

## Review from last lecture

An **alcohol** (R-OH) can be considered as a water molecule (H-OH) substituted with an alkyl group (-R) in place of a hydrogen (H).

An **alkyl** group (-R) is a group with a general formula  $C_nH_{2n+1}$  generally derived from hydrocarbons (compounds composed of only carbon and hydrogen). They are not found on their own but are found attached to other atoms.

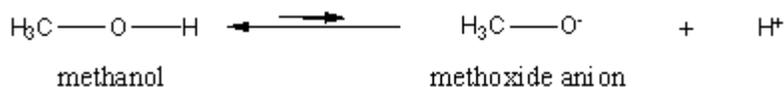
An example of an alkyl group is a  $CH_3-$  group. This is called a methyl group, a derivative of methane. To name this group, you take the parent alkane (methane in this case), drop *-ane* (meth-), and add *yl* (methyl). Similarly, a  $CH_3CH_2-$  is an ethyl group derived from ethane.

An **alkoxy** group is an alkyl group with an oxygen atom attached. Like the alkyl groups, these are also found attached to other groups.

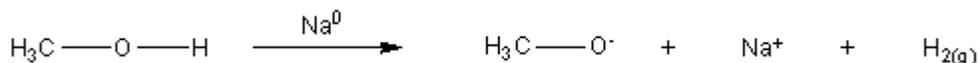
An example of an alkoxy group is a  $CH_3O-$  group. This is called a methoxy group. Similar to the naming of alkyl groups, we drop *-ane* of parent alkane, and add *oxy* at the end.

## Demo-In-Class

Methanol dissociates spontaneously to form a negative charged methoxy species called **methoxide** anion.



When sodium metal is added to methanol, we saw the metal sizzles on top of the methanol solution. (Sodium is an electron donor, it donates electron to make  $H^-$ , a hydride ion (a reduction process). The hydride ion then deprotonates the hydrogen on methanol to form hydrogen gas ( $H_2$ ).



The hydrogen gas formed can react (burn) with the oxygen in the atmosphere to form water (note the equation shown above is not balanced).

When potassium metal is added to methanol, the metal sizzles around the flask. The reduction process is more rapid than with sodium, since we observed that the potassium metal disappeared a lot faster than sodium metal (all potassium metal has reacted). This is expected since potassium is lower down in the periodic table than sodium. The electrostatic force binding the electron to the nucleus is weaker as we go further down the group. As a result, the electron is more readily removed as part of a reaction (it can donate electrons more readily), hence it is more reactive.

With water, when sodium is added, we saw the metal sizzles initially, then we heard a loud pop, witnessed a spark, and there was a small amount of smoke/gas given off. The reaction of water with sodium is more vigorous than methanol. (Caution! Sodium reacts violently with water, so don't try this at home).

When potassium metal is added to water, there was rapid evolution of hydrogen gas, and then the reaction was over (if a bigger piece of potassium metal was added, we would see an open flame or explosion take place. However, for our safety, a smaller piece of metal was used). Potassium reacted a lot faster and more vigorously than sodium. Hence there was more gas evolved, and metal disappeared fast (no sizzle was even observed before it disappeared).

## Physical Properties of Alcohols and Acidity

Examine the comparison of molecules below:

<i>Name</i>	Methanol	Ethane
<i>Formula</i>	CH <sub>3</sub> OH	CH <sub>3</sub> CH <sub>3</sub>
<i>Molecular Weight (g/mol)</i>	32	30
<i>Boiling Point (° C)</i>	65	-89

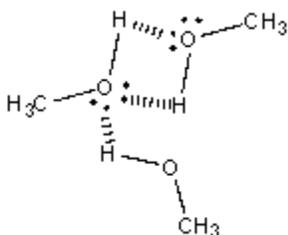
Ethane has almost the same molecular weight as methanol. However, the boiling point is much lower than methanol.

Similarly, propane has approximately the same molecular weight as ethanol, but the boiling point is significant lower than ethanol:

<i>Name</i>	Ethanol	Propane
<i>Formula</i>	CH <sub>3</sub> CH <sub>2</sub> OH	CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>
<i>Molecular Weight (g/mol)</i>	32	30
<i>Boiling Point (° C)</i>	78.5	-44.5

*Why are the boiling points so different?*

Answer: Alcohols are polar and able to form hydrogen bonds.



