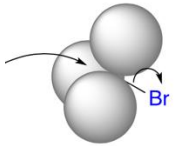
Bioorganic Chemistry

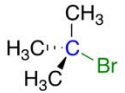
Lecture 7

S_N1 vs S_N2

Predicting the mechanism

tertiary alkyl halide





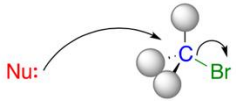
Factors favoring the S_N1 pathway:

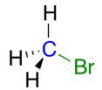
hindered electrophile
potential for a tertiary, secondary, or resonance-stabilized carbocation intermediate
uncharged nucleophile
protic solvent such as water

Factors favoring the S_N2 pathway:

Unhindered (methyl or primary) electrophile
powerful, anionic nucleophile
polar aprotic solvent

methyl halide

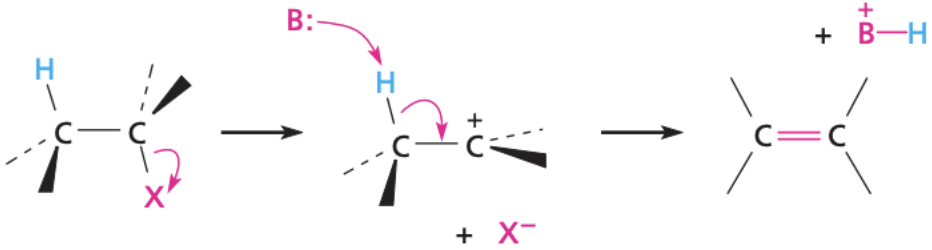




It is important to remember that many of these reaction pathways are just conceptual models and many reactions will fall somewhere in between.

Eliminations

E1 Reaction: C–X bond breaks first to give a carbocation intermediate, followed by base removal of a proton to yield the alkene.



Carbocation

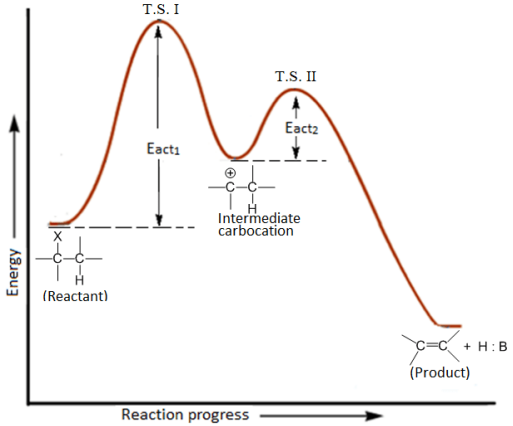
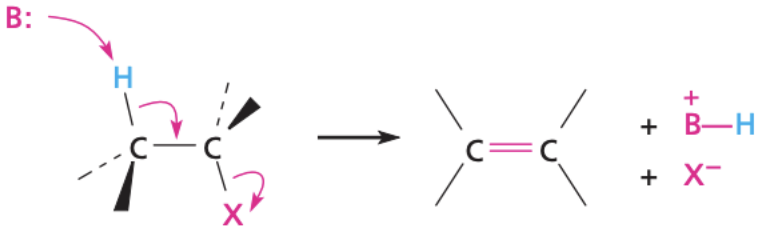


Fig. Potential energy diagram for E_1 reaction

E2 Reaction: C–H and C–X bonds break simultaneously, giving the alkene in a single step without intermediates.



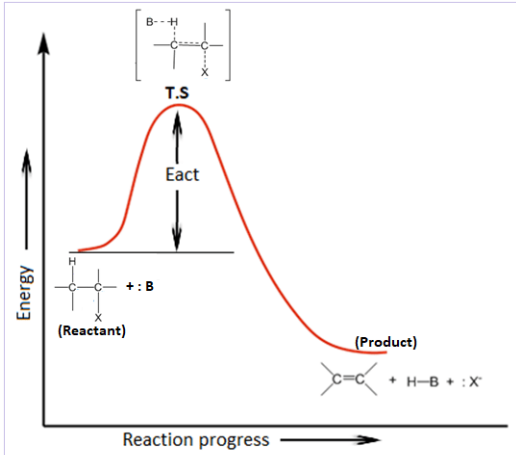
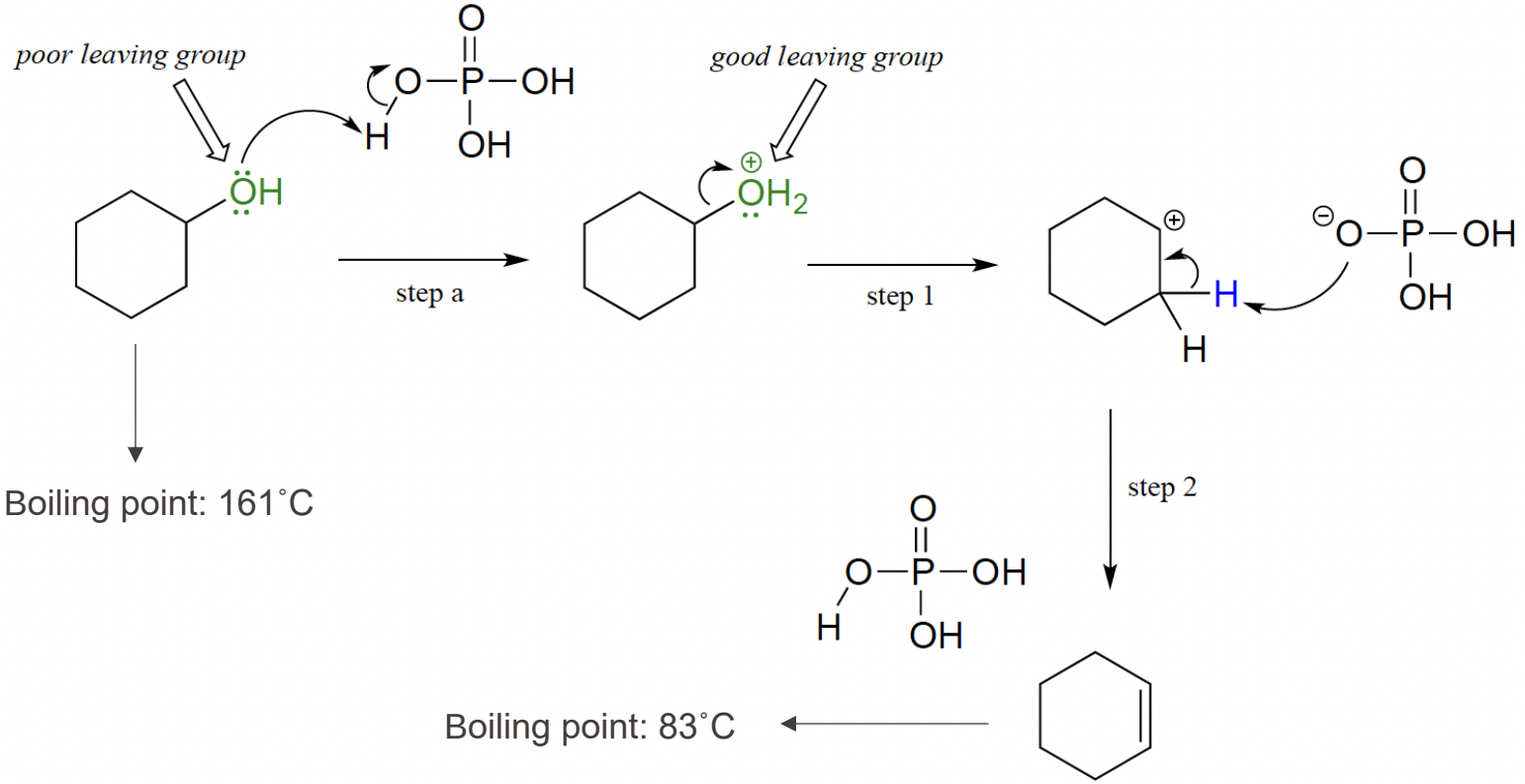


