The Payne rearrangement:
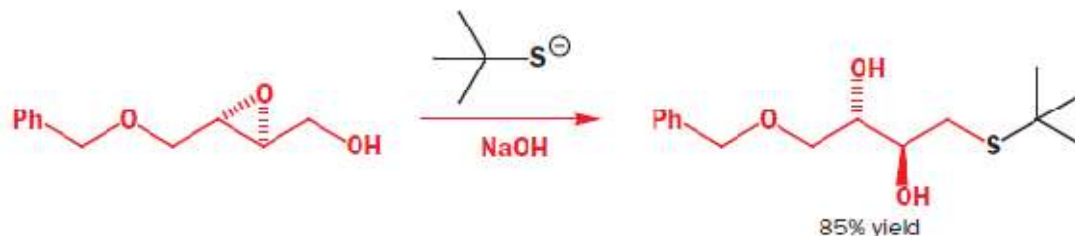
**Is the reaction of 2,3-epoxy alcohol in the base to form 1,2-epoxy-3-ol (as known epoxide migrationm).**

85% yield

The **thiolate nucleophile** has **not opened the epoxide** directly but instead appears to have displaced **HO⁻a very bad leaving group**, almost **no nucleophile will displace OH⁻**. To explain that, happens another rearrangement, this time involving **oxygen**. The epoxide through reactive as an electrophile, suffers from being **secondary at both electrophilic centers**. **t-BuS⁻ is a bulky nucleophile**, so **a direct attack on the epoxide is slow**. Instead, under the basic conditions of the reaction, the **neighbouring alkoxide group attacks intramolecularly to make a new, rearranged epoxy alcohol**. This rearrangement is called the Payne rearrangement.

Mechanism:
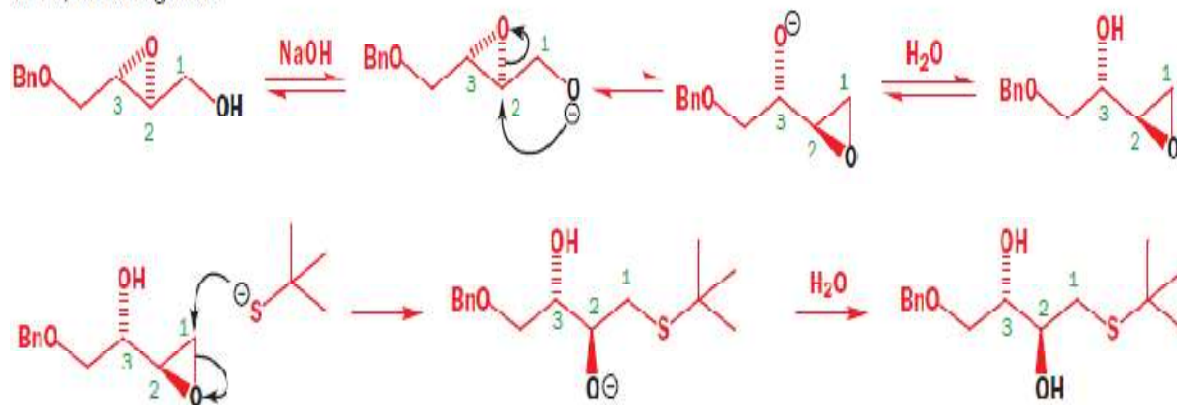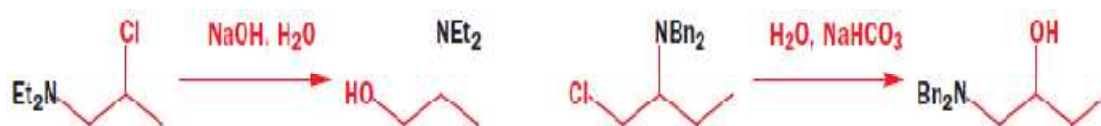

Now have a reactive, primary electrophilic site, which undergoes an S_N2 reaction with the t-BuS⁻ under the conditions of the rearrangement.

Note: The black **OH**, which **started on the carbon labeled 1, has ended up on carbon 2**.

- **The nucleophile can affect the direction of rearrangement.**

Examples: Compare these reactions:

In the **first reaction**, the **amine migrates from the primary to the secondary** position; in the other from **secondary to primary**. Both go through very **similar aziridinium intermediates**, so the difference must be due to the **regioselectivity with which this aziridinium opens** in each case.

