= $P_C$ up (sustained), [SID] up, $[H^+]$ up slightly.
Chronic respiratory alkalosis	= $P_C$ down (sustained), [SID] down, $[H^+]$ down slightly.

In all four of these situations, the  $P_C$  change is the primary or initiating cause of the  $[H^+]$  change, and in the chronic cases, the [SID] change is a compensating mechanism.

The acute situations may, and in fact must, arise frequently, whenever normal regular breathing is interrupted, as in speaking, singing, under-water swimming, playing wind instruments, or any activity that involves spasmotic hypo- or hyperventilation. Chronic situations of hypoventilation, and therefore above normal  $P_C$ , may occur following trauma to the chest that makes breathing painful, or in severe lung disease that interferes

**Figure 9.3.** The  $[H^+]-P_{CO_2}$  diagram for plasma with superimposed areas to indicate common ranges of values for patients with [SID] abnormalities, labeled metabolic acidosis and alkalosis. Compare with Figure 9.2. Modified from [1].



with normal  $\text{CO}_2$  transfer from plasma to air. Breathing abnormalities of psychic origin are also sometimes the cause of respiratory acidosis or alkalosis.

The differences in the time scales of the  $P_{\text{C}}$  changes and the [SID] response by the kidneys require caution in clinical treatment. An abrupt return of respiration, and therefore  $P_{\text{C}}$ , to normal in a patient with chronic respiratory alkalosis will result in a “metabolic” acidosis in that patient, as the subnormal [SID] can only be returned to normal by the kidneys in hours. Similarly, a rapidly corrected chronic respiratory acidosis will result in “metabolic” alkalosis.

We may summarize the major role of the kidneys in acid–base balance as the primary determiners of inorganic strong ion concentrations, and therefore of [SID], in the circulating plasma. No single organ is solely responsible for the value of [SID], however. The GI tract and tissue cells may both contribute indirectly or directly to changing its value. Disturbances in acid–base balance due to [SID] changes are generally called “metabolic,” as noted above, regardless of their relationship to actual metabolic events. Figure 9.3 presents on the plasma  $[\text{H}^+]$ — $P_{\text{C}}$  diagram the clinical areas for such [SID]-based disturbances. In this case, the distinction between acute and chronic is not significant because [SID] does not change rapidly. The striking difference between these areas and those in Figure 9.2 for  $P_{\text{C}}$ -based disturbances is that  $P_{\text{C}}$  changes relatively little in response to the plasma  $[\text{H}^+]$  changes produced by the abnormal [SID] values. Respiratory compensation for [SID] disturbances is not as effective as the kidneys’ [SID] compensation for sustained  $P_{\text{C}}$  disturbances.

The kidney still compensates for [SID] changes, nonetheless, by changing plasma [SID] appropriately so as to move plasma  $[\text{H}^+]$  back toward normal, whenever it is altered by effects of other organs. One of the most important of those is the GI tract, so we examine its role in acid–base disturbances in the next section.

#### 9.4. THE GASTROINTESTINAL (GI) TRACT

The GI tract is important in acid–base balance because it deals directly with strong ions. It does so differently in different regions along its length, so it is useful to consider four separate parts that are quantitatively important in their effects on plasma [SID].

First is the stomach.  $\text{Cl}^-$  is removed from plasma circulating through the gastric mucosa, and secreted into the lumen as gastric acid. [SID] in that plasma therefore increases. The effect on the total circulating plasma volume is small, but detectable; [SID] rises slightly and  $[\text{H}^+]$  falls correspondingly. The classical name for this phenomenon is “the alkaline tide” at the beginning of a meal when gastric acid secretion is maximal.

Normally, this sequestered  $\text{Cl}^-$  returns to the plasma when it is absorbed in the small intestine an hour or so after being secreted. It thus leaves the plasma temporarily, but does not leave the body.

This series of events is disrupted severely in the case of prolonged vomiting. Now the sequestered  $\text{Cl}^-$  is lost from the body and never returned to the plasma, so that plasma [SID] may show a significant elevation, which produces a fall in plasma  $[\text{H}^+]$  (rise in pH). The patient will be said to have a "metabolic alkalosis." The important point to understand is that the alkalosis in the plasma is due to loss of  $\text{Cl}^-$  from the plasma, not the loss of  $\text{H}^+$  from the stomach, as textbooks often imply.

