CHE 2060: Principles of Organic Chem

6. Nucleophilic substitution reactions
Introduction: Why aren't identical twins identical? Just ask SAM.
6.1: Two mechanistic models for nucleophilic substitution
- 6.1A: The SN2 mechanism
- 6.1B: The SN1 mechanism

6.2: All about nucleophiles (Nu:)
- What is a nucleophile vs. a base?
- Protonation state
- Periodic trends in nucleophilicity
- Resonance effects on nucleophilicity
- Steric effects on nucleophilicity

6.3: All about electrophiles (E+)
- Steric hindrance at the electrophile
- Carbocation stability

6.4: Leaving groups
6.5: Regiospecificity of SN1 reactions with allylic electrophile
6.6: SN1 or SN2? Predicting the mechanism
6.7: Biological nucleophilic substitution reactions *optional sidebar*
- 6.7A: A biochemical SN2 reaction
- 6.7B: A biochemical SN1 reaction
- 6.7C: A biochemical SN1/SN2 hybrid reaction

6.8: Nucleophilic substitution in the lab
- 6.8A: The Williamson ether synthesis
- 6.8B: Turning a poor leaving group into a good one: tosylates

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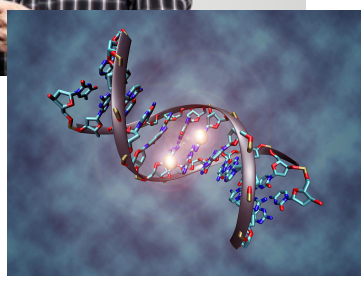
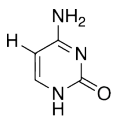
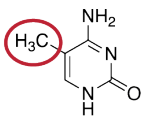
6. Nucleophilic substitution reactions

Introduction: Identical twins, epigenetics and SAM





Cytosine



methylated Cytosine

https://en.wikipedia.org/wiki/DNA_methylation

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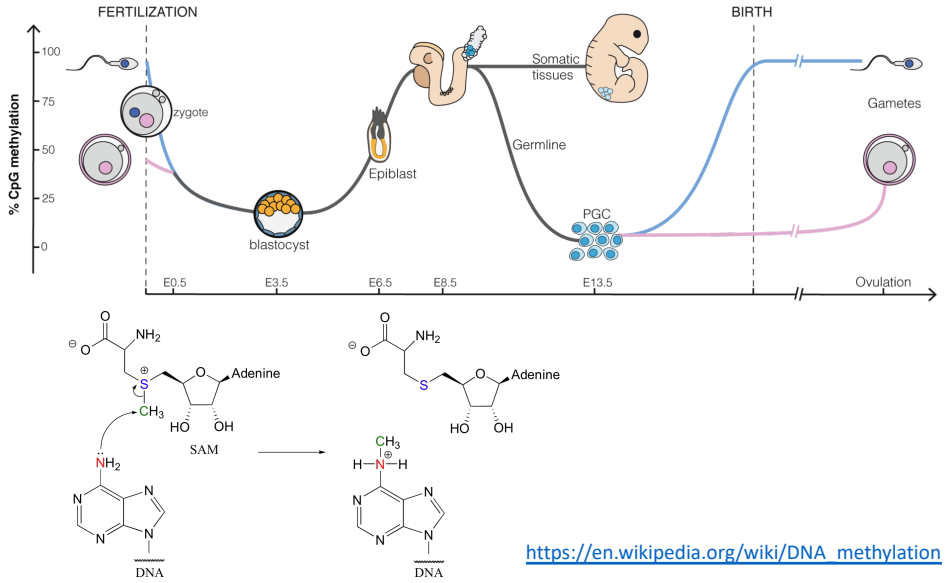
6. Nucleophilic substitution reactions

Introduction: Identical twins, epigenetics and SAM



https://en.wikipedia.org/wiki/DNA_methylation

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6. Nucleophilic substitution reactions

Big ideas:

1. ***SN mechanisms depend on the strength of Nu:, stability of E+ and quality of LGs.***
2. ***Carbocations are intermediates whose 'stability' depends on their structures.***

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6. Nucleophilic substitution reactions

6.1A: The SN2 mechanism

Resources for students:
'Guide (summary) comparing SN1 and SN2 reactions and mechanisms'
'Diagnostic chart for substitution, addition and elimination reactions'
'Substitution reaction mechanism animations'

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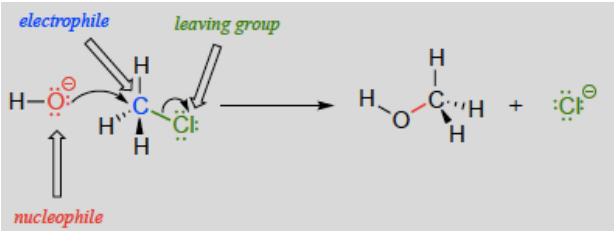
SN2: a concerted mechanism

The one-step, or **concerted**, nucleophilic substitution mechanism is called **SN2**.

- Bond are simultaneously broken and made.

sustitution nucléophilique 2



The '2' in SN2 means that the reaction mechanism is **bimolecular**: *depends on the collision rate of two molecules.*

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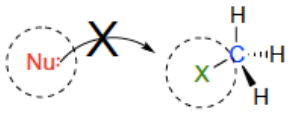
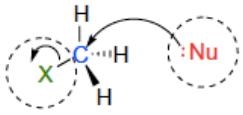
‘Backside’ attack

The orientation of the biomolecular collision of SN2 reactions is critical.

- The Nu: must attack from the side opposite the E+’s LG.
  - aka **‘attack from the back’**

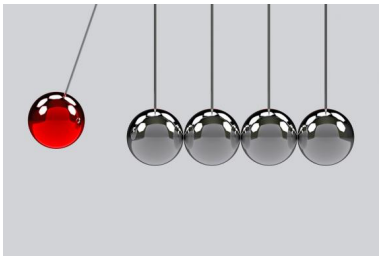


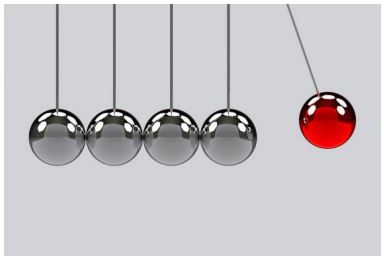
nucleophilic attack is blocked from the front side . . .



. . .so attack occurs from the back side

Analogy: *executive pendulum*





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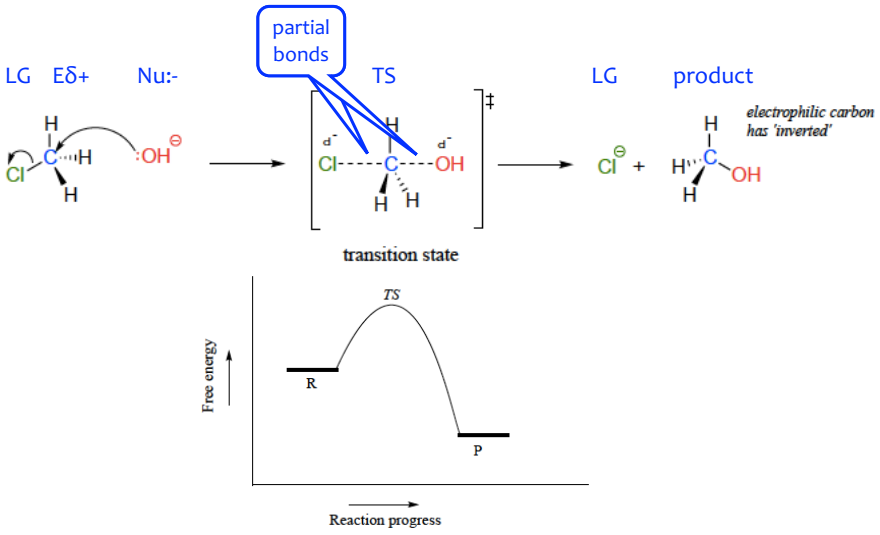
SN2 mechanism

- Attack from the back by the Nu: and loss of LG are **simultaneous**.
  - Single, concerted step.
- TS is (trigonal) planar; Nu: and LG are partially bonded.



