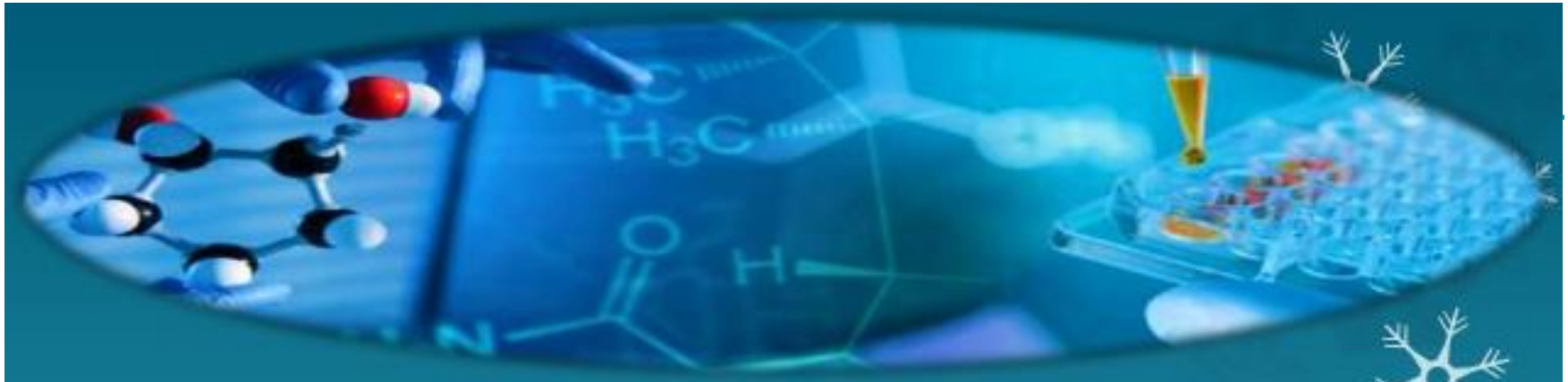


Prodrugs

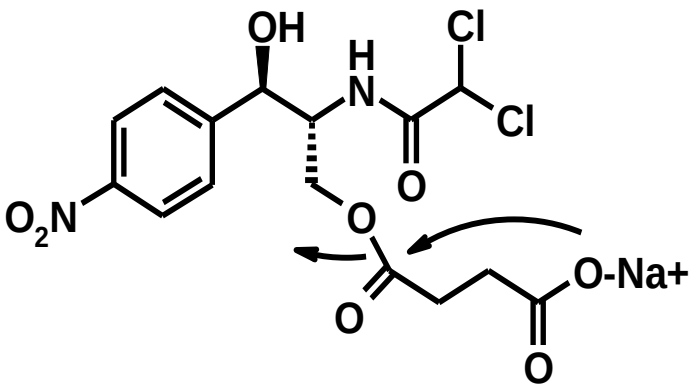
Dr. Basma Al-Qadi

The promoiety should be:

- Easily and completely removed after it has served its function.
- Should be nontoxic.
- Type of promoiety chosen is a function of properties desired?

  If it is desirable to increase water solubility, then a promoiety containing an ionizable function or numerous polar functional groups is used. If, on the other hand, the goal is to increase lipid solubility or decrease water solubility, a nonpolar promoiety is appropriate.

Administration of a drug parenterally may cause pain at the site of injection, especially if the drug begins to precipitate out of solution and damage the surrounding tissue. This situation can be remedied by preparing a drug with increased solubility in the administered solvent.

