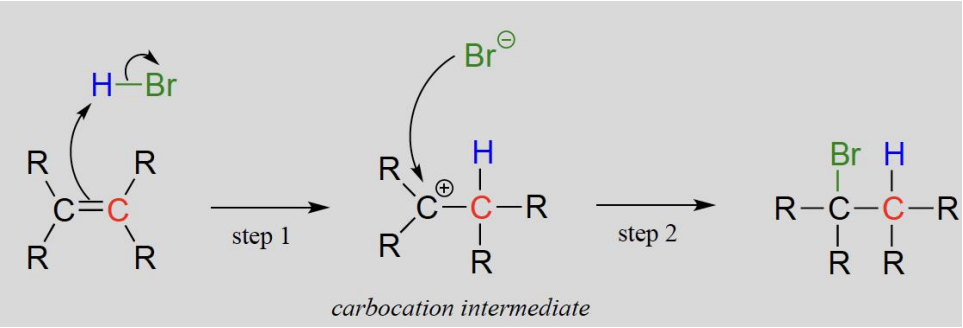
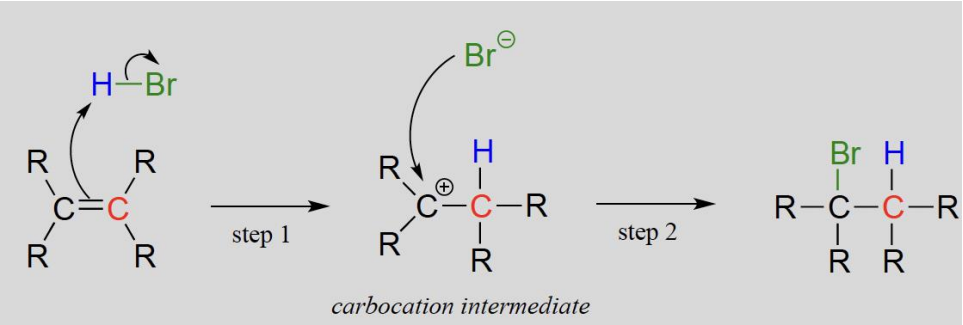
Bioorganic Chemistry

Lecture 8

Electrophilic reactions

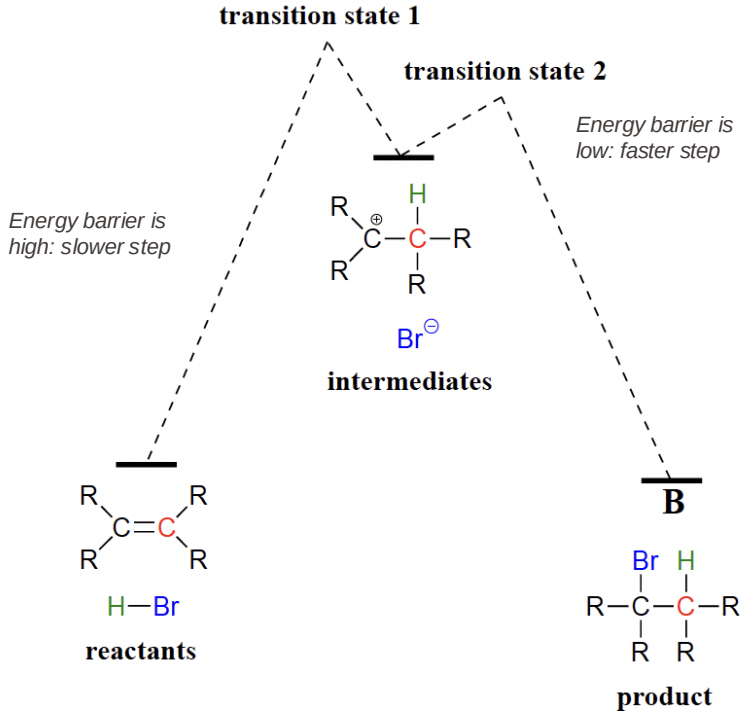


Electrophilic Addition of HBr - Overview

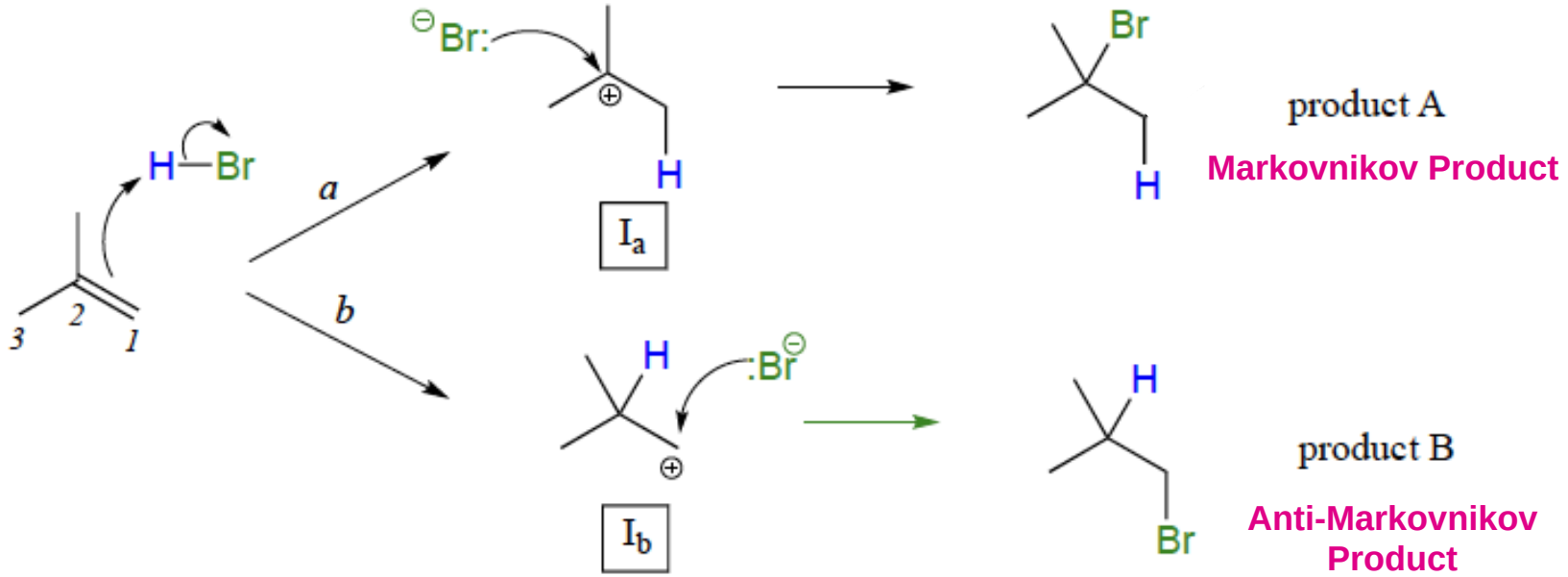


Step1: π - electrons of the alkene act as a base and extract the acidic proton of HBr
-> incomplete octet and a positive formal charge (high energy)

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



Electrophilic Addition – Markovnikov's Rule

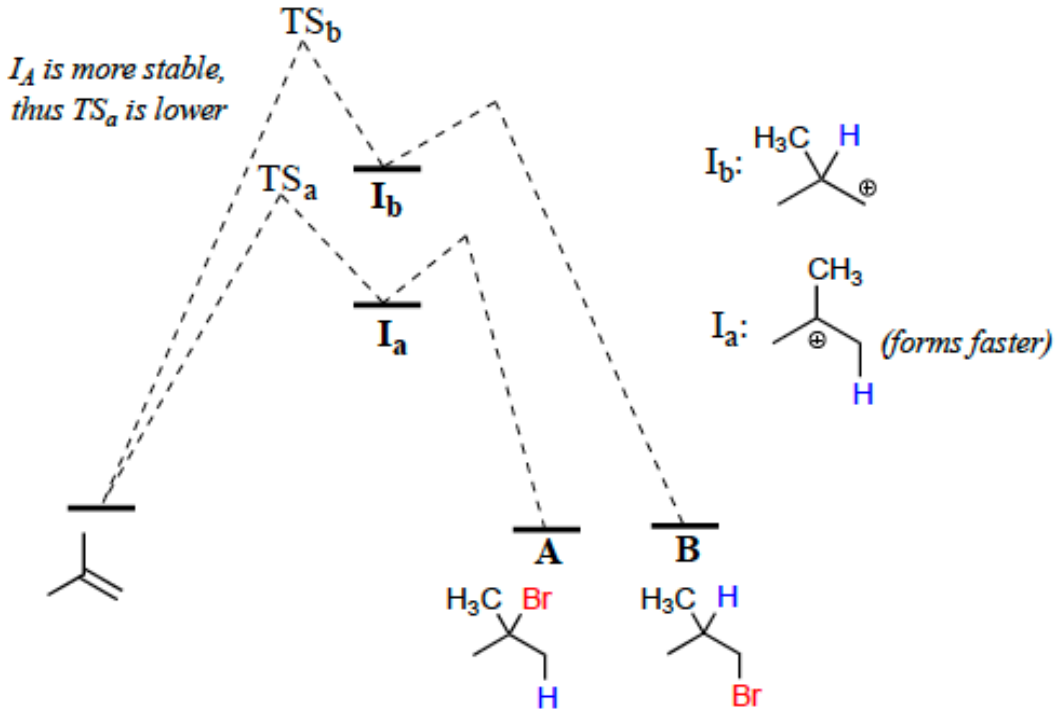


Markovnikov's rule

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!

