Chemistry II (Organic): Introduction to Stereoelectronics

STRUCTURE: Conformational analysis and ground state stereoelectronics of selected functional groups

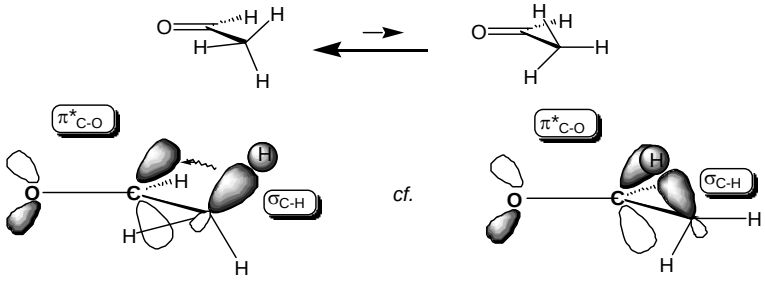
Dr Alan Spivey; Office: 834 C1; e-mail: a.c.spivey@imperial.ac.uk; Tel.: 45841

Note on assigning hybridisation states to heteroatoms:

As a 'rule of thumb', when assigning hybridisation states to heteroatoms, each heteroatom adopts the same hybridisation state the carbon to which it is bonded. If it is bonded to more than one carbon then it will have the same hybridisation state as the 'least hybridised' carbon atom to which it is attached.

ALDEHYDES AND KETONES:

Aldehydes and ketones can be treated in much the same way as alkenes. They tend to adopt allylically eclipsed conformations to maximise $\sigma_{C\text{-}H/C}$->$\pi^*_{C\text{-}O}$ ***hyperconjugative*** stabilising interactions. These interactions also account for the greater stability of ketones relative to aldehydes.



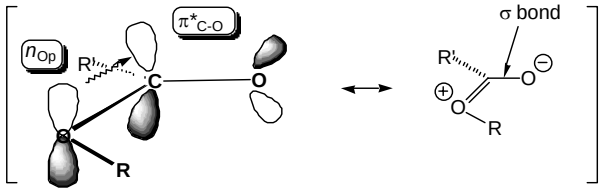
$A^{1,3}$ eclipsed conformation (good orbital alignment)

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

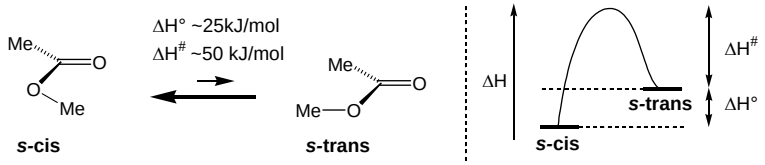
However, ***$A^{1,3}$ strain*** is less significant in these compounds relative to alkenes as the sp^2 hybrid lone pairs on the carbonyl oxygen are 'small' relative to the substituents on an alkene.

ESTERS:

Carboxylic esters prefer to adopt conformations in which all the atoms of the functional group are in a common plane. These planar conformations are stabilised by n_{Op}->$\pi^*_{C\text{-}O}$ ***resonance***. There are two such planar conformations: *s*-cis and *s*-trans. Because the p-orbital on oxygen is symmetrical resonance does not favour either relative to the other.

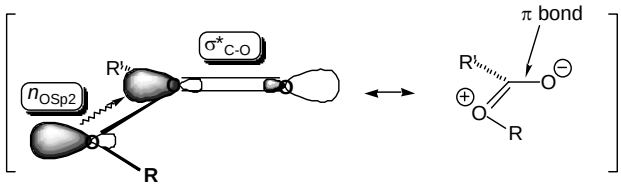


However, the thermochemical data provided for methyl acetate (below) clearly indicate that there is a relatively strong enthalpic preference for the *s-cis* conformer over the *s*-trans one although the barrier to rotation about the acyl oxygen bond (i.e. interconversion) is relatively low (*cf.* an amide, see later).

