

Chemical Introduction: Sources, Classification and Chemical Properties of Drugs

1.1 Introduction

Pharmacology can be divided into two major areas, pharmacodynamics (PD) – the study of what a drug does to the body and pharmacokinetics (PK) – the study of what the body does to the drug. Drug disposition is a collective term used to describe drug absorption, distribution, metabolism and excretion whilst pharmacokinetics is the study of the rates of these processes. By subjecting the observed changes, for example, in plasma concentrations as a function of time, to mathematical equations (models), pharmacokinetic parameters such as elimination half-life ($t_{1/2}$), volume of distribution (V) and plasma clearance (CL) can be derived. Pharmacokinetic modelling is important for the:

- Selection of the right drug for pharmaceutical development
- Evaluation of drug delivery systems
- Design of drug dosage regimens
- Appropriate choice and use of drugs in the clinic.

These points will be expanded in subsequent chapters.

A drug is a substance that is taken, or administered, to produce an effect, usually a desirable one. These effects are assessed as physiological, biochemical or behavioural changes. There are two major groups of chemicals studied and used as drugs. First, there is a group of pharmacologically interesting endogenous substances, for example acetylcholine, histamine and noradrenaline. Second, there are the non-endogenous, or 'foreign' chemicals (xenobiotics), which are mostly products of the laboratories of the pharmaceutical industry.

There are numerous ways in which drugs interact with physiological and biochemical process to elicit their responses. Many of these interactions are with macromolecules, frequently proteins and nucleic acids. *Receptors* are transmembrane proteins, with endogenous ligands typified by acetylcholine and noradrenaline (norepinephrine). Although substances may be present naturally in the body, they are considered drugs when they are administered, such as when adrenaline is injected to alleviate anaphylactic shock. Drugs can either mimic (agonists) or inhibit (antagonists) endogenous neurotransmitters. Salbutamol is a selective β_2 -agonist whereas propranolol is a non-selective β -blocker. Some receptors are *ligand-gated ion channels*, for example the cholinergic nicotinic receptor, which is competitively antagonized by (+)-tubocurarine. *Enzymes*, either membrane bound or soluble, can be inhibited – for example neostigmine inhibits acetylcholinesterase

and aspirin inhibits cyclooxygenase. Other proteins that may be affected are *voltage-gated (regulated) ion-channels* – a typical one being voltage-gated sodium channels which are blocked by local anaesthetics such as lidocaine (lignocaine). Antimalarials, chloroquine, for example, intercalate in DNA. Some drugs work because of their physical presence – often affecting pH or osmolarity – for example antacids to reduce gastric acidity or sodium bicarbonate to increase urinary pH and thereby increase salicylate excretion (Section 3.3.1.5).

1.1.1 Source of drugs

Primitive therapeutics relied heavily on a variety of mixtures prepared from botanical and inorganic materials. The botanical materials included some extremely potent plant extracts, with actions for example on the brain, heart and gastrointestinal tract, and also some innocuous potions, which probably had little effect. The inorganic materials were generally alkalis, which did little more than partially neutralize gastric acidity. Potassium carbonate (potash, from wood fires) was chewed with coca leaves to hasten the release of cocaine. Inevitably, the relative importance of these materials has declined, but it should be recognized that about a dozen important drugs are still obtained, as purified chemical constituents, from botanical sources and that alkalis still have a very definite value in certain conditions. Amongst the botanical drugs, are the alkaloids: morphine is still obtained from opium, cocaine is still obtained from coca leaves, and atropine is still obtained from the deadly nightshade (belladonna). Although the pure compounds have been prepared synthetically in the laboratory, the most economical source is still the botanical material. Similarly, glycosides such as digoxin and digitoxin are still obtained from plants. These naturally occurring molecules often form the basis of semisynthetic derivatives – it being more cost-effective than synthesis *de novo*.

Similar considerations apply with some of the drugs of zoological origin. For instance, while the consumption of raw liver (an obviously zoological material) was once of great importance in the treatment of anaemia, modern treatment relies on cyanocobalamin, which occurs in raw liver, and on hydroxycobalamin, a semisynthetic analogue. Another zoological example is insulin, which was obtained from the pancreatic glands of pigs (porcine insulin) but can now be genetically engineered using a laboratory strain of *Escherichia coli* to give human insulin.

Most other naturally occurring drugs, including antibiotics (antimicrobial drugs of biological origin) and vitamins, are generally nowadays of known chemical structure, and although their synthesis in the laboratory is in most cases a chemical possibility, it is often more convenient and economical to extract them from natural sources. For the simpler molecules the converse may be true, for example chloramphenicol, first extracted from the bacterium, *Streptomyces venezuelae*, is totally synthesized in the laboratory. For some antibiotics, penicillins and cephalosporins for example, the basic nucleus is of natural origin, but the modern drugs are semisynthetic modifications of the natural product.

Amongst the naturally occurring drugs are the large relative molecular mass (M_r) molecules, such as peptides, proteins (including enzymes), polysaccharides and antibodies or antibody fragments. Some of these macromolecules, snake venoms and toxins such as botulinum toxin ($M_r \sim 150,000$) have long been known. The anticoagulant, heparin, is a heavily sulfated polysaccharide ($M_r \sim 3,000\text{--}50,000$). Peptide hormones used as drugs include insulin and human growth hormone. Streptokinase, urokinase and tissue plasminogen activator (tPA) are enzymes used as thrombolytic agents. Other therapeutic enzymes are the pancreatic enzymes given to sufferers of cystic fibrosis. Antibodies are a recent addition to macromolecular drugs. Digoxin-specific antibodies, or light-chain fragments (F_{ab}) containing the specific binding site, are used to treat poisoning by cardiac glycosides. Advances in molecular biology have led to the introduction of a number of monoclonal antibodies with a range of targets: various cancers, viruses, bacteria, muscular dystrophy, the cardiovascular and immune systems, to name but some. Furthermore, the antibodies can be

modified to carry toxins, cytokines, enzymes and radioisotopes to their specific targets. Monoclonal antibodies have the suffix *-mab* and the infix indicates the source of the antibody and the intended target; *-u-* indicates human and *-tu(m)-* that the target is a tumour. Thus, trastuzumab is a monoclonal antibody directed at (breast) cancer that has been ‘humanized’, *-zu-*; that is over 95% of the amino acid sequence is human. The prefix is unique to the drug.

With only minor exceptions, drugs are chemicals with known structures. Some of them are simple, some complex. Some of them are purely synthetic; some are obtained from crude natural products and purified before use. Most are organic chemicals, a few are inorganic chemicals. With all drugs, the emphasis is nowadays on a pure active constituent, with carefully controlled properties, rather than on a mysterious concoction of unknown potency and constitution.

1.2 Drug nomenclature and classification

Drug names can lead to confusion. Generally a drug will have at least three names, a full chemical name, a proprietary name, i.e. a trade name registered to a pharmaceutical company, and a non-proprietary name (INN) and/or an approved name. Names that may be encountered include the British Approved Name (BAN), the European Pharmacopoeia (EuP) name, the United States Adopted Name (USAN), the United States Pharmacopoeia (USP) name and the Japanese Approved Name (JAN). The WHO has been introducing a system of recommended INNs (rINN) and it is hoped that this will become the norm for naming drugs, replacing alternative systems. For example, lidocaine is classed as a rINN, USAN and JAN, replacing the name lignocaine that was once a BAN. Often ‘ph’ is replaced by ‘f’, as in cefadroxil, even though the group name is cephalosporins. We have elected to use amphetamine rather than amfetamine. Generally, the alternatives obviously refer to the same drug, such as ciclosporin, cyclosporin and cyclosporine. There are some notable exceptions, pethidine is known as meperidine in the United States and paracetamol as acetaminophen. Even a simple molecule like paracetamol may have several chemical names but the number of proprietary names or products containing paracetamol is even greater, including Panadol, Calpol, Tylenol, Anadin Extra. Spelling can also lead to apparent anomalies. For example, cefadroxine is a cephalosporin (Table 1.2). Therefore it is necessary to use an unequivocal approved name whenever possible.