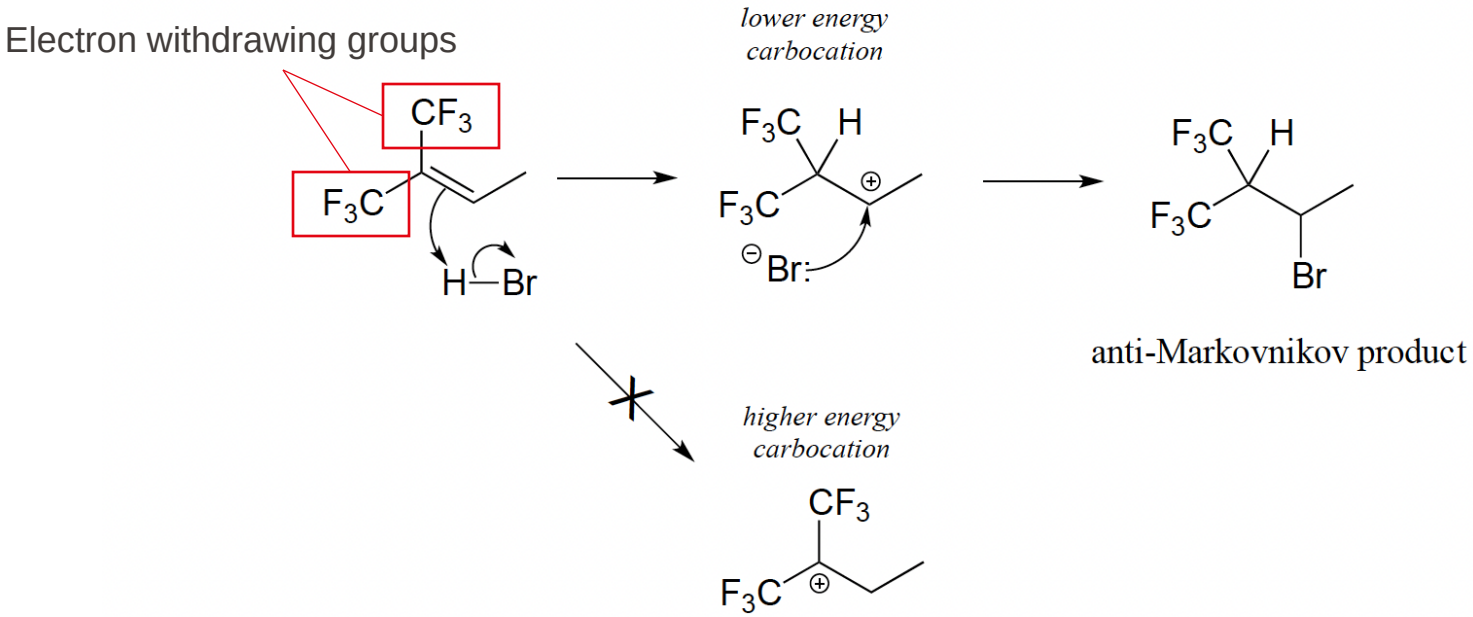
Electrophilic Addition – Regioselectivity



Regioselectivity

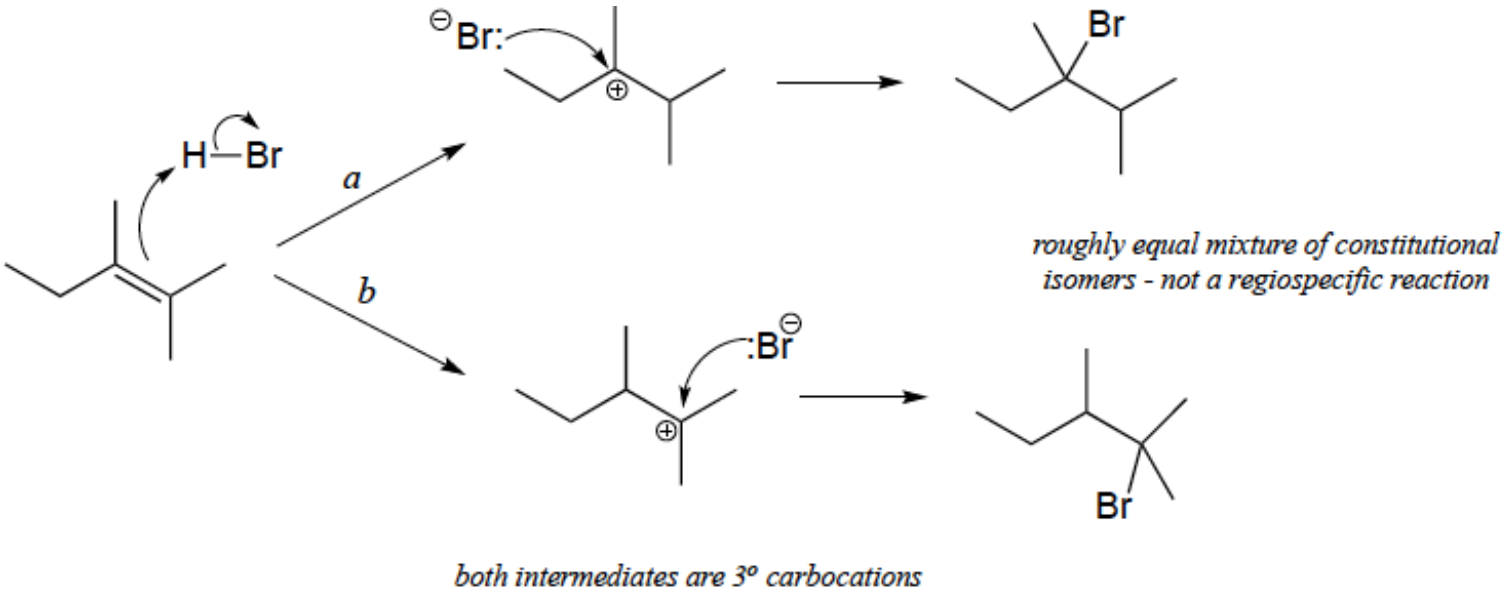
When an asymmetrical alkene undergoes electrophilic addition, the product that predominates is the one that results from the more stable of the two possible carbocation intermediates.

Electrophilic Addition – Markovnikov's Rule



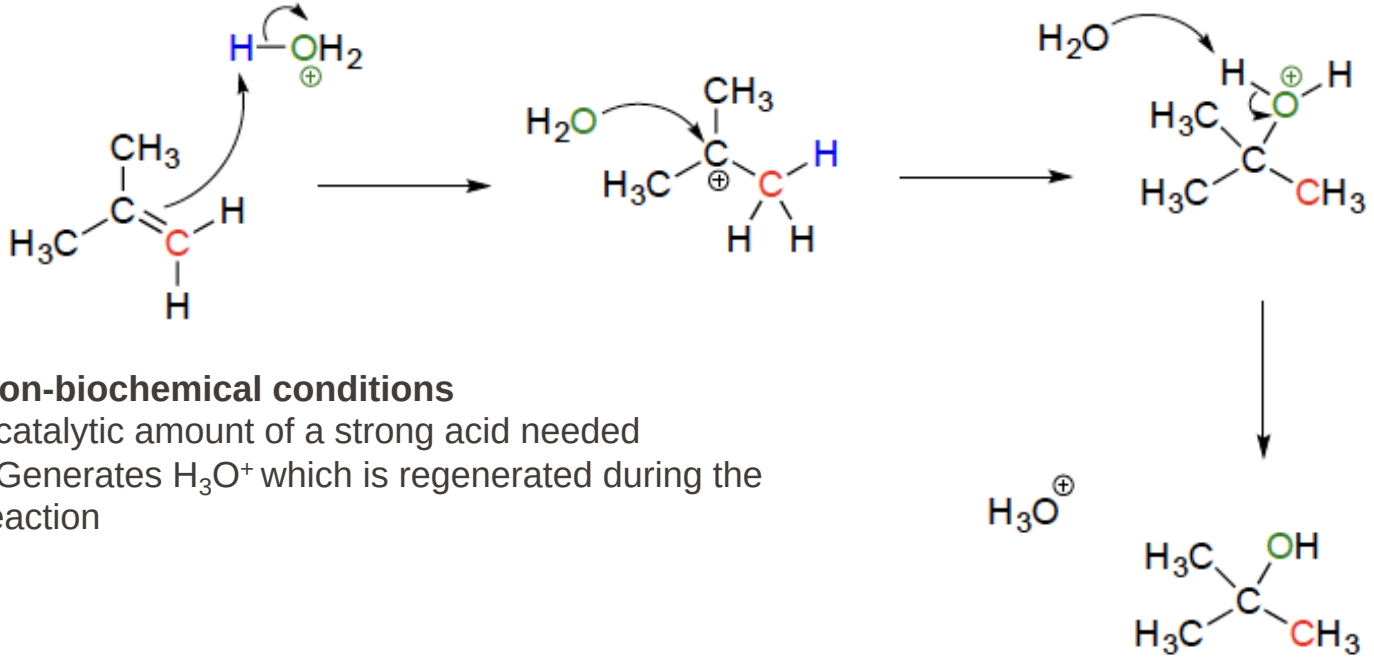
Under certain conditions (like the presence of electronegative withdrawing groups) the less substituted carbocation is formed faster leading to the **anti-Markovnikov product**

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?

