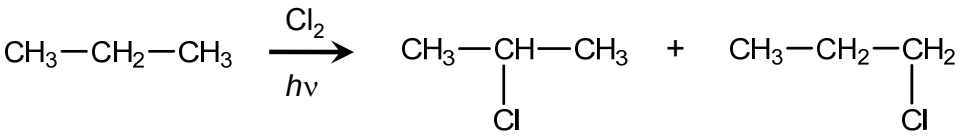
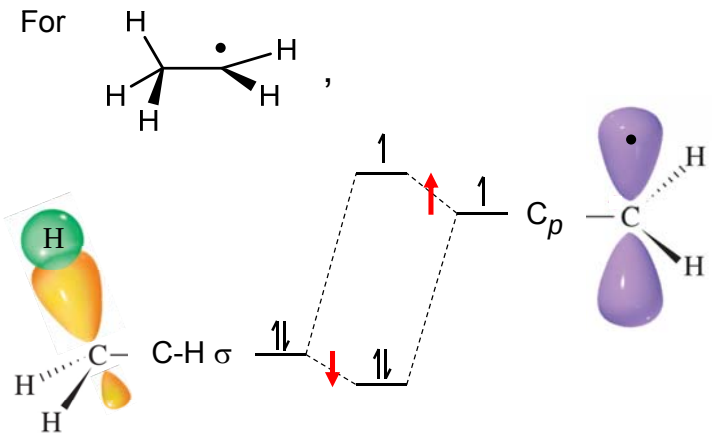
Selectivity in Radical Halogenation



Expected from statistical distribution:	25% (2/8 H's)	75% (6/8 H's)
Observed:	60%	40%

Radical halogenation is selective for the most substituted C-H.

More Substituted Radicals Are More Stable (by Hyperconjugation)



Two electrons decrease in energy, one electron increases in energy.

Net effect is **stabilization**.

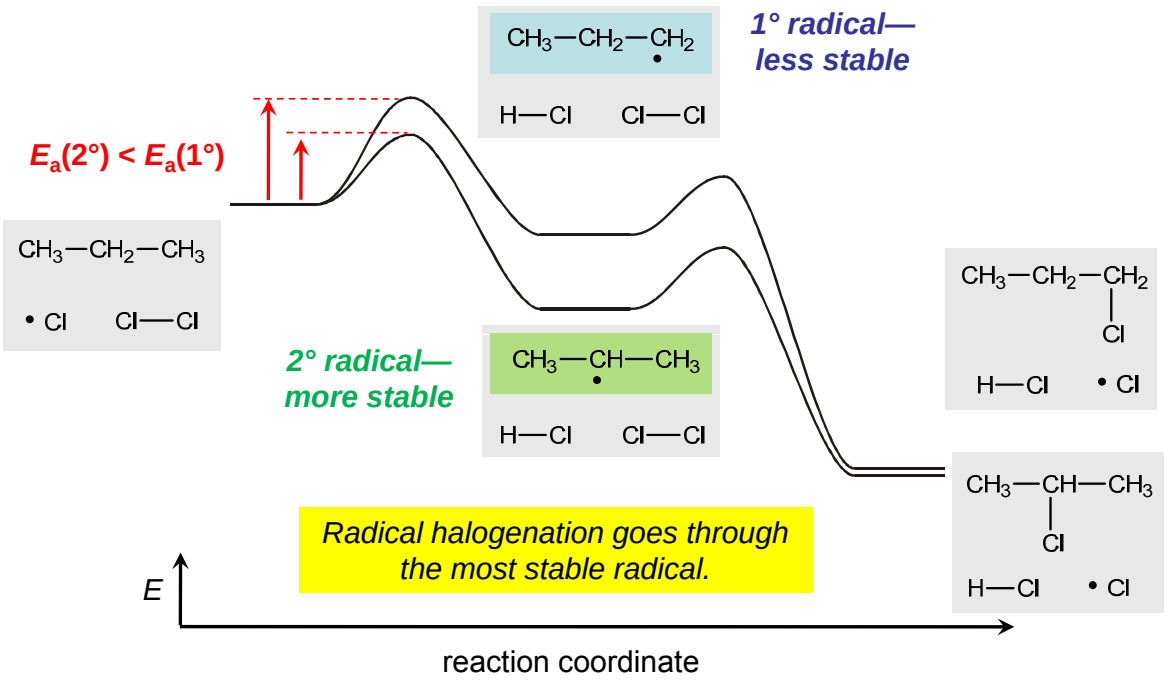
Stability trend for $R_3C\bullet$: 3° > 2° > 1° > CH_3

