

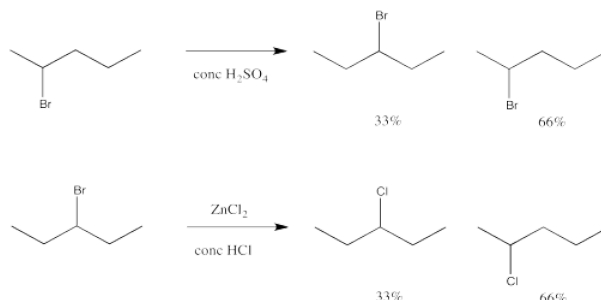
4.5: Regiochemistry

Regiochemistry is the term for where changes take place in a reaction. It can be another indication of how the reaction occurred.

In aliphatic nucleophilic substitution, the answer seems pretty obvious: the reaction takes place at the electrophilic carbon, the one attached to the electronegative halogen. That's where the leaving group is. When the leaving group is replaced, that's where the nucleophile will be. But this isn't always true.

- In an S_N2 reaction, the nucleophile is always found on the carbon where the leaving group used to be.
- In an S_N1 reaction, the nucleophile is usually found on the carbon where the leaving group used to be. Sometimes it moves.

Under some circumstances, unexpected changes occur. The following two reactions are examples of such surprises. These reactions happen to take place via an S_N1 mechanism.



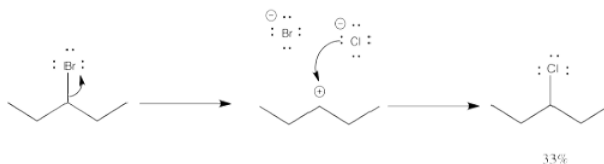
So, the regiochemistry of this reaction may be more complicated than we thought.

What is happening in these two reactions? In one of them, the bromine is just hopping from one place to another along the molecule. Some of the original compound remains, too, so there is a mixture. If you look carefully, though, the bromine has switched places with a hydrogen atom. It doesn't seem like that hydrogen atom could come off very easily.

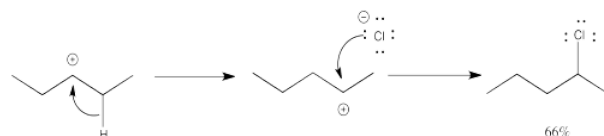
In the other reaction, something very similar is happening. Bromide and chloride both have lone pairs, so they can both be nucleophiles as well as leaving groups, and one can replace the other. There is lots of chloride around, so it beats any bromide to the electrophilic carbon. Once again, though, some of the chloride seems to end up in the wrong place.

This sort of behaviour is characteristic of carbocations. It is called a rearrangement, in which part of the molecule unexpectedly switches places.

Again, one of the products forms in a simple enough way.



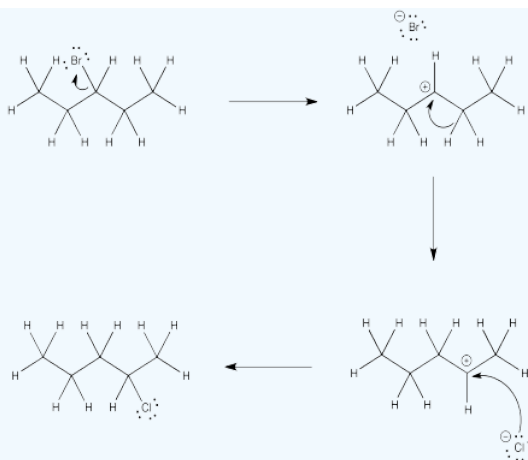
The formation of the other product involves a "1,2-hydride shift". In this event, a hydrogen anion hops from one carbon to the next, leaving a cation where it used to be.



? Exercise 4.5.1

Draw the reaction above with all the hydrogens drawn in the structures, to confirm the formal charges and the positions of the hydrogens.

