27

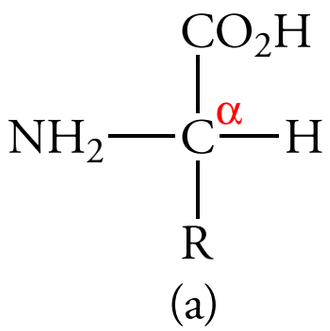
Amino Acids, Peptides, and Proteins

Ribbon model of human myoglobin

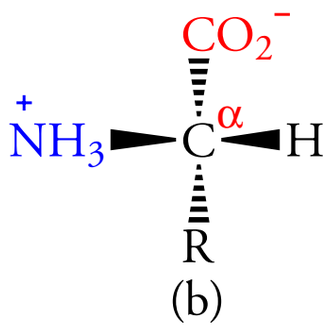
27.1 STRUCTURES OF THE α-AMINO ACIDS

Figure 27.1 Chirality of the α-Amino Acids

(a) Planar projection of an L-amino acid in unionized form. (b) The α-carboxyl group and the α-amino group are ionized in aqueous solution at pH 7. (c)The configuration of the α-amino acids isolated from proteins is opposite to the configuration of the reference compound D-glyceraldehyde. (d) Molecular model of L-serine, whose side chain is a CH_2OH group.



(a)



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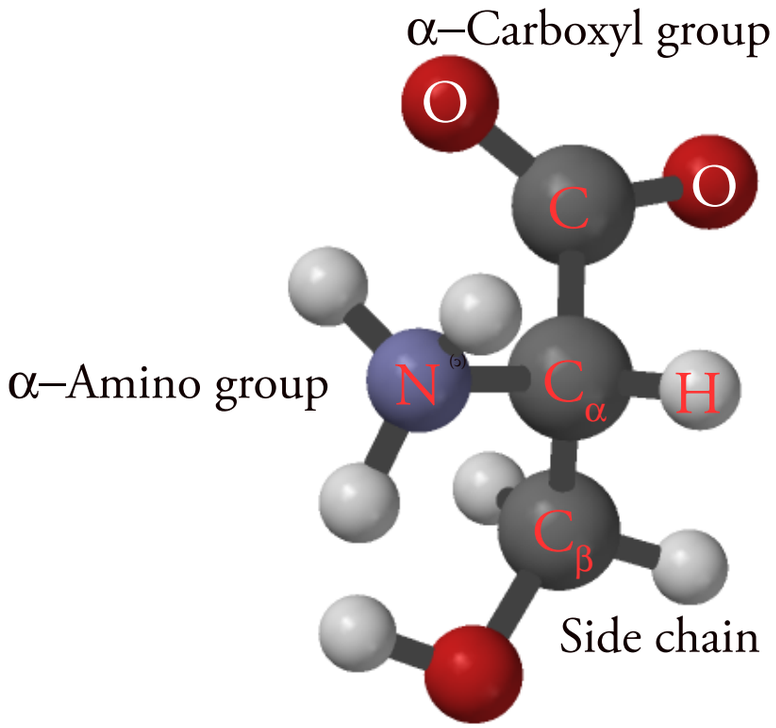

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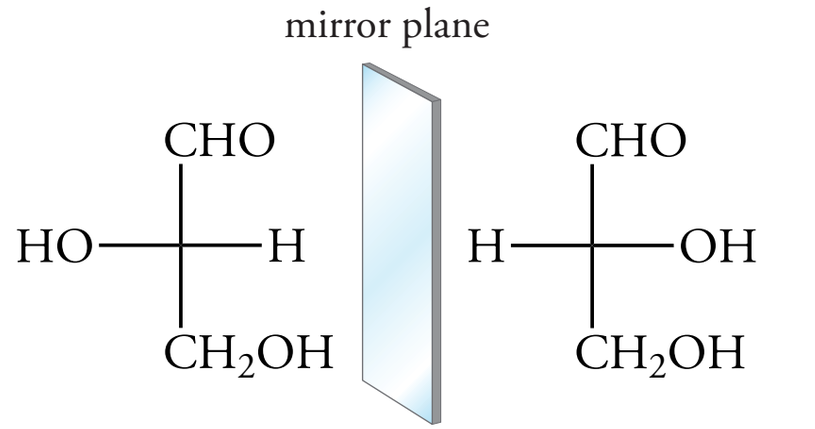
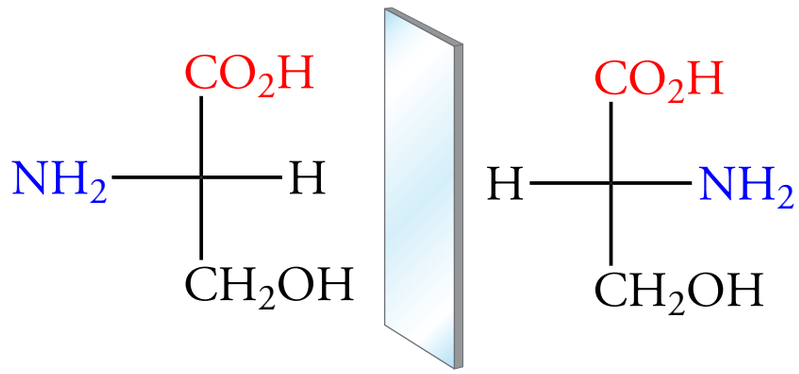


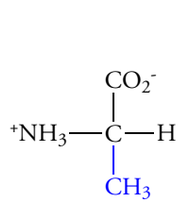


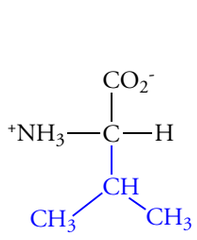
(d)

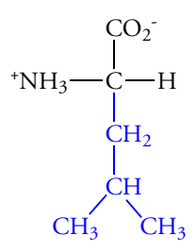
27.1 STRUCTURES OF THE α-AMINO ACIDS

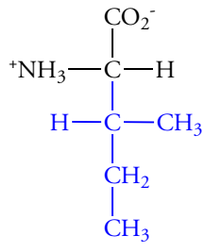
Figure 27.2 Structures of the α-Amino Acids at pH 7
At pH the α-amino and α-carboxyl groups are both ionized. The amino acids are classified by their side chain polarities. The amino acids have both on-letter and three-letter abbreviations.

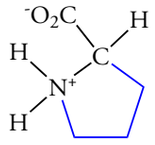
Nonpolar (hydrophobic) side chains

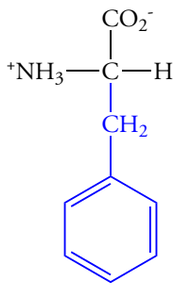

Alanine (A) (Ala)

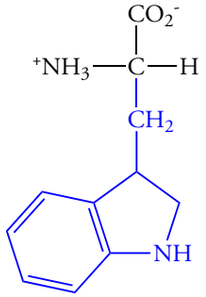

Valine (V) (Val)

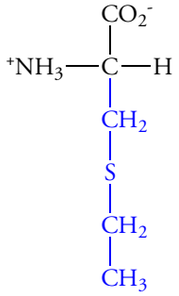

Leucine (L) (Leu)

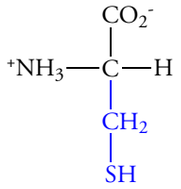

Isoleucine (Ile) (I)

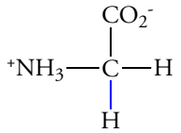

Proline (P) (Pro)


Phenylalanine (F) (Phe)

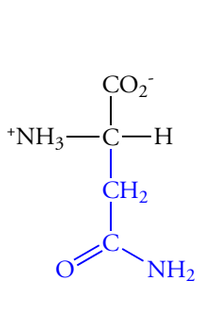

Tryptophan (W) (Trp)

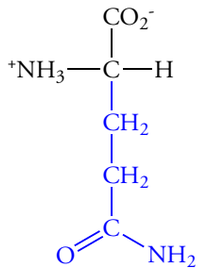

Methionine (M) (Met)

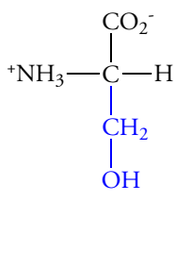

Cysteine (C) (Cys)

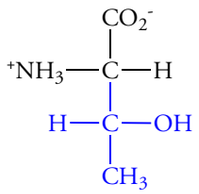

Glycine (G) (Gly)

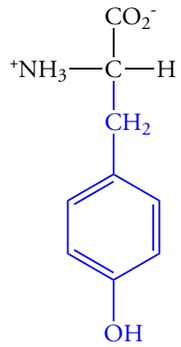
Polar, neutral (hydrophilic) side chains


Asparagine (N) (Asn)

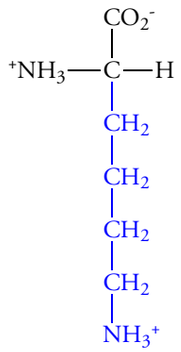

Glutamine (Q) (Gln)

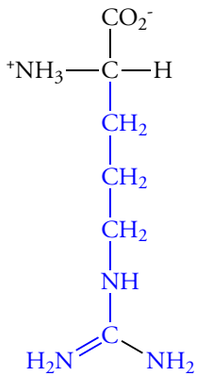

Serine (S) (Ser)

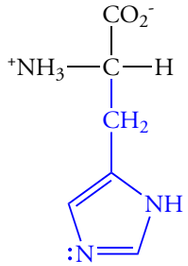

Threonine (Thr) (T)


Tyrosine (Y) (Tyr)

