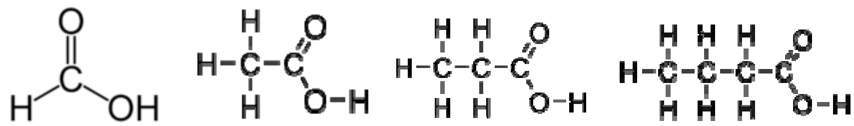
CHAPTER 4
CARBOXYLIC ACIDS

4.1 NAMING CARBOXYLIC ACIDS AND CARBOXYLATE IONS

To generate the systematic name of carboxylic acids, drop the -e of the corresponding alkane and add -oic acid. The older common names must simply be memorized. You should know the common as well as systematic names for the carboxylic acids containing up to 4 C atoms.



Systematic:	methanoic acid	ethanoic acid	propanoic acid	butanoic acid
Common:	formic acid	acetic acid	propionic acid	butyric acid

To name the carboxylate ions take the name of the acid, drop “ic” and add “ate”.

Ions:	$H\text{-}C(=O)\text{-}O^-$	$CH_3C(=O)\text{-}O^-$	$CH_3CH_2C(=O)\text{-}O^-$	$CH_3(CH_2)_2C(=O)\text{-}O^-$
Systematic:	methanoate ion	ethanoate ion	propanoate ion	butanoate ion
Common:	formate ion	acetate ion	propionate ion	butyrate ion

Even when no positive ion is explicitly shown next to the negatively charged carboxylate ion, there must be a positive ion to balance the negative charge, even if it is not shown.

When the positive ion is shown, it is normally placed adjacent to the negatively charged O- of the carboxylate ion. There is an **ionic** bond between the negatively charged O atom of the carboxylate ion and the positively charged ion.

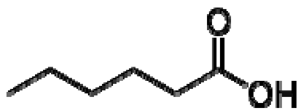
In the examples shown below the positive ion is a Na^+ ion.

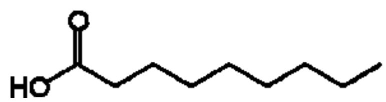
Systematic: sodium methanoate sodium ethanoate sodium propanoate sodium butanoate

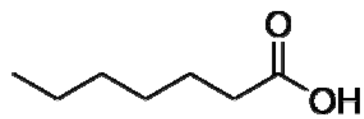
Common: sodium formate   sodium acetate   sodium propionate   sodium butyrate

The positive ion name goes first just like in inorganic compounds (e.g. sodium chloride, potassium fluoride) even if the positive ion is shown at the right of the carboxylate, as it is in the above structures.

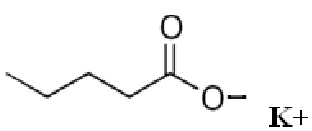
Name the following:

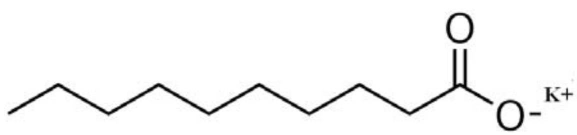




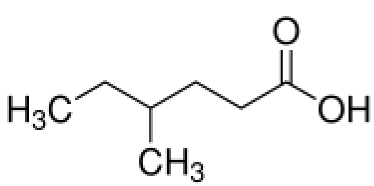


$CH_3(CH_2)_4\overset{\overset{O}{\|}}{C}\text{-}O^-\ \ Na^+$ $CH_3(CH_2)_7\overset{\overset{O}{\|}}{C}\text{-}O^{-1}\,K^{+1}$

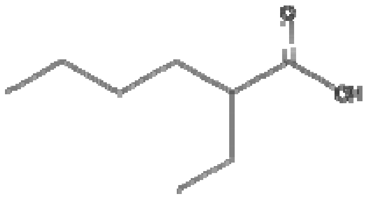
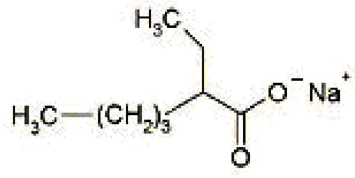




Numbering of C chains with carboxylic acid functional groups starts from the carboxylic acid end of the molecule, even if that assigns larger numbers to other alkyl groups.   Examples:



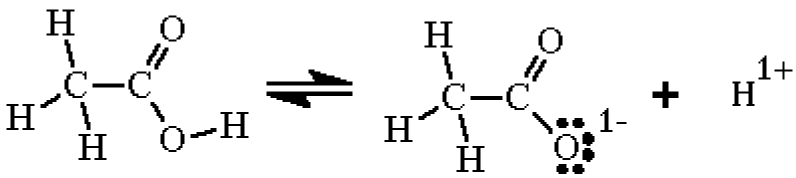
is 4-methyl hexanoic acid (and the carboxylic acid is understood to be on C#1, without explicitly numbering it.)
It is **not** named 3-methyl-6-hexanoic acid.
Likewise the structures below are 2-ethylhexanoic acid and sodium 2-ethyl hexanoate.

4.2 Structure and acidic properties of carboxylic acids

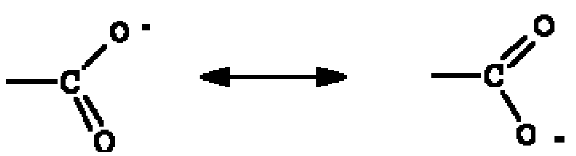
The OH group in a carboxylic acid is different from an OH in an alcohol. The OH group in a carboxylic acid is weakly acidic: it dissociates **reversibly** with water to form a carboxylate ion and a hydrogen ion:

dissociation of acetic acid

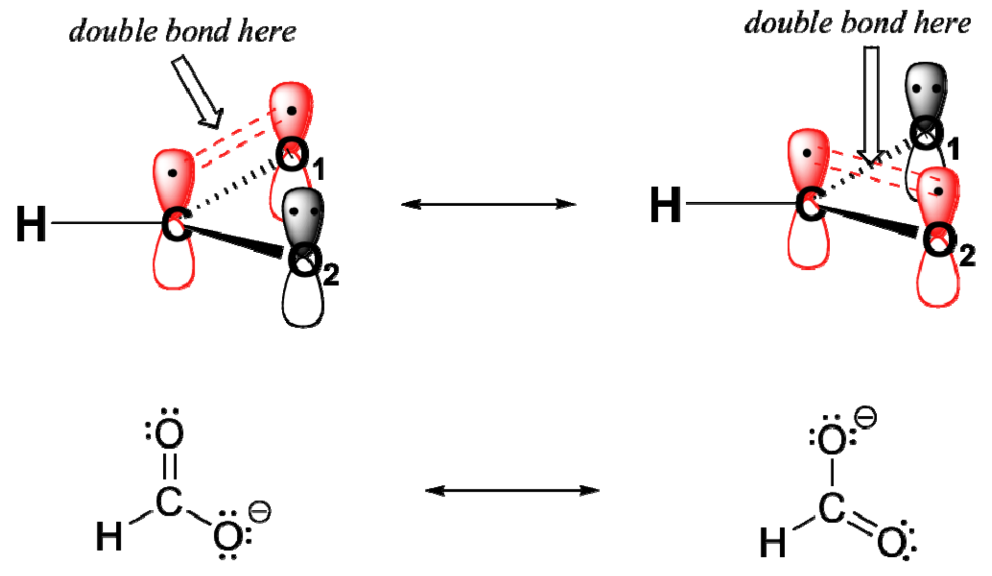


only 4 out of 100 molecules dissociate

When the bond lengths of the 2 C-O bonds of the carboxylic acid are measured experimentally the C=O is significantly shorter (and stronger) than the C-O bond of the C-O-H. However when the bond lengths of the C=O and C-O^{-1} bonds in the **carboxylate ion** are determined, they are found to be the same, and intermediate between that expected for a C=O and a C-O bond. The explanation for this is similar to that used to explain the C-C bond lengths of benzene. In terms of **resonance** structures we have two equally possible structures for a carboxylate ion and the true molecule appears to be an intermediate between them.



Alternatively we can look at the p orbital overlap as being shared between the C atom and **both** O atoms, similarly to the discussion with benzene.



A B

Creative commons: Chemwiki:ucdavis

This resonance spreads the negative charge between the two O atoms of the carboxylate ion and makes the carboxylate ion more stable. Chemists use this feature to explain why the OH bond in a carboxylic acid is considerably more acidic than the OH bond in an alcohol.

Being an acid, carboxylic acids can undergo **neutralization** reactions with bases, forming water and a salt of a weak acid.

$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}H \;+\; Na^{+} \;+\; OH^{-} \;\longleftrightarrow\; R\text{-}\overset{\overset{O}{\|}}{C}\text{-}O^{-1}\;Na^{+1} \;+\; H\text{-}O\text{-}H$$

Examples:

Write the equation for the neutralization of
a) acetic acid with potassium hydroxide.
b) butyric acid with sodium hydroxide

Answers:

a) $CH_3\overset{\overset{O}{\|}}{C}OH \;+\; K^{+} \;+\; OH^{-1} \longleftrightarrow CH_3\overset{\overset{O}{\|}}{C}O^{-1}\;K^{+} \;+\; H_2O$

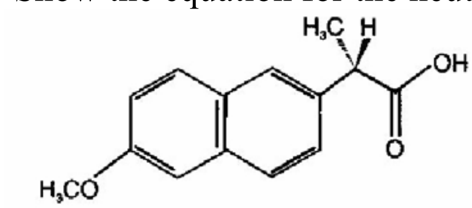
b) $CH_3(CH_2)_2\overset{\overset{O}{\|}}{C}OH \;+Na^{+} \;+\; OH^{-1} \longleftrightarrow CH_3(CH_2)_2\overset{\overset{O}{\|}}{C}O^{-1}\;Na^{+} \;+\; H_2O$

Write the equation for the neutralization of

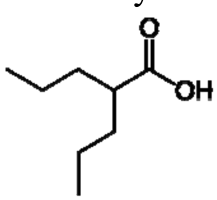
a) butanoic acid with lithium hydroxide.
b) propanoic acid with potassium hydroxide
c) formic acid with sodium hydroxide
d) Naproxen (Aleve) has the formula shown below. Circle the carboxylic acid functional group. What other functional groups are in the molecule? What is the 2 aromatic ring system called?

Naproxen is frequently administered as naproxen sodium in which the naproxen has been neutralized with sodium hydroxide, because the carboxylate is less irritating to the stomach than the carboxylic acid and it is more water soluble. In the case of drug names the positive ion is often put after the name of the negative ion: naproxen sodium.

Show the equation for the neutralization with sodium hydroxide.



e) Valproic acid is the common name for an anti-seizure medication and has the formula shown below. Give the systematic name for valproic acid Circle the carboxylic acid functional group. It is frequently administered as valproate sodium in which the valproic acid has been neutralized with sodium hydroxide. Show the equation for the neutralization

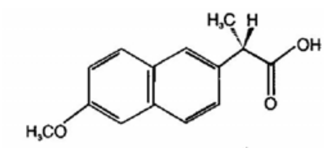
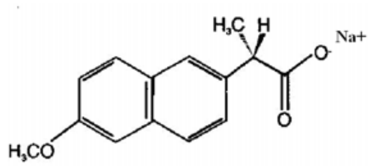


Answers:

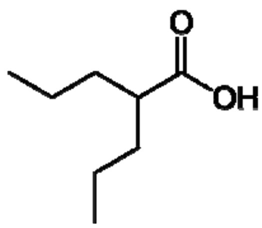
a) $CH_3(CH_2)_2\overset{\overset{O}{\|}}{C}OH + Li^{+} + OH^{-1} \longrightarrow CH_3(CH_2)_2\overset{\overset{O}{\|}}{C}O^{-1}\ Li^{+1} + H_2O$

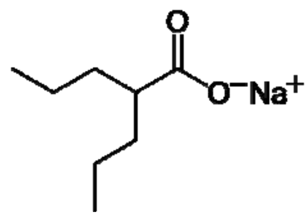
b) $CH_3CH_2\overset{\overset{O}{\|}}{C}OH + K^{+} + OH^{-1} \longrightarrow CH_3CH_2\overset{\overset{O}{\|}}{C}O^{-1}\ K^{+1} + H_2O$

c) $H\overset{\overset{O}{\|}}{C}OH + K^{+} + OH^{-1} \longrightarrow H\overset{\overset{O}{\|}}{C}O^{-1}\ K^{+1} + H_2O$

d)  + Na^+ + OH^{-1} —> 

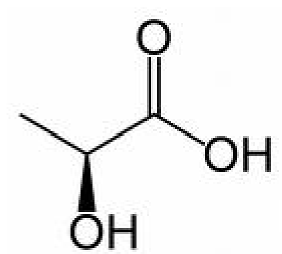
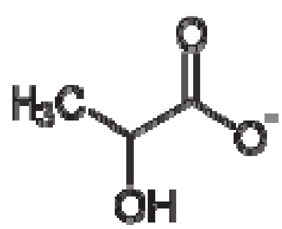
e)



+ Na + OH^{-1} —> 

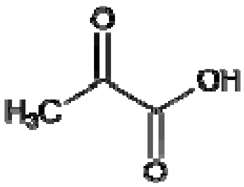
In most human tissues the pH is slightly alkaline (e.g. the pH in arterial blood is 7.4) and most physiologically important carboxylic acids in the body exist primarily in the carboxylate ion form rather than in the carboxylic acid form.

Many texts talk about **lactic acid** build up in the blood during anaerobic exercise when it fact most (about 99.99%) of the lactic acid exists primarily in the ionic **lactate ion** form in the blood.

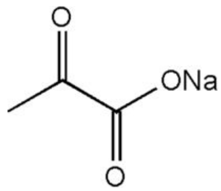
 <________> 

Lactic acid Lactate ion

Don’t worry about it if you see one source refer to lactic acid and another to lactate.
Other common carboxylic acids in the body include citric acid, pyruvic acid and many others; like lactic acid they actually exist in the body primarily as carboxylate ions: citrate ions and pyruvate ions.



Pyruvic acid

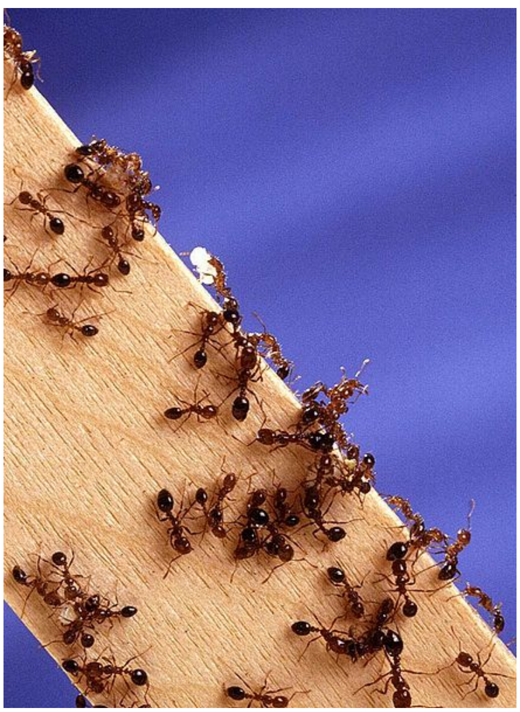


pyruvate

You are likely to see both the acid and ion form names of these physiological acids and you should be comfortable switching back and forth.

4.3 Common carboxylic acids with practical uses.

Methanoic acid (formic acid) is an acid found in some ants' sting . The name formic acid comes from the Latin for ant: formica). The pain associated with brushing nettles is also due to formic acid released from the tiny hollow hairs on the surface of the leaves.



Creative commons: Fire ants Author: FangHong USDA

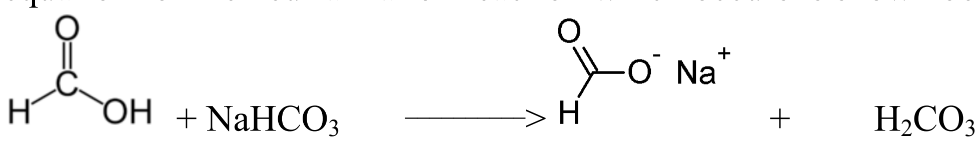
The Ant

The ant has made himself illustrious
Through constant industry industrious.

So what?
Would you be calm and placid
If you were full of formic acid?

-- Ogden Nash   Thanks to Seth Anthony!

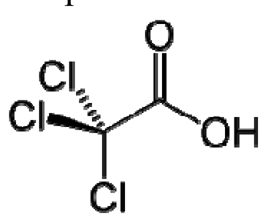
If one rubs a sodium bicarbonate paste on the afflicted surface **quickly**, it will neutralize the formic acid and some of the pain will be eliminated. The equation for the neutralization reaction which occurs is shown below.



What are the names of the two products formed?

Ethanoic acid (acetic acid) is the primary acid in vinegar (the term acetic comes from Latin acetabulum-a shallow cup used in Roman times for vinegar).