When a group migrates from a **primary to a secondary carbon**, we say the **rearrangement has a primary migration origin and a secondary migration terminu**s. The migrating group moves from the migration origin to the migration terminus.

Mechanism:
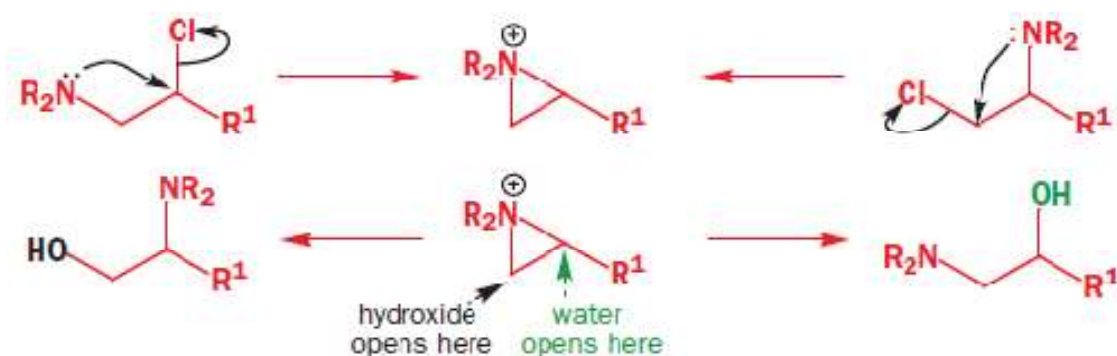
The only important difference is the **nucleophile** used in the reaction. **Hydroxide opens the aziridinium at the less hindered end; water opens the aziridinium ion at the more hindered (more substituted) end**. the aziridinium ion compound containing two alternative leaving groups one from a primary centre and one from a secondary. Primary centres can take part in fast S_N2 reactions, but cannot undergo S_N1. Secondary centres can undergo either S_N1 or S_N2 reactions, but, in general, do neither very well. Now, the **rate of an S_N2 reaction depends on the nucleophile, so a good nucleophile (like HO^-) can do fast S_N2 reactions, while a bad one (like H_2O) cannot**. The **fastest reaction HO^- can do then is S_N2 at the primary centre**. Water, on the other hand, takes part only reluctantly in substitution reactions but this does not matter if they are **S_N1 reactions because their rates are independent of**

nucleophiles. **H₂O waits until the leaving group has left of its own accord, to give a cation**, which rapidly grabs any nucleophile water, and will do just as well as HO⁻. This can happen only at the **secondary centre because the primary cation is too unstable to form**.
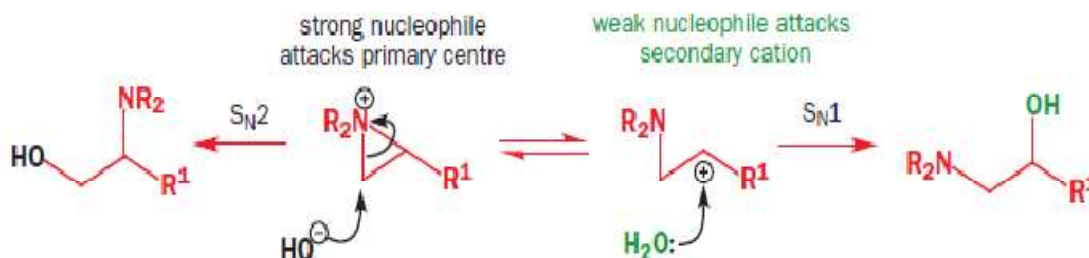

All the **rearrangements** have occurred during **substitution reactions**. All happened **because the reaction with rearrangement is faster than a reaction without rearrangement**, **rearrangement occurs because of a kinetic preference for the rearrangement pathway**. You could see these reactions as 'special case' examples of **neighbouring group participation in both participation and rearrangement**, the **neighbouring group speeds up the reaction**, but in rearrangement reactions, the neighbouring group gets rather more than it bargained for and ends up elsewhere in the molecule. Both proceed through a **cyclic transition state or intermediate**, and it is simply the way in which that **transition state or intermediate collapses that determines whether rearrangement occurs**.

<u>**Rearrangement by migration of alkyl groups:**</u>

Alkyl groups can rearrange.

