Structural and Physicochemical Profiling of Morphine and Related Compounds of Therapeutic Interest

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Abstract: A concise account of the physicochemical properties of morphine and its derivatives of therapeutic interest is provided. Such properties include macroscopic and microscopic acid/base parameters, lipophilicity, solubility, permeability that all influence the fate of drugs in the body. The dependence of these parameters on pH is discussed and subsequent implications in drug administration and formulation are presented.

Key Words: Morphine, pharmacokinetic properties, physicochemical profiling, acid/base properties, lipophilicity, solubility, permeability, stability.

FUNDAMENTALS OF THE SELECTED OPIOID ANALGESICS

Opioids, the chemical substances of morphine-like action have long been used to treat severe acute and chronic pain. There are a number of broad classes of opioids. Morphine and codeine, the best known opiate alkaloids, naturally occur in opium, the air-dried sap from the unripe capsules of *Papaver somniferum*. Their semi-synthetic derivatives include oxycodone and heroin. Fully synthetic opioids, such as methadone, are also of valuable therapeutic use. Endogenous opioid peptides, e.g. endorphins, enkephalins are products of the body and the structural similarity between their tyrosine terminal and the related morphine moieties accounts for the resembling biological effects of opioids. Although the term opiate is often used as a synonym for opioid, it is actually limited to the natural opium alkaloids and their semi-synthetics derivatives.

Opioids bind to specific opioid receptors in the central nervous system and in other body compartments, like the gastrointestinal tract. There are three principal classes of opioid receptors, μ, κ, δ (mu, kappa, delta), all of them are G-protein coupled receptors acting on GABAergic neurotransmission [1].

The structure of the opioids discussed in this review can be seen in Fig. (**1**). Morphine, the prototype narcotic drug is the standard in all opioid tests. It interacts predominantly with the μ-opioid receptor. Activation of the μ-opioid receptors is associated with analgesia, sedation, euphoria, physical dependence, and respiratory depression. Morphine is primarily metabolized into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in phase II metabolization by the enzyme UDP-glucuronosyl transferase-2B7 [2]. The biotransformation of morphine occurs primarily in the liver but it may also take place in the brain and the kidneys [3]. M6G has been found to be a potent analgesic, relatively more selective for mu-receptors than for delta- and kappa-receptors, whereas M3G does not appear to compete for opioid receptor binding. The significance of M6G formation on the observed effect of a dose of morphine is the subject of debates among pharmacologists [2, 4].

Codeine (3-O-methylmorphine) is widely used for its antitussive, analgesic, and antidiarrheal properties. Although codeine can be extracted from opium, codeine is mainly produced from morphine by O-methylation. Codeine is metabolised *in vivo* in the liver to codeine-6-glucuronide (~70%) and also to morphine, its parent compound (5-10%) [5]. Ethylmorphine, another synthetic derivative, is used in ophthalmology and metabolises in the liver to morphine. The semi-synthetic diacetylmorphine (heroin) is even more potent than morphine and acts faster due to the two acetyl groups which increase its lipid solubility, thus the molecule enters the brain more rapidly [6]. However, its highly addictive capacity makes its sale and use prohibited in many countries [1]. Heroin undergoes fast hydrolysis in the body, predominantly *via* 6-acetylmorphine to morphine [7].

Oxymorphone (14-hydroxydihydromorphinone) is a powerful semi-synthetic opioid analgesic, like its methylether oxycodone, which acts partly through its metabolite oxymorphone.

The effects of morphine can be reversed with opioid antagonists. Naloxone is a competitive antagonist on the μ-opioid receptor, used specifically in emergency to counteract life-threatening depression of the central nervous and respiratory system after overdosing morphine. The chemical structure of naloxone resembles that of oxymorphone, the only difference being the substitution of the N-methyl group with an allyl (prop-2-enyl) group. Naltrexone appears to be a relatively pure opioid antagonist, with enhanced efficacy and duration of action over naloxone, and is used primarily in the treatment of alcohol and opioid dependence. Naltrexone is a

