CH4103 Organic and Biological Chemistry
LCM Lectures 1-8

Dr Louis C. Morrill
School of Chemistry, Cardiff University
Main Building, Rm 1.47B
MorrillLC@cardiff.ac.uk

Autumn Semester

For further information see Learning Central: CH4103/Learning Materials/LCM

Unit 1: Recap

In Unit 1 with Dr Elliott you have learnt some key fundamentals in O-Chem:

- Drawing and naming organic compounds (Lecture 1)
- Molecular shape and hybridisation - sp^3, sp^2 and sp (Lecture 2)
- Constitutional and stereoisomers (Lectures 3-7)
- Conformations of acyclic and cyclic organic structures (Lectures 4 and 5)
- Conjugation and resonance (Lecture 8)
- Reactive intermediates – carbocations, carbanions and radicals (Lectures 8 and 9)
- Acids and bases – pH and pK_a (Lecture 9)

These are the first tools in your synthetic toolbox and are essential knowledge – please revise these topics diligently. Further supporting learning materials can be found on Learning Central and within *Organic Chemistry 2nd Ed.* (J. Clayden, N. Greeves and S. Warren) – Chapters 1-8.

Unit 2: Lecture Synopsis

- **Lecture 1: Describing an Organic Reaction.** Homolytic vs heterolytic bond breaking, bond dissociation energy (BDE), enthalpy and ΔH°, entropy and ΔS°, Gibbs free energy and ΔG°, equilibria.

- **Lecture 2: Reaction Kinetics and the Hammond Postulate.** Differentiating thermodynamics and kinetics, rate laws, activation energy (E_a), the Arrhenius equation, free energy diagrams, intermediates and transition states, the Hammond postulate.

- **Lecture 3: Curly Arrows for Electron Movement.** How molecules interact, nucleophiles and electrophiles, use of curly arrows to represent electron movement, curly arrows for nucleophilic attack / substitution, loss of a leaving group / elimination, proton transfers and carbocation rearrangements.

- **Lectures 4 and 5: Introduction to Substitution Reactions – S_N1 and S_N2.** Rate laws, free energy diagrams, curly arrow pushing mechanisms, molecular orbital analysis, intermediates and transition states, regioselectivity, stereoselectivity, factors that determine mechanism (substrate, nucleophile, solvent and leaving group).

Unit 2: Lecture Synopsis

- **Lecture 6 and 7: Introduction to Elimination Reactions – E1, E1$_{CB}$ and E2.** Rate laws, free energy diagrams, curly arrow pushing mechanisms, molecular orbital analysis, intermediates and transition states, regioselectivity, stereoselectivity, factors that determine mechanism (substrate, nucleophile, solvent and leaving group).

- **Lecture 8: Predicting Substitution vs Elimination.** Synthetic analysis and strategy – how to predict which type of substitution or elimination mechanism will dominate under a given set of reaction conditions.

- **Feedback Tutorial:** Questions on Lectures 1-3.

- **Workshop:** Answers to be completed beforehand. Feedback provided during workshop. Questions on Lectures 1-5.

- **In Unit 1 we learnt how to draw organic molecules realistically and what determines molecular shape and structure. In Unit 2 we will learn how these organic molecules can react together and how molecular shape and structure determine reactivity, adding yet more tools to our synthetic toolbox.**

Unit 2: Additional Resources

- **Recommended Reading:** *Organic Chemistry 2nd Ed.* (J. Clayden, N. Greeves and S. Warren, Oxford University Press, 2012, ISBN 978-0-19-927029-3). Chapters 6, 12, 15 and 17. Specific chapters and pages will be indicated as further reading in each lecture. Practice questions at http://www.oxfordtextbooks.co.uk/orc/clayden2e/ username: clayden2e password: compound

- **Molecular Model Kits:** These are available from the teaching labs and are invaluable for all organic chemistry courses. It is highly recommended that you make good use of these to visualise the molecules discussed in this course.

- **Learning Central:** I have set up a folder on Learning Central that will contain all information for this course including handouts and lecture capture. I have also set up a number of online tests that will reinforce your learning throughout the course.

- **Tutorials and Workshops:** In addition to the questions set, please take advantage of these opportunities to ask questions about any aspect of the course.

- **Me:** Should you not be able to find an answer to a question that specifically relates to this course, please email (MorrillLC@cardiff.ac.uk) or visit (1.47B) anytime. **In addition, I will specifically keep Monday 4-6pm free each week for office visits.**

CH4103 Organic and Biological Chemistry
LCM Lecture 1

Dr Louis C. Morrill
School of Chemistry, Cardiff University
Main Building, Rm 1.47B
MorrillLC@cardiff.ac.uk

Autumn Semester

Lecture 1 Preparation

To best prepare yourself for the contents of this lecture, please refresh

- Bonding in organic compounds (Unit 1, Lecture 2)
- Electronegativity and bond polarisation (Unit 1, Lecture 3)
- Reactive intermediates – radical stability (Unit 1, Lecture 8)

Lecture 1: Describing Organic Reaction Mechanisms

Key learning objectives:

- Understand the difference between homolytic vs heterolytic bond breaking
- Understand the importance of bond dissociation energy (BDE) how these values relate to bond strength and radical stability
- Enthalpy and $\Delta H°$ – predicting $\Delta H°$ for a chemical reaction, identifying a reaction as exothermic or endothermic, practical implications
- Entropy and $\Delta S°$ – the change in disorder during a process
- Gibbs free energy and $\Delta G°$ – determining whether a process is exergonic or endergonic
- Equilibria and its relationship to $\Delta G°$

Homolytic and Heterolytic Bond Breaking

- Bonds can be broken **homolytically** or **heterolytically**.

- **Homolytic bond cleavage (Homolysis):** When a bond breaks and the atoms get one bonding electron each. The products formed are **radicals**, which may be atoms or molecules, but must contain an unpaired electron.

Single-headed Fishhook Arrows

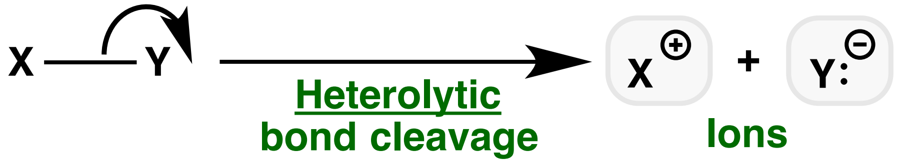
Homolytic bond cleavage

Radicals

One electron chemistry

- **Heterolytic bond cleavage (Heterolysis):** When a bond breaks and one atom gets both bonding electrons. The products formed are **ions**.

Double-headed Arrows



Heterolytic bond cleavage

Ions

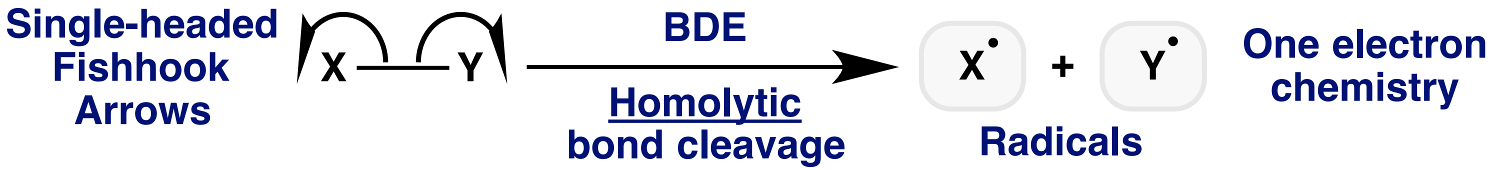
Two electron chemistry

- **Bond dissociation energy (BDE)** for bond breaking represents the energy required for **homolytic** cleavage

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 37 pp. 970-979.

Bond Dissociation Energies

- **Bond dissociation energy** for bond breaking represents the energy associated with **homolytic** cleavage



$$X{-}Y \xrightarrow[\text{Homolytic bond cleavage}]{\text{BDE}} X^{\bullet} + Y^{\bullet}$$

Single-headed Fishhook Arrows

Radicals

One electron chemistry

- The bond dissociation energies (BDEs) quoted in tables represent the homolytic breaking of a bond into two **radicals.**
- Therefore the bond dissociation energy reflects the stability of the radicals formed.
- High BDE = Strong Bond = Poorly stabilised radicals formed e.g. $H^{\bullet}$, $Me^{\bullet}$, $Ph^{\bullet}$ etc.
- Low BDE = Weak Bond = Highly stabilised radicals formed e.g. *t*-$Bu^{\bullet}$, $Bn^{\bullet}$, $I^{\bullet}$ etc.

For a recap of radical stabilisation, please refer to MCE lecture 8

Bond Dissociation Energies

- **Bond dissociation energy** for a selection of common bonds. The formation of highly stabilised radicals (e.g. *t*-Bu$^{\bullet}$, Bn$^{\bullet}$, I$^{\bullet}$) leads to lower BDEs

Decreasing BDE

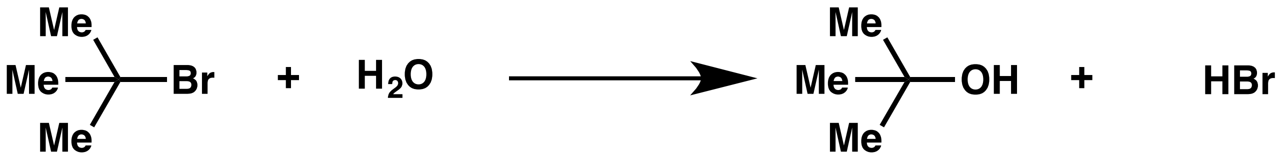
Form highly stabilised radicals upon homolytic bond cleavage (*t*-Bu$^{\bullet}$, Bn$^{\bullet}$, Allyl$^{\bullet}$, I$^{\bullet}$)

	kJ/mol		kJ/mol		kJ/mol		kJ/mol
Bonds to H		**Bonds to Me**		**Bonds to *i*-Pr**		**C-C Bonds**	
H—H	435	Me—H	435	*i*-Pr—H	397	Me—Me	368
Me—H	435	Me—F	456	*i*-Pr—F	444	Me—Et	356
Et—H	410	Me—Cl	351	*i*-Pr—Cl	335	Me—*i*-Pr	351
i-Pr—H	397	Me—Br	293	*i*-Pr—Br	285	Me—CH=CH_2	385
t-Bu—H	381	Me—I	234	*i*-Pr—I	222	Me—C≡CH	489
Ph—H	473						
Bn—H	356						
 H	464						
 H	364	**Bonds to Et**		**Bonds to *t*-Bu**		**X-X Bonds**	
F—H	569	Et—H	410	*t*-Bu—H	381	F—F	159
Cl—H	431	Et—F	448	*t*-Bu—F	444	Cl—Cl	242
Br—H	368	Et—Cl	339	*t*-Bu—Cl	331	Br—Br	192
I—H	297	Et—Br	285	*t*-Bu—Br	272	I—I	151
HO—H	498	Et—I	222	*t*-Bu—I	209	HO—OH	213

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 37 pp. 970-979.

Predicting ΔH° for a Reaction

- **Enthalpy (H°)** is a measure of **heat**.
- **Change in enthalpy (ΔH°)** is the **heat given out or taken up in a chemical reaction**.
- By considering bond dissociation energies, we can predict the **change in enthalpy (ΔH°)** for a given reaction.



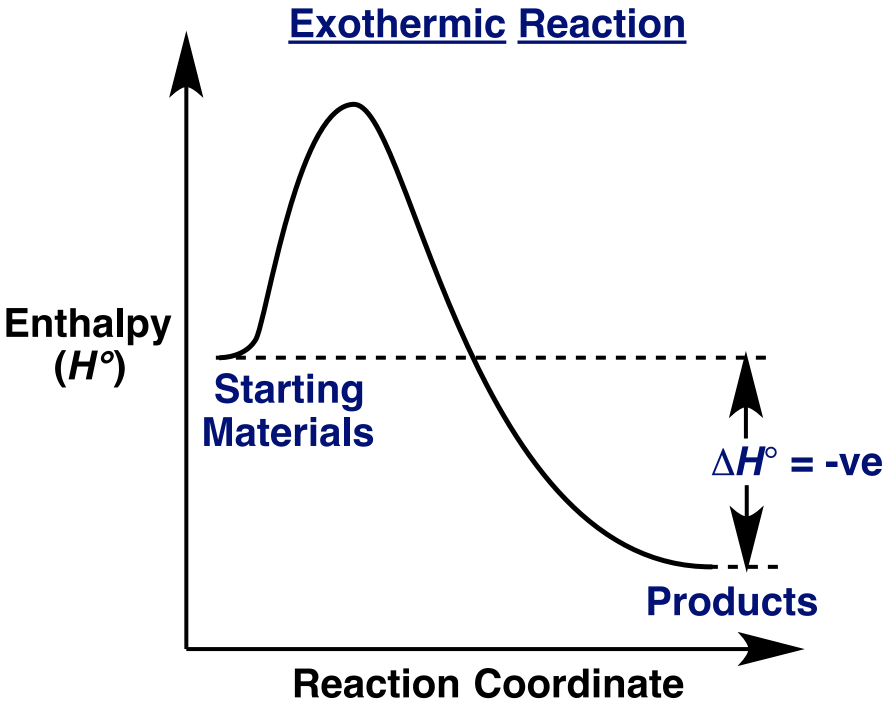
***t*-Butyl bromide** **Water** ***t*-Butyl alcohol** **hydrogen bromide**

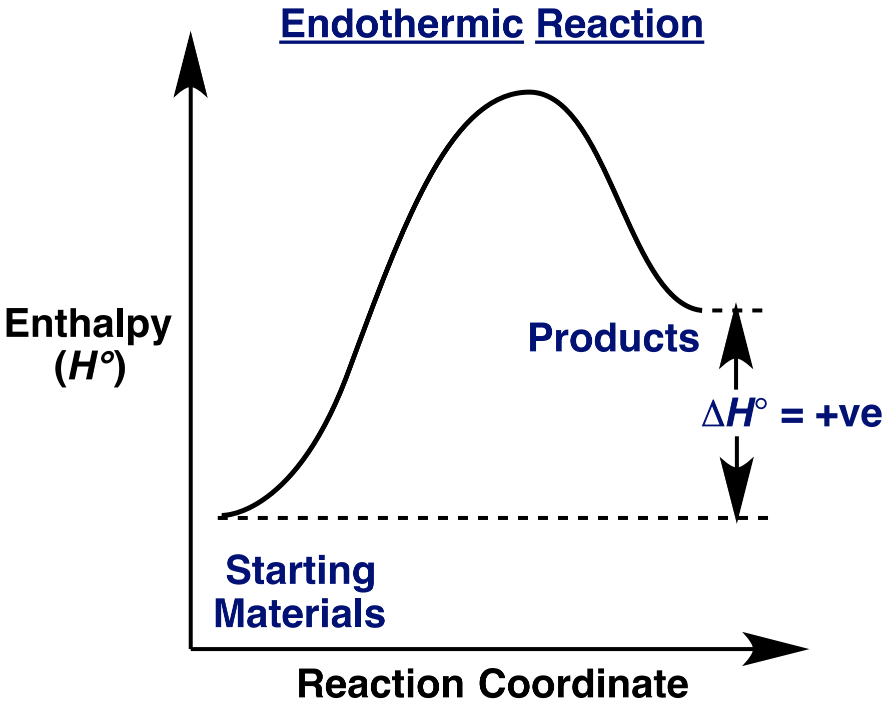
Step 1: Identify the bonds broken/made and their associated BDEs	**Bonds broken**	**BDE (kJ/mol)**	**Bonds formed**	**BDE (kJ/mol)**
	***t*-Bu—Br**	**+272**	***t*-Bu—OH**	**-381**
	HO—H	**+498**	**Br—H**	**-368**
Step 2: Add the values for all bonds broken and formed	**Energy in (Bonds Broken)** **= 272 + 498** **= 770 kJ/mol**		**Energy out (Bonds Formed)** **= -381 - 368** **= -749 kJ/mol**	
Step 3: Calculation	**ΔH° = Energy in + Energy out = 770 - 749 = +21 kJ/mol** **Endothermic Reaction**			

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Exothermic and Endothermic

- The change in enthalpy (Δ*H*°) is the heat given out or taken up in a chemical reaction and indicates whether a given reaction is **exothermic** or **endothermic**.





The reaction has a negative Δ*H*° therefore exothermic and causes the surrounding temperature to INCREASE

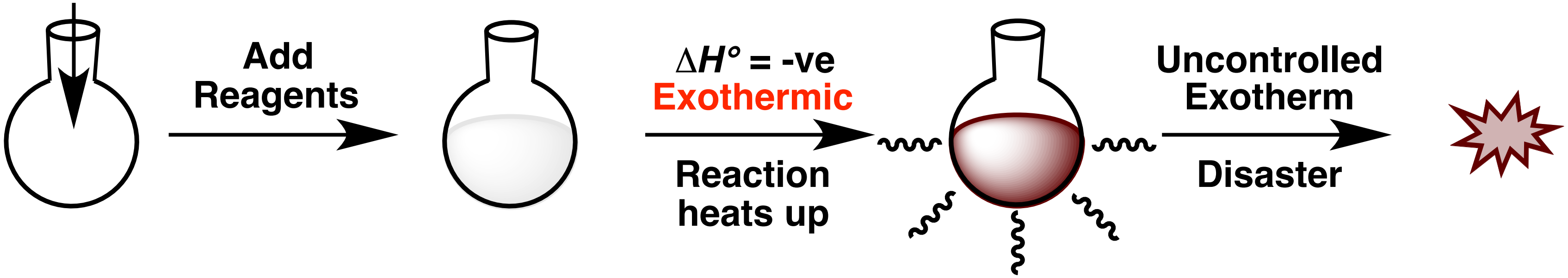
The reaction has a positive Δ*H*° therefore endothermic and causes the surrounding temperature to DECREASE

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Practical Importance of ΔH°

- In the lab, knowing whether ΔH° for a reaction is +ve (endothermic) or –ve (exothermic) can be very useful. Why?
- Let’s first consider an **exothermic** reaction – i.e. you know the ΔH° is –ve.

Not accounting for potential exotherms = bad experimental technique

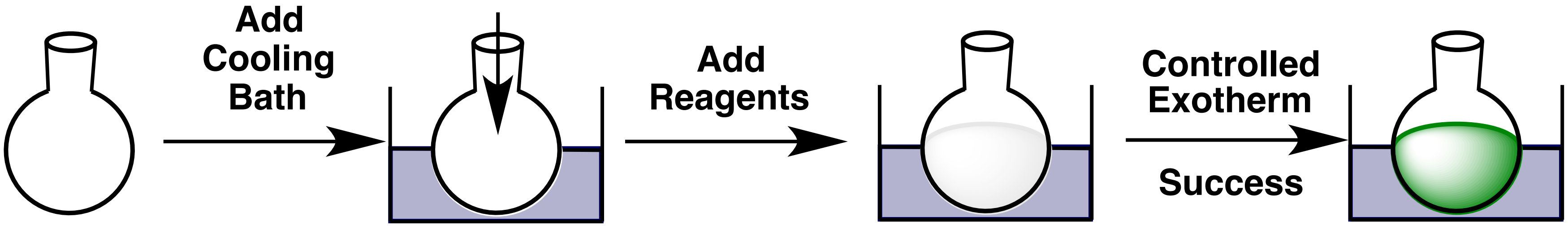


Add Reagents

ΔH° = -ve
Exothermic
Reaction heats up

Uncontrolled Exotherm
Disaster

Accounting for potential exotherms = excellent experimental technique



Add Cooling Bath

Add Reagents

Controlled Exotherm
Success

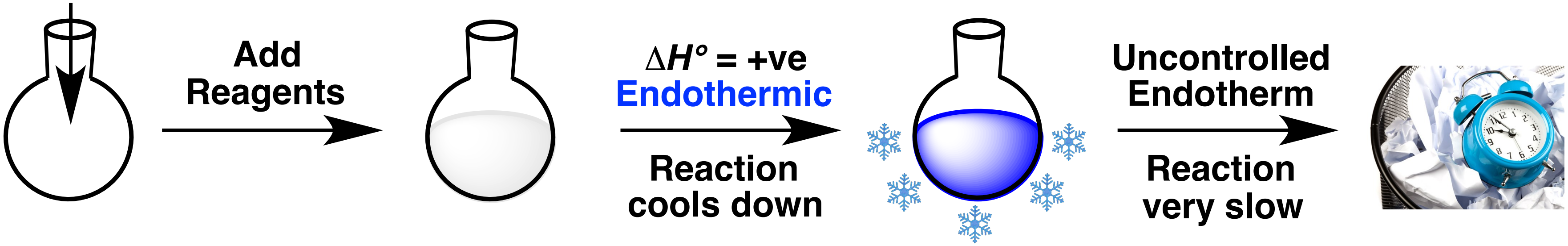
For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Practical Importance of $\Delta H°$

- In the lab, knowing whether $\Delta H°$ for a reaction is +ve (endothermic) or –ve (exothermic) can be very useful. Why?

- Let's now consider an **endothermic** reaction – i.e. you know the $\Delta H°$ is +ve.

Not accounting for potential endotherm = bad experimental technique



Add Reagents

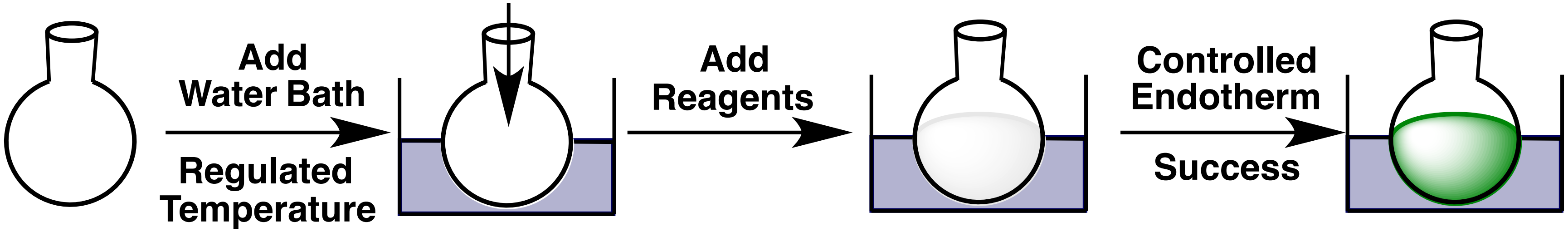
$\Delta H°$ = +ve
Endothermic

Reaction cools down

Uncontrolled Endotherm

Reaction very slow

Accounting for potential endotherms = excellent experimental technique



Add Water Bath

Regulated Temperature

Add Reagents

Controlled Endotherm

Success

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

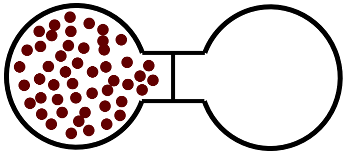
Entropy and ΔS°

- **Entropy (S°)** is a measure of the **disorder in the system**.

- **Change in enthalpy (ΔS°)** is the change in disorder between starting materials and products.

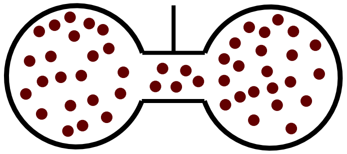
- Consider the free expansion of a gas. Opening the valve results in the gas filling both chambers, resulting in an **increase in disorder (+ve ΔS°)**.

Valve Closed (A)



Lower disorder (S°)

Valve Open (B)



Higher disorder (S°)

- The process of opening the valve (A ➔ B) results in an increase in entropy (+ve ΔS°).

- To determine the total change in entropy (ΔS°_{tot}) for a chemical reaction we must take account of the entropy change for both the system (ΔS°_{sys}) **AND** its surroundings (ΔS°_{surr}).

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Gibbs Free Energy and $\Delta G°$

- Let’s derive the Gibbs free energy equation:

$$\Delta S°_{tot} = \Delta S°_{surr} + \Delta S°_{sys} \qquad \text{Where } \Delta S°_{surr} = -\frac{\Delta H°_{sys}}{T}$$

$$\text{Therefore: } \Delta S°_{tot} = -\frac{\Delta H°_{sys}}{T} + \Delta S°_{sys}$$

$$-T\Delta S°_{tot} = \Delta H°_{sys} - T\Delta S°_{sys}$$

$$\Delta G° = \Delta H°_{sys} - T\Delta S°_{sys}$$

$\Delta G°$ = Gibbs free energy (kJ mol^{-1})
$\Delta H°$ = Enthalpy change (kJ mol^{-1})
$\Delta S°$ = Entropy change (J K^{-1})
T = Temperature (K)

- **The change in Gibbs free energy ($\Delta G°$)** is equal to the change in enthalpy for the system ($\Delta H°_{sys}$) minus temperature (T) multiplied by the change in entropy for the system ($\Delta S°_{sys}$).

- A negative $\Delta G°$ value corresponds to an **exergonic** process whereas a positive $\Delta G°$ value corresponds to a process that is **endergonic**.