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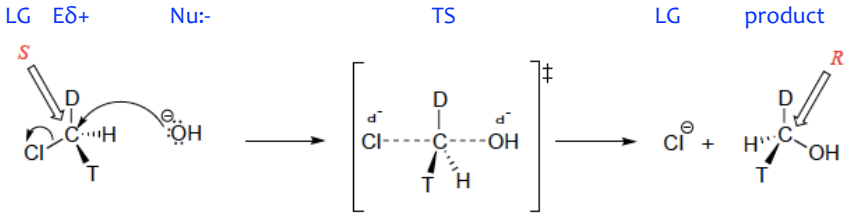
SN2 inversion

Chiral inversion: *if the substrate (E+) is chiral, SN2 reactions create a product with the opposite chirality*



Here two of the substrate's hydrogen atoms have been replaced by hydrogen isotopes, deuterium and tritium, to create chirality.

Notice attack from the back places the substituting group on the side of the molecule opposite the leaving group.

- Imagine the TS's trigonal planar group as a sheet of paper.
  - Nu:- attacks from behind and…
  - … pushes the LG off of the other side.

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6. Nucleophilic substitution reactions

6.1B: The SN1 mechanism

Resources for students:
'Guide (summary) comparing SN1 and SN2 reactions and mechanisms'
'Diagnostic chart for substitution, addition and elimination reactions'
'Substitution reaction mechanism animations'

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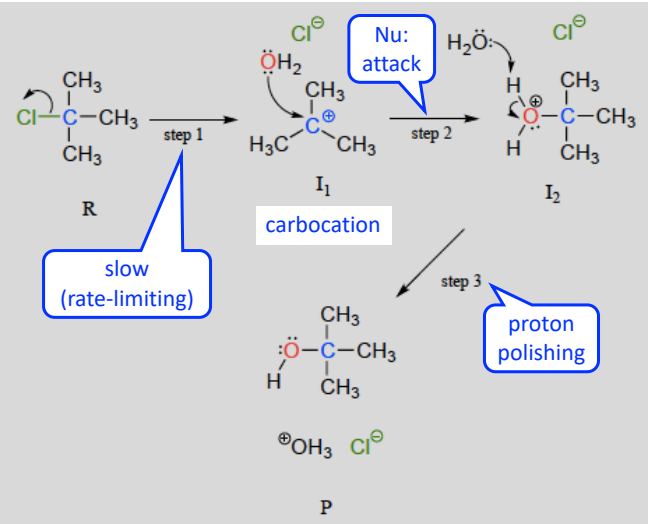
SN1 reactions

The two-step nucleophilic substitution mechanism is called **SN1**.



sustitution nucleophilique 1

NB: SN1 reactions don't cause stereo-chemical inversion.

The '1' in SN1 means that the rate-limiting step is **unimolecular**: *depends on a reaction happening in a single molecule.*

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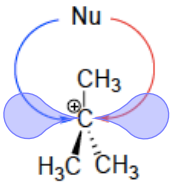
SN1 stereochemistry

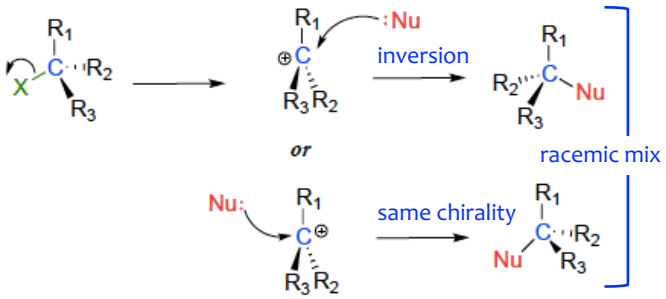
The stereochemistry of SN1 reactions is dictated by their **trigonal planar carbocation** intermediate.

- The positive charge is 'held' in an unhybridized p orbital.



The Nu: can 'attack' the carbocation from either side.

- **If** the substrate is chiral, **both enantiomers** are made.



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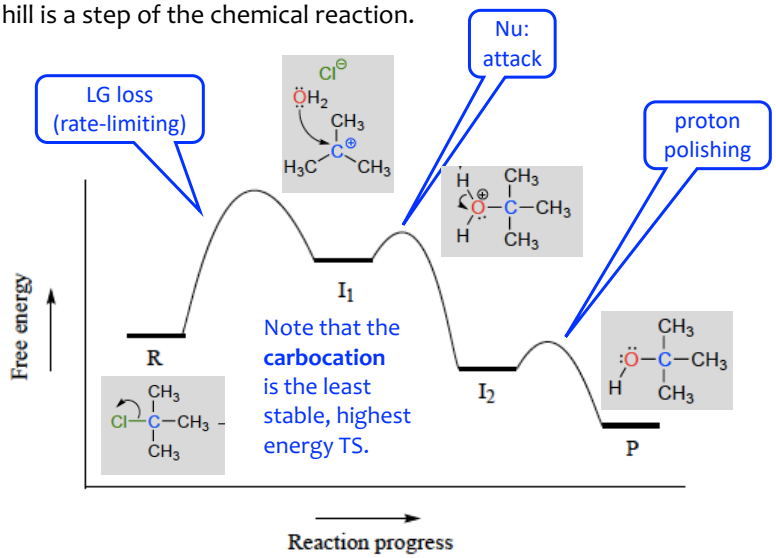
SN1 reaction coordinate diagram

- Each 'flat' area represents a chemical species: reactant, intermediate or product.
- Each hill is a step of the chemical reaction.



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Hydrolysis (& solvolysis)

Hydrolysis: *reactions in which water is used as the reactant to break a chemical bond*

- *Hydro = water*
- *Lysis = to break*

Notice that the SN2 and SN1 reactions used as examples here are hydrolysis reactions.

Solvolysis: *reactions in which the solvent (not necessarily water) is used as the reactant to break a chemical bond*

- The solvent is often an alcohol.

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Try this

Draw a mechanism for the SN1 solvolysis of tert-butyl chloride in methanol. What new functional group has been formed?

The product is an ether!

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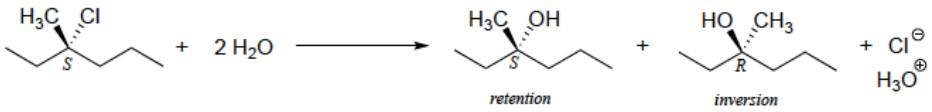
Lab chemistry vs. biochemistry

In the lab, many reactions are performed **without enzymes**.

In these cases, if the substrate is chiral, both enantiomers are produced



But **biochemical** reactions **use enzymes**.

- Enzymes themselves are chiral and can recognize only one chiral substrate.
- And enzymes produce only **one enantiomer**.

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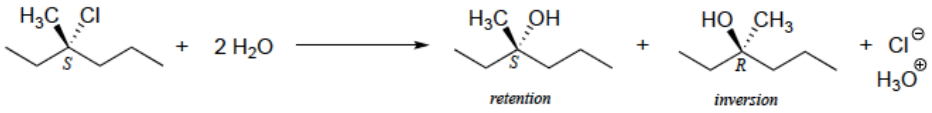
Try this



(a) Draw a complete mechanism for this SN1 hydrolysis reaction.
(b) Draw dash wedge structures representing TS1 and TS2 in the reaction.
(c) What is the expected optical rotation of the product mixture?
(d) Could the two organic products be separated on a silica column chromatography that requires different physical properties, specifically different overall polarity?

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Try this

(a) Draw the product(s) of the SN2 hydrolysis of (R)-3-chloro-3-methyl heptane.
(b) What can you predict, if anything, about the optical rotation of the product(s)?

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Try this

(a) Draw the product(s) of the hydrolysis of (3R,5R)-3-chloro-3,5-dimethyl heptane.
(b) What can you predict, if anything, about the optical rotation of the product(s)?