<u>**Example:**</u> is a **nucleophilic substitution** under conditions (Ag⁺, H₂O) designed to encourage **S_N1** reactions (**excellent leaving group, poor nucleophile**), **without Ag⁺ nothing happens at all**. Compounds like this, with a **t-butyl group** next to the **electrophilic center**, are notoriously slow to undergo **substitution reactions**. They **can't do S_N2, they are too hindered**; they **can't do S_N1, the cation you would get is primary**.
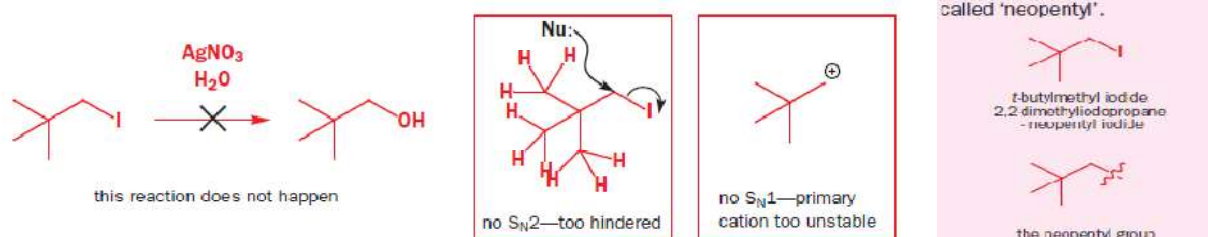
In fact, a rearrangement occurs. One of the **methyl groups moves ('migrates') from carbon 2 to carbon 1**, the new **OH group taking its place at carbon 2**.
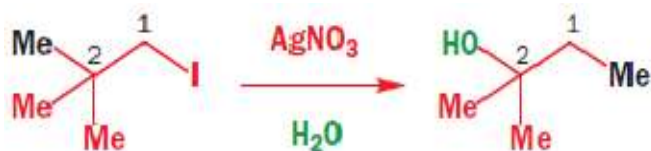
That it has **happened because S_N1 and S_N2 are both so slow that this new rearrangement mechanism is faster than either**. **Adding Ag^+ makes I^- desperate to leave**, but unassisted this would mean the **formation of a primary carbocation**. The molecule does the only thing it can to stop this happening and uses **the electrons in an adjacent C–C bond to assist the departure of I^-**. Having participated, the **methyl group continues to migrate to carbon 1 because by doing so it allows the formation of a stable tertiary carbocation**, which then captures water in a step reminiscent of the second half of an S_N1 reaction.
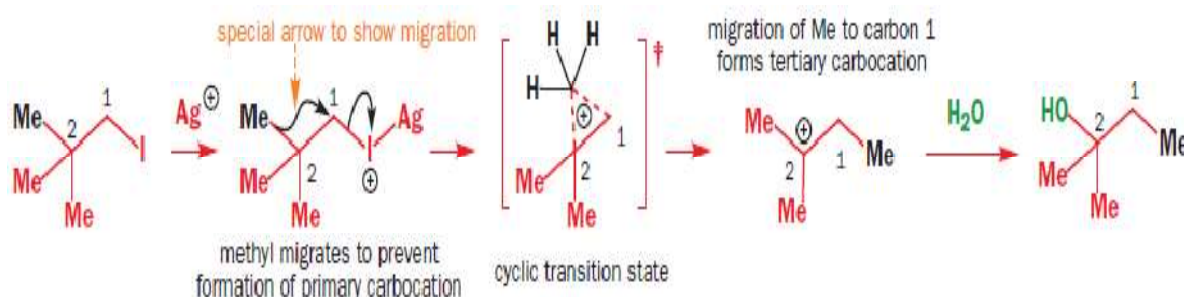
In the migration step we used a **slightly unusually curved curly arrow to represent the movement of a group (Me) along a bond taking its bonding electrons with it**. We shall use this type of **arrow when a group migrates from one atom to another during a rearrangement**.

Often, you will see this rearrangement represented in a different way. Both are correct, but we feel that the first is more intuitively descriptive.

Note: **Some of the cyclic species you have seen so far** (**aziridinium, ions, epoxides**) **are intermediates**; this **cyclic species is probably only a transition state**.

