* محاضرة (٣) منار الشربجي.

* الأحماض الضعيفة ال PKa لهم أعلى من ⑩ زي ١٢ وفوق.

- لا حدا يخربط إذا PKa = 12 يعني base (انتباه)

- الحمض مركب قادر على إعطاء ال H^+، مثال: عندي كحول R-OH عنده القدرة على إعطاء (H) لكن بأنه صعب وال PKa اله عالية لكن مش معناها إنه (فقدانه (H) صعب بالتالي)

تحول القاعدة بسبب ارتفاع PKa وهو يعتبر حمض لكن ضعيف والكحولات بالحقيقة ال PKa الها ~50 بس لا تفقد الهيدروجين إطلاقاً.

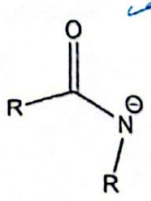
- الأحماض الضعيفة هي مركبات ال PKa=14 يعني حبة الدواء بس تعرض المعدة اللي PH الها ٢ ومرورها للأمعاء ال PH الها طول الأمعاء ال PH 8 تبعها منخفضة / لما PH أقل من PKa معناها الدنيا حامضية :
يعني (حمض PKa العالي شاف الدنيا حامضية بس ما يتأين) وال bioavailability العالية إذا استوفى شرط الثاني لل permeation

Weak acids

- 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 on
- such as optimal hydrophilic/hydrophobic properties represented by lipinski's rule of 5. (we will discuss it later on)
- 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

- **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**



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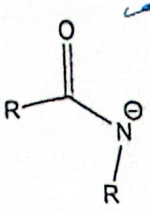
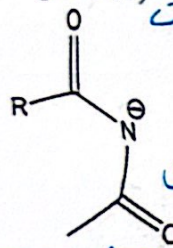
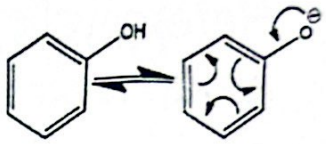


Weak acids

Imides (pKa=8-10)



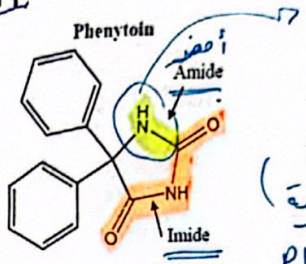
Phenols (pKa=17)



- **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.
- **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**

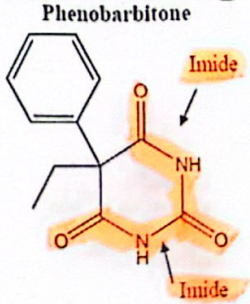
Examples

- **Phenytoin** (antiepileptic)
- 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.



