

CHEM95002:
Orbitals in Organic Chemistry- Stereoelectronics

***LECTURE 2 Stereoelectronics of Ground States –
Conformational Analysis***

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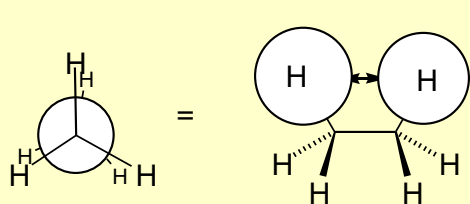
Feb 2020

Format & scope of lecture 2

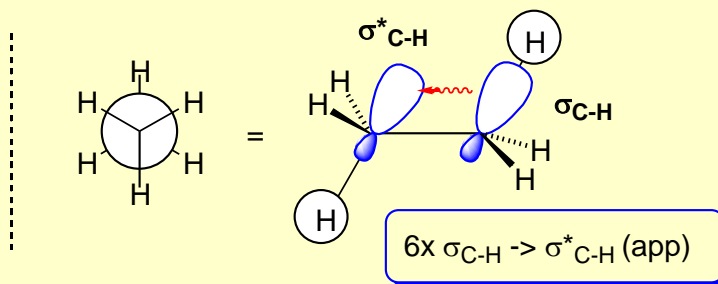
- ***The conformation of hydrocarbons***
 - Ethane & alkanes
 - Propene & alkenes
 - A^{1,2} and A^{1,3} strain
 - 1,3-Dienes & biaryls
- ***The conformation of functional groups***
 - Aldehydes & ketones
 - Esters & lactones
 - the ester anomeric effect
 - Amides
 - Acetals
 - the anomeric effect, Bohlmann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

Saturated hydrocarbons - ethane

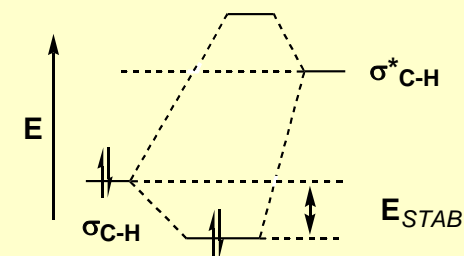
- **Ethane** prefers to adopt a **staggered** rather than **eclipsed** conformation because:
 - 1) The **eclipsed conformers** are **destabilised** by **steric interactions**
 - *i.e.* by non-bonded, van der Waals repulsions between the atoms concerned
 - 2) The **staggered conformers** are **stabilised** 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



van der Waals repulsions are maximised when eclipsed (shown)



'Cieplak' stereoelectronic stabilisation is maximised when staggered (all six interacting bonds are anti periplanar)



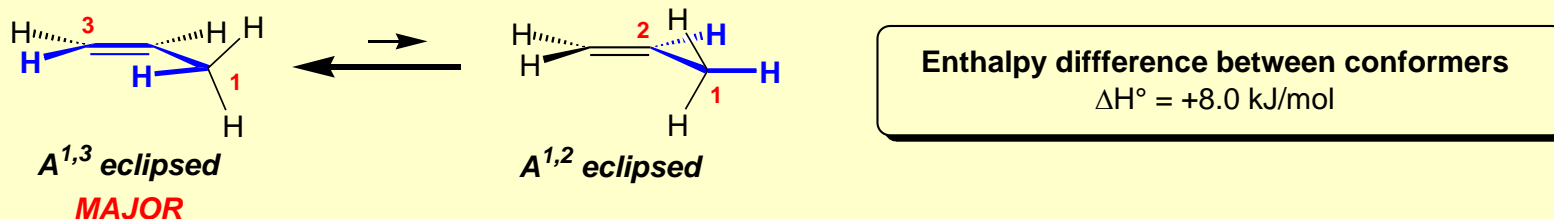
steric destabilisation of eclipsed conformations

stereoelectronic stabilisation of staggered conformations

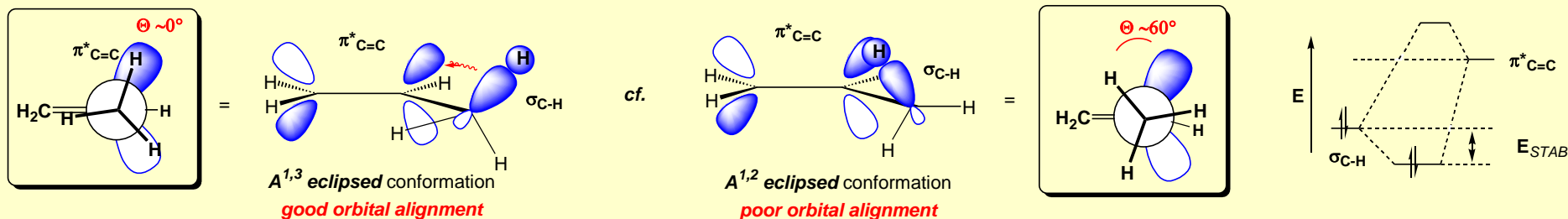
- For theoretical discussions of the relative importance of these effects see
 - L. Goodman *Nature* **2001**, 411, 539 ([DOI](#)) and 565 ([DOI](#))
 - P.R. Schreiner *Angew. Chem. Int. Ed.* **2002**, 41, 3579 ([DOI](#))
 - F.M. Bickelhaupt *Angew. Chem. Int. Ed.* **2003**, 42, 4183 ([DOI](#))
 - F. Weinhold *Angew. Chem. Int. Ed.* **2003**, 42, 4188 ([DOI](#))
- **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 14.8kJ/mol)



