Weak acids

unionized along the GI

Any functional group with proton

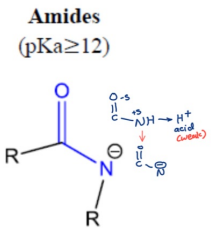
- There **pKa is 12 or more**, which means in the GIT (pH= 1-8) the
- conditions are constantly acidic shifting equilibrium toward HA, therefore weak acids are permanently unionized across GIT so they've well bioavailability not necessarily excellent but they're better candidate to be absorbed orally because there are other important factors controlling bioavailability we mentioned, and we'll discuss in more details later.
- such as optimal hydrophilic/hydrophobic properties represented by **lipinski's rule of 5**. (we will discuss it later)

- For example, if the compound is unionized and highly insoluble in water for some reason it won't be bioavailable, therefore we should keep in mind to check on all the factors to judge bioavailability.

Weak acids

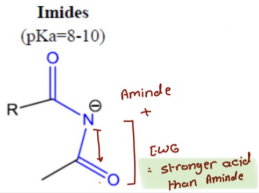
1) Amides

Amides by looking at their conjugate base, they contain an electron withdrawing carbonyl building up a -ve charge on N, yet N isn't strong electronegative enough to stabilize -ve charge efficiently therefore considered a weak acids; their **pKa is 12 or more**.

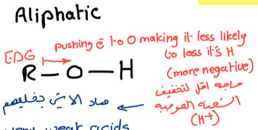


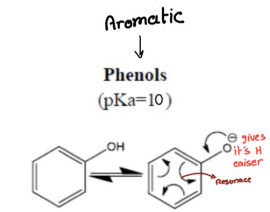
2) Imides

- **Imides** in fact are also considered weak acids even though they contain 2 electron withdrawing carbonyl which can further stabilize -ve charge on N; their **pKa=8-10** so imides are stronger acids than amides but still considered fairly weak acids.

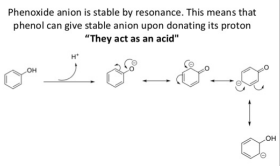


3) Alcohols



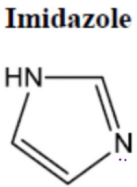


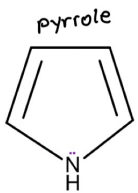
Alcohols are very weak acids with **pKa= 25** and it's impossible to be ionized under normal physiological conditions; **Phenols** instead are considered weak acids because the -ve charge on the O is stabilized by the conjugated benzene ring resonance; their **pKa=10**



4) Imidazole and pyrrole

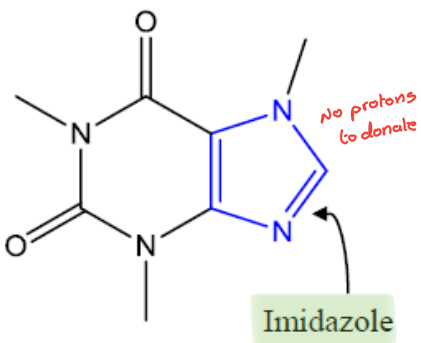
- Heterocyclic nitrogen structures such as in **Imidazole** group is also considered quite weak acid.



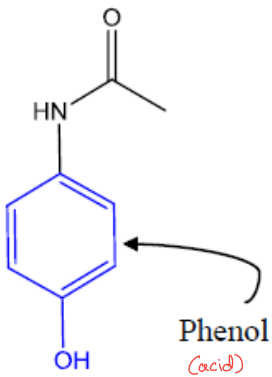


- So, we mentioned **Amides, Imides, Phenols and Imidazoles** as examples on functional groups which represent **weak acids.** Also, **Alcohols** are very weak acids.
- Therefore, if found in a chemical structure, it's expected to be unionized through GIT.

