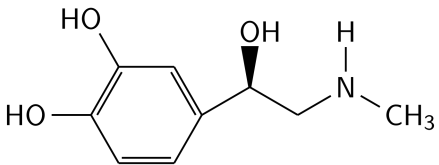
Organic chemistry for bioinformatics
Part 3: Reactions, dynamics, enzymes

After today you can

- decide whether a stereocentre is R or S
- explain why some reactions happen and others don't
- read an energy diagram: direction vs. speed
- explain how enzymes make reactions possible
- read a pathway as a chain of reaction types

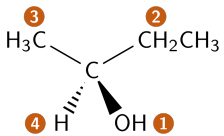


adrenaline: today we see how the cell makes it

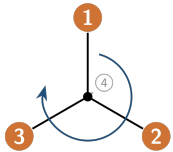
Slides developed with the help of Claude (Anthropic), an AI assistant; content checked by S. J. Prohaska (2026).

R or S in two steps

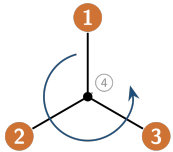
1. **rank** the four groups (CIP rules, lecture 2): higher atomic number first; tie → next sphere; a double bond counts its partner twice
2. **look** with group 4 pointing away from you: 1 → 2 → 3 clockwise = R, anticlockwise = S



(*S*)-2-butanol: H points away



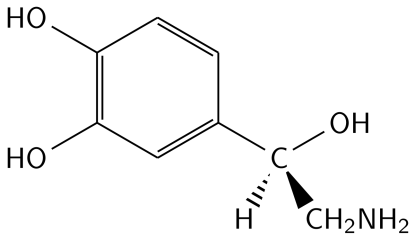
R: clockwise



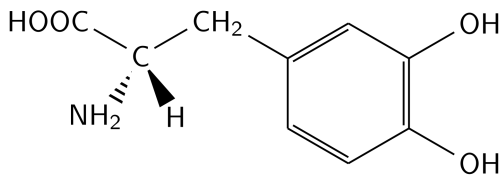
S: anticlockwise

Action – R or S? Ask the die

Your die is an **(R)** model: with 4 pointing away, $1 \rightarrow 2 \rightarrow 3$ runs clockwise. Rank the groups, hold the die like the molecule: does it match, or is the molecule its mirror image?



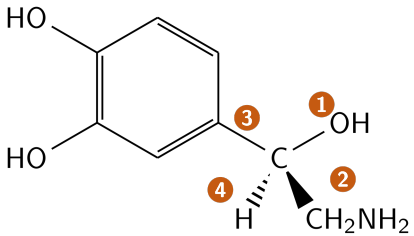
noradrenaline



L-DOPA

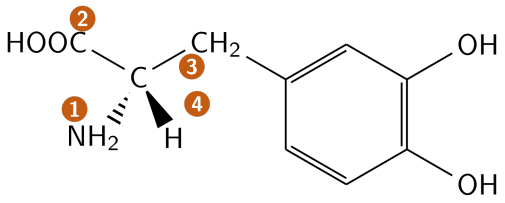
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noradrenaline

OH > CH_2NH_2 > ring > H

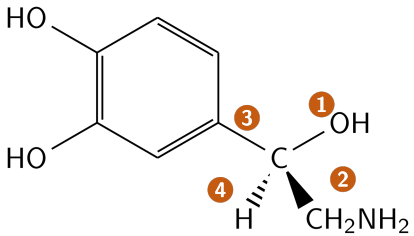


L-DOPA

NH_2 > COOH > CH_2–ring > H

Action – R or S? Ask the die

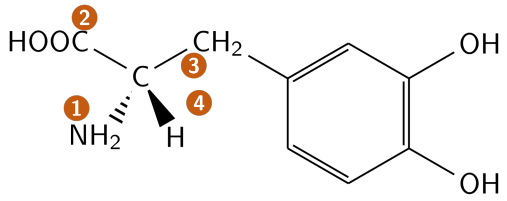
Your die is an **(R)** model: with 4 pointing away, $1 \to 2 \to 3$ runs clockwise. Rank the groups, hold the die like the molecule: does it match, or is the molecule its mirror image?



noradrenaline

$OH > CH_2NH_2 >$ ring $> H$

(R): matches the die



L-DOPA

$NH_2 > COOH > CH_2$–ring $> H$

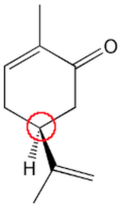
(S): mirror image

Why it matters: enzymes are chiral

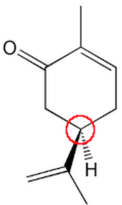
- enzymes are made of L-amino acids: they are chiral themselves
- so they tell the two mirror images apart, like a left glove and a left hand
- cells make L-DOPA, not D-DOPA, and (R)-noradrenaline, not (S)
- our noses do it too: the two carvones smell different



caraway



(S)-carvone



(R)-carvone



spearmint

What is a chemical reaction?

