CHEM60001:
An Introduction to Reaction Stereoelectronics

LECTURE 2 *Stereoelectronics of Ground States – Conformational Analysis*

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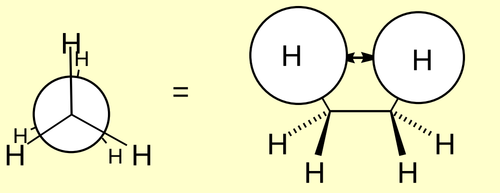
Format & scope of lecture 2

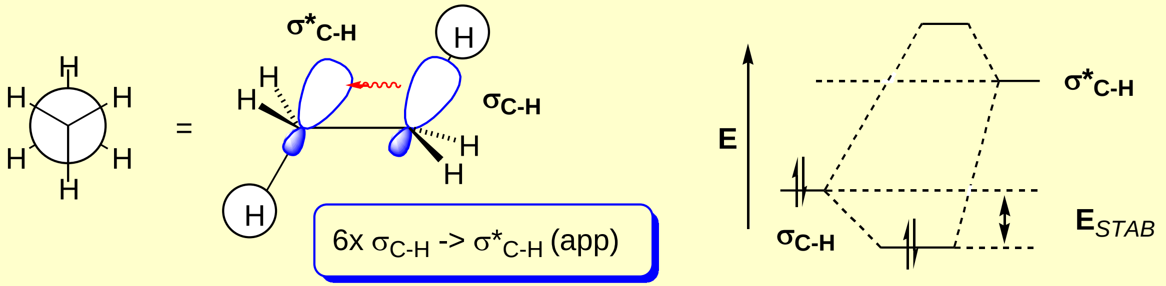
- ***The conformation of hydrocarbons***
  - Ethane & alkanes
  - Propene & alkenes
    - $A^{1,2}$ and $A^{1,3}$ strain
  - 1,3-Dienes & biaryls
- ***The conformation of functional groups***
  - Aldehydes & ketones
  - Esters & lactones
    - the ester anomeric effect
- ***The conformation of functional groups***
  - 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
maximised when eclipsed (shown)



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

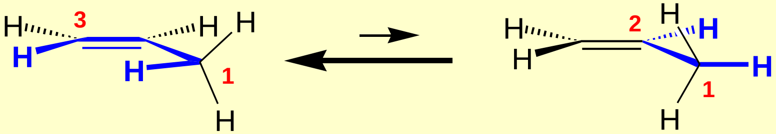
steric destabilisation of eclipsed conformations

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)



***$A^{1,3}$* eclipsed**

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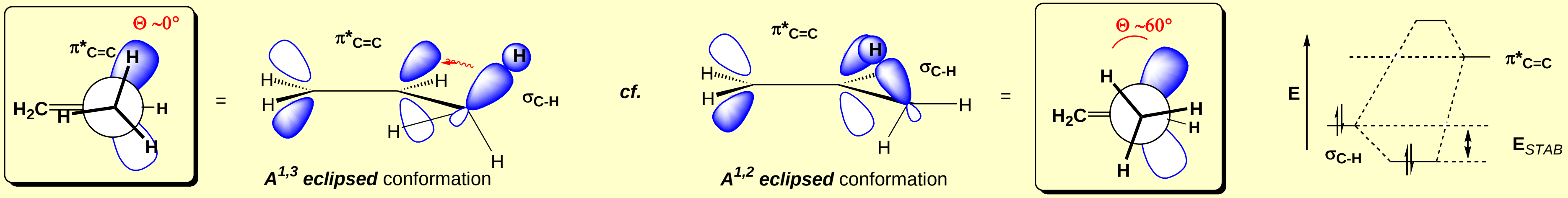
***$A^{1,2}$* eclipsed**

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



***$A^{1,3}$* eclipsed** conformation
good orbital alignment

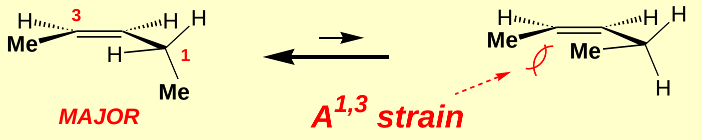
***$A^{1,2}$* eclipsed** conformation
poor orbital alignment

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

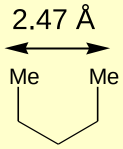
  - ***NB. Steric effects dominate for groups larger than hydrogen...***

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

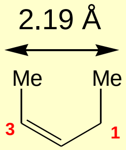
- ***Steric** interactions (i.e. **van der Waals** forces) dominate affairs when groups other than H are involved*
  - ***$A^{1,3}$ strain*** is the destabilising eclipsing interaction shown below:
    - As C=C double bonds are shorter than C-C single bonds, ***$A^{1,3}$ strain*** in the illustrated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

