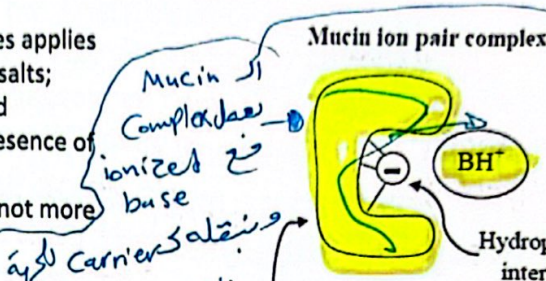
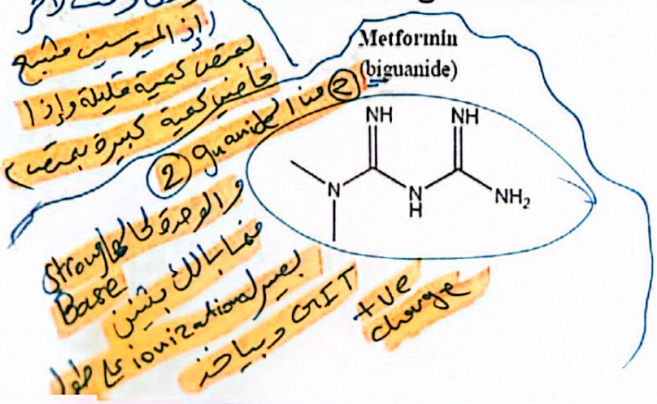
- So, both Guanidine and Amidine if they were found in a chemical structure we can conclude that this structure is permanently cationic (+vely charged) through all the GIT, therefore we expect them to be not available for absorption **BUT** that's not the case,
- **Strong bases actually are of poor bioavailability,** unlike strong acids which are completely not available for absorption This poor bioavailability of strong bases is due to the presence of **Mucin** which is a hydrophobic protein produced by GIT cells bearing a -ve charge on its interior while its exterior is hydrophobic therefore it's able to form complexes with the +vely charged bases forming **ion-pair complexes** protecting them from water and they're hydrophobic enough to cross the GIT cellular membrane.

What applies to strong bases applies for quaternary ammonium salts; they're permanently ionized however because of the presence of mucin we do have some bioavailability however it's not more than 40%.

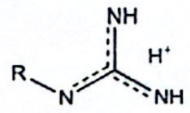


- **EXAMPLES**
- **Metformin** (diabetic medication) its trade name is Glucophage ® ; it has biguanide groups in its structure so it's a strong base with pKa 12 yet it's administered orally!
- It is given in high doses and the physician needs time adjusting the dose for a particular patient due to its **erratic** bioavailability as the presence of biguanide groups make it permanently ionized and permanently +vely charged as well as variation in the amount of mucin among individuals

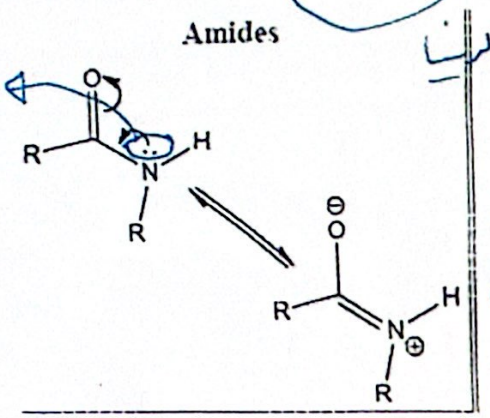


Side note...

The proton in strong bases rotate among the basic groups and so called tautomerism which is best drawn as below structure:



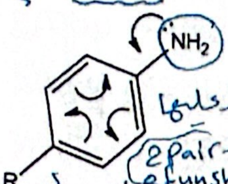
- Some functional groups with weak basic character are
- **Amides**. You may say it's a weak acid as we discussed
- previously when compared to carboxylic acids. BUT
- compared to amines, the amide's pair of electrons is
- unavailable for donation and they're being withdrawn by the carbonyl so they're 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.



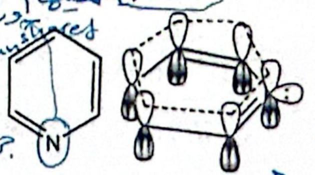
Other weak bases are aromatic amines

such as:

Anilines



Pyridine



- **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.

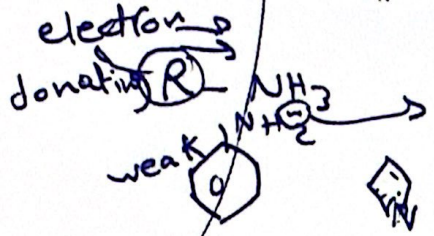
- **Pyridine**, is also considered a moderate base with **pKa= 5-7**; when looking at the 3D structure you'll notice that the orbital of the pair unshared electrons is out of the conjugated system and available for donation therefore considered bases, yet unlike amines' N with sp3 (s orbital is 1/4 of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

Other weak bases are aromatic amines

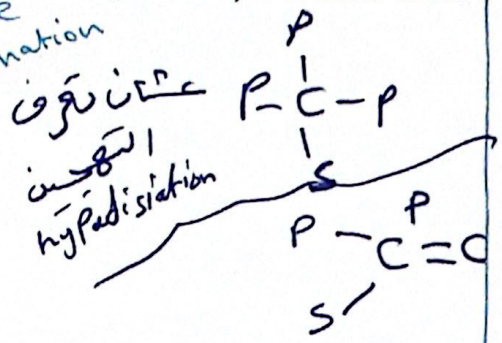
such as:

- **Pyrrol** the N is sp3 hybridized yet 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).



