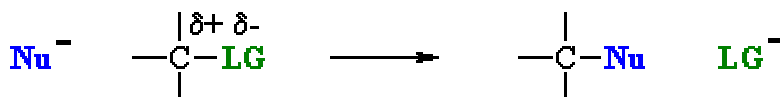


Nucleophilic Substitution and Elimination

What does the term "*nucleophilic substitution*" imply?

- A **nucleophile** is an the electron rich species that will react with an electron poor species
- A **substitution** implies that one group replaces another.

Nucleophilic substitution reactions occur when an electron rich species, the **nucleophile**, reacts at an electrophilic saturated C atom attached to an electronegative group (important), the **leaving group**, that can be displaced as shown by the general scheme:



The electrophilic C can be recognised by looking for the polar σ bond due to the presence of an electronegative substituent (esp. C-Cl, C-Br, C-I and C-O)

Nucleophilic substitution reactions are an important class of reactions that allow the interconversion of functional groups.

Of particular importance are the reactions of alkyl halides (**R-X**) and alcohols (**R-OH**)

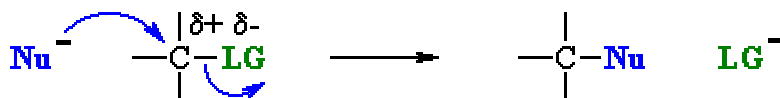
For alcohols, the range of substitution reactions possible can be increased by utilising the tosylates (**R-OTs**), an alternative method of converting the **-OH** to a better leaving group.

SN2 mechanism

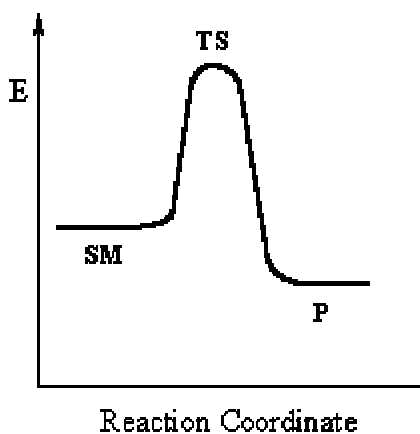
SN2 indicates a *substitution, nucleophilic, bimolecular* reaction, described by the expression rate = $k [\text{Nu}][\text{R-LG}]$.

This implies that the rate determining step involves an interaction between these two species, the nucleophile and the organic substrate.

This pathway is a concerted process (single step) as shown by the following reaction coordinate diagrams, where there is simultaneous attack of the nucleophile and displacement of the leaving group.



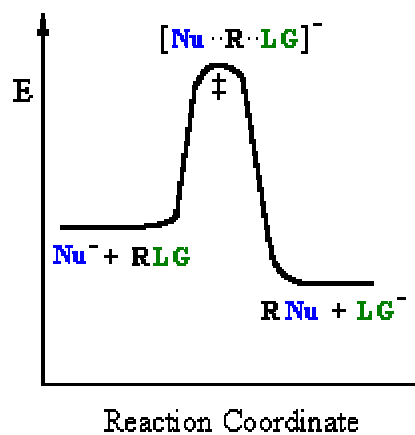
The nucleophile attacks at the carbon with the partial positive charge as a result of the polar σ bond to the electronegative atoms in the leaving group.



General case

Single step reactions have no intermediates and a single transition state (TS).

In an SN2 there is simultaneous formation of the carbon-nucleophile bond and breaking of the carbon-leaving group bond, hence the reaction proceeds via a TS in which the central C is partially bonded to five groups.



SN2 reaction

Let's look at how the various components of the reaction influence the reaction pathway:

R-

Reactivity order : $\text{CH}_3^- > \text{CH}_3\text{CH}_2^- > (\text{CH}_3)_2\text{CH}^- > (\text{CH}_3)_3\text{C}^-$

In an SN2 reaction, the transition state has 5 groups around the central C atom. As a consequence of the steric requirements at this center, less highly substituted systems (*i.e.* more smaller H groups) will favour an SN2 reaction by making it easier to achieve the transition state.



LG

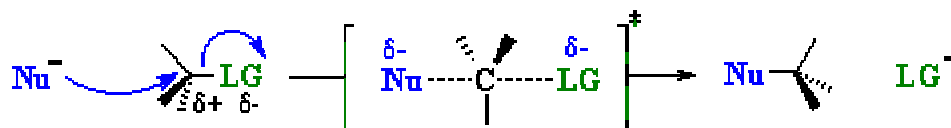
The C-LG bond is broken during the rate determining step so the rate does depend on the nature of the leaving group. However, if a leaving group is too good, then an SN1 reaction may result.

