6. Acids & Bases
Proton Transfer Equilibria: The simplest chemical reactions, and the underpinning of Brønsted acid/base catalysis

- Proton transfer equilibria are among the simplest of all chemical reactions and play a decisive role in countless synthetic and biosynthetic transformations.

- Protonation or deprotonation of functional groups in organic molecules is a fundamental means of activating such molecules toward chemical reactions.

- This activation mode underpins Brønsted acid and Brønsted base catalysis – the most common catalytic paradigm in organic chemistry (and certainly in biochemistry).

- The theory of acids and bases originated in 1884 from Arrhenius, and was later refined and generalised by Brønsted and Lowry in 1923:

  - A Brønsted acid is a molecule or ion that serves as a proton (H⁺) donor.*
  - A Brønsted base is a molecule or ion that serves as a proton (H⁺) acceptor.

- Following this definition, an acid-base reaction is as follows:

  $\text{A} + \text{H}^+ + \text{B} \rightleftharpoons \text{A}^+ + \text{H}^+ \text{B}^-$

  Where:
  - $\text{A}$ is an acid.
  - $\text{B}$ is a base.
  - $\text{A}^+$ is the conjugate acid.
  - $\text{B}^-$ is the conjugate base.

Take-home message: A Brønsted acid-base reaction involves the transfer of a proton (H⁺) from one molecule to another. Protonating or deprotonating a functional group on an organic molecule can dramatically increase chemical reactivity, and this is the basis for Brønsted acid or base catalysis.

*Although the species liberated by the acid is formally a H⁺ ion (hydrogen ion or proton), the species actually present in aqueous solution is the hydronium ion, H₃O⁺. In reality, a proton is bound to several H₂O molecules, such that other formulas such as H₅O₂⁺, H₇O₃⁺ and H₉O₄⁺ are increasingly accurate descriptions of the environment of a proton in water.
Quantifying Brønsted Acidity of A Solution: The pH scale

- The pH scale, formulated independently by Hans Friedenthal in 1904 and by Søren Sørensen of the Danish Carlsberg Laboratories in 1909, provides a quantitative measure of the proton concentration, [H⁺], in solution.

  \[ \text{pH} = -\log_{10}[H^+] \]

- Because the equation features the negative of the logarithm, a smaller (or more negative) pH denotes a higher [H⁺] concentration.

- In aqueous solution, the [H⁺] concentration is related to the [OH⁻] concentration by the self-ionisation constant of H₂O in water (often referred to, somewhat mysteriously, as the "ionic product of water" and given a unique symbol \( K_w \) – see below).

- Recall that equilibrium constants are strictly defined in terms of activities, \( a_X \), and that only very dilute species can be approximated by their molar concentration. This does not apply to the bulk solvent, and the activity of pure water is defined as unity (i.e., 1).*

\[
\begin{align*}
\text{H}_2\text{O} + \text{H}_2\text{O} & \leftrightharpoons \text{OH}^- + \text{H}_3\text{O}^+ \\
K_w &= \frac{a_{\text{OH}^-} a_{\text{H}_3\text{O}^+}}{(a_{\text{H}_2\text{O}})^2} \\
&\approx \frac{[\text{OH}^-] [\text{H}_3\text{O}^+]}{(a_{\text{H}_2\text{O}})^2} = [\text{OH}^-] [\text{H}_3\text{O}^+] = 1.0 \times 10^{-14} \quad \text{(at 298 K)}
\end{align*}
\]

- The pH of an aqueous solution is defined as neutral when \([\text{OH}^-] = [\text{H}_3\text{O}^+]\), giving a pH of 7 at 298 K (derived from \( K_w = 1.0 \times 10^{-14} \)).

- The pH of an aqueous solution is defined as acidic when the pH is <7 ([OH⁻] < [H₃O⁺]) and alkaline when the pH is >7 ([OH⁻] > [H₃O⁺]).

**Take-home message**: The pH value of an aqueous solution defines the H⁺ (strictly H₃O⁺) ion concentration present. The so-called "ionic product of water", \( K_w \), is the self-ionisation constant of H₂O in water that determines how much free H₃O⁺ is present when \([\text{OH}^-] = [\text{H}_3\text{O}^+]\). When the [OH⁻] and [H₃O⁺] concentrations are not equal to one another, the solution is either acidic (high [H₃O⁺]) or alkaline (high [OH⁻]).

*Contrary to what many textbooks show, \( K_w \) is dimensionless (no units of mol² dm⁻₆). This is because each activity/concentration term in an equilibrium constant is actually divided by the activity/concentration of its standard reference state (e.g., 1.0 mol dm⁻³ for a standard solution). This is also why the activity of a pure substance is defined as unity, because you are dividing its reference state activity by its reference state activity. Many chemists forget this!
Quantifying Brønsted Acidity of A Molecule: The $pK_a$ scale

- Relative (thermodynamic) acidities of different acids in a given solvent may be defined by measuring the extent of reaction that each acid undergoes with a common base.

- Typically, the base selected also doubles as the reaction solvent. $H_2O$ is often the choice of base/solvent, except when measuring the strength of very strong or very weak acids (see later).

- For an acid, $HA$, its strength (in $H_2O$) is defined by the extent of deprotonation by $H_2O$ (in $H_2O$ as the solvent) and is given by the acidity constant (or acid dissociation constant), $K_a$. The stronger the acid, the larger (more positive) the $K_a$ value.

$$HA + H_2O \overset{K_a}{\leftrightarrow} A^- + H_3O^+ \quad K_a = \frac{[A^-][H_3O^+]}{[HA]a_{H_2O}}$$

where $a_{H_2O} = 1$

- Variation in the order of magnitude of $K_a$ values is staggering: values ranging from about $10^{-60}$ to $10^{15}$ are known! To make the numbers more manageable, acid strengths are normally quoted as $pK_a$ values where:

$$pK_a = -\log_{10}K_a$$

- Note that stronger acids have smaller (or more negative) $pK_a$ values than weaker acids.

Take-home message: The Brønsted acidity of a molecular species is quantified by its acidity constant (acid dissociation constant), $K_a$. Remember that $K_a$, as for any equilibrium constant, is dimensionless, and be careful not to make the common error of including $[H_2O] = 55$ mol dm$^{-3}$ in the calculation.* A much more convenient (compressed) scale than $K_a$ is to use $pK_a$ values (in a given solvent).

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*It is a very common error, even in many textbooks, to use the molar concentration of water (55.5 M) in the $K_a$ calculation, leading to incorrect $K_a$ values. At such a high concentration, we must use the activity of $H_2O$, and for pure $H_2O$ this is defined as unity (i.e., 1) (see J. Chem. Educ. 2005, 82, 999).

