5. Reactions
The Gibbs Energy of Reaction ($\Delta r G$): A measure of thermodynamic driving force for a chemical reaction

- Some chemical reactions do not go to 100% completion – a (dynamic) equilibrium mixture of reactants and products results.
- Thermodynamics, and more precisely the Gibbs energy ($G$),* allows us to calculate the precise composition of this equilibrium mixture and how the position of equilibrium (i.e., molar composition of the mixture) will respond to changes in pressure and temperature.
- The Gibbs energy of reaction ($\Delta r G$) refers to the difference in partial molar Gibbs energies of the reactants and products at a given composition of the reaction mixture (i.e., not under standard conditions). It is also defined mathematically as the gradient of a plot of Gibbs energy versus extent of reaction (see a physical chemistry textbook, e.g., Atkins).
- The standard Gibbs energy of reaction ($\Delta r G^0$) refers to the Gibbs energy change per mole of reaction for pure reactants and products at standard conditions (i.e., 298 K, 100 kPa, 1 M of each reactant and product).
- A reaction only proceeds in the forward direction (spontaneous) when $\Delta r G < 0$, and reaches equilibrium when $\Delta r G = 0$.

*Gibbs energy ($G$) is often called "free energy", because it is effectively the energy leftover from the enthalpy ($H$) once the necessary portion has been subtracted to increase the disorder (entropy, $S$) of the system overall (i.e., $G = H - TS$). This is in accordance with the second law of thermodynamics.

Take-home message: A reaction is thermodynamically-favoured overall if $\Delta r G^0 < 0$ (i.e., negative), as the position of equilibrium will then lie towards the products. At a given composition, the direction of reaction is determined by $\Delta r G$. 

\[ G = H - TS \]
Equilibrium Constants \((K)\): Quantification of the position of equilibrium and the approximate use of molar concentrations

- The equilibrium constant \((K)\) for a dynamic equilibrium is defined as follows (where lowercase letters denote stoichiometry coefficients):

\[
\begin{align*}
\text{aA} + \text{bB} & \rightleftharpoons \text{cC} + \text{dD} \\
K = \frac{[\text{c}]^a [\text{d}]^b}{[\text{a}]^a [\text{b}]^b}
\end{align*}
\]

(at low conc)

- Strictly, \(K\) depends on the activity \((a_x)\) of each species – an "effective concentration" taking into account the non-ideality of the solution (i.e., strong solute-solute interactions). If a particular species is present in low concentration, its activity can be approximated by its molar concentration \(([X])\) (in mol dm\(^{-3}\)). For a pure substance under standard conditions, its activity is defined as unity (i.e., 1).

- Equilibrium constants are insensitive to concentration or pressure changes, but they are sensitive to temperature changes (see van't Hoff equation). Note also that the identity of the reaction solvent, even if it does not appear in the equilibrium constant, can affect \(K\).

- In accord with Le Chatelier's principle, increasing the concentration of one or more species will cause the relative concentrations (i.e., position of equilibrium) to adjust, in order to keep the value of \(K\) unchanged (remember its a constant!).

From \([\text{N}_2]_{\text{init}} = 0.10\ \text{M}\) and \([\text{H}_2]_{\text{init}} = 0.10\ \text{M}\):

\[
\begin{align*}
\text{N}_2 + 3\text{H}_2 & \rightleftharpoons 2\text{NH}_3 \\
0.099 & \quad 0.097 \quad 0.002 \\
K = 0.04 & \quad [0.002]^2 = 0.04 \\
1.00 & \quad 0.092 \quad 0.0055 \\
\end{align*}
\]

increase \([\text{N}_2]_{\text{init}}\) \(10\times\)

\[
\begin{align*}
\text{N}_2 + 3\text{H}_2 & \rightleftharpoons 2\text{NH}_3 \\
1.00 & \quad 0.092 \quad 0.0055 \\
K = 0.04 & \quad [0.0055]^2 = 0.04 \\
0.099 & \quad 0.097 \quad 0.002
\end{align*}
\]

\(~3\times\) as much product \(\text{NH}_3\)

- The equilibrium constant \((K)\) is related to both \(\Delta_rG^0\) and also to the forward and backward rate constants, \(k_{\text{fwd}}\) and \(k_{\text{rev}}\):

\[
\Delta_rG^0 = -RT \ln K \quad \text{relationship of } K \text{ to } \Delta_rG^0
\]

- relationship of \(K\) to \(k_{\text{fwd}}\) and \(k_{\text{rev}}\):

\[
K = \frac{k_{\text{fwd}}}{k_{\text{rev}}}
\]

Take-home message: The equilibrium constant \((K)\) is sensitive only to temperature, but changes in concentrations can alter the position of equilibrium (Le Chatelier's principle). It is also related to \(\Delta_rG^0\) and to the forward and backward rate constants, \(k_{\text{fwd}}\) and \(k_{\text{rev}}\).
Driving Reversible Reactions to Completion: Removing a (side) product or using a large excess of a reactant

There are sometimes occasions in organic synthesis where we need to drive reversible reactions to completion in order to maximise product yield. One strategy is to remove one or more of the products from the reaction mixture, and so prevent the reverse reaction from happening.