A rigid system for the classification of drugs will never be devised. Increasingly, it is found that drugs possess actions which would permit their categorization in several groups in any one particular classification system. This is shown most strikingly by the use of lidocaine for both local anaesthetic and cardiac effects. Additionally, with constant changes in drug usage, it is not uncommon to find drugs of several different types in use for the same purpose. The number of examples within each type is of course very large. However, drugs are commonly grouped according to one of two major systems. These are on the basis of action or effect, and on the basis of chemistry. It is not possible to include all drugs in either of these groupings, and so a hybrid classification is necessary if all possibilities are to be considered. Table 1.1 shows an abbreviated pharmacological listing. The interpretation of this is quite straightforward, and it is presented as a general aid to the reader of later chapters of this book. Most of the examples quoted in later chapters are mentioned. Not so straightforward is the chemical listing shown in Table 1.2. It will be immediately noticed that while all of the groups of drugs in Table 1.2 are represented in Table 1.1, all of the types in Table 1.1 are not represented in Table 1.2, as a great many drugs are of chemical types of which there is only a single example, and Table 1.1 is only concerned with those chemical groups of drugs which are commonly known by their chemical names. Commonly encountered chemical groups are exemplified in Table 1.3.

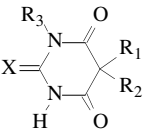
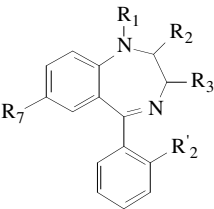
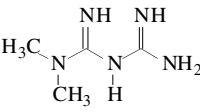
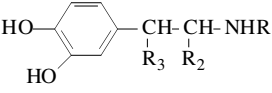
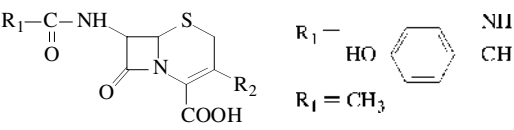
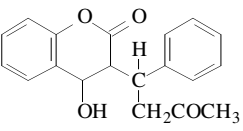
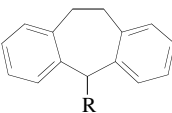
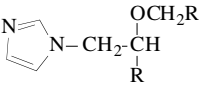
1.3 Properties of molecules

Drug molecules may be converted to other molecules either by spontaneous change (i.e. decomposition) or by enzymatic transformation. Enzymes are such efficient catalysts that the rate of a reaction may be increased

Table 1.1 Abbreviated listing of drug groups categorized on the basis of pharmacological use or clinical effect, with examples, or cross-referenced to the chemical types of Table 1.2

THE CENTRAL NERVOUS SYSTEM	PERIPHERAL SYSTEMS
General anaesthetics	Drugs acting at synapses and nerve endings
I Gases – e.g. nitrous oxide	I Acetylcholine and analogues (parasympathomimetic agents)
II Volatile liquids – e.g. halothane	II Anticholinesterase drugs – e.g. physostigmine
III Intravenous anaesthetics, including some barbiturates	III Inhibitors of acetylcholine at parasympathomimetic nerve endings – e.g. atropine
Hypnotics including some barbiturates and some benzodiazepines, and newer examples such as zolpidem	IV Drugs acting at ganglia – e.g. nicotine
Sedatives including certain barbiturates, phenothiazines and benzodiazepines	V Drugs acting at adrenergic nerve endings, including catecholamines and imidazolines
Tranquillizers	VI Neuromuscular blocking drugs – e.g. suxamethonium
I Major, including certain phenothiazines and butyrophenones	Drugs acting on the respiratory system
II Minor, including certain benzodiazepines	I Bronchodilators – e.g. salbutamol
III Other, newer, examples, such as olanzepine	II Drugs affecting allergic responses – e.g. disodium cromoglycate
Antidepressants	III Oral antiasthmatics e.g. montelukast
I Dibenzazepines – e.g. nortriptyline	Autacoids and their antagonists
II Monoamine oxidase inhibitors – e.g. tranlycypromine	I Histamine and 5-hydroxytryptamine
III Lithium	II Antihistamines – e.g. diphenhydramine
IV Other newer examples, such as fluoxetine	Drugs for the treatment of gastrointestinal acidity
Central nervous system stimulants	e.g. ranitidine and omeprazole
I Amphetamine-related compounds – e.g. methylphenidate and amphetamine	Cardiovascular drugs
II Hallucinogens – e.g. lysergic acid diethylamide	I Digitalis and digoxin
III Xanthines – e.g. caffeine	II Antiarrhythmic drugs – e.g. quinidine
Analgesics	III Antihypertensive drugs, including angiotensin-converting enzyme (ACE) inhibitors (‘prils’)
I Narcotics – e.g. morphine and pethidine	IV Vasodilators – e.g. glyceryl trinitrate
II Mild analgesics, including salicylates	V Anticoagulants, including heparin and coumarins.
Miscellaneous centrally acting drugs, including respiratory stimulants (analeptics), anticonvulsants, certain muscle relaxants, drugs for Parkinson’s disease, antiemetics, emetics and antitussives	VI Diuretics, including thiazidiazines
CHEMOTHERAPY	VII Lipid lowering drugs (e.g. ‘statins’)
Drugs used in the chemotherapy of parasitic diseases, including arsenicals	VIII Thrombolytics (e.g. tissue plasminogen activator)
Drugs used in the chemotherapy of microbial diseases, including penicillins, cephalosporins and sulfonamides	Local anaesthetics – e.g. lidocaine (lignocaine)
Drugs used in the treatment of viral diseases, such as aciclovir	Locally acting drugs
Drugs used in the treatment of fungal diseases, e.g. miconazole	e.g. gastric antacids and cathartics
Drugs used in the treatment of cancer, such as alkylating agents, antimetabolites, anthracycline derivatives, trastuzumab, hormone antagonists	Endocrinology
	Hormones, hormone analogues and hormone antagonists, including steroids, sulfonyleureas and biguanides (e.g. glipizide, thyroxine and insulin)
	Biological response modifiers
	e.g. interferon, adalimumab
	Immunosuppressants
	e.g. ciclosporin

Table 1.2 Some groups of drugs classified on chemical structure rather than pharmacological properties or uses

Group	Parent structure	Chemical example	Uses and examples
Barbiturates		Phenobarbital $R_1 = C_2H_5$ $R_2 = C_6H_5$ $R_3 = H$ $X = O$	As hypnotics and sedatives (pentobarbital) As anticonvulsants (phenobarbital) As general anaesthetics (thiopental)
Benzodiazepines		Lorazepam $R_1 = H$ $R_2 = O$ $R_3 = OH$ $R_7 = Cl$ $R'_2 = Cl$	As anxiolytics (diazepam) As hypnotics (temazepam)
Biguanides		Metformin (as drawn)	As oral hypoglycaemics
Catecholamines		Adrenaline $R_1 = CH_3$ $R_2 = H$ $R_3 = OH$	Sympathomimetic amines
Cephalosporins		Cefadroxil $R_1 = CH_3$	As antimicrobial drugs
Coumarins		Warfarin (as drawn)	As anticoagulants
Dibenzazepines		Nortriptyline $R =$ $=CH(CH_2)_2NHCH_3$	As antidepressants
Imidazoles		Miconazole $R = Cl$	As antifungal drugs

