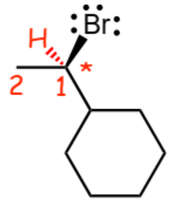
Alkyl Halides — Substitution and Elimination

1 Nomenclature

- Look for the longest chain that **contains** the **maximum number** of functional groups, in this case the halogen is the functional group and so even though the cyclohexane has more carbon atoms, the main chain is the two carbon ethane chain, the structure is named as a substituted alkyl bromide.



(1R)-bromo-1-cyclohexylethane

named as a substiuted alkyl halide

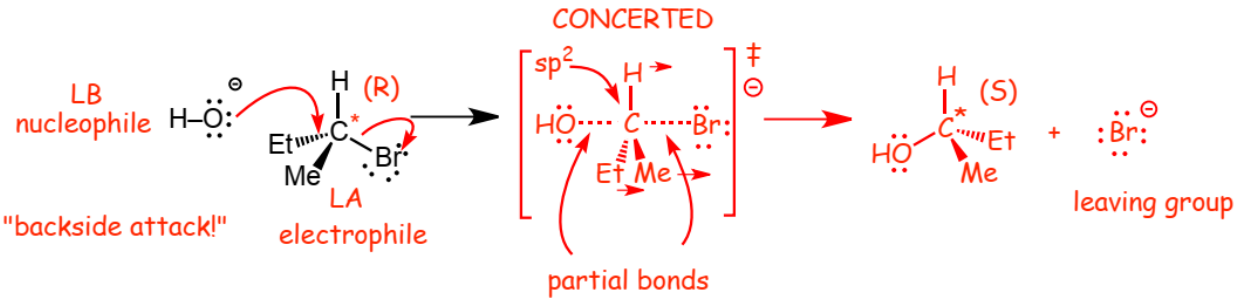
therefore, cyclohexane is a substituent!

2 Second Order Nucleophilic Substitution (SN2) Reaction

Substitution by **making a new bond at the same time** as **breaking the old bond**

- **Substitution requires a bond to be broken and a new bond to be formed.**
- The **lowest** energy way of doing this (unless precluded by steric or other effects, see later) is to **make the new bond** (getting some energy "back") at the same time as **breaking the old bond, this is SN2.**

Example:



- Reactions in which all bonds are made and broken at the same time are called **concerted.**
- This is fundamentally just a Lewis acid/base reaction of a kind we have seen previously, the Lewis base has the high energy chemically reactive electrons, which are used to make a new bond to the Lewis acid, and a stronger bond is formed (C-O in the example above) and a weaker bond is broken (C-Br above)
- The HO^- is the Lewis Base and also the **Nucleophile.**
- The halide is the Lewis acid/electrophile.
- The Br^- anion is the **Leaving Group.**

- This reaction "goes" because….

1) A weaker bond is converted into a stronger bond:

C-Br: B.D.E. ~ 65 kcal/mol (weaker bond)

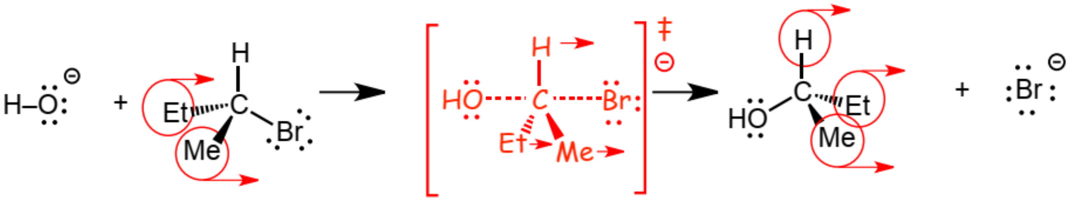
HO-C: B.D.E. ~ 90 kcal/mol (stronger bond)

2) A stronger base (^-OH) is converted into a weaker base (Br^-).

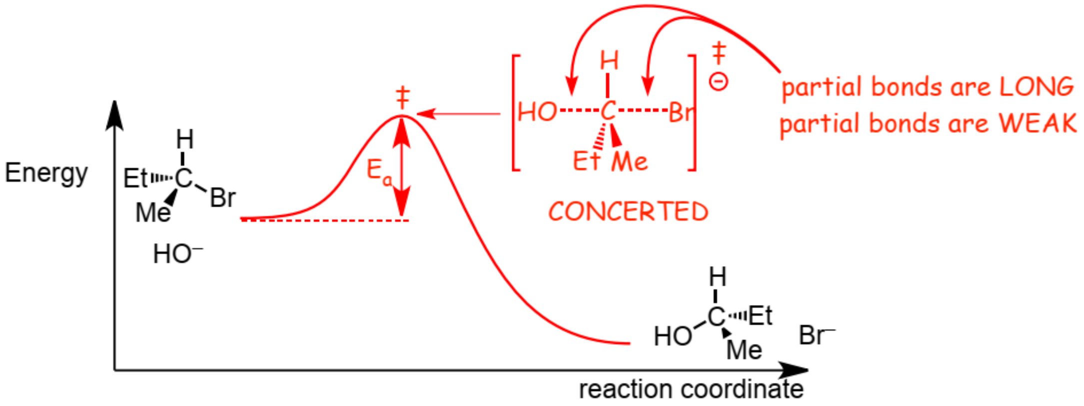
3) HIGHER energy electrons are converted into **lower** energy electrons.

- The reaction also proceeds with inversion (i.e. **backside attack**, think about an umbrella turning inside out in the wind), **called a Walden inversion**.

WALDEN INVERSION

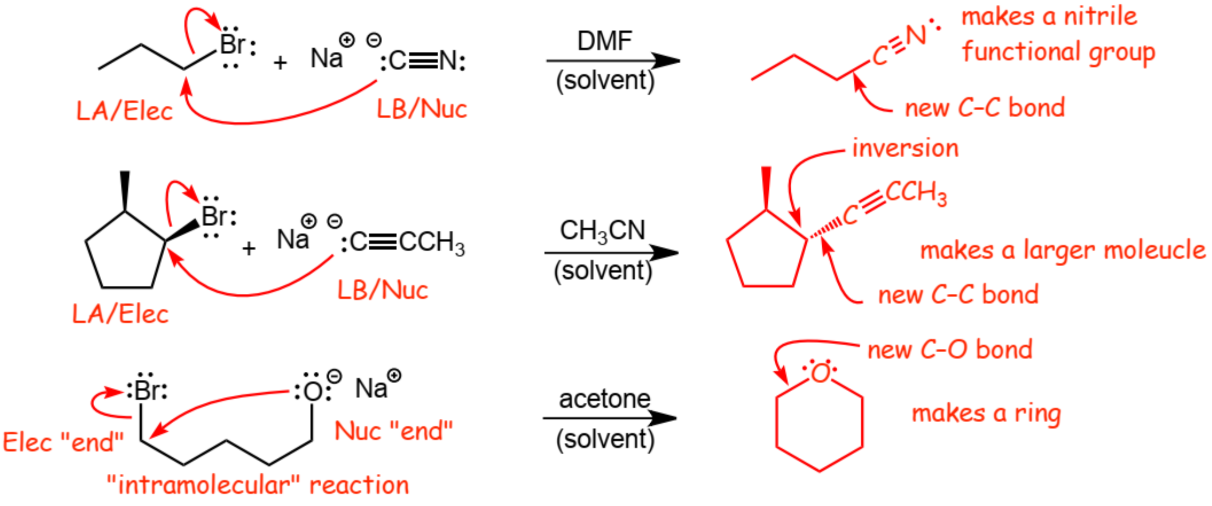


Often this will lead to a change in absolute configuration, i.e. R to S or *vice versa*, but not necessarily!