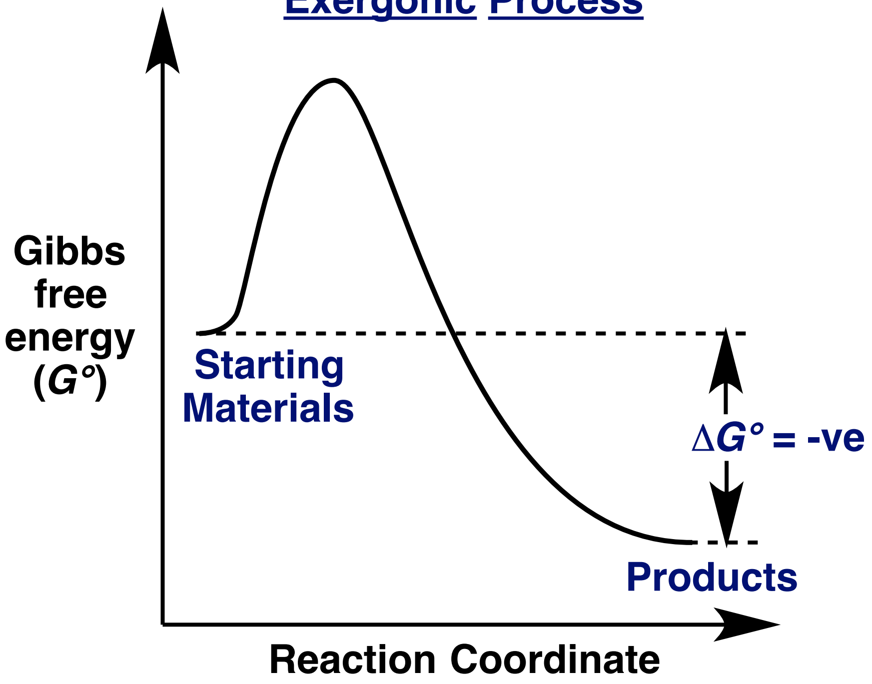
- Hence, exothermic processes (-ve $\Delta H°$) and those that involve an increase in entropy (+ve $\Delta S°$) give a large and negative $\Delta G°$, favouring the products at equilibrium.

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Gibbs Free Energy and Δ*G*°

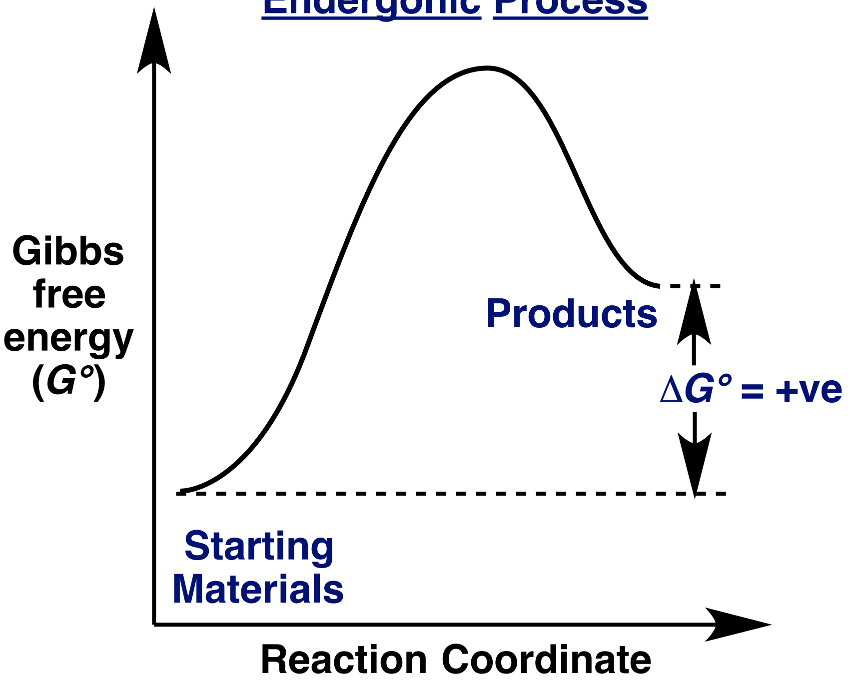
- The change in Gibbs free energy (Δ*G*°) at a given temperature indicates whether a given process is **exergonic** or **endergonic**.

Exergonic Process



If a process at a given temperature has a negative Δ*G*°, the process is EXERGONIC and will favour the products at equilibrium.

Endergonic Process

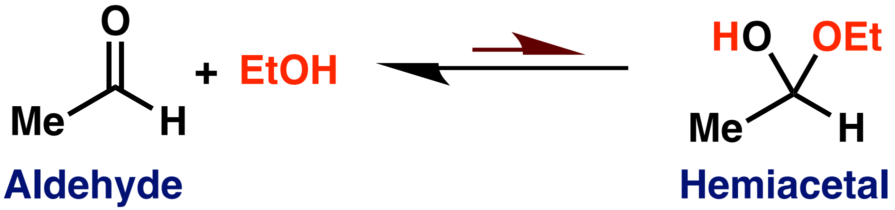


If a process at a given temperature has a positive Δ*G*°, the process is ENDERGONIC and will favour the starting materials at equilibrium.

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Worked Example 1 – Enthalpy vs Entropy

- Consider the reversible addition of ethanol to acetaldehyde (**intermolecular** hemiacetal formation). Rationalise why the starting aldehyde is favoured.



Starting aldehyde is favoured

Step 1: Predict Δ*H*°

Bonds broken	BDE (kJ/mol)	Bonds formed	BDE (kJ/mol)
C=O	+740	2 x C–O	-381
RO–H	+438	RO–H	-438

Δ*H*° = Energy in + Energy out = 1178 - 1200 = -22 kJ/mol
Slightly Exothermic Reaction

Step 2: Predict Δ*S*°
In the forward reaction we are converting 2 molecules into 1 therefore there is a decrease in disorder (-ve Δ*S*°)

Step 3: Predict Δ*G*°
Remember the equation Δ*G*° = Δ*H*°-*T*Δ*S*°
Δ*H*° is small and negative, Δ*S*° is large and negative → Δ*S*° term dominates
Therefore we expect a positive value of Δ*G*° and starting aldehyde to be favoured

Worked Example 2 – Enthalpy vs Entropy

- Now consider the reversible **intramolecular** hemiacetal formation. Rationalise why the product hemiacetal aldehyde is favoured.

Aldehyde **Hemiacetal**

Product hemiacetal is favoured

	Bonds broken	BDE (kJ/mol)	Bonds formed	BDE (kJ/mol)
Step 1: Predict Δ*H*°	C=O	+740	2 x C–O	-381
	RO–H	+438	RO–H	-438

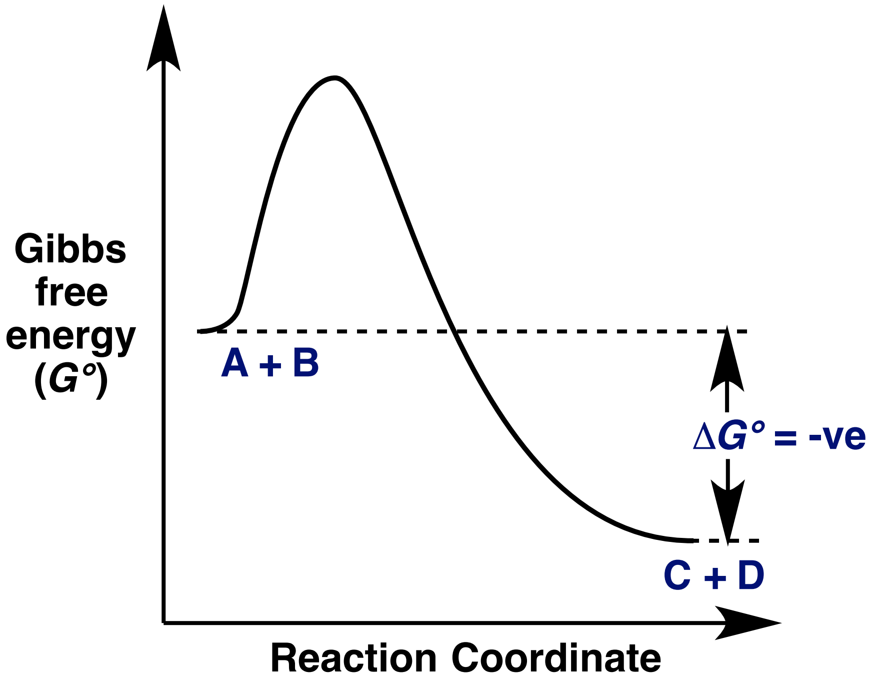
Δ*H*° = Energy in + Energy out = 1178 - 1200 = -22 kJ/mol
Slightly Exothermic Reaction

Step 2: Predict Δ*S*°
Δ*S*° is close to zero as there is no change in the number of molecules in this reaction

Step 3: Predict Δ*G*°
Remember the equation Δ*G*° = Δ*H*°-*T*Δ*S*°
Δ*H*° is small and negative, Δ*S*° is close to zero → Δ*H*° term dominates
Therefore we expect a negative value of Δ*G*° and product hemiacetal to be favoured

Gibbs Free Energy and Equilibria

- Consider an exergonic process with a negative change in Gibbs free energy (–ve $\Delta G°$).



$$A + B \rightleftharpoons C + D$$

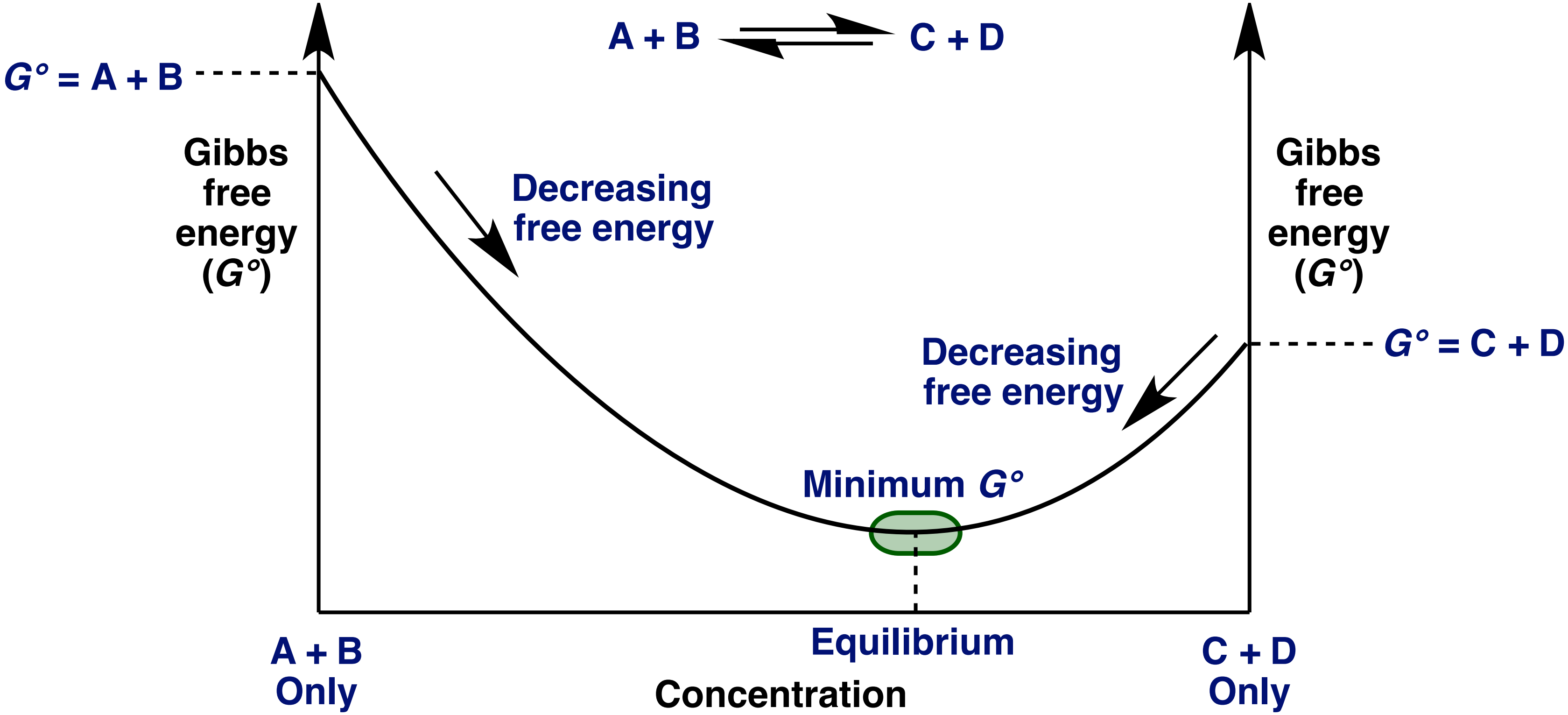
- Q) Will every molecule of A and B be converted to products?

- A) No. An equilibrium state will eventually be reached. An exergonic process will simply favour the products meaning that there will be more products than reactants

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Gibbs Free Energy and Equilibria

- Equilibrium is the state with the lowest overall free energy (minimum value of *G*).



- Remember that equilibrium is dynamic and is reached when the rate of both the forward and reverse reactions are equal.

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Gibbs Free Energy and Equilibria

- An equilibrium constant (K_{eq}) is used to show the degree to which a reaction favours products or reactants and can be related to the change in Gibbs free energy ($\Delta G°$).

$$A + B \rightleftharpoons C + D \qquad K_{eq} = \frac{[\text{Products}]}{[\text{Reactants}]} = \frac{[C][D]}{[A][B]} \qquad \Delta G° = -RT\ln K_{eq}$$

	$\Delta G°$ (kJ/mol)	K_{eq}	% Products At Equilibrium
-ve $\Delta G°$ Favouring Products	-17	10^{3}	99.9
	-11	10^{2}	99
	-6	10^{1}	90
Equilibrium	0	1	50
+ve $\Delta G°$ Favouring Reactants	+6	10^{-1}	10
	+11	10^{-2}	1
	+17	10^{-3}	0.1

- K_{eq}, $\Delta G°$, $\Delta H°$ and $\Delta S°$ are thermodynamic parameters that describe equilibria. They **DO NOT** describe reaction kinetics (the rate of a reaction). Discussed in Lecture 2

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

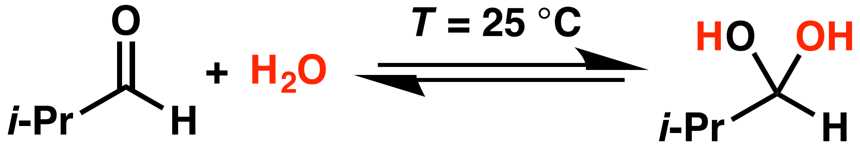
Worked Example 3 – Hydration of an Aldehyde

- Gibbs free energy ($\Delta G°$) is related to the equilibrium constant (K_{eq}) by the following equation:

$$\Delta G° = -RT\ln K_{eq}$$

$\Delta G°$ = Change in Gibbs free energy
R = Gas constant (8.314 J K^{-1} mol^{-1})
T = Temperature in kelvin (not °C)
K_{eq} = Equilibrium constant

- Consider the reversible addition of water to an aldehyde (hydration of an aldehyde). Note that pure solids and liquids (water) are **NOT** included in the equilibrium constant



Aldehyde **Hydrate**

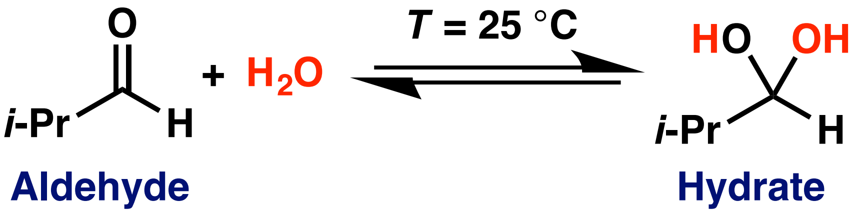
$$K_{eq} = \frac{[\text{Products}]}{[\text{Reactants}]} = \frac{[\text{Hydrate}]}{[\text{Aldehyde}]} = \text{ca. } 0.5$$

- Q1) What is the approximate ratio of aldehyde to hydrate in the equilibrium mixture?
- Q2) What is the corresponding value for $\Delta G°$? Is the process exergonic or endergonic?
- Q3) Sketch a suitable energy diagram indicating $\Delta G°$ for this process.

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Worked Example 3 – Hydration of an Aldehyde

- Q1) What is the approximate ratio of aldehyde to hydrate in the equilibrium mixture?
- A1) K_{eq} = ca. 0.5 therefore twice as much aldehyde as hydrate.



Aldehyde **Hydrate**

$$K_{eq} = \frac{[\text{Products}]}{[\text{Reactants}]} = \frac{[\text{Hydrate}]}{[\text{Aldehyde}]} = \text{ca. } 0.5$$

- Q2) What is the corresponding value for $\Delta G°$? Is the process exergonic or endergonic?
- A2) $\Delta G° = +1.72\ \text{kJ mol}^{-1}$ therefore endergonic

$$\Delta G° = -RT\ln K_{eq}$$
$$\Delta G° = -(8.314) \times 298 \times \ln(0.5)$$
$$\Delta G° = 1717\ \text{J mol}^{-1} = 1.72\ \text{kJ mol}^{-1}$$

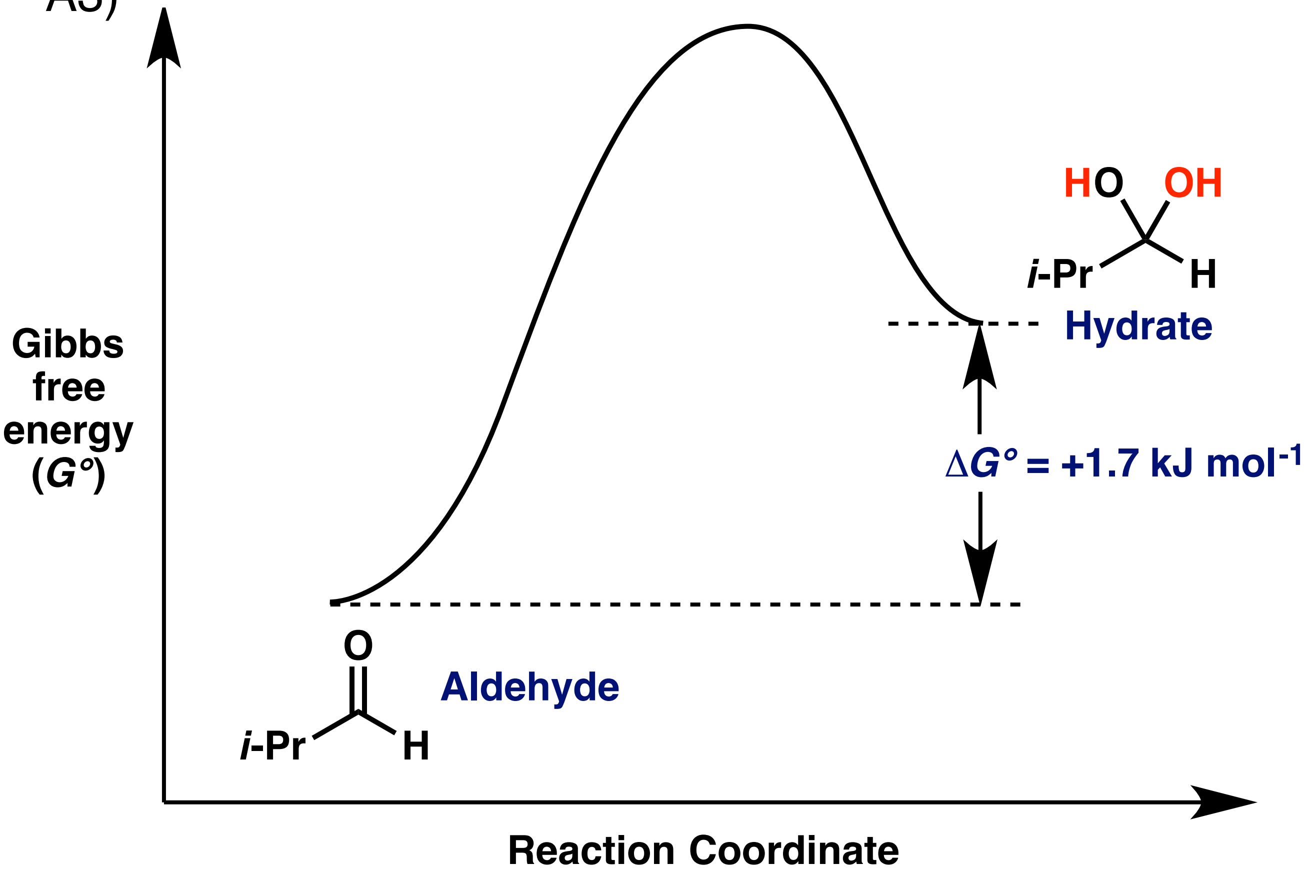
Endergonic Process (+ve $\Delta G°$)

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Worked Example 3 – Hydration of an Aldehyde

- Q3) Sketch a suitable Gibbs free energy diagram indicating Δ*G°* for this process.

- A3)



Process at 298 K has a positive Δ*G°* (+1.7 kJ mol^{-1}) therefore endergonic and favours the starting aldehyde.

Note: The reaction coordinate is an arbitrary scale used for diagrammatic purposes online

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249.

Lecture 1: Describing Organic Reaction Mechanisms

- **Key learning objectives:**
- Understand the difference between homolytic vs heterolytic bond breaking
- Understand the importance of bond dissociation energy (BDE) how these values relate to bond strength and radical stability
- Enthalpy and $\Delta H°$ – predicting $\Delta H°$ for a chemical reaction, identifying a reaction as exothermic or endothermic, practical implications
- Entropy and $\Delta S°$ – the change in disorder during a process
- Gibbs free energy and $\Delta G°$ – determining whether a process is exergonic or endergonic
- Equilibria and its relationship to $\Delta G°$

Lecture 1 Revision

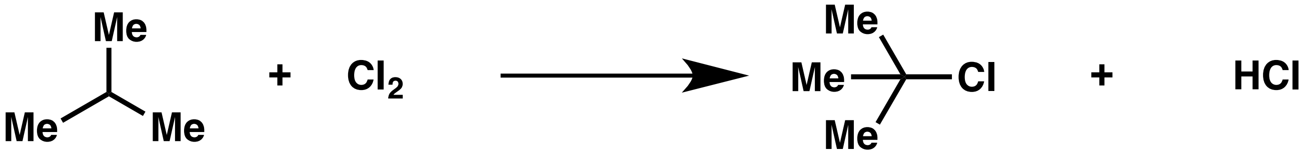
To reinforce your understanding of the contents of this lecture, please refer to:

- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 240-249 and Chapter 37 pp. 970-979.
- Practice questions provided on the next two slides.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e   Password: compound
- CH4103 Online Test 1
- CH4103 Tutorial 2
- CH4103 Workshop 2

Lecture 1 Practice Questions / Guided Self-Study

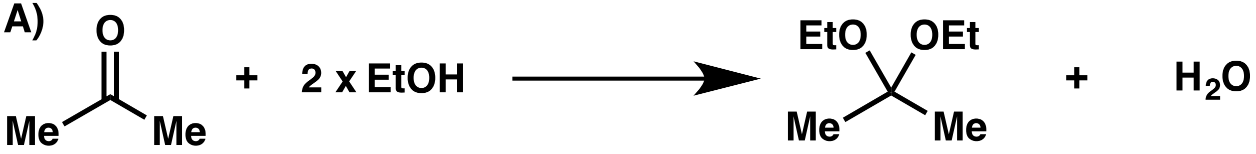
For further practice, attempt the following questions in your own time:

- Q1) Using the table on slide 6, predict the $\Delta H°$ for the following reaction and indicate whether the forward reaction is exothermic or endothermic. Represent this graphically using an enthalpy energy diagram.

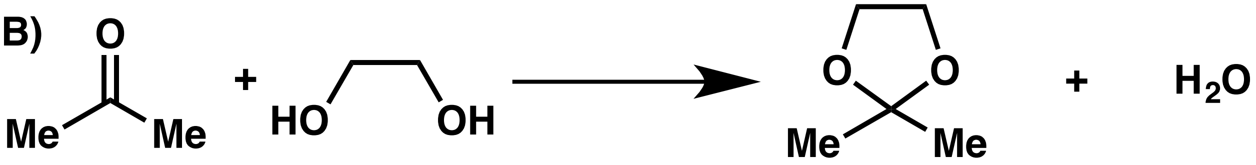


- Q2) For processes A and B below, would you expect the $\Delta S°$ value for the forward reaction to be +ve, -ve or close to 0?