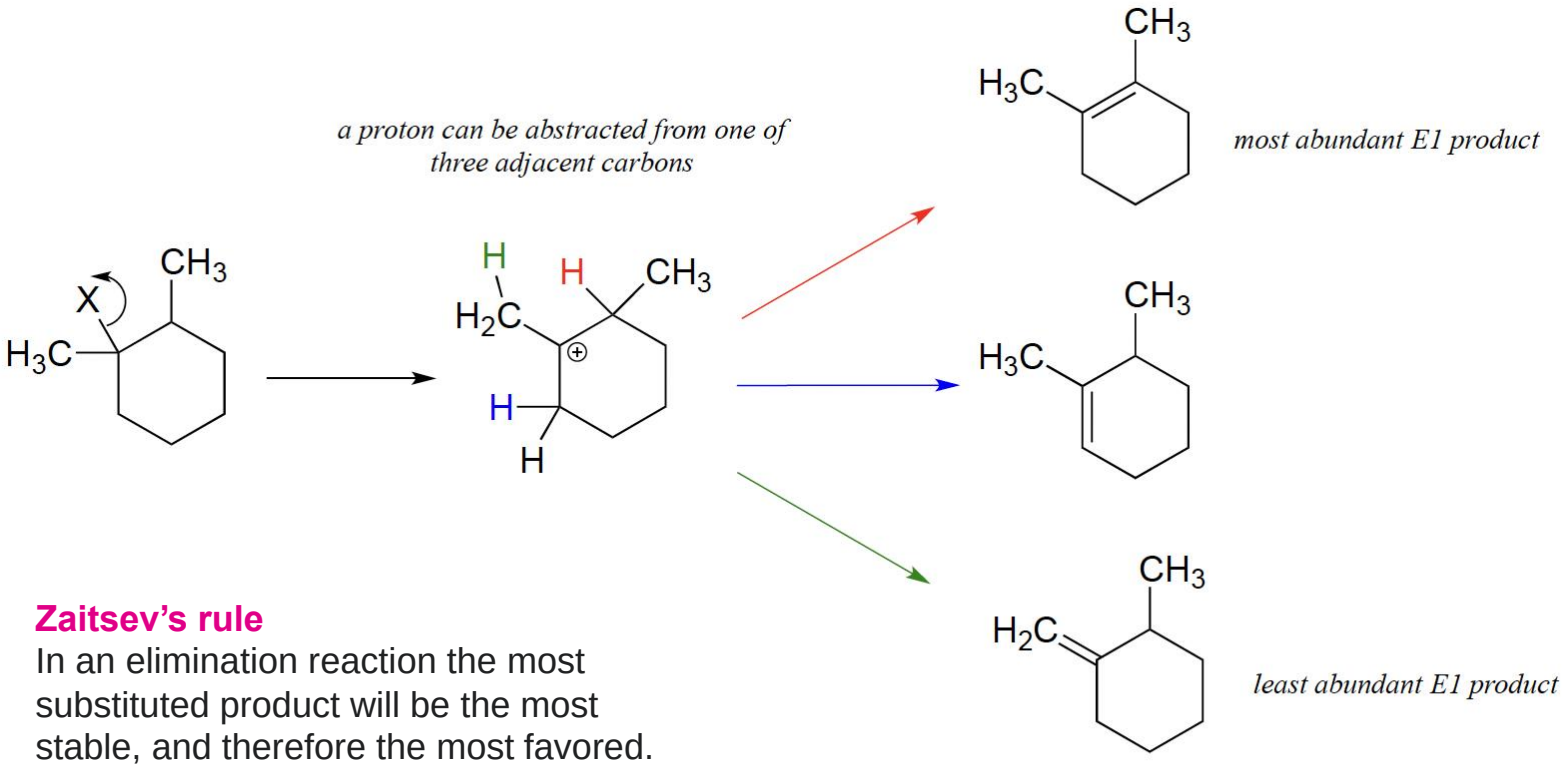
Fig. Potential energy diagram for E_2 reaction.

Solvent effects or catalytic acid can facilitate E1



How can I separate the reagents from the products ?

Eliminations – Zaitsev's rule



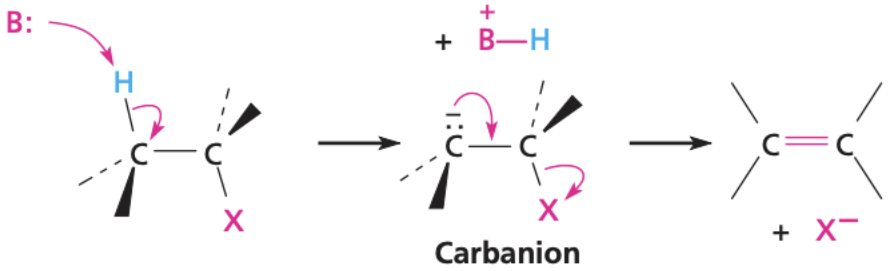
Zaitsev's rule

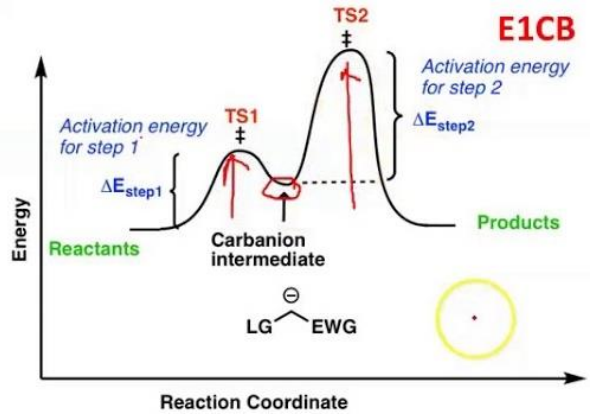
In an elimination reaction the most substituted product will be the most stable, and therefore the most favored. However, there are many exceptions!

Let’s do a few together

The E1cb Elimination

E1cB Reaction: C–H bond breaks first, giving a carbanion intermediate that loses X^- to form the alkene.

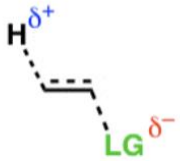




Protons in neighbourhood of a Carbonyl group are highly acidic (~pK_a≈20) and can be abstracted by a Base
-> The Anion is stable enough so the leaving group stays, it can delocalize to the Carbonyl

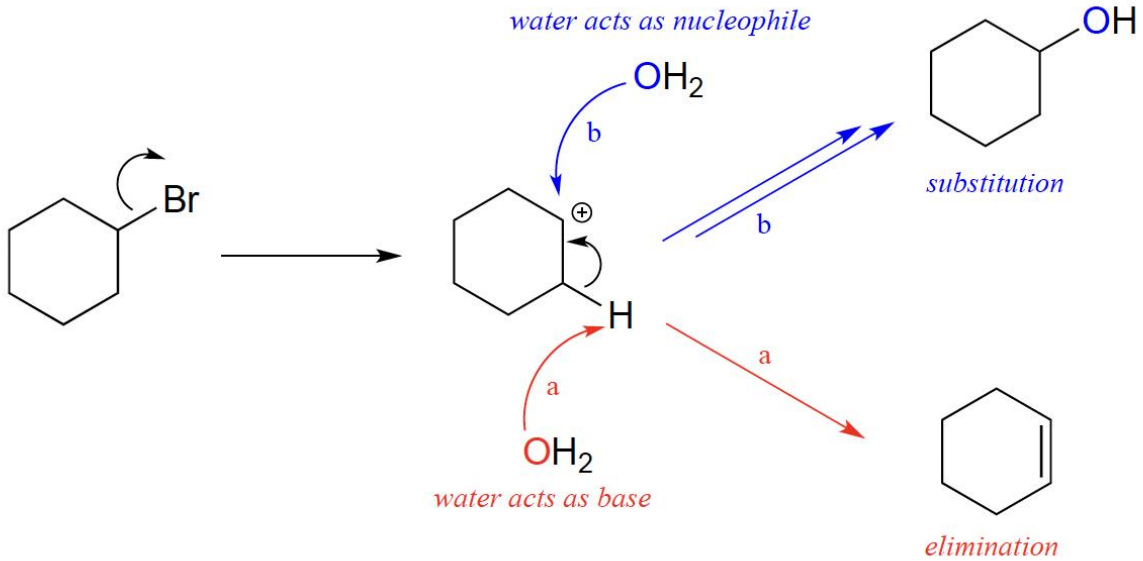
Eliminations - Summary

Comparing the E1, E2, and E1cB Mechanisms

E1	E2	E1cB
Two steps 1) C–LG breaks 2) C–H breaks C–C (pi) forms	**One** step C–H breaks, C–C (pi) forms C–LG breaks, all at same time	**Two** steps 1) C–H breaks 2) C–LG breaks C–C (pi) forms
		
Carbocation intermediate	**No** intermediate (concerted)	**Carbanion** intermediate
Carbocation stabilized by electron **donating** groups		Carbanion stabilized by electron **withdrawing** groups
Assisted by **good** leaving groups		Assisted by **poor** leaving groups
No strict requirement on stereochemistry of C–H and C–LG	C–H and C–LG are **anti**	No strict requirement on stereochemistry of C–H and C–LG

Elimination vs Substitution

The reagents employed remain consistent for both substitution and elimination reactions. Regardless of the scenario, a blend of both reactions occurs, yielding a combination of substitution and elimination products. The predominant outcome is determined by various influencing factors.



