CHEM95002:
Orbitals in Organic Chemistry- Stereoelectronics

LECTURE 2 *Stereoelectronics of Ground States – Conformational Analysis*

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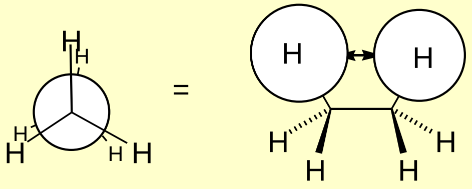
Format & scope of lecture 2

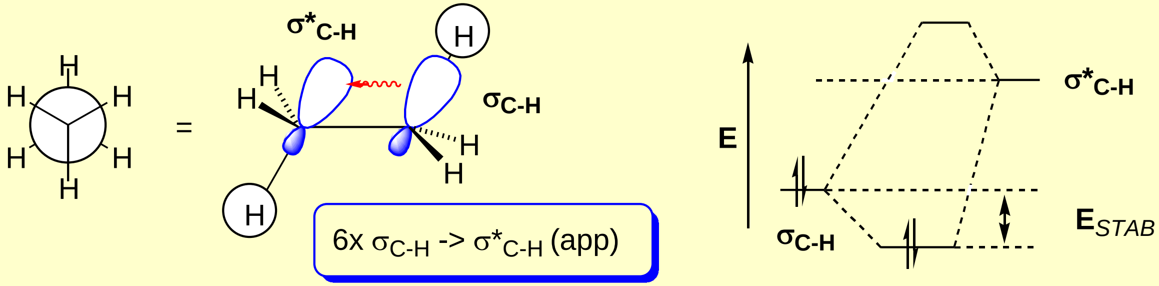
- ***The conformation of hydrocarbons***
  - Ethane & alkanes
  - Propene & alkenes
    - $A^{1,2}$ and $A^{1,3}$ strain
  - 1,3-Dienes & biaryls
- ***The conformation of functional groups***
  - Aldehydes & ketones
  - Esters & lactones
    - the ester anomeric effect
  - Amides
  - Acetals
    - the 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 **σ → σ*** ***stereoelectronic interactions***
    - *i.e.* in a staggered conformation all the bonds on adjacent carbons are ***anti periplanar*** to each other allowing six σ → σ* stabilising interactions



van der Waals repulsions are
<u>maximised</u> when <u>eclipsed</u> (shown)



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

steric destabilisation of eclipsed conformations

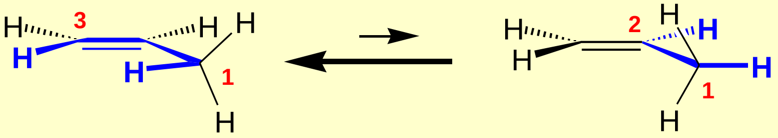
stereoelectronic stabilisation of staggered conformations

  - 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)



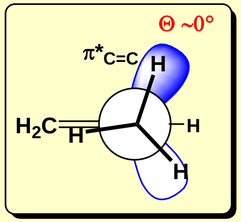
$A^{1,3}$ eclipsed

MAJOR

$A^{1,2}$ eclipsed

Enthalpy diffference between conformers
$\Delta H° = +8.0$ kJ/mol

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



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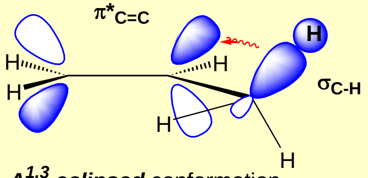
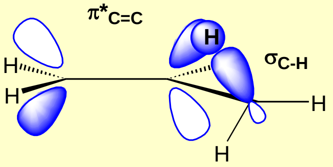


$A^{1,3}$ eclipsed conformation

good orbital alignment

cf.



$A^{1,2}$ eclipsed conformation

poor orbital alignment

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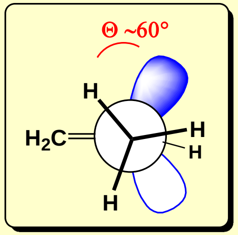
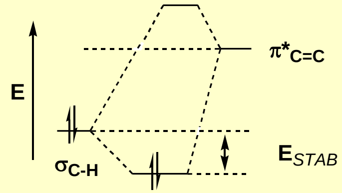


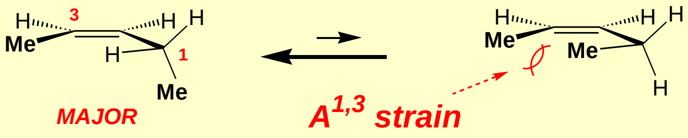


NB. There are two concurrent interactions:on the top face (as indicated) *and* on the bottom face

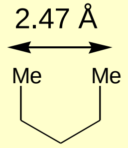
  - ***NB. Steric effects dominate for groups larger than hydrogen...***

