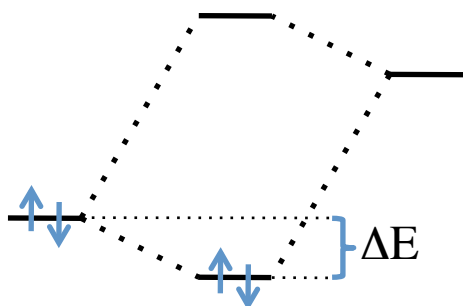


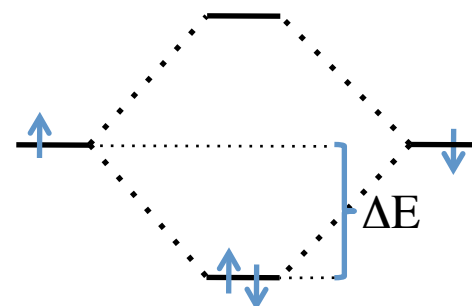
Radical Reactions

Remember that reactions are controlled by the HOMO of one molecule reacting with a LUMO of a second molecule

The closer in energy these two molecular orbitals are in energy before mixing, the more energy gain results due to the greater amount of mixing



As the OMO is closer in energy to the UMO there will be the more energy gain due to the better mixing of the orbitals

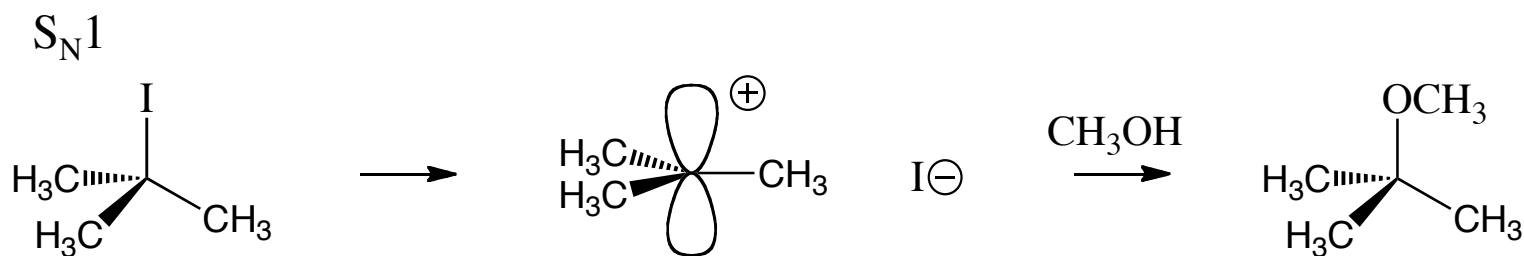
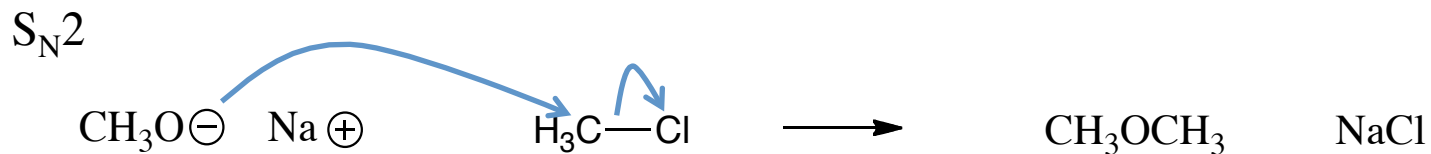


When two SOMO (singly occupied molecular orbitals) react, however, each electron will go down in energy considerably

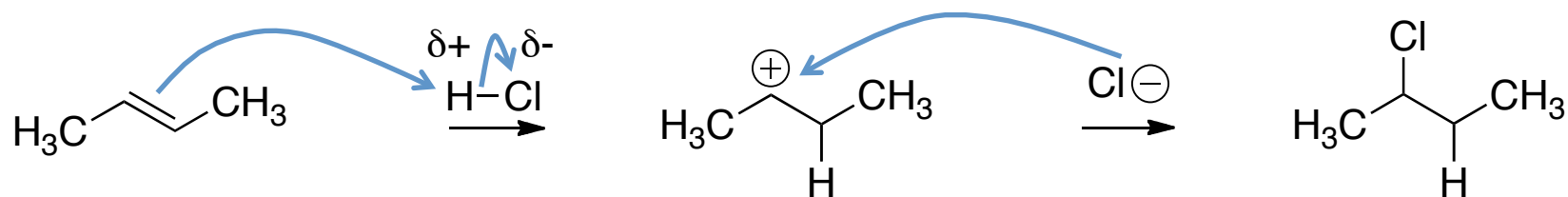
Radicals are thus generally unstable species and cannot be stored as they will simply react with themselves to form a new covalent bond (called dimerization)

Radical Reactions

Almost all of the reactions observed so far have involved charged structures at some point along the reaction coordinate



Alkene reactions

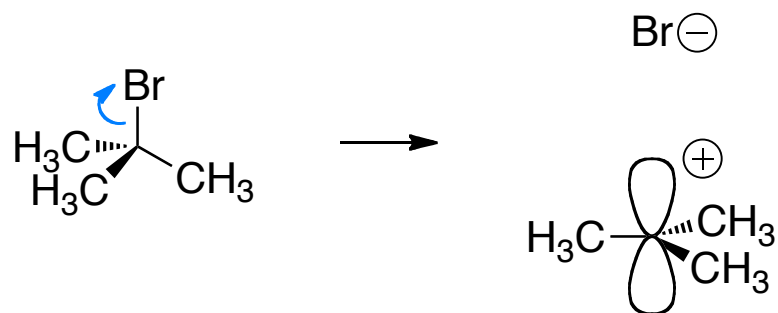


While the majority of organic reactions involve charged structures, there are some reactions that only have uncharged radical structures

Radical Reactions

The bond can break in different ways depending upon how the electrons move:

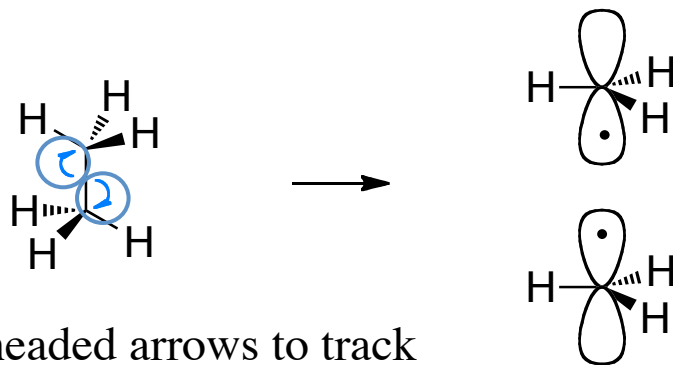
Heterolytic cleavage: both electrons move to one atom



Generates a cation and anion

Route for “polar” reactions
(S_N2 , S_N1 , E1, E2, alkene)

Homolytic cleavage: one electron moves to each atom from initial bond



Generates two radicals

Used in bond strength tables
(Bond Dissociation Energy, BDE)

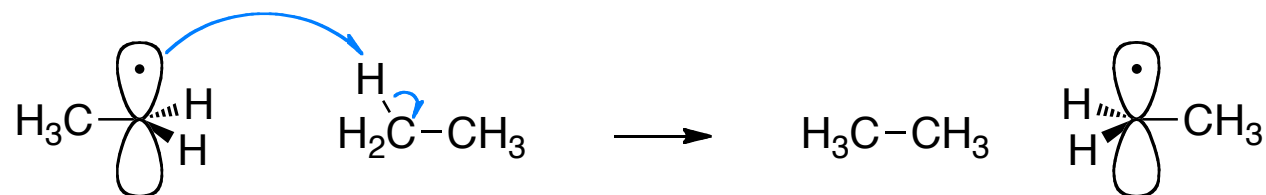
Use single-headed arrows to track
movement of one electron

