

# NUCLEOPHILIC SUBSTITUTION REACTIONS ①

Building upon:

- Rate equations
- Carbocation stability
- Alkynes as nucleophiles

Learning Objectives:

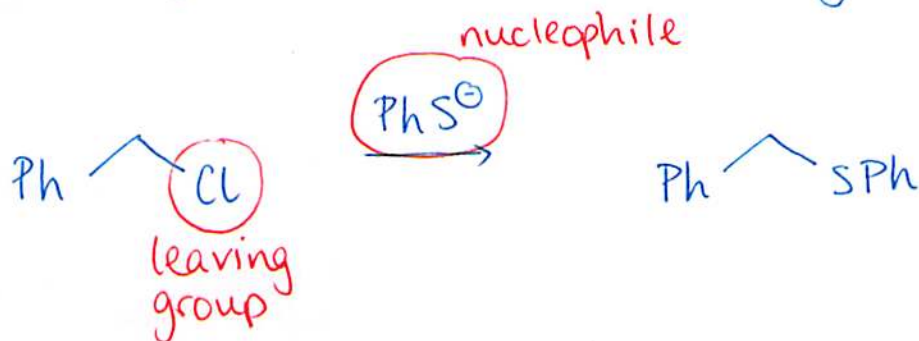
- State what type of reactions alkyl halides undergo
- Draw mechanisms for  $S_N1$  and  $S_N2$  reactions
- Predict, given reagents and conditions, whether a reaction will go by an  $S_N1$  or  $S_N2$  mechanism

Alkyl Halides



How can we make alkyl halides?  
→ look over alkene + alkane reactions

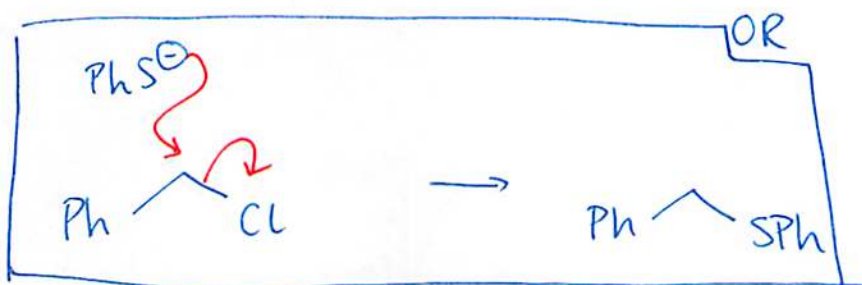
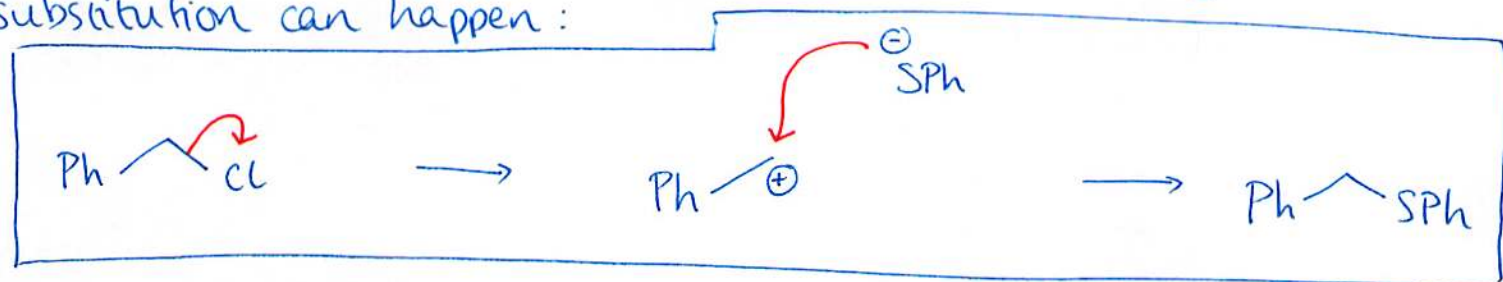
The  $\delta^+$  carbon can be attacked by a nucleophile...



