

IChO 1986

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Problem 1: Platinum(II) antitumour complexes: isomers, hydrolysis and DNA binding

Compounds containing divalent platinum with the general formula $\text{PtX}_2(\text{amine})_2$ ($\text{X} = \text{Cl}_2$, SO_4^{2-} , malonate, etc.) have met a lot of scientific interest because of their biological activity, particularly in view of their properties in the treatment of tumours. The best known compound used clinically is $\text{PtCl}_2(\text{NH}_3)_2$. This compound, in which platinum is coordinated in a planar square, has two geometrical isomers of which only one shows the antitumour activity.

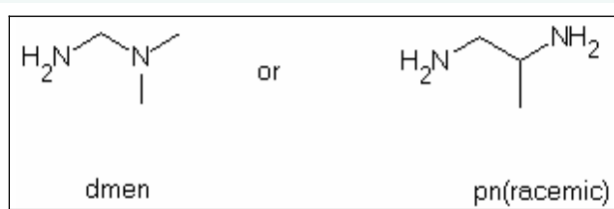
1.1 Sketch the spatial structures of the two possible isomers.

1.2 How many isomers has $\text{PtBrCl}(\text{NH}_3)_2$? Sketch all of them.

It is possible to replace the amine ligands by one ligand containing two donor atoms (N). Then one obtains a chelating ligand, such as 1,2-diaminoethane (en).

1.3 Show graphically that $\text{PtBrCl}(\text{en})$ has only one stable structure.

The ligand en can be substituted via methylation to form dmen or pn (racemic).



1.4 Give spatial structures of all isomers of the following compounds: $\text{PtCl}_2(\text{dmen})$, $\text{PtCl}_2(\text{pn})$, $\text{PtBrCl}(\text{dmen})$ and $\text{PtBrCl}(\text{pn})$.

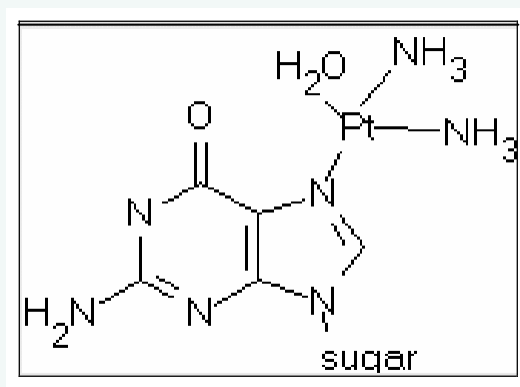
These compounds can isomerise in aqueous solution through dissociation of a ligand and transient replacement of the stronger ligands by the weak ligand water. Cl^- and Br^- are replaced relatively easily, but it is more difficult to replace the amine ligands, which usually requires heating.

1.5 Considering each of the isomers in the previous questions a-d, indicate which isomers can be converted to another at room temperature. Give both the original molecule and the products.

1.6 $\text{PtCl}_2(\text{en})$ reacts with Br^- in a molar proportion of 1:2 at room temperature. Which compound would you expect to form in what proportion? You can assume that the $\text{Pt}-\text{Br}$ and $\text{Pt}-\text{Cl}$ bonds are equally strong and that there is no perturbing influence from hydrolysis.

1.7 Using the equation to express chemical equilibrium, show that hydrolysis hardly ever occurs in blood but that it does occur in the cells. Note: $\text{PtCl}_2(\text{NH}_3)_2$ hydrolyses to and 2Cl^- . In cells the Cl^- concentration is low; in blood it is fairly high.

After hydrolysis in the tumour cell a reactive platinum ion is formed to which two NH_3 groups are still bound, as it was found in the urine of patients treated with this compound. The reactive platinum ion appears to be bound to cellular DNA, where the bonding occurs via guanine to one of the N-atoms.



As a result of the two reactive sites of platinum and the two unreactive NH_3 ligands, it can form additionally a second bond to DNA. Research has shown that this happens in particular with a second guanine base from the same strand of DNA.

1.8 Show by calculations which of the two isomers in question a) can form this bond.

(Note: $\text{Pt}-\text{N}$ distance = 210 pm, DNA base distance = 320 pm).

Official English text of the problem.

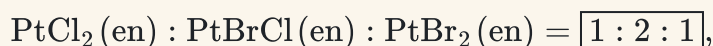
Answers

The named structures and their stereochemical SMILES are given individually in the solution.

- **1.1:** Two isomers: **cisplatin**, with adjacent ammonia ligands, and **transplatin**, with opposite ammonia ligands.
- **1.2:** **Two** isomers: cis- and trans-diamminebromidochloridoplatinum(II).
- **1.3:** **One** configurational isomer: the two nitrogen donors of en occupy adjacent sites; bromide and chloride occupy the remaining adjacent sites.
- **1.4:** The numbers of isomers are:

Compound	Number	Relationship
$\text{PtCl}_2(\text{dmen})$	1	One configuration
$\text{PtCl}_2(\text{pn})$	2	One enantiomeric pair
$\text{PtBrCl}(\text{dmen})$	2	Two geometrical arrangements
$\text{PtBrCl}(\text{pn})$	4	Two enantiomeric pairs

- **1.5:** The two mixed-halide dmen isomers interconvert. For mixed-halide pn, the two halide arrangements interconvert **separately within each carbon configuration**, *R* or *S*. No other distinct isomers listed above interconvert through the stipulated room-temperature halide-exchange process.
- **1.6:** The equilibrium platinum-containing mixture is



corresponding to **25%, 50%, and 25%**, respectively. - **1.7:** Aquation releases chloride. High chloride concentration in blood shifts the equilibrium toward the original complex; lower chloride concentration in cells favours aquation. The diaqua/original-complex activity ratio varies as $a_{\text{Cl}^-}^{-2}$.

1.8: Cisplatin fits the proposed adjacent-guanine cross-link: its two binding sites give a donor separation of approximately **297 pm**, compared with **420 pm** for transplatin and the supplied DNA spacing of **320 pm**.

Solution

The structures below count **configurational isomers**, excluding rapidly interconverting conformations of the chelate rings.

In the SMILES, $\rightarrow$ denotes a donor-to-metal coordination bond. Platinum is represented as Pt^{2+} , and coordinated halides retain their formal negative charges. The square-planar descriptor @SP1 places neighbours 1 and 3 opposite one another, and neighbours 2 and 4 opposite one another, in their SMILES order. These strings specify coordination geometry and carbon configuration; they do not fix ring puckering.

The ligand and small-species identities used below are:

Name	SMILES
Ammonia	N
Water	O
Chloride ion	[Cl-]
Bromide ion	[Br-]
Ethane-1,2-diamine, en	NCCN
<i>N,N</i> -Dimethylethane-1,2-diamine, dmen, as implied by methylation of en	NCCN(C)C
(<i>R</i>)-Propane-1,2-diamine, (<i>R</i>)-pn	NC[C@@H](C)N
(<i>S</i>)-Propane-1,2-diamine, (<i>S</i>)-pn	NC[C@H](C)N

Racemic pn contains equal amounts of its *R* and *S* enantiomers.

1.1 — The two isomers of $\text{PtCl}_2(\text{NH}_3)_2$

Place platinum at the centre of a square, with its four donor atoms above, right, below and left, all in one plane.

Name	Ligands clockwise from above platinum	SMILES
Cisplatin , cis-diamminedichloridoplatinum(II)	NH ₃ , NH ₃ , Cl, Cl	[NH3]->[Pt@SP1+2](<-[NH3])(<-[Cl-])<-[Cl-]
Transplatin , trans-diamminedichloridoplatinum(II)	NH ₃ , Cl, NH ₃ , Cl	[NH3]->[Pt@SP1+2](<-[Cl-])(<-[NH3])<-[Cl-]

The two ammonia ligands are separated by 90° in the cis isomer and 180° in the trans isomer. These exhaust the possibilities for two pairs of identical ligands in a square plane.

1.2 — Isomers of PtBrCl(NH₃)₂

The two identical ammonia ligands can again be adjacent or opposite.

Name	Ligands clockwise from above platinum	SMILES
cis-Diamminebromidochloridoplatinum(II)	NH ₃ , NH ₃ , Br, Cl	[NH3]->[Pt@SP1+2](<-[NH3])(<-[Br-])<-[Cl-]
trans-Diamminebromidochloridoplatinum(II)	NH ₃ , Br, NH ₃ , Cl	[NH3]->[Pt@SP1+2](<-[Br-])(<-[NH3])<-[Cl-]

Interchanging bromide and chloride within either arrangement does not generate an additional isomer: the resulting drawing can be superimposed on the original by rotating the molecule. Thus there are **two isomers**.

1.3 — Why PtBrCl(en) has one stable configuration

The short —CH₂CH₂— bridge of en makes a five-membered chelate ring with platinum. Its two nitrogen donors must occupy adjacent coordination sites; a trans arrangement is not compatible with a stable en chelate.

For the requested sketch, put one nitrogen above platinum and the other to its right. Connect them through the —CH₂CH₂— chain outside that corner. Put chloride below platinum and bromide to its left.

The product is **bromidochlorido(ethane-1,2-diamine)platinum(II)**:

N1CCN->[Pt@SP1+2](<-[Cl-])(<-[Br-])<-1

The two ends of en are equivalent. Consequently, reversing the bromide/chloride placement produces an equivalent structure, leaving **one configurational isomer**.

1.4 — All isomers of the four substituted-chelate complexes

Use the following common drawing convention:

- Put donor N_a above platinum and donor N_b to its right.
- Connect them by the ligand's carbon backbone.
- Put the two halides below and to the left of platinum.
- The lower halide is therefore trans to N_a ; the left-hand halide is trans to N_b .

For **dmen**, N_a is the primary amino donor and N_b is the dimethylamino donor. For **pn**, N_a is attached to the terminal methylene carbon, while N_b is attached to the stereogenic carbon.

Define the mixed-halide arrangements as:

$$\begin{aligned} A : & \quad \text{Cl trans to } N_a, \quad \text{Br trans to } N_b, \\ B : & \quad \text{Br trans to } N_a, \quad \text{Cl trans to } N_b. \end{aligned}$$

The complete set is:

Name and label	Configuration	SMILES
Dichlorido(dmen)platinum(II)	Single configuration	<chem>N1CCN(C)(C)->[Pt@SP1+2](<-[Cl-])(<-[Cl-])<-1</chem>
Dichlorido[(R)-pn]platinum(II)	<i>R</i>	<chem>N1C[C@@H](C)N->[Pt@SP1+2](<-[Cl-])(<-[Cl-])<-1</chem>
Dichlorido[(S)-pn]platinum(II)	<i>S</i>	<chem>N1C[C@H](C)N->[Pt@SP1+2](<-[Cl-])(<-[Cl-])<-1</chem>
Bromidochlorido(dmen)platinum(II), <i>D_A</i>	Arrangement <i>A</i>	<chem>N1CCN(C)(C)->[Pt@SP1+2](<-[Cl-])(<-[Br-])<-1</chem>
Bromidochlorido(dmen)platinum(II), <i>D_B</i>	Arrangement <i>B</i>	<chem>N1CCN(C)(C)->[Pt@SP1+2](<-[Br-])(<-[Cl-])<-1</chem>
Bromidochlorido[(R)-pn]platinum(II), <i>P_{R,A}</i>	<i>R, A</i>	<chem>N1C[C@@H](C)N->[Pt@SP1+2](<-[Cl-])(<-[Br-])<-1</chem>
Bromidochlorido[(S)-pn]platinum(II), <i>P_{S,A}</i>	<i>S, A</i>	<chem>N1C[C@H](C)N->[Pt@SP1+2](<-[Cl-])(<-[Br-])<-1</chem>
Bromidochlorido[(R)-pn]platinum(II), <i>P_{R,B}</i>	<i>R, B</i>	<chem>N1C[C@@H](C)N->[Pt@SP1+2](<-[Br-])(<-[Cl-])<-1</chem>
Bromidochlorido[(S)-pn]platinum(II), <i>P_{S,B}</i>	<i>S, B</i>	<chem>N1C[C@H](C)N->[Pt@SP1+2](<-[Br-])(<-[Cl-])<-1</chem>

For an explicit spatial description of the pn stereocentre, its substituent priorities are

amino nitrogen > methylene–amino group > methyl group > hydrogen.

With hydrogen directed away from the viewer, the first three groups run clockwise for *R* and counterclockwise for *S*.

