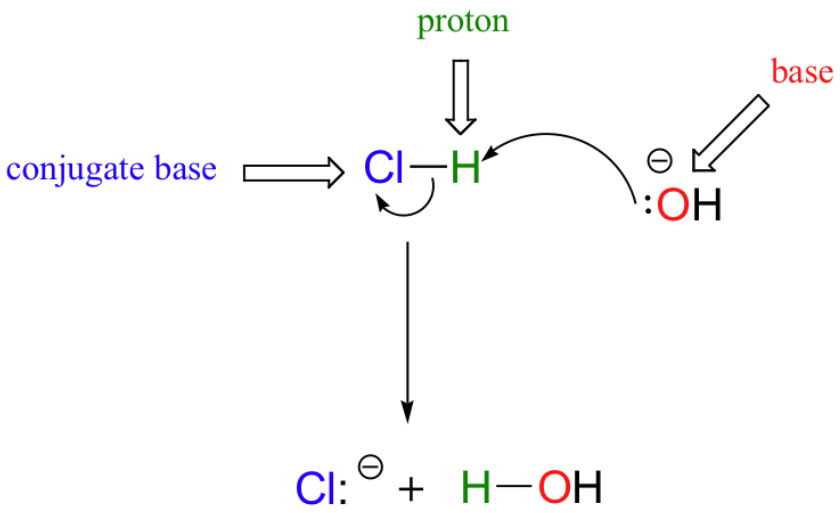
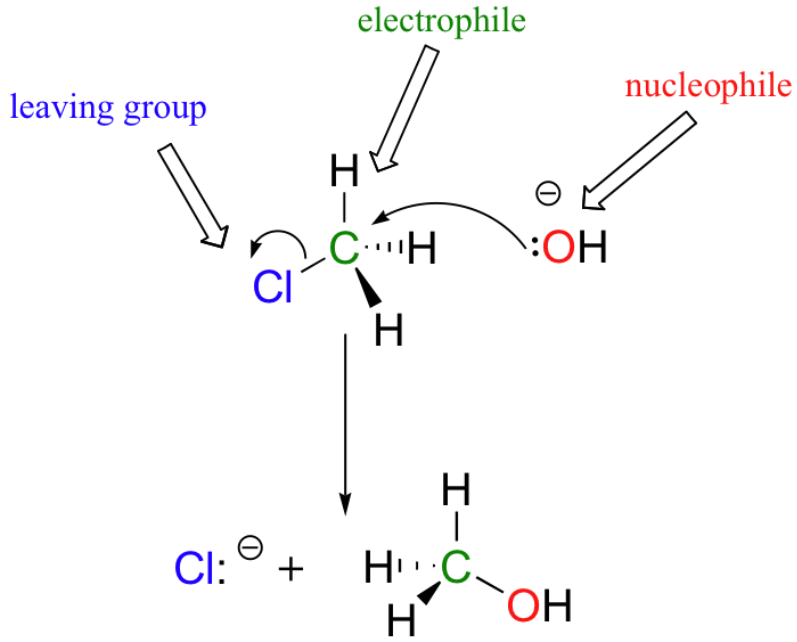
Overview of Nucleophilic Substitution

Recall that, in many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.



acid-base reaction



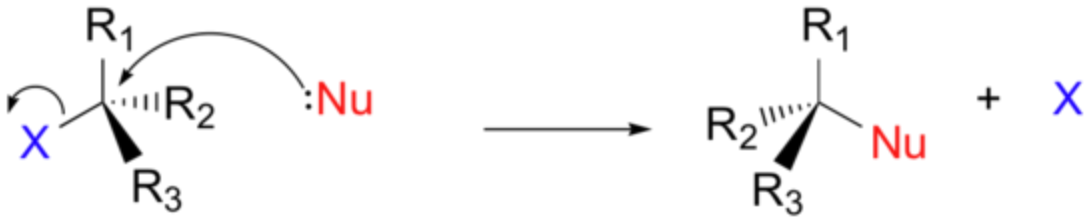
nucleophilic substitution

In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base.

In the next few sections, we are going to be discussing some general aspects of nucleophilic substitution reactions, and in doing so it will simplify things greatly if we can use some abbreviations and generalizations before we dive into real examples.

Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. In the same way, we will see later that nucleophiles and leaving groups are sometimes protonated and sometimes not, so for now, for the sake of simplicity, we will not include protons on 'Nu' or 'X'. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Finally, in order to keep figures from becoming too crowded, we will use in most cases the line structure convention in which the central, electrophilic carbon is not drawn out as a 'C'.

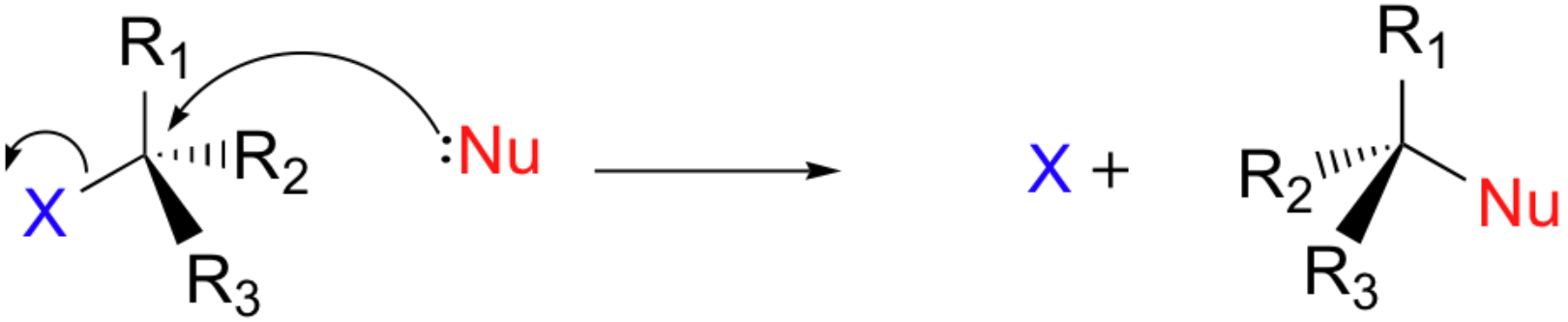
Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction. Note that this representation does not include the charges that would be present on Nu and X.



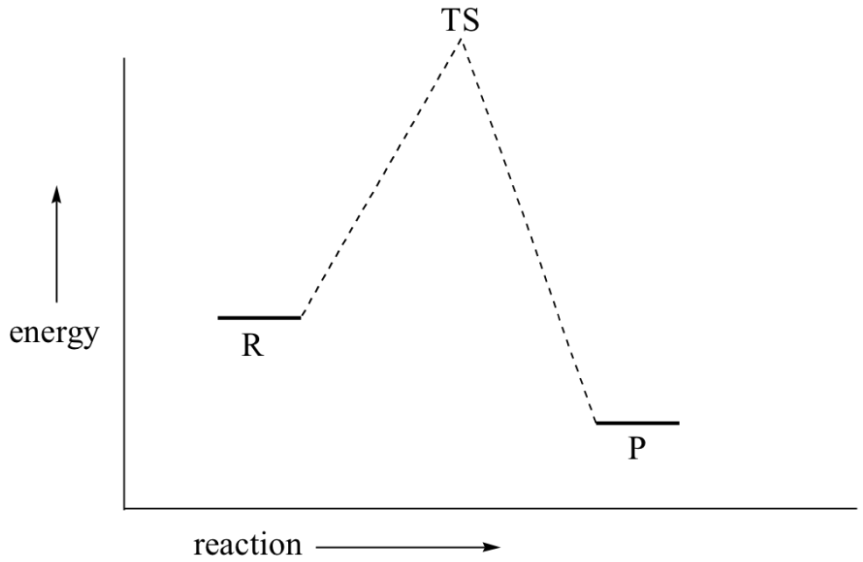
Physical chemistry for SN2 and SN1 reactions

The S_N2 Reaction

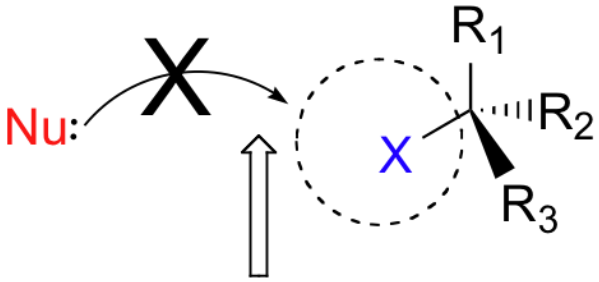
There are two mechanistic models for how a nucleophilic substitution reaction can proceed at an alkyl halide (or similar) – S_N2 and S_N1. In the first picture, S_N2, the reaction takes place in a single step, and bond-forming and bond-breaking occur simultaneously.



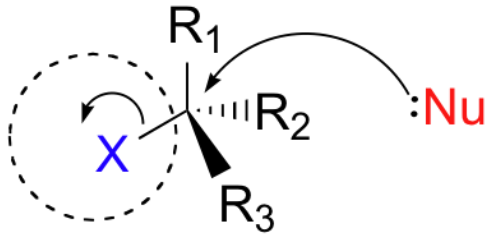
This is called an '**associative'**, or '**S_N2'** mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.



If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group – which is also an electron-rich group – blocks the way.

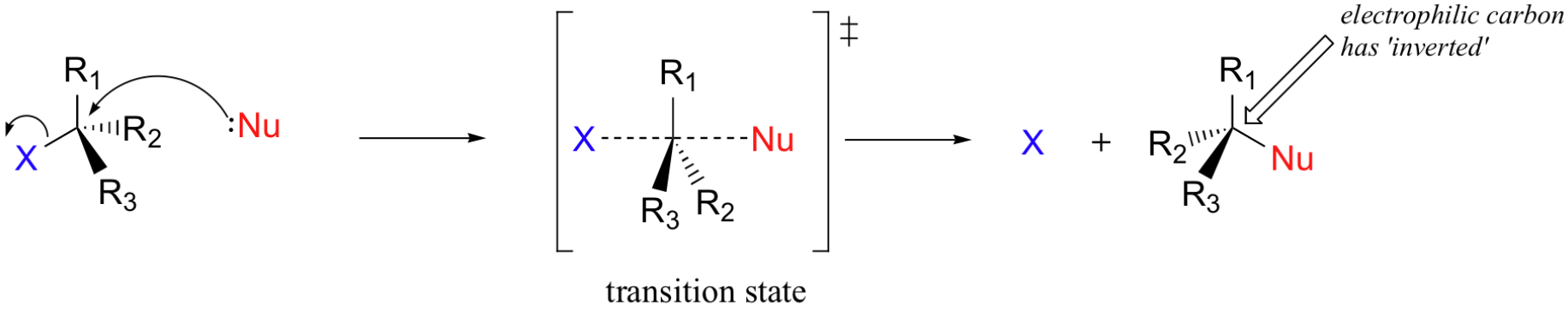


nucleophilic attack is blocked from the front side . . .



. . .so attack occurs from the back side

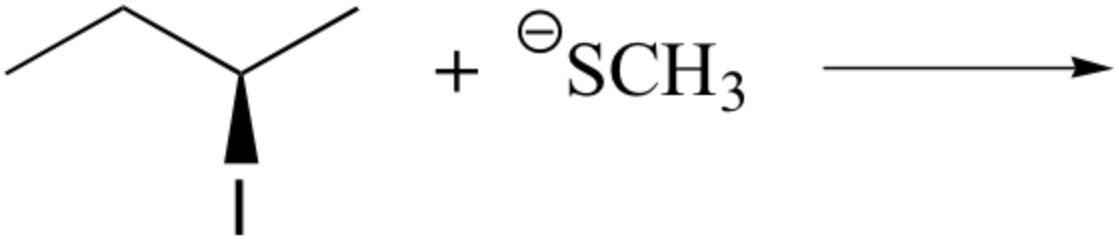
The result of this backside attack is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. At the transition state, the electrophilic carbon and the three 'R' substituents all lie on the same plane.



What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product.

EXERCISE

Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



EXERCISE

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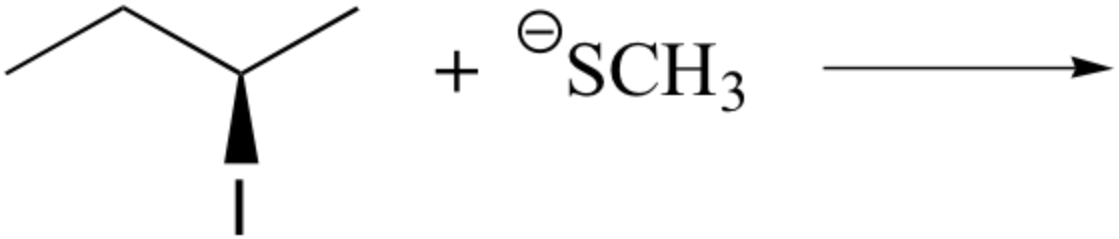
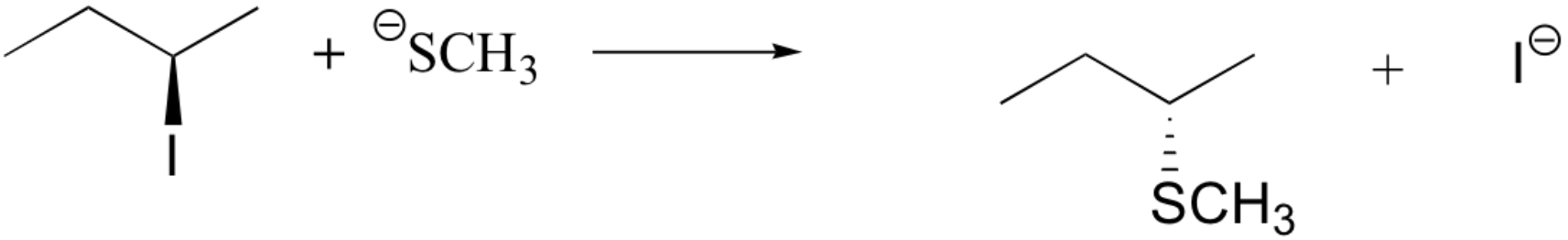
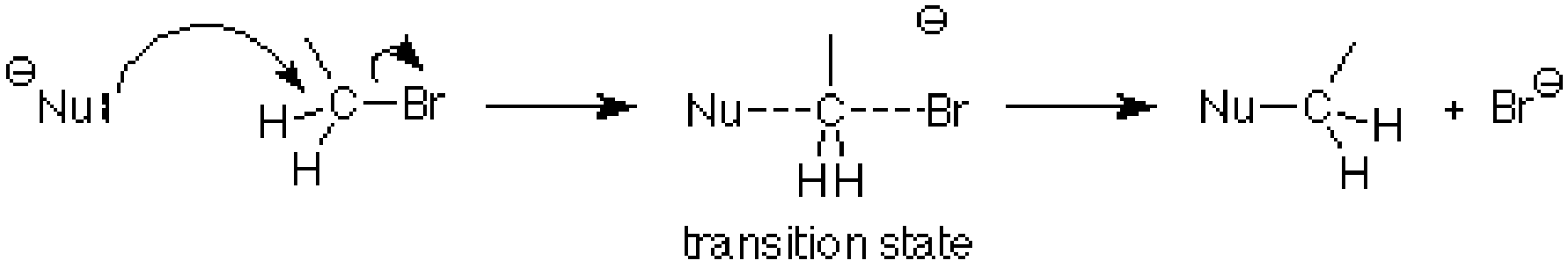


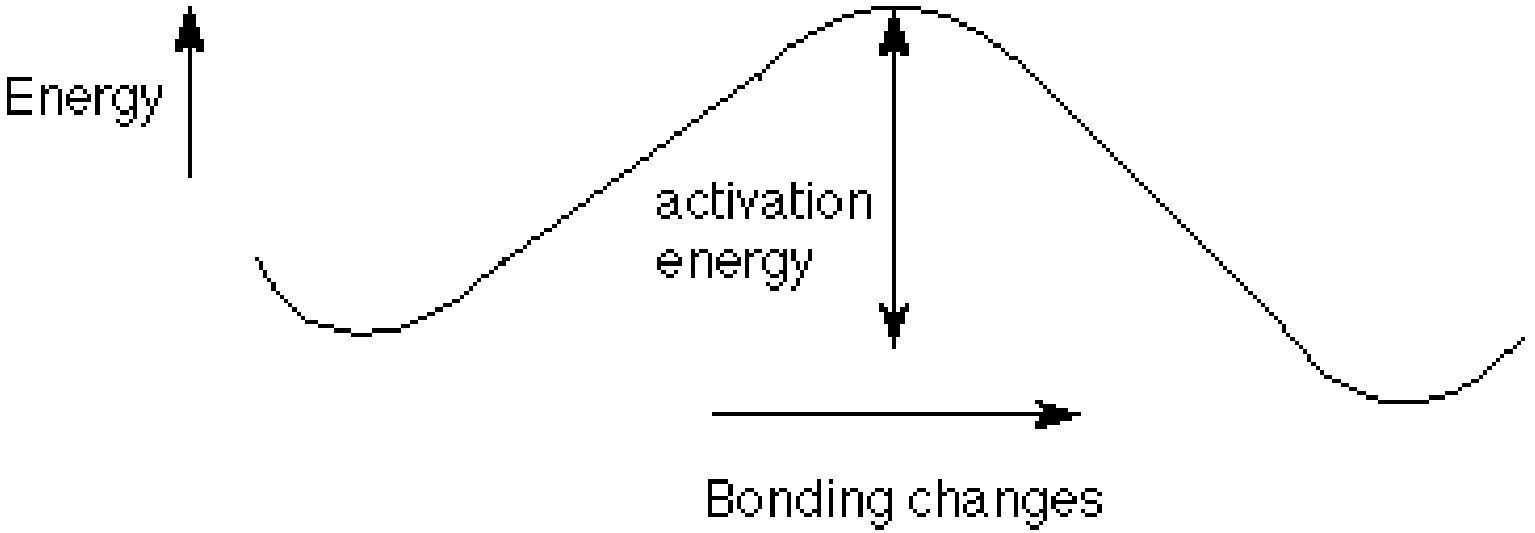
Notice that the reaction occurs with inversion of configuration: the leaving group (I) was pointing *out* of the plane of the page, while the nucleophile (CH_3S^-) attacks from *behind*, and ends up pointing *into* the plane of the page.