Radical Reactions

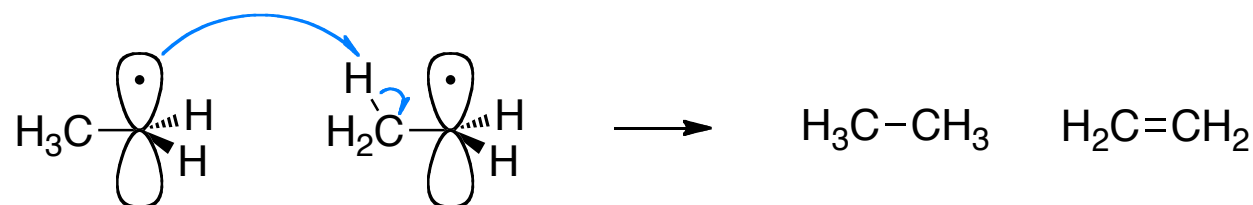
Similar to carbocations, radicals are unstable species and generally will not be present in a final product but rather as a high energy intermediate structure along a reaction pathway

When present, the high energy radical can react in different ways

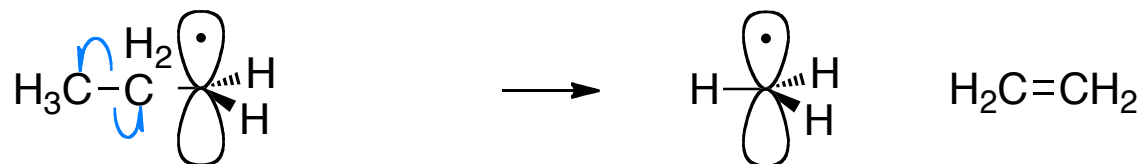
Hydrogen abstraction



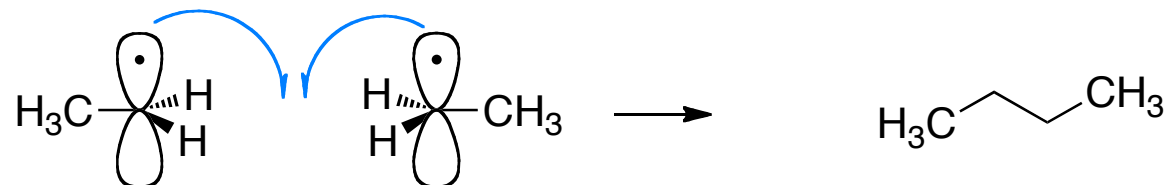
Disproportionation



β cleavage



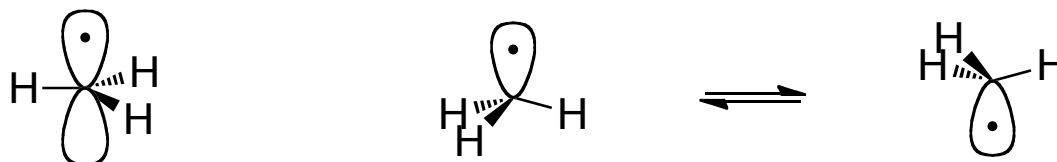
Dimerization



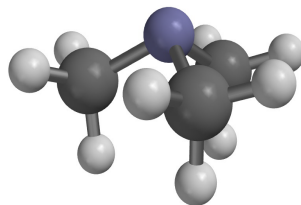
Structure and Stability of Radicals

The structure of radicals resemble the structure for carbocations

The radical resembles a sp^2 hybridized carbon with the substituents in a plane



Some argue* that the structure though is more of an equilibrium between two nearly planar structures which on average resemble a planar structure (similar to amines going through an inversion)

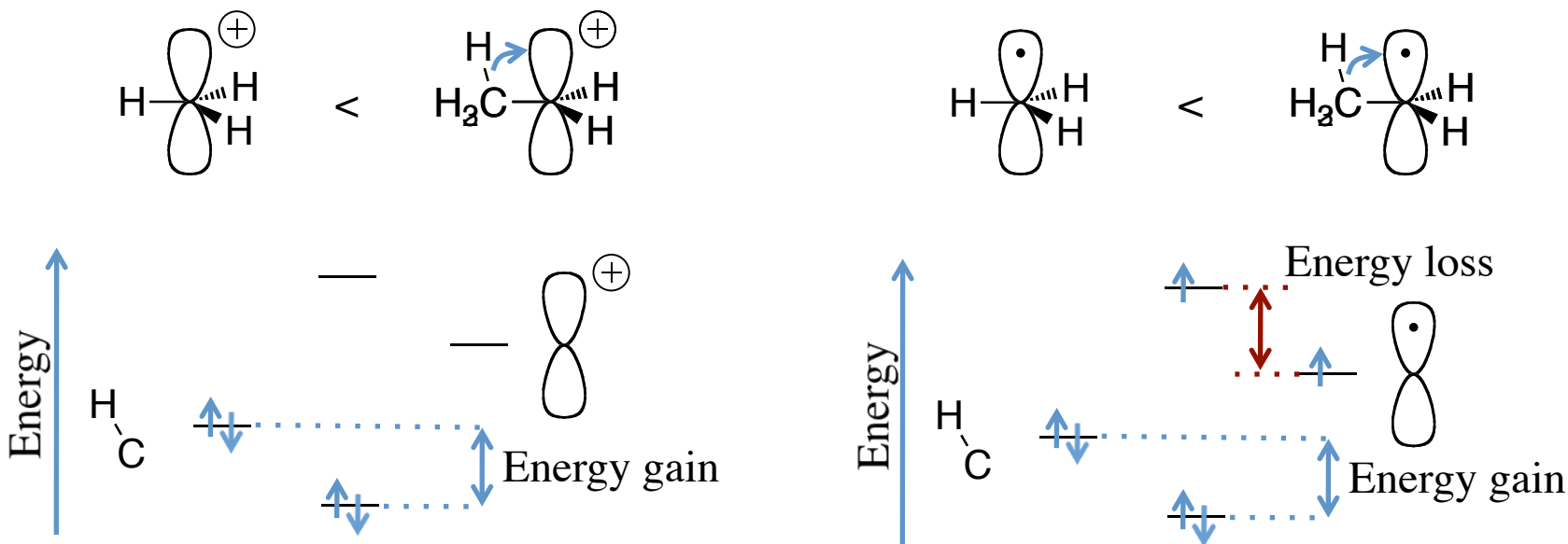


*Organic chemists still argue over many things, there is always another experiment to try and prove a hypothesis

Structure and Stability of Radicals

Radicals also follow a similar stability trend compared to carbocations

Remember with carbocations that the stability of the cation increases with more alkyl substituents due to the increase in hyperconjugation effects



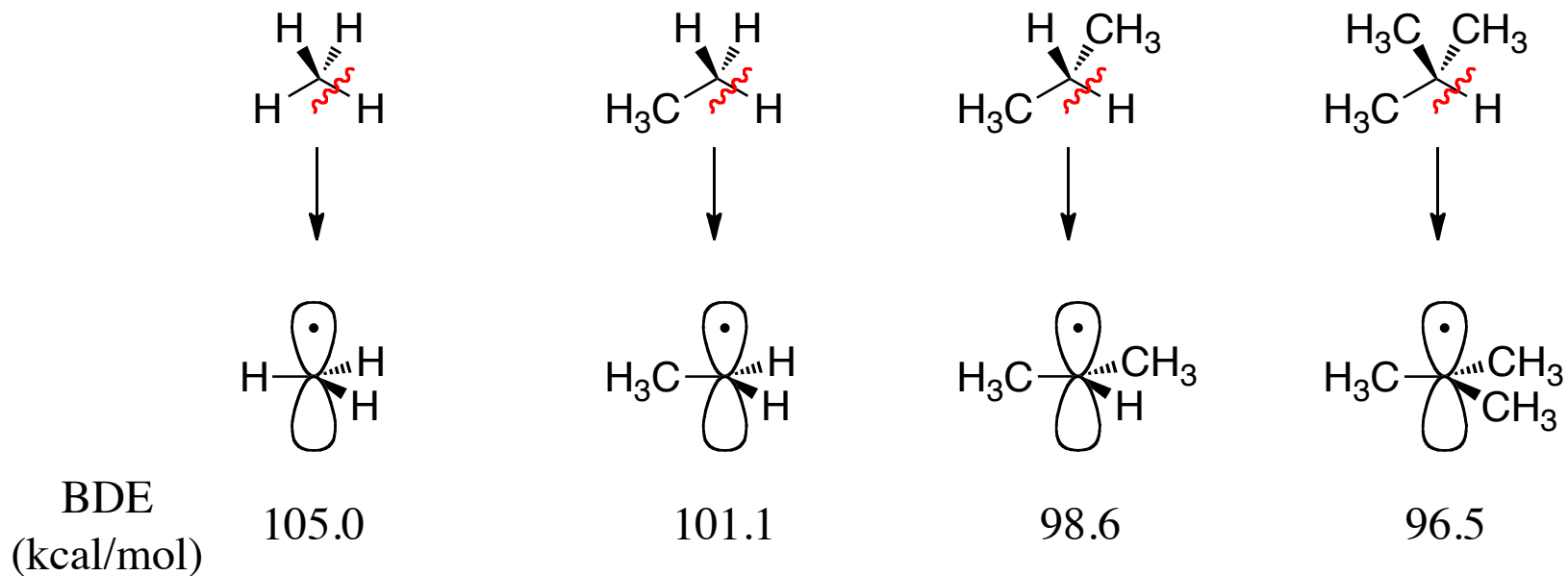
Only energy gain, therefore all hyperconjugation stabilizes and $3^\circ > 2^\circ > 1^\circ$

