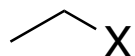


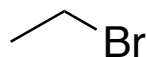
Substituted Alkanes



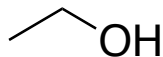
While alkanes have very few reactions that occur, combustion and some radical reactions, substituted alkanes display a variety of reactions and properties

Often the amount of information in organic chemistry feels overwhelming, how to learn all of these reactions for substituted alkanes for example, the key point is learning the similarity of reactions – often a set of substituted alkanes will behave in a similar manner

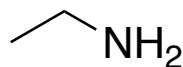
When looking at an organic molecule, the first point should be the ability to recognize what functional groups are present



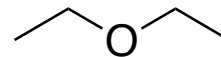
Alkyl halide



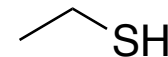
Alcohol



Amine



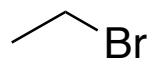
Ether



Thiol

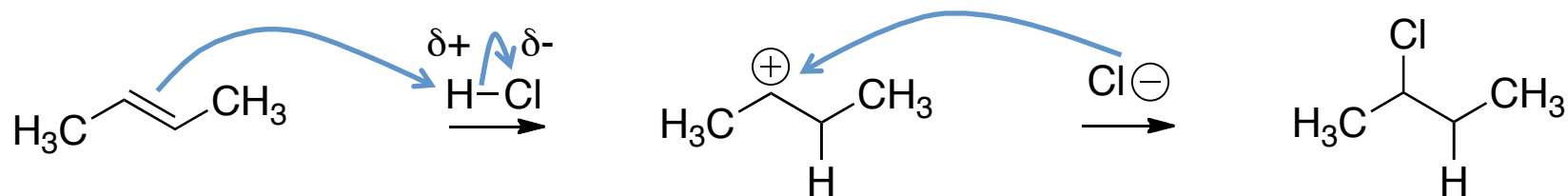
Alkyl Halides

Anytime a halogen is attached to an alkane an alkyl halide is formed



Alkyl halides are a very important functional group due to its ability to undergo a variety of reactions that will be discussed in later chapters

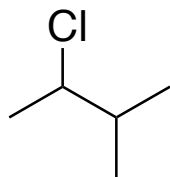
Have already observed a method to form alkyl halides from alkenes with an addition reaction



When using unsymmetrical alkenes, the regioproduct can be predicted due to the stability of the carbocation formed in the rate determining step

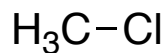
Alkyl Halides

Alkyl halides are named by finding the longest carbon chain for the root name, then when a halogen is attached the halo (fluoro, chloro, bromo, iodo) present is a prefix with the proper point of substitution given

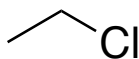


2-Chloro-3-methylbutane
(chloro is alphabetically before methyl)

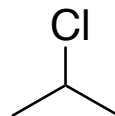
The alkyl halides are also distinguished by the amount of substitution at the halogen site



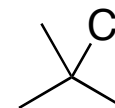
Methyl chloride



1° chloride

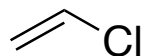


2° chloride



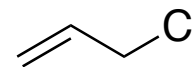
3° chloride

(The type of reactions that a given alkyl halide will undergo is dependent upon the substitution)



vinyl chloride

-vinyl refers to when chloride is attached to sp^2 hybridized carbon



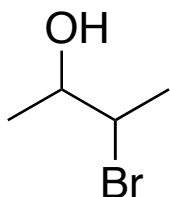
allyl chloride

-allyl refers to carbon *adjacent* to alkene

Alcohols

Alcohols have a higher priority in naming than any other substituted alkane

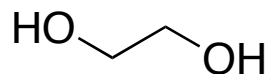
Find the longest continuous carbon chain containing the alcohol,
then remove last -e of alkane name and replace with -ol



3-bromo-2-butanol

With multiple alcohol substituents, the naming follows the same rules with a diol appendage

Unless the two alcohols are 1,2 substituted, then often use the glycol common name



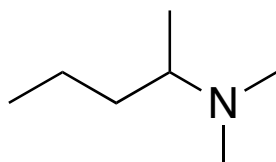
Ethylene glycol

(glycols are a type of vicinal diols – vicinal means “on adjacent atoms”,
while geminal means “on the same atom”)

Amines

Amines are named similarly to alcohols, but use –amine suffix instead of -ol

If an alkyl substituent is attached to the nitrogen, then use a N-alkyl designation



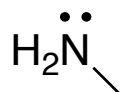
N,N-dimethyl-2-pentanamine

Amines are also characterized by the substitution pattern

-Ammonia has no alkyl substituents while replacing successive hydrogens with alkyl groups leads to 1°, 2° and 3° amines



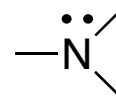
Ammonia



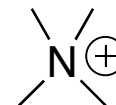
1° amine



2° amine



3° amine



Ammonium ion

With amines can obtain the fully alkylated product that has four alkyl substituents
-called ammonium derivative and has a positive charge (must have counterion)

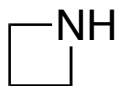
Cyclic Amines

There are many biologically relevant cyclic compounds that contain an amine functionality

