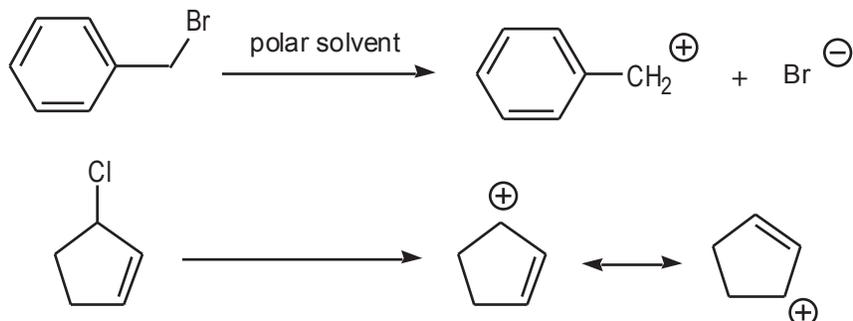


Some substrates, whether they are sterically hindered or not, may prefer to undergo S_N1 reactions if they can dissociate into very stable carbocations in the presence of the solvent. In most cases this involves resonance-stabilized cations.

EXAMPLES OF S_N1 SUBSTRATES THAT FORM STABLE CARBOCATIONS



2. NATURE OF THE NUCLEOPHILE. Both S_N1 and S_N2 reactions prefer small nucleophiles. Large nucleophiles have more difficulty accessing the electrophilic center in the substrate. They also have increased tendency to act as Bronsted bases, seeking acidic protons rather than electrophilic centers due to the lower activation energy of acid-base reactions compared to nucleophilic substitutions.

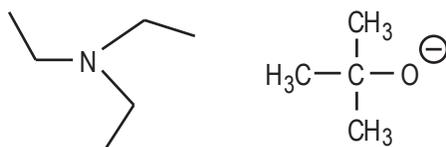
Small, strong nucleophiles that favor S_N2 reactions are shown below. Most of them have a **localized** negative charge. It is also better if they are weak bases, such as bromide and iodide ions, but they can be strong bases such as hydroxide and alkoxide ions (conjugate bases of alcohols).



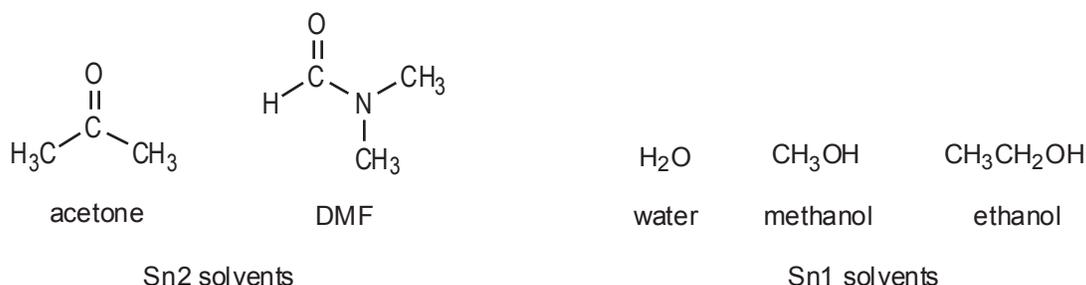
Weak, small nucleophiles that favor S_N1 reactions are shown below. Notice that several are the conjugate acids of strong nucleophiles. They are also typically neutral, but some have a **delocalized** negative charge.



Large nucleophiles, especially if they are strong, have a tendency to act as Bronsted bases rather than as nucleophiles. They should be avoided if a nucleophilic reaction is desired. Examples are:



3. SOLVENT USED. It has already been mentioned that Sn2 mechanisms are favored by low to moderate polarity solvents such as acetone and N,N-dimethylformamide (DMF). Sn1 mechanisms are favored by moderate to high polarity solvents such as water and alcohols. It is frequently the case that in Sn1 reactions the solvent also doubles as the nucleophile. Water and alcohols are prime examples of this practice.



4. LEAVING GROUP. The nature of the leaving group has more of an effect on the reaction rate (faster or slower) than it does on whether the reaction will follow an Sn1 or an Sn2 mechanism. The most important thing to remember in this regard is that **good leaving groups are weak bases**.

- All halogens, except for fluorine, are good leaving groups
- Groups that leave as resonance stabilized ions are also weak bases and therefore good leaving groups.
- Water is a good leaving group frequently used to prepare alkyl chlorides and bromides from alcohols.