Higher alkenes – *$A^{1,2}$ vs $A^{1,3}$ strain*

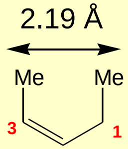
- ***Steric** interactions (i.e. **van der Waals** forces) dominate affairs when groups other than H are involved*
  - ***$A^{1,3}$ strain*** is the destabilising eclipsing interaction shown below:
    - As C=C double bonds are shorter than C-C single bonds, ***$A^{1,3}$ strain*** in the illustrated conformation of 2-pentene is ***more destabilising*** than the ***syn-pentane*** interaction in the illustrated conformation of *n*-pentane



Enthalpy diffference between conformers
ΔH° = +16.3 kJ/mol

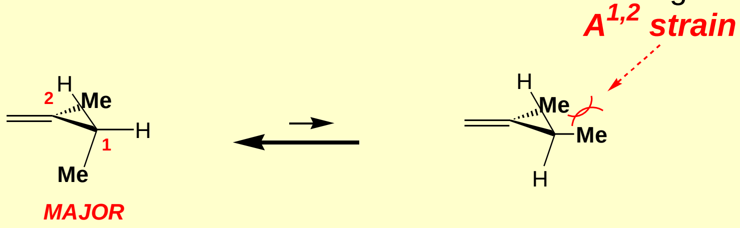


syn-pentane interaction
(+15.4 kJ/mol)
in *n*-pentane

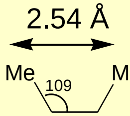


$A^{1,3}$ strain
(+16.3 kJ/mol)
in 2-pentene

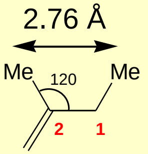
  - ***$A^{1,2}$ strain*** is the destabilising eclipsing interaction shown below:
    - As the C-C-C angle at an sp^3 carbon (~109°) is smaller than at an sp^2 carbon (~120°), ***$A^{1,2}$ strain*** in the illustrated conformation of 2-Me-but-1-ene is less destabilising than the eclipsing interaction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



Enthalpy diffference between conformers
ΔH° = +12.6 kJ/mol



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

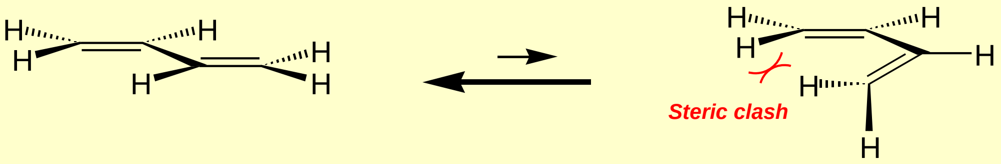


$A^{1,2}$ strain
(+12.6 kJ/mol)
2-Me-but-1-ene

  - 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:

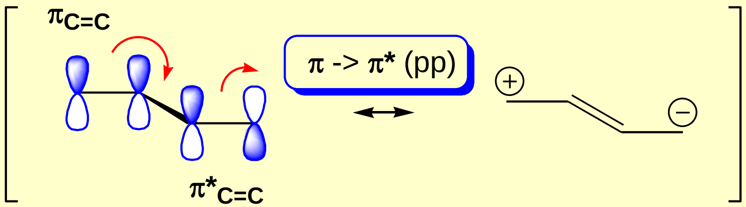


s-trans
MAJOR

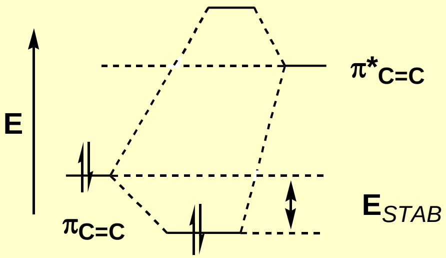
s-cis

Enthalpy diffference between conformers
ΔH° = +25 kJ/mol

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



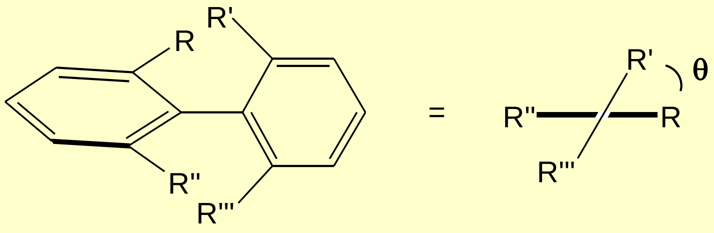
Maximum $\pi_{C=C}$ -> $\pi^*_{C=C}$ stabilisation
for periplanar alkenes
(*i.e.* best overlap)



