MEDCHEM 562
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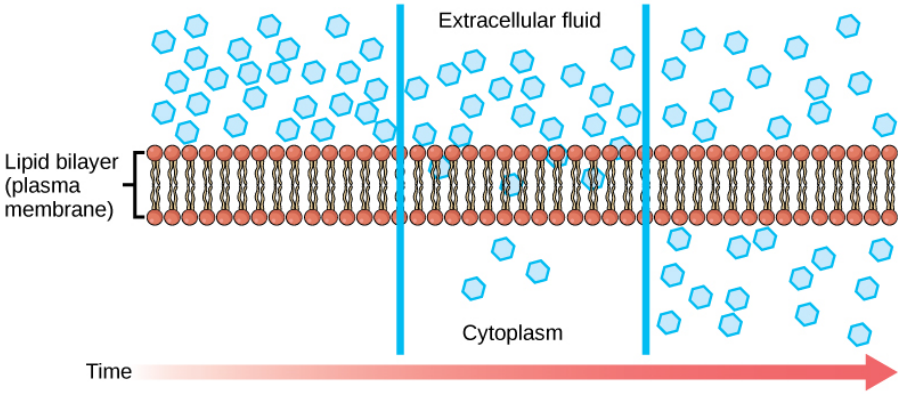
Lecture 1 & 2

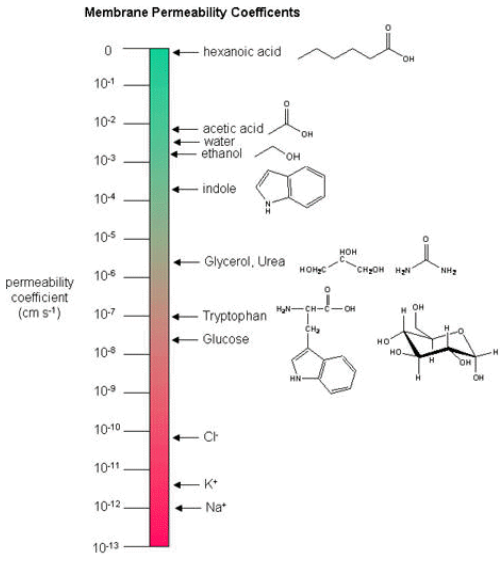
Physicochemical Properties of Drugs and Drug Disposition

The ADME properties of most drugs strongly depends on the ability of the drug to pass through membranes via simple diffusion.

Below we see how the concentration of a hypothetical solute changes with time until it reaches equilibrium. The rate of diffusion observed is an important physicochemical property of both the solute (charge, size, lipophilicity) and the membrane. Note that the time required to reach equilibrium will vary widely from drug to drug. Fortunately we can use equilibrium properties (lipophilicity and charge) to understand and predict most of absorption without resorting to higher-order time based modeling of the rates of diffusion.



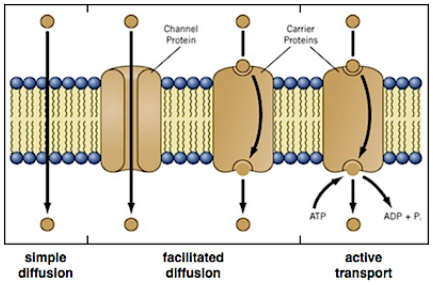
Solutes must have a meaningful solubility in aqueous solution and in lipid in order to pass from one compartment to another. Formulation for dissolution is important here.



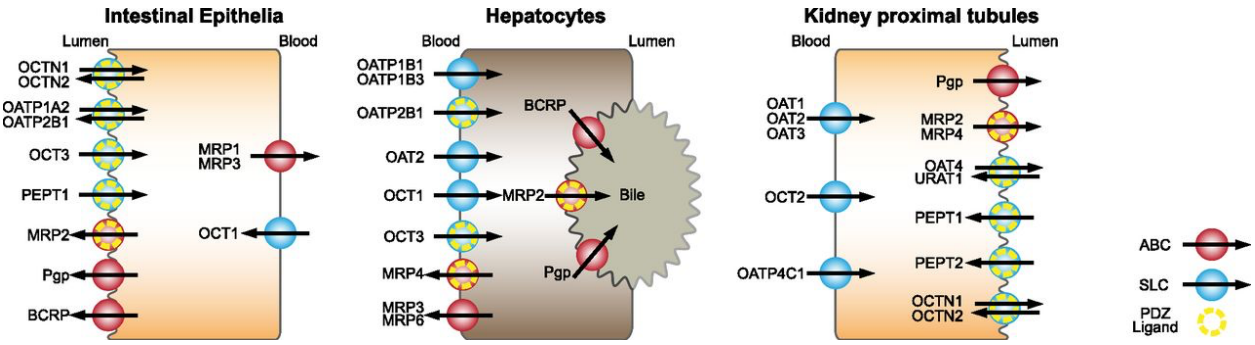
Charged solutes/drugs do not pass directly through membranes.