Trichloroacetic acid(TCA) is a stronger acid than acetic acid. It is used to chemically burn warts and for facial peels. It is potentially as corrosive as sulfuric acid and needs to be treated with care! As is the case with phenol, the concentration of the trichloroacetic acid and the amount of time the skin is exposed need to be monitored carefully.



A quote from some internet ads given below.

Nomelan Phenol Solution Peels
Photodamage, Hyperpigmentation
• **Phenol Light 60ml**
Indications
Photo types I, II III (blondes) not sensitive
Superficial hyperpigmentation
Acne-prone
Freckles

Key ingredients:

15% TCA
8% Phenol
Retinoic acid
Phytic acid
Glycolic acid
Salicylic acid
Ascorbic acid
Mandelic acid

TCA
TCA removes ageing layers of skin that are damaged by various organic or external processes. It coagulates cutaneous proteins by destroying the epidermal layer, which is later replaced by a new epidermis and new connective tissue.

Phenol
produces a powerful keratolytic effect while destroying cell sulfides of the keratin layer.

Alpha-hydroxyacids mix
Characterized by their humectant, keratoplastic, keratolytic, and sebum-regulating properties. They also improve the quality of the elastin fibers that tend to become longer, less fragmented, and more undulated.

Salicylic acid
Keratolytic properties are directly related to the intercellular cement of the corneocytes. Its comedolytic properties are due to its capacity to mix with the follicle

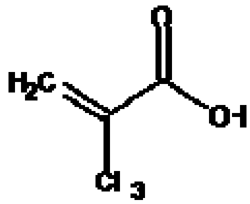
Phytic acid
Used as a bleaching agent. It blocks iron and receives melanin during its formation.

Retinoic acid
Retin-A Regulates keratinization, enhancing the cellular renovation process. Retinoic acid improves the appearance and overall quality of the skin. Retinoic acid nourishes the skin, prevents wrinkles, diminishes the depth of existing wrinkles, and improves the elasticity of aging skin while stimulating fibroblasts.
It synthesizes connective tissue molecules, particularly collagen. In addition, it regulates melanocyte activity and attenuates spots caused by excessive exposure to UV rays.

Propanoic acid (propionic acid) is an acid produced by several species of the bacteria genus *Propionibacterium. Propionibacterium acnes* grows on people's skins and uses oils from the sebaceous glands as an energy source. It also produces propionic acid as a product and is responsible for causing acne. Propionibacterium freudenreichii is a bacterium that produces the CO_2 gas bubbles in Swiss cheese and the propionic acid is partially responsible for the unique flavor of Swiss cheese.

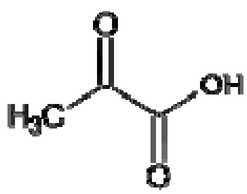
2-propenoic acid

The molecule **2-propenoic acid** has the structure:

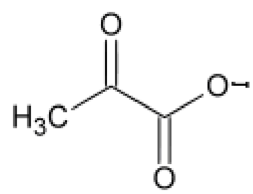


and the common name **methacrylic acid**. It is used for making acrylic polymers such as those that make artificial nails.

Pyruvic acid has both a ketone and a carboxylic acid functional group is formed from the metabolism of glucose and other sugars. As discussed in section 4.2, it actually exists primarily as pyruvate ion at physiological pH (pH 7.4).



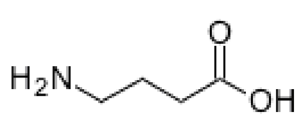
or



Butanoic acid (butyric acid) was first isolated from rancid butter (from the Latin butyrum = butter). It is also found in vomit, Parmesan cheese and is produced by **colonic bacteria** from various types of dietary fiber. A variety of contradictory claims are found in the research literature as to whether butanoic (butyric) acid in the colon increases or decreases the risk of colon cancer.

4-aminobutanoic acid (Gamma aminobutyric acid or GABA)

$$\underset{\gamma}{NH_2CH_2}\,\underset{\beta}{CH_2}\,\underset{\alpha}{CH_2}\overset{O}{\overset{\|}{C}}OH$$

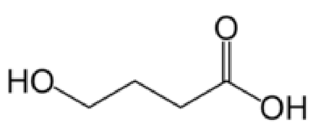


This molecule contains an amine group on the fourth C from the carboxylic acid group. Like the previous example the numbering starts at the carboxylic acid group. The "amine" functional group name is changed to amino when it is part of a bigger molecule. Hence we have 4-aminobutanoic acid.

An older naming system names the C atoms "downstream" from the carboxylic acid functional group as alpha(α), beta(β), and gamma(γ C atoms. The α C is the C adjacent to the C in the carboxylic acid functional group).

Hence the older (but commonly used) name for this molecule is **gamma aminobutyric acid, abbreviated GABA.** This molecule is a very common (and important) neurotransmitter in the brain which can cause **lowering of CNS activity.** It is readily available over the counter as a "dietary supplement" to treat depression, PTSD, anxiety, and many other conditions. GABA does not appear to cross the blood brain barrier, making it questionable whether it has any effect beyond placebo for these various CNS problems.(Valium).

4-hydroxybutanoic acid (gammahydroxybutyric acid, GHB)



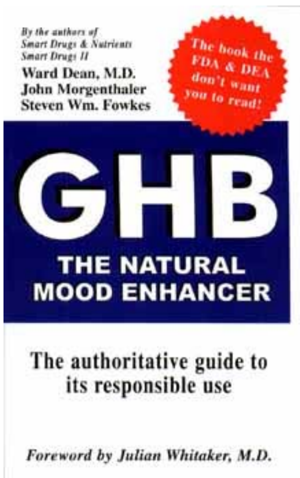
4-hydroxybutanoic acid or 4-hydroxybutyric acid is better known by its common name of **gamma hydroxybutyric acid** and its abbreviation, **GHB.**

$$\mathrm{HO}\underset{\gamma}{\mathrm{CH_2}}\underset{\beta}{\mathrm{CH_2}}\underset{\alpha}{\mathrm{CH_2}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{OH}$$

The drug is often neutralized with sodium hydroxide to produce the sodium salt of GHB.

$$\mathrm{HO}\underset{\gamma}{\mathrm{CH_2}}\underset{\beta}{\mathrm{CH_2}}\underset{\alpha}{\mathrm{CH_2}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{OH} \;+\; \mathrm{NaOH} \longrightarrow \mathrm{HOCH_2CH_2CH_2}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{O^{-1}}\ \mathrm{Na^{+1}}$$

It has been a popular recreational drug with street names such as Juice, Liquid Ecstasy, G, and Fantasy. It can cause feelings of euphoria, increased libido, and sociability. It can also cause amnesia, unconsciousness at higher dosages, leading to its use as a date rape drug. It has a structure very similar to GABA and acts to decrease the activity of the central nervous system (CNS) and high dosages (or susceptible individuals) can lead to extreme reduction in breathing rate (respiratory depression) which can cause death.



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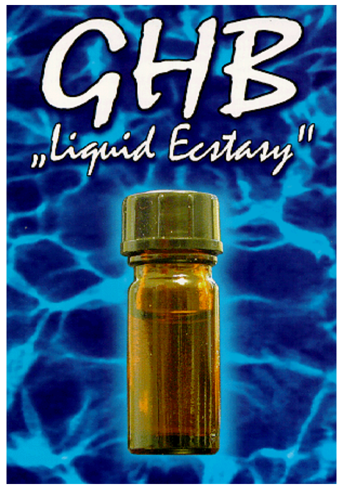

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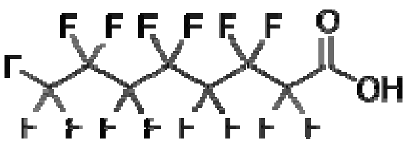
fnnc.org

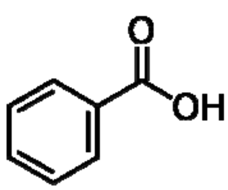
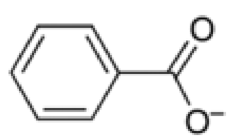
Perfluorooctanoic acid (PFOA)

Perfluorooctanoic acid (PFOA) is a molecule of octanoic acid that has had **all** the H atoms replaced with F atoms.



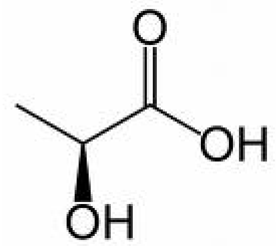
PFOA is used to make grease resistant carpeting, food packaging and Teflon. There is particular concern about its use in packages of microwavable popcorn as the perfluoroctanoic acid can leach into the popcorn at high temperatures. It has been classified as a "likely carcinogen", meaning that it has been found to be a carcinogen in animal tests although there is not enough data to determine whether it is a carcinogen for humans. Like chlorinated compounds, fluorinated compounds are only very slowly metabolized, and thus have the potential of accumulating in the environment. Dupont, the major manufacturer of Teflon, has agreed to reformulate the way Teflon and grease resistant PFOA are made so as to eliminate emissions into the environment.

Benzoic acid is a mold inhibitor and can be neutralized with NaOH to form sodium benzoate in a neutralization reaction.

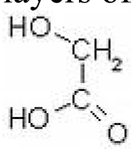
 + NaOH ———>  $Na^+ + H_2O$

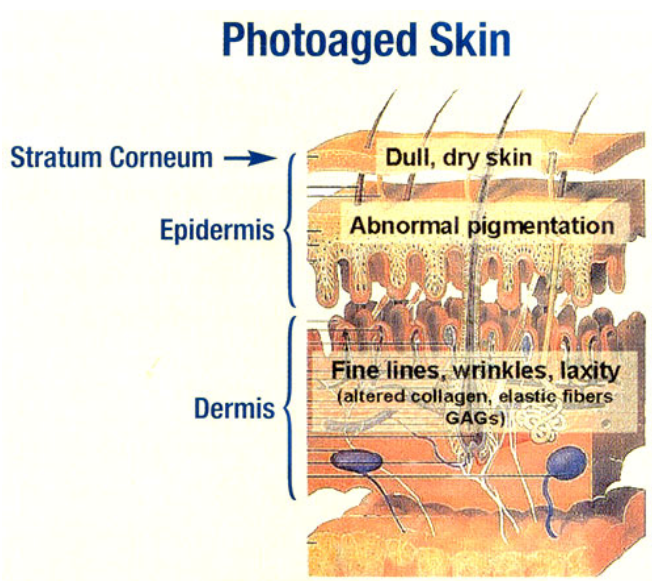
The sodium benzoate is more water soluble than benzoic acid (because the ion wants to be in water even more than the polar OH group). Sodium benzoate is also used as a food preservative, inhibiting mold growth.

Lactic acid (2-hydroxypropanoic acid) is produced by Lactobacillus acidophilus in yogurt and by your muscle cells during anaerobic exercise. It is also used in a variety of skin care products.



Glycolic acid (2-hydroxy acetic acid) is sold in a variety of skin care products for removing wrinkles and making skin look younger. It works the same way as phenol and trichloroacetic acid, dissolving away the outer layers of skin, but it is milder in its action.


Glycolic acid



botonics.co.uk

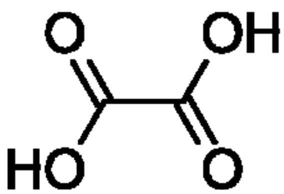
Oxalic acid is found in rhubarb (especially the leaves), and in lesser amounts in spinach, beets and some other plants. It has 2 carboxylic acid groups and can be neutralized completely to form the oxalate ion.

Creative commons:Author Maksim

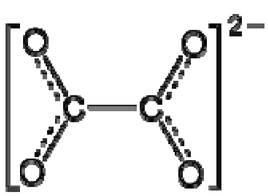
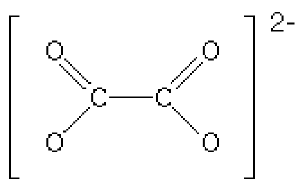
Creative commons: Arria Belli

Oxalic acid

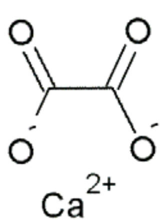
sodium oxalate



+ 2 NaOH —>

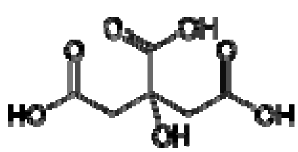
Na_2  or Na_2  + 2 H_2O

The oxalate ion can combine with Ca^{+2} ions to form insoluble calcium oxalate, the most common compound in kidney stones.



Patients who have had one kidney stone are at increased risk of additional kidney stones and are advised to avoid foods high in oxalate. Cooking destroys oxalic acid, so cooked rhubarb and spinach do not contain oxalic acid (or at least not as much). In high concentrations oxalic acid (oxalate ion) can form crystals with Ca^{+2} rapidly, causing kidney damage. There have been a few isolated cases of dietary oxalic acid poisoning due to consumption of substantial amounts of raw rhubarb leaves. Oxalic acid is also available in hardware stores for cleaning off iron stains.

Citric acid is found in berries, fruits, especially lemons and oranges; it is found in small quantities in all cells because its a essential component in the citric acid cycle (also called the tricarboxylic acid cycle or Krebs cycle), an essential part of glucose metabolism. Based on the structure of citric acid, why is the Krebs cycle also called the tricarboxylic acid cycle?



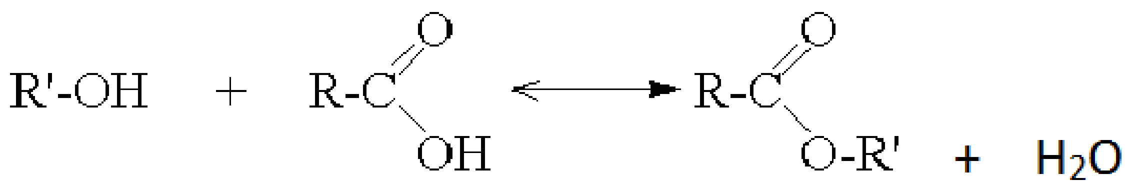
10-undecenoic acid (undecylenic acid) is a monounsaturated 11 C carboxylic acid which is used to treat epidermal fungal infections like athlete's foot. It is the active ingredient in several over the counter products

hotfrog.com.mx

zetacleartoenailfunguscure.info

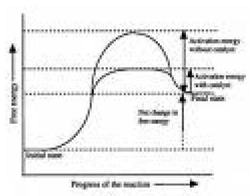
4.4 Formation of Esters from Carboxylic Acids and Alcohols

Carboxylic acids can react with alcohols to form esters, a reaction called **esterification.**

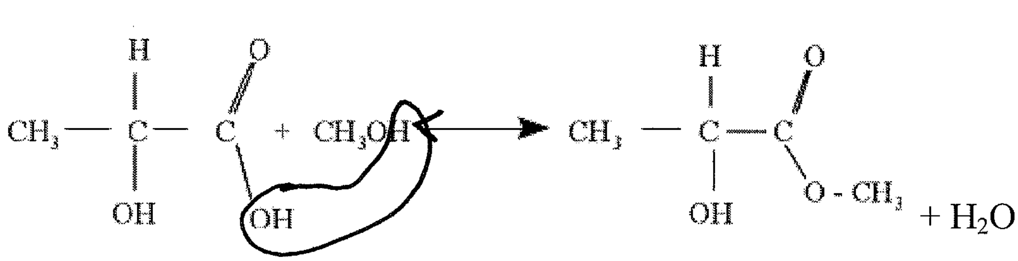


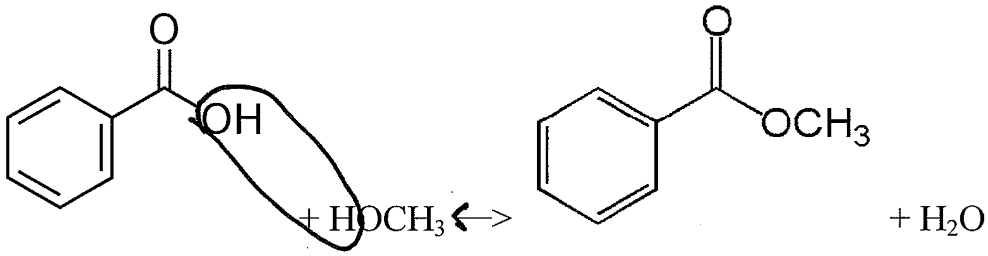
alcohol acid ester

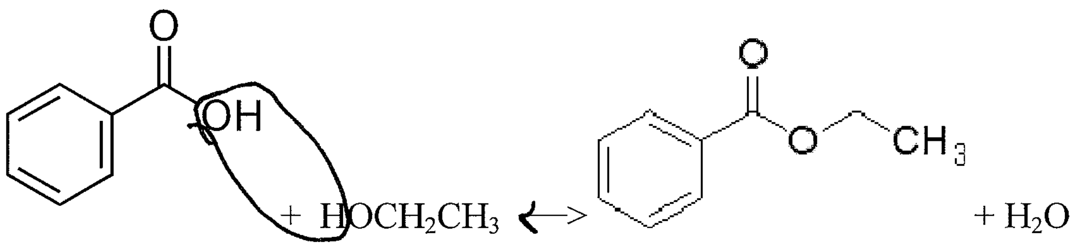
This is an endergonic (endothermic) reversible reaction with a high activation energy barrier in the absence of a catalyst. The esterification reaction profile is



In the forward direction it is called an **esterification** reaction, because it produces an ester. In the reverse direction it is called a **hydrolysis** reaction because it breaks up the ester and adds a water molecule in the process. Note that a water molecule is removed in the process of forming the ester from the carboxylic acid and the alcohol. The water comes from removing an OH group on the carboxylic acid and combining it with a H. One can show this using “lasso” chemistry as shown



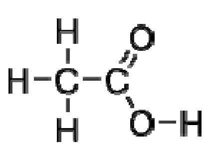


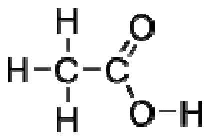
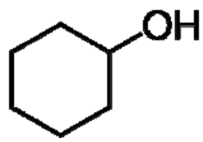


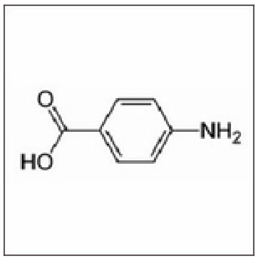
+ H_2O

(One might wonder how the ester gets formed in the first place, given that it is uphill from the carboxylic acid and alcohol molecules. In fact in biological systems the carboxylic acids are not the reactive molecule itself. The carboxylic acid is activated (energy level raised) by attaching a group which raises its energy level. It is this activated carboxylic acid which reacts with the alcohol and due to the high energy of the activated carboxylic acid, this reaction is exergonic. Once formed the ester often has an activation energy barrier that is high enough that hydrolysis will not occur unless a specific ***esterase*** *enzyme is present.)*

Draw the products of the following reactions

 + $HOCH_3$ $\xrightarrow[H^+]{}$

 +  — H^+—>

 + $HOCH_2CH_3$ — H+———>

Para aminobenzoic acid + ethanol —> benzocaine(product)

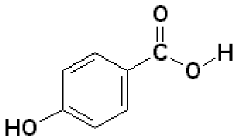
Benzocaine is commonly used as a topical ester local anesthetic to reduce the pain of sunburn and to temporarily reduce dental pain.

