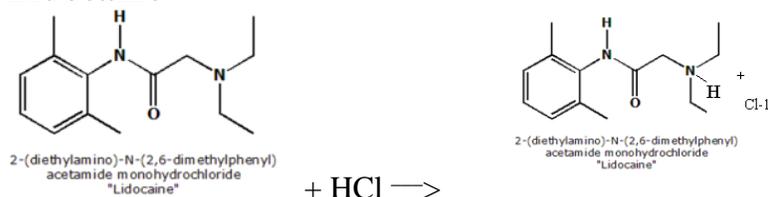


## 7.4 Drugs as amines

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.

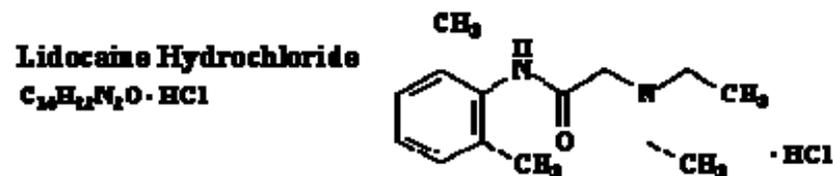
### Lidocaine



Lidocaine + hydrochloric acid

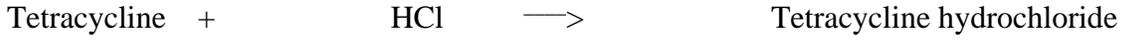
Lidocaine hydrochloride

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

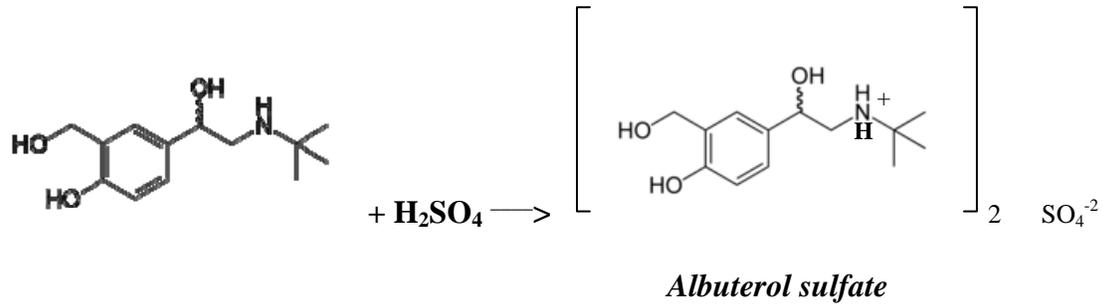


### Tetracycline

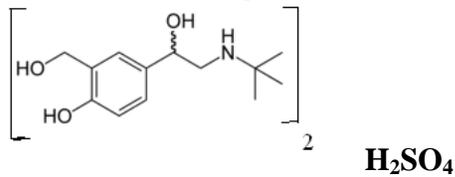




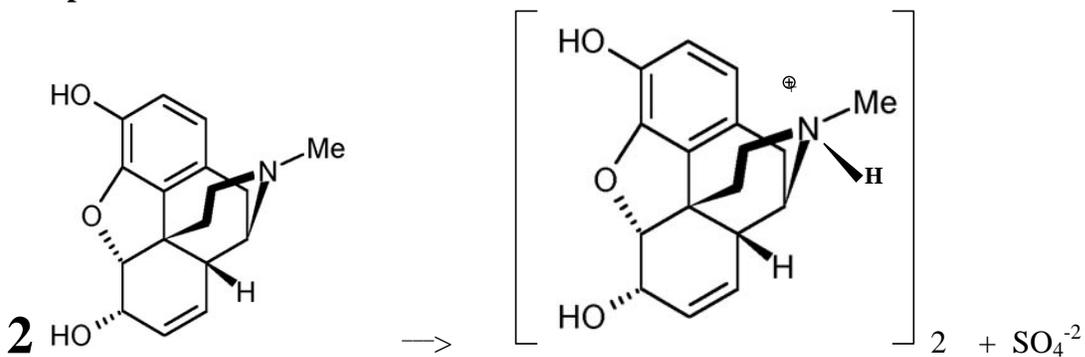
### Albuterol



But it is commonly written as

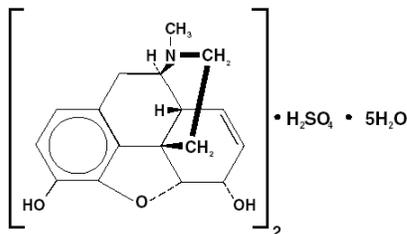


### Morphine

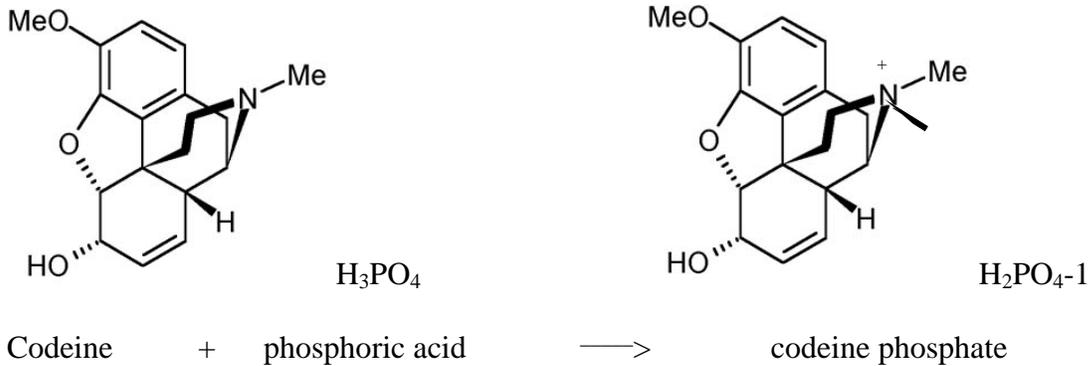


(The positive charge of the morphine ammonium ion is really balanced by a hydrogen sulfate with a -1 charge rather than sulfate with a -2 charge, but that is glossed over)

The sulfuric acid is usually written separately without showing the actual reaction. The 5  $\text{H}_2\text{O}$  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

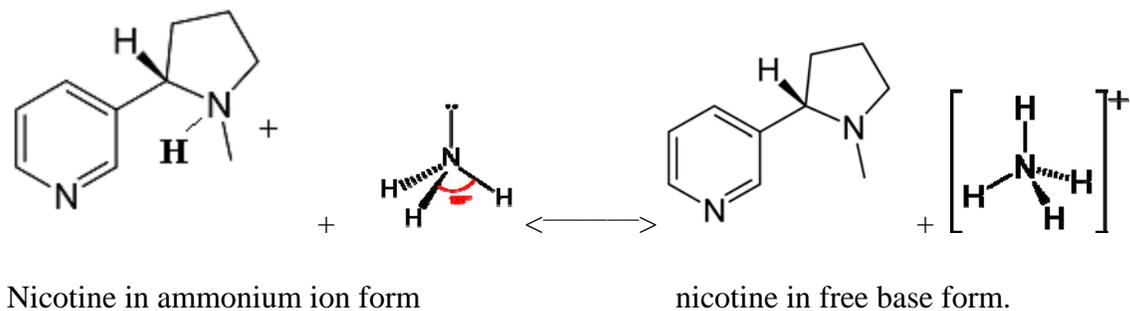


(The positive charge of the codeine ammonium is really balanced by a dihydrogen phosphate with a -1 charge rather than phosphate with a -3 charge, but that is glossed over)

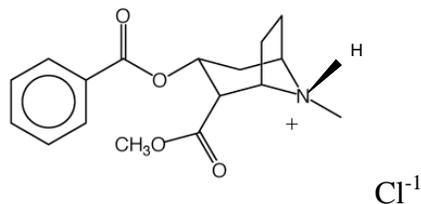
Although the ionic form of the drug is more water soluble, the **free amine or free base** form is more soluble in membranes and can dissolve through the interior of membranes faster, and that's important biologically.