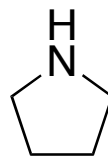
The naming almost always follows a common naming scheme, but the compounds are also named by using “aza” (meaning nitrogen containing) analogue of all carbon framework



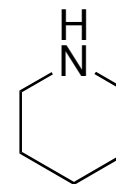
Aziridine
(azacyclopropane)



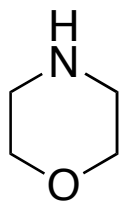
Azetidine
(azacyclobutane)



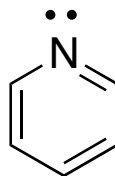
Pyrrolidine
(azacyclopentane)



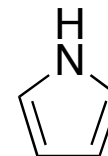
Piperidine
(azacyclohexane)



Morpholine
(oxygen has priority
over nitrogen)



Pyridine

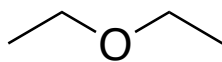


Pyrrole

Ethers

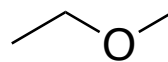
Ethers are organic compounds with two alkyl groups attached to an oxygen
-water has no alkyl groups attached and alcohols have one alkyl group attached

The two alkyl groups can be the same group (symmetrical) or different (unsymmetrical)



Diethyl ether

Ethoxyethane



Ethyl methyl ether

Methoxyethane

Nomenclature

There are different ways to name ethers

-common names

Use alkyl alkyl ether system

(if same substituent use di- appendage, if different then alphabetize)

-IUPAC names

Alkoxy alkane system

Find longest continuous chain with the alkoxy substituent

Name using same rules for alkanes learned previously

Cyclic Ethers

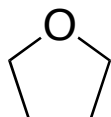
There are many types of cyclic ethers depending upon the ring size



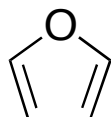
Epoxide



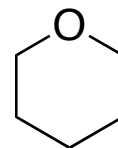
Oxetane



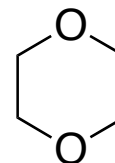
Tetrahydrofuran
(THF)



Furan



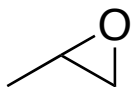
Tetrahydropyran
(THP)



1,4-Dioxane

Epoxides are a very important class of cyclic ethers
(they will undergo reactions that are impossible for other ethers)

The naming of epoxides follow a variety of methods



1,2-epoxypropane

1) Consider epoxide as substituent with an “epoxy” prefix

Propylene oxide

2) Common name uses alkene to synthesize epoxide with “oxide” name

2-Methyloxirane

3) Use “oxirane” as root and everything else is a substituent
(oxygen has 1 numbering in oxirane ring)

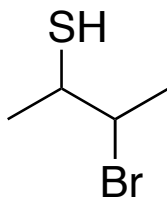
Thiols and Thioethers

Thiols and thioethers are the sulfur analogs of alcohols and ethers

The properties of thiols and thioethers are generally similar to alcohols and ethers, but some differences are predictable due to the replacement of oxygen with sulfur