Answer

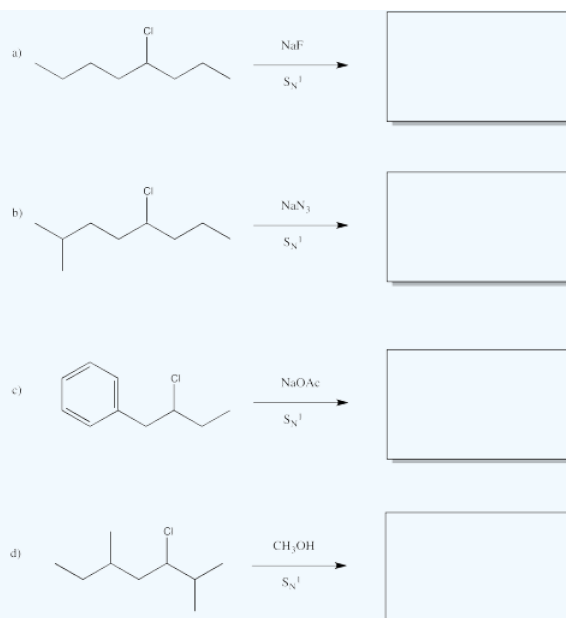


? Exercise 4.5.2

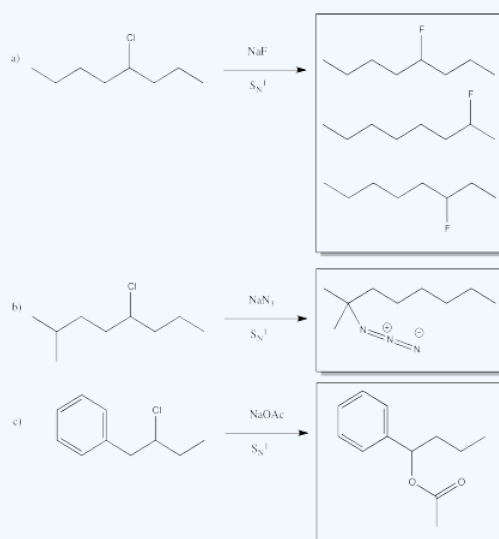
Explain the observed product ratios in the above reaction.

? Exercise 4.5.3

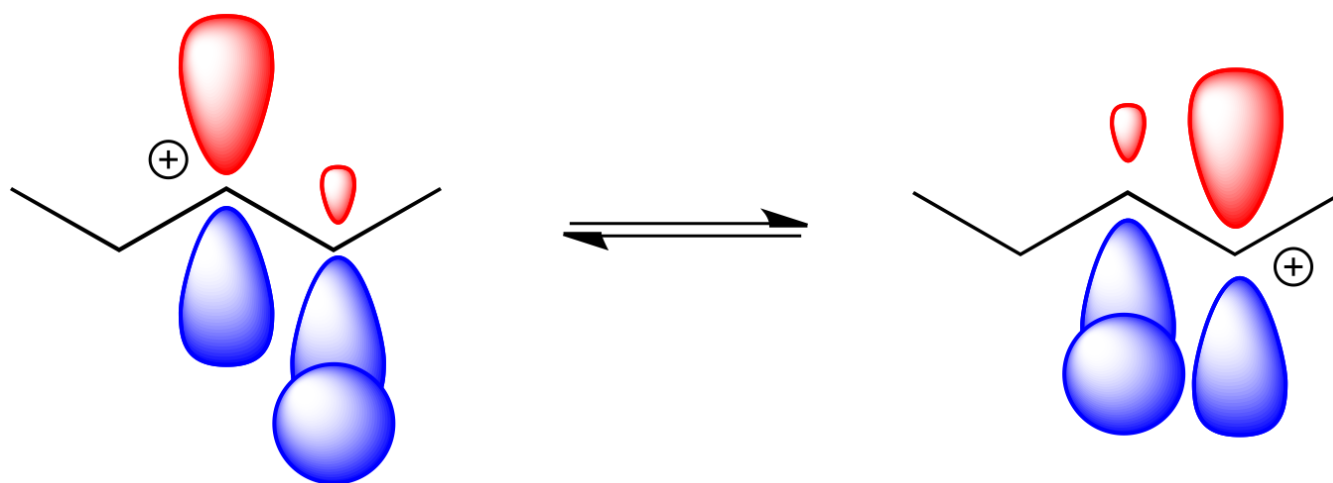
Predict the products of the following reactions.



