

Chapter 26 – Biomolecules: Amino Acids, Peptides and Proteins

Chapter Outline

I. Amino acids (Sections 26.1 – 26.4).

A. Structure of amino acids (Section 26.1).

1. Amino acids exist in solution as zwitterions.
 - a. Zwitterions are internal salts and have many of the properties associated with salts.
 - i. They have large dipole moments.
 - ii. They are soluble in water.
 - iii. They are crystalline and high-melting.
 - b. Zwitterions can act either as acids or as bases.
 - i. The -CO_2^- group acts as a base.
 - ii. The ammonium group acts as an acid.
2. All natural amino acids are α -amino acids: the amino group and the carboxylic acid group are bonded to the same carbon.
3. All but one (proline) of the 20 common amino acids are primary amines.
4. All of the amino acids are represented by both a three-letter code and a one-letter code.
5. All amino acids except glycine are chiral.
 - a. Only one enantiomer (L) of each pair is naturally-occurring.
 - b. In Fischer projections, the carboxylic acid is at the top, and the amino group points to the left.
 - c. α -Amino acids are referred to as L-amino acids.
6. Side chains can be acidic or basic.
 - a. Fifteen of the amino acids are neutral.
 - b. Two (aspartic acid and glutamic acid) are acidic.

At pH = 7.3, their side chains exist as carboxylate ions.
 - c. Three (lysine, arginine and histidine) are basic.
 - i. At pH = 7.3, the side chains of lysine and arginine exist as ammonium ions.
 - ii. Histidine is not quite basic enough to be protonated at pH = 7.3.
 - iii. The double-bonded nitrogen in the histidine ring is basic.
 - d. Cysteine and tyrosine are weakly acidic.

B. The Henderson–Hasselbalch equation and isoelectric points (Section 26.2).

1. The Henderson–Hasselbalch equation.
 - a. If we know the values of pH and $\text{p}K_a$, we can calculate the percentages of protonated, neutral and deprotonated forms of an amino acid.
 - b. If we do these calculations at several pH values, we can construct a titration curve for each amino acid.
2. The isoelectric point (pI) is the pH at which an amino acid exists as a neutral, dipolar zwitterion.
 - a. pI is related to side chain structure.
 - i. The 15 amino acids that are neutral have pI near neutrality.
 - ii. The two acidic amino acids have pI at a lower pH.
 - iii. The 3 basic amino acids have pI at a higher pH.
 - b. For neutral amino acids, pI is the average of the two $\text{p}K_a$ values.
 - i. For acidic amino acids, pI is the average of the two lowest $\text{p}K_a$ values.
 - ii. For basic amino acids, pI is the average of the two highest $\text{p}K_a$ values.
 - c. Proteins have an overall pI .

3. Electrophoresis allows the separation of amino acids by differences in their pI .
 - a. A buffered solution of amino acids is placed on a paper or gel.
 - b. Electrodes are connected to the solution, and current is applied.
 - c. Negatively charged amino acids migrate to the positive electrode, and positively charged amino acids migrate to the negative electrode.
 - d. Amino acids can be separated because the extent of migration depends on pI .
 - C. Synthesis of α -amino acids (Section 26.3).
 1. The Hell–Volhard–Zelinskii method and the phthalimide method.
 - a. An α -bromo acid is produced from a carboxylic acid by α -bromination.
 - b. Displacement of $-\text{Br}$ gives the α -amino acid.
 2. The amidomalonate synthesis.
 - a. An alkyl halide reacts with the anion of diethyl amidomalonate.
 - b. Hydrolysis of the adduct yields the α -amino acid.
 3. Reductive amination.
 - a. Reductive amination of an α -keto carboxylic acid gives an α -amino acid.
 - b. This method is related to the biosynthetic pathway for synthesis of amino acids.
 4. All of the methods listed above produce a racemic mixture of amino acids.
 - D. Enantioselective synthesis of amino acids.
 1. Resolution of racemic mixtures:
 - a. The mixture can react with a chiral reagent, followed by separation of the diastereomers and reconversion to amino acids.
 - b. Enzymes selectively catalyze reactions that form one of the enantiomers, but not the other.
 2. Enantioselective synthesis.
 - a. Enantioselective hydrogenation of Z -enamido acids produces chiral α -amino acids.
 - b. The most effective catalysts are complexes of rhodium (I), cyclooctadiene and a chiral diphosphine.
- II. Peptides (Sections 26.4 – 26.8).
- A. Peptide structure (Section 26.4).
1. Peptide bonds.
 - a. A peptide is an amino acid polymer in which the amine group of one amino acid forms an amide bond with the carboxylic acid group of a second amino acid.
 - b. This amino acid sequence is known as the backbone of the peptide or protein.
 - c. Rotation about the amide bond is restricted.
 2. The N-terminal amino acid of the polypeptide is always drawn on the left.
 3. The C-terminal amino acid of the polypeptide is always drawn on the right.
 4. Peptide structure is described by using three-letter codes, or one-letter codes, for the individual amino acids, starting with the N-terminal amino acid.
 5. Disulfide bonds.
 - a. Two cysteines can form a disulfide bond ($-\text{S}-\text{S}-$).
 - b. Disulfide bonds can link two polypeptides or introduce a loop in a polypeptide chain.

B. Structure determination of peptides (Sections 26.5 – 26.6).

1. Amino acid analysis (Section 26.5).
 - a. Amino acid analysis provides the amount of each amino acid present in a protein or peptide.
 - b. First, all disulfide bonds are broken and all peptide bonds are hydrolyzed.
 - c. The mixture is placed on a chromatography column, and the residues are eluted.
 - d. As each amino acid elutes, it undergoes reaction with ninhydrin, which produces a purple color that is detected and measured spectrophotometrically.
 - e. Amino acid analysis is reproducible on properly maintained equipment; residues always elute at the same time, and only small sample sizes are needed.
2. The Edman degradation (Section 26.6).
 - a. The Edman degradation removes one amino acid at a time from the $-\text{NH}_2$ end of a peptide.
 - i. The peptide is treated with phenylisothiocyanate, which reacts with the amino-terminal residue.
 - ii. The PITC derivative is split from the peptide.
 - iii. The residue undergoes rearrangement to a PTH, which is identified chromatographically.
 - iv. The shortened chain undergoes another round of Edman degradation.
 - b. Since the Edman degradation can only be used on peptides containing fewer than 50 amino acids, a protein must be cleaved into smaller fragments.
 - i. Partial acid hydrolysis is unselective.
 - ii. The enzyme trypsin cleaves proteins at the carboxyl side of arg and lys residues.
 - iii. The enzyme chymotrypsin cleaves proteins at the carboxyl side of Phe, Tyr and Trp residues.
 - c. The complete amino acid sequence of a protein results from determining the individual sequences of peptides and overlapping them.

C. Synthesis of peptides (Sections 26.7 – 26.8).

1. Laboratory synthesis of peptides (Section 26.7).
 - a. Groups that are not involved in peptide bond formation are protected.
 - i. Carboxyl groups are often protected as methyl or benzyl esters.
 - ii. Amino groups are protected as Boc derivatives.
 - b. The peptide bond is formed by coupling with DCC.
 - c. The protecting groups are removed.
 - i. Boc groups are removed by brief treatment with trifluoroacetic acid.
 - ii. Esters are removed by mild hydrolysis or by hydrogenolysis (benzyl).
2. Automated peptide synthesis – Merrifield technique (Section 26.8).
 - a. The carboxyl group of a Boc-protected amino acid is attached to a polystyrene resin.
 - b. The resin is washed, and the Boc group is removed.
 - c. A second Boc-protected amino acid is coupled to the first, and the resin is washed.
 - d. The cycle is repeated as many times as needed.
 - e. Finally, treatment with anhydrous HF removes the final Boc group and frees the polypeptide.

III. Proteins (Section 26.9).

A. Classification of proteins.

1. Fibrous proteins consist of long, filamentous polypeptide chains.
2. Globular proteins are compact and roughly spherical.

B. Protein structure.

1. Levels of protein structure.

- a. Primary structure refers to the amino acid sequence of a protein.
- b. Secondary structure refers to the organization of segments of the peptide backbone into a regular pattern, such as a helix or sheet.
- c. Tertiary structure describes the overall three-dimensional shape of a protein.
- d. Quaternary structure describes how polypeptide subunits aggregate into a larger structure.

2. Examples of structural features.

a. α -Helix

- i. An α -helix is a right-handed coil; each turn of the coil contains 3.6 amino acids.
- ii. The structure is stabilized by hydrogen bonds between amide N-H groups and C=O groups four residues away.

b. β -Pleated sheet.

- i. In a β -pleated sheet, hydrogen bonds occur between residues in adjacent chains.
- ii. In a β -pleated sheet, the peptide chain is extended, rather than coiled.

c. Tertiary structure.

- i. The nonpolar amino acid side chains congregate in the center of a protein to avoid water.
- ii. The polar side chain residues are on the surface, where they can take part in hydrogen bonding and salt bridge formation.
- iii. Other important features of tertiary structure are disulfide bridges, hydrogen bonds between amino acid side chains and salt bridges.

3. Denaturation of proteins.

- a. Modest changes in temperature and pH can disrupt a protein's tertiary structure.
 - i. This process is known as denaturation.
 - ii. Denaturation doesn't affect protein primary structure.
- b. Denaturation affects both physical and catalytic properties of proteins.
- c. Occasionally, spontaneous renaturation can occur.

C. Enzymes (Sections 26.10 – 26.11).

1. Description of enzymes and cofactors (Section 26.10).

- a. An enzyme is a substance (usually protein) that catalyzes a biochemical reaction.
- b. An enzyme is specific and usually catalyzes the reaction of only one substrate.
Some enzymes, such as papain, can operate on a range of substrates.

c. Function of enzymes.

- i. Enzymes form an enzyme-substrate complex, within which the conversion to product takes place.
- ii. Enzymes accelerate the rate of reaction by lowering the energy of the transition state.

d. Enzymes are grouped into 6 classes according to the reactions they catalyze.

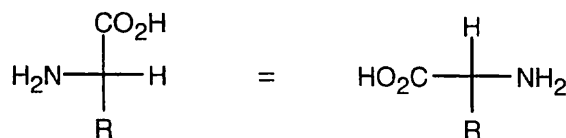
- i. Oxidoreductases catalyze oxidations and reductions.
- ii. Transferases catalyze the transfer of a group from one substrate to another.
- iii. Hydrolases catalyze hydrolysis reactions.
- iv. Isomerases catalyze isomerizations.
- v. Ligases catalyze bond formation between two molecules.
- vi. Lyases catalyze the loss of a small molecule from a substrate.

- e. The name of an enzyme has two parts, ending with *-ase*.
 - i. The first part identifies the substrate.
 - ii. The second part identifies the enzyme's class.
 - f. Most enzymes are globular proteins, and many consist of a protein portion (apoenzyme) and a cofactor.
 - i. Cofactors may be small organic molecules (coenzymes) or inorganic ions.
 - ii. Many coenzymes are vitamins.
2. How enzymes work – citrate synthase (Section 26.11).
- a. Citrate synthase catalyzes the aldol-like addition of acetyl CoA to oxaloacetate to produce citrate.
 - b. Functional groups in a cleft of the enzyme bind oxaloacetate.
 - c. Functional groups in a second cleft bind acetyl CoA.
The two reactants are now in close proximity.
 - d. Two enzyme amino acid residues generate the enol of acetyl CoA.
 - e. The enol undergoes nucleophilic addition to the ketone carbonyl group of oxaloacetate.
 - f. Two enzyme amino acid residues deprotonate the enol and protonate the carbonyl oxygen.
 - g. Water hydrolyzes the thiol ester, releasing citrate and CoA.

Solutions to Problems

- 26.1** Amino Acids with aromatic rings: Phe, Tyr, Trp, His.
 Amino acids containing sulfur: Cys, Met.
 Amino acids that are alcohols: Ser, Thr (Tyr is a phenol.)
 Amino acids having hydrocarbon side chains: Ala, Ile, Leu, Val, Phe.

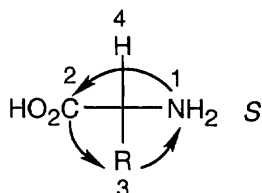
26.2



A Fischer projection of the α -carbon of an L-amino acid is pictured above.