Alcohols are strongly associated with each other both through dipole-dipole attraction (weaker intermolecular force) and hydrogen bonding (a stronger intermolecular force). The presence of the electronegative oxygen atom polarizes the bonds, and produce dipole moments. The basic oxygen atoms also form partial bonds to the acidic hydroxyl hydrogens of another molecule (shown as dotted line in the figure above). Together, these factors raise the boiling points of alcohols far above their parent alkanes, with the hydrogen-bonding being the most significant and powerful factor.

Review from previous term, there are **three** fundamental non-covalent bonding forces:

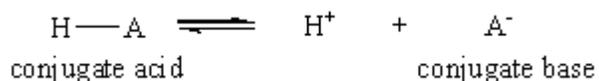
1. Hydrogen bonding (occur with hydrogen attached directly to electronegative atoms such as O, N, or halogen).
2. Dipole-dipole interaction
3. London forces (temporary dipole interactions, which is the basis for hydrophobic forces). This is comparatively a weak intermolecular force on a per atom basis, but large hydrophobic (non-polar) sections of molecules interact strongly and can overcome hydrogen bonding between two atoms in the same molecules.

### Physical Properties:

1. The polarity of alcohols make them quite soluble in (or miscible with) water if the number of carbons on the alcohol is less than 4. Butanol and higher alcohols are still soluble in water, but no longer infinitely miscible (completely soluble at all proportions)
2. The melting point and boiling point for an alcohol is higher than its parent alkane (as seen from our comparison above).
3. The density of alcohol is less than 1 (and hence less than water. If the given alcohol is not miscible with water ( $C > 5$ ), it will be floating on top of water)

### Acidity

Let's review some basic definitions



HA is the conjugate acid of  $\text{A}^-$ , and  $\text{A}^-$  is the conjugate base of HA.

The equilibrium constant, or acidity constant,  $K_a$ , for this reaction can be expressed as:

$$K_a = [\text{H}^+][\text{A}^-] / [\text{HA}]$$

For example: the dissociation of methanol



$$K_a = [\text{H}^+][\text{CH}_3\text{O}^-] / [\text{CH}_3\text{OH}] = 10^{-16}$$

The oxygen of the OH group in methanol is partially negative charged and the hydrogen is partially positively charged. The O-H bond is easy to break and it can break spontaneously. When methanol with OH is put in a solution of methanol with O-D (deuterium), the hydrogen will exchange rapidly against deuterium.

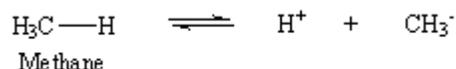
By analogy with pH, we can define a quantity  $pK_a$ , which is often used.

$$pK_a = -\log K_a$$

**Generally, the stronger the acid, the lower the  $pK_a$ .**

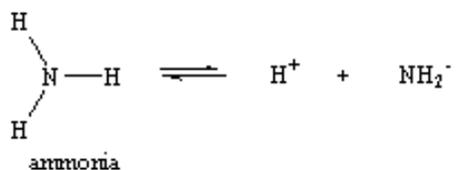
The  $pK_a$  value for methanol is 16, for water is 15.7 (know these values for exam). Since the  $pK_a$  value of water is less than methanol, the dissociation of methanol is harder than water and water is a stronger acid than methanol. We generally consider compounds with  $pK_a$  lower than water to be acidic, and those with  $pK_a$  higher than water to be non-acidic

Examples:



The  $pK_a$  value of methane is about 45. It is not acidic.

What happens when we replace the carbon with nitrogen, a heteroatom?