A)



B)



Lecture 1 Practice Questions / Guided Self-Study

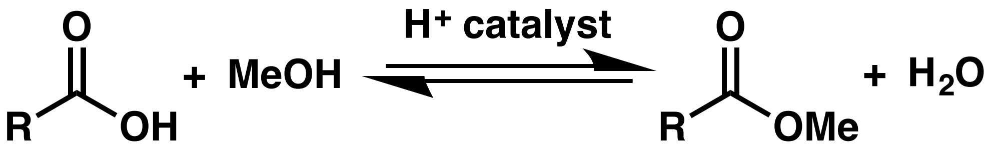
For further practice, attempt the following questions in your own time:

- Q3) Using the information provided, calculate $\Delta G°$ (in kJ mol^{-1}) for the following reaction and indicate whether the forward reaction is exergonic or endergonic.

$$NH_4NO_{3(s)} \xrightarrow{H_2O} NH_4^{+}{}_{(aq)} + NO_3^{-}{}_{(aq)}$$

$\Delta H° = 28.05$ kJ mol^{-1}
$\Delta S° = 108.7$ J K^{-1}
$T = 298$ K

- Q4) Consider the following reversible ester formation and the corresponding equilibrium. How might you alter the equilibrium position to favour the ester product?



$$K_{eq} = \frac{[RCO_2Me][H_2O]}{[RCO_2H][MeOH]} = \text{ca. } 1$$

CH4103 Organic and Biological Chemistry
LCM Lecture 2

Dr Louis C. Morrill
School of Chemistry, Cardiff University
Main Building, Rm 1.47B
MorrillLC@cardiff.ac.uk

Autumn Semester

Lecture 2 Preparation

To best prepare yourself for the contents of this lecture, please refresh

- Bonding in organic compounds (Unit 1, Lecture 2)
- Reactive intermediates – carbocations (Unit 1, Lecture 8)
- Thermodynamics (K_{eq}, $\Delta G°$, $\Delta H°$ and $\Delta S°$) and equilibria (Unit 2, Lecture 1)
- Energy diagrams (Unit 2, Lecture 1)

Lecture 2: Reaction Kinetics and the Hammond Postulate

Key learning objectives:

- Be able to clearly differentiate between thermodynamics and kinetics
- Rate laws – 1st, 2nd and 3rd order
- Activation energy (E_a) – the minimum amount of energy required for reaction
- Relating the rate constant (k) to the activation energy (E_a) – the Arrhenius equation
- The definitions of intermediates and transition states
- The Hammond postulate – early ("reagent like") and late ("product like") transition states

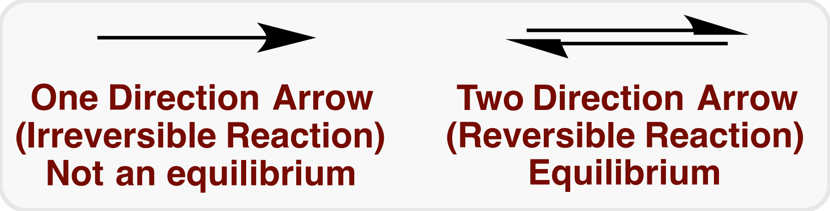
For further information see Learning Central: CH4103/Learning Materials/LCM

Reaction Kinetics

- In Lecture 1 we showed that a –ve $\Delta G°$ value indicates that a process favours the formation of products at equilibrium, i.e. it is exergonic. This does **NOT** tell us anything about the **RATE** of the process.

- In the laboratory reactions are often heated. This is often done to **speed up reactions** (kinetics) rather than to alter the **equilibrium position** (thermodynamics). Many reactions are irreversible with reactants and products not in equilibrium.

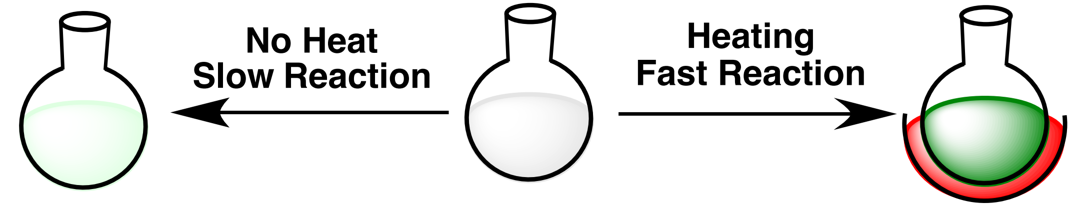
$$\mathrm{A + B} \xrightarrow[\text{Irreversible Reaction}]{} \mathrm{C}$$



One Direction Arrow (Irreversible Reaction) Not an equilibrium

Two Direction Arrow (Reversible Reaction) Equilibrium

Increasing Rate of Reaction by Heating



No Heat
Slow Reaction

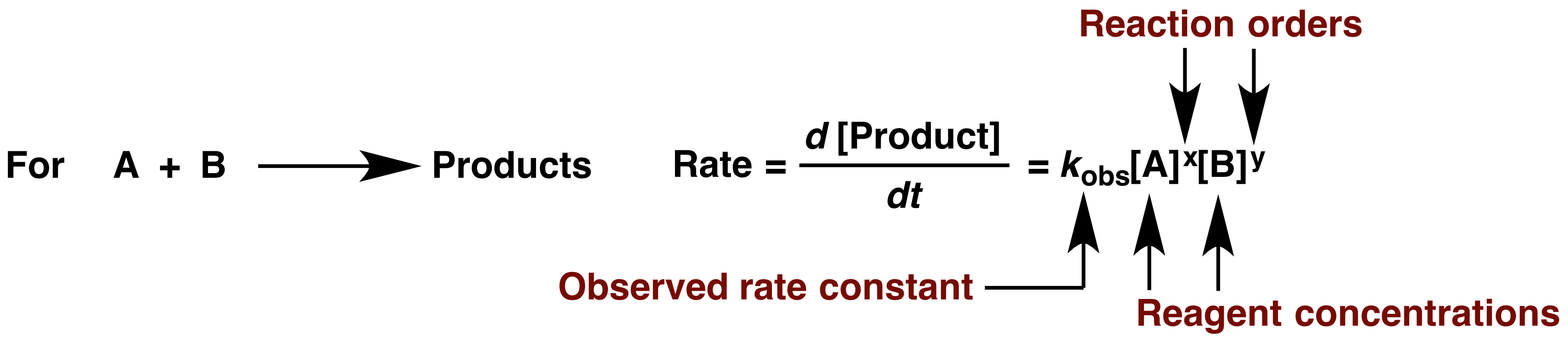
Heating
Fast Reaction

- Higher *T* results in molecules having higher kinetic energy. Therefore a higher number of molecular collisions have sufficient force for reaction, **increasing the rate**.

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

Reaction Kinetics – Rate Laws

- The kinetics of any given reaction is characterised by its **rate law**.
- This equation describes the relationship between the reactants and the **rate of product formation** (i.e. rate of reaction).



Reaction orders

$$\text{For} \quad A + B \longrightarrow \text{Products} \qquad \text{Rate} = \frac{d\,[\text{Product}]}{dt} = k_{obs}[A]^{x}[B]^{y}$$

Observed rate constant

Reagent concentrations

- The reaction orders exhibited by the reagents is important when considering the mechanism of a reaction.
- The reaction order for each reagent tells us how many molecules of that reagent participate in the rate determining step.
- Let’s now consider the rate law for 1st, 2nd and 3rd order reactions.

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

Reaction Kinetics – Rate Laws

- **First Order** – Only one molecule of reagent A participates in the rate determining step

$$\text{For}\quad A + B \longrightarrow \text{Products}\qquad \text{Rate} = \frac{d\,[\text{Product}]}{dt} = k_{obs}[A]^1$$

- **Second Order** – Only one molecule of reagent A and one molecule of reagent B participate in the rate determining step

$$\text{For}\quad A + B \longrightarrow \text{Products}\qquad \text{Rate} = \frac{d\,[\text{Product}]}{dt} = k_{obs}[A]^1[B]^1$$

- **Third Order** – Only one molecule of reagent A and two molecules of reagent B participate in the rate determining step

$$\text{For}\quad A + B \longrightarrow \text{Products}\qquad \text{Rate} = \frac{d\,[\text{Product}]}{dt} = k_{obs}[A]^1[B]^2$$

Rate = Rate of reaction (mol L^{-1} s^{-1})
[A] and [B] = Concentration of A and B (mol L^{-1})
x and y = Reaction order in A and B (integers, no unit)

k_{obs} = Rate constant (units below)
1st Order (s^{-1})
2nd Order (L mol^{-1} s^{-1})
3rd Order (L^2 mol^{-2} s^{-1})

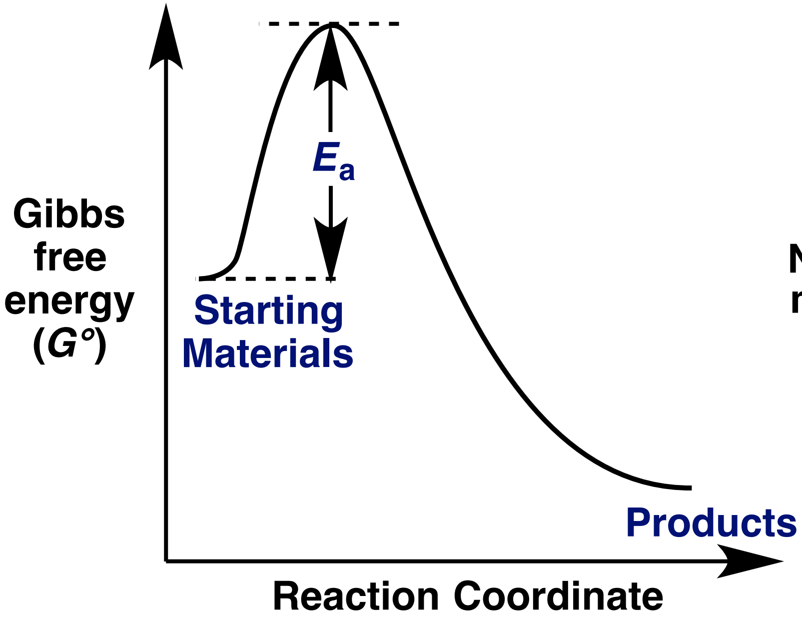
For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

Reaction Kinetics – Activation Energy (E_a)

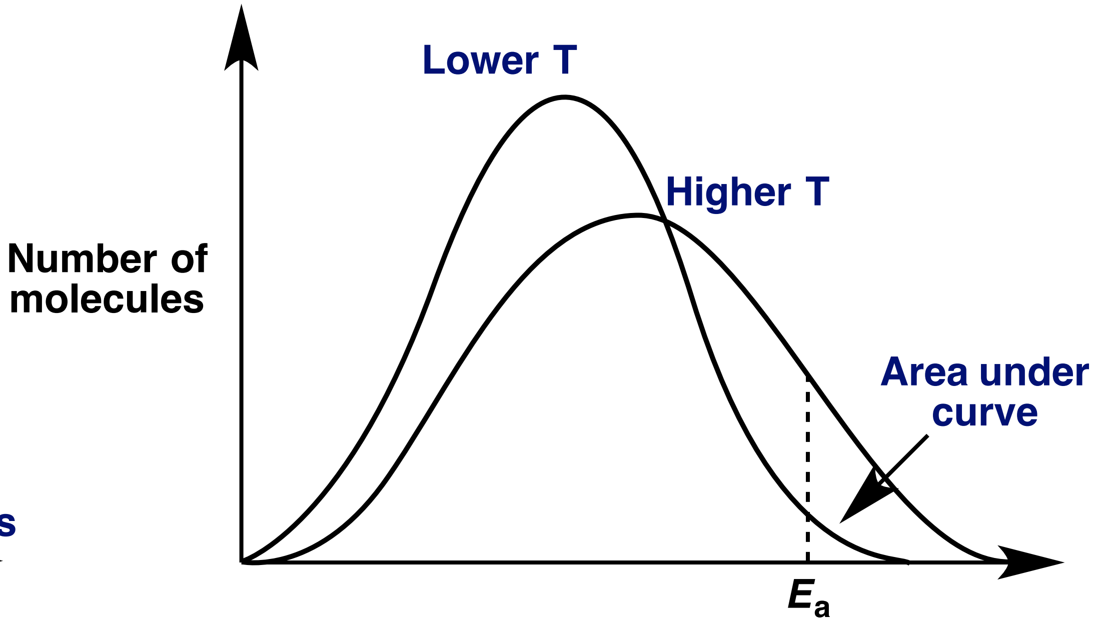
- The rate constant, *k*, is related to the minimum amount of energy required to bring about the reaction, the activation energy (E_a), by the Arrhenius equation.

$$k = Ae^{-E_a/RT}$$

k = Rate constant (units depend on reaction order)
A = Pre-exponential factor (units as for rate constant)
E_a = Activation energy (kJ mol^{-1})
R = Gas constant (8.314 J K^{-1} mol^{-1})
T = Temperature (K)



As E_a ↑, k ↓, rate ↓



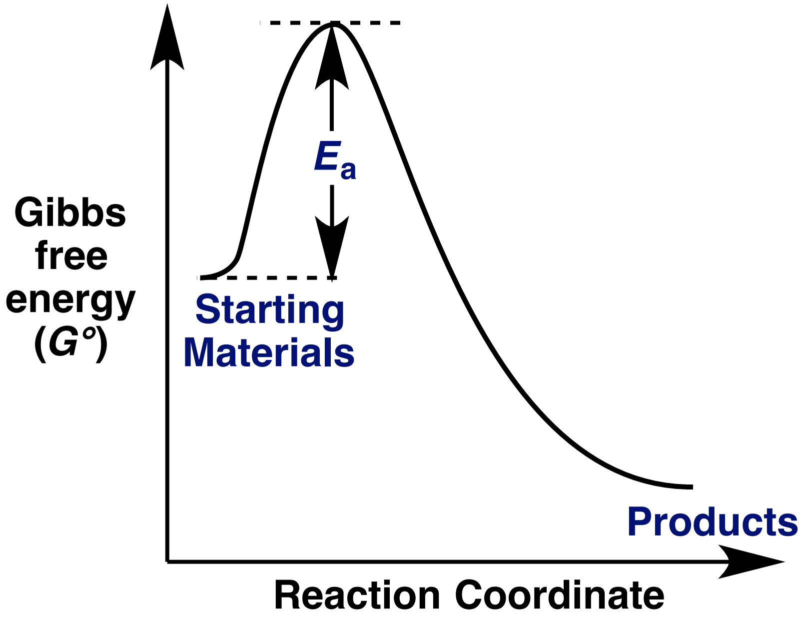
As T ↑, k ↑, rate ↑

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

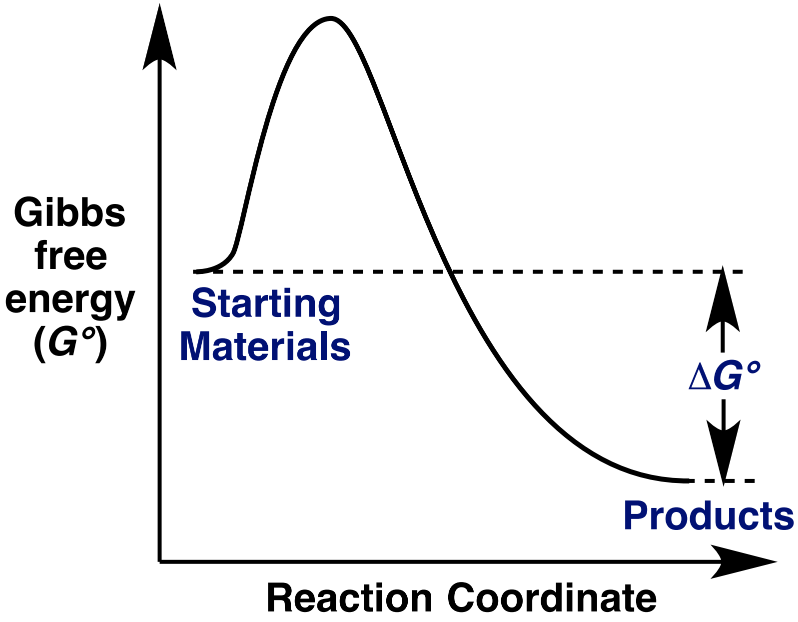
Reaction Kinetics vs Thermodynamics

- We must be able to clearly differentiate between **kinetics** and **thermodynamics**.
- **Kinetics** is concerned with reaction rates – how fast do we get there?
- **Thermodynamics** is concerned with equilibria – favour starting materials or products?

Kinetics - Rate of Reaction



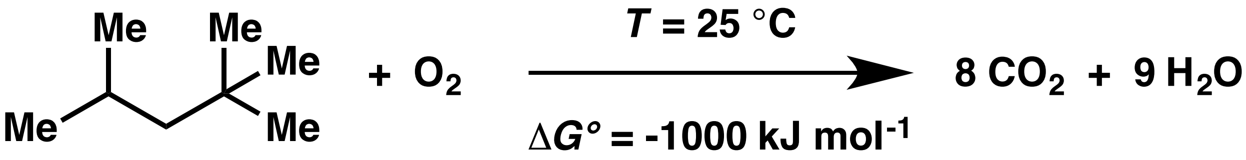
Thermodynamics - Equilibrium



For further reading refer to *Organic Chemistry 2^nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

Worked Example 1 – Kinetics vs Thermodynamics

- Consider the combustion 2,2,4-trimethylpentane (the major component of petrol):



2,2,4-trimethylpentane

- This massive **negative** value for $\Delta G°$ suggests that the process is exergonic and should favour the products at equilibrium.

- However, we put it into our fuel tanks everyday and nothing happens?

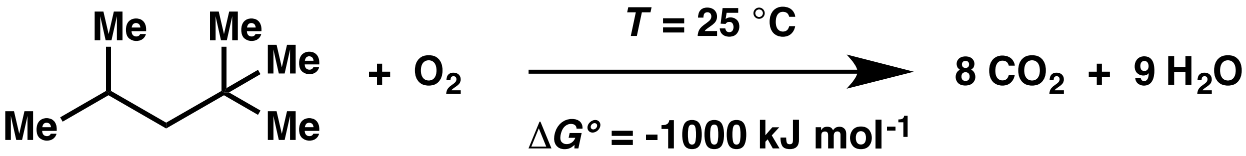
- Therefore, the mixture of 2,2,4-trimethylpentane and oxygen cannot be at equilibrium.

- Indeed a certain amount of energy (the activation energy, E_a) is needed to reach equilibrium. Without this burst of energy, the petrol is stable in the presence of O_2.

- The mixture of 2,2,4-trimethylpentane and oxygen is said to be **thermodynamically unstable** with respect to the products of the reaction, CO_2 and H_2O, but **kinetically stable**.

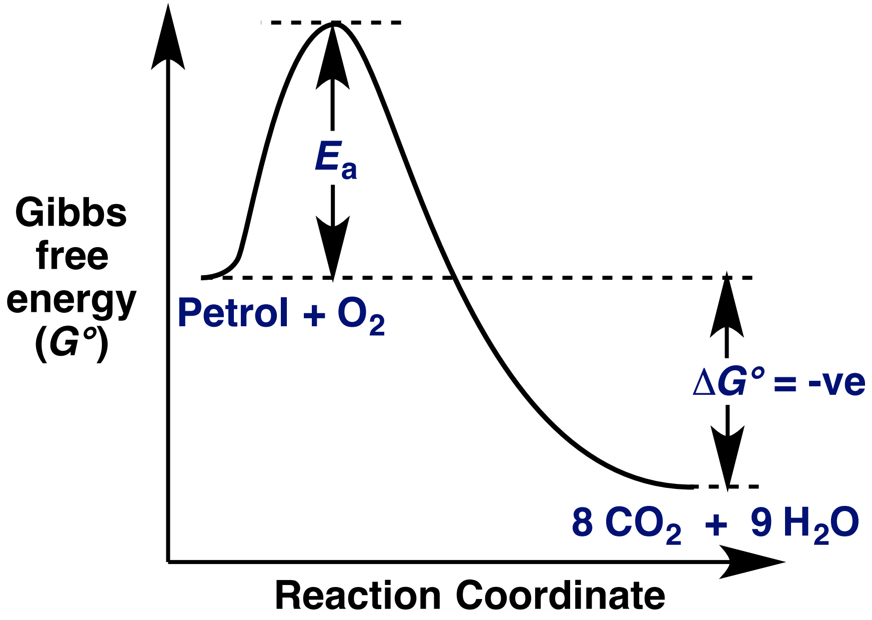
Worked Example 1 – Kinetics vs Thermodynamics

- Consider the combustion 2,2,4-trimethylpentane (the major component of petrol):



2,2,4-trimethylpentane

- The mixture of 2,2,4-trimethylpentane and oxygen is **thermodynamically unstable** but **kinetically stable**. We can think of this in terms of an energy diagram:



E_a = Activation energy for conversion of reactants to products

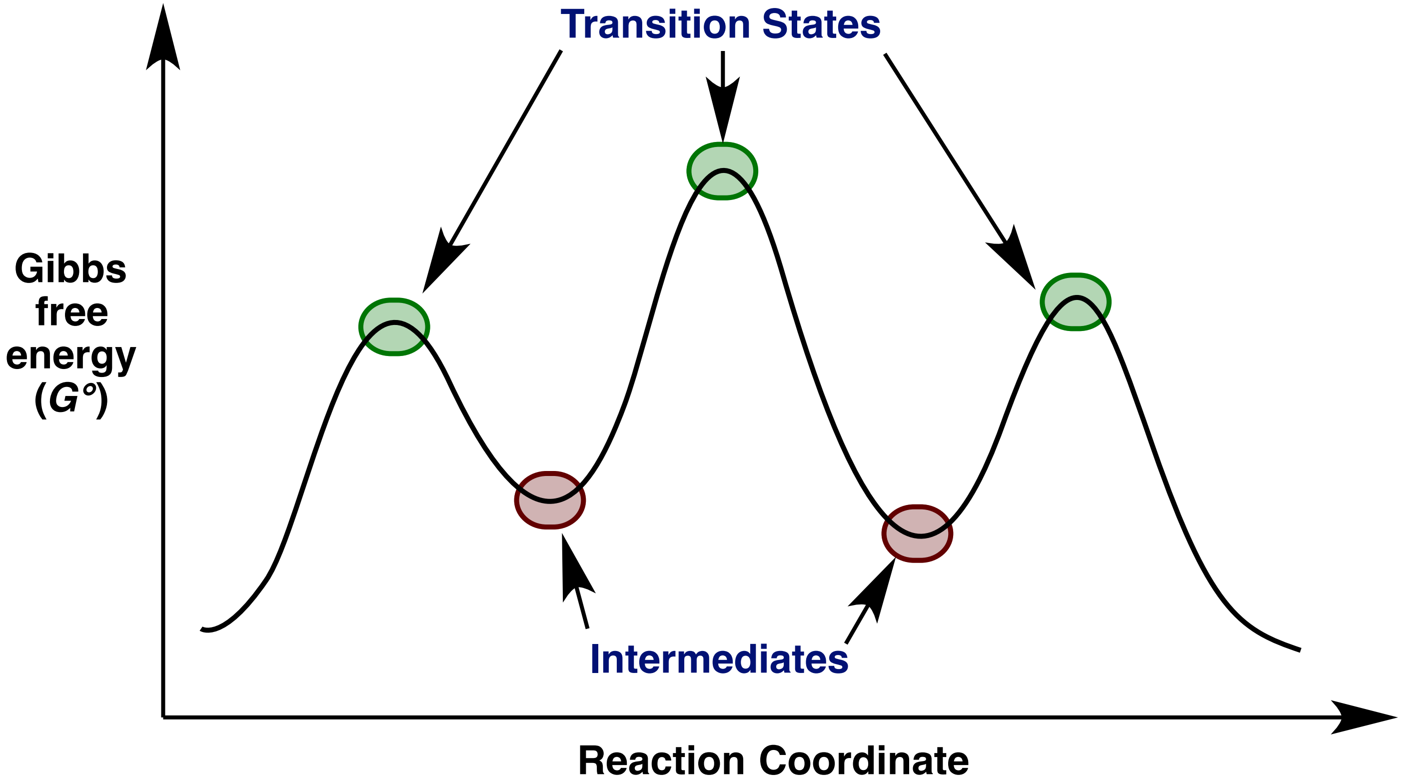
$\Delta G°$ = -ve therefore the products are thermodynamically favoured

In a car engine, the spark plug provides the needed energy and combustion occurs

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

Intermediates vs Transition States

- We must also be able to clearly differentiate between **intermediates** and **transition states**.
- Consider the following energy diagram with transition states and intermediates indicated:

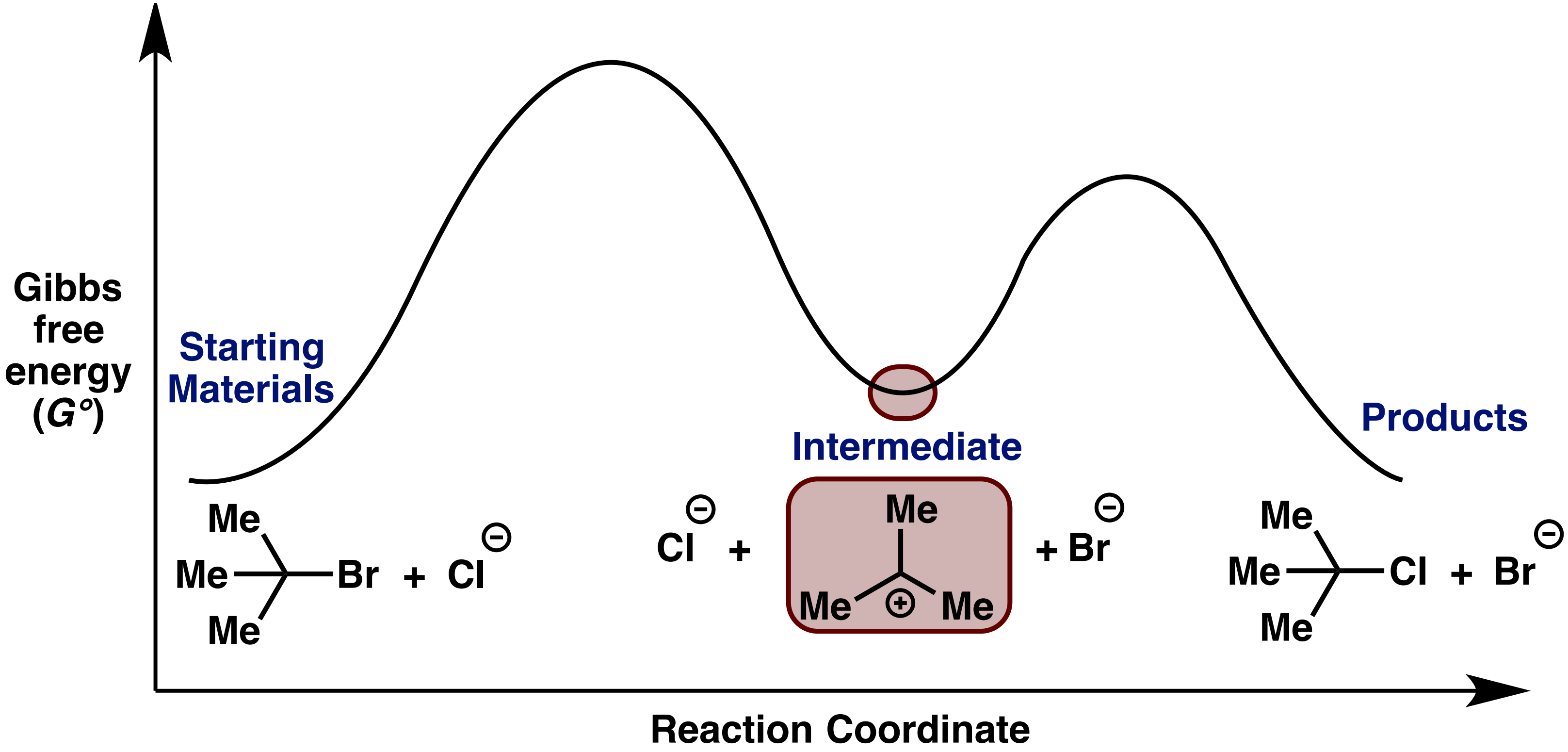


For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

Intermediates

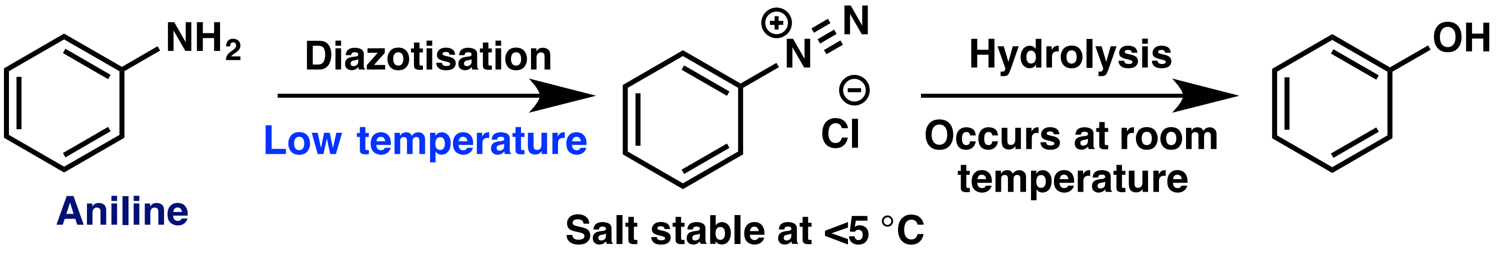
- An **intermediate** is a molecule or ion that appears at a localised energy minimum. Intermediates generally exist long enough to be observed and can in principle be isolated.

