Revised Third Edition

Medicinal Chemistry

Alaa malkawi

3. **Permeation** by partitioning (major)

The 3rd route of absorption

- Permeation is to cross the membrane by dissolving in the phospholipid bilayer in a process called **partitioning**.

يعني التوزع ← الدواء بين الحالة المائية والدهنية عشان هيك لازم يكون Balanced عنا Hydrophilic & Phobic Properties حتى يوصل بالأخير للدورة الدموية

- If a drug has optimal hydrophilic/hydrophobic properties, then the drug can partition itself and dissolve in both phases (water and oil) to certain limit. After dissolving in water outside the cell it starts to partition in both phases, and then after saturating the oil phase (phospholipid bilayer) it starts to partition toward the other water phase inside the cell.

diffusion

3. Permeation by partitioning (major)

الدوا خارج الخلية رح يدوب بالوسط المائي بعدين يصير له Partitioning وينتقل لداخل الخلية بعدين للخارج مرة اخرى

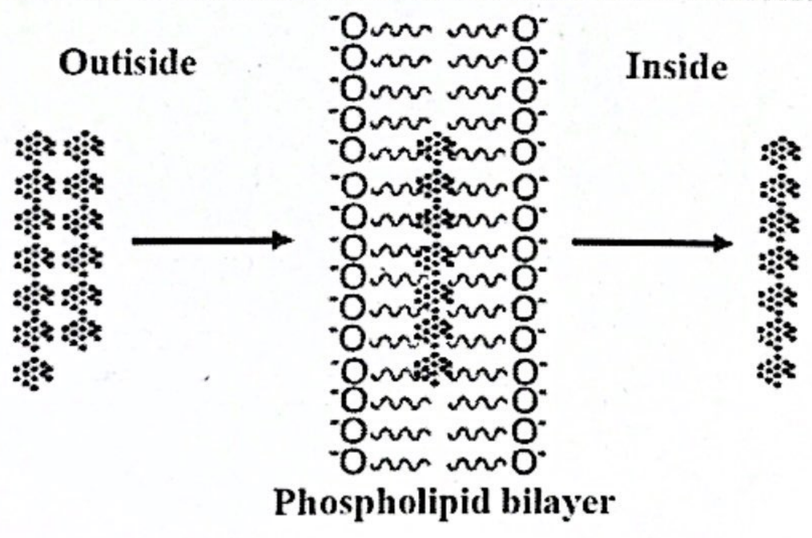
In order for partitioning to occur, 2 conditions must exist:

a. The drug must be unionized

If it was ionized: the +vely charged drug will be adsorbed to the -vely charged phospholipid bilayer heads; while repulsion between -vely charged drugs and the –vely charged phospholipid bilayer heads. Also the charge will make the drug hydrophilic therefore insoluble in the lipid bilayer.

b. The drug must have optimal Hydrophilic/Hydrophobic properties

In order to get partitioned between water and fatty layers.



strong acid → يتأين تماماً عنده قدره عاليه على اعطاء البروتون

$HA \rightarrow H^+ + A^-$

↙ اتجاه واحد للسرهم

يلي بحدد قوة قوه الحمض او قدرته على التأين

$pKa = -\log ka$ هوه ال pKa

النواتج $= \frac{[A^-][H]^+}{[HA]}$ المتفاعلات

* كل دواء اله pKa محددة *

احنا بندرس ال diffusion واشترطنا حتى يصير عنا diffusion يكون الدوا unionized

acid in acidic conditions ← unionized يكون حتى

Base in Basic conditions

* عشان يصير عنا Ionization (تيأين)

الدوا يجب ان يشعر ان محيطه مخالف لطبيعته

stomech بال pKa=2 ← strong acid عنا هاد

↳ which is acidic PH = 3 → PH > pka

This acid is stronge enough = حتى

يشوف انو الوسط اللي فيه PH=3 وسط قاعدي ويصيرله

↳ Ionization

* صيغة الدوا بتأين بشكل كامل بال stomech

intestine

stronge acid can't be absorbed *

كمان هون $AH \rightarrow A^- + H^+$

* هون شايف الوسط Basic يعني H^+ قليلة فرح يضل يضغ عليه H^+ (Basic $\rightarrow$ H^+ منخفض)

يعني رح يضل يتأين حتى يصير عنا Complete Ionization

Acid drug in acidic environment : non ionised [HA] = absorbed
Acid drug in basic environment : ionised [A-] = cleared
Base drug in acidic environment : ionised [BH+] = cleared
Base drug in basic envioronment : non ionised [B] = absorbed

- **Drug ionization**
- We can classify the drugs found in pharmacopeia according to ionization to 3 classes:

* بنقسمهوا (S/I/W) حسب قدرتهم على التأين

- 1. Strong acids and bases. → بتأين بسهولة
- 2. Weak acids and bases. → مابتأين
- 3. Intermediate acids and bases. بسهوله

2 factors affect the ionization of the drug? [1] pka
[2] PH of the media

لـ الجزء الي اله pka محددة رح يتصرف بالمعدة (which is acidic) بطريقة مختلفة عن intestine (which is basic)

حسب برونستد لوري
الماده القادره على اعطاء بروتون: Acid

$$HA \rightarrow A^- + H^+$$

Base: ماده قادرة على استقبال البروتون

$$NH_3 \rightarrow NH_4^+ + H^-$$

- **Strong acids and bases**
- **Strong acids...**
- Their **pKa is 2 or less**, and the stomach pH= ~~1-3~~ 3 while intestine pH= ~~7-8~~ 7-8; the pH through all the GIT is higher than the pKa which represents basic conditions for this strong acid shifting the equilibrium toward A- side, therefore it will be ionized through all the GIT and its ionization accounts for high hydrophilicity making it unavailable for absorption through oral route.

- **EXAMPLES**
- **Sulfonic acid group** pKa<1 so it's always ionized and we expect the drug carrying sulfonic acid group to be totally ionized through the GIT therefore orally unavailable.

