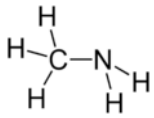
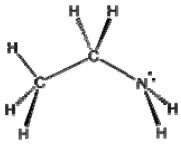
CHAPTER 7
AMINES

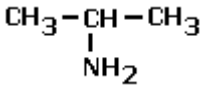
Many amines are found in natural products and many of them are biologically active when ingested or injected. There has been a long-standing interest in these compounds and they are collectively referred to as **alkaloids,** because of the basic (alkaline) properties resulting from the amine group. Morphine, quinine, lysergic acid, mescaline, and strychnine are just a few of the best known alkaloids that have been isolated from various plants. Amine drug compounds are often very bitter and are often combined with something very sweet to partially cover the bitterness (as in cough syrups) or taken in capsule form so that they aren't tasted at all.

7.1 NAMING

Primary amines





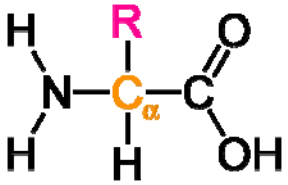


CH_3NH_2 $CH_3CH_2NH_2$ CH_3 $CH_2CH_2NH_2$ $CH_3CH(NH_2)CH_3$

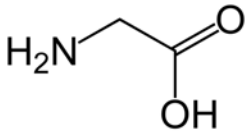
aminomethane aminoethane 1-aminopropane 2-aminopropane

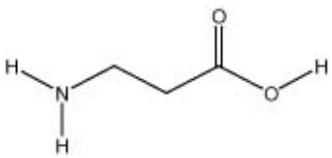
(Numbers are optional in the first two molecules because there are no alternative possibilities).

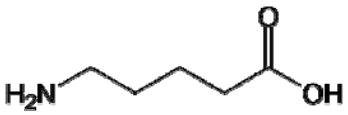
Molecules containing both amine groups and carboxylic acids are common biological molecules. Alpha amino acids are the building blocks of proteins.
The general structure for an alpha amino acid is:



Naming amino acids:







2-aminoethanoic acid 3-aminopropanoic acid 5-aminopentanoic acid

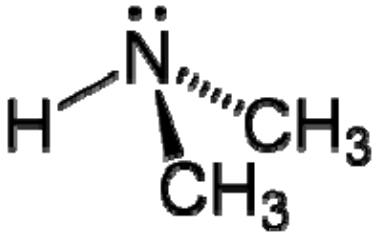
Glycine
An alpha(α) amino acid a β amino acid a δ amino acid
The carboxylic acid functional group takes precedence over the amino group for being assigned the lowest number.
Multiple amine groups are treated similar to previous functional groups.

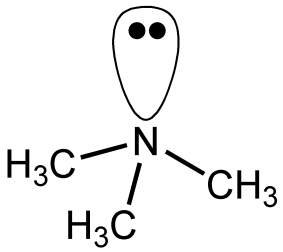
Systematic: 1,4 diaminobutane 1,5 diaminopentane
Common: putrescine cadaverine

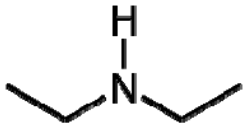
These two diamino compounds are formed by bacterial action on proteins particularly in meat. They contribute to the smell of spoiled meat and can cause food poisoning if one eats spoiled meat.

Naming Secondary and Tertiary Amines

When there is more than one alkyl chain on the N atom, the method of naming changes:







CH_3 CH_3 H
$H\text{-}N\text{-}CH_3$ $CH_3\text{-}N\text{-}CH_3$ -C-C-N-C-C-

dimethylamine trimethyl amine diethylamine.

7.2 Amines as bases.

Amines are weak bases, like ammonia:

Ammonia: $NH_3 + H_2O \longleftrightarrow NH_4^+ + OH^{-1}$

Amine: $R\text{-}NH_2 + H\text{-}O\text{-}H \leftrightarrow R\text{-}NH_3^+ + OH^-$

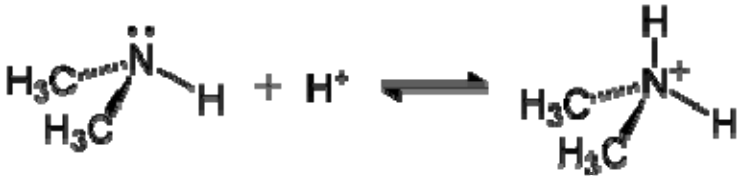
Amines undergo **neutralization** reactions with acids to form alkylammonium ions

General: $R\text{-}NH_2 + H^+ + Cl^{-1} \leftrightarrow R\text{-}NH_3^+ + Cl^-$

a) $CH_3NH_2 + HCl \longleftrightarrow CH_3NH_3^+ \ Cl^{-1}$

Methylamine hydrochloric acid methylammonium chloride

b) dimethylamine $+ H^+ \longleftrightarrow$ dimethylammonium ion



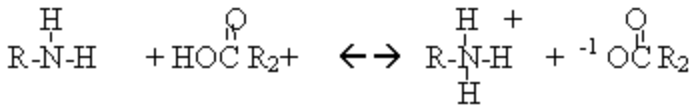
www.answers.com/topic/ammonium

Write the equation for the neutralization of trimethylamine with HCl

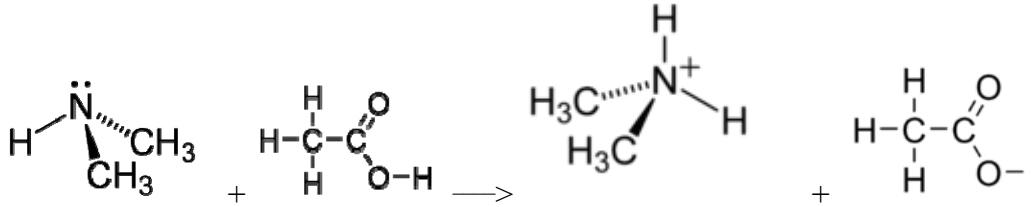
A molecule with two amine groups can react with **two** molecules of HCl or other acid.

$NH_2(CH_2)_4NH_2 + 2\ HCl \longleftrightarrow Cl^{-1} \ ^+NH_3(CH_2)_4NH_3^+ \ Cl^{-1}$

Neutralization of an amine with a carboxylic acid at room temperature



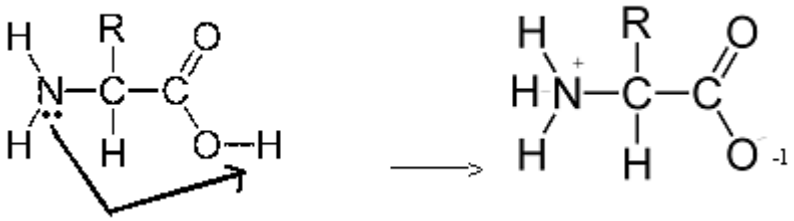
Sample problem:
Write the equation for the neutralization of acetic acid with dimethylamine.



Dimethylammonium acetate

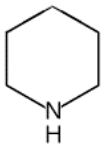
Practice problem:
Write the equation for the neutralization of trimethylamine with formic acid.

This neutralization reaction can occur in amino acids within the same molecule:

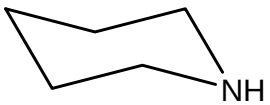


Amine groups in Rings

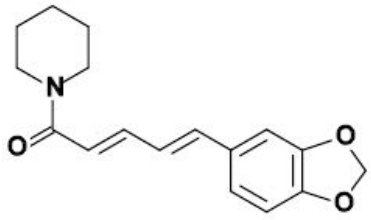
N can also exist in rings such as the 6-membered ring **piperidine.** Even though it is frequently drawn flat, it has a conformation similar to cyclohexane.



really looks like



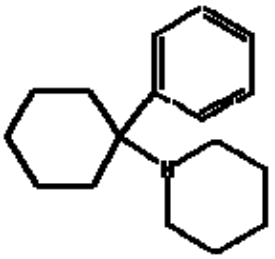
One example of a molecule containing the piperidine ring is **piperine,** the primary molecule responsible for giving black pepper its flavor.



Redraw the piperidine ring showing its actual conformation. What will the bond angle of the other two rings in the molecule be? Are the double bonds between the two ring systems in the cis or trans configuration?

PCP (ANGEL DUST)

Another example of a molecule containing a piperidine ring is **phencyclidine (a shortened version of** phenylcyclohexylpiperidine**),** better known by its street name of PCP or "angel dust". Name the 3 rings in this molecule. Redraw the molecule showing the real shape of each of the rings. Are there any chiral centers in this molecule?