The Cl group has been replaced by the SPh. This is a substitution reaction

(2)

It turns out there is not just one mechanism by which substitution can happen:



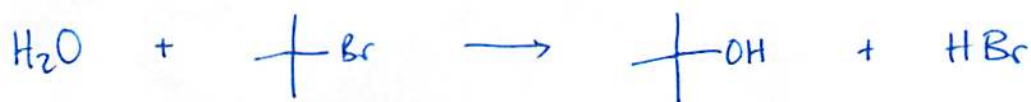
How do we know there are two different mechanisms?

Kinetic Evidence

look over kinetics from Gen Chem 2.



$$\text{rate} = k [\text{OH}^-] [\text{CH}_3\text{Br}]$$



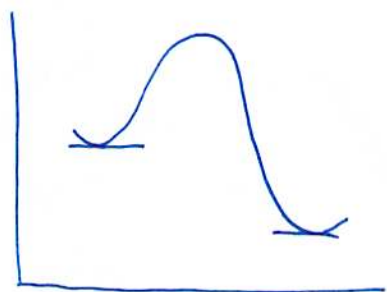
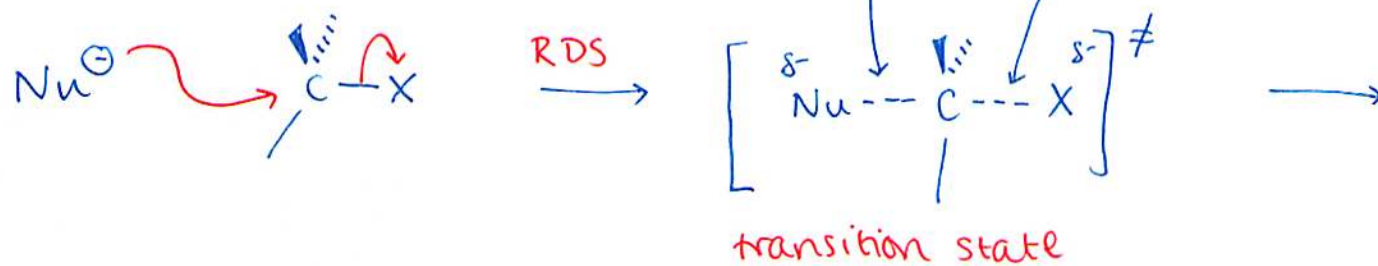
$$\text{rate} = k [(\text{CH}_3)_3\text{Br}]$$

So some nucleophilic substitutions are 1<sup>st</sup> order and some are 2<sup>nd</sup> order.

This implies there must be two different mechanisms.

# The S<sub>N</sub>2 Mechanism

substitution  
nucleophilic  
bimolecular

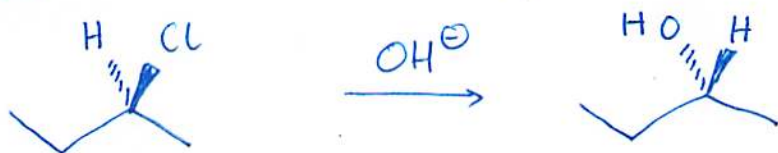


- Single step
- Backside attack  
(180° away from LG)
- Two molecules in the RDS

The nucleophile must attack from the back because it must interact with the C-X σ\* orbital.



If the carbon is a stereogenic centre, backside attack will result in an inversion of stereochemistry.