مابتاخده ← orally

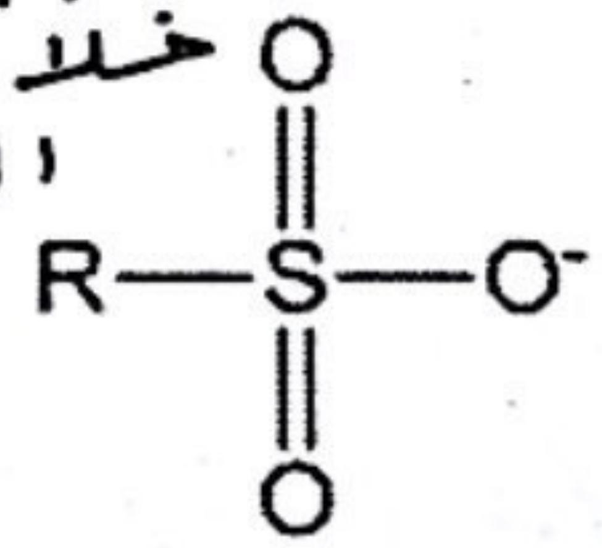
* مو موجود *

Summary examples on strong acids expected to be orally not available

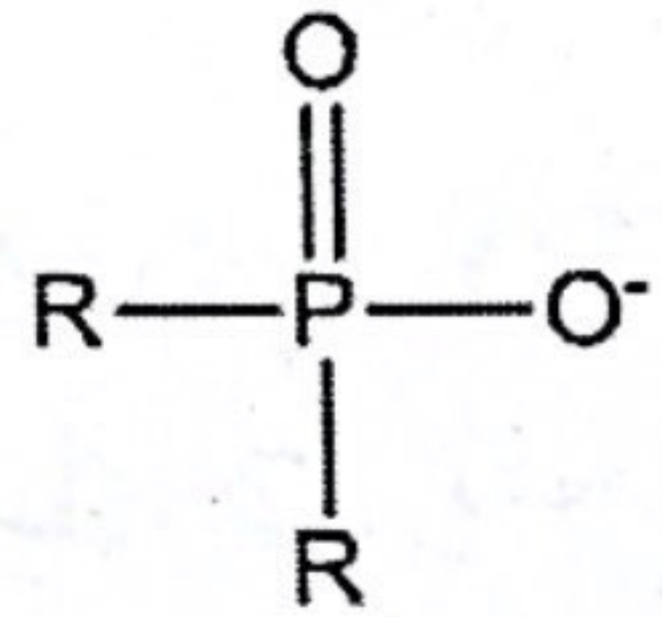
اذا كانت ← على اي مركب **Sulfonic acid** مستحيل تتم امتصاصه بسبب تأيّنه الكامل خلال جميع اجزاء ال GI

pKa < 1

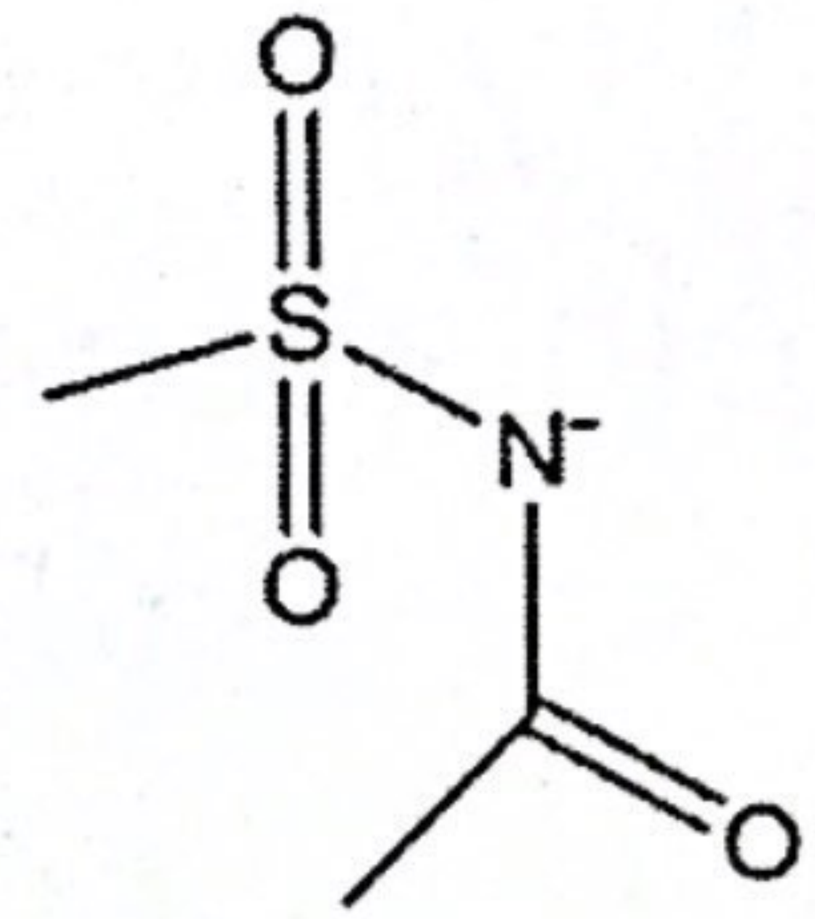
will not be absorbed



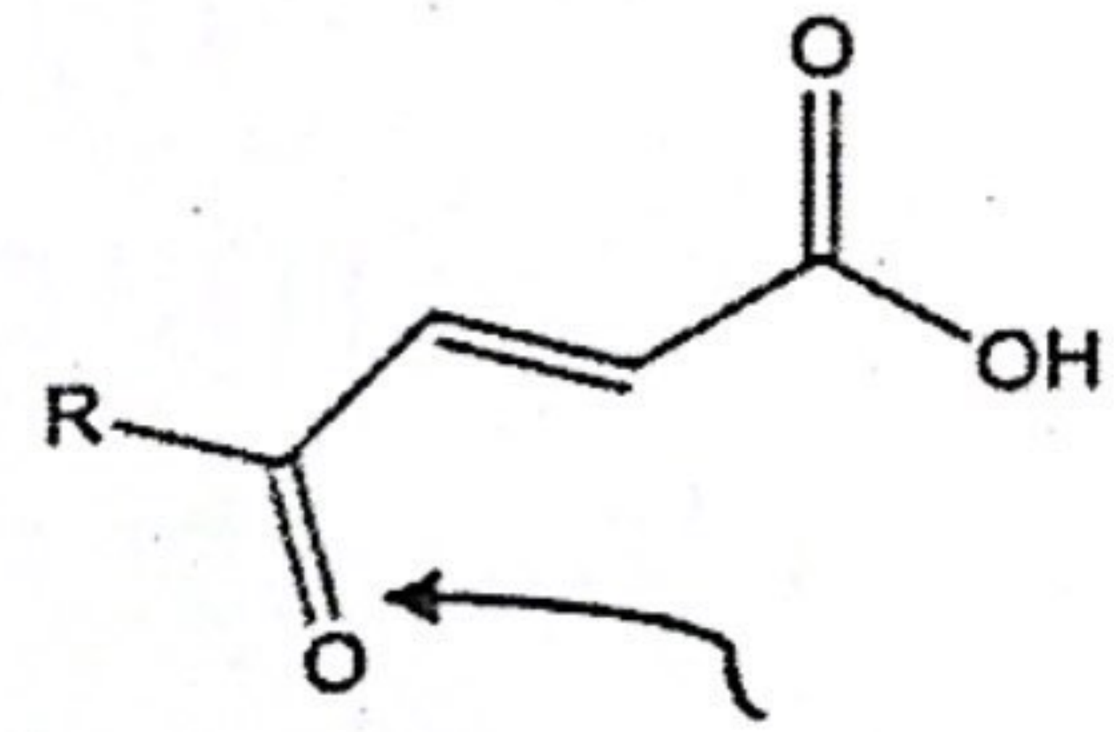
Phosphoric acid



Sulfonamides (with carbonyl at N)