Figure 9.3 indicates that plasma  $[\text{H}^+]$  does not fall as much as expected from the [SID] change, due to respiratory compensation.  $P_{\text{C}}$  rises as [SID] rises, so that a "respiratory acidosis" is superimposed on the "metabolic alkalosis." Because [SID] changes are necessarily slow and  $P_{\text{C}}$  changes rapid, there is no basis in this situation for distinguishing between "acute" and "chronic" situations; any [SID] disturbance is "chronic" so far as the response of the respiratory system is concerned. After prolonged vomiting, plasma analyses should show a lowered  $[\text{Cl}^-]$  (hypochloremia), above normal [SID] (metabolic alkalosis), above normal  $P_{\text{C}}$  (respiratory acidosis), and moderately lowered  $[\text{H}^+]$  (increased pH).

The second portion of the GI tract involved in acid-base balance is the pancreas. This gland manufactures and secretes into the small intestine a complex fluid that contains many digestive enzymes and has a [SID] value well above that of plasma, primarily due to its low  $[\text{Cl}^-]$ . Plasma perfusing this gland has its [SID] correspondingly lowered by extraction of  $\text{Na}^+$  but not  $\text{Cl}^-$ . This process peaks in activity some time after the "alkaline tide" due to stomach  $\text{Cl}^-$  secretion, and helps to restore plasma [SID] to normal.

In the duodenum, acid gastric fluid ([SID] very low or negative) mixes with the pancreatic secretion ([SID] large) to produce a fluid called chyme, which normally has a resultant [SID] value close to that of plasma. The precise value of chyme [SID], and therefore of chyme  $[\text{H}^+]$ , fluctuates with the strong ion composition of the diet, the size and timing of meals, the relative amounts of gastric and pancreatic secretion, and many other factors. It has no direct effect on plasma  $[\text{H}^+]$  for the same reason that urine  $[\text{H}^+]$  does not. What happens to the chyme in the remaining two sections of the GI tract is significant for plasma [SID], however.

The small intestine, duodenum, jejunum, and ileum, is the major site of absorption of strong ions from chyme into plasma. Here the  $\text{Cl}^-$  that was sequestered in the gastric acid and the  $\text{Na}^+$  that was removed from plasma to make alkaline pancreatic juice are returned to the plasma. Strong ions taken in with food are also absorbed and make direct contributions to plasma [SID]. Absorption from the small intestine is generally a slow process, taking place over the course of hours after each

meal, so that plasma [SID] changes take place equally slowly. The kidneys therefore are able to keep pace with the strong ion inputs and keep plasma [SID] near normal by appropriately eliminating into the urine excess  $\text{Cl}^-$  or  $\text{Na}^+$  or  $\text{K}^+$ .  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  in the diet are nutritionally very important, and they are also absorbed in the small intestine, but in small amounts compared to the alkali cations and  $\text{Cl}^-$ . They normally make only minor contributions to plasma [SID], so that small fluctuations in their plasma concentrations, if they do occur, can have slight acid-base significance.

The fourth important region is the large intestine or colon. The major physiological process taking place here is water absorption, but strong ions also move between plasma and colon contents, in both directions. Most of the  $\text{Cl}^-$  in the chyme is normally absorbed in the small intestine, so that chyme entering the colon has a high [SID], and the major strong ion exchanges with the plasma involve  $\text{Na}^+$  and  $\text{K}^+$ . Again the process is normally a slow one, and the colon and kidneys can interact via their effects on plasma [SID] in such a way that [SID] is appropriately regulated. Strong ions not absorbed from the colon are simply eliminated from the body in the feces.

The mechanisms by which these strong ion interactions are regulated are not yet fully understood, but their importance is underlined in two pathological situations that interfere with them. One is diarrhea, during which intestinal fluid passes through the colon too fast to be properly processed, so that water is lost from the body, and less  $\text{Na}^+$  and  $\text{K}^+$  are absorbed. The acid-base result is a fall in plasma [SID], the clinically well-known "metabolic acidosis" following diarrhea. This is just the opposite of the "metabolic alkalosis" following vomiting, for now strong cations are being lost from the body rather than  $\text{Cl}^-$ , so plasma [SID] falls and  $[\text{H}^+]$  rises.