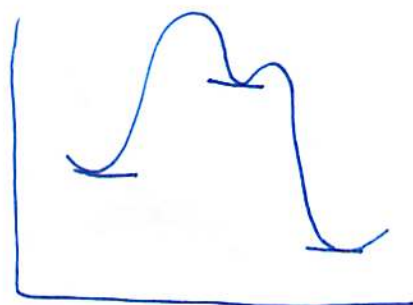
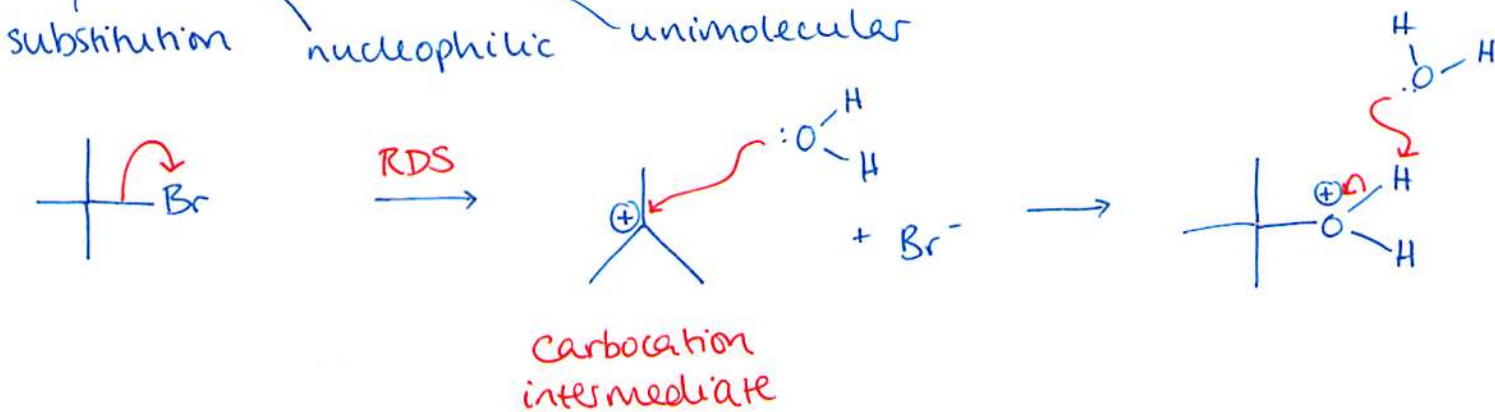


assign R or S labels to the starting material and product.



# The S<sub>N</sub>1 Mechanism

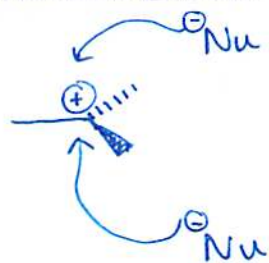
substitution  
nucleophilic  
unimolecular



- Goes through a carbocation intermediate
- Rate is independent of the nature of the nucleophile
- Fastest if a stable carbocation is formed.

The carbocation intermediate is planar. Therefore nucleophilic attack from above or below is equally likely.

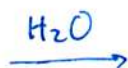
If the carbon is a stereogenic centre, this will lead to racemization



top or bottom attack equally likely.



one enantiomer



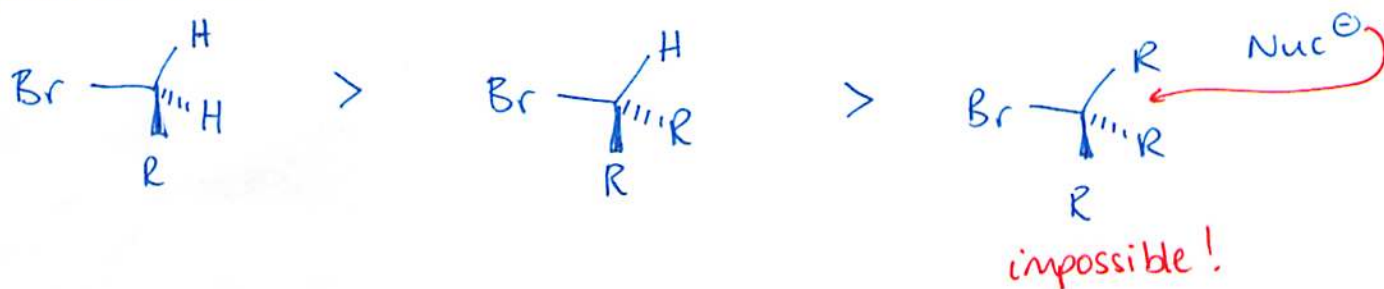
racemic mixture

So the stereochemistry of the product can help you determine if S<sub>N</sub>1 or S<sub>N</sub>2 took place.

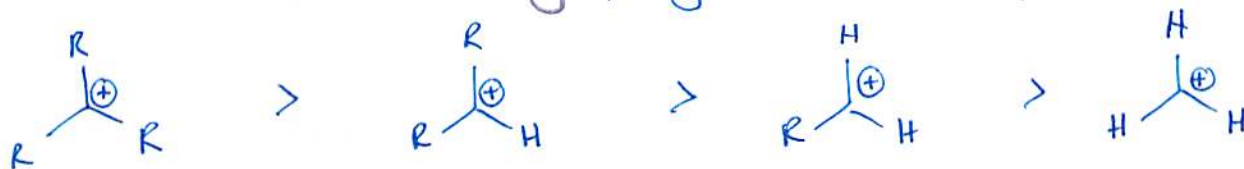
How can you determine whether a reaction proceeds via  $S_N1$  or  $S_N2$ ?