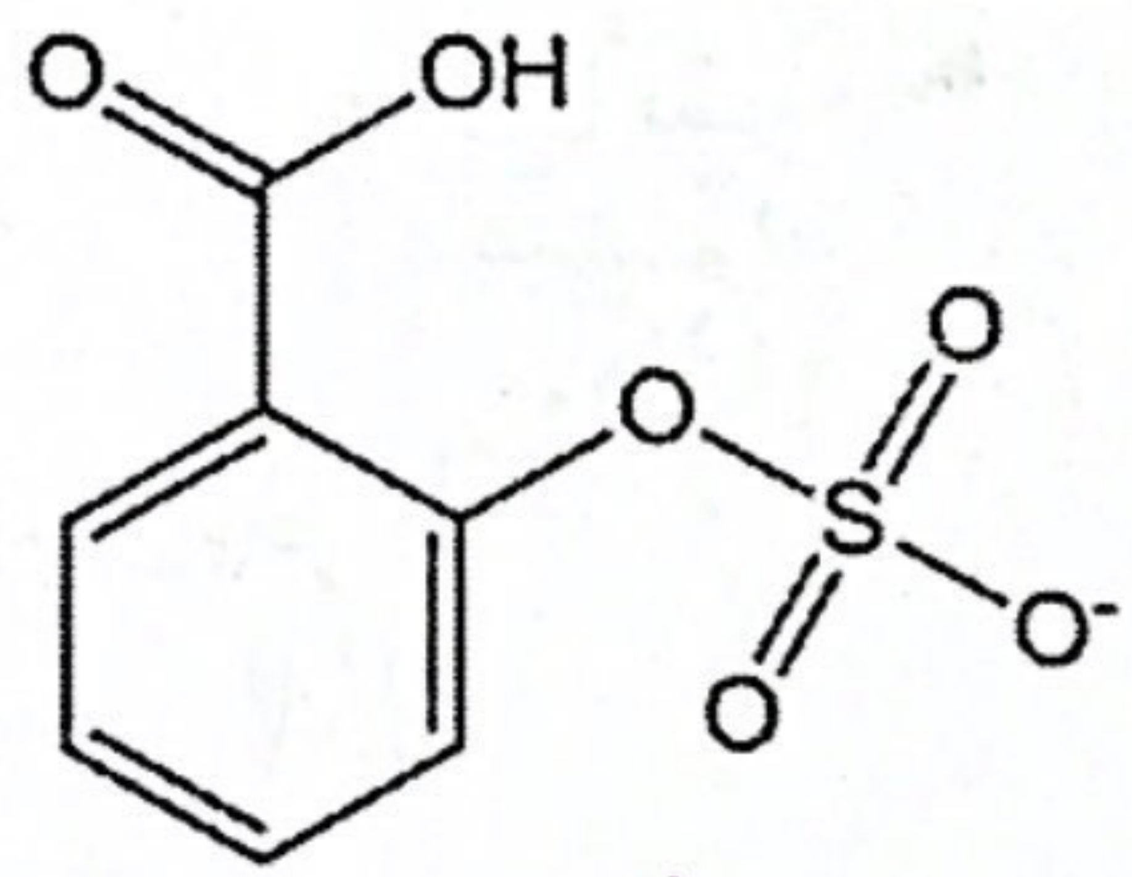


Carboxylic acid (conjugated to EWD)

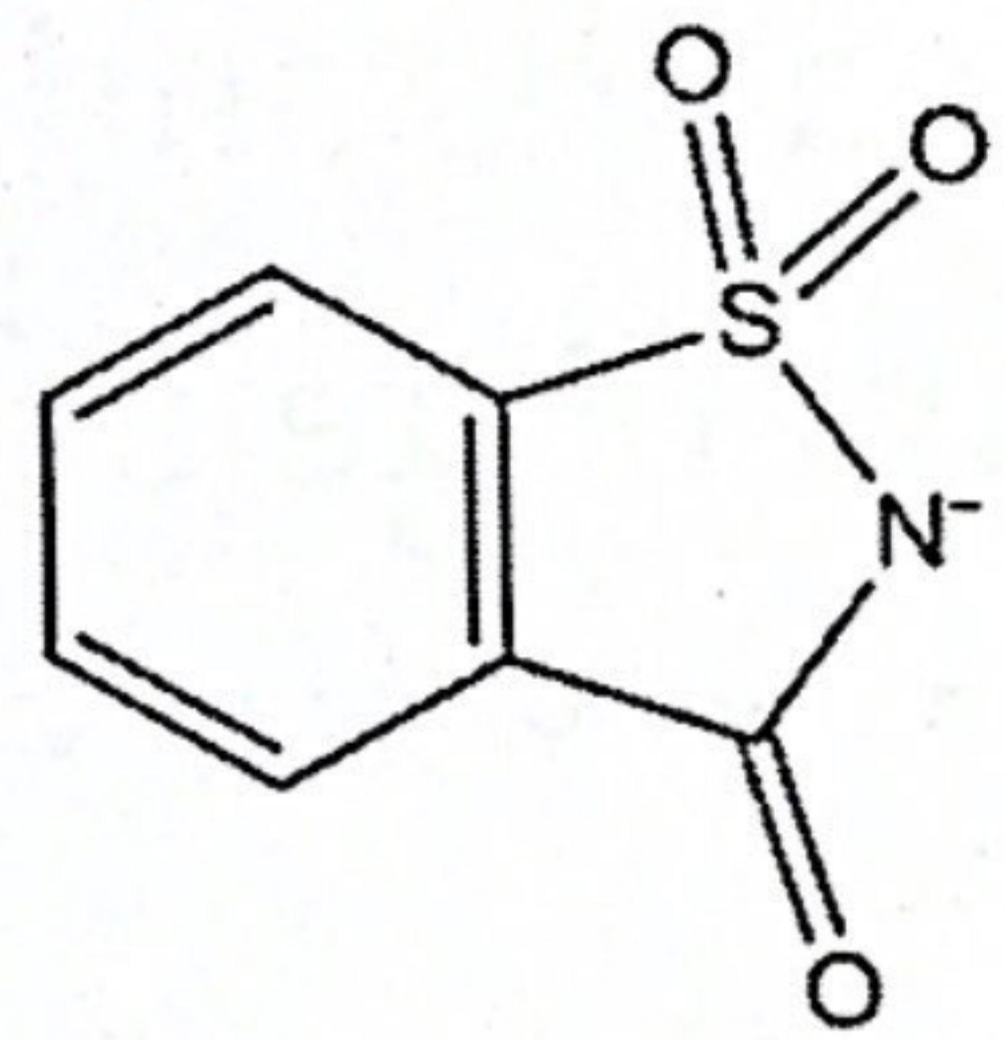


EW carbonyl

Sulfosalicylic acid



Saccharine



roduction

sulfonic+ salicylic acid → anti inflamatory agents ← الالتهاب ← لازم يعالجوه متى

anti Bacterial ← infection

it will not be absorbed through the GI tract

بنعطي لامراض الجهاز الهضمي

ال inflammatory Bowel (IBD)

