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The Science and Practice of Pharmacy

21st EDITION



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21ST EDITION

Remington

**The Science and Practice
of Pharmacy**



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Preface to the Twenty-First Edition

For over 100 years and throughout 20 previous editions, *Remington: The Science and Practice of Pharmacy* has stood as the definitive text and reference source of all aspects of the science and practice of pharmacy. In this new edition, you will find a text that is practice-oriented while maintaining its traditionally reliable coverage of scientific aspects. The 21st edition keeps pace with the changes in pharmacy curriculum and professional pharmacy practice in general.

In the years since the first publication of *Remington's Pharmaceutical Sciences*, there have been many changes in the field of pharmacy and pharmacy practice. Although this edition of *Remington* maintains the general philosophy of previous editions, several changes have been made to present fresh and new information and to take advantage of the advances made in recent years. Each section of the book has been critically reviewed and revised to reflect the emerging trends in the field. The overall organization of the book is the same as the previous editions.

The biggest change in the 21st edition is in the *Pharmacy Practice* section. This section has been reorganized and expanded to reflect the changing realities of contemporary practice. The integration of new scientific information into clinical practice is often difficult, and one of the key purposes of this section is to help clinicians translate these scientific advances into clinical practice and care of patients. This section brings the reader up to date on the latest trends and approaches. New chapters have been added that cover the areas of:

- The application of ethical principles to practice dilemmas
- Statistics applied to pharmacy practice
- Technology and automation
- Professional communication
- Medication errors
- Re-engineering pharmacy practice
- Management of special risk medicines
- Specialization of pharmacy practice
- Disease state management
- Emergency patient care
- Wound care

The *Pharmaceutical and Medicinal Agents* section is the most very useful part of the book in terms of core drug information. For this edition, we've added more than 100 new drug monographs, and the previously existing material has been up-

dated. We realize that this is a section that is nearly impossible to keep current, and we've tried to include as many new drugs as possible. Because of space constraints, we were limited to the most important or most widely used drugs.

Another significant addition to this edition is the expansion of the *Pharmacodynamics and Pharmacokinetics* section to include the new, growing area of Pharmacogenomics. This chapter highlights many of the important advances including: practical applications and technological considerations, molecular diagnostics for optimizing drug therapy, and pharmacogenomics and drug development.

Many people were involved in creating this edition. I am grateful to all the Section Editors and authors for their skillful review of the literature and for incorporating their own unique perspectives and experience into their chapters. With this edition, we welcome five new Section Editors. They represent a wide geographic diversity and spectrum of experience. We also have approximately 100 new authors who represent over 32 universities as well as positions in governmental agencies and private industry.

I also gratefully acknowledge the extensive contributions of the authors and Section Editors of previous editions of *Remington* for laying the foundation for the current volume. I recognize that we all stand upon the shoulders of giants and are supported by those leaders who taught and inspired many previous generations.

I especially thank Alfonso R Gennaro, PhD for his continued support. Dr. Gennaro was *Remington* editor for the past four editions. No one is more familiar with *Remington* than he is. Dr. Gennaro has been instrumental in the creation and review of the drug monographs. Ensuring scientific accuracy is critical in a book such as *Remington*, and he has been very generous with his time and expertise in this area.

A heartfelt thanks also goes to Mr. John Hoover, author and indexer, who has been involved with *Remington* since the 1960s and has provided editorial guidance at every step of the process.

It is a pleasure and honor to work on a book with such a long and rich tradition.

Randy Hendrickson
Editor

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Organic Pharmaceutical Chemistry

Alfonso R Gennaro, PhD



It is not the purpose of this chapter to provide a fundamental treatment of organic chemistry. Readers are expected to have pursued the usual basic courses in organic chemistry and be cognizant of the various advanced texts and other readily available works of reference. (See Bibliography) Accordingly, this chapter is restricted primarily to a listing of the more prominent structural types of organic compounds, a brief presentation of the various nomenclature systems and of the major chemical classes of official (USP/NF) pharmaceuticals, followed by a discussion on the identification of organic functional groups and the possible assignment of an approximate acidic, basic, or neutral value to these groups. A detailed treatment of the individual pharmaceuticals is provided at other locations in this book (refer to the index).

TYPES OF ORGANIC COMPOUNDS

A comprehensive understanding of organic chemistry would be extremely difficult were it not for the fact that the hundreds of thousands of known compounds fall conveniently into a very much smaller number of general types based on molecular structure. Similarities and differences among the physical and chemical properties of the diverse compounds thus become more apparent and understandable, and this is useful both in providing explanations for observed phenomena and in making predictions for possible applications of known compounds and compounds projected for synthesis.

Organic compounds may be classified in many ways, the desired intricacy of any particular scheme depending on the purpose of performing the classification. Thus, for one purpose it may suffice to construct a single, broad class of hydroxy compounds, while for other purposes it is desirable to subdivide this broad class into alcohols and phenols and perhaps even subdivide these further into subclasses of alcohols and phenols. It is appropriate here, for purposes of convenient reference, to list those types of compounds most commonly encountered in the systematic study of organic chemistry and to display their general (type) formulas. The types of compounds that are pertinent, especially to pharmacy, are treated in greater detail later in the chapter where examples of official drugs belonging to each class also are provided.

To enhance the utility of this chapter as a reference tool, the listing in Appendix A is alphabetical rather than by any chemical classification scheme. Prefatorily, the following explanatory notes are provided.

Unless otherwise specified, the formulas shown are for compounds containing only one of the particular functional groups involved. Formulas for compounds containing more than one of the same functional group can be derived easily.

Naturally occurring classes of compounds such as carbohydrates, proteins, alkaloids, glycosides, or lipids are not treated

as types of compounds in this classification. A separate, more detailed presentation of these is provided in Chapter 26.

Although a few heterocyclic types such as imines (azacyclic), anhydrides of dibasic acids (oxacyclic), lactides (dioxacyclic) automatically enter into the listing, it will be observed that parent heterocycles in general (eg, thiophene, pyridine, dioxane) are not included. Heterocycles represented in official drugs are listed later in the chapter.

In type formulas, such as in Appendix A, the symbol R is employed conventionally to denote a hydrocarbon radical. Unless otherwise specified, it may be aliphatic, alicyclic, or aromatic, and its valence varies to satisfy the requirements of its attachment to the rest of the molecule. The degree of saturation in R does not enter into the scheme. When a formula contains more than one R, the radicals may be either identical or different. In a few instances it is possible, that even if two monovalent Rs are replaceable by a single divalent R, the same type of compound is retained, as with aliphatic ketones ($R_2C=O$) and cyclic ketones ($R=C=O$).

The type formulas assume a useful broader meaning if R, instead of being restricted to designate only a hydrocarbon radical, is permitted to (1) be a residue from a heterocycle and (2) carry substituent groups. The latter definition automatically extends the listing to embrace polyfunctional compounds, but it also introduces the complicating feature of the *order of precedence* of functional groups. This matter is discussed later in the chapter.

Unless otherwise specified, the symbol X stands for a member of the halogen family. In addition to the type formulas, one or more specific examples of each type of compound also are provided, showing how the formulas usually appear in somewhat condensed form and illustrating the manner in which the type names become parts of individual compound names. However, it should be remembered that, although correct, such names are not always the preferred names in modern nomenclature practice.

A linear formula with a horizontal line above the symbols indicates a ring structure; the line is a bond joining the two atoms at each end. For example, $CH_2CH_2CH_2CH_2COO$ is δ -valerolactone. The oxygen atom on the right end is bonded to the carbon atom on the left end, forming a 6-membered ring.

The only formulas and structures that will be depicted will be those of pharmaceutical interest.

NOMENCLATURE OF ORGANIC COMPOUNDS

In the early decades of organic chemistry, newly discovered compounds commonly were provided with names which indicated either the source or some outstanding property of the

compound. Thus, marsh gas, wood alcohol, salicylic acid, cadaverine, morphine, chlorophyll, and thousands of other similar names were invented. As more and more compounds were isolated or synthesized, it became apparent, however, that some systematic manner of naming organic compounds in terms of their structure would have to be devised. Early systems of nomenclature, while adequate for the period in which they were invented, soon required modification as the number of known compounds increased. The result has been that the system (or rather the combination of systems) now in use represents an evolution covering many decades.

That a truly effective system of nomenclature is bound to be very complex becomes obvious when one reflects that it must not only discriminate, unequivocally, among the many millions of compounds already known, but also must allow adequate provision for encompassing new compounds, which are being synthesized by the thousands each year. Fundamentally, therefore, such discrimination means that each specific name coined through the system must account for (1) the quantitative elementary composition (molecular formula) and (2) all of the structural features for one, and only one, specific compound.

The IUPAC and CAS Systems of Nomenclature

Of the various comprehensive systems which had been proposed, and used to a varying extent, the two most widely employed and most thoroughly updated through revision and enlargement are those devised by the International Union of Pure and Applied Chemistry (IUPAC) and the Chemical Abstracts Service (CAS). Each of these systems represents an implementation of the rules devised by the IUPAC Commission on the Reform of the Nomenclature of Organic Chemistry, which has been engaged actively and continuously in the subject for many decades.