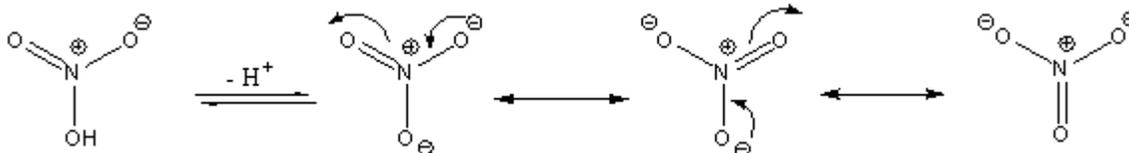
The  $pK_a$  value of ammonia is 36, which is 9 orders of magnitude ( $10^9$ ) more acidic than methane. This is because the nitrogen atom is more electronegative than carbon and able to stabilize the negative charge better. However, ammonia is still a very weak acid. The acidity of ammonia ( $\text{NH}_3$ ) should not be confused with the acidity of the ammonium ion ( $\text{NH}_4^+$ ) which has a  $pK_a$  of 9.26. Biologists and biochemists frequently speak of the  $pK_a$  of ammonia and amines, but what they are considering is the  $pK_a$  of the protonated form (conjugate acid), in the case of ammonia, the ammonium ion.

*Based on  $pK_a$  values, is oxygen more or less electron withdrawing than nitrogen?*

Answer: Oxygen is more electron withdrawing. It has lower  $pK_a$  value, able to stabilize the negative charge more.

Recall from last term, **the stability of the conjugate anion determines the acidity of a compound**. The more stabilized the anion is, more acidic the molecule is.

Example:

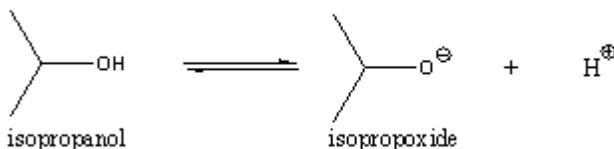


Nitric acid is very acidic ( $pK_a < -1$ ), because its conjugate anion is very stable (through resonance delocalization).

More examples:

Name	Structure	$pK_a$	
methanol	$H_3C-OH$	16	
ethanol	$CH_3-CH_2-OH$	17	
isopropyl alcohol		18	
tert-butanol		19	

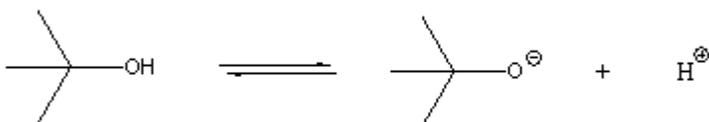
What do these  $pK_a$  values mean in reactions?



Isopropanol dissociates to form isopropoxide anion and a proton. However, the dissociation constant is  $1 \times 10^{-18}$ . Hence, most of the molecules exist in the isopropanol form and only one part in  $10^{18}$  is ionized. The equilibrium for this reaction lies far to the left.

There are two alkyl groups attached to the central carbon bearing oxygen in isopropanol. The alkyl groups (methyls) donate electron density to that carbon (an inductive effect) that is already next to a negative charged center (O). Since negative charges repel each other, the anion is less stabilized. Therefore, the anion is even less likely to form (less stabilized than if the alkyl groups (methyls) in isopropanol were missing).

Methanol ( $pK_a$  16) is 100 times ( $10^2$ ) more acidic than isopropanol, since it has only hydrogens (a less donating group) attached to the carbon bearing the negative oxygen in the corresponding anion)



For *tert*-butanol (*tert*-butyl alcohol), there are three alkyl groups (methyls) that donate electron density to the carbon next to a negative charged group (inductive donation of

electrons destabilizes the anion). Therefore, it is less likely to dissociate ( $pK_a$  19) and the molecule is even less likely to ionize (less acidic).

Consider the example below:

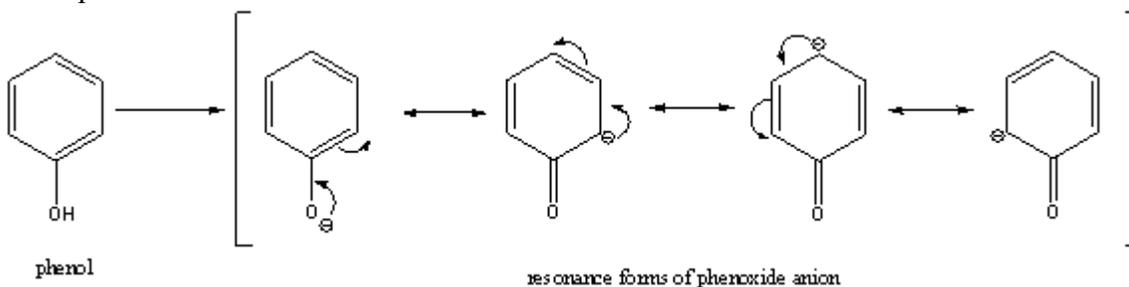


Where does the equilibrium lie in the above reaction?

