Substitution Reactions
4 - Exceptions in Substitution Reactions

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Factors Affecting S_N2 and S_N1 Reactions

There are four factors involved in substitution reactions: substrate, nucleophile, leaving group and solvent. Here we will go into detail on how nature of substrate and nucleophile determine the mechanism and consequently the product(s) formed. Some reactions will be more favorable than others depending on these factors. Favorable means, giving good yield and work as predicted.

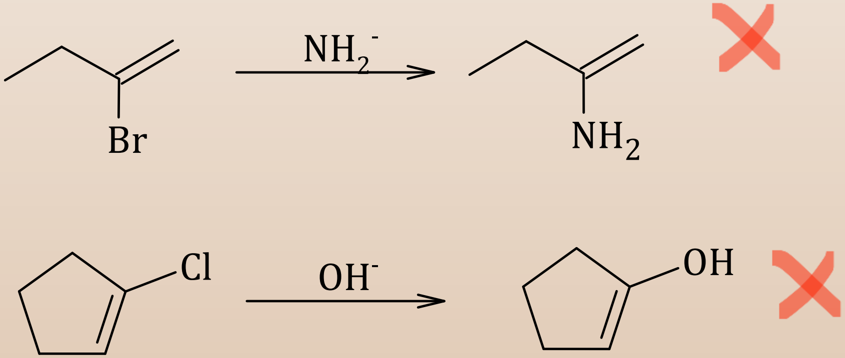
1. Nature of the Substrate (Subs)
    a) Electron rich substrate
    b) Steric hinderance
    c) Resonance
    d) Rearrangement
2. Strength of the Nucleophile (Nu^-)
    a) Sterically hindered Nu-
    b) Solvent as Nu-
    c) Resonance
3. Leaving Group (LG)

    Making a bad LG a good one.

1 - Substrate – a) Electron Rich for S_N^2

Electron rich substrates e.g., alkenes with the LG on the double bond are not good substrates as the Nu is also electron rich and hence it will not attack the electron rich carbon.

Both reactions below will not work.

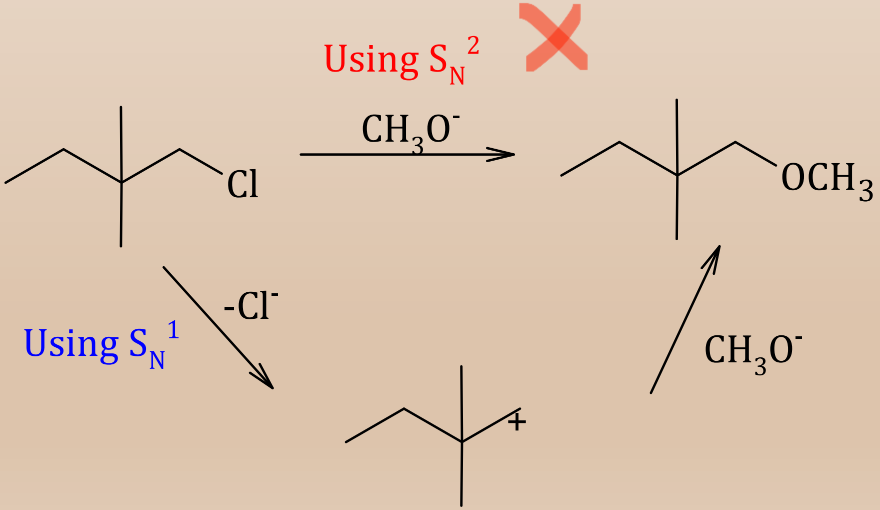


1 – Substrate - b) Steric Hindrance – S_N2

- This is more critical for S_N2 as Nu approaches from the back side hence the electrophilic carbon should not be hindered.
- Best substrates for S_N2 are primary halides.