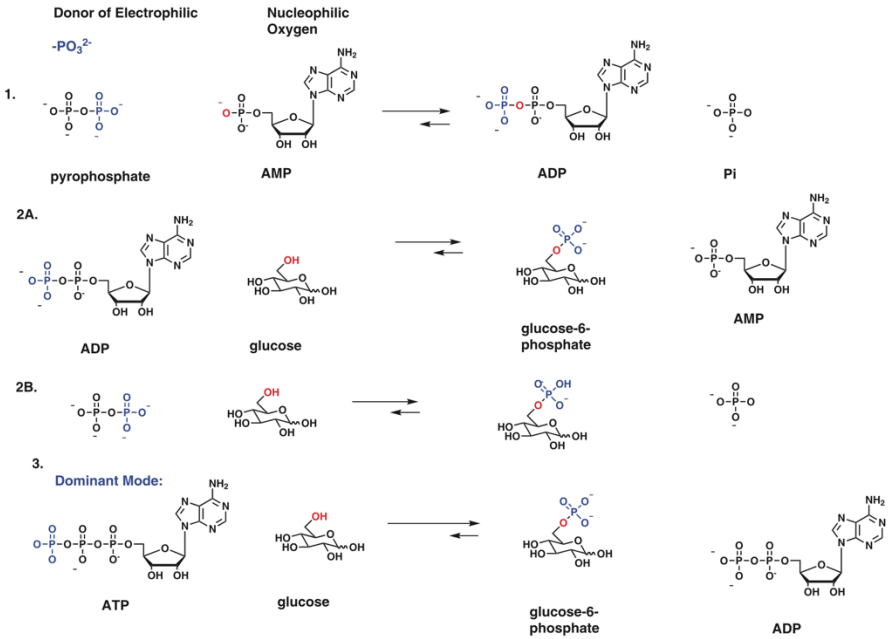
Phosphates in biology

Table 1. Examples of phosphates in biochemistry.

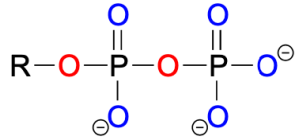
Phosphate	Acid derivative
DNA	Diester of phosphoric acid
RNA	Diester of phosphoric acid
ATP	Anhydride of phosphoric acid
Creatine phosphate	Amide of phosphoric acid
Phosphoenolpyruvate	Enol ester of phosphoric acid
Pyridoxal phosphate	Phenol ester of phosphoric acid
Nicotine adenine dinucleotide	Ester 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

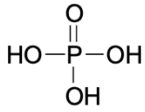
F. H. WESTHEIMER



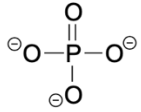
A few nomenclatures



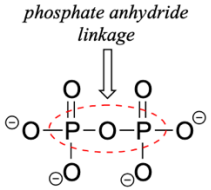
red = bridging oxygen
blue = non-bridging oxygen



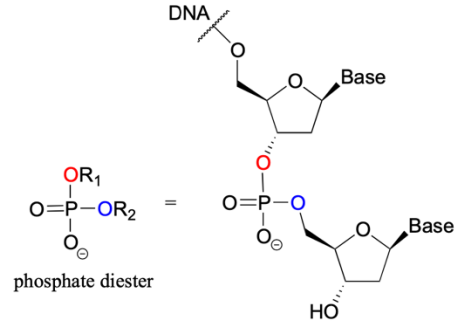
phosphoric acid



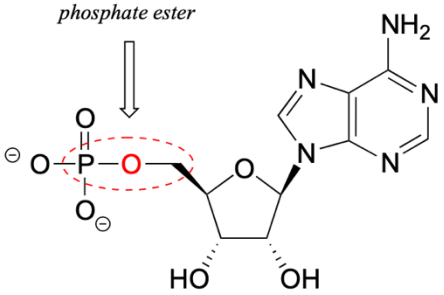
inorganic phosphate (P_i)



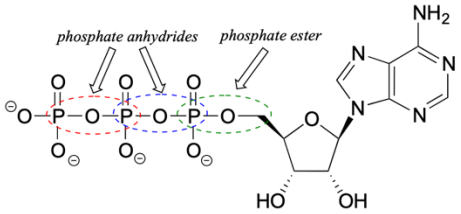
inorganic pyrophosphate (PP_i)



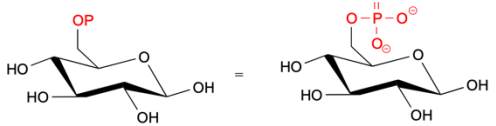
phosphate diester



adenosine monophosphate (AMP)



adenosine triphosphate (ATP)

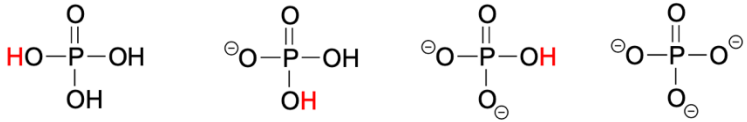


glucose-6-phosphate

isopentenyl diphosphate

Acid constants & protonation states

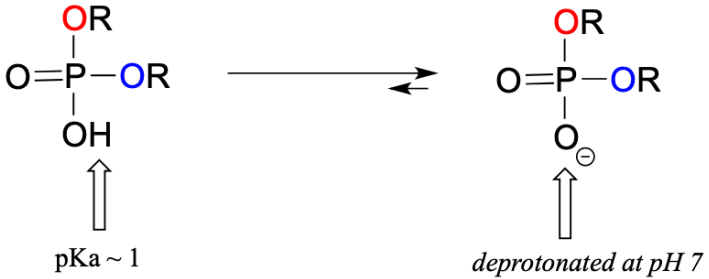
Phosphoric acid is triprotic



H_3PO_4 pKa = 1.0 | $H_2PO_4^{-1}$ pKa = 6.5 | HPO_4^{-2} pKa = 13.0 | PO_4^{-3}

At pH=7 more than half will be at the HPO_4^{-2} state

Phosphate diesters are negative at pH 7



-Phosphates are very common leaving groups meaning that they are weakly basic.

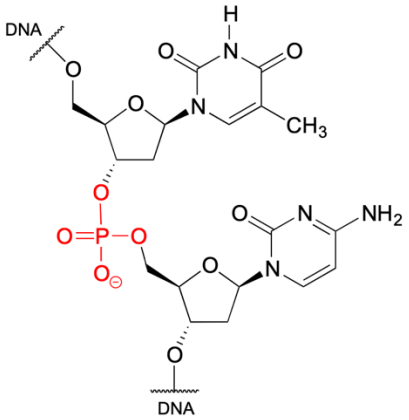
Why Phosphorylation?

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

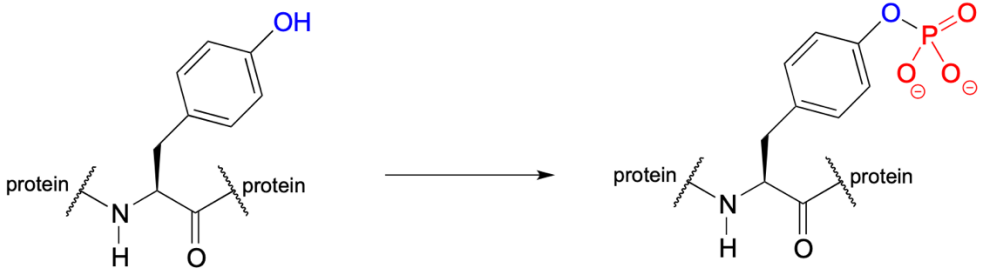
Great historic paper:
Westheimer: Why Nature Chose Phosphates (1987) Science, 235 (4793),1173-8

