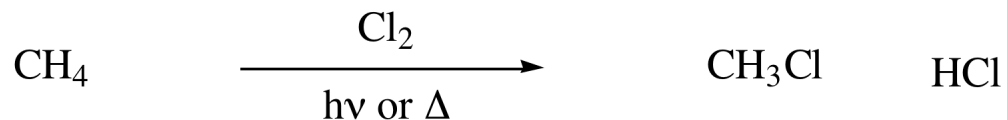


Studying an Organic Reaction

How do we know if a reaction can occur?

And – if a reaction can occur what do we know about the reaction?



Information we want to know:

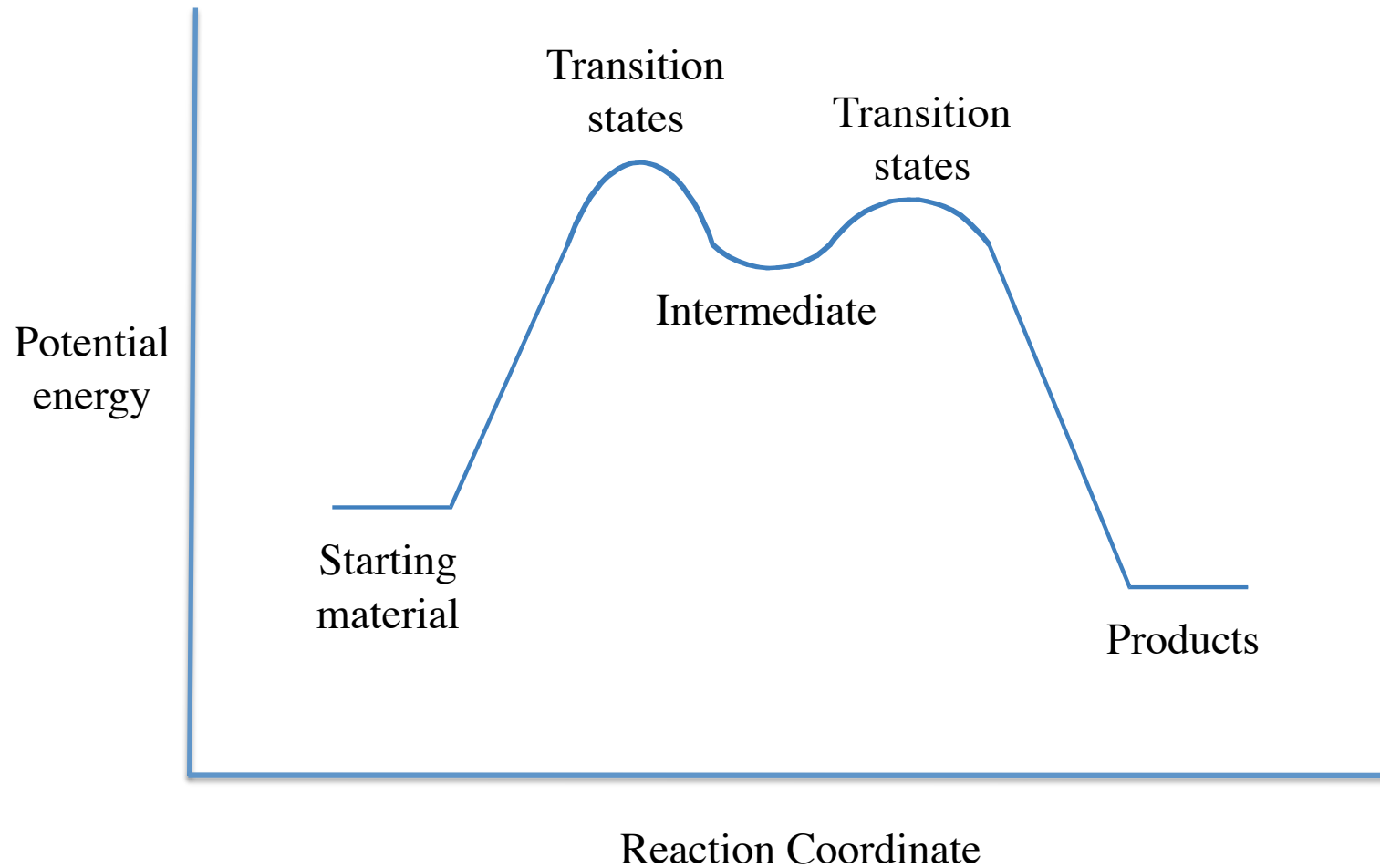
How much heat is generated?

How fast is the reaction?

Will a catalyst speed up the reaction?
(and if so what should the catalyst be?)

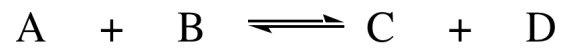
Are any intermediates generated?

All of this information is included in an Energy Diagram



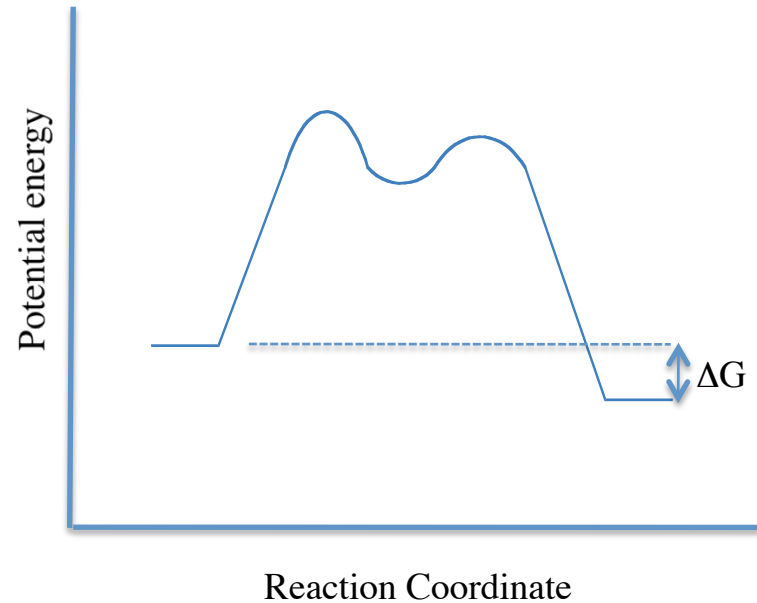
Equilibrium Constants

Equilibrium constants (K_{eq}) indicate thermodynamically whether the reaction is favored in the forward or reverse direction and the magnitude of this preference



$$K_{eq} = \frac{[C][D]}{[A][B]}$$

= ([products]) / ([starting material])



Gibb's Free Energy

The K_{eq} is used to determine the Gibb's free energy

$$\Delta G = (\text{free energy of products}) - (\text{free energy of starting materials})$$

If we use standard free energy then ΔG° (25°C and 1 atm)

$$K_{eq} = e^{(-\Delta G^\circ/RT)}$$

or

$$\Delta G^\circ = -RT(\ln K_{eq}) = -2.303 RT(\log_{10} K_{eq})$$

A favored reaction thus has a negative value of ΔG° (energy is released)

Contributions to Free Energy

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

The free energy term has two contributions: enthalpy and entropy

Enthalpy (ΔH°): heat of a reaction (due to bond strength)

Exothermic reaction: heat is given off by the reaction ($-\Delta G^\circ$)

Endothermic reaction: heat is consumed by the reaction ($+\Delta G^\circ$)

Entropy (ΔS°): a measure of the freedom of motion

- Reactions (and nature) always prefer more freedom of motion

Organic reactions are usually controlled by the enthalpy

Bond Dissociation Energies

The free energy of organic reactions is often controlled by the enthalpic term

-The enthalpic term in organic reactions is often controlled by the energy of the bonds being formed minus the energy of the bonds being broken