- The **$A^{1,3}$ eclipsed** conformation allows for better overlap of the orbitals for stabilising $\sigma_{C-H} \rightarrow \pi^*_{C=C}$ **hyperconjugation/ σ -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



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

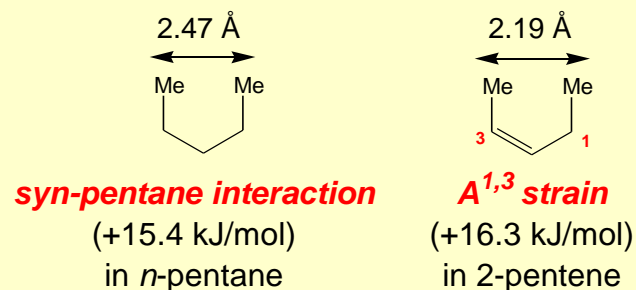
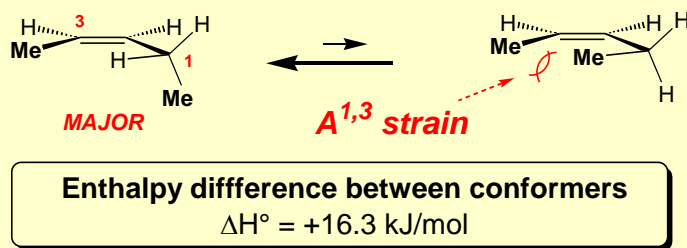
- **NB.** Steric effects dominate for groups larger than hydrogen...

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

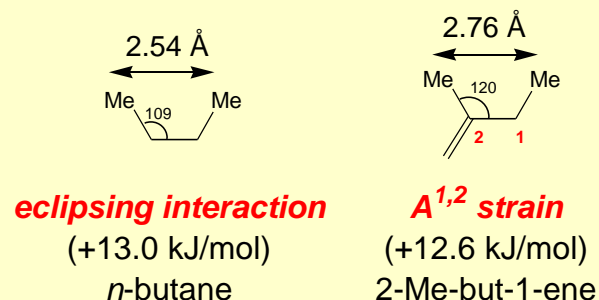
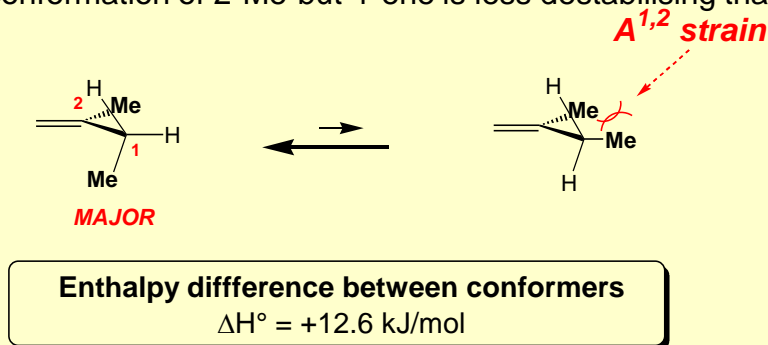
– $A^{1,3}$ **strain** is the destabilising eclipsing interaction shown below:

- 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



– $A^{1,2}$ **strain** is the destabilising eclipsing interaction shown below:

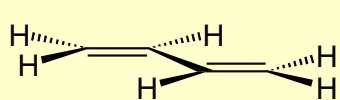
- As the C-C-C angle at an sp^3 carbon ($\sim 109^\circ$) is smaller than at an sp^2 carbon ($\sim 120^\circ$), $A^{1,2}$ **strain** in the illustrated conformation of 2-Me-but-1-ene is less destabilising than the eclipsing interaction in the illustrated conformation of *n*-butane



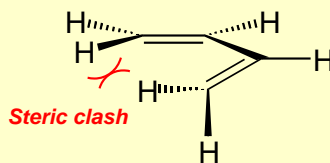
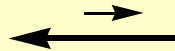
- For a given pair of groups (e.g. Me \leftrightarrow Me, above), $A^{1,3}$ **strain** is more destabilising than $A^{1,2}$ **strain**. The lowest energy conformation adopted by complex alkenes is that in which both $A^{1,2}$ & $A^{1,3}$ **strains** are minimised

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
MAJOR

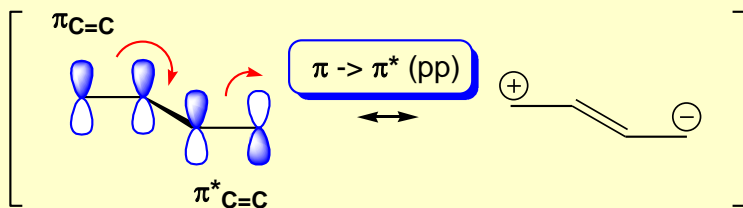


s-cis

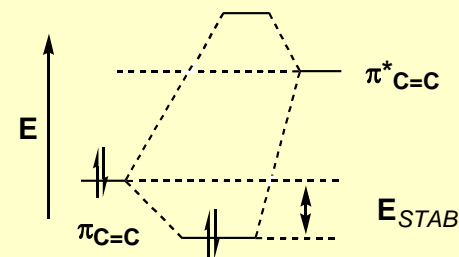
Enthalpy difference between conformers

$$\Delta H^\circ = +25 \text{ kJ/mol}$$

- **Co-planarity** of the π bonds allows for optimal overlap of the orbitals for $\pi_{\text{C}=\text{C}} \rightarrow \pi^*_{\text{C}=\text{C}}$ resonance stabilisation