بهاد المرض بصير جهاز المناعة يتعرف على خلايا الامعاء على انها جسم غريب فبصير يهاجمها وبصير inflammation

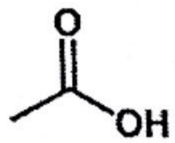
للانو الامعاء كلشي بمر فيها بكتريا feces بصير عند inflammation + infection المرض جداً صعب ومؤلم

هدول الدواين مالازم يصيرلهم امتصاص ليوصلو منطقة الامعاء وهناك تتكسر الروابط فيهم ويتم امتصاصهم Localy

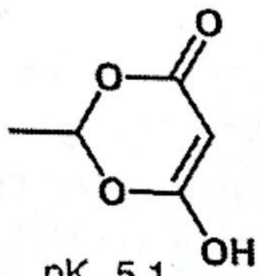
Acidic bioisosteres

تكملة

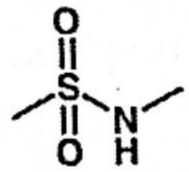
Acidic bioisosteres



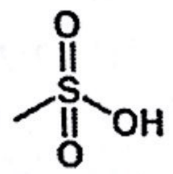
pK_a 4.75
tPSA 37.3
cLogP -0.19
CMR 1.29



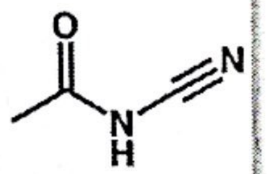
pK_a 5.1
tPSA 55.7
cLogP -0.26
CMR 2.86



pK_a 10.7
tPSA: 46.17
CLogP: -0.868
CMR: 2.3462

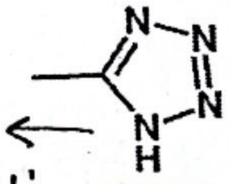


pK_a -1.9
tPSA: 54.37
CLogP: -2.424
CMR: 1.6668

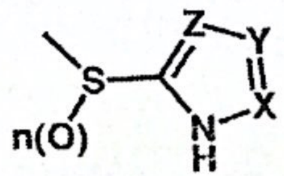


pK_a 8.2
tPSA: 52.89
CLogP: -1.594
CMR: 1.9871

Tetrazole isotere for carboxylic acid

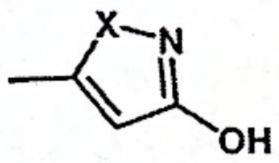


pK_a 4.5
tPSA: 49.11
cLogP: -0.194
CMR: 1.9486



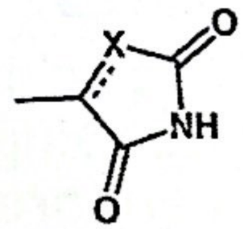
pKa 4.7 - 11.6

X, Y, Z = N, C, CO



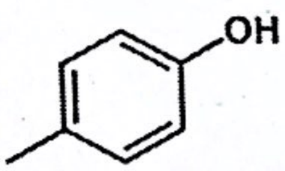
pKa 3.4 - 5.0

X = O, S, NMe



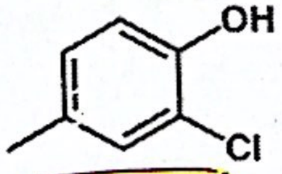
pKa 5.0 - 6.5

X = O, S, N, C



pKa 9.9

Phenols



pKa 8.5

with drawing groups

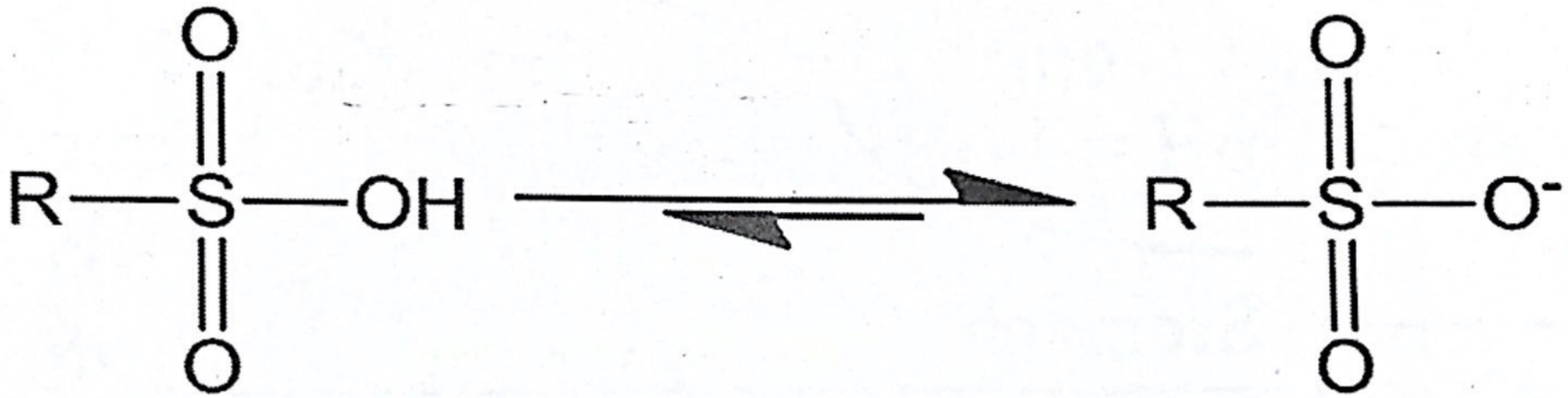
Scanned with CamScanner

ماحد عنده مشكله بامتصاصه

- Salicylic acid is the active form of Aspirin (acetylsalicylic acid), salicylic acid is absorbed through the GIT; if I want to treat a local inflammatory condition in the GIT such as Crohn's disease or ulcerative colitis, we can attach a sulfonic acid group to salicylic acid forming **sulfosalicylic acid** which is not absorbed orally and treat inflammation of the GIT in a local sense minimizing side effects.