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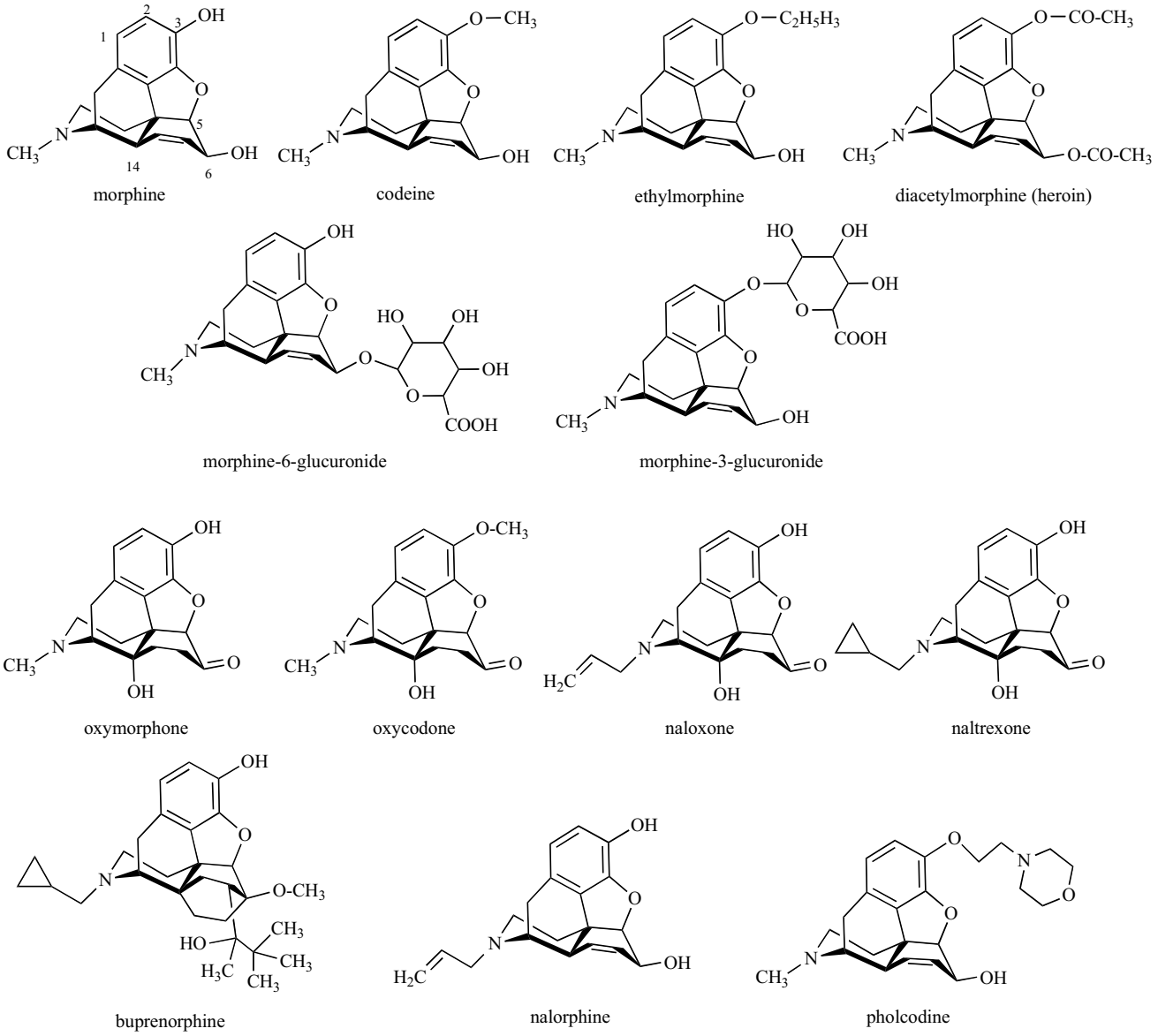

Fig. (1). The structure of the opiods discussed.

substituted oxymorphone where the methyl substituent of the tertiary amino group is replaced with a cyclopropylmethyl group.

The semi-synthetic buprenorphine, about 30 times more potent than morphine, has partial agonist activity at μ-opioid receptors, but it acts as antagonist on κ-opioid receptors. Nalorphine (N-allyl-normorphine) also acts at two opioid receptors, at the mu receptor it has antagonistic effects and at the kappa receptors it exerts agonistic characteristics. Pholcodine (3-O-morpholinoethylmorphine) is a semisynthetic morphine derivative used as an antitussive agent that has no analgesic effects.

The analgesic activity compared to morphine is represented in Table **1** [1]. However, much of the differences in analgesic potency are due to pharmacokinetic and distribution properties, and they do not necessarily show the differences in receptor interactions.

PHYSICOCHEMICAL PROPERTIES AND THEIR IMPORTANCE IN DRUG ACTION

The most important and commonly measured physicochemical properties influencing the pharmacokinetic behavior of drugs are the acid-base properties, lipophilicty, solubility and permeability, all related to passive absorption [8]. Fast and reliable determination methods of the above properties have been developed in order to drop problematic molecules at an early stage of drug development, before testing drug candidates on the various, expensive biological screenings. FDA's Biopharmaceutics Classification System (BCS) is an attempt to rationalize the critical components related to oral absorption, and it embraces permeability and solubility, with qualifications related to pH and dissolution [9].

These physicochemical constants can be characterized at several levels. The majority of the published constants are macroscopic, they characterize the molecule as a whole. Mi-

Table 1. The Analgesic Activity of the Opiods Discussed Compared to Morphine

Compound Name	Analgesic Activity Compared to Morphine
morphine	100
codeine	15
ethylmorphine	1
diacetylmorphine	200-300
oxymorphone	250
oxycodone	530
buprenorphine	≈ 3000

croscopic constants provide a more detailed view: they specify the protonation state of individual functional groups, while submicroscopic constants provide information about the conformation as well [10].

ACID/BASE CHARACTER

The acid/base character determines the charge state of a molecule in a solution of a particular pH. Protonation processes can be regarded either from the point of view of proton association or proton dissociation. In the former case protonation constants (K), in the latter case dissociation constants (K_a) characterize the process. In this review we regard these processes from the point of view of proton association and use log$K$, the logarithm of the protonation macroconstant. log$K$ values can help to predict ADME (absorption, distribution, metabolism, excretion) properties of potential drugs due to the pH gradient of 1.7-8.0 present in the human gastrointestinal tract. In addition, log$K$ data can be used for better understanding the binding mechanisms of therapeutic events and also for the optimization of chemical reactions.

log$K$ values are measured at the constant ionic medium reference state (the ionic strength of the solution must be kept at 0.15 mol/l of KCl or NaCl, the physiological level) [8, 11]. The log$K$ values of the opiods discussed are in Table **2**.

All of these compounds have a basic tertiary amino group, and some of them have a phenolate group in C3. The tertiary amino and phenolate sites are of comparable basicity. The glucuronic acid conjugates of morphine have an additional, weakly basic carboxylate site, so the macroscopic acid/base characterization of M6G takes three protonation constants.

The basicity of monoprotic molecules can be compared by these macroconstants. Oxycodone has a surprisingly high basicity relative to codeine, despite the presence of an electron withdrawing keto group in C6. This is probably due to intramolecular hydrogen bonds between the tertiary amino and C14 hydroxyl groups. The hydrogen bond is stronger in the cationic from than in the deprotonated free base and hence a base strengthening effect is observed.