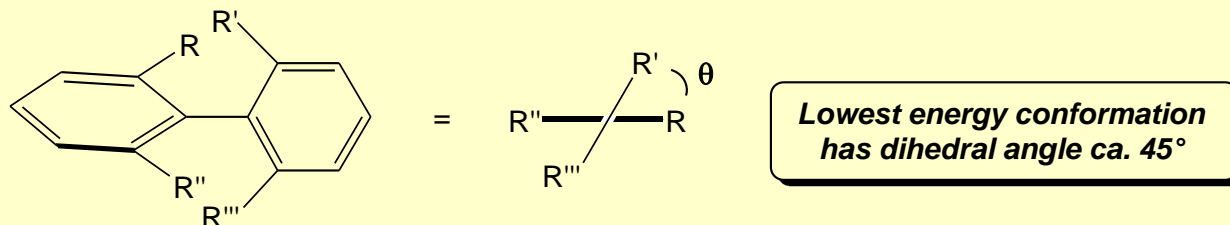
Maximum $\pi_{\text{C}=\text{C}} \rightarrow \pi^*_{\text{C}=\text{C}}$ stabilisation
for periplanar alkenes
(i.e. best overlap)



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

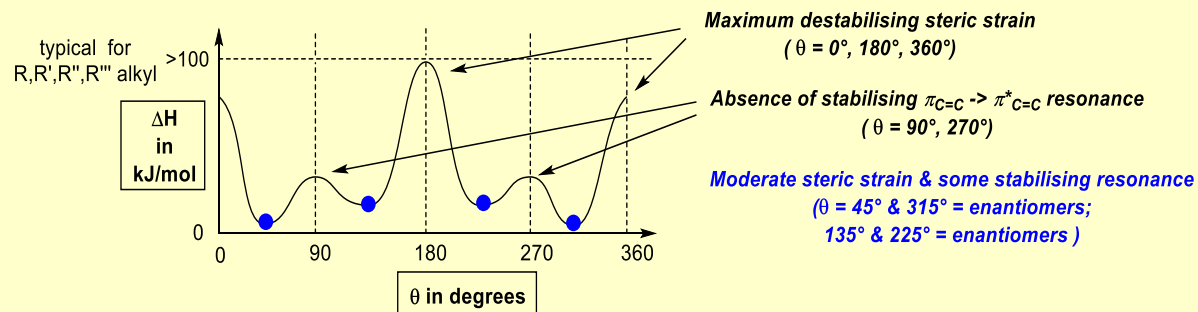
Unsaturated hydrocarbons - *biaryls*

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



– This is a compromise between:

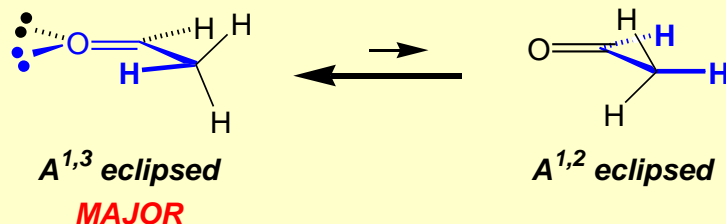
- Stabilising $\pi_{C=C} \rightarrow \pi^*_{C=C}$ resonance when coplanar
- Destabilising steric interactions between adjacent *ortho* aromatic substituents when coplanar



- 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**

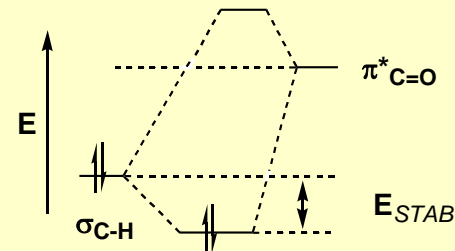
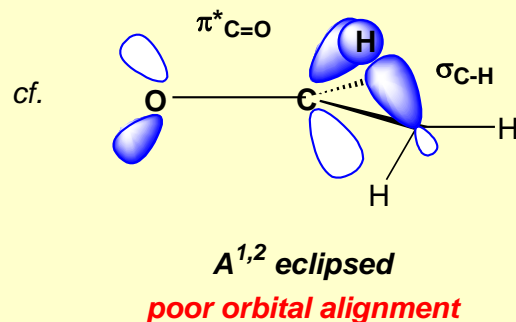
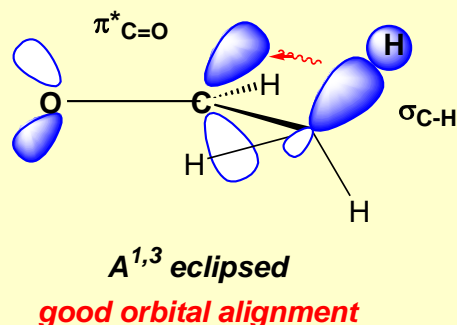
Functional groups – aldehydes & ketones