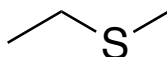
Nomenclature

Thiols are named exactly like alcohols but use a -thiol suffix instead of -ol



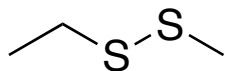
3-bromo-2-butanethiol

Thioethers are named like ethers, but use “sulfide” root



Ethyl methyl sulfide

Disulfides are commonly seen in biological molecules, more stable than peroxides



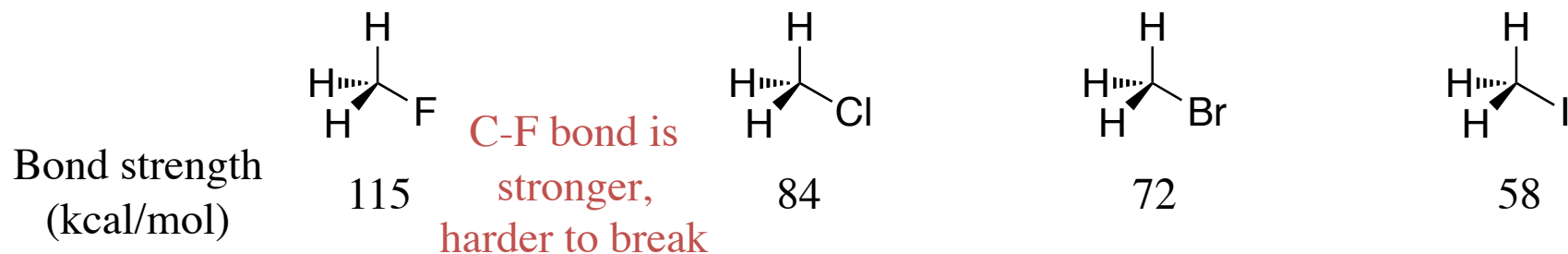
Ethyl methyl disulfide

Structure of Substituted Alkanes

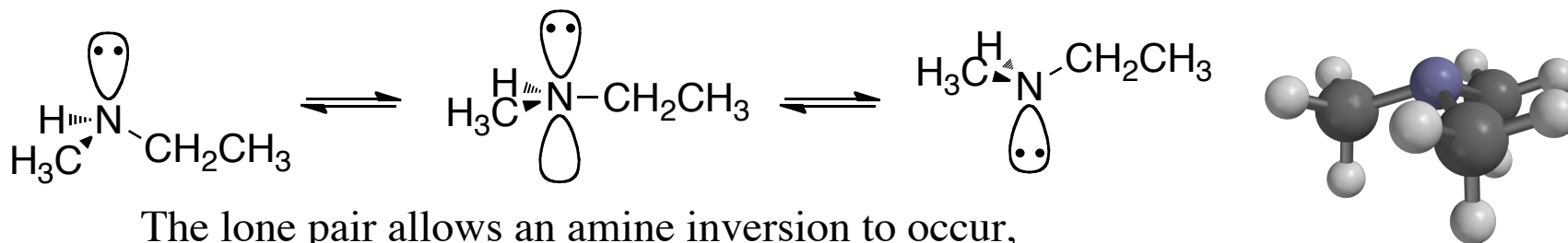
In substituted alkanes, the carbon attached to the substituent is always approximately sp^3 hybridized, but due to the unsymmetrical nature of the carbon (there are not 4 identical substituents on the carbon due to the substituent) the geometry is not a perfect tetrahedral

Some observations concerning structure of substituted alkanes:

Amongst alkyl halides, as the halogen becomes larger the orbital overlap to form the carbon-halogen bond is less and thus the bond is weaker (as well as the bond length larger)



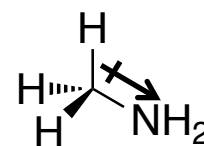
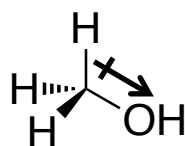
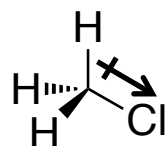
Alkyl amines are also approximately sp^3 hybridized, but instead of 4 covalent bonds to carbon, with ammonia, 1° , 2° or 3° amines have a lone pair on nitrogen



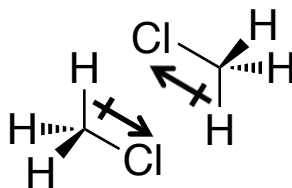
The lone pair allows an amine inversion to occur, stereocenters on nitrogen thus become inverted

Polarity of Substituted Alkanes

Since almost all substituents on the alkane (halides, oxygen, nitrogen, sulfur) are more electronegative than carbon, a bond dipole is introduced and the electrons are “on time average” closer to the substituent than the carbon



The polarity causes the molecules to associate in solution, causing a higher boiling point than compounds with no or little dipoles (like hydrocarbons)

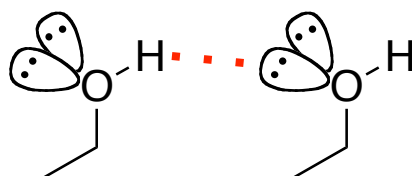


Hydrogen Bonding

In addition to the effect of dipole-dipole interactions to raise boiling point, molecules that can hydrogen bond also have a higher boiling point

Hydrogen bonding has a greater effect than dipole-dipole interactions, each hydrogen bond is worth ~ 5 kcal/mol in energy

A hydrogen bond is an interaction between a weakly acidic hydrogen and a lone pair of electrons on a different atom

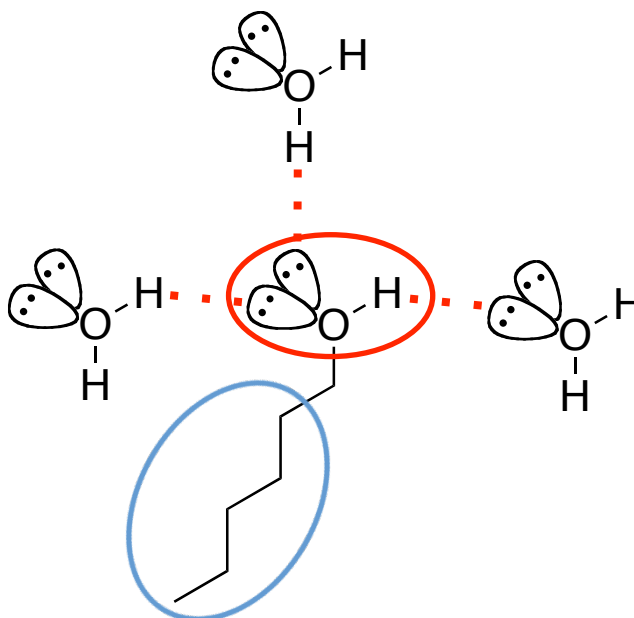


A C-H bond is not acidic enough for hydrogen bonding to occur, typically the hydrogen is attached to an oxygen (as in alcohols) or a nitrogen (as in amines)

Compound	Boiling Point ($^{\circ}$ C)
CH ₃ CH ₃	-88.6
CH ₃ NH ₂	-6.3
CH ₃ OH	65

Hydrogen Bonding Effects on Solubility

When a compound can hydrogen bond, it generally will increase the solubility in water due to the compound hydrogen bonding with the water molecules



For a given alcohol, there are a total of 3 hydrogen bonds possible (each ~ 5 kcal/mol)

The alkyl chain, however, is not soluble in water
-as the tail becomes larger, the water solubility decreases

Hydrophobic – “water hating”

Hydrophilic – “water loving”

Acidity of Substituted Alkanes

How to predict the relative strength of acids?

