

Nucleophilic substitution at saturated carbon

17

Connections

Building on:

- Attack of nucleophiles on carbonyl groups **ch6, ch9, ch12, & ch14**
- Attack of nucleophiles on double bonds conjugated with carbonyl groups **ch10**
- Substitution at carbonyl groups **ch12**
- Substitution of the oxygen atom of carbonyl groups **ch14**
- Stereochemistry **ch16**
- Transition states, intermediates, and rate expressions **ch13**

Arriving at:

- Nucleophilic attack on *saturated* carbon atoms, leading to substitution reactions
- How substitution at a saturated carbon atom differs from substitution at C=O
- Two mechanisms of nucleophilic substitution
- Intermediates and transition states in substitution reactions
- How substitution reactions affect stereochemistry
- What sort of nucleophiles can substitute, and what sort of leaving groups can be substituted
- The sorts of molecules that can be made by substitution, and what they can be made from

Looking forward to:

- Elimination reactions **ch19**
- Substitution reactions with aromatic compounds as nucleophiles **ch22**
- Substitution reactions with enolates as nucleophiles **ch26**
- Retrosynthetic analysis **ch30**

Nucleophilic substitution

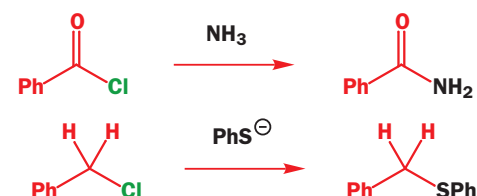
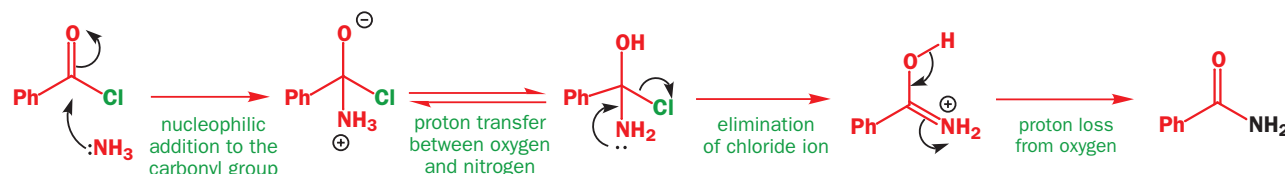
Substitution is the replacement of one group by another. In Chapter 12 we discussed nucleophilic substitution at the carbonyl group, this sort of thing.

The phenyl and carbonyl groups remain in the molecule but the Cl group is replaced by the NH₂ group. We called the molecule of ammonia (NH₃) the **nucleophile** and the chloride was called the **leaving group**. In this chapter we shall be looking at similar reactions at saturated carbon atoms, this sort of thing.

During this reaction, the methyl group remains the same and so does the CH₂ group, but the Cl group is replaced by the PhS group: it is a **substitution reaction**. The reaction happens at the CH₂ group—a *saturated* carbon atom—so the reaction is a **nucleophilic substitution at a saturated carbon atom**. This reaction and the one above may look superficially the same but they are quite different. We also changed the reagent for the substitution at a saturated carbon, because NH₃ would not give a good yield of MeCH₂NH₂ in the second type of reaction. The requirements for good reagents are different in substitution at the carbonyl group and at saturated carbon.

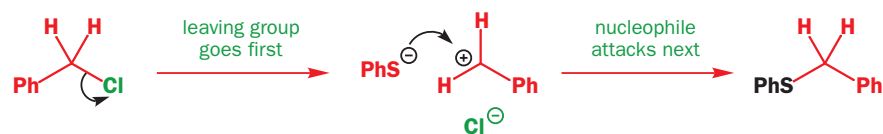
The main change is, of course, the absence of the carbonyl group. Mechanistically this is an enormous difference. The mechanism for the first reaction is:

mechanism of nucleophilic substitution at the carbonyl group

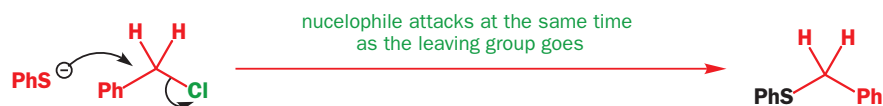


It is immediately obvious that the first step is no longer possible at a saturated carbon atom. The electrons cannot be added to a π bond as the CH_2 group is fully saturated. The nucleophile cannot add first and the leaving group go later because this would give a 5-valent carbon atom. Two new and different mechanisms become possible. Either the leaving group goes first and the nucleophile comes in later, or the two events happen at the same time. The first of these possibilities you will learn to call the $\text{S}_{\text{N}}1$ mechanism. The second mechanism, which shows that the only way the carbon atom can accept electrons is if it loses some at the same time, you will learn to call the $\text{S}_{\text{N}}2$ mechanism. You will see later that both mechanisms are possible here.

the $\text{S}_{\text{N}}1$ mechanism



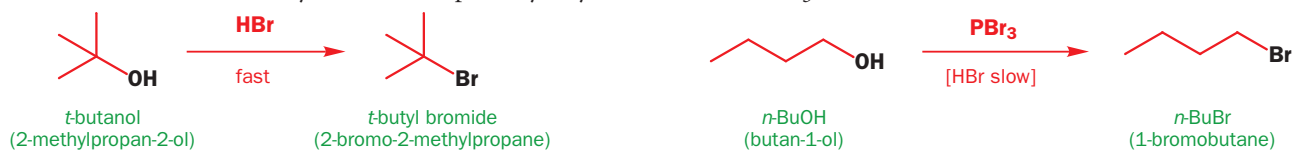
the $\text{S}_{\text{N}}2$ mechanism



We shall spend some time looking at the differences between these mechanisms. But first we must establish how we know that there are two mechanisms.

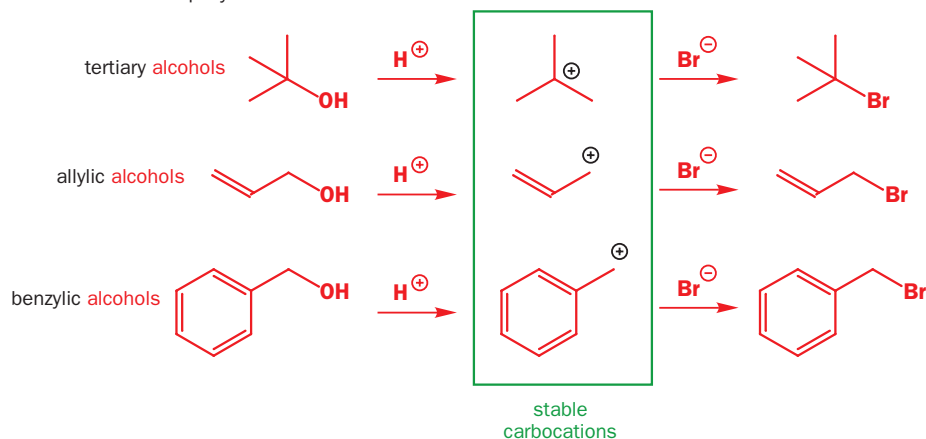
If we look at a commonly used nucleophilic substitution, the replacement of OH by Br, we find that two quite different reaction conditions are used. Tertiary alcohols react rapidly with HBr to give tertiary alkyl bromides. Primary alcohols, on the other hand, react only very slowly with HBr and are usually converted to primary alkyl bromides with PBr_3 .

The mechanism of the PBr_3 reaction will be discussed when we come to $\text{S}_{\text{N}}2$ reactions later in this chapter.



If we collect together those alcohols that react rapidly with HBr to give good yields of alkyl bromides, we find one thing in common: they can all form stable carbocations, that is, cations where the positive charge is on the carbon atom.

alcohols that react rapidly with HBr



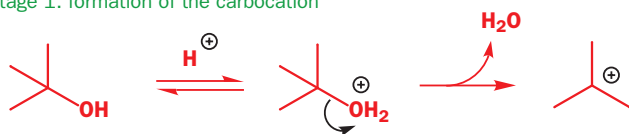
Carbocation stability

These carbocations are *relatively* stable as far as carbocations go. But you would not be able to keep even these 'stable' carbocations in a bottle on the shelf. The concept of more and less stable carbocations is important in understanding the $\text{S}_{\text{N}}1$ reaction.

They *can* form carbocations, but *do* they? It is one thing to suggest the existence of a reactive intermediate, another to prove that it is formed. We shall spend some time showing that carbocations do really exist in solution and more time showing that they are indeed intermediates in this mechanism for substitution that you will learn to call the $\text{S}_{\text{N}}1$ mechanism.

the S_N1 mechanism for nucleophilic substitution at saturated carbon

stage 1: formation of the carbocation



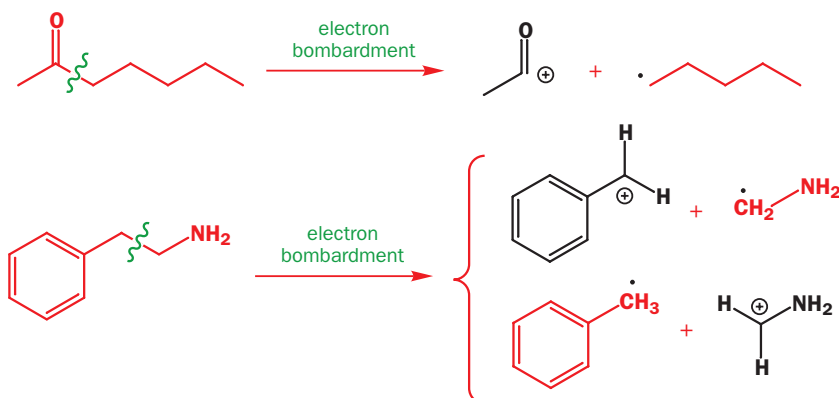
stage 2: capture of the carbocation by the nucleophile



Structure and stability of carbocations

We shall break off this mechanistic discussion to establish the nature of carbocations as ions that can be isolated and as intermediates in substitution reactions. We have seen in Chapter 3 that cations can easily be made in the gas phase by electron bombardment. We met these cations among others.

carbocations formed in the mass spectrometer

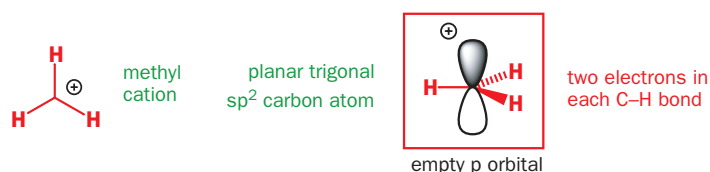
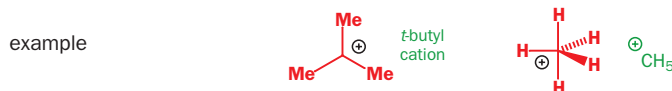


We also met the unusual cation CH_5^+ . This cation shares *eight* electrons among five bonds and has a full outer shell like that of the ammonium ion NH_4^+ . We call CH_5^+ a **carbonium** ion. The three ions formed in the mass spectrometer have only *three* bonds to the positively charged centre, only *six* electrons in the outer shell, and are electron-deficient. We call these ions **carbenium** ions and we may call both types **carbocations**. Table 17.1 gives a summary of the two types of carbocations.

It is the carbenium ions that interest us in this chapter because they are the intermediates in some nucleophilic substitutions. The simplest possible carbenium ion would be CH_3^+ , the methyl cation, and it would be planar with an empty p orbital.

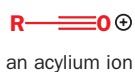
Table 17.1 Carbocations: carbenium ions and carbonium ions

Property	Carbenium ions	Carbonium ions
number of bonds to C^+	3	5
electrons in outer shell	6	8
empty orbital?	yes, a p orbital	no
electron-deficient?	yes	no

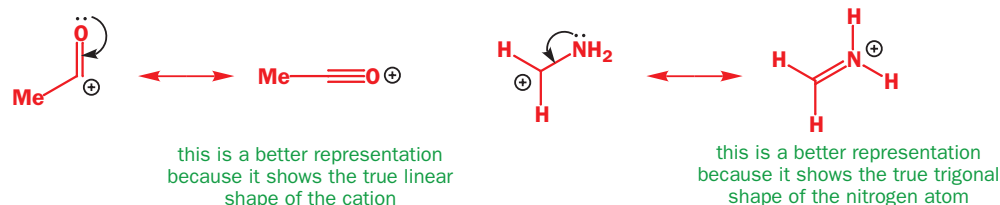


Carbocation stability

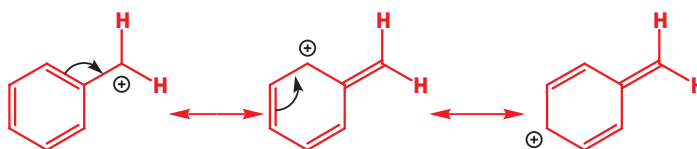
Avoid any controversy by calling all cations where the charge is on a carbon atom *carbocations*.



We did not meet this cation when we were discussing mass spectra, but we did meet the three ions on p. 000. The methyl cation is so unstable that it is rarely formed even in the gas phase. Each of these three ions are formed because they have extra stabilization of some sort. The first is an acylium ion which is actually linear with most of the positive charge on the oxygen atom. It is more an oxonium ion than a carbocation. The third ion also has the positive charge carried by a heteroatom—this time it is nitrogen and the cation is more stable. It is much better to have a positive charge on nitrogen than on carbon. Notice that in both of the ‘preferred representations’ no atom is electron-deficient: all of the C, N, and O atoms have eight electrons.



The second ion has no heteroatom but it has a benzene ring and the positive charge is delocalized around the ring, especially into the 2- and the 4- positions.



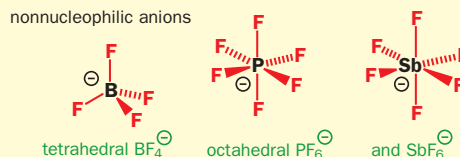
Thus, none of these three ions is a simple carbenium ion with the charge localized on an electron-deficient carbon atom. Most stable carbocations have extra stabilization of this sort. But even these relatively stable cations cannot be detected in normal solutions by NMR. This is because they are so reactive that they combine with even weak nucleophiles like water or chloride ions. Yet due to Olah's discovery of superacid (also called ‘magic acid’) in the 1960s we know that carbocations can exist in solution (you can read about this in the box). But are they formed as intermediates in substitution reactions?

George Olah was born in Hungary in 1927 but emigrated to the USA and did most of his work at Case Western Reserve University in Ohio. He got the Nobel prize for his work on cations in 1994. He now works at the University of Southern California.

Stable carbocations in superacid media

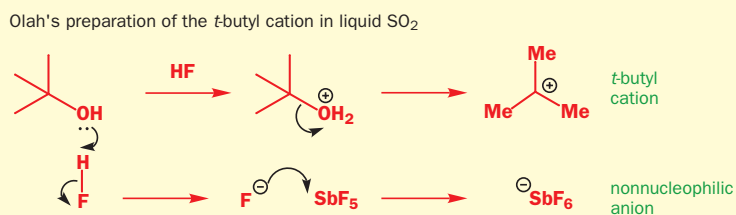
Olah's idea was to have a solution containing no nucleophiles. This sounds a bit tricky as any cation must have an anion to balance the charge and surely the anion will be a nucleophile? Well, nearly all anions are nucleophiles but there are some that

consist of a negatively charged atom surrounded by tightly held halogen atoms. Examples include BF_4^- , PF_6^- , and SbF_6^- . The first is small and tetrahedral and the others are larger and octahedral.



In these anions, the fluorine atoms are very tightly held around the central atom, which carries the formal negative charge. The negative charge does not correspond to a lone pair of electrons (cf. the role of NaBH_4 in carbonyl reductions) and so there is nothing to act as a nucleophile. It was important too to have a nonnucleophilic solvent and low temperatures, and liquid SO_2 at -70°C proved ideal.

With these conditions, Olah was able to make carbocations from alcohols. He treated *t*-butanol with SbF_5 and HF in liquid SO_2 . This is the reaction.



The proton NMR of this cation showed just one signal for the three methyl groups at 4.15 p.p.m., quite far downfield for C–Me groups. The ^{13}C spectrum also showed downfield Me groups at 47.5 p.p.m., but the key evidence was the shift of the central carbon atom, which came at an amazing 320.6 p.p.m., way downfield from anything we have met before. This carbon is very deshielded—it is positively charged and electron-deficient.

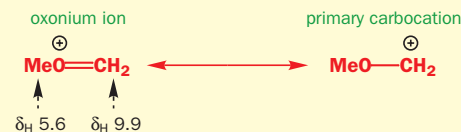
Carbocations do exist in solution! Under these conditions acylium ions were also stable and their IR spectra could be run. Even crystals could be prepared so that no doubt remains that these are oxonium ions: both the bond length and the CO stretch are more triple-bond-like than carbon monoxide (see Table 17.2).

Table 17.2 Does the acylium ion have a triple bond?

	acylium ion $\text{Me}-\text{C}\equiv\text{O}^{\oplus}$	carbon monoxide $\ominus\text{C}\equiv\text{O}^{\oplus}$
$\nu_{\text{CO}}, \text{cm}^{-1}$	2294	2170
CO bond length, Å	1.108	1.128

More important data were NMR spectra: both ^1H and ^{13}C NMRs could be run in liquid SO_2 at -70°C . The proton NMR of the MeOCH_2^+ cation showed a methyl group with a large downfield shift and a CH_2 group that resembled an electron-deficient alkene

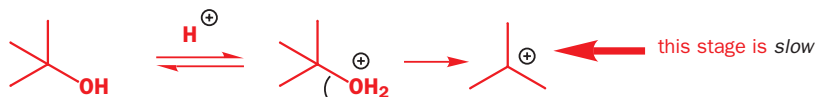
rather than a saturated carbon atom. The cation is delocalized but the oxonium ion representation is better.



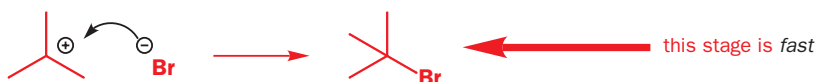
If we mix *t*-BuOH and HBr in an NMR tube and let the reaction run inside the NMR machine, we see no signals belonging to the cation. This proves nothing. We would not expect a reactive intermediate to be present in any significant concentration. There is a simple reason for this. If the cation is unstable, it will react very quickly with any nucleophile around and there will never be any appreciable amount of cation in solution. Its rate of formation will be less, much less, than its rate of reaction. We need only annotate the mechanism you have already seen.

the S_N1 mechanism for nucleophilic substitution at saturated carbon

stage 1: formation of the carbocation



stage 2: capture of the carbocation by the nucleophile

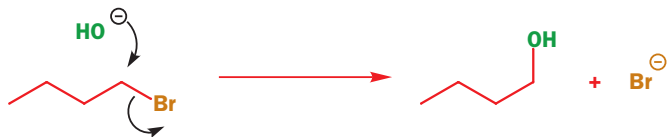


It is comforting that carbocations can be prepared, even under rather artificial conditions, but we shall need other kinds of evidence to convince ourselves that they are intermediates in substitution reactions. It is time to return to the mechanistic discussion.