Answer: It lies far to the right.

**The reaction of a stronger base (tert-butoxide) and a stronger acid (methanol) to a weaker base (methoxide) and weaker acid (tert-butanol) is very fast.**

Example:

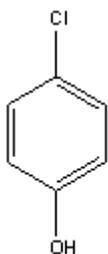


Phenol has a  $pK_a$  value of 10 (given this information, you should immediately recognize that it is much more acidic (about 6 orders of magnitude) than water ( $pK_a$  15.7) and methanol ( $pK_a$  16) since it has a lower  $pK_a$  value). As phenol is more acidic, this means that its conjugate anion is more stable. The phenoxide anion is stabilized through resonance (shown above). It has 4 resonance forms, and therefore, more ability to spread the negative charge and be stabilized.

Where does the equilibrium lie for ionization of phenol to phenoxide and a proton ( $H^+$ )?

Answer: It lies far to the left (not ionized). Even though phenol is  $10^6$  more acidic than water, its  $pK_a$  of 10 tells you that the acidity constant is  $10^{-10}$  or that only one part in  $10^{10}$  is ionized, the rest exists as phenol with H attached to oxygen.

Consider the following example:

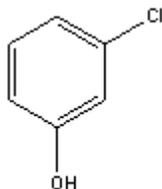


*p*-chlorophenol

The  $pK_a$  value for *p*-chlorophenol is approximately 9.3.

*Is the anion more or less stabilized compared to phenol?*

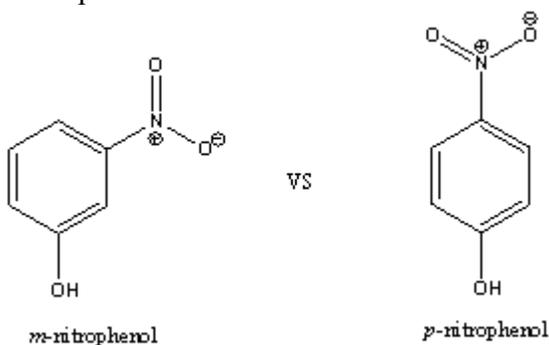
Answer: more stabilized. The chlorine atom is electron withdrawing, able to stabilize the negative charge at *para* position through inductive withdrawing effect. However, it also has weak resonance donating effect. The inductive effect of chlorine wins over resonance effect in this case (contrast this with electrophilic aromatic substitution where the resonance donating effect wins out against inductive effect).



*m*-chlorophenol

*m*-chlorophenol has a  $pK_a$  value of 9.1. It is more acidic than *p*-chlorophenol by a little bit. Chlorine is electron withdrawing, making the anion more stable. However, unlike *p*-chlorophenol, it cannot donate the lone pair through resonance to destabilize the negative charge. Therefore, it is slightly more acidic than *p*-chlorophenol.

Example:



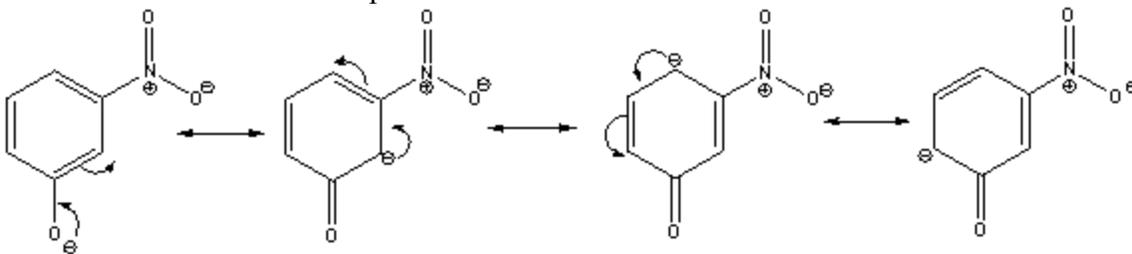
*m*-nitrophenol has a  $pK_a$  value of 9.3, whereas the *p*-nitrophenol has  $pK_a$  value is 7.2.

