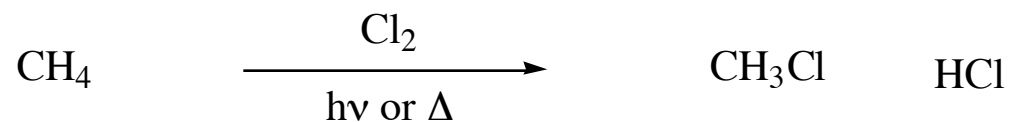


Study of Reactions

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

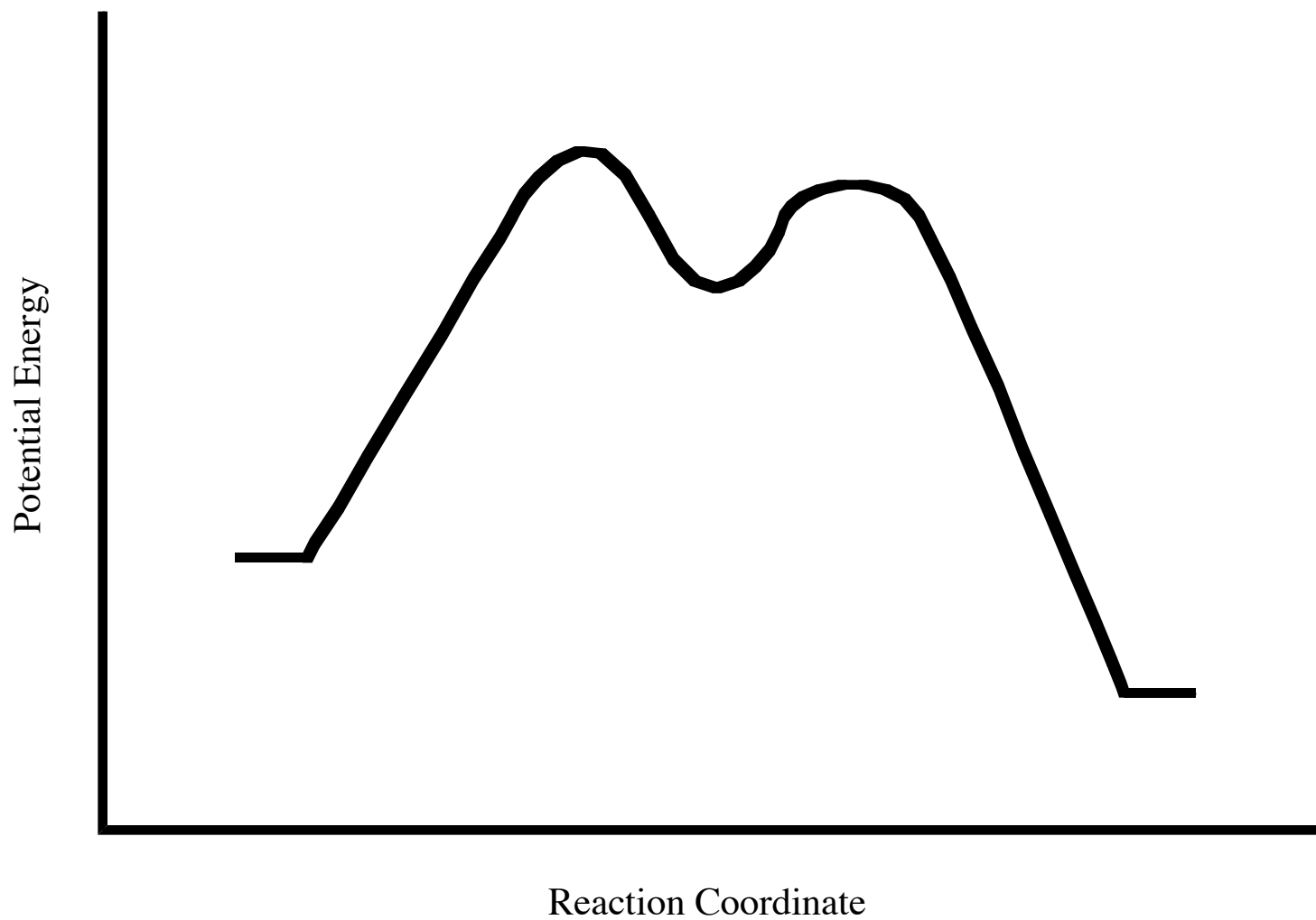
how fast is the reaction

will a catalyst speed up the reaction

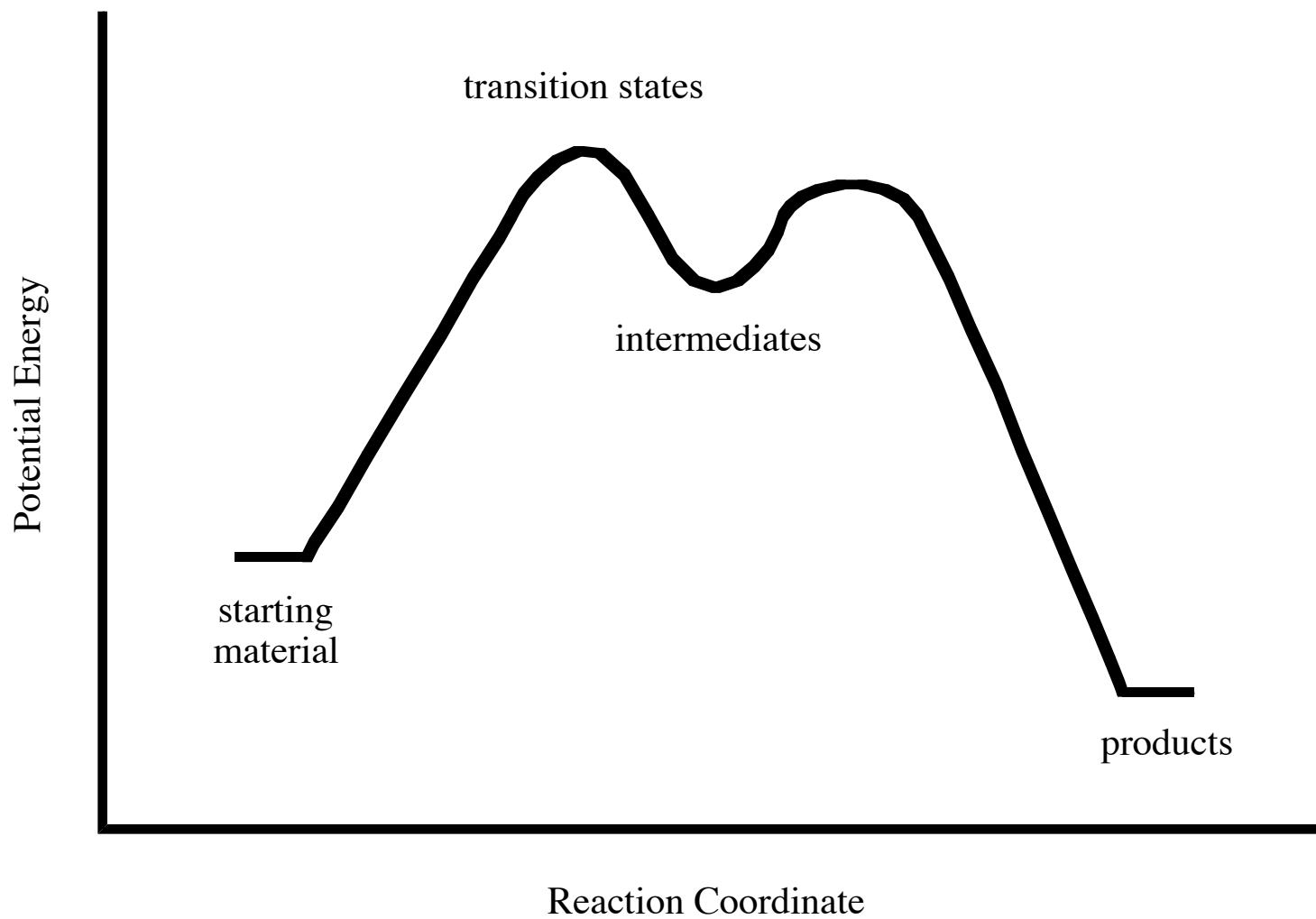
(and if so what should the catalyst be)