A good example is acid-catalysed acetalisation of carbonyl compounds, to convert them into acetals (a reaction you'll meet in semester 2). The process is mechanistically reversible, and it can be made to run in the reverse direction, with excess water present. To make the reaction irreversible, the water produced is removed from the reaction by distilling it into a Dean-Stark trap (see photo on right).

Another example is the Finkelstein reaction (see right), which converts an alkyl chloride to an alkyl iodide using NaI in acetone as the solvent. Because C–I bonds are much weaker than C–Cl bonds, the reaction is actually thermodynamically uphill, but it is driven to the right because NaCl is much less soluble than NaI in acetone, and it is removed by precipitation.

Another useful strategy, if one of the reactants is low molecular weight, is to use a large excess of that reactant. Based on Le Chatelier’s principle, this pushes the position of equilibrium to the right. This strategy is sometimes referred to as a mass action effect.

The Fischer esterification with small alcohols (e.g., MeOH, EtOH) works on this principle (see left).

Take-home message: Reversible reactions can be driven to the right by either removing a (side) product (e.g., by distillation, precipitation) or by using a large excess of a reactant (mass action effect).
Almost all chemical reactions have an **activation barrier** to reaction, even when they are thermodynamically-favoured, because there is an energetic price to pay for bringing molecules close together (i.e., electron-electron repulsion), aligning them appropriately, and starting to break their chemical bonds.

This is illustrated in a **reaction energy profile**, which shows how the Gibbs energy for the reaction of individual molecules changes as a function of the **reaction coordinate** (i.e., the extent of bond breakage and formation).

The simplest energy profile is one for a reaction that comprises only a single **elementary step** (i.e., no intermediates). An energy maximum on the profile is referred to as a **transition state (TS)**, which is a transient entity whose existence lasts no longer than the timescale of a molecular vibration (~$10^{-13}$ s).

The **Gibbs energy of activation** ($\Delta G^\ddagger$),* is the energy required to reach the TS from the reactants - this is the barrier that must be surmounted for the reaction to proceed. Note that the standard Gibbs energy of reaction ($\Delta_r G^o$) is shown on the same diagram, so these energy profiles actually show us both the kinetic and thermodynamic parameters of a reaction (and we will use them regularly).

Take-home message 1: Chemical reactions possess an activation barrier that is quantified as the Gibbs energy of activation ($\Delta G^\ddagger$) (at least for a single-step reaction).

Take-home message 2: Reaction energy profiles show us how the Gibbs energy of individual molecules varies as bond breaking/making proceeds. They also depict the thermodynamics of the reaction ($\Delta_r G^o$).

Take-home message 3: Energy maxima on the reaction profile are called transition states (TSs) and they exist no longer than a molecular vibration (~$10^{-13}$ s).

*Although most textbooks neglect to mention it, $\Delta G^\ddagger$ is not mathematically identical to the Arrhenius “activation energy” ($E_a$) derived from collision theory, even for a reaction comprising only a single elementary step. For a unimolecular reaction, the precise mathematical relationship is $\Delta G^\ddagger = E_a - T(R + S^\ddagger)$, and for a bimolecular reaction it is $\Delta G^\ddagger = E_a - T(2R + S^\ddagger)$. It's honestly best not to worry about this...
Rate Laws and Rate Constants ($k$): Quantification of the rate of a reaction (or a given step within a multi-step reaction)

- The rate law for a reaction defines the mathematical relationship between the reaction rate (in mol$^{-1}$ dm$^{-3}$ s$^{-1}$ = M$^{-1}$ s$^{-1}$) and the molar concentrations* of each chemical species involved in the reaction. Each concentration is raised to a power (termed the order in that component), which can be 0, 1, 2 or even a non-integral or negative number.

- The proportionality constant between the reaction rate and the molar concentrations is called the rate constant, $k$. The units of $k$ depend on the precise rate equation, including how many concentration terms there are and what powers (orders) they are raised to.

- An elementary step of a reaction is a single mechanistic step in the overall reaction mechanism (i.e., one transition state). It can be unimolecular (one molecule only) or bimolecular (two molecules involved); termolecular steps (three molecules involved) are very rare.

- A reaction comprised of two or more elementary steps is termed a multi-step reaction. [Do not confuse "multi-step reaction" with "multi-step synthesis" - the meaning of "step" in each case is different].

- The rate constant, $k$, for an elementary step has a negative exponential relationship with the activation Gibbs energy, $\Delta G^\ddagger$, for that step.

$$ k \propto \exp \left( \frac{-\Delta G^\ddagger}{RT} \right) $$

- Thus, the smaller the value of $\Delta G^\ddagger$, the larger the rate constant, $k$, and the faster the elementary step.

