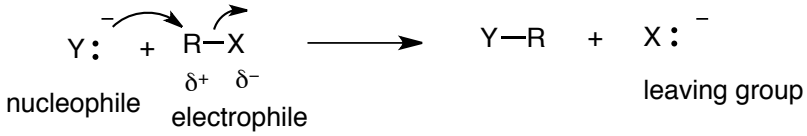
Chapter 6
Nucleophilic Substitution

In this chapter we re-examine nucleophilic substitution reactions in more detail, paying particular attention to stereochemistry and other details of the reaction mechanism. We will look at what makes a good nucleophile and we will examine solvent effects on substitution reactions.

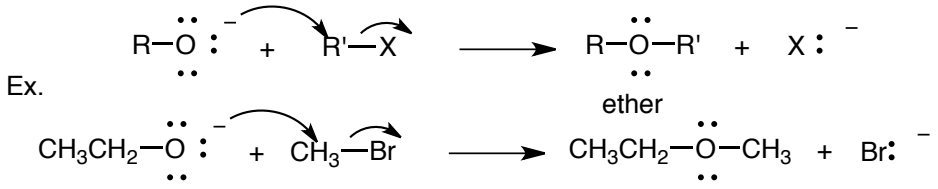
We will also see that substitution reactions compete with elimination reactions and we will study the conditions that favor substitution versus elimination and conditions that favor elimination over substitution.

With alkyl halides, the R-X bond is partially polarized with the R-group having a partial positive charge and the X group having a partial negative charge. The Y-group is the nucleophile and the R-group, with its partial The X-group is the leaving group and leaves with the two electrons in the R-X bond. The new R-Y bond is formed with the two electrons that come from the nucleophile Y. The nucleophile, by definition, donates two electrons to the electrophile. In order to be a nucleophile, it must have two electrons. In a later section we will discuss what it is that makes a good nucleophile.

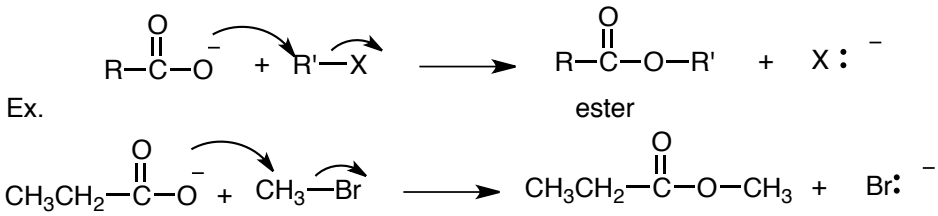


Examples of common nucleophiles:

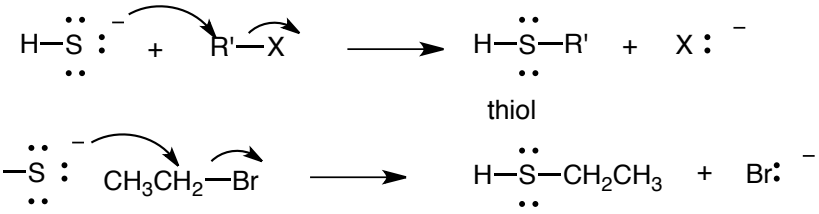
(1) Alkoxides, RO^-, used to make ethers.



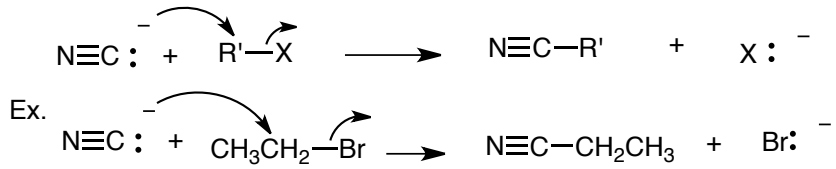
(2) Carboxylate, RCO_2^-, used to make carboxylic acid esters.



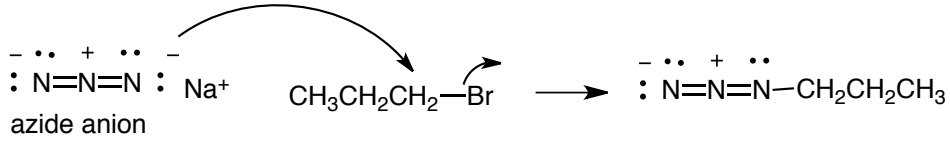
(3) Hydrogen sulfide anion, HS^-, used to make thiols.



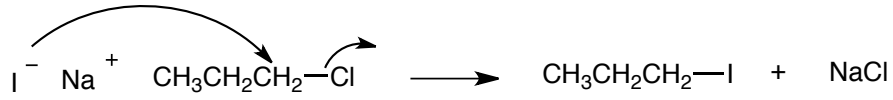
(4) Cyanide anion, NC^-, used to make alkyl cyanides.



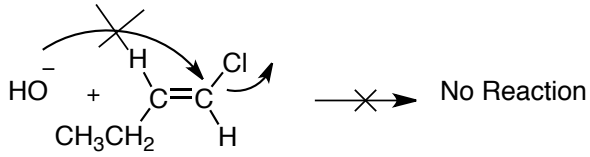
(5) Azides

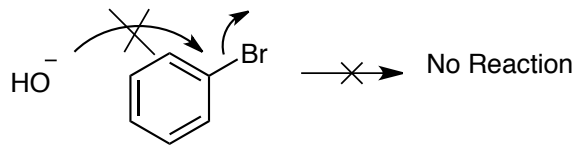


(6) Iodides



Substitution reactions cannot be done at sp^2 carbon centers.



