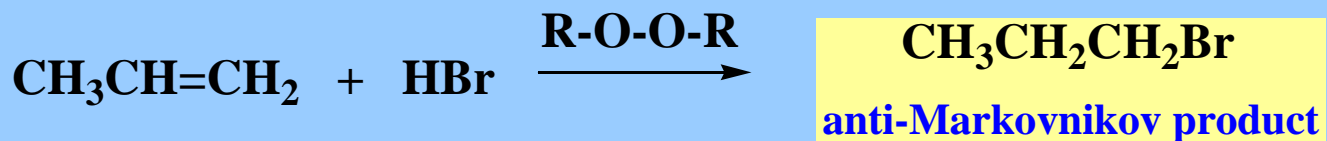


Regioselective Reactions

These Markovnikov additions are examples of **regioselective reactions**. When a reaction can potentially give two or more constitutional isomers, but yields one, or predominantly only one, it is regioselective.

An Apparent Exception to Markovnikov's Rule

The ionic addition of HX (HCl, HBr, HI) follows the Markovnikov rule. But for many years, HBr seemed to be an exception *in some reactions*. Finally, in the 1930s, it was demonstrated that the exceptions that gave anti-Markovnikov additions were due to the presence of peroxides (R-O-O-R) that initiated a different reaction. This free radical addition of HBr to alkenes will be discussed later.



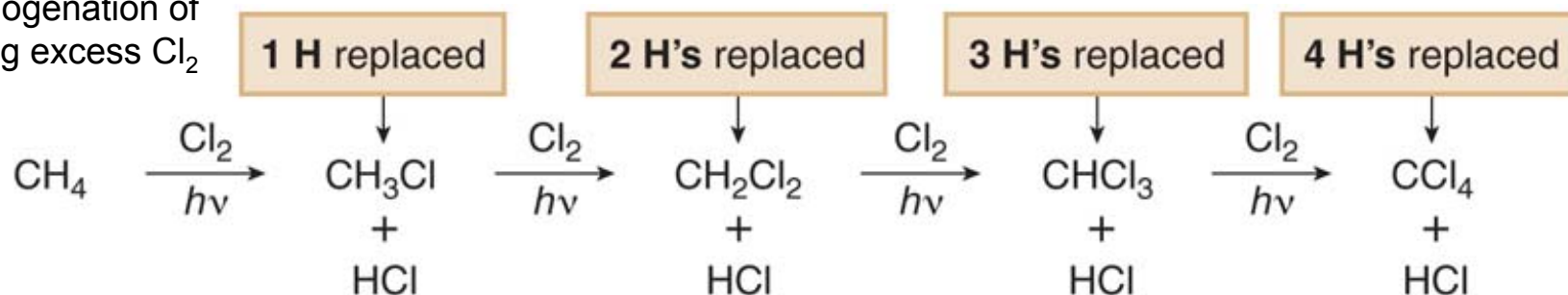
Radical Reactions

Halogenation of Alkanes

- When a single hydrogen atom on a carbon has been replaced by a halogen atom, **monohalogenation** has taken place.
- When excess halogen is used, it is possible to replace more than one hydrogen atom on a single carbon with halogen atoms.
- Monohalogenation can be achieved experimentally by adding halogen X_2 to an excess of alkane.
- When asked to draw the products of halogenation of an alkane, draw the products of monohalogenation only, unless specifically directed to do otherwise.

Figure 15.2

Complete halogenation of CH_4 using excess Cl_2



Radical Reactions

Halogenation of Alkanes—Reaction Mechanism

- **Three facts about halogenation suggest that the mechanism involves radical, not ionic, intermediates:**

| Fact | Explanation |
|---|---|
| [1] Light, heat, or added peroxide is necessary for the reaction. | <ul style="list-style-type: none">• Light or heat provides the energy needed for homolytic bond cleavage to form radicals. Breaking the weak O–O bond of peroxides initiates radical reactions as well. |
| [2] O ₂ inhibits the reaction. | <ul style="list-style-type: none">• The diradical O₂ removes radicals from a reaction mixture, thus preventing reaction. |
| [3] No rearrangements are observed. | <ul style="list-style-type: none">• Radicals do not rearrange. |

Radical Reactions—Mechanism

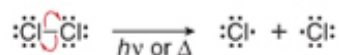
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Mechanism 15.1 Radical Halogenation of Alkanes

Initiation

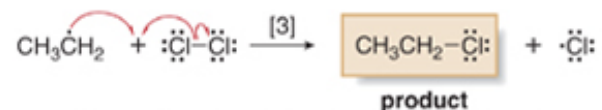
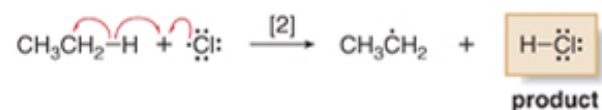
Step [1] Bond cleavage forms two radicals.



- The reaction begins with homolysis of the weakest bond in the starting materials using energy from light or heat.
- Thus, the Cl–Cl bond ($\Delta H^\circ = 58$ kcal/mol), which is weaker than either the C–C or C–H bond in ethane ($\Delta H^\circ = 88$ and 98 kcal/mol, respectively), is broken to form two chlorine radicals.

Propagation

Steps [2] and [3] One radical reacts and a new radical is formed.

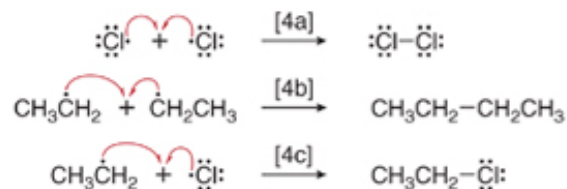


Repeat Steps [2], [3], [2], [3], again and again.

- The Cl \cdot radicals are highly reactive (they lack an octet of electrons), so they abstract a hydrogen atom from ethane (Step [2]). This forms H–Cl and leaves one unpaired electron on carbon, generating the ethyl radical (CH₃CH₂ \cdot).
- CH₃CH₂ \cdot is highly reactive, so it can abstract a chlorine atom from Cl₂ (Step [3]), forming CH₃CH₂Cl and a new chlorine radical (Cl \cdot).
- The Cl \cdot radical formed in Step [3] is a reactant in Step [2], so Steps [2] and [3] can occur repeatedly without an additional initiation reaction (Step [1]).
- In each propagation step, one radical is consumed and one radical is formed. The two products—CH₃CH₂Cl and HCl—are formed during propagation.

Termination

Step [4] Two radicals react to form a σ bond.