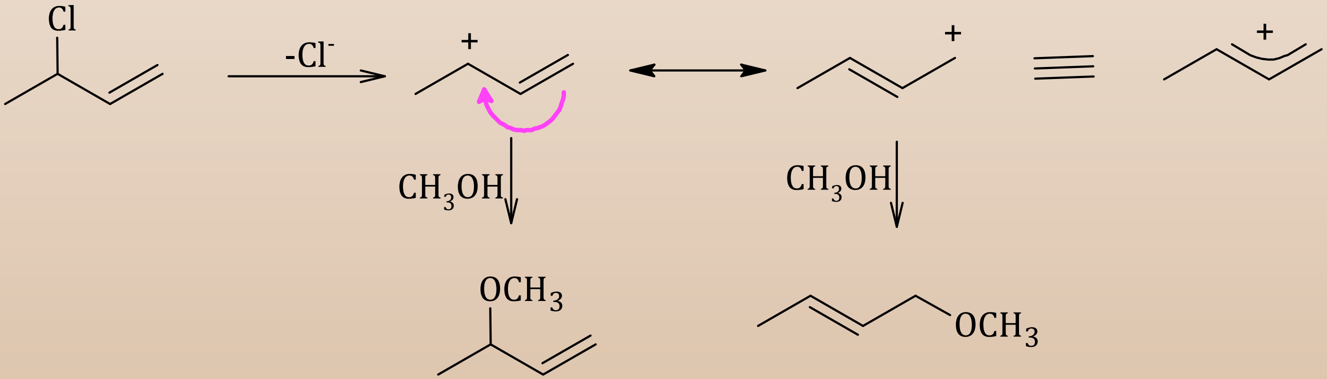
  $1^o > 2^o > 3^o$

- Exceptions in mechanism can occur if the LG is hindered. In the reaction below Subs is 1^o but hindered, so the preferred mechanism is S_N1. And s will also not be favorable since cation is primary. This just means this reaction is not favorable to give the product as written. (Note: There can be other products formed which we will learn later).



1 – Substrate - c) Resonance – S_N1

- Resonance is possible more in ions, cations or anions, hence it is found more in S_N1 mechanisms, as the intermediate is a carbocation.
- S_N2 mechanism is not affected by resonance as there is no carbocation.
- To predict if resonance will occur, look for double bonds near the LG. (*Note: LG cannot be on the double bond, see the "electron rich substrate" in slide 3*). In the reaction below, S_N1 mechanism will occur because the transitions state is resonance stabilized.

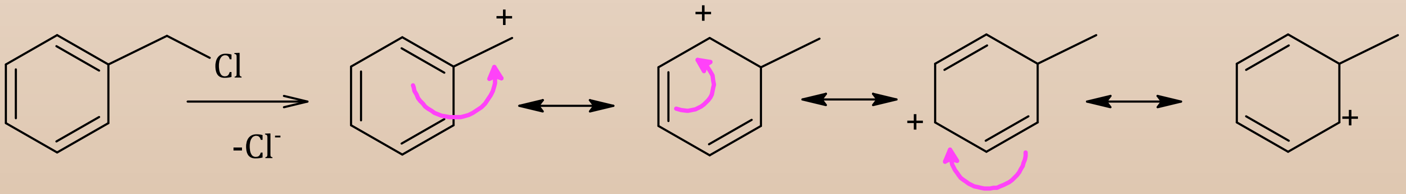


1. Will both products form? Yes, generally.
2. In equal proportion? That depends on the stability of the resonance structure, the more stable it is the more the product will form.

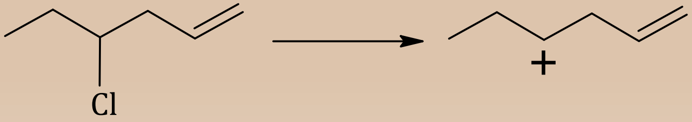
1 – Substrate - c) Resonance..Contd

When a substrate has been identified as a possible resonance substrate (by the placement of the double bond) then write out the carbocation and draw out all the resonance structures before writing the products.

- Practically, the only way to prove there is resonance in any reaction is to carry out the reaction and isolate and study the number and types of products formed.
- One has to write ALL the resonance contributors to estimate the number of products. Below are all resonance structures for benzylic cation.

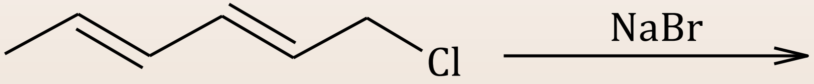


- The substrate below cannot have resonance structures as the double bond is too far from the carbocation, hence the mechanism here will be S_N2.



