

Remington's  
Pharmaceutical  
Sciences

Eighteenth Edition

# Remington's Pharmaceutical Sciences

18

**18<sup>TH</sup>**  
EDITION

# Remington's

**ALFONSO R. GENARO**

*Editor, and Chairman  
of the Editorial Board*

# Pharmaceutical Sciences

1990

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**Remington's Pharmaceutical Sciences . . . a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.**

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## Preface to the First Edition

The rapid and substantial progress made in Pharmacy within the last decade has created a necessity for a work treating of the improved apparatus, the revised processes, and the recently introduced preparations of the age.

The vast advances made in theoretical and applied chemistry and physics have much to do with the development of pharmaceutical science, and these have been reflected in all the revised editions of the Pharmacopoeias which have been recently published. When the author was elected in 1874 to the chair of Theory and Practice of Pharmacy in the Philadelphia College of Pharmacy, the outlines of study which had been so carefully prepared for the classes by his eminent predecessors, Professor William Procter, Jr, and Professor Edward Parrish, were found to be not strictly in accord, either in their arrangement of the subjects or in their method of treatment. Desiring to preserve the distinctive characteristics of each, an effort was at once made to frame a system which should embody their valuable features, embrace new subjects, and still retain that harmony of plan and proper sequence which are absolutely essential to the success of any system.

The strictly alphabetical classification of subjects which is now universally adopted by pharmacopoeias and dispensaries, although admirable in works of reference, presents an effectual stumbling block to the acquisition of pharmaceutical knowledge through systematic study; the vast accumulation of facts collected under each head being arranged lexically, they necessarily have no connection with one another, and thus the saving of labor effected by considering similar groups together, and the value of the association of kindred subjects, are lost to the student. In the method of grouping the subjects which is herein adopted, the constant aim has been to arrange the latter in such a manner that the reader shall be gradually led from the consideration of elementary subjects to those which involve more advanced knowledge, whilst the groups themselves are so placed as to follow one another in a natural sequence.

The work is divided into six parts. Part I is devoted to detailed descriptions of apparatus and definitions and comments on general pharmaceutical processes.

The Official Preparations alone are considered in Part II. Due weight and prominence are thus given to the Pharmacopoeia, the National authority, which is now so thoroughly recognized.

In order to suit the convenience of pharmacists who prefer to weigh solids and measure liquids, the official formulas are expressed, in addition to parts by weight, in *avoirdupois weight* and *apothecaries' measure*. These equivalents are

printed in *bold type* near the margin, and arranged so as to fit them for quick and accurate reference.

Part III treats of Inorganic Chemical Substances. Precedence is of course given to official preparation in these. The descriptions, solubilities, and tests for identity and impurities of each substance are systematically tabulated under its proper title. It is confidently believed that by this method of arrangement the valuable descriptive features of the Pharmacopoeia will be more prominently developed, ready reference facilitated, and close study of the details rendered easy. Each chemical operation is accompanied by equations, whilst the reaction is, in addition, explained in words.

The Carbon Compounds, or Organic Chemical Substances, are considered in Part IV. These are naturally grouped according to the physical and medical properties of their principal constituents, beginning with simple bodies like cellulose, gum, etc, and progressing to the most highly organized alkaloids, etc.

Part V is devoted to Extemporaneous Pharmacy. Care has been taken to treat of the practice which would be best adapted for the needs of the many pharmacists who conduct operations upon a moderate scale, rather than for those of the few who manage very large establishments. In this, as well as in other parts of the work, operations are illustrated which are conducted by manufacturing pharmacists.

Part VI contains a formulary of Pharmaceutical Preparations which have not been recognized by the Pharmacopoeia. The recipes selected are chiefly those which have been heretofore rather difficult of access to most pharmacists, yet such as are likely to be in request. Many private formulas are embraced in the collection; and such of the preparations of the old Pharmacopoeias as have not been included in the new edition, but are still in use, have been inserted.

In conclusion, the author ventures to express the hope that the work will prove an efficient help to the pharmaceutical student as well as to the pharmacist and the physician. Although the labor has been mainly performed amidst the harassing cares of active professional duties, and perfection is known to be unattainable, no pains have been spared to discover and correct errors and omissions in the text. The author's warmest acknowledgments, are tendered to Mr A B Taylor, Mr Joseph McCreery, and Mr George M Smith for their valuable assistance in revising the proof sheets, and to the latter especially for his work on the index. The outline illustrations, by Mr John Collins, were drawn either from the actual objects or from photographs taken by the author.

Philadelphia, October, 1885

JPR.

## Preface to the Eighteenth Edition

In anticipation of setting forth this *Preface* and prior to gathering thoughts on paper (or more accurately, the word processor!), this Editor paused to reread the preface to the first edition of *Remington*, published in 1885. Since it appears on the preceding page of this book it is recommended highly. The first paragraph would be just as suitable today as penned by Professor Remington 105 years ago.

Each decade transcends the previous one and the pharmaceutical and health sciences are not laggards. Every revision of *Remington* has encompassed new viewpoints, ideas, doctrines or principles which, perhaps, were inconceivable for the previous edition. It is a tribute to the authors and editors that they have kept abreast of the burgeoning literature in their respective fields of expertise.

Change not withstanding, the organization of this edition is similar to its immediate predecessors, being divided into 9 Parts, each subdivided into several chapters. Every chapter has been culled, revised and rewritten to update the material presented.

Two new chapters are evident; *Biotechnology and Drugs* (Chapter 74) and *Drug Education* (Chapter 99). Three chapters of the previous edition, which embraced *Interfacial and Particle Phenomena* and *Colloidal and Coarse Dispersions* have been winnowed and combined into a single chapter entitled, *Disperse Systems* (Chapter 19).

The current revision contains an additional 21 pages. A large amount of space (about 19 pages) gleaned from the review and condensation process, coupled with the extra pages, have been devoted primarily to expanding the contents of Part 6, *Pharmaceutical and Medicinal Agents* and Part 9, *Pharmaceutical Practice*.

Excessive duplication of text is the bane of any editor dealing with a multitude of authors. While some duplication in the discussion of rudimentary concepts is beneficial, there has been a special effort to cross-reference and eliminate unnecessary repetition. Space is at such a premium that it is hoped the reader will not be offended by being diverted to a different section of the text in order to obtain supplementary information.

Photographs which depicted the typical "black box" have been eliminated almost completely and replaced by line drawings or schematic diagrams which are instructive rather than picturesque.

Most of the drug monographs have been revamped not only as a means of updating, but to gain a degree of uniformity. All structural formulas are now in the standard *USAN* form. Duplication of chemical names has been minimized and the inclusion of trade names increased. No attempt has been made to ferret out every trade name by which a product is known, and only the most common are mentioned. The standard format for the major monographs is: Official Name, chemical name (*CAS*—inverted), trade name(s) and manufacturer(s), structural formula, *CAS* (*Chemical Abstracts System*) registry number (in brackets), molecular formula and formula weight (in parenthesis). This is followed by the method of preparation (or a reference if the method is lengthy), physical description, solubility, uses, dose and dosage forms.

The number of authors remains at 97, however, 36 new authors have joined as contributors to *Remington*. As the credentials of the new authors touch upon many areas of pharmacy, every section of the book has been invigorated by the incorporation of updated and fresh concepts.

As one primarily responsible for the production of a comprehensive text devoted to the science and practice of pharmacy, the wisdom of Dr Eric Martin, editor of the 13th Edition, in creating an Editorial Board to share the enormous burden, has been evident constantly. Each of the section editors labored diligently to comply with the logistics of maintaining a smooth flow of manuscripts and proofs. Also, each section editor doubled as an author or coauthor of one or more chapters. It would be remiss not to extend special mention to this group of dedicated people.

Four members of the Editorial Board are serving for the first time after having been authors for several editions. Dr Ara DerMarderosian of PCP&S, Editor for Part 1; Dr Daniel Hussar, also of PCP&S, Part 9; Dr Edward Rippie of the University of Minnesota, Part 2; and Dr Joseph Schwartz of PCP&S, Part 8. Each of the new members literally "jumped into the fray," gave much of their precious time and have become "blooded" members of the staff.

The stalwarts of the Editorial Board surviving the tribulations of one or more previous editions of this work demand singular attention. Dr Grafton Chase of PCP&S for Part 5, *Radioisotopes in Pharmacy & Medicine*; Dr Thomas Medwick of Rutgers University for Part 3, *Pharmaceutical Chemistry* and Part 4, *Testing and Analysis*; and Dr Gilbert Zink of PCP&S for Part 7, *Biological Products*.

Two dauntless, prolific contributors claim special recognition. Drs Stewart Harvey and Ewart Swinyard, both of the University of Utah, have served on the Editorial Board for twenty and twenty-five years respectively. They bear the burden of Part 6, *Pharmaceutical & Medicinal Agents*, which comprises over one-third of the book. Their diligence and meticulous attention to detail has eased the task of this Editor. Our relationship over the past several decades has been one of exceptional pleasure.

The Mack Publishing Company, through Messers Paul Mack and David Palmer, continues its unrelenting support, which has endured through many, many editions of this publication. Special commendation must be extended to Ms Nancy Smolock, of the Mack organization, as she was the person who interfaced with the Editorial Board. She was competent, cooperative and much too tolerant of the many requests made of her.

As with any publication a few of the editorial staff bear the brunt of the unglamorous, but absolutely essential, chores associated with the production of this voluminous tome. It mandates a close working relationship and, at times, restraint and concession to sustain the harmony necessary to function efficiently. One often encounters the aphorism usually attributed to administrators, "When three managers meet to discuss a problem there arise four points-of-view." Fortunately, this dilemma did not surface in the association of this Editor with Mr John Hoover and Ms Bonnie Packer.

After shepherding this publication through four editions, the Twelfth to Fifteenth, following a short hiatus for the Sixteenth, Mr Hoover returned in a lesser capacity with the Seventeenth revision. With the current edition he resumes the role of Managing Editor and his experience in pharmacy, journalism and the publishing business, have provided the capabilities needed to translate a disarranged manuscript into a format acceptable by the publisher and pleasing to the reader.

Ms Packer accepted the assignment of scrutinizing every word of text in the proof stages. Combining her skills in the



health and social sciences, she assumed the charge of reading primarily for comprehension and clarity of presentation, while concurrently uncovering typographical, spelling and grammatical errors which, although unpardonable, are ever-present. As a consequence of her deliberations, passages were often rephrased and refined to portray a concept from the viewpoint of the student, for whom this work primarily is directed.

The *Index* was developed by Mr Hoover, with the assis-

tance of Ms Packer. Much use was made of the computer in ensuring that a complete, practical and useful index was created. It is the opinion of this Editor that a major weakness encountered in most reference books is a perfunctory, casual index which amounts to little more than an expanded table of contents. Users of the index of this book will find it "friendly."

*Philadelphia, February, 1990*

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## CHAPTER 16

# Solutions and Phase Equilibria

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## Solutions and Solubility

A solution is a chemically and physically homogeneous mixture of two or more substances. The term solution generally denotes a homogeneous mixture that is liquid even though it is possible to have homogeneous mixtures which are solid or gaseous. Thus, it is possible to have solutions of solids in liquids, liquids in liquids, gases in liquids, gases in gases and solids in solids. The first three of these are most important in pharmacy and ensuing discussions will be concerned primarily with them.

In pharmacy different kinds of liquid dosage forms are used and all consist of the dispersion of some substance or substances in a liquid phase. Depending on the size of the dispersed particle they are classified as *true solutions*, *colloidal solutions* or *suspensions*. If sugar is dissolved in water, it is supposed that the ultimate sugar particle is of molecular dimensions and that a *true solution* is formed. On the other hand, if very fine sand is mixed with water, a *suspension* of comparatively large particles, each consisting of many molecules, is obtained. Between these two extremes lie *colloidal solutions*, the dispersed particles of which are larger than those of true solutions but smaller than the particles present in suspensions. In this chapter only true solutions will be discussed.

It is possible to classify broadly all solutions as one of two types.

In the first type, although there may be a lesser or greater interaction between the dispersed substance (the solute) and the dispersing medium (the solvent), the solution phase contains the same chemical entity as found in the solid phase and, thus, upon removal of the solvent, the solute is recovered unchanged. One example would be sugar dissolved in water where, in the presence of sugar in excess of its solubility, there is an equilibrium between sugar molecules in the solid phase with sugar molecules in the solution phase. A second example would be dissolving silver chloride in water. Admittedly, the solubility of this salt in water is low, but it is finite. In this case the solvent contains silver and chloride ions and the solid phase contains the same material. The removal of the solvent yields initial solute.

In the second type the solvent contains a compound which is different from that in the solid phase. The difference between the compound in the solid phase and solution is due generally to some chemical reaction that has occurred in the solvent. An example would be dissolving aspirin in an aqueous solvent containing some basic material capable of reacting with the acid aspirin. Now the species in solution would not only be undissociated aspirin, but aspirin also as its anion, whereas the species in the solid phase is aspirin in only its undissociated acid form. In this situation, if the solvent were removed, part of the substance obtained (the salt of aspirin) would be different from what was present initially in the solid.

### Solutions of Solids in Liquids

#### Reversible Solubility without Chemical Reaction

—From a pharmaceutical standpoint solutions of solids in liquids, with or without accompanying chemical reaction in

the solvent, are of the greatest importance, and many quantitative data on the behavior and properties of such solutions are available. This discussion will be concerned with definitions of solubility, the rate at which substances go into solution and with temperature and other factors which control solubility.

**Solubility**—When an excess of a solid is brought into contact with a liquid, molecules of the former are removed from its surface until equilibrium is established between the molecules leaving the solid and those returning to it. The resulting solution is said to be saturated at the temperature of the experiment, and the extent to which the solute dissolves is referred to as its *solubility*. The extent of solubility of different substances varies from almost imperceptible amounts to relatively large quantities, but for any given solute the solubility has a constant value at constant temperature.

Under certain conditions it is possible to prepare a solution containing a larger amount of solute than is necessary to form a saturated solution. This may occur when a solution is saturated at one temperature, the excess of solid solute removed and the solution cooled. The solute present in solution, even though it may be less-soluble at the lower temperature, does not always separate from the solution and there is produced a *supersaturated solution*. Such solutions, formed by sodium thiosulfate or potassium acetate, for example, may be made to deposit their excess of solute by vigorous shaking, scratching the side of the vessel in contact with the solution or introducing into the solution a small crystal of the solute.

**Methods of Expressing Solubility**—When quantitative data are available, solubilities may be expressed in many ways. For example, the solubility of sodium chloride in water at 25° may be stated as

1. 1 g of sodium chloride dissolves in 2.786 mL of water. (An approximation of this method is used by the USP.)
2. 35.89 g of sodium chloride dissolves in 100 mL of water.
3. 100 mL of a saturated solution of sodium chloride in water contains 31.71 g of solute.
4. 100 g of a saturated solution of sodium chloride in water contains 26.47 g of solute.
5. 1 L of a saturated solution of sodium chloride in water contains 5.425 moles of solute. This also may be stated as a saturated solution of sodium chloride in water is 5.425 molar with respect to the solute.

In order to calculate 3 from 1 or 2 it is necessary to know the density of the solution, in this case 1.198 g/mL. To calculate 5, the number of grams of solute in 1000 mL of solution (obtained by multiplying the data in (3) by ten) is divided by the molecular weight of sodium chloride, namely, 58.45.

Several other concentration expressions are used. Molality is the number of moles of solute in 1000 g of solvent and could be calculated from the data in 4 by subtracting grams

The author acknowledges the kind assistance of Dr Gordon L. Flynn, University of Michigan, in the revision of parts of this chapter.

Table I—Descriptive Terms for Solubility

Descriptive Terms	Parts of Solvent for 1 Part of Solute
Very soluble . . . . .	Less than 1
Freely soluble . . . . .	From 1 to 10
Soluble . . . . .	From 10 to 30
Sparsely soluble . . . . .	From 30 to 100
Slightly soluble . . . . .	From 100 to 1000
Very slightly soluble . . . . .	From 1000 to 10,000
Practically insoluble, or insoluble . . . . .	More than 10,000

of solute from grams of solution to obtain grams of solvent, relating this to 1000 g of solvent and dividing by molecular weight to obtain moles.

Mole fraction is the fraction of the total number of moles present which are moles of one component. Mole % may be obtained by multiplying mole fraction by 100. Normality refers to the number of gram equivalent weights of solute dissolved in 1000 mL of solution.

In pharmacy, use also is made of three other concentration expressions. Percent by weight (% w/w) is the number of grams of solute per 100 g of solution and is exemplified by 4 above. Percent weight in volume (% w/v) is the number of grams of solute per 100 mL of solution and is exemplified by 3 above. Percent by volume (% v/v) is the number of milliliters of solute in 100 mL of solution, referring to solutions of liquids in liquids. The USP indicates that the term "percent," when unqualified, means percent weight in volume for solutions of solids in liquids and percent by volume for solutions of liquids in liquids.

When, in pharmacopeial texts, it has not been possible, or in some instances not desirable, to indicate exact solubility, a descriptive term has been used. Table I indicates the meaning of such terms.

**Rate of Solution**—It is possible to define quantitatively the rate at which a solute goes into solution. The simplest treatment is based on a model depicted in Fig 16-1. A solid particle dispersed in a solvent is surrounded by a thin layer of solvent having a finite thickness,  $l$  in cm. The layer is an integral part of the solid and, thus, is referred to characteristically as the "stagnant layer." This means that regardless of how fast the bulk solution is stirred the stagnant layer remains a part of the surface of the solid, moving wherever the particle moves. The thickness of this layer may get smaller as the stirring of the bulk solution increases, but it is important to recognize that this layer will always have a finite thickness however small it may get.

Using Fick's First Law of Diffusion the rate of solution of the solid can be explained, in the simplest case, as the rate at which a dissolved solute particle diffuses through the stagnant layer to the bulk solution. The driving force behind the movement of the solute molecule through the stagnant layer is the difference in concentration that exists between the concentration of the solute,  $C_1$ , in the stagnant layer at the surface of the solid and its concentration,  $C_2$ , on the farthest side of the stagnant layer (see *Diffusion in Liquids*, page 221). The greater this difference in concentration ( $C_1 - C_2$ ), the faster the rate of solution.



Fig 16-1. Physical model representing the dissolution process.

According to Fick's Law, the rate of solution also is directly proportional to the area of the solid,  $A$  in  $\text{cm}^2$ , exposed to solvent and inversely proportional to the length of the path through which the dissolved solute molecule must diffuse. Mathematically, then, the rate of solution of the solid is given by

$$\text{Rate of solution} = \frac{DA}{l} (C_1 - C_2) \quad (1)$$

where  $D$  is a proportionality constant called the diffusion coefficient in  $\text{cm}^2/\text{sec}$ . In measuring the rate of solution experimentally, the concentration  $C_2$  is maintained at a low value compared to  $C_1$  and hence considered to have a negligible effect on the rate. Furthermore,  $C_1$  most often is the saturation solubility of the solute. Hence Eq 1 is simplified to

$$\text{Rate of solution} = \frac{DA}{l} (\text{saturation solubility}) \quad (2)$$

Equation 2 quantitatively explains many of the phenomena commonly observed that affect the rate at which materials dissolve.

1. Small particles go into solution faster than large particles. For a given mass of solute, as the particle size becomes smaller, the surface area per unit mass of solid increases; Eq 2 shows that as area increases, the rate must increase proportionately. Hence, if a pharmacist wishes to increase the rate of solution of a drug, its particle size should be decreased.

2. Stirring a solution increases the rate at which a solid dissolves. This is because the thickness of the stagnant layer depends on how fast the bulk solution is stirred; as stirring rate increases, the length of the diffusional path decreases. Since the rate of solution is proportional inversely to the length of the diffusional path, the faster the solution is stirred, the faster the solute will go into solution.

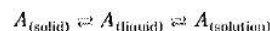
3. The more soluble the solute, the faster is its rate of solution. Again, Eq 2 predicts that the larger the saturation solubility, the faster the rate.

4. With a viscous liquid the rate of solution is decreased. This is because the diffusion coefficient is proportional inversely to the viscosity of the medium; the more viscous the solvent, the slower the rate of solution.

#### Heat of Solution and Temperature Dependency

Turning from the kinetic aspects of dissolution, this discussion will be concerned with the situation where there is thermodynamic equilibrium between solute in its solid phase and the solute in solution. (It is assumed that there is an amount of solid material in excess of the amount that can go into solution; hence, a solid phase is always present.) As defined earlier, the concentration of solute in solution at equilibrium is the saturation solubility of the substance.

When a solid (Solute A) dissolves in some solvent two steps may be considered as occurring: the solid absorbs energy to become a liquid and then the liquid dissolves.



For the overall dissolution the equilibrium existing between solute molecules in the solid and solute molecules in solution may be treated as any equilibrium. Thus, for Solute A in equilibrium with its solution



Using the Law of Mass Action an equilibrium constant for this system can be defined, just as any equilibrium constant may be written as

$$K_{\text{eq}} = \frac{a_{(\text{solution})}}{a_{(\text{solid})}}$$

where  $a$  denotes the activity of the solute in each phase. Since the activity of a solid is defined as unity

$$K_{\text{eq}} = a_{(\text{solution})}$$

Because the activity of a compound in dilute solution is approximated by its concentration and, because this concentration is the saturation solubility,  $K_S$ , the van't Hoff Equation (for a more complete treatment, see Ref 1, page 113) may be used, which defines the relationship between an equilibrium constant (here, solubility) and absolute temperature.

$$\frac{d \log K_S}{dT} = \frac{\Delta H}{2.3RT^2} \quad (3)$$

where  $d \log K_S/dT$  is the change of  $\log K_S$  with a unit change of absolute temperature,  $T$ ;  $\Delta H$  is a constant which in this situation is the heat of solution for the overall process (solid  $\rightleftharpoons$  liquid  $\rightleftharpoons$  solution); and  $R$  is the gas constant, 1.99 cal/mole/deg. Equation 3, a differential, may be solved to give

$$\log K_S = -\frac{\Delta H}{2.3RT} + J \quad (4)$$

where  $J$  is a constant. A more useful form of this equation is

$$\log \frac{K_{S,T_2}}{K_{S,T_1}} = \frac{\Delta H(T_2 - T_1)}{2.3RT_1 T_2} \quad (5)$$

where  $K_{S,T_1}$  is the saturation solubility at absolute temperature  $T_1$  and  $K_{S,T_2}$  is the solubility at temperature  $T_2$ . Through the use of Eq 5, if  $\Delta H$  and the solubility at one temperature are known, the solubility at any other temperature can be calculated.

**Effect of Temperature**—As is evident from Eq 4, the solubility of a solid in a liquid depends on the temperature. If, in the process of solution, heat is absorbed (as evidenced by a reduction in temperature),  $\Delta H$  is by convention positive and the solubility of the solute will increase with increasing temperature. Such is the case for most salts, as is shown in Fig 16-2, in which the solubility of the solute is plotted as the ordinate and the temperature as the abscissa, and the line joining the experimental points represents the solubility curve for that solute.

If a solute gives off heat during the process of solution (as evidenced by an increase in temperature),  $\Delta H$  is, by convention, negative and solubility decreases with an increase in temperature. This is the case with calcium hydroxide and, at higher temperatures, with calcium sulfate. (Because of the slight solubility of these substances their solubility curves are not included.) When heat is neither absorbed nor given

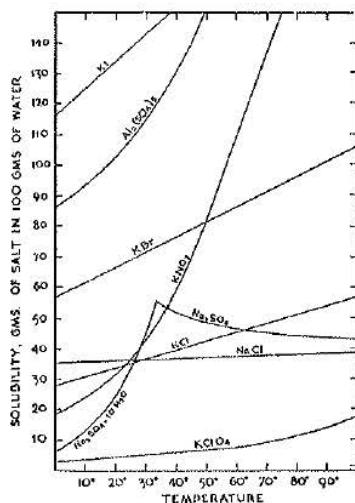


Fig 16-2. Effect of heat on solubility.

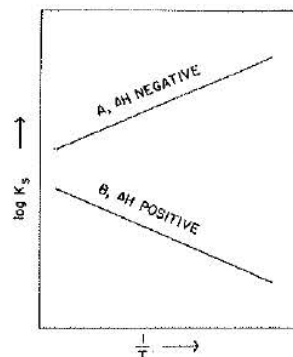


Fig 16-3. Typified relationship between the logarithm of the saturation solubility and the reciprocal of the absolute temperature.

off, the solubility is not affected by variation of temperature as is nearly the case with sodium chloride.

Solubility curves usually are continuous as long as the chemical composition of the solid phase in contact with the solution remains unchanged, but if there is a transition of the solid phase from one form to another, a break will be found in the curve. Such is the case with  $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ , which dissolves with absorption of heat up to a temperature of  $32.4^\circ$ , at which point there is a transition of the solid phase to anhydrous sodium sulfate,  $\text{Na}_2\text{SO}_4$ , which dissolves with evolution of heat. This change is evidenced by increased solubility of the hydrated salt up to  $32.4^\circ$ , but above this temperature the solubility decreases.

These temperature effects are what would be predicted from Eq 4. When the heat of solution is negative, signifying that energy is released during dissolution, the relation between  $\log K_S$  and  $1/T$  is typified in Fig 16-3 (Curve A), where as  $1/T$  increases,  $\log K_S$  increases. It can be seen that with increasing temperature ( $T$  itself actually increases proceeding left in Fig 16-3, A) there is a decrease in solubility. On the other hand, when the heat of solution is positive—that is, when heat is absorbed in the solution process—the relation between  $\log K_S$  and  $1/T$  is typified in Fig 16-3, B. Here, as temperature increases ( $1/T$  decreases), the solubility increases.

**Effect of Salts**—The solubility of a nonelectrolyte, in water, either is decreased or increased generally by the addition of an electrolyte; it is only rarely that the solubility is not altered. When the solubility of the nonelectrolyte is decreased, the effect is referred to as *salting-out*; if it is increased, it is described as *salting-in*. Inorganic electrolytes commonly decrease solubility, though there are some exceptions to the generalization.

Salting-out occurs because the ions of the added electrolyte interact with water molecules and, thus, in a sense reduce the amount of water available for solution of the nonelectrolyte. (Refer to the section on *Thermodynamics of the Solution Process*, page 215, for another view.) The greater the degree of hydration of the ions, the more the solubility of the nonelectrolyte is decreased. If, for example, one compares the effect of equivalent amounts of lithium chloride, sodium chloride, potassium chloride, rubidium chloride and cesium chloride (all of which belong to the family of alkali metals and are of the same valence type), it is observed that lithium chloride decreases the solubility of a nonelectrolyte to the greatest extent and that the salting-out effect decreases in the order given. This is also the order of the degree of hydration of the cations; lithium ion, being the smallest ion and, therefore, having the greatest density of positive charge per unit of surface area (see also Chapter 13 under *Electronegativity Values*), is the most extensively



hydrated of the cations while cesium ion is hydrated the least. Salting-out is encountered frequently in pharmaceutical operations.

Salting-in, commonly occurs when either the salts of various organic acids or organic-substituted ammonium salts are added to aqueous solutions of nonelectrolytes. In the first case the solubilizing effect is associated with the anion and in the second, with the cation. In both cases the solubility increases as the concentration of added salt is increased. The solubility increase may be relatively great, sometimes amounting to several times the solubility of the nonelectrolyte in water.

#### Solubility of Solutes Containing Two or More Species

In cases where the solute phase consists of two or more species (as in an ionizable inorganic salt), when the solute goes into solution, the solution phase often contains each of these species as discrete entities. For some such substance,  $AB$ , the following relationship for the solution process may be written.



Since there is an equilibrium between the solute and saturated solution phases, the Law of Mass Action defines an equilibrium constant,  $K_{eq}$

$$K_{eq} = \frac{a_{A(solution)} \cdot a_{B(solution)}}{a_{AB(solid)}} \quad (6)$$

where  $a_{A(solution)}$ ,  $a_{B(solution)}$  and  $a_{AB(solid)}$  are the activities of  $A$  and  $B$  in solution and of  $AB$  in the solid phase. Recall from the earlier discussion that the activity of a solid is defined as unity, and that in a very dilute solution (eg, for a slightly soluble salt), concentrations may be substituted for activities and Eq 6 then becomes

$$K_{eq} = C_A C_B$$

where  $C_A$  and  $C_B$  are the concentrations of  $A$  and  $B$  in solution. In this situation  $K_{eq}$  has a special name, the *solubility product*,  $K_{SP}$ . Thus

$$K_{SP} = C_A C_B \quad (7)$$

This equation will hold true theoretically only for slightly soluble salts.

As an example of this type of solution, consider the solubility of silver chloride

$$K_{SP} = [Ag^+][Cl^-]$$

where the brackets [ ] designate concentrations.

At 25° the solubility product has a value of  $1.56 \times 10^{-10}$ , the concentration of silver and chloride ions being expressed in moles/liter. The same numerical value applies also to solutions of silver chloride containing an excess of either silver or chloride ions. If the silver-ion concentration is increased by the addition of a soluble silver salt, the chloride-ion concentration must decrease until the product of the two concentrations again is equal numerically to the solubility product. In order to effect the decrease in chloride-ion concentration, silver chloride is precipitated and, hence, its solubility is decreased. In a similar manner an increase in chloride-ion concentration by the addition of a soluble chloride effects a decrease in the silver-ion concentration until the numerical value of the solubility product is attained. Again, this decrease in silver-ion concentration is brought about by the precipitation of silver chloride.

The solubility of silver chloride in a saturated aqueous solution of the salt may be calculated by assuming that the concentration of silver ion is the same as the concentration of chloride ion, both expressed in moles/liter, and that the concentration of dissolved silver chloride is numerically the

same since each silver chloride molecule gives rise to one silver ion and one chloride ion. Since

$$[\text{dissolved AgCl}] = [Ag^+] = [Cl^-]$$

the solubility of  $AgCl$  is equal to  $\sqrt{1.56 \times 10^{-10}}$ , which is  $1.25 \times 10^{-5}$  mole/liter. Multiplying this by the molecular weight of silver chloride (143) we obtain a solubility of approximately 1.8 mg/liter.

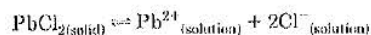
For a salt of the type  $PbCl_2$  the solubility product expression takes the form

$$[Pb^{2+}][Cl^-]^2 = K_{SP}$$

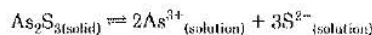
while for  $As_2S_3$  it would be

$$[As^{3+}]^2[S^{2-}]^3 = K_{SP}$$

because from the Law of Mass Action

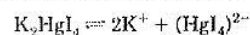


and



For further details of methods of using solubility-product calculations, the reader is referred to books on qualitative or quantitative analysis or physical chemistry.

Recall that the solubility-product principle is valid for aqueous solutions of slightly soluble salts, provided the concentration of added salt is not too great. Where the concentrations are high, deviations from the theory occur and these have been explained by assuming that in such solutions the nature of the solvent has been changed. Frequently, deviations also may occur as the result of the formation of complexes between the two salts. An example of increased solubility, by virtue of complex-ion formation, is seen in the effect of solutions of soluble iodides on mercuric iodide. According to the solubility-product principle it might be expected that soluble iodides would decrease the solubility of mercuric iodide, but because of the formation of the more soluble complex salt  $K_2HgI_4$ , which dissociates as follows



the iodide ion no longer functions as a common ion.

Practical applications of the solubility-product principle are found in qualitative and quantitative analysis whenever an excess of a precipitant is added in order to diminish, by common-ion effect, the solubility of the precipitate.

It is possible to formulate some general rules regarding the effect of the addition of soluble salts to slightly soluble salts where the added salt does not have an ion common to the slightly soluble salt. If the ions of the added soluble salt are not highly hydrated (see *Effect of Salts on the Solubility of Nonelectrolytes*, page 209), the solubility product of the slightly soluble salt will increase because the ions of the added salt tend to decrease the interionic attraction between the ions of the slightly soluble salt. On the other hand, if the ions of the added soluble salt are hydrated, water molecules become less available and the interionic attraction between the ions of the slightly soluble salt increases with a resultant decrease in solubility product. Another way of considering this effect is discussed later (*Thermodynamics of the Solution Process*, page 215).

The effect of temperature is, in general, what would be expected; increasing the temperature of the solution results in an increase of the solubility product.

**Solubility Following a Chemical Reaction**—Thus far in this chapter the discussion has been concerned with solubility that comes about because of interplay of entirely physical forces. The dissolution of some substance resulted from overcoming the physical interactions between solute mole-

cules and solvent molecules by the energy produced when a solute molecule interacted physically with a solvent molecule. The solution process, however, can be facilitated also by a chemical reaction. Almost always the chemical enhancement of solubility in aqueous systems is due to the formation of a salt following an acid-base reaction.

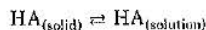
An alkaloidal base, or any other nitrogenous base of relatively high molecular weight, generally is slightly soluble in water, but if the pH of the medium is reduced by addition of acid, the solubility of the base is increased, considerably so, as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water. Conversely, the solubility of a salt of an alkaloid or other nitrogenous base is reduced as pH is increased by addition of alkali.

The solubility of slightly soluble acid substances is, on the other hand, increased as the pH is increased by addition of alkali, the reason again being that a salt, relatively soluble in water, is formed. Examples of acid substances whose solubility is thus increased are aspirin, theophylline and the penicillins, cephalosporins and barbiturates. Conversely, the solubility of salts of the same substances is decreased as the pH decreases.

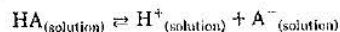
Among some inorganic compounds a somewhat similar behavior is observed. Tribasic calcium phosphate,  $\text{Ca}_3(\text{PO}_4)_2$ , for example, is almost insoluble in water, but if an acid is added its solubility increases rapidly with a decrease in pH. This is because hydrogen ions have such a strong affinity for phosphate ions forming nonionized phosphoric acid, that the calcium phosphate is dissolved in order to release phosphate ions. Or, stated in another way, the solubilization is an example of a reaction in which a strong acid (the source of the hydrogen ions) displaces a weak acid.

In all of these examples solubilization occurs as the result of an interaction of the solute with an acid or a base and that the species in solution is *not* the same as the undissolved solute. Compounds which do not react with either acids or bases are slightly, or not at all, influenced in their aqueous solubility by variations of pH. Such effects as may be observed are generally due to ionic *salt effects*.

It is possible to analyze quantitatively the solubility following an acid-base reaction by considering it as a two-step process. The first example is an organic acid, designated as HA, that is relatively insoluble in water. Its two-step dissolution can be represented as



followed by



The equilibrium constant for the first step is the solubility of HA ( $K_S = [\text{HA}]_{(\text{solution})}$ ), just as was developed earlier when no chemical reaction took place, and the equilibrium constant for the second step is the dissociation constant of the acid is

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]}$$

Since the total amount of compound *in solution* is the sum of nonionized and ionized forms of the acid, the total solubility may be designated as  $S_{t(\text{HA})}$ , or

$$S_{t(\text{HA})} = [\text{HA}] + [\text{A}^-] = [\text{HA}] + K_a \frac{[\text{HA}]}{[\text{H}^+]} \quad (8)$$

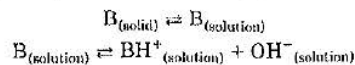
Since  $K_S = [\text{HA}]$ , Eq 8 becomes

$$S_{t(\text{HA})} = K_S \left( 1 + \frac{K_a}{[\text{H}^+]} \right) \quad (9)$$

Equation 9 is very useful since it equates the total solubility

of an acid drug with the hydrogen-ion concentration of the solvent. If the water solubility,  $K_S$ , and the dissociation constant,  $K_a$ , are known, the total solubility of the acid can be calculated at various hydrogen-ion concentrations. Equation 9 demonstrates quantitatively how the total solubility of the acid increases as the hydrogen-ion concentration decreases (that is, as the pH increases).

It is possible to develop an equation similar to Eq 9 for the solubility of a basic drug, B, such as a relatively insoluble nitrogenous base (an alkaloid, for example), at various hydrogen-ion concentrations. The solubility of the base in water may be represented in two steps, as



Again, if  $K_S$  is the solubility of the free base in water and  $K_b$  is its dissociation constant

$$K_b = \frac{[\text{BH}^+][\text{OH}^-]}{[\text{B}]}$$

the total solubility of the base in water  $S_{t(\text{B})}$  is given by

$$\begin{aligned} S_{t(\text{B})} &= [\text{B}] + [\text{BH}^+] = [\text{B}] + \frac{K_b[\text{B}]}{[\text{OH}^-]} = \\ &K_S \left( 1 + \frac{K_b}{[\text{OH}^-]} \right) \quad (10) \end{aligned}$$

It is convenient to rewrite Eq 10 in terms of hydrogen-ion concentration by making use of the dissociation constant for water

$$K_w = [\text{H}^+][\text{OH}^-] = 1 \times 10^{-14}$$

Equation 10 then becomes

$$S_{t(\text{B})} = K_S \left( 1 + \frac{K_b}{K_w/[\text{H}^+]} \right) = K_S \left( 1 + \frac{K_b[\text{H}^+]}{K_w} \right) \quad (11)$$

Equation 11 quantitatively shows how the total solubility of the base increases as the hydrogen-ion concentration of the solvent increases. If  $K_S$  and  $K_b$  are known, it is possible to calculate the total solubility of a basic drug at various hydrogen-ion concentrations using this equation.

