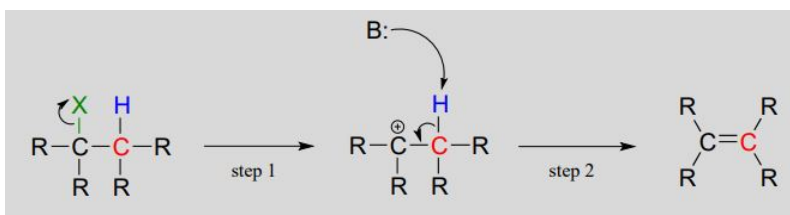


14.3: Elimination by the E1 Mechanism

E1 elimination - An overview

The reverse of electrophilic addition is called E1 elimination. We will begin by looking at some non-biochemical E1 reactions, as the E1 mechanisms is actually somewhat unusual in biochemical pathways.

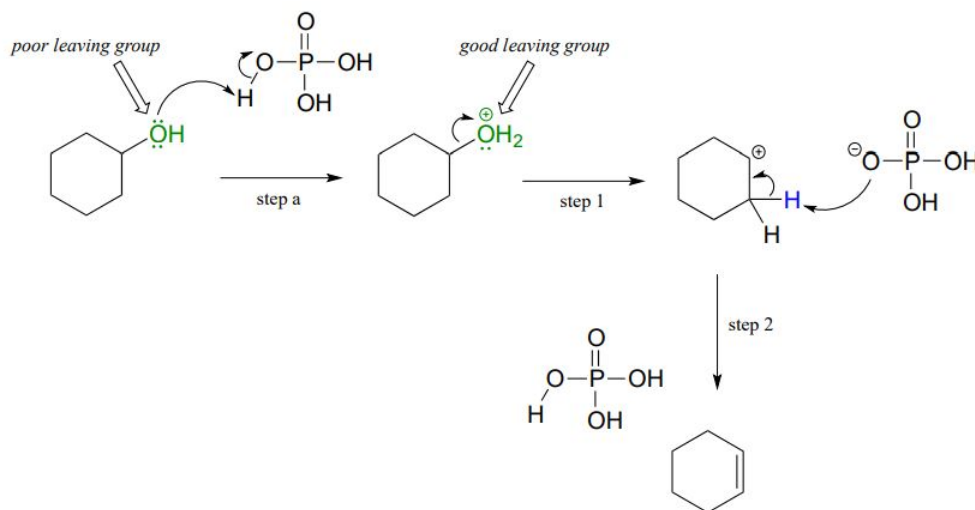
E1 elimination:



An E1 elimination begins with the departure of a leaving group (designated 'X' in the general figure above) and formation of a carbocation intermediate (step 1). Abstraction of a proton from an adjacent carbon (step 2) sends two electrons down to fill the empty p orbital of the carbocation, forming a new p bond. The base in this step may be the leaving group, or another basic species in solution.

E1 elimination does not occur when the leaving group is bonded to a primary carbon, unless the carbon is in the allylic or benzylic position. Recall that a primary carbocation, unless stabilized by resonance, is highly unstable and an unlikely reaction intermediate.

E1 eliminations can occur at secondary carbons, however. If cyclohexanol is heated with a catalytic amount of phosphoric acid, elimination of water (dehydration) results in cyclohexene as the product. The role of the phosphoric acid is to protonate the alcohol ('step a' below), making it a viable leaving group.



