CHEM50002:
Orbitals in Organic Chemistry- Stereoelectronics

LECTURE 2 Stereoelectroncis 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 anomic effect, Bohlmann IR bands
  – $X\cdot C\cdot C\cdot Y$ and $R\cdot X\cdot Y\cdot R'$ 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 $\sigma \rightarrow \sigma^*$ **stereoelectronic interactions**
    - *i.e.* in a staggered conformation all the bonds on adjacent carbons are **anti periplanar** to each other allowing six $\sigma \rightarrow \sigma^*$ stabilising interactions

\[
\begin{align*}
\text{van der Waals repulsions are} & \quad \text{maximised when} \quad \text{eclipsed} \quad \text{(shown)} \\
\text{steric destabilisation of eclipsed conformations} & \quad \text{stereoelectronic stabilisation of staggered conformations}
\end{align*}
\]

- For theoretical discussions of the relative importance of these effects see
  - L. Goodman *Nature* **2001**, 411, 539 ([DOI](https://doi.org/)) and 565 ([DOI](https://doi.org/))
  - P.R. Schreiner *Angew. Chem. Int. Ed.* **2002**, 41, 3579 ([DOI](https://doi.org/))
  - F.M. Bickelhaupt *Angew. Chem. Int. Ed.* **2003**, 42, 4183 ([DOI](https://doi.org/))

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

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

```
Enthalpy difference between conformers
$\Delta H^\circ = +16.3$ kJ/mol
```

- $A^{1,2}$ strain is the destabilising eclipsing interaction shown below:
  - As the C-C-C angle at an sp$^3$ carbon (~109°) is smaller than at an sp$^2$ 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

```
Enthalpy difference between conformers
$\Delta H^\circ = +12.6$ kJ/mol
```

- 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 \( \pi \) bonds allows for optimal overlap of the orbitals for \( \pi_{C=C} \rightarrow \pi^*_{C=C} \) resonance stabilisation
  - Maximum \( \pi_{C=C} \rightarrow \pi^*_{C=C} \) stabilisation for periplanar alkenes (i.e. best overlap)
  - The **s-trans** conformation is preferred over the **s-cis** conformation because it suffers less **strain**

\[
\begin{align*}
\Delta H^\circ &= +25 \text{ kJ/mol} \\
\pi_{C=C} &\rightarrow \pi^*_{C=C} \\
\text{Maximum } \pi_{C=C} \rightarrow \pi^*_{C=C} \text{ stabilisation for periplanar alkenes (i.e. best overlap)} \\
\text{The s-trans conformation is preferred over the s-cis conformation because it suffers less strain}
\end{align*}
\]
Unsaturated hydrocarbons - biaryls

- **Biaryls** prefer to adopt **non-planar** conformations in which the **dihedral angle** is \( \sim 45^\circ \)

\[
\begin{align*}
\text{R} & \quad \text{R'} \\
\text{R''} & \quad \text{R'} \\
\text{R'''} & \quad \theta \\
\end{align*}
\]

This is a compromise between:
- Stabilising \( \pi_{C=C} \rightarrow \pi_{C=C}^* \) resonance when coplanar
- Destabilising steric interactions between adjacent \textit{ortho} aromatic substituents when coplanar

- If at least three \textit{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

  ![Conformations](image.png)

  - As for allylic systems, $A^{1,3}$ **eclipsed** conformations allow stabilising $\sigma_{C-H/C} \rightarrow \pi^*_{C=O}$ **hyperconjugation**/$\sigma$-**conjugation**
    - 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)

  ![Orbital Alignment](image.png)

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

  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
Functional groups - esters

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

![Ester Conformers](image)

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

![Resonance](image)

- 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 ($\Delta H^o \sim 25kJmol^{-1}$ cf. $\sim 10kJmol^{-1}$ for amides) although the barrier to rotation about the acyl oxygen bond (i.e. interconversion) is relatively low ($\Delta H^\# \sim 50kJmol^{-1}$ cf. $\sim 85kJmol^{-1}$ for amides)
There are three factors which favour the s-cis over the s-trans conformer:

- There is a $n_{\text{sp}^2} \rightarrow \sigma^{*}_{\text{C-O}}$ anomeric effect which stabilises the s-cis form.

- 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).

- 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).

*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.*
Evidence for the ester anomeric effect

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

  \[ \text{F} - \text{O} \rightarrow \text{R} \quad \text{s-cis} \quad \text{s-trans (MAJOR)} \]

  - 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)

  \[ \text{R} - \text{O} - \text{F} \left( \sigma^* \right) \quad \text{n} \rightarrow \sigma^* \text{ (app)} \]

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

**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’).
Functional groups - lactones

- **5- & 6-Membered lactones** contain an ester function with an enforced s-trans conformation so anomic \( n_{\text{sp}^2} \rightarrow \sigma^*_{\text{C-O}} \) stabilisation is not possible

![s-trans](image.png)

- 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 anomic \( n_{\text{sp}^2} \rightarrow \sigma^*_{\text{C-O}} \) 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 anomic stabilisation \( (n_{\text{sp}^2} \rightarrow \sigma^*_{\text{C-O}}) \) 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 $pK_a$ (RSH) ~10 cf. $pK_a$ (ROH) ~16

- **high acidity of protons $\alpha$ 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 ($n_S$) [cf. $n_O$] and the carbonyl anti bonding orbital $\pi^*_C=O$
Functional groups - *amides*

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

  ![Diagram of amide conformations with relative stabilities](image)

  - **Co-planarity** is stabilised by $n_{Np} \rightarrow \pi^*_C=O$ resonance which is stronger than the corresponding $n_{Op} \rightarrow \pi^*_C=O$ resonance in esters because the nitrogen lone pair is a better donor than the oxygen lone pair
    - This is manifested in the high barrier to rotation about the acyl nitrogen bond ($\Delta H^\# \sim 85 \text{kJmol}^{-1}$, cf. $\sim 50 \text{kJmol}^{-1}$ for esters)

  - The **s-cis** conformer is preferred over the **s-trans** conformer but the enthalpic difference in ground state energy is less pronounced than in the case of esters ($\Delta H^0 \sim 10 \text{kJmol}^{-1}$, cf. $\sim 25 \text{kJmol}^{-1}$ 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):

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

    *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 $n_{ossp3} \rightarrow \sigma^*_{C-X}$ 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

NB. There are 2 of the indicated gauche interactions for isomer C: looking along the 'red' bond (as shown) and also looking along the 'blue' bond (not shown)
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 generalised anomeric effect](image)

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

![Diagram of fluoro sugar bond lengths](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 $n_{Nsp3} \rightarrow \sigma^*_{C-H}$ 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)

\[ \text{aphyllin} \text{ cis-fused} \]
\[ \text{17-oxo-sparteine} \text{ trans-fused} \]
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*)

  ![Diagram of gauche effect](image)

  - **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)

  ![Diagram of hypercoordination](image)
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 (H$_2$O$_2$) and hydrazine (H$_2$NNH$_2$)

- **Disulfides** adopt a *quasi gauche* conformation (dihedral angle $\Theta_{C-S-S-C}$ of $\sim$90º, cf. $\sim$60º as expected)
  - This is because sulfur is in the second row of the periodic table and the geometry of the sp$^3$ sulfur centres are distorted such that the angle between the lone pairs is $>$109º and that between the two substituents is $<$109º. Anti-periplanarity for $2\times n_S \rightarrow \sigma^*_{S-C}$ interactions results in the observed conformational geometry
1,2-, 1,3- & 1,4-Diheteroatom arrays - summary

1,4- array:

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

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

1,3- array:

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

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

1,2- array:

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

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