Another cause of this same situation is frequent tap-water enemas. Filling the colon with water and then eliminating it removes  $\text{Na}^+$  and  $\text{K}^+$  directly, just as a stomach tube draining gastric fluid will eliminate  $\text{Cl}^-$ . Both procedures will result in [SID] abnormalities, and therefore upset acid-base balance. The enema effect is easily prevented by using an appropriately balanced solution containing  $\text{Na}^+$  and  $\text{K}^+$  as the enema fluid. Such solutions are now readily available commercially. The acid-base effects of gastric lavage generally must be counteracted by appropriate changes (ie, increased  $\text{Cl}^-$  but not  $\text{Na}^+$ ) in the intravenous fluids that are usually infused into the patient during the same period.

The contributions of the GI tract to whole-body acid-base balance may now be summarized in three categories.

1. Temporary and usually small plasma [SID] changes due to temporary sequestration of  $\text{Cl}^-$  in gastric juice and  $\text{Na}^+$  in pancreatic juice.
2. Absorption of  $\text{Na}^+$ ,  $\text{Cl}^-$ , and  $\text{K}^+$  from the small intestine and of  $\text{Na}^+$  and  $\text{K}^+$  from the large intestine.

3. Pathological changes in plasma [SID] due to interference with any of these normal processes, notably in diarrhea, vomiting, tap-water enemas, and gastric lavage.

The overwhelming quantitative importance of [SID] and  $P_C$  in determining plasma  $[H^+]$  justify our ignoring, as we have done so far, the acid-base consequences of acids in the diet. Many foods, especially fresh fruits, contain high concentrations of weak and not so weak organic acids, for example, citric, acetic, and lactic. These are not important for acid-base balance because their rates of digestion and absorption in the small intestine are sufficiently slow compared to plasma circulation and liver metabolism that their concentrations in the circulating plasma never rise enough to make any significant change in  $[A_{TOT}]$ , if they are weak, or [SID] if they are strong. So long as they are still in the chyme, they cannot affect plasma [SID],  $P_C$ , or  $[A_{TOT}]$ , or, therefore,  $[H^+]$ . Once they get into the plasma, they are kept at such a low concentration that they can be ignored. This generalization is not true for tissue-produced lactate, however, as we shall see below.

A closely related question concerns antacids, substances taken by mouth to "neutralize gastric acid" or "reduce gastric acidity." There are two major classes of antacid substances, and the acid-base differences between them are important. The simplest, at first glance, is solid sodium bicarbonate, baking soda,  $NaHCO_3$ . Ingestion of solid  $NaHCO_3$  simply raises  $[Na^+]$  in the stomach and converts the normal negative [SID] "hydrochloric acid" there to an alkaline, positive [SID] " $Na^+ + Cl^-$ " solution. Stomach  $[H^+]$  is thereby reduced enormously, and this may have a beneficial effect on "heartburn," "gastric distress," or pain from a gastric ulcer. The hazard of this substance is that most of this extra  $Na^+$  will be absorbed from the small intestine into the plasma and will place an increased  $Na^+$  load on both the ECF volume and plasma [SID] regulating functions of the kidneys. This substance should clearly be strictly avoided by persons with hypertension or heart failure. The second, and physiologically far superior, category of antacid includes substances such as  $CaCO_3$ ,  $Mg(OH)_2$ ,  $Al(OH)_3$ , and mixtures of them. These substances will also raise [SID] and lower  $[H^+]$  in the stomach because of their strong ions, but they are not absorbed to any significant extent in the small intestine, so they do not place any extra load on the kidneys'  $Na^+$  and  $Cl^-$  regulating functions. Just like the acids in foods, these substances have important effects on the  $[H^+]$  of gastric juice and chyme, but essentially none on plasma. They therefore do not affect whole-body acid-base balance.

In both categories of antacid, the anions are weak and insignificant, except for their contributions to the physiological, rather than acid-base, neutrality of the substances involved. So far as the effect on gastric [SID] goes,  $NaOH$  would be just as effective as  $NaHCO_3$ ;  $NaOH$  cannot be

used, obviously, because it is a violently corrosive substance (lye). Similarly,  $\text{Ca}(\text{OH})_2$  is moderately corrosive at high concentrations (slaked lime), so  $\text{CaCO}_3$  is the substance to use, but the “active ingredient” is the strong ion,  $\text{Ca}^{2+}$ .