Bond Dissociation Enthalpies

BDE: Enthalpy required to break a bond into component radicals (A—B → A• + •B)

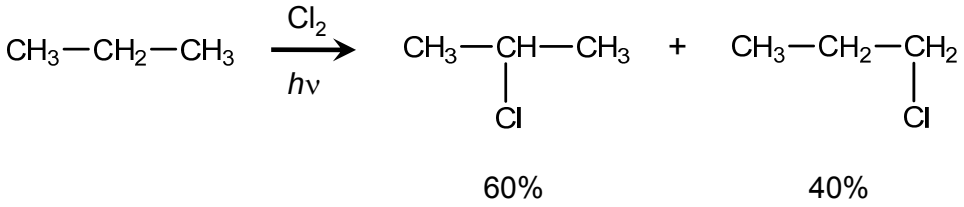
Bond	BDE (kcal/mol)	Bond	BDE (kcal/mol)
Cl—Cl	58	CH_3—Cl	84
H—Cl	103	CH_3CH_2—Cl	81
CH_3—H	**104**	$(CH_3)_2CH$—Cl	80
CH_3CH_2—H	**98**	$(CH_3)_3C$—Cl	79
$(CH_3)_2CH$—H	**95**	CH_3—Br	70
$(CH_3)_3C$—H	**91**	CH_3CH_2—Br	68
$C_6H_5CH_2$—H	88	$(CH_3)_2CH$—Br	68
CH_2=CH-CH_2—H	86	$(CH_3)_3C$—Br	65

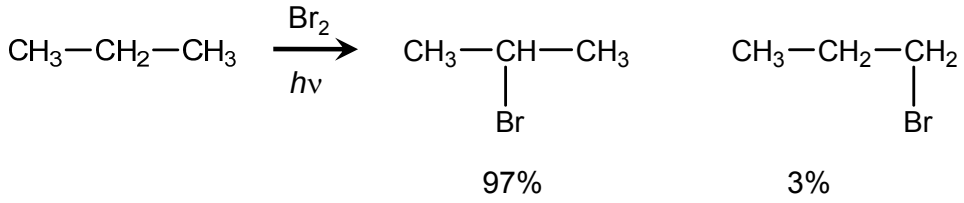
Selectivity in Radical Halogenation



Selectivity in Radical Halogenation

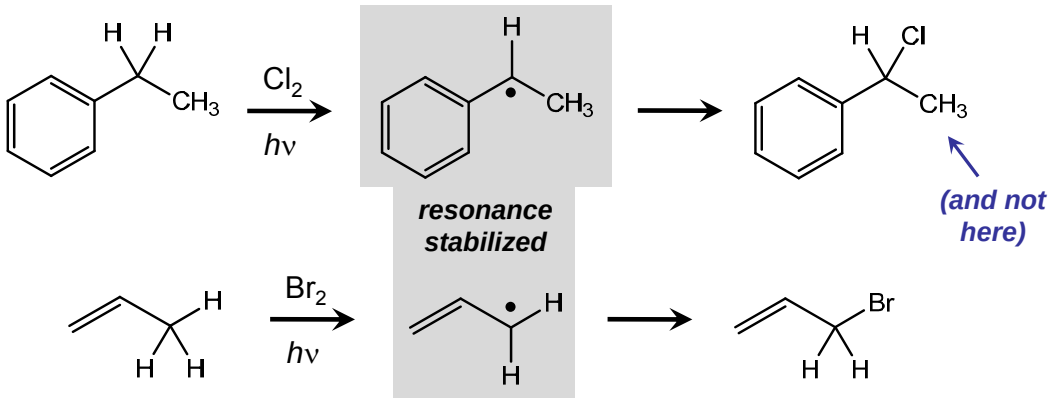
• Bromination is even more selective than chlorination.