The S_N1 and S_N2 mechanisms for nucleophilic substitution

The evidence that convinced chemists about these two mechanisms is kinetic: it relates to the rate of the reactions. It was discovered, chiefly by Hughes and Ingold in the 1930s, that some nucleophilic substitutions are first-order, that is, the rate depends only on the concentration of the alkyl halide and *does not depend on the concentration of the nucleophile*, while in other reactions the rate depends on the concentrations of *both* the alkyl halide and the nucleophile. How can we explain this result? In the S_N2 mechanism there is just one step.

the S_N2 mechanism: reaction of *n*-BuBr with hydroxide ion



This step must therefore be the **rate-determining step**, sometimes called the slow step. The rate of the overall reaction depends only on the rate of this step. Kinetic theory tells us that the rate of a reaction is proportional to the concentrations of the reacting species such that

$$\text{rate of reaction} = k[n\text{-BuBr}][\text{HO}^-]$$

Quantities in square brackets represent concentrations and the proportionality constant *k* is called the rate constant. If this mechanism is right, then the rate of the reaction will be simply and linearly proportional to both [*n*-BuBr] and to [HO⁻]. And it is. Ingold measured the rates of reactions like these and found that they were second-order (proportional to two concentrations) and he called this mechanism Substitution, Nucleophilic, 2nd Order or S_N2 for short. The rate equation is usually given like this, with *k*₂ representing the second-order rate constant.

$$\text{rate} = k_2[n\text{-BuBr}][\text{HO}^-]$$

Usefulness and significance of the rate expression

Now what use is this equation and what does it signify? It is useful because it gives us a test for the S_N2 mechanism. It is usually carried out by varying both the concentration of the nucleophile and the concentration of the carbon electrophile in two separate series of experiments. The results of these experiments would be plotted on two graphs, one for each series. Supposing we wished to see if

Edward David Hughes (1906–63) and Sir Christopher Ingold (1893–1970) worked at University College, London in the 1930s. They first thought of many of the mechanistic ideas that we now take for granted.

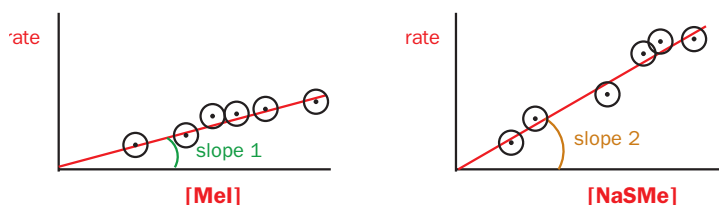
There is more about the relationship between reaction rates and mechanisms in Chapter 13.

Please note how this symbol is written. The S and the N are both capitals and the 2 is a subscript.

the reaction between NaSMe (an ionic solid—the nucleophile will be the anion MeS^-) and MeI were indeed $\text{S}_{\text{N}}2$ as we would expect.



First, we would keep the concentration of NaSMe constant and vary that of MeI and see what happened to the rate. Then we would keep the concentration of MeI constant and vary that of MeSNa and see what happened to the rate. If the reaction is indeed $\text{S}_{\text{N}}2$ we should get a linear relationship in both cases.



Each point on the slope represents a different experiment in which the rate of reaction is measured at a certain concentration of each of the reagents. All the points on the left-hand graph are measured with the concentration of NaSMe the same, but with different concentrations of MeI. On the right-hand graph, the points are measured with the concentration of MeI the same, but with different concentrations of NaSMe.

The first graph tells us that the rate is proportional to $[\text{MeI}]$, that is, $\text{rate} = k_a[\text{MeI}]$ and the second graph that it is proportional to $[\text{MeSNa}]$, that is, $\text{rate} = k_b[\text{MeSNa}]$. But why are the slopes different? If you look at the rate equation for the reaction, you will see that we have incorporated a constant concentration of one of the reagents into what appears to be the rate constant for the reaction. The true rate equation is

$$\text{rate} = k_2[\text{MeSNa}][\text{MeI}]$$

If $[\text{MeSNa}]$ is constant, the equation becomes

$$\text{rate} = k_a[\text{MeI}] \text{ where } k_a = k_2[\text{MeSNa}]$$

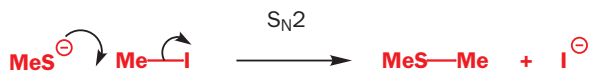
If $[\text{MeI}]$ is constant, the equation becomes

$$\text{rate} = k_b[\text{MeSNa}] \text{ where } k_b = k_2[\text{MeI}]$$

If you examine the graphs you will see that the slopes are different because

$$\text{slope 1} = k_a = k_2[\text{MeSNa}], \text{ but slope 2} = k_b = k_2[\text{MeI}]$$

We can easily measure the true rate constant k_2 from these slopes because we know the constant values for $[\text{MeSNa}]$ in the first experiment and for $[\text{MeI}]$ in the second. The value of k_2 from both experiments should be the same! The mechanism for this reaction is indeed $\text{S}_{\text{N}}2$: the nucleophile MeS^- attacks as the leaving group I^- leaves.



So the usefulness of the rate equation is that it gives us a test for the $\text{S}_{\text{N}}2$ mechanism. But the equation has a meaning beyond that test.

Significance of the $\text{S}_{\text{N}}2$ rate equation

The significance of the equation is that performance of the $\text{S}_{\text{N}}2$ reaction depends both on nucleophile and on the carbon electrophile. We can make a reaction go better by changing either. If we want to displace I^- from MeI by an oxygen nucleophile we might consider using any of those in Table 17.3.

Table 17.3 Oxygen nucleophiles in the $\text{S}_{\text{N}}2$ reaction

Oxygen nucleophile	$\text{p}K_a$ of conjugate acid ^a	Rate in $\text{S}_{\text{N}}2$ reaction
HO^-	15.7 (H_2O)	fast
RCO_2^-	about 5 (RCO_2H)	reasonable
H_2O	-1.7 (H_3O^+)	slow
RSO_2O^-	0 (RSO_2OH)	slow

^a See Chapter 8 for discussion of $\text{p}K_a$ values.

The same reasons that made hydroxide ion basic (chiefly that it is unstable as an anion and therefore reactive!) make it a good nucleophile. Basicity is just nucleophilicity towards a proton and nucleophilicity towards carbon must be related. You saw in Chapter 12 that nucleophilicity towards the carbonyl group is directly related to basicity. The same is not quite so true for nucleophilic attack on the saturated carbon atom as we shall see, but there is a relationship nonetheless. So if we want a fast reaction, we should use NaOH rather than, say, Na₂SO₄ to provide the nucleophile.

But that is not our only option. The reactivity and hence the structure of the carbon electrophile matter too. If we want reaction at a methyl group we can't change the carbon skeleton, but we can change the leaving group. Table 17.4 shows what happens if we use the various methyl halides in reaction with NaOH.

Thus the fastest reaction will be between MeI and NaOH and will give methanol.



We shall discuss nucleophilicity and leaving group ability in more detail later. For the moment, the most important aspect is that the rate of an S_N2 reaction depends on both the nucleophile and the carbon electrophile (and hence the leaving group). Changing the nucleophile or the electrophile changes the value of k_2 .

● The rate of an S_N2 reaction depends upon:

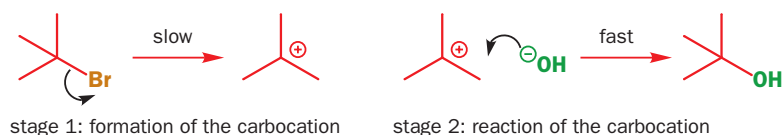
- The nucleophile
- The carbon skeleton
- The leaving group

It also depends, as do all reactions, on factors like temperature and solvent.

Kinetics for the S_N1 reaction

We shall start with a similar reaction to the S_N2 reaction discussed a few pages back, but we shall replace *n*-butyl bromide with tertiary butyl bromide (*t*-BuBr).

the S_N1 mechanism: reaction of *t*-BuBr with hydroxide ion



The formation of the cation is the rate-determining step. You can look at this in two ways. Either you could argue that a cation is an unstable species and so it will be formed slowly from a stable neutral organic molecule, or you could argue that the cation is a very reactive species and so all its reactions will be fast, regardless of the nucleophile. Both arguments are correct. In a reaction with an unstable intermediate, the formation of that intermediate is usually the rate-determining step.

The rate of disappearance of *t*-BuBr is simply the rate of the slow step. This is why the slow step is called the 'rate-determining' step. It is a unimolecular reaction with the simple rate equation

$$\text{rate} = k_1[t\text{-BuBr}]$$

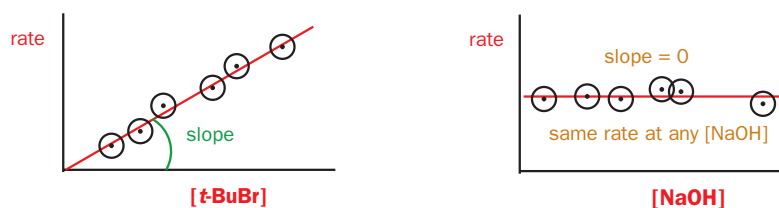
If this is not obvious to you, think of a crowd of people trying to leave a railway station (such as a metro or underground station in a city) through the turnstiles. It doesn't matter how fast they walk away afterwards, it is only the rate of struggling through the turnstiles that determines how fast they leave the station.

Once again, this rate equation is useful because we can determine whether a reaction is S_N1 or S_N2. We can plot the same graphs as we plotted before. If the reaction is S_N2, the graphs look like

Table 17.4 Halide leaving groups in the S_N2 reaction

Halide X in MeX	pK _a of conjugate acid HX	Rate of reaction with NaOH
F	+3	very slow indeed
Cl	-7	moderate
Br	-9	fast
I	-10	very fast

those we have just seen. But if it is S_N1 , they look like this when we vary $[t\text{-BuBr}]$ at constant $[\text{NaOH}]$ and then vary $[\text{NaOH}]$ at constant $[t\text{-BuBr}]$.



The slope of the first graph is simply the first-order rate constant because

$$\text{rate} = k_1[t\text{-BuBr}]$$

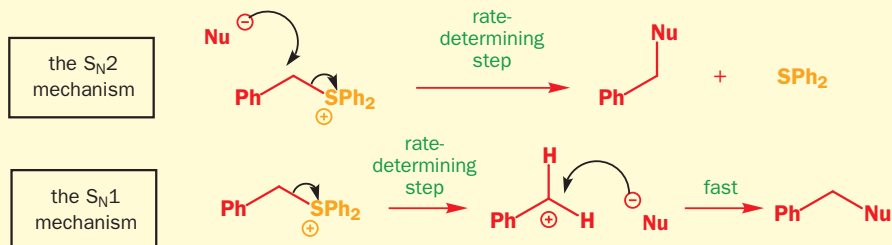
But the slope of the second graph is zero! The rate-determining step does not involve NaOH so adding more of it does not speed up the reaction. The reaction shows first-order kinetics (the rate is proportional to one concentration only) and the mechanism is called S_N1 , that is, Substitution, Nucleophilic, 1st order.

This observation is very significant. It is not only the *concentration* of the nucleophile that doesn't matter—its *reactivity* doesn't matter either! We are wasting our time adding NaOH to this reaction—water will do just as well. All the oxygen nucleophiles in Table 17.3 react at the *same* rate with $t\text{-BuBr}$ though they react at very different rates with MeI.

Stereoisomers and constitutional isomers

We can see the changeover from S_N1 to S_N2 in the reactions of a single compound if we choose one that is

good at both mechanisms, such as a benzyl sulfonium salt. Both mechanisms are available for this compound.



Weak nucleophiles react by the S_N1 mechanism while strong ones react by S_N2 . We can tell which is which simply by looking at the rates of the reactions (see Table 17.5).

The first three nucleophiles react at the same rate within experimental error while the last two are clearly faster. The first three nucleophiles react at the same rate because they react by the S_N1 mechanism whose rate does not depend on the nucleophile. All the nucleophiles in fact react by S_N1 at the same rate (about $4.0 \times 10^{-5} \text{ s}^{-1}$) but good nucleophiles also react by S_N2 . The S_N2 rate for hydroxide is about 70 and for PhS^- about 107. Compare these relative rates with those in Table 17.6 for reactions with MeBr where they all react at different rates by the S_N2 reaction.

Table 17.5 Rate of reaction ($10^5 k, \text{ s}^{-1}$) of nucleophiles with $\text{PhCH}_2\text{S}^+\text{Ph}_2$

Nucleophile	AcO^-	Cl^-	PhO^-	HO^-	PhS^-
rate	3.9	4.0	3.8	74	107

Table 17.6 Relative rate of reaction (water = 1) of nucleophiles with MeBr





Nucleophile	AcO^-	Cl^-	PhO^-	HO^-	PhS^-
rate	900	1100	2000	1.2×10^4	5×10^7

How can we decide which mechanism (S_N1 or S_N2) will apply to a given organic compound?

The most important factor is the structure of the carbon skeleton. A helpful generalization is that compounds that can form relatively stable cations generally do so and react by the S_N1 mechanism while the others have to react by the S_N2 mechanism.

In fact, the structural factors that make cations unstable also lead to faster S_N2 reactions. Cations are more stable if they are heavily substituted, that is, tertiary, but this is bad for an S_N2 reaction because the nucleophile would have to thread its way into the carbon atom through the alkyl groups. It is better for an S_N2 reaction if there are only small hydrogen atoms on the carbon atom—methyl groups react fastest by the S_N2 mechanism. The effects of the simplest structural variations are summarized in Table 17.7 (where R is a simple alkyl group like methyl or ethyl).

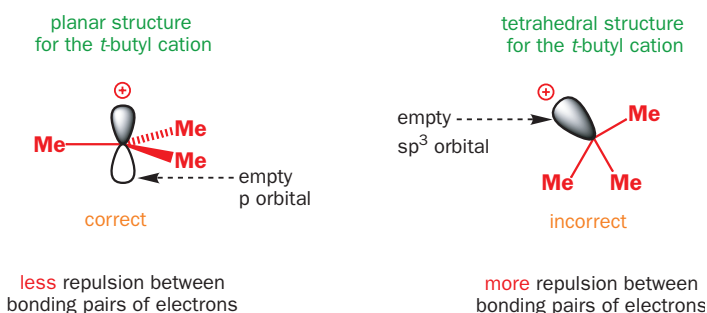
Table 17.7 Simple structures and choice of S_N1 or S_N2 mechanism

structure				
type	methyl	primary	secondary	tertiary
S_N1 reaction?	no	no	yes	good
S_N2 reaction?	good	good	yes	no

The only doubtful case is the secondary alkyl derivative, which can react by either mechanism, though it is not very good at either. The first question you should ask when faced with a new nucleophilic substitution is: ‘Is the carbon electrophile methyl, primary, secondary, or tertiary?’ This will start you off on the right foot, which is why we introduced these important structural terms in Chapter 2.

Stability and structure of tertiary carbocations

So why are tertiary cations relatively stable whereas the methyl cation is never formed in solution? Any charged organic intermediate is inherently unstable because of the charge. A carbocation can be formed only if it has some extra stabilization. The *t*-butyl cation that we met earlier in this chapter is planar. Indeed it is a universal characteristic of carbocations that they are planar. The basic instability of the carbocation comes from its electron deficiency—it has an empty orbital. The energy of the unfilled orbital is irrelevant to the overall stability of the cation—it’s only the energy of the orbitals with electrons in that matter. For any cation the most stable arrangement of electrons in orbitals results from making filled orbitals as low in energy as possible to give the most stable structure, leaving the highest-energy orbital empty. Thus, of the two structures for the *t*-butyl cation, the planar one has the lower-energy filled orbitals (sp^2) and a higher-energy empty p orbital while the tetrahedral one has higher-energy filled orbitals (sp^3) and a lower-energy empty sp^3 orbital.



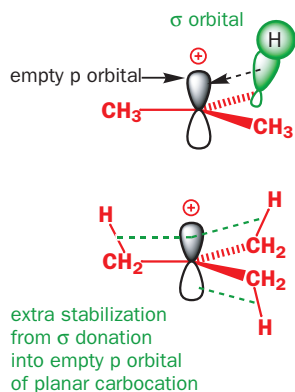
The diagram shows another reason why the planar structure is more stable than the tetrahedral structure for a carbocation. It is better for the filled orbitals to be:

- of the lowest possible energy (so that they contribute most to stability)
- as far from each other as possible (so that they repel each other as little as possible)

Both requirements are fulfilled in the planar structure for the carbocation.

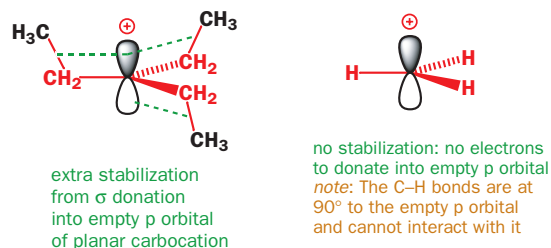
Stabilization of tertiary carbocations by C–H or C–C bonds

Extra stabilization comes to the planar structure from weak donation of σ bond electrons into the empty p orbital of the cation. Three of these donations occur at any one time in the *t*-butyl cation. It



doesn't matter if the C–H bonds point up or down; one C–H bond on each methyl group must be parallel to one lobe of the empty p orbital at any one time. The top diagram shows one overlap in orbital terms and the bottom diagram three as dotted lines.

There is nothing special about the C–H bond in donating electrons into an empty orbital. A C–C bond is just as good and some bonds are much better (C–Si). But there must be a bond of some sort—a hydrogen atom by itself has no lone pairs and no σ bonds so it cannot stabilize a cation.



If a tertiary cation cannot become planar, it is not formed. A classic case is the cage halide below, which does not react with nucleophiles either by S_N1 or by S_N2 . It does not react by S_N1 because the cation cannot become planar nor by S_N2 because the nucleophile cannot approach the carbon atom from the right direction (see below).



In almost all cases, tertiary alkyl halides react rapidly with nucleophiles by the S_N1 mechanism. The nature of the nucleophile is not important: it does not affect the rate and carbocations are reactive enough to combine with even quite weak nucleophiles.

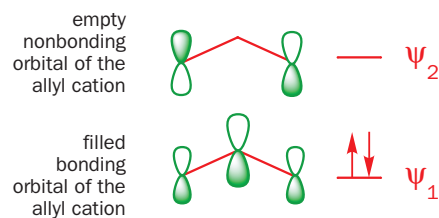
Allylic and benzylic cations

More effective stabilization is provided by genuine conjugation with π or lone-pair electrons. The allyl cation has a filled (bonding) orbital containing two electrons delocalized over all three atoms and an important empty orbital with coefficients on the end atoms only. It's this orbital that is attacked by nucleophiles and so it's the end carbon atoms that are attacked by nucleophiles. The normal curly arrow picture tells us the same thing.

the allyl cation
curly arrows



molecular orbitals



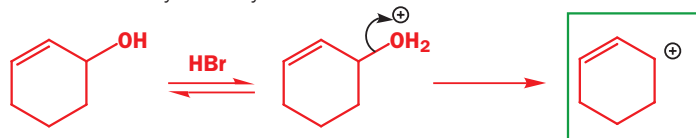
A symmetrical allyl cation can give one product only by the S_N1 reaction. We have already discussed the formation of the cyclohexenyl cation (Chapter 7) and that is a good example. The two delocalized structures are identical and the π bond is shared equally among the three atoms.

the cyclohexenyl cation

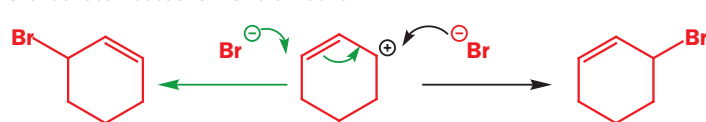


Treatment of cyclohexenol with HBr gives the corresponding allylic bromide. Only one compound is formed because attack at either end of the allylic cation gives the same product.

formation of the cyclohexenyl cation



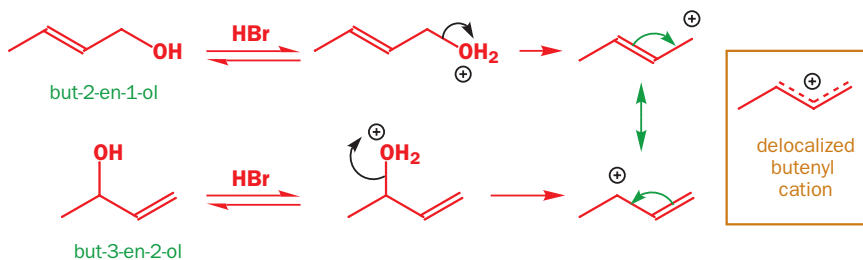
two identical reactions with bromide ion



▶ Many textbooks say that alkyl groups are fundamentally electron-donating and thus stabilize cations. This statement does contain some truth but it is important to understand the way in which they really donate electrons—weakly by σ conjugation into empty p orbitals.