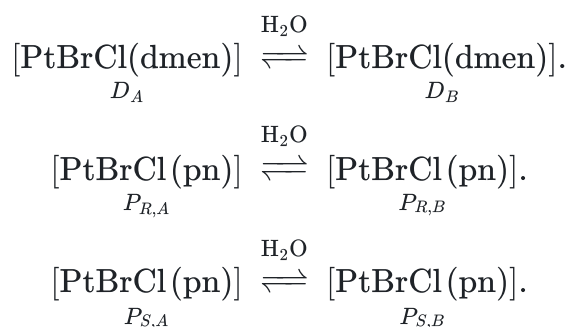
The counts follow directly:

- PtCl2(dmen): The chlorides are identical, and dmen has no configurationally stereogenic centre. There is **one** isomer.
- PtCl2(pn): The chlorides are identical, but pn has one stereogenic carbon. There are **two**, an *R/S* enantiomeric pair.
- PtBrCl(dmen): The two nitrogen donors differ, so arrangements *A* and *B* are distinct. There are **two geometrical isomers**.
- PtBrCl(pn): Each halide arrangement occurs with either carbon configuration. There are **four isomers**, forming the enantiomeric pairs (*P_{R,A}*, *P_{S,A}*) and (*P_{R,B}*, *P_{S,B}*).

1.5 — Room-temperature interconversions

Under the problem's substitution model, room-temperature exchange preserves the platinum–nitrogen framework. It also preserves the configuration of the pn carbon atom.

Temporary replacement of the halides by water, followed by halide rebinding, can exchange which halide occupies each available site. Thus the following net isomerizations are possible; the labels refer to the fully specified structures in 1.4:



These net equations are balanced: water mediates the exchange and is not consumed overall.

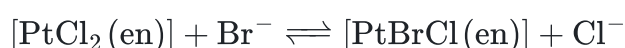
For completeness, the other cases are:

Earlier complex	Consequence of halide exchange alone
cis-/trans-PtCl ₂ (NH ₃) ₂	No interconversion: the relative ammonia positions remain unchanged.
cis-/trans-PtBrCl(NH ₃) ₂	No interconversion: swapping halides does not change the relative ammonia positions.
PtBrCl(en)	Returns the same configurational isomer.
PtCl ₂ (dmen)	Returns the same configurational isomer.
<i>R/S</i> -PtCl ₂ (pn)	No interconversion: halide exchange does not invert the stereogenic carbon.

Similarly, $P_{R,A}$ or $P_{R,B}$ does not become either S isomer by this process.

1.6 — Reaction of PtCl₂(en) with two equivalents of bromide

The balanced exchange equilibria are



and



The additional named structures are:

Name	SMILES
Dichlorido(ethane-1,2-diamine)platinum(II)	N1CCN->[Pt@SP1+2](<-[Cl-])(<-[Cl-])<-1
Dibromido(ethane-1,2-diamine)platinum(II)	N1CCN->[Pt@SP1+2](<-[Br-])(<-[Br-])<-1

The mixed-halide complex was specified in 1.3.

Initially, each mole of platinum complex supplies two moles of chloride, and two moles of bromide are added. Thus the total amounts of the two halides are equal.

Using the intended equal-affinity, independent-site approximation, equal total amounts imply equal equilibrium free-halide concentrations. Each of the two halide sites therefore has probability 1/2 of containing either halide:

$$P(\text{two chlorides}) = \left(\frac{1}{2}\right)^2 = \frac{1}{4},$$

$$P(\text{one of each}) = 2 \left(\frac{1}{2}\right) \left(\frac{1}{2}\right) = \frac{1}{2},$$

$$P(\text{two bromides}) = \left(\frac{1}{2}\right)^2 = \frac{1}{4}.$$

Therefore,

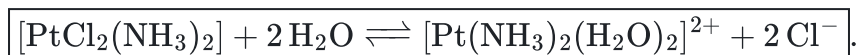
$$\boxed{\text{PtCl}_2(\text{en}) : \text{PtBrCl}(\text{en}) : \text{PtBr}_2(\text{en}) = 1 : 2 : 1}.$$

Per mole of initial platinum complex, the final amounts are 0.25, 0.50, and 0.25 mol, respectively, together with 1.0 mol each of free chloride and free bromide.

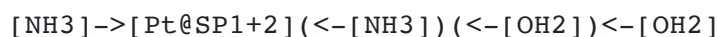
The factor of two for the mixed complex counts two equivalent site assignments; it does **not** imply two distinct mixed-halide en isomers.

1.7 — Hydrolysis in blood and in cells

Writing the replacing water ligands explicitly, the overall aquation equilibrium is



For cisplatin, the product is **cis-diamminediaquaplatinum(II) ion**:



The equilibrium constant is

$$K = \frac{a_{[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}} a_{\text{Cl}^-}^2}{a_{[\text{PtCl}_2(\text{NH}_3)_2]} a_{\text{H}_2\text{O}}^2}.$$

Taking water activity as approximately unity,

$$\boxed{\frac{a_{[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}}}{a_{[\text{PtCl}_2(\text{NH}_3)_2]}} = \frac{K}{a_{\text{Cl}^-}^2}}.$$

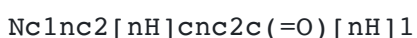
Thus:

- **Blood:** high chloride activity suppresses aquation through the common-ion effect.
- **Cells:** lower chloride activity favours the reactive aquated complex.

For example, a tenfold decrease in chloride activity increases this diaqua/original-complex ratio by a factor of $10^2 = 100$. The supplied information establishes the direction of the effect; numerical hydrolysis fractions would require equilibrium constants and concentrations.

1.8 — Which isomer can cross-link the two guanines?

The binding atom shown is guanine's **N7**. Guanine, as a free-base reference, has SMILES:



In DNA, its N9 position is attached to the sugar. The whole DNA molecule cannot be assigned a unique SMILES without specifying its sequence and structure.

After aquation, the two replaceable ligands occupy the positions originally occupied by the chlorides. Therefore the two guanine-binding sites are cis for cisplatin and trans for transplatin.

For two platinum–nitrogen bonds of length r , enclosing angle θ , the nitrogen–nitrogen distance is

$$d = \sqrt{r^2 + r^2 - 2r^2 \cos \theta} = 2r \sin \frac{\theta}{2}.$$

Using $r = 210$ pm:

For **cisplatin**, $\theta = 90^\circ$:

$$d_{\text{cis}} = \sqrt{2}(210 \text{ pm}) \approx \boxed{297 \text{ pm}}.$$

For **transplatin**, $\theta = 180^\circ$:

$$d_{\text{trans}} = 2(210 \text{ pm}) = \boxed{420 \text{ pm}}.$$

The supplied DNA base spacing is 320 pm, much closer to the cis separation. Equivalently, an exact donor separation of 320 pm with two 210 pm bonds would require

$$\theta = 2 \arcsin \left(\frac{320}{420} \right) \approx 99^\circ,$$

which is close to a cis angle.

Thus **cisplatin is the isomer consistent with the proposed cross-link between nearby guanines on the same DNA strand**, with some structural adjustment implicit in the approximate distance comparison.

The solution was checked against the official solution. Where this solution differs from the official solution, the official solution contains an error or a misprint.

Problem 2: Sodium triphosphate in detergents: complexation of Ca^{2+} and Mg^{2+}

The compound $\text{Na}_5\text{P}_3\text{O}_{10}$ is used as an additive for detergents to bind the Ca^{2+} and Mg^{2+} ions present in water in order to prevent the precipitation of their fatty acid salts on the laundry.

2.1 Draw the structure of the ions $(\text{P}_3\text{O}_{10})^{5-}$ and $(\text{P}_3\text{O}_9)^{3-}$ assuming that P-P bonds do not occur.

2.2 Assuming an octahedral coordination of the Mg^{2+} ion give a drawing of the $\text{Mg}(\text{P}_3\text{O}_{10})(\text{H}_2\text{O})_n^{3-}$ ion also indicating the value for n .

The complex ions of Mg^{2+} and Ca^{2+} and triphosphate are well soluble in water. They are, among other things, responsible for the wild growth of algae in surface waters. They could be removed by precipitation as an insoluble compound.

2.3 Give some possibilities (ions) to precipitate the triphosphates bound to Ca^{2+} or Mg^{2+} .

2.4 Calculate the mass of $\text{Na}_5\text{P}_3\text{O}_{10}$ (in grams) necessary in a washing machine to reduce the amount of Ca^{2+} in 20 litres of city water (0.225 g/l) to an acceptable maximum of 0.02 g/l. Effects of pH, the precipitation of $\text{Ca}(\text{OH})_2$, and possible effects by other positive ions, can be

neglected. The following data is given:

$$K_1 = \frac{[\text{Ca}^{2+}][\text{P}_3\text{O}_{10}^{5-}]}{[\text{CaP}_3\text{O}_{10}^{3-}]} = 1.0 \times 10^{-6}$$

Molar mass of $\text{Na}_5\text{P}_3\text{O}_{10}$ is 366 g mol^{-1} , the molar mass of Ca is 40 g mol^{-1} .

Official English text of the problem.

Answers

- 2.1 Triphosphate(5-),** $\text{P}_3\text{O}_{10}^{5-}$, has an open chain of three phosphorus atoms joined by oxygen bridges. SMILES: [O-]P(=O)([O-])OP(=O)([O-])OP(=O)([O-])[O-].
Cyclotriphosphate(3-), also called trimetaphosphate, $\text{P}_3\text{O}_9^{3-}$, has a six-membered ring of alternating phosphorus and oxygen atoms. SMILES: [O-]P1(=O)OP(=O)([O-])OP(=O)([O-])O1.
- 2.2** $n = 1$. The **aquatriphosphatmagnesate(II) ion**, $[\text{Mg}(\text{P}_3\text{O}_{10})(\text{H}_2\text{O})]^{3-}$, has five triphosphate oxygen donors and one water oxygen donor around octahedral magnesium. Dative-bond SMILES: [Mg+2]1234(<-[OH2])<-[O-]P(=O)([O-]->1)OP(=O)([O-]->2)OP(=O)([O-]->3)[O-]->4.
- 2.3** Suitable qualitative examples are **iron(III) ions**, Fe^{3+} , [Fe+3], and **aluminium(III) ions**, Al^{3+} , [Al+3], which can precipitate triphosphate in poorly soluble solids.
- 2.4** The required minimum mass is 37.6 g, approximately 38 g, of **sodium triphosphate**, $\text{Na}_5\text{P}_3\text{O}_{10}$. Ionic SMILES: [Na+] . [Na+] . [Na+] . [Na+] . [Na+] . [O-]P(=O)([O-])OP(=O)([O-])OP(=O)([O-])[O-].

Solution

2.1 — Structures of the phosphate ions

Each phosphorus(V) atom has approximately tetrahedral oxygen coordination. The tetrahedra connect through bridging oxygen atoms, giving $\text{P}-\text{O}-\text{P}$ links.

Three separate tetrahedra contain twelve oxygen positions. Sharing an oxygen between two phosphorus atoms reduces the number of distinct oxygen atoms by one.

For **triphosphate**, $\text{P}_3\text{O}_{10}^{5-}$, two oxygen bridges are therefore required:

$$12 - 2 = 10.$$

The structure is an open $\text{P}-\text{O}-\text{P}-\text{O}-\text{P}$ chain. In a conventional Lewis structure:

- Each terminal phosphorus has one $\text{P}=\text{O}$ group, two terminal O^- groups, and one bridging oxygen.
- The middle phosphorus has one $\text{P}=\text{O}$ group, one terminal O^- group, and two bridging oxygens.

Thus there are five negatively charged terminal oxygens and an overall charge of $5-$. To draw the ion, draw the three connected phosphorus tetrahedra and place these terminal groups on them. "Open chain" describes connectivity; the chain need not be straight or planar.

For **cyclotriphosphate**, $\text{P}_3\text{O}_9^{3-}$, three bridges are required:

$$12 - 3 = 9.$$

Draw a closed six-membered ring with alternating phosphorus and oxygen atoms. Each phosphorus carries one additional terminal $\text{P}=\text{O}$ group and one terminal O^- group. The three negatively charged oxygens give the overall charge $3-$.

The localized double bonds and charges are conventional Lewis representations; resonance distributes bonding and charge among terminal oxygens.

2.2 — The magnesium complex

In the intended idealised model, triphosphate is **pentadentate**: all five formally negatively charged terminal oxygen atoms coordinate to one magnesium(II) ion, Mg^{2+} , [$\text{Mg}+2$].