In case of the diprotic molecules the two macroconstants cannot be assigned to specific groups, because the basicity of the phenolate and amino sites both contribute to both successive macroconstants to comparable extent. Macroconstants, in principle, are measures of the basicity of the molecule as a whole. The basicity of individual protonation sites can be correctly characterized in terms of microscopic protonation constants (microconstants) [12], which quantitate the proton-binding capability of submolecular basic units, when the protonation states of all other sites are definite in the molecule [10]. Also, they are the analytical tools to calculate the concentration of the various protonation forms, including the minor one(s). One significance of microspeciation lies in the fact that not necessarily the major species is the reactive one in the highly specific, structure-controlled biochemical processes [13]. An important derivative parameter of the microconstants is the interactivity parameter ($\Delta\log k$). It quantitates how much the basicity at one protonation site decreases upon the protonation of an other site, and vice versa. The relationships between macro- and microconstants have long been known [12], and the theory and practice of proton microspeciation based on NMR-pH titrations and literature data on complete microspeciations of small ligands have recently been surveyed [14].

Fig. (**2**) shows the microconstants and microspecies of morphine, including the zwitterionic and noncharged protonation isomers. Reported microconstants and the related interactivity parameters are presented in Table **3**. The actual form of the interactivity parameter for the phenolate and amino groups are as follows:

$$\Delta \log k_{O-N} = \log k^{O} - \log k_{N}^{O} = \log k^{N} - \log k_{O}^{N} \qquad (1)$$

These microconstants show that the basicity of the amino and phenolate site is within an order of magnitude, and depends heavily on temperature and ionic strength. At body temperature the noncharged protonation isomer has slightly higher concentration over the zwitterionic one. The interactivity parameter is relatively invariant. It is perturbed to a lesser extent by the protonation and the concomitant electron withdrawing effects of other groups than the microconstants themselves.

The microscopic protonation constants of pholcodine have also been reported. The basicity of the piperidine nitrogen in pholcodine, however, exceeds about 38 times that of the morpholine nitrogen [15]. As the first macroconstant is the sum of the microconstants describing the initial protonation of the piperidine and morpholine nitrogen [12], the microconstants of the dominant pathway do not differ practically from the macroconstants of the molecule.

In the knowledge of these macro- and microconstants the mole fraction of each species can readily be calculated and the pH-dependent distribution of macro-and microspecies can be constructed [10] for morphine (Fig. (**3**)) and for morphine-6-glucuronide (Fig. (**4**)). Fig. (**3**) shows that in the blood plasma, at pH near 7.4, a substantial portion (7.9%) of morphine is in the noncharged form, the very microspecies that can most likely penetrate membranes, including the BBB. (See also the chapter Lipophilicity.) Fig. (**4**) shows

Table 2. The log*K* Values of the Opiods Discussed

Compound	logK_1	logK_2	logK_3	T (°C)	Ionic Strength (M)	Ref.
morphine	9.76	8.02		20	<0.01	[25]
	9.51	8.31		20	0.06	[65]
	9.46	8.13		25	0.001	[66]
	9.42	8.19		25	0.10	[67]
	9.34	8.18		25	0.10	[68]
	9.26	8.18		25	0.15	[66]
	9.62	8.37		25	0.20	[62]
	9.54	8.34		25	0.20	[69]
	9.19	7.91		37	<0.005	[70]
	9.63	7.93		37	<0.01	[25]
	9.50	8.21		37	0.10	[67]
M6G	9.42	8.22	2.77	25	0.15	[66]
M3G	8.21	2.86		25	0.15	[66]
codeine	8.18			20	<0.01	[25]
	8.22			25	0.15	[66]
	8.30			25	0.20	[62]
	7.86			37	<0.005	[70]
	8.10			37	<0.01	[25]
ethylmorphine	8.33			20	0.06	[65]
	7.96			37	<0.005	[70]
diacetylmorphine	7.95			25	0.15	[66]
	7.63			37	<0.005	[70]
6-acetylmorphine	9.55	8.19		25	0.15	[66]
	9.53	7.90		37	<0.005	[70]
oxymorphone	9.71	8.25		20	<0.01	[25]
	9.54	8.17		37	<0.01	[25]
oxycodone	8.53			37	<0.005	[70]
naloxone	9.44	7.94		20	<0.01	[25]
	9.25	7.82		37	<0.01	[25]
naltrexone	9.93	8.38		20	<0.01	[25]
	9.51	8.13		37	<0.01	[25]
buprenorphine	9.62	8.31		25	0.15	[66]
nalorphine	9.36	7.73		20	<0.01	[25]
	9.28	7.59		37	<0.01	[25]
pholcodine	8.39	6.67		25	0.15	[15]
	9.27	7.96		37	<0.005	[70]

