

Isomerism (Structural and Stereoisomerism)

Last-minute revision: the key ideas, standard results and traps of every part. The formula sheet is the last page.

If you only have five minutes

- Isomers: same molecular formula. Structural (chain, position, ring-chain, functional, metamerism, tautomerism) vs stereo (geometrical, optical, conformational).
- D.B.E. = $\frac{\sum n(v-2)}{2} + 1$: O adds nothing; each D.B.E. is a ring or a π bond.
- Tautomerism needs an α -H and an EWG; enol helped by chelation, conjugation, aromaticity, non-polar solvents.
- Geometrical: restricted rotation + two different groups per end. m.p. trans higher, b.p. cis higher.
- Chiral: no plane or centre of symmetry. $[\alpha] = \frac{\alpha_{\text{obs}}}{l \times c}$ with l in dm.
- Optical isomers: 2^n only for unsymmetrical molecules; meso forms reduce the count.
- Fischer: 180° keeps the molecule, 90° gives the enantiomer. D/L $\neq$ d/l.
- Butane: anti > gauche > partly > fully eclipsed. Cyclohexane: chair; big groups equatorial; 1,3: cis is e,e.

1 Isomers: Chain, Position and Ring-Chain

- Isomers: same molecular formula, different structure and properties (ethanol vs dimethyl ether).
- Structural: chain, position, ring-chain, functional, metamerism, tautomerism. Stereo: geometrical, optical (configurational) and conformational.
- Chain: different skeleton (n-butane / isobutane). Position: same skeleton, group or C=C moved.
- Ring-chain: alkene vs cycloalkane (C_4H_8 : but-1-ene, cyclobutane, methylcyclopropane).

STANDARD RESULTS

n-Propyl and isopropyl alcohol: position isomers.

TRAPS

- ✗ Calling "but-3-ene" a new isomer. Number from the other end first: it is but-1-ene.
- ✗ Calling an alkene and a cycloalkane chain isomers. They are ring-chain isomers (functional isomers if ring-chain is not an option).

2 Functional Isomerism

- Functional isomers: same formula, different functional group.
- $C_nH_{2n+2}O$: alcohols and ethers. $C_nH_{2n}O$: aldehydes, ketones, unsaturated alcohols and ethers, cyclic ethers and alcohols.
- $C_nH_{2n}O_2$: acids, esters, hydroxy carbonyls. C_nH_{2n-2} : alkynes, dienes, cycloalkenes.
- Pairs: $-CN/-NC$, $-NO_2/-ONO$, $1^\circ/2^\circ/3^\circ$ amines, oxime/amide, thiol/thioether; C_7H_8O : benzyl alcohol, cresols, anisole.

STANDARD RESULTS

Propan-1-amine and propan-2-amine are position isomers, not functional isomers.

TRAPS

- ✗ Listing only the aldehyde and ketone for $C_nH_{2n}O$. Unsaturated alcohols, unsaturated ethers and cyclic compounds fit too.
- ✗ Forgetting hydroxy carbonyls for $C_nH_{2n}O_2$. 2-Hydroxypropanal and 1-hydroxypropan-2-one are $C_3H_6O_2$.

3 Metamerism

- Metamerism: same homologous series, different alkyl groups around a polyvalent group.
- Ethers, thioethers, ketones, amines, amides and esters all show it.
- Pentan-2-one / pentan-3-one: metamers and position isomers; pick metamerism if offered.
- Book convention: methyl propyl and isopropyl methyl ketone are called metamers (others say chain isomers).

STANDARD RESULTS

Metamers of ethyl propionate: $CH_3COOC_3H_7$ and $C_3H_7COOCH_3$.

TRAPS

- ✗ Calling pentan-2-one and pentan-3-one only position isomers. They are metamers too; choose metamerism if it is offered.
- ✗ Including an acid among metamers of an ester. An acid is a functional isomer; metamers keep the same functional group.