**Take-home message:** Rate laws relate the reaction rate to concentrations of all components, with the rate constant being the proportionality constant. Because of the (exponential) relationship of $k$ to $\Delta G^\ddagger$, factors that stabilise the TS will speed up that elementary step of the reaction.

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* As for equilibrium constants, one should strictly use the "activity" ($a_X$) of each species – an "effective concentration" taking into account solute-solute interactions – but in most cases the molar concentration $[X]$ (in mol dm$^{-3}$) is an acceptable substitute.
Kinetic Stability: Thermodynamically-favourable reactions with a high kinetic barrier

- Although the relative height of the forward and reverse energy barriers is dependent on thermodynamics, their absolute height is not.
- It is perfectly possible (and indeed common) to have reactions with a strong thermodynamic driving force, but a very high kinetic barrier.
- Reactants that are thermodynamically unstable with respect to products, but are unable to react by virtue of a high kinetic barrier are termed **kinetically stable**.
- **Combustion** of hydrocarbons in air is a good example of this. The reaction releases a lot of energy (highly exergonic) but it requires a great deal of energy input to surmount the activation barrier.

We will see later that reactions that are thermodynamically-favoured but kinetically unfeasible are ideal candidates for **catalysis**.

**Take-home message**: Reactants with a high activation barrier to an otherwise favourable reaction are termed kinetically stable.
Reversible vs Irreversible Reactions: Can the reaction go backwards as well as forwards?

- If a reaction is strongly exergonic ($\Delta_r G^0 \ll 0$) such that the products are far, far more thermodynamically-stable than the reactants, then the barrier for the reverse reaction may be insurmountable, relative to the available thermal energy. If this is the case, then the reaction is irreversible. A dynamic equilibrium cannot be established here, because there is no reverse reaction operating.

- If a reaction is only weakly exergonic ($\Delta_r G^0 < 0$) or weakly endergonic ($\Delta_r G^0 > 0$), then both the forward and reverse barriers may be surmountable, relative to the available thermal energy (though this is not always the case, as we'll see). If these conditions are met, then the reaction is reversible, and if left for a sufficient amount of time, it will reach dynamic equilibrium.

Note that these definitions depend on the available (average) thermal energy. If the temperature is raised sufficiently, a formerly irreversible process could potentially become reversible.

**Take-home message:** Whether a reaction is reversible or irreversible depends on the intrinsic thermodynamics, and also on the available (average) thermal energy, relative to the barrier height. For reversibility, there must be sufficient thermal energy to surmount both the forward and reverse barriers.
**Thermodynamic Control:** Formation of the most thermodynamically stable product by letting a reversible reaction reach equilibrium

- An important consequence of reversibility is the potential for a reaction with several possible outcomes to converge onto a single major product, where that product is more thermodynamically stable than the other possibilities.

- A reaction run under these conditions, to allow reversibility and thus generation of the thermodynamic product, is said to be under thermodynamic control. [This does not apply to all reactions - we shall see soon that some are under "kinetic control"].

- You will meet many reactions in organic chemistry that are run under thermodynamic control. Under such conditions, various side-reactions can (and likely do) happen, but their reversibility means that the reaction always finds its way back onto the 'main path' (i.e., the side-reactions are akin to mechanistic cul-de-sacs - greyed out in the example below).

This is a named reaction called the **Robinson annulation** that you will meet in semester 2

From the "Conjugation" lectures, you should now understand why this is the thermodynamic product...

**Take-home message:** A reaction run under reversible conditions, to generate the most stable product, is under thermodynamic control. In this scenario, any side-reactions are reversible and thermodynamically unfavourable (effectively mechanistic 'cul-de-sacs'), and the reaction will be able to avoid forming these undesired products (e.g., the Robinson annulation - that you will meet in Yr 2 - is an example).
Kinetic Control: Formation of the fastest-formed product only

- If a reaction is irreversible, then the major product (if there is more than one potential outcome) is inevitably the product that forms the fastest. This is termed the kinetic product and the reaction is said to be operating under kinetic control.

- For reversible reactions, 'thermodynamic control' is only possible if there is a kinetically-accessible pathway to the most stable product (sometimes there isn't!) and the reaction is allowed to equilibrate. Some reactions, although reversible, are mechanistically constrained to give only the kinetic product (see bottom right for an example).

- In some cases the kinetic product is the least stable product, but in other cases it can be the most stable - it just depends on the reaction. So it is perfectly possible to have a reversible reaction, at equilibrium, where the thermodynamic product also happens to be the kinetic product. The concepts are not mutually exclusive.

