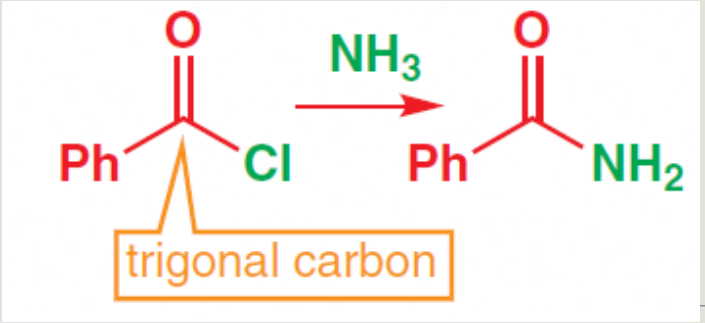
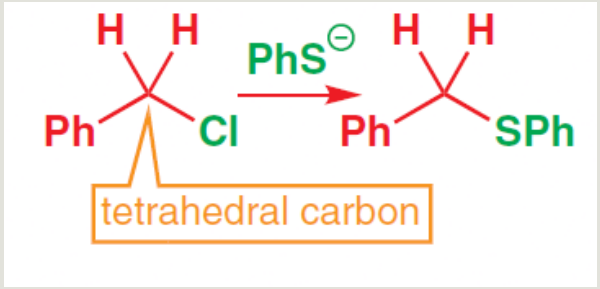
Nucleophilic aliphatic substitution

RASHMI PUNDEER
PROFESSOR, DEPARTMENT OF CHEMISTRY
INDIRA GANDHI UNIVERSITY, MEERPUR, REWARI, HARYANA



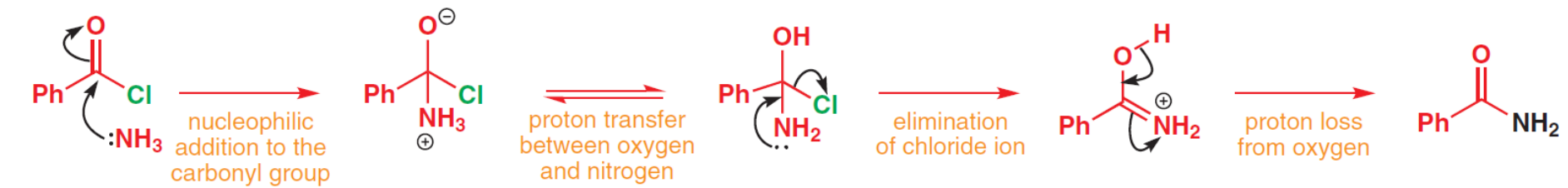
1. Substitution is the replacement of one group by another.



2. Substitution because the Cl group is replaced by the NH2 group.
3. ammonia (NH3) is **nucleophile** and the chloride is the **leaving group**.
4. In first reaction, the substitution reactions took place at the *trigonal* (sp2) carbon atom of a carbonyl group.
5. Second reaction is also substitution reaction, because the Cl group is replaced by the PhS group. But the CH2 group at which the reaction takes place is a *tetrahedral* (sp3), or *saturated*, carbon atom, rather than a C=O group.

The requirements of good reagents are also different in substitutions at carbonyl groups and at saturated carbon—that's why the nucleophile is changed from NH3 to PhS−: ammonia would not give a good yield of PhCH2NH2 in the second reaction

Nucleophilic substitution at carbonyl

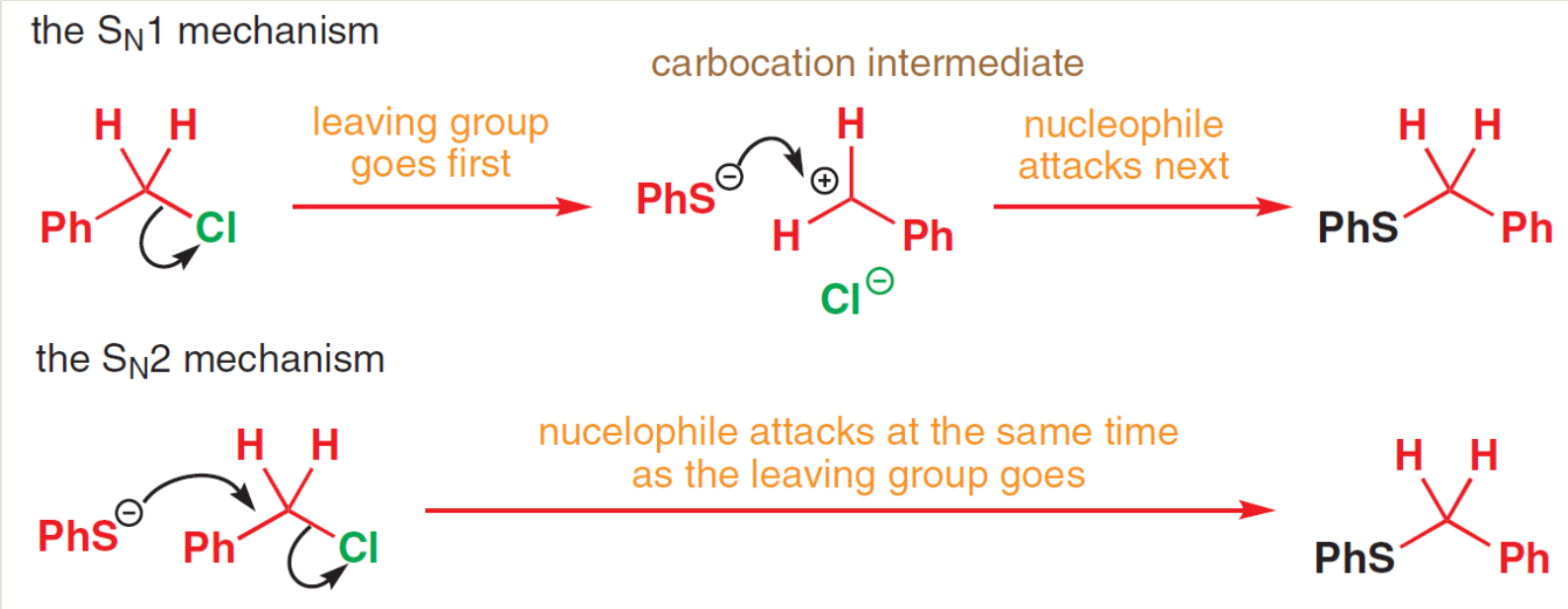


In the first step the nucleophile attacks the C=O π bond

the first step is no longer possible at a saturated carbon atom.

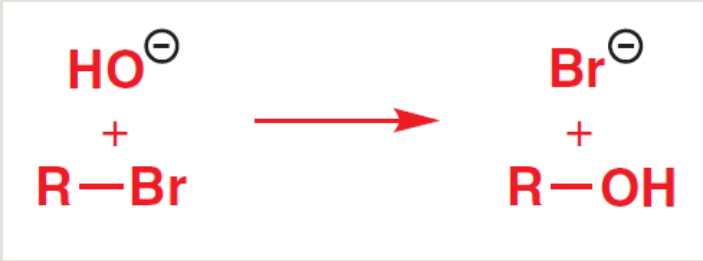
The electrons cannot be added to a π bond as the CH2 group is fully saturated.

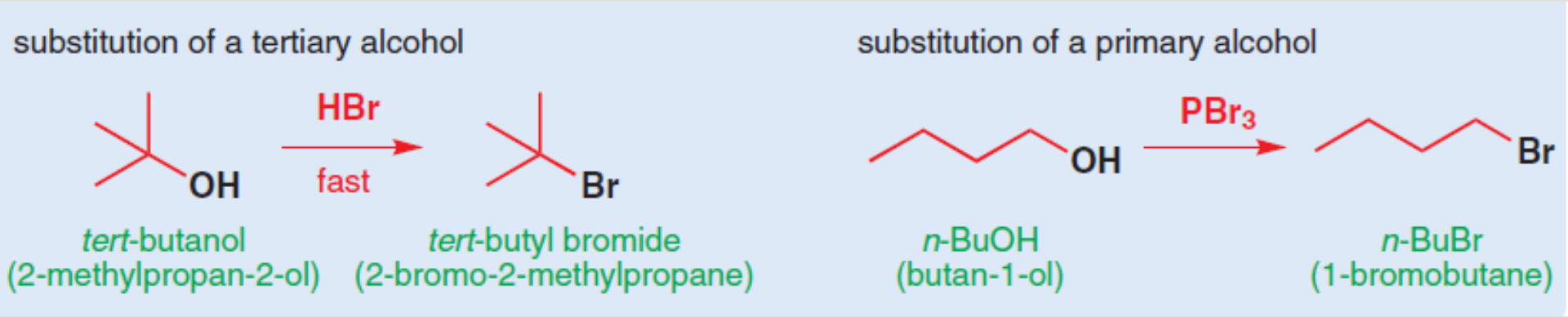
In fact there is no way for the nucleophile to add before the leaving group departs (as it did in the reaction above) because this would give an impossible five-valent carbon atom.



- 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, we learn to call the SN1 mechanism.
- The second mechanism, which shows how the neutral carbon atom can accept electrons provided it loses some at the same time, we learn to call the SN2 mechanism.

Replacement of OH by Br





i. If we know which mechanism a compound reacts by, we know what sort of conditions to use to get good yields in substitutions.

ii. For example, if we look at a commonly used nucleophilic substitution, the replacement of OH by Br, we will find that two quite different reaction conditions are used depending on the structure of the alcohol.