4 Tautomerism and Keto-Enol Equilibrium

- Tautomers: dynamic equilibrium by a mobile H; dyad (1 $\rightarrow$ 2) and triad (1 $\rightarrow$ 3).
- Keto more stable by ≈ 18 kcal/mol ($C=O$ π stronger than $C=C$ π).

- Enol favoured by chelation, conjugation, aromaticity, ketone (not ester) C=O, non-polar solvents.
- Acid: protonate O, then lose α -H. Base: remove α -H (enolate), then protonate O.
- No α -H (benzaldehyde, benzophenone, p-benzoquinone) or bridgehead α -H: no tautomerism.

STANDARD RESULTS

Acetylacetone $\approx$ 76 % enol; ethyl acetoacetate $\approx$ 7 %; phenol 100 %.

Ethyl acetoacetate: 0.4 % (water) $\rightarrow$ 46 % (hexane).

TRAPS

- ✗ **Assuming a more polar solvent gives more enol.** Polar protic solvents H-bond to the keto C=O; non-polar solvents or the gas phase raise the enol content.
- ✗ **Treating a bridgehead α -H as enolisable.** The C=C would sit at a bridgehead, which Bredt's rule forbids.

5 Other Types of Tautomerism

- Para: H from the para carbon; dienone $\rightleftharpoons$ phenol, 4-pyridone $\rightleftharpoons$ 4-hydroxypyridine.
- Nitrite $\rightleftharpoons$ nitro, nitro $\rightleftharpoons$ aci-nitro, nitroso $\rightleftharpoons$ oxime (oxime more stable).
- Imine $\rightleftharpoons$ enamine, azo $\rightleftharpoons$ hydrazone, amide $\rightleftharpoons$ imidol (amide dominates).
- Test: same formula, one H moved, double bond shifted, nothing else changed.

TRAPS

- ✗ **Calling nitroethane and ethyl nitrite tautomers.** An ethyl group, not an H, is attached differently: they are functional isomers.
- ✗ **Forgetting the double bond must shift with the H.** A tautomer pair differs only by one moved H and a matching shift of the double bond.

6 Degree of Unsaturation and Counting Isomers

- D.B.E. = $\Sigma n(v - 2)/2 + 1$; O and S add 0, halogens act like H.
- Each D.B.E. is a ring or a π bond; C $\equiv$ C counts 2.
- Count skeleton by skeleton, every distinct position, compare names.
- Default: leave out tautomers, include ring-chain isomers.

STANDARD RESULTS

C₄H₉Br: 4 · C₃H₆O: 7 (9 with enols) · C₅H₈ without rings: 9 · pentyl alcohols: 8.

TRAPS

- ✗ **Giving oxygen a contribution in D.B.E.** For divalent atoms $v - 2 = 0$.
- ✗ **Counting the same skeleton numbered from the other end.** Name every structure and compare names.

7 Geometrical (cis-trans) Isomerism

- Needs restricted rotation (C=C, C=N, N=N, ring) and two different groups on each end.
- abC=Cde: cis/trans can't be used; E/Z needed. Cis-trans isomers are diastereomers.
- trans: higher m.p., more stable, μ can be 0. cis: higher b.p., μ , solubility.
- Oximes: syn/anti; Beckmann: the anti group migrates.
- KMnO₄ syn, Br₂ anti: cis + syn and trans + anti $\rightarrow$ meso.
- Polyenes: 2ⁿ (ends differ); same ends: 2ⁿ⁻¹ + 2^{^(n/2-1)} (even), 2ⁿ⁻¹ + 2^{^((n-1)/2)} (odd).

STANDARD RESULTS

Maleic m.p. 403 K, fumaric 575 K. cis $\rightleftharpoons$ trans needs $\approx$ 62 kcal/mol.

TRAPS

- ✗ **Mixing up m.p. and b.p.** m.p.: trans higher · b.p.: cis higher.
- ✗ **Using the symmetrical polyene formula when the ends differ.** Different ends: 2ⁿ.
- ✗ **Naming a ketoxime syn or anti without the reference group.** State which group is syn or anti to the OH.