The two systems are identical in many respects. The CAS system intentionally departs from that of IUPAC wherever such departure contributes to the main purpose of *Chemical Abstracts*—indexing the world's chemical literature. Recognizing the desirability to maintain compatibility between the two systems, however, CAS identifies each such departure and displays the alternative IUPAC treatment.

Because of the difficulty in converting many structural formulas into unique, descriptive names, CAS now assigns a *Registry Number* to every chemical compound (organic and inorganic). All editions of the USAN (see Chapter 27) and commencing with USP XIX and NF XIV, all monographs for pure chemical entities carry the CAS Registry Number, which uniquely identifies every compound. In the same editions of USP and NF, "New Chemical Abstracts Names" were assigned. Also, CAS has completely revised the older system (which parallels IUPAC rules) so that computer searches may be made using nomenclature fragments, rather than topological features, to locate molecular fragments as well as complete molecules.

It obviously is inappropriate and space-prohibitive to include in this text a discussion of the multiplicity of details in either of these two systems. Suffice it to state that, from a structural viewpoint, each system adequately must describe for each compound the following:

- Composition and configuration of the carbon skeleton
- Interruptions of the carbon skeleton by heteroatoms
- State of hydrogenation of the skeleton
- Presence and location of substituents, i.e., atoms or groups of atoms (radicals) functioning in place of hydrogen
- Features of stereoisomerism

The reader desirous of the details of the systems should consult the continuing series of reports issued by the IUPAC Commission on the Nomenclature of Organic Chemistry, and the CAS publication entitled *The Naming and Indexing of Chemical Compounds from Chemical Abstracts*. The latter, which first

appeared as an introduction to the subject index of volume 56 of *Chemical Abstracts*, has undergone very extensive revision and enlargement. The introduction to the subject index of volume 66 provides a useful summary treatment. The publication of the American Chemical Society, *The Ring Index*, also offers a very detailed systematic presentation of closed-chain systems identified through the literature up to 1963.

Because of major changes in nomenclature and indexing procedures, mainly dictated by computerization of nomenclature and two-dimensional structures, each quinquennial index to *Chemical Abstracts* is accompanied by an index guide that allows the user to follow the transition between the old and new (or modified) nomenclature.

Three general features common to both systems deserve special comment, specifically the employment of trivial names, the order of precedence of functional groups, and permissive ambiguity.

TRIVIAL NAMES—A *trivial name* is one that does not describe a compound rigidly in terms of the absolute structure notations embodied in the system, but rather has earned worldwide recognition as being specific for that compound. Acetic acid (for ethanoic acid), purine (for 7H-imidazo[4,5-d]pyrimidine), and pregnane (for 10 β ,13 β -dimethyl-17 β -ethyl-9 α ,14 α ,5 β ,8 β -perhydrocyclopenta[α]phenanthrene) are common examples. Without allowing for the judicious employment of such trivial names, any scheme of nomenclature would be hopelessly complex and of little, if any, practical use. On the other hand, the wholesale, indiscriminate admission of trivial names to a system equally is disastrous.

Arriving at a satisfactory compromise between these two extremes obviously requires detailed deliberation, and the compromise position taken by IUPAC also has been adopted by CAS: trivial names admitted by IUPAC are also those admitted by CAS. However, with the advent of computer techniques, long or unwieldy names are handled with relative ease. Thus, trivial and systematic names are assuming equal importance, because a trivial-name index cannot be computer-searched to locate fragments of two-dimensional structures as these fragments are not evident in the name. But with long, systematic names, every portion of a parent molecule, substituent, functional group, and so on is apparent in the name and will yield to the computer search.

PRECEDENCE ORDER OF FUNCTIONAL GROUPS—

An *order of precedence* (priority) for functional groups is necessary to manage polyfunctional compounds systematically. As a simple example, in the absence of a systematic method, the compound $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ could be named either as an aminopropanol or as a hydroxypropylamine. But in the order of precedence, hydroxyl is higher than amino and, because the system requires that only the function of highest priority shall be represented by the suffix part of the name, the systematic name becomes 3-amino-1-propanol. The order of precedence of functional groups is described clearly (see Table 1 of the introduction to the subject index of *Chemical Abstracts*, volume 66, or the *11th Collective Index*, volumes 96 to 105, Appendix IV, *Chemical Substance Index Names*) and is identical in both the IUPAC and CAS systems.

PERMISSIVE AMBIGUITY—*Ambiguity* (lack of complete structural specificity) is permitted to the extent that it reflects structural features of a compound that either are unknown or have not yet been incorporated into the system. Prohibition of such ambiguity would disallow the cataloging of a very significant percentage of known compounds, especially among those that involve features of stereoisomerism.

Compendial Nomenclature

The lack of adherence to the principles of systematic nomenclature, in both the commercial and academic worlds, has led to a multiplicity in the types of chemical names in actual use. It is not at all unusual to find a specific compound referred to by several

different names, each of which is correct chemically. This, of course, creates a very confused state that, if it persists in the indexing literature, often renders searching via nomenclature extremely difficult, and frequently, impossible. It is for this reason that, wherever possible, *Chemical Abstracts* translates the non-systematic nomenclature of the author into its CAS equivalent.

Recognizing the advantages of adhering to a standard system of nomenclature, the official compendia (USP/NF) elected to adopt names preferred by CAS. The principle of operation is simply that either the title or one of the subtitles of an official chemical must be the currently preferred CAS name. It is well to observe that the structural relationships established on the basis of the principal functional group automatically may hide relationships involving functional groups of lesser priority (eg, amphetamine is named as a derivative of phenethylamine, whereas hydroxyamphetamine becomes a derivative of phenol; similarly, sulfamerazine is named as a derivative of sulfanilamide, whereas phthalylsulfacetamide becomes a derivative of phthalanilic acid). Beginning with USP XIX and NF XIV each monograph carries the "new CAS name" along with the CAS preferred name currently in use. Also included is the *Chemical Abstracts System Registry Number*, which provides a unique identifier and simplifies locating a specific compound or drug in the literature, especially using a computer search.

Chemical Syllables

In addition to whatever numbers, numerical syllables, and individual Greek and English letters are required, systematic chemical names consist of a collection of syllables, each of which carry a chemical connotation of some sort. Many, such as chloro-, hydroxy-, and methyl-, clearly indicate specific elements or radicals.

Many others, such as andro- (from the Greek, "man"), tauro- (Latin, "bull"), neo- (Greek, "new"), or pseudo- or ψ (Greek, "false"), are of no chemical significance from a structural viewpoint, but often are very useful in forming the so-called trivial or common names for complex molecules such as androsterone, taurocholic acid, neoantergan, pseudoglobulin—the correct chemical names for these structures are often extremely cumbersome. Because of their lack of structural chemical significance, however, these will not be discussed further here.

The third group of these syllables consists of miscellaneous prefixes and suffixes and is of sufficient importance to warrant abbreviated treatment, because, like those of the first group, these have structural significance and often constitute a necessary part of systematic chemical names. A list of the more commonly encountered ones of this group is provided in Appendices B and C. Many of these have multiple meanings, and the definitions given herein represent the most common sense in which they are used in organic chemistry. Those shown in italics are used commonly in italicized form and/or enclosed in parentheses when used in organic nomenclature. It also must be remembered that the precise meanings shown here do not always apply to trivial names (eg, the meaning of -ene or of -ylene does not apply to acetylene; similarly, the meaning of -ol (alcohol) does not apply to benzol). Caution always must be exercised in attempting to attach significance to the various parts of such common names.

The systematic treatment of cyclic systems uses a generous miscellany of syllables with specific meanings; for listings and explanations, consult the *Ring Index* and Appendix E.

RADICALS AND GROUPS IN ORGANIC CHEMISTRY

Through the concept and use of radicals and groups, a logical and very helpful classification of the huge number of organic compounds is possible. Furthermore, knowledge of the chemical properties of commonly used individual radicals makes pos-

sible either a prediction or an explanation of the chemical properties of compounds because, in general, the chemical properties of a compound are completely or partially the combined properties of the radicals present in the molecule.

Several hundred different radicals have been recognized, named, and classified. A comprehensive list ordered by both names and formulas is published periodically as part of the *Collective Index to Chemical Abstracts*, as *Appendix IV*, in the *Chemical Substance Index Names* found in the index guide for volumes 96 to 105 of *Chemical Abstracts*.

For purposes of convenient reference, a list of radicals and groups frequently encountered in pharmaceutical chemistry is provided in Appendix D. Classification into chemical types has been sacrificed in favor of an alphabetical arrangement. Included in the list are many inorganic radicals that frequently are present in organic combination.