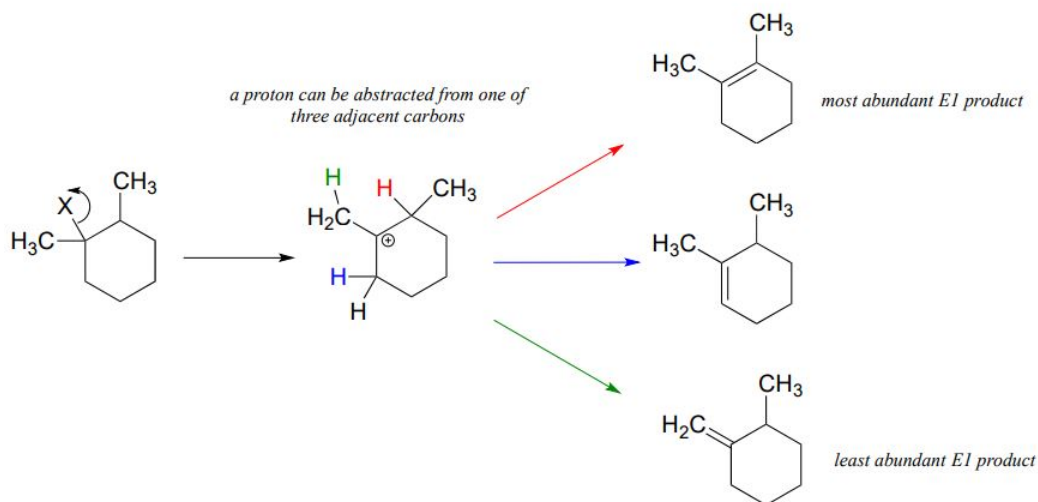
The reaction is reversible, but if cyclohexene is distilled away from the reaction mixture as it forms, the equilibrium can be driven towards product (you may want to review Le Chatelier's principle in your General Chemistry textbook). Separation of cyclohexene (boiling point 83°) from cyclohexanol (boiling point 161°) is simple because of the large difference in boiling points between the two liquids.

? Exercise 14.3.1

When the laboratory reaction described above is run to completion, a viscous 'goop' is usually left over in the distillation flask, which hardens upon cooling. Draw a mechanism showing how this 'goop' might form, and explain why it hardens upon cooling.

Regiochemistry of E1 elimination

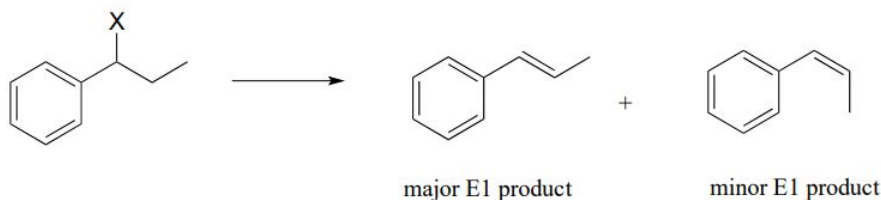
Nonenzymatic E1 reactions can often result in a mixture of more than one alkene product. Elimination of 'HX' from the following starting compound, for example, could yield three different possible alkene products.



Notice in the figure above that the three possible E1 products do not form in equal abundance. The most abundant alkene product is that which is most substituted: in other words, the alkene in which the two sp^2 carbons are bonded to the fewest hydrogen atoms. In this case, the most substituted alkene has zero hydrogen substituents. The least substituted - and least abundant - alkene product has two hydrogen substituents, while the middle alkene has one hydrogen substituent. This trend is observed generally with nonenzymatic E1 elimination reactions, and is known as Zaitsev's rule after the Russian chemist Alexander Zaitsev.

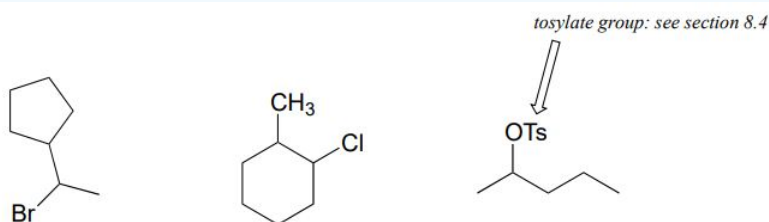
Stereochemistry of E1 elimination

Nonenzymatic E1 reactions can also result in both *cis* and *trans* alkenes. Keeping in mind that in general *trans* alkenes are more stable than *cis* alkenes, we can predict that *trans* alkenes will predominate in the product mixture.



? Exercise 14.3.2

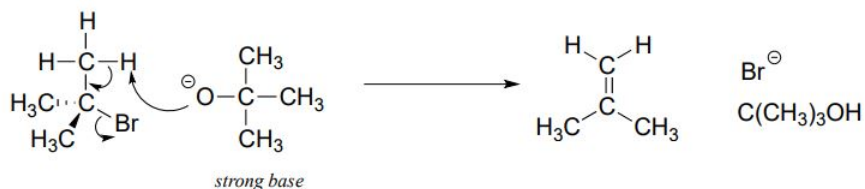
Draw the structures of all possible E1 products starting with the compounds below, and rank them in order of highest to lowest abundance.