■ We discussed conjugation in allyl cations in Chapter 7.

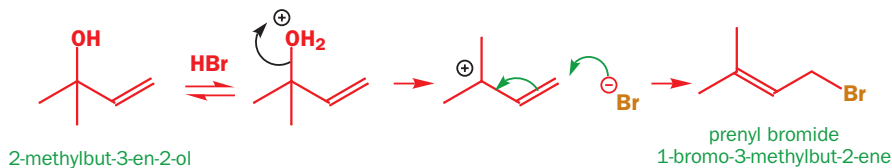
Sometimes when the allylic cation is unsymmetrical this can be a nuisance as a mixture of products may be formed. It doesn't matter which of the two butenols you treat with HBr; you get the same cation.



When this cation reacts with Br^- , about 80% goes to one end and 20% to the other, giving a mixture of butenyl bromides. Notice that we have chosen one localized structure for our mechanisms. The choice is meaningless since the other structure would have done as well. It's just rather too difficult to draw mechanisms on the delocalized structure.

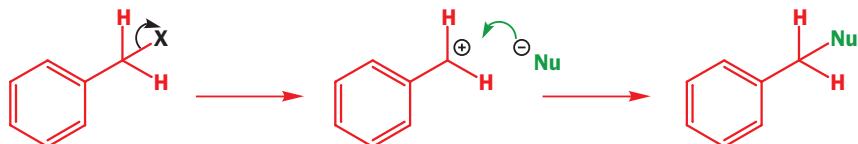


Sometimes this ambiguity is useful. The tertiary allylic alcohol 2-methylbut-3-en-2-ol is easy to prepare and reacts well by the S_N1 mechanism because it is both tertiary and allylic. The allylic carbocation intermediate is very unsymmetrical and reacts only at the less substituted end to give 'prenyl bromide'.



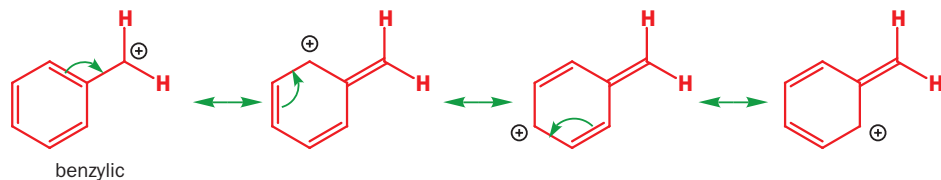
The benzyl cation is about as stable as the allyl cation but lacks its ambiguity of reaction. Though the positive charge is delocalized around the benzene ring, the benzyl cation almost always reacts on the side chain.

formation and reaction of the benzyl cation



If you draw the arrows for the delocalization, you will see that the positive charge is spread right round the ring, to three positions in particular.

delocalization in the benzyl cation

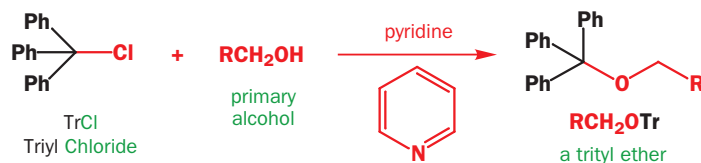


An exceptionally stable cation is formed when three benzene rings can help to stabilize the same positive charge. The result is the triphenylmethyl cation or, for short, the trityl cation. The symbol Tr (another of these 'organic elements') refers to the group Ph_3C . Trityl chloride is used to form an ether with a primary alcohol group by an S_N1 reaction. Here is the reaction.

▶ The **regioselectivity** (where the nucleophile attacks) is determined by steric hindrance: attack is faster at the less hindered end of the allylic system.

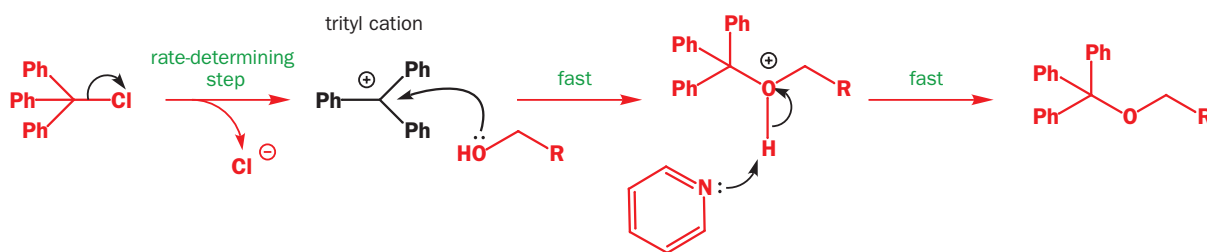
■ Prenyl bromide is a building block for making the class of natural products known as terpenes and discussed in Chapter 49. We come back to reactions of allylic compounds in Chapter 23.

■ This sort of delocalization will be given special importance in Chapter 22



You will notice that pyridine is used as solvent for the reaction. Pyridine (a weak base, pK_a 5.5; see Chapter 8) is not strong enough to remove the proton from the primary alcohol (pK_a about 15), and there would be no point in using a base strong enough to make RCH_2O^- as the neutral alcohol is as good in an $\text{S}_{\text{N}}1$ reaction. Instead the TrCl ionizes first to trityl cation, which now captures the primary alcohol and finally pyridine is able to remove the proton from the oxonium ion. Pyridine does not catalyse the reaction; it just stops it becoming too acidic by removing the HCl formed. Pyridine is also a convenient polar organic solvent for ionic reactions.

$\text{S}_{\text{N}}1$ formation of trityl ethers:



Rate data for substituted allylic chlorides compared with benzylic chlorides and simple alkyl chlorides on solvolysis in 50% aqueous ethanol give us some idea of the magnitude of stabilization (Table 17.8). These rates are mostly $\text{S}_{\text{N}}1$, but there will be some $\text{S}_{\text{N}}2$ creeping in with the primary compounds. Note the wide range of rates.

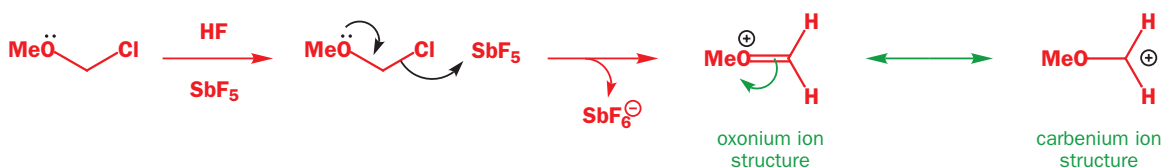
■ A **solvolysis reaction** is a reaction in which the solvent is also the nucleophile.

Table 17.8 Rates of solvolysis of alkyl chlorides in 50% aqueous ethanol at 44.6 °C

Compound	Relative rate	Comments
	0.07	primary chloride: probably all $\text{S}_{\text{N}}2$
	0.12	secondary chloride: can do $\text{S}_{\text{N}}1$ but not very well
	2 100	tertiary chloride: very good at $\text{S}_{\text{N}}1$
	1.0	primary but allylic: $\text{S}_{\text{N}}1$ all right
	91	allylic cation is secondary at one end
	130 000	allylic cation is tertiary at one end: compare with 2100 for simple tertiary
	7 700	primary but allylic and benzylic

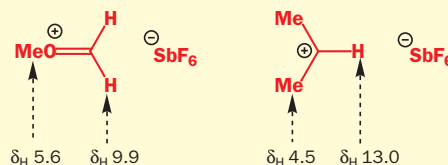
One type of carbocation remains to be discussed, the type with an electron-donating group on the same atom as the leaving group. A classic case is MeOCH_2Cl , which loses chloride ion in polar solvents and which can be converted in good yield (89%) to a stable cation using Olah's methods described on p. 000. Even though it is primary (so you might expect $\text{S}_{\text{N}}2$), substitution reactions of

this chloroether, 'methoxymethyl chloride' (or 'MOM chloride') follow the S_N1 mechanism and go via this cation.



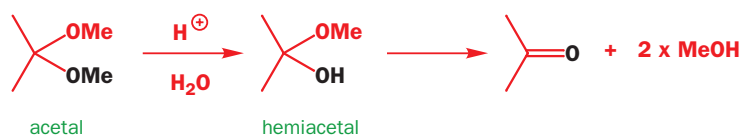
The methoxymethyl cation

This cation can be drawn either as an oxonium ion or as a primary carbenium ion. The oxonium ion structure is the more realistic. Primary carbenium ions are not known in solution, let alone as isolable intermediates, and the proton NMR spectrum of the cation compared with that of the isopropyl cation (this is the best comparison we can make) shows that the protons on the CH_2 group resonate at 9.9 p.p.m. instead of at the 13.0 p.p.m. of the true carbenium ion.



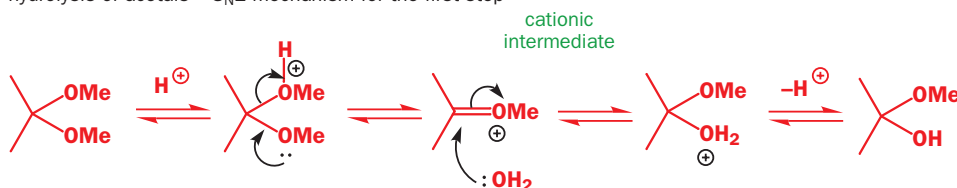
The first step in the hydrolysis of acetals is similar. One alkoxy group is replaced by water to give a hemiacetal.

hydrolysis of acetals – the first step



We considered the mechanism for this reaction in Chapter 14 but did not then concern ourselves with a label for the first step. It has, in fact, an S_N1 style of rate-determining step: the decomposition of the protonated acetal to give an oxonium ion. If you compare this step with the decomposition of the chloroether we have just described you will see that they are very similar.

hydrolysis of acetals – S_N1 mechanism for the first step



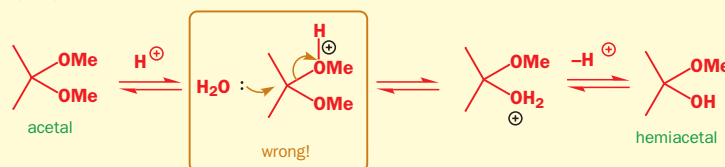
A common mistake

Students of organic chemistry often make a mistake with this mechanism and draw the displacement of the first molecule of methanol by water as an S_N2 reaction.

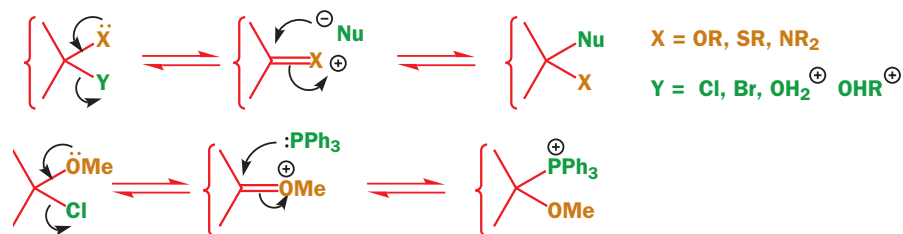
When we discuss the S_N2 reaction shortly you will see that

an S_N2 mechanism is unlikely at such a crowded carbon atom. However, the main reason why the S_N2 mechanism is wrong is that the S_N1 mechanism is so very efficient with a neighbouring MeO group. The S_N2 mechanism doesn't get a chance.

hydrolysis of acetals – *incorrect* S_N2 mechanism for the first step



This mechanism for the S_N1 replacement of one electronegative group at a carbon atom by a nucleophile where there is another electronegative group at the same carbon atom is very general. You should look for it whenever there are two atoms such as O, N, S, Cl, or Br joined to the same carbon atom. The better leaving groups (such as the halogens) need no acid catalyst but the less good ones (N, O, S) usually need acid. Here is a summary diagram and a specific example.



We now have in Table 17.9 a complete list of the sorts of structures that normally react by the $\text{S}_{\text{N}}1$ mechanism rather than by the $\text{S}_{\text{N}}2$ mechanism.

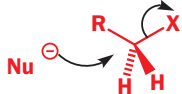
● **Table 17.9** Stable carbocations as intermediates in $\text{S}_{\text{N}}1$ reactions

Type of cation	Example 1	Example 2
simple alkyl	tertiary (good) t-butyl cation Me_3C^+ =	secondary (not so good) i-propyl cation Me_2CH^+ =
conjugated	allylic 	benzylic
heteroatom-stabilized	oxygen-stabilized (oxonium ions) 	nitrogen-stabilized

The $\text{S}_{\text{N}}2$ reaction

Small structures that favour the $\text{S}_{\text{N}}2$ reaction

Notice that we said *simple* alkyl groups: of course, primary allylic, benzylic, and RO or R_2N substituted primary derivatives may react by $\text{S}_{\text{N}}1$!



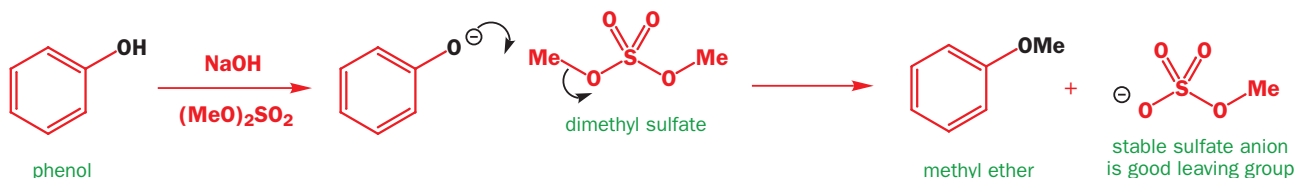
uncluttered approach for nucleophile in $\text{S}_{\text{N}}2$ reactions of methyl compounds ($\text{R}=\text{H}$) and primary alkyl compounds ($\text{R}=\text{alkyl}$)

Among simple alkyl groups, methyl and primary alkyl groups always react by the $\text{S}_{\text{N}}2$ mechanism and never by $\text{S}_{\text{N}}1$. This is partly because the cations are unstable and partly because the nucleophile can push its way in easily past the hydrogen atoms.

Thus, a common way to make ethers is to treat an alkoxide anion with an alkyl halide. If the alkyl halide is a methyl compound, we can be sure that this will be by the $\text{S}_{\text{N}}2$ mechanism. A strong base, here NaH, will be needed to form the alkoxide ion (Chapter 6) and methyl iodide is a suitable electrophile.



With phenols, NaOH is a strong enough base and dimethyl sulfate, the dimethyl ester of sulfuric acid, is often used as the electrophile. These variations do not affect the mechanism. As long as we have a good nucleophile (here reactive RO^-), a methyl electrophile, and a good leaving group (here an iodide or a sulfate anion), the $\text{S}_{\text{N}}2$ mechanism will work well.



The nature of the nucleophile and the leaving group and the structure of the compound under attack all affect the S_N2 mechanism because its rate expression is

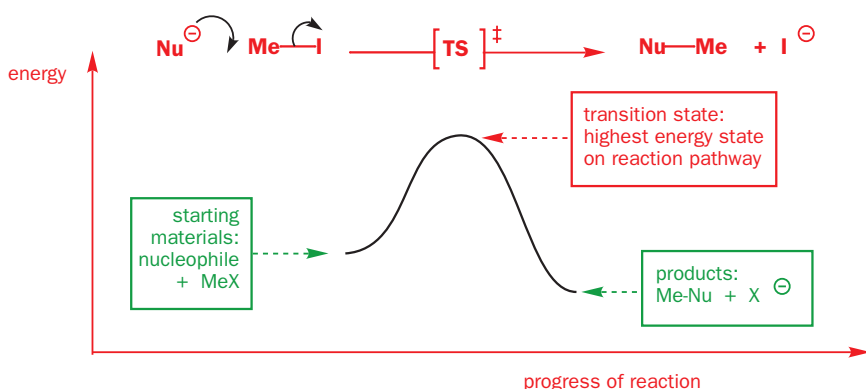
$$\text{rate} = k_2[\text{nucleophile}][\text{MeX}]$$

This expression shows that the rate of an S_N2 reaction is proportional both to the concentration of the nucleophile and to the concentration of the alkyl halide (MeX). The alkyl halide combines the carbon skeleton and the leaving group in the same molecule. We must consider all three factors (nucleophile, carbon skeleton, and leaving group) in an S_N2 reaction. So it was worth removing the proton from the alcohol or the phenol in these ether syntheses because we get a better nucleophile that way. We established on p. 000 that this was not worth doing in an S_N1 reaction because the nucleophile is not involved in the rate-determining step.

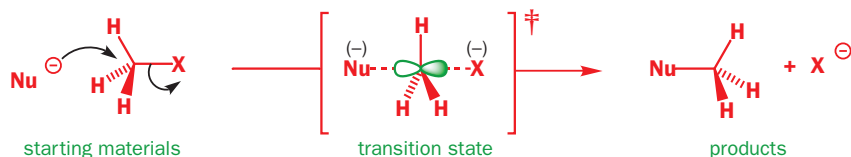
The transition state for an S_N2 reaction

Another way to put this would be to say that the nucleophile, the methyl group, and the leaving group are all present in the transition state for the reaction as explained in Chapter 13. This is the point about halfway through the slow step where the combined reagents reach their highest energy.

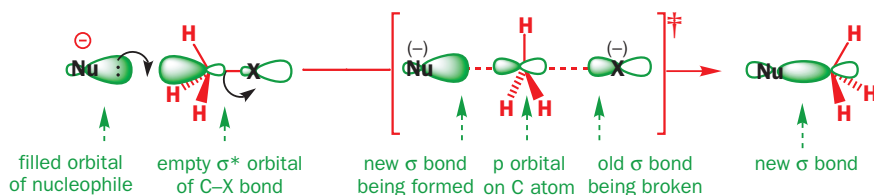
energy diagram for an S_N2 reaction



A transition state is not an intermediate. It can never be isolated because any change in its structure leads to a lower-energy state. In an S_N2 reaction any molecule at the transition state cannot stay there—it must roll down the slope towards products or back to starting materials. So what does it look like and why are we interested in it? The transition state in an S_N2 reaction is about halfway between the starting materials and the products. The bond to the nucleophile is partly formed and the bond to the leaving group is partly broken. It looks like this.



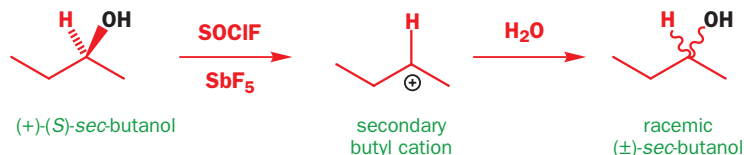
The dashed bonds indicate partial bonds (the C—Nu bond is partly formed and the C—X bond partly broken) and the charges in brackets indicate substantial partial charges (about half a minus charge each in this case as they must add up to one!). Transition states are often shown in square brackets and marked with the symbol ‡. Another way to look at this situation is to consider the orbitals. The nucleophile must have lone-pair electrons, which will interact with the σ* orbital of the C—X bond.



