CHEM50002: Orbitals in Organic Chemistry- Stereoelectronics

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\textsuperscript{1,2} and A\textsuperscript{1,3} strain
  – 1,3-Dienes & biaryls

• The conformation of functional groups
  – Aldehydes & ketones
  – Esters & lactones
    • the ester anomeric effect
  – 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 $\sigma \rightarrow \sigma^*$ **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

van der Waals repulsions are maximised when **eclipsed** (shown)

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steric destabilisation of eclipsed conformations  

For theoretical discussions of the relative importance of these effects see
- L. Goodman *Nature* 2001, 411, 539 ([DOI](https://doi.org/10.1038/35075600)) and 565 ([DOI](https://doi.org/10.1038/35075600))

- **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)

  ![Diagram showing $A^{1,3}$ eclipsed and $A^{1,2}$ eclipsed conformations](image)

  ```
  Enthalpy difference between conformers
  $\Delta H^\circ = +8.0$ 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 $\sim 109^\circ$ angle subtended by the ‘lobes’ of the $\pi^*_{C=C}$ orbital relative to the C=C axis

  ![Diagram showing overlap of orbitals](image)

  ```
  NB. There are two concurrent interactions: on the top face (as indicated) and on the bottom face
  ```

  – **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

```
  Me Me Me Me
Me Me
H H
H H

MAJOR
```

$A^{1,3}$ strain

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

```
  Me Me
Me Me

syn-pentane interaction
(+15.4 kJ/mol)
in n-pentane
```

```
Me Me 3
Me 1

A^{1,3} strain
(+16.3 kJ/mol)
in 2-pentene
```

- $A^{1,2}$ 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 illustarted conformation of n-butane

```
  Me H
Me 2

MAJOR
```

$A^{1,2}$ strain

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

```
  Me Me
Me Me

eclipsing interaction
(+13.0 kJ/mol)
n-butane
```

```
  Me Me
Me Me

A^{1,2} strain
(+12.6 kJ/mol)
2-Me-but-1-ene
```

- 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:

  ![s-trans](image)

  ![s-cis](image)

  Enthalpy difference between conformers
  \[ \Delta H^\circ = +25 \text{ kJ/mol} \]

- **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°

  ![Dihedral Angle Diagram]

  Lowest energy conformation has dihedral angle ca. 45°

  - 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

  ![Energy Diagram]

  Maximum destabilising steric strain ($\theta = 0°, 180°, 360°$)

  Absence of stabilising $\pi_{C=C} \rightarrow \pi^*_{C=C}$ resonance ($\theta = 90°, 270°$)

  Moderate steric strain & some stabilising resonance
  ($\theta = 45° & 315° =$ enantiomers; $135° & 225° =$ enantiomers)

  ![Energy Chart Diagram]

- 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
  
  ![Diagram](image)

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

  ![Diagram](image)

  - **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 a planar conformation with an s-cis conformation about the acyl oxygen single bond:**

  ![Diagram of ester conformation](image)

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

  ![Resonance diagram](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 ($\Delta H^o \sim 25\text{kJmol}^{-1}$ 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)
There are **three factors** which favour the **s-cis** over the **s-trans** conformer:

- There is a $n_{\text{Osp}^2} \rightarrow \sigma^*_{\text{C-O}}$ **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).
Evidence for the ester anomeric effect

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

  - 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.

\[ \text{NB. the cis and trans designations here are relative to the carbonyl group and not strictly according to CIP rules (where F>O in 'priority')} \]
Functional groups - *lactones*

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

- As a result, lactones have some different properties to corresponding acyclic esters:
  - *The \( sp^2 \) hybrid, non-carbonyl oxygen lone pair in a lactone is more basic/nucleophilic than in an acyclic ester* - because the lone pair is ‘more available’ for interaction with protons/metal cations etc.
  
  - *Lactones are more susceptible to nucleophilic attack at the carbonyl carbon than acyclic esters* - because anomic \( n_{\text{Osp}}^2 \rightarrow \sigma^*_{\text{C-O}} \) 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* - \([\text{pKa} \sim 22 \text{ (lactone)} \text{ cf. } \text{pKa} \sim 25 \text{ (acyclic ester)}]\) because for acyclic esters the anomic effect contributes to the transfer of electron density from the non-carbonyl oxygen to the carbonyl one, rendering it less able to accept electron density during \( \alpha \)-deprotonation. In a lactone, the anomic effect is absent so the carbonyl oxygen is better able to accept electron density from deprotonation.
Functional groups - *amides*

- **Amides** prefer to adopt a **planar** conformation with an **s-cis** conformation about the acyl oxygen single bond:

  - **Co-planarity** is stabilised by $\pi_{N\sigma} \rightarrow \pi^*_{C=O}$ *resonance* which is stronger than the corresponding $\pi_{O\sigma} \rightarrow \pi^*_{C=O}$ 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 ($\Delta H^\# \approx 85 \text{kJmol}^{-1}$, cf. $\approx 50 \text{kJmol}^{-1}$ 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 ($\Delta H^0 \approx 10 \text{kJmol}^{-1}$, 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 nitrogen is NOT sp$^3$ hybridised*
The anomic effect – *6-ring acetals*

- **6-ring acetals prefer to adopt chair conformations in which the anomic 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:

![Diagram showing the anomic effect in 6-ring acetals](image)

- **Two factors favour the α-anomer:**
  - An $n_{\text{sp}3} \rightarrow \sigma^{*}_{\text{C-X}}$ **anomeric effect** which stabilises the α-anomer
    - The better the $\sigma^{*}_{\text{C-X}}$ orbital is as an acceptor, the stronger the effect

![Diagram showing the anomeric effect](image)

  - 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)

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

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 $n_{\text{Nsp}3} \rightarrow \sigma^{*}_{C-H}$ **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](http://dx.doi.org/10.1002/anie.201600158))
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)

\[
\begin{align*}
\text{anti} \quad \text{gauche} & \quad \text{major} \\
\text{donor} \quad \text{acceptor} & \\
\text{C-C/H = best } \sigma \text{ donor} & \\
\text{C-X/Y = best } \sigma \text{ acceptor} & \\
\end{align*}
\]

- **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** ($\text{H}_2\text{NNH}_2$)

- **Disulfides** adopt a **quasi gauche** conformation (dihedral angle $\Theta_{\text{C-S-S-C}}$ of ~90°, cf. ~60° as expected)
  - This is because sulfur is in the second row of the periodic table and the geometry of the sp³ 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
1,2-, 1,3- & 1,4-Diheteroatom arrays - summary

**1,4-**

\[ \text{Diheteroatom array} \]

\[ \sigma \]

C-H/C = best σ donor
C-Y = best σ acceptor

**1,3-**

\[ \text{Diheteroatom array} \]

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