(continued)

Table 1.2 (Continued)

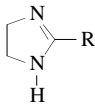
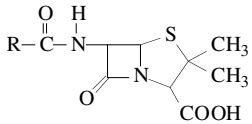
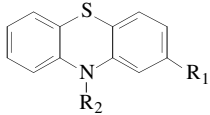
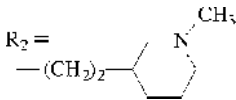
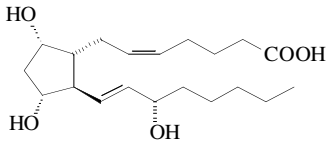
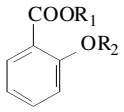
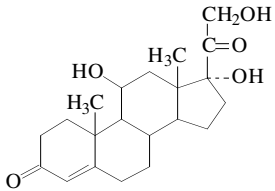
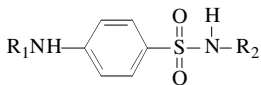
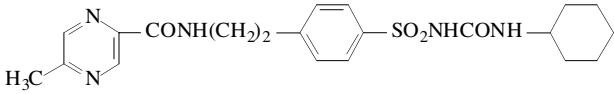
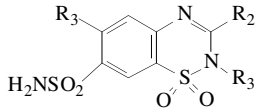
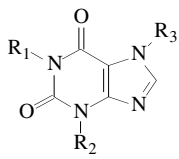
Group	Parent structure	Chemical example	Uses and examples
Imidazolines		Clonidine	As antihypertensive drugs
Macromolecules: Polysaccharides, peptides, proteins, enzymes, antibodies		Heparin, insulin, trastuzumab	In control of blood clotting, diabetes, cancer, rheumatoid arthritis and other conditions
Penicillins		Penicillin G	As antimicrobial drugs
Phenothiazines		Thioridazine R ₁ = SCH ₃ R ₂ = 	As antihistamines (promethazine) As antipsychotics (thioridazine) As antiemetics (trifluoperazine)
Prostaglandins		PGF _{2z} (as drawn)	As uterine stimulants and other procedures
Salicylates		Aspirin R ₁ = H R ₂ = COCH ₃	As antipyretic, anti-inflammatory and antipyretic drugs
Steroids		Hydrocortisone (as drawn)	Anti-inflammatory drugs
Sulfonamides		Sulfacetamide R ₁ = H R ₂ = COCH ₃	As antimicrobial drugs

Table 1.2 (Continued)

Group	Parent structure	Chemical example	Uses and examples
Sulfonylureas	Glipizide (As drawn)		As oral hypoglycaemic drugs
			
Thiadiazines		Chlorthiazide	As diuretics
		R ₁ = H R ₂ = H R ₃ = Cl	
Xanthines		Theophylline	As respiratory stimulants and bronchodilators
		R ₁ = CH ₃ R ₂ = CH ₃ R ₃ = H	

by the order of 10^{13} times – in other words some reactions would not, for all practical purposes, proceed but for the presence of enzymes. The role of enzymes in the metabolism of drugs is considered in Section 3.2.

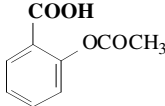
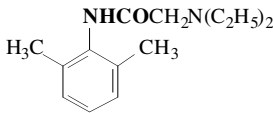
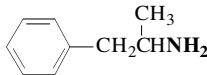
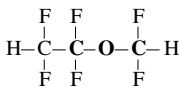
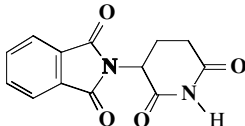
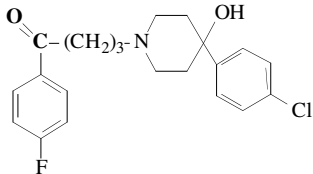
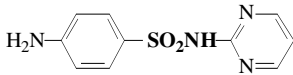
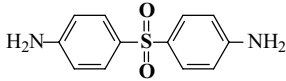
1.3.1 Decomposition of drugs

Spontaneous decomposition needs to be taken into consideration during manufacture, storage and use of drugs as well as during bioanalysis, when the products may be mistakenly thought to be metabolites. Although the same compounds may be produced by metabolism, there are occasions, for example, when substances identified in biological fluids arise from decomposition rather than metabolism. Decomposition may result in visible changes and odours when drugs are stored. The reactions tend to be accelerated by the presence of one or more of the following: catalysts, light, heat and moisture.

1.3.1.1 Hydrolysis

Esters and, to a lesser extent, amides are hydrolysed, particularly if catalysed by the presence of acids or bases. Aspirin (acetylsalicylic acid) is hydrolysed to salicylic acid and acetic acid, giving bottles of aspirin a smell of vinegar. Procaine is hydrolysed to *p*-aminobenzoic acid and *N*-dimethyl-2-aminoethanol, whilst cocaine is hydrolysed to benzoylecgonine.

Table 1.3 Some important functional groups found in drug molecules

Type of compound	Functional group	Specific example	
		Name	Formula
Acids e.g. carboxylic acids	–COOH	Aspirin (also an ester)	
Alcohols	–OH	Choral hydrate	$\text{CCl}_3\text{C}(\text{OH})_2$
Amides	–CONH–	Lidocaine (also an amine)	
Bases e.g. amines	–NRR'	Amphetamine	
Esters	–COO–	Suxamethonium chloride (also a quaternary ammonium compound)	$\text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$ $\text{CH}_2\text{COOCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$ 2Cl^-
Ethers	–C–O–C–	Enflurane	
Imides	–CONHCO–	Thalidomide	
Ketones	–CO–	Haloperidol (also an amine and an alcohol)	
Sulfonamides	–SO ₂ NH–	Sulfadiazine (also an amine)	
Sulfones	–SO ₂ –	Dapsone (also an amine)	
Small neutral molecules		Nitrous oxide	N_2O
Inorganic salts		Sodium bicarbonate	NaHCO_3
		Lithium carbonate	Li_2CO_3

1.3.1.2 Oxidation

Several drugs are readily oxidized, including phenothiazines, which form the corresponding 5-sulfoxides, via coloured semiquinone free radicals. Phenothiazines with an electron-withdrawing group in the 2-position, tend to be more stable, thus promethazine (2-H) is more readily oxidized (to a blue product) than chlorpromazine (2-Cl) which gives a red semiquinone radical. Methylene blue is a phenothiazine (Figure 1.1)

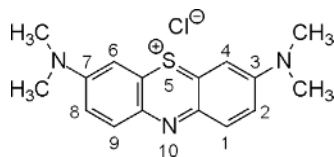
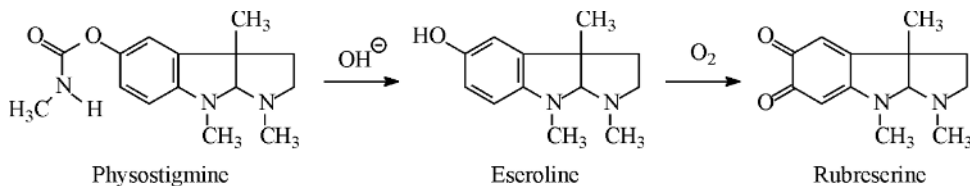


Figure 1.1 Formula of methylene blue (methylthioninium chloride). Other therapeutic phenothiazines usually have 10-substituents and often substituents at position 2.

that is used in medicine as a contrast agent, and as a treatment for methaemoglobinaemia, which is both a congenital and a drug-induced disorder. In this book it appears as an example of tri-exponential plasma concentration decay after intravenous doses (Figure 5.2), and as a valuable tool for laboratory modelling of drug disposition.