- Even though the transition state apparently has one more bond than either the reactants or the products, the partial bonds are very **long** and thus **weak**, partial bonds thus have very high energy electrons which is why the transition state is higher in energy than either reactants or products (2 weak partial bonds add up to less than one real bond).

Examples of SN2 Reactions: Give the major organic product in the following reactions:
- We understand these SN2 reactions a simple Lewis acid/base processes
- We can identify the Lewis base/**nucleophile** as the reactant with the high energy electrons.
- The Lewis acid/nucleophile must react with the Lewis acid/**electrophile**.



Important: SN2 reactions are one of the most important ways of **making new bonds**, i.e. of transforming one organic molecule into another one

- Here we made a **new functional group** (nitrile), we made a new C-C bond (larger molecule), we also made a ring structure, **we will use SN2 a lot!**

2.1 Nucleophilicity versus Basicity and SN2

Why the Name Second Order Nucleophilic Substitution (S_N2)?

S - Substitution reaction.

N - Nucleophile does the substitution (like a Lewis base, but see below).

2- kinetically 2nd order, **two molecules** are involved in the **rate determining step** (the only step).

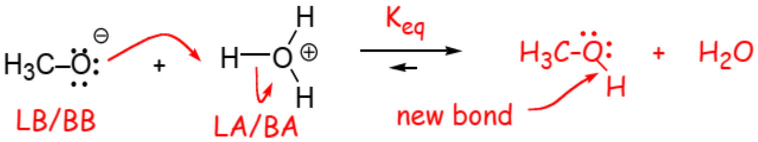
- The halide **and** the nucleophile (2 molecules) are involved in the rate determining step and so the reaction rate depends upon the concentration of them both, the reactions is kinetically **second** (2nd) order.

$$\text{rate} = \overset{\text{rate constant}}{k}\ [\text{nucleophile}]\,[\text{halide}]$$

- An increase in the concentration of **either** or **both** the nucleophile and halide results in a proportional increase in reaction rate, the rate depends upon the concentration of **both reactants**.

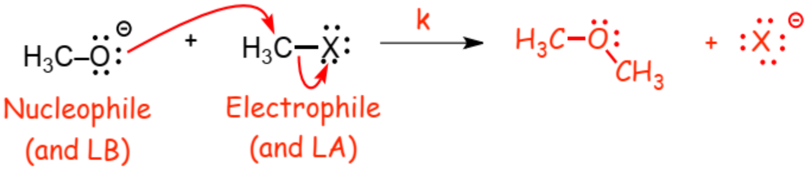
What is a Nucleophile and How is it Different from/Same as a Base?

The definition of a base is based on thermodynamics (K_{eq})



- **Lewis/Brønsted base** strength measured by size of K_{eq} (**thermodynamic definition**).
- **stronger base** means stronger new bond means **more exothermic reaction** larger Keq.
- **weaker** base means weaker new bond means **less exothermic** (or more endothermic) smaller Keq.

The definition of a nucleophile is based on kinetics (k):



- **Nucleophile** strength measured by size of rate constant k (**kinetic definition**).
- **A stronger nucleophile** means smaller Ea (stronger partial bonds), larger k, **faster reaction** rate.
- **A weaker** nucleophile means larger Ea (weaker partial bonds), smaller k, **slower reaction** rate.

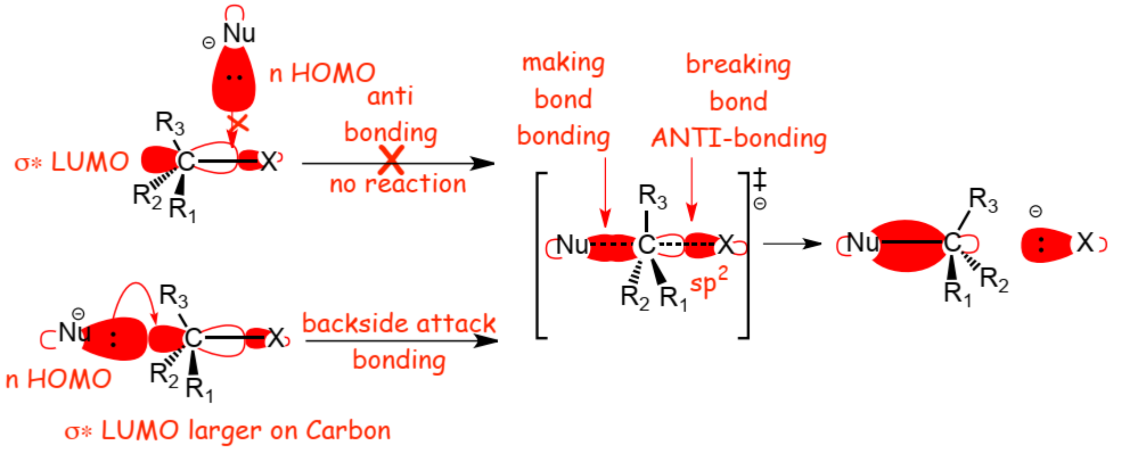
All nucleophiles are Lewis bases, the Hammond postulate says that strong bases should also be strong nucleophiles, and this is generally true, although **we will meet a few important exceptions later…..**

Lewis Base / Nucleophile (nucleus loving), donates electrons
Lewis Acid / Electrophile (electron loving), accepts electrons

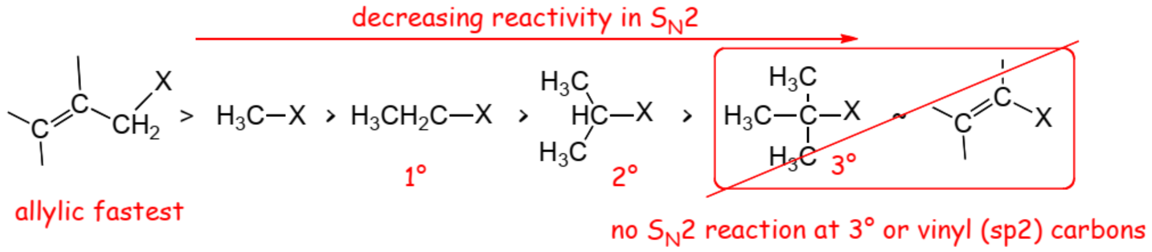
Why are we concerned with kinetics now when we used to be only concerned with the acid/base understanding of reactivity? We have already seen that when there are competing reactions, the fastest one "wins" (e.g. the most stable intermediate is formed fastest), in other words MOST organic reactions are controlled by kinetics, their reactions are **kinetically controlled**. For this reason, it makes sense to start talking about nucleophiles and electrophiles, because their definition is based on kinetics. Of course, most strong nucleophiles react fast **because** they are also strong bases and have very exothermic reactions (although there are some exceptions). We will use the terms nucleophile/electrophile and Lewis base/acid interchangeably.