2 electrons stabilized and one destabilized – overall still an energy gain, therefore all hyperconjugation stabilizes and $3^\circ > 2^\circ > 1^\circ$

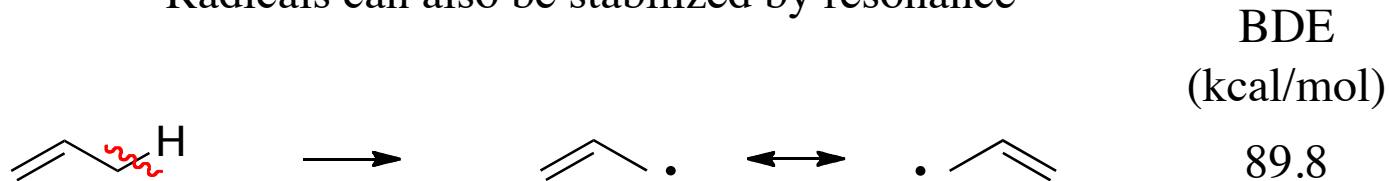
With anions, however, overall hyperconjugation is destabilizing as 2 electrons will raise in energy, therefore for anions hyperconjugation is bad and $3^\circ < 2^\circ < 1^\circ$

Structure and Stability of Radicals

The stability caused by the hyperconjugation can be seen by comparing the bond dissociation energies for related compounds



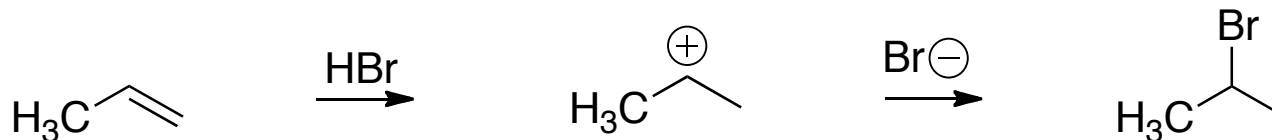
Radicals can also be stabilized by resonance



Resonance has a bigger effect on stability than hyperconjugation
(in this example a 1° radical in resonance is more stable than an isolated 3° radical)

Radical Addition to Alkenes

We have observed that when alkenes react with hydrohalic acid, a Markovnikov addition occurs through a polar mechanism



If the reaction is run with peroxides present, however, the opposite regiochemistry is obtained

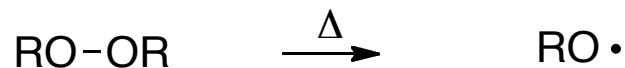


The mechanism must be changing due to the peroxide present because the 2° cation is more stable than the 1° cation, therefore first step must not be addition of proton to form cation

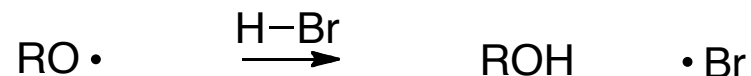
*peroxides are compounds that have a O-O single bond

Radical Addition to Alkenes

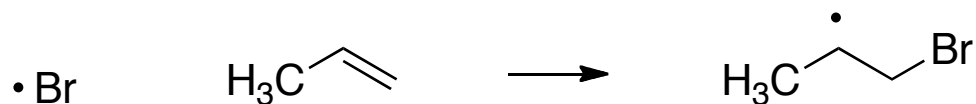
The key is the presence of the peroxide which contains a very weak O-O single bond, this bond breaks under thermal conditions to form oxygen radicals



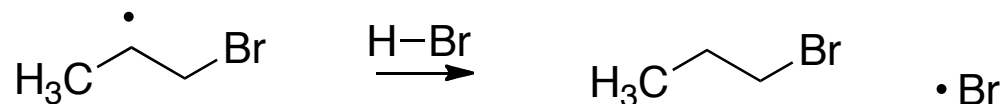
The oxygen radical then reacts with the HBr present



The bromine radical then reacts with the alkene present to form a carbon radical



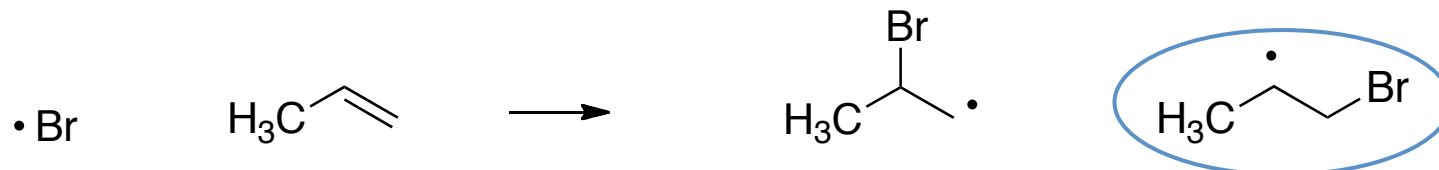
The unstable carbon radical abstracts a hydrogen (not a proton!) from HBr



Because a bromine radical is regenerated, it can react with another alkene to propagate the steps, therefore only a very small amount of initial radicals are needed to run the reaction

Radical Addition to Alkenes

The regiochemistry is therefore controlled by the formation of the carbon radical



Since a 2° radical is more stable than a 1° radical the preferred product for this reaction has the bromine attached to the less substituted carbon (Anti-Markovnikov)

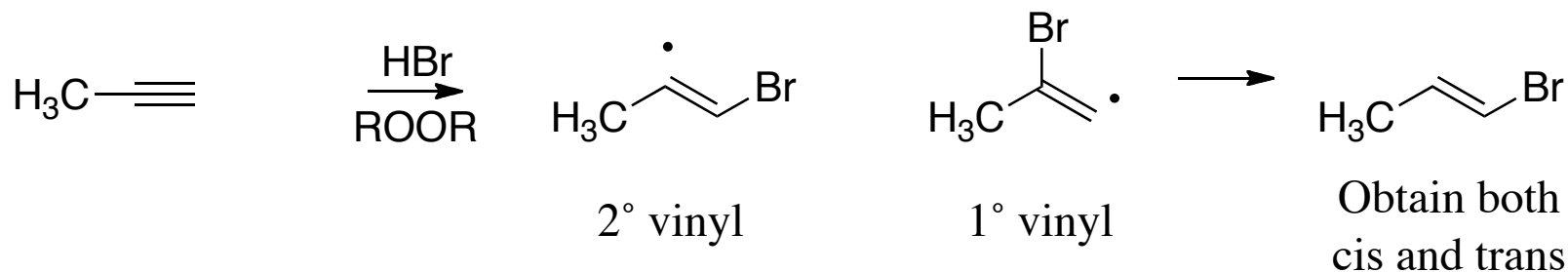
The most stable intermediate is still generated! The intermediate formed though has changed

This reaction, however, only gives the Anti-Markovnikov product for HBr addition, not with either HCl or HI

Only with HBr addition are both propagation steps exothermic, therefore either HCl or HI will prefer the Markovnikov product regardless of whether peroxide is present

