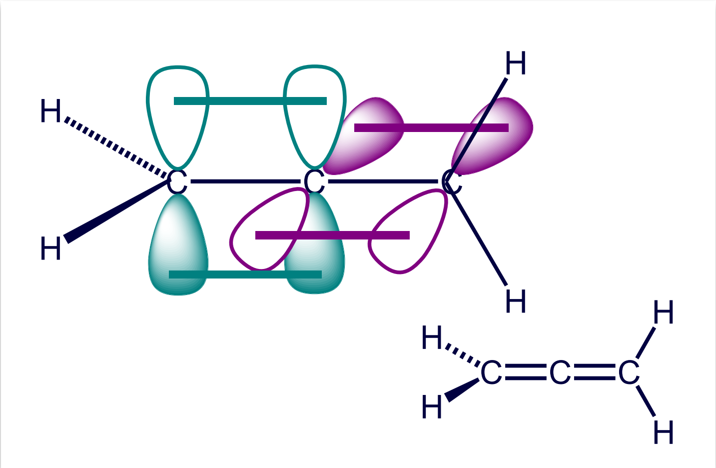
Introduction to Organic Chemistry

First Year – 7 lectures

Handout 1 - Bonding

Dr Jonathan Burton



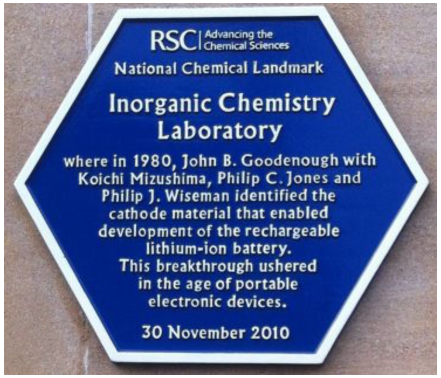
- *Organic Chemistry* J. Clayden, N. Greeves, S. Warren
- *Stereochemistry at a Glance* J. Eames & J. M. Peach
- *The majority of organic chemistry text books have good chapters on the topics covered by these lectures*

- *Eliel* Stereochemistry of Organic Compounds (advanced reference text)

UNIVERSITY OF OXFORD

Nobel Prize for Chemistry 2019 - for the development of lithium-ion batteries

- **John Goodenough** – head of the ICL Oxford 1976-1986 – discovered and developed Li_xCoO_2 as the cathode material of Li-ion batteries
- **Stanley Whittingham** – undergraduate and graduate student in chemistry at Oxford - worked on the precursor to Li_xCoO_2
- **Akira Yoshino** – developed the direct precursor to the lithium ion battery that was commercialised by SONY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where in 1980, John B. Goodenough with Koichi Mizushima, Philip C. Jones and Philip J. Wiseman identified the cathode material that enabled development of the rechargeable lithium-ion battery.
This breakthrough ushered in the age of portable electronic devices.

30 November 2010

Mat. Res. Bull., Vol. 15, pp. 783-789, 1980. Printed in the USA.
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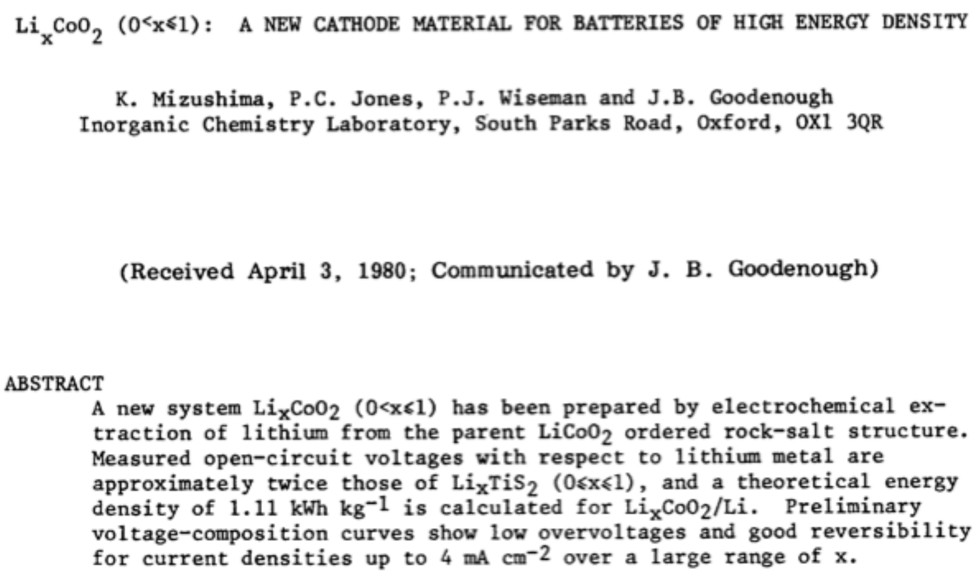

Li_xCoO_2 (0<x≤1): A NEW CATHODE MATERIAL FOR BATTERIES OF HIGH ENERGY DENSITY

K. Mizushima, P.C. Jones, P.J. Wiseman and J.B. Goodenough
Inorganic Chemistry Laboratory, South Parks Road, Oxford, OX1 3QR

(Received April 3, 1980; Communicated by J. B. Goodenough)

ABSTRACT

A new system Li_xCoO_2 (0<x≤1) has been prepared by electrochemical extraction of lithium from the parent $LiCoO_2$ ordered rock-salt structure. Measured open-circuit voltages with respect to lithium metal are approximately twice those of Li_xTiS_2 (0≤x≤1), and a theoretical energy density of 1.11 kWh kg^{-1} is calculated for Li_xCoO_2/Li. Preliminary voltage-composition curves show low overvoltages and good reversibility for current densities up to 4 mA cm^{-2} over a large range of x.

Course Outline

These seven lectures will focus on bonding, stereochemistry, and an introduction to mechanism (curly arrows). All of these areas are crucial to being able to rationalise, and more importantly predict, what will happen when organic molecules are treated with any of a plethora of reagents used by organic chemists and chemists in general. Aspects of bonding will receive much more in-depth treatments in both the 'inorganic' and 'physical and theoretical' lecture courses throughout the degree and here we will meet simple, but useful views of bonding, that are fit for our purposes. 'Curly arrow' mechanisms will be met in virtually all of the organic chemistry lecture courses and this course will introduce the key basic principles for drawing reasonable curly arrow mechanisms. Uniquely, this course will provide virtually all of the content you require regarding stereochemistry. Stereochemistry is chemistry in three-dimensions and developing skills to be able to manipulate molecules in 3-D in one's own head will prove important. Practising organic chemists frequently build 'ball-and-stick' models of molecules to better aid visualisation and a cheap, plastic molecular model kit can be very useful when working though stereochemical problems and will be useful throughout your degree – a decent one can be purchased here: https://www.cochranes.co.uk/show_product.asp?id=399&catid=44

Synopsis

Bonding – Lewis structures and bonding, formal charge, basic VSEPR, hybridisation, molecular orbitals, structures of some functional groups, drawing organic molecules, skeletal representations

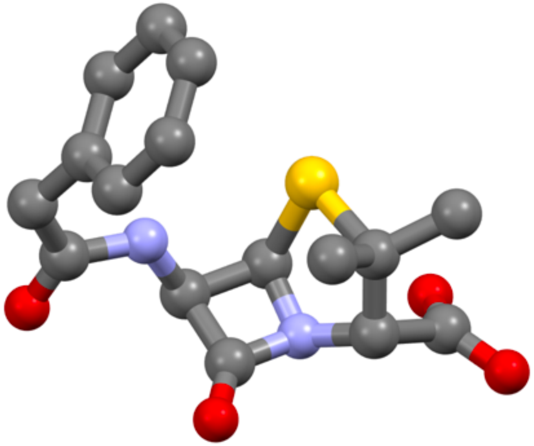
Stereochemistry – conformation, stereochemical definitions, optical activity, configuration, chirality, enantiomers and diastereomers, CIP rules, compounds with more than one stereocentre, meso compounds, racemisation, planar and helical chirality, resolution, relative and absolute configuration

Mechanism – acid base reactions, curly arrows, delocalisation

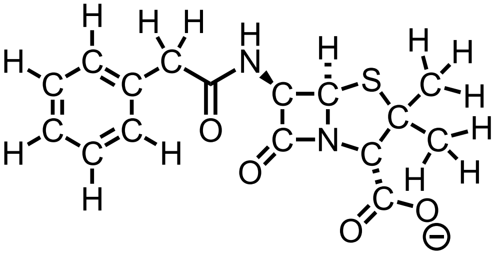
Two of Oxford's Nobel Laureates

Dorothy Hodgkin

- Dorothy Crowfoot Hodgkin (1910-1994)
- Read Chemistry at Oxford (Somerville College)
- Chemistry Tutor Somerville College
- Nobel Prize 1964 for "her determinations by X-ray techniques of the structures of important biochemical substances"
- 1945 – determined the structure of penicillin



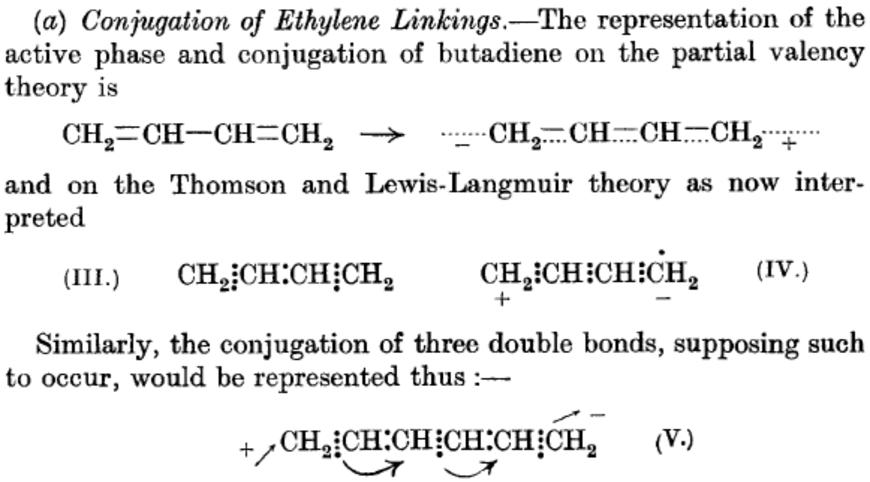
hydrogen atoms omitted for clarity



Two of Oxford’s Nobel Laureates

Robert Robinson

- Sir Robert Robinson (1886-1975)
- Waynflete Professor of Organic Chemistry 1930-1954
- Nobel Prize 1947 for “investigations on plant products of biological importance, especially the alkaloids”
- Inventor of the ‘curly arrow’



(*a*) *Conjugation of Ethylene Linkings.*—The representation of the active phase and conjugation of butadiene on the partial valency theory is

$$CH_2{=}CH{-}CH{=}CH_2 \longrightarrow \underset{-}{\cdots}CH_2\overset{-}{\cdots}CH\overset{-}{\cdots}CH\overset{-}{\cdots}CH_2\underset{+}{\cdots}$$

and on the Thomson and Lewis-Langmuir theory as now interpreted

$$\text{(III.)}\quad CH_2\vdots CH{:}CH\vdots CH_2 \qquad \underset{+}{CH_2}\vdots CH\vdots CH\vdots \underset{-}{\dot{C}H_2}\quad \text{(IV.)}$$

Similarly, the conjugation of three double bonds, supposing such to occur, would be represented thus :—

$$^{+}\nearrow CH_2\vdots CH{:}CH\vdots CH{:}CH\vdots \overset{\nearrow\ -}{CH_2}\quad \text{(V.)}$$

Atoms

- **Bohr atomic model** - electrons moving in specific orbits, s, p, d, f.

atomic number = number of protons

Quantum number	max. no. of electrons in shell								
1	2e	^{1}H · $1s^1$							^{2}He : $1s^2$
2	8e	^{3}Li · $2s^1$	^{4}Be : $2s^2$	^{5}B ⁝ $2s^2,2p^1$	^{6}C ⁞ $2s^2,2p^2$	^{7}N ⁞· $2s^2,2p^3$	^{8}O ⁞: $2s^2,2p^4$	^{9}F ⁞⁝ $2s^2,2p^5$	^{10}Ne ⁞⁞ $2s^2,2p^6$
3	8e	^{11}Na	^{12}Mg	^{13}Al	^{14}Si	^{15}P	^{16}S	^{17}Cl	^{18}Ar

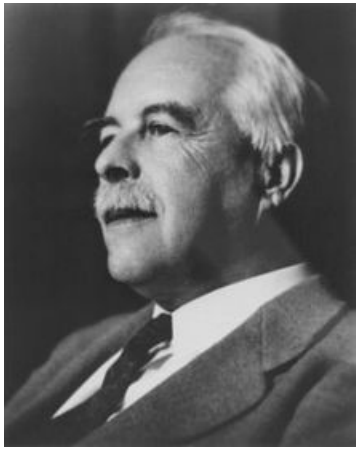
electrons in outer shell (valence shell)

- **Lewis Bonding Theory** (1916) – historic and useful

- Bonding = achievement of completely filled (or empty) valence shells by sharing (covalent bonds) or transfer of electrons (ionic bonds) between atoms

- **Lewis** bonding forms a simple basis for the qualitative understand of the structures and properties of organic molecules

- you will meet more sophisticated theories of bonding – particularly molecular orbital theory – as the course progresses



Gilbert. N. Lewis

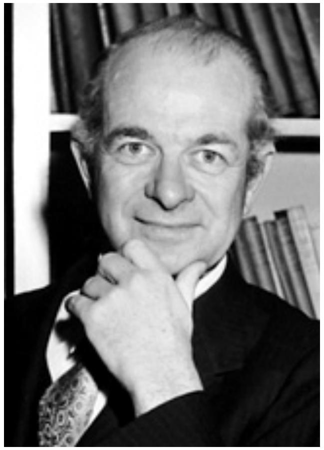
Atoms

- **Electronegativity** (χ chi) – measure of the relative ability of an atom to attract valence electrons to itself (Pauling Scale 1932, empirical)

increasing electronegativity →

H 2.2						
Li 1.0	Be 1.6	B 2.0	C 2.6	N 3.0	O 3.4	F 4.0
Na 0.9	Mg 1.3	Al 1.6	Si 1.9	P 2.2	S 2.6	Cl 3.2
						Br 2.9
						I 2.6

↑ *increasing electronegativity*



Linus Pauling

- the following order of electronegativities can be useful to remember: F > O > Cl > N

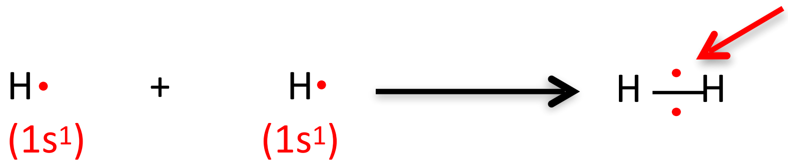
- **Ionic Bonds**
- usually occur between atoms at opposite ends of the periodic table i.e. between atoms that have very different electronegativities
- the atoms involved in ionic bonding achieve filled shells by the transfer of electrons (usually 1 or 2 electrons)
- examples $Li^{\oplus}\ F^{\ominus}$ $Na^{\oplus}\ Cl^{\ominus}$

$$^{3}Li + {}^{9}F \longrightarrow {}^{3}Li^{+}\ {}^{9}F^{-}$$

$$(2s^{1}) \quad (2s^{2},2p^{5}) \qquad (2s^{0} \quad 2s^{2},2p^{6})$$

Covalent bonds

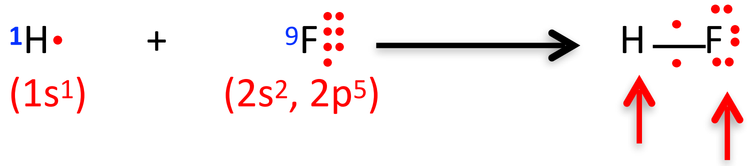
- generally between atoms of similar electronegativity – sharing of electrons



covalent bond

- each H atom has 2 electrons around it

i.e. 1st quantum number shell is full

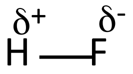


- both atoms have filled shells

2 electrons around H

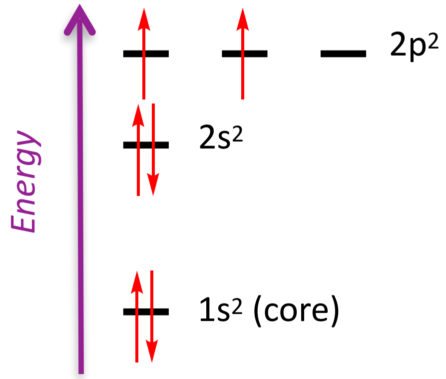
8 electrons around F

- in H—F the atoms have a large difference in nuclear charge and hence electronegativity
- the shared pair is therefore not equally distributed but displaced towards F – this is bond polarisation by the inductive effect leading to a permanent dipole

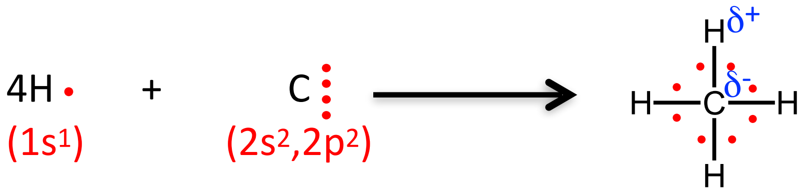


$$\overset{\delta+}{\mathrm{H}}\text{—}\overset{\delta-}{\mathrm{F}}$$

- the Greek letter δ (delta) is used to indicate a partial charge
- organic molecules are held together by covalent bonds
- carbon is in the middle of the period, with no great difference in electonegativity with other elements
- very difficult to form stable closed shell by ionisation i.e. C^{4+} and C^{4-}



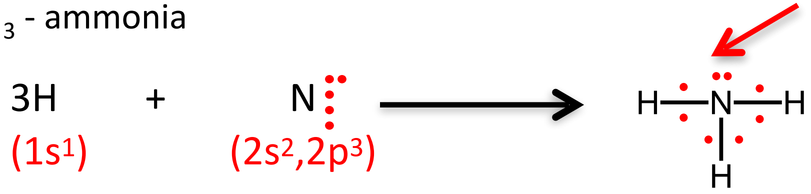
- CH_4 - methane
- bonds formed by the combination of 4 H atoms ($1s^1$) and 1 C atom ($2s^2$, $2p^2$)



C – 8 electrons
H – 2 electrons

- electronegativity of carbon and hydrogen are similar $\chi_c = 2.6$, $\chi_H = 2.2$,
- bonds slightly polarised

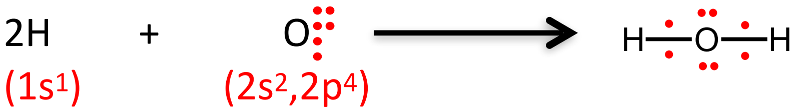
- NH_3 - ammonia



lone pair – not involved in covalent bond

N – 8 electrons
H – 2 electrons

- H_2O - water



O – 8 electrons
H – 2 electrons

2 lone pairs

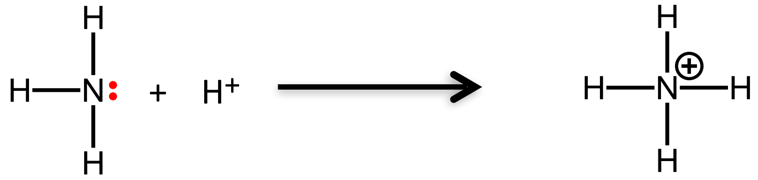
Rules for Lewis structures

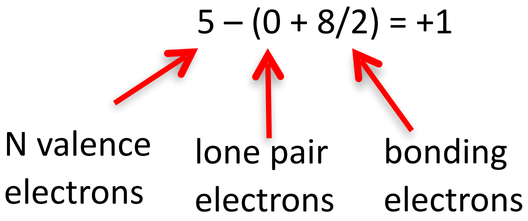
- line —— = shared pair = covalent bond – **no more drawing dots for electrons in bonds**
- •• = unshared pair or lone pair
- formal charge on atom = number of valence electrons – (number of lone pair electrons + ½ bonding pair electrons)
- for 2nd row elements Li → F the sum of the number of bonds plus the number of lone pairs cannot exceed 4

i.e. no more than 8 electrons around the atom – Lewis octet rule

- formal charge – charge assigned to each atom in a molecule assuming the electrons in the bonds are shared equally between atoms regardless of electronegativity – bookkeeping tool to denote relationship between the bonding electrons and those 'formally' belonging to each atom – a useful formalism but must be interpreted with care

- formal charge on atom = number of valence electrons – (number of lone pair electrons + number of bonds)



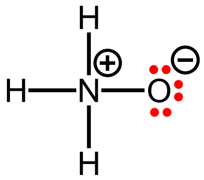


5 – (0 + 8/2) = +1

N valence electrons

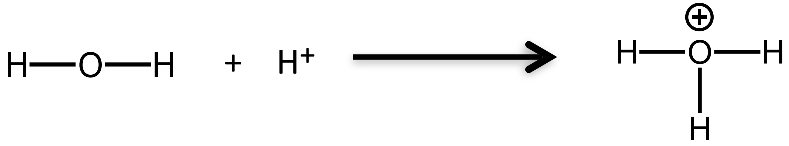
lone pair electrons

bonding electrons



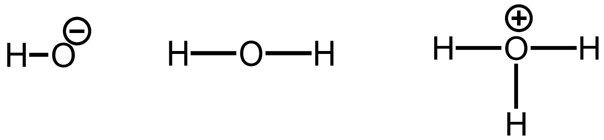
for N 5 – (0 + 8/2) = +1

for O 6 – (6 + 2/2) = -1

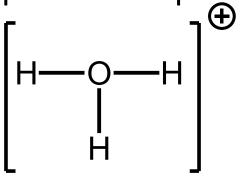


for O 6 – (2 + 6/2) = +1

- (organic) chemists do not work out the formal charge on atoms, they just remember that whenever oxygen has 8 electrons around it, and has 1, 2, or 3 bonds, it is negative, neutral or positive respectively



hydronium ion



- more generally, whenever an atom has 8 electrons around it, and has one more bond than its neutral state, it will be positively charged, and one fewer bonds it will be negative