2.2 Understanding SN2 Reactivity: Molecular Orbitals and Steric Effects

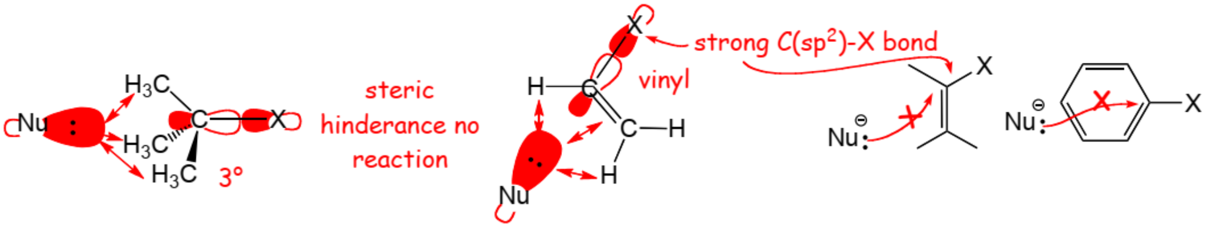
- Here we will use a more detailed form of Lewis acid/base theory that considers the important **molecular orbitals**, i.e. **F**rontier **M**olecular **O**rbital theory (**FMO** Theory).
- Making **bonds between atoms** requires overlap of **atomic orbitals** in phase to generate a **new bonding molecular orbital.**
- Here, we need to make a **bond** between two molecules.
- Making a **bond between molecules** requires overlapping **molecular orbitals** in phase to generate a **new bonding molecular orbital.**
- FMO theory looks at the overlap between **molecular** orbital with the **highest energy electrons** (the **HOMO**) of nucleophile, with the **lowest energy molecular** orbital of the electrophile (the **LUMO**).
- The HOMO is where the reactive Lewis basic electrons "are", the anti-bonding LUMO is the only orbital that the electrons can "go to" in the electrophile, all of the bonding orbitals are full of electrons.



- This provides the **best explanation for "backside attack"**, HOMO/LUMO overlap best at the carbon "end" of the halide LUMO.
- For this reason, reaction suffers "steric hindrance" when R1, R2, R3 are large.



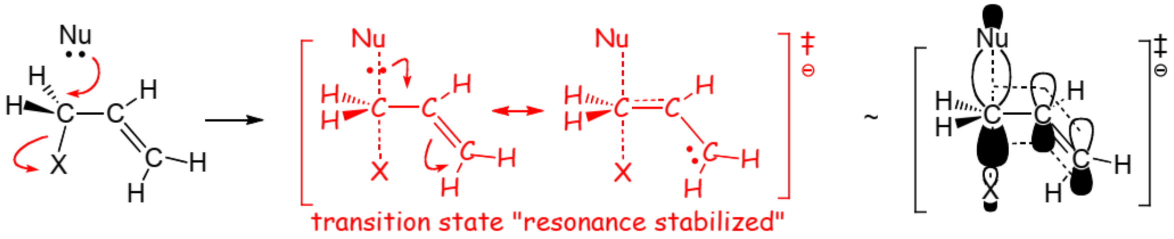
- SN2 reactions get slower with increasing steric hindrance at the backside of the carbon of the electrophile.
- To the extent that there is **no SN2 reaction** at a **tertiary** halide.
- SN2 reactions at **methyl** and **allylic** carbons are particularly facile (see below).
- There is **no SN2 at a tertiary or vinyl carbons** because the nucleophile cannot get close enough to form reasonable partial bonds in the transition state due to a steric effect at the other alkyl substituents on the C atoms.



- The vinyl C(sp2)-X sigma* orbital is smaller than a C(sp3)-X sigma* orbital, weakens any potential partial bond
- The vinyl C(sp2)-X bond is stronger than a corresponding C(sp3)-X bond.

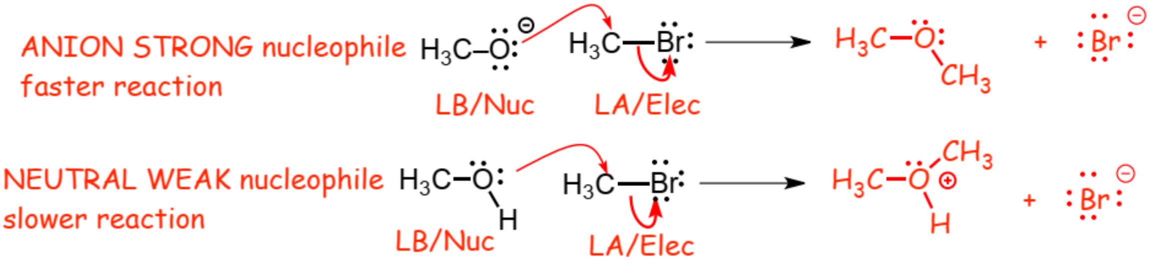
SN2 at the allylic position is FASTEST because the **transition state is resonance stabilized**, lowering the energy of the electrons in the transition state.

- A lower energy transition state means a smaller activation energy which results in a faster reaction……



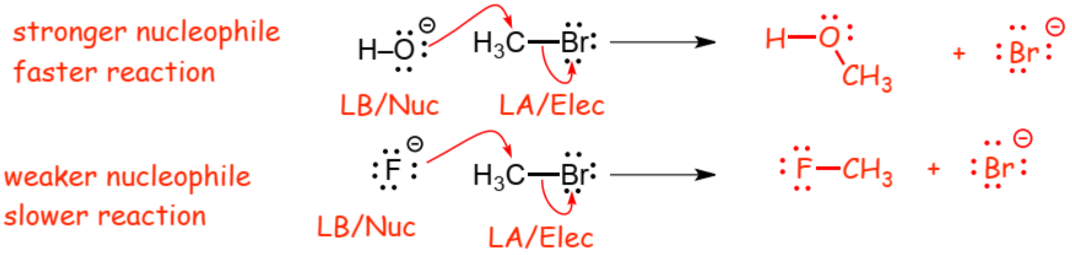
2.3 Factors Controlling SN2 Reactivity: Nucleophilicity

- **Good nucleophiles are almost always good Lewis bases (but see further below….).**
- **Comparing same atom (charged versus non-charged)**: Anions make stronger nucleophiles than neutrals.



- **Nucleophilicity is the same as basicity here!**
- higher energy electrons on negatively charged oxygen both react faster and have more exothermic reactions, are good Lewis bases AND good nucleophiles, this is true **in all solvents (see later)**

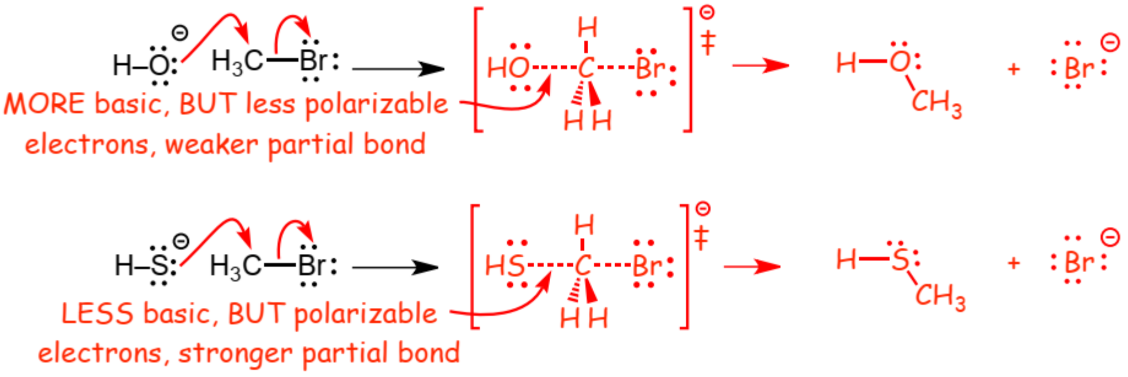
Comparing similarly sized atoms (**across** the periodic table)**:** Electronegative atoms make poor nucleophiles