Greater than 80% of all drugs contain one or more ionizable functional groups. Only the uncharged form of a drug that is in equilibrium with the charged form, can pass through a membrane by simple diffusion. Thus it is important to be able to recognize the fraction of a drug that will be charged in a given compartment such as the intestinal lumen, the kidney tubules and the blood. Therefore it is important that you be able to relate drug structure to charged state at the pH of physiological fluids. For ionizable drugs the percent of drug that is not ionized and therefore available for diffusion through a membrane will depend upon the pH of the compartment(s).

However, charged forms of drugs can pass through membranes via the many influx and efflux transporters. Transporters are critical to the ADME properties of many drugs and other biochemical. For instance the absorption of amino acids (zwitter-ionic) and simple sugars (very polar) from the diet requires transporters. Some efflux transporters (Pgp) can actually reduce absorption. Fortunately these transporters sometimes act on an entire class of drugs.



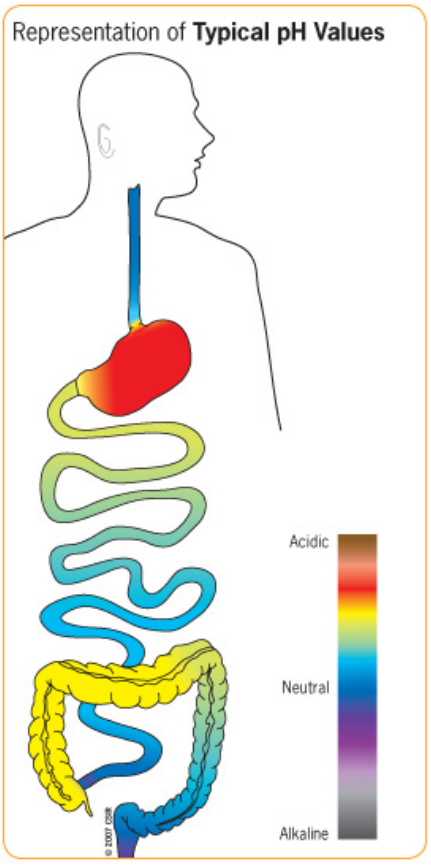
Fortunately these transporters sometimes act on an entire class of drugs. Unfortunately drugs that are substrates for the transporters are also inhibitors of the same transporter. So drug-drug interactions can be problematical.



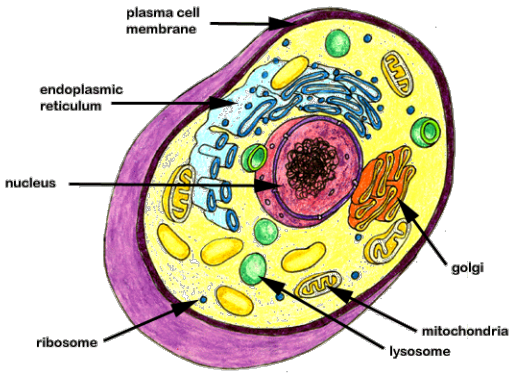
Note that the pH in the lumen of the intestine and the lumen of the kidney varies so the rates of passive diffusion will be pH dependent for and absorption and reabsorption respectively.

ADME

Absorption: The majority of drugs are administered orally and absorbed from the GI tract. There is negligible absorption in the stomach though dissolution does occur here. As you have learned many factors control the absorption profile of drugs. These include rates of drug dissolution, lipid solubility (logP), ionization state (pKa) and the location of the drug along the GI tract all affect the net rate of diffusion of a drug through the intestinal membranes into the portal blood (absorption). The two opposing membranes (apical and basolateral) are highly differentiated with respect to membrane proteins and contain different types of transporters that move essential nutrients and some drugs. As we will see later the site of absorption in the intestine can be predicted from the ionization properties of the drug. This partially controls the time to peak concentrations after a dose. A continuous pH gradient exists along the GI tract…….Duodenum (proximal) pH 5 to Illeum (distal) pH 7 or so. As we

