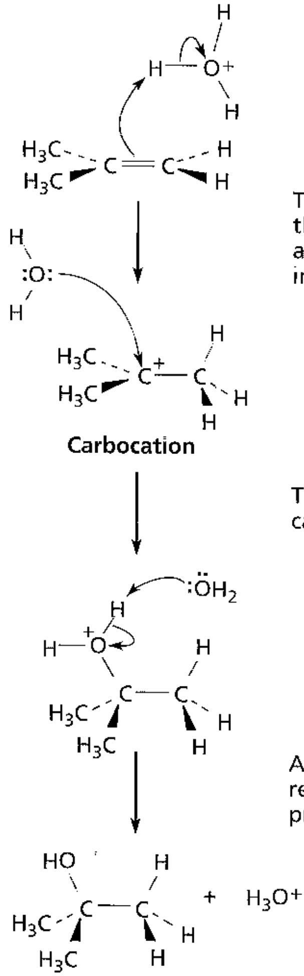
1.3 Mechanisms: Electrophilic Addition Reactions

Chemical reactions carried out in living organisms follow the same rules of reactivity as reactions carried out in the laboratory. The "solvent" is often different, the temperature is often different, and the catalyst is certainly different, but the reactions occur by the same fundamental mechanisms. That's not to say that *all* bioorganic reactions have obvious laboratory counterparts—some of the most chemically interesting biotransformations cannot be duplicated in the laboratory without an enzyme because too many side reactions would occur. Nevertheless, the chemical mechanisms of biotransformations can be understood and accounted for by organic chemistry. In this and the remaining sections of Chapter 1, we'll look at some fundamental organic reaction mechanisms, beginning with the electrophilic addition reactions of C=C bonds.

An **electrophilic addition reaction** is initiated by addition of an electrophile to an unsaturated (electron-rich) partner, usually an alkene, and leads to formation of a saturated product. In the laboratory, for example, water undergoes an acid-catalyzed electrophilic addition to 2-methylpropene to yield 2-methyl-2-propanol. The reaction takes place in three steps and proceeds through a positively charged, carbocation intermediate (Figure 1.4). In the first step, electrons from the nucleophilic C=C bond attack an electrophilic hydrogen atom of H_3O^+, forming a C—H bond. The intermediate carbocation then reacts with water as nucleophile, giving first a protonated alcohol and then the neutral alcohol after a proton-transfer step that regenerates H_3O^+. Note that the initial protonation takes place on the less highly substituted carbon of the double bond, leading to the more highly substituted, more stable, carbocation.

Biological examples of electrophilic addition reactions occur frequently in the biosynthetic routes leading to steroids and other terpenoids, although they are less common elsewhere. The electrophile in such reactions is a positively charged or positively polarized carbon atom, which often adds to a C=C bond within the same molecule. As an example, α-terpineol, a substance found in pine oil and used in perfumery, is derived biosynthetically from linalyl diphosphate by an internal electrophilic addition reaction. Following formation of an allylic carbocation by dissociation of the diphosphate (here abbreviated PPO),



The electrophile H_3O^+ is attacked by the nucleophilic double bond, forming a C—H bond and giving a carbocation intermediate.

The nucleophile H_2O attacks the electrophilic carbocation, forming a C—O bond.

A proton-transfer reaction with water regenerates H_3O^+ and yields the alcohol product.

FIGURE 1.4 The mechanism of the acid-catalyzed electrophilic addition of water to 2-methylpropene. The reaction involves a carbocation intermediate.

electrophilic addition to the nucleophilic C═C bond at the other end of the molecule occurs, giving a second carbocation that then reacts with nucleophilic water. A proton transfer from the protonated alcohol to water yields α-terpineol (Figure 1.5). We'll see more such examples when we look at steroid biosynthesis in Section 3.5.

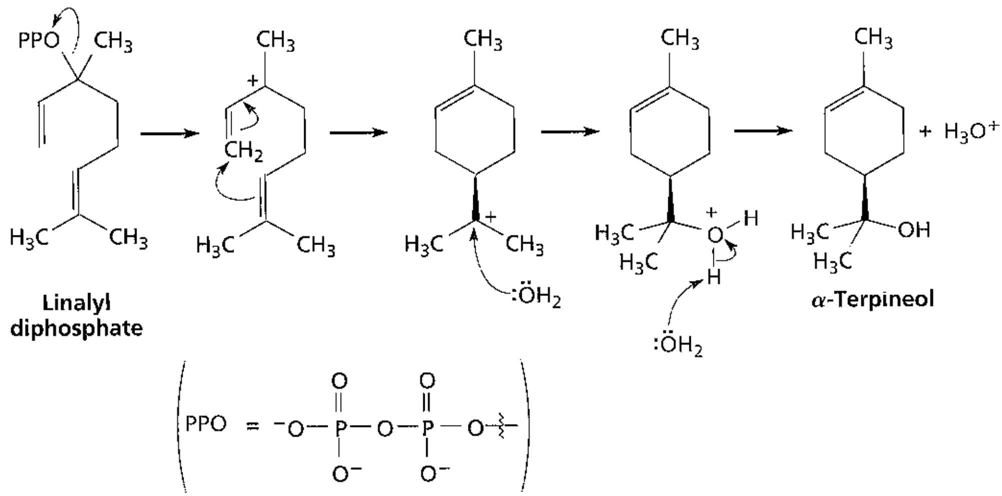


FIGURE 1.5 The biosynthesis of α-terpineol from linalyl diphosphate occurs by an electrophilic addition reaction.

1.4 Mechanisms: Nucleophilic Substitution Reactions

A **nucleophilic substitution reaction** is the substitution of one nucleophile (the *leaving group*) by another on a saturated, sp^3-hybridized carbon atom: Br^- by OH^-, for example. Nucleophilic substitution reactions in the laboratory generally proceed by either an **S_N1 mechanism** or an **S_N2 mechanism** depending on the reactants, the solvent, the pH, and other variables. S_N1 reactions usually take place with tertiary or allylic substrates and occur in two steps through a carbocation intermediate. S_N2 reactions usually take place with primary substrates and take place in a single step without an intermediate.

The mechanism of a typical S_N1 reaction is shown in Figure 1.6. As indicated, the substrate undergoes a spontaneous dissociation to generate a carbocation intermediate, which reacts with the substituting nucleophile to give product.

The mechanism of a typical S_N2 process is shown in Figure 1.7 for the reaction of hydroxide ion with (*S*)-2-bromobutane. The reaction takes place in a single step when the incoming nucleophile uses a lone pair of electrons to attack the