

POSSIECHEM

Organic Chemistry I: Structure, Stereochemistry and Acidity

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Before you start

This is the first of four organic chemistry courses, and it teaches you to read a structure: which functional groups are there, how the atoms are hybridised and shaped in 3D, what the molecule is called, how it twists and flips, why some molecules come as mirror images, what makes a ring aromatic, and why some molecules let go of a proton far more easily than others. It is written for a bachelor student in year 1 or 2. It stops before the reactions begin: those start in Organic Chemistry II: Reactions and Mechanisms.

What you need first

This is not an entry point. You should already be comfortable with:

Concept	Where you learn it
Atomic orbitals, electron configuration, electronegativity, periodic trends	Chemistry 1
Lewis structures, formal charge, VSEPR, resonance structures	Chemistry 1
Chemical equilibrium, Brønsted acids and bases, Ka and pKa	Chemistry 1 (or 2)
$E = h\nu$, $c = \lambda\nu$, Avogadro's constant	Chemistry 1; secondary-school physics
London, dipole and hydrogen-bond forces	Chemistry 1

How to use this course

Read the chapters in order: each one leans on the ones before it. Every structure is drawn at the same scale, and every atom the text talks about carries its number on the drawing, so you can follow along with a pencil.

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CHAPTER 1

Families of organic compounds

> **This chapter:** a map of the territory. Which families of organic compounds exist, what their functional groups look like, and which group wins the name when a molecule has more than one. **You need:** Lewis structures (Chemistry 1).

1.1 Hydrocarbons

Hydrocarbons are the simplest organic molecules: **only carbon and hydrogen**, nothing else. They come in two camps, **aliphatic** hydrocarbons and **aromatic** hydrocarbons (benzene and its relatives).

The aliphatic ones have two shapes. **Acyclic** hydrocarbons are open chains, either linear or branched. **Cyclic** hydrocarbons close the chain into a ring. In both shapes the molecule is either **saturated** (only single bonds, as many hydrogens as the carbons can hold) or **unsaturated** (at least one double or triple bond):

	Open chain	Ring
Saturated (only C–C)	alkane	cycloalkane
Unsaturated, with a C=C bond	alkene	cycloalkene
Unsaturated, with a C≡C bond	alkyne	cycloalkyne

Figure 1.1 shows one of each. Look at the cycloalkyne: a triple bond wants its four atoms in a straight line, so a ring has to be big before it can hold one at all. With eight carbons the triple bond is already bent out of line, and that strain is why eight is about the smallest ring that survives on a shelf.

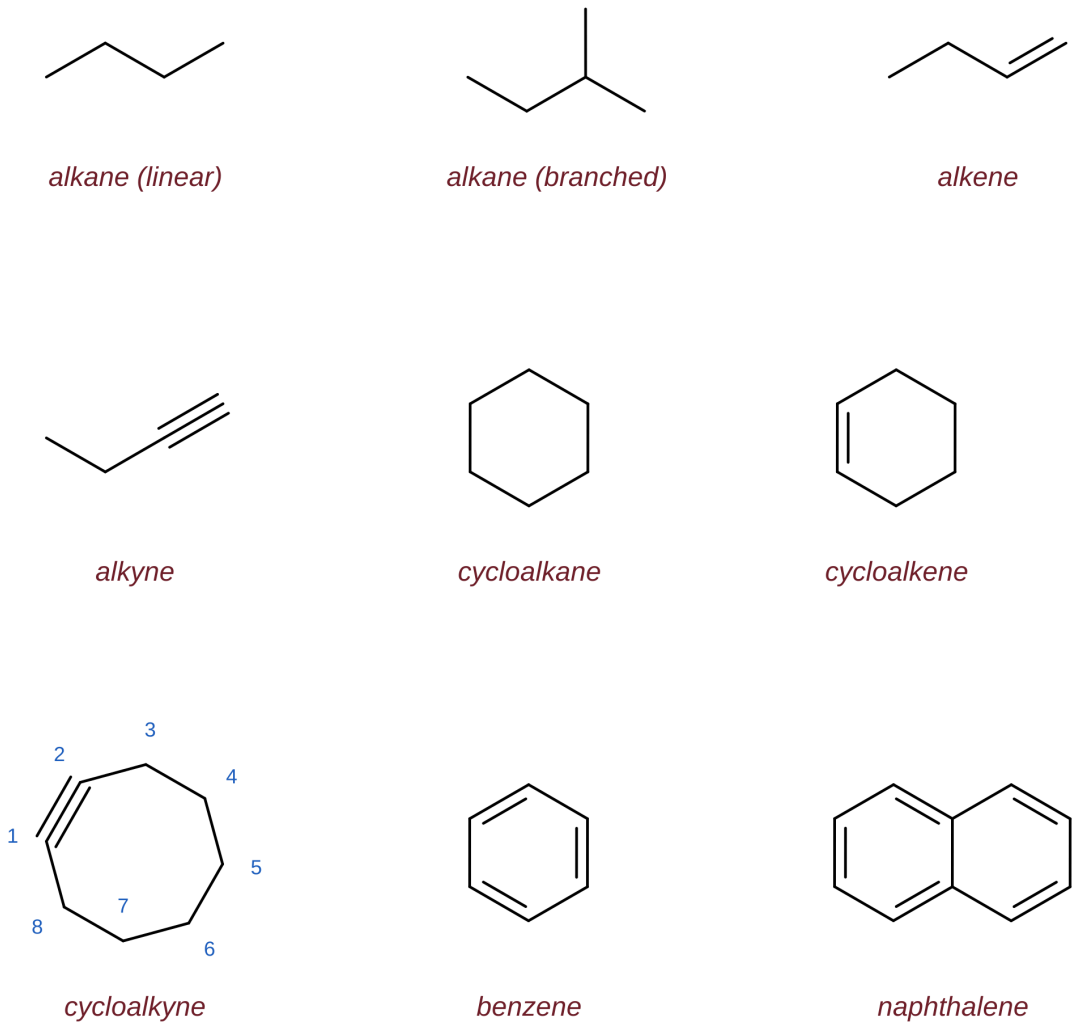


Figure 1.1. One example of each aliphatic family (linear and branched alkane, alkene, alkyne, cycloalkane, cycloalkene, cycloalkyne), then two aromatic examples: benzene and naphthalene. The cycloalkyne is cyclooctyne, numbered C1 to C8: its C–C≡C angle is about 160°, not 180°.

Aromatic hydrocarbons are the benzene-related compounds. Chapter 6 explains what earns a ring that label.

1.2 Hydrocarbon derivatives

Replace a hydrogen by something else and you have a hydrocarbon derivative. That something else is the **functional group**: the bit of the molecule that decides how it behaves. The hydrocarbon part it hangs on is written **R**, the *residue*: any carbon chain or ring we do not care about right now. A second one is R′, a third R″. They can turn out to be identical, but they do not have to be.

We sort the families by the heteroatom involved: halogens, oxygen, nitrogen, nitrogen with oxygen, sulfur, and phosphorus.

With halogens. The haloalkanes have a halogen (F, Cl, Br or I) on a carbon. Figure 1.2 shows all four.

With oxygen, single bonds only. An alcohol has an OH on a carbon. An ether has an O between two carbons. An acetal has one carbon carrying two O–R groups at once. If that carbon also carries an H it is an acetal in the older, narrow sense; if it carries a second carbon group it is a ketal. Current IUPAC usage calls both acetals. Chapter 9 makes them from aldehydes and ketones.

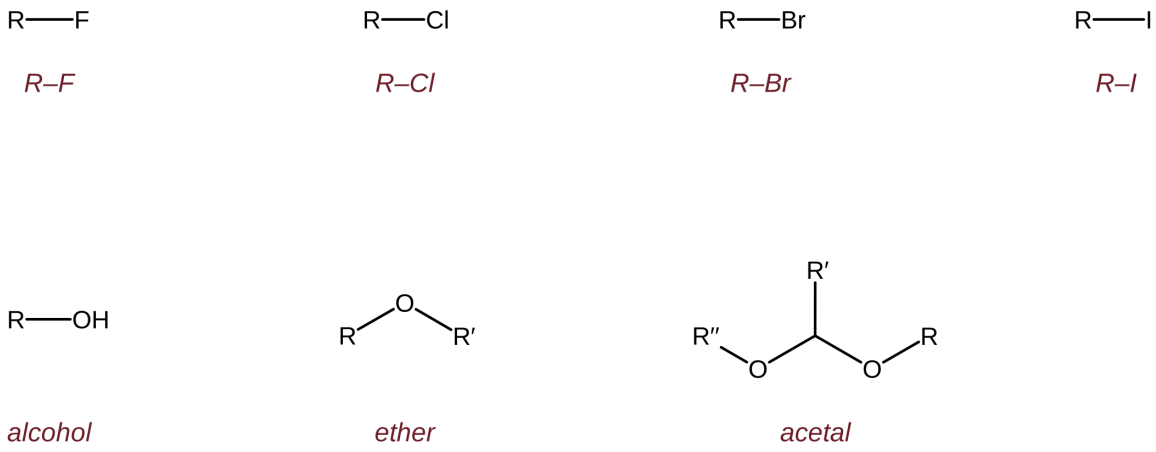


Figure 1.2. The four haloalkanes (top row), then the oxygen families with single bonds only: alcohol, ether and acetal.

With oxygen, the carbonyl family (Figure 1.3). The C=O group, the carbonyl group, is the busiest address in organic chemistry. In an aldehyde the carbonyl carbon carries an H, in a ketone it sits between two carbons. A carboxylic acid has an OH on the carbonyl carbon; an ester swaps that OH for an O–carbon, an anhydride for a second carboxylate, and an acid chloride for a chlorine. These three, together with the amides below, are the **carboxylic acid derivatives**: take the acid and swap its OH for something else.

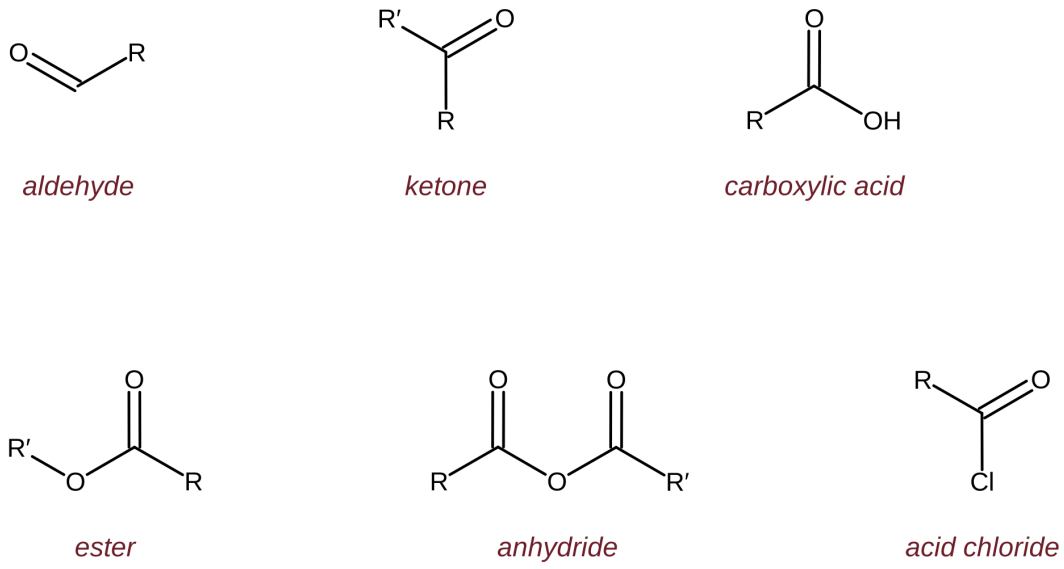


Figure 1.3. The carbonyl family: aldehyde, ketone, carboxylic acid, ester, anhydride and acid chloride.

With nitrogen (Figure 1.4, top row). An amine has a nitrogen with three single bonds to H or to carbon groups. An imine has a C=N double bond. A nitrile has a C≡N triple bond; it is also called a cyanide.

> **Watch out.** Primary, secondary and tertiary mean different things for amines and for alcohols. For an alcohol you count the carbons attached to the carbon that carries the OH. For an amine you count the carbon groups on the nitrogen itself, so an amine with one R is a primary amine, however branched that R is.

With nitrogen and oxygen (Figure 1.4, rest). An amide has a nitrogen on the carbonyl carbon, and is called primary, secondary or tertiary by how many carbon groups sit on that nitrogen. A carbamate, also called a urethane, is an ester and an amide at once: an O–carbon and an N on the same carbonyl carbon. A nitro compound has an NO_2 group on a carbon; it is drawn with a positive nitrogen and a negative oxygen, because nitrogen with five bonds does not exist.

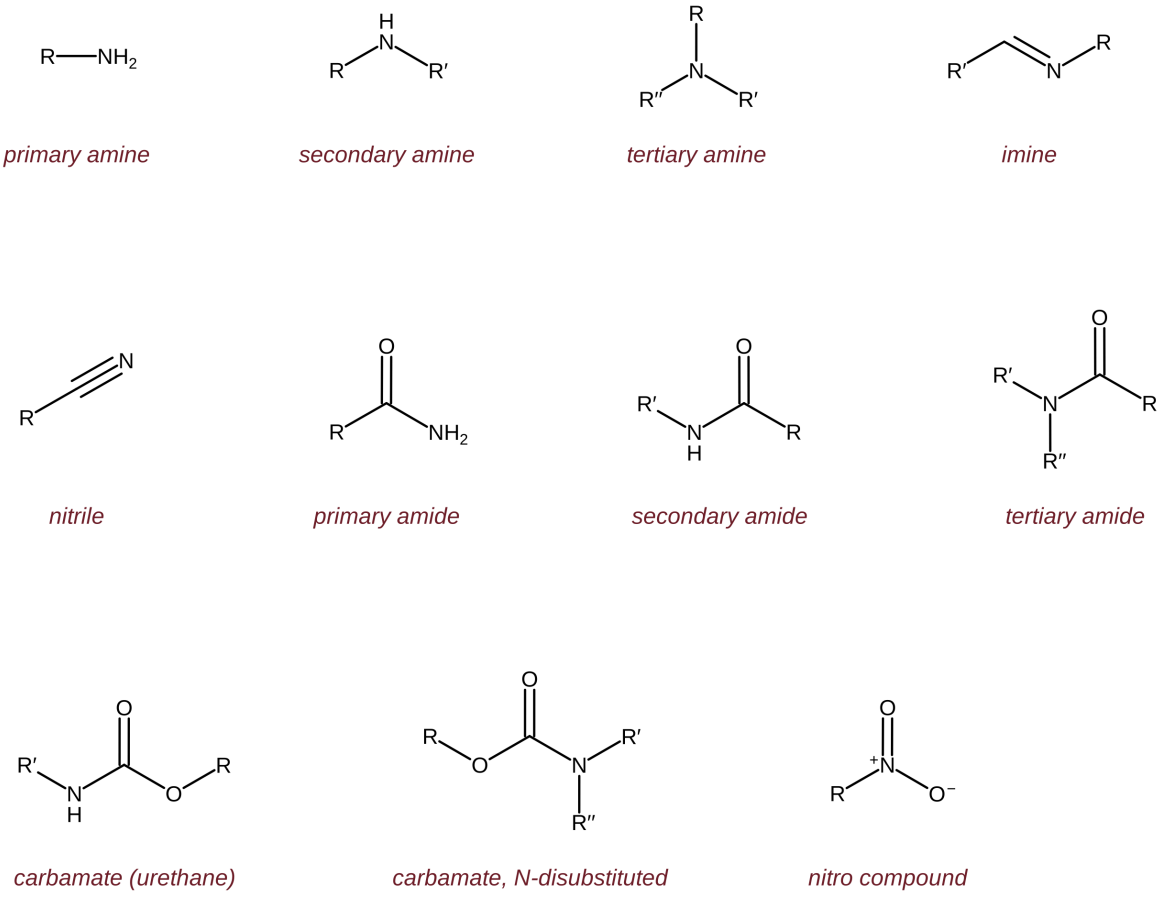


Figure 1.4. Nitrogen families: amines and imine (top row), nitrile and amides (middle row), carbamates and the nitro compound (bottom row).

With sulfur and phosphorus (Figure 1.5). Sulfur plays the same game as oxygen: a thiol (older name: mercaptan) is the sulfur version of an alcohol, a thioether the sulfur version of an ether, and a disulfide has two sulfurs bonded to each other. A sulfonic acid has a sulfur car-

rying two S=O bonds and an OH. Phosphorus gives phosphines (also called phosphanes), with three carbon groups on P; phosphites, with three O–R groups on P; and phosphates, which are phosphites with an extra P=O.

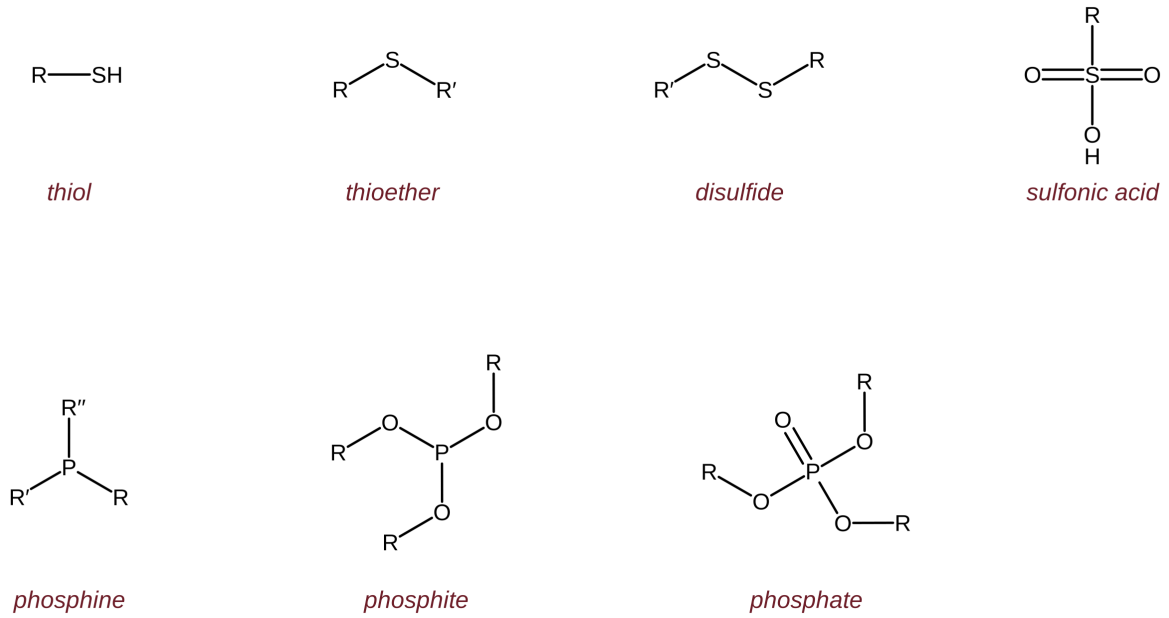


Figure 1.5. Sulfur families (top row) and phosphorus families (bottom row).

1.3 Which group wins?

When a molecule carries more than one functional group, it is named after the highest one on the list below, the **principal group**. Almost every other group is demoted to a prefix. Ethers and halogens are not even allowed a suffix: they are always prefixes. Alkenes and alkynes show up inside the name of the chain (-ene, -yne). Chapter 3 puts this list to work.

Rank	Family	Named with
1	carboxylic acid	-oic acid (on a ring: -carboxylic acid)
2	sulfonic acid	-sulfonic acid
3	anhydride	-oic anhydride
4	ester	-oate
5	acid chloride	-oyl chloride
6	amide	-amide
7	nitrile	-nitrile
8	aldehyde	-al
9	ketone	-one

Rank	Family	Named with
10	alcohol	-ol
11	thiol	-thiol
12	amine	-amine
13	ether	alkoxy- (prefix only)
14	alkene	-ene
15	alkyne	-yne
16	alkane	-ane
17	halogen	fluoro-, chloro-, bromo-, iodo- (prefix only)

Exercises

Exercise 1.1. The six hydrocarbons of Figure 1.6 are labelled a to f. For each one say whether it is acyclic or cyclic, saturated or unsaturated, and aliphatic or aromatic, and give its family.

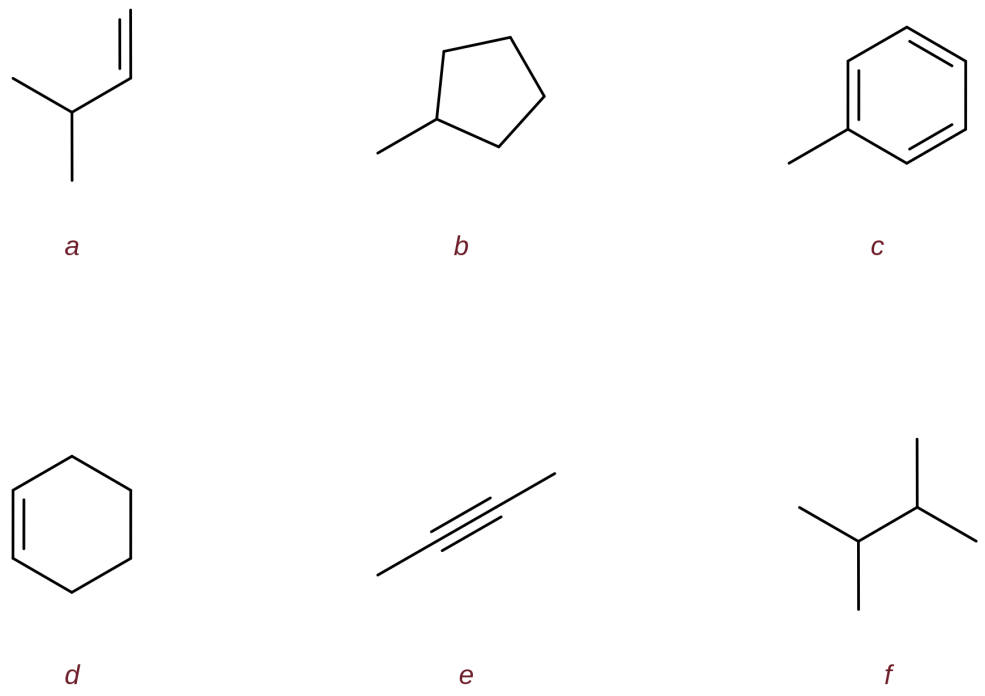


Figure 1.6. The hydrocarbons of Exercise 1.1.

Exercise 1.2. (a) Name every functional-group family in the five molecules of Figure 1.7. (b) Which of the five carry a carboxylic acid derivative?

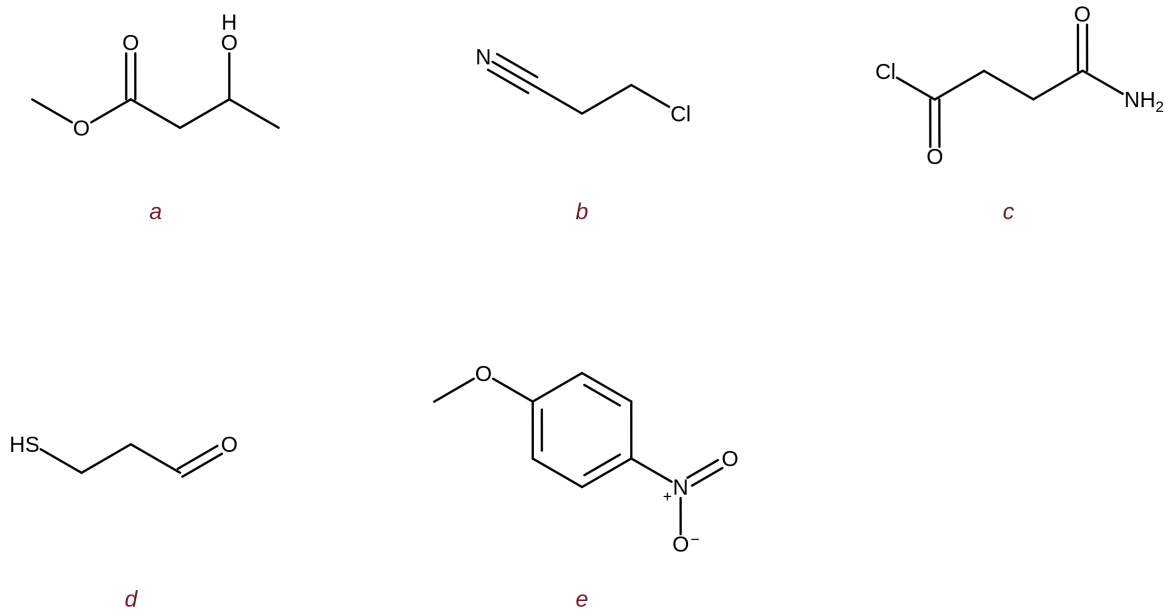


Figure 1.7. The molecules of Exercise 1.2. The nitro group in e is drawn the way Section 1.2 says it must be: a positive nitrogen and a negative oxygen.

Exercise 1.3. Figure 1.8 shows nine molecules with an OH or an N on a carbon skeleton. For each one say what it is (alcohol, amine or amide) and whether it is primary, secondary or tertiary.

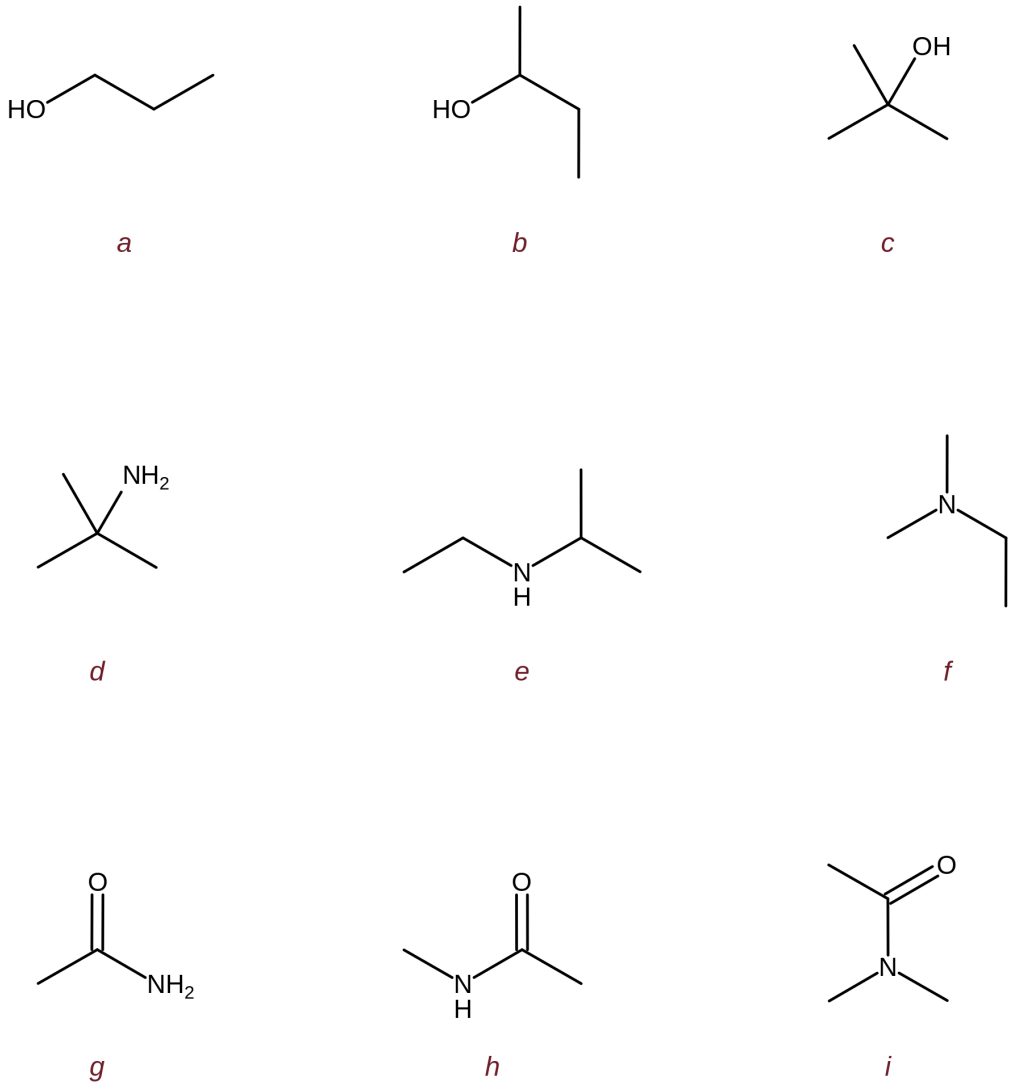


Figure 1.8. The molecules of Exercise 1.3.

Exercise 1.4. Each molecule of Figure 1.9 carries two functional groups. Which family is the principal group (the one that gets the suffix), and which family is demoted?

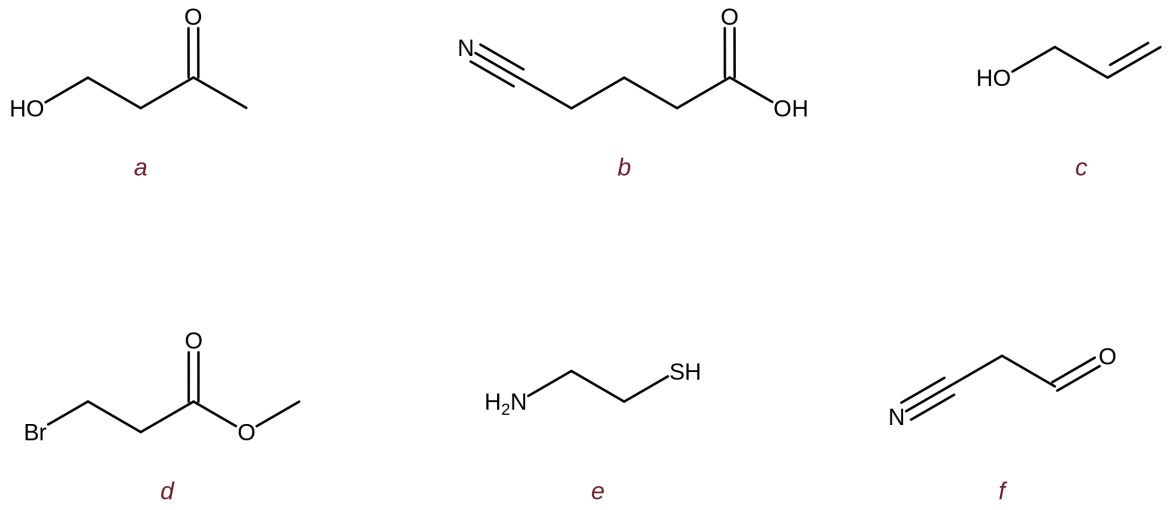


Figure 1.9. The molecules of Exercise 1.4.

Exercise 1.5. Draw one molecule for each description: (a) a tertiary amide with four carbons in total; (b) a secondary amine with four carbons in total; (c) an ester with the formula $C_4H_8O_2$ that has a methyl group on the oxygen; (d) a molecule with a ketone and a primary alcohol. More than one answer is possible for every part.

Solutions

Exercise 1.1. Look for rings first, then for double or triple bonds, then for a benzene-type ring.

Molecule	Acyclic or cyclic	Saturated or unsaturated	Aliphatic or aromatic	Family
a	acyclic	unsaturated (C=C)	aliphatic	alkene
b	cyclic	saturated	aliphatic	cycloalkane
c	cyclic	not applicable	aromatic	aromatic hydrocarbon (benzene ring)
d	cyclic	unsaturated (C=C)	aliphatic	cycloalkene
e	acyclic	unsaturated (C≡C)	aliphatic	alkyne
f	acyclic	saturated	aliphatic	alkane

Molecule c is the one that does not fit the pattern: its ring has double bonds on paper, but a benzene-type ring is not called unsaturated in the aliphatic sense. It is simply aromatic (Chapter 6 says why). The methyl group on the ring of c does not change that, and neither does the methyl group on b.

Exercise 1.2. (a) Read each molecule group by group:

- **a:** an ester (the C=O with an O–carbon on it) and an alcohol. The OH sits on a carbon that carries two other carbons, so it is a secondary alcohol.
- **b:** a haloalkane (a chloroalkane) and a nitrile.
- **c:** an acid chloride and an amide. The nitrogen of the amide carries no carbon group, so it is a primary amide.
- **d:** a thiol and an aldehyde.
- **e:** a nitro compound, an ether and an aromatic ring.

(b) The carboxylic acid derivatives are the esters, anhydrides, acid chlorides and amides: that is **a** (ester) and **c** (acid chloride and amide). The nitrile in b and the aldehyde in d are not derivatives of the acid in this sense: the aldehyde has an H where the acid has an OH, and the nitrile has no C=O at all.

Exercise 1.3. For an alcohol count the carbons on the carbon that carries the OH. For an amine count the carbon groups on the nitrogen itself. For an amide count the carbon groups on the nitrogen besides the carbonyl carbon.

Molecule	Family	Count	Class
a	alcohol	the OH carbon has 1 carbon on it	primary
b	alcohol	2 carbons	secondary
c	alcohol	3 carbons	tertiary
d	amine	1 carbon group on N, however branched	primary
e	amine	2 carbon groups on N	secondary
f	amine	3 carbon groups on N	tertiary
g	amide	none (NH_2)	primary
h	amide	1	secondary
i	amide	2	tertiary

The trap is d. The carbon next to the nitrogen carries three other carbons, so it is a tertiary *carbon*, and an alcohol with that skeleton would be tertiary. But the amine has just one carbon group on its nitrogen: it is a primary amine.

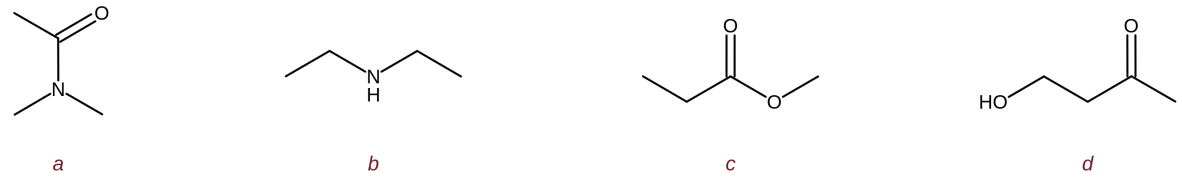
Exercise 1.4. Go down the priority list of Section 1.3 and take the higher of the two.

Molecule	Principal group	Demoted
a	ketone (rank 9)	alcohol (rank 10)
b	carboxylic acid (rank 1)	nitrile (rank 7)
c	alcohol (rank 10)	alkene: it is not a prefix but shows up as *-en-* inside the chain
d	ester (rank 4)	halogen: prefix only, whatever else is there

Molecule	Principal group	Demoted
e	thiol (rank 11)	amine (rank 12)
f	nitrile (rank 7)	aldehyde (rank 8)

Molecule f is the surprising one: most people expect the aldehyde to win because it looks more reactive, but the list is about naming, not about reactivity, and the nitrile ranks higher.

Exercise 1.5. One possible set of answers is drawn in Figure 1.10.



a b c d

Figure 1.10. One possible answer to each part of Exercise 1.5.

Check each one by counting. (a) The carbonyl carbon, its methyl group and the two methyl groups on nitrogen make four carbons; nitrogen carries two carbon groups besides the carbonyl, so it is a tertiary amide. (b) Two ethyl groups on one nitrogen: four carbons, two carbon groups on N, so secondary. (c) The carbonyl carbon, the carbon next to it and the carbon after that make three, and the methyl on oxygen makes four; with two oxygens the formula is $C_4H_8O_2$. Ethyl acetate would also fit the formula, but it has an ethyl group on the oxygen and not a methyl. (d) A ketone in the middle of the chain and an OH on the end carbon, which carries only one other carbon: a primary alcohol.

CHAPTER 2

Bonding and hybridisation

> **This chapter:** how an atom decides the shape of its surroundings. σ and π bonds, the three hybridisations of carbon, and what a lone pair does to nitrogen and oxygen. **You need:** atomic orbitals, electron configurations and VSEPR (Chemistry 1).

2.1 σ bonds and π bonds

Every bond between two atoms starts as a **σ bond**: two orbitals overlapping head-on, along the line between the nuclei. A single bond is one σ bond and nothing more. A double bond is a σ bond plus a **π bond**, and a triple bond is a σ bond plus two π bonds. A π bond is two p orbitals overlapping side by side, above and below the σ axis. It sits off the line between the nuclei, which makes it weaker and more exposed than the σ bond underneath it.

Figure 2.1 shows both cases. In ethene the σ framework (C1, C2 and the four hydrogens) lies in one plane, and the π bond is a cloud above that plane and another below it. In ethyne the σ axis is a straight line, and the two π bonds sit at right angles to each other, so together they wrap around the bond like a collar.

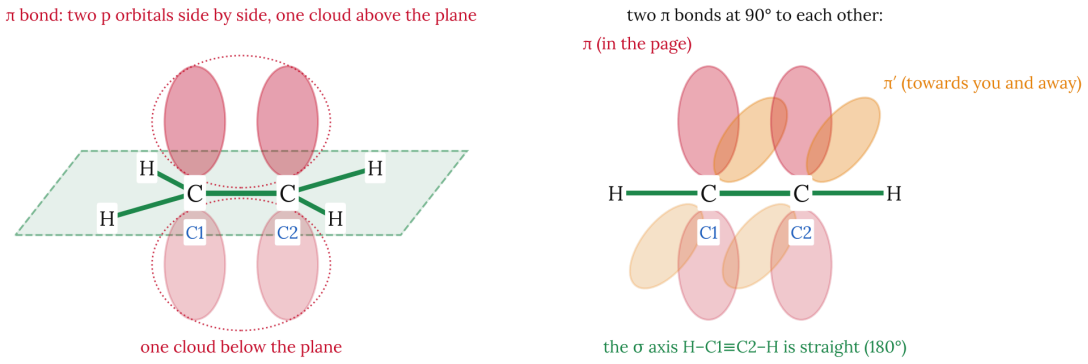


Figure 2.1. σ and π bonds in ethene (left) and ethyne (right). Green: the σ framework. Red and orange: the π clouds, one pair above and below the plane in ethene, two pairs at 90° to each other in ethyne.

The hybridisation of an atom follows from a simple count: **the number of σ bonds plus the number of lone pairs around the atom is the number of hybrid orbitals it makes.** Four groups give sp^3, three give sp^2, two give sp. π bonds do not count: they are made from the p orbitals that the hybridisation leaves over. (A lone pair that can join a π system changes the count; Chapter 6 comes back to it.)

Hybridisation	σ bonds on a carbon	π bonds on a carbon	Geometry	Bond angle
sp	2	2	linear	180°
sp^2	3	1	trigonal planar	120°
sp^3	4	0	tetrahedral	109.5°

For carbon this boils down to a shortcut: a triple bond (or two double bonds on the same carbon) makes it sp, one double bond makes it sp^2, and a neutral carbon with only single bonds is sp^3.

2.2 Carbon: sp^3, sp^2 and sp

Ground-state carbon is $2s^2 2p^2$: two unpaired electrons, so it should make two bonds. Yet carbon makes four. The way out is a two-step trick. First **promotion**: one 2s electron hops into the empty 2p orbital, which costs some energy that the two extra bonds repay many times over. Then **hybridisation**: the s orbital and some of the p orbitals blend into new, equal orbitals. Mix s with three p and you get four **sp^3** orbitals. Mix s with two p and you get three **sp^2** orbitals, with one p left over. Mix s with one p and you get two **sp** orbitals, with two p left over. The hybrid orbitals make the σ bonds, and the left-over p orbitals make the π bonds. Figure 2.2 follows the electrons through all three cases. The more s character a hybrid has, the lower its energy, which is why the sp orbitals sit lowest.