Creative commons: r [Kelly Sue DeConnick]

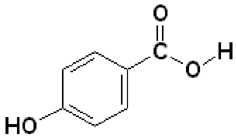
kaboodle.com

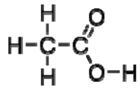
senses.typepad.com

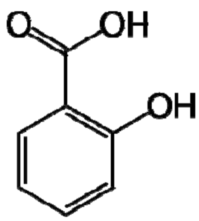
Note that the benzene ring has both an alcohol and a carboxylic acid functional group in the next four problems. Which group on the benzene ring will react in each of the above examples? Remember that you need an alcohol and a carboxylic acid in order to form an ester!



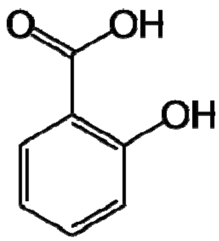
+ $HOCH_3$ $\xrightarrow{H+}$

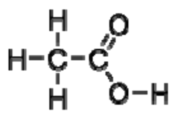


+  $\xrightarrow{H+}$

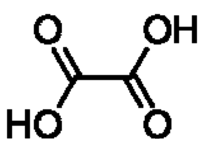


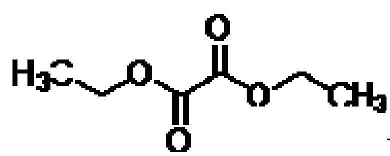
+ $HOCH_3$ ⟶

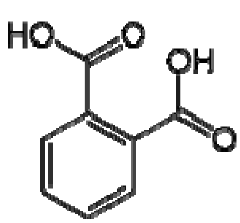


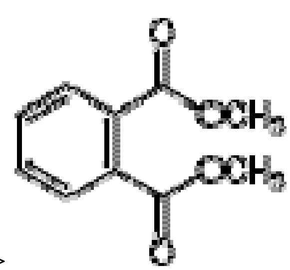
+  H^+⟶

If there are two carboxylic acid functional groups in the molecule, it can react with 2 alcohol molecules and form a **diester.**

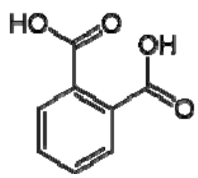
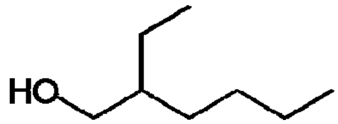
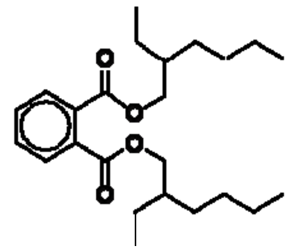


+ 2 $HOCH_2CH_3$ ⟶  + 2 H_2O



+2 $HOCH_3$ ⟶  + 2 H_2O

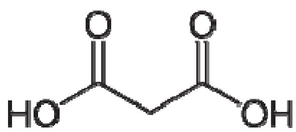
(ortho) phthalic acid

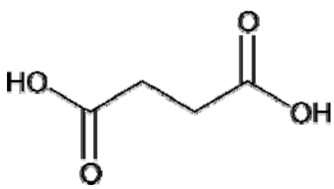
 + 2  ⟶  + 2 H_2O

Phthalic acid 2-ethylhexanol DEHP

What is DEHP used for?

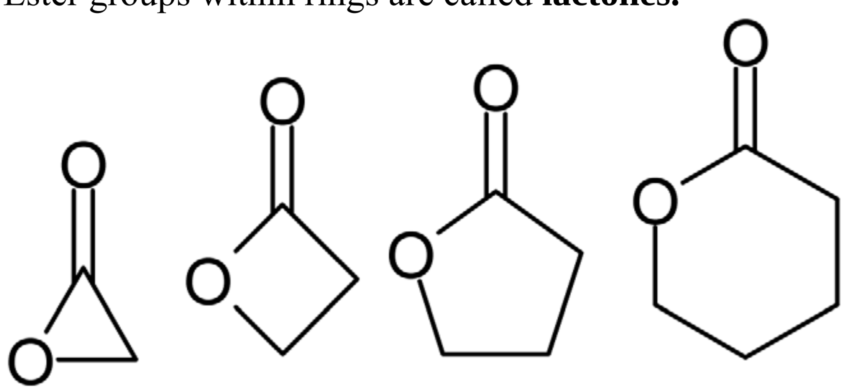
Practice problems

 + 2 $HOCH_3$ ⟶

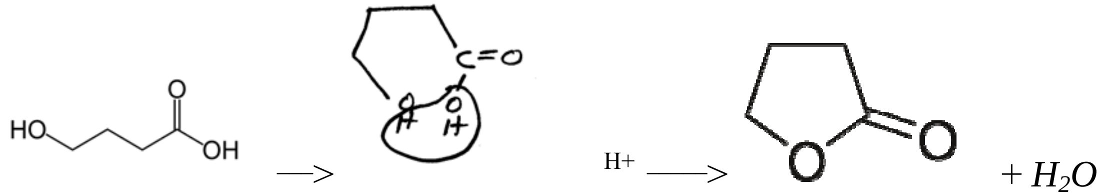
 + 2 $HOCH_2CH_3$ ⟶

Lactones

Ester groups within rings are called **lactones.**

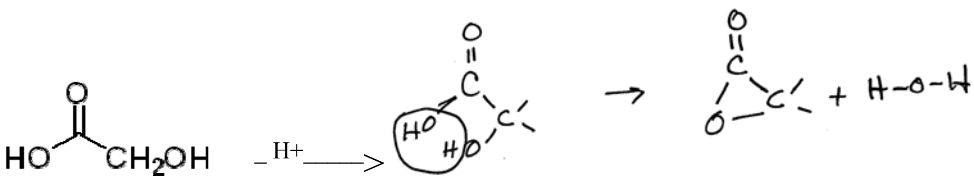


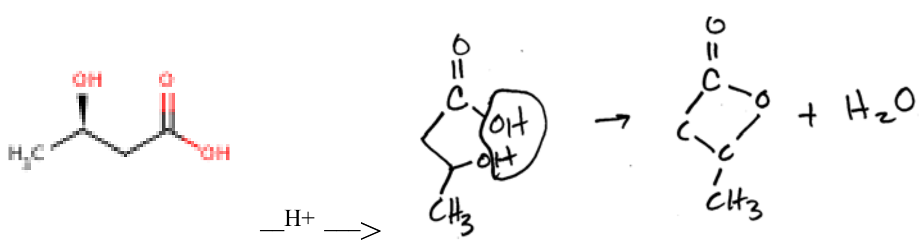
A lactone is made by forming an ester group from a carboxylic acid and alcohol on the same molecule, forming a ring in the process.



We've seen the above reactant molecule before, gamma hydroxybutyric acid (GHB). It is a sedative that was readily available in health food stores until 2000 when it was made illegal (schedule I) due to increasingly widespread abuse, particularly as a "date rape" drug. It is easily synthesized and is commonly made in "kitchen labs". GHB can be made into the GHB lactone form shown above. It may be sold as a paint stripper "solvent" without any claims of pharmacological properties (wink, wink!). In the body the ester is hydrolyzed by an enzyme back into gamma hydroxybutyric acid.

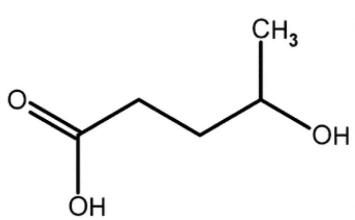
Additional sample problems of lactone formation



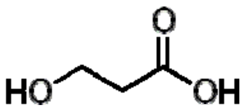


Will the above lactones be stable? Why or why not?

Form lactones from the following molecules.

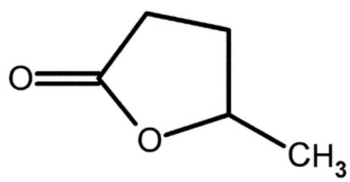
a) 

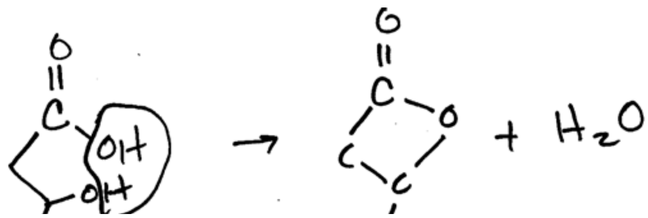
__H+___>

b)  $\xrightarrow{H^+}$

Why won't the last product be stable?

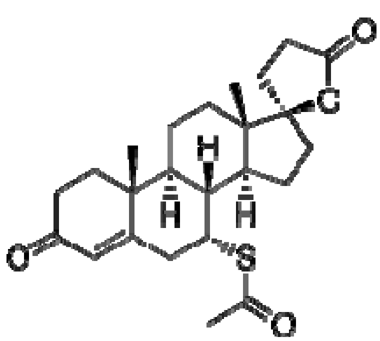
Answers:

a) 

b) 

4-membered ring will have bond angle strain.

Spironolactone(Aldactone) is a potassium sparing diuretic which is also used for treating congestive heart failure and off-label (not officially approved by FDA) to reduce excessive hair growth. Circle the lactone ring. What other functional groups are in spironolactone?



4.5 NAMING OF ESTERS

Esters are named on the basis of the alcohol and the carboxylic acid from which they are formed. The naming system is a little complex , but once you've got the idea, it is straightforward.

1) Identify the portion of the ester that came from the carboxylic acid, and that which came from an alcohol.
2) Take the name of the IONIC form of the carboxylic acid.

3) In front of that, put the name of the alkyl group which came from the alcohol.

These rules are best illustrated with examples:

$H-\overset{H}{\underset{H}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3$	$CH_3CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$	$CH_3CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3$
Methyl ethanoate or Methyl acetate	ethyl ethanoate or ethyl acetate	propyl ethanoate or propyl acetate

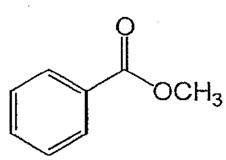
$H-\overset{H}{\underset{H}{C}}-O-\overset{O}{\overset{\|}{C}}-H$	$CH_3O\overset{O}{\overset{\|}{C}}CH_3$	$CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_3$	$CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$
Methyl methanoate Methyl formate	methyl ethanoate methyl acetate	methyl propanoate methyl propionate	methyl butanoate methyl butyrate

Name the following:

$CH_3(CH_2)_2O\overset{O}{\overset{\|}{C}}(CH_2)_3CH_3$ $CH_3(CH)_4O-\overset{O}{\overset{\|}{C}}-CH_2CH_3$

$CH_3(CH_2)_2O\overset{O}{\overset{\|}{C}}-CH_2CH_2CH_3$ $CH_3CH_2O\overset{O}{\overset{\|}{C}}-H$

$CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_3$



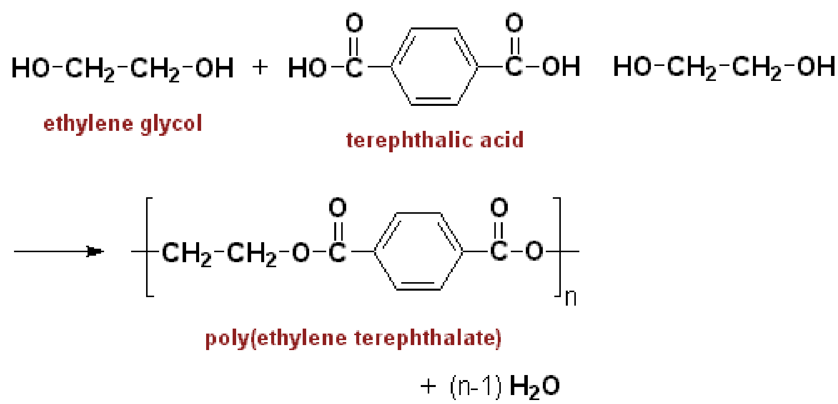
Answers:

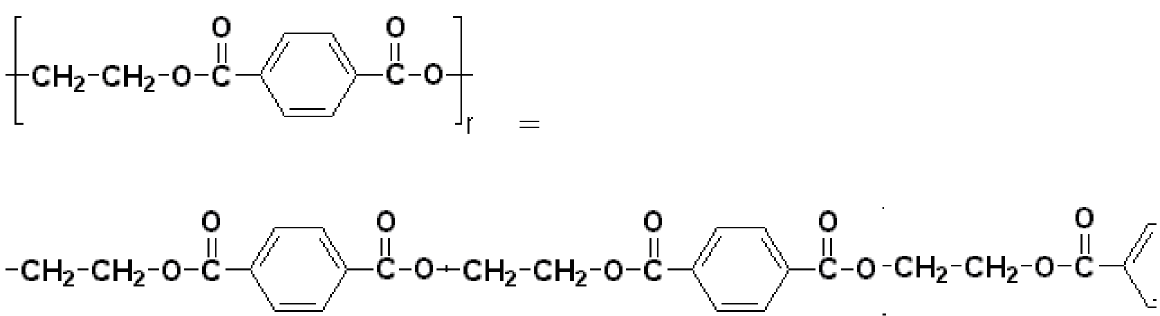
Propyl pentanoate	pentyl propanoate
propyl butanoate(butyrate)	ethyl methanoate(formate)
propyl propanoate(propionate)	
methyl benzoate	

4.6 FORMATION OF ESTER POLYMERS

a)One can form **polyester polymers** by reacting multiple molecules and covalently linking them together by ester linkages. Water is produced as a product along with the ester polymer and these types of polymers are called **condensation polymers.**

Polyethylene terephthalate(PET or PETE) is a common example of a polyester made from the dicarboxylic acid, terephthalic acid (paraphthalic acid), and ethylene glycol (the active ingredient in antifreeze). It is used in plastic bottles and a variety of clothes, suits, curtains. As a fiber, PETE is often labeled as Dacron and is frequently interspersed with fibers of wool or cotton in clothes and other cloth products.

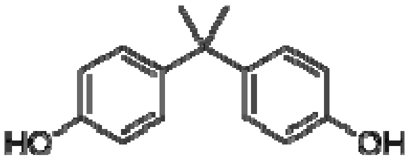




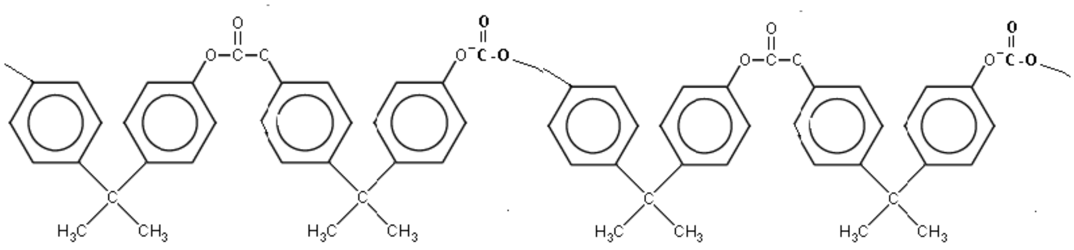
In plastics recycling PETE is labeled as #1.

b)Polycarbonate plastics

Most polycarbonate plastics are made from the monomer, bisphenol-A.