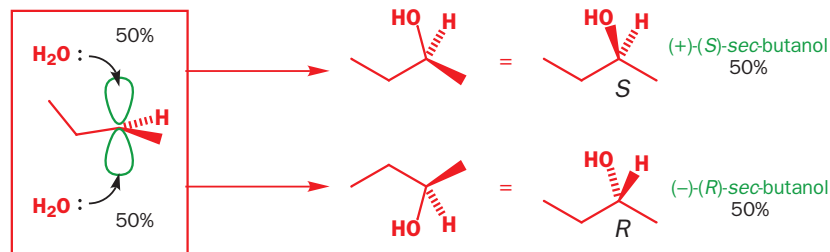
In the transition state there is a p orbital at the carbon atom in the middle that shares one pair of electrons between the old and the new bonds. Both these pictures suggest that the transition state for an S_N2 reaction has a more or less planar carbon atom at the centre with the nucleophile and the leaving group arranged at 180° to each other.

Stereochemistry and substitution

If this is true, it has a very important consequence. The nucleophile attacks the carbon atom on the opposite side from the leaving group and the carbon atom turns inside out as the reaction goes along, just like an umbrella in a high wind. If the carbon atom under attack is a stereogenic centre (Chapter 16), the result will be inversion of configuration. This is easily proved by a simple sequence of reactions. We start by looking at the stereochemistry of an S_N1 reaction.

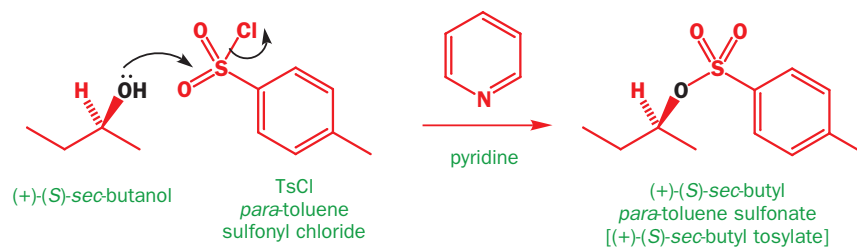


Starting with the optically active secondary alcohol *sec*-butanol (or butan-2-ol, but we want to emphasize that it is *secondary*), the secondary cation can be made by the usual method and has a characteristic ^{13}C NMR shift. Quenching this cation with water regenerates the alcohol but without any optical activity. Water has attacked the two faces of the planar cation with exactly equal probability as we described in Chapter 16. The product is an exactly 50:50 mixture of (*S*)-butanol and (*R*)-butanol. It is *racemic*.

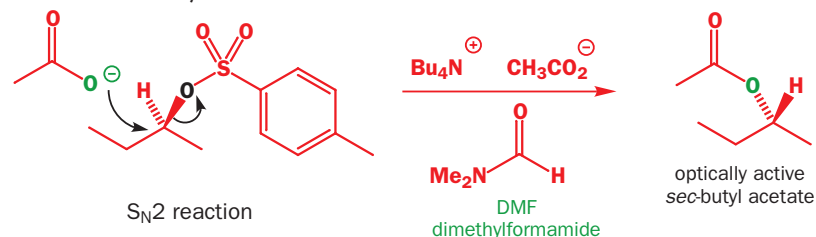


■ TsCl and its synthesis is discussed later in this chapter and in Chapter 22.

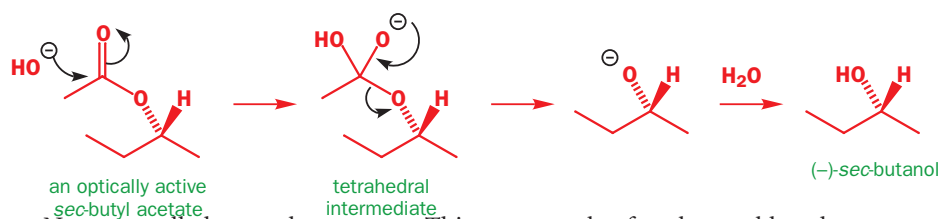
If, however, we first make the *para*-toluene sulfonate ('tosylate') by nucleophilic attack of the OH group on the sulfonyl chloride TsCl in pyridine solution, the sulfonate will be formed with retention as no bonds have been formed or broken at the chiral carbon atom. This is a substitution reaction too, but at sulfur rather than at carbon.



Now we can carry out an S_N2 reaction on the sulfonate with a carboxylate anion. A *tetra*-alkyl ammonium salt is often used in the polar solvent DMF to get a clean reaction. This is the key step and we don't want any doubt about the outcome.



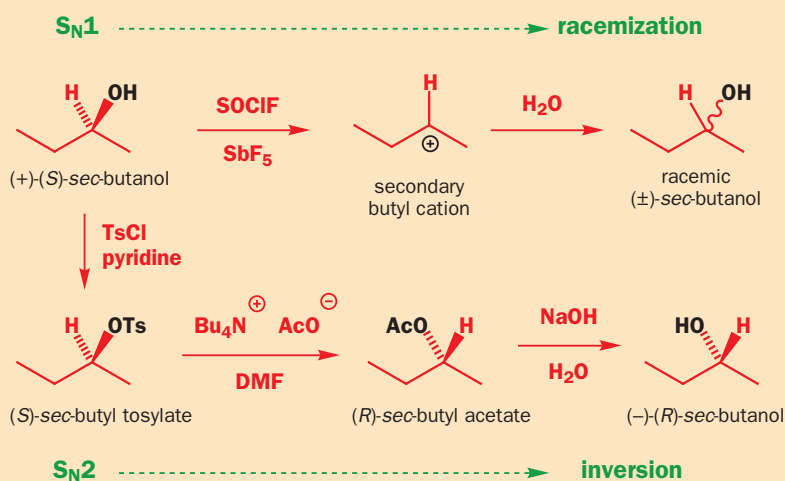
The product is optically active and we can measure its rotation. But this tells us nothing. Unless we know the true rotation for pure *sec*-butyl acetate, we don't yet know whether it is optically pure nor even whether it really is inverted. But we can easily find out. All we have to do is to hydrolyse the ester and get the original alcohol back again. We know the true rotation of the alcohol—it was our starting material—and we know the mechanism of ester hydrolysis (Chapter 12)—nucleophilic attack occurs at the carbonyl carbon and retention must be the stereochemical outcome as no reaction occurs at the stereogenic centre.



Now we really know where we are. This new sample of *sec*-butanol has the same rotation as the original sample, *but with the opposite sign*. It is (-)-(*R*)-*sec*-butanol. It is optically pure and inverted. Somewhere in this sequence there has been an inversion, and we know it wasn't in the formation of the tosylate or the hydrolysis of the acetate as no bonds are formed or broken at the stereogenic centre in these steps. It must have been in the S_N2 reaction itself.

● This is a general conclusion.

- The S_N2 reaction goes with inversion of configuration at the carbon atom under attack but the S_N1 reaction generally goes with racemization

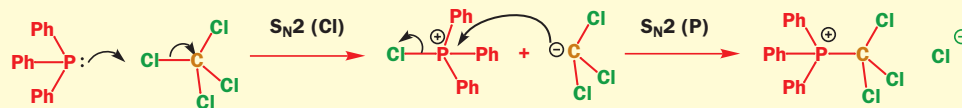


Substitution reactions at other elements

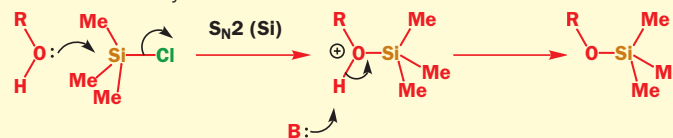
S_N2 reactions can occur at elements other than carbon. Common examples in organic chemistry are silicon, phosphorus, sulfur, and the halogens. The formation of the tosylate above by attack of the alcohol on TsCl is an example of an S_N2 reaction at sulfur. Later in this chapter you will see that alcohols attack phosphorus very easily and that we use the reaction between ROH and PBr₃ to make alkyl bromides. Alcohols also react rapidly with Si-Cl compounds such as Me₃SiCl to give silyl ethers by an S_N2 reaction at silicon. You have already seen several examples of silyl ether formation (p. 000, for example), though up to

For an example of an S_N2 reaction at chlorine we can choose a reaction we will need later in the book. Triphenyl phosphine reacts with CCl₄ to give a phosphonium salt by what looks like an S_N2 reaction at carbon.

In fact there is no room around the carbon atom of CCl₄ for any nucleophile, let alone such a large one as PPh₃ and the reaction occurs by two separate S_N2 steps: one at chlorine and one at phosphorus.



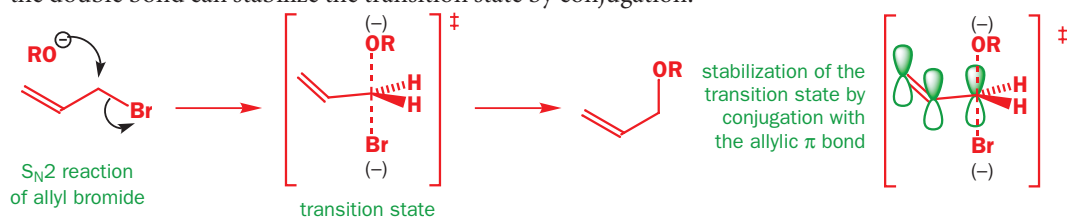
this point we have not discussed the mechanism. Here it is: B: represents a base such as triethylamine.



Structural variation and the S_N2 mechanism

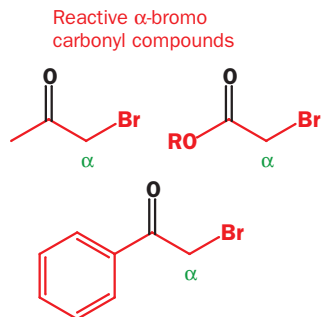
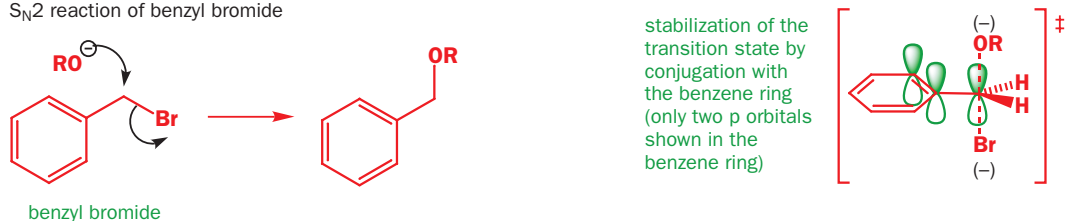
We have already established that methyl and primary alkyl compounds react well by the S_N2 mechanism, while secondary alkyl compounds *can* do so. There are other important structural features that also encourage the S_N2 mechanism. Two, allyl and benzyl compounds, also encourage the S_N1 mechanism.

Here you see a typical S_N2 reaction of allyl bromide. We have drawn the transition state for this reaction. This is not because we want to encourage you to do this for all S_N2 reactions but so that we can explain the role of the allyl system. Allyl compounds react rapidly by the S_N2 mechanism because the double bond can stabilize the transition state by conjugation.



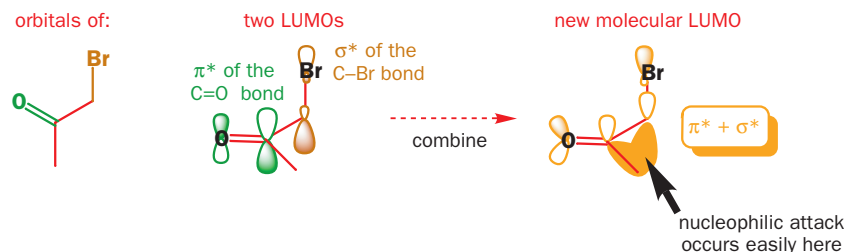
The benzyl group acts in much the same way using the π system of the benzene ring for conjugation with the p orbital in the transition state.

S_N2 reaction of benzyl bromide



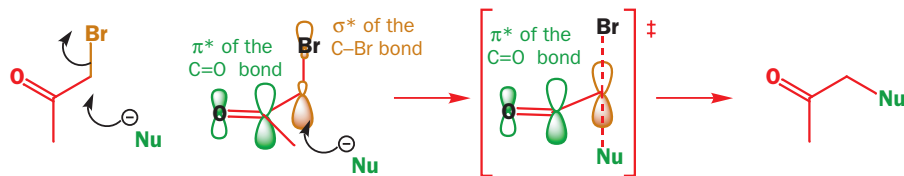
Since the p orbital in question has electrons in it—it shares a pair of electrons with the nucleophile and the leaving group—more effective conjugation is possible with an electron-deficient π bond. The most important example is the carbonyl group: carbon electrophiles like those in the margin give the fastest S_N2 reactions.

With α -bromo carbonyl compounds, substitution leads to two electrophilic groups on neighbouring carbon atoms. Each has a low-energy empty orbital, π^* from C=O and σ^* from C–Br (this is what makes them electrophilic), and these can combine to form a molecular LUMO ($\pi^* + \sigma^*$) lower in energy than either. Nucleophilic attack will occur easily where this new orbital has its largest coefficients, shown in orange in the diagram.

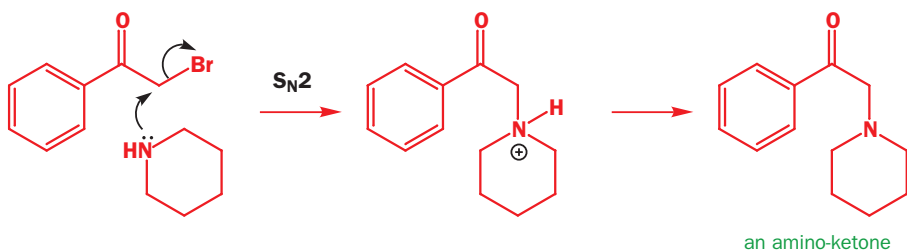


This orange area is on one side of the carbonyl group and in the usual place at the back of the C–Br bond. Each group has become more electrophilic because of the presence of the other—the C=O group makes the C–Br bond more reactive and the Br makes the C=O group more reactive. Another way to put this is that the carbonyl group stabilizes the transition state by overlap of its π^* orbital with the full p orbital of the carbon atom under attack. The nucleophile may well attack the carbonyl group but this will be reversible whereas displacement of bromide is irreversible.

transition state for nucleophilic attack on an α -bromo-ketone



There are many examples of this type of reaction. Reactions with amines go well and the amino-ketone products are widely used in the synthesis of drugs.



Variation of rate with structure

Some actual data may help at this point. The rates of reaction of the following alkyl chlorides with KI in acetone at 50 °C broadly confirm the patterns we have just analysed. These are relative rates with respect to *n*-BuCl

as a 'typical primary halide'. You should not take too much notice of precise figures but rather observe the trends and notice that the variations are quite large—the full range from 0.02 to 100 000 is eight powers of ten.

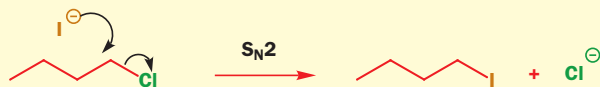


Table 17.10 Relative rates of S_N2 reactions of alkyl chlorides with the iodide ion

Alkyl chloride	Relative rate	Comments
Me—Cl	200	least hindered alkyl chloride
	0.02	secondary alkyl chloride; slow because of steric hindrance
	79	allyl chloride accelerated by π conjugation in transition state
	200	benzyl chloride slightly more reactive than allyl: benzene ring better at π conjugation than isolated double bond
Me—O—CH ₂ —Cl	920	conjugation with oxygen lone pair accelerates reaction
	100 000	conjugation with carbonyl group much more effective than with simple alkene or benzene ring. These α -carbonyl halides are the most reactive of all

Summary of structural variations and nucleophilic substitution

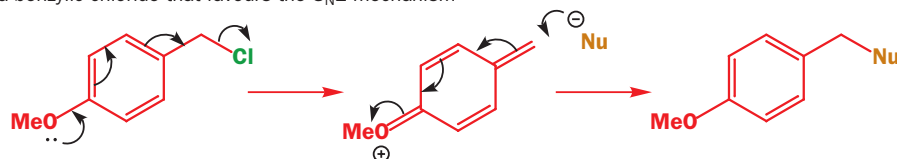
We are now in a position to summarize those effects we have been discussing over the last few pages on both mechanisms. It is simplest to list the structural types and rate each reaction qualitatively.

● **Table 17.11** Structural variations for the S_N1 and S_N2 reactions

Type of electrophilic carbon atom	S_N1 reaction	S_N2 reaction
methyl ($\text{CH}_3\text{-X}$)	no	very good
primary alkyl ($\text{RCH}_2\text{-X}$)	no	good
secondary alkyl ($\text{R}_2\text{CH-X}$)	yes	yes
tertiary alkyl ($\text{R}_3\text{C-X}$)	very good	no
allylic ($\text{CH}_2=\text{CH-CH}_2\text{-X}$)	yes	good
benzylic ($\text{ArCH}_2\text{-X}$)	yes	good
α -carbonyl ($\text{RCO-CH}_2\text{-X}$)	no	excellent
α -alkoxy ($\text{RO-CH}_2\text{-X}$)	excellent	good
α -amino ($\text{R}_2\text{N-CH}_2\text{-X}$)	excellent	good

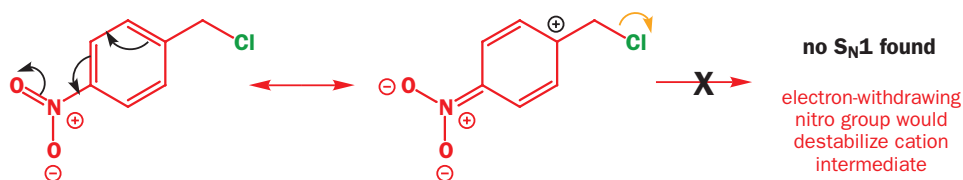
You must not regard this list as fixed and inflexible. The last five types will also be either primary, secondary, or tertiary. If they are primary, as shown, they will favour S_N2 more, but if they are tertiary they will all react by the S_N1 mechanism except the tertiary α -carbonyl ($\text{RCO-CR}_2\text{-X}$) compounds, which will still react by the S_N2 mechanism, if rather slowly. If they are secondary they might react by either mechanism. Similarly, a benzylic compound that has a well placed electron-donating group able to make an electronic connection with the leaving group will favour the S_N1 mechanism.

a benzylic chloride that favours the S_N1 mechanism

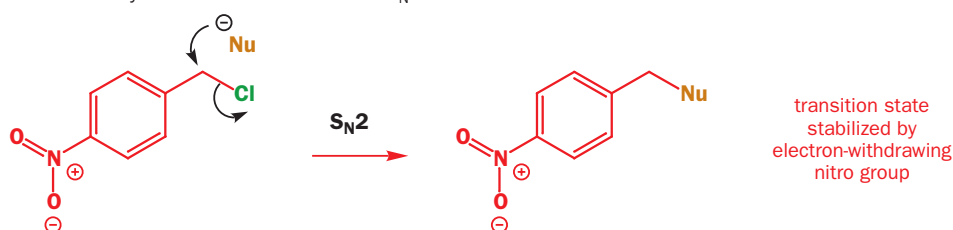


On the other hand, a 4-nitrobenzyl chloride is likely to react by the S_N2 mechanism as the strongly electron-withdrawing nitro group would destabilize the carbocation intermediate of the S_N1 mechanism.

a benzylic chloride that disfavours the S_N1 mechanism



the same benzylic chloride that favours the S_N2 mechanism

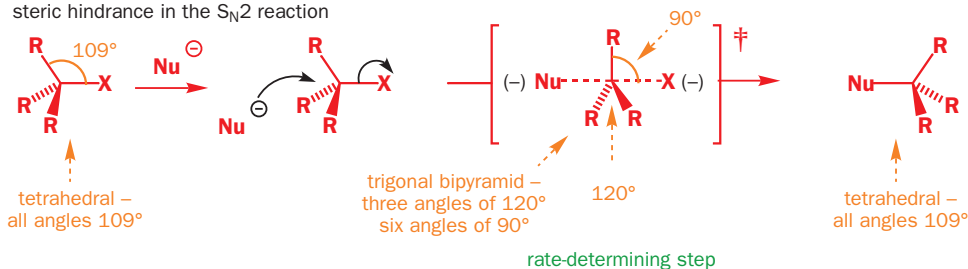


▶ Rate measurements for these two compounds are very revealing. We can force them to react by S_N1 by using methanol as the solvent (p. 000). If we set the rate of substitution of the benzyl compound with methanol at 25 °C at 1.0, then the 4-MeO benzyl compound reacts about 2500 times faster and the 4-NO₂ benzyl compound about 3000 times more slowly.