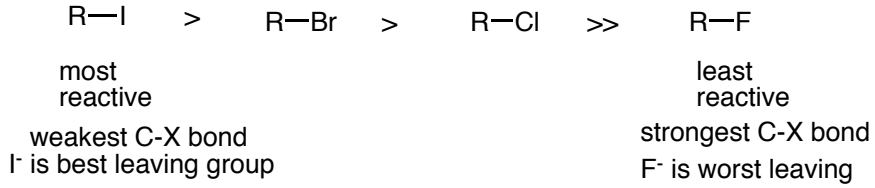


There are two main reasons for this.

(1) The sp^2 carbon-halogen bond is stronger than an sp^3 carbon-halogen bon and therefore harder to break. This increased bond strength is due to the increased electronegativity of the sp^2 carbon.

(2) The second reason is due to electron-electron repulsion of the incoming nucleophile with the π-electrons of the double bond. The nucleophile must approach from the backside (as we will discuss later) and therefore it must approach through the electron cloud of the π-electrons.

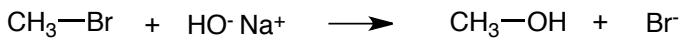
The relative reactivity of the halogens to nucleophilic substitution reactions correlates with the C-X bond strengths.



R-I is seven times more reactive than R-Br and 50-100 times more reactive R-Cl. Iodide is the best leaving group and fluoride is the worst leaving since it is the strongest base of the halogens. Remember, iodide anion, I^-, is about 10^{13} times a weaker base than fluoride anion, F^-. Recall that the weaker the base - i.e. the more stable the anion - the better it is as a leaving group. So, iodide is one of the weakest bases and one of the best leaving groups.

Mechanism for S_N2 Reactions

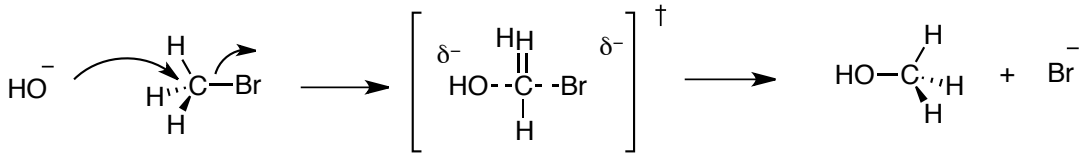
Kinetics: for the following reaction



Rate = $k[CH_3Br][HO^-]$

This is a second order reaction, bimolecular, where both the substrate, CH_3Br, and the nucleophile, NaOH, enter into the rate equation.

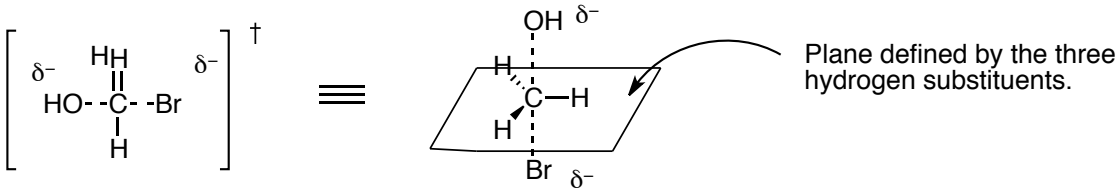
The reaction occurs in one step with the nucleophile coming in from the backside of the substrate on an angle of 180°. Note that the leaving group leaves with its lone pair of electrons.



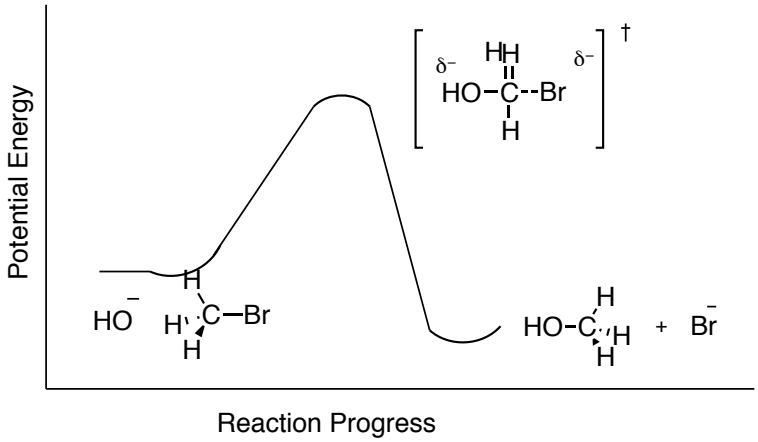
The substituents move in the transition state.

The substituents, in this case the three hydrogens, move in the transition state. Initially they are pointing at the nucleophile. They then move or flatten out so that in the transition state all three of the hydrogens are in the same plane. The incoming nucleophile and the leaving group are perpendicular to this plane. In the final product, the three hydrogens then point away from the new substituent.

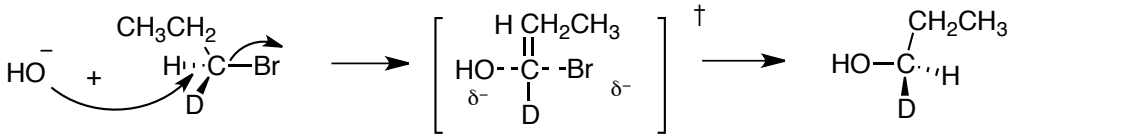
Another view of the transition state illustrates this.