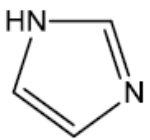
Caffeine



Paracetamol



Imidazole



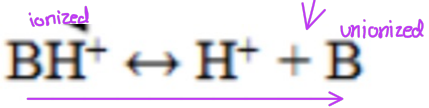
يعني إذا شفت واحد من هدول الاربعه موجود بتركيب الدواء هعرف إنو حمض ضعيف ما رح يتأين وانو سيتم امتصاصه جيدا

- What makes any chemical group basic is its ability to donate pair of unshared electrons.

Weak bases

Any F.G with a N

- Their **pKa is 1 or less**; they're completely the opposite of strong bases like guanidine or amidine which as we said their pKa is 12 or more.
- That means inside all the GIT (pH=1-8) the conditions are constantly basic shifting the equilibrium toward B therefore weak bases are permanently unionized across GIT and so they're better candidates for oral absorption.



*Note
EDG → ↑ basicity / ↓ Acidity
EWG → ↓ basicity / ↑ Acidity

weak bases

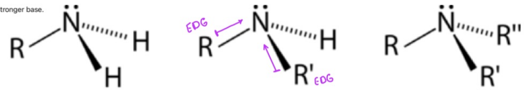
Aliphatic > Aromatic

Amines

intermedial base بشكل عام يعتبر

Amines are the most important basic functional group in most chemical structures, because its N is able to share pair of unshared electrons unlike O in case of alcohols, which has 2 pairs of unshared electrons but doesn't share them, because O is more electrophilic.

Higher pKa of the conjugate acid = stronger base.



primary amine < secondary amine > tertiary amine

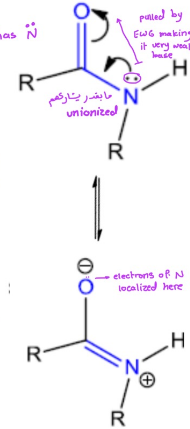
more basic (intermedit not weak)

طيب هاد عندو 3EDG ليه أكثر من 2 less basic?
الجواب: steric hindrance (more bulky less sharing capacity)

Amide

weak acid : has proton
weak base : has N

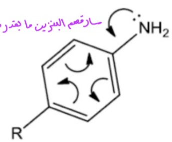
- **Amide** functional group have weak basic character! You may say it's a weak acid as we discussed before, when compared to carboxylic acids, BUT compared to amines, the amide's pair of electrons is less available for donation, and they're being withdrawn by the carbonyl.
- So, they're actually not available for donation because of resonance with the nearby carbonyl.
- So, Amides are also weak bases with **pKa 1 or less** therefore unionized in GIT.



aromatic amines

Aniline

(intermedial to weak)

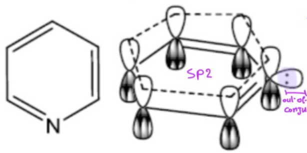


Aniline, the pair of electrons of the N enter the resonance of the benzene ring therefore weaker base than amines (pKa=9.5; moderate base); Aniline **pKa=5-6** and varies with substitution; it's considered a moderate base.

Pyridine

(intermedial to weak)

Sp3 easier to give lone pair than sp2

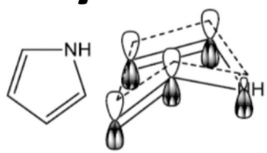


Pyridine, is also considered a moderate base with **pKa= 5-7**; when looking at the 3D structure you'll notice that the orbital of the pair of unshared electrons is out of the conjugated system and available for donation therefore considered bases, yet unlike amines' N with sp3 (s orbital is 1/4 of total sp3), while pyridine N is sp2 (s orbital is 1/3 of total sp2) therefore the pair of unshared electrons are closer to the N of pyridine and so less available for donation than amines; so pyridine (pKa=5-7) is weaker base than amines (pKa=9.5).