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

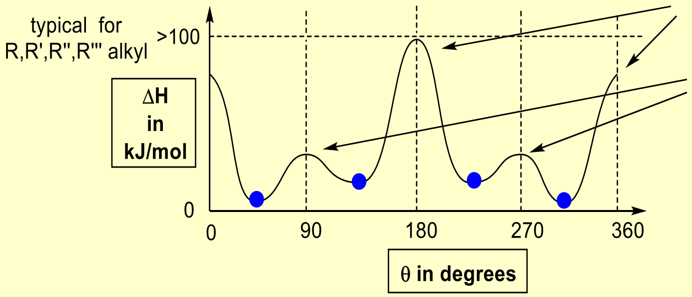
Unsaturated hydrocarbons - *biaryls*

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



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



Maximum destabilising steric strain
(θ = 0°, 180°, 360°)

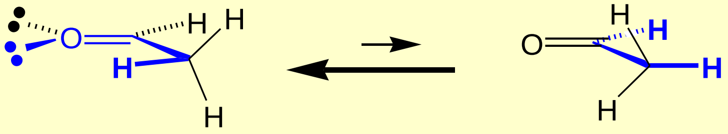
Absence of stabilising $\pi_{C=C}$ -> $\pi^*_{C=C}$ resonance
(θ = 90°, 270°)

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

- 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*



$A^{1,3}$ eclipsed

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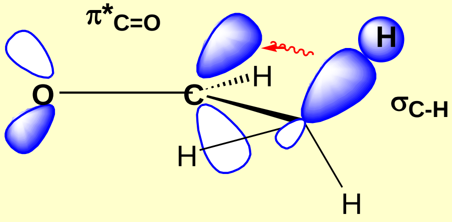
$A^{1,2}$ eclipsed

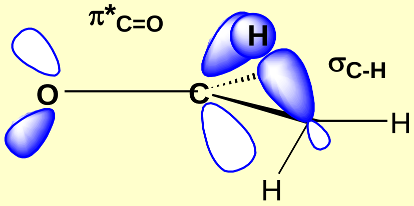
  - As for allylic systems, ***$A^{1,3}$ eclipsed*** conformations allow stabilising $\sigma_{C\text{-}H/C} \rightarrow \pi^*_{C=O}$ ***hyperconjugation/ σ-conjugation***
    - These interactions are more significant than the corresponding interactions in an allylic system because the $\pi^*_{C=O}$ orbital 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)



$A^{1,3}$ eclipsed

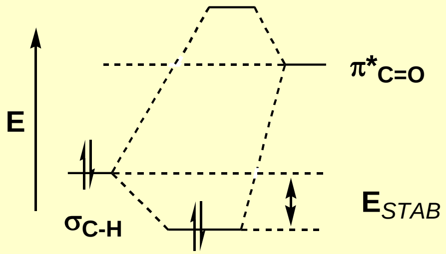
good orbital alignment

cf.



$A^{1,2}$ eclipsed

poor orbital alignment

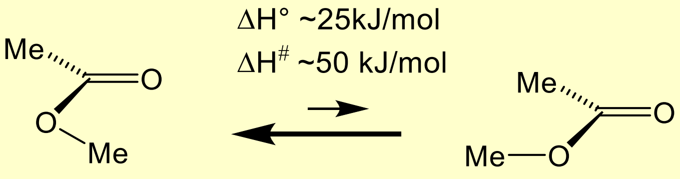


NB. of course there are two identical interactions: on the top and bottom faces

  - 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:*



***s*-cis**
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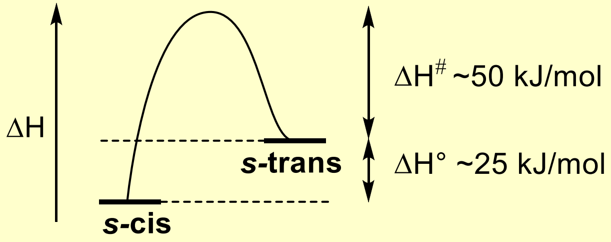
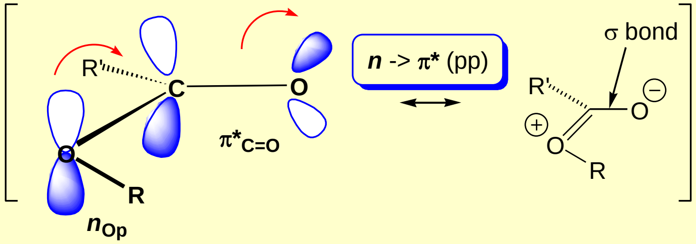
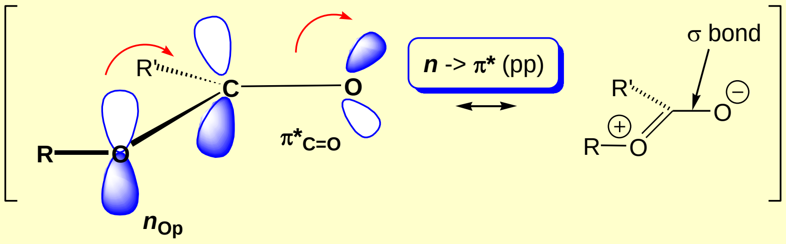
***s*-trans**