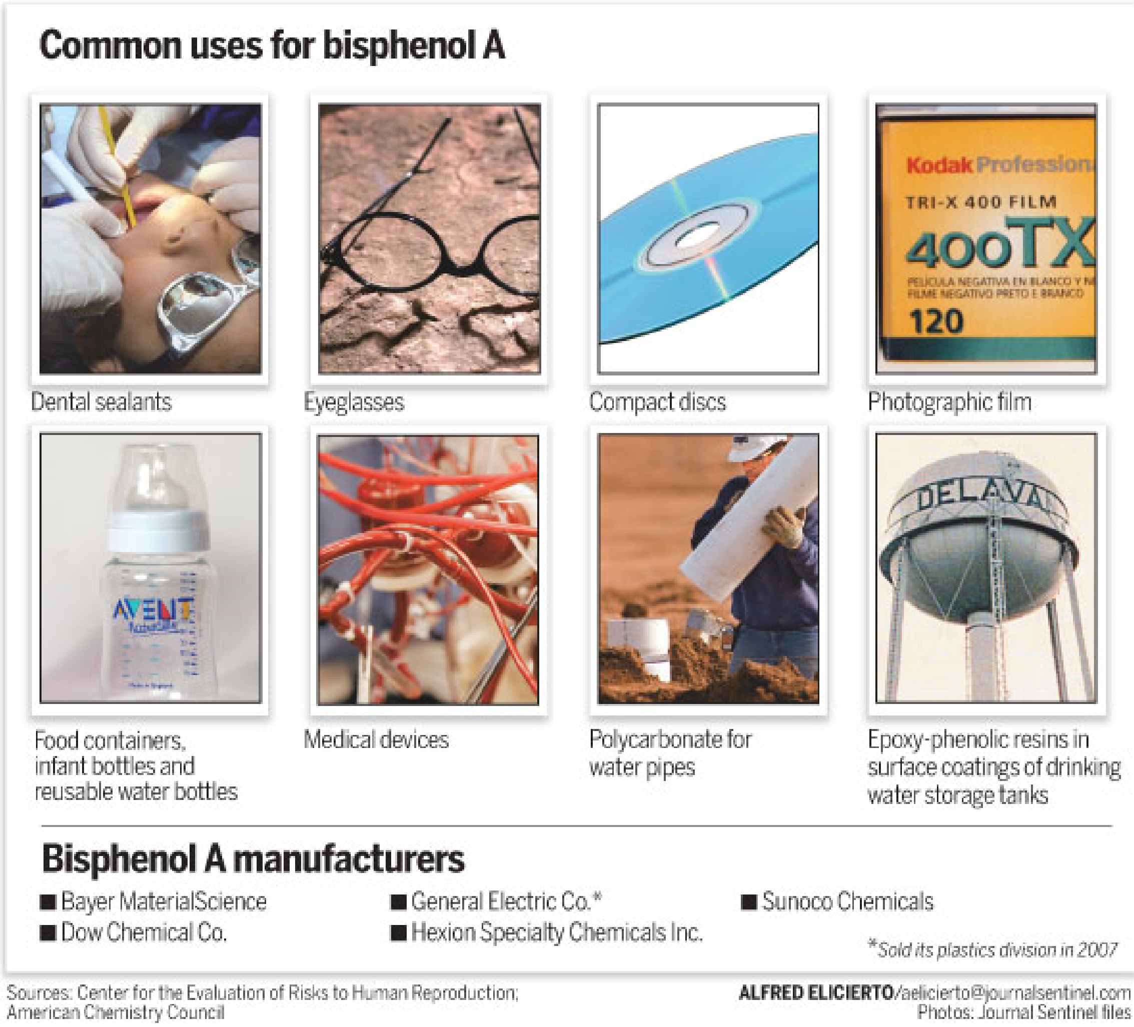
The bisphenolA monomers are then linked with carbonyl (C=O) groups to make **polycarbonate** plastics.



Polycarbonate plastics are light and very strong and flexible; they have been extremely widely used to make water bottles, baby bottles, epoxy resins inside cans, as well as CDs and DVDs.

Creative commons: Nuno Nogueira (Nmnogueira)

Broken sphere



withonebreath.wordpress.com
Milwaukee Journal Sentinel

Creative commons: Howie Le

Creative commons:
Calliditas

There is increasing concern that small amounts of bisphenol A that leach out of these bottles and can linings may be **endocrine disruptors**. They do not have a separate recycling number of themselves and get labeled as 7 (others).

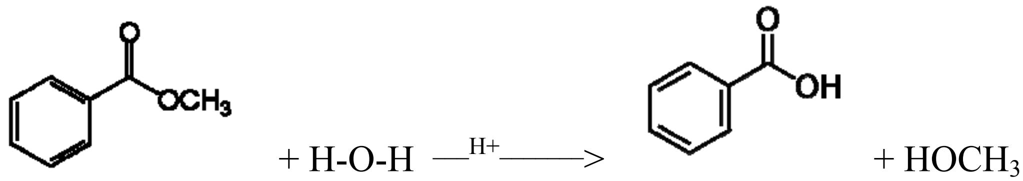
inspiredwater.org

epicplastic.com Creative commons: CAMBLLE

Food Safety Bill's Ban on BPA Resisted

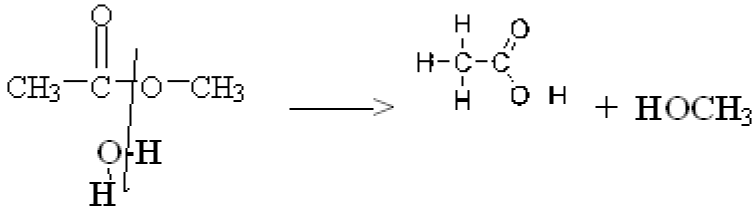
4.7 HYDROLYSIS OF ESTERS

Hydrolysis of esters is just the reverse of esterification:

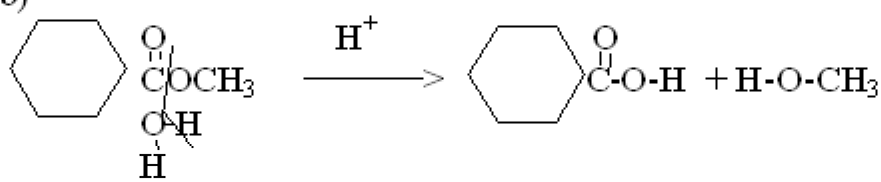


It may be easier to see how the ester is split in two by placing the H-O-H molecule strategically under the ester functional group, as shown.

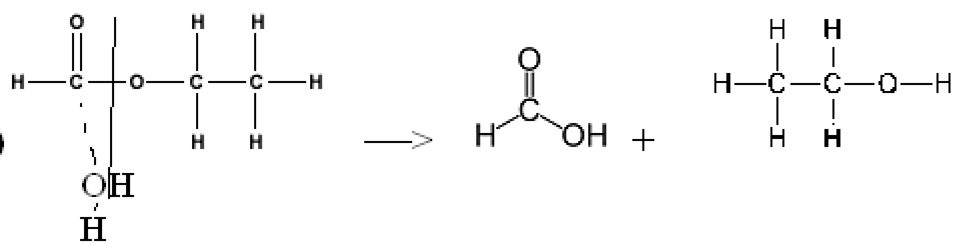
a)



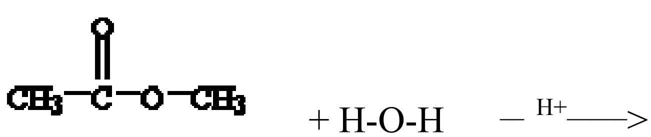
b)

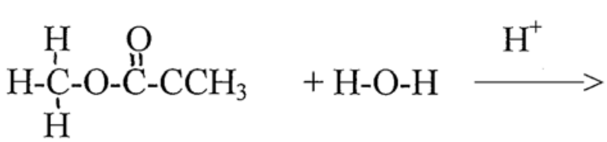


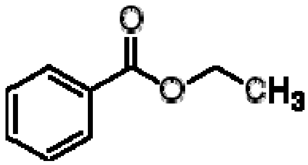
c)



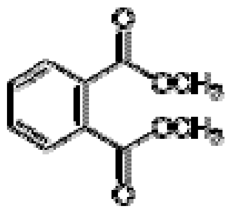
Try showing the hydrolysis for the following:



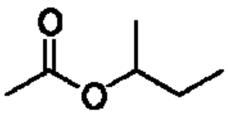




+ $H_2O \xrightarrow{H^+}$

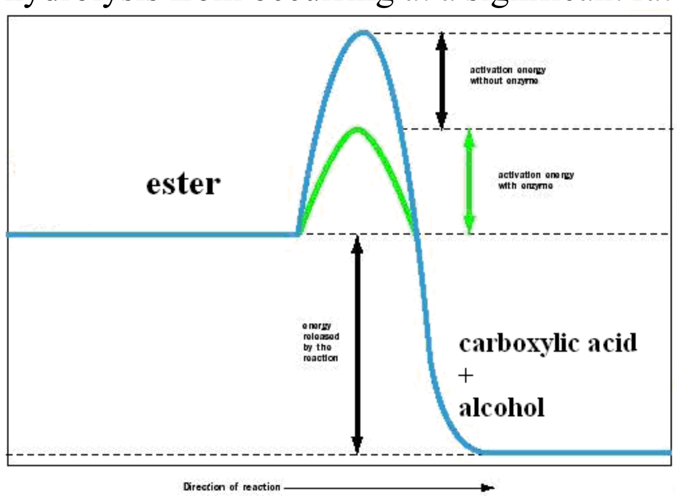


+ 2 $H_2O \xrightarrow{H^+}$

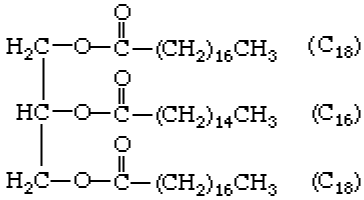


+ H-O-H $\xrightarrow{H^+}$

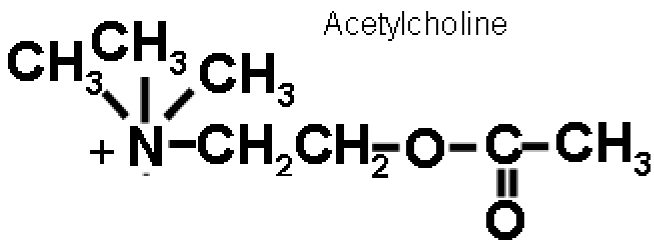
Hydrolysis of esters is an **exergonic reaction** . However in the absence of a catalyst the activation energy barrier is often high enough to prevent hydrolysis from occurring at a significant rate.

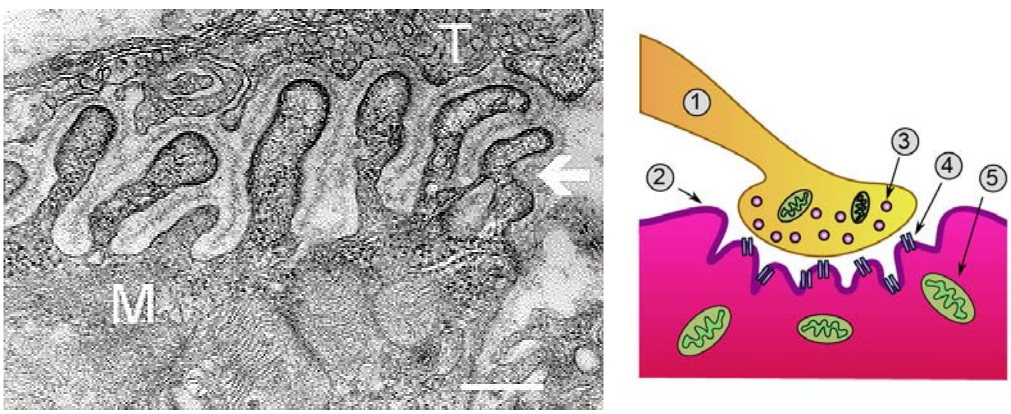


There are in fact a lot of stable ester compounds in biological organisms that do not hydrolyze at an appreciable rate unless a specific **esterase** enzyme is available to lower that activation energy barrier. Fats(triglycerides) contain 3 ester groups, but in the absence of esterase enzymes they hydrolyze only very slowly at typical biological temperatures and pH and can be stored in your body for long periods of time.



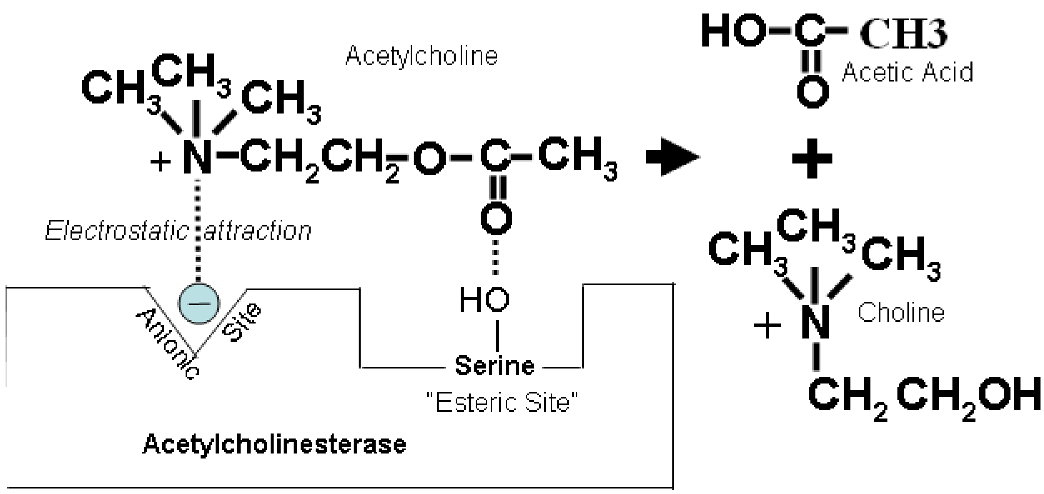
Acetylcholine(structure shown below) is a neurotransmitter released at the **neuromuscular junction** and elsewhere. Acetylcholine is released from the ends of neurons at muscle. The acetylcholine binds to receptors in the membrane of the muscle cells and stimulates contraction of the muscle. contains 2 functional groups. Name them.





Wikipedia:"neuromuscular junction"

It is important that this activity not continue indefinitely and so an enzyme **acetylcholinesterase** is present which catalyzes the hydrolysis of the acetylcholine ester bond.



Adapted from: www.atsdr.cdc.gov/.../pam_medications.html

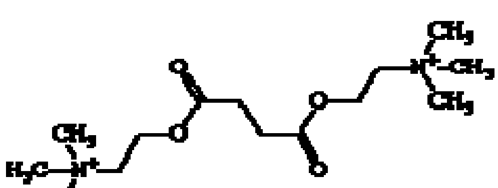
The separate product molecules no longer bind to the acetylcholine receptor site. Thus hydrolysis terminates the activity of the acetylcholine.

or written another way

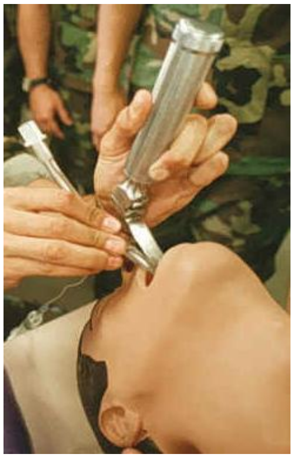
$$\mathrm{CH_3\overset{+CH_3}{\underset{Cl^-\ CH_3}{N}}CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3 + H_2O} \xrightarrow{\text{acetylcholinesterase}}$$

$$\mathrm{CH_3\overset{+CH_3}{\underset{Cl^-\ CH_3}{N}}CH_2CH_2OH + HO\overset{O}{\overset{\|}{C}}CH_3}$$

Succinyl choline (sometimes abbreviated sux) is an IV neuromuscular **blocker** sometimes used to relax the muscles during surgery. Succinyl choline (or molecules like it) can be used to relax the tracheal muscles when inserting a plastic tube into the trachea to ensure an adequate air supply **(intubation**). This may be done either to allow mechanical respiration during surgery or to overcome airway obstructions due to trauma or other causes.

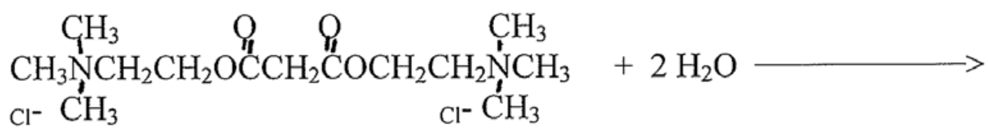


Succinylcholine

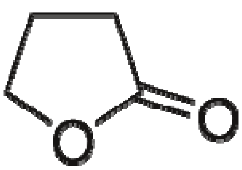
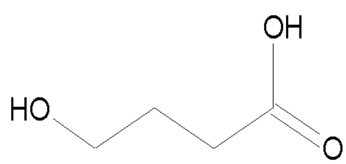


Creative commons: PD-LAYOUT; PD-USGOV-MILITARY-MARINES.