- bonds break and new bonds form: the atoms are rearranged into new molecules
- the atoms themselves stay: none is created, destroyed or turned into another element
- **law of conservation of mass** (Lavoisier, 1789): mass of the reactants = mass of the products
- a **chemical equation**: reactants (left) → products (right)

example

$$\text{acid} + \text{alcohol} \rightleftharpoons \text{ester} + \text{water}$$

$$CH_3COOH + C_2H_5OH \rightleftharpoons CH_3COOC_2H_5 + H_2O$$

atoms	left	right
C	$2 + 2 = 4$	$4 + 0 = 4$
H	$4 + 6 = 10$	$8 + 2 = 10$
O	$2 + 1 = 3$	$2 + 1 = 3$

forward reaction: condensation
reverse reaction: hydrolysis

Every reaction can run in both directions, indicated by the equilibrium arrow ($\rightleftharpoons$).

Stoichiometry: counting molecules with moles

Balanced equation: coefficients make the atoms add up

$$C_6H_{12}O_6 + O_2 \longrightarrow CO_2 + H_2O$$

C: 6, H: 12, O: 8 C: 1, H: 2, O: 3

What is a mole?

- a counting unit, like a dozen:
  1 mol $= 6.022 \times 10^{23}$ particles
- **molar mass** = mass of 1 mol

1 mol of C = 12 g
1 mol of H = 1 g
1 mol of O = 16 g

glucose $C_6H_{12}O_6$:
$6 \cdot 12 + 12 \cdot 1 + 6 \cdot 16 = 180$ g/mol

Stoichiometry: counting molecules with moles

Balanced equation: coefficients make the atoms add up

$$C_6H_{12}O_6 + O_2 \longrightarrow CO_2 + H_2O$$

C: 6, H: 12, O: 8 C: 1, H: 2, O: 3

$$C_6H_{12}O_6 + 6\,O_2 \longrightarrow 6\,CO_2 + 6\,H_2O$$

C: 6, H: 12, O: 18 C: 6, H: 12, O: 18

glucose is burnt in our cells (respiration)

- coefficients = ratios of molecules = mole ratios:
  1 glucose : 6 O_2 : 6 CO_2 : 6 H_2O

	glucose	O_2	CO_2	H_2O
mol	1	6	6	6
g	180	$6 \cdot 32 = 192$	$6 \cdot 44 = 264$	$6 \cdot 18 = 108$

What is a mole?

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glucose $C_6H_{12}O_6$:
$6 \cdot 12 + 12 \cdot 1 + 6 \cdot 16 = 180$ g/mol

left: $180 + 192 =$ **372 g**
right: $264 + 108 =$ **372 g**
mass is conserved

Three questions decide whether a reaction happens

1. **Is there a partner?**
   an electron-rich atom (nucleophile) meets an electron-poor atom (electrophile)

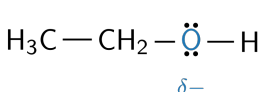
2. **Can something leave?**
   a stable leaving group: H_2O good, OH^- poor, phosphate very good

3. **Is it downhill, and is the barrier low enough?**
   ΔG (thermodynamics, part C) and activation energy (kinetics, part C)

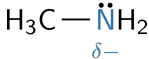
Functional groups (lecture 2) answer questions 1 and 2: they decide which reactions a molecule can take part in.

Partners: nucleophile meets electrophile

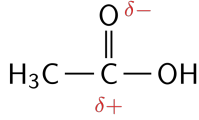
- polar bonds (electronegativity, lecture 1): O and N pull electrons, C next to them becomes $\delta+$
- nucleophile: a free electron pair (lone pair), e.g. on the O of an alcohol or the N of an amine
- electrophile: an electron-poor atom, e.g. the C of C=O
- a curved arrow shows an electron pair moving: from the nucleophile to the electrophile



ethanol: nucleophile

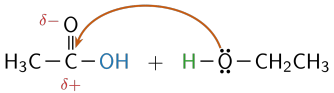


methylamine: nucleophile



acetic acid: electrophile at C

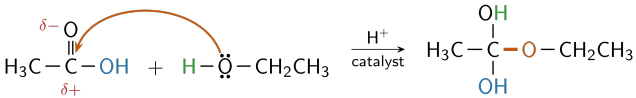
One mechanism in full: an ester forms



1. the O of ethanol (nucleophile) attacks the $\delta+$ C of the acid

H^+ is a **catalyst**: it shuttles the protons (H^+) between the oxygens and is given back at the end, so it does not appear in the balance. The individual proton steps: backup slide.