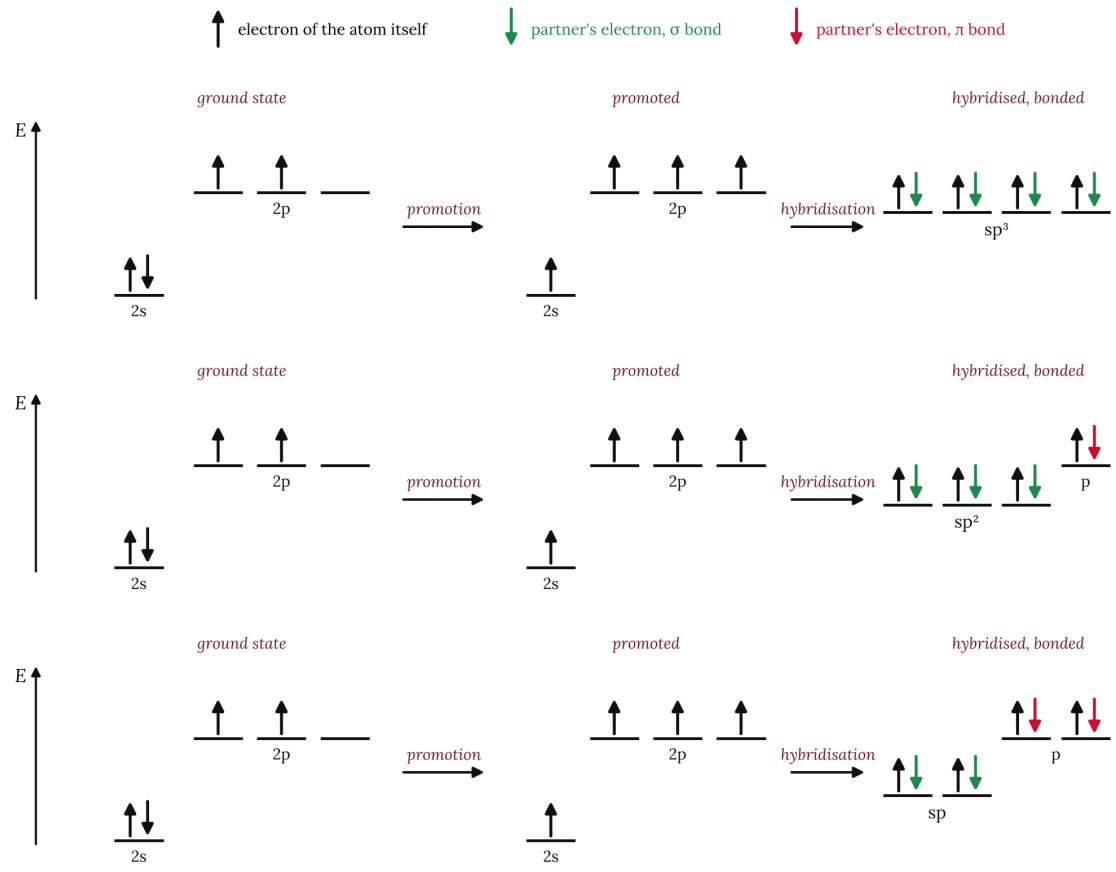


Figure 2.2. Carbon from ground state to hybridised: promotion of one 2s electron, then mixing of s with three, two or one p orbital. The left-over p orbitals (sp² and sp) make the π bonds.

Example 2.1. Give the hybridisation of every carbon in the molecule of Figure 2.3.

Count the σ bonds and π bonds on each carbon, hydrogens included:

Carbon	σ bonds	π bonds	Hybridisation
C1	4	0	sp^3
C2	2	2	sp
C3	2	2	sp
C4	3	1	sp^2
C5	3	1	sp^2
C6	4	0	sp^3
C7	4	0	sp^3
C8	4	0	sp^3

So the triple bond (C2 and C3) is sp, the double bond (C4 and C5) is sp^2, and everything with only single bonds is sp^3. Figure 2.3 colours them: purple for sp, red for sp^2, yellow for sp^3.

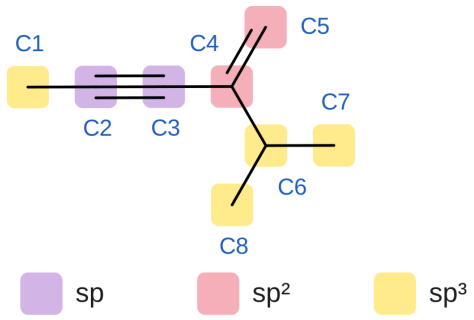


Figure 2.3. The molecule of Example 2.1 with its carbons numbered and coloured by hybridisation: purple sp, red sp^2, yellow sp^3.

2.3 Nitrogen and oxygen: ammonia and water

Nitrogen and oxygen hybridise too, and their lone pairs count as groups. Nitrogen has five valence electrons. In ammonia it makes three σ bonds and keeps one lone pair: four groups, so sp^3. Oxygen has six valence electrons. In water it makes two σ bonds and keeps two lone pairs: again four groups, again sp^3. Figure 2.4 shows the orbital diagrams: in each case the four sp^3 orbitals are filled with the atom's own electrons, and the bonding ones also receive an electron from a hydrogen.

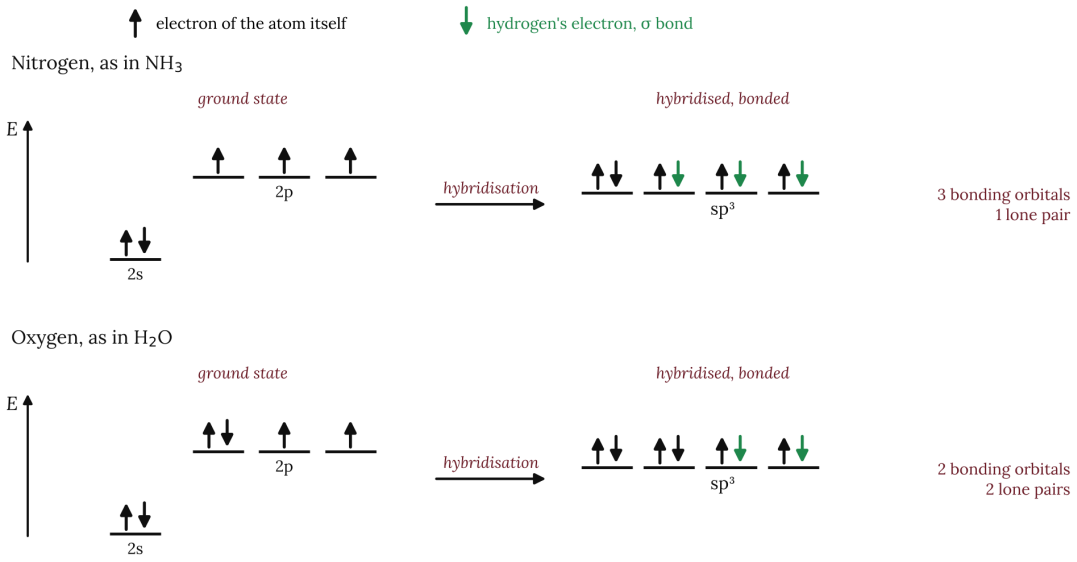


Figure 2.4. Nitrogen (ammonia) and oxygen (water): both end up sp^3, but with one and two lone pairs. Black electrons belong to the atom itself, green ones come from hydrogen.

> **Watch out.** Hybridisation counts groups of electrons around an atom, not neighbouring atoms. Oxygen in water has only two atoms attached and is still sp^3, because its two lone pairs count too.

Four sp³ orbitals point to the corners of a tetrahedron (methane, on the left of Figure 2.5, has all four bonded to hydrogen), but when we describe a shape we only look at the atoms, and a lone pair is not an atom. In ammonia one corner is taken by a lone pair, so the three hydrogens form a pyramid with nitrogen at the top. In water two corners are taken, so the molecule is bent (Figure 2.5). The H–N–H angle in ammonia is about 107° and the H–O–H angle in water about 104.5°: close to the tetrahedral 109.5°, but not quite. A lone pair is held by one nucleus only, so it spreads out more and pushes harder than a bonding pair, which is shared between two nuclei. The repulsion between a lone pair and a bonding pair is therefore stronger than between two bonding pairs, and it squeezes the bonds closer together. Water has two lone pairs and is squeezed a little more than ammonia.

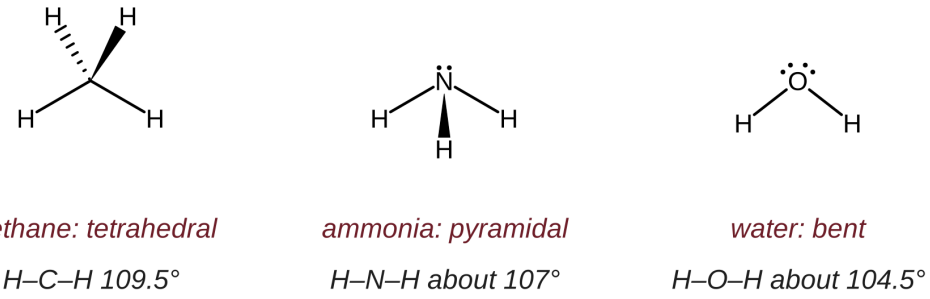


Figure 2.5. Same four sp³ orbitals, different shapes: methane has no lone pair and is tetrahedral, while the lone pairs of ammonia and water take up room but are not atoms, so ammonia is pyramidal and water is bent.

Exercises

Exercise 2.1. Figure 2.6 shows a molecule with its carbons numbered C1 to C6. Give the hybridisation of every carbon, of the nitrogen and of the oxygen.

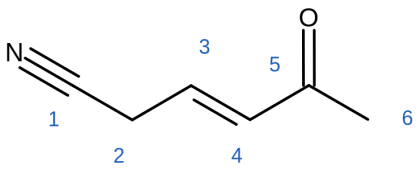


Figure 2.6. The molecule of Exercises 2.1 and 2.2, carbons numbered in blue.

Exercise 2.2. Count the σ bonds and the π bonds in the molecule of Figure 2.6. The bonds to hydrogen count too.

Exercise 2.3. For the atom marked 1 in each species of Figure 2.7, give the hybridisation, the shape of the atoms around it and the bond angle (about, or exactly).

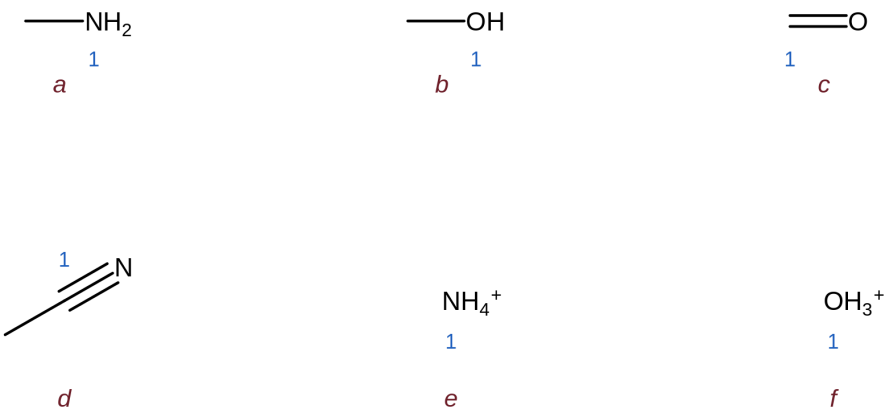


Figure 2.7. The species of Exercise 2.3. Carbons carry as many hydrogens as they need for four bonds, as always in a line drawing.

Exercise 2.4. (a) The H–N–H angle in ammonia is about 107°. In the ammonium ion, NH_4^+, it is 109.5°. Why? (b) The H–O–H angle in water is about 104.5°, smaller than in ammonia. Why?

Exercise 2.5. Complete the table for a carbon atom.

Hybridisation	Hybrid orbitals made	p orbitals left over	π bonds it can make
sp^3			
sp^2			
sp			

Solutions

Exercise 2.1. Count the σ bonds and the lone pairs on each atom; their sum is the number of groups, and the number of groups gives the hybridisation (two is sp, three is sp^2, four is sp^3). Figure 2.8 shows the result.

Atom	σ bonds	Lone pairs	Groups	Hybridisation
C1 (nitrile carbon)	2 (N and C2)	0	2	sp
C2	4 (C1, C3 and two H)	0	4	sp^3
C3	3 (C2, C4 and H)	0	3	sp^2
C4	3 (C3, C5 and H)	0	3	sp^2
C5 (carbonyl carbon)	3 (C4, C6 and O)	0	3	sp^2
C6	4 (C5 and three H)	0	4	sp^3
N	1 (C1)	1	2	sp
O	1 (C5)	2	3	sp^2

The two heteroatoms are the interesting ones. The nitrogen of a nitrile is sp, like the carbon it is bonded to: one σ bond and one lone pair make two groups, and the two π bonds do not count. The carbonyl oxygen makes only one σ bond, yet it is sp^2: its two lone pairs count as groups, so one σ bond plus two lone pairs makes three groups. The π bond is built from the leftover p orbital and, as always, does not count.

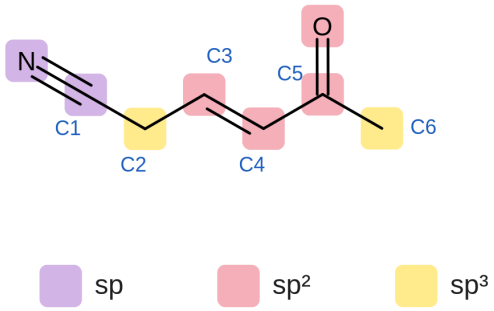


Figure 2.8. The molecule of Exercise 2.1 coloured by hybridisation: purple sp, red sp^2, yellow sp^3.

Exercise 2.2. Every multiple bond is one σ bond plus one or two π bonds. The triple bond C1≡N gives 1 σ and 2 π, the double bond C3=C4 gives 1 σ and 1 π, and the double bond C5=O gives 1 σ and 1 π. So there are 2 + 1 + 1 = **4 π bonds**. For the σ bonds, count the single bonds and add one for each multiple bond: C1–C2, C2–C3, C4–C5 and C5–C6 are 4; C2 carries 2 H, C3 and C4 one H each and C6 three H, which is 7 C–H bonds; add the three σ bonds of the multiple bonds, giving 4 + 7 + 3 = **14 σ bonds**.

A quick check: the molecule is C_6H_7NO, so it has 6 + 7 + 1 + 1 = 15 atoms. A molecule without rings needs one σ bond fewer than it has atoms to hold everything together: 14. The remaining bonds are π bonds, and the four of them match the count above.

Exercise 2.3.

Species	Atom 1	Groups around it	Hybridisation	Shape	Angle
a	N	3 σ bonds + 1 lone pair = 4	sp^3	trigonal pyramidal	a little under 109.5°, about 107° to 110°
b	O	2 σ bonds + 2 lone pairs = 4	sp^3	bent	about 108°, a little under 109.5°
c	C	3 σ bonds = 3	sp^2	trigonal planar	about 120°
d	C	2 σ bonds = 2	sp	linear	180°
e	N	4 σ bonds = 4	sp^3	tetrahedral	109.5°
f	O	3 σ bonds + 1 lone pair = 4	sp^3	trigonal pyramidal	a little under 109.5° in the simple picture (measured values are around 110° to 113°)

In species a, b and f the lone pair counts as a group but is not an atom, so the shape of the atoms is one step down from the tetrahedron of the groups: the amine is a pyramid, methanol is bent. In e there is no lone pair, and the four groups are four atoms, so the shape is the full tetrahedron.

Exercise 2.4. (a) In ammonium all four groups around nitrogen are identical N–H bonding pairs, so nothing pushes harder than anything else and the angle is the tetrahedral 109.5°. In ammonia one of the four groups is a lone pair. A lone pair is held by one nucleus only, so it spreads out more and pushes harder than a bonding pair, which is shared between two nuclei. It squeezes the three N–H bonds a little closer together: 107°.

(b) Water has two lone pairs on the oxygen where ammonia has one on the nitrogen. Two lone pairs squeeze the two O–H bonds more than one lone pair squeezes three N–H bonds, so the angle is smaller still: 104.5°.

Exercise 2.5.

Hybridisation	Hybrid orbitals made	p orbitals left over	π bonds it can make
sp^3	4	0	0
sp^2	3	1	1
sp	2	2	2

The three columns are one idea: a carbon has four orbitals to give out (one s and three p), and every p orbital that is not mixed into a hybrid is free to make a π bond. For sp that means two π bonds, either a triple bond, or two double bonds on the same carbon as in an allene.

CHAPTER 3

Naming

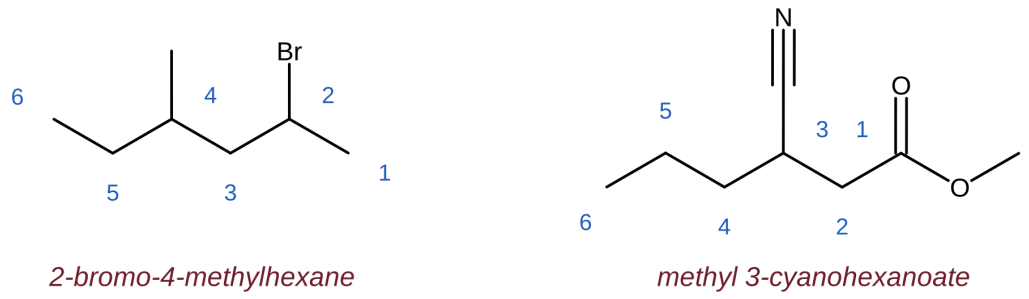
> **This chapter:** how a structure becomes a name and a name becomes a structure, and the rules that decide which chain, which direction and which order. **You need:** Chapter 1 (the families and the priority list).

3.1 The recipe

A name is built in four moves, always in this order:

1. **Find the parent.** The longest chain (or the ring) that carries the main group. Hexane, decane, cyclohexane.
2. **Pick the suffix.** The group with the highest rank on the priority list of Chapter 1 becomes the ending: -ol, -one, -oate, -amide. Every other group becomes a prefix, and ethers and halogens are always prefixes.
3. **Number.** Start from the end that gives the suffix the lowest number. Then double bonds, then the prefixes. Compare the sets of numbers one by one, at the first point where they differ: {2,4} beats {3,5}, and {2,9} beats {3,4}, because 2 is lower than 3.
4. **Write.** The prefixes go in front in alphabetical order, each with its number. The multipliers di-, tri-, tetra- do not count for the alphabet: dimethyl sorts under m.

Example 3.1. Name the molecule on the left of Figure 3.1.



2-bromo-4-methylhexane *methyl 3-cyanohexanoate*

Figure 3.1. The molecules of Examples 3.1 and 3.2, numbered the way the name needs.

There is no suffix group here: bromine is a prefix, so the parent is just the longest chain, hexane. Numbered from the right, the bromine sits on C2 and the methyl on C4: {2,4}. Numbered from the left it would be {3,5}. So {2,4} it is. Alphabetical order puts bromo before methyl: **2-bromo-4-methylhexane**.

3.2 A suffix group takes charge: esters

Example 3.2. Name the molecule on the right of Figure 3.1.

This molecule has an ester and a nitrile. The ester ranks higher, so it gets the suffix and the nitrile becomes the prefix *cyano*. An ester has a two-word name. The group on the oxygen comes first (methyl). The acid part comes second, as the chain with the ending -oate. The numbering of an ester always starts from the carbon of the ester group itself, so C1 is the C=O carbon. The nitrile carbon is not part of the chain, because cyano hangs on it as a substituent. That leaves six carbons: hexanoate, with the cyano group on C3. The name is **methyl 3-cyanohexanoate**.

3.3 When it gets crowded

Example 3.3. Name the molecule of Figure 3.2.

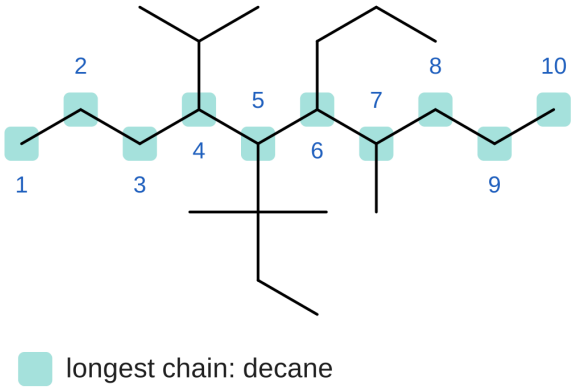


Figure 3.2. The molecule of Example 3.3. The highlighted chain is the longest one; the blue numbers are the ones that give the name.

Start with the longest chain. Count carefully: it has ten carbons, and every other route through the branches gives at most nine. So the parent is decane.

Next the numbering. Numbered as drawn, the substituents sit on 4, 5, 6 and 7. Numbered from the other end they also sit on 4, 5, 6 and 7:

Position	Numbered as in Figure 3.2	Numbered from the other end
4	isopropyl	methyl
5	1,1-dimethylpropyl	propyl
6	propyl	1,1-dimethylpropyl
7	methyl	isopropyl

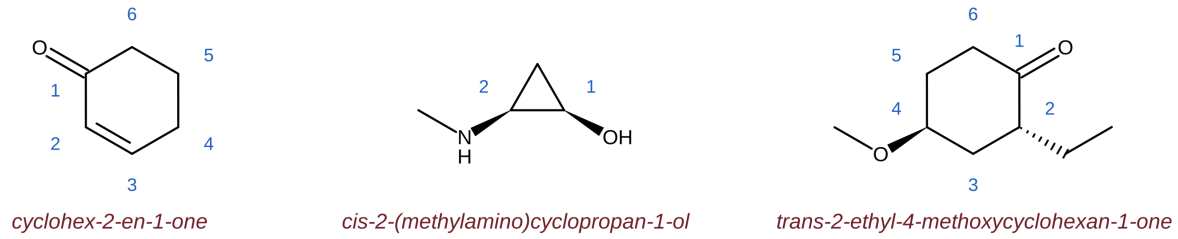
A tie. The tie-break is the alphabet: the substituent that comes first alphabetically gets the lowest number. The first one is *dimethylpropyl* (see below why it sorts under d), which gets 5 as drawn and 6 the other way. So we number as drawn, and the name, with the prefixes in alphabetical order, is **5-(1,1-dimethylpropyl)-4-isopropyl-7-methyl-6-propyldecane**.

Two things about that name. A substituent that is itself a branched chain gets its own numbers, counted from the carbon that is attached to the main chain, and it goes in brackets: in 1,1-dimethylpropyl, C1 is the carbon on the main chain, the propyl chain runs C1–C2–C3, and C1 also carries two methyls. And such a compound substituent is sorted under the first letter of its *complete* name, so here the *di* does count. Simple substituents are easier: isopropyl sorts under i, tert-butyl under b (tert- is ignored), and dimethyl under m. (The newest IUPAC recommendations call 1,1-dimethylpropyl 2-*methylbutan*-2-*yl*; the older name is still very common.)

> **Watch out.** Do not sort by the last word of a substituent. 1,1-Dimethylpropyl is not a kind of propyl for the alphabet: it goes under d, in front of isopropyl, not next to propyl.

3.4 Rings, and cis and trans in the name

Example 3.4. Name the first molecule of Figure 3.3.



cyclohex-2-en-1-one *cis-2-(methylamino)cyclopropan-1-ol* *trans-2-ethyl-4-methoxycyclohexan-1-one*

Figure 3.3. Examples 3.4 to 3.6. A wedge points towards you, a dashed bond away from you.

The ring is the parent: cyclohexane. The ketone has the highest rank, so it is the suffix and its carbon is C1: -1-*one*. The double bond gets the lowest number that is left, so we count towards it, and it sits between C2 and C3: -2-*ene*. The locant of the double bond goes in front of the *en*, and the locant of the ketone in front of the *one*: **cyclohex-2-en-1-one**.

Example 3.5. Name the second molecule of Figure 3.3.

The parent is cyclopropane. Alcohol outranks amine, so the alcohol is the suffix, on C1, and the amine becomes a prefix on C2. The methyl hangs on the nitrogen, so the prefix is *methylamino*, and since it is a compound prefix it goes in brackets. Both bonds are wedges: both substituents point towards you, on the same side of the ring. That is **cis**. The name is **cis-2-(methylamino)cyclopropan-1-ol**.

Example 3.6. Name the third molecule of Figure 3.3.

The parent is cyclohexane again, and the ketone is the suffix, C1. Counting towards the ethyl gives the ethyl C2 and the methoxy group C4, which is {2,4}; counting the other way would give {4,6}. Remember that an ether is always a prefix, so the OMe becomes *methoxy*. Alphabetically, ethyl comes before methoxy. The ethyl is on a dashed bond (behind the paper) and the methoxy on a wedge (in front of the paper): opposite sides of the ring, so **trans**. The name is **trans-2-ethyl-4-methoxycyclohexan-1-one**.

cis and trans only mean something when the substituents are fixed relative to each other, as they are in a ring. (For double bonds the same idea comes back as E and Z, in Chapter 5.)

3.5 From name to structure

The other direction is just the recipe in reverse: **draw the parent first, number it, then hang the substituents on their numbers.** Nobody is asking you to see the whole molecule at once.

Example 3.7. Draw 5-chloro-3-methyl-4-propyloctane.

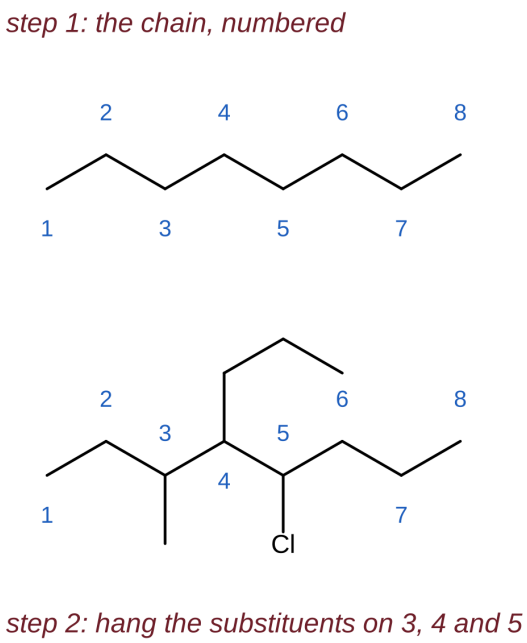


Figure 3.4. From name to structure: first the numbered chain, then the substituents.

Octane is eight carbons in a row: draw them and number them (Figure 3.4, step 1). Then put a methyl on 3, a propyl on 4 and a chlorine on 5 (step 2). Finally, check your own drawing by naming it again: if you find a longer chain than the octane you started with, then the name you were given was not a proper one.

3.6 A bit of nomenclature: the two words of an ester

Back to esters, because their names are a neat example of a name that splits in two parts. In ethyl acetate (Figure 3.5), the *acetate* part is everything that comes from the acid: the CH_3, the C=O and the oxygen that binds it to the rest. The *ethyl* is the group on that oxygen. Acetate is the common name for the ethanoate you get from the recipe above, and it is accepted by IUPAC; the systematic name is ethyl ethanoate.

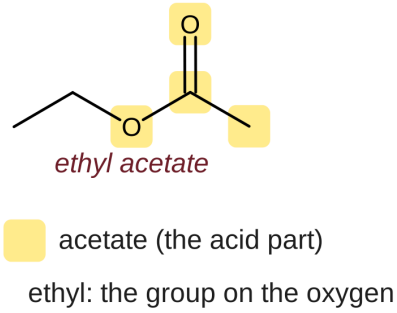


Figure 3.5. Ethyl acetate: the yellow part is the acetate, the group on the oxygen is the ethyl.

Exercises

Exercise 3.1. Name the six molecules of Figure 3.6. For molecule d, say whether it is cis or trans.

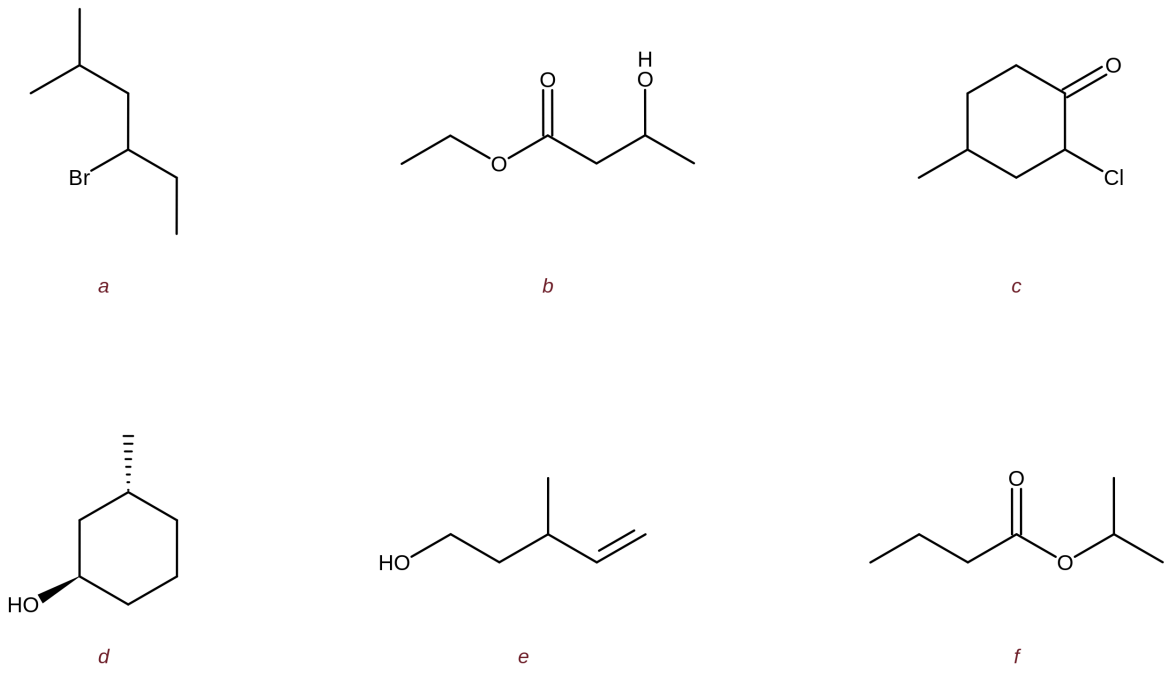


Figure 3.6. The molecules of Exercise 3.1. A wedge points towards you, a dashed bond away from you.

Exercise 3.2. Draw the four molecules below. Number the parent chain or ring first, as in Figure 3.4, and then hang the substituents on their numbers. Afterwards, name your drawing again: you should get the same name back.

(a) 3-ethyl-2,2-dimethylpentane
(b) propyl 4-chlorobutanoate
(c) *cis*-3-methylcyclopentan-1-ol
(d) 2-methylbut-3-en-2-ol

Exercise 3.3. Each of the four molecules of Figure 3.7 has been given a wrong name below. Find the mistake in each name and give the correct one.

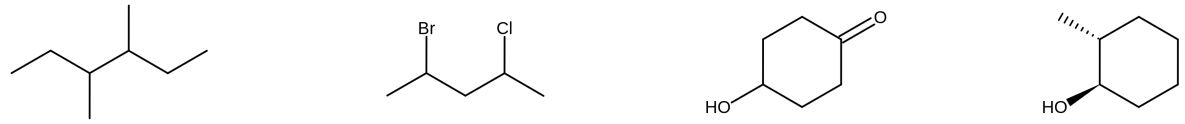


Figure 3.7. The molecules of Exercise 3.3.

(a) 2-ethyl-3-methylpentane
(b) 4-bromo-2-chloropentane
(c) 4-oxocyclohexan-1-ol
(d) *cis*-2-methylcyclohexan-1-ol

Exercise 3.4. Name the molecule of Figure 3.8. Watch the chain: the longest route through the carbons bends, and there is more than one way to follow it.

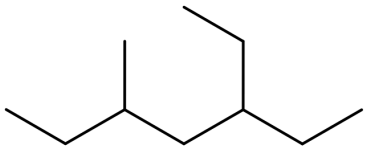
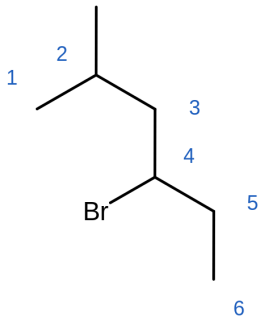


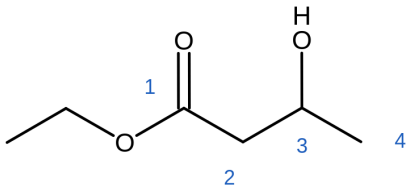
Figure 3.8. The molecule of Exercise 3.4.

Solutions

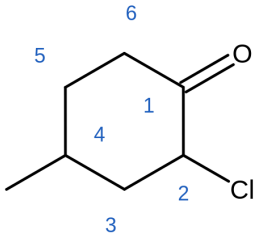
Exercise 3.1. Figure 3.9 shows every molecule with the numbering its name needs.



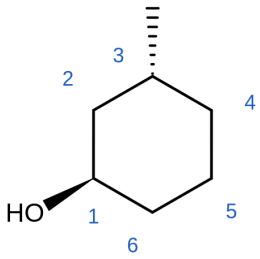
4-bromo-2-methylhexane



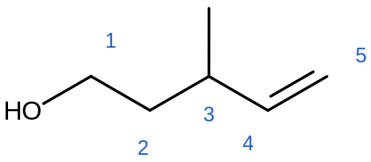
ethyl 3-hydroxybutanoate



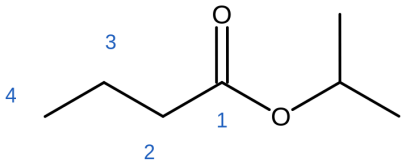
2-chloro-4-methylcyclohexan-1-one



trans-3-methylcyclohexan-1-ol



3-methylpent-4-en-1-ol



isopropyl butanoate

Figure 3.9. The answers to Exercise 3.1, numbered the way the name needs.

(a) No suffix group, so the parent is the longest chain: six carbons, running through the isopropyl end. Numbered from the isopropyl end, the methyl sits on C2 and the bromine on C4: {2,4}. Numbered from the other end it would be {3,5}. The set {2,4} is lower, so the isopropyl end is C1. Bromo comes before methyl in the alphabet: **4-bromo-2-methylhexane**. The numbers follow the chain; the order of the words follows the alphabet. Those are two separate decisions.

(b) The ester outranks the alcohol, so it gets the suffix and the OH becomes *hydroxy*. C1 is the C=O carbon; the chain is four carbons, with the hydroxy on C3. The ethyl on the oxygen goes first: **ethyl 3-hydroxybutanoate**.

(c) The ketone is the suffix, so C1 is the C=O carbon of the ring. Counting towards the chlorine gives the chlorine C2 and the methyl C4: {2,4}. Counting the other way gives {4,6}. So **2-chloro-4-methylcyclohexan-1-one**.

(d) The alcohol is the suffix and its carbon is C1. The methyl is two carbons away whichever way you count, but it is C3 one way and C5 the other, and we take the lower: C3. The OH is on a wedge and the methyl on a dashed bond, so they are on opposite sides of the ring: **trans-3-methylcyclohexan-1-ol**.

(e) The parent chain has to contain both the OH and the double bond: five carbons, with the methyl hanging off. The alcohol gets the lowest number, so the OH carbon is C1, and the double bond ends up between C4 and C5. The methyl is on C3: **3-methylpent-4-en-1-ol**.

(f) The ester has two words. The group on the oxygen is the isopropyl. The acid part is four carbons including the C=O carbon: butanoate. The name is **isopropyl butanoate**. (The systematic name for isopropyl is propan-2-yl, which gives propan-2-yl butanoate; both are in use.)

Exercise 3.2. Figure 3.10 shows the four drawings with their numbering.

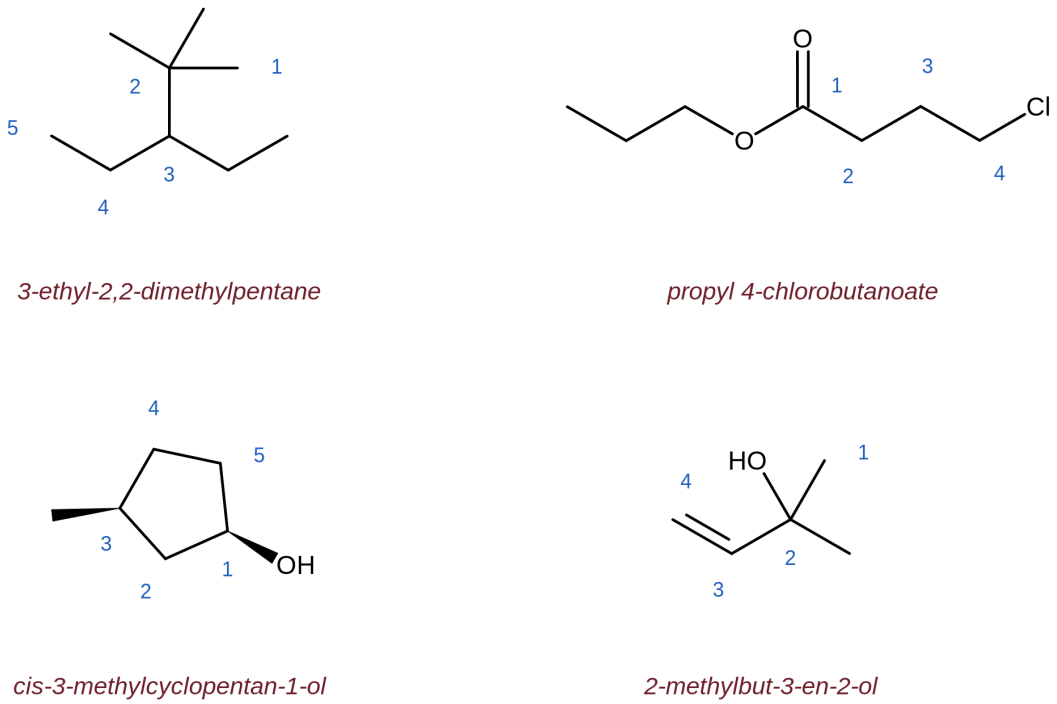


Figure 3.10. The answers to Exercise 3.2.

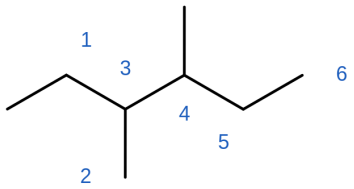
(a) Draw five carbons in a row and number them. Put two methyl groups on C2 and an ethyl group on C3. Check your drawing by naming it again: the longest chain is five carbons (you can also go from a methyl on C2, through C3 and out along the ethyl, and that is five as well), so the pentane stands.

(b) An ester: the acid part is the four-carbon chain butanoate, with C1 the C=O carbon and the chlorine on C4, the far end. The propyl hangs on the oxygen.

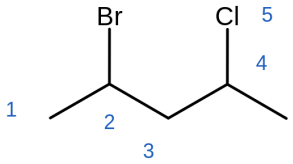
(c) Draw a five-membered ring and number it so that the OH carbon is C1. Put a methyl on C3. *cis* means both groups point the same way, so draw both on wedges.

(d) Four carbons in a row. The alcohol takes the lowest number it can, and that is C2 (counting from the other end it would be C3), so C1 is the methyl at the end of the chain. The double bond then sits between C3 and C4. The OH goes on C2, together with one more methyl: the 2-methyl of the name.

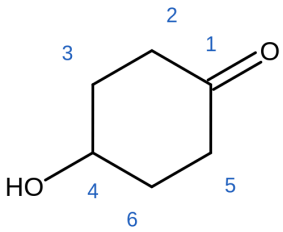
Exercise 3.3. Figure 3.11 shows the molecules with their correct numbering.



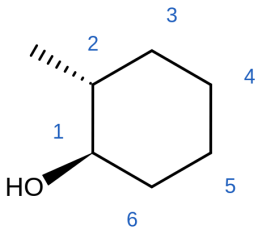
3,4-dimethylhexane



2-bromo-4-chloropentane



4-hydroxycyclohexan-1-one



trans-2-methylcyclohexan-1-ol

Figure 3.11. The answers to Exercise 3.3, numbered the way the name needs.

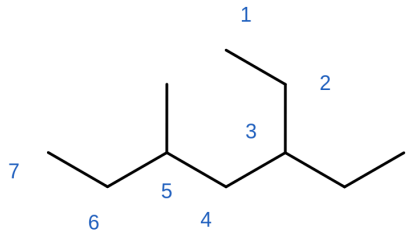
(a) The name picks a chain of five carbons, but there is a chain of six: the ethyl group of that name is part of the longest chain. Always take the longest chain first. With the six-carbon chain the two methyls sit on C3 and C4 whichever end you count from: **3,4-dimethylhexane**.

(b) Both directions give the substituents {2,4}, so numbering cannot break the tie. The alphabet does: the substituent that comes first alphabetically gets the lowest number. Bromo comes before chloro, so the bromine is on C2: **2-bromo-4-chloropentane**.

(c) The name treats the alcohol as the suffix and the ketone as the prefix *oxo*. But the ketone outranks the alcohol: it gets the suffix, and the OH becomes the prefix *hydroxy*. The ketone carbon is C1, so the OH ends up on C4: **4-hydroxycyclohexan-1-one**.

(d) The numbering and the constitution are right, but the wedge and the dashed bond are on opposite sides of the ring, so the compound is **trans**-2-methylcyclohexan-1-ol. Only the cis/trans label was wrong.

Exercise 3.4. Figure 3.12 shows the molecule with the numbering that gives its name.



3-ethyl-5-methylheptane

Figure 3.12. The answer to Exercise 3.4. The numbers run along one of the two seven-carbon chains.