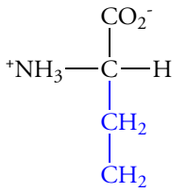
Basic Amino Acids

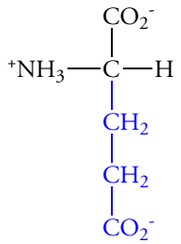

Lysine (Lys) (K)


Arginine (Arg) (R)


Histidine (His) (H)

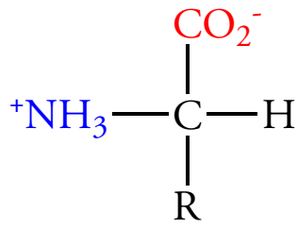
Acidic Amino Acids


Aspartate (Asp) (D)

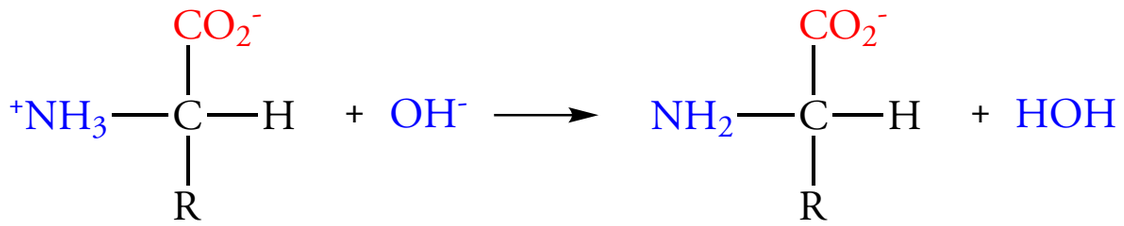

Glutamate (Glu) (E)

27.2 ACID-BASE EQUILIBRIA OF α-AMINO ACIDS

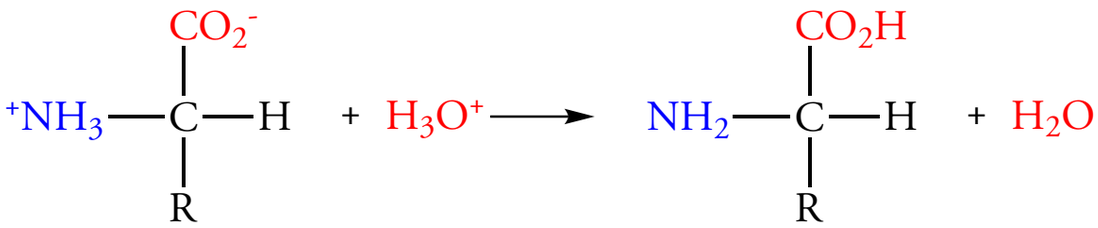
Ionic Form of Amino Acids



structure of a dipolar ion (zwitterion)



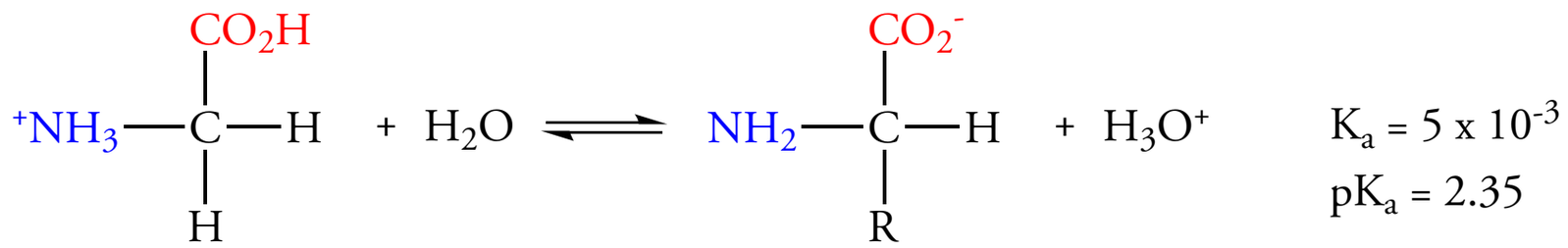
zwitterion conjugate base



zwitterion conjugate acid

27.2 ACID-BASE EQUILIBRIA OF α-AMINO ACIDS

pK_a Values of α-Amino Acids

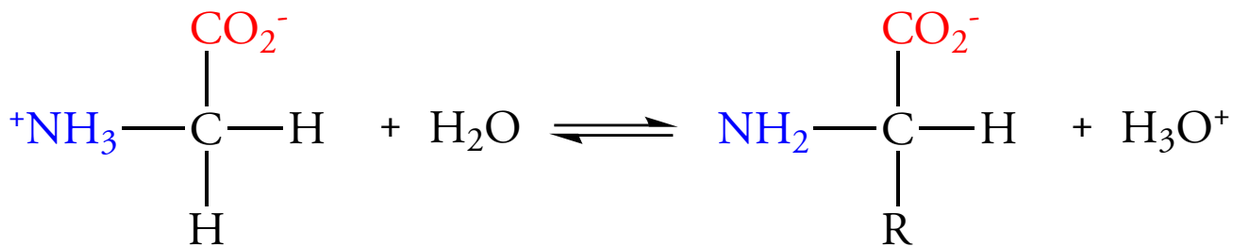


conjugate acid of glycine

dipolar form of glycine

$K_a = 5 \times 10^{-3}$

$pK_a = 2.35$



dipolar form of glycine

conjugate base of glycine

$K_a = 1.6 \times 10^{-10}$

$pK_a = 9.78$

27.2 ACID-BASE EQUILIBRIA OF α-AMINO ACIDS

pK_a Values of α-Amino Acids

27.1
pK_a Values of Acidic and Basic Groups in α–Amino Acids

Amino Acid	α–CO_2H group	α–NH_3^+ group	Side chain
Glycine	2.35	9.78	
Alanine	2.35	9.87	
Valine	2.29	9.72	
Leucine	2.33	9.74	
Isoleucine	2.32	9.76	
Methionine	2.17	9.27	
Proline	1.95	10.64	
Phenylalanine	2.58	9.24	
Tryptophan	2.43	9.44	
Serine	2.19	9.44	
Threonine	2.09	9.10	
Cysteine	1.89	10.78	8.53
Tyrosine	2.20	9.11	10.11
Asparagine	2.02	8.80	
Glutamine	2.17	9.13	
Aspartate	1.99	10.00	3.96
Glutamate	2.13	9.95	4.32
Lysine	2.16	9.20	10.80
Arginine	1.82	8.99	12.48
Histidine	1.81	9.15	6.00

27.3 ISOIONIC POINT AND TITRATION OF α-AMINO ACIDS

Isoionic Points of Amino Acids

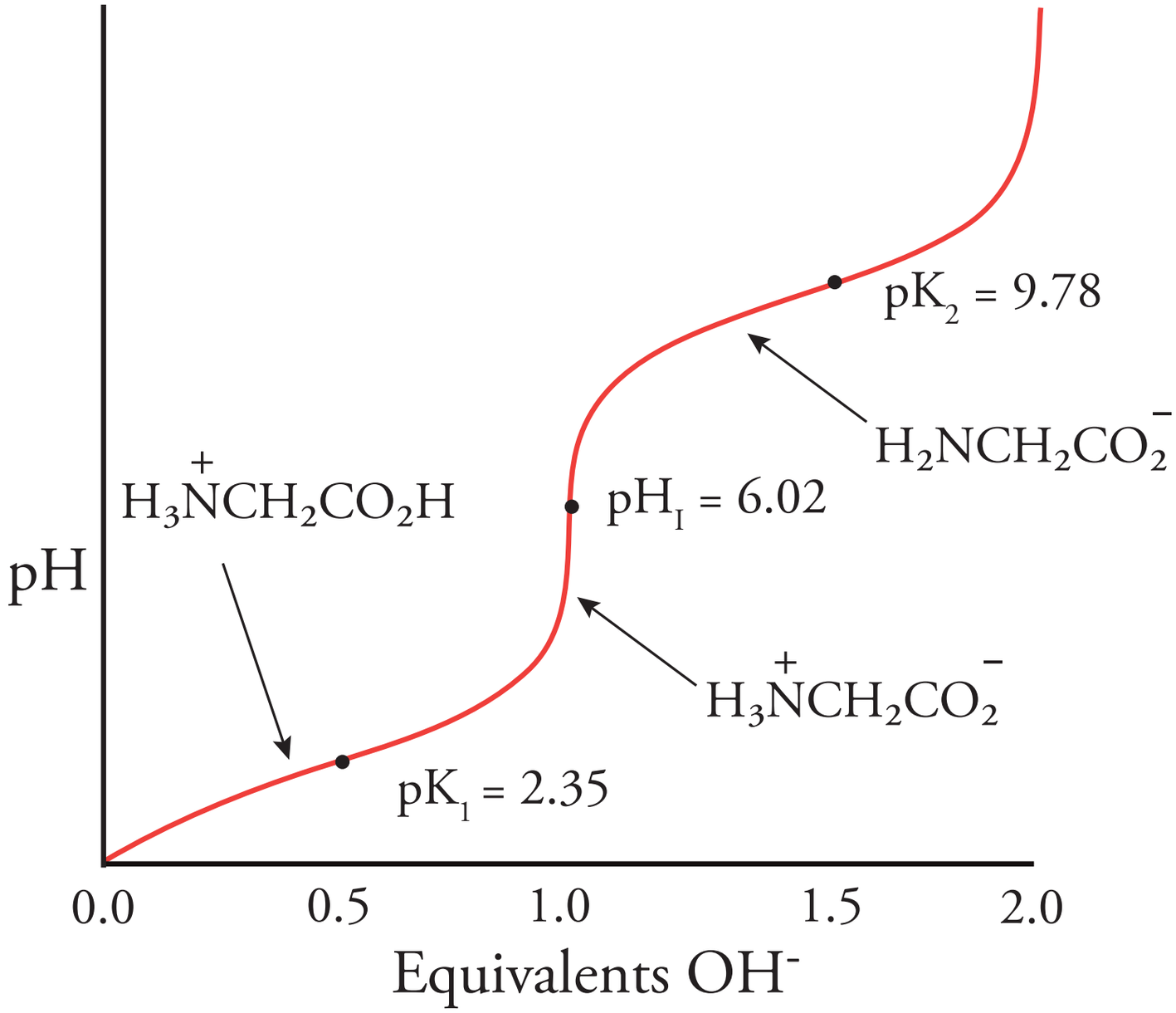
Table 27.2
Isoionic Points

Amino Acid	pH_I
Glycine	5.97
Alanine	6.10
Valine	5.96
Leucine	5.98
Isoleucine	6.02
Methionine	5.74
Proline	6.30
Phenylalanine	5/48
Tryptophan	5.89
Serine	5.68
Threonine	5.60
Cysteine	5.07
Tyrosine	5.66
Asparagine	5.41
Glutamine	5.65
Aspartic acid	2.77
Glutamic acid	3.22
Lysine	9.74
Arginine	10.76
Histidine	7.59