Phosphates in biology

Base-pair linkage



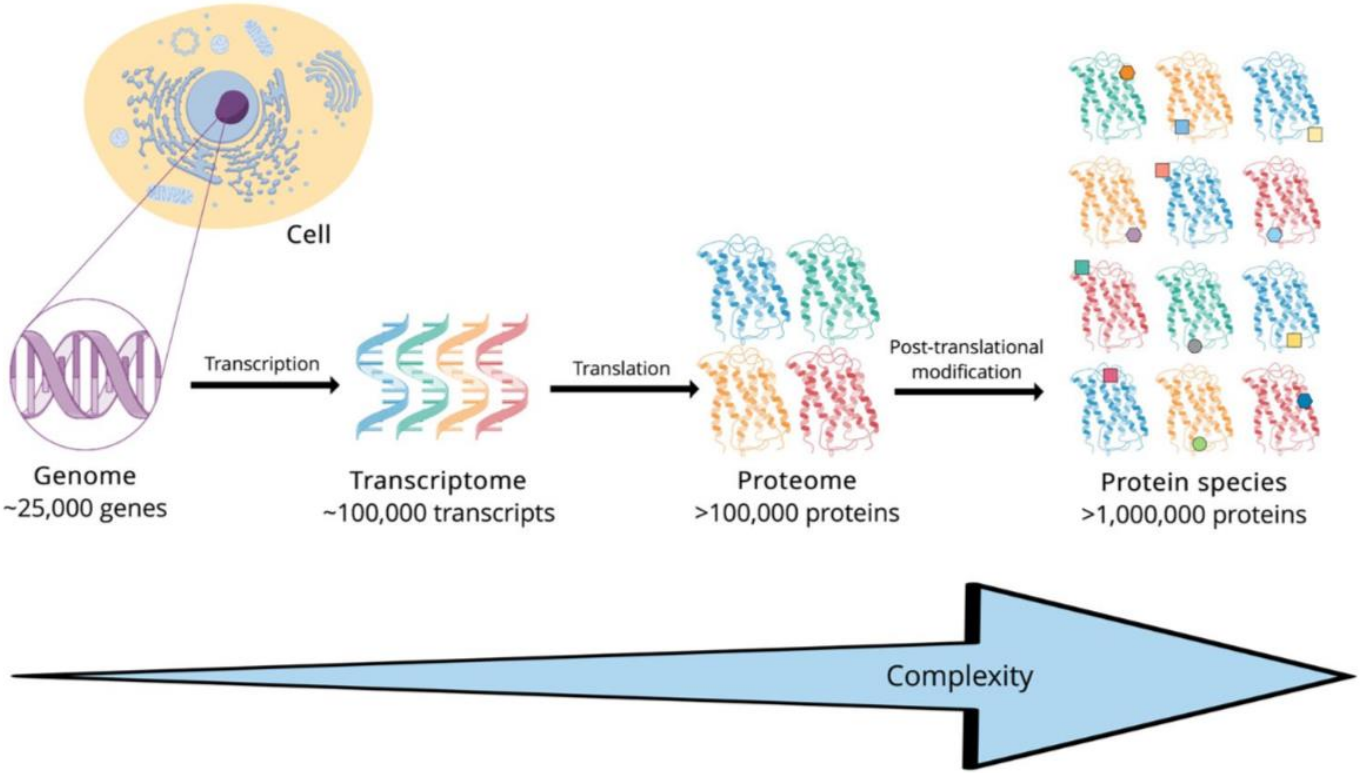
Controlling protein activity



tyrosine residue

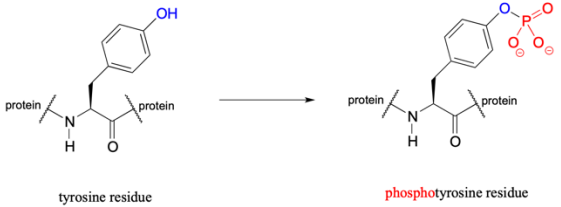
phosphotyrosine residue

What are post-translational modifications



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



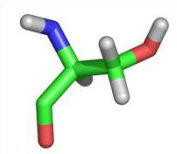
tyrosine residue

phosphotyrosine residue

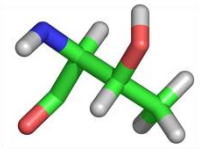
Theoretical considerations on phosphorylation:

- 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!

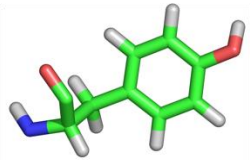
Serine



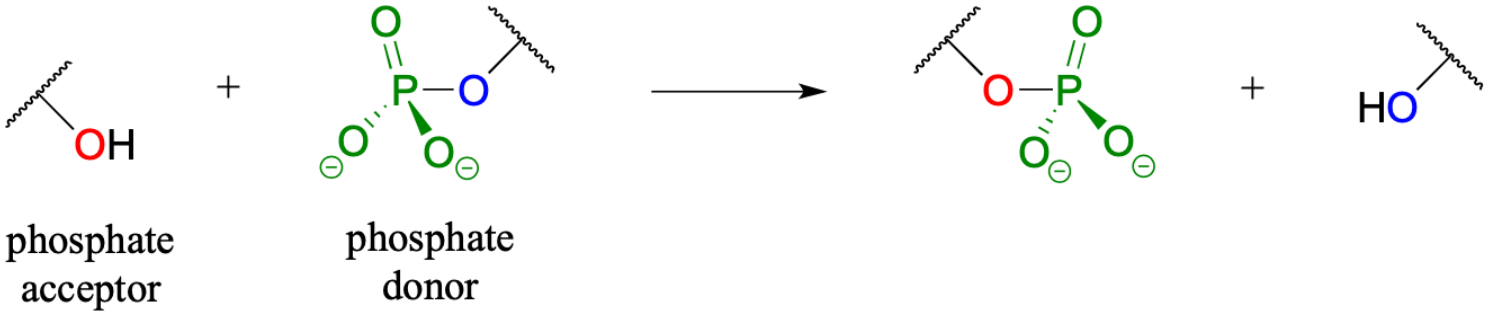
Threonine



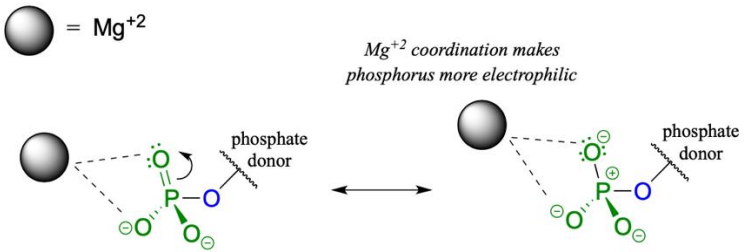
Tyrosine



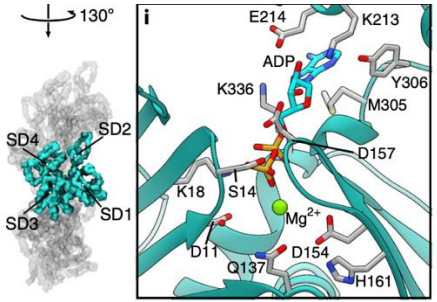
Phosphate transfer reactions – overview



-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:

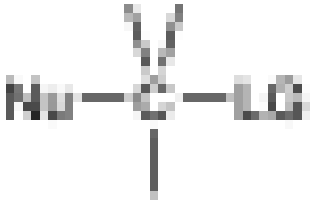
D then **A**

S_N1

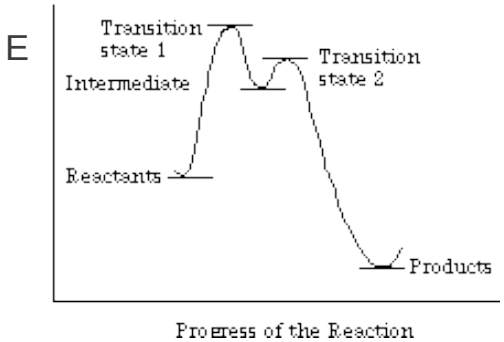
Trivalent *Intermediate*

A then **D**

Happens, but not with carbon

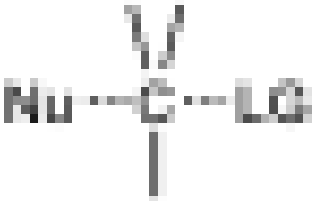


Pentavalent *Intermediate*

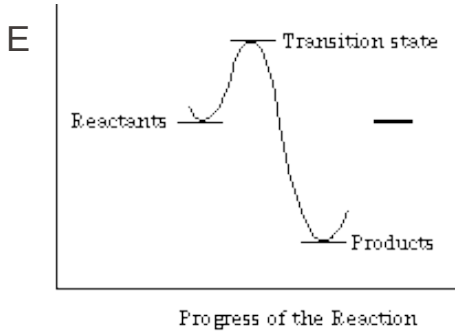


Simultaneous "**Concerted**" (make as you break)

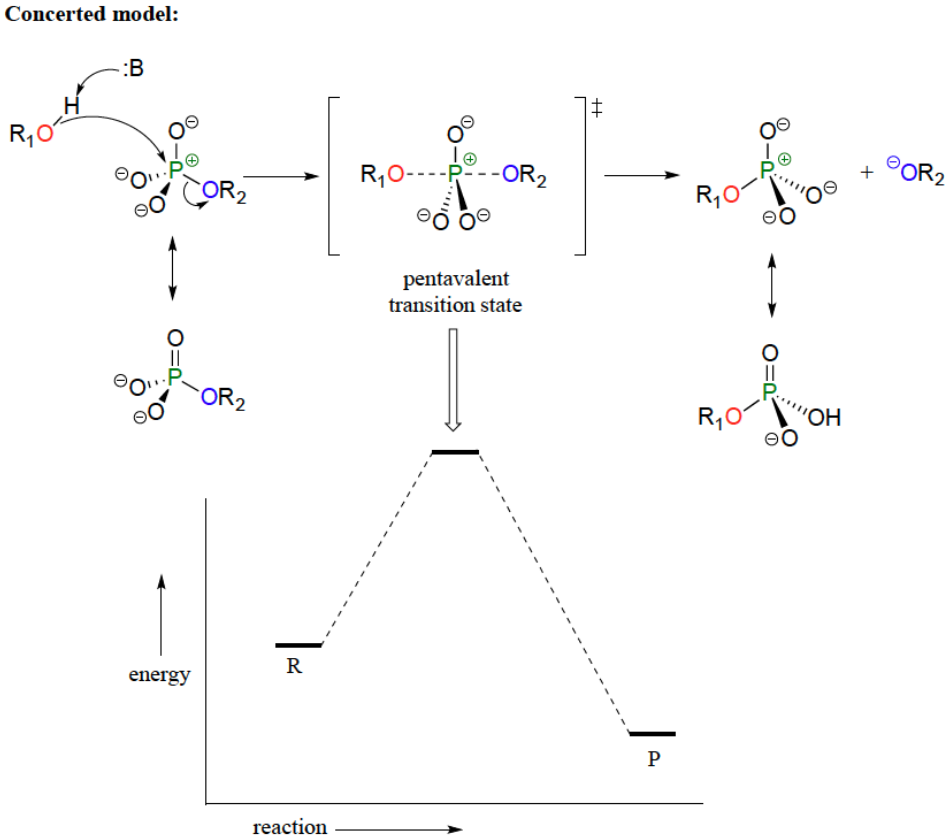
S_N2



Transition State



Mechanism of Phosphotransfer



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

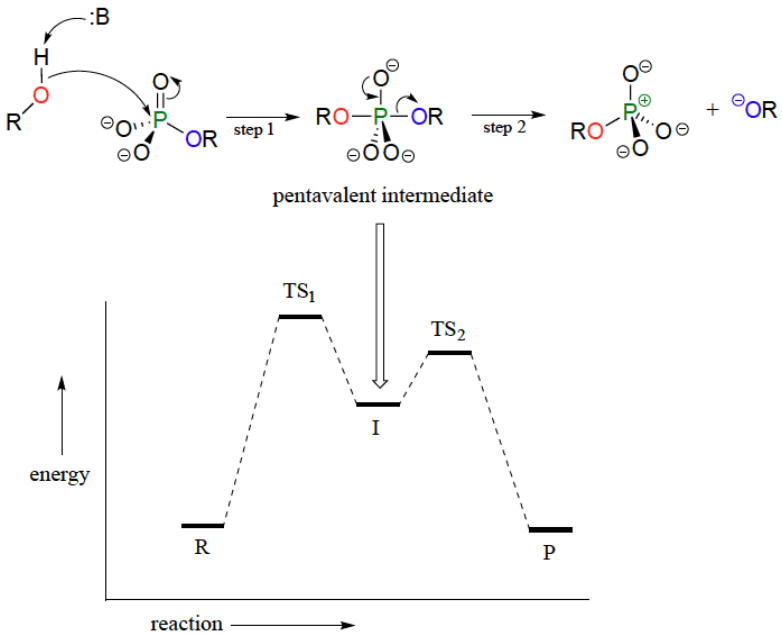
-Nucleophile attacks the phosphorus atom from the opposite side