The longest chain has seven carbons, and there are two ways to follow seven carbons through the drawing. Both leave the same two groups over: a methyl and an ethyl. So the parent is heptane, and the name is built from one methyl and one ethyl whichever route you pick.

Now the numbering. Counted from one end, the ethyl is on C3 and the methyl on C5: {3,5}. Counted from the other end, the methyl is on C3 and the ethyl on C5: also {3,5}. A tie. The alphabet breaks it: ethyl comes before methyl, so the ethyl gets the lower number, 3. The name is **3-ethyl-5-methylheptane**.

CHAPTER 4

Conformations

In Chapter 3 the molecules got names. In this chapter they start to move. Everything here follows from one fact: a single bond is free to turn, and a ring is not free to do whatever it likes, so it has to find a shape. You need the sp^3 carbon of Chapter 1 (four bonds, tetrahedral, 109.5°) and the naming habits of Chapter 3; nothing else.

4.1 Configuration versus conformation

Two words that look like twins and are not. Both describe how the atoms of a molecule sit in space, and both are kinds of stereoisomerism. The difference is how you get from one arrangement to the other.

Conformations of one molecule turn into each other by rotation around a single bond. Nothing breaks, so it costs little and it happens all the time. Configurations cannot be interconverted this way: to go from one to the other you would have to break bonds. A cis and a trans alkene are two configurations; the two ends of a butane chain twisting around the middle bond are two conformations of one and the same molecule.

4.2 Three ways to draw one bond

To show what a molecule looks like around one bond there are three standard drawings, and you should be able to jump between them without thinking. Take 2,2-dimethylbutane and look at the bond between C2 and C3 (Figure 4.1, top row).

The **Natta projection** is the zigzag you already know, with wedges and hashes for the groups that leave the plane. C2 carries a wedged and a hashed methyl; C1, C2, C3 and C4 stay in the plane of the paper.

The **sawhorse** looks at the C2–C3 bond from the side and a bit from above. The front carbon (C2) is at the lower right, the back carbon (C3) at the upper left, and the long line between them is the bond you are looking along. Each carbon gets its three other groups: C2 holds C1 and the two methyls, C3 holds two H and C4.

The **Newman projection** looks straight down the bond. The front carbon is the point in the middle where three bonds meet; the back carbon is the circle behind it, and its bonds start at the edge of the circle. A Newman projection is a sawhorse seen from the end.

The bottom row of Figure 4.1 does the same for 2,3-dimethylbutane, again along C2–C3. The two methyls sit on opposite faces in the Natta drawing, which is the conformation drawn in the sawhorse and the Newman projection: every group has its partner on the other carbon directly opposite it (180°, *anti*).

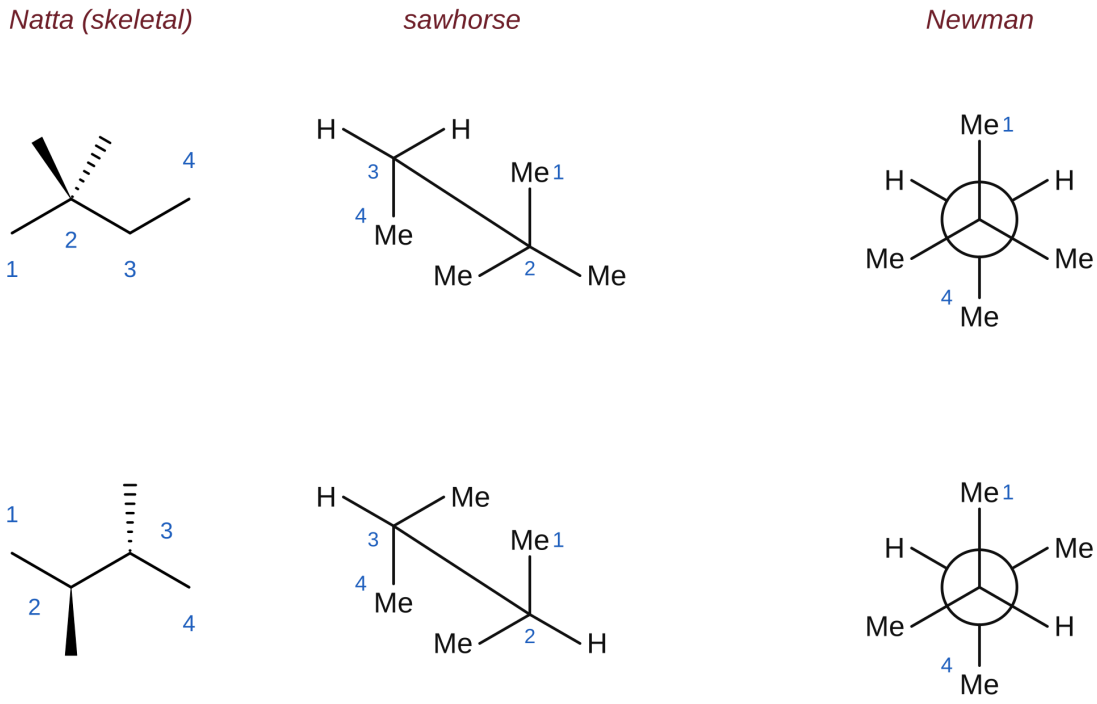


Figure 4.1. The same bond in three drawings: Natta (left), sawhorse (middle), Newman (right). Top: 2,2-dimethylbutane along C2–C3. Bottom: 2,3-dimethylbutane along C2–C3, in the conformation where every group is anti to its partner.

4.3 Turning around a single bond

Hold the front carbon still and turn the back carbon. Every 60° the picture flips between two looks (Figure 4.2). In an **eclipsed** conformation each back group sits straight behind a front group (in the Newman drawing the back bonds are drawn slightly rotated, otherwise you could not see them). In a **staggered** conformation each back group sits in the gap between two front groups.

Staggered is the low-energy form: the groups are as far from each other as they can get. Eclipsed is the top of the hill. Plot the energy against the angle and you get a wave. Two more words: two groups 60° apart are *gauche*, two groups 180° apart are *anti*.

For 2,2-dimethylbutane the front carbon holds three identical groups (C1 and the two methyls), so after every 120° the molecule looks exactly like it did before. The profile therefore has three equal maxima and three equal minima, and that is what Figure 4.2 shows. If the carbons carried different groups, as in 2,3-dimethylbutane, the three staggered forms would no longer be equal: anti is lower than gauche.

How high is the hill? For ethane about 12 kJ mol^{-1}. That is small enough to climb many billions of times per second at room temperature, which is why you normally cannot separate conformations of an open chain, and why a single bond counts as freely rotating.

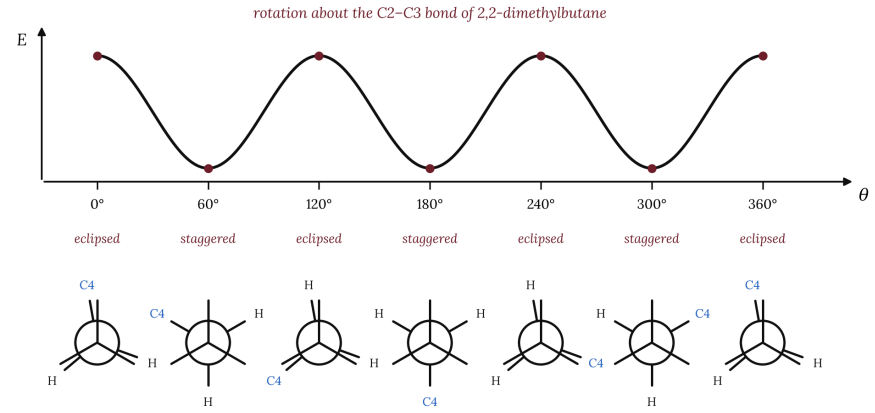


Figure 4.2. Rotation around the C2–C3 bond of 2,2-dimethylbutane: three equal maxima (eclipsed) and three equal minima (staggered).

4.4 The chair

Cyclohexane drawn as a flat hexagon would have 120° angles, where an sp³ carbon wants 109.5°, and every pair of neighbouring C–H bonds would be eclipsed. The ring dodges both by puckering into the **chair**: all angles about 109.5° and every bond staggered.

A chair has two kinds of positions. The six **axial** bonds are vertical, parallel to the axis of the ring, pointing up and down alternately from carbon to carbon. The six **equatorial** bonds point out around the equator of the ring, slightly up or down; in the drawing each one is parallel to two ring bonds, the ones one step removed from its carbon.

The chair can turn itself inside out: the **ring flip** (Figure 4.3). Every axial position becomes equatorial and every equatorial becomes axial. Up stays up and down stays down; the only thing that changes is how the group sits on the ring. In the figure, the carbons are numbered C1 to C6 and the two hydrogens on C3 are coloured and labelled ax (axial) and eq (equatorial): the orange one is axial before the flip and equatorial after it, the yellow one is equatorial before and axial after. On the way the ring passes through twisted half-chair and boat-like shapes, and the top of the hill (the half-chair, about 45 kJ mol⁻¹), so at room temperature the flip happens about a hundred thousand times per second.

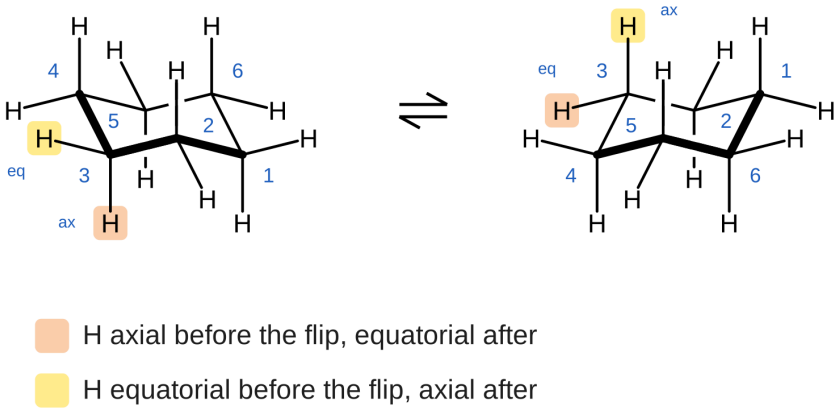


Figure 4.3. Ring flip of cyclohexane. Orange: the hydrogen that is axial in the left chair; yellow: the one that is equatorial in the left chair.

4.5 Groups on a chair

Put something bigger than H on the ring and the two chairs stop being equal. An axial group sits on the same side of the ring as the two axial hydrogens on the carbons two bonds further round the ring, and it bumps into them (a **1,3-diaxial interaction**). An equatorial group points away into free space. So the chair with the group equatorial is the favoured one, and how much it is favoured is the **A-value**: the energy of the axial chair minus the energy of the equatorial chair, for that group on cyclohexane. Table 4.1 gives rough values.

Table 4.1. Approximate A-values.

Group	A-value / kJ mol^{-1}
Br	about 2
Cl	about 2
OH	about 4
CH_3	about 7
C_6H_5 (phenyl)	about 12
$C(CH_3)_3$ (*tert*-butyl)	20 or more

Watch out. *Up* and *down* say which face of the ring a group is on; *axial* and *equatorial* say how it sits on one particular chair. An up group is axial on one carbon and equatorial on the next, and a ring flip swaps it. Cis and trans are about up and down, so a ring flip never changes them. What the faces tell you about the chairs:

- 1,2-cis: one axial, one equatorial. 1,2-trans: both equatorial or both axial.
- 1,3-cis: both equatorial or both axial. 1,3-trans: one axial, one equatorial.
- 1,4-cis: one axial, one equatorial. 1,4-trans: both equatorial or both axial.

Example 4.1. Draw both chairs of the molecule on the left of Figure 4.4 and say which is favoured.

The bromine on C1 and the methyl on C2 are both up, so the ring is 1,2-cis, and one of the two groups is always axial. In the left chair Br is equatorial and methyl axial; after the flip Br is axial and methyl equatorial. The A-value of methyl (about 7 kJ mol^{-1}) is much bigger than that of bromine (about 2), so the chair with methyl equatorial and bromine axial wins.

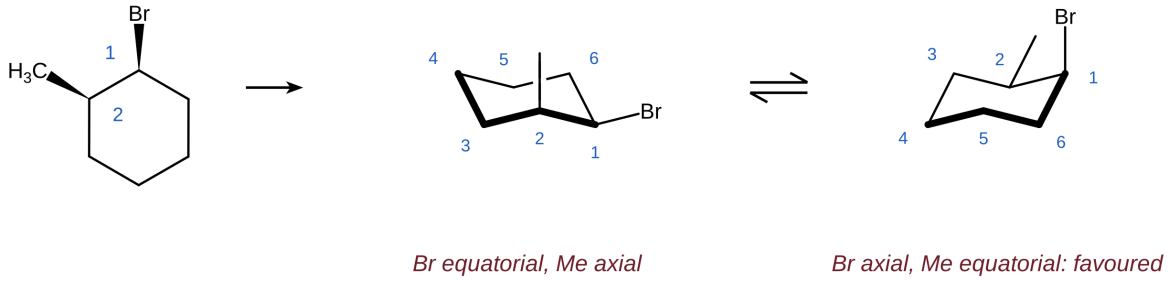


Figure 4.4. Flat ring (left) and the two chairs of the same molecule. Methyl prefers the equatorial position far more than bromine does.

Example 4.2. Draw both chairs of the molecule on the left of Figure 4.5 and say which is favoured.

Phenyl up on C1 and methyl down on C2 make the ring 1,2-trans: both equatorial or both axial. With two groups that both dislike the axial position there is no contest. The diequatorial chair has nothing axial at all; the diaxial chair pays for both groups, roughly the sum of their A-values, about 19 kJ mol^{-1}.

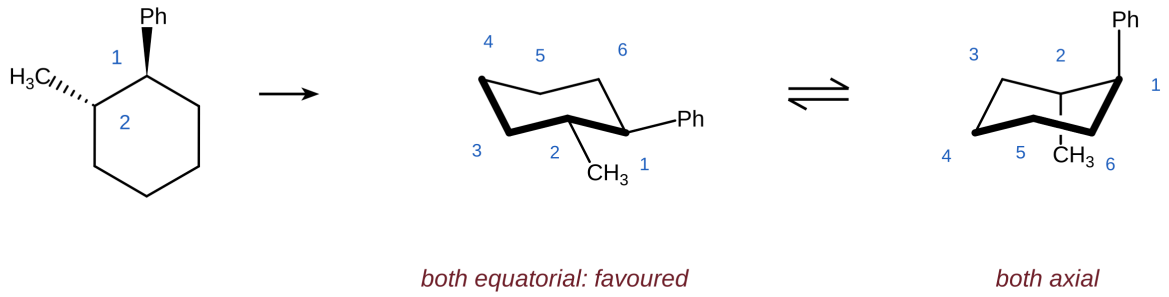


Figure 4.5. Trans-1,2: both groups equatorial (left chair) or both axial (right chair).

Example 4.3. Draw both chairs of the molecule on the left of Figure 4.6 and say which is favoured.

Both chlorines are up, on C1 and C3, so the ring is 1,3-cis: both equatorial or both axial. In the diaxial chair the two axial chlorines point up from carbons that are two bonds apart, so they sit right next to each other (and each also meets the axial H on C5). That is worse than just adding two small A-values, so the diequatorial chair is strongly favoured.

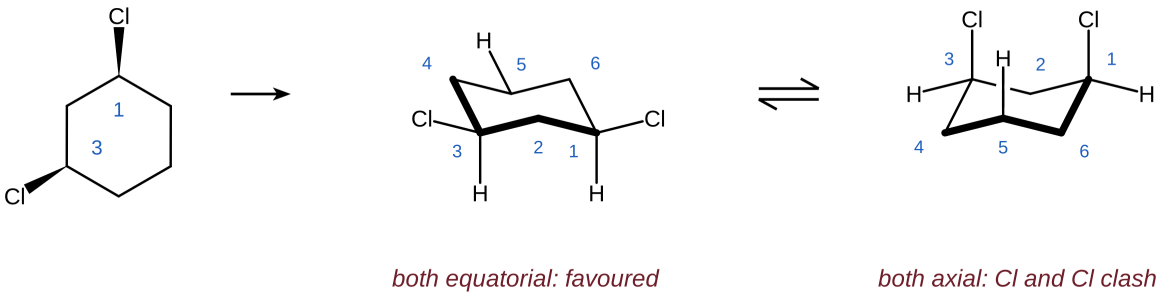


Figure 4.6. Cis-1,3: both equatorial (left chair) or both axial (right chair), where the two chlorines clash.

Example 4.4. Both groups sit on C1 of the ring in Figure 4.7. Which chair is favoured?

One carbon, two groups: in either chair one of them has to be axial. The *tert*-butyl group has one of the biggest A-values there is, so it must be equatorial. That leaves the tert-butoxy group axial, and that is acceptable: between the ring and the big *tert*-butyl there is an oxygen, so the bulky part lies one atom further away from the axial hydrogens, and the oxygen itself is small. Size is not the whole story, position matters too.

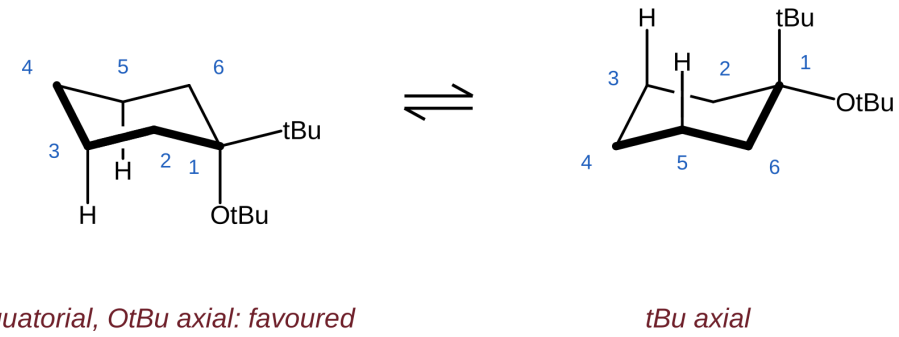


Figure 4.7. tert-Butyl equatorial and tert-butoxy axial (left) is the favoured chair.

Example 4.5. Draw glucose (the β-D-pyranose) as a flat ring and as both chairs.

In the flat ring of Figure 4.8 a wedge is a group pointing up and a hash a group pointing down: OH on C1 and C3 up, OH on C2 and C4 down, CH_2OH on C5 up. Put the ring in a chair with the ring oxygen at the back right and look at what happens: all five groups come out equatorial. Flip it and all five are axial, with every group meeting its 1,3-diaxial neighbours. That is why this sugar is so at home in the left chair, and why it is by far the most abundant one in nature. (The hydrogens are left out in Figure 4.8 to keep the groups readable.)

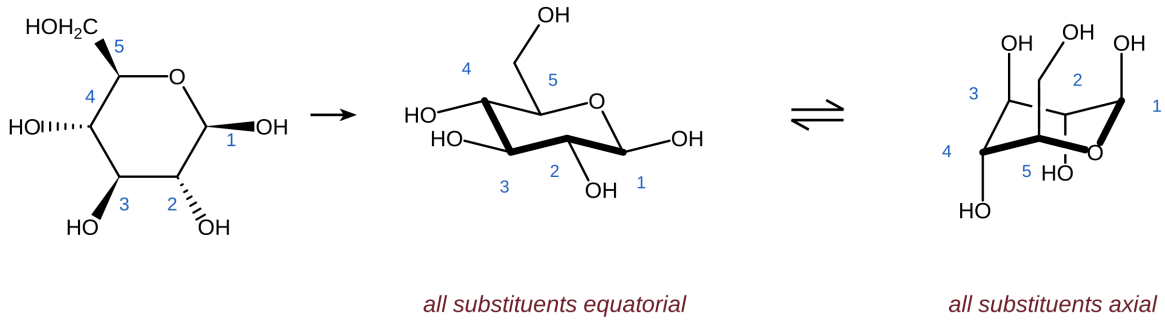


Figure 4.8. β-D-Glucopyranose: all substituents equatorial (left chair) or all axial (right chair).

4.6 Two rings sharing a bond: decalin

Decalin is two cyclohexane chairs that share a bond. The two hydrogens on the shared carbons (orange in Figures 4.9 and 4.10) are either on opposite faces (**trans**) or on the same face (**cis**), and that decides everything.

In **trans-decalin** (Figure 4.9) each ring is attached to the other through two equatorial bonds. There is only one chair–chair shape, and a ring flip is impossible: it would make both connecting bonds axial, and two axial bonds on neighbouring carbons point in opposite directions, 180° apart. The chain of four carbons that closes the second ring cannot reach across that. The ring would not connect. With both rings sitting equatorially on each other it is also the more stable isomer, by roughly 11 kJ mol^{-1}.

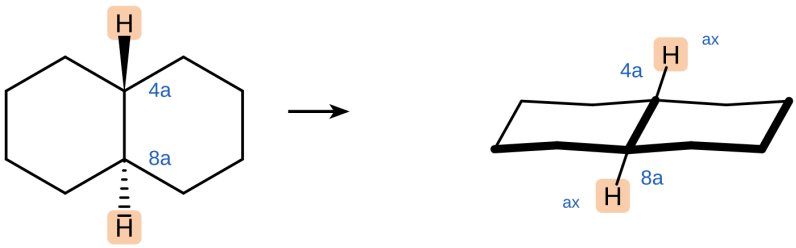


Figure 4.9. trans-Decalin: the hydrogens on the shared carbons (orange) are on opposite faces; the two rings are locked.

In **cis-decalin** (Figure 4.10) each ring is attached to the other by one axial and one equatorial bond. Here the ring flip is possible (both rings flip together), and it gives the other, equally good, chair–chair shape. But in either shape one bond of each ring is axial on the other ring, so there is always a steric clash with axial hydrogens, and the molecule never gets as comfortable as trans.

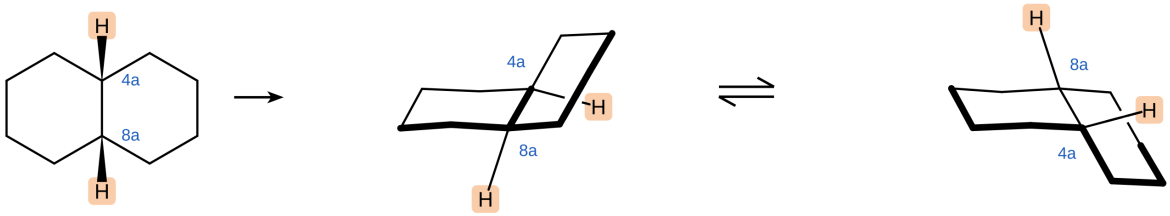
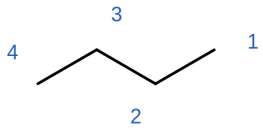


Figure 4.10. cis-Decalin: the hydrogens on the shared carbons (orange) are on the same face; the ring flip is possible and gives an equivalent shape.

Exercises

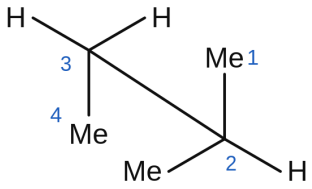
Exercise 4.1. Figure 4.11 shows butane with its carbons numbered. Look along the C2–C3 bond, with C2 in front. Draw the Newman projection of (a) the anti conformation, (b) a gauche conformation, (c) an eclipsed conformation in which each CH_3 eclipses an H, and (d) the eclipsed conformation in which the two CH_3 groups eclipse each other. Put the four in order of increasing energy and say why.



butane

Figure 4.11. Butane, the molecule of Exercise 4.1.

Exercise 4.2. Figure 4.12 shows 2-methylbutane in a sawhorse, looking along the C2–C3 bond with C2 in front. (a) Draw the Newman projection of this conformation. (b) Turn the back carbon by 120° and then by 120° again, and draw the other two staggered conformations. (c) In each of the three, count the CH_3/CH_3 pairs that are gauche. Which conformations are the most stable, and why are two of them equal in energy?



2-methylbutane, bond C2–C3

Figure 4.12. The sawhorse of Exercise 4.2. Carbons C1 to C4 of the chain are numbered in blue.

Exercise 4.3. Figure 4.13 shows four substituted cyclohexanes as flat rings: a wedge is a group on the upper face, a dashed bond a group on the lower face. For each one, draw both chair conformations, label every substituent axial or equatorial, say which chair is favoured, and estimate how much more stable it is with the A-values of Table 4.1.

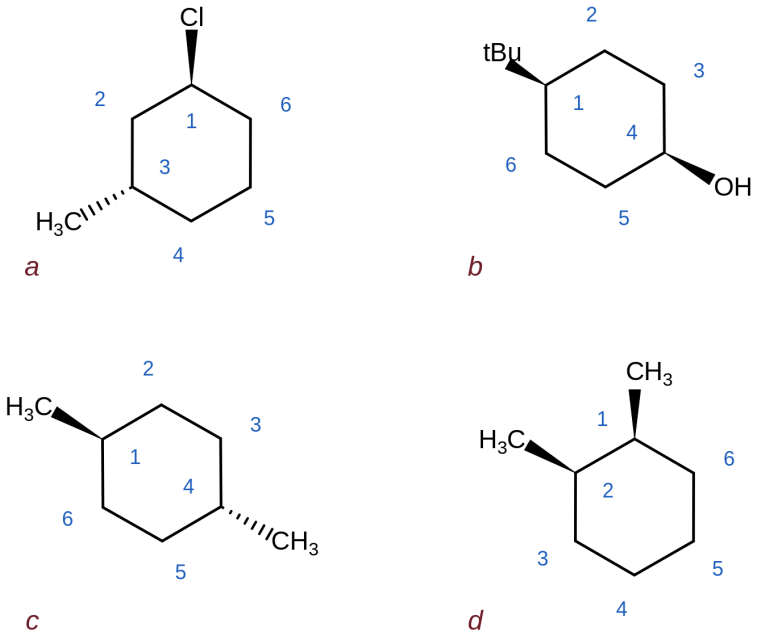


Figure 4.13. The four molecules of Exercise 4.3.

Exercise 4.4. Figure 4.14 shows β-D-galactopyranose as a flat ring. It differs from the glucose of Figure 4.8 in one place only: the OH on C4. Draw both chairs. How many groups are axial in each? Which chair is favoured?

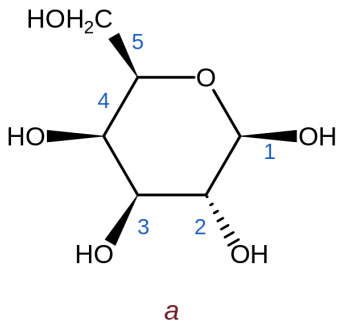


Figure 4.14. β-D-Galactopyranose, the molecule of Exercise 4.4. Ring carbons C1 to C5 are numbered in blue.

Exercise 4.5. Look at the decalins of Figures 4.9 and 4.10. (a) Which of the two can undergo a ring flip, and why can the other not? (b) Which is the more stable one, and by about how much? (c) Why is the more stable one more stable?

Solutions

Exercise 4.1. Figure 4.15 shows the four conformations. Rotating the back carbon around the C2–C3 bond turns one into the next.

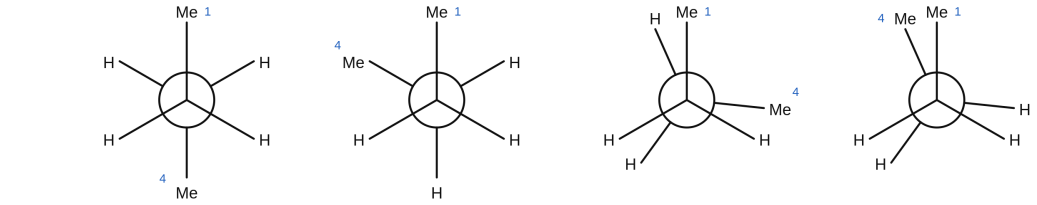


Figure 4.15. The answers to Exercise 4.1: butane along C2–C3, with C2 in front. Energies are relative to the anti conformation.

The order is **anti < gauche < eclipsed (CH₃ over H) < eclipsed (CH₃ over CH₃)**. Staggered conformations are always below eclipsed ones (Section 4.3). Among the staggered ones, anti keeps the two methyl groups as far apart as they can get, 180°. In the gauche conformation they are only 60° apart and they get in each other's way, which costs about 4 kJ mol⁻¹. Among the eclipsed ones, the worst is the one that puts the two largest groups right on top of each other: about 19 kJ mol⁻¹, against about 16 when each methyl eclipses an H. (The numbers are rough; the order is what to remember.)

Exercise 4.2. Figure 4.16 shows all three staggered conformations, with C2 in front and C3 behind.

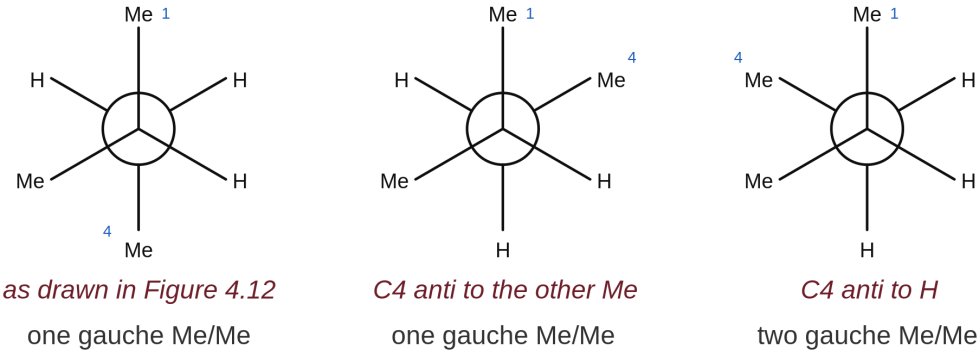


Figure 4.16. The answers to Exercise 4.2: the three staggered conformations of 2-methylbutane about C2–C3.

(a) The first projection is the conformation of Figure 4.12: on the front carbon C1 is on top, the second methyl lower left and H lower right. On the back carbon C4 points down and the two hydrogens point up. C4 sits straight under C1 (anti) and next to the other methyl (gauche).

(b) Turning the back carbon by 120° in one direction puts C4 upper right, straight opposite the second methyl; turning it by another 120° puts C4 upper left, opposite the H.

(c) In the first conformation C4 is anti to C1 and gauche to the other methyl: **one** gauche CH_3/CH_3 pair. In the second, C4 is anti to the other methyl and gauche to C1: again **one**. In the third, C4 is anti to H, so it is gauche to both methyls: **two**. The first two are the most stable, and the third is about 4 kJ mol^{-1} higher, the cost of one extra gauche CH_3/CH_3 pair. The first two are equal in energy because C1 and the second methyl on C2 are the same group (both are CH_3), so the two conformations are mirror images of each other.

Exercise 4.3. Figure 4.17 and Figure 4.18 show both chairs of every molecule. In the flat rings of Figure 4.13 a wedge is up and a dashed bond is down, and the rules in Section 4.5 turn that into axial and equatorial.

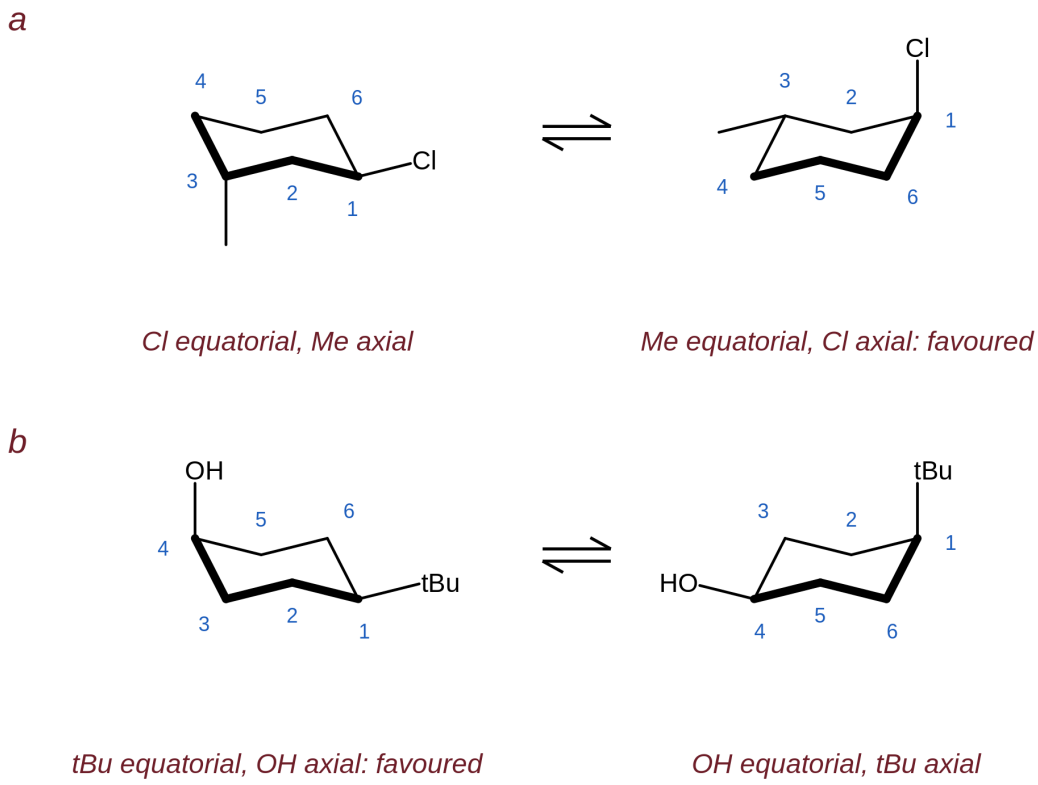


Figure 4.17. The answers to Exercise 4.3 (a) and (b).

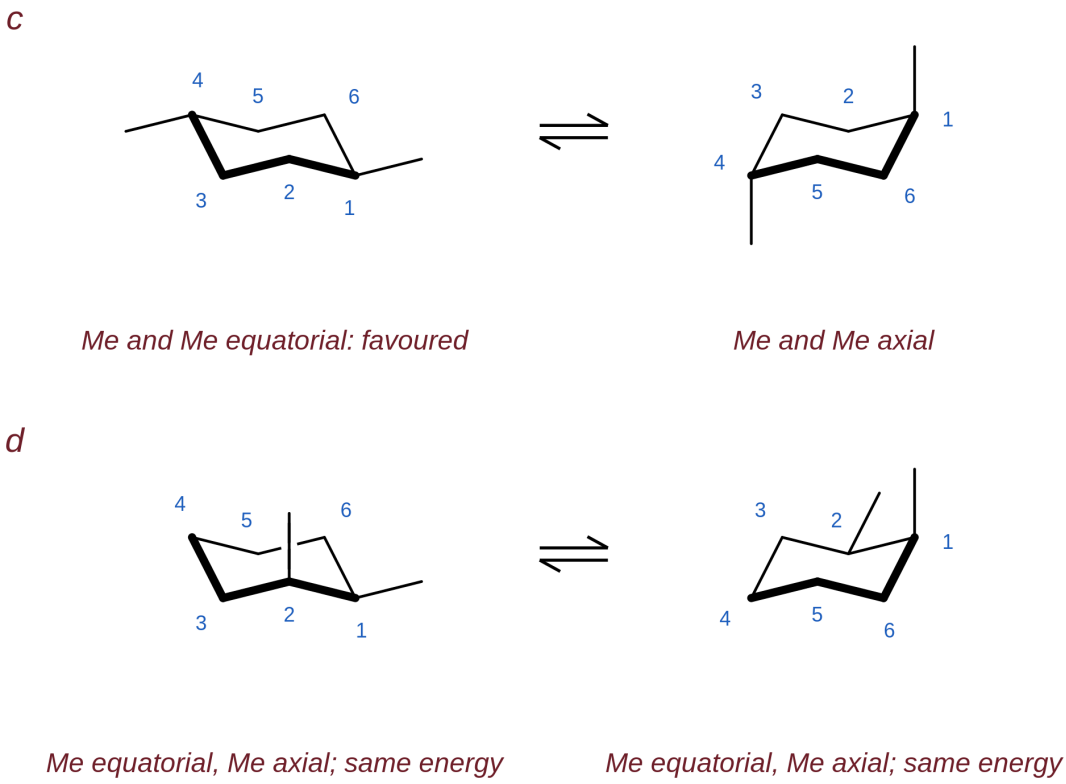


Figure 4.18. The answers to Exercise 4.3 (c) and (d).

(a) Cl is up on C1, CH_3 is down on C3. Groups on C1 and C3 that are on opposite faces are 1,3-trans, so in each chair one group is axial and the other equatorial. The chair with CH_3 equatorial and Cl axial wins, because the A-value of CH_3 (about 7 kJ mol^{-1}) is larger than that of Cl (about 2). It is more stable by about 7 − 2 = **5 kJ mol^{-1}**.

(b) tBu and OH are both up, on C1 and C4: 1,4-cis, so again one is axial and one equatorial. The *tert*-butyl group has by far the largest A-value (20 or more), so it takes the equatorial position and the OH goes axial. The favoured chair is more stable by about 20 − 4 = **16 kJ mol^{-1}** or more. The other chair is so unfavourable that for practical purposes the molecule exists in the first one only.

(c) The two methyls are on opposite faces on C1 and C4: 1,4-trans, so both equatorial or both axial. The diequatorial chair has nothing axial at all. The diaxial chair pays twice the A-value of CH_3, about 7 + 7 = **14 kJ mol^{-1}**.

(d) Both methyls are up, on C1 and C2: 1,2-cis, so in each chair one is axial and the other equatorial. Each chair pays the A-value of one methyl, so the two chairs have **the same energy**, and the ring flips back and forth between two chairs that are mirror images of each other. In the left chair of Figure 4.18 the axial methyl on C2 stands in front of the C5–C6 bond; the small gap in that bond says that it is behind.

Exercise 4.4. Figure 4.19 shows both chairs.

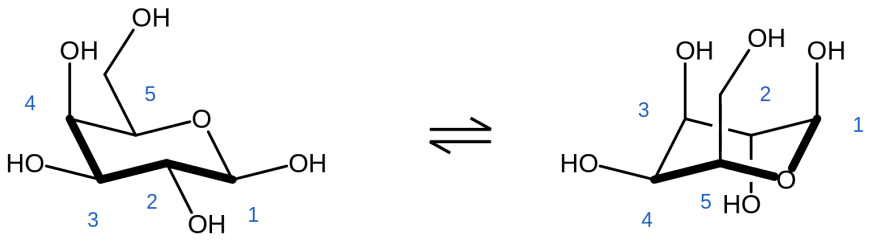


Figure 4.19. The answers to Exercise 4.4: both chairs of β-D-galactopyranose.

In the flat ring, the OH groups on C1, C3 and C4 and the CH_2OH on C5 are up and the OH on C2 is down. Put the ring in the chair with the ring oxygen at the back right, as for glucose in Figure 4.8. Then every group is equatorial except the OH on C4: in glucose that one is down, and down on C4 is equatorial; in galactose it is up, and up on C4 is **axial**. So the left chair has **one** axial group, and the right chair, after the flip, has the other **four** axial (the OH groups on C1, C2 and C3 and the CH_2OH) and only the OH on C4 equatorial. The left chair is strongly favoured. The one axial OH on C4 costs it a little (about 4 kJ mol^{-1}, the A-value of OH), which is why galactose is a slightly less comfortable sugar than glucose.

Exercise 4.5.

(a) **cis-Decalin** can flip, **trans-decalin** cannot. In *trans*-decalin each ring is attached to the other through two equatorial bonds. A flip would make both of them axial, and two axial bonds on neighbouring carbons point in opposite directions, 180° apart. The chain of four carbons that closes the second ring cannot reach across that, so the ring would not connect. In *cis*-decalin each ring is attached through one axial and one equatorial bond, and a flip turns that into one equatorial and one axial: another chair–chair shape just as good as the first.

(b) **trans-Decalin** is the more stable one, by roughly 11 kJ mol^{-1}.

(c) Because both rings sit on each other through equatorial bonds, nothing is axial across the ring fusion. In *cis*-decalin one bond of each ring is axial on the other ring, so there is always a clash with axial hydrogens, in either chair–chair shape.

CHAPTER 5

Stereochemistry

In Chapter 4 a molecule changed shape by turning around its single bonds, and every shape could turn into every other without breaking anything. This chapter is about the shapes that cannot. Two molecules can have the same atoms connected in the same order and still be different molecules, because the groups sit differently in space and no amount of turning will make one into the other. That sounds like a subtlety, but it is often the difference between a medicine that works and one that does nothing, or something worse.

The chapter takes four steps. Section 5.1: when are two molecules mirror images that do not overlap? Sections 5.2 to 5.4: how do you give them different names? Section 5.5: when does one turn into the other by itself? Sections 5.6 and 5.7: what changes when there are several such centres, or a double bond? You need the tetrahedral carbon of Chapter 2, the numbering habits of Chapter 3 and the cis and trans of Chapter 4.