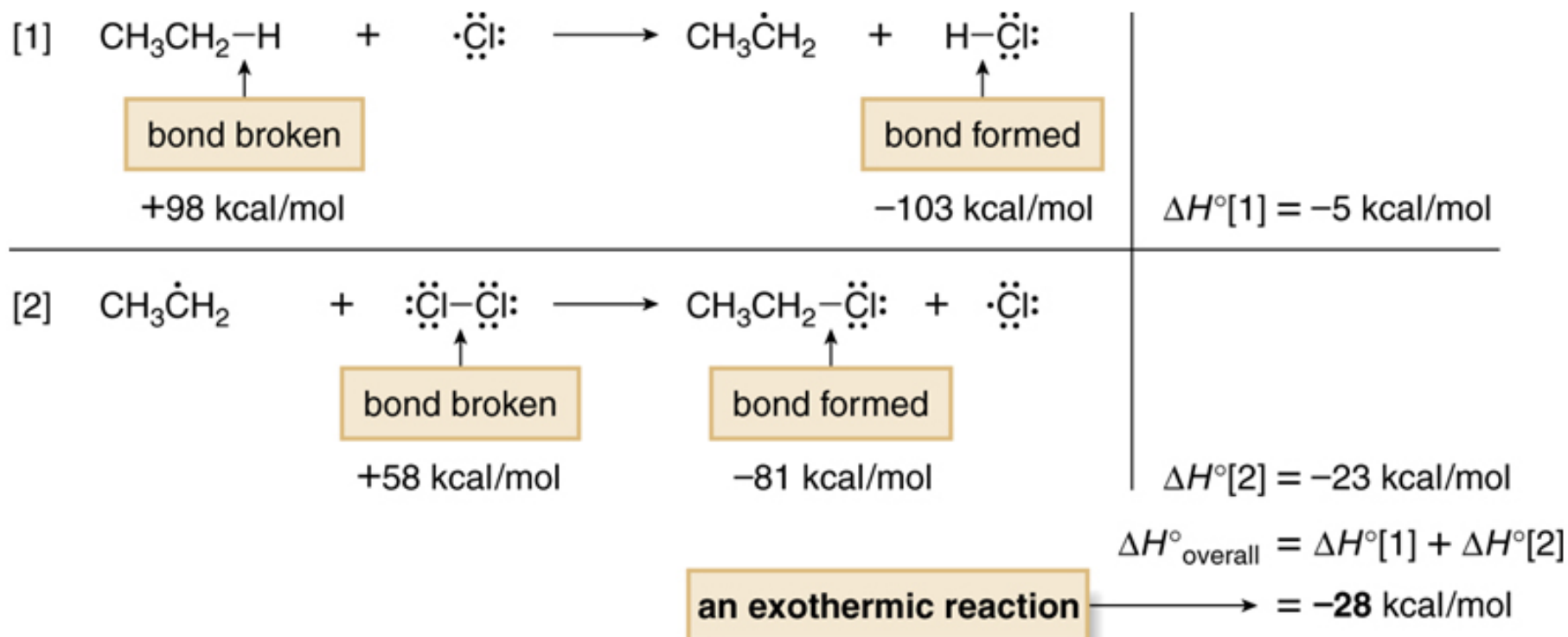
- To terminate the chain, two radicals react with each other in one of three ways (Steps [4a, b, and c]). Because these reactions remove reactive radicals and form stable bonds, they prevent further propagation via Steps [2] and [3].

Radical Reactions

Halogenation of Alkanes—Reaction Mechanism

Figure 15.3

Energy changes in the propagation steps during the chlorination of ethane

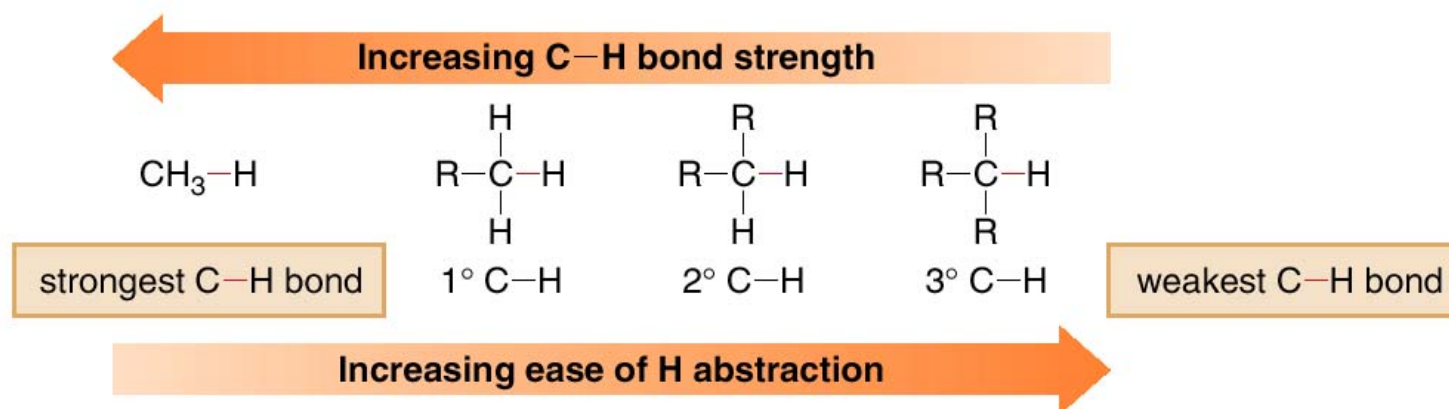


Radical Reactions

Halogenation of Alkanes

- Since the observed ratio between $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$ and $(\text{CH}_3)_2\text{CHCl}$ is 1:1, the 2° C—H bonds must be more reactive than the 1° C—H bonds.

- The weaker the C—H bond, the more readily the hydrogen atom is removed in radical halogenation.

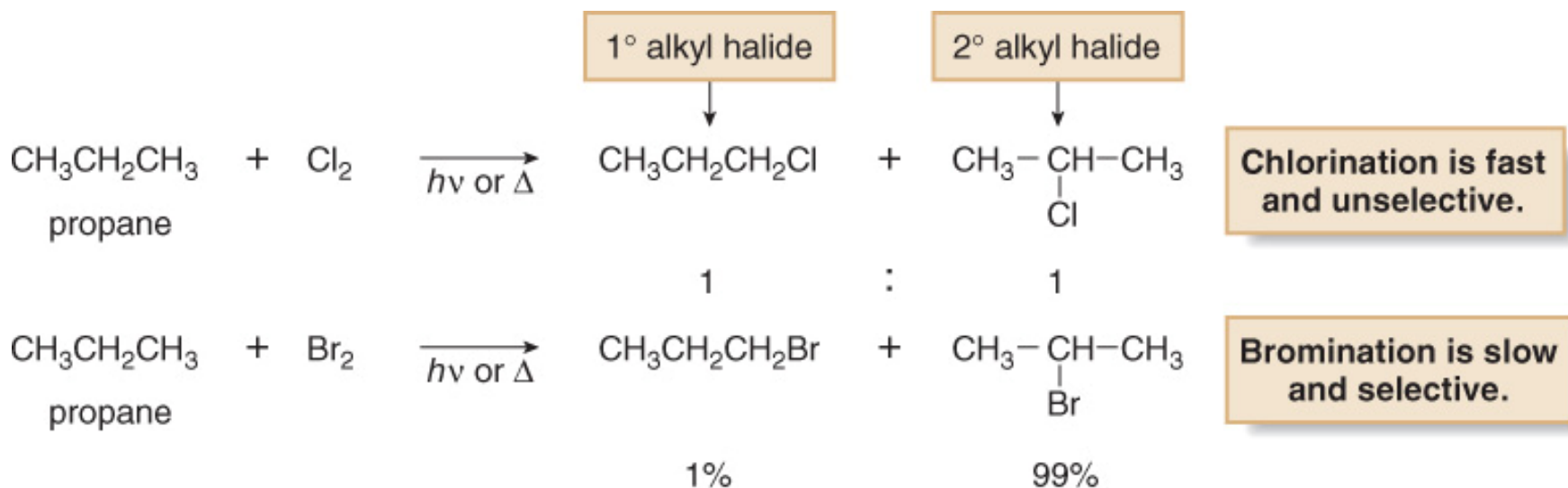


- Thus, when alkanes react with Cl_2 , a mixture of products results, with more product formed by cleavage of the weaker C—H bond than you would expect on statistical grounds. ⁶