27.3 ISOIONIC POINT AND TITRATION OF α-AMINO ACIDS

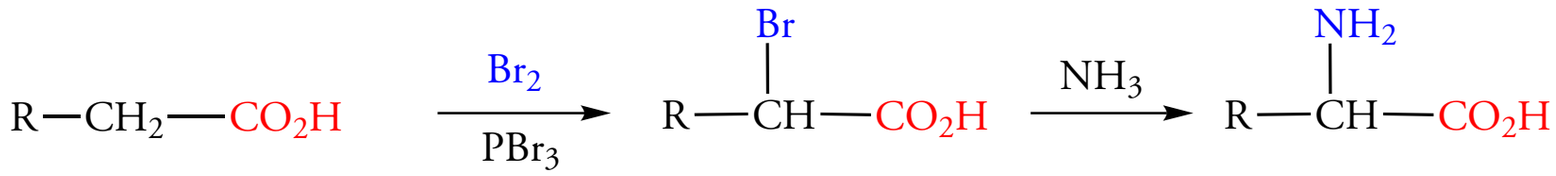
Titration of Amino Acids

Figure 27.3 Titration Curve of Glycine

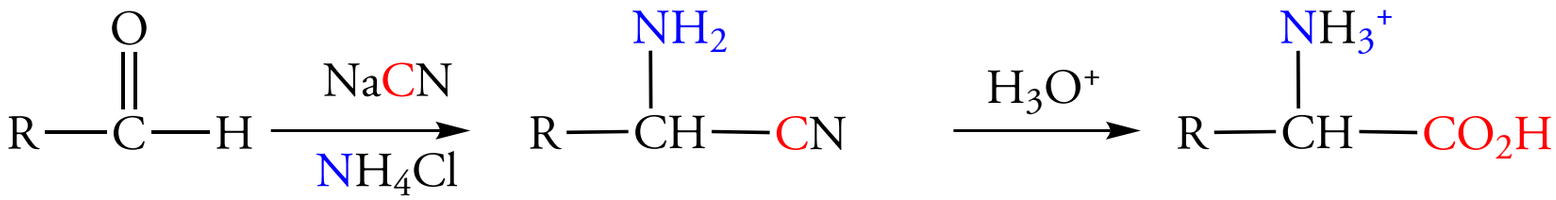


27.4 SYNTHESIS OF α-AMINO ACIDS

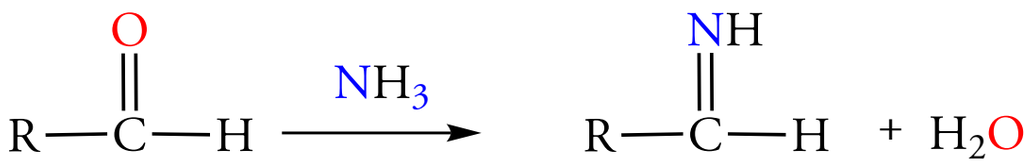
Amination of α-Halocarboxylic Acids

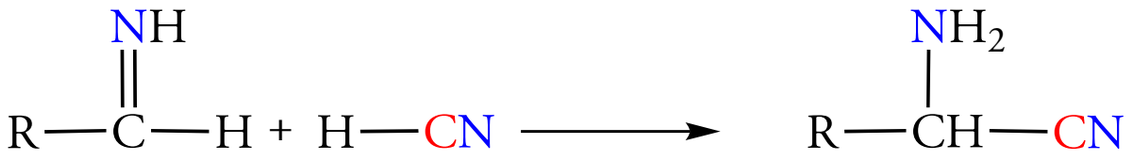


The Strecker Synthesis



(an α-amino nitrile)

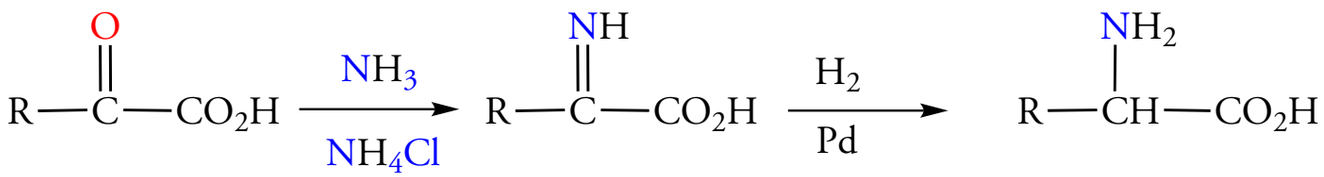




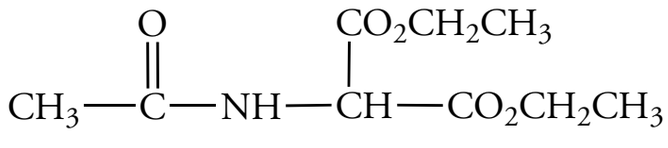
27.4 SYNTHESIS OF α-AMINO ACIDS

Reductive Amination and Acetamidomalonate Synthesis

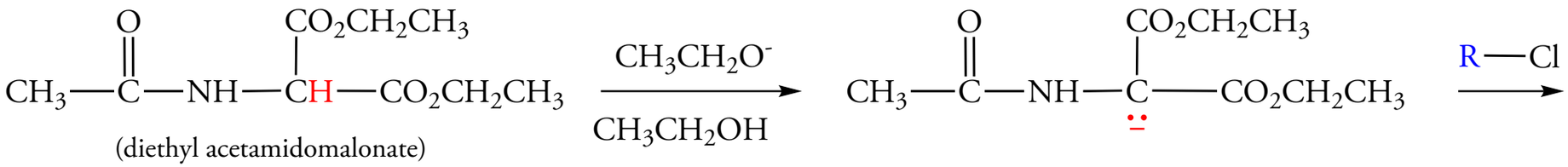
Reductive Amination



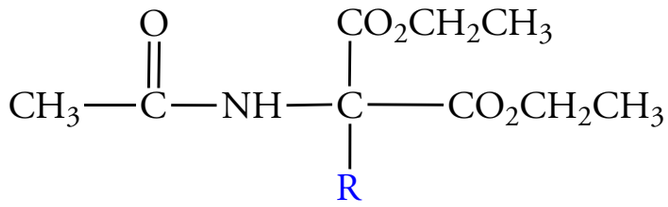
Acetamidomalonate Synthesis

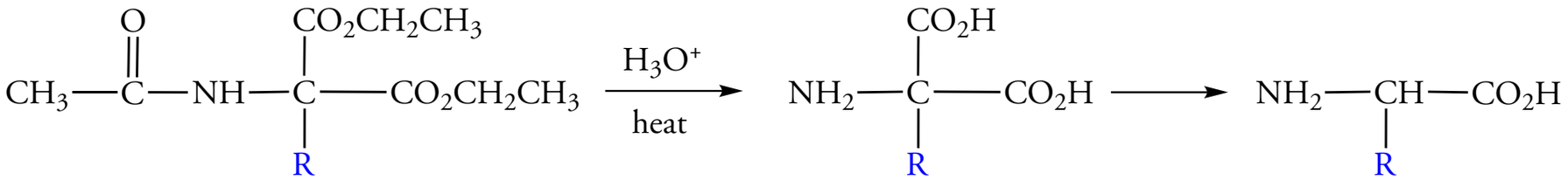


(diethyl acetamidomalonate)