Selectivity in Radical Halogenation

• Halogenation at allylic, benzylic sites is particularly preferred.



Resonance is usually more stabilizing than substitution.
This explains low BDEs of allylic, benzylic C-H bonds.

Bond Dissociation Enthalpies

BDE: Enthalpy required to break a bond into component radicals (A—B → A• + •B)

Bond	BDE (kcal/mol)	Bond	BDE (kcal/mol)
Cl—Cl	58	CH_3—Cl	84
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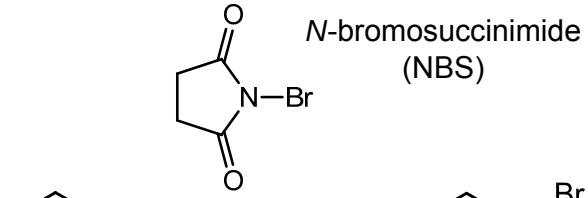
CH_2=CH-CH_2—H	**86**	$(CH_3)_3C$—Br	65

Allylic and Benzylic Bromination with NBS

Problem: Br_2 also reacts with double bonds.

Solution: Use a different reagent (w/ the same mechanism).

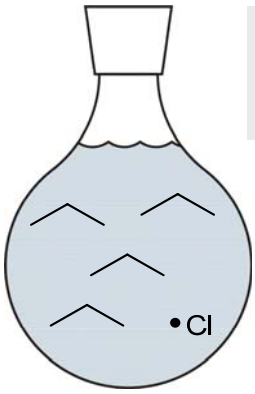


exclusively.

- NBS also halogenates benzylic positions.
- Will not halogenate unactivated C-H's.
- Requires either light ($h\nu$) or a chemical radical source (e.g., AIBN) to provide R•.

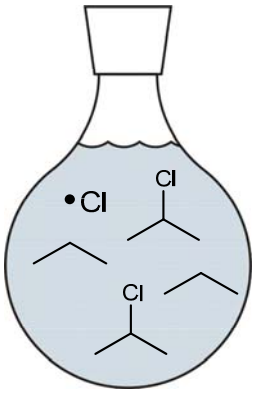
Multiple Halogenations

Problem: Once one C-H has been converted to a C-X, another one can be. This can lead to a mixture of products.



At the beginning of the reaction, Cl• will always find starting material.

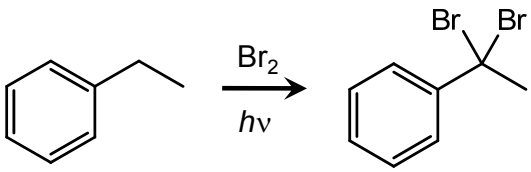
But as the halogenation proceeds, Cl• will encounter and react with molecules that are already chlorinated.



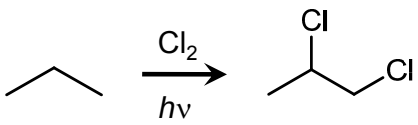
Solution: Monohalogenated product can be made by incomplete reaction, followed by purification of product from starting material.

Multiple Halogenations

Solution: Multiply halogenated products can also be made, as long as the pattern of selectivity allows it.



…is possible (because of selectivity for benzylic position), but…



…is not possible (would not happen selectively).