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Can you?

(1) Explain what both SN reactions have in common?

(2) Differentiate between SN2 and SN1 reactions?

(3) Recognize SN2 vs. SN1 by looking at a reaction coordinate diagram?

(4) Explain how the chirality of products of SN1 and SN2 reactions differ?

(5) Draw mechanisms of SN1 and SN2 reactions?

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6. Nucleophilic substitution reactions

6.2: All about nucleophiles

Resources for students: 'Guide to strength of Nu:, E+ and LG'

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What do you need to know about Nu: ?

1. How do you know whether a reactant is acting as a Nu: or a base?

- By its actions: bases remove a H atom while Nu:s do more.

2. Who are Nu: ? Many Nu: use **N, O** and **S atoms** to hold lone pairs.

- Water
- Alcohols
- Phenols
- Amines
- Thiols
- Carbohydrates (aldehydes and ketones)

Nu: strength?

3. Negatively charged > neutral >>> positively charged (better deprotonated)

4. Rows: strength decreases going left to right.

5. Columns:

In protic solvents, Nu: strength increases ↓

In polar aprotic solvents, Nu: strength increases ↑

6. Resonance stabilization weakens Nu:s.

7. Steric hinderance weakens Nu:s.

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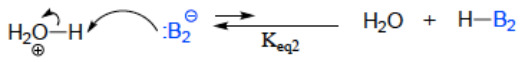
1. Acting as a Nu: or a base?

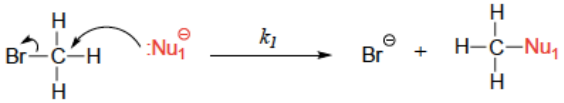
Both bases and nucleophiles (Nu:) are characterized by lone pairs. And bases can act as Nu: and Nu: can act as bases. **So, how can they be distinguished?**

Functional test:

- Bases remove only a hydrogen ion.
- Nu: do more.
    - In SN reactions, Nu: are added to the reactant in place of the LG.



Acting as a base



Acting as Nu:

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2. Who are Nu: ?

Many Nu: use **N, O and S atoms** to hold lone pairs.

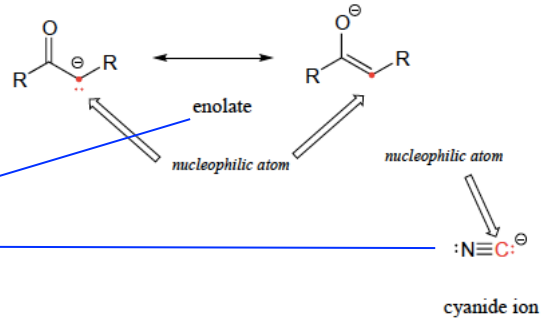
- Water
- Alcohols
- Phenols
- Amines
- Thiols
- (Carbohydrates)

Laboratory Nu: also include halide ions and azide:

- I^{-1}
- Br^{-1}
- Cl^{-1}
- F^{-1}
- N_3^{-1} (azide)

Carbon Nu: are less common.

- Enolate ions
- Cyanide ions (CN^{-1})



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3. (-) charged Nu: are stronger

Negatively charged (deprotonated) Nu: (-) are several orders of magnitude stronger than uncharged (protonated) Nu:.

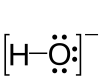
SN2 reactions require **strong Nu:(-)**

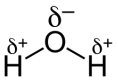
SN1 reactions can use **weaker Nu:**

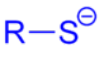
stronger Nu:(-)

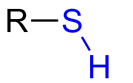
weaker Nu:

Often, negative charge indicates the stronger Nu:

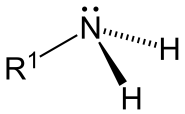


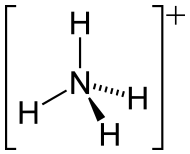






Here lack of + charge makes the stronger Nu:





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4. Nu: strength decreases across rows →

Within rows, **trends in Nu: strength mirror trends in basicity.**

- Left to right, each element in a row has one more proton.
- As atoms gain protons, they are less willing to donate electrons to form dative bonds (aka act as Nu:).

The horizontal periodic trend in nucleophilicity

more nucleophilic $NH_2^- > OH^- > F^-$ *less nucleophilic*

more nucleophilic $R\text{-}NH_2 > R\text{-}OH$ *less nucleophilic*

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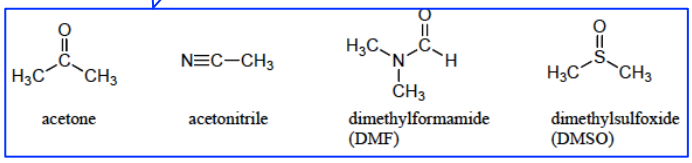
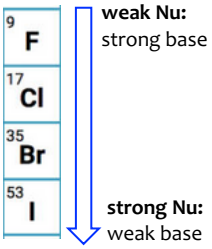
5. Nu: strength & columns

The strength of **bases decreases down a column:** larger ions have more surface are with which to accommodate lone pairs and are therefore more stable.

Nu: strength in columns **depends on the solvent**.

1. **Protic solvents:** *reactive, polar H (like water)*
2. **Aprotic solvent:** *no reactive, polar, H*





For **protic solvents,** Nu: strength increases ↓ **columns.**

- Because protic solvents (acids) react with and 'kill' a Nu: that is also a strong base.

For **polar aprotic solvents,** Nu: and base strength increase ↑ **columns.**

- Because aprotic solvents don't react with (or 'kill') a Nu: that is also a base.

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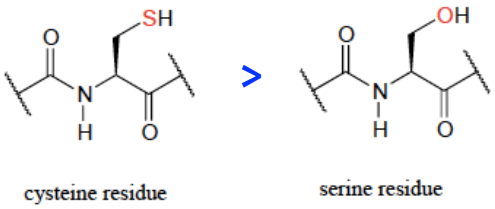
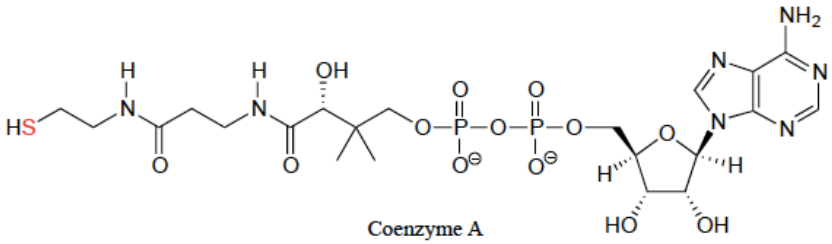
5. Example

For biochemical reactions it's critical to remember that **thiols are stronger Nu: than alcohols.**

- Weaker base ~ stronger Nu:



CoA:
Ubiquitous
Made from vit B5
Used in 4% of enzymatic rxns



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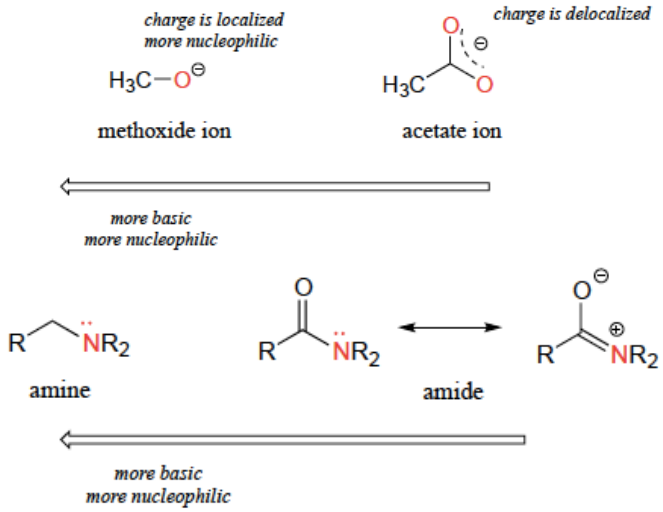
6. Resonance stabilization weakens Nu:

Remember that for bases, resonance stabilizes anions and makes groups less likely to donate lone pairs; stabilization weakens bases.