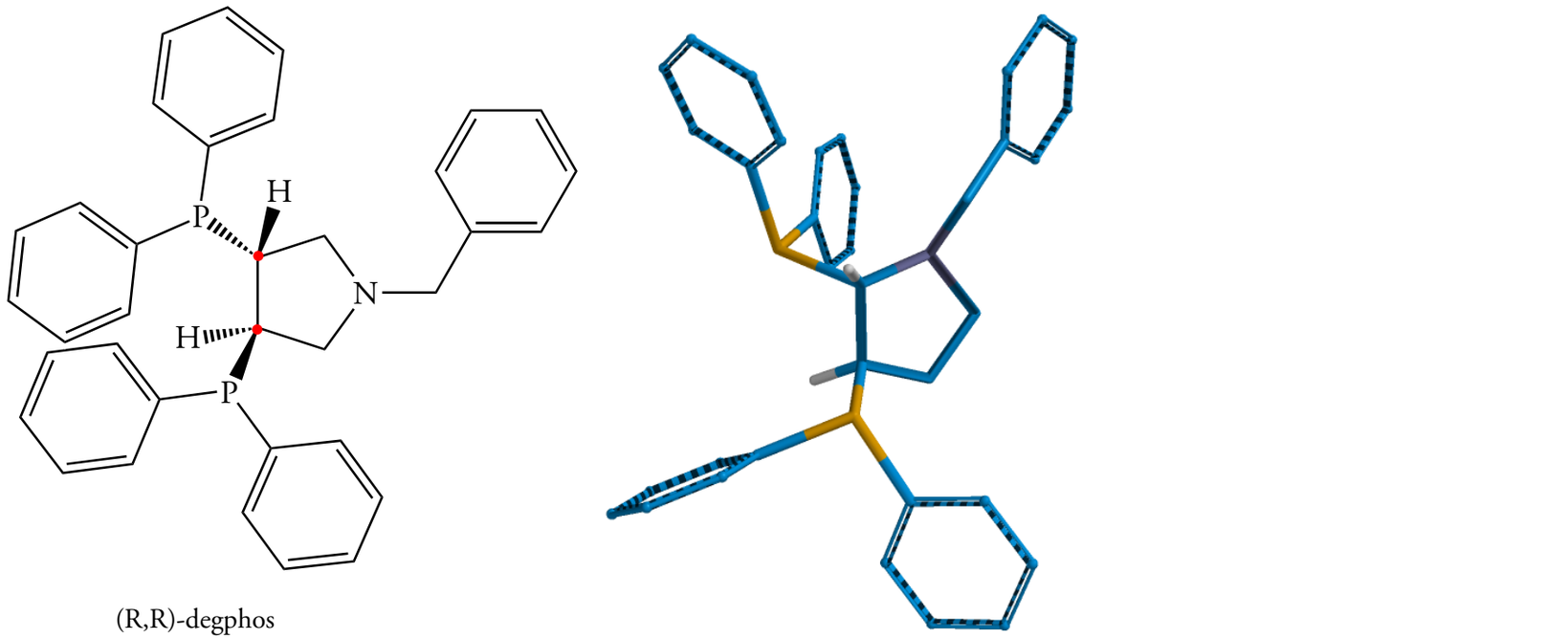
(diethyl acetamidomalonate)