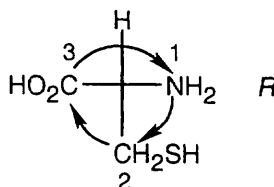
For most L-amino acids:

Group Priority	
-NH ₂	1
-CO ₂ H	2
-R	3
-H	4

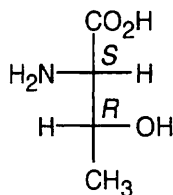
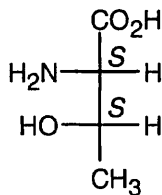
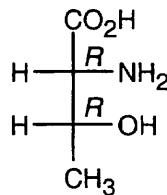


For cysteine:

Group Priority	
-NH ₂	1
-CH ₂ SH	2
-CO ₂ H	3
-H	4

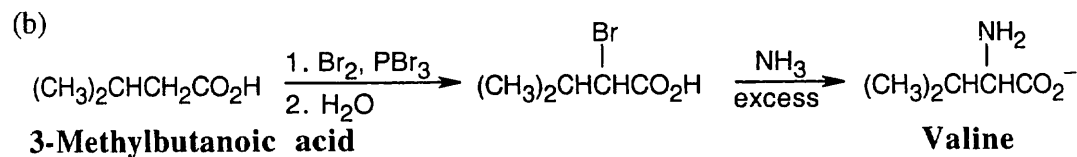
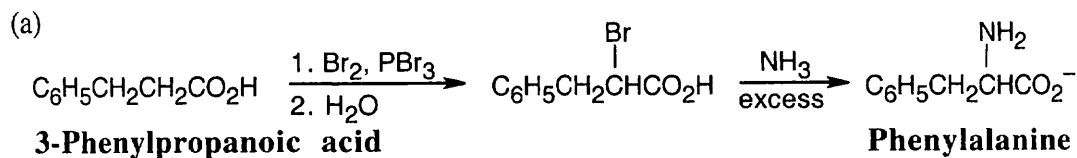


26.3

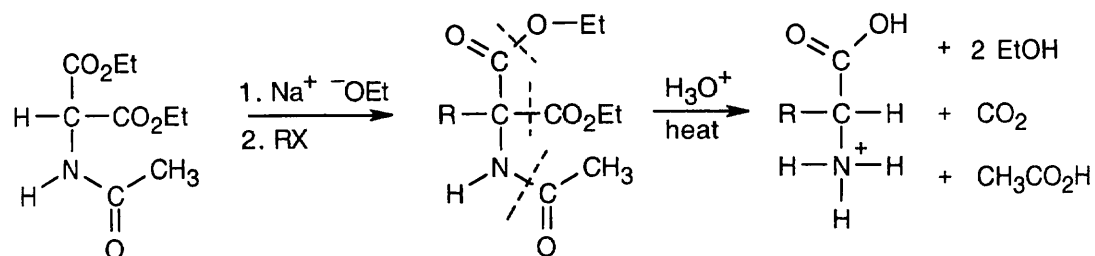
**L-Threonine****Diastereomers of L-Threonine**

26.4 On the low pH (acidic) side of pI , a protein has a net positive charge, and on the high pH (basic) side of pI , a protein has a net negative charge. Thus, hemoglobin ($pI = 6.8$) has a net positive charge at $pH = 5.3$ and a net negative charge at $pH = 7.3$.

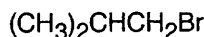
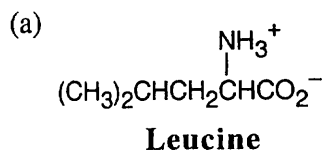
26.5 This method of amino acid synthesis is simple and uses methods we have already studied. The phthalimide synthesis can also be used to introduce the amino group. Remember that only racemic amino acids are produced by this method.

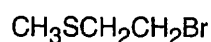
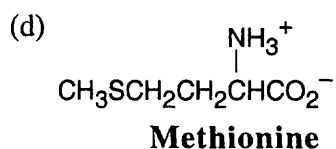
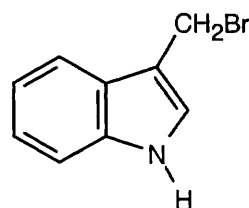
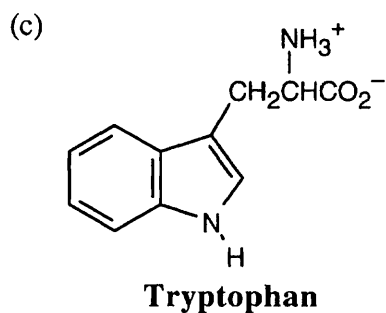
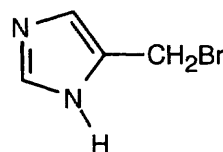
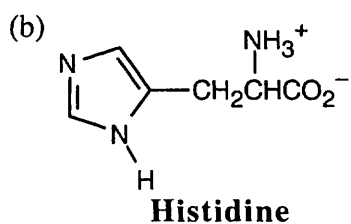


26.6

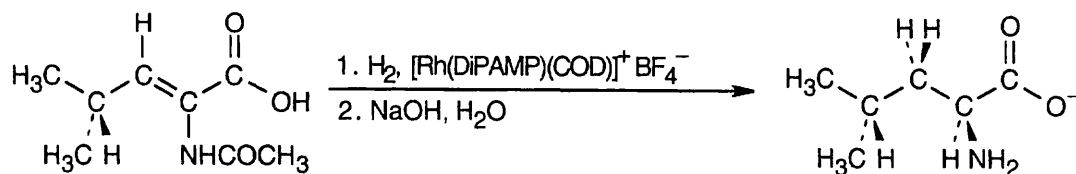


In the amidomalonate synthesis, shown above, an alkyl halide RX is converted to $\text{RCH}(\text{NH}_3^+)\text{CO}_2\text{H}$. Choose an alkyl halide that completes the structure of the target amino acid.

*Amino Acid**Halide*

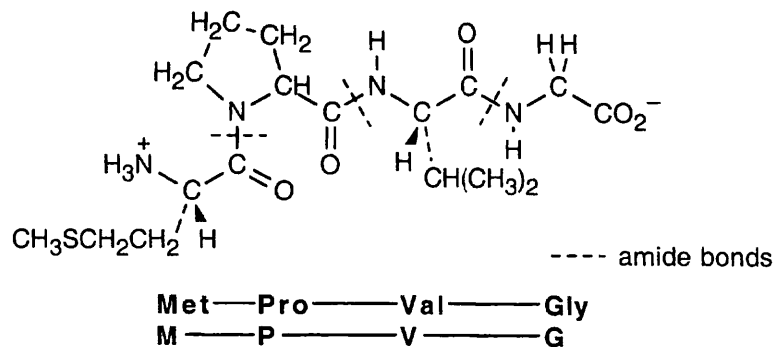


26.7 The precursor to an amino acid prepared by enantioselective hydrogenation has a Z double bond conjugated with a carboxylic acid carbonyl group.

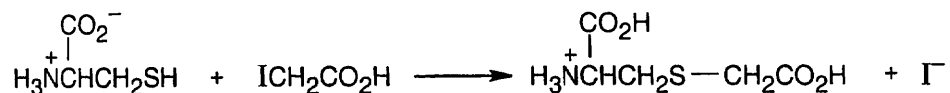


26.8 Val-Tyr-Gly (VYG) Tyr-Gly-Val (YGV) Gly-Val-Tyr (GVY)
 Val-Gly-Tyr (VGY) Tyr-Val-Gly (YVG) Gly-Tyr-Val (GYV)

26.9

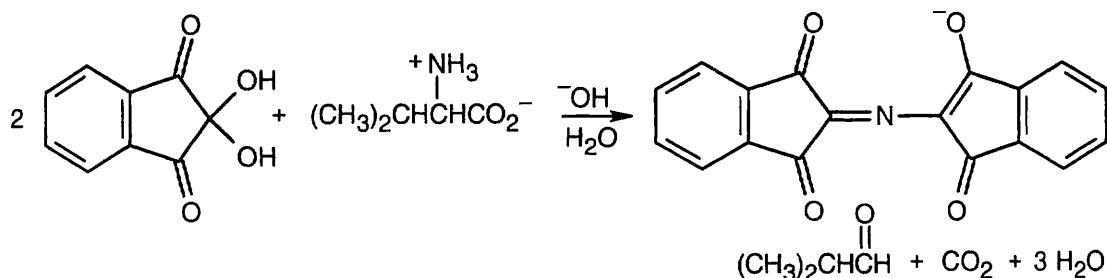


26.10

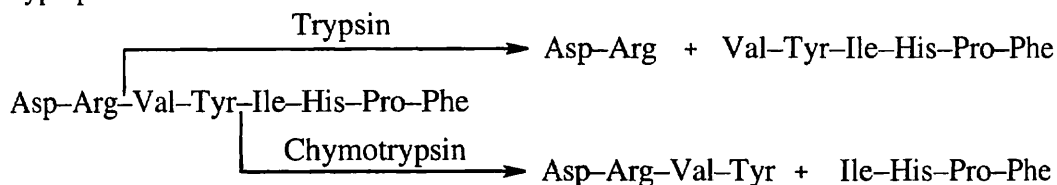


The cysteine sulfur is a good nucleophile, and iodide is a good leaving group.

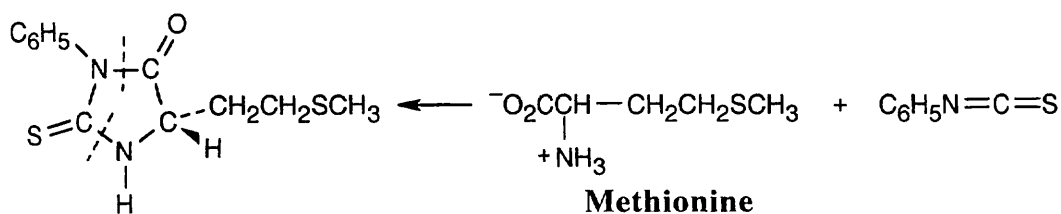
- 26.11** One product of the reaction of an amino acid with ninhydrin is the extensively conjugated purple ninhydrin product. The other major product is the aldehyde derived from the side chain of the amino acid. When valine reacts, the resulting aldehyde is 2-methylpropanal. The other products are carbon dioxide and water.



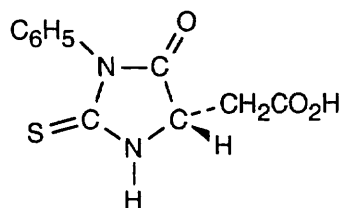
- 26.12** Trypsin cleaves peptide bonds at the carboxyl side of lysine and arginine. Chymotrypsin cleaves peptide bonds at the carboxyl side of phenylalanine, tyrosine and tryptophan.



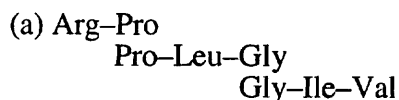
- 26.13** The part of the PTH derivative that lies to the right of the indicated dotted lines comes from the N-terminal residue. Complete the structure to identify the amino acid, which in this problem is methionine.



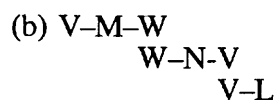
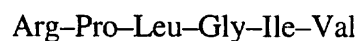
- 26.14** The N-terminal residue of angiotensin II is aspartic acid. Replace the -R group of the PTH derivative in Figure 26.4 with $-\text{CH}_2\text{CO}_2\text{H}$ to arrive at the correct structure.