- Tertiary alcohols react rapidly with HBr to give tertiary alkyl bromides.
- Primary alcohols, react only very slowly with HBr and are usually converted to primary alkyl bromides with PBr3.

The reason is that the first example is an SN1 reaction while the second is an SN2 reaction

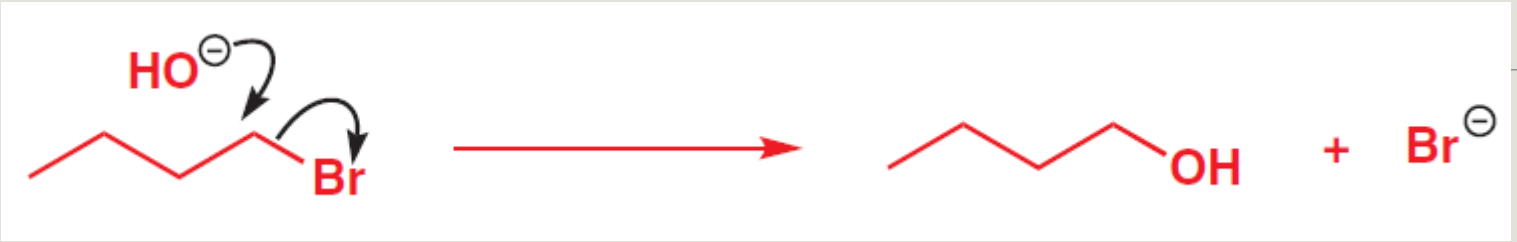
some nucleophilic substitutions are first order (that is, the rate depends only on the concentration of the alkyl halide and does not depend on the concentration of the nucleophile)

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while others are second order (the rate depends on the concentrations of both the alkyl halide and the nucleophile

Substitution, Nucleophilic, 2nd order

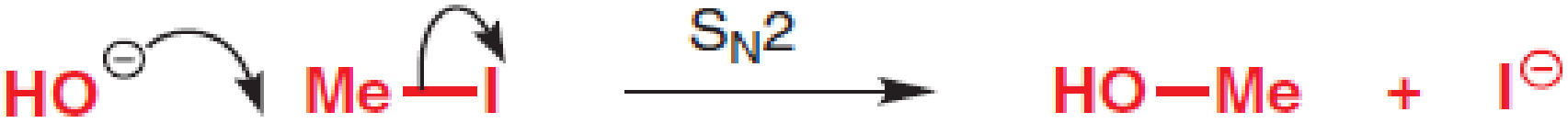
(One-step SN2 mechanism for substitution of *n*-butyl bromide by hydroxide)



With only one step, that step must be the **rate-determining step**.

The rate of the overall reaction depends only on the rate of this step, and kinetic theory tells us that the rate of a reaction is proportional to the concentrations of the reacting species:

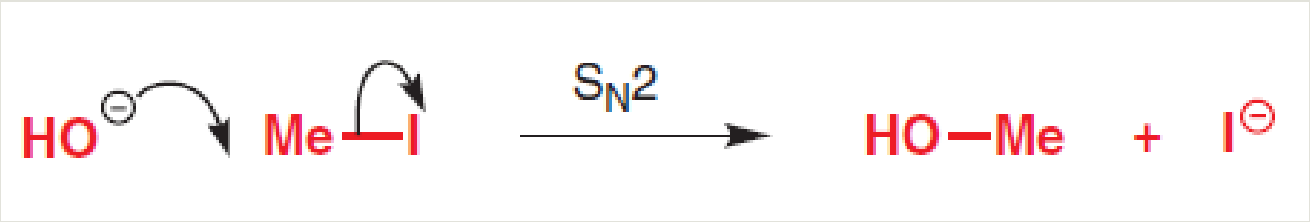
$$\text{rate of reaction} = k[\text{n-BuBr}][HO^-]$$



a. Performance of an SN2 reaction depends **both on the nucleophile and on the carbon electrophile**. We can therefore make a reaction go better (speed it up or improve its yield) by changing either.
b. For example, if we want to displace I– from MeI using an oxygen nucleophile we might consider using any of those in the table.

Oxygen nucleophiles in the S_N2 reaction

Oxygen nucleophile	pK_a of conjugate acid	Rate in S_N2 reaction
HO^-	15.7 (H_2O)	fast
RCO_2^-	about 5 (RCO_2H)	moderate
H_2O	–1.7 (H_3O^+)	slow
RSO_2O^-	0 (RSO_2OH)	slow



1. 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.

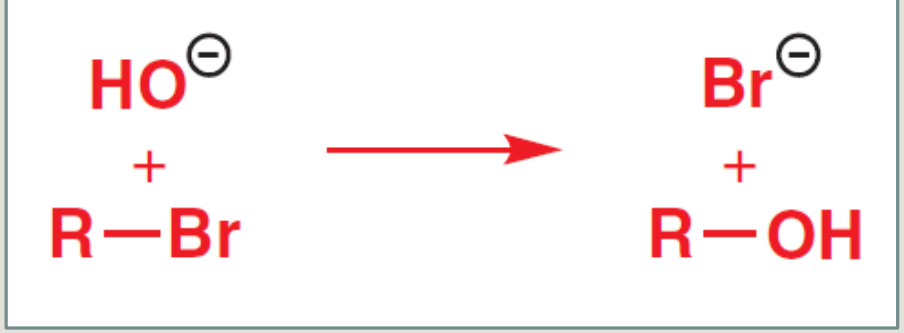
2. The table below shows what happens if we use the various methyl halides in reaction with NaOH. The best choice for a fast reaction (greatest value of *k*2) will be to use MeI and NaOH to give methanol.

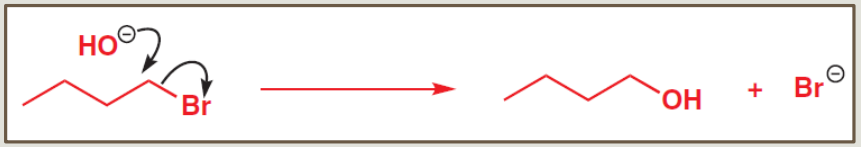
Halide X in MeX	pK_a of conjugate acid HX	Rate of reaction with NaOH
F	+3	very slow indeed
Cl	–7	moderate
Br	–9	fast
I	–10	very fast

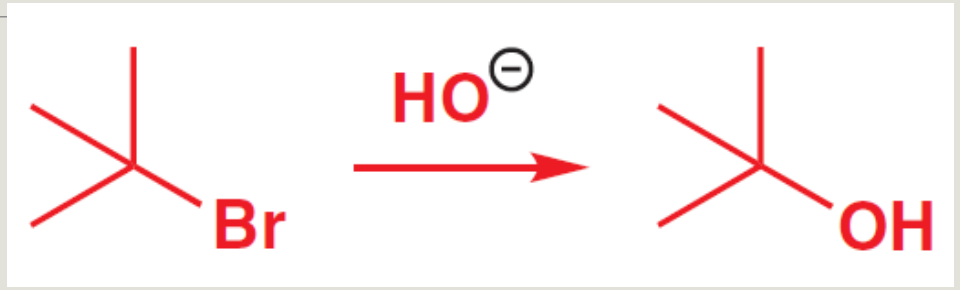
The rate of an S_N2 reaction depends on:

- **the nucleophile**
- **the carbon skeleton**
- **the leaving group**

along with the usual factors of temperature and solvent.

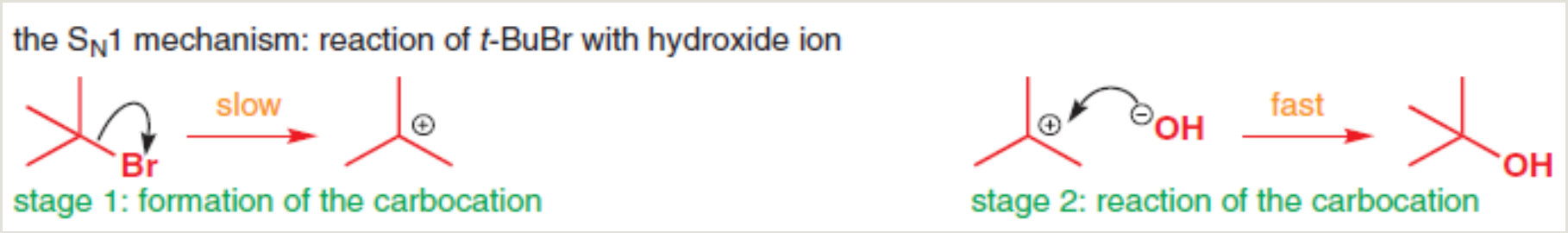






If we replace the substitution of *n*-butyl bromide with a substitution of *t*-butyl bromide, kinetically, this reaction is first order: its rate depends only on the concentration of *tert*-BuBr-it doesn't matter how much hydroxide we add: the rate equation is

rate = $k1[t\text{-BuBr}]$



- reaction happens in two steps: first the bromide leaves, to generate a carbocation, and only then does the hydroxide ion move in to attack, forming the alcohol.

Substitution, Nucleophilic, 1st order: S_N1

rate is proportional to one concentration only)

In the S_N1 mechanism, the formation of the cation is the rate-determining step.

This makes a good sense: a carbocation is an unstable species and so it will be formed slowly from a stable neutral organic molecule.