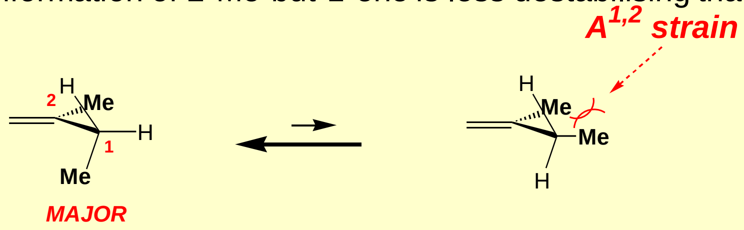


syn-pentane interaction
(+15.4 kJ/mol)
in *n*-pentane

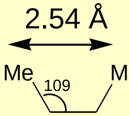


$A^{1,3}$ strain
(+16.3 kJ/mol)
in 2-pentene

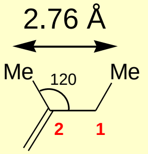
  - ***$A^{1,2}$ strain*** is the destabilising eclipsing interaction shown below:
    - As the C-C-C angle at an sp^3 carbon (~109°) is smaller than at an sp^2 carbon (~120°), ***$A^{1,2}$ strain*** in the illustrated conformation of 2-Me-but-1-ene is less destabilising than the eclipsing interaction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



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



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

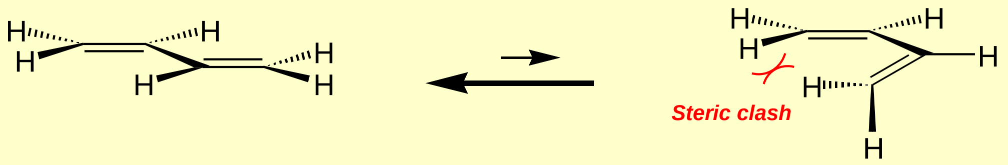


$A^{1,2}$ strain
(+12.6 kJ/mol)
2-Me-but-1-ene

  - 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
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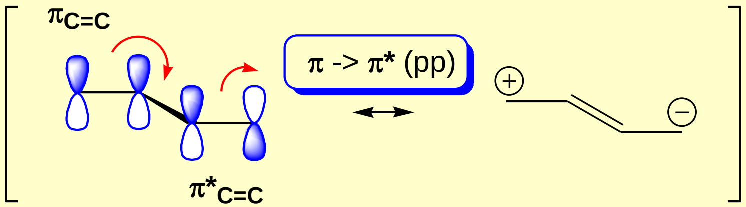
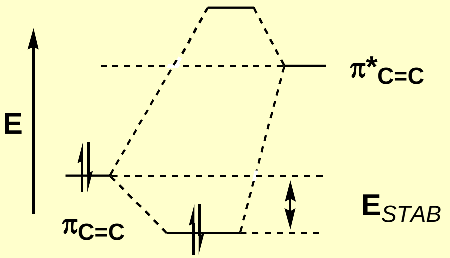
s-cis

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



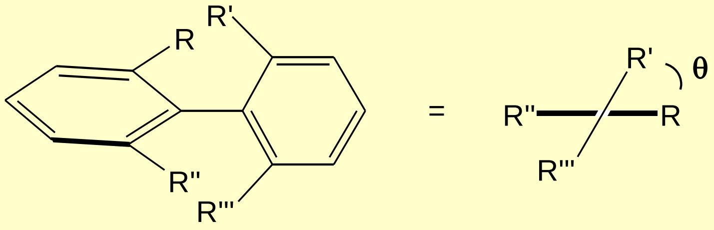
Maximum $\pi_{C=C}$ -> $\pi^*_{C=C}$ stabilisation
for periplanar alkenes
(*i.e.* best overlap)