26.15 Line up the fragments so that the amino acids overlap.



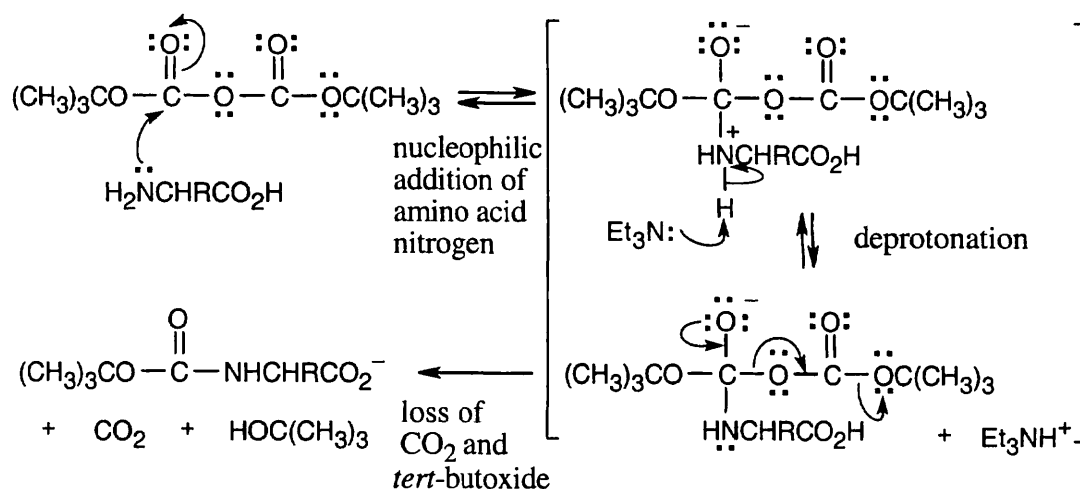
The complete sequence:



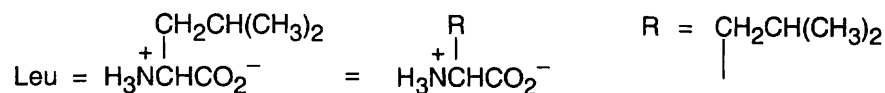
The complete sequence:



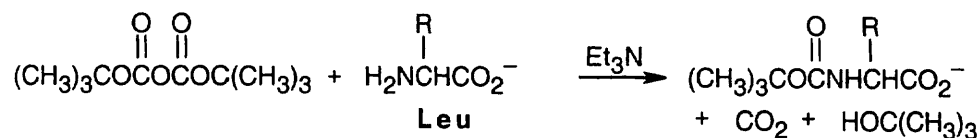
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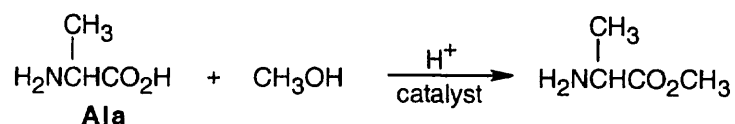
26.17



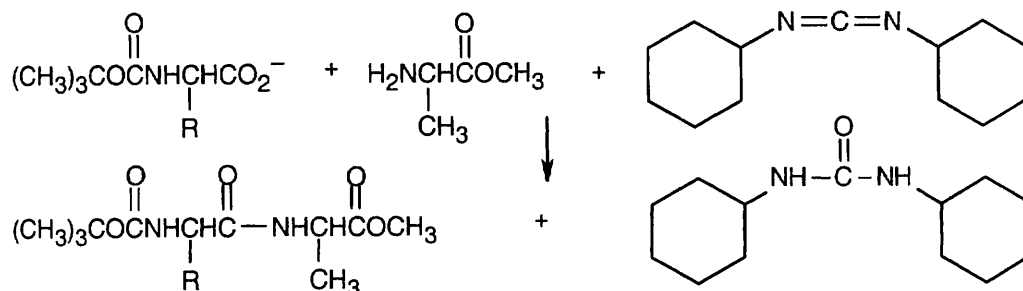
1. Protect the amino group of leucine.



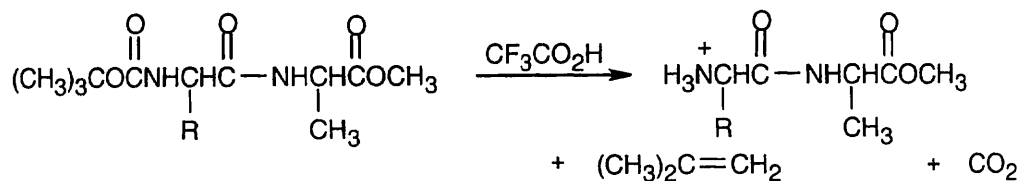
2. Protect the carboxylic acid group of alanine.



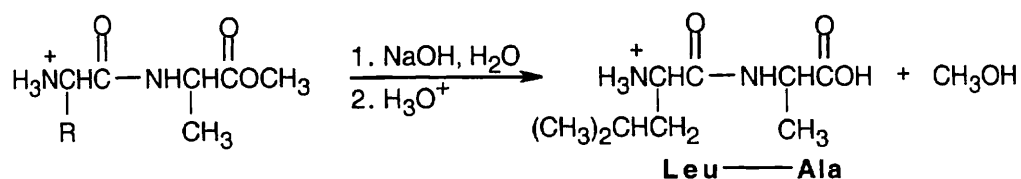
3. Couple the protected amino acids with DCC.



4. Remove the leucine protecting group.



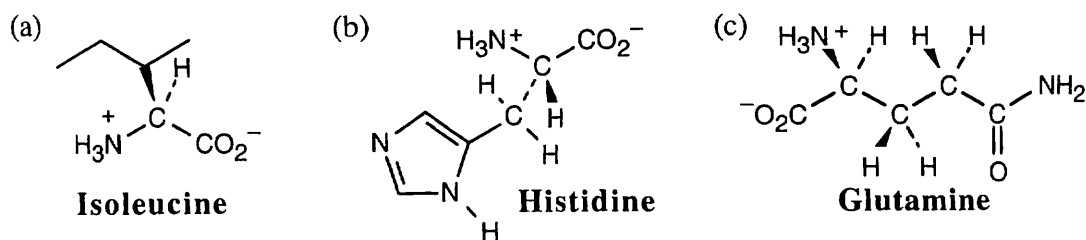
5. Remove the alanine protecting group.



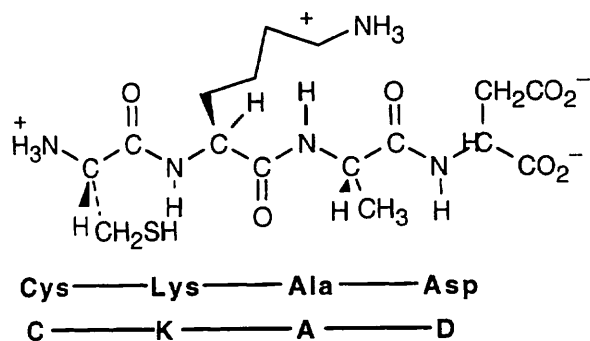
- 26.18** (a) Pyruvate decarboxylase is a lyase.
 (b) Chymotrypsin is a hydrolase.
 (c) Alcohol dehydrogenase is an oxidoreductase.

Visualizing Chemistry

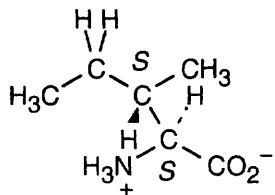
26.19



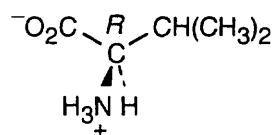
26.20



26.21

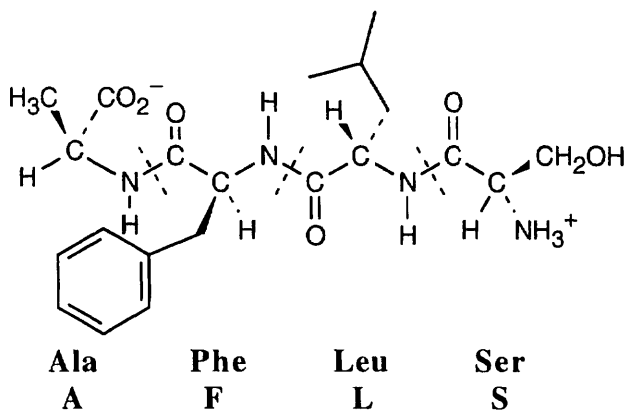


26.22 It's possible to identify this representation of valine as the D enantiomer by noting the configuration at the chirality center. The configuration is *R*, and thus the structure is D-valine.



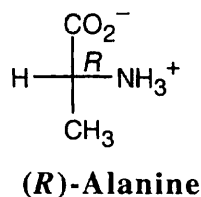
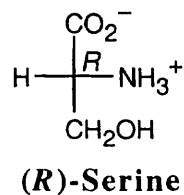
D-Valine
(*R*)-Valine

26.23 After identifying the amino acid residues, notice that the tetrapeptide has been drawn with the amino terminal residue on the right. To name the sequence correctly, the amino terminal residue must be cited first. Thus, the tetrapeptide should be named Ser-Leu-Phe-Ala.



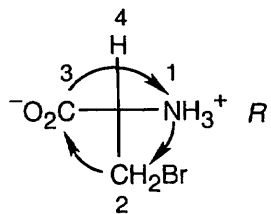
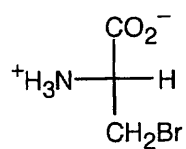
Additional Problems

26.24



Both (*R*)-serine and (*R*)-alanine are D-amino acids.

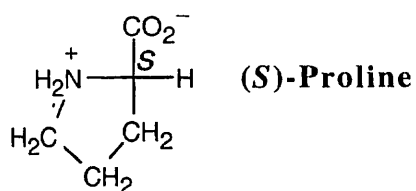
26.25



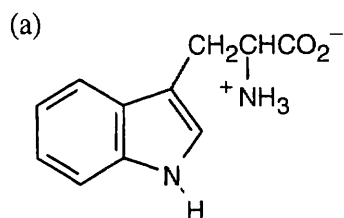
L-Bromoalanine
(R)-Bromoalanine

This L "amino acid" also has an *R* configuration because the $-\text{CH}_2\text{Br}$ "side chain" is higher in priority than the $-\text{CO}_2\text{H}$ group.

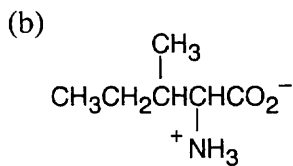
26.26



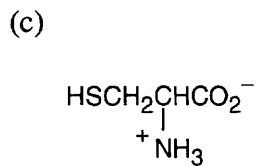
26.27



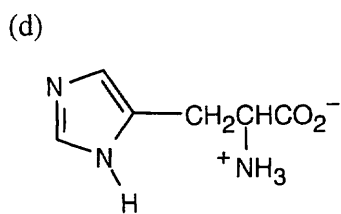
Tryptophan (Trp)



Isoleucine (Ile)

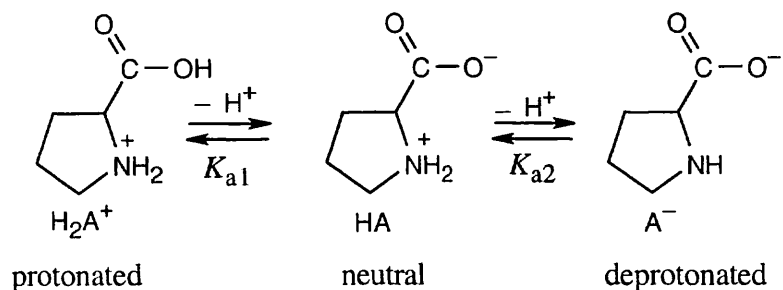


Cysteine (Cys)



Histidine (His)

26.28



At pH = 2.50:

$$\log \frac{[\text{HA}]}{[\text{H}_2\text{A}^+]} = \text{pH} - \text{p}K_{\text{a1}} = 2.50 - 1.99 = 0.51; \frac{[\text{HA}]}{[\text{H}_2\text{A}^+]} = 3.24$$

At pH = 2.50, approximately three times as many proline molecules exist in the neutral form as exist in the protonated form.