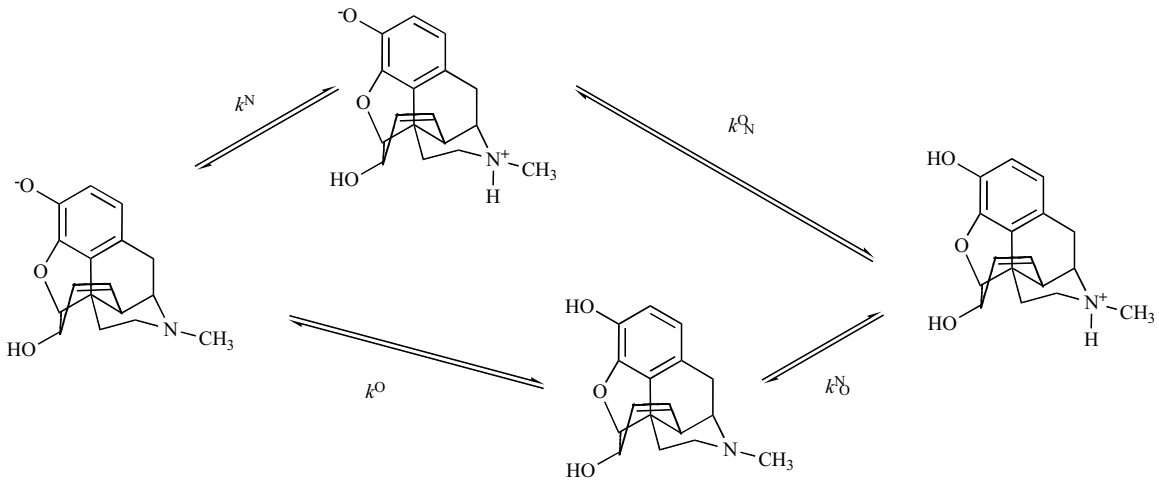

Fig. (2). The microspeciation scheme of morphine.

Table 3. Logarithmic Values of the Microscopic Protonation Constants of Morphine as in Fig. (2) and the Interactivity Parameter for the Phenolate and Amino Groups

k^N	k^O	k^O_N	k^N_O	$\Delta logk$	T (°C)	Ionic Strength (M)	Ref.
8.95	9.37	8.87	8.45	0.50	20	0.06	[65]
9.29	9.18	8.59	8.70	0.59	25	0.20	[69]
9.24	8.95	8.37	8.66	0.58	25	0.10	[67]
9.12	9.27	8.59	8.44	0.68	37	0.10	[67]

that in the blood plasma morphine-6-glucuronide occurs predominantly (86.7%) in the zwitterionic form.

LIPOPHILICITY

Lipophilicity is a molecular property of immense importance in medicinal chemistry and biochemistry. The ability of drugs to diffuse passively through biological membranes depends to a major extent on their lipophilicity [16]. The pH-partition hypothesis postulates that various microspecies of ionisable solutes have very different membrane-penetrating capability. In fact, it is the uncharged form that can penetrate membranes most. Consequently, the absorption of ionizable drugs may be location specific: absorption mainly takes place in compartment(s) where the local pH ensures the

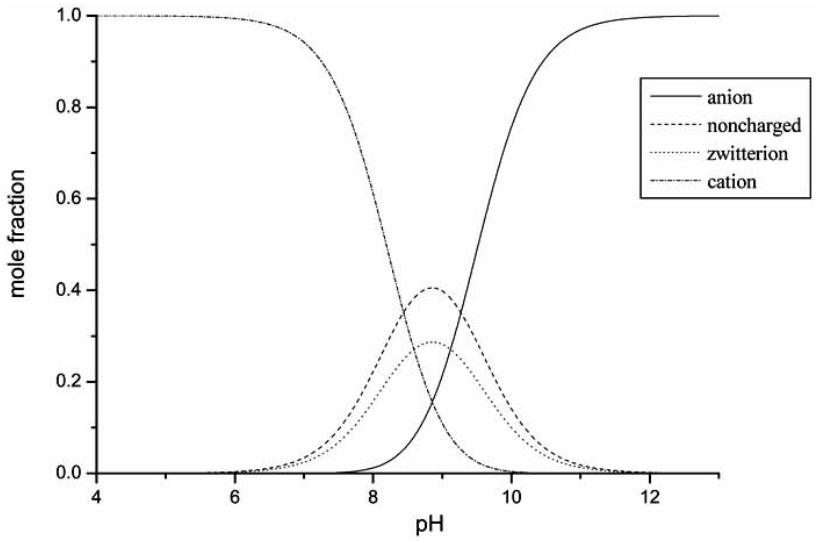

Fig. (3). The microspecies distribution diagram of morphine at 37 °C.

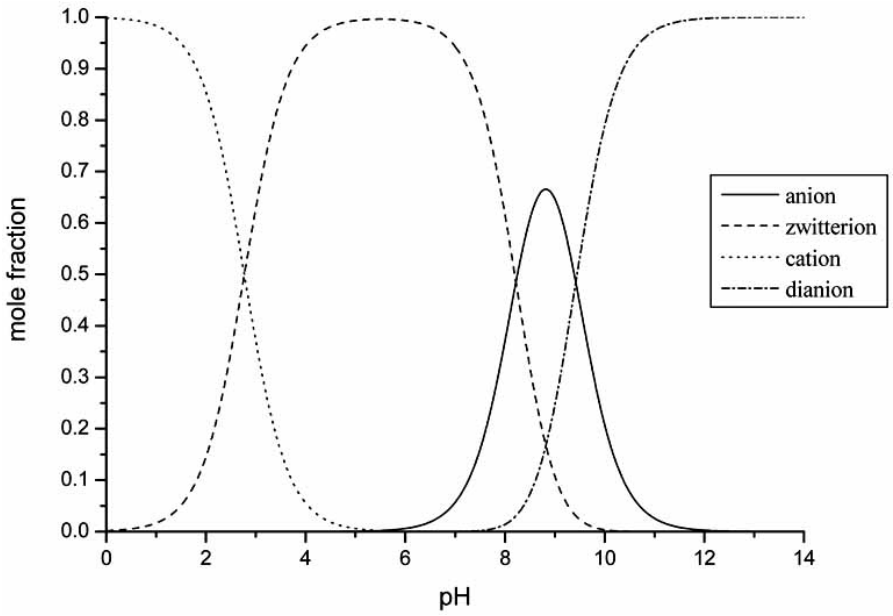

Fig. (4). The macrospecies distribution diagram of morphine-6-glucuronide at 25 °C.

maximum concentration of the uncharged form relative to the ionized forms [17]. In addition, lipophilicity is becoming a tool in unravelling biologically relevant intramolecular interactions [18-20] and intermolecular forces of recognition [21].