Equations 9 and 11 have assumed that the salt formed following a chemical reaction is infinitely soluble. This, of course, is not an acceptable assumption as suggested and demonstrated by Kramer and Flynn.<sup>2</sup> Rather, for an acidic or basic drug there should be a pH at which *maximum solubility* occurs where this solubility remains the sum of the solution concentrations of the free and salt forms of the drug at that pH. Using a basic drug, B, as the example, this would mean that a solution of B, at pH values greater than the pH of maximum solubility, would be saturated with free-base form but not with the salt form and the use of Eq 11 would be valid for the prediction of solubility. On the other hand, at pH values less than the pH of maximum solubility, the solution would be saturated with salt form and Eq 11 is no longer really valid. Since in this situation the total solubility of the base,  $S_{t(\text{B})}$ , is

$$S_{t(\text{B})} = [\text{B}] + [\text{BH}^+]_s$$

where the subscript, *s*, designates a solution saturated with salt, the correct equation to use at pH values less than the pH maximum would be

$$S_{t(\text{B})} = [\text{BH}^+]_s \left( 1 + \frac{[\text{OH}^-]}{K_b} \right) = [\text{BH}^+]_s \left( 1 + \frac{K_w}{K_b[\text{H}^+]} \right) \quad (12)$$



A relationship similar to Eq 12 likewise can be developed for an acidic drug at pHs greater than its pH of maximum solubility.

**Effecting Solution of Solids in the Prescription Laboratory.**—The method usually employed by the pharmacist when soluble compounds are to be dissolved in water in compounding a prescription requires the use of the mortar and pestle. The ordinary practice is to crush the substance into fragments in the mortar with the pestle and pour the solvent on it, meanwhile stirring with the pestle until solution is effected. If definite quantities are used, and the whole of the solvent is required to dissolve the given weight of the salt, only a portion of the solvent should be added first and, when this is saturated, the solution is poured off and a fresh portion of solvent added. This operation is repeated until the solid is dissolved entirely and all the portions combined. Other methods of effecting solution are to shake the solid with the liquid in a bottle or flask or to apply heat to the substances in a suitable vessel. Substances vary greatly in the rate at which they dissolve; some are capable of producing a saturated solution quickly, others require several hours to attain saturation. All too often, in their haste to prepare a saturated solution, pharmacists fail to obtain the required degree of solution of solute.

With hygroscopic substances like pepsin, silver protein compounds and some others, the best method of effecting solution in water is to place the substance directly upon the surface of the water and then stir vigorously with a glass rod. If the ordinary procedure, such as using a mortar and pestle, is employed with these substances, gummy lumps are formed which are exceedingly difficult to dissolve.

The solubility of chemicals and the miscibility of liquids are important physical factors for the pharmacist to know, as they often have a bearing on intelligently and properly filling prescriptions. Mainly for the information of the pharmacist, the USP provides tabular data indicating the degree of solubility or miscibility of many official substances.

**Determination of Solubility.**—For the pharmacist and pharmaceutical chemist the question of solubility is of paramount importance. Not only is it necessary to know solubilities when preparing and dispensing medicines, but such information is necessary to effect separation of substances in qualitative and quantitative analysis. Furthermore, the accurate determination of the solubility of a substance is one of the best methods for determining its purity.

The details of the determination of the solubility are affected markedly by the physical and chemical characteristics of the solute and solvent and also by the temperature at which the solubility is to be determined. Accordingly, it is not possible to describe a universally applicable method but, in general, the following rules must be observed in solubility determinations.

1. The purity of both the dissolved substance and the solvent is essential, since impurities in either affect the solubility.
2. A constancy of temperature must be maintained accurately during the course of the determination.
3. Complete saturation must be attained.
4. Accurate analysis of the saturated solution and correct expression of the results are imperative.

Consideration should be given also to the varying rates of solution of different compounds and to the marked effect of the degree of fineness of the particles on the time required for the saturation of the solution.

Many of the solubility data of USP have been determined with regard to the exacting requirements mentioned above.

**Phase-Solubility Analysis.**—This procedure is one of the most useful and accurate methods for the determination of the purity of a substance. It involves the application of precise solubility methods to the principle that constancy of solubility, in the same manner as constancy of melting point,

indicates that a material is pure or free from foreign admixture. It is important to recognize that the technique can be used to obtain the exact solubility of the pure substance without the necessity of the experimental material itself being pure.

The method is based on the thermodynamic principles of heterogeneous equilibria which are among the soundest of theoretical concepts of chemistry. Thus, it does not depend on any assumptions regarding kinetics or structure of matter, but is applicable to all species of molecules, and is sufficiently sensitive to distinguish between optical isomers. The requirements for an analysis are simple, since the equipment needed is basic to most laboratories and the quantities of substances required are small.

The standard solubility method consists of five steps:

1. Mixing, in separate systems, increasing amounts of a substance with measured amounts of a solvent.
2. Establishment of equilibrium for each system at identical constant temperature and pressure.
3. Separation of the solid phase from the solutions.
4. Determination of the concentration of the material dissolved in the various solutions.
5. Plotting the concentration of the dissolved material per unit of solvent (y-axis, or solution concentration) against the mass of material per unit of solvent (x-axis or system concentration).

The solubility method has been established on the sound theoretical principles of the Gibbs phase rule:  $F = C - P + 2$ , which relates  $C$ , the number of components,  $F$ , the degrees of freedom (pressure, temperature and concentration) and  $P$ , the number of phases for a heterogeneous equilibrium. Since solubility analyses are carried out at constant temperature and pressure, a pure solid in solution would show only one degree of freedom, because only one phase is present at concentrations below saturation. This is represented by section  $AB$  in Fig 16-4. For a pure solid in a saturated solution at equilibrium (Fig 16-4,  $BC$ ), two phases are present, solid and solution; there is no variation in concentration and thus, at constant temperature and pressure, no degrees of freedom.

The curve  $ABC$  of Fig 16-4 represents the type of solubility diagram obtained for: (1) a pure material, (2) equal amounts of two or more materials having identical solubilities or (3) a mixture of two or more materials present in the

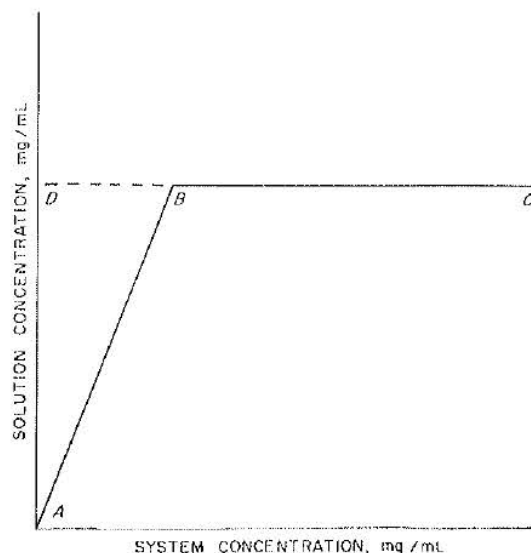


Fig 16-4. Phase-solubility diagram for a pure substance.

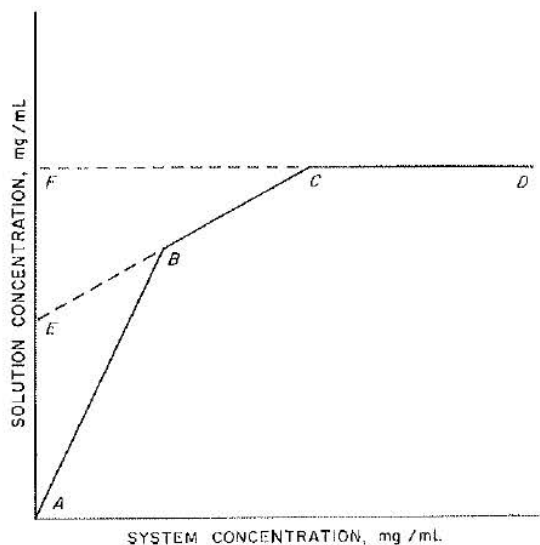


Fig 16-5. Type of solubility curve obtained when a substance contains one impurity.

unique ratio of their solubilities. These latter two cases are rare and often may be detected by a change in solvent system.

Line segment *BC* of Fig 16-4, since it has no slope, usually indicates purity. If, however, this section *does* exhibit a slope, its numerical value indicates the fraction of impurity present. Line segment *BC*, extrapolated to the *y* axis at *D*, is the actual solubility of the pure substance.

A representative type of solubility curve, which is obtained when a substance contains one impurity, is illustrated in Fig 16-5. Here, at *B*, the solution becomes saturated with one component. From *B* to *C* there are two phases present: a solution saturated with Component I (usually the major component) containing also some Component II (usually the minor component), and a solid phase of Component I. The one degree of freedom revealed by the slope of the line segment *BC* is the concentration of Component II, which is the impurity (usually the minor component). A mixture of *d* and *l* isomers could have such a curve, as would any simple mixtures in which the solubilities are independent of each other.

The section *CD* indicates that the solvent is saturated with both components of the two-component mixture. Here, three phases are present: a solution saturated with both components and the two solid phases. No variation of concentration is possible, hence, no degree of freedom is possible (indicated by the lack of slope of section *CD*). The distance *AE* on the ordinate represents the solubility of the major component, and the distance *EF*, the solubility of the minor component.

The fact that the equilibration process is time-consuming, requiring as long as 3 weeks in certain cases, is offset by the fact that all of the sample can be recovered after a determination. This adds to the general usefulness of the method, particularly in cases where the substance is expensive or difficult to obtain. A use for the method other than the determination of purity or of solubility is to obtain especially pure samples by recovering the solid residues at system concentration corresponding to points on section *BC* in Fig 16-5. Thus, the method is useful not only as a quantitative analytical tool, but also for purification.

## Solutions of Liquids in Liquids

**Binary Systems**—Under this title the following types of liquid-pairs may be recognized.

1. Those which are soluble completely in each other in all proportions. Examples: alcohol and water; glycerin and water; alcohol and glycerin.
2. Those which are soluble in each other in definite proportions. Examples: phenol and water; ether and water; nicotine and water.
3. Those which are imperceptibly soluble in each other in any proportion. Examples: castor oil and water; liquid petrolatum and water.

The mutual solubility of liquid pairs of Type 2 has been studied extensively and found to show interesting regularities. If a series of tubes containing varying, but known, percentages of phenol and water are heated (or cooled, if necessary) just to the point of formation of a homogeneous solution, and the temperatures at such points noted, there will be obtained, upon plotting the results, a curve similar to that in Fig 16-6.<sup>3</sup> On this graph the area inside the curve represents the region where mixtures of phenol and water will separate into two layers, while in the region outside of the curve homogeneous solutions will be obtained. The maximum temperature on this curve is called the *critical solution temperature*, that is, the temperature above which a homogeneous solution occurs regardless of the composition of the mixture. For phenol and water the critical solution temperature occurs at a composition of 34.5% phenol in water.

Temperature versus composition curves, as depicted in Fig 16-6, provide much useful information in the preparation of homogeneous mixtures of substances showing mutual-solubility behavior. At room temperature (here assumed to be 25°), by drawing a line parallel to the abscissa at 25°, we find that we actually can prepare two sets of homogeneous solutions, one containing from 0 to about 7.5% phenol and the other containing phenol from 72 to about 95% (its limit of solubility). At compositions between 7.5 and 72% phenol at 25° two liquid layers or phases will separate. In sample tubes containing a concentration of phenol in this two-layer region at 25° one layer always will be phenol-rich and always contain 72% phenol while the other layer will be water-rich and always contain 7.5% phenol. These values are obtained by interpolation of the two points of intersection of the line drawn at 25° with the experimental curve. As it may be deduced, at other temperatures, the composition of the two layers in the two-layer region is determined by the points of intersection of the curve with a line (called

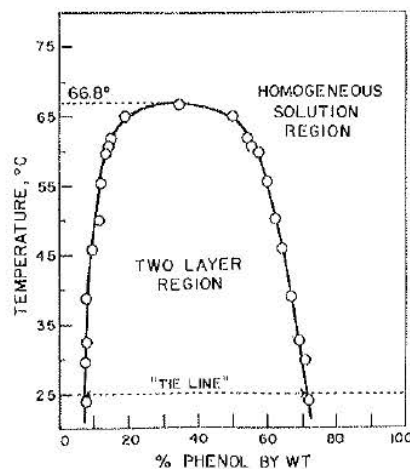


Fig 16-6. Phenol-water solubility.<sup>3</sup>

the "tie line") drawn parallel to the abscissa at that temperature. The relative amounts of the two layers or phases, phenol-rich and water-rich in this example, will depend on the concentration of phenol added. As expected, the proportion of phenol-rich layer relative to the water-rich layer increases as the concentration of phenol added increases. For example, at 20% phenol in water at 25° there would be more of the water-rich layer than of the phenol-rich layer, while at 50% phenol in water there would be more of the phenol-rich layer. The relative proportion of each layer may be calculated from such tie lines at any temperature and composition as well as the amount of phenol present in each of the two phases. To determine how these calculations are made and for further discussion of this topic the student should consult Ref 1, page 79.

A simple and practical advantage in the use of phase diagrams is pointed out in Ref 1. Based on diagrams such as Fig 16-6, they point out that the most concentrated stock solution of phenol that perhaps should be used by pharmacists is one containing 76% *w/w* phenol in water (equivalent to 80% *w/o*). At room temperature this mixture is a homogeneous solution and will remain homogeneous to around 3.5°, at which temperature freezing occurs. It should be noted that Liquefied Phenol USP contains 90% *w/w* phenol and freezes at 17°C. This means that if the storage area in the pharmacy falls to about 63°F, the preparation will freeze, resulting in a stock solution no longer convenient to use.

In the case of phenol and water the mutual solubility increases with increase in temperature and the critical solution temperature occurs at a relatively high point. In a certain number of cases, however, the mutual solubility increases with decrease in temperature and the critical solution temperature occurs at a relatively low value. Most of the substances which show lower critical solution temperatures are amines as, for example, triethylamine with water.

In addition to pairs of liquids which show *either* upper or lower critical solution temperatures, there are other pairs which show *both* upper and lower critical solution temperatures and the mutual solubility curve is of the closed type. An example of this type of liquid pair is found in the case of nicotine and water (Fig 16-7). Mixtures of nicotine and water represented by points within the curve will separate into two layers, but mixtures represented by points outside of the curve are perfectly miscible with each other.

In a discussion of solutions of liquids in liquids it is evident that the distinction between the terms solute and solvent loses its significance.

For example, in a solution of water and glycerin, which shall be considered to be the solute and which the solvent? Again, when two liquids are soluble only partially in each other the distinction between solute and solvent might be reversed easily. In such cases the term solvent usually is given to the constituent present in larger quantity.

**Ternary Systems**—The addition of a third liquid to a binary liquid system to produce a ternary or three-component system can result in several possible combinations.

If the third liquid is soluble in only one of the two original liquids or if its solubility in the two original liquids is markedly different, the mutual solubility of the original pair will be decreased. An upper critical solution temperature will be elevated and a lower critical solution temperature lowered. On the other hand, the addition of a liquid having roughly the same solubility in both components of the original pair will result in an increase in their mutual solubility. An upper critical solution temperature then will be lowered and a lower critical solution temperature elevated.

An equilateral-triangle graph may be used to represent the situation in which a third liquid is added to a partially miscible liquid pair, the third liquid being miscible with each member of the original pair. In this type of graph, each side of the triangle represents 0% of one of the components and the apex opposite that side represents 100% of that component. The reader is referred to textbooks on experimental physical chemistry for details of the construction and use of graphs of this type.

Two other possibilities exist in ternary liquid systems: that in which two components are completely miscible and the third is partially miscible with each, and that in which all combinations of two of the three components are only partially miscible.

### Solutions of Gases in Liquids

Nearly all gases are more or less soluble in liquids. One has but to recall the solubility of carbon dioxide, hydrogen sulfide or air in water as common examples.

The amount of gas dissolved in a liquid in general follows *Henry's law*, which states that *the weight of gas dissolved by a given amount of a liquid at a given temperature is proportional to its pressure*. Thus, if the pressure is doubled, twice as much gas will dissolve as at the initial pressure. The extent to which a gas is dissolved in a liquid, at a given temperature, may be expressed in terms of the *solubility coefficient*, which is the volume of gas measured under the conditions of the experiment, that is, absorbed by one volume of the liquid. The degree of solubility also is expressed sometimes in terms of the *absorption coefficient*, which is the volume of gas, reduced to standard conditions, dissolved by one volume of liquid under a pressure of one atmosphere.

Although Henry's law expresses fairly accurately the solubility of slightly soluble gases, it deviates considerably in the case of very soluble gases such as hydrogen chloride and ammonia. Such deviations most frequently are due to chemical interaction of solute and solvent.

The solubility of gases in liquids *decreases* with a *rise* in temperature and, in general, also when salts are added to the solvent, the latter effect being referred to as the *salting-out* of the gas.

Solutions of gases potentially are dangerous when exposed to warm temperatures because of the liberation and expansion of the dissolved gas which may cause the container to burst. Bottles containing such solutions (eg, strong ammonia solution) should be cooled before opening, if practical, and the stopper should be covered with a cloth before attempting its removal.

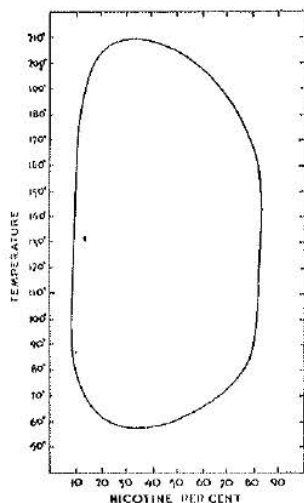


Fig 16-7. Nicotine-water solubility.

### Thermodynamics of the Solution Process

In the discussions under this heading the solute is assumed to be in the liquid state, hence, the heat of solution ( $\Delta H'$ ) is a term different from that in Eq 3 ( $\Delta H$ ). The heat of solution for a solid solute going into solution as defined in Eq 3 is the net heat effect for the overall dissolution

$$A_{(\text{solid})} \rightleftharpoons A_{(\text{liquid})} \rightleftharpoons A_{(\text{solution})}$$

Considering only the process

$$A_{(\text{liquid})} \rightleftharpoons A_{(\text{solution})}$$

and assuming that the solute is a liquid (or a supercooled liquid in the case of a solid) at a temperature close to room temperature, where the energy needed for melting (heat of fusion) is not being considered.

For a physical or chemical reaction to occur spontaneously at a constant temperature and pressure, the net free-energy change,  $\Delta G$ , for the reaction should be negative (see *Thermodynamics*, Chapter 15). Furthermore, it is known that the free-energy change depends on heat-related enthalpy ( $\Delta H'$ ) and order-related entropy ( $\Delta S$ ) factors as seen in

$$\Delta G = \Delta H' - T\Delta S \quad (13)$$

where  $T$  is the temperature. Recall, also, that the relation between free energy and the equilibrium constant,  $K$ , for a reaction is given by

$$\Delta G = -RT \ln K \quad (14)$$

Equations 13 and 14 certainly apply to the solution of a drug. Since the solubility is, in reality, an equilibrium constant, Eq 14 indicates that the greater the negative value of  $\Delta G$ , the greater the solubility.

The interplay of these two factors,  $\Delta H'$  and  $\Delta S$  in Eq 13, determines the free-energy change and, hence, whether or not dissolution of a drug will occur spontaneously. Thus, if in the solution process  $\Delta H'$  is negative and  $\Delta S$  positive, dissolution is favored since  $\Delta G$  will be negative.

As the heat of solution is quite significant in the dissolution process one must look at its origin. (For an excellent and more complete discussion of the interactions and driving forces underlying the dissolution process, see Higuchi.<sup>4</sup>) The mechanism of solubility involves severing of the bonds that hold together the ions or molecules of a solute, the separation of molecules of solvent to create a space in the solvent into which the solute can be fitted and the ultimate response of solute and solvent to whatever forces of interaction may exist between them. In order to sever the bonds between molecules or ions of solute in the liquid state, energy must be supplied, as is the case also when molecules of solvent are to be separated. If heat is the source of energy it is apparent that both processes require the absorption of heat.

Solute-solvent interaction, on the other hand, generally is accompanied by the evolution of heat since the process occurs spontaneously. In effecting solution there is, accordingly, a heat-absorbing effect and a heat-releasing effect to be considered beyond those required to melt a solid. If there is no, or very little, interaction between solute and solvent, the only effect will be that of absorption of heat to produce the necessary separations of solute and solvent molecules or ions. If there is a significant interaction between solute and solvent, the amount of heat in excess of that required to overcome the solute-solute and the solvent-solvent forces is liberated. If the opposing heat effects are equal, there will be no change of temperature.

When  $\Delta H'$  is zero, and there is no volume change, an *ideal solution* is said to exist since the solute-solute, solvent-solvent and solute-solvent interactions are the same. For such

an ideal solution, the solubility of a solid can be predicted from its heat of fusion (the energy needed to melt the solid) at temperatures below its melting point. The student is referred to Ref 1, page 281 to see how this calculation is made.

When the heat of solution has a positive (energy absorbed) or negative (energy liberated) value, the solution is said to be a *nonideal solution*. A negative heat of solution favors solubility while a positive heat works against dissolution.

The magnitude of the various attractive forces involved between solute, solvent and solute-solvent molecules may vary greatly and thus could lead to varying degrees of positive or negative enthalpy changes in the solution process. The reason for this is that the molecular structure of the various solutes and solvents determining the interactions can themselves vary greatly. (For a discussion of these effects, see Ref 1, page 41.)

The solute-solute interaction that must be overcome can vary from the strong ion-ion interaction (as in a salt), to the weaker dipole-dipole interaction (as in nearly all organic medicinals that are not salts), to the weakest induced dipole-induced dipole interaction (as with naphthalene).

The attractive forces in the solvent that must be overcome are, most frequently, the dipole-dipole interaction (as found in water or acetone) and the induced dipole-induced dipole interaction (as in liquid petrolatum).

The energy-releasing solute-solvent interactions that must be taken into account may be one of four types. In decreasing energy of interaction these are ion-dipole interactions (eg, a sodium ion interacting with water), dipole-dipole interactions (eg, an organic acid dissolved in water), dipole-induced dipole interaction, to be discussed later (eg, an organic acid dissolved in carbon tetrachloride) and induced dipole-induced dipole interactions (eg, naphthalene dissolved in benzene).

Since the energy-releasing solute-solvent interaction should approximate the energy needed to overcome the solute-solute and solvent-solvent interactions, it should be apparent why it is not possible to dissolve a salt like sodium chloride in benzene. The interaction between the ions and benzene does not supply enough energy to overcome the interaction between the ions in the solute and therefore gives rise to a positive heat of solution. On the other hand, the interaction of sodium and chloride ions with water molecules does provide an amount of energy approximating the energy needed to separate the ions in the solute and the molecules in the solvent.

Consideration must next be given to entropy effects in dissolution processes. Entropy is an indicator of the disorder or randomness of a system. The more positive the entropy change ( $\Delta S$ ) is, the greater the degree of randomness or disorder of the reaction system and the more favorably disposed is the reaction. Unlike  $\Delta H'$ , the entropy change (an entropy of mixing) in an ideal solution, is not zero, but has some positive value since there is an increase in the disorderliness or entropy of the system upon dissolution. Thus, in an ideal solution with  $\Delta H'$  zero and  $\Delta S$  positive,  $\Delta G$  would have a negative value and the process, therefore, would be spontaneous.

In a nonideal solution, on the other hand, where  $\Delta H'$  is not zero,  $\Delta S$  can be equal to, greater than or less than the entropy of mixing found for the ideal solution. A nonideal solution with an entropy of mixing equal to that of the ideal solution is called a "regular solution." These solutions usually occur with nonpolar or weakly polar solutes and solvents. Such solutions are accompanied by a positive enthalpy change, implying that the solute-solvent molecular interaction is less than the solute-solute and solvent-solvent molecular interactions. Regular solutions are amenable to rigorous physical chemical analysis which will not be covered



in this chapter but which can be found in outline form in Ref 1, page 282.

The possibility exists in a nonideal solution that the entropy change is greater than for an ideal solution. Such a solution occurs when there is an association among solute or solvent molecules. In essence, then, the dissolution process occurs when one begins at a relatively ordered (low entropy) state and progresses to a disorderly (high entropy) state. The overall entropy change is positive, greater than that of the ideal case, and favorable to dissolution. As may be expected, the enthalpy change in such a solution is positive since association in a solute or solvent must be overcome. The facilitated solubility of citric acid (an unsymmetrical molecule), as compared to inositol (a symmetrical molecule), may be explained on the basis of such a favorable entropy change.<sup>4</sup>

The solubility of citric acid is greater than that of inositol, yet, on the basis of their heats of solution, inositol should be more soluble. One may regard this phenomenon in another way. The reason for the higher solubility of citric acid is that although there is no hindrance in the transfer of a citric acid molecule as it goes from the solute to the solution phase, when the structurally unsymmetrical citric acid attempts to return to the solute phase from solution, it must assume an orientation that will allow ready interaction with polar groups already oriented. If it does not have the required orientation, it will not return readily to the solute, but it will remain in solution, thus bringing about a solubility larger than expected on the basis of heat of solution.

On the other hand, the structurally symmetrical inositol, as it leaves the solution phase, can interact with the solute phase without requiring a definite orientation; all orientations are equivalent. Hence, inositol can enter the solute phase without hindrance and, therefore, no facilitation of its solubility is observed.

In general, unsymmetrical molecules tend to be more soluble than symmetrical molecules.

Another type of nonideal solution occurs where there is an entropy change less than that expected of an ideal solution. Such nonideal behavior can occur with polar solutes and solvents. In a nonideal solution of this type there is significant interaction between solute and solvent. As may be expected, the enthalpy change ( $\Delta H'$ ) in such a solution is negative and favors dissolution, but this effect is tempered by the unfavorable entropy change occurring at the same time. The reason for the lower-than-ideal entropy change can be visualized where the equilibrium system is more orderly and has a lower entropy than that expected for an ideal solution. The overall entropy change of solution, thus, would be less and not favorable to dissolution. One may rationalize the lower-than-expected solubility of lithium fluoride on the basis of this phenomenon. Compared with other alkali halides, it has a solubility lower than would be expected based solely on enthalpy changes. Because of the small size of ions in this salt there may be considerable ordering of water molecules in the solution. This effect must, of course, lead to a lowered entropy and an unfavorable effect on solubility. The effect of soluble salts on the solubility of nonelectrolytes (page 209) or slightly soluble salts (page 210) may be considered a result of an unfavorable entropy effect.

### Pharmaceutical Solvents

The discussion will focus now on solvents available to pharmacists and, in particular, on their interactions and properties of these solvents. It is most important that the pharmacist obtain an understanding of the possible differences in solubility of a given solute in various solvents since

he most often is called on to select a solvent which will dissolve the solute. A knowledge of the properties of solvents will allow the intelligent selection of suitable solvents.

### Molecular Interactions

The solvent-solvent interaction is, in pharmaceutical solvents, always made up of a dipole-dipole interaction (Keesom Force) and an induced dipole-induced dipole interaction (London Force). It is important to keep in mind that both forces are always present; the contribution that each of these forces makes toward the overall attractive force depends on the structure of the solvent molecule. Some solvents have interactions which predominantly involve the Keesom Force (eg, water), while others are predominantly composed of the London Force (eg, chloroform); usually, both forces will be found.

**Dipole-Dipole Forces**—The unequal sharing of the electron pair between two atoms due to a difference in their electronegativity brings about a separation of the positive and negative centers of electricity in the molecule, causing it to become polarized; that is, to assume a partial ionic character. The molecule then is said to be a *permanent dipole* and the substance described as being a *polar compound*.

The greater the difference in the electronegativities of the constituent atoms, the greater the inequality of sharing of the electron pair, the greater the distance between the positive and negative centers of electricity in the molecule and the more polar the resulting molecule. As the character of the bonds are intermediate between those existing in nonpolar compounds and those occurring in ionic salts, it is to be expected that the properties of polar compounds should be intermediate between those of the two other classes. Such, in fact, generally is the case.

Coordinate covalent compounds all are very strongly polar because both of the electrons constituting the bonding pair have been contributed by a donor atom which, in effect, loses an electron and becomes positively charged, while the acceptor atom may be considered to gain an electron and become negatively charged.

While, in general, the electronegativities of different kinds of atoms are different, and the expectation is, therefore, that all molecules containing two or more different atoms will be polar, many such molecules actually are nonpolar. Thus, while the electronegativity of chlorine is appreciably different from that of carbon, the molecule of carbon tetrachloride,  $\text{CCl}_4$ , is nonpolar because the symmetrical arrangement of chlorine atoms about the carbon atom is such as to cancel the effects of the difference in the electronegativity of the constituent atoms. The same is true in the case of methane,  $\text{CH}_4$ , and for hydrocarbons generally. But the molecules  $\text{CH}_3\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$  and  $\text{CHCl}_3$  definitely are polar because of the unsymmetrical distribution of the forces within the molecule.

A knowledge of the degree of polarity of various molecules usually is available in the measurement of the *dipole moment*,  $\mu$ , of the molecules. This quantity is defined as the product of one of the charges on the molecule and the distance between the two average centers of positive and negative electricity. Measurements of the dipole moment of a substance are made, when possible, on the vapor of the substance but, when not possible, a dilute solution of the substance in a nonpolar solvent is employed. Table II lists the values of the dipole moment for a number of substances.

As stated previously, the molecules of nonpolar substances are characterized by weak attractions for one another, while molecules of polar substances exhibit a relatively strong attraction, which is all the more powerful the greater the dipole moment. The reason for this is readily apparent; the dipoles tend to align themselves so that the opposite charges of two different molecules are adjacent. They affect

Table II—Dipole Moments

Substance	Electrostatic Units ( $\mu \times 10^{18}$ )
Water	1.85
Acetone	2.8
Methyl alcohol	1.68
Ethyl alcohol	1.70
Phenol	1.70
Ethyl ether	1.14
Aniline	1.51
Nitrobenzene	4.19
<i>o</i> -Dinitrobenzene	6.0
<i>m</i> -Dinitrobenzene	3.8
<i>p</i> -Dinitrobenzene	0.3
Benzene	0
Methane	0
Chloromethane	1.86
Dichloromethane	1.58
Chloroform	1.05
Carbon tetrachloride	0
Carbon monoxide	0.11
Carbon dioxide	0
Oxygen	0
Hydrogen	0
Hydrogen chloride	1.03
Hydrogen bromide	0.78
Hydrogen iodide	0.38
Hydrogen sulfide	0.96
Hydrogen cyanide	2.93
Ammonia	1.49

each other in somewhat the same manner as do two bar magnets, the opposite poles of which are adjacent. While thermal agitation tends to break up the alignment or association of the dipoles, there is, nevertheless, a resultant significant intermolecular force present.

**Induced Dipole-Induced Dipole Forces**—It is of interest to inquire at this point what force does exist between the molecules of compounds which are nonpolar, eg, those which have zero dipole moment. If some attractive force did not exist, the molecules could not be expected to cling together, as in the solid and liquid states. Although the attraction is relatively slight, there is a force that arises from momentary polarization of the molecules because of electronic oscillations which are taking place continuously within the molecules. The *temporary dipoles* thus produced induce opposite polarizations in adjacent molecules and the net effect is that there is a small but definite attractive force between the molecules to keep them together in the liquid and solid states. This attraction resulting from mutual polarization commonly is referred to as the London Force and as an induced dipole-induced dipole force.

**The Hydrogen Bond**—The attraction between oppositely charged ends of two dipoles is accentuated when the positive end of one dipole contains a hydrogen atom and the negative end of the other dipole contains an atom of fluorine, oxygen or nitrogen. In such instances the nucleus of the hydrogen atom—which is a proton—appears to be able to bind together the negative end of the molecule, of which it is a part, with the negative end of the adjacent molecule. This may be represented by Fig 16-8.

Since the proton is the smallest positively charged atomic particle, it can draw together two negatively charged atoms

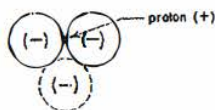
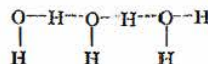


Fig 16-8. Hydrogen bonding.

or ions more closely than can any other—and necessarily larger—positively charged particle. Not more than two negative atoms are capable of being attracted at any given instant, as is evident from Fig 16-8, where a third negative atom is shown to be restricted physically from direct contact with the proton. Water is an excellent example of a substance, the molecules of which are associated through the formation of such a bond—called the *hydrogen bond*. An illustration of such bonding in the case of water may be represented as

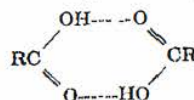


Each dotted line represents the bond or “bridge” established by the hydrogen atom of one water molecule with the oxygen atom of another. It is to be noted that the water molecule is pictured as an angular, rather than as a linear, molecule (H—O—H). This is in accord with the bond angles imposed by the directional character of the bonding orbitals making up the molecule (see Chapter 22). By virtue of its kernel containing six unneutralized protons, not only the valence electrons of the oxygen atom, but also those of the hydrogen atoms are attracted so strongly to the oxygen atom as to make the latter charged negatively, while the rest of the molecule is charged positively.

The hydrogen bond is not a strong bond, but it plays an important role in determining the properties of substances in which it occurs. For example, it primarily is responsible for the unusual properties of water. If the substance  $H_2O$  followed the course of the related substances  $H_2Te$ ,  $H_2Se$  and  $H_2S$ , in so far as the physical properties of these latter substances are concerned, the freezing point of water would be about  $100^\circ$  and its boiling point about  $-80^\circ$ . The unexpectedly high values actually observed are attributed to hydrogen bonding between molecules of water. To break such bonds, as for example in vaporizing water in the form of single  $H_2O$  molecules during the process of boiling, more energy is required than would be necessary if the water molecules were not linked by hydrogen bonds.

The molecules of at least the low-molecular-weight alcohols similarly are joined by hydrogen bonds to form a lattice-like structure.

Another example of the manner in which the hydrogen bond functions is seen in the case of carboxylic acids. Such acids usually exist in dimeric form, the two molecules being joined by hydrogen bonding, which may be depicted as



This tendency is so pronounced in the case of acetic acid that even in the vapor state the substance exists in dimeric aggregation.

#### Classification

On the basis of the forces of interaction occurring in solvents one may broadly classify solvents as one of three types:

1. *Polar solvents*—those made up of strong dipolar molecules having hydrogen bonding (water or hydrogen peroxide).
2. *Semipolar solvents*—those also made up of strong dipolar molecules but which do not form hydrogen bonds (acetone or pentyl alcohol).
3. *Nonpolar solvents*—those made up of molecules having a small or no dipolar character (benzene, vegetable oil or mineral oil).

Naturally, there are many solvents that may fit into more than one of these broad classes; for example, chloroform is a weak dipolar compound but generally is considered nonpo-



lar in character, and glycerin could be considered a polar or semipolar solvent even though it is capable of forming hydrogen bonds.

### Types

**Water**—Water is a unique solvent. Besides being a highly associated liquid, giving rise to its high boiling point, it has another very important property, a high dielectric constant. The dielectric constant ( $\epsilon$ ) indicates the effect that a substance has, when it acts as a medium, on the ease with which two oppositely charged ions may be separated. The higher the dielectric constant of a medium, the easier it is to separate two oppositely charged species in that medium. The dielectric constants of a number of liquids are given in Table III. The values listed are relative to a vacuum which, by definition, has a dielectric constant of unity. According to Coulomb's Law the force of attraction ( $F$ ) between two oppositely charged ions is

$$F = \frac{Z_1 Z_2}{\epsilon r^2} \quad (15)$$

where  $Z_1$  and  $Z_2$  are the charges on the ions,  $r$  is the distance separating the oppositely charged ions and  $\epsilon$  is the dielectric constant of the medium. Equation 15 indicates that the force of interaction between the oppositely charged ions is proportional inversely to the dielectric constant of the medium. Thus, the interactive force between a sodium and chloride ion in water at a distance  $r$  would be  $1/80$  that of the same ions in a vacuum separated the same distance. Looking at this example in another way, Coulomb's Law suggests that it is much easier to keep sodium and chloride ions apart in water than in a vacuum. Consider another example: the relative ease with which the ions of sodium chloride may be kept apart the same distance in water, as compared to olive oil, would occur in the ratio of 80/3.1; that is, it is 80/3.1 times easier to keep these ions apart in water than it is in olive oil. The ease of solubilizing salts in solvents like water and glycerin can be explained on the basis of their high dielectric constant. In general, also, the more polar the solvent, the greater its dielectric constant.