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

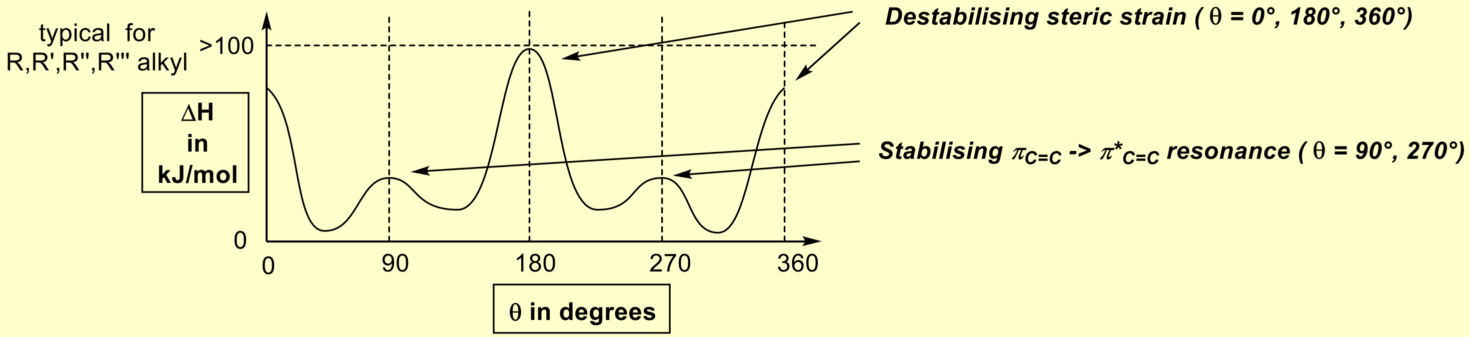
Unsaturated hydrocarbons - *biaryls*

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



Lowest energy conformation has dihedral angle ca. 45°

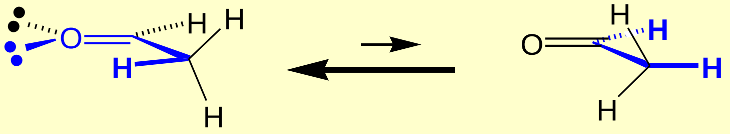
  - This is a compromise between:
    - Stabilising $\pi_{C=C} \rightarrow \pi^*_{C=C}$ resonance when coplanar
    - Destabilising steric interactions between adjacent *ortho* aromatic substituents when coplanar



  - 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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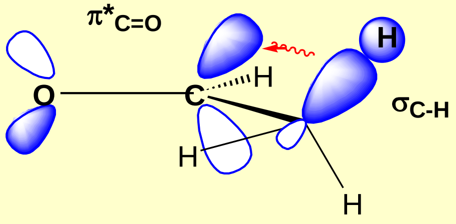
A^{1,2} eclipsed

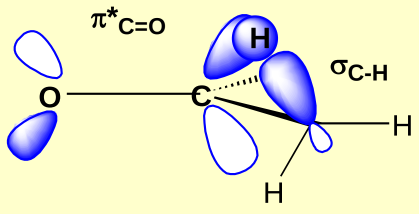
  - As for allylic systems, ***A^{1,3} eclipsed*** conformations allow stabilising $\sigma_{C\text{-}H/C} \rightarrow \pi^*_{C=O}$ ***hyperconjugation/ σ-conjugation***
    - These interactions are more significant than the corresponding interactions in an allylic system because the $\pi^*_{C=O}$ orbital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

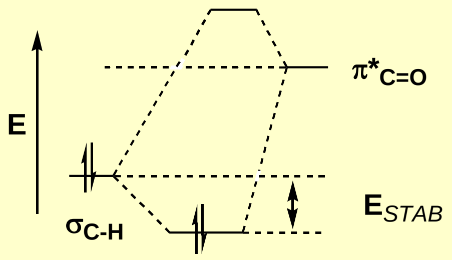
good orbital alignment

cf.



A^{1,2} eclipsed

poor orbital alignment

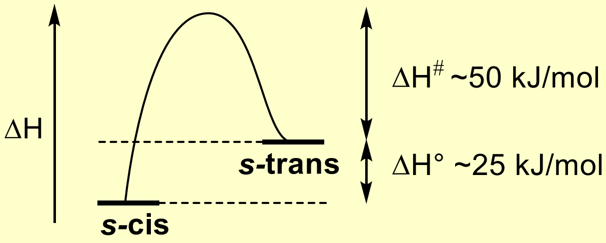


NB. of course there are two identical interactions: on the top and bottom faces

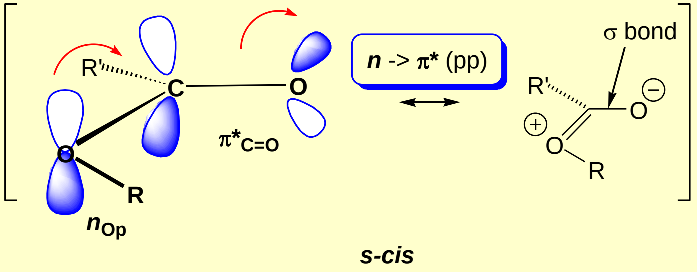
  - Moreover, ***A^{1,3} strain*** is less significant in these compounds relative to allylic compounds as the sp^2 hybrid lone pairs on the carbonyl oxygen are 'small' relative to any substituent on an alkene