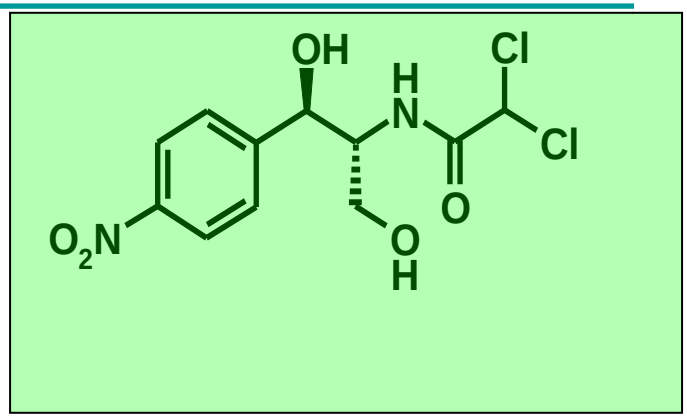


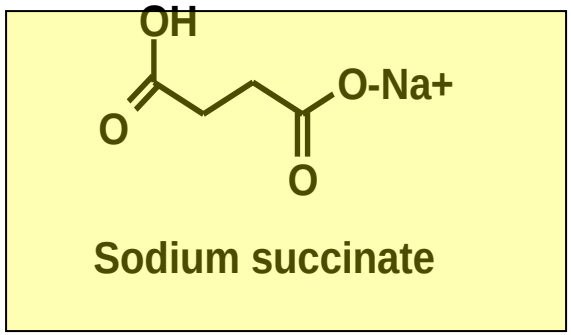
Chloramphenicol Succinate

Esterase

or Water

Chloramphenicol

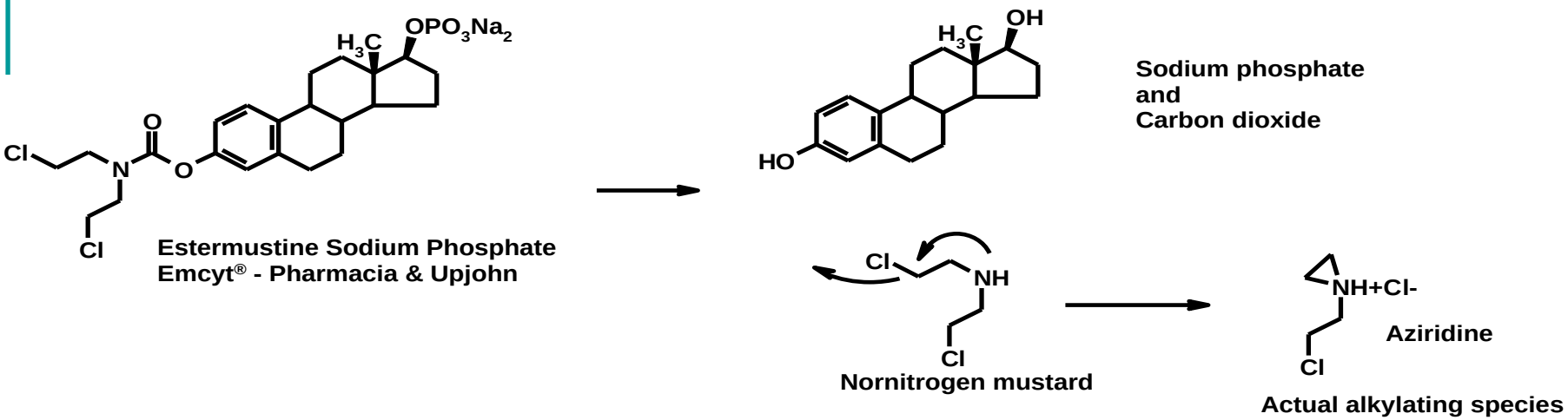




Sodium succinate

- **Enzymatic and intramolecular spontaneous hydrolysis**
- **Increased water solubility, ester itself is inactive as an antibiotic**
- **Promoiety should be nontoxic and easily excreted**
- **Type of promoiety chosen is a function of properties desired**

Mutual Prodrug



- **Used for metastatic carcinoma of the prostate**
- **Promoiety also a drug!**
- **Prodrug is selectively taken up into estrogen receptor positive cells then urethane linkage is hydroylzed**
  - **17-alphaestradiol slow prostate cell growth**
  - **Nornitrogen mustard is a weak alkylating agent**

•Note that phosphorylation of the estradiol can be used to increase the water solubility, which also constitutes a prodrug modification. Both types of esters (carbamates and phosphates) are hydrolyzed by chemical or enzymatic means.

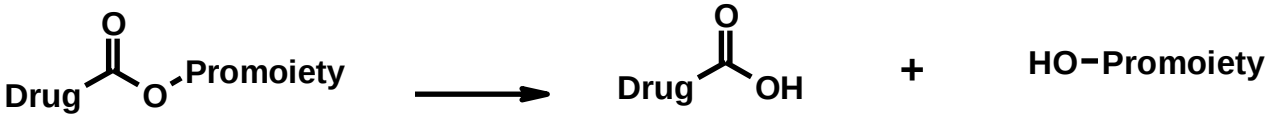
Estramustine is composed of a phosphorylated steroid (17 α - estradiol) linked to a normustard [NH(CH2CH2Cl)2] through a carbamate linkage.