**This is a greater span than that encompassed by distance measurements starting from the radius of a hydrogen atom and extending to the diameter of the known universe!
**Enthalpic and Entropic Contributions to X–H Acidity**

- There are two main contributions to the Gibbs free energy change, $\Delta G^\circ$, for the loss of a proton from a molecule by heterolytic cleavage of an X–H bond:

  - **Enthalpic contribution**, $\Delta H^\circ$, consisting of:
    - Loss in bond enthalpy* due to cleavage of the X–H bond (always endothermic)
    - Enthalpy of anion formation, which can be further partitioned into the intrinsic stability of the anion $X^-$ (in the gas phase), plus the solvation enthalpy of the anion (this can be endothermic or exothermic, depending on whether the medium stabilises or destabilises charged intermediates relative to neutral ones)**

  - **Entropic contribution**, $\Delta S^\circ$, due to change in the entropy (order) of the system, and this is usually dominated by entropically-unfavourable solvent-ordering (see right). For example, solvation of an ion leads to organisation of solvent molecules around the charged centre. Another cause of solvent-ordering is the "hydrophobic effect", in which water molecules form an ordered ‘cage-like’ structure around a hydrocarbon residue.

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**Take-home message**: The acidity ($pK_a$) of a molecule X–H is governed by a balance of enthalpic factors (i.e., anion stability, anion solvation) and entropic factors (i.e., solvent-ordering). Note that both of these factors are sensitive to the medium (solvent), which is why $pK_a$ values themselves are highly solvent-sensitive (i.e., $pK_{a,H_2O} \neq pK_{a,DMSO}$).

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*Bond enthalpies (or "bond dissociation energies", BDEs) are always for homolytic cleavage, because heterolytic cleavages are so sensitive to the medium (due to separation of charge) that it would be impossible to tabulate a single value for a given bond. Of course, the mechanism of proton loss does not actually involve radical intermediates, but as the Gibbs energy is a state function, it is perfectly valid to hypothetically partition it into values for homolytic fission followed by generation of charged species (via an electron transfer).

**If the acidic species is already charged (e.g., a hydronium ion, $H_3O^+$), we must consider whether the medium stabilises a neutral species more than a charged one; the arguments are identical, simply applied in reverse.
**Shorthand Icons for Stabilising and Destabilising Effects**

- There are often multiple different effects influencing X–H acidity, sometimes in an opposing manner, so I will employ shorthand icons throughout these slides to give a visual summary of the effects involved, and their influence on $\Delta H^\circ$ and $\Delta S^\circ$ for ionisation.

- Inductive (I) and mesomeric (M) effects:

  - Inductive (I) and mesomeric (M) effects:

    - Inductive effect (I):
      
      $\Delta H_{\text{stab}} \leftarrow X$

    - Mesomeric effect (M):
      
      $\Delta H_{\text{stab}} \leftarrow X$

- Field effects* (with an induced or permanent dipole):

  - Field effects:

    - Dipole stabilisation:
      
      $\Delta H_{\text{stab}} \leftarrow X$

- Solvation effects:

  - Solvation effects:

    - Hydrophobic effect on solvation:
      
      $\Delta H_{\text{sol}} \leftarrow X$

    - Effect of electronegative group on solvation:
      
      $\Delta H_{\text{sol}} \leftarrow X$

    - Effect of charge delocalisation on solvation:
      
      $\Delta S_{\text{sol}} \leftarrow X$

* A "field effect" is a repulsive or attractive electrostatic interaction that occurs *through space* in a molecule. It is often impossible to separate out the inductive (through bond) and field effect (through space) contributions for electronegative groups.
Across a period the acidity of X–H bonds increases because:

- Electronegativity (EN) increases, so the conjugate base anions X– become more stable.
- Charge density of the conjugate base anions X– does increase slightly, lowering the acidity of the X–H species,* but the increase is outweighed by increasing EN because covalent radii do not vary greatly across a p block period.
- X–H bond strength does increase, but the increase is not sharp and this trend is outweighed by the increasing stability of the conjugate base anion X–.

Down a group the acidity of X–H bonds increases because:

- X–H bond strength decreases markedly down a group, much more so than across a period.
- Charge density of the conjugate base anions X– decreases sharply as the covalent radii increase, raising the acidity of the X–H species.*
- Electronegativity does decrease, but this is outweighed by the above two factors.

**Take-home message:** Increasing EN is the dominant factor across a period and this causes the acidity of X–H bonds to increase, despite steadily increasing X–H bond strengths and charge densities. Thus, counterintuitively, the strongest acids also have the strongest bonds (H–O 111 kcal mol⁻¹ and H–F 135 kcal mol⁻¹). Down a group, the significant decrease in bond strength coupled with decreasing charge density causes the acidity of X–H bonds to increase, despite decreasing electronegativity. Thus, alcohols (O–H) are considerably less acidic than the corresponding thiols (S–H).

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*Ignoring solvation effects, an ion with a lower charge density is more stable than one with a higher charge density, as the charge is more diffuse and internal electrostatic repulsive forces are smaller. However, in an anion-stabilising solvent such as water, the enthalpy of solvation becomes more favourable as charge density increases, so might this cancel out the other effect? It turns out not, because as charge density increases, the solvent molecules become more tightly bound, increasing the solvent-ordering and decreasing the entropy of the system. This entropic effect is perhaps the dominant reason why lower charge densities are favoured in solution.
Effect of Electronegative Groups on $X$-$H$ Acidity: Is it as simple as just the inductive effect?

- Electronegative atoms/groups increase the acidity of nearby $X$-$H$ bonds, as demonstrated by the $pK_a$ data for ionisation of halogenated carboxylic acids in water. Note that the effect drops off quickly as the number of intervening $\sigma$-bonds increases.

<table>
<thead>
<tr>
<th>$pK_a$ (in $H_2O$)</th>
<th>4.8</th>
<th>4.5</th>
<th>4.0</th>
<th>2.9</th>
<th>1.3</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="MeCOOH" /></td>
<td><img src="image" alt="ClCOOH" /></td>
<td><img src="image" alt="ClCOOH" /></td>
<td><img src="image" alt="ClCOOH" /></td>
<td><img src="image" alt="ClCOOH" /></td>
<td><img src="image" alt="ClCOOH" /></td>
<td><img src="image" alt="ClCOOH" /></td>
</tr>
</tbody>
</table>

The usual explanation is that dispersal of the negative charge onto more electronegative atoms by the inductive effect (−I) is enthalpically-stabilising, but we must also consider solvation.*

Dispersing the negative charge reduces the enthalpic gain from solvation by $H_2O$, and this almost cancels the intrinsic enthalpic gain from the −I effect. Thus, $\Delta H^o \sim 0$ for ionisation of carboxylic acids, regardless of substituents (see table).

- However, the dispersal of the negative charge also helps to minimise entropically-unfavourable solvent-ordering, and so the main contribution to the acidity trend turns out to be entropic.

**Take-home message**: Inductively-withdrawing (−I) atoms/groups increase the acidity of nearby $X$–$H$ bonds. Though often attributed to enthalpic stabilisation of the negative charge (electrostatics), solvation of the anion by $H_2O$ must be considered. At least for protic solvents like $H_2O$, the data indicate that the entropic contribution due to solvent-ordering is likely the major contributor to the observed trends.

*"Actual effects controlling the acidity of carboxylic acids" J. Chem. Ed. 1971, 48, 338
Effect of Alkyl Groups on X–H Acidity: Again, is it as simple as just the inductive effect?

