LECTURE 2 Stereoelectronics of Ground States – Conformational Analysis

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Format & scope of lecture 2

- **The conformation of hydrocarbons**
  - Ethane & alkanes
  - Propene & alkenes
    - $A^{1,2}$ and $A^{1,3}$ strain
  - 1,3-Dienes & biaryls
- **The conformation of functional groups**
  - Aldehydes & ketones
  - Esters & lactones
    - the ester anomeric effect
- **The conformation of functional groups**
  - Amides
  - Acetals
    - the anomeric effect, Bohlmann IR bands
  - X-C-C-Y and R-X-Y-R’ systems
    - gauche conformations
Saturated hydrocarbons - ethane

- **Ethane** prefers to adopt a **staggered** rather than **eclipsed** conformation because:
  
  - 1) The **eclipsed conformers** are **destabilised** by **steric interactions**
    - *i.e.* by non-bonded, van der Waals repulsions between the atoms concerned
  
  - 2) The **staggered conformers** are **stabilised** by \( \sigma \to \sigma^* \) **stereoelectronic interactions**
    - *i.e.* in a staggered conformation all the bonds on adjacent carbons are **anti periplanar** to each other allowing six \( \sigma \to \sigma^* \) stabilising interactions

\[
\text{van der Waals repulsions are maximised when eclipsed (shown)}
\]

\[
\begin{align*}
\text{steric destabilisation of eclipsed conformations} & \quad \text{stereoelectronic stabilisation of staggered conformations} \\
\end{align*}
\]

- For theoretical discussions of the relative importance of these effects see
  
  - L. Goodman *Nature* 2001, 411, 539 (DOI) and 565 (DOI)
  
  
  

- **NB. Steric effects dominate for groups larger than hydrogen**
Unsaturated hydrocarbons – propene

- **Propene** prefers to adopt **A\textsubscript{1,3} eclipsed** conformations rather than **A\textsubscript{1,2} eclipsed** conformations
  - The barrier to rotation is 8.0 kJ/mol (cf. propane 14.8 kJ/mol)

- The **A\textsubscript{1,3} eclipsed** conformation allows for better overlap of the orbitals for stabilising \( \sigma_{C-H} \rightarrow \pi^{*}_{C=C} \) **hyperconjugation/\( \sigma \)-conjugation**
  - This better overlap is a consequence of the ~109° angle subtended by the 'lobes' of the \( \pi^{*}_{C=C} \) orbital relative to the C=C axis

- **NB.** Steric effects dominate for groups larger than hydrogen...
Higher alkenes – $A^{1,2}$ vs $A^{1,3}$ strain

- **Steric interactions** (i.e. van der Waals forces) dominate affairs when groups other than H are involved
  - $A^{1,3}$ strain is the destabilising eclipsing interaction shown below:
    - As C=C double bonds are shorter than C-C single bonds, $A^{1,3}$ strain in the illustrated conformation of 2-pentene is more destabilising than the syn-pentane interaction in the illustrated conformation of $n$-pentane

  ![Eclipsing Interactions Diagram](image)

  **Enthalpy difference between conformers**
  \[ \Delta H^\circ = +16.3 \text{ kJ/mol} \]

  $A^{1,3}$ strain

  - $A^{1,2}$ strain is the destabilising eclipsing interaction shown below:
    - As the C-C-C angle at an sp³ carbon (~109°) is smaller than at an sp² carbon (~120°), $A^{1,2}$ strain in the illustrated conformation of 2-Me-but-1-ene is less destabilising than the eclipsing interaction in the illustrated conformation of $n$-butane

  ![Eclipsing Interactions Diagram](image)

  **Enthalpy difference between conformers**
  \[ \Delta H^\circ = +12.6 \text{ kJ/mol} \]

  $A^{1,2}$ strain

  - For a given pair of groups (e.g. Me ↔ Me, above), $A^{1,3}$ strain is more destabilising than $A^{1,2}$ strain. The lowest energy conformation adopted by complex alkenes is that in which both $A^{1,2}$ & $A^{1,3}$ strains are minimised
Unsaturated hydrocarbons – 1,3-dienes

- **1,3-Dienes** prefer to adopt **s-trans** conformations in which both double bonds are **co-planar**
  - e.g. butadiene:
    - **Co-planarity** of the π bonds allows for optimal overlap of the orbitals for \( \pi_{\text{C=C}} \rightarrow \pi^*_{\text{C=C}} \) resonance stabilisation
  - The **s-trans** conformation is preferred over the **s-cis** conformation because it suffers less **strain**
Unsaturated hydrocarbons - *biaryls*