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



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

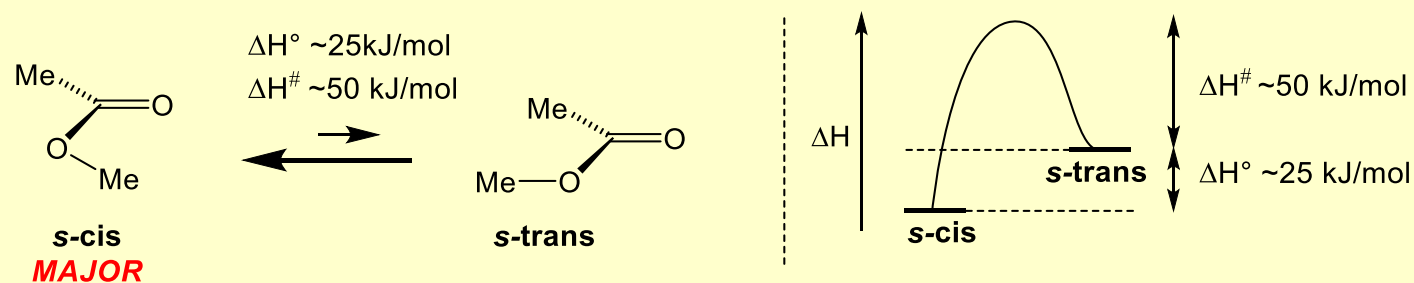


NB. of course there are two identical interactions: on the top and bottom faces

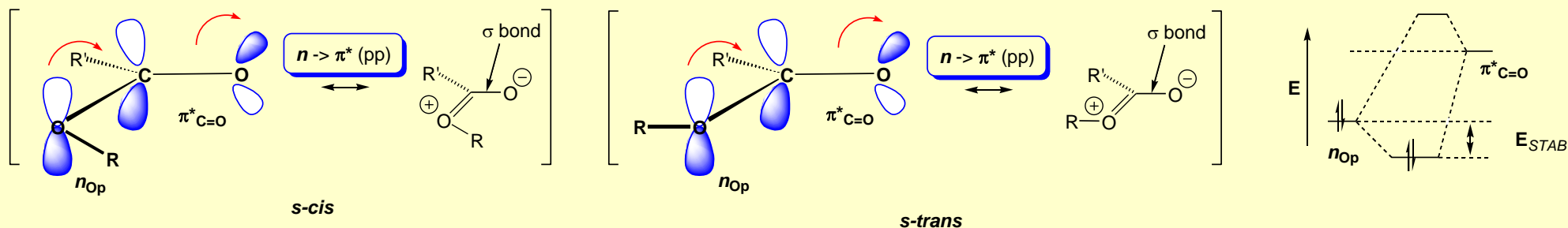
- Moreover, **$A^{1,3}$ strain** is less significant in these compounds relative to allylic compounds as the sp^2 hybrid lone pairs on the carbonyl oxygen are 'small' relative to any substituent on an alkene

Functional groups - esters

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



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

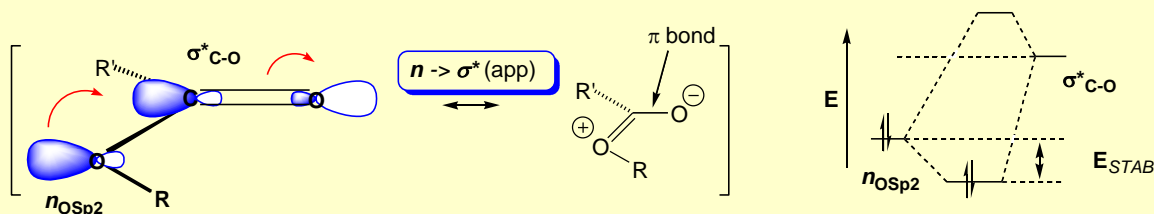


- Because the p-orbital on oxygen is symmetrical resonance does not favour s-cis over s-trans or *vice versa*
- However, there is a relatively strong enthalpic preference for the **s-cis** conformer over the **s-trans** one ($\Delta H^\circ \sim 25 \text{ kJ mol}^{-1}$ cf. $\sim 10 \text{ kJ mol}^{-1}$ for amides) although the barrier to rotation about the acyl oxygen bond (*i.e.* interconversion) is relatively low ($\Delta H^\ddagger \sim 50 \text{ kJ mol}^{-1}$ cf. $\sim 85 \text{ kJ mol}^{-1}$ for amides)

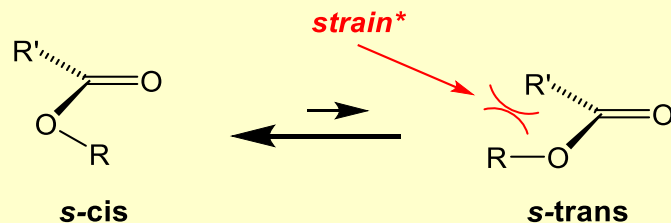
Functional groups – esters cont.

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

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

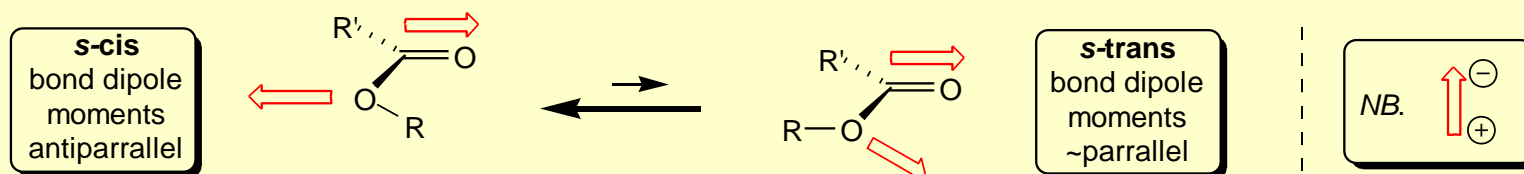


- There is significant '**A^{1,2} strain**' in the **s-trans** form (the sp^2 hybrid lone pair on the carbonyl oxygen is 'small' relative to a substituent bonded to the acyl carbon atom)