The classical parameter of lipophilicity is log*P*, the logarithm of the partition coefficient, the concentration ratio of a solute in equilibrium between two immiscible solvents. For molecules that exist in solution in various ionization states, log*P* refers to the partition of one single electrical state. In other words, log*P* is a pH-independent parameter. The value of log*P* however, depends to some extent on the type and concentration of the background salt used in the aqueous phase of the partition experiments [22, 23]. Typically KCl of 0.15 mol/l is chosen as the background electrolyte. Octanol is the most often used organic solvent, and the octanol-water partition coefficient is the prime descriptor of lipophilicity in QSAR studies [24].

For a long time the importance of the lipophilicity of ionizable drugs and solutes has been underestimated, due mainly to the lack of reliable methods to determine the partition coefficients of the ionic forms.

Partition coefficient of the noncharged and ionized species can be designated as P^N and P^I respectively. Since the concentration of the variously charged (cationic, noncharged, anionic) forms depends on pH, the observed partition is a function of pH. *D*, the distribution coefficient (also named as conditional, observed or apparent partition coefficient) can be calculated as follows:

$$D = x_i P_i \quad (2)$$

where x_i is the molar fraction (or relative concentration) of the given species in water. In the knowledge of log P^N and log P^I lipophilicity profiles can be constructed (the variation of log*D* as a function of pH in the aqueous phase). Table **4** lists the octanol-water log*P* and log*D* values of the opiods discussed.

Standard methods (shake-flask, dual-phase potentiometry) are not suitable to determine log*P* values below -2. In the octanol/water system in the presence of 0.15 M KCl in the aqueous phase, the $\log P^N - \log P^I$ difference is typically around 3-4 [11].

It has been customary to measure distribution coefficients at 20-25 °C, and to use the numerical results obtained at these temperatures in discussing pharmacological implications. However, as data in Table **4** show, the raising of temperature from 20 °C to 37 °C results in significant increases in the distribution coefficients, ranging from 21% for morphine to 200% for naltrexone. The non-regularity of the increases with temperature emphasizes that careful attention needs to be paid to the temperature dependence of these properties.

The onset and duration of narcotic agonist and antagonist activity are related to lipid solubility. The significantly higher apparent lipophilicity of naloxone compared to naltrexone (based on their distribution coefficient) explains why naloxone has a more rapid onset for antagonist activity and likewise a shorter duration of action [25].

Fig. (**5**) shows the lipophilicity profile of morphine and morphine-6-glucuronide. Such profiles are essential in the interpretation of the pharmacokinetic, toxicokinetic and even pharmacodynamic properties [26]. The lipophilicity profile of morphine has a maximum point corresponding to the partitioning of the noncharged species. Other zwitterionic compounds, like buprenorphine have similar profiles. Note that the log*D* maximum value is necessarily below of the log*P* value of the neutral species. This results from the fact that cationic and anionic species of lower log*P* value always exist

Table 4. Octanol-Water log*P* and log*D* Values of the Opiods Discussed

Compound	log*P* Cation	log*P* Neutral	log*P* Anion	log$D_{7.4}$	T (°C)	Ionic Strength (M)	Ref.
morphine	<–2	+0.89	<–2	–0.07	25	0.15 KCl	[66]
		+0.78		+0.07	20	<0.01	[25]
				+0.10	37	0.10	[71]
		+0.79		+0.15	37	<0.01	[25]
M6G	<–2	–0.76	–1.21	–0.79	25	0.15 KCl	[66]
M3G	<–2	–1.10	–1.45	–1.12	25	0.15 KCl	[66]
codeine	<–2	+1.19	none	+0.22	25	0.15 KCl	[66]
		+1.07	none	+0.23	20	<0.01	[25]
		+1.14	none	+0.36	37	<0.01	[25]
diacetylmorphine	–0.94	+1.58	none	+0.85	25	0.15 KCl	[66]
				+1.10	37	0.10	[71]
6-acetylmorphine	<–2	+1.55	–0.42	+0.61	25	0.15 KCl	[66]
oxymorphone		+0.58		–0.33	20	<0.01	[25]
				0.00	37	0.10	[71]
		+0.83		–0.01	37	<0.01	[25]
oxycodone			none	+0.21	37	0.10	[71]
naloxone		+1.77		+1.12	20	<0.01	[25]
		+2.09		+1.53	37	<0.01	[25]
naltrexone		+1.66		+0.64	20	<0.01	[25]
		+1.92		+1.12	37	<0.01	[25]
buprenorphine	+0.45	+4.98	+3.24	+3.93	25	0.15 KCl	[66]
nalorphine		+1.76		+1.26	20	<0.01	[25]
		+1.86		+1.45	37	<0.01	[25]

beside the neutral species, which is of greater importance when the two aqueous log*K*s are in close overlap. It is also apparent that the distribution coefficient of these amphoteric compounds is extremely pH-sensitive in the 7.1-7.7 pH range which includes the physiological pH. There is an approximate 300-400 % increase in the distribution coefficient between the low and high pH values. This strong pH dependence has significant implication for proper scaling of drug dosage under various clinical situations. For example, administering narcotic drugs to obstetrical patients in labour needs extreme care, since the pH in the foetus is lower than in the mother [27].