- Alkyl substitution decreases the acidity of nearby X–H bonds, as demonstrated by the $pK_a$ data for ionisation of carboxylic acids in water.
- The usual textbook explanation is that alkyl groups are more inductively-donating (+I) than hydrogen, despite the fact that carbon has a higher electronegativity than hydrogen (2.55 vs 2.20). It is reasoned that carbon draws some electron density from its attached hydrogens, so that it bears a very slight negative charge. This would then lead to electrostatic repulsion with the anionic centre.
- However, alkyl substitution has been found to increase the acidity of carboxylic acids in the gas phase,* which has been ascribed to a field effect. Carbon atoms are more polarisable than hydrogen atoms, and an induced dipole can stabilise the adjacent negative charge.
- Alkyl groups also exert a weak +M mesomeric effect via hyperconjugation (from C–H or C–C bonds). For carboxylic acids, this effect is more stabilising when the carboxyl group is in the un-ionised form (i.e., $\pi^+\text{C}=\text{O}$ is lower in energy), so it enthalpically discourages ionisation.
- Finally, increased alkyl substitution leads to a hydrophobic effect that lowers the solvation enthalpy. Moreover, the H$_2$O molecules form an ordered 'cage-like' structure around the alkyl chain, and this solvent-ordering becomes increasingly entropically-disfavourable.**

<table>
<thead>
<tr>
<th></th>
<th>$\Delta H^\circ$</th>
<th>$-T\Delta S^\circ$</th>
<th>$\Delta G^\circ$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–CO$_2$H</td>
<td>+0.1</td>
<td>-1.45</td>
<td>-1.38</td>
<td>3.75</td>
</tr>
<tr>
<td>Et–CO$_2$H</td>
<td>-0.6</td>
<td>+0.7</td>
<td>+0.08</td>
<td>4.82</td>
</tr>
<tr>
<td>Me–CO$_2$H</td>
<td>-0.7</td>
<td>-0.8</td>
<td>+0.12</td>
<td>4.85</td>
</tr>
<tr>
<td>Me–Me–CO$_2$H</td>
<td>-0.6</td>
<td>+1.0</td>
<td>+0.37</td>
<td>5.03</td>
</tr>
</tbody>
</table>

*“Acidities of substituted acetic acids” J. Mol. Struct. THEOCHEM 1988, 168, 141
Effect of Hybridisation on X–H Acidity: Electronegativity (and the inductive effect) is highly sensitive to atomic hybridisation

- Another factor influencing X–H bond acidity is the hybridisation of the X atom. The higher the %-s character of the X hybrid orbital involved in bonding to the acidic H atom, the more acidic that proton is (or rather, the more stable the conjugate base).

- This effect is rather powerful and has its origins in the fact that s orbitals are more penetrating than p orbitals (see radial distribution functions), and so hybrids with a higher %-s character are exposed to a larger percentage of the nuclear charge.

<table>
<thead>
<tr>
<th>X–H hybrid</th>
<th>C(sp)–H</th>
<th>C(sp²)–H</th>
<th>C(sp².4)–H</th>
<th>C(sp³)–H</th>
<th>N(sp)–H</th>
<th>N(sp²)–H</th>
<th>N(sp³)–H</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKₐ (H₂O)</td>
<td>24–25</td>
<td>41–50</td>
<td>44–46</td>
<td>47–48</td>
<td>−10</td>
<td>5.2</td>
<td>10.7</td>
</tr>
</tbody>
</table>

- Note how (relatively) easy it is to deprotonate the terminal C–H bond of an alkyne. This is usually done with BuLi or EtMgBr and the corresponding acetylide anions are very useful carbon nucleophiles for forming C–C bonds (as you’ll see later in the course).

- Thus, an atom’s electronegativity is not a fixed value for that element - it is related to the atom’s hybridisation.

- This is also manifested in the inductive effect (−I), with the σ-electron-withdrawing power following the trend sp > sp² > sp³.

<table>
<thead>
<tr>
<th></th>
<th>pKₐ (H₂O)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C≡CHOH</td>
<td>13.6</td>
<td>C≡CHOH</td>
<td>MeC≡CHOH</td>
<td>MeC≡CO₂H</td>
</tr>
<tr>
<td></td>
<td>15.5</td>
<td></td>
<td>16.1</td>
<td>2.59</td>
</tr>
<tr>
<td></td>
<td>16.1</td>
<td></td>
<td></td>
<td>4.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.82</td>
</tr>
</tbody>
</table>

Take-home message: The higher the %-s character of the X hybrid orbital involved in bonding to an acidic H atom, the more acidic that proton is. The inductive effect of an atom also increases significantly along the series sp > sp² > sp³.
Effect of Heavier p-Block Elements on X–H Acidity

- Second-row p-block elements (or those in the third or fourth row) can weakly stabilise an \( \alpha \)-carbanion, such that \( \alpha \)-C–H bonds are acidified to varying degrees. For heteroelements at their lowest oxidation level (e.g., sulfides, phosphides) the effect is not that dramatic, but two such groups can have a quite significant effect on C–H acidity (e.g., dithioacetals).

\[
\begin{array}{cccc}
\text{CH}_4 & \text{MeS} \text{H} & \text{SSS} & \text{H} \\
pK_a (\text{in DMSO}) & \sim 56 & 45 & 39 \\
\end{array}
\]

- Early explanations for this phenomenon suggested interaction of the carbanion with an empty 3\(d\) orbital on the adjacent heteroatom (see right), but high-level calculations show that 3\(d\) orbitals are simply too high in energy for any efficient interaction.

- A better explanation is based on the polarisability of the valence electron clouds in heavier elements.*

- Induced dipoles in readily-polarisable atoms adjacent to a localised negative charge can give rise to quite significant stabilisation (field effect) and this can dwarf the effect of inductive stabilisation based on electronegativity. Consider the relative acidities of iodoform and fluoroform (below).

\[
\begin{array}{cccc}
\text{H} & \text{I} & \text{H} & \text{F} \\
pK_a & 22.5 & 30.5 \\
\end{array}
\]

\(pK_a\) values measured in CyNH\(_2\); see: *J. Am. Chem. Soc.* 1976, 98, 5229

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However, polarisability is clearly not the whole story. Those $\alpha$-C–H bonds that are aligned antiperiplanar to an X–C bond (where X is the heavy $p$-block element) are significantly more acidic than those that are gauche (see right).

This is another example of a stereoelectronic effect - a phenomenon in which molecular stability or reactivity is contingent on the alignment of two or more orbitals.

The stabilisation arises due to donation of the carbanion electron pair into the X–C $\sigma^*$ antibonding orbital (see below). This is an example of negative hyperconjugation ($\sigma$-conjugation) and can be classified as a (weak) $\text{M}^{\text{mesomeric effect}}$.

If so, why is this effect not operative with first-row elements, where X = N or O, for example? Aren’t these more electronegative than second-row elements, which ought to lower the X–C $\sigma^*$ energy?

The reason is that the orbitals of heavier elements overlap much less well with C than first-row elements, so there is less interaction and the X–C $\sigma^*$ antibonding orbital is not raised as high in energy (see earlier lectures on "Orbitals").