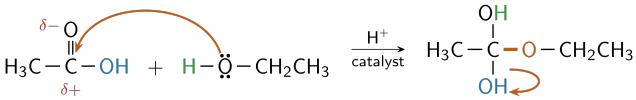
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2. a new C–O bond (orange): a tetrahedral intermediate, C now has four partners; the H of ethanol has moved to the former C=O oxygen

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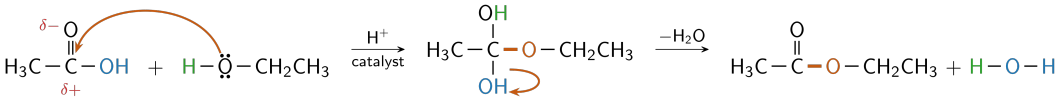
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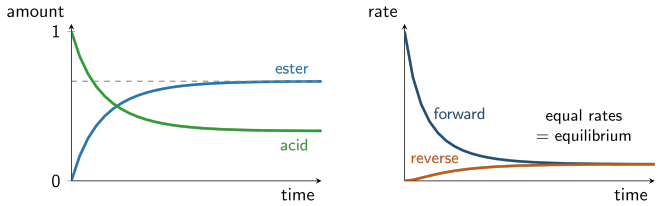
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3. the acid's OH leaves together with that H: as water, a good leaving group
4. C=O forms again: **ethyl ethanoate** (an ester) + water; all atoms are accounted for

H^+ is a **catalyst**: it shuttles the protons (H^+) between the oxygens and is given back at the end, so it does not appear in the balance. The individual proton steps: backup slide.

Equilibrium: both directions, all the time



- forward and reverse reactions run at the same time; at equilibrium both rates are equal: nothing has stopped, but nothing changes overall

$$K = \frac{[\text{ester}]\,[\text{water}]}{[\text{acid}]\,[\text{alcohol}]} = \frac{k_{\text{forward}}}{k_{\text{reverse}}}$$

K: equilibrium constant (for a given temperature)
[ester]: concentration of ester at equilibrium, in mol/L
k_{forward}, k_{reverse}: rate constants of the two directions

- ester: $K \approx 4$. From 1 mol acid + 1 mol ethanol, 2/3 mol ester ($\approx 67\,\%$) is present at equilibrium
- remove the water, and more ester forms (the equilibrium is pushed)

Why two thirds become ester

Start with 1 mol acid and 1 mol ethanol, no water.
Let x = ester formed at equilibrium; each ester also makes one water and uses one acid and one alcohol:

	acid	alcohol	ester	water
start	1	1	0	0
equilibrium	$1-x$	$1-x$	x	x

1. into K (the volume cancels):

$$K = \frac{x \cdot x}{(1-x)(1-x)} = \frac{x^2}{(1-x)^2} = 4$$

2. square root on both sides:

$$\frac{x}{1-x} = 2$$

3. solve:
$x = 2 - 2x \;\Rightarrow\; 3x = 2 \;\Rightarrow\; \boxed{x = 2/3}$

- two thirds of the acid becomes ester, one third stays: the dashed line on slide 10
- $2/3$ depends on the starting amounts; K does not: excess ethanol or removing water gives more than $2/3$, with the same K

The curves on slide 10 are an ODE model

Mass-action kinetics

a rate = rate constant × the concentrations of the molecules that must meet

$$v_f = k_f\,[\text{acid}][\text{alcohol}] = k_f\,(1-x)^2$$

$$v_r = k_r\,[\text{ester}][\text{water}] = k_r\,x^2$$

the ester concentration $x(t)$ changes by the difference:

$$\frac{dx}{dt} = k_f\,(1-x)^2 - k_r\,x^2, \qquad x(0) = 0$$

The parameters

- start: 1 mol/L acid, 1 mol/L ethanol
- $k_f = 1$, $k_r = 0.25 \to K = k_f/k_r = 4$
- time and rates in arbitrary units: the shape is real, the time scale is not

The two plots

- left: ester $= x(t)$, acid $= 1 - x(t)$
- right: $v_f(t)$ and $v_r(t)$
- where they meet, $dx/dt = 0$: equilibrium

Solving the ODE

Numerically: Euler steps

```
kf, kr = 1.0, 0.25
x, dt = 0.0, 0.01
for step in range(600):
    vf = kf * (1 - x)**2
    vr = kr * x**2
    x = x + dt * (vf - vr)
print(x)        # 0.6656...
```

this is how the plots were made (`t` from 0 to 6)

Exactly: the right side factorises

$$\frac{dx}{dt} = (1 - 1.5\,x)(1 - 0.5\,x)$$

separate the variables, partial fractions, integrate:

$$x(t) = \frac{2\,(e^t - 1)}{3\,e^t - 1}$$

$x(0) = 0$, $x(t) \to 2/3$ for $t \to \infty$: the same as with K

- every reaction gives one such term: a pathway or a network of reactions becomes a system of coupled ODEs
- this is how reaction networks are modelled in systems biology

Hydrolysis: the way back

- hydrolysis = splitting a bond with water: the reverse of condensation
- ester + water → acid + alcohol; amide + water → acid + amine
- in water, hydrolysis is **downhill**: proteins, fats, DNA "should" fall apart

a peptide bond without an enzyme, in water at 25 °C:
half-life about **400 years**

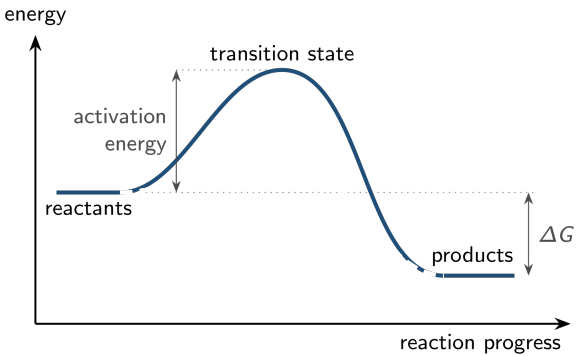
- downhill is not the same as fast: the barrier decides the speed → part C

Three zoom levels of one process

level	looks at	answers
mechanism (how?)	one reaction, step by step	which bonds break and form, in which order, through which intermediates
kinetics (how fast?)	many molecules over time	how fast? which product first?
thermodynamics (how far?)	the whole system at the end	where does it end up, whatever the path?