Radical Reactions

Chlorination versus Bromination

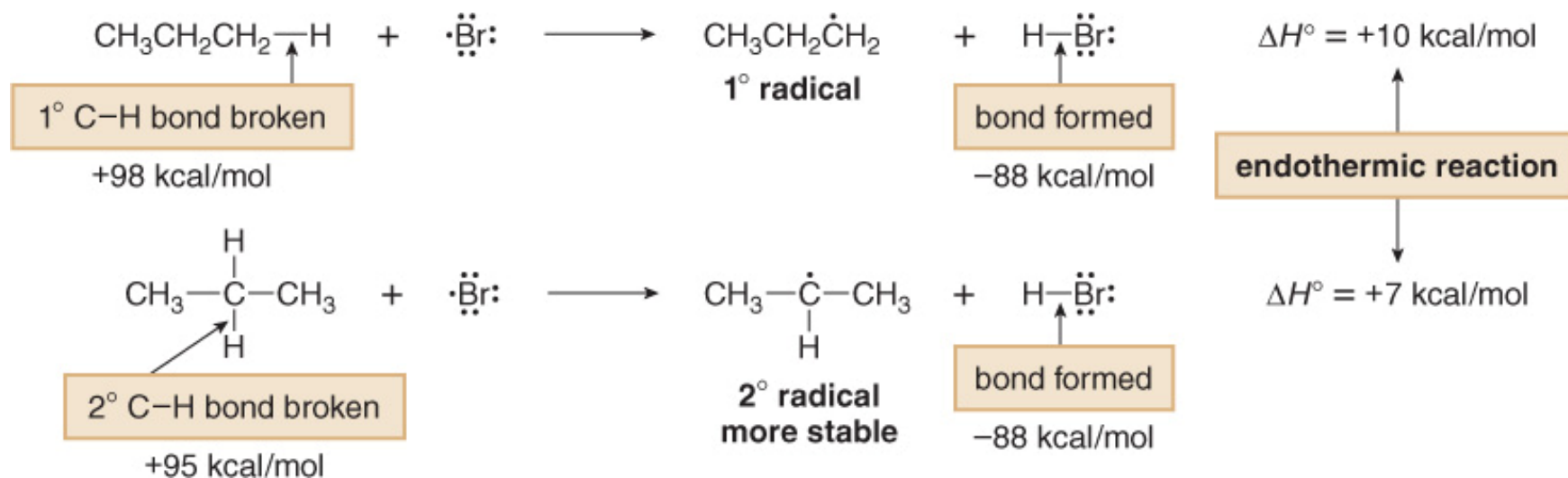
- Although alkanes undergo radical substitutions with both Cl_2 and Br_2 , chlorination and bromination exhibit two important differences.
 1. Chlorination is faster than bromination.
 2. Chlorination is unselective, yielding a mixture of products, but bromination is often selective, yielding one major product.



Radical Reactions

Chlorination versus Bromination

- The differences in chlorination and bromination can be explained by considering the energetics of each type of reaction.
- Calculating the ΔH° using bond dissociation energies reveals that abstraction of a 1° or 2° hydrogen by Br^\bullet is endothermic, but it takes less energy to form the more stable 2° radical.



Radical Reactions

Chlorination versus Bromination

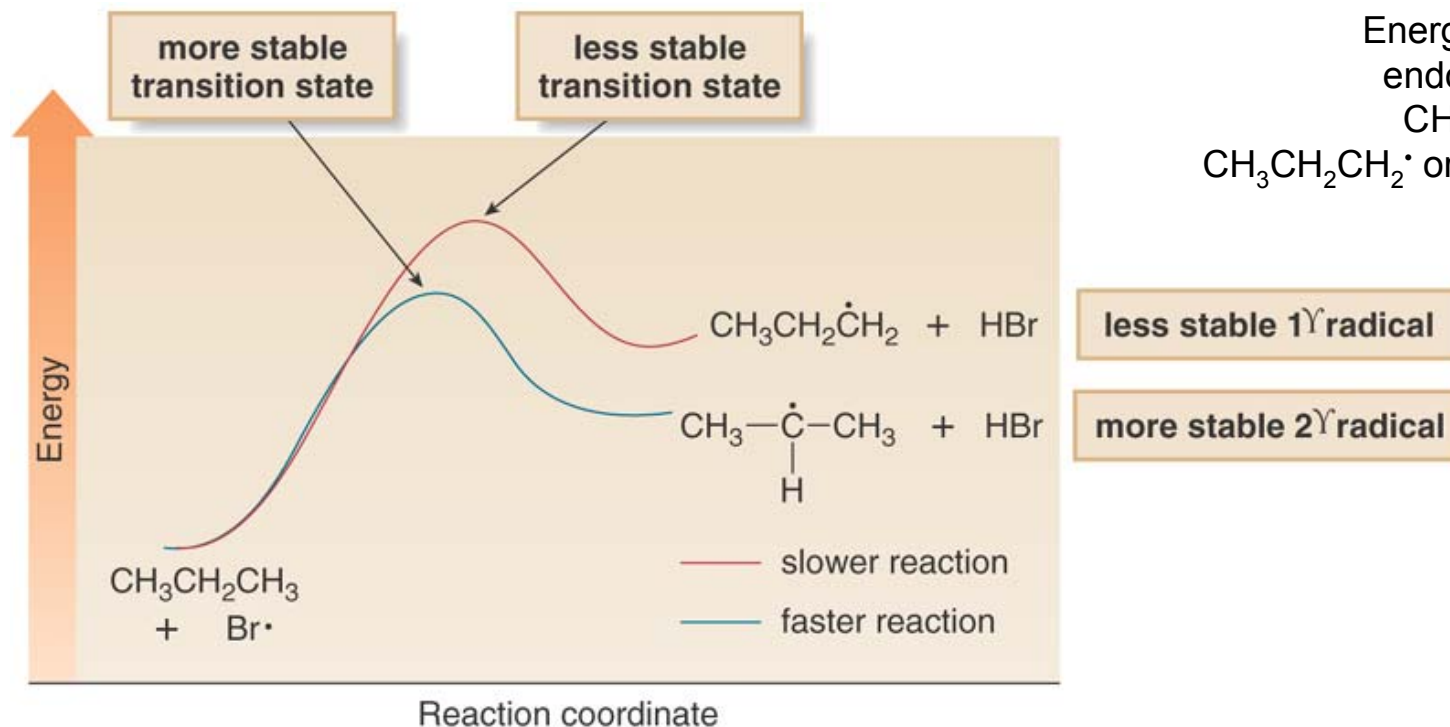
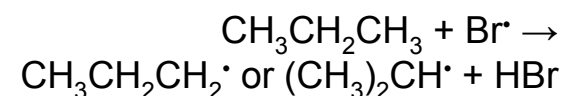


Figure 15.5

Energy diagram for the endothermic reaction:



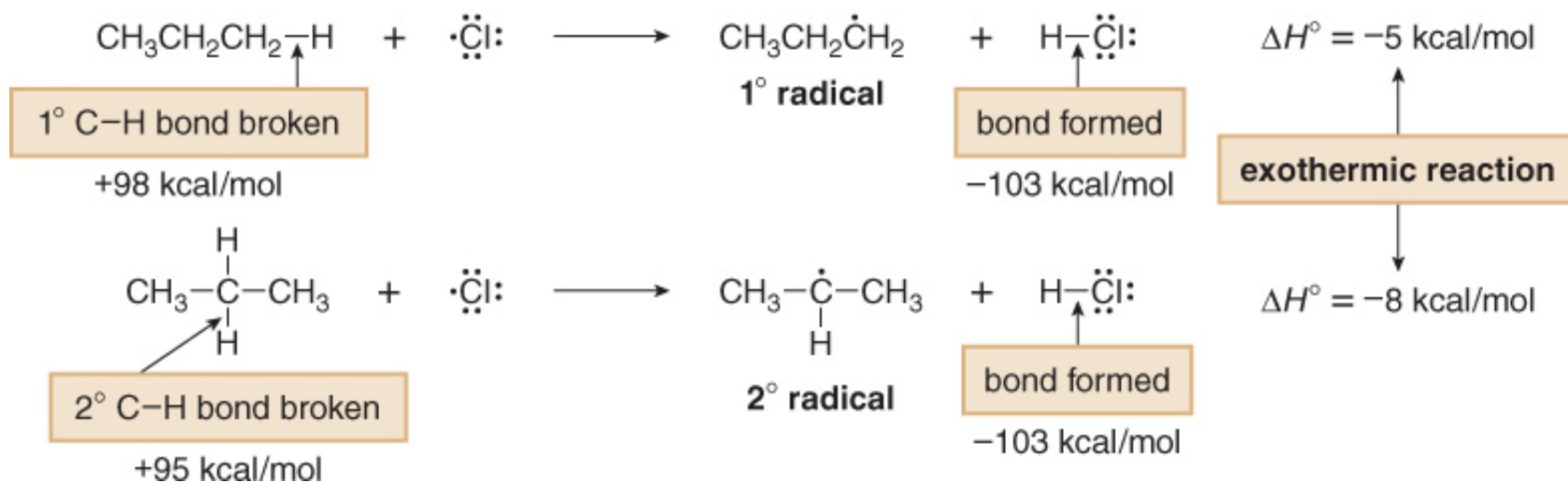
- The transition state to form the less stable 1° radical ($\text{CH}_3\text{CH}_2\dot{\text{C}}\text{H}_2$) is higher in energy than the transition state to form the more stable 2° radical [$(\text{CH}_3)_2\dot{\text{C}}\text{H}$]. Thus, **the 2° radical is formed faster.**

Conclusion: Because the rate-determining step is endothermic, the more stable radical is formed faster, and often a single radical halogenation product predominates.

Radical Reactions

Chlorination versus Bromination

- Calculating the ΔH° using bond dissociation energies for chlorination reveals that abstraction of a 1° or 2° hydrogen by $\text{Cl}\cdot$ is exothermic.



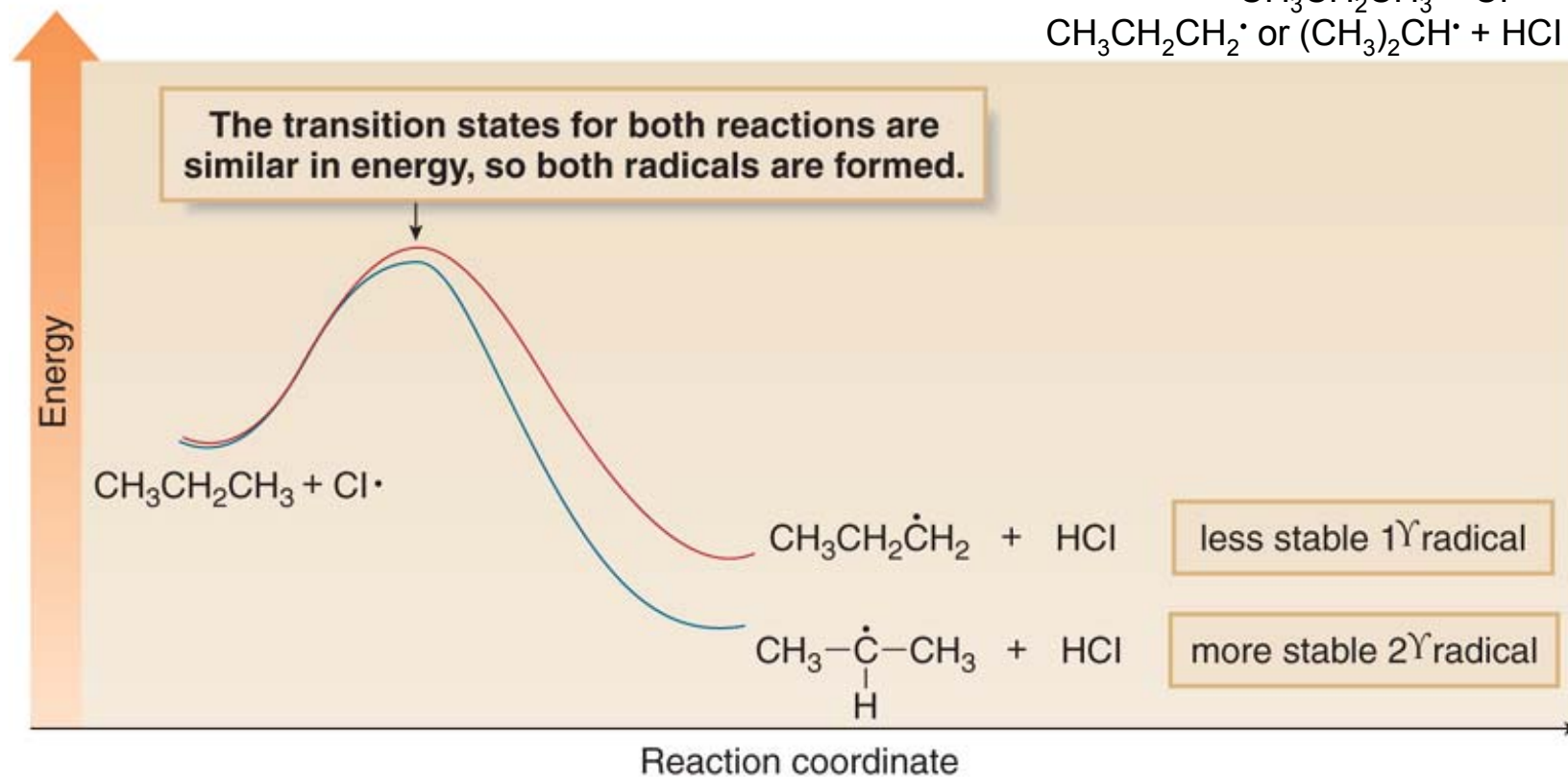
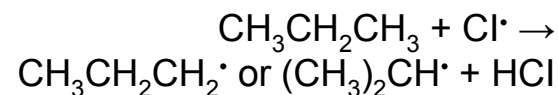
- Since chlorination has an exothermic rate-determining step, the transition state to form both radicals resembles the same starting material, $\text{CH}_3\text{CH}_2\text{CH}_3$. Thus, the relative stability of the two radicals is much less important, and both radicals are formed.