- **Biaryls** prefer to adopt *non-planar* conformations in which the **dihedral angle** is ~45°

![Diagram of biaryl conformations]

- This is a compromise between:
  - Stabilising \( \pi_C=C \rightarrow \pi^*_C=C \) resonance when coplanar
  - Destabilising steric interactions between adjacent *ortho* aromatic substituents when coplanar

![Graph showing energy changes with dihedral angle]

- If at least three *ortho* substituents are large then the co-operative steric interactions restrict C-C bond rotation to such an extent that the two conformers become **configurationally stable** and, provided the groups are different, can be isolated as enantiomers known as **atropisomers**
Functional groups – *aldehydes & ketones*

- **Alkyl aldehydes & ketones** prefer to adopt $A^{1,3}$ *eclipsed* conformations

  ![Eclipsed Conformations](image)

  $A^{1,3}$ *eclipsed*  
  **MAJOR**  
  $A^{1,2}$ *eclipsed*

  - As for allylic systems, $A^{1,3}$ *eclipsed* conformations allow stabilising $\sigma_{C-H/C} \rightarrow \pi^*_{C=O}$ *hyperconjugation*:
    - These interactions are more significant than the corresponding interactions in an allylic system because the $\pi^*_{C=O}$ orbital is a better acceptor (*i.e.* is lower in energy) than a $\pi^*_{C=C}$ orbital
    - These interactions also account for the greater stability of ketones relative to aldehydes (*i.e.* Deslongchamps theory: more interactions for the ketone)

  ![Hyperconjugation](image)

  - Moreover, $A^{1,3}$ *strain* is less significant in these compounds relative to allylic compounds as the $sp^2$ hybrid lone pairs on the carbonyl oxygen are ‘small’ relative to any substituent on an alkene

  ![Strain](image)

  **NB.** of course there are two identical interactions: on the top and bottom faces
Functional groups - esters

- **Esters** prefer to adopt **s-cis** conformations in which all atoms of the group are **co-planar**

  \[
  \begin{align*}
  \text{s-cis} & \quad \Delta H^\circ \sim 25 \text{kJ/mol} \\
  \text{s-trans} & \quad \Delta H^\circ \sim 50 \text{kJ/mol}
  \end{align*}
  \]

  - **Co-planarity** is stabilised by \( n_{\text{Op}} \rightarrow \pi^*_{\text{C}=\text{O}} \) resonance

  \[
  \begin{align*}
  \text{s-cis} & \quad n \rightarrow \pi^* (\text{pp}) \\
  \text{s-trans} & \quad n \rightarrow \pi^* (\text{pp})
  \end{align*}
  \]

  - Because the p-orbital on oxygen is symmetrical resonance does not favour s-cis over s-trans or vice versa

  - However, there is a relatively strong enthalpic preference for the **s-cis** conformer over the **s-trans** one (\( \Delta H^\circ \sim 25 \text{kJmol}^{-1} \) cf. \( \sim 10 \text{kJmol}^{-1} \) for amides) although the barrier to rotation about the acyl oxygen bond (*i.e.* interconversion) is relatively low (\( \Delta H^\# \sim 50 \text{kJmol}^{-1} \) cf. \( \sim 85 \text{kJmol}^{-1} \) for amides)
Functional groups – esters cont.

- **There are three factors which favour the s-cis over the s-trans conformer:**
  - There is a $n \rightarrow \sigma^*$ **anomeric effect** which stabilises the s-cis form

![Diagram of anomeric effect]

- There is significant ‘$A^{1,2}$ strain’ in the s-trans form (the sp$^2$ hybrid lone pair on the carbonyl oxygen is ‘small’ relative to a substituent bonded to the acyl carbon atom)

![Diagram of $A^{1,2}$ strain]

- The s-cis form has a significantly **smaller overall dipole moment** relative to the s-trans form
  - There is a general preference for conformers with minimum overall dipole (minimum overall charge separation)

![Diagram of bond dipole moments]
Evidence for the ester anomeric effect

- **Fluorocarbonates** prefer to adopt an *s-trans* conformation:

  ![Diagram of s-cis and s-trans conformations](image)

  - Here, the $\sigma^*$ orbital of the C-F bond is a better acceptor than the $\sigma^*$ orbital of the C-O bond (*i.e.* lower in energy because F is more electronegative than O)

  - Hence, in these compounds there is a stronger **anomeric stabilisation** of the *s-trans* conformation than of the *s-cis* conformation.