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

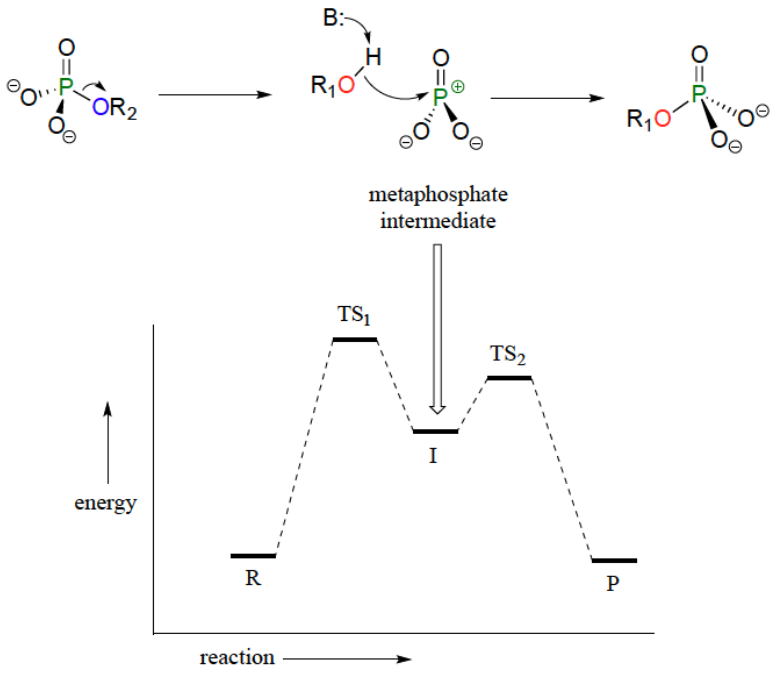
-Phosphorus undergoes a temporary change in bonding, shifting back to its initial tetrahedral state after the nucleophile and leaving group alteration.

Mechanism of Phosphotransfer

Addition-elimination model:



Elimination-addition model:



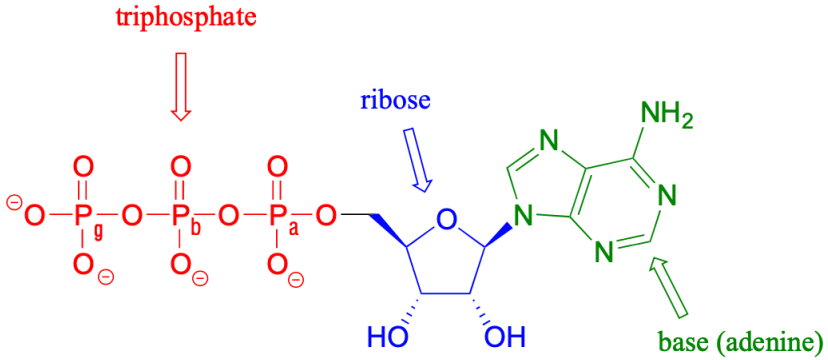
- There is still debate to which real mechanism is happening in the phosphor transfer reaction
- For now we will accept the concerted model as the one that is occurring

The reaction of life: ATP as a biological Phosphate Donor

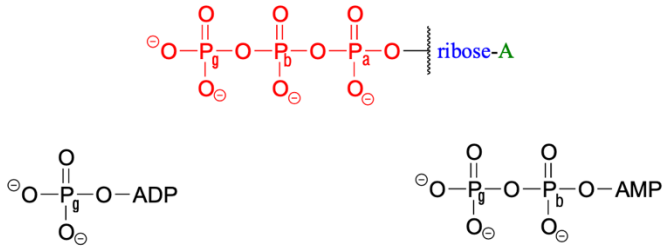
-The most important phosphate donor is a adenosine triphosphate

-ATP is used as the energetic currency in biological processes

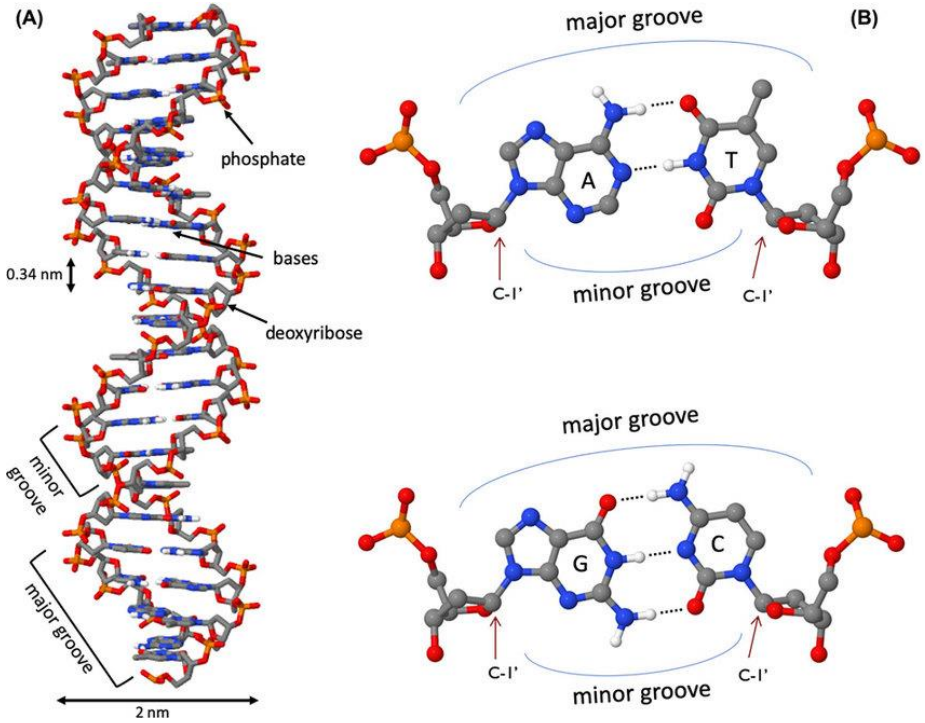
-ATP hydrolysis is one of the most important reactions in biology



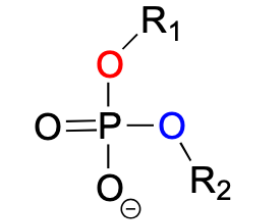
One can represent these molecules in different ways



Phosphate groups in DNA

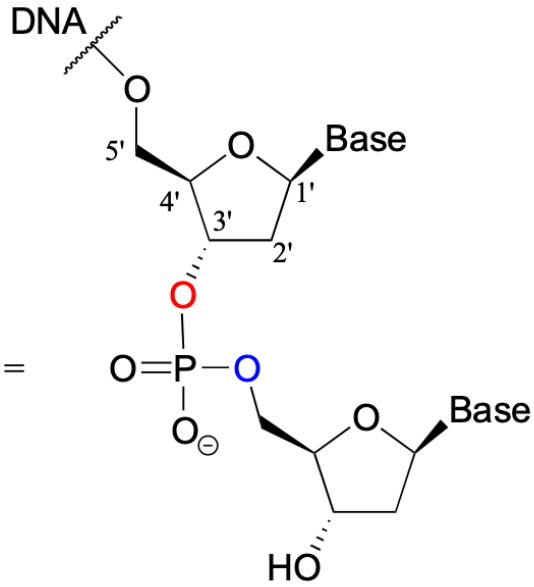


-Phosphate diesters play a critical role in nature by connecting individual nucleotides in DNA and RNA via a sugar-phosphate backbone