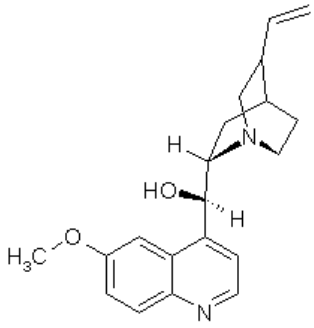


justice.gov

Phencyclidine was developed in the 1950's as an intravenous anesthetic but never was put on the market because early clinical trials found frequent adverse effects (agitation, delusions and sometimes violent behavior) occurred as patients came out from anesthesia. PCP is most typically dissolved in solution and then soaked in tobacco or marijuana to be smoked. The effects of phencyclidine tend to be very erratic among individuals and although a few people enjoy the hallucinations of strength, power and invulnerability, many people find the drug causes anxiety attacks, paranoia, suicidal thoughts and violent hostility. PCP first became available on the streets in the 1960's. According to the 2004 Monitoring the Future Survey, 1.7% of high school seniors have tried PCP at least once. Results of the 2003 National Survey on Drug Use and Health indicated that 3.0% of the population over 12 have tried PCP at least once.

Quinine

A third medically important molecule containing the piperidine ring is **quinine,** the first drug used to treat malaria. It is isolated from the bark of the Cinchona tree found in the Andes. It is added at 83 ppm (parts per million) to tonic water and is responsible for the bitter taste of tonic water. (This concentration is much less than that needed to treat malaria. You would have to drink a LOT of tonic water to treat malaria!) Quinine at therapeutic doses is *extremely* bitter and can cause nausea and vomiting; other adverse effects include excessive sweating, tinnitus (ringing of the ears), blurred vision, headache, and dizziness. This assemblage of adverse effects is referred to as **cinchonism.** With numerous adverse effects, quinine has largely been replaced by other drugs for the treatment of malaria. It was marketed for treating nocturnal leg cramps until 1994 before being banned by the FDA. It has a rather complex structure with multiple rings and several chiral centers. Label the chiral centers.



Quinine

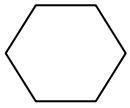
wikipedia.org/wiki/Image:Tonic_water_uv.jpg

7.3 Solubility of Amines

Amines are similar to alcohols in terms of their solubility. One polar amine group can pull about 4 C atoms of hydrophobic alkyl chain into water.

$CH_3CH_2CH_2NH_2$

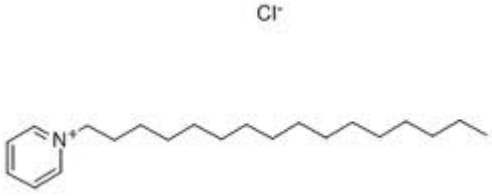
1 aminopropane
very soluble in water.



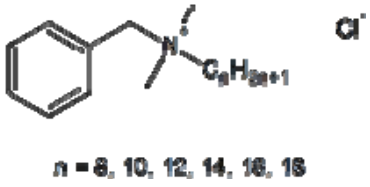
1-aminocyclohexane (cyclohexylamine)
not very soluble in water

When an amine is converted into an **alkylammonium** ion (by the addition of acid) the ionic ammonium ion is much more effective at pulling non-polar groups(up to ~15-18 C atoms) into aqueous solution, just as was the case for carboxylate ions. They do this by forming micelles, just like the carboxylate ions.

Several germicidal detergents use ammonium ion based detergents.



Cetylpyridinium chloride
(Cepacol mouthwash)



Benzalkonium chloride (Zephiran)
topical antiseptic and hair conditioners

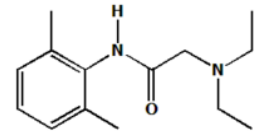
Hair conditioners also contain positively charged benzalkylammonium ions which stick to the negatively charged surface of hairs and coat the hair, reducing static repulsion between strands of hair and improving the shine of the hair.

7.4 Drugs as amines

Many drugs (probably 85% of the drugs on the market) contain amine groups covalently bonded to groups that are relatively hydrophobic. Most of these drugs are administered in the ammonium ion form. This accomplishes two objectives. 1) It makes the drug more water soluble (very important if the drug is going to be injected IV!!). 2) It converts the amine (which is usually a liquid oil) into the ionic ammonium ion form (which is a solid). Formation of the ionic ammonium ion makes the drug molecule less susceptible to oxidation by oxygen. This increases the shelf life of the drug considerably, and is one reason why most drugs, even those not given IV, are made in the ionic ammonium ion form. The solid powder is more readily mixed with solid filler and made into tablets The most common acids used to neutralize the amine group of the drug are hydrochloric acid and sulfuric acid (and occasionally phosphoric acid). Drugs that are neutralized with hydrochloric acid usually have **hydrochloride** attached after their name. Drugs neutralized with sulfuric acid have the name **sulfate** attached after their name. Addition of phosphoric acid produces a drug **phosphate**. Carboxylic acids are occasionally used.

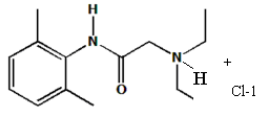
Some specific examples are shown.

Lidocaine



2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide monohydrochloride "Lidocaine"

+ HCl —>



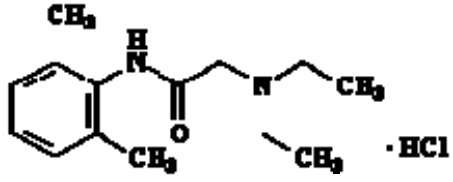
2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide monohydrochloride "Lidocaine"

Lidocaine + hydrochloric acid Lidocaine hydrochloride

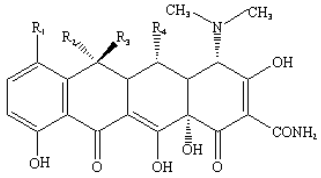
On the websites the acid is usually shown separately without having reacted with the amine group.

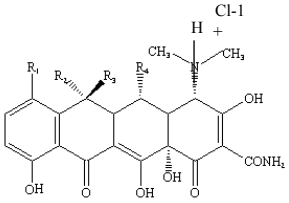
Lidocaine Hydrochloride

$C_{14}H_{22}N_2O \cdot HCl$



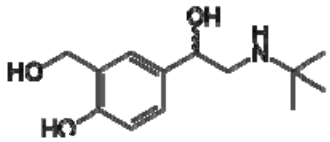
Tetracycline



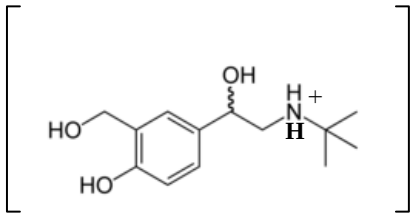


Tetracycline + HCl ⟶ Tetracycline hydrochloride

Albuterol



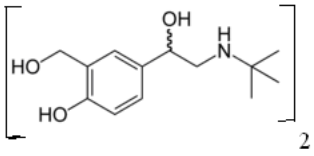
+ H_2SO_4 ⟶



2 SO_4^{-2}

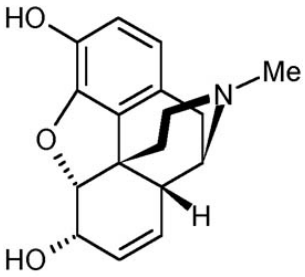
Albuterol sulfate

But it is commonly written as

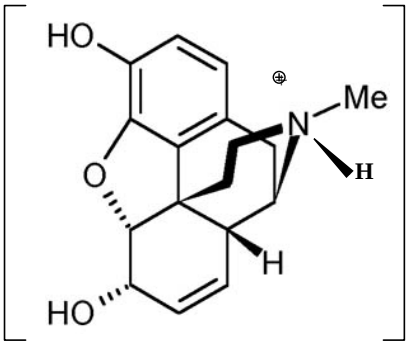


H_2SO_4

Morphine



2 ⟶

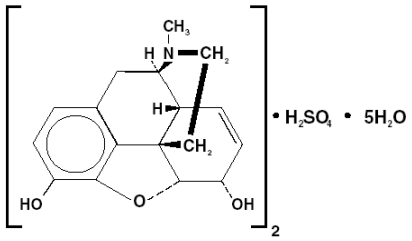


2 + SO_4^{-2}

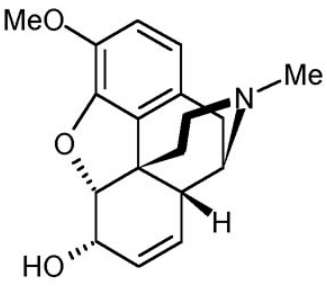
2 morphine + H_2SO_4 ⟶ Morphine sulfate(MS)

(The positive charge of the morphine ammonium ion is really balanced by a hydrogen sulfate with a -1 charge rather than sulfate with a -2 charge, but that is glossed over)

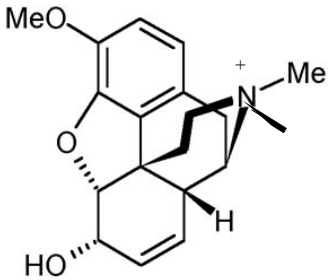
The sulfuric acid is usually written separately without showing the actual reaction. The 5 H_2O shown below is due to 5 water molecules in the crystal structure of morphine, like the waters of hydration in copper sulfate crystals in lab.