**Take-home message:** The 'kinetic product' of a reaction is the product that forms the fastest from the starting materials. A reaction that can only give the kinetic product is said to be operating under 'kinetic control'. Whilst this applies to all irreversible reactions, it can also apply to reversible reactions if there is no mechanistic pathway to the more stable product. Whether the kinetic product happens to be the least or most stable product (e.g., stereoisomer) will depend on the reaction - both scenarios are possible.
Kinetic Selectivity and $\Delta \Delta G^\dagger$: A two product reaction as a simple case

- For the simplest case of two competing pathways, the selectivity (product ratio) of a kinetically-controlled reaction is defined as the relative ratio of the two rate constants, which is in turn related to the quantity $\Delta \Delta G^\dagger$.

- This equation also reveals the important point that selectivity is typically increased as the temperature is lowered (which is why chemists often cool down reactions where selectivity is important).

\[
\Delta \Delta G^\dagger = \Delta G^\dagger_1 - \Delta G^\dagger_2
\]

- Because the relationship is exponential, the energy differences ($\Delta \Delta G^\dagger$) required for high selectivity are surprisingly small (0.5–5.0 kcal mol$^{-1}$), especially when compared to the strengths of C–C bonds (80–90 kcal mol$^{-1}$).

<table>
<thead>
<tr>
<th>$\Delta G^\dagger$ (kcal mol$^{-1}$)</th>
<th>Selectivity (at 25 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>54 : 46</td>
</tr>
<tr>
<td>0.5</td>
<td>70 : 30</td>
</tr>
<tr>
<td>1.0</td>
<td>84 : 16</td>
</tr>
<tr>
<td>1.8</td>
<td>95 : 5</td>
</tr>
<tr>
<td>3.4</td>
<td>99.7 : 0.3</td>
</tr>
</tbody>
</table>

Take-home message: Selectivity for a reaction that can form two possible products is defined by the relative ratio of the rate constants, and it tends to increase at lower temperatures. Because of the exponential relationship between $\Delta \Delta G^\dagger$ and $k$, only very tiny energy differences between TSs (2–3 kcal mol$^{-1}$) can give rise to significant selectivities.
Kinetic vs Thermodynamic Products: For some reversible reactions, either kinetic or thermodynamic control is possible

- Some (though not all) reversible reactions can be run under either kinetic or thermodynamic control, depending on the conditions employed.
- In such cases, kinetic control can be achieved by choosing conditions that prevent/minimise equilibration, such as a short reaction time and/or lowering the temperature.
- Thermodynamic control is achieved by doing the opposite: encouraging equilibration by raising the temperature (to speed up the reaction in both directions) and/or leaving it for long enough to reach its equilibrium position.

Take-home message: For some reversible reactions, either kinetic or thermodynamic control can be possible, depending on whether the conditions are chosen to encourage or prevent equilibration. This phenomenon can be very useful in organic synthesis.
Multi-Step Reactions with Intermediates

- So far we have focused on reactions with a single elementary step, but many organic reactions are multi-step processes that proceed via one or more intermediates - species on the reaction pathway that are formed but continue to react further to give the final product.

- There is an important distinction to be made between isolable intermediates (i.e., those you can potentially isolate and store) and reactive intermediates (i.e., those with only a fleeting existence).

![Image](image_url)

- Reactive intermediates are short-lived, high-energy, highly reactive things like carbocations and radicals, which are electron-deficient species that exist only transiently in a reaction and never accumulate.

**Take-home message:** Many organic reactions comprise more than one elementary step, and proceed via one or more intermediates. Sometimes these are stable, isolable entities in their own right, and the reaction can potentially be stopped at this point (e.g., by controlling temperature or time). When the intermediates are short-lived and high-energy, they are termed reactive intermediates, and these in general are transitory and never accumulate (e.g., carbocations, radicals).
The Rate-Determining Step (RDS): A flawed but deeply embedded concept for multi-step reactions

- Because multi-step reactions are kinetically complex, chemists have long sought to simplify the problem by identifying a single step of such processes that exerts the greatest influence on the overall reaction rate: the so-called rate-determining step (RDS).
- A major problem with this concept is that many multi-step reactions have rate laws featuring multiple rate constants (e.g., $k_1$, $k_{-1}$, $k_2$, $k_{-2}$, $k_3$) with equal weighting, so it isn’t always possible for a single elementary step to be said to ‘control’ the overall rate.
- That said, the RDS concept has stuck, and it is featured uncritically in many undergraduate textbooks. You will also meet this concept when discussing substitution/elimination mechanisms (e.g., $S_{N1}$, $S_{N2}$, E1, E2), where it does actually have some merit.
- There are two different (!) definitions for the RDS in common use (which should already sound the alarm bells):

  **Common definition 1.** The RDS is the step with the largest activation barrier ($\Delta G^\ddagger$)

  **Common definition 2.** The RDS is the step with the highest-energy transition state on the reaction coordinate

- Depending on the precise reaction energy profile, these definitions are sometimes both true, and sometimes conflicting (see below). The far right profile also highlights the fallacy of the idea that only one step controls the overall rate, as its abundantly clear here that A $\rightarrow$ B is just as kinetically-relevant as B $\rightarrow$ C.