**Take-home message**: Second-row $p$-block elements (or those in the third or fourth row) can partly stabilise an $\alpha$-carbanion, such that $\alpha$-C–H bonds are acidified to varying degrees. For heteroelements at their lowest oxidation level (e.g., sulfides, phosphides) the effect is not that dramatic, but two such groups can have a quite significant effect on C–H acidity (e.g., dithioacetals). Polarisability effects provide one explanation, but there is also a contribution from a stabilising $n_C \rightarrow \sigma^*_{X–C}$ mesomeric ($\text{M}^{\text{mesomeric}}$) effect.

"A theoretical analysis of the factors determining the conformations and stabilities of oxy- and thiocarbanions" J. Am. Chem. Soc. 1976, 98, 5435

Effect of $\pi$-Conjugation with C-Type Groups on X–H Acidity: Moderate anion-stabilisation

- As you saw in the "Conjugation" notes, groups such as phenyl or vinyl can stabilise cations, anions, or radicals by exerting a moderate mesomeric effect (either $\pm M$ or $-M$). These "electronically-flexible" groups are sometimes termed C-type substituents.

- C-type substituents like phenyl groups stabilise anions by a $-M$ mesomeric effect (i.e., interaction of the anion lone pair with an empty $\pi^*$ orbital), but this is much weaker than for $\pi$-acceptor Z-groups (see later). There is also an entropic benefit from reduced solvent-ordering that accompanies negative charge delocalisation.

- The $sp^2$-hybridised carbon of the C-type group also exerts a substantial inductive ($-I$) effect, which further stabilises the anion.

Incidentally, the $pK_a$ of acetone enol is almost identical to phenol. This shows that the number of resonance forms you can draw does not necessarily determine the anion stability (and note that all but one of the above phenolate anion resonance forms disrupts aromaticity).

Take-home message: C-type conjugating groups (e.g., phenyl, vinyl) exert only a moderate $-M$ effect on anions, but they do exhibit a fairly strong inductive ($-I$) effect (due to $sp^2$ carbon), so together this makes them moderately acidifying. As always with conjugation, some degree of charge delocalisation reduces unfavourable solvent-ordering, but this may not be significant for the phenolate anion.
Effect of Aromaticity on $X-H$ Acidity

- You will study aromaticity in more detail in semester 2, but you can think of it for now as a 'special' stabilisation of cyclic conjugated molecules with $4n+2$ $\pi$-electrons.
- If the conjugate base of an acid is aromatic, the p$K_a$ value is significantly lowered.
- For this reason, cyclopentadiene ($pK_a = 15$ in $H_2O$) is almost as acidic as water itself, despite it being a hydrocarbon!
- On the other hand, if the conjugate base is anti-aromatic* (i.e., cyclic with $4n$ $\pi$-electrons), the p$K_a$ value is significantly raised.

<table>
<thead>
<tr>
<th></th>
<th>$pK_a$ (in $H_2O$)</th>
<th>$6\pi$ electrons</th>
<th>$8\pi$ electrons</th>
<th>$4\pi$ electrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>H H</td>
<td>15</td>
<td>aromatic</td>
<td>anti-aromatic</td>
<td>anti-aromatic</td>
</tr>
<tr>
<td>H H</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H H</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This aromaticity effect can explain the surprisingly high acidity of some molecules relative to closely-related compounds (see right).

<table>
<thead>
<tr>
<th></th>
<th>$pK_a$ (in DMSO)</th>
<th>$14\pi$ electrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>H H</td>
<td>32</td>
<td>aromatic</td>
</tr>
<tr>
<td>H H</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>H H</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Take-home message:** If the conjugate base of an acid is aromatic, the p$K_a$ value is significantly lowered. On the other hand, if the conjugate base is anti-aromatic (i.e., cyclic with $4n$ $\pi$-electrons), the p$K_a$ value is significantly raised.

*You likely haven't yet met the concept of "anti-aromaticity". Leaving aside the fact that it is a controversial idea, the basic premise is that it is essentially the opposite to aromaticity (i.e., special destabilisation as opposed to stabilisation). You will learn more about it in semester 2.
**Effect of \( \pi \)-Conjugation with Z-Type Groups on X–H Acidity: Strong anion-stabilisation**

- One of the best ways to stabilise the anion of a deprotonated molecule is to conjugate it with a Z-type substituent, such as a carbonyl, cyano, or nitro group (see below). Such groups exert a strong \(-M\) mesomeric effect and also a strong \(-I\) inductive effect. You can think of Z-groups a bit like an electron pair "sink".

- The \(-M\) effect is so strong because the (empty) \( \pi^* \)-orbital of the Z-group is inherently low in energy for an antibonding orbital, so the filled-empty orbital interaction with the anion lone pair is particularly strong (see MO scheme below right).

- For efficient conjugation, rehybridisation of the anionic centre from \( sp^3 \) to \( sp^2 \) is required for good overlap with the \( \pi^* \)-orbital of the stabilising group. You saw the same phenomenon with heteroatom lone pairs (e.g., amines vs amides) in the "Conjugation" lectures.

- Delocalisation of the negative charge serves to reduce the charge density and thus minimises entropically-unfavourable solvent-ordering.

- The effect of multiple Z-groups attached to the anion is cumulative, so two Z-groups are far more acidifying than one (see box on left).

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**Take-home message:** Electron-withdrawing Z-type groups (e.g., carbonyl, cyano, nitro) exert both a strong \(-M\) effect and a strong \(-I\) effect, so they greatly increase the acidity of adjacent C–H bonds. Delocalisation again reduces unfavourable solvent-ordering.
Stereoelectronic Requirement for C–H Deprotonation \( \alpha \) to Z-Groups: Orbital alignment is crucial

- **Stereoelectronics** is the term for the dependence of a molecule’s stability or reactivity on the spatial alignment of two (or more) of its orbitals. It is couched in the fact that orbital-orbital interaction – be it stabilising or destabilising – is at its strongest when overlap between the interacting orbitals is maximised.

- This is a key consideration in virtually all chemical reactions (and is the subject of a dedicated lecture series in Yr 2), and **deprotonation** reactions are no different.

- When a C–H bond is conjugated with an anion-stabilising Z-group, the stereoelectronic requirement for C–H deprotonation is precisely the same as that for **hyperconjugation** - the \( \alpha \)-C–H bond must overlap with the \( \pi^* \) orbital of the Z-group.

- If it is difficult or even impossible for this alignment to occur, based on the structure of the molecule, then the C–H bond will exhibit very low (or even no detectable) C–H acidity.

\[
\text{Take-home message:} \quad \text{During a C–H deprotonation, there is a strong stereoelectronic requirement for alignment of the C–H \( \sigma \)-bonding orbital with the \( \pi^* \) orbital of the conjugated, anion-stabilising group. If it is difficult or even impossible for this alignment to occur, based on the structure of the molecule, then the C–H bond will exhibit very low (or even no detectable) C–H acidity.}
\]
**Effect of Cationic or Higher Oxidation Level S- or P-based Z-Type Groups on X–H Acidity**

- Cationic or higher oxidation level S- or P-based groups are also effective Z-type groups.