$\overset{\ominus}{N}H_2$ NH_3 $\overset{\oplus}{N}H_4$

- best guide to actual charge distribution is electronegativity

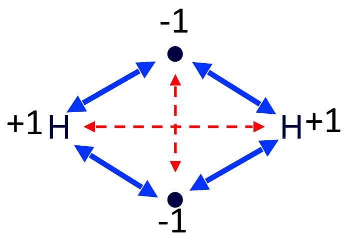
- in the hydronium ion the formal positive charge is drawn on oxygen

- in reality the oxygen, being more electronegative than hydrogen, does not have a positive charge and the positive charge is spread out over the 3 hydrogen atoms

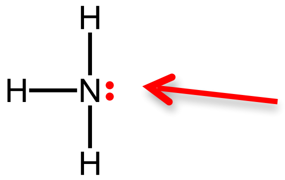
- physical origin of bonding forces (simplified) – if two atoms form a bond, the bonded state must be more stable then the separated atoms

- in covalent bonds the repulsion between the electrons and between the nuclei is balanced by the attraction of the electrons to the positive nuclei at the stable internuclear distance – the bond length

- H_2
- attraction – each electron sees 2 positive nuclei (↔)
- repulsion – electron-electron and nucleus-nucleus (⇠⇢)

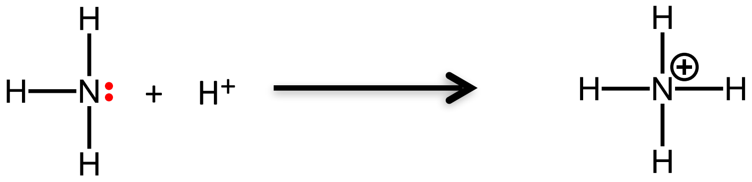


- lone pairs, a.k.a. non-bonded pairs, formally interact with only one positive nucleus, hence their interelectron repulsion is greater than for a bond pair – they are higher in energy and more available for bonding



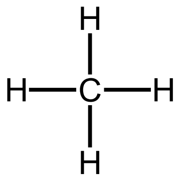
electron-electron repulsion in lone pair

- reactions which reduce this electron-electron repulsion are favoured

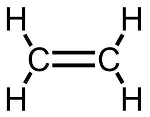


- in the product the lone pair electrons are now a bond pair and see 2 positive nuclei
- this is the Lewis basicity of lone pairs - frequently the reactive site of a molecule towards electrophiles

- Lewis structures are useful in predicting the bonding in molecules but they tell us nothing of the shape of the molecules



methane



ethene (ethylene)

$H-C\equiv C-H$

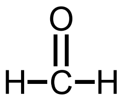
ethyne (acetylene)

$H-C\equiv N$

hydrogen cyanide

$H_2C=C=CH_2$

allene



$H-\overset{\overset{O}{\|}}{C}-H$

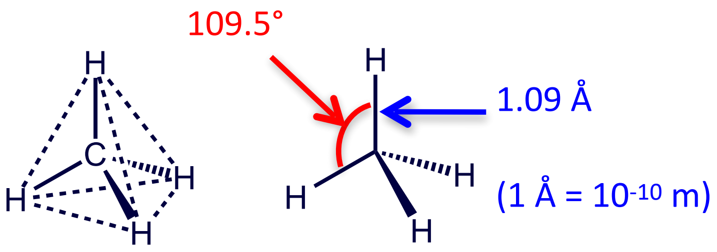
formaldehyde (methanal)

- the shapes of the vast majority of organic compounds are determined by repulsion between electrons in the valance shell (VSEPR - valence shell electron pair repulsion)

- i.e. bond pair – bond pair repulsions   bond pair – lone pair repulsions   lone pair – lone pair repulsions

- geometry of molecules is determined by minimising the above interactions

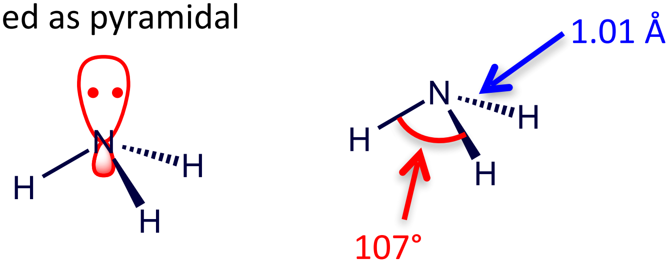
- for methane, CH_4, there are 4 bonding pairs of electrons and they repel each other to be as far apart as possible leading to the tetrahedral structure of methane



(1 Å = 10^{-10} m)

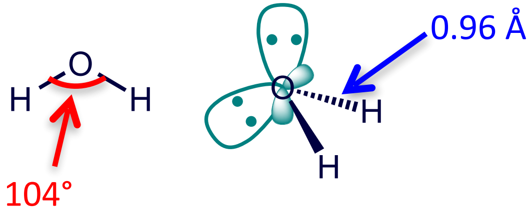
- tetrahedral geometry, 109.5° H-C-H bond angle

- with ammonia there are still four ‘groups’ to place around the central nitrogen atom – 3 bond pairs and 1 lone pair NH_3 is therefore based on a tetrahedron – its shape is described as pyramidal



- 107° H-C-H bond angle N–H bond length = 1.01 Å

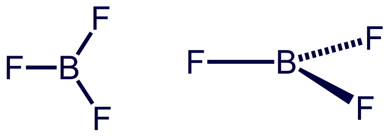
- similarly with water there are still four ‘groups’ to place around the central oxygen atom – 2 bond pairs and 2 lone pairs – water H_2O is therefore also based on a tetrahedron – its shape is described as bent



- bond angles decrease in the order CH_4, NH_3, H_2O because:

lone pair / lone pair repulsions *are greater than*
lone pair / bond pair repulsions *which are greater than*
bond pair / bond pair repulsions

- some examples
- BF_3 $3F$ $(2s^2,2p^5)$ + B $(2s^2,2p^1)$ $\longrightarrow$

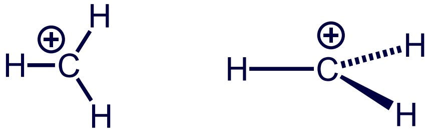


- planar 120° bond angle

B – 6 electrons (no lone pair)

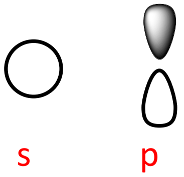
F – 8 electrons

- CH_3^+



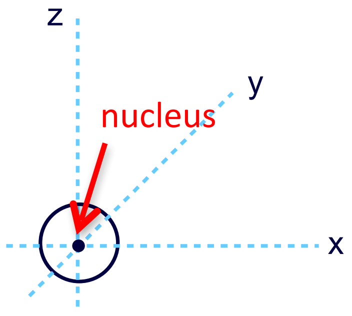
- planar 120° bond angle, C – 6 electrons (no lone pair), H – 2 electrons

- **Quantum Numbers and Atomic Orbitals**
- atomic orbitals – mathematical functions (wave functions) related to the probability of finding an electron in a particular region of space – for organic chemistry we will generally be concerned with s and p-orbitals

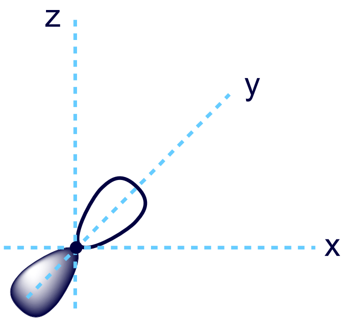


- atomic orbitals come in sets associated with the principal quantum number n = 1, 2, 3,…
- an atom's highest principal quantum number determines the valence shell of the atom - only these orbitals are generally involved in bonding
- each row of the periodic table indicates a different principal quantum number
- for hydrogen the principal quantum number is 1 giving rise to the familiar 1s orbital
- for carbon the principal quantum number is 2 giving rise to the familiar 2s and three 2p orbitals

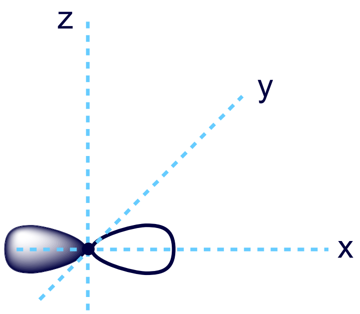
- 's' and 'p' orbitals



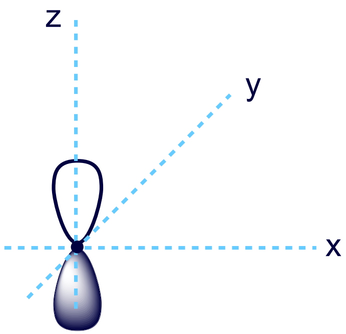
s



p_y



p_x



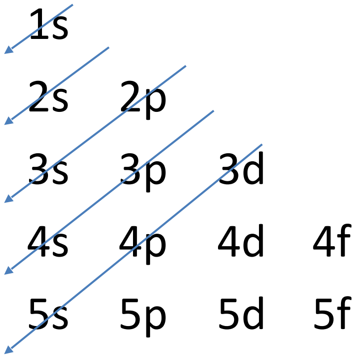
p_z

- s-orbitals - spherical
electron density decreases
in moving away from the nucleus

- there are three p-orbitals, p_x, p_y and p_z, orthogonal to each other

- p-orbitals have phase (sign) and a node at the nucleus (where the wavefunction changes sign) – the electron density is zero at a node

- the order of occupancy of atomic orbitals for a ground state configuration follows the Aufbau principle



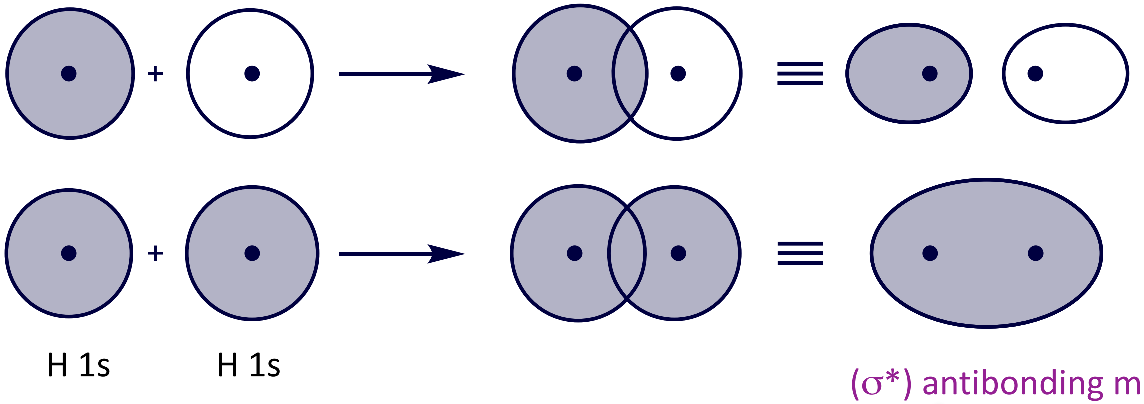
- ground state electronic configuration

i) orbitals filled lowest energy to highest energy following the arrows from top to bottom i.e. 1s, 2s, 2p, 3s, 3p, 4s, 3d, 4p, etc.

ii) maximum two electrons in each orbital which must have opposite spins (Pauli exclusion principle)

iii) empty orbitals of equal energy (e.g. 3 x 2p orbitals) take one electron each before pairing occurs (Hund's rule of maximum multiplicity)

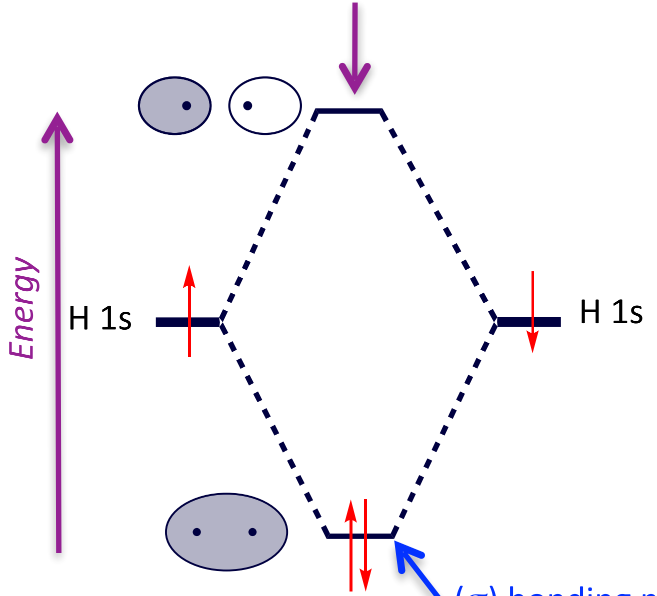
- **Molecular Orbitals** (simplified – an organic chemistry view)
- molecular orbitals are formed from combining atomic orbitals – we will look at H_2
- overlap of two hydrogen 1s atomic orbitals leads to two molecular orbitals, one lower in energy, and one higher in energy, than the original atomic orbitals
- electrons are fed into the lowest energy molecular orbital first



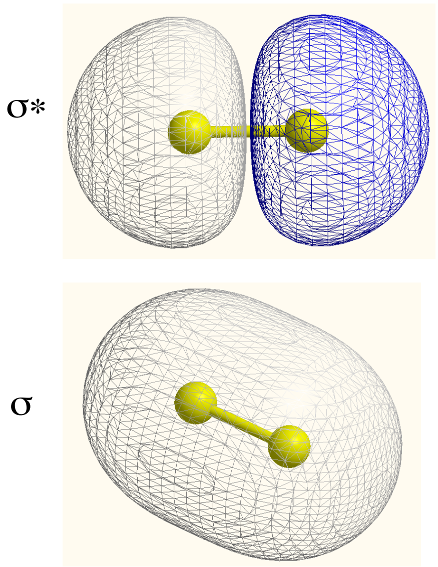
- destructive overlap of atomic orbitals leads to *anti-bonding* molecular orbital (internuclear node)
- constructive overlap of atomic orbitals leads to *bonding* molecular orbital

- molecular orbital diagram for H_2
- energy released in combining two hydrogen atoms to give H_2 is the bond strength = 432 kJmol^{-1}
- bonding molecular orbital in H_2 has cylindrical symmetry and is termed a σ-orbital (sigma orbital) – c.f. – s-atomic orbital
- in H_2 this orbital can be viewed as the (Lewis) bond and is called a σ-bond although the electron density is distributed over the whole molecule

(σ*) antibonding molecular orbital (empty)



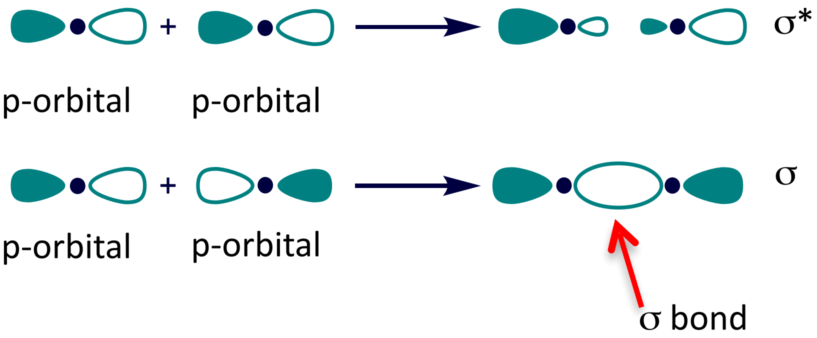
(σ) bonding molecular orbital (full)



- combinations of p-orbitals

(with all orbitals, the strongest bonding occurs when maximum overlap of (atomic) orbitals occurs)

- in a similar manner we can combine p-orbitals to make bonding and antibonding σ-molecular orbitals



- destructive overlap of atomic orbitals

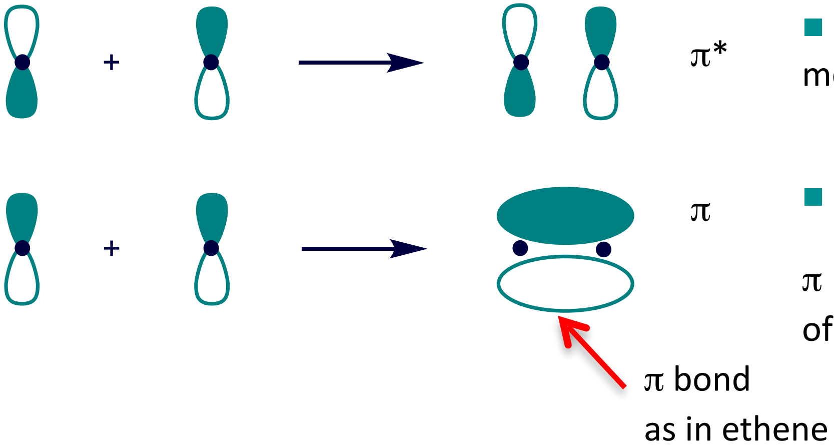
leads to *anti-bonding* σ^* molecular orbital – internuclear node

- constructive overlap of atomic orbitals leads to a *bonding* σ

molecular orbital - often drawn as 

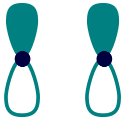
so the provenance of the molecular orbital is clear

- π-bonding – p-orbitals can also overlap edge on which leads to π-bonds – weaker than the corresponding σ-bonds as the orbital overlap is not as good

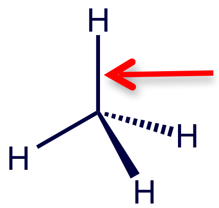


- destructive overlap of atomic orbitals leads to an *anti-bonding* π^* molecular orbital – internuclear node

- constructive overlap of atomic orbitals leads to a *bonding*

π molecular orbital - often drawn as  so the provenance of the molecular orbital is clear

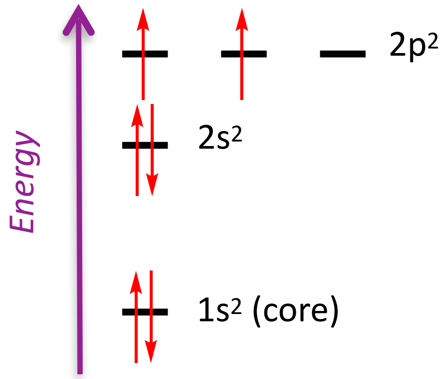
- returning to CH_4 (methane)



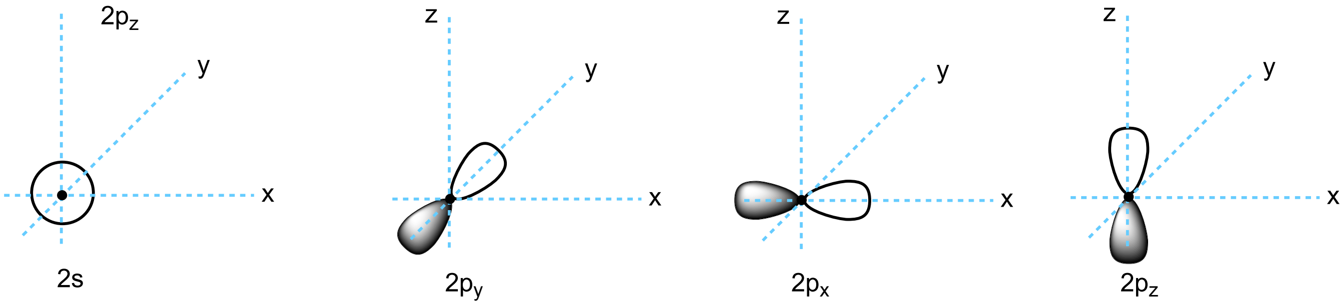
2 centre, 2 electron bond

- organic chemists generally draw Lewis structures where the line connecting the atoms represents a localised 2 centre, 2-electron bond. How can we rationalise this with a molecular orbital view of bonding involving overlap of orbitals?

- methane – CH_4



- carbon ground state $1s^2$, $2s^2$, $2p^2$ – the 1s electrons are core leaving the 2s and 2p valence electrons for bonding
- the 2s orbital is spherical (non-directional) and the three 2p orbitals point along their respective axes (i.e. at 90° to one another)

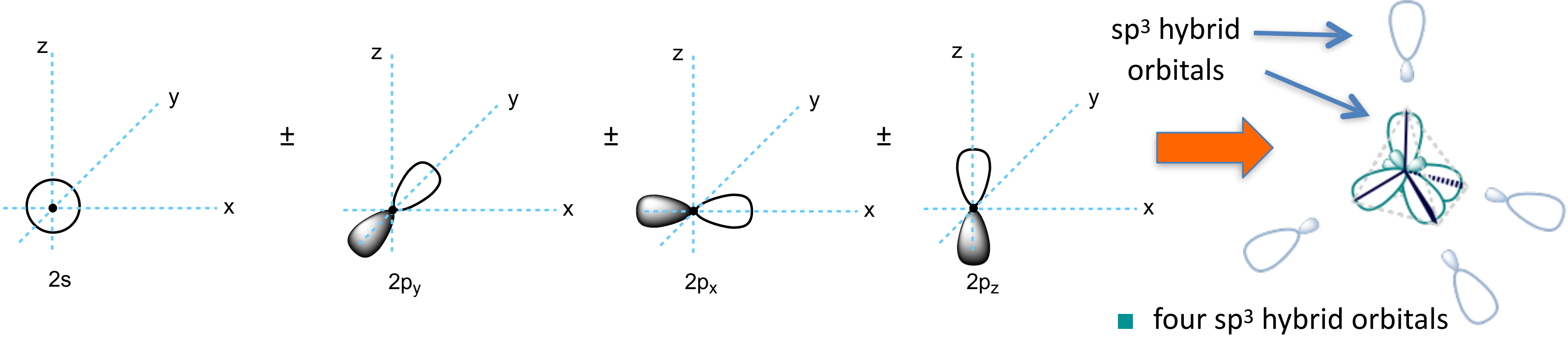


- how can s and p atomic orbitals accommodate the tetrahedral structure of methane (and the structures of many organic molecules)?