This is a one-step reaction so the potential energy versus reaction progress diagram will show one energy maximum and one transition state.



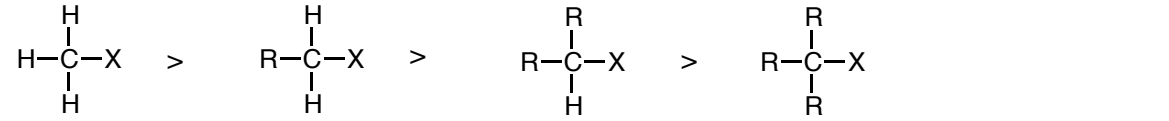
Since the substituents move in the transition state, an optically active substrate will undergo inversion of configuration.



(S)-1-bromo-1-deuteriopropane (R)-1-deutreio-1-propanol

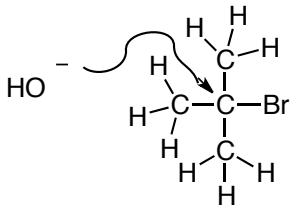
Steric Effects

S_N2 reactions are very sensitive to steric hindrance. Tertiary substrates react very slowly by the S_N2 mechanism, if at all. The best substrates are methyl and primary alkyl halides. Secondary substrates will react by the S^N2 mechanism but will do so relatively slowly.



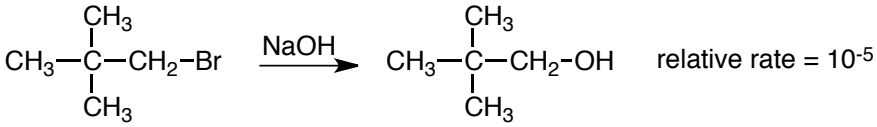
least crowded, most reactive — primary — secondary — tertiary — least reactive by S_N2 most crowded

The nucleophile must approach the electrophilic carbon from the backside. With tertiary substrates this approach is very crowded and the reaction is very slow.

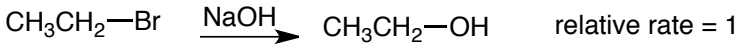


The backside approach is very hindered in tertiary substrates.

And neopentyl bromide also reacts very slowly, even though it is a primary alkyl halide, partially blocked by the methyl groups on C2. Neopentyl bromide reacts about 10^{-5} times more slowly than ethyl bromide.



relative rate = 10^{-5}

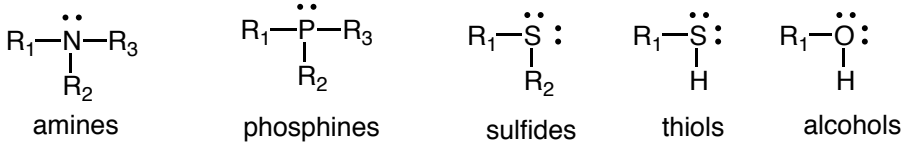


relative rate = 1

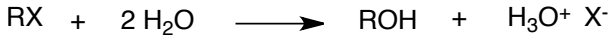
Nucleophilicity

We will now look at what makes a good nucleophile. By definition a nucleophile is a species that donates electrons to the electrophile. To be a nucleophile, a species must have at least a lone pair of electrons that it can donate. It does not have to be an anion.

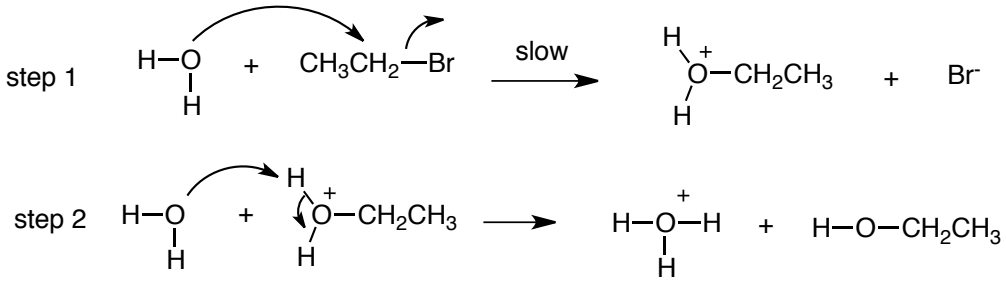
For example, all of the following are good nucleophiles:



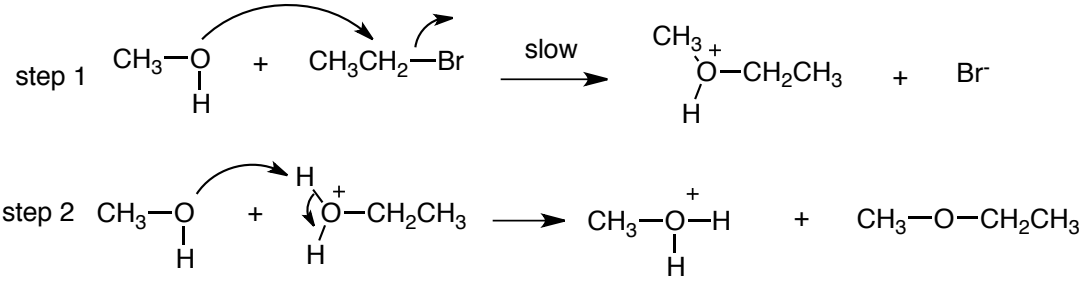
Solvolysis reactions are those in which the solvent is also the nucleophile. These are common in water and alcohol solvents.