**Take-home message:** The rate-determining step (RDS) in multi-step reactions is a widely cited concept, albeit without a single, robust definition. It does however have merit in some cases, and you will meet it when discussing $S_{N1}$/$S_{N2}$ and E1/E2 reactions.
An Aside (Non-Examinable) - The Concept of 'Rate-Determining States': The concept of a rate-determining step is not generalisable

- The usefulness of the RDS concept, and how to define the RDS, has long been debated.*
- Kozuch has come to the conclusion that the concept of the RDS is fundamentally flawed, and that a more physically meaningful concept is to discuss rate-determining states - one an energy minima (DI) and one a maxima (DTS) - where the steps inbetween these states are all kinetically-relevant.**

Kozuch's definition: Rate-determining states are the transition state and reactant/intermediate which exert the strongest effect on the overall rate with a differential change of their Gibbs energies.**

- In examples 1–3 (right), the DI and DTS are directly connected, with no intervening states, so the concept of a rate-determining step (RDS) is applicable here.
- Examples 1 and 2 are representative of SN2/E2 and SN1/E1 reactions, respectively, which is why the RDS concept has merit for those reactions.
- In examples 4–6, the DI and DTS are not directly connected, so the rate-determining states define more of a rate-determining 'zone'.

Take-home message: The rate-determining step (RDS) concept holds true in some cases, but not in others. A more generalisable concept is that of Kozuch's rate-determining states.

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**"The rate-determining step is dead. Long live the rate-determining state!" ChemPhysChem 2011, 12, 1413 (Kozuch et al.)
The Hammond Postulate: The concept of ‘early’ or ‘late’ transition states

- On the basis that many organic reactions have a clearly identifiable rate-determining step (RDS), we should next consider what governs the energy of the transition state (TS) for that step. After all, the TS energy governs the height of the activation barrier and thus the rate.

- To truly understand the TS, we need to better understand its structure and the nature of its bonding. Unfortunately, TSs cannot be directly observed, as they by definition exist for a time shorter than the timescale of a molecular vibration (~10^{-13} s).

- Fortunately, there is a very simple assumption that we can make, called Hammond's postulate:

  **Hammond's postulate:** The structure of the TS resembles most closely the species on the reaction coordinate that it is closest to in energy. For *exergonic* steps (\( \Delta_r G^0 < 0 \)), the TS most resembles the reactant(s) ("early TS") whereas for *endergonic* steps (\( \Delta_r G^0 > 0 \)), the TS most resembles the intermediate/product ("late TS")

\[ \text{TS is “carbocation-like”, so features that stabilise the corresponding carbocation intermediate will also stabilise the TS} \]

\[ \text{TS is “ketone-like”, so it can be modelled as if the ketone geometry is undistorted from } sp^2- \text{ becomes important in Felkin-Anh model (Yr 2)} \]

**Take-home message:** The Hammond postulate allows one to infer the structure of the TS from the species closest in energy.

Frontier Molecular Orbital (FMO) Theory (Revisited): An approximation to predict and understand chemical reactivity

- Recall that interaction between the frontier molecular orbitals (HOMO of donor and LUMO of acceptor) is an important (and often controlling) part of the total orbital interaction between two molecules.

- The strength of the interaction (and thus the stabilisation of the transition state) is related to the HOMO-LUMO energy separation. Thus, of the two HOMO-LUMO interactions which are in general possible, it is the one with the smallest energy separation that dominates.

- The most reactive nucleophiles have a high-energy HOMO, and the most reactive electrophiles have a low-energy LUMO.
**Brønsted Acid and Base Activation: Increasing electrophilicity or nucleophilicity of functional groups**

- Many reactions between **electrostatically-neutral** protic nucleophiles (\(\text{Nu-H}\)) and electrophiles (\(\text{E}\)) are too slow to be synthetically useful, because the \(\text{HOMO}_{\text{Nu}}\)\(-\text{LUMO}_{\text{E}}\) gap is relatively large, and so the TS is quite high in energy, leading to a slow rate.

- Such reactions can be accelerated by using a **Brønsted base** to **deprotonate the nucleophile**, raising its HOMO energy [i.e., increased electron density on the Nu atom repels and raises the energy of any other lone pairs(s)] and conferring it a **negative charge**. For example, treatment of an alcohol with a sufficiently powerful base (e.g., \(\text{NaH}\)) generates a much more nucleophilic alkoxide anion.