### 9.5. CLINICAL IMPLICATIONS

In clinical situations, decisions must be based on the data available. For circulating plasma, those data almost always include  $[\text{H}^+]$  (pH),  $P_{\text{C}}$ , and [total  $\text{CO}_2$ ], the latter often expressed as  $[\text{HCO}_3^-]$ . In nonurgent situations, values for  $[\text{Na}^+]$ ,  $[\text{Cl}^-]$ ,  $[\text{K}^+]$ , and frequently  $[\text{lactate}^-]$  are usually listed as well. From these numbers and the plasma  $[\text{H}^+]$ - $P_{\text{C}}$  diagram, a thorough and clinically useful understanding of the nature and cause of any abnormal acid-base status is easily gained. The clinical experience summarized in the areas presented in Figures 9.2 and 9.3 is extremely valuable in this process, and Figure 9.4, which combines them, will be found essential to the following discussion.

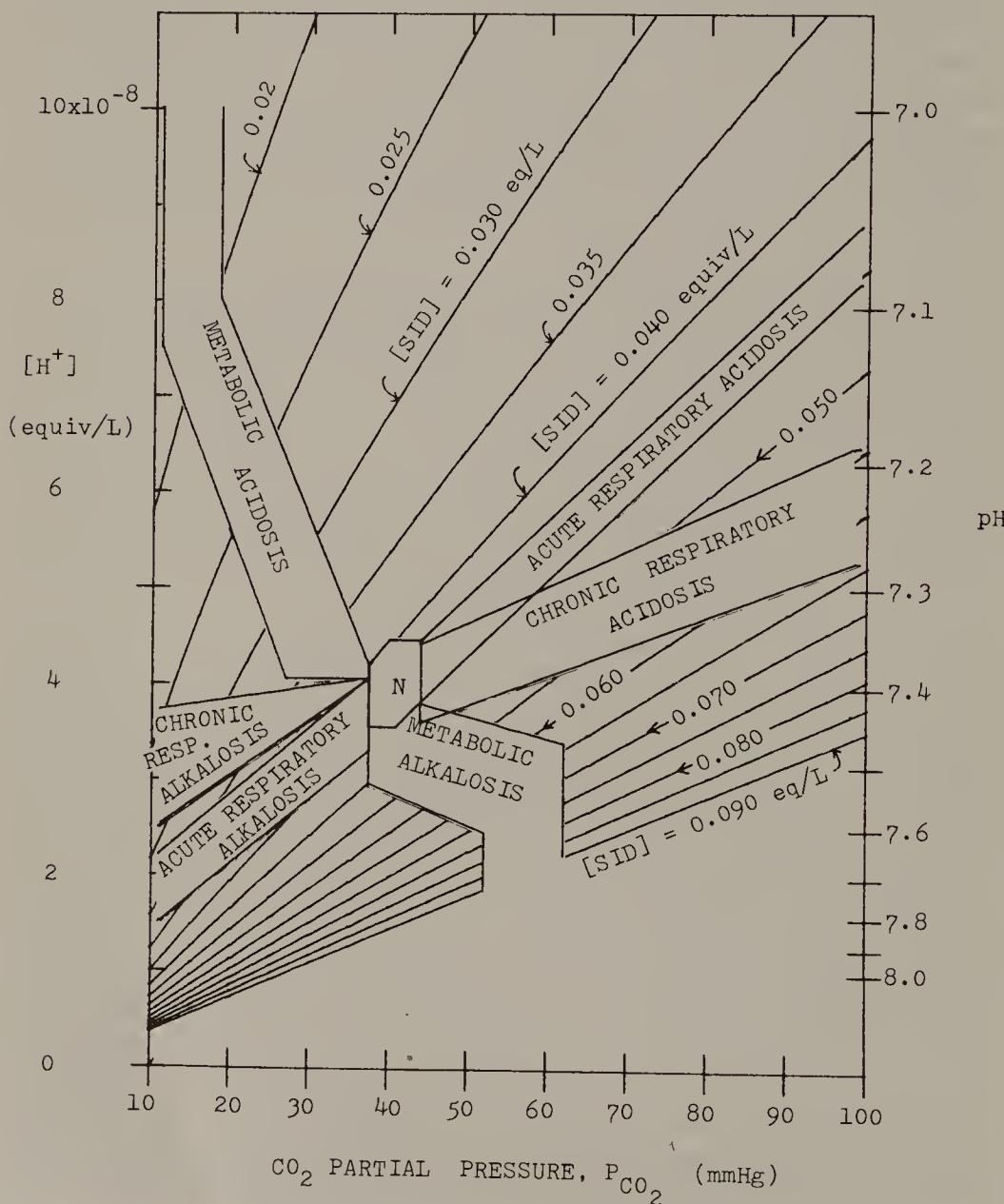
The  $[\text{H}^+]$  (or pH) and the  $P_{\text{C}}$  values are the most revealing. Plotting them on Figure 9.4 tells us at once the value of [SID], and by position with respect to the clinically established areas, identifies the major problem as respiratory or strong ion (“metabolic”) in origin. For example, if a patient’s plasma pH = 7.2, ( $[\text{H}^+] = 6.3 \times 10^{-8}$  Eq/liter), and  $P_{\text{C}} = 70$  mm Hg, then [SID] from Figure 9.4 is normal at 0.043 Eq/liter, and the acid-base problem is simply the high  $P_{\text{C}}$ . The next step is not to treat the high  $[\text{H}^+]$  but to determine the cause of the high  $P_{\text{C}}$  and correct that.  $[\text{H}^+]$  will then quickly return to normal. This patient would be described as having pure acute respiratory acidosis.