The usual bases employed to deprotonate α-C–H bonds of \( pK_{a,DMSO} > 20 \) are what we would call 'strong' bases - things like \( t\)-BuOK or LDA (see above right). Also common are NaH and BuLi, both of which are much stronger than theoretically necessary (overkill?) but they have the advantage of producing inert, gaseous by-products (i.e., \( H_2 \) or butane) - what you might call "clean" deprotonations.

- **Inductive (I) and field effects** play a significant role in C–H acidity of these compounds, but negative hyperconjugation \((n_C \rightarrow \sigma^*)\) also contributes (a \(-M\) effect). In the case of sulfones, the significant interaction is \( n_C \rightarrow \sigma^*_{S-C} \) (see *Tetrahedron* 2015, 71, 9061).

**Take-home message:** Phosphine oxides, sulfoxides, and sulfones are effective Z-type groups, albeit to a lesser degree than carbonyl groups of ketones. The origin of stabilisation is a mixture of inductive, field, and mesomeric (negative hyperconjugation) effects. Cationic sulfonium or phosphonium groups are even more acidifying on α-C–H bonds.
**Effect of \( \pi \)-Conjugation with X-Type Groups on X–H Acidity:** Either anion-destabilising or moderately anion-stabilising

- The influence of X-type substituents on the acidity of conjugated C–H (or X–H) bonds is more complex than for Z- or C-type groups.
- It depends on whether the X-type group is a strong or a weak \( \pi \)-donor (\(+M\) effect) and also on its inductive effect (\(-I\)).
- A \(+M\) effect towards the lone pair of a conjugate base anion is **destabilising**, because it is a repulsive 4-electron interaction.

### Strong \( \pi \)-donor, electronegative X-type groups (\(X = OR, NR_2\))

![Diagram](image)

- However, the \(-I\) effect for electronegative X-type groups (i.e., heteroatoms) has a **stabilising** influence.
- Thus, the effect of a conjugated X-group on acidity will depend on whether it is remote or proximal (see right).
- Note that the opposing weak \(+M\) and strong \(-I\) effects of a \(p\)-F group on a benzene ring essentially cancel one another out.

### Weak \( \pi \)-donor, electronegative X-type groups (e.g., \(X = F, Cl, Br, I\))

- Acidity

### Weak \( \pi \)-donor, non-electronegative X-type groups (e.g., \(X = Me, Et\))

- Acidity

<table>
<thead>
<tr>
<th>pK(_a) values (in DMSO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X = H), 18.0</td>
</tr>
<tr>
<td>(X = F), 18.0</td>
</tr>
<tr>
<td>(X = Me), 18.9</td>
</tr>
<tr>
<td>(X = OMe), 19.1</td>
</tr>
<tr>
<td>(X = NMe_2), 19.8</td>
</tr>
<tr>
<td>(X = H), 25</td>
</tr>
<tr>
<td>(X = NMe_2), 24</td>
</tr>
<tr>
<td>(X = OMe), 23</td>
</tr>
<tr>
<td>(X = F), 22</td>
</tr>
</tbody>
</table>

**Take-home message:** The effect of X-type substituents on the acidity of conjugated C–H (or X–H) bonds depends on the identity of the X-type group, and whether it is remote or proximal. They generally decrease acidity, but a strong inductive effect can override this.
**Effect of Solvent on X–H Acidity**

- In the ionisation of an acid in solution, the acid donates a proton to the medium. The more basic the medium, the larger the dissociation constant ($K_a$). The ability of the medium to stabilise the conjugate base also plays an important role in the promotion of ionisation (i.e., ion-dipole interactions, dielectric constant).

- **Acids are normally stronger in H₂O than DMSO** (i.e. the $pK_a$ values in H₂O are lower, or more negative) because H₂O has a higher dielectric constant and can solvate anions by hydrogen-bonding, whereas anions in DMSO are largely unsolvated (“naked”) and therefore more basic (see right, and values below).*

<table>
<thead>
<tr>
<th>Substrate</th>
<th>DMSO</th>
<th>H₂O</th>
<th>$\Delta pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>31.2</td>
<td>14.0</td>
<td>17.2</td>
</tr>
<tr>
<td>MeOH</td>
<td>29.0</td>
<td>15.3</td>
<td>13.7</td>
</tr>
<tr>
<td>PhCOMe</td>
<td>24.6</td>
<td>17.0</td>
<td>7.6</td>
</tr>
<tr>
<td>PhOH</td>
<td>18.0</td>
<td>9.9</td>
<td>8.1</td>
</tr>
<tr>
<td>MeNO₂</td>
<td>17.2</td>
<td>10.0</td>
<td>7.2</td>
</tr>
<tr>
<td>H₂S</td>
<td>14.7</td>
<td>7.0</td>
<td>7.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>DMSO</th>
<th>H₂O</th>
<th>$\Delta pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.1</td>
<td>16.0</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>16.4</td>
<td>13.3</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>13.3</td>
<td>8.9</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>11.1</td>
<td>11.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

- An increase in anion size (e.g., HO⁻ vs HS⁻) or delocalisation of the negative charge lessens the $pK_a$ difference between DMSO and H₂O, because hydrogen-bonding by H₂O is most effective when the anion charge density is high (see left).

- For acids stronger than H₃O⁺ or weaker than H₂O, $pK_a$ values in water as the medium cannot be determined directly. Values outside the 0–16 value range are extrapolated (estimated).

- DMSO (or sometimes other aprotic solvents like MeCN or THF) are typically used to measure $pK_a$ values of weaker acids (in the value range 0–33 for DMSO).

**Take-home message**: $pK_a$ values are highly sensitive to the identity of the solvent, with most reported values given in H₂O or DMSO. In general, acids are stronger in H₂O than DMSO due to a higher dielectric constant (78 vs 47) and anion solvation by hydrogen-bonding, but the effect is weaker for less charge-dense anions (e.g., delocalised). Always use or compare $pK_a$ values in the appropriate solvent!

*The same reasoning accounts for the lower nucleophilicity of anions (e.g., F⁻) in H₂O as opposed to non-protic solvents like DMSO.
Effect of Intramolecular Hydrogen-Bonding on X–H Acidity

- Compared with benzoic acid ($pK_a = 4.2$ in $H_2O$), the meta and para isomers of hydroxybenzoic acid and benzenedicarboxylic acid display expected changes in acidity, due to combined inductive and mesomeric effects.

- However, the ortho isomers are both ~15 times more acidic, even through the hydroxyl and carboxyl substituents have opposite influences in the para-location.

Intramolecular hydrogen bonding of an ortho OH donor to the carbonyl oxygen of the -CO$_2$H group, acting as an acceptor, increases the acidity of the carboxyl OH. This is illustrated on the right for salicylic acid.

This intramolecular hydrogen bonding also explains the decreased acidity of the remaining acidic function (i.e., the phenolic OH in salicylic acid and the second carboxyl group in phthalic acid).

