CHEM95002: Orbitals in Organic Chemistry- Stereoelectronics

LECTURE 2 Stereoelectronics of Ground States – Conformational Analysis

Alan C. Spivey
a.c.spivey@imperial.ac.uk

Imperial College
London

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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
  - 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

For theoretical discussions of the relative importance of these effects see
- L. Goodman *Nature* **2001**, 411, 539 ([DOI](https://doi.org/10.1038/35074758)) and 565 ([DOI](https://doi.org/10.1038/35074758))

- **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 $\sigma_{C-H} \rightarrow \pi^*_{C=\text{C}}$
  - This better overlap is a consequence of the $\sim 109^\circ$ angle subtended by the ‘lobes’ of the $\pi^*_{C=\text{C}}$ 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](image)

  $\Delta H^\circ = +16.3 \text{ kJ/mol}$

  - $A^{1,2}$ 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](image)

  $\Delta H^\circ = +12.6 \text{ kJ/mol}$

  - 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:

    ![Diagram of 1,3-Dienes]

    - **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

    ![Maximum πC=C → π*C=C stabilisation for periplanar alkenes]

    - **s-trans** conformation is preferred over the **s-cis** conformation because it suffers less **strain**

    ![Enthalpy difference between conformers](ΔH° = +25 kJ/mol)
Unsaturated hydrocarbons - biaryls

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

  - This is a compromise between:
    - Stabilising $\pi_{\text{C=C}} \rightarrow \pi^*_{\text{C=C}}$ resonance when coplanar
    - Destabilising steric interactions between adjacent *ortho* aromatic substituents when coplanar

- 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 of $A^{1,3}$ eclipsed conformations]

  - 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)

  ![Diagram of $A^{1,3}$ eclipsed conformations with hyperconjugation]

  **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

  ![Diagram of resonance stabilization](image)

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

  ![Diagram of stability](image)

  - 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)
Functional groups – esters cont.

There are three factors which favour the s-cis over the s-trans conformer:

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

2. 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).

3. 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 oxygen is NOT $sp^3$ hybridised.*
Evidence for the ester anomeric effect

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

  ![Diagram](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

  **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 anomeric $n_{\text{Os}} \rightarrow \sigma_{\text{C-O}}^*$ stabilisation is not possible

\[
\begin{array}{c}
\text{s-trans} \\
\end{array}
\]

- As a result, lactones have some different properties to corresponding acyclic esters:
  - *The sp\textsuperscript{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.
  
  \[
  \begin{array}{c}
  \text{O} \\
  \text{O} \\
  \end{array}
  \]

  - *Lactones are more susceptible to nucleophilic attack at the carbonyl carbon than acyclic esters* - because anomeric $n_{\text{Os}} \rightarrow \sigma_{\text{C-O}}^*$ 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)

  \[
  \begin{array}{c}
  \text{O} \\
  \end{array}
  \]

  - *Lactones are more prone to enolisation than acyclic esters* - [$p\text{Ka} \sim 22$ (lactone) *cf.* $p\text{Ka} \sim 25$ (acyclic ester)] because for acyclic esters the anomeric 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 anomeric effect is absent so the carbonyl oxygen is better able to accept electron density from deprotonation. The carbonyl is more like that of a ketone than an ester.
Functional groups - **amides**

- **Amides** prefer to adopt a **planar** conformation with an **s-cis** conformation about the acyl nitrogen single bond:
  
  ![Amide Conformations](image)

  - **Co-planarity** is stabilised by $n_{N\rightarrow} \pi^*_{C=O}$ **resonance** which is stronger than the corresponding $n_{O\rightarrow} \pi^*_{C=O}$ 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 ($\Delta H^\circ \sim 10 \text{kJmol}^{-1}$, 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):

    ![A1,2 Strain](image)

    *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 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:

![Diagram showing chair conformations for 6-ring acetals and cyclohexanes]

- **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

![Diagram showing anomeric effect and bond dipole moments for α- and β-anomers]

- 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 $n_{Nsp3} \rightarrow \sigma^{*}_{C-H}$ 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)
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](image.png)

  *NB. dipoles of C-X & C-Y bonds shown in red*

- **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](https://doi.org/10.1021/ol0000255))

  ![Diagram](image.png)

  *Donor = OR, NR$_2$  
  Acceptor = P, Si*
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 \( n \to \sigma^* \) (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 \( \Theta_{\text{C}-\text{S}-\text{S}-\text{C}} \) of \( \approx 90^\circ \), cf. \( \approx 60^\circ \) 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\( \times \) \( n_\text{S} \to \sigma^*_{\text{S}-\text{C}} \) interactions results in the observed conformational geometry
1,2-, 1,3- & 1,4-Diheteroatom arrays - summary

1,4-

\[ \text{app} \]

\[ \sigma \]

\[ \text{C-H/C = best } \sigma \text{ donor} \]

\[ \text{C-Y = best } \sigma \text{ acceptor} \]

\[ \text{gauche preference} \]

\[ 2x \ (\sigma \rightarrow \sigma^*) \]

1,3-

\[ \text{app} \]

\[ n \]

\[ n_x \text{ and } n_y \text{ = best donors} \]

\[ \text{C-Y and C-X = best } \sigma \text{ acceptors} \]

\[ \text{the anomic effect} \]

\[ 2x \ (n \rightarrow \sigma^*) \]

1,2-

\[ \text{app} \]

\[ n \]

\[ n_x \text{ and } n_y \text{ = best donors} \]

\[ \text{C-C/H = best } \sigma \text{ acceptors} \]

\[ \text{gauche preference} \]

\[ 2x \ (n \rightarrow \sigma^*) \]