For example, a hydrolysis reaction in water:



A methanolysis reaction in methanol:

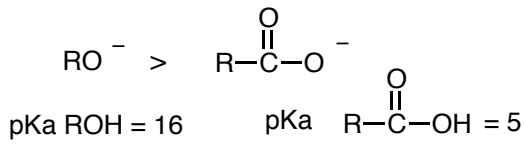


Nucleophilicity is a measure of the strength of the nucleophile. We do not have an exact scale that measures the strength of a nucleophile the way we do for measuring the strength of acids using the pKa scale but we can make some generalizations.

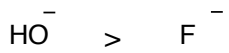
General Rules for Predicting the Strength of a nucleophile:

(1) If the attacking atom in two nucleophiles is the same in each and one of them has a charge, the nucleophile with the charge will be the stronger nucleophile.

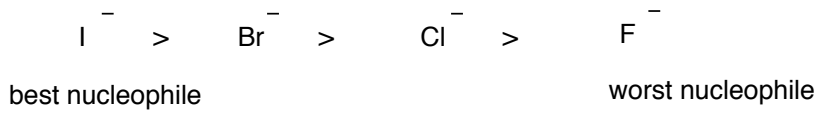
(2) If the attacking atom in two nucleophiles is the same, the more basic the atom, the better the nucleophile.



This is also true for atoms in the same row: the stronger the base, the better the nucleophile.



This is true only for atoms in the same row. It is not true when going down a column. For example, among the halogens, iodide is the best nucleophile and fluorine is the worst.



This trend is also true for other columns. For example, HS^- is a better nucleophile than HO^-.

Probably the main reason for this has to do with solvation. For reactions in solution the small, highly electronegative fluorine anion is tightly surrounded by solvent molecules and so is less available to react as a nucleophile. Its electrons are not free to react because they are partially bound to the solvent molecules surrounding them.

In the gas phase, where there is no solvent, the reactivity order is exactly the opposite: $F^- > Cl^- > Br^- > I^-$.

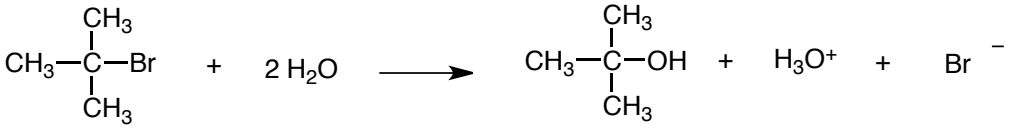
The Relative Nucleophilicity of Some Common Nucleophiles:

		Relative Reactivity
Very Good Nucleophiles:	I^- HS^- RS^-	$> 10^5$
Good Nucleophiles	Br^- HO^- RO^- $N\equiv C:^-$ N_3^-	10^4
Fair Nucleophiles	NH_3 Cl^- F^- RCO_2^-	10^3
Weak Nucleophiles	H_2O ROH	1
Very Weak	RCO_2H	10^{-2}

S_N1 Reactions

Tertiary alkyl halides do not undergo S_N2 reactions easily and in fact they react by the S_N1 mechanism.

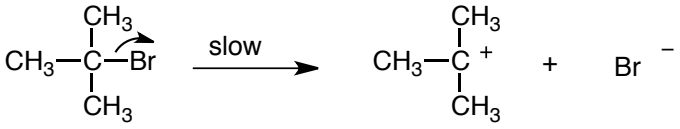
For the following reaction, it was found that the reaction rate is first order in 2-methyl-2-bromopropane (*t*-butyl bromide). The rate is independent of the concentration of the nucleophile, which is water in this case. It is a unimolecular reaction (substitution nucleophilic unimolecular)



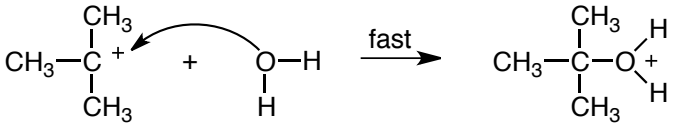
Rate = $k[(CH_3)_3CBr]$

Mechanism:

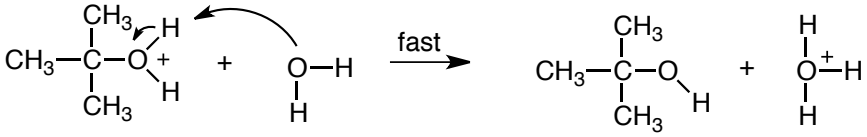
Step 1: The first step is simply unimolecular ionization of the *t*-butyl bromide to form a tertiary carbocation and bromide anion. The carbocation and bromide anion are stabilized by electrostatic interactions with the solvent, which is water in this case. This step is slow, since it is energetically unfavorable (endothermic). A bond is being broken but no bond is being formed.