سؤال امتحان
① peripendicular عموديات
② sp2 : s → 1:3

Pyrrole

weak base

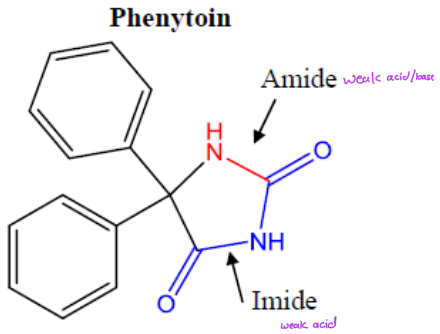


- **Pyrrole**, the N is sp3 hybridized. Yet, the pair of electrons are part of the aromatic ring conjugation, therefore not available for donation.
- So, pyrrole is a much weaker base; it's very weak and belong to the group of compound that's permanently unionized

أمثله Examples

١

- **Phenytoin** (antiepileptic) مضاد صرع
- Its structure contains both amide and imide functionalities. so it's both weak acid and weak base; phenytoin is totally absorbed, totally distributed, and can cross the blood brain barrier that is even tighter than GIT membrane.



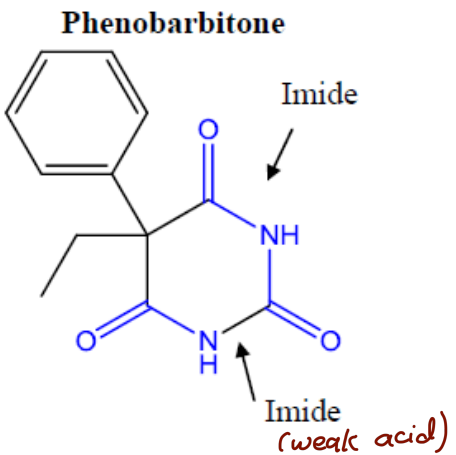
Examples

2

- **Phenobarbitone**
  - Very similar to phenytoin; its structure contains 2 imides; the N pair of electrons is being withdrawn by 2 carbonyl so it's a weak acid. Therefore, permanently unionized through GIT and gets absorbed readily.

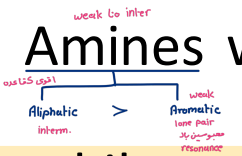
معلومة ★

N less likely to give it's H than O
bc: it's less electronegative



To summarize

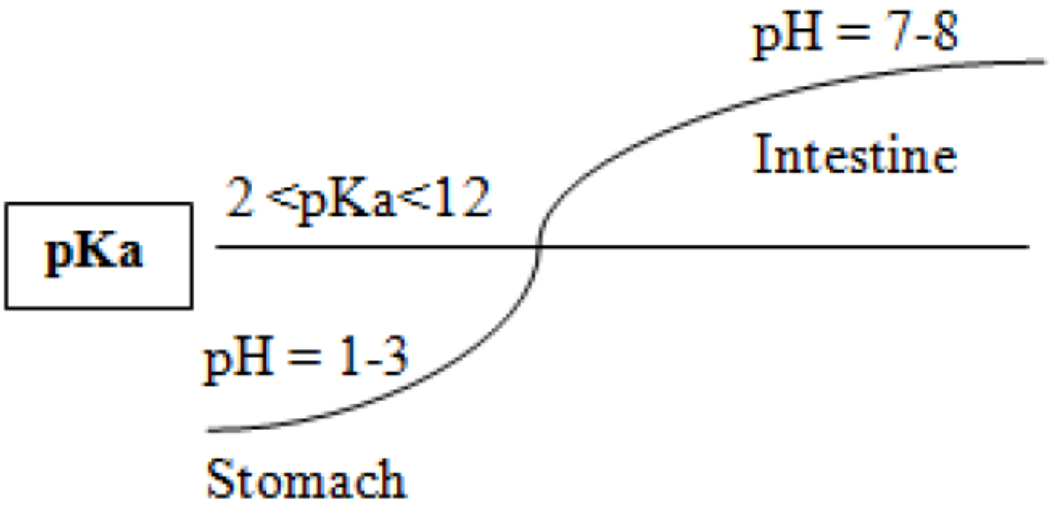
- So far, we have discussed the following:
- - Strong bases: Guanidine and Amidine.
- - Weak acids: Amides, Imides, Phenols and Imidazole.
- - Weak bases : Amides, Imides and aniline.
- - Moderate bases: Aniline, Pyridine and Amines were discussed for comparison.