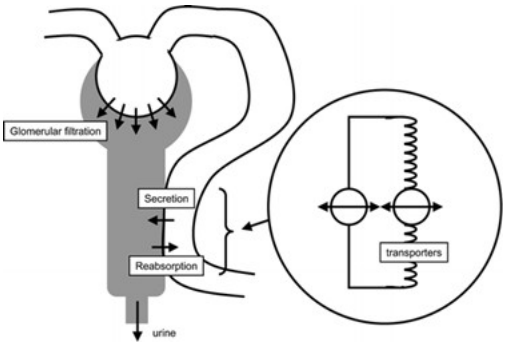


Drug Distribution: Drugs are distributed into various compartments in the body where they find targets that include surface, nuclear and cytosolic receptors as well as the metabolic enzymes. These drug targets may be extracellular or intracellular. In many cases these drugs must pass through additional membranes such as the blood brain barrier as well as the cytoplasmic and nuclear membranes of the cell and/or invading microorganisms or cancer cells. Generally uncharged lipophilic drugs have large volumes of distribution



Metabolism: Most metabolic enzymes that biotransform drugs and often activate prodrugs are located in the hepatoctyes. Generally, but not always, metabolism creates more polar less active metabolites that are readily excreted. This means that metabolism generally marks the termination of drug effect. Metabolism usually controls the rate at which a drug disappears from the body. It also can control systemic bioavailability of an oral dose. Lastly metabolism can be used to activate prodrugs to bioactive forms.

Excretion: Drugs are largely excreted as their metabolites and as well as unchanged drug by the kidneys. Among other factors, renal clearance of unchanged drug and metabolites depends upon the extent to which drugs are reabsorbed from the filtrate back into the systemic circulation. Charged drugs are not passively reabsorbed and are excreted in the urine. Thus the percent of drug ionized in the lumen (pH 5-8) will control urinary excretion. We also see biliary excretion via transporters located on the cannicular membrane of the hepatocytes.



Ionization State of the Drug: The ADME properties of a drug depend heavily upon the ionization state of the drug in the physiological fluids. The extent of ionization depends on the functional group pKa value(s) and the pH of the aqueous phase of interest. We usually use pH of 7.4 as a reference value.

The pH of other biological fluids can be significantly different. What this means is that a pH gradient often exists across a membrane. For ionizable drugs a pH gradient often determines total concentration of drug on each side of a membrane and the direction of movement of a solute through the membrane.

Here are the pH values for various fluids. The transition from low pH to high pH in the GI tract is particularly important to understand.

Blood and intracellular fluid pH =:	7.4
Urine pH =:	5-8 (normal is 7)
GI tract pH =:	1-7 (stomach 1; intestine 5-7)
Duodenum=	5
Illeum	7
CSF: pH =	7.3

We can use the Henderson-Hasselbalch equation to determine the precise ratio of the concentrations of the conjugate acid and conjugate base at a particular pH. You should know this equation

$$pKa = pH - \log \frac{[\text{conjugate base}]}{[\text{conjugate acid}]}$$

As you should definitely know by now, when the pH of a solution is equal to the pKa of the functional group the ratio of the conjugate base to the conjugate acid is equal to 1.

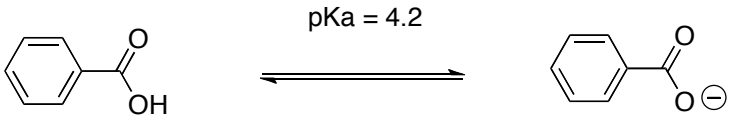
When the pH of the solution is significantly different from the pKa of a drug we can calculate the conjugate base/conjugate acid ratio in that environment.

$$\frac{[\text{conjugate base}]}{[\text{conjugate acid}]} = 10^{(pH - pKa)}$$

Here we are primarily interested in the ratio of unionized drug to ionized drug so we also need to know whether the conjugate acid is charged (e.g. an amine) or neutral (e.g. a carboxylic acid).

While this equation has many uses (e.g. calculation of arterial blood gases and pH) we will only be interested in determining the fraction of drug in the ionized and non-ionized states.