- Alternatively, a **Brønsted acid** can be used to **protonate the electrophile**, lowering its LUMO energy and conferring it a **positive charge**. For example, treatment of a ketone with a sufficiently powerful acid (e.g., \(\text{H}_2\text{SO}_4\)) generates a small amount of the much more electrophilic oxocarbenium ion.

\[
\begin{align*}
\text{alcohol} & \quad \overset{\text{NaH}}{\longrightarrow} \quad \text{alkoxide anion} \\
\text{lower HOMO (}\pi\text{)} & = \text{weaker Nu} \\
\text{higher HOMO (}\pi\text{)} & = \text{stronger Nu} \\
\text{ketone} & \quad \underset{\text{H}_2\text{SO}_4}{\rightleftharpoons} \quad \text{oxocarbenium ion} \\
\text{higher LUMO (}\pi^*\text{)} & = \text{weaker E} \\
\text{lower LUMO (}\pi^*\text{)} & = \text{stronger E}
\end{align*}
\]

- For this to work, the Brønsted base or acid activator must be sufficiently reactive to deprotonate or protonate, respectively, the substrate (see "Acids & Bases" notes). It doesn't necessarily need to be quantitative, but the equilibrium quantity of activated species must be high enough to drive the reaction.

- It is not uncommon to achieve rate enhancements of the order of \(\sim 10^6\) using this approach, compared to reactions of the neutral substrates.

- Naturally, you cannot use both strong acid and base simultaneously (a **common student error**!) - it is one or the other!

**Take-home message**: Brønsted acids and bases can significantly increase the reactivity of electrophiles and nucleophiles, respectively, by proton transfer. This isn't universal - the acid or base must be sufficiently powerful, and some Nu/E are just too hard to activate this way.
**Catalysis**: Speeding up reactions that are kinetically slow or impossible by adding a catalyst

- We met earlier the concept of kinetic stability - that is, the height of an activation barrier making a reaction too slow to be feasible/useful, even if thermodynamically favoured.
- In such circumstances, it may be possible to identify a catalyst to accelerate the reaction. This is a substance that increases the rate of a chemical reaction without itself undergoing any permanent chemical change (i.e., it gets regenerated at the end of the mechanism).
- Part of the attraction of catalysis is that a catalyst can be used in substoichiometric quantities. This is called the catalyst loading and is often expressed as a mol% value (e.g., 0.05 equiv wrt substrate = 5 mol%).

- A more active catalyst has a higher turnover number (TON - no. product molecules made per molecule of catalyst) and can typically be used at a lower loading.
- Many (non-transition metal) catalysts work simply by raising the HOMO of the nucleophile or lowering the LUMO of the electrophile, such that the reaction follows the same basic mechanism but with a lower activation barrier.
- It is also possible to catalyse reactions not by simply accelerating an existing pathway (the so-called background reaction), but by opening up a brand new pathway altogether. You will see in Year 2 that transition metal catalysts often work on this basis.

- Another attractive aspect of catalysis is that the catalyst can potentially be designed to control aspects of kinetic selectivity of the reaction, such as which regioisomer or stereoisomer (even enantiomer) is formed.

*Take-home message*: A catalyst increases the rate of a kinetically slow/unfeasible reaction without itself undergoing permanent change, so it can be utilised in small quantities. It lowers the activation barrier either by HOMO/LUMO activation of the Nu/E, or by opening up a new and mechanistically-distinct pathway. Catalysts can also potentially be used to control aspects of kinetic selectivity (e.g., regio/stereoselectivity).

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*This is particularly useful when the catalyst is very expensive (e.g., precious metal-based). However, there is nothing in the definition of a catalyst that says it must be used in substoichiometric quantities - it can in principle be equimolar to the substrate or even in excess. For that reason, the term "catalytic amount", though often used, is meaningless.
**Brønsted Acid and Base Catalysis: Catalytic proton transfer in organic reaction mechanisms**

- We have introduced the concepts of Brønsted acid or base activation and also the idea of catalysis, so it will come as no surprise that these phenomena can be combined to give us our most commonly exploited catalysis mode: Brønsted acid or base catalysis.

- There are hundreds of cases that we could exemplify, but a good example of an acid-catalysed process is the tautomerisation of ketones to their enol form. Remember that catalysts cannot change the position of equilibrium, so although the enol is formed much faster, it is still only ever present in vanishingly small amounts.

- Incidentally, keto-enol tautomerisation is also catalysed by Brønsted bases, such as hydroxide ion.*

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{OH} & \quad \text{HO}_2 \\
(>99.9\%) & \quad (<0.1\%) \\
\text{Keto form} & \quad \text{Enol form} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{OH} & \quad \text{HO} \\
\text{enolate} & \quad \text{enol form} \\
(p_{K_a} = 20) & \quad (p_{K_a} = 11) \\
\end{align*}
\]

- A great deal of organic chemistry involves the carbonyl group (as will become clear in Yr 2), and many of those reactions involve either protonation of the C=O oxygen under acidic conditions or formation of an enolate under basic conditions, so these catalysis modes are something you'll be seeing a lot more of.