- one approach, initially proposed by Pauling, is the idea of hybridisation – a method of creating orbitals that reproduces the observed shapes of molecules

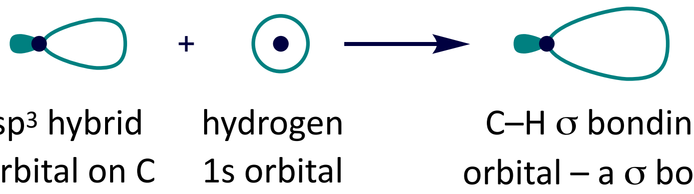
- atomic orbitals are just mathematical functions, so we can add and subtract them (as we have done to form simple molecular orbitals)
- full molecular orbital analysis (2nd year lecture course) is another approach

- hybridisation
- mixing the 2s and three 2p orbitals gives four sp^3 hybrids that point towards the corners of a tetrahedron



- four sp^3 hybrid orbitals

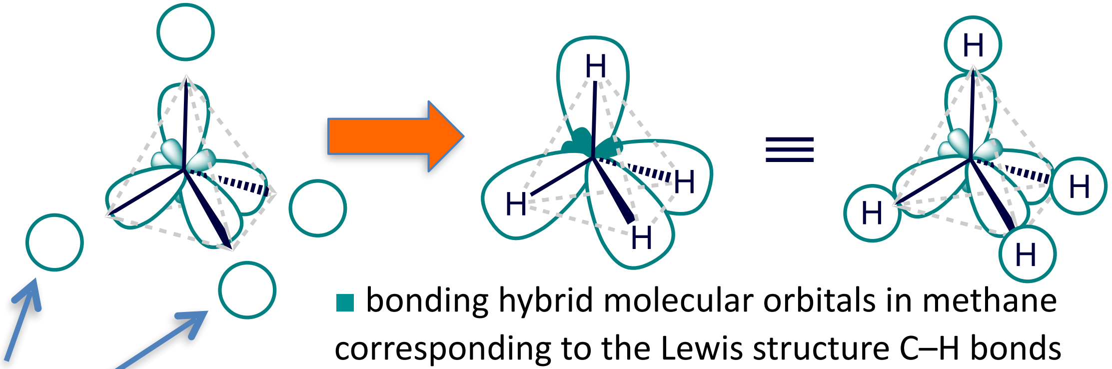
- these hybrid orbitals can overlap with the hydrogen 1s orbitals to form C–H σ-bonding orbitals (and the corresponding σ* antibonding orbitals)



- constructive overlap of hybrid orbital with 1s atomic orbital leads to a *bonding* σ molecular orbital (σ bond) - often drawn as  so the provenance of the molecular orbital is clear

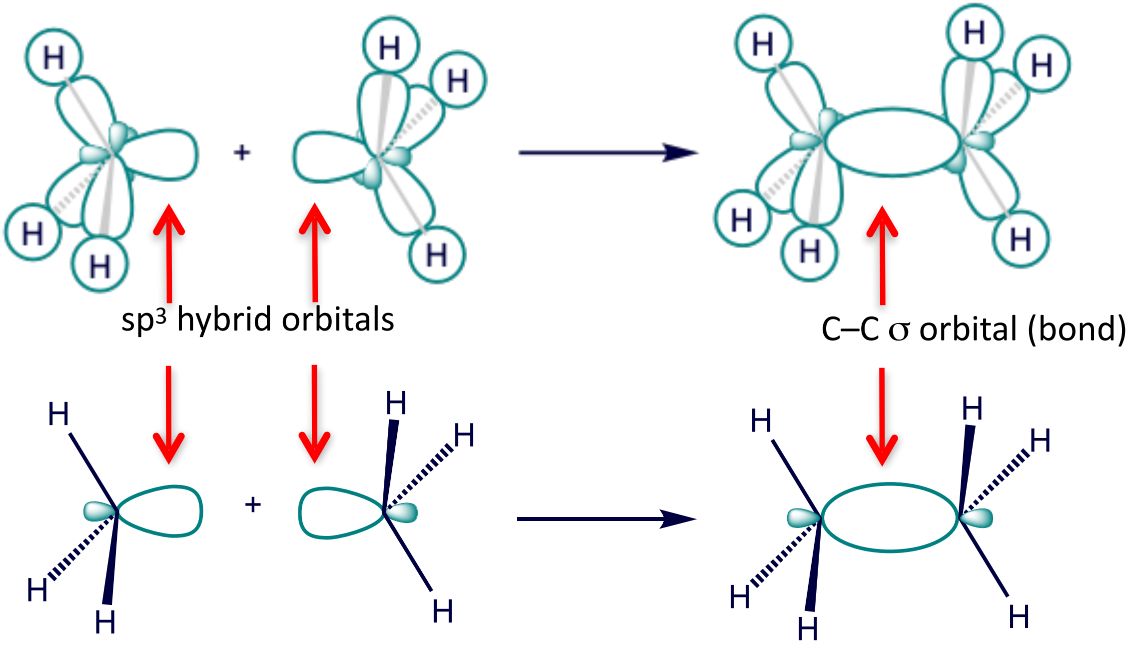
- the four sp^3 hybrid orbitals on carbon overlap with the 1s orbitals of the four hydrogen atoms to give methane

- the carbon atom is said to be sp^3 hybridised



- bonding hybrid molecular orbitals in methane corresponding to the Lewis structure C–H bonds each bond = 435 $kJmol^{-1}$

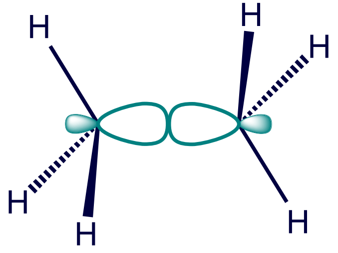
- as hybrid orbitals are directional they provide much better overlap with the 1s orbitals of the hydrogen atoms
- ethane – C_2H_6 – sp^3 hybrid orbitals can overlap with each other as in the C–C bond in ethane to give a bonding σ molecular orbital



sp^3 hybrid orbitals

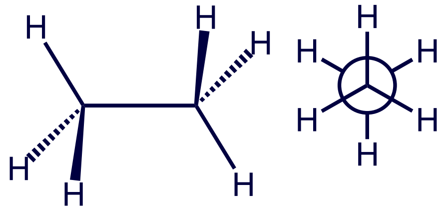
C–C σ orbital (bond)

- constructive overlap of hybrid orbitals leads to *bonding* σ molecular orbital - often drawn as below so the provenance of the molecular orbital is clear

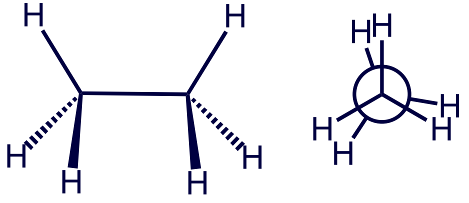


- rotation around the C–C axis does not alter the overlap of the sp^3 orbitals (the C–C σ orbital) and occurs readily to give a variety of *conformers* of ethane – more of this later

- staggered conformation

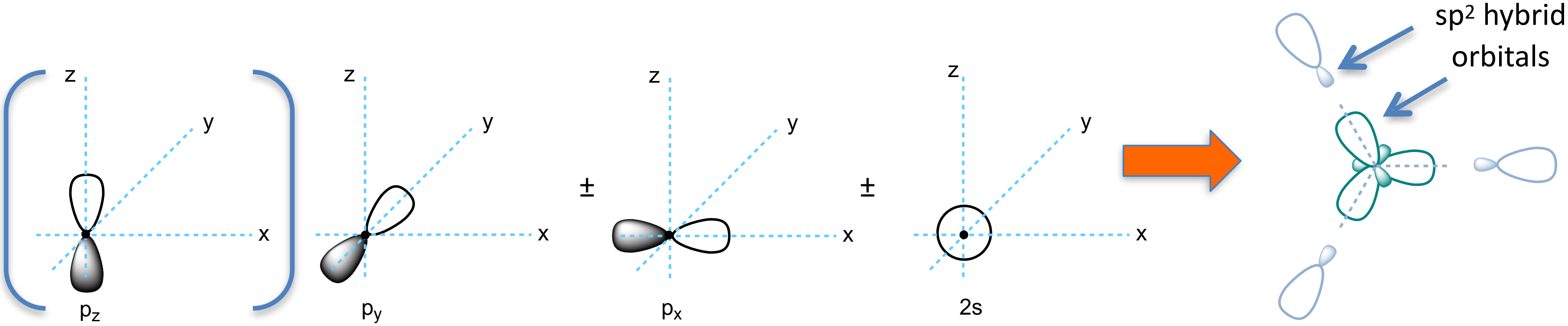


- eclipsed conformation



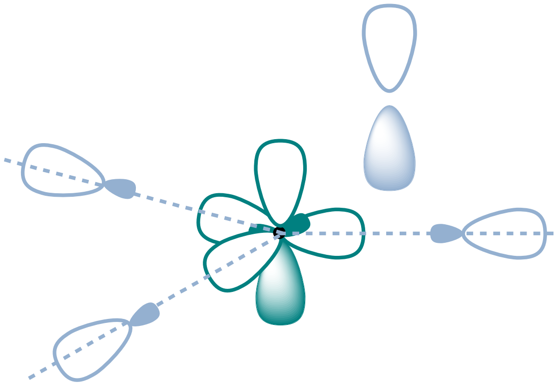
- the “end-on” views are termed Newman projections

- hybridisation – sp^2
- mixing the 2s and **two** 2p orbitals gives **three** sp^2 hybrids that lead to trigonal geometry (120° bond angles)



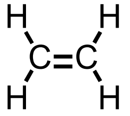
- three sp^2 hybrid orbitals (drawn in xy plane)

- forming three sp^2 hybrids leaves one p-orbital perpendicular to the plane containing the hybrid orbitals

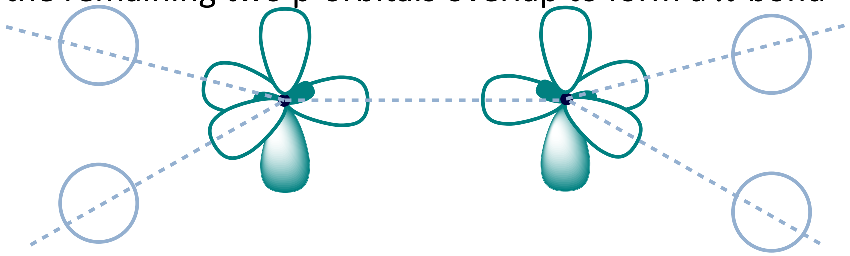


- three sp^2 hybrid orbitals and perpendicular p-orbital around central (carbon) atom

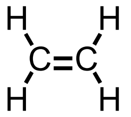
- the bonding in ethene/ethylene (C_2H_4) is a result of overlap of sp^2 hybridised carbon atoms with each other to form the C–C σ-bond, and with four hydrogen 1s orbitals to form the four C–H σ-bonds



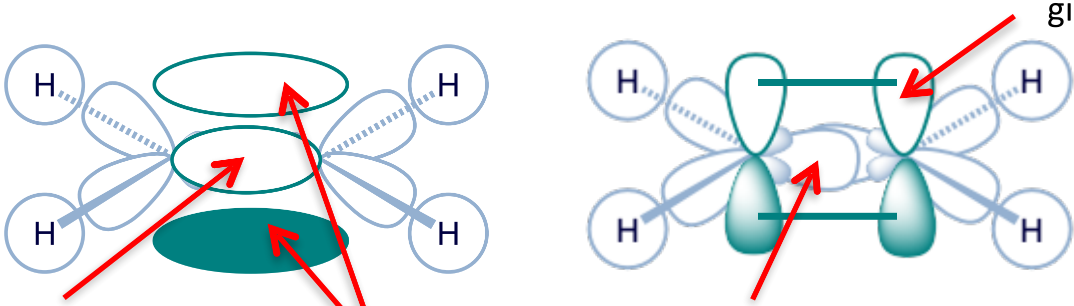
- the remaining two p-orbitals overlap to form a π-bond



- overlap of the sp^2 hybrid orbitals leads to three σ-bonds – two C–H bonds and one C–C bond
- overlap of the remaining perpendicular 'p'-orbitals gives a π-bond



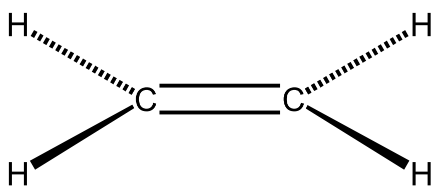
overlap of 'p' orbitals gives C–C π-bond



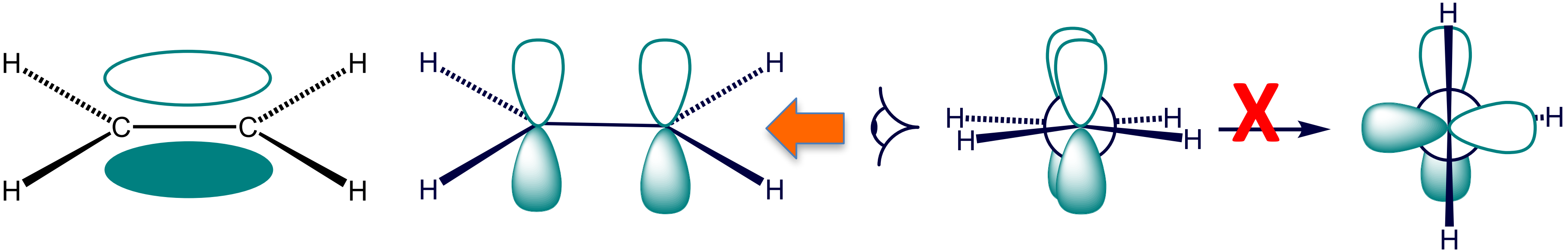
C–C σ-bond

the two lobes of the C–C π-bond

overlap of sp^2 hybrid orbitals gives C–C σ-bond



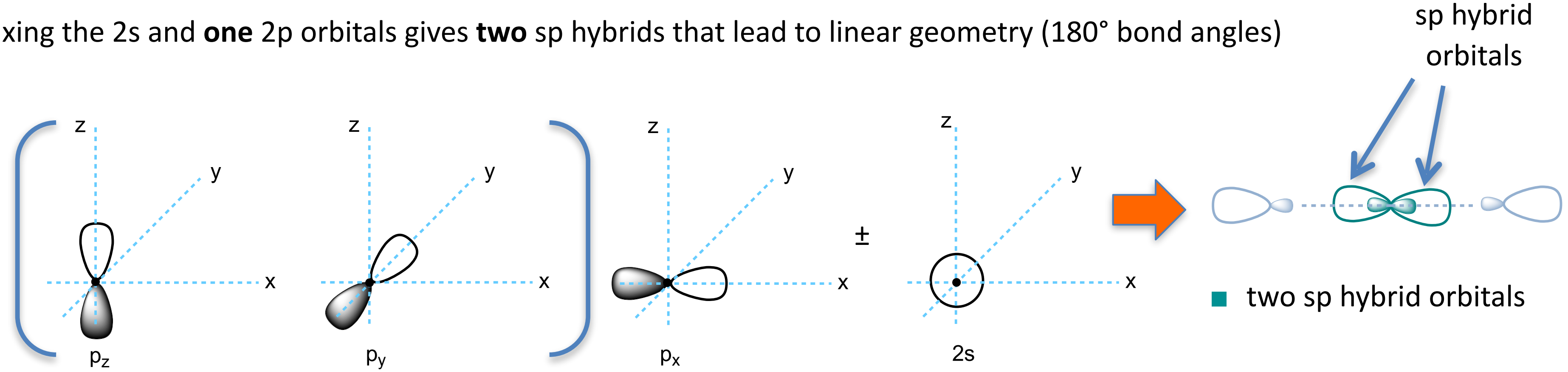
- the π-bond leads to electron density above and below the molecular plane
- rotation about the C–C axis is impossible as this would reduce overlap of the p-orbitals and would break the π-bond



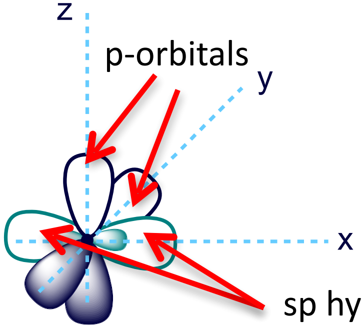
- as before the π-molecular orbital (π-bond) is generally drawn as two separate p-atomic orbitals for clarity

- rotation about C–C axis would break the π-bond and does not occur
- hence alkenes are configurationally stable (i.e. *cis* and *trans*)

- hybridisation – sp
- mixing the 2s and **one** 2p orbitals gives **two** sp hybrids that lead to linear geometry (180° bond angles)



- two sp hybrid orbitals

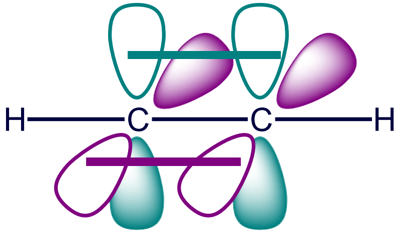


- forming two sp hybrids leaves two p-orbitals which can form π-bonds

H–C≡C–H

- the two sp hybrid orbitals are arranged 180° apart
- this is the bonding arrangement found in ethyne (acetylene) with the sp hybrids overlapping with the hydrogen 1s orbitals (not shown) the remaining p orbitals overlapping to form the two π-bonds
- the triple bond in acetylene is made up from one σ-bond and two orthogonal π-bonds, the carbons are said to be sp hybridised

H–C≡C–H



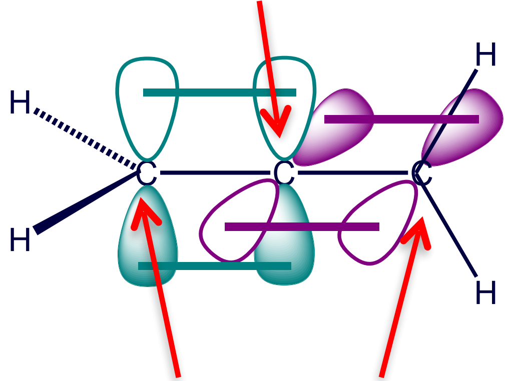
- view without σ-orbitals

- a quick method to work out the hybridisation of an atom is to count the number of substituents on that atom (including lone pairs of electrons), remembering that in the bonded environment second row elements have 8 electrons around them (there are exceptions to this method which we will meet later)

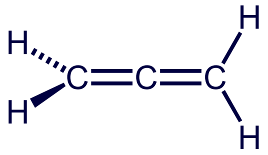
4 substituents = sp^3 hybridised, 3 substituents = sp^2 hybridised, 2 substituents = sp hybridised

- allene CH_2=C=CH_2 – what is its molecular shape?
  - terminal carbons bonded to 2 hydrogen atoms (σ-bonds) and double bonded to central carbon (σ-bond and π-bond) – ∴ terminal carbon atoms are sp^2 hybridised
  - central carbon bonded to 2 substituents ∴ has linear geometry ∴ sp hybridised
  - central carbon forms a single σ-bond with each terminal carbon (sp-sp^2 hybrid orbital overlap)

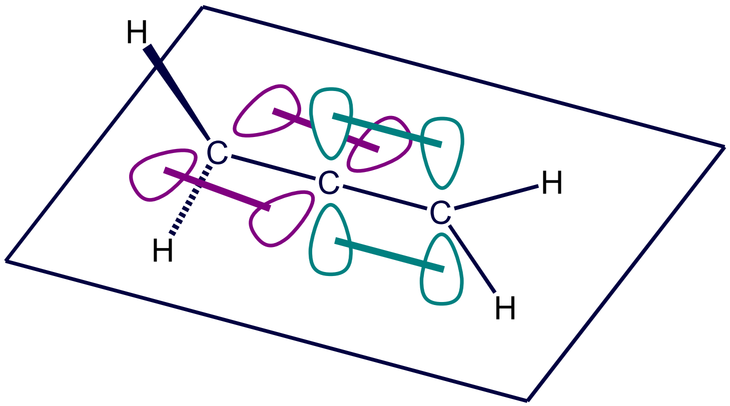
sp hybridised carbon
(c.f. acetylene)



sp^2 hybridised carbon
(c.f. ethene)

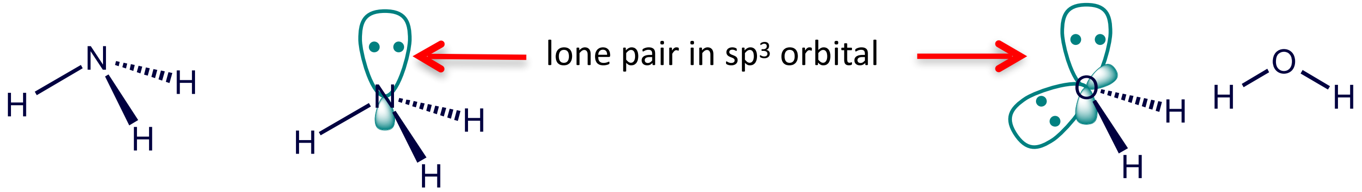


- no free rotation
- CH_2 groups are perpendicular



- alternative perspective

- hybridisation can be used with atoms other than carbon
- the nitrogen atom in ammonia can be viewed as sp^3 hybridised as can the oxygen atom in water although the H-X-H bond angle is slightly less than 109° due to lone pair–bond pair repulsion

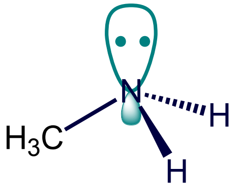


lone pair in sp^3 orbital

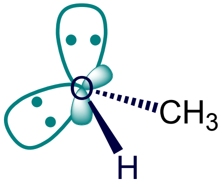
N-atom is sp^3 hybridised

O-atom is sp^3 hybridised

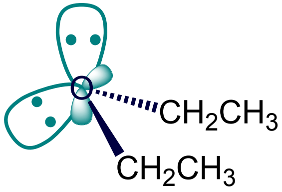
- similarly for amines, alcohols, ethers etc.



methylamine

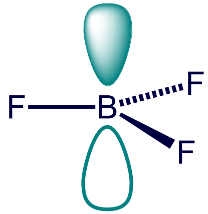


ethanol

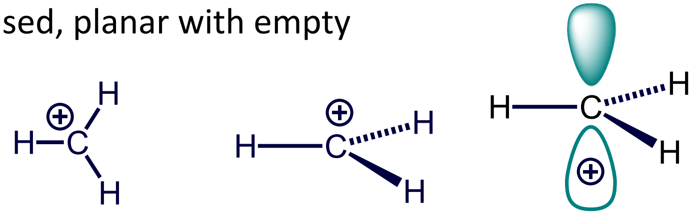


diethylether

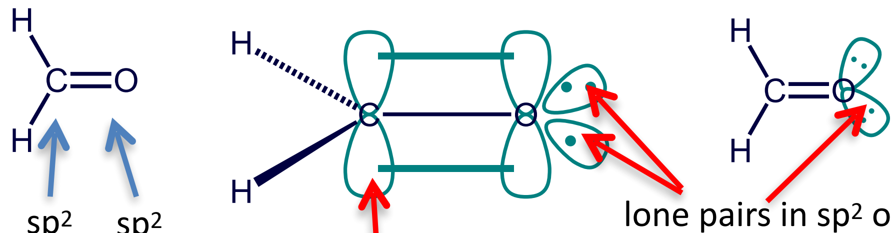
- BF_3 – three substituents around boron – no lone pair ∴ planar, sp^2 hybridised, planar with empty p-orbital on boron