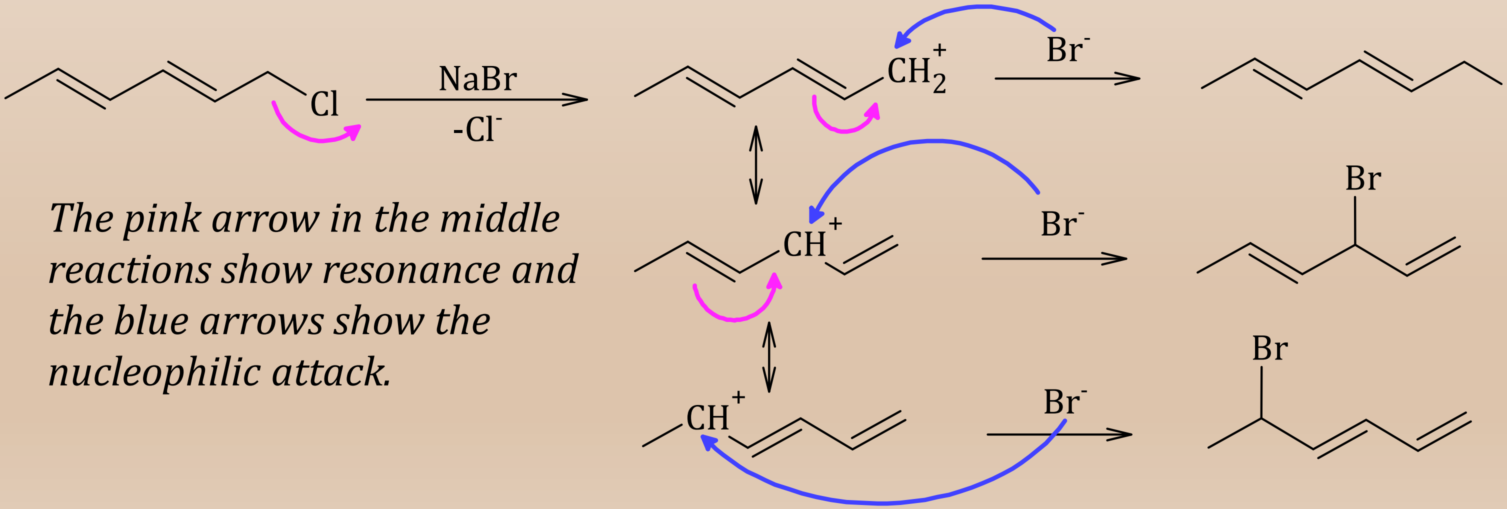
Solved Problem: Allylic LG and Resonance

Give the mechanism and show all the products formed from the substrate given below with sodium bromide?



ANSWER

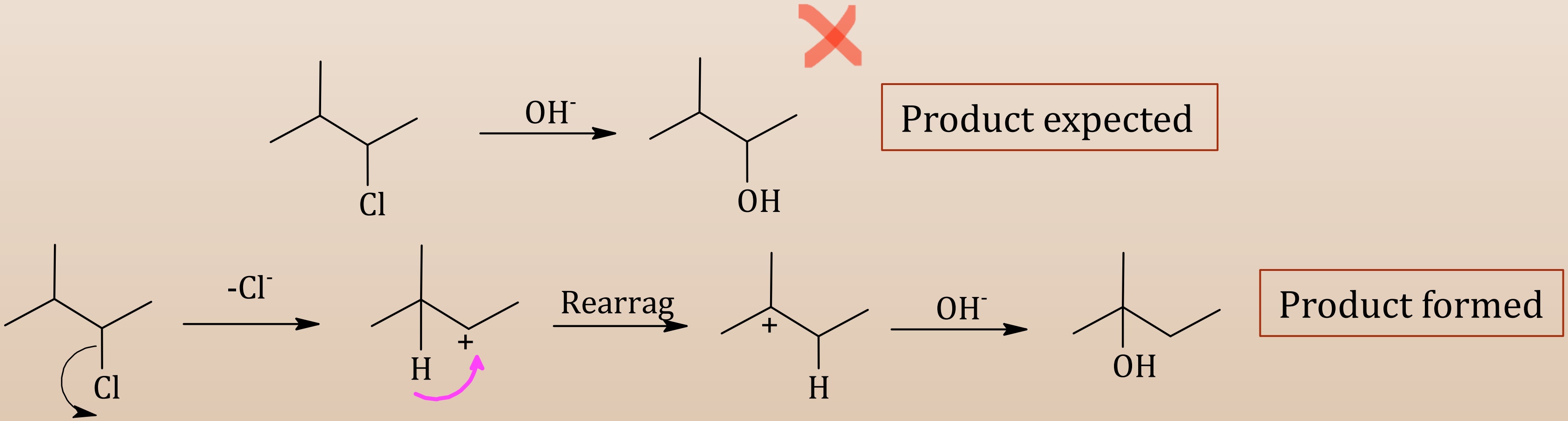
There are two double bonds and an allylic halide. This indicates that the cation can undergo resonance once the leaving group leaves. Since there are three different resonance structures, there are three products. All three should be formed in equal quantities as all resonance structures are equal in stability.



The pink arrow in the middle reactions show resonance and the blue arrows show the nucleophilic attack.

1 – Substrate - d) Rearrangement – S_N1

- Rearrangement happens in S_N1 reactions only because of carbocation formation.
- Carbocations have different stabilities, 3° > 2° > 1°, so if possible, rearrangement will occur to form more stable carbocation.
- This changes the carbon skeleton, thus giving a different product than expected.