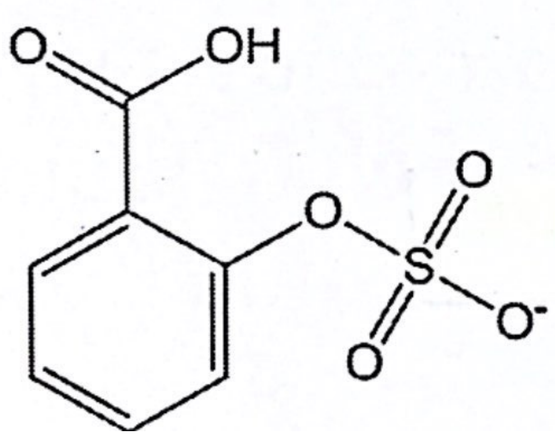
IBD

اذا صابين بهدول المرضين بنعطيهم Sulfocylic acid لانو مابدنا يتم امتصاصهم



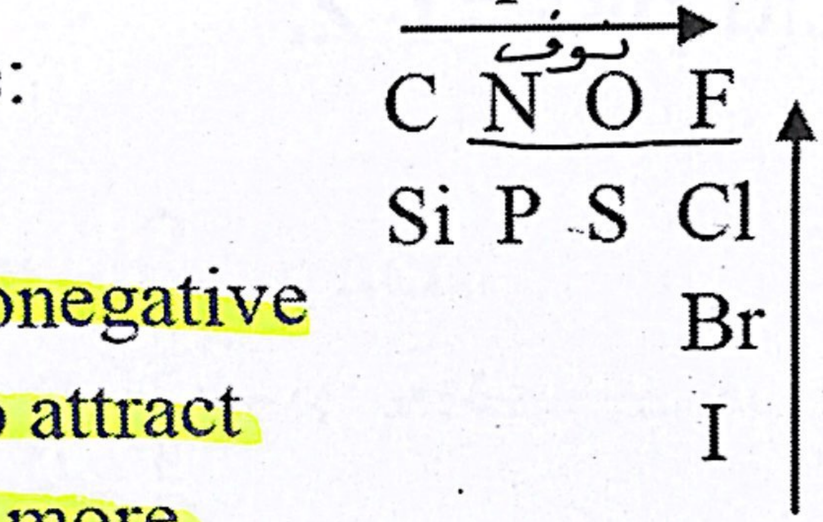
Sulfonic acid

Sulfosalicylic acid



Electronegativity

we most concern about this part of the periodic table:



ele. withdrawing group ← الهالوجينات
electronegativity لانو عاليه كل ما اتجهنا بإتجاه ال (F)

higher electronegative atoms tend to attract the electrons more.

Ex. O withdraw electrons from S in sulfonic acid.

Strong acids...

pH = 7-8

Intestine

pH = 1-3

Stomach

pKa
pKa≤2

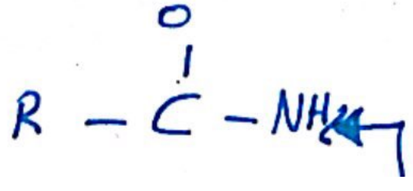
* stomech/intestine سواء بال pH
يتكون اعلى من pka للدوا
(للحمض)

* حمض وشايف الوسط قاعدي *

* دح يضل يضغ بروتون حتى يعطي الوسط القاعدي
H^+
(نفس اللي شرحناه بالاعلى)

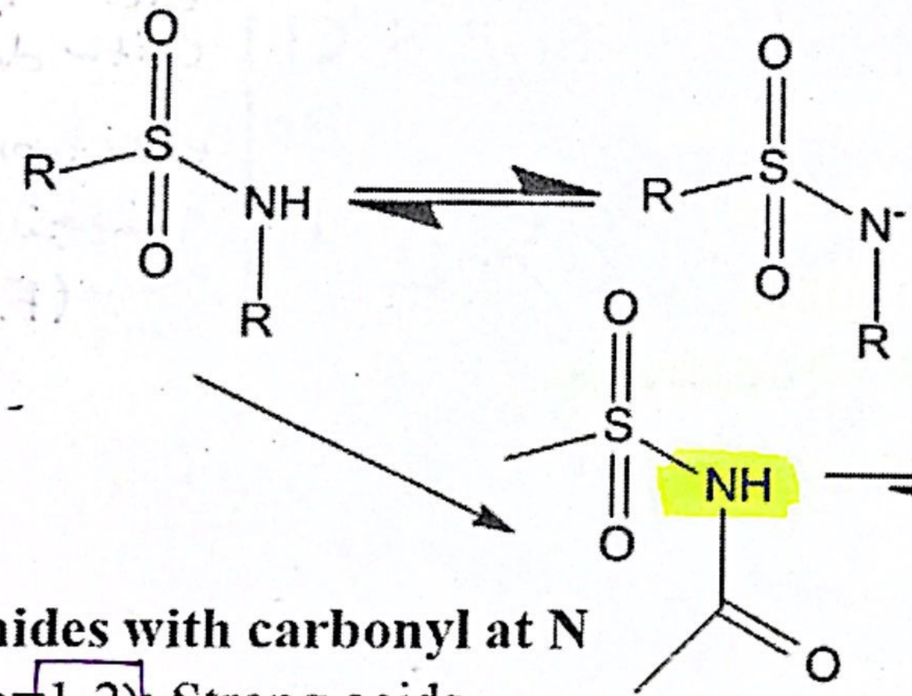
$$HA \leftrightarrow A^- + H^+$$

Strong acids (pH>pKa)



- Another group is **sulfonamids** which is per say an intermediate acid **pKa=7**, but if we attach an extra carbonyl to its nitrogen it becomes strong acid **pKa=1-2**.

* موكل sulfonamidesال strong acids



Sulfonamides with carbonyl at N

(pKa=1-2); Strong acids

* لما ارتبطت مع with drawing group ال pka نزلت

Sulfonamides

(pKa=7); Intermediate acids

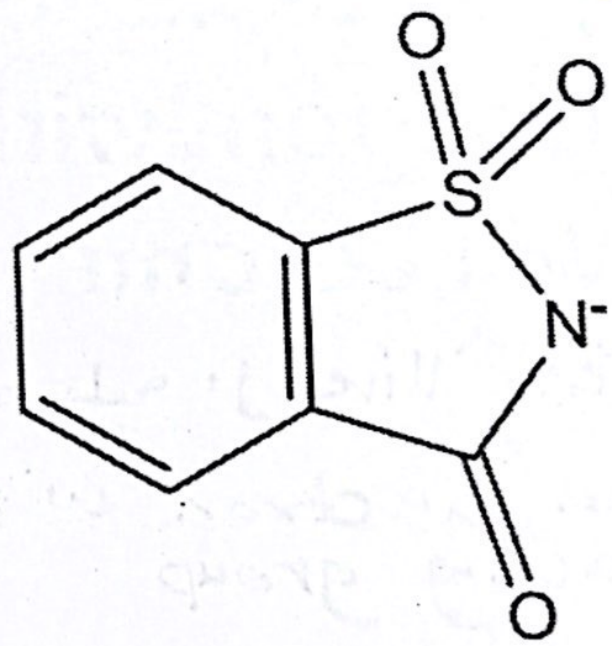
* لما يرتبط مع ele withdrawing group زي حالة الsaccharine بصير فقدان ال H اللي مرتبط على N اسهل لانها سحبت الكترونات الرابطه فصارت الرابطه بين ال N/H ضعيفة

* فلما يزيد اعطاء ال H^+ بصير stronger

- **sulfonamide with the carbonyl at the N** is nearly as strong as the sulfonic acid with a pKa=1-2; therefore, its **orally unavailable**.

An example is **Saccharine** produced as Na-Saccharine which is a diabetic sweetening agent; diabetic patient can feel its sweetness without concerning about elevating blood sugar levels because it's eliminated through the fecal system without being absorbed.