The energies of bonds is called the Bond Dissociation Energy

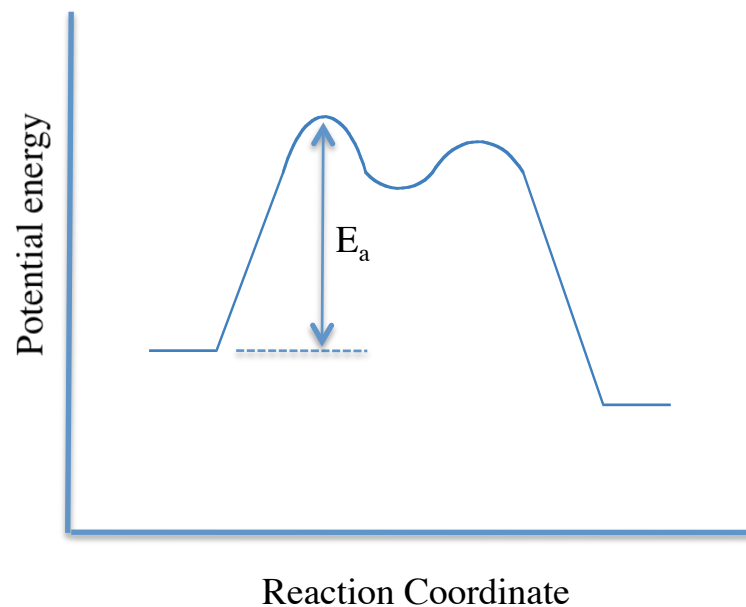
Many types of bonds have been recorded (both experimentally and computationally)
we can therefore predict the equilibrium of a reaction by knowing these BDE's

Kinetics

A second important feature is the
RATE of a reaction

The rate is not determined by K_{eq} ,
But instead by the energy of activation
(E_a)

Knowing the E_a of a reaction tells us
how fast a reaction will occur



Rate Equation

The rate of a reaction can be written in an equation that relates the rate to the concentration of various reactants



$$\text{Rate} = k_r [A]^a [B]^b$$

The exponents are determined by the number of species involved for the reaction step
- The exponents also indicate the “order” of the reaction with respect to A and B

Overall order of the reaction is a summation of the order for each individual reactant

Relationship between Rate and Energy of Activation

Referring back to our energy diagram the rate can be related to the energy of activation (E_a)

$$k_r = Ae^{(-E_a/RT)}$$

A is the Arrhenius “preexponential” factor

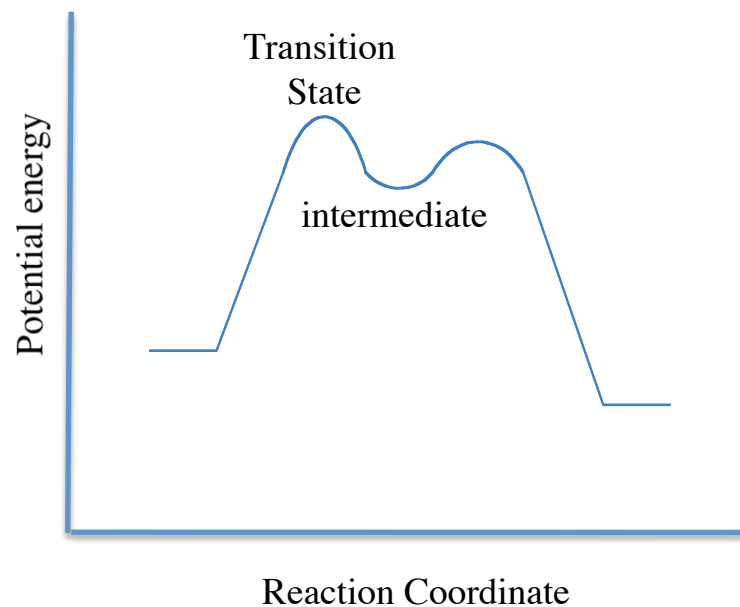
E_a is the minimum kinetic energy required to cause the reaction to proceed

Transition States vs. Intermediates

A transition state is an unstable species
(it has no measurable lifetime)

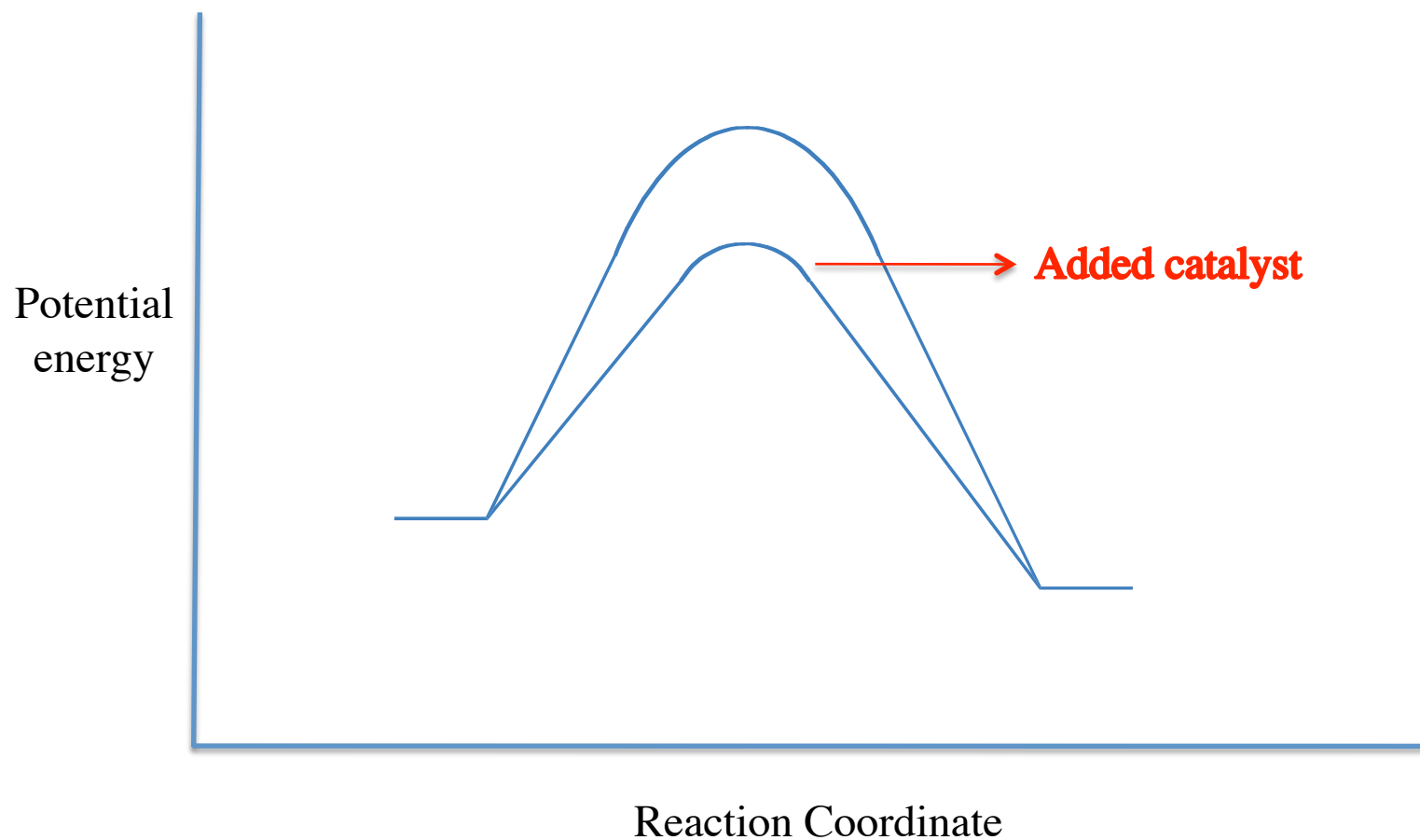
An intermediate has a measureable lifetime
(it can be isolated in theory)