phosphate diester

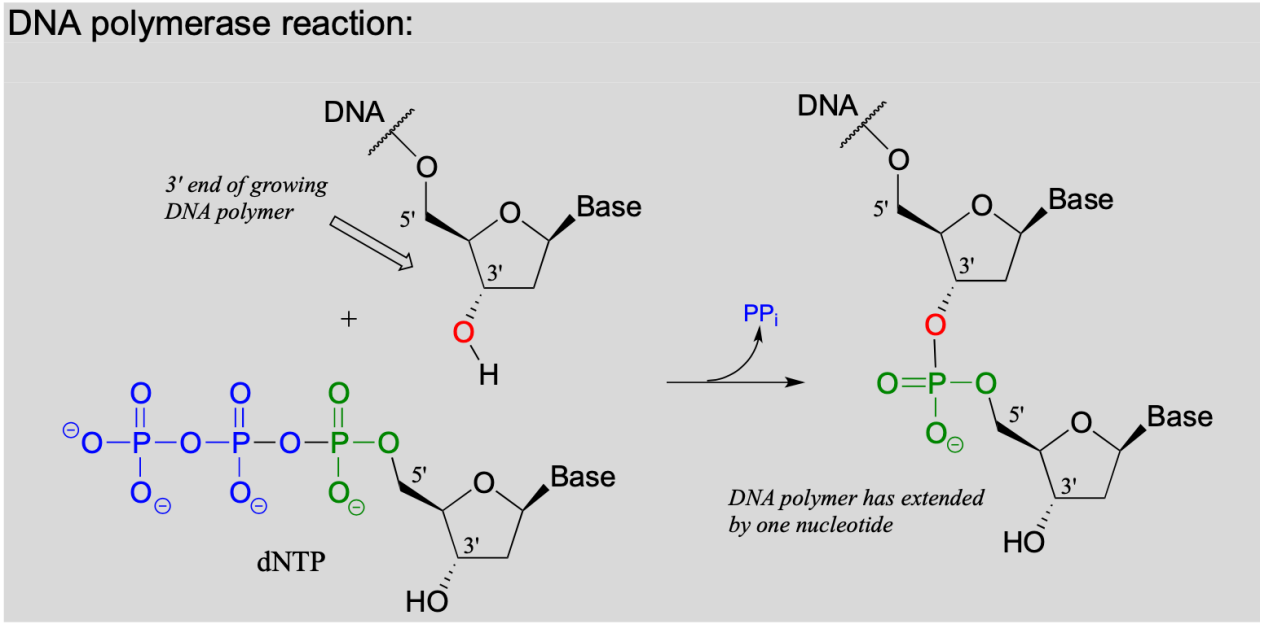
=



Phosphate chemistry in DNA synsthesis

-One of the first steps of a cloning procedure is to “copy” a DNA strand

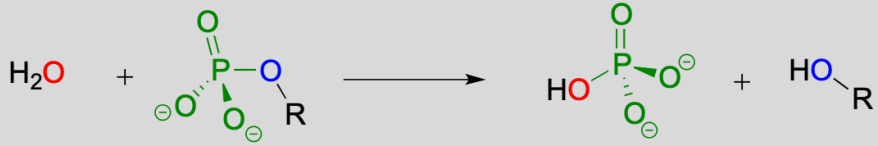
-3’ hydroxyl group of the growing strand of DNA attacks the α-phosphate



Hydrolysis of organic phosphates

- Enzymes called **phosphatases** catalyze dephosphorylation reactions

Phosphatase reaction:



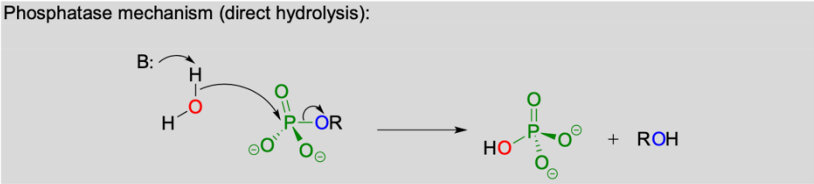
-The reactions catalyzed by kinases and phosphatases are not the reserve of one another

-Kinases irreversibly transfer phosphate groups from ATP to various acceptors

-Phosphatases transfer phosphate groups from organic compounds to water (hydrolysis reactions)

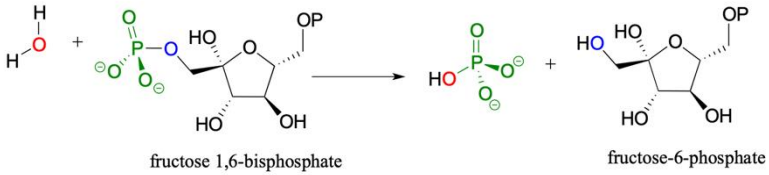
Two possibilities for the phosphate hydrolysis

- Direct hydrolysis

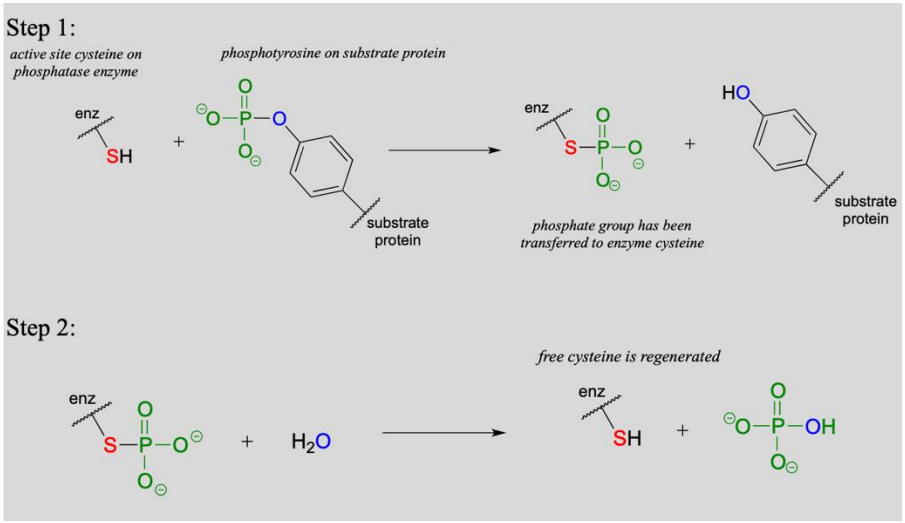


-the phosphate group is removed by direct attack of a water molecule

- Example on the gluconeogenesis pathway



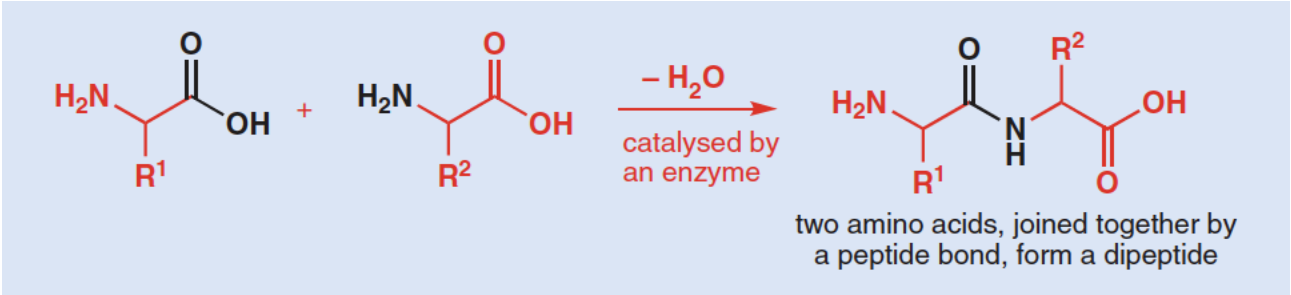
-Indirect phosphatase reaction

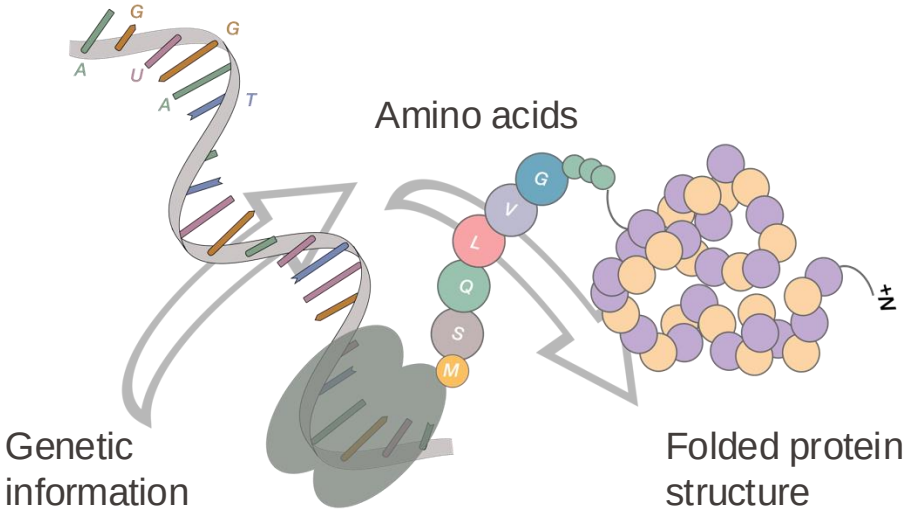


-First phase – nucleophilic enzyme group attacks the phosphate group
-Second phase – the phosphorylated residue is hydrolyzed
-Phosphate group has still being transferred to water

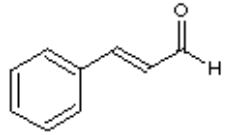
Questions?