8 Optical Activity, Symmetry and Chirality

- d (+) clockwise, l (-) anticlockwise; depends on substance, λ , C, solvent, l, T.
- $[\alpha] = \alpha_{\text{obs}}/(l \times C)$, l in dm.
- Chiral: no plane, centre or alternating axis of symmetry; dissymmetry $\rightleftharpoons$ enantiomers.
- One C*: always active; two or more: maybe (meso).
- Isotopes count; R₄N⁺ can be chiral; simple amines invert; compare ring paths.

STANDARD RESULTS

Sucrose $[\alpha] \approx +66.5^\circ$, 9 chiral centres.

TRAPS

- ✗ **Taking the path length in cm.** $[\alpha]$ uses l in decimetres: a 20 cm tube is l = 2.
- ✗ **Assuming two chiral centres always mean optical activity.** Meso compounds have chiral centres and a plane of symmetry: inactive.
- ✗ **Treating a ring carbon as achiral without checking.** Compare the two ring paths around it.

9 Optical Isomerism Without a Chiral Carbon

- Allene abC=C=Cab: perpendicular ends, chiral.
- Even number of cumulated C=C: possibly chiral; odd: cis-trans.
- Alkylidene cycloalkanes and spiranes: active if each end has two different groups.

- Biphenyls: bulky ortho groups block rotation; each ring needs two different ortho groups.

TRAPS

- ✗ **Assuming every cumulene is chiral.** Count the double bonds: odd numbers give a flat molecule (cis-trans).
- ✗ **Calling a biphenyl chiral when one ring has two identical ortho groups.** Each ring needs two different ortho groups.

10 Lactic Acid, Tartaric Acid and Counting Stereoisomers

- Lactic acid: one C*, d (+), l (-), racemic ($\pm$).
- Tartaric acid: (+), (-), meso (plane of symmetry) and racemic mixture.
- Unsymmetrical: 2^n . Symmetrical even: $a = 2^{n-1}$, $m = 2^{(n/2-1)}$. Odd: $a = 2^{n-1} - 2^{((n-1)/2)}$, $m = 2^{((n-1)/2)}$.
- Racemic forms $r = a/2$; odd symmetrical chains have a pseudo-asymmetric centre.

STANDARD RESULTS

Glucose 16 · sorbitol 10 · pentitol 4 · $n = 5$ symmetric acid 16.

TRAPS

- ✗ **Applying 2^n to a symmetrical molecule.** Identical halves give meso forms; the total is fewer than 2^n .
- ✗ **Confusing meso with racemic.** Meso: one compound, internal compensation. Racemic: a mixture, external compensation.

11 Racemic Mixtures, Optical Purity and Configuration

- Racemic: equal d and l, inactive by external compensation; racemisation via flat intermediates (S_N1).
- No bond to C* broken $\rightarrow$ configuration retained, even if the sign changes.
- % ee = $(n_1 - n_2)/(n_1 + n_2) \times 100 = [\alpha]_{\text{obs}}/[\alpha]_{\text{pure}} \times 100$.
- Resolution: chiral base $\rightarrow$ diastereomeric salts $\rightarrow$ crystallise $\rightarrow$ acid; also biochemical, mechanical, chromatography.
- Asymmetric synthesis: enzymes give one enantiomer; H_2/Ni gives the racemate.
- Walden: PCl_5 , KOH invert; moist Ag_2O doesn't.

STANDARD RESULTS

ee 50 % $\rightarrow$ 75 % major, 25 % minor.

TRAPS

- ✗ **Assuming a change of sign means a change of configuration.** (-)-2-methylbutan-1-ol $\rightarrow$ (+)-1-chloro-2-methylbutane keeps its configuration.

- ✗ **Reporting the ee as the percentage of the major enantiomer.** ee 50 % means 75 % of the major form.

12 Diastereomers, Fischer Projections and D/L Configuration

- Fischer: C* at the crossing, chain vertical with the most oxidised C on top, vertical bonds back, horizontal forward.
- 180° rotation: same molecule. 90° or swapping two groups: enantiomer.
- Diastereomers: stereoisomers that aren't mirror images; different physical properties.
- Erythro: similar groups on the same side; threo: opposite.
- D/L from glyceraldehyde (OH right = D); sugars: last-but-one carbon. D/L $\neq$ d/l.