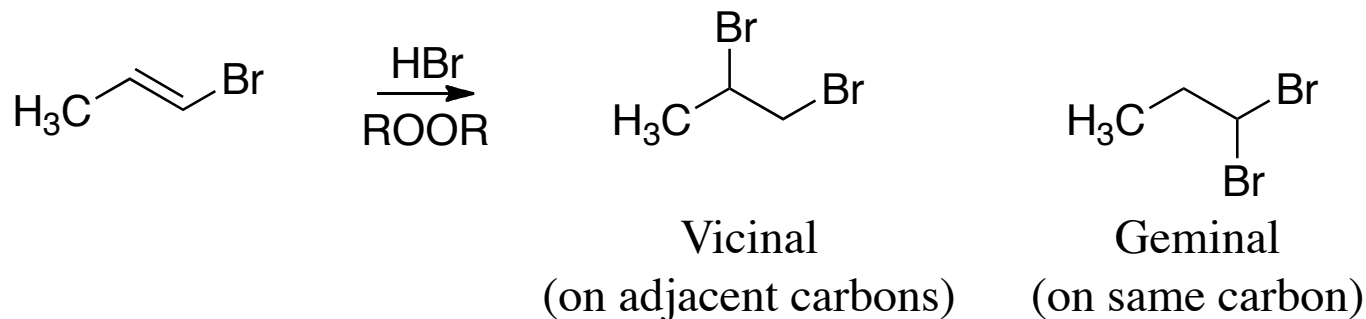
Radical Addition to Alkynes

A similar reaction occurs when HBr is reacted in the presence of peroxides with alkynes



The 2° vinyl radical is more stable than the 1° vinyl radical, thus controlling regiochemistry

Due to the second π bond, HBr can add a second equivalent to obtain a dibrominated product



The radical in resonance with the bromine is more stable than the isolated radical

Therefore the vicinal dibromide is favored over the geminal
(opposite from HBr addition without peroxide)

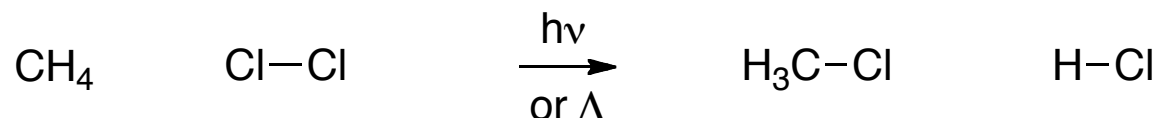
Photohalogenation of Alkanes

Alkanes are relatively unreactive

They will not react in S_N2 , S_N1 , E2 or E1 due to not have a leaving group attached

They also will not undergo alkene or alkyne reactions since they do not have π bonds

One of the few reactions they do undergo, however, is halogenation



When photolyzed, an alkane will react with halogen gas to generate a halogen substituted alkane

As chemists we want to know the mechanism of this reaction (or how does the energy diagram appear)

What we know:

Reaction does not proceed in the dark or in the cold

Reaction occurs with wavelengths corresponding to Cl_2 absorption

Quantum yield is greater than 1

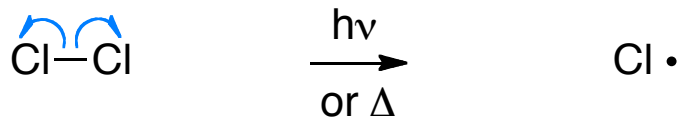
(therefore more moles of product are obtained than moles of photons of light used)

Photohalogenation of Alkanes

This data implies:

- 1) The chlorine molecule absorbs the light to initiate the reaction
- 2) The reaction proceeds in a chain mechanism

To initiate:

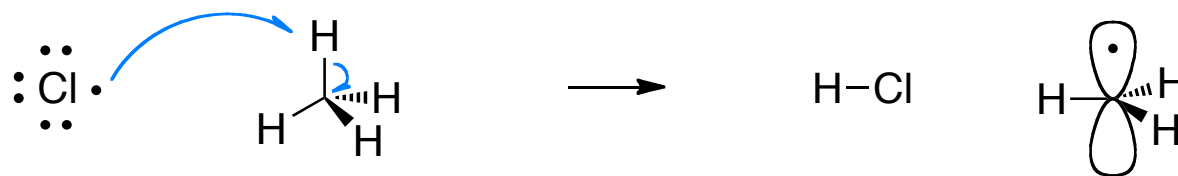


Full Lewis dot structure

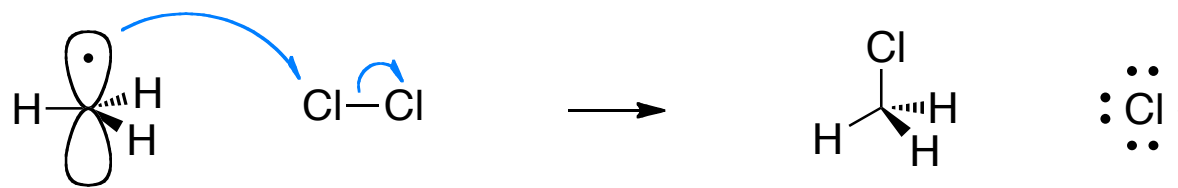
This chlorine radical is a reactive species – it wants to fill its octet

Photohalogenation of Alkanes

The chlorine radical will react with methane to generate a methyl radical



The methyl radical (also a reactive species) will react further

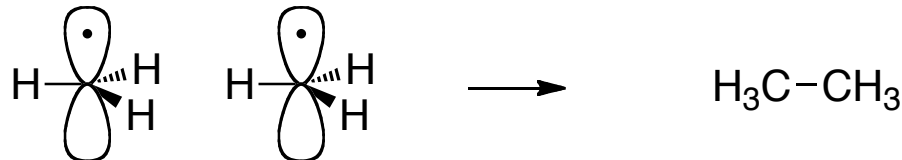
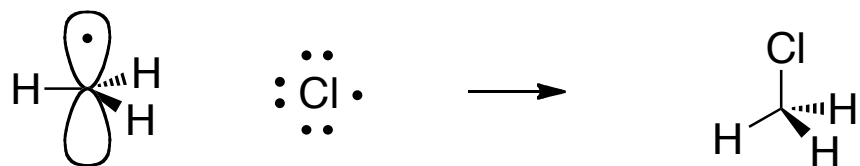


This step creates chloromethane and another reactive species in chlorine radical that will continue the radical chain process

These steps are called propagation steps
(the step creates the same number of reactive intermediates as it begins with)

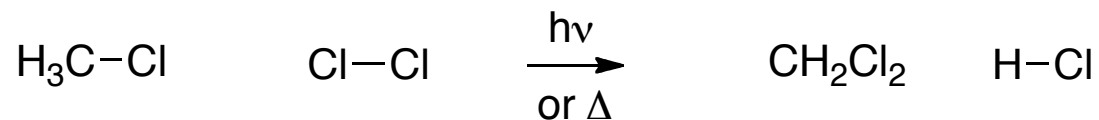
Photohalogenation of Alkanes

A radical chain process will continue until a termination step
(whenever two radicals combine to form less reactive species)



For this reaction any step that destroys radicals will cause the reaction to terminate

Depending upon the number of equivalents, additional halogenations can occur



Photohalogenation of Alkanes

Same Mechanism Can Occur with F₂, Br₂ and I₂

What is the difference compared to Cl₂?

-BOND DISSOCIATION ENERGIES

What is the E_a for the rate-determining step?

Starting material	transition state	E _a (Kcal/mol)
F• + CH ₄	F...H...CH ₃	1.2
Cl• + CH ₄	Cl...H...CH ₃	4
Br• + CH ₄	Br...H...CH ₃	18
I• + CH ₄	I...H...CH ₃	34

Therefore fluorine reacts the fastest and iodine the slowest

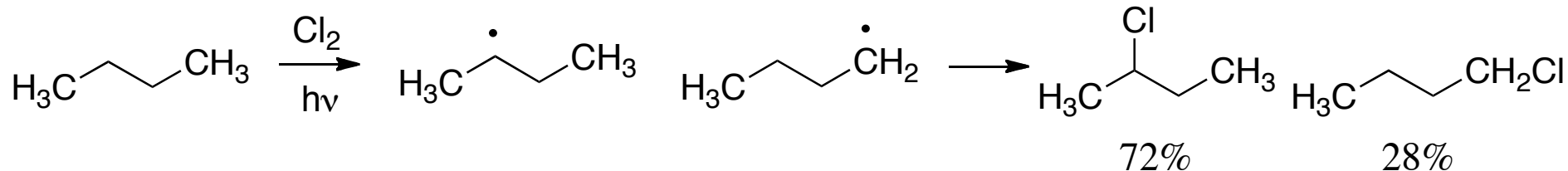
In practice this means that chlorination and bromination are the only reactions run in the lab, fluorination is too fast (potentially explosive) and iodination takes too long

Photohalogenation of Alkanes

If methane is reacted, therefore, either chloromethane or bromomethane can be prepared (with the bromination being a slower reaction than chlorination)

What occurs if other alkanes are photohalogenated?