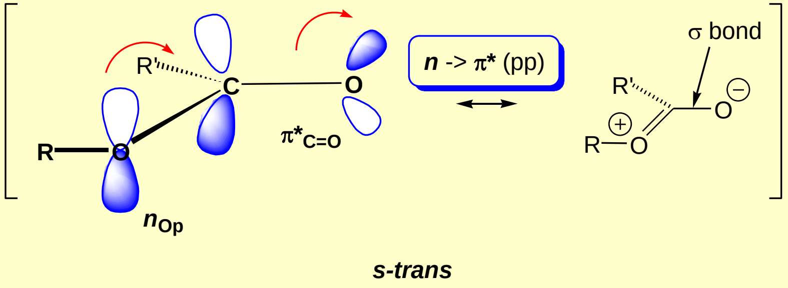
Functional groups - *esters*

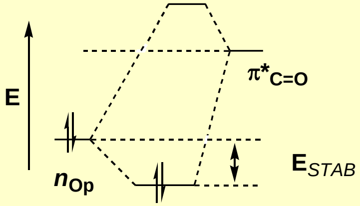
- ***Esters*** *prefer to adopt* ***s-cis*** *conformations in which all atoms of the group are* ***co-planar***



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



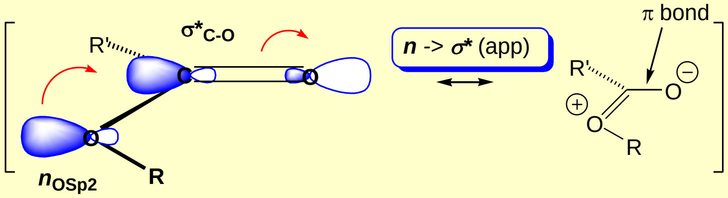


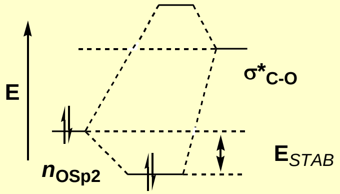


  - Because the p-orbital on oxygen is symmetrical resonance does not favour *s*-cis over *s*-trans or *vice versa*
  - However, there is a relatively strong enthalpic preference for the ***s*-cis** conformer over the ***s*-trans** one (ΔH° ~25kJmol^{-1} *cf.* ~10kJmol^{-1} for amides) although the barrier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

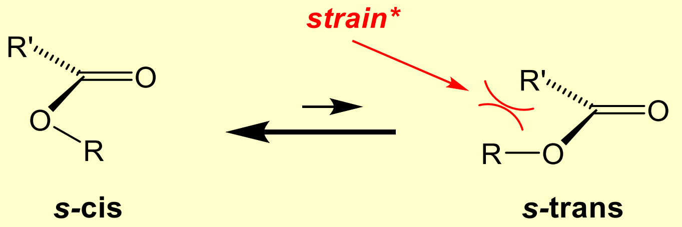
Functional groups – *esters cont.*

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





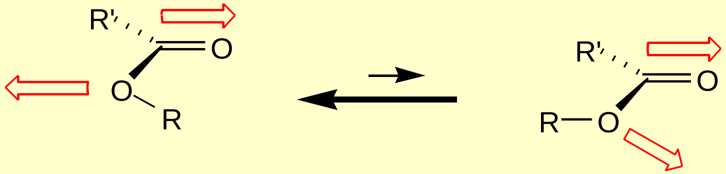
  - There is significant '***A*^{1,2} *strain'*** in the **s-trans** form (the sp^2 hybrid lone pair on the carbonyl oxygen is 'small' relative to a substituent bonded to the acyl carbon atom)



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

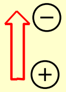
  - The **s-cis** form has a significantly ***smaller overall dipole moment*** relative to the **s-trans** form
    - There is a general preference for conformers with minimum overall dipole (minimum overall charge separation)

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



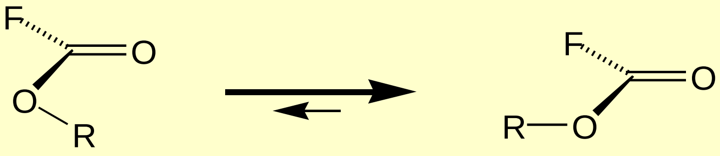
***s*-trans**
bond dipole
moments
~parrallel

NB.



Evidence for the ester anomeric effect

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



***s*-cis**

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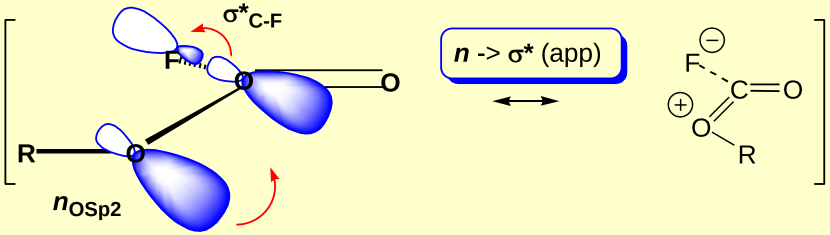
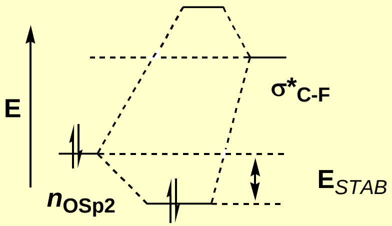
NB. the *cis* and *trans* designations here are relative to the carbonyl group and not strictly according to CIP rules (where F>O)