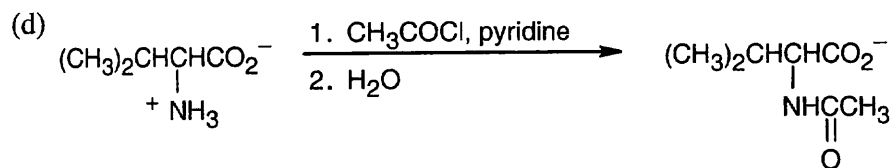
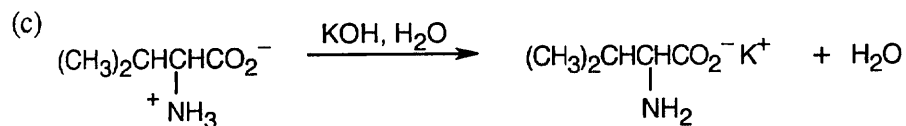
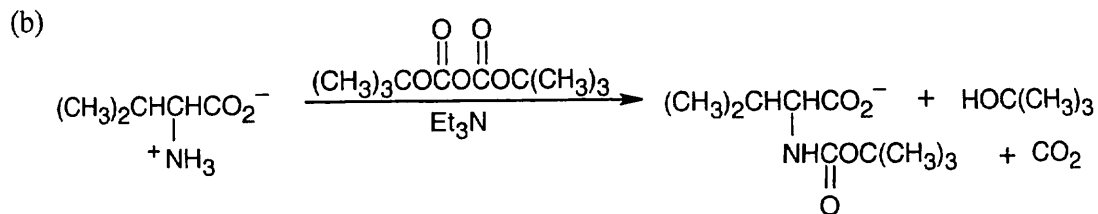
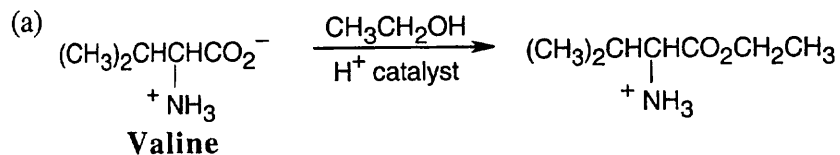
At pH = 9.70:

$$\log \frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} - \text{p}K_{\text{a2}} = 9.70 - 10.60 = -0.90; \frac{[\text{A}^-]}{[\text{HA}]} = 0.126$$

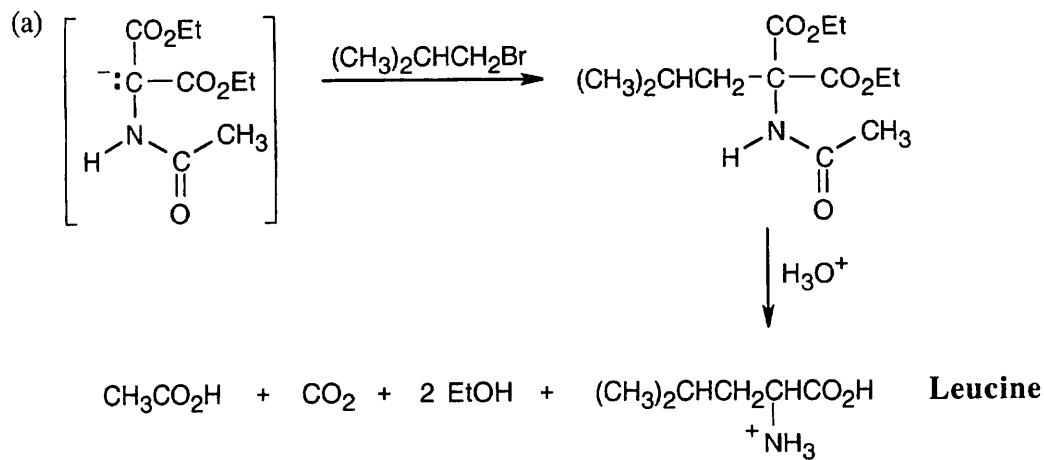
At pH = 9.70, the ratio of deprotonated proline to neutral proline is approximately 1:8.

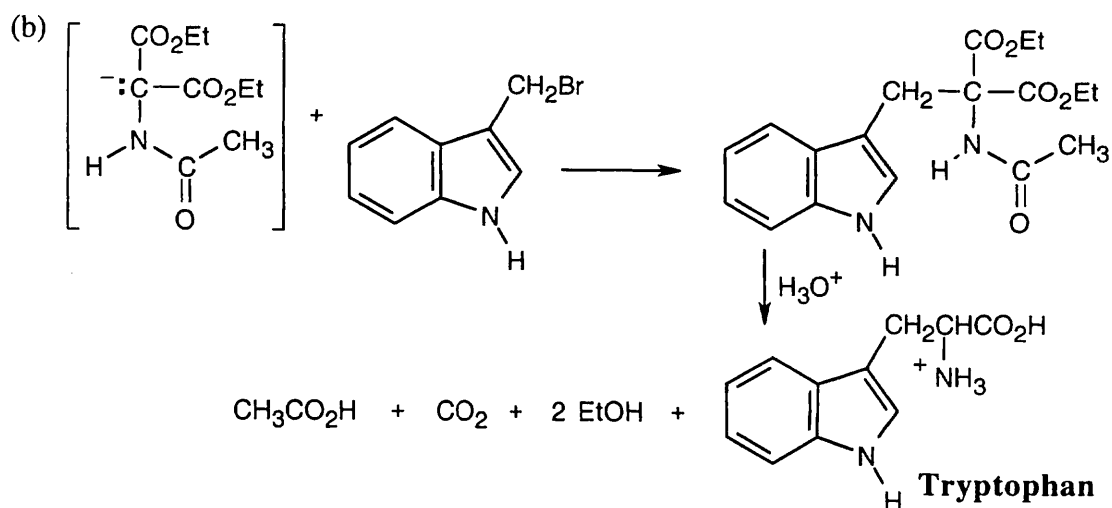
26.29	(a) Val-Leu-Ser	V-L-S	Ser-Val-Leu	S-V-L
	Val-Ser-Leu	V-S-L	Leu-Val-Ser	L-V-S
	Ser-Leu-Val	S-L-V	Leu-Ser-Val	L-S-V
	(b) Ser-Leu-Leu-Pro	S-L-L-P	Leu-Leu-Ser-Pro	L-L-S-P
	Ser-Leu-Pro-Leu	S-L-P-L	Leu-Leu-Pro-Ser	L-L-P-S
	Ser-Pro-Leu-Leu	S-P-L-L	Leu-Ser-Leu-Pro	L-S-L-P
	Pro-Leu-Leu-Ser	P-L-L-S	Leu-Ser-Pro-Leu	L-S-P-L
	Pro-Leu-Ser-Leu	P-L-S-L	Leu-Pro-Leu-Ser	L-P-L-S
	Pro-Ser-Leu-Leu	P-S-L-L	Leu-Pro-Ser-Leu	L-P-S-L

26.30

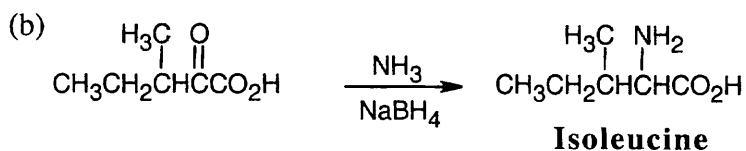
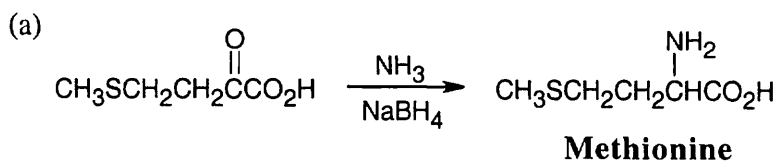


26.31 The diethylamidomalonate anion is formed by treating diethylamidomalonate with sodium ethoxide.

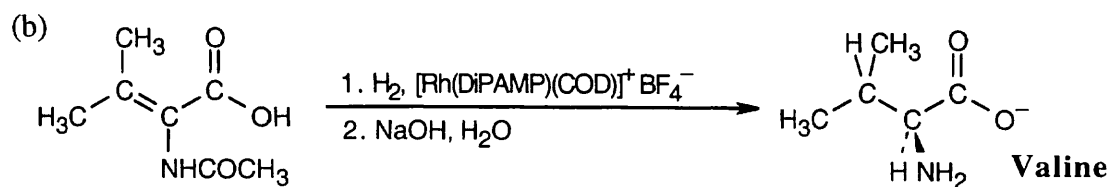
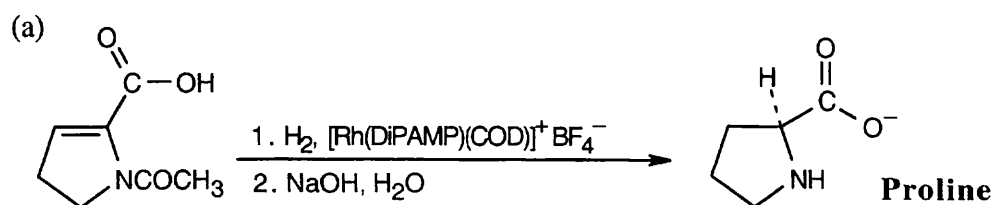




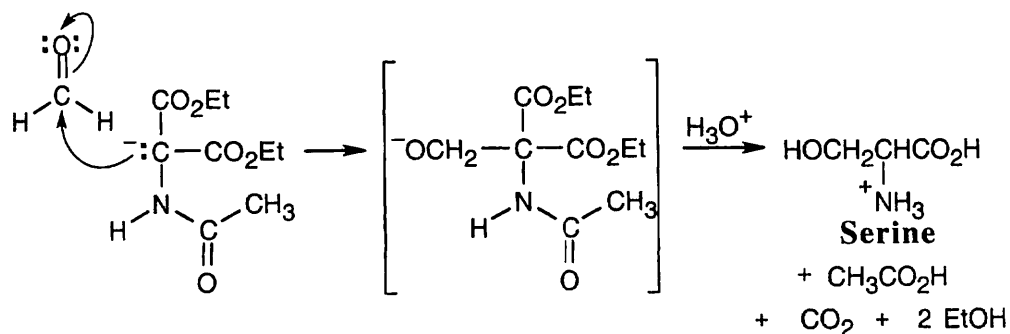
26.32



26.33

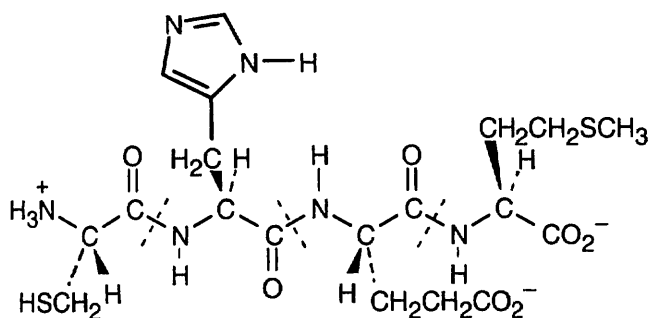


26.34



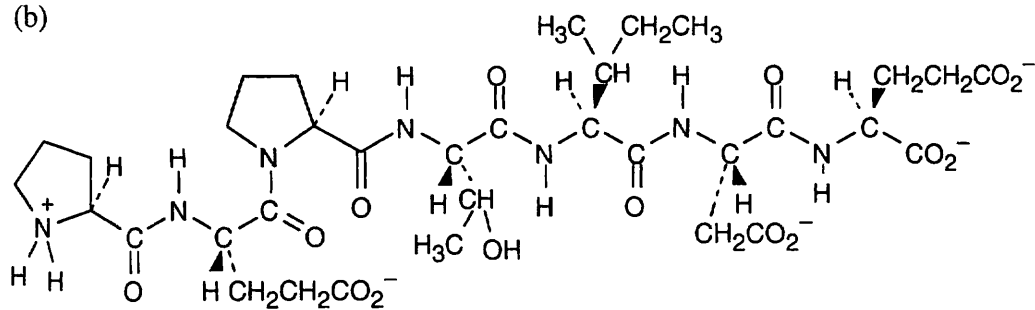
26.35

(a)



Cys — His — Glu — Met
C — H — E — M

(b)



P — E — P — T — I — D — E
Pro — Glu — Pro — Thr — Ile — Asp — Glu

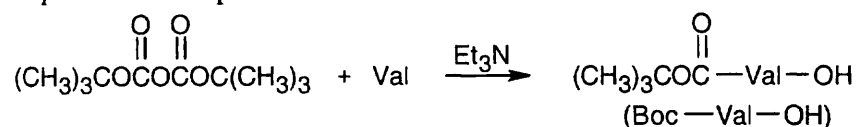
26.36

The tripeptide is cyclic.

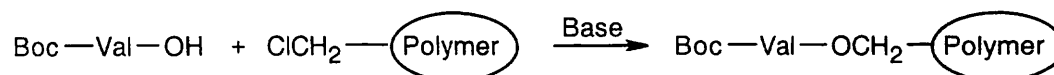


26.37

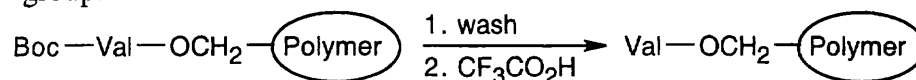
Step 1: Valine is protected as its Boc derivative.



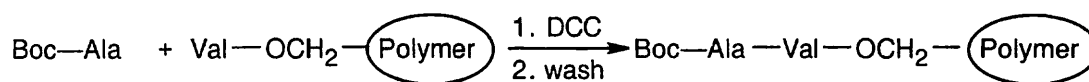
Step 2: Boc—Val bonds to the polymer in an $\text{S}_{\text{N}}2$ reaction.



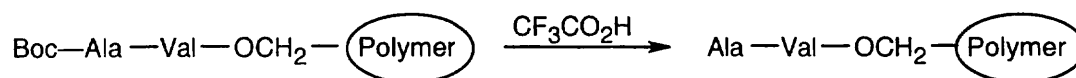
Step 3: The polymer is first washed, then is treated with $\text{CF}_3\text{CO}_2\text{H}$ to cleave the Boc group.