- Bonds are **NOT** in the process of breaking or forming within **intermediates**.

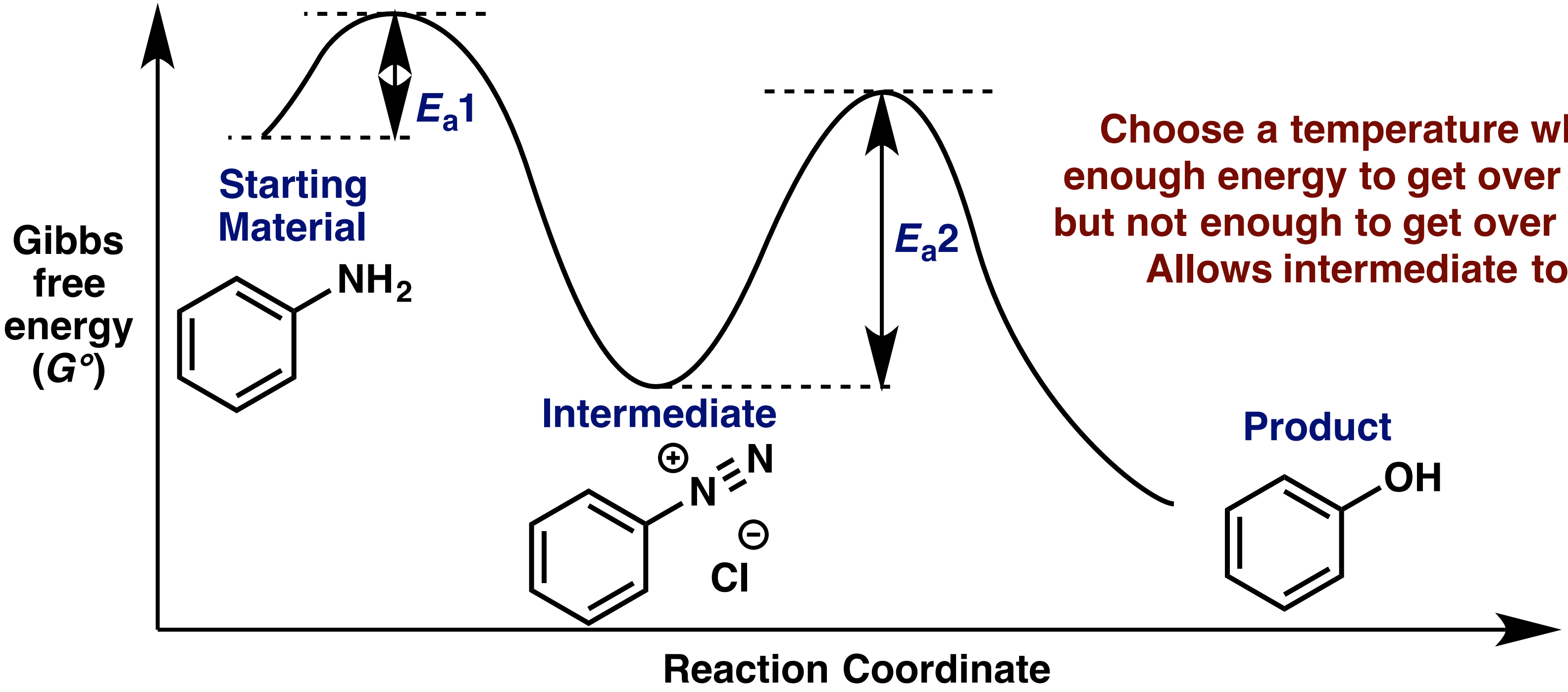


Worked Example 2 – Isolating Intermediates

- Consider the conversion of aniline to the corresponding diazo compound:



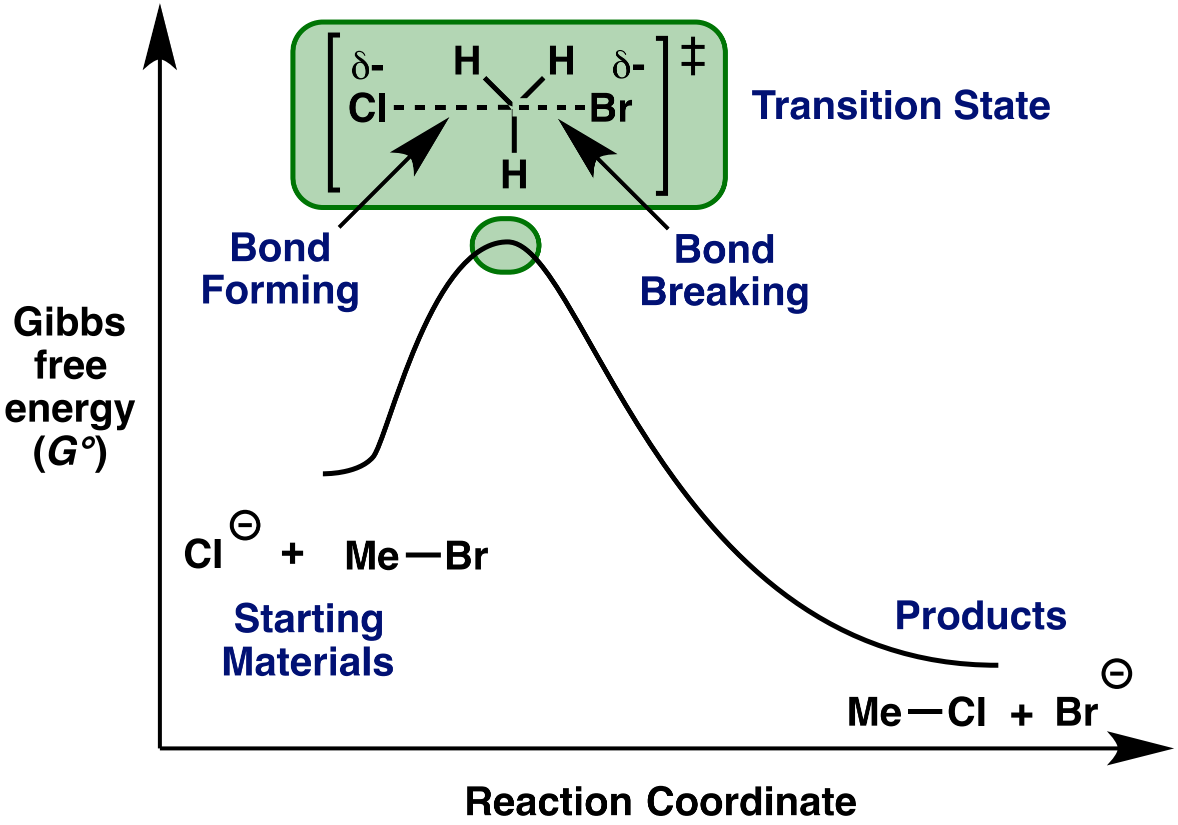
- Why is the diazotisation step carried out at lower temperature?



Choose a temperature which provides:
enough energy to get over 1st barrier (E_a1)
but not enough to get over 2nd barrier (E_a2)
Allows intermediate to be isolated

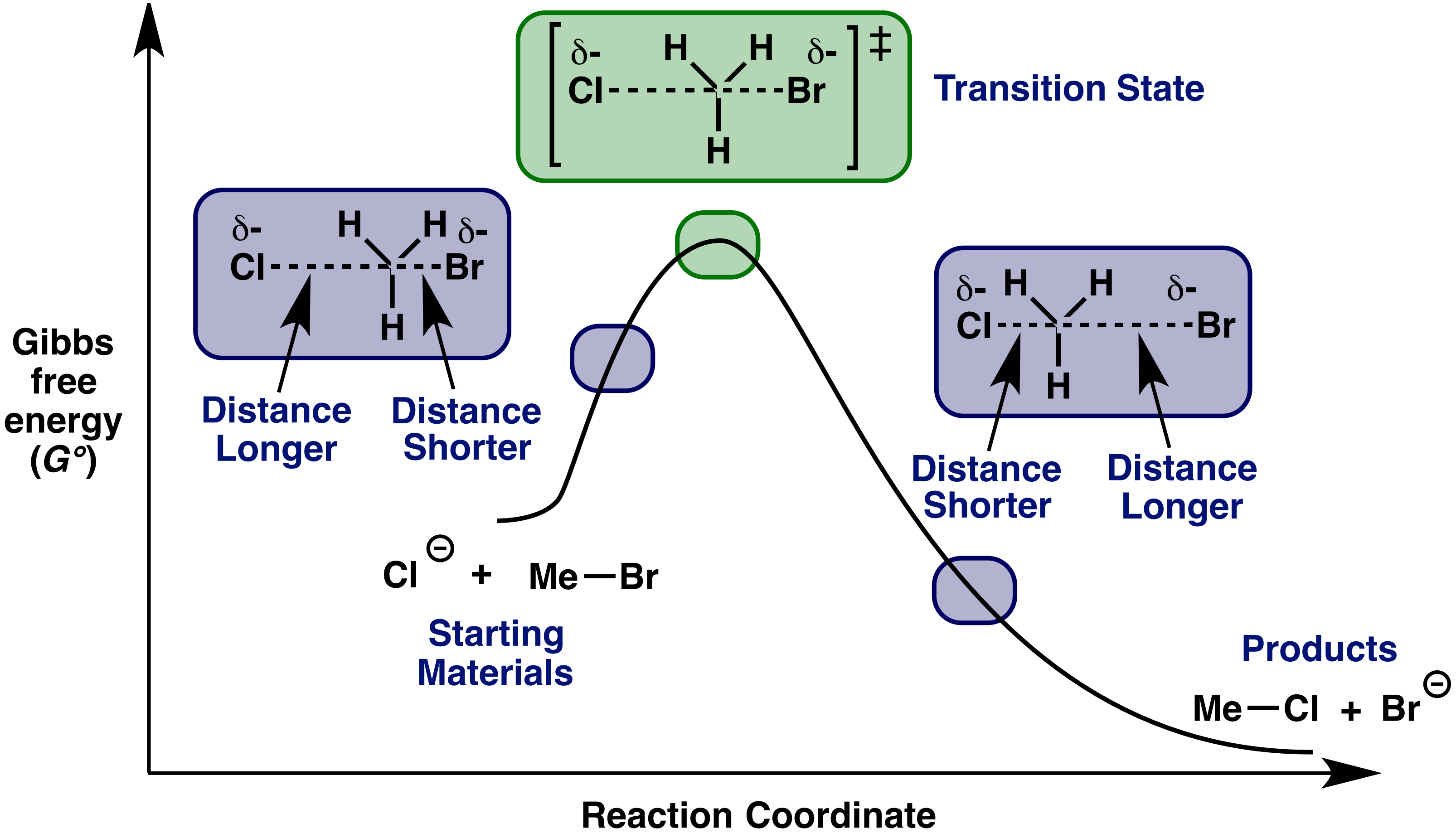
Transition States

- A **transition state** represents an energy maximum. They exist for an extremely short period of time and can never be isolated or observed directly.
- **Transition states** contain bonds that are partially formed and/or partially broken.



Transition States

- It is reasonable to suggest that two points on an energy diagram that are **close in energy** should be **similar in structure**. This idea is the basis of the **Hammond postulate**.

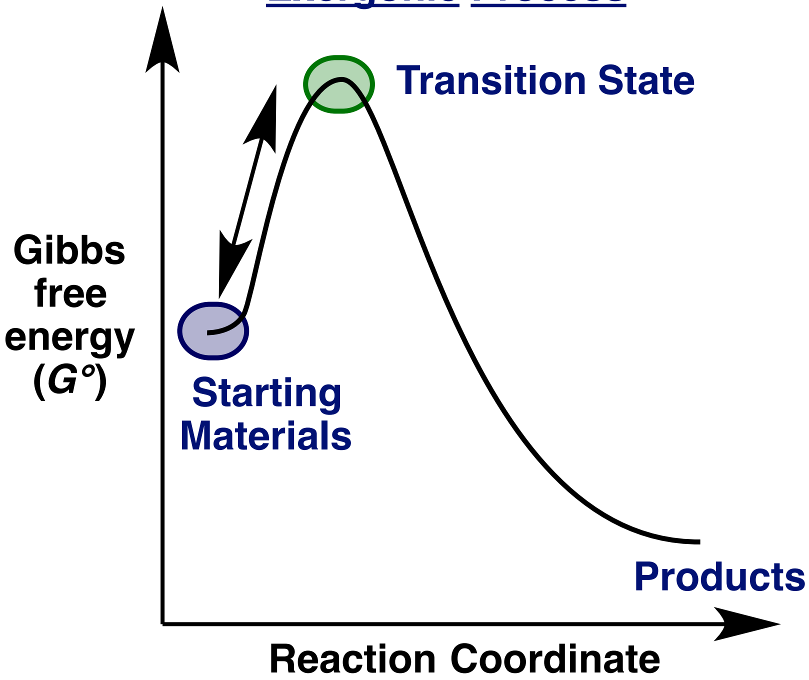


For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267.

The Hammond Postulate

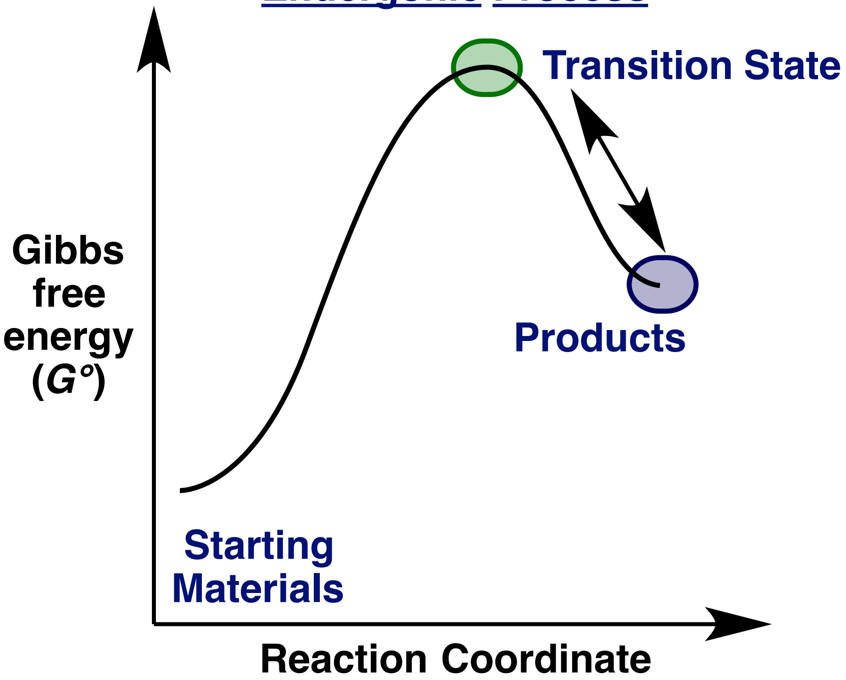
- The **Hammond postulate** gives information about the structure of transition states. It states that a transition state will resemble the observable structure that is closest in energy. This may be starting materials, intermediates or products.

Exergonic Process



Transition state is early and is similar in structure to the starting materials.

Endergonic Process



Transition state is late and is similar in structure to the products.

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 37 pp. 989.

Lecture 2: Reaction Kinetics and the Hammond Postulate

Key learning objectives:

- Be able to clearly differentiate between thermodynamics and kinetics
- Rate laws – 1st, 2nd and 3rd order
- Activation energy (E_a) – the minimum amount of energy required for reaction
- Relating the rate constant (k) to the activation energy (E_a) – the Arrhenius equation
- The definitions of intermediates and transition states
- The Hammond postulate – early (“reagent like”) and late (“product like”) transition states

Lecture 2 Revision

To reinforce your understanding of the contents of this lecture, please refer to:

- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 12 pp. 250-267 and Chapter 37 pp. 989.
- Practice questions provided on the next slide.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e   Password: compound
- CH4103 Online Test 2
- CH4103 Tutorial 2
- CH4103 Workshop 2

Lecture 2 Practice Questions / Guided Self-Study

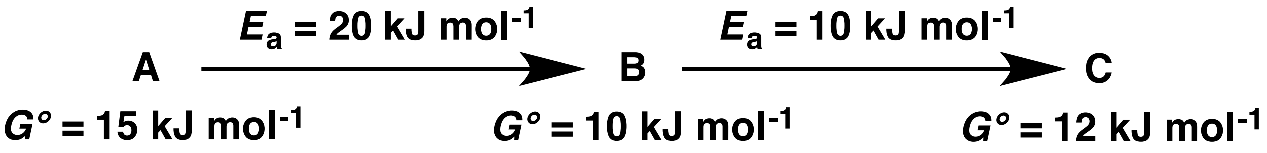
For further practice, attempt the following questions in your own time:

- Q1) Given the reaction and rate data below answer the following questions:
- A) Give the rate equation
- B) Determine the rate constant
- C) Determine the initial rate of reaction when $[NH_4^+] = 0.05$ M and $[NO_2^-] = 0.04$ M

$$NH_4^+ + NO_2^- \longrightarrow N_2 + 2H_2O$$

Experiment	$[NH_4^+]$	$[NO_2^-]$	Rate
1	0.010 M	0.020 M	0.020 M s^{-1}
2	0.015 M	0.020 M	0.030 M s^{-1}
3	0.010 M	0.010 M	0.005 M s^{-1}

- Q2) Determine the rate constant for a reaction if the temperature is 298 K, activation energy is 200 kJ mol^{-1} and the pre-exponential factor is 9 $M^{-1}s^{-1}$
- Q3) Sketch an energy diagram for the following process indicating activation energies and the locations of any transition states or intermediates



$$\underset{G^\circ = 15\ \text{kJ mol}^{-1}}{A} \xrightarrow{E_a = 20\ \text{kJ mol}^{-1}} \underset{G^\circ = 10\ \text{kJ mol}^{-1}}{B} \xrightarrow{E_a = 10\ \text{kJ mol}^{-1}} \underset{G^\circ = 12\ \text{kJ mol}^{-1}}{C}$$

CH4103 Organic and Biological Chemistry
LCM Lecture 3

Dr Louis C. Morrill
School of Chemistry, Cardiff University
Main Building, Rm 1.47B
MorrillLC@cardiff.ac.uk

Autumn Semester

Lecture 3 Preparation

To best prepare yourself for the contents of this lecture, please refresh

- Bonding in organic compounds (Unit 1, Lecture 2)
- Atomic and molecular orbitals (Unit 1, Lecture 2)
- Molecular shape and hybridisation (Unit 1, Lecture 2)
- Sigma and pi bonds (Unit 1, Lecture 2)
- Electronegativity and bond polarisation (Unit 1, Lecture 3)
- Reactive intermediates – carbocations (Unit 1, Lecture 8)
- Reaction thermodynamics (Unit 2, Lecture 1) and kinetics (Unit 2, Lecture 2)

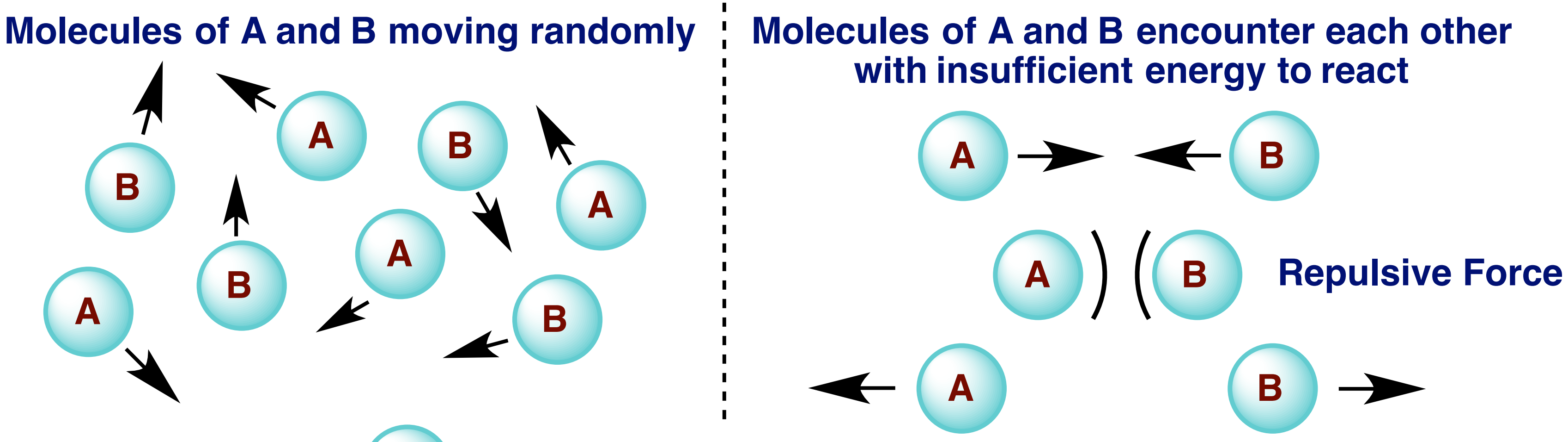
Lecture 3: Curly Arrows for Electron Movement

Key learning objectives:

- Understand repulsive and attractive interactions that can exist between molecules
- Understand the ways in which molecules can react with each other
- The definitions of nucleophiles and electrophiles
- Be able to identify nucleophiles and electrophiles
- Using curly arrows to represent electron movement
- Be able to draw curly arrow mechanisms for fundamental processes including nucleophilic attack, loss of a leaving group, proton transfers and sigma bond migration
- Be able to identify the orbitals associated with a curly arrow

Why Molecules Generally *Don't* React

- Molecules are coated with a layer of electrons that occupy bonding and non-bonding orbitals.
- As a result, the surface of each molecule is negatively charged and most molecules repel each other.