Carboxylic acid example:



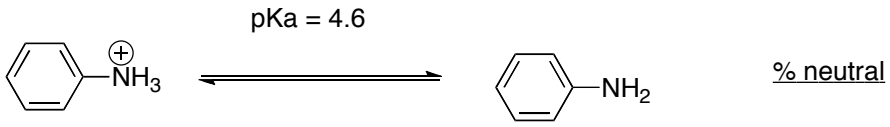
1	pH =7.4	1500	0.07%
1	pH = 4.2	1	50%

Lower pH favors the neutral conjugate acid

For benzoic acid (left column of the following table; pKa = 4.2) the protonated conjugate acid form is neutral and the benzoate anion conjugate base is negatively charged. We can calculate that the ratio of benzoate anion to benzoic acid (neutral) at pH 7.4 is 1 x $10^{3.2}$ or roughly 1500:1. Thus carboxylic acid drugs are negatively charged in the blood and penetration into tissues will be dependent on the lipophilicity (log P) of the conjugate acid…. which is neutral. Also these types of drugs tend to be bound to plasma proteins (albumin) and have high unbound volumes of distribution. Almost all of this compound is in the anion form that cannot pass through membranes. If we consider the GI tract which is more acidic at the upper end this ratio shifts in favor of the neutral species. For instance at pH = 4.2 approximately 50% is present as the neutral form and absorption of carboxylate containing drugs in general is fine as long as there are not other ionizable groups such as is present in amino acids.

The presence of other ionizable groups complicates the relationship. For instance, amino acids are amphoteric (zwitterionic) and always charged. Amino acids can only only pass membranes via transporters and we see examples where transporter deficiencies for particular essential amino acids can cause disease due to a lack of adequate levels of the amino acid absorbed from the diet. Many drugs are zwitterionic due to critical binding interactions with the target.

Aromatic amine example:

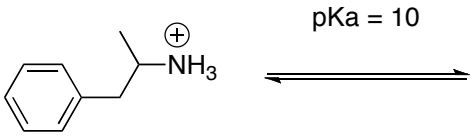


1	pH = 7.4	280	99.6%
2.5	pH = 4.2	1	30%

Lower pH favors the charged conjugate acid

The pKa of aniline is 4.6, which is very similar to benzoic acid. However in the case of aniline the conjugate acid, the anilinium ion, is charged and the conjugate base, aniline is neutral. This is opposite to benzoic acid that has a similar pKa see above. We can calculate the ratio of the conjugate base (aniline) to the conjugate acid (anilinium ion) at pH 7.4 as above which yields a ratio of 1 x $10^{2.8}$ or roughly 280:1 in favor of the neutral form. Thus we would expect that absorption of an aniline type drug to be rapid and to occur towards the distal (more basic) portion of the GI tract. We would also expect log P to be less problematical as a determinant of absorption and distribution since the neutral form usually predominates along the GI tract.

Aliphatic amine example:

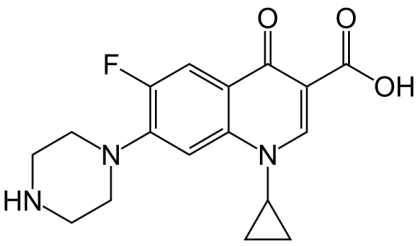


400	pH =7.4	1	0.25%
600000	pH = 4.2	1	nil

Lower pH favors the charged conjugate acid

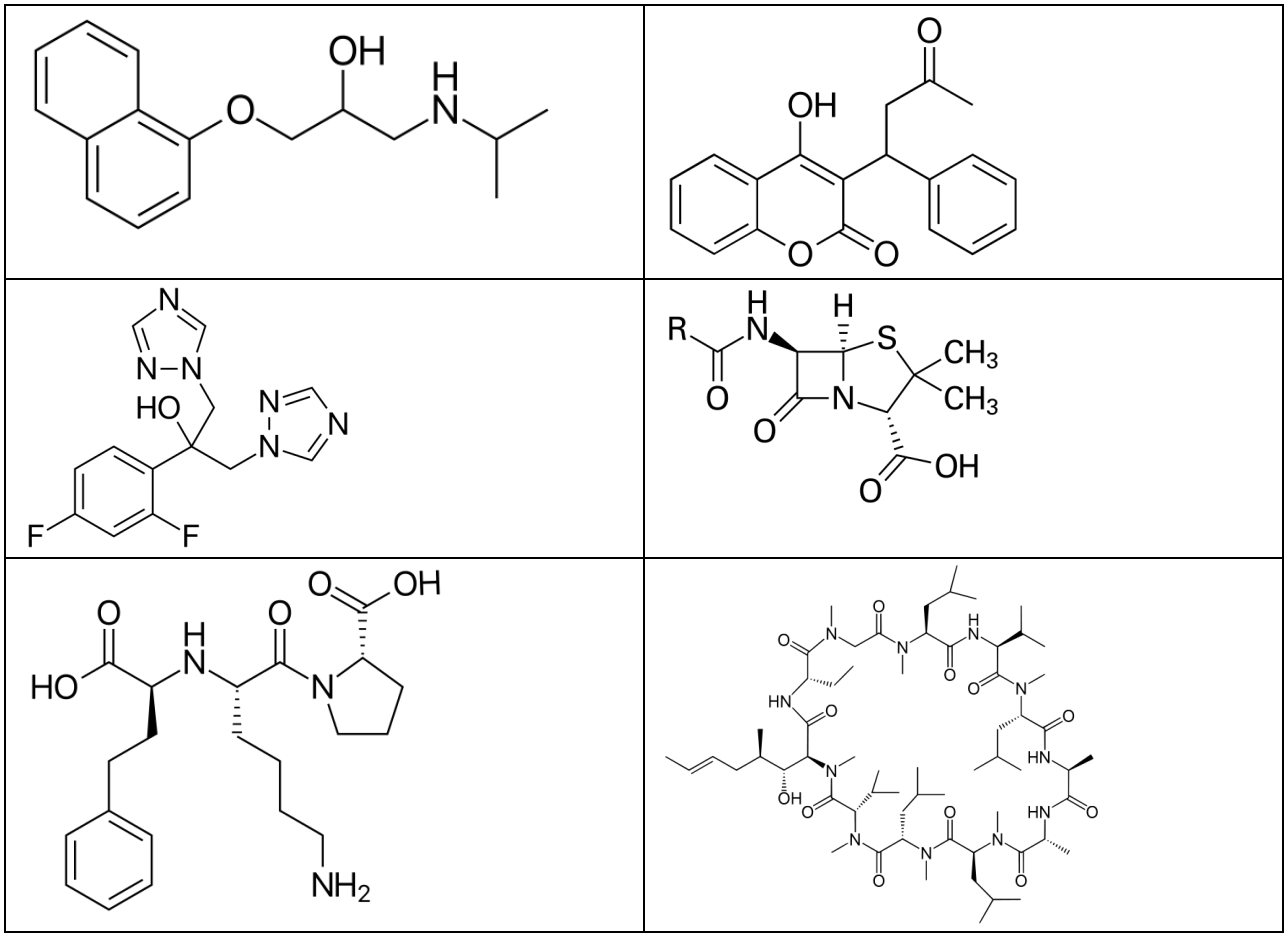
The pKa of amphetamine is 10 thus the charged conjugate acid predominates at most physiological pH values. The neutral conjugate bases of amine drugs are generally highly lipid soluble and most simple amines are well absorbed in the distal GI. The blood brain barrier is more problematical for agents that must be neuroactive agents.

Multiple ionizable groups are often present in drugs.



Ciprofloxacin is zwitterionic due to three ionizable groups (carboxylic acid (pKa = 4.5); aliphatic amine (pKa = 9-10); aromatic amine (pKa 4.5). It bears at least one charge over the pH range of interest (2-9) and will not pass through membranes. Thus one would predict poor bioavailability. Note that ciprofloxacin is absorbed from the GI tract due to the action of uptake transporters however the bioavailability is limited (60%) by absorption.

Note: The structures of most drugs are usually shown as the neutral species along with an associated pKa. This can be confusing/irritating if it is not readily apparent whether the neutral species is the conjugate acid (phenols, aliphatic or aromatic carboxylic acids, sulphonamides, imide (barbituates)) or the conjugate base (aromatic amines, alkylamines, pyridines, imidazoles, azole). Obviously if you are given the name of a drug and it's pKa without structural information (is it an acid or a base?) you cannot know how it will behave at different pH values and what the ionization state is at pH 7.4. Sometimes this can be really difficult, particularly on exams. Over the course of the next three quarters you will see many examples where the pKa's of functional groups drive important properties such as receptor affinity, protein binding, absorption and exretion so you will develop a working knowledge of common functional group pKa as you go along and an intuition about ionizable groups in general.



Some characteristic functional groups and pKa's are shown below. The list is not exhaustive by any means but should trigger your long-term memory from MedChem 400.