are any intermediates generated

All of this Information is Included in an Energy Diagram

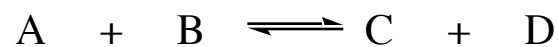


First Need to Know what Each Point on Diagram Represents

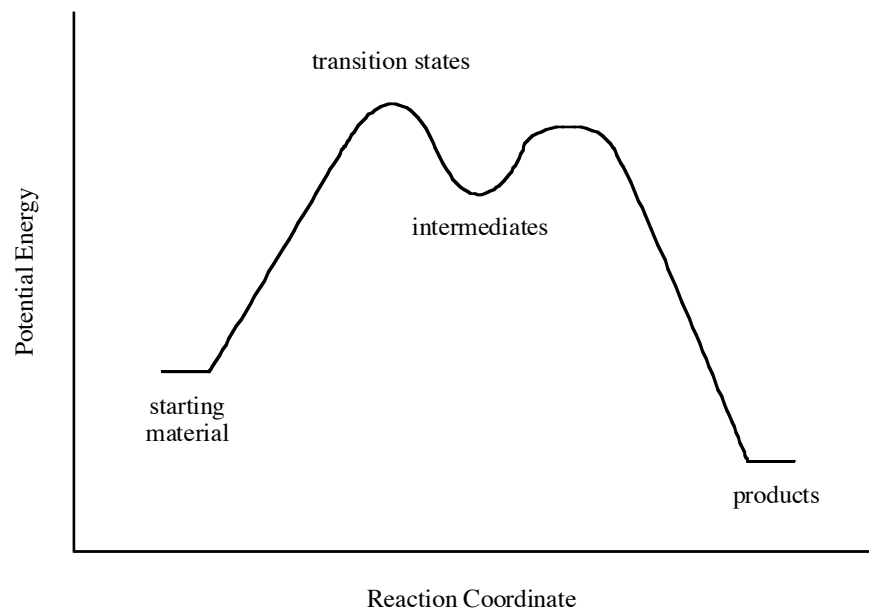


Equilibrium Constants

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



$$K_{eq} = \frac{[C][D]}{[A][B]}$$
$$= \frac{\text{(products)}}{\text{(reactants)}}$$



Gibb's Free Energy

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

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

if we use standard free energy (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 ($-\Delta H^\circ$)

endothermic reaction: heat is consumed by a reaction ($+\Delta H^\circ$)

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

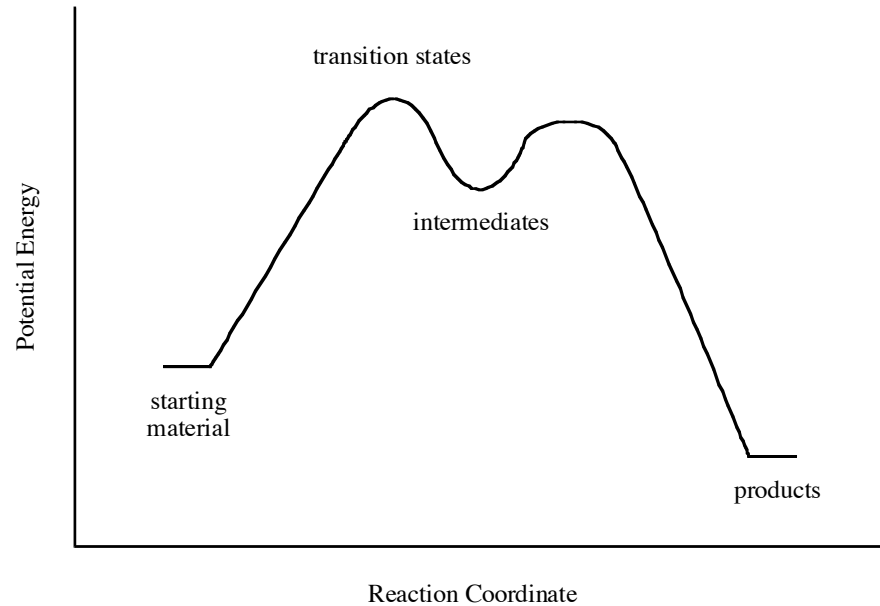
many types of bonds have been recorded (both experimentally and computationally)
we can therefore predict the equilibrium of a reaction by knowing these BDE's

Kinetics

a second important feature is the
RATE of a reaction

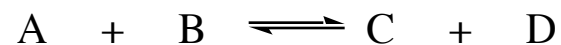
the rate is not determined by K_{eq}
but instead by the energy of activation
(E_a)

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 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)

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

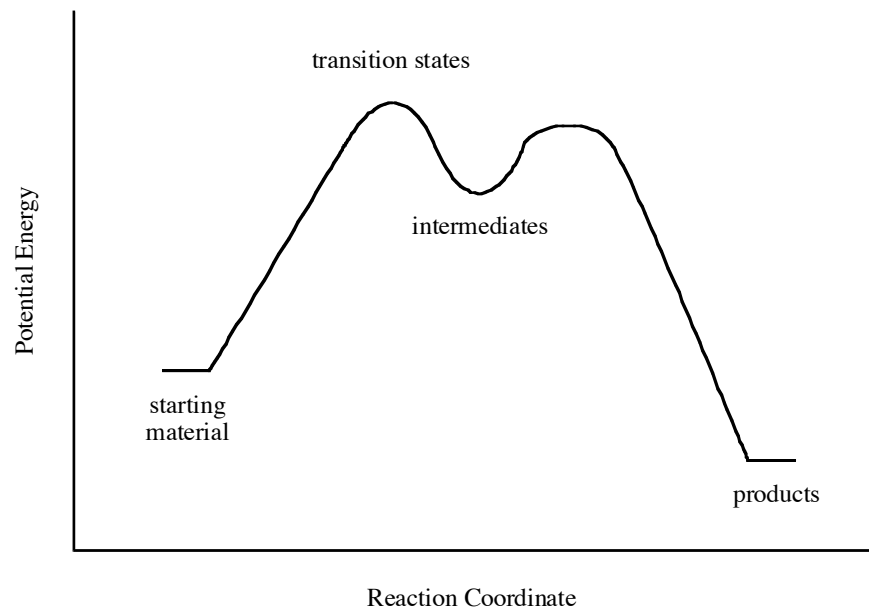
E_a is the minimum kinetic energy required to cause the reaction to proceed