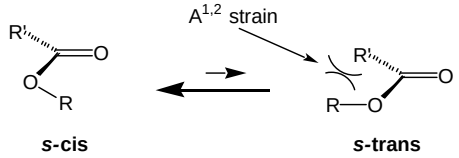


There are three factors which are responsible for this situation:

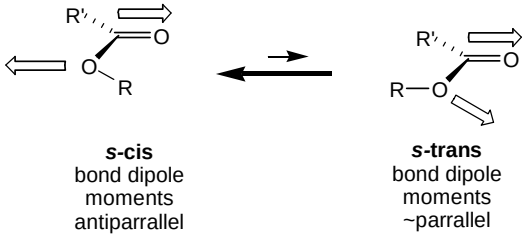
- Firstly, there is a n_{Osp2}->σ^*_{C-O} ***anomeric effect*** which stabilises the *s*-cis form.



- Secondly, there is significant ***A^{1,2} strain*** in the *s*-trans form (the sp^2 hybrid lone pairs on the carbonyl oxygen are 'small' relative to any substituent bonded to the acyl carbon atom).

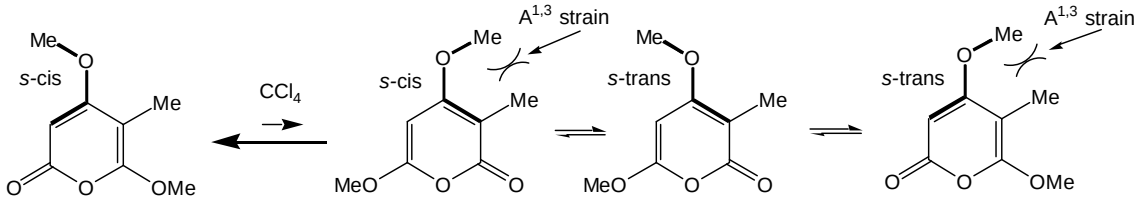


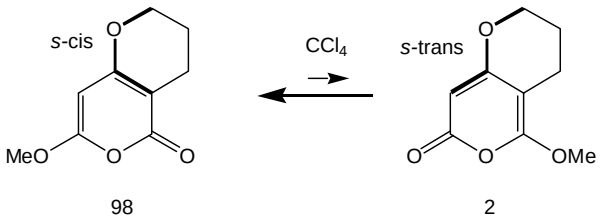
- Thirdly, the *s*-cis form has a significantly ***smaller overall dipole moment*** relative to the *s*-trans form. There is a general preference for conformers with minimum overall dipole (minimum overall charge separation).



α,β-UNSATURATED ESTERS:

The situation outlined for esters can be extrapolated to α,β–unsaturated cases. The following experimental equilibrium ratios for conformers of certain pyrones nicely exemplify this:

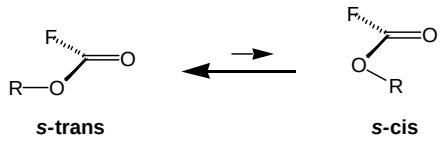




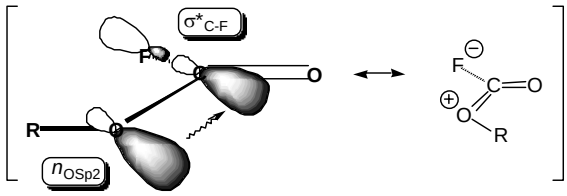
In these 'vinologous' cases it is of course a n_{Osp2}->σ^*_{C-C} ***anomeric effect*** which stabilises the *s*-cis form.

FLUOROCARBONATES

Evidence for the importance of an ***anomeric effect*** in stabilising the *s*-cis conformation of esters relative to the *s*-trans form comes from conformational analysis of fluorocarbonates. These compounds prefer to adopt an *s*-trans conformation.



This preference can be rationalised by realising that 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.