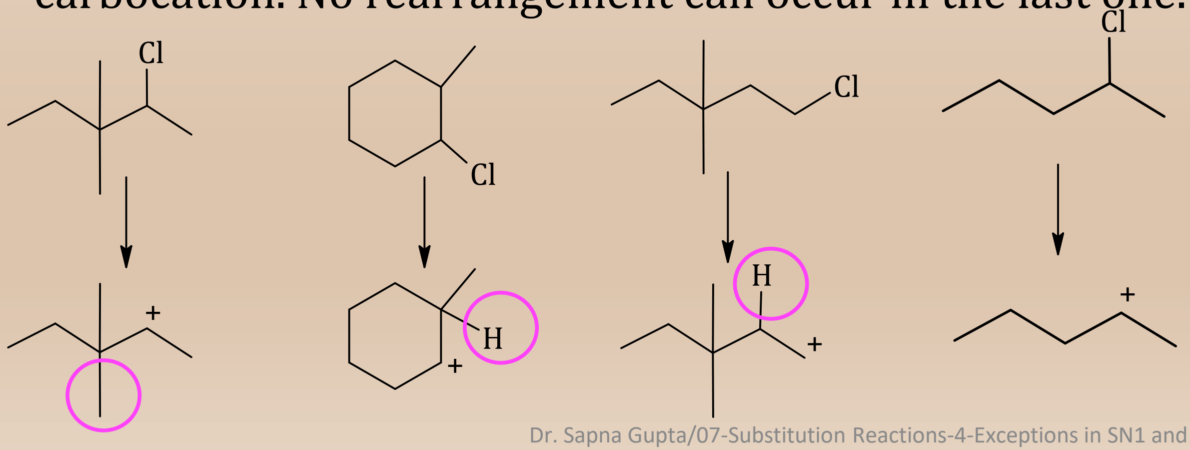
Product expected

Product formed

1 – Substrate - d) Rearrangement…contd

Follow these rules to help you with rearrangement:

- Shift occurs only to form a more stable ion.
- The only groups that can shift are H, CH_3 and Ph (C_6H_5). Don’t move Et, Pr etc. groups. In some cases, ring expansion or shrinking can occur to form stable ions.
- Shift can happen only once.
- <u>Predicting rearrangement</u>: The best way to do this is to draw the carbocation and then see if a more stable cation is possible by moving above groups, if yes, move it and see if you are forming a more stable carbocation.
- In the examples below the circled groups can be moved to create a more stable carbocation. No rearrangement can occur in the last one.



No rearrangement possible as only a 2° carbocation will form after H-shift.

1 – Substrate - d) Rearrangement…Last Word

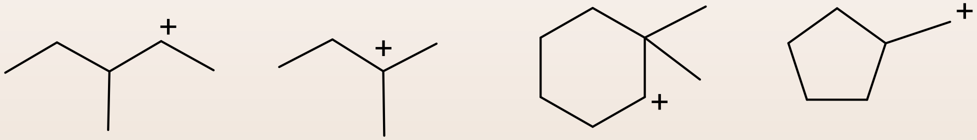
What kind of questions can you expect for rearrangement? How to approach a rearrangement problem? How to even know it's a rearrangement or resonance question?

First follow the guidelines I have provided you and look at the substrate carefully:

1. First in both resonance and rearrangement, the mechanism is always S_N1.
2. Does it have a double bond? If yes, where? Is the LG on the double bond, then there is no reaction. If LG is one carbon over, then yes there can be resonance structures. If the double bond is too far from LG then simple S_N1 or S_N2 depending on the other factors.
3. Is the LG 3° ? Then no rearrangement occurs.
4. If LG is 1° or 2° then look at the carbons next to electrophilic carbon and see you can move a H or Me or Ph to create a more stable carbocation. If yes, then write out the carbocation and show the shift to draw out the shift.
5. Now regarding questions: a) Sometimes I ask you to write ALL the products for a reaction. I am hinting that either resonance or rearrangement is possible, and b) I will give you all the products and ask you to propose a mechanism.

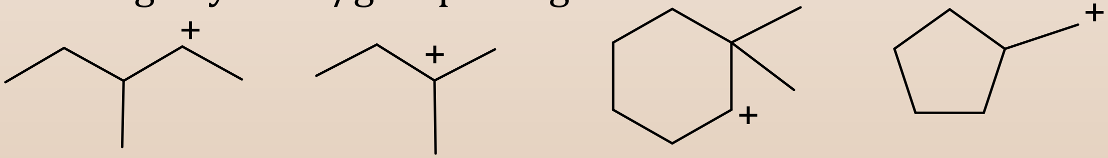
Solved Problem: Possibility of rearrangement

From the following carbocations, which ones are capable of rearrangement?