Carbocations rearrange:

It is possible to run the NMR spectra of **carbocations by using a polar but nonnucleophilic solvent such as liquid SO2 or SOClF**. **Treating an alkyl halide RX with the powerful Lewis acid SbF5 under these conditions gives a solution of a carbocation**: the **carbocation reacts neither with solvent nor the SbF5X⁻ counterion because neither is nucleophilic**. and the chemical shifts in both the ^{13}C and ^{1}H-NMR spectra of the **t-butyl cation are very large**, particularly the ^{13}C shift at the positively charged center.
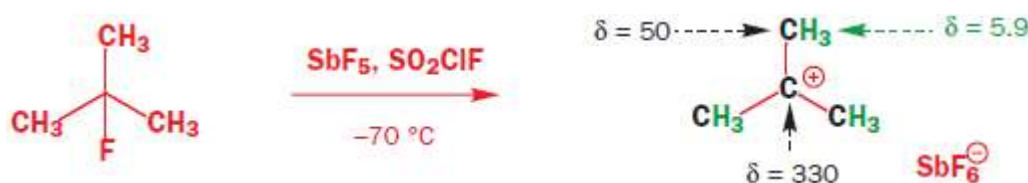
NMR can be **used to follow the course of rearrangement reactions involving carbocations**. We can illustrate this with an experiment that tries to make the neopentyl cation by the **substitution reaction**. This time the starting material and solvent are slightly different, but the outcome is nonetheless most revealing. Dissolving neopentyl tosylate in fluorosulfonic acid (a strong, nonnucleophilic acid) at −77°C gives a 77% yield of a **cation** whose spectrum is shown below. Assigning the peaks is not hard once you know that the same spectrum is obtained when 2,2-dimethyl-2-butanol is dissolved in fluorosulfonic acid with SbF5 added.
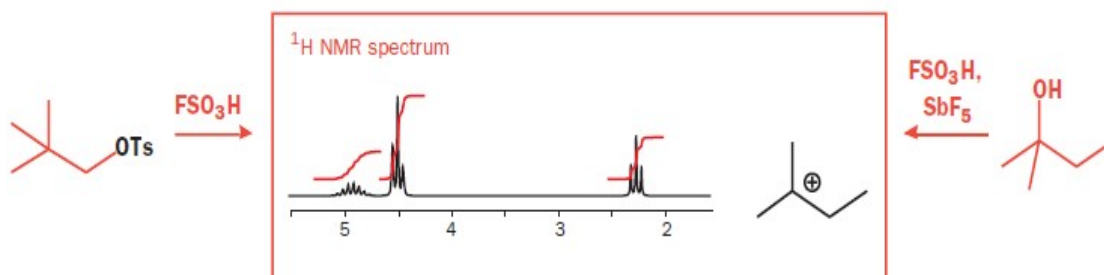
Clearly, both spectra are of the tertiary 2-methylbutyl cation and the neopentyl cation never saw the light of day. The **reaction is the same rearrangement that you saw in the substitution reaction of neopentyl**

iodide, but here the rate of **rearrangement can be measured and it is extremely fast**.

Neopentyl tosylate reacts to form a cation under these conditions about 104 times as **fast** as **ethyl tosylate**, even though both tosylates are primary. This massive rate difference shows that if **migration of an alkyl group can allow rearrangement to a more stable carbocation**, it will happen, and happen rapidly.


Note: In fact, all **seven possible isomers** of pentyl alcohol ($C_5H_{11}OH$) give this **same spectrum** under these conditions at temperatures greater than –30 °C.

Primary cations can **never be observed by NMR** they are too **unstable**. But **secondary cations** can be provided if the **temperature is kept low** enough. *sec*-Butyl chloride in SO_2ClF at –78 °C gives a **stable**, observable action. But, as the cation is warmed up, it rearranges to the t-butyl cation. This rearrangement truly is a carbocation rearrangement: the starting material is an observable carbocation, and so is the product.
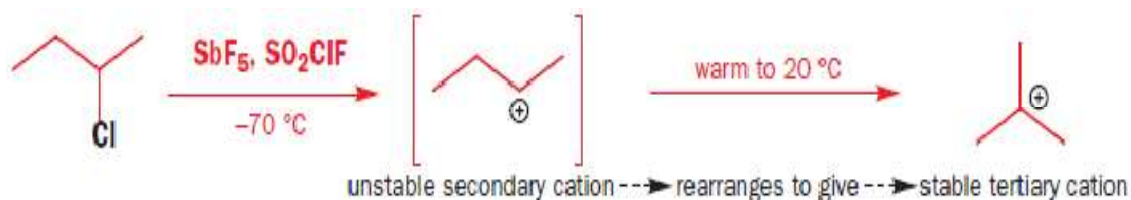

Note: Should be **number the carbon atoms in starting material and product** before you try to work out the **mechanism**.