Steric hindrance in nucleophilic substitution

We have already considered the inversion of stereochemistry necessary in an S_N2 mechanism, but there is another steric effect, the rather cruder steric hindrance. In the approach to the S_N2 transition state, the carbon atom under attack gathers in another ligand and becomes (briefly) five-coordinate. The angles between the substituents decrease from tetrahedral to about 90°.

steric hindrance in the S_N2 reaction

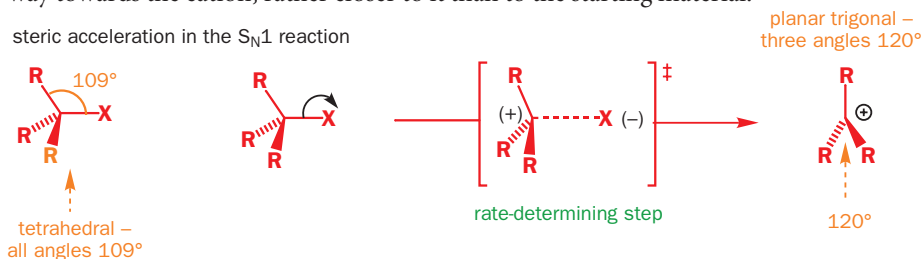


In the starting material there are four angles of about 109°. In the transition state (enclosed in square brackets and marked ‡ as usual) there are three angles of 120° and six angles of 90°, a significant increase in crowding. The larger the substituents R, the more serious this is. We can easily see the effects of steric hindrance if we compare these three structural types:

- methyl: CH₃–X: very fast S_N2 reaction
- primary alkyl: RCH₂–X: fast S_N2 reaction
- secondary alkyl: R₂CH–X: slow S_N2 reaction

The opposite is true of the S_N1 reaction. The slow step is simply the loss of the leaving group. The starting material is again tetrahedral (four angles of about 109°) and in the intermediate cation there are just three angles of 120°—fewer and less serious interactions. The transition state will be on the way towards the cation, rather closer to it than to the starting material.

steric acceleration in the S_N1 reaction



Even in the transition state, the angles are increasing towards 120° and all interactions with the leaving group are diminishing as it moves away. There is steric *acceleration* in the S_N1 reaction rather than steric *hindrance*. This, as well as the stability of *t*-alkyl cations, is why *t*-alkyl compounds react by the S_N1 mechanism.

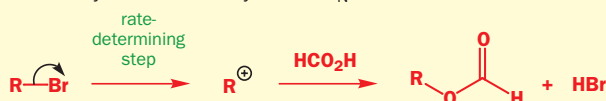
You will often read that *t*-alkyl compounds do not react by the S_N2 mechanism because the steric hindrance would be too great. This is a reasonable assumption given that secondary alkyl compounds are already reacting quite slowly. The truth is that *t*-alkyl compounds react so fast by the S_N1 mechanism that the S_N2 mechanism wouldn't get a chance *even if it went as fast as it goes with methyl compounds*. The nucleophile would have to be about 100 molar in concentration to compensate for the difference in rates and this is impossible! Even pure water is only 55 molar (Chapter 8). You see only the faster of the two possible mechanisms.

- If there are two *steps* in a single mechanism, the *slower* of the two determines the rate of the overall reaction
- If there are two different *mechanisms* available under the reaction conditions, only the *faster* of the two actually occurs.

Rates of S_N1 and S_N2 reactions

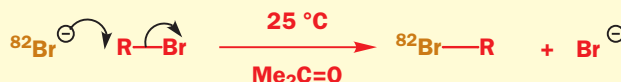
Here is a simple illustration of these effects. The green curve in Figure 17.1 (next page) shows the rates (*k*₁) of an S_N1 reaction: the conversion of alkyl bromides to alkyl

formate esters in formic acid at 100 °C. Formic acid is very polar and, though a weak nucleophile, is adequate for an S_N1 reaction.



The red curve in Figure 17.1 shows the rates of displacement of Br[−] by radioactive ⁸²Br[−] in acetone at 25 °C by the S_N2 mechanism, the rates (*k*₂) being multiplied by 10⁵ to bring both curves on to the same

graph. The actual values of the rate constants are not important. Table 17.12 gives the relative rates compared with that of the secondary halide, *i*PrBr, set at 1.0 in each case.



Rates of S_N1 and S_N2 reactions (contd)

Both curves are plotted on a log scale, the \log_{10} of the actual rate being used on the y-axis. The x-axis has no real significance; it just shows the four points corresponding to

the four basic structures: MeBr, MeCH₂Br, Me₂CHBr, and Me₃CBr. The values plotted are given in Table 17.12

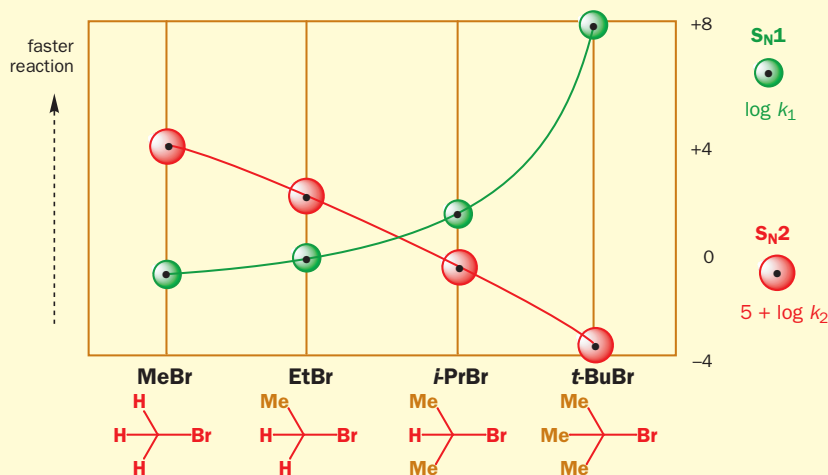
Table 17.12 Rates of S_N1 and S_N2 reactions of simple alkyl bromides

alkyl bromide	CH ₃ Br	CH ₃ CH ₂ Br	(CH ₃) ₂ CHBr	(CH ₃) ₃ CBr
type	methyl	primary	secondary	tertiary
k_1, s^{-1}	0.6	1.0	26	10^8
$10^5 k_2 (lm^{-1} s^{-1})$	13 000	170	6	0.0003
relative k_1	2×10^{-2}	4×10^{-2}	1	4×10^6
relative k_2	6×10^3	30	1	5×10^{-5}

The reactions were chosen to give as much S_N1 reaction as possible in one case and as much S_N2 reaction as possible in the other case. Formic acid is a very polar solvent but a poor nucleophile; this gives the maximum opportunity for a cation to form. Bromide ion is a good nucleophile and acetone is polar enough to dissolve the reagents but not so polar that ionization is encouraged. Of

course, you will understand that we cannot prevent the molecules doing the 'wrong' reaction! The values for the ' S_N1 ' reaction of MeBr and MeCH₂Br are actually the low rates of S_N2 displacement of the bromide ion by the weak nucleophile HCO₂H, while the ' S_N2 ' rate for *t*-BuBr may be the very small rate of ionization of *t*-BuBr in acetone.

Figure 17.1: S_N1 and S_N2 rates for simple alkyl bromides



The actual values of the rate constants are not important. The graph in Figure 17.1 has been plotted to put the rates of the S_N2 and S_N1 reactions of the secondary alkyl

bromide at about the same level to give a graphical illustration of the *relative* speed of the S_N2 reaction with MeBr and the *relative* speed of the S_N1 reaction of *t*-BuBr.

Solvating polar compounds or transition states

Three things are important:

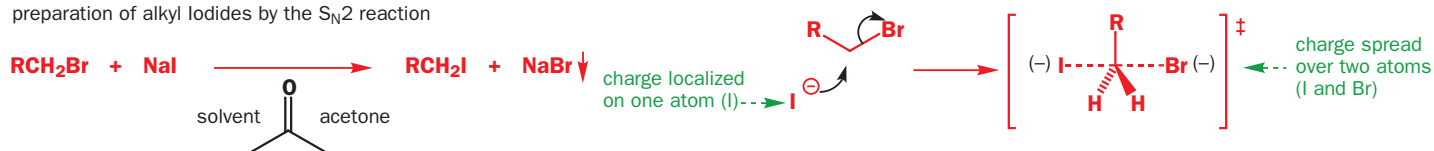
- Polarity—simply measured by dipole moment. The + end of the dipole stabilizes full or partial anions and the – end of the dipole stabilizes full or partial cations
- Electron donation to cationic centres by lone-pair electrons
- Hydrogen bonding to stabilize full or partial anions

Solvent effects

In the box above, you can see acetone used as a solvent for an S_N2 reaction and formic acid (HCO₂H) as solvent for the S_N1 reaction. These are typical choices: a less polar solvent for the S_N2 reaction (just polar enough to dissolve the ionic reagents) and a polar protic solvent for the S_N1 reaction. The S_N1 reaction fairly obviously needs a polar solvent as the rate-determining step usually involves the formation of ions and the rate of this process will be increased by a polar solvent. More precisely, the transition state is more polar than the starting materials and so is stabilized by the polar solvent. Hence solvents like water or carboxylic acids (RCO₂H) are ideal.

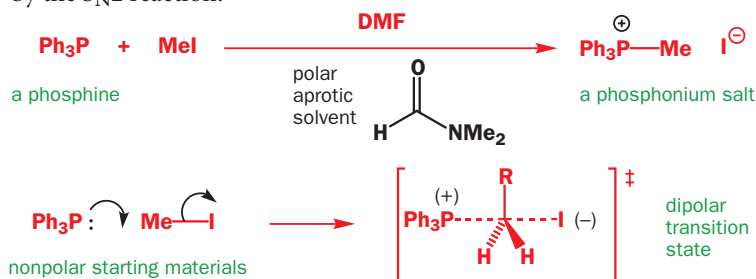
It is less obvious why a less polar solvent is better for the S_N2 reaction. The most common S_N2 reactions use an anion as the nucleophile and the transition state is less polar than the localized anion as the charge is spread between two atoms.

preparation of alkyl iodides by the S_N2 reaction



A polar solvent solvates the anionic nucleophile and slows the reaction down. A nonpolar solvent destabilizes the starting materials more than it destabilizes the transition state and speeds up the reaction. There is another reason for using acetone for this particular reaction. NaI is very soluble in acetone but NaBr is rather insoluble. The NaBr product precipitates out of solution which helps to drive the reaction over to the right.

If an S_N2 reaction has neutral starting materials and an ionic product, then a polar solvent is better. A good choice is DMF, a polar aprotic solvent often used for the synthesis of phosphonium salts by the S_N2 reaction.

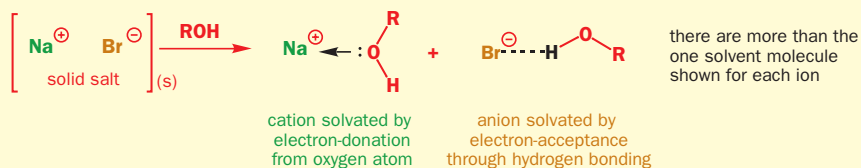


Polar aprotic solvents

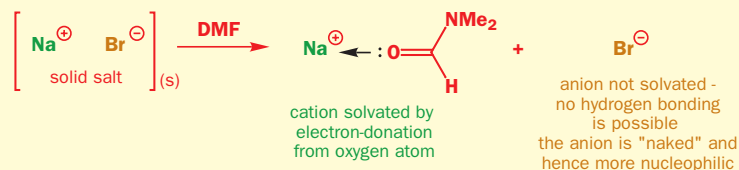
Water, alcohols, and carboxylic acids are polar protic solvents able to form hydrogen bonds (**hydroxylic solvents**). They solvate both cations and anions well. A nucleophilic reagent such as bromide ion must be accompanied by a cation, say, the sodium ion, and hydroxylic solvents dissolve salts such as NaBr by hydrogen bonding to the anion and electron donation to the cation. This is solvation by a polar protic solvent. These solvents do not 'ionize' the salt, which already exists in the solid state as ions; they separate and solvate the ions already present.

Polar aprotic solvents, on the other hand, have dipole moments and are still able to solvate cations by electron donation from an oxygen atom, but they lack the ability to form hydrogen bonds because any hydrogen atoms they may have are on carbon. Examples include DMF and DMSO (dimethyl sulfoxide).

solvation of salts by hydrophilic solvents



solvation of salts by polar aprotic solvents



We have considered the important effects of the basic carbon skeleton on the S_N1 and S_N2 reactions and we shall now consider the remaining two possible structural variations: the nucleophile and the leaving group. We shall tackle the leaving group first because it plays an important role in both S_N1 and S_N2 reactions.

The leaving group

We have mostly seen halides and water from protonated alcohols as leaving groups in both S_N1 and S_N2 reactions. Now we need to establish the principles that make for good and bad leaving groups. We might be considering an S_N1 reaction.



Or we might be considering an S_N2 reaction—both have a leaving group, which we are representing as ‘X’ in these mechanisms. In both cases the C–X bond is breaking in the slow step.



Starting with the halides, two main factors are at work: the strength of the C–halide bond and the stability of the halide ion. The strengths of the C–X bonds have been measured and are listed in Table 17.13. How shall we measure anion stability? One way, which you met in Chapter 8, was to use the pK_a values of the acids HX. We established in Chapter 8 that bond strength can be used to explain pK_a values so these two factors are not independent.

It is clearly easiest to break a C–I bond and most difficult to break a C–F bond. Iodide sounds like the best leaving group. We get the same message from the pK_a values: HI is the strongest acid, so it must ionize easily to H^+ and I^- . This result is quite correct—iodide is an excellent leaving group and fluoride a very bad one with the other halogens in between.

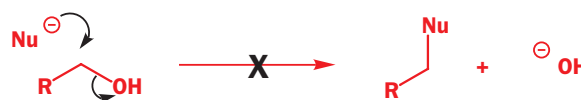
Table 17.13 Halide leaving groups in the S_N1 and S_N2 reactions

Halide (X)	Strength of C–X bond, ¹ kJ mol ⁻¹	pK_a of HX
fluorine	118	+3
chlorine	81	-7
bromine	67	-9
iodine	54	-10

Nucleophilic substitutions on alcohols

Now what about leaving groups joined to the carbon atom by a C–O bond? There are many of these but the most important are OH itself, the carboxylic esters, and the sulfonate esters. First we must make one thing clear. In spite of what you may suppose, alcohols do *not* react with nucleophiles. Why not? Hydroxide ion is very basic, very reactive, and a bad leaving group. If the nucleophile were strong enough to produce hydroxide ion, it would be more than strong enough to remove the proton from the alcohol.

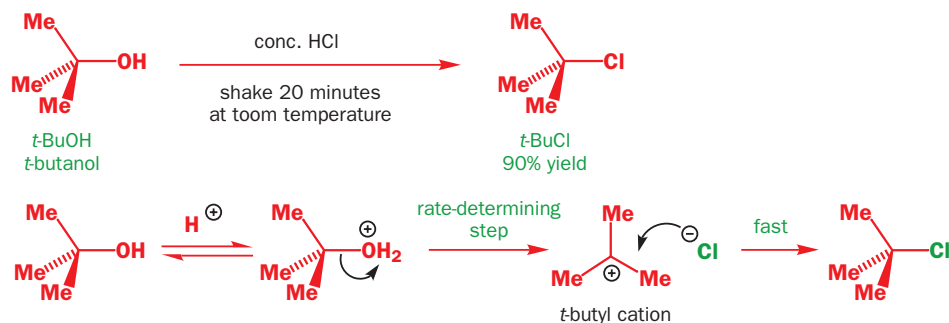
S_N2 displacement of hydroxide ion is *not* a known reaction



if the nucleophile reacts, it attacks the *proton* instead

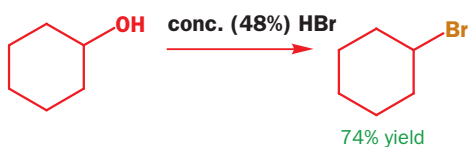


But we want to use alcohols in nucleophilic substitution reactions because they are easily made. The simplest answer is to protonate the OH group with strong acid. This will work only if the nucleophile is compatible with strong acid, but many are. The preparation of *t*-BuCl from *t*-BuOH simply by shaking it with concentrated HCl is a good example. This is obviously an S_N1 reaction with the *t*-butyl cation as intermediate.

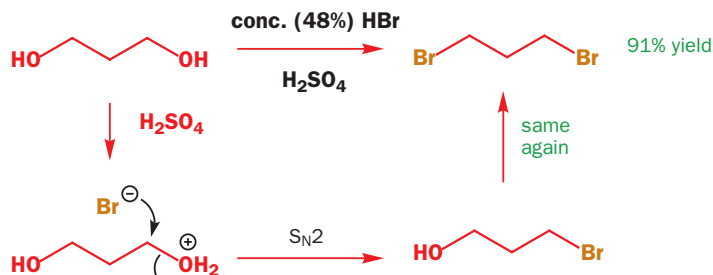


Similar methods can be used to make secondary alkyl bromides with HBr alone and primary alkyl bromides using a mixture of HBr and H_2SO_4 . The second is certainly an S_N2 reaction and we show just one stage in a two-step process that is very efficient.

substituting a secondary alcohol in acid

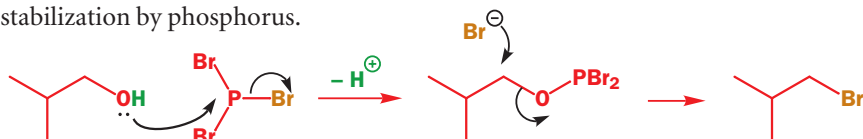


substituting a primary alcohol in acid



Another way is to convert the OH group into a better leaving group by combination with an element that forms very strong bonds to oxygen. The most popular choices are phosphorus and sulfur. Making primary alkyl bromides with PBr₃ usually works well.

The phosphorus reagent is first attacked by the OH group (an S_N2 reaction at phosphorus) and the displacement of an oxyanion bonded to phosphorus is now a good reaction because of the anion stabilization by phosphorus.