The E2 elimination mechanism

When a strong base is combined with an alkyl halide (or alkyl tosylate/mesylate), elimination generally occurs by the E2 pathway, in which proton abstraction and loss of the leaving group occur simultaneously, without an intervening carbocation intermediate:

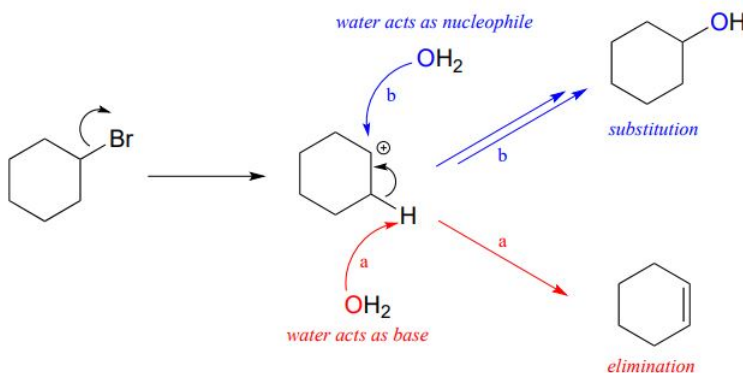
bond-breaking and bond-forming occurs simultaneously, no carbocation intermediate



Just like in the S_N2 mechanism, the '2' in the E2 designation refers to the idea that the rate-determining (and only) step of the reaction is a collision between the two reacting molecules, in this case bromocyclohexane and methoxide ion.

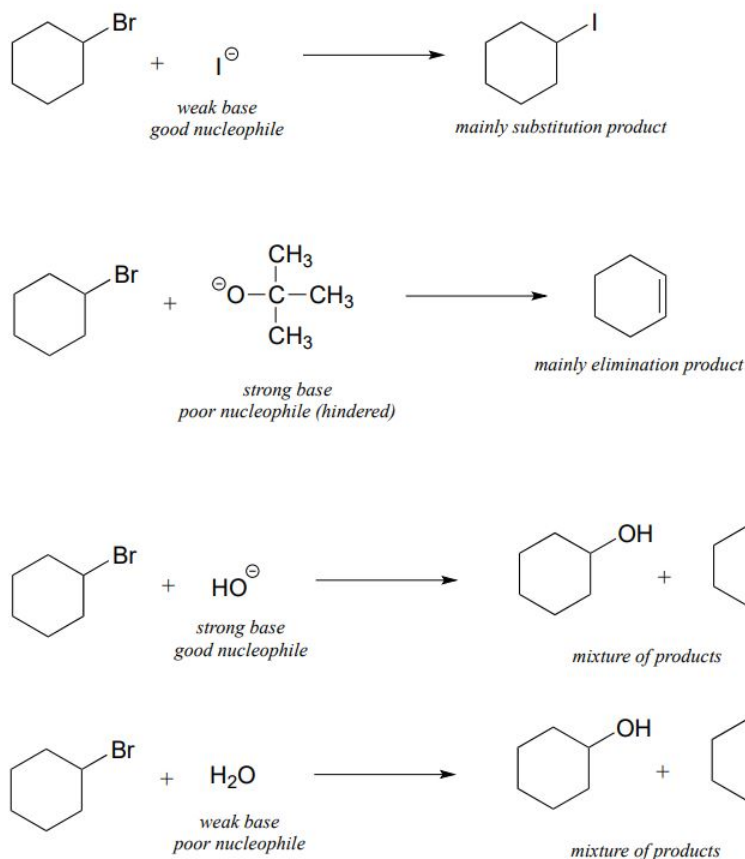
Competition between elimination and substitution

Consider a reaction between water and bromocyclohexane. Based on what we have just learned, a likely product would be the alkene formed from an E1 elimination reaction (pathway (a) in red below).

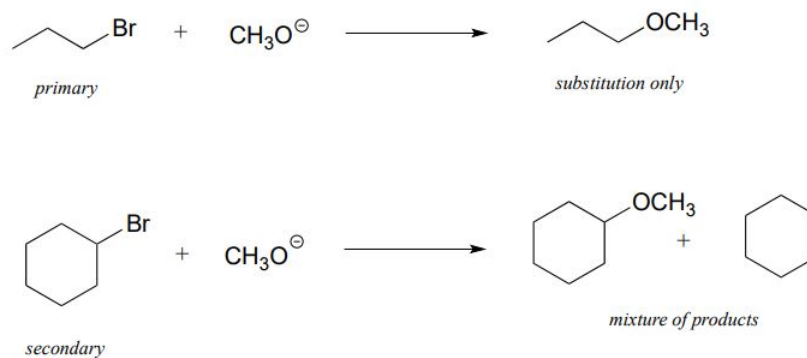


However, the reaction could take another course: what if the water molecule, instead of acting as a base, were to act as a nucleophile (pathway (b) in blue)? This should look familiar - it is simply an S_N1 reaction (section 8.1). In fact, the reaction would result in a mixture of elimination (E1) and substitution (S_N1) products. This is a common theme: elimination and substitution often compete with each other.