Physostigmine is oxidized to rubreserine, which is a deep brown-red colour. The first stage is probably hydrolysis to eseroline:



Adrenaline oxidizes in a similar manner to a brown-red material, adrenochrome.

1.3.1.3 Photodecomposition

Most compounds are photosensitive if irradiated with intense light of the appropriate wavelength. Some drugs are unstable in natural light, notably the 1,4-dihydropyridine calcium channel blocking drugs such as nifedipine. These drugs have to be formulated and handled in a darkroom under sodium light. Similarly, it is recommended that blood samples taken for nitrazepam or clonazepam analysis are protected from light to avoid photodecomposition.

1.3.1.4 Racemization

Optically active drugs (Section 1.8.2) may undergo racemization. For example during extraction from belladonna (–)-hyoscyamine may be converted to atropine [(±)-hyoscyamine].

1.4 Physicochemical interactions between drugs and other chemicals

In the present context we are principally concerned with interactions between relatively small drug molecules and relatively large endogenous molecules such as proteins e.g. enzymes, receptors and ion

channels. The majority of drug–receptor interactions are reversible although some covalent reactions are known, for example non-competitive antagonism.

1.4.1 Chemical bonding and interactions between molecules

The interaction between atoms and molecules is basically electrostatic. The positively charged nuclei of atoms would repel each other if it were not for electrons sharing the space between them such that an electron from one atom is attracted to the nucleus of another. *Ionic bonds* occur when one atom completely donates one or more electrons to another atom, such as in sodium chloride. In the solid the ions are arranged so that the structure is held together by the electrostatic attraction of the oppositely charged ions. Bonds are described as (*non-polar*) *covalent* when atoms of similar electronegativities share electrons more or less equally, or *polar covalent* when the electronegativity of one atom is appreciably greater than the other. The nature of these bonds is somewhere between that of covalent and ionic bonds. The electrons in polar covalent bonds are attracted to the more electronegative atom creating a dipole, i.e. an asymmetric electric charge. The electron-withdrawing effect of oxygen in water molecules results in a strong dipole whereas in methane, CH₄, the electron density is evenly distributed so there is no dipole (Figure 1.2).

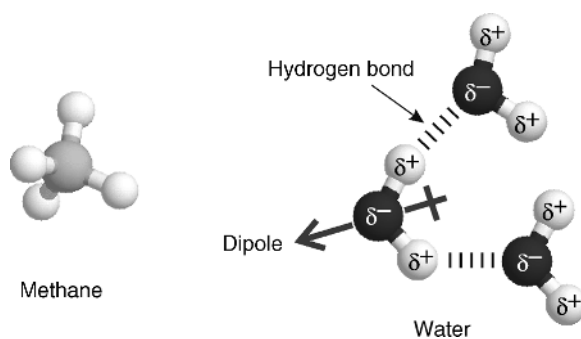


Figure 1.2 Comparison of non-polar methane (CH₄) and water (H₂O) where differences in charge densities between the more electronegative oxygen and hydrogen produces a dipole. Hydrogen bonding occurs between the slightly negatively charged oxygen and the slightly positively charged hydrogen.

Dipoles are responsible for the attractions between molecules. Molecules can align dipole to dipole, the more negative end of one being attracted to the more positive end of another; or a dipole in one molecule can induce a complementary one in an adjacent molecule. The differences in valence electron densities in the more electronegative elements, nitrogen, oxygen and fluorine, leads to *hydrogen bonding* (Figure 1.2) which in some instances can be as strong as some covalent bonds. *Van der Waals* forces arise because the density of the valence electron cloud around an atom can fluctuate causing a temporary dipole which may then induce a dipole in a neighboring atom. These are the weakest but most common forms of attractions between atoms. Another form of bonding is the *hydrophobic bonding* seen in proteins, where hydrophobic regions come together with the exclusion of water.

All the forms of bonding described above are encountered in pharmacology. Covalent binding of groups to enzymes and receptors occurs, such as acetylation of the serine groups in cyclooxygenase by aspirin. Ionic interaction is responsible for the binding of acidic drugs to albumin and of bases to α_1 -acid glycoprotein. Hydrophobic binding is also important for binding of molecules to proteins. Similarly, these interactions occur when drugs bind to the active sites of enzymes and to receptors.

1.4.2 Solubility

The physicochemical interactions described above affect the solubility of molecules (solutes) in solvents. The dipole moment and hydrogen bonding in water make this a polar solvent and polar solutes readily dissolve in water, including salts. These solutes are described as hydrophilic – water loving. Organic solvents such as heptane are apolar because they have neither dipoles nor hydrogen bonding. Apolar solvents are very poorly soluble in water and vice versa, water being essentially insoluble in the organic solvent. The two liquids are said to be *immiscible*. Non-polar, non-ionized molecules tend to dissolve readily in organic solvents and lipids, and are referred to as hydrophobic or lipophilic – lipid loving.

To be transferred across lipid membranes drugs must be soluble in the barrier layer of fluid bathing the membrane. Consequently, drugs with low aqueous solubility may be poorly absorbed from the gastrointestinal tract. This can be exploited. An example is sulfasalazine, which is minimally absorbed after oral administration, and is used to treat ulcerative colitis.

1.5 Law of mass action

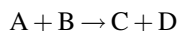
The Law of Mass Action states: ‘the rate at which a chemical reaction proceeds is proportional to the active masses (usually molar concentrations) of the reacting substances’. This means that a non-reversible reaction proceeds at an ever-decreasing rate as the quantity of the reacting substances declines. The Law of Mass Action is easily understood if the assumption is made that, for the reaction to occur, collision between the reacting molecules must take place. It follows that the rate of reaction will be proportional to the number of collisions. The number of collisions will be proportional to the molar concentrations of the reacting molecules.

If a single substance X is in process of transformation into another substance Y, and if at any moment the active mass of X is represented by [X] (usually expressed in moles per litre) then we have:



and the rate of reaction at any time point = $k[X]$ where k is the velocity, or rate, constant. This constant varies with temperature and the nature of the reacting substance.

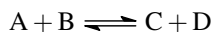
If two substances A and B are reacting to form two other substances C and D, and if the concentrations of the reactants at any particular moment are [A] and [B] then:



and the rate of reaction = $k[A][B]$.

1.5.1 Reversible reactions and equilibrium constants

Consider the reaction:



The rate of the forward reaction is:

$$\text{forward rate} = k_1[A][B] \quad (1.1)$$

whilst the backward rate is:

$$\text{backward rate} = k_{-1}[C][D] \quad (1.2)$$

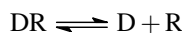
where k_1 and k_{-1} , are the rate constants of the forward and backward reactions, respectively. As the reaction proceeds, the concentrations of the original substances A and B diminish and the rate of the forward reaction decreases. At the same time, the substances C and D are produced in ever-increasing quantities so that the rate at which they form A and B increases. Eventually equilibrium is reached when the forward and backward rates are equal:

$$k_1[A][B] = k_{-1}[C][D] \quad (1.3)$$

The equilibrium constant, K , is the ratio of the forward and backward rate constants, so rearranging Equation 1.3 gives:

$$K = \frac{k_1}{k_{-1}} = \frac{[C][D]}{[A][B]} \quad (1.4)$$

The term *dissociation constant* is used when describing the equilibrium of a substance which dissociates into smaller units, as in the case, for example, of an acid (Section 4.6). The term is also applied to the binding of a drug, D, to a macromolecule such as a receptor, R, or plasma protein. The complex DR dissociates:



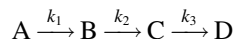
So:

$$K = \frac{[D][R]}{[DR]} \quad (1.5)$$

An association constant is the inverse of a dissociation constant.