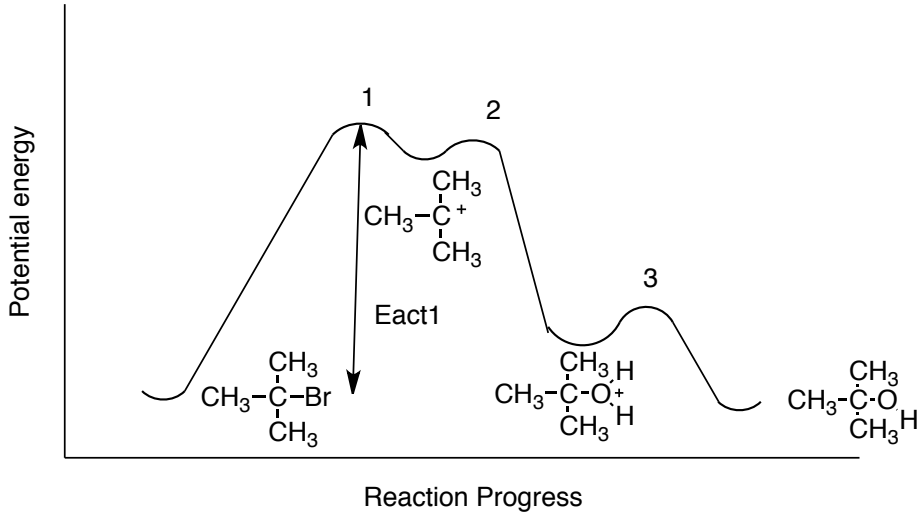
Step 2 is fast. The carbocation is attacked by water. This step is fast and energetically favorable. A strong C-O bond is formed.



Step 3 is a rapid proton transfer step in which the extra proton attached to the oxygen is transferred to another molecule of water. Usually, the proton transfer steps are the fastest reactions in chemistry, particularly in this case where the protons are already hydrogen-bonded to water.

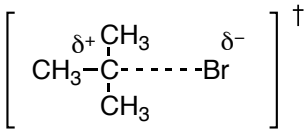


The potential energy versus reaction progress diagram shows up the energy relations between the various steps.



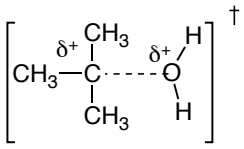
Since there are three steps in this reaction, there are three transition states. In the first step, we are simply breaking the C-Br bond and so in the transition state we have a lengthened C-Br bond with considerable charge build up on the bromine (negative charge) and on the tertiary carbon (positive charge). Hammond's postulate allows us to predict this build-up of charge in the transition state. Since we know that the first step is endothermic, Hammonds postulate tells us that this step will have a late transition state and that it will resemble the product carbocation in structure. Therefore, there will be a lot of positive charge in the first transition state.

Transition state 1



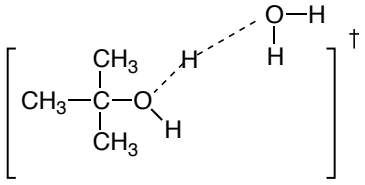
The second and third transition states both resemble the starting materials since these reactions are fast, and exothermic.

Transition state 2



exothermic reaction, early transition state, little build up of charge

Transition State 3



exothermic reaction, early transition state, little build up of charge

The reaction rates for S_N1 reactions are determined by the rate of formation of the carbocation. As we have learned, the more stable carbocation forms fastest because it is lower in energy. Therefore tertiary substrates, which form tertiary carbocations in the first step, react the fastest by the S_N1 mechanism. This is very rapid at room temperature.

Reactivity order for alkyl substrates:

R_3CX	>	R_2CHX	>	RCH_2X	>	CH_3X
tertiary		secondary		primary		methyl
reacts fastest, forms most stable carbocation						

The reactivity order for S_N2 reactions is exactly the opposite:

CH_3X	>	RCH_2X	>	R_2CHX	>	R_3CX
methyl		primary		secondary		tertiary
least hindered						most hindered

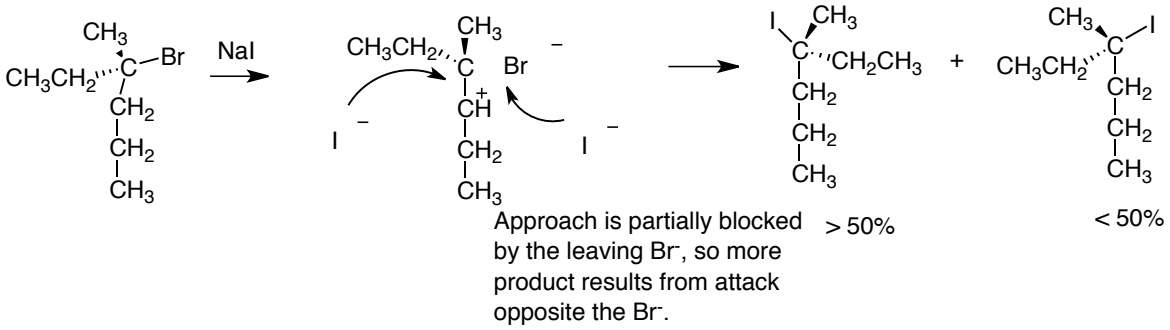
In general:

Methyl and primary alkyl halides never react by S_N1 mechanisms, always by S_N2.
Tertiary alkyl halides never react by S_N2 mechanisms, always by S_N1.
Secondary alkyl halides can give a mixture of S_N1 and S_N2 but it depends to a large extent on the nucleophile:

- Good nucleophiles tend to give mainly S_N2.
- Poor/weak nucleophiles tend to give mainly S_N1 (as in solvolysis reactions).