There is a very close relationship between dielectric constant and the two types of interactions found in all solvents; that is, the dipole-dipole interaction (Keesom) and the induced dipole-induced dipole interaction (London). The dielectric constant is related to these two forces through a quantity called *total molar polarization*,  $P$ , which is a measure of the relative ease with which a charge separation may be made within a molecule. The total molar polarization is given by

Table III—Dielectric Constants (at 20°)

Hydrogen cyanide	116
Water	80
Glycerin	46
Ethylene glycol	41
Methyl alcohol	33
Ethyl alcohol	25
<i>n</i> -Propyl alcohol	22
Acetone	21
Aniline	7.0
Chloroform	5.0
Castor oil	4.6
Ethyl ether	4.3
Octyl alcohol	3.4
Olive oil	3.1
Benzene	2.2
Turpentine oil	2.2
Carbon tetrachloride	2.2
Octane	1.9

$$P = \frac{\epsilon - 1}{\epsilon + 2} \cdot \frac{M}{D} \quad (16)$$

where  $\epsilon$  is the dielectric constant of the substance,  $M$  is the molecular weight and  $D$  is the density. (For further details, see Ref 1, page 114.) Total molar polarization is in turn composed of two terms

$$P = P_a + P_\mu = \frac{4}{3} \pi N \alpha + \frac{4}{3} \pi N \left( \frac{\mu^2}{3kT} \right) \quad (17)$$

where  $P_a = 4/3 \pi N \alpha$  is the contribution due to induced polarization (the London contribution), and where

$$P_\mu = \frac{4}{3} \pi N \left( \frac{\mu^2}{3kT} \right)$$

is the contribution due to the permanent dipole (the Keesom contribution),  $N$  is Avogadro's Number,  $\alpha$  is a constant called the polarizability (related to the induced dipole),  $\mu$  is the dipole moment,  $k$  is the Boltzmann constant ( $1.38 \times 10^{-16}$  erg/mole/deg) and  $T$  is the absolute temperature. Grouping all constant terms, it is possible to rewrite Eq 17 as

$$P = A + B/T$$

and substituting Eq 16, yields

$$\frac{\epsilon - 1}{\epsilon + 2} \cdot \frac{M}{D} = A + \frac{B}{T} \quad (18)$$

The first term on the right-hand side is the contribution to the dielectric constant of the London dispersions; it is not temperature-dependent. The second term on the right-hand side is the contribution to the dielectric constant of the Keesom dispersions. This latter contribution is temperature-dependent because the contribution from the permanent dipole depends on the dipoles aligning themselves, which tendency is opposed by thermal agitation. Thus, it is apparent from Eq 18 (and from common sense) that as temperature increases, the dielectric constant of dipolar solvents will tend to decrease.

Equation 18 also indicates that solvents which have large dipole moments tend to have large dielectric constants because of the contribution of the  $P_\mu$  term (Eq 17). Water, which has a very large dielectric constant, is estimated to have  $2/3$  of its molecular interaction due to a dipole-dipole interaction and  $1/3$  due to the induced dipole-induced dipole interaction. On the other hand, compounds such as benzene, with a dipole moment of zero, will have small dielectric constants since the contribution by the  $P_\mu$  term will drop out of Eq 18.

There is an important concept that should be considered which has been introduced to pharmaceutical systems.<sup>5</sup> It must be recognized that pharmacists frequently are concerned with dissolving relatively nonpolar drugs in aqueous or mixed polar aqueous solvents. To understand what may be happening in such cases, factors concerned with the entropic effects arising from interactions originating with the nonpolar solutes must be considered. Previously it had been noted that the favorable entropic effect on dissolution was due to the disruption of associations occurring among solute or solvent molecules. Now, consider the effects on solubility due to solute interactions in the solution phase. Since the solutes under discussion are relatively nonpolar, the interactions are of the London Force type or a *hydrophobic association*. This hydrophobic association in aqueous solutions may cause significant structuring of water with a resultant ordered or low-entropy system, unfavorable to solution. As is known, the solution of an essentially nonpolar molecule in water is not a favorable process. It should be stressed that this is due to not only an unfavorable enthalpy change but also an unfavorable entropy change generated by

water-structuring. Such an unfavorable entropy change is quite significant in the solution process. As an example of this effect, the aqueous solubility of a series of alkyl *p*-aminobenzoates shows a ten million-fold decrease in solubility in going from the 1-carbon analog to the 12-carbon analog. These findings demonstrate clearly the considerable effect that hydrophobic associations can have.

**Alcohols**—*Ethanol*, as a solvent, is next in importance to water. An advantage is that growth of microorganisms does not occur in solutions containing alcohol in a reasonable concentration.

Resins, volatile oils, alkaloids, glycosides, etc are dissolved by alcohol, while many therapeutically inert principles, such as gums, albumin and starch, are insoluble, which makes it more useful as a "selective" solvent. Mixtures of water and alcohol, in proportions varying to suit specific cases, are used extensively. They are often referred to as *hydroalcoholic* solvents.

*Glycerin* is an excellent solvent, although its range is not as extensive as that of water or alcohol. In higher concentrations it has preservative action. It dissolves the fixed alkalis, a large number of salts, vegetable acids, pepsin, tannin, some active principles of plants, etc, but it also dissolves gums, soluble carbohydrates, starch, etc. It is also of special value as a simple solvent, as in phenol glycerite, or where the major portion of the glycerin simply is added as a preservative and stabilizer of solutions that have been prepared with other solvents (see *Glycerines*, Chapter 84).

*Propylene glycol*, which has been used widely as a substitute for glycerin, is miscible with water, acetone or chloroform in all proportions. It is soluble in ether and will dissolve many essential oils but is immiscible with fixed oils. It is claimed to be as effective as ethyl alcohol in its power of inhibiting mold growth and fermentation.

*Isopropyl alcohol* possesses solvent properties similar to those of ethyl alcohol and is used instead of the latter in a number of pharmaceutical manufacturing operations. It has the advantage in that the commonly available product contains not over 1% of water, while ethyl alcohol contains about 5% water, often a disadvantage. Isopropyl alcohol is employed in some liniment and lotion formulations. It cannot be taken internally.

**General Properties**—Low-molecular-weight and polyhydroxy alcohols form associated structures through hydrogen bonds just as in water. When the carbon-atom content of an alcohol rises above five, generally only monomers then are present in the pure solvent. Although alcohols have high dielectric constants, compared to other types of solvents, they are small compared to water. As has been discussed, the solubility of salts in a solvent should be paralleled by its dielectric constant. That is, as the dielectric constant of a series of solvents increases, the probability of dissolving a salt in the solvent increases. This behavior is observed for the alcohols. Table IV, taken from Higuchi,<sup>4</sup> shows how the solubility of salts follows the dielectric constant of the alcohols.

As mentioned earlier, absolute alcohol rarely is used pharmaceutically. However, hydroalcoholic mixtures such as elixirs and spirits frequently are encountered. A very useful generalization is that the dielectric properties of a mixed solvent, such as water and alcohol, can be approximated as the weighted average of the properties of the pure components. Thus, a mixture of 60% alcohol (by weight) in water should have a dielectric constant approximated by

$$\epsilon_{(\text{mixture})} = 0.6(\epsilon_{(\text{alcohol})}) + 0.4(\epsilon_{(\text{water})})$$

$$\epsilon_{(\text{mixture})} = 0.6(25) + 0.4(80) = 47$$

The dielectric constant of 60% alcohol in water is found

Table IV—Solubilities of Potassium Iodide and Sodium Chloride in Several Alcohols and Acetone<sup>a</sup>

Solvent	g KI/ 100 g Solvent	g NaCl/ 100 g Solvent
Water	148	35.9
Glycerin	...	8.3 (20°)
Propylene Glycol	50	7.1 (30°)
Methanol	17	1.4
Acetone	2.9	...
Ethanol	1.88	0.065
1-Propanol	0.44	0.0124
2-Propanol	0.18	0.003
1-Butanol	0.20	0.005
1-Pentanol	0.089	0.0018

<sup>a</sup> All measurements are at 25°C unless otherwise indicated.

experimentally to be 43, which is in close agreement with that just calculated. The dielectric constant of glycerin is 46, close to the 60% alcohol mixture. One would, therefore, expect a salt like sodium chloride to have about the same solubility in glycerin as in 60% alcohol. The solubility of sodium chloride in glycerin is 8.3 g/100 g of solvent and in 60% alcohol about 6.3 g/100 g of solvent. This agreement would be even closer if comparisons were made on a volume rather than weight basis. At least qualitatively it can be said that the solubility of a salt in a solvent or a mixed solvent very closely follows the dielectric constant of the medium or, conversely, that the polarity of mixed solvents is paralleled by their dielectric constant, based on salt solubility.

Although the dielectric constant is useful in interpreting the effect of mixed solvents on salt solubility, it cannot be applied properly to the effect of mixed solvents on the solubility of nonelectrolytes. It was seen earlier that unfavorable entropic effects can occur upon dissolution of relatively nonpolar nonelectrolytes in water. Such an effect due to hydrophobic association considerably affects solubility. Yalkowsky<sup>5</sup> studied the ability of cosolvent systems to increase the solubility of nonelectrolytes in polar solvents where the cosolvent system essentially brings about a reduction in structuring of solvent. Thus, by increasing, in a positive sense, the entropy of solution by using cosolvents, it was possible to increase the solubility of the nonpolar molecule. Using as an example the solubility of alkyl *p*-aminobenzoates in propylene glycol-water systems, Yalkowsky<sup>5</sup> reported that it is possible to increase the solubility of the nonelectrolyte by several orders of magnitude by increasing the fraction of propylene glycol in the aqueous system. Sometimes, it is found that, as a good first approximation, the logarithm of the solubility is related linearly to the fraction of propylene glycol added by

$$\log S_f = \log S_{f=0} + \epsilon f$$

where  $S_f$  is the solubility in the mixed aqueous system containing the volume fraction  $f$  of nonaqueous cosolvent,  $S_{f=0}$  is the solubility in water and  $\epsilon$  is a constant (not dielectric constant) characteristic of the system under study. Specifically, when a 50% solution of propylene glycol in water is used, there is a 1000-fold increase in solubility of dodecyl *p*-aminobenzoate, in comparison to pure water.

In a series of studies, Martin *et al.*<sup>16</sup> have made attempts to predict solubility in mixed solvent systems through an extension of the "regular solution" theory. The equations are logarithmic in nature and can reduce in form to the equations of Yalkowsky.<sup>5</sup>

**Acetone and Related Semipolar Materials**—Even though acetone has a very high dipole moment ( $2.8 \times 10^{-18}$  esu), as a pure solvent it does not form associated structures.





Fig 16-9. The charge separation in acetone.

This is evidenced by its low boiling point ( $57^\circ$ ) in comparison with the boiling point of the lower-molecular-weight water ( $100^\circ$ ) and ethanol ( $79^\circ$ ). The reason why it does not associate is because the positive charge in its dipole does not reside in a hydrogen atom (Fig 16-9), precluding the possibility of its forming a hydrogen bond. However, if some substance which is capable of forming hydrogen bonds, such as water or alcohol, is added to acetone, a very strong interaction through hydrogen bonding will occur (see *Mechanism of Solvent Action* below). Some substances which are semipolar and similar to acetone are aldehydes, low-molecular-weight esters, other ketones and nitro-containing compounds.

**Nonpolar Solvents**—This class of solvents includes fixed oils such as vegetable oil, petroleum ether (ligroin), carbon tetrachloride, benzene and chloroform. On a relative basis there is a wide range of polarity among these solvents; for example, benzene has no dipole moment while that of chloroform is  $1.05 \times 10^{-18}$  esu. But even the polarity of these compounds normally classified as nonpolar is still in line with the dielectric constant of the solvent. The relation between these quantities is seen best through a quantity called *molar refraction*. The molar refraction (or *refractivity*),  $R$ , of a compound is given by

$$R = \frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{D} \quad (19)$$

where  $n$  is the refractive index of the liquid,  $M$  is its molecular weight and  $D$  is its density. The similarity between Eq 19 and Eq 16 is to be noted and, indeed, in refractive index measurements using very long wavelengths of light,  $n^2 = \epsilon$ . Thus, molar refraction under these conditions approximates total molar polarization. Since, in the more nonpolar solvents there is generally no dipole moment,  $\mu$ , total molar polarization reflects polarization due only to the induced dipoles possible. Thus

$$P_\alpha = \frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{D} = \frac{\epsilon - 1}{\epsilon + 2} \cdot \frac{M}{D} = \frac{4}{3} \pi N \alpha \quad (20)$$

It is evident from this that the refractive index of a nonpolar compound reflects its relative polarity. For example, the more-polar benzene ( $\epsilon = 2.2$ ) has a higher refractive index, 1.501, than the less-polar hexane ( $\epsilon = 1.9$ ), whose refractive index is 1.375.

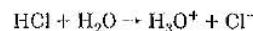
It should be emphasized again that when a solvent (such as chloroform) has highly electronegative halogen atoms attached to a carbon atom also containing at least one hydrogen atom, such a solvent will be capable of forming strong hydrogen bonds with solutes which are polar in character. Thus, through the formation of hydrogen bonds such solvents will dissolve polar solutes. For example, it is possible to dissolve alkaloids in chloroform.

#### Mechanism of Solvent Action

A solvent may function in one, or more, of several ways. When an ionic salt is dissolved, eg, by water, the process of solution involves separation of the cations and anions of the salt with attendant orientation of molecules of the solvent about the ions. Such orientation of solvent molecules about the ions of the solute—a process called *solvation* (*hydration*, if the solvent is water)—is possible only when the solvent is highly polar, whereby, the dipoles of the solvent are attracted to and held by the ions of the solute. The solvent also

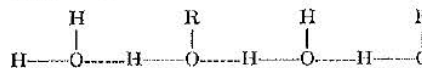
must possess the ability to keep the solvated, charged ions apart with minimal energy. The role of the dielectric constant in keeping this energy to a minimum has been discussed earlier.

A polar liquid such as water may exhibit solvent action also by virtue of its ability to break a covalent bond in the solute and bring about ionization of the latter. For example, hydrogen chloride dissolves in water and functions as an acid as a result of



The ions formed by this preliminary reaction of breaking the covalent bond subsequently are maintained in solution by the same mechanism as ionic salts.

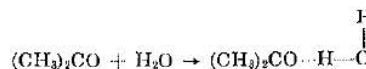
Still another mechanism by which a polar liquid may act as a solvent is that involved when the solvent and solute are capable of being coupled through hydrogen-bond formation. The solubility of the low-molecular-weight alcohols in water, for example, is attributed to the ability of the alcohol molecules to become part of a water-alcohol association complex.



As the molecular weight of the alcohol increases, it becomes progressively less polar and less able to compete with water molecules for a place in the lattice-like arrangement formed through hydrogen bonding; high-molecular-weight alcohols are, therefore, poorly soluble or insoluble in water. When the number of carbon atoms in a normal alcohol reaches five, its solubility in water is reduced materially.

When the number of hydroxyl groups in the alcohol is increased, its solubility in water generally is increased greatly; it is principally, if not entirely, for this reason that such high-molecular-weight compounds as sugars, gums, many glycosides and synthetic compounds, such as the polyethylene glycols, are very soluble in water.

The solubility of ethers, aldehydes, ketones, acids and anhydrides in water, and in other polar solvents, also is attributable largely to the formation of an association complex between solute and solvent by means of the hydrogen bond. The molecules of ethers, aldehydes and ketones, unlike those of alcohols, are not associated themselves, because of the absence of a hydrogen atom which is capable of forming the characteristic hydrogen bond. Notwithstanding, these substances are more or less polar because of the presence of a strongly electronegative oxygen atom, which is capable of association with water through hydrogen-bond formation. Acetone, for example, dissolves in water, in all likelihood, principally because of the following type of association:



The maximum number of carbon atoms which may be present per molecule possessing a hydrogen-bondable group, while still retaining water solubility, is approximately the same as for the alcohols.

Although nitrogen is less electronegative than oxygen and, thus, tends to form weaker hydrogen bonds, it is observed that amines are at least as soluble as alcohols containing an equivalent chain length. The reason for this is that alcohols form two hydrogen bonds with a net interaction of 12 kcal/mole. Primary amines can form three hydrogen bonds; two amine protons are shared with the oxygens of two water molecules, and the nitrogen accepts one water proton. The net interaction for the primary amine is between 12 and 13 kcal/mole and, hence, it shows an equal or greater solubility compared with corresponding alcohols.

The solvent action of nonpolar liquids involves a somewhat different mechanism. Because they are unable to form dipoles with which to overcome the attractions between ions of an ionic salt, or to break a covalent bond to produce an ionic compound or form association complexes with a solute, nonpolar liquids are incapable of dissolving polar compounds. They only can dissolve, in general, other nonpolar substances in which the bonds between molecules are weak. The forces involved usually are of the induced dipole-induced dipole type. Such is the case when one hydrocarbon is dissolved in another, or an oil or a fat is dissolved in petroleum ether. Sometimes it is observed that a polar substance, such as alcohol, will dissolve in a nonpolar liquid, such as benzene. This apparent exception to the preceding generalization may be explained by the assumption that the alcohol molecule induces a temporary dipole in the benzene molecule which forms an association complex with the solvent molecules. A binding force of this kind is referred to as a *permanent dipole-induced dipole force*.

**Some Useful Generalizations**—The preceding discussion indicates that enough is known about the mechanism of solubility to be able to formulate some generalizations concerning this important physical property of substances. Because of the greater importance of organic substances in the field of medicinal chemistry, certain of the more useful generalizations with respect to organic chemicals are presented here in summary form. It should be remembered, however, that the phenomenon of solubility usually involves several variables, and there may be exceptions to general rules.

One general maxim which holds true in most instances is: *the greater the structural similarity between solute and solvent, the greater the solubility*. As often stated to the student, "like dissolves like." Thus, phenol is almost insoluble in petroleum ether but is very soluble in glycerin.

Organic compounds containing polar groups capable of forming hydrogen bonds with water are soluble in water, providing that the molecular weight of the compound is not too great. It is demonstrated easily that the polar groups OH, CHO, COH, C(OH), CH<sub>2</sub>OH, COOH, NO<sub>2</sub>, CO, NH<sub>2</sub> and SO<sub>3</sub>H tend to increase the solubility of an organic compound in water. On the other hand, nonpolar or very weak polar groups, such as the various hydrocarbon radicals, reduce solubility; the greater the number of carbon atoms in the radical, the greater the decrease in solubility. Introduction of halogen atoms into a molecule in general

Table V—Demonstration of Solubility Rules

Chemical Compound	Solubility <sup>a</sup>
Aniline, C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	28.6
Benzene, C <sub>6</sub> H <sub>6</sub>	1430
Benzoic acid, C <sub>6</sub> H <sub>5</sub> COOH	275
Benzyl alcohol, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> OH	25
1-Butanol, C <sub>4</sub> H <sub>9</sub> OH	12
<i>t</i> -Butyl alcohol, (CH <sub>3</sub> ) <sub>2</sub> COH	Miscible
Carbon tetrachloride, CCl <sub>4</sub>	2000
Chloroform, CHCl <sub>3</sub>	200
Fumaric acid, <i>trans</i> -butenedioic acid	150
Hydroquinone, C <sub>6</sub> H <sub>4</sub> (OH) <sub>2</sub>	14
Maleic acid, <i>cis</i> -butenedioic acid	5
Phenol, C <sub>6</sub> H <sub>5</sub> OH	15
Pyrocatechol, C <sub>6</sub> H <sub>4</sub> (OH) <sub>2</sub>	2.3
Pyrogallol, C <sub>6</sub> H <sub>3</sub> (OH) <sub>3</sub>	1.7
Resorcinol, C <sub>6</sub> H <sub>4</sub> (OH) <sub>2</sub>	0.9

<sup>a</sup> The number of ml. of water required to dissolve 1 g. of solute.

tends to decrease solubility because of an increased molecular weight without a proportionate increase in polarity.

The greater the number of polar groups contained per molecule, the greater the solubility of a compound, provided that the size of the rest of the molecule is not altered; thus, pyrogallol is much more soluble in water than phenol. The *relative positions* of the groups in the molecule also influence solubility; thus, in water, resorcinol (*m*-dihydroxybenzene) is more soluble than catechol (*o*-dihydroxybenzene), and the latter is more soluble than hydroquinone (*p*-dihydroxybenzene).

Polymers and compounds of high molecular weight generally are insoluble or only very slightly soluble.

High melting points frequently are indicative of low solubility for organic compounds. One reason for high melting points is the *association* of molecules and this cohesive force tends to prevent dispersion of the solute in the solvent.

The *cis* form of an isomer is more soluble than the *trans* form. See Table V.

*Solvation*, which is evidence of the existence of a strong attractive force between solute and solvent, enhances the solubility of the solute, provided there is not a marked ordering of the solvent molecules in the solution phase.

*Acids*, especially strong acids, usually produce water-soluble salts when reacted with nitrogen-containing organic bases.

## Colligative Properties of Solutions

Up to this point concern has been with dissolving a solute in a solvent. Having brought about the dissolution, the solution, quite naturally, has a number of properties which are different from that of the pure solvent. Of very great importance are the *colligative properties* which a solution possesses.

The colligative properties of a solution are those that depend on the *number* of solute particles in solution, irrespective of whether these are molecules or ions, large or small. Ideally, the effect of a solute particle of one species is considered to be the same as that of an entirely different kind of particle, at least in dilute solution. Practically, there may be differences which may become substantial as the concentration of the solution is increased.

The colligative properties which will be considered are:

1. Osmotic pressure.
2. Vapor-pressure lowering.
3. Boiling-point elevation.
4. Freezing-point depression.

Of these four, all of which are related, osmotic pressure has the greatest direct importance in the pharmaceutical sciences. It is the property that largely determines the physiological acceptability of a variety of solutions used for therapeutic purposes.

### Osmotic-Pressure Elevation

**Diffusion in Liquids**—Although the property of diffusion is rapid in gaseous systems, it is not limited to such systems. That molecules or ions in liquid systems possess this same freedom of movement may be demonstrated by placing carefully a layer of water on a concentrated aqueous solution of any salt. In time it will be observed that the boundary between solvent and solution widens gradually since salt moves into the water layer and water migrates from its layer into the salt solution below. Eventually, the composition of the new solution will become uniform throughout. This experiment indicates that *substances tend to move or diffuse from regions of higher concentration to regions of lower concentrations* so that differences in concentration eventually disappear.

**Osmosis**—In carrying out the experiment just described, it is impossible to distinguish between the diffusion of the solute and that of the solvent. However, by separating the solution and the solvent by means of a membrane that is permeable to the solvent, but not to the solute (such a membrane is referred to as a *semipermeable* membrane), it is possible to demonstrate visibly the diffusion of solvent into the concentrated solution, since volume changes will occur. In a similar manner, if two solutions of different concentra-

tion are separated by a membrane, the solvent will move from the solution of lower solute concentration to the solution of higher solute concentration. This diffusion of solvent through a membrane is called *osmosis*.

There is a difference between the activity or escaping tendency of the water molecules found in the solvent and salt solution separated by the semipermeable membrane. Since *activity*, which is related to water concentration, is higher on the pure solvent side, water moves from solvent to solution in order to equalize escaping-tendency differences. The difference in *escaping-tendency* gives rise to what is referred to as the *osmotic pressure* of the solution, which might be visualized as follows. A semipermeable membrane is placed over the end of a tube and a small amount of salt solution placed over the membrane in the tube. The tube then is immersed in a trough of pure water so that the upper level of the salt solution initially is at the same level as the water in the trough. With time, solvent molecules will move from solvent into the tube. The height of the solution will rise until the *hydrostatic pressure* exerted by the column of solution is equal to the *osmotic pressure*.

**Osmotic Pressure of Nonelectrolytes**—From quantitative studies with solutions of varying concentration of a solute that does not ionize, it has been demonstrated that *osmotic pressure is proportional to the concentration of the solute*; i.e., twice the concentration of a given nonelectrolyte will produce twice the osmotic pressure in a given solvent. (This is not strictly true in solutions of fairly high solute concentration, but does hold quite well for dilute solutions.)

Furthermore, the osmotic pressures of solutions of different nonelectrolytes are proportional to the number of molecules in each solution. Stated in another manner, the osmotic pressures of two nonelectrolyte solutions of the same molal concentration are identical. Thus, a solution containing 34.2 g of sucrose (mol wt 342) in 1000 g of water has the same osmotic pressure as a solution containing 18.0 g of anhydrous dextrose (mol wt 180) in 1000 g of water. These solutions are said to be *isosmotic* with each other because they have identical osmotic pressures.

A study of the results of osmotic-pressure measurements on different substances led the Dutch chemist Jacobus Henricus van't Hoff, in 1885, to suggest that the solute in a solution may be considered as being analogous to the molecules of a gas and the osmotic pressure as being produced by the bombardment of the semipermeable membrane by the molecules of solute. According to van't Hoff's theory the osmotic pressure of a solution is equal to the pressure which the dissolved substance would exert in the gaseous state if it occupied a volume equal to the volume of the solution. From this it follows that, just as in the case of a gas, there is a proportionality between pressure and concentration of dissolved substance. This proportionality is illustrated well by the values of the osmotic pressure of solutions of sucrose at 0° as determined by the Earl of Berkeley and EGJ Hartley and shown in Table VI.

In column *PV* of Table VI a quantitative confirmation, at least for fairly dilute solutions, of van't Hoff's oversimplified

Table VI—Osmotic Pressure of Sucrose Solutions

Conc. (g/L), C	Vol in L in Which 1 g Mole is Dissolved, V <sup>a</sup>	Pressure in Atmos P	P/C	PV
10.00	34.2	0.65	0.065	22.2
20.00	17.1	1.27	0.064	21.7
45.00	7.60	2.91	0.065	22.1
93.75	3.65	6.23	0.067	22.7

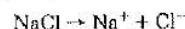
<sup>a</sup> These figures were obtained by calculating the volume of solution in which 342 (mol wt) g of sucrose would be dissolved.

though useful generalization is shown by the constancy of the values of the product *PV*. Recall that the product of the pressure and the volume of a gas, at constant temperature, is likewise constant (Boyle's law).

Van't Hoff also deduced that the osmotic pressure must be proportional to the absolute temperature, just as in Charles' law for gases, which deduction was confirmed by the experiments of several workers. From this it follows that the equation  $PV = nRT$  is valid for dilute solutions of nonelectrolytes just as a similar equation is valid for gases. However, even as Boyle's law does not apply to gases under high pressures and at low temperatures, so van't Hoff's equation for osmotic pressure does not apply in concentrated solutions.

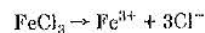
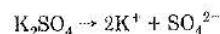
**Osmotic Pressure of Electrolytes**—In discussing the generalizations concerning the osmotic pressure of solutions of nonelectrolytes it was stated that the osmotic pressures of two solutions of the same molal concentration are identical. This generalization, however, cannot be made for solutions of electrolytes, i.e., acids, alkalies and salts (see Chapter 17).

For example, sodium chloride is assumed to ionize as



It is evident that each molecule of sodium chloride that ionizes produces two ions and, if sodium chloride is completely ionized, there will be twice as many particles as would be the case if it were not ionized at all. Furthermore, if each ion has the same effect on osmotic pressure as a molecule, it might be expected that the osmotic pressure of the solution would be twice that of a solution containing the same molal concentration of nonionizing substance.

For solutions which yield more than two ions as, for example



it is to be expected that the complete dissociation of the molecules would give rise to osmotic pressures that are three and four times, respectively, the pressure of solutions containing an equivalent quantity of a nonionized solute. Accordingly, the equation  $PV = nRT$ , which may be employed to calculate the osmotic pressure of a dilute solution of a nonelectrolyte, also may be applied to dilute solutions of electrolytes if it is changed to  $PV = inRT$ , where the value of *i* approaches the number of ions produced by the ionization of the strong electrolytes cited in the preceding examples. For weak electrolytes *i* represents the total number of particles, ions and molecules together, in the solution, divided by the number of molecules that would be present if the solute did not ionize. The experimental evidence indicates that in dilute solutions, at least, the osmotic pressures approach the predicted values. It should be emphasized, however, that in more concentrated solutions of electrolytes the deviations from this simple theory are considerable, due to interionic attraction, solvation and other factors.

**Biological Aspects of Osmotic Pressure**—Osmotic-pressure experiments were made as early as 1884 by the Dutch botanist Hugo de Vries in his study of plasmolysis, which term is applied to the contraction of the contents of plant cells placed in solutions of comparatively high osmotic pressure. The phenomenon is caused by the osmosis of water out of the cell through the practically semipermeable membrane surrounding the protoplasm. If suitable cells (eg, the epidermal cells of the leaf of *Tradescantia discolor*) are placed in a solution of higher osmotic pressure than that of the cell contents, water flows out of the cell, causing the contents to draw away from the cell wall. On the other hand, if the cells are placed in solutions of lower osmotic pressure, water enters the cell, producing an expansion



which is limited by the rigid cell wall. By immersing cells in a series of solutions of varying solute concentration, a solution may be found in which plasmolysis is barely detectable or absent. The osmotic pressure of such a solution is then the same, or very nearly the same, as that of the cell contents, and it is then said that the solution is *isotonic* with the cell contents. Solutions of greater concentration than this are said to be *hypertonic* and solutions of lower concentration, *hypotonic*.

Red blood cells, or erythrocytes, have been studied similarly by immersion into solutions of varying concentration of different solutes. When introduced into water or into sodium chloride solutions containing less than 0.90 g of solute per 100 mL, human erythrocytes swell, and often burst, because of the diffusion of water into the cell and the fact that the cell wall is not sufficiently strong to resist the pressure. This phenomenon is referred to as *hemolysis*. If the cells are placed in solutions containing more than 0.90 g of sodium chloride per 100 mL, they lose water and shrink. By immersing the cells in a solution containing exactly 0.90 g of sodium chloride in 100 mL, no change in the size of the cells is observed; since in this solution the cells maintain their "tone," the solution is said to be *isotonic* with human erythrocytes. For the reasons indicated it is desirable that solutions to be injected into the blood should be made isotonic with erythrocytes. The manner in which this may be done is described in Chapter 79.

**Distinction between Isoosmotic and Isotonic**—The terms isoosmotic and isotonic are not to be considered as equivalent, although a solution often may be described as being both isoosmotic and isotonic. If a plant or animal cell is in contact with a solution that has the same osmotic pressure as the cell contents, there will be no net gain or loss of water by either solution *provided* the cell membrane is impermeable to all the solutes present. Since the volume of the cell contents remains unchanged, the "tone", or normal state, of the cell is maintained, and the solution in contact with the cell may be described not only as being isoosmotic with the solution in the cell, but also as being isotonic with it. If, however, one or more of the solutes in contact with the membrane can pass through the latter, it is evident that the volume of the cell contents will change, thus altering the "tone" of the cell; in this case the two solutions may be isoosmotic, yet not be isotonic.

It is possible that some substances used in an injection dosage form can cause hemolysis of red blood cells, even when their concentrations are such as to produce solutions theoretically isoosmotic with the cells, because the solutes diffuse through the membrane of the cells. For example, a 1.8% solution of urea has the same osmotic pressure as a 0.9% solution of sodium chloride, but the former solution produces hemolysis of red blood cells; obviously the urea solution is not isotonic with the cells. To determine if a solution is isotonic with erythrocytes, it is necessary to determine the concentration of solute at which the cells retain their normal size and shape. A simple method for doing this was devised by Setnikar and Temelcou,<sup>7</sup> who determined the concentration of a solution at which red blood cells maintained a volume equal to that occupied in an isotonic solution of sodium chloride. The red cell volumes were determined by centrifuging suspensions of them in different solutions, using a hematocrit tube.

### Vapor-Pressure Lowering

When a nonvolatile solute is dissolved in a liquid solvent the vapor pressure of the solvent is lowered. This easily can be described qualitatively by visualizing solvent molecules on the surface of the solvent, which normally could escape

into the vapor, being replaced by solute molecules which have little if any vapor pressure of their own. For ideal solutions of nonelectrolytes the vapor pressure of the solution follows Raoult's law

$$P_A = X_A P_A^\circ \quad (21)$$

where  $P_A$  is the vapor pressure of the solution,  $P_A^\circ$  is the vapor pressure of the pure solvent and  $X_A$  is the mole fraction of solvent. This relationship states that the vapor pressure of the solution is proportional to the number of molecules of solvent in the solution. Rearranging Eq 21 gives

$$\frac{P_A^\circ - P_A}{P_A^\circ} = (1 - X_A) = X_B \quad (22)$$

where  $X_B$  is the mole fraction of the solute. This equation states that the lowering of vapor pressure in the solution relative to the vapor pressure of the pure solvent—called simply the *relative vapor-pressure lowering*—is equal to the mole fraction of the solute. The *absolute* lowering of vapor pressure of the solution is defined by

$$P_A^\circ - P_A = X_B P_A^\circ \quad (23)$$

**Example**—Calculate the lowering of vapor pressure and the vapor pressure at 20° of a solution containing 50 g of anhydrous dextrose (mol wt 180.16) in 1000 g of water (mol wt 18.02). The vapor pressure of water at 20°, in absence of air, is 17.535 mm.

First, calculate the lowering of vapor pressure, using Eq 23, in which  $X_B$  is the mole fraction of dextrose, defined by

$$X_B = \frac{n_B}{n_A + n_B}$$

where  $n_A$  is the number of moles of solvent and  $n_B$  is the number of moles of solute. Substituting numerical values

$$n_B = \frac{50}{180.2} = 0.278$$

$$n_A = \frac{1000}{18.02} = 55.5$$

$$X_B = \frac{0.278}{55.5 + 0.278} = 0.00498$$

the lowering of vapor pressure is

$$\begin{aligned} P_A^\circ - P_A &= 0.00498 \times 17.535 \\ &= 0.0873 \text{ mm} \end{aligned}$$

The vapor pressure of the solution is

$$\begin{aligned} P_A &= 17.535 - 0.0873 \\ &= 17.448 \text{ mm} \end{aligned}$$

### Boiling-Point Elevation

In consequence of the fact that the vapor pressure of any solution of a nonvolatile solute is less than that of the solvent, the boiling point of the solution—the temperature at which the vapor pressure is equal to the applied pressure (commonly 760 mm)—must be higher than that of the solvent. This is clearly evident in Fig 16-10.

The relationship between the elevation of boiling point and the concentration of nonvolatile, nonelectrolyte solute may be derived from the Clausius-Clapeyron equation (see Chapter 15), which is

$$\frac{dP}{dT} = \frac{P \cdot \Delta H_{\text{vap}}}{RT^2} \quad (24)$$

Replacing the differential expression  $dP/dT$  by  $\Delta P/\Delta T_b$ , where  $\Delta P$  is the lowering of vapor pressure and  $\Delta T_b$  is the

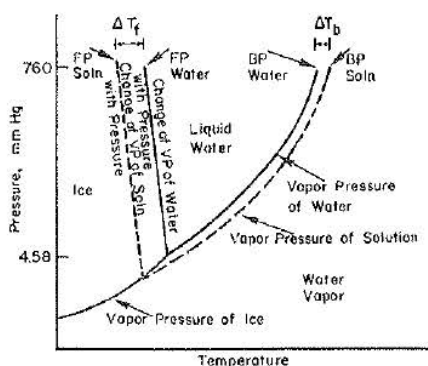


Fig 16-10. Vapor-pressure-temperature diagram for water and an aqueous solution, illustrating elevation of boiling point and lowering of freezing point of the latter.

elevation of boiling point, and introducing  $P_A^\circ$ , the vapor pressure of the solvent at its boiling point  $T_b$ , results in

$$\frac{\Delta P}{\Delta T_b} = \frac{P_A^\circ \cdot \Delta H_{\text{vap}}}{RT_b^2} \quad (25)$$

Since the lowering of vapor pressure in an ideal solution is

$$\Delta P = X_B P_A^\circ \quad (26)$$

substitution of this equation into Eq 25, with rearrangement to provide a solution for  $\Delta T_b$ , gives

$$\Delta T_b = \frac{RT_b^2}{\Delta H_{\text{vap}}} X_B \quad (27)$$

This equation may be used to calculate the elevation of the boiling point if the concentration of solute is expressed as the mole fraction. A more common expression, however, is in terms of the molality  $m$  (the number of gram-moles of solute per 1000 g of solvent), which relationship is derived as

$$X_B = \frac{n_B}{n_A + n_B} = \frac{m}{1000/M_A + m} \approx \frac{m}{1000/M_A} \quad (28)$$

In these equations  $M_A$  is the molecular weight of the solvent. When the solutions are dilute, so that  $m$  is small, it may be neglected in the denominator (*but not in the numerator!*) to give the approximate equivalent in Eq 28. Substituting this equivalent into Eq 27 gives

$$\Delta T_b = \frac{RT_b^2 M_A m}{1000 \Delta H_{\text{vap}}} \quad (29)$$

Grouping the constants into a single term results in

$$\Delta T_b = K_b m \quad (30)$$

where

$$K_b = \frac{RT_b^2 M_A}{1000 \Delta H_{\text{vap}}} \quad (31)$$

and is called the molal boiling-point elevation constant.