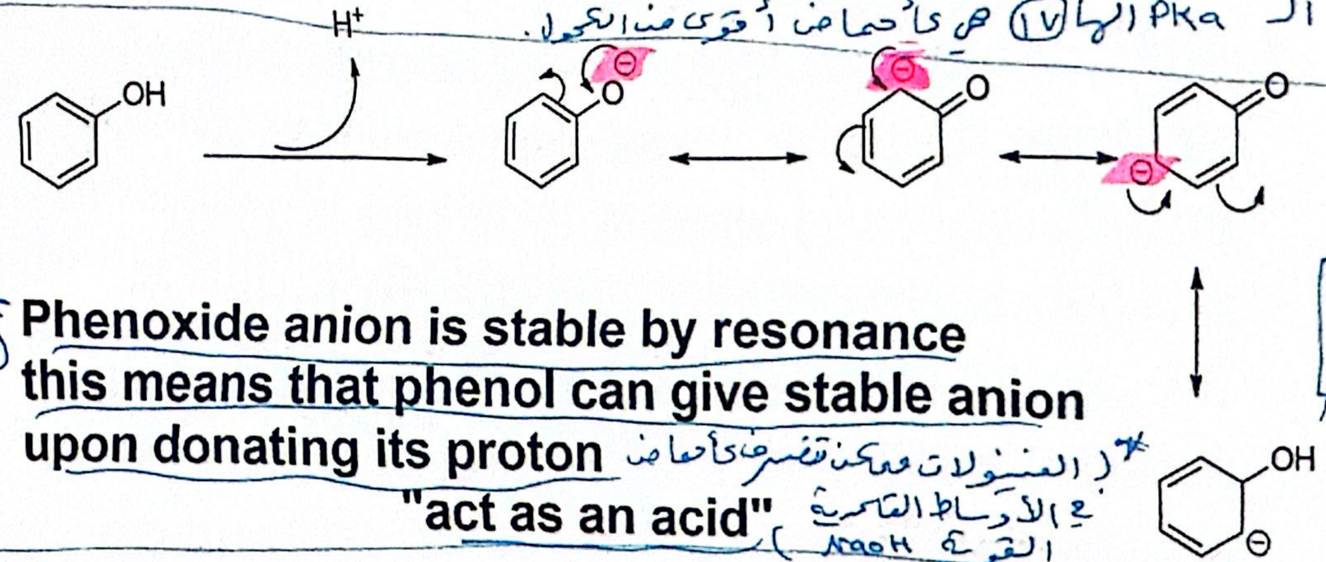
Examples

- **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.



+ ٤ هاي حالة دوران الإلكترونات بهاي الطريقة ع الشحنة السالبة اللي على الـ Phenoxide حتعطي stability
by resonance هاد سبب وتفسير الفينولات بتتأين أما الاكحولات لا..

١ * الـ Phenol أقوى كأحماض من الكحولات Alcohol (R-OH) لا يتأين نهائياً ولكن الفينول
الـ PKa الها ١٧ هي كأحماض أقوى من الكحول.



* Phenoxide anion is stable by resonance
this means that phenol can give stable anion
upon donating its proton
"act as an acid"

* (الفينولات ممكن تتصرف كأحماض في الأوساط القاعدية القوية ع NaOH)

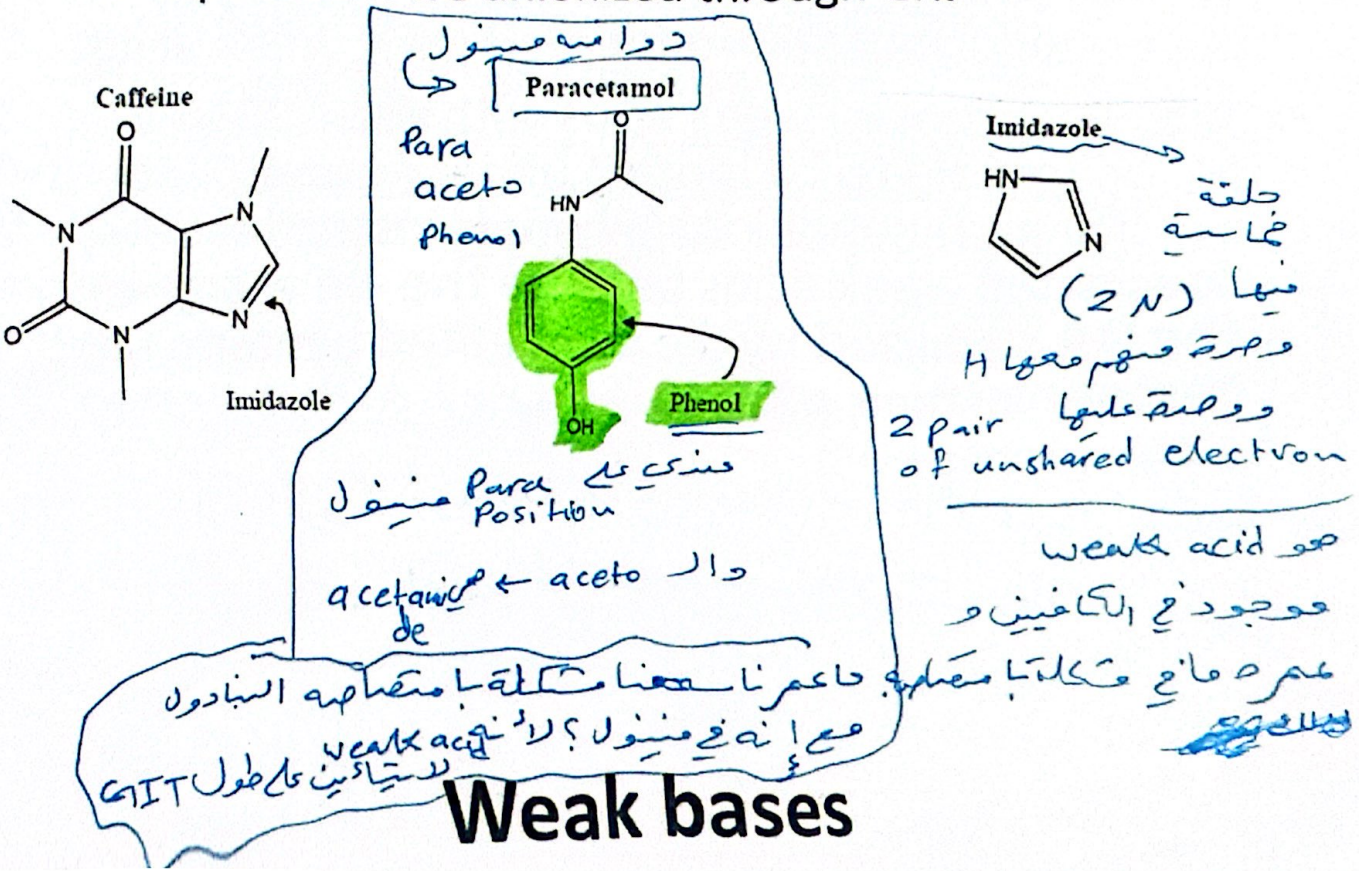
* (الكحولات حتى ع NaOH لا تتصرف كأحماض)