Octahedral coordination requires six donor atoms. Water, H_2O , 0, supplies the remaining donor:

$$5 + n = 6 \quad \implies \quad \boxed{n = 1}.$$

The charge is

$$(+2) + (-5) + 0 = -3,$$

so the complex is $[\text{Mg}(\text{P}_3\text{O}_{10})(\text{H}_2\text{O})]^{3-}$.

A precise drawing can be constructed as follows:

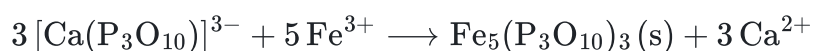
1. Place magnesium at the centre of an octahedron.
2. Put the oxygen donor from the middle phosphorus at the upper axial vertex and the water oxygen at the opposite axial vertex.
3. Put the four negatively charged oxygens from the two terminal phosphorus atoms at the four equatorial vertices. The two donors belonging to each terminal phosphorus occupy adjacent vertices.
4. Retain the two oxygen bridges connecting the three phosphorus atoms.

The three conventional $\text{P}=\text{O}$ oxygens and the two bridging oxygens do not coordinate in this model. The arrows in the supplied SMILES encode oxygen-to-magnesium coordination bonds; the octahedral arrangement is specified by the description above. Other denticities are possible in real complexes, but in the idealised model in which all five negatively charged oxygen atoms coordinate, $n = 1$.

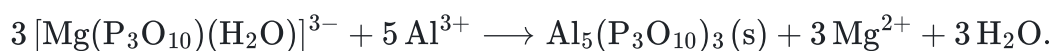
2.3 — Precipitation

Iron(III) and aluminium(III) ions have a strong affinity for phosphate oxygen donors and can form poorly soluble triphosphate-containing solids. Precipitation draws triphosphate out of the soluble calcium or magnesium complexes.

Writing the insoluble trivalent-metal triphosphates formally as $\text{Fe}_5(\text{P}_3\text{O}_{10})_3$ and $\text{Al}_5(\text{P}_3\text{O}_{10})_3$, representative balanced equations are



and

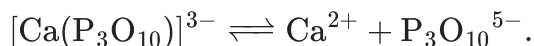


Either precipitating cation can be considered for either hardness-ion complex. These equations describe idealised displacement and precipitation stoichiometry; the precise solid phase depends on the solution conditions.

2.4 — Required sodium triphosphate mass

The specified calcium limit concerns **free calcium(II)**, Ca^{2+} , $[\text{Ca}^{2+}]$. Complexation reduces its free concentration while retaining calcium in solution.

The equilibrium is



The calcium(II)–triphosphate complex has composition SMILES $[\text{Ca}^{2+}] \cdot [\text{O}-]\text{P}(=\text{O})([\text{O}-])\text{OP}(=\text{O})([\text{O}-])\text{OP}(=\text{O})([\text{O}-])[\text{O}-]$; this notation omits coordination bonds, whose arrangement is unnecessary for the calculation.

The initial total calcium concentration is

$$c_{\text{Ca,tot}} = \frac{0.225 \text{ g L}^{-1}}{40 \text{ g mol}^{-1}} = 5.625 \times 10^{-3} \text{ mol L}^{-1}.$$

For the minimum dose, the final free calcium concentration equals the acceptable maximum:

$$[\text{Ca}^{2+}] = \frac{0.020 \text{ g L}^{-1}}{40 \text{ g mol}^{-1}} = 5.00 \times 10^{-4} \text{ mol L}^{-1}.$$

Because each complex contains one calcium ion, the calcium balance gives

$$\begin{aligned} &= c_{\text{Ca,tot}} - [\text{Ca}^{2+}] \\ &= 5.625 \times 10^{-3} - 5.00 \times 10^{-4} \\ &= 5.125 \times 10^{-3} \text{ mol L}^{-1}. \end{aligned}$$

Some triphosphate must remain free to establish the specified equilibrium. Using the given dissociation constant, with concentrations expressed in mol L^{-1} ,

$$\begin{aligned} &= K_1 \frac{[\text{CaP}_3\text{O}_{10}^{3-}]}{[\text{Ca}^{2+}]} \\ &= (1.0 \times 10^{-6}) \frac{5.125 \times 10^{-3}}{5.00 \times 10^{-4}} \\ &= 1.025 \times 10^{-5} \text{ mol L}^{-1}. \end{aligned}$$

The total triphosphate concentration required is consequently

$$\begin{aligned} c_{\text{triphosphate,tot}} &= [\text{CaP}_3\text{O}_{10}^{3-}] + [\text{P}_3\text{O}_{10}^{5-}] \\ &= 5.13525 \times 10^{-3} \text{ mol L}^{-1}. \end{aligned}$$

Each mole of sodium triphosphate supplies one mole of triphosphate. Thus, using the supplied molar mass,

$$\begin{aligned} m &= (20 \text{ L})(5.13525 \times 10^{-3} \text{ mol L}^{-1})(366 \text{ g mol}^{-1}) \\ &= 37.59003 \text{ g}. \end{aligned}$$

Therefore,

$$m(\text{Na}_5\text{P}_3\text{O}_{10}) \approx 37.6 \text{ g} \quad (\text{about } 38 \text{ g}).$$

The solution was checked against the official solution.

Problem 3: Particle-in-a-box model of conjugated dyes and retinal

In order to explain why dyes are coloured, they can be considered as rod-like, one-dimensional molecules over which the electrons are distributed. The wave lengths of the electrons should fit to the available space which is the length l . When absorbing light, an electron makes a transition from a lower to a higher energy state. The energy difference is given by:

$$\Delta E = h \times \text{coverlambda} \quad \text{where } \lambda = \frac{h}{p}$$

3.1 Give a general expression for possible wavelengths of the electron as a function of the length l .

In the 'particle in the box' model, only the variations in the kinetic energy of the electrons are considered.

3.2 Give an expression for the possible energies that electrons in the molecule can have (as a function of l).

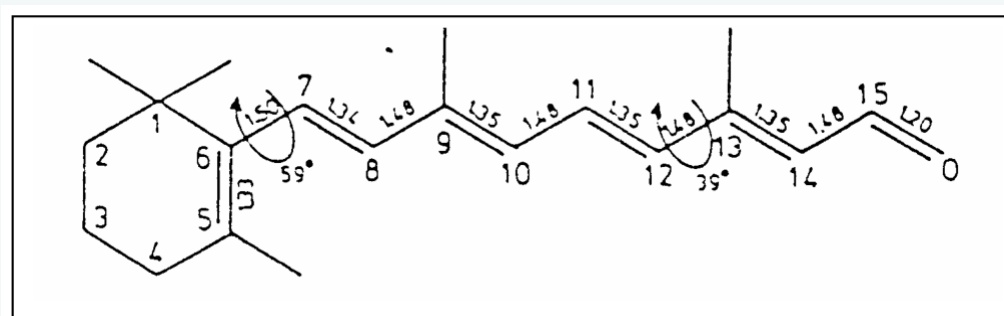
3.3 Show that for a chain of length l with k electrons, the longest wavelength absorption occurs at:

$$\lambda = \frac{8mcl^2}{h(k+1)} \quad \text{for even values of } k$$

3.4 Derive an expression for the wavelength of the first electronic transition as a function of the number of C-atoms for even values of n .

3.5 Calculate the minimum number of C-atoms (conjugated systems) to obtain a visible colour. C-C bond length is 142 pm.

The retina in the human eye contains rhodopsin, a light absorbent.



The molecule in the part of C-atoms 7 through 12 is planar. The angle between the bonds C5-C6, C7-C8, C11-C12 and C13-C14 is about 39°. According to the 'particle in the box' theory fragment C7 through C12 should absorb at about 213 nm. In reality the absorption of retinal occurs at 308 nm.

3.6 Give a reason for the longer wavelength that is observed in practice using the above mentioned theories.

3.7 When retinal is bound to opsin to form rhodopsin, the absorption occurs around 600 nm. Which atoms must be forced into one plane by the protein? Show by calculation that it's true.

Official English text of the problem.

Answers

- **3.1** $\lambda_{e,j} = \frac{2l}{j}$, where $j = 1, 2, 3, \dots$

- **3.2** $E_j = \frac{j^2 h^2}{8m_e l^2}$.

- **3.3** The lowest excitation is $j = k/2 \rightarrow k/2 + 1$, giving $\lambda_{\max} = \frac{8m_e c l^2}{h(k+1)}$.

- **3.4** With a the carbon-carbon bond length, $l = (n-1)a$ and $k = n$, so

$$\lambda_{\text{first}} = \frac{8m_e c a^2}{h} \frac{(n-1)^2}{n+1}.$$

- **3.5** $n_{\min} = 10$ conjugated carbon atoms. The predicted absorption is approximately 490 nm; eight carbon atoms give 362 nm.

- **3.6** Twisting reduces, but does not eliminate, orbital overlap. Delocalization therefore extends beyond C7-C12, lowering the excitation energy and increasing the absorption wavelength.

- **3.7** Within the stated model, the entire conjugated skeleton—**C5 through C15 and the terminal oxygen in the drawing**—must be coplanar. It contains 12 conjugated electrons over approximately 1.54 nm, giving $\lambda \approx 600 \text{ nm}$.

Solution

Write λ_e for an electron's de Broglie wavelength and λ_{ph} for the absorbed photon's wavelength. The two relevant relations are

$$p = \frac{h}{\lambda_e}, \quad \Delta E = \frac{hc}{\lambda_{\text{ph}}}.$$

For numerical calculations, use

$$h = 6.626 \times 10^{-34} \text{ J s}, \quad m_e = 9.109 \times 10^{-31} \text{ kg}, \quad c = 2.998 \times 10^8 \text{ m s}^{-1}.$$

3.1

For a particle confined by impenetrable ends at $x = 0$ and $x = l$, the wavefunction must vanish at both ends. Thus an integral number of half-wavelengths fits into the box:

$$l = j \frac{\lambda_{e,j}}{2}.$$

Consequently,

$$\boxed{\lambda_{e,j} = \frac{2l}{j}}, \quad j = 1, 2, 3, \dots$$

The corresponding standing waves are proportional to $\sin(j\pi x/l)$. The value $j = 0$ would give an identically zero wavefunction and is excluded.

3.2

The permitted momentum magnitudes are

$$p_j = \frac{h}{\lambda_{e,j}} = \frac{j\hbar}{2l}.$$

Taking the potential energy inside the box as zero, the energy is entirely kinetic:

$$E_j = \frac{p_j^2}{2m_e}.$$

Therefore,

$$\boxed{E_j = \frac{j^2 \hbar^2}{8m_e l^2}}, \quad j = 1, 2, 3, \dots$$

3.3

Each spatial energy level accommodates two electrons with opposite spins. For an even number k of electrons in the ground state, the occupied levels are

$$j = 1, 2, \dots, \frac{k}{2}.$$

The smallest possible excitation promotes an electron from the highest occupied level to the lowest unoccupied level:

$$\frac{k}{2} \longrightarrow \frac{k}{2} + 1.$$

This adjacent-level transition is dipole allowed. Its energy is

$$\begin{aligned} \Delta E_{\min} &= E_{k/2+1} - E_{k/2} \\ &= \frac{\hbar^2}{8m_e l^2} \left[\left(\frac{k}{2} + 1 \right)^2 - \left(\frac{k}{2} \right)^2 \right] \\ &= \frac{\hbar^2(k+1)}{8m_e l^2}. \end{aligned}$$

Since the longest photon wavelength corresponds to the smallest excitation energy,

$$\boxed{\lambda_{\max} = \frac{hc}{\Delta E_{\min}} = \frac{8m_e c l^2}{\hbar(k+1)}}.$$

3.4

An unbranched conjugated chain containing n carbon atoms has $n - 1$ bonds along its backbone. Using the chain's contour length as the one-dimensional box length,

$$l = (n - 1)a,$$

where a is the common carbon–carbon bond length. Each conjugated carbon supplies one π electron, so $k = n$.