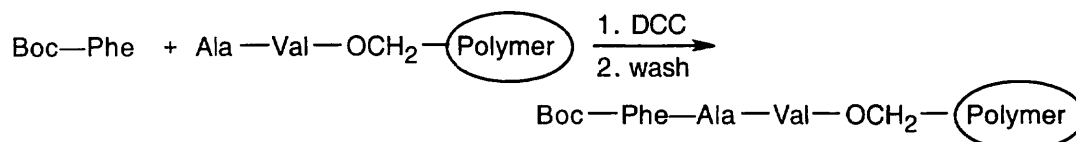
Step 4: A Boc-protected Ala is coupled to the polymer-bound valine by reaction with DCC. The polymer is washed.



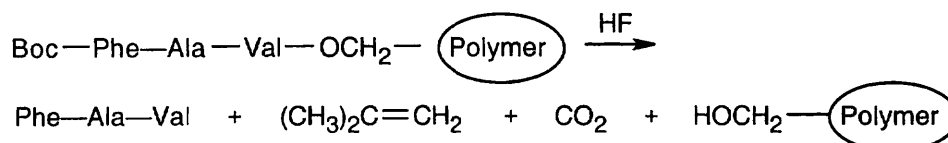
Step 5: The polymer is treated with $\text{CF}_3\text{CO}_2\text{H}$ to remove Boc.



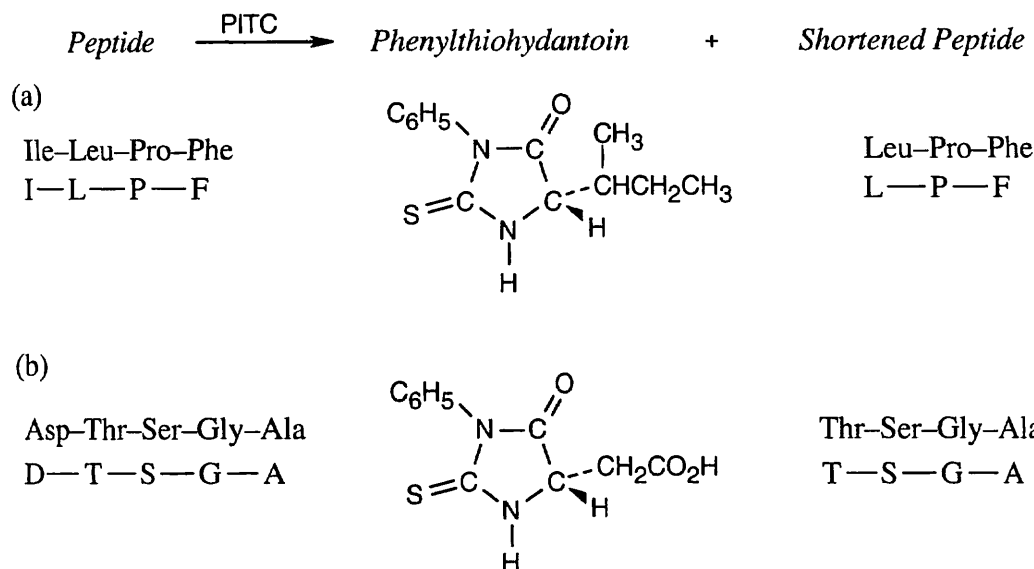
Step 6: A Boc-protected Phe is coupled to the polymer by reaction with DCC. The polymer is washed.



Step 7: Treatment with anhydrous HF removes the Boc group and cleaves the ester bond between the peptide and the polymer.



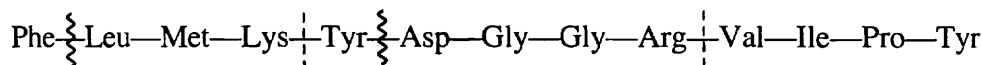
26.38



26.39 Aldehydes and ketones can undergo nucleophilic addition reactions. In particular, aldehydes and ketones can react with amines to form imines and enamines, reactions that might compete with formation of amide bonds between amino acids. Because of this reactivity, aldehydes and ketones are unlikely to be found in amino acid side chains.

26.40 A proline residue in a polypeptide chain interrupts α -helix formation because the amide nitrogen of proline has no hydrogen that can contribute to the hydrogen-bonded structure of an α -helix.

26.41



Cleaved by trypsin = ----

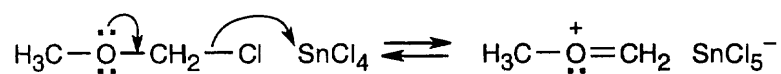
Cleaved by chymotrypsin = ~~~~

26.42 (a) Hydrolases catalyze the cleavage of bonds by addition of water (hydrolysis).
 (b) Lyases catalyze the elimination of a small molecule (H_2O , CO_2) from a molecule.
 (c) Transferases catalyze the transfer of a functional group between substrates.

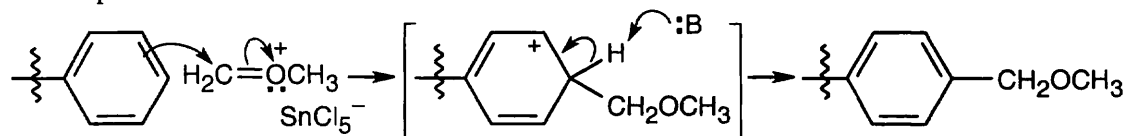
26.43 Amino acids with polar side chains are likely to be found on the outside of a globular protein, where they can form hydrogen bonds with water and with each other. Amino acids with nonpolar side chains are found on the inside of a globular protein, where they can avoid water. Thus, aspartic acid (b) and lysine (d) are found on the outside of a globular protein, and valine (a) and phenylalanine (c) are likely to be found on the inside.

26.44

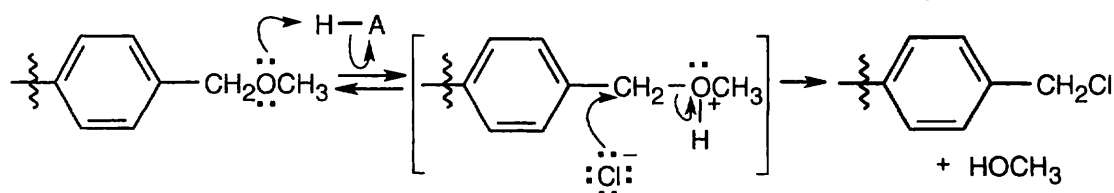
Formation of cation:



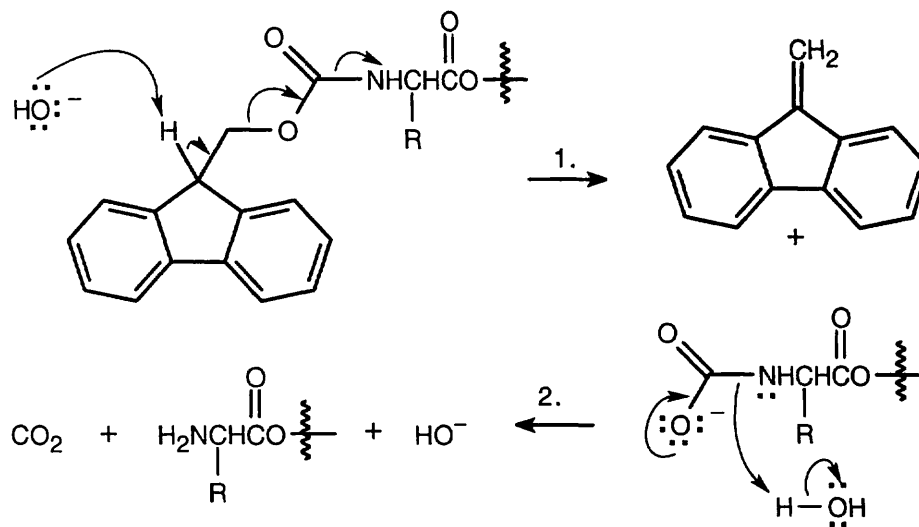
Electrophilic aromatic substitution:



Protonation of the ether oxygen, followed by displacement of methanol by Cl^- .



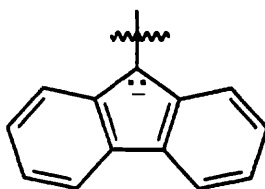
26.45



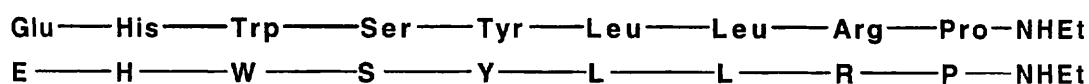
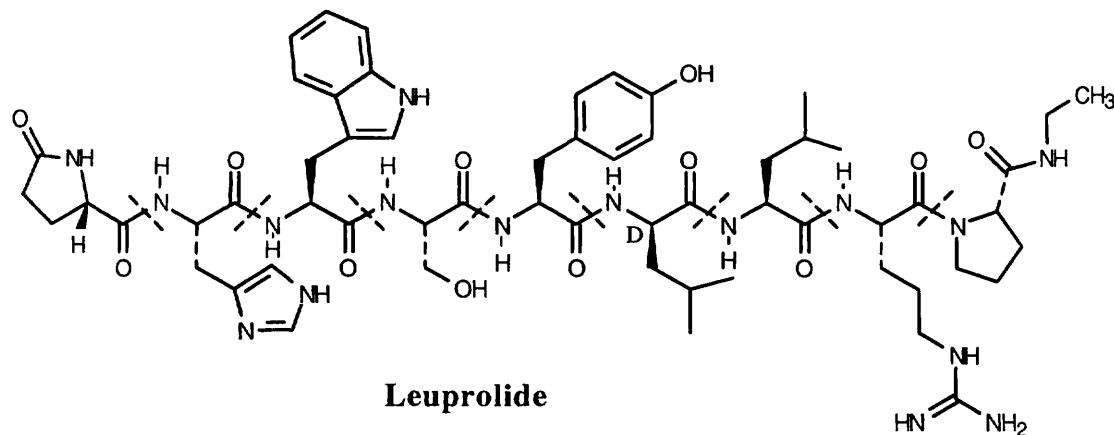
Step 1: NaOH brings about elimination of the carboxylated peptide.

Step 2: Loss of CO_2 .

The Fmoc group is acidic because the resulting anion is similar to the cyclopentadienyl anion, which is resonance-stabilized and is aromatic.



26.46



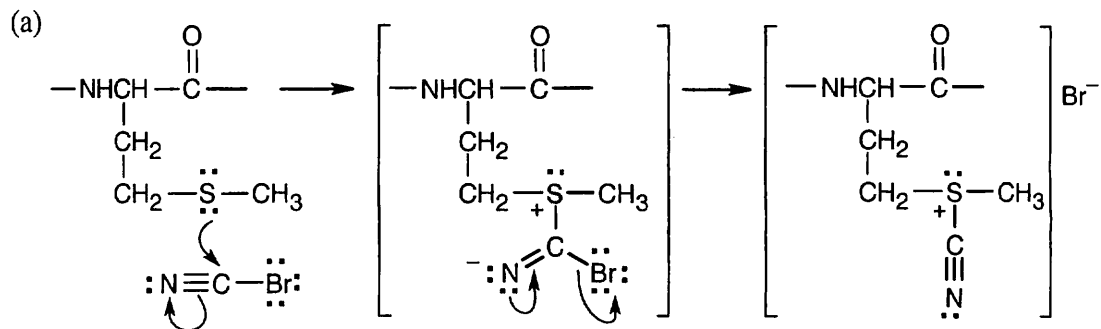
(a) The N-terminal glutamic acid is a cyclic lactam. The C-terminal proline is an *N*-ethyl amide.

(b) One of the leucines (indicated above) has D stereochemistry.

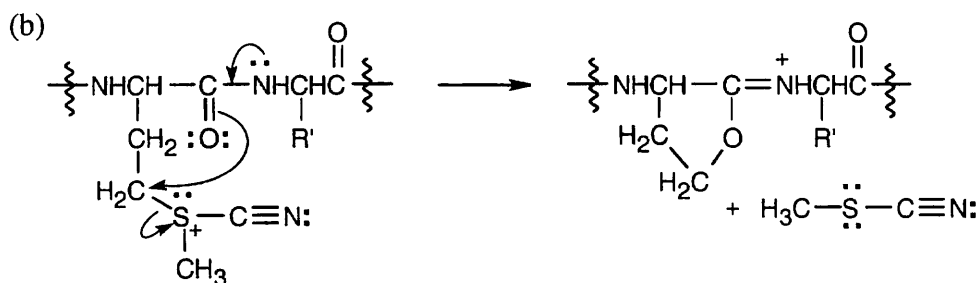
(c) See above.

(d) The charge on a peptide is due to the side chains. According to Table 26.1, the only side chain that is charged at neutral pH is arginine. Thus, leuprolide has a charge of +1 at neutral pH.