The value of this constant for water, which boils at 373.1° K, has a heat of vaporization of 539.7 cal/g and a molecular weight of 18.02, is

$$K_b = \frac{1.987 \times 373.1^2 \times 18.02}{1000 \times 18.02 \times 539.7} = 0.513^\circ \quad (32)$$

Notwithstanding that  $K_b$  is called a molal boiling-point elevation constant, it should not be interpreted as the actual rise of boiling point for a 1-molal solution. Such solutions are generally too concentrated to exhibit the ideal behavior

assumed in deriving the equation for calculating the theoretical value of the constant. In dilute solutions, however, the actual boiling-point elevation, *calculated to a 1-molal basis*, approaches the theoretical value, the closer the more dilute the solution.

The elevation of boiling point of a dilute solution of a nonelectrolyte solute may be used to calculate the mol wt of the latter. In a solution containing  $w_B$  g of solute of  $M_B$  in  $w_A$  g of solvent the molality  $m$  is

$$m = \frac{1000 w_B}{w_A M_B} \quad (33)$$

substituting this into Eq 30 and rearranging gives

$$M_B = \frac{K_b 1000 w_B}{w_A \Delta T_b} \quad (34)$$

### Freezing-Point Depression

The freezing point of a solvent is defined as the temperature at which the solid and liquid forms of the solvent coexist in equilibrium at a fixed external pressure, commonly 1 atm (760 mm of mercury). At this temperature the solid and liquid forms of the solvent must have the same vapor pressure, for if this were not so, the form having the higher vapor pressure would change into that having the lower vapor pressure.

The freezing point of a solution is the temperature at which the solid form of the pure solvent coexists in equilibrium with the solution at a fixed external pressure, again commonly 1 atm. Since the vapor pressure of a solution is lower than that of its solvent, it is obvious that solid solvent and solution cannot coexist at the same temperature as solid solvent and liquid solvent; only at some lower temperature, where solid solvent and solution do have the same vapor pressure, is equilibrium established. A schematic pressure-temperature diagram for water and an aqueous solution, not drawn to scale and exaggerated for the purpose of more effective illustration, shows the equilibrium conditions involved in both freezing-point depression and boiling-point elevation (Fig 16-10).

The freezing-point lowering of a solution may be quantitatively predicted for ideal solutions, or dilute solutions which obey Raoult's law, by mathematical operations similar to (though somewhat more complex than) those used in deriving the boiling-point elevation constant. The equation for the freezing point lowering,  $\Delta T_f$ , is

$$\Delta T_f = \frac{RT_f^2 M_A m}{1000 \Delta H_{\text{fus}}} = K_f m \quad (35)$$

where

$$K_f = \frac{RT_f^2 M_A}{1000 \Delta H_{\text{fus}}} \quad (36)$$

The value of  $K_f$  for water, which freezes at 273.1° K and has a heat of fusion of 79.7 cal/g, is

$$K_f = \frac{1.987 \times 273.1^2 \times 18.02}{1000 \times 18.02 \times 79.7} = 1.86^\circ \quad (37)$$

The molal freezing-point depression constant is not intended to represent the freezing-point depression for a 1-molal solution, which is too concentrated for the premise of ideal behavior to be applicable. In dilute solutions the freezing-point depression, calculated to a 1-molal basis, approaches the theoretical value, the agreement between experiment and theory being the better the more dilute the solution.

The freezing point of a dilute solution of a nonelectrolyte solute may be used, as was the boiling point, to calculate the molecular weight of the solute. The applicable equation is

$$M_B = \frac{K_f 1000 w_B}{w_A \Delta T_f} \quad (38)$$

The molecular weight of organic substances soluble in molten camphor may be determined by observing the freezing point of a mixture of the substance with camphor. This procedure, called the *Rast method*, uses camphor because it has a very large molal freezing-point-depression constant, about  $40^\circ$ . Since the "constant" may vary with different lots of camphor and with variations of technique, the method should be standardized using a solute of known molecular weight.

Freezing-point determinations of molecular weights have the advantage over boiling-point determinations of greater accuracy and precision by virtue of the larger magnitude of the freezing-point depression compared to boiling-point elevation. Thus, in the case of water the molal freezing-point depression is approximately 3.5 times greater than the molal boiling-point elevation.

### Relationship between Osmotic Pressure and Vapor-Pressure Depression

The lowering of vapor pressure and the development of osmotic pressure in a solution are both manifestations of the basic condition that the free energy of solvent molecules in the pure solvent is greater than the free energy of solvent molecules in the solution. Consequently, solvent molecules will transfer spontaneously, if given an opportunity, from solvent to solution until equilibrium conditions are established. The transfer can take place either through a membrane permeable only to solvent molecules or, if such contact between solvent and solution is not available, by distillation of solvent from pure solvent to solution, if access through a vapor phase is provided.

If an experiment is performed with two sets of vessels containing solution and solvent, as illustrated in Fig 16-11, differing only in that the long tube of one set has a semipermeable membrane attached to its lower end, while in the

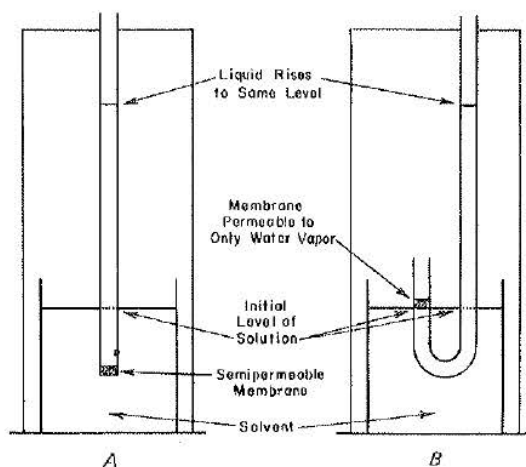


Fig 16-11. Transfer of solvent to equal volumes of solution. A: Osmotically, through a semipermeable membrane separating solution and solvent. B: By distillation, through a membrane separating solution and solvent vapor.

other a hypothetical membrane separates the vapor phases, in time the same hydrostatic pressure should develop in both cases. For a definite volume, eg, a mole, of solvent transferred to the solution by distillation the change of free energy,  $\Delta G$ , in the process is

$$\Delta G = RT \ln \frac{P_A}{P_A^\circ} \quad (39)$$

where  $P_A$  is the vapor pressure of the solution and  $P_A^\circ$  is the vapor pressure of the solvent.

For the transfer of the same volume of solvent by osmosis the free-energy change is

$$\Delta G = -\bar{V}_A \pi \quad (40)$$

where  $\bar{V}_A$  is the partial molal volume of solvent (the volume of 1 mole of solvent in the solution) and  $\pi$  is the osmotic pressure of the solution. Since the free-energy change is the same in both processes

$$-\bar{V}_A \pi = RT \ln \frac{P_A}{P_A^\circ} \quad (41)$$

rearranging the equation yields

$$\pi = \frac{RT}{\bar{V}_A} \ln \frac{P_A^\circ}{P_A} \quad (42)$$

With this equation the osmotic pressure of a solution may be calculated if its vapor pressure and the partial molal volume of the solvent are known, not only when the solution is sufficiently dilute that Raoult's law is obeyed but also when the concentration is so high as to introduce substantial deviation from the law.

From Eq 42, which has some resemblance to van't Hoff's empirical equation  $\pi V = nRT$  for dilute solutions, the latter equation may be derived as follows. If a solution is sufficiently dilute to correspond to Raoult's law, then

$$P_A = X_A P_A^\circ = (1 - X_B) P_A^\circ \quad (43)$$

and then Eq 42 may be written

$$\pi = -\frac{RT}{\bar{V}_A} \ln(1 - X_B) \quad (44)$$

When  $X_B$  is small (as in a dilute solution), the term  $-\ln(1 - X_B)$  can be shown to be approximately equal to  $X_B$ , so that

$$\pi = \frac{RT}{\bar{V}_A} X_B \quad (45)$$

In dilute solutions the approximations  $X_B = n_B/n_A$  (where  $n_B$  and  $n_A$  are the moles of solute and solvent, respectively) and  $\bar{V}_A = V/n_A$  (where  $V$  is the volume of solution) may be introduced, yielding

$$\pi V = n_B RT \quad (46)$$

which is van't Hoff's equation.

### Ideal Behavior and Deviations

In setting out to derive mathematical expressions for colligative properties, such phrases as "for ideal solutions" or "for dilute solutions" were used to indicate the limitations of the expressions. Samuel Glasstone defines an ideal solution as "one which obeys Raoult's law over the whole range of concentration and at all temperatures" and gives as specific characteristics of such solutions their formation only from constituents which mix in the liquid state without heat change and without volume change. These characteristics reflect the fact that addition of a solute to a solvent produces no change in the forces between molecules of the solvent.

Thus, the molecules have the same *escaping-tendency* in the solution as in the pure solvent and the vapor pressure above the solution is proportional to the ratio of the number of solvent molecules in the surface of the solution to the number of the molecules in the surface of the solvent—which is the basis for Raoult's law.

Any change in intermolecular forces produced by mixing the components of a solution may result in deviation from ideality; such a deviation may be expected particularly in solutions containing both a polar and a nonpolar substance. Solutions of electrolytes, except at high dilution, are especially prone to depart from ideal behavior, even though allowance is made for the additional particles that result from ionization. When solute and solvent combine to form solvates, the escaping-tendency of the solvent may be reduced in consequence of the reduction in the number of free molecules of solvent; thus, a negative deviation from Raoult's law is introduced. On the other hand, the escaping-tendency of the solvent, in a solution of nonvolatile solute, may be increased because the cohesive forces between molecules of solvent are reduced by the solute; this results in a positive deviation from Raoult's law. Chapter 17 considers deviations from ideality in more detail.

While few solutions exhibit ideal behavior over a wide range of concentration, most solutions behave ideally at least in high dilution, where deviations from Raoult's law are negligible.

**Comparison of Colligative Properties**—In view of the established interrelationships of the colligative properties of ideal solutions or very dilute real solutions, it is possible to predict, by calculation, the magnitude of all these properties of such solutions if the concentration of the nonelectrolyte solute is given. Also, if the magnitude of one of the properties, eg, the freezing point, is known for a solution of unspecified concentration, it is possible to calculate the vapor pressure, boiling point and osmotic pressure, provided the solution is ideal or sufficiently dilute to show negligible deviation from ideality. To what upper limit of concentration a nonideal solution remains "sufficiently dilute" to show ideal behavior is difficult to specify. The answer depends at least in part on the degree of agreement expected between experimental and theoretical values. Certainly, a 1-molal concentration is much too concentrated for a nonideal solution to show conformance with ideal behavior and even in 0.1-molal concentration, deviations are significant and for some purposes may be excessive.

In dealing with colligative properties of solutions which do not behave ideally, caution should be exercised in attempting to predict the magnitude of other colligative properties from one that has been determined experimentally. Earlier, an equation was derived for calculating the vapor pressure of a solution from its osmotic pressure, or *vice versa*, this equation being valid even with solutions showing substantial departures from ideal behavior. The equation is limited, however, to a comparison of these colligative properties at the same temperature. The degree of deviation from ideal behavior for one colligative property will be exactly the same for another only when the temperature is the same for both. It does not follow that the degree of deviation of the colligative properties of a given nonideal solution will be the same for all the properties since at least two of these (freezing point and boiling point) must be determined at quite different temperatures. While in dilute solutions the intermolecular (and/or interionic) forces and interactions may change little over the temperature interval between freezing and boiling, in concentrated solutions the change may be marked. In the absence of adequate knowledge about the forces and interactions involved, only by experiment can one establish the magnitude of the colligative properties of other than very dilute nonideal solutions. It is important to keep

this in mind in estimating the osmotic pressure of a nonideal solution at body temperature from a freezing point determined some 37° lower. While in many cases—possibly the majority of them—such an estimate is warranted by virtue of essential constancy of the various forces and interactions over a wide range of temperature, this is not always the case and the estimate may be significantly inaccurate.

**Colligative Properties of Electrolyte Solutions** [See Chapter 17]—Earlier in this chapter attention was directed to the increased osmotic pressure observed in solutions of electrolytes, the enhanced effect being attributed to the presence of ions, each of which acts, in general, in the same way as a molecule in developing osmotic pressure. Similar magnification of vapor-pressure lowering, boiling-point elevation and freezing-point depression occurs in solutions of electrolytes. Thus, at a given constant temperature the abnormal effect of an electrolyte on osmotic pressure is paralleled by abnormal lowering of vapor pressure; the other colligative properties are, subject to variation of effect with temperature, comparably intensified. In general the magnitude of each colligative property is proportional to the total number of particles (molecules and/or ions) in solution.

While in very dilute solutions the osmotic pressure, vapor-pressure lowering, boiling-point increase and freezing-point depression of solutions of electrolytes would approach values 2, 3, 4, etc times greater for NaCl, Na<sub>2</sub>SO<sub>4</sub> and Na<sub>3</sub>PO<sub>4</sub> than in solutions of the same molality of a nonelectrolyte, two other effects are observed as the concentration of electrolyte is increased. The first effect results in less than 2-, 3- or 4-fold intensification of a colligative property. This reduction is ascribed to interionic attraction between the positively and negatively charged ions, in consequence of which the ions are not completely dissociated from each other and do not exert their full effect in lowering vapor pressure, etc. This deviation generally increases with increasing concentration of electrolyte. The second effect intensifies the colligative properties and is attributed to the attraction of ions for solvent molecules, which holds the solvent in solution and reduces its escaping-tendency, with consequent enhancement of the vapor-pressure lowering. Solvation also may reduce interionic attraction and thereby further lower the vapor pressure. These factors (and possibly others) combine to effect a progressive reduction in the molal values of colligative properties as the concentration of electrolyte is increased to 0.5 to 1 molal, beyond which the molal quantities either increase, sometimes quite abruptly, or remain almost constant.

### Activity and Activity Coefficient

Various mathematical expressions are employed to relate properties of chemical systems (equilibrium constants, colligative properties, pH, etc) to the stoichiometric concentration of one or more molecular, atomic or ionic species. In deriving such expressions it either is stated or implied that they are valid only so long as intermolecular, interatomic and/or interionic forces may be ignored or remain constant, under which restriction the system may be expected to behave ideally. But intermolecular, interatomic and/or interionic forces do exist, and not only do they change as a result of chemical reaction but also with variation in the concentration or pressure of the molecules, atoms or ions under observation. In consequence, mathematical expressions involving stoichiometric concentrations or pressures generally have limited applicability. The conventional concentration terms, while providing a count of molecules, atoms or ions per unit volume, afford no indication of the physical or chemical activity of the species measured, and it is this activity which determines the physical and chemical properties of the system.



In recognition of this, GN Lewis introduced both the quantitative concept and methods for evaluation of activity as a true measure of the physical or chemical activity of molecular, atomic or ionic species, whether in the state of gas, liquid or solid, or whether present as a single species or in a mixture. Activity may be considered loosely as a corrected concentration or pressure which takes into account not only the stoichiometric concentration or pressure but also any intermolecular attractions, repulsions or interactions between solute and solvent in solution, association and ionization. Thus, activity measures the net effectiveness of a chemical species. Because only relative values of activity may be determined, a *standard state* must be chosen for quantitative comparisons to be made. Indeed, because activity measurements are needed for many different types of systems, several standard states must be selected. Since this discussion is concerned mainly with solutions, the standard state for the solvent is pure solvent, while for the solute it is a hypothetical solution with free energy corresponding to unit molality under conditions of ideal behavior of the solution. The relationship of activity to concentration is measured in terms of an activity coefficient which is discussed in Chapter 17.

### Practical Applications of Colligative Properties

One of the most important pharmaceutical applications of colligative properties is in the preparation of isotonic intravenous and isotonic lacrimal solutions, the details of which are discussed in Chapter 79.

Other applications of the colligative properties are found in experimental physiology. One such application is in the immersion of tissues in salt solutions, which are isotonic with the fluids of the tissue, in order to prevent changes or injuries that may arise from osmosis.

The colligative properties of solutions also may be used in determining the molecular weight of solutes or, in the case of electrolytes, the extent of ionization. The method of determining molecular weight depends on the fact that each of the colligative properties is altered by a constant value when a definite number of molecules of solute is added to a solvent [See Chapter 17]. For example, in dilute solutions the freezing point of water is lowered at the rate of 1.855° for each

gram-molecular weight of a nonelectrolyte dissolved in 1000 g of water.\*

The constant 1.855° is commonly called the *molar freezing-point depression* of water. To find the molecular weight of a nonelectrolyte, therefore, all that is necessary is to determine the freezing point of a dilute aqueous solution of known concentration of the nonelectrolyte and, by proportion, to calculate the quantity that would produce, theoretically, a depression of 1.855° when 1000 g of water is used as the solvent. If the substance is insoluble in water, it may be dissolved in another solvent, in which case, however, the freezing-point depression of a solution corresponding to a gram-molecular weight of the solute in 1000 g of solvent will be some value other than 1.855°. In the case of benzene, for example, this value is 5.12°; carbon tetrachloride, 2.98°; phenol, 7.27° and camphor, about 40° (see *Freezing-Point Depression*, in this chapter).

The boiling-point elevation may be used similarly for determining molecular weights. The boiling point of water is raised at the rate of 0.52° for each gram-molecular weight of solute dissolved in 1000 g of water,\* the corresponding values for benzene, carbon tetrachloride and phenol being 2.57°, 4.88° and 3.60°, respectively. The observation of vapor-pressure lowering and osmotic pressure likewise may be used to calculate molecular weights.

To determine the extent to which an electrolyte is ionized, it is necessary to know its molecular weight, as determined by some other method, and then to measure one of the four colligative properties. The deviation of the results from similar values for nonelectrolytes then is used in calculating the extent of ionization.

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\* These constants apply only to solutions that are considerably more dilute than 1 molar; a substantial deviation would be observed if a 1-molar solution were to be used.



## CHAPTER 17

# Ionic Solutions and Electrolytic Equilibria

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## Electrolytes

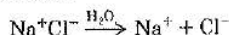
In the preceding chapter, attention was directed to the colligative properties of nonelectrolytes, or substances whose aqueous solutions do not conduct electricity. Substances whose aqueous solutions conduct electricity are known as electrolytes, and are typified by inorganic acids, bases and salts. In addition to the property of electrical conductivity, solutions of electrolytes exhibit anomalous colligative properties.

### Colligative Properties

In general, for nonelectrolytes, a given colligative property of two equimolar solutions will be identical. This generalization, however, cannot be made for solutions of electrolytes.

Van't Hoff pointed out that the osmotic pressure of a solution of an electrolyte is considerably greater than the osmotic pressure of a solution of a nonelectrolyte of the same molal concentration. This anomaly remained unexplained until 1887 when Arrhenius proposed a hypothesis which forms the basis for our modern theories of electrolyte solutions.

This theory postulated that when electrolytes are dissolved in water they split up into charged particles known as ions. Each of these ions carries one or more electrical charges, with the total charge on the positive ions (cations) being equal to the total charge on the negative ions (anions). Thus, although a solution may contain charged particles, it remains neutral. The increased osmotic pressure of such solutions is due to the increased number of particles formed in the process of ionization. For example, sodium chloride is assumed to dissociate as



It is evident that each molecule of sodium chloride which is dissociated produces two ions and, if dissociation is complete, there will be twice as many particles as would be the case if it were not dissociated at all. Furthermore, if each ion has the same effect on osmotic pressure as a molecule, it might be expected that the osmotic pressure of the solution would be twice that of a solution containing the same molal concentration of a nonionizing solute.

Osmotic-pressure data indicate that, in very dilute solutions of salts which yield two ions, the pressure is very nearly double that of solutions of equimolar concentrations of nonelectrolytes. Similar magnification of vapor-pressure lowering, boiling-point elevation and freezing-point depression occurs in dilute solutions of electrolytes.

Van't Hoff defined a factor  $i$  as the ratio of the colligative effect produced by a concentration  $m$  of electrolyte, divided by the effect observed for the same concentration of nonelectrolyte, or

$$i = \frac{\pi}{(\pi)_0} = \frac{\Delta P}{(\Delta P)_0} = \frac{\Delta T_b}{(\Delta T_b)_0} = \frac{\Delta T_f}{(\Delta T_f)_0} \quad (1)$$

in which  $\pi$ ,  $\Delta P$ ,  $\Delta T_b$  and  $\Delta T_f$  refer to the osmotic pressure, vapor-pressure lowering, boiling-point elevation and freezing-point depression, respectively, of the electrolyte. The terms  $(\pi)_0$ , etc refer to the nonelectrolyte of the same concentration. In general, with strong electrolytes (those assumed to be 100% ionized), the van't Hoff factor is equal to the number of ions produced when the electrolyte goes into solution (2 for NaCl and MgSO<sub>4</sub>, 3 for CaCl<sub>2</sub> and Na<sub>2</sub>SO<sub>4</sub>, 4 for FeCl<sub>3</sub> and Na<sub>3</sub>PO<sub>4</sub>, etc).

In very dilute solutions the osmotic pressure, vapor-pressure lowering, boiling-point elevation and freezing-point depression of solutions of electrolytes approach values 2, 3, 4 or more times greater (depending on the type of strong electrolyte) than in solutions of the same molality of nonelectrolyte, thus confirming the hypothesis that an ion has the same primary effect as a molecule on colligative properties. It bears repeating, however, that two other effects are observed as the concentration of electrolyte is increased.

The first effect results in less than 2-, 3- or 4-fold intensification of a colligative property. This reduction is ascribed to interionic attraction between the positively and negatively charged ions, in consequence of which the ions are not dissociated completely from each other and do not exert their full effect on vapor pressure and other colligative properties. This deviation generally increases with increasing concentration of electrolyte.

The second effect intensifies the colligative properties and is attributed to the attraction of ions for solvent molecules (called solvation, or, if water is the solvent, hydration), which holds the solvent in solution and reduces its escaping tendency, with a consequent enhancement of the vapor-pressure lowering. Solvation also reduces interionic attraction and, thereby, further lowers the vapor pressure.

### Conductivity

The ability of metals to conduct an electric current results from the mobility of electrons in the metals. This type of conductivity is called *metallic* conductance. On the other hand, various chemical compounds—notably acids, bases and salts—conduct electricity by virtue of ions present or formed, rather than by electrons. This is called *electrolytic* conductance, and the conducting compounds are electrolytes. While the fact that certain electrolytes conduct electricity in the molten state is important, their behavior when dissolved in a solvent, particularly in water, is of greater concern in pharmaceutical science.

The electrical conductivity (or conductance) of a solution of an electrolyte is merely the reciprocal of the resistance of the solution. Hence, to measure conductivity is actually to

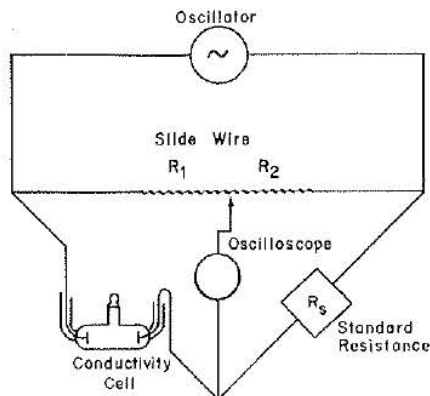


Fig 17-1. Alternating current Wheatstone bridge for measuring conductivity.

measure electrical resistance, commonly with a Wheatstone-bridge apparatus, and then to calculate the conductivity. Fig 17-1 is a representation of the component parts of the apparatus.

The solution to be measured is placed in a glass or quartz cell having two inert electrodes, commonly made of platinum or gold and coated with spongy platinum to absorb gases, across which passes an alternating current generated by an oscillator at a frequency of about 1000 Hz. The reason for using alternating current is to reverse the electrolysis that occurs during flow of current and which would cause polarization of the electrodes and lead to abnormal results. The size of the electrodes and their distance apart may be varied to reduce very high resistance and increase very low resistance in order to increase the accuracy and precision of measurement. Thus, solutions of high conductance (low resistance) are measured in cells having small electrodes relatively far apart, while solutions of low conductance (high resistance) are measured in cells with large electrodes placed close to each other.

Electrolytic resistance, like metallic resistance, varies directly with the length of the conducting medium and inversely with its cross-sectional area. The known resistance required for the circuit is provided by a resistance box containing calibrated coils. Balancing of the bridge may be achieved by sliding a contact over a wire of uniform resistance until no (or minimum) current flows through the circuit, as detected either visually with a cathode-ray oscilloscope or audibly with earphones.

The resistance, in ohms, is calculated by the simple procedure used in the Wheatstone-bridge method. The reciprocal of the resistance is the conductivity, the units of which are *reciprocal ohms* (also called *mhos*). As the numerical value of the conductivity will vary with the dimensions of the

conductance cell, the value must be calculated in terms of *specific conductance*,  $L$ , which is the conductance in a cell having electrodes of 1-sq cm cross-sectional area and 1 cm apart. If the dimensions of the cell used in the experiment were known, it would be possible to calculate the specific conductance, but this information actually is not required, because it is possible—and much more convenient—to calibrate a cell by measuring in it the conductivity of a standard solution of known specific conductance and then calculating a “cell constant.” Since this constant is a function only of the dimensions of the cell, it can be used to convert all measurements in that cell to specific conductivity. Solutions of known concentration of pure potassium chloride are used as standard solutions for this purpose.

**Equivalent Conductance**—In studying the variation of conductance of electrolytes with dilution it is essential to make allowance for the degree of dilution in order that the comparison of conductances may be made for identical amounts of solute. This may be achieved by expressing conductance measurements in terms of *equivalent conductance*,  $\Lambda$ , which is obtained by multiplying the specific conductance,  $L$ , by the volume in milliliters,  $V_e$ , of solution containing 1 g-eq of solute. Thus

$$\Lambda = LV_e = \frac{1000L}{C} \quad (2)$$

where  $C$  is the concentration of electrolyte in the solution in g-Eq/L, ie, the normality of the solution. For example, the equivalent conductance of 0.01  $N$  potassium chloride solution, which has a specific conductance of 0.001413 mho/cm may be calculated in either of the following ways

$$\Lambda = 0.001413 \times 100,000 = 141.3 \text{ mho cm}^2/\text{eq}$$

or

$$\Lambda = \frac{1000 \times 0.001413}{0.01} = 141.3$$

**Strong and Weak Electrolytes**—It is customary to classify electrolytes broadly as *strong electrolytes* and *weak electrolytes*. The former category includes solutions of strong acids, strong bases and most salts; the latter includes weak acids and bases, primarily organic acids, amines and a few salts. The usual criterion for distinguishing between strong and weak electrolytes is the extent of ionization. An electrolyte existing entirely or very largely as ions is considered a strong electrolyte, while one that is a mixture of a substantial proportion of molecular species along with ions derived therefrom is a weak electrolyte. For the purposes of this discussion, classification of electrolytes as strong or weak will be on the basis of certain conductance characteristics exhibited in aqueous solution.

The equivalent conductances of a number of electrolytes, at different concentrations, are given in Table I and for certain of these electrolytes again in Fig 17-2, where the

Table I—Equivalent Conductances at 25°

g-Eq/L	HCl	HAc	NaCl	KCl	NaI	KI	NaAc
Inf dil	426.1	390.6*	126.5	149.9	126.9	150.3	91.0
0.0005	422.7	67.7	124.5	147.8	125.4	...	89.2
0.001	421.4	49.2	123.7	146.9	124.3	...	88.5
0.005	415.8	22.9	120.6	143.5	121.3	144.4	85.7
0.01	412.0	16.3	118.5	141.3	119.2	142.2	83.8
0.02	407.2	11.6	115.8	138.3	116.7	139.5	81.2
0.05	399.1	7.4	111.1	133.4	112.8	135.0	76.9
0.1	391.3	5.2	106.7	129.0	108.8	131.1	72.5

\* The equivalent conductance at infinite dilution for acetic acid, a weak electrolyte, is obtained by adding the equivalent conductances of hydrochloric acid and sodium acetate and subtracting that of sodium chloride (see text for explanation).

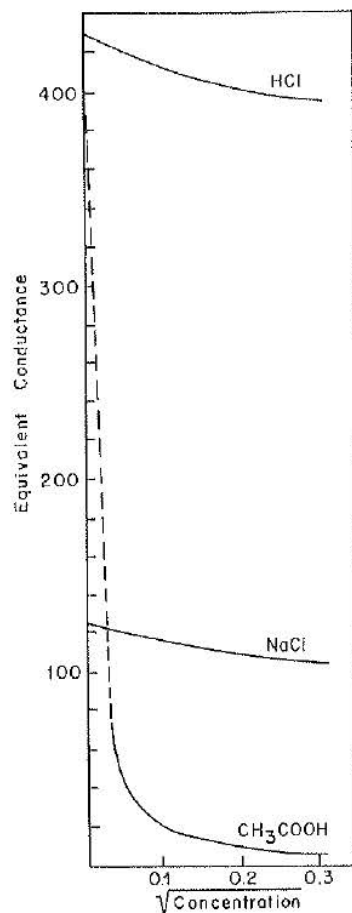


Fig 17-2. Variation of equivalent conductance with square root of concentration.

equivalent conductance is plotted against the square root of concentration. By plotting the data in this manner a linear relationship is observed for strong electrolytes, while a steeply rising curve is noted for weak electrolytes; this difference is a characteristic which distinguishes strong and weak electrolytes. The interpretation of the steep rise in the equivalent conductance of weak electrolytes is that the degree of ionization increases with dilution, becoming complete at infinite dilution. Interionic interference effects generally have a minor role in the conductivity of weak electrolytes. With strong electrolytes, which usually are completely ionized, the increase in equivalent conductance results not from increased ionization but rather from diminished ionic interference as the solution is diluted, in consequence of which ions have greater freedom of mobility, i.e., increased conductance.

The value of the equivalent conductance extrapolated to infinite dilution (zero concentration), designated by the symbol  $\Lambda_0$ , has a special significance. It represents the equivalent conductance of the completely ionized electrolyte when the ions are so far apart that there is no interference with their migration due to interionic interactions. It has been shown, by Kohlrausch, that the equivalent conductance of an electrolyte at infinite dilution is the sum of the equivalent conductances of its component ions at infinite dilution, expressed symbolically as

Table II—Equivalent Ionic Conductivities at Infinite Dilution, at 25°

Cations	$l_0$	Anions	$l_0$
H <sup>+</sup>	349.8	OH <sup>-</sup>	198.0
Li <sup>+</sup>	38.7	Cl <sup>-</sup>	76.3
Na <sup>+</sup>	50.1	Br <sup>-</sup>	78.4
K <sup>+</sup>	73.5	I <sup>-</sup>	76.8
NH <sub>4</sub> <sup>+</sup>	61.9	Ac <sup>-</sup>	40.9
$\frac{1}{2}\text{Ca}^{2+}$	59.5	$\frac{1}{2}\text{SO}_4^{2-}$	79.8
$\frac{1}{2}\text{Mg}^{2+}$	53.0		

$$\Lambda_0 = l_0(\text{cation}) + l_0(\text{anion}) \quad (3)$$

The significance of Kohlrausch's law is that each ion, at infinite dilution, has a characteristic value of conductance that is independent of the conductance of the oppositely charged ion with which it is associated. Thus, if the equivalent conductances of various ions are known, the conductance of any electrolyte may be calculated simply by adding the appropriate ionic conductances. Since the fraction of current carried by cations (*transference number of the cations*) and by anions (*transference number of anions*) in an electrolyte may be determined readily by experiment, ionic conductances are known. Table II gives the equivalent ionic conductances at infinite dilution of some cations and anions. It is not necessary to have this information in order to calculate the equivalent conductance of an electrolyte, for Kohlrausch's law permits the latter to be calculated by adding and subtracting values of  $\Lambda_0$  for appropriate electrolytes. For example, the value of  $\Lambda_0$  for acetic acid may be calculated as

$$\Lambda_0(\text{CH}_3\text{COOH}) = \Lambda_0(\text{HCl}) + \Lambda_0(\text{CH}_3\text{COONa}) - \Lambda_0(\text{NaCl})$$

which is equivalent to

$$l_0(\text{H}^+) + l_0(\text{CH}_3\text{COO}^-) = l_0(\text{H}^+) + l_0(\text{Cl}^-) + l_0(\text{Na}^+) + l_0(\text{CH}_3\text{COO}^-) - l_0(\text{Na}^+) - l_0(\text{Cl}^-)$$

This method is especially useful for calculating  $\Lambda_0$  for weak electrolytes such as acetic acid. As is evident from Fig 17-2, the  $\Lambda_0$  value for acetic acid cannot be determined accurately by extrapolation because of the steep rise of conductance in dilute solutions. For strong electrolytes, on the other hand, the extrapolation can be made very accurately. Thus, in the example above, the values of  $\Lambda_0$  for HCl, CH<sub>3</sub>COONa and NaCl are determined easily by extrapolation since the substances are strong electrolytes. Substitution of these extrapolated values, as given in Table II, yields a value of 390.6 for the value of  $\Lambda_0$  for CH<sub>3</sub>COOH.

**Ionization of Weak Electrolytes**—When Arrhenius introduced his theory of ionization he proposed that the degree of ionization,  $\alpha$ , of an electrolyte is measured by the ratio

$$\alpha = \Lambda/\Lambda_0 \quad (4)$$

where  $\Lambda$  is the equivalent conductance of the electrolyte at any specified concentration of solution and  $\Lambda_0$  is the equivalent conductance at infinite dilution. As strong electrolytes were not then recognized as being 100% ionized, and interionic interference effects had not been evaluated, he believed the equation to be applicable to both strong and weak electrolytes. Since it now is known that the apparent variation of ionization of strong electrolytes arises from a change in the mobility of ions at different concentrations, rather than from varying ionization, the equation is not applicable to strong electrolytes. It does provide, however, a generally acceptable approximation of the degree of ionization of weak

electrolytes, for which deviations resulting from neglect of activity coefficients and of some change of ionic mobilities with concentration are, for most purposes, negligible. The following example illustrates the use of the equation to calculate the degree of ionization of a typical weak electrolyte.

*Example*—Calculate the degree of ionization of  $1 \times 10^{-3} N$  acetic acid, the equivalent conductance of which is 48.15 mho  $\text{cm}^2/\text{Eq}$ . The equivalent conductance at infinite dilution is 390.6 mho  $\text{cm}^2/\text{Eq}$ .

$$\alpha = \frac{48.15}{390.6} = 0.12$$

$$\% \text{ ionization} = 100\alpha = 12\%$$

The degree of dissociation also can be calculated using the van't Hoff factor,  $i$ , and the following equation

$$\alpha = \frac{i - 1}{\nu - 1} \quad (5)$$

where  $\nu$  is the number of ions into which the electrolyte dissociates.

*Example*—A  $1.0 \times 10^{-3} N$  solution of acetic acid has a van't Hoff factor equal to 1.12. Calculate the degree of dissociation of the acid at this concentration.

$$\alpha = \frac{i - 1}{\nu - 1} = \frac{1.12 - 1}{2 - 1} = 0.12$$

This result agrees with that obtained using equivalent conductance and Eq 4.

## Modern Theories

The Arrhenius theory explains why solutions of electrolytes conduct electricity, why they exhibit enhanced colligative properties and essentially is satisfactory for solutions of weak electrolytes. Several deficiencies, however, do exist when it is applied to solutions of strong electrolytes. It does not explain the failure of strong electrolytes to follow the law of mass action as applied to ionization; discrepancies exist between the degree of ionization calculated from the van't Hoff factor and the conductivity ratio for strong electrolyte solutions having concentrations greater than about 0.5  $M$ .