This is also true of Nu: → stabilization weakens Nu:.



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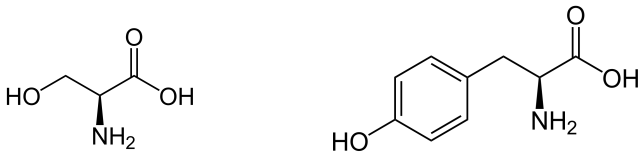
6. Try this

Which amino acid has the more nucleophilic side chain - serine or tyrosine? Explain.



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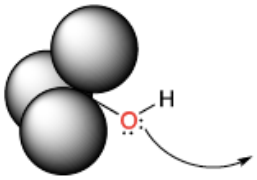
7. Steric hindrance weakens Nu:

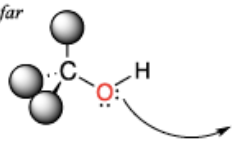
Steric hindrance: *crowding by bulky functional groups or molecules*

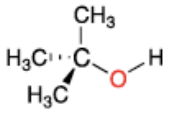
Large or bulky groups tend to **get in the way** in reactions and **slow** or prevent reactions from happening.

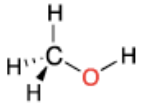
large methyl groups hinder nucleophilic attack



small hydrogens cause far less hindance







So, while their OH functional groups are identical, the bulky **tert-butyl alcohol is a weaker Nu:** than the more compact methanol.

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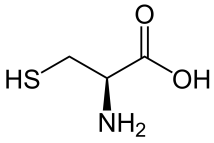
7. Try this

Which is the better nucleophile?

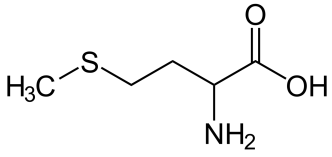
(a) A cysteine side chain or a methionine side chain?

(b) A serine or a threonine?

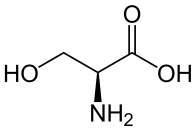
Explain.



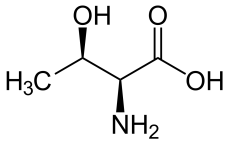
cysteine



methionine



serine



threonine

32

All together! Try this

In each of the following pairs of molecules/ions, which is expected to react more rapidly with CH_3Cl in acetone solvent? Explain your choice.

(a) phenolate (deprotonated phenol) or benzoate (deprotonated benzoic acid)?

(b) water or hydronium ion?

(c) trimethylamine or triethylamine?

(d) chloride anion or iodide anion?

(e) CH_3NH^- or $CH_3CH_2NH_2$?

(f) acetate or trichloroacetate?

(g) aniline or 4-methoxyaniline?

(h) phenolate or 2,6-dimethylphenolate?

33

Can you?

(1) Understand why stronger bases are stronger Nu:?

(2) Distinguish between Nu: and base by their function (what they do)?

(3) Understand that stronger Nu: react more quickly?

(4) List atoms commonly, and uncommonly, that act as Nu:?

(5) Relate Nu: strength to state of protonation?

(6) Relate Nu: strength to state of protonation?

(7) Understand how and why protic solvents change Nu: strength?

(8) Describe a few aprotic solvents and explain why they are aprotic?

(9) Understand why resonance stabilization weakens Nu:?

(10) Understand why bulky Nu: react more slowly?

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6. Nucleophilic substitution reactions

6.3: All about electrophiles

Resources for students: 'Guide to strength of Nu:, E+ and LG'

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What do you need to know about E+ ?

Factors that affect E+ strength or speed or reaction:

1. Steric hindrance weakens E+ for SN2 but not SN1.

2. Structure:

- E+ must be **sp^3** for either SN1 or SN2.
- **SN1** speed and likelihood of reaction: 3° > 2° 1° > methyl.
- **SN2** speed and likelihood of reaction: methyl > 1° > 2° > 3°.

3. Electron withdrawing groups ↓ E+ stability (↓ SN1, ↑ SN2).

4. Resonance stabilizing carbocation charge ↑ stability (↑ SN1, ↓ SN2).

5. Electron donating groups in resonance with carbo+ stabilize it (↑ SN1, ↓ SN2).

6. Vinyl carbocations are not stable! (↓ SN1, ↑ SN2).

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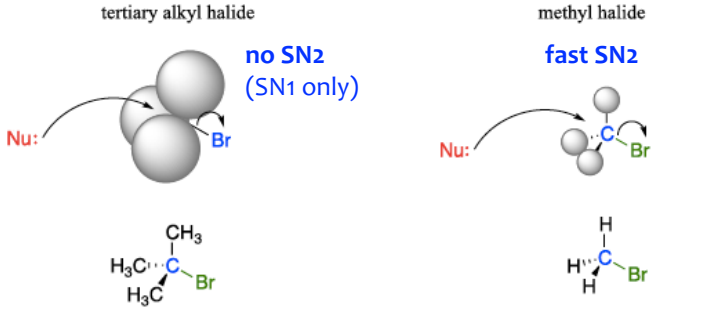
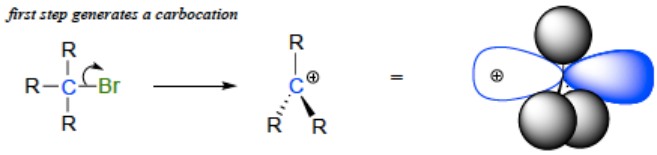
1. Steric hindrance weakens SN2 E+

What if the substrate (the E+) is bulky?

- Bulkiness **hinders the Nu:** from accessing its carbon target in **SN2 reactions.**



But for **SN1 rxns,** E+ bulkiness **isn't a factor** because carbocations are only 2D!



37

1. Try this

Which would be expected to react more rapidly in an SN2 reaction with an azide ion (N_3^{-1}) nucleophile in acetone solvent?

- 1-bromo-2,2-dimethylbutane
- 1-bromo-3-methylbutane

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2. Structure: methyl, 1°, 2° and 3° E+

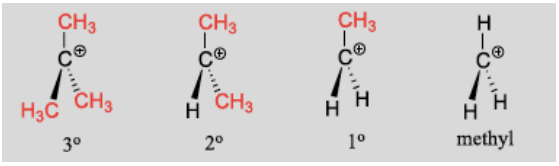
Substrate (E+) carbons can be classified using one of these terms:

- **Methyl** — H substituents only
- **Primary (1°)** — 1 R substituent
- **Secondary (2°)** — 2 R substituents
- **Tertiary (3°)** — 3 R substituents

all sp^3

increasing bulkiness

increasing stability



3° structure allows greater delocalization (sharing) of the carbocation's + charge.
- Thus ↑ stability.

Speed of SN2 reactions ↑ as bulkiness ↑ (Nu: access is hindered)
- Methyl > 1° > 2° (no 3°)

Speed of SN1 reactions ↓ as stability ↑ (E+ exists long enough to meet Nu:)
- 3° > 2° (no 1° or methyl)
- Think about dating: stability is attractive!

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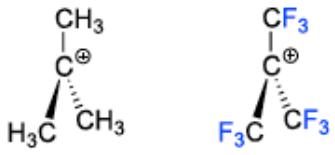
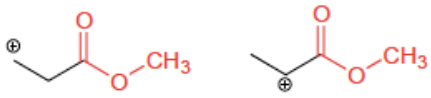
3. E- w/drawing groups

Addition of electron withdrawing groups **destabilizes carbocations** because they effectively increase the positive charge.

less stable



And as with all inductive effects, **distance matters**.
- So, the closer the group, the greater the effect.



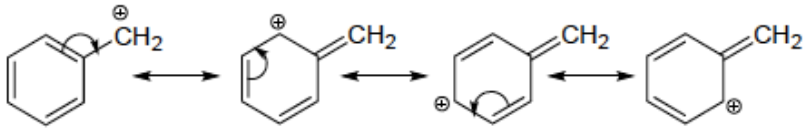
The destabilized carbocation ↓ SN1 and makes SN2 more likely.