5.1 Mirror images

Look at the top row of Figure 5.1. Carbon C2 carries four different things: a hydroxyl group, a nitrile, an ethyl group and a hydrogen. Draw the molecule, draw its reflection in a mirror, and try to put one on top of the other. It can't be done, however you turn them, so they are two different molecules. They are **enantiomers**, and a carbon like C2 is a **stereocentre** (also called a chiral centre or stereogenic centre): a centre where swapping two groups gives a different molecule. A molecule that cannot be laid on top of its own mirror image is **chiral**, from the Greek word for hand. Your hands are the proof: identical in every way, and nobody has ever managed to put a left glove on a right hand.

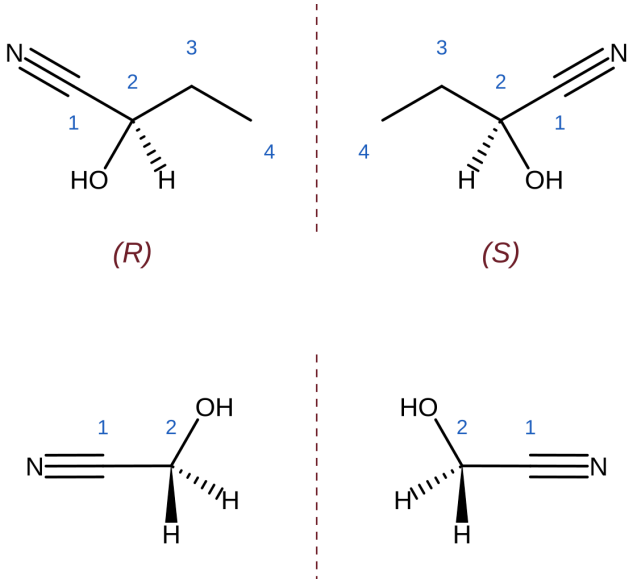


Figure 5.1. The dashed line is the mirror. Top: C2 carries four different groups, so the two sides are different molecules (enantiomers). Bottom: C2 carries two hydrogens; turn the right-hand molecule around and it lies exactly on the left-hand one, so there is only one molecule. The labels (R) and (S) in the top row are explained in Section 5.2; for now they only say that the two molecules are different.

The bottom row of the figure shows what happens when you take the ethyl group away. C2 now carries two hydrogens, the mirror image is the same molecule, and there is nothing to separate. **A stereocentre needs four different groups.** Three different groups and one repeated is not enough.

A single stereocentre makes a molecule chiral. With several stereocentres it depends, and we come back to that in Section 5.6.

Two enantiomers have identical physical properties: the same melting point, boiling point, solubility, everything except how they rotate polarised light. What tells them apart is a *chiral environment*, something that is itself handed, such as another chiral molecule. Your body is full of those: it is built from only one of the two mirror-image forms of each chiral amino acid, so it treats the two enantiomers of a molecule as two different substances. That is why a medicine can work as one enantiomer while its mirror image does nothing, or something nasty. Your nose works the same way. The two mirror images in Figure 5.2 differ in nothing but their handedness, and one smells of spearmint, the other of caraway.

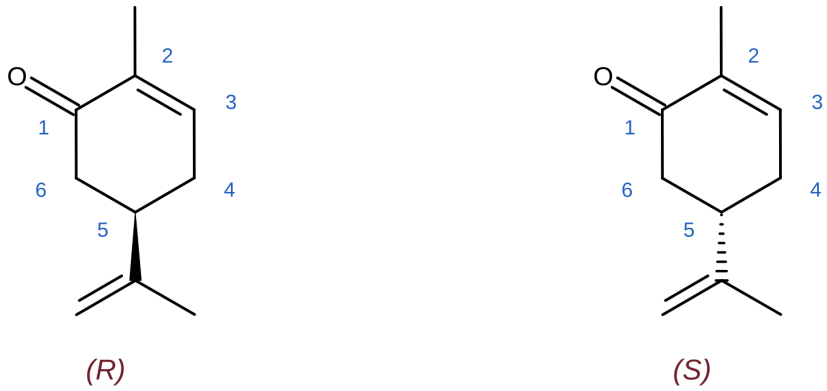


Figure 5.2. The two enantiomers of carvone. The left-hand one, (R), smells of spearmint; the right-hand one, (S), smells of caraway. The ring carbons are numbered C1 to C6; the stereocentre is C5.

A 50:50 mixture of an enantiomer and its mirror image is called a **racemate** (a racemic mixture). A racemate is not a third kind of molecule, it is just a mixture with no net preference for either hand. When the two are not 50:50 the sample has an **enantiomeric excess**, *ee*, which says how far it is from a racemate:

$$ee = \frac{|n_R - n_S|}{n_R + n_S} \times 100\,\%$$

A sample of 80 % of one enantiomer and 20 % of the other has an ee of 80 − 20 = 60 %.

Chemists measure the difference with light. A chiral compound is **optically active**: it rotates the plane of polarised light, and its mirror image rotates it by exactly the same angle in the opposite direction. A clockwise rotation is written + and an anticlockwise one −; the sign has to be measured, and it has nothing to do with R and S (Section 5.2). The **specific rotation** takes out how much sample you used:

$$[\alpha]^{T}_{\mathrm{D}} = \frac{\alpha}{c \cdot l}$$

Here α is the measured rotation in degrees, c the concentration in g mL⁻¹, l the path length in dm, T the temperature and D the sodium D line (589 nm) the light comes from. You will rarely need the formula itself. What matters is that a racemate does not rotate at all (the two rotations cancel), and that the rotation of a mixture is proportional to its ee, so at the same concentration and path length

$$ee = \frac{\alpha_{\text{mixture}}}{\alpha_{\text{pure enantiomer}}}$$

Example 5.1. The pure (R)-enantiomer of a compound rotates polarised light by −23.1°. A mixture of its two enantiomers, measured under the same conditions, rotates it by −8.2°. What fraction of the molecules is (S)?

The rotation of the mixture is 8.2 / 23.1 = 0.355 of that of the pure enantiomer, so the ee is 35.5 %. The excess is (R), because the mixture rotates in the same direction as pure (R). An excess of 0.355 means that the fraction of (R) is (1 + 0.355) / 2 = 67.7 % and the fraction of (S) is (1 − 0.355) / 2 = 32.3 %. Check: together they make 100 %, and their difference is 35.5 %, the ee. So **32.3 % of the molecules are (S)**.

5.2 R and S: the CIP rules

Two enantiomers need two names, and "left" and "right" will not do for a molecule you cannot hold. The names come from a recipe by Cahn, Ingold and Prelog, the **CIP rules**: give the four groups on a stereocentre a priority from 1 (highest) to 4 (lowest), look at the centre with group 4 pointing away from you, and read 1 → 2 → 3. Clockwise is **R** (*rectus*, right), anticlockwise is **S** (*sinister*, left). Figure 5.3 shows both for a carbon that carries Br, Cl, F and H.



Figure 5.3. The recipe. The burgundy circled digits are the priorities (Br 1, Cl 2, F 3, H 4). H is on the hash, so it points away from you and you read 1 → 2 → 3 as drawn: clockwise (R) on the left, anticlockwise (S) on the right. The right-hand molecule is the mirror image of the left-hand one.

Three steps give the label: rank the four groups, turn the molecule so that group 4 points away from you, and follow 1 → 2 → 3. The work is in the first step, and these are the rules for it.

Key result. The CIP rules.

1. Look at the four atoms directly attached to the stereocentre. The higher the atomic number, the higher the priority (I > Br > Cl > S > P > F > O > N > C > H).
2. A tie is settled by going outward. Compare the sets of atoms one step further out, highest atom first (so (O, C, H) beats (C, C, C), because O beats C at the first position). Still tied? Go another step out along the highest-ranked branches first.
3. A double bond counts twice: the atom at the other end is copied onto each of the two atoms, and a triple bond counts three times. These copies carry no substituents of their own.
4. If all else is equal, the heavier isotope wins (D > H).

What if group 4 is not at the back? Looking at the centre from the opposite side reverses the direction, so if group 4 points at you (on a wedge), read the direction you see and flip the answer. A related fact worth knowing: swapping any two groups on a stereocentre turns R into S and the other way round.

Watch out. R and S are names given by the rules above. They do not tell you the sign of the optical rotation (+ or −), which has to be measured, and they are not the same thing as D and L. Changing one group can also change the label without changing the shape at all, because the label depends on the priorities and not only on where the groups sit.

Example 5.2. Assign R or S to the stereocentre C2 of the molecule in Figure 5.4.

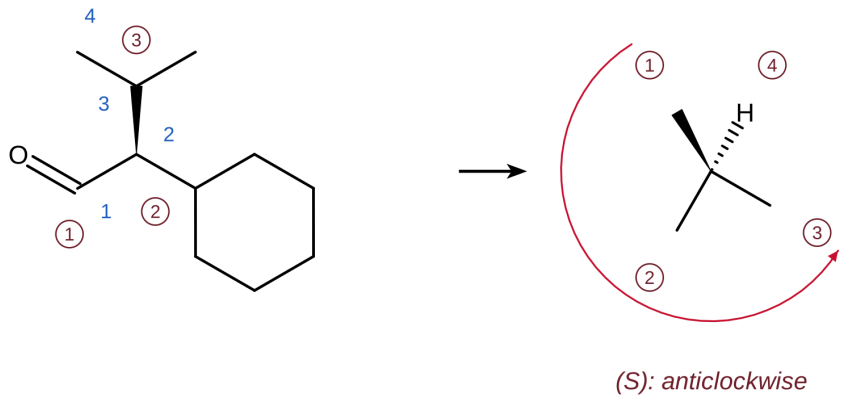


Figure 5.4. Left: the molecule, carbons numbered in blue, the CIP priorities as burgundy circled digits. Right: the same centre as a template, hydrogen on the hash. The isopropyl group is on the wedge, so the hydrogen that is not drawn points away from you.

Priorities. C2 carries the aldehyde carbon C1, the carbon of the cyclohexyl ring, the isopropyl carbon C3 and a hydrogen. The hydrogen is lowest, 4. C1 carries (O, O, H), because the C=O is counted twice, so it is 1. The ring carbon and C3 both carry (C, C, H): a tie, so go one

step further out. The two ring carbons next to the attachment point each carry (C, H, H); the two methyl groups of the isopropyl each carry (H, H, H). The ring wins: cyclohexyl is 2 and isopropyl is 3.

Direction. The hydrogen is not drawn, but the isopropyl bond is on a wedge and the other two bonds lie in the plane, so the hydrogen must point away from you. That is the template on the right. 1 → 2 → 3 runs anticlockwise, so the centre is **(S)**.

Example 5.3. Assign R or S to both stereocentres C2 and C3 of the molecule in Figure 5.5.

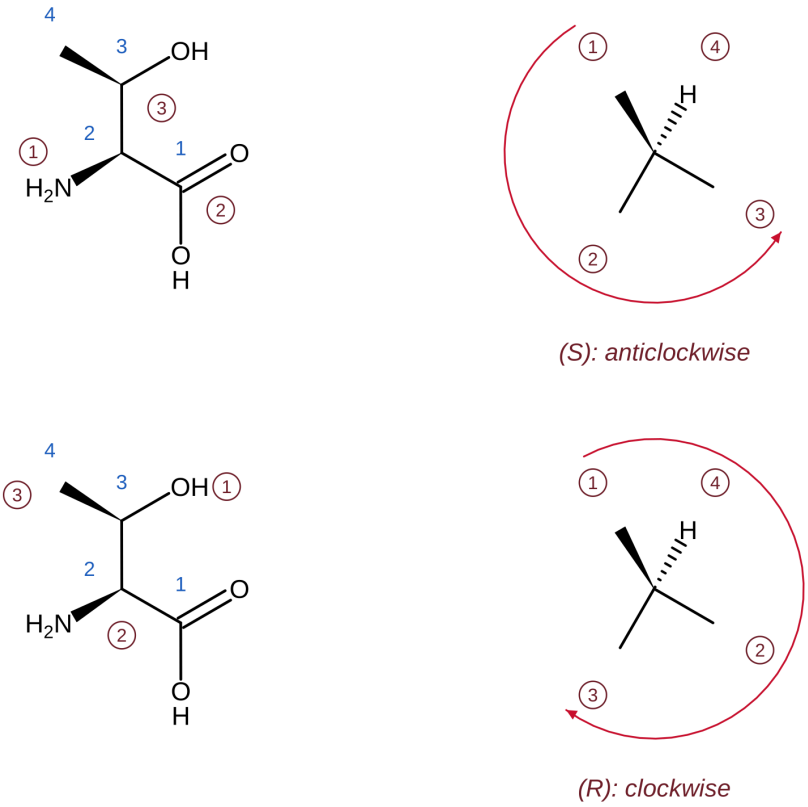


Figure 5.5. Top: the priorities at C2 and the template, anticlockwise. Bottom: the priorities at C3 and the template, clockwise. Burgundy circled digits are CIP priorities, blue digits number the carbons. This is the natural form, L-threonine.

Take the centres one at a time, and ignore the other one while you do.

C2. The nitrogen is 1 (N beats C). The carboxyl carbon carries (O, O, O) and C3 carries (O, C, H); they tie at the first atom and the carboxyl wins at the second, so the carboxyl is 2 and C3 is 3. The hydrogen is 4. The template reads anticlockwise: **(S)**.

C3. The oxygen is 1, C2 with (N, C, H) is 2, the methyl group with (H, H, H) is 3 and the hydrogen is 4. The template reads clockwise: **(R)**.

The molecule is (2S,3R), which is the name of the natural amino acid L-threonine.

Example 5.4. Assign R or S to the stereocentre of the molecule in Figure 5.6. Here the lowest priority is not a hydrogen.

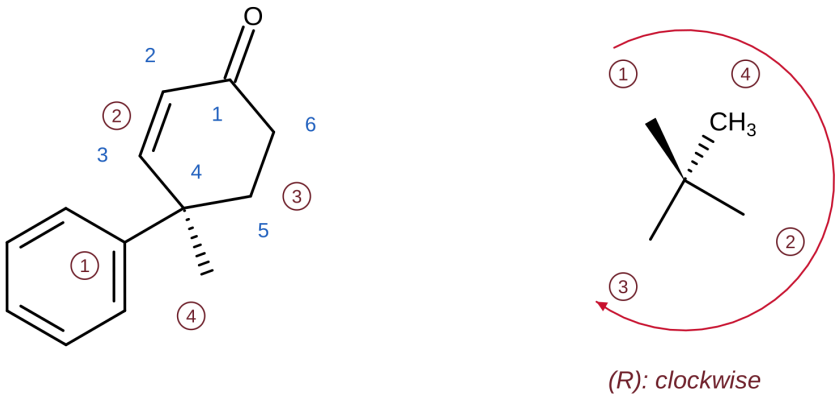


Figure 5.6. (R)-4-Methyl-4-phenylcyclohex-2-en-1-one. Ring carbons C1 to C6 numbered in blue, priorities as burgundy circled digits. The methyl group is on the hash, so it points away and the template is read directly.

C4 has no hydrogen. Its four neighbours are the phenyl carbon, the ring carbon C3 of the C=C, the ring carbon C5 and the methyl group. The phenyl carbon carries (C, C, C), the best of the set, so it is 1. C3 is next: it is double-bonded to C2, so it carries (C, C, H) with the duplicate. C5 carries (C, H, H), the methyl group (H, H, H). The order is phenyl 1, C3 2, C5 3, methyl 4. The methyl group is the lowest priority and already on the hash, so the template is read as it is: clockwise, **(R)**.

Example 5.5. Assign R or S to the stereocentres C1 and C2 of the cyclopropane in Figure 5.7.

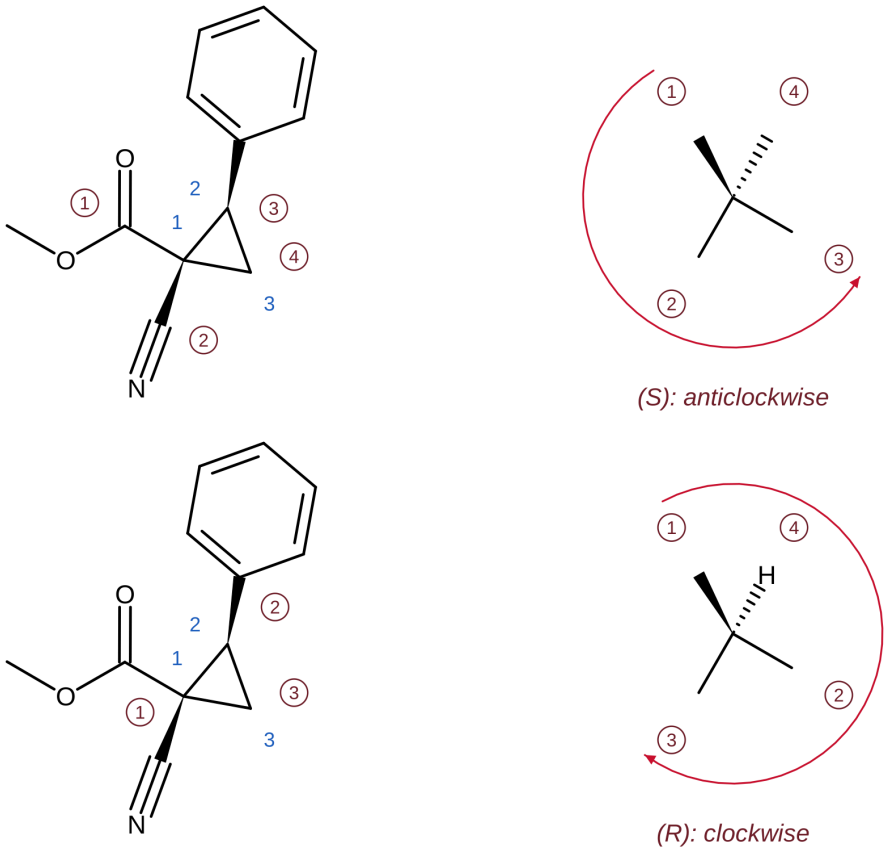


Figure 5.7. Methyl (1S,2R)-1-cyano-2-phenylcyclopropane-1-carboxylate. Top: the priorities at C1 and the template, anticlockwise. Bottom: the priorities at C2 and the template, clockwise. Blue digits number the ring carbons, burgundy circled digits are CIP priorities.

At C1 there are no hydrogens. The ester carbon with (O, O, O) beats the nitrile carbon with (N, N, N), so the ester is 1 and the nitrile 2. Of the two ring carbons, C2 carries (C, C, H) and C3 carries (C, H, H), so C2 is 3 and C3 is 4. Turn the centre so that the lowest priority, C3, points away (the template), and 1 → 2 → 3 reads anticlockwise: **(S)**. At C2 the hydrogen is 4. C1 and the phenyl carbon both carry (C, C, C), a tie, so compare the branches one step further out, best branch first. The best branch of C1 is the ester carbon with (O, O, O); the best branch of the phenyl ring is an ortho carbon with (C, C, H). Oxygen beats carbon at the first position, so C1 wins: C1 is 1, phenyl is 2, C3 is 3. The template reads clockwise: **(R)**.

5.3 The Fischer projection

Wedges and hashes are fine for one or two stereocentres. For a chain of them, chemists (and above all sugar chemists) use a shorthand from the 19th century that is still going strong: the **Fischer projection**. It is a cross. The carbon chain runs vertically with the most oxidised carbon at the top, and the stereocentre sits at the crossing. The rule that makes it work: **horizontal bonds point towards you, vertical bonds point away from you.** Figure 5.8 shows the translation in three steps.

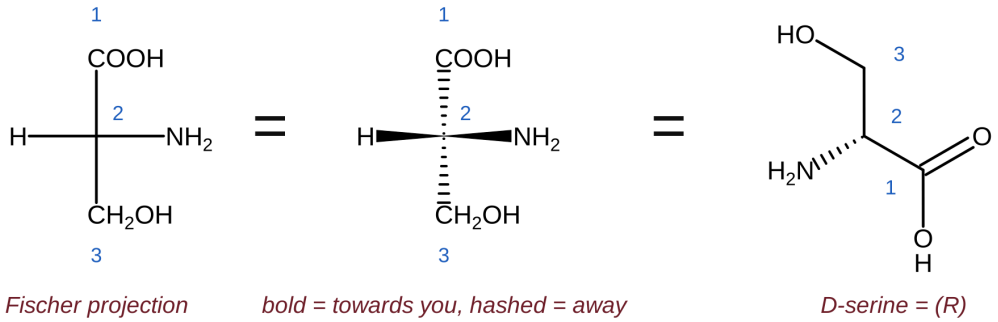


Figure 5.8. Left: the Fischer projection. Middle: the same molecule with the rule written into the bonds: bold means towards you, hashed means away. Right: the same molecule as a normal line drawing, D-serine. The carbons C1 to C3 are numbered in blue.

Reading R or S from a Fischer projection tests everything so far. The priorities are NH_2 1, COOH 2, CH_2OH 3 and H 4. The hydrogen sits on a horizontal bond, so it points towards you: the wrong way round for reading, which means you read the direction you see and flip the answer. Going from 1 (right) to 2 (top) to 3 (bottom) you see anticlockwise. Flipped, that is **(R)**. This is D-serine, with its NH_2 on the right. Its mirror image, with the NH_2 on the left, is the natural L-serine, (S).

Two moves leave the molecule unchanged.

- Turn the whole projection by 180° in the plane of the paper. Nothing changes.
- Swap two groups twice (any even number of swaps): you get the original back. A single swap gives the mirror image (R becomes S).

> **Watch out.** Turning a Fischer projection by 90° changes which bonds point towards you and which away, so it gives you the *enantiomer*, not the same molecule. Never turn it by 90°, and never lift it off the paper.

5.4 A chiral molecule without a stereocentre

A stereocentre is not the only way to make a molecule chiral. What matters is whether the molecule can be placed on its mirror image, and a molecule without a single stereocentre can still fail that test. The classic case is the **allene**, a chain with two double bonds that share a carbon, C=C=C. The central carbon is sp-hybridised, so the three carbons lie on a straight line, and its two π bonds are perpendicular to each other. The result is that the groups on C2 lie in one plane and the groups on C4 in the plane at right angles to it.



Figure 5.9. The two enantiomers of an allene, C1 to C5 numbered in blue. The groups on C2 (CH_3 and H) are in the plane of the paper; the groups on C4 are one in front, one behind. Each end carries two different groups, so the molecule has axial chirality: left (Sa), right (Ra).

If either end of the allene carried two identical groups, the molecule would have a mirror plane and there would be no enantiomers. With two different groups at each end, as in Figure 5.9, there are two. The molecule has an *axis* of chirality, the C=C=C line, instead of a centre. The label is assigned like this: look along the axis, from either end. The two groups on the near carbon are ranked 1 and 2 (by the usual CIP rules), and both outrank the two groups on the far carbon, which are 3 and 4. Follow 1 → 2 → 3: clockwise is **Ra**, anticlockwise is **Sa**. The small *a* says that the chirality is axial. A third kind, planar chirality, appears in some ring systems where part of the molecule is held on one side of a flat unit; you will meet it far less often than the other two.

5.5 Does the stereocentre stay put? Nitrogen, sulfur and carbon

A nitrogen with three different groups looks like a stereocentre: three groups and a lone pair make four different things around a pyramid. Yet amines are not sold as separate enantiomers, and the reason is that the pyramid does not stay put. The nitrogen flips through the plane of its three substituents, like an umbrella in the wind, and comes out on the other side as the mirror image. This is **nitrogen inversion**. In the middle of the flip the nitrogen is flat and sp^2-hybridised, with the lone pair in a p orbital, and that flat arrangement is the transition state (Figure 5.10).

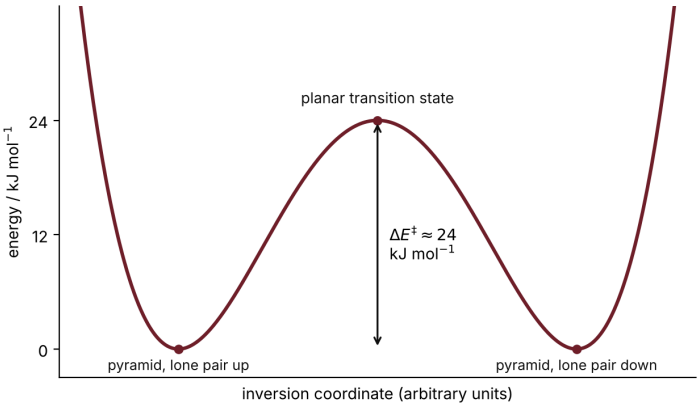


Figure 5.10. Energy during nitrogen inversion. The two minima are the two pyramids, which are mirror images of each other; the maximum is the planar transition state, about 24 kJ mol⁻¹ higher, the barrier of an amine of the ammonia type.

A barrier of about 24 kJ mol⁻¹ is nothing. At room temperature the molecule has enough thermal energy to cross it a few hundred million times per second, so the two enantiomers of a simple amine interconvert faster than anyone can separate them, and the sample behaves as a racemate. A rough rule: a barrier below roughly 100 kJ mol⁻¹ means that you cannot isolate the two forms at room temperature. For a nitrogen that is locked in a ring junction and cannot flatten, the story changes, and it can be a stable stereocentre.

Sulfur is different. A sulfoxide has sulfur with three substituents (the oxygen and two carbon groups) and a lone pair, which is the same picture as the amine. The S=O bond is better written S⁺–O⁻, but whichever way you draw it the sulfur is pyramidal with a lone pair. Its inversion barrier is not 24 kJ mol⁻¹ but around 150 kJ mol⁻¹ or more, and so the sulfur is a perfectly good stereocentre that does not racemise at room temperature. In the CIP rules the lone pair counts as the lowest priority, 4, like a hydrogen. In Figure 5.11 the oxygen is 1, the phenyl carbon 2, the methyl carbon 3, and the lone pair, 4, points towards you in the left-hand drawing, where the methyl is on the hash, so you read the direction you see and flip it; in the right-hand drawing the methyl is on the wedge, so the lone pair points away and you read the direction as drawn.

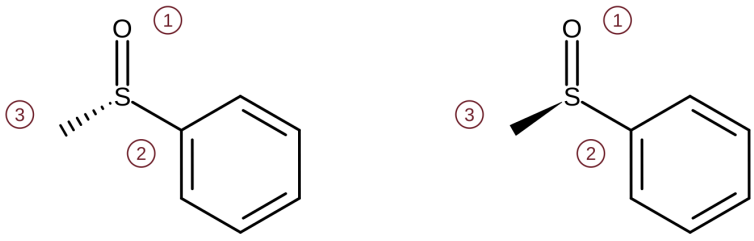


Figure 5.11. The two enantiomers of a sulfoxide. Burgundy circled digits are the CIP priorities; the lone pair on sulfur is the lowest priority, 4. Left (S), right (R).

A carbon does not invert at all. It has four bonds and no lone pair; to flip it would have to pass through a flat four-bonded carbon, which costs far more energy than the C–C bond is worth, so the molecule falls apart long before. A tetrahedral stereocentre stays as it is until a bond actually breaks.

The nitrogen of an imine, C=N, behaves differently from an amine. It is sp^2 with its lone pair in the plane, and to invert it would have to pass through a linear, sp-hybridised arrangement, which costs far more than the flat state of an amine. At room temperature the groups on a C=N therefore usually stay on their side, and, just as on a C=C, the two arrangements can be told apart as E and Z. That is the subject of Section 5.7.

Centre	Pathway	Barrier	Consequence
N in an amine	flat sp^2 transition state	about 24 kJ mol^{-1}	inverts fast, racemic at room temperature
S in a sulfoxide	flat transition state	about 150 kJ mol^{-1} or more	stable stereocentre
sp^3 carbon	none without breaking a bond	not applicable	stable stereocentre

5.6 More than one stereocentre

Every stereocentre can be set in two ways, so a molecule with n stereocentres has at most 2^n stereoisomers. One centre gives two, two centres give four, three give eight. The word *at most* is there for a reason, and Figure 5.12 shows it.

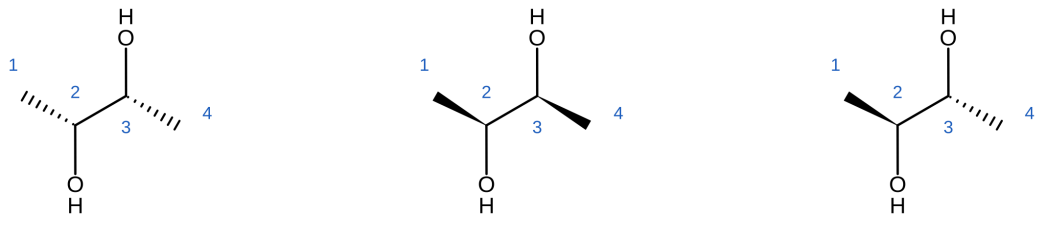


Figure 5.12. The stereoisomers of a chain of four carbons with an OH on C2 and on C3, carbons numbered C1 to C4 in blue. Left and middle: (2R,3R) and (2S,3S), mirror images of each other. Right: (2S,3R), which is its own mirror image: a meso compound.

Two stereocentres should give four isomers, but this molecule has three. The left and middle drawings are mirror images of each other, a pair of enantiomers. The right-hand drawing has an R at one centre and an S at the other, and the two halves of the molecule are exact mirror images of each other, so the whole molecule is its own mirror image. A molecule like that is **meso**. It has two stereocentres and is not chiral, and it does not rotate polarised light. (2R,3S) would be the mirror image of (2S,3R), but they are the same molecule, which is why the

fourth isomer is missing. A meso compound is always a symmetrical molecule, and the quickest test is to look for the mirror plane, or to draw the mirror image and see if you can turn it into the original.

The meso compound is related to the other two in a different way from how they are related to each other. Two stereoisomers that are mirror images of each other are **enantiomers**. Two stereoisomers that are *not* mirror images of each other are **diastereomers**. The meso compound is a diastereomer of both the (2R,3R) and the (2S,3S) form. This difference matters in the lab: enantiomers have identical physical properties, but diastereomers have different melting points, boiling points and solubilities, so they can be separated by ordinary methods such as crystallisation and chromatography.

> **Key result.** Stereoisomers are either enantiomers (mirror images: every centre inverted) or diastereomers (not mirror images: at least one centre the same and at least one different). With n stereocentres there are at most 2^n stereoisomers; symmetry, as in a meso compound, reduces the number.

A ring behaves in the same way, with one extra twist: the groups on the ring can be on the same face (cis) or on opposite faces (trans), the cis and trans of Chapter 4.

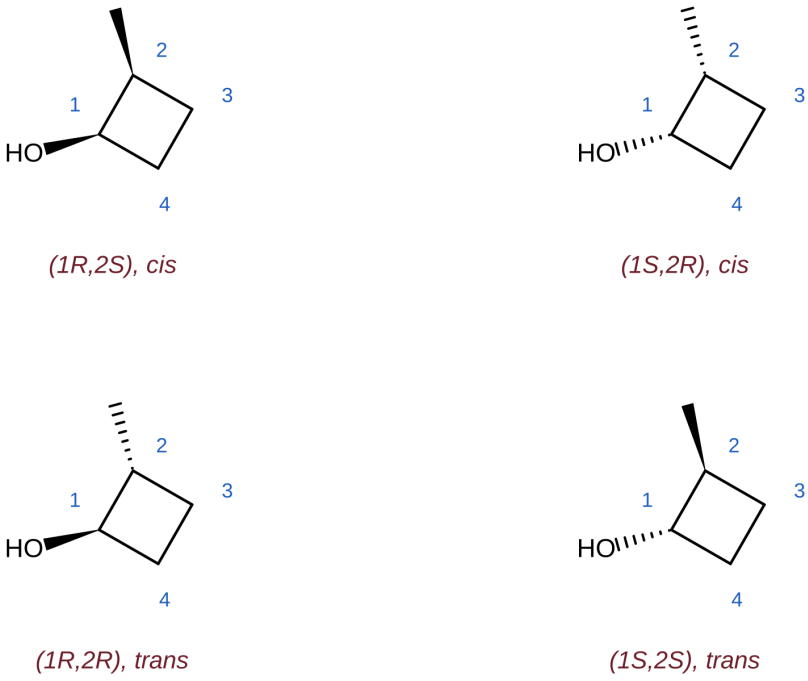


Figure 5.13. The four stereoisomers of a four-membered ring with an OH on C1 and a methyl group on C2, ring carbons numbered C1 to C4 in blue. Top row: the two cis isomers, which are mirror images of each other. Bottom row: the two trans isomers, also mirror images of each other.

Both ring carbons C1 and C2 are stereocentres and this time there is no symmetry, so all $2^2 = 4$ isomers exist. They fall into two pairs of enantiomers: the cis pair on top, the trans pair below. Each cis isomer is a diastereomer of each trans isomer. Notice that cis and trans do not translate into R and S in a simple way. Here cis is (1R,2S) or (1S,2R) and trans is (1R,2R) or (1S,2S), but that comes from the priorities in this particular molecule; with other groups it can be the other way round. You have to work it out each time.

5.7 E and Z

There is one more kind of stereoisomerism, and it is the oldest one you know: around a double bond. The atoms on a C=C cannot turn around it, because that would break the π bond, so two groups can be on the same side or on opposite sides of it. In Chapter 4 these were cis and trans, which works well as long as each carbon has one obvious group. With several different groups it does not, and again the CIP rules help. At each end of the double bond, rank the two groups, 1 and 2, with the rules of Section 5.2. If the two number 1 groups are on the **same** side, the double bond is **Z** (German *zusammen*, together); if they are on **opposite** sides, it is **E** (*entgegen*, opposite).

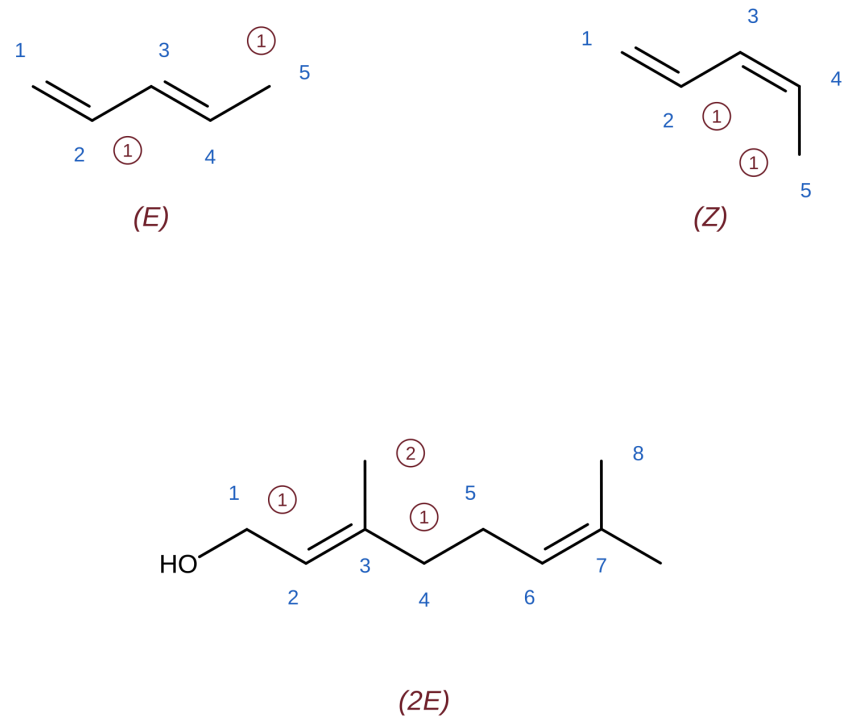


Figure 5.14. Top: the two stereoisomers around the C3=C4 bond of a five-carbon chain, carbons C1 to C5 numbered in blue. The priority-1 groups (burgundy circled digits) are C2 and C5. They are on opposite sides in the left-hand isomer (E) and on the same side in the right-hand one (Z). Bottom: a molecule with two double bonds, carbons C1 to C8, of which only one can be E or Z.

The top of the figure applies the rule. At C3 the groups are the carbon C2 and a hydrogen, so C2 is 1. At C4 they are the carbon C5 and a hydrogen, so C5 is 1. In the left isomer C2 and C5 are on opposite sides: E. In the right one they are on the same side: Z. The terminal double bond C1=C2 has two hydrogens on C1, so it has no E and Z form at all. A double bond needs two different groups on *each* of its carbons.

The bottom of the figure has two double bonds. At C2=C3, C2 carries C1 and a hydrogen, so C1 is 1. C3 carries the methyl group and C4; C4 has (C, H, H) and the methyl has (H, H, H), so C4 is 1 and the methyl is 2. C1 and C4 are on opposite sides: **2E**. The other double bond, C6=C7, has two methyl groups on C7, which cannot be told apart, so it has no E or Z: only the first double bond gets a label.

E and Z isomers are not mirror images of each other, so they are diastereomers with different physical properties, and the same goes for cis and trans on a ring. Whatever the origin of the stereoisomerism (a centre, an axis, a ring, a double bond), the question to ask first is the same: are the two molecules mirror images of each other or not?

Exercises

Exercise 5.1. Figure 5.15 shows six molecules. Which of them have a stereocentre? Mark every stereocentre, and for the molecules without one say why there is none.

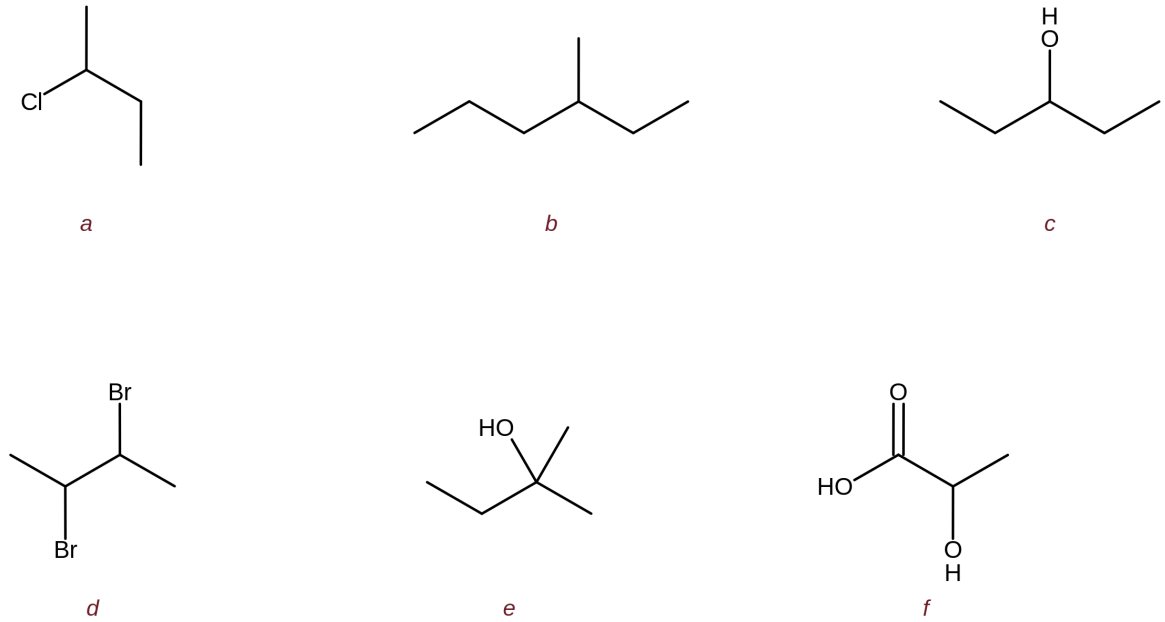


Figure 5.15. The six molecules of Exercise 5.1.

Exercise 5.2. Figure 5.16 shows four stereocentres, each on a wedge drawing with the carbons numbered in blue. Assign R or S to each, with the CIP rules of Section 5.2. The lowest priority is not drawn in any of the four; it is the hydrogen.

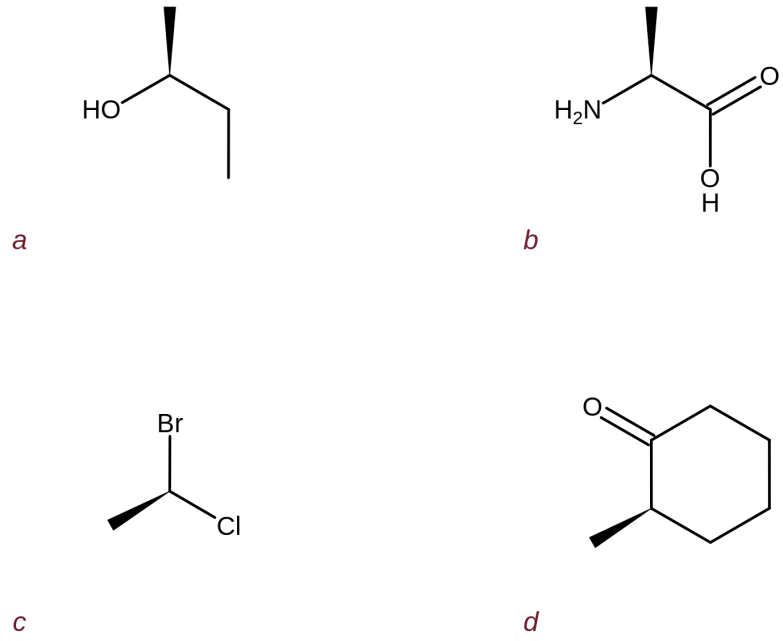


Figure 5.16. The four stereocentres of Exercise 5.2. Carbons are numbered in blue.