These deficiencies can be explained by the following observations

1. In the molten state, strong electrolytes are excellent conductors of electricity. This suggests that these materials are already ionized in the crystalline state. Further support for this is given by X-ray studies of crystals, which indicate that the units comprising the basic lattice structure of strong electrolytes are ions.

2. Arrhenius neglected the fact that ions in solution, being oppositely charged, tend to associate through electrostatic attraction. In solutions of weak electrolytes, the number of ions is not large and it is not surprising that electrostatic attractions do not cause appreciable deviations from theory. In dilute solutions, in which strong electrolytes are assumed to be 100% ionized, the number of ions is large, and interionic attractions become major factors in determining the chemical properties of these solutions. These effects should, and do, become more pronounced as the concentration of electrolyte or the valence of the ions is increased.

It is not surprising, therefore, that the Arrhenius theory of partial ionization involving the law of mass action and neglecting ionic charge does not hold for solutions of strong electrolytes. Neutral molecules of strong electrolytes, if they do exist in solution, must arise from interionic attraction rather than from incomplete ionization.

**Activity and Activity Coefficients**—Due to increased electrostatic attractions as a solution becomes more concentrated, the concentration of an ion becomes less efficient as a measure of its net effectiveness. A more efficient measure of the physical or chemical effectiveness of an ion is known as its *activity*, which is a measure of an ion's concentration related to its concentration at a universally adopted refer-

ence-standard state. The relationship between the activity and the concentration of an ion can be expressed as

$$a = m\gamma \quad (6)$$

where  $m$  is the molal concentration,  $\gamma$  is the activity coefficient and  $a$  is the activity. The activity also can be expressed in terms of molar concentration,  $c$ , as

$$a = fc \quad (7)$$

where  $f$  is the activity coefficient on a molar scale. In dilute solutions (below 0.01  $M$ ) the two activity coefficients are identical, for all practical purposes.

The activity coefficient may be determined in various ways, such as measuring colligative properties, electromotive force, solubility, distribution coefficients, etc. For a strong electrolyte, the mean ionic activity coefficient,  $\gamma_{\pm}$ , or  $f_{\pm}$ , provides a measure of the deviation of the electrolyte from ideal behavior. The mean ionic activity coefficients on a molal basis for several strong electrolytes are given in Table II. It is characteristic of the electrolytes that the coefficients at first decrease with increasing concentration, pass through a minimum and finally increase with increasing concentration of electrolyte.

**Ionic Strength**—Ionic strength is a measure of the intensity of the electrical field in a solution and may be expressed as

$$\mu = \frac{1}{2} \sum c_i z_i^2 \quad (8)$$

where  $z_i$  is the valence of ion  $i$ . The mean ionic activity coefficient is a function of ionic strength as are such diverse phenomena as solubilities of sparingly soluble substances, rates of ionic reactions, effects of salts on pH of buffers, electrophoresis of proteins, etc.

The greater effectiveness of ions of higher charge type on a specific property, compared with the effectiveness of the same number of singly charged ions, generally coincides with the ionic strength calculated by Eq 8. The variation of ionic strength with the valence (charge) of the ions comprising a strong electrolyte should be noted.

For univalent cations and univalent anions (called univalent or 1-1) electrolytes, the ionic strength is identical with molarity. For bivalent cation and univalent anion (bivalent or 2-1) electrolytes, or univalent cation and bivalent anion (univalent or 1-2) electrolytes, the ionic strength is three times the molarity. For bivalent cation and bivalent anion (bibivalent or 2-2) electrolytes, the ionic strength is four times the molarity. These relationships are evident from the following example.

*Example*—Calculate the ionic strength of 0.1  $M$  solutions of NaCl,  $\text{Na}_2\text{SO}_4$ ,  $\text{MgCl}_2$  and  $\text{MgSO}_4$ , respectively. For

$$\text{NaCl} \quad \mu = \frac{1}{2} (0.1 \times 1^2 + 0.1 \times 1^2) = 0.1$$

$$\text{Na}_2\text{SO}_4 \quad \mu = \frac{1}{2} (0.2 \times 1^2 + 0.1 \times 2^2) = 0.3$$

$$\text{MgCl}_2 \quad \mu = \frac{1}{2} (0.1 \times 2^2 + 0.2 \times 1^2) = 0.3$$

$$\text{MgSO}_4 \quad \mu = \frac{1}{2} (0.1 \times 2^2 + 0.1 \times 2^2) = 0.4$$

The ionic strength of a solution containing more than one electrolyte is the sum of the ionic strengths of the individual salts comprising the solution. For example, the ionic strength of a solution containing NaCl,  $\text{Na}_2\text{SO}_4$ ,  $\text{MgCl}_2$  and  $\text{MgSO}_4$ , each at a concentration of 0.1  $M$ , is 1.1.

**Debye-Hückel Theory**—The Debye-Hückel equations which are applicable only to very dilute solutions (about 0.02  $\mu$ ), may be extended to somewhat more concentrated solutions (about 0.1  $\mu$ ) in the simplified form

$$\log f_i = \frac{-0.51 z_i^2 \sqrt{\mu}}{1 + \sqrt{\mu}} \quad (9)$$



Table III—Values of Some Salting-Out Constants for Various Barbiturates at 25°

Barbiturate	KCl	KBr	NaCl	NaBr
Amobarbital	0.168	0.095	0.212	0.143
Aprobarbital	0.136	0.062	0.184	0.120
Barbital	0.092	0.042	0.136	0.088
Phenobarbital	0.092	0.034	0.132	0.078
Vinbarbital	0.125	0.036	0.143	0.096

The mean ionic activity coefficient for aqueous solutions of electrolytes at 25° can be expressed as

$$\log f_{\pm} = \frac{-0.51 z_+ z_- \sqrt{\mu}}{1 + \sqrt{\mu}} \quad (10)$$

in which  $z_+$  is the valence of the cation and  $z_-$  is the valence of the anion. When the ionic strength of the solution becomes high (approximately 0.3 to 0.5), these equations become inadequate and a linear term in  $\mu$  is added. This is illustrated for the mean ionic activity coefficient

$$\log f_{\pm} = \frac{-0.51 z_+ z_- \sqrt{\mu}}{1 + \sqrt{\mu}} + K_s \mu \quad (11)$$

in which  $K_s$  is a "salting-out" constant chosen empirically for each salt. This equation is valid for solutions with ionic strength up to approximately 1.

**Salting-Out Effect.**—The aqueous solubility of a slightly soluble organic substance generally is affected markedly by the addition of an electrolyte. This effect particularly is noticeable when the electrolyte concentration reaches 0.5 *M* or higher. If the aqueous solution of the organic substance has a dielectric constant lower than that of pure water, its solubility is decreased and the substance is "salted-out." The use of high concentrations of electrolytes, such as ammonium sulfate or sodium sulfate, for the separation of proteins by differential precipitation is perhaps the most striking example of this effect. The aqueous solutions of a few substances such as hydrocyanic acid, glycine and cystine have a higher dielectric constant than that of pure water, and these substances are "salted-in." These phenomena can be expressed empirically as

$$\log S = \log S_0 \pm K_s m \quad (12)$$

in which  $S_0$  represents the solubility of the organic substance in pure water and  $S$  is the solubility in the electrolyte solution. The slope of the straight line obtained by plotting  $\log S$  versus  $m$  is positive for "salting-in" and negative for salting-out. In terms of ionic strength this equation becomes

$$\log S = \log S_0 \pm K_s' \mu \quad (13)$$

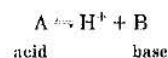
where  $K_s' = K_s$  for univalent salts,  $K_s' = K_s/3$  for univalent salts and  $K_s' = K_s/4$  for bivalent salts. The salting-out constant depends on the temperature as well as the nature of both the organic substance and the electrolyte. The effect of the electrolyte and the organic substance can be seen in Table III. In all instances, if the anion is constant, the sodium cation has a greater salting-out effect than the potassium cation, probably due to the higher charge density of the former. Although the reasoning is less clear, it appears that for a constant cation, chloride anion has a greater effect than bromide anion upon the salting-out phenomenon.

### Acids and Bases

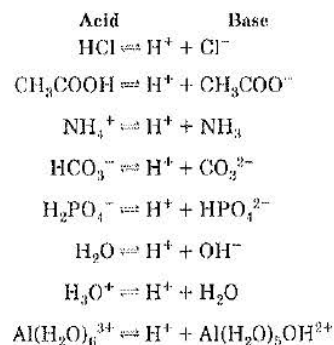
Arrhenius defined an acid as a substance that yields hydrogen ions in aqueous solution and a base as a substance

that yields hydroxyl ions in aqueous solution. Except for the fact that hydrogen ions neutralize hydroxyl ions to form water, no complementary relationship between acids and bases (such as that between oxidants and reductants, for example) is evident in Arrhenius' definitions for these substances; rather, their oppositeness of character is emphasized. Moreover, no account is taken of the behavior of acids and bases in nonaqueous solvents. Also, while acidity is associated with so elementary a particle as the proton (hydrogen ion), basicity is attributed to so relatively complex an association of atoms as the hydroxyl ion. It would seem that a simpler concept of a base could be devised.

**Proton Concept.**—In pondering the objections to Arrhenius' definitions, Brønsted and Bjerrum in Denmark and Lowry in England developed, and in 1923 announced, a more satisfactory, and more general, theory of acids and bases. According to this theory an acid is a substance capable of yielding a proton (hydrogen ion), while a base is a substance capable of accepting a proton. This complementary relationship may be expressed by the general equation

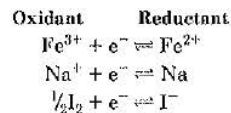


The pair of substances thus related through mutual ability to gain or lose a proton is called a *conjugate acid-base pair*. Specific examples of such pairs are

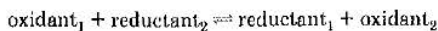


It is apparent that not only molecules but also cations and anions may function as acids or bases.

The complementary nature of the acid-base pairs listed is reminiscent of the complementary relationship of pairs of oxidants and reductants where, however, the ability to gain or lose one or more electrons—rather than protons—is the distinguishing characteristic.

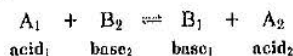


However, these examples of acid-base pairs and oxidant-reductant pairs represent reactions that are possible in principle only. Ordinarily acids will not release free protons any more than reductants will release free electrons. That is, protons and electrons, respectively, can be *transferred* only from one substance (an ion, atom or molecule) to another. Thus, it is a fundamental fact of chemistry that oxidation of one substance will occur only if reduction of another substance occurs simultaneously. Stated in another way, electrons will be released from the reductant (oxidation) only if an oxidant capable of accepting electrons (reduction) is present. For this reason oxidation-reduction reactions must involve two conjugate oxidant-reductant pairs of substances



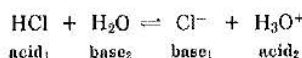
where Subscript 1 represents one conjugate oxidant-reductant pair and Subscript 2 represents the other.

Similarly, an acid will not release a proton unless a base capable of accepting it is present simultaneously. This means that any actual manifestation of acid-base behavior must involve interaction between two sets of conjugate acid-base pairs, represented as



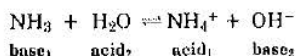
In such a reaction, which is called *protolysis* or a *protolytic reaction*,  $A_1$  and  $B_1$  constitute one conjugate acid-base pair and  $A_2$  and  $B_2$  the other; the proton given up by  $A_1$  (which thereby becomes  $B_1$ ) is transferred to  $B_2$  (which becomes  $A_2$ ).

When an acid, such as hydrochloric, is dissolved in water, a protolytic reaction occurs.

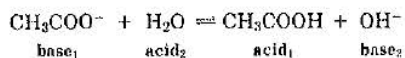


The ionic species  $\text{H}_3\text{O}^+$ , called *hydronium* or *oxonium* ion, always is formed when an acid is dissolved in water. Often, for purposes of convenience, this is written simply as  $\text{H}^+$  and is called hydrogen ion, although the "bare" ion practically is nonexistent in solution.

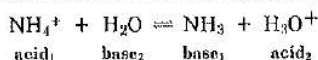
When a base, eg, ammonia, is dissolved in water the reaction of protolysis is



The proton theory of acid-base function makes the concept of hydrolysis superfluous. When, for example, sodium acetate is dissolved in water, this acid-base interaction occurs

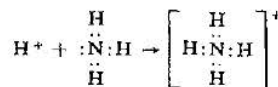


In an aqueous solution of ammonium chloride the reaction is

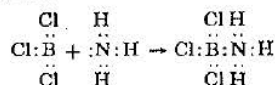


Transfer of protons (protolysis) is not limited to dissimilar conjugate acid-base pairs. In the preceding examples  $\text{H}_2\text{O}$  sometimes behaves as an acid and at other times as a base. Such an amphoteric substance is called, in Brønsted's terminology, an *amphiprotic substance*.

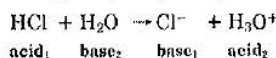
**Electron-Pair Concept**—While the proton concept of acids and bases provides a more general definition for these substances, it does not indicate the basic reason for proton transfer, nor does it explain how such substances as sulfur trioxide, boron trichloride, stannic chloride or carbon dioxide—none of which is capable of donating a proton—can behave as acids. Both deficiencies of the proton theory are avoided in the more inclusive definition of acids and bases proposed by Lewis in 1923. In 1916 he proposed that sharing of a pair of electrons by two atoms established a bond (covalent) between the atoms; therefore, an acid is a substance capable of sharing a pair of electrons made available by another substance called a base, thereby forming a coordinate covalent bond. The base is the substance that donates a share in its electron pair to the acid. The following equation illustrates how Lewis' definitions explain the transfer of a proton (hydrogen ion) to ammonia to form ammonium ion.



The reaction of boron trichloride, which according to the Lewis theory is an acid, with ammonia is similar, for the boron lacks an electron pair if it is to attain a stable octet configuration, while ammonia has a pair of electrons which may be shared, thus



**Leveling Effect of a Solvent**—When the strong acids such as  $\text{HClO}_4$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{HCl}$  or  $\text{HNO}_3$  are dissolved in water the solutions—if they are of identical normality and are not too concentrated—all have about the same hydrogen-ion concentration, indicating the acids to be of about the same strength. The reason for this is that each one of the acids undergoes practically complete protolysis in water.

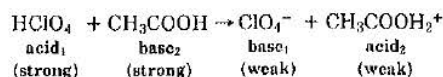


This phenomenon, called the leveling effect of water, occurs whenever the added acid is stronger than the hydronium ion. Such a reaction manifests the tendency of proton-transfer reactions to proceed spontaneously in the direction of forming a weaker acid or weaker base.

Since the strongest acid that can exist in an amphiprotic solvent is the conjugate acid form of the solvent, any stronger acid will undergo protolysis to the weaker solvent acid. Since  $\text{HClO}_4$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{HCl}$  or  $\text{HNO}_3$  are all stronger acids than the hydronium ion, they are converted in water to the hydronium ion.

When the strong bases sodium hydride, sodium amide or sodium ethoxide are dissolved in water, each reacts with water to form sodium hydroxide. These reactions illustrate the leveling effect of water on bases. Since the hydroxide ion is the strongest base which can exist in water, any base stronger than the hydroxide ion undergoes protolysis to hydroxide.

Intrinsic differences in the acidity of acids become evident if they are dissolved in a relatively poor proton acceptor such as anhydrous acetic acid. Perchloric acid ( $\text{HClO}_4$ ), a strong acid, undergoes practically complete reaction with acetic acid



but sulfuric acid and hydrochloric acid behave as weak acids. It is because perchloric acid is a very strong acid when dissolved in glacial acetic acid that it has found many important applications in analytical chemistry as a titrant for a variety of substances which behave as bases in acetic acid. Because of its ability to differentiate the acidity of various acids, it is called a *differentiating solvent for acids*; this property results from its relatively weak proton-acceptor tendency. A solvent that differentiates basicity of different bases must have a weak proton-donor tendency; it is called a *differentiating solvent for bases*. Typical of solvents in this category is liquid ammonia. Solvents that have both weak proton-donor and proton-acceptor tendencies are called *aprotic solvents* and may serve as differentiating solvents for both acids and bases; they have little if any action on solutes and serve mainly as inert dispersion media for the solutes. Useful aprotic solvents are benzene, toluene or hexane.

**Ionization of Acids and Bases**—Acids and bases commonly are classified as strong or weak acids and strong or



weak bases depending on whether they are ionized extensively or slightly in aqueous solutions. If, for example, 1 *N* aqueous solutions of hydrochloric acid and acetic acid are compared, it is found that the former is a better conductor of electricity, reacts much more readily with metals, catalyzes certain reactions more efficiently and possesses a more acid taste than the latter. Both solutions, however, will neutralize identical amounts of alkali. A similar comparison of 1 *N* solutions of sodium hydroxide and ammonia reveals the former to be more "active" than the latter, although both solutions will neutralize identical quantities of acid.

The differences in the properties of the two acids is attributed to differences in the concentration of hydrogen (more accurately hydronium) ion, the hydrochloric acid being ionized to a greater extent and, therefore, containing a higher concentration of hydrogen ion than acetic acid. Similarly, most of the differences between the sodium hydroxide and ammonia solutions are attributed to the higher hydroxyl-ion concentration in the former.

The ionization of incompletely ionized acids may be considered a reversible reaction of the type

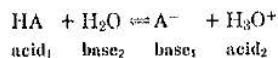


where HA is the molecular acid and A<sup>-</sup> is its anion. An equilibrium expression based on the law of mass action may be applied to the reaction

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \quad (14)$$

where  $K_a$  is the ionization or dissociation constant, and the brackets signify concentration. For any given acid in any specified solvent and at any constant temperature,  $K_a$  remains relatively constant as the concentration of acid is varied, provided the acid is weakly ionized. With increasingly stronger acids, however, progressively larger deviations occur.

Although the strength of an acid commonly is measured in terms of the ionization or dissociation constant defined in Eq 14, the process of ionization probably is never as simple as shown above. A proton simply will not detach itself from one molecule unless it is accepted simultaneously by another molecule. When an acid is dissolved in water, the latter acts as a base, accepting a proton (Brønsted's definition of a base) by donating a share in a pair of electrons (Lewis' definition of a base). This reaction may be written



Application of the law of mass action to this reaction gives

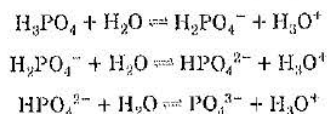
$$K = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}][\text{H}_2\text{O}]} \quad (15)$$

since  $[\text{H}_2\text{O}]$  is a constant this equation may be written

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \quad (16)$$

This equation is identical with Eq 14 because  $[\text{H}_3\text{O}^+]$  is numerically equal to  $[\text{H}^+]$ .

Acids which are capable of donating more than one proton are termed *polyprotic*. The ionization of a polyprotic acid occurs in stages and can be illustrated by considering the equilibria involved in the ionization of phosphoric acid



Application of the law of mass action to this series of reactions gives

$$K_1 = \frac{[\text{H}_2\text{PO}_4^-][\text{H}_3\text{O}^+]}{[\text{H}_3\text{PO}_4]} \quad (17)$$

$$K_2 = \frac{[\text{HPO}_4^{2-}][\text{H}_3\text{O}^+]}{[\text{H}_2\text{PO}_4^-]} \quad (18)$$

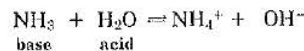
$$K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]}{[\text{HPO}_4^{2-}]} \quad (19)$$

If the three expressions for the ionization constants are multiplied together, an overall ionization,  $K$ , can be obtained

$$K = K_1 K_2 K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]^3}{[\text{H}_3\text{PO}_4]} \quad (20)$$

Each of the successive ionizations is suppressed by the hydronium ion formed from preceding stages according to Le Chatelier's principle. The successive dissociation constants always decrease in value, since successive protons must be removed from species that are always more negatively charged. This can be seen from the data in Table IV, in which  $K_1$  for phosphoric acid is approximately 100,000 times greater than  $K_2$ , which is in turn approximately 100,000 times greater than  $K_3$ . Although successive dissociation constants are always smaller, the difference is not always as great as it is for phosphoric acid. Tartaric acid, for example, has  $K_1 = 9.12 \times 10^{-4}$  and  $K_2 = 4.27 \times 10^{-5}$ .

Ionization of a base can be illustrated by using the specific substance  $\text{NH}_3$  for an example. According to Brønsted and Lewis, when the base  $\text{NH}_3$  is dissolved in water, the latter acts as an acid, donating a proton to  $\text{NH}_3$ , which accepts it by offering a share in a pair of electrons on the nitrogen atom. This reaction is written



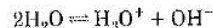
The equilibrium expression for this reaction is

$$K = \frac{[\text{NH}_4^+][\text{OH}^-]}{[\text{NH}_3][\text{H}_2\text{O}]} \quad (21)$$

with  $[\text{H}_2\text{O}]$  constant this expression may be written

$$K_b = \frac{[\text{NH}_4^+][\text{OH}^-]}{[\text{NH}_3]} \quad (22)$$

**Ionization of Water**—Although it is a poor conductor of electricity, pure water does ionize through a process known as *autoprotolysis*, in the following manner



Application of the law of mass action to this reaction gives

$$K = \frac{[\text{H}_3\text{O}^+][\text{OH}^-]}{[\text{H}_2\text{O}]^2} \quad (23)$$

where  $K$  is the equilibrium constant for the reaction. Since the concentration of  $\text{H}_2\text{O}$  (molecular water) is very much greater than either the hydronium-ion or hydroxyl-ion concentrations, it can be considered to be constant and can be combined with  $K$  to give a new constant,  $K_w$ , known as the *ion product of water*, and Eq 23 becomes

$$K_w = [\text{H}_3\text{O}^+][\text{OH}^-] \quad (24)$$

The numerical value of  $K_w$  varies with temperature; at 25° it is approximately equal to  $1 \times 10^{-14}$ .

Since the autoprotolysis of pure water yields one hydronium ion for each hydroxyl ion produced,  $[\text{H}_3\text{O}^+]$  must be equal to  $[\text{OH}^-]$ . At 25° each has a value of  $1 \times 10^{-7}$  moles/

Table IV—Dissociation Constants in Water at 25°

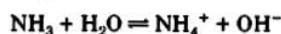
Substance		K
Weak Acids		
Acetic		$1.75 \times 10^{-5}$
Acetylsalicylic		$3.27 \times 10^{-4}$
Barbital		$1.23 \times 10^{-8}$
Barbituric		$1.05 \times 10^{-4}$
Benzoic		$6.30 \times 10^{-5}$
Benzyl penicillin		$1.74 \times 10^{-3}$
Boric	$K_1$	$5.8 \times 10^{-10}$
Caffeine		$1 \times 10^{-14}$
Carbonic	$K_1$	$4.31 \times 10^{-7}$
	$K_2$	$4.7 \times 10^{-11}$
Citric (1H <sub>2</sub> O)	$K_1$	$7.0 \times 10^{-4}$
	$K_2$	$1.8 \times 10^{-5}$
	$K_3$	$4.0 \times 10^{-7}$
Dichloroacetic		$5 \times 10^{-2}$
Ethylenediaminetetra- acetic acid (EDTA)	$K_1$	$1 \times 10^{-2}$
	$K_2$	$2.14 \times 10^{-3}$
	$K_3$	$6.92 \times 10^{-7}$
	$K_4$	$5.5 \times 10^{-11}$
Formic		$1.77 \times 10^{-4}$
Glycerophosphoric	$K_1$	$3.4 \times 10^{-2}$
	$K_2$	$6.4 \times 10^{-7}$
Glycine	$K_1$	$4.5 \times 10^{-3}$
	$K_2$	$1.7 \times 10^{-10}$
Lactic		$1.39 \times 10^{-4}$
Mandelic		$4.29 \times 10^{-4}$
Monochloroacetic		$1.4 \times 10^{-3}$
Oxalic (2H <sub>2</sub> O)	$K_1$	$5.5 \times 10^{-2}$
	$K_2$	$5.3 \times 10^{-6}$
Phenobarbital		$3.9 \times 10^{-8}$
Phenol		$1 \times 10^{-10}$
Phosphoric	$K_1$	$7.5 \times 10^{-3}$
	$K_2$	$6.2 \times 10^{-8}$
	$K_3$	$2.1 \times 10^{-13}$
Picric		$4.2 \times 10^{-1}$
Propionic		$1.34 \times 10^{-5}$
Saccharin		$2.5 \times 10^{-2}$
Salicylic		$1.06 \times 10^{-3}$
Succinic	$K_1$	$6.4 \times 10^{-5}$
	$K_2$	$2.3 \times 10^{-6}$
Sulfadiazine		$3.3 \times 10^{-7}$
Sulfamerazine		$8.7 \times 10^{-8}$
Sulfapyridine		$3.6 \times 10^{-9}$
Sulfathiazole		$7.6 \times 10^{-8}$
Tartaric	$K_1$	$9.6 \times 10^{-4}$
	$K_2$	$4.4 \times 10^{-5}$
Trichloroacetic		$1.3 \times 10^{-1}$
Weak Bases		
Acetanilide		$4.1 \times 10^{-14}$ (40°)
Ammonia		$1.74 \times 10^{-5}$
Apomorphine		$1.0 \times 10^{-7}$
Atropine		$4.5 \times 10^{-5}$
Benzocaine		$6.0 \times 10^{-12}$
Caffeine		$4.1 \times 10^{-14}$ (40°)
Cocaine		$2.6 \times 10^{-6}$
Codeine		$9 \times 10^{-7}$
Ephedrine		$2.3 \times 10^{-5}$
Morphine		$7.4 \times 10^{-7}$
Papaverine		$8 \times 10^{-9}$
Physostigmine	$K_1$	$7.6 \times 10^{-7}$
	$K_2$	$5.7 \times 10^{-13}$
Pilocarpine	$K_1$	$7 \times 10^{-8}$
	$K_2$	$2 \times 10^{-13}$
Procaine		$7 \times 10^{-6}$
Pyridine		$1.4 \times 10^{-9}$
Quinine	$K_1$	$1.0 \times 10^{-6}$
	$K_2$	$1.3 \times 10^{-10}$
Reserpine		$4 \times 10^{-8}$
Strychnine	$K_1$	$1 \times 10^{-6}$
	$K_2$	$2 \times 10^{-12}$
Theobromine		$4.8 \times 10^{-14}$ (40°)
Thiourea		$1.1 \times 10^{-15}$
Urea		$1.5 \times 10^{-14}$

liter ( $1 \times 10^{-7} \times 1 \times 10^{-7} = K_w = 1 \times 10^{-14}$ ). A solution in which  $[H_3O^+]$  is equal to  $[OH^-]$  is termed a *neutral* solution.

If an acid is added to water, the hydronium-ion concentration will be increased and the equilibrium between hydronium and hydroxyl ions will be disturbed *momentarily*. To restore equilibrium, some of the hydroxyl ions, originally present in the water, will combine with a *part* of the added hydronium ions to form nonionized water molecules, until the product of the concentrations of the two ions has been reduced to  $10^{-14}$ . When equilibrium again is restored, the concentrations of the two ions no longer will be equal. If, for example, the hydronium-ion concentration is  $1 \times 10^{-3} N$  when equilibrium is established, the concentration of hydroxyl ion will be  $1 \times 10^{-11}$  (the product of the two concentrations being equal to  $10^{-14}$ ). Since  $[H_3O^+]$  is much greater than  $[OH^-]$ , the solution is said to be *acid* or *acidic*.

In a similar manner, the addition of an alkali to pure water momentarily disturbs the equilibrium between hydronium and hydroxyl ions. To restore equilibrium, some of the hydronium ions originally present in the water will combine with part of the added hydroxyl ions to form nonionized water molecules. The process continues until the product of the hydronium and hydroxyl ion concentrations again is equal to  $10^{-14}$ . Assuming that the final hydroxyl-ion concentration is  $1 \times 10^{-4} N$ , the concentration of hydronium ion in the solution will be  $1 \times 10^{-10}$ . Since  $[OH^-]$  is much greater than  $[H_3O^+]$ , the solution is said to be *basic* or *alkaline*.

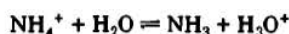
**Relationship of  $K_a$  and  $K_b$ .**—A particularly interesting and useful relationship between the strength of an acid and its conjugate base, or a base and its conjugate acid, exists. For illustration, consider the strength of the base  $NH_3$  and its conjugate acid  $NH_4^+$ , in water. The behavior of  $NH_3$  as a base is expressed by



for which the equilibrium, as formulated earlier is

$$K_b = \frac{[NH_4^+][OH^-]}{[NH_3]} \quad (25)$$

The behavior of  $NH_4^+$  as an acid is represented by



the equilibrium constant for which is

$$K_a = \frac{[NH_3][H_3O^+]}{[NH_4^+]} \quad (26)$$

Multiplying Eqs 25 and 26

$$K_a K_b = \frac{[NH_3][H_3O^+][NH_4^+][OH^-]}{[NH_4^+][NH_3]} \quad (27)$$

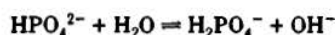
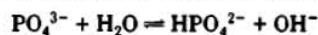
It is obvious that the product

$$K_w = K_a K_b \quad (28)$$

where  $K_w$  is the ion product of water as defined in Eq 24.

The utility of this relationship, which is a general one for any conjugate acid-base pair, is evident from the following deductions: (1) the strength of an acid may be expressed in terms either of the  $K_a$  or the  $K_b$  of its conjugate base, or *vice versa*; (2) the  $K_a$  of an acid may be calculated if the  $K_b$  of its conjugate base is known, or *vice versa* and (3) the stronger an acid is, the weaker its conjugate base, or *vice versa*.

Bases which are capable of interacting with more than one proton are termed *polyacidic*, and can be illustrated by





Applying the law of mass action to this series of reactions, and using the concepts outlined in Eqs 25 to 28, it becomes obvious that the relationship between the various  $K_a$  and  $K_b$  values for phosphoric acid are

$$K_w = K_{a1} \times K_{b3} = K_{a2} \times K_{b2} = K_{a3} \times K_{b1} \quad (29)$$

where  $K_{a1}$ ,  $K_{a2}$  and  $K_{a3}$  refer to the equilibria given by Eqs 17, 18 and 19, respectively;  $K_{b1}$ ,  $K_{b2}$  and  $K_{b3}$  refer to the reaction of  $\text{PO}_4^{3-}$ ,  $\text{HPO}_4^{2-}$  and  $\text{H}_2\text{PO}_4^-$ , respectively, with water.

**Electronegativity and Dissociation Constants**—Table IV gives the dissociation constants of several weak acids and weak bases, in water, at 25°. As pointed out previously, strong acids and strong bases do not obey the law of mass action, so that dissociation constants cannot be formulated for these strong electrolytes.

From an inspection of this table it is evident that great variations occur in the strength of weak acids and weak bases. The effect of various substituents on the strength of acids and bases depends on the electronegativity of the substituent atom or radical. For example, the substitution of one chlorine atom into the molecule of acetic acid increases the degree of ionization of the acid. Substitution of two chlorine atoms further increases the degree of ionization, and introduction of three chlorine atoms produces a still stronger acid. Acetic acid ionizes primarily because the oxygen atom adjacent to the hydrogen atom of the carboxyl group has a stronger affinity for electrons than has the hydrogen atom. Thus, when acetic acid is dissolved in water the polar molecules of the latter have a stronger affinity for the hydrogen of acetic acid than the latter. The acetic acid ionizes as a consequence of this difference in affinities. When an atom of chlorine is introduced into the acetic acid molecule, forming  $\text{ClCH}_2\text{COOH}$ , the electrons in the molecule are attracted very strongly to the chlorine because of its relatively high electronegativity, the bond between the hydrogen and the oxygen in the carboxyl group thereby weakened and the degree of ionization increased. Introduction of two, or three chlorine atoms weakens the bond further and increases the strength of the acid. On the other hand, substitution of chlorine into the molecule of ammonia reduces the strength of the base because of its decreased affinity for the hydrogen ion.

**Ionic Strength and Dissociation Constants**—Most solutions of pharmaceutical interest are in a concentration range such that the ionic strength of the solution may have a marked effect on ionic equilibria and observed dissociation constants. One method of correcting dissociation constants for solutions with an ionic strength up to about 0.3 is to calculate an apparent dissociation constant,  $pK_a'$  as

$$pK_a' = pK_a + \frac{0.51(2Z-1)\sqrt{\mu}}{1+\sqrt{\mu}} \quad (30)$$

in which  $pK_a$  is the tabulated thermodynamic dissociation constant,  $Z$  is the charge on the acid and  $\mu$  is the ionic strength.

*Example*—Calculate  $pK_a'$  for succinic acid at an ionic strength of 0.1. Assume that  $pK_2$  is 5.63. The charge on the acid species is -1.

$$\begin{aligned} pK_2' &= 5.63 + \frac{0.51(-2-1)\sqrt{0.1}}{1+\sqrt{0.1}} \\ &= 5.63 - 0.37 = 5.26 \end{aligned}$$

**Determination of Dissociation Constants**—Although the dissociation constant of a weak acid or base can be obtained in a wide variety of ways including conductivity measurements, or ultraviolet or visible absorption spectrom-

etry, the most widely used method is potentiometric pH measurement (see *Potentiometry*, page 244). The simplest method involving potentiometric pH measurement is based on the measurement of the hydronium-ion concentration of a solution containing equimolar concentrations of the acid and a strong-base salt of the acid. The principle of this method is evident from an inspection of Eq 16; when equimolar concentrations of HA (the acid) and  $\text{A}^-$  (the salt) are present, the dissociation constant,  $K_a$ , numerically is equal to the hydronium-ion concentration (also, the  $pK_a$  of the acid is equal to the pH of the solution). Although this method is simple and rapid, the dissociation constant obtained is not sufficiently accurate for many purposes.

In order to obtain the dissociation constant of a weak acid with a high degree of accuracy and precision, a dilute solution of the acid (about  $10^{-3}$  to  $10^{-4}$  M) is titrated with a strong base, and the pH of the solution taken after each addition of base. The resulting data can be handled in a wide variety of ways, perhaps the best of which is the method proposed by Benet and Goyan.<sup>1</sup> The proton balance equation for a weak acid, HA, being titrated with a strong base such as KOH, would be

$$[\text{K}^+] + [\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{A}^-] \quad (31)$$

in which  $[\text{K}^+]$  is the concentration of the base added. Equation 31 can be rearranged to give

$$Z = [\text{A}^-] = [\text{K}^+] + [\text{H}_3\text{O}^+] - [\text{OH}^-] \quad (32)$$

When a weak monoprotic acid is added to water, it can exist in the unionized form, HA, and in the ionized form,  $\text{A}^-$ . After equilibrium is established, the sum of the concentrations of both species must be equal to  $C_a$ , the stoichiometric (added) concentration of acid or

$$C_a = [\text{HA}] + [\text{A}^-] = [\text{HA}] + Z \quad (33)$$

The term,  $[\text{HA}]$ , can be replaced using Eq 16 to give

$$C_a = \frac{[\text{H}_3\text{O}^+]Z}{K_a} + Z \quad (34)$$

which can be rearranged to

$$Z = C_a - \frac{Z[\text{H}_3\text{O}^+]}{K_a} \quad (35)$$

According to Eq 35, if  $Z$ , which is obtained from the experimental data using Eq 32, is plotted versus the terms  $Z/[\text{H}_3\text{O}^+]$ , a straight line results with a slope equal to  $1/K_a$ , and an intercept equal to  $C_a$ . In addition to obtaining an accurate estimate for the dissociation constant, the stoichiometric concentration of the substance being titrated is obtained also. This is of importance when the substance being titrated cannot be purified, or has an unknown degree of solvation. Similar equations can be developed for obtaining the dissociation constant for a weak base.<sup>1</sup>

The dissociation constants for diprotic acids can be obtained by defining  $P$  as the average number of protons dissociated per mole of acid or

$$P = Z/C_a \quad (36)$$

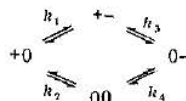
and

$$\frac{[\text{H}_3\text{O}^+]^2 P}{(2-P)} = K_1 K_2 + \frac{K_1 [\text{H}_3\text{O}^+] (1-P)}{(2-P)} \quad (37)$$

A plot of Eq 37 should yield a straight line with a slope equal to  $K_1$  and an intercept of  $K_2$ ; dividing the intercept by the slope yields  $K_2$ .