On the other hand, if a patient with the same plasma pH of 7.2 shows a  $P_{\text{C}}$  of 20 mm Hg, then Figure 9.4 tells us that [SID] = 0.024 Eq/liter, far below normal, so the patient has “metabolic acidosis.” Attempting to restore  $P_{\text{C}}$  to normal in this case would be a very bad thing to do, for if [SID] stayed at 0.024 Eq/liter,  $[\text{H}^+]$  would then rise to  $1.0 \times 10^{-7}$  Eq/liter, pH 7.0. The next step is obviously to determine why [SID] is abnormal. Data from the patient’s history and most recent physical examination may be crucial. For example, has the patient had diarrhea recently? If electrolyte analyses are available, the next question is what is the value of  $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$ , which we call for convenience the inorganic [SID], compared to the effective [SID] value given by the patient’s position on Figure 9.4? A disparity of more than a few milliequivalents per liter must mean that other strong ions are present. If lactate has been assayed, does it account for the difference? Does the history or physical suggest likely candidates, such as acetylsalicylate from aspirin poisoning, for example? Many toxic substances when ingested result in

significant concentrations in the plasma of anions whose presence may be measured in this way.

If inorganic [SID] is equal to the value found from Figure 9.4, then the next step is to identify the cause of the abnormal  $[Na^+]$  or  $[Cl^-]$  or  $[K^+]$ . Vomiting? Enemas? Diet? Self-medication? Is kidney function normal? Is the patient receiving intravenous infusions? Should their composition

**Figure 9.4.** Summary diagram, combining the information in Figures 9.2 and 9.3. This diagram tells the whole story of acid-base balance and what can go wrong with it. See text.



or amount be altered? Temporary correction of the abnormal  $[H^+]$  may be achieved by infusing  $Na^+$ , via  $NaHCO_3$  solution, but it must be remembered that the whole 16.5 liters of ECF has this abnormal [SID] value, and also that raising  $[Na^+]$  in this way may be a bad thing to do because of its effects on ECF volume and the additional  $Na^+$  load it places on the kidney.

If organic anions are present, as indicated by a significant organic component of the [SID] value from Figure 9.4, then the next step is to identify their nature and source. Lactate may be identified easily, and the keto-acids of diabetic acidosis are always prime suspects, but drug intoxication is also high on the list. In some cases, dialysis may be necessary to eliminate the abnormal anions, whereas in others they may be slowly removed by the liver and kidneys. In any event, it is essential to treat the cause of the abnormal [SID]. The abnormal [SID] itself should be thought of as the primary symptom and the abnormal  $[H^+]$  as a secondary symptom.