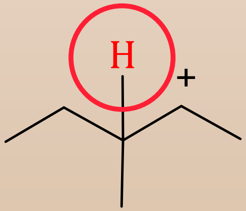


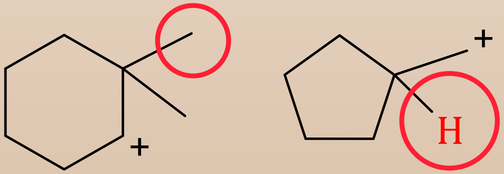
ANSWER

First see if it is a 3° cation, that is most stable and will not undergo rearrangement. Then see if moving any atom/group will give a more stable carbocation.



3° cation – already stable. No rearrangement

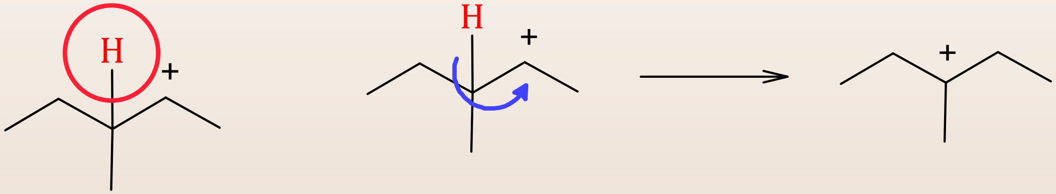


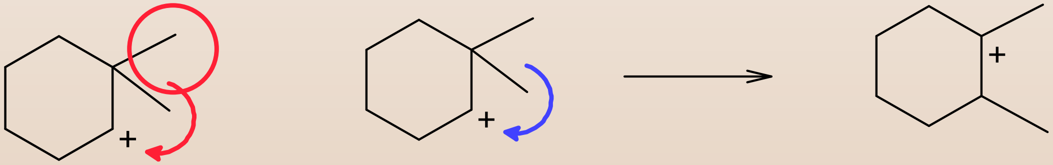


In the rest of the intermediates the cation is 1° or 2° hence can rearrange. The circled Hs or CH3 can be shifted to give a more stable carbocation.

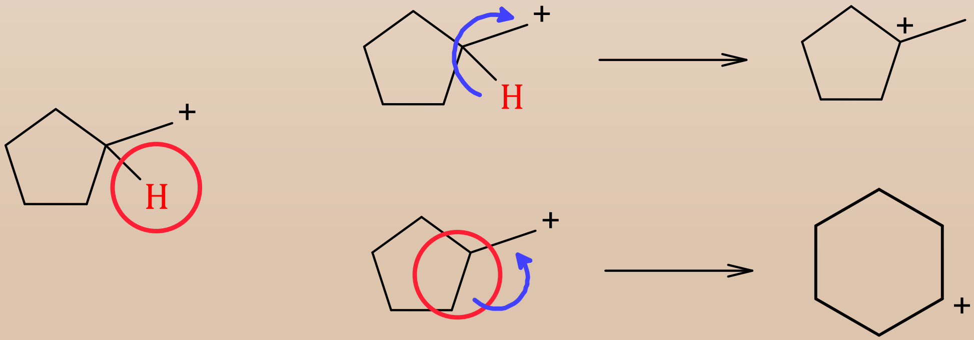
Go to the next slide to see the rearrangements.

Here is how you should be shifting the groups to create a more stable carbocation.





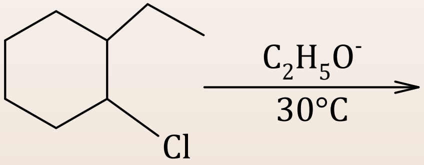
Note here that both methyl groups are identical so you can move whichever one.



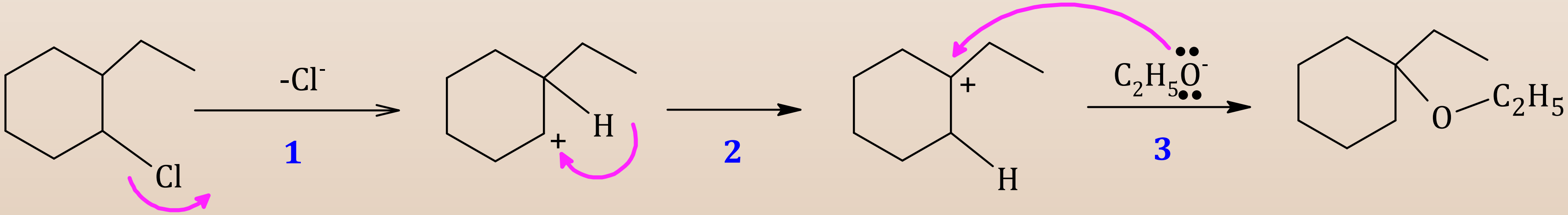
There are two rearrangements possible here; the top one is a H-shift to create a 3° cation; the bottom one is moving the bond within the ring to create a ring expansion and give a 2° cation. Both can occur, but 3° cation is more stable.