Codeine



H_3PO_4



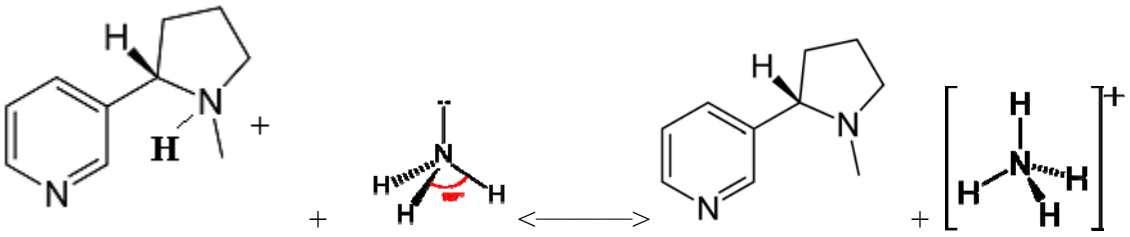
H_2PO_4-1

Codeine + phosphoric acid ⟶ codeine phosphate

(The positive charge of the codeine ammonium is really balanced by a dihydrogen phosphate with a -1 charge rather than phosphate with a -3 charge, but that is glossed over)

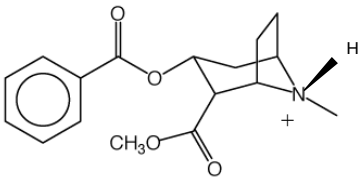
Although the ionic form of the drug is more water soluble, the **free amine or free base** form is more soluble in membranes and can dissolve through the interior of membranes faster, and that's important biologically.
The free amine form is also more volatile (evaporates more readily) so that if a drug is smoked (e.g. tobacco, marijuana, crack cocaine) more of the free base form of the drug appears in the smoke and can enter the lungs if the drug is in the free amine (free base) form. The drug also passes through the lung membranes more readily than the ionic form of the drug, and the free base form can also dissolve through the "blood-brain barrier" (really a membrane) more readily. Thus drugs whose action is in the central nervous system tend to be much more potent and rapidly acting when administered in the free base form.

Tobacco companies have utilized this information by processing tobacco to convert the ionic form of nicotine found in tobacco into the free base form. This has most typically been done by adding ammonia or a molecule which produce ammonia upon heating. The non-bonding pair of electrons on the ammonia can pull off a H ion from the amine group of the nicotine ammonium ion and convert it back to the amine. In the process the ammonia becomes an ammonium ion. The reaction is shown below.



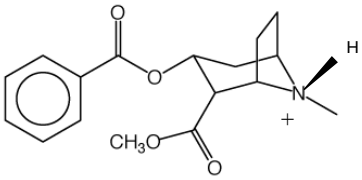
Nicotine in ammonium ion form nicotine in free base form.

The above concept has applications in illegal drug use also. Cocaine is normally purified from coca leaves as the hydrochloride salt, shown below.

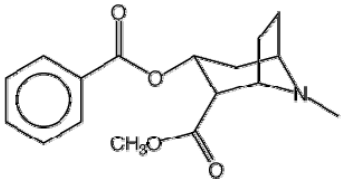


Cl^{-1}

The ammonium ion form of cocaine is then converted to the free base form by the addition of sodium bicarbonate, baking soda ($NaHCO_3$)



Cl^{-1} + $NaHCO_3$ ⟶

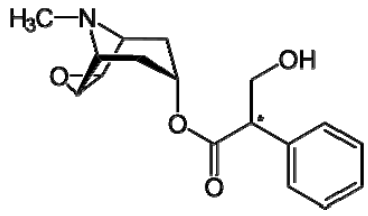


+ H_2CO_3 + NaCl ⟶ CO_2 + H_2O + NaCl

Although the ionic form is more soluble in water (and blood) its passage through membranes is somewhat slower. Cocaine in the free base (free amine) form evaporates more readily, passes through lung membranes and blood brain barrier faster and can give a faster, more intense "rush" when inhaled. The conversion of the hydrochloride form of the drug into the free base form is most easily accomplished by dissolving the drug in water, neutralizing the HCl with a base such as $NaHCO_3$ and then adding a more lipophilic solvent such as ether to preferentially dissolve the more hydrophobic free base form of the drug. The ether can then be evaporated off leaving the free base form of the drug. Residual bicarbonate salts in the free base can decompose during heating to form CO_2 gas bubbles, producing a popping sound, hence the term **"crack" cocaine**. Speeding up the evaporation of the ether with a BIC lighter is extremely hazardous to ones health, as was demonstrated by Richard Pryor.

Creative Commons: Author: Alan Light

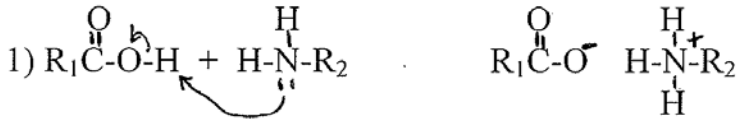
Drugs designed for topical (transdermal) use for absorption through the skin may also be more effective if given in the free amine form (the more lipophilic form) rather than the ionic (more hydrophilic form) because they will dissolve through thhe epidermal oil layer more effectively. Examples include:
1) scopolamine is used for motion sickness. It is often given as a transdermal patch which allows the drug to be slowly absorbed through the skin.



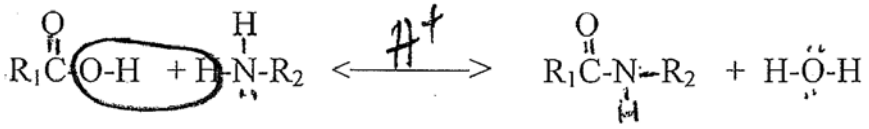
2) Rogaine which is applied to the scalp to promote hair growth.
3) fentanyl (Duragesic) a potent opioid drug for severe pain relief which is available in transdermal form and
4) Nicoderm, Habitrol and other nicotine patches.

7.5 Reactions of Carboxylic Acids and Amines

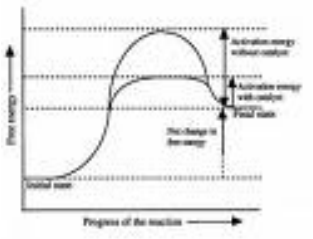
1) at **low temperature** a simple acid-base reaction occurs



2) at **high temperatures** or with suitable enzymes they form an amide and water.