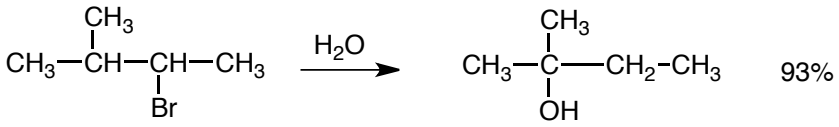
Stereochemistry of S_N1 Reactions

Usually we see at least some racemization of chiral substrates in S_N1 conditions but we usually do not get an exactly 50:50 mixture of the two isomers. Generally, the leaving group partially shields one side of the carbocation so that there is a slight predominance of attack of the nucleophile from the side away from the leaving group.

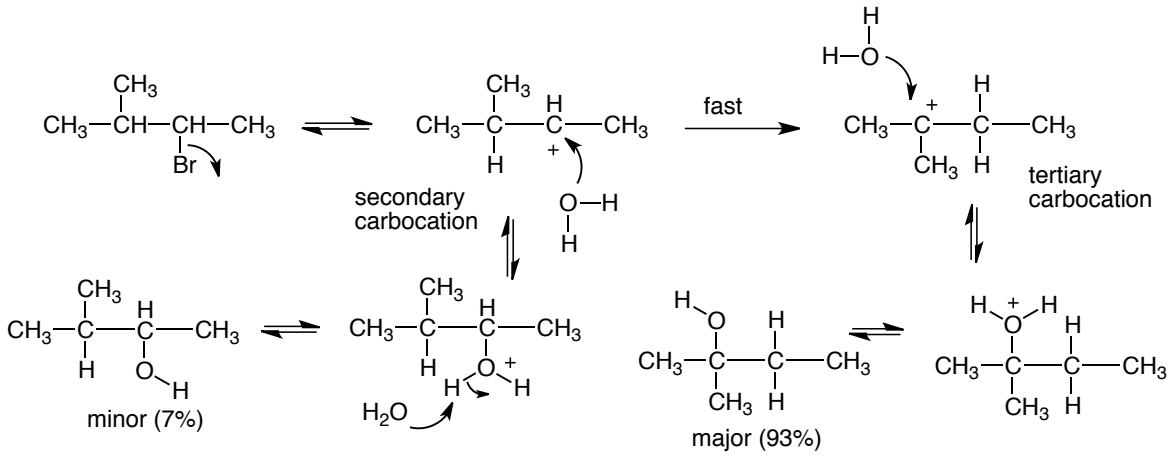


Rearrangements

Since there is a carbocation intermediate, rearrangements will occur. For example, in the following solvolysis reaction, most of the product results from the rearrangement of the secondary carbocation to the tertiary carbocation by means of a hydride shift in this case. This step is very fast since a higher energy species is being converted to a lower energy species.



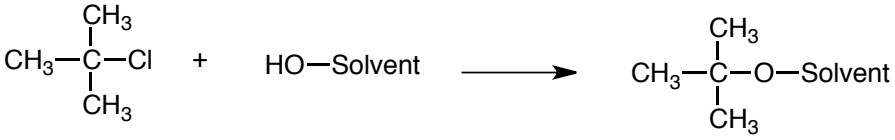
The mechanism is shown below. Here we see a hydride shift, since this converts the secondary carbocation into the tertiary. Migration of a methyl group does not occur since this would not result in a lower energy carbocation (i.e. secondary to secondary).



Solvents Effects

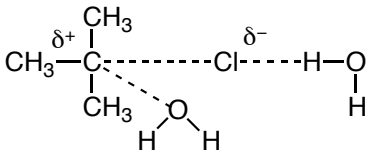
S_N1 Reactions:

The solvent can have a large effect on the rate of the substitution reaction. In general, the rate of a S_N1 reaction increases dramatically with increasing solvent polarity. For the following reaction, look at the increase in rate as the solvent polarity increases.



	Solvent	Polarity	Rate
acetic acid	CH_3COOH	6	1
methanol	CH_3OH	33	4
formic acid	$HCOOH$	58	5×10^3
water	H_2O	78	5×10^5

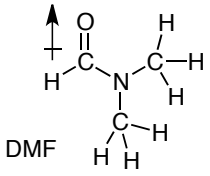
A polar protic solvent helps to stabilize both the anion and cation that develop in the transition state and so lowers the energy of the transition states, thereby increasing the rate.



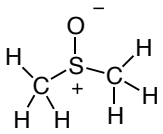
S_N2 Reactions:

For S_N2 reactions, the rate is greatly increased by using a polar aprotic solvent. Polar aprotic solvents do not undergo hydrogen bonding since, by definition, they do not have polarized hydrogens. Therefore, these solvents are good at solvating cations but not good at solvating anions. This leaves the anion relatively free to react with the substrate.

Two common examples of polar aprotic solvents are DMF (dimethyl formamide) and DMSO (dimethyl sulfoxide).



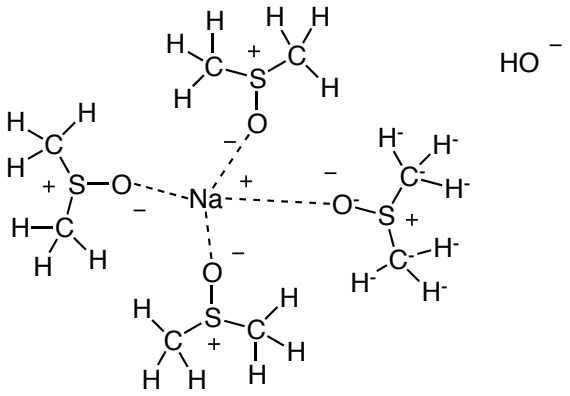
DMF



DMSO

In both of these solvents there is a strong dipole moment (they are polar) but there is no hydrogoen attached to an electronegative atom, so they are aprotic. Furthermore, the positive charged part of the molecule is partially blocked by steric hindrance in both cases while the negative portion of the molecule in each case is relatively accessible.