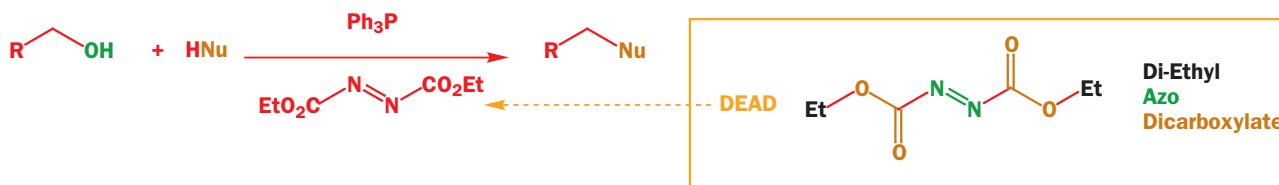


The Mitsunobu reaction is a modern S_N2 reaction using phosphorus chemistry

So far we have seen methods of displacing the OH group by first converting it to something else—a better leaving group like Br, for example. There is one recent invention that allows us to put an alcohol straight into a reaction mixture and get an S_N2 product in one operation. This is the **Mitsunobu reaction**. The alcohol becomes the electrophile, the nucleophile can be whatever you choose, and there are two other reagents.

■ Oyo Mitsunobu was born in 1934 in Japan and works at the Aoyama Gakuin University in Tokyo. He is one of the few modern chemists to have a famous reaction named after him. Please note the spelling of his name: MitsUnObU.

a Mitsunobu reaction

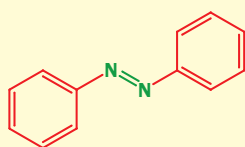


One of these reagents, Ph₃P, triphenylphosphine, is a simple phosphine, rather like an amine but with P instead of N. The other deserves more comment. Its full name is diethyl azodicarboxylate, or DEAD.

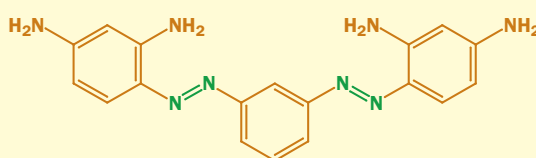
Azo compounds

The 'azo' in the name of DEAD refers to two nitrogen atoms joined together by a double bond and compounds such as azobenzene are well known. Many dyestuffs have

an azo group in them—Bismarck Brown (mentioned in Chapter 1) is used to dye kippers.



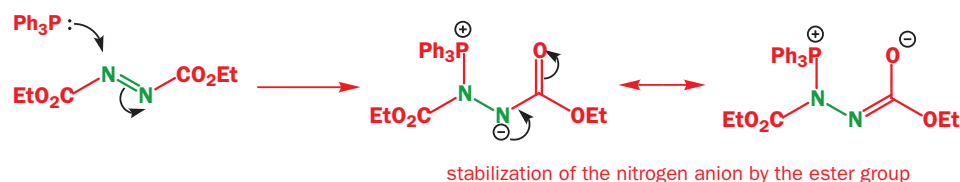
azobenzene



Bismarck Brown Y: an azo dye

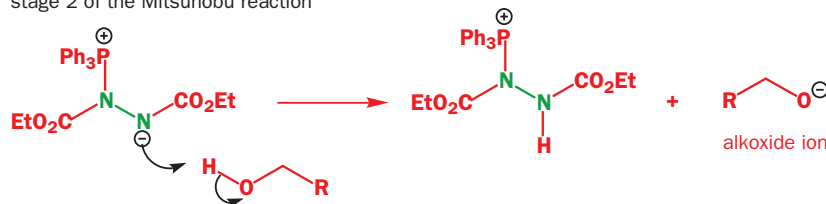
So how does the Mitsunobu reaction work? The first step involves neither the alcohol nor the nucleophile. The phosphine adds to the weak N=N π bond to give an anion stabilized by one of the ester groups.

stage 1 of the Mitsunobu reaction



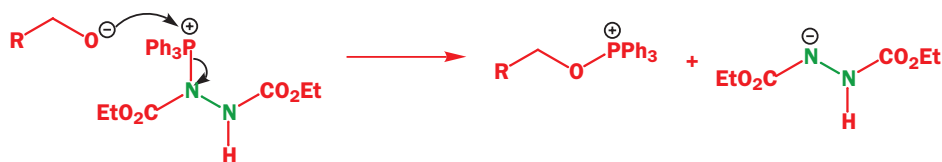
The anion produced by this first stage is basic enough to remove a proton from the alcohol. This is always what will happen if a strong nucleophile is combined with an alcohol and previously this was a fatal disadvantage when we wanted an $\text{S}_{\text{N}}2$ reaction. But wait and see.

stage 2 of the Mitsunobu reaction



Oxygen and phosphorus have a strong affinity as we saw in the conversion of alcohols to bromides with PBr_3 and in the Wittig reaction (Chapter 14, p. 000) and so the new alkoxide ion immediately attacks the positively charged phosphorus atom displacing a second nitrogen anion stabilized in the same way as the first. This is an $\text{S}_{\text{N}}2$ reaction at phosphorus.

stage 3 of the Mitsunobu reaction



The second basic nitrogen anion removes a proton from the nucleophile, which has been patiently waiting in disguised form as HNu while all this is going on. The true nucleophile is now revealed as an anion.

stage 4 of the Mitsunobu reaction



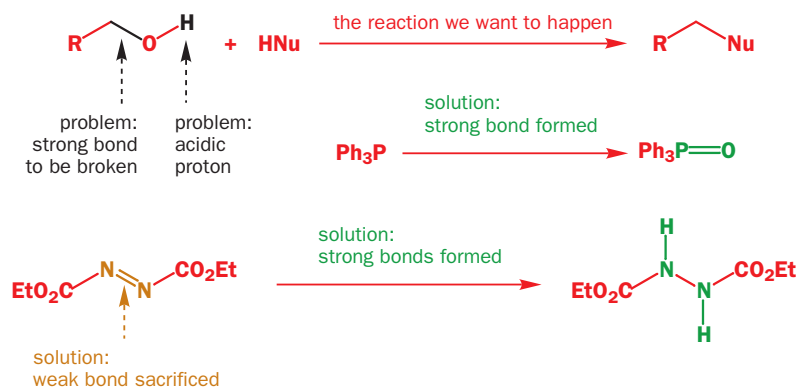
Finally, the anion of the nucleophile attacks the phosphorus derivative of the alcohol in a normal $\text{S}_{\text{N}}2$ reaction at carbon with the phosphine oxide as the leaving group. We have arrived at the products.

stage 5 of the Mitsunobu reaction



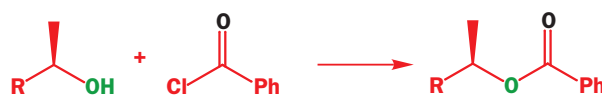
The whole process takes place in one operation. The four reagents are all added to one flask and the products are the phosphine oxide, the reduced azo diester with two NH bonds replacing the $\text{N}=\text{N}$ double bond, and the product of an $\text{S}_{\text{N}}2$ reaction on the alcohol. Another way to look at this reaction is that a molecule of water must formally be lost: OH must be removed from the alcohol and H from the nucleophile. These atoms end up in very stable molecules—the $\text{P}=\text{O}$ and $\text{N}-\text{H}$ bonds are very stable while the $\text{N}=\text{N}$ bond was weak. This compensates for the sacrifice of the strong $\text{C}-\text{O}$ bond in the alcohol.

the Mitsunobu reaction – summary



If this is all correct, then the vital S_N2 step should lead to inversion as it always does in S_N2 reactions. This turns out to be one of the great strengths of the Mitsunobu reaction—it is a reliable way to replace OH by a nucleophile with inversion of configuration. The most dramatic example is probably the formation of esters from secondary alcohols with inversion. Normal ester formation leads to retention as the C–O bond of the alcohol is not broken.

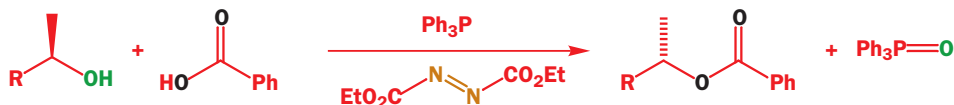
ester formation from a secondary alcohol with retention



● The Mitsunobu reaction is used to replace OH by another group with inversion of configuration.

In the Mitsunobu reaction, the C–O bond of the alcohol is broken because the alcohol becomes the electrophile and the acid derivative must be a nucleophile so an acid is better than an acid chloride. The ester is formed with inversion. Note the fate of the oxygen atoms.

ester formation from a secondary alcohol with inversion by the Mitsunobu reaction

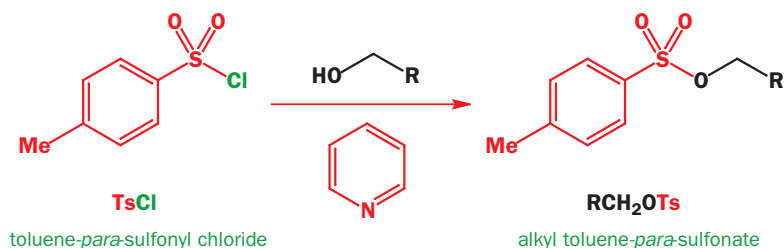


The Mitsunobu reaction is by no means the only way to turn OH groups into leaving groups and a method based on sulfur chemistry is as important.

Tosylate, TsO^- , is an important leaving group made from alcohols

The most important of all these leaving groups are those based on sulfonate esters. The intermediates in the PBr_3 reaction are unstable, but it is usually easy to make stable, usually crystalline toluene-*para*-sulfonates from primary and secondary alcohols. We met these derivatives on p. 000. These isolable but reactive compounds are so popular that they have been given a trivial name ('tosylates') and the functional group has been allocated an 'organic element' symbol Ts. This is what it means.

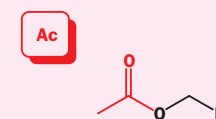
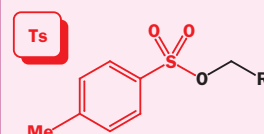
■ Sulfonic acids are strong acids ($\text{p}K_a$ from Chapter 8) and so any sulfonate is a good leaving group. Another closely related leaving group, methane sulfonate or MsO^- is discussed in Chapter 19 under elimination reactions.



▶ **Warning of wrong labelling!**

Ts = toluene-*para*-sulfonyl

Ac = acetyl



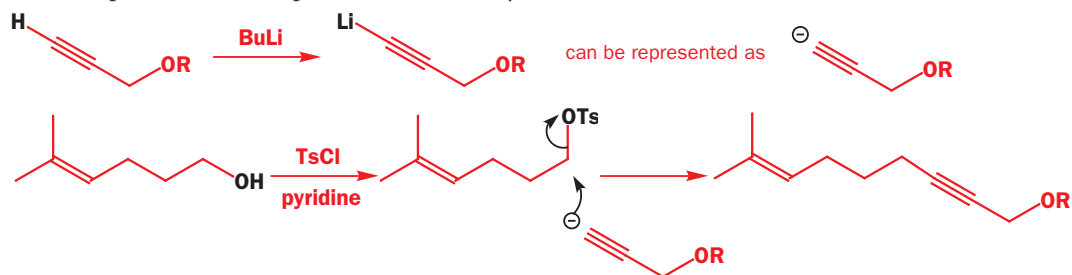
this compound is RCH_2OTs *not* RCH_2Ts this compound is RCH_2OAc *not* RCH_2Ac

The leaving groups are toluene-*para*-sulfonate, TsO^- , and acetate, AcO^- , but the substituents are toluene-*para*-sulfonyl, Ts- , and acetyl, Ac- .

You have already seen the tosyl group used in the inversion sequence on p. 000, where it was displaced by as weak a nucleophile as acetate. This should alert you to the fact that TsO^- can be displaced by almost anything. We choose some examples in which new carbon–carbon bonds are formed. This will be an important topic later in the book when we meet enolate anions (Chapter 21) but our two examples here use sp anions derived from nitriles and acetylenes.

Cyanide ion is a good small nucleophile and displaces tosylate from primary carbon atoms and adds one carbon atom to the chain. As the cyanide (nitrile) group can be converted directly to a carboxylic acid or ester (Chapter 14) this sequence is a useful chain extension.

Corey's synthesis of leukotrienes, human metabolites that control many important natural defence reactions like inflammation, involves the lithium derivative of an alkyne prepared by deprotonation with the very strong base butyllithium. The tosyl derivative of a primary alcohol reacts with this lithium derivative and a perfectly normal $\text{S}_{\text{N}}2$ reaction follows. The alkyne provides the carbanion (Chapter 8) for the displacement of the tosylate.

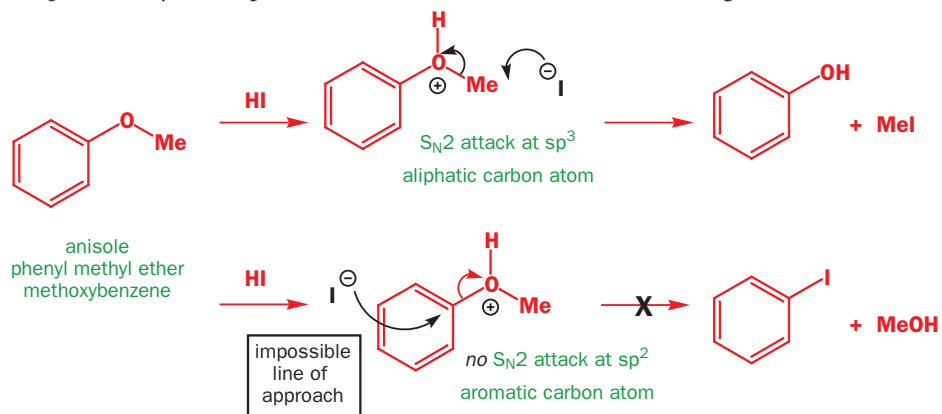


■ Elias J. Corey (1928–), PhD from MIT, works at Harvard University. He invented the disconnection approach to the design of organic synthesis. His group has invented many of the most important modern methods of synthesis, and have made an enormous number of complex compounds. He won the Nobel prize in 1990.

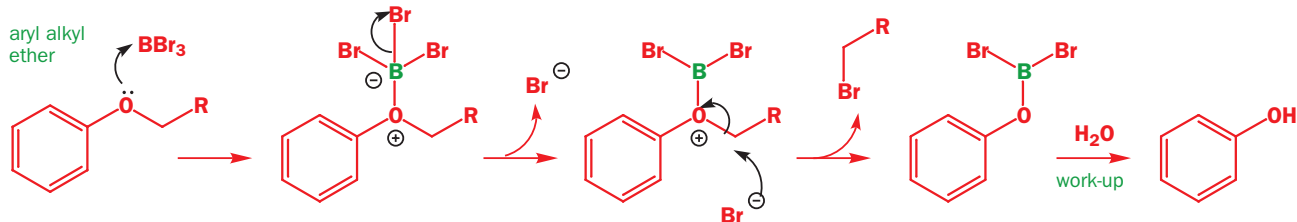
■ Leukotrienes will be discussed in detail in Chapter 51. They are C_{20} chain compounds, normally with three double bonds as their name suggests.

Ethers as electrophiles

Ethers are stable molecules, which do not react with nucleophiles: they must be stable because THF and Et_2O are used as solvents. But we can make them react by using an acid with a nucleophilic counterion (HBr or HI, for example) and then nucleophilic attack will occur preferentially at the more susceptible carbon atom. Aryl alkyl ethers cleave only on the alkyl side. We shall explain in Chapter 23 why nucleophilic attack does not occur on a benzene ring.

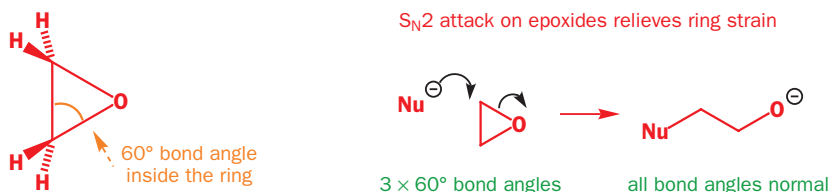


So far we have used only protic acids to help oxygen atoms to leave. Lewis acids work well too, and the cleavage of aryl alkyl ethers with BBr_3 is a good example. Trivalent boron compounds have an empty p orbital so they are very electrophilic and prefer to attack oxygen. The resulting oxonium ion can be attacked by Br^- in an $\text{S}_{\text{N}}2$ reaction.

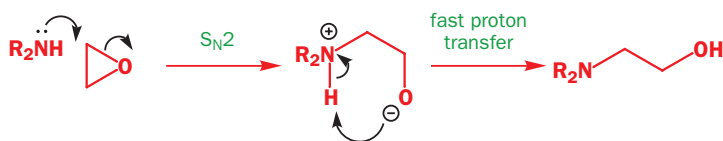


Epoxides

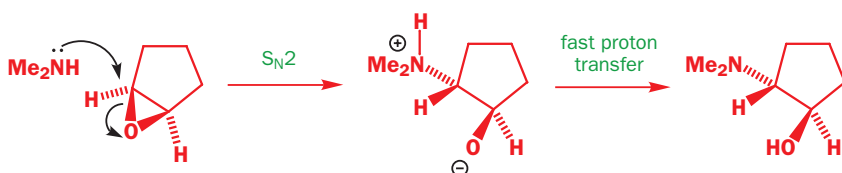
One type of ether reacts in nucleophilic substitution without acids or Lewis acids. The leaving group is genuinely an alkoxide anion RO^- . Obviously, some extra special feature must be present in these ethers making them unstable and this feature is ring strain. They are the three-membered cyclic ethers called **epoxides** (or oxiranes). You will see how to make these compounds in Chapter 20. The ring strain comes from the angle between the bonds in the three-membered ring which has to be 60° instead of the ideal tetrahedral angle of 109° . You could subtract these numbers and say that there is ‘ 49° of strain’ at each carbon atom, making about 150° of strain in the molecule. This is a lot. The idea of strain is that the molecule wants to break open and restore the ideal tetrahedral angle at all atoms. This can be done by one nucleophilic attack.



Epoxides react cleanly with amines to give amino-alcohols. We have not so far featured amines as nucleophiles because their reactions with alkyl halides are often bedevilled by overreaction (see the next section), but with epoxides they give good results.



It is easy to see that inversion occurs in these $\text{S}_{\text{N}}2$ reactions if we put the epoxide on the side of another ring. With a five-membered ring only *cis*-fusion of the epoxide is possible and nucleophilic attack with inversion gives the *trans* product. As the epoxide is *up*, attack has to come from underneath. Notice that the new C–N bond is *down* and that the H atom at the site of attack was *down* in the epoxide but is *up* in the product. Inversion has occurred.



The product of this reaction is used in the manufacture of the antidepressant drug eclanamine by the Upjohn Company. Because the starting material must be a single diastereoisomer (the *cis* or *syn* isomer) and inversion has occurred at one carbon atom, the product must be the *trans* or *anti* diastereoisomer. The starting material cannot be a single enantiomer as it is not chiral (it has a plane of symmetry). Though the product is chiral, it cannot be optically active as no optically active reagents have gone into the reaction (Chapter 15). The biological activity in the drug requires this diastereoisomer.

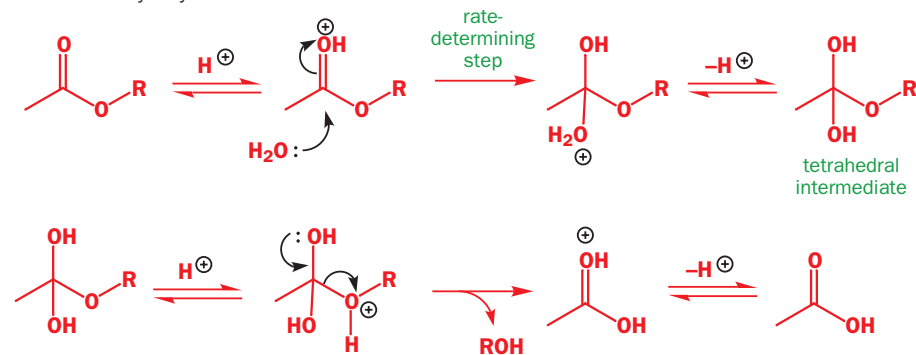
Esters

Nucleophilic attack on esters in acidic or basic solution normally occurs at the carbonyl group (Chapter 12). We are going to concentrate here on what happens to the hydrolysis of simple esters in acid solution as the alkyl group varies in size.