Substitution into the result of 3.3 gives

$$\lambda_{\text{first}}(n) = \frac{8m_e c a^2 (n-1)^2}{h(n+1)}, \quad n \text{ even.}$$

For $a = 142 \text{ pm} = 1.42 \times 10^{-10} \text{ m}$,

$$\frac{8m_e c a^2}{h} = 6.648 \times 10^{-8} \text{ m} = 66.48 \text{ nm}.$$

Hence

$$\lambda_{\text{first}}(n) = (66.48 \text{ nm}) \frac{(n-1)^2}{n+1}.$$

3.5

Taking approximately 400 nm as the short-wavelength boundary of visible light requires

$$66.48 \frac{(n-1)^2}{n+1} \geq 400.$$

The equality gives $n \approx 8.60$. Because n must be even, the first candidate is $n = 10$. Checking the neighboring even values:

Conjugated carbon atoms n	Box length l	First absorption wavelength
8	994 pm	362 nm
10	1278 pm	490 nm

Thus eight carbon atoms still give ultraviolet absorption, whereas ten give visible absorption:

$$n_{\text{min}} = 10.$$

Using 380 nm instead of 400 nm for the visible boundary gives the same minimum.

3.6

The molecule drawn is **retinal**, with an all-trans polyene configuration, represented by the SMILES O=C/C=C(\C)/C=C/C=C(\C)/C=C/C1=C(C)CCCC1(C)C.

This SMILES specifies connectivity and double-bond configuration; it does not specify the single-bond torsion angles shown in the figure.

Restricting the box to C7–C12 assumes that the conjugated electrons cannot extend beyond that fragment. However, the neighboring double bonds are separated from it by single bonds about which the molecule is twisted. A twist of the stated magnitude reduces the overlap of neighboring p orbitals but does not make that overlap zero.

Consequently, the electronic states extend beyond C7–C12 into the neighboring conjugated groups. The greater effective delocalization length lowers the first excitation energy, so

$$\Delta E \downarrow \implies \lambda_{\text{ph}} = \frac{hc}{\Delta E} \uparrow.$$

This explains qualitatively why the observed 308 nm is longer than the stated isolated-fragment prediction of 213 nm. The simple model and torsion angles alone do not determine the precise observed wavelength.

3.7

To maximize conjugation in the model, the protein must bring the complete conjugated skeleton into one plane:

- the ring double bond, C5=C6;
- the chain carbons C7–C15;
- the terminal carbonyl oxygen in the supplied drawing.

Thus the relevant plane contains **C5–C15 and O**. The saturated ring carbons C1–C4 and the methyl carbons do not belong to this conjugated electron system.

There are six conjugated double bonds: five carbon–carbon double bonds and one carbon–oxygen double bond. Therefore,

$$k = 6 \times 2 = 12 \text{ electrons.}$$

Adding the labelled bond lengths along the conjugated path from C5 to O gives approximately

$$l = l_{5,6} + l_{6,7} + \cdots + l_{14,15} + l_{15,O} \simeq 1.54 \text{ nm.}$$

The predicted absorption is therefore

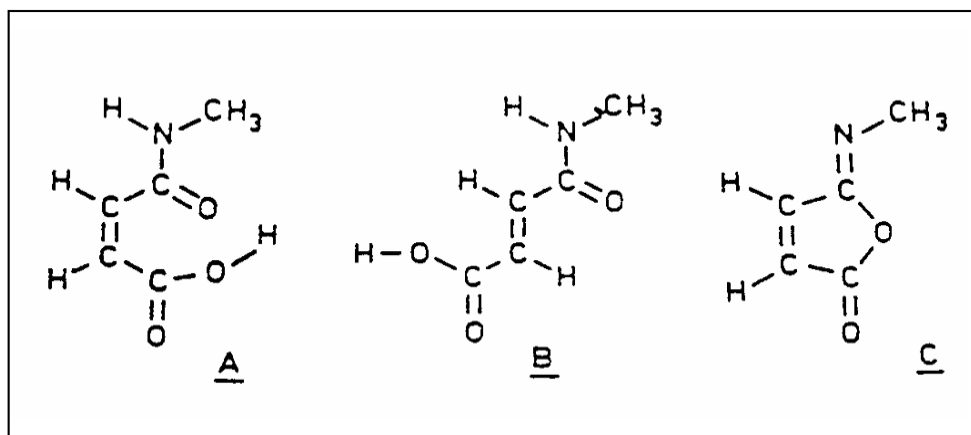
$$\begin{aligned} \lambda_{\max} &= \frac{8m_e c l^2}{h(k+1)} \\ &\simeq \frac{8(9.109 \times 10^{-31} \text{ kg})(2.998 \times 10^8 \text{ m s}^{-1})(1.54 \times 10^{-9} \text{ m})^2}{(6.626 \times 10^{-34} \text{ J s})(13)} \\ &\simeq 6.0 \times 10^{-7} \text{ m} \\ &= \boxed{6.0 \times 10^2 \text{ nm}}. \end{aligned}$$

This agrees with the problem's value of about 600 nm.

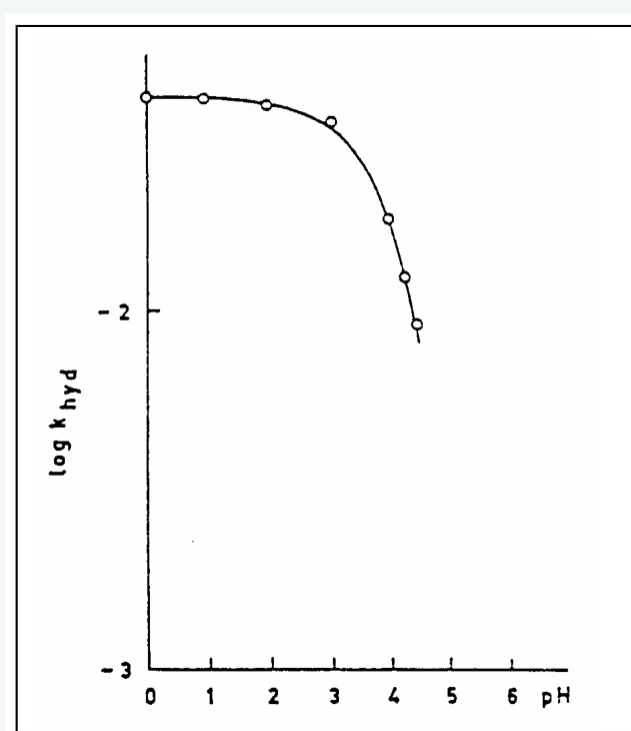
The solution was checked against the official solution.

Problem 4: Intramolecular catalysis of amide hydrolysis (an enzyme model)

The high efficiency of catalysis by enzymes is mainly due to an enzyme-reactant complex in which the reacting group is placed in a favourable position for the reaction with respect to the catalyzing groups of the enzyme. Studies are carried out with model compounds in which a catalyzing group has been introduced in the proximity of the reaction centre of the molecule. As an example we consider the hydrolysis of the amide bond in compound **A**. This reaction proceeds in water at 39 °C and pH = 2 more than a million times faster than the hydrolysis of compound **B**.



The relation between the rate constant k_{hyd} and pH for the hydrolysis of **A** at 39 °C is shown in figure below.



Further observation:

Addition of water to the iso-imide **C** gives a rapid reaction, which initially yields **A**. Subsequently, hydrolysis of **A** occurs. The amid carbonyl group in **A** is labelled with ^{13}C and the hydrolysis is allowed to take place in H_2^{18}O at pH = 2 and 39 °C. The diacid formed upon hydrolysis is isolated, converted into a disilver salt and completely decarboxylated with bromine in an anhydrous reaction medium. The carbon dioxide formed is a mixture of particles of masses 44, 45, 46 and 47 which are formed in equal amounts.

4.1 Why is the hydrolysis of **A** so much faster than that of **B**?

4.2 Explain why the rate of hydrolysis of **A** is independent on pH in the range between pH = 0 to pH = 2.

4.3 Why does k_{hyd} decrease so rapidly at pH values higher than 3.

4.4 Give a detailed reaction mechanism for the hydrolysis of **A**. Indicate which step in the reaction is rate determining.

4.5 Show that the observations further made are consistent with the reaction mechanism given under d.

Official English text of the problem.

Answers

- **4.1:** The cis arrangement in **A** permits neighbouring-carboxyl-group participation through a five-membered cyclic intermediate. The trans arrangement in **B** prevents this favourable pathway.
- **4.2:** The neighbouring carboxyl group is predominantly protonated and supplies the proton needed internally. The rate therefore approaches a pH-independent limiting value.
- **4.3:** Carboxyl-group ionization suppresses this pathway. Approximately,

$$k_{\text{hyd}} = \frac{k_0}{1 + 10^{\text{pH} - \text{p}K_a}}.$$

- **4.4:** Reversible cyclization gives a tetrahedral intermediate. Slow, proton-assisted C–N cleavage forms **maleic anhydride**, O=C1OC(=O)C=C1, which rapidly hydrolyses to **maleic acid**, O=C(O)/C=C\C(=O)O.
- **4.5:** Hydration of **C** can give the same tetrahedral intermediate, which readily returns to **A**. Subsequent hydrolysis through the symmetric anhydride places the incoming oxygen-18 at either carboxyl group with equal probability, giving carbon dioxide of nominal masses 44, 45, 46, 47 in the ratio 1 : 1 : 1 : 1.

Solution

4.1 — Origin of the acceleration

The two starting compounds are:

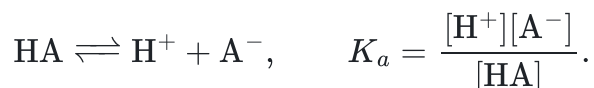
Compound	Name and alkene configuration	SMILES
A	N-Methylmaleamic acid; the carboxyl and amide groups are cis	<chem>CNC(=O)/C=C\C(=O)O</chem>
B	N-Methylfumaramic acid; the carboxyl and amide groups are trans	<chem>CNC(=O)/C=C/C(=O)O</chem>

In **A**, the neighbouring carboxyl group can approach the amide carbonyl and participate in an **intramolecular nucleophilic acyl substitution**. Ring closure produces a favourable five-membered intermediate. The carboxyl group also supplies a proton that assists departure of the nitrogen-containing group.

This arrangement gives both favourable positioning and a high effective local concentration of the participating group. In **B**, the alkene holds the two substituents on opposite sides. The corresponding five-membered ring cannot form while retaining that trans double-bond geometry. Consequently, **B** lacks the strongly accelerated intramolecular pathway.

4.2 — The pH-independent region

Write HA for neutral **A**, and A^- for its conjugate base, **N-methylmaleamate**, CNC(=O)/C=C\C(=O)[O-]. Their equilibrium is



Here the hydrogen ion is H^+ , $[H^+]$.

The efficient pathway requires the **protonated carboxyl group**: it provides neighbouring-group attack together with internal proton transfer. It does not require an additional hydronium ion in the rate-determining conversion.

Neglecting the much slower background hydrolysis, let k_0 be the limiting first-order rate constant of this pathway. Then

$$v = k_0[HA] = k_{\text{hyd}}([HA] + [A^-]),$$

so

$$k_{\text{hyd}} = k_0 \frac{[H^+]}{K_a + [H^+]} = \frac{k_0}{1 + 10^{\text{pH} - \text{p}K_a}}.$$

Between pH 0 and 2, the neutral acid predominates, and therefore

$$[H^+] \gg K_a \implies k_{\text{hyd}} \approx k_0.$$

This accounts for the plateau.

4.3 — Decrease above pH 3

As the pH rises, an increasing fraction of **A** becomes its carboxylate anion. Although a carboxylate oxygen is nucleophilic, the group has lost the acidic proton required for the efficient coupled proton-transfer and amide-cleavage pathway.

The fraction of reactive neutral acid therefore falls sharply. In the higher-pH limit,

$$k_{\text{hyd}} \approx k_0 \frac{[H^+]}{K_a},$$

and consequently

$$\log_{10} k_{\text{hyd}} \approx \log_{10} k_0 + \text{p}K_a - \text{pH}.$$

Thus the idealized descending branch approaches a slope of -1 : a one-unit increase in pH gives approximately a tenfold decrease in this contribution to the rate.

4.4 — Detailed mechanism and rate-determining step

The important cyclic species are:

Symbol	Species	SMILES
T	Cyclic tetrahedral intermediate, 5-hydroxy-5-(methylamino)furan-2(5H)-one	<chem>CNC1(O)OC(=O)C=C1</chem>
T_N	Proton-transfer form of T , with an ammonium group and an alkoxide oxygen	<chem>C[NH2+]C1([O-])OC(=O)C=C1</chem>
D	Maleic anhydride	<chem>O=C1OC(=O)C=C1</chem>

The transient stereochemistry at the tetrahedral carbon does not affect the argument; the SMILES for **T** and **T_N** leave it unspecified.