The energy of activation refers to the energy difference between the starting material and the transition state along the reaction coordinate



Effect of Catalyst

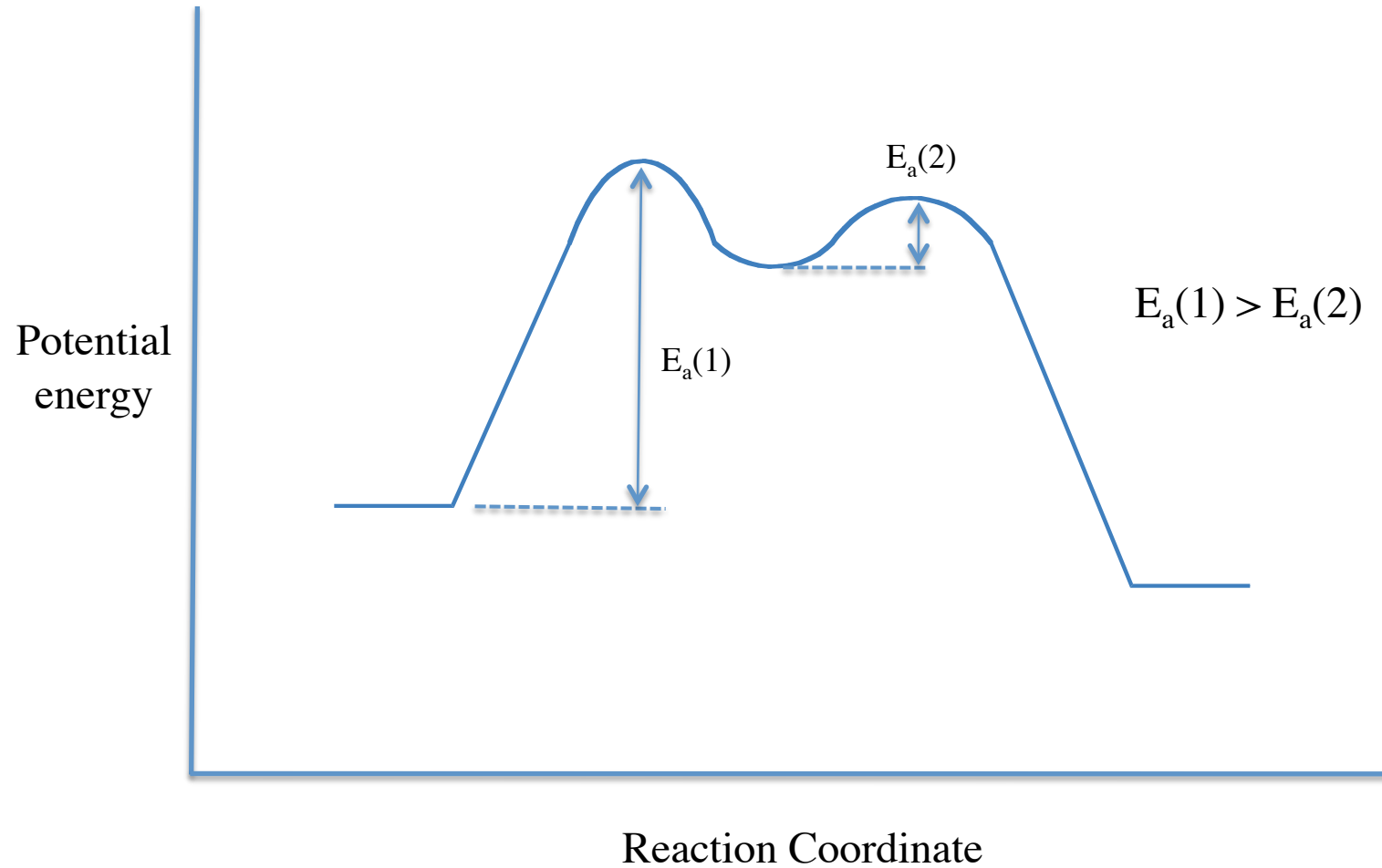
A catalyst only affects the energy of activation
(starting material and product energies are unaffected, therefore K_{eq} is the same)



A catalyst therefore needs to stabilize the transition state structure
-not starting material or products

Multistep Reactions

In a multistep reaction, the overall reaction rate is determined by the highest energy barrier along the reaction coordinate

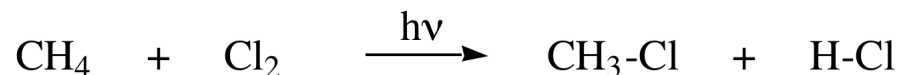


Referred to as the rate determining step

Let's Look at the Reactions of Alkanes

Most alkanes are relatively inert

Halogenation is one reaction type for alkanes



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

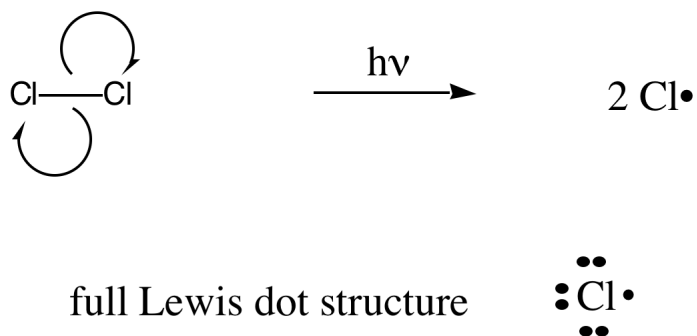
Reaction occurs with wavelengths corresponding to Cl_2 absorption

Quantum yield is greater than 1
(therefore more moles of product are obtained than moles of photons of light used)

This data implies:

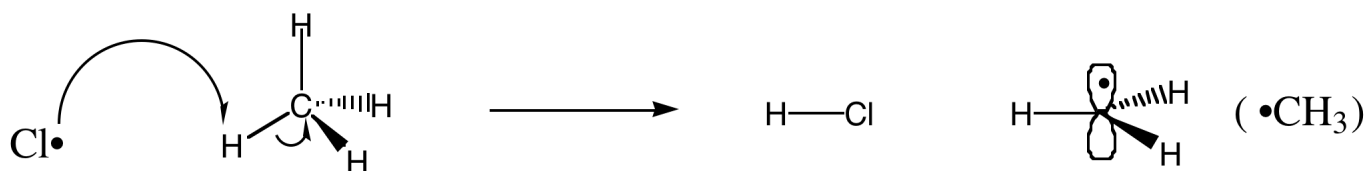
- 1) The chlorine molecule absorbs the light to initiate the reaction
- 2) The reaction proceeds in a chain mechanism

To initiate:

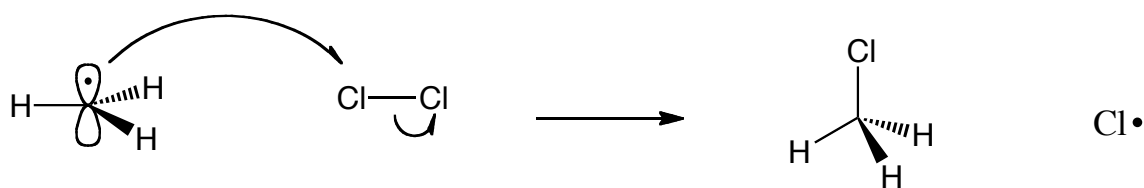


This chlorine radical is a reactive species – it wants to fill its octet

The chlorine radical will react with methane



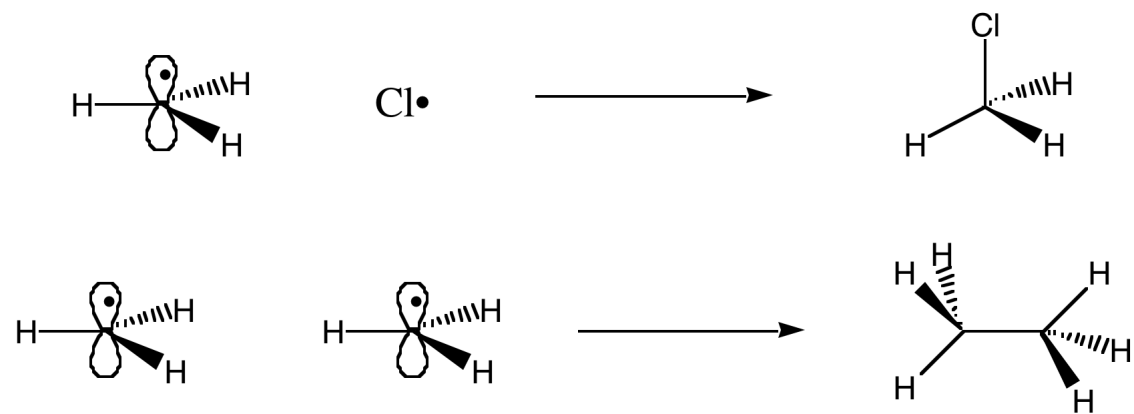
The methyl radical (also a reactive species) will react further



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

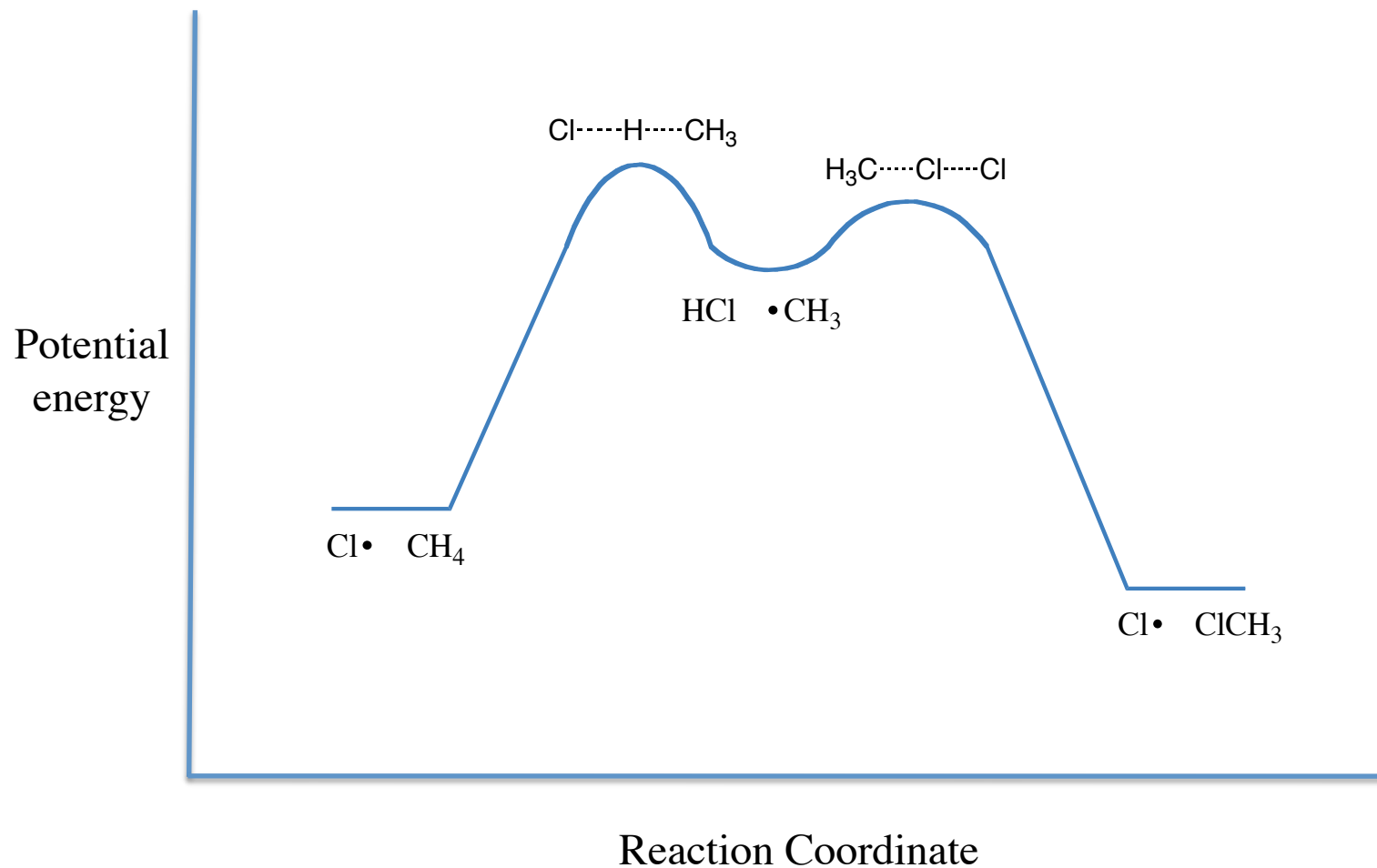
These steps are called propagation steps
(the step creates the same number of reactive intermediates as it begins with)

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

How Does this Mechanism Look Like in an Energy Diagram?



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?

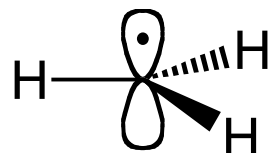
Starting material	transition state	E _a (Kcal/mol)
F• + CH ₄	F...H...CH ₃	1.2
Cl• + CH ₄	Cl...H...CH ₃	4
Br• + CH ₄	Br...H...CH ₃	18
I• + CH ₄	I...H...CH ₃	34

Therefore fluorine reacts the fastest and iodine the slowest

Stability of Reactive Intermediates

Methyl radical ($\text{CH}_3\bullet$) is a reactive intermediate
(its outer shell is not filled)

Structure: sp^2 hybridized with single electron in remaining p orbital



This species is electron deficient
(only 7 electrons in the outer shell)

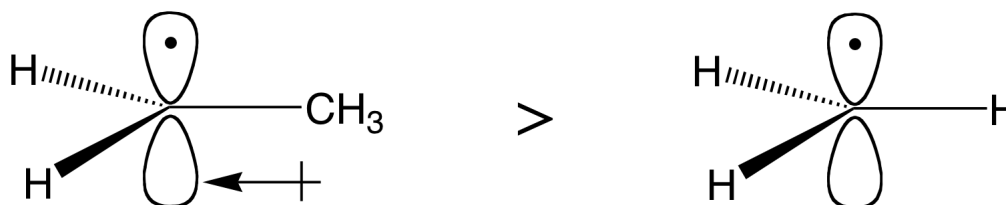
How can we Stabilize $\text{CH}_3\cdot$?