- Be clear that not all reactions involving acids or bases are catalytic in these substances - many are stoichiometric and the acid/base is fully consumed in the process (e.g., addition of HBr across an alkene, reaction of NaOH with an acid chloride).

- Strictly speaking, acid/base catalysis that involves pre-equilibrium protonation or deprotonation of a molecule (to generate intermediates that are typically charged) is called specific acid/base catalysis. It differs from 'general' acid/base catalysis (see next slide).

**Take-home message:** (Specific) Brønsted acid or base catalysis involves the pre-equilibrium protonation or deprotonation to activate a substrate, immediately prior to the product-forming step. It is particularly common in the chemistry of the carbonyl group.

*This is a rare case where the quantity of catalyst (hydroxide) can influence the equilibrium, because the enol is more acidic than the keto form, and so raising the pH converts more enol to enolate than it does ketone. Le Chatelier tells us this will displace the equilibrium position further towards the enol.
**General Acid and Base Catalysis:** Catalytic acids/bases that act on the transition state rather than (de)protonate the substrate

- Though less potent than specific acid/base catalysis, catalysis with 'weak' acids/bases is possible, whereby the (de)protonation is **concerted** with the bond making/breaking steps. In essence, the catalyst serves to stabilise the TS rather than pre-activate the substrate.

- This is termed **general acid/base catalysis**, and is ubiquitous in Nature, as biology doesn't have access to harsh acids or bases. Enzymes work on this principle, pre-organising the catalytic residue and substrate to overcome the entropic barrier, and frequently using **both** general acid and base activation simultaneously.

**Take-home message:** General acid/base catalysis uses weaker acids or bases to stabilise the TS rather than pre-activate the substrate. It is most commonplace in biology, underpinning the catalytic activity of enzymes. [See advanced text for how to probe it experimentally]
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Transformation Types: A classification system based upon bonds broken and formed

- Without a means of classification, organic chemistry would just be a vast collection of seemingly isolated reactions.
- However, there are only four basic kinds of overall transformations: additions, eliminations, substitutions, and rearrangements.

- In an addition reaction, two starting materials combine to give a single product. Usually a \( \pi \)-bond in one molecule is replaced by two new \( \sigma \)-bonds:

  ![Addition Reaction](image)

- In an elimination reaction, one starting material is divided into two products. Usually two \( \sigma \)-bonds in one molecule are replaced by a new \( \pi \)-bond:

  ![Elimination Reaction](image)

- In a substitution reaction, one atom/group on a molecule is replaced with a different atom/group:

  ![Substitution Reaction](image)

- In a rearrangement reaction, one starting material gives one product with a different structure:

  ![Rearrangement Reaction](image)

Additions, eliminations, and substitutions are inclusive of reactions that change the oxidation level of the molecule (oxidations and reductions), but they can also be redox-neutral, depending on the type of bonds formed/broken. Rearrangements are inherently redox-neutral with respect to the whole molecule, but they may involve oxidation of one functional group with concomitant reduction of the other.

Some transformations constitute examples of more than one of these classes. For example, the reaction of esters with Grignard reagents gives alcohols in what is a substitution reaction and an addition reaction.
Mechanism Types: Another classification system based upon reaction mechanisms

A second way to classify reactions is according to the type of mechanism that is operative (provided it is known of course!). Although there are hundreds, if not thousands, of organic reactions, they all proceed via one of the mechanistic types shown below.*

- A polar (sometimes called an ionic) mechanism proceeds by the movement of pairs of electrons from a nucleophile (i.e., filled orbital = HOMO) to an electrophile (i.e., empty orbital = LUMO). Polar reactions are often assisted (accelerated) by either basic or acidic conditions. Most of the reactions you will meet in Year 1 fall into this class.

- A radical mechanism proceeds by the movement of single electrons, and therefore involves radicals as reactive intermediates. New bonds are often formed by the reaction of a radical with a neutral molecule. These reactions often (but not always) proceed via a chain process.

- A pericyclic mechanism proceeds via a cyclic transition state (TS) with continuous orbital overlap between all the bonds that are breaking/forming. These processes are governed by "orbital symmetry" rules that determine whether a particular process is allowed or forbidden, based on the number of electrons involved in the TS and the topology of the interacting orbitals.

- An organometallic mechanism proceeds via intermediates bearing one or more covalent bonds between carbon and a transition metal (TM). These mechanisms typically involve multiple steps, featuring changes in ligation and oxidation state of the metal, and they can often be made catalytic in the TM.** Processes involving only "polar organometallics" (i.e., those based on non-redox-active main group metals like Li and Mg) are considered as polar (ionic) reactions. You will meet organometallic mechanisms in Year 2, in the context of palladium-catalysed cross-coupling.