We saw in earlier discussion about the evolution of models for acid/base reactions and how these models introduced the term pK_a which is indicative of the acidity for a compound

As the pK_a becomes lower, the compound is more acidic

-Common point is the ability to stabilize a negative charge
(molecules that can handle more excess electron density after deprotonation are stronger acids)

There are many factors that affect the ability of a molecule to stabilize a negative charge

It is important, therefore, to recognize the differences between two compounds and then be able to predict which factor would have a greater influence on acidity

The assigned book uses an acronym to remember these factors: ISHARE

*I*nduction

*S*ize

*H*ybridization

*A*romaticity

*R*esonance

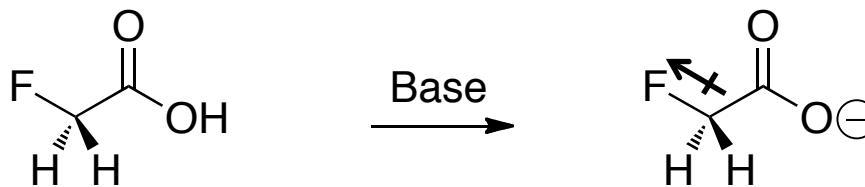
*E*lectronegativity

Induction

Induction refers to electron movement “through bonds”

-All bonds between different atoms are polar and the electrons are closer to the more electronegative atom “on time average”

As the electronegative atom is further removed, the inductive effect is less (inductive stabilization is through bonds, therefore if there are more bonds to transverse the effect is less)



X

pKa

H

4.8

I

3.2

F

2.6

The electronegative fluorine pulls electron density away from carboxylate

Size

Placing negative charge on larger atoms stabilizes excess charge

As the atom becomes larger (meaning atoms in different rows and thus a bigger shell where the excess negative charge is located) the electrons experience less electron repulsion in bigger volume and more stabilization due to more positively charged protons in nucleus

				pK _a
HF	\rightleftharpoons	F ⁻	H ⁺	3.2
HCl	\rightleftharpoons	Cl ⁻	H ⁺	-7
HBr	\rightleftharpoons	Br ⁻	H ⁺	-9
HI	\rightleftharpoons	I ⁻	H ⁺	-10

Consider size of atom where charge is located

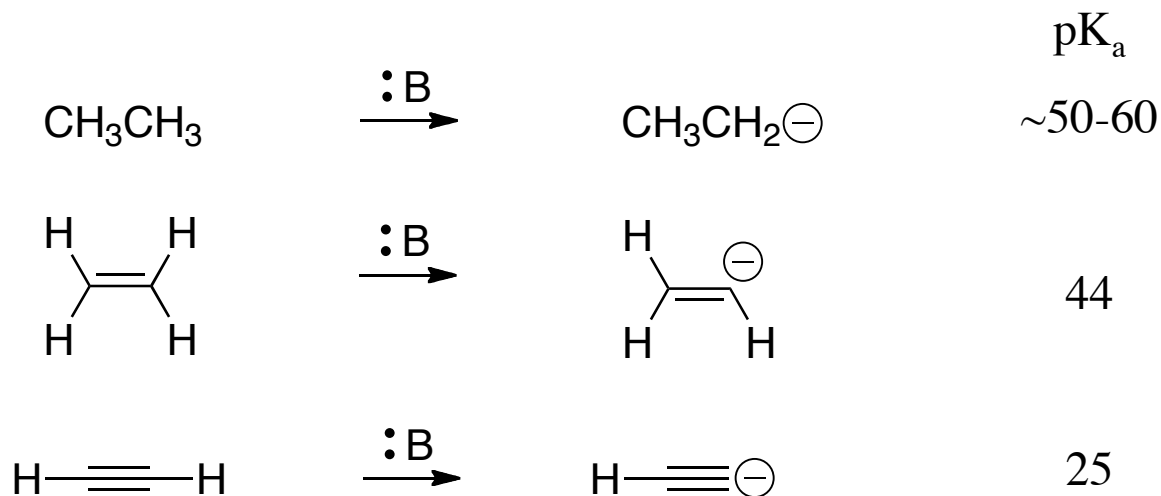
This trend usually is relevant when comparing atoms in the same column (as the atom becomes larger going down a column, the excess negative charge is more stabilized)

Hybridization

As a C-H bond changes from a sp^3 to sp^2 to sp hybridization (hybridization of carbon hydrogen is attached) the orbital has more s character
-As s character increases the orbital is more stable (s is lower in energy than p) and the electrons are closer to the nucleus

As the resultant lone pair of electrons (the pair formed after the proton is abstracted in an acid-base reaction) becomes closer to the positively charged nucleus the lone pair is **MORE STABLE**

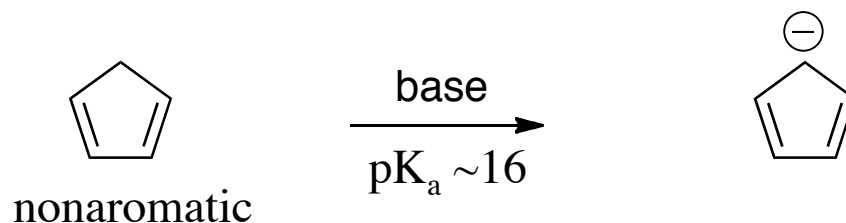
As the stability of the deprotonated form increases the conjugate is more acidic