Take-home message: In some cases, intramolecular hydrogen bonding can perturb the acidity of functional groups such as carboxylic acids. You can think of this as being akin to an intramolecular ‘solvation’ effect.
Quantifying Brønsted Basicity: The $pK_{bH}$ scale

- By analogy to the $pK_a$ scale for acids, relative (thermodynamic) basicities of different bases in $H_2O$ may be quantified using $pK_b$ values, which measure the extent of deprotonation of $H_2O$ (in $H_2O$ as the solvent):

$$K_b = \frac{[BH^+] [OH^-]}{[B] a_{H_2O}} \quad \text{where} \quad a_{H_2O} = 1 \quad \Rightarrow \quad pK_b = -\log_{10}K_b$$

- Stronger bases have smaller (or more negative) $pK_b$ values than do weaker bases. Simple algebra shows that the $pK_b$ of a given base in $H_2O$ can be related to the $pK_a$ of its conjugate acid, the $pK_{aH}$, by the ionic product of water, $K_w$ (see right).

- Organic chemists almost invariably report basicity using $pK_{aH}$ values, as this means that we only need to learn one scale (i.e., $pK_a$)! Stronger bases have higher (or more positive) $pK_{aH}$ values than weaker bases (i.e., a protonated strong base holds 'tightly' to its proton).

- A given deprotonation reaction will only be favoured if the $pK_{aH}$ of the base is more positive than the $pK_a$ of the acid. If $pK_{aH}(\text{base}) >> pK_a(\text{acid})$ the deprotonation will be irreversible.

- To calculate the order of magnitude of the equilibrium constant for an acid-base reaction, use the following equation:

$$K_{eq} = 10^{[pK_{aH}(\text{base}) - pK_a(\text{acid})]}$$

**Take-home message:** Organic chemists normally report basicity using $pK_{aH}$ values, rather than $pK_b$. A given deprotonation will only be favoured if the $pK_{aH}$ of the base is more positive than the $pK_a$ of the acid. If $pK_{aH}(\text{base}) >> pK_a(\text{acid})$ the deprotonation will be irreversible.

Be careful with amphoteric molecules (e.g., amines, alcohols) which can be either protonated or deprotonated. For example, the $pK_a$ of ammonia (which describes its deprotonation to the amide anion, $NH_2^-$) is 38, whereas its $pK_{aH}$ (which describes the deprotonation of its conjugate acid, the ammonium ion, $NH_4^+$) is 9.2. Annoyingly, chemists sometimes (incorrectly) refer to the $pK_{aH}$ of a base as its $pK_a$. 
Amines as Bases: Effect of alkyl substituents, electronegative groups, and hybridisation on amine basicity

- We have seen that X–H bond acidity is perturbed by alkyl substituents (decreased acidity) and also by electronegative atoms/groups (increased X–H acidity). Although this is often attributed solely to the inductive effect (I), the reality is that these outcomes are due to a complex interplay of inductive, field, mesomeric, and solvation effects. Entropy changes can play an especially important role in solution.

- The same is true for the effect of alkyl or electronegative substituents on amine basicity (which is inversely related to the acidity of their conjugate acid ammonium ions, R₃N⁺–H). In general alkyl substitution slightly increases amine basicity, but the trend in solution is not linear, and secondary amines end up being the most basic. Proximal electronegative atoms/groups always decrease amine basicity.

<table>
<thead>
<tr>
<th>pKₐ in H₂O</th>
<th>9.2</th>
<th>10.6</th>
<th>11.0</th>
<th>10.7</th>
</tr>
</thead>
</table>

- The hybridisation of the nitrogen atom strongly affects its electronegativity and by extension its basicity. The higher the %s character of the N hybrid orbital holding the lone pair, the more tightly the electron pair is bound and the less basic the amine (see right).

- Hence, pyridine is almost 10⁶ times less basic than triethylamine in H₂O.

- Note that nitriles are very difficult to protonate, and are effectively non-basic.

**Take-home message:** Alkyl substituents on nitrogen generally increase amine basicity, whereas electronegative atoms/groups do the opposite. Hybridisation of N has a powerful effect on its basicity, with higher %s character giving much less basic nitrogen atoms.

Amines as Bases: Effect of $\pi$-conjugation with C- or Z-type groups and aromaticity on amine basicity

- Conjugation of the N lone pair with a phenyl group (a C-type substituent), as in aniline, is a stabilising interaction ($n_N \rightarrow \pi^*$) that significantly lowers the basicity of the nitrogen (i.e., because protonation removes the stabilisation).

- Similarly, if the N lone pair is involved in maintaining the aromaticity of the molecule, as in pyrrole, then the basicity is extremely low (effectively non-basic).

\[
\begin{array}{ccc}
\text{MeNH}_2 & \text{aniline} & \text{pyrrole} \\
pK_{aH} \text{ values (in H}_2\text{O)} & 10.6 & 4.6 & -3.8 \\
\end{array}
\]

Conjugation of the N lone pair with a carbonyl group (a Z-type substituent), as in the amide functional group, is an even more stabilising interaction ($n_N \rightarrow \pi^*_\text{C=O}$) than that in aniline, because the $\pi^*$ orbitals of Z-type groups are lower in energy.

- For this reason, amides are non-basic at N. They can be protonated under strongly acidic conditions, but only at oxygen rather than nitrogen, because this maintains the stabilising $n_N \rightarrow \pi^*_\text{C=O}$ interaction.

\[
\begin{array}{ccc}
\text{an amide} & \text{pK}_{aH} \text{ (in H}_2\text{O)} = -0.2 \\
\end{array}
\]

Take-home message: Conjugation of the N lone pair with C-type substituents (e.g., phenyl) significantly lowers N basicity, and the effect is stronger still with Z-type groups (e.g., C=O) to the extent that amides are non-basic at N. Under very acidic conditions, amides can protonate to a small degree, but they do so at the carbonyl oxygen. Aromaticity (as in pyrrole) also greatly lowers N basicity.
**Amidines and Guanidines:** The imino analogues of amides and ureas are stronger bases even than alkylamines

- An **amidine** is the imino analogue of an amide, with a C=NR group replacing the carbonyl. By analogy to amides, amidines are only protonated at the imino nitrogen, because this maintains a stabilising $n_N \rightarrow \pi^*_{C=\text{N}}$ interaction. They are however much stronger bases than amides ($pK_{\text{aH}} \sim 13.5$ versus $-0.2$ for an amide), and they are even more basic than alkylamines ($pK_{\text{aH}} \sim 11$).