Rate law for the S_N2 reaction

Earlier we saw that the energy required to reach the transition state comes from the energy with which the nucleophile and the alkyl halide collide. The requirement for a collision also means that the frequency with which the nucleophile and the alkyl halide collide is important. This frequency is primarily controlled by concentration.





If the concentration of the alkyl halide is high, then there will be many opportunities for a nucleophile to collide with an alkyl halide molecule. The rate of the reaction will increase proportionately as the alkyl halide concentration is made higher. When this is the case the reaction is said to be first order in alkyl halide. Similarly an increase in the nucleophile concentration will result in a proportionate increase in the rate, so the reaction is also first order in nucleophile. Overall, the rate depends on the concentration of **both** reactants, and the reaction is said to be second order. This can be summarized in the *rate equation* or *rate law.*

$$\text{Rate} = k[RX][Nu^-]$$

It is the second order behavior (requirement for two molecules to collide in the critical transition state) which is designated by the "2" in S_N2.

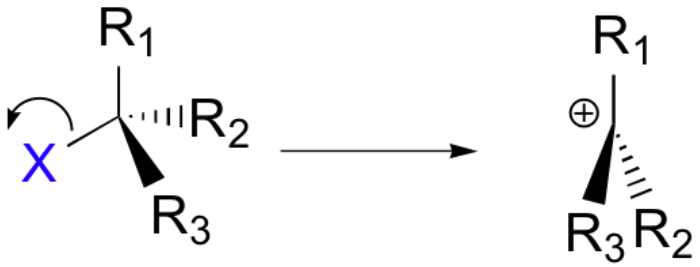
THE S_N2 REACTION

In summary, we see that for the SN2 reaction:

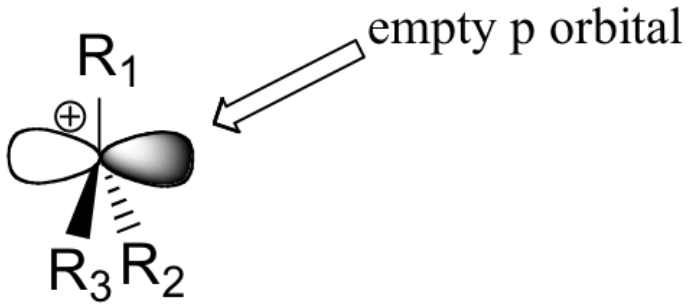
1. The reaction is “concerted” – it has only one step in the mechanism
2. The reaction rate depends on the concentration of both the electrophile (the alkyl halide or similar) and the nucleophile.
3. The nucleophile attacks the “back side” of the electrophile, with the leaving group leaves from the “front”. This also means that if the leaving group is leaving from a chiral carbon, the stereochemistry at that center is inverted,

The S_N1 Reaction

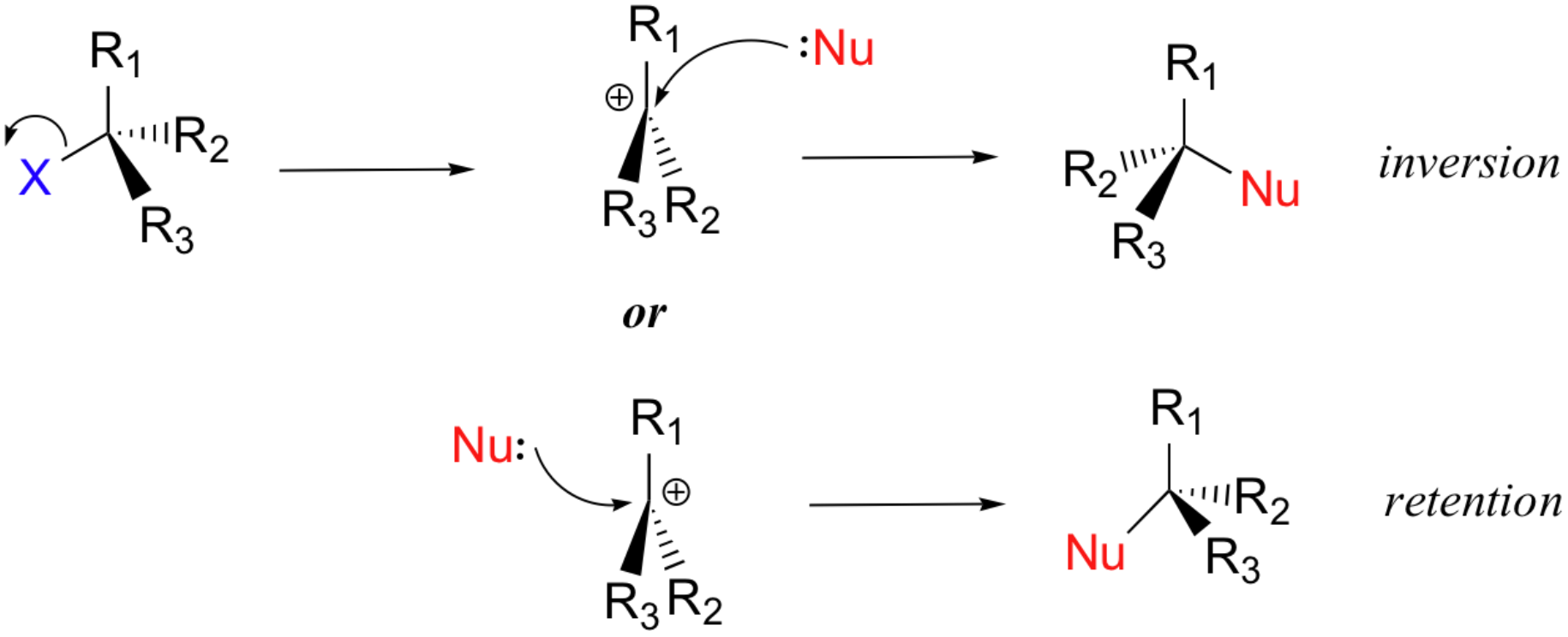
A second model for a nucleophilic substitution reaction is called the '**dissociative'**, or '**S_N1'** mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



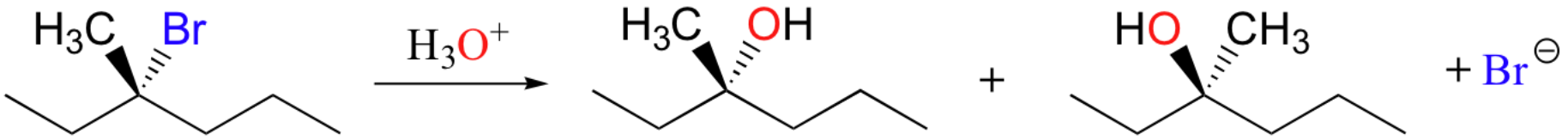
This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with flat (trigonal planar) geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.



We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, the product has become racemic and optically inactive. As an example, the tertiary alkyl bromide below would be expected to form a racemic mixture of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



EXERCISE

Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

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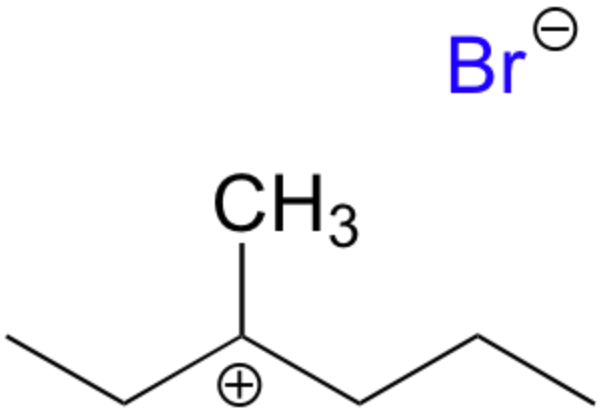
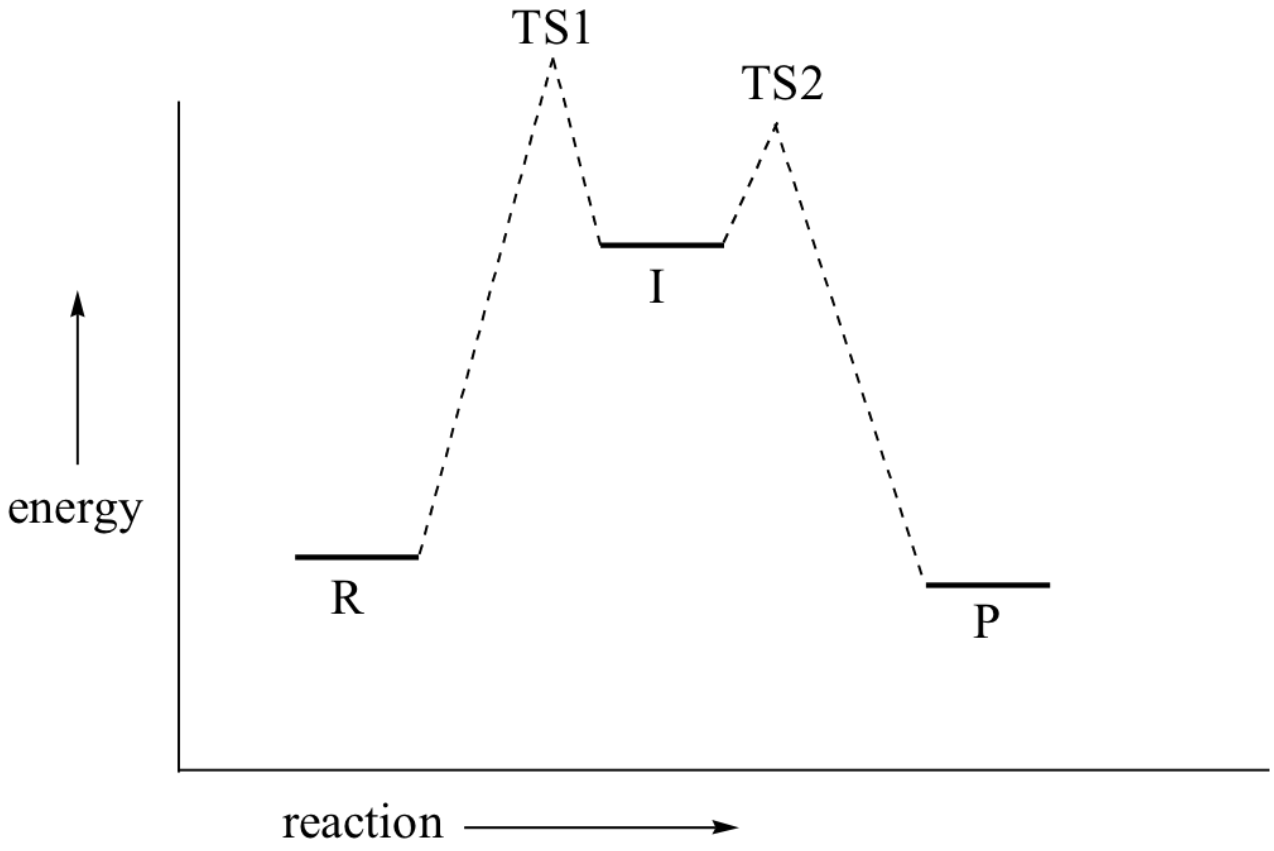
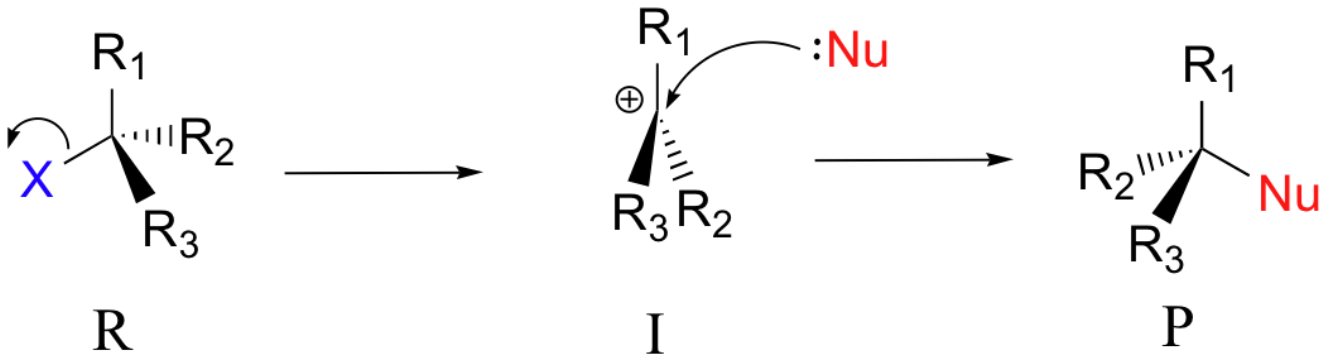
The intermediate species is a carbocation that forms after the bromine leaves:



In the S_N1 reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms is that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discrete bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. The S_N1 reaction involves both a heterolysis step and a coordination step, as well as (usually) at least one acid-base step. The carbocation species is the reactive intermediate in the S_N1 reaction. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of "mountain valley" in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.


TS1
TS2
I
energy
R
P
reaction


R1
R2
X
R3
R
R1
:Nu
R3
R2
I
R1
R2
Nu
R3
P

EXERCISE

Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

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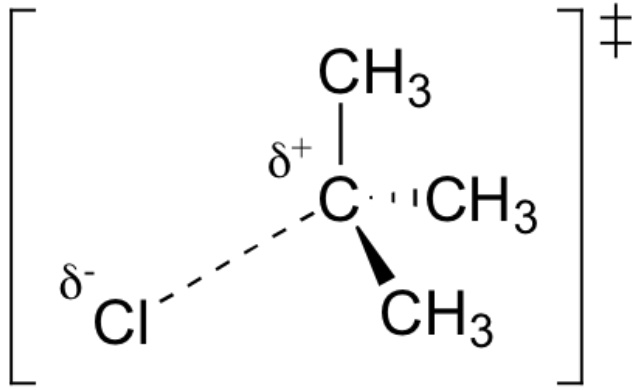
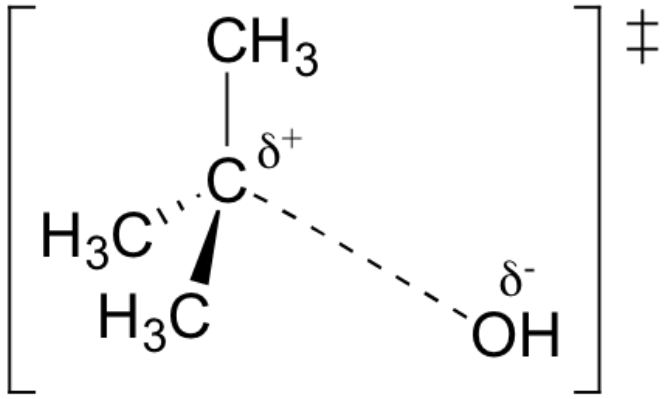
Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

TS1:



TS2:



Recall (from Hammond's postulate) that the first heterolysis step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for the first step is higher than that for the second step. Also recall that an S_N1 reaction has *first order* kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding.

EXERCISE

Consider two nucleophilic substitutions that occur uncatalyzed in solution. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.