Aromaticity

Aromaticity refers to specific cyclic compounds that are flat, have a p orbital on every atom of the ring, and have $4n+2$ number of electrons conjugated in the ring
-we will learn about these compounds in later chapters

If compounds can become “aromatic” after deprotonation, therefore changing from a nonaromatic to an aromatic compound upon loss of proton, the acidity is dramatically changed

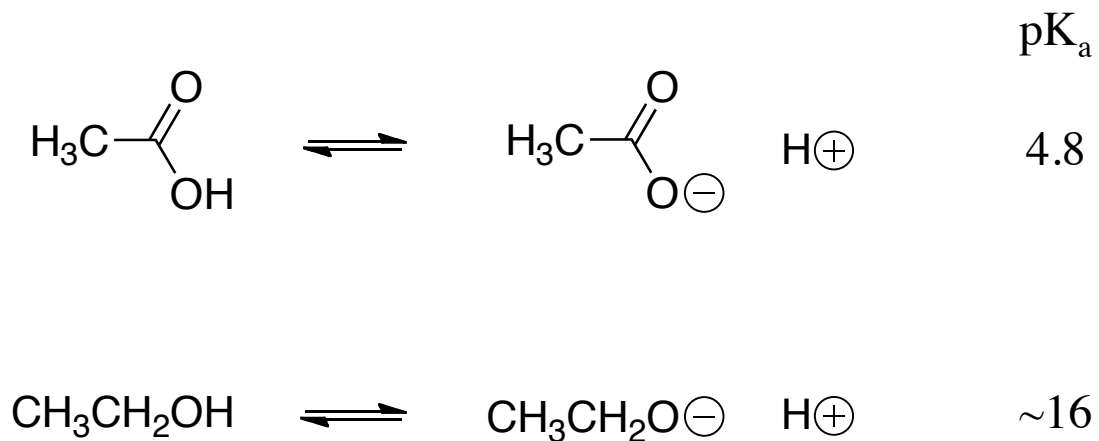


Cyclopentadiene is nonaromatic since there is not a p orbital on one of the carbons in the ring while cyclopentadienyl anion is aromatic

Resonance

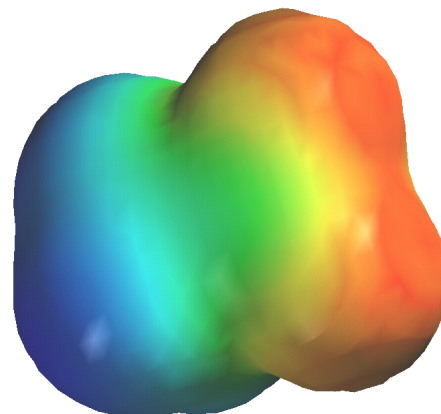
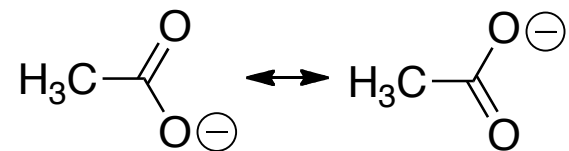
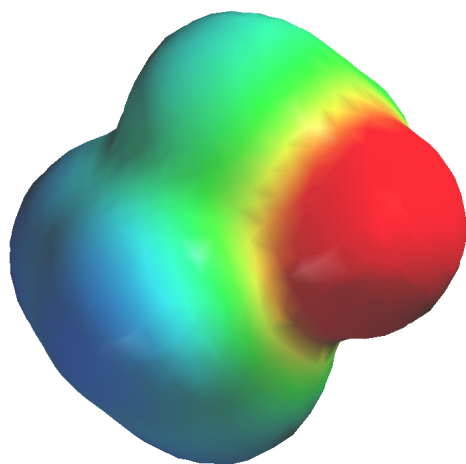
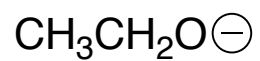
Resonance allows a formal negative charge to be “delocalized” over more than one atom
-this stabilizes the anion by spreading the excess charge over more than one atom

Consider pK_a of organic molecules



Both structures place a negative charge on oxygen after loss of proton,
but the pK_a difference is greater than 11