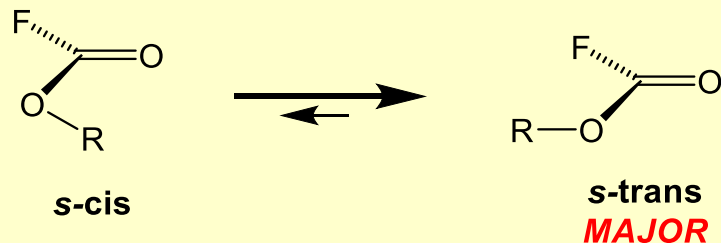
* NB. This strain is often referred to as $A^{1,2}$ -strain despite the fact that the non-carbonyl oxygen is NOT sp^3 hybridised

- 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)



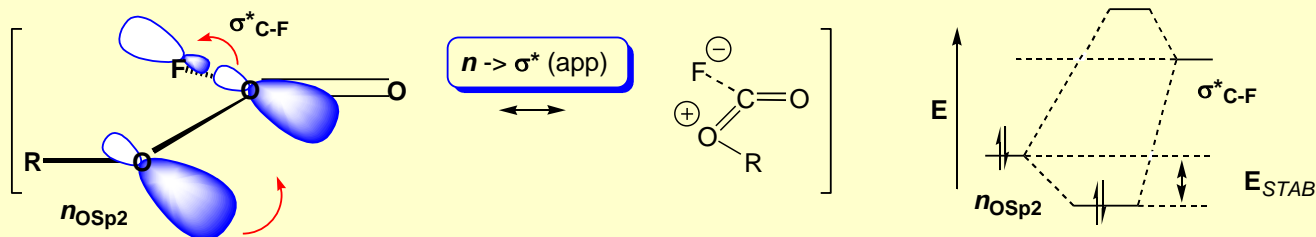
Evidence for the ester anomeric effect

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



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')

- Here, the σ^* orbital of the C-F bond is a better acceptor than the σ^* 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

Functional groups - *lactones*

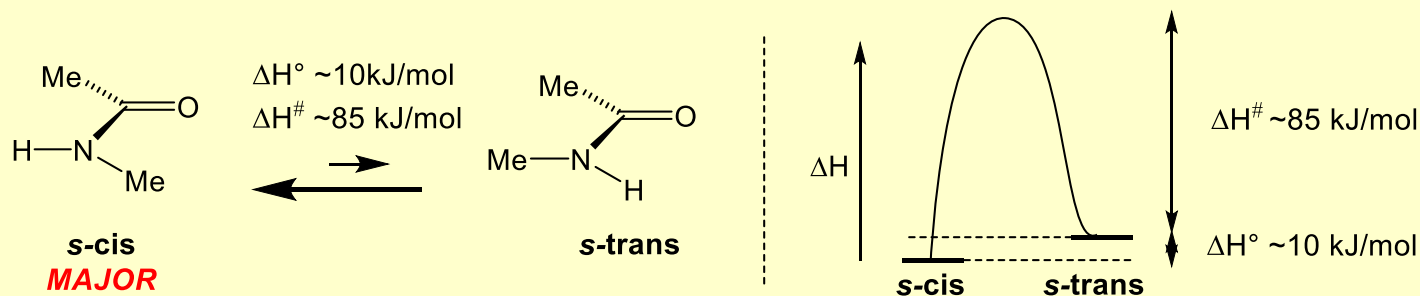
- **5- & 6-Membered lactones** contain an ester function with an enforced **s-trans** conformation so **anomeric $n_{\text{Osp}^2} \rightarrow \sigma^*_{\text{C-O}}$ stabilisation** is not possible



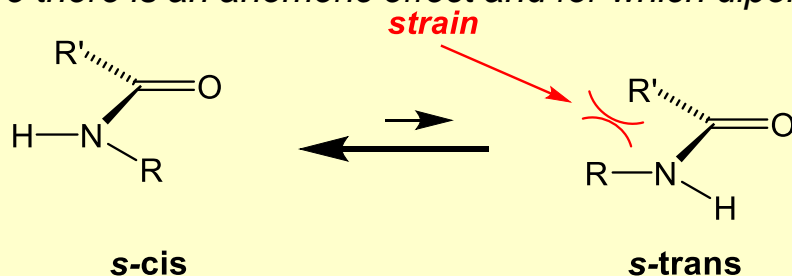
- As a result, lactones have some different properties to corresponding acyclic esters:
 - **The sp^2 hybrid, non-carbonyl oxygen lone pair in a lactone is more basic/nucleophilic than in an acyclic ester** - because the lone pair is 'more available' for interaction with protons/metal cations etc.
 - **Lactones are more susceptible to nucleophilic attack at the carbonyl carbon than acyclic esters** - because anomeric $n_{\text{Osp}^2} \rightarrow \sigma^*_{\text{C-O}}$ 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** - [pKa ~22 (lactone) *cf.* pKa ~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 α -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:



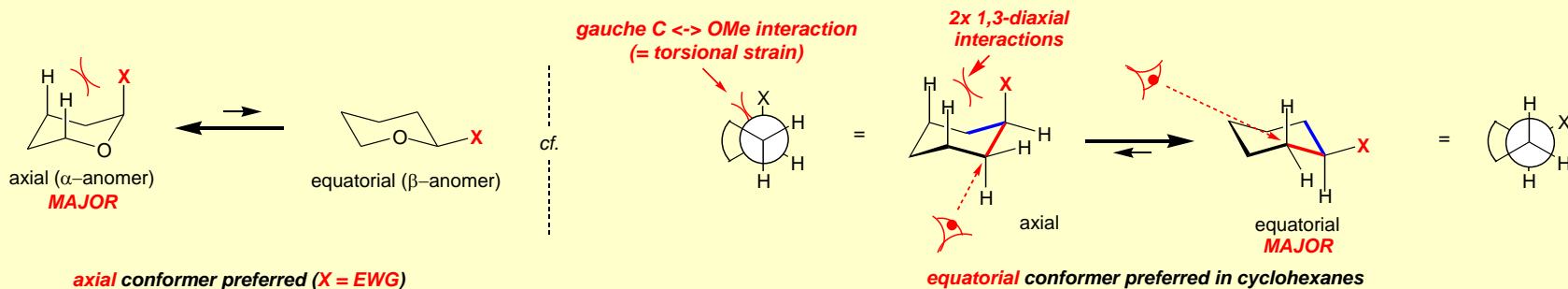
- **Co-planarity** is stabilised by $n_{\text{Np}} \rightarrow \pi^*_{\text{C=O}}$ **resonance** which is stronger than the corresponding $n_{\text{Op}} \rightarrow \pi^*_{\text{C=O}}$ resonance in esters because the nitrogen lone pair is a better donor than the oxygen lone pair
 - This is manifested in the high barrier to rotation about the acyl nitrogen bond ($\Delta H^\ddagger \sim 85 \text{ kJ/mol}^{-1}$, cf. $\sim 50 \text{ kJ/mol}^{-1}$ 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 ($\Delta H^\circ \sim 10 \text{ kJ/mol}^{-1}$, cf. $\sim 25 \text{ kJ/mol}^{-1}$ 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 anomeric effect – 6-ring acetals

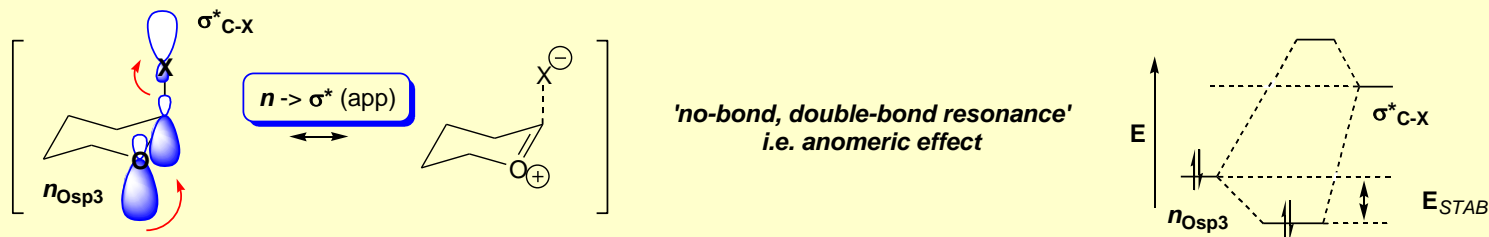
- **6-ring acetals prefer to adopt chair conformations in which the anomeric oxygen is axial**
 - This is in contrast to the situation for cyclohexanes in which the substituent adopts an equatorial position 1) to avoid unfavourable 1,3-diaxial or '1,3-flagpole' interactions, & 2) to minimise gauche interactions:



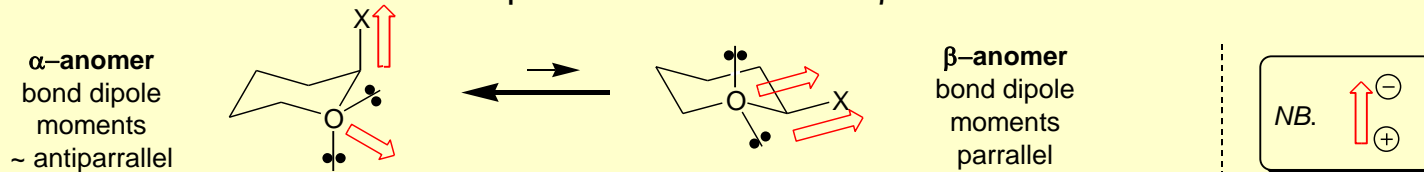
NB. There are 2 of the indicated gauche interactions for isomer C: looking along the 'red' bond (as shown) and also looking along the 'blue' bond (not shown)