**Micro Dissociation Constants**—The dissociation constants for polyprotic acids, as determined by potentiometric titration, are generally known as macro, or titration con-

stants. Since it is known that carboxyl groups are stronger acids than protonated amino groups, there is no difficulty in assigning  $K_1$  and  $K_2$ , as determined by Eq 37 to the carboxyl and amino groups, respectively, of a substance such as glycine hydrochloride. In other chemicals or drugs such as phenylpropanolamine, in which the two acidic groups are the phenolic and the protonated amino group, the assignment of dissociation constants is more difficult. This is because, in general, both groups have dissociation constants of equal magnitude. Thus, there will be two ways of losing the first proton and two ways of losing the second, resulting in four possible species in solution. This can be illustrated using the convention of assigning a + to a positively charged group, a 0 to an uncharged group and a - to a negatively charged group. Thus, +0 would represent the fully protonated phenylpropanolamine, +- the dipolar ion, 00 the uncharged molecule and 0-, the anion. The total ionization scheme, therefore, can be written



The micro constants are related to the macro constants as

$$K_1 = k_1 + k_2 \quad (38)$$

$$K_1 K_2 = k_1 k_3 = k_2 k_4 \quad (39)$$

It can be seen from Eq 38 that unless  $k_1$  or  $k_2$  is very much smaller than the other, the observed macro constant is a composite of the two and cannot be assigned to one or the other acidic group in a nonambiguous way.

Methods for determining  $k_1$  are given by Riegelman<sup>2</sup> and Niebergall *et al.*<sup>3</sup> Once  $k_1$ ,  $K_1$  and  $K_2$  have been determined, all of the other micro constants can be obtained from Eqs 38 and 39.

## pH

The numerical values of hydronium-ion concentration may vary enormously; for a normal solution of a strong acid the value is nearly 1, while for a normal solution of a strong base it is approximately  $1 \times 10^{-14}$ ; ie, a variation of 100,000,000,000,000 between these two limits. Because of the inconvenience of dealing with such large numbers, Sørensen, in 1909, proposed that hydronium-ion concentration be expressed in terms of the logarithm (log) of its reciprocal. To this value he assigned the symbol pH. Mathematically it is written

$$\text{pH} = \log \frac{1}{[\text{H}_3\text{O}^+]} \quad (40)$$

and since the logarithm of 1 is zero, the equation also may be written

$$\text{pH} = -\log[\text{H}_3\text{O}^+] \quad (41)$$

from which it is evident that pH also may be defined as the negative logarithm of the hydronium-ion concentration. In general, this type of notation is used to indicate the negative logarithm of the term that is preceded by the "p," which gives rise to the following

$$\text{pOH} = -\log[\text{OH}^-] \quad (42)$$

$$\text{pK} = -\log K \quad (43)$$

Thus, taking logarithms of Eqs 26 and 28 gives

$$\text{p}K_a + \text{p}K_b = \text{p}K_w \quad (44)$$

$$\text{pH} + \text{pOH} = \text{p}K_w \quad (45)$$

The relationship of pH to hydronium-ion and hydroxyl-ion concentrations may be seen in Table V.

The following examples illustrate the conversion from exponential to "p" notation

1. Calculate the pH corresponding to a hydronium-ion concentration of  $1 \times 10^{-4}$  g-ion/L.

Solution:

$$\begin{aligned}
 \text{pH} &= \log \frac{1}{1 \times 10^{-4}} \\
 &= \log 10,000 \text{ or } \log (1 \times 10^4) \\
 \log (1 \times 10^4) &= +4 \\
 \text{pH} &= 4
 \end{aligned}$$

Table V—Hydronium-Ion and Hydroxyl-Ion Concentrations

	pH	Normality in Terms of Hydronium Ion	Normality in Terms of Hydroxyl Ion
Increasing acidity	0	1	$10^{-14}$
	1	$10^{-1}$	$10^{-13}$
	2	$10^{-2}$	$10^{-12}$
	3	$10^{-3}$	$10^{-11}$
	4	$10^{-4}$	$10^{-10}$
Neutral point	5	$10^{-5}$	$10^{-9}$
	6	$10^{-6}$	$10^{-8}$
Increasing alkalinity	7	$10^{-7}$	$10^{-7}$
	8	$10^{-8}$	$10^{-6}$
	9	$10^{-9}$	$10^{-5}$
	10	$10^{-10}$	$10^{-4}$
	11	$10^{-11}$	$10^{-3}$
	12	$10^{-12}$	$10^{-2}$
	13	$10^{-13}$	$10^{-1}$
	14	$10^{-14}$	1

2. Calculate the pH corresponding to a hydronium ion-concentration of 0.000036 N (or g-ion/L). (Note—This more frequently is written as a number multiplied by a power of 10, thus,  $3.6 \times 10^{-5}$  for 0.000036.)

Solution

$$\begin{aligned}
 \text{pH} &= \log \frac{1}{3.6 \times 10^{-5}} \\
 &= \log 28,000 \text{ or } \log (2.8 \times 10^4) \\
 \log (2.8 \times 10^4) &= \log 2.8 + \log 10^4 \\
 \log 2.8 &= +0.44 \\
 \log 10^4 &= +4.00 \\
 \text{pH} &= 4.44
 \end{aligned}$$

This problem may also be solved as follows

$$\begin{aligned}
 \text{pH} &= -\log (3.6 \times 10^{-5}) \\
 \log 3.6 &= +0.56 \\
 \log 10^{-5} &= -5.00 \\
 &= -4.44 = \log (3.6 \times 10^{-5}) \\
 \text{pH} &= -(-4.44) = +4.44 = 4.44
 \end{aligned}$$

The following examples illustrate the conversion of "p" notation to exponential notation:

1. Calculate the hydronium-ion concentration corresponding to a pH of 4.44.



*Solution*

$$\text{pH} = \log \frac{1}{[\text{H}_3\text{O}^+]}$$

$$4.44 = \log \frac{1}{[\text{H}_3\text{O}^+]}$$

$$\frac{1}{[\text{H}_3\text{O}^+]} = \text{antilog of } 4.44 = 28,000 \text{ (rounded off)}$$

$$[\text{H}_3\text{O}^+] = \frac{1}{28,000} = 0.000036 \text{ or } 3.6 \times 10^{-5}$$

This calculation also may be made as

$$+4.44 = -\log [\text{H}_3\text{O}^+]$$

$$\text{or } -4.44 = +\log [\text{H}_3\text{O}^+]$$

In finding the antilog of  $-4.44$  it should be kept in mind that the *mantissa* (the number to the right of the decimal point) of a log to the base 10 (the common or Briggsian logarithm base) is *always positive* but that the *characteristic* (the number to the left of the decimal point) may be *positive or negative*. As the entire log  $-4.44$  is negative, it is obvious that one cannot look up the antilog of  $-4.44$ . However, the number  $-4.44$  also may be written  $(-5.00 + 0.56)$  or, as more often written,  $5.56$ , where the bar across the characteristic indicates that it alone is negative, while the rest of the number is positive. Looking up the antilog of  $0.56$  it is found to be  $3.6$  and, as the antilog of  $-5.00$  is  $10^{-5}$ , it follows that the hydronium-ion concentration must be  $3.6 \times 10^{-5}$  moles/l.

2. Calculate the hydronium-ion concentration corresponding to a pH of 10.17.

*Solution*

$$10.17 = -\log [\text{H}_3\text{O}^+]$$

$$-10.17 = \log [\text{H}_3\text{O}^+]$$

$$-10.17 = (-11.00 + 0.83) = \bar{1}1.83$$

The antilog of  $0.83 = 6.8$

The antilog of  $-11.00 = 10^{-11}$

The hydronium-ion concentration is therefore  $6.8 \times 10^{-11}$  moles/l.

In the section on *Ionization of Water* it was shown that the hydronium-ion concentration of pure water, at  $25^\circ$ , is  $1 \times 10^{-7}$  *N*, corresponding to a pH of 7.\* This figure, therefore, is designated as the neutral point and all values below a pH of 7 represent acidity; the smaller the number, the greater the acidity. Values above 7 represent alkalinity; the larger the number, the greater the alkalinity. The pH scale usually runs from 0 to 14, but mathematically there is no reason why negative numbers or numbers above 14 should not be used. In practice, however, such values are never encountered because solutions which might be expected to have such values are too concentrated to be ionized extensively or the interionic attraction is so great as to materially reduce ionic activity.

It should be emphasized strongly that the generalizations stated concerning neutrality, acidity and alkalinity hold exactly only when (1) the solvent is water, (2) the temperature is  $25^\circ$  and (3) there are no other factors to cause deviation from the simply formulated equilibria underlying the definition of pH given in the preceding discussion.

### Species Concentration

When a weak acid,  $\text{H}_n\text{A}$ , is added to water,  $n + 1$  species, including the unionized acid, can exist. After equilibrium is

\* The pH of the purest water obtainable, so-called "conductivity" water, is 7.0 when the measurement is carefully made under conditions to exclude carbon dioxide and prevent errors inherent in the measuring technique (such as acidity or alkalinity of the indicator). Upon agitating this water in the presence of carbon dioxide in the atmosphere (equilibrium water) the value drops rapidly to 5.7, which is the pH of nearly all distilled waters that have been exposed to the atmosphere for even a short time.

established, the sum of the concentrations of all species must be equal to  $C_a$ , the stoichiometric (added) concentration of acid. Thus, for a triprotic acid  $\text{H}_3\text{A}$

$$C_a = [\text{H}_3\text{A}] + [\text{H}_2\text{A}^-] + [\text{HA}^{2-}] + [\text{A}^{3-}] \quad (46)$$

In addition, the concentrations of all acidic and basic species in solution vary with pH, and can be represented solely in terms of equilibrium constants and the hydronium-ion concentration. These relationships may be expressed as

$$[\text{H}_n\text{A}] = [\text{H}_3\text{O}^+]^n C_a/D \quad (47)$$

$$[\text{H}_{n-j}\text{A}^{-j}] = [\text{H}_3\text{O}^+]^{n-j} K_1 \dots K_j C_a/D \quad (48)$$

in which  $n$  represents the total number of dissociable hydrogens in the parent acid,  $j$  is the number of protons dissociated,  $C_a$  is the stoichiometric concentration of acid and  $K$  represents the acid dissociation constants. The term  $D$  is a power series in  $[\text{H}_3\text{O}^+]$  and  $K$ , starting with  $[\text{H}_3\text{O}^+]$  raised to the  $n$ th power. The last term is the product of all the dissociation constants. The intermediate terms can be generated from the last term by substituting  $[\text{H}_3\text{O}^+]$  for  $K_n$  to obtain the next-to-last term, then substituting  $[\text{H}_3\text{O}^+]$  for  $K_{n-1}$  to obtain the next term, etc, until the first term is reached. The following examples show the denominator,  $D$ , to be used for various types of acids

$$\text{H}_3\text{A}: D = [\text{H}_3\text{O}^+]^3 + K_1[\text{H}_3\text{O}^+]^2 + K_1K_2[\text{H}_3\text{O}^+] + K_1K_2K_3 \quad (49)$$

$$\text{H}_2\text{A}^-: D = [\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2 \quad (50)$$

$$\text{HA}^{2-}: D = [\text{H}_3\text{O}^+] + K_a \quad (51)$$

The numerator, in all instances, is  $C_a$  multiplied by the term from the denominator that has  $[\text{H}_3\text{O}^+]$  raised to the  $n - j$  power. Thus, for diprotic acids such as carbonic, succinic, tartaric, etc

$$[\text{H}_2\text{A}] = \frac{[\text{H}_3\text{O}^+]^2 C_a}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2} \quad (52)$$

$$[\text{HA}^-] = \frac{K_1[\text{H}_3\text{O}^+] C_a}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2} \quad (53)$$

$$[\text{A}^{2-}] = \frac{K_1K_2 C_a}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2} \quad (54)$$

*Example*—Calculate the concentrations of all succinic acid species in a  $1.0 \times 10^{-2}$  *M* solution of succinic acid at pH 6.0. Assume that  $K_1 = 6.4 \times 10^{-5}$  and  $K_2 = 2.3 \times 10^{-6}$ .

Eqs 52–54 have the same denominator,  $D$ , which can be calculated as

$$\begin{aligned} D &= [\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2 \\ &= 1.0 \times 10^{-12} + 6.4 \times 10^{-5} \times 1.0 \times 10^{-6} + 6.4 \times \\ &\quad 10^{-5} \times 2.3 \times 10^{-6} \\ &= 1.0 \times 10^{-12} + 6.4 \times 10^{-11} + 14.7 \times 10^{-11} \\ &= 21.2 \times 10^{-11} \end{aligned}$$

Therefore

$$[\text{H}_2\text{A}] = \frac{[\text{H}_3\text{O}^+]^2 C_a}{D} = \frac{1.0 \times 10^{-12} \times 1.0 \times 10^{-2}}{21.2 \times 10^{-11}} = 4.7 \times 10^{-6} \text{ M}$$

$$[\text{HA}^-] = \frac{K_1[\text{H}_3\text{O}^+]C_a}{D} = \frac{6.4 \times 10^{-11} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 3.0 \times 10^{-4} M$$

$$[\text{A}^{2-}] = \frac{K_1 K_2 C_a}{D} = \frac{14.7 \times 10^{-11} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 6.9 \times 10^{-5} M$$

### Proton Balance Equation

In the Brønsted-Lowry system the total number of protons released by acidic species must equal the total number of protons consumed by basic species. This results in a very useful relationship known as the proton balance equation (PBE), in which the sum of the concentration terms for species that form by proton consumption is equated to the sum of the concentration terms for species that are formed by the release of protons. The PBE forms the basis of a unified approach to pH calculations, since it is an exact accounting of all proton transfers occurring in solution.

When HCl is added to water, for example, it dissociates yielding one  $\text{Cl}^-$  for each proton released. Thus,  $\text{Cl}^-$  is a species formed by the release of a proton. In the same solution, and actually in all aqueous solutions



where  $\text{H}_3\text{O}^+$  is formed by proton consumption and  $\text{OH}^-$  is formed by proton release. Thus, the PBE is

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{Cl}^-] \quad (55)$$

In general, the PBE can be formed in the following manner

1. Start with the species added to water.
2. Place all species that can form when protons are released on the right side of the equation.
3. Place all species that can form when protons are consumed on the left side of the equation.
4. Add  $[\text{H}_3\text{O}^+]$  to the left side of the equation and  $[\text{OH}^-]$  to the right side of the equation. These result from the interaction of two molecules of water as shown above.

*Example*—When  $\text{H}_3\text{PO}_4$  is added to water, the species  $\text{H}_2\text{PO}_4^-$  forms with the release of one proton,  $\text{HPO}_4^{2-}$  forms with the release of two protons and  $\text{PO}_4^{3-}$  forms with the release of three protons to give the following PBE

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{H}_2\text{PO}_4^-] + 2[\text{HPO}_4^{2-}] + 3[\text{PO}_4^{3-}] \quad (56)$$

*Example*—When  $\text{Na}_2\text{HPO}_4$  is added to water, it dissociates into two  $\text{Na}^+$  and one  $\text{HPO}_4^{2-}$ . The sodium ion is neglected in the PBE since it is not formed from the release or consumption of protons. The species  $\text{HPO}_4^{2-}$ , however, may react with water to give  $\text{H}_2\text{PO}_4^-$  with the consumption of one proton,  $\text{H}_3\text{PO}_4$  with the consumption of two protons, and  $\text{PO}_4^{3-}$  with the release of one proton to give the following PBE

$$[\text{H}_3\text{O}^+] + [\text{H}_2\text{PO}_4^-] + 2[\text{H}_3\text{PO}_4] = [\text{OH}^-] + [\text{PO}_4^{3-}] \quad (57)$$

### Calculations

The pH of solutions of acids, bases and salts may be calculated using the concepts presented in the preceding sections.

#### Strong Acids or Bases

When a strong acid such as HCl is added to water, the following reactions occur



The proton balance equation for this system would be

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{Cl}^-] \quad (58)$$

In most instances ( $C_a > 4.5 \times 10^{-7} M$ ) the  $[\text{OH}^-]$  would be negligible compared to the  $[\text{Cl}^-]$  and the equation simplifies to

$$[\text{H}_3\text{O}^+] = [\text{Cl}^-] = C_a \quad (59)$$

Thus, the hydronium-ion concentration of a solution of a strong acid would be equal to the stoichiometric concentration of the acid. This would be anticipated, since strong acids generally are assumed to be 100% ionized.

The pH of a 0.005 M solution of HCl therefore is calculated as

$$\text{pH} = -\log 0.005 = 2.30$$

In a similar manner the hydroxyl-ion concentration for a solution of a strong base such as NaOH would be

$$[\text{OH}^-] = [\text{Na}^+] = C_b \quad (60)$$

and the pH of a 0.005 M solution of NaOH would be

$$\text{pOH} = -\log 0.005 = 2.30$$

$$\text{pH} = \text{p}K_w - \text{pOH} = 14.00 - 2.30 = 11.70$$

#### Weak Acids or Bases

If a weak acid, HA, is added to water, it will equilibrate with its conjugate base,  $\text{A}^-$ , as



Accounting for the ionization of water gives the following proton balance equation for this system

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{A}^-] \quad (61)$$

The concentration of  $\text{A}^-$  as a function of hydronium-ion concentration can be obtained as shown previously to give

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + \frac{K_a C_a}{[\text{H}_3\text{O}^+] + K_a} \quad (62)$$

Algebraic simplification yields

$$[\text{H}_3\text{O}^+] = K_a \frac{(C_a - [\text{H}_3\text{O}^+] + [\text{OH}^-])}{([\text{H}_3\text{O}^+] - [\text{OH}^-])} \quad (63)$$

In most instances for solutions of weak acids,  $[\text{H}_3\text{O}^+] \gg [\text{OH}^-]$  and the equation simplifies to give

$$[\text{H}_3\text{O}^+]^2 + K_a[\text{H}_3\text{O}^+] - K_a C_a = 0 \quad (64)$$

This is a quadratic equation\* which yields

$$[\text{H}_3\text{O}^+] = \frac{-K_a + \sqrt{K_a^2 + 4K_a C_a}}{2} \quad (65)$$

since  $[\text{H}_3\text{O}^+]$  can never be negative. Furthermore, if  $[\text{H}_3\text{O}^+]$  is less than 5% of  $C_a$ , Eq 64 is simplified further to give

\* The general solution to a quadratic equation of the form

$$aX^2 + bX + c = 0$$

is

$$X = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$



$$[\text{H}_3\text{O}^+] = \sqrt{K_a C_a} \quad (66)$$

It generally is preferable to use the simplest equation to calculate  $[\text{H}_3\text{O}^+]$ . However, when  $[\text{H}_3\text{O}^+]$  is calculated, it must be compared to  $C_a$  in order to determine whether the assumption  $C_a \gg [\text{H}_3\text{O}^+]$  is valid. If the assumption is not valid, the quadratic equation should be used.

*Example*—Calculate the pH of a  $5.00 \times 10^{-5} M$  solution of a weak acid having a  $K_a = 1.90 \times 10^{-5}$ .

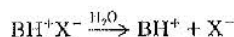
$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{K_a C_a} \\ &= 1.90 \times 10^{-5} \times 5.00 \times 10^{-5} \\ &= 3.08 \times 10^{-6} M \end{aligned}$$

Since  $C_a$  ( $5.00 \times 10^{-5} M$ ) is not much greater than  $[\text{H}_3\text{O}^+]$ , the quadratic equation (Eq 65) should be used

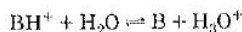
$$\begin{aligned} [\text{H}_3\text{O}^+] &= \frac{-1.90 \times 10^{-5} + \sqrt{(1.90 \times 10^{-5})^2 + 4(1.90 \times 10^{-5})(5.00 \times 10^{-5})}}{2} \\ &= 2.26 \times 10^{-5} M \\ \text{pH} &= -\log(2.26 \times 10^{-5}) = 4.65 \end{aligned}$$

Note that the assumption  $[\text{H}_3\text{O}^+] \gg [\text{OH}^-]$  is valid. The hydronium-ion concentration calculated from Eq 66 has a relative error of 36% when compared to the correct value obtained from Eq 65.

When a salt obtained from a strong acid and a weak base—e.g., ammonium chloride, morphine sulfate, pilocarpine hydrochloride, etc.—is dissolved in water, it dissociates as



in which  $\text{BH}^+$  is the protonated form of the base B, and  $\text{X}^-$  is the anion of a strong acid. Since  $\text{X}^-$  is the anion of a strong acid, it is too weak a base to undergo any further reaction with water. The protonated base, however, can act as a weak acid to give



Thus, Eqs 65 and 66 are valid, with  $C_a$  being equal to the concentration of the salt in solution. If  $K_a$  for the protonated base is not available, it can be obtained by dividing  $K_b$  for the base B, into  $K_w$ .

*Example*—Calculate the pH of a  $0.026 M$  solution of ammonium chloride. Assume that  $K_b$  for ammonia is  $1.74 \times 10^{-5}$  and  $K_w$  is  $1.00 \times 10^{-14}$ .

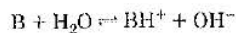
$$K_a = \frac{K_w}{K_b} = \frac{1.00 \times 10^{-14}}{1.74 \times 10^{-5}} = 5.75 \times 10^{-10}$$

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{K_a C_a} \\ &= \sqrt{5.75 \times 10^{-10} \times 2.6 \times 10^{-2}} \\ &= 3.87 \times 10^{-6} M \\ \text{pH} &= -\log(3.87 \times 10^{-6}) = 5.41 \end{aligned}$$

Since  $C_a$  is much greater than  $[\text{H}_3\text{O}^+]$  and  $[\text{H}_3\text{O}^+]$  is much greater than  $[\text{OH}^-]$ , the assumptions are valid and the value calculated for pH is sufficiently accurate.

#### Weak Bases

When a weak base, B, is dissolved in water it ionizes to give the conjugate acid as



The proton balance equation for this system is

$$[\text{BH}^+] + [\text{H}_3\text{O}^+] = [\text{OH}^-] \quad (67)$$

Substituting  $[\text{BH}^+]$  as a function of hydronium-ion concen-

tration and simplifying, in the same manner as shown for a weak acid, gives

$$[\text{OH}^-] = K_b \frac{(C_b - [\text{OH}^-] + [\text{H}_3\text{O}^+])}{([\text{OH}^-] - [\text{H}_3\text{O}^+])} \quad (68)$$

If  $[\text{OH}^-] \gg [\text{H}_3\text{O}^+]$ , as is true generally

$$[\text{OH}^-]^2 + K_b[\text{OH}^-] - K_b C_b = 0 \quad (69)$$

which is a quadratic with the following solution

$$[\text{OH}^-] = \frac{-K_b + \sqrt{K_b^2 + 4K_b C_b}}{2} \quad (70)$$

If  $C_b \gg [\text{OH}^-]$ , the quadratic equation simplifies to

$$[\text{OH}^-] = \sqrt{K_b C_b} \quad (71)$$

Once  $[\text{OH}^-]$  is calculated, it can be converted to pOH, which can be subtracted from pK<sub>w</sub> to give pH.

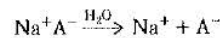
*Example*—Calculate the pH of a  $4.50 \times 10^{-2} M$  solution of a weak base having  $K_b = 2.00 \times 10^{-4}$ . Assume that  $K_w = 1.00 \times 10^{-14}$ .

$$\begin{aligned} [\text{OH}^-] &= \sqrt{K_b C_b} \\ &= \sqrt{2.00 \times 10^{-4} \times 4.50 \times 10^{-2}} \\ &= \sqrt{9.00 \times 10^{-6}} = 3.00 \times 10^{-3} M \end{aligned}$$

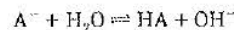
Both assumptions are valid.

$$\begin{aligned} \text{pOH} &= -\log 3.00 \times 10^{-3} = 2.52 \\ \text{pH} &= 14.00 - 2.52 = 11.48 \end{aligned}$$

When salts obtained from strong bases and weak acids (eg, sodium acetate, sodium sulfathiazole, sodium benzoate, etc) are dissolved in water, they dissociate as



in which  $\text{A}^-$  is the conjugate base of the weak acid, HA. The  $\text{Na}^+$  undergoes no further reaction with water. The  $\text{A}^-$ , however, acts as a weak base to give



Thus, Eqs 70 and 71 are valid, with  $C_b$  being equal to the concentration of the salt in solution. The value for  $K_b$  can be obtained by dividing  $K_w$  for the conjugate acid, HA, into  $K_a$ .

*Example*—Calculate the pH of a  $0.05 M$  solution of sodium acetate. Assume that  $K_a$  for acetic acid is  $1.75 \times 10^{-5}$  and  $K_w = 1.00 \times 10^{-14}$ .

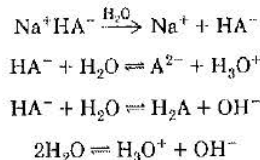
$$\begin{aligned} K_b &= \frac{K_w}{K_a} = \frac{1.00 \times 10^{-14}}{1.75 \times 10^{-5}} \\ &= 5.71 \times 10^{-10} \\ [\text{OH}^-] &= \sqrt{K_b C_b} = \sqrt{5.71 \times 10^{-10} \times 5.0 \times 10^{-2}} \\ &= 5.34 \times 10^{-6} M \end{aligned}$$

Both assumptions are valid

$$\begin{aligned} \text{pOH} &= -\log(5.34 \times 10^{-6}) = 5.27 \\ \text{pH} &= 14.00 - 5.27 = 8.73 \end{aligned}$$

### Ampholytes

Substances such as  $\text{NaHCO}_3$  and  $\text{NaH}_2\text{PO}_4$  are termed *ampholytes*, and are capable of functioning both as acids and bases. When an ampholyte of the type  $\text{NaHA}$  is dissolved in water, the following series of reactions can occur



The total proton balance equation (PBE) for the system is

$$[\text{H}_3\text{O}^+] + [\text{H}_2\text{A}] = [\text{OH}^-] + [\text{A}^{2-}] \quad (72)$$

Substituting both  $[\text{H}_2\text{A}]$  and  $[\text{A}^{2-}]$  as a function of  $[\text{H}_3\text{O}^+]$  (see Eqs 52 and 54), yields

$$[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]^2 C_s}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1 K_2} = \frac{K_w}{[\text{H}_3\text{O}^+]} + \frac{K_1 K_2 C_s}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1 K_2}$$

This gives a fourth-order equation in  $[\text{H}_3\text{O}^+]$ , which can be simplified using certain judicious assumptions to

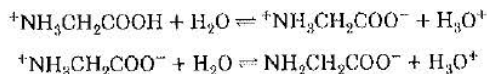
$$[\text{H}_3\text{O}^+] = \sqrt{\frac{K_1 K_2 C_s}{K_1 + C_s}} \quad (73)$$

In most instances,  $C_s \gg K_1$  and the equation further simplifies to

$$[\text{H}_3\text{O}^+] = \sqrt{K_1 K_2} \quad (74)$$

and  $[\text{H}_3\text{O}^+]$  becomes independent of the concentration of the salt. A special property of ampholytes is that the concentration of the species  $\text{HA}^-$  is maximum at the pH corresponding to Eq 74.

When the simplest amino acid salt, glycine hydrochloride, is dissolved in water, it acts as a diprotic acid and ionizes as



The form,  ${}^+ \text{NH}_3 \text{CH}_2 \text{COO}^-$ , is an ampholyte since it also can act as a weak base

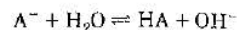
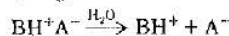


This type of substance, which carries both a charged acid and a charged basic moiety on the same molecule is termed a *zwitterion* and, since the two charges balance each other, the molecule acts essentially as a neutral molecule. The pH at which the *zwitterion* concentration is maximum is known as the isoelectric point, which can be calculated from Eq 74.

On the acid side of the isoelectric point, amino acids and proteins are cationic and incompatible with anionic materials such as the naturally occurring gums used as suspending and/or emulsifying agents. On the alkaline side of the isoelectric point, amino acids and proteins are anionic and incompatible with cationic materials such as benzalkonium chloride.

### Salts of Weak Acids and Weak Bases

When a salt such as ammonium acetate (which is derived from a weak acid and a weak base) is dissolved in water, it undergoes the following reactions



The total PBE for this system is

$$[\text{H}_3\text{O}^+] + [\text{HA}] = [\text{OH}^-] + [\text{B}] \quad (75)$$

Replacing  $[\text{HA}]$  and  $[\text{B}]$  as a function of  $[\text{H}_3\text{O}^+]$ , gives

$$[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+] C_s}{[\text{H}_3\text{O}^+] + K_a} = [\text{OH}^-] + \frac{K_a' C_s}{[\text{H}_3\text{O}^+] + K_a'} \quad (76)$$

in which  $C_s$  is the concentration of salt,  $K_a$  is the ionization constant of the conjugate acid formed from the reaction between  $\text{A}^-$  and water and  $K_a'$  is the ionization constant for the protonated base,  $\text{BH}^+$ . In general,  $[\text{H}_3\text{O}^+]$ ,  $[\text{OH}^-]$ ,  $K_a$  and  $K_a'$  usually are smaller than  $C_s$  and the equation simplifies to

$$[\text{H}_3\text{O}^+] = \sqrt{K_a K_a'} \quad (77)$$

*Example*—Calculate the pH of a 0.01 *M* solution of ammonium acetate. The ammonium ion has a  $K_a$  equal to  $5.75 \times 10^{-10}$ , which represents  $K_a'$  in Eq 77. Acetic acid has a  $K_a$  of  $1.75 \times 10^{-5}$ , which represents  $K_a$  in Eq 77

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{1.75 \times 10^{-5} \times 5.75 \times 10^{-10}} \\ &= 1.05 \times 10^{-7} \\ \text{pH} &= -\log (1.05 \times 10^{-7}) = 6.98 \end{aligned}$$

All of the assumptions are valid.

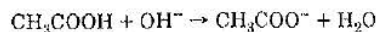
### Buffers

The terms *buffer*, *buffer solution* and *buffered solution*, when used with reference to hydrogen-ion concentration or pH, refer to the ability of a system, particularly an aqueous solution, to resist a change of pH on adding acid or alkali, or on dilution with a solvent.

If an acid or base is added to water, the pH of the latter is changed markedly, for water has no ability to resist change of pH; it is completely devoid of buffer action. Even a very weak acid such as carbon dioxide changes the pH of water, decreasing it from 7 to 5.7 when the small concentration of carbon dioxide present in air is equilibrated with pure water. This extreme susceptibility of distilled water to a change of pH on adding very small amounts of acid or base is often of great concern in pharmaceutical operations. Solutions of neutral salts, such as sodium chloride, similarly lack ability to resist change of pH on adding acid or base; such solutions are called unbuffered.

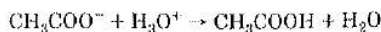
Characteristic of buffered solutions, which undergo small changes of pH on addition of acid or base, is the presence either of a weak acid and a salt of the weak acid, or a weak base and a salt of the weak base. An example of the former system is acetic acid and sodium acetate; of the latter, ammonium hydroxide and ammonium chloride. From the proton concept of acids and bases discussed earlier, it is apparent that such buffer action involves a conjugate acid-base pair in the solution. It will be recalled that acetate ion is the conjugate base of acetic acid, and that ammonium ion is the conjugate acid of ammonia (the principal constituent of what commonly is called ammonium hydroxide).

The mechanism of action of the acetic acid-sodium acetate buffer pair is that the acid, which exists largely in molecular (nonionized) form, combines with hydroxyl ion that may be added to form acetate ion and water, thus



while the acetate ion, which is a base, combines with hydrogen (more exactly hydronium) ion that may be added to

form essentially nonionized acetic acid and water, represented as



As will be illustrated later by an example, the change of pH is slight as long as the amount of hydronium or hydroxyl ion added does not exceed the capacity of the buffer system to neutralize it.

The ammonia-ammonium chloride pair functions as a buffer because the ammonia combines with hydronium ion that may be added to form ammonium ion and water, thus



Ammonium ion, which is an acid, combines with added hydroxyl ion to form ammonia and water, as

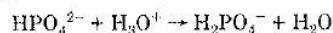


Again, the change of pH is slight if the amount of added hydronium or hydroxyl ion is not in excess of the capacity of the system to neutralize it.

Besides these two general types of buffers, a third appears to exist. This is the buffer system composed of two salts, as monobasic potassium phosphate,  $\text{KH}_2\text{PO}_4$ , and dibasic potassium phosphate,  $\text{K}_2\text{HPO}_4$ . This is not, however, a new type of buffer; it is actually a weak-acid-conjugate-base buffer in which an ion,  $\text{H}_2\text{PO}_4^-$ , serves as the weak acid, and  $\text{HPO}_4^{2-}$  is its conjugate base. When hydroxyl ion is added to this buffer the following reaction takes place



and when hydronium ion is added



It is apparent that the mechanism of action of this type of buffer is essentially the same as that of the weak-acid-conjugate-base buffer composed of acetic acid and sodium acetate.

**Calculations**—A buffer system composed of a conjugate acid-base pair,  $\text{NaA} - \text{HA}$  (such as sodium acetate and acetic acid), would have a PBE of

$$[\text{H}_3\text{O}^+] + [\text{HA}] = [\text{OH}^-] + [\text{A}^-] \quad (78)$$

Replacing  $[\text{HA}]$  and  $[\text{A}^-]$  as a function of hydronium-ion concentration gives

$$[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]C_b}{[\text{H}_3\text{O}^+] + K_a} = [\text{OH}^-] + \frac{K_a C_a}{[\text{H}_3\text{O}^+] + K_a} \quad (79)$$

where  $C_b$  is the concentration of the salt,  $\text{NaA}$ , and  $C_a$  is the concentration of the weak acid,  $\text{HA}$ . This equation can be rearranged to give

$$[\text{H}_3\text{O}^+] = K_a \frac{(C_a - [\text{H}_3\text{O}^+] + [\text{OH}^-])}{(C_b + [\text{H}_3\text{O}^+] - [\text{OH}^-])} \quad (80)$$

In general, both  $C_a$  and  $C_b$  are much greater than  $[\text{H}_3\text{O}^+]$ , which is in turn much greater than  $[\text{OH}^-]$ , and the equation simplifies to

$$[\text{H}_3\text{O}^+] = \frac{K_a C_a}{C_b} \quad (81)$$

or, expressed in terms of pH, as

$$\text{pH} = \text{p}K_a + \log \frac{C_b}{C_a} \quad (82)$$

This equation is generally called the Henderson-Hasselbalch equation. It applies to all buffer systems formed from a single conjugate acid-base pair, regardless of the nature of the salts. For example, it applies equally well to the follow-

ing buffer systems: ammonia-ammonium chloride, monosodium phosphate-disodium phosphate, phenobarbital-sodium phenobarbital, etc. In the ammonia-ammonium chloride system, ammonia is obviously the base and the ammonium ion is the acid ( $C_a$  equal to the concentration of the salt). In the phosphate system, monosodium phosphate is the acid and disodium phosphate is the base. For the phenobarbital buffer system, phenobarbital is the acid and the phenobarbital anion is the base ( $C_b$  equal to the concentration of sodium phenobarbital).

As an example of the application of this equation, the pH of a buffer solution containing acetic acid and sodium acetate, each in 0.1 M concentration, may be calculated. The  $K_a$  of acetic acid, as defined above, is  $1.8 \times 10^{-5}$ , at 25°.

**Solution**

First, the  $\text{p}K_a$  of acetic acid is calculated

$$\begin{aligned} \text{p}K_a &= -\log K_a = -\log 1.8 \times 10^{-5} \\ &= -\log 1.8 - \log 10^{-5} \\ &= -0.26 - (-5) = +4.74 \end{aligned}$$

Substituting this value into Eq 82

$$\text{pH} = \log \frac{0.1}{0.1} + 4.74 = +4.74$$

The Henderson-Hasselbalch equation predicts that any solutions containing the same molar concentration of acetic acid as of sodium acetate will have the same pH. Thus, a solution of 0.01 M concentration of each will have the same pH, 4.74, as one of 0.1 M concentration of each component. Actually, there will be some difference in the pH of the solutions, for the *activity coefficient* of the components varies with concentration. For most practical purposes, however, the approximate values of pH calculated by the equation are satisfactory. It should be pointed out, however, that the buffer of higher concentration of each component will have a much greater capacity for neutralizing added acid or base and this point will be discussed further under *Buffer Capacity*.

The Henderson-Hasselbalch equation is useful also for calculating the ratio of molar concentrations of a buffer system required to produce a solution of specific pH. As an example, suppose that an acetic acid-sodium acetate buffer of pH 4.5 is to be prepared. What ratio of the buffer components should be used?

**Solution**

Rearranging Eq 82, which is used to calculate the pH of weak acid-salt type buffers, gives

$$\begin{aligned} \log \frac{[\text{base}]}{[\text{acid}]} &= \text{pH} - \text{p}K_a \\ &= 4.5 - 4.76 = -0.24 = (9.76 - 10) \\ \frac{[\text{base}]}{[\text{acid}]} &= \text{antilog of } (9.76 - 10) = 0.575 \end{aligned}$$

The interpretation of this result is that the *proportion* of sodium acetate to acetic acid should be 0.575 mole of the former to 1 mole of the latter to produce a pH of 4.5. A solution containing 0.0575 mole of sodium acetate and 0.1 mole of acetic acid per liter would meet this requirement, as would also one containing 0.00575 mole of sodium acetate and 0.01 mole of acetic acid per liter. The actual concentration selected would depend chiefly on the desired buffer capacity.