But once formed, being very reactive, all its reactions will be fast, regardless of the nucleophile.

The rate of disappearance of *t*-BuBr is therefore simply the rate of the slow first step

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)

Indeed, SN1 substitution reactions are generally best done with weaker, non-basic nucleophiles to avoid the competing elimination reactions

The rate of an SN1 reaction depends on:

the nucleophile……NO

- **the carbon skeleton**

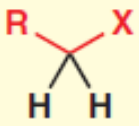
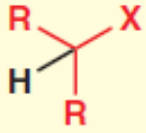
the leaving group

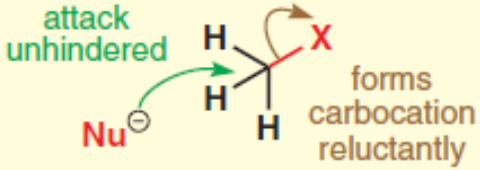
along with the usual factors of temperature and solvent.

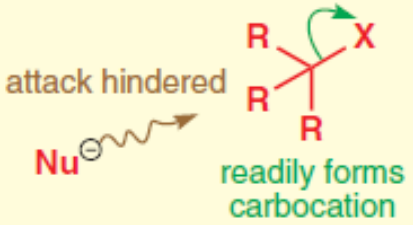
SN1 or SN2: carbon skeleton

- **S_N1 or S_N2?**

Simple structures and choice of S_N1 or S_N2 mechanism

Structure	Me—X			
type	methyl	primary	secondary	tertiary
S_N1 reaction?	no	no	moderate	excellent
S_N2 reaction?	good	good	moderate	no





Compounds that can form relatively stable carbocations generally do so and react by the S_N1 mechanism, while the others have no choice but to react by the S_N2 mechanism.

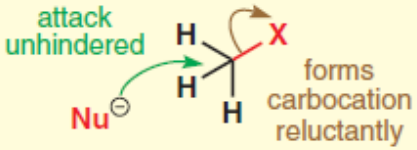
the most stable carbocations are the ones that have the most substituents, so the more carbon substituents at the reaction centre, the more likely the compound is to react by the S_N1

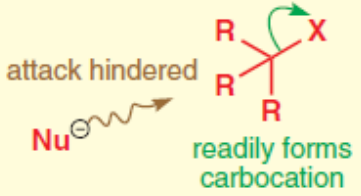
SN1 or SN2: carbon skeleton

- **S_N1 or S_N2?**

Simple structures and choice of S_N1 or S_N2 mechanism

Structure	Me—X	R, X, H, H	R, X, H, R	R, X, R, R
type	methyl	primary	secondary	tertiary
S_N1 reaction?	no	no	moderate	excellent
S_N2 reaction?	good	good	moderate	no





Structural factors that make cations stable usually also lead to slower SN2 reactions.

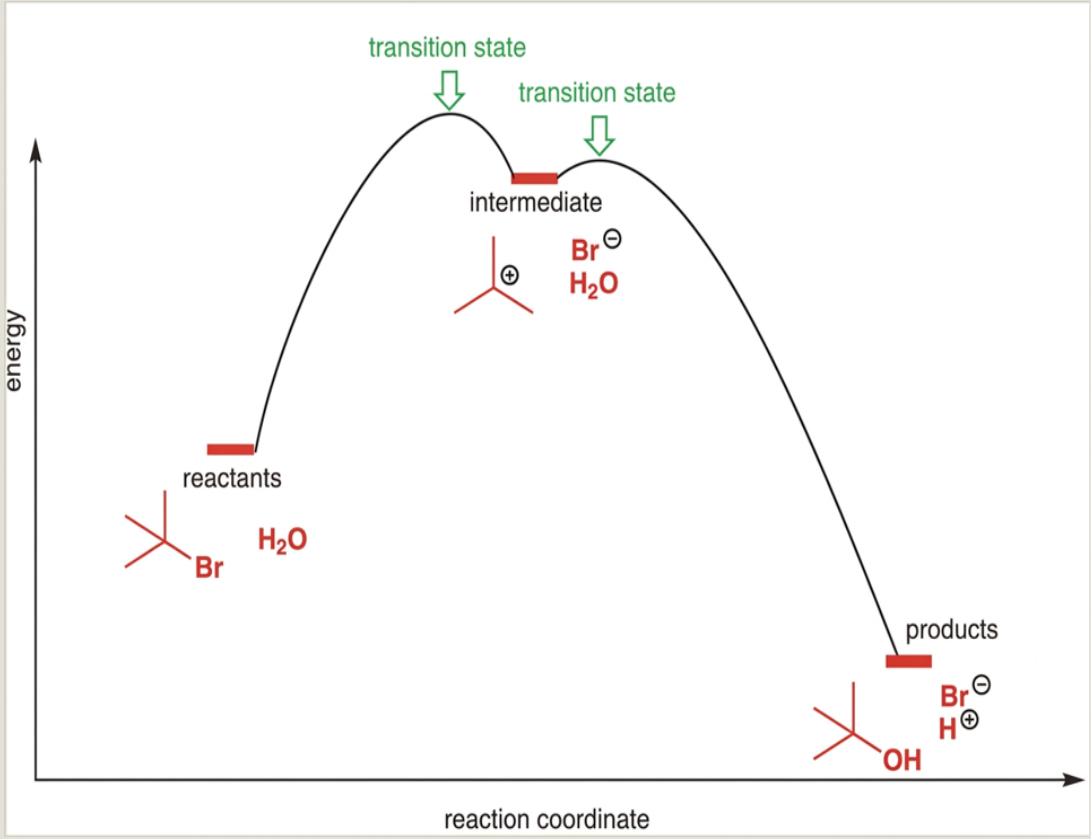
Heavily substituted compounds are good in SN1 reactions, but bad in an SN2 reaction because the nucleophile would have to squeeze its way into the reaction centre past the substituents.

It is better for an SN2 reaction if there are only hydrogen atoms at the reaction centre: methyl groups react fastest by the SN2 mechanism.

The only doubtful case is the secondary alkyl derivative, which can react by either mechanism, although it is not very good at either.

The first question you should ask when faced with a new nucleophilic substitution is this 'Is the carbon electrophile methyl, primary, secondary, or tertiary?'

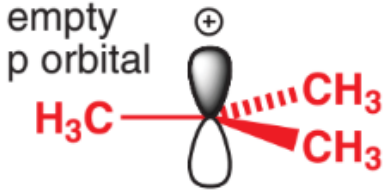
S_N1 Reaction



The carbocation is shown as an intermediate—a species with a finite (if short) lifetime
And because we know that the first step, the formation of the carbocation, is slow, that must be the step with the higher energy transition state.

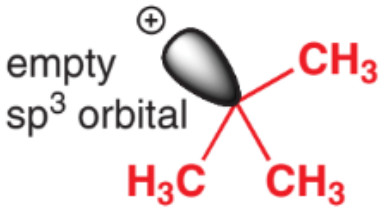
The energy of that transition state, which determines the overall rate of the reaction, is closely linked to the stability of the carbocation intermediate, and it is for this reason that the most important factor in determining the efficiency of an SN1 reaction is the stability of any carbocation that might be formed as an intermediate.

correct planar structure for the *t*-butyl cation



less repulsion between bonding pairs of electrons

incorrect tetrahedral structure for the *t*-butyl cation



more repulsion between bonding pairs of electrons

the electron-deficient central carbon atom has only six electrons, which it uses to form three σ bonds, and therefore also carries an empty p orbital.

Any carbocation will have a planar carbon atom with an empty p orbital. Think of it this way: only filled orbitals contribute to the energy of a molecule, so if you have to have an unfilled orbital (which a carbocation always does) it is best to make that unfilled orbital as high in energy as possible to keep the filled orbitals low in energy. p orbitals are higher in energy than s orbitals (or hybrid sp, sp2, or sp3 orbitals for that matter) so the carbocation always keeps the p orbital empty.

t-Butyl cation is stable enough to observe because of the work of George Olah, who won the Nobel Prize for Chemistry in 1994.

The challenge is that carbocations are very reactive electrophiles, so Olah's idea was to have a solution containing no nucleophiles.