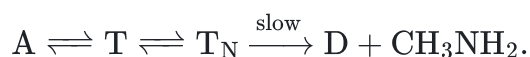
Reversible intramolecular addition. The hydroxyl oxygen of the neighbouring carboxyl group attacks the amide carbonyl carbon. The carbonyl π electrons move onto oxygen. Proton transfer from the participating carboxyl group to the former carbonyl oxygen gives **T**.

The newly formed ring contains, in sequence, the former amide carbonyl carbon, the two alkene carbons, the original carboxyl carbon and the participating oxygen. It is therefore five-membered.

Proton-assisted amide cleavage. Transfer of the hydroxyl proton in **T** to nitrogen gives the charge arrangement represented by **T_N**. The alkoxide oxygen then reforms the carbonyl while the C–N bond breaks, releasing **methylamine**, CN , and forming maleic anhydride **D**.

These proton-transfer and bond-cleavage events may be coupled; they need not involve an appreciable concentration of an isolated **T_N**.

The productive sequence is

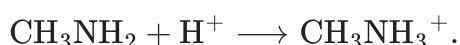


The **rate-determining productive step is the proton-assisted C–N cleavage leading to the anhydride**. The rapid return of the tetrahedral intermediate to **A**, discussed in 4.5, is consistent with this assignment.

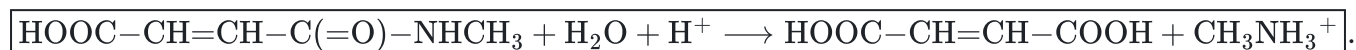
Rapid anhydride hydrolysis. Water, O , attacks an anhydride carbonyl. Addition and proton transfer give a tetrahedral hydrate, **5,5-dihydroxyfuran-2(5H)-one**, $\text{O}=\text{C1OC}(\text{O})(\text{O})\text{C}=\text{C1}$. Carbonyl reformation with cleavage of the acyl–oxygen bond opens the ring and gives maleic acid:



At pH 2, the released methylamine is protonated to **methylammonium**, $\text{C}[\text{NH}_3^+]$:



The balanced overall reaction under these acidic conditions is



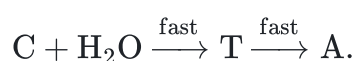
The alkene retains its cis configuration throughout.

4.5 — Consistency with the additional observations

Hydration of the iso-imide.

Compound **C** is **N-methylmaleic iso-imide**, $\text{C}/\text{N}=\text{C1}\backslash\text{OC}(=\text{O})\text{C}=\text{C1}$; this SMILES represents the imine arrangement drawn in the question.

Water addition at its imidoyl carbon, accompanied by proton transfer to nitrogen, gives the same tetrahedral intermediate **T**:



The corresponding molecular-formula balance is



In **T**, reformation of the amide carbonyl with cleavage of the ring's acyl–oxygen bond regenerates **A**. This route is faster than productive C–N cleavage. Thus **C** initially yields **A**, after which the slower anhydride-forming reaction occurs, exactly as observed.

Carbon-13 and oxygen-18 tracing.

The starting material is **amide-carbonyl-¹³C-labelled A**, CN[13C](=O)/C=C\C(=O)O. Its intramolecular reaction gives **carbonyl-¹³C-labelled maleic anhydride**, O=[13C]1OC(=O)C=C1.

Crucially, formation of the anhydride incorporates **no solvent oxygen**. The oxygen-18 enters during the subsequent reaction with **oxygen-18-labelled water**, [18OH2].

The two carbonyl sites of the unlabelled maleic anhydride skeleton are equivalent. Neglecting small isotope effects, water attacks either site with probability 1/2. Each product molecule contains one carbon-13 atom and one newly incorporated oxygen-18 atom.

Site attacked by labelled water	Maleic acid isotopomer formed	Carbon dioxide masses obtained from its two carboxyl groups
The carbon-13 carbonyl	Labels in the same carboxyl group: <chem>O=[13C]([18OH])/C=C\C(=O)O</chem>	47 and 44
The carbon-12 carbonyl	Labels in different carboxyl groups: <chem>O=[13C](O)/C=C\C(=O)[18OH]</chem>	45 and 46

Unmarked oxygens in these product SMILES represent the original oxygen-16 atoms in the idealized isotope accounting.

Conversion to the disilver salt—**disilver maleate**, [Ag+].[Ag+].[O-]C(=O)/C=C\C(=O)[O-], with the labels retained—does not change which oxygen atoms belong to each carboxyl carbon.

Decarboxylation with **bromine**, BrBr, in the anhydrous medium then releases those carboxyl units as carbon dioxide.

The resulting isotopologues are:

Carbon dioxide isotopologue	SMILES	Nominal mass / u	Fraction of total carbon dioxide
Carbon-12, oxygen-16 carbon dioxide, $^{12}\text{C}^{16}\text{O}_2$	<chem>[16O]=[12C]=[16O]</chem>	$12 + 16 + 16 = 44$	1/4
Carbon-13 carbon dioxide, $^{13}\text{C}^{16}\text{O}_2$	<chem>[16O]=[13C]=[16O]</chem>	$13 + 16 + 16 = 45$	1/4
Singly oxygen-18-labelled carbon dioxide, $^{12}\text{C}^{16}\text{O}^{18}\text{O}$	<chem>[16O]=[12C]=[18O]</chem>	$12 + 16 + 18 = 46$	1/4
Carbon-13 and oxygen-18-labelled carbon dioxide, $^{13}\text{C}^{16}\text{O}^{18}\text{O}$	<chem>[16O]=[13C]=[18O]</chem>	$13 + 16 + 18 = 47$	1/4

For n_0 moles of hydrolysed **A**, each pathway occurs for $n_0/2$ moles and produces one mole of each member of its carbon dioxide pair. Hence

$$n_{44} = n_{45} = n_{46} = n_{47} = \frac{n_0}{2}, \quad n_{\text{total}} = 2n_0.$$

Therefore,

$$n_{44} : n_{45} : n_{46} : n_{47} = 1 : 1 : 1 : 1.$$

Direct hydrolysis solely at the original amide carbonyl would place oxygen-18 only with carbon-13 and give masses 47 and 44. The additional, equally abundant masses 45 and 46 support hydrolysis through the symmetric anhydride.

The solution was checked against the official solution.

Problem 5: Lactic acid, its dilactide and polylactide, and the herbicide Barnon

Bacterial conversion of saccharose leads to (S)-(+)-2-hydroxypropanoic acid (L-(+)-lactic acid), which forms a cyclic ester out of two molecules. This dilactide can be polymerized to a polylactide, which is used in surgery.

5.1 Give the spatial structures and Fischer projection of L-(+)-lactic acid and its dilactide.

5.2 Sketch the structure of the polylactide discussed above (at least three units). What is its tacticity (iso-, syndio- or atactic)?

5.3 Draw the isomeric dilactides formed out of racemic lactic acid. Show the configuration of the chiral centres.

L-(+)-lactic acid is used for the preparation of the herbicide Barnon that is used against wild oats. In this case (+)-lactic acid is esterified with 2-propanol and then the hydroxyl group is treated with methanesulfonyl chloride. The product is then submitted to a S_N2 -reaction with 3-fluoro-4-chloro-phenylamine, where the methanesulfonate group leaves as CH_3SO_3^- . Finally a benzoyl group is introduced with the help of benzoyl chloride.

5.4 Draw the Fischer projection of the various consecutive reaction products.

Official English text of the problem.

Answers

- 5.1** L-(+)-lactic acid is **(S)-2-hydroxypropanoic acid**, $\text{C}[\text{C@H}](\text{O})\text{C}(=\text{O})\text{O}$. Its Fischer projection has CO_2H above, CH_3 below, hydroxyl left and hydrogen right. Its cyclic diester is **L,L-lactide**, **(3S,6S)-3,6-dimethyl-1,4-dioxane-2,5-dione**, $\text{C}[\text{C@@H}]1\text{OC}(=\text{O})[\text{C@H}](\text{C})\text{OC1=O}$.
- 5.2** The product is **isotactic poly(L-lactide)**: every stereogenic carbon has configuration *S*. A three-repeat fragment is $*\text{O}[\text{C@@H}](\text{C})\text{C}(=\text{O})\text{O}[\text{C@@H}](\text{C})\text{C}(=\text{O})\text{O}[\text{C@@H}](\text{C})\text{C}(=\text{O})^*$, where * denotes continuation of the chain.
- 5.3** There are **three stereoisomeric lactides**: L,L-lactide, $(3S,6S)$, given above; its enantiomer **D,D-lactide**, **(3R,6R)-3,6-dimethyl-1,4-dioxane-2,5-dione**, $\text{C}[\text{C@H}]1\text{OC}(=\text{O})[\text{C@@H}](\text{C})\text{OC1=O}$; and **meso-lactide**, **(3R,6S)-3,6-dimethyl-1,4-dioxane-2,5-dione**, $\text{C}[\text{C@@H}]1\text{OC}(=\text{O})[\text{C@@H}](\text{C})\text{OC1=O}$. The $(3S,6R)$ description represents the same meso compound.

- **5.4** The consecutive products are:

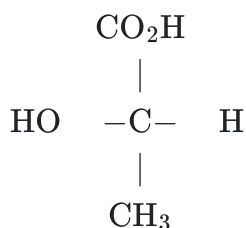
Step	Product	Stereochemical SMILES
1	Isopropyl (2S) -2-hydroxypropanoate	<chem>C[C@H](O)C(=O)OC(C)C</chem>
2	Isopropyl (2S) -2-[(methanesulfonyl)oxy]propanoate	<chem>C[C@H](OS(=O)(=O)C)C(=O)OC(C)C</chem>
3	Isopropyl (2R) -2-[(4-chloro-3-fluorophenyl)amino]propanoate	<chem>C[C@@H](Nc1cc(F)c(Cl)cc1)C(=O)OC(C)C</chem>
4	Barnon , isopropyl (2R) -2-[benzoyl(4-chloro-3-fluorophenyl)amino]propanoate	<chem>C[C@@H](N(c1cc(F)c(Cl)cc1)C(=O)c2ccccc2)C(=O)OC(C)C</chem>

Solution

5.1 — Lactic acid and its dilactide

In every Fischer projection below, **horizontal bonds point towards the observer and vertical bonds point away**.

The Fischer projection of L-(+)-lactic acid is



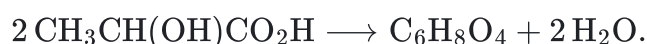
Its tetrahedral spatial structure is therefore specified by hydroxyl and hydrogen pointing towards the observer, with carboxyl and methyl pointing away in this projection.

The CIP priority order is

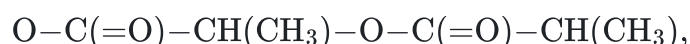


The carboxyl carbon outranks the methyl carbon because its attached-atom list is oxygen, oxygen, oxygen, whereas that of methyl is hydrogen, hydrogen, hydrogen. Accounting for hydrogen pointing towards the observer gives the stated *S* configuration.

Two lactic acid molecules form two ester bonds, eliminating two molecules of **water**, O:



The product is the six-membered cyclic diester L,L-lactide. Number its ring consecutively as



starting with oxygen at position 1 and closing the final carbon back to that oxygen. The stereogenic carbons are positions 3 and 6. Esterification preserves their configurations, giving (3*S*, 6*S*).

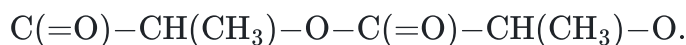
A precise perspective drawing can be constructed as follows:

- Draw a hexagon with O1 at the top and number clockwise.
- C2 and C5 carry the carbonyl oxygens.

- At both C3 and C6, draw methyl on a hashed wedge pointing away and hydrogen on a solid wedge pointing towards the observer.

In this convention the two methyl groups are **cis**.

For a cyclic Fischer projection, write the following ring path vertically, from top to bottom:



Join the bottom oxygen to the top carbonyl carbon by an external return bond. At **both** stereogenic crosses, place **hydrogen on the left and methyl on the right**. Each cross then has a carbonyl carbon above and an ester oxygen below, giving *S* at both centres. This specifies configuration without assigning a particular ring conformation.

5.2 — Polylactide structure and tacticity

Opening the lactide rings produces the polyester backbone



This explicitly shows three lactyl repeat units. Every displayed $\text{CH}(\text{CH}_3)$ centre has configuration *S*, as encoded in the fragment SMILES in the Answers.