Consider reacting butane



There are two different radical intermediates that can be generated, which produce two different products from this reaction

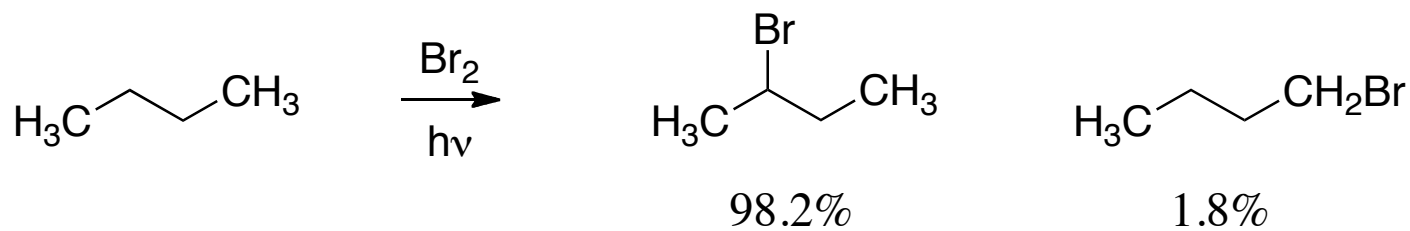
Since the 2° radical is more stable than the 1° radical, the 2° site is favored over the 1°

But the 2-chlorobutane is not obtained exclusively, a significant fraction of 1-chlorobutane is also obtained (in chlorination reactions with multiple radical positions, a mixture of products are obtained)

The selectivity also needs to consider the possible radical sites, therefore $72/28$ ($6/4$) = 3.9 (secondary site reacts 3.9 times faster than primary site)

Photohalogenation of Alkanes

A major difference occurs, however, if a bromination reaction is performed



Instead of obtaining a mixture of products, in essence only the product from the most stable radical intermediate is obtained (selectivity for bromination is $98.2/1.8$ ($6/4$) = 82, 2° carbon reacts 82 times faster than 1° in bromination)

Selectivity of Photohalogenation Reactions

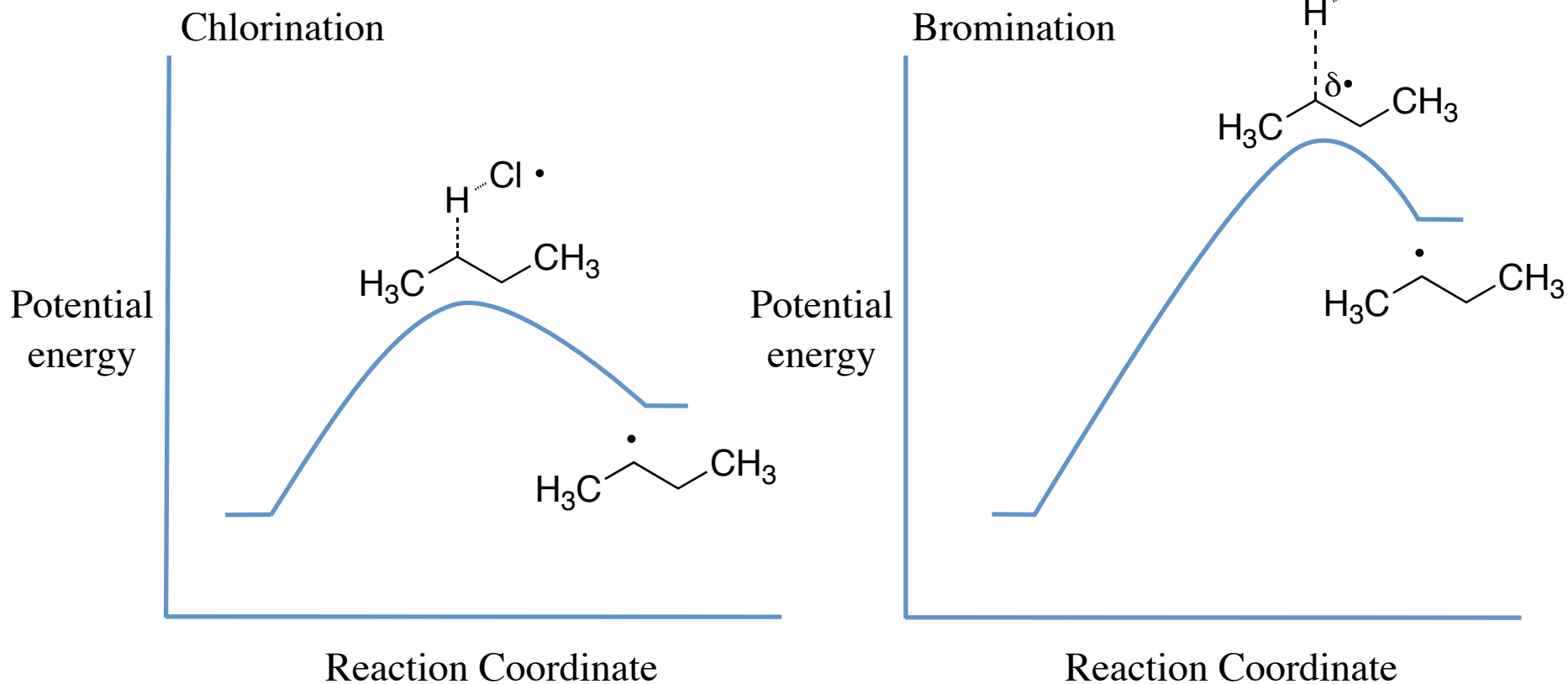
Halogen	1°	2°	3°
F	1	1.2	1.4
Cl	1	3.9	5.1
Br	1	82	1600

reactivity



selectivity

Photohalogenation of Alkanes



Consider the reaction coordinate diagram for a photochlorination versus a photobromination

Both generate a radical as the intermediate structure

The photochlorination is faster, therefore the E_a is smaller

According to Hammond postulate, therefore the transition state for the slower bromination will resemble the radical intermediate more than chlorination and thus the carbon will have more radical character for the bromination than chlorination

Reactivity vs. Selectivity

Another way to use the Hammond postulate in organic reactions is to compare reactivity versus selectivity

Reactivity: how fast is the reaction
(how large is the E_a in the energy diagram)

Selectivity: if more than one site is available for reaction the ratio between each product obtained determines the selectivity
(the difference in E_a for each competing path in the energy diagram)

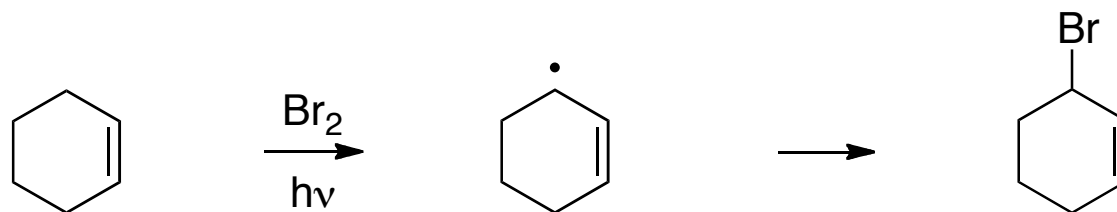
This leads to an almost universal statement in organic chemistry:

FOR A GIVEN REACTION THE MORE REACTIVE, THE LESS SELECTIVE

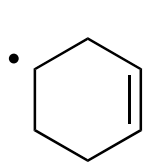
Allylic Halogenation

Due to the selectivity in photobromination reactions,
only the product resulting from the most stable radical intermediate is obtained