The slow step is the addition of water, which increases the crowding at the central carbon atom. As the alkyl group R is made larger, the reaction gets slower and slower. Then a dramatic thing happens. If the alkyl group R is made *tertiary*, the reaction suddenly becomes very fast indeed—faster than when R was methyl under the same conditions. Clearly, the mechanism has changed. It is no

■ We first discussed the idea of ring strain in Chapter 6, p. 000. The true origin of strain is the poor overlap between the orbitals forming the σ bonds inside the three-membered ring. This is discussed in Chapter 15 where another piece of evidence for ring strain is the peculiar chemical shifts in the proton NMR spectra of epoxides and other three-membered rings.

normal ester hydrolysis in acid solution

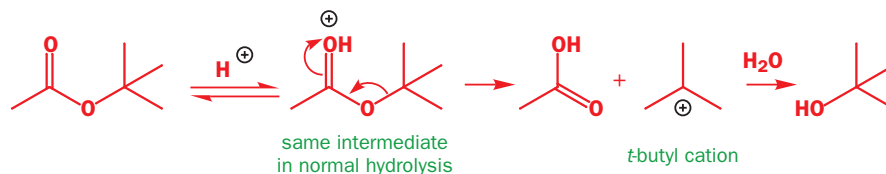


▶ ***t*-Butyl esters**

If you have several ester groups in a molecule and want to remove one without disturbing the others, then a *t*-butyl ester is the answer as it can be 'hydrolysed' in acid solution under very mild conditions. *t*-Butyl esters are used in protecting groups because they are so easily hydrolysed and this aspect of their chemistry is discussed in Chapter 24.

longer the normal ester hydrolysis but has become an S_N1 reaction at the alkyl group. It is still a substitution reaction but at the saturated carbon atom rather than at the carbonyl group. The first step is the same, but the protonated ester is a good leaving group and so the intermediate decomposes to the *t*-alkyl cation without needing water at all.

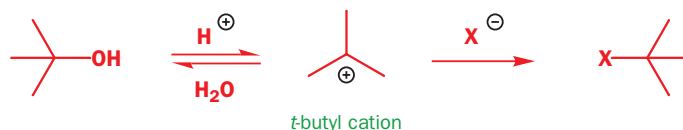
the S_N1 mechanism for *t*-alkyl ester hydrolysis in acid solution



Nucleophiles

We have established that the nucleophile is not important in the *rate* of an S_N1 reaction. We need now to discuss two ways in which it is important. Both concern the nature of the product. A better nucleophile will not accelerate the S_N1 reaction but it may determine which product is formed. In the reactions of tertiary alcohols with concentrated HCl or HBr there is always more water than halide ion present and yet the *t*-alkyl halide is formed in good yield.

reaction of tertiary alcohols with hydrogen halides



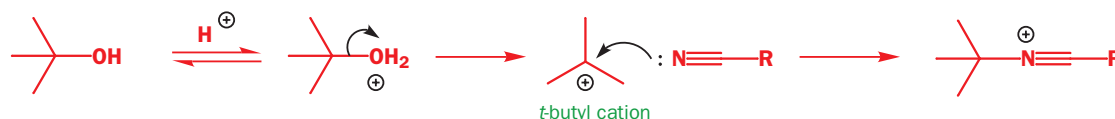
This is partly because the halide ion is a better nucleophile than water for a carbocation as both are charged and partly because, if water does act as a nucleophile, it merely regenerates the starting material, which may react again.

A more interesting result of the unimportance of the nucleophile in the rate is that very poor nucleophiles indeed may react in the absence of anything better. In Chapter 8 we established that nitriles are only weakly basic because the lone pair of electrons on the nitrogen atom is in a low-energy *sp* orbital. They are not good nucleophiles either.

nitriles are only weakly basic



If we dissolve *t*-butanol in a nitrile as solvent and add strong acid, a reaction does take place. The acid does not protonate the nitrile, but does protonate the alcohol to produce the *t*-butyl cation in the usual way. This cation is reactive enough to combine with even such a weak nucleophile as the nitrile.

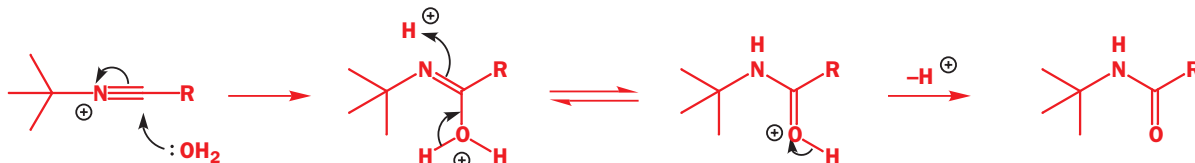


nitriles



lone pair in *sp* orbital

The resulting cation is captured by the water molecule released in the first step and an exchange of protons leads to an amide.



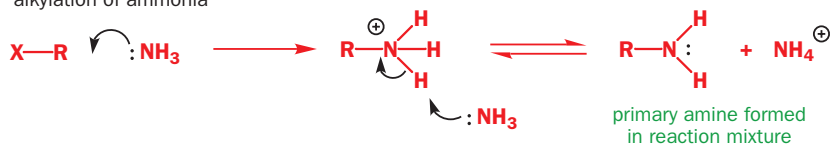
The overall process is called the **Ritter reaction** and is one of the few reliable ways to make a C–N bond to a tertiary centre.

Nucleophiles in the S_N2 reaction

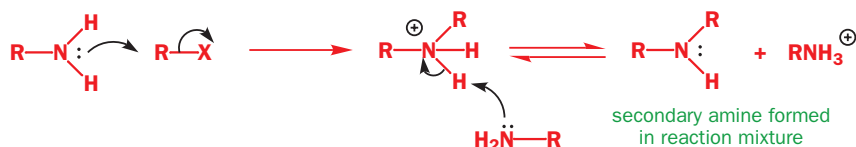
Nitrogen nucleophiles

Reactions between ammonia and alkyl halides rarely lead to single products. The problem is that the primary amine product is at least as nucleophilic as the starting material and is formed in the reaction mixture so that it in turn reacts with the alkyl halide.

alkylation of ammonia

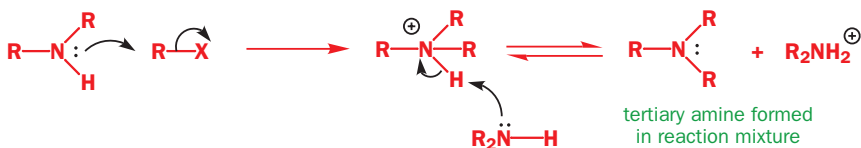


alkylation of the primary amine

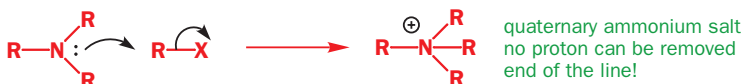


Even this is not all! If the alkylation were to continue, the secondary and the tertiary amines would be produced all together in the reaction mixture. The reaction comes to an end only when the *tetra*-alkylammonium salt R₄N⁺ is formed. This salt could be the product if a large excess of alkyl halide RI is used, but other more controlled methods are needed for the synthesis of primary, secondary, and tertiary amines.

alkylation of the secondary amine



alkylation of the tertiary amine

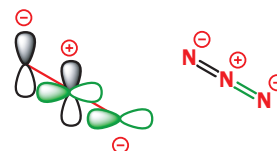


One solution for primary amines is to replace ammonia with azide ion N₃⁻. This is a linear triatomic species, nucleophilic at both ends—a little rod of electrons able to insert itself into almost any electrophilic site. It is available as the water-soluble sodium salt NaN₃.

Azide reacts only once with alkyl halides because the product, an alkyl azide, is no longer nucleophilic.



structure of azide ion N₃⁻



You should compare the structure of azide with those of ketene (p.000) and allene (p.000).

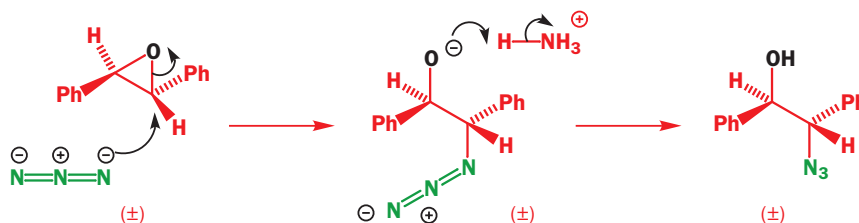
A warning about azides

Azides can be converted by heat—or even sometimes just by a sharp blow—suddenly into nitrogen gas. In other words they are potentially explosive, particularly inorganic (that is, ionic) azides and small covalent organic azides.

The alkyl azide produced can be reduced to the primary amine by a number of methods such as catalytic hydrogenation (Chapter 24) or LiAlH_4 (Chapter 12). This method has a similar philosophy to the reductive amination discussed in Chapter 14.

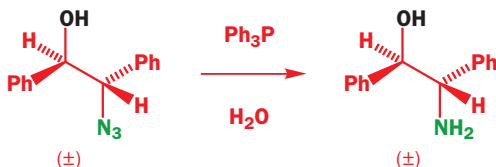


Azide reacts cleanly with epoxides too: here is an example with some stereochemistry in an open-chain epoxide.

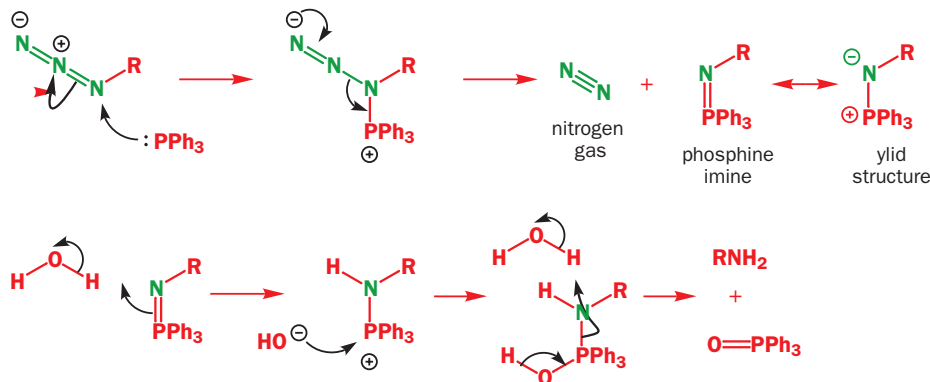


The epoxide is one diastereoisomer (*trans*) but racemic and the symbol (\pm) under each structure reminds you of this (Chapter 15). Azide attacks at either end of the three-membered ring (the two ends are the same) to give the hydroxy-azide. The reaction is carried out in a mixture of water and an organic solvent with ammonium chloride as buffer to provide a proton for the intermediate.

Next, triphenylphosphine in water was used for reduction to the primary amine. This process might remind you of the Mitsunobu reaction earlier in this chapter.



One possible mechanism follows. What is certainly true is that a molecule of nitrogen is lost and a molecule of water is ‘dismembered’ and shared between the reagents. The phosphorus atom gets the oxygen and the nitrogen atom gets the two hydrogens. These (P=O and N–H rather than N–O and P–H) are the stronger bonds.

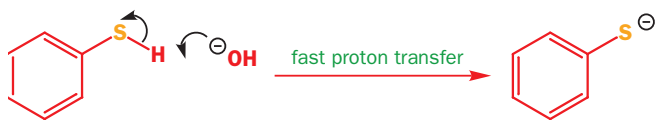


Sulfur nucleophiles are better than oxygen nucleophiles in $\text{S}_{\text{N}}2$ reactions

Thiolate anions make excellent nucleophiles in $\text{S}_{\text{N}}2$ reactions on alkyl halides. It is enough to combine the thiol, sodium hydroxide, and the alkyl halide to get a good yield of the sulfide.

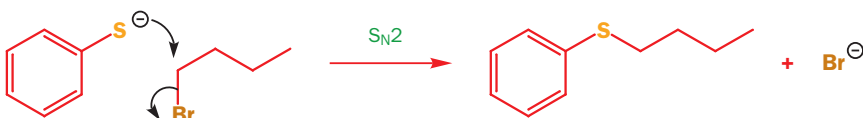


There is no competition between hydroxide and thiol because thiols are more acidic than water ($\text{p}K_{\text{a}}$ of RSH is typically 9–10, $\text{p}K_{\text{a}}$ of PhSH is 6.4, $\text{p}K_{\text{a}}$ of H_2O is 15.7; Chapter 8) and there is a rapid proton transfer from sulfur to oxygen.

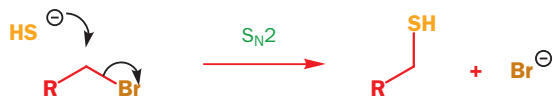


The thiolate anion produced then acts as a nucleophile in the S_N2 reaction.

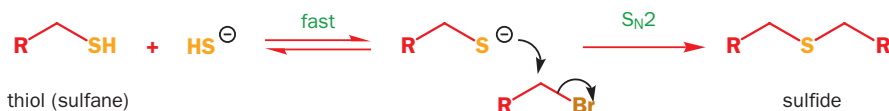
the S_N2 reaction with a thiolate anion as nucleophile



But how do you make a thiol in the first place? The obvious way to make aliphatic thiols would be by an S_N2 reaction using NaSH on the alkyl halide.



This works well but, unfortunately, the product easily exchanges a proton and the reaction normally produces the symmetrical sulfide—this should remind you of what happened with amines!

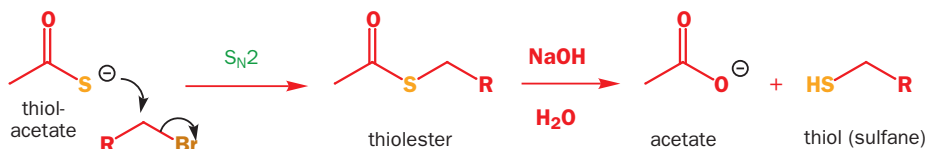


thiol (sulfane)

sulfide

The solution is to use the anion of thioacetic acid, usually the potassium salt. This reacts cleanly through the more nucleophilic sulfur atom and the resulting ester can be hydrolysed in base to liberate the thiol.

the S_N2 reaction with a thioacetate anion as nucleophile



Effectiveness of different nucleophiles in the S_N2 reaction

Just to remind you of what we said before: basicity is nucleophilicity towards protons and nucleophilicity towards the carbonyl group parallels basicity almost exactly.

During this chapter you have had various hints that nucleophilicity towards saturated carbon is not so straightforward. Now we must look at this question seriously and try to give you helpful guidelines.

1 If the atom that is forming the new bond to carbon is the same over a range of nucleophiles—it might be oxygen, for example, and the nucleophiles might be HO^- , PhO^- , AcO^- , and TsO^- —then nucleophilicity does parallel basicity. The anions of the weakest acids are the best nucleophiles. The order for the nucleophiles we have just mentioned will be: $\text{HO}^- > \text{PhO}^- > \text{AcO}^- > \text{TsO}^-$. The actual values for the rates of attack of the various nucleophiles on MeBr in EtOH relative to the rate of reaction with water (=1) are given in Table 17.14

Table 17.14 Relative rates (water = 1) of reaction with MeBr in EtOH

Nucleophile X	$\text{p}K_a$ of HX	Relative rate
HO^-	15.7	1.2×10^4
PhO^-	10.0	2.0×10^3
AcO^-	4.8	9×10^2
H_2O	-1.7	1.0
ClO_4^-	-10	0

2 If the atoms that are forming the new bond to carbon are *not* the same over the range of

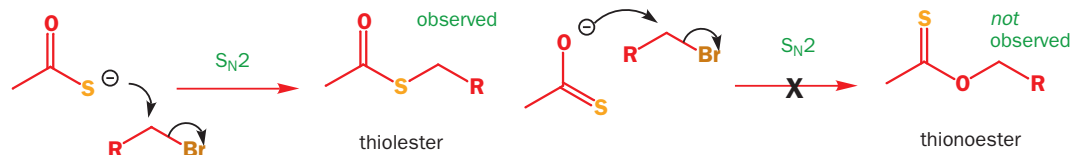
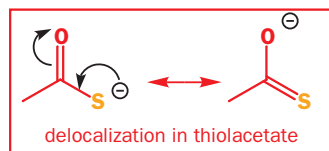
This was discussed in Chapter 12.

nucleophiles we are considering, then another factor is important. In the very last examples we have been discussing we have emphasized that RS^- is an excellent nucleophile for saturated carbon. Let us put that another way. RS^- is a better nucleophile for saturated carbon than is RO^- , even though RO^- is more basic than RS^- (Table 17.15).

Table 17.15 Relative rates (water = 1) of reaction with MeBr in EtOH

Nucleophile X	$\text{p}K_{\text{a}}$ of HX	Relative rate
PhS^-	6.4	5.0×10^7
PhO^-	10.0	2.0×10^3

You might have noticed that the thiolacetate ion could have reacted with an alkyl halide through sulfur or through oxygen:



▶ We had a similar discussion in Chapter 10 when we were considering nucleophiles attacking conjugated $\text{C}=\text{C}-\text{C}=\text{O}$ systems. Attack at $\text{C}=\text{O}$ in these systems tends to be electrostatically controlled, while nucleophilic attack at $\text{C}=\text{C}$ is under orbital (HOMO–LUMO) control.

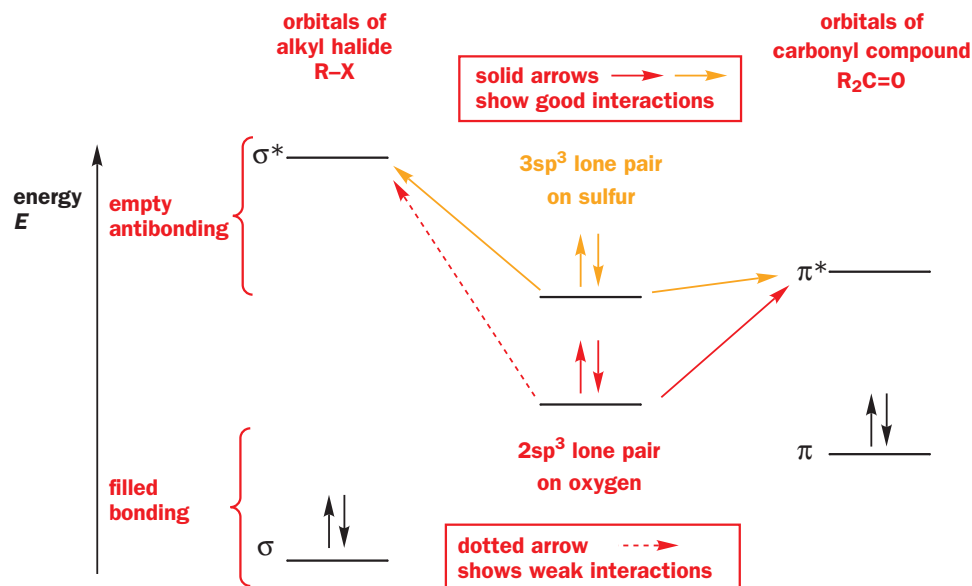
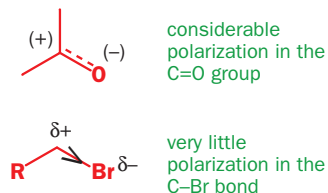
It is clear then that sulfur is a better nucleophile than is oxygen for saturated carbon. Why should this be? There are two main factors controlling bimolecular reactions: electrostatic attraction (simple attraction of opposite charges) and productive interactions between the HOMO of the nucleophile and the LUMO of the electrophile.