A: $CH_3I + CH_3S^{\ominus} \xrightarrow{S_N2}$

B: $(CH_3)_3CBr + CH_3SH \xrightarrow{S_N1}$

EXERCISE

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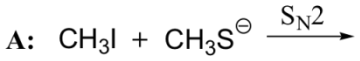
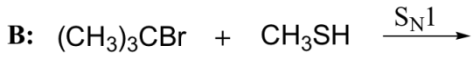




Reaction A is a concerted (one-step) reaction, essentially a collision between two species. Therefore, if the concentration of nucleophile (CH_3S^-) were doubled in the solution, the rate of the reaction should also double. You should recall learning about rate expressions in your general chemistry course – this is an example of a second order rate expression, where the rate depends on some rate constant (*k*) and the product of two concentration:

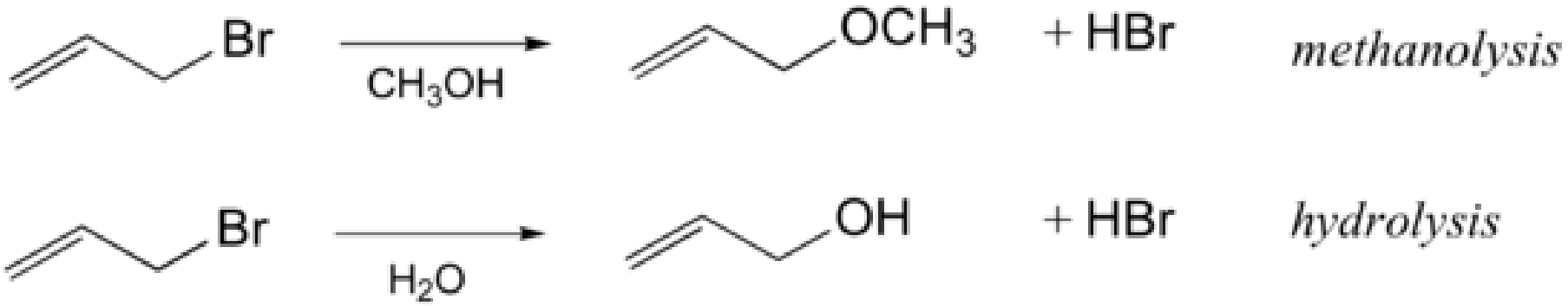
rate = $k[CH_3I]\,[CH_3S^-]$

(If this is unfamiliar to you, now would be a good time for a quick review of rate expressions in your general chemistry textbook!)

Reaction B is a two-step reaction. The first step – the breaking of the C-Br bond – is the slow, rate determining step, and does not involve the CH_3SH nucleophile at all. Therefore, changing the concentration of the nucleophile should have no effect on the rate of the reaction. (If the concentration of CH_3SH were doubled, the *second* step would occur twice as fast – but the rate of the first, slower step would not change, and so the overall rate of the reaction would not be affected). The rate expression in this case is first order (it depends on the concentration of only one reactant):

rate = $k[C(CH_3)_3Br]$

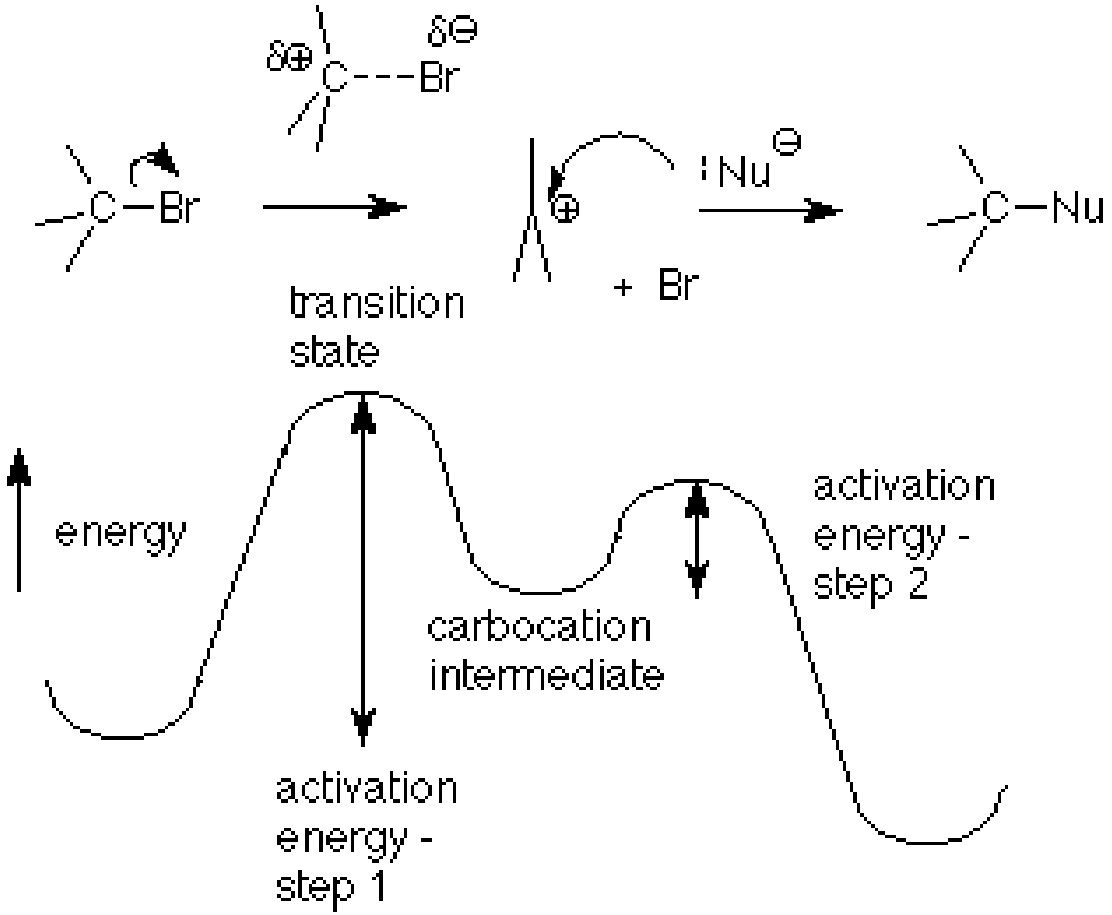
Many S_N1 reactions are of a class that are referred to as **solvolysis**, where a solvent molecule participates in the reaction as a nucleophile. The S_N1 reaction of allyl bromide in methanol is an example of what we would call **methanolysis**, while if water is the solvent the reaction would be called **hydrolysis**. In reactions like this that use an uncharged nucleophile, an acid-base step is needed after the coordination step, in order to remove H^+ and form the uncharged final product.



Because water and alcohols are relatively weak nucleophiles, they are less likely to react in an S_N2 fashion.

Rate law for the S_N1 reaction

The "1" in S_N1 means that only one molecule needs to be "activated" in order to reach the transition state. That molecule is the alkyl halide. The critical step in this mechanism is the first heterolysis step, in which the bond between the carbon atom and the halogen leaving group is broken. The transition state for this step has the bond stretched far enough that the halide ion is balanced between leaving as a stable chloride or bromide ion or slipping back into a covalent bond.



(The energy required to break this bond comes from random collisions with the solvent without the solvent reacting.) The activation energy for the first step is higher than for the second step (coordination), so the rate of the reaction is controlled by how many molecules get through the first step. Once a molecule is through the first step, it can react rapidly in the second step. We call the step which is slowest the "rate determining step." Notice that the rate determining step for this reaction doesn't involve the nucleophile. That means that changing the concentration of the nucleophile doesn't affect the rate. The only concentration which affects the rate is the concentration of the alkyl halide. We thus have a first order reaction, and the rate law includes only one reactant:

$$\text{Rate} = k[RX]$$

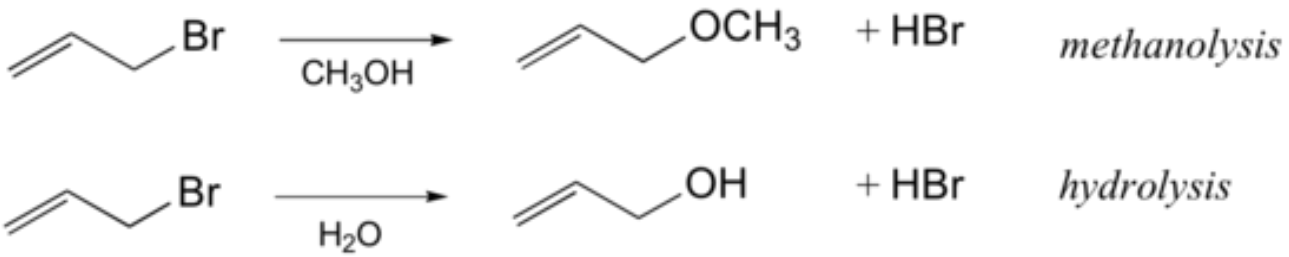
This also means that the strength of the nucleophile — its ability to use its electron pair to make a bond — isn't important in determining how fast the reaction goes. It's not involved in the rate determining step, so it has no effect on the energy of that transition state.

THE S_N1 REACTION

In summary, for the S_N1 reaction

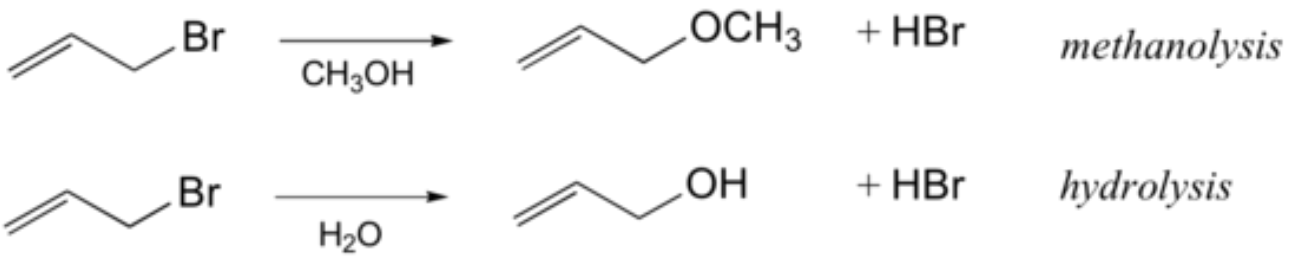
- The reaction involves at least two steps – heterolysis (to form the carbocation) and coordination (when the nucleophile bonds to the carbon). In addition, there are often acid-base steps needed in order to give uncharged products at the end.
- Because the rate determining step is the heterolysis step, the rate depends only on the alkyl halide, and the nucleophile has no effect on rate. This means that weak nucleophiles can work well in the S_N1 reaction.
- The nucleophile is free to approach the flat carbocation equally from either side in the coordination step. This means that if the substitution is occurring at a (single) chiral carbon, the product will be racemic (a 50:50 mixture of enantiomers).

EXERCISE



Draw a complete curved-arrow mechanism for the methanolysis reaction above.

EXERCISE



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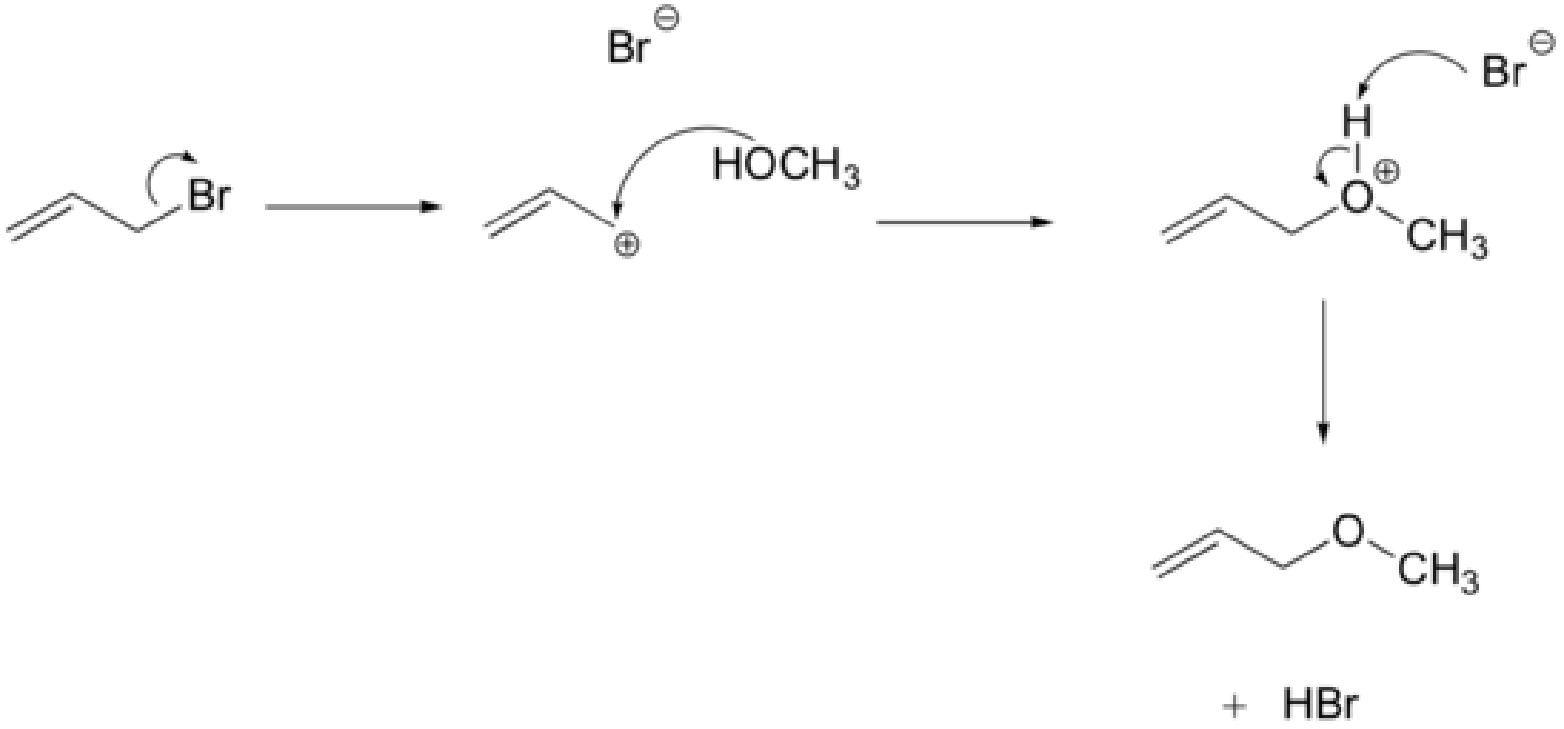
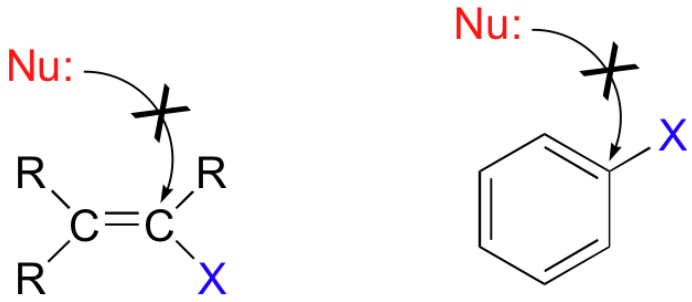


Nucleophilic Substitutions Do Not Occur At Sp^2-Hybridized Carbons

One more important point must be made before continuing: nucleophilic substitutions as a rule occur at sp^3-hybridized carbons, and *not* where the leaving group is attached to an sp^2-hybridized carbon::



Bonds on sp^2-hybridized carbons are inherently shorter and stronger than bonds on sp^3-hybridized carbons, meaning that it is harder to break the C-X bond in these substrates. In addition, sp^2 carbons are more electronegative, and therefore less electrophilic (δ+) than sp^3 carbons. S_N2 reactions of this type are unlikely also because the (hypothetical) electrophilic carbon is protected from nucleophilic attack by electron density in the pi bond. S_N1 reactions are highly unlikely, because the resulting carbocation intermediate, which would be sp-hybridized, would be very unstable.

Before we look at some real-life nucleophilic substitution reactions in the next chapter, we will spend some time in the remainder of this chapter focusing more closely on the three principal partners in the nucleophilic substitution reaction: the nucleophile, the electrophile, and the leaving group.