- CH_3^+ - three substituents around carbon – no lone pair ∴ planar, sp^2 hybridised, planar with empty p-orbital on carbon – other carbocations have similar planar structure



- hybridisation in functional groups (sites of chemical reactivity)
- formaldehyde (c.f. bonding in ethene)



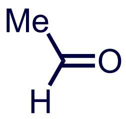
sp^2 sp^2

lone pairs in sp^2 orbital

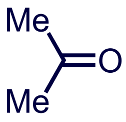
π-bond formed by overlap of adjacent p-orbitals

- bonding and reactivity is similar in aldehydes and ketones

acetaldehyde (ethanal)

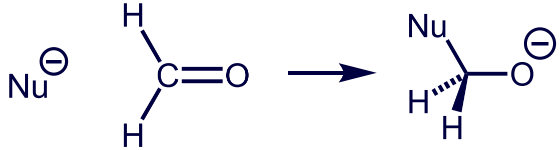


acetone (propanone)



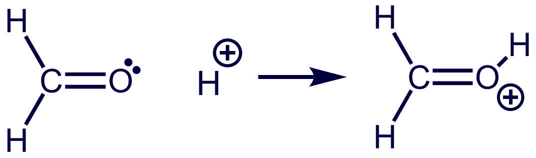
- electronegativity difference results in polarisation of C–O bond

- nucleophiles ∴ react on carbon and break the weaker π-bond

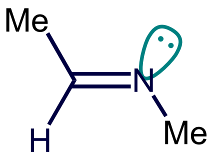


- conversely, lone pairs are sites of electron density

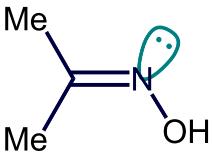
- electrophiles ∴ react on oxygen



- imines – planar, lone pair in sp^2 orbital

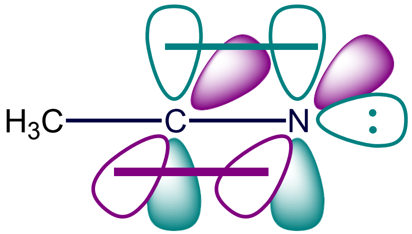


- oximes– planar, lone pair in sp^2 orbital



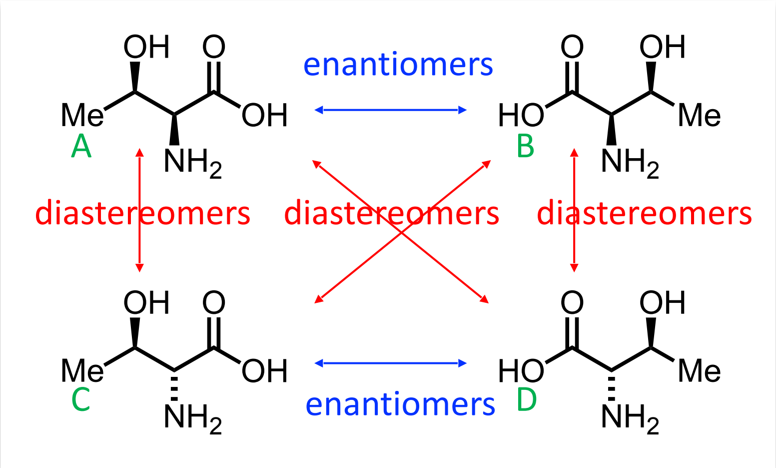
- nitriles – e.g. CH_3CN (c.f. bonding in acetylene)

lone pair in sp-orbital



Introduction to Organic Chemistry

Handout 2 – Stereochemistry



- *Organic Chemistry* J. Clayden, N. Greeves, S. Warren
- *Stereochemistry at a Glance* J. Eames & J. M. Peach
- *The majority of organic chemistry text books have good chapters on the topics covered by these lectures*

- *Eliel* Stereochemistry of Organic Compounds (advanced reference text)

- representations of formulae in organic chemistry

- skeletal representations are far less cluttered and as a result are much clearer than drawing all carbon and hydrogen atoms explicitly, they also give a much better representation of the likely bond angles and hence hybridisation states of the carbon atoms

- skeletal representations allow functional groups (sites of reactivity) to be clearly seen

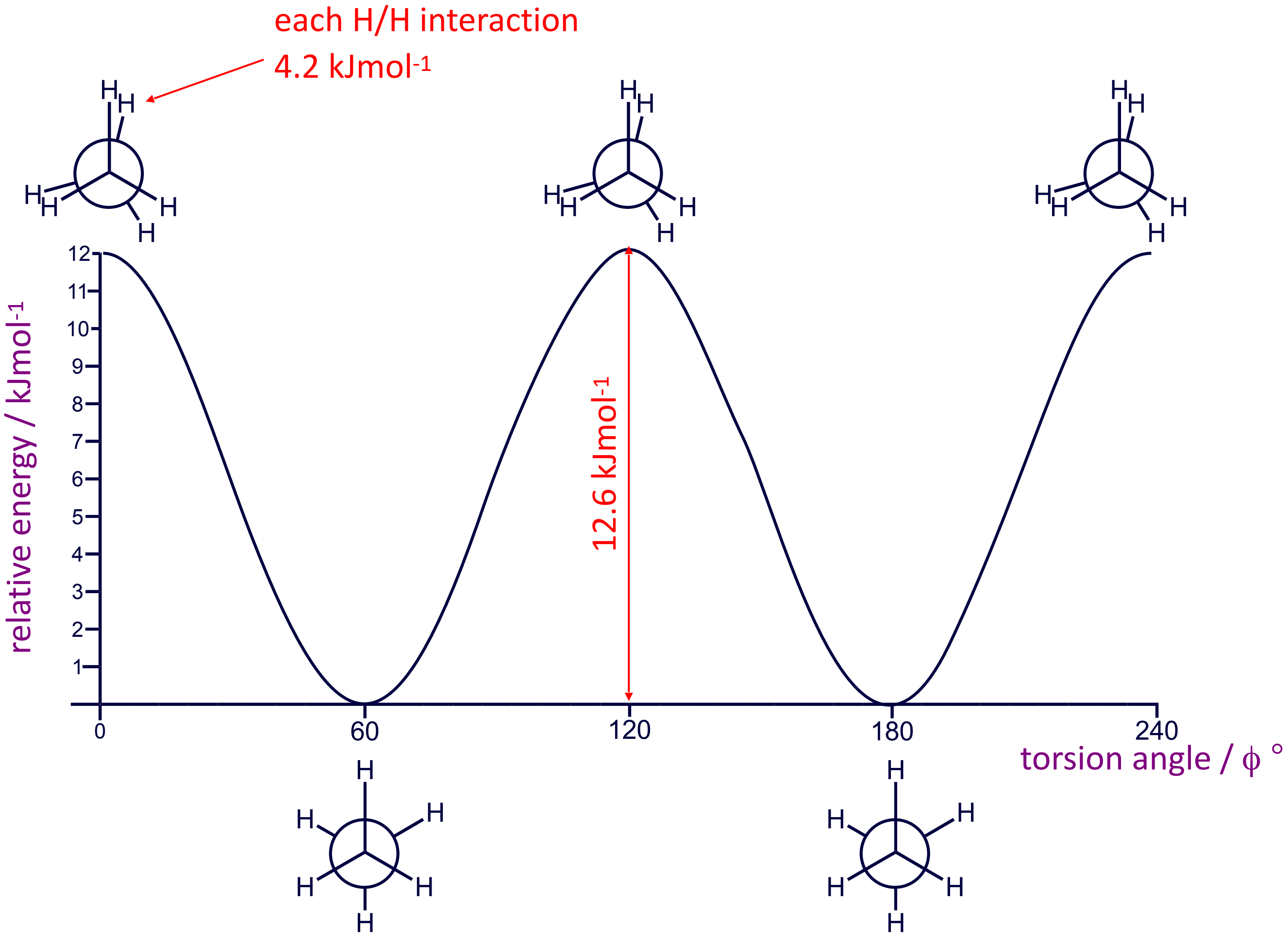
- guidelines for drawing skeletal structures

i) draw chains of atoms as zig-zags
ii) do not draw C atoms unless there is good reason to draw them
iii) do not draw C-H bonds unless there is good reason to draw then
iv) do not draw Hs attached to carbon atoms unless there is good reason to draw them
v) make drawings realistic

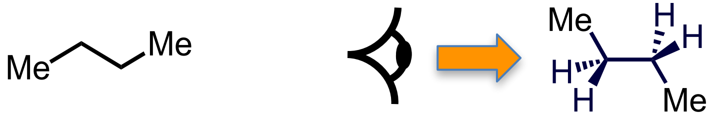
- representing structures in three dimensions

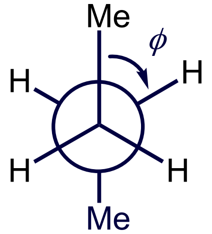
- a wedged bond  indicates the bond is projecting out in front of the plane of the paper
- a dashed bond  indicates the bond is projecting behind the plane of the paper
- a wavy bond  indicates one of two things: *either* unknown or unspecified stereochemistry *or* a mixture of two stereoisomers

- **conformation** – any spatial arrangement of atoms of a molecules that can be achieved by rotation about single bonds
- virtually an infinite number of conformations
- generally only the most and least stable conformations are discussed
- C_2H_6 - ethane

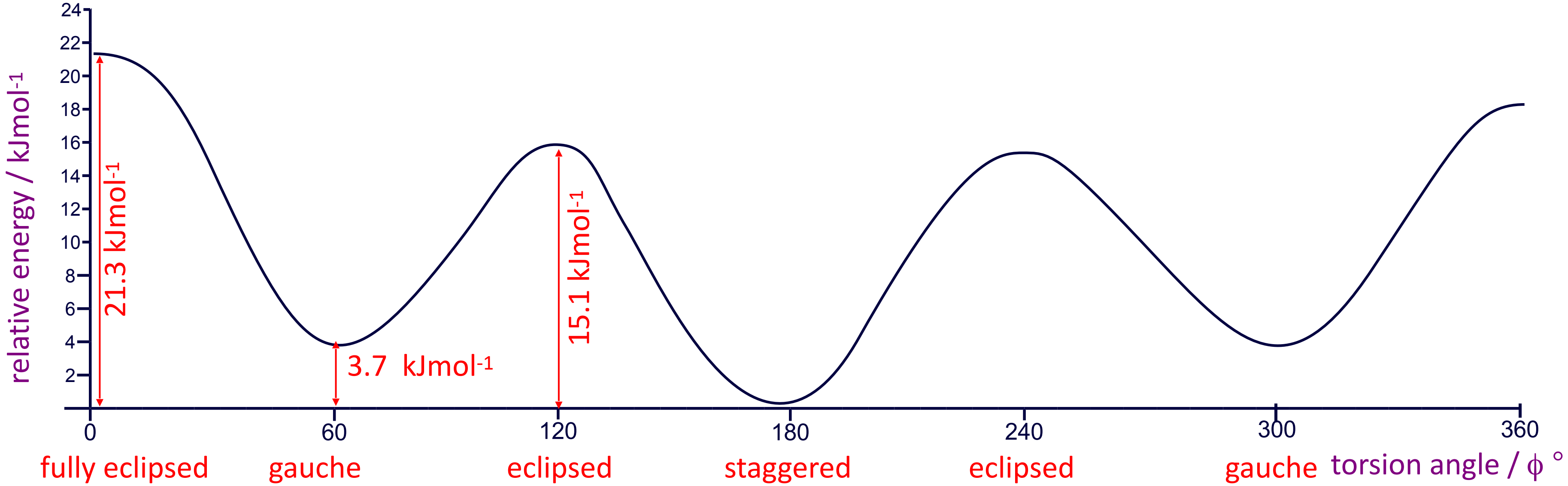


- conformational analysis of butane is similar to that of ethane





ϕ is the torsion angle



- staggered conformations are energy minima
- eclipsed conformations are energy maxima
- lowest energy conformation has Me groups as far apart as possible
- highest energy conformation has Me groups eclipsing one another

STEREOCHEMISTRY – from the Greek stereós (στερεός) meaning solid

- **isomers** – non-identical molecules with the same molecular formula

- **constitution** of a molecule is defined by the sequence of bonds (atom connectivity) between atoms without reference to their directions in space – constitutional isomers have the same molecular formula but different connectivity

- **stereoisomers** – isomers with the same connectivity – i.e. A linked to B linked to C etc., but different disposition of atoms in space

stereoisomers cannot be interconverted by rotation about single bonds (more later)

- stereoisomers can be divided into two mutually exclusive classes – enantiomers and diastereoisomers (diastereomers)

STEREOISOMERS

ENANTIOMERS

DIASTEREOISOMERS

- **enantiomers** (from the Greek for opposite – énanti (έναντι) – are stereoisomers which are related as non-superimposable object and mirror image (non-identical molecules related as object and mirror image)

- molecules (and objects) which have a non-superimposable mirror image are called ***chiral*** (from the Greek for hand – *chéri* (χέρι))

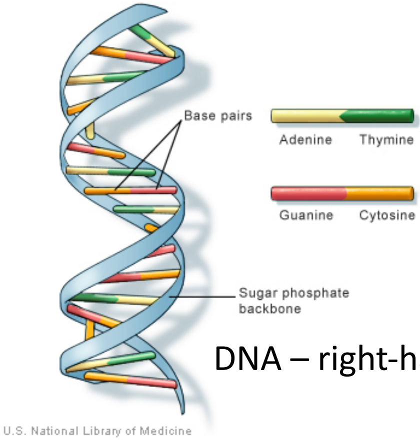
- a carbon atom (or other atom) bearing four different substituents is termed a ***stereogenic centre*** or ***stereocentre*** – frequently termed a chiral centre

- compounds in which one or more carbon atoms have four non-identical substituents are the largest class of chiral molecules

- conversely a molecule (or object) is termed ***achiral*** if it is superimposable on its mirror image

hands - chiral

screws – chiral – right-handed screw



U.S. National Library of Medicine

DNA – right-handed screw

golf clubs - chiral

snails – chiral –
usually right-handed helix

left-handed snails are rarer

tennis rackets - achiral

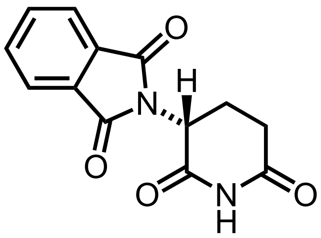
- enantiomers have the same physical and chemical properties in a non-chiral (*achiral*) environment – i.e. they are identical (in an achiral environment)

- enantiomers have *different* properties in a *chiral* environment e.g. an enzyme

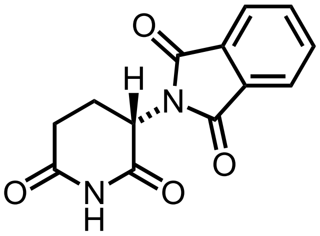
- separated enantiomers rotate the plane of *plane polarised light* in equal but opposite directions – this is optical activity and the sample is said to be optically active

- optical activity was first demonstrated by Pasteur in 1848 and led to the idea of tetrahedral carbon

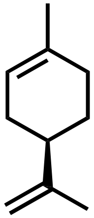
- Jean Baptiste Biot (1774-1862) first showed that some natural substances can rotate the plane of plane polarised light



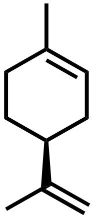
(+)-thalidomide, $[\alpha]_D^{21} = +63$ (*c* 2.03, DMF)
sedative, hypnotic, stops morning sickness



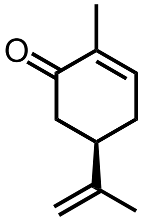
(–)-thalidomide, $[\alpha]_D^{21} = -63$ (*c* 2.03, DMF)
teratogen, foetal damage, congenital malformation



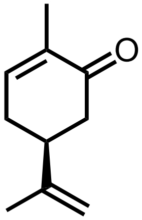
(+)-limonene
oranges



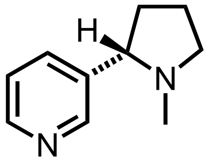
(–)-limonene
turpentine /
lemon



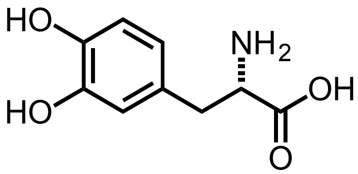
(–)-carvone
spearmint



(+)-carvone
caraway and dill

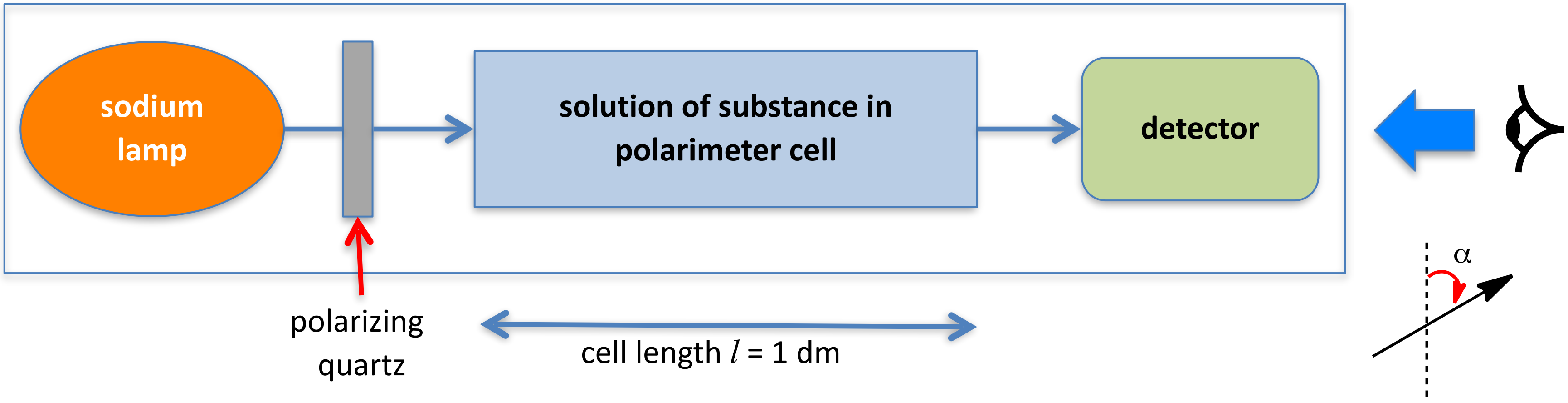


(*S*)-(–)-nicotine



L-DOPA

- optical rotation.
- schematic of a polarimeter



wavelength, λ

concentration of solution, *c* (g / mL)

sodium lamp

solution of substance in polarimeter cell

detector

polarizing quartz

cell length l = 1 dm

Specific rotation: $[\alpha]_D^T = \alpha / c \times l$

α = observed rotation

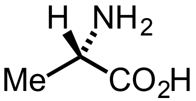
D = wavelength of sodium "D" line – 589 nm

c = concentration of solution in g / mL

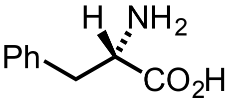
l = length of cell in dm (usually 1 dm)

T = temperature in °C

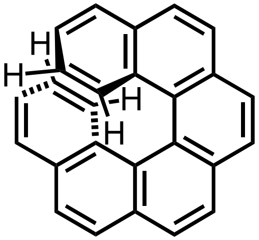
rotation to the right
dextrorotatory (+)
rotation to the left
levorotatory (-)



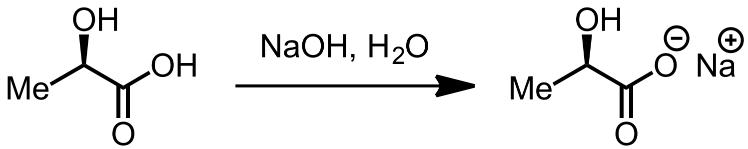
(S)-L-(+)-alanine
$[\alpha]_D$ = +14.7



(S)-L-(–)-phenylalanine
$[\alpha]_D$ = –35.2



hexahelicene
$[\alpha]_D$ = +3640!



(*R*)-D-(-)-lactic acid
$[\alpha]_D$ = -3.8

(*R*)-sodium lactate
$[\alpha]_D$ = +13.5

- there is no simple connection between structure and specific rotation; however, single enantiomers always show equal and opposite rotation if the specific rotation is measured under identical conditions

- the magnitude of the specific rotation depends on the wavelength, the temperature, the concentration and the solvent, among other things

- a 1:1 mixture of *enantiomers* is termed a ***racemic mixture*** (or ***racemate***), a *racemic mixture* is optically inactive – does not rotate the plane of plane polarised light

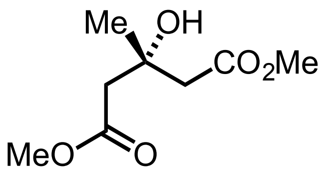
- *achiral* (non-chiral) molecules do *not* rotate the plane of plane polarised light and are optically inactive

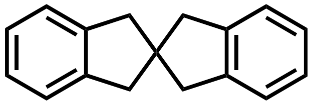
- if a reaction is to produce an excess of one enantiomer over the other then the reaction must be conducted in a chiral, non-racemic environment e.g. in the presence of an enzyme or enantiomerically enriched reagent or catalyst

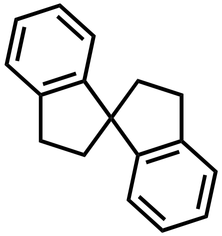
- *no* optically active material can be generated if all the staring material, reagents and conditions are either *achiral* or *racemic* i.e. optically inactive.
i.e. if a chiral compound is synthesised from achiral or racemic reactants, reagents and catalysts then it will be formed as a racemate

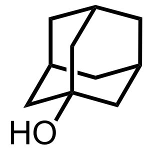
- *Note:* a sample of a chiral molecule may contain a single enantiomer or it may be a mixture of enantiomers, depending on how it was made

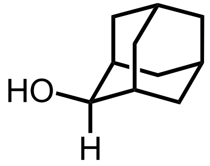
- which of the following molecules are chiral?