  \[ \text{ESTAB}_{s\text{-trans}} > \text{ESTAB}_{s\text{-cis}} \]

  - NB. the *cis* and *trans* designations here are relative to the carbonyl group and not strictly according to CIP rules (where F>O in 'priority')
• **5- & 6-Membered lactones** contain an ester function with an enforced s-trans conformation so anomeric $n_{Osp2} \rightarrow \sigma^*_{C-O}$ stabilisation is not possible

![s-trans](image)

• As a result, lactones have some different properties to corresponding acyclic esters:
  
  – **Lactones are more basic than acyclic esters** - because the oxygen sp$^2$ lone pair is ‘more available’ for interaction with protons (e.g. it is possible to form salts etc.)

  – **Lactones are more susceptible to nucleophilic attack at the carbonyl carbon than acyclic esters** - because anomeric $n_{Osp2} \rightarrow \sigma^*_{C-O}$ stabilisation results in ‘dilution’ of the dipole across the carbonyl in acyclic esters; this interaction is absent for lactones (i.e. they are more electrophilic)

  – **Lactones are more prone to enolisation than acyclic esters** - [pKa ~22 (lactone) cf. pKa ~25 (acyclic ester)] because for acyclic esters there is an energy penalty associated with loss of anomeric stabilisation ($n_{Osp2} \rightarrow \sigma^*_{C-O}$) in going to the enolate; this is not the case for lactones.
The Claisen Condensation - Why Thioesters?

- recall the chemistry of coenzyme A (1st lecture) – properties of alkyl thioesters (cf. alkyl esters)
  - good leaving group ability of RS: (cf. RO⁻)
    - due to pKₐ (RSH) ~10 cf. pKₐ (ROH) ~16

- high acidity of protons α to the carbonyl of thioesters (cf. ester) & weak C-S bond (cf. C-O bond):
  - due to poor orbital overlap between the lone pairs on sulfur (ₙₛ) [cf. ₙₒ] and the carbonyl anti bonding orbital π⁺_{C=O}

```
\[
\begin{align*}
\text{Nu:} & \quad \text{Nu:} \\
\text{SR} & \quad \text{SR} \\
\end{align*}
\]
```

- a good leaving group

```
\[
\begin{align*}
\text{Nu:} & \quad \text{Nu:} \\
\text{OR} & \quad \text{OR} \\
\end{align*}
\]
```

- a poorer leaving group

```
\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{S} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]
```

- less effective

```
\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]
```

- pKa = 20
  - acyl-sulfur bond weak

```
\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]
```

- pKa = 25
  - acyl-oxygen bond strong
Amides prefer to adopt s-cis conformations in which all atoms of the group are co-planar. Co-planarity is stabilised by $n_{\text{Np}} \rightarrow \pi^*_{\text{C}=\text{O}}$ resonance which is stronger than the corresponding $n_{\text{Op}} \rightarrow \pi^*_{\text{C}=\text{O}}$ resonance in esters because the nitrogen lone pair is a better donor than the oxygen lone pair.

- Co-planarity stabilises the s-cis conformer over the s-trans conformer, but the enthalpic difference in ground state energy is less pronounced than in the case of esters ($\Delta H^\circ \approx 10\text{kJmol}^{-1}$, cf. $\approx 25\text{kJmol}^{-1}$ for esters).

- This is because the only significant factor favouring the s-cis conformation over the s-trans is ‘$A^{1,2}$ strain’ (cf. esters where there is an anomeric effect and for which dipole effects are significant):

*NB*. This strain is often referred to as $A^{1,2}$-strain despite the fact that the non-carbonyl carbon is NOT $sp^3$ hybridised.
The anomic effect – 6-ring acetals

- **6-ring acetals prefer to adopt chair conformations in which the anomeric oxygen is axial**
  - This is in contrast to the situation for cyclohexanes in which the substituent adopts an equatorial position 1) to avoid unfavourable 1,3-diaxial or ‘1,3-flagpole’ interactions, & 2) to minimise gauche interactions:

- **Two factors favour the α-anomer:**
  - An $n_{sp^3} \rightarrow \sigma^*_{C-X}$ **anomeric effect** which stabilises the α-anomer
    - The better the $\sigma^*_{C-X}$ orbital is as an acceptor, the stronger the effect
  - The α-anomer has a smaller overall dipole moment than the β-anomer
The generalised anomeric effect & structural evidence