Chemical Notation Systems

The complexity and the cumbersome nature of modern organic chemical nomenclature have encouraged attempts to develop "shorthand expressions," variously referred to as notations, ciphers, codes, and alphametrics, which for certain purposes would be more convenient to use than the chemical names. Several systems have been proposed (eg, the NAS-NRC provided a comprehensive review of the history of the various systems), although none have fully survived. In general, they involved assigning chemical meanings to the characters usually available on, or readily adapted to, a standard typewriter or computer keyboard and devising rules for their use in constructing the notations. A recent addition to the nomenclature/notation foray is **SMILES**, an acronym for **Simplified Molecular Line Entry Specification**. This is a valence model of a structure, not a computer data structure, and is relatively simple to master. (A tutorial is available at <http://www.day-light.com/>.)

Final assessment of the overall utility of notations has yet to be made; they particularly are appealing because their brevity (compared with descriptive chemical nomenclature as illustrated in Table 25-1) greatly increases storage efficiency in printed indexes and computer memories and facilitates computerized searching. In addition, they automatically avoid the troublesome "trivial name feature" encountered in practical nomenclature. However, they are not pronounceable words and do not eliminate the need for descriptive chemical nomenclature in the written and spoken word.

Several of these notations have been found useful for retrieving compounds on a structural basis from specialized files of compounds stored in computers using the same notations. The extent to which techniques for accomplishing such retrieval may be applied usefully to a file comprising the universe of chemical compounds is the subject of considerable interest and study.

Special typewriters have been devised whereby structural formulas may be coded directly on punched tape and also stored in the memory of a computer in the form of a matrix (a connection table of atoms) that can be searched at any future time on an atom-by-atom basis. This technique permits retrieval of compounds on a highly intimate structural basis that need not involve either nomenclature or the above-mentioned notations. Auxiliary devices exist for regenerating the actual structural formulas of retrieved compounds either by actual printout or by display on a computer monitor screen.

Table 25-1. Illustrations of Notation Brevity

DESCRIPTIVE CAS NAME	SMILES NOTATION
1-Chloro-3-methylbutane	CCCC(C)C
4-Aminobenzoic acid	Nc1ccc(C(=O)O)CC1
1-Naphthalenemethanol	OCc1c2cccccc2c1

Organic Chemical Literature

The constantly accelerating rate of research and development during the past five decades has created severe literature problems, not only in the areas of basic chemistry but also in the other fields of science and technology where chemical information is primarily applied, rather than generated. The history of *Chemical Abstracts* (CA) illustrates the magnitude of this so-called "information explosion." Commencing in 1906, the Chemical Abstracts Service (CAS) required 32 years for CA to produce its first million abstracts (1938), but only 17 years for the second million (1955), 8 years for the third million (1963), 6 years for the fourth million (1969), 5 years for the fifth million (1974), and somewhat less than 5 years for the sixth million (1979). By late 1983 the seventh million was surpassed, and the 8-million mark was reached in early 1987. Over 10 million abstracts were published by the end of 1992. One prediction suggests 20 million abstracts will be achieved by the year 2005.

Currently, the volume of chemical literature is so great that many libraries simply do not have enough shelf space to accommodate bound volumes and have resorted to microfilming, microfiche or, more drastically, cancellation of hardcopy in favor of electronic journals. More important is the fact that selective retrieval of information from the hardcopy literature has become an extremely arduous task. As a consequence, various industrial, academic, and governmental institutions (several pharmaceutical firms actually pioneered the effort) have developed computerized systems of storage and retrieval of those kinds of chemical information pertinent to their specific interests.

Currently, *Chemical Abstracts* may be searched via *SciFinder* or *SciFinder Scholar* and information may be found at the website www.info.cas.org. This facility allows a very rapid and thorough search of CAS to date; the current information is available on computer even before the printed copy reaches the subscriber. The *Institute for Scientific Information* (ISI) in Philadelphia also has computerized its abstract journal, *Index Chemicus*, a text and substructure searchable database which has several million compounds in its registry, and is adding new compounds at a rate of about 200,000 per year (See www.isinet.com.) Computer programs are available to customers that provide the capability to search and retrieve compound data either on the basis of structural features, or properties, applications, and bibliographic information.

The huge and continuing flood of published literature also has taxed severely the abilities of abstracting services to keep current. The magnitude of the task is illustrated by the experience of CA, which shows that the approximate number of papers and patents abstracted annually increased from 50,000 in 1950 to 120,000 in 1959; 230,000 in 1968; 400,000 in 1973; over half a million in 1978; approached 750,000 in 1983; and exceeded 1 million in 1988. The lag between publication of original articles and that of their abstracts has been sufficiently severe to foster the production of various so-called "current awareness tools" and specialty publications such as *Index Chemicus* and *Current Contents of ISI* and *Chemical Titles*, *Chemical-Biological Activities* (CBAC), *Polymer Science and Technology* (POST), *Basic Journal Abstracts* (BJA), and *CA Condensates* of CAS; which also are computer-based publications.

ORGANIC PHARMACEUTICALS

The contrast between the drugs of today and those of yesterday is a dramatic one in several respects. A century ago, humans relied almost exclusively on nature to produce the organic drugs they needed, and the contributions of pharmacy were confined largely to the preparation of extracts, tinctures, or other dosage forms of the crude drugs, and to the isolation of active principles, especially alkaloids and glycosides.

Synthetic drugs began to appear at a noticeably accelerated rate in the 1920s, and this generally is attributed to the very large expansion of the American chemical industry fostered by World War I. Many observers view the advent of the sulfa drugs

in the early 1930s as the beginning of the modern era of synthetics.

The great majority of new basic drugs are distinct organic chemical compounds. Most of these are products of synthetic organic chemistry, although some, such as taxol, ACTH, and many of the antibiotics, hormones, and anticancer drugs are products of natural origin. Even with drugs of the latter group, however, the chemist has played a very important role in devising processes to produce them economically, not only in the large quantities required, but also in a sufficient state of purity. He also has succeeded in the deliberate chemical alteration of these naturally occurring compounds and produced derivatives that are either more potent or superior in some other respect (eg, dehydrocholic acid, dihydroergotamine, fluorocorticosteroids, semisynthetic penicillins, methyltestosterone).

Such molecular modification of known pharmacodynamic compounds, both natural and synthetic, constitutes one of the main kinds of research effort in the field of chemotherapy. Although it is true that such effort frequently results in cluttering the market with drugs that may not be superior to those being imitated, nevertheless, a critical review of the results achieved over the past half century provides abundant evidence that the effort yields a gratifying percentage of new, highly beneficial drugs (see Chapter 28). Many of the new admissions to the official compendia are of such genesis.

Chemical and Pharmacological Classifications

During the early years of the modern era of synthetic organic pharmaceuticals, it was common to classify these new drugs on a chemical basis. This was logical, not only because they were fundamentally the products of chemical research but also because the sciences of pharmacology and biochemistry were still in their early stages of development. Indeed, the ever-increasing need for more precise knowledge concerning the efficacy and safety of new drugs has fostered, to a significant degree, the rapid growth of these sciences to their present impressive status, and will undoubtedly continue to do so in the future. The most comforting result is that these complementary efforts continuously are providing medical science with better tools and knowledge to the end that effective prevention and treatment of human physiological and psychological ills constantly are becoming more and more of a science and less and less of an art.

The guiding hypothesis underlying all efforts to classify organic pharmaceuticals on a chemical basis is simply that some correlation will exist between the chemistry of the compounds and their actions and uses as medicinal agents. Early efforts to discover useful correlations were based largely on gross structural considerations with particular emphasis on the presence and location of chemically active (functional) groups. In a more sophisticated form, such efforts continue today, and the net result has been the accumulation of a very large body of knowledge on the broad subject of drug action. This knowledge materially strengthens the belief that the pharmacodynamics of drugs ultimately will be explicable in terms of their chemical characteristics. It also points indisputably to the fact that a complete understanding of the mechanisms of drug action is far in the future and that it will involve much more information than presently can be visualized from structural formulas and molecular models. (Refer to Chapter 28, *Structure-Activity Relationships and Drug Design*.)

It has become clear that the pharmacological actions of drugs must be viewed as functions of the *total* molecules. For example, all barbituric acids contain the malonylurea fragment, but the relative actions of the different barbiturates vary widely with respect to quantitiveness, onset time, and duration, depending upon substituents at the 1, 3, and 5 positions (Chapter 80, *Sedative and Hypnotic Drugs*). The official sulfa drugs provide another example. The antibacterial portion common to all sulfas is the parent compound sulfanilamide, but

chemical alterations at the N^1 and N^4 positions produce derivatives that differ importantly in their actions and chemotherapeutic applications.

Dependence of pharmacological activity on *total* molecular structure commonly is evident with drugs that are polyfunctional from a chemical viewpoint. The sulfa drugs provide a good example of this as elimination of either the amino or sulfonamido portions, or even a change in their relative positions, results in loss of bacteriostatic activity. Similarly, aspirin loses its analgesic action if either its carboxyl or acetoxy group is removed completely or if the relation of these groups is other than *ortho*.