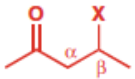
Elimination vs Substitution

Substitution and elimination reactions are strongly influenced by many experimental factors

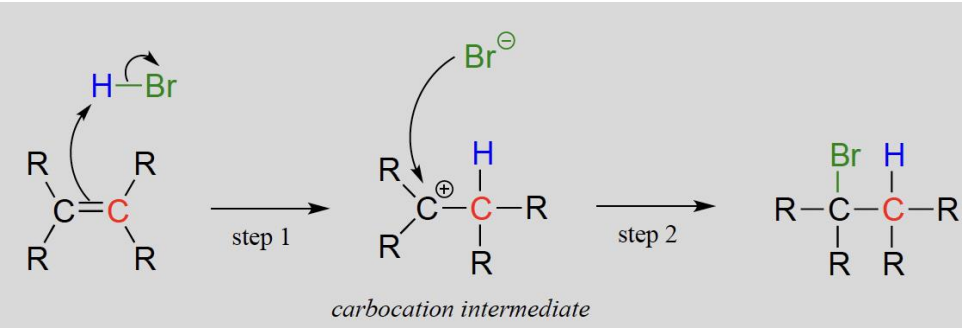
1. Increasing the temperature tends to increase elimination due to disorder / entropy effects (recall $\Delta G = \Delta H - T\Delta S$)

2. Increasing steric effects (look at both "R" and the "Nu/B") tends to increase elimination.

3. The basicity / nucleophilicity of the attacking species *i.e.* switching from ROH to RO- will increase the amount of elimination

		Poor nucleophile (e.g. H_2O, ROH)	Weakly basic nucleophile (e.g. I^-, RS^-)	Strongly basic, unhindered nucleophile (e.g. RO^-)	Strongly basic, hindered nucleophile (e.g. DBU, *t*-BuO^-)
methyl	$H_3C—X$	no reaction	S_N2	S_N2	S_N2
primary (unhindered)		no reaction	S_N2	S_N2	E2
primary (hindered)		no reaction	S_N2	E2	E2
secondary		S_N1, E1 (slow)	S_N2	E2	E2
tertiary		E1 or S_N1	S_N1, E1	E2	E2
β to anion-stabilizing group		E1cB	E1cB	E1cB	E1cB

Electrophilic reactions



Electrophile/Nucleophile Differences

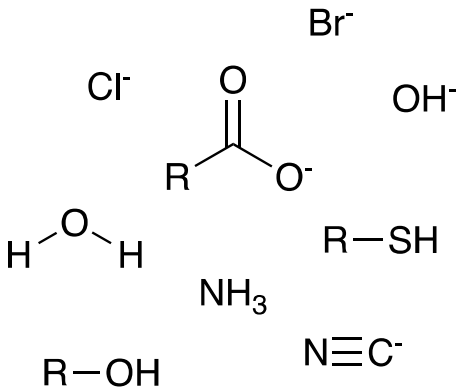
Nucleophile

Donates electron pair

Neutral or negatively charged

Undergoes Nucleophilic Substitutions/Additions

Called Lewis-Bases



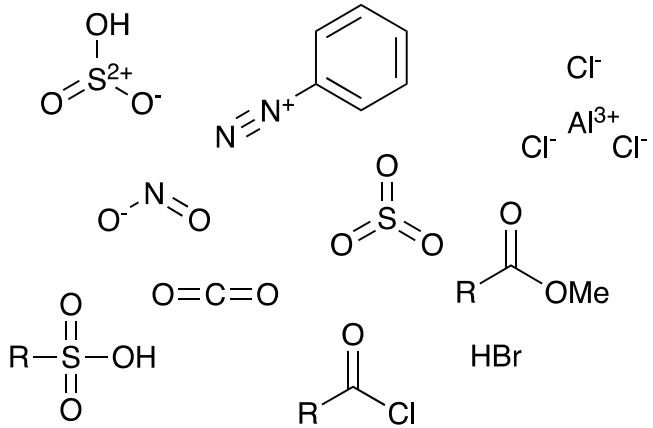
Electrophile

Accepts electron pair

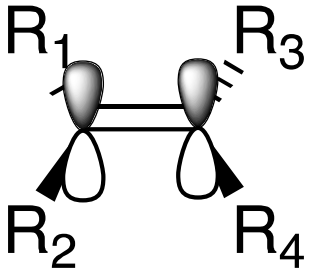
Neutral or positively charged

Undergoes Electrophilic Substitutions/Additions

Called Lewis Acids



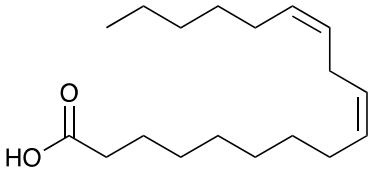
Carbon - Carbon Double Bonds



σ-Bond : ~350 kJ/mol
π-Bond : ~270 kJ/mol

Physical Properties of Alkenes

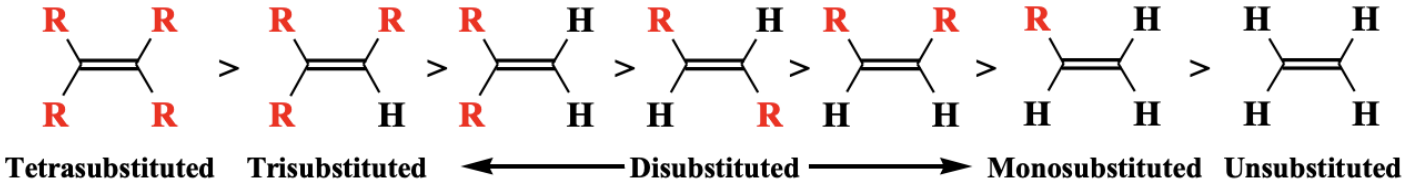
- Alkenes and alkynes with up to four carbons are typically gases at room temperature.
- They dissolve well in nonpolar solvents or those with low polarity.
- Their solubility in water is extremely limited.
- Additionally, their densities are lower than that of water.



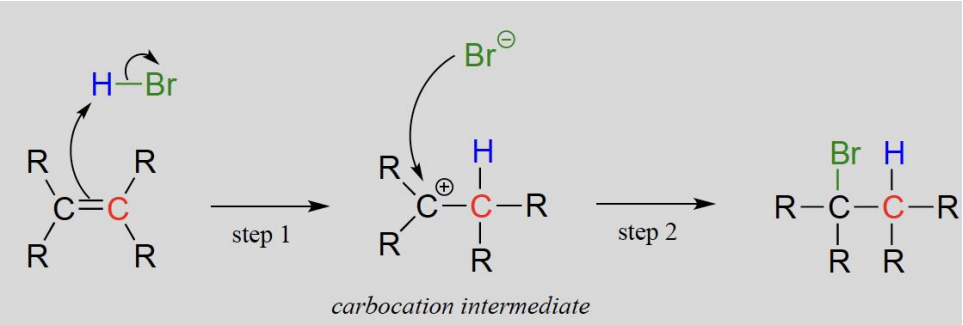
Linolic acid

Relative Stability of Alkenes

The greater the number of attached alkyl groups (i.e., the more substituted the carbon atoms of the double bond), the greater is the alkene's stability