Molecules of A and B moving randomly

Molecules of A and B encounter each other with insufficient energy to react

○ **= negatively charged electron cloud**

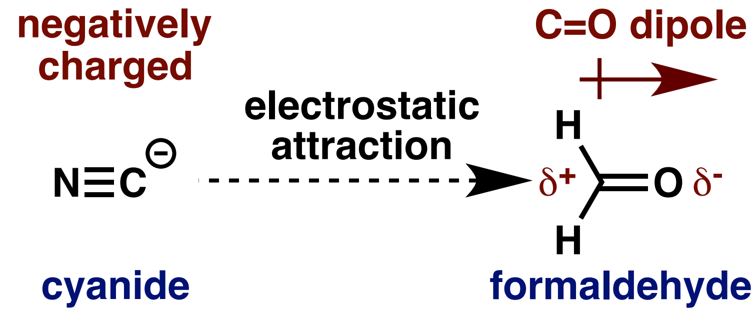
Reactions can only occur if molecules collide with enough energy to overcome this repulsion – **activation energy (E_a)**. Recap Unit 2 Lecture 2

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

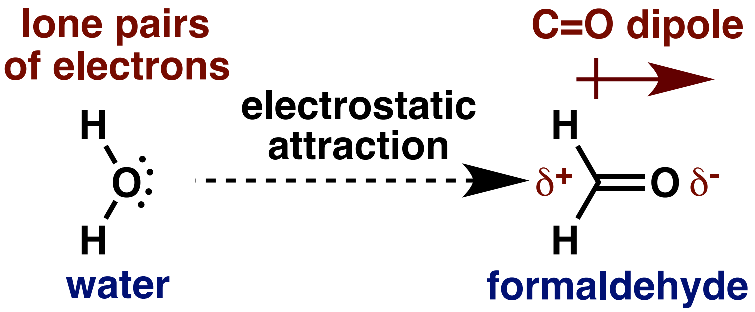
What Brings Molecules Together

- Electrostatic attraction brings molecules together

Charged Molecules

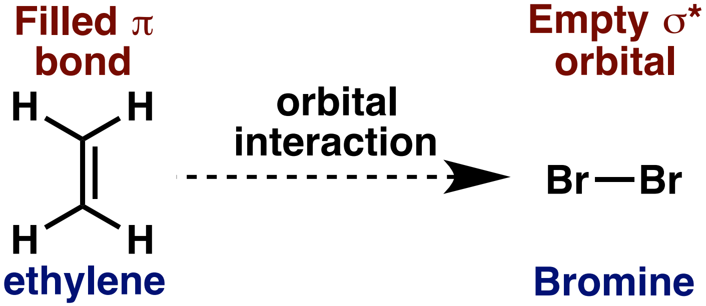


Neutral Molecules



Reminder: Electronegativities for carbonyl C=O polarisation
Oxygen - 3.44, Carbon - 2.55
Unit 1, Lecture 3

- Orbital overlap brings molecules together



hybridisation and molecular orbitals
Unit 1, Lecture 2

- Attractive forces help overcome electronic repulsion and lower activation energy, E_a

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

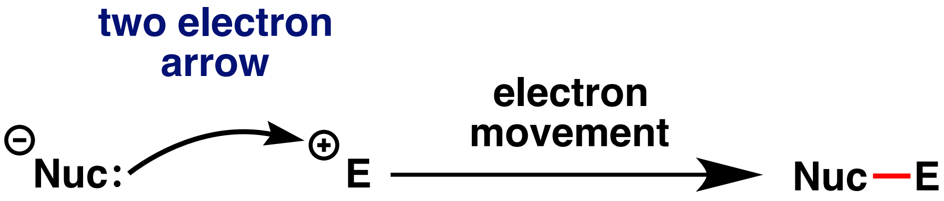
Nucleophiles and Electrophiles

- When attractive interactions bring two molecules close together, electrons can move from one molecule to another, resulting in a **reaction**

- A molecule that is **electron-rich** and can **donate** electrons is called a **nucleophile** – it *loves* to attack a *nucleus*

- A molecule that is **electron-poor** and can **accept** electrons is called an **electrophile** – it *loves* to accept *electrons*

- A bond forms when electrons move from a nucleophile to an electrophile



- In the upcoming slides, we will learn how to identify which molecules are **nucleophiles** (electron-rich) and which are **electrophiles** (electron-poor)

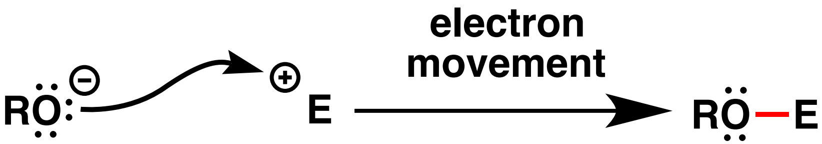
For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Identifying Nucleophiles

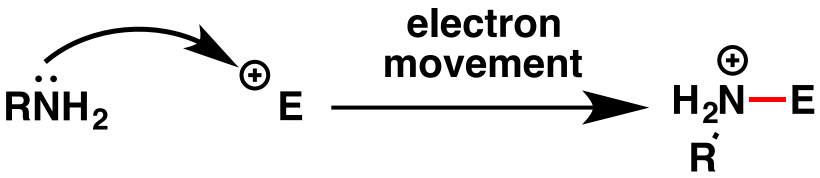
- A molecule that is **electron-rich** and can **donate** electrons is called a **nucleophile** – it *loves* to attack a *nucleus*

- A **nucleophile** is any molecule able to donate a pair of electrons from a filled high-energy orbital, forming a new bond

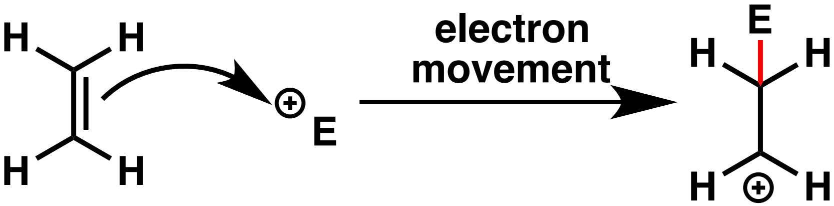
Negatively charged - lone pair of electrons



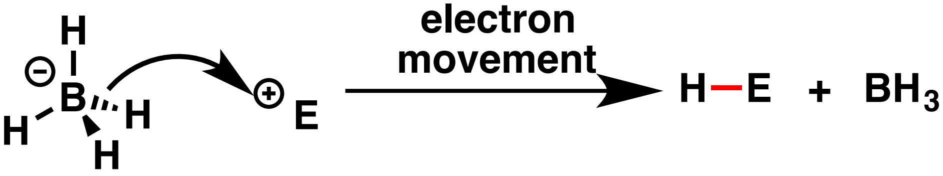
Neutral - lone pair of electrons



Filled π bond containing 2 electrons



Filled σ bond containing 2 electrons



- Let's consider a few examples of each class

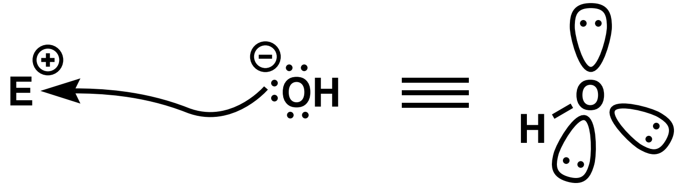
For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Identifying Nucleophiles

- **Nucleophiles** can donate a pair of electrons from their highest (energy) occupied molecular orbitals (HOMOs). Consider the following examples:

Negatively charged molecules

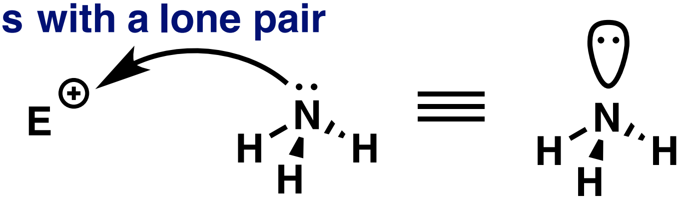
Hydroxide



oxygen atom sp^3 hybridised
HOMO = filled non-bonding sp^3 orbital

Neutral molecules with a lone pair

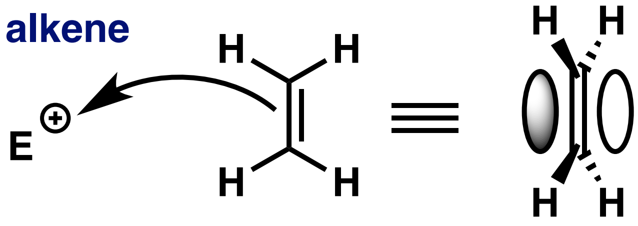
Ammonia



nitrogen atom sp^3 hybridised
HOMO = filled non-bonding sp^3 orbital

A π bond - e.g. an alkene

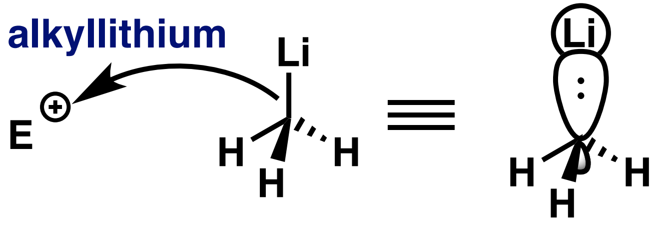
Ethene



carbon atoms sp^2 hybridised
HOMO = C=C π bond

A σ bond - e.g. an alkyllithium

methyllithium



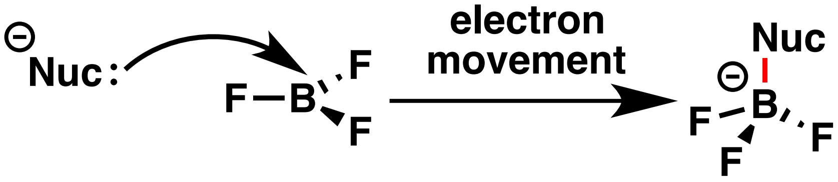
carbon atom sp^3 hybridised
HOMO = C-Li σ bond

Identifying Electrophiles

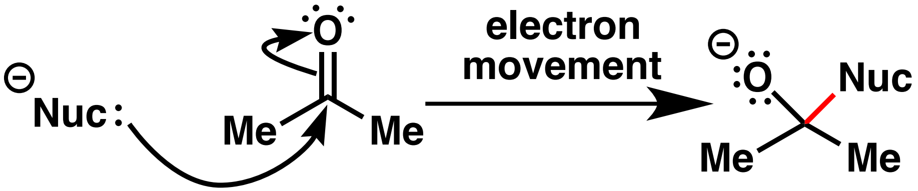
- A molecule that is **electron-poor** and can **accept** electrons is called an **electrophile** – it *loves* to accept *electrons*
- An **electrophile** is any molecule able to accept a pair of electrons into an empty low-energy orbital, forming a new bond

Positively charged - missing valence electrons

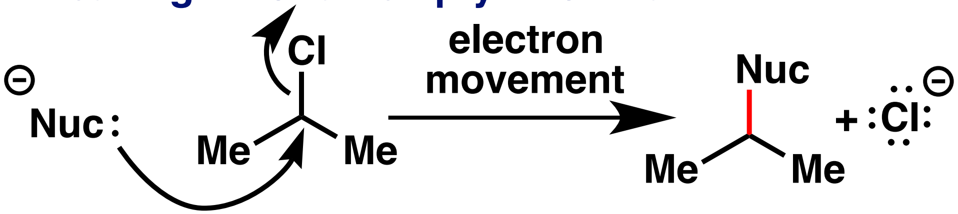
Neutral molecules - missing valence electrons



Breaking π bond - empty π* orbital



Breaking σ bond - empty σ* orbital



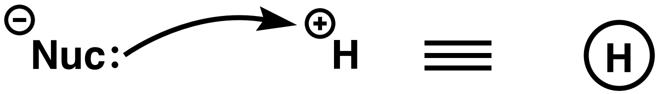
- Let's consider a few examples of each class

Identifying Electrophiles

- **Electrophiles** can accept a pair of electrons into their lowest (energy) unoccupied molecular orbitals (LUMOs). Consider the following examples:

Positively charged molecules with an empty orbital

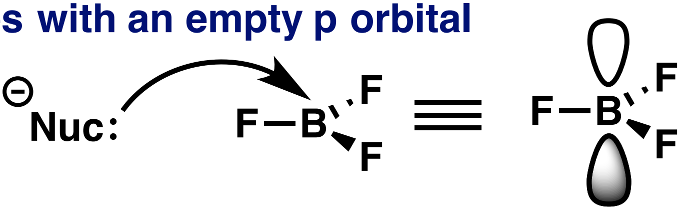
proton



LUMO = empty 1s orbital

Neutral molecules with an empty p orbital

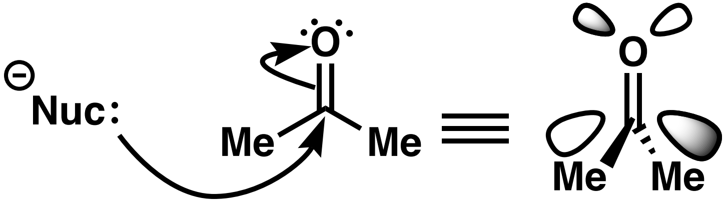
boron trifluoride



boron atom sp^2 hybridised
LUMO = empty 2p orbital

A π bond to an electronegative element

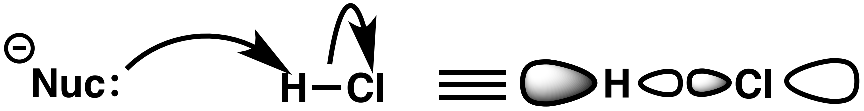
acetone



carbon atom sp^2 hybridised
LUMO = empty C=O π* orbital

A σ bond to an electronegative element

hydrogen chloride



LUMO = Empty H-Cl σ* orbital

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Mechanisms and Curly Arrow Pushing

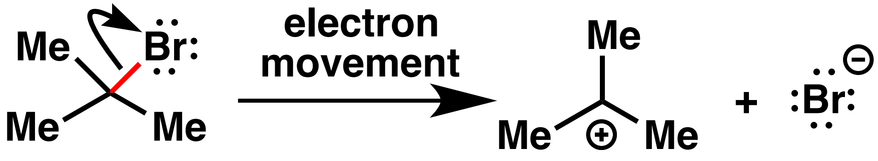
- You have now seen a few examples of curly arrows representing the **movement of electrons** during a reaction. Now we need to discuss this in detail.

- There are four main ways that electrons flow in ionic reactions:

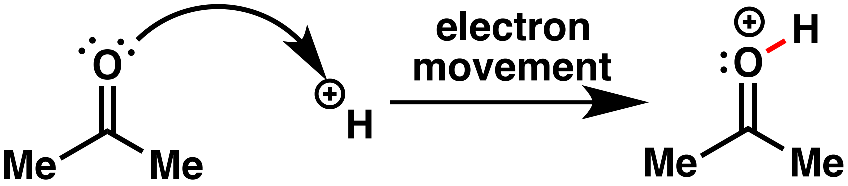
1) Nucleophilic attack
2) Loss of a leaving group
3) Proton transfers (acid/base)
4) Sigma bond migration

Nucleophilic attack

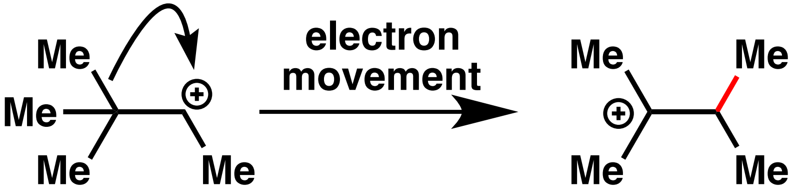
Loss of a leaving group



Proton transfers



Sigma bond migration



- Let's consider each of these in detail

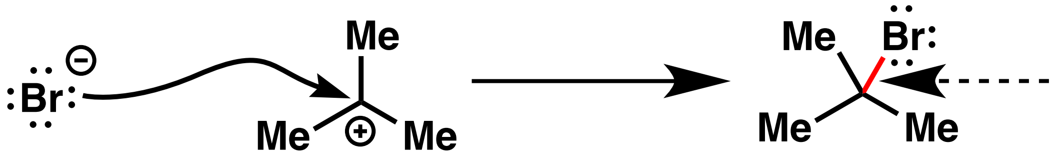
For further reading refer to *Organic Chemistry 2^nd^ Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Curly Arrow Pushing – Nucleophilic Attack

- A **curly arrow** represents the movement of a pair of electrons from a filled orbital into an empty orbital

- Once you have identified the nucleophile and electrophile, a curly arrow can be drawn that shows the **nucleophile attacking the electrophile**

Nucleophilic attack



new σ bond

bromide anion
nucleophile
(-ve charge)

tert-butyl cation
electrophile
(+ve charge)

nucleophile HOMO = filled 4p orbital
electrophile LUMO = empty 2p orbital

- The **tail of the arrow** starts on the electrons (negatively charged nucleophile)

- The **head of the arrow** ends on a nucleus (positively charged electrophile)

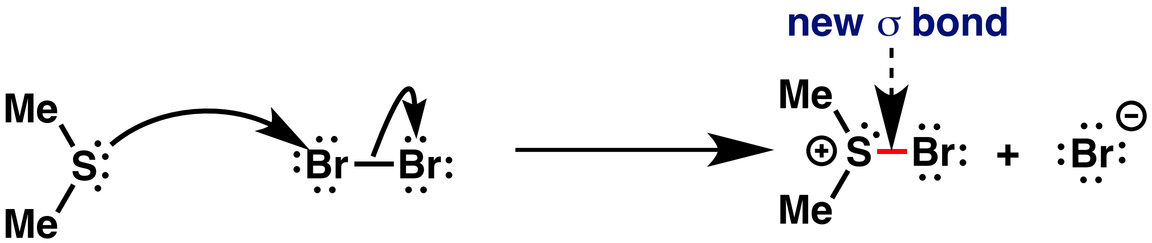
- Curly arrow starts at an electron-rich centre and ends at an electron-poor centre

- Remember that there are various types of nucleophiles and electrophiles

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Worked Example 1 – Nucleophilic Attack

- In this case we have a neutral nucleophile (dimethyl sulfide) and a neutral electrophile (bromine)



dimethyl sulfide
nucleophile
(neutral)

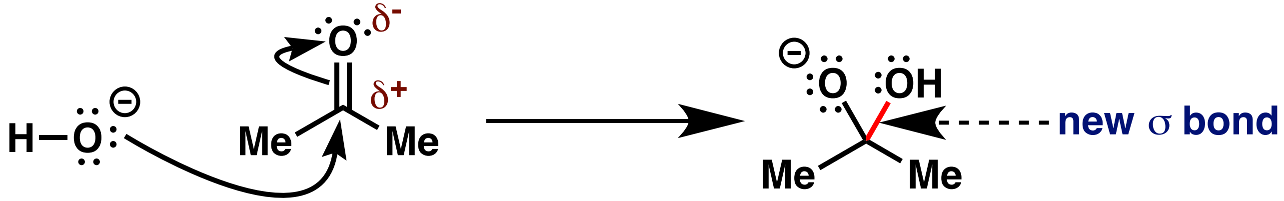
bromine
electrophile
(neutral)

nucleophile HOMO = filled non-bonding *S* sp^3 orbital
electrophile LUMO = empty Br-Br σ* orbital

- **First curly arrow –** there is a flow of electrons from the filled non-bonding sulfur sp^3 orbital into the empty Br-Br σ* orbital. This orbital interaction breaks the Br-Br σ bond and forms a new S-Br σ bond
- **Second curly arrow –** the Br-Br σ bond breaks with the two bonding electrons ending up on the negatively charged bromide anion
- The presence of two curly arrows does not mean that it occurs in two distinct steps. Indeed, as the new S-Br bond forms, the Br-Br bond breaks.

Worked Example 2 – Nucleophilic Attack

- In this case we have a negatively charge nucleophile (hydroxide anion) and a neutral electrophile (acetone)



hydroxide anion
nucleophile
(-ve charge)

acetone
electrophile
(neutral)

nucleophile HOMO = filled non-bonding *O* sp^3 orbital
electrophile LUMO = empty C=O π* orbital

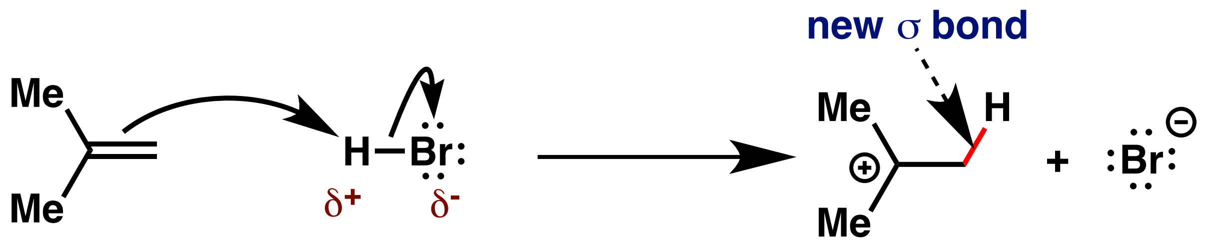
- **First curly arrow –** there is a flow of electrons from the filled non-bonding oxygen sp^3 orbital into the empty C=O π* orbital. This orbital interaction breaks the C=O π bond, leaving a C-O σ bond and forming a new C-O σ bond

- **Second curly arrow –** the C=O π bond breaks with the two electrons ending up on the negatively charged oxygen atom (alkoxide)

- Notice that the second curly arrow ends up delivering the electrons to an electronegative atom (oxygen), satisfying its desire for electron density

Worked Example 3 – Nucleophilic Attack

- In this case we have a neutral nucleophile (isobutylene) and a neutral electrophile (hydrogen bromide)



isobutylene
nucleophile
(neutral)

hydrogen bromide
electrophile
(neutral)

nucleophile HOMO = filled π bond
electrophile LUMO = empty H-Br σ* orbital

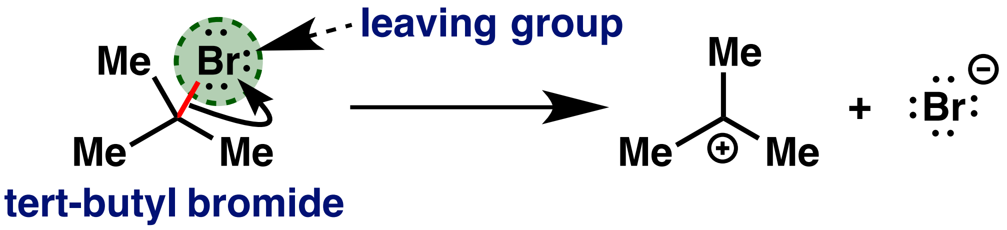
- **First curly arrow –** there is a flow of electrons from the filled C=C π bond into the empty H-Br σ* orbital. This orbital interaction breaks the H-Br σ bond, forming a new C-H σ bond

- **Second curly arrow –** the H-Br σ bond breaks with the two bonding electrons ending up on the negatively charged bromide anion

- Notice how in all examples charge is conserved – i.e. the overall charge of the starting materials is the same as the overall charge of the products

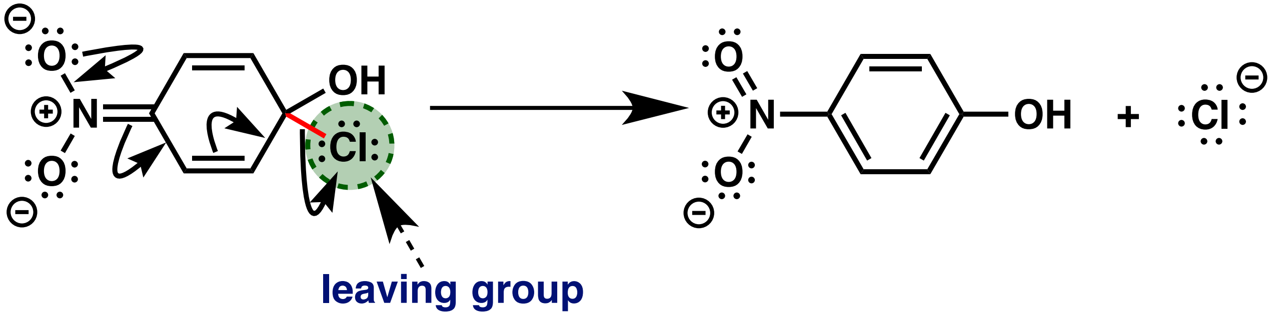
Curly Arrow Pushing – Loss of a Leaving Group

- Loss of a leaving group occurs when a bond breaks and one atom from the bond retains **both** electrons. The electrons move to the more electronegative atom



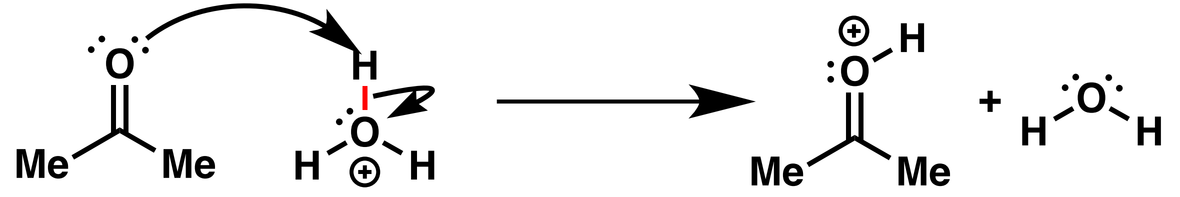
- **Curly arrow –** the C-Br σ bond breaks with the two bonding electrons ending up on the negatively charged bromide anion, resulting in a positively charged carbocation being formed

- As with nucleophilic attack, drawing a curly arrow pushing mechanism for the loss of a leaving group may require more than one arrow



Curly Arrow Pushing – Proton Transfer

- In acidic conditions a base can be **protonated** to form the **conjugate acid** when it uses a pair of electrons to remove H^+ from an acid. Remember that H^+ in aqueous solution is often drawn as H_3O^+ (aqueous cation)



acetone
nucleophile / base

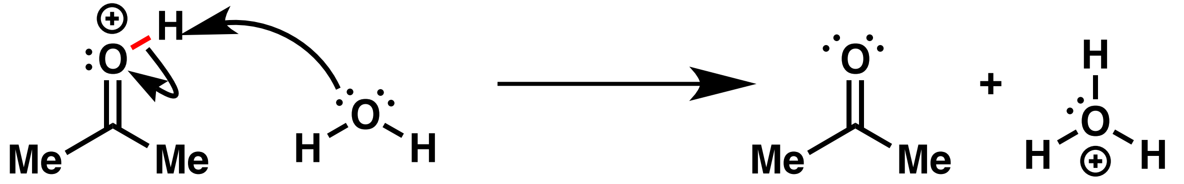
hydronium
electrophile / acid

conjugate acid

conjugate base

- **First curly arrow –** there is a flow of electrons from the filled non-bonding sp^2 orbital on oxygen into the empty O-H σ^* orbital. **Second curly arrow –** the O-H σ bond breaks with the two bonding electrons ending up on the neutral water molecule