Succinylcholine binds the same receptors as acetylcholine, but after initial muscle contraction it causes relaxation. Among other adverse effects, patients tend to feel post-operative muscle pain from the initial extensive muscle contraction. It is hydrolyzed by an enzyme in the blood stream called pseudocholinesterase. Draw the structure of the products formed from the hydrolysis of succinyl choline.

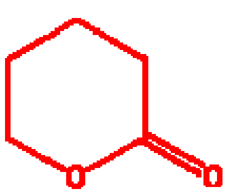


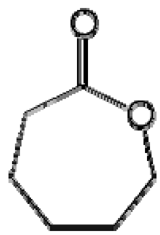
Lactones (ester rings) can be hydrolyzed in similar fashion

 + H-O-H $\xrightarrow{H+}$ 

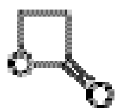
GHB lactone GHB

Try showing the hydrolysis product of the following:

 + H_2O $\xrightarrow{H+}$



$+ H_2O \xrightarrow{H+}$



$+ \quad \text{H-O-H} \xrightarrow{H+}$

Can you predict why the original molecule in the third hydrolysis might not be too stable?

Esters have fruity smells.

Esters are responsible for many of the fruity smells and flavors found in fruits. Ethyl butanoate is a major component of peach flavor. Pentyl propanoate is a major component of apricot flavor. Methyl and ethyl acetate are found in pineapple along with other esters.
Draw their structures.

Most fruit smells and flavors actually result from a combination of several different esters. When fruits start to spoil the esters are often hydrolyzed into alcohols and carboxylic acids. The carboxylic acids are responsible for the sharp unpleasant flavor associated with spoiled fruit.

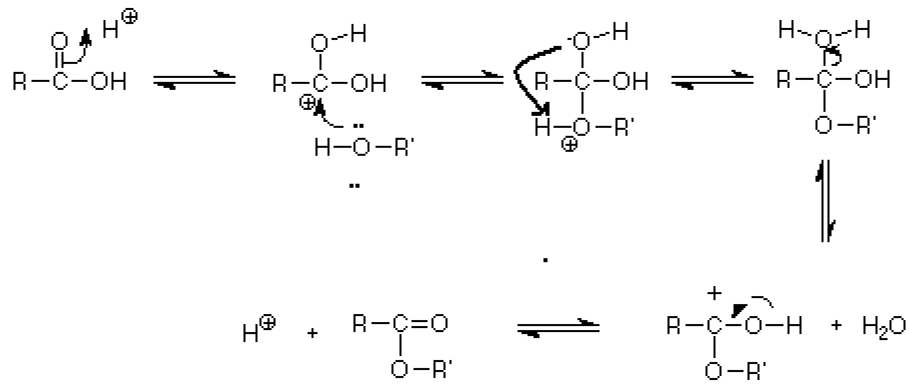
$$\underset{\text{fruity}}{R_1\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-O-}R_2} + H_2O \longrightarrow \underset{\text{sharp}}{R_1\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-O-H}} + R_2\text{-O-H}$$

Write the chemical equation for the hydrolysis of

a) methyl acetate (found in pineapples)
b) ethyl butanoate (in peaches)

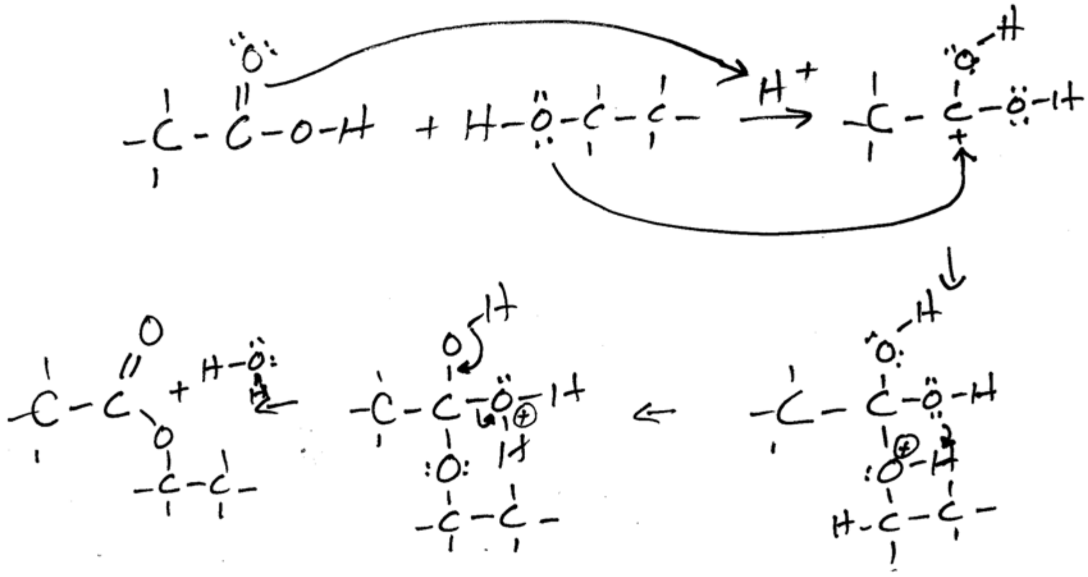
4.8 Reaction Pathway for Esterification

A somewhat simplified step- by- step reaction pathway for formation of an ester from a carboxylic acid and an alcohol is shown below.



Kirt Michael, Organic Chem Notes.

In the first step a pair of electrons of the carbonyl group pick up an hydrogen ion, forming a carbocation. The carbocation needs another pair of electrons and acquires them from a non-bonding pair of electrons on the O atoms of the alcohol. However this results in the O atom of the alcohol sharing three pairs of electrons instead of two and this puts a positive charge on the oxygen atoms. One of the OH groups on this intermediate can pick off the H , in the process forming a H-O-H "wannabe) with the oxygen atom still bonding to the C atom, and so it is also an oxonium ion. The H-O-H leaves, with the O atom taking the pair of electrons it shared with the C atom with it. This leaves the C with only 3 bonds, once again a carbocation! Since a hydrogen ion started off this whole process, it's only poetic justice that the hydrogen ion gets kicked out. The pair of electrons it shared then "flip back" and reform the double bond with the C atom. In the process the C=O carbonyl group is reformed and the hydrogen ion is regenerated; hence the hydrogen ion is a catalyst, since it was not used up in the reaction.
Let's look at the reaction pathway for reaction of acetic acid with ethanol to form ethyl acetate.

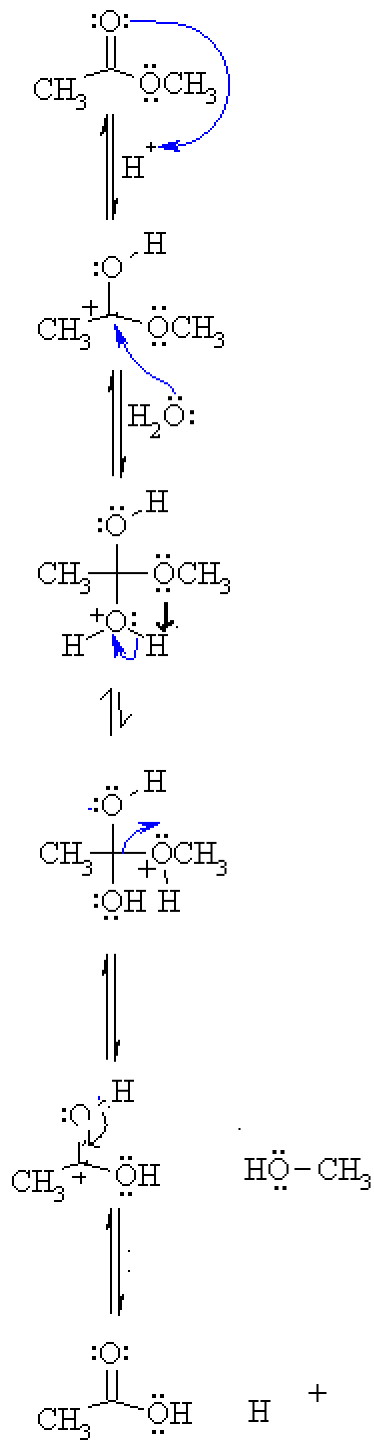


Go through and explain what is happening in each step of the above reaction, based on the general explanation given above.

Show the complete reaction pathway for the following reactions:

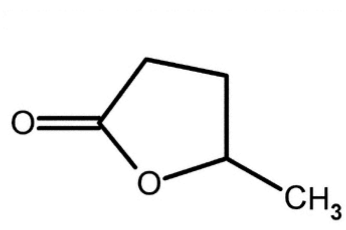
a) Butanoic acid and methanol with acid catalyst
b) Acetic acid and cyclohexanol with acid catalyst
c) Propanoic acid and ethanol with acid catalyst
d) 5-hydroxypentanoic acid

All of the above reactions are reversible and so ester hydrolysis with water back to a carboxylic acid and alcohol can occur by the same reaction pathway in reverse.
The reaction pathway for methyl acetate is shown.



Try doing the reaction pathway for the hydrolysis of

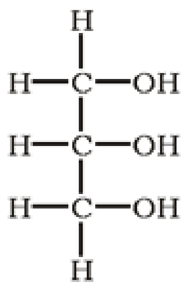
a) ethyl formate
b) propyl butanoate
c) butyl acetate
d)



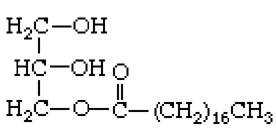
4.9 Triglycerides(Triacylglycerols)

One class of esters is particularly important in the nutritional areas and that is the class of esters formed from the alcohol glycerol (also called glycerin or 1,2,3 propanetriol).

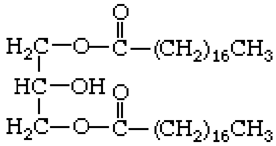
Figure 1. Structure of Glycerol



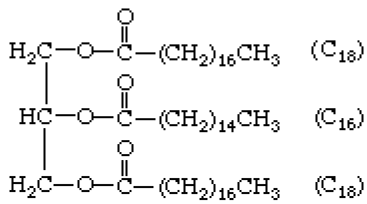
There are three alcohol groups here which can react with three long chain carboxylic acids, typically 12-20 Cs) called **fatty acids**. If one ester linkage is formed it is called a **monoglyceride or monoacylglycerol**. If two carboxylic acid molecules react to form two ester linkages it is called a **diglyceride or a diacyl glycerol.** If three carboxylic acids react to form three ester linkages, it is called a **triglyceride or a triacylglycerol**



Monoglyceride(monoacylglycerol)



Diglyceride(diacylglycerol)



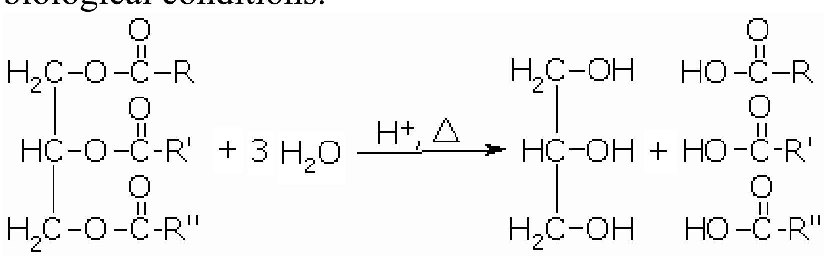
Triglyceride(triacylglycerol)

Fats and oils are both triglycerides; the only difference is that fats are solids at room temperature and oils are liquids at room temperature. The number of double bonds, i.e. the degree of unsaturation, is a major factor in determining the melting point. The higher the degree of unsaturation, the lower the melting point and the greater the tendency for the triglyceride to be liquid.

Certain brands of margarine commonly sold in grocery stores used to advertise that their products were fat free. If one read the label carefully, one found that monoglycerides and diglycerides were ingredients. Since monoglycerides and diglycerides are essentially equivalent to triglycerides in terms of their caloric value and their atherogenic potential, this claim was in fact quite misleading. Some brands of pastries and energy bars had similar claims. Stricter “truth in labeling” requirements have stopped this particular scam.

Hydrolysis of triglycerides

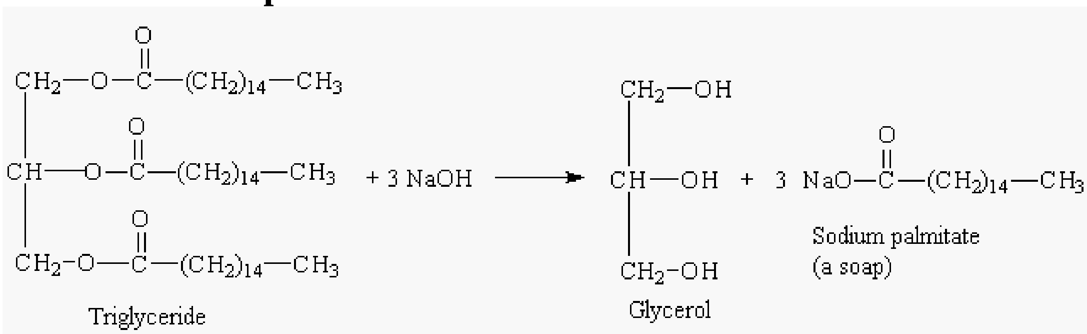
Triglycerides (fats) can be hydrolyzed to produce glycerol and 3 fatty acids in the presence of acid and heat or with a suitable **lipase** enzyme under biological conditions.



When these fatty acids are neutralized with base they produce carboxylate ions which are used as soaps.

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}H \;+\; Na^+ + OH^- \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}O^- \;\; Na^+ \;+\; H\text{-}\ddot{O}\text{-}H$$

The hydrolysis of triglycerides can also be carried out with base and this is the common way of doing it on an industrial scale. The hydrolysis and neutralization are carried out simultaneously and produces soap in a one step reaction called **saponification**.

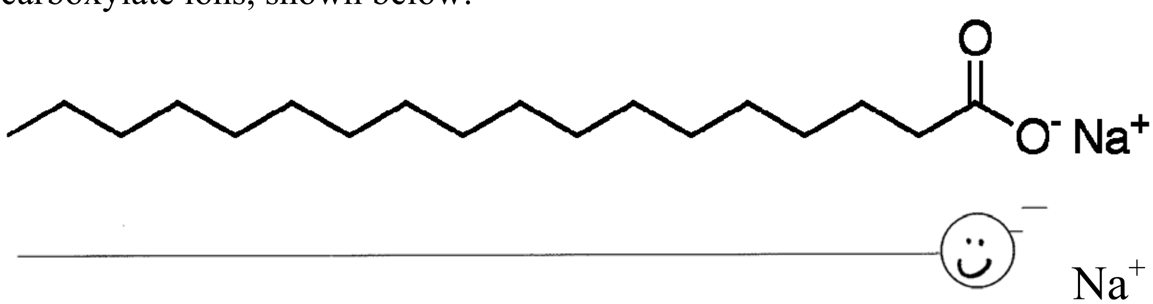


www.chem.latech.edu/.../L06U00Soap122.htm

4.10 Micelles and Soaps

The solubility of carboxylic acids is similar to that of alcohols and amines. The carboxylic acid is slightly more effective than an OH group in pulling a non-polar chain into water, but we will not worry about small differences and will stick to our 4:1 rule of thumb: one carboxylic acid functional group can solubilize a nonpolar chain of about 4 C atoms.
If we neutralize the carboxylic acid and convert it into a carboxylate ion, the ionic **carboxylate ion is much more effective** at pulling a non-polar chain into aqueous solution. The carboxylate ions can pull fairly long non-polar chains (up to about 18 C atoms) into solution. The carboxylate ions dissolve in solution by forming special structures called **micelles.** Micelles account for the cleaning action of soap and other similar molecules.