40

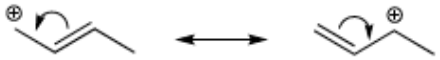
4. Resonance stabilizing the E+

If **resonance helps to delocalize the positive charge** of the carbocation, then it increases carbocation stability.

So substrate (E+) resonance can ↑ the rate of SN1 reactions.



benzylic carbocation



an allylic carbocation

41

4. Try this

Fill in the missing numbers in this statement: The conjugated p system in the benzylic carbocation above is composed of _____ p orbitals overlapping to share _____ π electrons.

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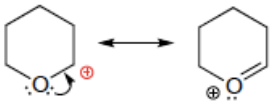
5. E- donating groups

While N and O are generally electron withdrawing, they can be **electron donating if in resonance** with the carbocation.

Electron donating groups stabilize the carbocation by countering +



more stable

less stable
(no resonance delocalization)

A more stable E+ would ↑ S_N1 vs. S_N2.

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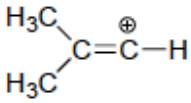
6. Vinylic carbocations are unstable!

Vinylic carbocations: *the + is found on a double-bonded C*

- **Very unstable!!**



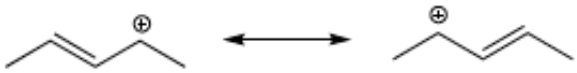
Explain why vinylic carbocations are unstable.
(Hint: think about hybridization and electronegativity)

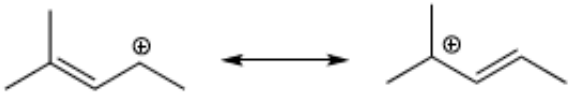
44

Combining factors?

Many of the factors that you've seen can be combined to affect the likelihood and speed for SN1 reactions.

Compare these two similar carbocations. Which is more stable?

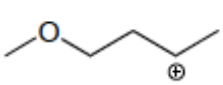




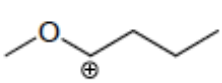
45

Try this

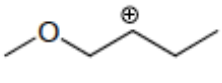
Rank the following carbocations from most to least stable:



A



B

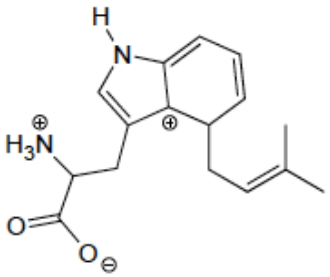


C

46

Try this

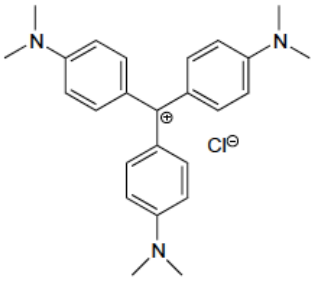
The carbocation below is an intermediate species in a reaction that is part of the biosynthesis of a hallucinogenic compound in a fungus.
Draw a resonance contributor that shows how it is stabilized by resonance with the nitrogen atom.



47

Try this

(a) Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.
(b) Notice that crystal violet is deeply colored. Explain why you could have predicted this from looking at its chemical structure.
(c) The conjugated system of crystal violet consists of how many overlapping p orbitals sharing how many π electrons?



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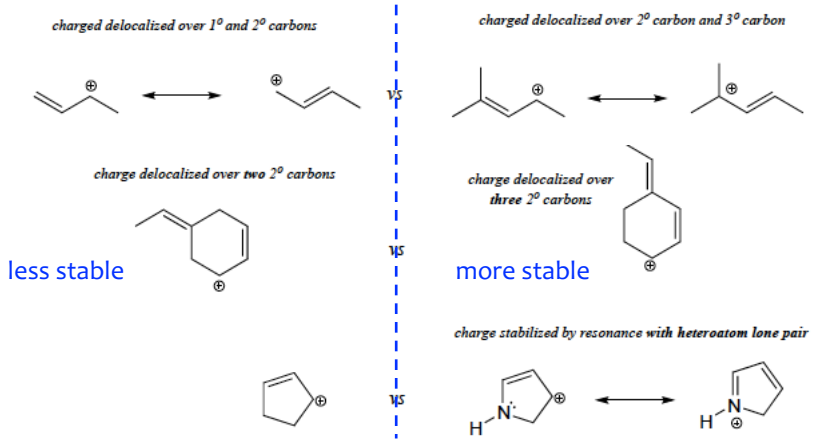
Carbocation stability summary

(1) 3° > 2° > 1° > methyl

(2) Electron donating groups increase stability; distance matters.

(3) Resonance that delocalizes + stabilizes carbocations.

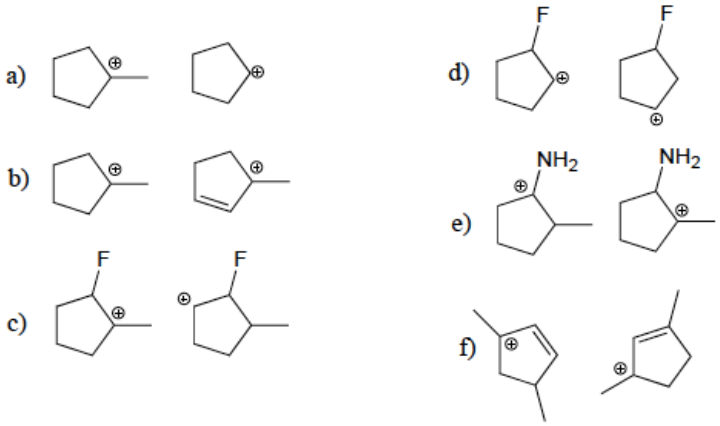
(4) Resonance that delocalizes + with lone pairs stabilizes carbocations.



49

Try this

State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.

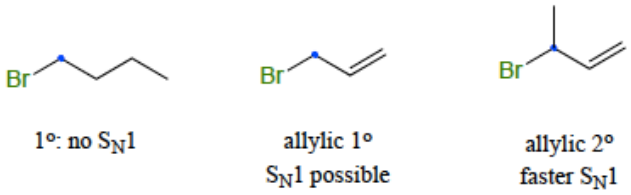


50

Summary: SN1 wants stable carbocations

SN1 reactions:

methyl	no SN1
1°	SN1 only if very stabilized
2°	✓ SN1
3°	✓ SN1



1°: no S_N1 | allylic 1° S_N1 possible | allylic 2° faster S_N1

51

Can you?

(1) Explain why bulky E+ react more slowly via the SN2 mechanism?

(2) Understand that SN2 reactions favor less bulky substrates: methyl > 1° > 2°?

(3) Understand that SN1 reactions like stable carbocations: 3° > 2° > 1° ?

(4) Explain why e- withdrawing substituents destabilize carbocations?

(5) Explain why resonance that delocalizes (+) stabilizes carbocations?

(6) Understand that e- donating groups in resonance can stabilize carbocations?

(7) Explain why vinylic carbocations are so unstable and don't react via SN?

(8) Summarize the factors that increase carbocation stability?

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6. Nucleophilic substitution reactions

6.4: All about leaving groups

Resources for students: 'Guide to strength of Nu:, E+ and LG'

53

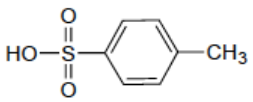
What makes a good leaving group?

Weaker bases make the best leaving groups because they have to be greedy and keep lone pairs rather than donating them.