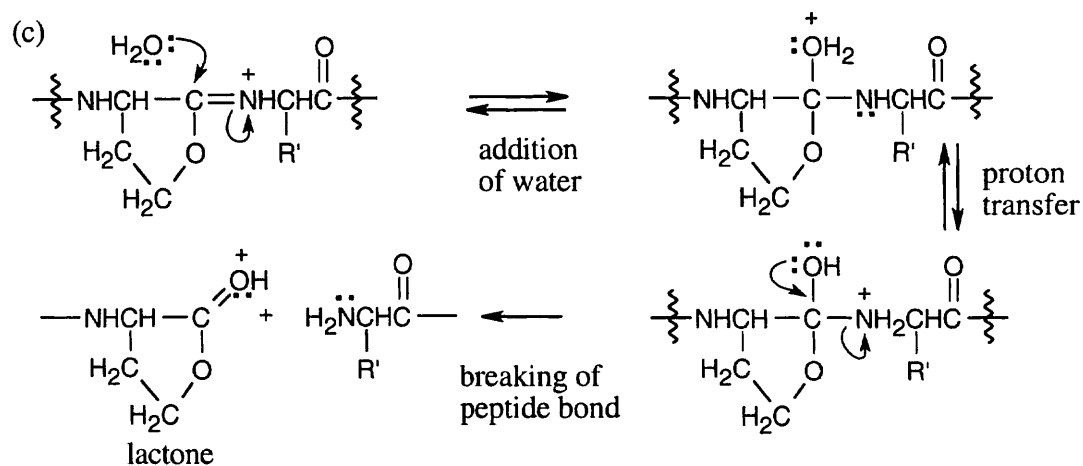
26.47



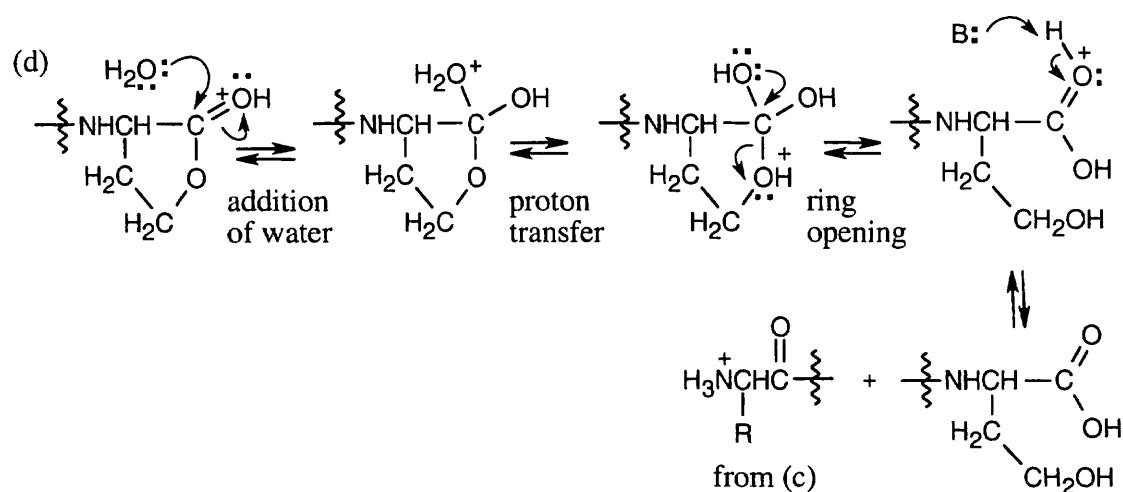
The first step is a substitution similar to the nucleophilic acyl substitution reactions that we studied in Chapter 21.



Internal S_N2 displacement of sulfide results in formation of a 5-membered ring containing an iminium group.

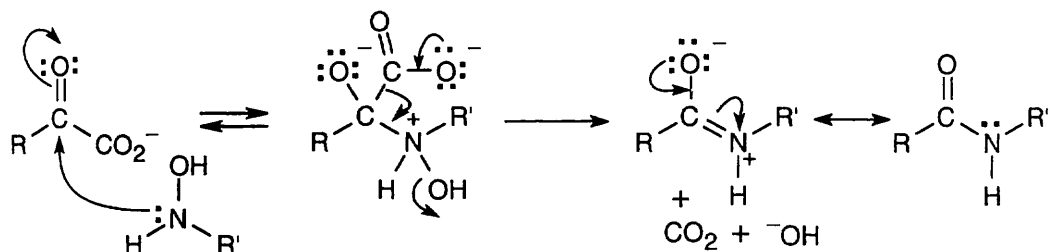


In this sequence of steps, water adds to the imine double bond, and the peptide bond is cleaved.

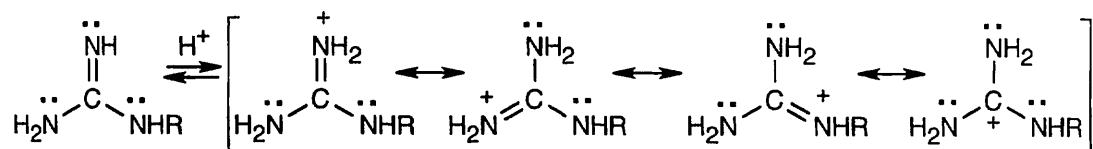


Water opens the lactone ring to give the product shown.

26.48



26.49



The protonated guanidino group can be stabilized by resonance.

26.50 100 g of cytochrome *c* contains 0.43 g iron, or 0.0077 mol Fe:

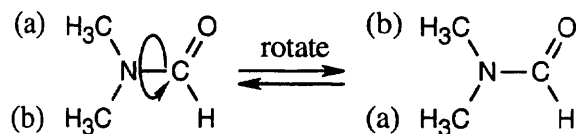
$$0.43 \text{ g Fe} \times \frac{1 \text{ mol Fe}}{55.8 \text{ g Fe}} = 0.0077 \text{ mol Fe}$$

Assuming that each mole of protein contains 1 mol Fe, then mol Fe = mol protein.

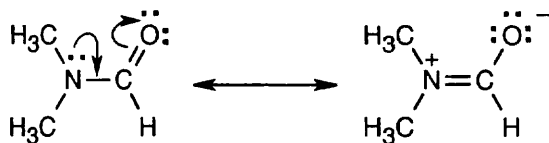
$$\frac{100 \text{ g Cytochrome } c}{0.0077 \text{ mol Fe}} = \frac{13,000 \text{ g Cytochrome } c}{1 \text{ mol Fe}}$$

Cytochrome *c* has a minimum molecular weight of 13,000 g/mol.

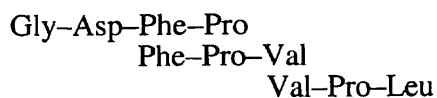
26.51 ^1H NMR shows that the two methyl groups of *N,N*-dimethylformamide are nonequivalent at room temperature. If rotation around the CO–N bond were unrestricted, the methyl groups would be interconvertible, and their ^1H NMR absorptions would coalesce into a single signal.



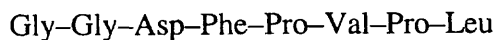
The presence of two methyl absorptions shows that there is a barrier to rotation around the CO–N bond. This barrier is due to the partial double-bond character of the CO–N bond, as indicated by the two resonance forms. Rotation to interconvert the two methyl groups is slow at room temperature, but heating to 180° supplies enough energy to allow rapid rotation and to cause the two NMR absorptions to coalesce.



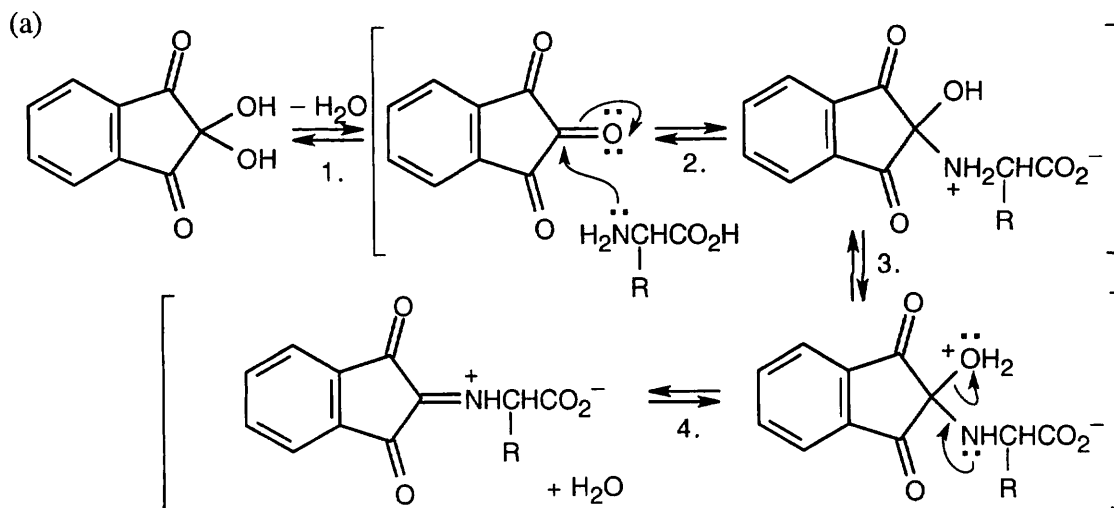
26.52 Gly



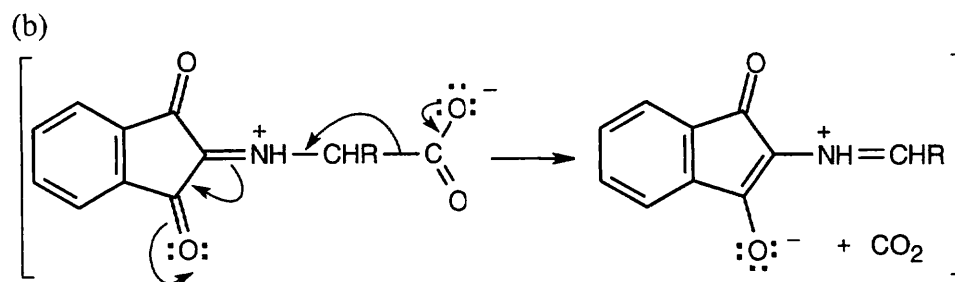
The complete sequence:



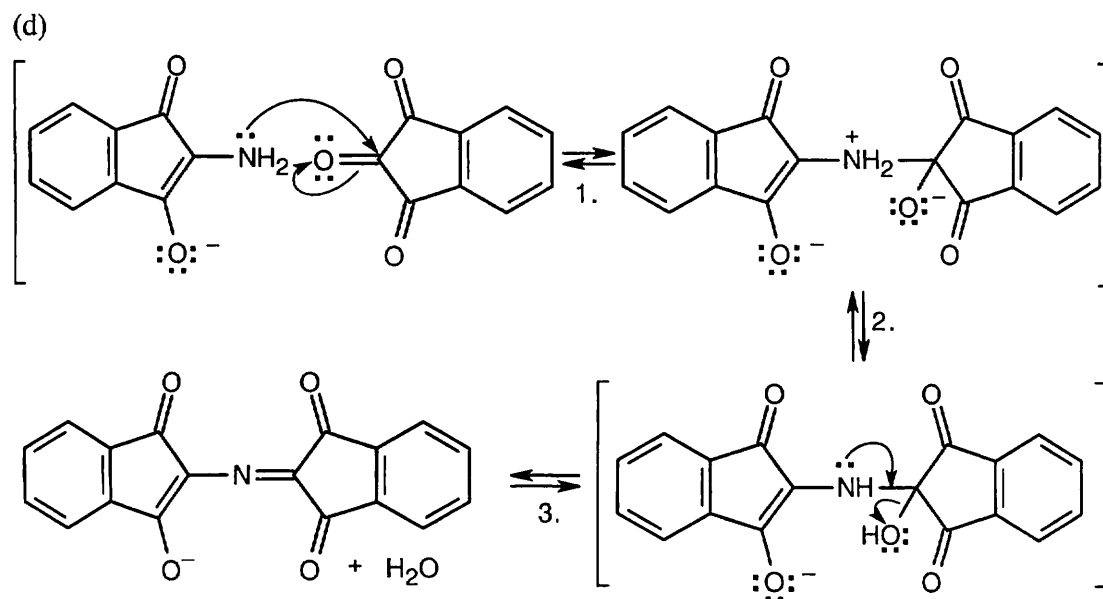
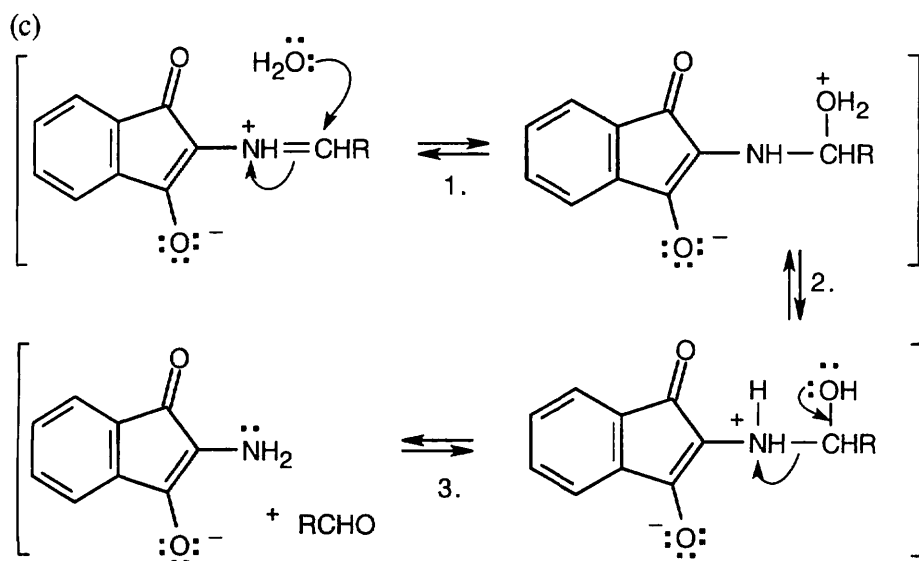
26.53