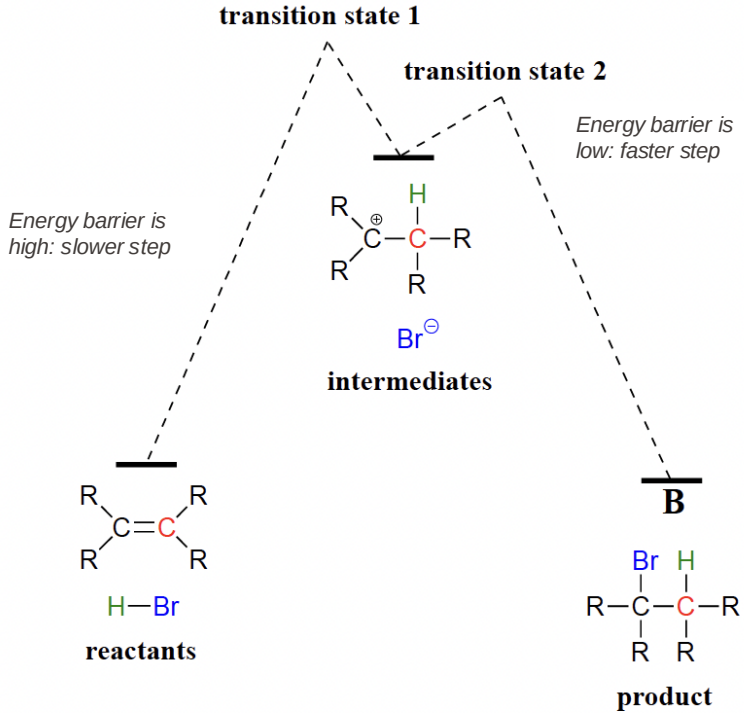


Electrophilic Addition of HBr - Overview

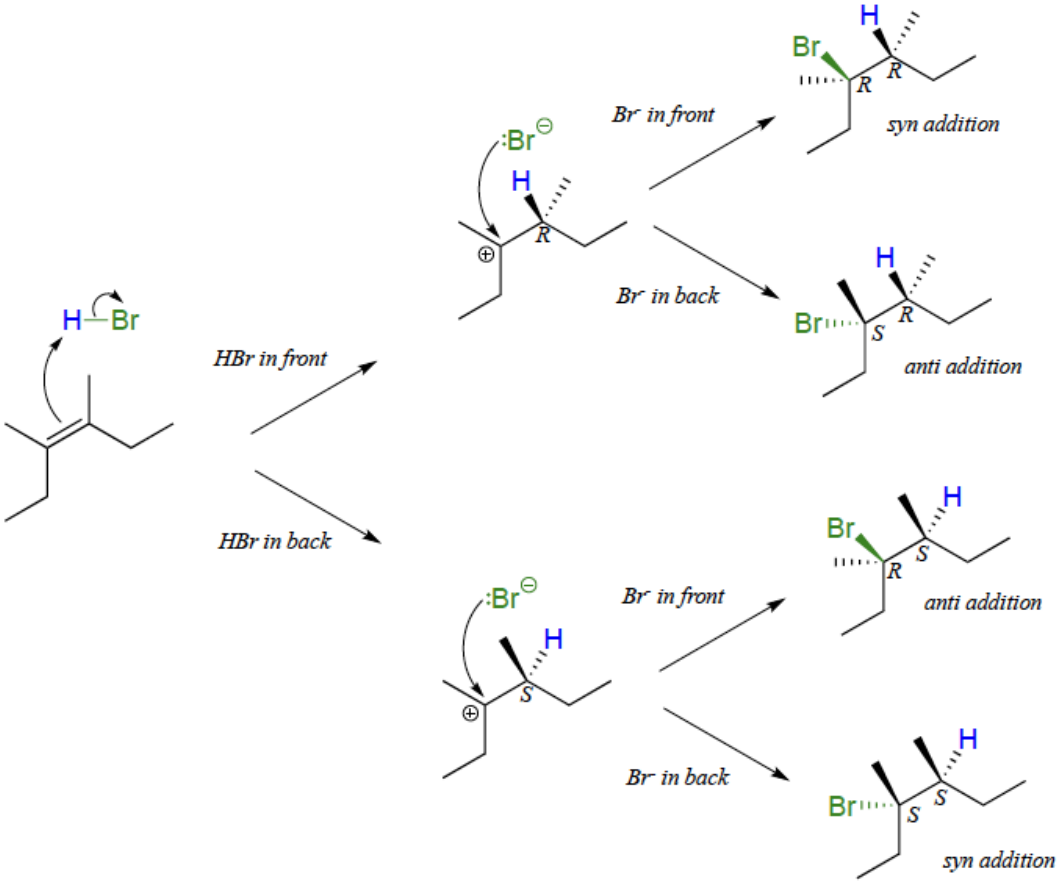


Step1: π - electrons of the alkene act as a base and extract the acidic proton of HBr
-> incomplete octet and a positive formal charge (high energy)

Step2: Nucleophilic bromide anion attacks the electrophilic carbocation to form a new carbon-bromine bond

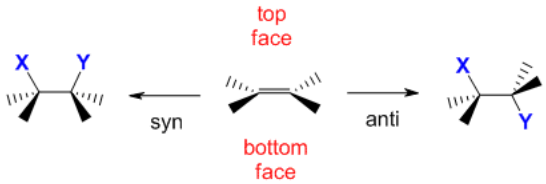


Electrophilic Addition – A view on Stereochemistry

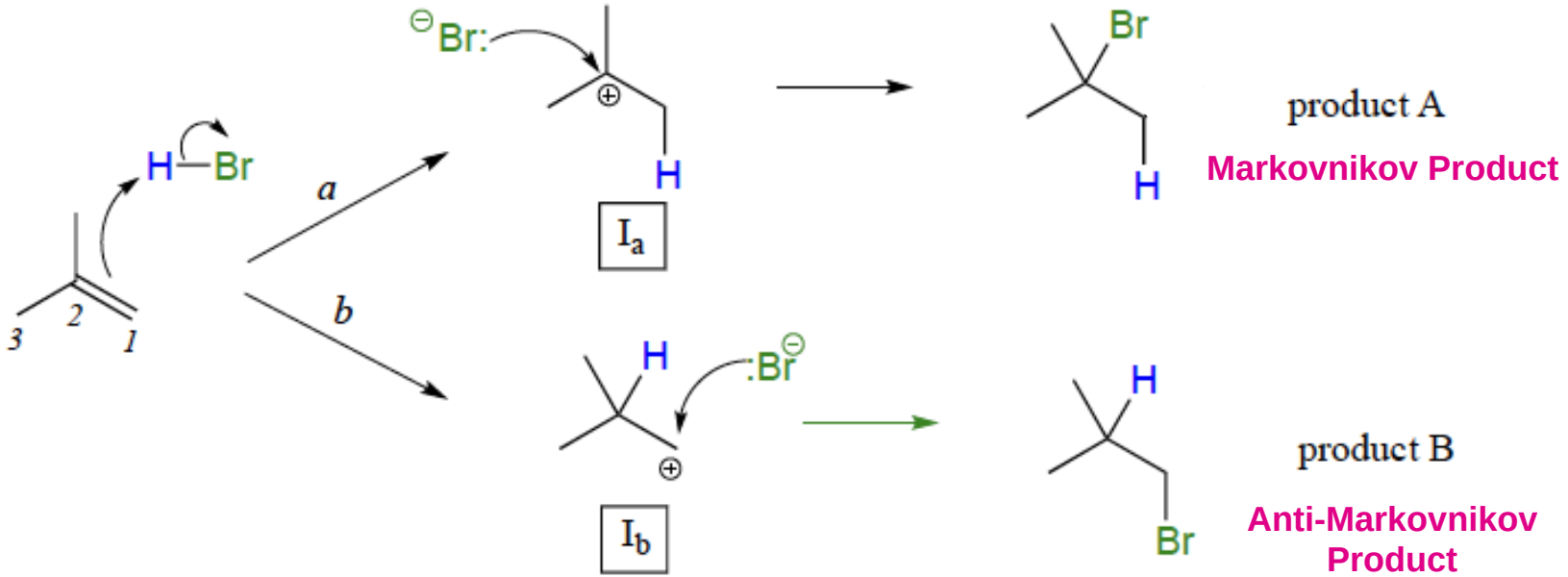


Introduction of potentially 2 new chiral centers

- ➔ No control on Stereochemistry in this reaction
- ➔ product mixture to consist of equal amounts of four different stereoisomers



Electrophilic Addition – Markovnikov's Rule

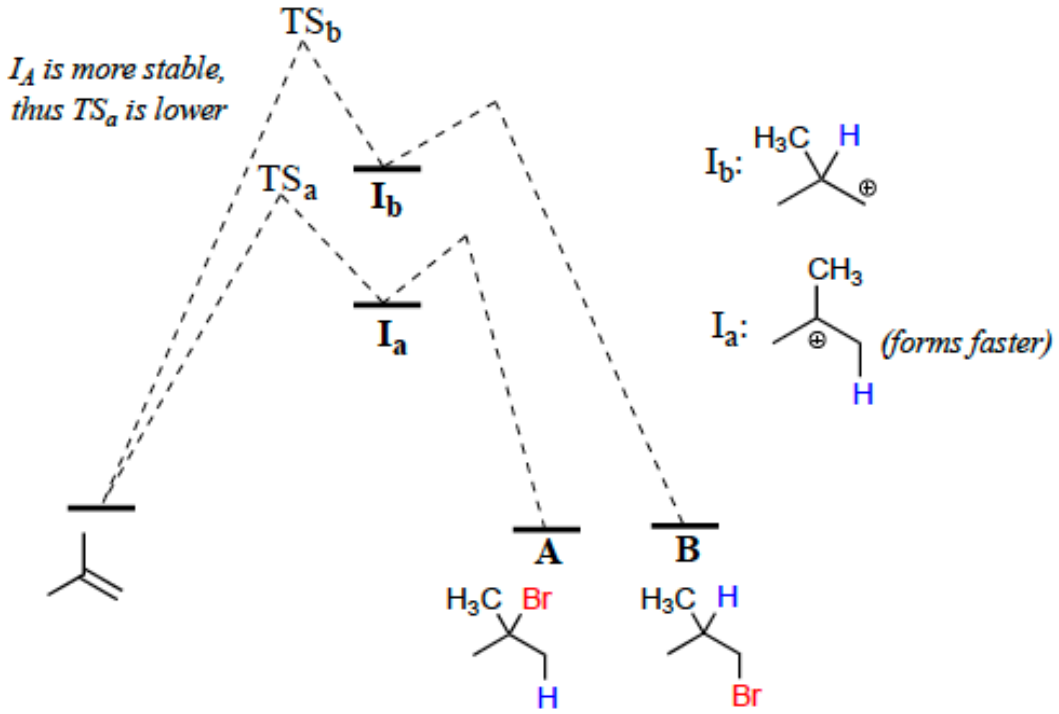


Markovnikov's rule

In the addition of HX to an alkene, the H attaches to the carbon with fewer alkyl substituents and the X attaches to the carbon with more alkyl substituents.

-> Rule of thumb!