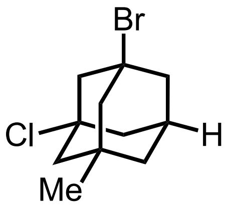


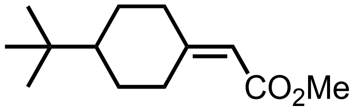












- **configuration** – the spatial arrangement of atoms that distinguishes stereoisomers

- tests for the presence of chirality

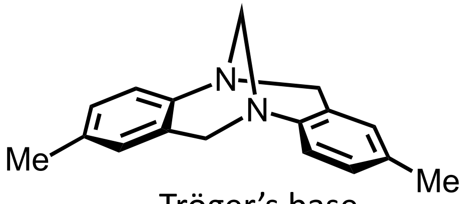
- if a molecule (or object) has a plane symmetry it **cannot be chiral**

- the presence of a stereogenic centre, a.k.a a stereocentre (i.e. a carbon with four different substituents, often called a chiral centre), is a reliable test for chirality if the molecule has **only one** stereocentre

- molecules with more than one stereocentre can be achiral (more of this later)

- the only reliable test to determine if a molecule is chiral, is the test of non-superimposability of the mirror image with the object

- chiral molecules are not restricted to those having a carbon atom carrying four different substituents
- sulfoxides, sulfinamides, phosphines and phosphine oxides can all be chiral and are frequently configurationally stable at room temperature
- the central atom (P or S) can carry four different substituents one of which can be a lone pair of electrons



Tröger’s base
a chiral molecule

- generally amines that have three different groups on nitrogen cannot be resolved into separate enantiomers as very rapid pyramidal inversion occurs at room temperature
- if the nitrogen substituents can be ‘tied-back’ to prevent pyramidal inversion then the amine may be resolved

- stereoisomers which are not related to each other as enantiomers are termed **diastereomers**

- all stereoisomers which are not related as non-superimposable object and mirror image are related as diastereomers

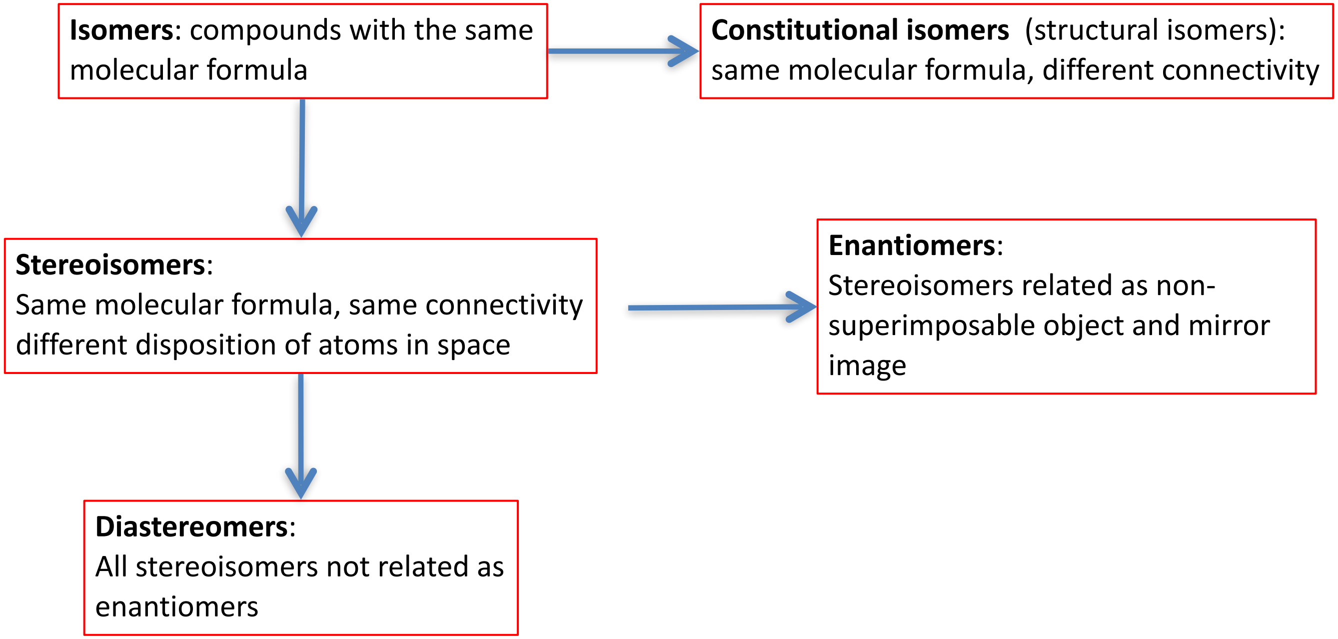
- *Note: it is the* ***relationships, enantiomeric and diastereomeric,*** *that are mutually exclusive*

i.e. two particular stereoisomers are ***either*** *enantiomers* or *diastereomers*; however, a molecule that is *enantiomeric* to one other molecule, may also be *diastereomeric* to other molecules

- diastereomers have different physical and chemical properties – different NMR spectra, IR spectra, melting point, boiling point etc. – they are ***different*** compounds

- remember enantiomers are related as non-superimposable object and mirror image and hence only have different properties in a chiral environment – they are identical in an achiral environment – more on this later

flow chart of isomers



Isomers: compounds with the same molecular formula

Constitutional isomers (structural isomers): same molecular formula, different connectivity

Stereoisomers:
Same molecular formula, same connectivity
different disposition of atoms in space

Enantiomers:
Stereoisomers related as non-superimposable object and mirror image

Diastereomers:
All stereoisomers not related as enantiomers

Cahn-Ingold-Prelog Sequence Rules

- it is important to be able to label the ***configuration*** of a *stereocentre* centre in much the same way as geometrical isomers of double bonds are termed ***cis*** and ***trans***

- *R* = Rectus (Latin for ‘right’) and *S* = Sinister (Latin for ‘left’) are used to label the configurations of *stereogenic* centres

- assign the priority of each atom directly attached to the stereocentre on the basis of atomic number – higher atomic number = higher priority

- if atoms directly attached to the stereocentre have the same atomic number move down each substituent one atom at a time until the *first* difference is reached, with higher atomic number always being the first point of difference
- same atomic number but different mass number – higher mass number takes priority e.g. T > D > H

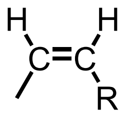
substituent	1st atom	2nd atom	priority

- draw molecule with the lowest priority substituent (priority d) at the rear

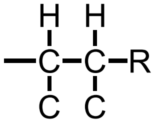
- a→b→c is clockwise the stereochemical descriptor is *R*
- a→b→c is anticlockwise the stereochemical descriptor is *S*

Cahn-Ingold-Prelog Sequence Rules - continued

Treat double and triple bonds as multiple single bonds:

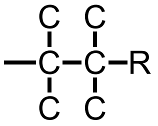


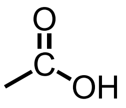
treat as



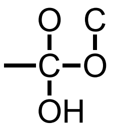
$-C\equiv C-R$

treat as



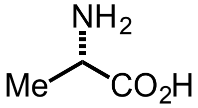


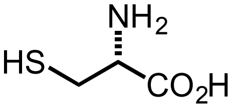
treat as

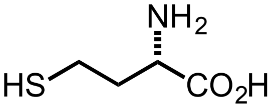


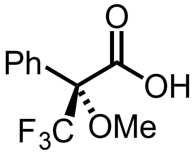
substituent	treat as	1st atom	2nd atom	priority

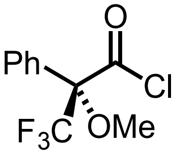
- assign *R* and *S* stereochemical descriptors to the following molecules

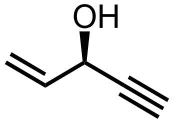


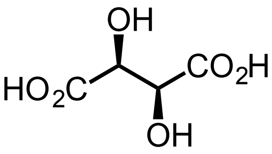


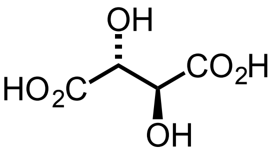


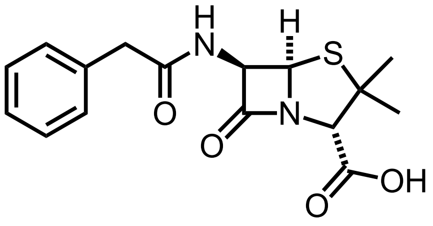












- *Cahn-Ingold-Prelog Sequence Rules - continued*
- the CIP rules can be extended to the assignment of double bond geometry.

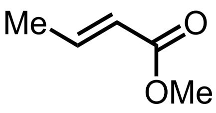
- look at one end of the double bond and decide which substituent has higher priority.

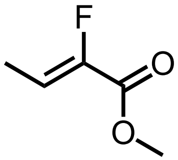
- look at the other end of the double bond and decide which substituent has higher priority.

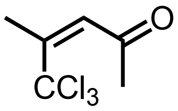
- double bond is (*Z*) if the the higher order substituents are on the same side of the double bond (**Zusammen** – together in German)

- double bond is (*E*) if the higher order substituents are on the opposite side of the double bond (**Entgegen** – opposite in German)

- assign (*E*) or (*Z*) to the following alkenes







- some useful stereochemical projections
- sawhorse projection – looking down the C–C bond with an angled projection

- Newman projection – looking down the C–C bond

- Fisher projections are no longer a useful stereochemical projection but are historically important

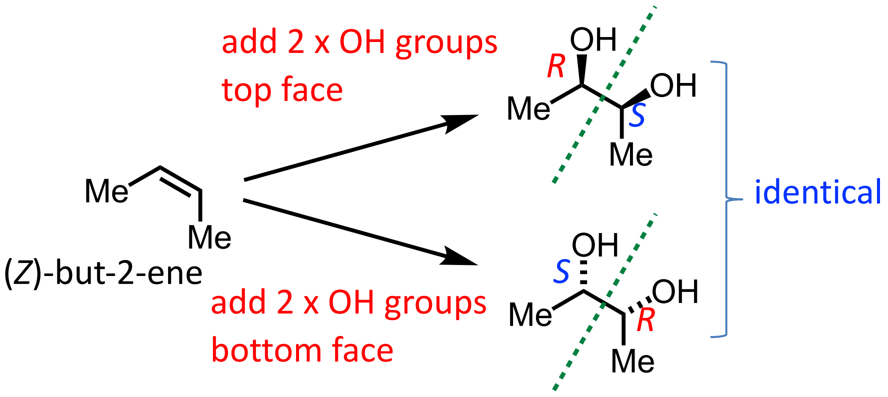
e.g. tartaric acid

- molecules with two stereocentres – we will use the dihydroxylation of alkenes using osmium tetroxide as an example
- OsO_4 is a reagent that adds two ‘OH’ groups to the same face of an alkene – ***syn*** addition (mechanism in later course)

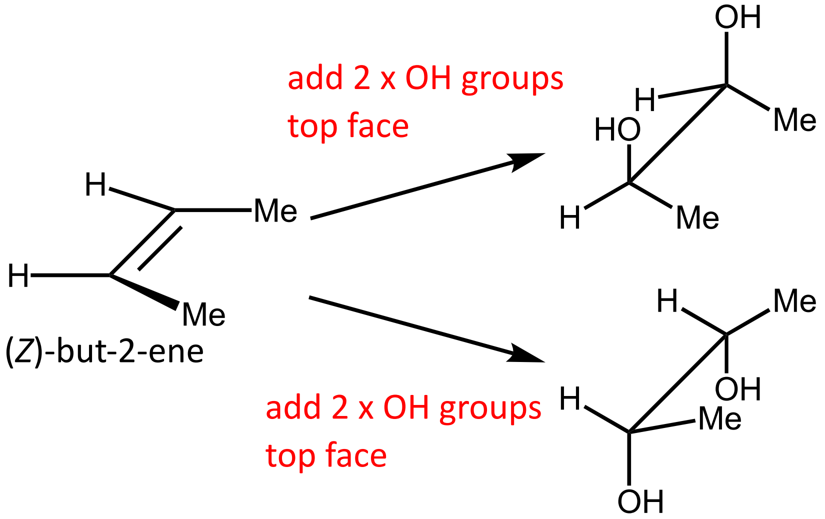
- three projections of the products formed from the ***syn***-addition of two OH groups to the top or bottom face of (*E*)-but-2-ene (*trans*-but-2-ene)
- the products formed from addition to either face of the alkene are different – they are stereoisomers – they are enantiomers

- *aside* - if two groups are added to the opposite faces of an alkene this is termed ***anti*** addition

- (*Z*)–but-2-ene



meso compound - **achiral**

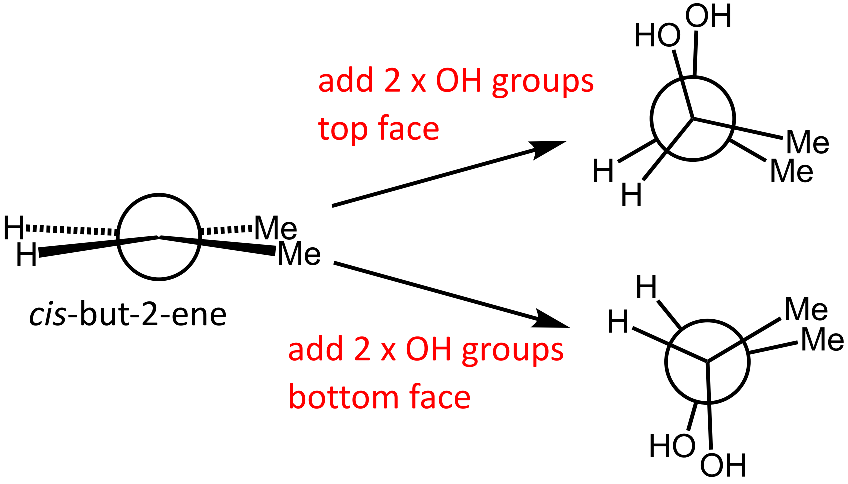


- three projections of the products formed from the ***syn***-addition of two OH groups to the top or bottom face of (*Z*)-but-2-ene (*cis*-but-2-ene)

- the products formed from addition to either face of the alkene are the same i.e. only one stereoisomer is formed

- this stereoisomer has a plane of symmetry and is thus achiral (not chiral and is optically inactive)

- this stereoisomer is termed a ***meso*** compound

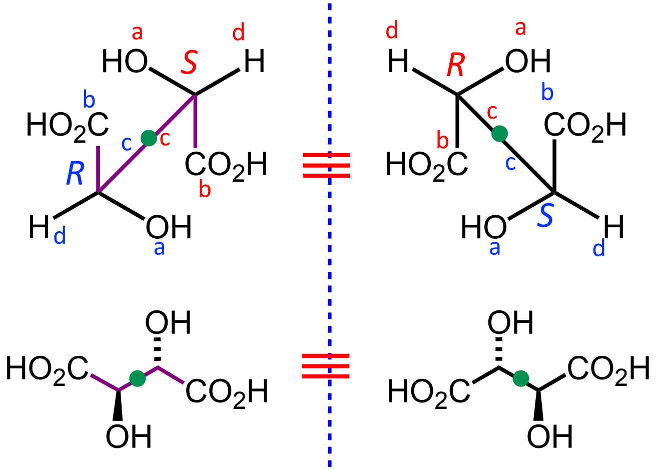


- there are therefore three stereoisomers of butane-2,3-diol

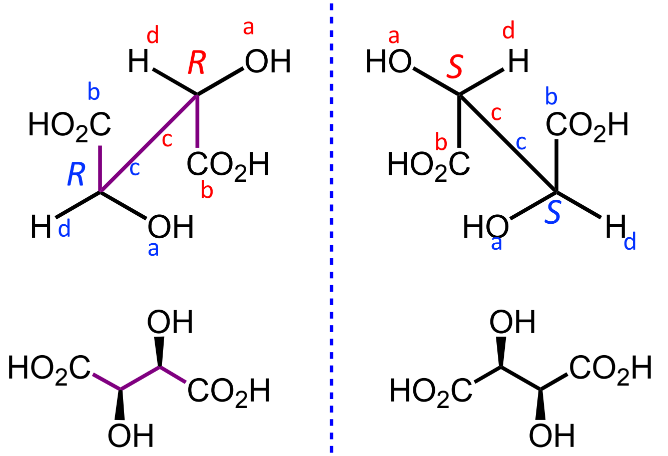
- a simple definition of a *meso* compound is a stereoisomer with two or more stereocentres but which is itself achiral

a fuller definition is that a ‘meso compound is an achiral member of a set of diastereomers that includes at least one chiral member’ *Elliel*

- 2-stereogenic centres – tartaric acid – potential descriptor combinations *RR, SS, RS, SR*



object and mirror image are the same
(superimposable) achiral,
meso, form *SR* = *RS* = *meso*

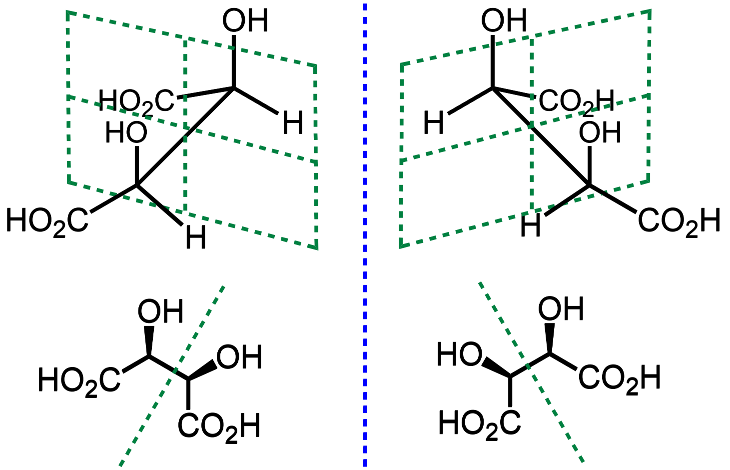


R, *R* *S*, *S*

pair of enantiomers
(non-superimposable object and mirror image)

- there are 3 steresiomers of tartaric acid, a pair of enantiomers, and the *meso*-form

- as drawn the conformers of the meso compound have a centre of inversion *i* (●)
- molecules (objects) with a centre of inversion cannot be chiral
- redrawing in a different conformation reveals a plane of symmetry (σ, often easier to spot than *i*) indicating that this stereoisomer is achiral



- if a molecule can gain access to a conformation which is superimposable on its mirror image then it will be **achiral**
- if a molecule can gain access to a conformation that has a plane of symmetry or centre of inversion (or more generally an improper axis of rotation S_n) then it will be **achiral**

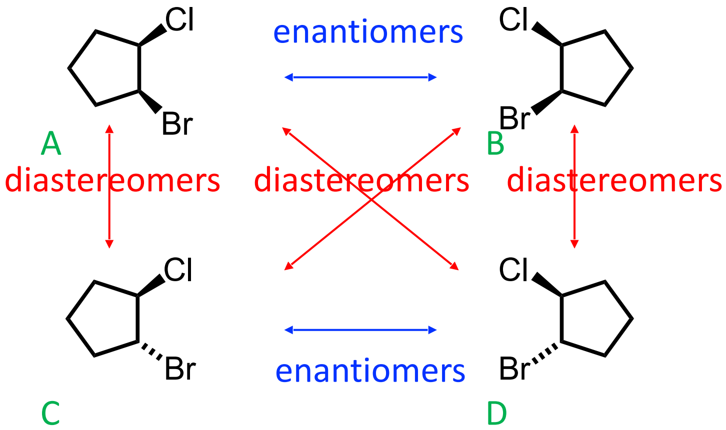
- 2-stereogenic centres - 1,2-dichlorocyclopropane – 3 stereoisomers

- in compounds with 2 stereocentres, when the groups are not the same there are always 4 stereoisomers

- if a compound has *n* stereogenic centres (or more generally stereogenic elements) then the maximum number of stereoisomers is 2^n

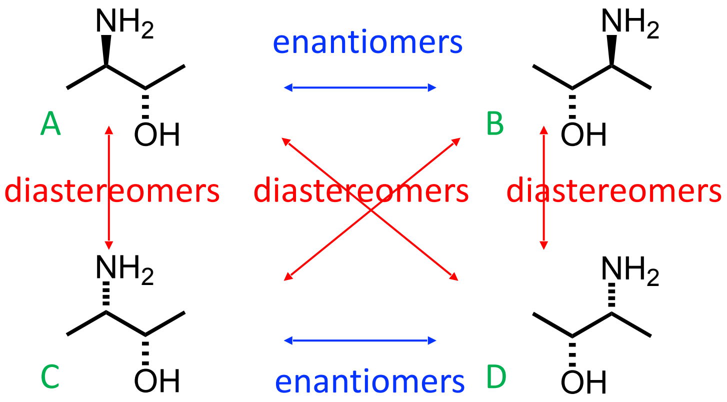
- 2-stereogenic centres – 1-bromo-2-chlorocyclopentane

4 stereoisomers, 2 pairs of enantiomers



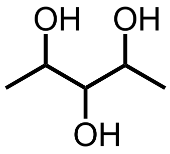
- 2-stereogenic centres – 3-aminobutan-2-ol

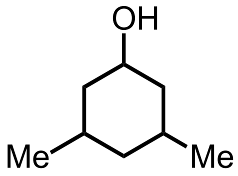
4 stereoisomers, 2 pairs of enantiomers

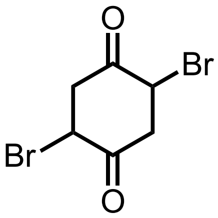


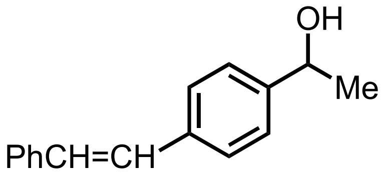
- for molecules with multiple stereocentres all stereocentres must be inverted to convert one enantiomer into the opposite enantiomer

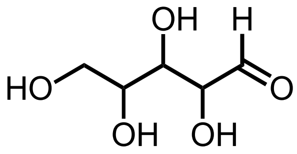
- draw all the stereoisomers of the following compounds. What are the stereochemical relationships between the various pairs of stereoisomers? Which of the stereoisomers are chiral? Identify any *meso* compounds