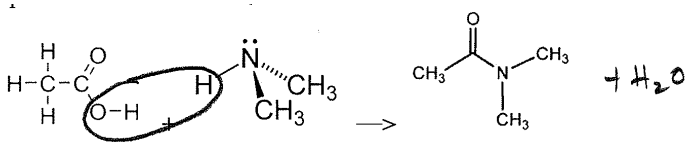


Notice that this second reaction is analogous to the formation of an ester from an alcohol and carboxylic acid in several ways:
1) A water molecule is "split out" when the two molecules react
2) The reaction is **endergonic reversible.**

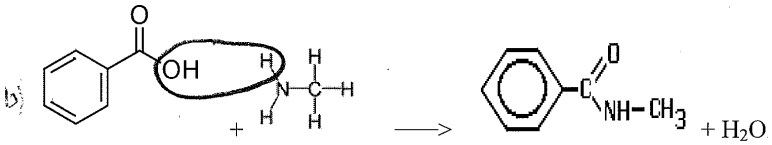


Sample problems:
Write the structure of the **amide products** formed from the following molecules at high temperature:

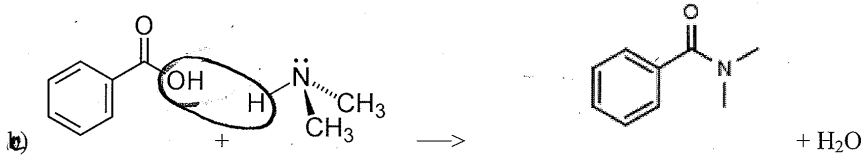
a)



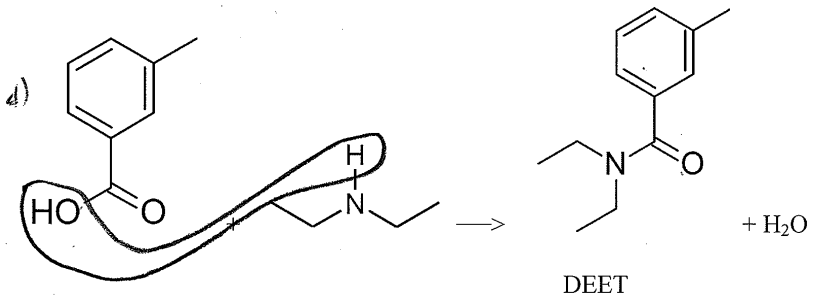
b)



c)



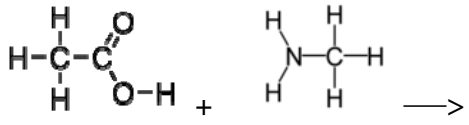
d)

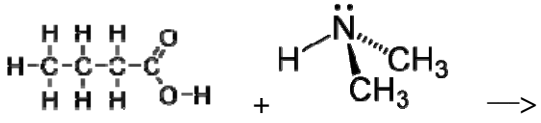


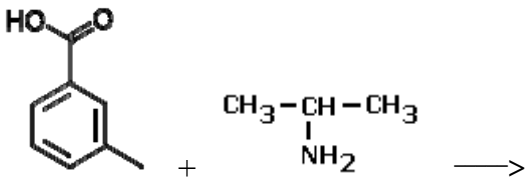
DEET
***N*,*N*-Diethyl-*meta*-toluamide**

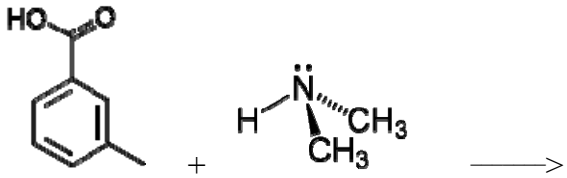
Practice problems

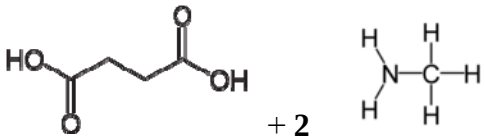
a)



b)  —>

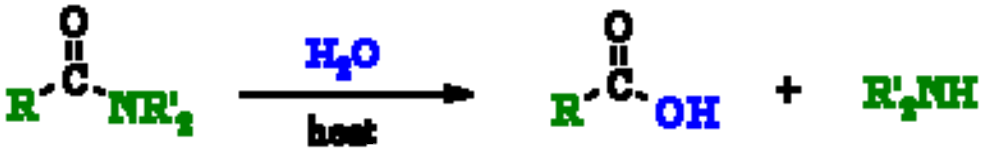
c)  —>

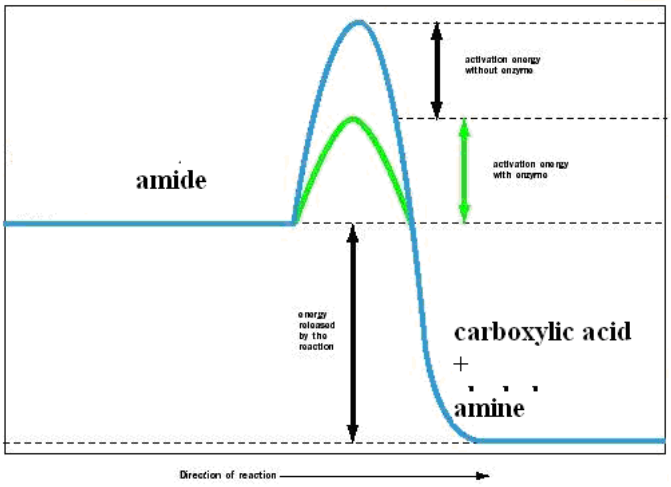
d)  ——>

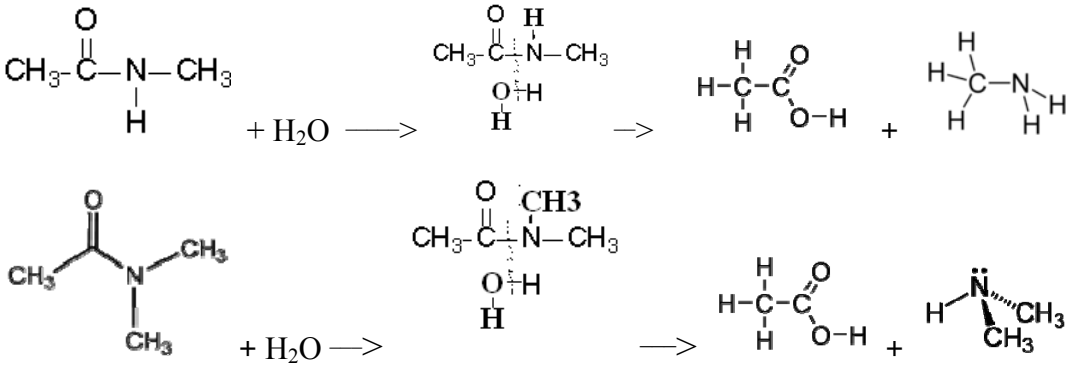
e) 

7.6 Hydrolysis of Amides

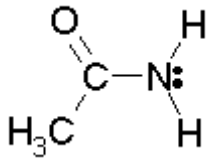
The reversibility of this reaction means that an amide can hydrolyze to form an amine and a carboxylic acid. This reaction is **reversible exergonic**.

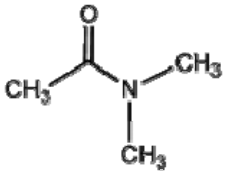


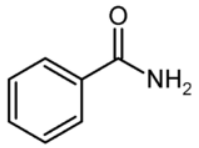


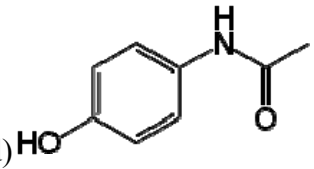


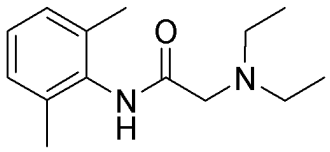
Write the amide **hydrolysis** reaction for the following amides:

a)  + H_2O —>

b)  + H_2O —>

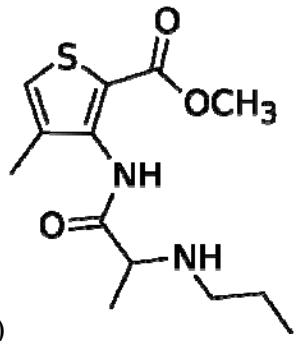
c)  + H_2O —>

d)  + H_2O —>

e)  + H_2O —>

lidocaine

Hydrolysis of lidocaine results in the inactivation of its activity as a local anesthetic.

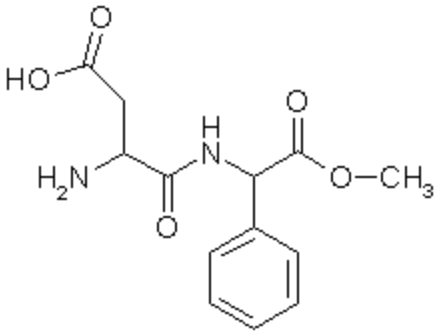
f) 

Articaine is being increasingly used as a local anesthetic in dental offices.

There are actually two hydrolyses that can occur in articaine. What are they?

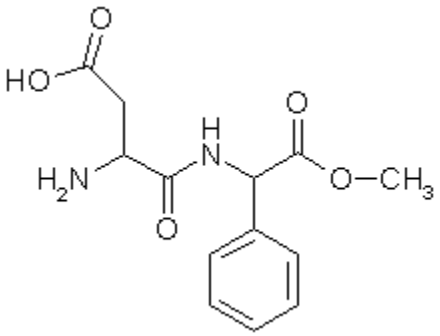
Aspartame Hydrolysis.