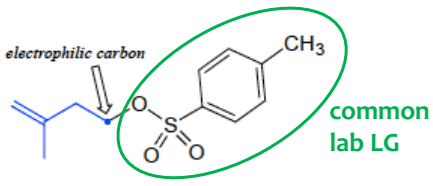
Best LG: $I^{-1} > Br^{-1} > Cl^{-1} >> F^{-1}$

Notice how leaving group strength or ability is reflected in the **speed of SN2 reaction** of these substrates**:**

Fastest SN2: $CH_3I > CH_3Br > CH_3Cl >> CH_3F$



para-toluenesulfonic acid
(pKa -2.8)

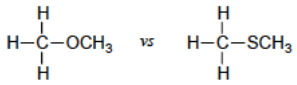


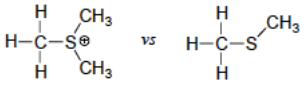
organic electrophile with *para*-toluenesulfonate leaving group

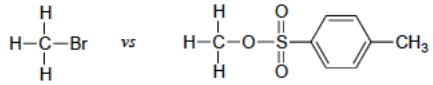
54

Try this

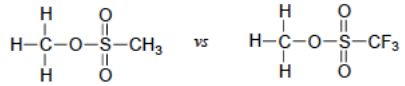
In each pair (A and B) below, which electrophile would be expected to react more rapidly with cyanide ion nucleophile in acetone solvent? Explain.

a) 

b) 

c) 

(hint - use a pKa table)

d) 

55

Can you?

(1) Explain why weak bases make the best leaving groups?

(2) Explain the halide trend in LGs?

(3) Explain why para-toluenesulfonic acid (tosyl, Tos) makes a great LG?

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6. Nucleophilic substitution reactions

6.5: Regiospecificity of SN1 with allylic E+s

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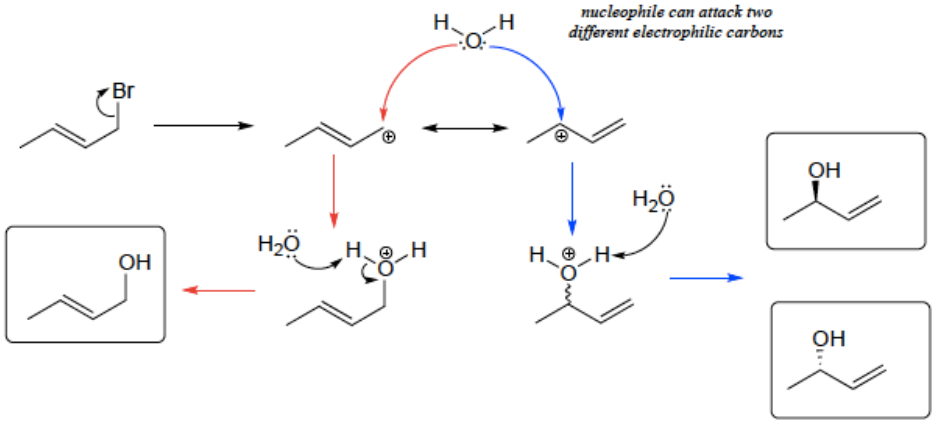
Regiospecificity

Regiospecificity: *the preference for one carbocation and outcome when several are possible*

Enzymatic reactions are far more regiospecific than chemical reactions.



Here SN1 chemical reaction of an allylic substrate produces **three possible products.** An enzymatic reaction would favor one product.

58

Can you?

(1) Define the term 'regiospecific'?

(2) Explain why enzymatic reactions are more regiospecific than chemical reactions?

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6. Nucleophilic substitution reactions

6.6: SN1 or SN2?

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SN1 or SN2

A number of factors need to be considered.

factor	SN1	SN2
number of steps	3	1 (concerted)
E+ (substrate)	sterically hindered	unhindered
E+ stability	3°, 2° or stabilized	1°, 2°°
Nu:	weak Nu:	strong Nu:(-)
LG	good	good
TS	carbocation	5-bond trigonal planar
solvent	protic	polar aprotic
If chiral products?	enantiomers	chiral inversion

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Can you?

(1) Create a list or matrix of the factors that determine whether nucleophilic substitution occurs via an SN1 or SN2 reaction mechanism?

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6. Nucleophilic substitution reactions

6.7A: A biochemical SN2 reaction

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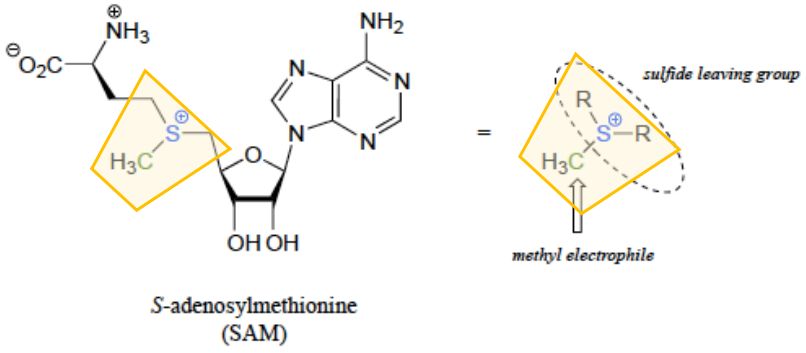
SAM: S-adenosyl methionine

SAM (S-adenosyl methionine): *a coenzyme used by enzymes to carry and donate methyl groups*



S-adenosylmethionine (SAM)

SAM-dependent methyl transferases are enzymes that use SAM to carry a methyl group that they add to substrate molecules like DNA.

- Methylation of DNA helps determine whether genes are expressed.

sidebar

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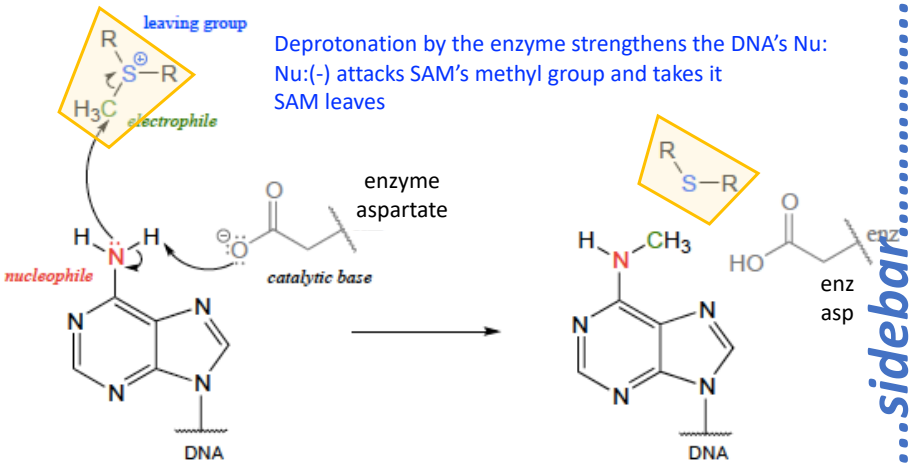
Methylation of DNA

SAM-dependent methyl transferases are enzymes that use SAM to carry a methyl group that they add to substrate molecules like DNA.

- Methylation of DNA helps determine whether genes are expressed.



Deprotonation by the enzyme strengthens the DNA's Nu:
Nu:(-) attacks SAM's methyl group and takes it
SAM leaves

sidebar

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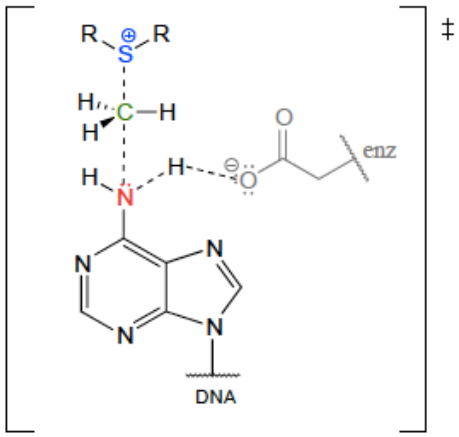
Methylation of DNA: mechanism, TS

If this is the likely transition state (TS) of the DNA methylation reaction, **which nucleophilic substitution reaction** is occurring?



This TS looks lie a concerted reaction with a trigonal planar intermediate.

SN2

sidebar

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Does the SN diagnostic chart work?