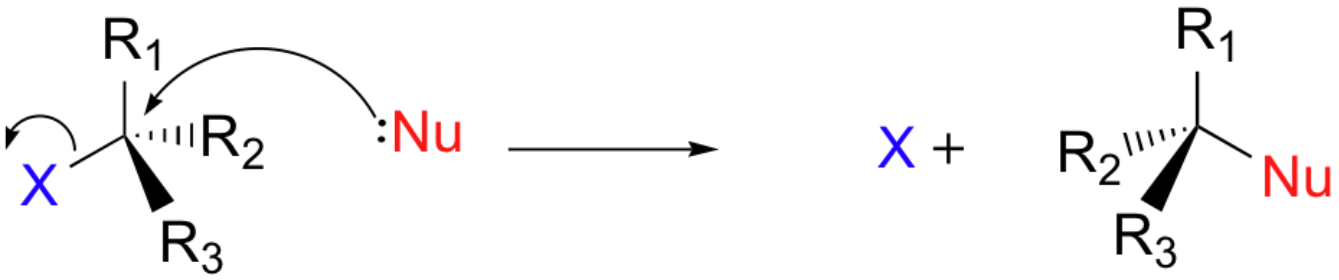
Factors affecting rate of nucleophilic substitution reactions

Designing A "Good" Nucleophilic Substitution

If you want to do well in this class, there are several things you need to work hard at: Being attentive in class, studying the notes and this textbook (especially before exams), practicing problems, and completing the quizzes and homeworks. As long as you do all of these things then you're likely to pass (though I can't give guarantees!). So there are many different factors that can affect your grade. In the same way, the outcome of a reaction (such as nucleophilic substition) depends on many different things – reactants, solvent, etc. When we want to make a chemical in a lab or on a chemical plant, we need to design the reaction so that it works well, and gives a good yield of the product in a reasonable time. The reactants and conditions we use will depend on what we're trying to do. In this section, we examine what factors will help an S_N2 or S_N1 reaction be successful.

Factors Affecting The S_N2 Reaction

As we saw in the previous section, in the S_N2 reaction the rate of reaction depends on both the electrophile (usually an alkyl halide) and the nucleophile.



In practice, the rates of S_N2 reactions vary enormously, and for a practicable procedure we need to make sure that the reaction will happen at a reasonable rate. So what makes for a good S_N2 reaction? We need to consider what makes a suitable nucleophile, and what makes a suitable electrophile.

Nucleophile strength

In **section 6.5**, we learnt what makes a nucleophile strong (reactive) or weak (unreactive). Anything which removes electron-density from the nucleophilic atom will make it less nucleophilic. We summarized the main points from 6.5 as follows:

- Charge – negatively charged => stronger nucleophile
- Within a row – more electronegative atom => weaker nucleophile
- Within a column, size of atom. Polar protic solvent, bigger atom is better; polar aprotic solvent, smaller atom is better.
- Resonance – if the nucleophilic lone pair can be delocalized by resonance, it will make it less nucleophilic
- Steric hindrance – a hindered nucleophilic atom will tend to be less reactive, particularly when attacking a crowded electrophile.

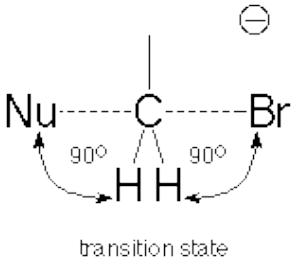
Regarding the solvent, polar aprotic solvents such as DMSO, DMF, acetone or acetonitrile are popular choices for S_N2 reactions, because rates are generally faster than with polar protic solvents (water, alcohols, etc.). This is because the nucleophile is almost "naked" in aprotic solvents, whereas in polar protic solvents it is surrounded by a cage of solvent molecules.

If we have a strong nucleophile, the S_N2 reaction will happen faster; a weak nucleophile will react more slowly and may not even react. So in general we want a strong nucleophile.

The electrophile

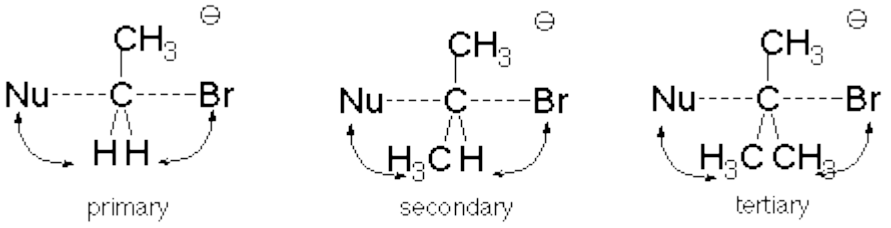
(a) Structure of the alkyl group

In the structure of the S_N2 transition state, there are 90° bond angles between the breaking bond to the leaving group and the three bonds which remain connected to the carbon as well as between the bond being made to the nucleophile and those same three bonds.



transition state

As long as the two of the groups attached to the carbon being attacked are small hydrogens, the repulsions which happen do not require much energy. If the groups attached to the carbon are larger, though, like methyl groups, the transition state energy increases, the activation energy increases, and the reaction becomes much slower.



primary secondary tertiary

transition states

This means that the reactivity order for alkyl halides in S_N2 reactions is:

methyl > primary > secondary > tertiary

The practical outcome of this is that S_N2 reactions are generally reliable only when the alkyl halide is primary, though under the correct conditions secondary halides can react well also.

(b) Leaving group ability – what makes a good leaving group?

In our general discussion of nucleophilic substitution reactions, we have until now been designating the leaving group simply as "X". As you may imagine, however, the nature of the leaving group is an important consideration: if the C-X bond does not break, the new bond between the nucleophile and electrophilic carbon cannot form, regardless of whether the substitution is S_N1 or S_N2. There are two main factors: The strength of the C-X bond, and the stability of the X group after it has left. It turns out that the two factors lead to the same prediction for halogen leaving group ability:

$$I > Br > Cl > F$$

C-X bond strength

Since the bond between the carbon and the leaving group is being broken in the transition state, the weaker this bond is the lower the activation energy and the faster the reaction. This leads to the following reactivity order for alkyl halides

RI > RBr > RCl > RF

Practically, alkyl fluorides are not used for S_N2 reactions because the C-F bond is too strong. Often alkyl iodides are reactive enough to be difficult to store, so the the common choices for reactions are alkyl chlorides and alkyl bromides.

Stability of the group after leaving

When the C-X bond breaks in a nucleophilic substitution, the pair of electrons in the bond goes with the leaving group. In this way, the leaving group is analogous to the conjugate base in a Brønsted-Lowry acid-base reaction. When we were evaluating the strength of acids in chapter 7, what we were really doing was evaluating the stability of the conjugate base that resulted from the proton transfer. All of the concepts that we used to evaluate the stability of conjugate bases we can use again to evaluate leaving groups – essentially they are one and the same. In other words, the trends in basicity are parallel to the trends in leaving group potential – the weaker the base, the better the leaving group. Just as with conjugate bases, the most important question regarding leaving groups is this: when a leaving group leaves and takes a pair of electrons with it, how well is the extra electron density stabilized?

In laboratory synthesis reactions, halides often act as leaving groups. Iodide, which is the *least* basic of the four main halides, is also the *best* leaving group – it is the most stable as a negative ion. Fluoride is the least effective leaving group among the halides, because fluoride anion is the most basic.

We already know that the use of polar, aprotic solvents increases the reactivity of nucleophiles in S_N2 reactions, because these solvents do not 'cage' the nucleophile and keep it from attacking the electrophile.

FACTORS FAVORING S_N2

To design an effective S_N2 reaction using an alkyl halide, we need:

- An unhindered alkyl halide (preferably methyl or primary, but secondary may be possible)
- A good leaving group (preferably I or Br)
- A strong nucleophile
- A suitable solvent – polar aprotic is most effective

Factors Affecting The S_N1 Reaction

As we learnt in **section 8.2**, the nucleophile has no effect on the rate of an S_N1 reaction. This means that we only need to consider the electrophile, usually an alkyl halide. Another feature of the S_N1 reaction is that it is often prone to side reactions, which is why it is less used in synthesis than the S_N2 reaction.

The electrophile

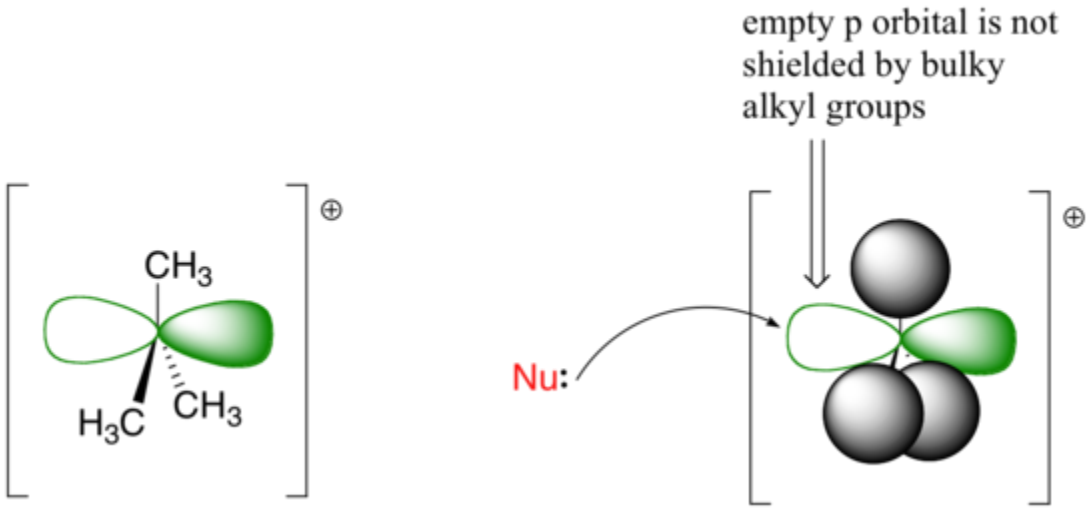
This topic was examined in general in section 6.5., and also considered above for S_N2. But a electrophile that is good for S_N2 is not necessarily good for S_{N1}, for reasons that will become clear. We also have a new factor to consider – the stability of the carbocation that is formed as a result of the heterolysis step.

(a) Structure of the alkyl group

In the vast majority of the nucleophilic substitution reactions you will see in this and other organic chemistry texts, the electrophilic atom is a carbon which is bonded to an electronegative atom, usually oxygen, nitrogen, sulfur, or a halogen. The concept of electrophilicity is relatively simple: an electron-poor atom is an attractive target for something that is electron-rich, *i.e*. a nucleophile. However, we must also consider the effect of steric hindrance on electrophilicity. In addition, we must discuss how the nature of the electrophilic carbon, and more specifically the stability of a potential carbocationic intermediate, influences the S_N1 reaction.

Steric effects on electrophilicity

In an S_N1 mechanism, the nucleophile attacks an sp^2-hybridized carbocation intermediate, which has trigonal planar geometry with 'open' 120 angles.

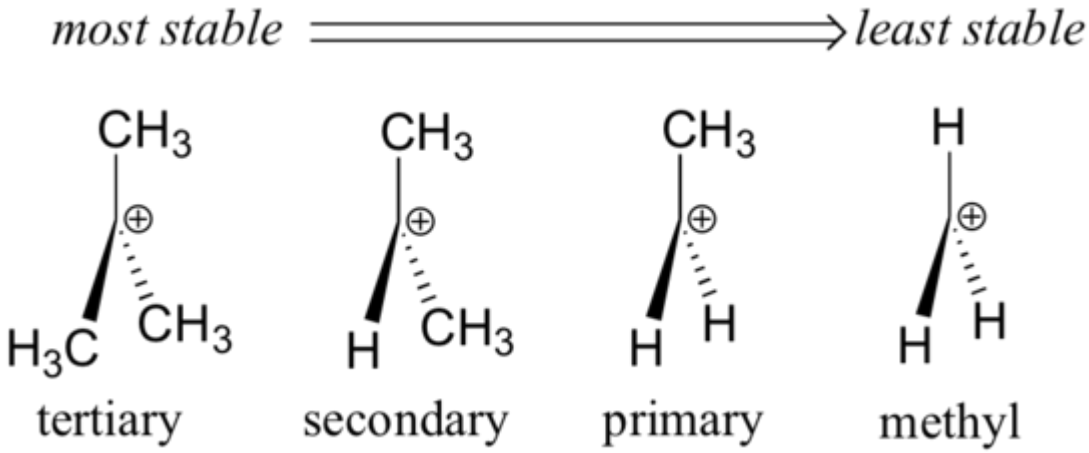


With this open geometry, the empty p orbital of the electrophilic carbocation is no longer significantly shielded from the approaching nucleophile by the bulky alkyl groups. A carbocation is a very potent electrophile, and the nucleophilic step occurs very rapidly compared to the first (ionization) step. This is in direct contrast to the S_N2 reaction, where bulky alkyl groups hinder the reaction.

Stability of carbocation intermediates

We know that the rate-limiting step of an S_N1 reaction is the first step – formation of the this carbocation intermediate. The rate of this step – and therefore, the rate of the overall substitution reaction – depends on the activation energy for the process in which the bond between the carbon and the leaving group breaks and a carbocation forms. According to Hammond's postulate (**section 5.5**), the more stable the carbocation intermediate is, the faster this first bond-breaking step will occur. In other words, the likelihood of a nucleophilic substitution reaction proceeding by a dissociative (S_N1) mechanism depends to a large degree on the stability of the carbocation intermediate that forms.

We previously considered carbocation stability in **section 6.5.**, and we found that in general, *more substituted carbocations are more stable*:

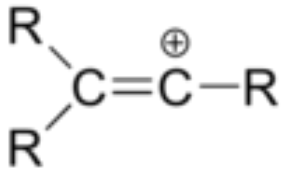


A positively charged species such as a carbocation is very electron-poor, and thus anything which donates electron density to the center of electron poverty will help to stabilize it. Conversely, a carbocation will be *destabilized* by an electron withdrawing group.

Stabilization of a carbocation can also occur through **resonance**, which allows the "burden" of the negative charge to be delocalized, or shared, onto more than one atom. Resonance effects as a rule are more powerful than inductive effects. For example, a cation next to a double bond will delocalize the charge via type IV resonance:

an allylic carbocation

Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are very unstable and thus unlikely to form as intermediates in any reaction.



a vinylic carbocation
(very unstable)

When considering the possibility that a nucleophilic substitution reaction proceeds *via* an S_N1 pathway, it is critical to evaluate the stability of the hypothetical carbocation intermediate. If this intermediate is not sufficiently stable, an S_N1 mechanism must be considered unlikely, and the reaction probably proceeds by an S_N2 mechanism.

Leaving group

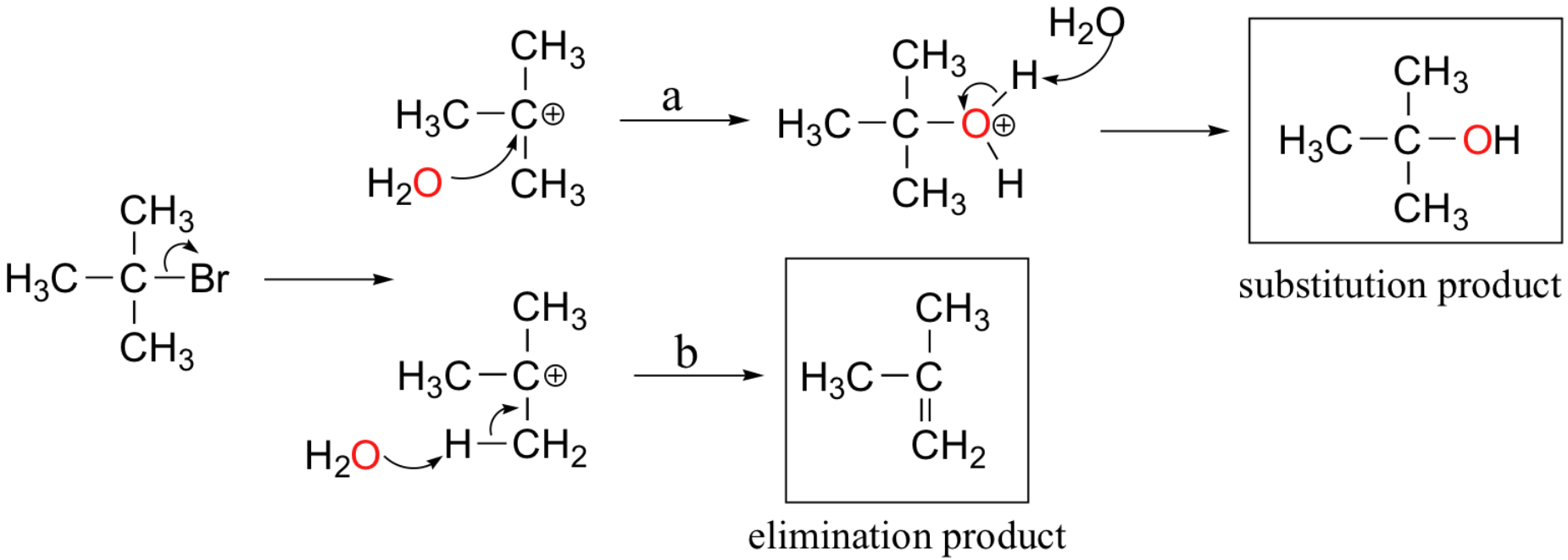
The C-X bond breaks in the rate determining step of S_N1, just as it does in S_N2, and in fact the rules are the same for determining a "good" leaving group. Again these are determined by the C-X bond strength and the stability of X after it has left. This means that we see the same trends as we did for S_N2, where the larger halogens make better leaving groups, i.e.,

$$I > Br > Cl > F$$

Side reactions in S_N1

(a) Elimination

In all of our discussion so far about nucleophilic substitutions, we have ignored another important possibility. In many cases, including the two examples above, substitution reactions compete with a type of reaction known as **elimination**. This will be covered in detail soon, in **section 8.5.** Consider, for example, the two courses that a reaction could take when 2-bromo-2-methylpropane reacts with water:



We begin with formation of the carbocation intermediate. In pathway 'a', water acts as a nucleophile – this is, of course, the familiar S_N1 reaction. However, a water molecule encountering the carbocation intermediate could alternatively act as a *base* rather than as a nucleophile, plucking a proton from one of the methyl carbons and causing the formation of a new carbon-carbon p bond. This alternative pathway is called an elimination reaction, and in fact with the conditions above, both the substitution and the elimination pathways will occur in competition with each other. Elimination can be minimized by keeping the reaction cold, but some of this side-reaction is often inevitable.