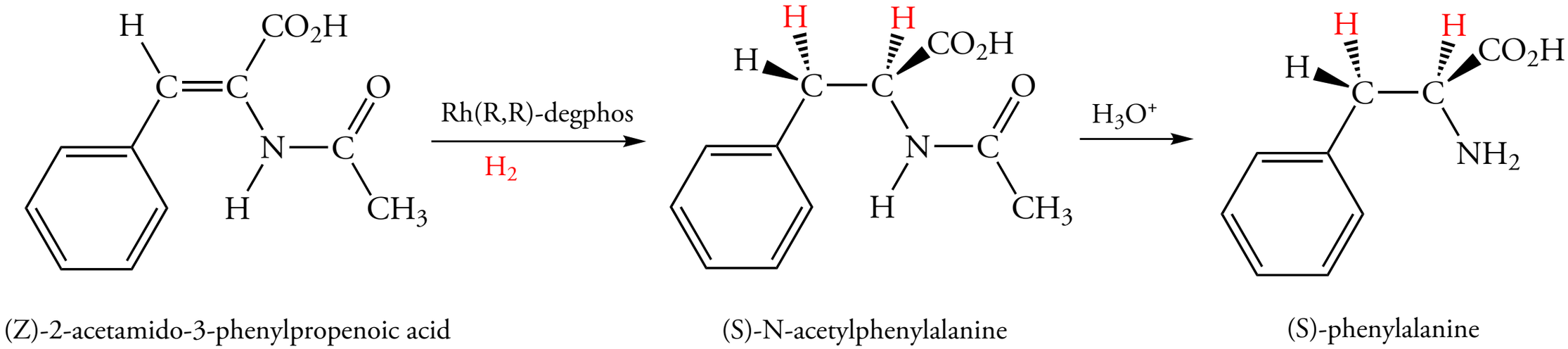


27.5 CHIRAL SYNTHESIS OF α-AMINO ACIDS

Figure 27.4 Structure of (R,R)-degphos



(R,R)-degphos



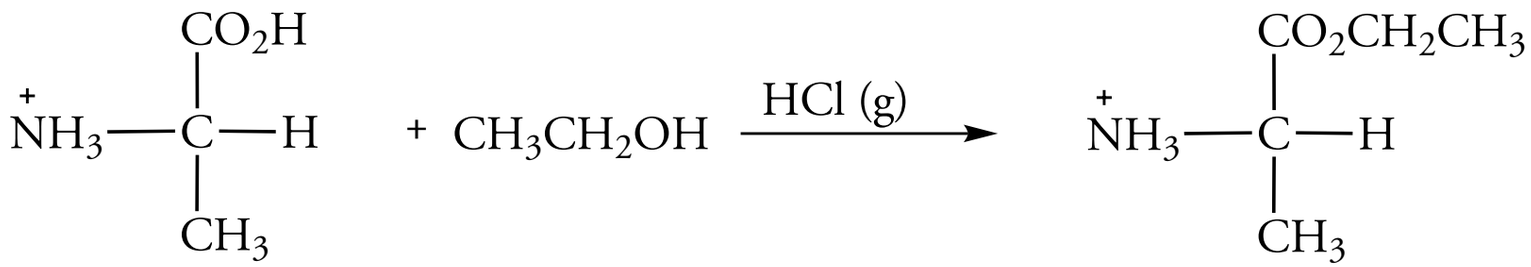
(Z)-2-acetamido-3-phenylpropenoic acid

(S)-N-acetylphenylalanine

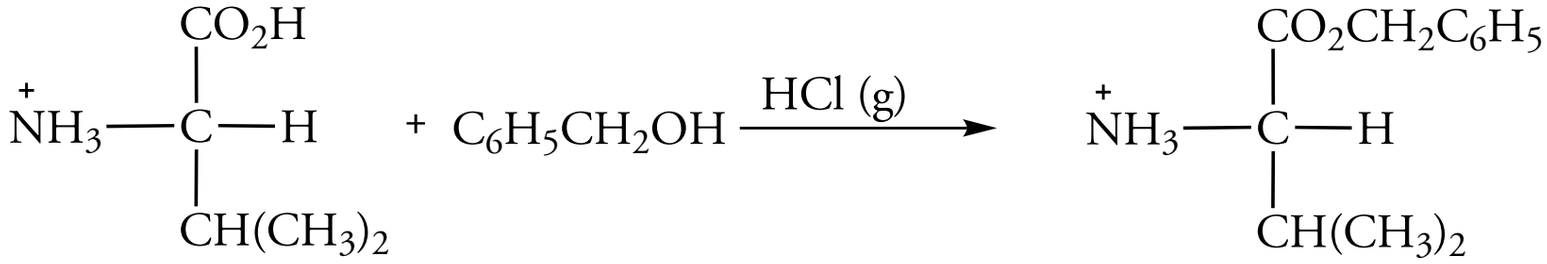
(S)-phenylalanine

27.6 REACTIONS OF α-AMINO ACIDS

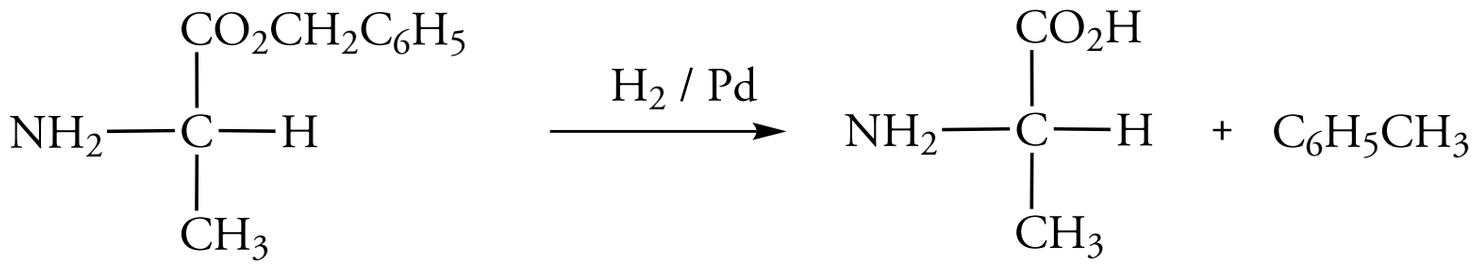
Esterification of the α-Carboxyl Group



alanine — alanine ethyl ester



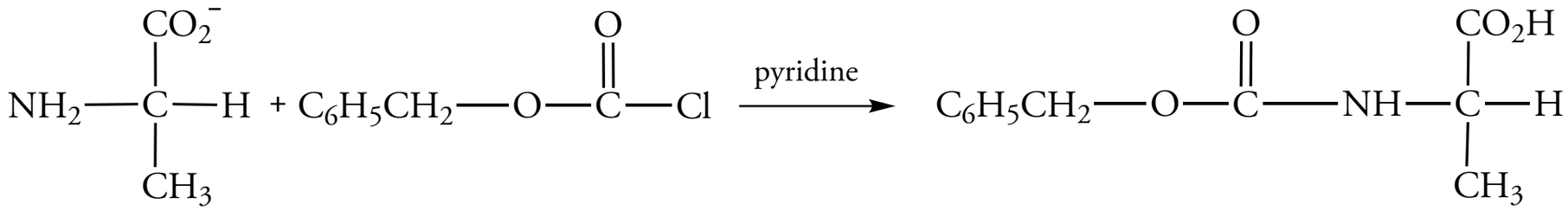
valine — valine benzyl ester



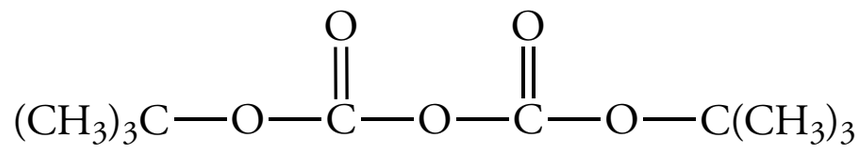
alanine benzyl ester — alanine

27.6 REACTIONS OF α-AMINO ACIDS

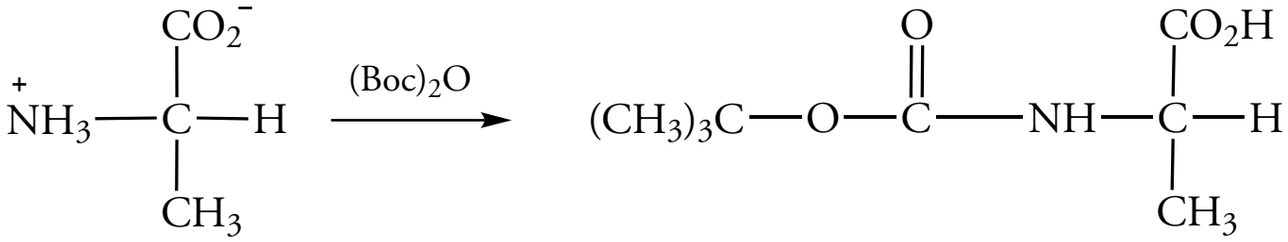
Acetylation of the α-Amino Group



alanine benzyl chloroformate N-benzyloxycarbonyl alanine (Cbz alanine)



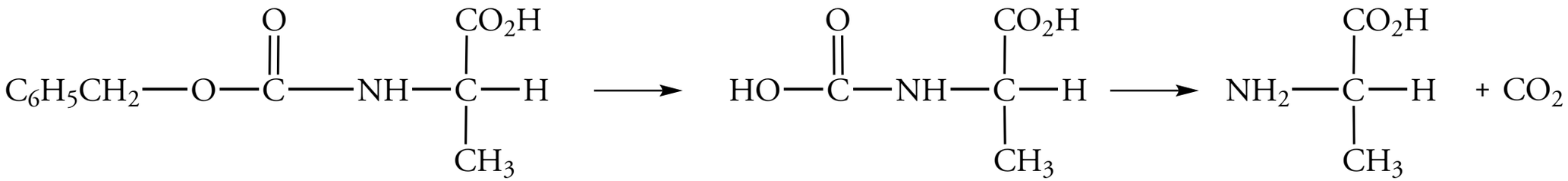
di-*tert*-butyldicarbonate
$(Boc)_2O$



alanine N-*tert*-butoxycarbonyl alanine (Boc alanine)

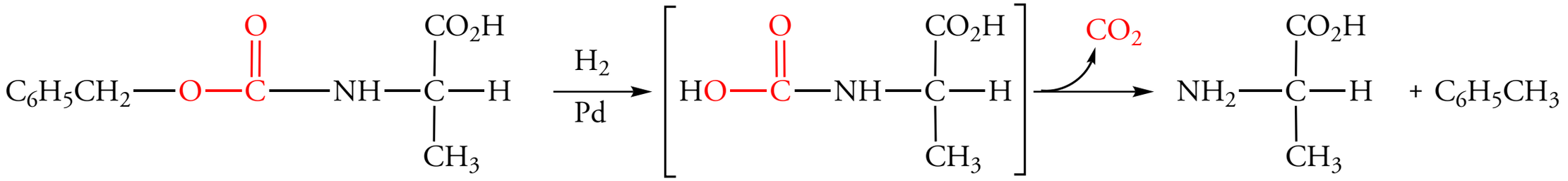
27.6 REACTIONS OF α-AMINO ACIDS

Acetylation of the α-Amino Group

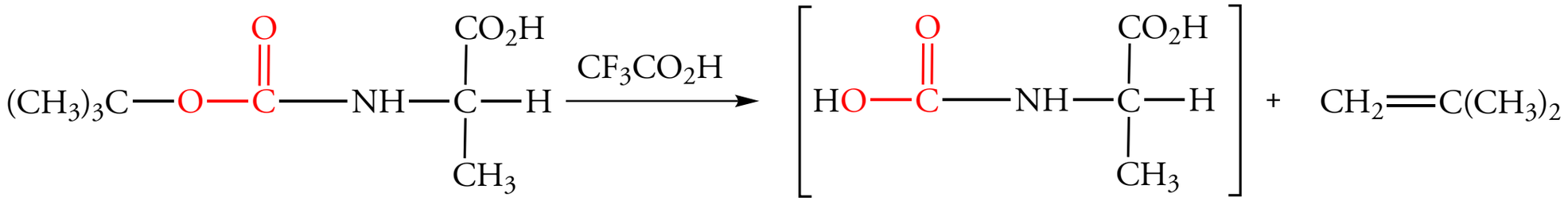


N-benzyloxycarbonyl alanine
(Cbz alanine)

a carbamic acid



N-benzyloxycarbonyl alanine
(Cbz alanine)



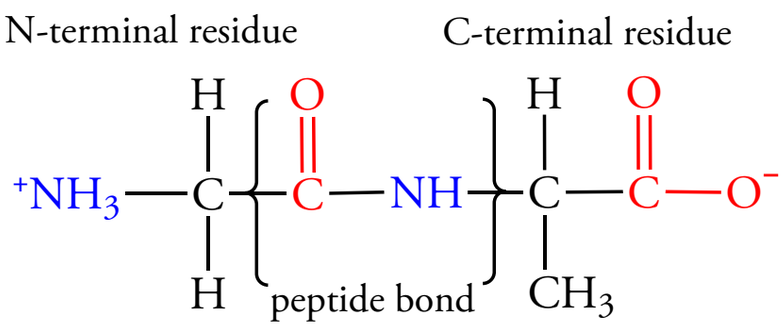
N-*tert*-butoxycarbonyl alanine
(Boc alanine)

27.7 PEPTIDES

Peptide Nomenclature

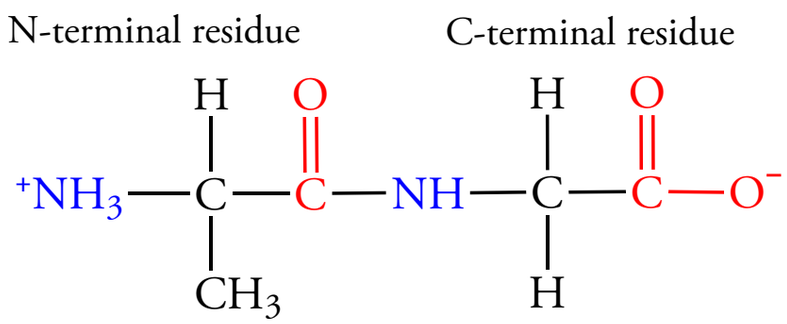
Figure 27.4 Peptide Nomenclature

(a) Structure of glycylalanine. The N-terminal α-amino group and the C-terminal α-carboxyl group and are ionized in aqueous solution at pH 7. Three-letter and one-letter abbreviations for the amino acids are commonly used. (b) Structure of alanylglycine. (c) An aminoacyl group consists of the —NH—CHR—CO— group of each amino acid in the peptide.



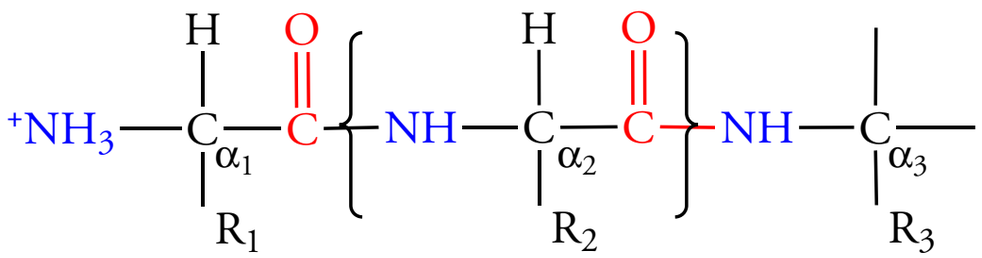
glycylalanine
(Gly-Ala or GA)

(a)



alanylglycine
(Ala-Gly or Ag)

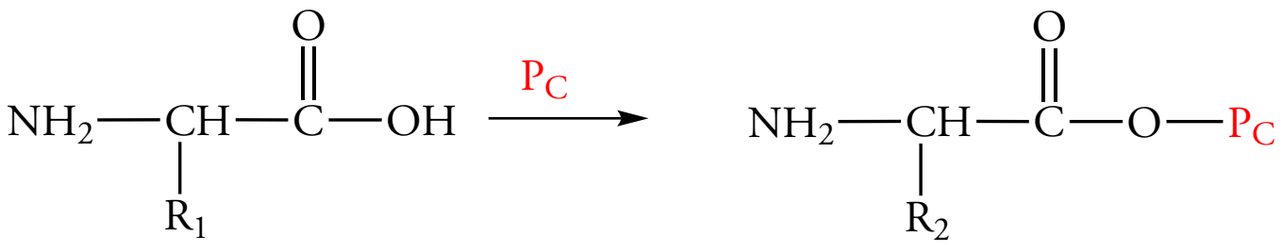
(b)