With rearrangements like this, it is best to **number the C atoms** so we see that the **methyl group** we have labeled 4 and the **H on C3 have changed places**. (**Note that C3 starts off as a CH$_2$ group and ends up as CH$_3$**).
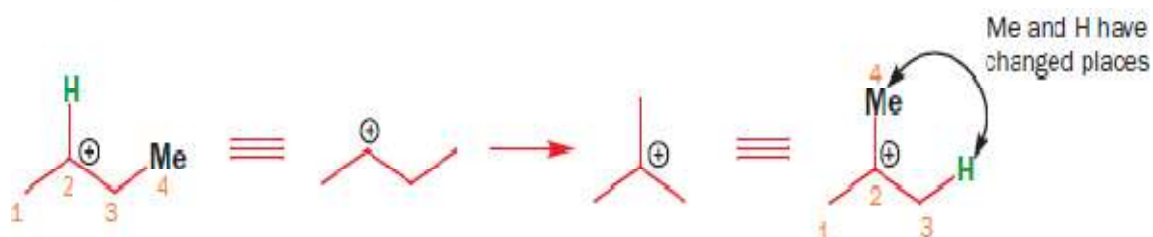

Mechanism: We can draw a mechanism for this in which **first the (Me) migrates, and then the hydride**. We say **hydride migration rather than hydrogen (or proton) because the H atom migrates with its pair of electrons**, by Using the arrows.
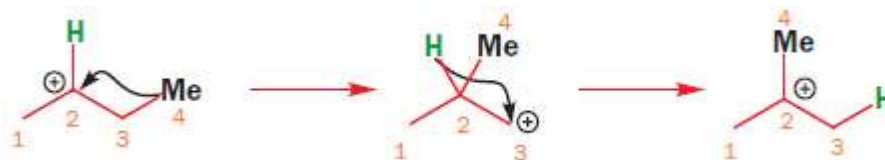
-As these rearrangements are a new type of reaction, we should just spend a moment looking at the molecular orbitals that are involved. For the first step, migration of the methyl group, the LUMO must clearly be the empty p orbital of the cation, and the HOMO is the C–C s bond, which is about to break.

The methyl group migrates smoothly from one orbital to another there are bonding interactions all the way. The next step, migration of H, is just the same except that the HOMO is now a C–H σ bond. The **methyl migration is unfavourable as it transforms a secondary cation into an unstable primary cation but the hydride migration puts that right as it gives a stable tertiary cation**. The whole reaction is under thermodynamic control.
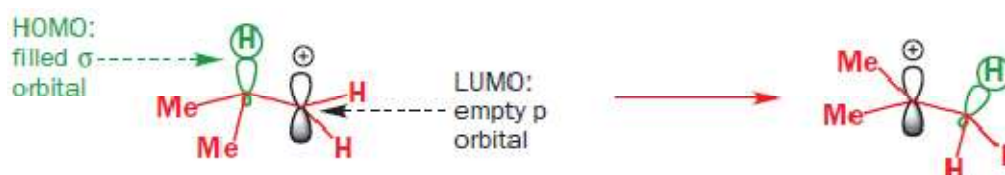
Wagner–Meerwein rearrangements:

Wagner–Meerwein rearrangement or Wagner–Meerwein shift is the carbocation rearrangements involving the migration of H or alkyl groups or **the migration of an alkyl group to a cationic center** don't just happen in NMR machines. They happen during normal reactions too, Wagner–Meerwein shifts have been studied extensively in the class of natural products.

Dr. Roaa Majid

Example: acid-catalyzed dehydration of the natural product camphenilol gives the alkene santene (a key component of the fragrance of sandalwood oil) in a reaction involving the migration of a methyl group.
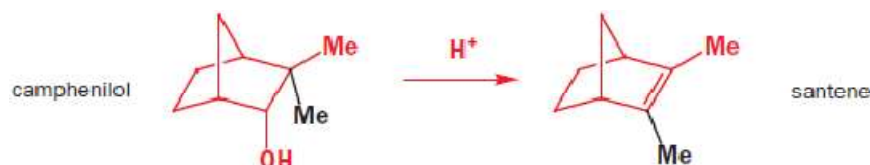

Mechanism: The **first formed cation cannot eliminate H⁺ in an E1 reaction because loss of the only available proton would give a very strained alkene**.
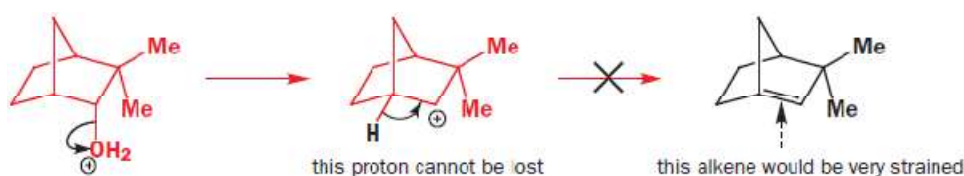