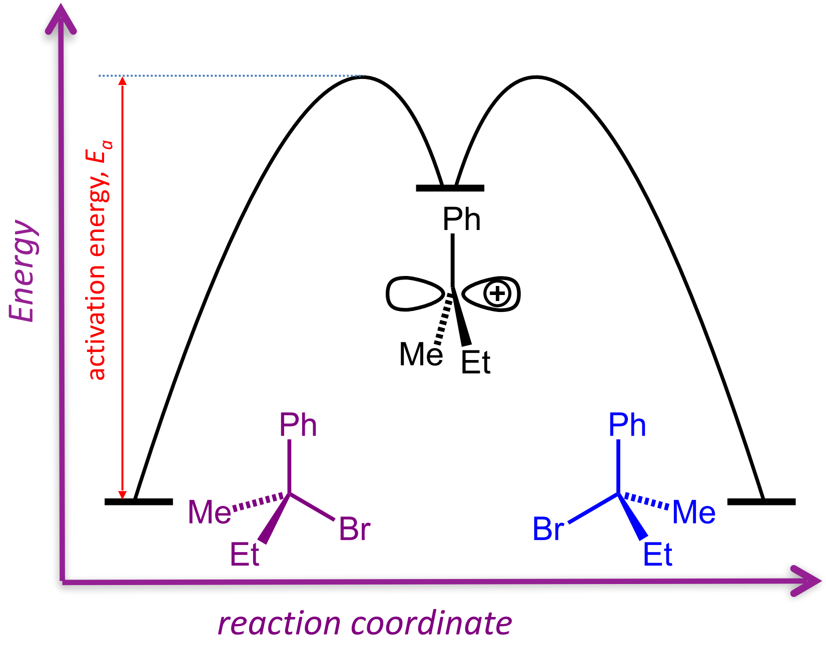
- to investigate how many stereoisomers a compound has the following method may be useful:

i) if a compound has *n* stereogenic centres (or more generally stereogenic elements) then the maximum number of stereoisomers will be 2^n – if you have more than 2^n you have made a mistake
ii) if the compound is acyclic draw it in zig-zag fashion
iii) identify the stereocentres
iv) decide how many diastereomers there are by putting substituents, with defined stereochemistry on the stereocentres
v) look for possible planes of symmetry (or centres of inversion) and hence decide which diastereomers are chiral – identify *meso* compounds – the presence of meso compounds reduces the number of stereoisomers
vi) draw the enantiomers of any chiral diastereomers by inverting *all* of the stereogenic centres - chiral steroisomers *always* come in pairs i.e. two enantiomers

- **racemisation** – the conversion of one enantiomer (or an excess of one enantiomer) into a 1:1 mixture of enantiomers (a racemate or racemic mixture)

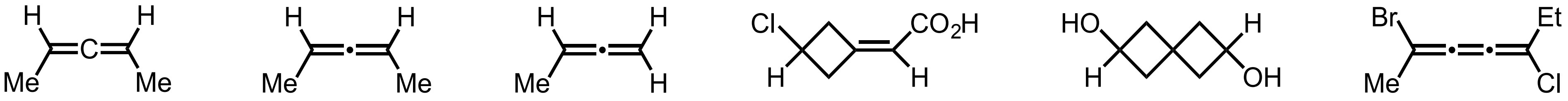
- e.g. S_N1 reaction (more of this in later courses)

- on recombination, Br^- has equal probability of attacking either side of the carbocation leading to a racemic mixture



- so far we have mainly looked at ‘central’ chirality – we will now briefly look at planar, axial and helical chirality
- chirality is a molecular property (in fact a property of an object) so it is not necessary for a molecule to posses a stereocentre (chiral centre) in order to be chiral

- the necessary and sufficient condition for a molecule to be chiral is that it is non-superimposable on its mirror image (i.e. that it lacks an improper axis of rotation (S_n))
- allenes



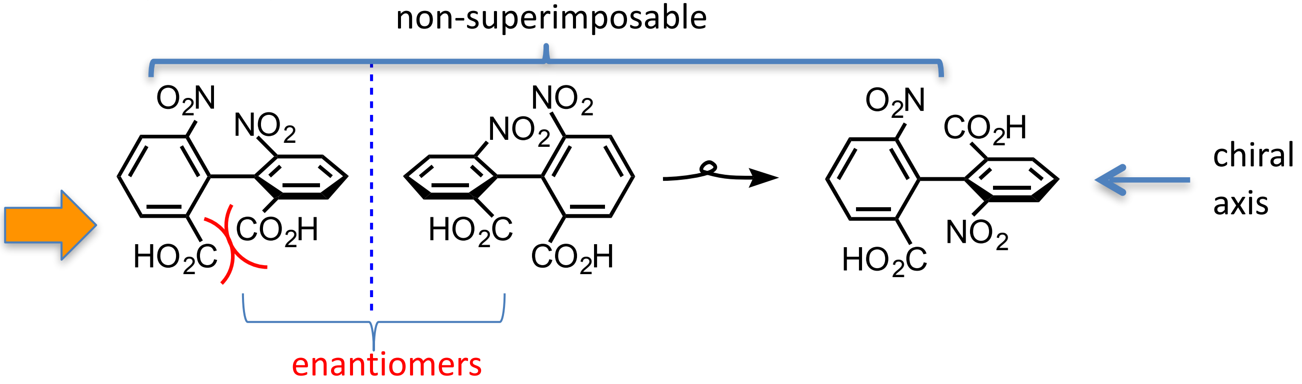
- which of the following molecules are chiral?

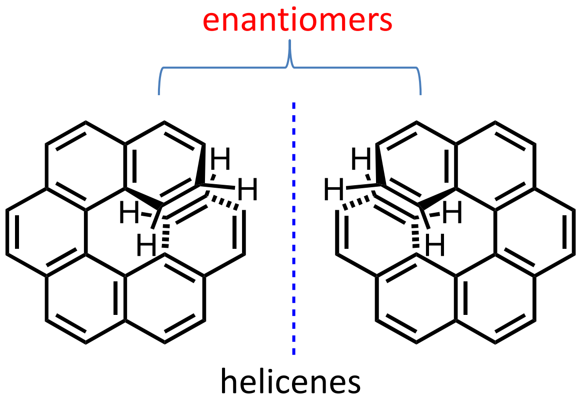
- atropisomers and axial chirality – biphenyls

- atropisomers may be defined as stereoisomers resulting from restricted rotation about single bonds

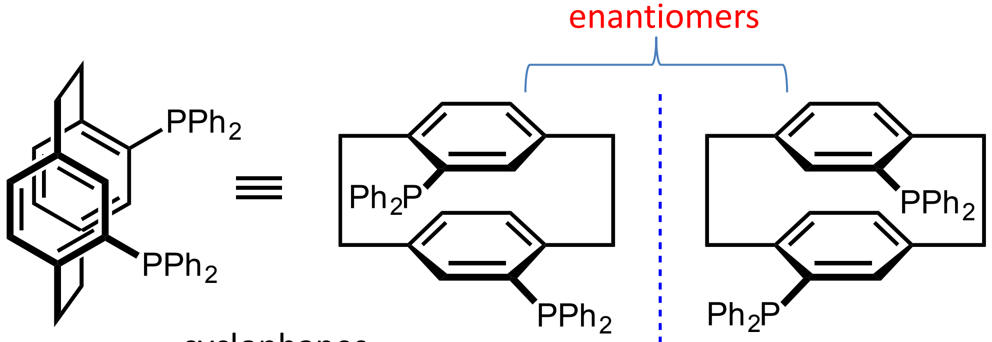
- the (arbitrary) definition of atropisomers is that they have a half life of at least 1000s at a given temperature (>90 kJ•mol^{-1} at 300 K) – the rotational barrier needs to be high enough that the separate isomeric species can be isolated

severe steric hindrance means rotation around the central C-C single bond only occurs at high temperature and this compound can be resolved

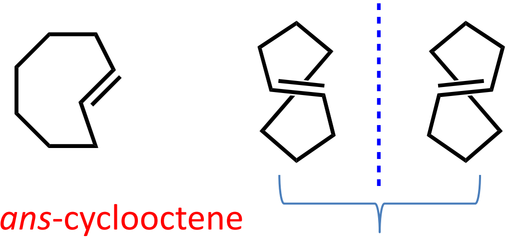




helicenes



cyclophanes



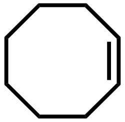
trans-cyclooctene

strained alkenes

enantiomers

- *trans*-cyclooctene is stable to racemisation indefinitely at 20 °C (chiral)

- *cis*-cyclooctene is achiral

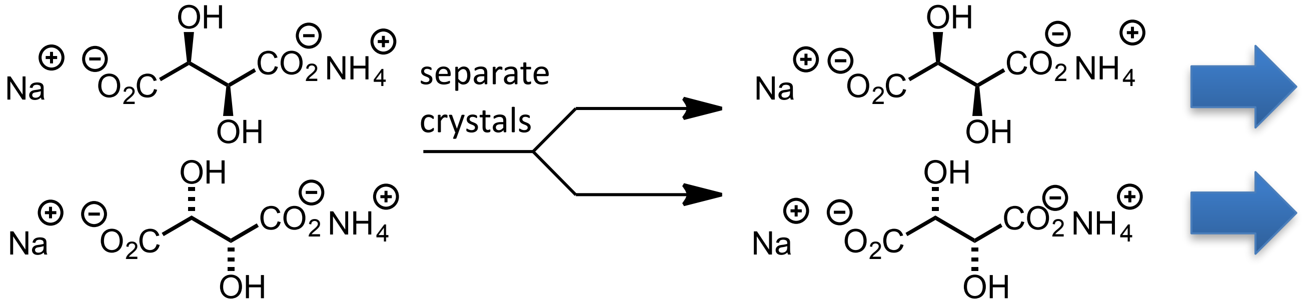


- **Resolution of Racemates** – separation of a 1:1 mixture of enantiomers i.e. (±) mixture, into pure (+) and (–) forms

- problem: enantiomers have identical physical properties therefore they are very difficult to separate

- if a racemate crystallises it can either crystallise so that each crystal contains both enantiomers (a racemic crystal) or such that each crystal is either (*R*) or (*S*) – this is termed a conglomerate and approximately 5-10% of chiral crystalline materials crystallise in this manner

- sodium ammonium tartrate crystallises as a conglomerate, which allowed Pasteur to separate the enantiomeric crystals by hand

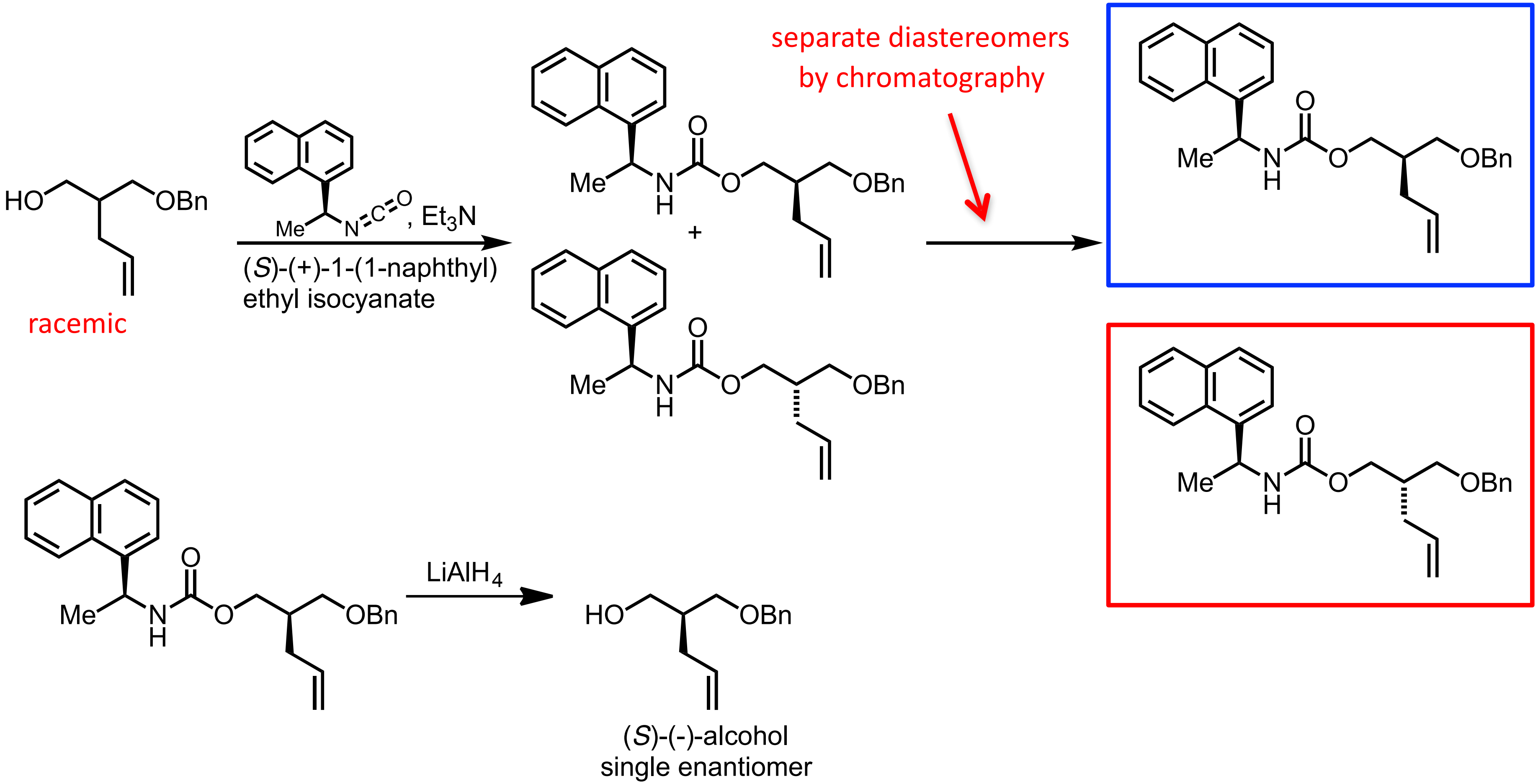


$[\alpha]_D^{20} = -12$ (c = 20 in water)
(–)-tartaric acid - unnatural

$[\alpha]_D^{20} = +12.4$ (c = 20 in water)
(+)-tartaric acid - natural

- this is not a general solution to the separation of enantiomers as:
  i) not all racemates are crystalline
  ii) the majority of chiral crystalline materials are not conglomerates

- separating diastereomers – diastereomers are different molecules, and have different physical properties,
- we should therefore expect to be able to separate diastereomers by standard methods including: chromatography on silica, crystallisation, distillation etc.
- this property of diastereomers indirectly allows the separation of mixtures of enantiomers
- a racemic mixture is a 1:1 mixture of enantiomers
- if we react the racemic mixture with a single enantiomer of a reagent we will produce diastereomers which are (at least theoretically) separable



racemic

, Et_3N

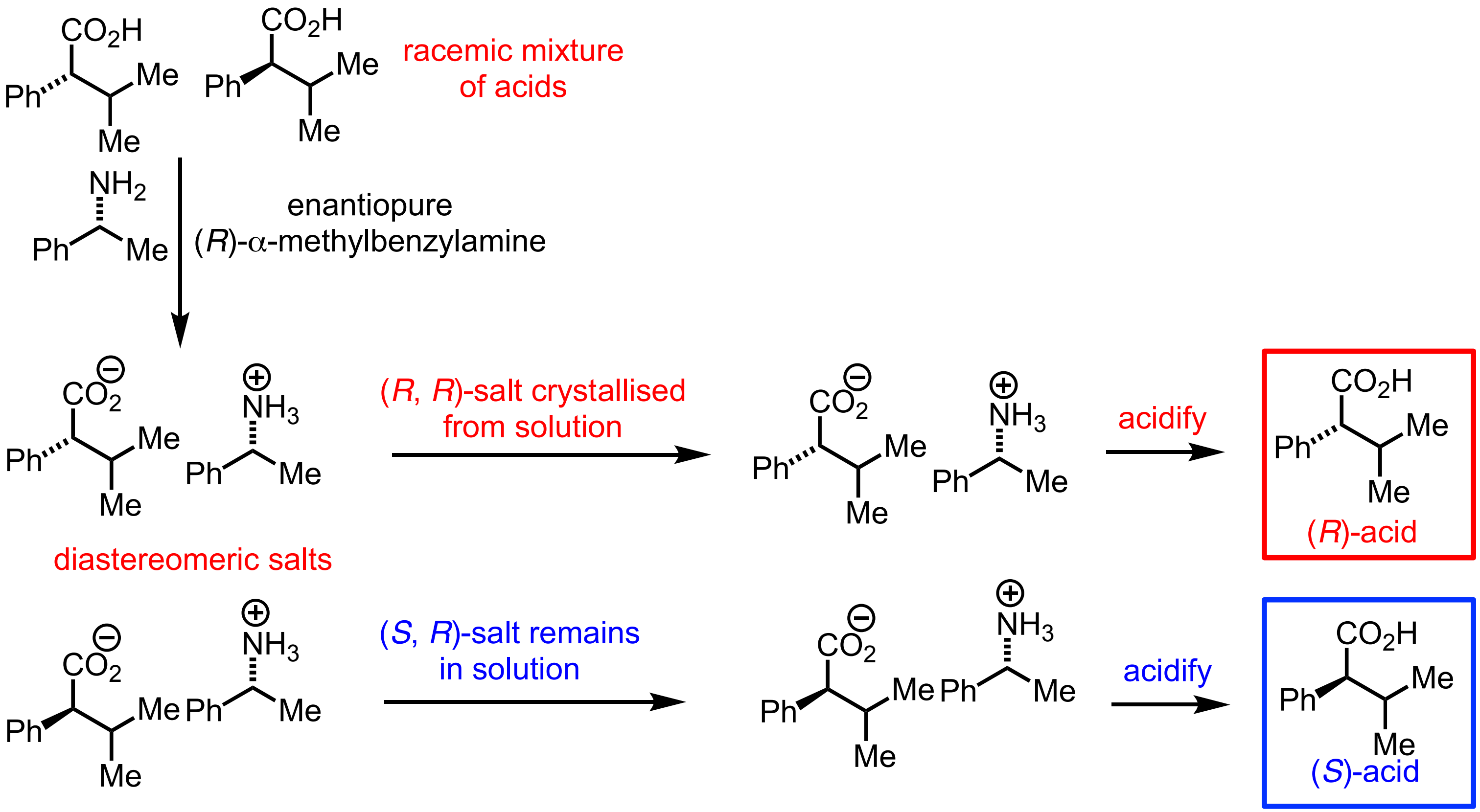
(*S*)-(+)-1-(1-naphthyl)
ethyl isocyanate

separate diastereomers
by chromatography

$LiAlH_4$

(*S*)-(-)-alcohol
single enantiomer

- it can be much more efficient to do a resolution by selective crystallisation of diastereomeric salts
- diastereomeric salts, much like diastereomers, have different physical properties including melting points and solubility and hence selective crystallisation is frequently possible



racemic mixture of acids

enantiopure (*R*)-α-methylbenzylamine

diastereomeric salts

(*R*, *R*)-salt crystallised from solution

(*S*, *R*)-salt remains in solution

acidify

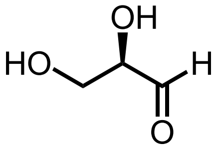
acidify

(*R*)-acid

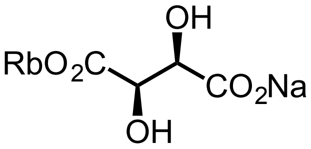
(*S*)-acid

absolute and relative configuration

- before 1951 we did not know the absolute configuration of any molecule i.e. we did not know what the actual 3-D arrangement of atoms was. For example we could not tell if (+)- tartaric acid was (*R, R*) or (*S*, *S*)
- Rosenhoff had arbitrarily assigned the absolute configuration of D-(+)-glyceraldehyde as (*R*)
- many compounds were assigned absolute configuration by tedious chemical degradation, if they were related to the assigned configuration of D-glyceraldehyde they were called D-compounds, regardless of the direction of optical rotation (if they were related to the enantiomer of D-glyceraldehyde they were called L-compounds)
- in 1951 **Johannes Martin Bijvoet** (1892-1980) used X-ray crystallography to assign the absolute configuration to sodium rubidium (+)-tartrate tetrahydrate – Rosenhoff had guessed correctly.



D-(+)-glyceraldehyde



(+)-tartaric acid
sodium rubidium salt
(*R*, *R*)

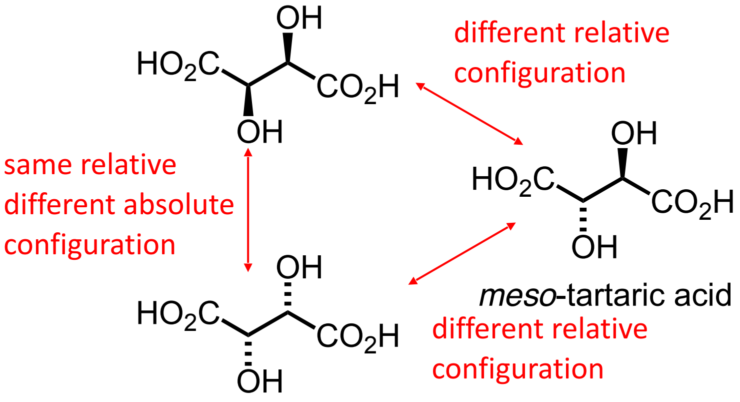
■ absolute and relative configuration

■ absolute and relative configuration can therefore be defined as follows:
if we know which enantiomeric series a molecule is in we know its absolute configuration

if we only know its relative configuration we only know how the stereogenic centres within a molecule are related to one another

■ to put it another way:
“When the stereochemistry drawn on a molecule means ‘this diastereomer’ we say we are representing **relative configuration**; when it means ‘this enantiomer of this diastereomer’ we say we are representing its **absolute configuration**” *from Clayden, Greeves, Warren*

(*R*, *R*)-tartaric acid



different relative configuration

same relative different absolute configuration

meso-tartaric acid

different relative configuration

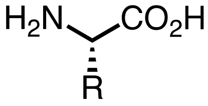
(*S*, *S*)-tartaric acid

■ generation of chirality – the chiral pool
As stated previously *no* optically active material can be generated if all the staring material, reagents and conditions are either *achiral* or *racemic* i.e. optically inactive.

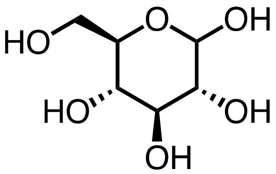
Ultimately to generate *non-racemic* material (material which is optically active) it is necessary to utilise molecules from the *chiral pool* i.e. from the vast array of *enantiopure* and *enantioenriched* molecules which occur in Nature

The Chiral Pool

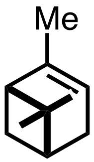
Amino acids



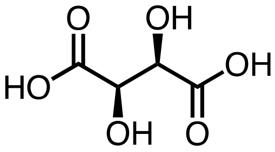
Sugars



Terpenes



Hydroxy acids etc.