Maybe the most important chapter – Carbonyl Chemistry

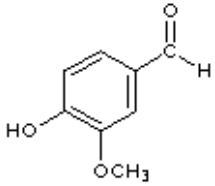




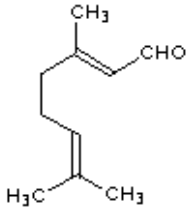
Maybe the most important chapter – Carbonyl Chemistry



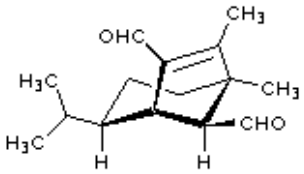
cinnamaldehyde
(cinnamon bark)



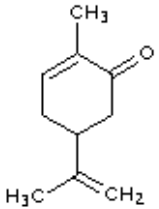
vanillin
(vanilla bean)



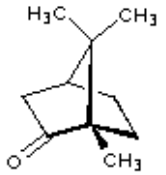
citral
(lemongrass)



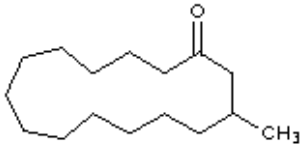
helminthosporal
(a fungal toxin)



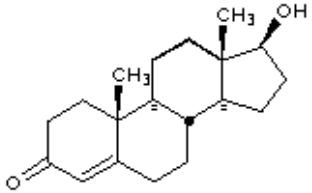
carvone
(spearmint & caraway)



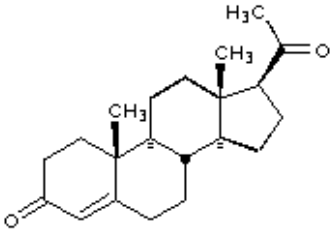
camphor
(camphor tree)



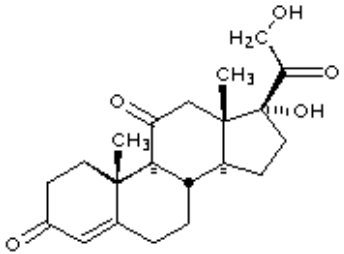
muscone
(musk deer)



testosterone
(male sex hormone)



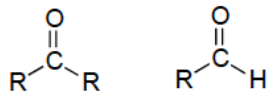
progesterone
(female sex hormone)



cortisone
(adrenal hormone)

Source: https://www2.chemistry.msu.edu/faculty/reusch/virttxtjml/aldket1.htm

Reactions directly at the Carbonyl group with acyl substituents

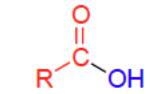


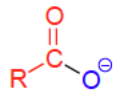
ketone

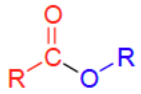
aldehyde

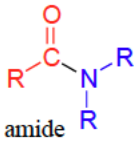
Carboxylic acid derivatives – Important nomenclature

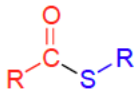
Simple carbonyls, in which the carbon of the C=O bond is attached to **other carbons** or to **hydrogens**
Carboxylic acid derivatives, or **carboxyloids**, in which the carbonyl carbon is attached to a "**heteroatom**"

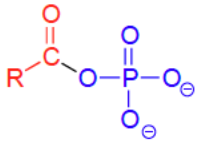

carboxylic acid

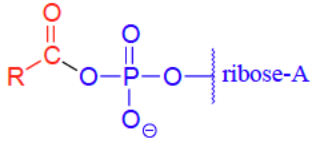

carboxylate


ester

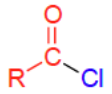

amide

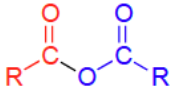

thioester

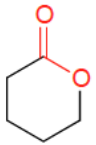

acyl phosphate

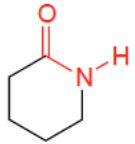


acyl-AMP

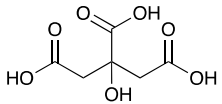

acid chloride

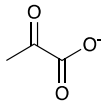

acid anhydride

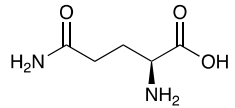

a lactone

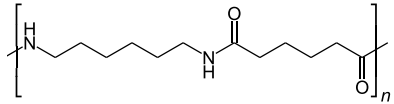

a lactam

Relevant molecules from life sciences


Citric acid


Pyruvate

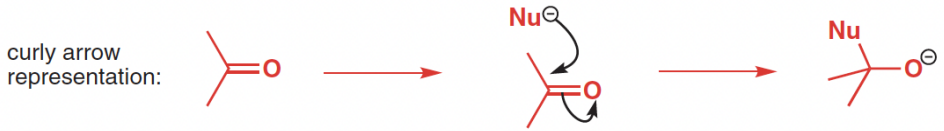

Glutamine

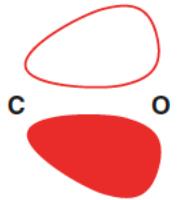

Polyamid 6.6

Original Nylon

Reactivity of Carbonyl Groups - Polarity

The polarized C=O bond gives the carbon atom some degree of positive charge, and this charge attracts negatively charged nucleophiles

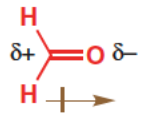




electronegativity difference means C=O π orbital is distorted towards O

electronegativity difference means C–O σ orbital is also distorted towards O

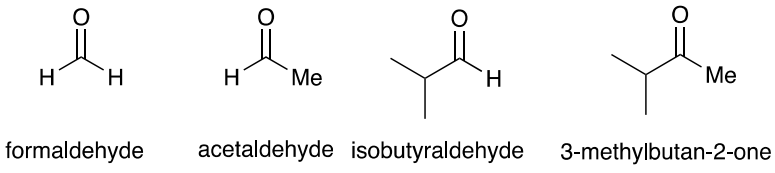
formaldehyde



the consequence: a dipole

Reactivity of Carbonyl Groups - Summary

Steric Effects

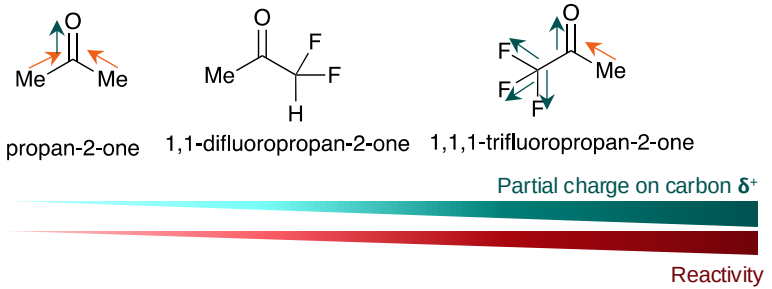


The less crowded the electrophile, the more reactive

➔ Aldehydes are more reactive than Ketones

Question: How easy can a reactant access the carbon?

Electronic Effects



The more positive the electrophile, the more easily it will react.

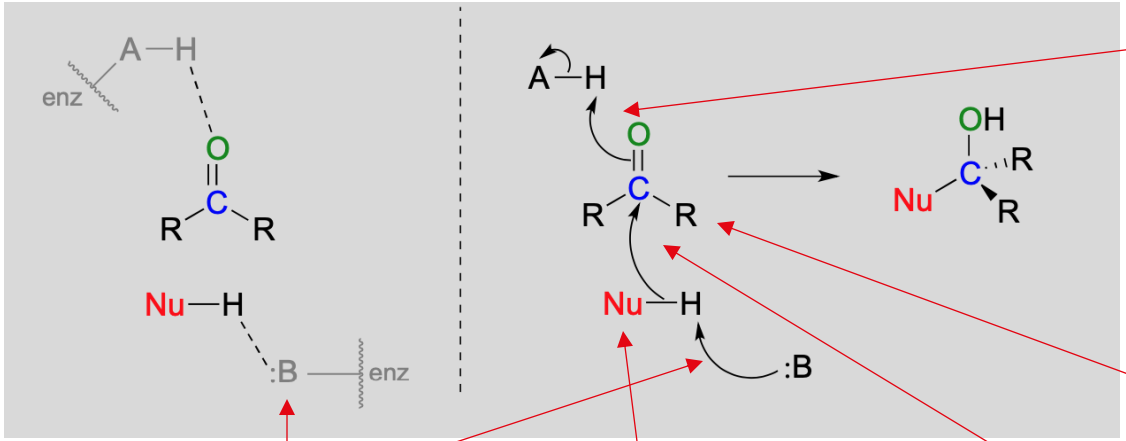
➔ Electron withdrawing groups increase reactivity
➔ Electron pushing groups reduce reactivity

Question: How stable is the positive charge on the carbon?

Carbonyl carbons are electrophiles

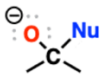
-Carbonyl carbons are excellent targets for attacks by electron-rich nucleophilic groups

-Let's start with an example from an enzyme



Attack of the oxygen to an hydrogen donor

Generation of a nucleophile in the sp3 carbon



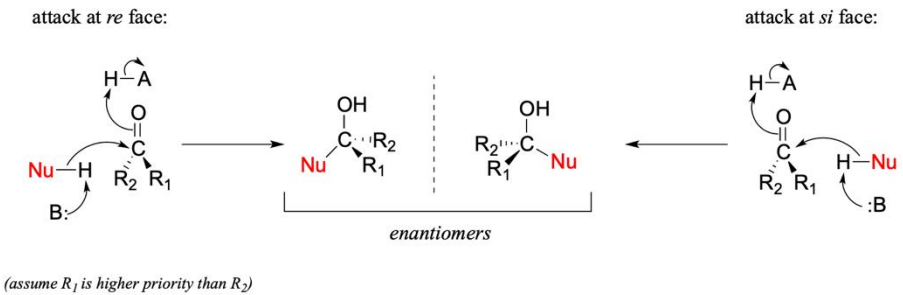
Basic group deprotonates nucleophile

Nucleophile becomes more reactive (Nu^-)

Attack to the electrophile

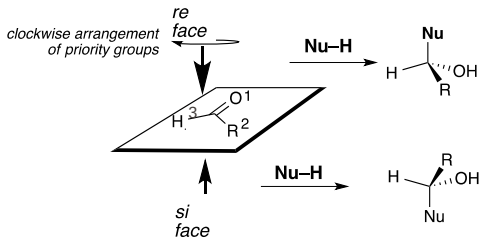
Stereochemistry on nucleophilic additions