The steroid portion of the molecule helps to:

- concentrate the drug in the prostate, where hydrolysis occurs to give the normustard and CO2.
- The I7 α -estradiol has an antiandrogenic effect on the prostate and thereby, slows the growth of the cancer cells.

Functional Groups in Prodrugs

- **Carboxylic acids and Alcohols:** **Most common type of prodrug**



or

-

- Prodrugs of agents that contain carboxylic acid or alcohol functionalities can often be prepared by conversion to an ester

- Ester prodrugs are the most common type of prodrug?

1. The ease with which the ester can be synthesized.
2. The ease with which the ester can be hydrolyzed to give the active drug.

- Hydrolysis of ester prodrugs are accomplished by:

1. Esterase enzymes present in plasma and other tissues e.g.

   a/ Ester hydrolase b/ Lipase

   c/ Cholesterol esterase d/ cholinesterase

   e/ acetyl cholinesterase f/ Carboxypeptidase

2. Microflora presents within the gut produce a wide variety of enzymes that can hydrolyze esters.
3. Chemical hydrolysis of the ester function may also occur to some extent.

- Manipulation of the steric and electronic properties of the promoiety allows:

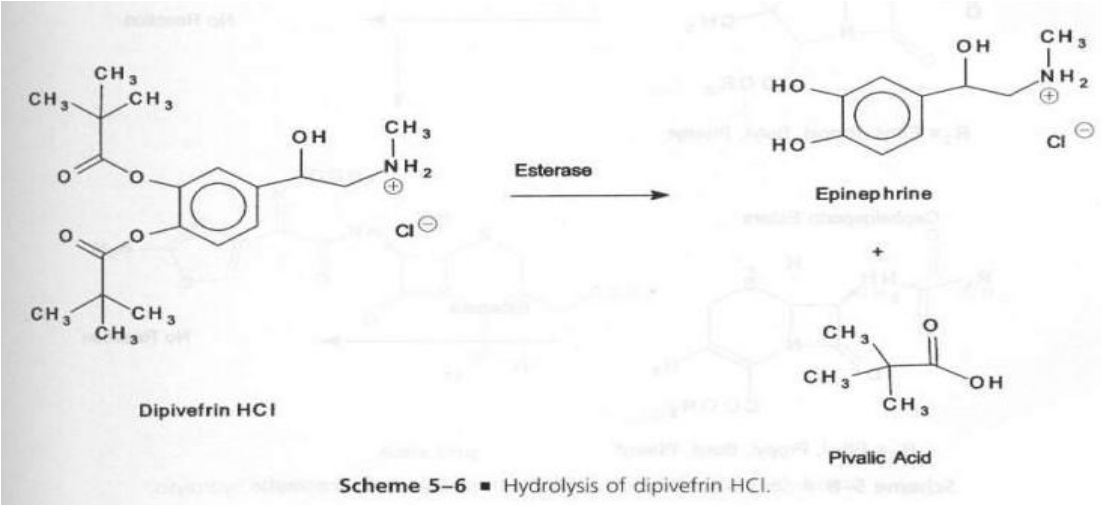
  1. Control of the rate of hydrolysis.
  2. Control of the extent of hydrolysis.
  3. Control when the active drug must be revealed at the correct point in its movement through the biological system.

- When it's desired to decrease water solubility, a nonpolar alcohol or carboxylic acid is chosen as the prodrug moiety which may yield a number of benefits including:

  1. Increased absorption, e.g. dipivefrin HCI.
  2. Decreased dissolution in the aqueous environment of the stomach.
  3. Longer duration of action.
  4. Mask an unpleasant taste of agents when given orally e.g. chloramphenicol palmitate.

Dipivefrin HCl is a prodrug of epinephrine with pivalic acid which is used in the treatment of open angle glaucoma.

- **The increased lipophilicity relative to epinephrine allows the agent, when applied, to move across the membrane of the eye easily and achieve higher intraocular concentrations. Hydrolysis of the ester functions then occurs in the cornea, conjunctiva, and aqueous humor to generate the active form, epinephrine.**



Scheme 5–6 ▪ Hydrolysis of dipivefrin HCl.