Aspartame (sold as Equal or NutraSweet) is an artificial sweetener commonly used in diet sodas. It is 200 times as sweet as sucrose. The structure of aspartame is shown below.



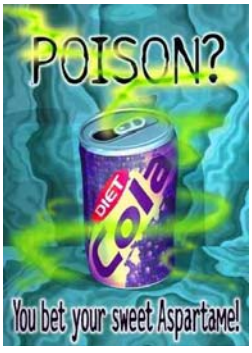
When left in aqueous solution, the **ester** linkage can hydrolyze to produce a dipeptide and methanol, neither of which is sweet. Diet sodas that are stored too long (6-12months), especially in a hot warehouse, lose their sweetness!

When diet sodas are consumed strong acid of the stomach can hydrolyze the ester linkage and peptidases in the small intestine can hydrolyze the amide bond. Draw the products that result from this.



$2\ H_2O$ —>

aspartamesafety.com



911bodyrescue.com

current.com

sankam.deviantart.com

The phenylalanine amino acid produced by the hydrolysis aspartame must be taken into account by people with the genetic disease phenylketonuria, although this disease is very rare (about one in 15,000 births in the US).

More attention has been directed to the methanol product. The methanol that is produced is metabolized by alcohol dehydrogenase in the liver into formaldehyde, which is further metabolized into formic acid by aldehyde dehydrogenase. In large quantities formaldehyde is a suspected carcinogen and formic acid can cause metabolic acidosis. The quantities that are consumed by most people are very small (17 mg of methanol per 12 oz diet soda). One would need to drink twenty one 12 oz diet sodas for life to reach the acceptable daily intake suggested by the FDA.

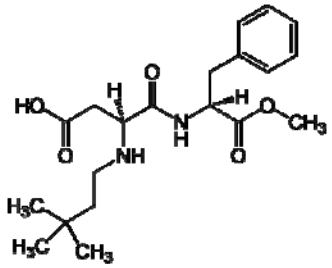
In fact methyl esters that provide the flavor of many fruits are hydrolyzed in the body into methanol in quantities that are equal or larger than the amount in an equivalent volume diet soda sweetened with aspartame. In terms of methanol toxicity, orange juice is as dangerous for our health as is the aspartame in diet soda! Nonetheless there have

been (and still are) major objections about the widespread use of aspartame as an artificial sweetener.

Note that the methanol that is produced is potentially toxic because it can be converted into formaldehyde by alcohol dehydrogenase. The manufacturer argues that the quantities that are likely to be consumed by most people are too small to be important. One argument points out that methanol is found in fresh orange juice at a concentration around 60 mg/L , about the same amount of methanol that would be obtained by drinking a liter of diet Coke! In addition a variety of methyl esters found in fruit (e.g. oranges, strawberries and pineapples) produce amounts of methanol comparable to that of diet sodas when they are hydrolyzed by acid in the stomach. If aspartame is to be banned on the basis of its methanol content, so should orange juice and pineapple juice!*

(*Source: Source:"Multivariate analysis for classification of commercial orange juice products by volatile constituents using Headspace Gas chromatography" by Philip E. Shaw, Manuel G. Moshonas and Bela S. Buslig in Chapter 4 of Fruit Flavors: Biogensis, Characterization and Authentication ed. By Russell L. Rouseff and Margaret M. Leahy, ACS Symposium 596.)

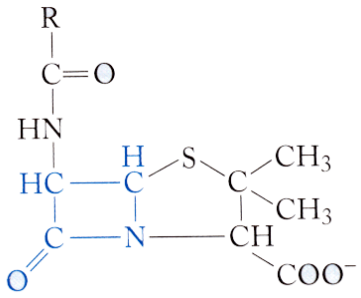
A new improved version of Aspartame, Neotame, is much sweeter(~10,000 times that of sucrose) than Aspartame and does not hydrolyze as quickly as Aspartame. Unfortunately it gives a bitter aftertaste that has hindered its acceptability to consumers. Comment on the relative size of the activation barrier for ester hydrolysis for Aspartame and Neotame. How is the structure of Neotame similar to Aspartame? How is it different?



Neotame

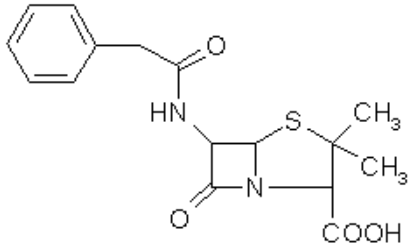
Penicillin hydrolysis

The general structure of **penicillin** and several specific penicillin drugs are shown below. Label the various functional groups.

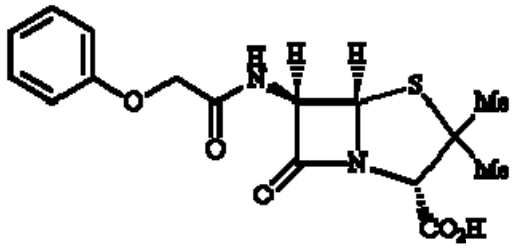


Penicillin

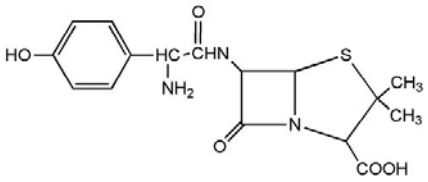
Penicillin is an unstable molecule. Can you see why?
There is in fact a whole family of penicillin drugs with different R groups. Currently the most commonly prescribed penicillin drug is **amoxicillin.**



Penicillin G



Penicillin V



Amoxicillin

The original penicillin marketed, penicillin G, was quite unstable in acid, which catalyzed the hydrolysis of the 4-membered amide ring. Write the structure of the hydrolyzed product. (Drawing the right hand side of the product molecule will be sufficient.)

As a result penicillin G (which is still occasionally used in the hospital setting) has to be given by injection. Research looking for more acid-stable penicillins has been successful and most of the penicillin drugs currently used (penicillin V and amoxicillin) survive exposure in the hydrochloric acid in the stomach. (Admittedly, since they all still have the strained 4-membered amide ring, it isn't obvious why that should be the case.)

The reactive 4 amide ring is sometimes referred to as a **β-lactam** ring. Amides in rings are referred to as lactams. This drug reacts with and destroys the transpeptidase enzymes in bacteria which crosslink the bacteria's **peptidoglycan** cell wall (a wall containing both peptide bonds and sugars). Many bacteria have developed a defense against this drug by making an enzyme, called **penicillinase or beta lactamase**, that catalyzes the hydrolysis of the amide linkage and open up the ring. Once the reactive ring has been hydrolyzed open, all antibiotic activity is lost. Pharmaceutical chemists have

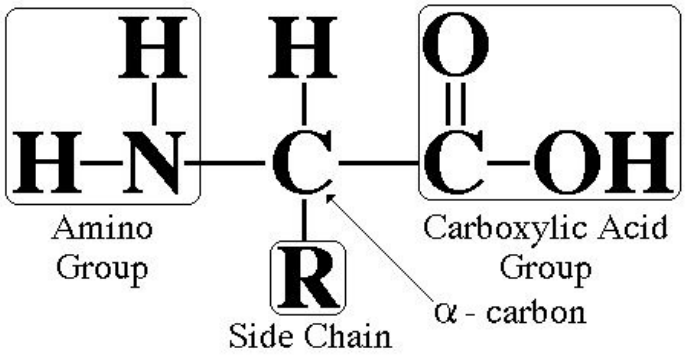
counterattacked by combing amoxicillin with a molecule called clavulanate which inhibits the beta lactamase enzyme.