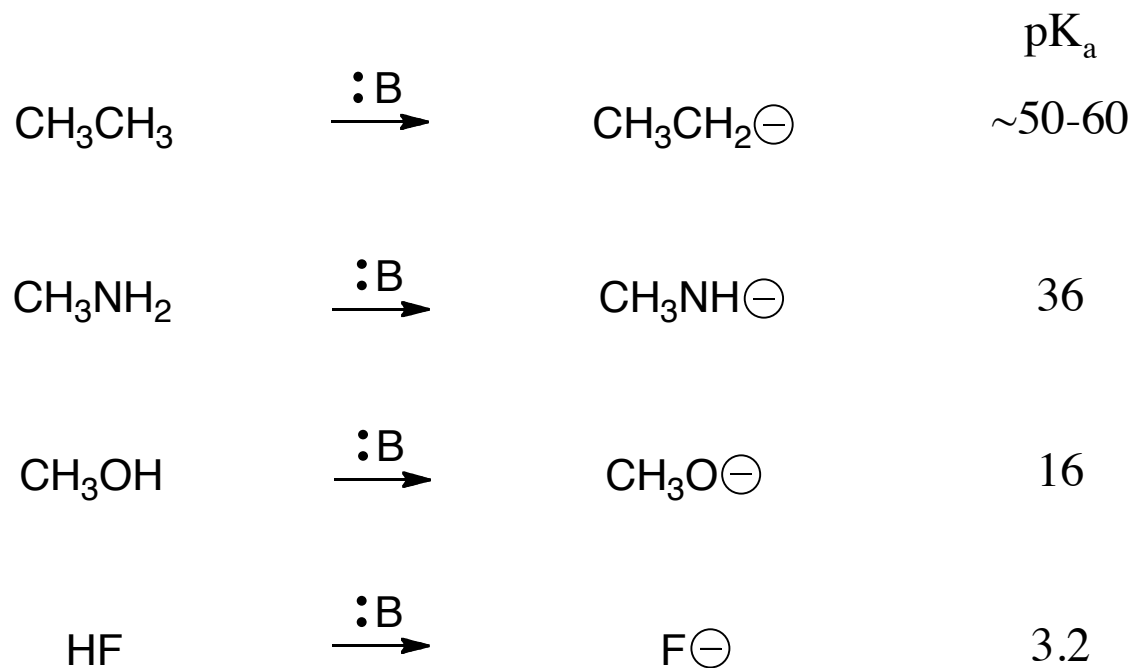
Comparison of Electron Density for Ethoxide versus Acetate anion



The excess negative charge is more stable on the acetate anion that can resonate, thus the conjugate acid is more acidic

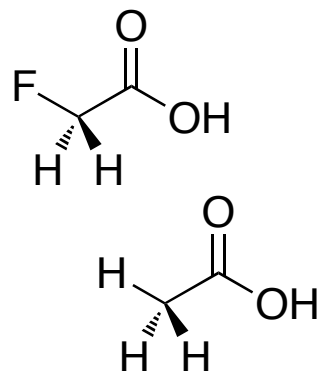
Electronegativity

Amongst atoms of similar size, the atom with a greater electronegativity will be a stronger acid



This comparison is typically made between atoms that bear the negative charge in the same row of the periodic table

Factors on Acidity of Organic Compounds



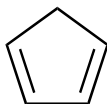
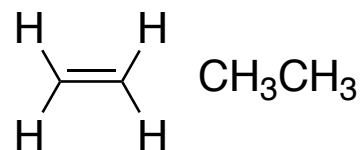
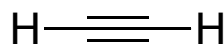
ISHARE

Inductive: electron withdrawing groups will stabilize a negative charge

HI HCl HF

Size: negative charge on larger atoms is more stable

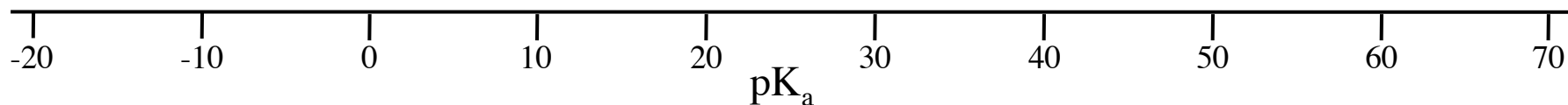
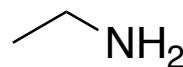
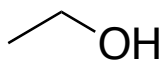
Hybridization: negative charge is more stable in orbital with greater s character



Aromaticity: aromatic anions are more stable

Resonance: anions in resonance are more stable than localized anions

Electronegativity: Anions on atoms in same row are more stable on more electronegative atom



Solubility Effects on Acidity

The ISHARE acronym helps to understand how to predict acidity differences between organic compounds

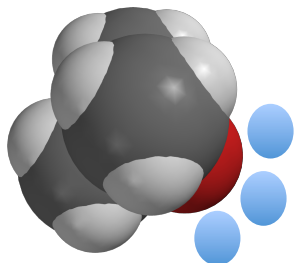
First determine what is the difference between the compounds in question (where is the charge located and how is it stabilized in the compounds) which will allow determination of which factor (induction, size, hybridization, aromaticity, resonance or electronegativity) is the most important

Must realize though that the pKa for a compound is determined in solution

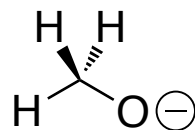
How the anion formed after deprotonation is stabilized in the solvent is critical to determine the change in pKa

Charged species are less stable than the neutral conjugates, therefore the solvent has a large effect on stabilizing the charges

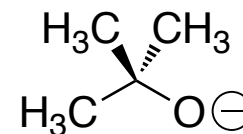
One way to see this effect is how alkyl substitution changes pKa