Similar dependence is common in the area of stereochemistry. Thus, the *trans* form of diethylstilbestrol is estrogenically potent whereas the *cis* form is not. This is reminiscent of the α - and β -forms of estradiol, the latter being about ten times as potent as the former. As an example involving diastereoisomers, the widely different mydriatic and pressor potencies of ephedrine and pseudoephedrine might be cited. Similar differences in physiological activity also are commonly observed between enantiomorphs. Thus, the D- and L-ephedrines differ markedly in mydriatic and pressor potencies; the D-forms of the α -amino acids are vastly inferior to the L-forms as nutrients, and (-)-epinephrine is more than 20 times as potent a sympathomimetic agent as the (+)-form.

From the preceding discussion, it is clear that difficulties may be encountered whenever one attempts to classify organic drugs on a chemical basis and obtain a system that simultaneously separates these drugs on a pharmacological basis. As will be seen in subsequent parts of this text, drugs that fall into the same chemical category often display, collectively, quite a number of different actions. Conversely, drugs of widely different chemical characteristics frequently provide the same kind of action when used as medicinal agents. Since, from a practical viewpoint, these agents are important because of the actions they provide (irrespective of their chemical composition), in subsequent chapters of this text drug monographs are grouped and presented on a pharmacological basis.

HETEROCYCLES PRESENT IN OFFICIAL PHARMACEUTICALS

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. Numerous examples occur, among the carbohydrates, essential amino acids, vitamins, alkaloids, glycosides, and antibiotics. The presence of heterocyclic structures in such diverse types of compounds is indicative strongly of the profound effects such structures exert on physiological activity, and recognition of this is reflected abundantly in efforts to find useful synthetic drugs. Examples include researches leading to a wide variety of modern drugs such as chlorthalidone (tranquilizer), methazolamide (carbonic anhydrase inhibitor), guanethidine (antihypertensive), stanozolol (anabolic), dapson (leprostatic), cyclophosphamide and thiopeta (antineoplastics), hydrochlorothiazide (diuretic and antihypertensive), imipramine (antidepressant), lucanthone (antischistosomal), and many others.

As is to be expected, this trend in research is reflected in the changing character of the contents of official drug compendia. Intensive research in diverse hetero areas continues to yield new medicinal agents, and Appendix E is designed to portray partially the spectrum of heterocycles presently represented in USP/NF drugs. The classification is patterned after that employed in the *Ring Index* and in *Chemical Abstracts*. The rings are presented in the order of increasing complexity. The boldface figures show the total number of atoms in the rings, and the number of boldface figures indicates the number of rings present in the systems. As an example, the notation 5, 6 indicates a system composed of two rings, one of which contains five atoms while the other one contains six atoms. The notations, such as C_3NS-C_6 , portray the kind and number of atoms present in the ring or rings. Associated with each of these formulas are the

graphic formulas and *Ring Index* names¹ of the individual heterocycles and, in italics, one or more examples of official drugs (or the portions of them) containing these heterocycles.

Structures and numbering schemes² are according to the *Ring Index* and thus do not portray any inherent features of stereospecificity.³ It will be observed that some of the names for the heterocycles are trivial (eg, pyrimidine, nortropane) while others are rigidly systematic. Trivial names are employed in the table wherever advisable; ie, wherever, through continued use, they have become recognized by chemists (as reflected by IUPAC adoption and *Chemical Abstracts* indexing) as denoting the structures to which they refer. In all other instances, systematic names must be used to distinguish between the heterocycle of interest and its isomeric forms. Presentation is exclusively on the basis of the *most complex ring "system"* containing the hetero atom or atoms; the term "system" meaning either a single ring or a combination of rings of the fused, bridged, or spiro types. For example, quinine is presented *only* as a quinoline derivative and *not* also as a pyridine derivative, even though quinoline also is a benzopyridine. Similarly, caffeine is presented *only* as a purine derivative and *not* as either a pyrimidine or an imidazole derivative, even though purine also is an imidazopyrimidine.

In a complete presentation of this type, drugs containing two or more *separate* hetero ring systems would appear under each of the systems; eg, quinine would emerge both as a quinoline and quinuclidine derivative. Wherever possible, only that portion of the official title is used that embraces the heterocycle; eg, thiamine is used instead of thiamine hydrochloride.

The final volume (IV) of the *Ring Index* was published in 1964 and index numbers are no longer assigned to ring structures by CAS. Identifiers for all compound types (including ring systems) have been organized into a *Parent Compound Handbook*, published by CAS, which consists of the following index categories.

Parent Name—This includes the names of all parent compounds and undefined natural products arranged in alphabetical order. Complex parent names are permuted so that root terms, buried in the names, may be located.

Parent Formula—Compounds are arranged according to the Hill system (carbon first, hydrogen second, with other elements following in alphabetic order), but omitting hydrogen atoms in the molecular formula. Ring systems are grouped in the same fashion as the *Ring Index* (see Appendix E) under the appropriate molecular formula.

Registry Number—These are arranged in ascending CAS registry number order with associated *Parent Compound Identifiers*.⁴

Stereoparent—This consists of *CAS Index Parents* whose names imply stereochemistry and whose structures are known. The arrangement is alphabetical with CA references for undefined or partially defined natural products.

¹Heterocyclic structures often are synthesized actually or theoretically by relatively simple chemical operations such as condensation or dehydrogenation of aliphatic structures. Because of this, many authors prefer to name such compounds in a manner designed to disclose the relationship to the aliphatics, rather than employ *Ring Index* or *CAS* nomenclature, as is used in Appendix D.

²Extreme caution must be exercised in interpreting position numbers (locants) as given the same compound by different texts, reference works or authors. The situation often exists in which two different numbering schemes, through long-continued usage, have become established firmly for a particular ring system. This leads to the use of different numbers as locants in an otherwise identical pair of names for the same compound. Also, authors frequently indulge in the reprehensible practice of inventing their own numbering schemes.

³The *Ring Index*, 2nd ed, Washington DC: American Chemical Society, 1960 and supplements. Also, for each annual, quinquennial and decennial Index to *Chemical Abstracts*.

⁴An identifier consists of a 5-letter code through which an entry may be found in the Parent Compound File. Each section of this file is assigned a range of identifiers by which the type of parent may be recognized. The ranges are:

BBBBB to BPZZY	Cage parents
BQBBR to BZZZZ	Acyclic stereo parents
CBBBC to DZZZZ	Cyclic stereo parents
FBBBB to ZZZZZ	Ring parents

Ring Analysis—This includes ring systems only, arranged by the classical *Ring Index* system and states the *CA* name and *Parent Compound Identifier*.

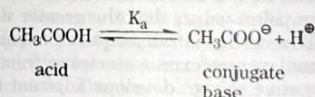
Ring Substructure—Rings are listed by;
A *component ring formula* for each individual ring system listed in the *Ring Analysis Index*, arranged according to the Hill system, but not including hydrogen atoms. All entries are permuted to allow searching on any atom.

The *current CA index name* of a ring parent and cyclic stereoparent; a *Parent compound Identifier*.

ACIDS AND BASES

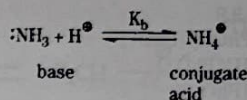
Organic pharmaceuticals are often complex molecules that have a variety of acidic and basic functional groups. The behavior of these groups in an aqueous environment will influence the activity of the drug, its transport through the body and its passage from one body compartment to another. There are two main theories of acids and bases, the *Brønsted* theory and the *Lewis* theory. According to the *Brønsted* theory an acid is a group that can donate a proton (a hydrogen ion), and a base is a group that can accept (bond to) a proton. Because a proton has no electrons, the base must be able to provide a pair of electrons to form a new bond. A *Lewis* acid is a group that can accept an electron pair and therefore must have an empty orbital. Groups that can donate an electron pair are termed *Lewis bases*. In this chapter the discussion will focus on *Brønsted* acids and bases. See also Chapter 17 *Ionic Solutions and Electrolytic Equilibria*.

Groups which function as acids must have a proton that can be removed in the presence of a base. In the laboratory extremely strong bases can be used in nonaqueous solvents to remove protons from alkyl groups and aromatic rings. Although such reactions are extremely important for drug synthesis, the concern of this chapter is with drugs in an aqueous environment. In water, the strongest base that can exist is hydroxide ion, OH^- , while the strongest acid is the hydrated proton or hydronium ion, H_3O^+ . Although there are several exceptions, most hydrogen atoms bonded to carbon are not sufficiently acidic to be removed in aqueous solution. In general hydrogen atoms bonded to O, N, S, and sometimes P (in general, any electronegative atom) are potentially removable in aqueous solution. When an acid donates a proton, a new species called the *conjugate base* of the acid is formed.



which has a charge one unit less than that of the acid from which it is derived. Thus, acetic acid, which is electrically neutral, dissociates to a proton and its conjugate base, acetate ion, which has a charge of -1 . An equilibrium is established between the acid and its conjugate base. The equilibrium constant, which is known as the acid dissociation constant (K_a), is a property of the acid in question. Because K_a values generally are exponential numbers, it is convenient to use $-\log K_a$ which is referred to as the $\text{p}K_a$ of the acid. In water, the $\text{p}K_a$ scale runs from 0 to 14 with the lowest values corresponding to the strongest acids. Refer to Chapter 17 for a more extensive treatment of this concept.