Radical Reactions

Chlorination versus Bromination

Figure 15.6

Energy diagram for the exothermic reaction:



Conclusion: Because the rate-determining step in chlorination is exothermic, the transition state resembles the starting material, both radicals are formed, and a mixture of products results. 11

Radical Reactions

Stereochemistry of Halogenation

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Table 15.1

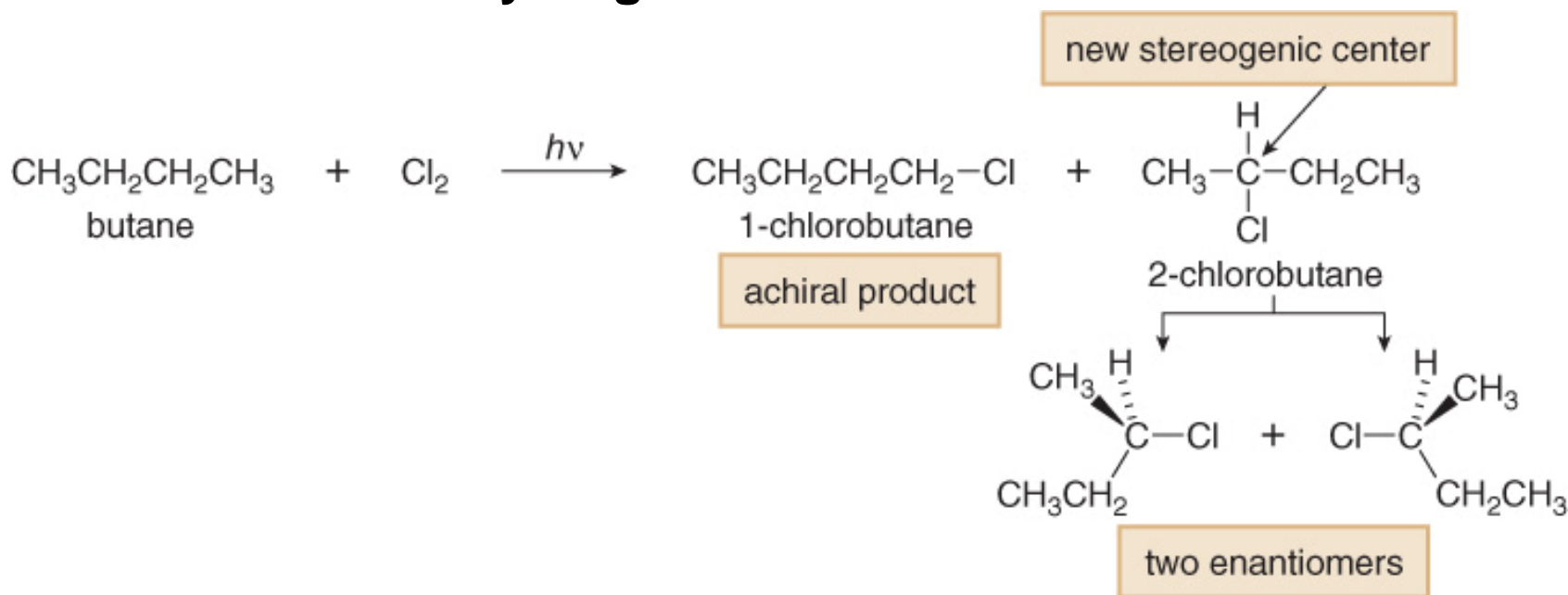
Rules for Predicting the Stereochemistry of Reaction Products

| Starting material | Result |
|-------------------|---|
| Achiral | <ul style="list-style-type: none">• An achiral starting material always gives either an achiral or a racemic product. |
| Chiral | <ul style="list-style-type: none">• If a reaction does not occur at a stereogenic center, the configuration at a stereogenic center is retained in the product.• If a reaction occurs at a stereogenic center, we must know the mechanism to predict the stereochemistry of the product. |

Radical Reactions

Stereochemistry of Halogenation

- Halogenation of an achiral starting material such as $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$ forms two constitutional isomers by replacement of either a 1° or 2° hydrogen.

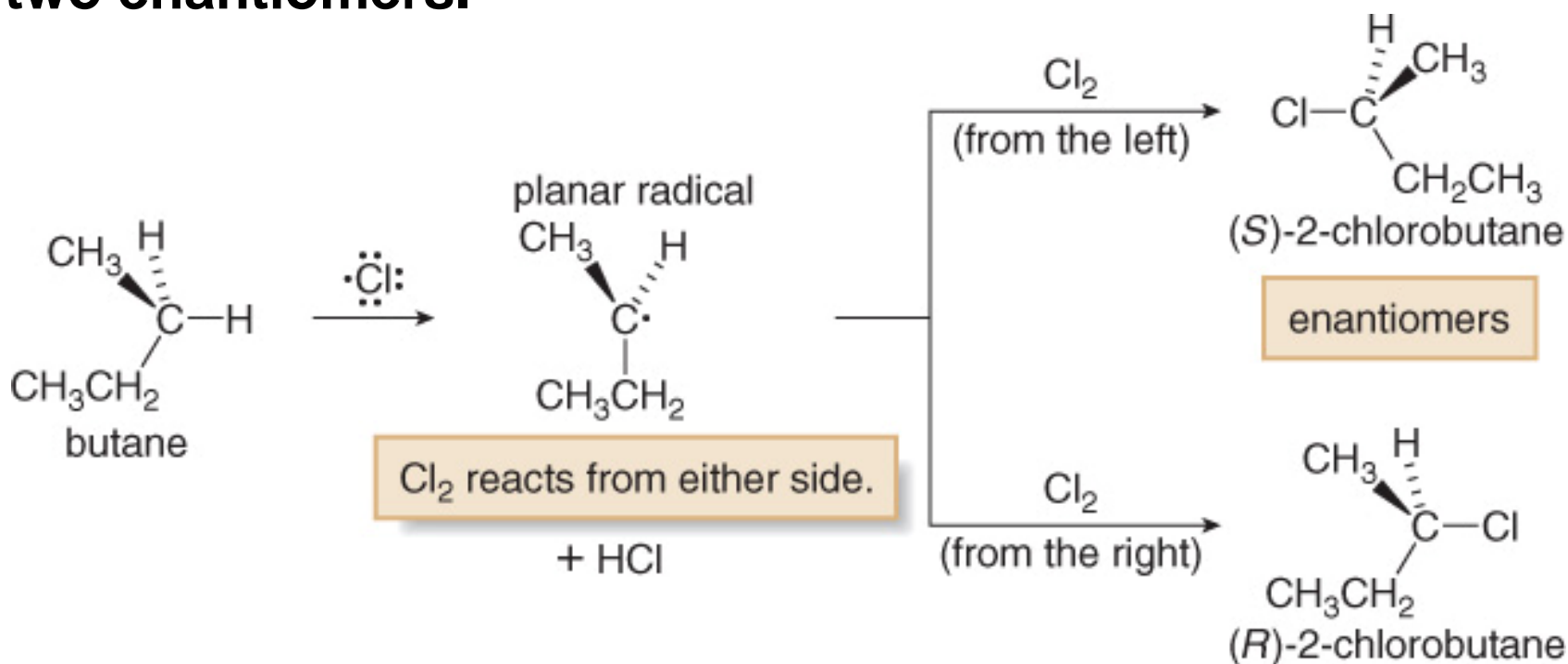


- 1-Chlorobutane has no stereogenic centers and is thus achiral.
- 2-Chlorobutane has a new stereogenic center, and so an equal amount of two enantiomers must form—a racemic mixture.