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.

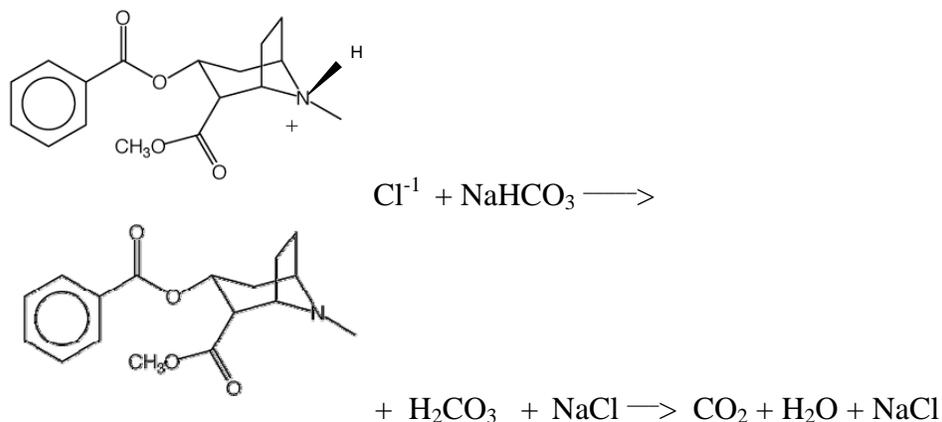
Tobacco companies have utilized this information by processing tobacco to convert the ionic form of nicotine found in tobacco into the free base form. This has most typically been done by adding ammonia or a molecule which produce ammonia upon heating. The non-bonding pair of electrons on the ammonia 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.



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



The ammonium ion form of cocaine is then converted to the free base form by the addition of sodium bicarbonate, baking soda ( $\text{NaHCO}_3$ )



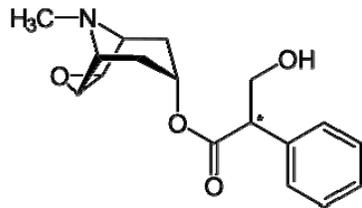
Although the ionic form is more soluble in water (and blood) its passage through membranes is somewhat slower. Cocaine in the free base (free amine) form evaporates more readily, passes through lung membranes and blood brain barrier faster and can give a faster, more intense “rush” when inhaled. The 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  $\text{NaHCO}_3$  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  $\text{CO}_2$  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 the 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.