1 (A)
Incorrect base-pairing would cause point mutations as a consequence of substitution of A for G during subsequent rounds of DNA replication.

1 (B)
(i) Because of mutations, the transcribed mRNA may contain incorrect codons in the coding regions in genomic DNA. Incorrect codons may lead to incorporation of incorrect amino acids in the polypeptide chains in proteins, during protein synthesis.

According to the standard genetic code (see page 2):
Incorporation of incorrect amino acids may result in incorrect protein structure, incorrect protein folding, or both.

For example, substitution of Ser by Pro may disrupt the structure of an $\alpha$ helix; substitution of a basic amino acid with a hydrophobic residue may perturb the tertiary structure of a protein; at active sites of enzymes, substitution of Ser with other amino acids could alter catalytic and kinetic properties of affected enzymes; substitution of a coding codon with a termination codon would produce truncated polypeptide chains, etc.

(ii) Substitution of A for G during the subsequent rounds of DNA replication may produce cryptic RNA splicing sites producing mRNAs encoding aberrant proteins.

(iii) Substitution of A for G in regulatory elements could cause anomalous patterns of gene expression.
The standard genetic code

<table>
<thead>
<tr>
<th>First Position (5' end)</th>
<th>Second Position</th>
<th>Third Position (3' end)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U</td>
<td>C</td>
</tr>
<tr>
<td>U</td>
<td>UUU Phe</td>
<td>UCU Ser</td>
</tr>
<tr>
<td></td>
<td>UUC Phe</td>
<td>UCC Ser</td>
</tr>
<tr>
<td></td>
<td>UUA Leu</td>
<td>UCA Ser</td>
</tr>
<tr>
<td></td>
<td>UUG Leu</td>
<td>UCG Ser</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>CCU Pro</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td>CUA Leu</td>
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<td></td>
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<td>CUG Leu</td>
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<td></td>
<td>A</td>
<td>AUA Thr</td>
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<td>AUA Thr</td>
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<tr>
<td></td>
<td>G</td>
<td>GUU Val</td>
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<td></td>
<td></td>
<td>GUC Val</td>
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<td></td>
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<td>GUA Val</td>
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<tr>
<td></td>
<td></td>
<td>GUG Val</td>
</tr>
</tbody>
</table>

2.

![Ethidium Bromide](image)

![Acridine Orange](image)

![Proflavine](image)
Due to their planar structure, Ethidium Bromide, Acridine Orange, and Proflavine intercalate between adjacent base pairs in double-helical DNA.

Intercalation of planar structure in DNA often causes frameshift mutation during DNA replication.

Frameshift mutations consist of addition or subtraction of 1 or 2 nucleotides in DNA, causing a shift in the reading frame in coding regions of genes. Recall that during protein synthesis, the codons in mRNAs are translated three letters at a time in a non-overlapping fashion.

Consequently, mRNAs that contain frameshift mutations would encode polypeptide chains containing aberrant amino acid sequences.

Addition or subtraction of 1 or 2 nucleotides in regulatory elements could cause anomalous patterns of gene expression.
(1. b) Ground state of $O_2$ is a triplet.
   Organic molecules are closed shell.
   Spin forbidden reaction with $O_2$.

(B). \[ O_2 \xrightarrow{e^-} O_2^- \xrightarrow{e^-} O_2^{2-} \xrightarrow{2H^+} H_2O_2 \xrightarrow{2e^-, 2H^+} 2H_2O \]

    $\text{H}^\text{II}$
    $\text{H}_2\text{O}_2$

(C). SOD, catalase.

(2).

PASO: trans. axial cysteine
Peroxidase: histidine (proximal)
(3). \[ 2\text{O}_2^- + 2\text{H}^+ \xrightarrow{\text{SOD}} \text{O}_2 + \text{H}_2\text{O}_2 \]

Mechanism:
\[ \text{Cu}^{2+} + \text{O}_2^- \rightarrow \text{Cu}^+ + \text{O}_2 \]
\[ \text{Cu}^+ + \text{O}_2^- \rightarrow \text{Cu(O}_2) \xrightarrow{2\text{H}^+} \text{Cu}^{2+} + \text{H}_2\text{O}_2 \]

Zn - is structural.

(4). Extradiol

Intradiol

Intradiol ligands on Fe^{III} (Tyr) stabilize Fe(III) oxidating state.
Theme: Electrophile-driven reactions (with a focus on recent ACS publications)

1. (24 pts.) For each reaction, draw the cationic intermediate formed immediately after electrophilic activation, and final product(s).

a)

\[
\begin{align*}
\text{CH}_3 &+ \quad \text{CH}_3 \quad + \quad \text{Cl} \\
\text{HCl} &\text{CH}_2\text{Cl}_2 \\
\end{align*}
\]

b)

\[
\begin{align*}
\text{OH} &\text{CH}_3\text{CN,}
\text{reflux} \\
\rightarrow &\text{H}_2\text{O} \\
\end{align*}
\]

c)

\[
\begin{align*}
\text{O} &\text{CH}_3 \quad \text{TMS} \quad \text{CH}_2\text{Cl}_2 \\
\rightarrow &\text{CH}_3 \quad \text{O} \\
\end{align*}
\]

d)

\[
\begin{align*}
\text{HO} \quad \text{CHCl}_3 \\
\text{H}_2\text{SO}_4 \quad \text{(cat.)} \\
\rightarrow \text{HO} \quad \text{O} \\
\end{align*}
\]
2. (30 pts.) Dobish and Johnston developed a chiral, bifunctional Brønsted acid–base complex \((J. \text{ Am. Chem. Soc.}, \text{2012, 134 (14), 6068–71})\) and applied it toward an asymmetric iodoabolactonization with enantiomeric excesses up to 98% ee \((\text{NIS} = \text{N-iodosuccinimide}; \text{TF} = \text{SO}_2\text{CF}_3)\). Without the chiral reagent, the reaction proceeds in good yield but with 0% ee.