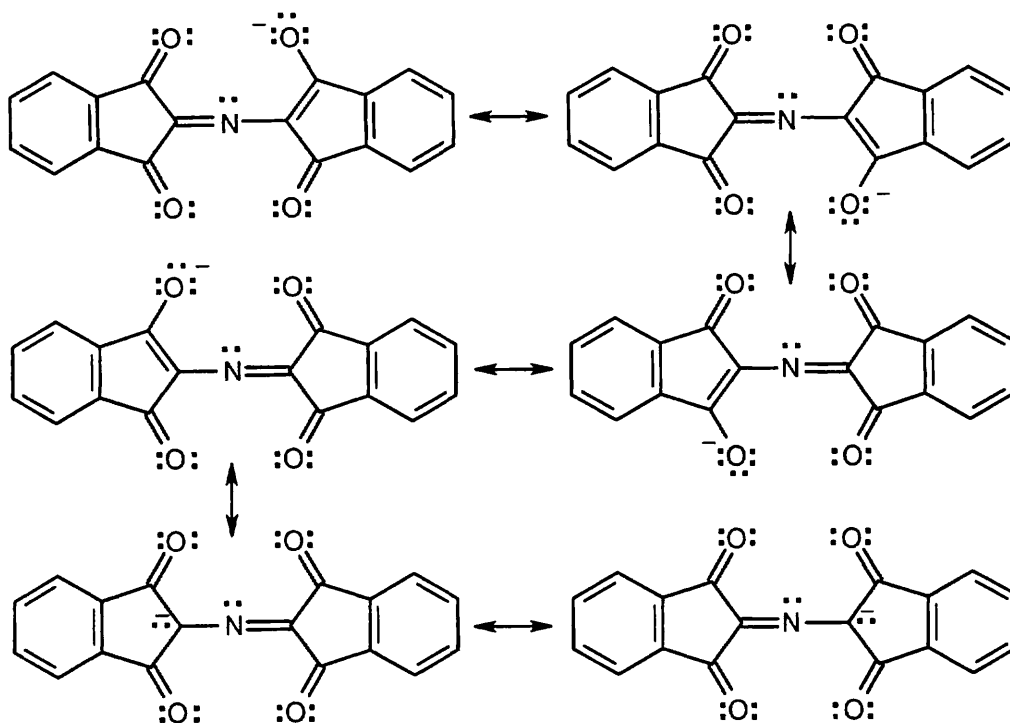
The steps involved in imine formation: (1) dehydration, (2) nucleophilic addition of the amino group of the amino acid, (3) proton transfer, and (4) loss of water.



Decarboxylation produces a different imine.

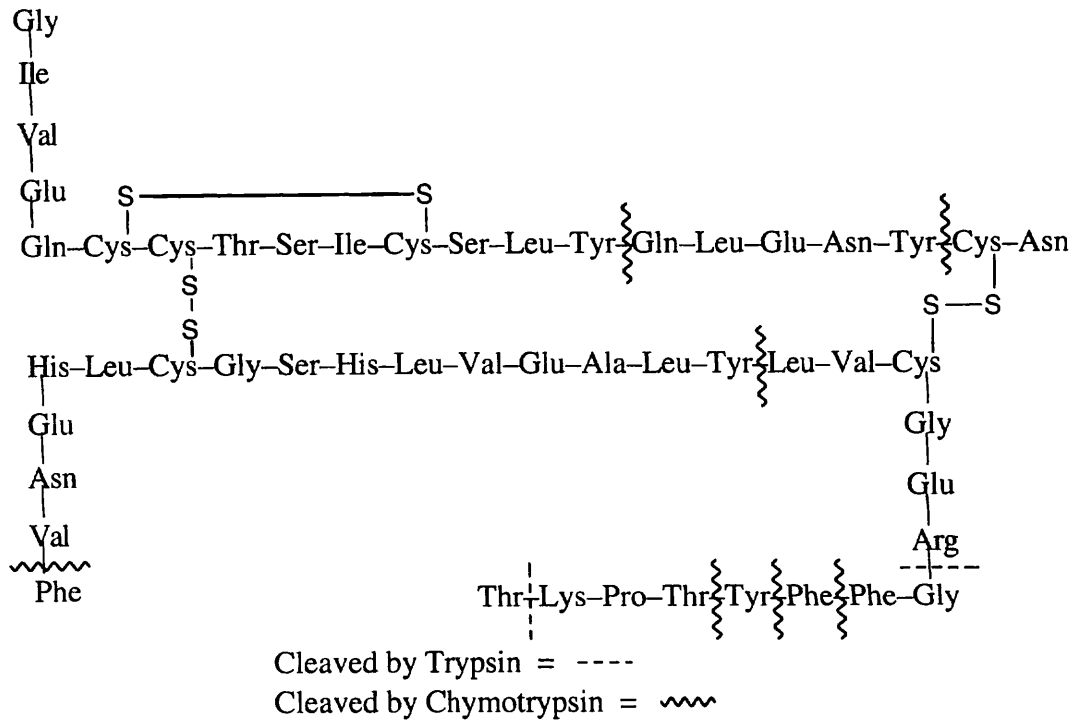


26.54



It is also possible to draw many other resonance forms that involve the π electrons of the aromatic 6-membered rings.

26.55



26.56 Ser-Ile-Arg-Val-Val-Pro-Tyr-Leu-Arg

26.57

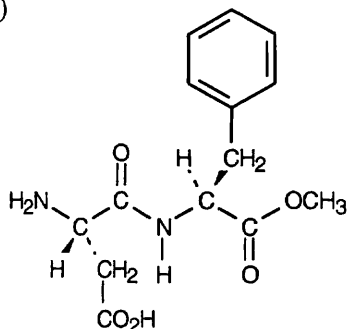
Reduced oxytocin: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH₂Oxidized oxytocin: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH₂

$$\begin{array}{c} \text{S} \text{-----} \text{S} \end{array}$$

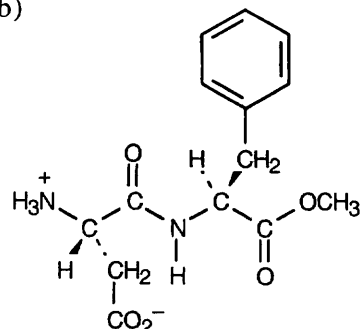
The C-terminal end of oxytocin is an amide, but this can't be determined from the information given.

26.58

(a)

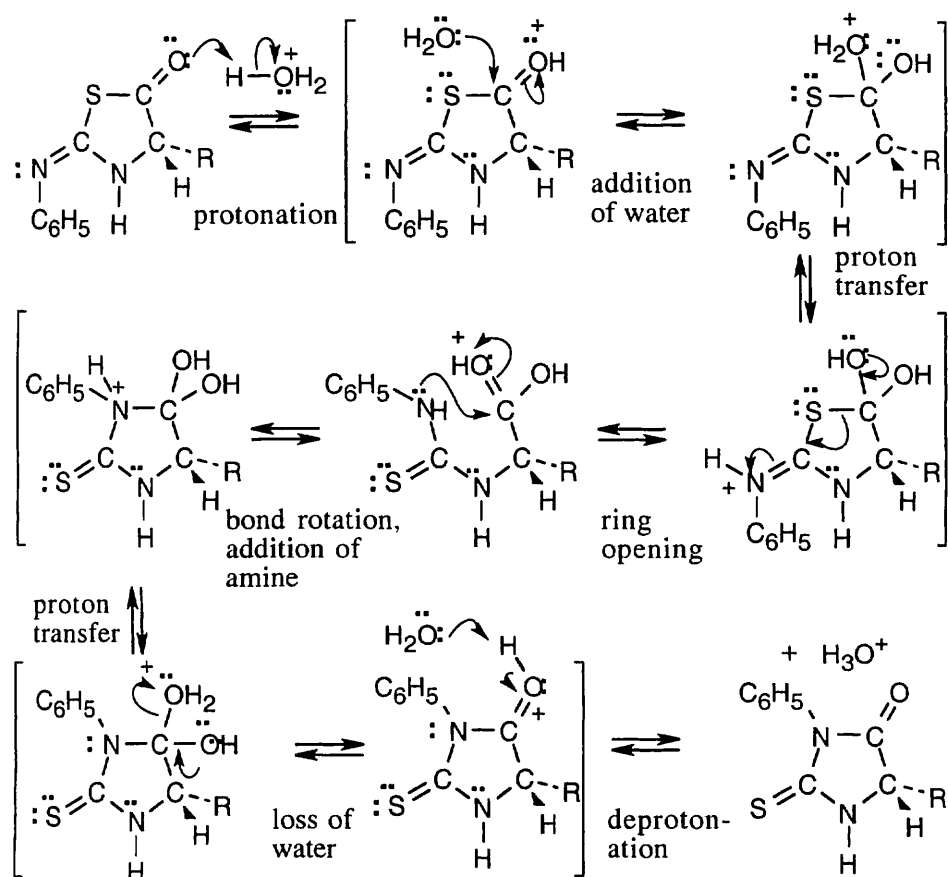
**Aspartame (nonzwitterionic form)**

(b)

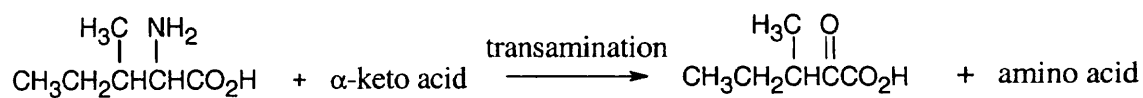
**Aspartame at pH = 5.9, 7.3**

At pH = 7.3, aspartame exists in the zwitterionic form, as it does at pH = 5.9.