For  $S_N2$  reactions, the nucleophile has to attack at the correct angle -  $180^\circ$  away from the leaving group and a 5 coordinate transition state is formed.

Therefore sterics play a critical factor  
Speed of  $S_N2$ :



For  $S_N1$  reactions, a carbocation is formed in the RDS, so carbocation stability plays a critical factor



	1° LG	2° LG	3° LG
$S_N1$	X	possible	✓
$S_N2$	✓	possible	X

So if you have a  $1^\circ$  or  $3^\circ$  LG, you can immediately state whether it is  $S_N1$  or  $S_N2$ .

But if it is  $2^\circ$ , then you must consider other factors...

There are always exceptions!  
Think about



⑥

## The strength of the Nucleophile

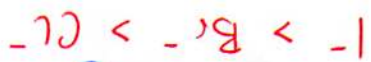
For  $S_N2$ , the rate is first order dependent on the concentration of the nucleophile.  
 For  $S_N1$ , the rate is independent of the nature of the nucleophile.

What makes a good nucleophile?

When the atom forming the bond to carbon stays the same, nucleophilicity correlates with basicity



Nucleophilicity increases going down a periodic group.



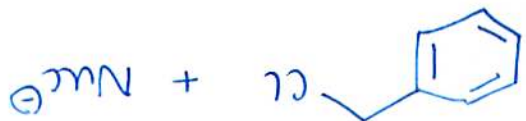
Negatively charged nucleophiles are usually more reactive than neutral nucleophiles.

For  $S_N2$ , a better nucleophile will react faster.

Although the rate of  $S_N1$  is independent of the nucleophile, a poorer nucleophile may favour  $S_N1$  because competing  $S_N2$  processes are slowed down so there is more time for carbocation formation.

The effect of changing the nucleophile:

nuc <sup>-</sup>	rate
AcO <sup>-</sup>	3.9
C <sup>-</sup>	4.0
PhO <sup>-</sup>	3.8
HO <sup>-</sup>	74
PhS <sup>-</sup>	107

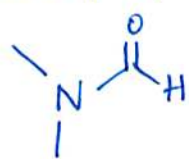


What can we learn from these rate data?

# The Solvent

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## Polar, aprotic solvents



DMF



DMSO



Acetonitrile

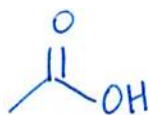


THF



acetone

## Polar protic solvents



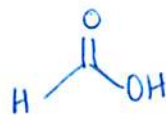
acetic acid



propanol



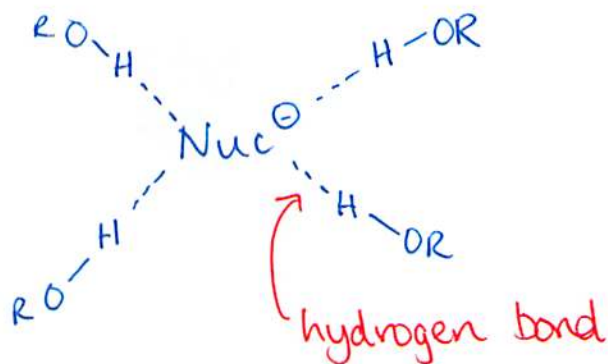
methanol



formic acid

Polar, aprotic solvents are good for  $S_N2$ .

This is because protic solvents solvate the nucleophile, making it less reactive.



"cage" around the nucleophile.

On the other hand, polar aprotic solvents solvate metal cations making the nucleophilic anions more available.



↳ more available as a nucleophile because the  $Na^+$  is solvated by the DMSO.

# The Leaving Group

For both  $S_N1$  and  $S_N2$ , a better LG will result in a faster reaction.

What makes a good LG?

	weak bond C-X bond	stability pKa of HX
F	118	+3
Cl	81	-7
Br	67	-9
I	54	-10



↑  
better LG

$OH^-$  is an extremely poor LG (what is the pKa of  $H_2O$ ?)

How can you make  $OH^-$  into a better LG?



Convert into a tosylate