Exercise 5.3. Figure 5.17 shows two Fischer projections. Assign R or S to the stereocentre of each, and redraw each one as a normal line drawing with a wedge or a hash.

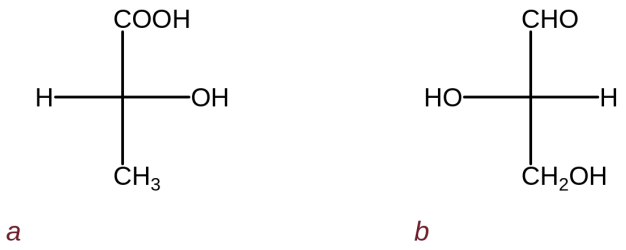


Figure 5.17. The two Fischer projections of Exercise 5.3.

Exercise 5.4. Molecule d of Figure 5.15, 2,3-dibromobutane, has two stereocentres. Draw all its stereoisomers, give each one an R or S at C2 and C3, and say which are enantiomers of each other, which one is meso, and how many stereoisomers there are in total.

Exercise 5.5. Assign E or Z to the double bond of each molecule in Figure 5.18.

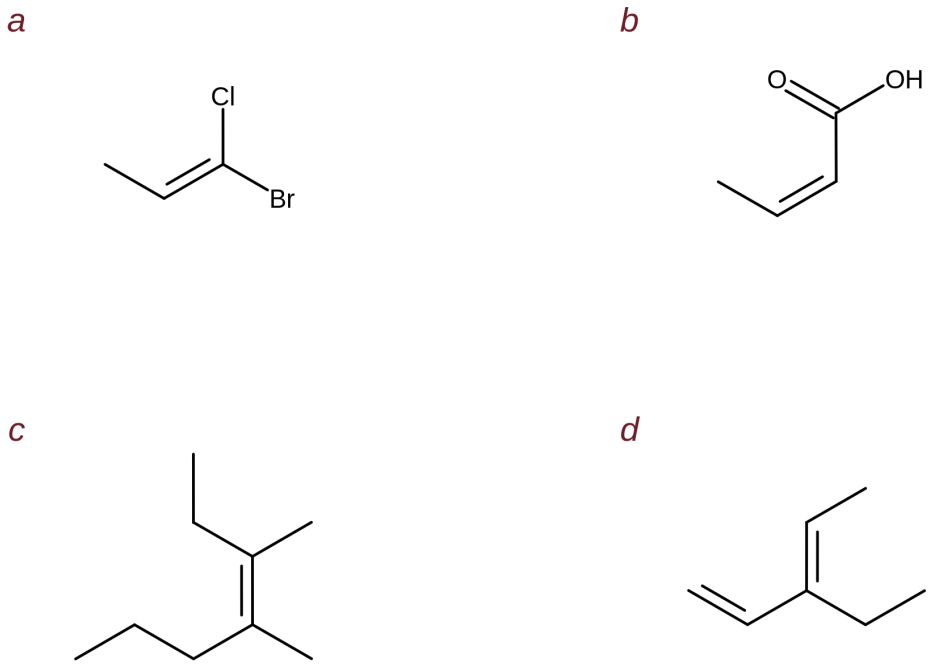
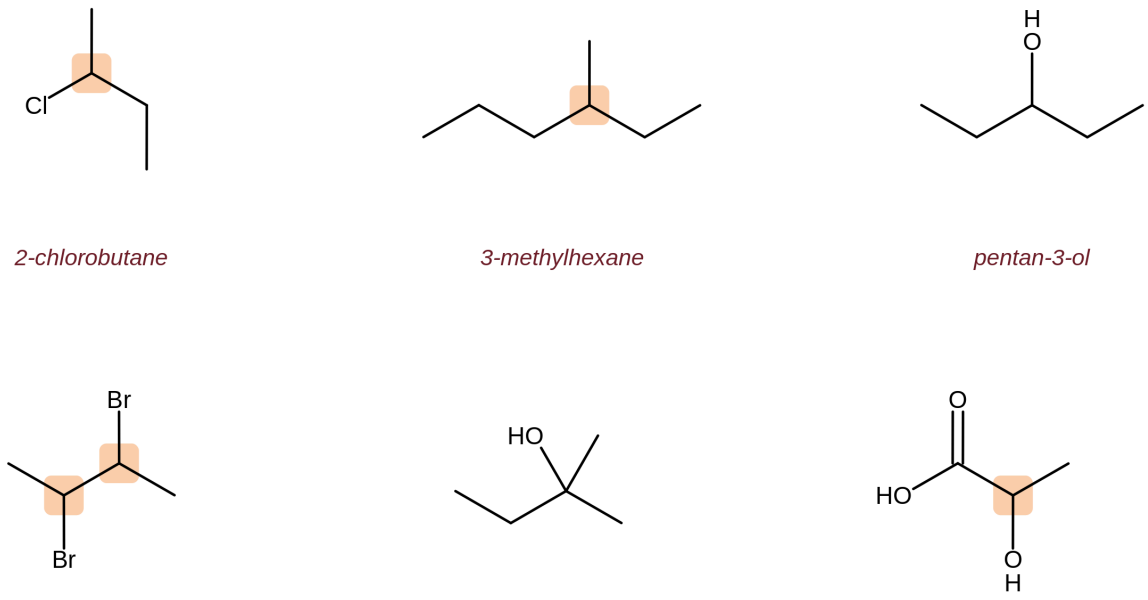


Figure 5.18. The four double bonds of Exercise 5.5.

Exercise 5.6. (a) The pure (R)-enantiomer of a compound has a specific rotation of +30.0°. A mixture of its two enantiomers, measured under the same conditions, has +12.0°. What is the ee, and what percentage of the molecules is (R)? (b) Figure 5.10 shows nitrogen inversion in an amine, and Figure 5.11 shows the two enantiomers of a sulfoxide. Why can the enantiomers of a sulfoxide be separated and those of an amine not?

Solutions

Exercise 5.1. A stereocentre needs four different groups (Section 5.1). Figure 5.19 marks the carbons that have them.



2-chlorobutane *3-methylhexane* *pentan-3-ol*

2,3-dibromobutane *2-methylbutan-2-ol* *2-hydroxypropanoic acid*

Figure 5.19. The answers to Exercise 5.1. The stereocentres are highlighted in orange.

(a) C2 carries Cl, H, a methyl group and an ethyl group: four different groups, so **C2 is a stereocentre**. (b) C3 carries H, a methyl group, an ethyl group and a propyl group: **a stereocentre**. (c) The carbon with the OH carries two ethyl groups, which are identical: **no stereocentre**. (d) C2 carries Br, H, a methyl group and the $CHBr–CH_3$ group, and C3 is the same seen from the other end: **two stereocentres**. (e) The carbon with the OH carries two methyl groups: **no stereocentre**. (f) C2 carries OH, H, a methyl group and the carboxyl group: **a stereocentre**.

Exercise 5.2. Figure 5.20 and Figure 5.21 show the priorities as burgundy circled digits, and next to each molecule the same centre as a template with the hydrogen on the hash. In each molecule the methyl group is on the wedge and the other groups are in the plane, so the hydrogen that is not drawn points away from you, which is exactly the template.

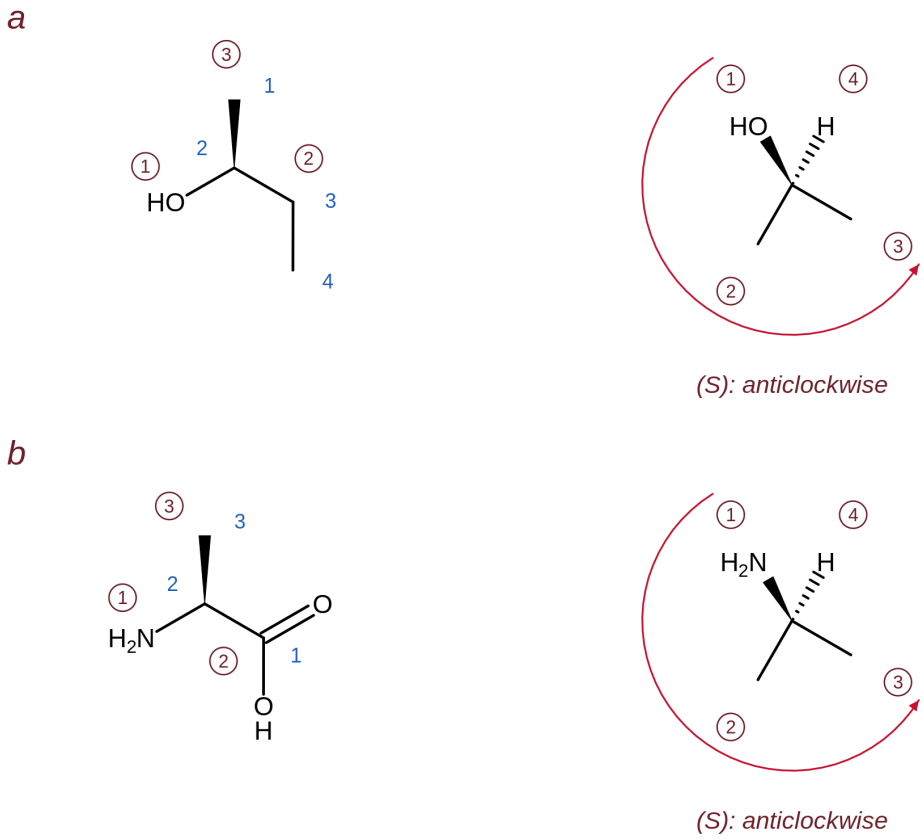


Figure 5.20. The answers to Exercise 5.2 (a) and (b). Carbons numbered in blue, CIP priorities as burgundy circled digits.

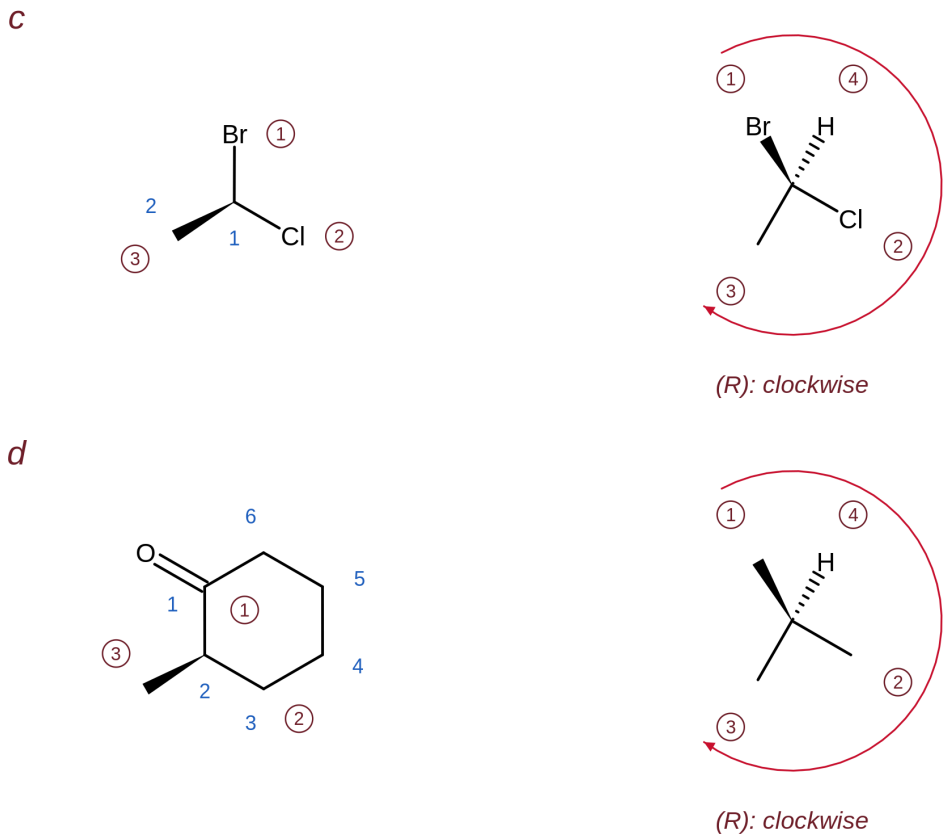


Figure 5.21. The answers to Exercise 5.2 (c) and (d).

(a) At C2 the OH is 1 (O beats C). The ethyl carbon C3 carries (C, H, H) and the methyl group C1 carries (H, H, H), so the ethyl group is 2 and the methyl group 3. The template reads anti-clockwise: **(S)**.

(b) At C2 the nitrogen is 1. The carboxyl carbon C1 carries (O, O, O) and the methyl group C3 carries (H, H, H), so C1 is 2 and C3 is 3. Anticlockwise: **(S)**. This is the natural amino acid L-alanine.

(c) Br is 1 and Cl is 2 (the higher the atomic number, the higher the priority), the methyl group is 3 and H is 4. Clockwise: **(R)**.

(d) At C2 the carbonyl carbon C1 carries (O, O, C) and wins, so it is 1. The ring carbon C3 carries (C, H, H) and is 2, the methyl group (H, H, H) is 3. Clockwise: **(R)**.

Exercise 5.3. In both projections the hydrogen sits on a horizontal bond, so it points towards you. Read the direction you see and flip it (Section 5.3). Figure 5.22 shows the same projections with the rule written into the bonds (horizontal bold, vertical hashed) and as a normal line drawing.

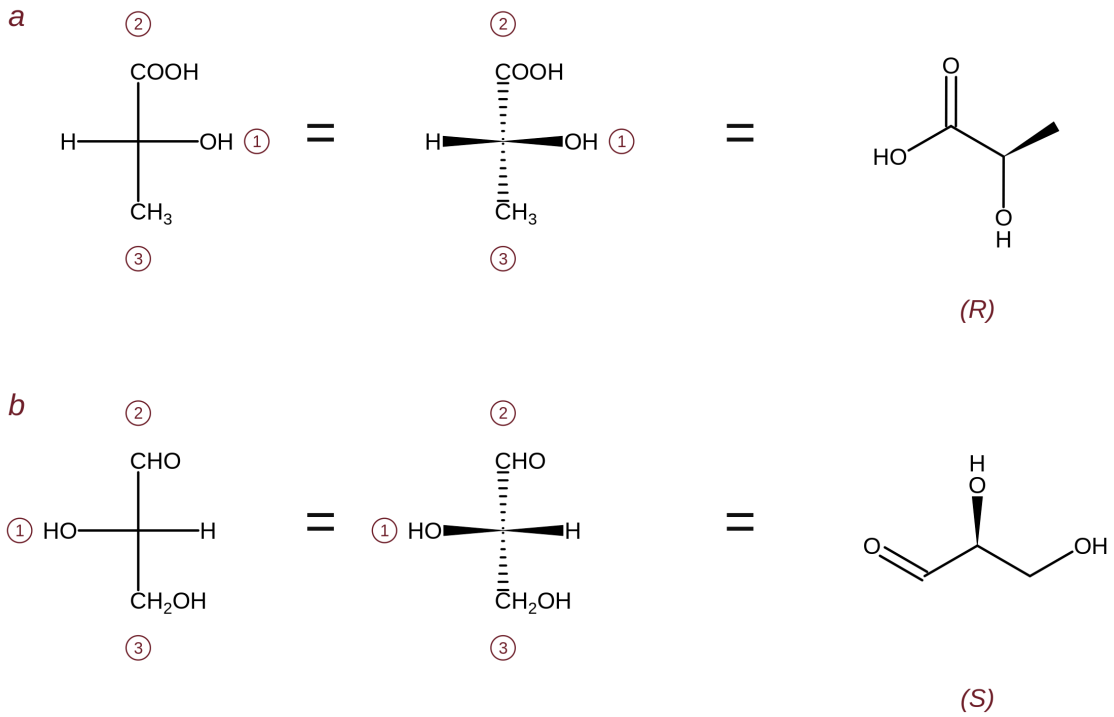


Figure 5.22. The answers to Exercise 5.3. Left: the Fischer projection with the CIP priorities as burgundy circled digits. Middle: the same molecule with the bonds drawn as the Fischer rule demands. Right: the normal line drawing.

(a) The OH on the right is 1, the carboxyl group on top is 2 (it carries (O, O, O)), the methyl group at the bottom is 3, and H is 4. Going from 1 (right) to 2 (top) to 3 (bottom) is anticlockwise as you see it. The hydrogen points towards you, so flip: **(R)**. This is D-lactic acid.

(b) The OH on the left is 1. The aldehyde group on top carries (O, O, H) and the CH_2OH at the bottom carries (O, H, H), so the aldehyde is 2 and the CH_2OH is 3. Going from 1 (left) to 2 (top) to 3 (bottom) is clockwise as you see it; flip: **(S)**. This is L-glyceraldehyde.

Exercise 5.4. There are **three** stereoisomers, not four, and they are shown in Figure 5.23.

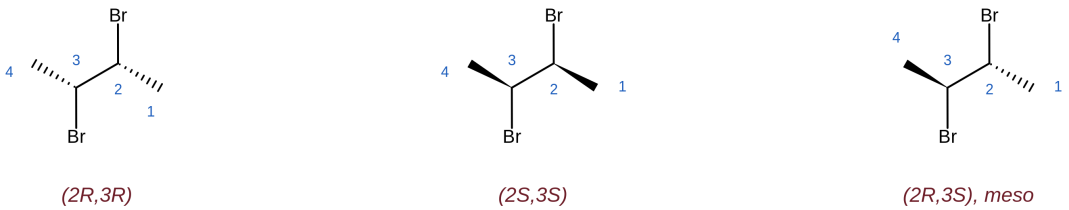


Figure 5.23. The answers to Exercise 5.4. The first two are mirror images of each other; the third is meso. Carbons numbered in blue.

(2R,3R) and (2S,3S) are **enantiomers**: every centre is inverted. The (2R,3S) isomer has an R at one centre and an S at the other, and the two halves of the molecule are mirror images of each other, so the molecule is its own mirror image: it is **meso**. It is a diastereomer of both of the others. The count of two stereocentres, $2^2 = 4$, drops to three because (2R,3S) and (2S,3R) are the same molecule.

Exercise 5.5. Figure 5.24 marks the higher-priority group on each carbon of the double bond with a circled 1. E means that the two marked groups are on opposite sides, Z that they are on the same side.

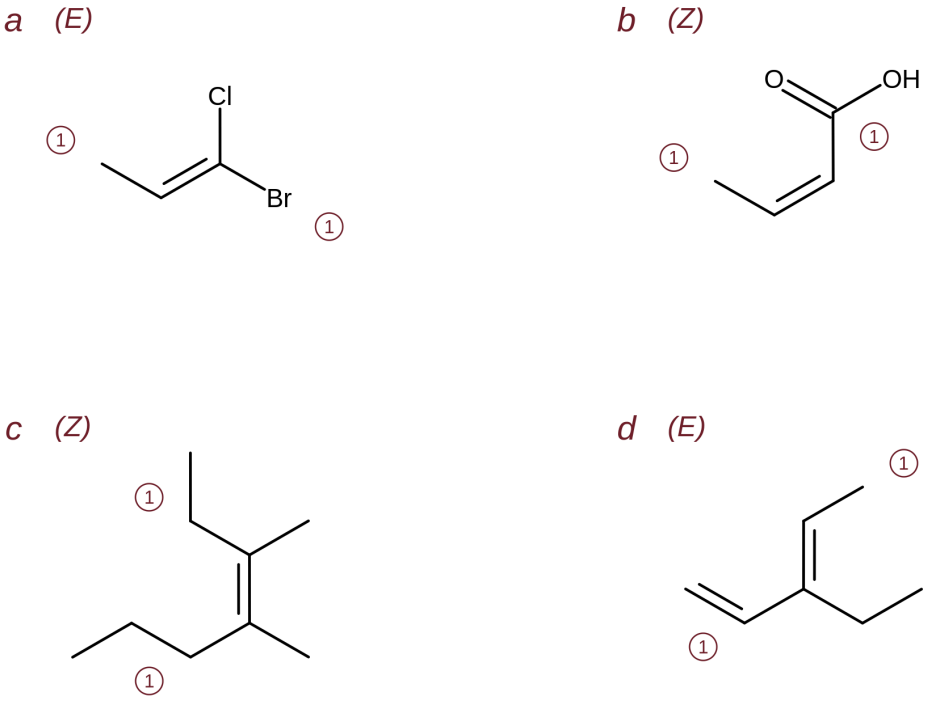


Figure 5.24. The answers to Exercise 5.5. The circled 1 marks the higher-priority group on each carbon of the double bond.

(a) On the carbon with Br and Cl, Br beats Cl, so Br is 1. On the other carbon the methyl group beats the hydrogen. Br and the methyl group are on opposite sides: **E**.

(b) The carboxyl group beats the hydrogen on one carbon and the methyl group beats the hydrogen on the other. Both are on the same side: **Z**.

(c) On one carbon the ethyl group (C, H, H) beats the methyl group (H, H, H). On the other the propyl group beats the methyl group in the same way. The ethyl group and the propyl group are on the same side: **Z**.

(d) On one carbon the methyl group beats the hydrogen. On the other carbon the vinyl group and the ethyl group both start with a carbon, so go one step out: the vinyl carbon carries (C, C, H) because the double bond counts twice, the ethyl carbon only (C, H, H). The vinyl group is 1. It is on the opposite side from the methyl group: **E**.

Exercise 5.6. (a) The rotation of the mixture is 12.0 / 30.0 = 0.40 of that of the pure (R)-enantiomer, so **ee = 40 %**, and the excess is (R) because the rotation has the same sign as the pure (R). The fraction of (R) is (1 + 0.40) / 2 = **70 %** and that of (S) is 30 %. Check: 70 − 30 = 40 %.

(b) The amine inverts through a flat transition state about 24 kJ mol^{-1} above the pyramid, a barrier that room temperature crosses hundreds of millions of times per second, so the two enantiomers turn into each other faster than anyone can separate them. For a sulfoxide the barrier is about 150 kJ mol^{-1} or more, which is crossed so rarely that each enantiomer can be isolated and stored.

CHAPTER 6

Conjugation, resonance and aromaticity

In Chapter 2 every double bond was a private affair between two carbons: one σ bond, one π bond, nothing more. This chapter is about what happens when π bonds and lone pairs start sharing their electrons over more than two atoms. That sharing is called **delocalisation**. It lowers the energy of a molecule, it flattens it, it decides which rings earn the label aromatic (the label Chapter 1 promised to explain), it keeps an amide group rigid, and it decides which light a molecule can swallow.

6.1 Isolated, conjugated and cumulated double bonds

Take a molecule with two C=C double bonds. What matters is how far apart they sit. In an **isolated** diene at least one sp^3 carbon separates them, in a **conjugated** diene exactly one single bond separates them, and in a **cumulated** diene they share a carbon. Repeat the conjugated pattern three times and you have a conjugated triene. Figure 6.1 shows one of each. (The double bond at the start of every chain, C1=C2, is a **terminal** double bond, because it ends in a $=CH_2$ group. One inside the chain, like C3=C4 in the conjugated example, is internal.)

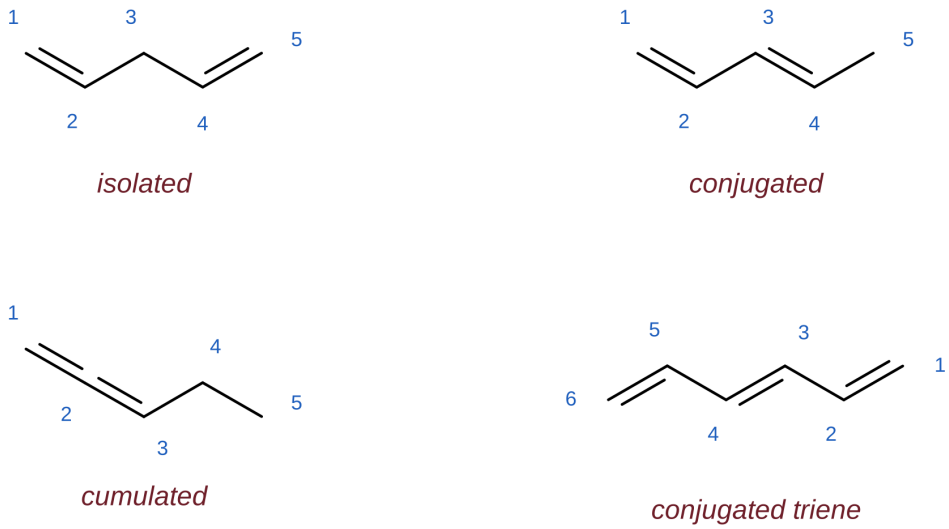


Figure 6.1. Top left: penta-1,4-diene, with the sp^3 carbon C3 between the two double bonds (isolated). Top right: (3E)-penta-1,3-diene, whose double bonds are separated by the single bond C2–C3 (conjugated). Bottom left: penta-1,2-diene, where C2 belongs to both double bonds (cumulated). Bottom right: (3E)-hexa-1,3,5-triene, a conjugated triene. Carbons are numbered in blue.

Which pentadiene is more stable? The conjugated one, and you can measure it. Hydrogenating either isomer gives the same product, pentane, but the isolated isomer releases about 254 kJ mol^{-1} and the conjugated one about 226 kJ mol^{-1}, so the conjugated isomer starts about 28 kJ mol^{-1} lower in energy. Roughly half of that is conjugation itself (the cleaner comparison, a diene with nothing else attached against two separate double bonds, gives about 15 kJ mol^{-1}). The rest comes from the methyl group sitting on a double bond, which helps a little too.

The reason is orbital overlap. Every sp^2 carbon has one p orbital, perpendicular to the plane of its three σ bonds. In the isolated diene the p orbitals of C1 and C2 overlap, and so do those of C4 and C5, but C3 is sp^3 and has no p orbital to bridge the gap: two small π systems, two electrons each. In the conjugated diene the p orbitals of C1, C2, C3 and C4 stand in a row, and C2 and C3 overlap as well, so the four π electrons live in one π system spread over four carbons. An electron with more room has lower energy. Think of a dance floor: the same crowd, but one big floor instead of two broom cupboards. A side effect is that the C2–C3 bond is no longer an ordinary single bond: in the simplest conjugated diene it is about 147 pm long, shorter than the 154 pm of a C–C bond between two sp^3 carbons (partly because sp^2 carbons carry more s character, partly because of the overlap).

The cumulated diene is the odd one out. Its central carbon C2 is sp hybridised and linear, and it uses two different p orbitals, one for each double bond, at right angles to each other. The two π bonds cannot overlap, so a cumulated diene is not conjugated. The same right angle makes the two ends of the molecule twist 90° relative to each other, which is the axis of chirality of Section 5.4.

Conjugation does not need two C=C bonds. A C=C next to a C=O, next to an aromatic ring or next to an atom with a lone pair is conjugated too, as soon as the p orbitals line up in a row. Longer chains of alternating double and single bonds are called conjugated polyenes, and Section 6.4 shows what they do to light.

Conjugation needs the p orbitals to be parallel, so the four carbons of a conjugated diene lie in one plane. With C1=C2 and C3=C4 in a plane, there are only two ways to hold the C2–C3 single bond flat (Figure 6.2): the two double bonds on opposite sides of it (**s-trans**) or on the same side (**s-cis**). The *s* stands for single bond: the prefix describes the arrangement around the single bond, the way cis and trans do around a double bond. The s-trans form is the more stable one, because in s-cis the two inner hydrogens, on C1 and C4, crowd each other. The two forms interconvert by turning around C2–C3. That bond has only a little double-bond character, so the barrier is low, a few tens of kJ mol^{-1}, and the turning happens easily at room temperature. Many reactions of dienes work only through the s-cis form, so the small fraction of molecules in it matters more than its size suggests.

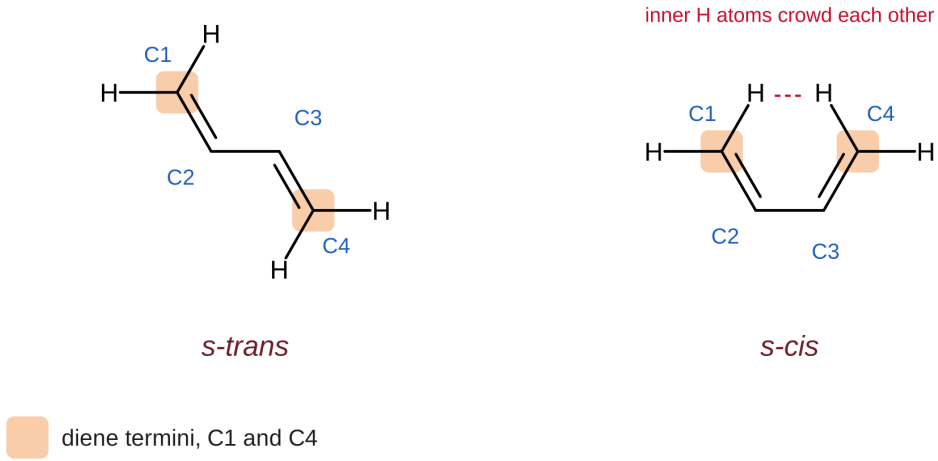


Figure 6.2. Buta-1,3-diene as s-trans (left) and s-cis (right), carbons C1 to C4 numbered in blue. The orange squares mark the two ends of the diene unit, C1 and C4. In s-cis the two inner hydrogens (dashed red line) crowd each other.

6.2 Resonance

A Lewis structure puts every electron pair in one place: on one atom, or between two atoms. That is a fine model until it is not. The amide group, a carbonyl carbon with a nitrogen attached, is the standard case. In structure A of Figure 6.3 the nitrogen has a lone pair and the carbon has a C=O. Now push two electron pairs, with two curved arrows: the nitrogen lone pair moves into the C1–N bond and turns it into a double bond, and the π electrons of the C=O move onto oxygen as a lone pair. The result is structure B, with O^- and N^+. No atom has moved. Only electrons did.

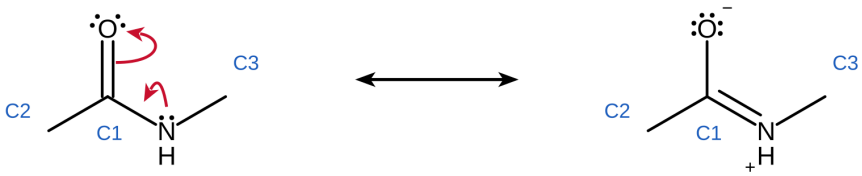


Figure 6.3. The two resonance structures of an amide group. C1 is the carbonyl carbon, C2 the methyl group on it and C3 the methyl group on nitrogen. The red curved arrows show the two electron pairs that move: the nitrogen lone pair becomes a C1–N π bond, and the C1=O π bond becomes a lone pair on oxygen.

Neither A nor B exists on its own. The real molecule is a **resonance hybrid** of the two, written with the double-headed arrow ↔ between them. It looks like A with a bit of B mixed in: A contributes most because it has no charges, but B contributes enough to matter, and three things you can measure show it.

- The C1–N bond is short, about 133 pm, against about 147 pm for a C–N single bond in an amine.
- C1, O, N, C2, C3 and the hydrogen on N all lie in one plane, and N is sp^2. Its lone pair sits in a p orbital and overlaps with the π bond of the C=O. This is the lone pair that joins a π system, which Chapter 2 promised to come back to: an amine nitrogen is sp^3 and pyramidal, an amide nitrogen is sp^2 and flat.
- Rotation around the C1–N bond is hindered. Turning the two ends would pull the p orbitals out of line and cut the partial double bond, which costs roughly 70 to 85 kJ mol^{-1}, so at room temperature the amide group does not spin freely.

Key result. Rules for resonance structures. (1) Only electrons move, never atoms: every structure has the same σ framework. (2) Curved arrows start at a lone pair or at a bond, never at an atom, and end at an atom or between two atoms. (3) The total number of electrons and the net charge stay the same. (4) No second-row atom (C, N, O) gets more than eight electrons. (5) A structure contributes more when it has more bonds, full octets, fewer charges, and any negative charge on the more electronegative atom. (6) The more structures a molecule has, and the more equal they are, the more stable it is.

Watch out. The arrow ↔ is not the equilibrium arrow ⇌. In an equilibrium two different molecules turn into each other; in resonance there is one molecule that a single Lewis structure cannot draw. A hybrid is not a mixture and not a flicker between two forms. It is a mule: one animal, with the traits of both parents.

A conjugated diene has resonance structures as well, but they need charges and cost a bond, so they hardly contribute. That is why conjugation in a diene is worth only about 15 kJ mol^{-1}. Benzene, in the next section, is the opposite case.

6.3 Aromaticity

Benzene has six carbons in a ring, all sp^2, all in one plane, and every carbon has a p orbital pointing up and down. All six overlap in a ring: a π system without a beginning or an end. Written with ordinary Lewis structures there are two ways to place the three double bonds, the Kekulé structures of Figure 6.4, and three curved arrows turn one into the other. Neither is right. In real benzene all six C–C bonds are equal, about 139 pm, between the 134 pm of a C=C and the 154 pm of a C–C bond between two sp^3 carbons.

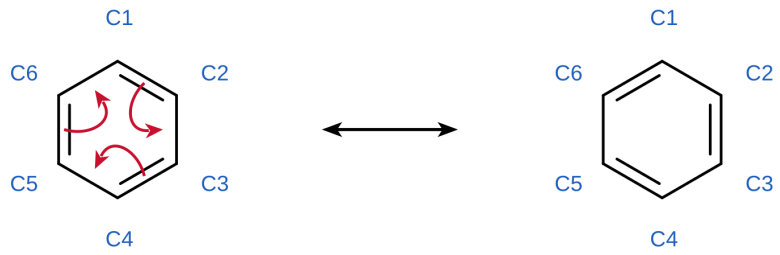


Figure 6.4. The two Kekulé structures of benzene, carbons C1 to C6 in blue. Three curved arrows turn the left structure into the right one. The real molecule is the hybrid of the two.

Here resonance pays off. Hydrogenating benzene releases about 208 kJ mol^{-1}, whereas three separate C=C bonds would release about 360 kJ mol^{-1}. Benzene is about 150 kJ mol^{-1} more stable than its Kekulé structures suggest, ten times the gain of a conjugated diene. This extra stability is what **aromaticity** means. Not every ring with alternating double bonds has it, though, and Hückel's rule says which ones do.

> **Key result.** A ring is **aromatic** when (1) it is cyclic and planar, (2) every ring atom has a p orbital, so every atom is sp² (or sp) hybridised and the π system is continuous, and (3) the π system holds 4n + 2 electrons:

$$4n + 2 \qquad (n = 0, 1, 2, \dots) \;\Rightarrow\; 2,\ 6,\ 10,\ 14,\ \dots\ \pi \text{ electrons}$$

Why 4n + 2? The p orbitals of the ring combine into π molecular orbitals: one lowest orbital, then pairs of orbitals with equal energy. Fill them with pairs of electrons and the shells close at 2, 6, 10, 14 electrons, that is at 4n + 2. Then every bonding orbital is full and no antibonding orbital is occupied, a little like a noble-gas configuration. The dance floor again: at 4n + 2 the floor is exactly full of couples. At 4n two electrons have no partner and stand in the corner, sulking; a planar, fully conjugated ring with 4n electrons is called antiaromatic and is unusually unstable.

Counting is the whole game, so here is how. Each ring atom that sits in the π system provides its p orbital (call it p_z, perpendicular to the ring) and some electrons to put in it. Figure 6.5 works it out for the four atom types that cover almost everything in this chapter. A carbon in a ring double bond has four valence electrons: three go into the sp² orbitals (the σ bonds) and one into p_z, so it counts 1. A pyrrole-type nitrogen, the N–H kind, has five valence electrons: one into each of three σ bonds and the remaining two as a lone pair in p_z, so it counts 2. A pyridine-type nitrogen, the C=N kind, has five valence electrons: its lone pair sits in an sp² orbital in the plane of the ring, pointing away from it, and it counts 1. An oxygen as in furan has six valence electrons: one lone pair in p_z (counts 2) and one in an sp² orbital in the plane (does not count). Only electrons in p_z are counted; in-plane lone pairs are not.

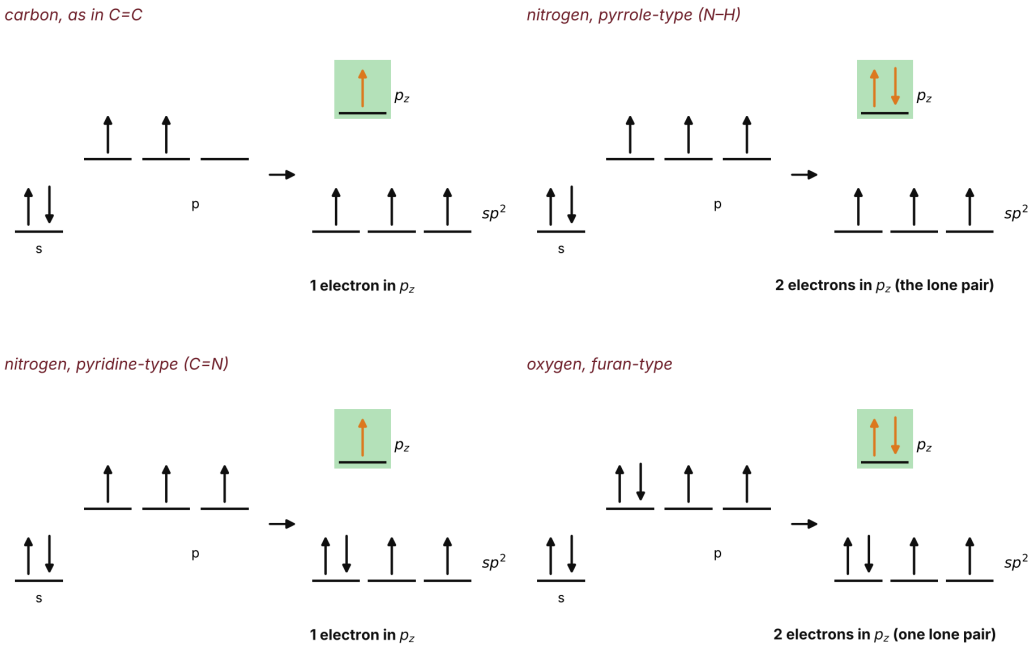


Figure 6.5. How many electrons each ring atom puts into the π system. Left of each arrow: the valence electrons of the free atom. Right: after hybridisation, three sp^2 orbitals (σ bonds and, if present, an in-plane lone pair) and one p_z orbital perpendicular to the ring. The p_z electrons (orange, on green) are the ones that are counted.

Figure 6.6 puts the counting to work. Toluene is aromatic: the ring has six π electrons and the methyl group hangs outside it, so its sp^3 carbon does not matter. Naphthalene, two rings fused, has five double bonds, so ten π electrons: 4n + 2 with n = 2, and all ten carbons are sp^2. In pyrrole the two double bonds give four electrons and the nitrogen lone pair gives two: 4 + 2 = 6. Furan does the same with oxygen. Imidazole and oxazole carry two heteroatoms each, of two different kinds: the N–H of imidazole and the O of oxazole give two electrons, the C=N nitrogen (N3) gives one. Pyrimidine has two pyridine-type nitrogens and three double bonds, so it counts six. A lone pair that joins the π system is no longer available for anything else; Chapter 8 returns to this when it asks which of these nitrogens can pick up a proton.