- part B was the mechanism: one reaction, arrow by arrow
- now we zoom out: rates (kinetics) and equilibria (thermodynamics)

The energy diagram



- ΔG: products minus reactants
  $\Delta G < 0$: downhill, runs by itself
  decides the direction and the equilibrium
- **activation energy**: the barrier on the way
  decides the speed
- **transition state**: the top of the barrier, half-formed bonds; the tetrahedral moment of slide 9 is close to it
- two independent numbers

How much, and how fast?

How much: ΔG° sets K

$$\Delta G^\circ = -RT \ln K$$

$R = 8.314$ J/(mol·K): gas constant; T: temperature in K (25 °C = 298 K)

ΔG° (kJ/mol)	K
+5.7	0.1
0	1
−5.7	10
−11.4	100
−34	1 000 000

every 5.7 kJ/mol = a factor of 10 (at 25 °C)

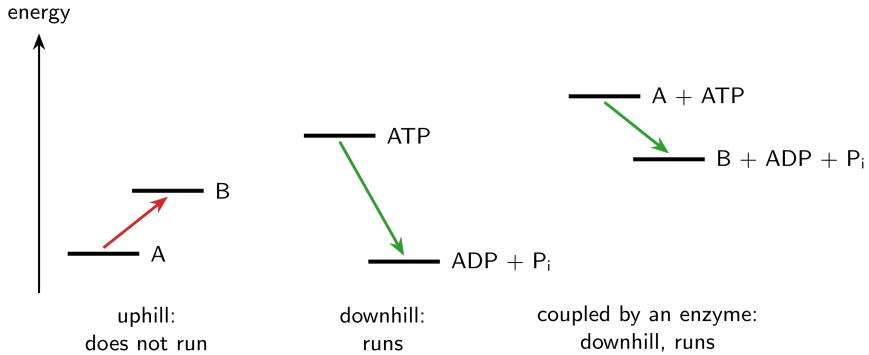
How fast: the barrier sets the rate

$$k = A\, e^{-E_a/RT}$$

k: rate constant; E_a: activation energy; A: how often molecules meet in a suitable orientation (pre-exponential factor)

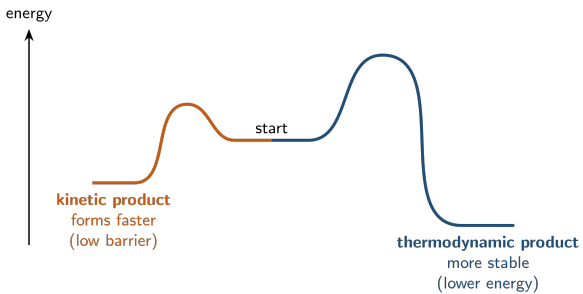
- a higher barrier → exponentially slower
- warmer → faster
- more molecules (higher concentration) → more encounters → faster

Coupling: uphill with help



- an uphill step runs when it is coupled to a downhill one: the ΔG add up
- the cell's standard downhill partner: **ATP** $\rightarrow$ ADP + P_i
- coupling needs a shared intermediate, e.g. an acid activated with ATP before an amide (peptide) bond forms (backup slide)

Kinetic or thermodynamic control?

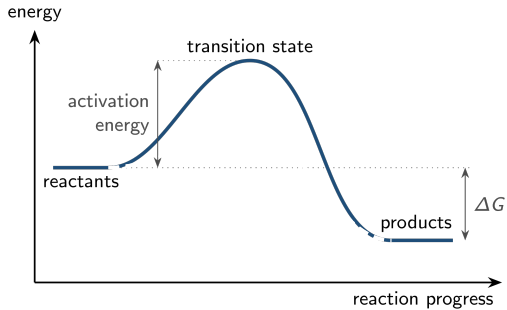


- what forms first is not always what is most stable
- peptide bonds in water: hydrolysis is downhill, yet they last about 400 years without an enzyme: kinetically stable
- protein folding: for many proteins, amyloid fibrils (as in Alzheimer's disease) are more stable than the native, functional fold; a high barrier keeps the protein in the native fold: kinetic control

Action – What does a catalyst change?

Vote in the Moodle poll, yes or no:

1. ΔG
2. activation energy
3. the equilibrium constant K
4. the forward rate
5. the reverse rate
6. time to reach equilibrium

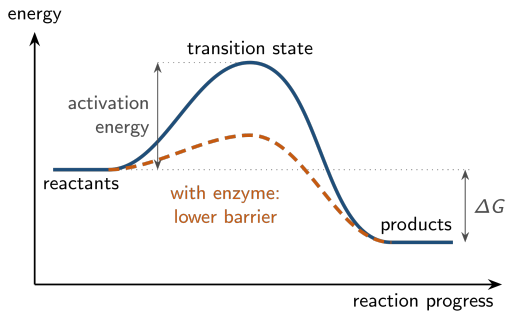


Action – What does a catalyst change?