Glossary of terms (working definitions)

achiral – not chiral *i.e.* molecule/object has a superimposable mirror image. If a molecule can gain access to a conformation which has a plane of symmetry (or centre of inversion) it will be *achiral*

chiral – molecules (and objects) which have a non-superimposable mirror image

chiral centre – see stereogenic centre

diastereomers – *stereoisomers* which are not related as *enantiomers*

enantioenriched – consisting of an excess of one *enantiomer*

enantiopure – consisting of a single *enantiomer*.

enantiomers - *stereoisomers* which are related as non-superimposable object and mirror image

epimer – *diastereomers* related by the difference in configuration at one *chiral centre*

meso compound - a *stereoisomer with two or more stereocentres but which is itself achiral (an achiral member of a set of diastereomers that includes at least one chiral member)*

optically active – rotates the plane of plane polarised light – can only occur with non-racemic samples

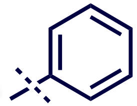
racemate or *racemic mixture* – 50:50 mixture of *enantiomers*; a *racemate* is *optically inactive*.

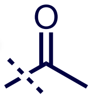
racemisation – the conversion of one *enantiomer* (or an excess of one *enantiomer*) into a 50:50 mixture of *enantiomers*

stereogenic centre (stereocentre) – an atom (generally carbon) with four *non-identical* substituents – also called a *chiral centre*

stereoisomers – isomers with the same connectivity – i.e. A linked to B linked to linked to C etc. but different disposition of atoms in space

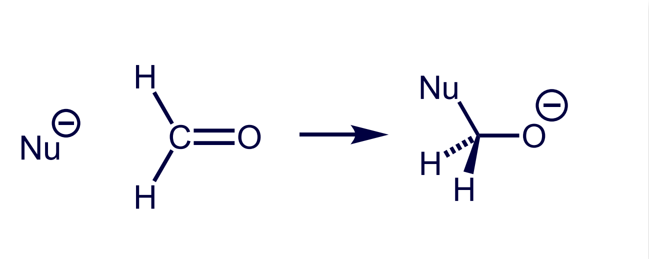
name of group	formula	abbreviation
methyl	$-CH_3$	Me
ethyl	$-CH_2CH_3$	Et
propyl	$-CH_2CH_2CH_3$	Pr
butyl	$-CH_2CH_2CH_2CH_3$	Bu
phenyl	$-C_6H_5$	Ph
acyl	CH_3CO	Ac





Introduction to Organic Chemistry

Handout 3 – Mechanism



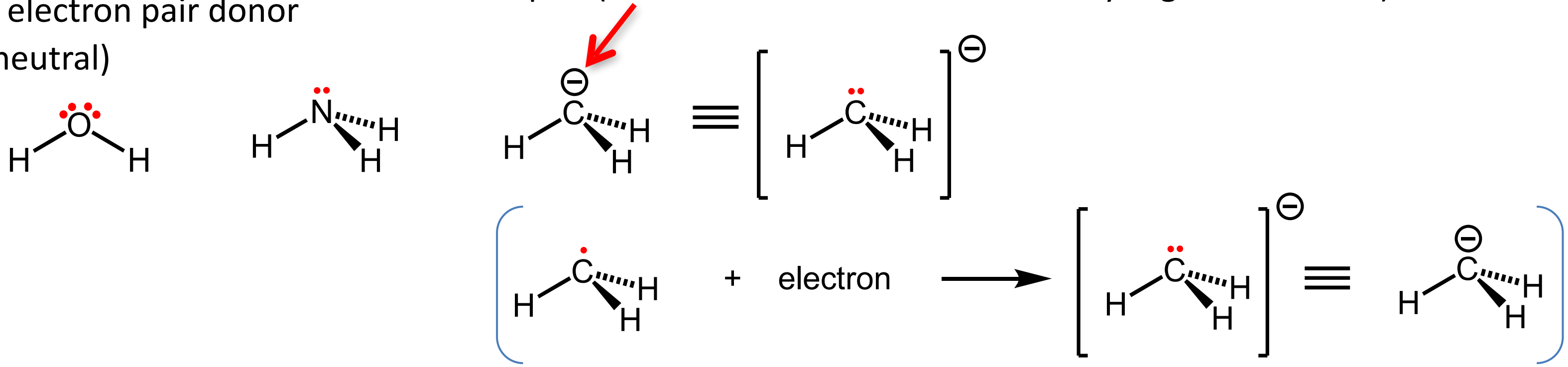
http://burton.chem.ox.ac.uk/teaching.html

- *Organic Chemistry* J. Clayden, N. Greeves, S. Warren
- *Stereochemistry at a Glance* J. Eames & J. M. Peach
- *The majority of organic chemistry text books have good chapters on the topics covered by these lectures*

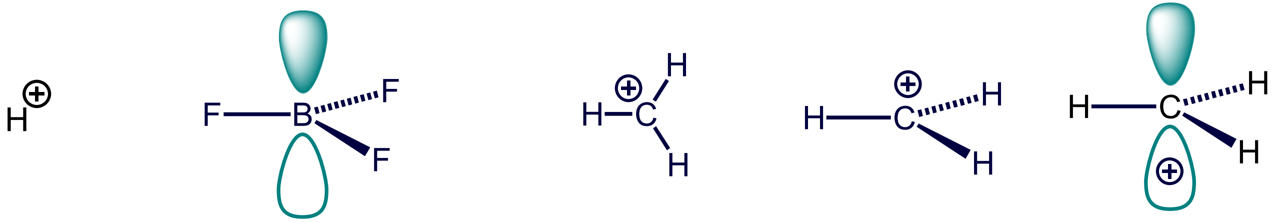
- *Eliel* Stereochemistry of Organic Compounds (advanced reference text)

- **acid base reactions**
- a Lewis base is an electron pair donor (can be charged or neutral)

when atom is negatively charged, the negative charge implies a lone pair (this is shorthand notation used by organic chemists)



- a Lewis acid is an electron pair acceptor (can be charged or neutral)



- acid base reactions

B is sharing an electron pair and therefore becomes positively charged

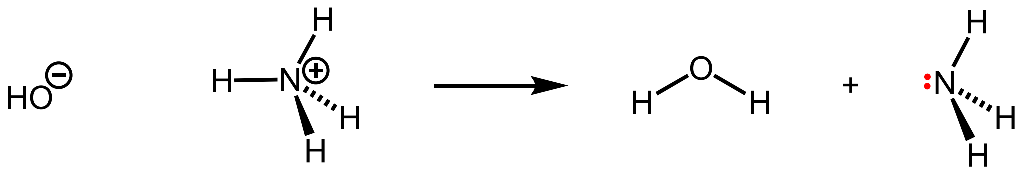
A is accepting an electron pair and therefore becomes negatively charged

- conservation of charge

CURLY ARROWS – indicate the movement of a ***pair*** of electrons

- the arrow starts at the origin of the pair of electrons (lone pair or bonding pair) and the head of the arrow indicates where the electrons end up (lone pair or bonding pair)

bond (electron pair) formed between N and H atoms

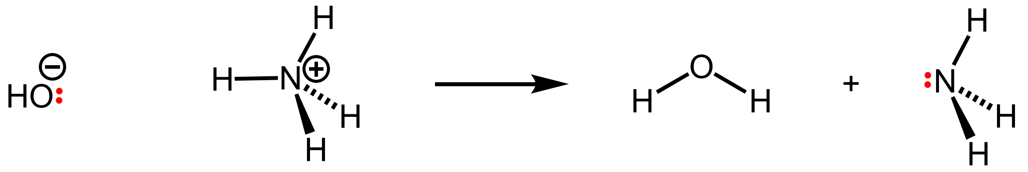


negative oxygen has donated electrons so becomes neutral

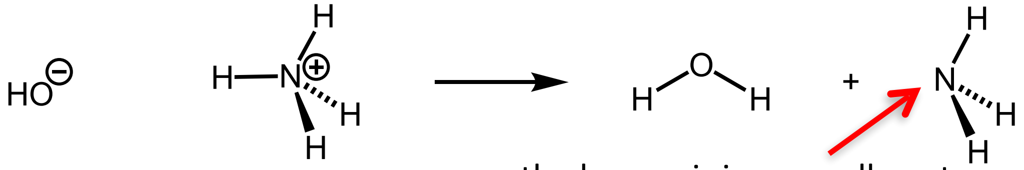
positive nitrogen has accepted electrons and becomes neutral

1st curly arrow starts from the negative charge which we treat as a lone pair
2nd curly arrow starts from the N–H bond pair

- strictly speaking the arrow starts from an actual lone pair but it is normal practice to draw it from the negative charge

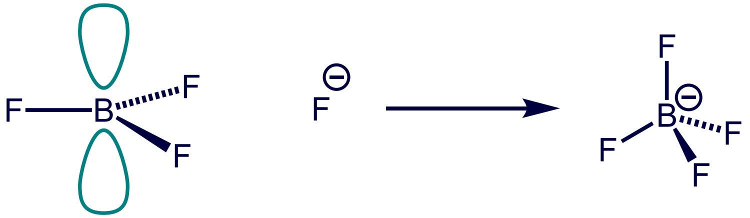


- drawing the curly arrow to point at the atom to which it is forming a bond is also common practice



the lone pair is generally not drawn explicitly

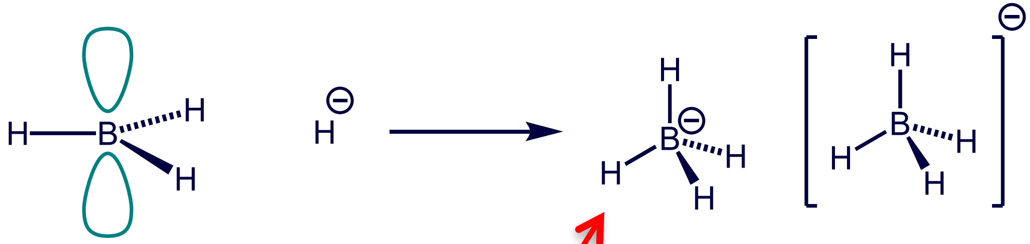
acid base reactions



planar,
B – 6e, sp^2

fluoride, 8e

tetrahedral
B – 8e, sp^3

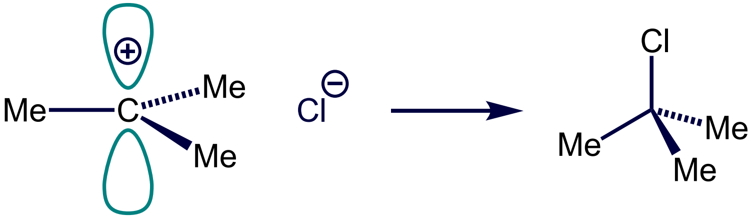


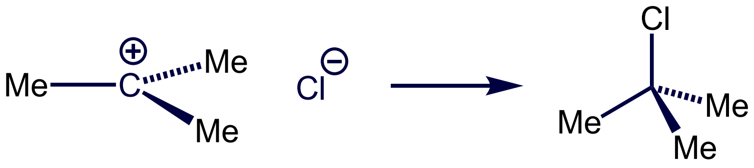
planar,
B – 6e, sp^2

hydride, 2e
($1s^2$)

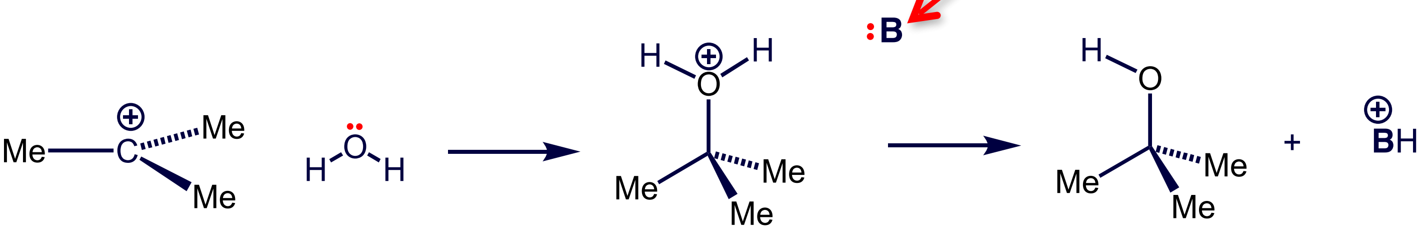
tetrahedral
B – 8e, sp^3

here the negative (formal) charge (although drawn on boron) does not represent a lone pair –
B has 8 electrons from the bonding pairs





a generic base

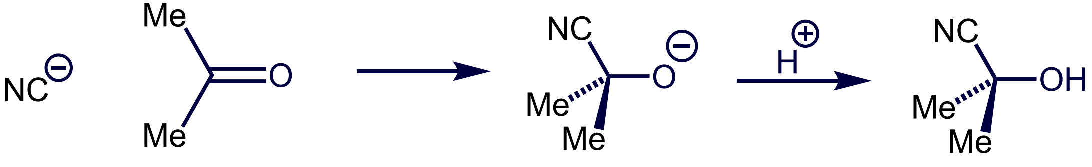


- a common error

$\mathrm{H}^{\oplus}$

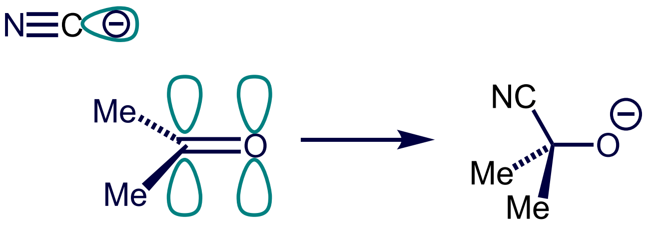
a curly arrow cannot begin from a proton – $\mathrm{H}^{\oplus}$ has no electrons

- further examples – some typical reactions of aldehydes and ketones



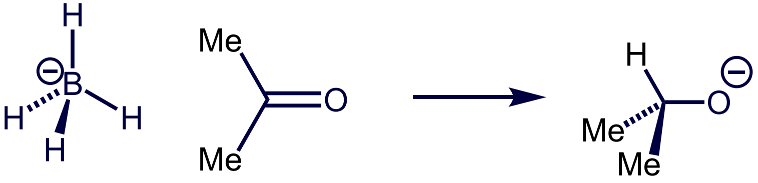
cyanohydrin

- orbitals



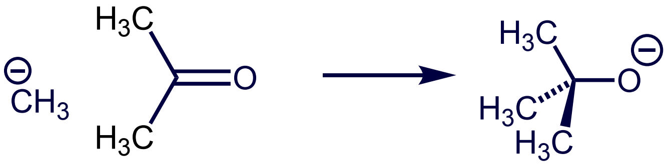
sp lone pair overlaps with π-orbitals

- $\text{Li}^{\oplus}\ \text{AlH}_4^{\ominus}$ or $\text{Na}^{\oplus}\ \text{BH}_4^{\ominus}$

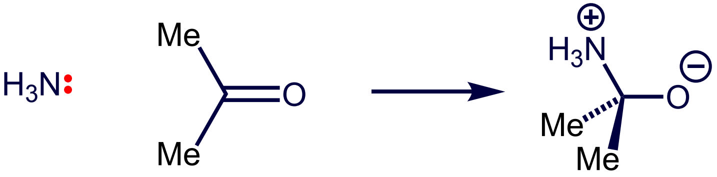


- arrow comes from a bond pair of electrons and transfers hydrogen with its pair of electrons i.e. as hydride $\text{H}^{\ominus}$ (*remember the negative charge on B does not represent a lone pair*)

- addition of a Grignard reagent – CH_3–MgBr

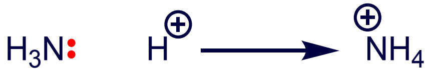


- addition of a neutral nucleophile



- delocalisation a.k.a resonance

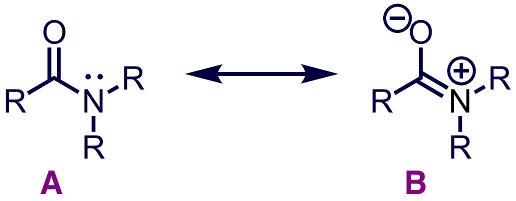
R = general alkyl group



$H_3N{:}\quad H^{\oplus} \longrightarrow NH_4^{\oplus}$

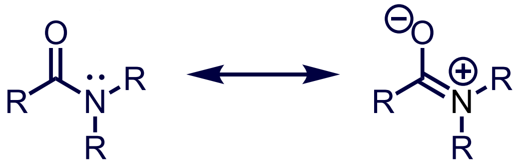
$R_3N{:}\quad H^{\oplus} \longrightarrow R_3NH^{\oplus}$

- amines are basic – the nitrogen lone pair is readily protonated
- amides, however, are essentially neutral – the lone pair is delocalised into the carbonyl group

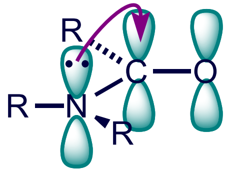


- lone pair in **A** is bonding pair in **B**
- neither **A** nor **B** actually exist – the real structure is a weighted average of structures **A** and **B** called a resonance hybrid
- structures **A** and **B**, are referred to as *resonance* structures
- *note – there **is not** an equilibrium between **A** and **B***
- individual Lewis structures do not accommodate the electron distribution in certain functional groups, and delocalisation (a.k.a. resonance) is a simple method to account for the actual electron distribution

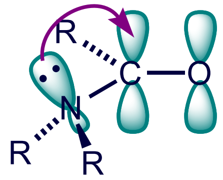
- effect on structure
- the curly arrows above represent the overlap of the nitrogen lone pair with the C-O π-orbitals
- the best overlap occurs if the N-lone pair is in a p-orbital, i.e. N is sp^2 hybridised



A **B**



N-sp^2 hybridised
N-lone pair in p-orbital



N-sp^3 hybridised
N-lone pair in sp^3-orbital

- the curly arrows above represent the overlap of the nitrogen lone pair with the C-O π-orbitals (the antibonding π* orbital)

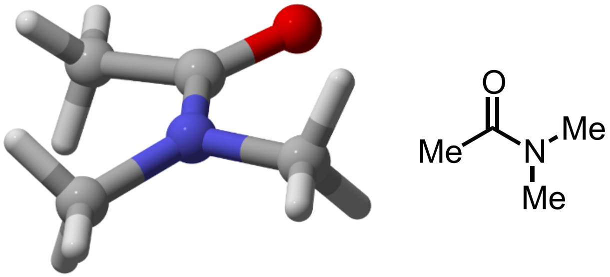
- the best overlap therefore is if the N-atom is sp^2 hybridised resulting in the N-lone pair being in a p-orbital with excellent overlap with the p-orbitals of the C–O π-system

- if the N-atom were sp^3 hybridised then the N-lone pair would be in an sp^3 orbital which would result in poorer overlap with the adjacent C-O π-system

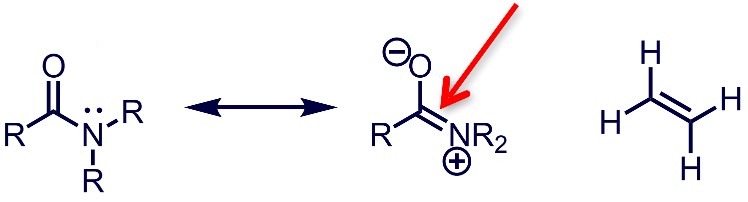
- generally better overlap (of full and empty orbitals) = greater stabilisation

- actual structure is composite of **A** and **B** – the geometry of amides is planar

restricted rotation
around C–N bond



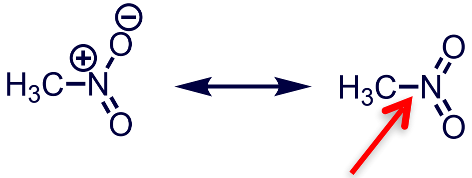
X-ray crystal structure of dimethyl acetamide



A **B**

C–N bond length: amines 1.47 Å, amides 1.33 Å

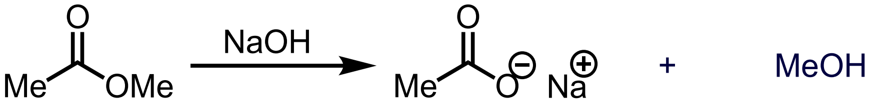
- some guidelines for drawing delocalised structures (resonance structures, canonical forms)
    - all resonance structure must be proper Lewis structures



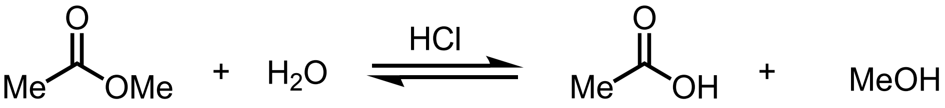
not a proper Lewis structure
N – 10 electrons

    - the positions of the nuclei must be the same in all structures
    - all structures must have the same number of paired/unpaired electrons
    - all atoms involved in delocalistion should be co-planar or nearly co-planar
    - the overall structure of the molecule is a weighted average of the various resonance structures – the more stable resonance structures contribute more to the overall structure of the molecule (and generally only the most stable resonance structures need to be considered)
    - charge separation is destabilising
    - the energy of the actual molecule is lower than any of the resonance structures

- some of the arrows of organic chemistry



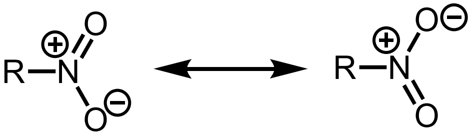
- reaction arrow **A** goes to **B**



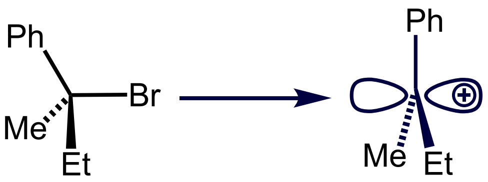
- equilibrium arrow - indicates a reversible reaction

equilibrium arrow strongly favouring products

equilibrium arrow strongly favouring reactants



- resonance arrow – indicates actual structure of the molecule is a hybrid of the structures shown