- Strong acids are totally not absorbed while strong bases have some absorption, due to the presence of mucin; weak acids and bases are totally unionized therefore are good candidates for absorption taking in concern the other factors that will be discussed later.

Intermediate acids and bases

pka: 2 – 12



Moderate acids and bases

Intermediate acids

In the stomach

In the stomach, conditions are acidic. Which means that the equilibrium is shifted toward HA therefore they're unionized and absorbed.

- Nevertheless, major absorption (50%) happens in the stomach, absorption isn't complete because the stomach is not designed for absorption itself:

1. It has small surface area,
2. Short transient time (around 6 hours)
3. Less blood supply compared to intestine which has large surface area, long transient time (around 12 hours) and highly vascularized.

- Under stomach conditions (acidic conditions), intermediate acids are unionized (HA) while in intestines (basic conditions) are ionized (A-). That's why nearly 50% of the administered dose is being absorbed in stomach even though transient time is short (around 3-6 hours) in stomach, on the other hand in intestines only 15% are absorbed

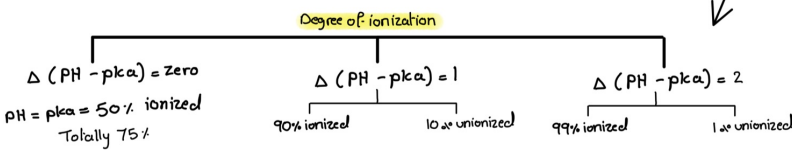
in intestines

On the other hand, conditions are basic in the intestines. So, the equilibrium is shifted toward A-. Therefore, minimal absorption happens.

- Through intestines even though it's mostly ionized because ionization is in equilibrium between HA and A- not absolute and a fraction of unionized form is always present (if pH=pKa then 50% is ionized; if pH>Pka with 1 unit then 90% is ionized and 10% unionized); intestines have:

1. large surface area
2. long transient time (around 12 hours).
3. Very good blood supply which aid in absorption. Eventually intermediate acids are

- approximately 60-75% absorbed provided that they satisfy Lipinski's rule of 5 which we'll discuss later on.



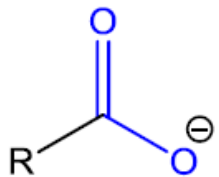
two groups

Functional groups that make drugs of intermediate acid character

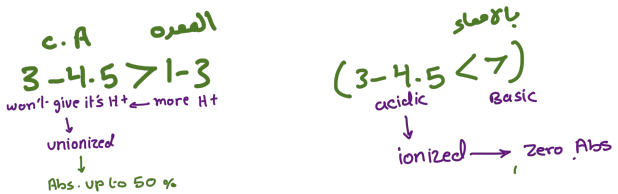
① Carboxylic acid

if present with EWG become strong acid

pKa = 3-4.5

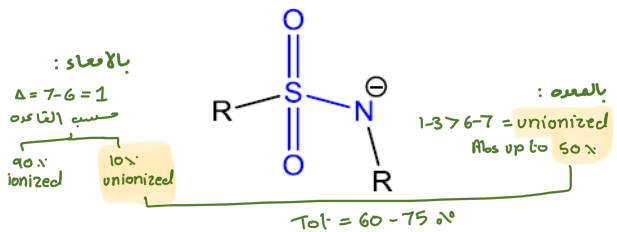


Carboxylic acid with **pKa=3-4.5** depending on the substitution if it's attached to an electron withdrawing group it becomes more acidic while if it's attached to electron donating group it becomes less acidic



② Sulfonamides (without EWD)