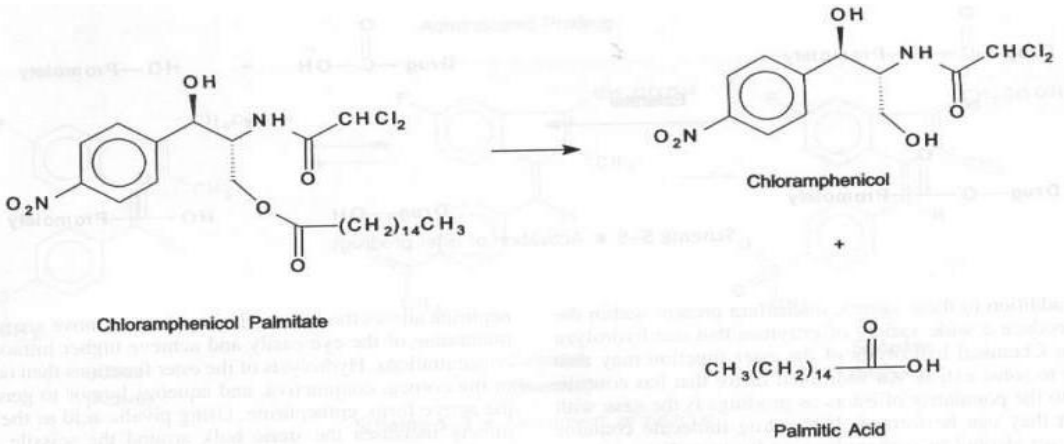
- Important of using pivalic acid in Dipivefrin HCl:

1. Increases the steric bulk around the scissile ester bond, which slows the ester hydrolysis relative to less bulky groups.

2. Protecting the catechol system as the diester prevents its oxidation and the resulting drug inactivation.

- **Chloramphenicol palmitate:**
- **Chloramphenicol has an unpleasant taste when given orally because the drug dissolves in the mouth and then is capable of interacting with taste receptors. This can present a significant problem, especially in pediatric patients, and may lead to low compliance.**
- **The hydrophobic palmitate ester does not dissolve to any appreciable extent in the mouth, so there is little chance for interaction with taste receptors.**

- The ester moiety is subsequently hydrolyzed in the GI tract, and the agent is absorbed as chloramphenicol.
- Listed below are a number of other agents that have been converted into ester prodrugs and other types of prodrugs to overcome an unpleasant taste:
- N-Acetyl sulfisoxazole
- Erythromycin estolate
- Clindamycin palmitate.

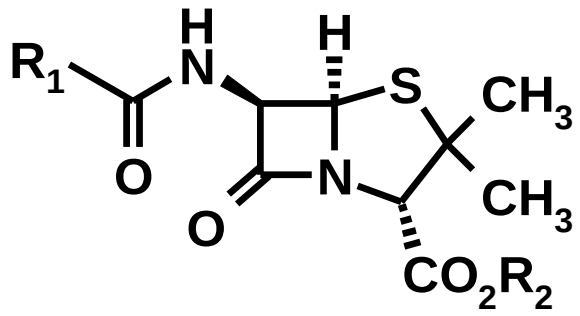


Scheme 5–7 ■ Hydrolysis of chloramphenicol palmitate.

Not all carboxylic esters are easily hydrolyzed in vivo

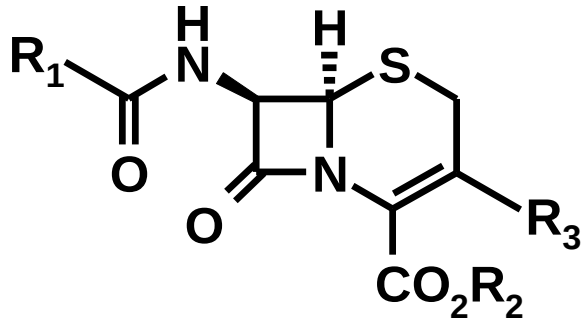
- Steric inhibition around the ester in some cases prevents the prodrug from being hydrolyzed.
- This is seen in the β-lactams, in which it is often desirable to increase the hydrophobicity of the agent to improve absorption or prevent dissolution in the stomach where acid-catalyzed decomposition may occur.
- Simple esters of the carboxylic acid moiety, however, are not hydrolyzed in vivo to the active carboxylate.