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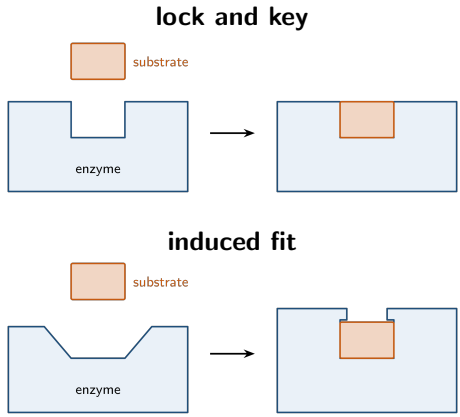
1. ΔG — no
2. activation energy — yes, lower
3. the equilibrium constant K — no
4. the forward rate — yes
5. the reverse rate — yes, by the same factor
6. time to reach equilibrium — yes, shorter

Enzymes are catalysts: faster, same end point.
Forward and reverse rate are multiplied by the same factor, so $K = k_{\text{forward}} / k_{\text{reverse}}$ stays the same.



How enzymes do it

- the active site binds the substrate
- it binds the **transition state** even better $\rightarrow$ lower barrier
- it holds nucleophile and electrophile in the right place and orientation
- groups of the enzyme in the active site act as acids, bases or nucleophiles (e.g. an OH group)
- **cofactors**, non-protein helpers, add chemistry the protein lacks: metal ions (Fe^{2+}, Cu) or small molecules such as NAD^+ (redox) and SAM (methyl groups)
- chiral: binds (R) or (S), not both



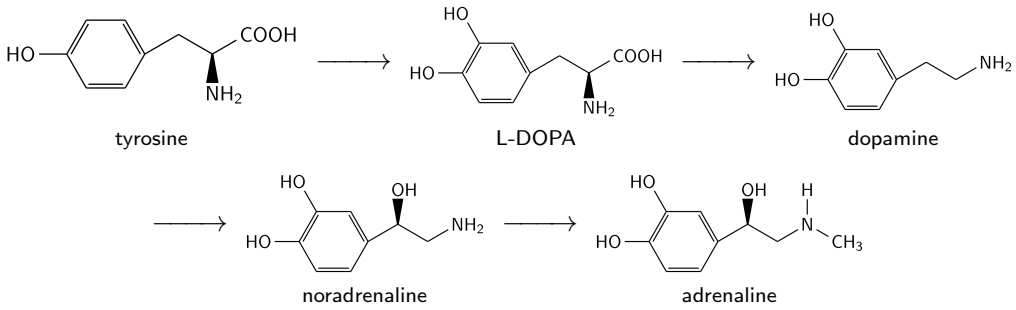
EC numbers: enzymes as a hierarchy

EC	reaction class
1	oxidoreductases (redox)
2	transferases (move a group)
3	hydrolases (split with water)
4	lyases (split without water)
5	isomerases (rearrange atoms within a molecule)
6	ligases (join, using ATP)
7	translocases (move across membranes)

- four levels, like a path in a file system:
  EC 2.1.1.28: transferase → one-carbon group → methyl → enzyme no. 28
- the number classifies the reaction, not the protein
- used in databases: KEGG, BRENDA, Rhea

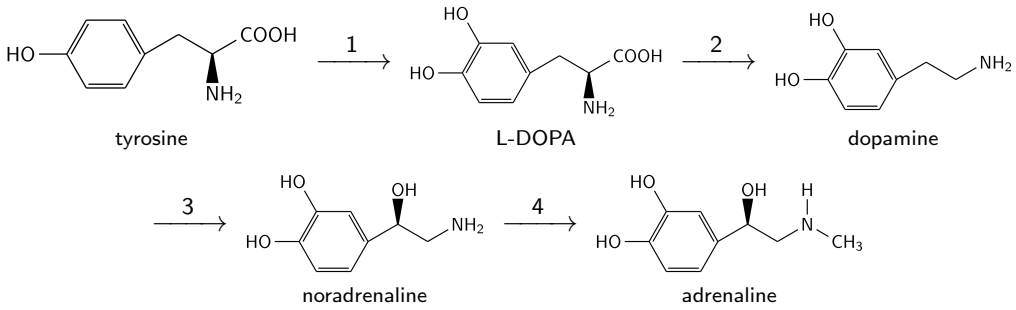
Enzymes are proteins that catalyse reactions; their names mostly end in -ase.