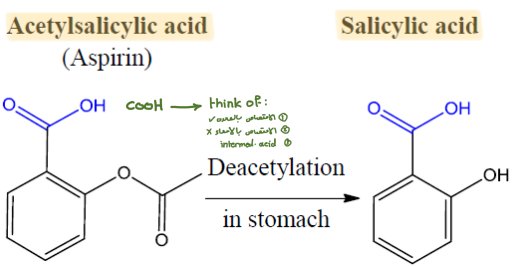
pKa = 6-7

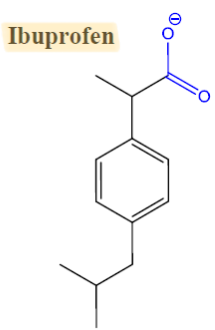


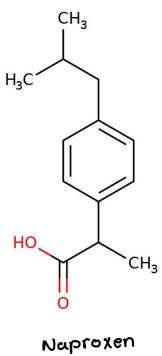
Sulfonamide, you remember from the previous lecture if the R group is an electron withdrawing group, then it will become strong acid as in case of Saccharin but Sulfonamides without having an electron withdrawing group on R their **Pka=6-7** they're intermediate acidic therefore they're unionized in the stomach and in the intestine is ionized on the N.

EXAMPLES

- Drugs containing carboxylic acid like **salicylic acid** which is a non-steroidal anti-inflammatory drug NSAID when attached to acetyl group it becomes **acetylsalicylic acid** which is found in **Aspirin,** an anti inflammatory, used as analgesic, and as antiplatelet. In fact, all the family of NSAIDs are characterized by the presence of aromatic ring attached with a carboxylic acid. Therefore, if you attach a carboxylic acid with an aromatic ring in any configuration, you'll form an NSAID, such as **ibuprofen**.





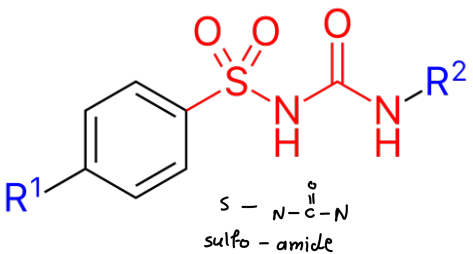


pka (6-7) — Abs in the stomach; minimal Abs in the instine

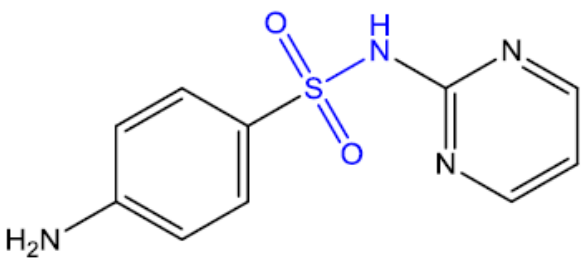
(2)

- Drugs containing sulfonamides are usually used as antibacterial agents. However, some sulfonamide drugs are used as anti-diabetics (Sulfonylurea (السكري): pKa ~ 3.8-6), anti cancer agents and diuretics (Thiazides: pKa ~ 6.8-9.8).
- Example of antibacterial agent: **Sulfadiazine**.