Each lactide supplies two lactyl repeats. Ignoring initiator-dependent end groups, the balanced repeat-unit stoichiometry is



Normal ring-opening polymerization cleaves an ester bond at the acyl group without substituting at a stereogenic carbon. Thus the configurations are retained, and no small molecule is eliminated during this polymerization step.

Because all stereogenic repeat units have the same configuration, the polymer is **isotactic**.

5.3 — Lactides from racemic lactic acid

Racemic lactic acid contains equal amounts of the *S* acid and **D-(R)-lactic acid**, $\text{C}[\text{C}@@\text{H}](\text{O})\text{C}(=\text{O})\text{O}$.

Pairing the two configurations gives *SS*, *RR*, *SR*, and *RS*. The two ring positions are equivalent, so *SR* and *RS* describe one meso compound. Consequently, there are three distinct stereoisomers.

Using the numbered hexagon and cyclic Fischer convention specified in 5.1:

Lactide	Configuration	Perspective: methyl bonds at C3, C6	Cyclic Fischer: methyl positions at C3, C6
L,L-lactide	(3 <i>S</i> , 6 <i>S</i>)	Both hashed wedges, away	Right, right
D,D-lactide	(3 <i>R</i> , 6 <i>R</i>)	Both solid wedges, towards	Left, left
meso-Lactide	(3 <i>R</i> , 6 <i>S</i>)	Solid wedge, hashed wedge	Left, right

At each centre, hydrogen occupies the position opposite methyl.

The *SS* and *RR* compounds are **enantiomers**. The *RS* compound is **achiral and meso**, and is a diastereomer of each member of the enantiomeric pair. Its two methyl groups are trans in the stated hexagon convention.

Each formation reaction has the condensation stoichiometry given in 5.1: two lactic acid molecules yield one lactide and two water molecules.

5.4 — Consecutive products in the Barnon synthesis

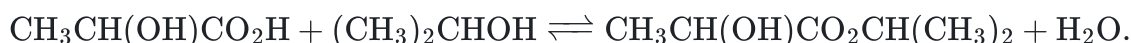
Let Ar denote the **4-chloro-3-fluorophenyl group**, with fluorine at position 3 and chlorine at position 4 relative to the carbon bonded to nitrogen.

For every product, draw the Fischer projection with $\text{CO}_2\text{CH}(\text{CH}_3)_2$ at the top and CH_3 at the bottom. The horizontal substituents are:

Product	Left	Right	Configuration
Isopropyl lactate	OH	H	<i>S</i>
Its methanesulfonate ester	$\text{CH}_3\text{SO}_2\text{O}$, bonded through oxygen	H	<i>S</i>
Aniline substitution product	H	NHAr , bonded through nitrogen	<i>R</i>
N-Benzoylated product, Barnon	H	$\text{N}(\text{Ar})\text{C}(=\text{O})\text{C}_6\text{H}_5$, bonded through nitrogen	<i>R</i>

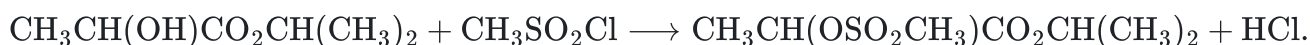
The balanced equations below show acid equivalents explicitly; the problem does not specify an acid-accepting base.

Step 1: esterification. Reaction with **propan-2-ol**, $\text{CC}(\text{O})\text{C}$, gives isopropyl *S*-lactate:



The reaction occurs at the carboxyl group. No bond at the stereogenic carbon is replaced, so its configuration remains *S*.

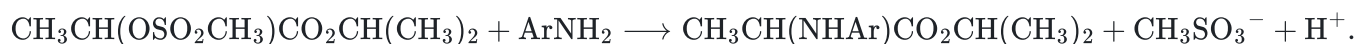
Step 2: methanesulfonylation. The alcohol reacts with **methanesulfonyl chloride**, $\text{CS}(=\text{O})(=\text{O})\text{Cl}$:



The formal acid by-product is **hydrogen chloride**, Cl .

The hydroxyl oxygen forms a bond to sulfur; the original bond between oxygen and the stereogenic carbon remains intact. Configuration is therefore retained: *S*.

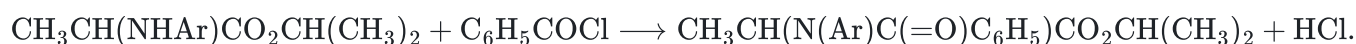
Step 3: nucleophilic substitution. The nucleophile is **4-chloro-3-fluoroaniline**, Nc1cc(F)c(Cl)cc1 . Its nitrogen attacks the stereogenic carbon from the side opposite the leaving group:



The leaving group is **methanesulfonate**, $\text{CS}(=\text{O})(=\text{O})[\text{O}-]$. The **hydrogen ion**, $[\text{H}^+]$, accounts formally for deprotonation of the nitrogen after substitution.

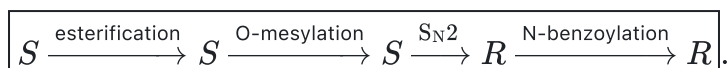
Backside attack gives **Walden inversion**. In both substrate and product the heteroatom substituent has highest priority, followed by the ester carbonyl carbon, methyl, and hydrogen. Thus inversion changes the designation from *S* to *R*. With the vertical Fischer groups fixed, hydrogen is now left and the amino substituent right.

Step 4: benzoylation. The secondary amine reacts with **benzoyl chloride**, $\text{O}=\text{C}(\text{Cl})\text{c1ccccc1}$:



Benzoylation replaces the nitrogen-bound hydrogen with a benzoyl group, producing a tertiary amide. The stereogenic carbon undergoes no substitution, so its configuration remains *R*.

The complete configuration sequence is therefore



The solution was checked against the official solution.

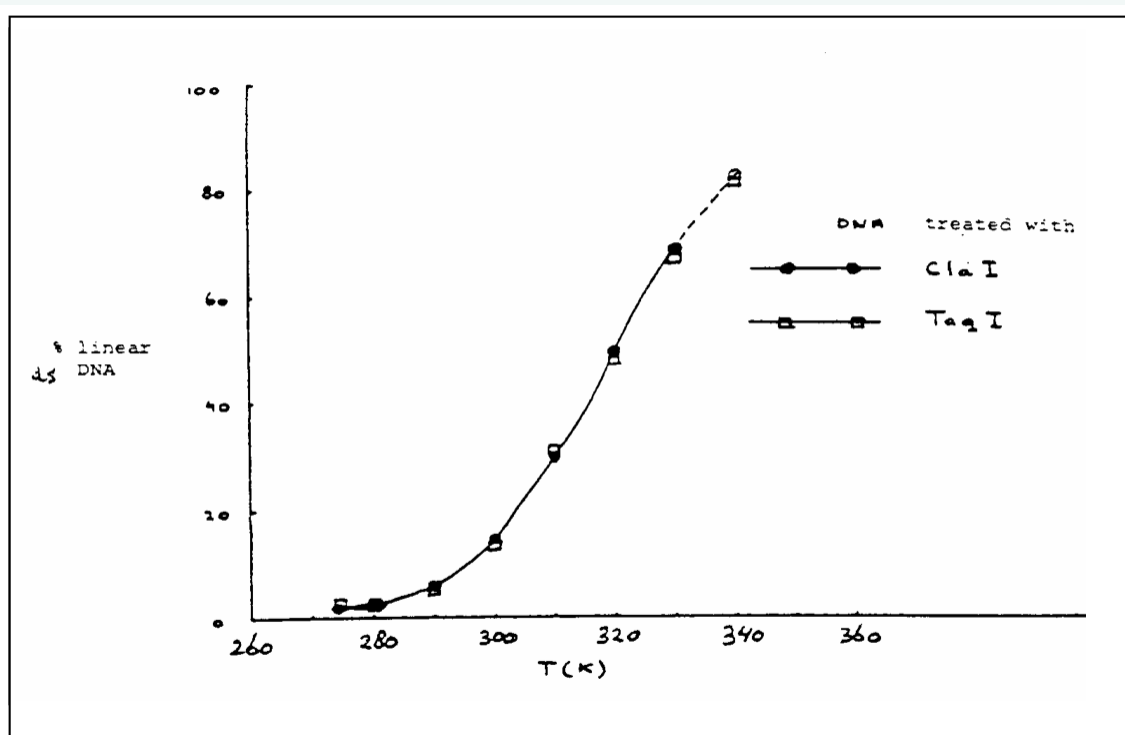
Problem 6: Restriction endonucleases Cla I and Taq I and recombinant DNA

In recombinant DNA technology specific endonucleases can recognize and hydrolyse the phosphoric ester bound in each of both strands. Cla I for example hydrolyses the bond between two nucleotides in the sequence:



6.1 Give the base sequence of the complementary strand in the 5' - 3' direction and indicate with arrows the location where the hydrolysis by Cla I would occur.

6.2 How often on average will this sequence occur in one strand of DNA molecule of 10^5 base pairs? You can assume that the four bases occur equally often and that they randomly distribute in the two chains.

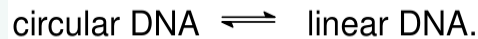


Taq I hydrolyses a long double strand DNA molecule into fragments which are on average 256 base pairs long. The 3' end of these fragments treated by cleavage turns out to be a thymine(T)- and the 5' end a cytosine(C)- end.

6.3 How long is the sequence recognized by Taq I?

6.4 Give the two possible base sequences (in the direction 5' - 3') which form the recognition pattern for Taq I (must obviously have some symmetry).

The DNA of a phage which occurs as a close circle contains only 5'-pApTpCpGpApT-3' sequence in each of the two strands. After treatment with ClaI equilibrium is established:



6.5 Give a schematic drawing of the circular and linear molecules. Indicate the bases adjacent to the cleaving site in both strands. Indicate also the 3' and 5' ends.

In Fig. 1 the percentage of linear DNA is given as a function of temperature, measured in a solution of 0.15 M NaCl buffered with citrate at pH = 6.5. With Taq I as cleavage enzyme, the same curve is obtained.

6.6 Is the reaction as written endothermic or exothermic? Explain your answer.

6.7 Show, considering the information given, which of the two base sequences of the answer to **6.4** is the correct one.

6.8 What would look the curve for Taq I like if the recognition pattern would have been the other possibility of d)?

A large DNA molecule is cut into fragments with the aid of Cla I. One fragment is isolated, purified and mixed in the ratio of 1:1 with phage DNA which was also cleaved with Cla I. Thereby recombinant molecules can be formed through the reaction:



6.9 Would the enthalpy of this reaction be positive, negative or about zero? Explain your answer.

6.10 Which combination of temperature, DNA concentration and ionic strength (high or low in each case) will give the maximum percentage of recombinant molecules?

Official English text of the problem.

Answers

- **6.1:** The complementary strand, written 5' → 3', is also 5'-AT ↓ CGAT-3'. Cla I produces two-nucleotide **5'-CG cohesive ends**.
- **6.2:** Approximately **24 occurrences** in one strand: $10^5/4^6 \approx 24.4$.
- **6.3:** **Four nucleotides per strand**, corresponding to a four-base-pair recognition site.
- **6.4:** 5'-T ↓ CGA-3' and 5'-GAT ↓ C-3'.
- **6.5:** Cutting the single site opens the circular duplex into one linear molecule with a **5'-CG overhang at each end**, terminal 5'-phosphorylated C residues, and terminal 3'-hydroxyl T residues.
- **6.6:** Circular → linear is **endothermic**, $\Delta H > 0$.
- **6.7:** Taq I recognizes 5'-TCGA-3' and cleaves T ↓ C.

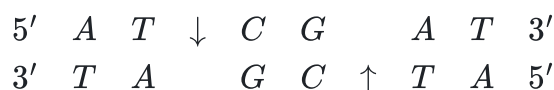
- **6.8:** The alternative would give a similar rising curve **shifted toward lower temperatures**.
- **6.9: Negative enthalpy**, $\Delta H < 0$, for association of the open, cleaved molecules through their cohesive ends.
- **6.10: Low temperature, low DNA concentration, and high ionic strength.** Dilution suppresses formation of chains containing several DNA molecules; excessive dilution would also suppress the initial phage–fragment association.

Solution

6.1

The base symbols denote residues of adenine, A (Nc1ncnc2[nH]cnc12); thymine, T (Cc1c[nH]c(=O)[nH]c1=O); cytosine, C (Nc1cc[nH]c(=O)n1); and guanine, G (Nc1nc2[nH]cnc2c(=O)[nH]1). The SMILES in this sentence describe the corresponding free nucleobases.

