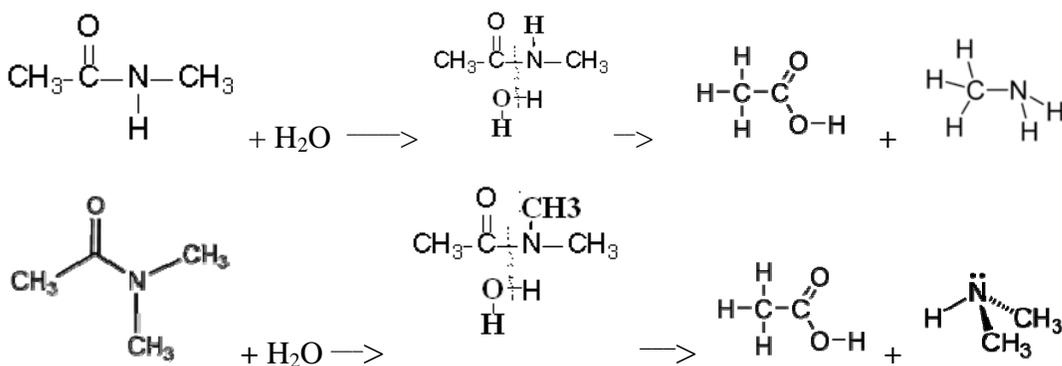
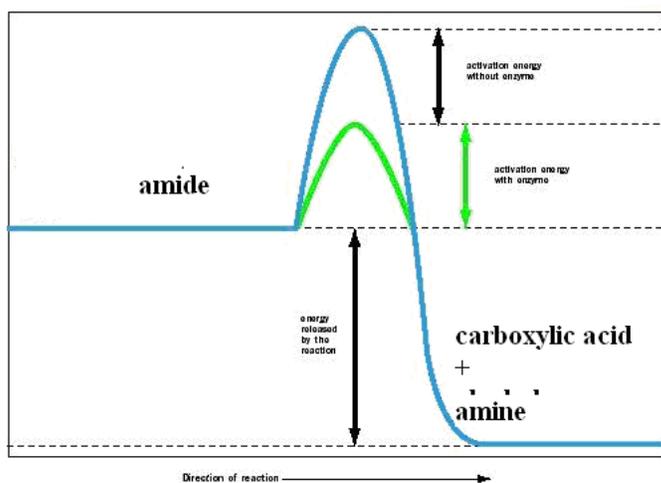
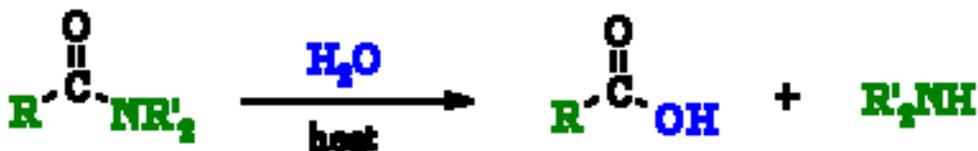
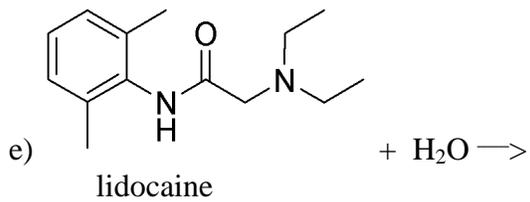
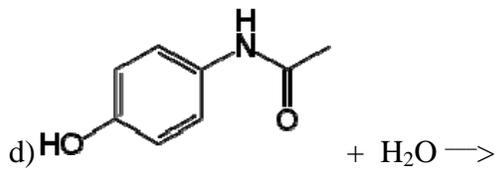
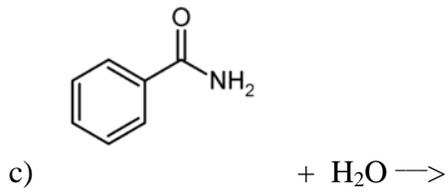
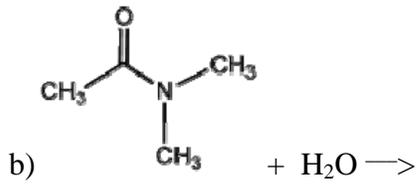
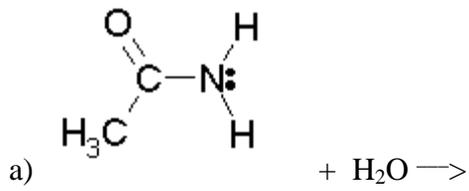


7.6 Hydrolysis of Amides

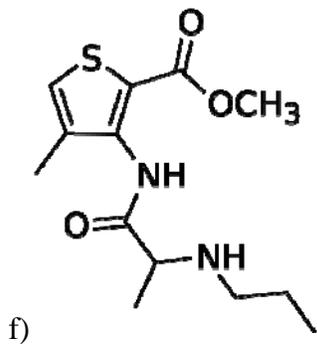
The reversibility of this reaction means that an amide can hydrolyze to form an amine and a carboxylic acid. This reaction is **reversible exergonic**.