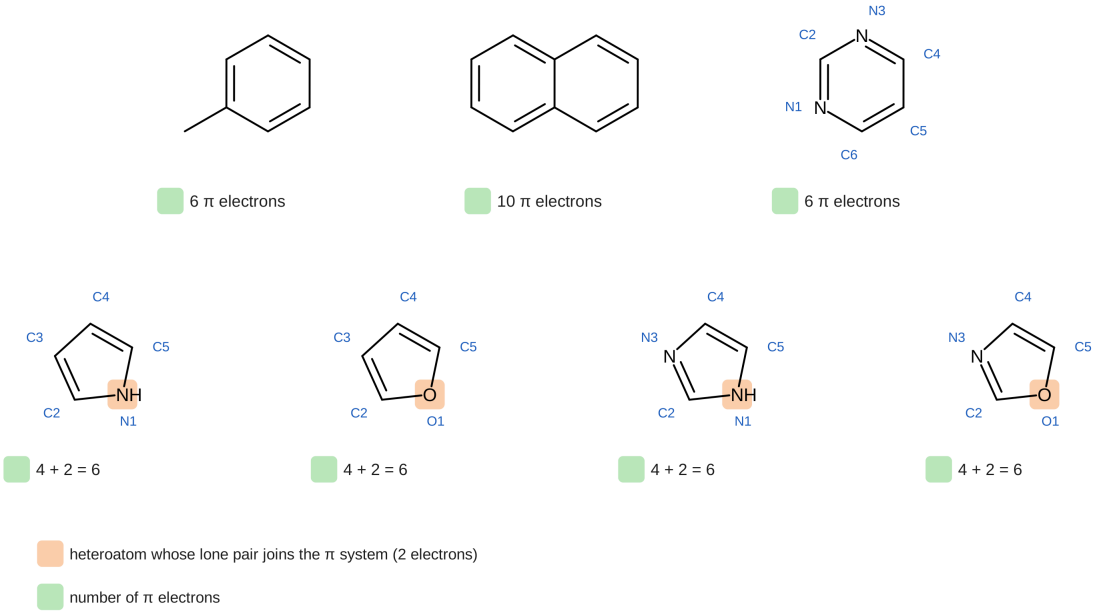


Figure 6.6. Aromatic rings and their π-electron count (green). Top: toluene (6), naphthalene (10) and pyrimidine (6). Bottom: pyrrole, furan, imidazole and oxazole, each 4 + 2 = 6, with ring atoms numbered from the heteroatom. Orange marks the heteroatom whose lone pair joins the π system and gives two electrons.

Example 6.1. Is imidazole aromatic? Check the three conditions in Figure 6.6. Cyclic and planar: yes, a five-membered ring of five atoms. Every ring atom sp²: C2, C4 and C5 are in double bonds, N3 is in the C2=N3 double bond, and N1 carries a lone pair that can sit in a p orbital, so all five atoms have a p orbital. Count the electrons: C4=C5 gives 2, C2=N3 gives 2, the lone pair on N1 gives 2, total 6 = 4·1 + 2. Imidazole is aromatic. The lone pair on N3 lies in the plane and is not counted.

Six electrons are not enough on their own. Figure 6.7 shows three rings that are not aromatic although every one of them contains double bonds, and the reason is always the same yellow square: an sp³ carbon in the ring. It has no p orbital, so the chain of p orbitals is broken and nothing runs round the ring. Cyclopenta-1,3-diene has only four π electrons, and its CH_2 (C5) has no p orbital and no electron to give, so there is only the one Lewis structure and no resonance. 7-Bromocyclohepta-1,3,5-triene has six π electrons, but C7 carries the Br and is sp³, so the ring is not fully conjugated. The bicyclic ring on the right also has six π electrons, spread over three double bonds, but four of its carbons (C3, C4, C7 and C8) are sp³.

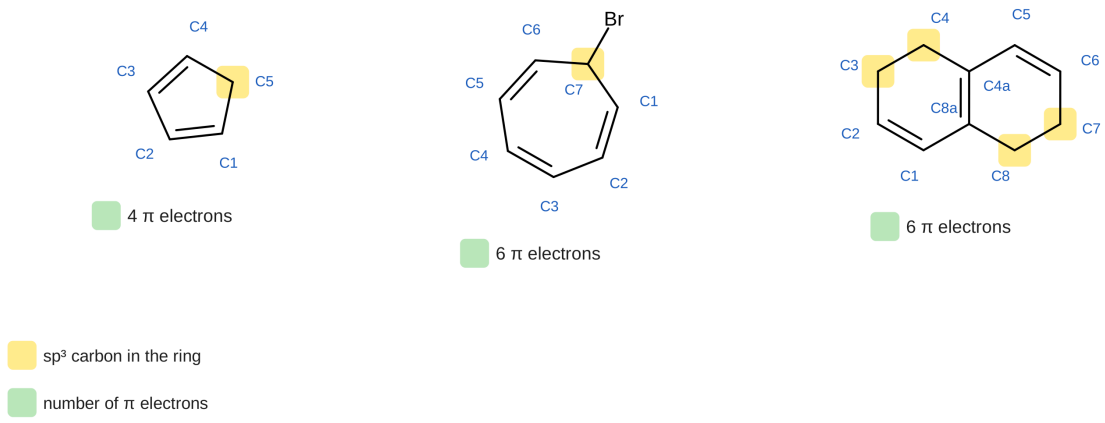


Figure 6.7. Three rings that are not aromatic: cyclopenta-1,3-diene, 7-bromocyclohepta-1,3,5-triene and a bicyclic ring with three double bonds. The sp³ carbons are marked yellow, and the π-electron count is green. A single sp³ carbon in the ring is enough to stop the conjugation.

> **Watch out.** Counting to 4n + 2 is only the last step. First look at the ring itself: if one ring atom is sp³, stop, the ring is not aromatic, whatever the count. An sp³ carbon outside the ring, like the methyl group of toluene, does not matter at all.

One ring in the family looks wrong at first sight: a seven-membered ring with a C=O. The C=O is polarised, with the π electrons pulled towards oxygen, and the ring can take the hint, as the next example shows.

Example 6.2. Why does tropone (cyclohepta-2,4,6-trien-1-one, Figure 6.8) behave as if it had some aromatic character? Push the π electrons of the C=O onto oxygen with one curved arrow. The oxygen becomes O^- and the carbonyl carbon C1 becomes C^+. In this dipolar resonance structure the ring has three C=C bonds, which is six π electrons, spread over seven p orbitals: six electrons for seven carbons with an empty p orbital on C1, which is exactly the situation of the cycloheptatrienyl (tropylium) cation, an aromatic ion. The dipolar structure is a real contributor, because it is the one that gives the ring its sextet, and that is why tropone is more stable than you would expect and why it has a large dipole moment.

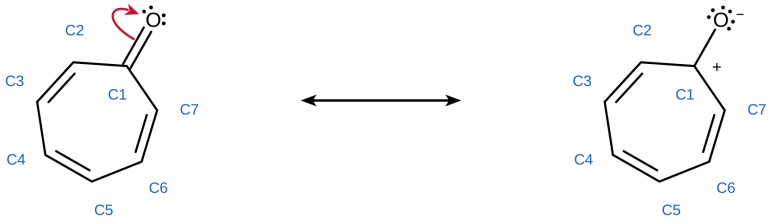


Figure 6.8. Tropone and its dipolar resonance structure, carbons C1 to C7 numbered. One curved arrow moves the π electrons of the C=O onto oxygen; the ring then has six π electrons over seven carbons.

6.4 Light and π → π* transitions

A π bond comes with an empty partner. When two p orbitals overlap, they form a bonding π orbital and an antibonding π* orbital. In the ground state the electrons sit in π, and the highest filled orbital is called the **HOMO**; the lowest empty orbital, usually a π*, is the **LUMO**. If a photon has exactly the energy of the gap, a molecule can swallow it and lift one electron from HOMO to LUMO (Figure 6.9). For a simple π → π* transition the gap is of the order of 500 to 600 kJ mol^{-1}.

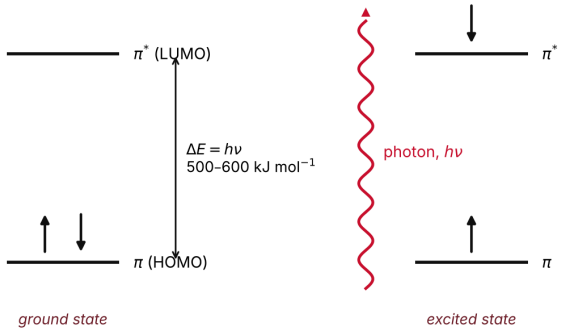


Figure 6.9. A π → π transition: a photon whose energy equals the gap lifts one electron from the highest occupied π orbital (HOMO) to the lowest unoccupied π* orbital (LUMO). The π level is left with one electron.*

Example 6.3. Which wavelength lifts an electron from HOMO to LUMO if the π → π* gap is 500 to 600 kJ mol^{-1}? A photon carries

$$\Delta E_{\text{photon}} = h\nu = \frac{hc}{\lambda}$$

so the wavelength is λ = hc/ΔE. The gap is given per mole, and a photon lifts a single electron, so ΔE must be per electron: divide by Avogadro's number, or, what is the same thing, multiply the photon energy by N_A to get J/mol:

$$\lambda = \frac{hcN_\mathrm{A}}{\Delta E} = \frac{6.626 \times 10^{-34}\ \mathrm{J\,s} \times 2.998 \times 10^{8}\ \mathrm{m\,s^{-1}} \times 6.022 \times 10^{23}\ \mathrm{mol^{-1}}}{500 \times 10^{3}\ \mathrm{J\,mol^{-1}}} = 2.39 \times$$

For 600 kJ mol⁻¹ the same calculation gives 199 nm. A simple π → π* transition therefore absorbs at a couple of hundred nanometres, in the ultraviolet, where our eyes see nothing. Conjugation moves the absorption: the more π orbitals overlap, the closer HOMO and LUMO get, and the longer the wavelength that fits the gap. The simplest conjugated diene (Figure 6.2) absorbs near 217 nm and the conjugated triene of Figure 6.1 near 258 nm. Keep adding double bonds and the absorption crawls into the visible, which is why the coloured organic molecules, dyes and pigments, are practically all long conjugated systems.

Example 6.4. What does a microwave of 2500 MHz do? The photon energy per mole is

$$\Delta E = h\nu N_\mathrm{A} = 6.626 \times 10^{-34}\ \mathrm{J\,s} \times 2500 \times 10^{6}\ \mathrm{s^{-1}} \times 6.022 \times 10^{23}\ \mathrm{mol^{-1}} = 1.0\ \mathrm{J\,mol}$$

That is half a million times smaller than a π → π* gap. A microwave photon cannot lift an electron and cannot break a bond. It is only strong enough to change the way a molecule rotates, which is how a microwave oven warms the water in your soup.

Exercises

Exercise 6.1. Figure 6.10 shows six molecules with their carbons numbered. (a) Classify the double bonds of each molecule as isolated, conjugated or cumulated. (b) Which of the conjugated molecules cannot adopt the s-trans arrangement around the single bond between its double bonds, and why? (c) One molecule contains an sp-hybridised carbon: which one, and what is the C=C=C angle?

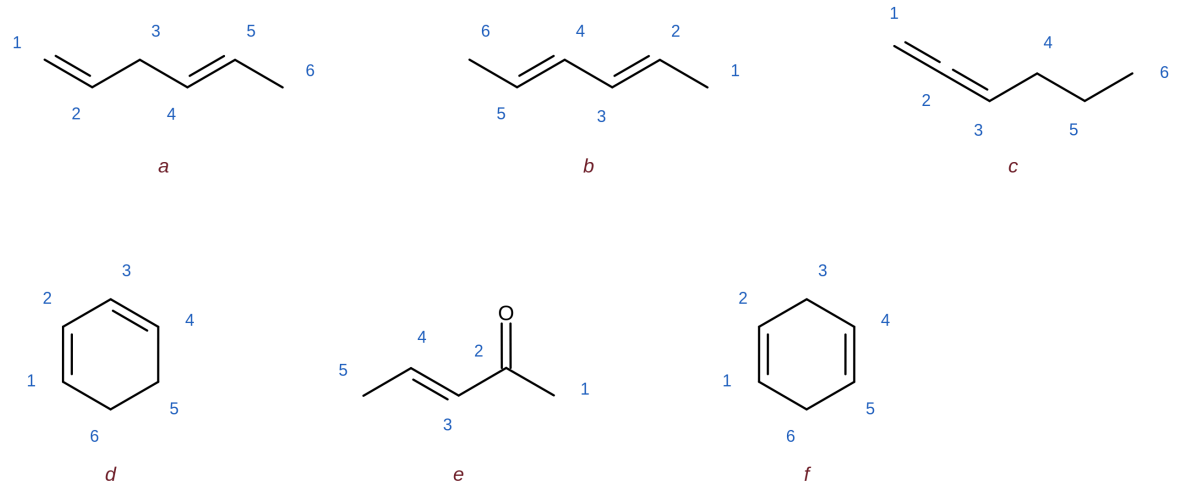


Figure 6.10. The six molecules of Exercise 6.1. Carbons are numbered in blue.

Exercise 6.2. Figure 6.11 shows one resonance structure of each of three species. For each one, draw the other resonance structure and the curved arrows that turn the first into the second. Which species have two equivalent structures? In the one that does not, which structure contributes more?

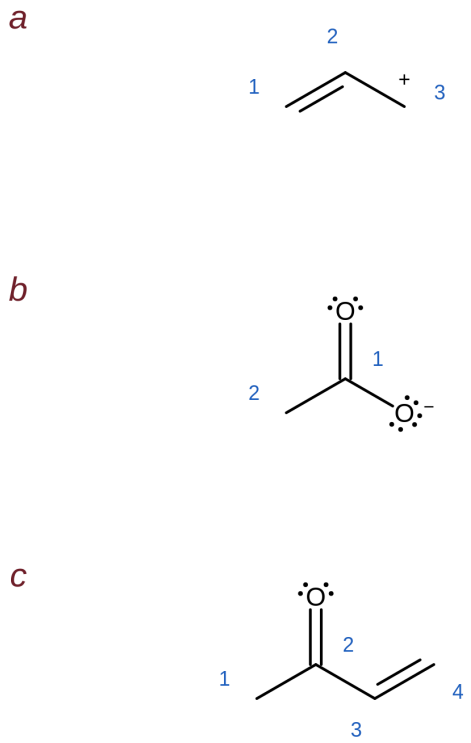


Figure 6.11. The three species of Exercise 6.2. Carbons are numbered in blue.

Exercise 6.3. Figure 6.12 shows six rings. For each one, decide whether it is aromatic by checking the three conditions of Section 6.3, and give the number of π electrons.

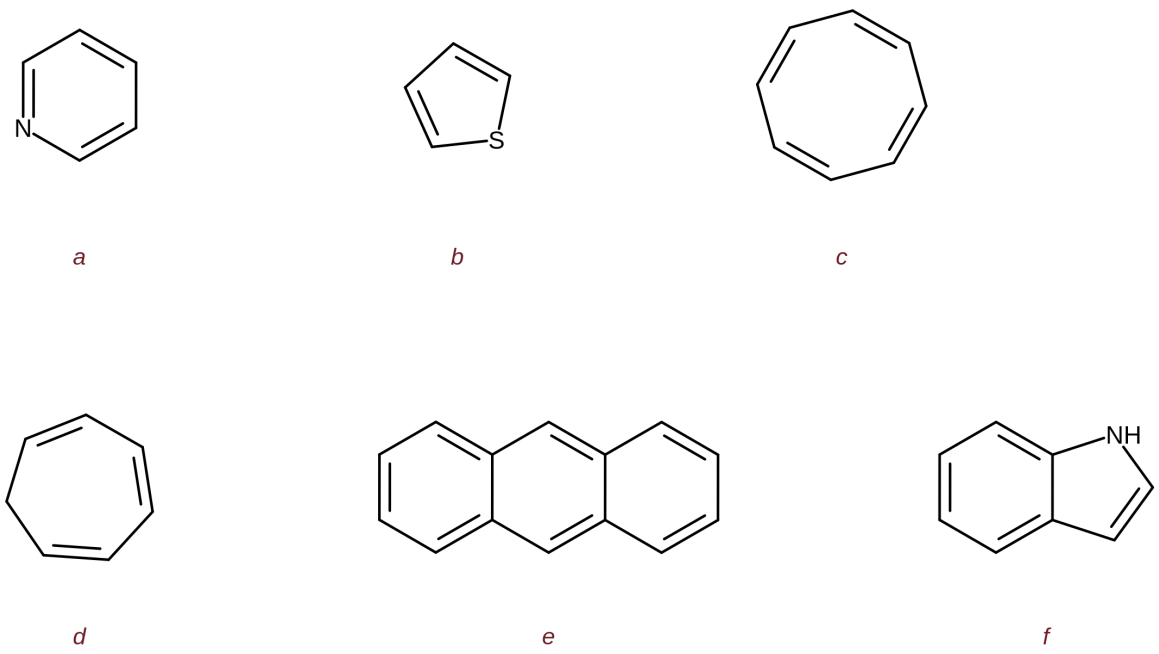


Figure 6.12. The six rings of Exercise 6.3.

Exercise 6.4. (a) A conjugated polyene has a $\pi \rightarrow \pi^*$ gap of 330 kJ mol^{-1}. At which wavelength does it absorb, and in which region of the spectrum is that? (b) How much energy per mole of photons does visible light of 500 nm carry?

Exercise 6.5. Figure 6.13 shows trimethylamine (a) and N,N-dimethylacetamide (b). For the nitrogen of each: what is its hybridisation, is it pyramidal or flat, in which orbital does its lone pair sit, and is rotation around the bond from N to a methyl carbon (a) or to the carbonyl carbon (b) free?



Figure 6.13. The two molecules of Exercise 6.5.

Solutions

Exercise 6.1. Figure 6.14 marks the double bonds: orange for conjugated, teal for isolated, green for cumulated.

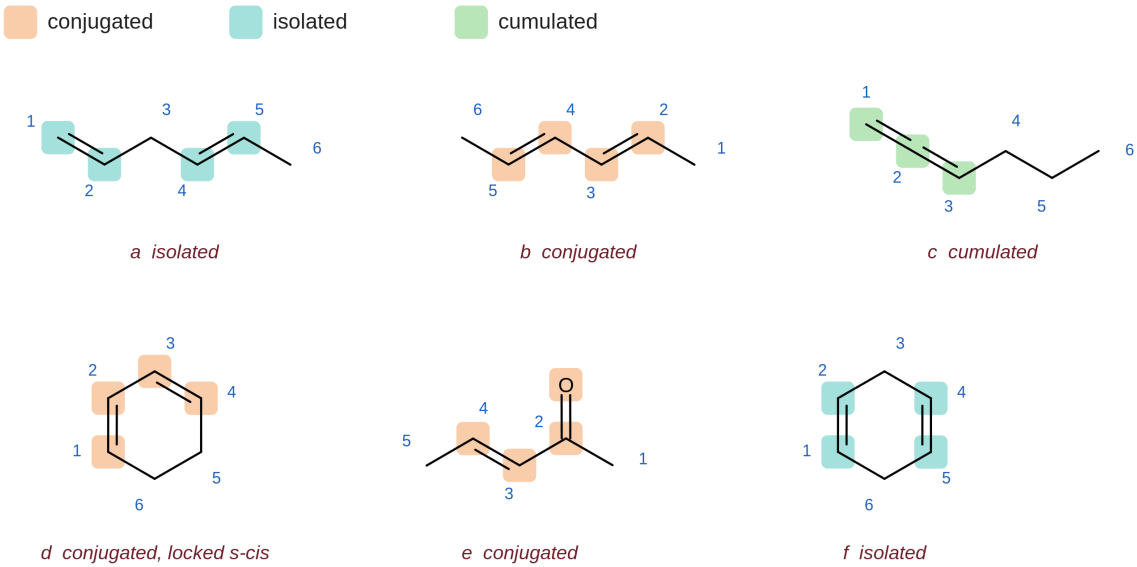


Figure 6.14. The answers to Exercise 6.1. Orange: conjugated. Teal: isolated. Green: cumulated.

(a) In **a** the sp³ carbon C3 sits between C1=C2 and C4=C5: **isolated**. In **b** the double bonds C2=C3 and C4=C5 are separated by exactly one single bond, C3–C4: **conjugated**. In **c** C2 belongs to both double bonds: **cumulated**. In **d** C1=C2 and C3=C4 are separated by the single

bond C2–C3: **conjugated**. In **e** the C=C (C3=C4) and the C=O (C2=O) are separated by the single bond C2–C3, so the four p orbitals of O, C2, C3 and C4 stand in a row: **conjugated**, and conjugation does not need two C=C bonds. In **f** the sp^3 carbons C3 and C6 separate the double bonds on both sides: **isolated**.

(b) Molecule **d** cannot. The two double bonds sit inside a six-membered ring, so C1 and C4 are held on the same side of the C2–C3 bond: the diene is **locked s-cis**. Molecules **b** and **e** can turn around their single bond and can be s-cis or s-trans.

(c) Molecule **c**. Its central carbon C2 is sp-hybridised, so the C1=C2=C3 angle is **180°**, and the two double bonds use two different p orbitals at right angles, so they are not conjugated.

Exercise 6.2. Figure 6.15 shows the arrows and the second structure of each species.

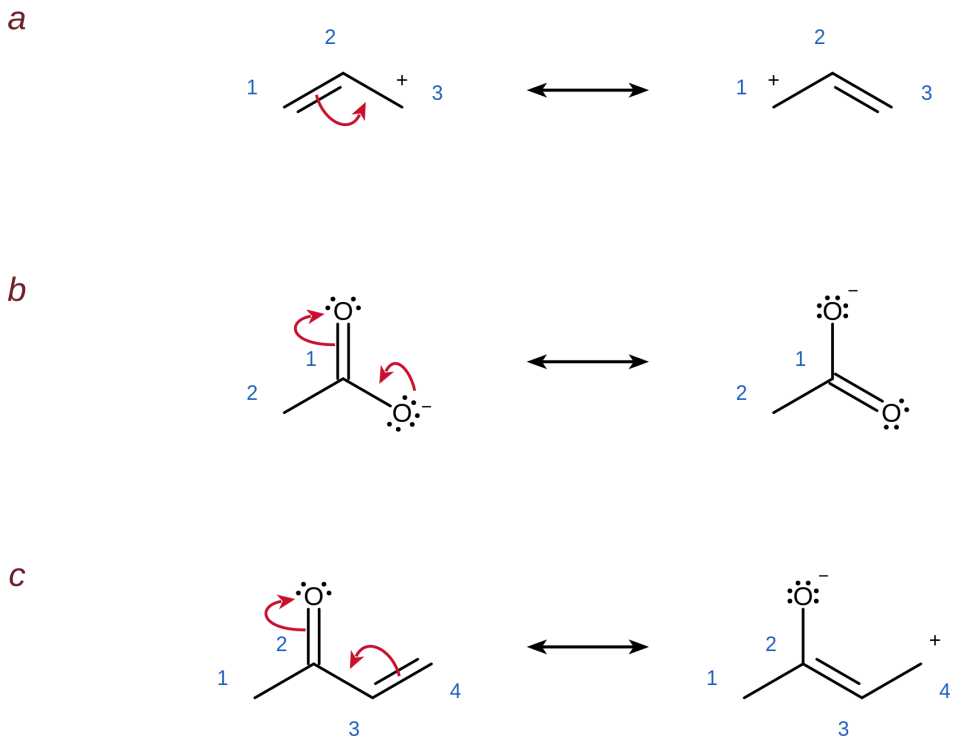


Figure 6.15. The answers to Exercise 6.2. Carbons numbered in blue; red arrows show the electron pairs that move.

(a) The π bond C1=C2 moves into the C2–C3 bond, so it becomes C2=C3, and the positive charge ends up on C1. The two structures are **equivalent**: the positive charge is shared equally by the two ends, half on C1 and half on C3.

(b) The lone pair on the negative oxygen moves into the C1–O bond, and the C1=O π bond moves onto the other oxygen as a lone pair. The two structures are **equivalent**: the two C–O bonds have the same length, between that of a single and a double bond, and each oxygen carries half of the negative charge.

(c) Two electron pairs move. The π bond C3=C4 moves into the C2–C3 bond, giving C2=C3, and the π bond C2=O moves onto oxygen as a lone pair, giving O^-. The second structure has a negative O and a positive C4, charges that the first does not have, so the two are **not equivalent**. The first structure, without charges, contributes **most**. The second still counts: it tells you that C4 is the electron-poor end of the C=C.

Exercise 6.3. Figure 6.16 gives the verdict for each ring.

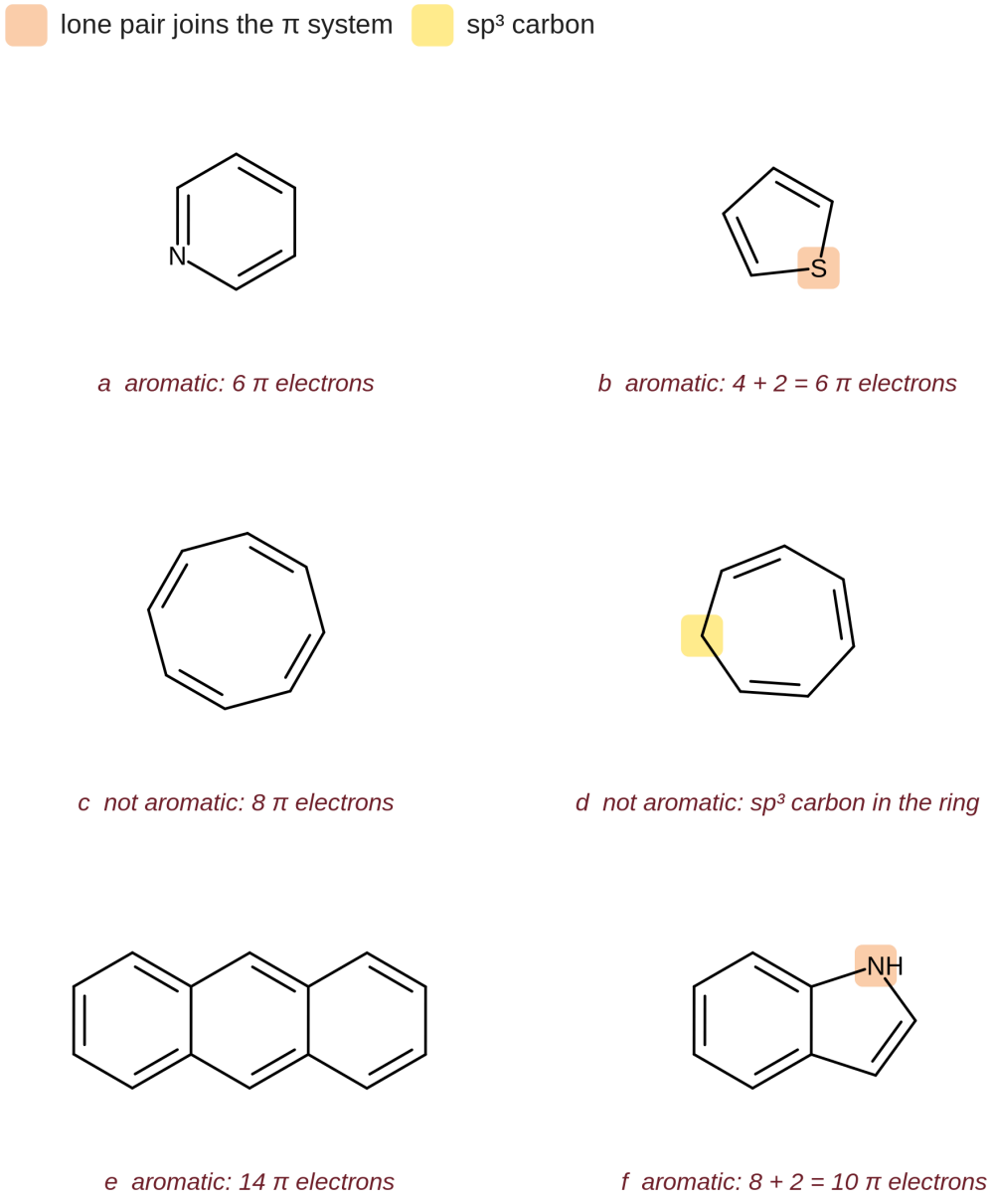


Figure 6.16. The answers to Exercise 6.3. Orange: a heteroatom whose lone pair joins the π system. Yellow: an sp^3 carbon in the ring.

(a) The ring has three double bonds, so **6 π electrons**. The nitrogen is sp^2 and its lone pair lies in the plane of the ring, in an sp^2 orbital, so it is not part of the π system and adds nothing: **aromatic**.

(b) The two C=C bonds give 4 electrons and a lone pair on sulfur sits in a p orbital and gives 2: 4 + 2 = **6**, so **aromatic**.

(c) Four double bonds make **8 π electrons**, which is 4n and not 4n + 2: **not aromatic**. The ring also folds into a tub instead of lying flat.

(d) The CH_2 carbon is sp^3 and has no p orbital, so the chain of p orbitals is broken. **Not aromatic**, whatever the electron count (it is 6).

(e) Seven double bonds give **14 π electrons**, which is 4·3 + 2, and all fourteen carbons are sp^2: **aromatic**.

(f) The four C=C bonds give 8 electrons, and the lone pair of the NH adds 2: 8 + 2 = **10**, which is 4·2 + 2: **aromatic**.

Exercise 6.4. (a) The gap is given per mole, so the wavelength is

$$\lambda = \frac{hcN_\mathrm{A}}{\Delta E} = \frac{0.1196\ \mathrm{J\,m\,mol^{-1}}}{330 \times 10^3\ \mathrm{J\,mol^{-1}}} = 3.63 \times 10^{-7}\ \mathrm{m} = 363\ \mathrm{nm}$$

where $h\,c\,N_\mathrm{A} = 6.626 \times 10^{-34}\ \mathrm{J\,s} \times 2.998 \times 10^{8}\ \mathrm{m\,s^{-1}} \times 6.022 \times 10^{23}\ \mathrm{mol^{-1}} = 0.1196\ \mathrm{J\,m\,mol^{-1}}$. **363 nm** is in the near ultraviolet, just short of the violet end of visible light, which is why such a compound looks colourless or pale yellow.

(b) With the same constant,

$$\Delta E = \frac{hcN_\mathrm{A}}{\lambda} = \frac{0.1196\ \mathrm{J\,m\,mol^{-1}}}{500 \times 10^{-9}\ \mathrm{m}} = 2.39 \times 10^5\ \mathrm{J\,mol^{-1}} = 239\ \mathrm{kJ\,mol^{-1}}$$

So a gap of about **239 kJ mol⁻¹** absorbs green-blue light. A longer conjugated system has a smaller gap and absorbs at longer wavelengths, which is how a molecule gets a colour.

Exercise 6.5. (a) In trimethylamine the nitrogen is **sp^3** and **pyramidal**. Its lone pair sits in an sp^3 orbital pointing away from the three methyl groups, and it is not conjugated with anything, so **rotation around the N–C bonds is easy**.

(b) In N,N-dimethylacetamide the nitrogen is **sp^2** and **flat**. Its lone pair sits in a **p orbital** parallel to the π bond of the C=O and overlaps with it (the resonance of Figure 6.3), so the C–N bond is partly a double bond. Rotation around it is **hindered**, by roughly 70 to 85 kJ mol⁻¹, so at room temperature the two methyl groups on nitrogen stay in different places, one on the side of the oxygen and one on the side of the methyl group of the acetyl.

CHAPTER 7

Intermolecular forces

Everything so far was about what happens inside one molecule: which atoms are bonded, in which shape, with which electrons spread where. This chapter looks at what happens between molecules. The forces there are far weaker than a bond (breaking a C–C bond costs a few hundred kJ mol^{-1}, pulling two molecules apart a few to a few tens), but they decide whether a compound is a gas, a liquid or a solid, how high it boils and what it dissolves in. The easiest way to see them is the **boiling point**: to boil a liquid you pull its molecules apart from each other, and the more they stick together, the more heat that takes. The covalent bonds inside the molecules stay intact the whole time.

There are three kinds of attraction to know, in order of increasing strength: London forces, dipole–dipole forces and hydrogen bonds. Each section adds one to the list, and Figure 7.1 shows the whole story at once. Every compound in it has one, two or three carbons; read it by rows and by columns.

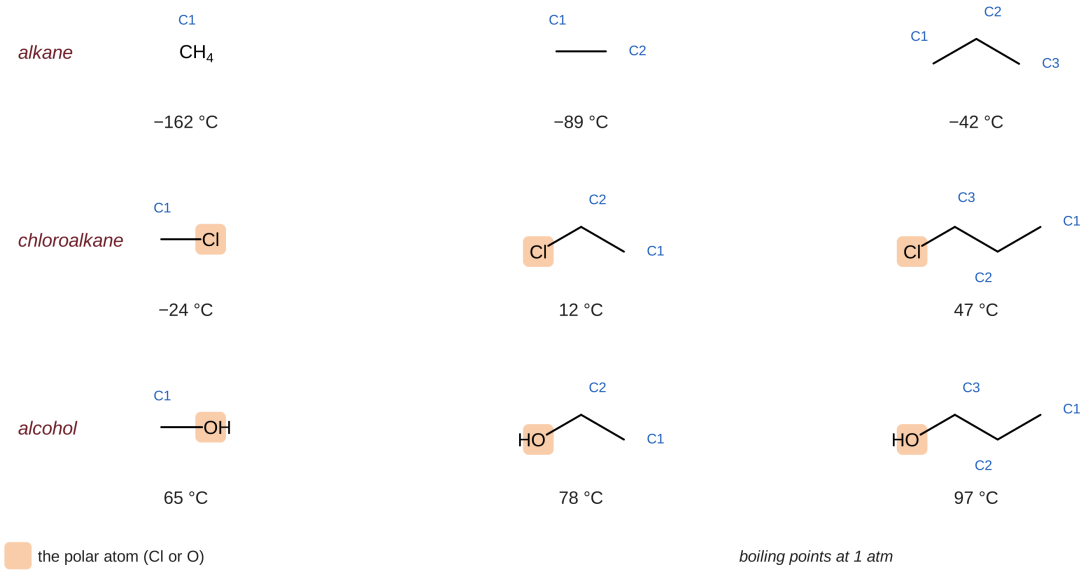


Figure 7.1. Boiling points (at 1 atm) of nine small molecules with one to three carbons, numbered in blue. Along each row the chain grows by one carbon and the boiling point rises. Down each column the same carbon skeleton gets a chlorine, then an OH, and the boiling point rises again. The polar atom, Cl or O, is marked orange.

7.1 London forces: size matters

Look at the top row of Figure 7.1. Methane, ethane and propane are all non-polar: just carbon and hydrogen, and C–H bonds are hardly polarised. Still, they stick to each other a little, because electrons are not frozen in place. At any instant the electrons of a molecule are slightly more on one side than on the other, and for that moment the molecule has a tiny dipole. It makes a neighbouring molecule do the same, with opposite sign facing it, and the two attract. A moment later the dipoles flip, and the attraction stays. These attractions are called **London forces** (also dispersion forces or induced-dipole forces; the general name for all attractions between molecules is **van der Waals forces**). Every molecule has them, polar or not.

The bigger the molecule, the stronger they are, for two reasons. A bigger molecule has more electrons that can shift, so its electron cloud is easier to deform: it is more **polarisable**. And a longer molecule touches its neighbours along a longer stretch. That is why the boiling point climbs along the top row: −162 °C, −89 °C, −42 °C. Add carbons and you reach liquids, then waxes. Shape counts as well: for the same number of carbons, a compact branched isomer touches its neighbours at fewer places than the straight chain and boils lower.

7.2 Polar bonds: dipole–dipole forces

Now the second row. Replace one H by Cl and the boiling point jumps by some 140 °C for the smallest molecule: chloromethane boils at −24 °C against −162 °C for methane. Part of this is simply size (Cl is a big atom with many electrons, so the molecule is far more polarisable). The other part is that chlorine is more electronegative than carbon. The two atoms in the C–Cl bond do not share their electrons equally: the bonding electrons sit closer to Cl, which becomes slightly negative (δ−), and the carbon slightly positive (δ+). The bond is **polar**, it has a **dipole** (drawn as an arrow with a crossed tail on the + end and the head on the − end, left of Figure 7.2), and the molecule as a whole is polar as well, as the dipoles do not cancel. Polar molecules line up δ+ against δ− with their neighbours, and this extra pull is the **dipole–dipole force**. It comes on top of the London forces, never instead of them.

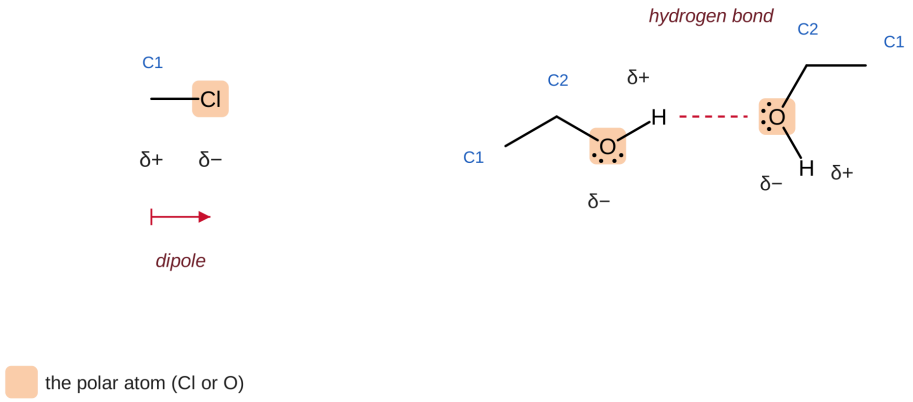


Figure 7.2. Left: the C1–Cl bond of chloromethane is polar. The partial charges δ+ and δ− and the dipole arrow point from carbon to chlorine. Right: a hydrogen bond (red dashed line) between the OH group of one ethanol molecule and the oxygen of another. Carbons C1 and C2 are numbered in blue, the oxygens are orange.

The same goes for every other polar group: C–O, C–N, C=O, C–Br. The size of the effect depends on how different the two electronegativities are. Fluorine is the exception to the rule "more electronegative, higher boiling point": a C–F bond is very polar, but fluorine holds its electrons so tightly that they are hardly polarisable, so the London forces stay small and a fluoroalkane boils lower than its chloro analogue (fluoromethane, −78 °C, against chloromethane, −24 °C).

7.3 Hydrogen bonds

The bottom row of Figure 7.1 shows the biggest jump so far. The alcohols have the same carbon skeleton as the chloroalkanes above them but boil 50 to 90 °C higher, even though an oxygen atom has fewer electrons than a chlorine atom, so London forces alone would predict the opposite. The extra ingredient is the hydrogen on the oxygen.

An O–H bond is strongly polar, with oxygen δ− and hydrogen δ+, and a hydrogen atom is small: it has no inner electrons, so its δ+ charge can come very close to a lone pair on a neighbouring oxygen. The resulting attraction, X–H···Y, is a **hydrogen bond**: the δ+ hydrogen of one molecule sits against a lone pair of a more electronegative atom of another (right of Figure 7.2). It is still an attraction between molecules and not a covalent bond. It is much weaker than a covalent bond but several times stronger than London or ordinary dipole forces between molecules of that size.

> **Key result.** A hydrogen bond needs two partners: a hydrogen on a very electronegative atom (N–H, O–H or F–H) as donor, and a lone pair on N, O or F as acceptor. A C–H bond does not count: carbon is not electronegative enough. Boiling points are therefore set by the sum of three things: London forces (size and shape), dipole–dipole forces (polar groups) and hydrogen bonds (O–H and N–H groups). When two compounds have about the same size, compare the polar groups first, then the hydrogen bonds.

Example 7.1. Explain the order of the boiling points of the three molecules of the right column in Figure 7.1: propane (−42 °C), 1-chloropropane (47 °C) and propan-1-ol (97 °C). All three have the same chain C1–C2–C3, so the London forces are about the same in size to begin with (the chlorine adds some). Propane has nothing but London forces, so it boils lowest. In 1-chloropropane the C3–Cl bond is polar, so dipole–dipole forces are added and the boiling point rises by almost 90 °C. In propan-1-ol the O–H group is polar and also has a δ+ hydrogen and two lone pairs on oxygen, so each molecule can form hydrogen bonds with its neighbours, and the compound boils higher still.

Example 7.2. Why does cyclohexanol (161 °C) boil higher than octane (126 °C), with the molecules of Figure 7.3? Octane is slightly larger (eight carbons against six in a ring), so its London forces are not smaller; if they were all that mattered octane should win. But octane has only C–H and C–C bonds: no polar bond, no OH group, no hydrogen bonds. Cyclohexanol has the OH group on C1, a polar C1–O bond and an O–H that forms hydrogen bonds. Those more than make up for the difference in size.

Example 7.3. Ethanol (78 °C) and dimethyl ether (−24 °C) have the same formula, C_2H_6O, yet differ by 100 °C (Figure 7.3). Both have a polar C–O bond, so both have dipole–dipole forces and about the same London forces. In ethanol the oxygen carries a hydrogen, so ethanol molecules form hydrogen bonds with each other. In dimethyl ether the oxygen sits between C1 and C2 and has no hydrogen: it can accept a hydrogen bond (it has lone pairs) but it cannot donate one, so it has none to offer to its own kind, and the liquid is held together by weaker forces.