![Mechanism diagram]

a) Present a mechanism for achiral iodolactonization, using bis-triflimidic acid as the catalyst (i.e., \(\text{HNTf}_2\) without StilbPBAM).

![Mechanism diagram]

a) Provide a rational explanation for chiral iodolactonization reported by the authors. Use your mechanism to support your argument (you do not need to provide a complex drawing).

**The StilbPBAM-H\(^+\) cation is a chiral Bronsted acid.**

Complexation with NIS creates a chiral environment during iodine transfer:

b) StilbPBAM plus TfOH or TfNH\(_2\) produced lactone with 46 or 24% ee, respectively. Interestingly, StilbPBAM alone (no extra acid) also produced lactone, but with 19% ee. Explain why the combination of StilbPBAM and \(\text{HNTf}_2\) is essential for high % ee, based on these observations.

**The carboxylic acid also serves as a proton donor to generate (some) StilbPBAM-H\(^+\), but less efficiently than TfOH, TfNH\(_2\), or Tf\(_2\)NH.** The high ee% in the latter case is based on the size of the NTf\(_2\) counteron, which has twice the steric bulk as OTf or NHTf and can reinforce the chiral environment created by StilbPBAM-H\(^+\).
3. (30 pts.) Han and Floreancig used DDQ (2,3-dichloro-5,6-dicyanoquinone) to drive an oxidative Prins cyclization reaction (Org. Lett., 2012, 14 (14), 3808–11). Their optimized reaction is performed at room temperature under anhydrous conditions using DDQ and 2,6-dichloropyridine (mild base) in 1,2-dichloroethane, to obtain a single stereoisomer in good yield. The internal alkyne in the macrolactone was found to be important for the efficient and stereocontrolled formation of the 6-membered ring.

![Chemical Structures](image)

a) Provide a detailed mechanism for the DDQ oxidation resulting in cationic intermediate A.

b) Provide a mechanism for converting A into the final product via intermediate B. Is an aqueous workup required to obtain the final product? Why or why not?

![Chemical Structures](image)

No aqueous workup is needed; acylium ion can be generated as a leaving group.
4. (16 pts.) For each reaction, explain why condition B is more efficient than condition A.

\[
\text{AgNO}_3 \text{ reacts with TBS-Cl to produce the more reactive "TBS-NO}_3\text{":}
\]

\[
t\text{BuMe}_2\text{SiCl} + \text{AgNO}_3 \rightarrow t\text{BuMe}_2\text{Si}^-\text{ONO}_2 + \text{AgCl(s)}
\]

b) \[
\begin{align*}
\text{chiral amine (3 mol\%)} & \quad \text{DMF, RT, 24 h} \\
\text{A) } & \quad \text{<5\% yield (racemic)} \\
\text{B) } & \quad \text{>99\% yield, 93\% ee}
\end{align*}
\]

Proline condenses with the methyl ketone to generate a chiral enamine intermediate:
1) \[ \left( \frac{\partial S}{\partial P} \right)_T = \left( \frac{\partial U}{\partial T} \right)_P = -\frac{dG}{dT} - VdP \]

b. \[ \left( \frac{\partial P}{\partial T} \right)_V = \frac{\partial}{\partial T} \left( \frac{\partial P}{\partial T} \right)_V = -\frac{VdP}{-V} = \frac{dP}{KT} \]

2) \[ \bar{V} = \left( \frac{\partial V}{\partial n_i} \right)_{T,P,n_i,n_j} \approx \frac{\Delta V}{\Delta n_i} \mid \begin{array}{c} \text{SO}_4^{2-} \\ \text{mgSO}_4 \\ \text{H}_2\text{O} \end{array} \]

So, the final volume is \[ 1000 - 0.14 \approx 999.86 \text{ cm}^3 \]

3) a. \[ \Delta U = \frac{3}{2} n R \Delta T^0 = 0 \]

b. \[ \Delta S = R \ln \left( \frac{\sqrt{2}}{V_i} \right) = R \ln \left( \frac{\sqrt{2}}{2} \right) \sim -R(0.69) \sim -5.8 \text{ J/K mol} \]

c. \[ \Delta A = \Delta U - T \Delta S = \Delta U - \Delta S \sim 2.9 \text{ kJ/mol} \]

d. \[ \Delta H = \Delta U + \Delta (PV) = \Delta U + \Delta (nRT) = 0 \]

e. \[ \Delta G = \Delta H - T \Delta S = 2.9 \text{ kJ/mol} \]