(b) Carbocation rearrangements

These will be covered very soon, in **section 8.4.** If the carbocation can easily rearrange to a more stable carbocation, then rearrangement products are likely to be important, and the reaction may lead to mixtures.

Solvent

The rates of S_N1 reactions are generally increased by the use of a highly polar solvent, including protic (hydrogen bonding) solvents such as water or ethanol. In essence, a protic solvent increases the reactivity of the leaving group in an S_N1 reaction, by helping to stabilize the products of the first (ionization) step. In the S_N1 mechanism, remember, the rate determining step does *not* involve the nucleophilic species, so any reduction of nucleophilicity does not matter. What matters is that the charged products of the first step – the carbocation intermediate and the anionic leaving group – are stabilized best by a highly polar, protic solvent.

FACTORS FAVORING S_N1

To design an effective S_N1 reaction using an alkyl halide, we need:

- A highly substituted alkyl halide (preferably tertiary or resonance-stabilized, but secondary may be possible), ideally one which will not lead to rearrangement
- A good leaving group (preferably I or Br)
- A non-basic nucleophile (to reduce the elimination side reaction)
- A suitable solvent – polar protic is most effective

Predicting S_N1 Vs. S_N2 Mechanisms

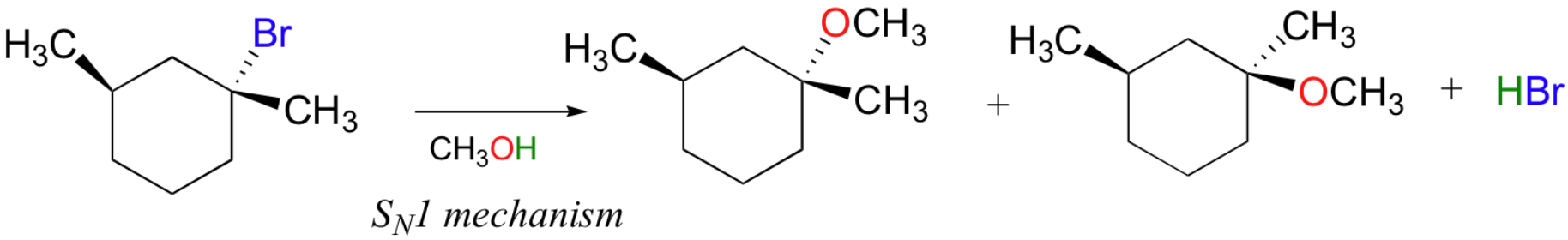
When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

1) **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary, allylic, or benzylic carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored.

2) **The nucleophile**: powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.

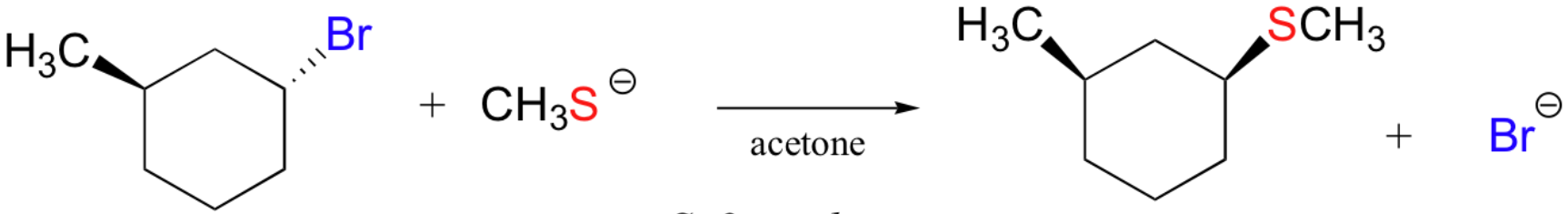
3) **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the carbocation intermediate. S_N1 reactions are frequently solvolysis reactions.

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.



S_N1 mechanism

In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar protic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.

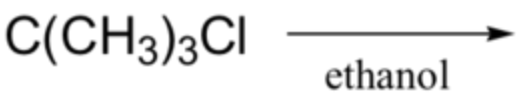


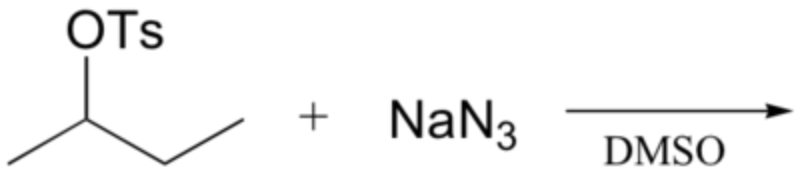
S_N2 mechanism

EXERCISE

Determine whether each substitution reaction shown below is likely to proceed by an S_N1 or S_N2 mechanism.

a)

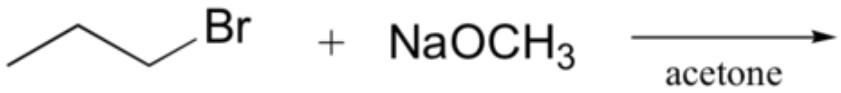
b) 

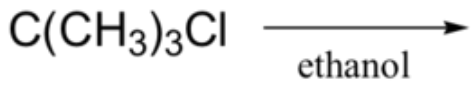
c) 

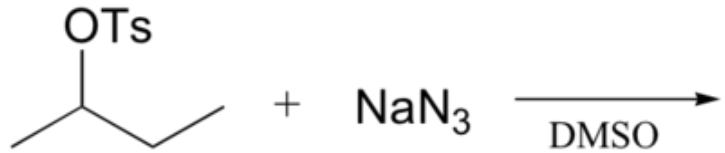
EXERCISE

Solution

Determine whether each substitution reaction shown below is likely to proceed by an S_N1 or S_N2 mechanism.

a) 

b) 

c) 

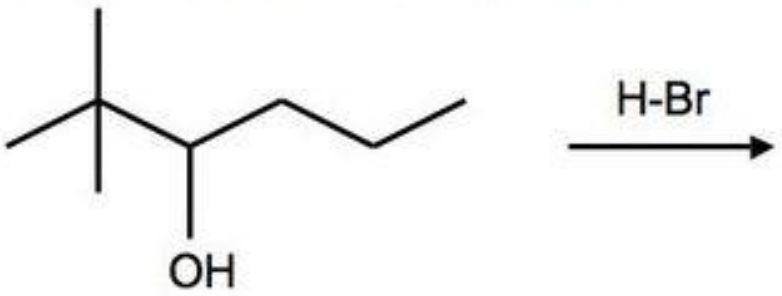
a) S_N2 (primary electrophile, strong nucleophile, polar aprotic solvent)

b) S_N1 (tertiary electrophile, weak nucleophile, protic solvent)

c) S_N2 (secondary electrophile, strong nucleophile, polar protic solvent)

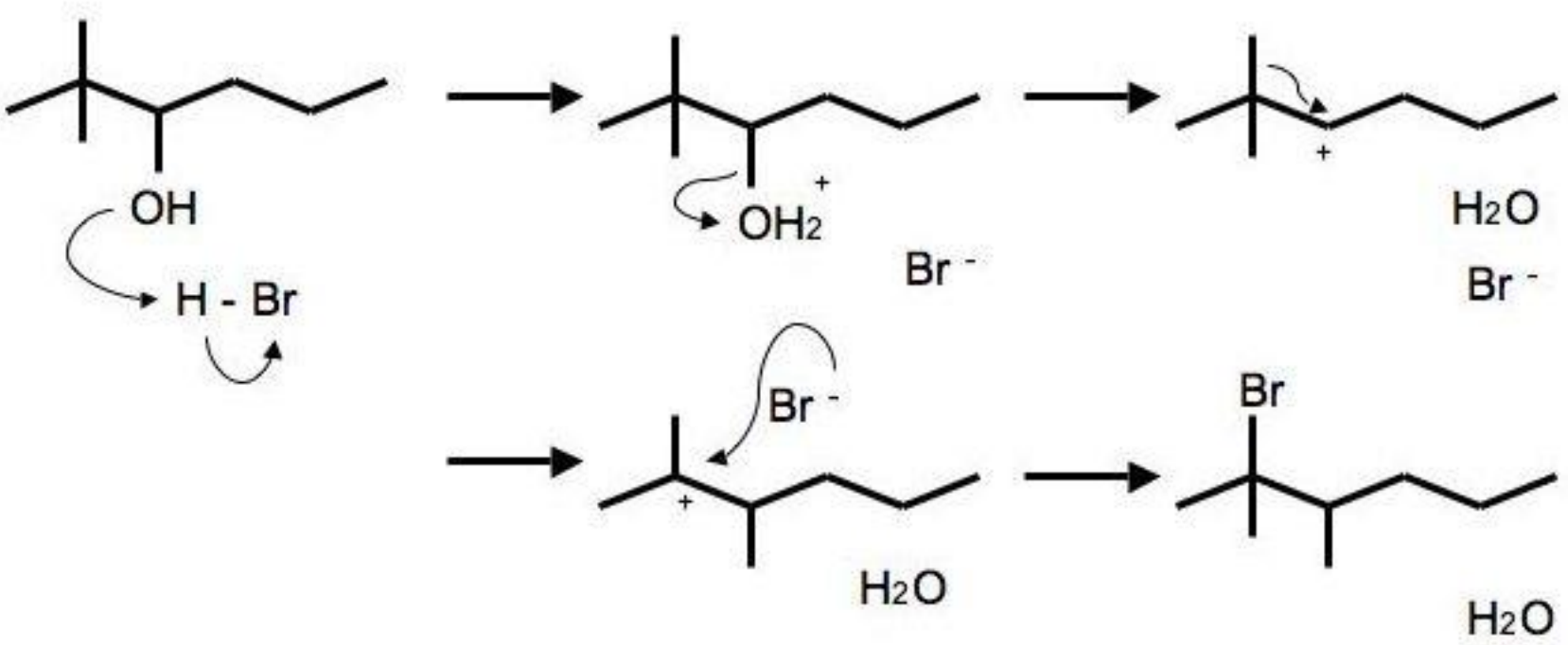
Problem

1) Please show the arrow pushing mechanism and the major final product:



Answers to Practice Problem

1)



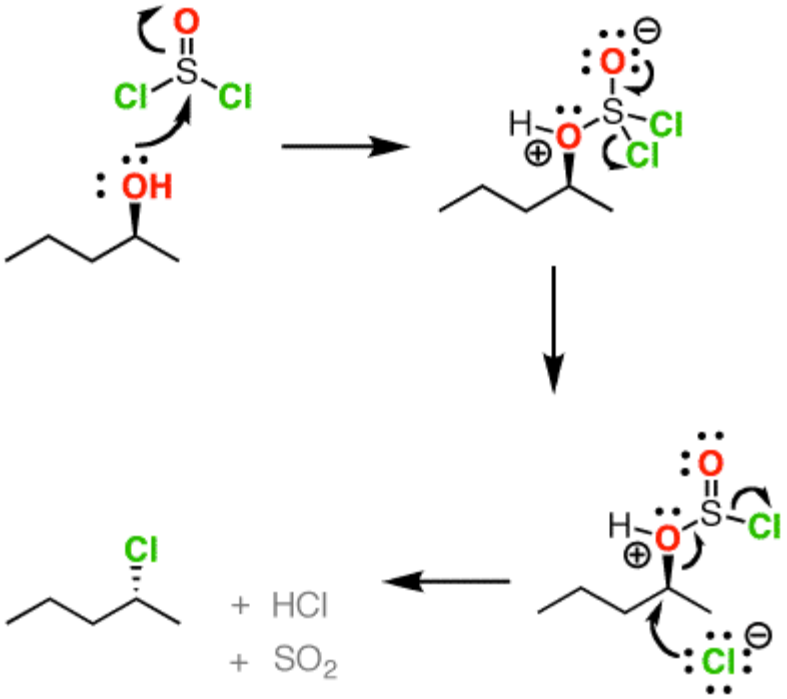
$SOCl_2$ Mechanism With Alcohols, With And Without Pyridine: Nucleophilic Substitution (S_N2) Versus Nucleophilic Substitution With Internal Return (SNi)

Most of the time, the reaction of alcohols with thionyl chloride is taught as an SN2 reaction. And indeed, on primary alcohols this is definitely the case.

The problem arises with secondary alcohols, where the reaction can be taught

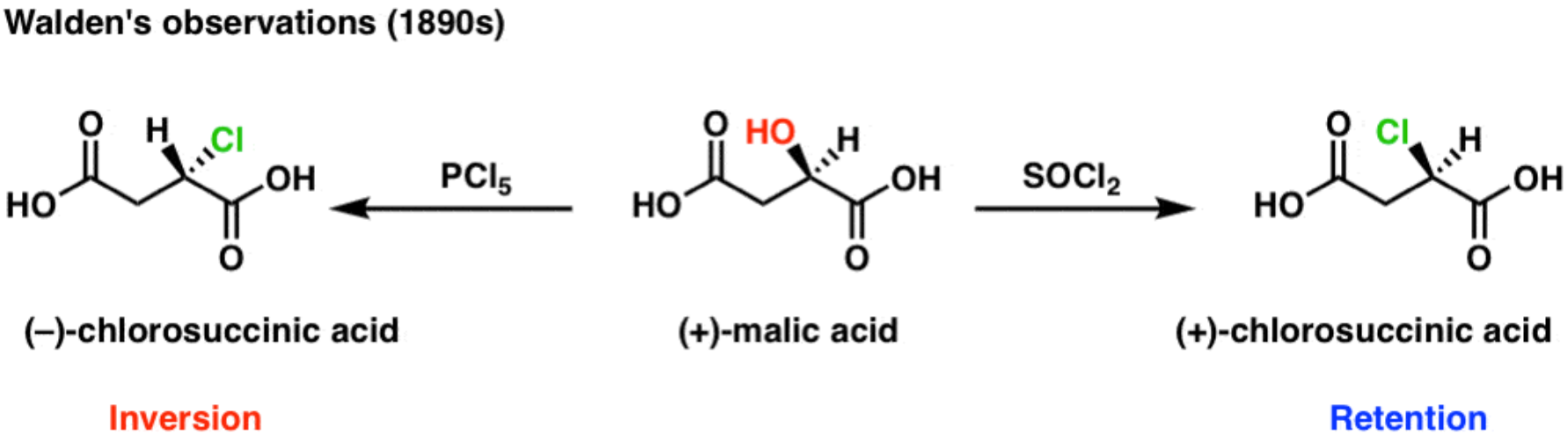
1. either as a classical SN2 with inversion, or…
2. as a reaction with *retention!?* via the SNi mechanism.

1. Conversion Of Alcohols To Chlorides With $SOCl_2$ Proceeds With Inversion…Right? Well, Maybe Not Always



2. What Really Happens In The Reaction of $SOCl_2$ With Secondary Alcohols: The S_Ni Mechanism

In the late 19th century, Paul Walden performed a series of fundamental experiments on the stereochemistry of various reactions of sugars (and sugar derivatives). Walden noted that when (+)-malic acid treated with PCl_5, the product was (–) chlorosuccinic acid – a process that proceeded with **inversion** of stereochemistry. When (+) malic acid was treated with thionyl chloride ($SOCl_2$), however the product was (+)-chlorosuccinic acid. This proceeds with **retention** of stereochemistry.



How can we understand this?

The reaction of malic acid with PCl_5 leading to inversion of stereochemistry is an example of what we now call the **S_N2 reaction**, and Walden was the first to make the observation that the stereochemistry is inverted. In fact the process of stereochemical inversion observed during the S_N2 reaction is sometimes called **Walden inversion** in his honor. By the time most students encounter $SOCl_2$ in their courses, the S_N2 is a familiar reaction.