In emergency situations, if Figure 9.4 or its equivalent is not available, a simple calculation can be done mentally to provide roughly the same information. It is based on our knowledge that to an excellent approximation in plasma,  $[SID] = [HCO_3^-] + [A_{TOT}]$ . If pH and  $P_C$  are known,  $[HCO_3^-]$  is easily calculated from Equation (7.2.4):  $[HCO_3^-] = K_C \times P_C / [H^+]$ . If  $[Na^+]$  and  $[Cl^-]$  have been measured, then  $[Na^+] - [Cl^-] - [HCO_3^-]$  should be a good approximation to  $[A^-]$ , which we know is normally close to 17 mEq/liter. This quantity is called the "anion gap." If it is very different from 17 mEq/liter, then we know that other ions must be present. The difference between this "anion gap" and 17 mEq/liter provides the same information as the quantity we called the organic [SID] value in the context of Figure 9.4, namely, whether or not organic acids are a significant component of the abnormal [SID] in metabolic acidosis.

Figure 9.4 also emphasizes the inherent, and surprising, simplicity of whole-body acid-base balance when it is understood in quantitative terms. Normal acid-base status, indicated by the area labeled "N" in Figures 9.2, 9.3, and 9.4, means plasma [SID] between 0.040 and 0.045 Eq/liter and plasma  $P_C$  between 37 and 44 mm Hg. Plasma  $[H^+]$  therefore is between  $3.6$  and  $4.4 \times 10^{-8}$  Eq/liter, pH 7.44 to 7.36. If  $[H^+]$  is found to be outside this range, then either [SID] or  $P_C$  or both must have changed from their normal values. Theoretically, because plasma is a solution, [SID] and  $P_C$  can assume any values, independently. In biological fact, however, the respiratory and renal compensating mechanisms in the body restrict the values usually seen to the pathological areas shown in Figure 9.4.

In the "metabolic" areas, [SID] is the primary problem, and the identity of the specific ions involved must be established before rational therapy can be planned. The  $P_C$  abnormality is not part of the pathology, but the

compensating mechanism that keeps plasma  $[H^+]$  from changing as much as it otherwise would as a result of the abnormal [SID] value.

In the “respiratory” areas, the primary problem is the  $P_C$  value, and the [SID] change this time is not pathological but imposed by the kidneys as a compensating mechanism to keep  $[H^+]$  from changing as much as it otherwise would due to the abnormal  $P_C$  value.

In both cases, it is the primary pathology that must be understood and treated, rather than the  $[H^+]$  change per se; the  $[H^+]$  change is a sign of that pathology. Figure 9.4, in this context, is a useful summary of how that sign is related to its causal pathology. In different words, it is a useful summary of what whole-body acid-base balance means and what can go wrong with it.

## 9.6. BUFFERS AND BICARBONATE: WHAT ARE THEIR ROLES?

It is helpful to recall two basic features of ionic solutions before addressing these questions. First, as we have seen numerous times,  $[H^+]$  in any solution at any instant is determined by, and only by, the current values of [SID],  $P_C$ , and  $[A_{TOT}]$  in that solution. Second, the important distinction between independent and dependent variables is that changes in dependent variables can only occur as a result of changes in independent ones. Dependent variables therefore cannot cause changes in each other.

Hemoglobin in RBCs is usually assigned an important role as a “buffer” for plasma in whole blood. Because it is in the RBC-ICF, not in the plasma, there is no way that hemoglobin can affect the [SID], the  $P_C$ , or the  $[A_{TOT}]$  of the plasma surrounding the RBCs, and therefore no way it can affect plasma  $[H^+]$ . In other words, it cannot possibly serve as a plasma “buffer.” It can only “buffer” RBC-ICF, and as we saw in Chapter 7, even there its role is small because of the overwhelming importance of the  $CO_2$  system. It might be supposed that hemoglobin could alter plasma [SID] by somehow changing its strong ion binding, but the total amount of hemoglobin present in the 2 liters of RBCs is so small compared to the total ECF volume of 16.5 liters with which the strong ions in plasma equilibrate that such binding changes could produce only minute [SID] changes in the plasma. Strong ion shifts between plasma and RBC-ICF, discussed in Chapter 8, do occur and affect plasma [SID] to a small degree while it is sequestered from the ISF, in either the venous or arterial pools, but these shifts are transient and not important for the kind of [SID] changes involved in Figure 9.4.