Nu

Since the nucleophile is involved in the rate determining step, the nature of the nucleophile is very important in an SN2 reaction. The more reactive the nucleophile, the more likely the reaction will be SN2 rather than SN1.

Stereochemistry

When the nucleophile attacks in an SN2 it is on the opposite side to the position of the leaving group. As a result, the reaction will proceed with an **inversion of configuration**.



Solvent

Polar aprotic solvents can be used to enhance the reactivity of the nucleophile and help promote an SN2 reaction.

Summary

This pathway is most common for systems with poorer leaving groups, 1° or 2° substrates and stronger nucleophiles.

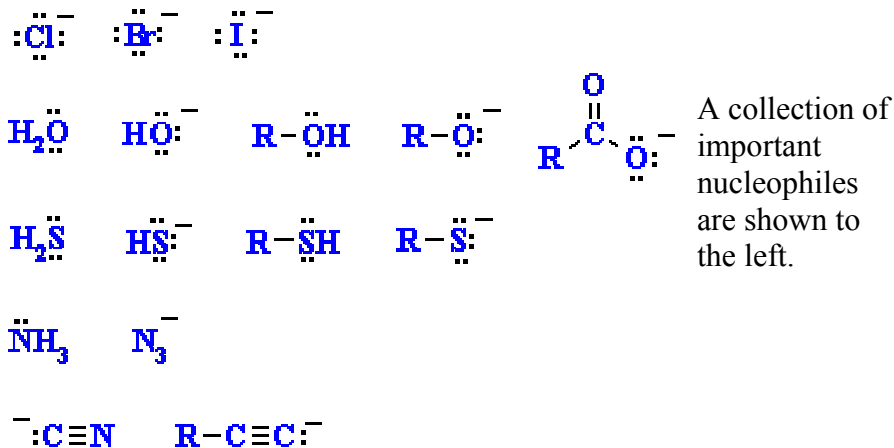
A typical example is the reaction of NaI with primary alkyl halides or tosylates.

Nucleophiles

Nucleophile means "*nucleus loving*" which describes the tendency of an electron rich species to be attracted to the positive nuclear charge of an electron poor species, the *electrophile*.

The **nucleophilicity** expresses the ability of the nucleophile to react in this fashion.

In general terms this can be appreciated by considering the availability of the electrons in the nucleophile. The more available the electrons, the more nucleophilic the system. Hence the first step should be to locate the nucleophilic center. At this point we will be considering Nu that contain lone pairs and may be anionic, however the high electron density of a C=C is also a nucleophile.



Nucleophilicity trends (compared with basicity)

1. Across a row in the periodic table nucleophilicity (lone pair donation) $C^- > N^- > O^- > F^-$ since increasing electronegativity decreases the lone pair availability. This is the **same order** as for basicity.
2. If one is comparing the same central atom, higher electron density will increase the nucleophilicity, *e.g.* an anion will be a better Nu (lone pair donor) than a neutral atom such as $HO^- > H_2O$. This is the **same order** as for basicity.
3. Within a group in the periodic table, increasing **polarisation** of the nucleophile as you go down a group enhances the ability to form the new C-X bond and increases the nucleophilicity, so $I^- > Br^- > Cl^- > F^-$. The electron density of larger atoms is more readily distorted *i.e.* polarised, since the electrons are further from the nucleus.
Note that is the **opposite order** to basicity (acidity increases down a group) where polarisability is much less important for bond formation to the very small proton.

Here is a table of relative nucleophilicities as measured in methanol (CH_3OH):

Very Good	I⁻, HS⁻, RS⁻
Good	Br⁻, HO⁻, RO⁻, NC⁻, N₃⁻
Fair	NH ₃ , Cl ⁻ , F ⁻ , RCO ₂ ⁻
Weak	H ₂ O, ROH
Very Weak	RCO ₂ H

Those nucleophiles that are **bold-faced** are particularly good since they are *weak* bases (no competing elimination reactions).

Leaving Groups

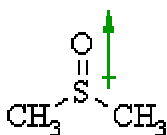
A **leaving group**, **LG**, is an atom (or a group of atoms) that is displaced as stable species taking with it the bonding electrons. Typically the leaving group is an anion (*e.g.* Cl^-) or a neutral molecule (*e.g.* H_2O). The better the leaving group, the more likely it is to depart. **A "good" leaving group can be recognized as being the conjugate base of a strong acid.** Here is a table classifying some common leaving groups that we will eventually meet.....