Since it is electron deficient we need to supply extra electron density to stabilize

Ways to add extra electron density:

1) Inductive effect

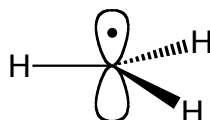
Have carbon-carbon bonds that can inductively supply electron density



Therefore more substituted radical sites are more stable

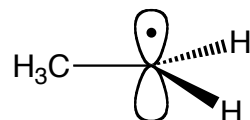
Remember the nomenclature for alkyl sites
-use same naming for radical sites

Methyl radical



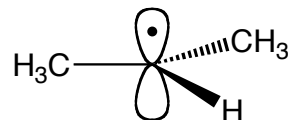
no alkyl substituents

primary radical (1°)



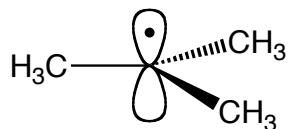
1 alkyl substituent

secondary radical (2°)



2 alkyl substituents

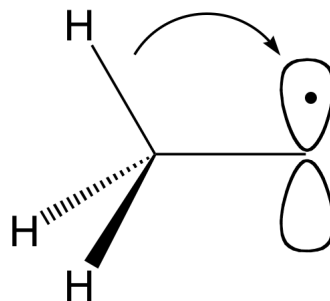
tertiary radical (3°)



3 alkyl substituents

2) Hyperconjugation

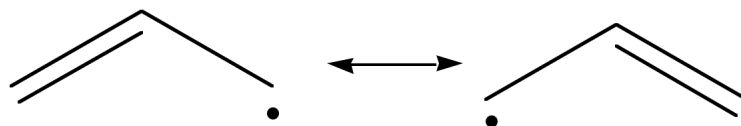
-Refers to neighboring C-H bond being able to donate electron density to electron deficient site



Hyperconjugation stability also increases with increasing number of substituents
(have more neighboring C-H bonds to potentially donate electron density)

3) Resonance

Unsaturated sites in conjugation with radical sites will offer stabilization by allowing electron deficient site to be spread over more atoms



Remember from previous discussions, resonance is primarily observed when there are p orbitals on adjacent sites due to π bonds or when there are atoms with lone pair of electrons adjacent to site

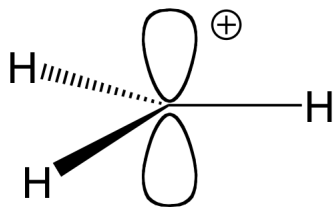
Must have p orbitals in conjugation

Other Reactive Species

Important to know the characteristics of these reactive species because many mechanisms have one somewhere along the reaction coordinate

CARBOCATIONS

Formal positive charge at a carbon site



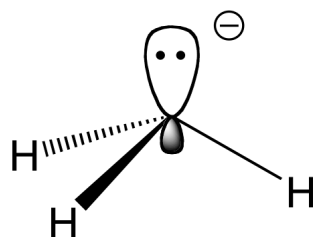
also sp^2 hybridized
only 6 electrons in outer shell

Carbocations are even more electron deficient than a radical site

Therefore same stability factors as a radical

CARBANIONS (carbon anions)

The carbon atom now has a filled outer shell of electrons

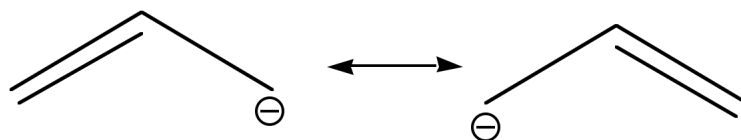


Remember that lone pairs of electrons generally fill hybridized orbitals
therefore the methyl carbanion is sp^3 hybridized
(changes to sp^2 if resonance is available with lone pair)

A carbanion is electron rich – it has an excess of electron density
therefore stability decreases with increasing number of substituents

Carbanions want to lower electron density
-not add more

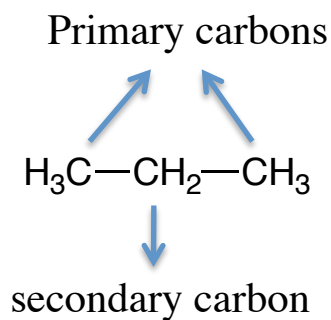
Resonance, though, still stabilizes a carbanion
-allows negative charge to delocalize over more atoms



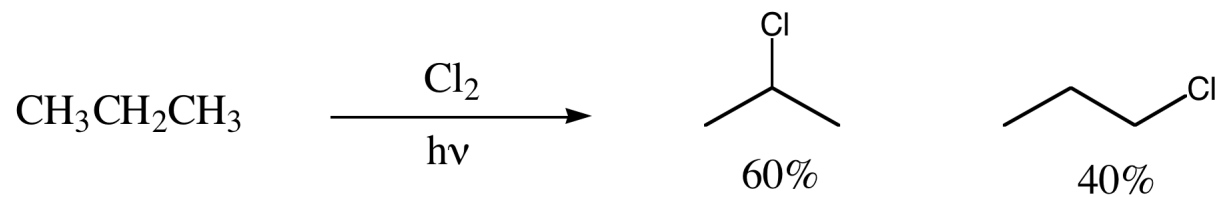
Similar to acid strengths observed earlier where delocalizing a negative charge
will make the conjugate more acidic

What happens when an alkane is reacted in a halogenation reaction when various alkyl sites could react?

For simplest example consider propane:



There are both primary and secondary carbon positions



2° site is favored over the 1° site

The energetic difference is greater than 60% / 40%

Must also consider the possible sites for reaction

In propane:

There are 6 primary hydrogens
and only 2 secondary hydrogens

$$40\% / 6 = 6.66\% \text{ per } 1^\circ \text{ hydrogen}$$

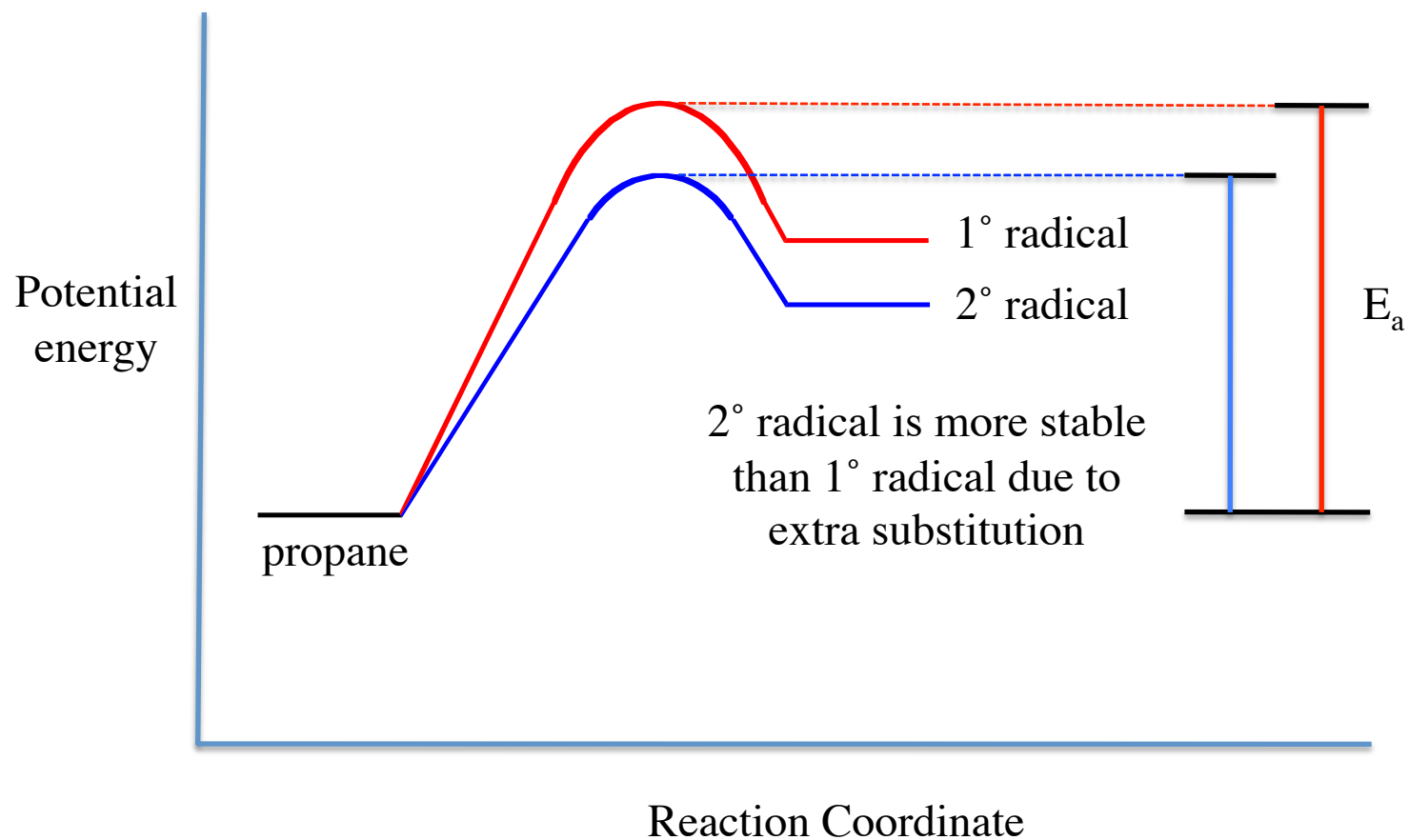
$$60\% / 2 = 30\% \text{ per } 2^\circ \text{ hydrogen}$$

