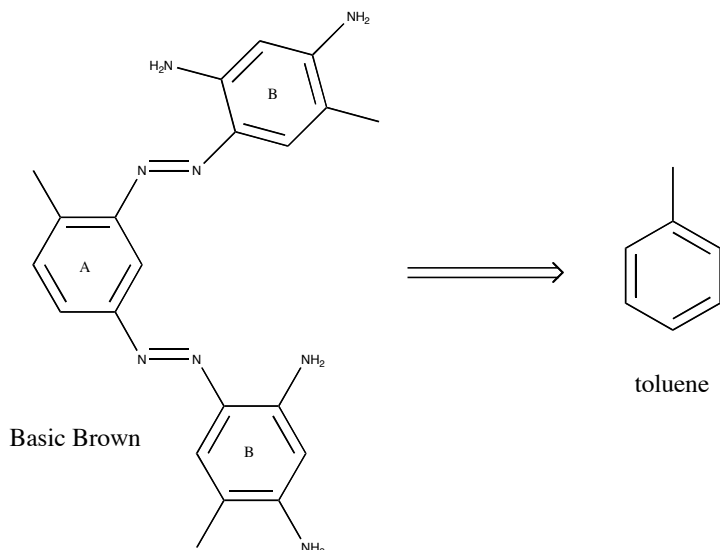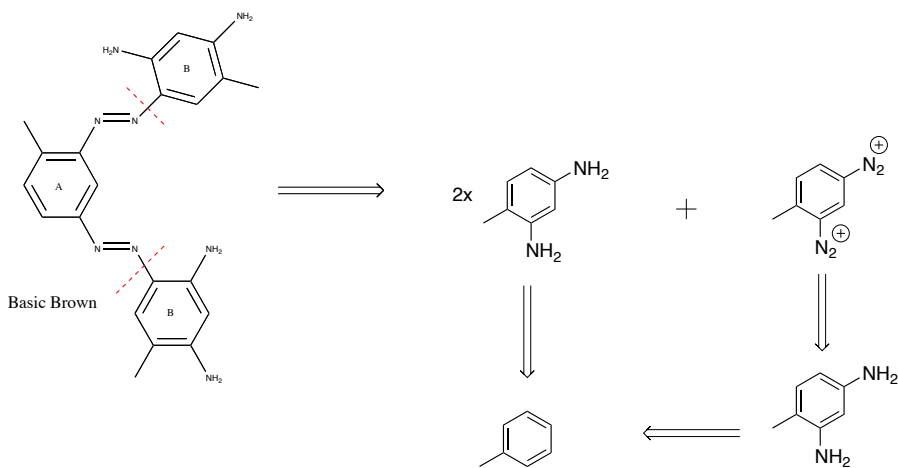## Reactions of Substituted Benzene – Continued

How can Basic Brown be synthesized from toluene? (The process of figuring out what starting materials could be used to synthesize a target molecule is known as **retrosynthesis**).
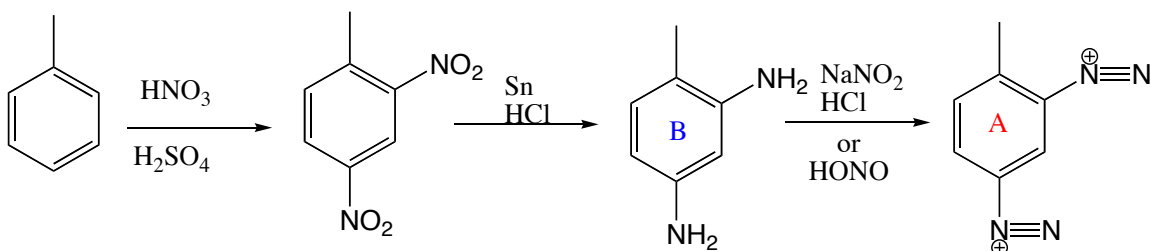

Using retrosynthesis we can break basic brown into intermediate compounds

It is easier to make the bond to the two B rings than it is to make the bond to ring A. The following rings (one of A and two of B) could be used to synthesize basic brown:
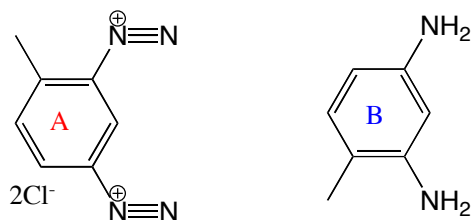
The forward reaction would be the following:

A and B will react with each other spontaneously to form basic brown.