  - 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

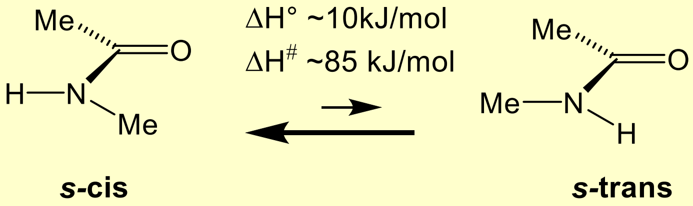
Functional groups - *lactones*

- ***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:*
  - ***Lactones are more basic than acyclic esters*** - because the oxygen sp^2 lone pair is ‘more available’ for interaction with protons (*e.g.* it is possible to form salts *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 there is an energy penalty associated with loss of anomeric stabilisation ($n_{Osp2} \rightarrow \sigma^*_{C\text{-}O}$) in going to the enolate; this is not the case for lactones.

Functional groups - *amides*

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



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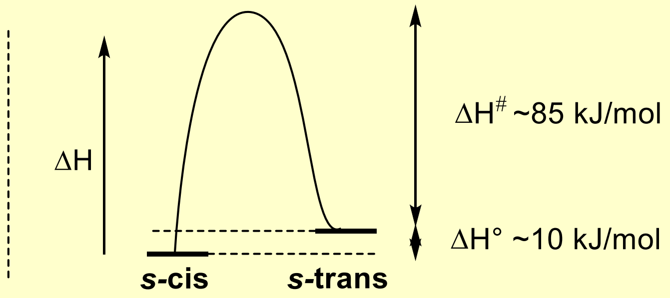
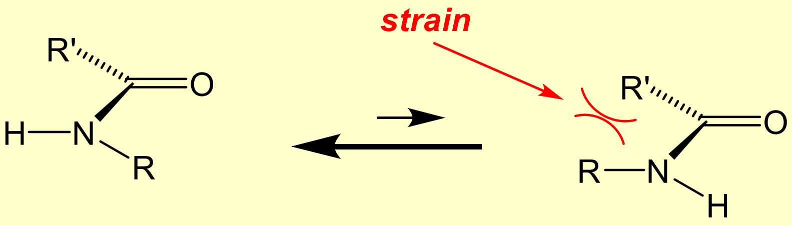
***s*-trans**



  - ***Co-planarity*** is stabilised by $n_{\mathrm{Np}} \rightarrow \pi^*_{\mathrm{C=O}}$ ***resonance*** which is stronger than the corresponding $n_{\mathrm{Op}} \rightarrow \pi^*_{\mathrm{C=O}}$ 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 ($\Delta H^{\#}$ ~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 ($\Delta H°$ ~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)*:



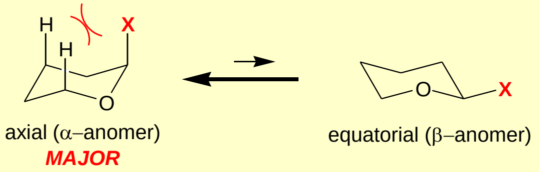
***s*-cis**

***s*-trans**

* *NB*. This strain is often referred to as *A^{1,2}*-strain de^{s}pite the fact that the non-carbonyl carbon is NOT *sp*^{3} hybridised

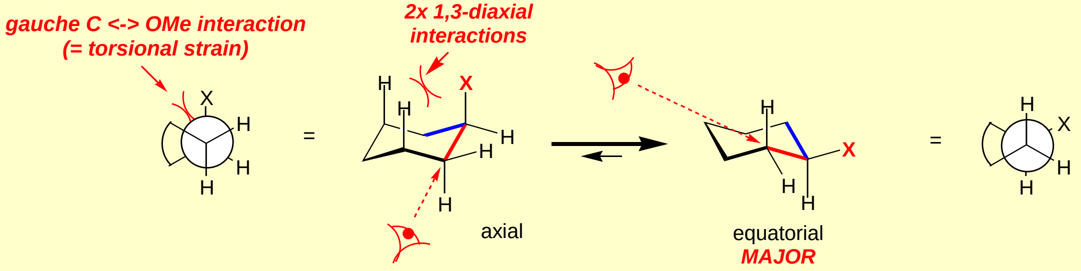
The anomeric effect – *6-ring acetals*

- ***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*)**

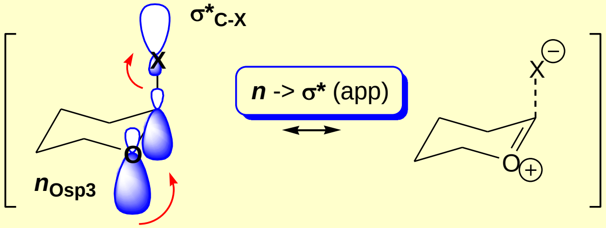
cf.