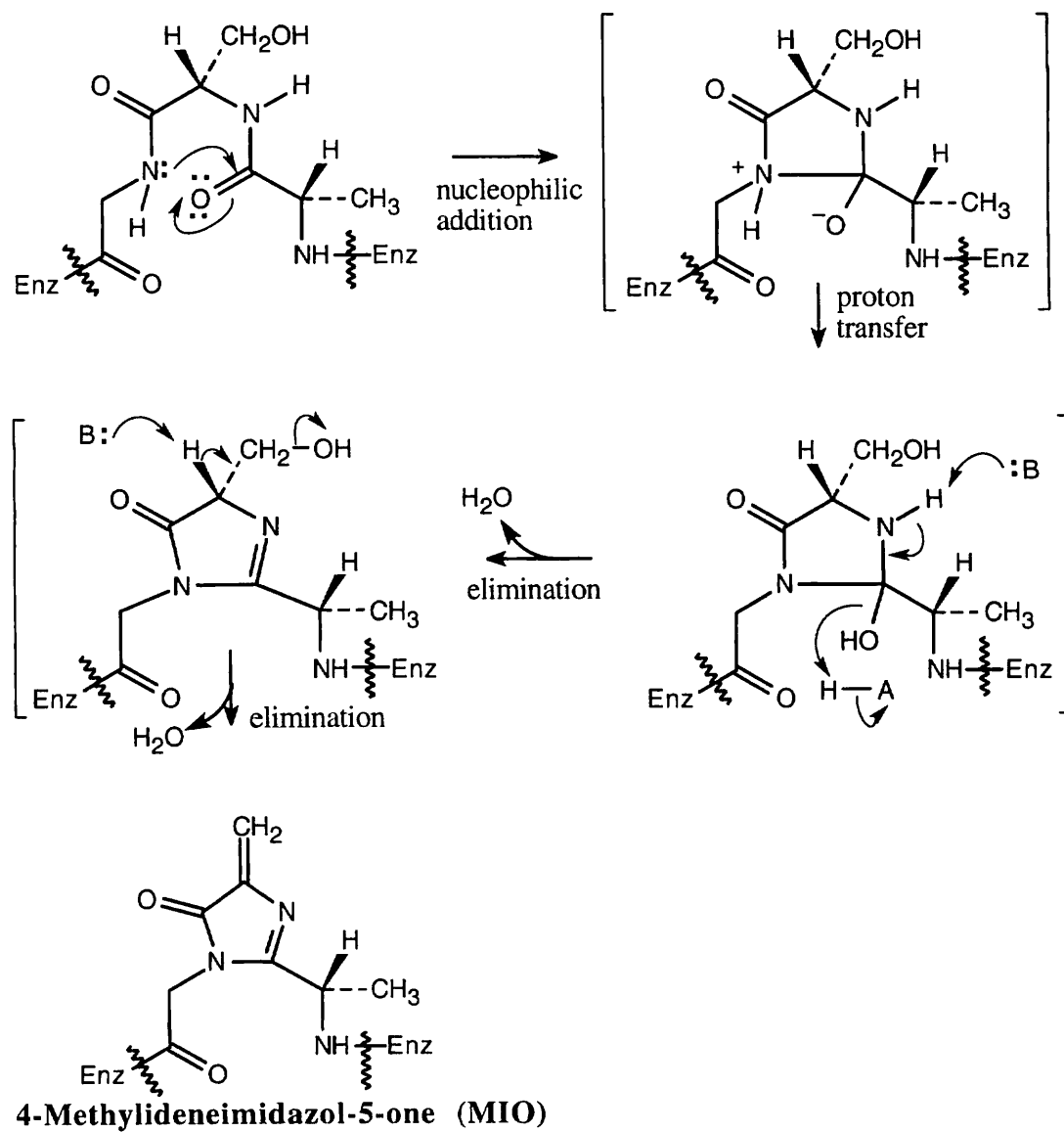
26.59



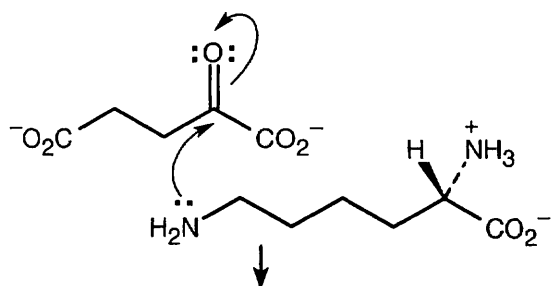
26.60



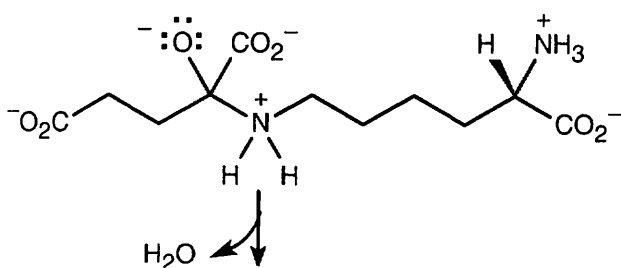
26.61



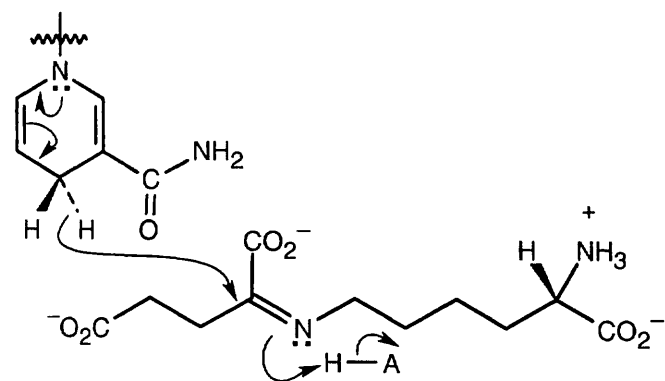
26.62



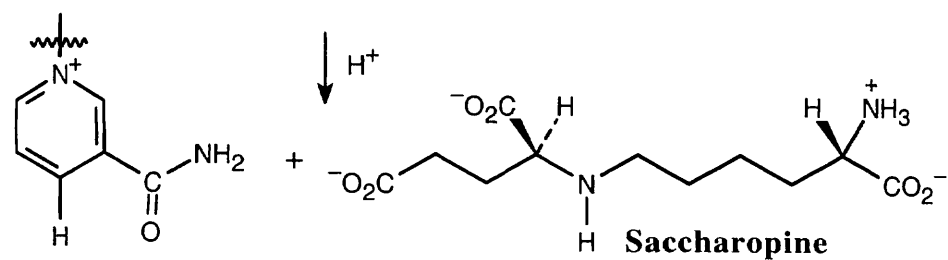
Nucleophilic addition of the amine to α -ketoglutarate.



Loss of water.



Reduction by NADPH/ H^+



Review Unit 10: Biomolecules I – Carbohydrates, Amino Acids, Peptides

Major Topics Covered (with vocabulary):

Monosaccharides:

carbohydrate monosaccharide aldose ketose Fischer projection D,L sugars pyranose furanose anomer anomeric center α anomer β anomer mutarotation glycoside Koenigs-Knorr reaction aldonic acid alditol reducing sugar aldaric acid Kiliani-Fischer synthesis Wohl degradation fucose glucosamine galactosamine neuraminic acid

Other sugars:

disaccharide 1,4' link cellobiose maltose lactose sucrose polysaccharide cellulose amylose amylopectin glycogen glycal assembly method deoxy sugar amino sugar cell-surface carbohydrate

Amino acids:

amino acid zwitterion amphoteric α -amino acid side chain isoelectric point (pI) electrophoresis Henderson-Hasselbalch equation amidomalonate synthesis reductive amination resolution enantioselective synthesis

Peptides:

residue backbone N-terminal amino acid C-terminal amino acid disulfide link amino acid analysis Edman degradation phenylthiohydantoin trypsin chymotrypsin peptide synthesis protection BOC derivative DCC Merrifield solid-phase technique

Proteins:

simple protein conjugated protein primary structure secondary structure tertiary structure quaternary structure α -helix β -pleated sheet salt bridge prosthetic group enzyme cofactor apoenzyme holoenzyme coenzyme vitamin isomerase hydrolase ligase lyase oxidoreductase transferase denaturation

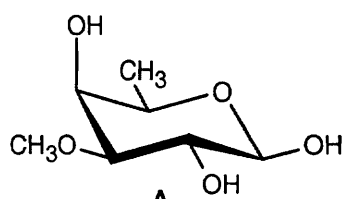
Types of Problems:

After studying these chapters, you should be able to:

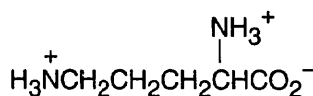
- Classify carbohydrates as aldoses, ketoses, D or L sugars, monosaccharides, or polysaccharides.
- Draw monosaccharides as Fischer projections or chair conformations.
- Predict the products of reactions of monosaccharides and disaccharides.
- Deduce the structures of monosaccharides and disaccharides.
- Formulate mechanisms for reactions involving carbohydrates.
- Identify the common amino acids and draw them with correct stereochemistry in dipolar form.
- Explain the acid-base behavior of amino acids.
- Synthesize amino acids.
- Draw the structure of simple peptides.
- Deduce the structure of peptides and proteins.
- Outline the synthesis of peptides.
- Explain the classification of proteins and the levels of structure of proteins.
- Draw structures of reaction products of amino acids and peptides.

Points to Remember:

- * Aldohexoses, ketohexoses and aldopentoses can all exist in both pyranose forms and furanose forms.
- * A reaction that produces the same functional group at both ends of a monosaccharide halves the number of possible stereoisomers of the monosaccharide.
- * The reaction conditions that form a glycoside are different from those that form a polyether, even though both reactions, technically, form $-OR$ bonds.
- * At physiological pH, the side chains of the amino acids aspartic acid and glutamic acid exist as anions, and the side chains of the amino acids lysine and arginine exist as cations. The imidazole ring of histidine exists as a mixture of protonated and neutral forms.
- * Since the amide backbone of a protein is neutral and uncharged, the isoelectric point of a protein or peptide is determined by the relative numbers of acidic and basic amino acid residues present in the peptide.
- * In the Merrifield technique of protein synthesis, a protecting group isn't needed for the carboxyl group because it is attached to the polymer support.

Self-Test:

Digitalin
(hydrolysis product of
digitoxigenin, a heart
medication)



Ornithine

Digitalin (**A**) is related to which D-aldohexose? Provide a name for **A**, including the configuration at the anomeric carbon. Predict the products of the reaction of **A** with: (a) CH_3OH , H^+ catalyst; (b) CH_3I , Ag_2O .

Vicianose (**B**) is a disaccharide associated with a natural product found in seeds. Treatment of **B** with CH_3I and Ag_2O , followed by hydrolysis, gives 2,3,4-tri-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-D-arabinose. What is the structure of **B**? Is **B** a reducing sugar?

Ornithine (**C**) is a nonstandard amino acid that occurs in metabolic processes. Which amino acid does it most closely resemble? Estimate pK_a values and pI for ornithine, and draw the major form present at $pH = 2$, $pH = 6$, and $pH = 11$. If ornithine were a component of proteins, how would it affect the tertiary structure of a protein?

Tyr–Gly–Gly–Phe–Leu–Arg–Arg–Ile–Arg–Pro–Lys–Leu–Lys–Trp–Asp–Asn–Gln
Porcine Dynorphin (D)

Dynorphin (**D**) is a neuropeptide. Indicate the *N*-terminal end and the *C*-terminal end. Show the products of cleavage with: (a) trypsin; (b) chymotrypsin. Show the *N*-phenylthiohydantoin that results from treatment of **D** with phenyl isothiocyanate. Do you expect **D** to be an acidic, a neutral or a basic peptide?

Kallidin (**E**) is a decapeptide that serves as a vasodilator. The composition of **E** is Arg₂ Gly Lys Phe₂ Pro₃ Ser. The *C*-terminal residue is Arg. Partial acid hydrolysis yields the following fragments:

Pro–Gly–Phe, Lys–Arg–Pro, Pro–Phe–Arg, Pro–Pro–Gly, Phe–Ser–Pro
 What is the structure of **E**.

Multiple choice:

- The enantiomer of α -D-glucopyranose is:
 (a) β -D-Glucopyranose (b) α -L-Glucopyranose (c) β -L-Glucopyranose (d) none of these
- All of the following reagents convert an aldose to an aldonic acid except:
 (a) dilute HNO_3 (b) Fehling's reagent (c) Benedict's reagent (d) aqueous Br_2
- Which two aldoses yield D-lyxose after Wohl degradation?
 (a) D-Glucose and D-Mannose (b) D-Erythrose and D-Threose (c) D-Galactose and D-Altrose (d) D-Galactose and D-Talose
- All of the following disaccharides are reducing sugars except:
 (a) Cellobiose (b) Sucrose (c) Maltose (d) Lactose
- Which of the following polysaccharides contains β -glycosidic bonds?
 (a) Amylose (b) Amylopectin (c) Cellulose (d) Glycogen
- To find the *pI* of an acidic amino acid:
 (a) find the average of the two lowest pK_a values (b) find the average of the two highest pK_a values (c) find the average of all pK_a values (d) use the value of the pK_a of the side chain.
- Which of the following techniques can synthesize a single enantiomer of an amino acid?
 (a) Hell–Volhard–Zelinskii reaction (b) reductive amination (c) amidomalonate synthesis (d) hydrogenation of a *Z* enamido acid
- The purple product that results from the reaction of ninhydrin with an amino acid contains which group of the amino acid?
 (a) the amino group (b) the amino nitrogen (c) the carboxylic acid group (d) the side chain
- Which of the following reagents is not used in peptide synthesis?
 (a) Phenylthiohydantoin (b) Di-*tert*-butyl dicarbonate (c) Benzyl alcohol (d) Dicyclohexylcarbodiimide
- Which structural element is not present in myoglobin?
 (a) a prosthetic group (b) regions of α -helix (c) hydrophobic regions (d) quaternary structure