Action – A pathway: from tyrosine to adrenaline



In pairs: which atoms change in each step? Pick a reaction type (hydroxylation · decarboxylation · methyl transfer) and an enzyme class (EC 1–7, slide 22)

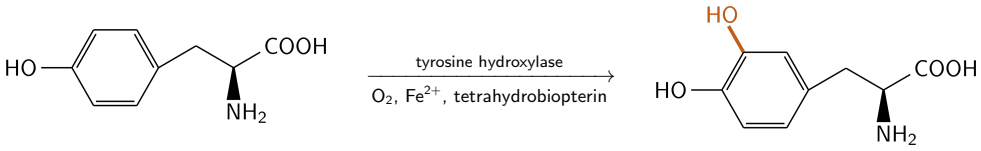
Action – A pathway: from tyrosine to adrenaline



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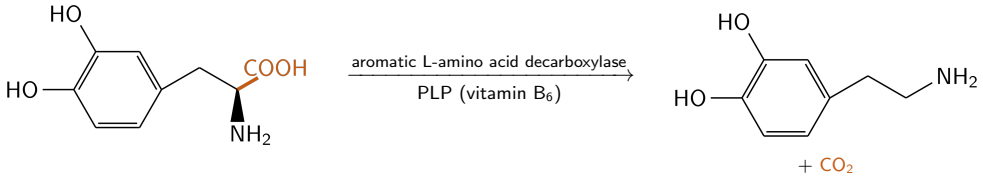
1, 3: hydroxylation, EC 1 (oxidoreductase)
2: decarboxylation, EC 4 (lyase)
4: methyl transfer, EC 2 (transferase)

Step 1: tyrosine → L-DOPA



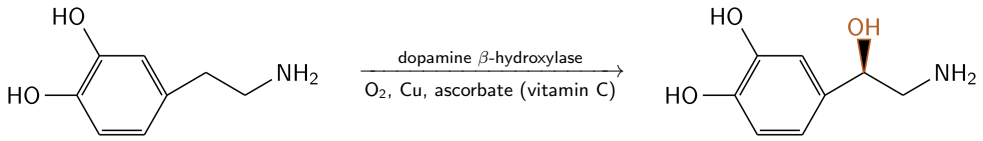
- **hydroxylation**: an OH is added to the ring, a redox reaction with O_2
- the enzyme activates O_2 with an iron ion; tetrahydrobiopterin delivers the electrons
- EC 1.14.16.2, an oxidoreductase
- the slowest step: it controls how much adrenaline the cell can make

Step 2: L-DOPA → dopamine



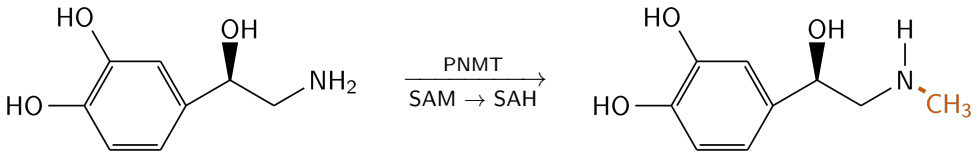
- **decarboxylation**: the COOH leaves as CO_2; CO_2 is a very stable leaving group
- the stereocentre is gone: dopamine has two H on that carbon
- EC 4.1.1.28, a lyase (splits a bond without water)

Step 3: dopamine → noradrenaline



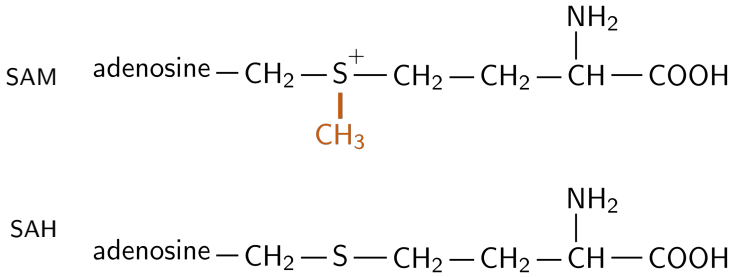
- **hydroxylation** again, now at the chain, next to the ring
- a new stereocentre: the enzyme makes only (R)
- EC 1.14.17.1, an oxidoreductase

Step 4: noradrenaline → adrenaline



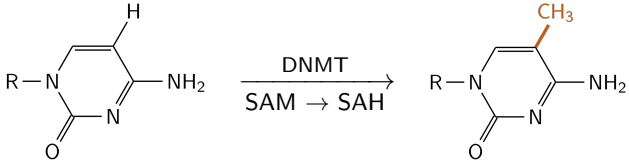
- **methyl transfer**: the CH_3 comes from SAM (next slide)
- EC 2.1.1.28, a transferase

SAM: the cell's methyl donor



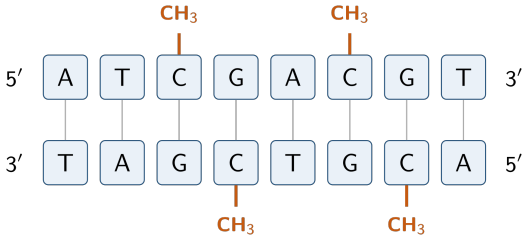
- SAM (S-adenosylmethionine) is made from methionine and **ATP**
- the N of noradrenaline (nucleophile) attacks the CH_3; the sulfur part is the leaving group: SAM becomes SAH (S-adenosylhomocysteine)
- the positive sulfur makes the CH_3 electron-poor: a good electrophile