Transition States vs. Intermediates

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

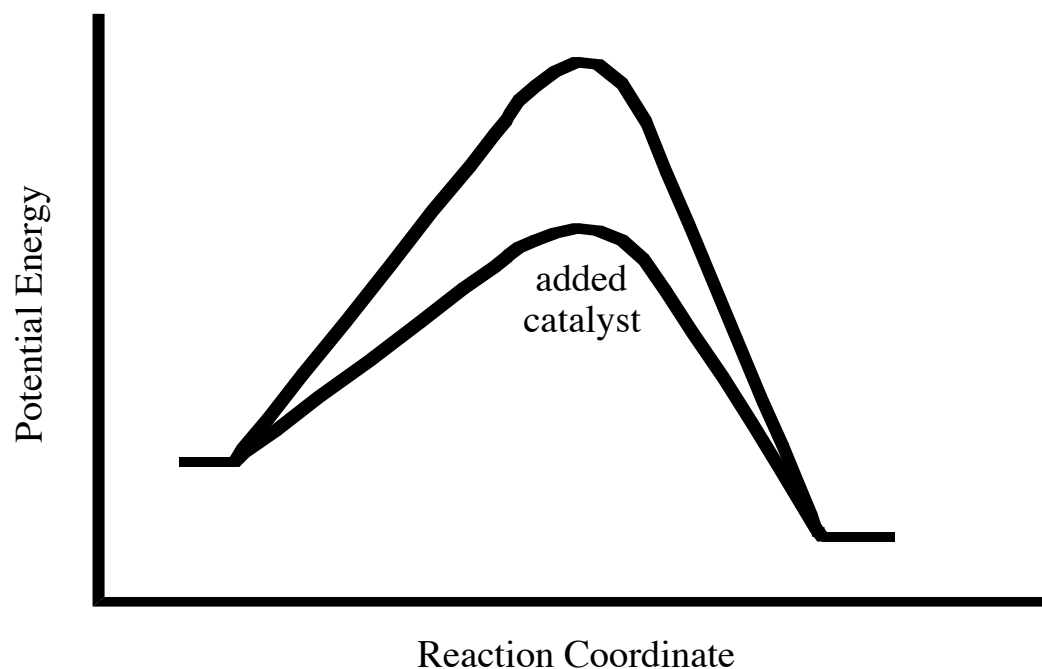
an intermediate has a measurable lifetime
(it can be isolated in theory)

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



Effect of Catalyst

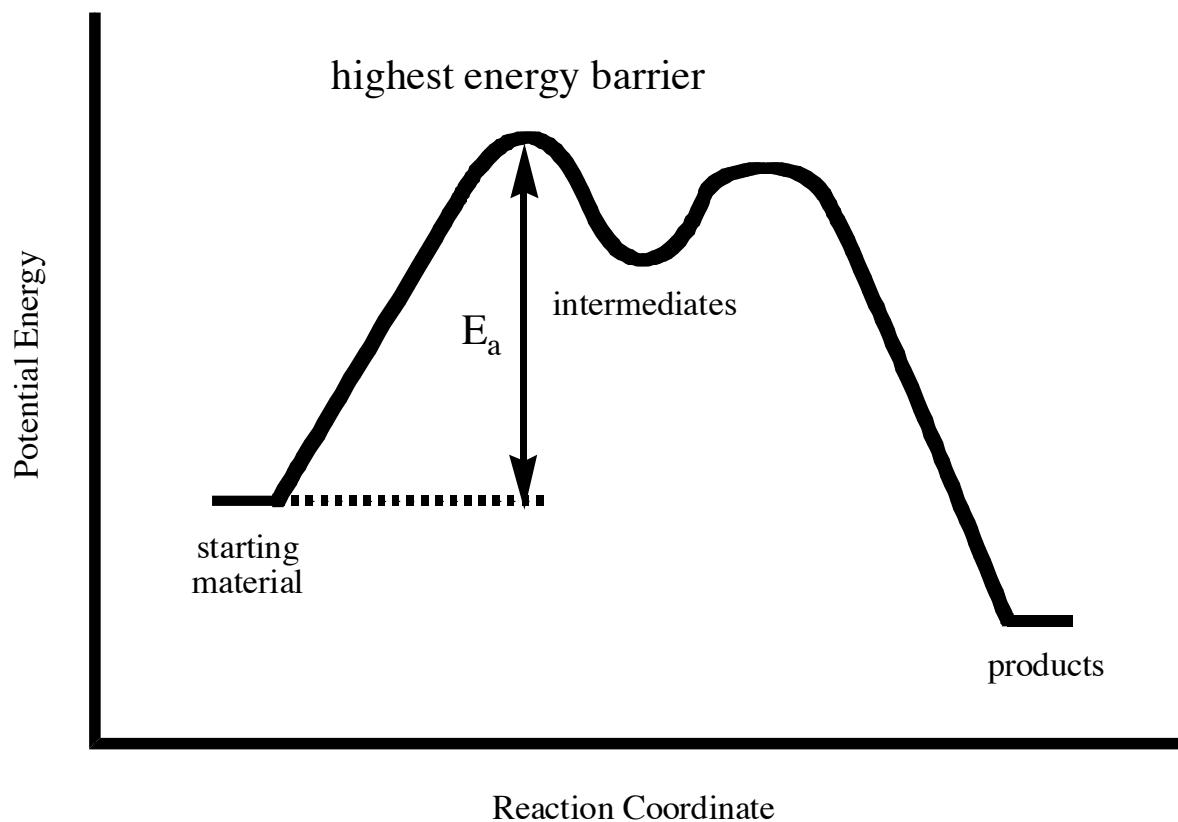
A catalyst only affects the energy of activation
(starting material and product energies are unaffected, therefore K_{eq} is the same)



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

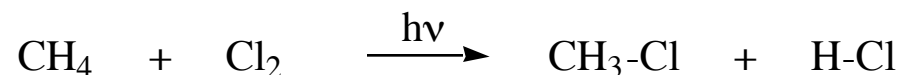


referred to as the rate determining step

Let's Look at the Reactions of Alkanes

most alkanes are relatively inert

halogenation is one reaction type of alkanes



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

we know:

reaction does not proceed in the dark or in the cold

reaction occurs with wavelengths corresponding to Cl_2 absorption

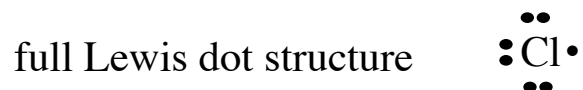
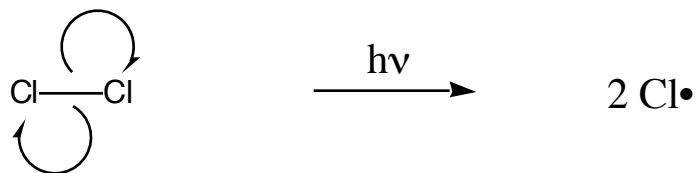
quantum yield is greater than 1

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

this data implies:

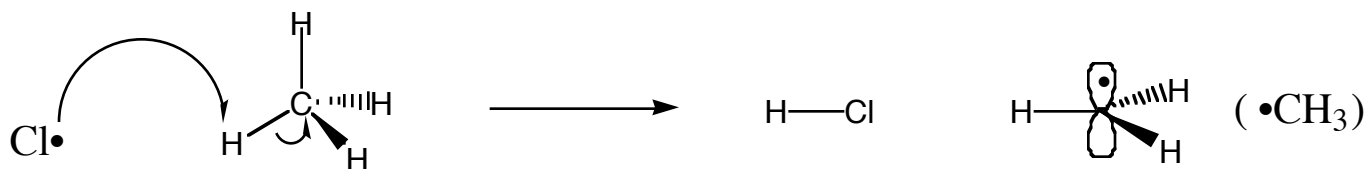
- 1) the chlorine molecule absorbs light to initiate the reaction
- 2) the reaction proceeds in a chain mechanism

to initiate:

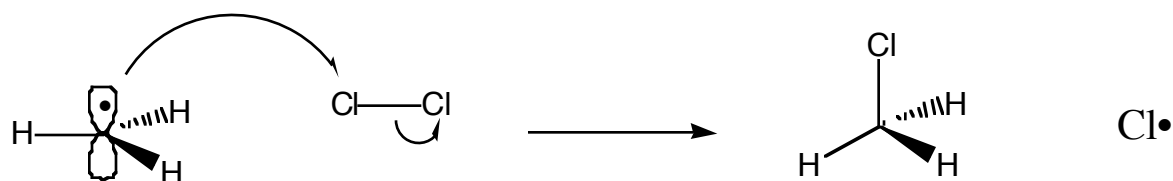


this chlorine radical is a reactive species - it wants to fill its octet

the chlorine radical will react with methane



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

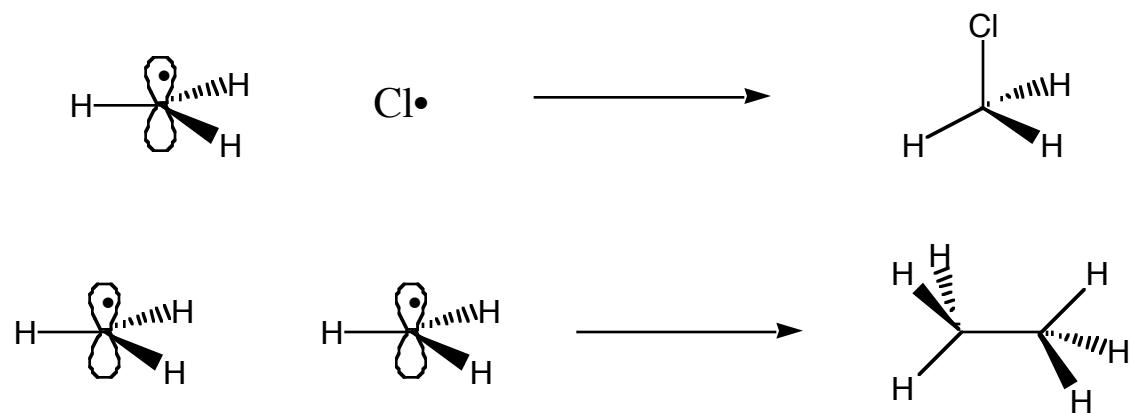


this step creates the product methylchloride (IUPAC: chloromethane) and another reactive species in chlorine radical which will continue the radical chain process

these steps are called propagation steps

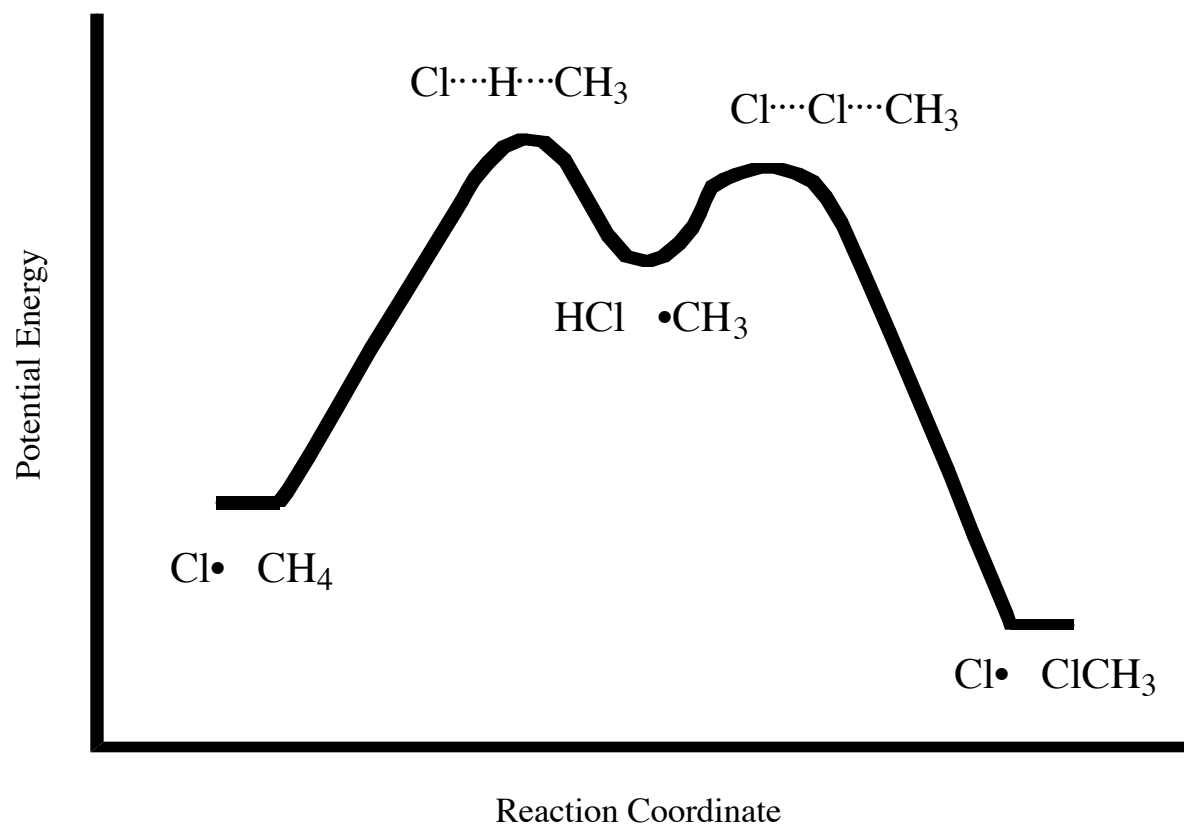
(the step creates the same number of reactive intermediates as it begins with)

A radical chain process continues until a termination step
(whenever a less number of reactive species are created)



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, 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

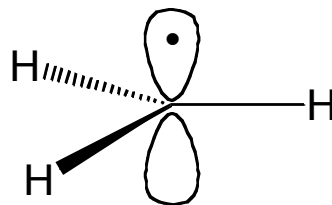
therefore fluorine is the fastest and iodine is the slowest