*Some multi-step mechanisms feature steps in more than one of these mechanistic classes. Thus, it’s possible to have multi-step reactions that involve sequential polar (ionic) and radical steps. Or sequential polar and pericyclic steps. Or metal-mediated/catalysed reactions that also involve radicals.

**Certain transition metal complexes (e.g., TiCl₄, FeCl₃) act only as Lewis acids in organic reactions, and others (e.g., TiCl₂, SmI₂) act as one-electron reducing agents like Na and Li. Reactions promoted by these compounds are classified in polar (ionic), pericyclic, or radical processes.
Choosing the appropriate **solvent** for a reaction is often critical for success. At a minimum, it must be dissolve the reactant(s) and reagent(s) and be chemically compatible with the reaction. Water is rarely ever a good choice, for both of these reasons.

Many polar solvents are incompatible with strong basic reagents (e.g., RLi, RMgBr) so the solvents of choice are almost invariably ethers (Et₂O or THF). Similarly, some solvents are incompatible with powerful acids (e.g., THF can polymerise).

Solvents can be **polar** or **non-polar** (as quantified by their **dielectric constant**, εᵣ) and either **protic** or **aprotic** (i.e., capable of H-bonding or not).

Sometimes the solvent can also be a reactant (e.g., **solvolysis reactions**).

The electrostatic attraction between separated charges (q) in a solvent of dielectric εᵣ is given by Coulomb’s law. Separated charges are more stable (i.e., interact less) in solvents with higher εᵣ. Thus, polar solvents are preferential for reactions involving charged intermediates.

\[
F = \frac{1}{4\pi\varepsilon_0\varepsilon_r} \frac{q_1q_2}{r^2}
\]

**Coulomb’s law**

**Take-home message:** The solvent is critically important for dissolving the reactant(s) and reagent(s), and it often plays either a direct or indirect role in the reaction itself (e.g., proton shuttle, provision of ion-stabilising environment). It must be chemically-compatible with the reaction (e.g., ethers are commonly used with reactive organometallics like RLi or RMgX, for example).

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*The term "hydroxylic" is also used for solvents with O–H bonds, such as water, alcohols, or acetic acid.*
Foundations of Organic Chemistry: Reactions

A. Cresswell

Organic chemists have conventions for how transformations are depicted, and which information is typically included (or omitted).

**Reaction Scheme Conventions**

- Organic chemists have conventions for how transformations are depicted, and which information is typically included (or omitted).

![Reaction Scheme](image)

**A reactant** is another term for the substrate (starting material) whereas a **reagent** is a substance (usually much lower in molecular weight) that causes a chemical change by transferring an atom/group to or from the substrate. We've already met **catalysts** (which are only relevant of course to catalytic reactions). An **additive** is a general term for something that isn't classed as a reagent but is still necessary for the reaction to proceed (e.g., an initiator that kicks off the reaction but is henceforth not involved).

- Sometimes a **sequence** of reactions is conducted where the initial product from the first step (or an intervening one) is not actually isolated but immediately reacted further by adding the next reagent(s). This may or may not involve removal of solvent and addition of a different solvent (depending on the circumstances and the stability of the entity).

- Compounds treated in this way are termed **intermediates** (not to be confused with **reactive intermediates** like carbocations or radicals, which only exist fleetingly). Square brackets are often included around intermediates to indicate that they are not isolated/purified prior to the next step. Sequences in which two or more reactions are conducted sequentially in the same flask are termed "one-pot" reactions.

**Take-home message**: Chemists have a number of conventions for how chemical transformations are drawn. Note that work-up steps (e.g., addition of a proton quench after an organometallic reaction) are often implied and not drawn in explicitly.
Revision Checklist

Revised?

- Gibbs energy of reaction ($\Delta_r G$) and the standard Gibbs energy of reaction ($\Delta_r G^0$); condition for spontaneity ($\Delta_r G < 0$) and equilibrium ($\Delta_r G = 0$); relationship of $\Delta G$ to $\Delta H$ and $\Delta S$

- Equilibria, including equilibrium constants ($K$), Le Chatelier's principle, and driving reversible reactions to completion

- Gibbs energy of activation ($\Delta G^\ddagger$) and rate constants ($k$), and the negative exponential relationship between the two

- Kinetic stability

- Reversible and irreversible reactions; thermodynamic and kinetic control; kinetic selectivity (for two product reaction)

- Intermediates in multi-step reactions; isolable versus reactive intermediates

- Rate-determining step (RDS) and its conceptual flaws; the Hammond postulate

- Frontier molecular orbital (FMO) theory (revisited)

- Brønsted acid or base activation (LUMO-lowering or HOMO-raising); importance in catalysis

- Transformation types (substitution, elimination, addition, rearrangement)

- Mechanism types (polar/ionic, radical, pericyclic, and organometallic)

- Organic solvents; polar vs non-polar solvents; protic vs aprotic solvents; importance of compatibility with reactants

- Conventions for drawing organic reaction schemes