Radical Reactions

Stereochemistry of Halogenation

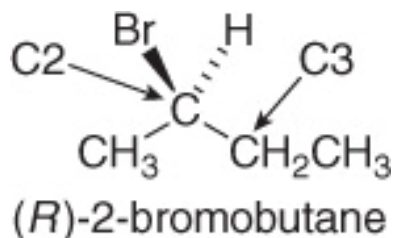
- A racemic mixture results because the first propagation step generates a planar sp^2 hybridized radical. Cl_2 then reacts with it from either side to form an equal amount of two enantiomers.



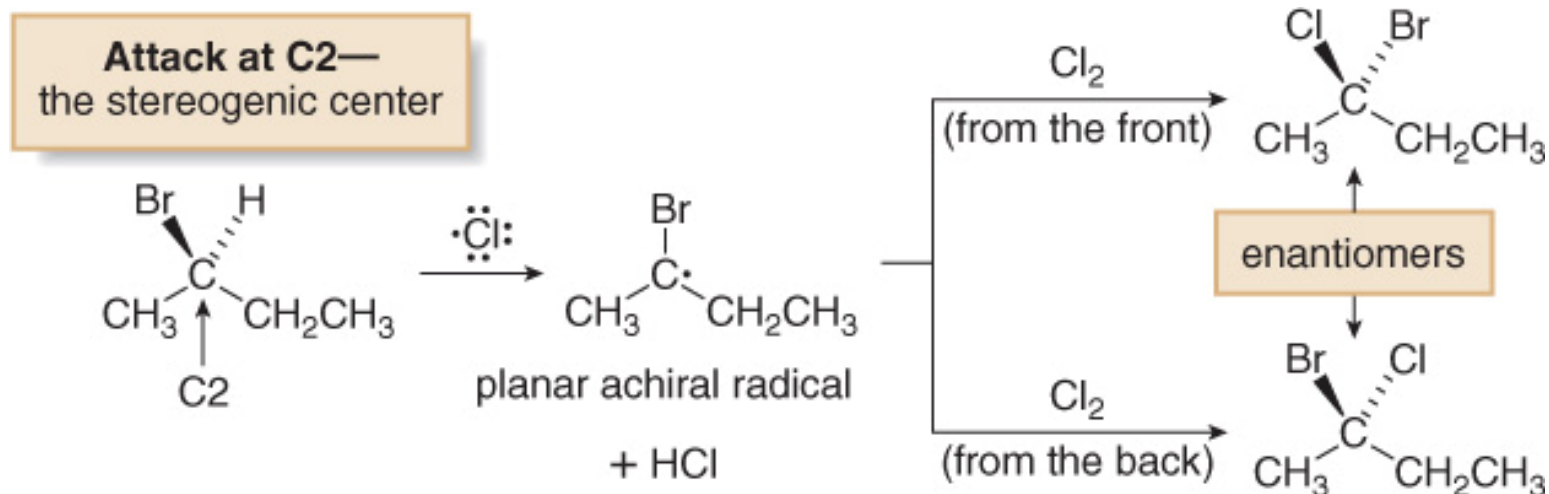
Radical Reactions

Stereochemistry of Halogenation

- Suppose we were to chlorinate the chiral starting material (*R*)-2-bromobutane at C2 and C3.



- Chlorination at C2 occurs at the stereogenic center.

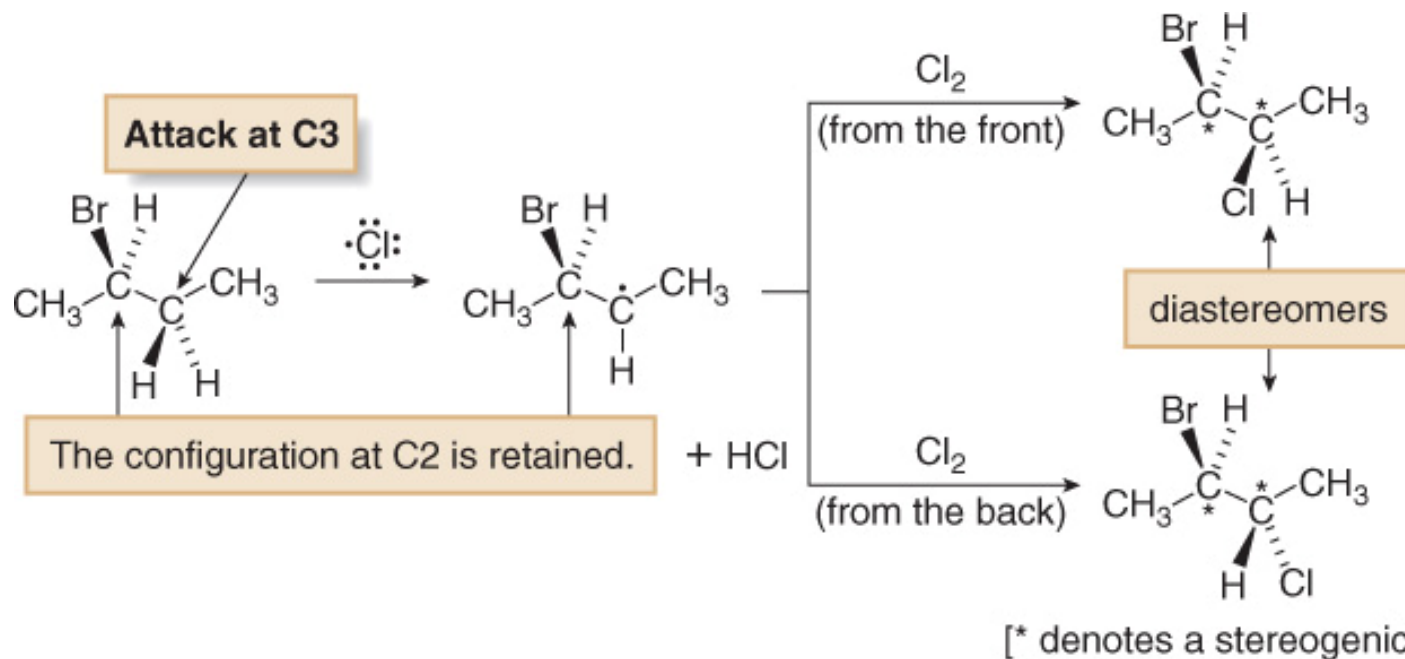


- Radical halogenation reactions at a stereogenic center occur with racemization.