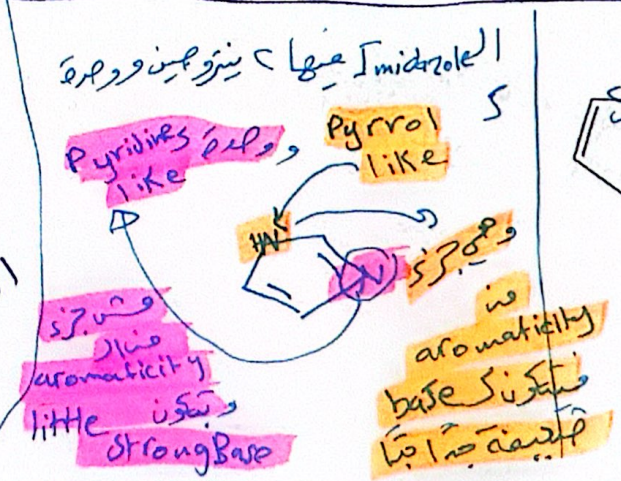
available for donation

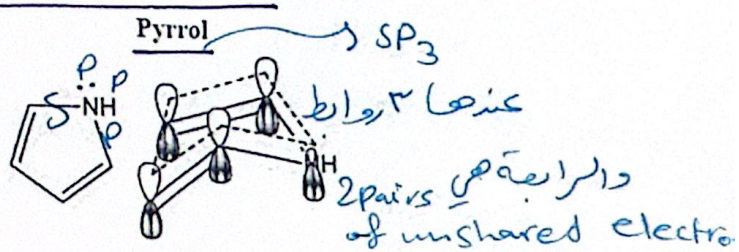


Pyridine ال *
(N)
Pyridine like
(N)
both of them not available for donation during acid - Base reaction
So, it consider weak or moderate Base

Other weak bases are aromatic amines such as:

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





ويتم مقارنتها

* لعبه بلايه الـ Pyrrol اقرأ واهار.

- احنا درسنا الـ pyridine هي aromatic ring وعليها (N) والـ Pyrrol هي aromatic ring وفيها (N)

pyridine → SP_2	Pyrrol → SP_3
من ناحية التهجين 2 pairs of unshared electron موجود في orbital خارجي	2pairs of unshared electron هون جزء من الـ aromaticity
فهو بين المتوسط الضعيف والأقوى كقاعدة من الـ Pyrrol لأنه	لأنه يعمل 2double Bon تشبههم 2pairs of un shared حتى يصير aromaticity كاملة.
2pairs فما بكون مكتفية aromaticity جزء من الـ aromaticity	ولأنهم جزء من الـ aromaticity 2pairs الـ فوقه مش متاحين للـ donation فهو very Weak Base.

Amazing

Weak bases

- 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.

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 absorbtivity 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 discussed later on.

TABLE 6-1 Values of K_a and pK_a for Various Acids[a]

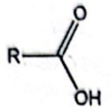
Acid	Conjugate Base	K_a	pK_a
Trifluoromethanesulfonic acid		1×10^{13}	−13
Sulfuric acid		1×10^{3}	−9
Hydrochloric acid	Cl^-	1×10^{7}	−7
Hydronium ion	H_2O	55	−1.7
Trichloroethanoic acid (Trichloroacetic acid)		0.17	0.77
Hydrofluoric acid	F^-	6.3×10^{-4}	3.2
Benzoic acid		6.3×10^{-5}	4.2
Ethanoic acid (Acetic acid)		1.8×10^{-5}	4.75
Hydrogen sulfide	HS^-	6.3×10^{-8}	7.2
Ammonium ion	NH_3	4×10^{-10}	9.4
Phenol		1×10^{-10}	10.0
Methylammonium ion	H_3C-NH_2	2.3×10^{-11}	10.63
2,2,2-Trifluoroethanol		4×10^{-13}	12.4
2-Chloroethanol		1.3×10^{-14}	12.9

Acid	Conjugate Base	K_a	pK_a
Methanol	CH_3O^-	3.2×10^{-16}	15.5
Water	HO^-	2×10^{-16}	15.7
Ethanol		1×10^{-16}	16
Propan-2-ol (Isopropyl alcohol)		3.2×10^{-17}	16.5
Methylpropan-2-ol (tert-butyl alcohol)		1×10^{-19}	19
Propanone (Acetone)		1×10^{-20}	20
Ethyne (Acetylene)	$HC \equiv C^-$	1×10^{-25}	25
Aniline (Phenylamine)		1×10^{-27}	27
Hydrogen gas	H^-	1×10^{-35}	35
N-Methylmethanamine (Dimethylamine)		1×10^{-38}	38
Ethene (Ethylene)	$H_2C=CH^-$	1×10^{-44}	44
Ethoxyethane (Diethyl ether)		$\sim 1 \times 10^{-45}$	~45
Methane	H_3C^-	1×10^{-48}	48
Ethane	$CH_3CH_2^-$	1×10^{-50}	50

very strong acid

very weak Base

Common acidic functional groups in pharmaceutical chemistry and their pKa values



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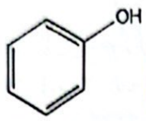

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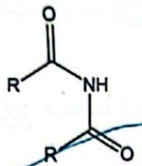
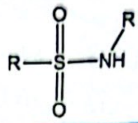


8-10



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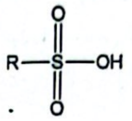

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Remember the followings

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