<u>Solved Problem: Rearrangment</u>

Write the mechanism of reaction of 2-chloro-1-ethylcyclohexane with ethoxide in ethanol.



ANSWER

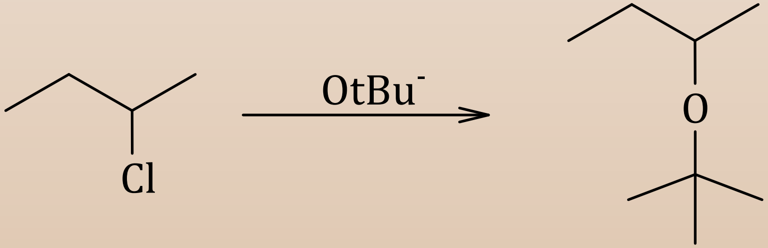


Step 1: LG leaves.
Step 2: H-shift to form a more stable carbocation.
Step 3: Nu- attacks the E+

2 - Nucleophile - a) Sterically Hindered Nu^-

A bulky nucleophile is only a concern in S_N^2 since the Nu^- needs to access the electrophilic carbon (α carbon).

- If the Nu^- is too big it will experience steric hinderance and those reactions will not be favorable in S_N^2 mechanism. This means either the yield will be lower, or the mechanism will proceed via S_N^1, which is dependent on the stability of the carbocation.
- The most problematic substrate is when the LG is 2^o which adds to the steric hinderance as shown below.

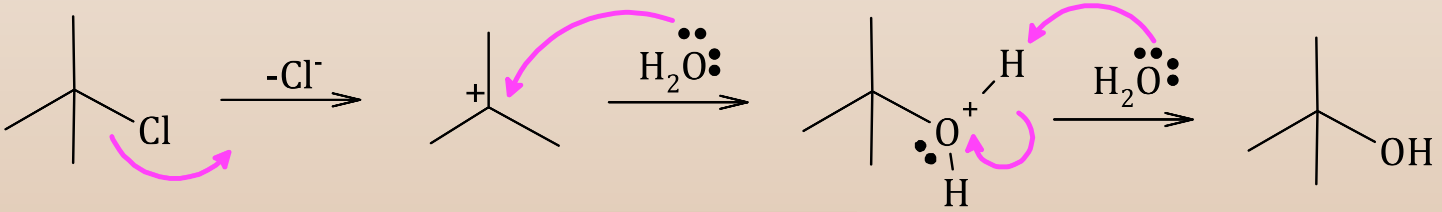


- Bulky Nu^- is not a problem for S_N^1 because carbocation is trigonal planar and can be accessed easily from either side in the planar structure.

2 - Nucleophile – b) Solvent as Nu^- – S_N1

<u>Solvolysis</u> occurs when the solvent behaves like the Nu^- reacts with the Subs.

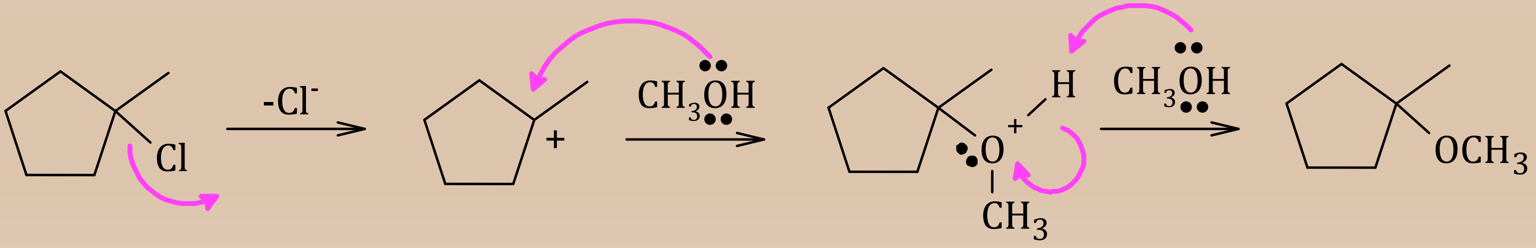
- Solvolysis happens only in S_N1 since Nu^- does not need to be strong since it is not part of the rate determining step. In fact, solvolysis is never observed in S_N2 reactions because a strong Nu^- is required. Solvents reacting as Nu^- are generally water and alcohols.
- Here are a couple of examples of solvolysis using water and methanol as solvents.