However, **migration of a methyl group both stabilizes the cation it becomes tertiary instead of secondary and allows E1 elimination of H⁺ to take place to give a stable alkene**.
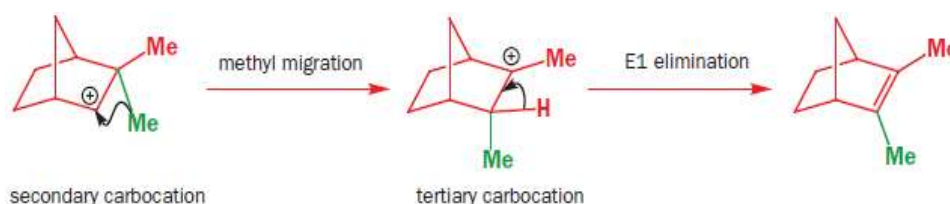
Example: acid-catalyzed dehydration, of isoborneol to camphene.
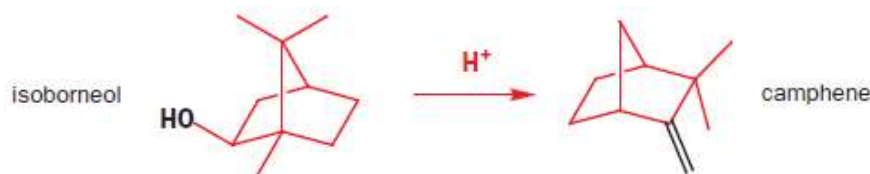

The example involves **one alkyl group migration only**. Firstly number the carbons atoms. We start numbering the starting material from the dimethyl group because it will be easy to spot in the product. The numbers just follow round the ring, with C8 being the methyl group attached to C5.
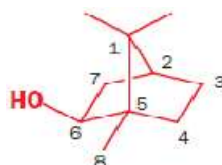
Use the substituents to help you some will have changed, C1 is still easy to spot as the carbon carries the dimethyl group.


Use connectivity to help you again, a C–C bond or two may have broken or formed, but most of the C–C bonds in the starting material will be there in the product. C1 and C2 will probably still be next door to one another C2 was a bridgehead carbon in the starting material, and there is a bridgehead C attached to C1 in the product; assume that's C2.
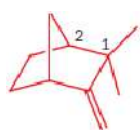

C3 and C4 were unsubstituted carbons in the starting material, and are identifiable in the product too. The other easily spotted atom is C7 an unsubstituted C attached to C2.
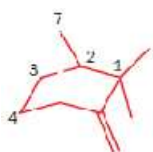

We can assume that C8 is the =CH2 carbon it was a methyl group but perhaps has become involved in an elimination. C5 was attached to C1, C4, C6, and C8: one of the remaining carbons is attached to C1 and C8, so that seems more likely to be C5, which leaves C6 as the bridgehead, attached as before to C7 and C5.
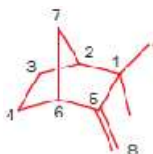
Now we can assess which old bonds have been broken and which new bonds have been formed.
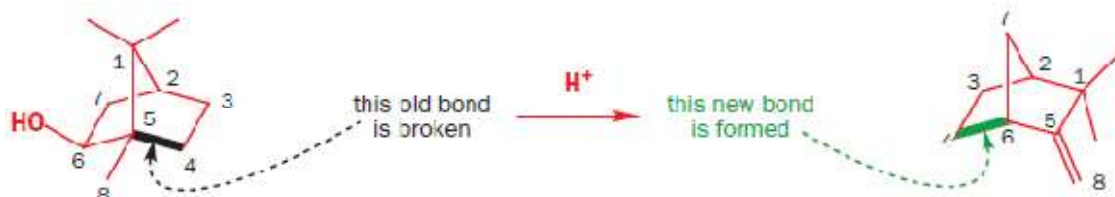
Mechanism: Numbering the atoms this way identifies the likely point of rearrangement the only bond broken is between C4 and C5. Instead we have a new one between C5 and C6: C4 appears to have migrated from C5 to C6. Now for the mechanism. The first step will, be loss of water to generate a secondary cation at C6. The cation is next to a quaternary centre, and migration of any of three bonds could generate a more stable tertiary carbocation. But we know that the new bond in the product is between C4 and C6, so let's migrate carbon 4, then lose a proton from C8.