- Because the N atom that is protonated is $sp^2$-hybridised, it makes more sense to compare amidines to pyridine ($pK_{\text{aH}} = 5.2$) than an alkylamine. On that basis, we can see that conjugating the imine-like nitrogen with an amino group (an X-type substituent) significantly increases the basicity. As ever, delocalisation of the positive charge will minimise entropically-disfavourable solvent-ordering.

$$\begin{align*}
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} & \xrightleftharpoons{+H^+} \text{R}'' \text{N}^+ \text{N}^+ \text{R'} \\
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} & \xrightarrow{+H^+} \left[ \begin{array}{c}
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} \\
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} \\
\text{R}'' \text{N}^+ \text{N}^+ \text{R'}
\end{array} \right] \\
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} & \equiv \text{R}'' \text{N}^+ \text{N}^+ \text{R'}
\end{align*}$$

**an amidine**

$pK_{\text{aH}}$ (in H$_2$O) $\sim 13.5$

- A **guanidine** - the imino analogue of a urea - has a $pK_{\text{aH}}$ of $\sim 15.0$, which makes it nearly as strong a base as NaOH (at least in water). On protonation, the positive charge is delocalised over all three nitrogens, which minimises solvent-ordering to an even greater degree.

$$\begin{align*}
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} & \xrightarrow{+H^+} \left[ \begin{array}{c}
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} \\
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} \\
\text{R}'' \text{N}^+ \text{N}^+ \text{R'}
\end{array} \right] \\
\text{R}'' \text{N}^+ \text{N}^+ \text{R'} & \equiv \text{R}'' \text{N}^+ \text{N}^+ \text{R'}
\end{align*}$$

**a guanidine**

$pK_{\text{aH}}$ (in H$_2$O) $\sim 15.0$

**Take-home message:** Amidines and guanidines are the imino analogues of amides and ureas respectively, and they are more strongly basic than alkylamines. They protonate exclusively on the imine-like nitrogen to give delocalised cations.
'Passive' (Auxiliary) Brønsted Bases: Bases used simply to 'mop up' acid produced during a reaction

- Neutral nitrogen bases are the strongest neutral bases encountered in organic chemistry. However, on the grand scale of basicity (with extremely powerful bases like BuLi at the extreme) they are typically considered as relatively 'weak' (or 'mild') bases.

- Pyridine and simple trialkylamines like Et₃N are often used as 'passive' (auxiliary) bases in organic reactions, where their role is simply to 'mop up' stoichiometric acid generated in the reaction (e.g., HCl from acylation of alcohols with acid chlorides).

<table>
<thead>
<tr>
<th>Base</th>
<th>pKₐ(H₂O)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine (Py)</td>
<td>5.2</td>
<td>common passive base, sometimes used as solvent</td>
</tr>
<tr>
<td>lutidine</td>
<td>6.8</td>
<td>less nucleophilic than Py, more compatible with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reactive electrophilic reagents</td>
</tr>
<tr>
<td>triethylamine (Et₃N)</td>
<td>10.7</td>
<td>common passive base, inexpensive and low bp</td>
</tr>
<tr>
<td>Hünig's base (DIPEA)</td>
<td>~11</td>
<td>less nucleophilic than Et₃N, more compatible with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reactive electrophilic reagents</td>
</tr>
<tr>
<td>Proton Sponge™</td>
<td>12.3</td>
<td>very non-nucleophilic, compatible with powerful</td>
</tr>
<tr>
<td></td>
<td></td>
<td>alkylating agents (e.g., Me₃O⁺)</td>
</tr>
</tbody>
</table>

Passive bases are not powerful enough to deprotonate the reactant itself (that would be an "active base" - see next slide). Consider the alcohol acylation reaction below. It is a very common student error to draw the Et₃N deprotonating the alcohol!

Take-home message: Pyridine and simple trialkylamines like Et₃N are often used as passive (auxiliary) bases in organic reactions, where their role is simply to 'mop up' stoichiometric acid generated in the reaction (e.g., HCl from acylation of alcohols with acid chlorides).
An 'active' base is defined as one that is strong enough to participate in the reaction itself, rather than just mopping up acid at the end.

For example, DBU (an amidine) is a commonly-used active base for the E2 elimination of alkyl halides (see later "Elimination" lectures).

For formation of stabilised carbanions (e.g., enolates), much stronger amide anion or alkoxide bases are needed, such as t-BuOK or lithium amides. [Do not confuse "amide" in this context with the FG of the same name!]

**Take-home message:** An active base is one that is strong enough to participate in the reaction itself, rather than just mopping up acid at the end. They tend to be anionic, such as amide bases (or hydroxide and alkoxide bases) but they can in some cases be neutral amines or amidines. It all depends on the $pK_a$ of the substrate. Amide or alkoxide bases are often used to generate stabilised carbanions like enolates.
**Lewis Acids and Bases: Electron-pair donor-acceptor complexes**

- The Brønsted-Lowry definition of acids and bases is limited to a proton (H\(^+\)) as the electron-pair acceptor.
- Lewis reasoned that the acid-base concept could be generalised to the interaction of an electron-pair donor (Lewis base) with any electron-pair acceptor (Lewis acid). The proton (H\(^+\)) is then merely a special case of the latter (in his own words, he helped overthrow the "modern cult of the proton!")

- A **Lewis acid (LA)** is a molecule or ion that serves as an electron-pair acceptor.
- A **Lewis base (LB)** is a molecule or ion that serves as an electron-pair donor.

- An exemplar Lewis acid-base reaction is the reaction of NH\(_3\) with BH\(_3\) to give the stable adduct H\(_3\)N•BH\(_3\) (see below).

- The terms Lewis base and Lewis acid are effectively synonymous with the terms **nucleophile** and **electrophile**, respectively. The relevant donor orbital on the LB is the HOMO and on the LA it is the LUMO.

- This type of interaction is sometimes called a **dative (coordinative) bond**, to distinguish it from a "conventional" covalent bond where one electron is contributed from each atom. One could debate whether this distinction truly is useful or even necessary.

**Take-home message:** A Lewis acid-base reaction involves the interaction of an electron-pair donor (Lewis base) with an electron-pair acceptor (Lewis acid). The bond formed is sometimes referred to as a "dative" bond, though it is nevertheless still a covalent bond.

*"Valence and the Structure of Atoms and Molecules", The Chemical Catalog Company, New York, 1923 (Lewis)
Charge Distribution in Lewis Acid-Base Complexes: Formal charges are very misleading

- When we draw a Lewis acid-base adduct like \( \text{H}_3\text{N} \cdot \text{BH}_3 \), where the acid and base species were originally both neutral, we place formal charges on the donor and acceptor atoms. Nitrogen ends up with a formal positive charge, and boron a formal negative charge (see right).

- However, as we’ve already learnt, formal charges are often misleading, and are frequently opposite to the real electrostatic charge on an atom. Because N is much more electronegative than B, the bonding electrons in the newly-formed N–B bond are skewed towards the N, giving it a partial negative charge and the B a partial positive charge.

- This uneven distribution of charge between N and B creates an attractive electrostatic interaction between these atoms.

- In response, the N–H bonds decrease in length and polarise towards N, to further enhance the negative charge on N and strengthen the B–N interaction. Likewise, the B–H bonds increase in length and draw electron density away from B to further supplement the B–N interaction.

- This redistribution of electron density to and from the attached ligands has implications for reactivity.

- In general, Lewis acid-base complexation renders the ligands attached to the donor atom more electrophilic (positively-charged), whereas the ligands attached to the acceptor atom become more nucleophilic (negatively-charged).

Take-home message: The formal charges in the adduct are misleading, and are more representative of the real electrostatic charges on the ligands attached to the donor-acceptor atoms. This has significant implications for the reactivity of those ligands.