Basic groups require a pair of electrons, which are used to bond with a proton. This electron pair can be either an unshared pair or a formal negative charge. Bases such as ammonia or amines bond with protons using the lone unshared pair of electrons on the nitrogen atom. Other bases, such as hydroxide, use the electron pair made available by dissociation of the cation, to bond with protons. When a neutral base accepts a proton its charge increases by one unit and a new species is formed, called the *conjugate acid* of the base.



Ammonium ion (+1 charge) is the conjugate acid of ammonia; water (0 charge) is the conjugate acid of hydroxide ion. The equilibrium constant for base dissociation is called the K_b of the base. In water, the $\text{p}K_b$ scale extends from 0 to 14 with low values representing the strongest bases. There is a relationship between the $\text{p}K_a$ of an acid and the $\text{p}K_b$ of its conjugate base in water.

$$\text{p}K_a(\text{acid}) + \text{p}K_b(\text{conjugate base}) = 14$$

A similar relationship holds for bases and their conjugate acids.

$$\text{p}K_b(\text{base}) + \text{p}K_a(\text{conjugate acid}) = 14$$

Acids are in equilibrium with their conjugate base forms. One of these species will be charged and the equilibrium ratio, therefore, will determine the extent to which the molecule is ionized in solution. This has profound implications in medicinal chemistry because the extent of ionization of a drug in the body will affect its transport from one compartment to another. Examination of the expression for acid dissociation shows that the equilibrium constant

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

Taking the logarithm of both sides of the equation gives

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

Multiplying both sides of the equation by -1 gives

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

Substitution of $\text{p}K_a$ for $-\log K_a$ and pH for $-\log [\text{H}^+]$ gives

$$\text{p}K_a = \text{pH} + \log [\text{HA}]/[\text{A}^-]$$

This is known as the *Henderson-Hasselbalch* equation and gives the relationship between the $\text{p}K_a$ of an acid⁵ and the ratio of its acid form to conjugate base form at a given pH . It is important to remember that while $\text{p}K_a$ is a property of the molecule, pH is a property of the medium (solvent). In this case (for electrically neutral acids) the ratio $[\text{HA}]/[\text{A}^-]$ is the ratio of [non-ionized]/[ionized] species.

A more general form of the equation can be expressed as

$$\text{p}K_a = \text{pH} + \log [\text{acid form}]/[\text{conjugate base form}]$$

This is easy to remember because the *base* goes in the *base*-ment. For charged acids, such as conjugate acids of amines, the equation appears as

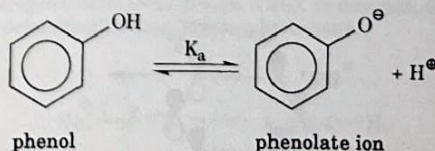
$$\text{p}K_a = \text{pH} + \log [\text{BH}^+]/[\text{B}]$$

Here, the ratio $[\text{BH}^+]/[\text{B}]$ equals the ratio of [ionized]/[nonionized] species.

The *Henderson-Hasselbalch* equation allows for calculation of the percent ionization of an acid at a given pH . This can be calculated as

$$\% \text{ ionization} = 100 [\text{ionized}]/([\text{ionized} + \text{non-ionized}])$$

An example of a *Henderson-Hasselbalch* calculation using phenol as the acid at pH 7.



⁵In medicinal chemistry only $\text{p}K_a$ is recognized to eliminate confusion. Those compounds with a $\text{p}K_a$ greater than $\text{p}K_w$ are bases; the greater the $\text{p}K_a$, the stronger the base. Henceforth, only $\text{p}K_a$ will be used.

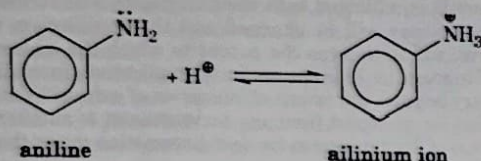
$$\begin{aligned} \text{p}K_a(\text{phenol}) &= 9.9 \\ 9.9 &= 7 + \log [\text{PhOH}]/[\text{PhO}^-] \\ 2.9 &= \log [\text{PhOH}]/[\text{PhO}^-] \\ 794 &= [\text{PhOH}]/[\text{PhO}^-] \end{aligned}$$

Thus, the ratio of phenol to phenolate ion (PhO^-) at pH 7 is 794:1, the compound is largely non-ionized. The percent ionization is calculated to be

$$\% \text{ ionization} = 100[1/(1 + 794)]$$

$$\% \text{ ionization} = 0.126\% \text{ at pH 7}$$

A second example is provided for the extent of ionization of aniline at pH 7. Aniline (PhNH_2) is a base with a $\text{p}K_a$ of 4.6 for the anilinium ion (PhNH_3^+). Using the Henderson-Hasselbalch equation gives



$$\begin{aligned} 4.6 &= 7 + \log [\text{PhNH}_3^+]/[\text{PhNH}_2] \\ -2.4 &= \log [\text{PhNH}_3^+]/[\text{PhNH}_2] \\ 0.004 &= [\text{PhNH}_3^+]/[\text{PhNH}_2] \end{aligned}$$

The ratio of ionized to non-ionized aniline at pH 7 equals 1:251. The percent ionization at pH 7 is

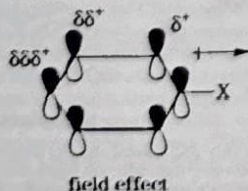
$$\% \text{ ionization} = 100 [1/(1 + 251)]$$

$$\% \text{ ionization} = 0.4\% \text{ at pH 7}$$

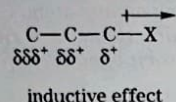
Some compounds have several acidic or basic groups or a combination of acidic and basic groups. In these cases, the $\text{p}K_a$ of the strongest acid is used for Henderson-Hasselbalch calculations because this is the group that will dissociate most readily. It also should be recognized that compounds that possess quaternary ammonium groups (N attached to four alkyl or aryl groups but not hydrogen) have a permanent +1 charge which is unaffected by the pH of the medium. Such compounds will always be 100% ionized and calculation of the extent of ionization of the molecule is unnecessary.

It was stated previously that in an aqueous environment hydrogen atoms attached to O, N, S, or P may be acidic and that an equilibrium is established between the acid form and its conjugate base. Groups that stabilize (lower the energy of) the conjugate base will drive the equilibrium farther to the right and thereby increase the strength of the acid. Such groups stabilize the conjugate base by providing a mechanism for the dispersal of any developing negative charge. Electronic effects from functional groups will therefore have an effect on the strength of nearby acidic and basic sites.

The electronic effects of functional groups can be divided into *field*, *inductive*, and *resonance* effects. The nature of these effects and how they are balanced, is the deciding factor for the type of electronic effect expressed by an individual functional group. *Field effects* are through-space effects on polarizability due to electronegativity differences.



Polarizability is the ease of distortion of the electron cloud. Attachment of a highly electronegative atom to a system will draw electron density toward that atom, thereby rendering other portions of the molecule positively charged. Field effects tend to decrease with increasing distance. *Inductive effects* are the polarization of bonds as a result of electronegativity differences.

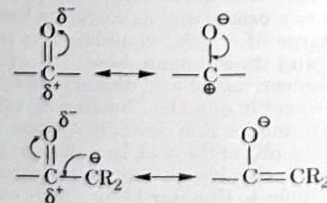


Thus an electronegative atom polarizes the bond attached to it by increasing the electron density in its vicinity. The opposite side of that bond acquires a degree of positive charge. This in turn polarizes the adjacent bond, and so on. These effects, which are transmitted through bonds, also decrease with distance from the electronegative atom.

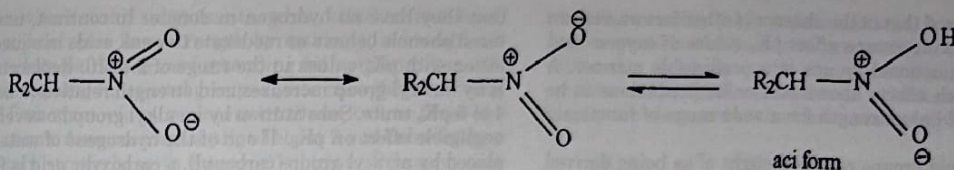
Resonance effects involve the actual movement of electrons through a π -bond system. The π -bond system acts as a conductor of electrons, much as wires conduct the flow of electricity, which can be moved in either direction depending on the needs of the system. This is especially prominent in conjugated systems (those with alternating double and single bonds). The movement of electrons through a conjugated system allows for charges to be dispersed over several atoms (delocalization). This lowers the energy of the system relative to an isolated charge. In contrast to field and inductive effects, resonance effects decrease much more slowly with distance. Stabilization increases as the number of atoms over which the charge is dispersed increases. Resonance effects generally contribute more extensively to the overall electronic effect of a functional group than do field or inductive effects.

