Format & scope of lecture 3

• **The conformation of functional groups**
  – Amides
  – Acetals
    • the anomeric effect, Bohlmann IR bands
  – X-C-C-Y and R-X-Y-R’ systems & nucleosides
    • gauche effects
Functional groups - amides

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

  - **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 ($\Delta H^o \sim 10\, \text{kJmol}^{-1}$, 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):
The anomeric 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 $n_{Osp3} \rightarrow \sigma^*_{C-X}$ **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)

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

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**Diagram**

- Generalised anomeric effect
  - Preferred conformation

**Bond Lengths**

- 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 $n_{N\text{sp}^3} \rightarrow \sigma^*_{C-H}$ **anomeric interactions** which weaken the acceptor (i.e. C-H) bonds
  - That these bands (2700-2800 cm$^{-1}$) only occur when there are at least 2 appropriately orientated C-H bonds presumably reflects the weak nature of the interaction
The gauche effect – 1,2-disubstituted ethanes

- **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**)

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

- **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)

\[
\begin{align*}
\text{Donor} = \text{OR, NR}_2 \\
\text{Acceptor} = \text{P, Si}
\end{align*}
\]
The gauche effect – *peroxides, hydrazines, disulfides*

- **X-Y containing compounds** (where X and Y are electronegative groups) also adopt **gauche** rather than **anti** conformations
  - Stabilisation accrues from $n \rightarrow \sigma^*$ interactions between antiperiplanar donor lone pairs on X and Y and acceptor bonds (also referred to as the gauche effect)
  - *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 $\sim 90^\circ$, 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 $2 \times n_\text{S} \rightarrow \sigma^*_\text{S-C}$ interactions results in the observed conformational geometry
1,2-, 1,3- & 1,4-Diheteroatom arrays - summary

1,4-  \[
\begin{array}{c}
\text{app} \\
\text{C/H} & \text{C/H} \\
X & Y
\end{array}
\]

= \[
\begin{array}{c}
\sigma \\
n \\
\text{C/H} & \text{C/H} \\
X & Y
\end{array}
\]

diameter \quad \text{app} \quad \text{app}

\begin{array}{c}
\text{gauche-favoured} \\
\text{X} & \text{Y}
\end{array}

\text{the gauche effect}

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

1,4-  \[
\begin{array}{c}
\text{C-H/C} = \text{best } \sigma \\
\text{C-Y} = \text{best } \sigma^* \\
\text{app} \\
\text{app}
\end{array}
\]

= \[
\begin{array}{c}
\text{gauche-favoured} \\
\text{X} & \text{Y}
\end{array}
\]

1,3-  \[
\begin{array}{c}
\text{app} \\
\text{app} \\
\text{X} & \text{Y}
\end{array}
\]

= \[
\begin{array}{c}
\text{app} \\
n \\
\text{X} & \text{Y}
\end{array}
\]

\begin{array}{c}
\text{nX} \text{ and } nY = \text{best donors} \\
\text{C-Y and C-X = best } \sigma^*_\text{ acceptors}
\end{array}

\text{the anomeric effect}

2x (n \rightarrow \sigma^*)

1,2-  \[
\begin{array}{c}
\text{app} \\
\text{X} & \text{Y} \\
\text{C/H} & \text{C/H}
\end{array}
\]

= \[
\begin{array}{c}
n \\
\text{X} & \text{Y} \\
\text{C/H} & \text{C/H}
\end{array}
\]

\begin{array}{c}
nX \text{ and } nY = \text{best donors} \\
\text{C-C/H = best } \sigma^*_\text{ acceptors}
\end{array}

\text{the gauche effect}

2x (n \rightarrow \sigma^*)
Nucleos(t)ides - gauche & anomeric effects

- The conformation of the furanosyl rings in RNA & DNA is important because small changes in conformation are amplified along a strand to give gross differences in structure and hence properties. Hydrogen bonding & dipole minimisation effects are important as are anomeric & gauche effects
  - There are two extreme conformers of nucleoside furanosyl rings that interconvert by Berry pseudorotation: a north-type (N) and a south-type (S)

- DNA tends to adopt an S-type conformation
  - The N-type conformation allows an $n_O \rightarrow \sigma^*_C-N$ anomeric interaction between a lone pair on the furanosyl ring oxygen and the C1-N glycosidic bond whereas the S-type conformation allows the oxygen substituents at C3' and C4' to benefit from a gauche effect. The gauche effect is the stronger and so an S-type conformation is generally preferred.

- RNA tends to adopt an N-type conformation
  - The additional C2' hydroxyl group allows additional gauche effects to operate as well as additional hydrogen bonding opportunities and the net result is that the N-type is generally preferred

- For a brief review see: Plavec ‘How do the Energetics of the Stereoelectronic Gauche and Anomeric Effects Modulate the Conformation of Nucleos(t)ides?’ Pure Appl. Chem. 1996, 68, 2137