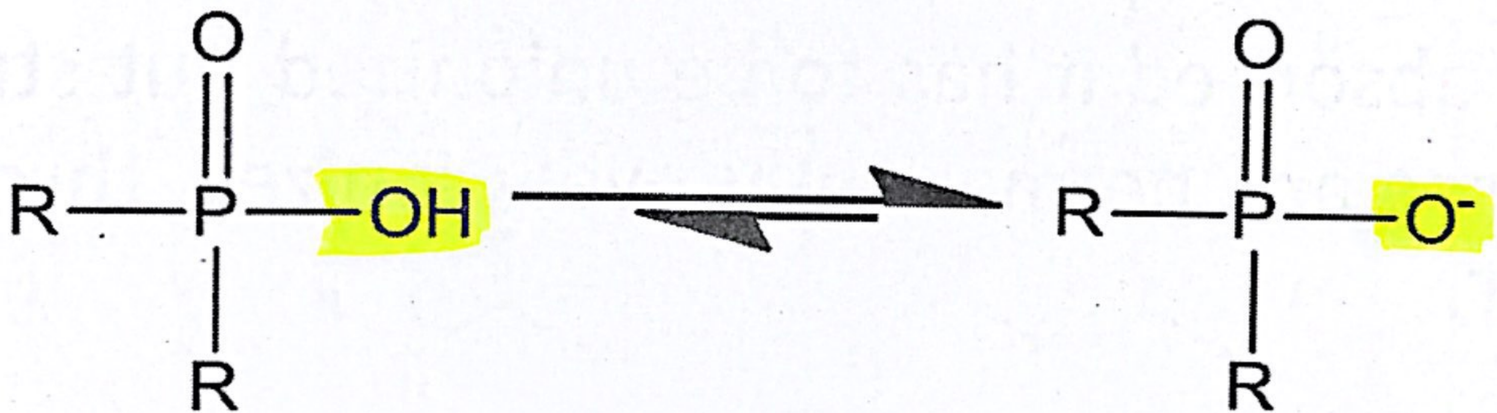
Saccharine → بديل للسكر
محلي صناعي



* ال saccharine من اطرحبات
الي مابدنا يتم امتصاصها
- يعني الي بستخدمه مع الشاي بحطه
ليحس بطعم الحلاوه وبعدين يتخلص
منه (ما يتم امتصاصه)

- Another example on strong acidic groups which if found in drugs they make them orally unavailable is **phosphoric acid**;.

Phosphoric acid



Another example on strong acidic groups

* ال carboxylic acid العادي موحض Intermedient acid قوي بل

- **Carboxylic acid** is another group to discuss, even though it's solely intermediate acid with **pKa=3-4.5** but if it was conjugated to an electron withdrawing group like carbonyl it will become a strong acid.

* لايضف ابداً ك strong acid ومثال عليه ال penicillins الي امتصاصهم جيد
لكن اذا كان conjucated ← to an electron with drawing group

الرابطة الي موجوده بين ال H/O بتضعف ← بالتالي بصير فقدان ال H اسهل وبصير stronger acid

$$R-\overset{\overset{O}{\|}}{C}-\underline{O\cdot H} \longrightarrow R-\overset{\overset{O}{\|}}{C}-O^{-} + H^{+}$$

لـ يتضعف هاي الرابطة وبنفقد البروتون

Completly Ionized through the GI Tract ←

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

عالية
strong Base للـ

pKa — pKa≥12

pH = 7-8

Intestine

pH = 1-3

Stomach

$BH^+ \leftarrow H^+ + B$

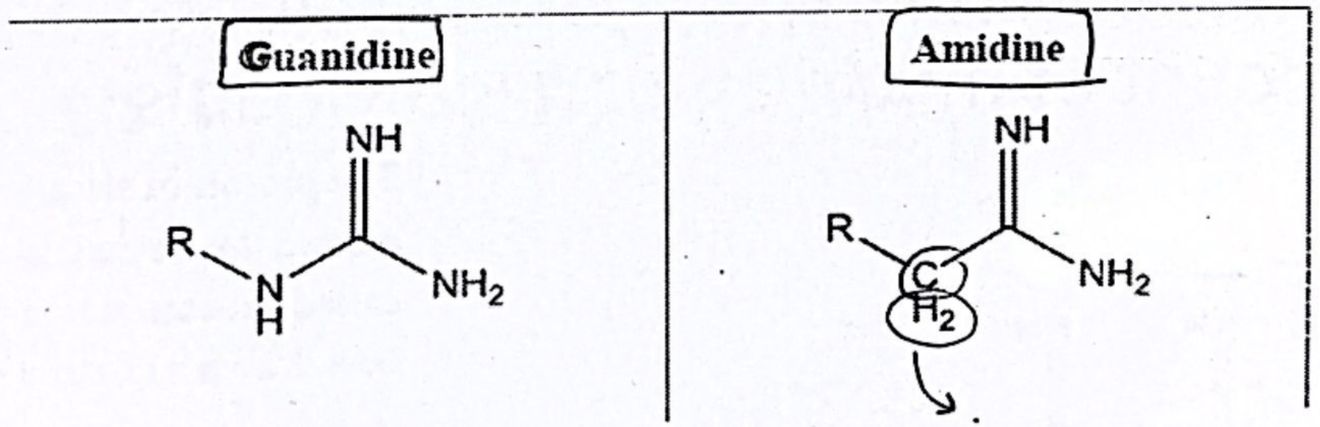
Strong bases (pH<pKa)

* عبارة عن Base بدو ياخد من الوسط H^+ حتى ليتأين

* حتى الـ Base ليتأين لازم يكون الوسط حمضي (مخالف لطبيعته) رح ليتأين على طول

- 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.

* همون بدنا نعتمد على لويس في تصنيف الـstrong Bases



نعسرها بس بدلنا ال NH ← CH_2

Base → ماده قادره على اعطاء 2 pairs of unchared electrons

* غنى system → جدا بالبروتونات

- 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.

عشان هيك بحتاج جرعة عالية من ال Metformin + بتختلف الجرعة لكل حد حسب وجود بروتين ال Mucin عنده