- **Two factors favour the α -anomer:**

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

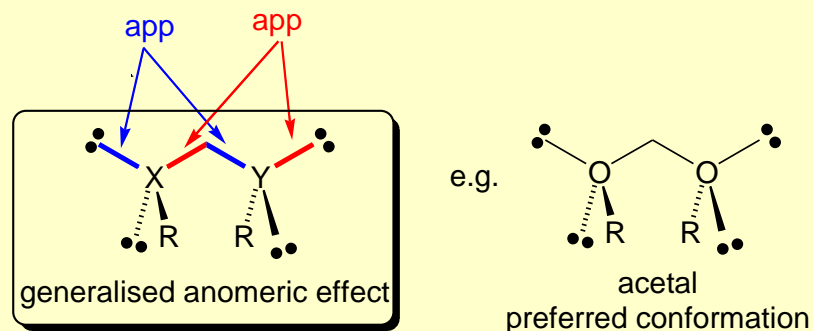


- The α -anomer has a smaller overall dipole moment than the β -anomer

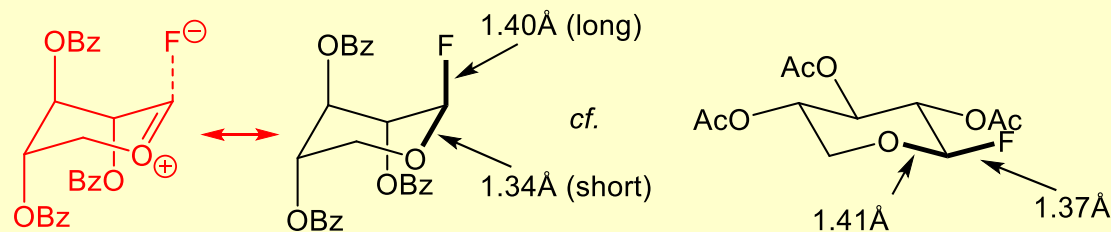


The generalised anomeric effect & structural evidence

- **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)



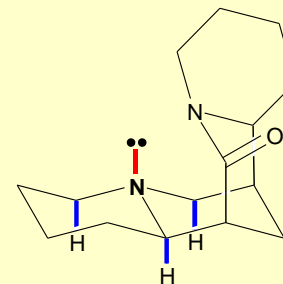
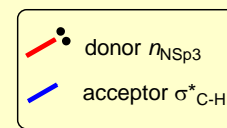
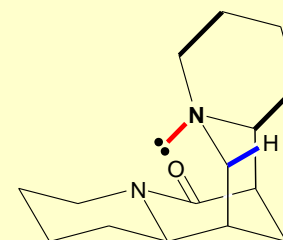
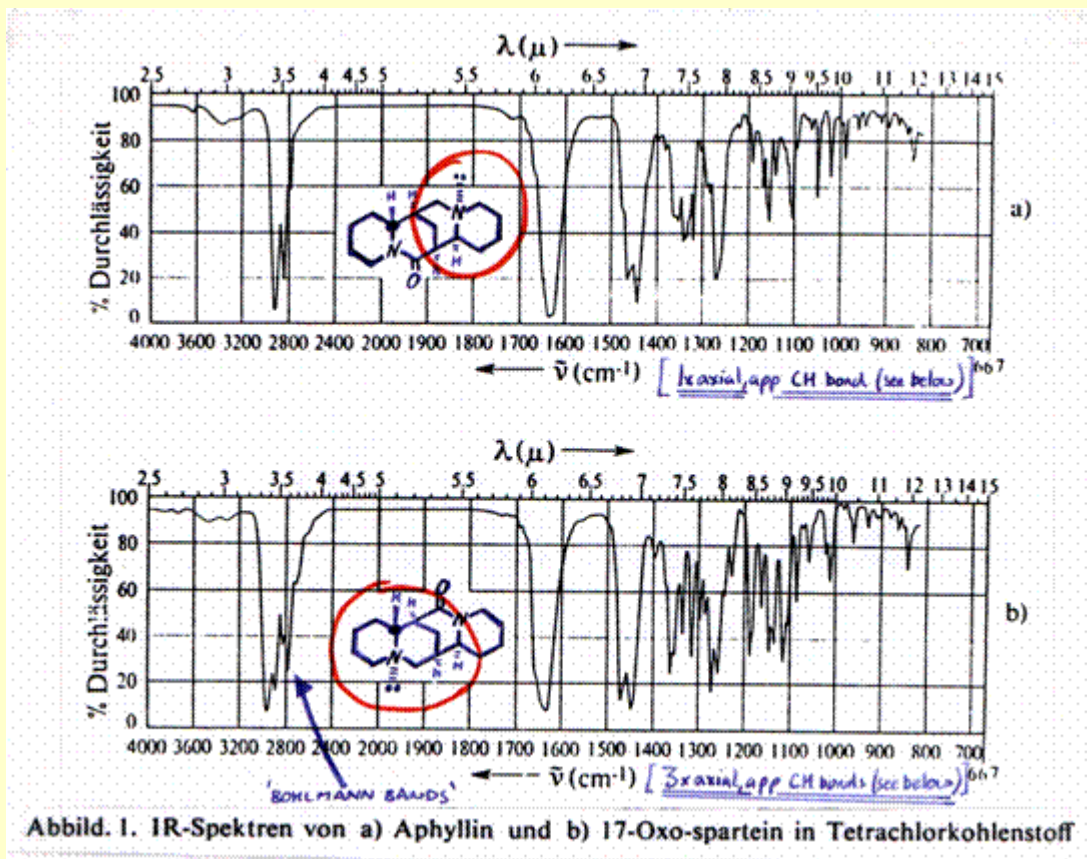
- **Evidence for the anomeric effect comes from e.g. bond length analysis of fluoro sugars**



X-ray bond lengths of fluorosugars...evidence for lengthening (and weakening) of the 'acceptor' C-F bond.