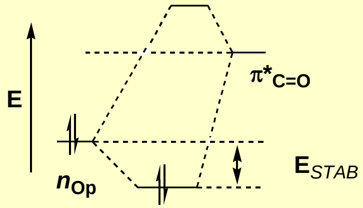
  - ***Co-planarity*** is stabilised by $n_{Op} \rightarrow \pi^*_{C=O}$ ***resonance***



s-cis



s-trans

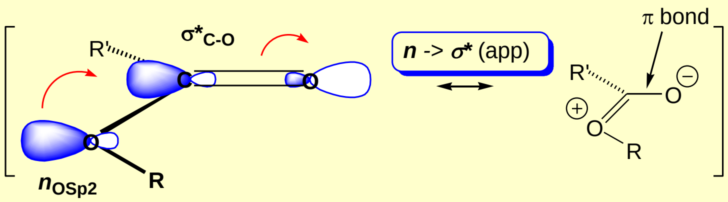


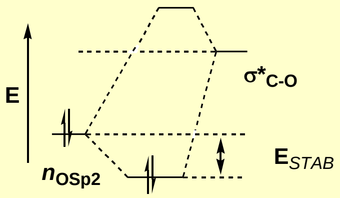
  - Because the p-orbital on oxygen is symmetrical resonance does not favour *s*-cis over *s*-trans or *vice versa*

  - However, there is a relatively strong enthalpic preference for the ***s*-cis** conformer over the ***s*-trans** one (ΔH° ~25kJmol^{-1} *cf.* ~10kJmol^{-1} for amides) although the barrier to rotation about the acyl oxygen bond (*i.e.* interconversion) is relatively low (ΔH$^{\#}$ ~50kJmol^{-1} *cf.* ~85kJmol^{-1} for amides)

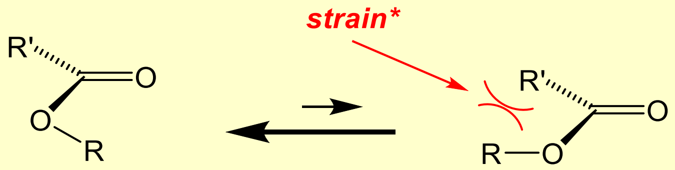
Functional groups – *esters cont.*

- *There are **three factors** which favour the **s-cis** over the **s-trans** conformer:*
  - There is a $n_{\mathrm{Osp^2}} \rightarrow \sigma^*_{\text{C-O}}$ ***anomeric effect*** which stabilises the ***s*-cis** form





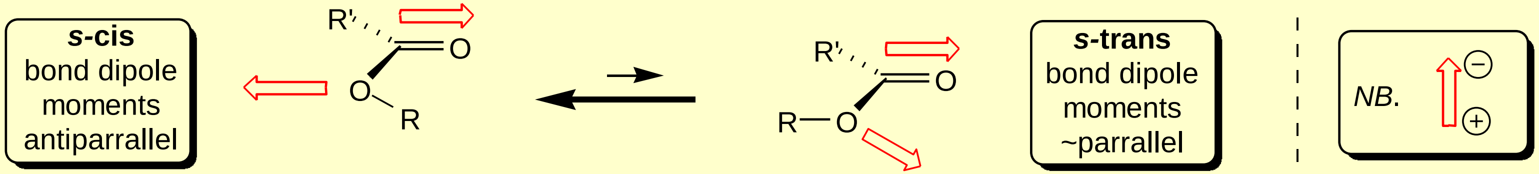
  - There is significant ‘***A*^{1,2} *strain’*** in the ***s*-trans** form (the sp^2 hybrid lone pair on the carbonyl oxygen is ‘small’ relative to a substituent bonded to the acyl carbon atom)



***s*-cis** ***s*-trans**

* *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)



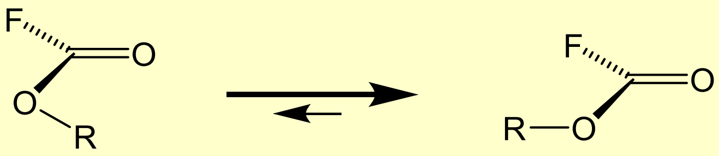
***s*-cis**
bond dipole
moments
antiparrallel

***s*-trans**
bond dipole
moments
~parrallel

NB.