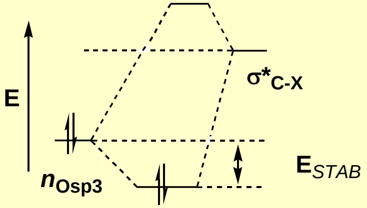
***equatorial* conformer preferred in cyclohexanes**

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

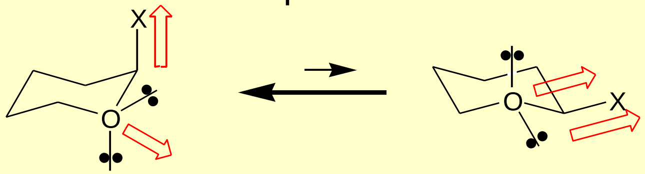


'no-bond, double-bond resonance'
i.e. anomeric effect

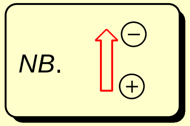


  - The α-anomer has a smaller overall dipole moment than the β-anomer

α–anomer
bond dipole
moments
~ antiparrallel

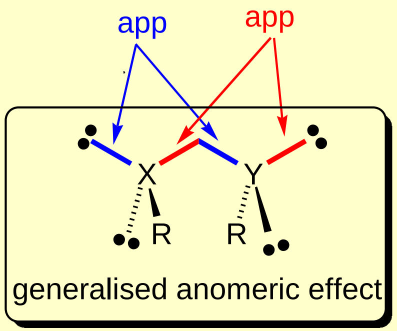


β–anomer
bond dipole
moments
parrallel



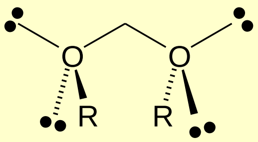
The generalised anomeric effect & structural evidence

- ***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)



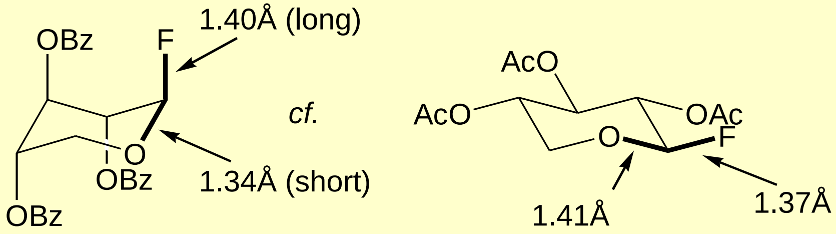
generalised anomeric effect

e.g.



acetal
preferred conformation

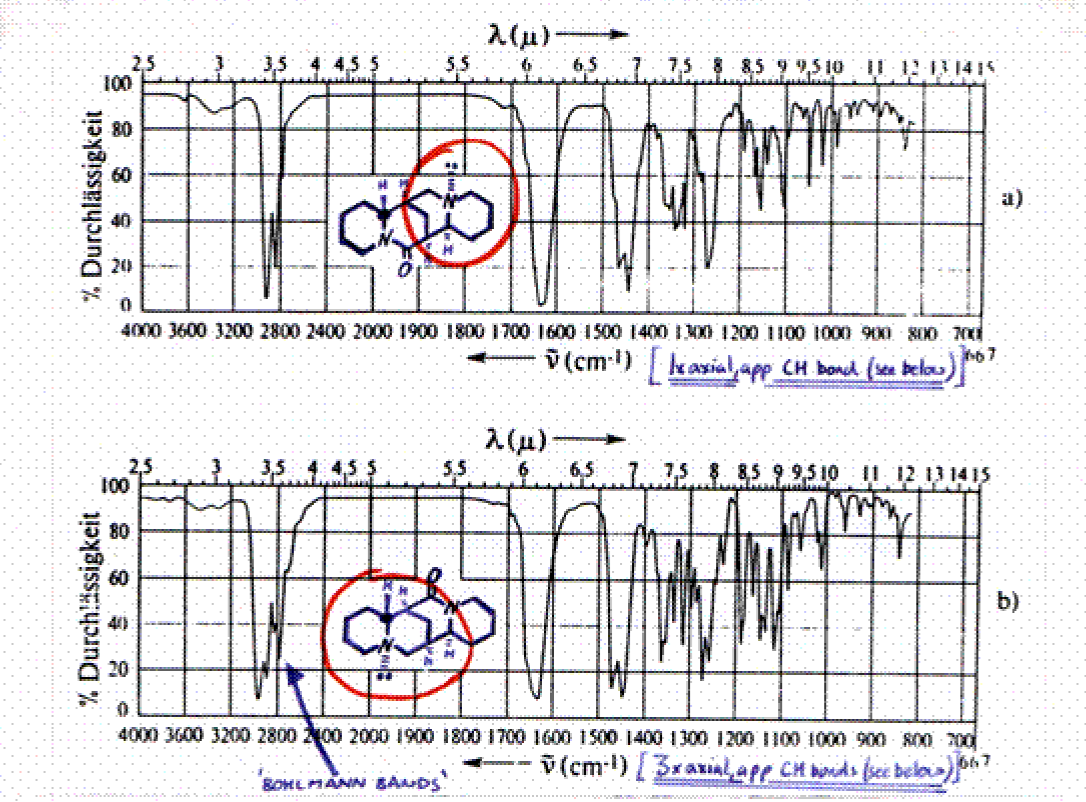
- ***Evidence for the anomeric effect comes from e.g. bond length analysis of fluoro sugars***