What is much more curious is the observation that malic acid treated with $SOCl_2$ leads to **substitution with retention**. Sharp readers may recall that "retention" of stereochemistry can be obtained if two successive S_N2 reactions occur [double inversion = retention]. Perhaps that is what is going on here? Maybe the carboxylic acid of malice acid can act as a nucleophile in a first (intramolecular) S_N2, and then Cl- coming in for the second?

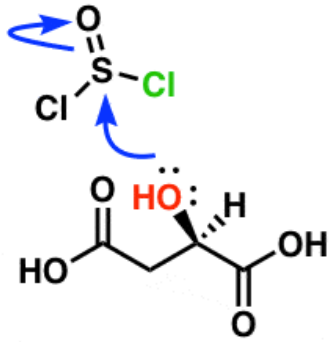
[double inversion = retention]

3. Nucleophilic Substitution With Internal Return: S_Ni

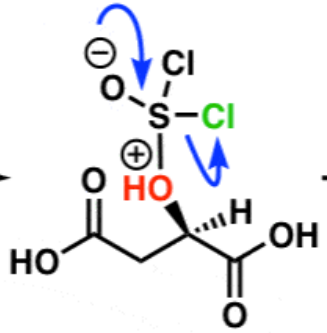
S_Ni or **Substitution Nucleophilic internal** stands for a specific but not often encountered nucleophilic aliphatic substitution reaction mechanism.

Good idea – but this retention of configuration **occurs even in cases where no group can possibly perform an intramolecular S_N2**. There must be something else going on. And after a lot of experimental work, this is the best proposal we have:

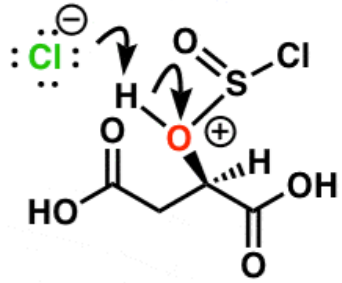
Why does $SOCl_2$ give retention ?



Attack of OH upon $SOCl_2$

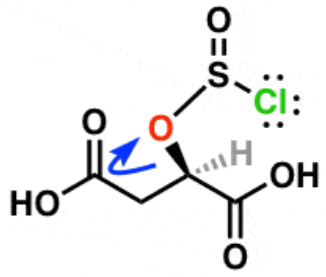


Expulsion of Cl- to form protonated chlorosulfite



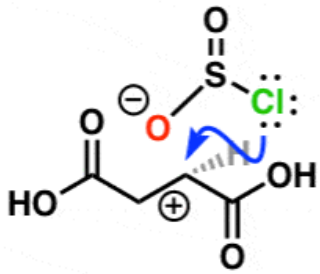
Neutralization to give chlorosulfite

The alcohol attacks $SOCl_2$ and after expulsion of Cl and deprotonation of O, a "chlorosulfite" is formed. The C–O bond breaks with expulsion of Cl^-, forming CO_2 and an "intimate" ion pair. Chloride then attacks the carbocation from the same face, resulting in "retention" of stereochemistry

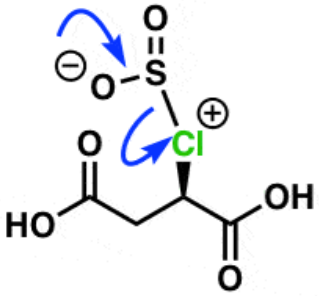


chlorosulfite

Departure of leaving group to form "intimate ion pair"



Chloride attacks carbocation on same face of "intimate" ion pair



Loss of SO_2

This is called the S_Ni mechanism, or, "Nucleophilic substitution with internal return"

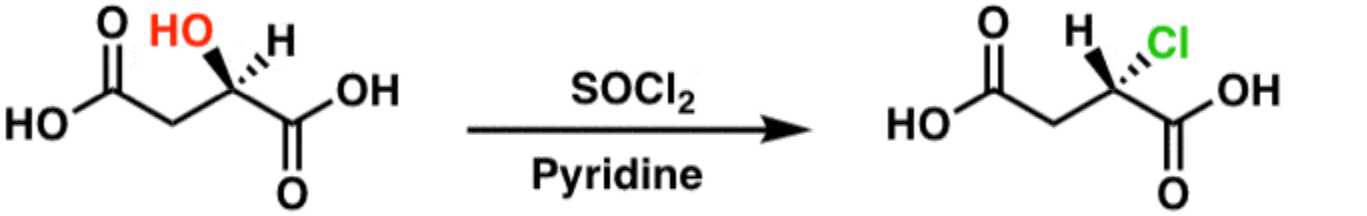
This is called, **S_Ni (nucleophilic substitution with internal return)**: what happens here is that $SOCl_2$ corrdinates to the alcohol, with loss of HCl and formation of a good leaving group ("chlorosulfite"). The chlorosulfite leaving group can spontaneously depart, forming a carbocation, and when it does so, an "intimate ion pair" is formed, where the carbocation and negatively charged leaving group are held tightly together in space. From here, the chlorine can act as a nucleophile – attacking the carbocation on the same face from which it was expelled – and after expulsion of SO_2, we have formation of an alkyl chloride with retention of configuration.

So the chlorosulfite leaving group (SO2Cl) is quite special in that it can deliver a nucleophile (chlorine) to the same face it departs from, with simultaneous loss of SO_2.

4.Why Adding $SOCl_2$ AND Pyridine Leads To Inversion via The S_N2 Mechanism

Here's the twist. As it turns out, the stereochemistry of this reaction can change to **inversion** if we add a mild base – such as pyridine.

Observation: When base is added, $SOCl_2$ now gives inversion



(+)-malic acid **(–)-chlorosuccinic acid**

Inversion

Retention of stereochemistry with $SOCl_2$ alone, inversion with $SOCl_2$ **and pyridine**. What's happening here? How does pyridine affect the course of this reaction?

Both reactions form the "chlorosulfite" intermediate. But when pyridine (a decent nucleophile) is present, it can attack the chlorosulfite, displacing chloride ion and forming a charged intermediate. Now, if the leaving group departs, forming a carbocation, **there's no lone pair nearby on the same face that can attack**.

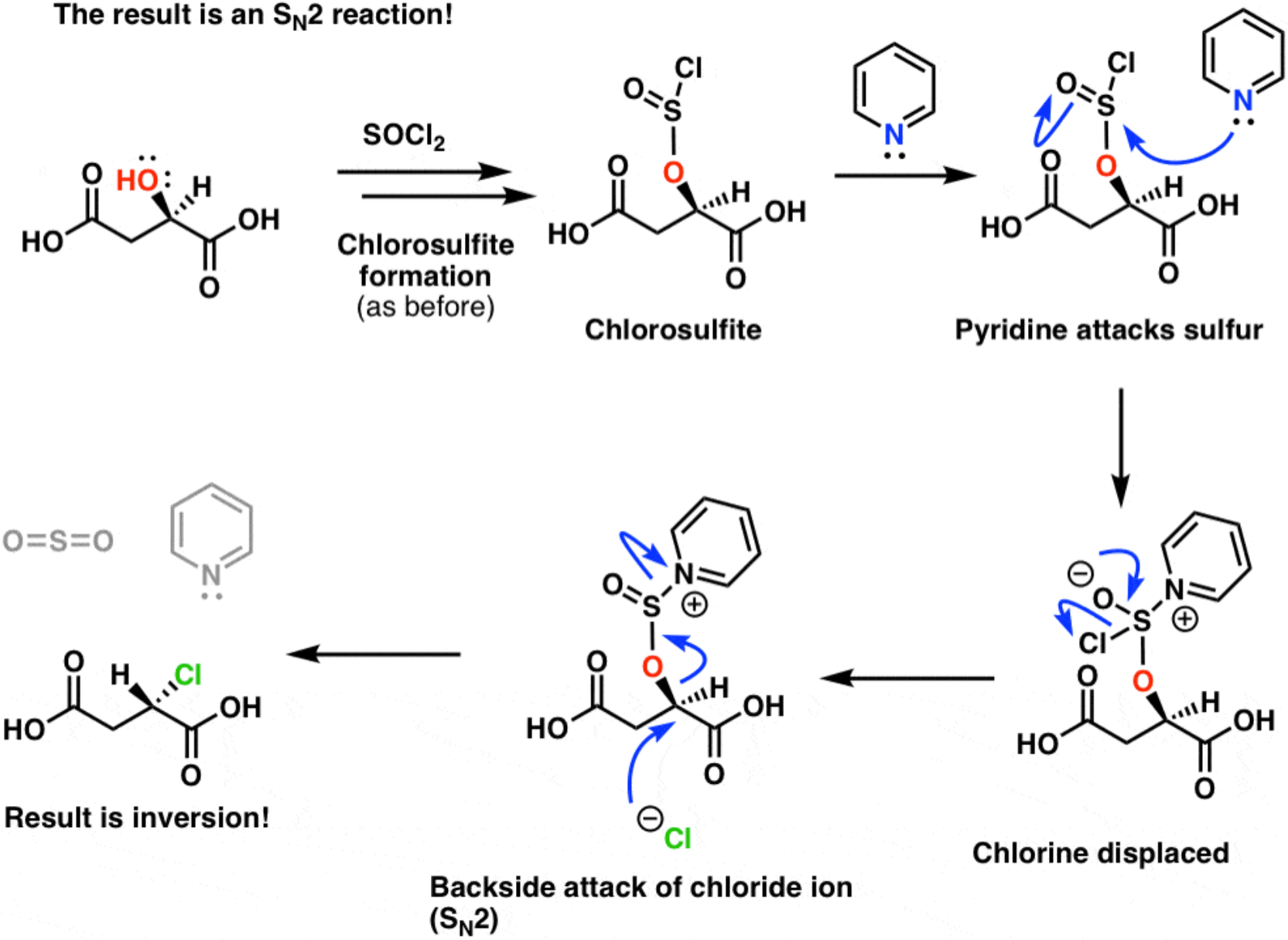
In other words, by displacing chloride ion, **pyridine shuts down the SNi mechanism**.

5. Adding Pyridine To SOCl2 Shuts Down The SNi Mechanism

Even though the SNi can't occur here, we still have a very good leaving group, and a decent nucleophile – chloride ion – and so **chloride attacks the carbon from the backside, leading to inversion of configuration and formation of a C-Cl bond**. This, of course, the S_N2 reaction.

Why inversion this time? Because pyridine displaces chlorine from sulfur, and "internal return" from the leaving group cannot occur

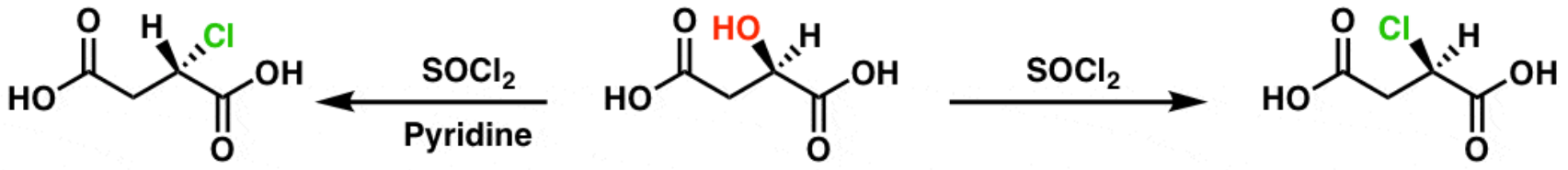
The result is an S_N2 reaction!



6. Summary: $SOCl_2$ And Alcohols, With Or Without Pyridine – S_N2 Versus S_Ni

The bottom line is this:
$SOCl_2$ plus alcohol gives **retention** of configuration, **$SOCl_2$ plus alcohol plus pyridine** gives **inversion** of configuration (S_N2)

Bottom Line (in real life)



(–)-chlorosuccinic acid **(+)-malic acid** **(+)-chlorosuccinic acid**

Inversion
(via S_N2)

Retention
(via S_Ni)

Beware - your course / textbook might treat this differently

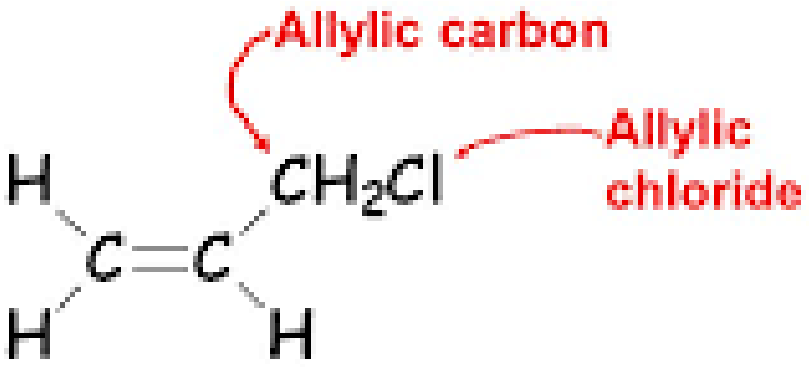
You might be asking, "how common is this SNi mechanism? Is it something which occurs in a large number of other reactions we commonly encounter in introductory organic chemistry?"
To be frank, not really. There are some cases where species called chloroformates can also undergo the SNi with loss of CO_2 but this isn't seen very often at all .

SN1`, SN2` and SNi` = Substitution with rearrangement

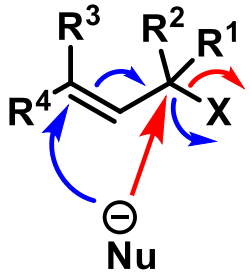
Nucleophilic substitution reaction= Allyl Halides

Other Organic Halides

- Allylic halide:
  - halogen is attached to a carbon that is attached to a C=C



1



—X , 1°-C, SP^3

3°-C, SP^2

$R^1 == R^2 == H$

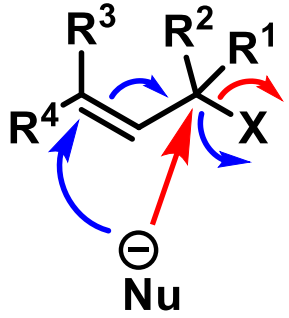
$R^3 \neq R^4 \neq H$

→ SN2

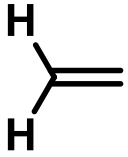
→ SN1' (Carbocation 1st , Then Nu, rearrangement

SN2 competes with SN1'

2



—X , 3°-C, SP^3



1°-C, SP^2

$R^1 == R^2 \neq H$

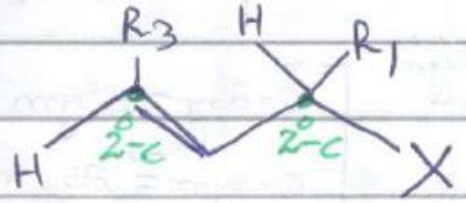
$R^3 == R^4 == H$

→ SN1 (Sterically crowded) 3°-C

→ SN2' (Sterically crowded)

SN1 competes with SN2'

3



$R_1 \neq H$; $R_2 = H$ → S_N1/S_N2 (equal stability)

2°-C

$R_3 \neq H$; $R_4 = H$ → S_N1'/S_N2' • (S_N2 proceeding, S_N1' too)

• It depends on "polarity"

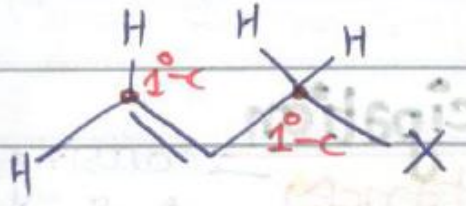
• (S_N1 proceeding, S_N2' too)

Polar solvent → S_N1 (dominant)

Low-P → (S_N2-d)

All '4' Mech are observed.

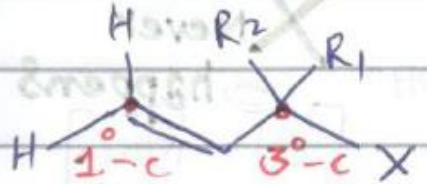
4



$R_1 = R_2 = R_3 = R_4 = H$ (1°-C) → S_N2

• chances of S_N1' poor 1°-C (v. poor) generated.