*Which one is more acidic?*

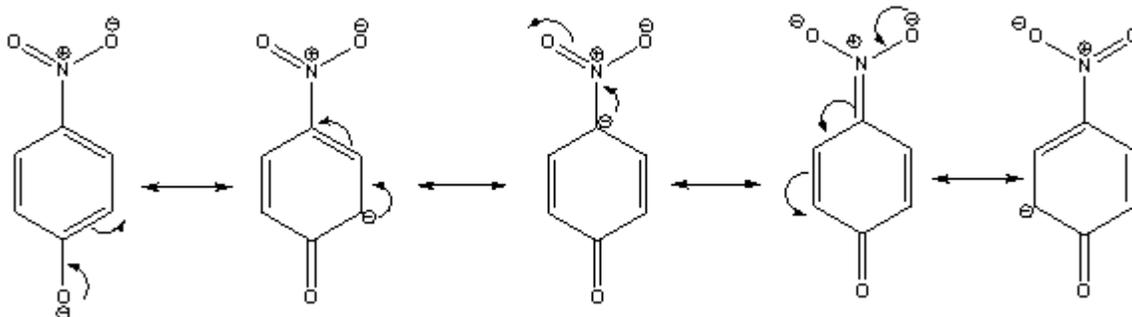
Answer: *p*-nitrophenol

Why? (Think about conjugate anion stabilization and resonance forms).

Resonance forms for *m*-nitrophenoxide anion:



Resonance forms for *p*-nitrophenoxide anion:



The nitro group offers an additional resonance form for *p*-nitrophenol that is not possible for *m*-nitrophenol (we are able to drive electrons all the way up to the nitro group for the *para*-substituted nitrophenol). Since there is one more reasonable resonance form and the *p*-nitrophenol  $pK_a$  7.2 is about 100 times ( $10^2$ ) more acidic than the *m*-nitrophenol with  $pK_a$  9.3 ( $pK_a$  9.3-7.2 = 2.1  $pK_a$  units)

If there are two nitro groups in the *ortho* and *para* positions of the phenoxide anion, the  $pK_a$  of the phenol (2,4-dinitrophenol) drops to 4.5. If three nitro groups are attached, the  $pK_a$  of the phenol becomes even lower (2,4,6-trinitrophenol has a  $pK_a$  of approximately 1). This is because *ortho* and *para* positions are where negative charge of the resonance form can be located, and addition of a nitro group is able to offer more stabilization. This phenomenon is not observed for the *meta* position.

## Stereochemistry -review

Stereochemistry refers to the three dimensional arrangement of atoms in space. Stereoisomers are different compounds (different physical properties) that have the same connectivity but a different 3D arrangement of atoms

A **chiral** molecule (or object) is one that has a non-superposable mirror image

An **achiral** molecule has mirror images that are superimposable, and it can be acted on by a chiral agent to make new chiral molecule.

A superimposable mirror image for an arbitrary molecule is shown below:

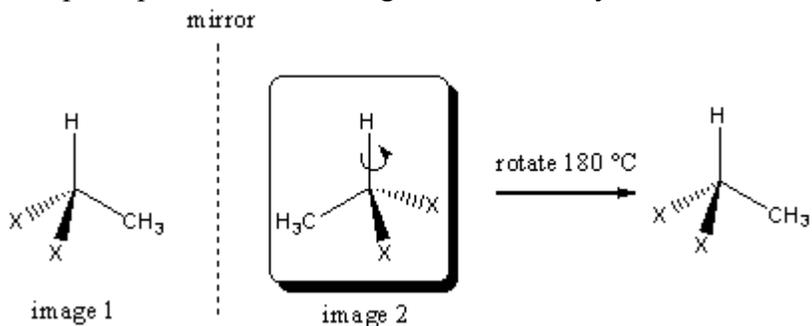
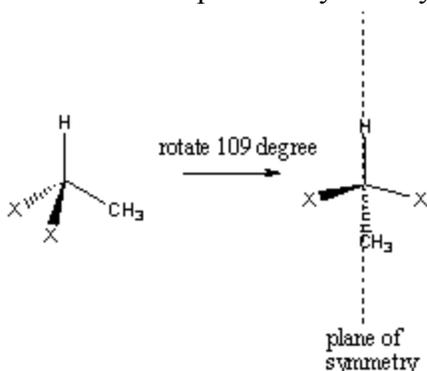


Image 1 and image 2 are mirror images of each other. The “imaginary” mirror is denoted by the dotted line. Comparison of the two images may not be obvious. So what we have done is rotate the C-H bond of image 2 for 180 degrees to put all the atoms in the same position as in image 1. We see that after the rotation, image 1 and image 2 are superimposable (superposable) with each other. Therefore, the arbitrary molecule is achiral.