Stability of Reactive Intermediates

methyl radical ($\text{CH}_3\bullet$) is a reactive intermediate

- its outer shell of electrons is not filled

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



this species is electron deficient

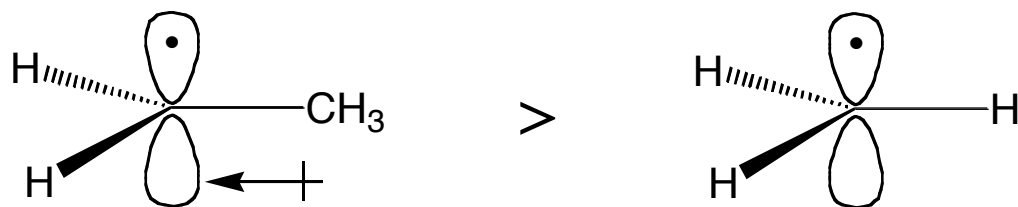
How can we Stabilize $\text{CH}_3\cdot$?

since it is electron deficient we need to supply electron density

ways to accomplish supplying increased electron density:

1) inductive effect

have carbon-carbon bonds which can inductively supply electron density



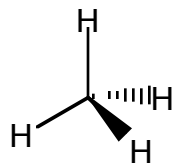
therefore more substituted radical sites are more stable

Remember the Nomenclature for Alkyl Sites

methane

no alkyl substituents

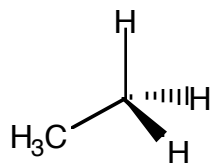
has 4 hydrogens



primary carbon (1°)

1 alkyl substituent

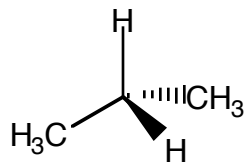
has 3 primary hydrogens



secondary carbon (2°)

2 alkyl substituents

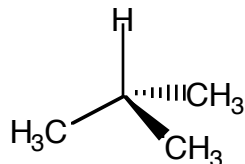
has 2 secondary hydrogens



tertiary carbon (3°)

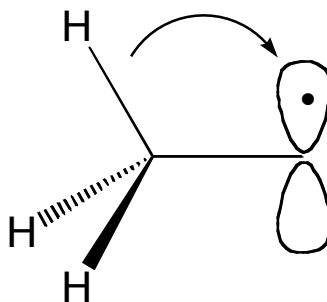
3 alkyl substituents

has 1 tertiary hydrogen



2) Hyperconjugation

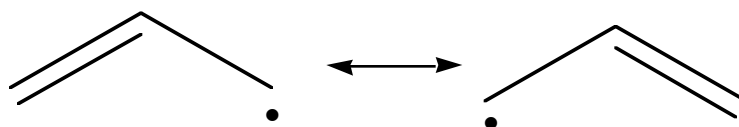
- refers to neighboring C-H bond being able to donate electron density to electron deficient site



hyperconjugation stability also increases with increasing number of substituents

3) Resonance

unsaturated sites in conjugation with radical sites will offer stability by allowing electron deficient site to be spread over various atoms



remember from previous discussions, resonance is primarily observed when there are multiple bonded carbon atoms adjacent to site or when there are atoms with lone pair of electrons adjacent to site

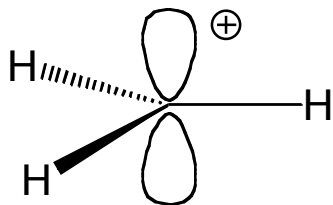
- must have p orbitals in conjugation

Other Reactive Species

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

CARBOCATIONS (carbonium ions)

positive charge at a carbon site



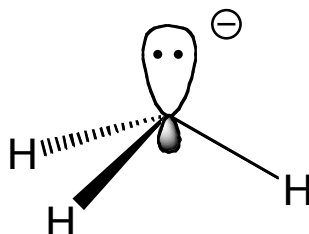
also sp^2 hybridized
only 6 electrons in outer shell

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



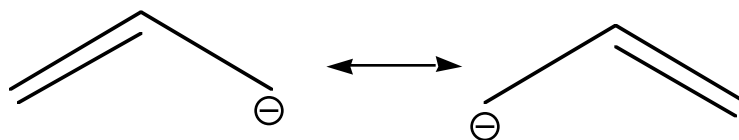
remember that lone pairs of electrons generally fill hybridized orbitals
therefore the methyl carbanion is sp^3 hybridized
(changes to sp^2 if resonance is available)

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 still stabilizes a carbanion

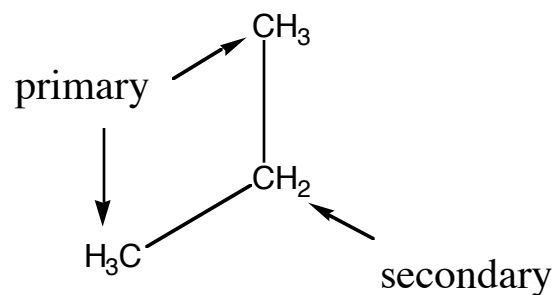
- allows the negative charge to delocalize over more atoms



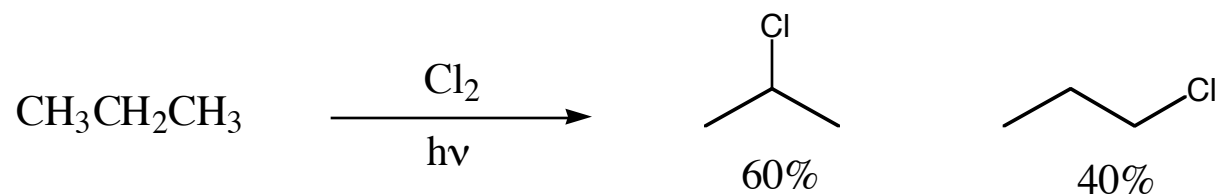
similar to acid strengths observed earlier in the class

What happens when an alkane is used with various substituent sites?

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

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

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

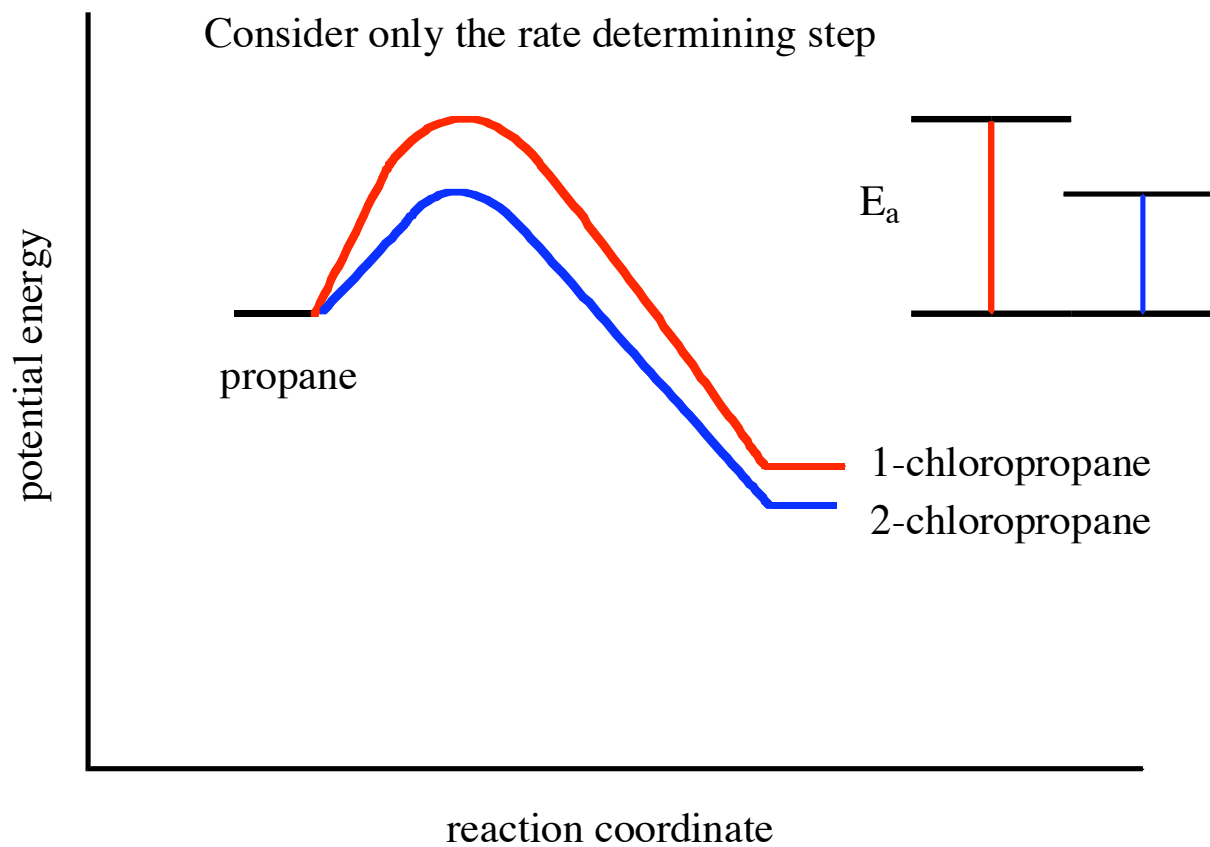
therefore the selectivity for 2° hydrogen over 1° hydrogen is greater