1.5.1.1 Sequential reactions

When a product, D, arises as a result of several, sequential reactions:



it cannot be formed any faster than the rate of at which its precursor, C, is formed, which in turn cannot be formed any faster than its precursor, B. The rates of each of these steps are determined by the rate constants, k_1 , k_2 and k_3 . Therefore, the rate at which D is formed will be the rate of the slowest step, i.e. the reaction with the lowest value of rate constant. Say for example, k_2 is the lowest rate constant, then the rate of formation of D is determined by k_2 and the reaction $B \rightarrow C$ is said to be the *rate-limiting* step.

1.5.2 Reaction order and molecularity

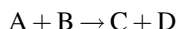
The order of a reaction is the number, n , of concentration terms affecting the rate of the reaction, whereas molecularity is the number of molecules taking part in the reaction. The order of a reaction is measured experimentally and because it is often close to an integer, 0, 1, or 2, reactions are referred to as zero-, first- or second-order, respectively. The reaction



is clearly monomolecular, and may be either zero- or first-order depending on whether the rate is proportional to X^0 or X^1 . The reactions



and



are both bimolecular and second-order providing the rate is proportional to $[X]^2$, in the first case, and to $[A][B]$, in the second. Note how the total reaction order is the sum of the indices of each reactant: rate $\propto [A]^1[B]^1$, so $n = 2$. However, if one of the reactants, say A, is present in such a large excess that there is no detectable change in its concentration, then the rate will be dependent only on the concentration of the other reactant, B, that is, the rate is proportional to $[A]^0[B]^1$. The reaction is first-order (rate $\propto [B]$) but still described as 'bimolecular'. Hydrolysis of an ester in dilute aqueous solution is a commonly encountered example of a bimolecular reaction which is first-order with respect to the concentration of ester and zero-order with respect to the concentration of water, giving an overall reaction order of 1.

Enzyme-catalysed reactions have reaction orders between 1 and 0 with respect to the drug concentration. This is because the Michaelis–Menten equation (Section 3.2.5) limits to zero-order when the substrate is in excess and the enzyme is saturated so that increasing the drug concentration will have no effect on the reaction rate. When the concentration of enzyme is in vast excess compared with the substrate concentration, the enzyme concentration is not rate limiting and the reaction is first-order. Thus, the reaction order of an enzyme-catalysed reaction changes as the reaction proceeds and substrate is consumed.

1.5.3 Decay curves and half-lives

As discussed above the rate of a chemical reaction is determined by the concentrations of the reactants and from the foregoing it is clear that a general equation relating rate of decline in concentration ($-dC/dt$), rate constant (λ), and concentration (C) can be written:

$$-\frac{dC}{dt} = \lambda C^n \quad (1.6)$$

Note the use of λ , to denote the rate constant when it refers to decay; the symbol is used for radioactive decay, when it is known as the decay constant. Use of λ for elimination rate constants is now the standard in pharmacokinetic equations.

1.5.3.1 First-order decay

Because first-order kinetics are of prime importance in pharmacokinetics, we shall deal with these first. For a first-order reaction, substituting $n = 1$ in Equation 1.6 gives:

$$-\frac{dC}{dt} = \lambda C \quad (1.7)$$

that is the rate of the reaction is directly proportional to the concentration of substance present. As the reaction proceeds and the concentration of the substance falls, the rate of the reaction decreases. This is exponential decay, analogous to radioactive decay where the probability of disintegration is proportional to

the number of unstable nuclei present. The first-order rate constant has units of reciprocal time (e.g. h^{-1}). Integrating Equation 1.7 gives:

$$C = C_0 \exp(-\lambda t) \quad (1.8)$$

which is the equation of a curve that asymptotes to 0 from the initial concentration, C_0 [Figure 1.3(a)]. Taking natural logarithms of Equation 1.8:

$$\ln C = \ln C_0 - \lambda t \quad (1.9)$$

gives the equation of a straight line of slope, $-\lambda$ [Figure 1.3(b)]. If common logarithms are used ($\log C$ versus t) the slope is $-\lambda/2.303$. Another way of presenting the data is to plot C on a logarithmic scale (using ‘semilog.’ graph paper — not shown). This approach was often used when computers were not readily available and is still frequently used to present data, for example Figure 2.10. Such plots allow computation of C_0 (read directly from the intercept) and the elimination half-life. However, a common misconception is to believe that the slope of this plot is $-\lambda/2.303$. The slope is the same as that of a C versus t plot, but it only appears to be linear — the graph is of the type shown in Figure 1.3(a), which could be viewed as a series of slopes of ever-decreasing magnitude. The slope that matters, permitting calculation of the rate constant and the half-life using linear regression, is that of a graph of $\ln C$ versus t [Figure 1.3(b)].

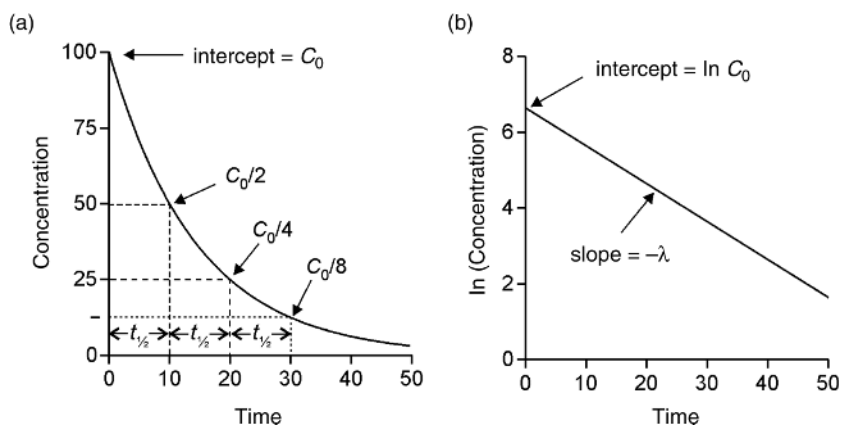


Figure 1.3 Curves for first-order decay plotted as (a) C versus t and (b) $\ln C$ versus t .

The half-life ($t_{1/2}$) is the time for the initial concentration (C_0) to fall to $C_0/2$, and substitution in Equation 1.9 gives:

$$t_{1/2} = \frac{\ln 2}{\lambda} = \frac{0.693}{\lambda} \quad (1.10)$$

as $\ln 2 = 0.693$. This important relationship, where $t_{1/2}$ is constant (independent of the initial concentration) and inversely proportional to λ , is *unique* to first-order reactions. Because $t_{1/2}$ is constant, 50% is eliminated in $1 \times t_{1/2}$, 75% in $2 \times t_{1/2}$, and so on. Thus, when five half-lives have elapsed less than 95% of the analyte remains, and after seven half-lives less than 99% remains.