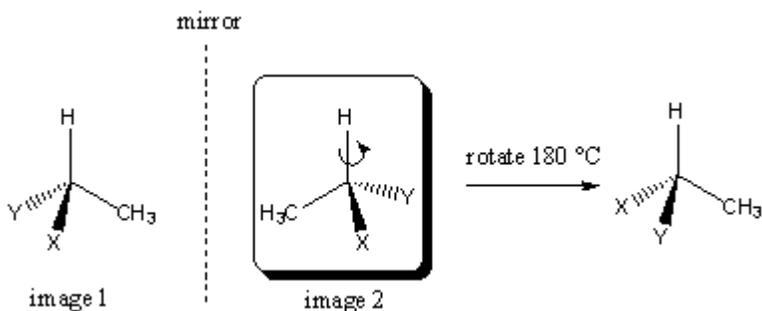
There is also a plane of symmetry in the molecule:



This molecule has a plane of symmetry shown by the dotted line. We can see that the left side of the molecule is identical to the right side (these are the X groups and they are symmetric).

A **chiral** molecule has a non-superimposable mirror image and does not have plane of symmetry. A simple example of a chiral object would be your hand. Your left hand is not superimposable onto your right hand. They are not identical.

A non-superimposable mirror image for an arbitrary molecule is shown below:



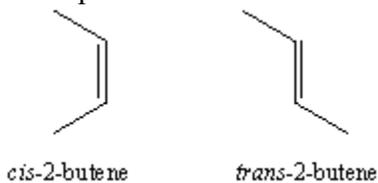
In this example, substituent X is not equivalent to substituent Y.

We have done the same thing for achiral molecule. Take the molecule, draw the mirror image of it. However, in this case, when we rotate image 2 of the molecule, we see that it is not the same as image 1. Although the H and CH<sub>3</sub> groups are in the same position, the X and Y substituents cannot be put to the same place. In image 1, X is pointed outward, whereas in image 2, X is pointed inward. The two mirror images are not superimposable with each other. Therefore, the molecule is chiral. There is also no plane of symmetry as X group is not the same as Y group.

Tetrahedral atoms (i.e. carbon) with 4 different groups attached are called a **stereogenic centers**. A chiral molecule usually (not always) has a stereogenic center.

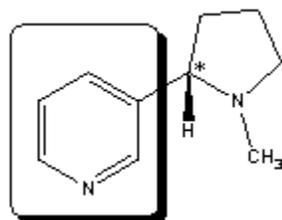
Stereoisomers that are non-superposable mirror image of each other are **enantiomers**. All other stereoisomers (which are not mirror images) are called **diastereomers** or **diastereoisomers**.

Example:



These *trans* and *cis* isomers are diastereomers. They are not mirror images.

Example:



The molecule shown is nicotine, a highly toxic and addictive compound.

*Is the ring highlighted aromatic?*

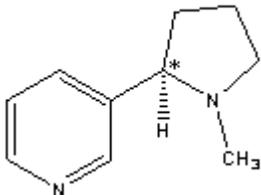
Answer: Yes. It is pyridine (an example from previous lecture on aromaticity)

*Does this molecule have stereogenic centers?*

Answer: Yes. The carbon highlighted with asterisk has 4 different groups attached.

*How do you draw the enantiomer of nicotine?*

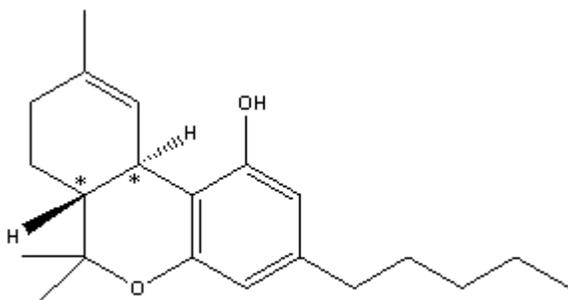
Redraw the molecule, and **invert/change all stereogenic centers**.