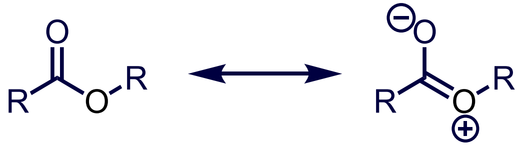


- curly arrows (double headed) – indicates movement of a pair of electrons

$Br{-}Br \longrightarrow Br^{\bullet} \quad + \quad Br^{\bullet}$

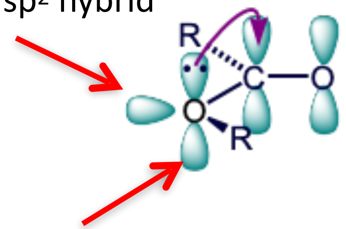
- curved single-headed arrow – indicates movement of single electrons (homolysis of the bond in this example)

- esters

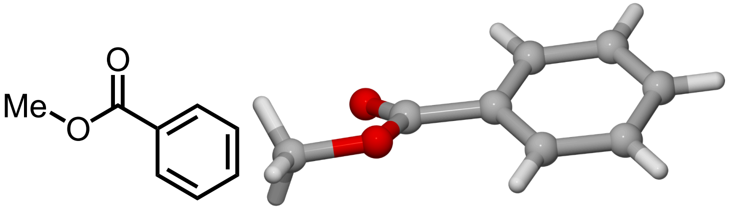


oxygen atom is sp^2 hybridised

one oxygen lone pair in sp^2 hybrid orbital

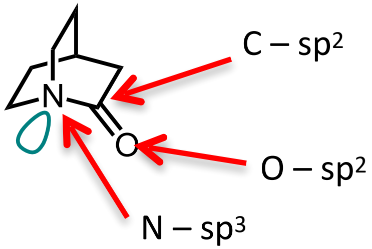


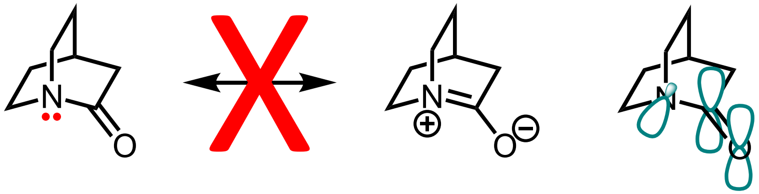
one oxygen lone pair in p-orbital



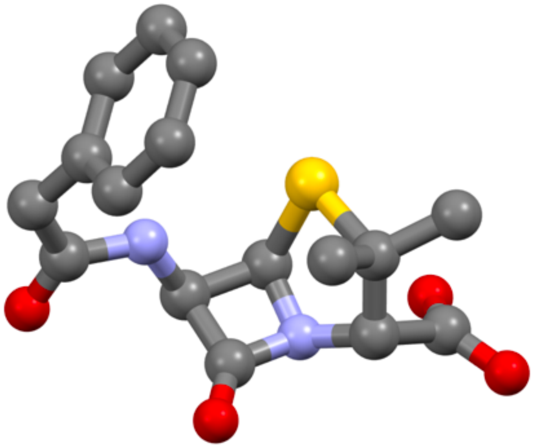
esters are generally planar

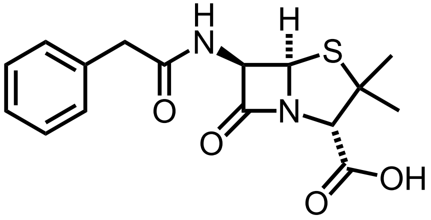
- an unusual amide





- impossible overlap of lone pair with π-orbitals

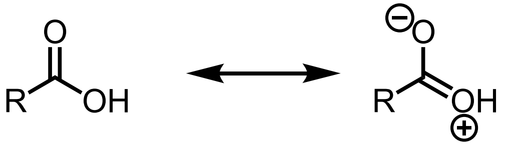




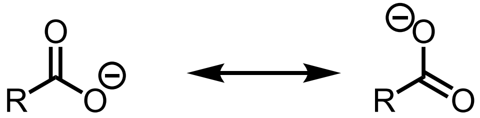
- the above amide is much more basic than a normal amide

- delocalisation in common functional groups

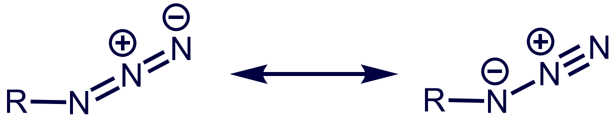
- carboxylic acids similarly



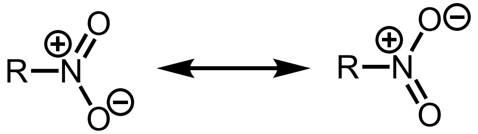
- carboxylate



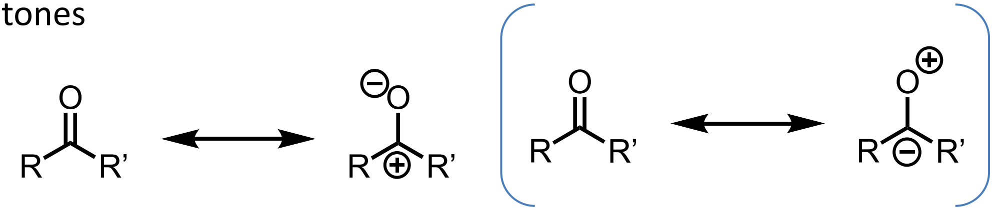
- azides



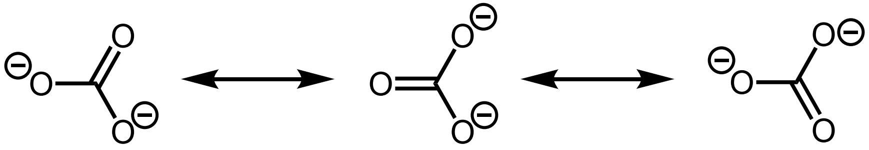
- nitro groups

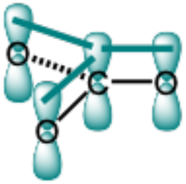


- ketones



- carbonate

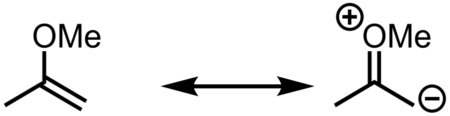




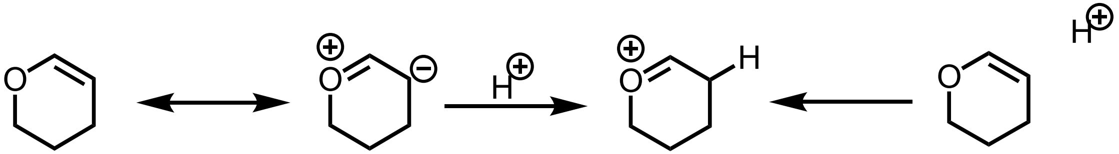
- diazo compounds

$H_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} \longleftrightarrow H_2\overset{\ominus}{C}{-}\overset{\oplus}{N}{\equiv}N$

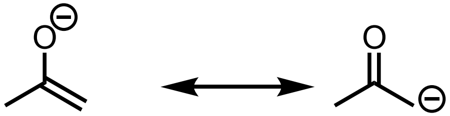
- in general if a π-system has an adjacent atom which carries a lone pair delocalisation of the lone pair into the π-system is possible



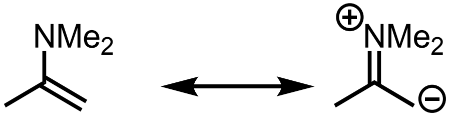
enol ether



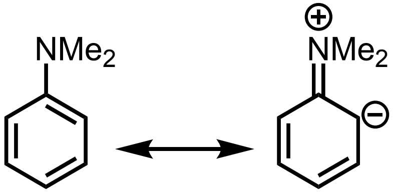
enol ether

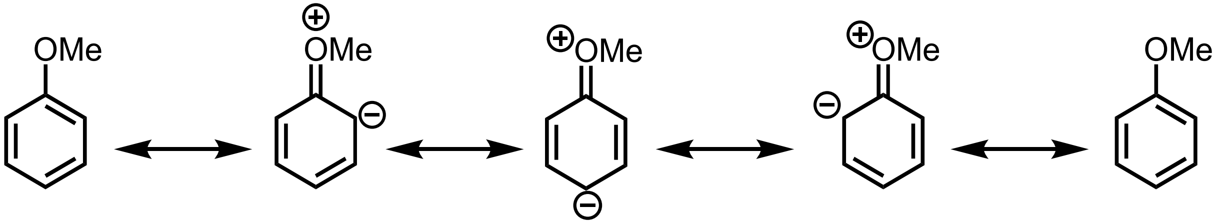


enolate anion



enamine

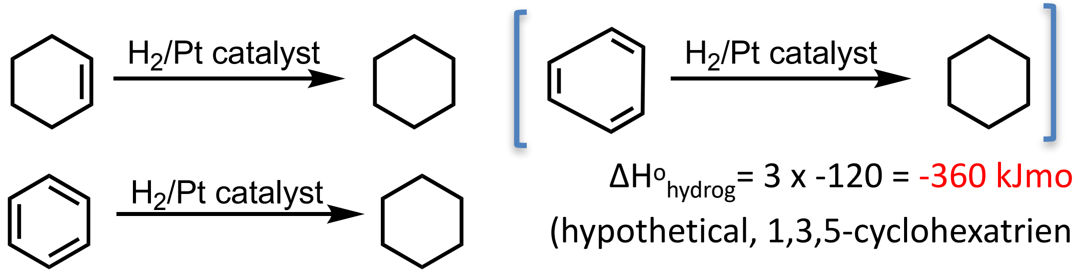




- double bond resonance
- benzene
- heats of hydrogenation

ΔH^o_{hydrog} = -120 kJmol^{-1}

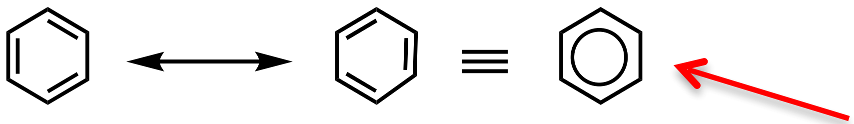
ΔH^o_{hydrog} = -210 kJmol^{-1}



ΔH^o_{hydrog} = 3 x -120 = -360 kJmol^{-1}

(hypothetical, 1,3,5-cyclohexatriene)

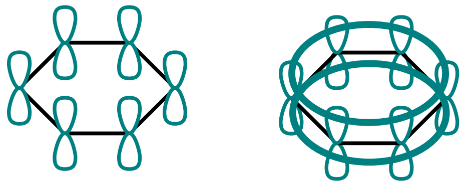
- benzene ≈150 kJmol^{-1} more stable than expected – (represents stability over hypothetical 1,3,5-cyclohextriene) – termed the *empirical resonance energy (values vary enormously)*



benzene best represented like this but cannot draw curly arrow mechanisms from this representation – we will therefore use the alternating double/single bond representation

C-C	sp^3-sp^3	1.54 Å
C-C	sp^3-sp^2	1.50 Å
C-C	sp^3-sp	1.47 Å
C-C	sp^2-sp^2	1.46 Å
C-C	benzene	1.39 Å
C=C		1.34 Å
C≡C		1.21 Å

- molecular orbital description

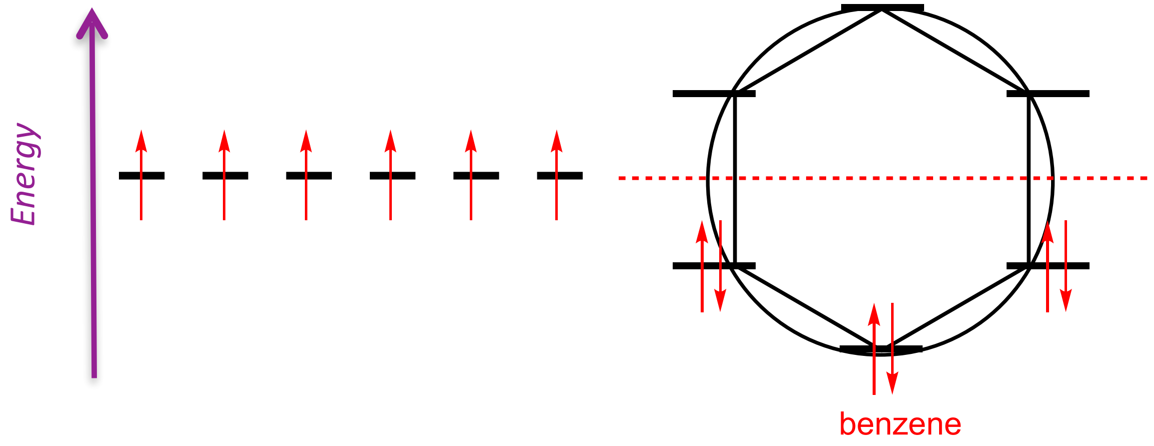


- all carbon atoms are sp² hybridised
- all bond angles are 120°

- there are six p-orbitals which overlap to give six molecular orbitals

Frost-Musulin Diagram – Frost Circle

- simple method to find the energies of the molecular orbitals for an aromatic compound
- inscribe the regular polygon, with one vertex pointing down centred at the energy of an isolated p-orbital
- each intersection of the polygon with the circumference of the circle corresponds to the energy of a molecular orbital



antibonding molecular orbital (empty)

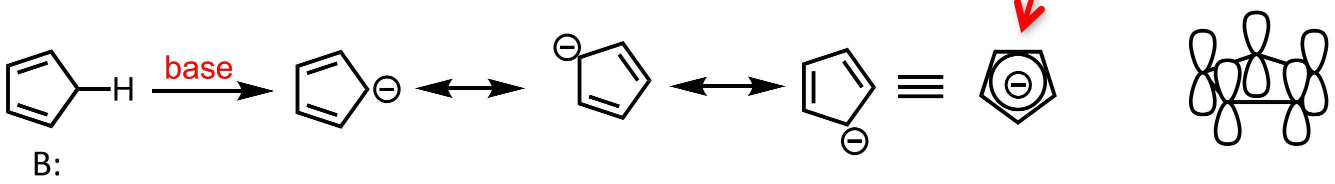
bonding molecular orbitals (full)

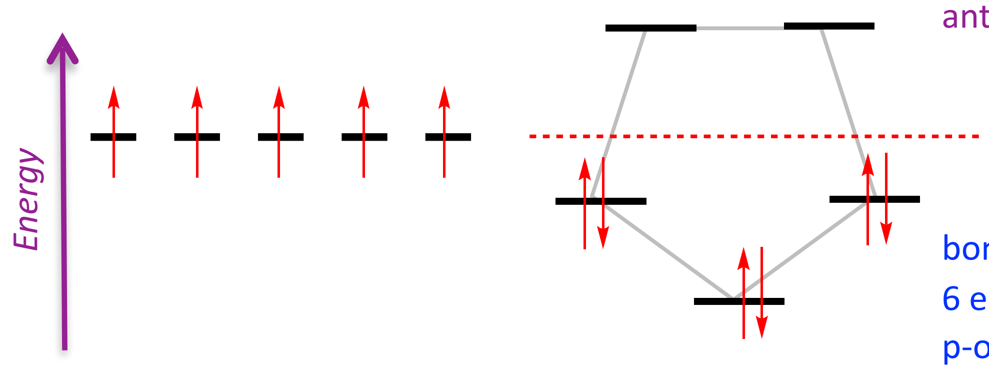
- the six electron are delocalised over the entire ring – benzene is described as aromatic with aromatic stabilisation

- for aromaticity require (4n +2) π-electrons cyclically conjugated
- other common aromatic systems

negative charge spread over 5 carbon atoms

- cyclopentadienyl anion – (4n +2), n = 1, 6π electrons

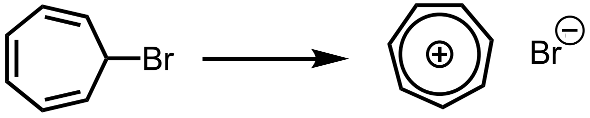




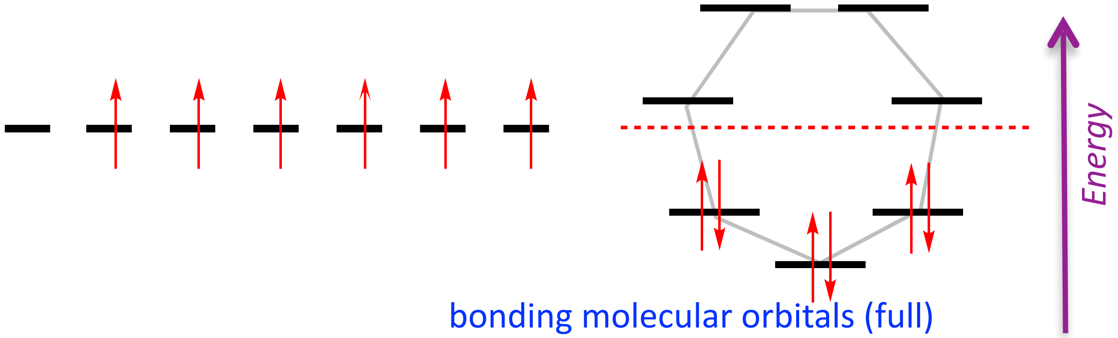
antibonding molecular orbital (empty)

bonding molecular orbitals (full)
6 electrons, 5 from the
p-orbitals one from the negative charge

- tropylium cation – (4n +2), n = 1, 6π electrons – aromatic



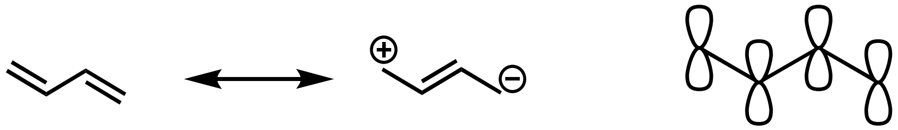
antibonding molecular orbital (empty)



bonding molecular orbitals (full)

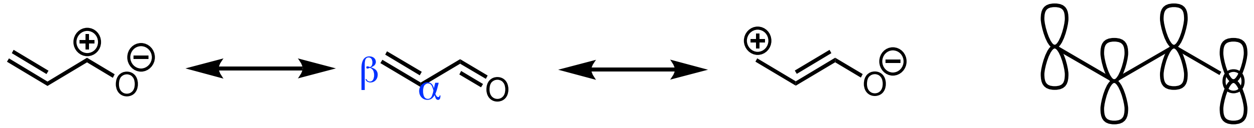
- delocalisation in conjugated alkenes (non-aromatic)

- dienes



- overlap of p-orbitals on central carbon leads to new extended molecular orbital – increased bonding

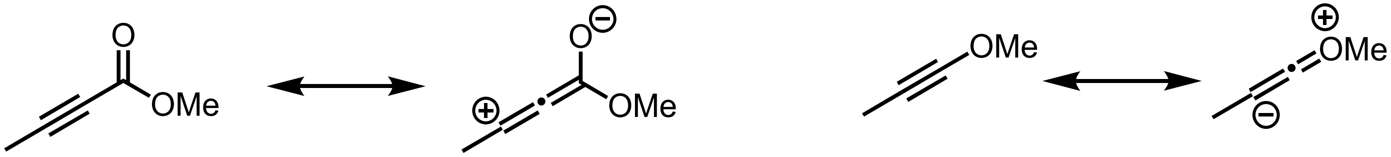
- α,β-unsaturated carbonyl compounds



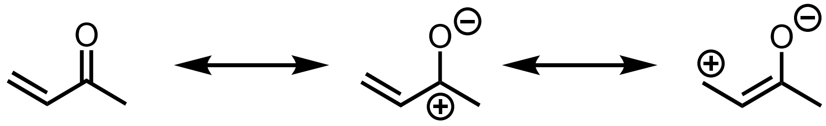
nucleophlies therefore react at the carbonyl carbon or the β-position

- similary with α,β-unsaturated nitro compounds and α,β-unsaturated nitriles

- or with triple bonded species

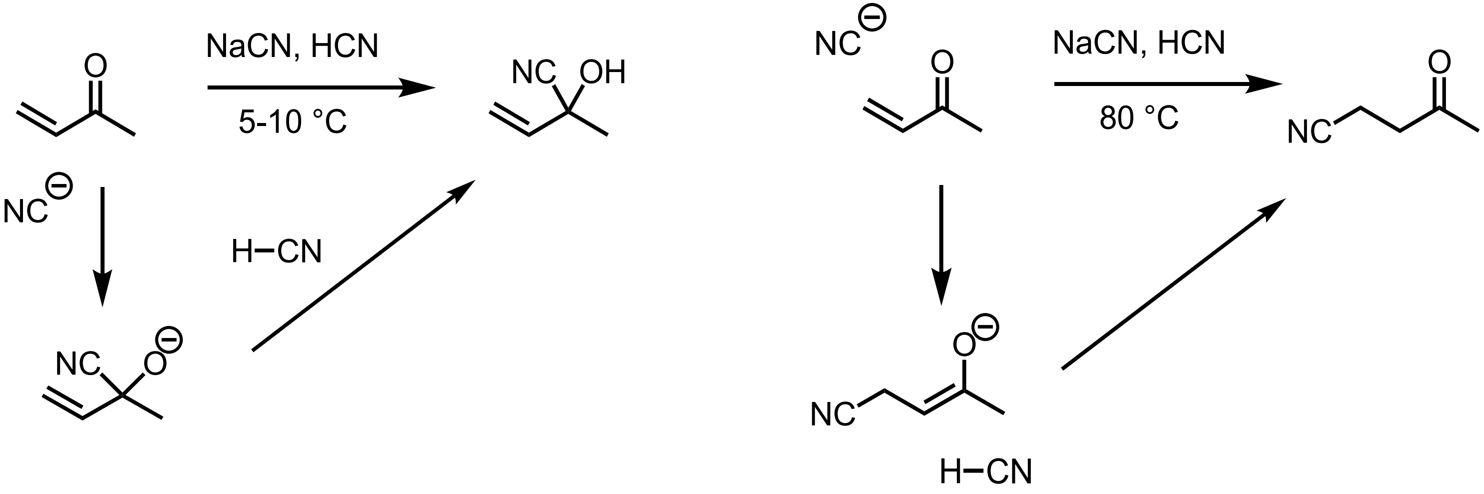


- some more simple reactions



- drawing delocalised structures, shows us where nucleophiles and electrophiles may attack substrates

- cyanide will add to the carbonyl carbon, or the β-position of an α,β-unsaturated ketones depending on the reaction conditions



- these reactions can be reversible