7.7 Reaction pathway for Amide Formation

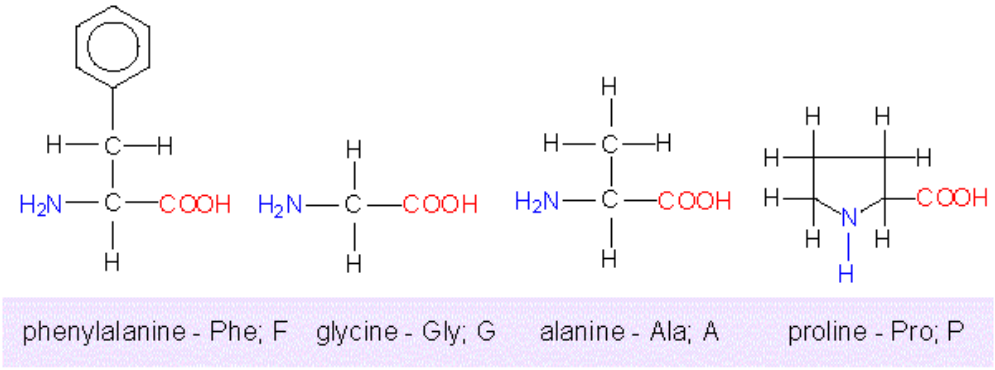
The reaction pathway for amide formation is very similar to that of ester formation, with the amine substituting for the alcohol in the reaction pathway.

Try the following problems showing the reaction pathway at both low temperature and high temperature:

7.8 Amino Acids and proteins. Alpha amino acids (often just referred to as amino acids are particularly important examples of amines and have the structure:

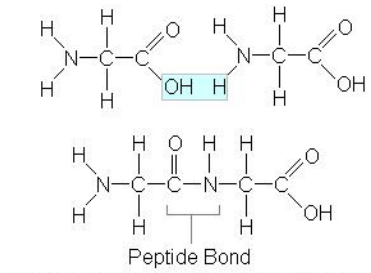


They contain both amine groups and carboxylic acids. There are 20 different common R groups on the primary amino acids. In most cases the R group is different than the other three groups and hence the alpha C has 4 different groups bonded to it and is a chiral center. The structure of some common amino acids are:



Notice that the central C has 4 different groups and hence is a chiral center in all of the above structures except glycine. Also note the common but confussing COOH notation for the carboxylic acid functional group.

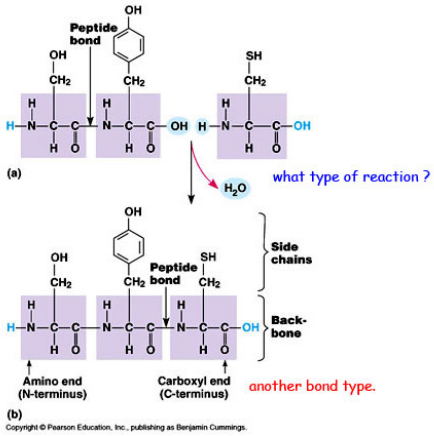
Two amino acids can link together head-to-toe to form an amide bond between them. The amide bond between two amino acids is called a **peptide bond** and we call the resulting molecule a **dipeptide**.



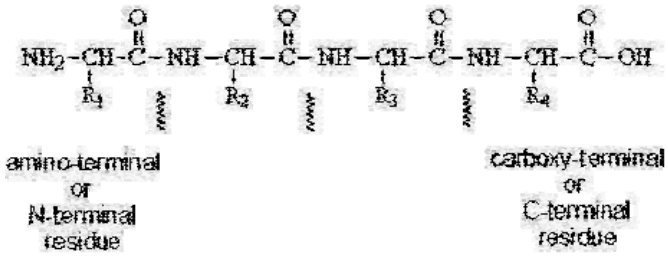
A molecule of water is removed from two glycine amino acids to form a peptide bond.

The resulting dipeptide still has an amine group on one end and a carboxylic acid on the other end so additional amino acids can be covalent bonded to both ends of the molecule. A molecule containing three amino acids is called a **tripeptide**; one with four amino acids is called a **tetrapeptide** and so forth. The end with a free amine group is called the N terminal end and the end with the free carboxylic acid group is called the C terminal end of the peptide.

Tripeptide

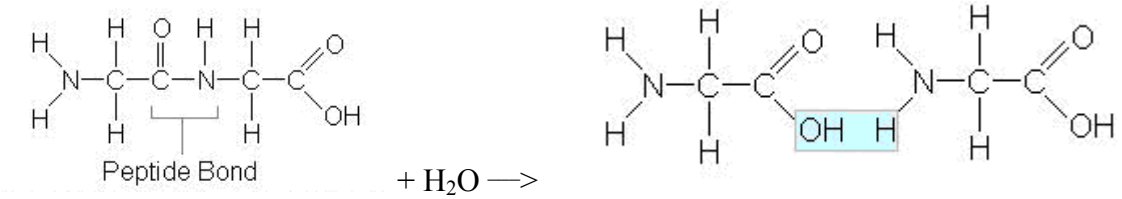


Tetrapeptide



Long chains of less than 50 amino acids are referred to as **polypeptides.** When 50 or more amino acids are linked together, it is commonly referred to as a **protein.**

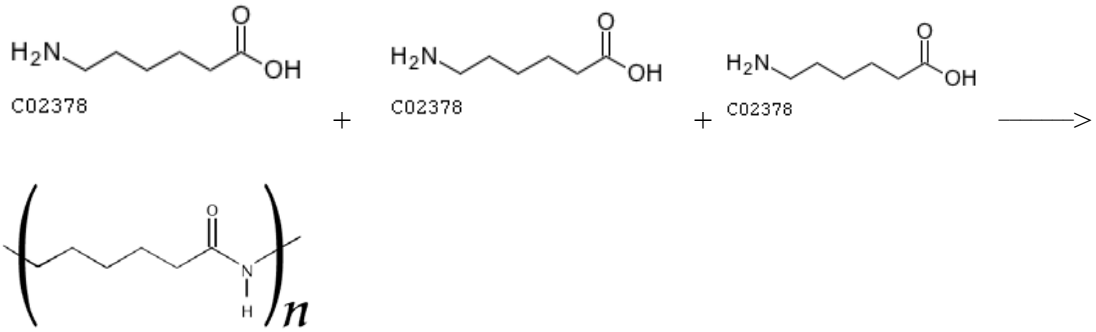
In the presence of acid catalysis and water amino acids linked by amide (peptide) bonds can hydrolyze back to separate amino acids:



This is in fact what happens when one eats proteins. They are hydrolyzed back to short peptides and amino acids with the help of HCl and the protease pepsin in the stomach and an additional collection of **protease** enzymes in the small intestine. The amino acids are absorbed and then rebuilt into proteins by your body.

7.9 Other polyamide polymers. Man-made polyamide polymers can be made by reacting the carboxylic acid and amine functional groups of multiple monomers and linking them together by means of amide linkages. Some well known examples are shown below:

Nylon 6

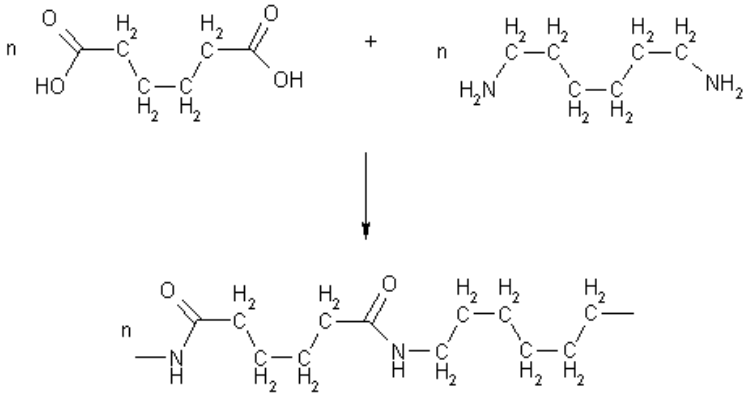


In Nylon6 the 6-carbon 6-aminohexanoic acid can react end to end in a fashion very similar to what we saw with amino acids and produce a long polyamide chain. It is referred to as Nylon 6 because the monomer has 6 C atoms.

Draw a representative structure of the polyamide formed from

a) 4-aminobutanoic acid, forming Nylon 4
b) 8-aminooctanoic acid, forming Nylon 8

Nylon 66 is formed from alternating subunits of hexanedioic acid (adipic acid) and 1,6 diaminohexane.(Developed and patented by Dupont in 1937)



In Nylon 66 the 6 C dicarboxylic acid(hexanedioic acid) is reacted with a 6-C 1,6-diaminohexane to form a molecule very similar but not identical to Nylon 6.