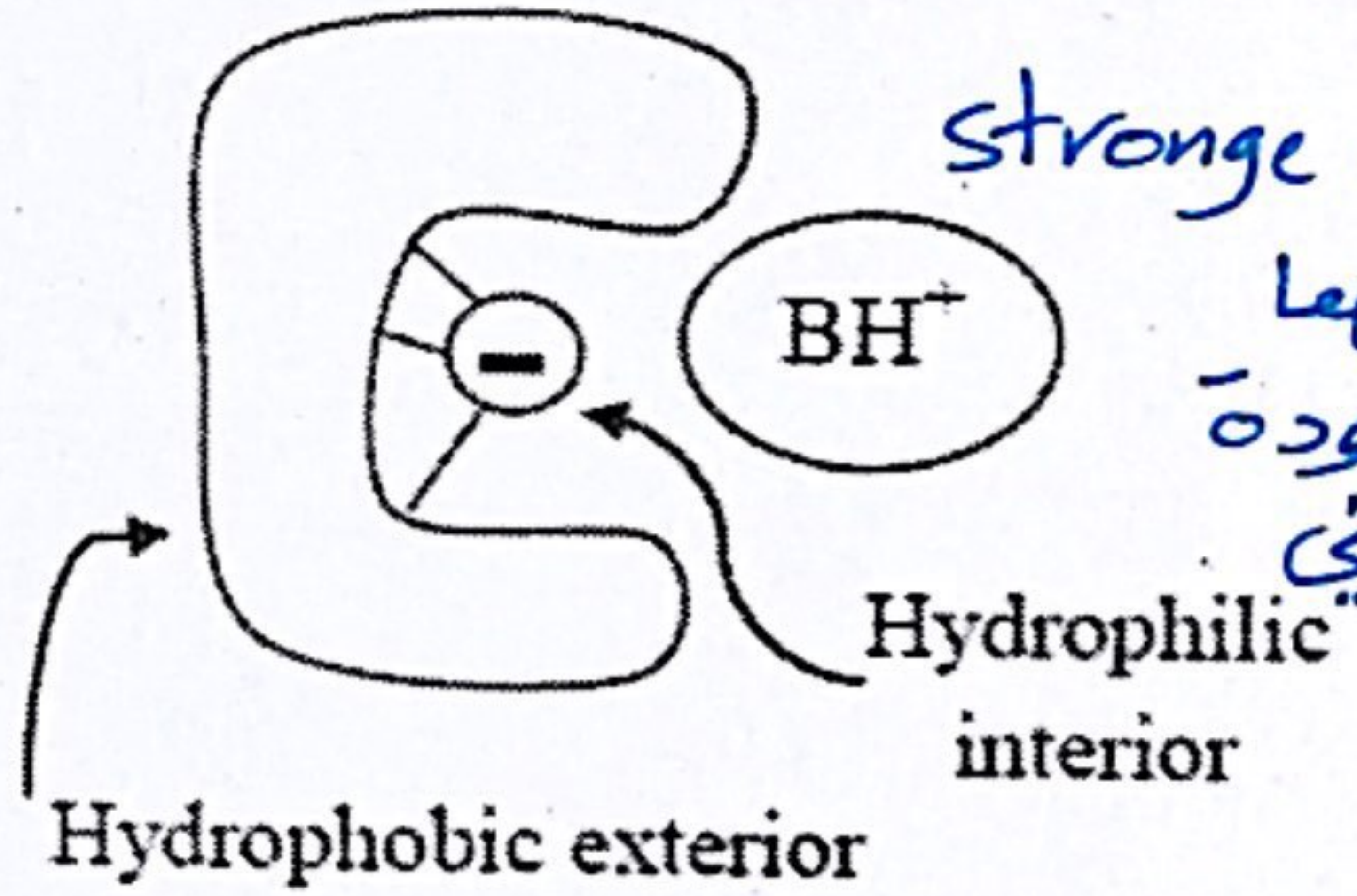
بساعد على الامتصاص

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%.

مثلاً لو اخدنا ال Metformin 1000 → بس 40% يتم امتصاصهم

Mucin ion pair complex

موجود ببطانة الامعاء



ربنا خلقه حتى ال Stronge Bases يتم امتصاصها بكميات محدودة من الانسان لتاني

* وظيفته بيرتبط مع القاعدة القوية وبلف عليها بخبي ال Ionization تبعها وبنقلها للـ phospholipid bilayer جواته negative charge

- **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!

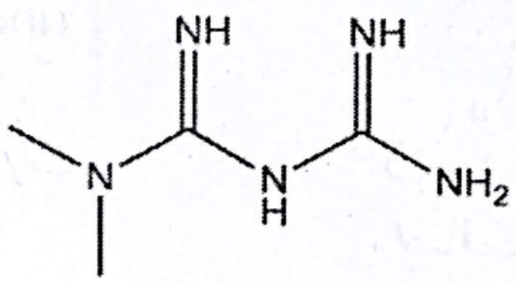
التجاري

- 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

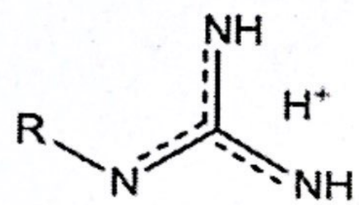
يعني يختلف من واحد لواحد ال Mucin يختلف لكل واحد

Metformin
(biguanide)

2 guanide



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



Weak acids

عالية 12 ≤ pKa

- 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.

[1] acid → pKa = 12 → acid فهموه وشايف الي حواليه حامضي فما بتأين unIonized

يعني شايف كتير في H^+ فما رح يفقد H^+

[2] كمان حكينا لازم يكون عنده Hydro philic /Phobic prop

العلماء ... حطوا قاعده لدراسة هدول الـprop

سموا القاعده lipinski's rule of five

[1] not more than 5 H.bond donors → الى همة زحفظها
[2] not more = 10 = acceptors → انو الي بعطي اقل من الي باخدو
[3] molecular weight < 500
[4] logp > 5

Weak acids

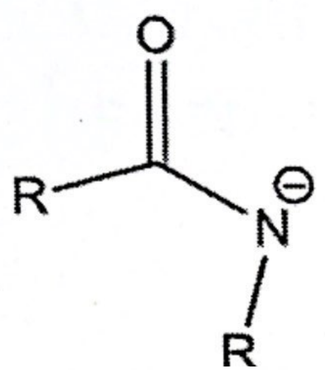
احياناً بعتبروهم weak acid / bases and its the same لانهم دائما unIonized

- **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**.

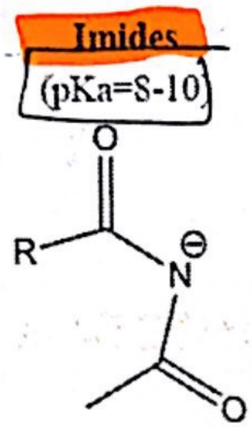
* اذا رح يعطى H^+ بنعتبره weak acid

* اذا رح يعطى 2 pairs of unshared electrons Base بنعتبره

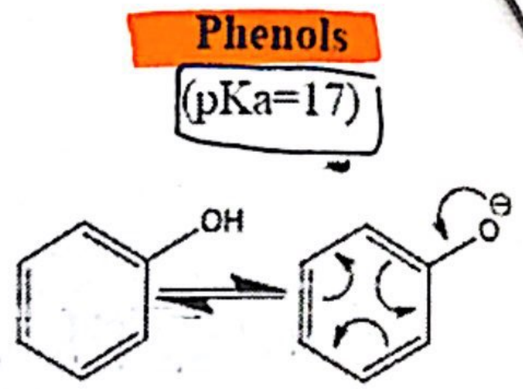
Amides
(pKa≥12)



الكاربونيل لصيه مجموعة تسحب الالكترونات



Weak acids



pKa الـ ← اله سوي اكتره acidic

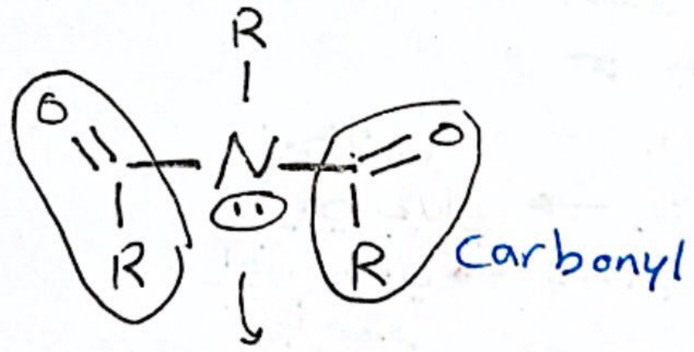
- **Imides** in fact are also considered weak acids even though they contain 2 electron withdrawing carbonyl which can further stabilize -ve charge on N; their **pKa=8-10** so imides are stronger acids than amides but still considered fairly weak acids.