- Proton transfer is **reversible**



electrophile / acid

nucleophile / base

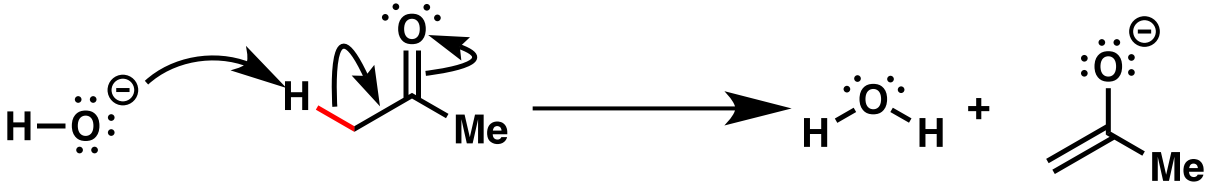
conjugate base

conjugate acid

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Curly Arrow Pushing – Proton Transfer

- In some cases multiple arrows may be necessary to show the complete electron flow when a proton is removed (deprotonation). Such electron flow can also be thought of as a proton transfer combined with resonance



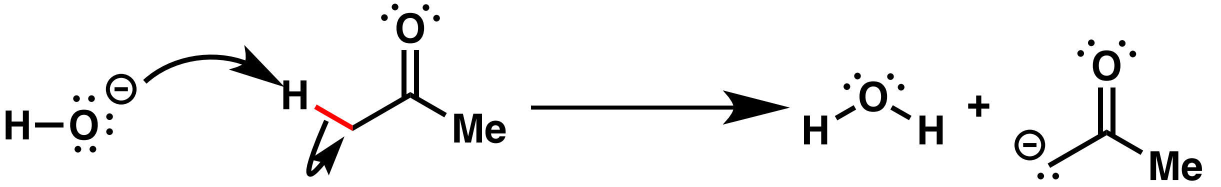
hydroxide anion nucleophile / base

acetone electrophile / acid

conjugate acid

conjugate base

Electron density flows up onto electronegative oxygen atom



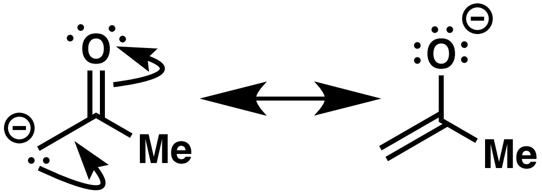
hydroxide anion nucleophile / base

acetone electrophile / acid

conjugate acid

conjugate base

These two curly arrows show the proton transfer step

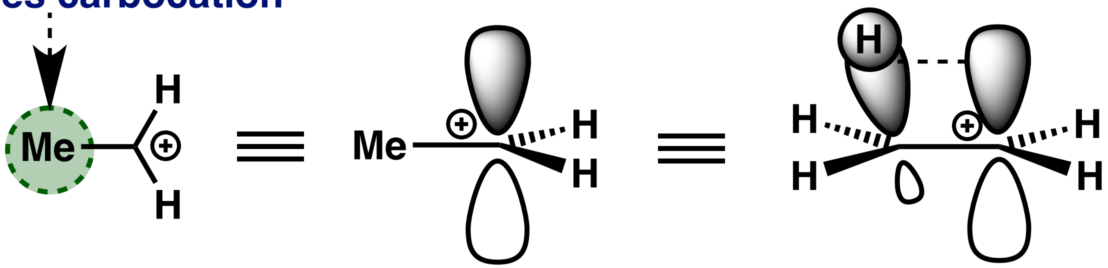


These two curly arrows show resonance

Resonance
Unit 1, Lecture 8

Curly Arrow Pushing – Sigma Bond Migration

- Carbocations can be stabilised by neighbouring groups through orbital overlap known as **hyperconjugation** (inductive effect)



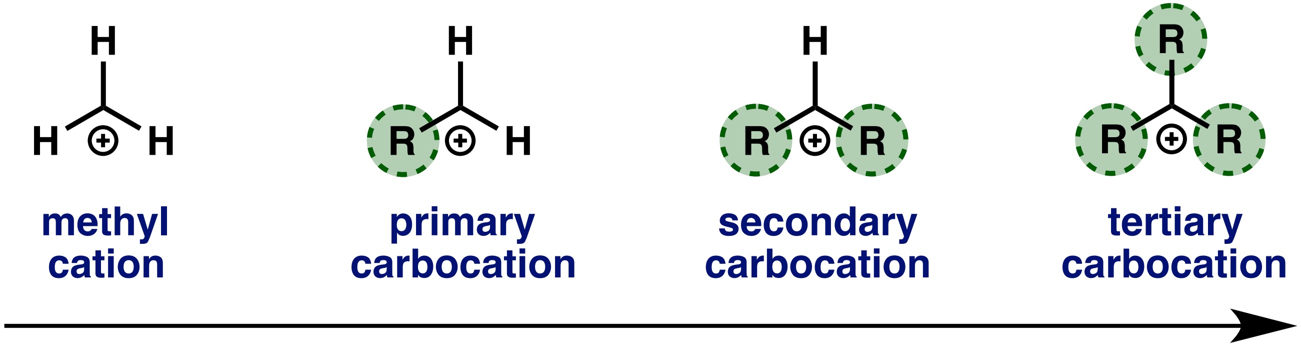
stabilises carbocation

primary carbocation

empty 2p orbital on carbon

donation from filled C-H σ orbital into empty 2p orbital

- **Hyperconjugation** explains the stability trend shown below.



methyl cation

primary carbocation

secondary carbocation

tertiary carbocation

Increasing Stability

recap

Reactive Intermediates Unit 1, Lectures 8 and 9

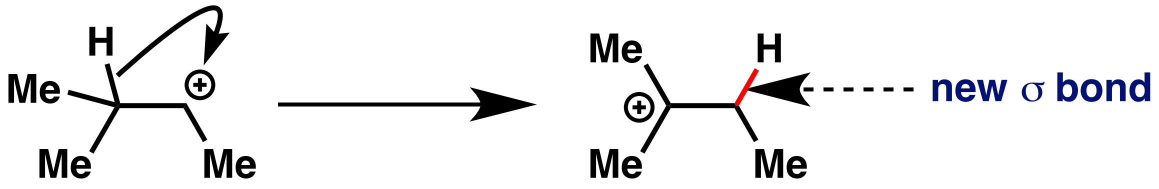
recap

Curly Arrow Pushing – Sigma Bond Migration

- If a carbocation can **intramolecularly** rearrange to become more stable, it will do so before reacting with an external nucleophile **intermolecularly**.

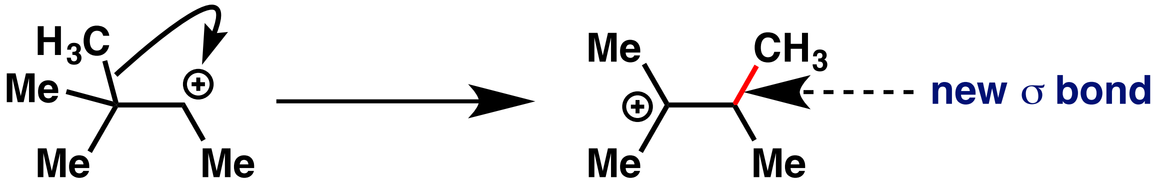
- There are two common types of carbocation rearrangements – **hydride shifts** and **alkyl shifts**. Shifts can only occur from the adjacent carbon due to orbital overlap

Hydride Shift



secondary carbocation **tertiary carbocation**

Alkyl Shift

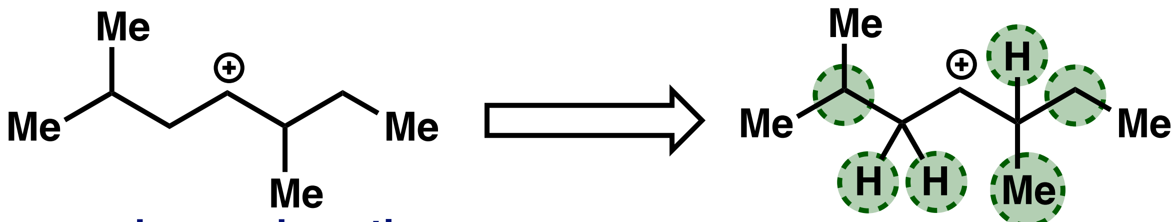


secondary carbocation **tertiary carbocation**

- **Curly arrow** – there is a flow of electrons from a filled bonding C-H (hydride shift) or C-C (alkyl shift) σ bond into the empty 2p orbital on carbon.

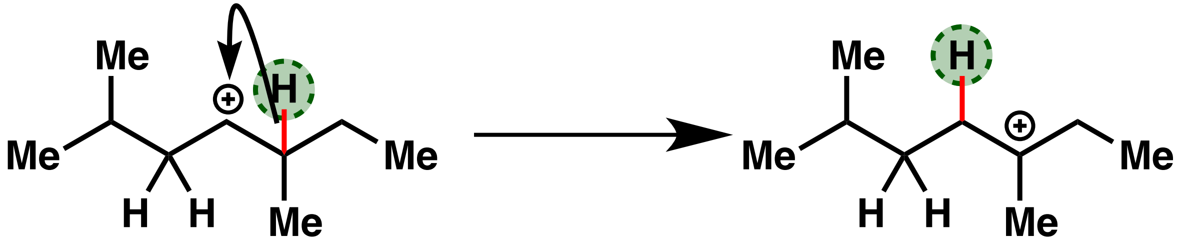
Curly Arrow Pushing – Sigma Bond Migration

- When you encounter a carbocation, you must consider all possible rearrangements (both hydride and alkyl shifts)



secondary carbocation

Identify all -H and -Alkyl groups on adjacent carbon atoms that are capable of shifting



secondary carbocation

tertiary carbocation

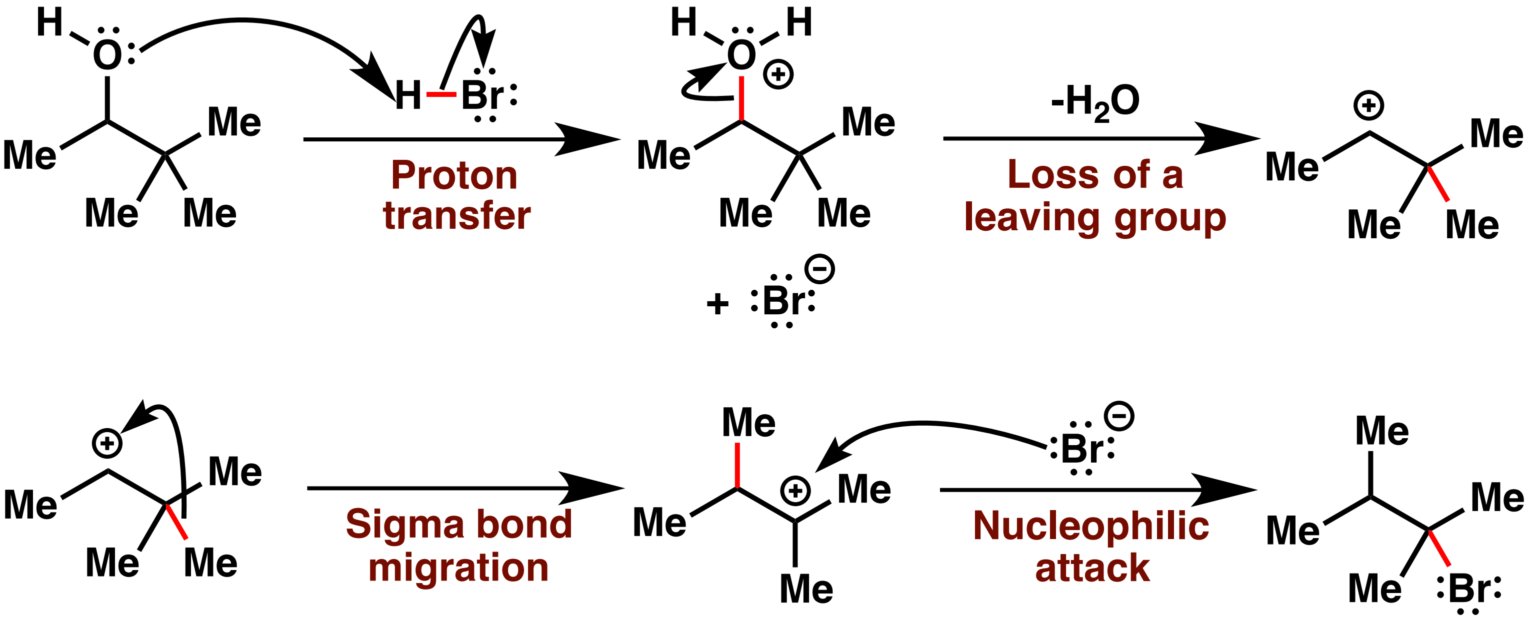
Identify which shift will give the most stable carbocation

- **Curly arrow** – there is a flow of electrons from a filled bonding C-H σ bond into the empty 2p orbital on carbon.

- Migration of any other highlighted substituent will result in the formation of a less stable secondary carbocation – convince yourself!

Worked Example 4 – Combining Curly Arrow Pushing

- We can now classify each step in the following mechanism:



- You should also be able to discuss each curly arrow in terms of the **filled and empty orbitals involved**.

- **Practice** curly arrow pushing mechanisms as much as possible – it is central to organic chemistry!

For further reading refer to *Organic Chemistry 2^{nd} Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Curly Arrow Pushing Rules – Summary

- A curly arrow shows the movement of a pair of electrons

- The start of the curly arrow shows the source of the electron pair, which is located within the highest energy occupied molecular orbital (HOMO) of the nucleophile and can be:
- 1) a **lone pair of electrons**
- 2) a π **bond**
- 3) a σ **bond**

- The end of the curly arrow shows the destination of the electron pair, which will be the lowest unoccupied molecular orbital (LUMO) of the electrophile and can be:
- 1) an empty **atomic orbital** where a new bond will be formed
- 2) a **π^* or σ^* antibonding orbital** where a new bond will be formed and an old bond will be broken
- 3) an **electronegative atom** that can support a negative charge

- Overall charge is always **conserved** in a reaction

- Avoid breaking the octet rule – **never** give C, N, O or F more than 8 valence electrons

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124.

Lecture 3: Curly Arrows for Electron Movement

Key learning objectives:

- Understand repulsive and attractive interactions that can exist between molecules
- Understand the ways in which molecules can react with each other
- The definitions of nucleophiles and electrophiles
- Be able to identify nucleophiles and electrophiles
- Using curly arrows to represent electron movement
- Be able to draw curly arrow mechanisms for fundamental processes including nucleophilic attack, loss of a leaving group, proton transfers and sigma bond migration
- Be able to identify the orbitals associated with a curly arrow

Lecture 3 Revision

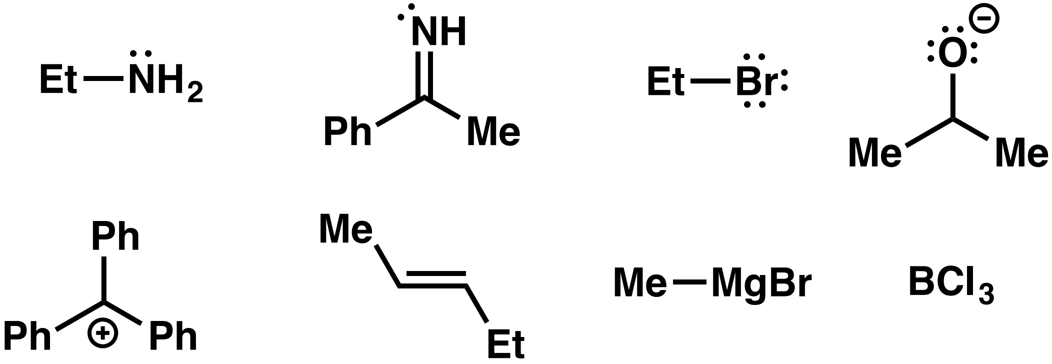
To reinforce your understanding of the contents of this lecture, please refer to:

- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 5 pp. 107-124 and Chapter 15 pp. 334-349.
- Practice questions provided on the next two slides.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e   Password: compound
- CH4103 Online Test 3
- CH4103 Tutorial 2
- CH4103 Workshop 2

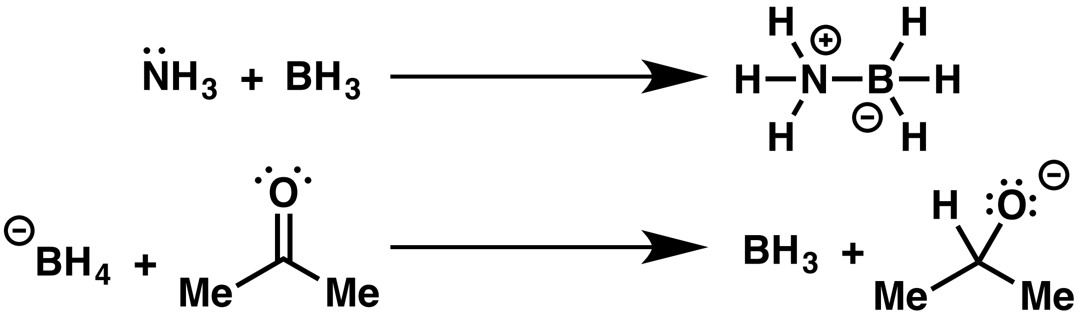
Lecture 3 Practice Questions / Guided Self-Study

For further practice, attempt the following questions in your own time:

- Q1) Classify each of the following molecules are either nucleophiles or electrophiles and identify the associated HOMO or LUMO



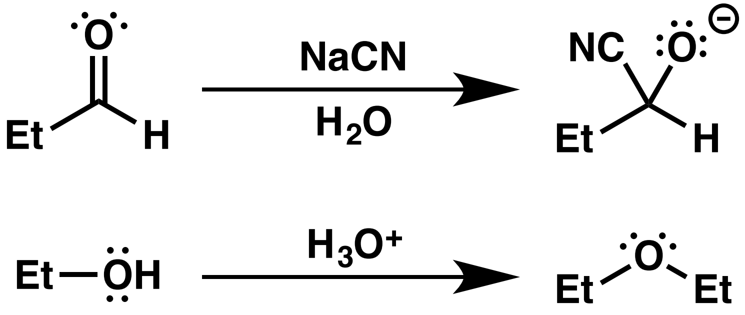
- Q2) For both of the reactions show below, identify the nucleophile and electrophile and their associated HOMOs and LUMOs, draw curly arrow mechanisms for the products formed.



Lecture 3 Practice Questions / Guided Self-Study

For further practice, attempt the following questions in your own time:

- Q3) Draw curly arrow pushing mechanisms for all steps to form the products shown. Classify all steps.



CH4103 Organic and Biological Chemistry
LCM Lecture 4

Dr Louis C. Morrill
School of Chemistry, Cardiff University
Main Building, Rm 1.47B
MorrillLC@cardiff.ac.uk

Autumn Semester

Lecture 4 Preparation

To best prepare yourself for the contents of this lecture, please refresh

- Atomic and molecular orbitals (Unit 1, Lecture 2)
- Molecular shape and hybridisation (Unit 1, Lecture 2)
- Sigma and pi bonds (Unit 1, Lecture 2)
- Electronegativity and bond polarisation (Unit 1, Lecture 3)
- Stereochemistry (Unit 1, Lecture 4-7)
- Reactive intermediates – carbocations (Unit 1, Lecture 8)
- Acids and bases – pK_a (Unit 1, Lecture 9)
- Reaction thermodynamics (Unit 2, Lecture 1) and kinetics (Unit 2, Lecture 2)
- Curly arrow pushing mechanisms (Unit 2, Lecture 3)

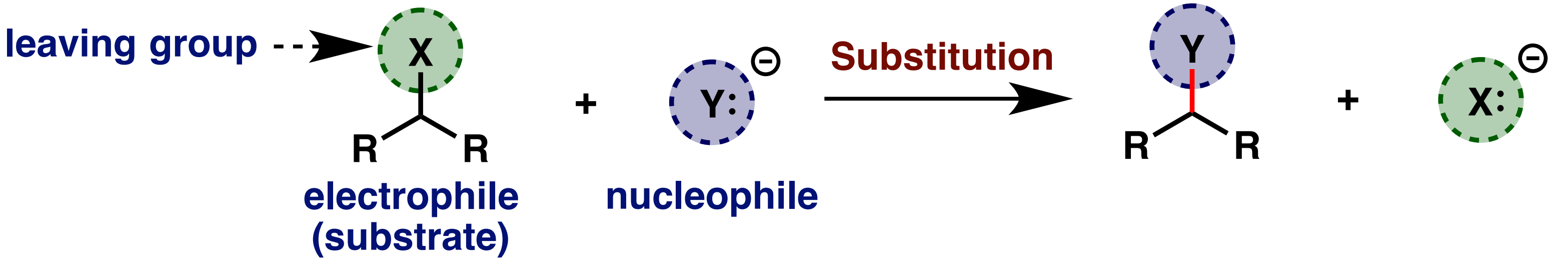
Lecture 4: Introduction to Substitution Reactions – S_N2

Key learning objectives:

- Know the difference between the possible mechanisms for nucleophilic substitution at saturated carbon – S_N2 and S_N1
- Understand what makes a good leaving group
- The rate law for a S_N2 reaction
- The free energy diagram for a S_N2 reaction
- The curly arrow pushing mechanism, molecular orbital analysis, transition state and stereochemical outcome of a S_N2 reaction
- The factors that favour a S_N2 mechanism including the nature of the substrate, nucleophile, solvent and leaving group

Nucleophilic Substitution at Saturated Carbon

- A substitution reaction exchanges one group for another



leaving group

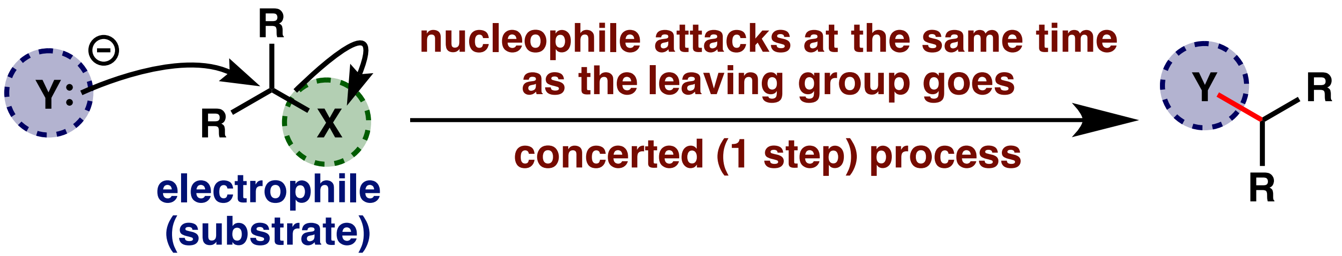
electrophile (substrate)

nucleophile

Substitution

- This process can happen in two separate ways:
- 1) Nucleophile attacks at the same time as the leaving group goes – **S_N2 mechanism**
- 2) Leaving group goes first, forming a carbocation intermediate that is attacked by a nucleophile in a second step – **S_N1 mechanism**

S_N2 mechanism

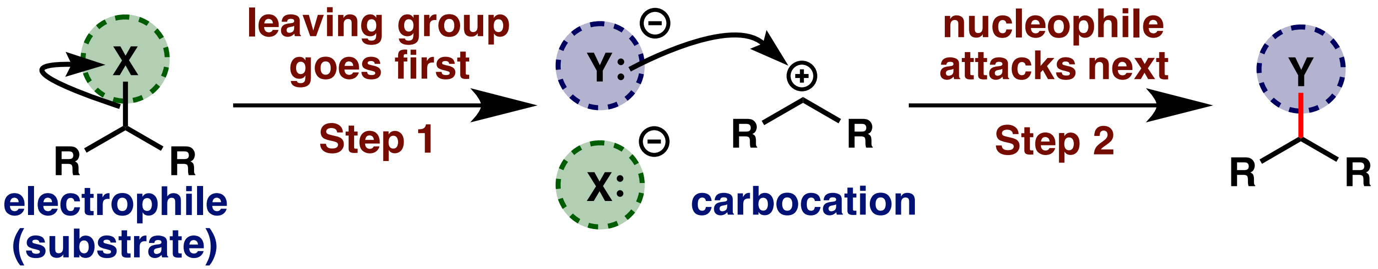


electrophile (substrate)

nucleophile attacks at the same time as the leaving group goes

concerted (1 step) process

S_N1 mechanism



electrophile (substrate)

leaving group goes first

Step 1

carbocation

nucleophile attacks next

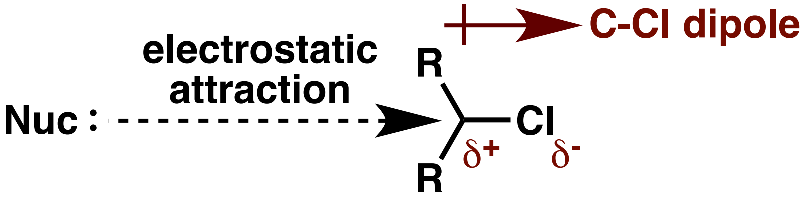
Step 2

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

Leaving Group in Substitution Reactions

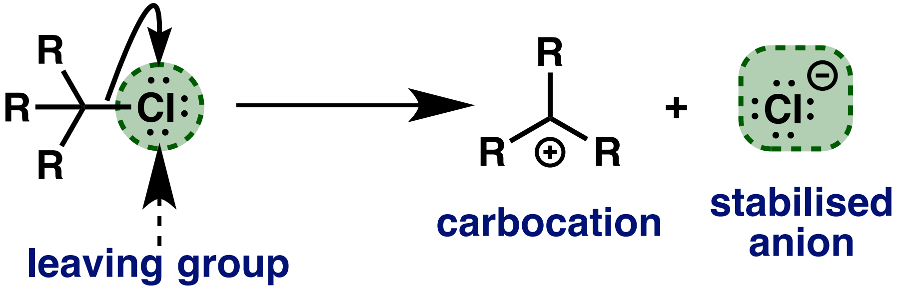
- Some leaving groups encourage a substitution reaction better than others. A leaving group must:

- 1) Be more electronegative than carbon, creating a partial positive charge (δ+) on carbon that will attract the negative charge of the nucleophile



Reminder: Electronegativities for C-Cl polarisation
Chlorine - 3.16, Carbon - 2.55
Unit 1, Lecture 3

- 2) Be able to stabilise the electrons it leaves with



For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

Leaving Group in Substitution Reactions

- A good leaving group is the conjugate base of a strong acid – i.e. acids with low pK_a

Stonger acids
Most stable conjugate base
(low pK_a)

↑

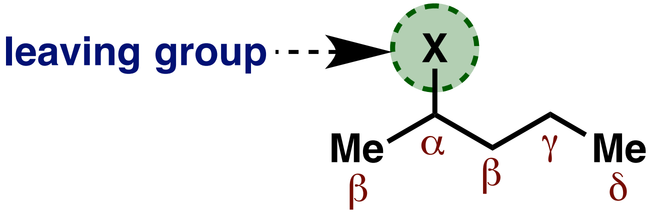
Weaker acids
Least stable conjugate base
(high pK_a)

Acid	pK_a	Conjugate Base / Leaving Group	Name	
HI	-10	I^-	Iodide	Good Leaving Groups
HBr	-9	Br^-	Bromide	
HCl	-8	Cl^-	Chloride	
$HOSO_2R$	-3	$^-OSO_2R$	Sulfonate	
H_3O^+	-1.7	H_2O	Water	
HF	+3.2	F^-	Fluoride	Bad Leaving Groups
H_2S	+7.0	HS^-	Thiolate	
HCN	+9.4	^-CN	Cyanide	
H_2O	+15.7	^-OH	Hydroxide	
$HOCH_2CH_3$	+15.9	$^-OCH_2CH_3$	Ethoxide	
HOR	+16 to +18	^-OR	Alkoxide	

recap **Reminder: acids and bases**
Unit 1, Lecture 9 recap

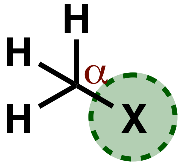
Substrates for Substitution Reactions

- The structure of the substrate is key in substitution reactions.
- Greek letters are often used to label the carbons of the alkyl group attached to the leaving group (X). Substitution reactions occur at the α **carbon**. Why?