Therefore the selectivity for 2° hydrogen over 1° hydrogen is greater

$$\text{Selectivity} = 30 / 6.66 = 4.5 \text{ } 2^\circ/1^\circ \text{ for chlorination}$$

What causes the selectivity?

Consider only the rate determining step in the energy diagram:

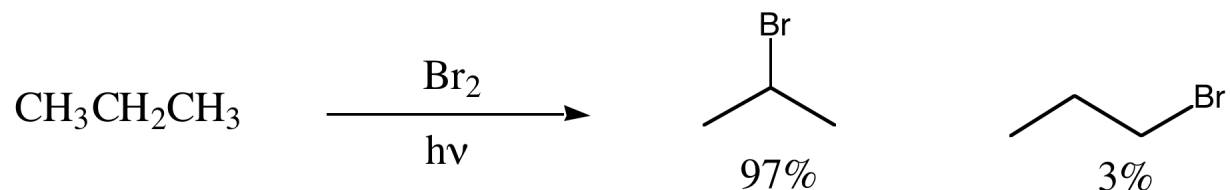


What Occurs with Bromination?

We already saw that bromination will be slower than chlorination
(there is a higher E_a for bromination than chlorination)

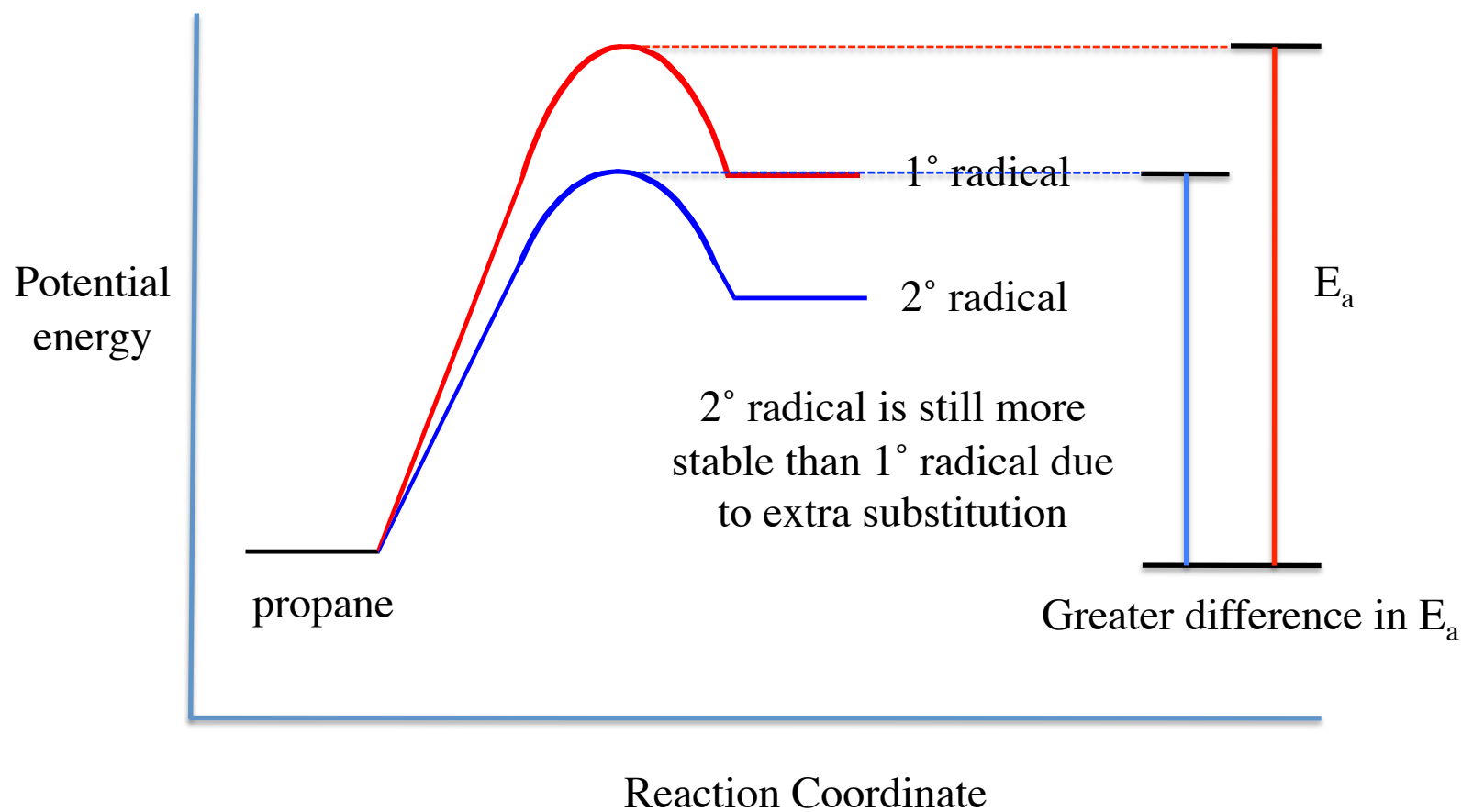
This requires the reaction to be heated in order to get the reaction to proceed

It is also found that brominations are much more selective



Almost entirely form the product resulting from the more stable radical
(usually for brominations only the most stable radical site is brominated!)

How Does the Energy Diagram Reflect this Selectivity?