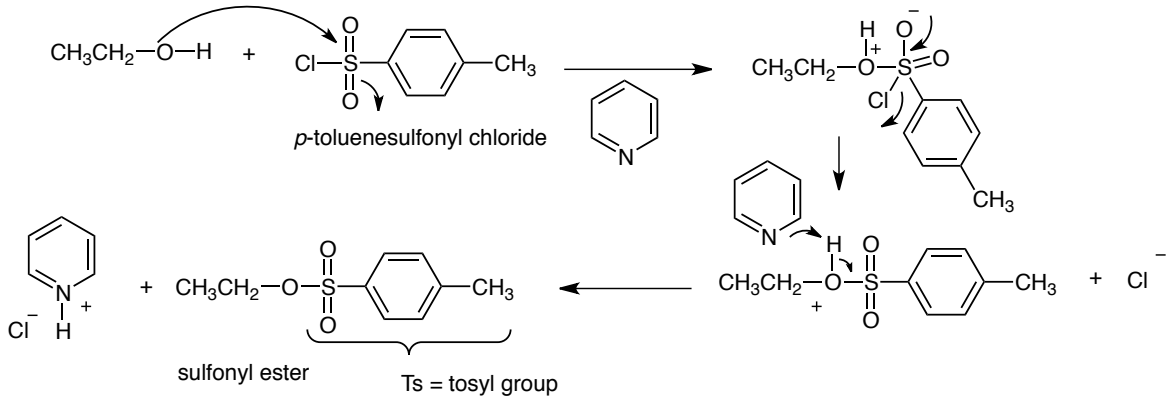
So, if sodium hydroxide, for example, is used as a nucleophile in DMSO, the hydroxide is very nucleophilic because the DMSO will tightly bind up the Na^+, but leave the HO^- relatively free.



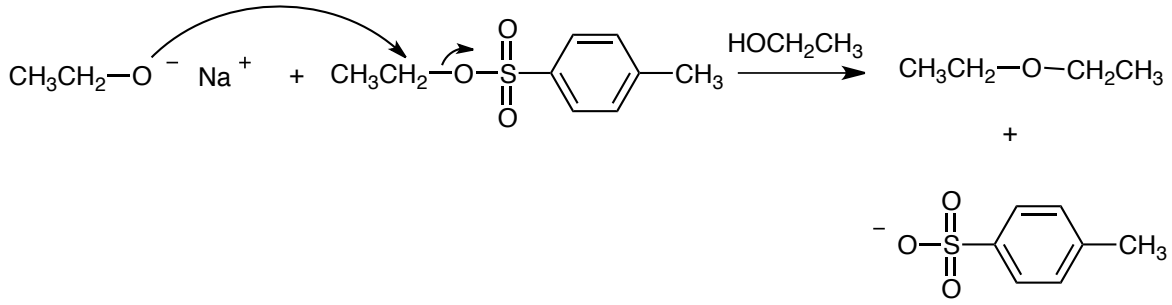
Sulfonate Esters

Alkyl sulfonates esters are also very good leaving groups, similar in leaving group ability to halogens. They are prepared from alcohols by reaction with a sulfonyl chloride. A common sulfonyl chloride is *p*-toluene sulfonyl chloride. Generally a mild, non-

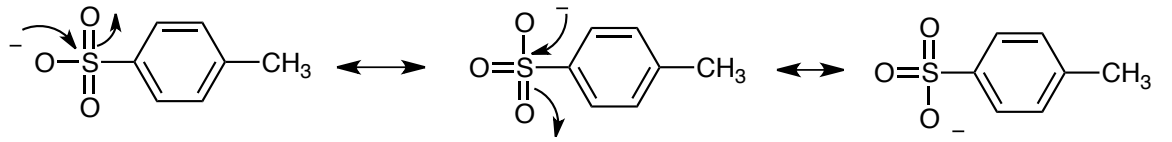
nucleophilic base such as pyridine or triethyl amine is used to neutralize the HCl that is formed in the reaction.



The sulfonyl ester can then be attacked by strongly basic nucleophiles to give substitution products with loss of the tosyl group.

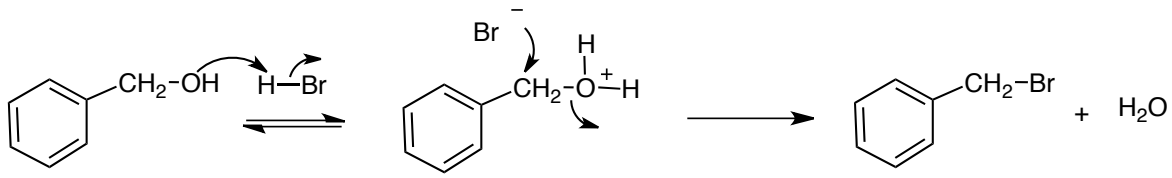


The tosyl group is a very good leaving group, equivalent to a halogen, because it forms a resonance-stabilized anion that is a weak base. Remember, by definition, a good leaving group is a weak base.