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



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

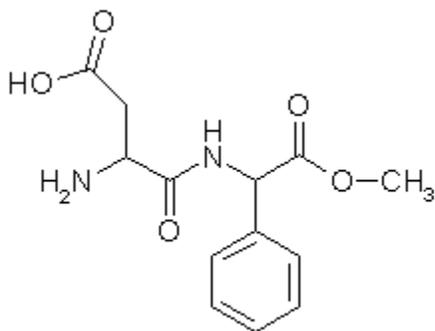


Articaine is being increasingly used as a local anesthetic in dental offices.

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

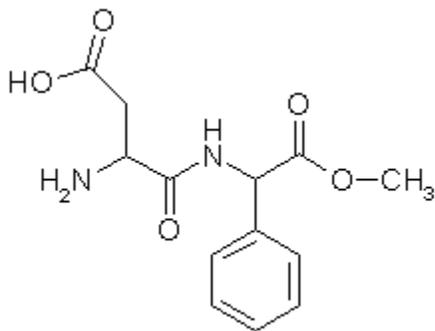
Aspartame Hydrolysis.

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.



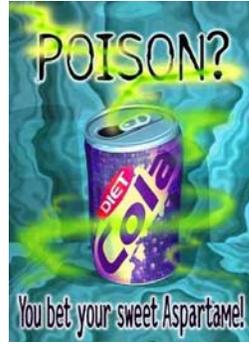
When left in aqueous solution, the **ester** linkage can hydrolyze to produce a dipeptide and methanol, neither of which is sweet. Diet sodas that are stored too long (6-12months), especially in a hot warehouse, lose their sweetness!

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.





aspartamesafety.com



911bodyrescue.com



current.com



News Item:
Scientists have discovered that red pandas prefer the taste of artificial sweeteners to actual sugar.
BBC News, 16 April 2009

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

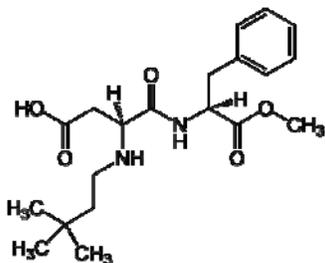
formaldehyde is a suspected carcinogen and formic acid can cause metabolic acidosis. The quantities that are consumed by most people are very small (17 mg of methanol per 12 oz diet soda). One would need to drink twenty one 12 oz diet sodas for life to reach the acceptable daily intake suggested by the 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: Biogenesis, Characterization and Authentication ed. By Russell L. Rouseff and Margaret M. Leahy, ACS Symposium 596.)

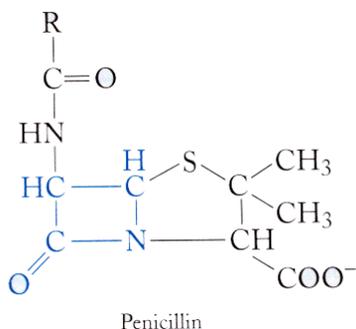
A new improved version of Aspartame, Neotame, is much sweeter (~10,000 times that of sucrose) than Aspartame and does not hydrolyze as quickly as Aspartame. Unfortunately it gives a bitter aftertaste that has hindered its acceptability to consumers. Comment on the relative size of the activation barrier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



Neotame

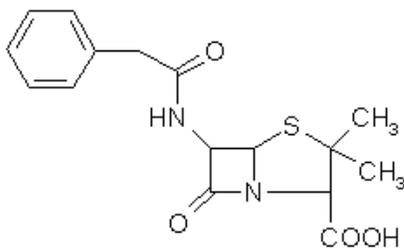
Penicillin hydrolysis

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

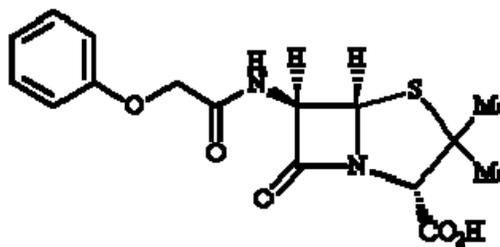


Penicillin is an unstable molecule. Can you see why?

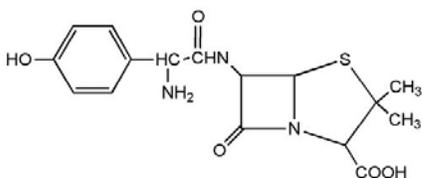
There is in fact a whole family of penicillin drugs with different R groups. Currently the most commonly prescribed penicillin drug is **amoxicillin**.



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.