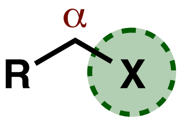


α = alpha position
β = beta position
γ = gamma position
δ = delta position

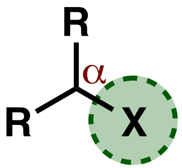
- The amount of branching at the α carbon greatly affects the reaction mechanism for substitution reactions. There are four types of substrate to consider:



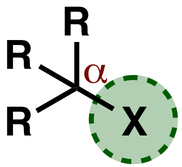
Methyl



Primary (1°)



Secondary (2°)



Tertiary (3°)

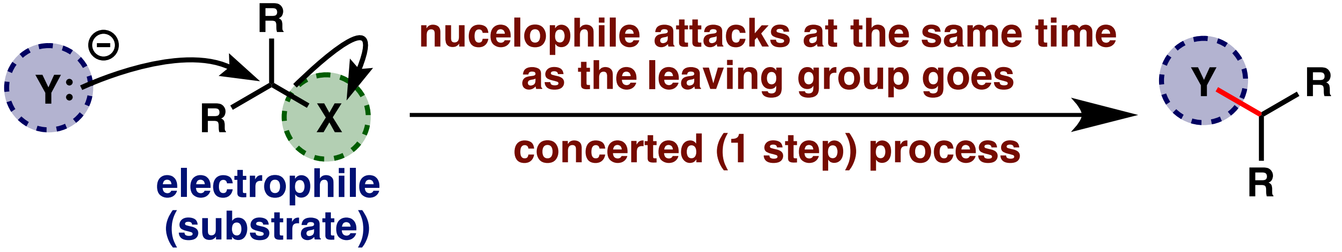
R ≠ H
X = Leaving Group

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

The S_N2 Reaction – Rate Law

- For many substitution reactions, the rate is proportional to **both the concentration of the nucleophile and the concentration of the substrate**, giving the following rate law:

Curly Arrow Pushing Mechanism



nucelophile attacks at the same time as the leaving group goes

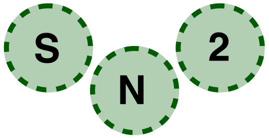
concerted (1 step) process

Rate Law

$$\text{Rate} = \frac{d\,[\text{Products}]}{dt} = k_{obs}[\text{nucleophile}]^1[\text{substrate}]^1$$

recap **Reaction Kinetics Unit 2, Lecture 2** recap

- This dependence implies that **both** species are involved in the rate determining step of the reaction, i.e. the step with the highest activation energy, E_a.



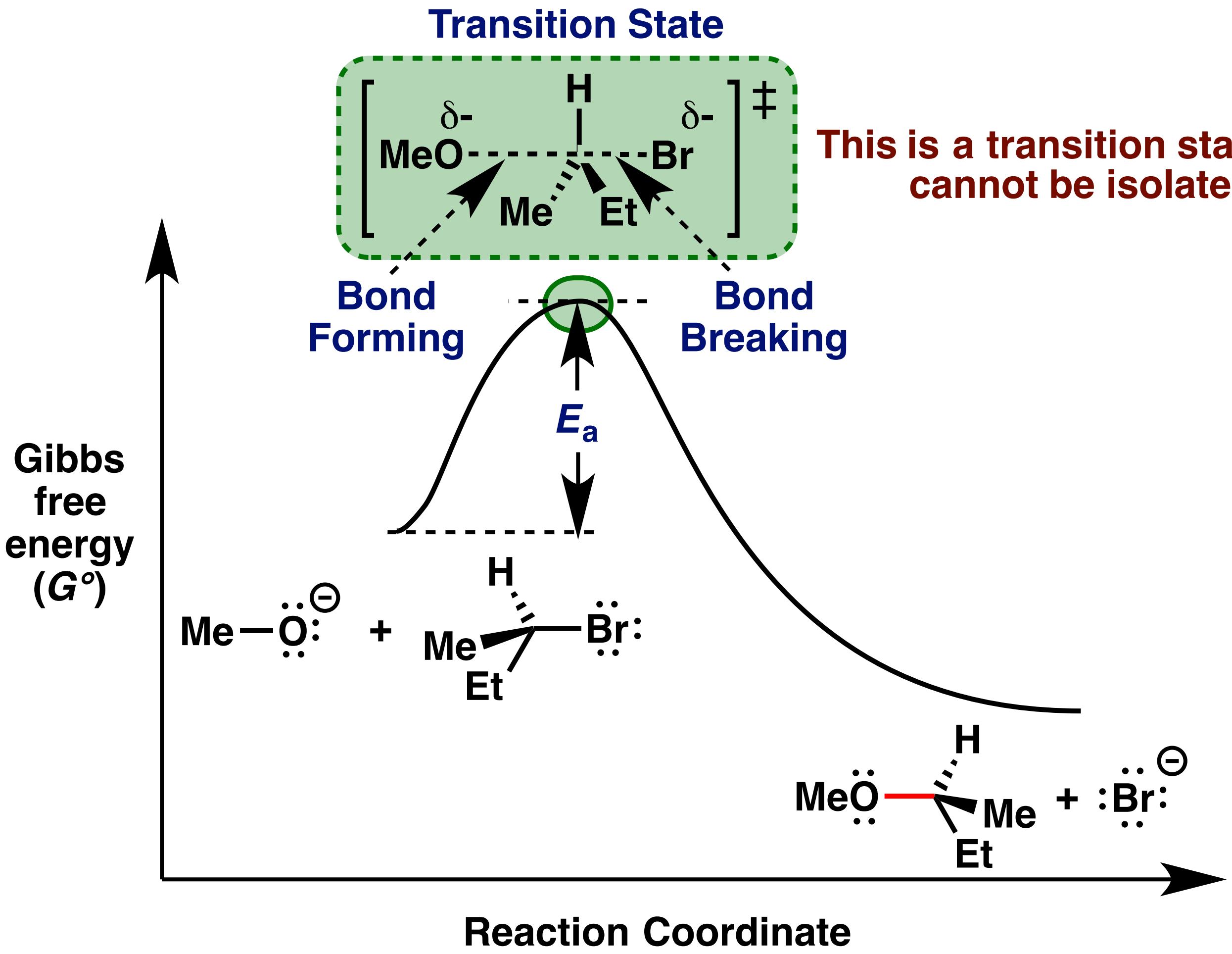
Substitution

Nucleophilic

Bimolecular - two species involved in rate-determining step

The S_N2 Reaction – Free Energy Diagram

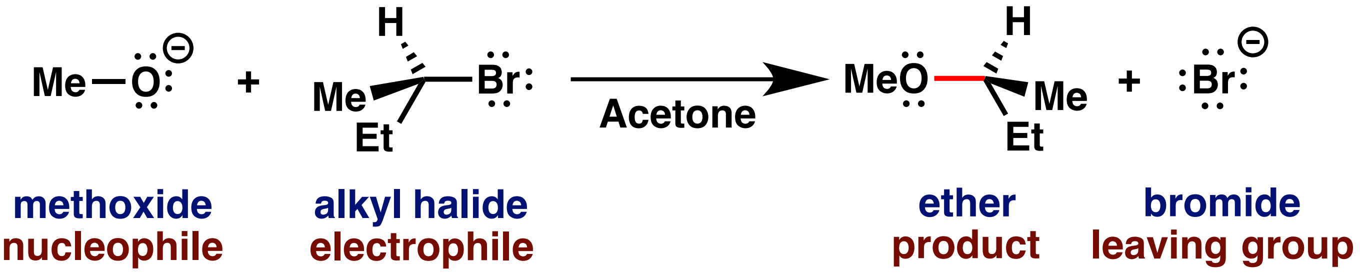
- The S_N2 reaction proceeds through a **five-coordinate transition state** that results in an inversion of configuration at the carbon centre



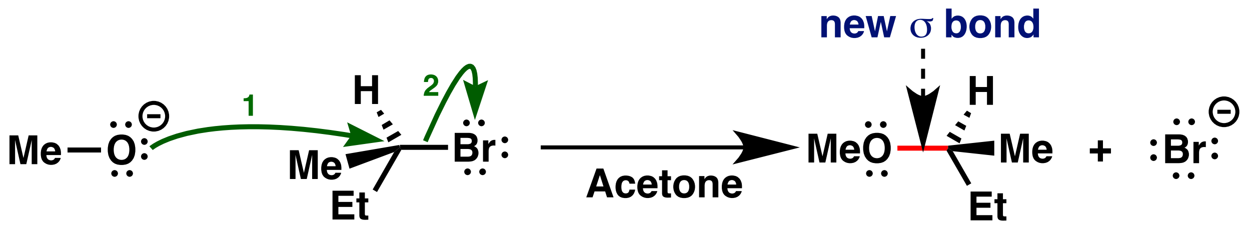
For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

The S_N2 Reaction – Curly Arrow Pushing Mechanism

- The Williamson ether synthesis forms an ether from an organohalide and a deprotonated alcohol (alkoxide). Consider the substitution reaction shown below:



- We should now be able to draw a curly arrow pushing mechanism and identify the key orbital interaction associated with this movement of electrons



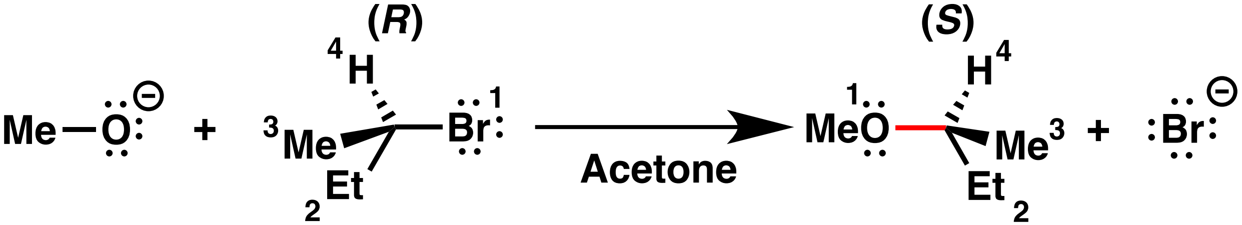
key orbital interactions

Curly arrow 1 - filled non-bonding O sp^3 orbital to empty C-Br σ^* orbital, forming new C-O σ bond

Curly arrow 2 - breaking of C-Br σ bond with two bonding electrons ending up on bromide anion

The S_N2 Reaction – Stereochemistry

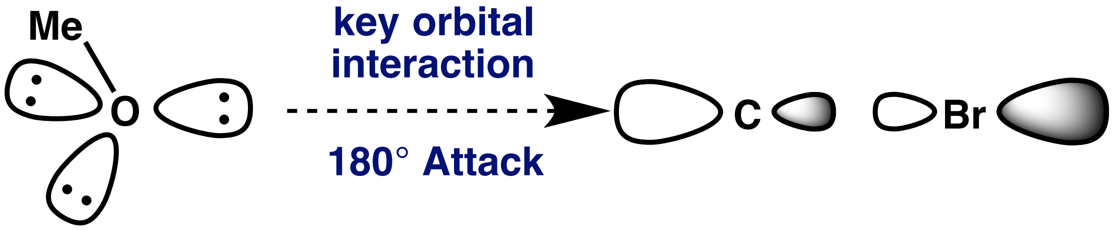
- The S_N2 reaction proceeds with **inversion of configuration** at the carbon centre



methoxide nucleophile | **alkyl halide electrophile** | **ether product** | **bromide leaving group**

Assigning Stereocentres
Unit 1, Lectures 4-7

- The nucleophile **must** attack opposite (180°) to the leaving group in order to donate electron density into the C-Br σ* orbital. This proceeds through a five coordinate transition state that results in an inversion of configuration at the carbon centre

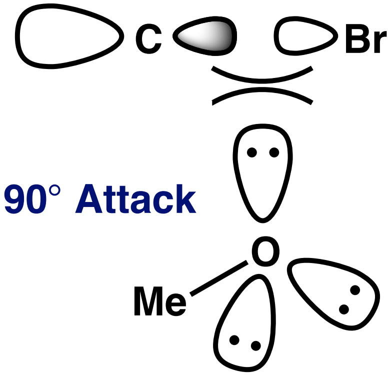


key orbital interaction

180° Attack

nucleophile HOMO = filled non-bonding O sp^3 orbital

electrophile LUMO = empty C-Br σ∗ orbital

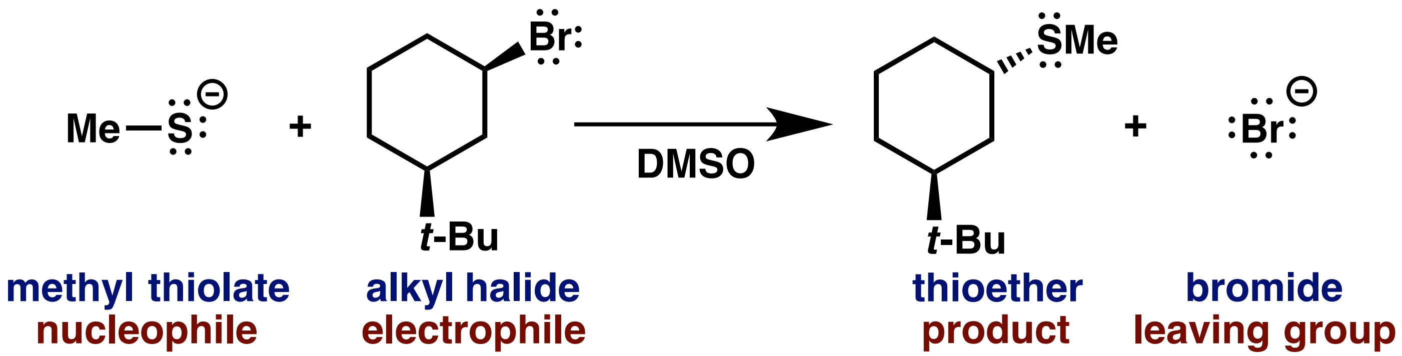


90° Attack

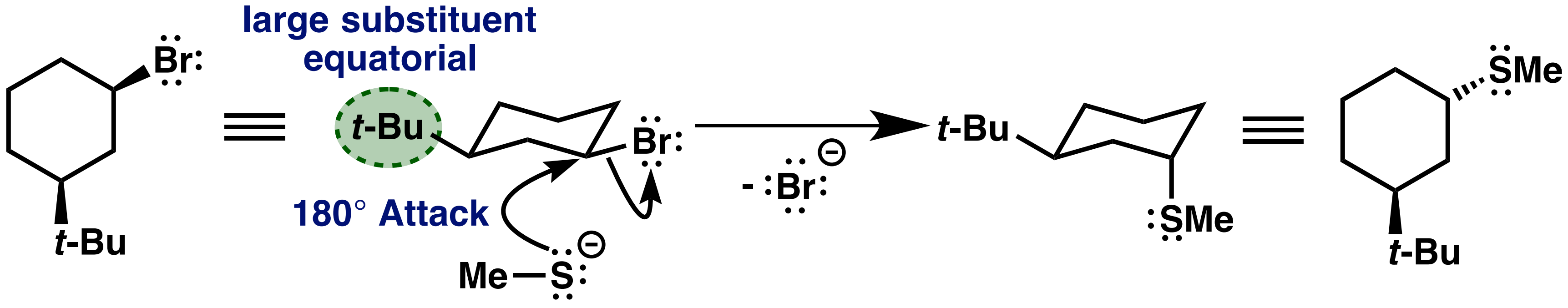
no net orbital overlap

Worked Example 1 – S_N2 on a Cyclic System

- Consider the following reaction involving a cyclic alkyl halide:



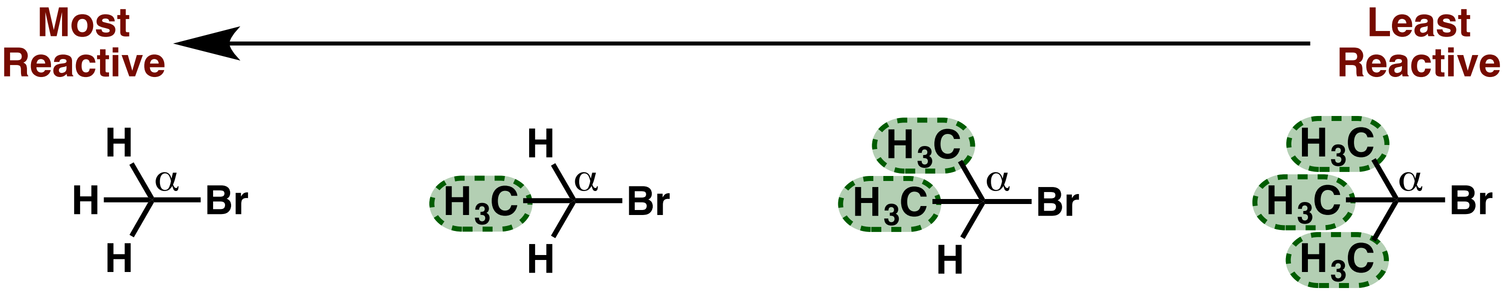
- We must be able to draw the molecule in 3-D and then show curly arrows



For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

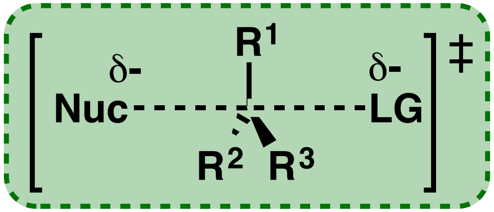
The S_N2 Reaction – Substrate Dependence (Sterics)

- The degree of **steric congestion** (size) within the substrate makes a big difference to the rate of a S_N2 reaction



	Methyl	**Primary (1°)**	**Secondary (2°)**	**Tertiary (3°)**
Relative Reactivity	**>1000**	**≈100**	**1**	**Too slow to measure**

- This trend can be easily understood – we are trying to create a carbon centre at the transition state that have **five** groups around it. The more steric congestion around the carbon centre, the more difficult it is for the nucleophile to reach the carbon

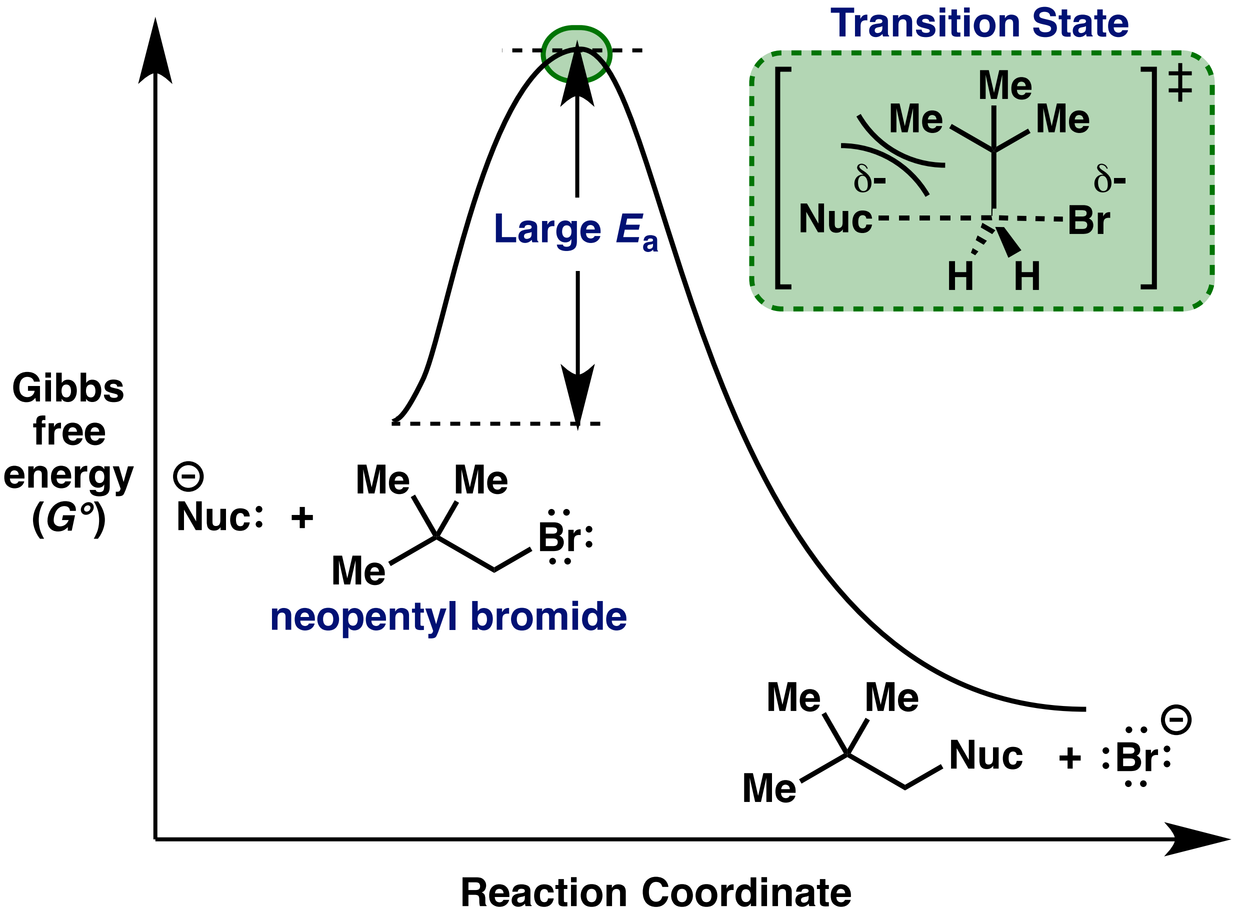


When R groups = H → fast reaction
When one or more R groups = alkyl → slower reaction

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

The S_N2 Reaction – Substrate Dependence (Sterics)

- **Neopentyl bromide** undergoes substitution extremely slowly despite being a primary alkyl halide. This is due to the large steric congestion in the transition state resulting in a large activation energy, E_a, for reaction.



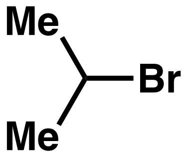
For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

The S_N2 Reaction – Substrate Dependence (Sterics)

- **Cyclohexyl bromide** undergoes substitution slower than isopropyl bromide despite both being secondary alkyl bromides. This is due to two axial hydrogen atoms interfering with the approach of the nucleophile in cyclohexyl bromide.

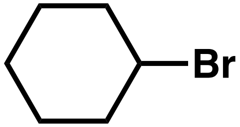
Relative Reactivity

1



isopropyl bromide

0.01

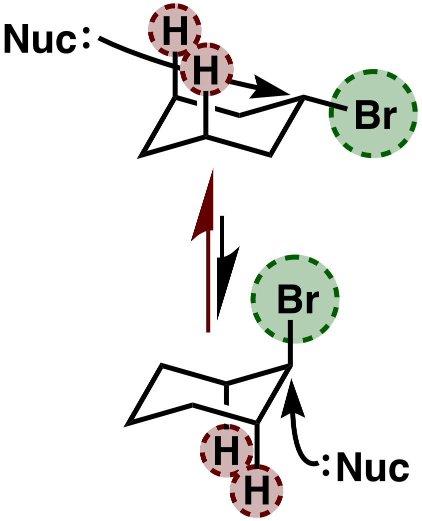


cyclohexyl bromide

Why is cyclohexyl bromide slower in substitution reactions?