When both elimination and substitution products are possible, however, we can often predict which reaction will predominate. In general, strong bases and hindered carbons favor elimination, while powerful nucleophiles and unhindered carbons favor substitution.



In addition, primary alkyl halides are much more likely to undergo substitution than elimination, even when the nucleophile is also a strong base, because the electrophilic carbon is unhindered and accessible to the nucleophile. Recall that the Williamson ether synthesis (section 8.8) is an efficient laboratory S_N2 reaction between a primary (or methyl) alkyl halide and an alkoxide. If a secondary alkyl halide is used, a substantial amount of elimination product will form (the electrophilic carbon is more hindered, and the alkoxide will act as a base as well as a nucleophile).



While competition between substitution and elimination pathways is an issue for chemists running reactions in the lab, the same cannot be said of biochemical reactions, as the architecture active site of enzymes have evolved to ensure the formation of only one product.

? Exercise 14.3.3

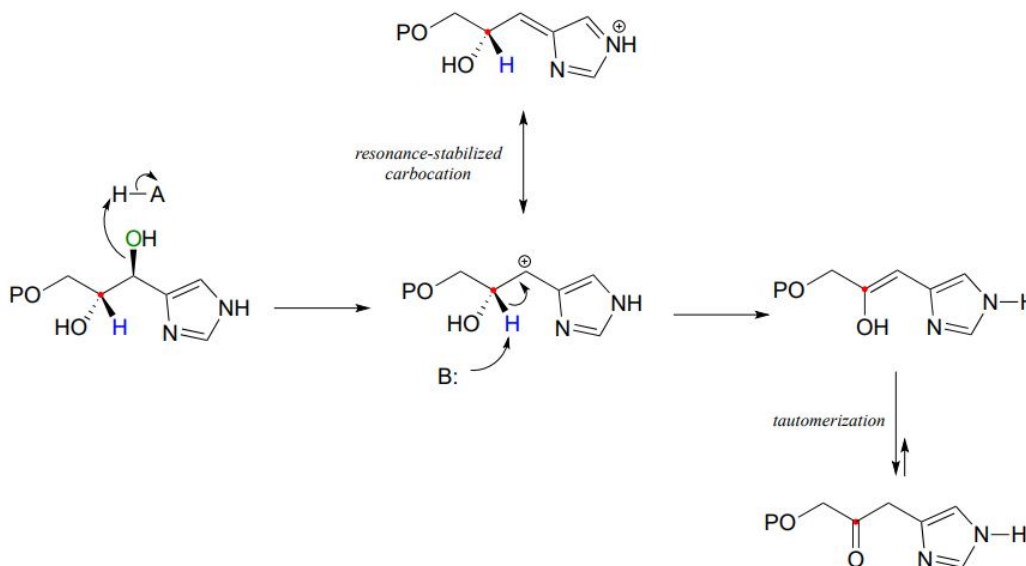
Predict the major organic product(s) of the following reactions. If the reaction is expected to result in a mixture of elimination and substitution product, show both.

- a. bromocyclopentane plus ethoxide
- b. 1-chlorohexane plus CH_3S^-
- c. 2-iodo-2-methylpentane plus hydroxide

Biochemical E1 elimination reactions

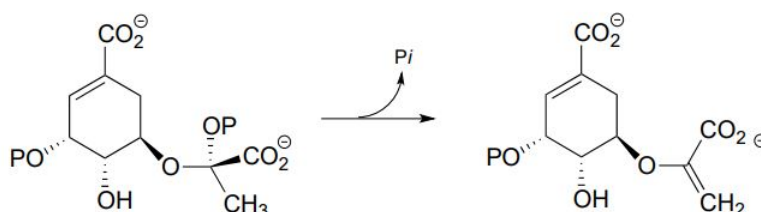
Looking through metabolic pathways in a biochemistry textbook, you'll see that almost all elimination reactions appear to be of the E1cb type, occurring on carbons in the $\alpha\beta$ position relative to a carbonyl or imine. A relatively small number of elimination steps, however, take place away from the electron-withdrawing influence of a carbonyl or imine, and these are of the carbocation-intermediate, E1 type. The E2 mechanism is very rare in biochemical pathways.