Radical Reactions

Stereochemistry of Halogenation

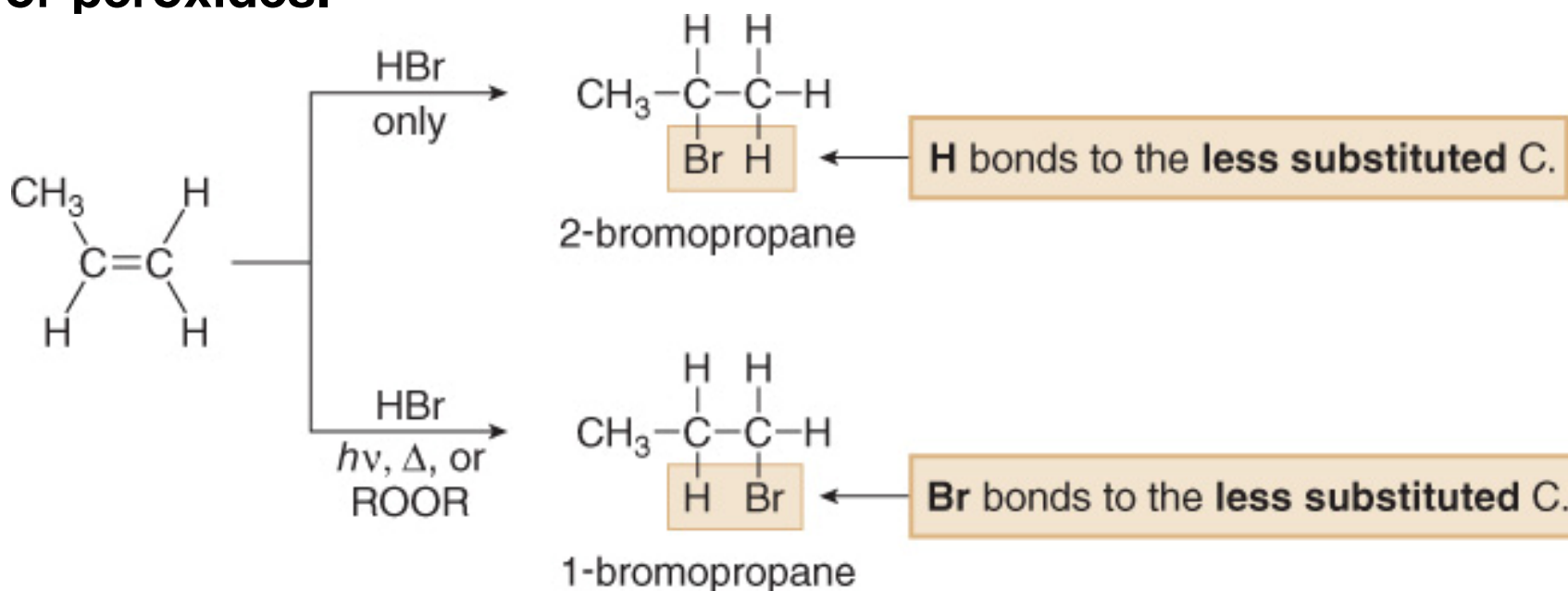
- Chlorination at C3 does not occur at the stereogenic center, but forms a new stereogenic center.
- Since no bond is broken to the stereogenic center at C2, its configuration is retained during the reaction.
- The trigonal planar sp^2 hybridized radical is attacked from either side by Cl_2 , forming a new stereogenic center.
- A pair of diastereomers is formed.



Radical Reactions

Radical Additions to Double Bonds

- HBr adds to alkenes to form alkyl bromides in the presence of heat, light, or peroxides.
- The regioselectivity of the addition to unsymmetrical alkenes is different from that in addition of HBr in the absence of heat, light or peroxides.



- The addition of HBr to alkenes in the presence of heat, light or peroxides proceeds via a radical mechanism.

Radical Reactions

Radical Additions to Double Bonds

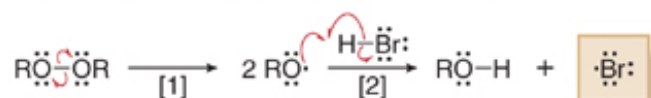
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Mechanism 15.4 Radical Addition of HBr to an Alkene

Initiation

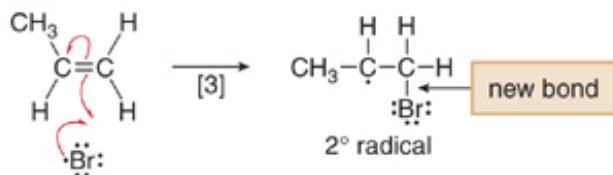
Steps [1] and [2] Abstraction of H from HBr occurs by a two-step process.



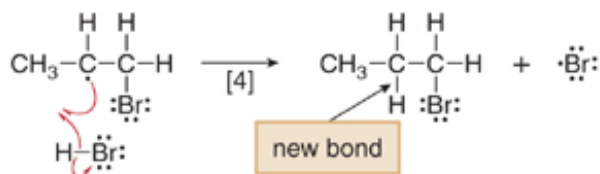
- With ROOR to initiate the reaction, two steps are needed to form Br \cdot . Homolysis of the weak O–O bond of the peroxide forms RO \cdot , which abstracts a hydrogen atom from HBr to form Br \cdot .

Propagation

Steps [3] and [4] The π bond is broken and the C–H and C–Br σ bonds are formed.



- Chain propagation occurs in two steps, and in each step one radical is consumed and another is formed.
- The first step of propagation forms the C–Br bond when the Br \cdot radical adds to the terminal carbon, leading to a 2° carbon radical.

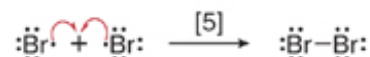


- The 2° radical abstracts a H atom from HBr, forming the new C–H bond and completing the addition reaction. Because a new Br \cdot radical is also formed in this step, Steps [3] and [4] occur repeatedly.

Repeat Steps [3], [4], [3], [4], and so forth.

Termination

Step [5] Two radicals react to form a bond.

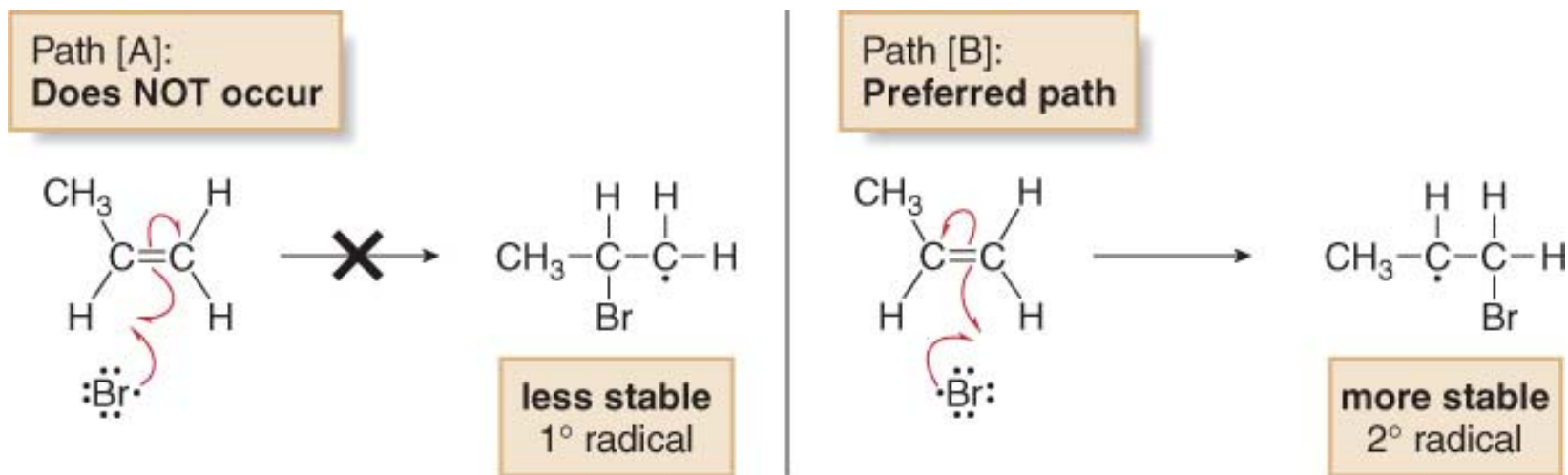


- To terminate the chain, two radicals (for example two Br \cdot radicals) react with each other to form a stable bond, preventing further propagation via Steps [3] and [4].