Evidence for the ester anomeric effect

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



***s*-cis**

***s*-trans**
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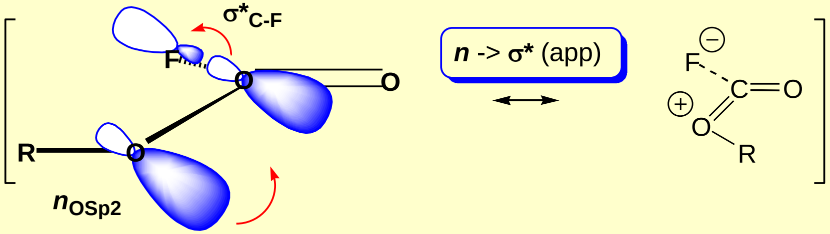
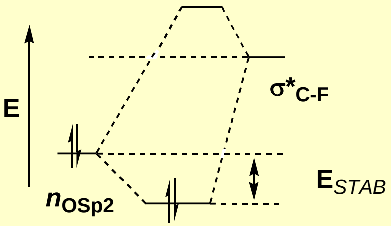
NB. the *cis* and *trans* designations
here are relative to the carbonyl group
and not strictly according to CIP rules
(where F>O in 'priority')

  - 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

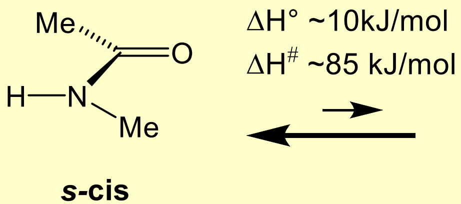
Functional groups - *lactones*

- ***5- & 6-Membered lactones*** *contain an ester function with an enforced* ***s-trans*** *conformation so* ***anomeric*** $\boldsymbol{n_{Osp2} \rightarrow \sigma^*_{C\text{-}O}}$ ***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 $n_{Osp2} \rightarrow \sigma^*_{C\text{-}O}$ 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.

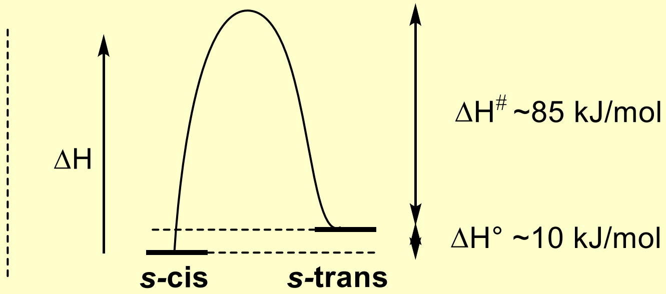
Functional groups - *amides*

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

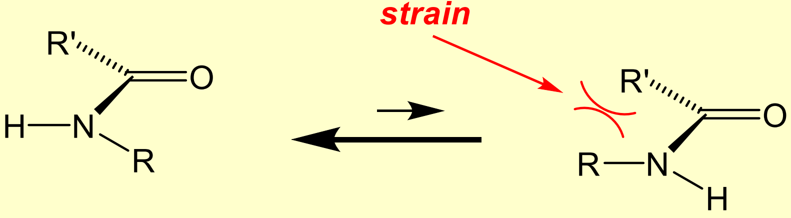


***s*-cis**
MAJOR

***s*-trans**



  - ***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 (ΔH# ~85kJmol^{-1}, *cf.* ~50kJmol^{-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 (ΔH° ~10kJmol^{-1}, *cf.* ~25kJmol^{-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)*:



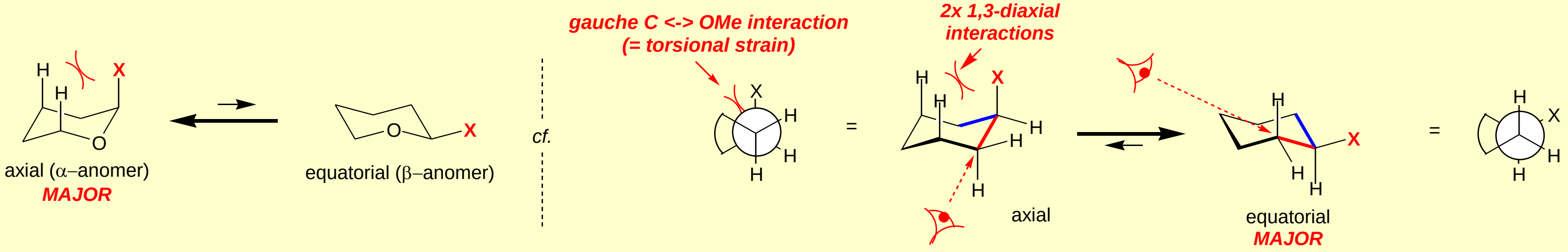
***s*-cis**

***s*-trans**

* *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:

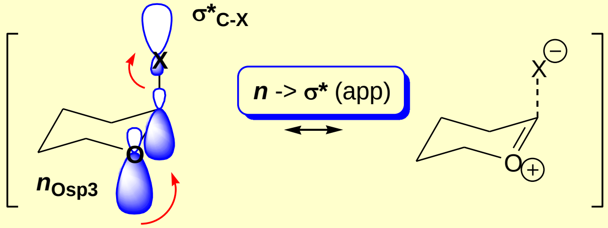


***axial* conformer preferred (*X = EWG*)**

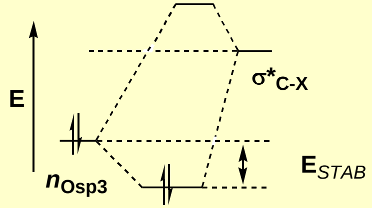
***equatorial* conformer preferred in cyclohexanes**