The 6 refers to the number of C atoms in each monomer. Nylon is in fact a general name for polymers similar to those shown, linked together by amide linkages. Nylon was first synthesized in 1935 by Walter Carothers, working for DuPont Corporation. It was rapidly perfected and used in nylon stockings, tooth brushes and more recently in dental floss and a large assortment of plastic devices.

teens4safecellphones.typepad.com

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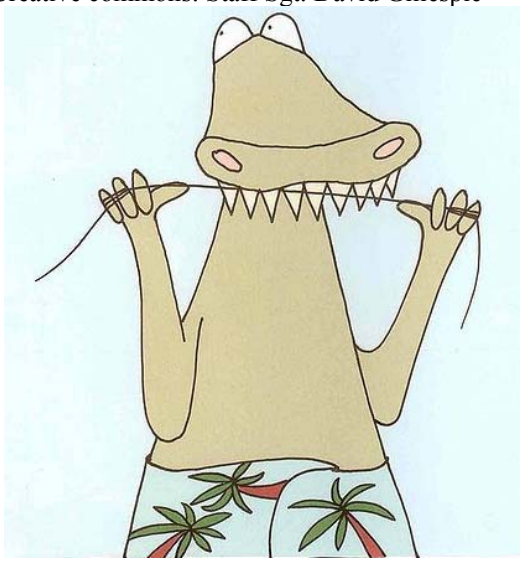


Creative commons: Author: Torill Kove

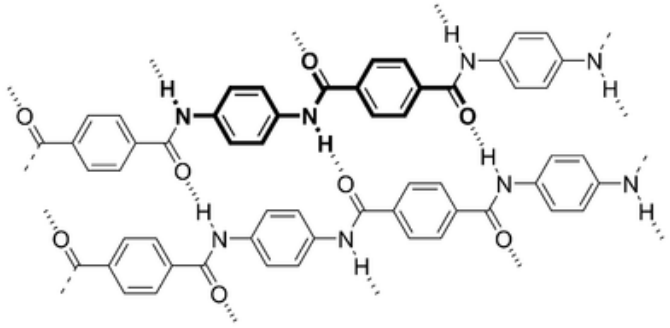
alessi-dental-floss.jpg.

Creative commons: shortszene

Specific properties of the nylon compound can be varied by adjusting the length of the C chains. Nylon 12 is used to make fuel and brake linings. An explosion in the only plant making nylon 12 (in Germany) has created a major shortage of brake lines for auto manufacturers.

Draw the starting molecules and final products for Nylon 44.

Kevlar is an extremely strong amide polymer made from 1,4 benzenedicarboxylic acid and 1,4-diaminobenzene. It is used in bulletproof vests, Kevlar belted radial tires, high performance skis, and other uses that require high strength and low weight. There are attractions between chains of Kevlar formed by the repeated attractions between the δ^- on the O of the C=O carbonyl group on one chain and the δ^+ on the H of a N atom on another chain. See diagram below.

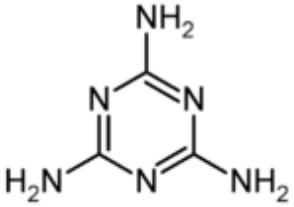


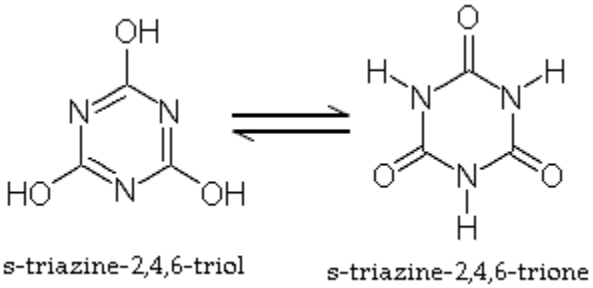
(So can aliphatic nylon)

Creative commons: Author: Cheryl Ransford

7.10 Protein enhancers and the pet food scare

In April 2007 an increase in pet deaths due to kidney failure was noticed and traced back to food imported from a plant in China. Initial reports suggested that the toxic ingredient was gluten, which is a major non-toxic protein constituent in wheat which helps make bread dough rise. Further investigation revealed that the ground wheat being added to the pet food was spiked with melamine, cyanuric acid and other chemicals Their structures are shown below





s-triazine-2,4,6-triol s-triazine-2,4,6-trione

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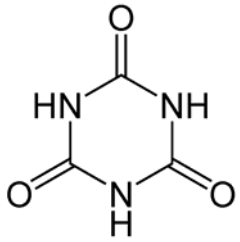
Melamine Cyanuric acid

The primary use of melamine is for making plastics(such as whiteboards) by polymerizing it with formaldehyde. So what was it doing in cat and dog food? Although the Chinese aren't talking, the following *plausible* (but unproven) scenario has been suggested. The Chinese have several huge plants making melamine (from coal) for the

plastic industry. An overcapacity of melamine production has resulted in more melamine production than is needed for making plastics. It has been known since the 1950's that ruminant animals (e.g. cows) fed melamine can convert melamine into amino acids with the help of bacteria in their rumens and the amino acids can then be converted into proteins such as muscle (i.e. meat!). Non-herbivores like cats and dogs cannot do this however, so melamine has no nutritional value to cats and dogs. On the other hand, toxicity tests on rats and cows did not find any evidence for toxicity either.

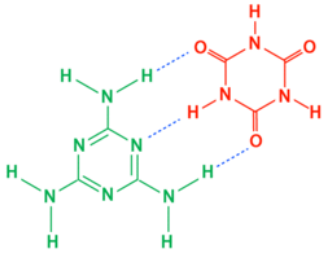
Small quantities of other chemicals besides melamine were found in the contaminated pet food suggesting that it was actually "melamine scrap", waste products from melamine synthesis. One of the other products in the food beside melamine was cyanuric acid. (structure shown above).



cyanuric acid

Analysis of the pet food showed that the "gluten" protein was in fact just wheat flour, which is mostly carbohydrate (only about 10% protein), and hence not as digestible by cats and dogs. The melamine was added to increase the ***apparent*** N content of the mislabeled wheat gluten to make it more closely resemble protein. Of the three primary nutrients (fat, carbohydrates, and proteins) only proteins contain N, so a chemical test measuring the amount of N in a food sample can be done to determine the % protein in the food. However if melamine is added to food, it will test much higher for N than the actual amount due to protein and that was the reason for adding the melamine. The wheat flour has much less protein than pure wheat gluten and would test low for protein and potentially be rejected. By adding melamine to the wheat flour the factory was able to use cheaper wheat flour combined with excess melamine and melamine waste products and meet the nitrogen content expected of protein.

Still, the available data suggests that both melamine and cyanuric acid *individually* have very low toxicity which led investigators to look at other products in the melamine waste. Crystals isolated from the kidneys of dead animals were found to contain both melamine and cyanuric acid and one possible explanation is that the melamine reacted with cyanuric acid by hydrogen bonding as shown below to form insoluble crystals that caused damage to the kidney nephrons.



7.11 Chloramine

The term chloramine unfortunately is often used to refer to both NH_2Cl and to any organic molecule which contain a Cl atom on the amine group.

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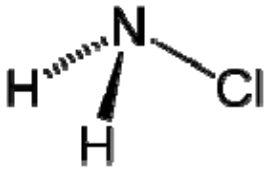
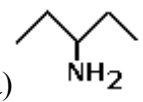


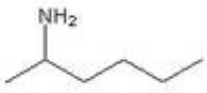
Chloramine

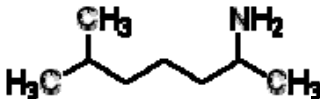
Chloramine is being used as a water disinfectant in many city public water systems. It is replacing chlorine because chlorine can react with organic compounds to form chlorinated compounds such as CCl_4(carbon tetrachloride)and $HCCl_3$(chloroform) which are carcinogenic in rats. As a result, the EPA has put limits on the amount of these compounds which can be in drinking water. Chloramines also act as water disinfectants. They are not as potent as chlorine, but they produce fewer chlorinated organic molecules and last longer while water is being transported through the large city water distribution system. Like chlorine, they must be removed before use in dialysis centers and in aquariums. (In both cases the chloramine comes in direct contact with blood either via the gills or the dialysis filter membranes.) Chloramine concentrations are limited to a maximum of 3 parts per million (ppm or mg/L). Higher concentrations, which may occur in poorly maintained swimming pools, may cause skin rash and irritation and burning eyes.