The lipophilicity profile of M6G is significantly different in its shape (Fig. (**5**)). It displays a broad region of maximum lipophilicity in the 3 to 8 pH range. It has unexpectedly high lipophilicity compared to the fact that it can predominantly found in the zwitterionic form in this pH region. It has been shown in pharmacological investigations that the zwitterions M3G and M6G can cross the blood-brain barrier [28]. Ions or otherwise hydrophilic molecules are generally not able to do so without the intervention of an active transport process. A hypothesis has been proposed to explain the enhanced lipophilicity of M6G and M3G. It was shown by conformational energy minimization calculations that both M6G and M3G can exist in stable "extended" and "folded" conformers, with intramolecular hydrogen bonds between the sugar COOH group and either the 3-phenolic OH or the 6-alcoholic OH groups stabilizing the folded form. The latter form was calculated to be more lipophilic than the extended form [29]. According to this hypothesis, M6G and M3G may act as molecular "chameleons", with an increased apparent lipophilicity in a lipid-like environment.

The lipophility order of these opioids can change dramatically in the acidic region, with absorption relevances to certain parts of the gastrointestinal tract.

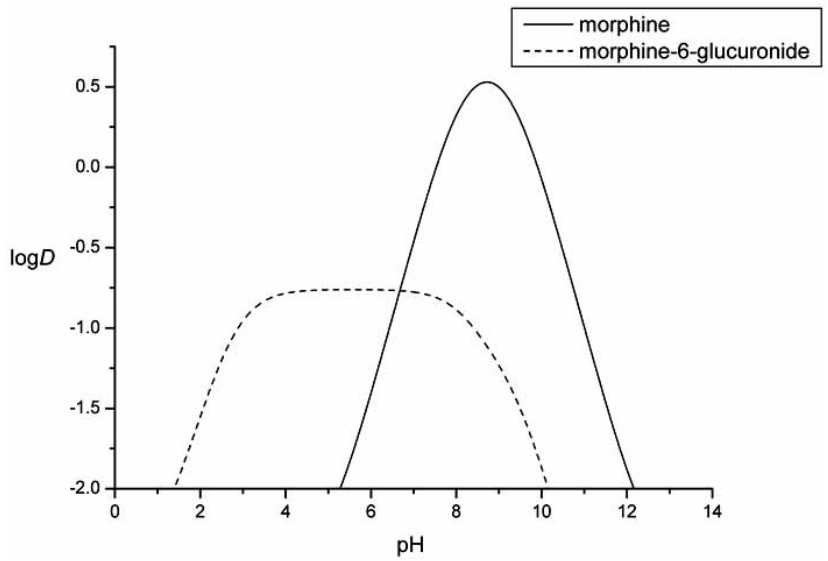

Fig. (5). Lipophilicity profile of morphine and morphine-6-glucuronide at 25 °C.

PARTITIONING INTO DIFFERENT ORGANIC SOLVENTS

For decades octanol has been the standard organic solvent of choice when it came to quantification of log*P* values. The structure of water-saturated octanol became better understood in recent years [30]. Inverted micellar aggregates are formed where water clusters are surrounded by about 16 molecules of octanol, with the polar hydroxyl groups pointing to the clusters and intertwined in a hydrogen-bonded network. The aliphatic tails form a hydrocarbon region with properties not too different from the hydrocarbon core of bilayers. In the past decade partition solvents other than octanol have been explored, such as various alkanes, 1,2-dichloroethane (DCE). The latter is often used in electrochemical methods that require a polarizable interphase, precluding the use of octanol/water and the liposome/water systems [31]. The log*P* of the cationic forms of some opioids was recently determined in the DCE-water system: codeine (log*P* = –2.00) and diacetylmorphine (log*P* = –0.58) are more lipophilic than morphine (log*P* = –4.55); while the lipophilicity of the phase I metabolite 6-acetylmorphine (log*P* = –2.45) is between that of heroin and morphine [32]. These results are in agreement with previous findings that heroin molecules can pass through the blood–brain barrier [33] and human skin [34] much faster than morphine [35].

PARTITIONING INTO LIPOSOMES

In contrast to the isotropic solvents used traditionally in lipophilicity studies, artificial and natural membranes are anisotropic media. Their use in lipophilicity studies has led to the concept of anisotropic lipophilicity, which should be viewed as being an intermediate case between partitioning and binding. This ambiguity is also evident in the literature, where drug-membrane interactions are discussed either as a binding or a partitioning process.

Liposomes are vesicles with walls of phospholipid bilayer. Their structural properties have recently been reviewed [36, 37]. The relative static permittivity in the region of the polar head groups of phospholipids is about 32 (same as that of methanol), whereas in the hydrocarbon core it is near 2 (same as dioxane) [38]. The abundance of available lipids and preparation techniques has resulted in a variety of liposome types. These are now employed as partition phases. The partitioning of ionized solutes depends also on the quality and size distribution of the liposomes. The majority of membrane lipids are comprised of a head group region with one or more charged units, typically either zwitterionic or anionic. Using the constant ionic medium reference state $\log P_{mem}^{SIP}$ can be defined as the partition coefficient of the surface ion-pair. The value of $\log P_{mem}^{SIP}$ depends on the background salt used, although the dependence is subtle (the counterion may be exchanged with the zwitterionic phosphatidylcholine head groups). Liposome-water log*P* values have only been published for morphine: $\log P_{mem}^{N} = 1.89$ and $\log P_{mem}^{SIP} = 1.02$ at 25 °C and 0.15 M KCl [11]. So $\log P_{mem}^{N}$ and $\log P_{mem}^{SIP}$ lie in the same order of magnitude. Thus, charged species partition into membranes about 100 times more strongly than is suggested by octanol. Partition measured in the liposome/water system may not always reflect transmembrane permeation [39] as solutes obviously associate with the membrane interface without entering the bilayer interior. This is a possible explanation for the significantly higher ionic partition coefficients obtained in liposomes compared to the octanol/water system [40, 41].