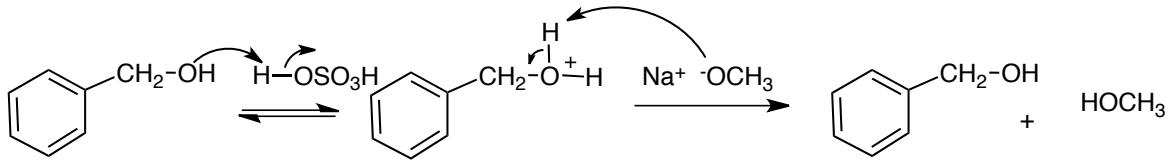
The (-) charge is spread out over all three oxygens and is thereby stabilized.

Note that the overall effect of making the alcohol into the tosylates is to convert the OH group into a good leaving group under mild, non-acidic conditions. As we have learned, we can convert the OH group into a good leaving group by protonation but this restricts the nucleophiles we can use to those that are very weakly basic such as the halogens.

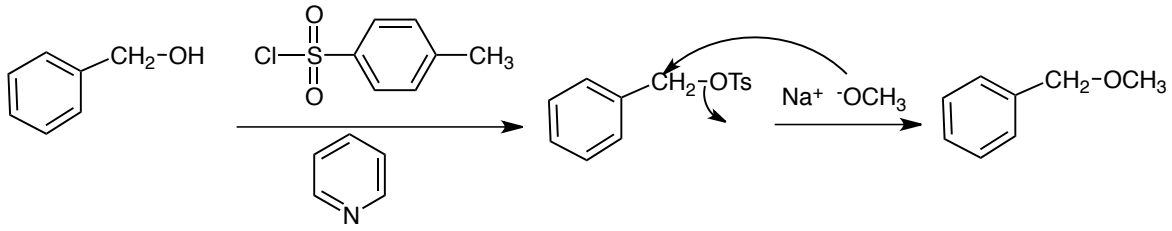


The Br^- is a very weak base and will not deprotonate the oxygen.

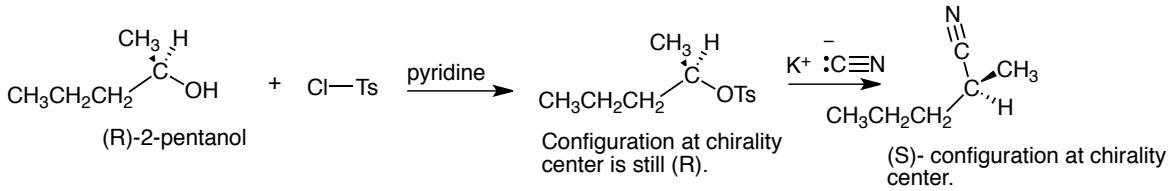
If we tried to do this same type of reaction with a more basic nucleophile like CH_3O^-, we would simply deprotonate the hydroxyl group in an acid-base reaction rather than a substitution reaction. Recall that the fastest reactions are always the proton transfer reactions.



So, if we first make the tosylates we can safely react it with the basic sodium methoxide and get an excellent yield of the substitution product.



Note that the stereochemistry of the C-O bond does not change when the tosylates is made but it does undergo inversion in the subsequent S_N2 reaction.



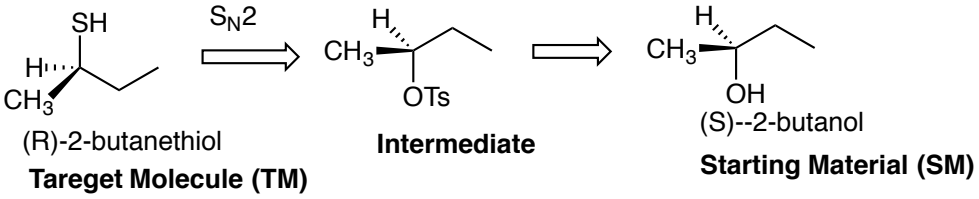
Introduction to Organic Synthesis: Retrosynthetic Analysis

One of the most important uses of organic chemistry and a major task of an organic chemist working in industry is the synthesis of new molecules, usually from smaller known molecules that are less expensive and commercially available. The small molecules

that are available from commercial chemical suppliers are called the **starting materials** (often abbreviated as **S.M.**) and the new, desired molecule is called the **target molecule (**or **T.M.)**. Very often in a complicated synthesis of say an important drug molecule it is not immediately obvious what the starting material or starting materials are because there can be more than one possible way to synthesize the molecule. It is therefore the task of the organic chemist to figure out what starting materials to use. We call this process **retrosynthetic analysis**, since we work backward from the known target molecule to the unknown starting material(s) in a series of **BACKWARD** steps (hence the name "retro").

This is illustrated below for the synthesis of (R)-2-butanethiol from (S)-2-butanol. It is customary to write the target molecule on the left and the starting material on the right with a new kind of arrow, a **backward arrow**.

Retrosynthetic Analysis



(R)-2-butanethiol
Tareget Molecule (TM)

Intermediate

(S)--2-butanol
Starting Material (SM)

Note the special arrow. It is a backward arrow.

⇨ Backward arrow

→ Forward arrow

In order to carry out this reaction the forward direction, the needed starting material is (S)-2-butanol.

Forward Synthesis