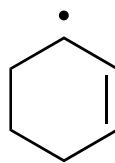
When an alkene is present, a radical in resonance with the alkene (allylic position)
is often more stable than an isolated radical site



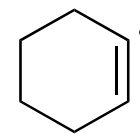
Of the three possible radical structures from cyclohexene, the allylic radical is the most stable



2° radical
Isolated radical



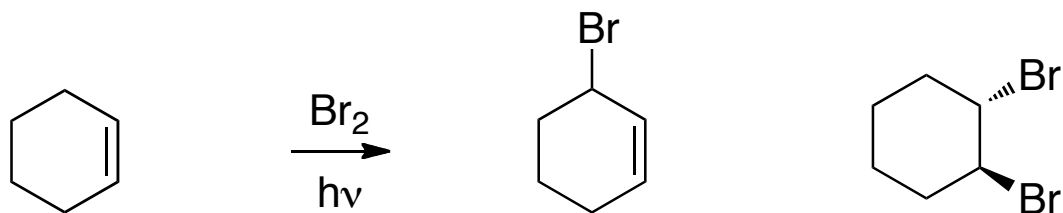
Allylic radical
Most stable due to
resonance



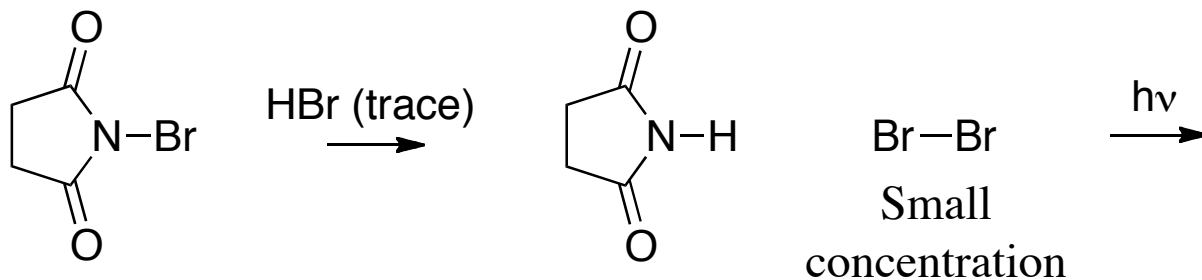
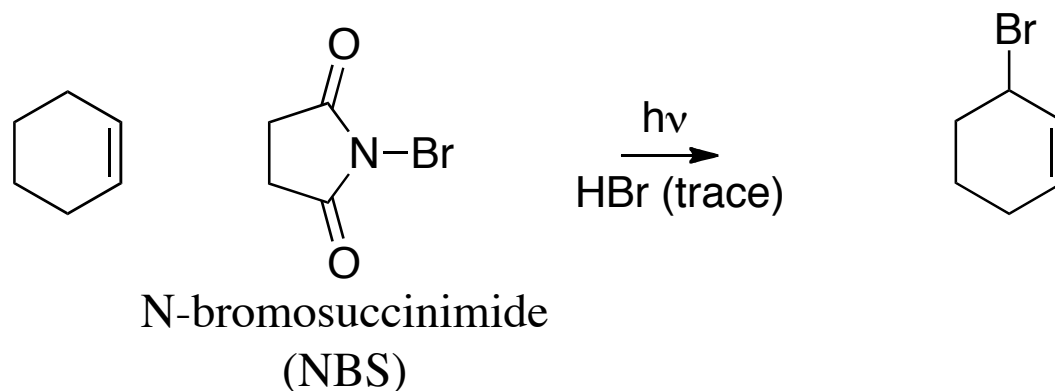
Vinyl radical
Least stable, typically vinyl
radicals not observed

Allylic Halogenation

A problem with reacting an alkene with bromine photolytically is that the dibromo addition to the alkene is a possible side reaction



To lower the amount of side reactions occurring, NBS is often used which causes a lower concentration of Br_2 present to hinder the side reaction

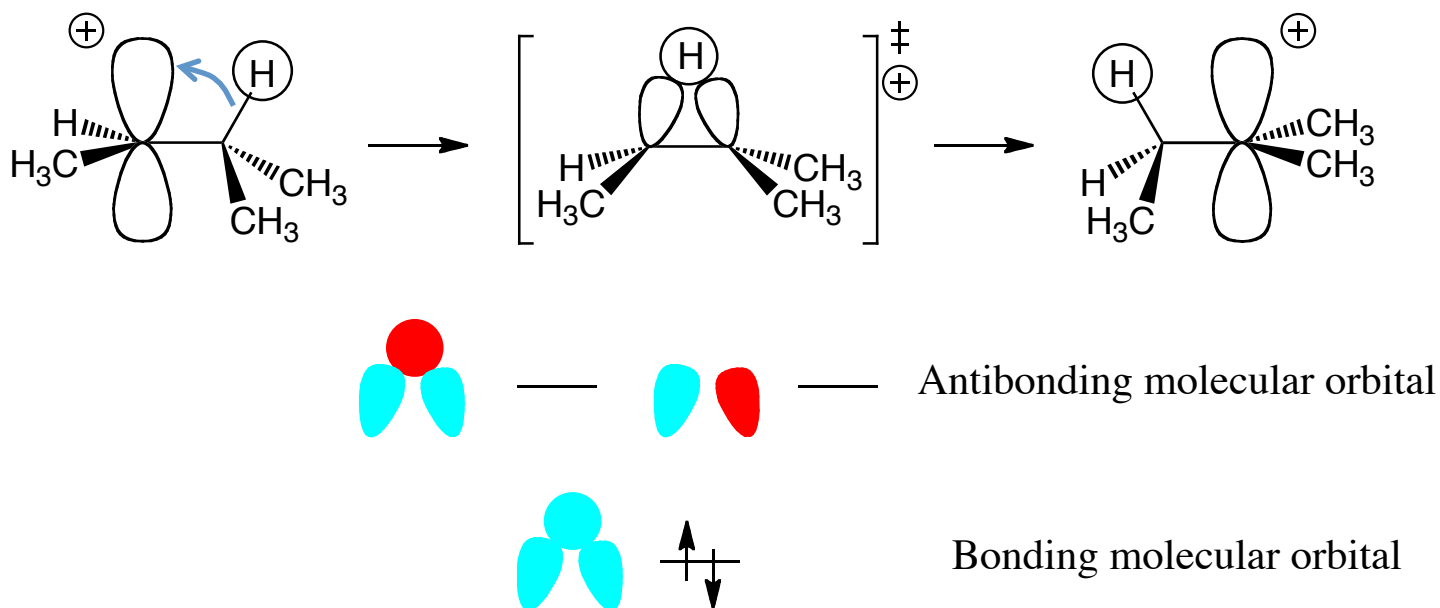


Rearrangements

Rearrangements only occur with cations, not with anions or radicals

Process occurs with an orbital on an adjacent atom interacting with the empty p orbital of the carbocation

Consider the orbital interactions for the transition state for this process

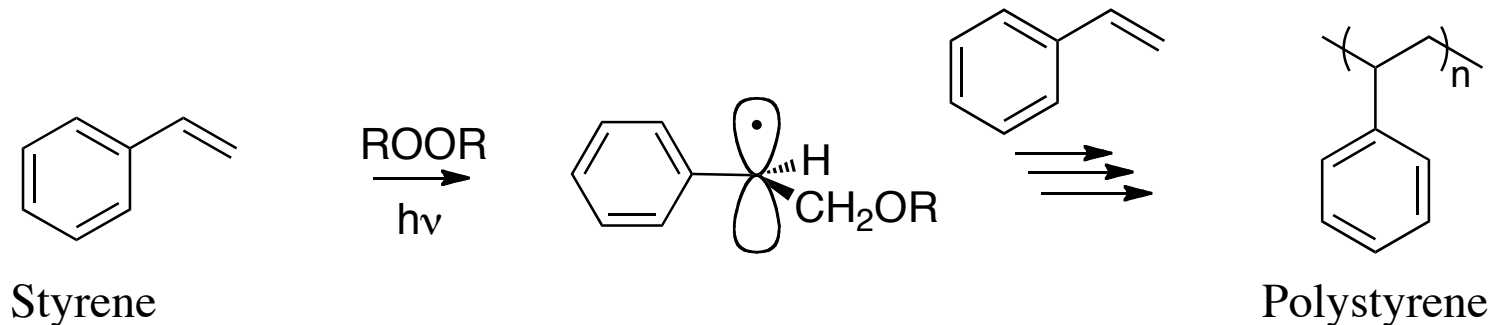


In a cation rearrangement, 2 electrons are involved in a bonding molecular orbital
In a radical or anion rearrangement, additional electrons would be placed in antibonding molecular orbitals (therefore a less stable process)