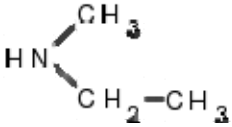
Amine Study Guide Question

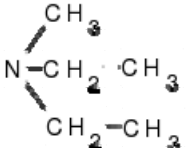
1. Name the following molecules:

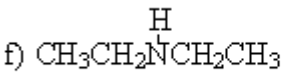
a) 

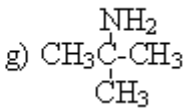
b) 

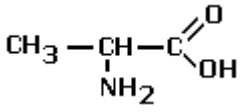
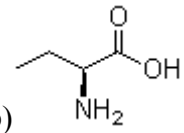
c) 

d) 

e) 

f) 

g) 

2. Name a)  b) 

3. Draw the structure of: a) trimethylamine b) ethylmethylamine c) ethyldimethylamine d) triethylamine e)dipropylamine f) tripropylamine g) 5-amino-2,3-dimethylhexane h) 2-amino pentanoic acid

4. Explain why 3-aminobutane is not a correct IUPAC name. Draw the structure and think about it.

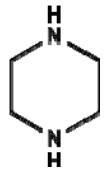
5. When triethylamine is dissolved in water, the pH of the solution is basic (alkaline). Explain why, writing the equation for the reaction which has occurred.

6. Draw piperidine a) in the "flat" shape and b) showing its true conformation. What is the bond angle in piperidine?

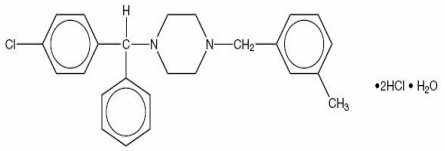
7. Give a practical use for piperine.

8. What was the original medical use for phencyclidine? Why was it never marketed? What are two "street names" for phencyclidine? What is the significance of the "phen" part of the name?

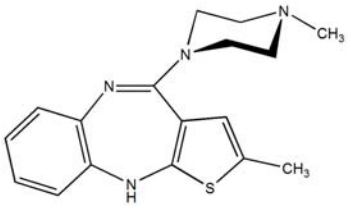
9. What is the medical use for quinine? What problems are there with taking quinine orally? What adverse effects can occur with quinine overdose? What common food product contains quinine (at very low concentrations)?



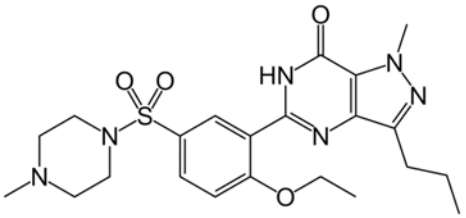
10. Piperazine (structure shown at right) is also found in many drug molecules. Draw piperazine in its real conformation. Identify the piperazine group in the drug molecules shown below.



Meclizine(Bonine) is used in treating nausea.

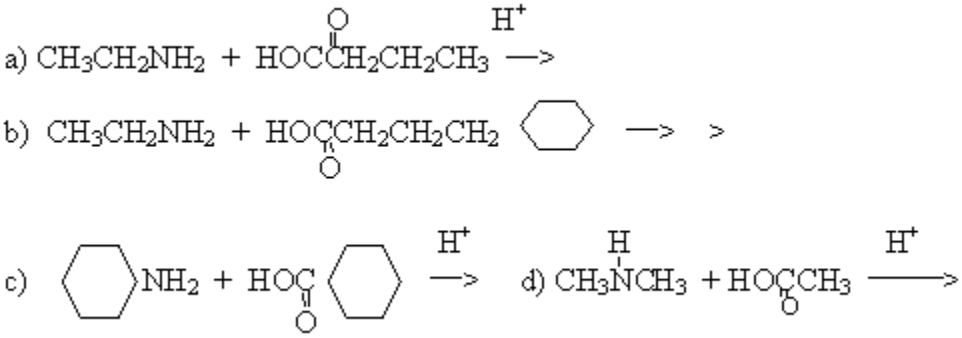


Olanzapine(Risperdal) is used to treat schizophrenia.



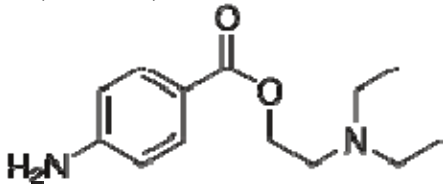
Sildenafil(Viagra) is used to treat erectile dysfunction.

11. Draw the structure of the **amide** formed:



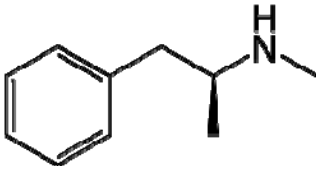
12. Show the products for the reactants shown below a) at low temperature where a simple acid-base reaction occurs b) at high temperature (or in the presence of a suitable catalyst) where formation of an amide occurs.

13. Write the structure of the product formed from the reaction of procaine (Novocaine) with hydrochloric acid. Would procaine or procaine hydrochloride be more soluble in water (or blood)?



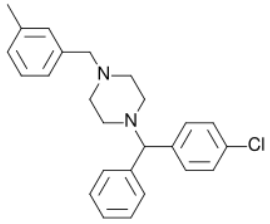
+ HCl⟶

14. Answer the previous question for methamphetamine (structure shown below). Which form is the free base form of meth?

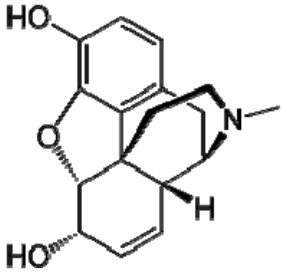


+ HCl ⟶

15. Meclizine (structure shown below) is an antihistamine and antiemetic that is administered as meclizine **di**hydrochloride. Suggest a reason why meclizine reacts with two molecules of HCl, based on its structure.



16.(skip) When morphine is extracted from the latex resin of opium poppies, the latex is normally dissolved in a solution of sulfuric acid.



1) Explain why the morphine will be soluble when an acid such as H_2SO_4 is added. Show the equation for the reaction that occurs. You do not have to draw the whole structure of morphine but show the portion that reacts.

Fiber and insoluble residue is filtered off and the aqueous solution is then made basic with a base such as sodium bicarbonate. This process causes the morphine alkaloid to precipitate.

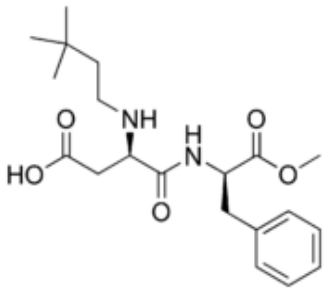
2) Write the equation for the reaction that occurs and explain why the addition of sodium bicarbonate makes the morphine less soluble in water.

The morphine precipitate is then redissolved in a solvent such as ether and crystallized upon evaporating off the ether.

3) Why is this form of the morphine soluble in ether but not in water?

17. Explain what happens to NutraSweet when it is ingested and the basis for concerns for aspartame toxicity if it is eaten in large quantities.

18. Neotame (structure shown below) has a structure similar to aspartame except that the N of the amide bond has an additional dimethyl butyl group attached. Give some of the advantages of neotame over aspartame.



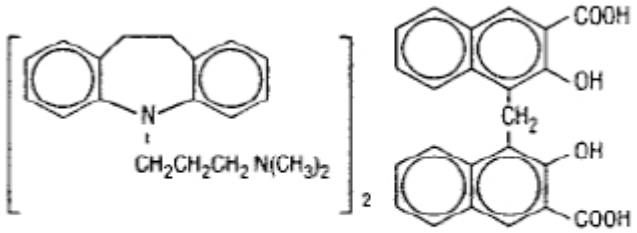
19. Explain why penicillin is a very reactive molecule. What is the specific name for the reactive ring? How do bacteria inactivate it? How can this inactivation be prevented?

20. What type of functional groups link the monomers of Nylon? How is the structure of Nylon 66 similar to that of amino acids? Name a dental use of nylon.

21. Explain the probable reason why melamine was added to pet food and what deficiency was being remedied. Would the melamine be of any nutritional value to cats and dogs? What animals could utilize the melamine and why? Discuss why or why melamine by itself is likely to be the cause of many pet deaths. What theory has been proposed?

22. What is the purpose of adding chloramine do drinking water? In what medical situations does it need to be removed?

23. The structure of the tricyclic antidepressant imipramine pamoate (Tofranil) is shown below. The actual drug molecule, imipramine, is shown on the left. Why is it called a tricyclic? The pamoate molecule is on the right. Suggest what the function of the



$(C_{19}H_{24}N_2)_2 \bullet C_{23}H_{16}O_6$ M.W. = 949.21

pamoate is.

24. The drug insert on donepezil(Aricept) (a drug for Alzheimer's) warns that people allergic to piperidine drugs should not use Aricept. Circle the piperidine ring in the structure of donepizil shown below. Draw the piperidine, showing its real shape .