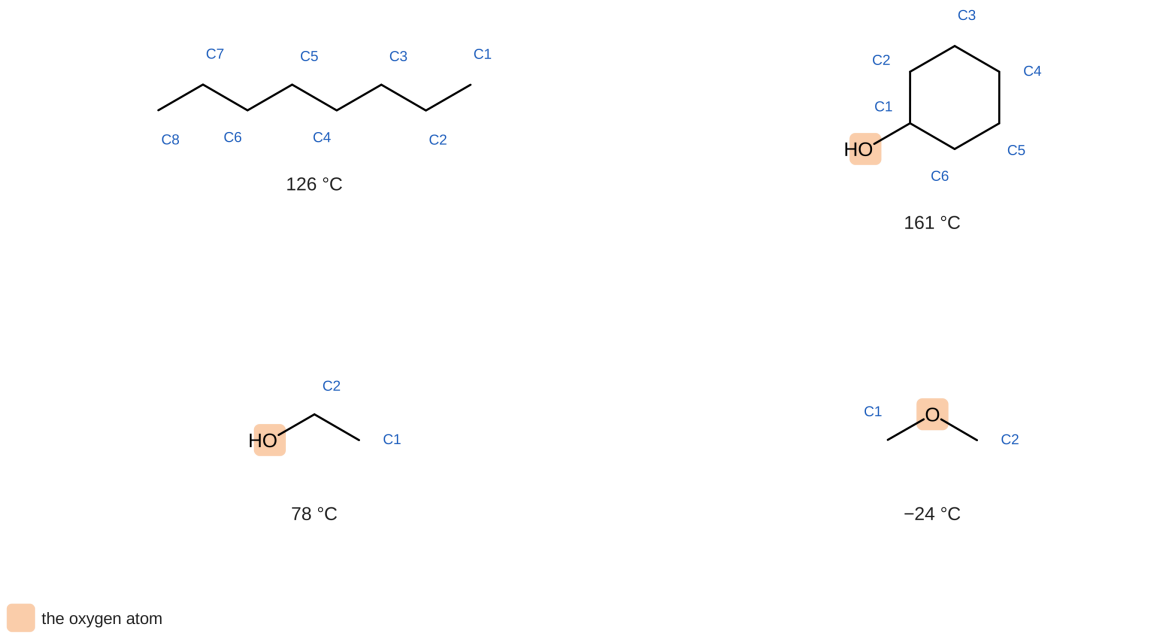


Figure 7.3. Examples 7.2 and 7.3. Top: octane (no OH group) and cyclohexanol (OH on C1). Bottom: ethanol and dimethyl ether, the same atoms put together in two different ways. The oxygen is orange; carbons are numbered in blue.

> **Watch out.** Do not say that the O–H bond breaks when an alcohol boils: boiling pulls the molecules apart and only breaks the hydrogen bonds between them, not the covalent bonds inside them. And "hydrogen bond" is not "any bond with a hydrogen in it": the hydrogen has to sit on N, O or F. A molecule with an oxygen but no O–H (an ether, a ketone) can accept hydrogen bonds from water but cannot form them with its own kind.

The same three forces explain what dissolves in what. A liquid dissolves another one when the attractions between the two kinds of molecule are about as strong as those within each: polar molecules mix with polar ones, and above all those that form hydrogen bonds with water, while non-polar chains stay together. That is why the small alcohols of Figure 7.1 mix with water in every ratio and the alkanes hardly mix at all; as the carbon chain gets longer and the OH group matters less, the alcohols turn away from water too. Chapter 8 uses the same idea once more when it asks which molecules can give away or pick up a proton.

Exercises

Exercise 7.1. Figure 7.4 shows nine molecules in three sets (a, b and c). Within each set, put the three molecules in order of increasing boiling point and say which forces decide the order.

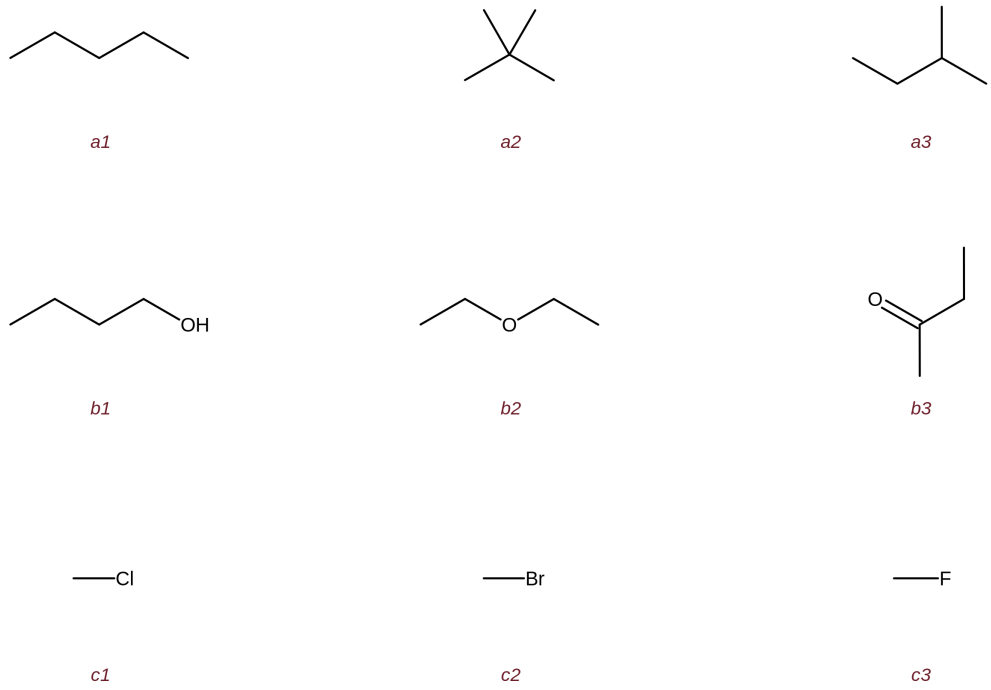


Figure 7.4. The three sets of Exercise 7.1.

Exercise 7.2. For each molecule of Figure 7.5, say whether it can donate a hydrogen bond, accept one, both, or neither.

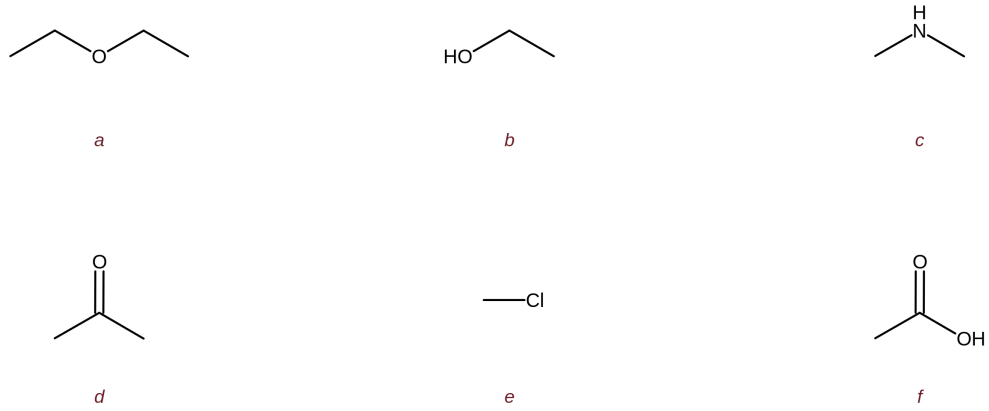


Figure 7.5. The six molecules of Exercise 7.2.

Exercise 7.3. Molecules a and b of Figure 7.6 have the same formula, $C_4H_{10}O$, and both are alcohols. Butan-1-ol (a) boils at 118 °C and 2-methylpropan-2-ol (b) at 82 °C. Explain the difference.

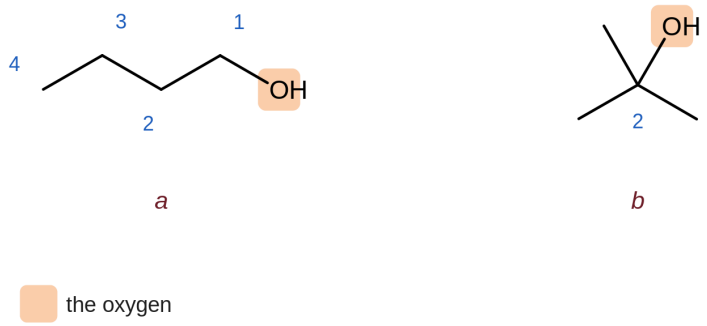


Figure 7.6. The two alcohols of Exercise 7.3. The oxygen is orange; carbons are numbered in blue.

Exercise 7.4. Which of the three molecules in Figure 7.7 mixes with water in every ratio, and which hardly dissolve in it at all? Explain.

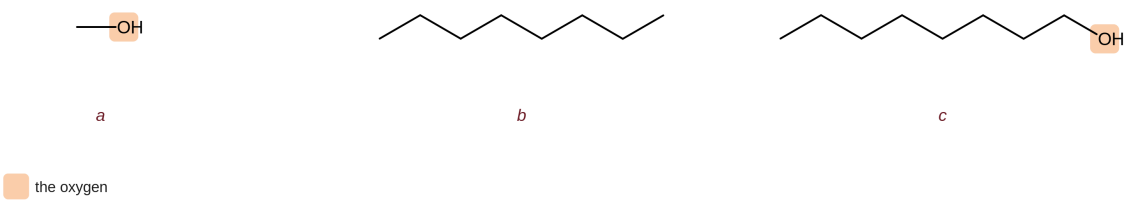


Figure 7.7. The three molecules of Exercise 7.4.

Solutions

Exercise 7.1. Figure 7.8 shows each set in order of increasing boiling point, with the boiling points at 1 atm.

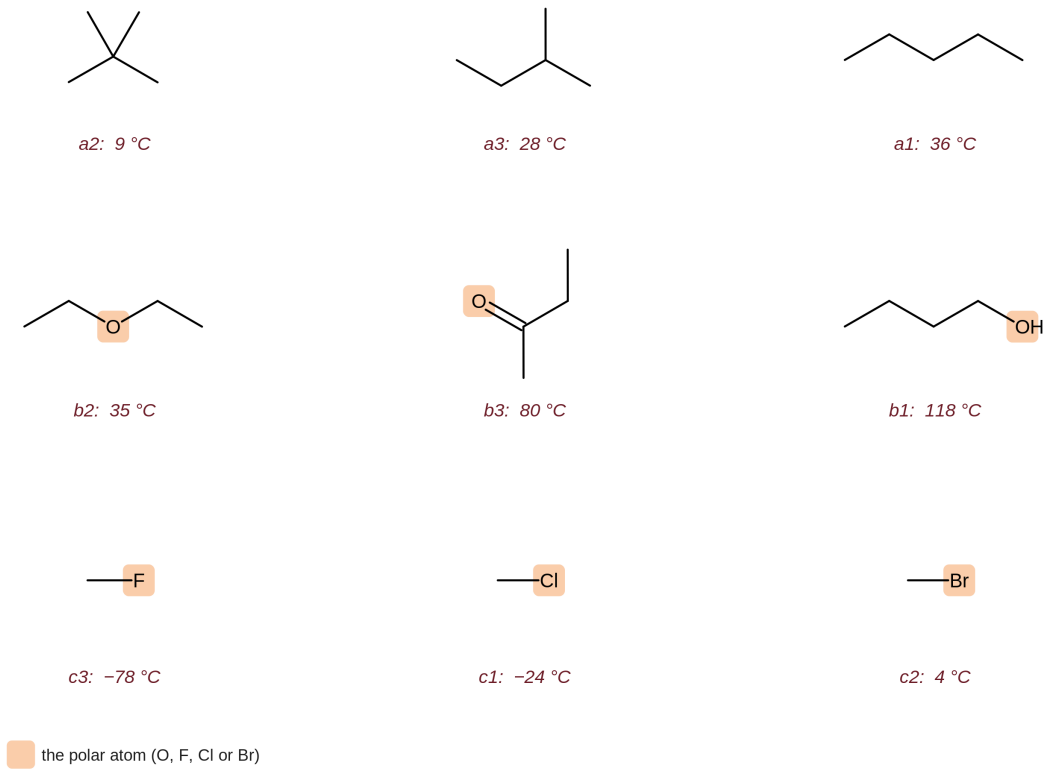


Figure 7.8. The answers to Exercise 7.1. The polar atom is highlighted in orange.

(a) The three molecules are isomers of C_5H_{12} with no polar bond, so only London forces act, and the number of atoms is the same. What differs is the shape: the more compact and branched the molecule, the fewer places it touches its neighbours. 2,2-Dimethylpropane is almost a ball (**9 °C**), 2-methylbutane is in between (**28 °C**) and unbranched pentane touches its neighbours along its whole length (**36 °C**).

(b) All three have four carbons, so the London forces are about equal. Diethyl ether has a polar C–O bond, so it has dipole–dipole forces (**35 °C**). Butanone has a C=O bond, which is more polar still (**80 °C**). Butan-1-ol has an O–H group and forms hydrogen bonds, which are stronger than ordinary dipole–dipole forces (**118 °C**).

(c) All three are polar. The order follows the size of the halogen, because a bigger atom with more electrons is more polarisable: bromomethane (**4 °C**) is highest and chloromethane (**−24 °C**) in the middle. Fluorine is the exception: its electrons are held so tightly that they are hardly polarisable, so fluoromethane boils lowest (**−78 °C**), in spite of the very polar C–F bond.

Exercise 7.2. A hydrogen bond needs a donor, a hydrogen on N, O or F, and an acceptor, a lone pair on N, O or F. Figure 7.9 highlights the atoms that can accept.

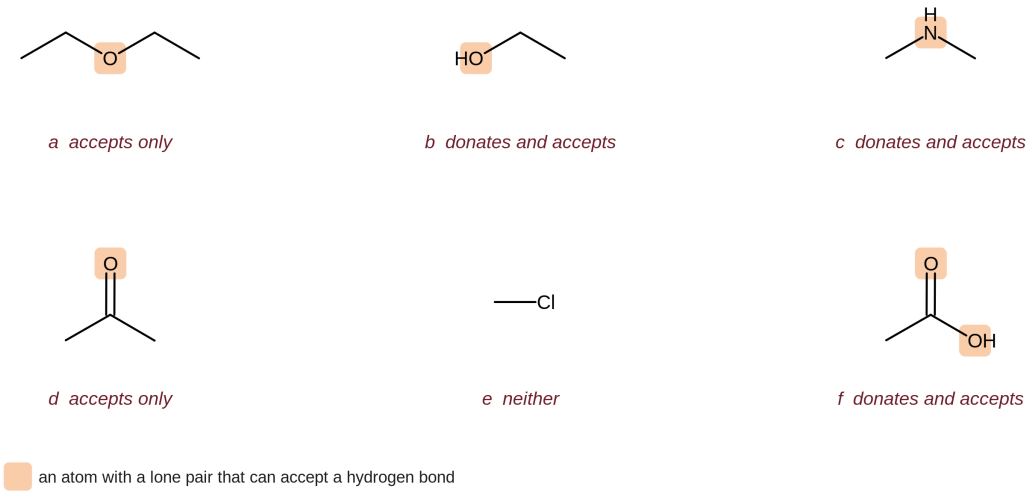


Figure 7.9. The answers to Exercise 7.2. Orange: an atom with a lone pair that can accept a hydrogen bond.

(a) Diethyl ether: the oxygen has lone pairs, so it **accepts**, but it has no hydrogen on O, and the hydrogens on carbon do not count: it cannot donate. (b) Ethanol: the OH hydrogen **donates** and a lone pair on the oxygen **accepts**. (c) Dimethylamine: the N–H hydrogen donates and the lone pair on nitrogen accepts, so **both**. (d) Acetone: the carbonyl oxygen accepts, but there is no hydrogen on O or N, so it **accepts only**. (e) Chloromethane: chlorine is not N, O or F and the hydrogens are on carbon, so **neither**. (f) Acetic acid: the OH hydrogen donates and the oxygens accept, so **both**.

Exercise 7.3. Both molecules are alcohols and can form hydrogen bonds, so the difference has to come from somewhere else. Molecule a is a chain that touches its neighbours along its whole length, so its London forces are larger. Molecule b is compact, almost a ball: three methyl groups sit on C2, they touch their neighbours at fewer places, and they also shield the OH group, so its hydrogen bonds form less easily. Both effects lower the boiling point of b, **82 °C** against **118 °C**.

Exercise 7.4. Methanol (a) mixes with water in every ratio: its OH group forms hydrogen bonds with water, and the single carbon is too small to matter. **Octane (b)** hardly dissolves at all: it has no polar bond and no OH, so nothing in it can replace the hydrogen bonds between the water molecules that it would have to push apart. **Octan-1-ol (c)** hardly dissolves either. It has an OH group like methanol, but the OH group is only a small part of a molecule with eight carbons, and the long chain turns away from water.

CHAPTER 8

Acids and bases

Almost every reaction in this book starts with a proton moving from one atom to another, so this chapter is about how to predict that move. One number does most of the work: the pKa. With it you can tell which proton in a molecule leaves first, which base is strong enough to take it, and which way an equilibrium will lie. The structure of the molecule (Chapters 1 to 7) tells you why the number is what it is.

8.1 Acids, bases and pKa

An **acid** gives away a proton, a **base** takes one. In water an acid HA hands its proton to the solvent, and how far that goes is measured by the acid dissociation constant and its logarithmic form, the **pKa**:

$$K_\mathrm{a} = \frac{[\mathrm{A^-}]\,[\mathrm{H_3O^+}]}{[\mathrm{HA}]}, \qquad \mathrm{p}K_\mathrm{a} = -\log_{10} K_\mathrm{a}$$

The pKa squeezes constants that differ by sixty orders of magnitude into a short scale. A small pKa means a strong acid (HCl, about −6); a large pKa means an acid that hardly wants to let go (methane, about 50). Every acid has a **conjugate base**, the particle left behind after the proton has gone, and the two run opposite: the stronger the acid, the weaker its conjugate base.

The same number also works when the base is not water. Take two acids, the one on the left of the equilibrium arrow and the one on the right. The acid with the lower pKa is the stronger one, so it is the one that is happy to give its proton away to the conjugate base of the other. The equilibrium therefore lies on the side of the weaker acid:

$$\mathrm{HA} + \mathrm{B^-} \rightleftharpoons \mathrm{A^-} + \mathrm{HB}, \qquad K = \frac{K_\mathrm{a}(\mathrm{HA})}{K_\mathrm{a}(\mathrm{HB})} = 10^{\,\mathrm{p}K_\mathrm{a}(\mathrm{HB}) - \mathrm{p}K_\mathrm{a}(\mathrm{HA})}$$

> **Key result.** The proton goes from the acid with the lower pKa to the base that is the conjugate of the acid with the higher pKa. A difference of one pKa unit is a factor of ten in K; a difference of three or more means the equilibrium lies almost completely on one side. When the two pKa values are close, you get a real mixture.

Figure 8.1 lines up the acidic hydrogen of nine kinds of molecule, from acetic acid (C1 is its carbonyl carbon) at about 5 to ethane at about 50. A few reference points outside the figure: HI about −10, HCl about −6, H_3O^+ −1.7, HF 3.2, NH_4^+ 9.25, water 15.7, NH_3 about 38, CH_4 about 50.

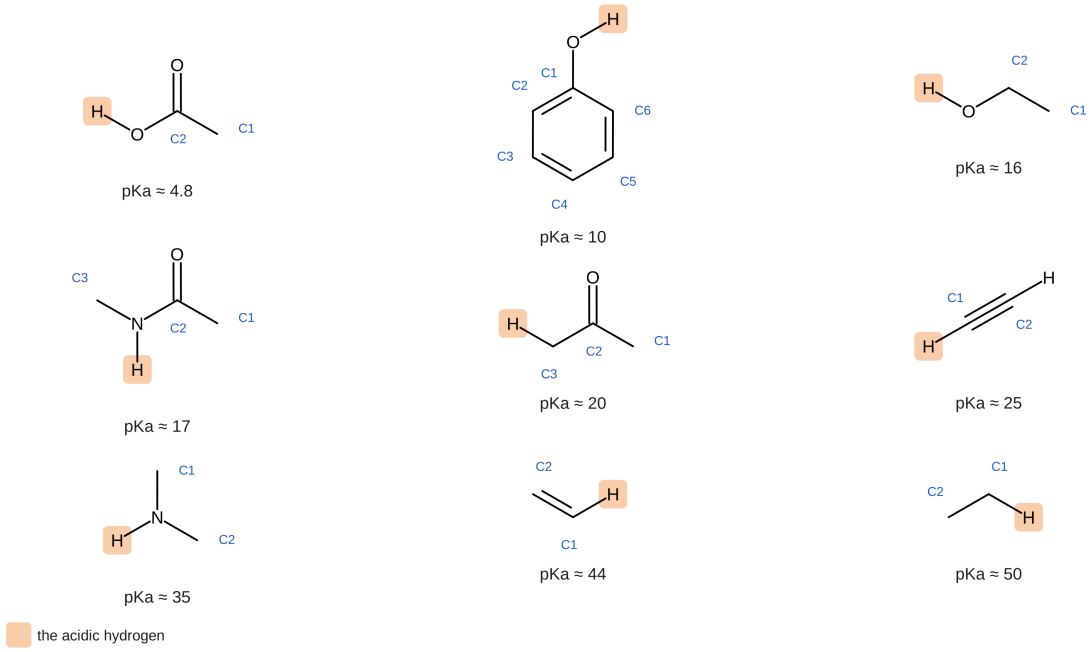


Figure 8.1. The acidic hydrogen (orange) of nine common groups, with the pKa of that hydrogen. Carbons are numbered C1, C2, … in each structure.

8.2 What makes an acid strong

An acid is strong when its conjugate base is stable. A proton that leaves, leaves its two bonding electrons behind, so the question is always: how comfortable is the negative charge on the atom that remains? Five things decide it.

The element carrying the charge. Along a row of the periodic table, the more electronegative the atom, the better it carries a negative charge: HF (pKa 3.2) > an alcohol, O–H (15 to 19) > an amine, N–H (about 35) > an alkane, C–H (about 50). In Figure 8.1 you can read this straight off the O–H of ethanol (16), the N–H of dimethylamine (35) and the C–H of ethane (50).

Down a group the trend turns around. Going down the periodic table the atoms get bigger, the negative charge spreads over a larger volume and the H–X bond gets weaker. HI is therefore a stronger acid than HF, and an S–H is more acidic than the O–H in the same place (a thiol, about 10, against an alcohol, about 16).

> **Watch out.** Electronegativity decides the order along a period, size and bond strength decide it down a group. Do not apply the first rule to the halogens: HF is the weakest of the hydrogen halides, not the strongest.

Hybridisation. For a C–H bond the acidity goes sp > sp² > sp³: ethyne about 25, ethene about 44, ethane about 50 (all in Figure 8.1). The lone pair of the carbanion that is left behind sits in the hybrid orbital that carried the bond. An sp orbital is 50% s, an sp² orbital 33% and an sp³

orbital 25%. An s orbital lies closer to the nucleus than a p orbital, so the more s character, the lower the energy of the lone pair and the happier the anion.

Induction. An electron-withdrawing group pulls electron density through the σ bonds and takes some of the charge off the atom that carries it. Acetic acid has a pKa of 4.76. Replace the three H of its methyl group (C2) with three fluorine atoms and the pKa falls to −0.25: trifluoroacetic acid is five pKa units stronger, a factor of 10^5 (Figure 8.2, top). The effect weakens quickly with every bond between the group and the acidic centre.

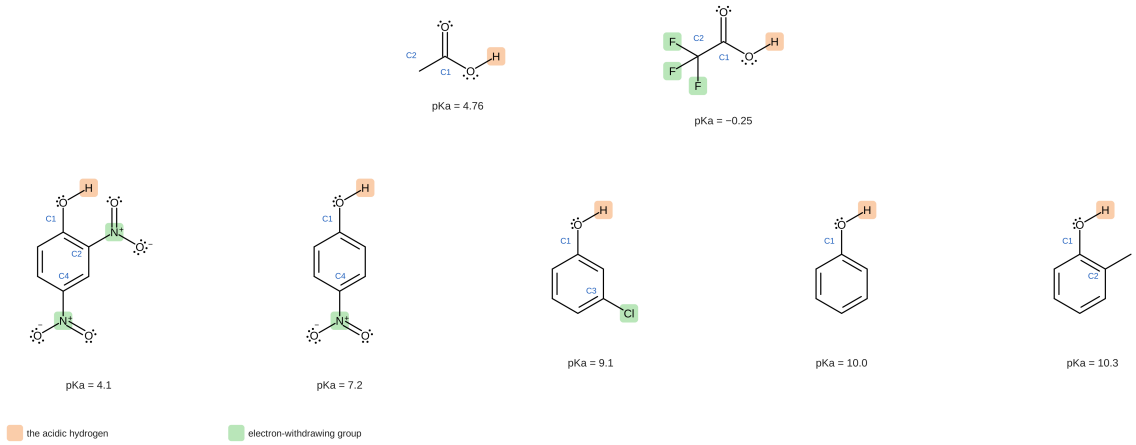


Figure 8.2. Top: induction makes trifluoroacetic acid much stronger than acetic acid. Bottom: five phenols in order of acidity; the substituent on C2, C3 or C4 (green) decides it. Orange: the acidic hydrogen. The ring carbons are numbered from the carbon that carries the OH (C1).

Resonance. If the negative charge can be spread over several atoms, the anion is stabilised far more than by any single atom. This is why acetic acid (about 5) is eleven pKa units, a factor of 10^{11}, more acidic than ethanol (16), although both lose an O–H proton. In ethoxide the charge sits on one oxygen. In acetate it is shared between two, and the two C–O bonds are identical (Figure 8.3, top; C1 is the carboxyl carbon).

Phenol (10) is about a million times more acidic than an alcohol, because the charge of phenolate can leave the oxygen and sit on C2, C4 and C6 of the ring (Figure 8.3, bottom). Resonance also explains the order in Figure 8.2. A nitro group joins the delocalisation: the charge can run all the way onto the nitro oxygens, so a nitro group on C4 lowers the pKa to 7.2, and two of them (C2 and C4) to 4.1. A chlorine on C3 cannot take part in the resonance, because no resonance form puts the charge on C3; it only withdraws electrons through the σ bonds, and the pKa drops just one unit, to 9.1. A methyl group pushes electrons towards the ring, which destabilises the anion a little, so the phenol with a methyl group on C2 comes out slightly above phenol itself, at 10.3.

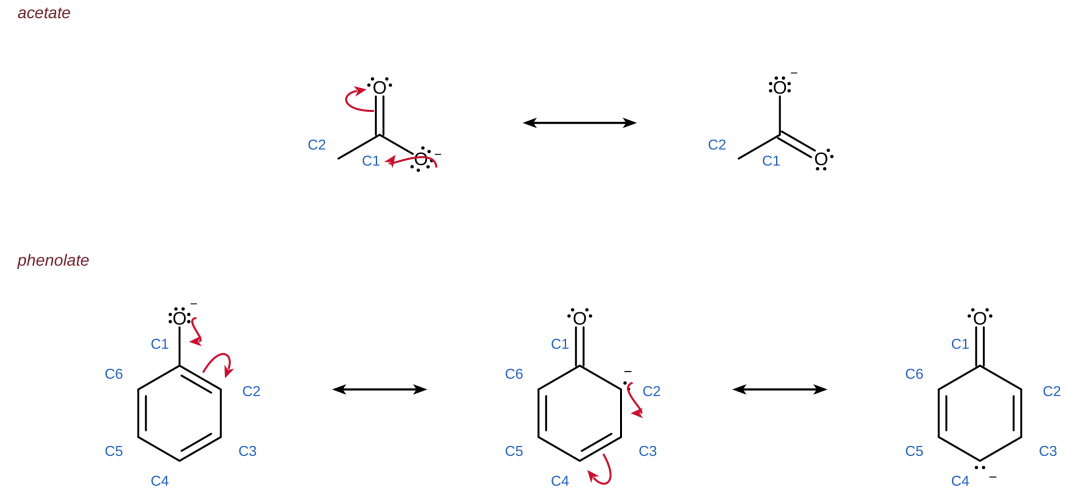


Figure 8.3. Resonance in acetate (top) and phenolate (bottom). Red arrows move electron pairs; in phenolate the charge ends up on C2 and then on C4 (and by the same steps on C6).

Sulfur and phosphorus acids. The strongest common organic acids carry the acidic O–H on an atom with several S=O or P=O bonds, so that the anion shares its charge over up to three oxygens. A sulfonic acid, such as the one at the left of Figure 8.4, has a pKa around −3 and is a strong acid like HCl. A sulfinic acid, with one S=O, is much weaker (about 2). A phosphonic acid, with one P=O and two O–H, gives up its first proton at about 1.8.

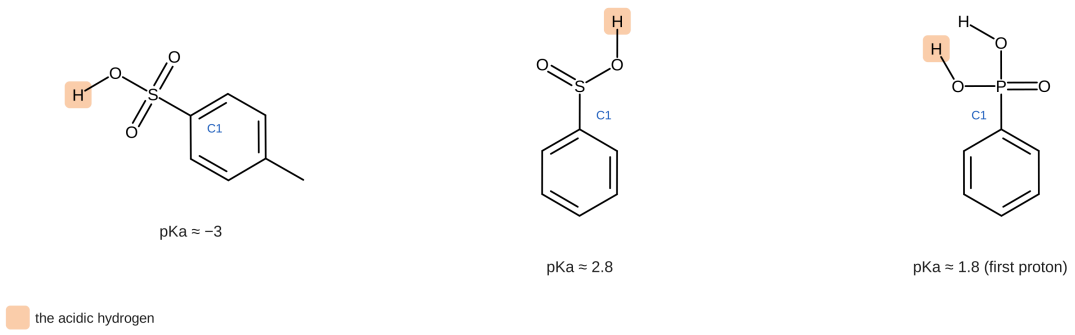


Figure 8.4. Three acids with an O–H on sulfur or phosphorus. The ring carbon bonded to S or P is C1. Orange: the acidic hydrogen.

> **Key result.** When you compare two acids, compare their conjugate bases. Ask in this order: which element carries the charge? Is it sp, sp² or sp³ if it is carbon? Is there an electron-withdrawing group near it? Can the charge be delocalised by resonance (and onto how many atoms)?

8.3 Acidic C–H next to a carbonyl

A C–H bond is normally almost not acidic at all (about 50), yet the hydrogens on the carbon next to a carbonyl group have a pKa of about 20. Figure 8.5 shows why, for the ketone with a CH_2 (C3) beside the C=O (C2). The base takes the proton of C3, the electrons of the C–H bond become the new C2=C3 π bond, and the C=O π bond shifts onto the oxygen. The result is an **enolate**, an anion that is spread over C3 and O.

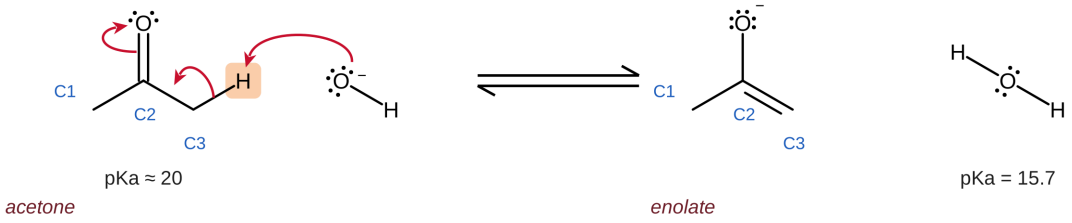


Figure 8.5. Deprotonation of the carbon next to a carbonyl. The base is hydroxide; its lone pair attacks the orange hydrogen on C3, the C3–H bond forms the C2=C3 double bond and the C2=O π bond moves onto oxygen. The pKa under each side is that of the acid: the ketone on the left (about 20) and water on the right (15.7).

Because water is a stronger acid (15.7) than the ketone (about 20), hydroxide only forms a little enolate: the exponent is 15.7 − 20 = −4.3, so $K \approx 5 \times 10^{-5}$, of the order of 10^{-4}. To make the enolate completely you need a base whose conjugate acid has a much higher pKa than 20; the bases in the next section do that. A C–H that sits between two carbonyl groups is stabilised twice and has a pKa of roughly 9 to 13.

8.4 Strong bases and predicting equilibria

A base is as strong as its conjugate acid is weak. A short list of bases that appear in the lab, with the pKa of the acid that forms when they take a proton:

Base	Conjugate acid	pKa of conjugate acid
acetate, trifluoroacetate	the carboxylic acids of Figure 8.2	4.76 and −0.25
carbonate	hydrogencarbonate	about 10
hydroxide	water	15.7
alkoxide, RO^-	alcohol, ROH	16 to 19
hydride, H^-	H_2	about 36
lithium diisopropylamide (LDA)	the amine that is LDA with H in place of Li	about 36

Base	Conjugate acid	pKa of conjugate acid
amide ion, NH_2^-	NH_3	about 38
organolithium, R–Li	the alkane R–H	about 50

Acetate and trifluoroacetate are very weak bases, carbonate and hydroxide are moderate, alkoxides are fine for acids that are stronger than an alcohol, and everything below that in the table is for deprotonating things that water or an alcohol can hardly touch. Hydroxide, carbonate and acetate are usually used as their lithium, sodium or potassium salts, which dissolve in water; the metal ion plays almost no part in the acid–base step.

Organolithium reagents are the strongest bases in common use. They are made from an alkyl chloride and lithium metal, R–Cl + 2 Li → R–Li + LiCl, and Figure 8.6 shows the three butyl versions: n-butyllithium, s-butyllithium (the C2 carbon carries the lithium) and t-butyllithium (C1 carries it). The negative charge sits on carbon, so the conjugate acid is an alkane with a pKa of about 50. **LDA**, in the same figure, is the hindered amide base: lithium sits on nitrogen between two isopropyl groups (C2 and C5 are the CH carbons), and the conjugate acid is diisopropylamine at about 36. Sodium hydride is strong for the same reason (its conjugate acid H_2 has a pKa of about 36) and has a bonus: the H_2 that forms bubbles away, so the deprotonation hardly runs backwards.

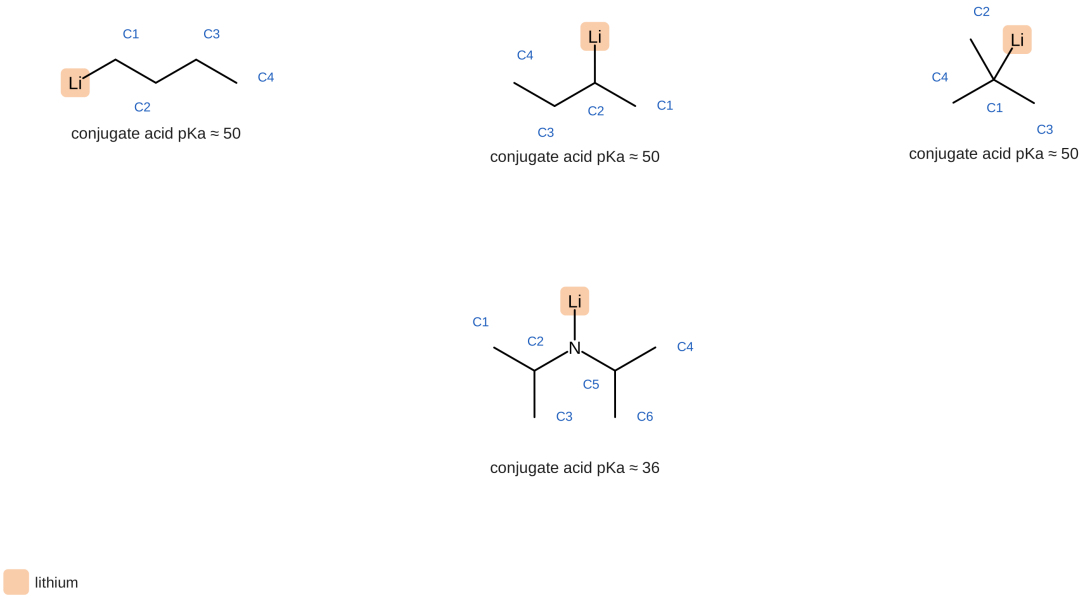


Figure 8.6. Organolithium bases (top) and LDA (bottom). Orange: lithium. The text gives the pKa of the acid that forms when each base takes a proton.

Predicting an equilibrium is now one subtraction. Write the acid–base reaction, put the pKa under each acid, and see which side holds the weaker acid.

Example 8.1. Phenol with pyridine (Figure 8.7, top). The acid on the left is phenol, pKa about 10; the acid on the right is the pyridinium ion, pKa about 5. The exponent is 5 − 10 = −5, so K = 10^{-5}, so the equilibrium lies far to the left. Pyridine is too weak a base to deprotonate phenol to any real extent.

Example 8.2. An amide with sodium amide, $NaNH_2$ (Figure 8.7, bottom). The amide N–H (pKa about 17, C1 to C3 numbered in the figure) is a far stronger acid than the ammonia that forms (about 38). The exponent is 38 − 17 = 21, so K = 10^{21}: the equilibrium lies completely on the side of the deprotonated amide.

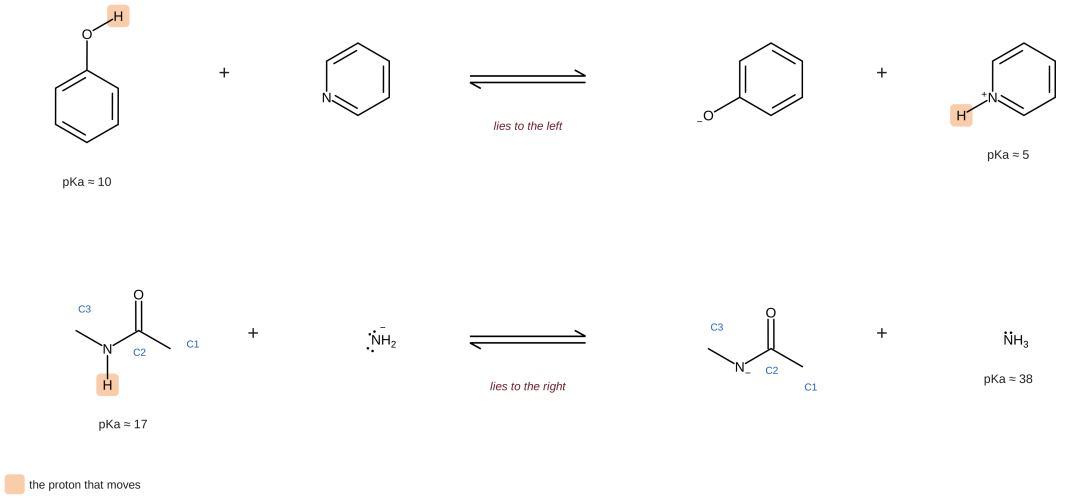


Figure 8.7. Two acid–base equilibria. Top: phenol and pyridine (lies to the left). Bottom: an amide and the amide ion NH_2^- (lies to the right). Orange: the proton that moves.

8.5 Basicity of amines and heterocycles

The table of acids works for bases too, if you read it from the other side. How basic a nitrogen is, is the pKa of its conjugate acid, the ammonium ion: a high pKa means a strong base. Figure 8.8 compares four.

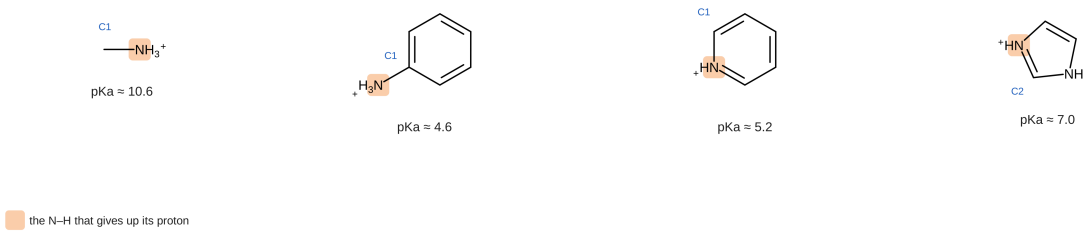


Figure 8.8. The conjugate acids of four nitrogen bases and their pKa. Orange: the N–H that is lost. C1 is the carbon on nitrogen (or, for imidazole, between the two nitrogens: C2).