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

What causes the selectivity?

the 2° radical formed is more stable than the 1° radical formed

what this means in an energy diagram:

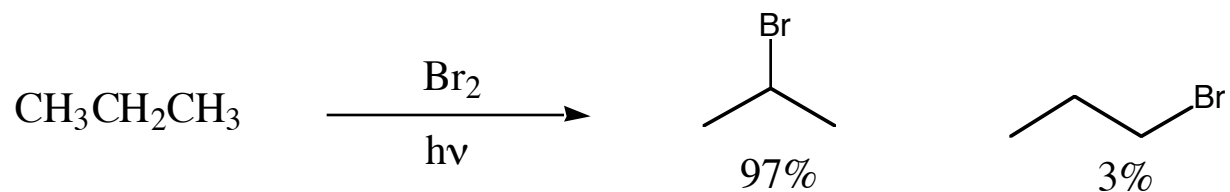


What Occurs with Bromination?

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

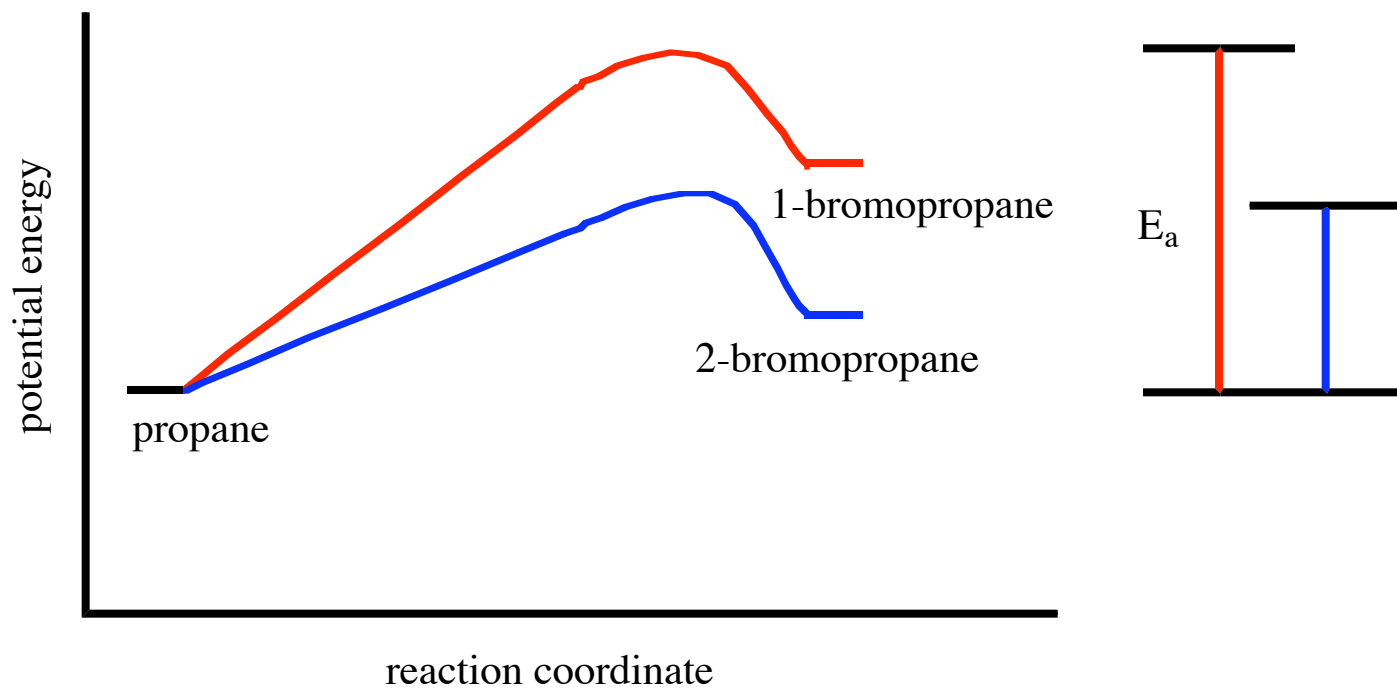
this requires the reaction to be heated in order to get the reaction to proceed

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 site is brominated

How Does the Energy Diagram Reflect this Selectivity



there is a greater difference in E_a for this endothermic reaction
compared to the exothermic chlorination reaction
-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° site
(same energy)

the product is different in energy 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 for reaction at
the 2° site relative to the 1° site

if the transition states are more “product like” the energy difference will be greater for
reaction at the 2° site relative to the 1° site

Reactivity vs. Selectivity

another way to relate the Hammond postulate to organic reactions is to compare reactivity versus selectivity

reactivity: how easily the reaction occurs
(how large is the E_a in the energy diagram)

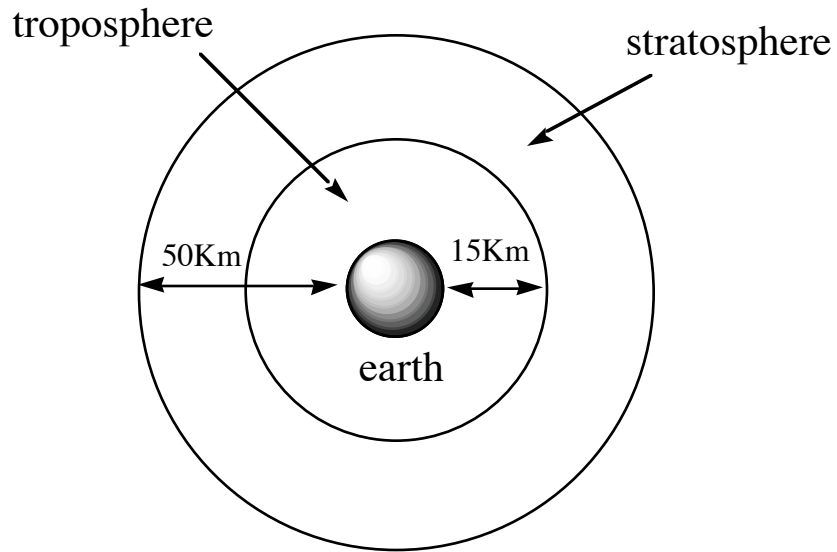
selectivity: if more than one site is available for attack in a given reaction the ratio of the products obtained determines the selectivity
(the difference in E_a between competing paths in the energy diagram)

an almost universal statement in organic chemistry:

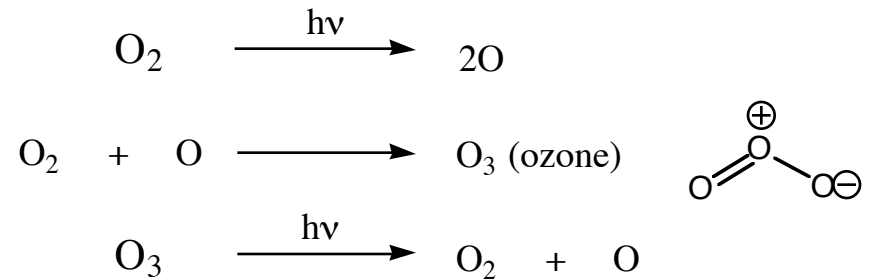
FOR A GIVEN REACTION THE MORE REACTIVE THE LESS SELECTIVE

Relevance of Radical Chemistry

Ozone Depletion



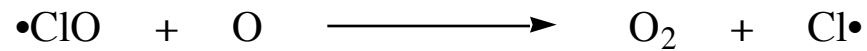
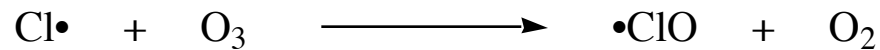
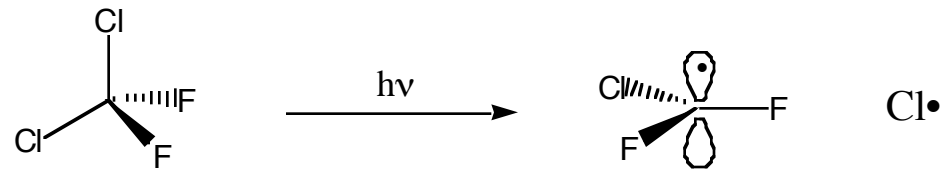
chemistry involved in stratosphere:



ozone absorbs light in the 200 - 300nm range

Carbon Compounds Can Also Interact with Ozone

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



therefore the concentration of ozone decreases and the 200nm - 300 nm sunlight is not blocked as efficiently

same type of chemistry occurs with bromine radicals (from halons)

As a result biological entities can be destroyed by the low wavelength light

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

a solution: replace chlorine containing carbon species
(and also bromine containing species)

possibilities:

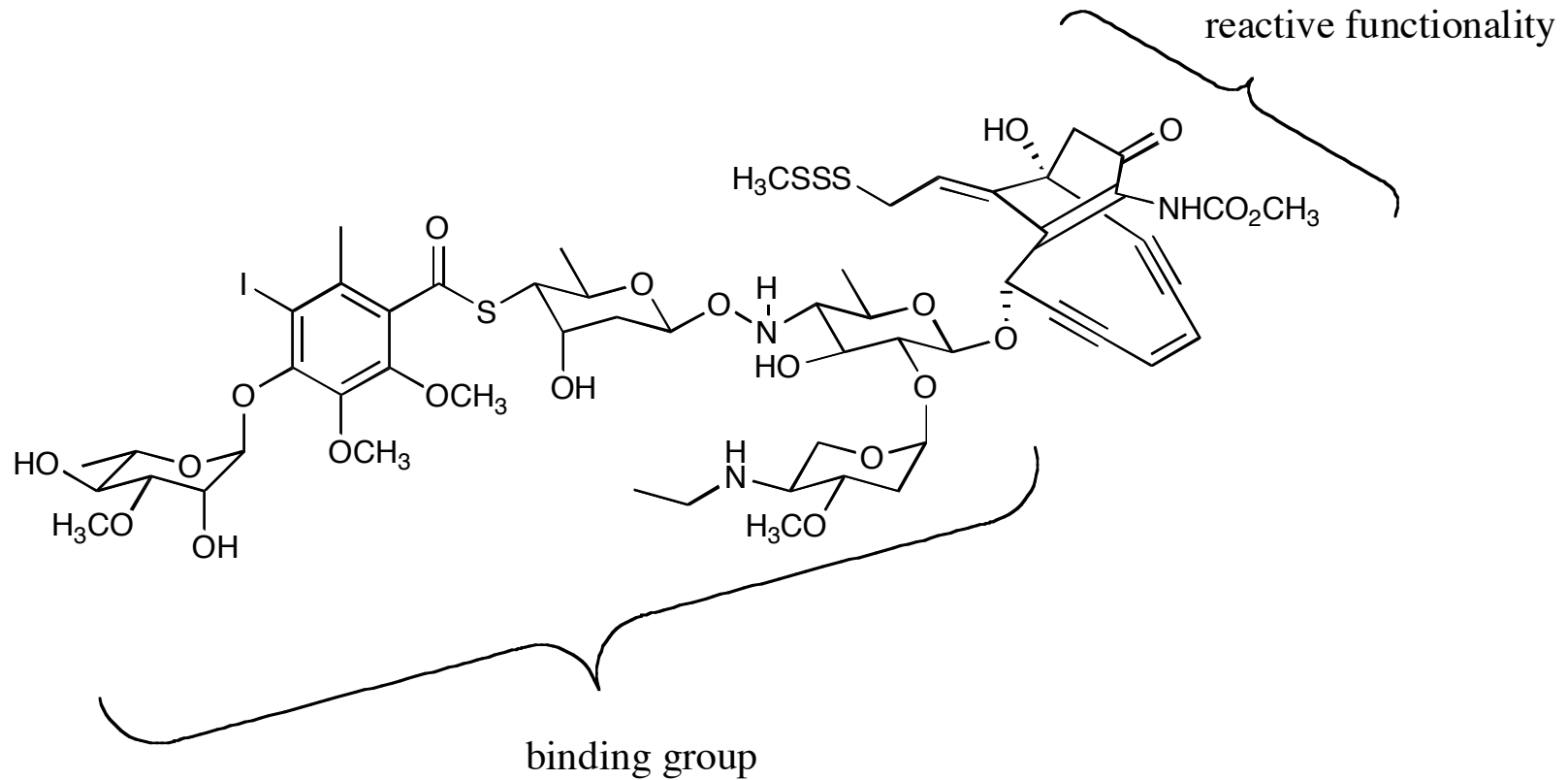
CH_2FCF_3 CHClF_2
HFC (hydrofluorocarbons)