The enantiomer of nicotine is not toxic and has no neurological effect.

**If not all stereogenic centers are inverted, we get diastereomers.**

Example:



tetrahydrocannabinol (THC)

This molecule is the active ingredient in marijuana.

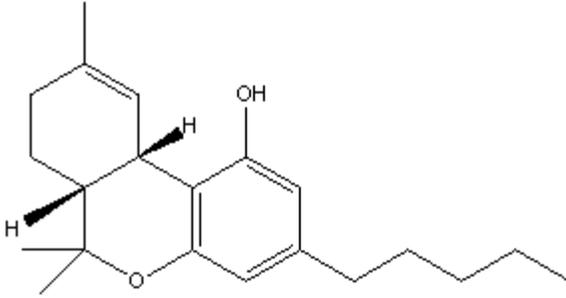
*Does this molecule have any aromatic rings?*

Answer: Yes. The phenol ring.

*How many stereogenic centers does it have?*

Answer: Two. They are marked by the asterisks.

To draw the enantiomer, change both stereogenic centers to opposing stereochemistry. To draw a diastereomer, change one or more but not all stereogenic centers. See below.



Is the molecule shown above the enantiomer of THC?

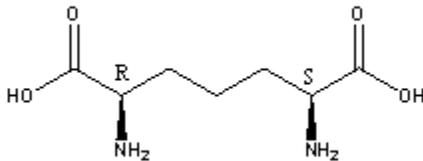
Answer: No. Only one stereogenic center is inverted and the above structure is a diastereomer. This molecule is biologically inactive.

### More Definitions

1:1 mixture of enantiomers is called a **racemic mixture** or **racemate**.

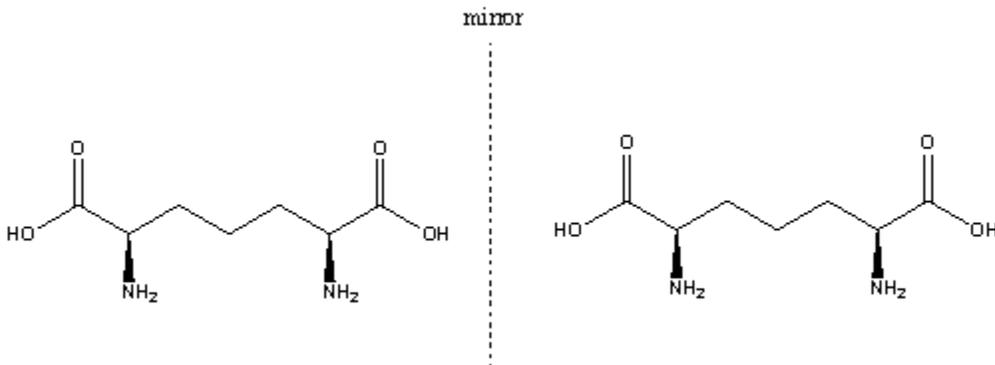
A **meso** compound has stereogenic centers, but it is achiral (the mirror images are superposable).

Example:

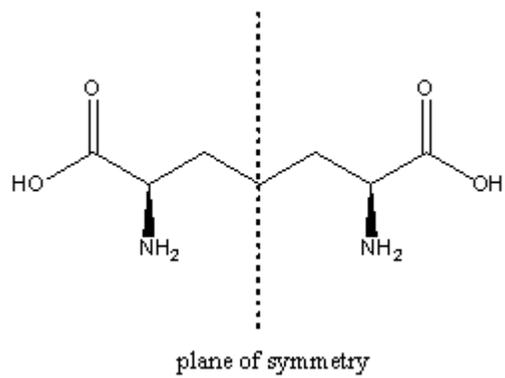


This molecule is called *meso*-diaminopimelic acid (*meso*-DAP).

It has 2 stereogenic centers (one is *S* configuration and the other is *R* configuration). However, the molecule is achiral. The mirror images for this molecule are superimposable (superposable).



As well, there is a plane of symmetry in the molecule (the left side is same as the right side with amine group both pointed outward), which is a certain indication that the molecule is achiral (not chiral)



We will discuss more about this in the next lecture.