Try using the table to diagnose the mechanism of the DNA methylation.

factor		SN1		SN2
number of steps		3	✓	1 (concerted)
E+ (substrate)	methyl	sterically hindered	✓	unhindered
E+ stability	1°	3°, 2° or stabilized	✓	1°, 2°
Nu:	$R\text{-}NH^{-1}$	weak Nu:	✓	strong Nu:(-)
LG	stable sulfide	good	✓	good
TS		carbocation	✓	5-bond trigonal planar
solvent		protic		polar aprotic
If chiral products?		enantiomers		chiral inversion

sidebar

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Termolecular mechanism

The DNA methylation uses a **termolecular mechanism**: *a mechanism involving three molecules.*

- Catalytic base — enzyme aspartate
- Nu: — DNA
- E+ — SAM

In a **test tube** getting those three molecules to come together in the perfect orientation would require high concentrations of all three molecules, lots of energy and a good dose of good luck.

An **enzyme** makes the reaction possible because it brings the three players together in the proper orientation.

- Binding increases the effective concentration of all three molecules.
- And the geometry of the enzyme's active site sets up perfect orientation.

sidebar

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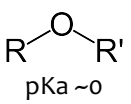
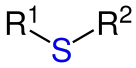
Try this

Think back to the acid-base chapter: the pKa of a protonated ether is approximately zero, indicating that an ether is a very weak base. Considering periodic trends in acidity and basicity, what can you say about the relative basicity of a sulfide (aka thioether)?



pKa ~0



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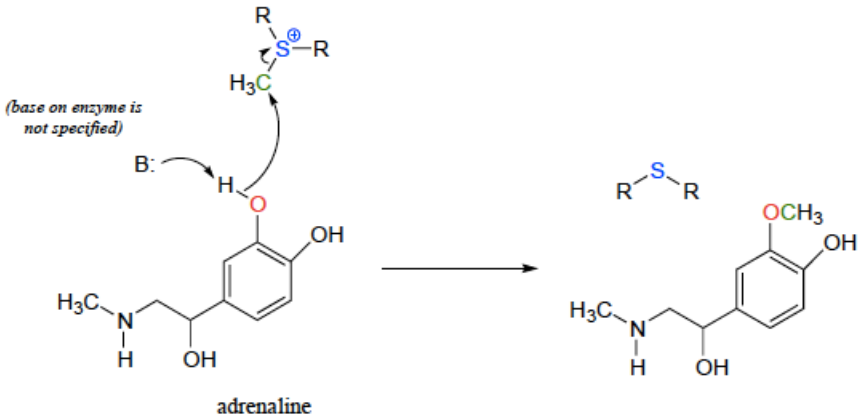
Catechol-O-methyltransfase

Catechol-O-methyltransferase also uses SAM to methylate epinephrine (aka adrenaline), tagging it for degradation.



adrenaline

What are the **similarities and differences** between the two reactions using SAM?

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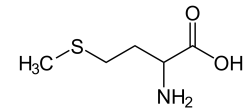
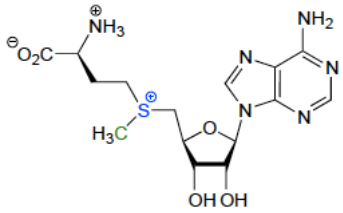
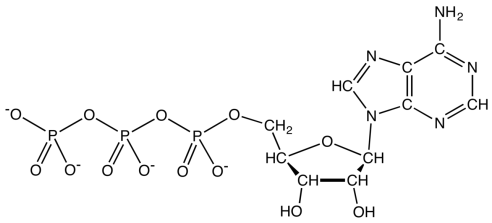
Try this

SAM is formed by a nucleophilic substitution reaction between methionine and adenosine triphosphate (ATP).
Draw a mechanism for this reaction, and explain why you chose either an SN1 or and SN2 pathway.





S-adenosylmethionine
(SAM)



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6. Nucleophilic substitution reactions

6.7B: A biochemical SN1 reaction

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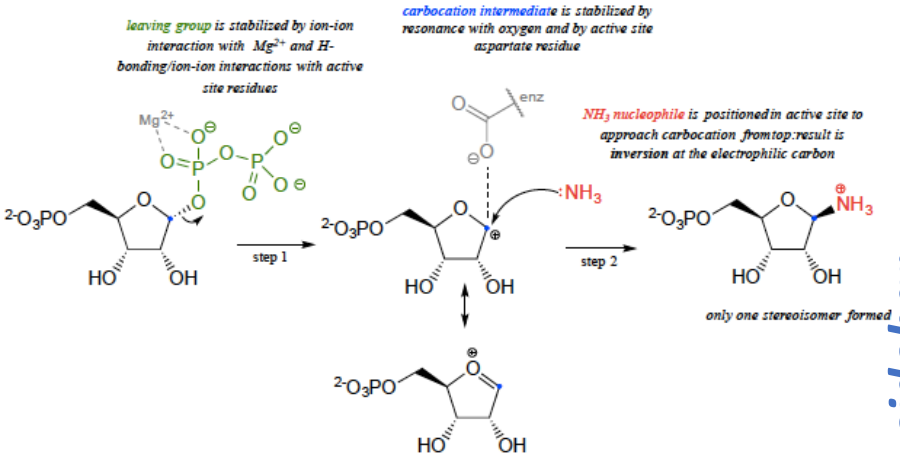
SN1 in nucleotide biosynthesis

How many characteristics of an SN1 reaction can you identify?



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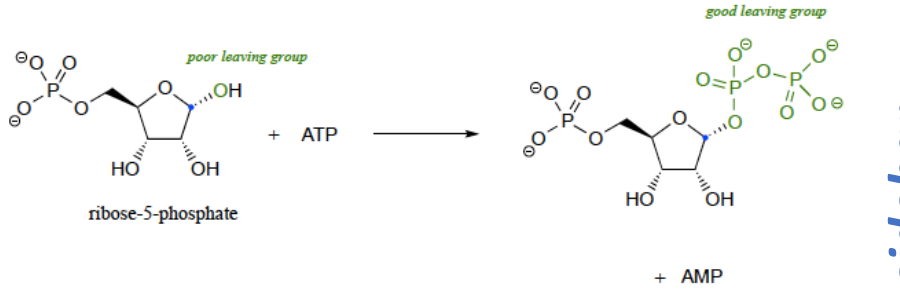
Prior step: improving the LG

The substrate in the SN1 nucleotide biosynthesis reaction, ribose-5-phosphate, has a poor leaving group and wouldn't undergo nucleophilic substitution.

Phosphorylation of ribose-5-phosphate by ATP **creates a far better leaving group** and allows the SN1 reaction to occur.



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6. Nucleophilic substitution reactions

6.7C: A biochemical hybrid SN1/SN2 reaction

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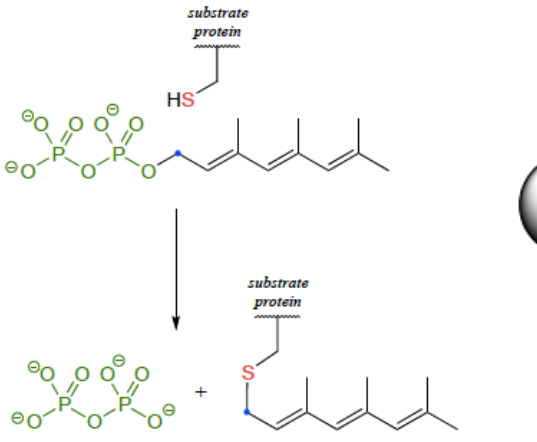
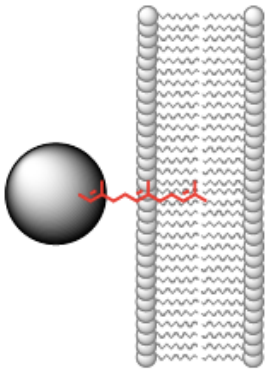
Adding a cell membrane anchor

Some proteins involved in **cell signaling** have to be located at the cell membrane in order to function. In order to create a **hydrophobic anchor** for those proteins, a 15-carbon **isoprene group** is added to a cysteine of the signaling protein. This reaction is called prenylation.



protein with modified cysteine side chain



membrane: lipid bilayer

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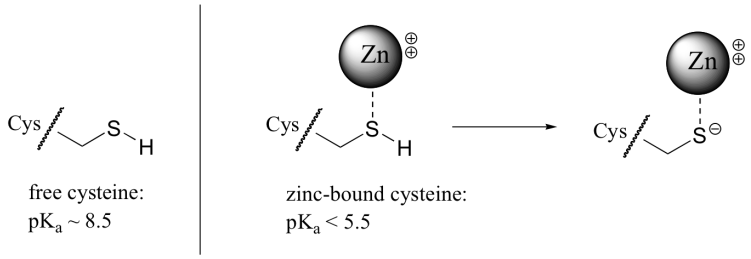
How does the enzyme add the anchor?