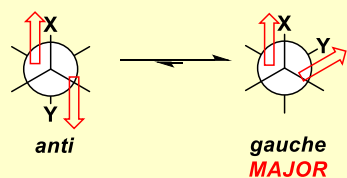
The anomeric effect – alkaloid ‘Bohlmann bands’

- **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 $n_{\text{Nsp}^3} \rightarrow \sigma^*_{\text{C-H}}$ **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
 - E. Winterfeldt *Liebigs Ann. Chem.* **1994**, I-XXXIV (retrospective on Ferdinand Bohlmann 1921-1991, [DOI](#))
 - For recent use during Terengganensine A synthesis see: J. Zhu *Angew. Chem. Int Ed.* **2016**, 55, 6556 ([DOI](#))

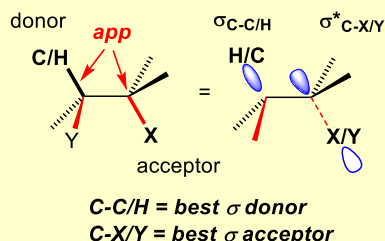


1,2-Disubstituted ethanes - *gauche* preference

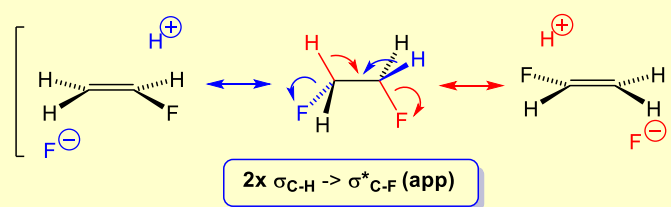
- **X-C-C-Y** containing compounds (where X and Y are electronegative groups) adopt **gauche** rather than **anti** conformations – **despite this conformation having a larger overall dipole**
 - Stabilisation accrues from $\sigma \rightarrow \sigma^*$ interactions between the best combinations of anti-periplanar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



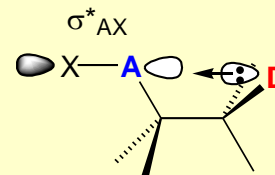
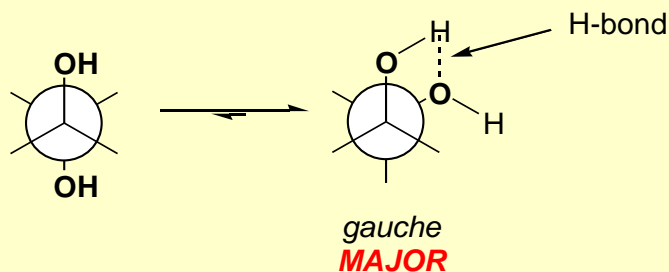
NB. dipoles of C-X & C-Y bonds shown in red



e.g. 1,2-difluoroethane



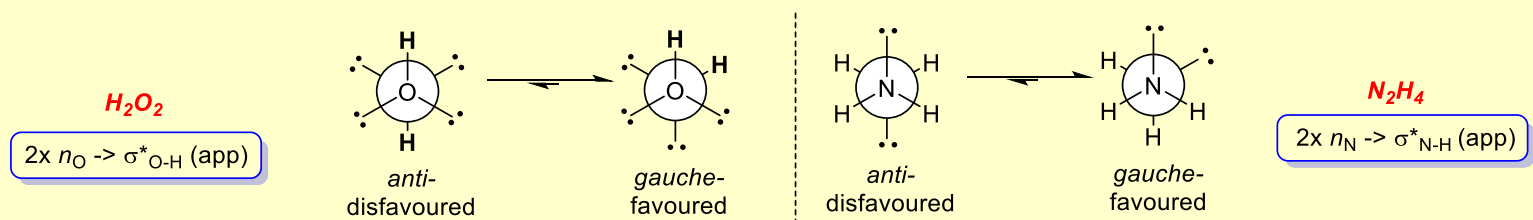
- NB. In the case of 1,2-ethanediol an **intramolecular H-bond** also stabilises the **gauche form**
- Also, 1,4-hypercoordination has been proposed as an additional factor stabilising **gauche conformations**, particularly when X or Y is a second row element: Inagaki *Org. Lett.* **1999**, 1, 1145 ([DOI](#))



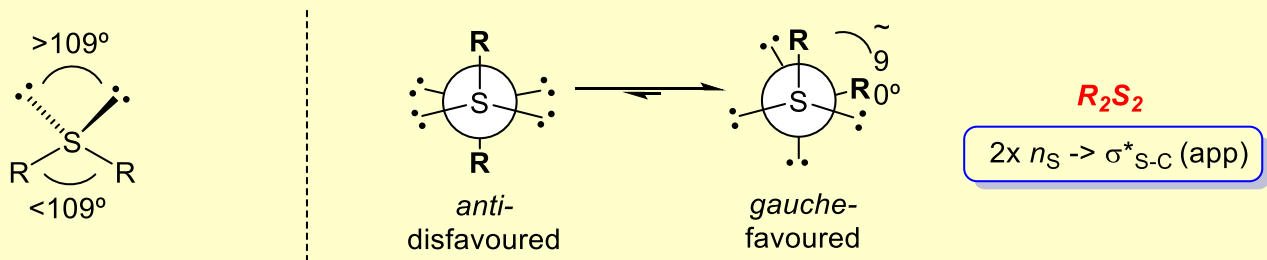
Donor = OR, NR₂
Acceptor = P, Si

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 $n \rightarrow \sigma^*$ (anomeric) interactions between antiperiplanar donor lone pairs on X and Y and acceptor bonds
 - e.g. **hydrogen peroxide** (H_2O_2) and **hydrazine** (H_2NNH_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 $2x n_{\text{S}} \rightarrow \sigma^*_{\text{S-C}}$ interactions results in the observed conformational geometry



1,2-, 1,3- & 1,4-Diheteroatom arrays - *summary*