5

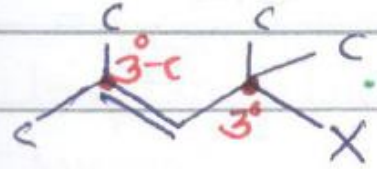


$R_1 = R^2 \neq H$

$R_2 = R_{2'} = H$

→ only S_N1

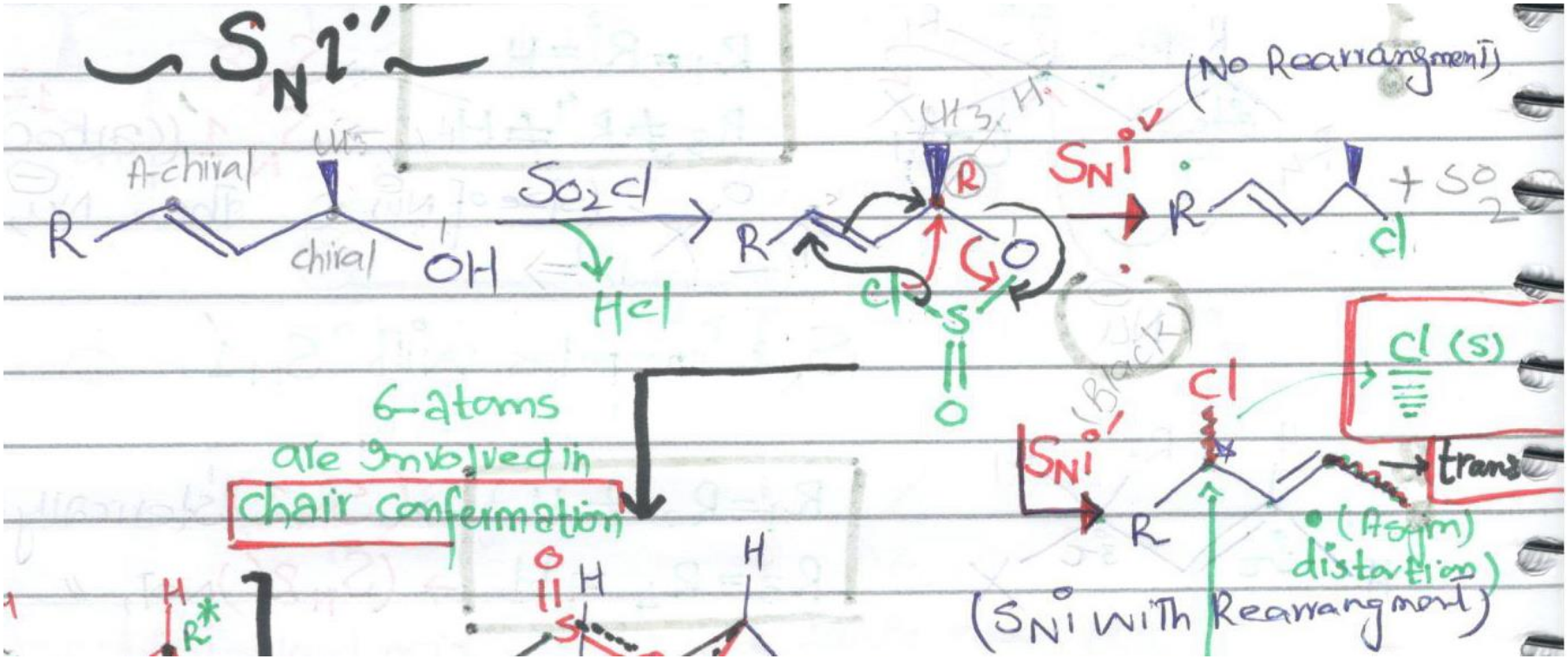
6



$R_1, R_2, R_3, R_4 \neq H$: S_N1/S_N1'

7

$R_1, R_2, R_3, R_4 = H$ • S_N2/S_N2'


SN2''
A-chiral
chiral
OH
SO2Cl
HCl
(No Rearrangment)
SNi
+ SO2
Cl
6-atoms
are involved in
Chair conformation
SNi'
Cl (s)
trans
(Asym)
distortion
(SNi with Rearrangment)

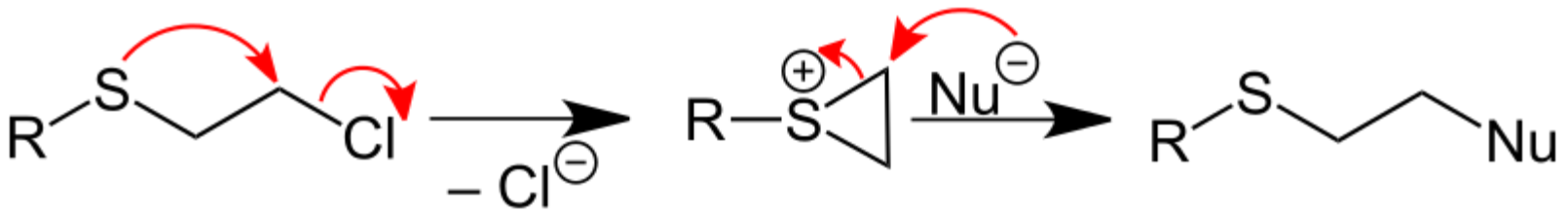
Neighbouring Group Participation (NGP) is observed in nucleophilic substitution **reactions**, where a **neighbouring group** helps in the removal of the leaving **group** to form a reactive intermediate that leads to the formation of the product. ... This is called anchimeric assistance from the **neighbouring group**

Neighbouring group participation (**NGP**) (also known as **anchimeric assistance**) in organic chemistry has been defined by IUPAC as the interaction of a reaction center with a lone pair of electrons in an atom or the electrons present in a sigma bond or pi bond contained within the parent molecule but not conjugated with the reaction centre.

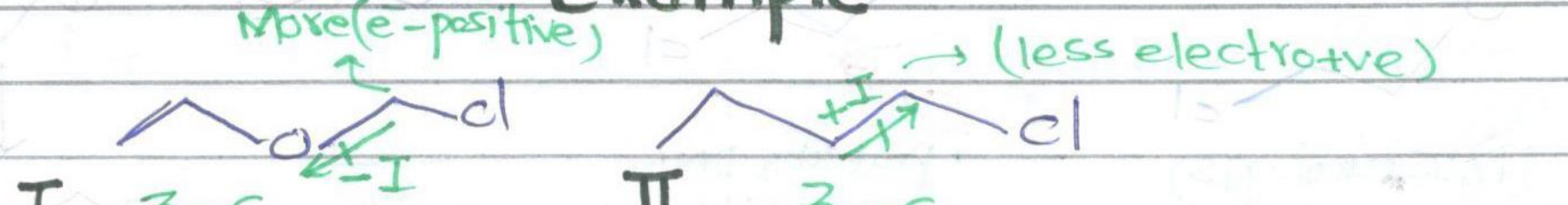
When NGP is in operation it is normal for the reaction rate to be increased. It is also possible for the stereochemistry of the reaction to be abnormal (or unexpected) when compared with a *normal* reaction.

NGP by heteroatom lone pairs

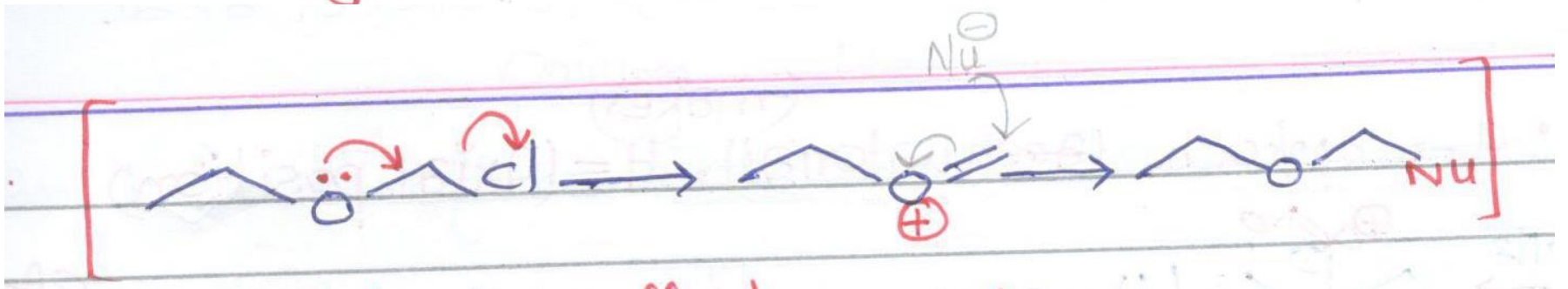
A classic example of NGP is the reaction of a sulfur or nitrogen mustard with a nucleophile, the rate of reaction is much higher for the sulfur mustard and a nucleophile than it would be for a primary alkyl chloride without a heteroatom.



Example



- Substitution Rate different
  - Involving heteroatom



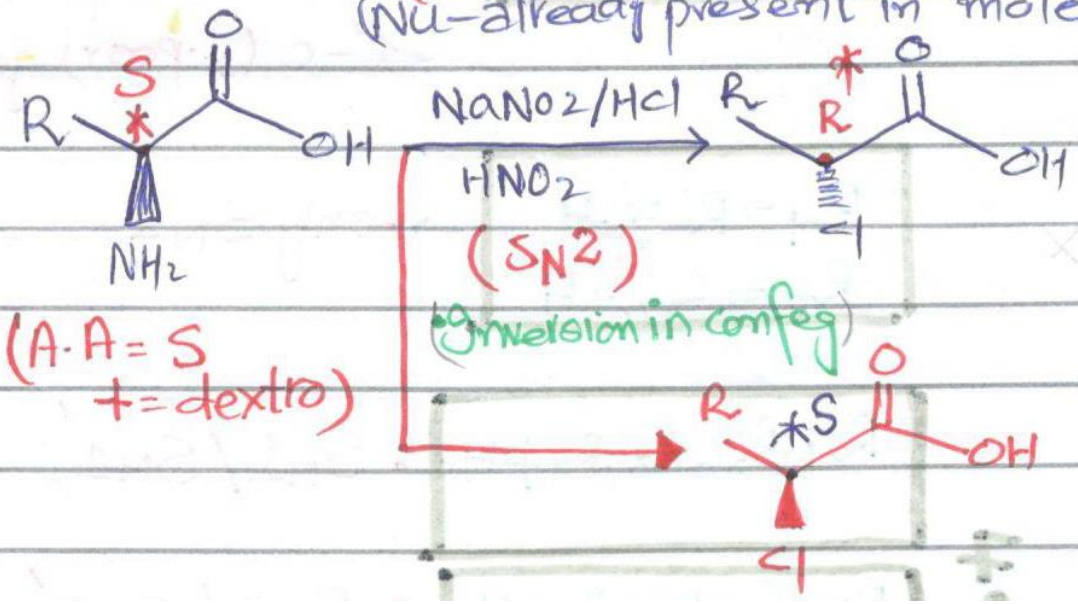
- O = e⁻ withdrawing effect. ← also
- not only anchimaric resistance.
- 1°-C following 'SN1' mechanism (not by 3°)
  why? (Bcz, there is internal Nu present, Stabalized +ve charge (1°- carbocation).

• Neighbouring grp Participation

OR (Anchimaric assistance) → causing abrupt ↑es in Reaction

(Nu- already present in molecule)

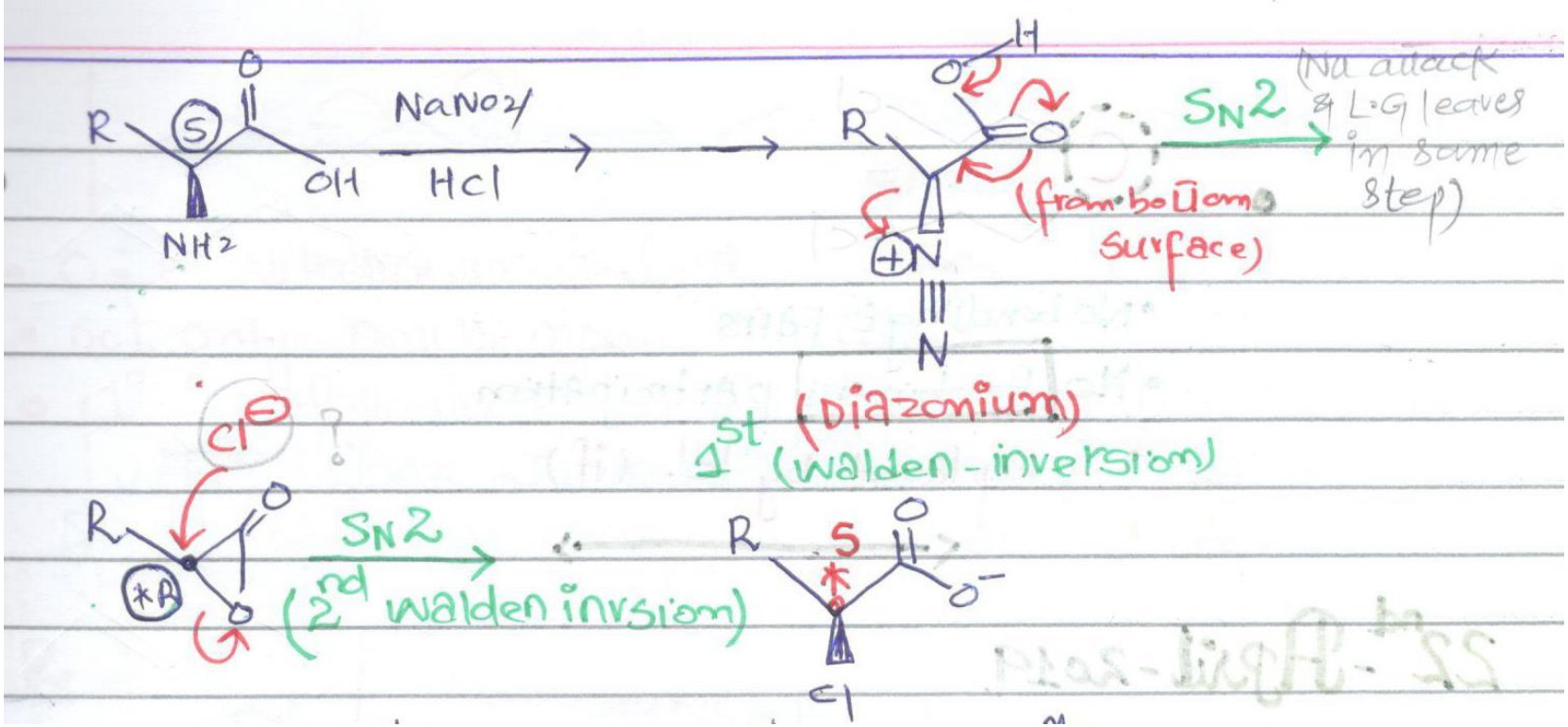
1~



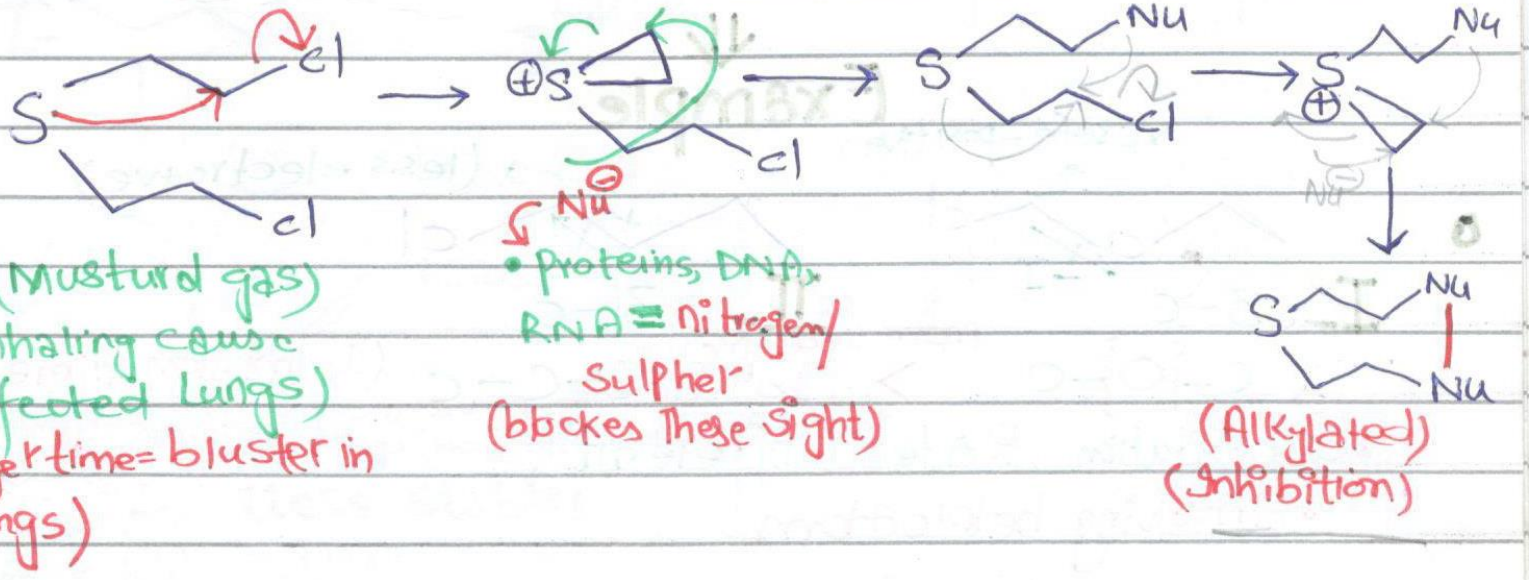
✗ Never happens

[Cl = NH2 both e⁻ = rich] ⊖ ⊕ NO Nu

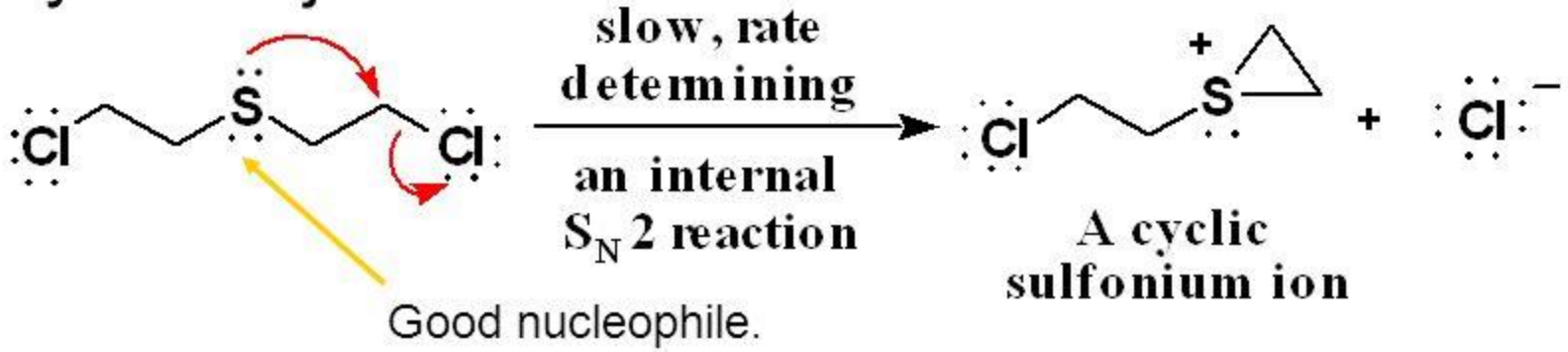
(A.A = S + = dextro)