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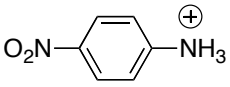
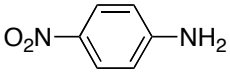
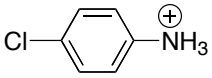
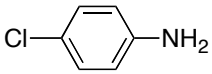
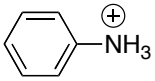
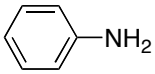
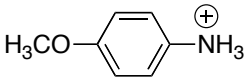
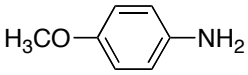
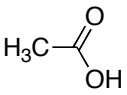
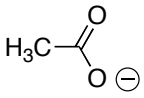
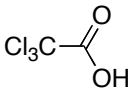
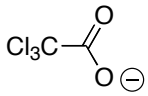
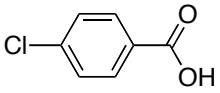
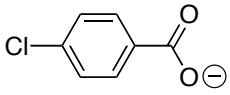
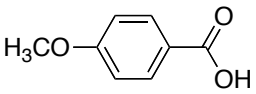
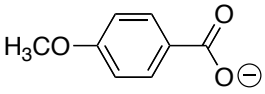
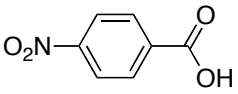
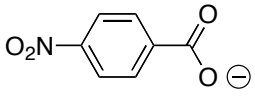
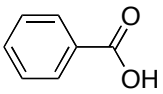
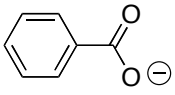
	1.0	
	4.0	
	4.6	
	5.3	
	4.8	
	0.8	
	4.0	
	4.5	
	3.4	
	4.2	

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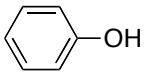
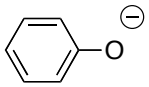
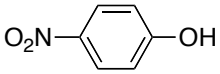
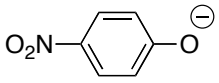
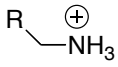
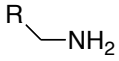
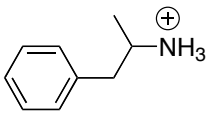
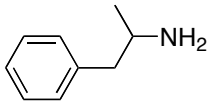
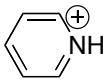
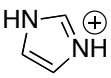
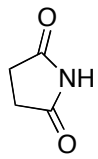
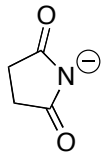
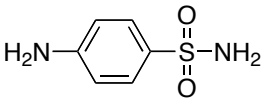
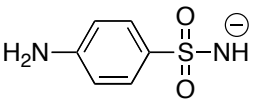
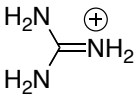
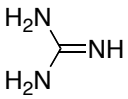
	9.6	
	7.2	
	10	
	10	
	5.0	
	7.0	
	10	
	11	
	14	
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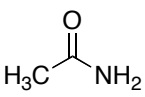
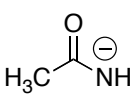
	18	

Some other trends of note

1. For series of similar compounds with different substituents, electron withdrawing groups tend to lower pKa values whether the effect is due to inductive effects or reasonance. Electron donating groups tend to raise pKa values.

2. The pKa's of aliphatic and aromatic carboxylic acids are similar (pKa = 3-5) and they are all referred to as weak acids (Strong acids have pKa's less than 2 and are always ionized).

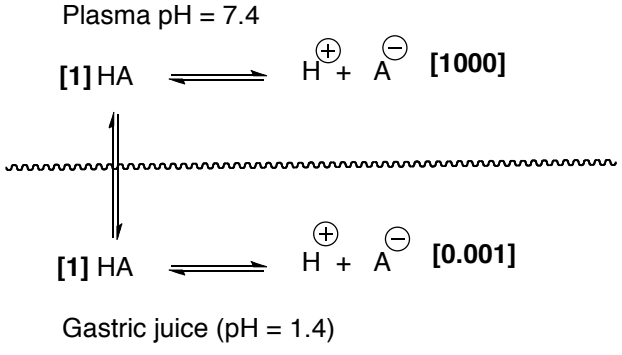
3. The pKa's for aromatic amines (3-5) are roughly 6 pKa units lower than aliphatic amines (8-10). Aromatic amines, pyridines and imidazoles are generally called weak bases. Aliphatic amines are called strong bases.