Among the functional groups which are classified as being electron-withdrawing are the carbonyl-based groups (aldehydes, ketones, esters, carboxylic acids, amides, etc), nitro, nitrile (cyano), sulfinyl, sulfonyl, halo, quaternary ammonium, trifluoromethyl, vinyl, ethynyl, and phenyl. The relative contributions of field, inductive, and resonance effects to the overall electronic effect of these functional groups is discussed below.

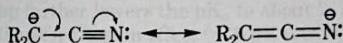
The carbonyl group ($\text{C}=\text{O}$) is an integral part of a large number of functional groups such as ketones, carboxylic acids, amides, esters, and carbamates. Field and inductive effects within this bond system arise because of the electronegativity difference between oxygen and carbon. Electrons in both the σ - and π -bonds are polarized so that the greater density occurs near oxygen. The carbon atom acquires a partial positive charge which can attract excess electrons from neighboring groups. If a negative charge develops adjacent to a carbonyl group, that charge is stabilized not only by electrostatic effects, but also by resonance, which can delocalize the negative charge onto the carbonyl oxygen.



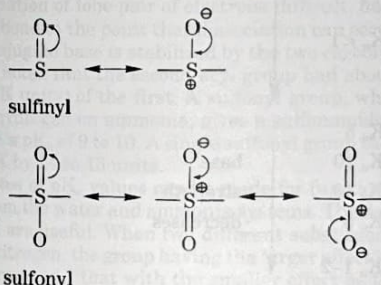
Another powerful electron-withdrawing group is the nitro group ($-\text{NO}_2$). Although this group is electrically neutral overall, the nitrogen always carries a positive charge that is balanced by a negative charge on one of the oxygen atoms. Two resonance structures can be drawn which distribute the negative charge over both oxygen atoms. The positively charged nitrogen can stabilize an adjacent negative charge by electrostatic attraction as well as by resonance.



A nitrile possesses a carbon–nitrogen triple bond. The electronegativity difference between carbon and nitrogen results in carbon having a partial positive charge. The larger effect of this functional group however, comes from resonance stabilization of an adjacent negative charge onto the nitrogen.



The difference between a sulfinyl and a sulfonyl group is that the former has one and the latter two S=O bonds. A major resonance form of the sulfinyl group has a S–O single bond with a formal positive charge on sulfur and a negative charge on oxygen. Sulfonyl has two such resonance structures. The preference for these structures over those with double bonds is a result of the relative inefficiency of *p*-orbital overlap due to the difference in size between sulfur and oxygen. Despite this, however, resonance stabilization of an adjacent negative charge does contribute to the electron-withdrawing capability of these functional groups.



The halides (F, Cl, Br, I) are much weaker electron withdrawing groups than might be expected. Fluorine, which is the most electronegative element, exerts strong field and inductive effects on an adjacent carbon atom. Additional electron density cannot be withdrawn by resonance because there are no available vacant orbitals. The lone-pair electrons on fluorine can however, be donated by resonance. As a result of this push–pull effect, the resonance and field (+ inductive) effects nearly cancel and fluorine usually exerts only a small electron-withdrawing effect.

electron-withdrawal by
field and inductive effects



electron-donation by
resonance

Chlorine is less efficient at donating electrons by resonance because of its size relative to carbon. It does exert substantial field and inductive effects, and therefore behaves as an electron-withdrawing group. The electronegativity difference between carbon and bromine is small, and electron-donation by resonance is inefficient. As a result, bromine generally behaves as a weak electron-withdrawing group. Iodine is weaker still because of decreased field and inductive effects.

Functional groups such as quaternary ammonium and trifluoromethyl exert their electronic effects primarily through field and inductive effects. The quaternary ammonium group has a permanent positive charge on nitrogen, which stabilizes an adjacent negative charge electrostatically. Because there are no lone-pair electrons or vacant orbitals, resonance with this group is not possible. Direct resonance with a trifluoromethyl group does not occur. The three highly electronegative fluorine atoms exert multiple field and inductive effects on the carbon atom to which they are attached, which can then in turn stabilize an adjacent negative charge in a similar fashion.

Unsaturated groups such as phenyl, vinyl or ethynyl can function as electron withdrawing groups by delocalizing any excess electron density throughout the π -system.

Functional groups, which are classified as being electron donating, include alcohols, ethers, amines, and alkyl groups. Each of these will stabilize a developing positive charge and, when attached to basic atoms, tend to increase the association constant.

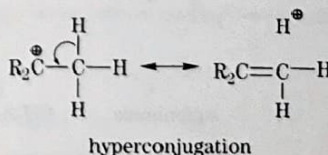
Alcohols and ethers have similar inductive effects to those present in carbonyl groups but experience decreased field effects due to the lack of a polarizable π -bond. Although carbonyl groups have the ability to delocalize excess electron density onto the oxygen, this is not possible for alcohols and ethers. Unshared electrons on the oxygen, however, can be delocalized by resonance to help stabilize a developing positive charge. In the process a new C=O bond is formed and the charge is delocalized onto oxygen. Although it is unfavorable to place a positive charge on an electronegative atom, this is compensated by the formation of a new bond. The predominance of resonance over field and inductive effects is observed by the fact that alcohols and ethers behave as electron-donating groups.



A similar situation exists for amino groups where the lone-pair electrons can be donated to form a C=N bond and thereby delocalize an adjacent positive charge onto the nitrogen. Because nitrogen is less electronegative than oxygen, it can better tolerate the charge. Amino groups are generally stronger electron donating substituents than either alcohols or ethers.



Alkyl groups, unlike alcohol or amino groups, do not have lone-pairs of electrons to donate. Instead, σ -bonding electrons, especially those from C–H bonds, can be donated in a process known as *hyperconjugation*, or *no-bond resonance*. Hyperconjugation allows an adjacent positive charge to be delocalized by resonance onto a proton. Such effects are greatest for methyl groups because the charge can be delocalized onto three different hydrogens. Methylene groups (CH_2), in contrast, allow for charge delocalization onto only two hydrogens.



hyperconjugation

It has been observed that in the absence of other factors, certain electron-withdrawing groups affect pK_a values of oxygen- and nitrogen-based functional groups in a predictable manner. A knowledge of such effects allows first-order predictions to be made of acid and base strength for a wide range of functional groups.

Some functional groups can be thought of as being derived from water by replacement of one or both hydrogens. Alcohols, for example, can be derived from water by replacement of one hydrogen by an alkyl group. Replacement of hydrogen by an aryl group (aromatic ring) gives a phenol. If both hydrogens are replaced by alkyl or aryl groups, an ether is formed. Water and simple alcohols are neutral (pK_a 14) with respect to their acid-base properties. Ethers are neutral by virtue of the fact

that they have no hydrogen to donate. In contrast, unsubstituted phenols behave as moderate to weak acids in aqueous solution with pK_a values in the range of 9 to 10. Replacement of H by an aryl group increases acid strength relative to water by 4 to 5 pK_a units. Substitution by an alkyl group however, has a negligible effect on pK_a . If one of the hydrogens of water is replaced by an acyl group (carbonyl), a carboxylic acid is formed. Such compounds typically have pK_a values in the range of 4 to 5. An acyl group therefore lowers the pK_a by 9 to 10 pK_a units. Substitution of a sulfonyl group for H increases acidity by 14 to 15 pK_a units. The resulting compounds, called sulfonic acids, are nearly as acidic as sulfuric acid in aqueous solution. A listing of the approximate pK_a values for a number of organic compounds is presented below.

ether	$H_3C-O-CH_3$	neutral	
alcohol	H_3C-O-H	neutral	
water	$H-O-H$	neutral	
phenol	$Ph-O-H$	pK_a 9-10	acid strength increases
carboxylic acid	$CH_3\overset{\overset{O}{\parallel}}{C}-O-H$	pK_a 4-5	
sulfonic acid	$CH_3\overset{\overset{O}{\parallel}}{S}(O)-O-H$	$pK_a < 1$	
ammonia	$H-NH_2$	pK_a 5	
1° amine	H_3C-NH_2	pK_a 10	base strength decreases
2° amine	$H_3C-NH-CH_3$	pK_a 10	
arylamine	$Ph-NH_2$	pK_a 5	
diarylamine	$Ph-NH-Ph$	pK_a 1-2	base
amide	$CH_3\overset{\overset{O}{\parallel}}{C}-NH_2$	neutral	acid
N-arylamide	$CH_3\overset{\overset{O}{\parallel}}{C}-NH-Ph$	pK_a 12-13	
imide	$CH_3\overset{\overset{O}{\parallel}}{C}-NH-\overset{\overset{O}{\parallel}}{C}CH_3$	pK_a 9	
sulfonamide	CH_3S-NH_2	pK_a 9	acid strength increases
N-arylsulfonamide	$CH_3S-NH-Ph$	pK_a 6-7	
sulfonimide	$CH_3S-NH-\overset{\overset{O}{\parallel}}{C}CH_3$	pK_a 4	

Electron-withdrawing substituents, when attached to a basic group, will decrease base strength by making it more difficult to donate lone-pair electrons for bonding with protons. Some nitrogen-containing functional groups can be thought of as being derived from ammonia by replacement of one, two, or three hydrogen atoms. Ammonia has a pK_a of about 9 and behaves as a moderately strong base in aqueous solution. Primary, secondary and tertiary alkyl amines can be formed from ammonia by replacement of one, two or three hydrogens, respectively, by alkyl groups. Such compounds have approximately the same base strength as ammonia in aqueous solution, indicating that the alkyl groups have little effect on pK_a .