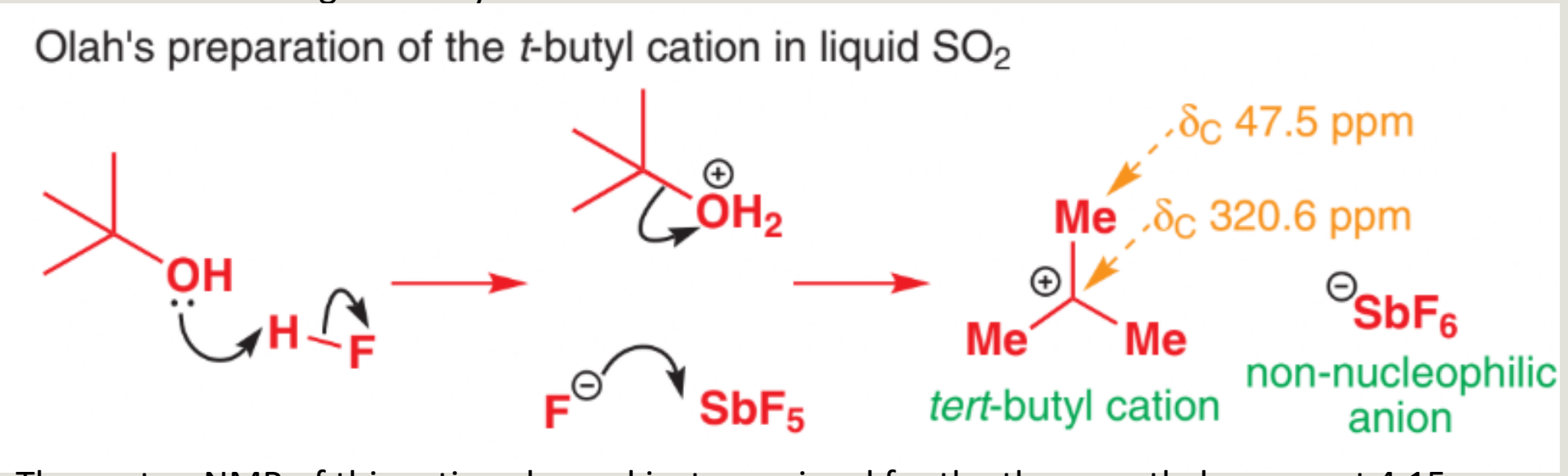
Any cation must have an anion to balance the charge, so the important advance was to find anions, consisting of a negatively charged atom surrounded by tightly held halogen atoms, which are just too stable to be nucleophilic. Examples include BF_4^- , PF_6^-, and Sb_6^-
The first is small and tetrahedral and the others are larger and octahedral.

In these anions, the negative charge does not correspond to a lone pair of electrons (they are like BH_4^- in this respect) and there is no orbital high enough in energy to act as a nucleophile.

By using a non-nucleophilic solvent, liquid SO2, at low temperature, Olah was able to turn alcohols into carbocations with these counterions.

This is what happens when tert-butanol is treated with SbF5 and HF in liquid SO2. The acid protonates the hydroxyl group, allowing it to leave as water, while the SbF5 grabs the fluoride ion, preventing it from acting as a nucleophile.

The cation is left high and dry.

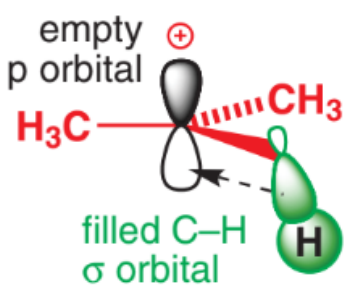


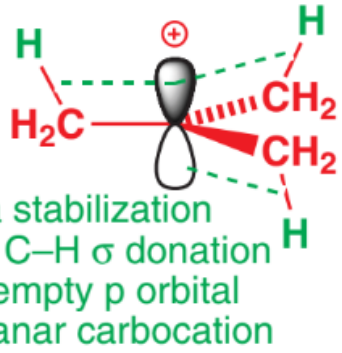
The proton NMR of this cation showed just one signal for the three methyl groups at 4.15 ppm, quite far downfield for C–Me groups.

The 13C spectrum also showed downfield Me groups at 47.5 ppm, but the key evidence that the cation was formed was the shift of the central carbon atom, which came at an amazing 320.6 ppm, way downfield. This carbon is very deshielded--it is positively charged and extremely electron deficient.

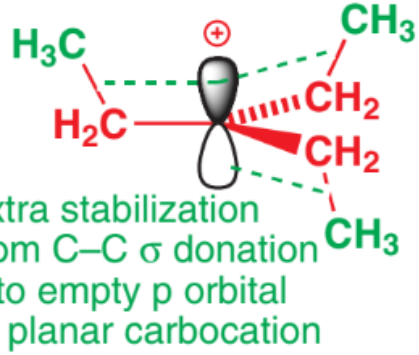
Any charged organic intermediate is inherently unstable because of the charge. A carbocation can be formed only if it has some extra stabilization, and extra stabilization can come to the planar carbocation structure from weak donation of σ bond electrons into the empty p orbital of the cation.

In the t-butyl cation, three of these donations occur at any one time: it doesn't matter if the C–H bonds point up or down; one C–H bond of each methyl group must be parallel to one lobe of the empty p orbital at any one time.





extra stabilization from C–H σ donation into empty p orbital of planar carbocation



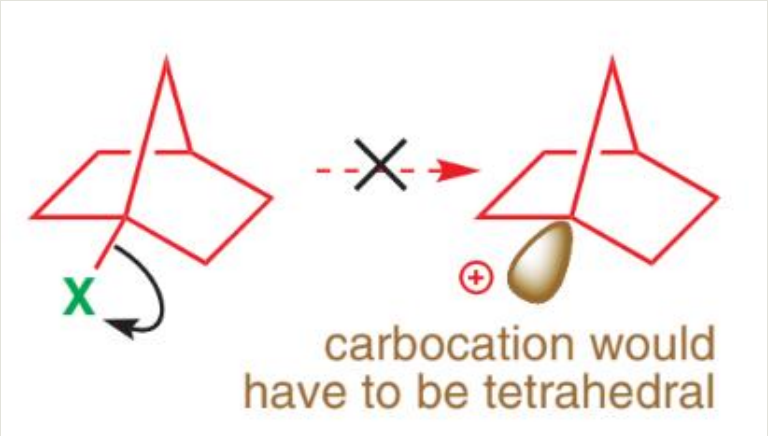
extra stabilization from C–C σ donation into empty p orbital of planar carbocation



C–H s bonds and empty p orbital are perpendicular: no donation possible

Planarity is so important to the structure of a carbocation that if a tertiary cation cannot become planar, it is not formed.

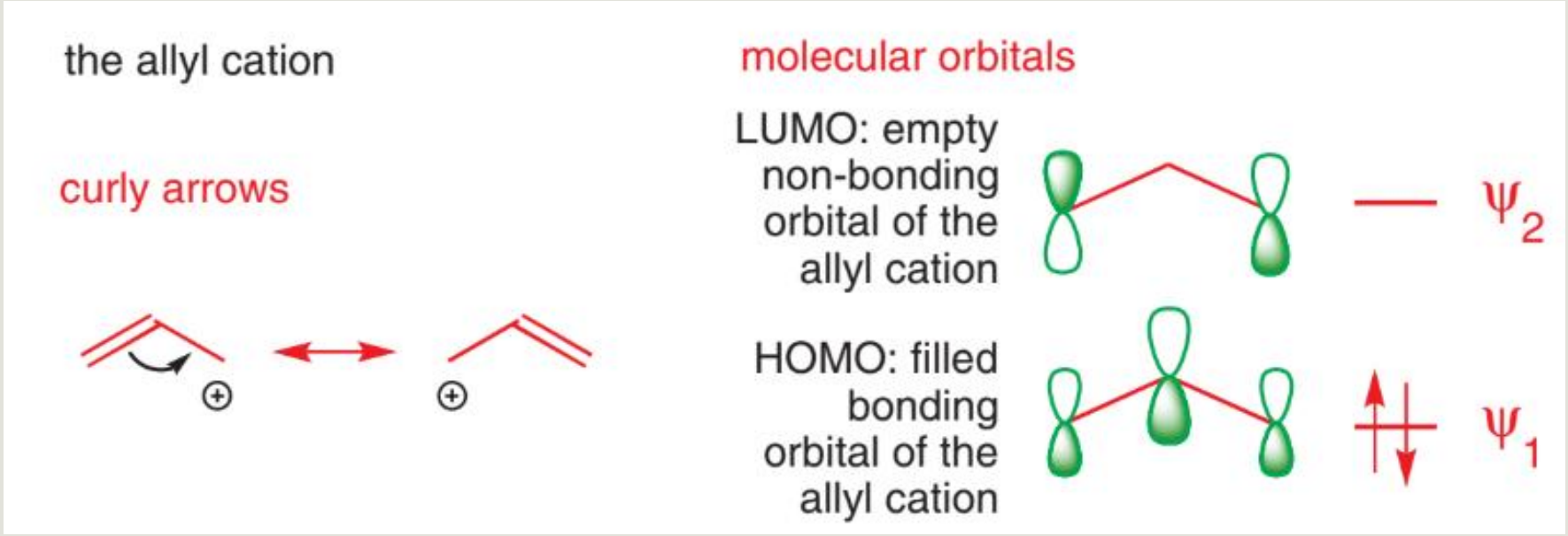
The structure (below), which does not react with nucleophiles either by SN1 or by SN2. It does not react by SN1 because the cation cannot become planar, nor by SN2 because the nucleophile cannot approach the carbon atom from the right direction.



