# Organic Reactions 1
## *Nucleophilic Substitution*

VANCOUVER
COMMUNITY
COLLEGE

There are four similar reactions that organic compounds can undergo: $S_N1$, $S_N2$, E1 and E2. This worksheet will cover the first two, the substitution reactions.

In both cases, one chemical group takes the place of another. One group is already part of an organic molecule. This group, because of its role in the reaction, is called the **leaving group**, and the remainder of the molecule is the **substrate**. The other group starts out as a negative ion. As such, it seeks out a positive charge, as you would find in a nucleus, and so it is called a **nucleophile**.

When discussing these kinds of reactions, you hear talk of "better nucleophiles" and "better leaving groups". It's worth remembering that when we discuss chemicals, it's usually in their role during the reaction, not their role after the reaction. One ion is a better nucleophile than another if it does a better job at taking its place in a larger molecule, for example, in an $S_N2$ reaction; one group makes a better leaving group than another if it does better as an independent anion, for example, in an $S_N1$ reaction.

## $S_N2$ REACTIONS: COLLISIONS

Nucleophilic substitution reactions (reactions in which one nucleophile replaces another) can happen in two ways. The easiest to imagine is the $S_N2$ reaction, which happens in a collision of two molecules like many reactions do. (That's what the "2" stands for: a bimolecular step is the main step.) A strong nucleophile, like an $OH^-$ ion approaches a substrate near a weaker nucleophile and takes over, ejecting the other group (the leaving group). How well this reaction goes depends on a number of factors.

● *Can the collision occur?* In this type of process, all the action happens at the carbon that the weaker nucleophile is bonded to, so if the incoming nucleophile can't get to it, the reaction's never going to happen. In a molecule where there are many other large structures bonded to that carbon, they're going to get in the way. In technical terms, there is **steric hindrance**. If the carbon is just methane, or it's a primary carbon (bonded to exactly one other carbon) there's lots of room and the $S_N2$ reaction is favoured. If it's a tertiary carbon (bonded to exactly three other carbons) there's so much steric hindrance, the $S_N2$ reaction is virtually impossible.

● *Is the incoming group a better nucleophile than what's already there?* It's not always the case that being a better nucleophile means being a worse leaving group and vice versa, but in $S_N2$ reactions it's helpful to think that way. If the nucleophile can't push out a leaving group, the reaction won't occur. Stronger nucleophiles (a) are electron rich, so the attraction to the nucleus of the carbon is stronger, (b) have lower electronegativity, so they can better polarize bonds during the reaction process, (c) are usually better bases, especially in solvents where there's no hydrogen bonding, and (d) are less massive, since bulky molecules have slower reaction rates.

*Authored by Darren Rigby*

If conditions are favourable, then the $S_N2$ reaction can proceed. The reaction occurs in one step (i.e. it's a **concerted** reaction). The nucleophile collides with the carbon and goes through a **transition state** where both the nucleophile and the leaving group are momentarily partially bonded to the carbon. This creates a sort of tipping point: the reaction might proceed, or the incoming nucleophile might get rejected. If the leaving group's bond dissociates, the configuration of the carbon has been reversed — an *R* carbon becomes an *S* and vice versa. If the substrates all have the same chirality before, then the chirality of the major product is very predictable.
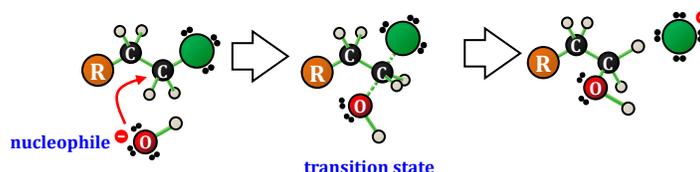
## $S_N1$ REACTIONS: DISSOCIATIONS

The other way the reaction can occur is in a two-step process in which the slow first step doesn't require any other molecule. (The "1" tells us the main step is unimolecular.) This step is a spontaneous dissociation — the leaving group just *leaves*, forming an anion and leaving the substrate as a **carbocation**, a carbon with a positive charge. The identity of the nucleophile is irrelevant because it bonds to the nucleophile in a later fast step. The conditions that make $S_N1$ reactions more likely include:

● *How strong is the leaving group?* If the leaving group isn't a stable ion on its own, it's unlikely to dissociate in the first place. Halides make very good leaving groups, especially those that are conjugate bases to the strong acids: $Cl^-$, $Br^-$, and $I^-$.

● *How stable is the carbocation?* In general, carbocations are under a lot of strain. (Had you heard of carbon making many ions before starting this unit? There's a reason….) A substrate can better handle that strain if there are other carbons around to help share the load, so, in perfect opposition to $S_N2$ reactions, tertiary carbons will have the easiest time sustaining a carbocation, and in primary carbons and methane derivatives, a carbocation would be too unstable to let the leaving group go.