SOLUBILITY

Solubility (*S*) is the concentration of the solute in equilibrium with its solid phase. Its knowledge is essential in designing the appropriate delivery system for a drug [11, 42].

The effective solubility is the sum of the concentrations of all the species dissolved in the solution. S_0 and S_I are the solubilities of the neutral and ionic species, respectively, where S_I depends on the background salt used.

Table **5** summarizes the solubility of the opiods discussed.

Table 5. The Solubility of the Opiods Discussed (e.g. 1 : 5,000 Indicates that 1 g is Soluble in 5,000 ml of the Solvent at 25 °C)

Compound	Solubility in Water	Solubility in Chloroform	Solubility in Ethanol	T (°C)	ref.
morphine	1 : 5,000	1 : 1,220	1 : 210	25	[1]
	0.149 g /l			20	[25]
	0.184 g /l			37	[25]
morphine HCl	1 : 17.5	insoluble	1: 52	25	[1]
morphine H_2SO_4	1 : 16	insoluble	1: 570	25	[1]
codeine	1 : 120	1 : 0.5	1 : 2	25	[1]
codeine H_3PO_4	1 : 2.5		1 : 325	25	[1]
codeine H_2SO_4	1 : 30	insoluble	1 : 1,280	25	[1]
oxycodone HCl	1 : 10			25	[1]
naloxone	0.134 g /l			20	[25]
	0.140 g /l			37	[25]

Since morphine is sparingly soluble in water, pharmaceutical companies produce sulfate and hydrochloride salts of the drug, both of which are about 300 times more water-soluble than the parent molecule. While the pH of a saturated morphine solution is 8.5, the salts are acidic with a pH about 5. As a consequence, these morphine salts are mixed with small amounts of NaOH to make them suitable for injection.

The solubility of codeine in water is about 42 times better than that of morphine, in spite of the presence of a free hydroxyl group in morphine that should enhance aqueous solubility through hydrogen bonding. But this additional hydrogen bond also exists and stabilises the crystal lattice of morphine, as indicated by its much higher melting point compared to codeine (255 °C *vs*. 155 °C), thus hampers dissolution [42].

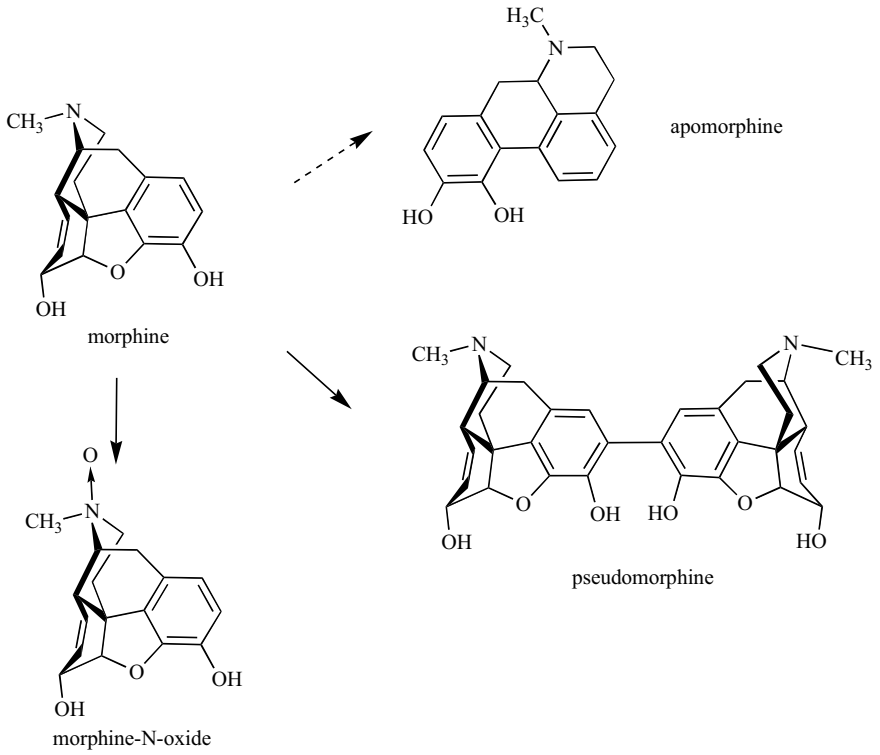

Fig. (6). Overall degradation of morphine under ambient conditions.