الكحولات ← العادية ليست احماض لكن كحول واحد يعتبر حمض وهو Phenol الـ وعليها & aromatic ring

- **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**

موجود بالدبتول

وعليها OH و الكترونات الرابطة مسحوبه على الـ aromatic فممكن ring Phinoxide لـ تتأين

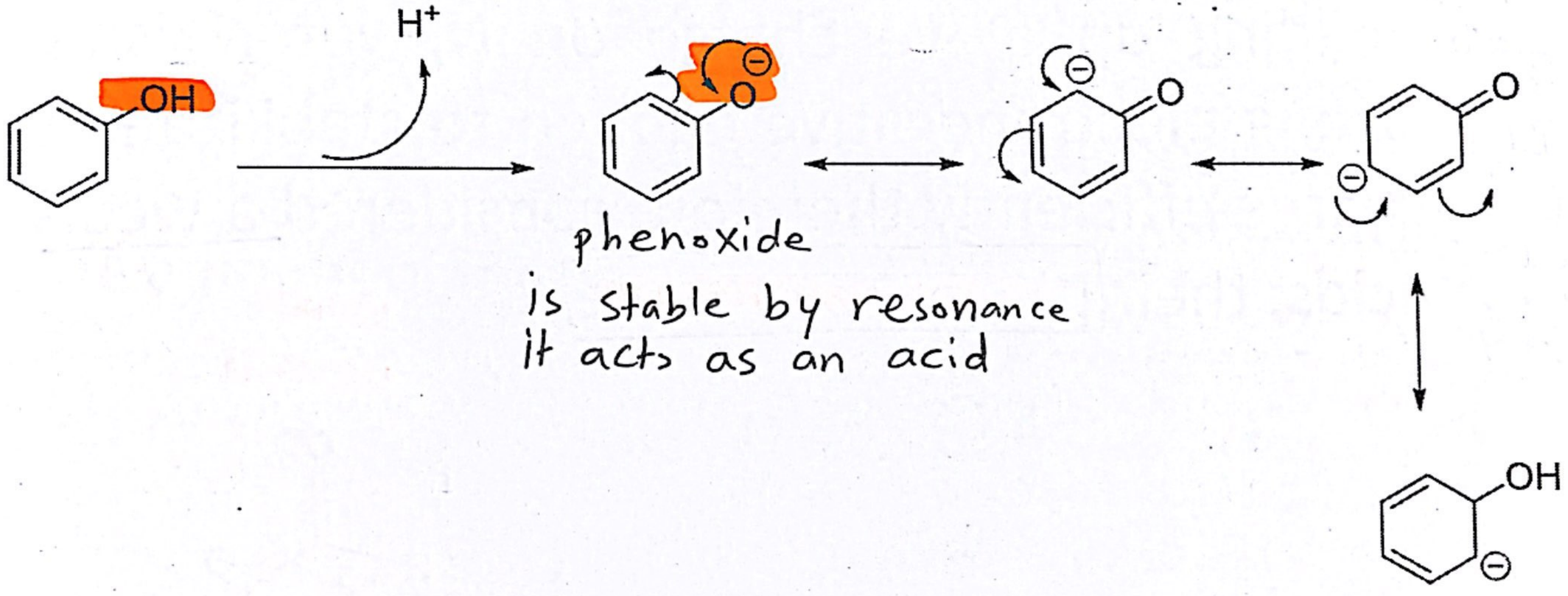


imides
2pairs of unshared electron عندو

وعنده 2 carbonyls رح تشد الكترونات الرابطة فرح تصير الرابطة ضعيفة فقدان H رح يصير اسهل

Phenoxide anion is stable by resonance. This means that phenol can give stable anion upon donating its proton

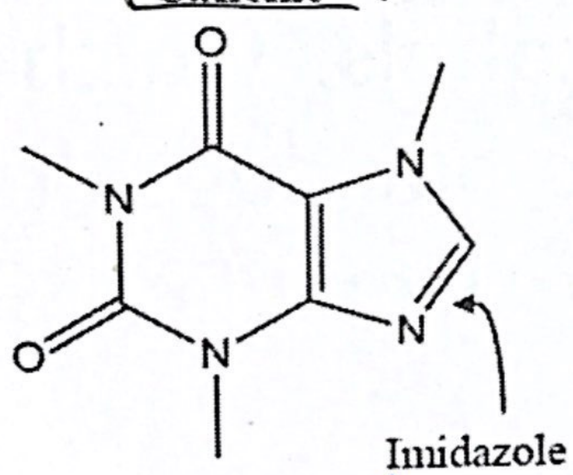
"They act as an acid"



phenoxide
is stable by resonance
it acts as an acid

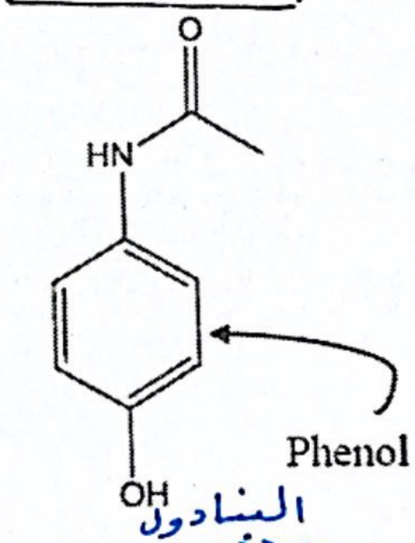
- Heterocyclic nitrogen structures such as in **Imidazole** group is also considered quite weak acid.
- So, we mentioned **Amides, Imides, Phenols and Imidazoles** as examples on functional groups which represent **weak acids.** Also, **Alcohols are very weak acids.** it's not even an acid
- Therefore, if found in a chemical structure, it's expected to be unionized through GIT.

Caffeine



طبيعتة حامضية
* امتصاصه سريع
زي الظبوة لما حد يشربها الصبح بيصيبه صداع لانو امتصاصة سريع

Paracetamol



البنادول
زي ~~الجديد~~ امتصاصه سريع

Imidazole → موجود بال Paracetmol و ال Caffeine