-Distinguishing *re* and *si* faces in of the planar sp2 carbon



-Remember we go from an sp2 to sp3 configuration of the carbon
-If the R groups are not equivalent – a chiral center is created
-The configuration of the chiral center depends on the face that is attacked

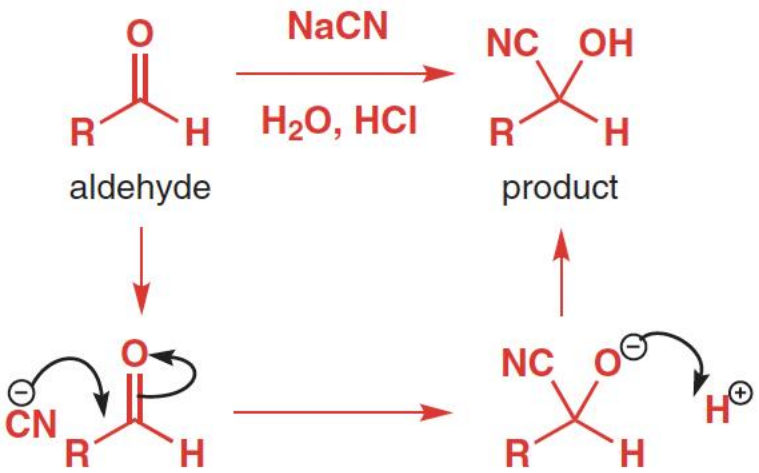
- Let's revise the faces assignment

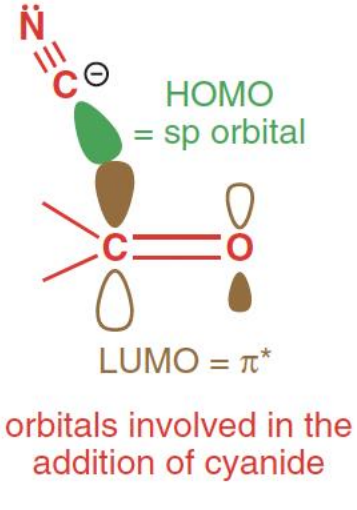


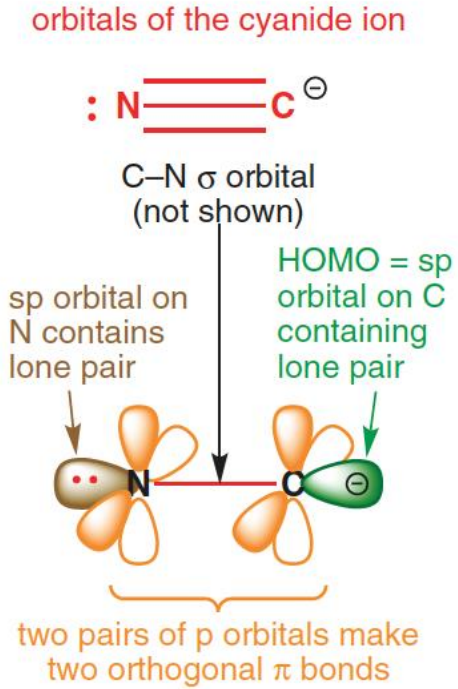
Cahn-Ingold-Prelog

1) rank substituents:
    1) Higher molecular weight
    2) If identical move to next atom away from chiral center
    3) Multiple bonds count as two identical substituent atoms

Addition of Cyanide to Aldehydes



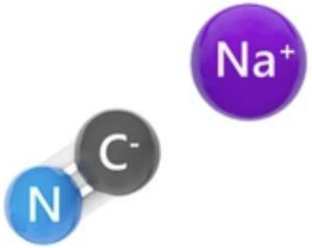




The important part is to reason about which species is the nucleophile

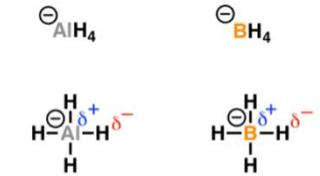
Some reagents that can be used for nucleophilic additions

NaCN



-Sodium positive ion
-Cyanide the negative electrophile

$NaAlH_4$/$NaBH_4$

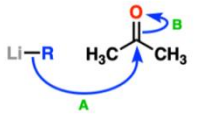


Electronegativities:

Aluminum: 1.6 Boron: 2.0
Hydrogen: 2.2 Hydrogen: 2.2

- Sodium positive ion => BH_4 is negative
- **However due to electronegativity differences the nucleophilic atom is hydrogen**

R-Li(organolithium)

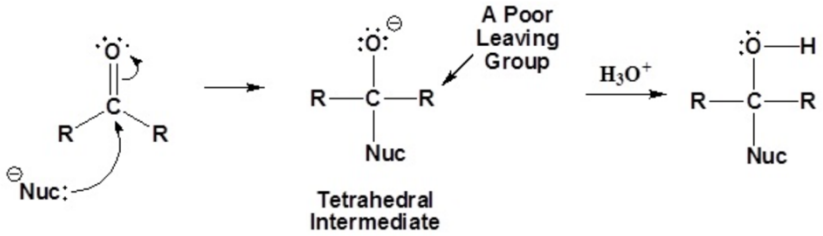


Note

R is a generic carbon group
e.g. CH_3, CH_2CH_3, $CH_2C_6H_5$, etc

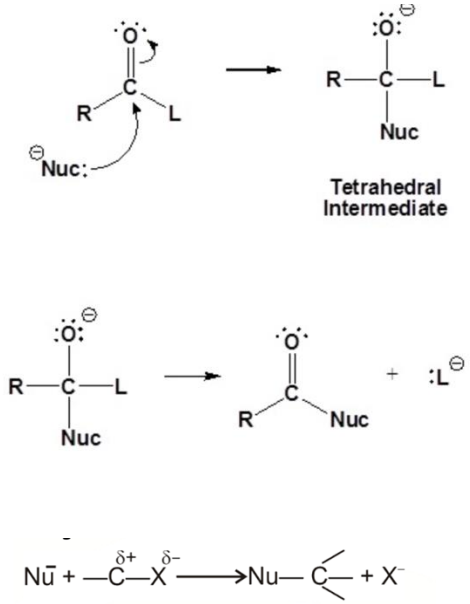
Comparing nucleophilic additions and nucleophilic substitutions

Addition



-pi bond reacts with a nucleophile leading to the diseapearence of a double bond and the creation of a new sigma bond

Substitutions

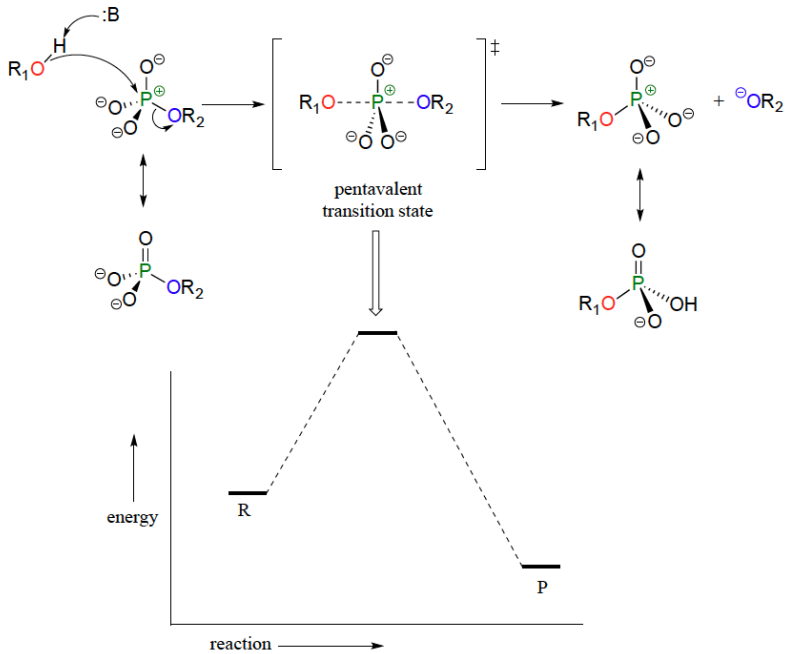


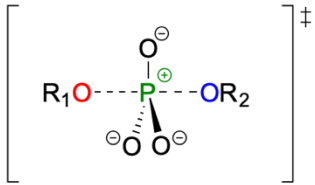
-Leaving group leaves

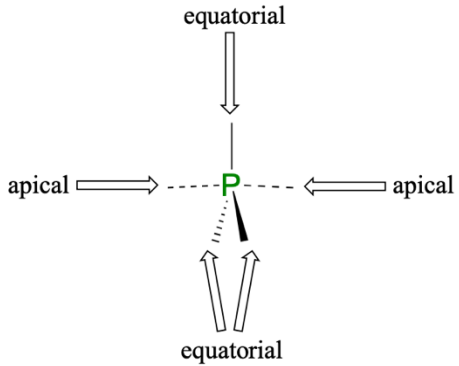
Questions?

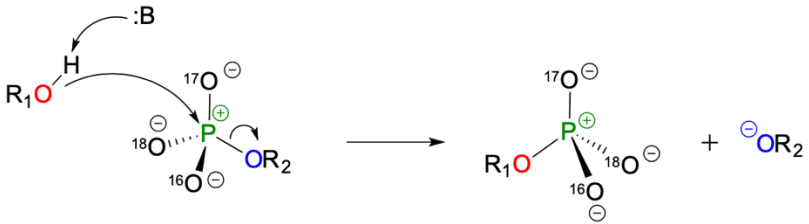
Mechanism of Phosphotransfer

Concerted model:









phosphate has *S* configuration

phosphate has *R* configuration