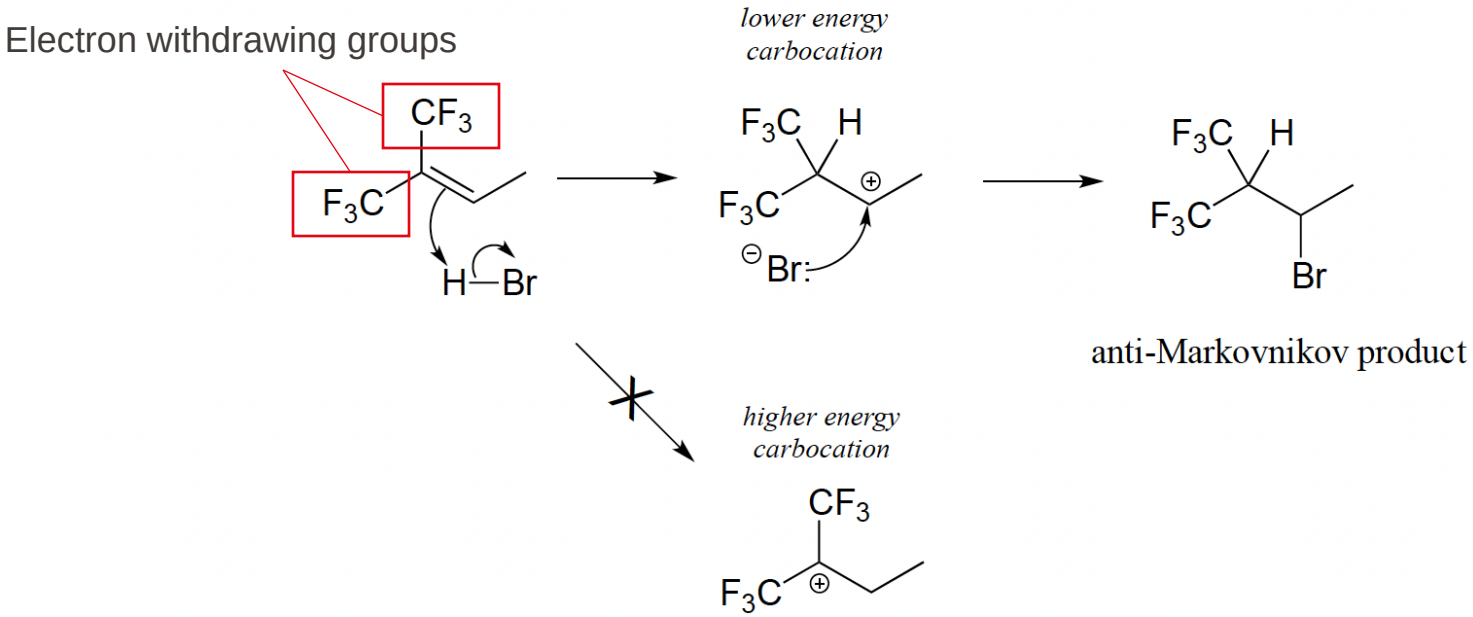
Electrophilic Addition – Regioselectivity



Regioselectivity

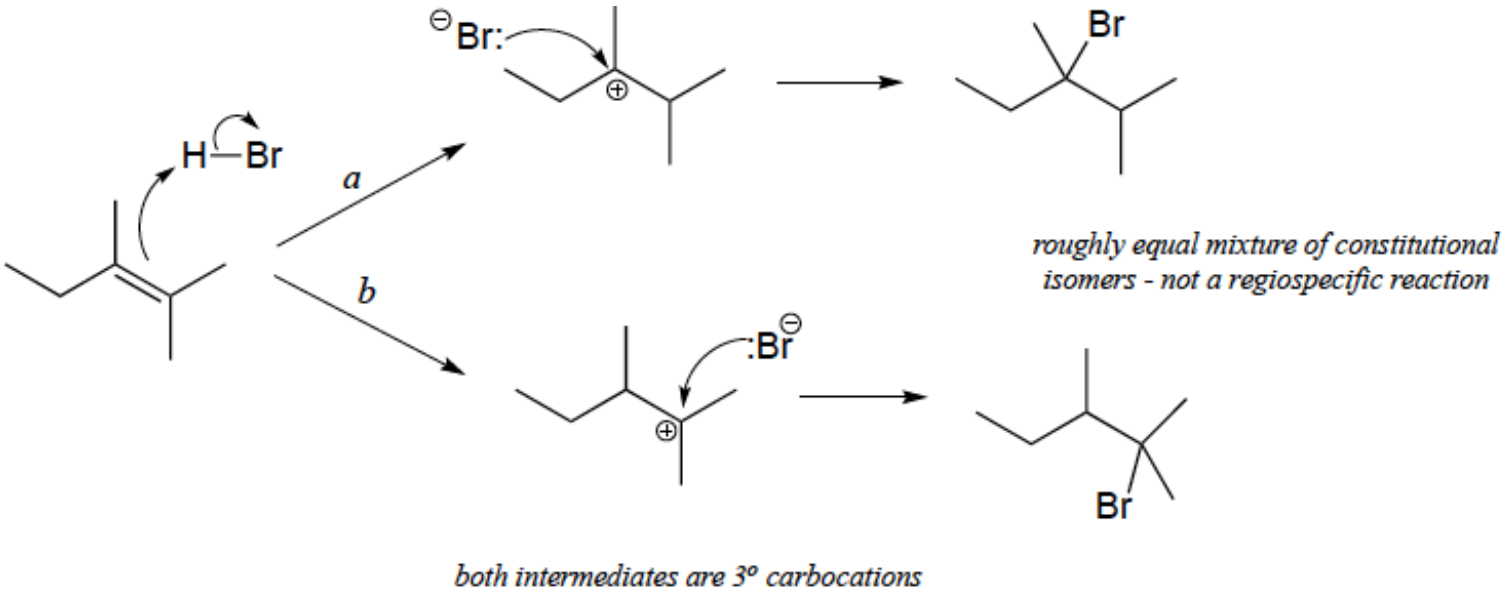
When an asymmetrical alkene undergoes electrophilic addition, the product that predominates is the one that results from the more stable of the two possible carbocation intermediates.

Electrophilic Addition – Markovnikov's Rule



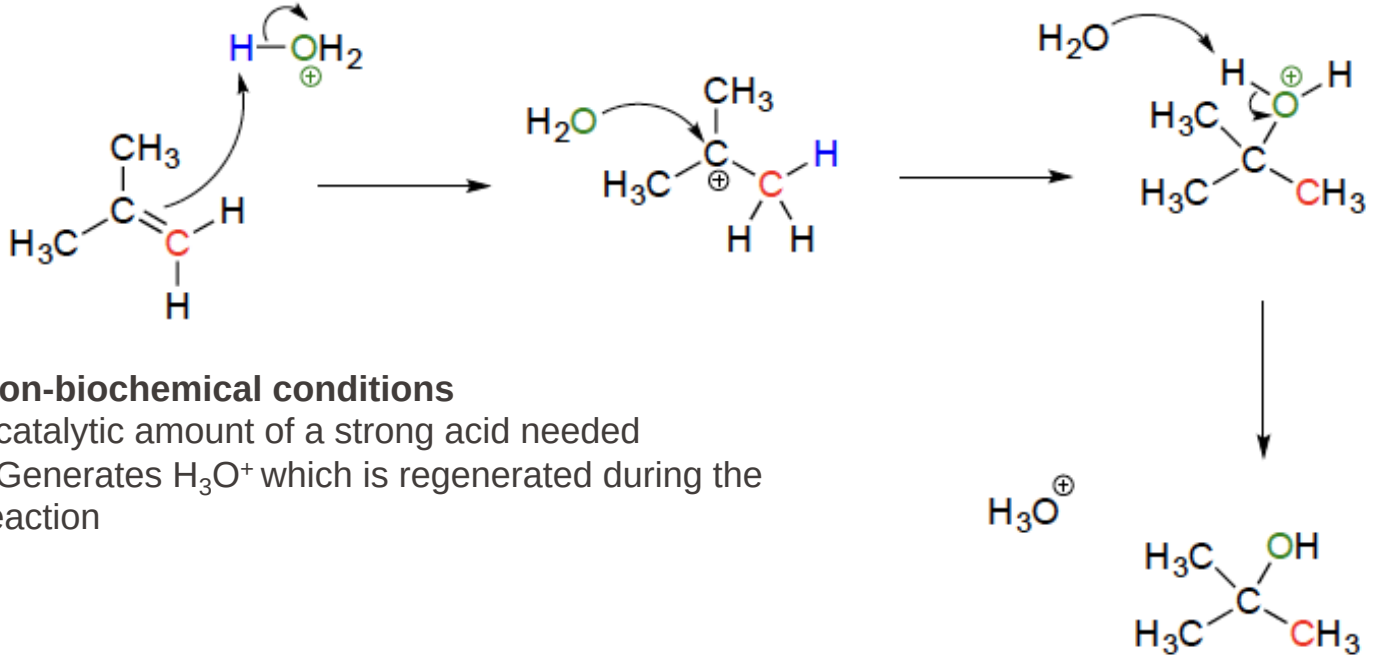
Under certain conditions (like the presence of electronegative withdrawing groups) the less substituted carbocation is formed faster leading to the **anti-Markovnikov product**

Electrophilic Addition – Markovnikov's Rule



If the two possible carbocation intermediates in an electrophilic addition reaction are of **similar stability**, the product will be a **mixture of constitutional isomers**.

Electrophile addition of water



Non-biochemical conditions

- catalytic amount of a strong acid needed
- Generates H_3O^+ which is regenerated during the reaction

Let's do one of these together

What to know

-Reactivity of the double bond

-Stereochemistry and regiochemistry of electrophilic reactions

-Markovnikov rule

-Addition reaction

-Elimination reactions

-Zaitsev’s rule

-Differences between the different elimination mechanisms

Questions?