Solvent stabilizes charge
Bulkier group blocks solvent



pKa 15.5

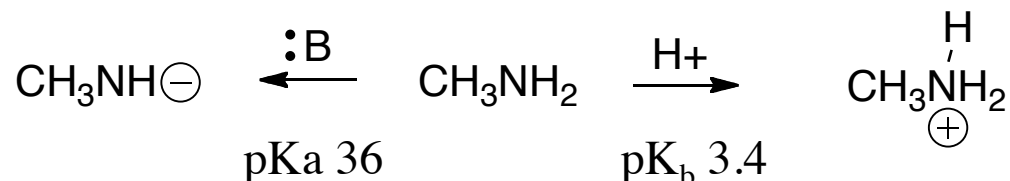


pKa 17.0

C-C bonds are considered electron donating,
but solvent effects are physical reason

Solubility Effects on Amine Basicity

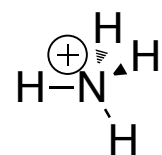
Amines can react with base to form an amide,
but amines can more easily accept a proton



The pK_b is a measure of basicity similar to pK_a for acidity
(pK_a + pK_b = 14)

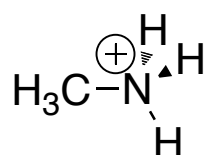
Similar to the alkyl substitution effects on acidity, amines experience a combination of effects
where differences in solvation changes the basicity

With amines, however, the effects oppose each other
(extra alkyl substitution stabilizes cations through hyperconjugation, but extra alkyl
substitution destabilizes charged cations by sterically hindering solvation)

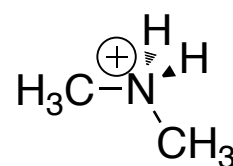


pK_b 4.8

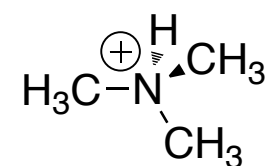
Easy to solvate,
No alkyl stabilization



pK_b 3.4



pK_b 3.2



pK_b 4.2

Hard to solvate,
large alkyl stabilization

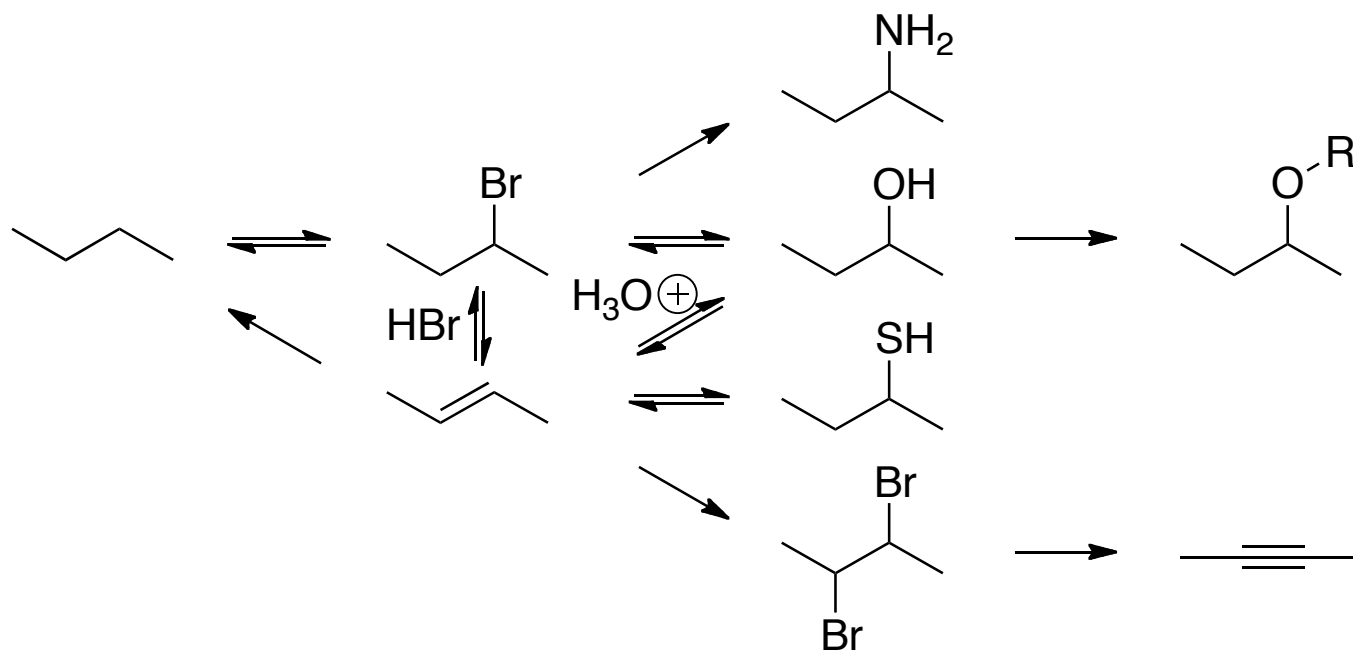
Formation of Substituted Alkanes

A variety of properties can thus be affected by changing the substitution on an alkane (solubility, acidity, reactivity, boiling point, etc.)