1.5.3.2 Zero-order decay

For a zero-order reaction, $n = 0$, and:

$$-\frac{dC}{dt} = \lambda C^0 = \lambda \quad (1.11)$$

Thus, a zero-order reaction proceeds at a *constant rate*, and the zero-order rate constant must have units of rate (e.g. $\text{g L}^{-1} \text{h}^{-1}$). Integrating Equation 1.11:

$$C = C_0 - \lambda t \quad (1.12)$$

gives the equation of a straight line of slope, $-\lambda$, when concentration is plotted against time [Figure 1.4(a)]. The half-life can be obtained as before, substituting $t = t_{1/2}$ and $C = C_0/2$, gives:

$$t_{1/2} = \frac{C_0}{2\lambda} \quad (1.13)$$

The zero-order half-life is inversely proportional to λ , but $t_{1/2}$ is also directly proportional to the initial concentration. In other words, the greater the amount of drug present initially, the longer the time taken to reduce the amount present by 50% [Figure 1.4(b)]. The term 'dose dependent half-life' has been applied to this situation as well as to Michaelis–Menten kinetics cases.

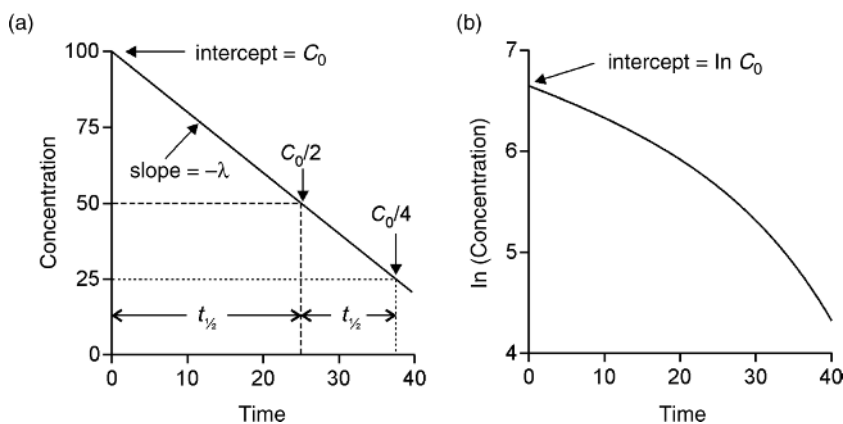


Figure 1.4 Curves for zero-order decay plotted as (a) C versus t and (b) $\ln C$ versus t .

1.5.3.3 Second-order decay

When $n \geq 2$, the integral of Equation 1.6 has a general solution, which when written in terms of λ is:

$$\lambda = \frac{1}{(n-1)t} \left(\frac{1}{C^{(n-1)}} - \frac{1}{C_0^{(n-1)}} \right) \quad (1.14)$$

So, when $n = 2$,

$$\lambda = \frac{1}{t} \left(\frac{1}{C} - \frac{1}{C_0} \right) \quad (1.15)$$

Substituting $C = C_0/2$ when $t = t_{1/2}$ and rearranging gives:

$$t_{1/2} = \frac{1}{\lambda C_0} \quad (1.16)$$

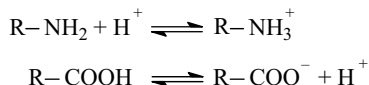
This is to be expected of second-order reactions because the probability of molecules colliding and reacting is much greater at higher concentrations.

Equations such as Equations 1.8 and 1.12 are referred to as *linear* equations. Note that in this context it is important not to confuse ‘linear’ with ‘straight-line’. While it is true that the equation of a straight-line is a linear equation, exponential equations are also linear. On the other hand, nonlinear equations are those where the variable to be solved for cannot be written as a linear combination of independent variables. The Michaelis–Menten equation is such an example.

Despite the importance of the elimination half-life of a drug in pharmacokinetics, it is, in fact, dependent on two other pharmacokinetic parameters, apparent volume of distribution (V) and clearance (CL). The apparent volume of distribution, as its name implies, is a quantitative measure of the extent to which a drug is distributed in the body (Section 2.4.1.1) whilst clearance can be thought of as an indicator of how efficiently the body’s eliminating organs remove the drug. Therefore the larger the value of CL , the shorter will be $t_{1/2}$. Changes in half-life are a result of changes in either V or CL or both (Section 4.2.1).

1.6 Ionization

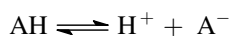
Ionization is a property of all electrolytes, whether weak and strong. For example, sodium chloride (NaCl) is essentially completely ionized in aqueous solutions (forming sodium and chloride ions, Na^+ and Cl^-). Amines and carboxylic acids are only partially ionized in aqueous solutions. Their ionization reactions can be represented as follows:



It will be noted that these ionization reactions are reversible, and the extent to which ionization takes place is determined by the $\text{p}K_a$ of the compound and the pH of the aqueous solution. The $\text{p}K_a$ of the compound is a measure of its inherent acidity or alkalinity, and it is determined by the molecular arrangement of the constituent atoms. It is the pH of the aqueous solution in which the compound is 50% ionized.

According to the Brønsted–Lowry theory, an acid is a species that tends to lose protons, and a base is a species that tends to accept protons. Acids and bases ionize in solution; acids donating hydrogen ions and bases accepting them. Thus in the examples above, R-NH_3^+ and R-COOH are acids, while R-NH_2 and R-COO^- are bases. Also, R-NH_3^+ and R-NH_2 , and R-COOH and R-COO^- , are termed ‘conjugate acid–base pairs’.

The term *strength* when applied to an acid or base refers to its tendency to ionize. If an acid, AH , is dissolved in water, the following equilibrium occurs:



The acid dissociation constant is:

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{AH}]} \quad (1.17)$$

Clearly the more the equilibrium is to the right, the greater is the hydrogen ion concentration, with a subsequent reduction in the concentration of non-ionized acid, so the larger will be the value of K_a . Taking logarithms (see Appendix 1 for details) of Equation 1.14, gives:

$$\log K_a = \log[\text{H}^+] + \log[\text{A}^-] - \log[\text{AH}] \quad (1.18)$$

and on rearrangement:

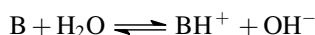
$$-\log[\text{H}^+] = -\log K_a + \log \frac{[\text{A}^-]}{[\text{AH}]} \quad (1.19)$$

Because, $-\log[\text{H}^+]$ is the pH of the solution:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{AH}]} = \text{p}K_a + \log \frac{[\text{base}]}{[\text{acid}]} \quad (1.20)$$

where $\text{p}K_a = -\log K_a$, by analogy with pH. Note that when $[\text{A}^-] = [\text{AH}]$ the ratio is 1 and because $\log(1) = 0$, the $\text{p}K_a = \text{pH}$, as stated earlier.

It is possible to calculate the equilibrium constant, K_b , for a base, B, ionizing in water:



However, one can consider the ionization of the conjugate acid, BH^+ and derive a $\text{p}K_a$ for it as above.

$$K_a = \frac{[\text{H}^+][\text{B}]}{[\text{BH}^+]} \quad (1.21)$$

Note how for a strong base, the concentration of BH^+ is high (high tendency to ionize) and so K_a is small.

$$\text{pH} = \text{p}K_a + \log \frac{[\text{B}]}{[\text{BH}^+]} = \text{p}K_a + \log \frac{[\text{base}]}{[\text{acid}]} \quad (1.22)$$

The use of terms such as weak and strong is fraught with danger. However, because the term ‘weak electrolyte’ is used for all partially ionized materials, the term weak should probably be applied to all acids and bases used as drugs. However, it should not be forgotten that high concentrations of organic acids and bases, in spite of the compounds being weak electrolytes, can appear ‘strong’ in the sense of being corrosive, removing rust, precipitating protein etc. These compounds, however, are obviously distinct from most inorganic acids (nitric, hydrochloric and perchloric acids) which have $\text{p}K_a$ values in the range -1 to -7 , and are effectively 100% dissociated at any pH. There are, also, certain weak electrolyte inorganic acids; carbonic acid ($\text{p}K_{a1} = 6.35$, $\text{p}K_{a2} = 10.25$) for example. The bicarbonate to CO_2 ratio is of major significance for buffering the pH of blood.