An adjacent C=C π system stabilizes a carbocation: allylic and benzylic carbocations

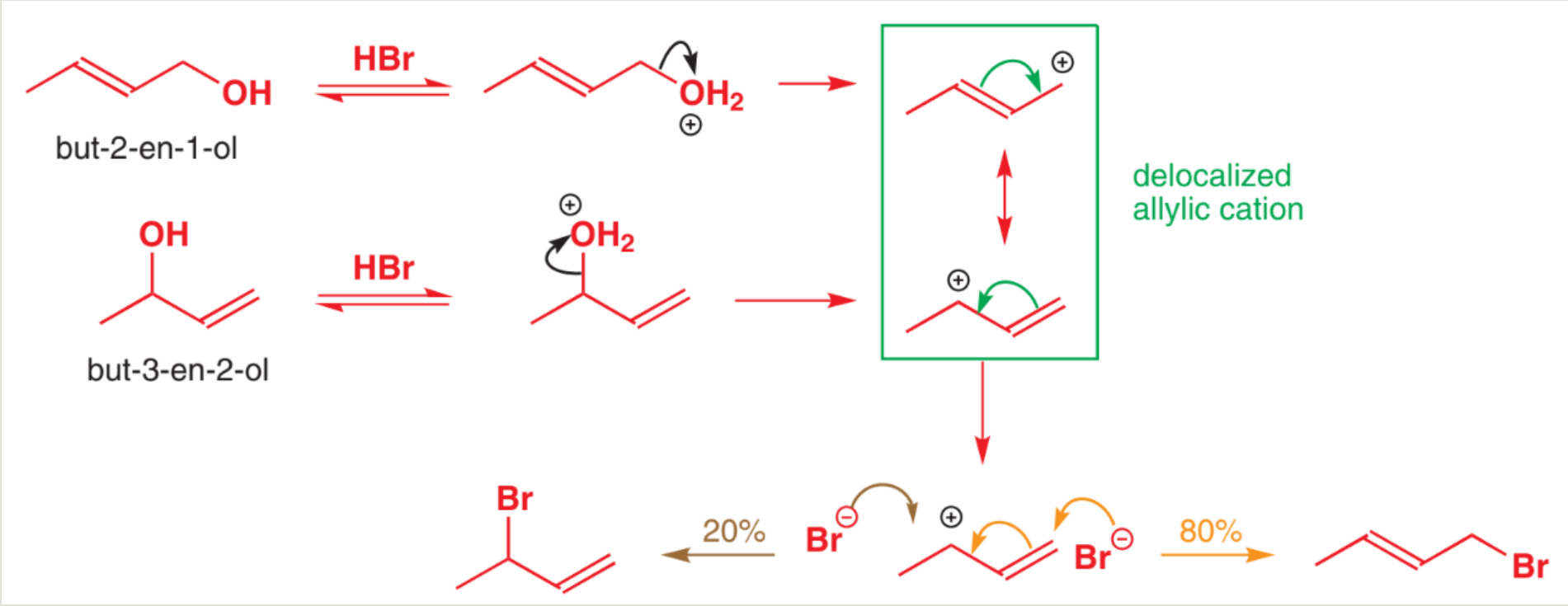
Tertiary carbocations are more stable than primary ones, but powerful stabilization is also provided when there is genuine conjugation between the empty p orbital and adjacent π or lone pair electrons.

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 (LUMO).

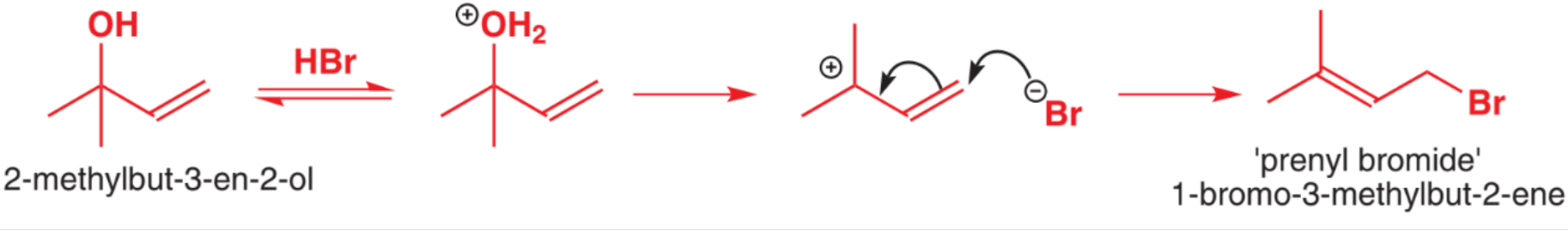


Allylic electrophiles react well by the SN1 mechanism because the allyl cation is relatively stable. Here's an example of a reaction working in the opposite direction from most of those you have seen so far—we start with the alcohol and form the bromide.

It doesn't matter which of these two butenols you treat with HBr, you get the same delocalized allylic cation.



When this cation reacts with Br−, about 80% goes to one end and 20% to the other, giving a mixture of butenyl bromides. This regioselectivity (where the nucleophile attacks) is determined by steric hindrance: attack is faster at the less hindered end of the allylic system.

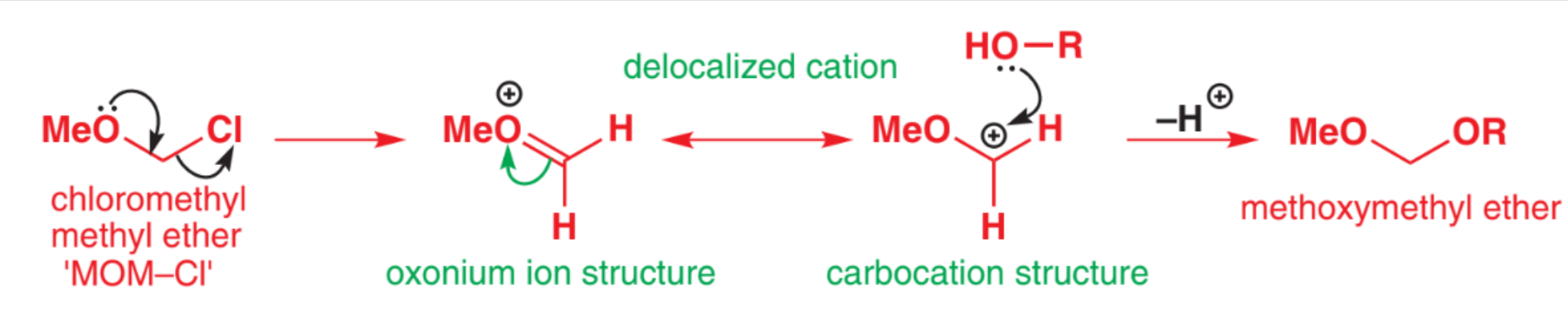


The tertiary allylic alcohol 2-methylbut-3-en-2-ol reacts well by the SN1 mechanism because it can form a stable carbocation that is both tertiary and allylic.

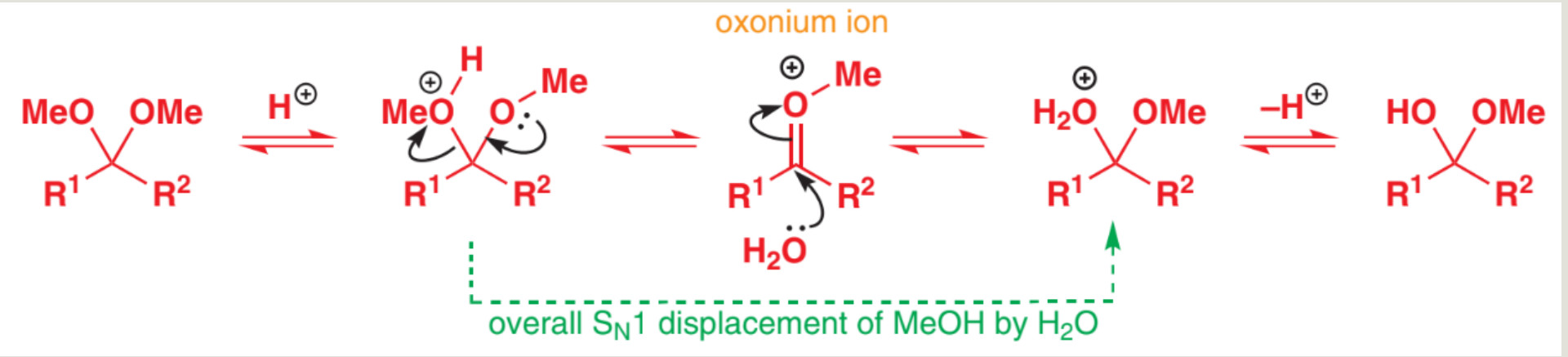
The allylic carbocation intermediate is unsymmetrical and reacts only at the less substituted end to give ‘prenyl bromide’.

Carbocations are stabilized by an adjacent lone pair

- The alkyl chloride known as methyl chloromethyl ether, MeOCH2Cl, reacts very well with alcohols to form ethers.
- Being a primary alkyl chloride, we might think that its reactions would follow an SN2 mechanism, but in fact it has characteristic SN1 reactivity.
- the reason for its preference for the SN1 mechanism is its ability to form a stabilized carbocation.
- Loss of the chloride ion is assisted by the adjacent lone pair, and we can draw the resulting cation either as an oxonium ion or as a carbocation.

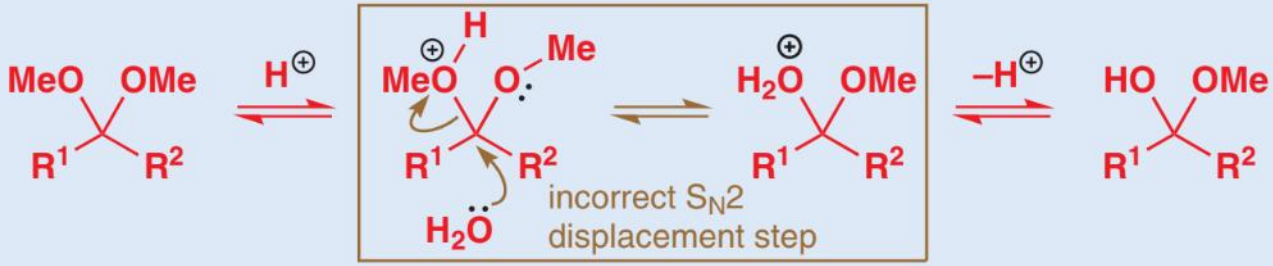


The first step in the hydrolysis of an acetal is a similar reaction, with one alkoxy group replaced by water to give a hemiacetal.
It is in effect an SN1 substitution reaction: the decomposition of the protonated acetal to give an oxonium ion. If you compare this step with the reaction of the chloroether, just described you will see that they are very similar



A common mistake

Don't be tempted to shortcut this mechanism by drawing the displacement of the first molecule of methanol by water as an S_N2 reaction.