The same chemistry on DNA: cytosine methylation



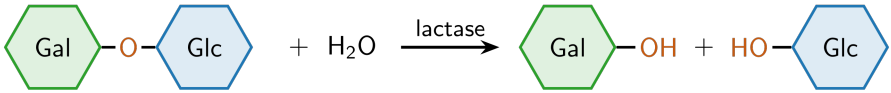
cytosine 5-methylcytosine

- DNA methyltransferases (DNMTs) put a CH_3 from SAM on C5 of cytosine
- in mammals mostly at **CpG**: a C followed by a G
- the methyl group does not change the base pairing, but it changes which genes are read



methylated CpG: both strands carry a methyl group

Lactase: digesting milk

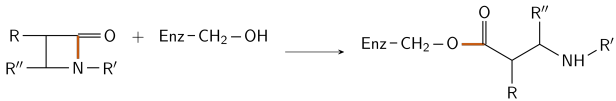


lactose (milk sugar) galactose + glucose

- **hydrolysis** of the bond between the two sugars: downhill, but far too slow without the enzyme
- the gut takes up only the single sugars
- without lactase, gut bacteria ferment the lactose: gas and discomfort (lactose intolerance)
- most adult mammals switch lactase off after weaning; in many humans it stays on (lactase persistence): a question of gene regulation (special lecture)
- EC 3.2.1.108, a hydrolase

Antibiotics: blocking the pathogen's enzymes

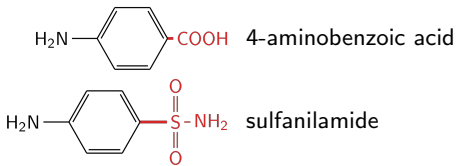
Penicillin: an amide in a four-membered ring (the β-lactam ring)



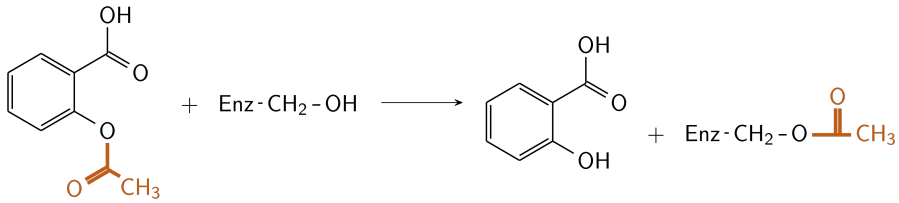
- the ring is under strain: its bond angles are squeezed to 90° (normally about 109–120°), so it opens easily and the amide is unusually reactive
- an OH of the enzyme that crosslinks the bacterial cell wall attacks the C=O: the ring opens, the enzyme stays blocked

Sulfonamides: mimic a folate building block

- they block folate synthesis in bacteria
- humans take folate from food: we are spared



Aspirin: switching an enzyme off for good



- aspirin hands its acetyl group to a serine OH of **cyclooxygenase** (COX)
- the same chemistry as slide 9: an OH (nucleophile) meets the C=O of an ester
- the enzyme is blocked: fewer prostaglandins, less pain, fever and inflammation
- platelets (cell fragments that start blood clotting) cannot make new COX: after one dose they stay blocked for their whole life of about 7–10 days; low-dose aspirin prevents blood clots

Summary and outlook

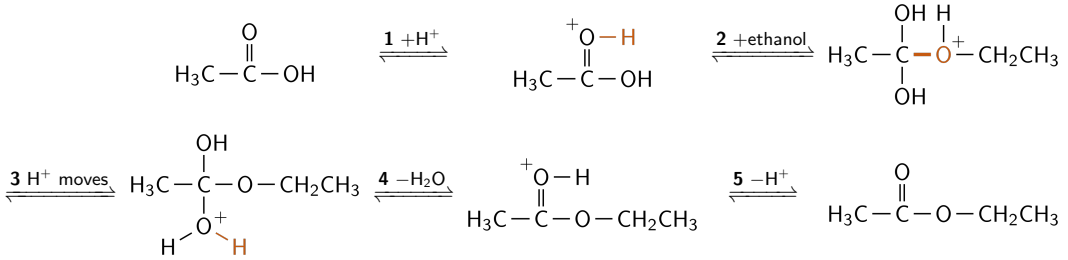
- functional groups decide what can react: partner, leaving group, energy
- ΔG decides the direction, the barrier decides the speed; at equilibrium forward and reverse rates are equal
- enzymes lower the barrier, not ΔG: they choose which reactions run
- pathways: chains of simple reaction types

The block: atoms → molecules → names and SMILES → reactions → enzymes → pathways

Next semester: RNA folding (thermodynamics, kinetics) · epigenetics (SAM, histone marks) · toxicology · metabolomics (KEGG, reaction networks)

These slides were made with an AI assistant (Claude). Every structure, R/S label and number was checked by hand: do the same with AI answers.