Lecture Outline 3: Alcohols, Ethers, Stereochemistry, Ketones, and Aldehydes

Nomenclature of Alcohols

Alcohols are compounds that have a hydroxyl group (-OH) bonded to a carbon atom (but not a carbonyl C=O). Alcohols can be thought of as organic derivatives of water in which one of the hydrogens is replaced by an organic group: H-O-H versus R-O-H. Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Ethanol is one of the simplest alcohols, finding use as a fuel additive, an industrial solvent, and key ingredient in many beverages (beer, wine etc).
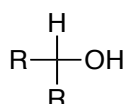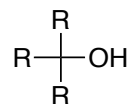

Ethanol
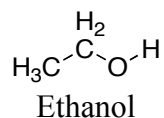
Naming Alcohols

Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl bearing carbon.
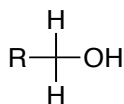
primary alcohol (1°)   secondary alcohol (2°)   tertiary alcohol (3°)

Simple alcohols are named using the IUPAC system as derivatives of the parent alkane, using the suffix *ol*:

1) Select the longest carbon chain containing the alcohol, and derive the parent name by replacing the -*e* ending of the corresponding alkane with –*ol.*
2) Number the alkane chain, beginning at the end closest to the hydroxyl group.
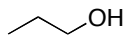3) Number the substituents according to their position on the chain.

For example:

H₃C–OH
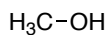
methanol
or methyl alcohol
or wood alcohol

ethanol
or ethyl alcohol
or grain alcohol

OH

n-propanol
or 1-propanol

OH

2-propanol
or isopropanol

OH
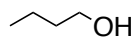
butanol
1-butanol
n-butanol

If there is more than 1 OH group:

2 OH's	diol (glycol)
3 OH's	triol
4 OH's	tetraol

Some simple and widely occurring alcohols have common names that are accepted by IUPAC. For example:

HO   OH
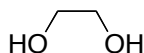
ethylene glycol
or 1,2-ethanediol
(antifreeze)
the freezing point is lower if mixed with water

OH

HO   OH

glycerol
or 1,2,3-propanetriol
or propane-1,2,3-triol
a precursor to fatty acids (esters)
is used for lubricants such as KY jelly

You need to know the following structures:

phenol

4-hydroxyphenol
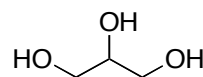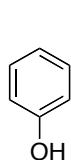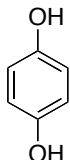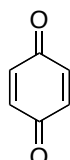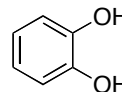or p-hydroxyphenol
or hydroquinone

quinone

catechol

A more difficult example is the name of the sex pheromone from the silk worm moth shown below.
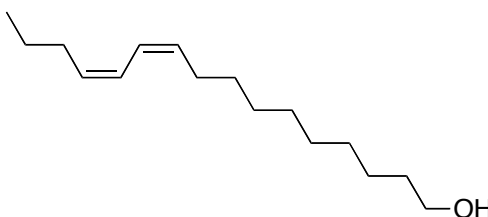
hexadeca-10Z,12Z-dien-1-ol

The longest chain is 16 carbons long, which is a hexadecane. The *-e* ending is dropped, and replaced with *–ol* to become hexadecan-1-ol. There are two cis double bonds present at positions 10 and 12. This information allows the compound to be named a 10,12-diene. Putting the overall name together then gives hexadeca-10Z, 12Z-dien-1-ol.

This molecule was discovered by Adolf Butenandt in 1959.
The word pheromone comes from Greek pherein (to carry) and horman (excitement)

Physical Properties of Alcohols and Acidity

Look at the following comparisons:

Name	Methanol	Ethane
Formula	CH_3OH	CH_3CH_3
Molecular Weight (g/mol)	32	30
Boiling Point (° C)	65	-89
State (at room temp)	liquid	gas

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:

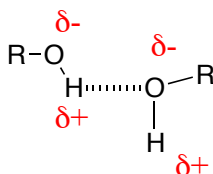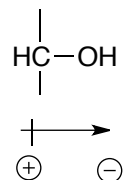| Name	Ethanol	Propane
Formula	CH_3CH_2OH	$CH_3CH_2CH_3$
Molecular Weight (g/mol)	38	44
Boiling Point (° C)	78.5	-44.5

Why are the boiling points so different?
Answer: Alcohols are polar and able to form hydrogen bonds.

Hydrogen Bond   Dipole

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). Linus Pauling described this.
2. Dipole-dipole interaction
3. London dispersion 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 concentrations)
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 g/cm^3 (and hence less than water. If the given alcohol is not miscible with water (Carbons >4), it will be floating on top of water)
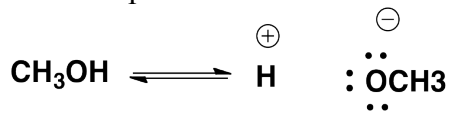
Acidity

Let's review some basic definitions
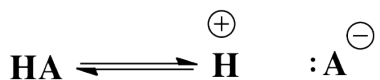
$$HA \rightleftharpoons \overset{\oplus}{H} \quad :\overset{\ominus}{A}$$

HA is the conjugate acid of A⁻, and A⁻ is the conjugate base of HA.