- **Nucleophilicity is the same as basicity here!**
- lower energy electrons on electronegative fluorine react slower and have less exothermic reactions, are weaker Lewis bases **and** less good nucleophiles, this is true **in all solvents**

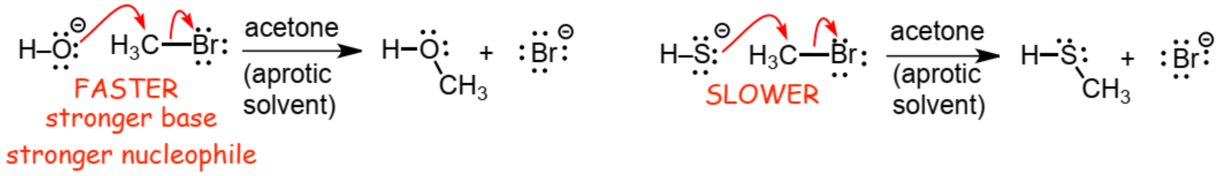
Comparing differently sized atoms (**down** the periodic table)

- **A new Concept**: Larger atoms have more polarizable electrons, they do not ha**ve to "get so close" to make a bond, can make "longer" bonds, and thus can make stronger partial bonds** in the transition state

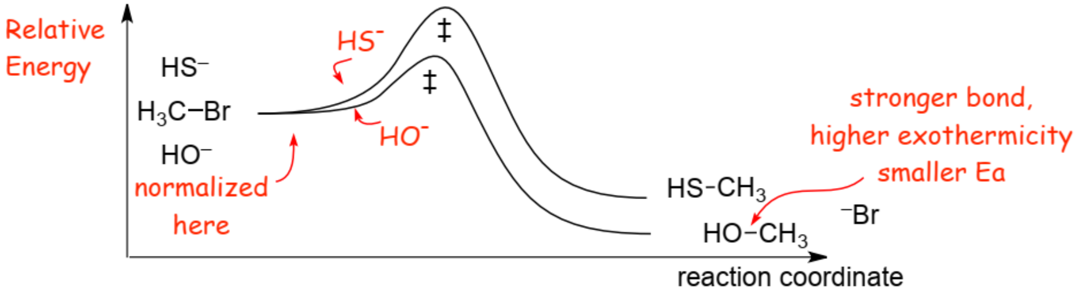


- So, which "wins", **basicity** or **nucleophilicity** because of the partial-bond strength? Unfortunately, which one wins **depends upon solvent (see later)**
- Here we will look at the case that is straightforward, **where nucleophilicity and basicity are the same**

Example: Compare these two reactions



- The larger S makes stronger partial bonds, but the stronger bonds in the product with O simply wins!
- **Nucleophilicity is the same as basicity here!**

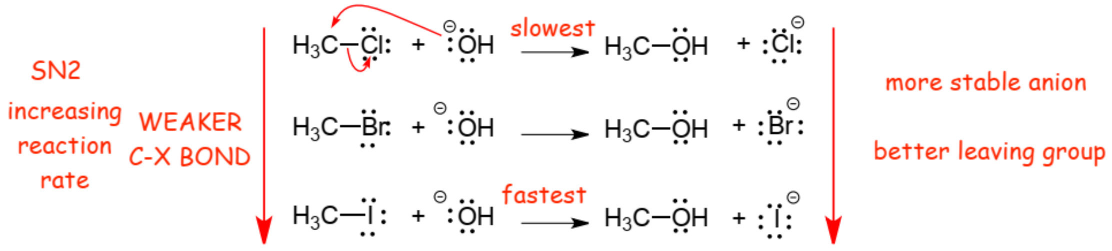


2.4 Factors Controlling SN2 Reactivity: Leaving Group Ability

Good leaving groups:

- Are **stable/less reactive** as an anion
- Are generally **weak bases** (i.e. they have WEAK bonds to, for example, H atoms)
- Polarize the C–LG bond (and are polarizable to make strong partial bonds in transition state)

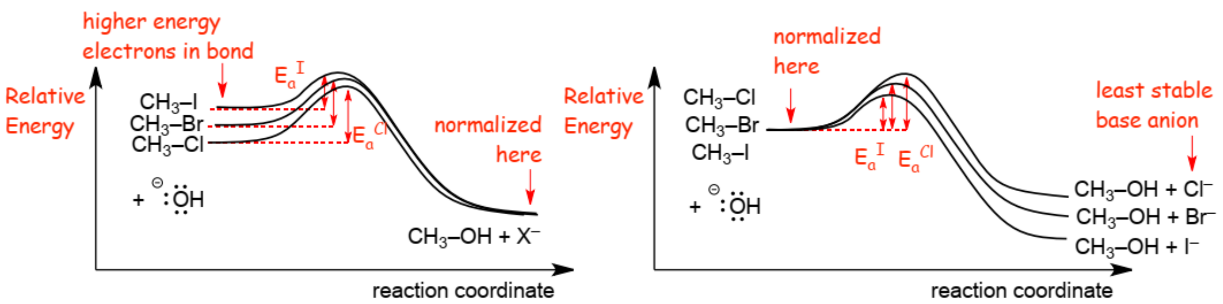
For Example:



- **Leaving Group ability increases** going down the periodic, as **anion stability increases**
- The **iodide anion** is stable and unreactive because it is a weak base, it makes **weak bonds** to H
- The **chloride anion** is **less** stable and is **more** reactive because it is somewhat stronger base, it makes somewhat **stronger bonds** to H

Reaction Energy Diagrams: Two Equally correct ways of illustrating this effect

- Which of the following energy diagrams best illustrates why iodide is a better leaving group than bromide etc.?



- **Both of these diagrams are equally correct**
- The diagram on the LEFT, the diagram shows the difference in the energies of the electrons on the bonds, the weaker (higher electron energy) bond is the most reactive (smallest Ea, largest reaction rate)

- The diagram on the **right** shows the difference in the stabilities of the anion leaving groups, the more stable the anion the smaller the Ea, the faster the reaction.
- **Remember**, the iodide anion is the most stable not because of particularly low electron energy in this case, but because if it reacts it can only make weak bonds because it is so large.

2.5 Factors Controlling SN2 Reactivity: Solvent Effects

- Nucleophile strength **depends upon solvent,** this is something new for us.
- Solvent effects on reactions can be **dramatic.**
- **But**, A complication: **solvent effects are different** for **nucleophiles of different sizes (see below).**

Polar protic (hydrogen-bonding) Solvents: Mostly alcohols and water.

- Polar protic solvents have **strong intermolecular ion-dipole forces** with dissolved anions in particular.
- These **ion-dipole interactions** solvent anions strongly (think about ionic compounds dissolved in water).
- The **stronger the IMF**, the **more solvated** the ion in the solvent since the interactions with the solvent lower the total electron energy more than for comparable weaker intermolecular forces.