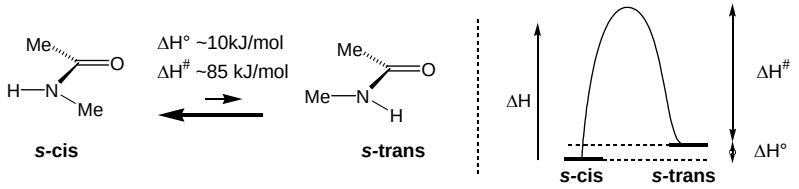
LACTONES:

Further evidence for the importance of the ***anomeric effect*** in dictating ester conformations comes from the study of 5- and 6-membered lactones. These contain an ester function with an enforced *s*-trans conformation. This means that anomeric n_{Osp2}->σ^*_{C-O} stabilisation is not possible. As a result lactone have some different properties to corresponding acyclic esters:

- the oxygen sp^2 lone pair is 'more available' for interaction with protons and so lactones are significantly more basic than acyclic esters (e.g. it is possible to form salts etc.).
- because anomeric n_{Osp2}->σ^*_{C-O} stabilisation results in 'dilution' of the dipole across the carbonyl, the absence of this interaction for lactones results in them being more susceptible to nucleophilic attack at the carbonyl carbon than acyclic esters.
- lactones are also more prone to enolisation than acyclic esters [pK_a ~25 (lactone) *cf.* pK_a ~30 (acyclic ester)] because for acyclic esters there is an energy penalty associated with loss of ***anomeric stabilisation*** (n_{Osp2}->σ^*_{C-O}) in going to the enolate; this is not the case for lactones.

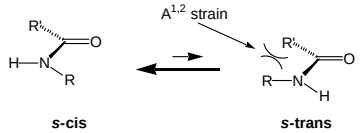
AMIDES:

Carboxylic amides, like esters, prefer to adopt conformations in which all the atoms of the functional group are in a common plane due to resonance. The **n_{Np}->π^*_{C-O} resonance** interaction in amides is stronger than the corresponding ***n_{Op}->π^*_{C-O} resonance*** interaction 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).



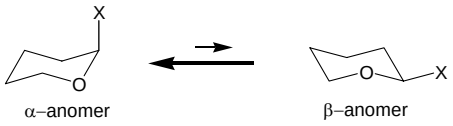
From the thermochemical data provided for *N*-methyl acetamide it can be seen that amides, like esters, prefer to adopt *s*-cis conformations but that enthalpic difference in ground state energy is less pronounced ($\Delta H°$ ~10kJmol^{-1}, *cf.* ~25kJmol^{-1} for esters). The reason for this is that there is no sp^2 lone pair on the nitrogen available for ***anomeric interaction*** with the carbonyl σ* orbital (or making a significant dipole). This means that the only factor favouring the *s*-cis conformation over the *s*-trans is:

- ***A*^{1,2} *Strain*** in the *s*-trans form:

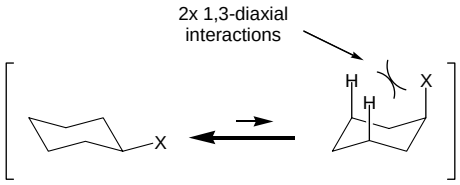


ACETALS (e.g. SUGARS):

Six membered ring cyclic acetals (e.g. hexoses) and related compounds having an exocyclic anomeric electron withdrawing group tend to adopt chair conformations in which the anomeric substituent is axial (***the anomeric effect***). This is in contrast to the situation for similarly substituted cyclohexanes in which the substituent adopts an equatorial position to avoid unfavourable ***1,3-diaxial or '1,3-flagpole' interactions***.



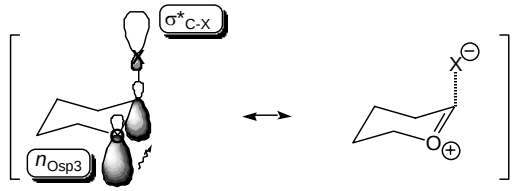
axial conformer preferred for
X=electron withdrawing group



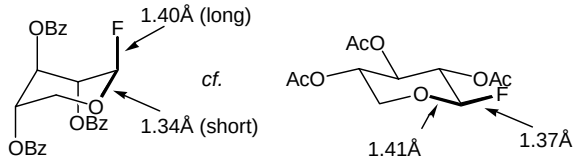
equatorial conformer preferred in cyclohexanes
(and indeed tendancy would be expected to be
exacerbated for sugars given that C-O bond length
is shorter than C-C)

There are two factors favouring the α–anomer:

- Firstly, there is a ***n_{Osp3}->σ^*_{C-X} anomeric effect*** which stabilises the α–anomer. The better the σ^*_{C-X} orbital is as an acceptor, the stronger the effect. Evidence for the anomeric effect comes from examination of bond lengths (e.g. for fluorosugars, shown below) which reflect the colloquial term 'no-bond, double-bond resonance' sometimes used for anomeric interactions:

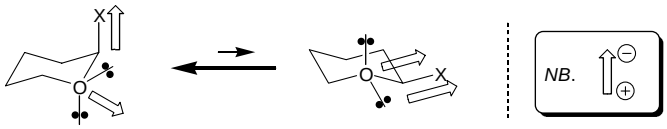


'no-bond, double-bond resonance'
i.e. anomeric effect



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

- Secondly, the α–anomer has a significantly ***smaller overall dipole moment*** relative to the β–anomer. Notice that the ring oxygen is ascribed sp^3 hybridisation and the dipole vector drawn bisecting the two sp^3 hybrid lone pairs.

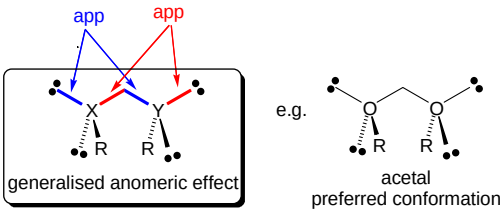


α–anomer
bond dipole
moments
~ antiparrallel

β–anomer
bond dipole
moments
parrallel

THE GENERALISED ANOMERIC EFFECT:

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):

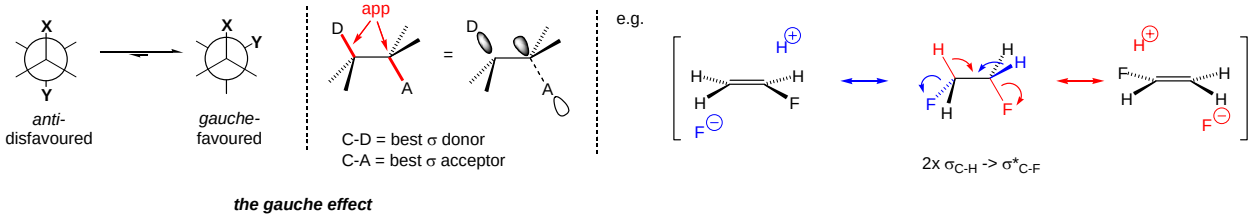


AMINES (e.g. ALKALOIDS):

The ***anomeric effect*** is also operative in certain geometrically rigid alkaloids and is manifested in a shift in the infra-red stretching frequencies of C-H bonds anti-periplanar to nitrogen lone pairs. The effect of these ***anomeric n_{Nsp3}->σ^*_{C-H} interactions*** (as in the case of the fluorosugars, see above), is to lengthen and therefore to weaken the acceptor (i.e. C-H) bonds. This results in a shift of the C-H stretching frequency to ***lower*** wavenumbers: the so called '***Bohlmann bands***' (see 'Anomeric effect' handout). That these bands only occur when there are at least 2 appropriately orientated C-H bonds presumably reflects the weak nature of the interaction. That these interactions are weak is not surprising given that although an sp^3 hybrid nitrogen lone pair is a good donor, a σ^*_{C-H} orbital is not a very good acceptor.

1,2-DI-SUBSTITUTED ETHANES

Compounds containing the X-C-C-Y constellation of functionality (where again X and Y are electronegative groups), such as 1,2-difluoroethane and 1,2-ethanediol (ethyleneglycol) adopt *gauche*- rather than *anti*-conformations. This *gauche* attractive interaction is stereoelectronic in origin and overcomes unfavourable steric and/or dipole interactions. The stabilisation accrues from σ -> σ* energy lowering interactions between the best combinations of antiperiplanar donor and acceptor bonds (the ***gauche effect***). Thus in the gauche conformation of 1,2-difluoroethane the C-H bonds serve as donors and the antiperiplanar C-F bonds as acceptors:

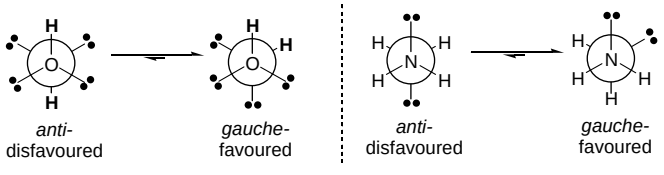


the gauche effect

It should be noted that in the case of 1,2-ethanediol there is the additional factor that the *gauche* conformation is stabilised by the presence of an intramolecular H-bond, which cannot form in the *anti*-conformation.