Esters Failure as Prodrugs



R_2 = ethyl, propyl, butyl, phenyl
Penicillin esters

Esterases → **NO REACTION!**



R_2 = ethyl, propyl, butyl, phenyl
Cephalosporin esters

Simple esters of β -lactams with resistance to enzymatic hydrolysis

- A solution to this problem was to use the so-called double ester approach, in which an additional ester or carbonate function is incorporated into the R_2 substituent further removed from the heterocyclic nucleus.
- Hydrolysis of such a function occurred readily, and the moiety was selected so that chemical hydrolysis of the second ester occurred quickly. This is seen in the cephalosporin cefpodoxime proxetil where a carbonate function was used.
- The carbonate is also susceptible to the action of esterase enzymes, and the unstable product undergoes further reaction to give the active carboxylate.
- This approach is frequently used to:

  1. Improve absorption.

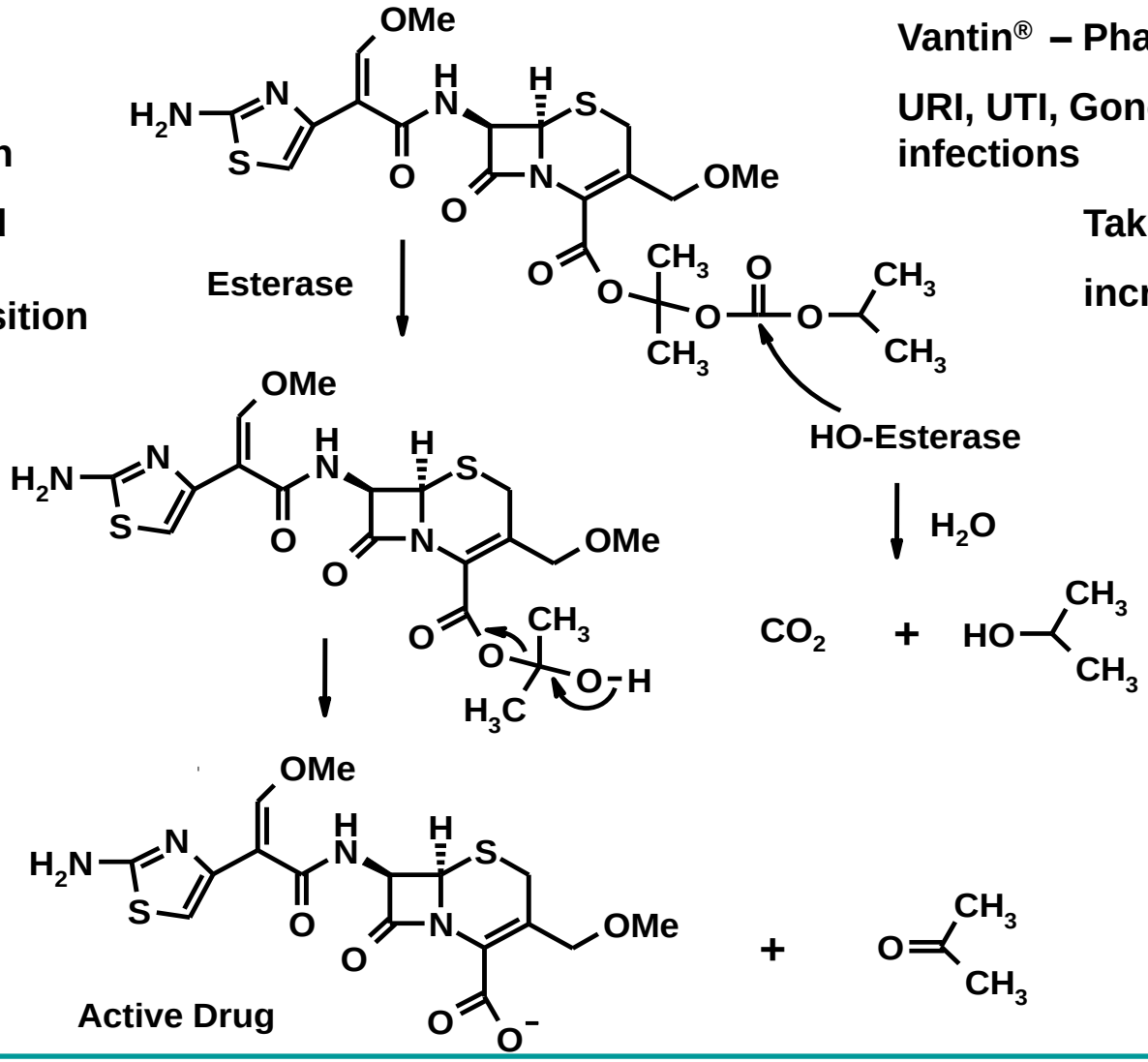
  2. Or prevent dissolution in the stomach and the subsequent acid-catalyzed decomposition of aminopenicillins and second- and third-generation cephalosporins so that these agents can be administered orally, e.g. Bacampicillin.