4. For most purposes the use of integer pKa values are sufficient for estimating % ionized. This makes it easy to calculate estimates of % unionized.

5. Lipophilicity is also important: Many drugs will pass passively and rapidly through membranes despite the fact that as little as 0.1% of the drug is in the uncharged form. This is because the relative lipophilicity of the uncharged form will contribute substantially to the overall rate of transfer across membranes (permeability).

7. Good systemic bioavailability is often hard to achieve. For some drug classes, both good bioavailability and pharmacological efficacy have not yet been achieved in a single compound.

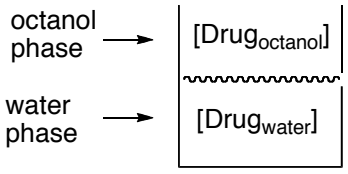
8. Important concept: When a membrane separates compartments of different pH the total concentration of an ionizable drug will be different in each compartment while the concentrations of the unionized species will be the same. This is particularly important in the GI tract lumen and kidney tubules which are adjacent to the blood. What is the pKa of the drug (HA) shown below? Would you expect reasonable absorption in the intestine? Gastric absorption is limiting for many drugs. Here the pH gradient drives absorption and final equilibrium strongly favors the blood. Now think about the kidney where the proximal tubule pH is variable but usually slightly acidic.



Lipophilicity

The relative physicochemical properties of a drug or series of drugs can be related to ADME and pharmacological effect. In drug design lead compounds are modified to optimize these properties as well as others (like minimizing off target effects). Here a basic core structure called a pharmacophore is systematically modified by changing functional groups, lipophilicity, solubility, size and pKa values. In some cases, ADME can also be improved by creating a prodrug or altering the formulation. You will learn about some successes and failures as you study the various drug classes. Lipophilicity is a major factor and has it's own language.

Log P is partition coefficient that is a quantitative measure of lipophilicity. Here the solubility of the unionized form of the drug in a lipid phase (octanol) and water is compared and expressed as a ratio. Octanol and water are immiscible, so the solution has two phases with the octanol on top. Typically the drug is dissolved in the more soluble solvent, equilbrium established and the concentrations of the non-ionized species in the two phases is measured. Log P is measured for only the non-ionized species.



$$P = \frac{[Drug_{octanol}]}{[Drug_{water}]} \qquad logP = \log \left[\frac{[Drug_{octanol}]}{[Drug_{water}]} \right]$$

Equal solubility in both phases gives a P = 1 and a log P = 0. Most drugs have positive log P values. Importantly Log P values are independent of pH.

Note that most drugs are partially ionized in water. This means that a direct measure of log P requires that we know the concentration of the non-ionized species and ignore the ionized species. Charged species are not soluble in octanol. While logP is known for many drugs based on experiment, we usually resort to a log P that has been calculated using a computer. This value is referred to a clogP (calculated log P).

Log D is a partition coefficient that is quantitative measure of the ratio of **total drug** in each phase. For non-ionizable drugs log D and log P are the same. For ionizable drugs log D is highly dependent on pH of the aqueous phase. Log D then is more representative of the partitioning between a membrane and the aqueous phase such as a drug in the GI tract. Lets look at an two examples. We use the earlier data at different pH values for benzoic acid and aniline.

	Benzoic Acid; pKa = 4.2; logP = 1.8				Aniline; pKa = 4.6; logP = 1.03			
pH	4.2		7.4		4.2		7.4	
Species	HA	A^-	HA	A^-	BH^+	B	BH^+	B
octanol	63	--	63	--	--	10.7	--	10.7
water	1	1	1	1500	2.5	1	.003	1
D	31.5		.042		3		10.7	
Log D	**1.5**		**-1.4**		**0.5**		**1.02**	
Log P	1.8		1.8		1.03		1.03	

We note that:

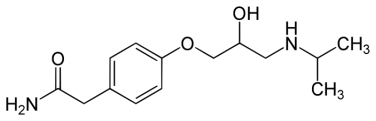
1. Log D for weak acids (conjugate acid is neutral) decreases as pH increases.

2. Log D for weak bases (conjugate acid is charged) increases as the pH increases.

3. Since log D is pH dependent the pH must be noted. Often seen in a subscript (Log $D_{7.4}$; Log $D_{4.2}$; etc).

4. pKa, logP and log D_{pH} values are related. If you know any two values you can calculate the third.