How does the enzyme lower the EA and add the isoprene anchor to the signaling protein?

1. **Increase the strength of the thiol Nu: of the cysteine R of the substrate.**
2. Decrease the basic strength of the diphosphate to make it a better LG.



A **Zn ion** in the enzyme's active site forms a dipolar bond with the thiol group from the substrate's cysteine.

- Interaction with Zn stabilizes the S and **lowers its pKa**.
- The sulfur donates its hydrogen converting the weak SH Nu: to a **very strong charged sulfur Nu:(-).**

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How does the enzyme add the anchor?

How does the enzyme lower the EA and add the isoprene anchor to the signaling protein?

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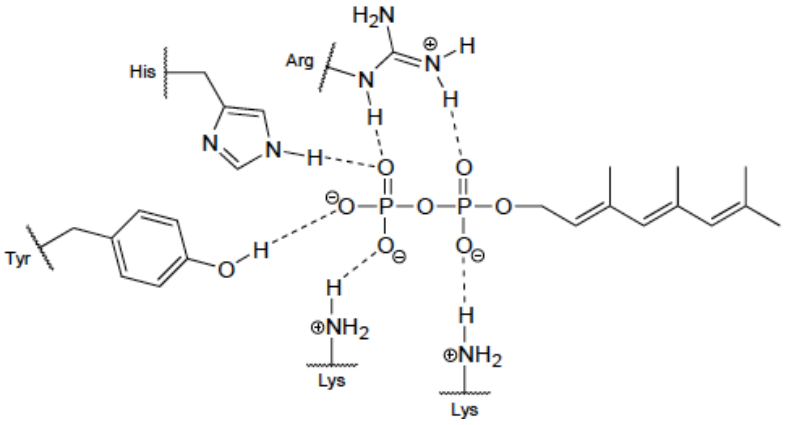

A number of the **enzyme's amino acids H-bond to the diphosphate,** decreasing its basicity and making it a better LG.

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So, is the reaction SN1 or SN2?

What do we know?

E+: primary allylic cation (stabilized)	either SN1 or SN2
Nu:-: very strong	SN1

Experimental evidence suggests that the reaction is mainly SN2 with elements of SN1.

- A hybrid!

In reality SN1 and SN2 are **models**, or **extremes**.

- Real nucleophilic substitution reactions may be SN1 or SN2 or fall in between.

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Can you?

(1) Describe the function of S-adenosyl methionine (SAM)?

(2) Explain whether SAM acts as the Nu: or E+ and why?

(3) Understand why SAM reacts by the SN2 mechanism?

(4) Understand that the strength of LG can be improved?

(5) Understand that SN1 vs SN2 are 'teaching paradigms' and that biological SN reactions are SN1/SN2 hybrids?

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6. Nucleophilic substitution reactions

6.8A: The Williamson ether synthesis

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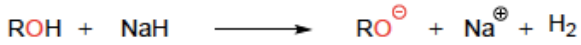
Williamson ether synthesis

The Williamson ether synthesis (1850) converts primary alcohols to ethers in two steps.

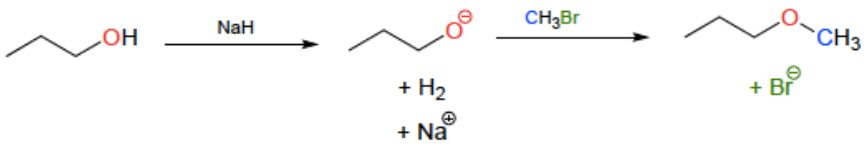
1. A strong base deprotonates the alcohol.



1. SN2: alkoxide substitutes for bromide.

Methyl bromide is used to carry the methyl group, acting a bit like SAM.

- These reactants wouldn't work in a cell or in the body!



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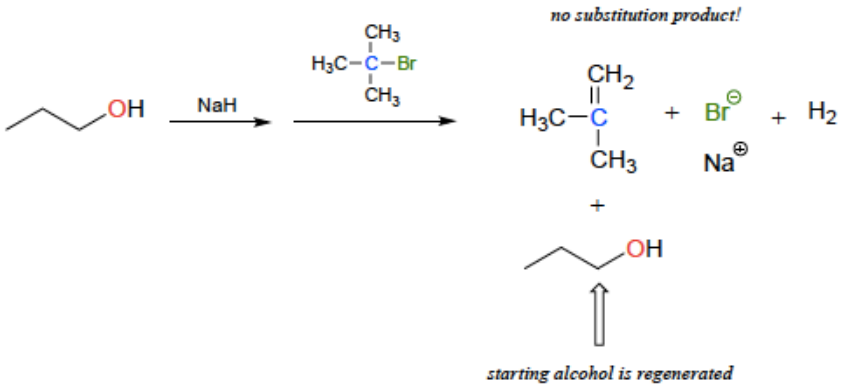
Williamson with 2° or 3° alkyl halides?

What would happen if 2° or 3° alkyl halides (the methyl carriers) were used as the substrate in a Williamson ether synthesis?

Rather than making ether by a substitution reaction, an **elimination reaction** would occur, producing an alkene.

- And the original primary alcohol substrate would be reproduced.



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Try this

A rookie organic chemist ran the reaction shown above, hoping to synthesize an ether. Instead, he got the alkene shown.
What alkyl halide/alcohol combination should he have used instead to get the ether product he was trying for?

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6. Nucleophilic substitution reactions

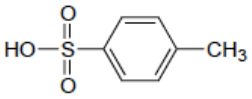
6.8B: Turning a poor leaving group into a good one - tosylates

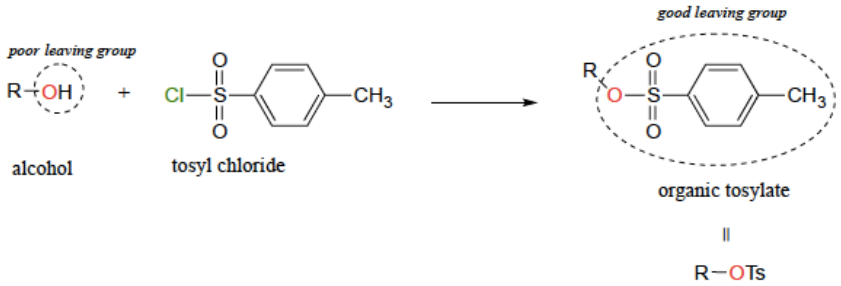
85

Tosylates are great LGs

If an organic chemist wants to convert a hydroxide to a better LG, she can convert it to an **organic tosylate:** *para-toluene sulfonate.*

Para–toluene sulfonic acid is a strong acid with a **pKa of 2.8**, so its conjugate base is a **weak base** and makes a good LG.





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Can you?

(1) Understand that the Williamson synthesis of ethers is a lab reaction?

(2) Understand that Williamson synthesis only works for 1° alcohol substrates?

(3) Understand that Williamson synthesis proceeds via a S_N2 reaction?

(4) Understand why para-toluene sulfonic acid creates a good leaving group?

(5) Understand how tosylates can improve OH leaving groups?

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