**Buffer Capacity**—The ability of a buffer solution to resist changes in pH upon addition of acid or alkali may be measured in terms of *buffer capacity*. In the preceding discussion of buffers, it has been seen that, in a general way, the concentration of acid in a weak-acid-conjugate-base buffer determines the capacity to "neutralize" added base,

while the concentration of salt of the weak acid determines the capacity to neutralize added acid. Similarly, in a weak-base-conjugate-acid buffer the concentration of the weak base establishes the buffer capacity toward added acid, while the concentration of the conjugate acid of the weak base determines the capacity toward added base. When the buffer is equimolar in the concentrations of weak acid and conjugate base, or of weak base and conjugate acid, it has equal buffer capacity toward added strong acid or strong base.

Van Slyke, the biochemist, introduced a quantitative expression for evaluating buffer capacity. This may be defined as the amount, in gram-equivalents (g-Eq) per liter, of strong acid or strong base, required to be added to a solution to change its pH by 1 unit; a solution has a buffer capacity of 1 when 1 L. requires 1 g-Eq of strong base or acid to change the pH 1 unit (in practice, considerably smaller increments are measured, expressed as the ratio of acid or base added to the change of pH produced). From this definition it is apparent that the smaller the pH change in a solution caused by the addition of a specified quantity of acid or alkali, the greater the buffer capacity of the solution.

The following numerical examples illustrate certain basic principles and calculations concerning buffer action and buffer capacity.

*Example 1*—What is the change of pH on adding 0.01 mole of NaOH to 1 L. of 0.10 *M* acetic acid?

(a) Calculate the pH of a 0.10 molar solution of acetic acid

$$[\text{H}_3\text{O}^+] = \sqrt{K_a C_a} = 1.75 \times 10^{-4} \times 1.0 \times 10^{-1} = 1.33 \times 10^{-3}$$

$$\text{pH} = -\log 1.33 \times 10^{-3} = 2.88$$

(b) On adding 0.01 mole of NaOH to a liter of this solution, 0.01 mole of acetic acid is converted to 0.01 mole of sodium acetate, thereby decreasing  $C_a$  to 0.09 *M*, and  $C_b = 1.0 \times 10^{-2}$  *M*. Using the Henderson-Hasselbach equation gives

$$\text{pH} = 4.76 + \log \frac{0.01}{0.09} = 4.76 - 0.95 = 3.81$$

The pH change is, therefore, 0.93 unit. The buffer capacity as defined above is calculated to be

$$\frac{\text{moles of NaOH added}}{\text{change in pH}} = 0.011$$

*Example 2*—What is the change of pH on adding 0.1 mole of NaOH to 1 L. of buffer solution 0.1 *M* in acetic acid and 0.1 *M* in sodium acetate?

(a) The pH of the buffer solution before adding NaOH is

$$\begin{aligned} \text{pH} &= \log \frac{[\text{base}]}{[\text{acid}]} + \text{p}K_a \\ &= \log \frac{0.1}{0.1} + 4.76 = 4.76 \end{aligned}$$

(b) On adding 0.01 mole of NaOH per liter to this buffer solution, 0.01 mole of acetic acid is converted to 0.01 mole of sodium acetate, thereby decreasing the concentration of acid to 0.09 *M* and increasing the concentration of base to 0.11 *M*. The pH is calculated as

$$\begin{aligned} \text{pH} &= \log \frac{0.11}{0.09} + 4.76 \\ &= 0.086 + 4.76 = 4.85 \end{aligned}$$

The change of pH in this case is only 0.09 unit, about  $\frac{1}{10}$  the change in the preceding example. The buffer capacity is calculated as

$$\frac{\text{moles of NaOH added}}{\text{change of pH}} = \frac{0.01}{0.09} = 0.11$$

Thus, the buffer capacity of the acetic acid-sodium acetate buffer solution is approximately 10 times that of the acetic acid solution.

As is in part evident from these examples, and may be further evidenced by calculations of pH changes in other systems, the degree of buffer action and, therefore, the buff-

er capacity, depend on the kind and concentration of the buffer components, the pH region involved and the kind of acid or alkali added.

**Strong Acids and Bases as "Buffers"**—In the foregoing discussion, buffer action was attributed to systems of (1) weak acids and their conjugate bases, (2) weak bases and their conjugate acids and (3) certain acid-base pairs which can function in the manner either of System 1 or 2.

The ability to resist change in pH on adding acid or alkali is possessed also by relatively concentrated solutions of strong acids and strong bases. If to 1 L. of pure water having a pH of 7.0 is added 1 mL. of 0.01 *M* hydrochloric acid, the pH is reduced to about 5.0. If the same volume of the acid is added to 1 L. of 0.001 *M* hydrochloric acid, which has a pH of about 3, the hydronium-ion concentration is increased only about 1% and the pH is reduced hardly at all. The nature of this buffer action is quite different from that of the true buffer solutions. The very simple explanation is that when 1 mL. of 0.01 *M* HCl, which represents 0.00001 g-Eq of hydronium ions, is added to the 0.0000001 g-Eq of hydronium ions in 1 L. of pure water, the hydronium-ion concentration is increased 100-fold (equivalent to 2 pH units), but when the same amount is added to the 0.001 g-Eq of hydronium ions in 1 L. of 0.001 *M* HCl, the increase is only 1/100 the concentration already present. Similarly, if 1 mL. of 0.01 *M* NaOH is added to 1 L. of pure water, the pH is increased to 9, while if the same volume is added to 1 L. of 0.001 molar NaOH, the pH is increased almost immeasurably.

In general, solutions of strong acids of pH 3 or less, and solutions of strong bases of pH 11 or more, exhibit this kind of buffer action by virtue of the relatively high concentration of hydronium or hydroxyl ions present. The USP includes among its *Standard Buffer Solutions* a series of hydrochloric acid buffers, covering the pH range 1.2 to 2.2, which also contain potassium chloride. The salt does not participate in the buffering mechanism, as is the case with salts of weak acids; instead, it serves as a nonreactive constituent required to maintain the proper electrolyte environment of the solutions.

## Determination of pH

### Colorimetry

A relatively simple and inexpensive method for determining the approximate pH of a solution depends on the fact that some conjugate acid base pairs (indicators) possess one color in the acid form and another color in the base form. Assume that the acid form of a particular indicator is red, while the base form is yellow. The color of a solution of this indicator will range from red, when it is sufficiently acid, to yellow, when it is sufficiently alkaline. In the intermediate pH range (the transition interval) the color will be a blend of red and yellow depending upon the ratio of the base to the acid form. In general, although there are slight differences between indicators, color changes apparent to the eye cannot be discerned when the ratio of base to acid form, or acid to base form exceeds 10:1. The use of Eq 82 indicates that the transition range of most indicators is equal to the  $\text{p}K_a$  of the indicator  $\pm 1$  pH unit, or a useful range of approximately 2 pH units. Standard indicator solutions can be made at known pH values within the transition range of the indicator, and the pH of an unknown solution determined by adding the indicator to it and comparing the resulting color with the standard solutions. Details of this procedure can be found in RPS-14. Another method for using these indicators is to apply them to thin strips of filter paper. A drop of the unknown solution is placed on a piece of the indicator paper and the resulting color compared to a color chart supplied with the indicator paper. These papers are available in a wide variety of pH ranges.



## Potentiometry

Electrometric methods for the determination of pH are based on the fact that the difference of electrical potential between two suitable electrodes dipping into a solution containing hydronium ions depends on the concentration (or activity) of the latter. The development of a potential difference is not a specific property of hydronium ions. A solution of any ion will develop a potential proportional to the concentration of that ion if a suitable pair of electrodes is placed in the solution.

The relationship between the potential difference and concentration of an ion in equilibrium with the electrodes may be derived as follows. When a metal is immersed into a solution of one of its salts, there is a tendency for the metal to go into solution in the form of ions. This tendency is known as the *solution pressure* of the metal and is comparable to the tendency of sugar molecules, for example, to dissolve in water. The metallic ions in solution tend, on the other hand, to become discharged by forming atoms, this effect being proportional to the *osmotic pressure* of the ions. In order for an atom of a metal to go into solution as a positive ion, electrons, equal in number to the charge on the ion, must be left behind on the metal electrode with the result that the latter becomes negatively charged. The positively charged ions in solution, however, may become discharged as atoms by taking up electrons from the metal electrode. Depending on which effect predominates, the electrical charge on the electrode will be either positive or negative and may be quantitatively expressed by the following equation proposed by Nernst in 1889

$$E = \frac{RT}{nF} \ln \frac{P}{p} \quad (83)$$

where  $E$  is the potential difference or electromotive force,  $R$  is the gas constant (8.316 joules),  $T$  is the absolute temperature,  $n$  is the valence of the ion,  $F$  is the Faraday of electricity (96,500 coulombs),  $p$  is the osmotic pressure of the ions and  $P$  is the solution pressure of the metal.

Inasmuch as it is impossible to measure the potential difference between one electrode and a solution with any degree of certainty, it is customary to use two electrodes and to measure the potential difference between them. If two electrodes, both of the same metal, are immersed separately in solutions containing ions of that metal, at osmotic pressures  $p_1$  and  $p_2$ , respectively, and connected by means of a tube containing a nonreacting salt solution (a so-called "salt-bridge"), the potential developed across the two electrodes will be equal to the difference between the potential differences of the individual electrodes; thus

$$E = E_1 - E_2 = \frac{RT}{nF} \ln \frac{p_1}{P_1} - \frac{RT}{nF} \ln \frac{p_2}{P_2} \quad (84)$$

Since both electrodes are of the same metal,  $P_1 = P_2$  and the equation may be simplified to

$$E = \frac{RT}{nF} \ln p_1 - \frac{RT}{nF} \ln p_2 = \frac{RT}{nF} \ln \frac{p_1}{p_2} \quad (85)$$

In place of osmotic pressures it is permissible, for dilute solutions, to substitute the concentrations  $c_1$  and  $c_2$  which were found (see Chapter 16, page 222) to be proportional to  $p_1$  and  $p_2$ . The equation then becomes

$$E = \frac{RT}{nF} \ln \frac{c_1}{c_2} \quad (86)$$

If either  $c_1$  or  $c_2$  is known, it is obvious that the value of the other may be found if the potential difference,  $E$ , of this cell can be measured.

For the determination of hydronium-ion concentration or pH, an electrode at which an equilibrium between hydrogen

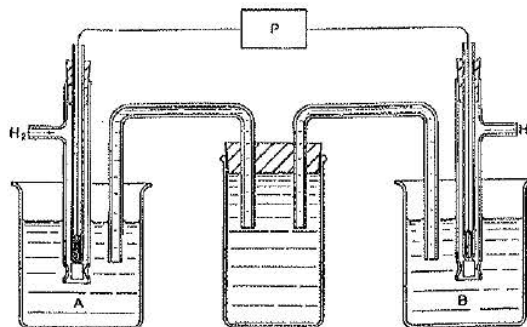


Fig 17-3. Hydrogen-ion concentration chain.

gas and hydronium ion can be established must be used in place of metallic electrodes. Such an electrode may be made by electrolytically coating a strip of platinum, or other noble metal, with platinum black and saturating the latter with pure hydrogen gas. This device functions as a *hydrogen electrode*. Two such electrodes may be assembled as shown in Fig 17-3.

In this diagram one electrode dips into Solution A, containing a known hydronium-ion concentration, and the other electrode dips into Solution B, containing an unknown hydronium-ion concentration. The two electrodes and solutions, sometimes called half-cells, then are connected by a bridge of neutral salt solution, which has no significant effect on the solutions it connects. The potential difference across the two electrodes is measured by means of a potentiometer,  $P$ . If the concentration,  $c_1$ , of hydronium ion in Solution A is 1  $N$ , Eq 86 simplifies to

$$E = \frac{RT}{nF} \ln \frac{1}{c_2} \quad (87)$$

or in terms of Briggsian logarithms

$$E = 2.303 \frac{RT}{nF} \log_{10} \frac{1}{c_2} \quad (88)$$

If for  $\log_{10} 1/c_2$  there is substituted its equivalent pH, the equation becomes

$$E = 2.303 \frac{RT}{nF} \text{pH} \quad (89)$$

and finally by substituting numerical values for  $R$ ,  $n$ ,  $T$  and  $F$ , and assuming the temperature to be 20°, the following simple relationship is derived

$$E = 0.0581 \text{ pH or pH} = \frac{E}{0.0581} \quad (90)$$

The hydrogen electrode dipping into a solution of known hydronium-ion concentration, called the *reference electrode*, may be replaced by a calomel electrode, one type of which is shown in Fig 17-4. The elements of a calomel electrode are mercury and calomel in an aqueous solution of potassium chloride. The potential of this electrode is constant, regardless of the hydronium-ion concentration of the solution into which it dips. The potential depends on the equilibrium which is set up between mercury and mercurous ions from the calomel, but the concentration of the latter is governed, according to the solubility-product principle, by the concentration of chloride ions, which are derived mainly from the potassium chloride in the solution. Therefore, the potential of this electrode varies with the concentration of potassium chloride in the electrolyte.

Because the calomel electrode always indicates voltages which are higher, by a constant value, than those obtained

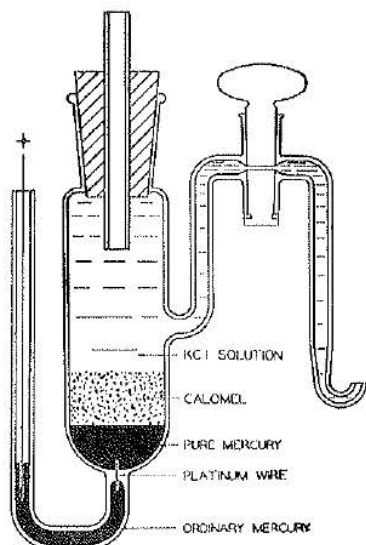


Fig 17-4. Calomel electrode.

when the normal hydrogen electrode chain shown in Fig 17-3 is used, it is necessary to subtract the potential due to the calomel electrode itself from the observed voltage. As the magnitude of this voltage depends on the concentration of potassium chloride in the calomel-electrode electrolyte, it is necessary to know the concentration of the former. For most purposes a saturated potassium chloride solution is used which produces potential difference of 0.2488 v. Accordingly, before using Eq 85 for the calculation of pH from the voltage of a cell made up of a calomel and a hydrogen electrode dipping into the solution to be tested, 0.2488 v must be subtracted from the observed potential difference. Expressed mathematically, Eq 91 is used for calculating pH from the potential difference of such a cell.

$$\text{pH} = \frac{E - 0.2488}{0.0581} \quad (91)$$

In measuring the potential difference between the electrodes, it is imperative that very little current be drawn from the cell, for with current flowing the voltage changes, owing to polarization effects at the electrode. Because of this it is not possible to make accurate measurements with a voltmeter which requires appreciable current to operate it. In its place a potentiometer is used which does not draw a current from the cell being measured.

There are many limitations to the use of the hydrogen electrode:

It cannot be used in solutions containing strong oxidants such as ferric iron, dichromates, nitric acid, peroxide or chlorine or reductants, such as sulfurous acid and hydrogen sulfide.

It is affected by the presence of organic compounds which are fairly easily reduced.

It cannot be used successfully in solutions containing cations that fall below hydrogen in the electrochemical series.

Erratic results are obtained in the measurement of unbuffered solutions unless special precautions are taken.

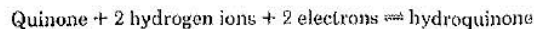
It is troublesome to prepare and maintain.

Since other electrodes more convenient to use now are available, the hydrogen electrode today is used rarely. Nevertheless, it is the ultimate standard for pH measurements.

To avoid some of the difficulties with the hydrogen electrode, the *quinhydrone* electrode was introduced and was popular for a long time, particularly for measurements of acid solutions. The unusual feature of this electrode is that it consists of a piece of gold or platinum wire or foil dipping

into the solution to be tested, in which has been dissolved a small quantity of quinhydrone. A calomel electrode may be used for reference, just as in determinations with the hydrogen electrode.

Quinhydrone consists of an equimolecular mixture of quinone and hydroquinone; the relationship between these substances and hydrogen-ion concentration is



In a solution containing hydrogen ions the potential of the quinhydrone electrode is related logarithmically to hydronium-ion concentration if the ratio of the hydroquinone concentration to that of quinone is constant and practically equal to one. This ratio is maintained in an acid solution containing an excess of quinhydrone, and measurements may be made quickly and accurately; however, quinhydrone cannot be used in solutions more alkaline than pH 8.

An electrode which, because of its simplicity of operation and freedom from contamination or change of the solution being tested, has replaced both the hydrogen and quinhydrone electrodes is the *glass electrode*. It functions by virtue of the fact that when a thin membrane of a special composition of glass separates two solutions of different pH there is developed across the membrane a potential difference which depends on the pH of both solutions. If the pH of one of the solutions is known, the other may be calculated from the potential difference. In practice, the glass electrode usually consists of a bulb of the special glass fused to the end of a tube of ordinary glass. Inside the bulb is placed a solution of known pH, in contact with an internal silver-silver chloride or other electrode. This glass electrode and another reference electrode are immersed in the solution to be tested and the potential difference is measured. A potentiometer providing electronic amplification of the small current produced is employed. The modern instruments available permit reading the pH directly and provide also for compensation of variations due to temperature in the range of 0-50° and to the small but variable asymmetry potential inherent in the glass electrode.

### Pharmaceutical Significance

In the broad realm of knowledge concerning the preparation and action of drugs few, if any, variables are so important as pH. For the purpose of this presentation, four principal types of pH-dependence of drug systems will be discussed: solubility, stability, activity and absorption.

#### Drug Solubility

If a salt, NaA, is added to water to give a concentration  $C_s$ , the following reactions occur



If the pH of the solution is lowered, more of the  $\text{A}^-$  would be converted to the unionized acid, HA, in accordance with Le Chatelier's principle. Eventually, a pH will be obtained, below which the amount of HA formed exceeds its aqueous solubility,  $S_0$ , and the acid will precipitate from solution; this pH can be designated as  $\text{pH}_p$ . At this point, at which the amount of HA formed just equals  $S_0$ , a mass balance on the total amount of drug in solution yields

$$C_s = [\text{HA}] + [\text{A}^-] = S_0 + [\text{A}^-] \quad (92)$$

Replacing  $[\text{A}^-]$  as a function of hydronium-ion concentration gives

$$C_s = S_0 + \frac{K_a C_s}{[H_3O^+]_p + K_a} \quad (93)$$

where  $K_a$  is the ionization constant for the conjugate acid, HA, and  $[H_3O^+]_p$  refers to the hydronium-ion concentration above which precipitation will occur. This equation can be rearranged to give

$$[H_3O^+]_p = K_a \frac{S_0}{C_s - S_0} \quad (94)$$

Taking logarithms gives

$$pH_p = pK_a + \log \frac{C_s - S_0}{S_0} \quad (95)$$

Thus, the pH below which precipitation occurs is a function of the amount of salt added initially, the  $pK_a$  and the solubility of the free acid formed from the salt.

The analogous equation for salts of weak bases and strong acids (such as pilocarpine hydrochloride, cocaine hydrochloride or codeine phosphate) would be

$$pH_p = pK_a + \log \frac{S_0}{C_s - S_0} \quad (96)$$

in which  $pK_a$  refers to the protonated form of the weak base.

*Example.*—Below what pH will free phenobarbital begin to precipitate from a solution initially containing 1.3 g of sodium phenobarbital/100 mL at 25°C? The molar solubility of phenobarbital is 0.0050 and its  $pK_a$  is 7.41. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

$$C_s = \frac{\text{g/l}}{\text{mol wt}} = \frac{13}{254} = 0.051 M$$

$$\begin{aligned} pH_p &= 7.41 + \log \frac{0.051 - 0.005}{0.005} \\ &= 7.41 + 0.96 = 8.37 \end{aligned}$$

*Example.*—Above what pH will free cocaine begin to precipitate from a solution initially containing 0.0294 mole of cocaine hydrochloride/L? The  $pK_b$  of cocaine is 5.59, and its molar solubility is  $5.60 \times 10^{-3}$ .

$$pK_a = pK_b - pK_b = 14.00 - 5.59 = 8.41$$

$$\begin{aligned} pH_p &= 8.41 + \log \frac{0.0056}{0.0294 - 0.0056} \\ &= 8.41 + (-0.63) = 7.78 \end{aligned}$$

#### Drug Stability

One of the most diversified and fruitful areas of study is the investigation of the effect of hydrogen-ion concentration on the stability or, in more general terms, the reactivity of pharmaceutical systems. The evidence for enhanced stability of systems when these are maintained within a narrow range of pH, as well as of progressively decreasing stability as the pH departs from the optimum range, is abundant. Stability (or instability) of a system may result from gain or loss of a proton (hydrogen ion) by a substrate molecule—often accompanied by an electronic rearrangement—which reduces (or increases) the reactivity of the molecule. Instability results when the substance desired to remain unchanged is converted to one or more other, unwanted, substances. In aqueous solution, instability may arise through the catalytic effect of acids or bases, the former by transferring a proton to the substrate molecule, the latter by accepting a proton.

Specific illustrations of the effect of hydrogen-ion concentration on the stability of medicinals are myriad; only a few will be given here, these being chosen to show the importance of pH adjustment of solutions that require sterilization.

Morphine solutions are not decomposed during a 60-min exposure at a temperature of 100° if the pH is less than 5.5; neutral and alkaline solutions, however, are highly unstable. Minimum hydrolytic decomposition of solutions of cocaine occurs in the range of pH of 2 to 5; in one study a solution of cocaine hydrochloride, initially at a pH of 5.7, remained stable during 2 months (although the pH dropped to 4.2 in this time), while another solution buffered to about pH 6 underwent approximately 30% hydrolysis in the same time. Similarly, solutions of procaine hydrochloride containing some hydrochloric acid showed no appreciable decomposition; when dissolved in water alone, 5% of the procaine hydrochloride hydrolyzed, while when buffered to pH 6.5, from 19 to 35% underwent decomposition by hydrolysis. Solutions of thiamine hydrochloride may be sterilized by autoclaving without appreciable decomposition if the pH is below 5; above this, thiamine hydrochloride is unstable.

The stability of many disperse systems, and especially of certain emulsions, is often pH-dependent. Information concerning specific emulsion systems, and the effect of pH upon them, may be found in Chapter 19.

#### Drug Activity

Drugs that are weak acids or weak bases, and hence may exist in ionized or nonionized form (or a mixture of both), may be active in one form but not in the other; often such drugs have an optimum pH range for maximum activity. Thus, mandelic acid, benzoic acid or salicylic acid have pronounced antibacterial activity in nonionized form but have practically no such activity in ionized form. Accordingly, these substances require an acid environment to function effectively as antibacterial agents. For example, sodium benzoate is effective as a preservative in 4% concentration at pH 7.0, in 0.06 to 0.1% concentration at pH 3.5 to 4.0 and in 0.02 to 0.03% concentration at pH 2.3 to 2.4. Other antibacterial agents, on the other hand, are active principally, if not entirely, in cationic form. Included in this category are the acridines and quaternary ammonium compounds.

#### Drug Absorption

The degree of ionization and lipid solubility of a drug are two important factors that determine the rate of absorption of drugs from the gastrointestinal tract and, indeed, their passage through cellular membranes generally. Drugs which are weak organic acids or bases, and which in nonionized form are soluble in lipids, apparently are absorbed through cellular membranes by virtue of the lipoidal nature of the membranes. Completely ionized drugs, on the other hand, are absorbed poorly, if at all. Rates of absorption of a variety of drugs are related to their ionization constants and in many cases may be predicted quantitatively on the basis of this relationship. Thus, not only the degree of the acidic or basic character of a drug but consequently also the pH of the physiological medium (gastric or intestinal fluid, plasma, cerebrospinal fluid, etc) in which a drug is dissolved or dispersed—since this pH determines the extent to which the drug will be converted to ionic or nonionic form—become important parameters of drug absorption. Further information on drug absorption is given in Chapter 35.

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## CHAPTER 19

# Disperse Systems

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## Interfacial Phenomena

Very often it is desirable or necessary in the development of pharmaceutical dosage forms to produce multiphasic dispersions by mixing together two or more ingredients which are not mutually miscible and capable of forming homogeneous solutions. Examples of such dispersions include suspensions (solid in liquid), emulsions (liquid in liquid) and foams (vapor in liquids). Because these systems are not homogeneous and thermodynamically stable, over time they will show some tendency to separate on standing to produce the minimum possible surface area of contact between phases. Thus, suspended particles agglomerate and sediment, emulsified droplets cream and coalesce and the bubbles dispersed in foams collapse, to produce unstable and nonuniform dosage forms. In this chapter the fundamental physical chemical properties of dispersed systems will be discussed, along with the principles of interfacial and colloidal physics and chemistry which underly these properties.

### Interfacial Forces and Energetics

In the bulk portion of each phase, molecules are attracted to each other equally in all directions, such that no resultant forces are acting on any one molecule. The strength of these forces determines whether a substance exists as a vapor, liquid or solid at a particular temperature and pressure.

At the boundary between phases, however, molecules are acted upon unequally since they are in contact with other molecules exhibiting different forces of attraction. For example, the primary intermolecular forces in water are due to hydrogen bonds, whereas those responsible for intermolecular bonding in hydrocarbon liquids, such as mineral oil, are due to London dispersion forces.

Because of this, molecules situated at the interface contain potential forces of interaction which are not satisfied relative to the situation in each bulk phase. In liquid systems such unbalanced forces can be satisfied by spontaneous movement of molecules from the interface into the bulk phase. This leaves fewer molecules per unit area at the interface (greater intermolecular distance) and reduces the actual contact area between dissimilar molecules.

Any attempt to reverse this process by increasing the area of contact between phases, ie, bringing more molecules into the interface, causes the interface to resist expansion and to

behave as though it is under a tension everywhere in a tangential direction. The force of this tension per unit length of interface generally is called the interfacial tension, except when dealing with the air-liquid interface, where the terms surface and surface tension are used.

To illustrate the presence of a tension in the interface, consider an experiment where a circular metal frame, with a looped piece of thread loosely tied to it, is dipped into a liquid. When removed and exposed to the air, a film of liquid will be stretched entirely across the circular frame, as when one uses such a frame to blow soap bubbles. Under these conditions (Fig 19-1A), the thread will remain collapsed. If now a heated needle is used to puncture and remove the liquid film from within the loop (Fig 19-1B), the loop will stretch spontaneously into a circular shape.

The result of this experiment demonstrates the spontaneous reduction of interfacial contact between air and the liquid remaining and, indeed, that a tension causing the loop to remain extended exists parallel to the interface. The circular shape of the loop indicates that the tension in the plane of the interface exists at right angles or normal to every part of the looped thread. The total force on the entire loop divided by the circumference of the circle, therefore, represents the tension per unit distance of surface, or the surface tension.

Just as work is required to extend a spring under tension, work should be required to reverse the process seen in Figs 19-1A and B, thus bringing more molecules to the interface. This may be seen quantitatively by considering an experiment where tension and work may be measured directly. Assume that we have a rectangular wire with one movable side (Fig 19-2). Assume further that by dipping this wire into a liquid, a film of liquid will form within the frame when it is removed and exposed to the air. As seen earlier in Fig 19-1, since it comes in contact with air, the liquid surface will tend to contract with a force,  $F$ , as molecules leave the surface for the bulk. To keep the movable side in equilibrium, an equal force must be applied to oppose this tension in the surface. We then may define the surface tension,  $\gamma$ , of the liquid as  $F/2l$ , where  $2l$  is the distance of surface over which  $F$  is operating ( $2l$  since there are two surfaces, top and bottom). If the surface is expanded by a very small distance,  $\Delta x$ , one can then estimate that the work done is

$$W = F\Delta x \quad (1)$$

and therefore

$$W = \gamma 2l\Delta x \quad (2)$$

Dr Zografi authored the section on *Interfacial Phenomena*. Dr Schott authored the section on *Colloidal Dispersions*. Dr Swarbrick authored the section on *Particle Phenomena and Coarse Dispersions*.



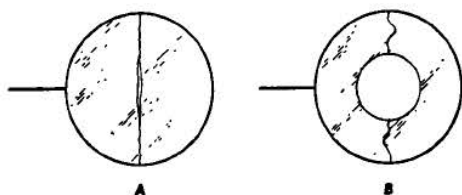


Fig 19-1. A circular wire frame with a loop of thread loosely tied to it: (A) a liquid film on the wire frame with a loop in it; (B) the film inside the loop is broken.<sup>1</sup>

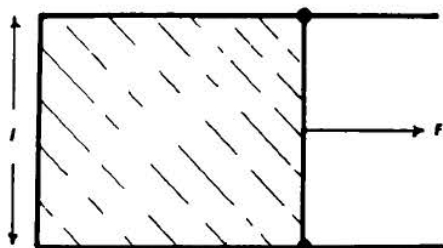


Fig 19-2. A movable wire frame containing a film of liquid being expanded with a force,  $F$ .

Since

$$\Delta A = 2l\Delta x \quad (3)$$

where  $\Delta A$  is the change in area due to the expansion of the surface, we may conclude that

$$W = \gamma\Delta A \quad (4)$$

Thus, the work required to create a unit area of surface, known as the surface free energy/unit area, is equivalent to the surface tension of a liquid system, and the greater the area of interfacial contact between phases, the greater the free-energy increase for the total system. Since a prime requisite for equilibrium is that the free energy of a system be at a minimum, it is not surprising to observe that phases in contact tend to reduce area of contact spontaneously.

Liquids, being mobile, may assume spherical shapes (smallest interfacial area for a given volume), as when ejected from an orifice into air or when dispersed into another immiscible liquid. If a large number of drops are formed, further reduction in area can occur by having the drops coalesce, as when a foam collapses or when the liquid phases making up an emulsion separate.

Surface tension is expressed in units of dynes/cm, while surface free energy is expressed in ergs/cm<sup>2</sup>. Since an erg is a dyne-cm, both sets of units are equivalent.

Values for the surface tension of a variety of liquids are given in Table I, while interfacial tension values for various liquids against water are given in Table II. Other combinations of immiscible phases could be given but most heterogeneous systems encountered in pharmacy usually contain water. Values for these tensions are expressed for a particular temperature. Since an increased temperature increases the thermal energy of molecules, the work required to bring molecules to the interface should be less, and thus the surface and interfacial tension will be reduced. For example, the surface tension of water at 0° is 76.5 dynes/cm and 63.5 dynes/cm at 75°.

As would be expected from the discussion so far, the relative values for surface tension should reflect the nature of intermolecular forces present; hence, the relatively large values for mercury (metallic bonds) and water (hydrogen bonds), and the lower values for benzene, chloroform, carbon tetrachloride and the *n*-alkanes. Benzene with  $\pi$  electrons

Table I—Surface Tension of Various Liquids at 20°

Substance	Surface tension, dynes/cm
Mercury	476
Water	72.8
Glycerin	63.4
Oleic acid	32.5
Benzene	28.9
Chloroform	27.1
Carbon tetrachloride	26.8
1-Octanol	26.5
Hexadecane	27.4
Dodecane	25.4
Decane	23.9
Octane	21.8
Heptane	19.7
Hexane	18.0
Perfluoroheptane	11.0
Nitrogen (at 75°K)	9.4

Table II—Interfacial Tension of Various Liquids against Water at 20°

Substance	Interfacial tension, dynes/cm
Decane	52.3
Octane	51.7
Hexane	50.8
Carbon tetrachloride	45.0
Chloroform	32.8
Benzene	35.0
Mercury	428
Oleic acid	15.6
1-Octanol	8.51

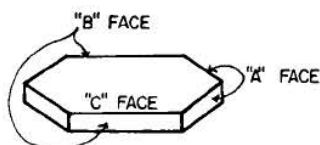
exhibits a higher surface tension than the alkanes of comparable molecular weight, but increasing the molecular weight of the alkanes (and hence intermolecular attraction) increases their surface tension closer to that of benzene. The lower values for the more nonpolar substances, perfluoroheptane and liquid nitrogen, demonstrate this point even more strongly.

Values of interfacial tension should reflect the differences in chemical structure of the two phases involved; the greater the tendency to interact, the less the interfacial tension. The 20-dynes/cm difference between air–water tension and that at the octane–water interface reflects the small but significant interaction between octane molecules and water molecules at the interface. This is seen also in Table II, by comparing values for octane and octanol, oleic acid and the alkanes, or chloroform and carbon tetrachloride.

In each case the presence of chemical groups capable of hydrogen bonding with water markedly reduces the interfacial tension, presumably by satisfying the unbalanced forces at the interface. These observations strongly suggest that molecules at an interface arrange themselves or orient so as to minimize differences between bulk phases.

That this occurs even at the air–liquid interface is seen when one notes the relatively low surface-tension values of very different chemical structures such as the *n*-alkanes, octanol, oleic acid, benzene and chloroform. Presumably, in each case, the similar nonpolar groups are oriented toward the air with any polar groups oriented away toward the bulk phase. This tendency for molecules to orient at an interface is a basic factor in interfacial phenomena and will be discussed more fully in succeeding sections.

Solid substances such as metals, metal oxides, silicates and salts, all containing polar groups exposed at their surface, may be classified as high-energy solids, whereas nonpo-

Fig 19-3. Adipic acid crystal showing various faces.<sup>2</sup>Table III—Values of  $\gamma_{sv}$  for Solids of Varying Polarity

Solid	$\gamma_{sv}$ (dynes/cm)
Teflon	19.0
Paraffin	25.5
Polyethylene	37.6
Polymethyl methacrylate	45.4
Nylon	50.8
Indomethacin	61.8
Griseofulvin	62.2
Hydrocortisone	68.7
Sodium Chloride	155
Copper	1300

lar solids such as carbon, sulfur, glyceryl tristearate, polyethylene and polytetrafluoroethylene (Teflon) may be classified as low-energy solids. It is of interest to measure the surface free energy of solids; however, the lack of mobility of molecules at the surface of solids prevents the observation and direct measurement of a surface tension. It is possible to measure the work required to create new solid surface by cleaving a crystal and measuring the work involved. However, this work not only represents free energy due to exposed groups but also takes into account the mechanical energy associated with the crystal (ie, plastic and elastic deformation and strain energies due to crystal structure and imperfections in that structure).

Also contributing to the complexity of a solid surface is the heterogeneous behavior due to the exposure of different crystal faces, each having a different surface free energy/unit area. For example, adipic acid,  $\text{HOOC}(\text{CH}_2)_4\text{COOH}$ , crystallizes from water as thin hexagonal plates with three different faces, as shown in Fig 19-3. Each unit cell of such a crystal contains adipic acid molecules oriented such that the hexagonal planes (faces) contain exposed carboxyl groups, while the sides and edges (A and B faces) represent the side view of the carboxyl and alkyl groups, and thus are quite nonpolar. Indeed, interactions involving these different faces reflect the differing surface free energies.<sup>2</sup>

Other complexities associated with solid surfaces include surface roughness, porosity and the defects and contamination produced during a recrystallization or comminution of the solid. In view of all these complications, surface free energy values for solids, when reported, should be regarded as average values, often dependent on the method used and not necessarily the same for other samples of the same substance.

In Table III are listed some approximate average values of  $\gamma_{sv}$  for a variety of solids, ranging in polarity from Teflon to copper, obtained by various indirect techniques.

### Adhesional and Cohesional Forces

Of prime importance to those dealing with heterogeneous systems is the question of how two phases will behave when brought in contact with each other. It is well known, for instance, that some liquids, when placed in contact with other liquid or solid surfaces, will remain retracted in the form of a drop (known as a lens), while other liquids may

exhibit a tendency to spread and cover the surface of this liquid or solid.

Based upon concepts developed to this point, it is apparent that the individual phases will exhibit a tendency to minimize the area of contact with other phases, thus leading to phase separation. On the other hand, the tendency for interaction between molecules at the new interface will offset this to some extent and give rise to the spontaneous spreading of one substance over the other.

In essence, therefore, phase affinity is increased as the forces of attraction between different phases (adhesional forces) become greater than the forces of attraction between molecules of the same phase (cohesional forces). If these adhesional forces become great enough, miscibility will occur and the interface will disappear. The present discussion is concerned only with systems of limited phase affinity, where an interface still exists.

A convenient approach used to express these forces quantitatively involves the use of the terms work of adhesion and work of cohesion.