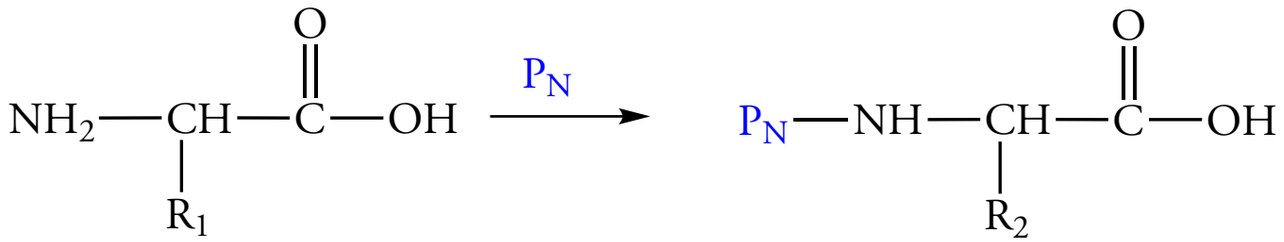


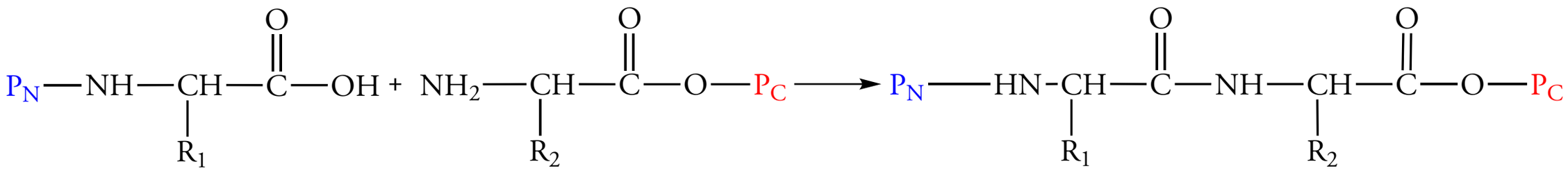
aminoacyl group

(c)

27.8 OVERVIEW OF PEPTIDE SYNTHESIS

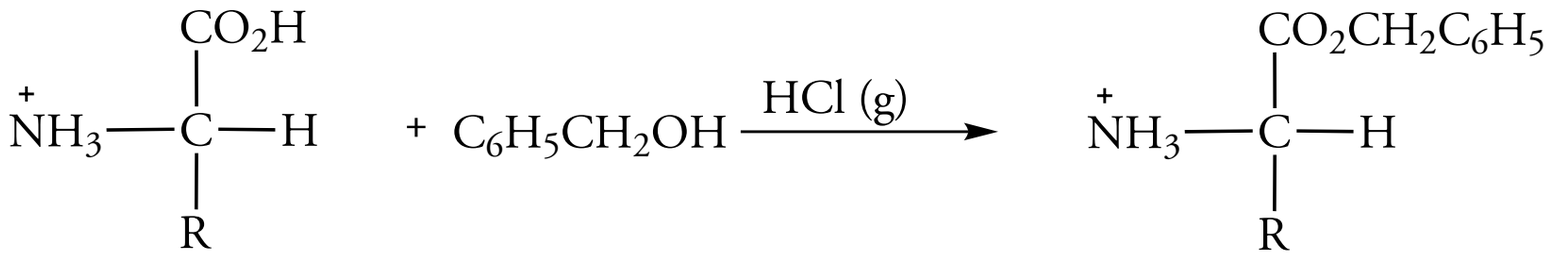




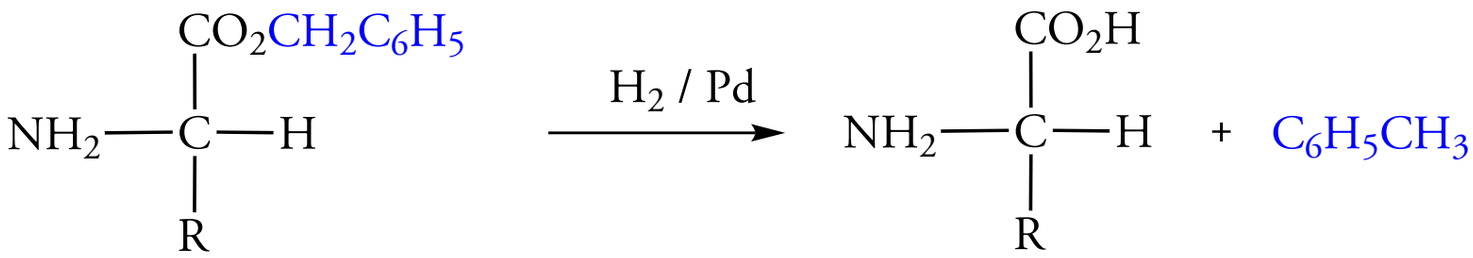


27.8 OVERVIEW OF PEPTIDE SYNTHESIS

Protecting the Carboxyl Group



benzyl ester

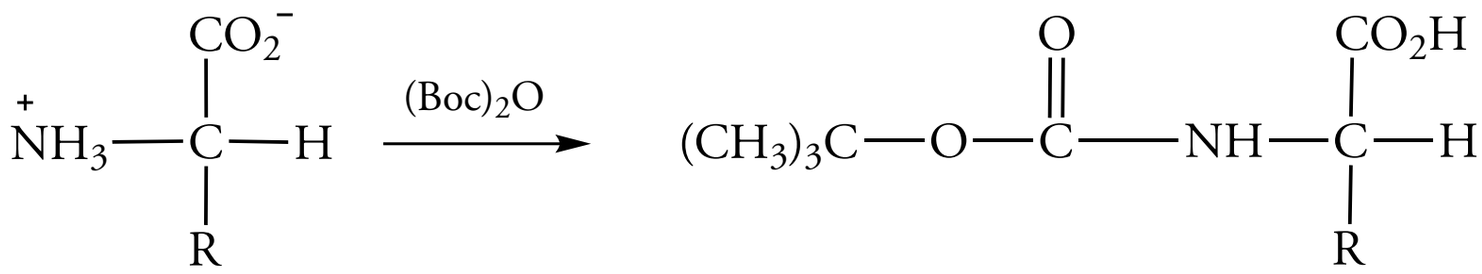


amino acid (or peptide) benzyl ester

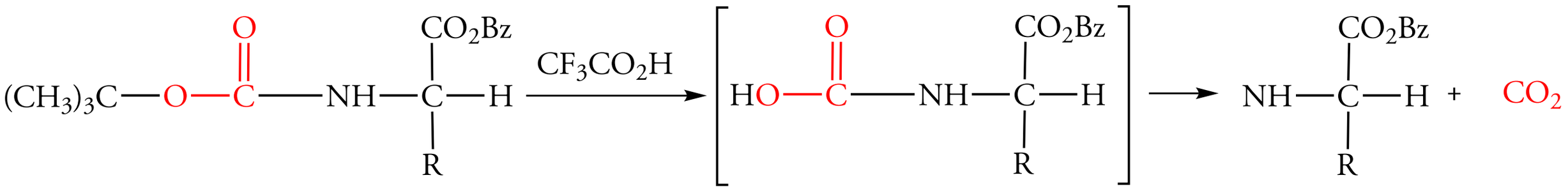
deprotected amino acid (or peptide)

27.8 OVERVIEW OF PEPTIDE SYNTHESIS

Protecting the Amino Group



N-*tert*-butoxycarbonyl amino acid
(a Boc-amino acid)



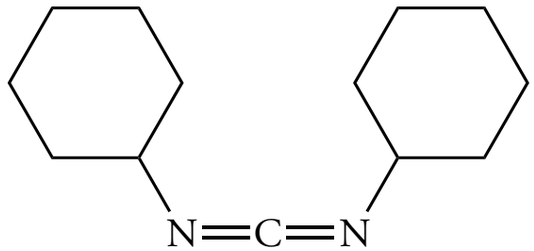
N-*tert*-butoxycarbonyl amino acid
(Boc-amino acid)

unstable carbamate derivative of
an amino acid

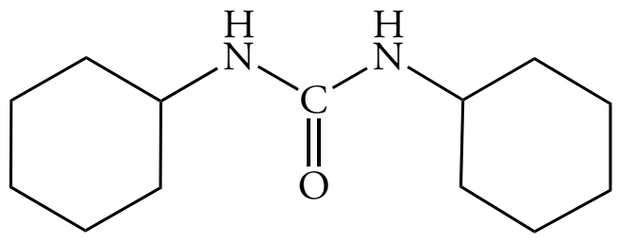
+ $CH_2{=}C(CH_3)_2$

27.8 OVERVIEW OF PEPTIDE SYNTHESIS

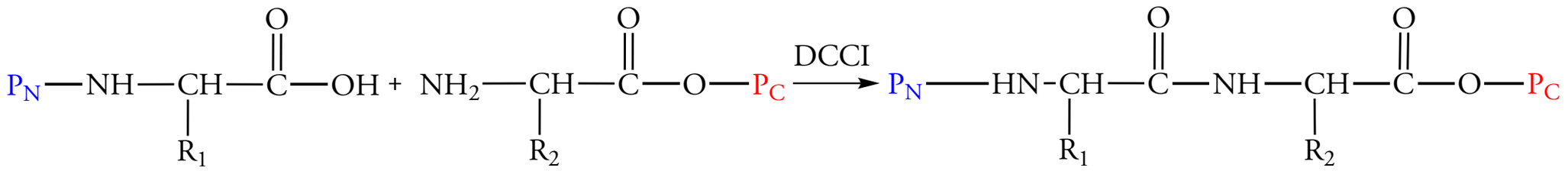
Peptide Bond Synthesis



dicyclohexylcarbodiimide
(DCCI)