Radical Polymerization

As observed previously with cations, radicals can also undergo a polymerization route

The key is generating a radical in the presence of a large concentration of alkene, the radical then reacts with a monomer alkene to regenerate a new radical

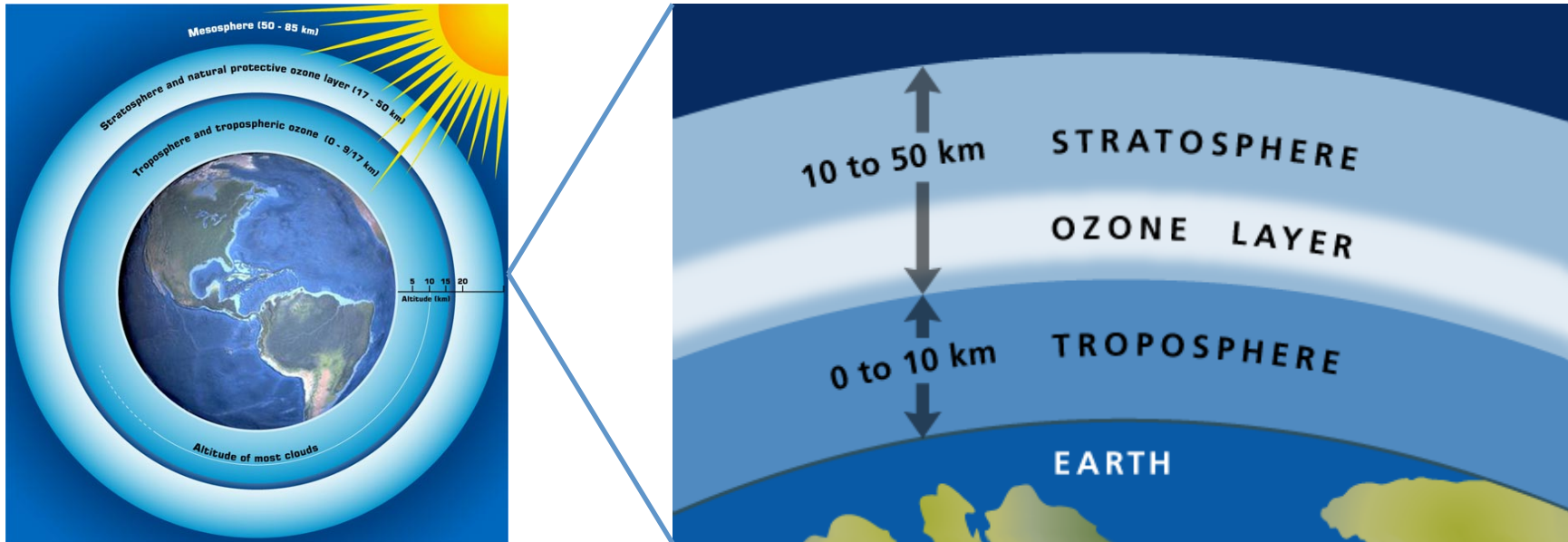


The process continues until the concentration of monomer alkene lowers and termination steps (where two radicals combine) compete in rate

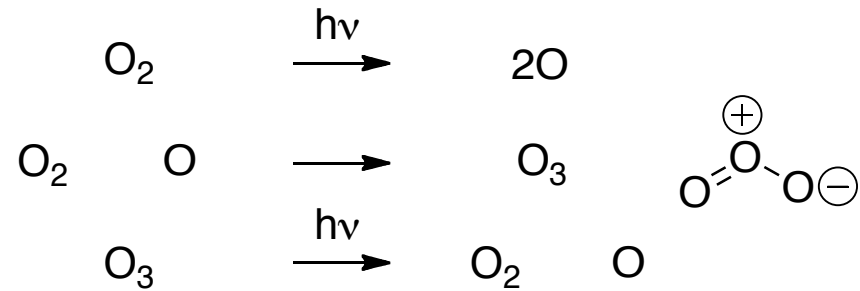
Overall radical polymerizations work well with monomers that can generate a stable radical, the regio and stereochemistry of the polymerization is controlled by the radical stability

Relevance of Radical Chemistry

Ozone Depletion



Chemistry involved in stratosphere

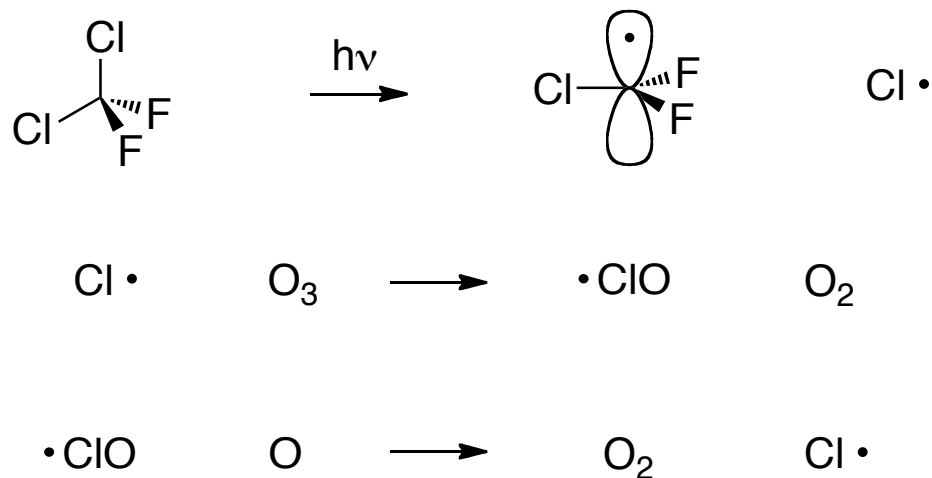


Ozone absorbs light in the 200 – 300 nm range

Ozone Depletion

Carbon Compounds can also React with Ozone

It was discovered that chlorofluorocarbons (CFCs or freons) can react with ozone



Therefore the concentration of ozone decreases with more CFCs in the stratosphere and the 200 – 300 nm sunlight is not blocked as efficiently

Same type of chemistry occurs with bromine radicals (called halons)

Ozone Depletion

Biological entities can be destroyed with low wavelength (high energy) sunlight

One estimate is that decreasing the ozone concentration by 1%
causes a 1-3 % increase in skin cancer