It should be noted that it is not possible from knowledge of the $\text{p}K_a$ alone to say whether a substance is an acid or a base. It is necessary to know how the molecule ionizes. Thiopental, $\text{p}K_a = 7.8$, forms sodium salts and so must be an acid, albeit a rather weak one. Diazepam, $\text{p}K_a = 3.3$, must be a base as it can be extracted from organic solvents into hydrochloric acid. Molecules can have more than one ionizable group; salicylic acid for example, has a carboxylic acid ($\text{p}K_a = 3.0$) and a weaker acidic phenol group ($\text{p}K_a = 13.4$). Morphine is amphoteric, that is it is both basic (tertiary amine, $\text{p}K_{a1} = 8.0$) and acidic (phenol $\text{p}K_{a2} = 9.9$) (Figure 1.5).

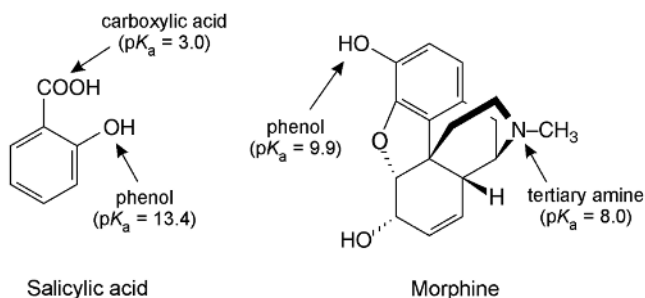


Figure 1.5 Ionizable groups of salicylic acid and morphine.

1.6.1 Henderson–Hasselbalch equation

Equation 1.20 is a form of the Henderson–Hasselbalch equation, which is important in determining the degree of ionization of weak electrolytes and calculating the pH of buffer solutions. If the degree of ionization is α , then the degree non-ionized is $(1 - \alpha)$ and, for an acid:

$$\text{pH} = \text{p}K_a + \log \frac{\alpha}{1-\alpha} \quad (1.23)$$

or

$$\log \frac{\alpha}{1-\alpha} = \text{pH} - \text{p}K_a \quad (1.24)$$

taking antilogarithms gives:

$$\frac{\alpha}{1-\alpha} = 10^{(\text{pH}-\text{p}K_a)} \quad (1.25)$$

on rearrangement:

$$\alpha = \frac{10^{(\text{pH}-\text{p}K_a)}}{1 + 10^{(\text{pH}-\text{p}K_a)}} \quad (1.26)$$

The equivalent equation for a base is:

$$\alpha = \frac{10^{(\text{p}K_a-\text{pH})}}{1 + 10^{(\text{p}K_a-\text{pH})}} \quad (1.27)$$

Although Equations 1.26 and 1.27 look complex, they are easy to use. Using the ionization of aspirin as an example: the $\text{p}K_a$ of aspirin is ~ 3.4 , so at the pH of plasma (7.4),

$$\text{pH} - \text{p}K_a = 7.4 - 3.4 = 4$$

$$\alpha = \frac{10^4}{1 + 10^4} = \frac{10000}{10001} = 0.9999$$

In other words aspirin is 99.99% ionized at the pH of plasma, or the ratio of ionized to non-ionized is 10,000 : 1. In gastric contents, pH 1.4, aspirin will be largely non-ionized; $1.4 - 3.4 = -2$, so the ratio of ionized to non-ionized is $1 : 10^{-2}$, i.e. there are 100 non-ionized molecules for every ionized one.

1.7 Partition coefficients

When an aqueous solution of a substance, such as drug, is shaken with an immiscible solvent (e.g. diethyl ether) the substance is extracted into the solvent until equilibrium between the concentration in the organic phase and the aqueous phase is established. Usually equilibration only takes a few seconds. For dilute

solutions the ratio of concentrations is known as the distribution, or partition coefficient, P :

$$P = \frac{\text{concentration in organic phase}}{\text{concentration in aqueous phase}} \quad (1.28)$$

Organic molecules with large numbers of paraffin chains, aromatic rings and halogens tend to have large values of P , whilst the introduction of polar groups such as hydroxyl or carbonyl groups generally reduces the partition coefficient. Drugs with high partition coefficients are lipophilic or hydrophobic, whereas those that are very water soluble and are poorly extracted by organic solvents are hydrophilic. Lipophilicity can have a major influence on how a drug is distributed in the body, its tendency to bind to macromolecules such as proteins and, as a consequence, drug activity. A relationship between partition coefficient and pharmacological activity was demonstrated as early as 1901, but it was Corwin Hansch in the 1960s who used regression analysis to correlate biological activity with partition coefficient. He chose *n*-octanol as the organic phase and this has become the standard for such studies (Figure 1.6). Because P can vary between <1 (poorly extracted by the organic phase) to several hundred thousand, values are usually converted to $\log P$, to encompass the large range (see Appendix).

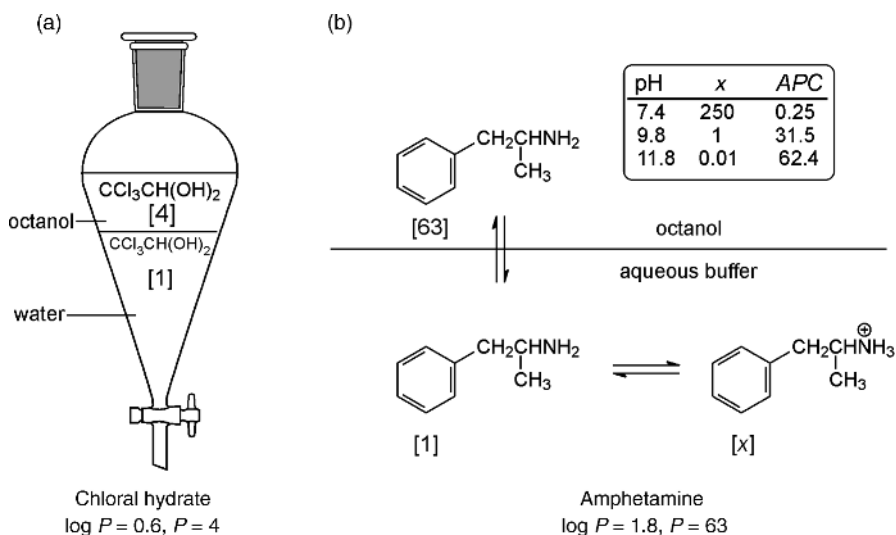


Figure 1.6 (a) Partitioning of chloral hydrate is unaffected by buffer pH. (b) Partitioning of non-ionized amphetamine remains constant, 63:1. However the ratio of ionized to non-ionized is affected by buffer pH and as a consequent affects the apparent partition coefficient (APC) and the proportion extracted (inset).

1.7.1 Effect of ionization on partitioning

Generally, ionized molecules cannot be extracted into organic solvents, or at least not appreciably. The most notable exception to this is the extraction of ion-pairs into solvents such as chloroform. Thus, for weak electrolytes the amount extracted will usually be dependent on the degree of ionization, which of course is a function of the pH of the aqueous solution and the $\text{p}K_a$ of the ionizing group as discussed above (Section 1.5.1), and the partition coefficient. If the total concentration (ionized + non-ionized) of solute in

the aqueous phase is measured and used to calculate an apparent partition coefficient, D , then the partition coefficient, P , can be calculated. For an acid:

$$P = D[1 + 10^{(\text{pH} - \text{p}K_a)}] \quad (1.29)$$

and for a base:

$$P = D[1 + 10^{(\text{p}K_a - \text{pH})}] \quad (1.30)$$

When the $\text{pH} = \text{p}K_a$ then, because $10^0 = 1$, $P = 2D$. When the pH is very much less than the $\text{p}K_a$, in the case of acids, or very much larger than the $\text{p}K_a$, in the case of bases, there will be no appreciable ionization and then D will be a good estimate of P [Figure 1.6(b)].