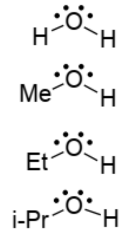
example polar protic solvents

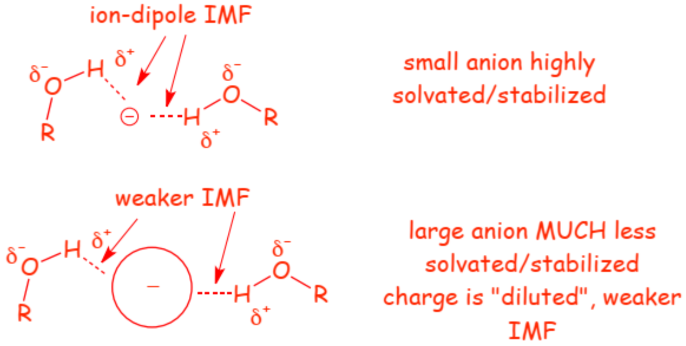
water

methanol

ethanol

i-propanol





- **Stronger solvation** lowers electron energy and **chemical reactivity**, anions in particular tend to be **less reactive in polar protic solvents.**
- **Polar protic solvents solvate small anions strongly, but solvate larger anions less strongly**, transition states are large, and are thus much less solvated.
- there is often a **large solvation energy difference** between reactants and the transition state, particularly when using small anionic nucleophiles in a **polar protic solvent.**
- Intermolecular **force** is actually an unfortunate term because force and energy are not the same thing, but it is not hard to understand that if an **IMF** is strong it is more likely to lower the energy of the relevant electrons more.

Polar Aprotic (Non-hydrogen-bonding) Solvents

- There are Several, you need to know these
- **Polar protic solvents** have **weaker intermolecular ion-dipole forces** with dissolved ions
- The **ion-dipole interactions** certainly solvent and stabilize ions, but there is no **H-bonding!**

example polar aprotic solvents

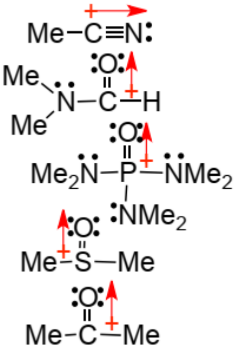
acetonitrile

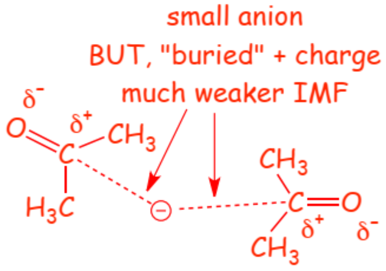
dimethylformamide (DMF)

hexamethylphosphoramide (HMPA)

dimethylsulfoxide (DMSO)

acetone





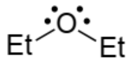
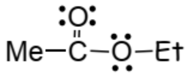
learn these by using them and working practice problems

- There is a usually a **smaller** energy difference between reactants and the transition state when SN2 reactions are performed in polar aprotic solvents, SN2 reactions in polar **aprotic** solvents are usually faster than in polar protic solvents (but see further below).
- You **need to know** the polar **aprotic** solvents, this is not easy because they are different structures, learn them by working with them.

Medium Polarity or Non-Polar Solvents

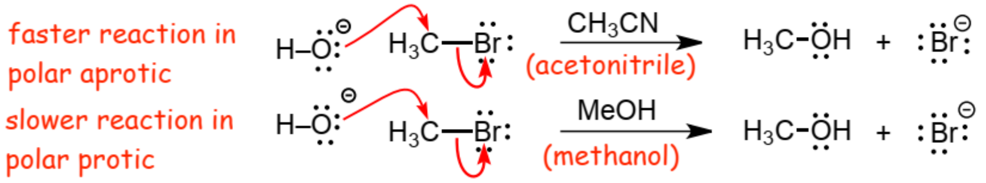
- These solvents should be very good for SN1 and SN2 reactions since they will solvate the anions so poorly, but that is the problem, they solvate ions so poorly that the reactants often simply don't dissolve in them!
- We do see these solvents quite often in organic reactions, in fact we have seen carbon tetrachloride, CCl4) already, as an inert (non-reactive) solvent in more than one reaction
- Some common low polarity solvents are summarized here but we will .not use them much for SN1/SN2.

example medium and nonpolar solvents

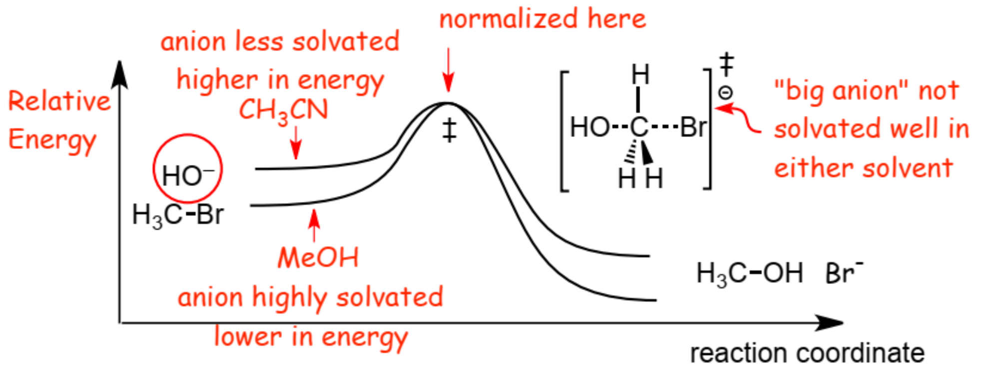
hexane	$CH_3(CH_2)_4CH_3$	diethyl ether	
chloroform	$CHCl_3$	carbon tetrachloride	CCl_4
benzene		cyclohexane	
ethyl acetate			

- Medium and in particular non-polar solvents are commonly used in organic chemistry, but not so much for SN2 reactions, since these often involve ionic reactants that will simply not dissolve in non-polar solvents.

Example Solvent Effects



- Explain the difference in reaction rates using a reaction energy diagram:

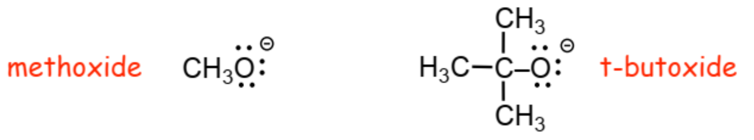


- Here we have **two** reactions on one diagram. The **absolute** energies of the two systems are very different, thus we need to **normalize** the energies and plot **relative energy**.
- Where to normalize? In general, we will want to emphasize the places where the energies are different and where they are similar. In this case, the energies at the start and end are different due to large differences in anionic solvation, and the energies at the transition states are more similar due to small differences in solvation, thus we normalize at the transition state.