- **An alkylamine** is the standard. Its ammonium ion has a pKa of about 11: the lone pair is localised on nitrogen, and the alkyl groups push electrons onto it.
- **Aniline** is a base of about 5 only (pKa of the anilinium ion 4.6), because the nitrogen lone pair is delocalised into the ring (Chapter 6); that same electron pair is needed to bind the proton, and it is more comfortable where it is.
- **Pyridine** (about 5): the lone pair of the pyridine nitrogen lies in the plane of the ring and is not part of the aromatic sextet (Chapter 6), so protonation keeps the ring aromatic. It is weaker than an alkylamine because that lone pair sits in an sp^2 orbital, with more s character than an sp^3 lone pair, and an s-rich lone pair is held tighter.
- **Imidazole** (about 7) is the best of the heterocycles: when its pyridine-type nitrogen picks up a proton, the cation has two equivalent resonance forms that share the charge over both nitrogens.
- Two nitrogens are hardly basic at all. The lone pair of the N–H of pyrrole (Figure 6.6) is part of the aromatic sextet, and protonating it would destroy the aromaticity; the lone pair of an amide nitrogen is delocalised onto the C=O oxygen (Chapter 6), so an amide is protonated on oxygen, and only in strong acid.

> **Watch out.** Two pKa values belong to an amine. The N–H of the amine itself (a proton leaving a neutral amine, about 35) is a hopeless acid. The N–H of its ammonium ion (about 11) is a decent weak acid. When a question asks about basicity, use the second.

Exercises

Exercise 8.1. In each pair in Figure 8.9, which compound is the stronger acid? Give the factor by which it is stronger, using the pKa values under the structures. In one sentence per pair, say why.

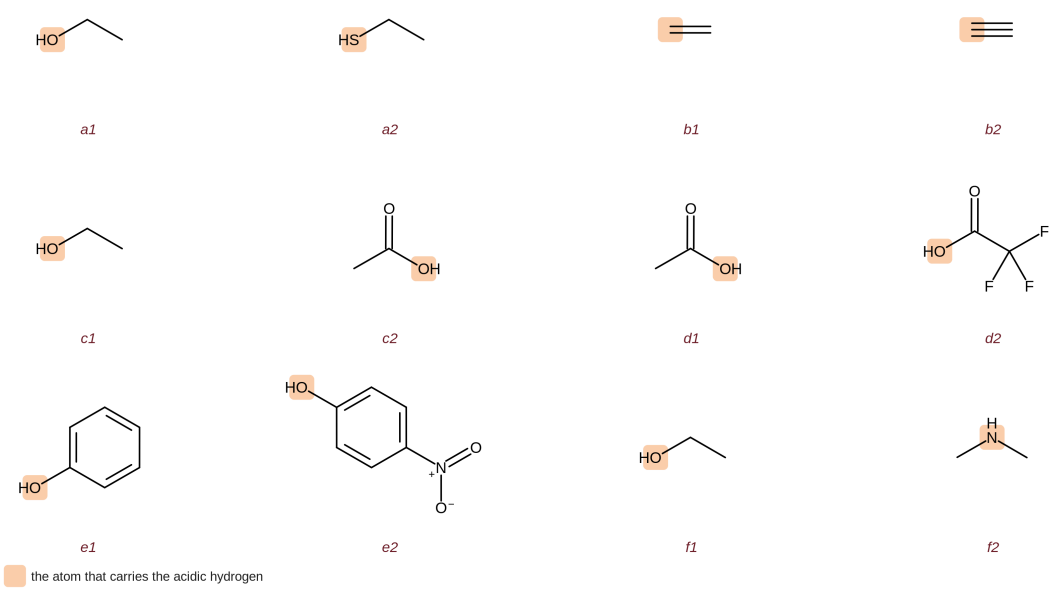


Figure 8.9. Six pairs of acids. The highlighted atom carries the hydrogen that leaves as H^+.

Exercise 8.2. Complete the three acid–base reactions in Figure 8.10: draw the two products, take the pKa of each acid from this chapter, work out the equilibrium constant K and say on which side the equilibrium lies.

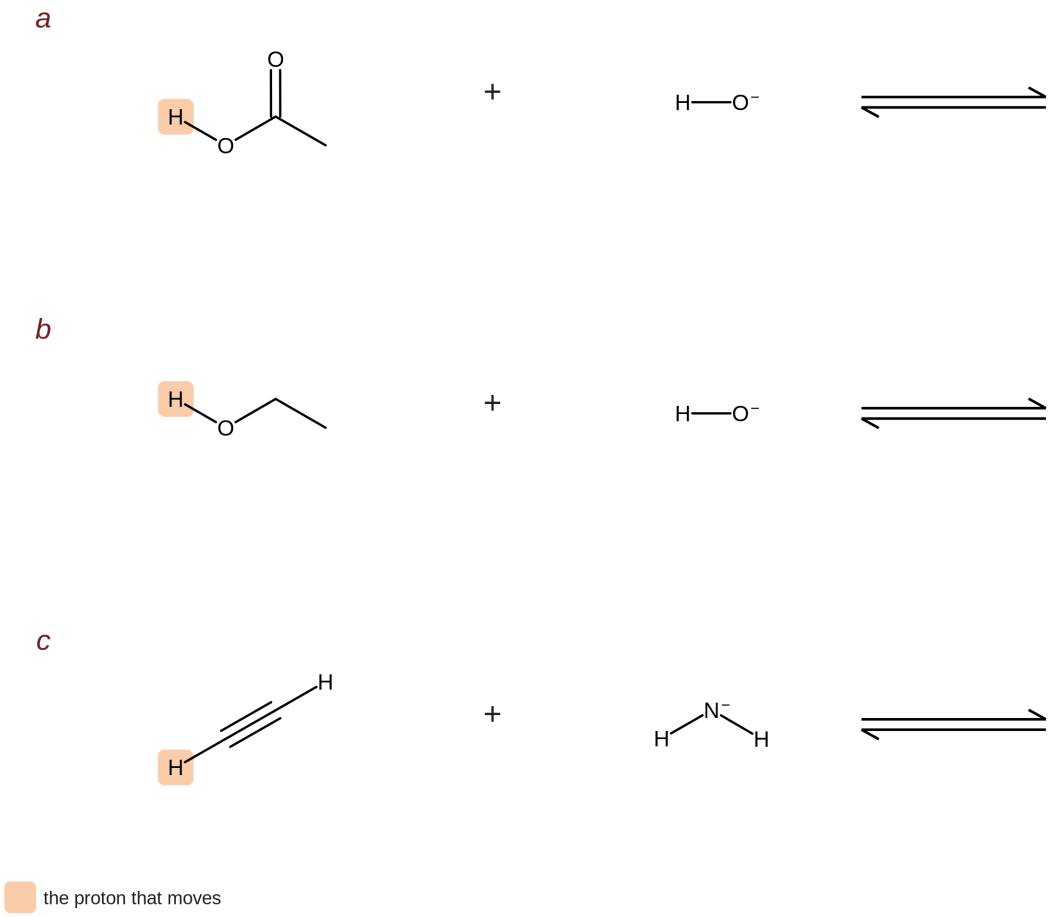


Figure 8.10. Three acid–base reactions. Only the reactants are given; the proton that moves is highlighted.

Exercise 8.3. Rank the five nitrogen compounds in Figure 8.11 from the weakest to the strongest base, and explain every step of the ranking in terms of where the lone pair on the highlighted nitrogen sits.

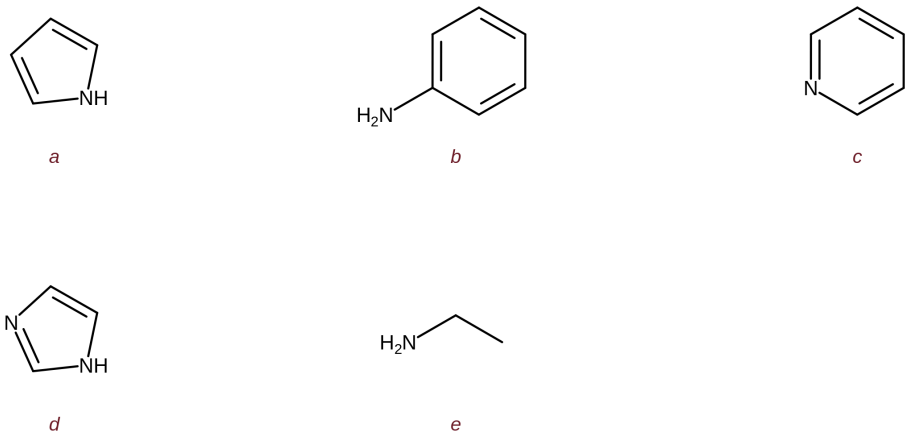
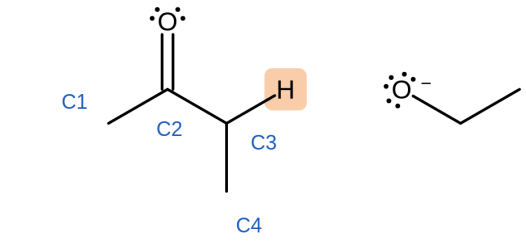


Figure 8.11. Five nitrogen bases. The highlighted nitrogen is the one that would take the proton.

Exercise 8.4. Ethoxide takes the hydrogen on C3 from the ketone in Figure 8.12. Draw the complete mechanism with curved arrows on these molecules, including the resonance that makes the product a stable anion. Then work out K for this step and say on which side the equilibrium lies.



pKa ≈ 20

butanone

Figure 8.12. The ketone and the base. C1 to C4 are numbered; the hydrogen on C3 is highlighted.

Solutions

Solution 8.1. The stronger acid is the one with the lower pKa; the factor is 10 to the power of the pKa difference (Figure 8.13).

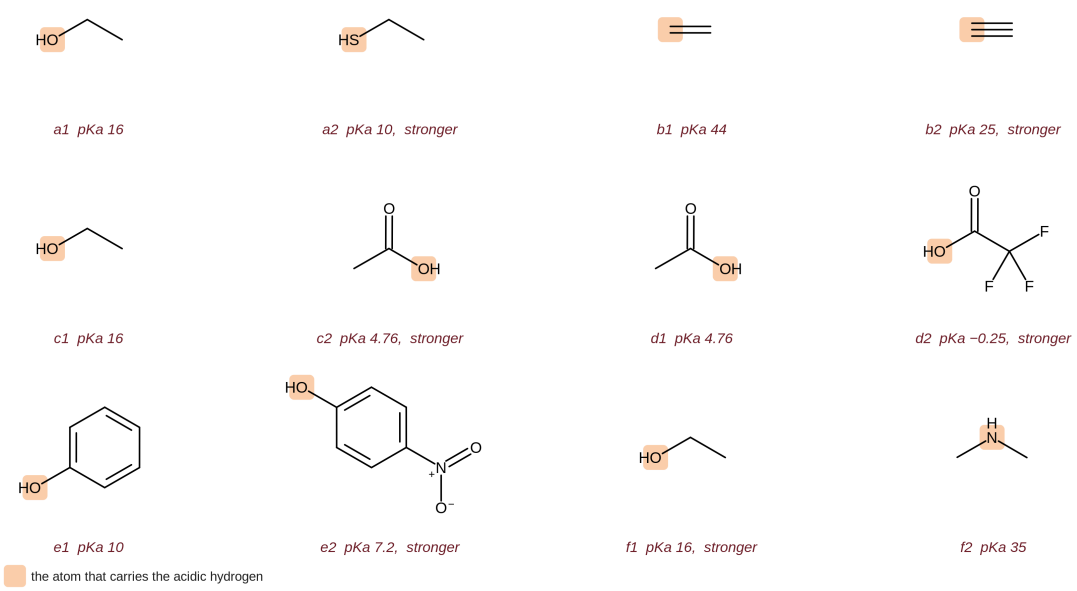


Figure 8.13. The stronger acid of each pair is marked.

- **a. a2 is stronger, by a factor 10^6** (16 − 10 = 6). Sulfur is larger than oxygen, so the negative charge in the thiolate is spread over a bigger volume, and the S–H bond is longer and weaker.
- **b. b2 is stronger, by a factor 10^{19}** (44 − 25 = 19). The lone pair of the anion sits in an sp orbital (50 % s) in the alkyne and in an sp^2 orbital (33 % s) in the alkene; the more s character, the closer the electrons are held to the nucleus.
- **c. c2 is stronger, by a factor 10^{11}** (16 − 4.76 = 11.2). The carboxylate charge is shared over two oxygens by resonance; the alkoxide charge has nowhere to go.
- **d. d2 is stronger, by a factor 10^5** (4.76 − (−0.25) = 5.0). The three fluorines pull electrons through the σ bonds (inductive effect) and stabilise the carboxylate.
- **e. e2 is stronger, by a factor of about 600** (10 − 7.2 = 2.8, so 10 raised to 2.8 is about 630). The nitro group sits para to the O^- and takes part of the charge by resonance.
- **f. f1 is stronger, by a factor 10^{19}** (35 − 16 = 19). Oxygen is more electronegative than nitrogen, so it carries the negative charge more comfortably.

Solution 8.2. For acid 1 + base ⇌ conjugate base 1 + acid 2, the equilibrium constant is K = 10 raised to the power (pKa of acid 2 − pKa of acid 1). The equilibrium lies on the side of the weaker acid (Figure 8.14).

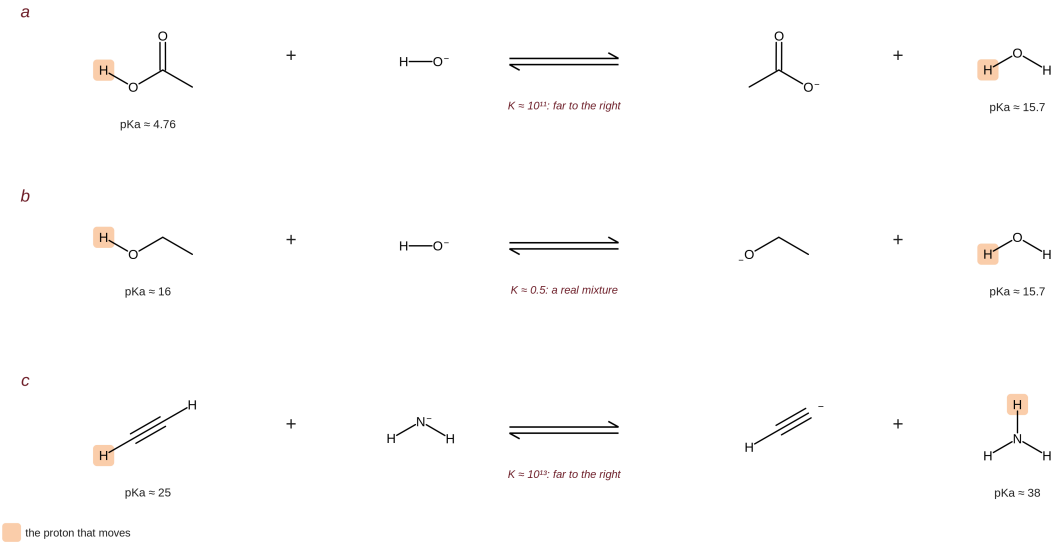


Figure 8.14. The three equilibria completed. The pKa under each acid is the one used in the calculation.

- **a.** The acid on the left has pKa 4.76 and the acid on the right (water) 15.7: the exponent is 15.7 − 4.76 = 10.9, so K ≈ 8 × 10^{10}, of the order of 10^{11}. **The equilibrium lies far to the right.** Hydroxide deprotonates the carboxylic acid completely for all practical purposes.
- **b.** pKa 16 on the left, 15.7 on the right: the exponent is 15.7 − 16 = −0.3, so K ≈ 0.5. **A real mixture of all four species**, with a slight preference for the left.
- **c.** pKa 25 on the left, 38 on the right: the exponent is 38 − 25 = 13, so K = 10^{13}. **The equilibrium lies far to the right.** Amide is a strong enough base to deprotonate the alkyne quantitatively; hydroxide is not (25 > 15.7, so the exponent would be 15.7 − 25 = −9.3 and K ≈ 5 × 10^{-10}).

Solution 8.3. Pyrrole (a) < aniline (b) < pyridine (c) < imidazole (d) < ethylamine (e) (Figure 8.15).

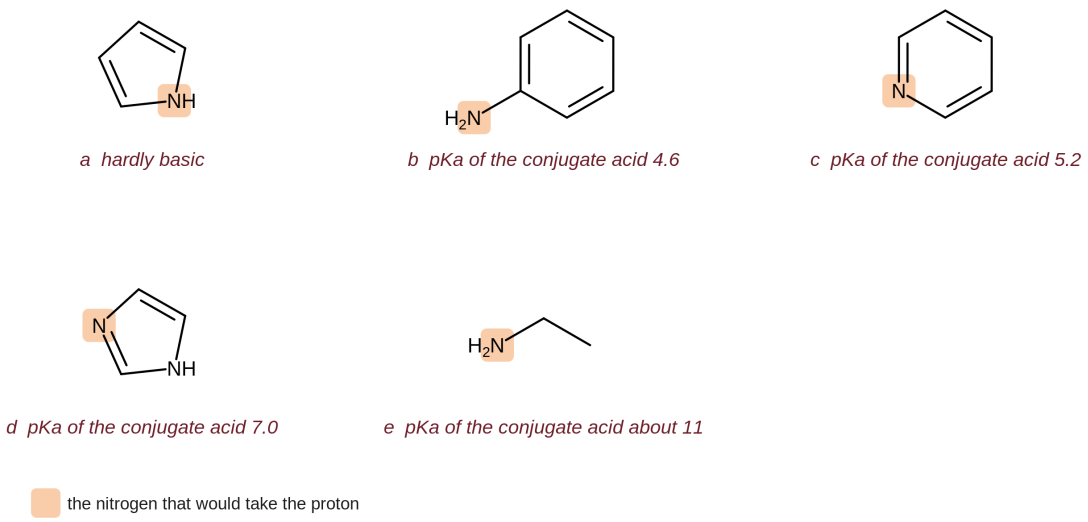


Figure 8.15. The five bases with the pKa of their conjugate acids. From a to e they run from the weakest to the strongest base.

- **Pyrrole is hardly basic.** The nitrogen lone pair is part of the aromatic sextet. Putting a proton on it would use up that pair and destroy the aromaticity.
- **Aniline** (conjugate acid 4.6): the lone pair is not part of a ring sextet, but it is conjugated with the ring and so delocalised over the ortho and para carbons. Less available, weaker base.
- **Pyridine** (5.2): the lone pair sits in an sp^2 orbital in the plane of the ring and does not take part in the aromatic π system, so protonation costs no aromaticity. But sp^2 holds the pair closer to the nucleus than sp^3 does, so it is a weaker base than an amine.
- **Imidazole** (7.0): the same kind of nitrogen as in pyridine, but after protonation the charge is shared between both nitrogens by resonance, which stabilises the conjugate acid.
- **Ethylamine** (about 11): a localised sp^3 lone pair, with an alkyl group that pushes electron density towards the nitrogen. The strongest of the five.

Solution 8.4. Three arrows, one electron pair each (Figure 8.16): the lone pair on the ethoxide oxygen forms the new O–H bond to the hydrogen on C3; the C3–H bond electrons move into the new C2=C3 π bond; and the C2=O π electrons move onto oxygen as a lone pair.

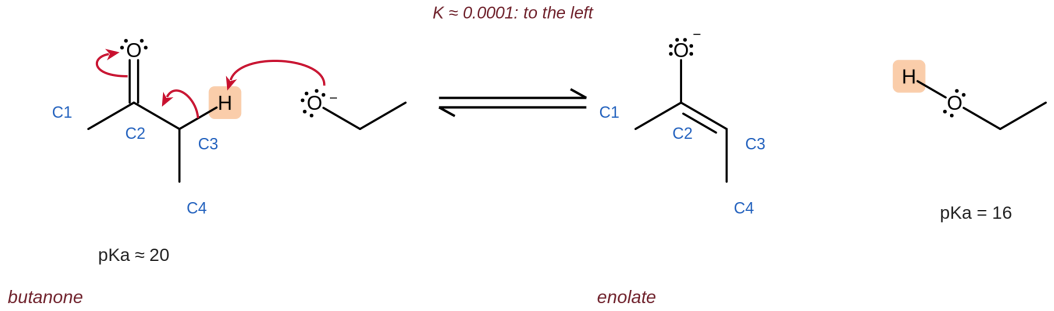


Figure 8.16. Deprotonation of the ketone on C3. The enolate on the right carries its charge on oxygen; the resonance form with the charge on C3 shows why the enolate is also a carbon nucleophile.

The negative charge ends up on oxygen, where a charge is comfortable, and is shared with C3 by resonance. The acids are the ketone (pKa about 20) and ethanol (16): the exponent is 16 − 20 = −4, so K = 10^{-4}. **The equilibrium lies on the left**: only about one molecule in ten thousand is deprotonated at any moment. That is still enough for the enolate to react with an electrophile, because the equilibrium refills as the enolate is consumed.

CHAPTER 9

Hemiacetals and acetals

An aldehyde or a ketone reacts with an alcohol, in the presence of a little acid, in two steps: first to a **hemiacetal**, then to an **acetal**. It is the first full mechanism of this book, and it is built from the pieces of the previous chapters: a lone pair that attacks, a cation made stable by a neighbouring oxygen, and a proton that moves back and forth between oxygens of very different basicity.

9.1 Hemiacetals and acetals

In a **hemiacetal** the carbon that used to be the carbonyl carbon carries an OH and an O–R group. In an **acetal** it carries two O–R groups, and no OH is left. (When the starting material is a ketone, the two compounds used to be called a hemiketal and a ketal; IUPAC now treats them as subclasses of hemiacetals and acetals. The mechanism is the same.) A hemiacetal is an alcohol and an ether on the same carbon; an acetal is two ethers on the same carbon.

The whole reaction, with the acid only as a catalyst, is:

$$\mathrm{R{-}CHO} \;+\; 2\,\mathrm{R'OH} \overset{\mathrm{H^+}}{\rightleftharpoons} \mathrm{R{-}CH(OR')_2} \;+\; \mathrm{H_2O}$$

We follow it on benzaldehyde and methanol. C1 is the carbon of the former C=O, C2 the methyl carbon of the first methanol and C3 that of the second. There are seven steps in three figures.

9.2 Making the hemiacetal

Methanol is a weak nucleophile and the C=O carbon of an aldehyde is only moderately electrophilic, so without acid the reaction hardly moves. The acid helps by making the carbonyl carbon far more electrophilic.

Step 1: protonation of the carbonyl oxygen. A lone pair of the carbonyl oxygen takes up H^+ (the first red arrow of Figure 9.1). The resulting cation has two resonance forms: C=O$^+$–H, and C$^+$–O–H with the positive charge on carbon. The truth is a hybrid of the two, and that is what matters: the positive charge now sits partly on C1, which has become a very good electrophile.

Step 2: the alcohol attacks. A lone pair of the methanol oxygen forms a new bond to C1, and at the same time the C=O π electrons move onto the oxygen, which becomes a neutral OH (two arrows in the second panel of Figure 9.1). The new oxygen now carries three bonds and a positive charge, an oxonium ion. C1 has turned from sp^2 (trigonal) into sp^3 (tetrahedral).

Step 3: loss of a proton. The O⁺–H bond breaks and its electrons stay on oxygen: a proton goes to the solvent (a methanol molecule or a trace of water) and the neutral **hemiacetal** is formed. For every proton that step 1 took out of the solution, step 3 gives one back, which is why the acid is only a catalyst.

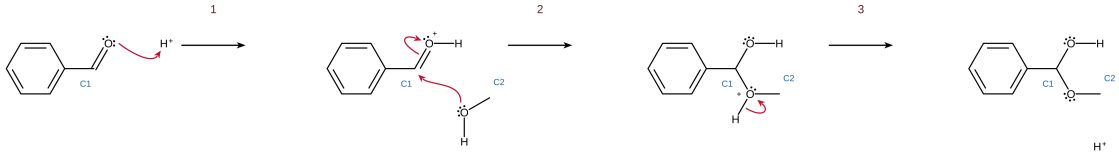


Figure 9.1. Steps 1 to 3: benzaldehyde and methanol give the hemiacetal. C1 is the carbonyl carbon of benzaldehyde, C2 the carbon of the methanol. Red arrows show the movement of electron pairs; the H⁺ on the right of the last panel is the catalyst, which returns to the solution.

> **Watch out.** An arrow that protonates a carbonyl starts at the lone pair on oxygen, not at the C=O double bond: the lone pair is the electron pair that is available, and the C=O π bond is still needed afterwards. A double bond first becomes the source of an arrow in step 2, once the oxygen already carries the proton.

9.3 From hemiacetal to acetal

A hemiacetal is mostly an intermediate: it stays in equilibrium with the aldehyde and the alcohol. To go further, the OH on C1 has to be replaced by OCH_3, and an OH is a poor leaving group: hydroxide would have to leave as HO^-, the conjugate base of water (pKa 15.7). The acid solves this in the same way as before.

Step 4: protonation of the OH. A lone pair of the OH oxygen takes up H^+ (Figure 9.2, left). The oxygen now holds three bonds and a positive charge, and what is going to leave is no longer HO^- but a neutral water molecule, the conjugate base of H_3O^+ (pKa −1.7), which is a very good leaving group.

Step 5: loss of water. A lone pair on the other oxygen (the OCH_3, with C2) moves in to form a C1=O⁺ double bond, while the C1–OH_2^+ bond breaks and the electrons go to oxygen: water leaves (Figure 9.2, two arrows). What is left is an **oxocarbenium ion**: C1 is now sp^2 again and the positive charge is shared between C1 and the oxygen. The lone pair of the neighbouring oxygen is what pays for the loss of water, and that is why an OR group on the carbon makes the departure so easy.

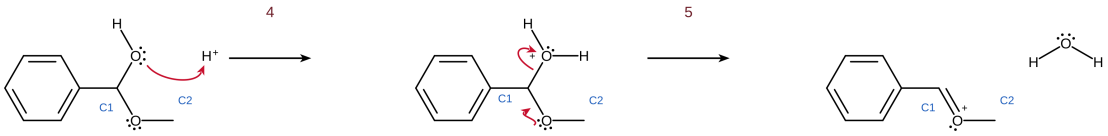


Figure 9.2. Steps 4 and 5: the hemiacetal is protonated on its OH group and loses water to give the oxocarbenium ion. In the last panel the water has left the ion and sits beside it.

Step 6: the second alcohol attacks. A second molecule of methanol (C3) uses a lone pair to bond to C1, and the C1=O⁺ π electrons go back onto the oxygen, so that this oxygen is neutral again (Figure 9.3, left). C1 is planar in the oxocarbenium ion, so methanol can approach from either face.

Step 7: loss of a proton. As in step 3, the O⁺–H proton leaves with its electrons staying on oxygen. The product is the **acetal**, with two OCH_3 groups on C1, and H^+ is back in solution (Figure 9.3, right).

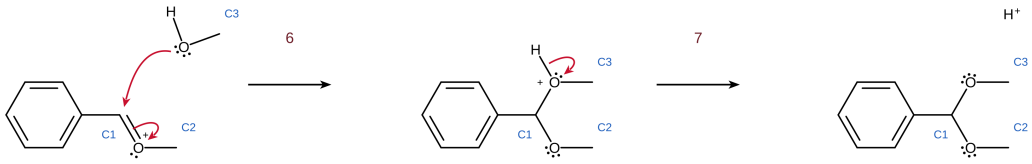


Figure 9.3. Steps 6 and 7: the oxocarbenium ion adds a second methanol (carbon C3) and loses a proton to give the acetal. The two OCH_3 groups on C1 are the signature of an acetal.

9.4 Why it needs acid, and how to steer it

All seven steps are reversible. Two consequences follow, and they are what you need to know when using acetals; a third paragraph explains why acid is needed at all.

Formation. The equilibrium is pushed towards the acetal by removing the water (a drying agent, molecular sieves, or distilling it off) or by using the alcohol in large excess. A hemiacetal on its own is usually not worth isolating; the exception is a ring, where the OH and the C=O sit in the same molecule and the ring-closed hemiacetal is the stable form. Sugars close their rings in exactly this way.

Hydrolysis. The reaction runs backwards, step for step, when an acetal is stirred with aqueous acid: protonation of an OR oxygen, loss of ROH to give the oxocarbenium ion, attack of water, loss of H^+. That is why an acetal is a protecting group for a carbonyl: it survives bases,

nucleophiles and organometallic reagents, and a drop of acid in water releases the carbonyl again.

Why acid and not base. Base deprotonates the alcohol, which gives a better nucleophile (a hemiacetal can still form), but it cannot make the carbonyl more electrophilic, and without acid no leaving group is made out of the OH of the hemiacetal, so the reaction stops there. An acetal cannot form under basic conditions, and is stable in them.

The acid itself needs to be strong, because the carbonyl oxygen is a very weak base: the pKa of a protonated aldehyde or ketone is around −7. Only a minute fraction of the carbonyl is protonated at any moment, but that fraction is enormously reactive, and the catalyst is regenerated at once. A strong, organic-soluble acid such as p-toluenesulfonic acid (Figure 8.4, pKa about −3) is the usual choice; the proton for steps 3 and 7 is taken up by methanol, whose protonated form has a pKa of about −2, so these steps run downhill.

Example 9.1. Benzaldehyde dissolved in methanol with a catalytic amount of an acid such as p-toluenesulfonic acid gives the hemiacetal quickly and the acetal of Figure 9.3 more slowly; to obtain it in good yield the water that forms is removed, or the methanol is used as the solvent. Adding a large excess of water and a little acid to the acetal sends the reaction back to benzaldehyde and methanol.

> **Key result.** Acid catalysis does two jobs: it makes the carbonyl carbon electrophilic (step 1) and it makes OH leave as water (step 4). Once the OH is protonated, a neighbouring oxygen lone pair drives the loss of water (step 5), and the proton that came in is given back to the solution in steps 3 and 7. Aldehyde or ketone + two alcohols ⇄ acetal + water: remove the water to form the acetal, add water and acid to take it back.

Exercises

Exercise 9.1. The acetal in Figure 9.4 is stirred in water with a little acid (drawn here as H_3O^+). Draw the mechanism of the first half of its hydrolysis, step by step with every curved arrow, until the hemiacetal is formed. Four steps are needed. The kinetics of this reaction for benzaldehyde acetals are described by Bull, Pletcher and Cordes (1970), see the References.

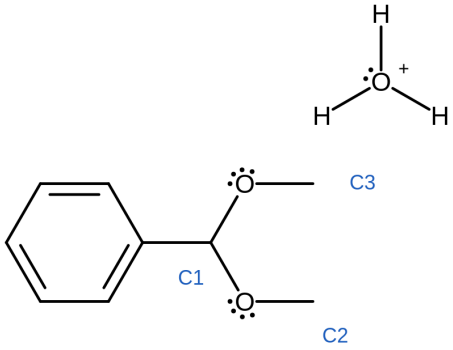


Figure 9.4. The acetal and the acid. C1 is the carbon that carried the C=O, C2 and C3 the two methyl carbons.

Exercise 9.2. The compound in Figure 9.5 has an aldehyde and an alcohol in the same molecule. With a trace of acid it closes to a ring. Draw the mechanism with every curved arrow, keep the carbon numbering, and say what the ring compound is called in the language of this chapter. Why does this reaction need no second molecule of alcohol? (This ring–chain equilibrium was studied by Hurd and Saunders, 1952.)

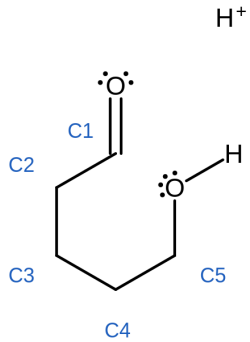


Figure 9.5. A hydroxy-aldehyde that can close onto itself. C1 is the aldehyde carbon, C5 carries the OH.

Exercise 9.3. The hemiacetal in Figure 9.6 has two oxygens that can take up a proton. Draw both protonated forms and, for each of them, the loss of the leaving group with the curved arrows. Which one leads on towards the acetal and which one leads back to the aldehyde?

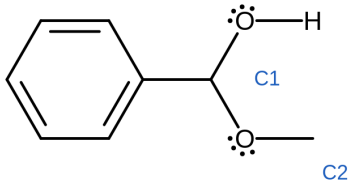


Figure 9.6. The hemiacetal. Its OH and its OCH_3 group can each be protonated.

Exercise 9.4. An acetal is (a) stirred with a strong base in water, (b) stirred with dilute aqueous acid. What happens in each case, and why?

Solutions

Solution 9.1. The hydrolysis is the formation read backwards (Figure 9.7). **Step 1:** a lone pair of one OCH_3 oxygen takes a proton from H_3O^+ (two arrows: lone pair to H, O–H bond of H_3O^+ to the lone pair of its oxygen). **Step 2:** a lone pair of the other OCH_3 oxygen forms the C1=O^+ double bond while the C1–O^+ bond of the protonated group breaks and methanol leaves; the result is the oxocarbenium ion. **Step 3:** a lone pair of water forms the new bond to C1, and the C1=O^+ π electrons move onto oxygen. **Step 4:** the O^+–H bond breaks, its electrons stay on oxygen, and H^+ leaves: the hemiacetal.

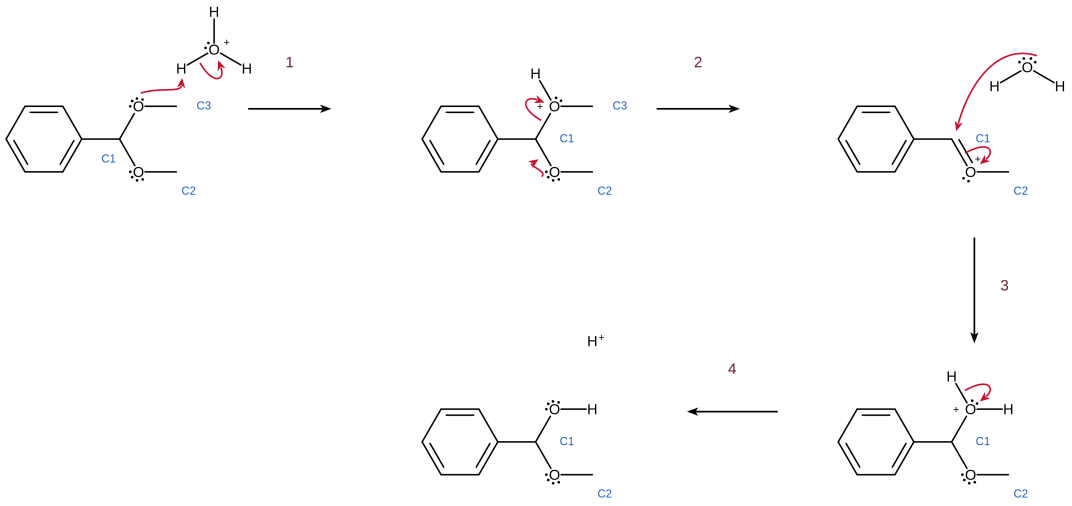


Figure 9.7. Hydrolysis of the acetal to the hemiacetal. Steps 1 and 2 are steps 7 and 6 of Figure 9.3 backwards, and steps 3 and 4 are steps 5 and 4 of Figure 9.2 backwards; methanol and water are the small molecules that leave and arrive.

The hemiacetal then goes on to the aldehyde by reversing steps 3, 2 and 1 of Figure 9.1. A large excess of water pushes the whole equilibrium in this direction.

Solution 9.2. The product is a cyclic hemiacetal (Figure 9.8). **Step 1:** a lone pair of the carbonyl oxygen takes up H^+. **Step 2:** a lone pair of the OH oxygen on C5 attacks C1 and closes the six-membered ring, while the C1=O^+ π electrons move onto oxygen, which becomes the OH on C1. **Step 3:** the ring oxygen loses its proton and H^+ leaves. The ring contains C1 to C5 and the ring oxygen.

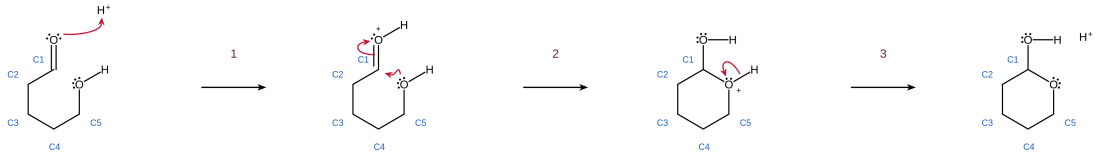


Figure 9.8. Ring closure of the hydroxy-aldehyde. C1 now carries an OH and the ring oxygen: the signature of a hemiacetal.

No second alcohol is needed because the alcohol is already in the molecule, a few bonds from the carbonyl: the attack is intramolecular, and a six-membered ring closes without strain. That is why ring-closed hemiacetals can be the stable form, and why sugars, which have the same C1 to C5 pattern, live mostly as rings.

Solution 9.3. Protonation of the OH leads on towards the acetal; protonation of the OCH_3 leads back to the aldehyde (Figure 9.9).

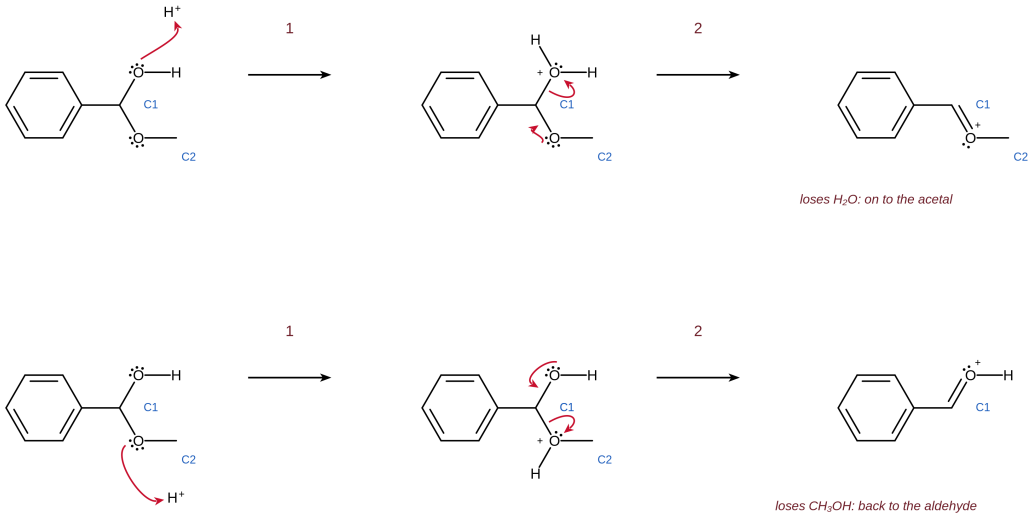


Figure 9.9. Top: OH protonated, water leaves, oxocarbenium ion. Bottom: OCH_3 protonated, methanol leaves, protonated aldehyde.

In the top row the proton goes on the OH oxygen; a lone pair of the OCH_3 oxygen pushes in to form C1=O^+ while water leaves. The OCH_3 group stays on C1, so this ion can add a second methanol (steps 6 and 7) to give the acetal. In the bottom row the proton goes on the OCH_3 oxygen; a lone pair of the OH oxygen pushes in while methanol leaves. What is left is a protonated aldehyde, which is simply where the reaction started. Both protonations happen all the time and both are reversible; only the first one gets you further.

Solution 9.4. (a) Nothing happens, and an acetal is stable in base. Hydroxide finds no acidic hydrogen on carbon to take, cannot protonate an acetal oxygen, and the acetal carbon is not electrophilic enough to attack: the OR group would have to leave as RO^-, a very poor leaving group (pKa of an alcohol about 16), and nothing in the solution can make it better. **(b) It hydrolyses.** The acid protonates an OR oxygen, the group leaves as a neutral alcohol, and the oxocarbenium ion takes up water (Solution 9.1); in a large excess of water the equilibrium lies on the side of the carbonyl compound and the alcohol.

References

The exercises on the acid-catalysed chemistry of aldehydes and acetals (Chapter 9) follow the reactions reported in these papers.

1. Hurd, C. D.; Saunders, W. H. Ring–chain tautomerism of hydroxy aldehydes. *J. Am. Chem. Soc.* **1952**, 74, 5324–5329. https://doi.org/10.1021/ja01141a030
2. Bull, H. G.; Pletcher, T. C.; Cordes, E. H. Secondary deuterium isotope effects for hydrolysis of acetals and orthoformates. *J. Chem. Soc. D* **1970**, 527–528. https://doi.org/10.1039/C29700000527

Index of mechanisms and derivations

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- Acid–base equilibria with a proton moving between two species: section 8.4 and Solution 8.2.
- Acid-catalysed formation of a hemiacetal: section 9.2 (steps 1 to 3, Figure 9.1).
- Acid-catalysed formation of an acetal through the oxocarbenium ion: section 9.3 (steps 4 to 7, Figures 9.2 and 9.3).
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- Isolated against conjugated double bonds, from heats of hydrogenation: section 6.1.
- The resonance energy of benzene, from heats of hydrogenation: section 6.3.
- The wavelength of a $\pi \rightarrow \pi^*$ transition from an energy per mole: section 6.4 and Example 6.3.
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