The equilibrium constant, or acidity constant, K_a, for this reaction can be expressed as:
$K_a = [H^+] [A^-] / [HA]$

For example: the dissociation of methanol

$$CH_3OH \rightleftharpoons \overset{\oplus}{H} \quad :\overset{\ominus}{\underset{..}{\overset{..}{O}}}CH3$$

$K_a = [H^+][CH_3O^-] / [CH_3OH] = 10^{-16}$

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.
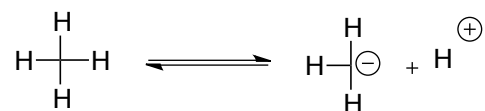The pK_a value for methanol is 16, for water is 15.7 (know these values). Since the pK_a value of water is less than methanol, the dissociation of methanol is harder than water and water is a stronger acid than methanol.

Remember that the pK_a and pK_w for water are not the same.
$K_w = [H^+][OH^-]$,
$K_a = [H^+][OH^-]/(H_2O)$

Examples:

$$\underset{H}{\overset{H}{H-\underset{|}{\overset{|}{C}}-H}} \rightleftharpoons \underset{H}{\overset{H}{H-\underset{|}{\overset{|}{C}}\ominus}} + \overset{\oplus}{H}$$

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

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

$$\underset{H}{\overset{}{H-\underset{|}{N}-H}} \rightleftharpoons \underset{H}{\overset{}{H-\underset{|}{N}\ominus}} + \overset{\oplus}{H}$$
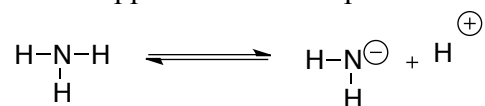
The pK_a value of ammonia is 36, which is 9 orders of magnitude (10^9) more acidic than methane. This is because the nitrogen atom is more electronegative than carbon and able to stabilize the negative charge better. However, ammonia is still a very weak acid. The acidity of ammonia (NH_3) should not be confused with the acidity of the ammonium ion (NH_4^+) which has a pK_a of 9.26.

Based on pK_a values, is oxygen more or less electron withdrawing than nitrogen?
Answer: Oxygen is more electron withdrawing. It has lower pKa value, able to stabilize the negative charge more.

Name	Structure	pKa	Less acidic
methane	CH_4	46	
ammonia	NH_3	36	
water	HOH	15.7	
hydrofluoric acid	HF	3.2	More acidic

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.

Name	Structure	pKa	
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?
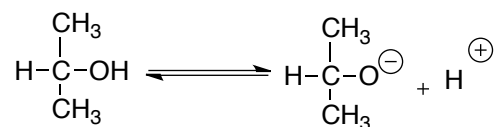
Isopropanol dissociates to from isopropoxide anion and a proton. However, the dissociation constant is 1×10^{-18}. Most of the molecules exist in the isopropanol form and only one part in 10^{18} is ionized. The equilibrium for this reaction lies far to the left.

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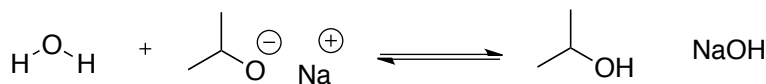
Methanol (pK$_a$ 16) is 100 times (10^2) more acidic than isopropanol, since it has only hydrogens (a less donating group) attached to the carbon bearing the negative oxygen in the corresponding anion)

H–C(–H)(–H)–OH ⇌ H–C(–H)(–H)–O$^{\ominus}$ + H$^{\oplus}$
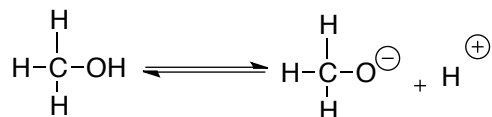
For *tert*-butanol (tert-butyl alcohol), there are three alkyl groups (methyls) that donate electron density to the carbon next to a negative charged group (inductive donation of electrons destabilizes the anion). Therefore, it is less likely to dissociate (pK$_a$ 19) and the molecule is even less likely to ionize (less acidic).

H$_3$C–C(CH$_3$)(CH$_3$)–OH ⇌ H$_3$C–C(CH$_3$)(CH$_3$)–O$^{\ominus}$ + H$^{\oplus}$
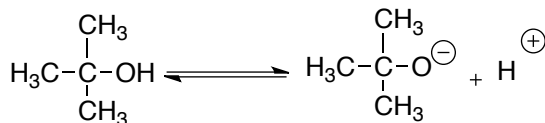
Consider the example below:

H–O–H + (CH$_3$)$_2$CH–O$^{\ominus}$ Na$^{\oplus}$ ⇌ (CH$_3$)$_2$CH–OH   NaOH

Where does the equilibrium lie in the above reaction?
Answer: It lies far to the right.

The reaction of a stronger base (isopropoxide) **and a stronger acid** (water) **to a weaker base** (sodium hydroxide) **and weaker acid** (isopropanol) **is very fast.**