2.6 Differences Between Nucleophilicity and Basicity

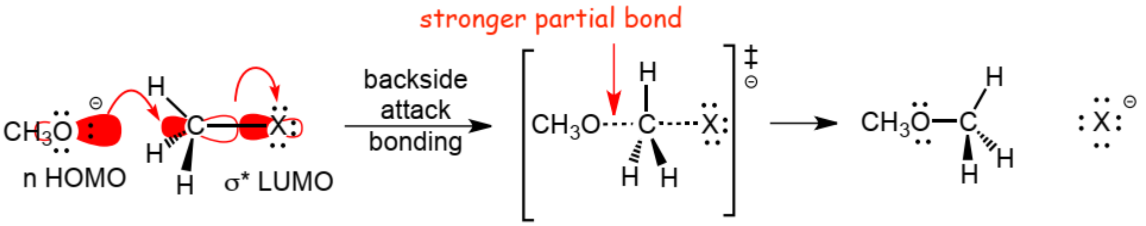
Bulky bases are strong bases but weak nucleophiles

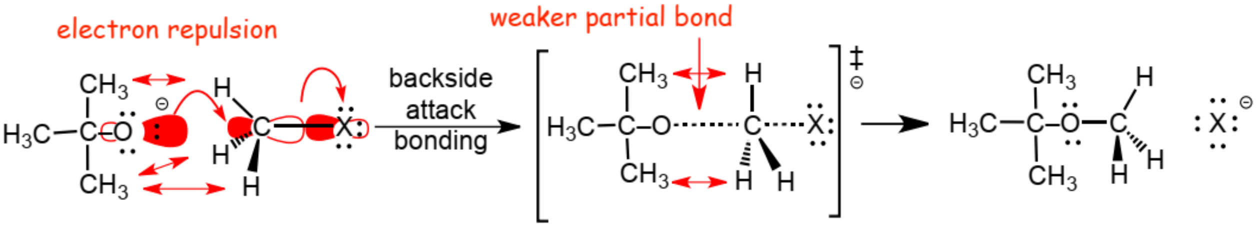
- Compare methoxide and t-butoxide:



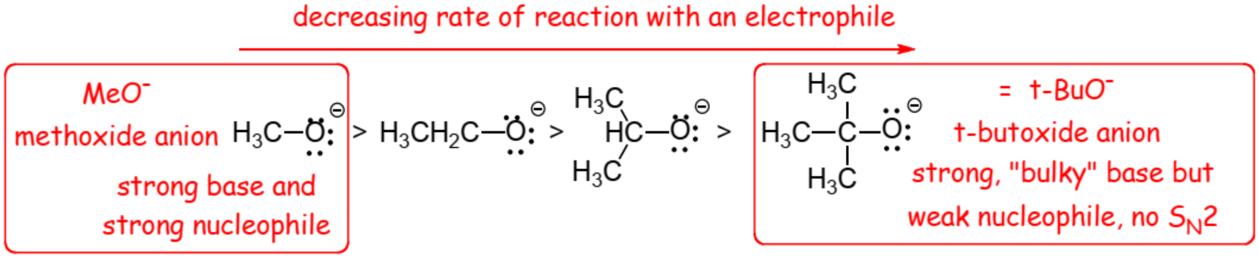
equally strong bases, both make equally strong bonds to H^+

- Both are equally strong Bronsted bases, both make equally strong bonds to a proton (H^+)
- **But**, t-butoxide is a much weaker nucleophile than methoxide, due to electron repulsion/steric effects, it makes a weak O-C partial bond in the transition state in an SN2 reaction





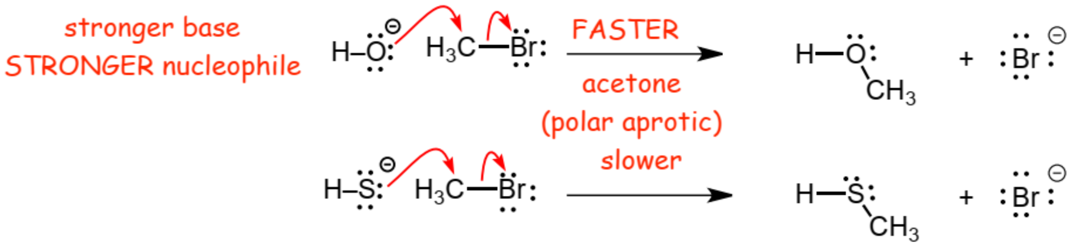
- This steric effect results in the following nucleophilicity trend, note that all are equally strong bases



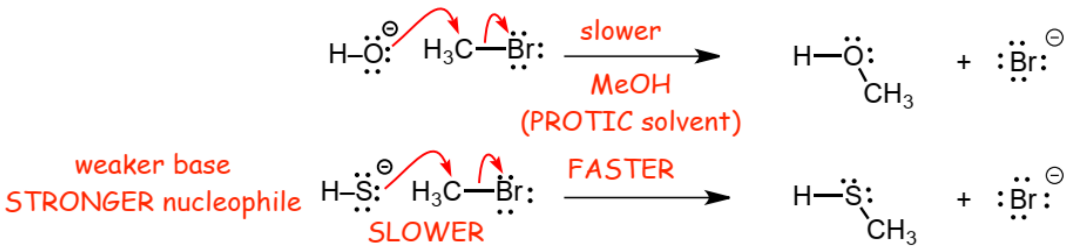
- **SN2 is not possible using the t-butoxide anion**
- We will use bulky bases to our advantage in controlling the competition between SN2 and E2 reactions frequently, see later

Nucleophile strength can depend upon solvent, this is something new for us

- **Reminder**: Larger atoms have more polarizable electrons, they do not have **to "get so close" to make a bond, they can make "longer" bonds, and thus can make stronger partial bonds** in the transition state
- But, the oxygen anion makes stronger bonds, it is smaller, and so which wins?
- We already saw a comparison between these two reactions **in a polar aprotic solvent**
- In the **polar aprotic solvent** the smaller **anion making the stronger bond in the product wins, the stronger base is the stronger nucleophile.**

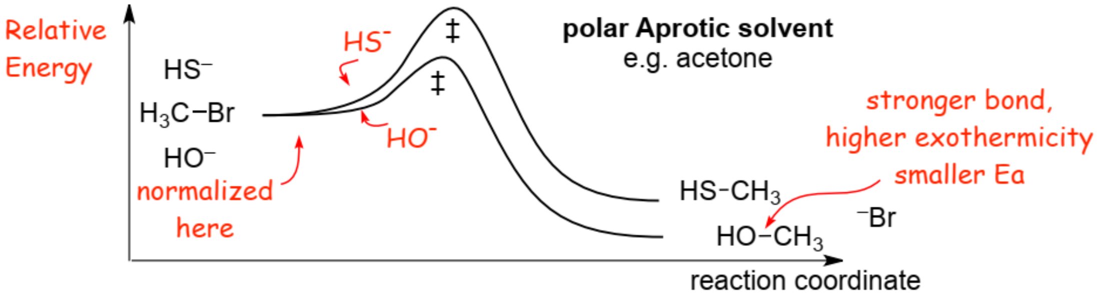


- However, in a **polar protic solvent** the **larger anion making stronger bonds in the transition state wins, the weaker base is the stronger nucleophile.**