The work of adhesion,  $W_a$ , is defined as the energy per  $\text{cm}^2$  required to separate two phases at their boundary and is equal but opposite in sign to the free energy/ $\text{cm}^2$  released when the interface is formed. In an analogous manner the work of cohesion for a pure substance,  $W_c$ , is the work/ $\text{cm}^2$  required to produce two new surfaces, as when separating different phases, but now both surfaces contain the same molecules. This is equal and opposite in sign to the free energy/ $\text{cm}^2$  released when the same two pure liquid surfaces are brought together and eliminated.

By convention, when the work of adhesion between two substances, A and B, exceeds the work of cohesion for one substance, eg, B, spontaneous spreading of B over the surface of A should occur with a net loss of free energy equal to the difference between  $W_a$  and  $W_c$ . If  $W_c$  exceeds  $W_a$ , no spontaneous spreading of B over A can occur. The difference between  $W_a$  and  $W_c$  is known as the spreading coefficient, S; only when S is positive will spreading occur.

The values for  $W_a$  and  $W_c$  (and hence S) may be expressed in terms of surface and interfacial tensions, when one considers that upon separation of two phases, A and B,  $\gamma_{AB}$  ergs of interfacial free energy/ $\text{cm}^2$  (interfacial tension) are lost, but that  $\gamma_A$  and  $\gamma_B$  ergs/ $\text{cm}^2$  of energy (surface tensions of A and B) are gained; upon separation of bulk phase molecules in an analogous manner,  $2\gamma_A$  or  $2\gamma_B$  ergs/ $\text{cm}^2$  will be gained. Thus

$$W_a = \gamma_A + \gamma_B - \gamma_{AB} \quad (5)$$

and

$$W_c = 2\gamma_A \text{ or } 2\gamma_B \quad (6)$$

For B spreading on the surface of A, therefore

$$S_B = \gamma_A + \gamma_B - \gamma_{AB} - 2\gamma_B \quad (7)$$

or

$$S_B = \gamma_A - (\gamma_B + \gamma_{AB}) \quad (8)$$

Utilizing Eq 8 and values of surface and interfacial tension given in Tables I and II, S can be calculated for three representative substances—decane, benzene, and oleic acid—on water at 20°.

$$\text{Decane: } S = 72.8 - (23.9 + 52.3) = -3.4$$

$$\text{Benzene: } S = 72.8 - (28.9 + 35.0) = 8.9$$

$$\text{Oleic acid: } S = 72.8 - (32.5 + 15.6) = 24.7$$

As expected, relatively nonpolar substances such as decane exhibit negative values of S, whereas the more polar materials yield positive values; the greater the polarity of the mole-

cule, the more positive the value of  $S$ . The importance of the cohesive energy of the spreading liquid may be noted also by comparing the spreading coefficients for hexane on water and water on hexane:

$$S_{H/W} = 72.8 - (18.0 + 50.8) = 4.0$$

$$S_{W/H} = 18.0 - (72.8 + 50.8) = -105.6$$

Here, despite the fact that both liquids are the same, the high cohesion and air-liquid tension of water prevents spreading on the low-energy hexane surface, while the very low value for hexane allows spreading on the water surface. This also is seen when comparing the positive spreading coefficient of hexane to the negative value for decane on water.

To see whether spreading does or does not occur, a powder such as talc or charcoal can be sprinkled over the surface of water such that it floats; then, a drop of each liquid is placed on this surface. As predicted, decane will remain as an intact drop, while hexane, benzene and oleic acid will spread out, as shown by the rapid movement of solid particles away from the point where the liquid drop was placed originally.

An apparent contradiction to these observations may be noted for hexane, benzene and oleic acid when more of each substance is added, in that lenses now appear to form even though initial spreading occurred. Thus, in effect a substance does not appear to spread over itself.

It is now established that the spreading substance forms a monomolecular film which creates a new surface having a lower surface free energy than pure water. This arises because of the apparent orientation of the molecules in such a film so that their most hydrophobic portion is oriented towards the spreading phase. It is the lack of affinity between this exposed portion of the spread molecules and the polar portion of the remaining molecules which prevents further spreading.

This may be seen by calculating a final spreading coefficient where the new surface tension of water plus monomolecular film is used. For example, the presence of benzene reduces the surface tension of water to 62.2 dynes/cm so that the final spreading coefficient,  $S_F$ , is

$$S_F = 62.2 - (28.9 + 35.0) = -1.7$$

The lack of spreading exhibited by oleic acid should be reflected in an even more negative final spreading coefficient, since the very polar carboxyl groups should have very little affinity for the exposed alkyl chain of the oleic acid film. Spreading so as to form a second layer with polar groups exposed to the air would also seem very unlikely, thus leading to the formation of a lens.

### Wetting Phenomena

In the experiment described above it was shown that talc or charcoal sprinkled onto the surface of water float despite the fact that their densities are much greater than that of water. In order for immersion of the solid to occur, the liquid must displace air and spread over the surface of the solid; when liquids cannot spread over a solid surface spontaneously, and, therefore,  $S$ , the spreading coefficient, is negative, we say that the solid is not wetted.

An important parameter which reflects the degree of wetting is the angle which the liquid makes with the solid surface at the point of contact (Fig 19-4). By convention, when wetting is complete, the contact angle is zero; in nonwetting situations it theoretically can increase to a value of  $180^\circ$ , where a spherical droplet makes contact with solid at only one point.

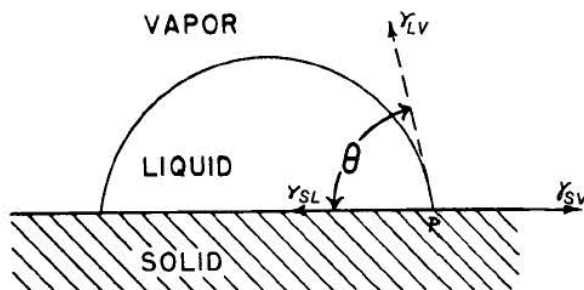


Fig 19-4. Forces acting on a nonwetting liquid drop exhibiting a contact angle of  $\theta$ .<sup>3</sup>

In order to express contact angle in terms of solid-liquid-air equilibria, one can balance forces parallel to the solid surface at the point of contact between all three phases (Fig 19-4), as expressed in

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos \theta \quad (9)$$

where  $\gamma_{SV}$ ,  $\gamma_{SL}$ , and  $\gamma_{LV}$  represent the surface free energy/unit area of the solid-air, solid-liquid, and liquid-air interfaces, respectively. Although difficult to use quantitatively because of uncertainties with  $\gamma_{SV}$  and  $\gamma_{SL}$  measurements, conceptually the equation, known as the Young equation, is useful because it shows that the loss of free energy due to elimination of the air-solid interface by wetting is offset by the increased solid-liquid and liquid-air area of contact as the drop spreads out.

The  $\gamma_{LV} \cos \theta$  term arises as the horizontal vectorial component of the force acting along the surface of the drop, as represented by  $\gamma_{LV}$ . Factors tending to reduce  $\gamma_{LV}$  and  $\gamma_{SL}$ , therefore, will favor wetting, while the greater the value of  $\gamma_{SV}$  the greater the chance for wetting to occur. This is seen in Table IV for the wetting of a low-energy surface, paraffin (hydrocarbon), and a higher energy surface, nylon, (polyhexamethylene adipamide). Here, the lower the surface tension of a liquid, the smaller the contact angle on a given solid, and the more polar the solid, the smaller the contact angle with the same liquid.

With Eq 9 in mind and looking at Fig 19-5, it is now possible to understand how the forces acting at the solid-

Table IV—Contact Angle on Paraffin and Nylon for Various Liquids of Differing Surface Tension

Substance	Surface tension, dynes/cm	Contact angle Paraffin	Nylon
Water	72.8	105°	70°
Glycerin	63.4	96°	60°
Formamide	58.2	91°	50°
Methylene iodide	50.8	66°	41°
$\alpha$ -Bromonaphthalene	44.6	47°	16°
<i>tert</i> -Butylnaphthalene	33.7	38°	spreads
Benzene	28.9	24°	"
Dodecane	25.4	17°	"
Decane	23.9	7°	"
Nonane	22.9	spreads	"

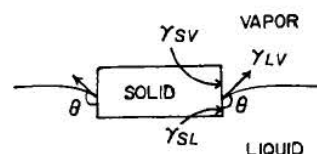


Fig 19-5. Forces acting on a nonwetting solid at the air-liquid-vapor interface: contact angle  $\theta$  greater than  $90^\circ$ .

**Table V—Critical Surface Tensions of Various Polymeric Solids**

Polymeric Solid	$\gamma_c$ , Dynes/cm at 20°
Polymethacrylic ester of $\phi'$ -octanol	10.6
Polyhexafluoropropylene	16.2
Polytetrafluoroethylene	18.5
Polytrifluoroethylene	22
Poly(vinylidene fluoride)	25
Poly(vinyl fluoride)	28
Polyethylene	31
Polytrifluorochloroethylene	31
Polystyrene	33
Poly(vinyl alcohol)	37
Poly(methyl methacrylate)	39
Poly(vinyl chloride)	39
Poly(vinylidene chloride)	40
Poly(ethylene terephthalate)	43
Poly(hexamethylene adipamide)	46

liquid-air interface can cause a dense nonwetted solid to float if  $\gamma_{SL}$  and  $\gamma_{LV}$  are large enough relative to  $\gamma_{SV}$ .

The significance of reducing  $\gamma_{LV}$  was first developed empirically by Zisman when he plotted  $\cos \theta$  vs the surface tension of a series of liquids and found that a linear relationship, dependent on the solid, was obtained. When such plots are extrapolated to  $\cos \theta$  equal to one or a zero contact angle, a value of surface tension required to just cause complete wetting is obtained. Doing this for a number of solids, it was shown that this surface tension (known as the critical surface tension,  $\gamma_c$ ) parallels expected solid surface energy  $\gamma_{SV}$ ; the lower  $\gamma_c$ , the more nonpolar the surface.

Table V indicates some of these  $\gamma_c$  values for different surface groups, indicating such a trend. Thus, water with a surface tension of about 72 dynes/cm will not wet polyethylene ( $\gamma_c = 31$  dynes/cm), but heptane with a surface tension of about 20 dynes/cm will. Likewise, Teflon (polytetrafluoroethylene) ( $\gamma_c = 19$ ) is not wetted by heptane but is wetted by perfluoroheptane with a surface tension of 11 dynes/cm.

One complication associated with the wetting of high-energy surfaces is the lack of wetting after the initial formation of a monomolecular film by the spreading substance. As in the case of oleic acid spreading on the surface of water, the remaining liquid retracts because of the low-energy surface produced by the oriented film. This phenomenon, often called autophobic behavior, is an important factor in many systems of pharmaceutical interest since many solids, expected to be wetted easily by water, may be rendered hydrophobic if other molecules dissolved in the water can form these monomolecular films at the solid surface.

### Capillarity

Because water shows a strong tendency to spread out over a polar surface such as clean glass (contact angle  $0^\circ$ ), one would expect to observe the meniscus which forms when water is contained in a glass vessel such as a pipet or buret. This behavior is accentuated dramatically if a fine-bore capillary tube is placed into the liquid (Fig 19-6); not only will the wetting of the glass produce a more highly curved meniscus, but the level of the liquid in the tube will be appreciably higher than the level of the water in the beaker.

The spontaneous movement of a liquid into a capillary or narrow tube due to surface forces is defined as capillarity and is responsible for a number of important processes involving the penetration of liquids into porous solids. In contrast to water in contact with glass, if the same capillary is placed into mercury (contact angle on glass:  $130^\circ$ ), not

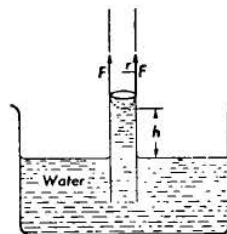


Fig 19-6. Capillary rise for a liquid exhibiting zero contact angle <sup>1</sup>

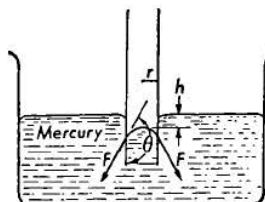


Fig 19-7. Capillary fall for a liquid exhibiting a contact angle,  $\theta$ , which is greater than  $90^\circ$ .<sup>1</sup>

only will the meniscus be inverted (see Fig 19-7), but the level of the mercury in the capillary will be lower than in the beaker. In this case one does not expect mercury or other *nonwetting* liquids to easily penetrate pores unless external forces are applied.

To quantitate the factors giving rise to the phenomenon of capillarity, let us consider the case of a liquid which rises to a height,  $h$ , above the bulk liquid in a capillary having a radius,  $r$ . If (as shown in Fig 19-6) the contact angle of water on glass is zero, a force,  $F$ , will act upward and vertically along the circle of liquid-glass contact. Based upon the definition of surface tension this force will be equal to the surface tension,  $\gamma$ , multiplied by the circumference of the circle,  $2\pi r$ . Thus

$$F = \gamma 2\pi r \quad (10)$$

This force upward must support the column of water, and since the mass,  $m$ , of the column is equal to the density,  $d$ , multiplied by the volume of the column,  $\pi r^2 h$ , the force  $W$  opposing the movement upward will be

$$W = mg = \pi r^2 dgh \quad (11)$$

where  $g$  is the gravity constant.

Equating the two forces at equilibrium gives

$$\pi r^2 dgh = \gamma 2\pi r \quad (12)$$

so that

$$h = \frac{2\gamma}{rdg} \quad (13)$$

Thus, the greater the surface tension and the finer the capillary radius, the greater the rise of liquid in the capillary.

If the contact angle of liquid is not zero (as shown in Fig 19-8), the same relationship may be developed, except the

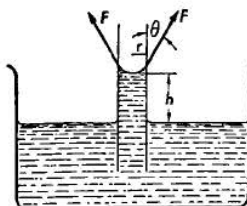


Fig 19-8. Capillary rise for a liquid exhibiting a contact angle,  $\theta$ , which is greater than zero but less than  $90^\circ$ .<sup>1</sup>



vertical component of  $F$  which opposes the weight of the column is  $F \cos \theta$  and, therefore

$$h = \frac{2\gamma \cos \theta}{rdg} \quad (14)$$

This indicates the very important fact that if  $\theta$  is less than  $90^\circ$ , but greater than  $0^\circ$ , the value of  $h$  will decrease with increasing contact angle until at  $90^\circ$  ( $\cos \theta = 0$ ),  $h = 0$ . Above  $90^\circ$ , values of  $h$  will be negative, as indicated in Fig 19-7 for mercury. Thus, based on these equations we may conclude that capillarity will occur spontaneously in a cylindrical pore even if the contact angle is greater than zero, but it will not occur at all if the contact angle becomes  $90^\circ$  or more. In solids with irregularly shaped pores the relationships between parameters in Eq 14 will be the same, but they will be more difficult to quantitate because of nonuniform changes in pore radius throughout the porous structure.

### Pressure Differences across Curved Surfaces

From the preceding discussion of capillarity another important concept follows. In order for the liquid in a capillary to rise spontaneously it must develop a higher pressure than the lower level of the liquid in the beaker. However, since the system is open to the atmosphere, both surfaces are in equilibrium with the atmospheric pressure. In order to be raised above the level of liquid in the beaker and produce a hydrostatic pressure equal to  $hgd$ , the pressure just below the liquid meniscus, in the capillary,  $P_1$ , must be less than that just below the flat liquid surface,  $P_0$ , by  $hgd$ , and therefore

$$P_0 - P_1 = hgd \quad (15)$$

Since, according to Eq 14

$$h = \frac{2\gamma \cos \theta}{rgd}$$

then

$$P_0 - P_1 = \frac{2\gamma \cos \theta}{r} \quad (16)$$

For a contact angle of zero, where the radius of the capillary is the radius of the hemisphere making up the meniscus,

$$P_0 - P_1 = \frac{2\gamma}{r} \quad (17)$$

The consequences of this relationship (known as the Laplace equation) are important for any curved surface when  $r$  becomes very small and  $\gamma$  is relatively significant. For example, a spherical droplet of air formed in a bulk liquid and having a radius,  $r$ , will have a greater pressure on the inner concave surface than on the convex side, as expressed in Eq 17.

Another direct consequence of what Eq 17 expresses is the fact that very small droplets of liquid, having highly curved surfaces, will exhibit a higher vapor pressure,  $P$ , than that observed over a flat surface of the same liquid at  $P'$ . The equation (Eq. 18) expressing the ratio of  $P/P'$  to droplet radius,  $r$ , and surface tension,  $\gamma$ , is called the Kelvin equation where

$$\log P/P' = \frac{2\gamma M}{2.303RT\rho r} \quad (18)$$

and  $M$  is the molecular weight,  $R$  the gas constant in ergs per mole per degree,  $T$  is temperature and  $\rho$  is the density in  $\text{g/cm}^3$ . Values for the ratio of vapor pressures are given in Table VI for water droplets of varying size. Such ratios indicate why it is possible for very fine water droplets in

**Table VI—Ratio of Observed Vapor Pressure to Expected Vapor Pressure of Water at  $25^\circ$  with Varying Droplet Size**

$P/P'$ <sup>a</sup>	Droplet size, $\mu\text{m}$
1.001	1
1.01	0.1
1.1	0.01
2.0	0.005
3.0	0.001
4.2	0.00065
5.2	0.00060

<sup>a</sup>  $P$  is the observed vapor pressure and  $P'$  is the expected value for "bulk" water.

clouds to remain uncondensed despite their close proximity to one another.

This same behavior may be seen when measuring the solubility of very fine solid particles since both vapor pressure and solubility are measures of the escaping tendency of molecules from a surface. Indeed, the equilibrium solubility of extremely small particles has been shown to be greater than the usual value noted for coarser particles; the greater the surface energy and smaller the particles, the greater this effect.

### Adsorption

#### Vapor Adsorption on Solid Surfaces

It was suggested earlier that a high surface or interfacial free energy may exist at a solid surface if the unbalanced forces at the surface and the area of exposed groups are quite great.

Substances such as metals, metal oxides, silicates, and salts—all containing exposed polar groups—may be classified as high-energy or hydrophilic solids; nonpolar solids such as carbon, sulfur, polyethylene, or Teflon (polytetrafluoroethylene) may be classified as low-energy or hydrophobic solids (Table III). Whereas liquids satisfy their unbalanced surface forces by changes in shape, pure solids (which exhibit negligible surface mobility) must rely on reaction with molecules either in the vapor state or in a solution which comes in contact with the solid surface to accomplish this.

Vapor adsorption is the simplest model demonstrating how solids reduce their surface free energy in this manner.

Depending on the chemical nature of the adsorbent (solid) and the adsorbate (vapor), the strength of interaction between the two species may vary from strong specific chemical bonding to interactions produced by the weaker more nonspecific London dispersion forces. Ordinarily, these latter forces are those responsible for the condensation of relatively nonpolar substances such as  $\text{N}_2$ ,  $\text{O}_2$ ,  $\text{CO}_2$  or hydrocarbons.

When chemical reaction occurs, the process is called chemisorption; when dispersion forces predominate, the term physisorption is used. Physisorption occurs at temperatures approaching the liquefaction temperature of the vapor, whereas, for chemisorption, temperatures depend on the particular reaction involved. Water-vapor adsorption to various polar solids can occur at room temperature through hydrogen-bonding, with binding energies intermediate to physisorption and chemisorption.

In order to study the adsorption of vapors onto solid surfaces one must measure the amount of gas adsorbed/unit area or unit mass of solid, at different pressures of gas. Since such studies usually are conducted at constant temperature, plots of volume adsorbed vs pressure are referred to as adsorption isotherms. If the physical or chemical adsorption process is monomolecular, the adsorption iso-

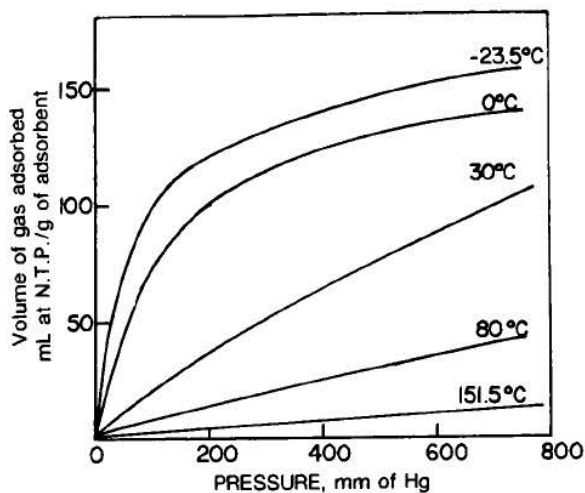


Fig 19-9 Adsorption isotherms for ammonia on charcoal.<sup>4</sup>

therm should look like those shown in Fig 19-9. Note the significant increase in adsorption with increasing pressure, followed by a leveling off. This leveling off is due either to a saturation of available specific chemical groups, as in chemisorption, or to the entire available surface being covered by physically adsorbed molecules. Note also the reduction in adsorption with increasing temperature which occurs because the adsorption process is exothermic. Often in the case of physical adsorption at low temperatures, after adsorption levels off, a marked increase in adsorption occurs, presumably due to multilayered adsorption. In this case vapor molecules essentially condense upon themselves as the liquefaction pressure of the vapor is approached. Figure 19-10 illustrates one type of isotherm generally seen with multilayered physisorption.

In order to have some quantitative understanding of the adsorption process and to be able to compare different systems, two factors must be evaluated; it is important to know what the capacity of the solid is or what the maximum amount of adsorption is under a given set of conditions and what the affinity of a given substance is for the solid surface or how readily does it adsorb for a given amount of pressure? In effect, this second term is the equilibrium constant for the process.

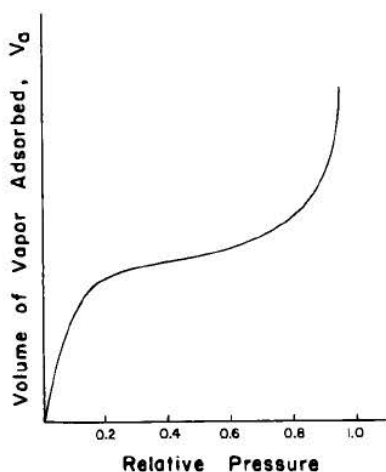


Fig 19-10. Typical plot for multilayer physical adsorption of a vapor on a solid surface.

A significant development along these lines was introduced by Langmuir when he proposed his theory of monomolecular adsorption. He postulated that for adsorption to occur a solid must contain uniform adsorption sites, each capable of holding a gas molecule. Molecules colliding with the surface may bounce off elastically or they may remain in contact for a period of time. It is this contact over a period of time that Langmuir termed adsorption.

Two major assumptions were made in deriving the equation: (1) only those molecules striking an empty site can be adsorbed, hence, only monomolecular adsorption occurs, and (2) the forces of interaction between adsorbed molecules are negligible and, therefore, the probability of a molecule adsorbing onto or desorbing from any site is independent of the surrounding sites.

The derivation of the equation is based upon the relationship between the rate of adsorption and desorption, since at equilibrium the two rates must be equal. Let  $\mu$  equal the number of molecules striking each sq cm of surface/sec. From the kinetic theory of gases

$$\mu = \frac{p}{(2\pi mkT)^{1/2}} \quad (19)$$

where  $p$  is the gas pressure,  $m$  is the mass of the molecule,  $k$  is the Boltzmann gas constant, and  $T$  is the absolute temperature. Thus, the greater  $p$ , the greater the number of collisions. Let  $\alpha$  equal the fraction of molecules which will be held by the surface; then  $\alpha\mu$  is equal to the rate of adsorption on the bare surface. However, if  $\theta$  is the fraction of the surface already covered, the rate of adsorption actually will be

$$R_a = \alpha\mu(1 - \theta) \quad (20)$$

In a similar manner the rate of molecules leaving the surface can be expressed as

$$R_d = \gamma\theta \quad (21)$$

where  $\gamma$  is the rate at which molecules can leave the surface and  $\theta$  represents the number of molecules available to desorb. The value of  $\gamma$  strongly depends on the energy associated with adsorption; the greater the binding energy, the lower the value of  $\gamma$ . At equilibrium,  $R_a = R_d$  and

$$\gamma\theta = \alpha\mu(1 - \theta) \quad (22)$$

Isolating the variable term,  $\theta$ , and combining all constants into  $k$ , the equation can be written as

$$\theta = \frac{kp}{1 + kp} \quad (23)$$

and, since  $\theta$  may be expressed as

$$\theta = \frac{V_a}{V_m} \quad (24)$$

where  $V_a$  is the volume of gas adsorbed and  $V_m$  is the volume of gas covering all of the sites, Eq. 23 may be written as

$$V_a = \frac{V_m kp}{1 + kp} \quad (25)$$

A test of fit to this equation can be made by expressing it in linear form

$$\frac{p}{V_a} = \frac{1}{V_m k} + \frac{p}{V_m} \quad (26)$$

The value of  $k$  is, in effect, the equilibrium constant and may be used to compare affinities of different substances for the solid surface. The value of  $V_m$  is valuable since it indicates the maximum number of sites available for adsorption. In the case of physisorption the maximum number of sites is

actually the total surface area of the solid and, therefore, the value of  $V_m$  can be used to estimate surface area if the volume and area/molecule of vapor are known.

Since physisorption most often involves some multilayered adsorption, an equation, based on the Langmuir equation, the B.E.T. equation, is normally used to determine  $V_m$  and solid surface areas. Equation 27 is the B.E.T. equation:

$$V_a = \frac{V_m c p}{(p_0 - p)[1 + (C - 1)(p/p_0)]} \quad (27)$$

where  $c$  is a constant and  $p_0$  is the vapor pressure of the adsorbing substance.<sup>5</sup> The most widely used vapor for this purpose is nitrogen, which adsorbs nonspecifically on most solids near its boiling point at  $-195^\circ$  and appears to occupy about  $16 \text{ \AA}^2/\text{molecule}$  on a solid surface.

#### Adsorption from Solution

By far one of the most important aspects of interfacial phenomena encountered in pharmaceutical systems is the tendency for substances dissolved in a liquid to adsorb to various interfaces. Adsorption from solution is generally more complex than that from the vapor state because of the influence of the solvent and any other solutes dissolved in the solvent. Although such adsorption is generally limited to one molecular layer, the presence of other molecules often makes the interpretation of adsorption mechanisms much more difficult than for chemisorption or physisorption of a vapor. Since monomolecular adsorption from solution is so widespread at all interfaces, we will first discuss the nature of monomolecular films and then return to a discussion of adsorption from solution.

#### Insoluble Monomolecular Films

It was suggested above that molecules exhibiting a tendency to spread out at an interface might be expected to orient so as to reduce the interfacial free energy produced by the presence of the interface. Direct evidence for molecular orientation has been obtained from studies dealing with the spreading on water of insoluble polar substances containing long hydrocarbon chains, eg, fatty acids.

In the late 19th century Pockels and Rayleigh showed that a very small amount of olive or castor oil—when placed on the surface of water—spreads out, as discussed above. If the amount of material was less than could physically cover the entire surface only a slight reduction in the surface tension of water was noted. However, if the surface was compressed between barriers, as shown in Fig 19-11, the surface tension was reduced considerably.

Devaux extended the use of this technique by dissolving small amounts of solid in volatile solvents and dropping the solution onto a water surface. After assisting the water-insoluble molecules to spread, the solvent evaporated, leaving a surface film containing a known amount of solute.

Compression and measurement of surface tension indicated that a maximum reduction of surface was reached when the number of molecules/unit area was reduced to a value corresponding to complete coverage of the surface. This suggested that a monomolecular film forms and that surface

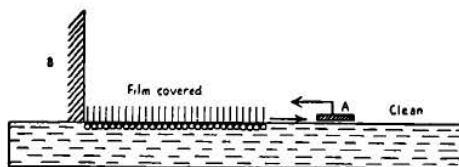


Fig 19-11. Insoluble monomolecular film compressed between a fixed barrier, B, and a movable barrier, A.<sup>6</sup>

tension is reduced upon compression because contact between air and water is reduced by the presence of the film molecules. Beyond the point of closest packing the film apparently collapses very much as a layer of corks floating on water would be disrupted when laterally compressed beyond the point of initial physical contact.

Using a refined quantitative technique based on these studies, Langmuir<sup>7</sup> spread films of pure fatty acids, alcohols, and esters on the surface of water. Comparing a series of saturated fatty acids, differing only in chain length, he found that the area/molecule at collapse was independent of chain length, corresponding to the cross-sectional area of a molecule oriented in a vertical position (see Fig 19-11). He further concluded that this molecular orientation involved association of the polar carboxyl group with the water phase and the nonpolar acyl chain out towards the vapor phase.

In addition to the evidence for molecular orientation, Langmuir's work with surface films revealed that each substance exhibits film properties which reflect the interactions between molecules in the surface film. This is best seen by plotting the difference in surface tension of the clean surface,  $\gamma_0$ , and that of the surface covered with the film,  $\gamma$ , vs the area/molecule,  $A$ , produced by film compression (total area  $\div$  the number of molecules). The difference in surface tension is called the surface pressure,  $\pi$ , and thus

$$\pi = \gamma_0 - \gamma. \quad (28)$$

Figure 19-12 depicts such a plot for a typical fatty acid monomolecular film. At areas greater than  $50 \text{ \AA}^2/\text{molecule}$  the molecules are far apart and do not cover enough surface to reduce the surface tension of the clean surface to any extent and thus the lack of appreciable surface pressure. Since the molecules in the film are quite free to move laterally in the surface, they are said to be in a two-dimensional "gaseous" or "vapor" state.

As the intermolecular distance is reduced upon compression, the surface pressure rises because the air-water surface is being covered to a greater extent. The rate of change in  $\pi$  with  $A$ , however, will depend on the extent of interaction between film molecules; the greater the rate of change, the more "condensed" the state of the film.

In Fig 19-12, from  $50 \text{ \AA}^2$  to  $30 \text{ \AA}^2/\text{molecule}$ , the curve shows a steady increase in  $\pi$ , representative of a two-dimensional "liquid" film, where the molecules become more restricted in their freedom of movement because of interactions. Below  $30 \text{ \AA}^2/\text{molecule}$  the increase in  $\pi$  occurs over a narrow range of  $A$ , characteristic of closest packing and a two-dimensional "solid" film.

Any factor tending to increase polarity or bulkiness of the molecule—such as increased charge, number of polar groups, reduction in chain length, or the introduction of

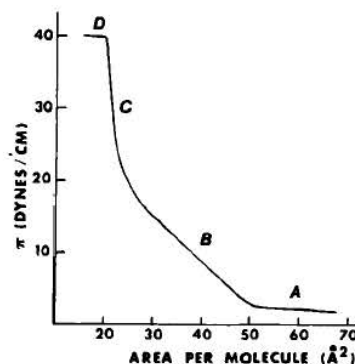


Fig 19-12. A surface pressure-area curve for an insoluble monomolecular film: Region A, "gaseous" film; Region B, "liquid" film; Region C, "solid" film; Region D, film collapse



aromatic rings, side chains, and double bonds—should reduce molecular interactions, while the longer the alkyl chain and the less bulky the polar group, the closer the molecules can approach and the stronger the extent of interaction in the film.

#### Soluble Films and Adsorption from Solution

If a fatty acid exhibits highly "gaseous" film behavior on an aqueous surface, we should expect a relatively small change in  $\pi$  with  $A$  over a considerable range of compression. Indeed, for short-chain compounds—eg, lauric acid (12 carbons) and decanoic acid—not only is the change in  $\pi$  small with decreasing  $A$  but at a point just before the expected closest packing area the surface pressure becomes constant without any collapse.

If lauric acid is converted to the laurate ion, or if a shorter chain acid such as octanoic acid is used, spreading on water and compression of the surface produces no increase in  $\pi$ ; the more polar the molecule (hence, the more "gaseous" the film), the higher the area/molecule where a constant surface pressure occurs.

This behavior may be explained by assuming that polar molecules form monomolecular films when spread on water but that, upon compression, they are caused to enter the aqueous bulk solution rather than to remain as an intact insoluble film. The constant surface pressure with increased compression arises because a constant number of molecules/unit area remain at the surface in equilibrium with dissolved molecules. The extent of such behavior will be greater for substances exhibiting weaker intermolecular interaction and greater water solubility.

Starting from the other direction, it can be shown that short-chain acids and alcohols (when dissolved in water) reduce the surface tension of water, thus producing a surface pressure, just as with insoluble films (see Eq 28). That dissolved molecules are accumulating at the interface in the form of a monomolecular film is suggested from the similarity in behavior to systems where slightly soluble molecules are spread on the surface. For example, compressing the surface of a solution containing "surface-active" molecules has no effect on the initial surface pressure, whereas increasing bulk-solution concentration tends to increase surface pressure, presumably by shifting the equilibrium between surface and bulk molecules.

At this point we may ask, why should water-soluble molecules leave an aqueous phase and accumulate or "adsorb" at an air-solution interface? Since any process will occur spontaneously if it results in a net loss in free energy, such must be the case for the process of adsorption.

A number of factors will produce such a favorable change in free energy. First, the presence of the oriented monomolecular film reduces the surface free energy of the air-water interface. Second, the hydrophobic group on the molecule is in a lower state of energy at the interface, where it no longer is as surrounded by water molecules, than when it is in the bulk-solution phase. Increased interaction between film molecules also will contribute to this process.

A further reduction in free energy occurs upon adsorption because of the gain in entropy associated with a change in water structure. Water molecules, in the presence of dissolved alkyl chains are more highly organized or "ice-like" than they are as a pure bulk phase; hence, the entropy of such structured water is lower than that of bulk water.

The process of adsorption requires that the "ice-like" structure "melt" as the chains go to the interface and, thus, an increase in the entropy of water occurs. The adsorption of molecules dissolved in oil can occur but it is not influenced by water structure changes and, hence, only the first factors mentioned are important here.

It is very rare that significant adsorption can occur at the hydrocarbon-air interface since little loss in free energy can occur by bringing hydrocarbon chains with polar groups attached to this interface; however, at oil-water interfaces the polar portions of the molecule can interact with water at the interface, leading to significant adsorption.

Thus, whereas water-soluble fatty acid salts are adsorbed from water to air-water and oil-water interfaces, their undissociated counterparts, the free fatty acids, which are water insoluble, form insoluble films at the air-water interface, are not adsorbed from oil solution to an oil-air interface, but show significant adsorption at the oil-water interface when dissolved in oil.

From this discussion it is possible also to conclude that adsorption from aqueous solution requires a lower solute concentration to obtain the same level of adsorption if the hydrophobic chain length is increased or if the polar portion of the molecule is less hydrophilic. On the other hand, adsorption from nonpolar solvents is favored when the solute is quite polar.

Since soluble or adsorbed films cannot be compressed, there is no simple direct way to estimate the number of molecules/unit area coming to the surface under a given set of conditions. For relatively simple systems it is possible to estimate this value by application of the Gibbs equation, which relates surface concentration to the surface-tension change produced at different solute activities. The derivation of this equation is beyond the scope of this discussion, but it arises from a classical thermodynamic treatment of the change in free energy when molecules concentrate at the boundary between two phases. The equation may be expressed as

$$\Gamma = - \frac{a}{RT} \frac{d\gamma}{da} \quad (29)$$

where  $\Gamma$  is the moles of solute adsorbed/unit area,  $R$  is the gas constant,  $T$  is the absolute temperature and  $d\gamma$  is the change in surface tension with a change in solute activity,  $da$ , at activity  $a$ . For dilute solutions of nonelectrolytes, or for electrolytes when the Debye-Hückel equation for activity coefficient is applicable, the value of  $a$  may be replaced by solute concentration,  $c$ . Since the term  $dc/c$  is equal to  $d \ln c$ , the Gibbs equation is often written as

$$\Gamma = - \frac{1}{RT} \frac{d\gamma}{d \ln c} \quad (30)$$

In this way the slope of a plot of  $\gamma$  vs  $\ln c$  multiplied by  $1/RT$  should give  $\Gamma$  at a particular value of  $c$ . Figure 19-13 depicts typical plots for a series of water-soluble surface-active agents differing only in the alkyl chain length. Note the

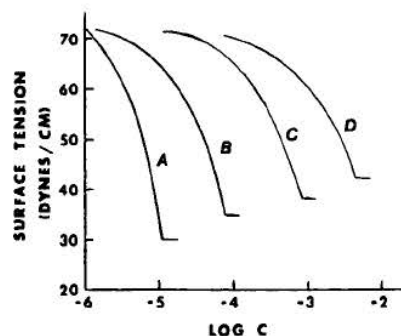


Fig 19-13. The effect of increasing chain length on the surface activity of a surfactant at the air-aqueous solution interface (each figure depicted to differ by two methylene groups with A, the longest chain, and D, the shortest).