Replacement of one hydrogen of ammonia by an unsubstituted aryl group gives a very weak base with a $pK_a \approx 4$. A second aryl group further lowers the pK_a to about 2. A single aryl substituent therefore has an effect (≈ 5 pK units), while a second such group displays an effect that is half again as great (2 to 3 pK units). The effect of a third group is not as easily quantified because of nonlinear effects such as steric hindrance.

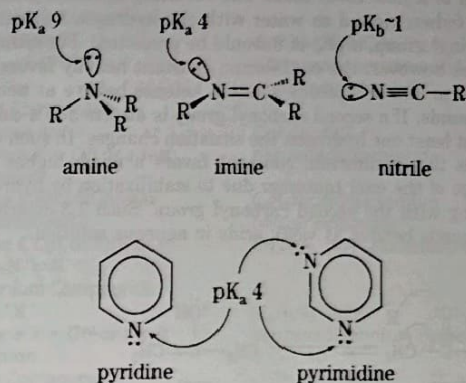
Replacement of one of the ammonia hydrogen atoms by an acyl group gives an amide. Such compounds are virtually neutral in aqueous medium, suggesting that the acyl group decreased the pK_a by 3 to 4 units, the same magnitude as it increased acid strength in the water model. The electron withdrawing carbonyl group restrains the lone pair electrons of the nitrogen atom to such an extent that it can no longer abstract protons.

Substitution of a second acyl group on ammonia gives an imide. Imides behave as acids in aqueous solution with pK_a values of about 9. The second electron withdrawing group not only makes donation of lone pair of electrons difficult, but weakens the N—H bond to the point that dissociation can occur. The resulting conjugate base is stabilized by the two carbonyl groups. It is to be noted that the second acyl group had about half the effect (5 pK units) of the first. A sulfonyl group, when substituted for hydrogen on ammonia, gives a sulfonamide, which is acidic with a pK_a of 9 to 10. A single sulfonyl group therefore alters the pK by 14 to 15 units.

Estimates of pK_a values can be made for functional groups derived from the water and ammonia systems. The data seen in Table 25-2 are useful. When two different substituents are attached to nitrogen, the group having the larger effect is taken as the first group and that with the smaller effect as the second group. Thus, *N*-methylaniline is calculated to have a pK_a of about 4 (using the first group value for the aryl substituent) and not pK_a of 5 to 6, as would be obtained if the methyl group were taken for the first group. *It is important to realize however, these estimates exclude steric and other electronic effects and may vary from the actual (experimental) values by several pK units.*

Hybridization also can affect base strength as observed in the series amine, imine, nitrile where the hybridization of nitrogen changes from sp^3 to sp^2 to sp . Although amines function as moderately strong bases ($pK_a \approx 9$), imines are much weaker with pK_a values near 4. Nitriles are essentially neutral ($pK_b \sim 1$). The effect of hybridization is to shorten the bond length and the general trend is that bond length decreases and electronegativity increases as the percent of *s*-character of the bond increases (25% for sp^3 ; 33% for sp^2 ; and 50% for sp). The shorter bond lengths and higher electronegativity associated with the nitrogen atom of nitriles results in the lone-pair being held much closer to nitrogen than it is for imines or amines. Since, basicity is a func-

tion of how readily the lone-pair is shared, it is reasonable that amines would be the most basic, and nitriles the weakest bases, within this series. Aromatic nitrogen atoms, such as found in pyridine and pyrimidine, are also sp^2 hybridized and are similar to imines with regard to their base-strength ($pK_a \approx 4$).



Two functional groups that are common in pharmaceuticals are amidine and guanidine. Refer to Appendix A of this chapter for a listing of functional groups and names. These can be considered as amino derivatives of imines. Amidines, which have a single amino group attached to the imine carbon, are strong bases with pK_a values near 11. Guanidines are even more basic ($pK_a \approx 13$) and have two amino groups attached to the imine carbon. The higher basicity of these functional groups as compared to imines is due to two factors: (1) the effect of the electron-donating amino nitrogen(s), which can increase electron density at the imino nitrogen by resonance, and (2) the conjugate acid form is stabilized by charge delocalization among each of the nitrogens again as a result of resonance. These effects are more pronounced for guanidines, which have an additional resonance structure available. In these functional groups it is the doubly-bound nitrogen that serves as the basic site. The single-bonded nitrogen is neutral due to the electron-withdrawing effect of the double bond and the lack of resonance stabilization for the conjugate acid form of this nitrogen. It is important to note, however, that if the amino nitrogen carries at least one hydrogen, tautomeric structures are possible in which either nitrogen can be bonded to hydrogen, with the other then becoming the basic site.

Tautomers are structures that differ in the placement of one small group or atom, usually hydrogen. In amidines, hydrogen can shift rapidly back and forth between the two nitrogen atoms (with the consequent relocation of a pair of electrons) unless structural features favor a particular tautomeric structure.

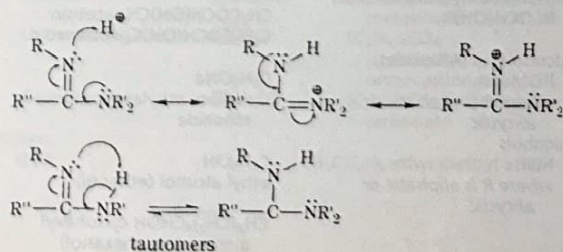
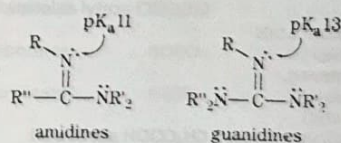
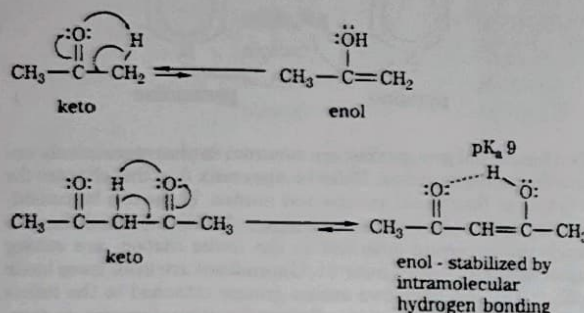


Table 25-2. pK Effect of Functional Groups as Substituents on H_2O and NH_3

FUNCTIONAL GROUP	EFFECT AS FIRST GROUP, PK UNITS	EFFECT AS SECOND GROUP, PK UNITS
H Alkyl	0	0
Aryl, vinyl	4	2-3
Acyl	10	5
Sulfonyl	15	7-8

Another situation where tautomerization occurs involves protons on carbons adjacent to a carbonyl group. Ketones, for example, have two tautomeric structures known as the *keto* and *enol* forms. In the enol form, a hydrogen from an adjacent carbon migrates onto the carbonyl oxygen, with concomitant formation of a new C=C bond. The resulting hydroxyl group is acidic (when viewed as water with one hydrogen substituted by a vinyl group, a pK_a of 9 would be predicted). For ordinary ketones however, the equilibrium constant heavily favors the keto form and in aqueous solution ketones behave as neutral compounds. If a second carbonyl group is attached to a carbon with at least one hydrogen the situation changes. In such compounds the equilibrium constant favors a much higher percentage of the enol tautomer due to stabilization by hydrogen bonding with the second carbonyl group. Such 1,3-dicarbonyl compounds behave as weak acids in aqueous solution.



SUMMARY

With the ability of the modern computer to manipulate millions of bits of data in a trice, the prediction of many physical and chemical constants for known and potential chemical entities, solely based on data available in a library of known information has really come to the fore. There exist programs that predict quite accurate values for pK_a , log P (octanol-water partition coefficient), fragmentation patterns for compounds in mass spectra, the interpretation of IR and NMR spectra, and so on, coupled with extensive databases of experimentally derived constants. (One such program may be viewed at <http://www.acdlabs.com/>.)