STANDARD RESULTS

One C* + one cis-trans C=C: 4 stereoisomers.

W = 3-chloropent-1-ene $\rightarrow$ achiral Y; X = 4-chloropent-2-ene $\rightarrow$ chiral Z.

TRAPS

- ✗ **Turning a Fischer projection by 90°.** That gives the enantiomer; only 180° keeps the molecule.
- ✗ **Linking D with (+).** D/L is configuration and d/l is the sign of rotation; they are unrelated.

13 Conformations of Ethane, Propane and Butane

- Conformations interconvert by rotation; they can't be isolated.
- $\theta = 0^\circ$ eclipsed, 60° staggered; sawhorse and Newman projections.
- Ethane barrier ≈ 12.5 kJ/mol; propane ≈ 14.2 kJ/mol.
- Butane: anti 0, gauche 3.8, partially eclipsed 14.6, fully eclipsed 18.4 kJ/mol.
- Internal H-bond (ethane-1,2-diol, 2-fluoroethanol): gauche preferred.
- $\mu = \mu_a x_a + \mu_g x_g$; symmetric anti has $\mu = 0$.

STANDARD RESULTS

1,2-Dichloroethane: $x_g = 0.18$, $x_a = 0.82$.

TRAPS

- ✗ **Expecting anti to always win.** Groups that attract (internal H-bond) make gauche the most stable.
- ✗ **Forgetting the anti term vanishes.** A symmetric anti conformer has $\mu = 0$.

14 Conformations of Cyclohexane

- Baeyer: $d = \frac{1}{2}(109^\circ 28' - \text{angle})$; cyclopropane most strained; fails for cyclohexane (puckers).
- Chair: staggered, strain-free; boat: eclipsed + flagpole H (1.83 Å).

- Boat $\approx$ 29.9 kJ/mol above chair; barrier 37.7–46.0 kJ/mol.
- 6 axial + 6 equatorial H; ring flip swaps them.
- Substituents prefer equatorial (1,3-diaxial clashes): methyl 95 % e; tert-butyl never axial.
- 1,2: trans e,e · 1,3: cis e,e · 1,4: trans e,e.

STANDARD RESULTS

Stability: chair > twist boat > boat > half chair.

TRAPS

✗ **Concluding cyclohexane is strained.** It puckers into a chair with $109^{\circ}28'$ angles.

✗ **Assuming trans is always the more stable disubstituted isomer.** For 1,3-disubstitution, cis is diequatorial and more stable.

Isomerism (Structural and Stereoisomerism)

$$v - 2C + 2N + 1O, S, O, H, X - 1$$

$$\text{Na D-line } \lambda = 5893 \text{ \AA}$$

Notation C* chiral centre · a active forms · m meso forms · r = a/2 racemic forms · a/e axial/equatorial

1 Isomers: Chain, Position and Ring-Chain

- Chain: skeleton differs · position: group moves · ring-chain: open vs ring (call it functional if ring-chain isn't an option).

2 Functional Isomerism

- $C_nH_{2n+2}O$ alcohol/ether · $C_nH_{2n}O$ carbonyls, unsat. alcohols/ethers, rings · $C_nH_{2n}O_2$ acids, esters, hydroxy carbonyls · C_nH_{2n-2} alkynes, dienes, cycloalkenes.

3 Metamerism

- Metamers: same functional group (–O–, –S–, –NH–, –CO–, –COO–), different alkyl groups on its two sides. Offered? Prefer metamerism over position.

4 Tautomerism and Keto-Enol Equilibrium

Enol order: $CH_3COCH_3 < CH_3COCH_2COOC_2H_5 < C_6H_5COCH_2COOC_2H_5 < CH_3COCH_2CHO < CH_3COCH_2COCH_3 < C_6H_5COCH_2COCH_3 < \text{cyclohexane-1,3-dione} < C_6H_5COCH_2COC_6H_5$

- Needs an α -H + EWG; never at a bridgehead. Polar protic solvent lowers enol %.