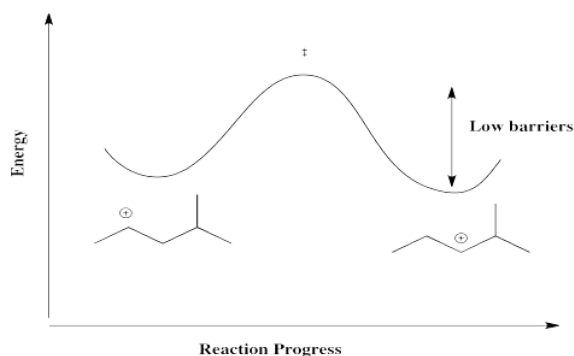
Answer



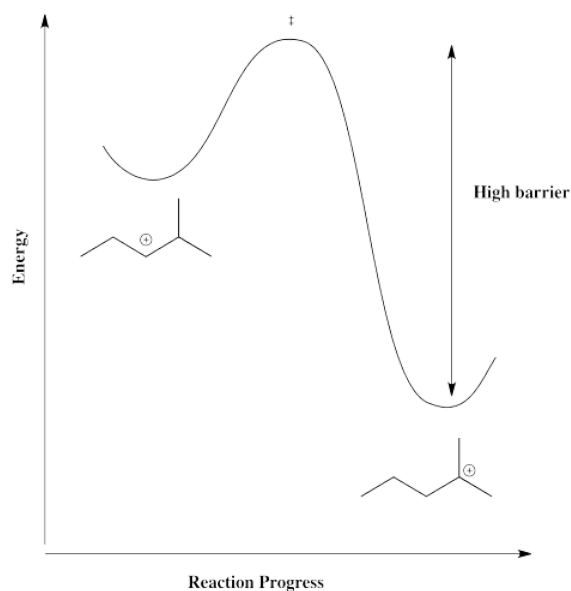
The hydride can hop one carbon away because of the proximity to the empty p orbital with which it can overlap and form a new bond.



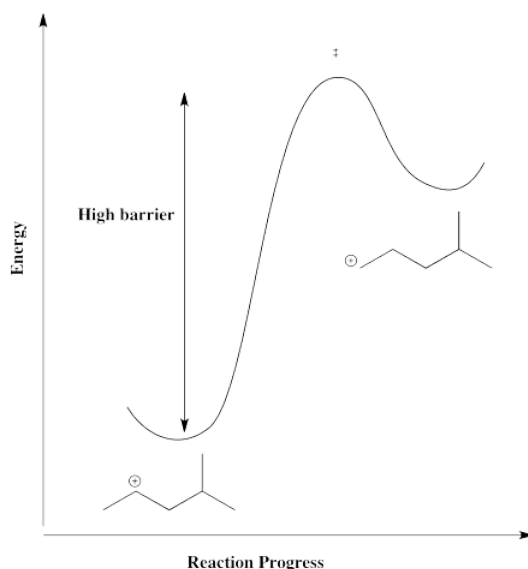
The barrier for a hydride shift is not very high, provided a carbocation is available on the very next carbon. As a result, an equilibrium between cations is established pretty quickly. Below, there is an equilibrium between two secondary cations on the 2-methylpentyl skeleton.



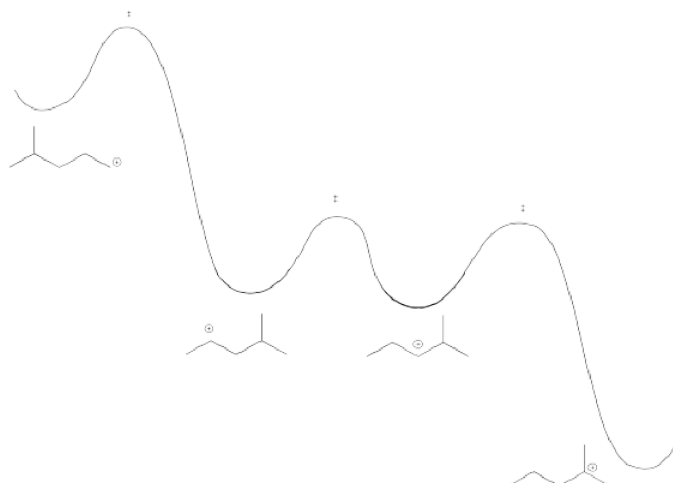
However, that particular structure has another possible cation that is more stable. Once a tertiary cation forms, the hydride isn't likely to hop back.



On the other hand, there is also a primary position. A hydride shift could give a primary cation, but that isn't likely to happen, because it would be too far uphill.

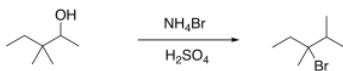


Altogether, there is an energy surface linking several different possible cations. In this case, however, one tertiary cation would quickly dominate.



It isn't just hydride ions that are able to undergo 1,2-migrations. Alkyl anions (such as methyl, CH_3^-) and aryl anions (such as phenyl, C_6H_5^-) can also undergo 1,2-shifts, rearranging to give stable cations.

For example, the following reaction is apparently just a substitution of a bromo group for a hydroxy group. The regiochemistry indicates a cation was formed, however, because the new group is found at the site of the most stable carbocation.



The mechanism here involves protonation of the hydroxy group; the reaction takes place in strong, concentrated acid. The resulting cation is able to undergo a 1,2-methyl shift leading to a new carbocation. The bromide ion connects at that new position.



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