اقرأ أولاً الشرح عالترقيم

٢ يعني لو جبت الفينول وحطيته NaOH ، تتكون الأيون ، لكن إذا جبت أي كحول وحطيته NaOH
ما رح يتأين بوجود Strong base.

٣ سؤال: ليش عمل مجموعة الـ (OH) الهيدروكسيل الموجودة على aromatic ring متأينة في حين
مجموعة الـ OH الموجودة على Aliphateic Alcohol غير متأينة؟؟؟ هوا الـ stability تبعت الأيون اللي بيتكون
اللي هو الـ (Phenoxide) ، فكرتنا HA ⇌ A⁻ + H⁺ فالـ A⁻ بتمثل الـ Phenoxide ففي حالة الفينول فتكون
stable لأنو صار عليها Resonance ، تكملة ...

- Heterocyclic nitrogen structures such as in **Imidazole** group is also considered quite weak acid.
- So we mentioned as examples on functional groups
- which represent weak acids are Amides, Imides, Phenols and Imidazoles, also Alcohols which are very weak acids; therefore if found in a chemical structure
- it's expected to be unionized through GIT.



Weak bases

* متى يكون المركب قاعدي ؟ لما يكون عنده القدرة على إعطاء 2Pairs of unshared electron

What is a basic compound

- What makes any chemical group basic is its ability to donate pair of unshared electrons; **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 it don't share them because O is more electrophilic.

{ أهمهم الأمينات

في شرح عالفترالهاي السلايد بعدها

محاضرة ٣ تكملة من ال base هلاء:

*أشهر قاعدة هي الأمونيا NH_3 وعلى 2 pair of unshared electron وعليها 3 H

*عنا strong base و weak base و intermediate base ال 6 لقدر يعطي strong base 2 pair unshared of (e)

بشكل كبير وال PKa لل strong base = 14 أو أكثر فكلما زادت القاعدة أقوى

فال PKa إلها أقل. القاعدة المتوسطة ال PKa إلها (10 – 7) = PKa

weak base ال PKa إلها تحت السبعة (7) القاعدة ضعيفة مو قادرة تعطي few pairs unshared electron فمش عندها تجمع لأنه القاعدة ما بتتحول لضعف

*القاعدة القوية اللي PKa = 14 لما تتواجد في الجهاز الهضمي شو بصير (الجهاز الهضمي بيلش من المعدة PKa = 2 للأمعاء PH = 8)

فنشا نية الدنيا PH أقل من PKa يعني ١٢ في الدنيا (حمضية)

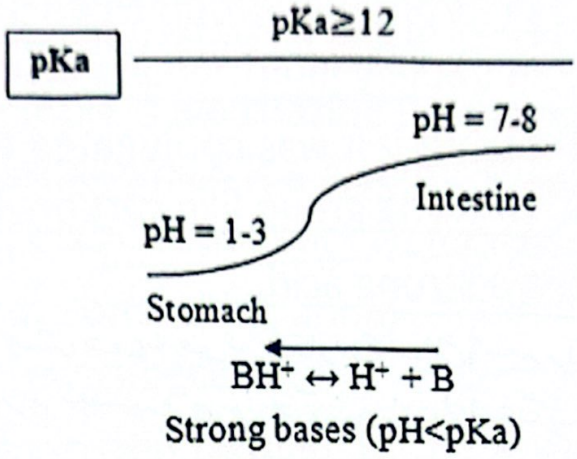
يعني base وين ما عنا الدنيا حامضية فحتكون (ionized) على طول GIT