Solutions: replace chlorine (and bromine) containing carbon species

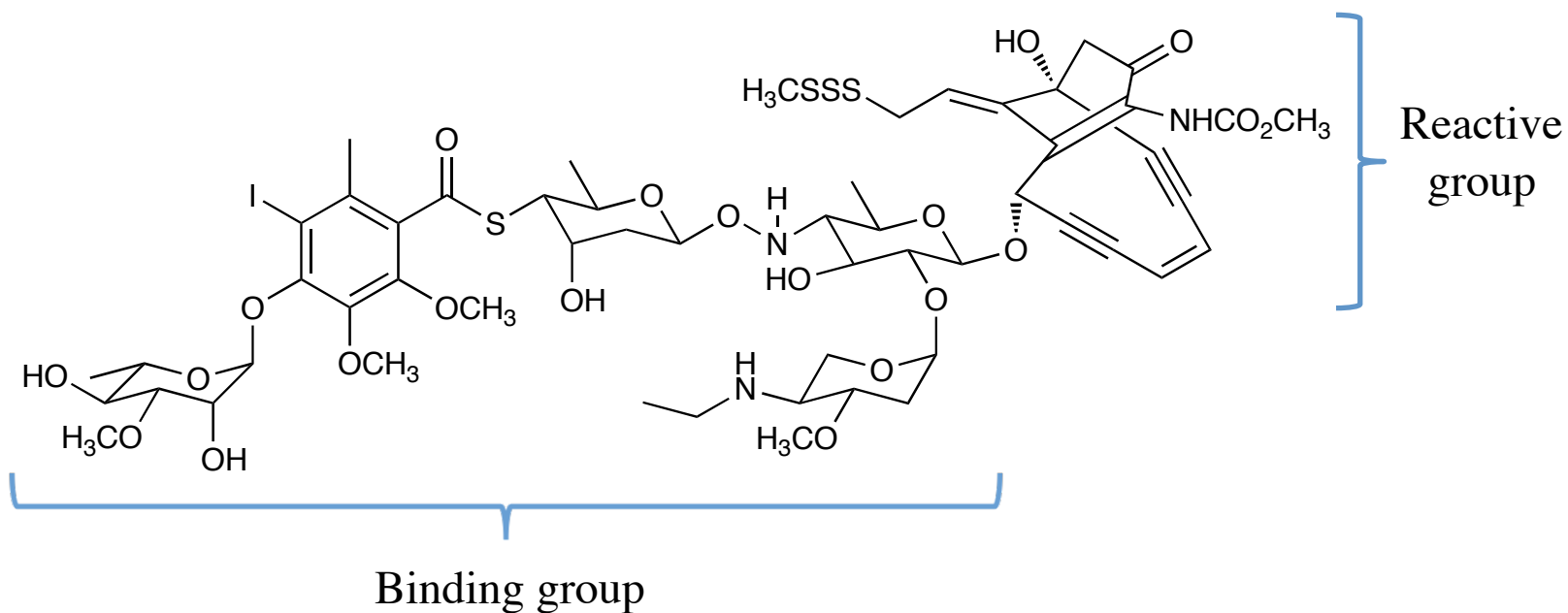
Possibilities:

CHClF_2 less chlorine
 CH_2FCF_3 HFC (hydrofluorocarbons)

Radical Interactions in Drug Development

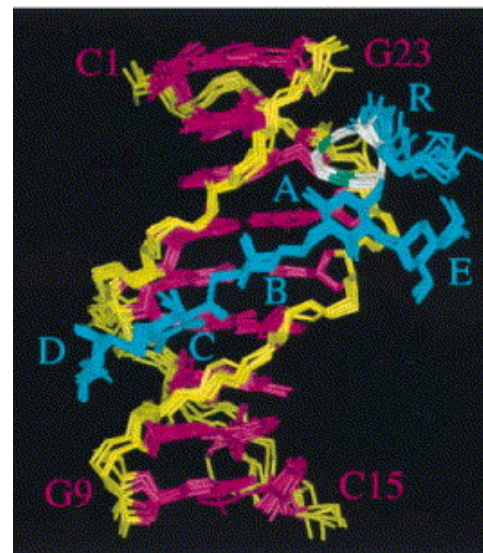
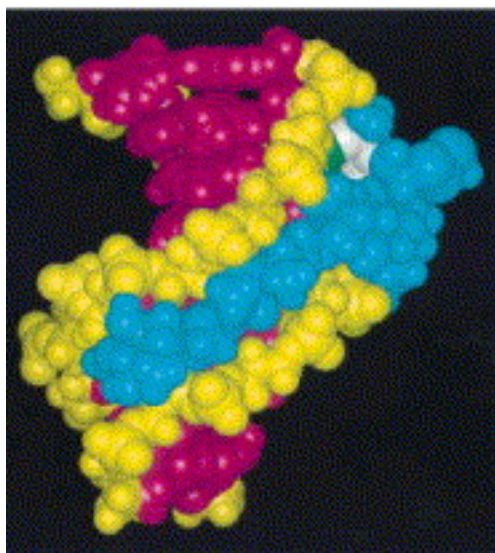
As observed, radicals are reactive species
-when generated near biological targets, irreversible damage may occur

An example: Calicheamicin γ_1



Radical Interactions in Drug Development

Calicheamicin binds specifically with the minor groove of DNA



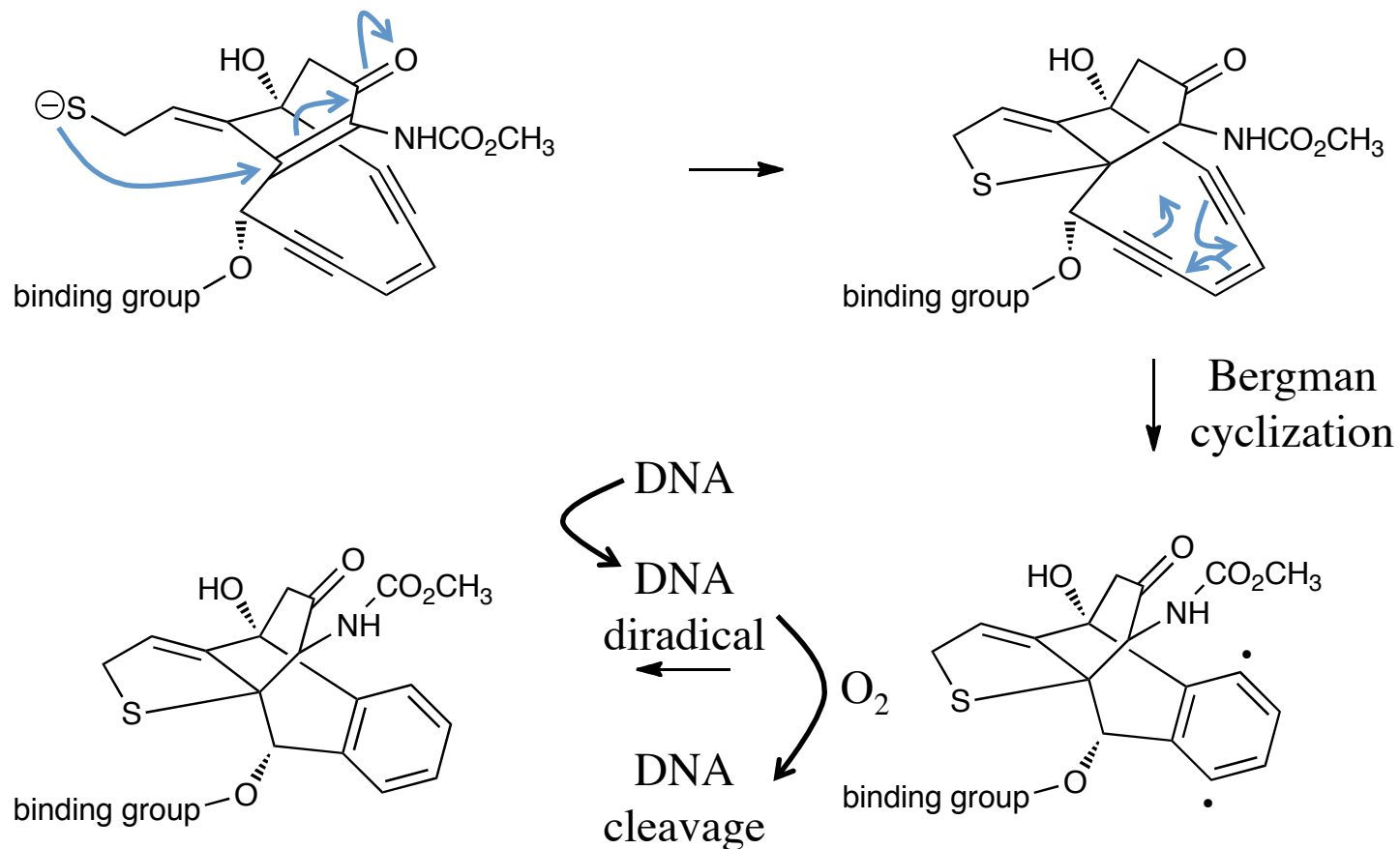
Yellow and magenta correspond to DNA backbone,
Blue is Calicheamicin

The binding of Calicheamicin brings reactive group (white in picture)
near DNA backbone

*R.A. Kumar, N. Ikemoto, D.J. Patel, *J. Mol. Biol.*, **1997**, 265, 187.

Radical Interactions in Drug Development

Reactive part (called enediyne) forms a diradical



This DNA cleavage can kill cancer cells – used in drug Mylotarg for acute leukemia