Step 1: loss of LG to form the carbocation

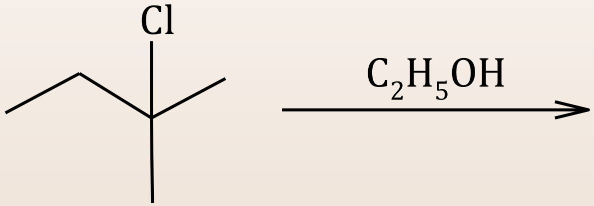
Step 2: Solvent as Nu- attacks the carbocation

Step 3: Deprotonation of the oxonium ion

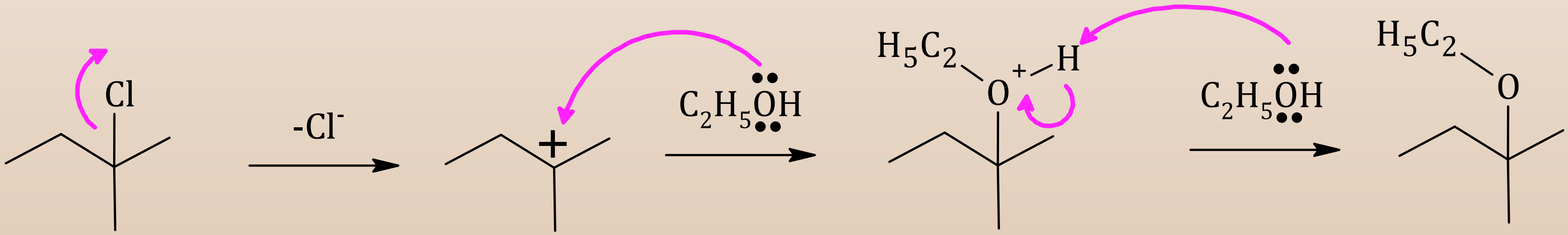


Solved Problem: Solvolysis

Give the mechanism of the reaction 2-chloro-2-methylbutane with ethanol (C_2H_5OH).



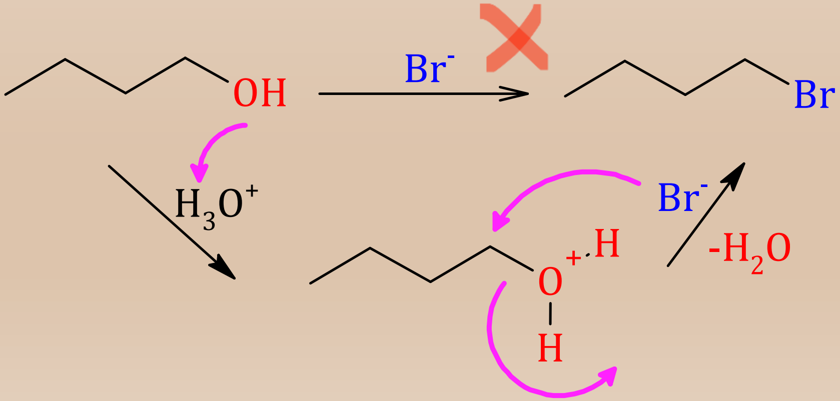
ANSWER



3) Leaving Group (LG) - Making a Bad LG a Good One

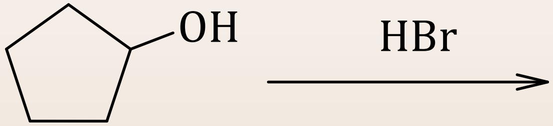
Generally, when doing reactions, one would want to start with the right Subs and Nu, however, in some cases when there is no choice, then a bad LG (strong base) can be converted into a good one (weak base). This conversion lets chemists carry out substitution reactions – both S_N1 and S_N2.

- Not all LGs can be made into good LGs.
- The one we will focus here is converting an alcohol (OH^- LG) into water (H_2O LG) a neutral LG, thus weaker base than OH^- thus a good LG. H_2O can be substituted with even weak Nu^-. See example below.
- Reaction conditions for this reaction are acidic – either start with H_2SO_4 followed by using NaBr or use HBr (hydrobromic acid) for the reaction below.

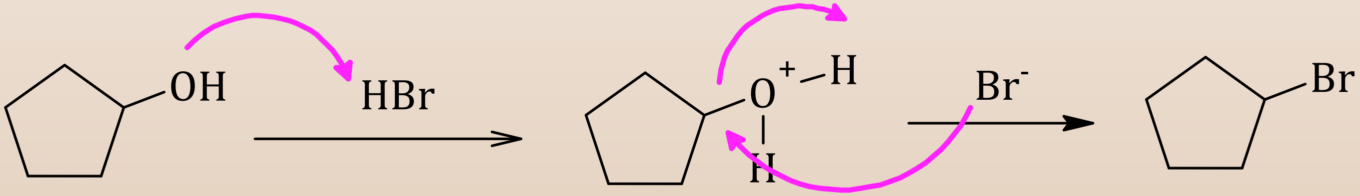


Solved Problem: Making a bad LG into a good one

Give the mechanism of the reaction of cyclopentanol with hydrobromic acid?