Reactions of nucleophiles with protons and with carbonyl groups are heavily influenced by electrostatic attraction (as well as by HOMO–LUMO interactions). The proton is, of course, positively charged. The carbonyl group too has a substantial positive charge on the carbon atom, which comes from the uneven distribution of electrons in the $\text{C}=\text{O}$ π bond (Chapter 4).

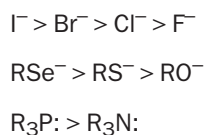
There is, of course, also some polarity in the bond between a saturated carbon atom and a leaving group, say, a bromine atom, but this is a much smaller effect leading only to very small charge separation represented as δ^+ . In alkyl iodides, one of the best electrophiles in $\text{S}_{\text{N}}2$ reactions, there is in fact almost no dipole at all—the electronegativity of C is 2.55 and that of I is 2.66. Electrostatic attraction is unimportant in $\text{S}_{\text{N}}2$ reactions.

So what does matter? Only HOMO–LUMO interactions matter. In nucleophilic attack on the carbonyl group, the nucleophile added in to the low-energy π^* orbital. In attack on a saturated carbon atom, the nucleophile must donate its electrons to the σ^* orbital of the $\text{C}-\text{X}$ bond as we discussed in Chapter 10.

typical arrangement of molecular energy levels



The higher-energy ($3sp^3$) lone-pair electrons on sulfur overlap better with the high-energy σ^* orbital of the C–X bond than do the lower-energy ($2sp^3$) lone-pair electrons on oxygen because the higher energy of the sulfur electrons brings them closer in energy to the C–X σ^* orbital. Notice that both elements overlap well with the lower-energy π^* orbital. The conclusion is that nucleophiles from lower down the periodic table are more effective in S_N2 reactions than those from the top few rows. Typically, nucleophilic power towards saturated carbon goes like this.



Nucleophiles in substitution reactions

Some rates (relative to that of water = 1) of various nucleophiles towards methyl bromide in ethanol are shown in Table 17.16.

Table 17.16 Relative rates (water = 1) of reaction of nucleophiles with MeBr in EtOH

nucleophile	F [−]	H ₂ O	Et ₃ N	Br [−]	PhO [−]	EtO [−]	I [−]	PhS [−]
relative rate	0.0	1.0	1400	5000	2.0×10^3	6×10^4	1.2×10^5	5.0×10^7

You have met a similar sequence before in Chapter 10, and it would be useful to review the terms we used then. Nucleophiles like $\text{R}_3\text{P}:$ and RS^- , the ones that react well with saturated carbon, are referred to as **soft nucleophiles** and those that are more basic and react well with carbonyl groups referred to as **hard nucleophiles**. These are useful and evocative terms because the soft nucleophiles are rather large and flabby with diffuse high-energy electrons while the hard nucleophiles are small with closely held electrons and high charge density. When we say ‘hard’ (nucleophile or electrophile) we refer to species whose reactions are dominated by electrostatic attraction and when we say ‘soft’ (nucleophile or electrophile) we refer to species whose reactions are dominated by HOMO–LUMO interactions.

Just to remind you: reactions dominated by electrostatic attraction also need to pass electrons from HOMO to LUMO, but reactions that are dominated by HOMO–LUMO interactions need have *no* contribution from electrostatic attraction.

- It is worth summarizing the characteristics of the two types of nucleophile.

Hard nucleophiles X

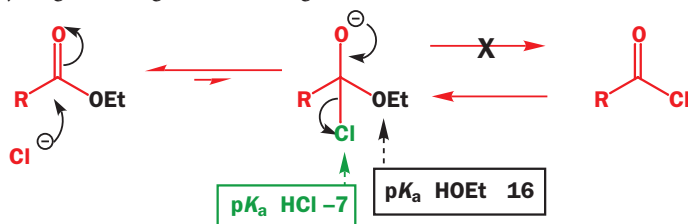
small
charged
basic (HX weak acid)
low-energy HOMO
like to attack C=O
such as RO^- , NH_2^- , MeLi

Soft nucleophiles Y

large
neutral
not basic (HY strong acid)
high-energy HOMO
like to attack saturated carbon
such as RS^- , I^- , R_3P

Nucleophiles and leaving groups compared

In nucleophilic attack on the carbonyl group, a good nucleophile is a bad leaving group and vice versa because the intermediate chooses to expel the best leaving group. If that is the nucleophile, it just goes straight back out again.



Chloride ion will always be the best leaving group from the intermediate, however it is formed, and the attempt to make an acid chloride from an ester with NaCl is doomed. Chloride is a good leaving group from C=O and a bad nucleophile towards C=O while EtO⁻ is a bad leaving group from C=O and a good nucleophile towards C=O.

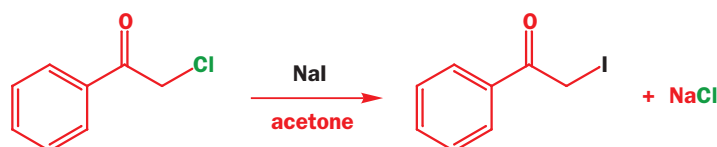
The S_N2 reaction is different because it does not have an intermediate. Therefore anything that lowers the energy of the transition state will speed up both the forward and the back reactions. We need to consider two results of this: the rate of the reaction and which way it will go.

Iodide ion is one of the best nucleophiles towards saturated carbon because it is at the bottom of its group in the periodic table and its lone-pair electrons are very high in energy. This is in spite of the very low basicity of iodide (Table 17.17). It reacts rapidly with a variety of alkyl derivatives and alkyl iodides can be made by displacement of chloride or tosylate by iodide.

Table 17.17 Relative rates (water = 1) of reaction with MeBr in EtOH

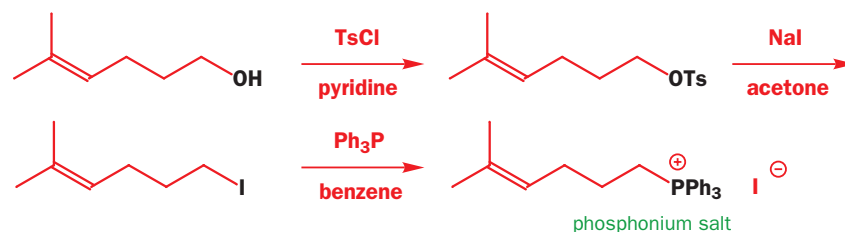
Nucleophile X	pK _a of HX	Relative rate
I ⁻	-10	1.2 × 10 ⁵
Br ⁻	-9	5.0 × 10 ³
Cl ⁻	-7	1.1 × 10 ³
F ⁻	+3	0

▶ The first of these reactions is assisted by precipitation of NaCl from acetone, which drives the reaction along.

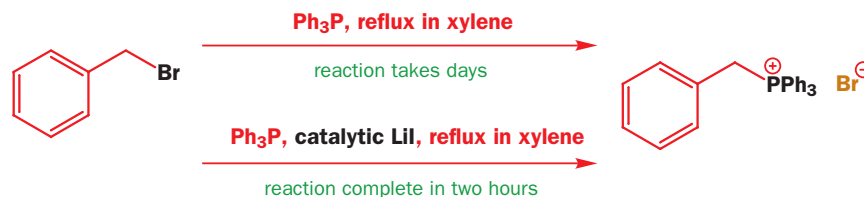


But why are these alkyl iodides made? They are needed for reactions with other nucleophiles in which iodide is again displaced. As well as being one of the best nucleophiles for saturated carbon, iodide ion is one of the best leaving groups from saturated carbon (see p. 000). Yields are often higher if the alkyl iodide is prepared than if the eventual nucleophile is reacted directly with the alkyl tosylate or chloride.

An example is the synthesis of the phosphonium salt used by Corey in a synthesis of terpenes (Chapter 51). An unsaturated primary alcohol was first made into its tosylate, the tosylate was converted into the iodide, and the iodide into the phosphonium salt.



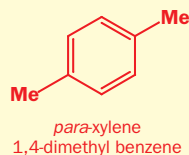
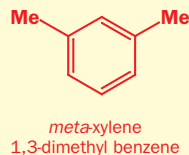
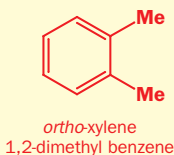
However, iodine is expensive and a way round that problem is to use a catalytic amount of iodide. The next phosphonium salt is formed slowly from benzyl bromide but the addition of a small amount of LiI speeds up the reaction considerably.



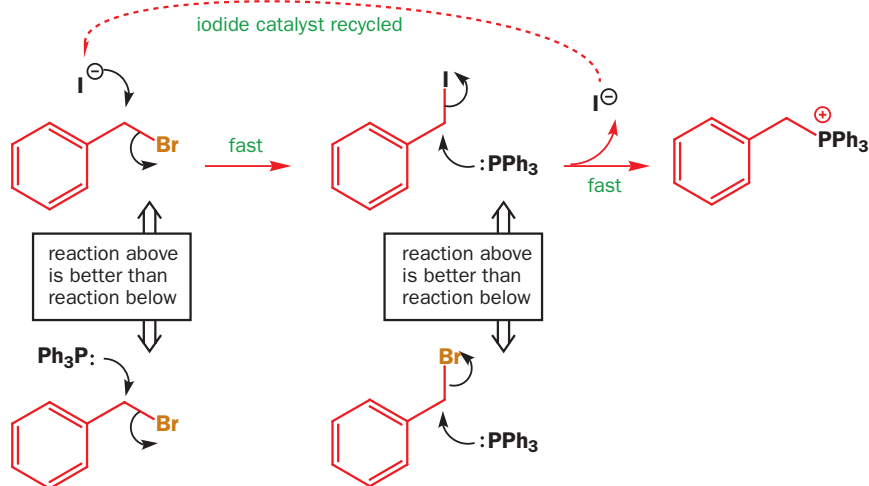
Xylenes

The solvent 'xylene' needs some explanation. Xylene is the trivial name for dimethyl benzene and there are three isomers. Mixed xylenes are isolated cheaply from oil and often used as a relatively high boiling solvent (b.p. about

140 °C) for reactions at high temperature. In this case, the starting materials are soluble in xylene but the product is a salt and conveniently precipitates out during the reaction.



The iodide reacts as a better nucleophile than Ph_3P and then as a better leaving group than Br^- . Each iodide ion goes round and round many times as a **nucleophilic catalyst**.



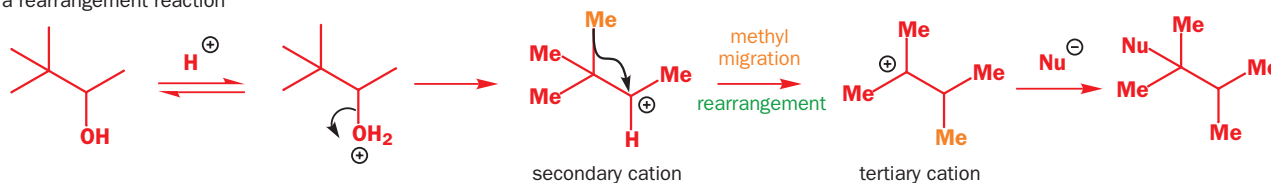
Looking forward: elimination and rearrangement reactions

Simple nucleophilic substitutions at saturated carbon atoms are fundamental reactions found wherever organic chemistry is practised. They are used in industry on an enormous scale to make 'heavy chemicals' and in pharmaceutical laboratories to make important drugs. They are worth studying for their importance and relevance.

There is another side to this simple picture. These were among the first reactions whose mechanisms were thoroughly investigated by Ingold in the 1930s and since then they have probably been studied more than any other reactions. All our understanding of organic mechanisms begins with $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions and you need to understand these basic mechanisms properly. Some of the more sophisticated investigations into nucleophilic substitutions have clouded the main issues by looking at minute details and we shall not discuss these.

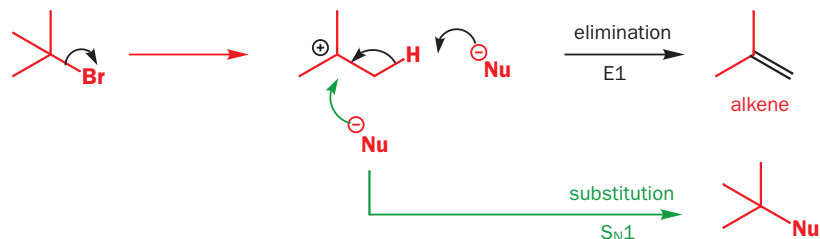
We shall, however, be returning to this sort of chemistry in several further chapters. The carbocations you met in this chapter are reactive species. One of the most convincing pieces of evidence for their formation is that they undergo reactions other than simple addition to nucleophiles. The carbon skeleton of the cation may rearrange.

a rearrangement reaction



You will meet rearrangements in several chapters later in the book especially Chapter 37. Another common fate of cations, and something that may also happen instead of an intended S_N1 or S_N2 reaction, is an elimination reaction where an alkene is formed by the nucleophile acting as a base to remove HX instead of adding to the molecule.

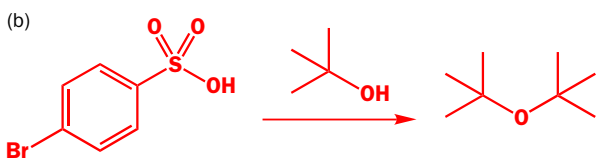
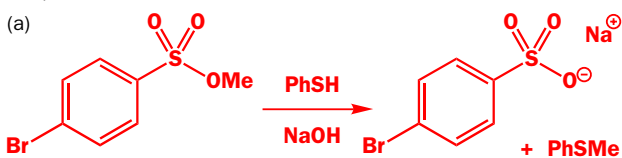
an elimination reaction (E1)



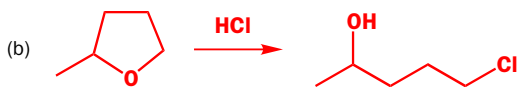
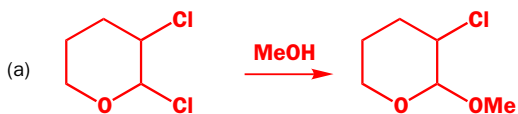
You will meet elimination reactions in the next chapter but one (19) after some further exploration of stereochemistry.

Problems

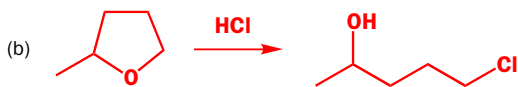
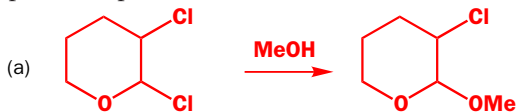
1. Suggest mechanisms for the following reactions, commenting on your choice of S_N1 or S_N2 .



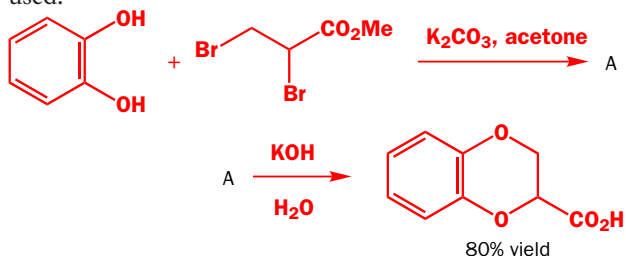
2. Draw mechanisms for the following reactions. Why were acidic conditions chosen for the first reaction and basic conditions for the second?



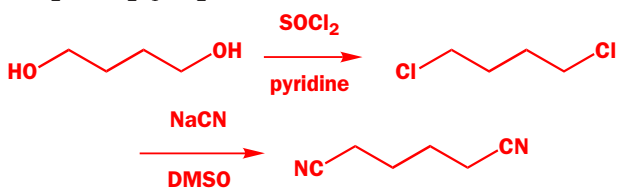
3. Draw mechanisms for these reactions, explaining why these particular products are formed.



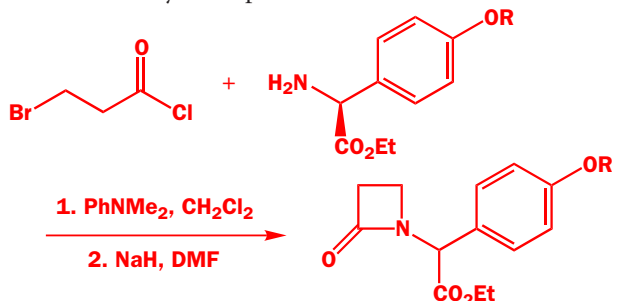
4. The chemistry shown here is the first step in the manufacture of Pfizer's doxazosin (Cardura), a drug for hypertension. Draw mechanisms for the reactions involved and comment on the bases used.



5. Suggest mechanisms for these reactions, commenting on the choice of reagents and solvents. How would you convert the final product into diethyl hexanedioate [diethyl adipate, $\text{EtO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{Et}$]?



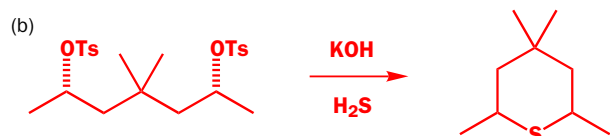
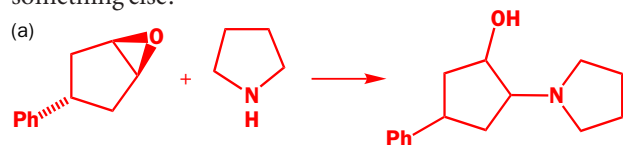
6. Draw mechanisms for these reactions and describe the stereochemistry of the product.



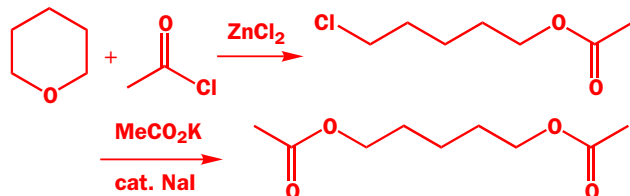
7. Suggest a mechanism for this reaction. You will find it helpful first of all to draw good diagrams of reagents and products.



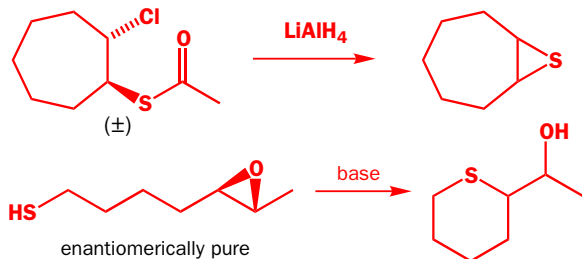
8. Predict the stereochemistry of these products. Are they single diastereoisomers, enantiomerically pure, or racemic, or something else?



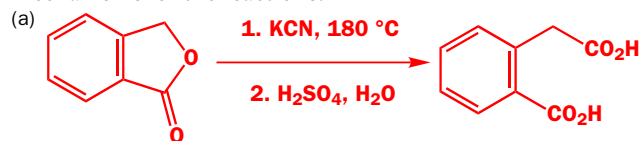
9. What are the mechanisms of these reactions, and what is the role of the ZnCl_2 in the first step and the NaI in the second?



10. Describe the stereochemistry of the products of these reactions.



11. Identify the intermediates in these syntheses and give mechanisms for the reactions.



12. State with reasons whether these reactions will be either $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$.