The other kind of buffer question concerns the weak acids in the plasma, and  $[A_{TOT}]$ . Why have they not been mentioned? The answer is that they have, in the sense that  $[A_{TOT}]$  is explicitly included, as it must be, in the calculations of Chapter 7 that produced the  $[H^+]-P_C$  curves. To talk about

this in terms of buffering contributes nothing but confusion to our attempts to understand acid–base balance in the body. Plasma  $[H^+]$  depends on all three of  $[SID]$ ,  $P_C$ , and  $[A_{TOT}]$ .  $[A_{TOT}]$  almost never changes, so that to concentrate on it, which is what the term “buffer” suggests, is not at all helpful.

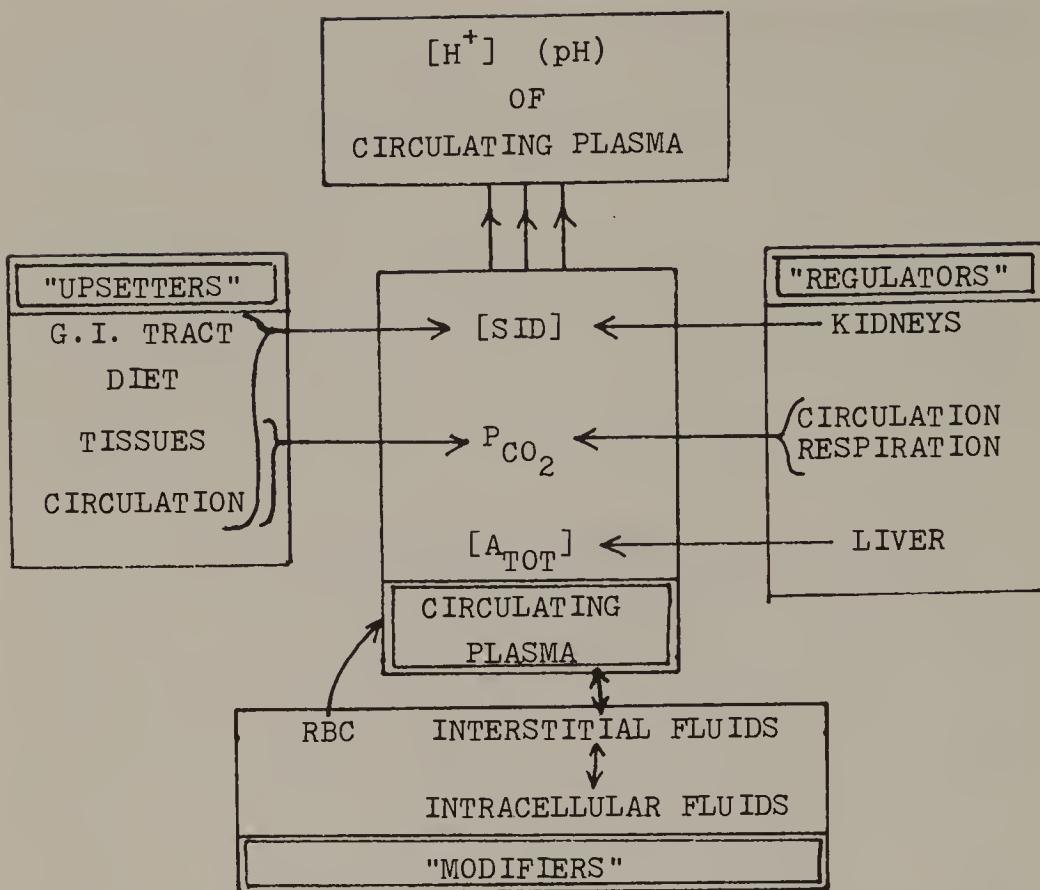
The role of  $[HCO_3^-]$  in plasma, or in any body fluid, is that of another dependent variable, along with  $[H^+]$ . Changes in  $[HCO_3^-]$  have to be understood in terms of changes in  $[SID]$ ,  $P_C$ , and possibly  $[A_{TOT}]$ , just as  $[H^+]$  changes do. We could plot  $[HCO_3^-]-P_C$  curves at constant  $[SID]$ , analogous to the  $[H^+]-P_C$  curves in Figure 9.4, and outline the areas of clinical interest, just as in that figure. The result would be, in logical terms, strictly equivalent to Figure 9.4, and could be used in just the same way, if we were interested in  $[HCO_3^-]$  for some reason. We are not. We are interested in  $[H^+]$ , because we have defined acid–base in terms of  $[H^+]$  and its dependence on the independent variables.  $[HCO_3^-]$  is not relevant to the relationship between  $[H^+]$ ,  $[SID]$ ,  $P_C$ , and  $[A_{TOT}]$ ; it is simply another dependent variable, just as  $[OH^-]$ ,  $[CO_3^{2-}]$ ,  $[A^-]$ , and  $[HA]$  are. If we want to understand the  $[H^+]$  behavior of plasma and define acid–base balance in terms of it, then the answer to the question “What is the role of  $[HCO_3^-]$ ? ” is very simply “None! ”. Figure 9.4 demonstrates this more clearly than a lot of words. It does not require, or make use of, or display  $[HCO_3^-]$ , and yet it tells the whole story of plasma  $[H^+]$  behavior.