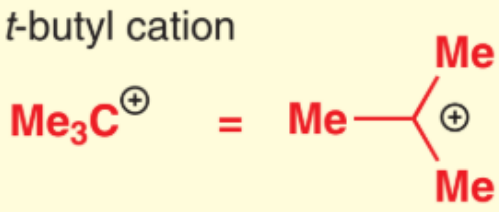
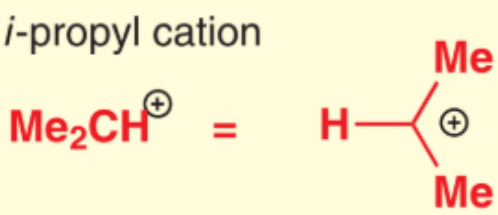
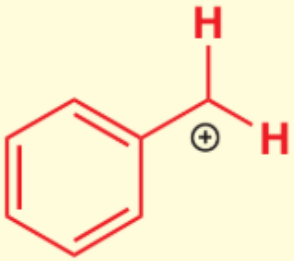
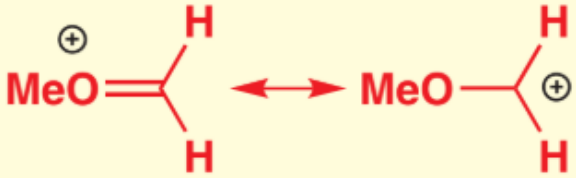
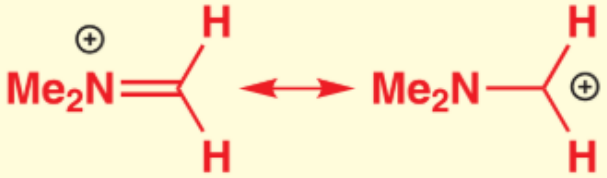
An S_N2 mechanism is unlikely at such a crowded carbon atom. However, the main reason why the S_N2 mechanism is wrong is that the S_N1 mechanism is so very efficient, with a neighbouring MeO group whose lone pair can stabilize the carbocation intermediate. The S_N2 mechanism doesn't get a chance.

This mechanism for the SN1 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.

We 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.



Stable carbocations as intermediates in S_N1 reactions

Type of cations	Example 1	Example 2
simple alkyl	tertiary (good) *t*-butyl cation 	secondary (not so good) *i*-propyl cation 
conjugated	allylic 	benzylic 
heteroatom-stabilized	oxygen-stabilized (oxonium ions) 	nitrogen-stabilized (iminium ions) 

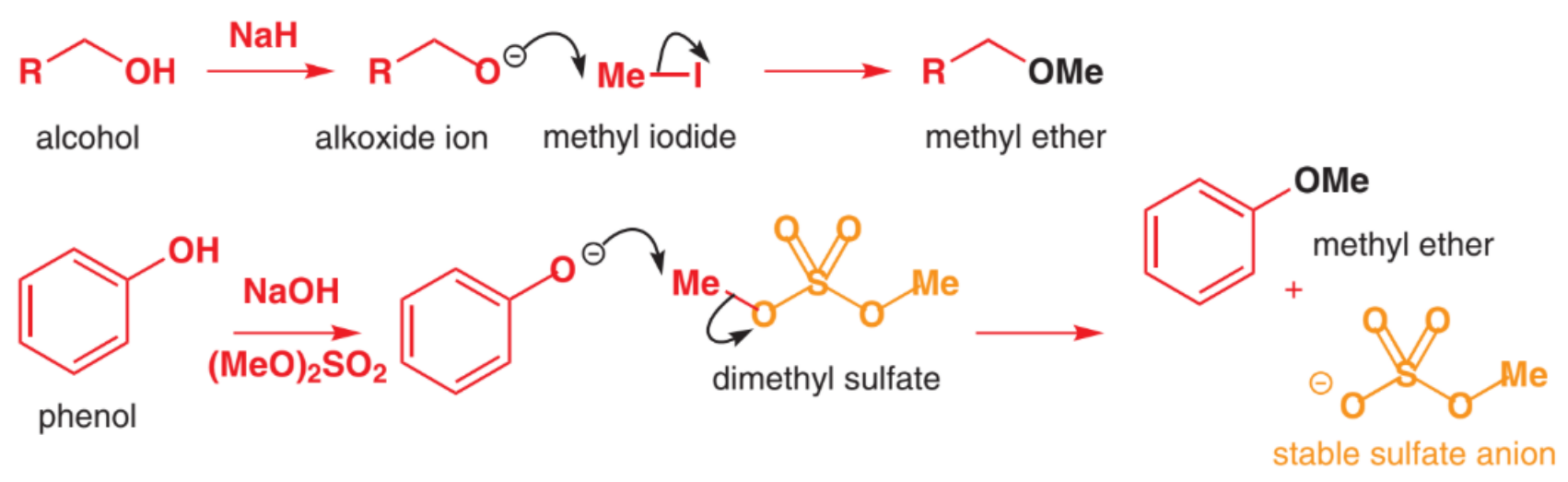
S_N2 Reaction

Among simple alkyl groups, methyl and primary alkyl groups always react by the SN2 mechanism and never by SN1. This is partly because the cations are unstable and partly because the nucleophile can push its way in easily past the hydrogen atoms.

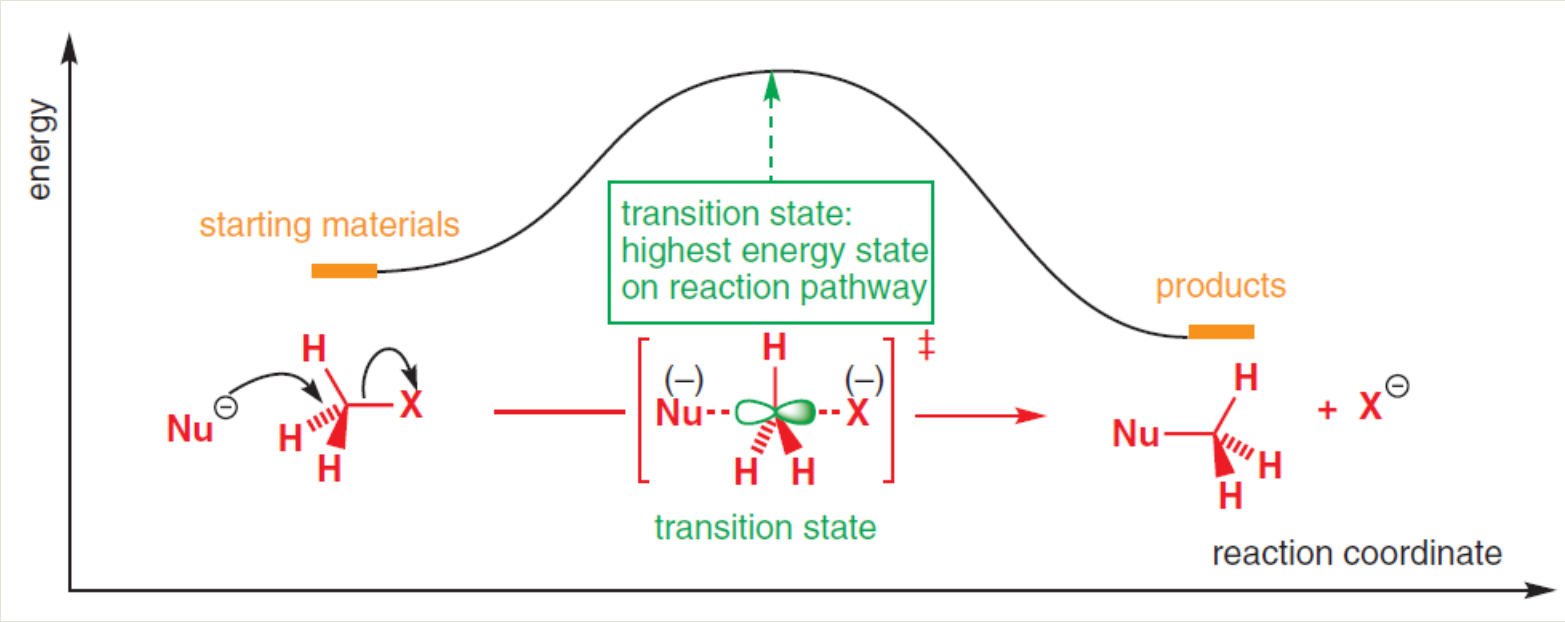
A common way to make ethers is to treat an alkoxide anion with an alkyl halide. If the alkyl halide is a methyl compound, we can be sure that the reaction will go by the SN2 mechanism.

A strong base, here NaH, will be needed to form the alkoxide ion, since alcohols are weak acids (pKa about 16). Methyl iodide is a suitable electrophile.