Lewis Acid and Lewis Base Activation: Increasing electrophilicity or nucleophilicity of functional groups

- You will meet many reactions in organic synthesis that rely upon the concept of Lewis acid activation, where the binding of a Lewis acid renders a functional group more electrophilic. This is most commonly encountered for the carbonyl group (see right), where Lewis acid binding increases the positive charge at the C=O carbon (or, stated in FMO terms, it lowers the energy of the π* LUMO).

\[
\text{LiBH}_4 \ (2 \text{ eqv}) \quad \begin{array}{c}
\text{R} \quad \text{OMe} \\
\text{H} \quad \text{B} \quad \text{H} \quad \text{H} \quad \text{H}
\end{array} \quad \text{OH} \\
\text{R} \quad \text{H} \quad \text{OH} \quad \text{LiBH}_4
\]

\text{reduction of an ester with lithium borohydride (Li}^+ \text{ as Lewis acid)}

- Though perhaps less common, you will also encounter Lewis base activation, particularly in the chemistry of organoboron and organosilicon compounds. For example, silyl enol ethers can be converted to "naked" (metal-free) enolates by reacting them with a fluoride Lewis base. This transfers negative charge onto the oxygen in a hypervalent silicate, so that it can be expelled as an oxyanion (see left).

\[
\text{OSiMe}_3 \quad \text{O} \quad \text{Me} \quad \text{3} \quad \text{Si} \quad \text{F}
\]

\text{transmetalation step of the Pd-catalysed Suzuki-Miyaura reaction}

- Some reactions involve dual Lewis acid-base activation, where formation of a LA-LB adduct activates both reaction partners simultaneously, and an intramolecular reaction ensues. A good example of this is the transmetalation step of the Pd-catalysed Suzuki-Miyaura reaction you’ll meet in Yr 2, involving aryl anion transfer from B to an electrophilic Pd^{II} centre (see right).

Take-home message: The interaction of Lewis acids (or Lewis bases) with certain functional groups can lead to enhancement of electrophilicity (or nucleophilicity), facilitating reactivity. Some reactions involve dual Lewis acid-base activation, making both reaction partners more reactive and enabling an intramolecular reaction to take place.


Lewis Acid and Lewis Base Catalysis: An example of an enantioselective reaction catalysed by a chiral Lewis acid

- In some reactions, the Lewis acid/base activator is not consumed and can thus function as a catalyst. This allows one to use the Lewis acid/base in substoichiometric quantities. This is termed Lewis acid/base catalysis.

- An example of Lewis acid catalysis could be AlCl₃ in a Friedel-Crafts alkylation of benzene with t-BuCl, but a more exciting example is to append a chiral, enantiopure ligand to the Lewis acid and use it to catalyse an enantioselective reaction, where we can control which enantiomer of the product is formed (often called "asymmetric catalysis").

- One rather sophisticated example of this is the use of a copper(II) Lewis acid catalyst bound to a chiral, enantiopure "BOX" ligand, which can catalyse a Diels-Alder cycloaddition reaction to give the product in almost 98% enantiopurity.

Take-home message: Some reactions can be catalysed by Lewis acids (or Lewis bases), rather than using them as stoichiometric activators/reagents. You will many examples of this, particularly with Lewis acids for the catalytic activation of carbonyl groups. It is also possible to use chiral, enantiopure Lewis acids (or bases) to catalyse enantioselective reactions.

Whether or not Lewis acids truly operate via LUMO-lowering as the origin of their catalytic activation has recently been called into question, and electron repulsion effects may in fact be the true origin; see: "The Pauli Repulsion-Lowering Concept in Catalysis" Acc. Chem. Res. 2021, 54, 1972
Revision Checklist

Revised?

☐ Brønsted acids and bases; the pH scale for solution acidity; the $pK_a$ scale for molecular acidity

☐ Enthalpic and entropic contributions to X–H acidity (X–H bond strength, $X^-$ anion stability, solvent-ordering)

☐ Periodic trends in X–H acidity

☐ Inductive and hybridisation effects on X–H acidity

☐ Effect of heavier $p$-block elements on X–H acidity

☐ Effect of conjugation on X–H acidity (C-, Z-, and X-type substituents); stereoelectronic constraints

☐ Effect of aromaticity on X–H acidity

☐ Solvation effects on X–H acidity; effects of intramolecular hydrogen-bonding

☐ The $pK_{aH}$ scale for molecular basicity

☐ Effect of inductive effects, hybridisation, and C- or Z-type conjugation on nitrogen atom basicity; amidines and guanidines

☐ Passive and active bases in organic chemistry

☐ Lewis acids and bases; charge distribution in LA–LB complexes and resultant activation; Lewis acid/base catalysis
## Compilation of $pK_a$ Values

(measurements <0 in H$_2$O and DMSO, and values >14 in H$_2$O and >35 in DMSO are extrapolated)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$pK_a$</th>
<th>H$_2$O</th>
<th>(DMSO)</th>
<th>Substrate</th>
<th>$pK_a$</th>
<th>H$_2$O</th>
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<th>Substrate</th>
<th>$pK_a$</th>
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<th>(DMSO)</th>
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<td>2.1, 7.2, 12.3</td>
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<td>HNO$_3$</td>
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<tr>
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<td>(0.9)</td>
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This data was sourced from https://organicchemistrydata.org/hansreich/resources/pka/.  *The $pK_a$ of H$_2$O is often cited as 15.7, but its true value is 14.0 (J. Chem. Educ. 2017, 94, 690). **The $pK_a$ of H$_3$O$^+$ is often cited as $-$1.7, but its true value is 0.0 (Analyst, 1998, 123, 409)
### PROTONATED NITROGEN SPECIES

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<td>DBU</td>
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<td>$3^\circ$ Et$_3$N$^+$-</td>
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<td>H$_2$N-H</td>
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<td>(41)</td>
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<tr>
<td>(i-Pr)$_2$N-H</td>
<td>36 (THF)</td>
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### AMIDES & CARBAMATES (N–H)

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### IMIDES (N–H)

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### SULFONIMIDES (N–H)

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<tr>
<td>Me–H</td>
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<td>Me</td>
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<tr>
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<tr>
<td>Allyl</td>
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<tr>
<td>Biphenyl</td>
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### ESTERS (α-C–H)

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<td>(15.7)</td>
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<td>(26.6)</td>
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### KETONES (α-C–H)

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<tbody>
<tr>
<td>i-PrO–C–Me</td>
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<td>MeO–C–Me</td>
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</tr>
<tr>
<td>MeO–C–Me</td>
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<td>(15.7)</td>
<td></td>
</tr>
<tr>
<td>MeO–C–Ph</td>
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<td>(19.8)</td>
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</tr>
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<td>MeO–C–Me</td>
<td>9</td>
<td>(13.3)</td>
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### AMIDES (α-C–H)

<table>
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<tbody>
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<tr>
<td>OMe–C–H</td>
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<td>MeO–C–H</td>
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<td>MeO–C–H</td>
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<td>(15.7)</td>
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<td>MeO–C–Me</td>
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<td>9</td>
<td>(13.3)</td>
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This data was sourced from [https://organicchemistrydata.org/hansreich/resources/pka/](https://organicchemistrydata.org/hansreich/resources/pka/). *For isobutane $pK_a$ of 71, see: *J. Am. Chem. Soc.* **1976**, **98**, 6076.