Backup: the ester mechanism with all proton steps (slide 9)



1. H^+ binds the C=O oxygen: the C becomes more electron-poor (a better electrophile)
2. the O of ethanol attacks the C (new C–O bond): tetrahedral intermediate
3. a proton moves from the ethanol O to one OH: OH becomes H_2O^+
4. water leaves, a good leaving group (OH^- would not); C=O forms again
5. the ester gives the H^+ back: the catalyst is regenerated

Every step is reversible ($\rightleftharpoons$): read from right to left, it is the acid-catalysed hydrolysis of the ester (slide 14).

Backup: why ethers don't just form

Nothing can leave

- alcohol + alcohol: the OH would have to leave as OH^-, a poor leaving group
- in the lab, ethers form from alcohols only with strong acid and heat (the acid turns OH into H_2O)

The cell's trick: activate with UTP

- C–O–C bonds between sugars (glycosidic bonds, e.g. in lactose, glycogen)
- first the sugar is activated with UTP:

  galactose-1-phosphate + UTP $\rightarrow$ UDP-galactose + PP_i
- UDP (a diphosphate) is a very good leaving group:

  UDP-galactose + glucose $\rightarrow$ lactose + UDP

Backup: why amides don't just form

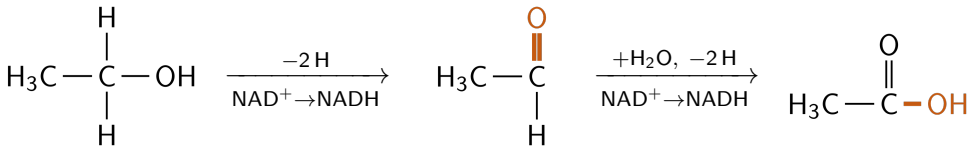
The acid–base reaction wins

- the amine takes the acid's H^+:
  $CH_3COOH + CH_3NH_2 \rightarrow CH_3COO^- + CH_3NH_3^+$
- the carboxylate (COO^-) is no longer an electrophile: the salt stays a salt

The cell's trick: activate with ATP

- first, the acid takes the AMP part of ATP:
  $R\text{–}COOH + ATP \rightarrow R\text{–}CO\text{–}AMP + PP_i$
- now the phosphate of AMP is the leaving group, a very good one
- then the amine attacks:
  $R\text{–}CO\text{–}AMP + H_2N\text{–}R' \rightarrow R\text{–}CO\text{–}NH\text{–}R' + AMP$
- proteins are made this way: amino acids are activated with ATP before the ribosome links them

Backup: redox, an alcohol is oxidised



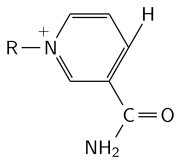
ethanol
C: −1

acetaldehyde
C: +1

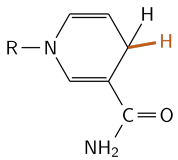
acetic acid
C: +3

- oxidation = losing electrons; in organic molecules: losing H or gaining O
- reduction = the reverse; both always happen together (**red**uction + **ox**idation)
- in cells, **NAD**$^+$ takes the electrons, as a hydride ion (H^-, one H with two electrons)

Backup: redox carriers, oxidized and reduced



$+ 2e^- + H^+$ ⇌

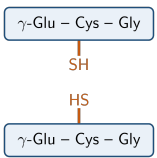


NAD(P)$^+$, oxidized

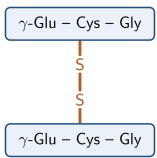
NAD(P)H, reduced

NAD$^+$ / NADH: takes electrons in oxidations
NADP$^+$ / NADPH: gives electrons in biosyntheses

same ring; H arrives as a hydride (H^-) at C4; R = ribose–ADP (NADP: one extra phosphate)



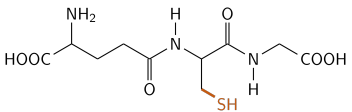
$- 2e^- - 2\,H^+$ ⇌



2 GSH, reduced

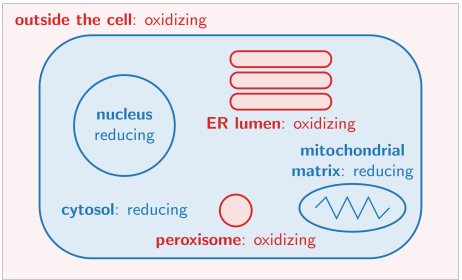
GSSG, oxidized

glutathione: a tripeptide with a free SH (cysteine)



two GSH are oxidized to one disulfide, GSSG

Backup: reducing and oxidizing compartments



	cytosol	ER lumen, outside
GSH : GSSG	$\approx$ 30–100 : 1	$\approx$ 1–3 : 1 (ER)
cysteines	free SH	disulfides (S–S)
example	most enzymes	insulin, antibodies

- two separate electron pools in the cytosol:

  NAD^+ : NADH several hundred : 1 (free): mostly oxidized, ready to take electrons (ethanol $\rightarrow$ acetaldehyde)

  NADPH : $NADP^+$: mostly reduced, ready to give electrons (biosynthesis, GSSG $\rightarrow$ 2 GSH)

- gut (colon): almost no O_2, reducing: anaerobic bacteria

Ratios are approximate textbook values; they vary with cell type and condition.