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Appendix A Types of Organic Compounds

CLASS	EXAMPLES	CLASS	EXAMPLE
Acetals RC(H or R)(OR) ₂ (cf Ketals)	CH ₃ CH(OCH ₃) ₂ acetaldehyde dimethyl acetal (1,1-dimethoxyethane)(CH ₃) ₂ C(OC ₂ H ₅) ₂ acetone diethyl acetal (2,2-diethoxypropane)	Aldehydes RCHO	CH ₃ CHO acetaldehyde
Acid Anhydrides 1. Of Monocarboxylic Acids RCOOCOR	(CH ₃ CO) ₂ O acetic (acid) anhydride	Alkoxides (see Alcoholates)	
2. Of Dicarboxylic Acids RCOOCO	CH ₂ CH ₂ COOCO succinic (acid) anhydride	Alkylhalosilanes R(SiH ₂) _n X where one or more H's may be substituted by additional R's or X's	CH ₃ SiH ₂ Cl methylchlorosilane
Acid Halides (Acyl Halides) RCOX	CH ₃ COCl acetyl chloride	Alkylsilanes R(SiH ₂) _n H where one or more H's may be substituted by additional R's	CH ₃ SiH ₃ methylsilane C ₂ H ₅ SiH ₂ SiH ₂ C ₂ H ₅ sym-diethyldisilane
Acids (Carboxylic) (other acids are listed under their characteristic names, eg, Sulfonic Acids, Thio Acids, etc) RCOOH	CH ₃ COOH acetic acid	Alkylsilanols Types here illustrated are limited to derivatives of silane; ie, (mono)-silane, SiH ₄ . There are similar derivatives of the di-, tri-, etc, silanes.	
Acyloins (α-Hydroxy Ketone) RCOCH(OH)R	CH ₃ COCH(OH)CH ₃ acetoin C ₆ H ₅ COCH(OH)C ₆ H ₅ benzoin	RSiH ₂ OH alkylsilanol R ₂ SiOH dialkylsilanediols R ₃ SiOH trialkylsilanol	RSi(OH) ₂ alkylsilanediols RSi(OH) ₃ alkylsilanetriols
Alcoholates (Alkoxides) ROMetal where R is aliphatic or alicyclic	C ₂ H ₅ ONa sodium ethylate sodium ethoxide	Alkylsiloxanes Various linear and cyclic types. (see Silicones). A common linear type consisting of condensation polymers of dialkylsilanediols is shown.	HO(SiR ₂ O) _n SiR ₂ OH
Alcohols ROH where R is aliphatic or alicyclic	C ₂ H ₅ OH ethyl alcohol (ethanol) CH ₂ (CH ₂) ₄ CHOH cyclohexyl alcohol (cyclohexanol)	Amides RCONH ₂ Amidines RC(=NH)NH ₂	CH ₃ CONH ₂ acetamide CH ₃ C(NH)NH ₂ acetamidine

Appendix A Continued

CLASS	EXAMPLES	CLASS	EXAMPLE
Amines $RN(H \text{ or } R)(H \text{ or } R)RNH_2$ types = Amino Compounds	CH_3NH_2 methylamine $(C_2H_5)_2NH$ diethylamine $CH_3N(C_2H_5)C_3H_7$ methylethylpropylamine	Diazoamino Compounds (Triazene Derivatives) $RN=NNHR$	$C_6H_5N=NNHC_6H_5$ diazaminobenzene or 1,3- diphenyltriazene
Amino Acids $R(NH_2)COOH$	$CH_2(NH_2)COOH$ aminoacetic acid	Diazo Compounds Type A $RNNX$ where $X = OH$ or a salt anion Type B $RN=NO$ Metal (diazoates) Type C $C(H \text{ or } R)(H \text{ or } R)-$ $=N^+=N^-$	$C_6H_5N=NCI$ benzenediazochloride $C_6H_5N=NONa$ sodium benzenediazoate $CH_2=N^+=N^-$ diazomethane
Ammonium Derivatives $[RH_3N]^+X^-$ where $X = OH$ or a salt anion and any or all H's may be R's. If N is a ring member, specific "ium" nomenclature is employed to denote the heterocycle.	$[(CH_3)_4N]^+I^-$ tetramethylammonium iodide $[(C_2H_5)_2N^+H_2]Cl^-$ diethylammonium chloride (diethylamine hydrochloride) $[CH=CHCH=CHCH=N^+-(CH_3)]Br^-$, 1-methyl pyridinium bromide	Diazonium Compounds $RN_2^+X^-$ where $X = OH$ or a salt anion Epoxy Compounds $CH_2(CH_2)_nCH_2O$ where $n = \text{zero or greater}$ and any or all H's may be R's	$[C_6H_5N_2]^+OH^-$ benzenediazonium hydroxide CH_2CH_2O epoxyethane $CH_3CHCH_2CH(CH_3)O$ 2,4-epoxypentane
Anilides $RCONHR'$ where NHR' is derived from aniline Note—If NHR' is derived from: toluidine xylylidine anisidine phenetidide	$CH_3CONHC_6H_5$ acetanilide Compounds are termed: toluidides xylylides anisidides phenetidides	Esters (of Carboxylic Acids) $RCOOR$ Esters (of Inorganic Oxy Acids) The listing here is intentionally limited to esters of the more impor- tant oxy acids of nitrogen, phosphorus, sulfur, boron, silicon, and carbon. In each instance, the type formula shown is for the ester which results from the replacement of all acidic H's by R's. Where more than one R is present, acid esters (ie, esters still containing one or more unreplaced H's) are possible.	$CH_3COOC_2H_5$ ethyl acetate
Anils (Schiff bases) $RCH=NR$	$C_6H_5CH=NC_6H_5$ N-Benzylideneaniline	Nitrates Nitrites (Ortho)phosphates Metaphosphates Pyrophosphates (Ortho)phosphites Hypophosphites cf Phosphonic Acids Sulfates Sulfites Orthoborates Metaborates Orthosilicates Metasilicates Orthocarbonates Carbonates	$CH_3CHCH_2CH(CH_3)O$ 2,4-epoxypentane $CH_3COOC_2H_5$ ethyl acetate
Azides (Acyl Azides) $RCON=N^+=N^-$ Azido Compounds $RN=N^+=N^-$ Azines $R_2C=NN=CR_2$	$CH_3CON=N^+=N^-$ acetyl azide $C_2H_5N=N^+=N^-$ azidoethane $(CH_3)_2C=NN=C(CH_3)_2$ acetone azine $C_6H_5N=NC_6H_5$ azobenzene $C_6H_5N=N(O)C_6H_5$ azoxybenzene	$RONO_2$ $RONO$ $(RO)_3PO$ $ROPO_2$ $(RO)_2PO-OR$ $—PO(OR)_2$ $P(OR)_3$ $H_2P(O)(OR)$ $(RO)_2SO_2$ $(RO)_2SO$ $B(OR)_3$ $ROBO$ $Si(OR)_4$ $(RO)_2SiO$ $C(OR)_4$ $(RO)_2CO$	$C_2H_5NO_3$, ethyl nitrate C_2H_5ONO , ethyl nitrite $(C_2H_5)_3PO_4$, (tri)ethyl phosphate $C_2H_5PO_3$, ethyl metaphosphate $(C_2H_5)_4P_2O_7$, (tetra)ethyl pyrophosphate $(C_2H_5)_3PO_3$, (tri)ethyl phosphite $C_2H_5H_2PO_2$, ethyl hypophosphite $(C_2H_5)_2SO_4$, (di)ethyl sulfate $(C_2H_5)SO_3$, (di)ethyl sulfite $(C_2H_5)_3BO_3$, (tri)ethyl orthoborate $C_2H_5BO_2$, ethyl metaborate $(C_2H_5)_4SiO_4$, (tetra)ethyl orthosilicate $(C_2H_5)_2SiO_3$, (di)ethyl metasilicate $(C_2H_5)_4CO_4$, (tetra)ethyl orthocarbonate $(C_2H_5)_2CO_3$, (di)ethyl carbonate
Azo Compounds $RN=NR$ Azoxy Compounds $RN=N(O)R$	$C_6H_5N=NC_6H_5$ azobenzene $C_6H_5N=N(O)C_6H_5$ azoxybenzene		
Benzils (Aromatic α -Diketones) $RCOCOR$ where R is aromatic Benzoin (Aromatic α -Hydroxy Ketones) $RCH(OH)COR$ where R is aromatic	$p-CH_3C_6H_4COCOC_6H_4CH_3$, p p',p'-dimethylbenzil $p-CH_3C_6H_4CH(OH)CO-C_6H_4CH_3$, p p',p' dimethylbenzoin or p-toluoïn		
Betaines $R_3N^+(CH_2)_nCOO^-$	$(CH_3)_3N^+CH_2CH_2COO^-$ β -alanine, trimethylbetaine		
Borates (see Esters) Carbonates (see Esters) Carbamines (see Isocyanides; Isonitriles) RNC	C_6H_5NC phenyl {carbamine, isocyanide or isonitrile C_6H_5OCN phenyl cyanate $CH_3C(CN)(OH)CH_3$ acetone cyanohydrin		
Cyanates $ROCN$ Cyanides (see Nitriles) Cyanohydrins $RC(CN)(OH)(H \text{ or } R)$		Ethers ROR	$CH_3OC_2H_5$ ethyl methyl ether