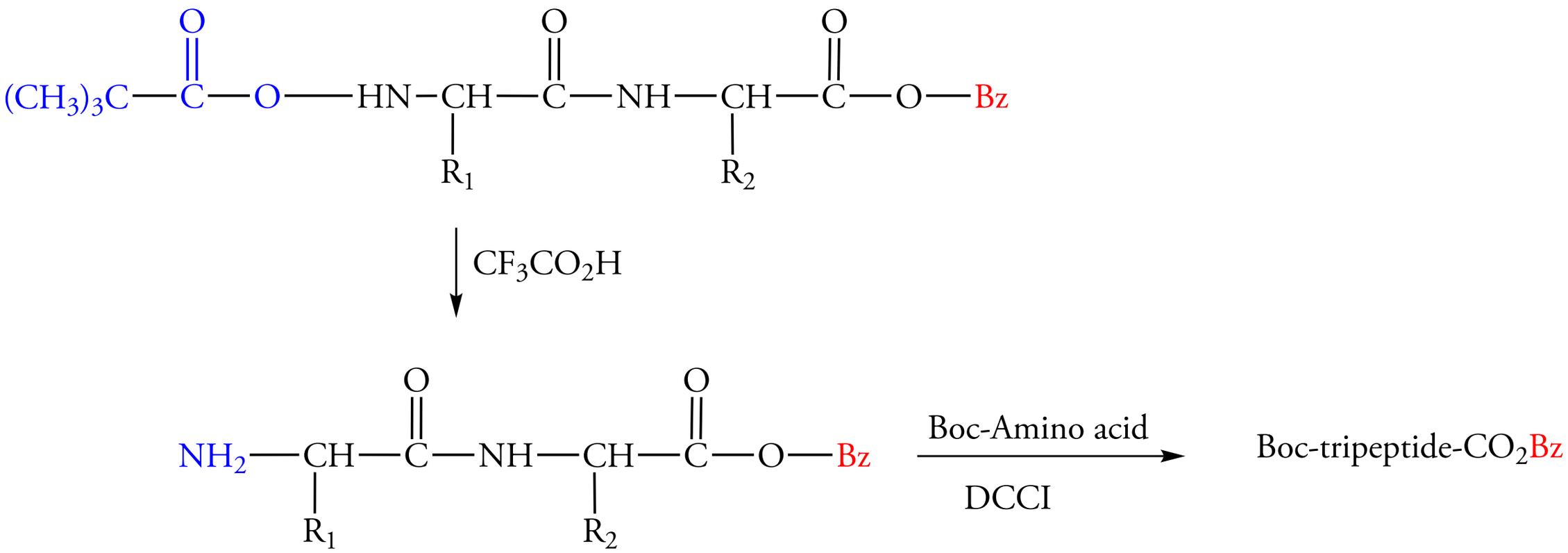


dicyclohexylurea



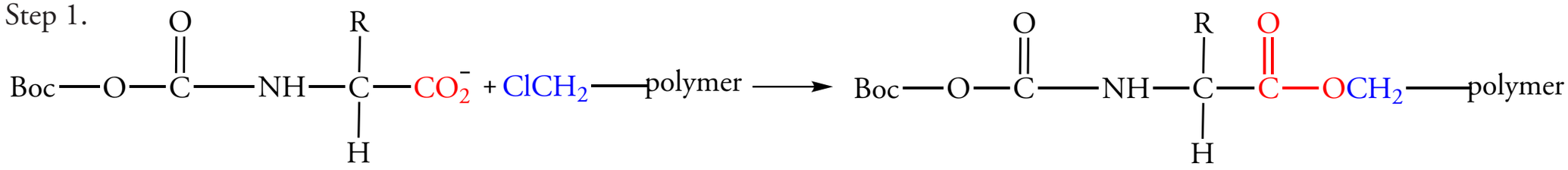
27.8 OVERVIEW OF PEPTIDE SYNTHESIS

Polypeptide Synthesis



27.9 SOLID PHASE PEPTIDE SYNTHESIS

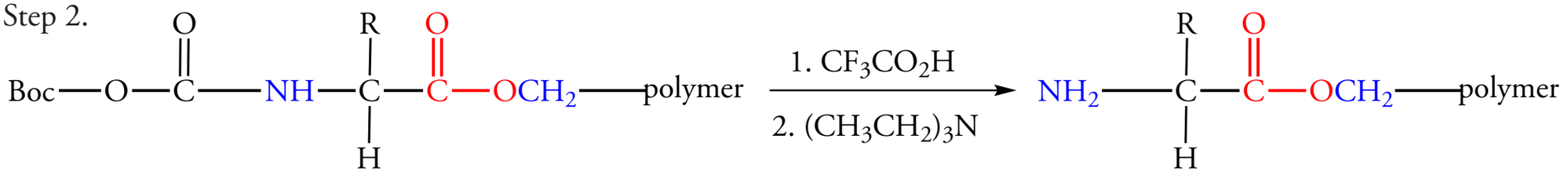
Step 1.



(N-protected Boc-amino acid)

(polymer bound N-protected Boc-amino acid)

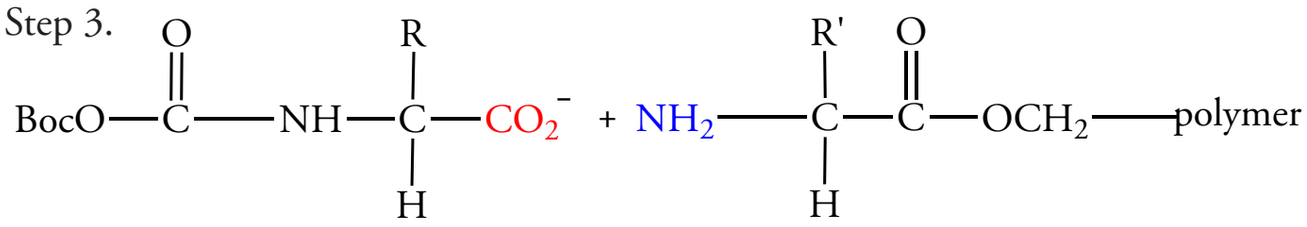
Step 2.



(polymer bound N-protected Boc-amino acid)

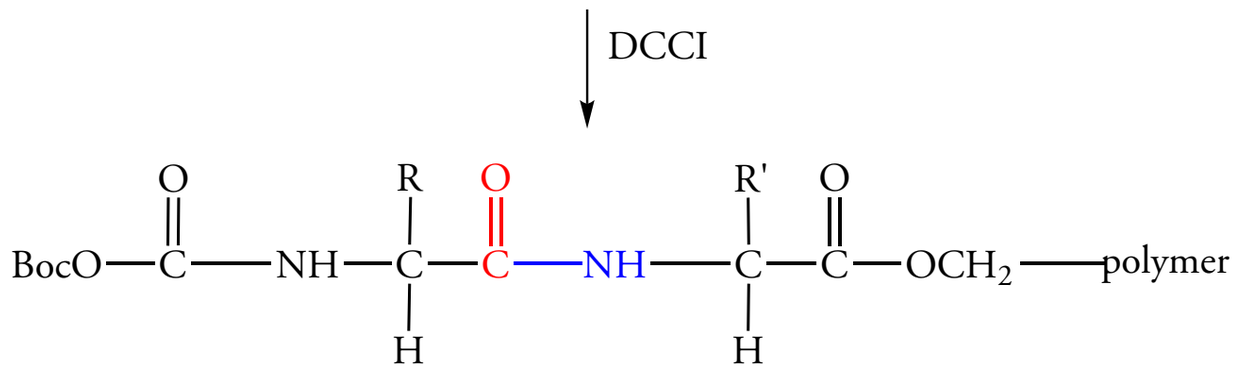
(polymer bound amino acid)

Step 3.



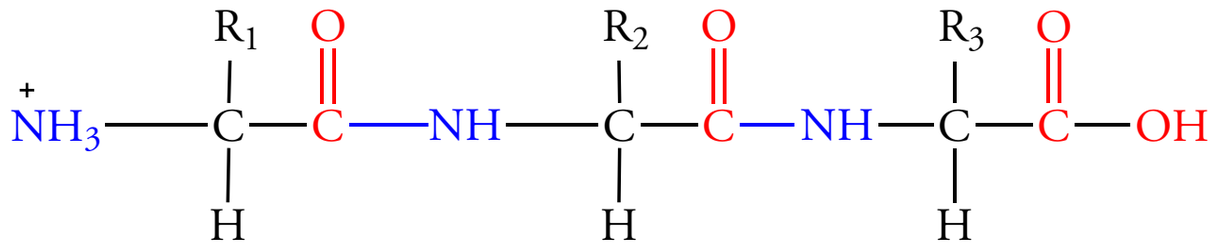
a Boc-amino acid

polymer bound amino acid



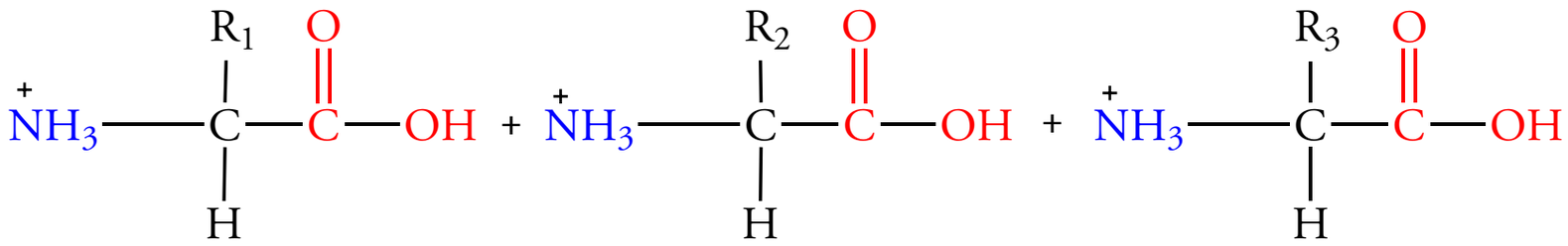
N-protected polymer bound dipeptide

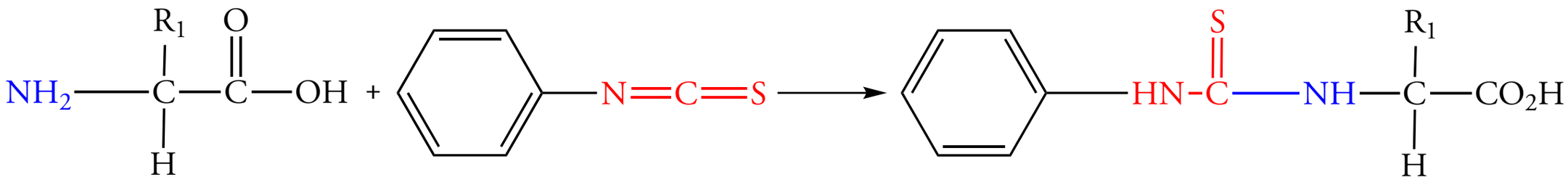
27.10 DETERMINATION OF THE AMINO ACID COMPOSITION OF PROTEINS