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 $n_{Osp3} \rightarrow \sigma^*_{C\text{-}X}$ ***anomeric effect*** which stabilises the α-anomer
    - The better the $\sigma^*_{C\text{-}X}$ orbital is as an acceptor, the stronger the effect

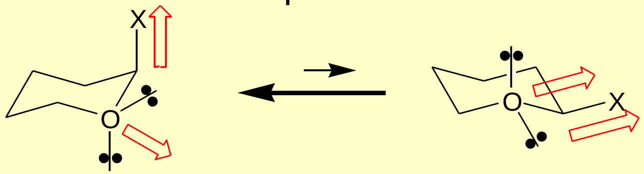


'no-bond, double-bond resonance' i.e. anomeric effect

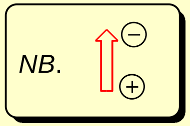


  - The α-anomer has a smaller overall dipole moment than the β-anomer

α–anomer
bond dipole
moments
~ antiparrallel

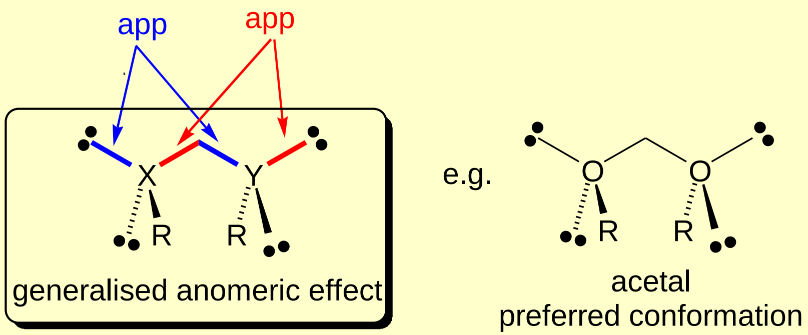


β–anomer
bond dipole
moments
parrallel

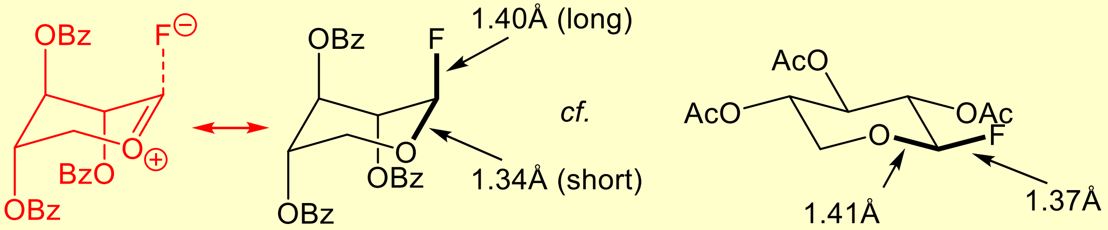


The generalised anomeric effect & structural evidence

- ***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)



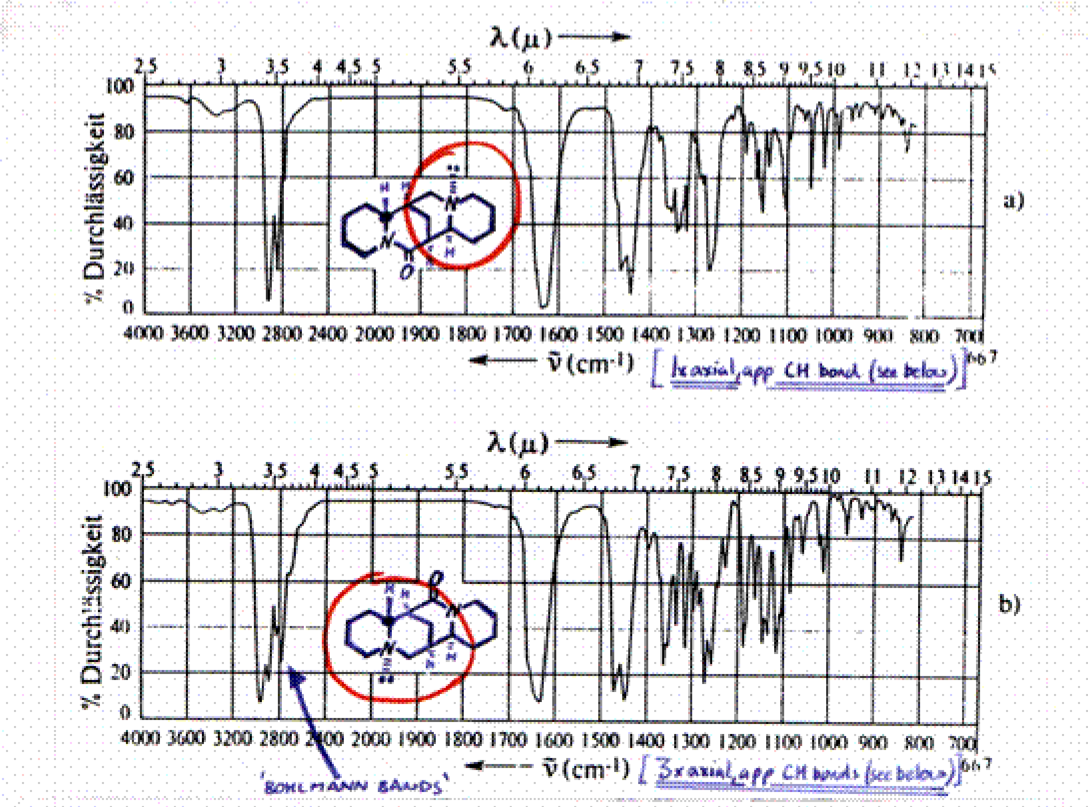
- ***Evidence for the anomeric effect comes from e.g. bond length analysis of fluoro sugars***