- **The anomeric effect in its most general form explains the conformational behaviour of systems containing two heteroatoms bound to a single carbon atom**
  - *i.e.* X-C-Y where X and Y are electronegative groups (*e.g.* acetals, where X = Y = O below)

![Diagram of the generalised anomeric effect with bond lengths](image)

- **Evidence for the anomeric effect comes from *e.g.* bond length analysis of fluoro sugars**

![Diagram of bond lengths in fluoro sugars](image)

X-ray bond lengths of fluorosugars...evidence for lengthening (and weakening) of the 'acceptor' C-F bond.
The anomeric effect – alkaloid ‘Bohlmann bands’

- **Geometrically rigid alkaloids** having at least **2 x C-H bonds anti-periplanar to nitrogen lone pairs** display characteristic low frequency infra-red stretching frequencies of the C-H bonds
  - This is because of multiple $\text{n}_{\text{Sp}3} \rightarrow \sigma^*_{\text{C-H}}$ **anomeric interactions** which weaken the acceptor (i.e. C-H) bonds
    - These bands (2700-2800 cm$^{-1}$) only occur when there are at least 2 appropriately orientated C-H bonds. Presumably due to the weak nature of the interaction
    - For recent use during Terengganensine A synthesis see: J. Zhu *Angew. Chem. Int Ed.* 2016, 55, 6556 (DOI)
1,2-Disubstituted ethanes - *gauche* preference

- **X-C-C-Y** containing compounds (where X and Y are electronegative groups) adopt *gauche* rather than *anti* conformations – *despite this conformation having a larger overall dipole*
  - Stabilisation accrues from $\sigma \rightarrow \sigma^*$ interactions between the best combinations of anti-periplanar donor and acceptor bonds (**the gauche effect**)

- **NB.** In the case of 1,2-ethanediol an *intramolecular H-bond* also stabilises the *gauche form*
- Also, 1,4-hypercoordination has been proposed as an additional factor stabilising *gauche conformations*, particularly when X or Y is a second row element: Inagaki *Org. Lett.* 1999, 1, 1145 (DOI)
**Peroxides, hydrazines, disulfides - gauche preference**

- **X-Y containing compounds** (where X and Y are electronegative groups) also adopt *gauche* rather than *anti* conformations
  - Stabilisation accrues from $n \rightarrow \sigma^*$ (anomeric) interactions between antiperiplanar donor lone pairs on X and Y and acceptor bonds
  - *e.g.* hydrogen peroxide ($\text{H}_2\text{O}_2$) and hydrazine ($\text{H}_2\text{NNH}_2$)

  ![Diagram of H$_2$O$_2$ and N$_2$H$_4$](image)

  - ***Disulfides*** adopt a *quasi gauche* conformation (dihedral angle $\Theta_{\text{C-S-S-C}}$ of $\sim 90^\circ$, cf. $\sim 60^\circ$ as expected)
    - This is because sulfur is in the second row of the periodic table and the geometry of the sp$^3$ sulfur centres are distorted such that the angle between the lone pairs is $>109^\circ$ and that between the two substituents is $<109^\circ$. Anti-periplanarity for $2 \times n_s \rightarrow \sigma^*_{\text{S-C}}$ interactions results in the observed conformational geometry

  ![Diagram of R$_2$S$_2$](image)
1,2-, 1,3- & 1,4-Diheteroatom arrays - summary

**1,4-**

\[
\begin{align*}
\text{app} & & \sigma \\
\text{X} & & \text{C/H} & & \text{C/H} \\
\text{Y} & & \text{C/H} & & \text{H/C} \\
\end{align*}
\]

\[
\begin{align*}
\text{gauche preference} \\
2x (\sigma \rightarrow \sigma^*)
\end{align*}
\]

C-H/C = best \(\sigma\) donor
C-Y = best \(\sigma\) acceptor

**1,3-**

\[
\begin{align*}
\text{app} & & \text{app} \\
\text{X} & & \text{R} & & \text{R} \\
\text{Y} & & \text{R} & & \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{the anomeric effect} \\
2x (n \rightarrow \sigma^*)
\end{align*}
\]

\(n_X\) and \(n_Y\) = best donors
C-Y and C-X = best \(\sigma\) acceptors

**1,2-**

\[
\begin{align*}
\text{app} & & \\
\text{X} & & \text{C/H} & & \text{C/H} \\
\end{align*}
\]

\[
\begin{align*}
\text{gauche preference} \\
2x (n \rightarrow \sigma^*)
\end{align*}
\]

\(n_X\) and \(n_Y\) = best donors
C-C/H = best \(\sigma\) acceptors