R
NH2
OH
NaNO2/
HCl
SN2
(Na attack & L.G leaves in same step)
(from bottom surface)
(Diazonium)
1st (Walden - inversion)
Cl
SN2
(2nd walden inversion)
R
S
Cl

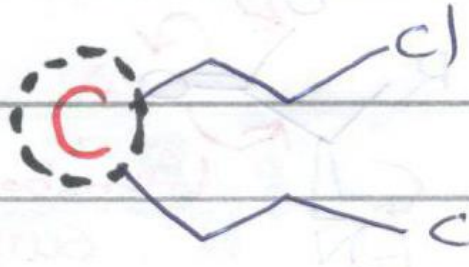
2-


S
Cl
Cl
(Mustard gas)
(inhaling cause affected Lungs)
Longer time = bluster in Lungs)
Nu
• Proteins, DNA, RNA = nitrogen/ Sulpher
(blockes these sight)
(Alkylated)
(Inhibition)

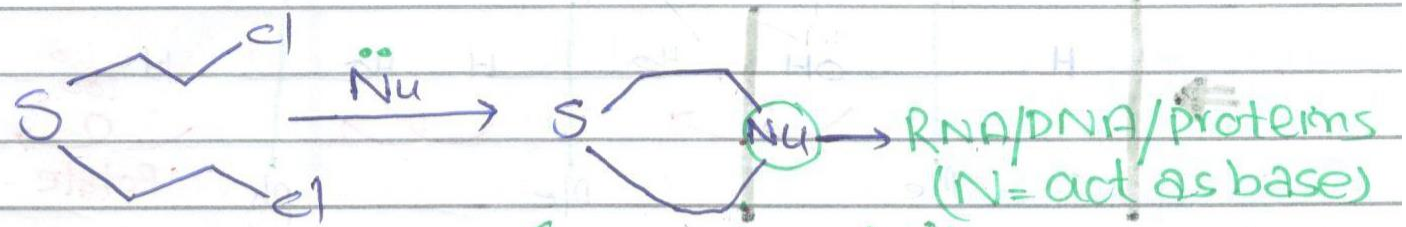
– the reason is **neighboring group participation** by the adjacent heteroatom



– proton transfer to "solvent" completes the reaction



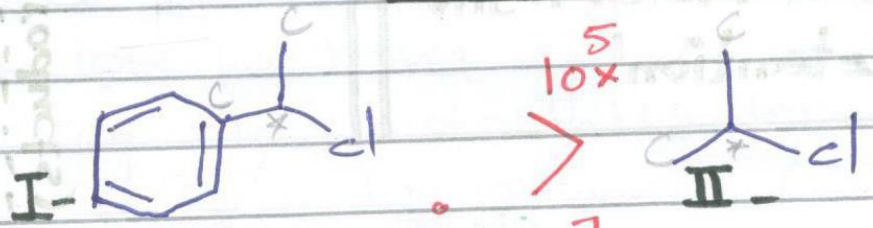
- No bonding $\bar{e}$-pairs
- No Anchimeric participation
- S Replaced by 'c'. (if)



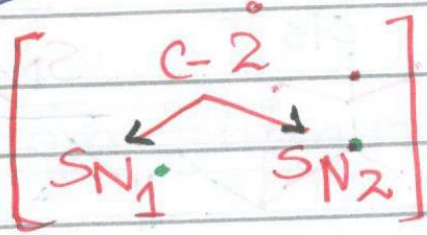
- 6-membered Ring

- Mustured colour.
  - ↳ Mustured Gas. (Resemblance with Cl_2).
- Germans = 'Yprite' (name) (With Sulpher).
- 4000-soldiers were killed.
- It follows two consective 'Walden Inversion'
- first 'Itself neighbouring Then' actual Nu'.

2.



1 o·1 million times faster!

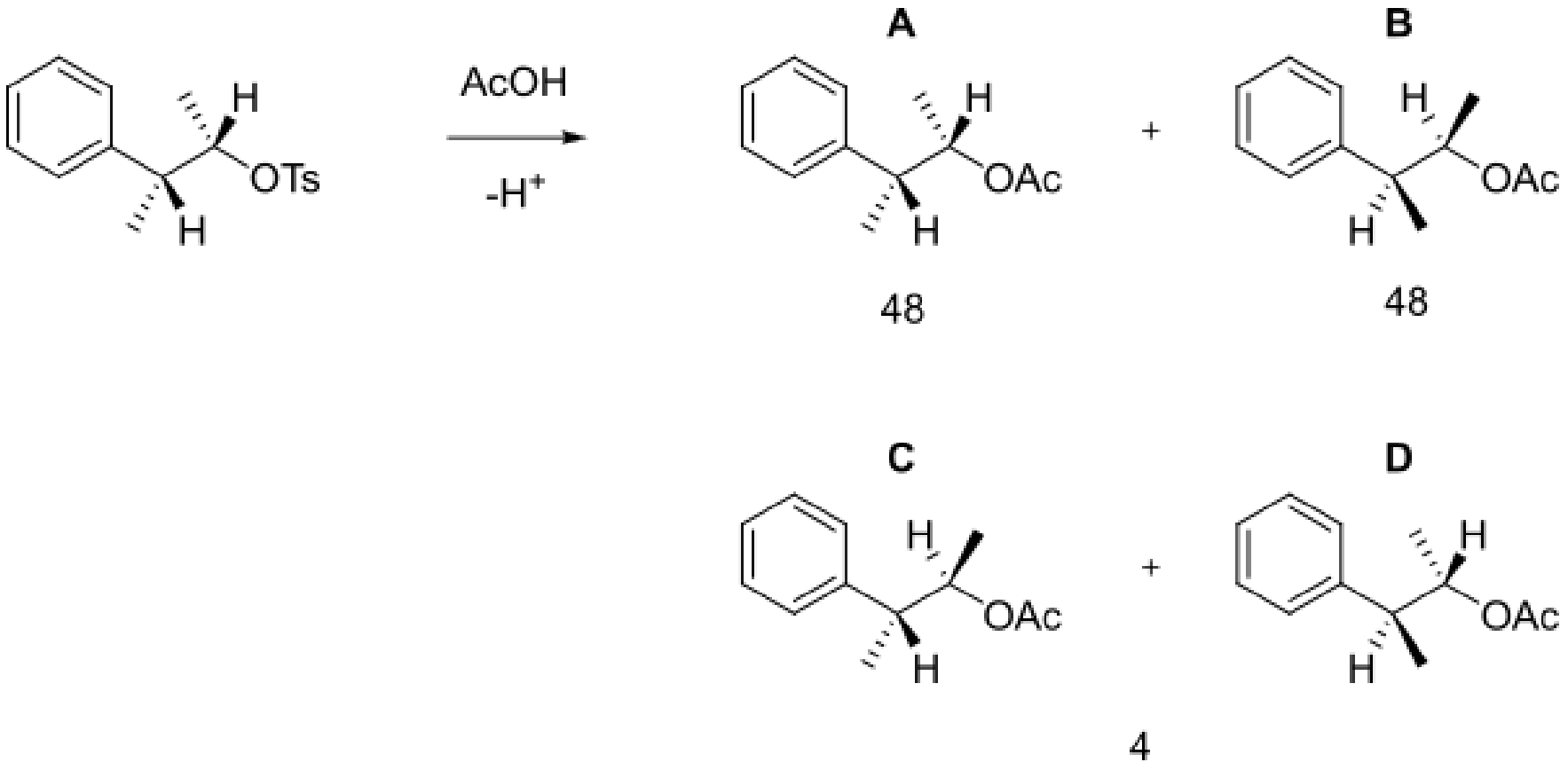


← but →

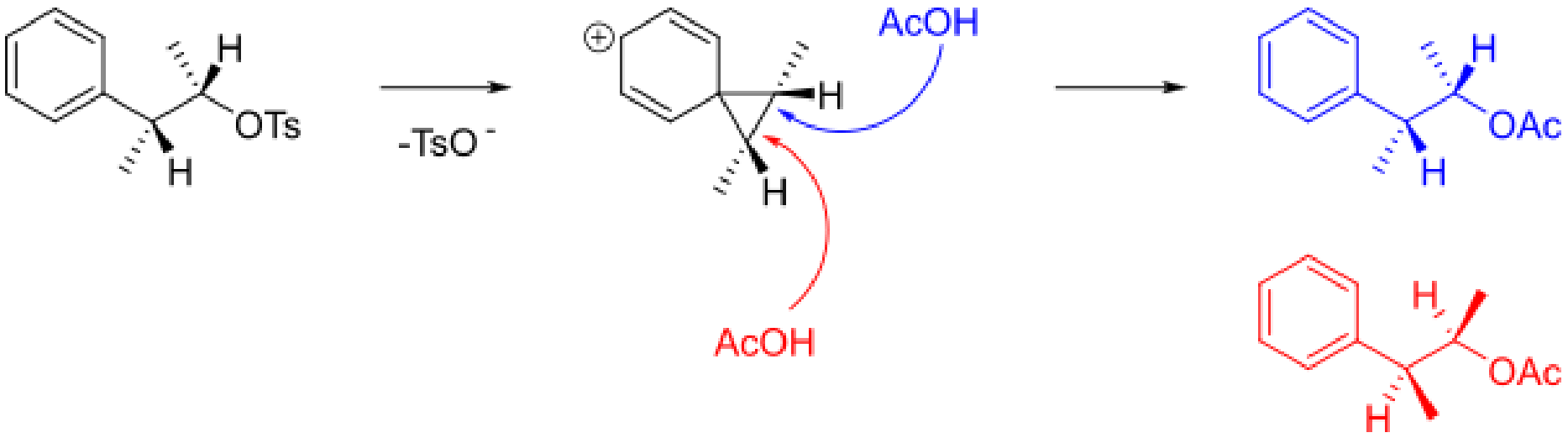
..

- Resonance Stalization(π-System)–I = S_N1
- only Hyperconjugation stabalization.–II

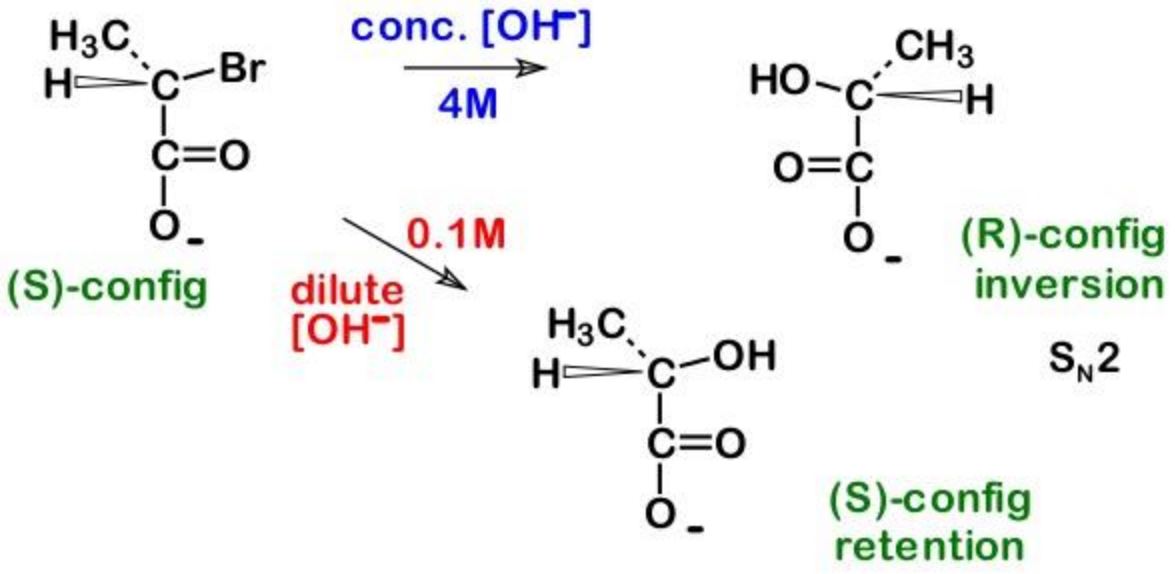
When the following tosylate reacts with acetic acid in solvolysis then rather than a simple S_N2 reaction forming B, a 48:48:4 mixture of A, B (which are enantiomers) and C+D was obtained



The mechanism which forms A and B is shown below.



α-Bromopropionate Ion



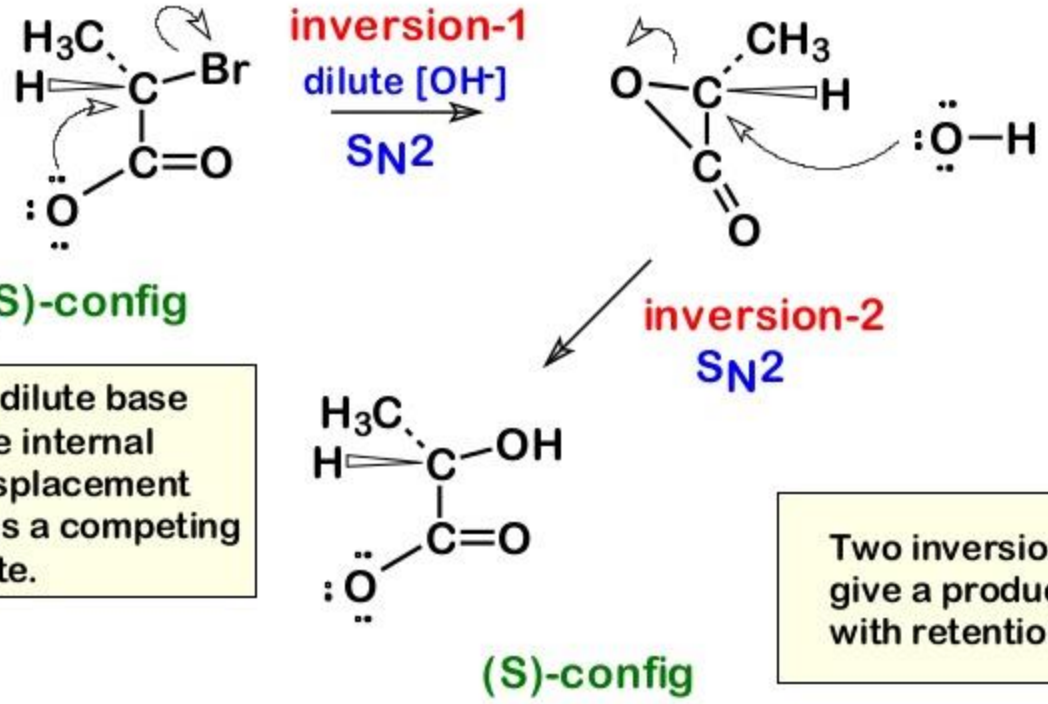
REACTION IN CONCENTRATED BASE

straightforward S_N2 displacement

S_N2 (rate = k[RBr] [OH]) is favored by high [OH]

REACTION IN DILUTE BASE

neighboring group participation



In dilute base the internal displacement has a competing rate.

Two inversions give a product with retention.