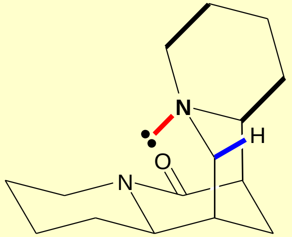
X-ray bond lengths of fluorosugars...evidence for lengthening
(and weakening) of the 'acceptor' C-F bond.

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 $n_{\mathrm{Nsp3}} \rightarrow \sigma^*_{\mathrm{C\text{-}H}}$ ***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)

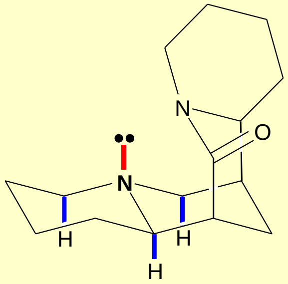


Abbild. 1. IR-Spektren von a) Aphyllin und b) 17-Oxo-spartein in Tetrachlorkohlenstoff



aphyllin
cis-fused

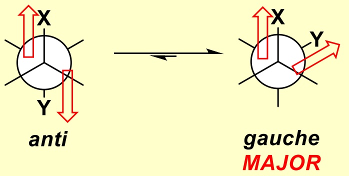
donor n_{NSp3}
acceptor $\sigma^*_{\mathrm{C\text{-}H}}$



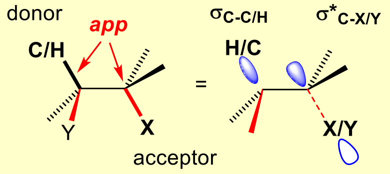
17-oxo-sparteine
trans-fused

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 σ → σ* interactions between the best combinations of anti-periplanar donor and acceptor bonds (***the gauche effect***)

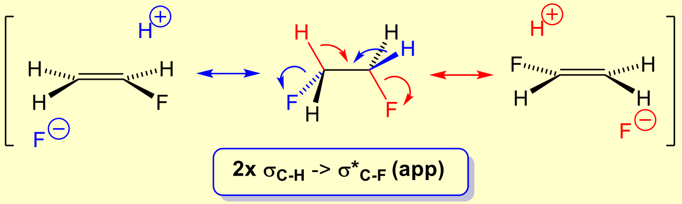


NB. dipoles of C-X & C-Y bonds shown in red



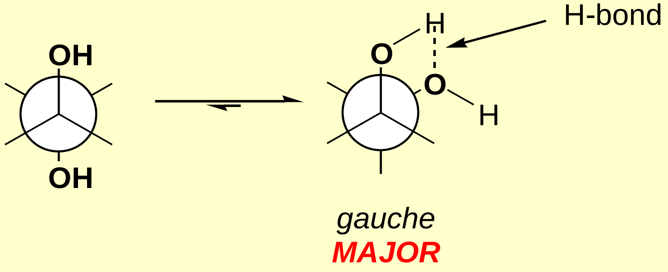
C-C/H = best σ donor
C-X/Y = best σ acceptor

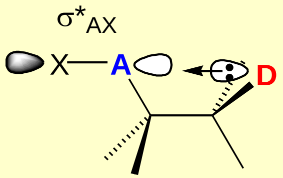
e.g. ***1,2-difluoroethane***



2x $\sigma_{C\text{-}H}$ -> $\sigma^*_{C\text{-}F}$ (app)

- *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**)