A pairs with T, and C pairs with G. The strands run antiparallel, so the aligned recognition site and cleavage positions are

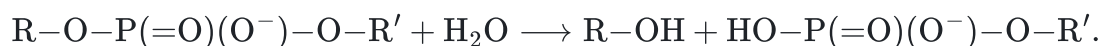


Reading the lower strand from its own 5' end gives



Thus ATCGAT is a **reverse-complement palindrome**. The staggered cuts leave two-nucleotide 5'-CG overhangs.

Each cleavage hydrolyses a phosphodiester linkage, producing a 3'-hydroxyl end and a 5'-phosphate end. A balanced representation, with R and R' standing for the sugar-containing DNA portions, is



This equation uses one possible protonation state of the terminal phosphate; the buffer controls subsequent proton exchange. Each double-strand cut consumes **two water molecules**. Water has SMILES O; the generic phosphodiester and phosphate monoester groups have SMILES *OP(=O)([O-])O* and *OP(=O)([O-])O, respectively, where $*$ denotes an unspecified DNA portion.

For structural identification, the recognition sequences can be represented as isolated **5'-phosphorylated, 3'-hydroxy oligodeoxynucleotides**. Their SMILES below encode the natural sugar stereochemistry and use neutral phosphate acid forms for notation. They do not encode duplex pairing or helicity. Complete SMILES for the phage and recombinant DNA cannot be specified because their remaining sequences are not given.

5'-Phosphorylated DNA hexamer d(ATCGAT):

```
O=P(O)(O)OC[C@H]1O[C@@H](n2cnc3c(N)ncnc32)C[C@@H]1OP(=O)(O)OC[C@H]1O[C@@H](n2cc(C)c(=O)[nH]c2=O)C[C@@H]1OP(=O)(O)OC[C@H]1O[C@@H](n2ccc(N)nc2=O)C[C@@H]1OP(=O)(O)OC[C@H]1O[C@@H](n2cnc3c(=O)[nH]c(N)nc32)C[C@@H]1OP(=O)(O)OC[C@H]1O[C@@H](n2cnc3c(N)ncnc32)C[C@@H]1OP(=O)(O)OC[C@H]1O[C@@H](n2cc(C)c(=O)[nH]c2=O)C[C@@H]1O
```

6.2

At a specified starting position, the probability of the particular six-base sequence is

$$p = \left(\frac{1}{4}\right)^6 = \frac{1}{4096}.$$

For a linear strand containing $N = 10^5$ nucleotides, there are $N - 6 + 1$ possible starting positions. Therefore,

$$\mathbb{E}[n] = (10^5 - 5) \frac{1}{4096} = 24.4128 \dots \approx \boxed{24 \text{ occurrences}}.$$

Neglecting the five terminal positions gives 24.4141, essentially the same result. The mean spacing is approximately 4096 base pairs.

There is no factor of two: the question asks about one strand, and the complementary occurrence identifies the same duplex site.

6.3

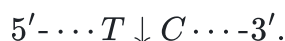
For a particular recognition sequence of length m , the occurrence probability is 4^{-m} . In a long DNA molecule, the mean fragment length is consequently approximately 4^m base pairs.

Thus,

$$4^m = 256 = 4^4, \quad \boxed{m = 4}.$$

6.4

A terminal 3'-T and terminal 5'-C mean that cleavage occurs at



A palindromic four-base recognition site has its first and fourth bases complementary, and its second and third bases complementary.

There are two possible placements of $T \downarrow C$:

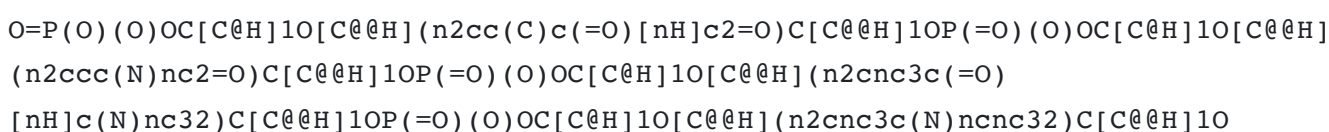
Position of $T \downarrow C$	Recognition sequence	Aligned complementary strand
First–second bases	5'-T $\downarrow$ CGA-3'	3'-AGC $\uparrow$ T-5'
Third–fourth bases	5'-GAT $\downarrow$ C-3'	3'-C $\uparrow$ TAG-5'

It cannot occupy the middle two positions because T and C are not complementary.

The two candidates therefore produce different cohesive ends:

- **TCGA:** two-nucleotide **5'-CG** overhangs.
- **GATC:** two-nucleotide **3'-AT** overhangs.

5'-Phosphorylated DNA tetramer d(TCGA):



5'-Phosphorylated DNA tetramer d(GATC):

```
O=P(O)(O)OC[C@H]1O[C@@H](n2cnc3c(=O)[nH]c(N)nc32)C[C@H]1OP(=O)(O)OC[C@H]1O[C@@H](n2cnc3c(N)ncnc32)C[C@H]1OP(=O)(O)OC[C@H]1O[C@@H](n2ccc(N)nc2=O)C[C@H]1O
```

6.5

The requested drawing should show the following.

For the **original circular molecule**, draw two continuous antiparallel circular strands. At the unique recognition site, place the paired bases and staggered cleavage positions exactly as in 6.1. The intact circle has no free 3' or 5' termini; these labels indicate strand direction.

For the **linear molecule**, open both backbones at those positions and separate the cohesive ends. Reading the resulting duplex from left to right:

- The upper strand starts 5'-pCGAT... and ends ...AT-3'.
- The lower strand starts 3'-TA... and ends ...TAGC-p-5'.

At the left end, the upper strand's initial CG projects beyond the lower strand. At the right end, the lower strand's terminal GC, read left to right, projects beyond the upper strand. Read in its own 5' → 3' direction, that overhang is also CG.

Thus every 5' terminus is a **phosphorylated C**, and every 3' terminus is a **T bearing a free hydroxyl group**.

After cleavage, these complementary overhangs can pair again to produce a **circular, annealed molecule with two backbone nicks**. This is the circular species participating in the temperature-dependent equilibrium:



Annealing alone does not restore the hydrolysed covalent bonds; covalent sealing would require an additional ligation step.

6.6

The fraction of linear DNA increases as the temperature increases. Heating therefore favours the forward direction,



so this direction is **endothermic**:

$$\boxed{\Delta H > 0}.$$

More formally, if f is the fraction of linear molecules,

$$K = \frac{[\text{linear DNA}]}{[\text{circular DNA}]} = \frac{f}{1-f}.$$

The graph shows K increasing with temperature. The van 't Hoff relation,

$$\frac{d \ln K}{dT} = \frac{\Delta H^\circ}{RT^2},$$

then gives $\Delta H^\circ > 0$.

Physically, opening the annealed circle disrupts the base pairing and stacking at its cohesive junction. This conclusion concerns **end dissociation**, not the initial phosphodiester hydrolysis.

6.7

Cla I produces 5'-CG overhangs. Closing their junction forms **two G–C base pairs**.

Of the two Taq I candidates:

- $T \downarrow CGA$ produces the same 5'-CG overhangs.
- $GAT \downarrow C$ produces 3'-AT overhangs, which would form two A–T pairs.

The identical temperature curves therefore select, within the model of the problem,



Indeed, this recognition sequence lies within the Cla I site:



Both enzymes consequently cut the same bonds at this site.

6.8

The alternative $GAT \downarrow C$ site would produce AT cohesive ends. Their annealing would form two A–T pairs instead of two G–C pairs.

A–T pairs have two hydrogen bonds each, whereas G–C pairs have three. In the intended comparison, the AT junction is less stable and dissociates at a lower temperature.

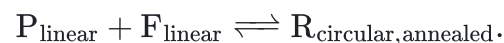
The requested curve should therefore be described as a **similar increasing, approximately sigmoidal curve shifted to the left**:

- At a given temperature in the transition region, the percentage of linear DNA would be higher.
- The temperature at which 50% is linear would be lower.

The supplied information does not determine the numerical shift.

6.9

Let P denote the open phage DNA, F the open fragment, and R the intended circular recombinant containing one of each:



Each molecule supplies two compatible cohesive ends. Formation of the recombinant circle produces **two cohesive junctions**, each containing two G–C pairs: four newly formed G–C pairs in total.

Base pairing and stacking release heat, so

$$\boxed{\Delta H < 0}.$$

There is no release of water in this annealing reaction. The backbone nicks remain unless a subsequent covalent ligation step is performed.

6.10

The intended qualitative combination is

low temperature; low DNA concentration; high ionic strength.

- **Low temperature:** Cohesive-end association is exothermic, so cooling favours the associated recombinant.
- **Low DNA concentration:** After one phage end joins one fragment end, the remaining two ends are tethered within the same combined molecule and can close it into a circle. At high concentration, they can instead encounter additional DNA molecules and form longer chains. Dilution suppresses these additional intermolecular encounters relative to intramolecular closure.
- **High ionic strength:** Salt, such as sodium chloride ($[Na^+] \cdot [Cl^-]$), screens electrostatic repulsion between the negatively charged phosphate backbones and stabilizes the paired cohesive ends.

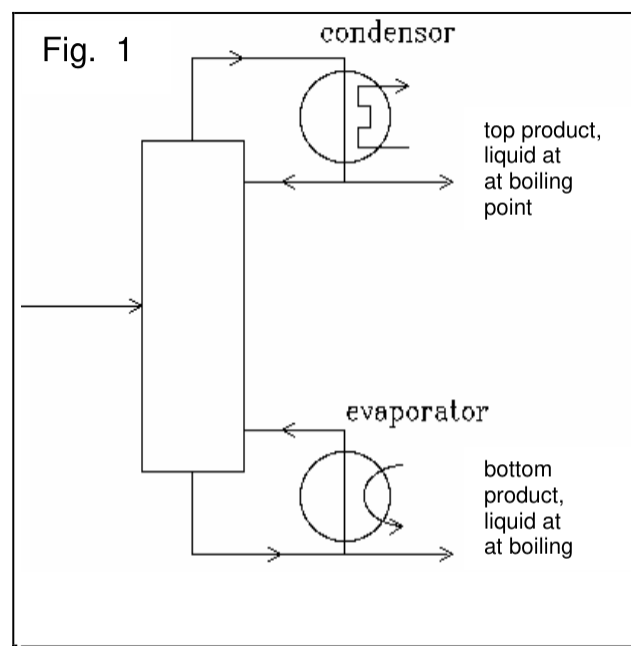
The concentration argument must therefore include both ends of each molecule. Applying mass action only to the first bimolecular association would overlook chain formation.

"Low concentration" does **not** mean unlimited dilution: excessive dilution suppresses the initial phage-fragment encounter and favours separate self-circularization. The useful condition is sufficiently dilute to suppress multimer formation while still permitting the initial association.

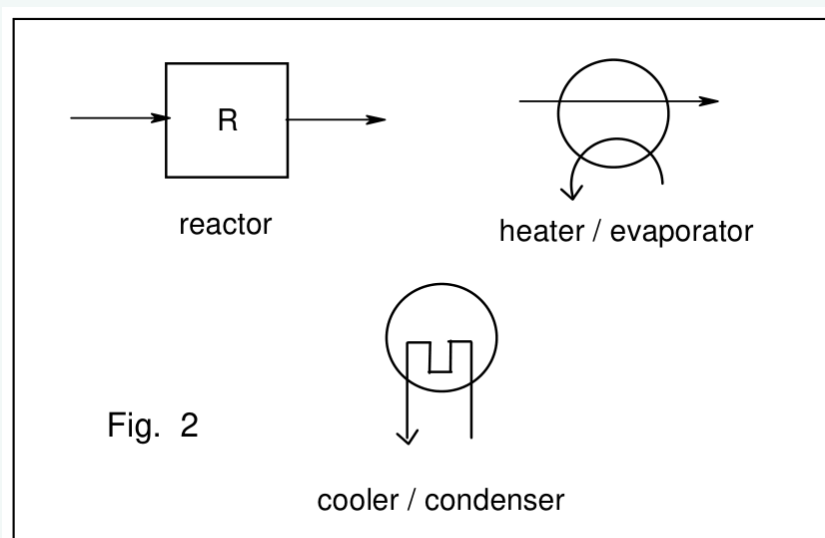
The solution was checked against the official solution.