β-Lactam prodrug – Double esters

Why?

Increase absorption

Avoid acid catalyzed decomposition



Vantin® – Pharmacia & Upjohn

URI, UTI, Gonorrhea, skin infections

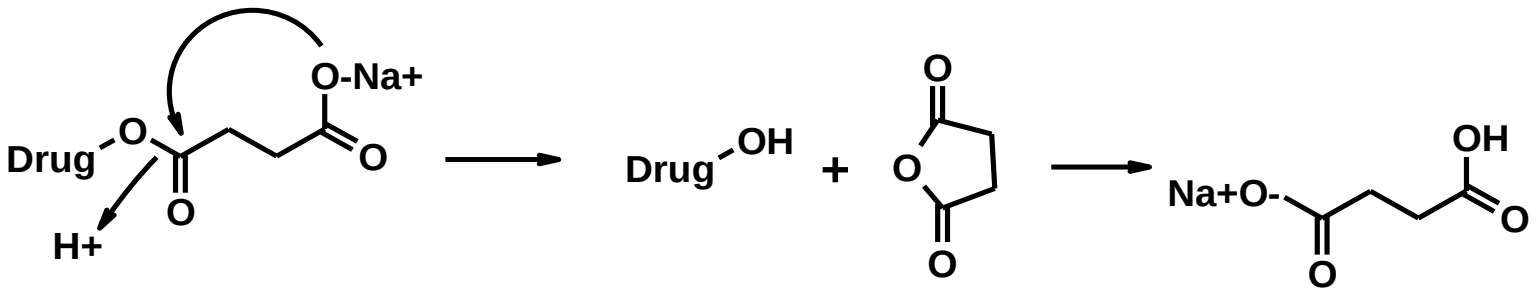
Taking with food increases absorption

- To increase the hydrophilicity of an agent, several different types of ester prodrugs have been used, including:

  1. succinates
  2. phosphates
  3. sulfonates.

- All are ionized at physiological pH and, therefore, increase the water solubility of the agents, making them more suitable for parenteral or oral administration when high water solubility is desirable.

Scheme: succinate, sulphate, and phosphate ester

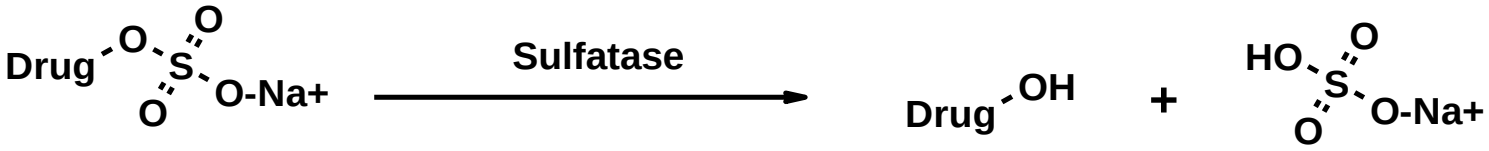


Sodium succinate prodrug

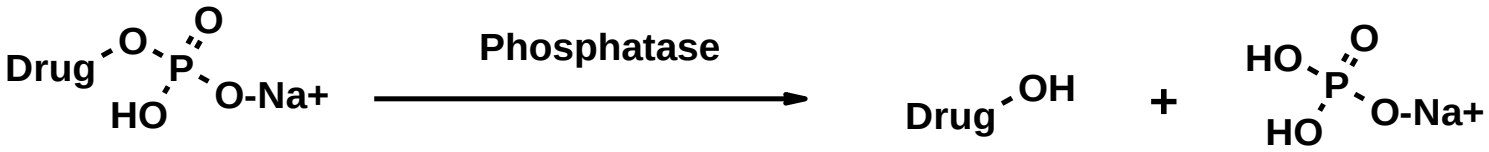
Sodium succinate

Unstable: use immediately

More stable: less prone to hydrolysis by water



Sulfate prodrug



Phosphate prodrug

- Succinate esters containing an ionizable carboxylate are useful when rapid in vivo hydrolysis of the ester functionally is required.
- The rapid hydrolysis is related to the intramolecular attack of the carboxylate on the ester linkage, which does not require the participation of enzymes

Scheme 5-12 • Intramolecular cleavage of succinate esters.

- As a result, these agents may be somewhat unstable in solution and should be dissolved immediately prior to administration.