The OH group in alcohols is not a good leaving group because it leaves as hydroxide ion, which is a strong base. However, if the hydroxyl group is protonated first with strong acid, it can leave as a water molecule, which is a good leaving group. Refer to the manuscript titled **Introduction to Lewis Acid-Base Chemistry** for a discussion and examples of this approach.

COMPETING (SIDE) REACTIONS IN NUCLEOPHILIC SUBSTITUTIONS

There are two major reactions that compete with nucleophilic substitutions. They are:

- CARBOCATION REARRANGEMENTS** (Sn1 only)
- ELIMINATION REACTIONS** (Sn1 and Sn2)

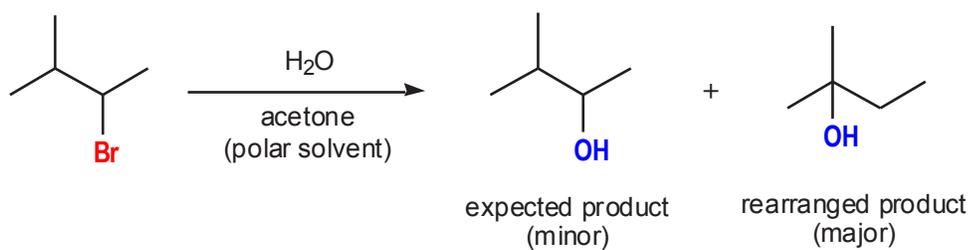
Carbocation rearrangements are examined first. Eliminations are examined in a separate paper.

CARBOCATION REARRANGEMENTS

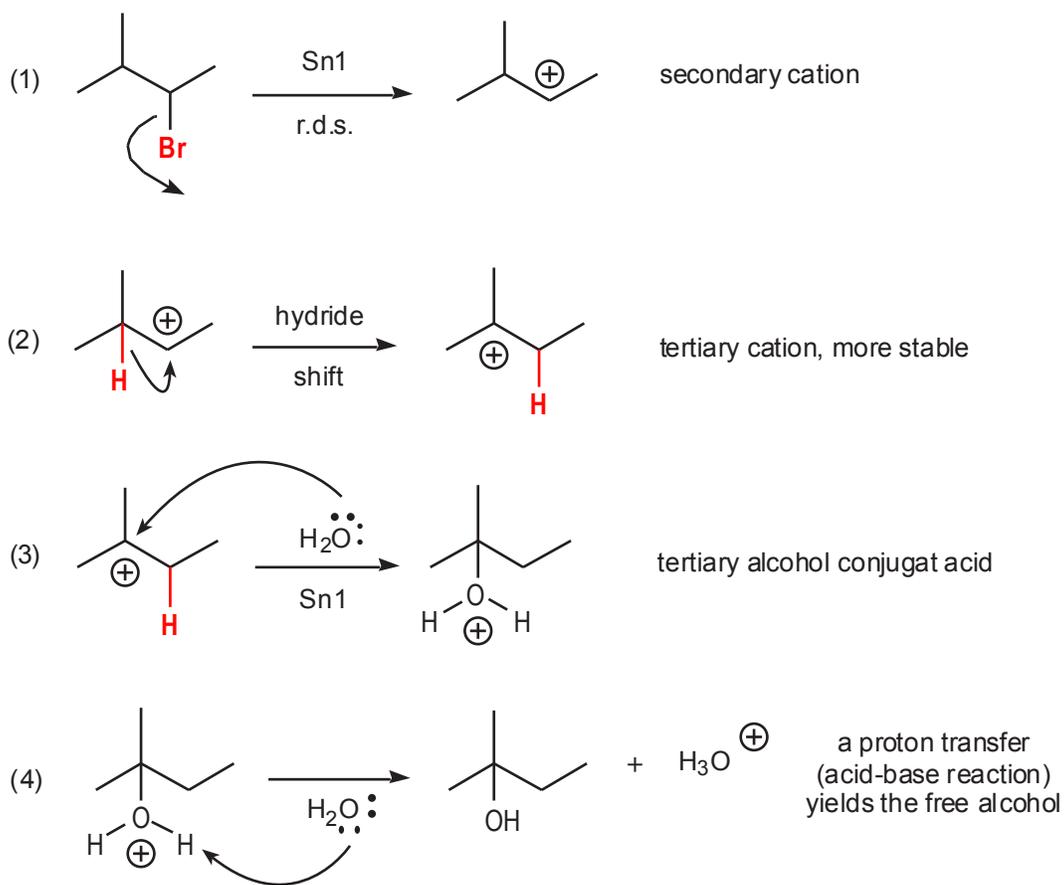
Carbocations only form in Sn1 reactions. Carbocations are prone to skeletal rearrangements if this produces a more stable cation. Carbocation rearrangements occur mainly by two processes:

- Hydride shift** - migration of a hydrogen atom with electrons to an adjacent carbon
- Alkyl shift** - migration of a carbon (usually as part of an alkyl group) with electrons to an adjacent carbon.