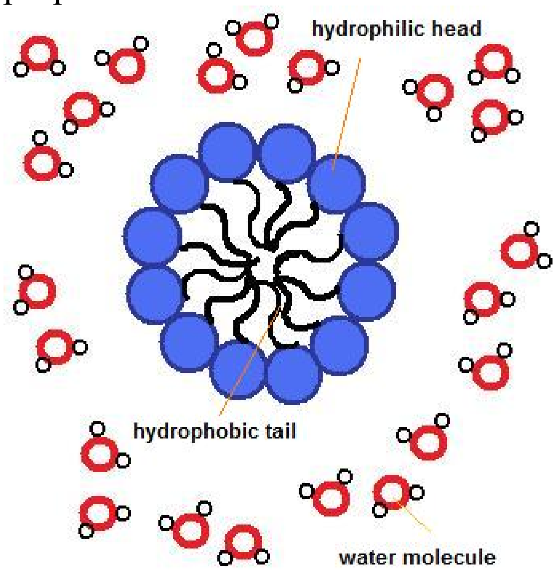
To discuss micelles, we will introduce a shorthand notation for the carboxylate ions, shown below:



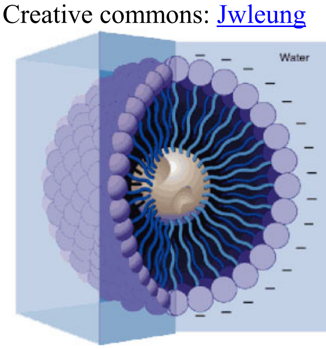
hydrophobic (lipophilic) **hydrophilic**

The portion that wants to dissolve in water is referred to as **hydrophilic** and is represented by a circle. The portion that does not want to dissolve in water is called **hydrophobic or lipophilic** and is represented by a line: the string on the balloon, so to speak. The negatively charged (anionic) carboxylate ion must have a positive ion (a cation) to balance its charge. When a K^+ is the ion, the result is soft soap; when Na^+ is the positive ion hard bar soap results. When Li^+ is the positive ion we end up with a hard soap with a very high melting point; this compound is not used for human cleaning action, but is added to some greases to provide cleaning action in axles!

A group of carboxylate ions form a micelle by forming a sphere with their **hydrophilic** portions in contact with the outside of the sphere and they hide their hydrophobic (**lipophilic)** portions inside the sphere. When one dissolves soap in water, the soap molecules form micelles and in fact the properties of micelles account for how soap works to dissolve grease.



Creative commons: Jwleung



grantscienceworld.com

Grease and fats are non-polar molecules and they won't dissolve in pure water. You can scrub that greasy plate in water all day long and all you'll get is a thin even distribution of grease on your plates. However, when you have soap dissolved in water micelles with nonpolar (hydrophobic) interiors are formed that can dissolve nonpolar compounds quite well. The grease molecules on the plate dissolve inside the soap micelles. Micelles cannot absorb an infinite amount of grease. As more non-polar molecules are added to the interior, the size of the micelle increases, but the number of hydrophilic groups on the surface does not. Eventually, the hydrophilic groups cannot solubilize the enlarging hydrophobic interior and a separate oil phase may start appearing in your dish water. Then its time for some new dish water!

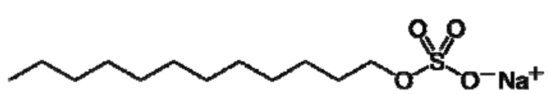
When the soap micelles dissolve fat into their hydrophobic (nonpolar) interiors, we say that the soap is **emulsifying** the oil or fat globules. The soap is pulling non-polar molecules into an aqueous solution where it would not normally be soluble. A solution containing micelles is referred to as an **emulsion.** Molecules that can form micelles are also referred to as **emulsifying agents, wetting agents, or surfactants (**a shortened word for surface active agent). If the surfactant molecule has a negative charge, it is referred to as an **anionic surfactant**; if the surfactant has a positive charge, it is called a **cationic surfactant**.

Soaps are by no means the only molecules that can form micelles. There are in fact a huge number of surfactants that have great importance in medical and everyday life. We'll look further into some of these important molecules.

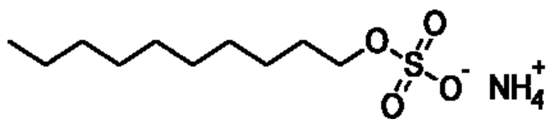
4.11 Detergents as surfactants

Dish and laundry detergents, shampoos, toothpaste and some laxatives also form micelles which act to emulsify grease and fats in an aqueous solution as well as provide foaming action! The structures of some detergents are shown:

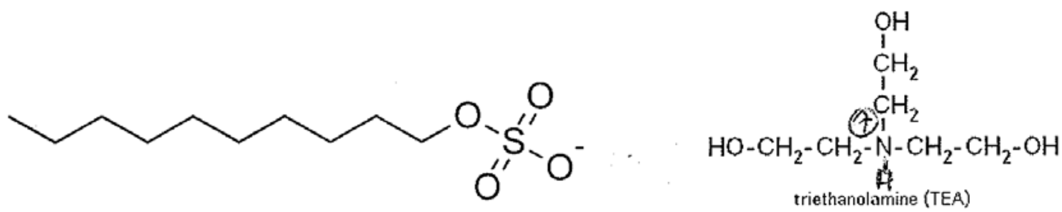
sodium dodecyl (lauryl) sulfate



Ammonium lauryl sulfate



TEA(triethanolamine) lauryl sulfate



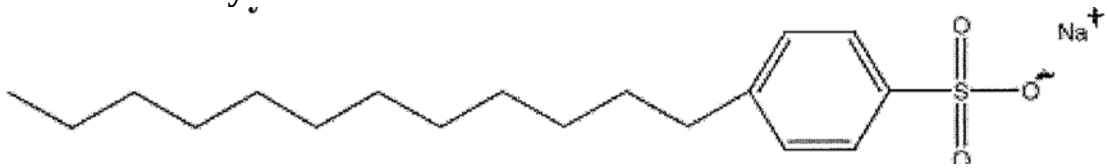
Sodium lauryl sulfate is commonly used as a “foaming agent” in toothpaste. There have been concerns that its presence in toothpaste may increase the incidence of oral canker sores. Several small studies indicated an increased incidence of canker sores in those using toothpaste with sodium lauryl sulfate, but another large study found no increase from use of toothpaste with sodium lauryl sulfate, so the jury is still out.

Creative commons

Sodium lauryl sulfate and closely related compounds like ammonium lauryl sulfate are also very commonly used in shampoos. On a molecule per molecule basis, they work more effectively under alkaline conditions, but that can cause stinging of the eyes and damage to the protein hair. The pH is often adjusted to be near neutrality which minimizes damage to the hair protein keratin. Baby’s shampoo in particular may be adjusted to the pH of tears (7.0 +/-0.5) to minimize stinging of the eyes.

All three of the above surfactants have the same lauryl sulfate ion, only differing in what positive ion balances the negative charge.

Sodium dodecyl benzene sulfonate



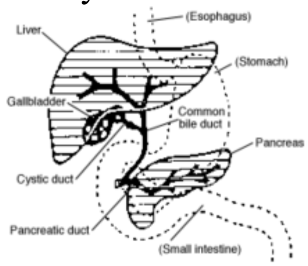
(Notice that **sulfates** have an O atom between the S and the C atoms, while **sulfonates** have the S atom bonded directly to the C atom. The removal of one O atom does not significantly change the surfactant action of the molecule however.)
Label the hydrophilic and hydrophobic portions in the above molecules.

Detergents have replaced soaps in many uses because soap molecules tend to form precipitates when dissolved in water containing +2 ions like Ca^{+2}, Mg^{+2}, and Fe^{+2} (hard water). This precipitate produces the scum that forms bathtub ring. It also accumulates on clothes if soap is used instead of detergent when doing laundry in hard water.

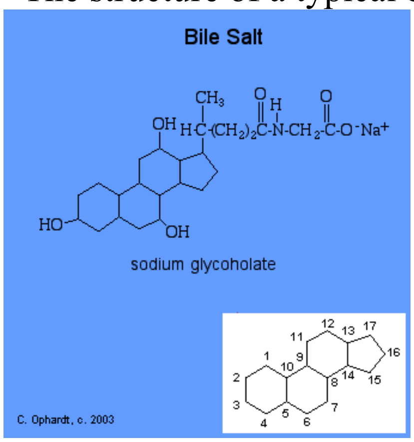
Detergents are made from petroleum and only came into common use after World War II. Although detergents do lose some cleansing action in the presence of +2 metal ions, they do not form insoluble precipitates nearly as readily as soaps do, so they have replaced soaps in many cleaning applications.
Before detergents were available, the pioneer women often preferred to do their laundry in rain water, if it was available. Rain water does not contain as many metal ions as well or stream water and hence does not have as igh a tendency to precipitate soap.
Pioneer women made soap by saving up the fat from slaughtered animals and from the frying pan. They then made lye (a mixture of NaOH and KOH) by filtering water through the ashes from the fireplace. They then added the lye to a kettle of fat and cooked it, thus saponifying the fat into soap. Frequently this soap contained an excess of lye. It was very hard on the skin!

4.12 Bile Salts

Dietary fat has to be emulsified in the small intestine in order to be absorbed into the blood stream. The first step of this emulsification is done by bile salts which are synthesized in the liver and then secreted into the bile duct. They are normally concentrated in the gall bladder and released when dietary fat is detected.



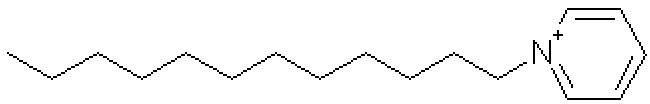
The structure of a typical bile salt, sodium glycholate, is shown below.

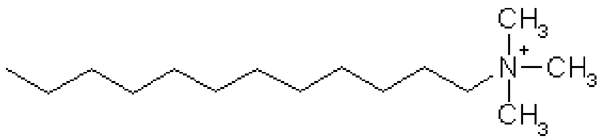


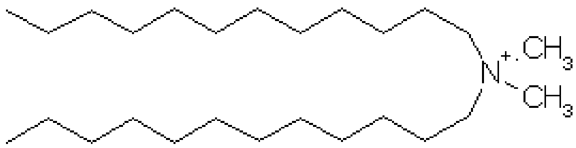
Label the hydrophilic and hydrophobic portions of the molecule.
Bile salts are synthesized in the liver from cholesterol and are secreted into the small intestine via the bile duct. Their presence in the small intestine helps in the absorption of fats and other fat soluble substances (such as the fat soluble vitamins). If the bile duct is blocked by a gallstone severe pain can result. In addition dietary fats do not get as effectively emulsified and absorbed and end up being excreted in the stools. This results in fatty stools that have lower density than normal (because of the low density of fat), a condition called **steatorrhea**. The most common solution to gall stone problems is to remove the gall bladder. Bile salts are no longer stored in the gall bladder but enter the small intestine on a more continuous basis. Most patients do not have any problem with having their gall bladder removed, although their absorption of fats may not be as efficient, especially with a high fat diet.

4.13 Cationic surfactants

The surfactants discussed so far all contain negatively charged hydrophilic groups, either carboxylate or sulfate ions. These types of surfactants are called **anionic surfactants**. Surfactants with positively charged hydrophilic groups (ammonium ions), called **cationic surfactants**, also exist, although they are less common.







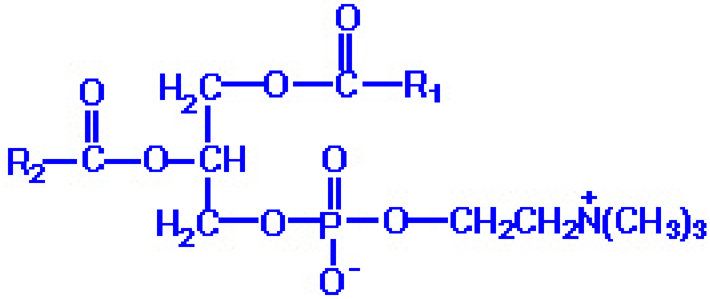
What functional group is found in the above two molecules?

Cationic surfactants are used as hair conditioners, fabric softeners, and germicidal soaps. Shampoos typically contain one or more anionic surfactants which remove accumulated dirt and sluffed skin particles, but also remove some of the natural sebum oil that coats hair.

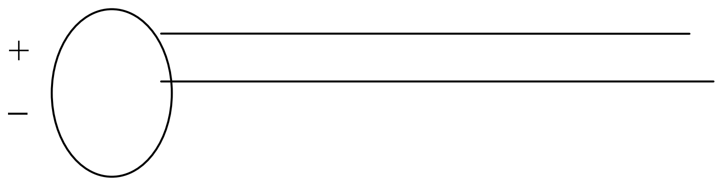
Hair conditioners add back oil to the hair after shampooing to keep it flexible and glossy. They often contain cationic surfactants because the hair has a negative charge which will attract and bind the cationic surfactant. Additional agents such as silicone products (e.g. dimethicone) are sometimes added to increase gloss.

4.14 Amphipathic surfactants

Amphipathic surfactants contain both a positive and negative charge on the hydrophilic portion of the surfactant. The most common amphipathic emulsifying agent is **lecithin (phosphatidyl choline)** whose structure is shown below.

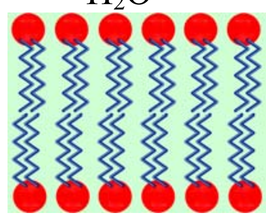


where R_1 and R_2 are usually 11-21 C atoms long.
It has both a positive quaternary ammonium ion and a negatively charged phosphate ester in its hydrophilic portion and is called **amphipathic** because of the dual charge.
Label the hydrophilic and hydrophobic portions. Lecithin has **two** long non-polar chains in contrast to the previous soaps and detergents we showed which only have one. As a result, the shorthand notation for lecithin is



Besides forming micelles, lecithin can also form lipid bilayers which also maximize “like dissolves like” solubility. Lipid bilayers are a primary component of cell membranes.

H_2O

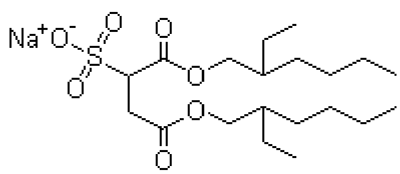


H_2O

Lecithin is a major component in biological membranes and is obtained commercially from egg yolks, soybeans, and other sources. It is a good emulsifying agent. It is used in salad dressings and mayonnaise to emulsify vinegar and oil, the two primary ingredients of salad dressings. In old fashioned vinegar and oil salad dressing there are two separate layers, vinegar and oil. When shaken vigorously, the two separate layers are broken up into tiny intermixed droplets, but the two layers separate out quickly. When lecithin or other surfactants are added, an emulsion is formed that has an opaque creamy consistency and does not separate into separate oil and water layers. In homemade salad dressing the active emulsifying agent is egg yolk, which is a very rich source of lecithin.

Lecithin is also found in some cake mixes. Cake mixes frequently contain both flour (hydrophilic) and shortening (fat). Mixing these together requires an emulsifying agent. Although cake mixes generally recommend the addition of an egg (which provides additional emulsifying action via lecithin), additional lecithin or other emulsifying agents are frequently included in the cake mix itself.

Several synthetic "detergent" molecules are used as laxatives and stool softeners. The structure of **dioctyl sodium sulfosuccinate** (abbreviated **DSS** for obvious reasons) or **docusate** (pronounced DOK you sate) is shown below. It is marketed under a variety of trade names and is recommended for the treatment of constipation and fecal impaction. Label the hydrophilic and hydrophobic portion of the molecule. It may act as a laxative by inhibiting water reabsorption as well as emulsifying the bowel contents.

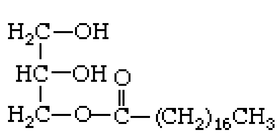


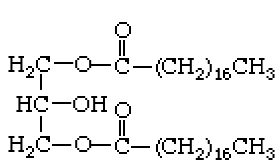
DSS is one of the major components of Corexit 9500, one of the dispersants used in the Gulf oil spill.

4.15 Nonionic emulsifying agents

In all of the above molecules the hydrophilic portion contains an ionic group. In general ionic groups are needed to make a good emulsifying agent. Nonionic surfactants do exist, although they are typically not as effective as ionic surfactants, and are frequently used in combination with ionic surfactants. They frequently have multiple polar groups in their hydrophilic end. The names and structures of three common non-ionic emulsifying agents are shown below. Label the hydrophilic and hydrophobic portions in each.

Monoglyceride **Diglyceride** **Polyethylene glycol (PEG)** ***ester***



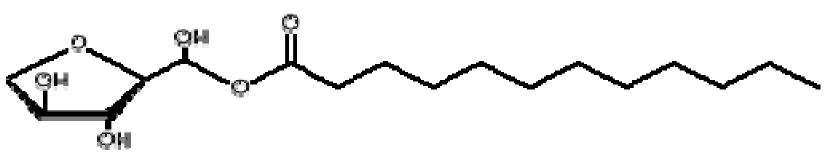


$$R - \overset{\displaystyle O}{\overset{\|}{C}}O(CH_2CH_2O)_nH$$

The ”n” in the formula for PEG esters can vary from 2-3 to over a hundred. When the n value is very large it makes a long chain which increases the viscosity (thickness) of the solution it is in. This property is taken advantage of when adding it to shampoos and laundry detergents to thicken the liquid as well as act as a detergent. PEG surfactants are used as OTC (over-the-counter) laxatives as well as in preparing for bowel preparation kits for colonoscopies to clear out the colon. Two such PEG products (PEG 3350) are the perversely named **GoLytely and HalfLytely**!(Half-Lytely is only half a gallon instead of a full gallon! Bisacodyl is added to finish the cleansing job)

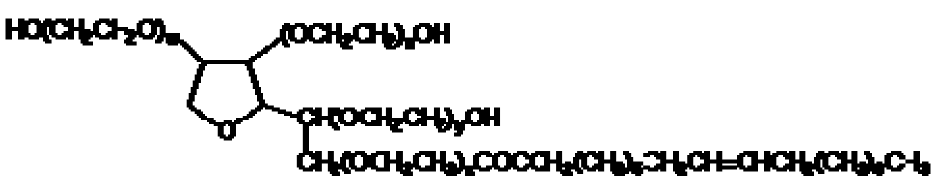
Another satisfied customer!