Unless stated otherwise, $\log P$ is taken to represent the logarithm of the true partition coefficient, i.e. when there is no ionization of the drug. However, for some weak electrolytes, biological activity may correlate better with the partition coefficient between octanol and $\text{pH} 7.4$ buffer solution. These values are referred to as $\log D$.

Differences in the pH of different physiological environments, e.g. plasma and gastric contents can have a major influence on the way drugs are absorbed and distributed. (Section 2.2.1.1).

1.8 Stereochemistry

Compounds with the same molecular formula, but with a different arrangement of atoms are isomers. Structural isomers have different arrangements of atoms, for example, ethanol ($\text{CH}_3\text{CH}_2\text{OH}$) and diethyl ether (CH_3OCH_3) are structural isomers and have distinct chemical properties. Stereoisomers have the same bond structure but the geometrical positioning of atoms in space differs.

1.8.1 *Cis-trans isomerism*

Cis-trans isomerism is most commonly encountered when chemical groups are substituted about a double $\text{C}=\text{C}$ bond. Because the bond is not free to rotate, structures with the substituents on the same side of the bond (*cis*-isomers) are distinct from those with substituents on opposite sides of the bond (*trans*-isomers) [Figure 1.7(a)]. This kind of isomerism can also occur in alicyclic compounds when the ring structure prevents free rotation of $\text{C}-\text{C}$ bonds. In the *E/Z* system of nomenclature, *Z*, from the German *zusammen*

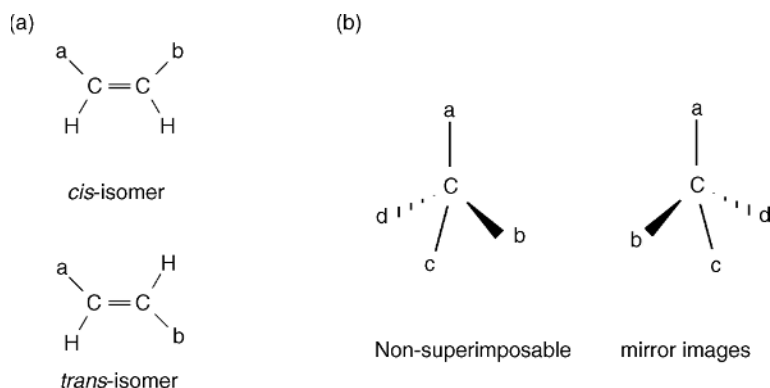


Figure 1.7 (a) *Cis-trans* isomerism occurs because the $\text{C}=\text{C}$ bond cannot rotate and so the molecules depicted are different. (b) Asymmetric substitution produces isomers that are mirror images. The wedge represents a bond coming out of the page, the broken line represents a bond that recedes behind the page and the carbon atom and other two bonds are in the plane of the page.

meaning together, corresponds to *cis*; whilst *E*, from the German *entgegen* meaning opposite, to *trans*. The *E/Z* system must be used when there are more than two different substituents. The groups are assigned a rank according to the Cahn–Ingold–Prelog (CIP) rules (Section 1.8.2). If substituents of higher priority are on the same side, the isomer is designated *Z*; if they are on opposite sides, it is the *E*-isomer. *Cis–trans* isomerism is encountered in pharmacology. For example, clopenthixol is a mixture of *cis/trans* isomers whereas zuclopenthixol is the purified *Z*-isomer.

1.8.2 Optical isomerism

When a molecule and its mirror image cannot be superimposed, the substance is said to be *chiral*, from the Greek, *cheir*, meaning hand. The distinctive feature of such molecules is that they rotate the plane of plane-polarized light. Asymmetric substitution about carbon produces optical isomers [Figure 1.7(b)]. Other elements that show optical isomerism include sulfur, phosphorus and nitrogen. Individual isomers are referred to as enantiomers. These can be identified by whether they rotate the light to the right (dextrorotatory) or to the left (laevorotatory). The symbols *d*- and *l*- may be used to indicate the direction of rotation but (+)- and (-)- are preferred. A racemic mixture, or racemate, a 50 : 50 mixture of each enantiomer, is identified by *dl*-, (\pm)-, or *rac*-. Sometimes it is clear when a drug is an enantiomer from its name, for example the cough suppressant, dextrophan, and its enantiomer, the analgesic, levorphanol. Often there is no indication, particularly with naturally occurring drugs. Morphine, hyoscine, cocaine and physostigmine are enantiomers. Similarly, many synthetic drugs are marketed as racemates without any indication, but there are examples of deliberate marketing of single isomers, sometimes for reasons connected with patents.

1.8.2.1 Absolute configuration

Although the rotation of plane-polarized light unequivocally defines a compound as one enantiomer or the other, it gives no indication of the spatial arrangement of the groups around the chiral centre – the *configuration*. Until the advent of X-ray crystallography, the absolute configurations of enantiomers were unknown. D-(+)-glyceraldehyde was arbitrarily defined as the D-configuration and all compounds derived from it were designated D-, irrespective of the optical activity, provided that the bonds to the asymmetric carbon remained intact. The naturally-occurring mammalian amino acids in proteins can be related to L-(–)-glyceraldehyde and form an L-series.

The use of D- or L- to define absolute configuration, is not readily applicable to all chiral molecules, and the CIP convention is generally used. The groups are assigned to a priority order according to sequence rules. Simply, the order is determined by the atomic numbers of the atoms attached to the chiral centre, priority being given to the higher numbers; for example O > N > C > H. When groups are attached by the same atom, then the next atom is considered, and so on in sequence until the order has been determined. The arrangement of groups around the chiral centre is ‘viewed’ with the group of least priority to the rear. Then the spatial arrangement of the groups is determined in decreasing priority order. If the direction is clockwise (i.e. to the right) the configuration is designated *R* (from the Latin, *rectus*, right). If the direction is anticlockwise the configuration is *S* (Latin, *sinister*, left). It must be noted that the D/L and R/S notations are not interchangeable. Using the CIP system, all L-amino acids are *S*-, with the exception of cysteine and cystine which, because they contain sulfur atoms (higher priority) that are connected to the chiral carbon, are designated *R*-.

1.8.3 Importance of stereochemistry in pharmacology

Obviously, the physical shape of a drug is important for it to bind to its receptors and so elicit a response. Because receptors are proteins, comprised of chiral amino acids, the spatial arrangement of the atoms in the

interacting drug will be crucial. There are numerous examples where stereoisomers show marked differences in their pharmacology. *R*-Thalidomide is sedative whereas the *S*-isomer inhibits angiogenesis, which is probably part of the mechanism of its teratogenic effect. However, because enzymes and transport systems are proteins, stereochemical differences may be shown in the way in which isomers are metabolized or distributed. With the advent of more convenient methods of measuring enantiomers, such as chiral high performance liquid chromatography phases, we are beginning to understand the full extent of differences in the pharmacokinetics of stereoisomers. The interaction between warfarin and phenylbutazone was not fully understood until it was shown that phenylbutazone selectively inhibits the metabolism of the more active *S*-isomer of warfarin.

Further reading and references

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