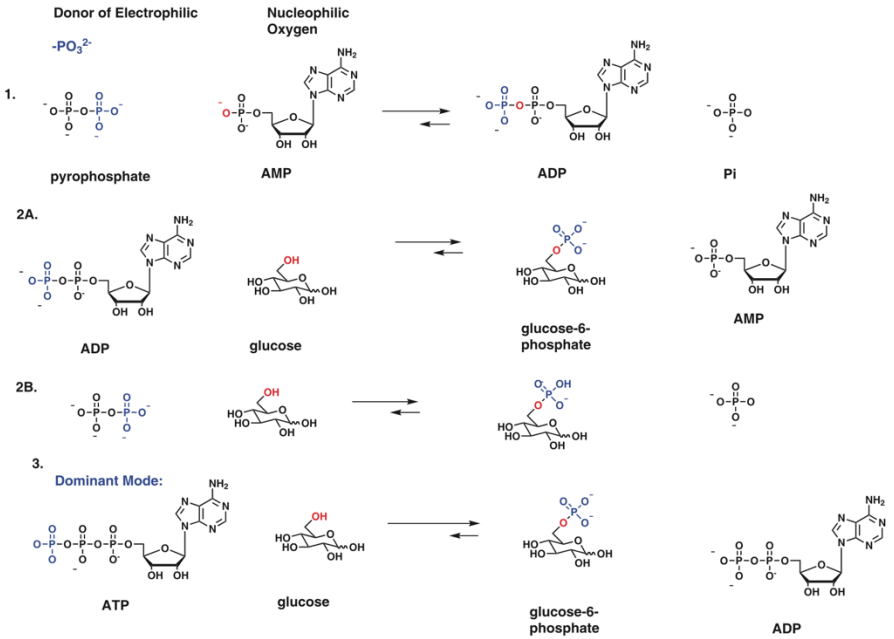
Phosphates in biology

Table 1. Examples of phosphates in biochemistry.

Phosphate	Acid derivative
DNA	Diester of phosphoric acid
RNA	Diester of phosphoric acid
ATP	Anhydride of phosphoric acid
Creatine phosphate	Amide of phosphoric acid
Phosphoenolpyruvate	Enol ester of phosphoric acid
Pyridoxal phosphate	Phenol ester of phosphoric acid
Nicotine adenine dinucleotide	Ester and anhydride of phosphoric acid
Fructose 1,6-diphosphate	Ester of phosphoric acid
Glucose-6-phosphate	Ester of phosphoric acid
Isopentenyl pyrophosphate	Ester of pyrophosphoric acid
Ribose-6-phosphate-1-pyrophosphate	Ester of phosphoric and pyrophosphoric acids

Why Nature Chose Phosphates

F. H. WESTHEIMER



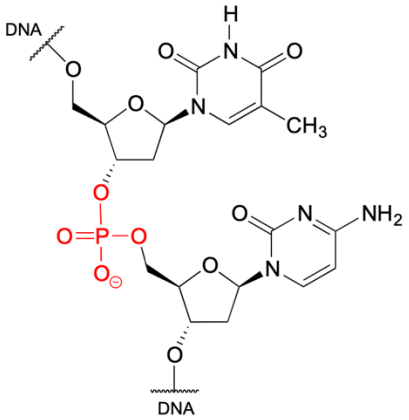
Why Phosphorylation?

1. Electrostatics: two negative charges
2. Specificity: >3 highly directional hydrogen bonds
3. Thermodynamic stability: -12 kcal/mol
4. Signal can be amplified
5. Adjustable kinetics (seconds to hours)
6. Availability: high intracellular ATP concentration

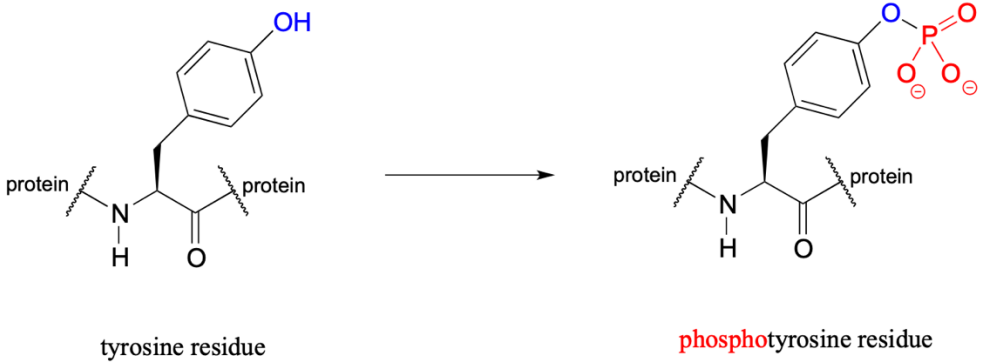
Great historic paper:
Westheimer: Why Nature Chose Phosphates (1987) Science, 235 (4793),1173-8