A quick way to tell whether a substrate will produce a carbocation prone to rearrangement is to look at the carbon that bears the leaving group. If this carbon is next to a higher order carbon (meaning secondary, tertiary, allylic, etc.) then the carbocation that results can rearrange to a more stable one, and will do so, probably yielding a product with different carbon connectivity. Examples follow.

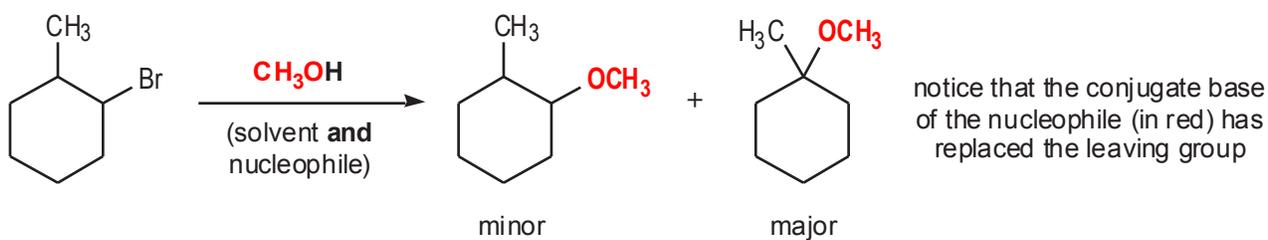


The leaving group (Br) is on a secondary carbon, but this carbon is next to a tertiary carbon. The nucleophile is water, therefore the expected product is an alcohol. The product will consist of a mixture of the expected secondary alcohol (minor) and a tertiary alcohol (major) due to the rearrangement to a more stable cation shown below.



The above example also shows the reason why, when the nucleophile is water or an alcohol, the group that replaces the leaving group in the product is the conjugate base of water (OH) or the alcohol (RO respectively).

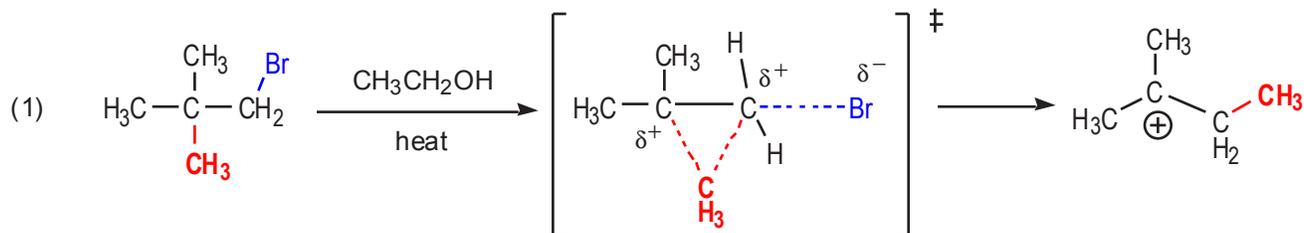
Another example illustrates a similar point. Can you provide a step by step mechanism (it might be in the test, you never know)?



Sn1 REACTIONS AND REARRANGEMENTS INVOLVING PRIMARY SUBSTRATES

Primary substrates normally do not follow Sn1 mechanisms because they do not form stable cations. However, a hindered primary substrate can be forced into an Sn1 mechanism if sufficient energy and time are allowed, for example boiling the substrate in a nucleophilic solvent such as ethanol.

The nucleophile cannot do a backside attack, and the substrate cannot form stable cations. In this case the substrate will begin to rearrange as the leaving group departs. This avoids formation of a primary cation. As the leaving group departs, a positive charge begins to develop on the carbon bearing the leaving group, and the rearrangement process starts, all in unison. The reaction of neopentyl bromide with ethanol illustrates this point.



As the positive charge develops on the primary carbon while bromine leaves, the methyl group is migrating to an adjacent position to form a more stable cation.