Problem 7: Continuous process $A + 2 B \rightleftharpoons 2 C$: flow sheet and energy balance

The equilibrium constant of the reaction $A(g) + 2 B(g) \rightleftharpoons 2 C(g)$ is $K_p = 10.0 \text{ MPa}^{-1}$. The starting materials are supplied at 25 °C and heated to 100 °C where complete equilibration takes place. Below 100 °C the reaction rate is negligibly small. The whole process is executed continuously in a stationary state. The boiling points at 0.1 MPa of A, B, and C are 40 °C, 80 °C, and 60 °C, respectively. The three compounds have the same heat of evaporation: $q \text{ J mol}^{-1}$. The heat capacities of A, B, and C may be neglected. A schematic diagram of a distillation is shown below (Fig. 1).



The total heat used at each of the two distillations is $3q \text{ J mol}^{-1}$ (of the top product). Apart from distillation columns (each with its own evaporator and condenser) the pieces of apparatus shown of Fig. 2 are available.



7.1 Draw a flow diagram of the process in which all flows are given (flow sheet) and in which the starting materials are used as efficiently as possible using as few pieces of apparatus as possible.

7.2 Express the equilibrium constant in terms of the degree of conversion and of total pressure for the case that the feed to the reactor is stoichiometric. What is the value of the degree of conversion when total pressure is 0.100 MPa?

7.3 Number all flows. Calculate the composition of each flow in mol s^{-1} for a rate of production of 1 mole of C per second under the conditions of part b.

7.4 In what respect can the reaction conditions influence the composition of the mixture that leaves the reactor? (Refer to question b.)

7.5 The process requires energy. For the conditions of b explain where energy should be supplied in the flow diagram drawn in part a. Derive an expression for the total energy needed.

Answers

- **7.1:** Combine fresh and recycled reactants in one evaporator, feed the vapor to the reactor, then separate the outlet in two columns: first take A overhead; then take C overhead from the remaining B/C mixture. Recycle all separated A and B. A separate reactor-outlet condenser can be omitted if the first column accepts vapor feed.
- **7.2:**

$$K_p = \frac{\alpha^2(3 - \alpha)}{P(1 - \alpha)^3}, \quad \alpha = \frac{1}{3} = 33.3\%.$$

- **7.3:** In mol s^{-1} , fresh feed is $0.500 \text{ A} + 1.00 \text{ B}$; recycle is $1.00 \text{ A} + 2.00 \text{ B}$; reactor feed is $1.50 \text{ A} + 3.00 \text{ B}$; reactor outlet is $1.00 \text{ A} + 2.00 \text{ B} + 1.00 \text{ C}$. The complete numbered stream table appears below.
- **7.4:** Higher pressure increases equilibrium conversion. The effect of temperature depends on the unspecified reaction enthalpy. Below 100°C , the composition is effectively frozen by the negligible reaction rate.
- **7.5:** Vaporization requires $4.50q \text{ J s}^{-1}$, and each column requires $3.00q \text{ J s}^{-1}$:

$$\dot{Q}_{\text{vaporization+distillation}} = 10.5q \text{ J s}^{-1}.$$

The additional signed reactor duty is

$$\dot{Q}_R = (0.500 \text{ mol s}^{-1}) \Delta_r H_g,$$

where $\Delta_r H_g$ is the enthalpy of the gas-phase reaction as written.

Solution

The symbols A, B, and C denote unspecified compounds. Their chemical names and SMILES cannot be inferred from the data.

7.1 — Flow sheet

At 0.100 MPa , the volatility order indicated by the boiling points is

$$\text{A } (40^\circ\text{C}) > \text{C } (60^\circ\text{C}) > \text{B } (80^\circ\text{C}).$$

Use the following arrangement, with the stream numbers also used in part 7.3:

1. Join fresh liquid A, stream **1**, and fresh liquid B, stream **2**, with the two liquid recycle streams **6** and **9**.
2. Send the combined liquid, stream **3**, through one common heater/evaporator. Its gaseous outlet, stream **4**, enters the reactor at 100°C .
3. Send the equilibrium reactor outlet, stream **5**, to the first distillation column.
4. In the first column, obtain pure A as the liquid top product, stream **6**, and recycle it to the feed junction. Send the bottom product containing B and C, stream **7**, to the second column.

5. In the second column, withdraw pure liquid C as the top product, stream **8**, and recycle pure liquid B, the bottom product, as stream **9**.

Thus the pure liquid outlet temperatures are 40 °C for recycled A, 60 °C for product C, and 80 °C for recycled B.

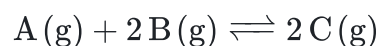
Complete recycling gives complete overall utilization of the starting materials, despite incomplete conversion during each reactor passage. Two ordinary columns with top and bottom products provide the required separation of the intermediate-boiling product.

For the fewest separate units, stream 5 can enter the first column as vapor: its built-in condenser supplies the necessary condensation duty. If liquid feed to that column is required, insert one cooler/condenser between the reactor and the first column. Its inlet and outlet have identical molar compositions.

Removing A first also gives the smaller distillation heating requirement, as shown in part 7.5.

7.2 — Equilibrium conversion

Let α be the fraction of the entering A converted. For a stoichiometric reactor feed initially containing n_0 mol of A, $2n_0$ mol of B, and no C,



gives the equilibrium amounts

$$n_A = n_0(1 - \alpha), \quad n_B = 2n_0(1 - \alpha), \quad n_C = 2n_0\alpha.$$

The total is

$$n_{\text{tot}} = n_0(3 - \alpha).$$

Consequently,

$$p_A = P \frac{1 - \alpha}{3 - \alpha}, \quad p_B = P \frac{2(1 - \alpha)}{3 - \alpha}, \quad p_C = P \frac{2\alpha}{3 - \alpha}.$$

Substitution into the equilibrium expression gives

$$K_p = \frac{p_C^2}{p_A p_B^2} = \boxed{\frac{\alpha^2(3 - \alpha)}{P(1 - \alpha)^3}}.$$

At $P = 0.100 \text{ MPa}$,

$$K_p P = (10.0 \text{ MPa}^{-1})(0.100 \text{ MPa}) = 1.00.$$

Therefore,

$$\begin{aligned} \alpha^2(3 - \alpha) &= (1 - \alpha)^3, \\ 3\alpha^2 - \alpha^3 &= 1 - 3\alpha + 3\alpha^2 - \alpha^3, \end{aligned}$$

and hence

$$\boxed{\alpha = \frac{1}{3} = 33.3\%}.$$

The equilibrium mole fractions are $y_A = 1/4$, $y_B = 1/2$, and $y_C = 1/4$. As a check,

$$K_p = \frac{(0.0250)^2}{(0.0250)(0.0500)^2} = 10.0 \text{ MPa}^{-1}.$$

7.3 — Numbered material balances

Producing 1.00 mol s^{-1} of C requires a reaction extent rate

$$\dot{\xi} = \frac{\dot{n}_C}{2} = 0.500 \text{ mol s}^{-1}.$$

Since one-third of the entering A reacts,

$$\dot{n}_{A,\text{in}} = \frac{\dot{\xi}}{\alpha} = \frac{0.500}{1/3} = 1.50 \text{ mol s}^{-1},$$

and the stoichiometric feed contains

$$\dot{n}_{B,\text{in}} = 3.00 \text{ mol s}^{-1}.$$

The reactor therefore discharges

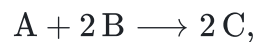
$$\begin{aligned}\dot{n}_{A,\text{out}} &= 1.50 - 0.500 = 1.00, \\ \dot{n}_{B,\text{out}} &= 3.00 - 2(0.500) = 2.00, \\ \dot{n}_{C,\text{out}} &= 2(0.500) = 1.00,\end{aligned}$$

all in mol s^{-1} .

The complete external stream table is:

Stream	Description	A, mol s^{-1}	B, mol s^{-1}	C, mol s^{-1}
1	Fresh liquid A	0.500	0	0
2	Fresh liquid B	0	1.00	0
3	Combined liquid feed to evaporator	1.50	3.00	0
4	Gaseous feed to reactor	1.50	3.00	0
5	Reactor outlet to first column	1.00	2.00	1.00
6	First-column top product; A recycle	1.00	0	0
7	First-column bottom product to second column	0	2.00	1.00
8	Second-column top product; final C	0	0	1.00
9	Second-column bottom product; B recycle	0	2.00	0

The fresh feed exactly replaces the reactants consumed. Thus the overall material balance corresponds to



with no reactants discarded.

7.4 — Influence of reaction conditions

For the specified stoichiometric feed,

$$K_p P = \frac{\alpha^2(3 - \alpha)}{(1 - \alpha)^3}.$$

The right-hand side increases with α over $0 < \alpha < 1$. Therefore, at fixed temperature, increasing pressure increases conversion. This agrees with the reduction from three gaseous reactant molecules to two gaseous product molecules.

Temperature changes K_p . The van 't Hoff relation is

$$\frac{d \ln K_p}{dT} = \frac{\Delta_r H_g}{RT^2}.$$

Accordingly:

- If the forward reaction is endothermic, increasing temperature increases equilibrium conversion.
- If it is exothermic, decreasing temperature increases equilibrium conversion.

The reaction enthalpy is not supplied, so the applicable direction cannot be determined. Moreover, below 100 °C the reaction is negligibly slow: cooling the outlet preserves its composition during separation.

Changing the reactant ratio also changes the equilibrium composition; an excess of one reactant generally increases the fractional conversion of the other. A catalyst or additional residence time cannot change the final equilibrium composition once equilibrium has been reached.

7.5 — Energy requirements

Let the molar latent heat be

$$L = q \text{ J mol}^{-1}.$$

Because heat capacities are neglected, there is no sensible-heating contribution from raising the feeds to 100 °C.

The common evaporator vaporizes all fresh and recycled reactants:

$$\dot{Q}_E = (1.50 + 3.00) \text{ mol s}^{-1} L = \boxed{4.50q \text{ J s}^{-1}}.$$

The first column produces 1.00 mol s^{-1} of overhead A, so its reboiler requires

$$\dot{Q}_{D1} = (1.00 \text{ mol s}^{-1})(3L) = \boxed{3.00q \text{ J s}^{-1}}.$$

The second column produces 1.00 mol s^{-1} of overhead C:

$$\dot{Q}_{D2} = \boxed{3.00q \text{ J s}^{-1}}.$$

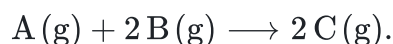
Thus the specified vaporization and distillation heating duties total

$$\boxed{\dot{Q}_{\text{physical}} = (4.50 + 3.00 + 3.00)q = 10.5q \text{ J s}^{-1}}.$$

Equivalently, these operations require $10.5q \text{ J}$ per mole of C.

The alternative separation order—first taking A + C overhead, then separating them—would have overhead rates of 2.00 and 1.00 mol s^{-1} . Its distillation duties would total $9.00q$, compared with $6.00q \text{ J s}^{-1}$ for the chosen order.

The reactor must also be maintained at 100 °C. Define $\Delta_r H_g$ as the molar enthalpy of



Its signed heat requirement is

$$\boxed{\dot{Q}_R = \dot{\xi} \Delta_r H_g = (0.500 \text{ mol s}^{-1}) \Delta_r H_g}.$$

The algebraic sum of the evaporator, reboiler, and reactor duties is therefore

$$\boxed{\dot{Q}_E + \dot{Q}_{D1} + \dot{Q}_{D2} + \dot{Q}_R = 10.5q \text{ J s}^{-1} + (0.500 \text{ mol s}^{-1}) \Delta_r H_g}.$$

An endothermic reaction requires additional heat at the reactor; an exothermic reaction requires heat removal there. With no heat recovery, the total positive heating demand is

$$\dot{Q}_{\text{heating}} = 10.5q \text{ J s}^{-1} + \max[0, (0.500 \text{ mol s}^{-1})\Delta_r H_g].$$

For an energy-balance check, the reactor outlet contains 4.00 mol s^{-1} of vapor. In the vapor-fed layout, the first column's condenser rejects $7.00q \text{ J s}^{-1}$: $4.00q$ from condensation of that feed plus its $3.00q$ reboiler input. The second condenser rejects $3.00q \text{ J s}^{-1}$. A separate effluent condenser would divide the first $7.00q$ into $4.00q + 3.00q$, leaving the total unchanged.

After subtracting condenser cooling, the overall net heat exchange is consequently

$$\dot{Q}_{\text{net}} = 0.500q \text{ J s}^{-1} + (0.500 \text{ mol s}^{-1})\Delta_r H_g.$$

The solution was checked against the official solution.