Phosphates in biology

Base-pair linkage



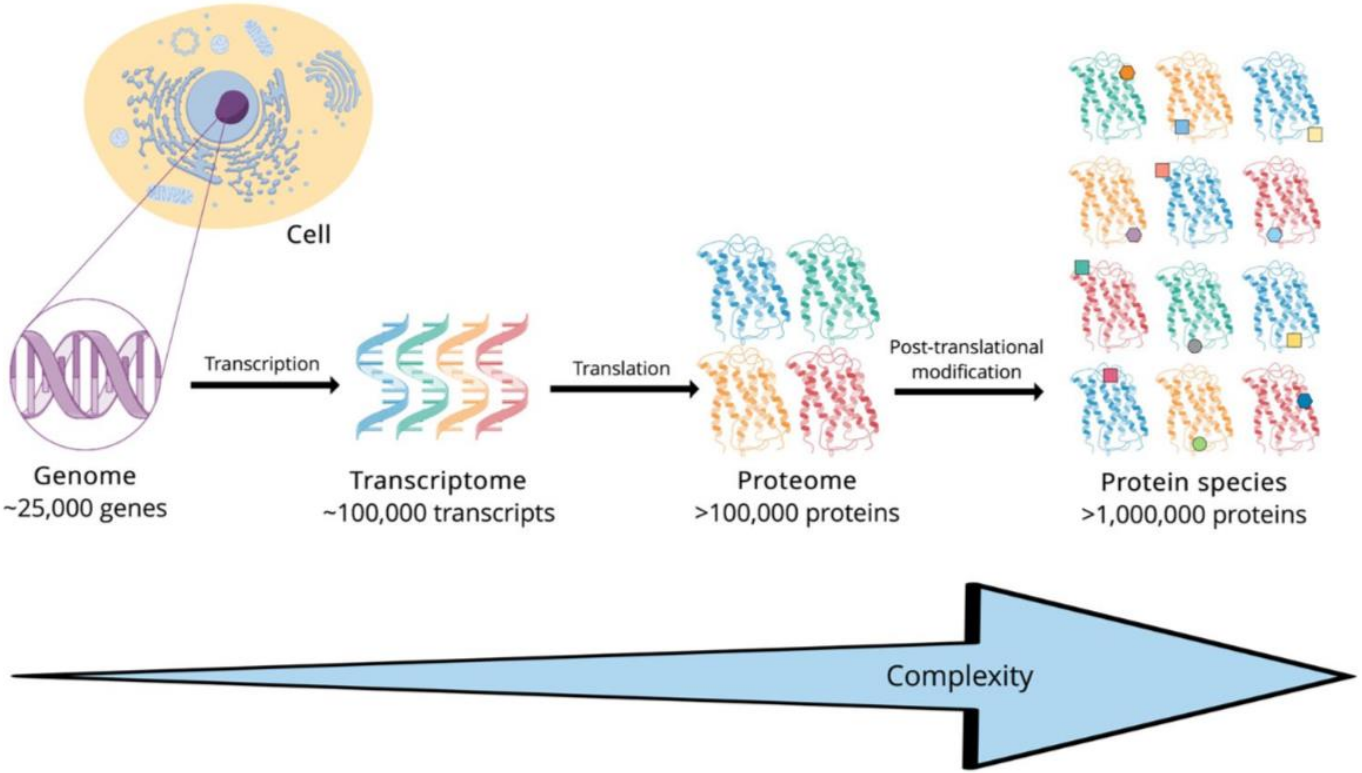
Controlling protein activity



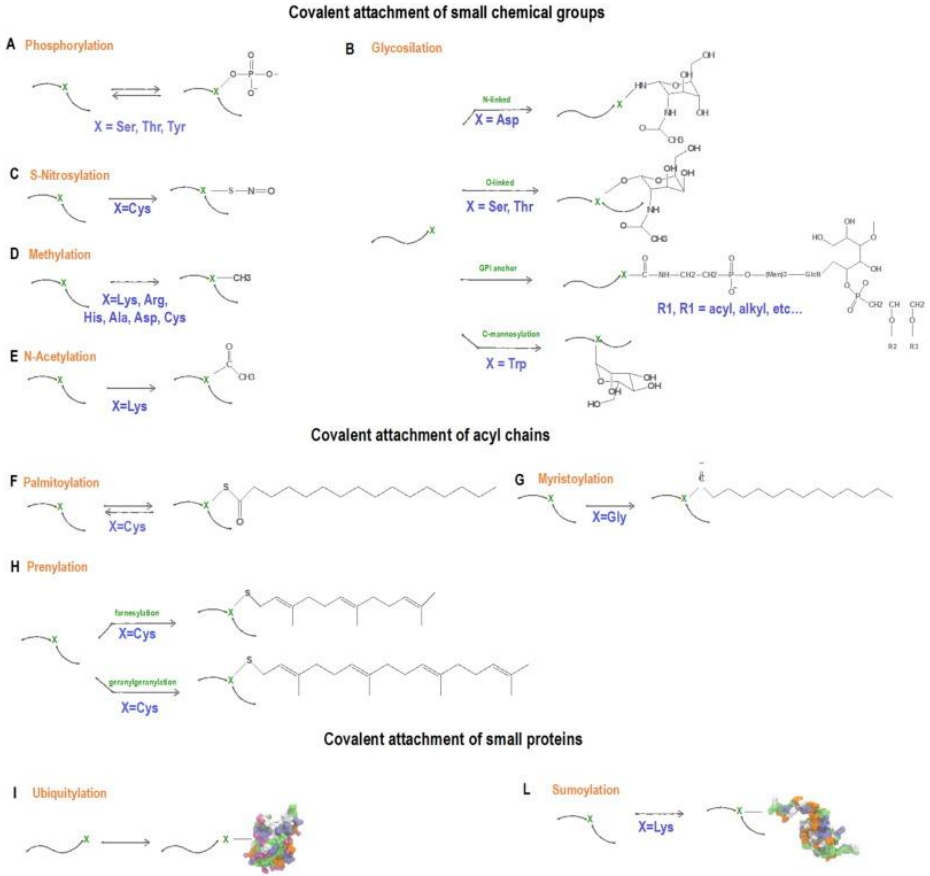
tyrosine residue

phosphotyrosine residue

What are post-translational modifications

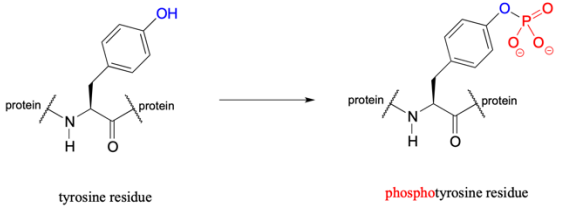


Chemically defined modifications are performed to the aminoacids



Protein Phosphorylation: General

- Most common post-translational modification
- Occur on hydroxyl (OH-) groups in Ser, Thr or Tyr (in eukaryotes)
- Also on His (but much less well studied)
- At least 30% of all human proteins are known to be phosphorylated at at least one residue



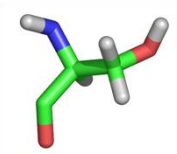
tyrosine residue

phosphotyrosine residue

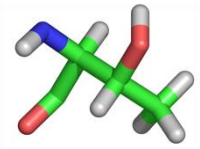
Theoretical considerations on phosphorylation:

- average length of protein is ~400 amino acids
- ~10.000 different proteins in a cell
- ~15% are Ser (6.6%), Thr (5.3%) or Tyr (2.9%) residues (see BCI)
- then there are ~600,000 potential phosphorylation sites!

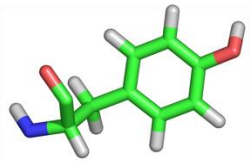
Serine



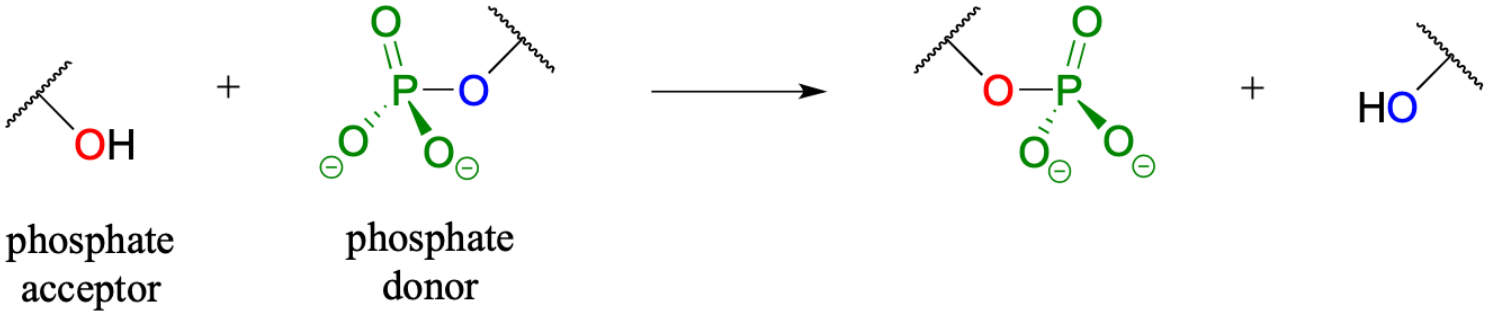
Threonine



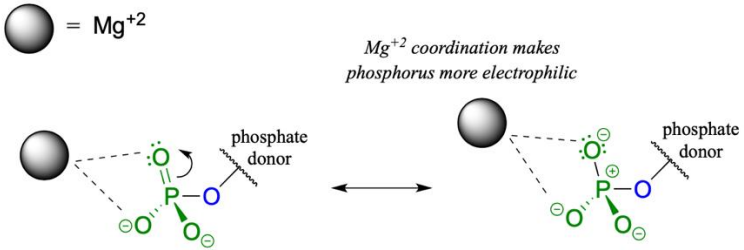
Tyrosine



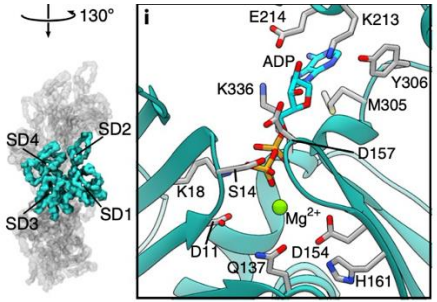
Phosphate transfer reactions – overview



-Electrophilicity of the phosphorus atom is enhanced by magnesium ions



-Magnesium ion pulls electron density away from the phosphorus making it more electrophilic



Remember

Break Bond (**D**issocitation)

Make Bond (**A**ssociation)

Combinations:

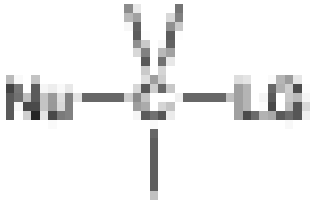
D then **A**

S_N1

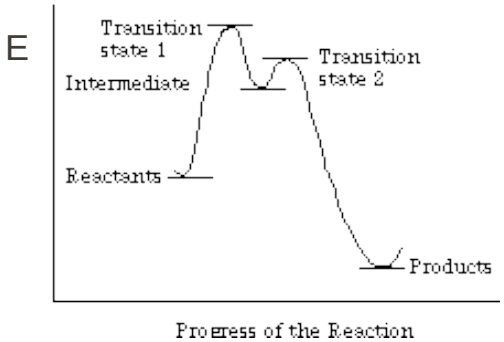
Trivalent *Intermediate*

A then **D**

Happens, but not with carbon

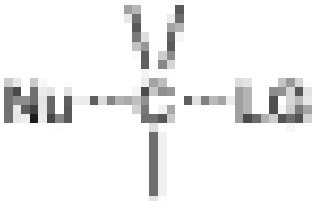


Pentavalent *Intermediate*

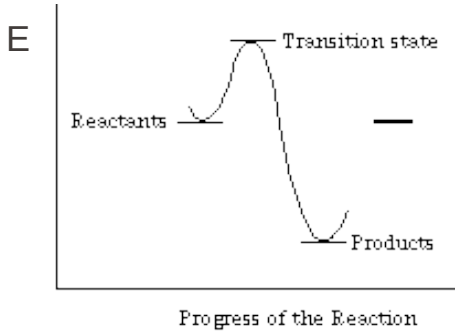


Simultaneous "**Concerted**" (make as you break)