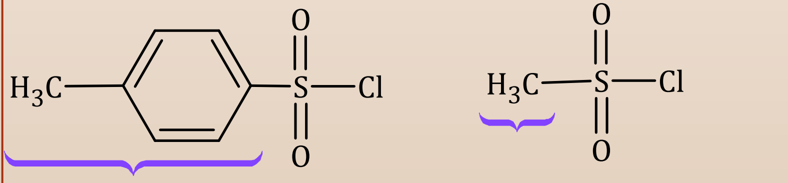


ANSWER



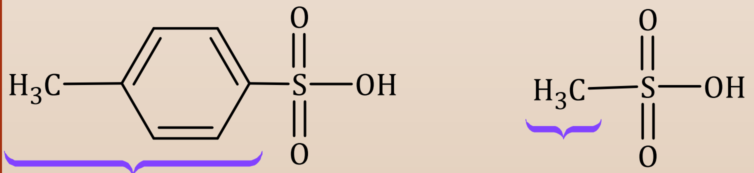
3) Leaving Group (LG) - Making a Bad LG a Good One…Tosylates and Mesylates

Another chemical used, besides haloacid, to convert an alcohol into a good LG is p-toluene sulfonyl chloride (pTsCl). It converts the OH group to a tosylate ($^{-}$OTs), which is great LG as it is a conjugate base of strong acid – p-toluene sulfonic acid, shown in the right box. Methyl sulfonyl chloride behaves the same as pTsCl. This reaction follows the S_N2 mechanism.



p-toluene sulfonyl chloride
pTsCl

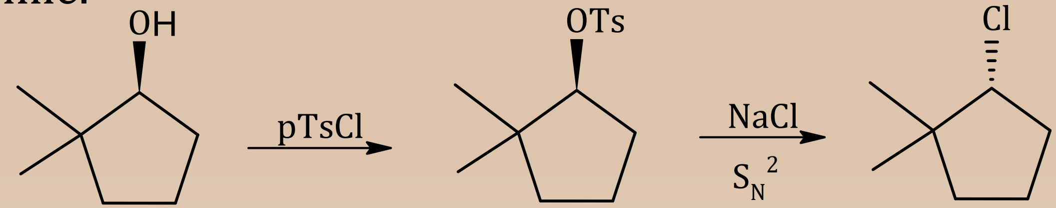
methyl sulfonyl chloride
MsCl



p-toluene sulfonic acid
pTsOH

methyl sulfonic acid
MsOH

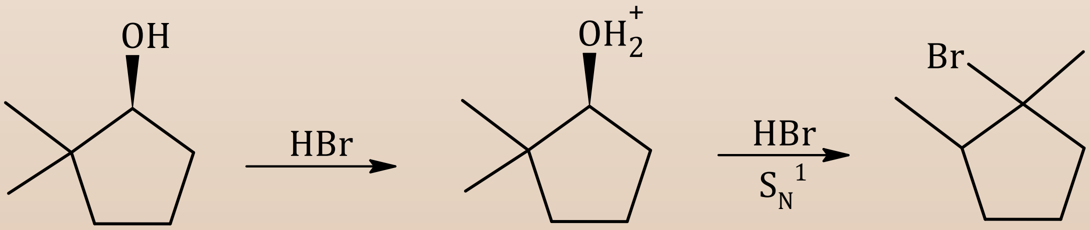
Here is an example of a chiral alcohol treated with TsCl* and undergoing S_N2 in the second step to give the chloride of inverse stereochemistry. Note that chloride is not a strong nucleophile.



This is covered more in Alcohols chapter.

3) Leaving Group (LG) - Making a Bad LG a Good One…Tosylates and Mesylates – Last Word

Tosylates reactions are S_N2 hence preventing rearrangement which is a characteristic of carbocations. The example below shows that if the reaction on the previous slide had been carried out in acidic conditions using hydrobromic acid, then a rearranged product would be obtained. (*Write the mechanism yourself*).



S_N2 and S_N1 Characteristics

	S_N2	S_N1
Substrate	Primary or methyl	Tertiary
Nucleophile	Strong nucleophile	Weak nucleophile (may also be solvent)
Solvent	Polar aprotic solvent	Polar protic solvent
Kinetics	[substrate][Nu^-]	[substrate]
Stereochemistry	Inversion	Racemic mixture
Rearrangement	No	Yes
Resonance	No	Yes, if double bonds present

Key Words/Concepts

- Substitution Reaction
- 1st order reaction (unimolecular)
- 2nd order reaction (bimolecular)
- Carbocation
- Resonance
- Steric hinderance
- Solvolysis
- Rearrangement