5 Other Types of Tautomerism

- N triads: nitrite-nitro, nitro-aci, nitroso-oxime, imine-enamine, azo-hydrazone, amide-imidol.

6 Degree of Unsaturation and Counting Isomers

$$\text{D.B.E.} = \frac{\sum n(v-2)}{2} + 1$$

- $v - 2: C + 2, N + 1, O/S 0, H/X - 1$. Each D.B.E. = ring or π bond. C_6H_8 (no rings) = 9; C_3H_6O = 7 (+2 enols).

7 Geometrical (cis-trans) Isomerism

$$N = 2^n \text{ (unsymmetrical)}$$

$$N = 2^{n-1} + 2^{n/2-1} \text{ (symmetrical, } n \text{ even)}$$

$$N = 2^{n-1} + 2^{(n-1)/2} \text{ (symmetrical, } n \text{ odd)}$$

- m.p. trans higher · b.p., μ cis higher · trans more stable. cis + syn $\rightarrow$ meso, trans + anti $\rightarrow$ meso.

8 Optical Activity, Symmetry and Chirality

$$[\alpha] = \frac{\alpha_{\text{obs}}}{l \times C}$$

- $[\alpha] = \alpha_{\text{obs}} / (l \times C)$, l in dm, C in g/mL; Na D-line 5893 Å. C* = four different groups.

9 Optical Isomerism Without a Chiral Carbon

- abC=C=Cab chiral; abC=C=C=Cab flat (cis-trans). Biphenyls: two different ortho groups on each ring.

10 Lactic Acid, Tartaric Acid and Counting Stereoisomers

$$a = 2^n, m = 0$$

$$a = 2^{n-1}, m = 2^{n/2-1}$$

$$a = 2^{n-1} - 2^{(n-1)/2}, m = 2^{(n-1)/2}$$

$$\text{total} = a + m$$

$$r = \frac{a}{2}$$

- Meso: internal compensation, one compound · racemic: external, a mixture. Tartaric: 3 stereoisomers.

11 Racemic Mixtures, Optical Purity and Configuration

$$\% ee = \frac{n_1 - n_2}{n_1 + n_2} \times 100$$

$$\% ee = \frac{[\alpha]_{\text{obs}}}{[\alpha]_{\text{pure}}} \times 100$$

$$[\alpha]_{\text{obs}} = \frac{\% ee}{100} \times [\alpha]_{\text{pure}}$$

- ee 25 % with $[\alpha]_{\text{pure}} 13.5^\circ \rightarrow [\alpha]_{\text{obs}} 3.375^\circ$. Sign change $\neq$ configuration change.

12 Diastereomers, Fischer Projections and D/L Configuration

- Fischer: vertical back, horizontal forward; 180° same, 90° enantiomer. Erythro: similar groups same side.

13 Conformations of Ethane, Propane and Butane

Stability: anti > gauche > partially eclipsed > fully eclipsed

$$\mu = \mu_{\text{anti}} X_a + \mu_{\text{gauche}} X_g$$

$$X_a + X_g = 1$$

- Ethane barrier 12.5 kJ/mol; butane gauche 3.8, partly eclipsed 14.6, fully eclipsed 18.4 kJ/mol.

14 Conformations of Cyclohexane

$$d = \frac{1}{2} (109^\circ 28' - \text{ring angle})$$

cyclopropane $24^\circ 44'$, cyclobutane $9^\circ 44'$, cyclopentane $0^\circ 44'$, cyclohexane $-5^\circ 16'$

Stability: chair > twist boat > boat > half chair

$$1,2: \text{trans} = ee/aa, \text{cis} = ae$$

$$1,3: \text{cis} = ee/aa, \text{trans} = ae$$

$$1,4: \text{trans} = ee/aa, \text{cis} = ae$$

- Big groups equatorial (CH_3 95 %). Diequatorial isomers: 1,2 trans · 1,3 cis · 1,4 trans.