Radical Reactions

Radical Additions to Double Bonds

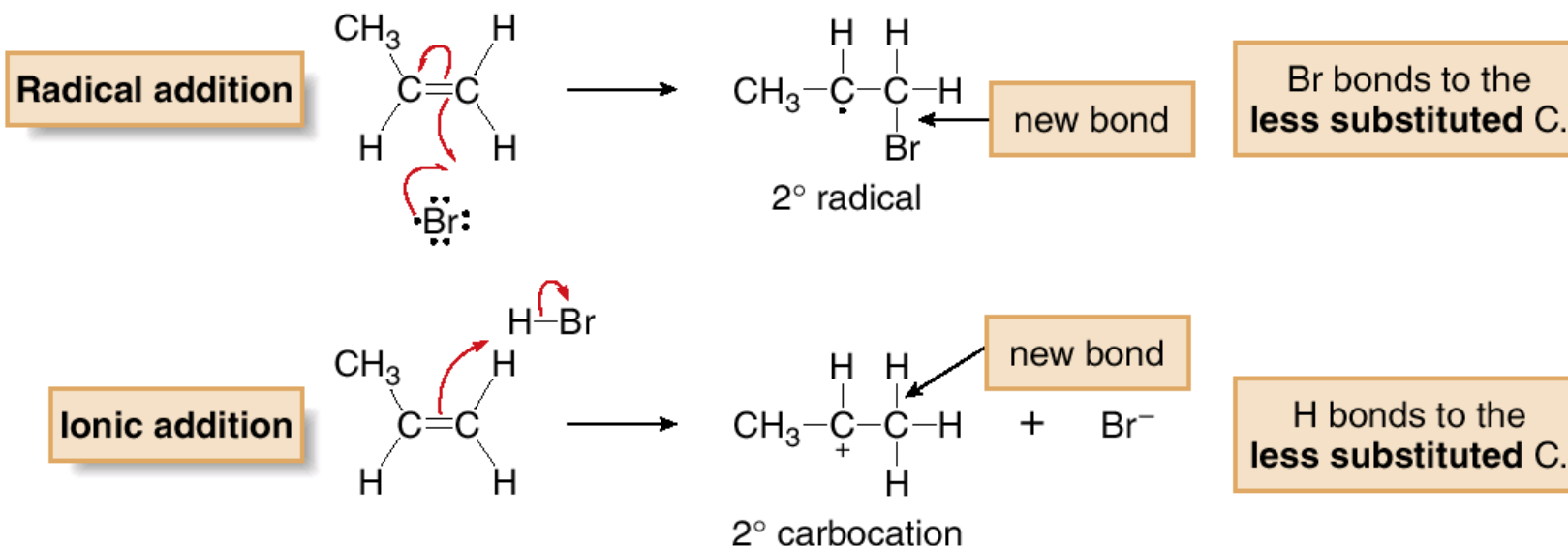
- Note that in the first propagation step, the addition of $\text{Br}\cdot$ to the double bond, there are two possible paths:
 1. Path [A] forms the less stable 1° radical.
 2. Path [B] forms the more stable 2° radical.
- The more stable 2° radical forms faster, so Path [B] is preferred.



Radical Reactions

Radical Additions to Double Bonds

- The radical mechanism illustrates why the regioselectivity of HBr addition is different depending on the reaction conditions.

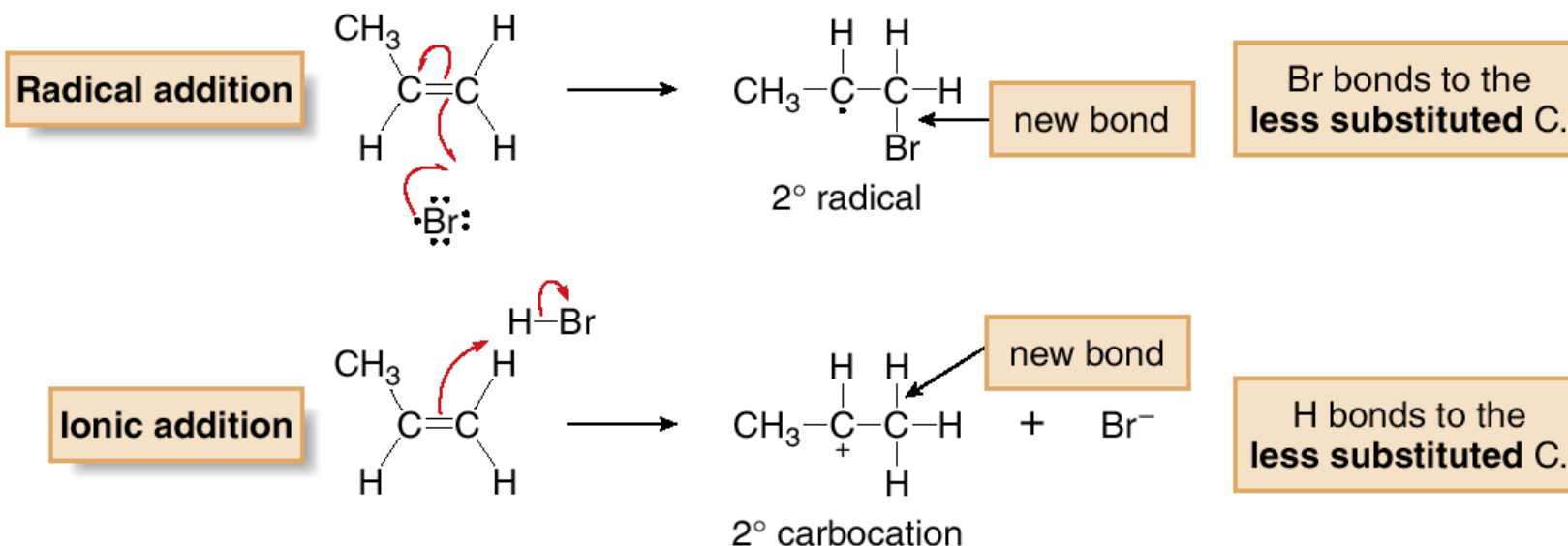


- In radical addition (HBr with added light, heat, or ROOR), *Br· adds first* to generate the more stable radical.
- In ionic addition (HBr alone), *H⁺ adds first* to generate the more stable carbocation.

Radical Reactions

Radical Additions to Double Bonds

- The radical mechanism illustrates why the regioselectivity of HBr addition is different depending on the reaction conditions.



- In radical addition (HBr with added light, heat, or ROOR), *Br· adds first* to generate the more stable radical.
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