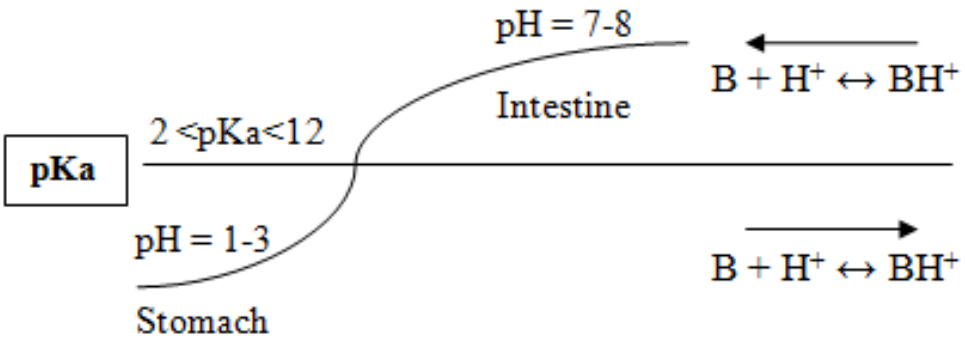
Sulfonylurea



Sulfadiazine



Intermediate bases



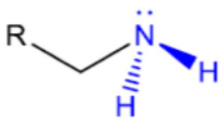
Intermediate bases

Intermediate bases have **ZERO** absorption in stomach, however significant absorption happen in the intestine provided that the compound satisfies Lipinski's rule of 5 because drugs are unionized and the intestines have long transient time, large surface area and very good blood supply so it's well designed for absorption, can reach 100% absorption.

Groups which make drugs with intermediate basic character,

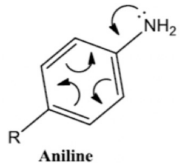
Amines

- most importantly are **Amines** which in fact are benchmark for organic bases; their **pKa=9-9.5**



Amine

Aniline

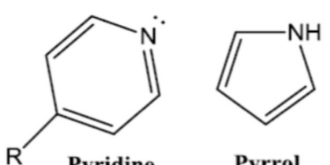


Aniline

- follow amines in order are **aromatic amines** like **Aniline**, they're weaker bases because their pair of electrons are involved in the aromatic system resonance and their **pKa= 5-7**

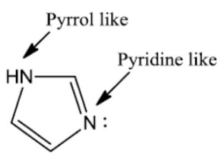
Pyridines

- **Pyridines** are weak bases with heterocyclic nitrogen discussed previously and we said that the pairs of electrons are not involved in the aromatic ring yet they're sp2 hybridized so electrons are closer to nucleus **pKa=5-6**



Pyridine **Pyrrol**

Imidazole



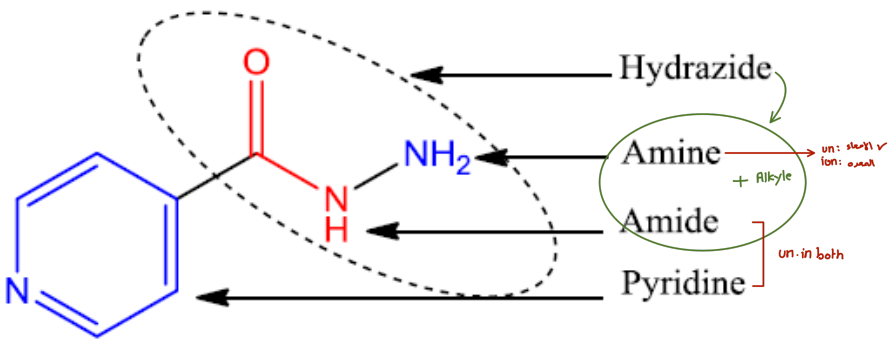
Imidazole

- Other heterocyclic compounds like **Imidazole** one of its N is pyridine like while the other is pyrrole like with the electrons being involved within the ring. So, they are not available for donation which makes pyrrole very weak base.
- It's very weak and belong to the group of compound that's permanently unionized.

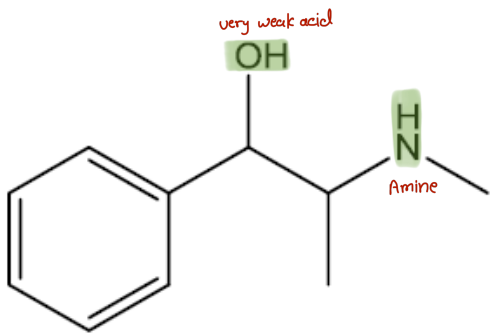
Intermediate Bases: Examples

Isoniazide (for tuberculosis)
contains pyridine N and hydrazide function (consecutive N attached to a carbonyl) containing amide which is a weak base, and an amine which is an intermediate base. Therefore, Isoniazide is a drug administered orally and well absorb in the intestine for sure.