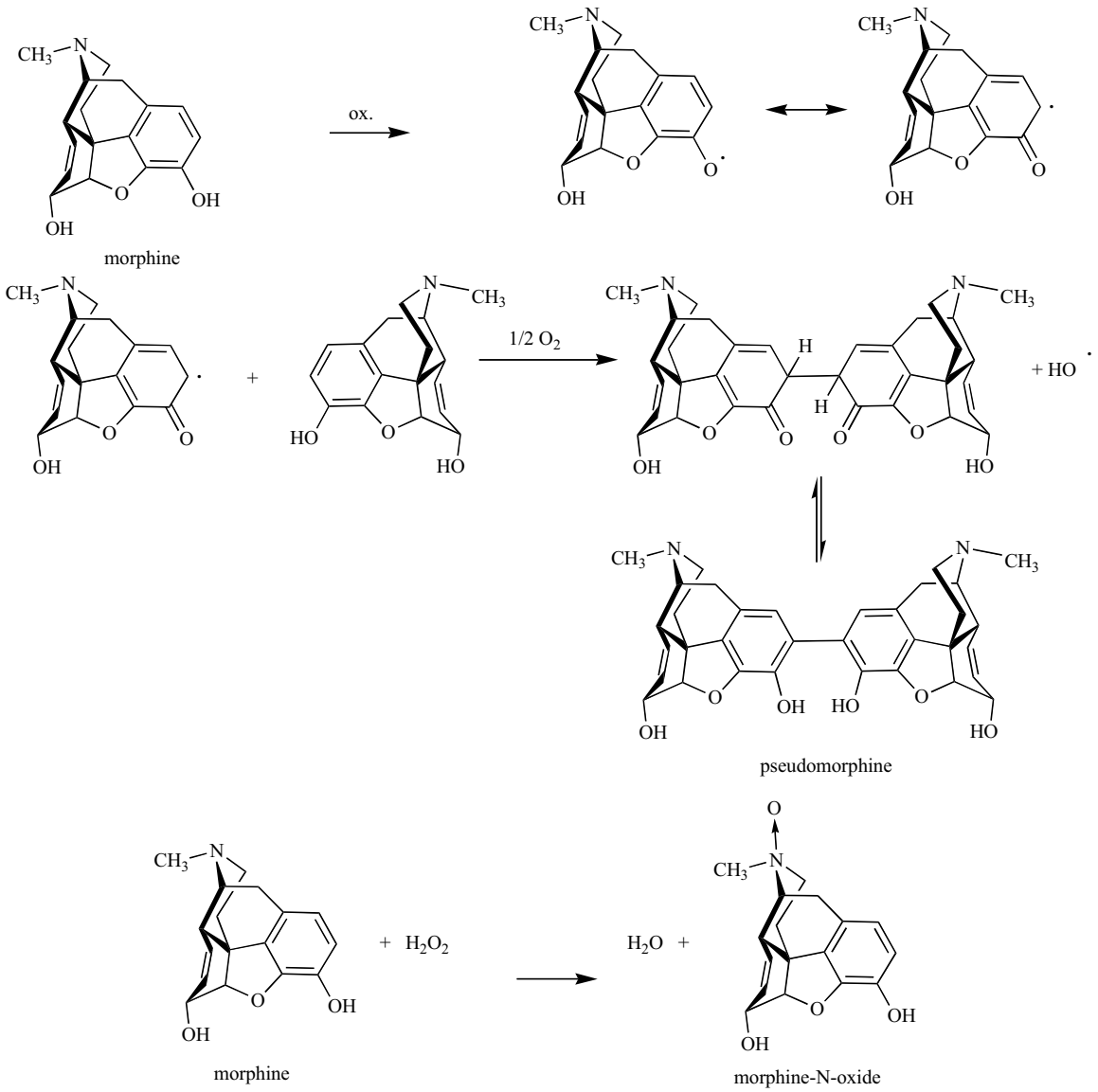

Fig. (7). Degradation mechanism of morphine.

The solubility of morphine base in many organic solvents has been determined [42], and the pH-dependence of the aqueous solubility of morphine [43] and buprenorphine [44] has also been investigated.

PERMEABILITY

Permeability (P_e) determines how quickly molecules can cross membrane barriers. It is a kinetic (not a thermodynamic) parameter, its dimension is cm/s.

The advantage of studying biological permeation with cell monolayers grown on polycarbonate filters is that they measure the transport of the drug across the cell membrane, instead of just its interaction with the lipid bilayer, as can be the case with liposomes. The transepithelial transport of morphine was recently investigated in Caco-2 (human colon adenocarcinoma) cells [45].

Microdialysis is an established, commercially available method to sample brain extracellular fluid. It provides the technology to determine the cerebral penetration of drugs and it measures biological markers of brain tissue injury [46]. Intracerebral microdialysis was utilised to obtain information on the transport of morphine across the blood-brain barrier [47].

STABILITY

The stability of morphine has been surveyed recently [48]. Morphine is degraded in aqueous solutions as indicated by the discoloration during storage. The degradation of morphine has been reported to result in three products, the third of them is produced under extreme circumstances. Under ambient conditions oxidation reactions take place resulting in the formation of pseudomorphine and morphine-N-oxide (Fig. (**6**)). Apomorphine is a product of laboratory decomposition for analytical purposes, in concentrated acids. Apomorphine, as ortho-diphenol easily oxidizes further, resulting in various green products.

The stability of morphine in aqueous solutions has been examined in detail and it is generally accepted that oxygen of air, sunlight, UV irradiation and metal ions can catalyse the degradation of morphine [49-54]. Since morphine contains a phenolic hydroxyl group its stability in aqueous solution is pH-dependent. In alkaline or neutral solutions morphine deteriorates rapidly at room temperature, whereas acidic solutions are relatively stable. In the presence of oxygen excess, the degradation rate and extent increases with increasing pH of the solutions. Presumably a free radical of morphine is formed that dimerizes with another morphine molecule to yield pseudomorphine (Fig. (**7**)) and the appearance of morphine-N-oxide can be explained by the formation of H_2O_2 [51, 55].

Several further aspects of morphine decomposition have been reported, such as the effect of hydrogen peroxide [56], anti-oxidants [57], the influence of gassing ampoules with nitrogen [58]. A study of the electrochemical oxidative behaviour of morphine involved the oxidation of phenolic and tertiary amine groups [59]. The decomposition of codeine has also been extensively studied [60] and codeine N-oxide was detected among the decomposition products [61]. Studies on the hydrolytic decomposition of diacetylmorphine and its derivatives showed that the major pathway of hydrolysis is through 6-acetylmorphine, the rate of hydrolysis is more than 4 times larger than in the case of the minor 3-acetylmorphine metabolite [7, 62]. The major degradation product of both naloxone and oxymorphone is the 2,2-dimer [63]. Buprenorphine also undergoes an acid-catalyzed rearrangement reaction when exposed to acid and heat [64].

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