With the more acidic phenols (pKa about 10), NaOH is a strong enough base and dimethyl sulfate, the dimethyl ester of sulfuric acid, is often used as the electrophile.



transition state for an SN2 reaction



- Nucleophile, the methyl group, and the leaving group are all present in the transition state for the reaction. The transition state is the highest energy point on the reaction pathway.
- In the case of an SN2 reaction it will be the point where the new bond from the nucleophile is partly formed while the old bond to the leaving group is not yet completely broken.
- The dashed bonds in the transition state 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).
- Transition states are often shown in square brackets and marked with the symbol ‡.

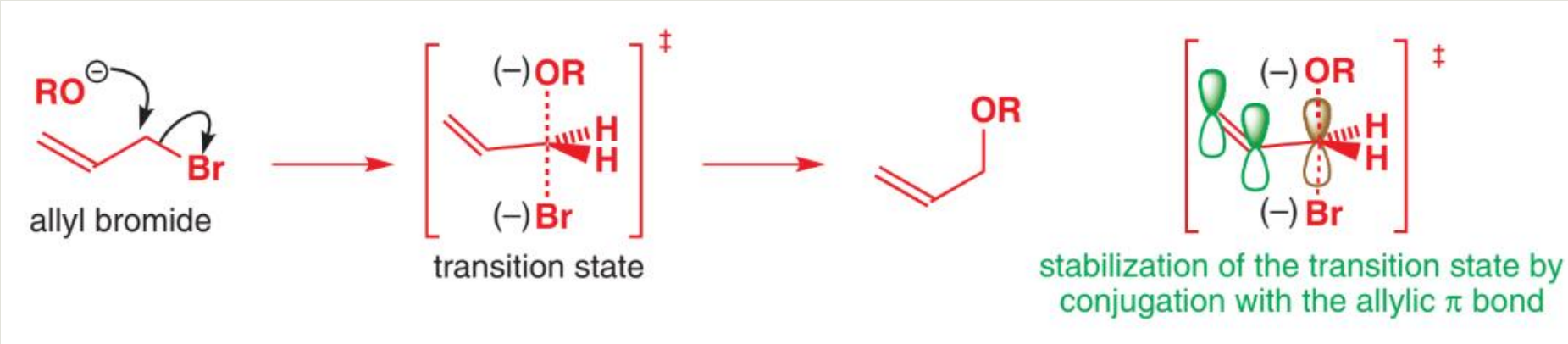
Adjacent C=C or C=O π systems increase the rate of SN2 reactions

Methyl and primary alkyl compounds react well by the SN2 mechanism, while secondary alkyl compounds undergo SN2 reactions only reluctantly.

- But there are other important structural features that also encourage the SN2 mechanism. Two of these, allyl and benzyl groups, also encourage the SN1 mechanism.

Allyl bromide reacts well with alkoxides to make ethers, and shown below is the typical SN2 mechanism for this reaction. Allyl compounds react rapidly by the SN2 mechanism because the π system of the adjacent double bond can stabilize the transition state by conjugation.

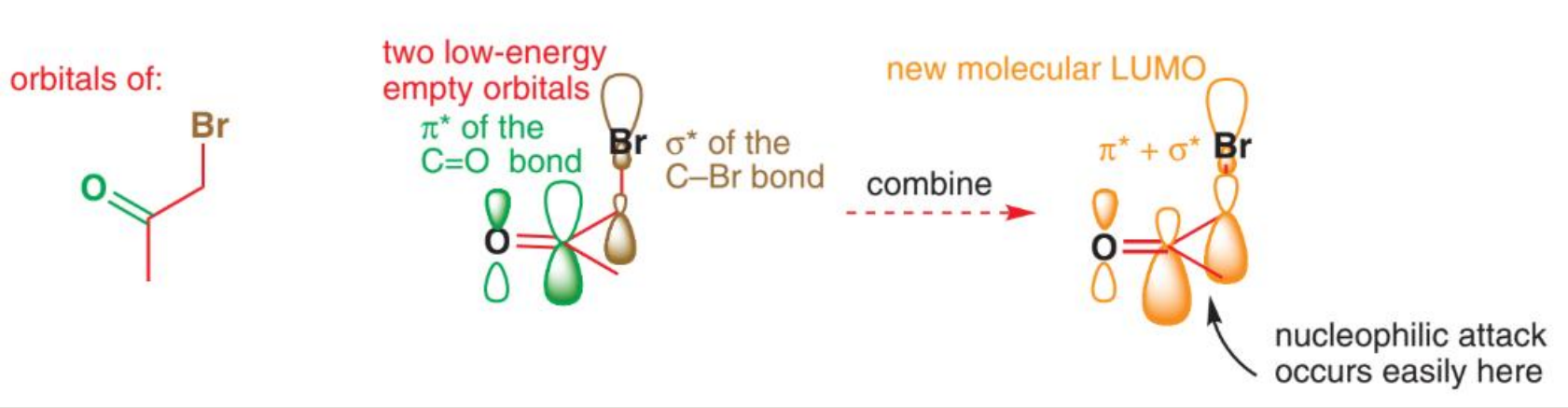
The p orbital at the reaction centre (shown in brown) has to make two partial bonds with only two electrons—it is electron deficient, and so any additional electron density it can gather from an adjacent π system will stabilize the transition state and increase the rate of the reaction.



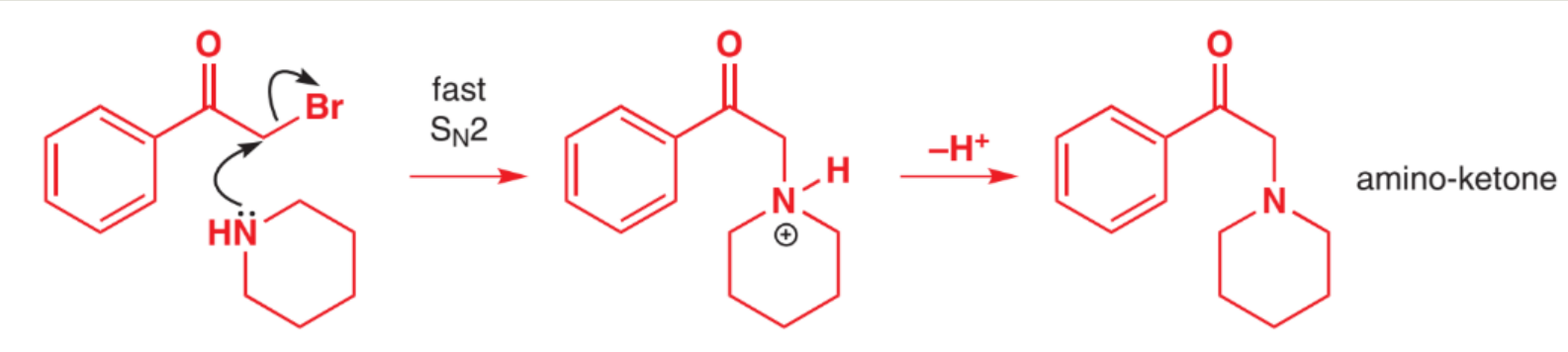
Among the fastest of all SN2 reactions are those where the leaving group is adjacent to a carbonyl group. With α-bromo carbonyl compounds, two neighbouring carbon atoms are both powerfully electrophilic sites.

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 new LUMO (π* + σ*) lower in energy than either.

Nucleophilic attack will occur easily where this new orbital has its largest coefficient, shown in orange on the diagram. The effect of this interaction between antibonding orbitals is that each group becomes 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. In fact, it may well be that the nucleophile will attack the carbonyl group, but this will be reversible whereas displacement of bromide is irreversible.



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

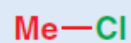
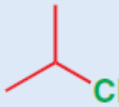
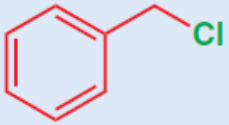
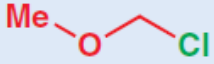
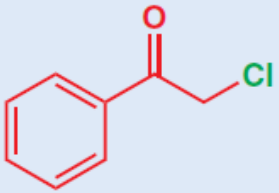


Quantifying structural effects on S_N2 reactions

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 illustrate the patterns of S_N2 reactivity 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.