Radical Interactions in Drug Development

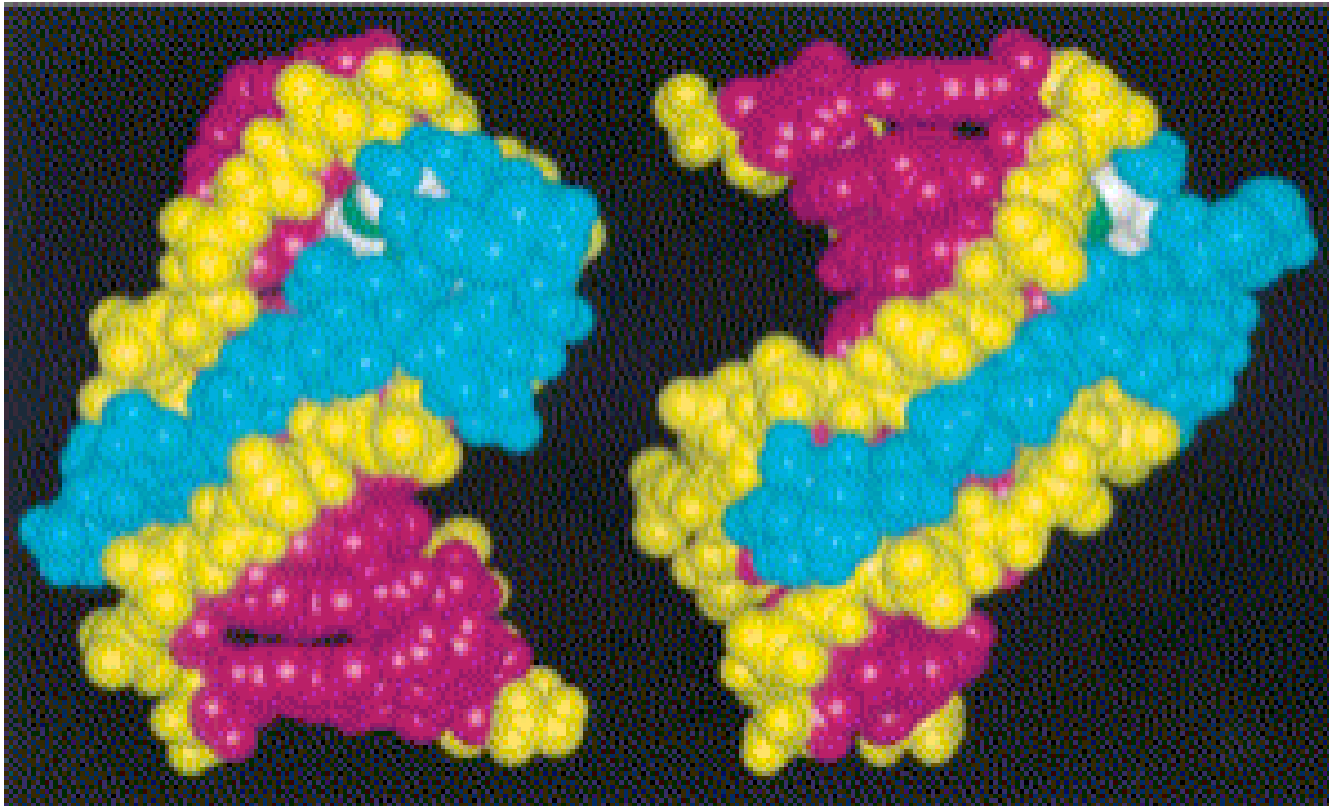
As observed radicals are reactive species

When generated near biological species irreversible damage may occur

An example: Calicheamicin γ_1^1



Calicheamicin binds specifically with the minor groove of DNA

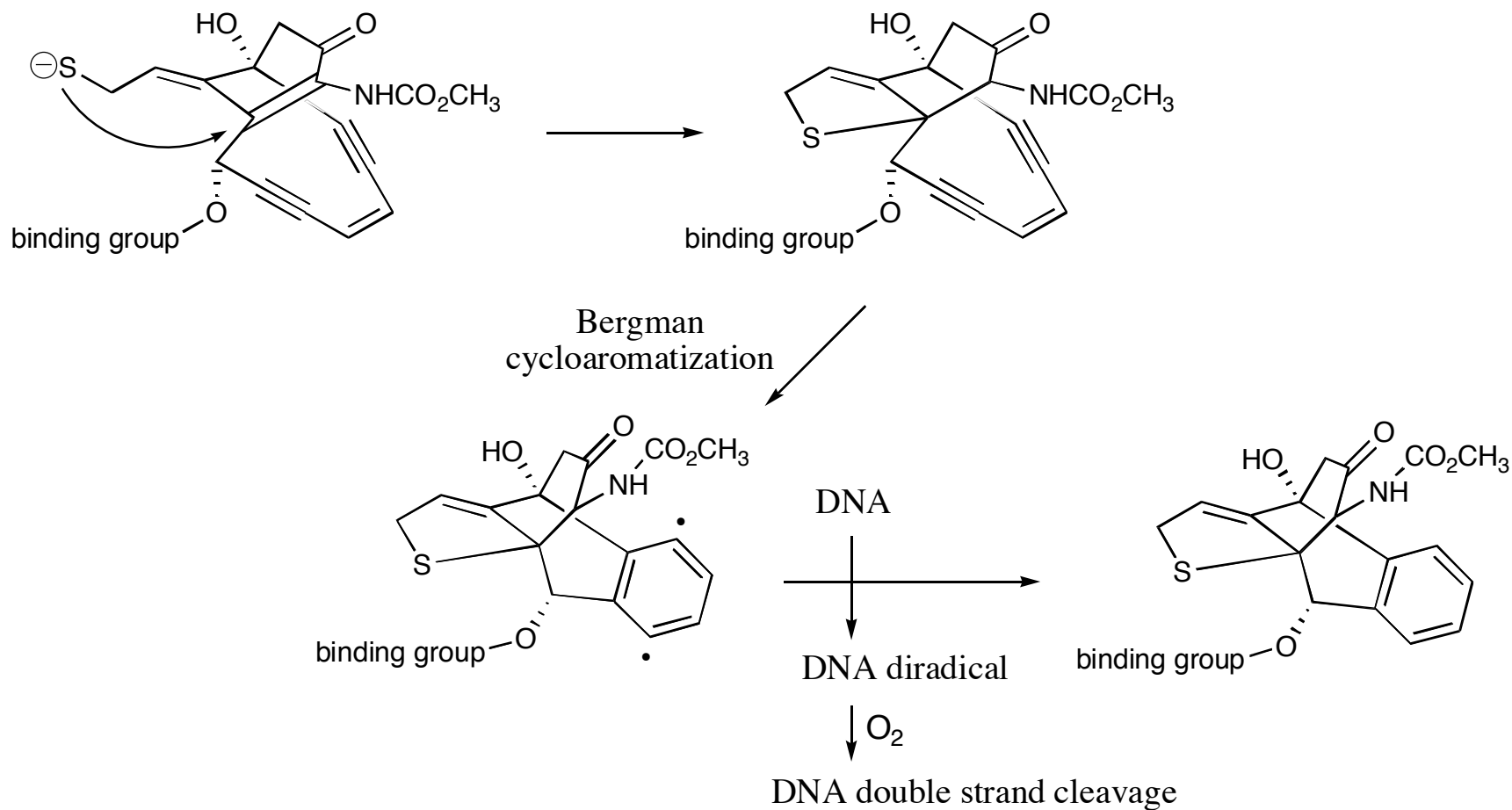


Yellow and magenta correspond to DNA backbone, blue is Calicheamicin

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