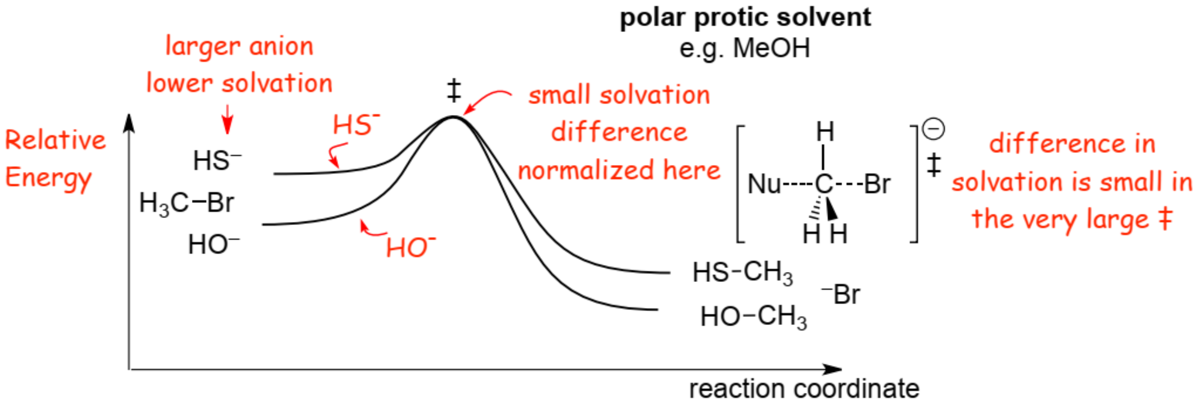


- The larger more polarizable sulfur anion forms stronger partial bonds in the transition state
- **And**, the larger sulfur anion is not solvated well (not stabilized) by the polar protic solvent, therefore, it is more reactive
- **Here, nucleophilicity is opposite to basicity, solvation and polarization effects "win" over exothermicity**
- Reaction energy diagram curves emphasize the difference in solvation of the nucleophilic ions

In a polar Aprotic solvent:



In a polar protic solvent:

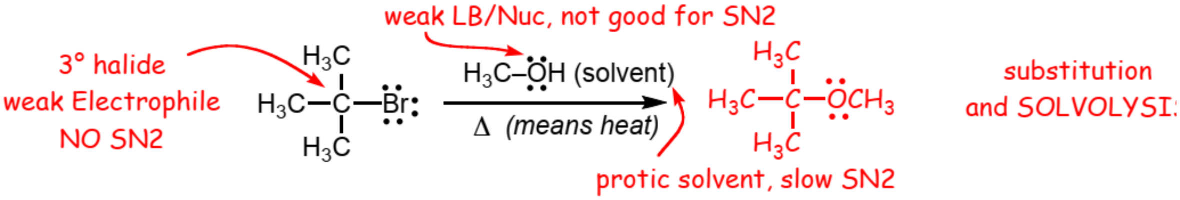


Summary:
- **Bulky bases such as t-butoxide are weak nucleophiles** (No SN2 with t-butoxide)
- **Nucleophilicity** is always the **same as basicity, except that larger anions are more nucleophilic than smaller anions in protic solvents** (but not in polar aprotic solvents)

Going down the periodic table often makes things complicated! Even worse, when NUETRAL nucleophiles are compared with different sized atoms, for example Me_2O versus Me_2S, then nucleophilicity is the same is all solvents, and Me_2O is weaker than Me2S because neutral structures are not as affected by solvent and the larg size and polarizability of the electrons on the larger atom wins out over electronegativity. However, I don't think i is really fair to ask you to know this detail, and so you should assume that nucleophilicity and basicity are the same EXCEPT for ions going down the periodic table in polar protic solvents, where it is reversed, this is the onl exception you need to know. Well, there is one more exception that we will met soon, which are the bulky bases but they are actually quite easy!

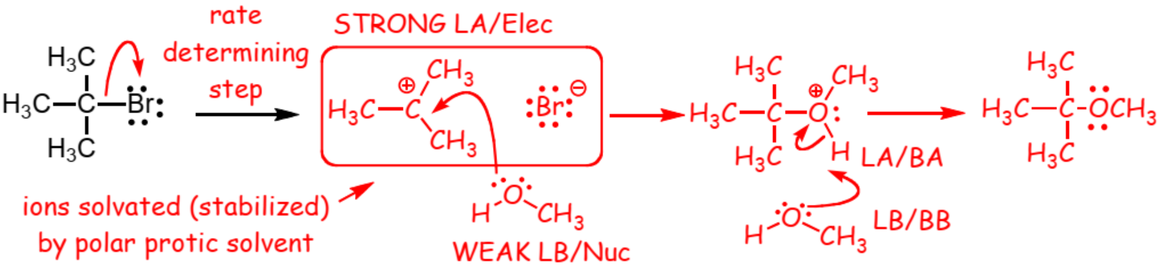
3 First Order Nucleophilic Substitution (SN1) Reaction

- What happens if we try to do an SN2 reaction with a very weak (e.g. neutral) nucleophile Lewis base?

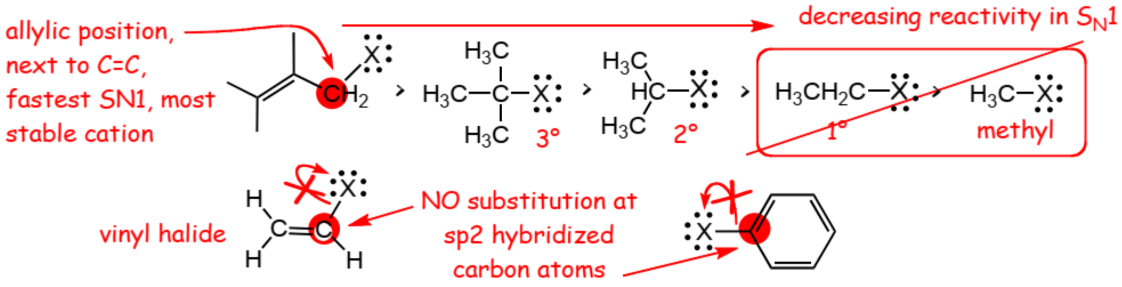


- here we have a nucleophilic substitution reaction BUT......
- we have a 3° halide which is a weak electrophile (backside attack is not possible), can't do SN2.
- H_3COH is a weak nucleophile (no negative charge on the oxygen), shouldn't do SN2.
- H_3COH is also a PROTIC solvent, which should be slow for SN2.
- here the solvent "helps" to break the C–Br bond, the reaction is a **solvolysis reaction** (lysis - bond breaking)

We need a new substitution **mechanism** to account for this: **The SN1 Mechanism.**



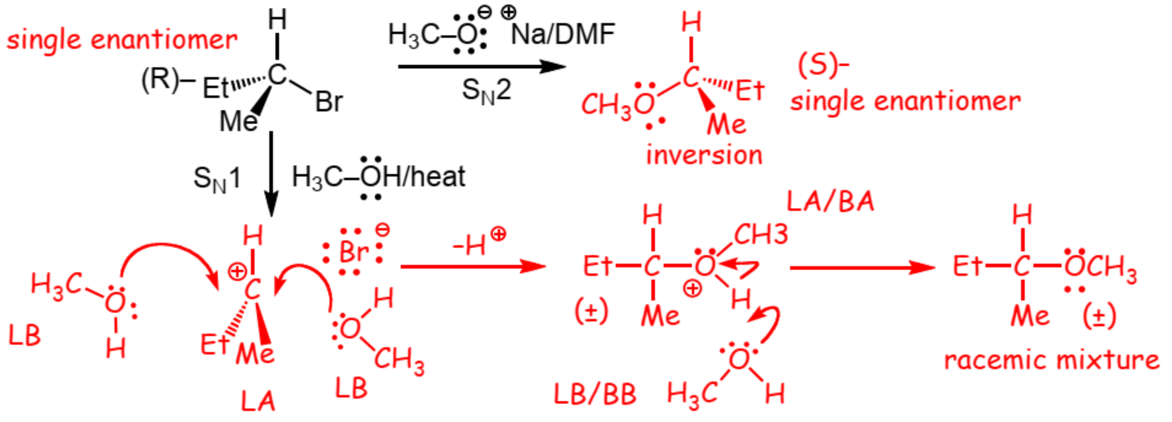
- Although the alcohol is a **weak LB/Nucleophile**, the first cation intermediate is a **STRONG LA/Electrophile**, and so nucleophilic addition at this step in the mechanism is fast.
- The SN1 reaction requires a polar protic solvent to stabilize the ionic (cation and halide) intermediates
- Usually requires heat (energy) to break the C–X bond unimolecularly.
- ONLY the halide (not the nucleophile) involved in the R.D.S., thus **SN1** (1 means only 1 reactant in the R.D.S.)
- Requires a stable intermediate cation, **no** SN1 for methyl or primary halides.