Relative rates of substitution reactions of alkyl chlorides with the iodide ion

Alkyl chloride	Relative rate	Comments
	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 a bit more reactive than allyl: benzene ring slightly better at π conjugation than isolated double bond
	920	conjugation with oxygen lone pair accelerates reaction (this is an S_N1 reaction)
	100,000	conjugation with carbonyl group much more effective than with simple alkene or benzene ring; these α-halo carbonyl compounds are the most reactive of all

The effect of solvent

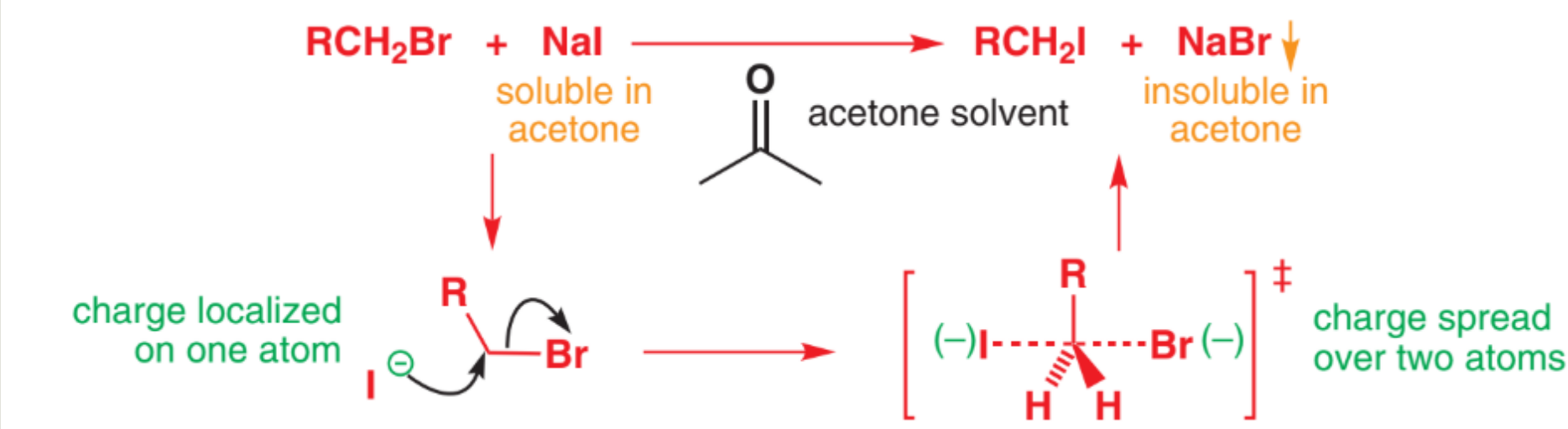
We will generally find SN2 reactions are carried out in aprotic, and often less polar, solvents. A common solvent for an SN2 reaction isacetone—just polar enough to dissolve the ionic reagents, but not as polar as, say, acetic acid, a common solvent for the SN1 reaction.

SN1 reactions are typically carried out in polar, protic solvents. It is fairly obvious why the SN1 reaction needs a polar solvent: the rate-determining step involves the formation of ions (usually a negatively charged leaving group and a positively charged carbocation) and the rate of this process will be increased by a polar solvent that can solvate these ions. 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.

The most common SN2 reactions use an anion as the nucleophile. The transition state is then less polar than the localized anion as the charge is spread between two atoms.

Here's an example: the formation of an alkyl iodide from an alkyl bromide. Acetone fails to solvate the iodide well, making it more reactive; the transition state is less in need of solvation, so overall the reaction is faster.

DMF and DMSO, the polar aprotic solvents we discussed in Chapter 12 (p. 255) are also good solvents for SN2 reactions because they dissolve ionic compounds well but fail to solvate anions well, making them more reactive.

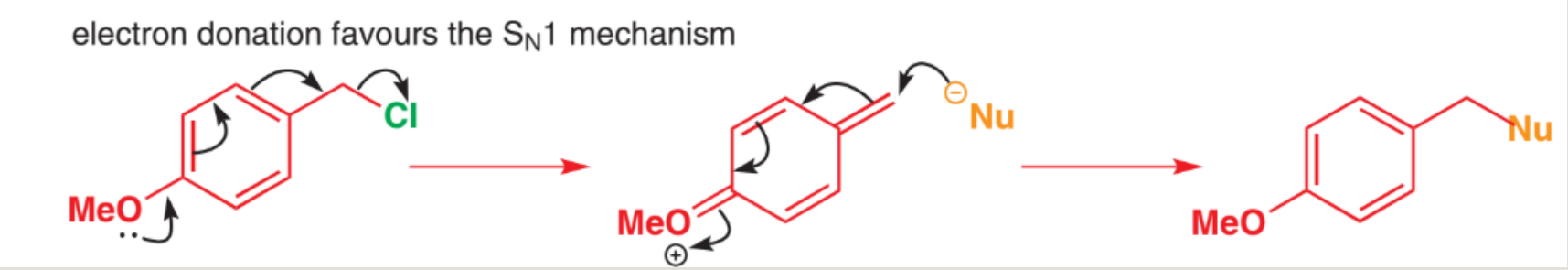


Electronic effects

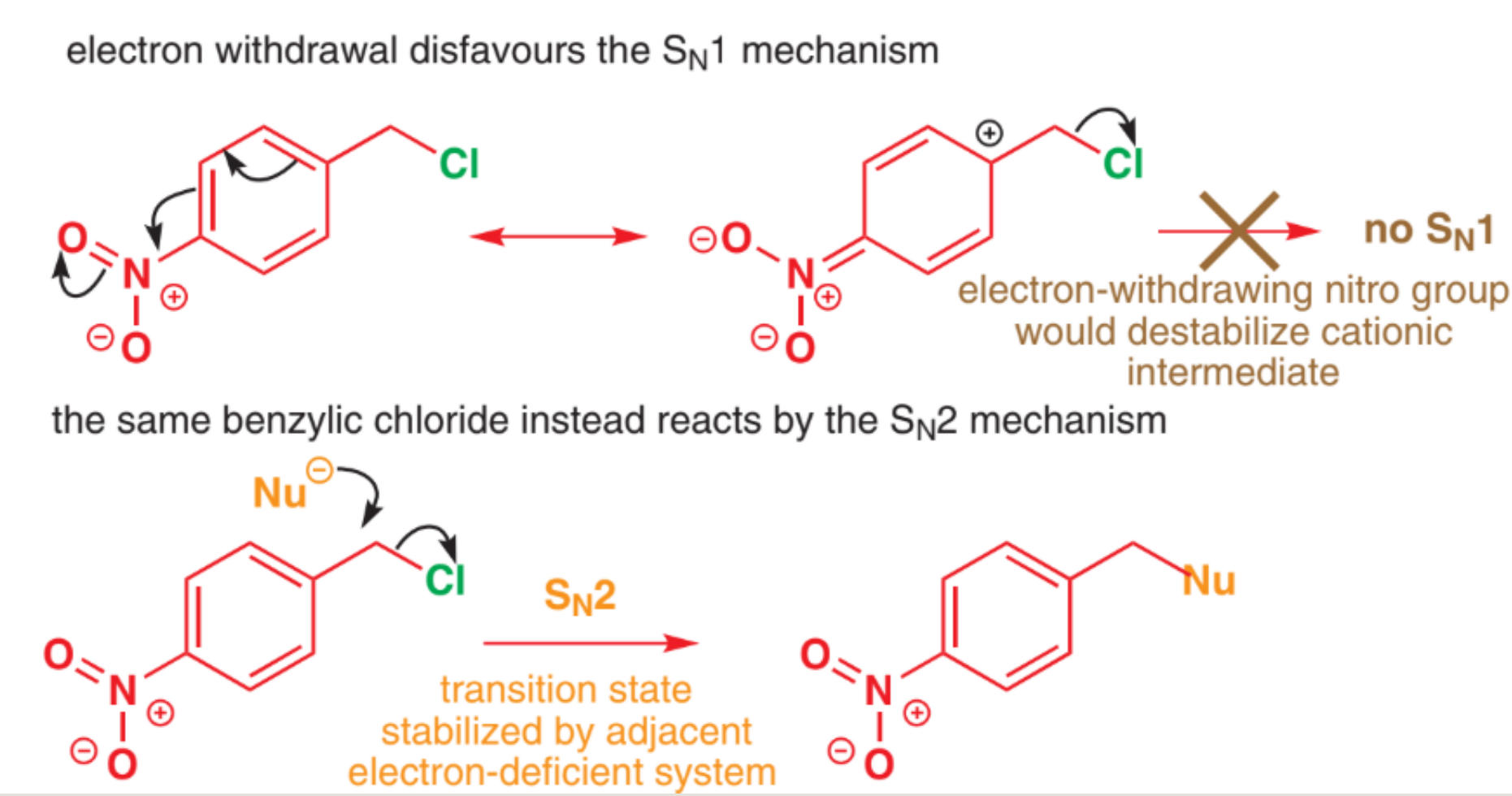
Electron-withdrawing or -donating groups can also tip finely balanced cases from one mechanism to another. For example, benzylic compounds react well by either SN1 or SN2, and a change of solvent, as just discussed, might switch them from one mechanism to another.

Alternatively, a benzylic compound that has a well-placed electron-donating group able to stabilize the cation will also favour the SN1 mechanism.

Thus 4-methoxybenzyl chloride reacts by SN1: the methoxy group stabilizing the cation intermediate by assisting departure of the chloride.

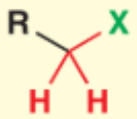


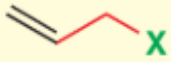
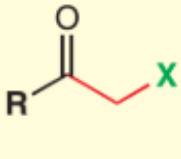
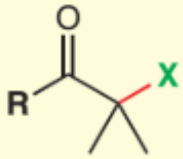
On the other hand, an electron-withdrawing group, such as a nitro group, within the benzylic compound will decrease the rate of the SN1 reaction and allow the SN2 mechanism to take over.



Summary of structural variations and nucleophilic substitution

We are now in a position to summarize the structural effects on both mechanisms we have been discussing over the last few pages. The table lists the structural types and rates each reaction qualitatively.

Electrophile	Me–X				
	methyl	primary	secondary	tertiary	'neopentyl'
S_N1 mechanism?	bad	bad	poor	excellent	bad
S_N2 mechanism?	excellent	good	poor	bad	bad

Electrophile					
	allylic	benzylic	α-alkoxy (adj. lone pair)	α-carbonyl	α-carbonyl and tertiary
S_N1 mechanism?	good	good	good	bad	bad
S_N2 mechanism?	good	good	okay but S_N1 better	excellent	possible

THANKS