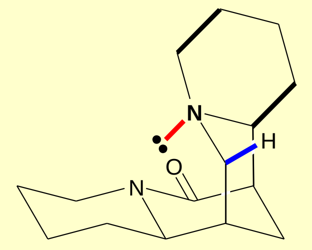
X-ray bond lengths of fluorosugars...evidence for lengthening
(and weakening) of the 'acceptor' C-F bond.

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)

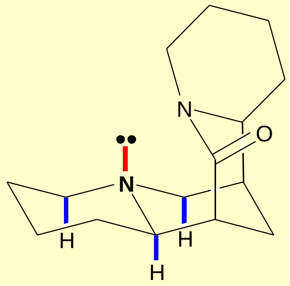


Abbild. 1. IR-Spektren von a) Aphyllin und b) 17-Oxo-spartein in Tetrachlorkohlenstoff



aphyllin
cis-fused

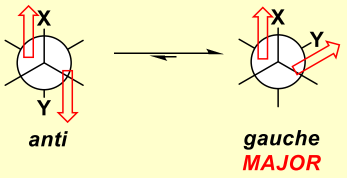
- donor n_{NSp3}
- acceptor $\sigma^*_{\mathrm{C\text{-}H}}$



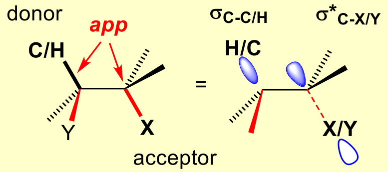
17-oxo-sparteine
trans-fused

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***)

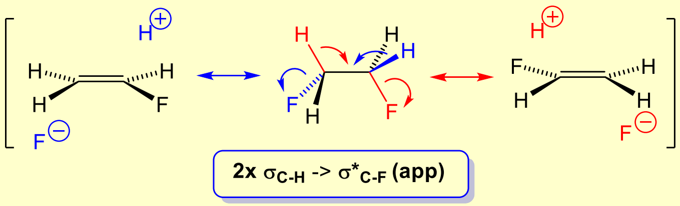


NB. dipoles of C-X & C-Y bonds shown in red

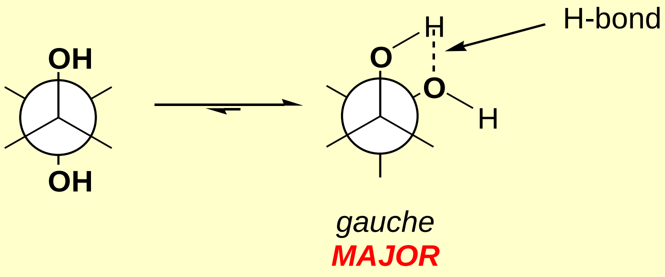


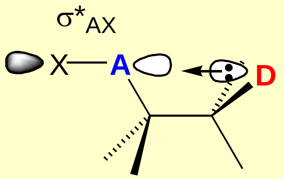
C-C/H = best σ donor
C-X/Y = best σ acceptor

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



- *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**)

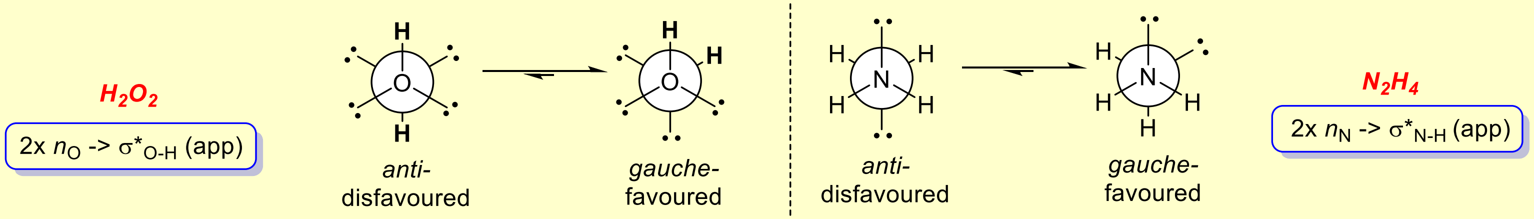




Donor = OR, NR_2
Acceptor = P, Si

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*$_O$ -> σ*$_{O-H}$ (app)