If an $S_N1$ reaction has begun, there's a positively charged, unstable ion just waiting for a nucleophile to come along. While it's waiting, its molecular geometry is trigonal planar, which means there are two flat sections to the molecule where the nucleophile can come in. There's no special reason for the nucleophile to pick one side over the other, so it will happen randomly. If the two resulting compounds are enantiomers of each other, then each enantiomer will occur about 50% of the time, resulting in a **racemic mixture** of the two.
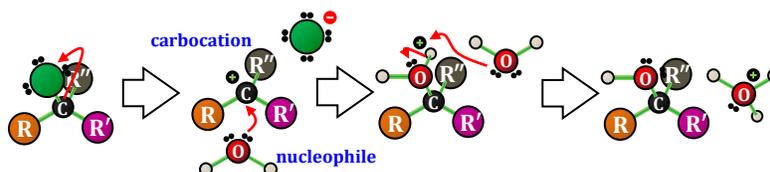
## SECONDARY CARBONS

If you've been reading carefully, you'll notice that nothing has been said about which reaction is favoured when the carbon with the leaving group is a secondary carbon (i.e., one with exactly two other carbons bonded to it). Secondary carbons can do either reaction, and frequently you get a little of each happening, though one might be somewhat favoured over the other. In practice, it's difficult to predict which one will occur in a given reaction.

## EXERCISES
A. Give the major product in the following $S_N2$ reactions (if an $S_N2$ reaction is possible).

1) $CH_3-C\ell$ + $HS^-$

2) $I-C(CH_3)_3$ + $H_2O$

3) + :C≡N⁻

4) + $NH_4^+$

5) + $OH^-$

6) + $Br^-$
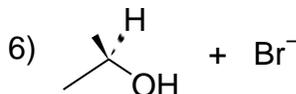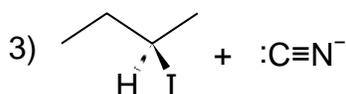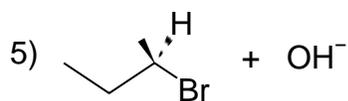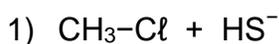
B. Give the major product(s) in the following $S_N1$ reactions (if an $S_N1$ reaction is possible).

1) $I-C(CH_3)_3$ + $NH_2^-$

2) + $CH_3O^-$

3) $CH_3(CH_2)_5CH_3$ + $OH^-$

4) + $OH^-$

5) + $OH^-$

6) + $Br^-$
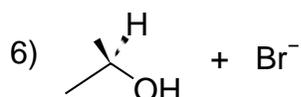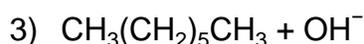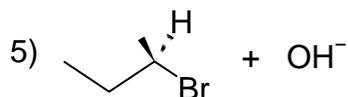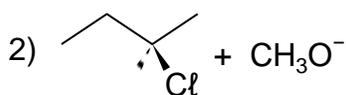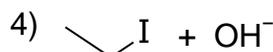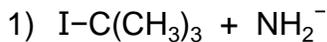
C. If the pK$_a$ of HR$_A$ is 2.6 and the pK$_a$ of HR$_B$ is 8.1, then would you consider R$_A^-$ or R$_B^-$ the better leaving group? Why?
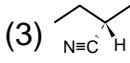
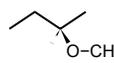D. If a sample of (S)-2-chloro-2-methylpropane were exposed to hydrochloric acid, how would you be able to tell?

**SOLUTIONS**

A:   (1) $CH_3SH$   (2) no reaction — steric hindrance   (3)  $_{N\equiv C}$ $_H$   (4) no reaction — terrible nucleophile   (5)  $^{OH}$ $_H$   (6) no reaction — nucleophile not strong enough; compare question A5

B:   (1) $C(CH_3)_3-NH_2$   (2)  $_{O-CH_3}$   (3) no reaction — no leaving group   (4) no reaction — carbocation will not form   (5)  $^{OH}$ $_H$ and  $^{HO}$ $_H$   (6) no reaction — poor leaving group

C:   A (conjugate) base is a better leaving group if it is more stable in its ion form, such as the conjugate base to a strong acid. $pK_a$ can be used as a measure of the strength of an acid. An acid is strong if it dissociates completely to products; the $K_a$ of a strong acid is a very large number. $pK_a = -\log (K_a)$, so the $pK_a$ of a strong acid is a negative number. Lower $pK_a$ values for acids go with more stable conjugate bases. Thus $R_A^-$ is more likely to be a better leaving group.

D:   The only possible leaving group in the sample is $C\ell^-$, but then it's being exposed to more $C\ell^-$ as the only possible nucleophile. This means that an $S_N2$ reaction cannot take place; the incoming $C\ell^-$ cannot be strong enough to make the chloro group leave. On the other hand, $S_N1$ reactions could take place. If the chloro group leaves spontaneously, and then a chloride ion attacks the substrate as a nucleophile, some of the resulting molecules will retain the (*S*) configuration the original sample had throughout, but about half the time the new molecule will have the (*R*) configuration. We will be able to tell that there was exposure to hydrochloric acid because the sample will be converted into a racemic mixture of the two configurations.