Let's look at some data for the absorption of various beta blockers which are all secondary aliphatic amines with no other ionizable groups. Atenolol below (pKa = 9.2).



Drug	LogP	Log D(7.4)	% Absorbed
Nadolol	0.56	-2.1	30%
Atenolol	.033	-1.7	50%
Acebutolol	1.77	-0.3	90%
Betaxolol	2.53	0.43	100%
Propranolol	2.9	0.79	100%

Here we see the effect of lipid solubility on extent of absorption from the intestine into the portal blood. As expected increased log P and log D confers better absorption. Since the pKa values for the amines are similar we see parallel changes in Log P and Log D. Also be careful to differentiate between % absorbed and bioavailability. The bioavailability of atenolol is 40 to 50%. The bioavailability of propranolol is around 25% due to hepatic first pass metabolism.

Many of the beta blockers are relatively resistant to metabolism and are then excreted unchanged in the urine. Based on the principles you learned about renal clearance it should be logical to you that the % unchanged in the urine for a class of drugs with similar structure should be inversely related to log P and log D. In this case that relationship is observed.

Drug	Log D(7.4)	% excreted unchanged
Sotalol	-1.7	80%
Practolol	-1.5	90%
Atenolol	-1.7	85%
Metoprolol	-0.5	10%
Betaxolol	0.43	15%

High lipophilicity can be a bad thing.

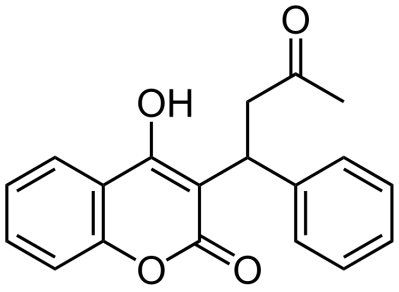
Highly lipophilic drugs (log P > 5, octanol/water ratio > 100,000 to 1) are normally readily absorbed if they can be dissolved, however they partition into the lipid compartments (large Vd), have long half-lives (difficult to dose) and may persist in the brain. Examples of these kinds of drugs are amiodarone (Log P = 7.8), Proxicromil (Log P = 4.9) and Penfluridol (Log P = 7).

ADME and Lipinski's Rules

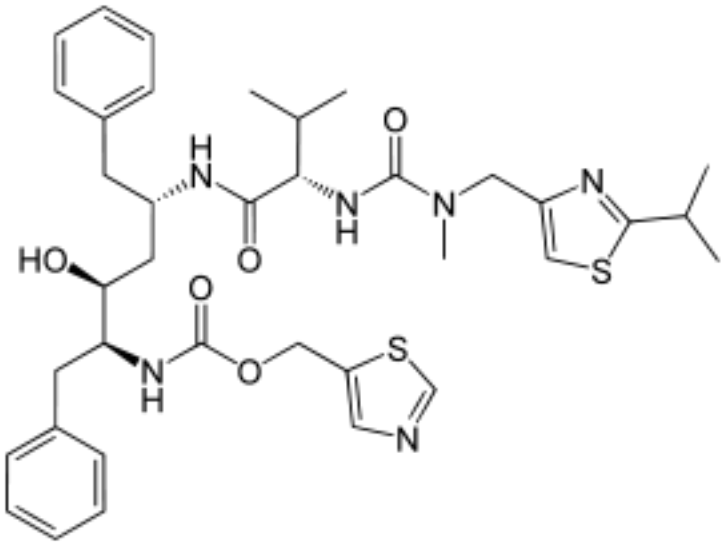
Lipinski's rule of was derived from analysis of large data base of known drugs and clinical failures for which extensive data had been collected. It was meant to provide a set of rules that could be used to guide the development of new drugs that would be orally active. These rules are empirical and impact each component of ADME to some extent. For instance an orally active drug has to escape first pass metabolism. They are most widely applied to creating drugs that are absorbed. These rules do not predict pharmacological activity (ie receptor binding). They are widely used in the industry and have undergone a number of refinements and additions. Obviously not all of the drugs on the market fit the rules.

Lipinski's rule states that, in general, an orally active drug has **no more than one violation** of the following criteria:

1. Not more than 5 hydrogen bond donors (R-O-H and R-N-H). (RTV = 4)
2. Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms) (RTV = 11)
3. A molecular weight less than 500 grams/mole (RTV= 728)
5. An octanol-water partition coefficient, log P, not greater than 5 (RTV = 7.5).



Warfarin



Ritonavir (RTV)