anti- disfavoured

gauche- favoured

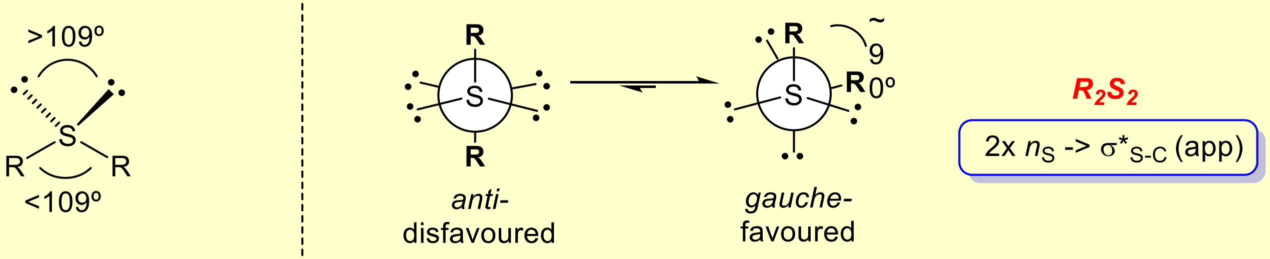
anti- disfavoured

gauche- favoured

N_2H_4

2x *n*$_N$ -> σ*$_{N-H}$ (app)

  - ***Disulfides*** adopt a ***quasi gauche*** conformation (dihedral angle $\Theta_{C-S-S-C}$ 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$_S$ → σ*$_{S-C}$ interactions results in the observed conformational geometry



anti- disfavoured

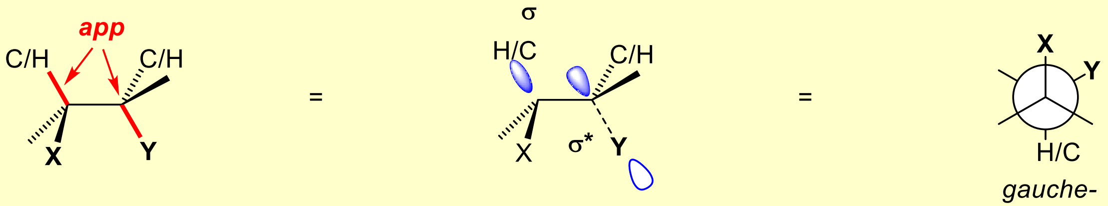
gauche- favoured

R_2S_2

2x *n*$_S$ -> σ*$_{S-C}$ (app)

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

1,4-

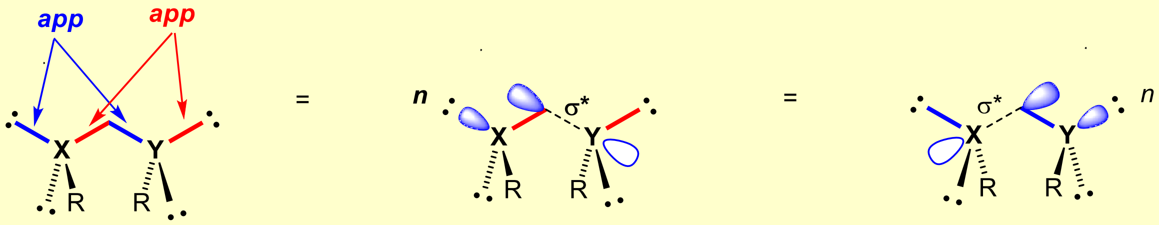


gauche-
favoured

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

gauche preference
2x (*σ* -> *σ)**

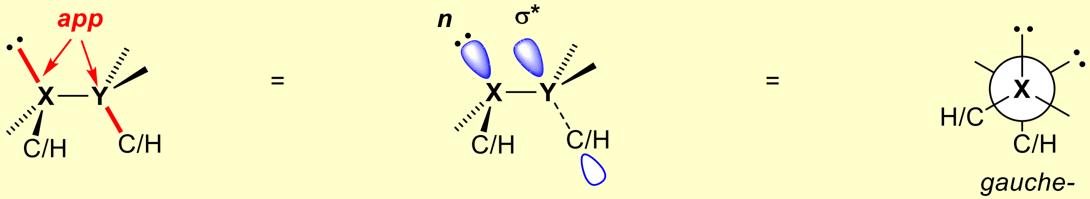
1,3-



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

the anomeric effect
2x (*n* -> *σ)**

1,2-



gauche-
favoured

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

gauche preference
2x (*n* -> σ*)