فالمفروض ما تنمتص لأنها ionized وعلى طول GIT ما بتم امتصاصهم زي القواعد القوية، لكن بعض الأدوية فيها زي strong base التي تتواجد بالإسكان ويتم امتصاصها

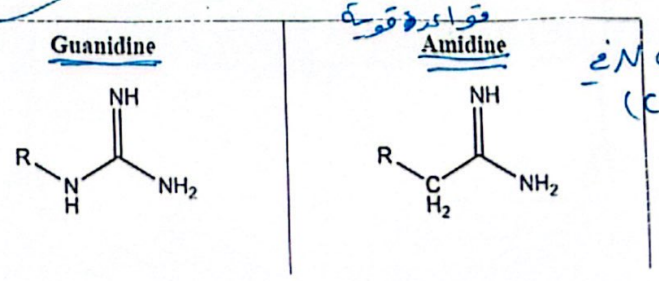
Strong bases...

- Strong bases have high **pKa 12**; in GIT
- (pH=1-8) the conditions are continuously acidic and the reaction is shifted toward BH+, as previously said, in order for a compound to be absorbed it has to be unionized but strong bases are permanently +vely ionized through GIT.

Absorption of strong bases

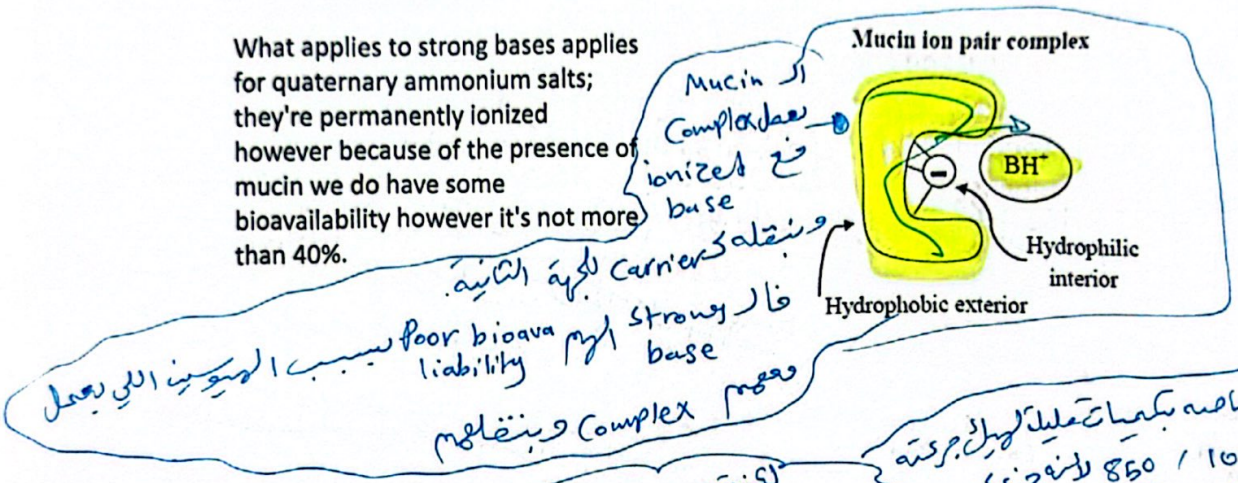


- There are some functional groups if found in a chemical structure they indicate that this structure is permanently +vely charged during passage of GIT; most important ones are
- **Guanidine** and **Amidine** both with pKa 12.



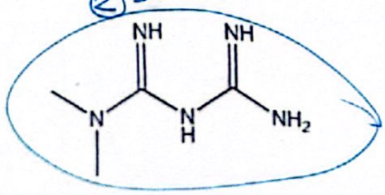
- So, both Guanidine and Amidine if they were found in a chemical structure we can conclude that this structure is permanently cationic (+vely charged) through all the GIT, therefore we expect them to be not available for absorption **BUT** that's not the case,
- **Strong bases actually are of poor bioavailability,** 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

Metformin
(biguanide)



Side note...

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