Historically,  $[HCO_3^-]$  was important as the major component of the directly measurable quantity [total  $CO_2$ ]. Once calculated from this quantity, it could then be combined with  $[H^+]$  to calculate  $P_C$ . Confusion therefore exists about its role; does it somehow represent  $P_C$ , or does it somehow represent  $[SID]$  because of its place in anion gap calculations? The information in Figure 9.4 is sometimes plotted as  $[H^+]$  versus  $[HCO_3^-]$ , for example, [1], or as  $[H^+]$  versus  $P_C$ , but with lines of constant  $[HCO_3^-]$  instead of constant  $[SID]$  [2]. Although there is nothing technically incorrect about such plots, they thoroughly obscure the causal relationships between  $[H^+]$ ,  $[SID]$ , and  $P_C$  and thereby make appropriate clinical procedures much more difficult to understand and to plan. If  $[H^+]$  is what we want to understand, the less said about  $[HCO_3^-]$  the better, once we have solved Equations (7.2.1)–(7.2.6).

## 9.7. SUMMARY

The major factors involved in whole-body acid–base balance may now be summarized in the following statements and in diagrammatic form in Figure 9.5.

1. Whole-body acid–base balance means, “What is happening to circulating plasma  $[H^+]$ , and why?”



**Figure 9.5.** Summary schematic diagram of whole body acid-base balance (to accompany Section 9.7). It illustrates the physiological and physical variations and interactions that determine plasma  $[H^+]$  (or pH).

2.  $[H^+]$  in the plasma is determined by  $[SID]$ ,  $P_{CO_2}$ , and  $[A_{TOT}]$  in the plasma. Its normal value is  $4.0 \times 10^{-8}$  Eq/liter, pH 7.4.
3. The strong ion composition of the diet, the function of the GI tract, the functions of other tissues, and local variations in tissue perfusion all may alter plasma  $[SID]$  from its normal value near 0.042 Eq/liter.
4. Variations in local tissue metabolism and perfusion can alter circulating plasma  $P_{CO_2}$  from its normal value near 40 mm Hg.
5. Plasma  $[SID]$  changes imposed by the "upsetters" in item 3 are modified by plasma interaction with interstitial fluid through tissue capillary membranes. Interstitial fluid in turn may interact with intracellular fluid through cell membranes.
6. Respiration in the lungs and general body circulation regulate alveolar and circulating plasma  $P_{CO_2}$ .

7. The kidneys regulate circulating plasma [SID] by differential reabsorption of  $\text{Na}^+$  and  $\text{Cl}^-$
8. When circulating plasma  $[\text{H}^+]$  changes due to  $P_{\text{CO}_2}$  changes, the kidneys slowly produce compensating [SID] changes (Figure 9.2).
9. When circulating plasma  $[\text{H}^+]$  changes due to [SID] changes, respiration in the lungs changes so as to produce compensating plasma  $P_{\text{CO}_2}$  changes (Figure 9.3).

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