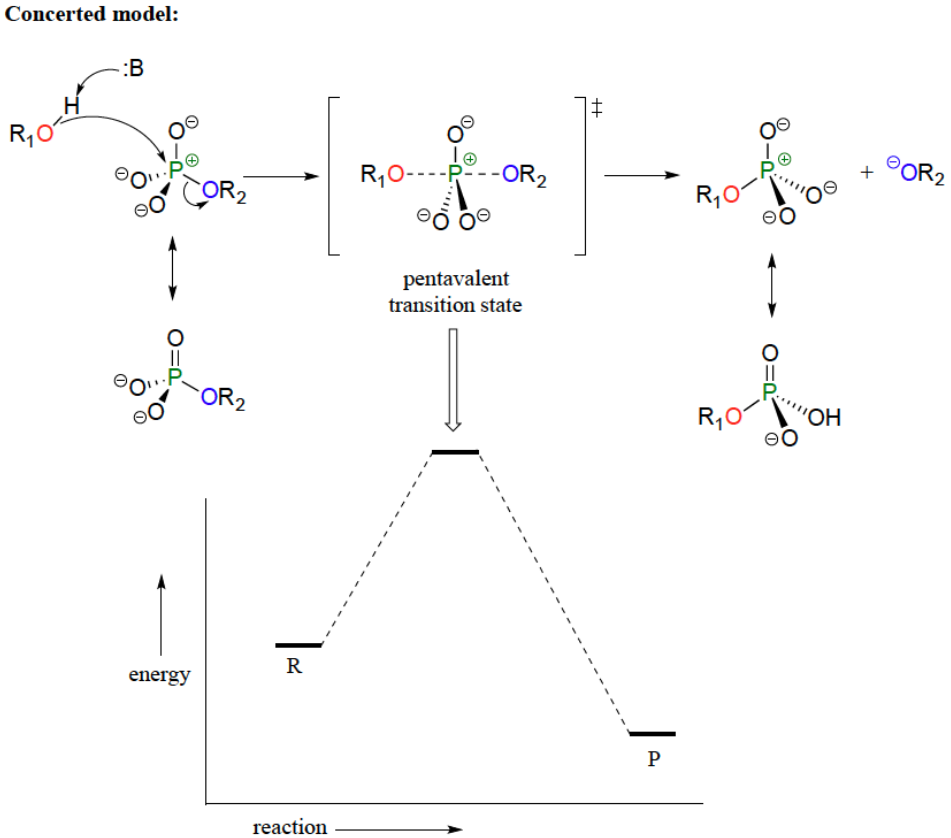
S_N2



Transition State



Mechanism of Phosphotransfer



-Phosphate transfer reaction can be thought of much like an SN2 reaction

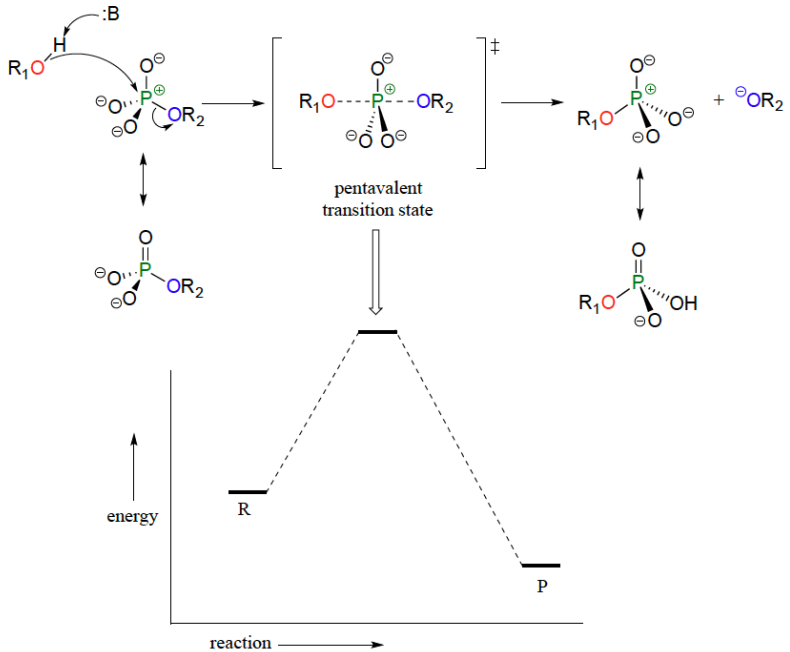
-Nucleophile attacks the phosphorus atom from the opposite side

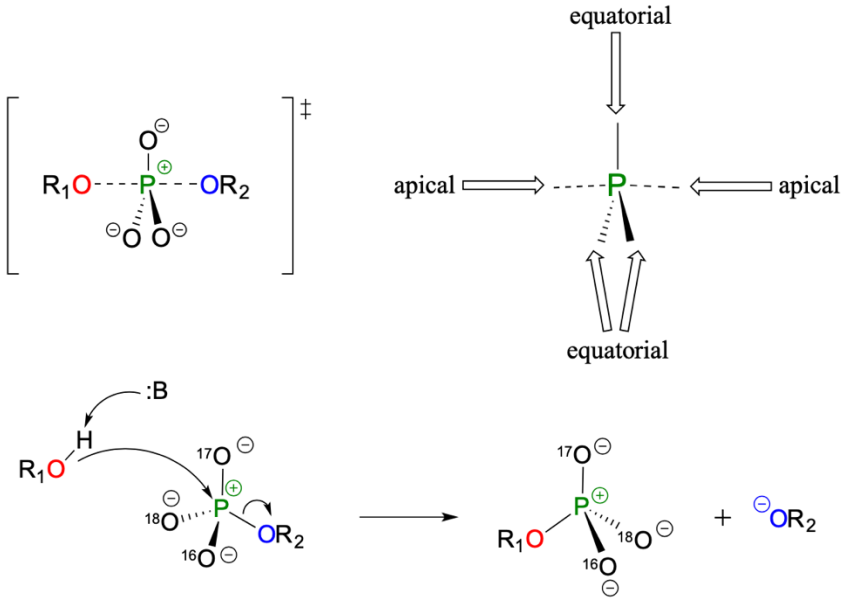
- **geometry** around the phosphorus atom shifts from **tetrahedral to trigonal bipyramidal** at the transition state with five bonds.

-Phosphorus undergoes a temporary change in bonding, shifting back to its initial tetrahedral state after the nucleophile and leaving group alteration.

Mechanism of Phosphotransfer

Concerted model:



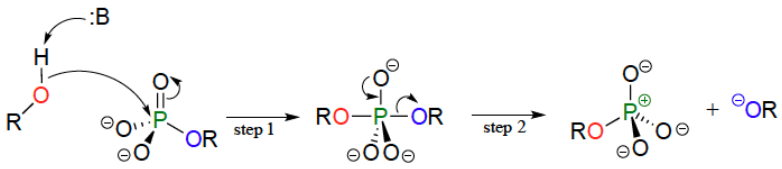


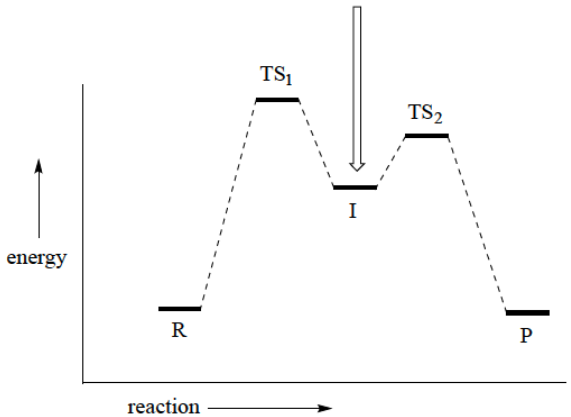
phosphate has *S* configuration

phosphate has *R* configuration

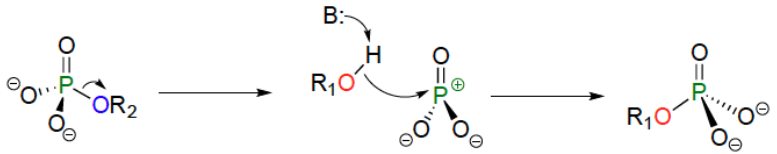
Mechanism of Phosphotransfer

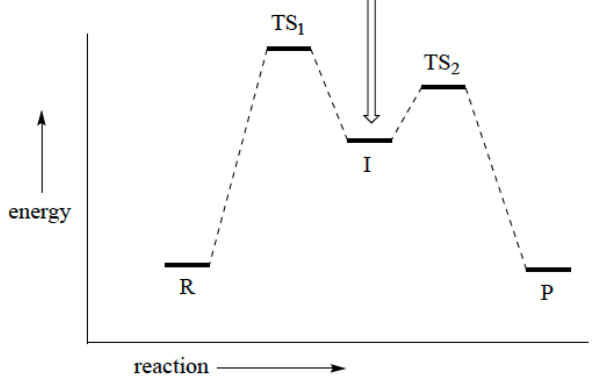
Addition-elimination model:





Elimination-addition model:





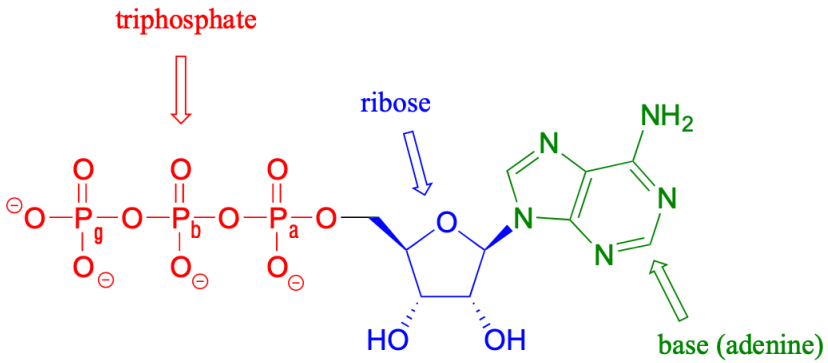
- There is still debate to which real mechanism is happening in the phosphor transfer reaction
- For now we ill accept the concerted model as the one that is occurring

The reaction of life: ATP as a biological Phosphate Donor

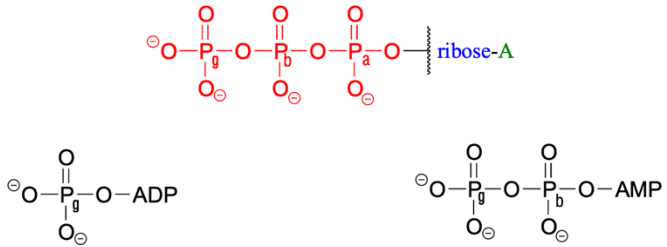
-The most important phosphate donor is a adenosine triphosphate

-ATP is used as the energetic currency in biological processes

-ATP hydrolysis is one of the most important reactions in biology



One can represent these molecules in different ways



Questions?