---

large substituent equatorial more stable but less reactive conformer



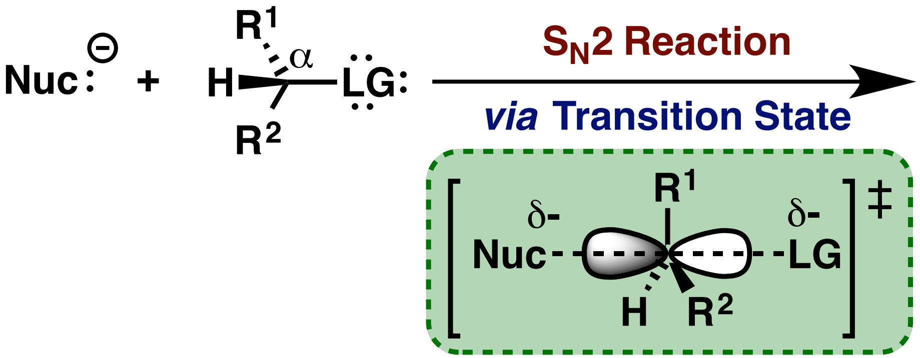
Axial hydrogen atoms hinder nucleophile approach

large substituent axial less stable but more reactive conformer

Nucleophile approach is relatively unhindered

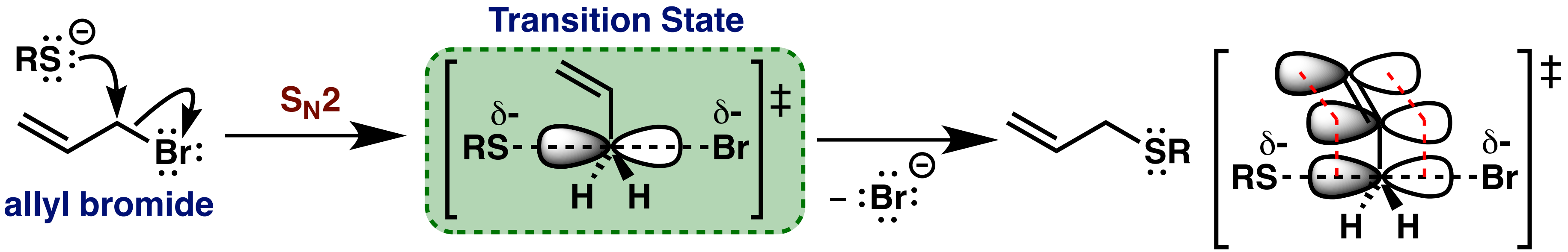
The S_N2 Reaction – Substrate Dependence (Electronics)

- During the S_N2 reaction, the hybridisation at carbon changes from sp^3 to sp^2 (with the $2p_z$ atomic orbital on carbon) back to sp^3. R groups that can facilitate this rehybridisation will lower the activation energy (E_a) resulting in faster reactions.



carbon sp^2 hybridised
$2p_z$ orbital on carbon

- Adjacent π systems (C=C, C=O etc.) attached to the carbon centre serve this role by orienting parallel to the $2p_z$ orbital and stabilising the transition state by conjugation. Important electrophiles of this type include allyl bromide and benzyl bromide

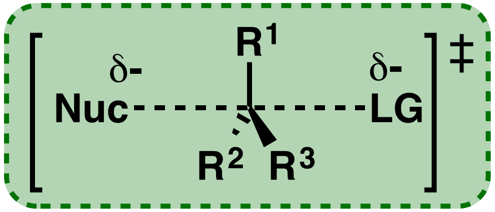


The S_N2 Reaction – Nucleophile

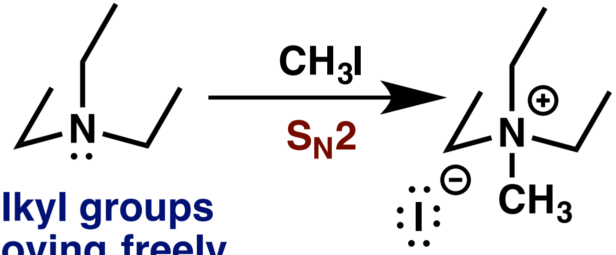
- In an S_N2 reaction a **good nucleophile** is essential – component of the rate equation

- Just as steric effects are important in the substrate, they are also important in the nucleophile.

- A less bulky nucleophile will result in a less congested transition state and a faster reaction due to better overlap of the nucleophile lone pair with the C-LG σ^* orbital

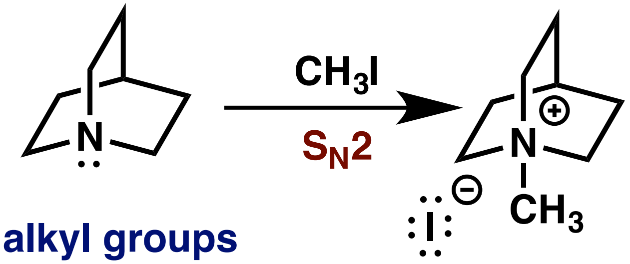


When Nuc = small → fast reaction
When Nuc = large / bulky → slower reaction



Relative Rate 1

alkyl groups moving freely more congested nucleophile



Relative Rate 252

alkyl groups pinned back less congested nucleophile

The S_N2 Reaction – Nucleophilicity

- Consider the following table of relative nucleophilicities in EtOH (polar protic solvent):

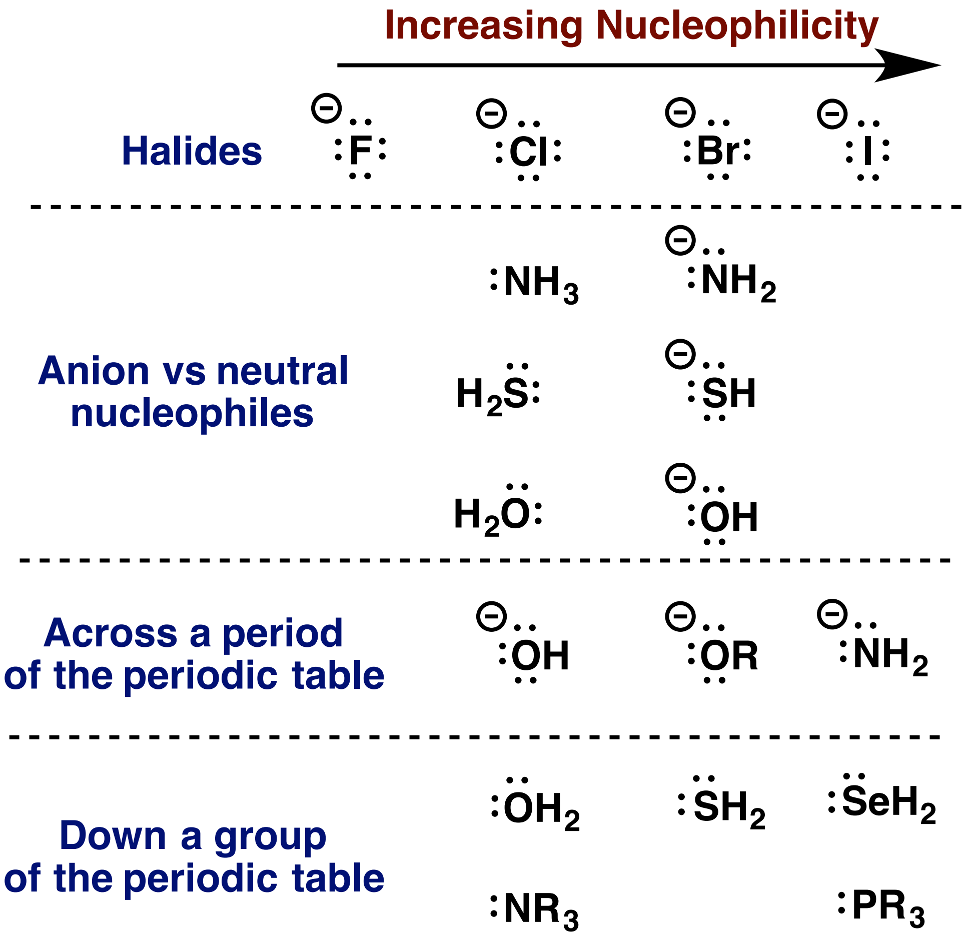
Best Nucleophiles

Species	Relative Nucleophilicity	Name	
NC^-	125000	cyanide	Excellent nucleophiles
HS^-	125000	thiolate	
I^-	80000	iodide	
HO^-	16000	hydroxide	Good nucleophiles
Br^-	10000	bromide	
N_3^-	8000	azide	
NH_3	8000	ammonia	
NO_2^-	5000	nitrite	
Cl^-	1000	chloride	Average nucleophiles
$CH_3CO_2^-$	650	acetate	
F^-	80	fluoride	
CH_3OH	1	methanol	
H_2O	1	water	

Poorer Nucleophiles

The S_N2 Reaction – Nucleophilicity

- In reality, nucleophilicity is difficult to quantify on a single scale and is affected by the choice of solvent. However, we can identify some general trends that are useful in identifying the best nucleophiles for a S_N2 reaction in EtOH (polar protic solvent)



Some of the best nucleophiles are:

1) based on atoms with large atomic radii - diffuse orbitals where electrons are far from postively charged nucleus resulting in high energy HOMO

2) negatively charged - electron rich

For S_N2 reaction a strong or moderate nucleophile is required for reaction

strong nucleophiles include:
RS^-, I^-, R_2N^-, R_2NH^-, RO^-, NC^-, N_3^-

moderate nucleophiles include:
RSH, Br^-, RCO_2^-

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

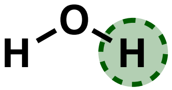
The S_N2 Reaction – Solvent

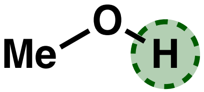
- Consider the following relative rates of an S_N2 reaction in different solvents:

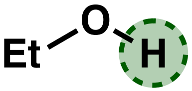
Solvent	CH_3OH **Polar Protic**	H_2O **Polar Protic**	DMSO **Polar Aprotic**	DMF **Polar Aprotic**	CH_3CN **Polar Aprotic**
Relative rate	1	7	1300	2800	5000

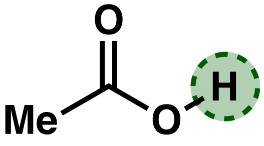
Increasing Reaction Rate →

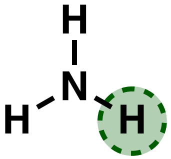
- Polar protic solvents contain at least one hydrogen atom connected directly to an electronegative atom


water

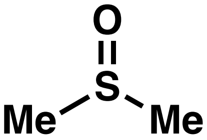

methanol

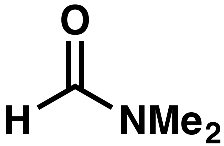

ethanol


acetic acid


ammonia

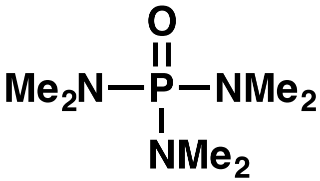
- Polar aprotic solvents contain no hydrogen atoms connected directly to an electronegative atom


dimethylsulfoxide (DMSO)


dimethylformamide (DMF)

Me—≡N

acetonitrile

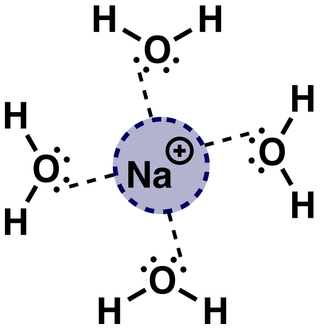

$\mathrm{Me_2N{-}P({=}O)(NMe_2){-}NMe_2}$

hexamethylphosphoramide (HMPA)

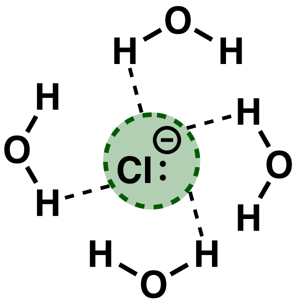
The S_N2 Reaction – Solvent

- For S_N2 reactions, polar aprotic solvents give the fastest reactions. **Polar** – for solubility of substrate and nucleophile, **aprotic** – due to solvation effects

- In polar protic solvents, cations and anions are both solvated, reducing the energy of the nucleophile HOMO (**decreased nucleophilicity**)

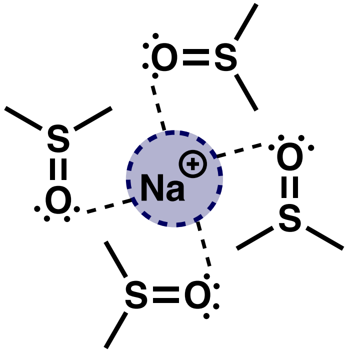


The lone pairs on the oxygen atoms of H_2O stabilise the cation

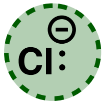


Hydrogen-bonding interactions stabilise the anion, reducing nucleophilicity

- In polar aprotic solvents, only cations are solvated, maintaining the energy and hence nucleophilicity of the anion.



The lone pairs on the oxygen atoms of DMSO stabilise the cation



The anion is not stabilised by the solvent as there are no hydrogen bond donors, maintaining nucleophilicity

The S_N2 Reaction – Leaving Group

- A good leaving group is the conjugate base of a strong acid – i.e. acids with low pK_a

Stonger acids
Most stable conjugate base
(low pK_a)

Weaker acids
Least stable conjugate base
(high pK_a)

Acid	pK_a	Conjugate Base / Leaving Group	Name
HI	-10	I^-	Iodide
HBr	-9	Br^-	Bromide
HCl	-8	Cl^-	Chloride
$HOSO_2R$	-3	$^-OSO_2R$	Sulfonate
H_3O^+	-1.7	H_2O	Water
HF	+3.2	F^-	Fluoride
H_2S	+7.0	HS^-	Thiolate
HCN	+9.4	^-CN	Cyanide
H_2O	+15.7	^-OH	Hydroxide
$HOCH_2CH_3$	+15.9	$^-OCH_2CH_3$	Ethoxide
HOR	+16 to +18	^-OR	Alkoxide

Good Leaving Groups

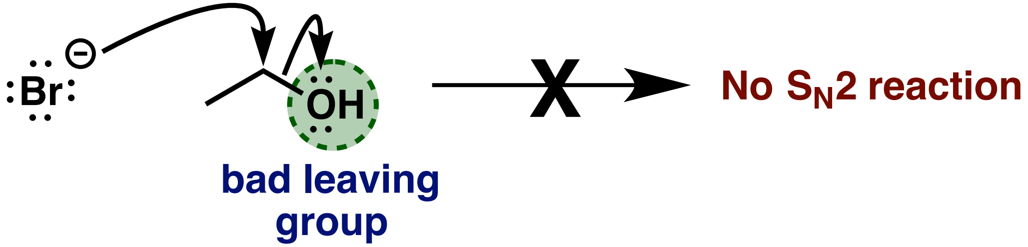
Bad Leaving Groups

Reminder: acids and bases
Unit 1, Lecture 9

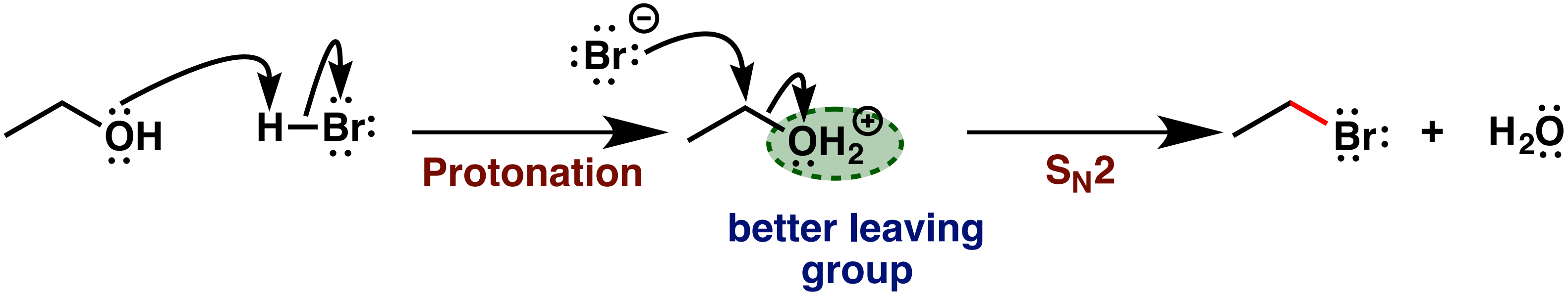
For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

The S_N2 Reaction – Leaving Group

- A good leaving group is the conjugate base of a strong acid – i.e. acids with low pK_a
- If we have a bad leaving group the S_N2 reaction will either be slow or not occur at all



- If we have a bad leaving group, we must change it into a better one

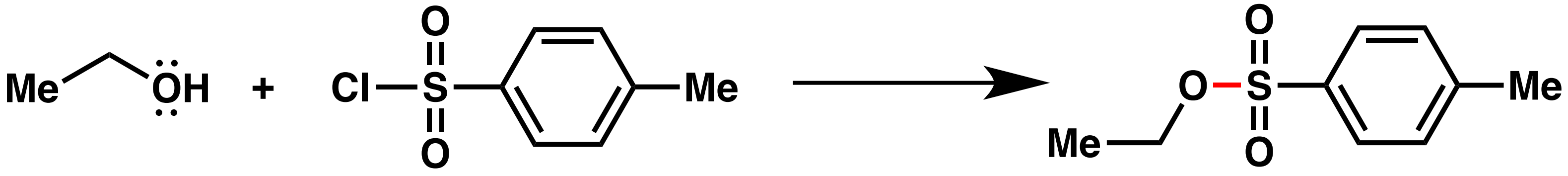


recap **Reminder: Curly Arrows**
Unit 2, Lecture 3 recap

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

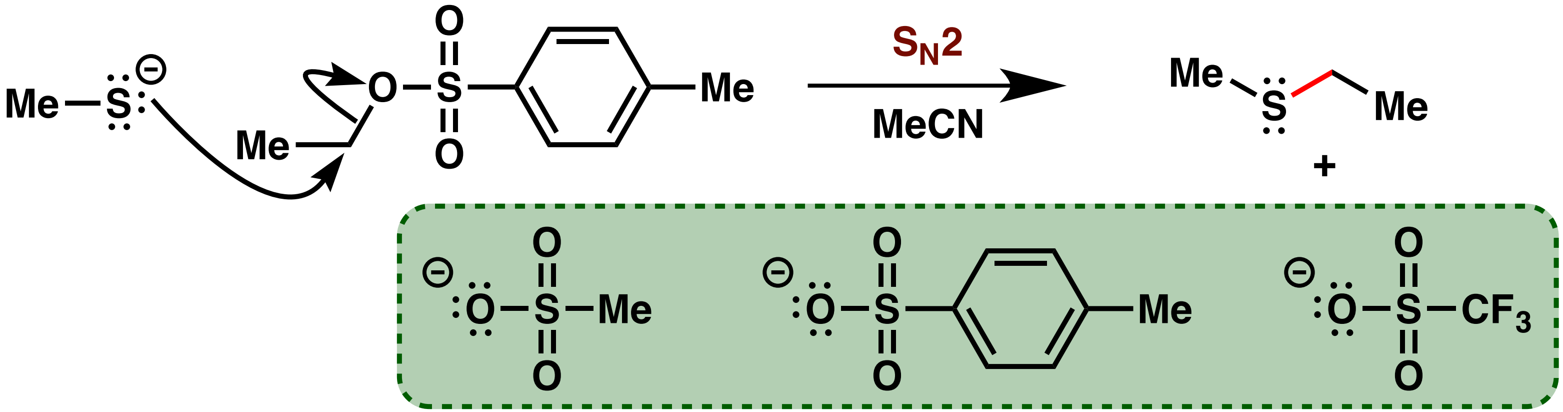
The S_N2 Reaction – Leaving Group

- Another good way of making a good leaving group from a hydroxyl is forming a **sulfonate ester**



ethanol **tosyl chloride** **ethyl tosylate**

activated species



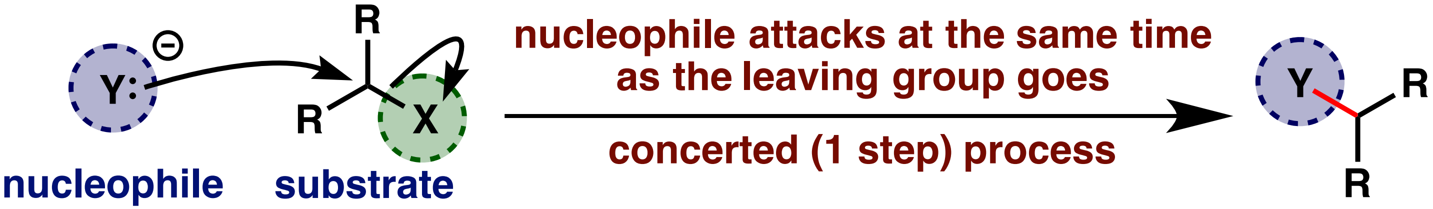
mesylate anion **tosylate anion** **triflate anion**

all are excellent leaving groups

- Always remember, if the site of S_N2 reaction is a stereogenic centre, the reaction will proceed with **inversion of configuration**

The S_N2 Reaction – Cheat Sheet

- For the S_N2 reaction, you must remember the following key information
- Mechanism:



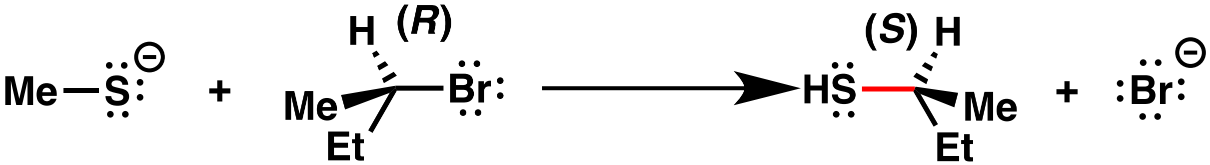
nucleophile **substrate**

nucleophile attacks at the same time as the leaving group goes

concerted (1 step) process

- Rate Law: $$\text{Rate} = \frac{d\,[\text{Products}]}{dt} = k_{obs}[\text{nucleophile}]^1[\text{substrate}]^1$$

- Stereospecific (inversion):



- Factors that favour an S_N2 mechanism:

Substrate
methyl, primary - good
allylic, benzylic - good
secondary - moderate
tertiary - bad

Nucleophile
highly nucleophilic, unhindered, often negatively charged
e.g. NC^-, RS^-, I^-, N_3^-

Solvent
polar aprotic
e.g. DMSO, DMF acetonitrile, acetone

Leaving Group
highly stabilised / conjugate acid has a low pK_a value
e.g. I^-, Br^-, $^-OSO_2R$

For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.

Lecture 4: Introduction to Substitution Reaction – S_N2

Key learning objectives:

- Know the difference between the possible mechanisms for nucleophilic substitution at saturated carbon – S_N2 and S_N1
- Understand what makes a good leaving group
- The rate law for a S_N2 reaction
- The free energy diagram for a S_N2 reaction
- The curly arrow pushing mechanism, molecular orbital analysis, transition state and stereochemical outcome of a S_N2 reaction
- The factors that favour a S_N2 mechanism including the nature of the substrate, nucleophile, solvent and leaving group

Lecture 4 Revision

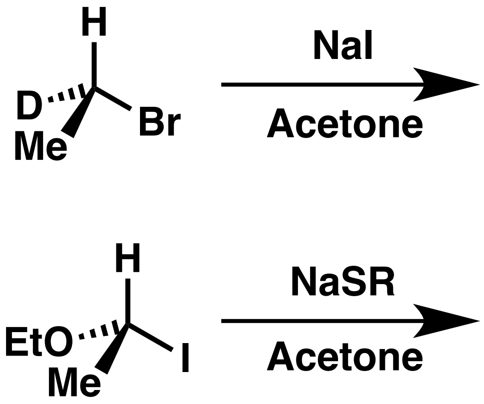
To reinforce your understanding of the contents of this lecture, please refer to:

- *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 15 pp. 328-359.
- Practice questions provided on the next two slides.
- Online practice questions http://www.oxfordtextbooks.co.uk/orc/clayden2e/
  Username: clayden2e   Password: compound
- Online practice questions http://www.chem.ox.ac.uk/vrchemistry/iom/#
- CH4103 Online Test 4
- CH4103 Workshop 2

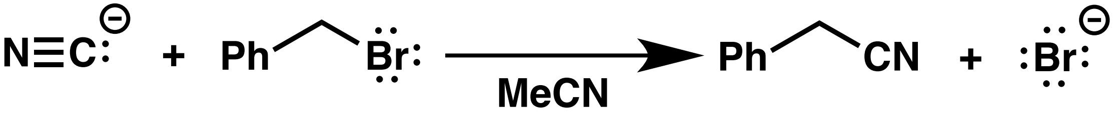
Lecture 4 Practice Questions / Guided Self-Study

For further practice, attempt the following questions in your own time:

- Q1) What are the stereochemical outcomes of these S_N2 reactions? Assign *R* or *S* descriptors to the starting material and product in each case



- Q2) Draw a curly arrow pushing mechanism for the following reaction. Is this reaction slower or faster than the same process with ethyl bromide. Why?



Lecture 4 Practice Questions / Guided Self-Study

For further practice, attempt the following questions in your own time:

- Q3) Draw curly arrow pushing mechanisms for all steps to form the products shown.