A key part of organic chemistry is learning how to transform an organic molecule into different functionality in order to change the properties of the molecule

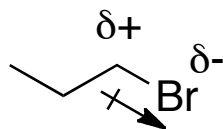
These reactions need to be predictable and in high yield for a practical outcome

As we continue in this course, we will learn how to transform hydrocarbons into any of the substituted alkanes



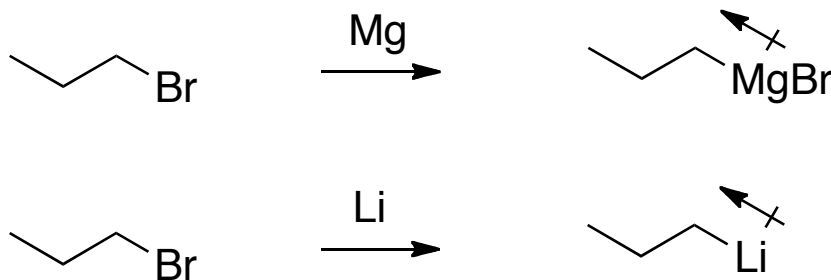
Organometallic Reagents

As observed for many substituted alkanes, the substituent is typically more electronegative than the carbon atom, thus the dipole creates a partial positive charge on carbon and partial negative charge on the substituent



In order to create a dipole in opposite direction, need to attach a substituent on carbon that is less electronegative

This is accomplished by using either a Grignard or organolithium reagent

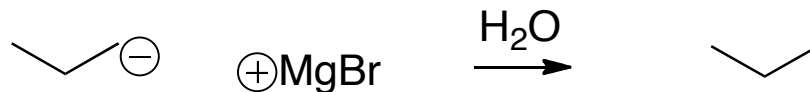


Organometallic Reagents

Due to the very high dipole of a carbon-magnesium bond (or carbon-lithium) and the dipole having the electrons closer to the more electronegative carbon on time average these compounds behave like carbon anions



These carbon anions can react with a variety of Lewis or Brønsted acids



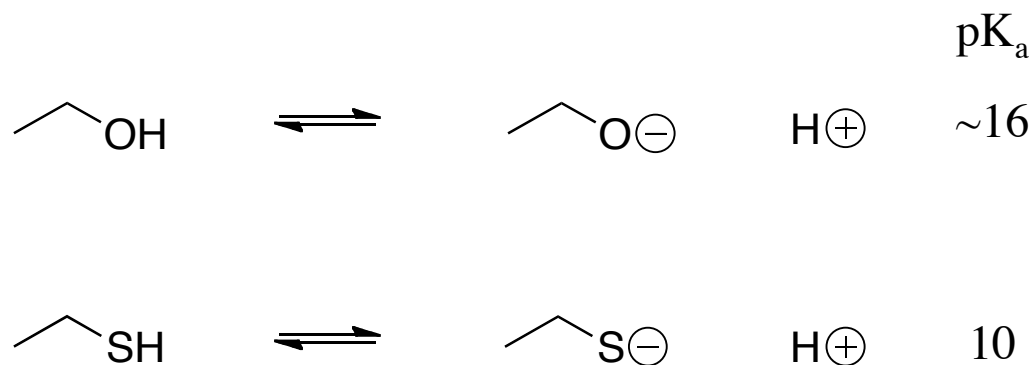
With any water present, the Grignard reagent will react with the proton to form an alkane

Overall this has formed an alkane from an alkyl halide, in later chapters we will observe Grignard reagents reacting with other Lewis or Brønsted acids to form other products

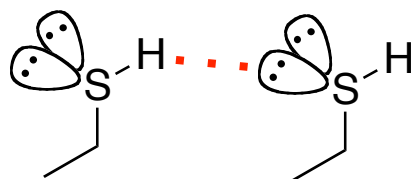
Thiols

Thiols follow the same trends observed for other substituted alkanes

Thiols are stronger acids than alcohols
due to charge being placed on larger sulfur and a weaker S-H bond

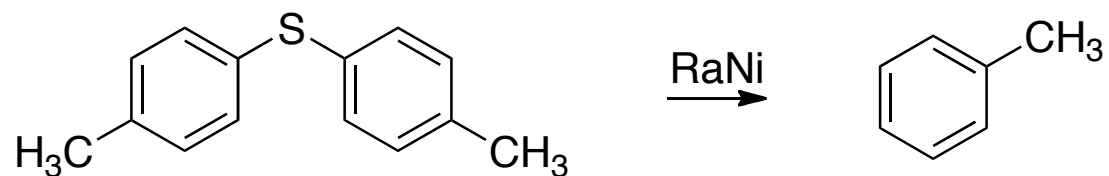
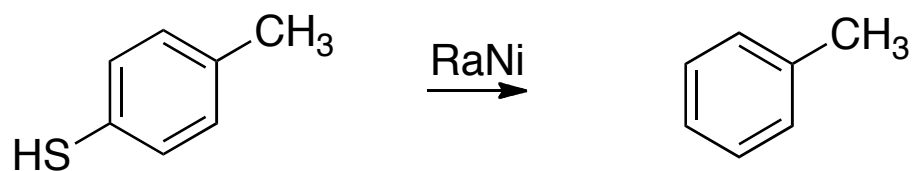


Thiols have less hydrogen bonding than alcohols
due to sulfur being less electronegative than oxygen



Thiols

One unique reaction with thiols compared to alcohols, however, is that sulfur containing compounds can be reduced with Raney nickel



Allows another method to form alkanes from substituted alkanes