migrate C4 from C5 to C6 to create tertiary cation
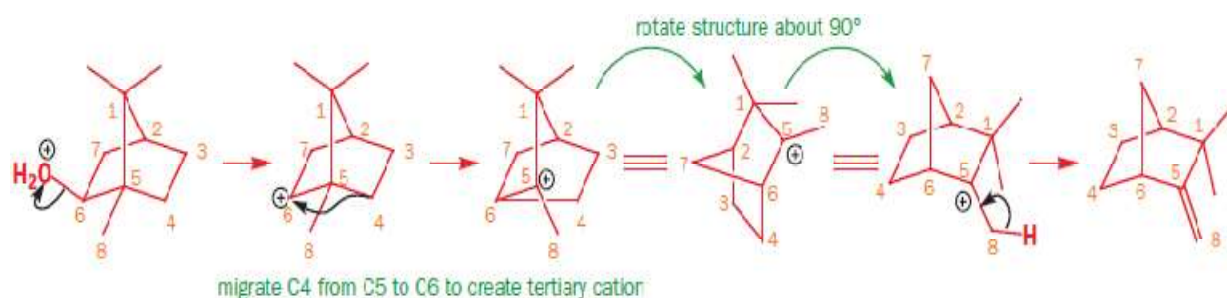
**Note: Alkyl migrations occur in order to make a carbocation more stable.**

-Why the alkyl group migrated in this example and not the methyl group, or the other alkyl group **all three possibilities give similar tertiary carbocations**, the reason involves the alignment of the orbitals involved.

Rearrangement by ring expansion:

More stable usually means **more substituted**, and **cations** can also be made **more stable** if they become **less strained**. example, **four-membered rings** adjacent to cations readily **rearrange** to **five-membered rings in order to relieve ring strain**.
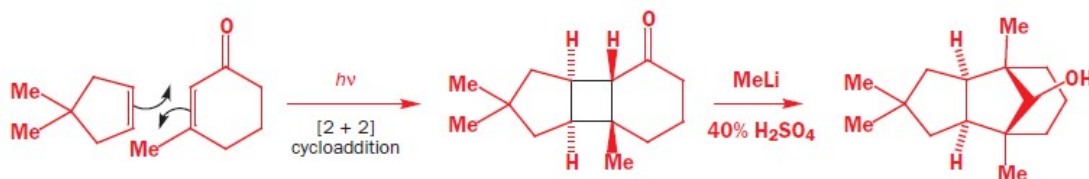

four-membered ring   five-membered ring
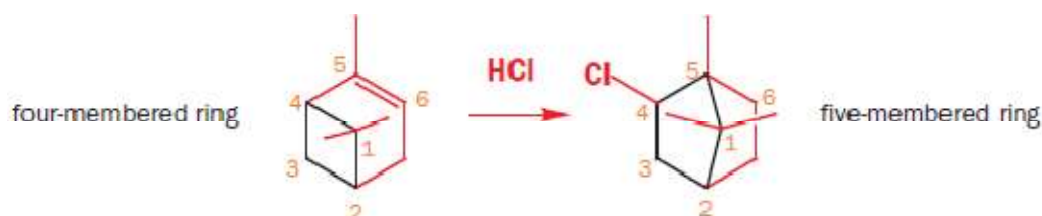
Note: This time the **cation is formed by protonation of an alkene, not departure of a leaving group**.

Mechanism:

protonation of alkene → alkyl migration → chloride addition to cation
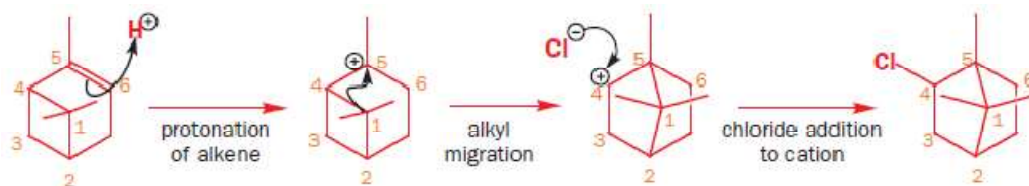
Note: Though the rearrangement step **transforms a stable tertiary cation into a less stable secondary cation, relief of strain in expansion from a four- to a five-membered ring makes the alkyl migration favourable**.