Other drugs are like **ephedrine**, **pseudoephedrine** and **natural alkaloids** all of them are amine containing compounds and absorbed in the intestines



Isoniazide

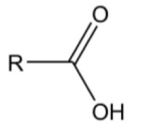


Ephedrine

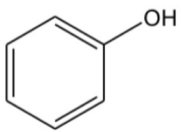
↓

Abs في الأمعاء

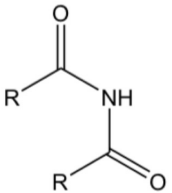
Common acidic functional groups in pharmaceutical chemistry and their pKa values



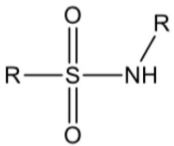
4-5 **Carboxylic acid**



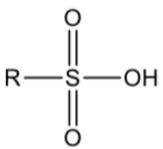
9.9 **Phenols**



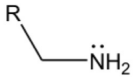
8-10 **Imides**



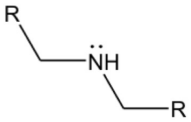
10 **Sulfonamind**



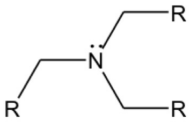
<2 **Sulfonic acid**



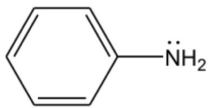
9.5
10.0 **Primary amine**



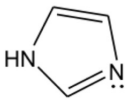
11
10.6-11.0 **Secondary amine**



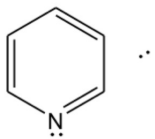
10-10.5
9.8-10.8 **Tertiary anime**



4.6 **Aniline**



6.5 **Pyridine**



5.2 **Imidazole**

Remember the followings

For acids:

1. *a high pka* means the species is predominantly unionised, is a bad proton donor, and a weak acid

2. *a low pka* means the species is predominantly ionised, is a good proton donor, and a strong acid

pH < pKa by 2 units, 99% unionised

pH > pKa by 2 units, 99% ionised

For bases:

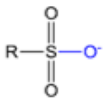
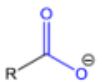
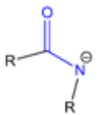
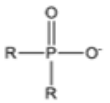
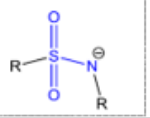
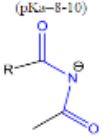
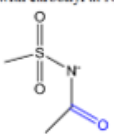
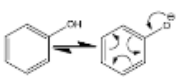
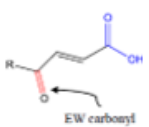
1. *a high pka* means the species is predominantly ionised, is a good proton acceptor, and a strong base

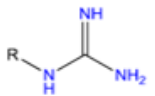
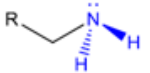
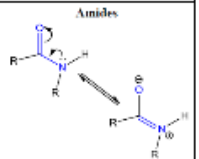
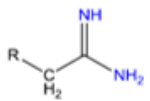
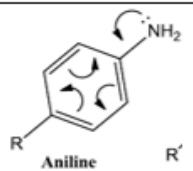
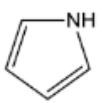
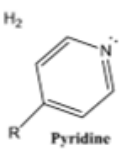
2. *a low pka* means the species is predominantly unionised, is a bad proton acceptor, and a weak base

pH < pKa by 2 units, 99% ionised

pH > pKa by 2 units, 99% unionised

Summary

Strong acids	Intermediate acids	Weak acids
Sulfonic acid 	**Carboxylic acid** (conjugated to EWD) 	**Amides** (pKa≥12) 
Phosphoric acid 	**Sulfonamides** (without EWD) 	**Imides** (pKa~8-10) 
Sulfonamides (with carbonyl at N) 		**Phenols** (pKa=17) 
Carboxylic acid (conjugated to EWD) 		**Imidazole**  and pyrrole

Strong bases	Intermediate bases	Weak bases
Guanidine 	 **Amine**	**Amides** 
Amidine 	 **Aniline** R′	 **Pyrrole**
	 **Pyridine**	
	Imidazole and pyrrole