Sorbitan esters are common emulsifying agents used in **cake mixes** and skin creams.



Sorbitan ester

Polysorbates have a polyethoxylated sorbitan bonded in an ester linkage to a long chain carboxylic (fatty) acid.

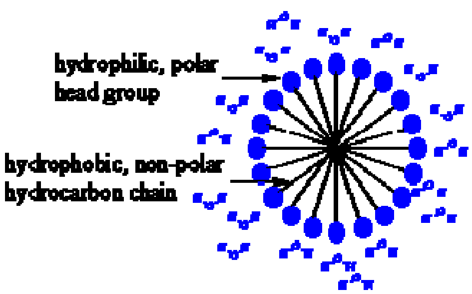


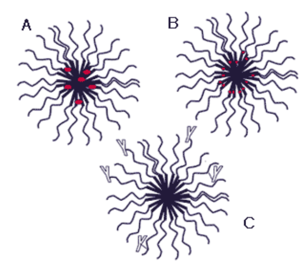
w + x + y + z = 20

Several variations on polysorbates have the numbers 20,40,60 or 80 after the name polysorbate. These refer to the total number of ethoxylate (O-CH_2CH_2O) units attached to the sorbitan ring. Thus polysorbate 80 has a total of 80 (O-CH_2CH_2O) attached to the 4 sites shown in the structure.

Water-in-oil emulsions

The micelles we have discussed so far contain a hydrophobic interior, hydrophilic exterior and exist in a water medium. These types of solutions are called **oil-in-water emulsions**. If one has a large quantity of oil and only a small quantity of water, together with an emulsifying agent, the emulsifying agents may surround small droplets of water suspended in hydrophobic oil environment (see below). This is called **a water-in-oil emulsion** or a reverse phase emulsion. This is fairly common in a variety of cosmetic products such as hand lotions and cold creams.



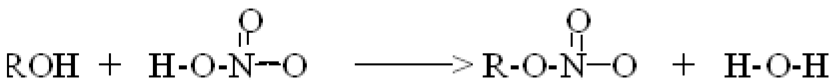


oil-in-water emulsion   water-in-oil emulsion

(Soaps are added to lubricating oils to make reverse micelles which form. The soaps used often use the lithium ion as their positive ion, producing a high melting point grease that will not melt away from the surfaces to be protected)

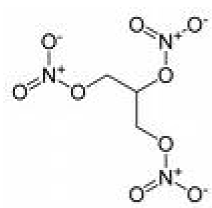
4.16 Nitrate Esters

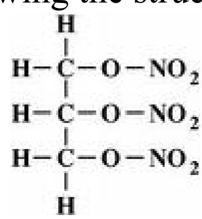
Esters of biological importance can also be formed from the inorganic acids nitric acid and phosphoric acid.



In nitrate esters the N=O bond is analogous to the C=O in regular esters.

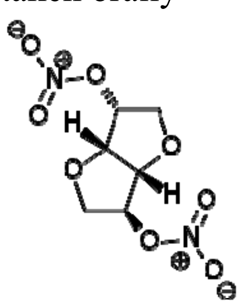
An important example of medically important nitrate esters is **nitroglycerin**. Although developed as an explosive, it also turns out to be an excellent **vasodilator**. Vasodilation allows more blood to flow and nitroglycerin is primarily used to treat angina. Angina occurs when the heart is not getting sufficient oxygenated blood, usually due to clogged coronary arteries. Here are two different ways of drawing the structure of nitroglycerin.





Unfortunately the liver has enzymes which can hydrolyze nitroglycerin (to glycerin and nitrate ions) so quickly that very little active drug actually gets to the coronary arteries when the drug is taken orally. As a result nitroglycerin is typically taken as a capsule that is placed under the tongue where it is absorbed directly into the bloodstream, bypassing the GI tract.

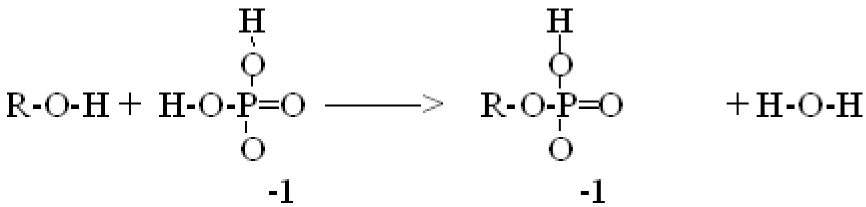
Isosorbide dinitrate is another nitrate ester molecule that can cause vasodilation which is not metabolized as quickly as nitroglycerin and can be taken orally



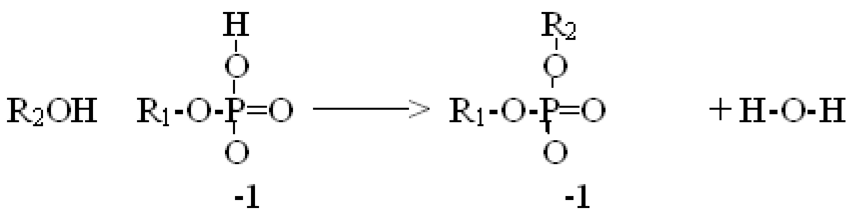
Isosorbide dinitrate

4.16 Phosphate esters

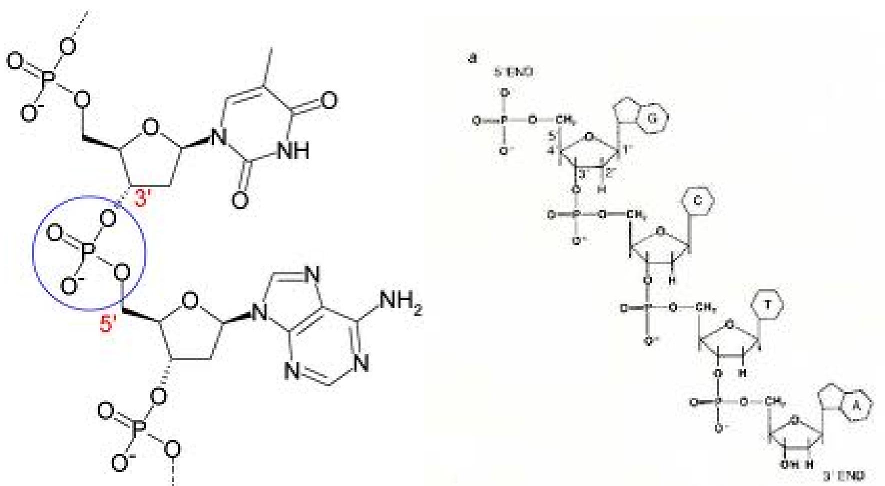
Similarly we can react phosphoric acid (really phosphate ions) with alcohol groups to form **phosphate esters**:



Again the P=O in the phosphate is analogous to the C=O in a regular ester. A phosphate ester can react with a second alcohol and form a **phosphodiester.**

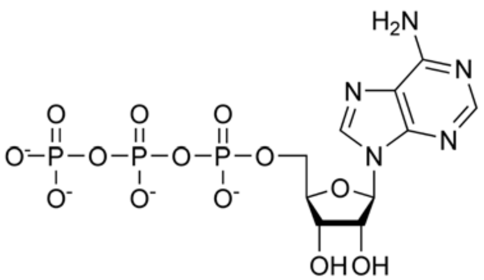


Alcohol   phosphate ester   phosphodiester



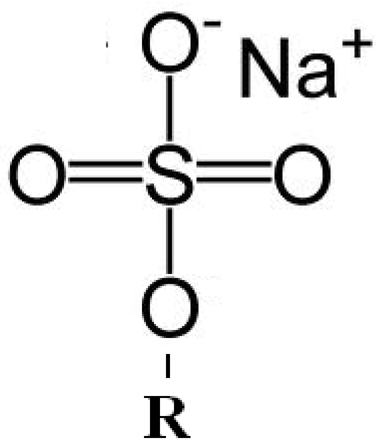
Phosphodiester bonds link the ribose sugars of DNA together.

Phosphate groups are used to activate (raise the energy level of) alcohol and other functional groups. Reacting two or three phosphate together forces the negatively charged phosphates closely together and requires energy (it is **endergonic)**! When the phosphate ions hydrolyze, energy is released (**exergonic**)! The most well known molecule that utilizes this principle is the major high energy molecule of the cell, **adenosine triphosphate**.



Adenosine triphosphate

Sulfate esters

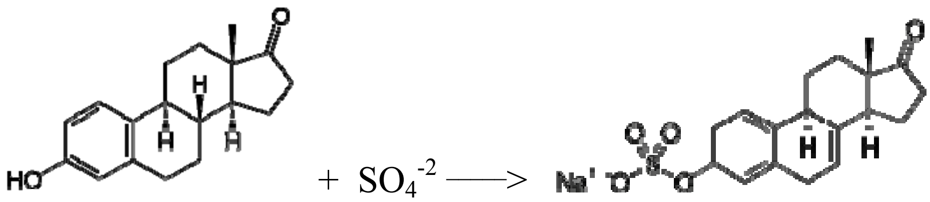


The liver metabolizes many hormones as well as drugs by adding a sulfate group onto an OH group of a molecule. The ionic sulfate group increases the water solubility and expedites excretion of the sulfated molecule in the urine or feces.

A medically important example is the metabolism of estrogens. The body does not want these hormones to stay active forever and one way of terminating their activity is to add either a **sulfate group** or a **glucuronic acid** onto an OH group of the estrogen, a process called **conjugation**. This not only increases the water solubility, but decreases the biological activity of the estrogen.

Example. The estrogen molecule estrone is metabolized in the liver into estrone sulfate which is readily excreted in the urine.

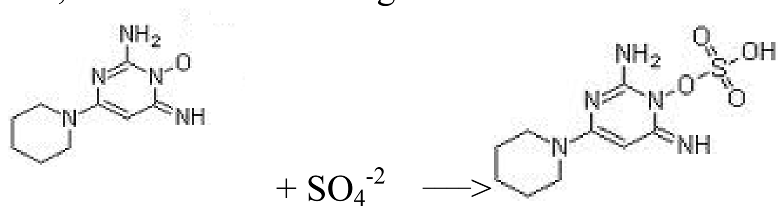
This excretion has been used pharmacologically. Pregnant mares excrete large amounts of sulfated estrone which can be purified from their urine and taken orally by menopausal women as Premarin. The Premarin can have its sulfate removed in the human liver and be regenerated into active estrone.



The estrogens with sulfate covalently attached are collectively referred to as **conjugated estrogens.** This is analogous to the term conjugated bilirubin which is used to describe a bilirubin molecule in which glucuronic acid has been covalently attached. Indeed the active ingredients of Premarin are listed as **conjugated estrogens**.

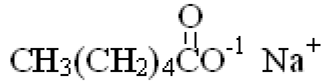
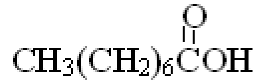
When taken orally, the sulfate group is removed from the conjugated estrogens to make them active again.

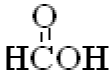
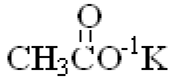
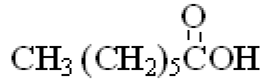
Sulfation of drugs does not always lead to inactivation. Minoxidil(Rogaine) is used in the treatment of male baldness. It turns out that minoxidil is actually a pro-drug and is sulfated on the O atom to produce minoxidil sulfate, the actual active drug.

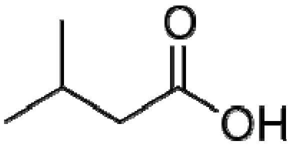
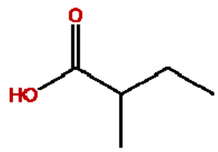


CARBOXYLIC ACIDS STUDY GUIDE

1. Name the following carboxylic acids and carboxylate ions:

2. Write the general chemical equation (using an R group) showing the formation of a hydrogen ion from a carboxylic acid. Is this reaction reversible or irreversible? Are carboxylic acids weak or strong acids in general? Compare the length of the two C-O bonds in the carboxylic acid with the C-O bond lengths in a carboxylate ion. Explain how resonance/delocalization explains the difference and why it stabilizes the carboxylate ion.

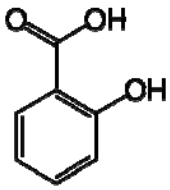
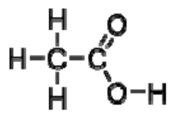
3. Write the chemical equation for the neutralization of a general carboxylic acid with NaOH.(Use an R + the carboxylic acid functional group.)

4. Give at least one practical use or natural source for
   a) formic acid
   b) acetic acid
   c) trichloroacetic acid
   d) propanoic acid
   e) pyruvic acid
   f) GABA
   g) GHB
   h) benzoic acid
   i) lactic acid
   j) glycolic acid
   k) oxalic acid
   l) citric acid
   m) undecylenic acid
5. Write the structure of the ester product and give the systematic or common name for the carboxylic acid reactants and the ester product.

a) $CH_3CH_2OH + HO\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{H^+}$

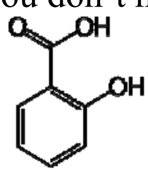
b) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH + HOCH_2CH_3 \xrightarrow{H^+}$

c) $CH_3(CH_2)_3CH_2OH + CH_3CH_2\overset{\overset{O}{\|}}{C}OH \xrightarrow{H^+}$

d)  +  $\xrightarrow[H^+]{}$

salicylic acid

(you don't need to name product of this reaction)

e)  + $HOCH_3$ $\xrightarrow[H^+]{}$

salicylic acid

f) $CH_3OH + HO\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{H^+}$

g) $CH_3CH_2OH + HO\overset{\overset{O}{\|}}{C}\text{-}H \xrightarrow{H^+}$

h) $CH_3CH_2CH_2CH_2OH + HO\overset{\overset{O}{\|}}{C}\text{-}H \xrightarrow{H^+}$

i) $CH_3CH_2CH_2OH + HO\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3 \xrightarrow{H^+}$

j) $CH_3OH + HO\overset{\overset{O}{\|}}{C}\ CH_2CH_2CH_2CH_3 \xrightarrow{H^+}$

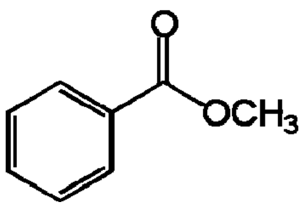
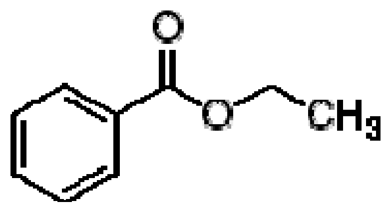
k) $CH_3CH_2CH_2OH + HO\overset{\overset{O}{\|}}{C}CH_2CH_3 \xrightarrow{H^+}$

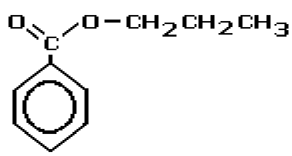
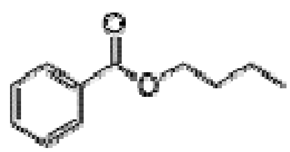
6. Name the following esters

$CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$ $CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_2CH_3$ $CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}OCH_2CH_3$

$CH_3(CH_2)_5O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_3$ $CH_3(CH_2)_6\overset{O}{\overset{\|}{C}}O(CH_2)_3CH_3$

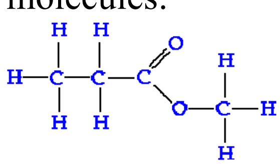
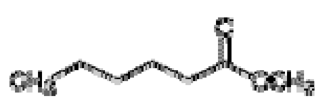
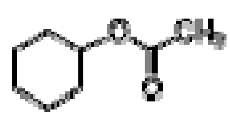
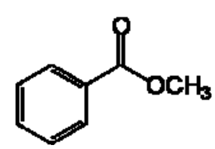
$CH_3(CH_2)_6\overset{O}{\overset{\|}{C}}OCH_2(CH_2)_2CH_3$ $CH_3(CH_2)_4O\overset{O}{\overset{\|}{C}}(CH_2)_5CH_3$

7. Name two examples of polyester polymers. Which one has become a matter of significant health concern. Name the component of concern and why the concern.