Example: In 1964, E.J. Corey published a synthesis of the natural product α-caryophyllene alcohol that made use of a similar ring expansion. The photochemical [2+2] cycloaddition in the synthesis of the starting material. Rearrangement of this tertiary alcohol in acid gives the natural product.

Mechanism: The **four-membered ring disappeared**, and **carbon 7 has migrated from carbon 6 to carbon 5**. **Loss of water** gives a **tertiary carbocation** that undergoes **rearrangement to a secondary carbocation** with expansion of a **four-** to a **five -membered ring**.


rearrangement relieves strain in this 4-membered ring
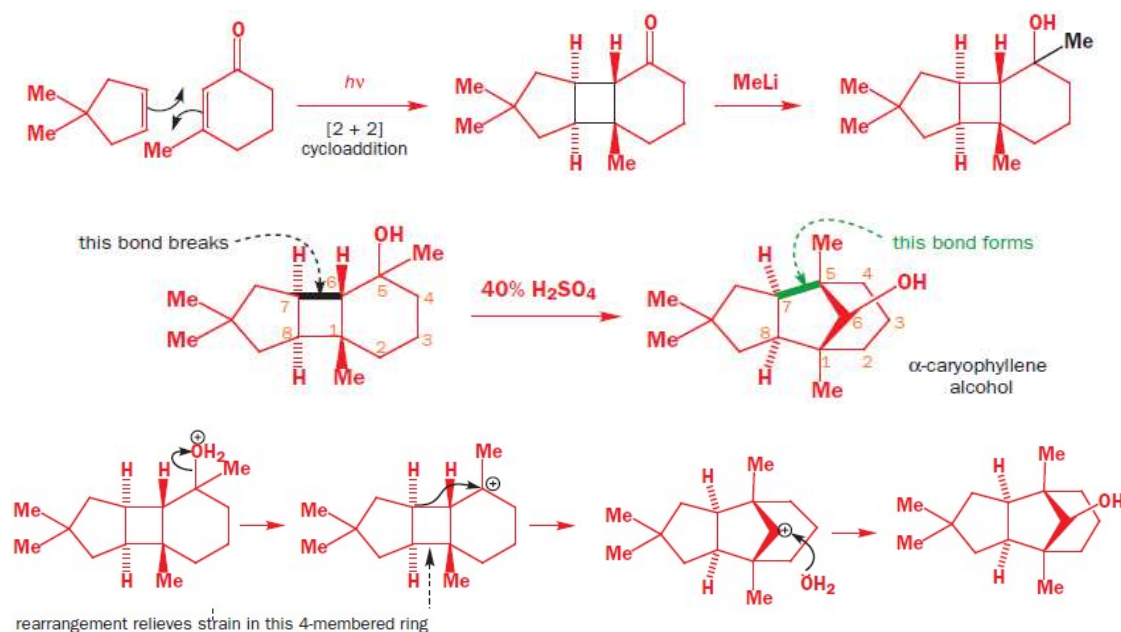
Note: Most compounds are kinetically stable precisely because spontaneous rearrangements to more thermodynamically stable compounds do not occur the kinetic barrier to rearrangement is too high. Carbocations are the most important class of species that habitually undergo rearrangement reactions, even at low temperature.

Carbocation rearrangements:

The ourpose of carbocation rearrangements is give single products in high yield. Excepte one reaction that cannot be done because of carbocation rearrangements: Friedel Crafts alkylation using primary alkyl halides.

Example:
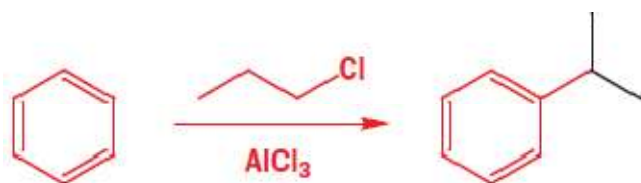
The Friedel–Crafts alkylation illustrates the problems of trying to use carbocation rearrangements to make single products in high yield. We can give three guidelines to spotting this type of reaction.

1- The rearrangement must be **fast** so that other reactions do not compete.
2- The product cation must be sufficiently **more stable** than the starting one so that the rearrangement happens in high yield.
3- Subsequent trapping of the product cation must be reliable: cations are **high-energy intermediates**, and are therefore unselective about how they react.

A reaction is no good if the cation reacts in more than one way it may react with a nucleophile, eliminate, or undergo further rearrangement but it must do only one of these, unlike this Friedel Crafts reaction.