As reaction becomes more endothermic there is a greater difference in E_a
- Causes a greater selectivity

Hammond Postulate

In an ENDOTHERMIC reaction, the transition state is closer to the PRODUCTS in energy and structure. In an EXOTHERMIC reaction, the transition state is closer to the REACTANTS in energy and structure

In the halogenation of propane the reactant is the same for both the 1° and 2° sites
(same energy)

The product is different in energy (which is actually the intermediate radical)
due to the stability of the radical at a 2° site relative to a 1° site

If the transition states are more “reactant like” the energy will be similar
and thus the selectivity will be low

If the transition states are more “product like” the energy difference will be greater
and thus the selectivity will be higher

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)

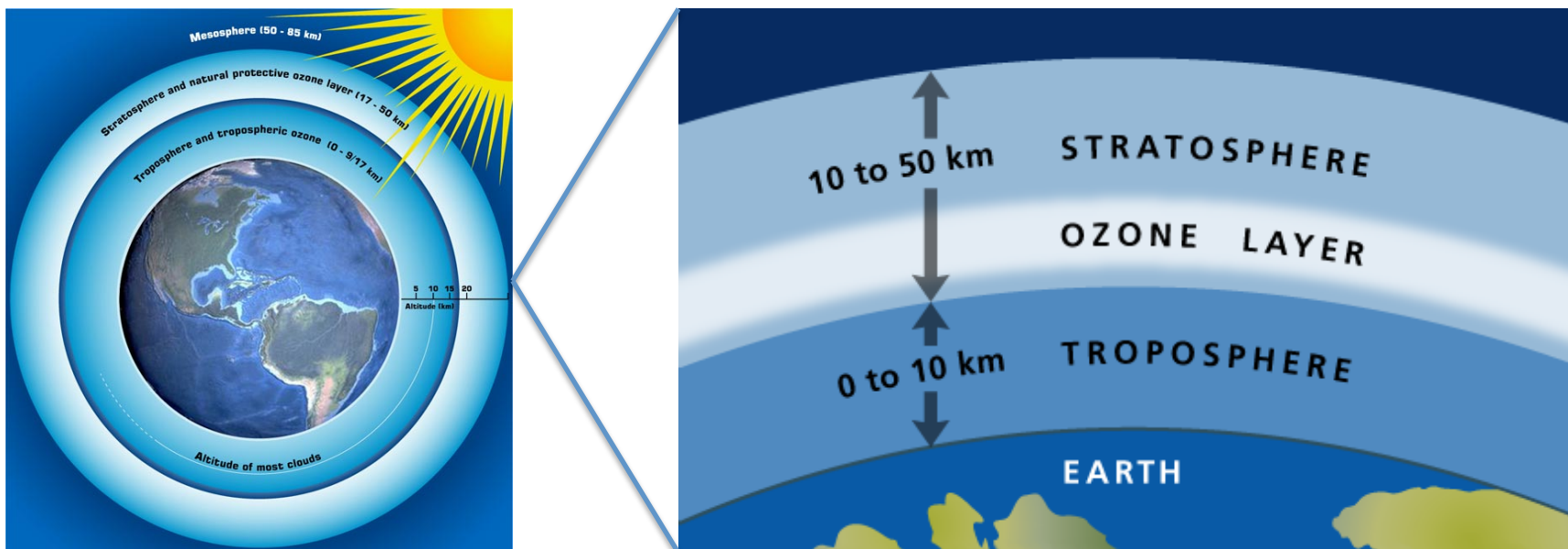
Selectivity: if more than one site is available for reaction the ratio between each product obtained determines the selectivity
(the difference in E_a for each competing path in the energy diagram)

This leads to an almost universal statement in organic chemistry:

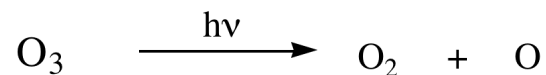
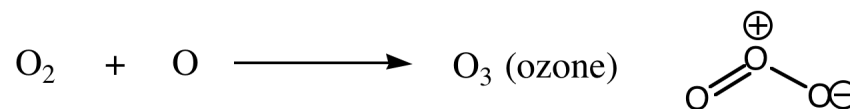
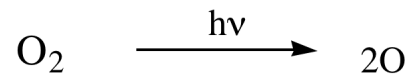
FOR A GIVEN REACTION THE MORE REACTIVE, THE LESS SELECTIVE

Relevance of Radical Chemistry

Ozone Depletion



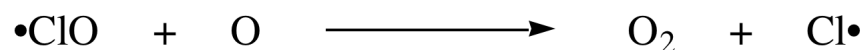
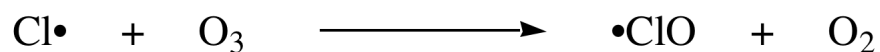
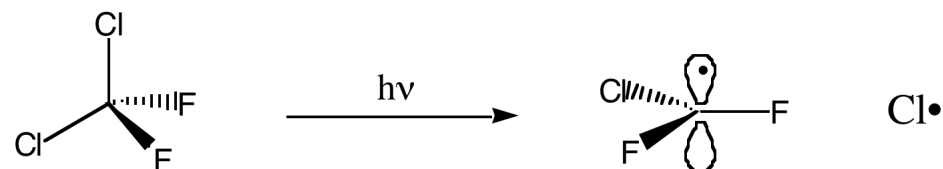
Chemistry involved in stratosphere



Ozone absorbs light in the 200 – 300 nm range

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)

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

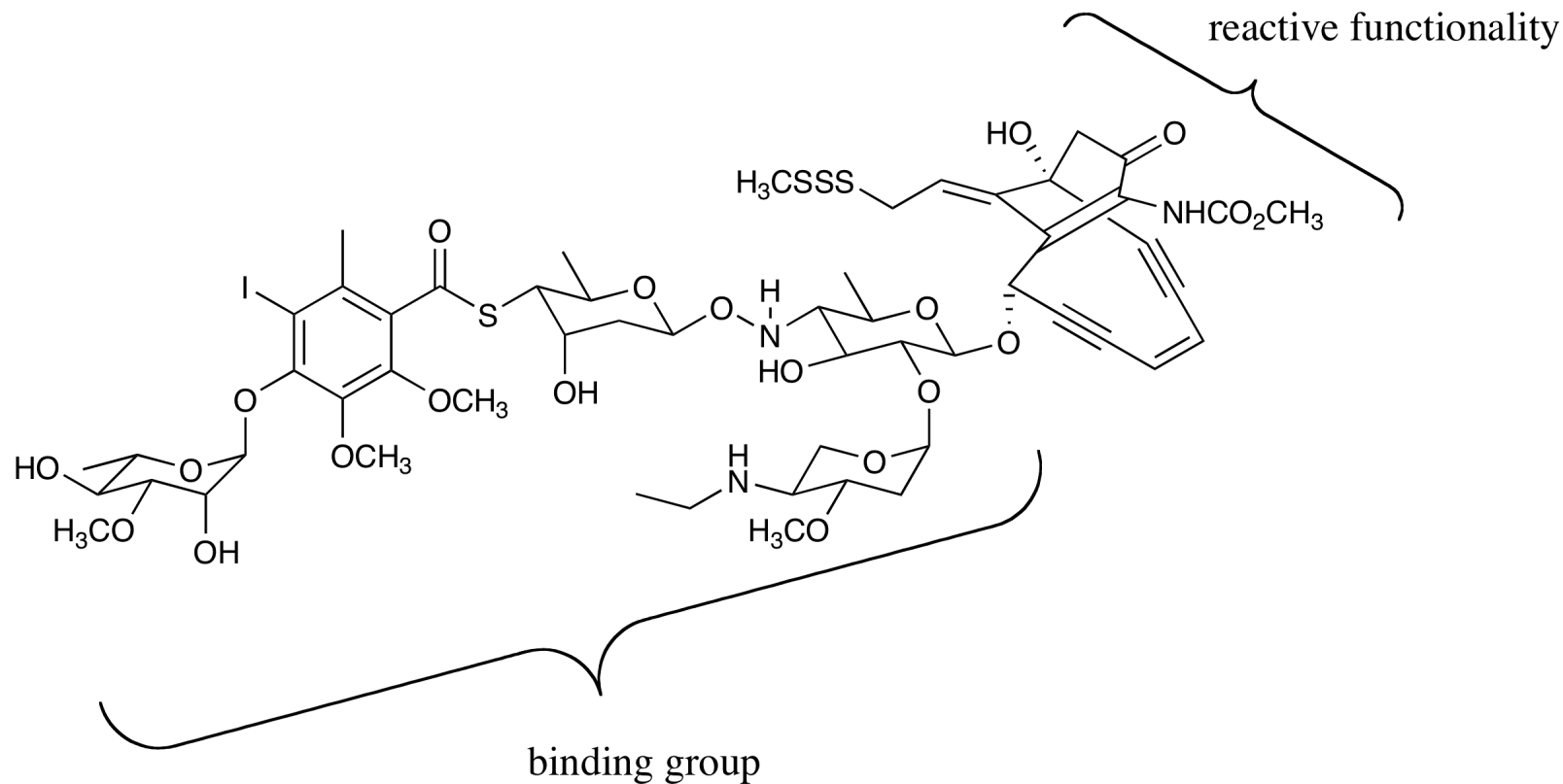
Possibilities:

CHClF_2 less chlorine
 CH_2FCF_3 HFC (hydrofluorocarbons)

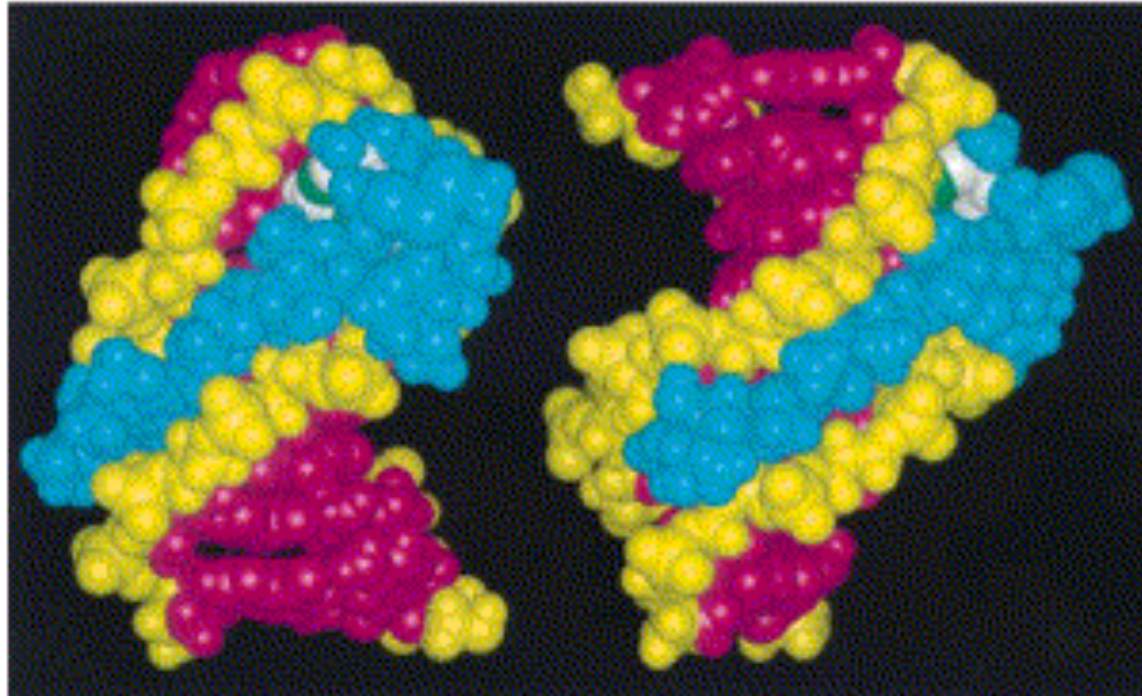
Radical Interactions in Drug Development

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

An example: Calicheamicin γ_1



Calicheamicin binds specifically with the minor groove of DNA

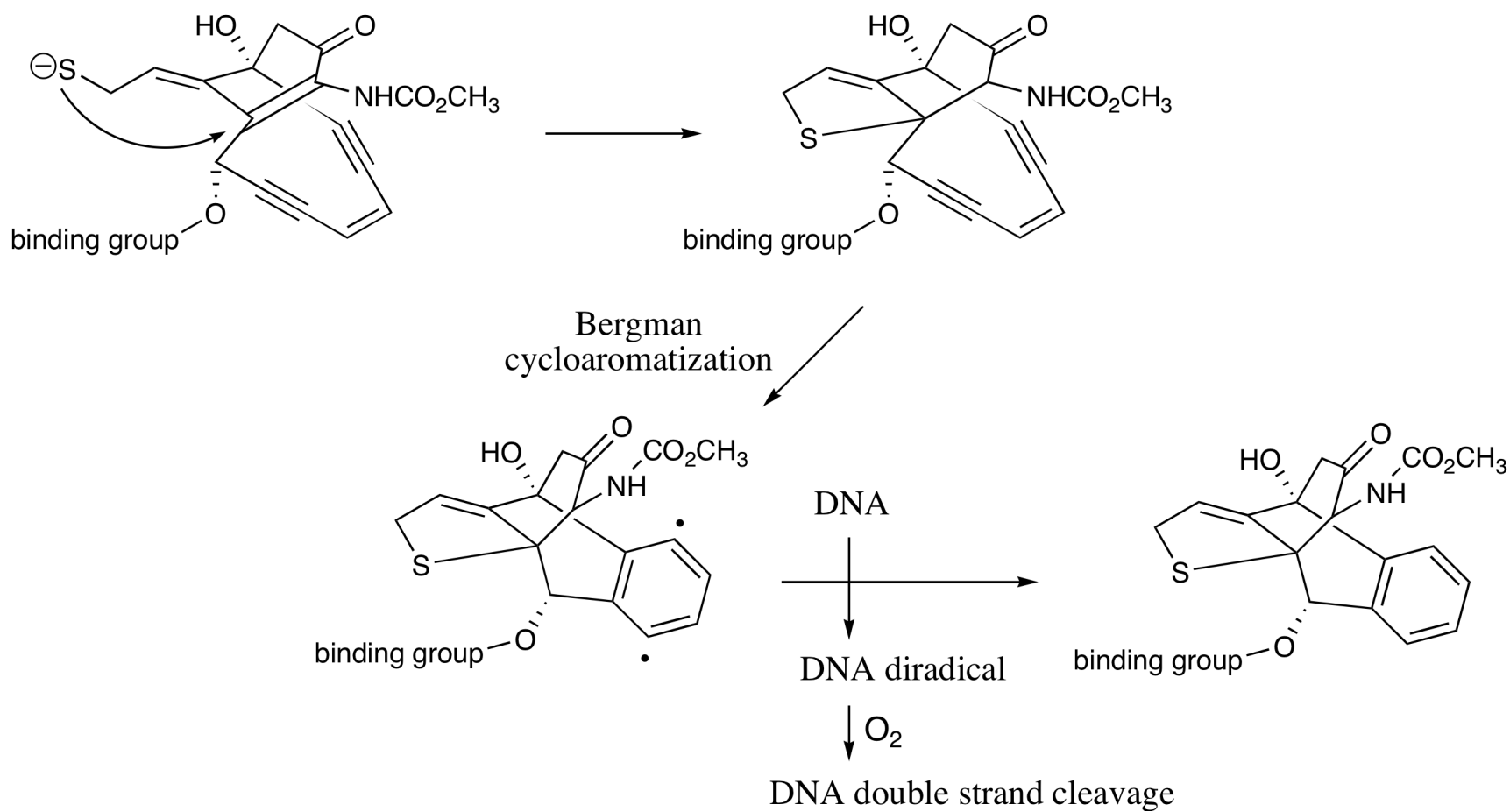


Yellow and magenta correspond to DNA backbone,
Blue is Calicheamicin

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.

Reactive part (called enediyne) forms a diradical



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