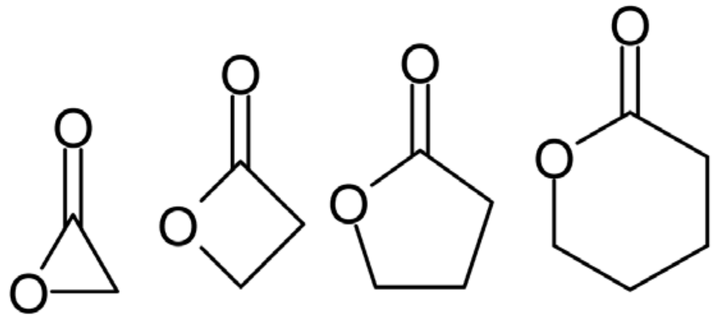
8.Write the products formed from acid catalyzed **hydrolysis** of the following molecules:

$CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$ $CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_2CH_3$ $CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}OCH_2CH_3$

$CH_3(CH_2)_5O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_3$ $CH_3(CH_2)_6\overset{O}{\overset{\|}{C}}O(CH_2)_3CH_3$

$CH_3(CH_2)_6\overset{O}{\overset{\|}{C}}OCH_2\,(CH_2)_2CH_3 \qquad CH_3(CH_2)_4\,O\overset{O}{\overset{\|}{C}}(CH_2)_5CH_3$

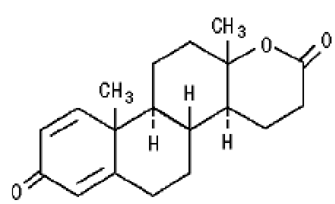


9. Is ester hydrolysis typically exergonic or endergonic? Why doesn't the hydrolysis occur spontaneously in many circumstances? What can be done to speed up the hydrolysis?

10. What important neurotransmitter contains an ester group? How is it inactivated?

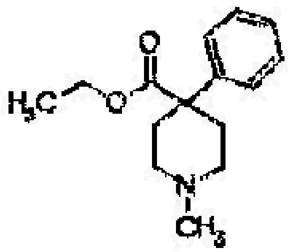
11. What functional groups are responsible for fruity smells and flavors? What chemical reaction causes these flavors to become sharp and unpleasant? What functional group is responsible for this?

12. Testolactone is a drug occasionally used in the treatment of post-menopausal breast cancer. Identify the various functional groups, including the lactone ring.

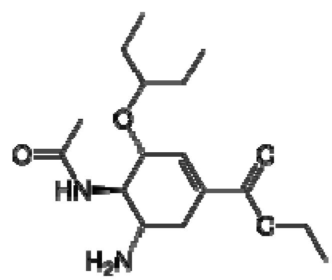


$C_{19}H_{24}O_3$ MW300.40 CAS-968-93-4

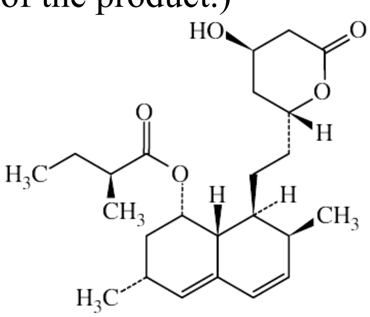
13. Meperidine(Demerol) is an opiate analgesic with structure shown below. Its metabolism is somewhat complex, but one step is ester hydrolysis. Show the products that will result from hydrolysis of the meperidine molecule.



14a. Oseltamavir (Tamiflu) has been widely used since 2001 to reduce the symptoms and severity of flu infection. Oseltamavir molecule itself is activated by hydrolyzing an ester linkage in the structure (shown below). Show the structure of the products which result from ester hydrolysis of oseltamavir. (You don't need to draw the structure of the whole carboxylic acid portion of the molecule, just the carboxylic acid and the ring it is attached to.)
Identify all the functional groups in Tamiflu.

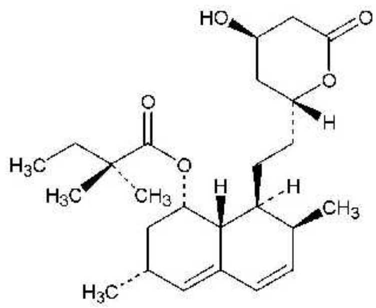


14b. Lovastatin(Mevacor) (structure shown below) is a drug commonly prescribed for lowering blood cholesterol. It has to be activated by hydrolysis of the ester linkage in the 6 membered ring. Show the structure of the hydrolyzed ring product. (You don't have to show the structure of rest of the product.)



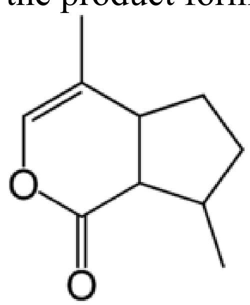
LOVASTATIN

14c Simvastatin (structure shown below) is another drug in the statin family that is commonly prescribed for lowering blood cholesterol. It has to be activated by hydrolysis of the ester linkage in the 6 membered ring. What do we call an ester linkage in a ring? Show the structure of the product.

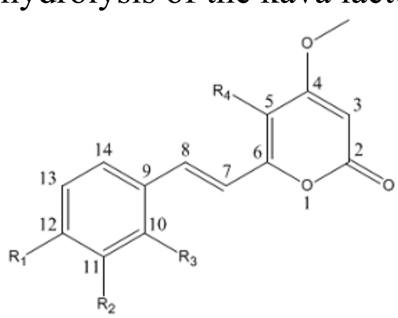


How does simvastatin differ from lovastatin in terms of its structure? This is a classic case of a "me too drug". When the patent on the original drug lovastatin ran out Merck came out with simvastatin which appears to be somewhat more effective but only has very minor differences in structure and hence was relatively easy to synthesize.

14d. Nepetolactone is the active ingredient in catnip. Show the structure of the product formed by the hydrolysis of the lactone ring.



14e) Kavalactone is regarded as the active ingredient in kava kava, a Polynesian drink. Show the structure of the product result from the hydrolysis of the kava lactone.



15. Show the products formed for the following:

a) $CH_3\overset{O}{\overset{\|}{C}}OH + HOCH_3 \xrightarrow{H^+}$

b) $HO\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OH + 2\,HOCH_3 \xrightarrow{H^+}$

c) $HOCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow{H^+}$

d) $HOCH_2CH_2\,CH_2CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow{H^+}$

16. Draw the structure of glycerol and of a monoglyceride, digyceride, and triglyceride

17. Explain why some food products' claims in the 90s and early 2000s of being "fat free" were misleading. What equivalent product did they contain?

18. Write the reaction for hydrolysis of a triglyceride. Draw a typical structure of a soap molecule (using R groups for the hydrophobic chains). Label the hydrophilic and hydrophobic portions.

19. What is meant by the term saponification? What is the structural and physical differences between a soft soap and a hard soap?

20. Explain how soaps work in terms of micelle formation.

21. What is meant by the term emulsion? emulsifying agent? surfactant?

22. Draw the structure of a detergent molecule and label the hydrophilic, lipophilic, and hydrophobic portions. How does the hydrophilic portion of the detergent differ from that of asoap? What advantages do detergents have over soaps?

23. Explain how the bile salts work. What physiological problems occur in the absence of bile salts?

24. What is the difference between an anionic surfactant, a cationic surfactant, and an amphipathic surfactant. Give examples of an anionic and amphipathic surfactant. Where are cationic surfactants often used?

25. Draw the structure of lecithin. Explain why lecithin is used in salad dressing and how it works. What common food product is added to home made salad dressing which is very rich in lecithin?

26. Name a surfactant (full name and abbreviation) that is used as a laxative. What medical procedure frequent uses it as a "prep"?

27. Why are nonionic surfactants often combined with ionic surfactants?

28. What is the difference between anionic and cationic surfactants?

29. What are some of the practical uses of cationic surfactants?

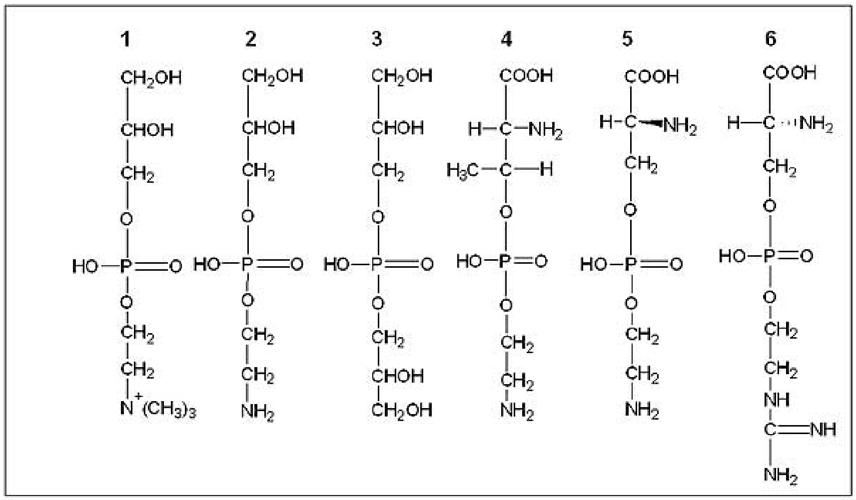
30. Draw an "oil-in-water" micelle and a "water-in-oil" micelle, making the differences clear. Where are "water-in-oil" emulsions commonly found?

31. Check the ingredients on your shampoo, dishwashing detergent, toothpaste and see how many surfactants discussed in this chapter you can find.

32. Give two examples of medically important nitrate esters. Why is one of them rarely if ever given orally?

33. Explain why the formation of polyphosphate esters is an endergonic process.

34. What sort of functional group do all the molecules below have in common?



35. What is a common physiological purpose for adding a sulfate group to a biological molecule? What is the generic name given for the addition of such a group? Give two examples where this reaction occurs in molecules we have talked about earlier.

Questions Digging deeper

36. Artemisinin is a compound isolated from a Chinese herb Artemisia which has traditional use for treating malaria and is also being investigated as an anti-cancer drug. Do a web search and learn more about this molecule and identify the various functional groups in the molecule.

37.The web sites below are to several studies looking at the effect of sodium lauryl sulfate on oral cankers. Review the essentials of these studies (number of patients, single blind, double blind, source of funding, statistical probability) and discuss your findings on strengths, weaknesses, and conflicting results.

1. ^ <A>> Herlofson B, Barkvoll P (1994). "Sodium lauryl sulfate and recurrent aphthous ulcers. A preliminary study. <http://www.wealthpartners.net/pdf/0535.pdf> " (PDF). Acta Odontol Scand 52 (5): 257-9. PMID 7825393 <http://www.ncbi.nlm.nih.gov/pubmed/7825393> .

2. ^ <A>> Herlofson B, Barkvoll P (1996). "The effect of two toothpaste detergents on the frequency of recurrent aphthous ulcers.". Acta Odontol Scand 54 (3): 150-3. PMID 8811135 <http://www.ncbi.nlm.nih.gov/pubmed/8811135> .

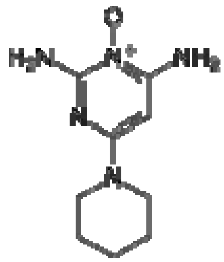
3. ^ <A>> Chahine L, Sempson N, Wagoner C (1997). "The effect of sodium lauryl sulfate on recurrent aphthous ulcers: a clinical study.". Compend Contin Educ Dent 18 (12): 1238-40. PMID 9656847 <http://www.ncbi.nlm.nih.gov/pubmed/9656847> .

4. ^ <A>> Healy CM, Paterson M, Joyston-Bechal S, Williams DM, Thornhill MH (1999). "The effect of a sodium lauryl sulfate-free dentifrice on patients with recurrent oral ulceration". Oral Dis 5 (1): 39-43. PMID 10218040 <http://www.ncbi.nlm.nih.gov/pubmed/10218040> .

38. The dose of oxalic acid needed to kill humans is estimated as approximately 375 mg of oxalic acid per kg weight of the person. How many grams would be needed to kill a person weighing 150 pounds? If the concentration of oxalic acid in rhubarb leaves is typically about 0.5%, how many grams of leaves would have to be eaten to risk death? How many pounds is that? (Remember 454 grams = 1 pound).

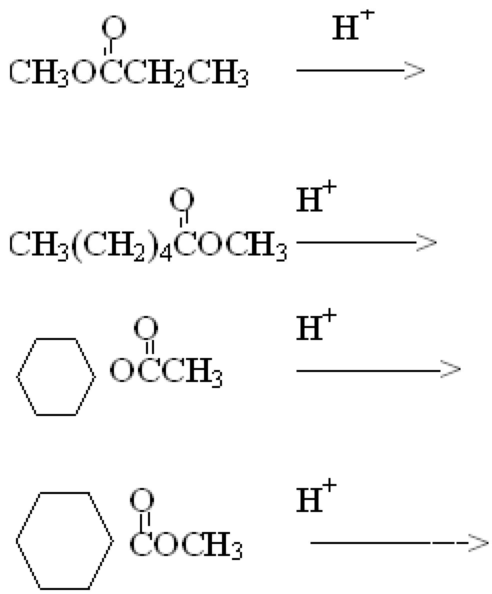
39.a) Write the equation for the reaction of benzoic acid with sodium hydroxide.
b) The product is frequently used as an alternative to benzoic acid to inhibit mold growth
c) What solubility advantages might the product have over benzoic acid.

40.Sulfation of drugs does not always lead to inactivation. Minoxidil(Rogaine) is used in the treatment of male baldness. It turns out that minoxidil is actually a pro-drug and is sulfated on the O atom to produce minoxidil sulfate, the actual active drug.

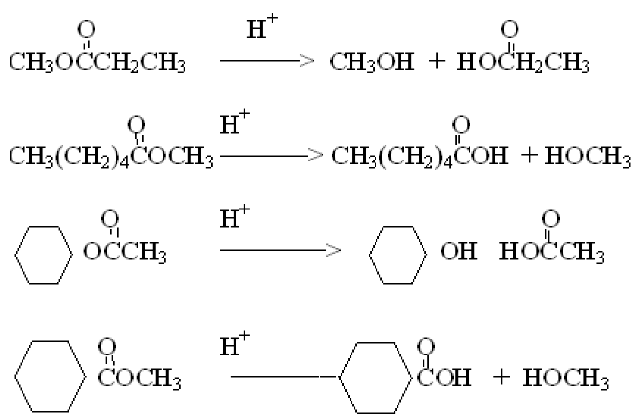


+ SO_4^{-2} —>

Additional hydrolysis problems.



Answers:



Skip answers below.

11. Esters are responsible for many fruity smells and flavors. Hydrolysis causes formation of carboxylic acids which have a sharp often unpleasant flavor.

13. Monoglycerides are essentially equivalent to triglycerides in terms of calorie/gram and in terms of atherogenic potential. Hence ,using mono- and diglycerides in place of triglycerides serves no useful nutritional purpose. But it does allow the manufacturer to claim that their product is “fat-free”.

14. Soft soaps have a potassium ion balancing the negatively charged carboxylate ion while hard bar soap has a sodium ion balancing the carboxylate ion.

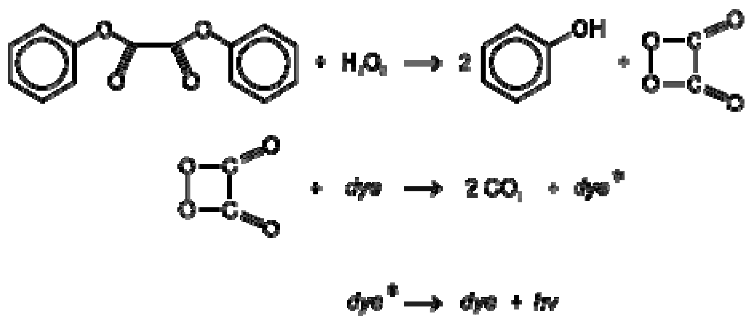
15. Lecithin is an emulsifying agent that emulsifies the vinegar (primarily water) and the oil in salad dressings.

16. DSS (dioctylsulfosuccinate) is used in Colace and other laxative products; PEG (polyethyleneglycol) is used in some preparations designed to cleanse the bowel prior to a GI exam.

17. Non-ionic surfactants are usually not as effective as ionic surfactants in forming micelles (particularly oil-in-water micelles). They are usually combined with ionic surfactants to improve micelle formation.

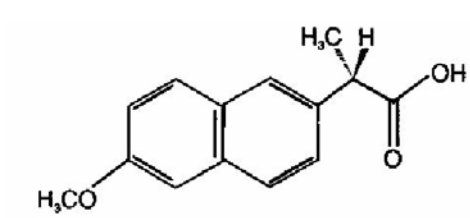
18.Water-in-oil emulsions are commonly found in hand lotions and cold creams.

19. Glow sticks work by undergoing the following reaction:

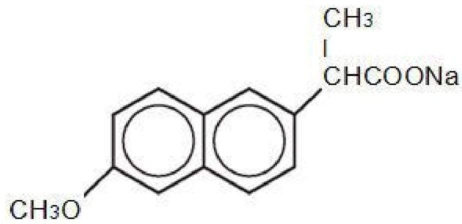


(The asterisk after the dye indicates a molecule with an excited electron.)

Explain why the molecule that reacts with the dye is particularly reactive. Compare the water solubility of naproxen and naproxen sodium (structures shown below) and explain.



Naproxen



Naproxen sodium