Excellent	TsO ⁻ , MsO ⁻ , NH ₃
Very Good	I ⁻ , H ₂ O
Good	Br ⁻
Fair	Cl ⁻
Poor	F ⁻
Very Poor	HO ⁻ , NH ₂ ⁻ , RO ⁻

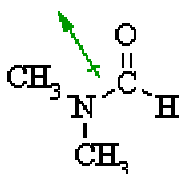
Solvent Effects

POLAR APROTIC SOLVENTS (*polar but no ability to be H-bond donor*)

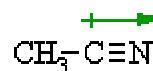
- have dipoles due to polar bonds
- **don't** have H atoms that can be donated into a H-bond
- examples are acetone, **acetonitrile**, **DMSO**, **DMF** (see below)
- anions **are not solvated** and are "**naked**" and reaction is not inhibited



dimethylsulfoxide



N,N-dimethylformamide

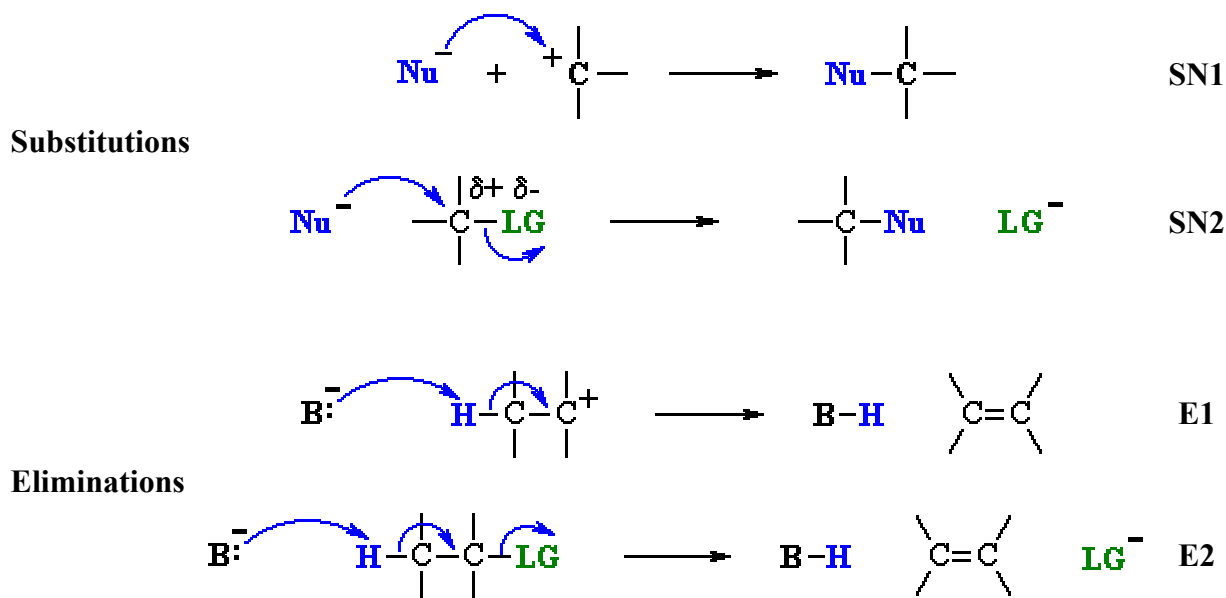


acetonitrile

Overall

- All nucleophiles will be *more reactive* in **aprotic** than **protic** solvents
- Those species that were most strongly solvated in **polar protic** solvents will "gain" the most reactivity in **polar aprotic** (*e.g.* F^-).
- **Polar aprotic solvents** are typically only used when a **polar protic solvent** gives poor results due to having a weak Nu, (*esp.* F^- , ^-CN , $^-RCO_2$)

Substitution versus Elimination



Substitution and elimination reactions are strongly influenced by many factors. Some of more important factors are outlined in the following table.

The significance of the effect is stated first, then the system that will favor the reaction is stated.

This should help you deal with the questions....

1. When does an anion function as a Nu: and when does it function as a Base?, and therefore,
2. When do I get substitution and when do I get elimination?

Reaction	Solvent	Nu or Base	Leaving Group	Substrate	Typical Conditions
SN1	Very Strong Polar solvents	Weak Good Nu and weak base	Strong Good LG	Strong 3° or resonance stabilised	AgNO ₃ / aq. EtOH
SN2	Strong Polar aprotic solvents	Strong Good Nu and weak base	Strong Good LG	Strong Methyl or 1°	NaI / Acetone
E1	Very Strong Polar solvents	Weak Weak base	Strong Good LG	Strong 3° or resonance stabilised	H ₂ SO ₄ , heat
E2	Strong Polar aprotic solvents	Strong Poor Nu and strong base	Strong Good LG	Strong 3°	KOH, heat,