PEROXIDES, HYDRAZINES AND DISULFIDES:

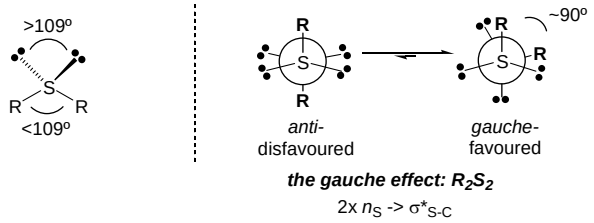
Compounds containing the X-Y constellation of functionality (where again X and Y are electronegative groups), such as hydrogen peroxide (H_2O_2) and hydrazine (H_2NNH_2) also adopt *gauche*- rather than *anti*-conformations. The stereoelectronic rationale for this is also referred to as the ***gauche effect***. For this type of structure it is the *lone pairs* on X and Y which constitute the best donor orbitals and the molecules adopt the gauche conformation to allow these orbitals to be antiperiplanar to the best acceptor σ*-orbitals (i.e. *n* -> σ* interactions):



the gauche effect: H_2O_2
2x n_O -> σ^*_{O-H}

the gauche effect: N_2H_4
2x n_N -> σ^*_{N-H}

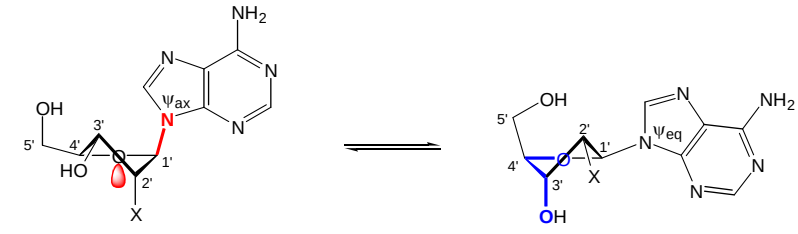
Disulfides are an interesting case. Because sulfur is in the second row of the periodic table the geometry of an sp^3 sulfur centre is distorted such that the angle between the lone pairs is >109º and that between the two substituents is <109º. A consequence of this is that when 2x n_S -> σ^*_{S-C} interactions operate in disulfides the resulting *gauche* conformation subtends a dihedral (C-S-S-C) angle of ~90º (*cf.* ~60º as expected):



NUCLEOSIDES AND NUCLEOTIDES:

The conformation of the pentafuranosyl ring (sugar skeleton) in RNA and DNA is very important because small changes in conformation, when repeated many times along the length of a strand, results in amplification of the effects to give gross differences in structure and therefore properties. Many factors influence the conformation of the pentafuranosyl ring including hydrogen bonding opportunities and dipole minimisation effects but stereoelectronics are also important. In particular, ***anomeric effects*** and ***gauche effects*** are known to be crucial.

There are two extreme conformers of nucleoside pentafuranosyl rings that interconvert by Berry pseudorotation: an N- or north-type and an S- or south-type.



DNA tends to adopt an S-type conformation whereas RNA tends to adopt an N-type conformation. The situation for DNA (no hydroxyl group at C2') is the simplest to analyse: the N-type conformation allows an n_O -> σ^*_{C-N} ***anomeric interaction*** between a lone pair on the pentafuranosyl ring oxygen and the C1-N glycosidic bond whereas the S-type conformation allows the oxygen substituents on the C3-C4 ring carbons to benefit from a ***gauche effect***. The gauche effect is the stronger and so an S-type conformation is generally preferred. For RNA there are additional ***gauche effects*** operating as well as additional hydrogen bonding opportunities and the net result is that the N-type is generally preferred.

*****