- No SN1 (OR SN2) at sp2 hybridized carbons, the C-X bond is too strong and the cations are too unstable
- **In general, SN1 will always occur in preference to SN1 since this makes a bond at the same time the bond is broken, unless SN2 is impossible (e.g. at a 3° carbon).**

3.1 Stereochemistry of SN1 Reactions: Racemization (?)

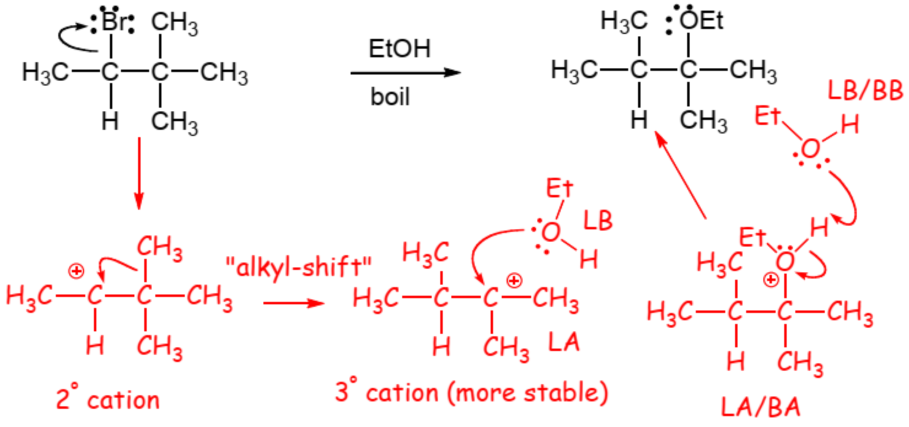
Example:



- We expect racemization, or at least **some loss of stereochemistry** for SN1 compared to SN2
- depending upon conditions/reactants, attack on the same side as the leaving group may be hindered, resulting in a slight excess of the inversion product
- in reality, however, it is not easy to predict exactly how much stereochemistry will be lost, and so we will use the "rule" in this course that **if the reaction goes via SN1 we will assume that racemization always occurs**

3.2 Cation Rearrangements in SN1 Reactions

Example:



- Once the cation is made it will react the same as any other cation, and so this cation will rearrange

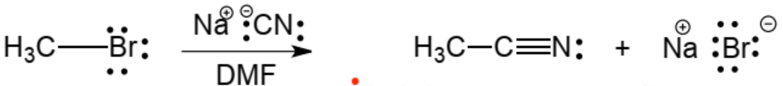
3.3 Distinguishing SN1 and SN2 Reactions

S_N2 favored by:
- 1° > 2° > 3°
- strong nucleophile
- polar aprotic solvent

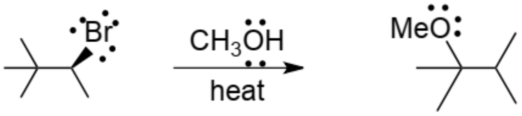
S_N1 favored by:
- 3° > 2° > 1°
- weak nucleophile
- polar protic solvent AND heat

- **Note**: the factors above favor the reactions by making them go faster, e.g. SN2 is **faster** at a primary carbon, SN1 is faster at a tertiary carbon, SN1 is faster in polar protic solvents etc.
- However, weak nucleophiles do not favor SN1 because they make SN1 reactions faster, they don't, but they do make competing SN2 reactions **slower.**
- SN2 reactions are not precluded by polar protic solvents, they are just faster in aprotic solvents

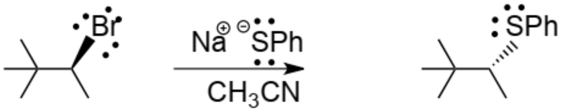
Examples: Assign the mechanism of the following reactions to S_N1 or S_N2



1° halide, strong Nu, polar aprotic - S_N2

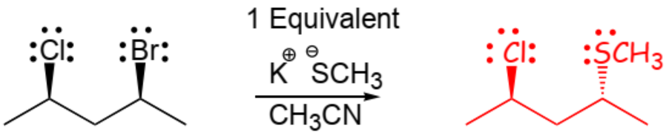


2° halide, weak Nu, polar protic/heat - S_N1 with rearrangement

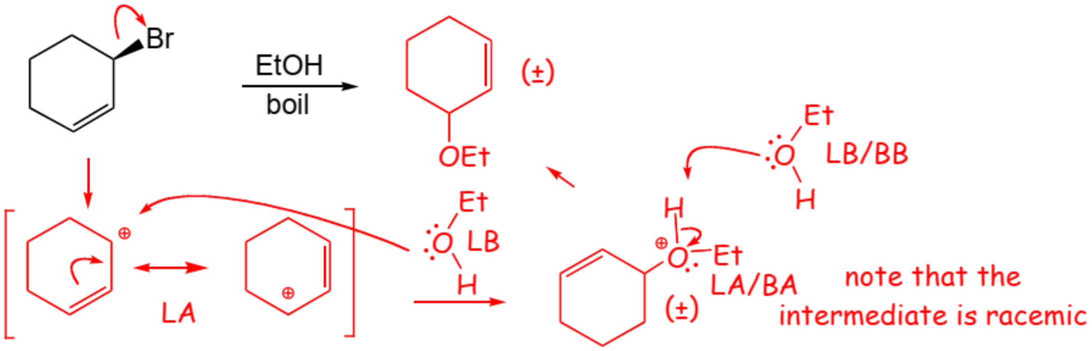


2° halide, strong Nu, polar aprotic - S_N2 (so NO rearrangement and inversion)

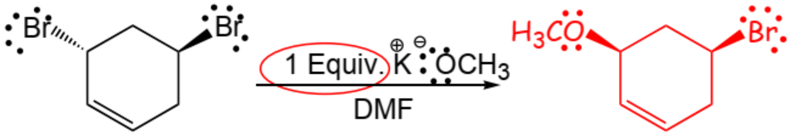
Example Problems: Give the major organic product of reactions



- Polar aprotic solvent, strong nucleophile, SN2, Br- better leaving group
- **1 equivalent means exactly the same number of nucleophiles as organic reactants**, which in this context means that there is only enough nucleophile to substitute one of the halide leaving groups



- Polar protic solvent and heat, no strong nucleophile and allylic halide, must be SN1. Need to draw the mechanism to be sure of the product!



- Polar aprotic solvent, strong nucleophile, SN2, allylic position more reactive.
- 1 **equivalent** will **only react** at the carbon where SN2 will be fastest, there is only enough reagent to react once.