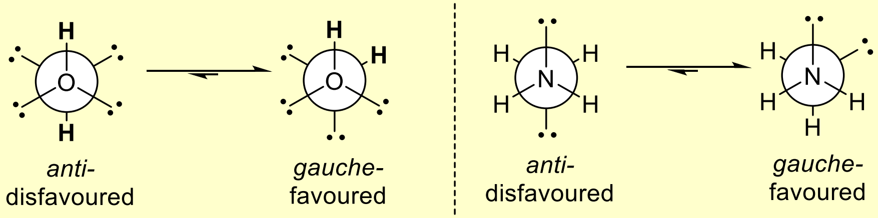
Donor = OR, NR_2
Acceptor = P, Si

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* → σ* (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)

H_2O_2

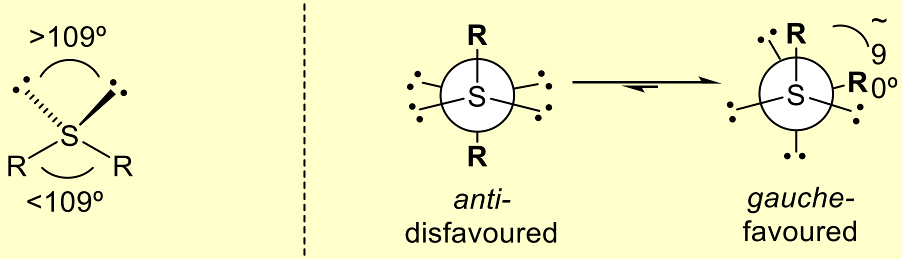
2x n_O -> $\sigma^*_{O\text{-}H}$ (app)



N_2H_4

2x n_N -> $\sigma^*_{N\text{-}H}$ (app)

  - ***Disulfides*** adopt a ***quasi gauche*** conformation (dihedral angle $\Theta_{C\text{-}S\text{-}S\text{-}C}$ of ~90º, *cf.* ~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× $n_S \rightarrow \sigma^*_{S\text{-}C}$ interactions results in the observed conformational geometry

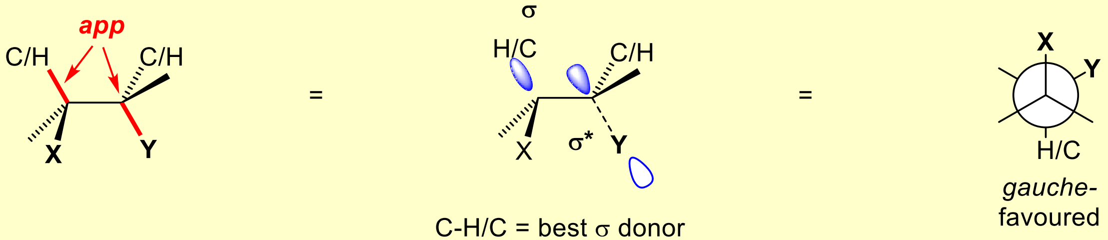


R_2S_2

2x n_S -> $\sigma^*_{S\text{-}C}$ (app)

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

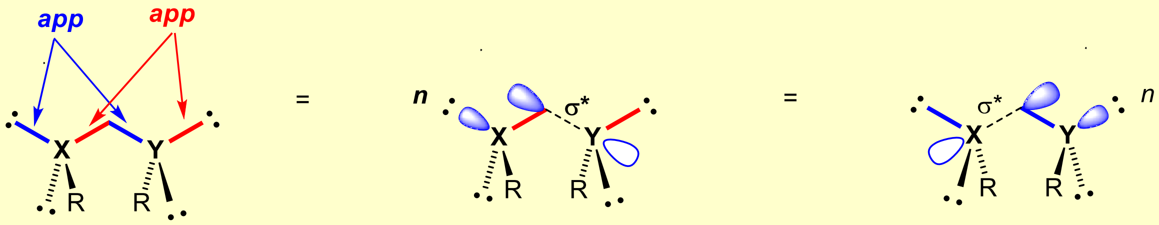
1,4-



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

gauche preference
2x (σ -> σ*)

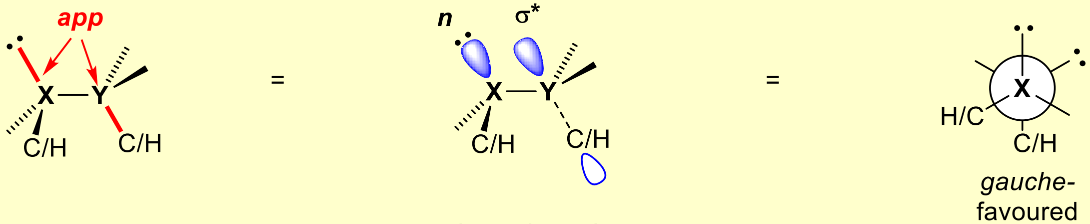
1,3-



n_X and n_Y = best donors
C-Y and C-X = best σ acceptors

the anomeric effect
2x (n -> σ*)

1,2-



n_X and n_Y = best donors
C-C/H = best σ acceptors

gauche preference
2x (n -> σ*)