A reaction in the histidine biosynthetic pathway (EC 4.2.1.19) provides an example of a biological E1 dehydration step:



Notice that an E1cb mechanism is not possible here - there is no adjacent carbonyl or imine and thus no possibility for a stabilized anionic intermediate. Instead, the first step is loss of water to form a resonance-stabilized carbocation intermediate. Deprotonation completes the E1 phase of the reaction to form an enol, which rapidly tautomerizes to a ketone.

Another example of a biological E1 reaction is found in the biosynthesis pathway for aromatic amino acids (EC 2.5.1.19):

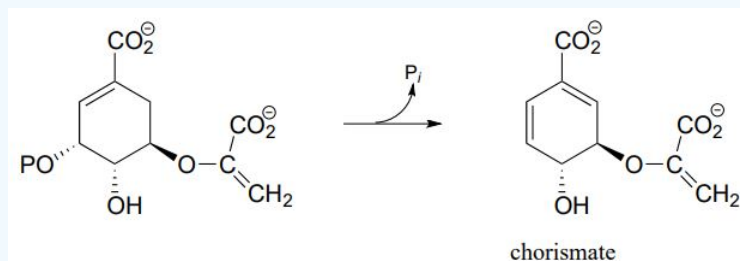


? Exercise 14.3.4

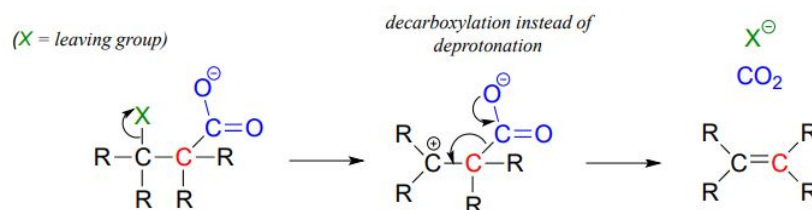
Draw a complete mechanism for the reaction above. Show how the carbocation intermediate is stabilized by resonance.

? Exercise 14.3.5

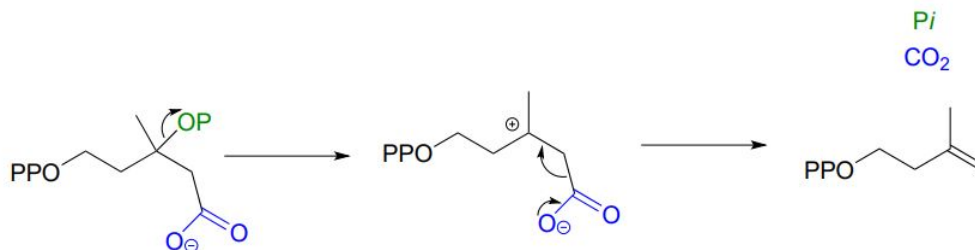
Another step (EC 4.2.3.5) in the aromatic acid biosynthesis pathway could be referred to as a conjugated E1 elimination of phosphate, the mechanistic reverse of electrophilic addition to a conjugated diene (section 14.1). Draw a complete mechanism for this reaction, showing two resonance contributors of the carbocation intermediate.



In section 13.3, we saw some Claisen condensation reactions in which the usual proton-abstraction step was replaced by decarboxylation. A similar thing can happen with E1 eliminations:

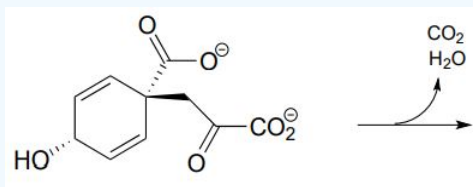


Isopentenyl diphosphate, the 'building block' for all isoprenoid compounds, is a product of this type of hybrid decarboxylation / elimination reaction (EC 4.1.1.33).



? Exercise 14.3.6

A conjugated decarboxylation/E1 elimination reaction (EC 4.2.1.51) occurs in the phenylalanine biosynthesis pathway.



- Predict the product, and draw a mechanism.
- What two main factors contribute to the 'driving force' for this reaction?

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