tripeptide

6 M HCl



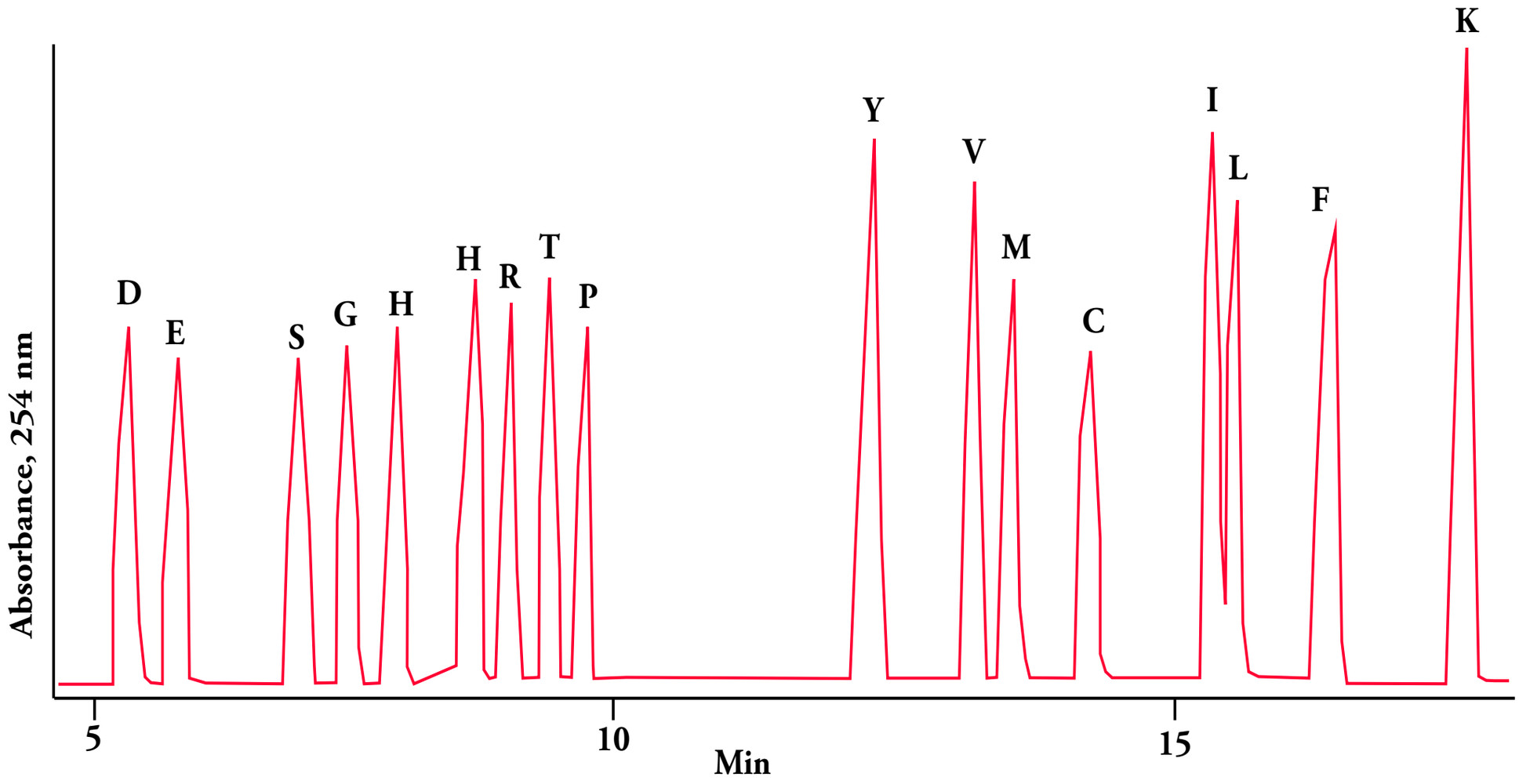


phenylisothiocyanate
(PICT)

phenylisothiocarbamyl amino acid
(PCT amino acid)

27.10 DETERMINATION OF THE AMINO ACID COMPOSITION OF PROTEINS

Figure 27.5 HPLC Separation of PCT Amino Acids



27.10 DETERMINATION OF THE AMINO ACID COMPOSITION OF PROTEINS

Table 27.4
Amino Acid Composition of Human Lysozyme

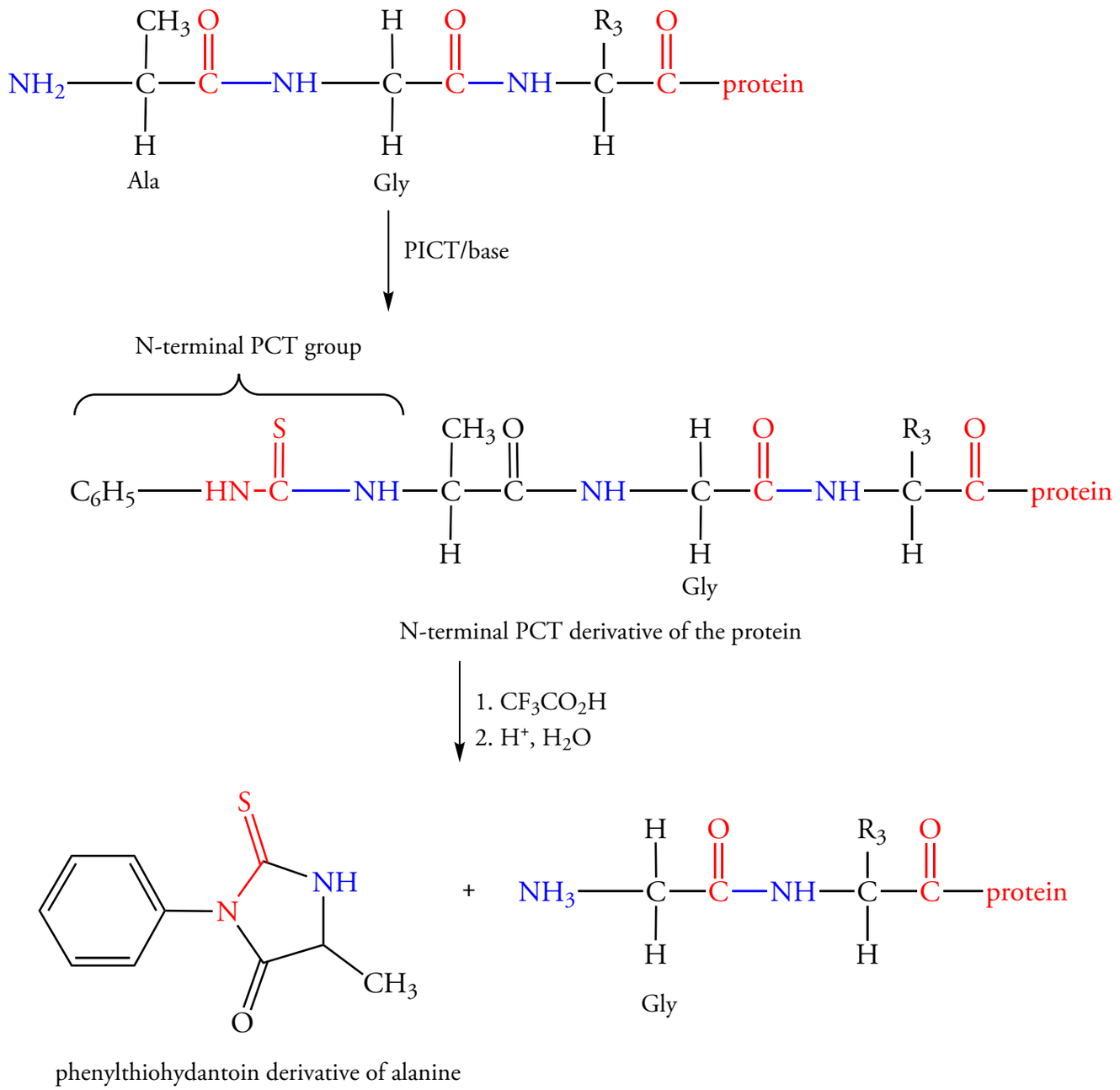
Amino Acid	Number of Amino Acids	Per Cent Composition
Ala	5	4.1
Arg	1	0.8
Asn	4	3.3
Asp	12	9.8
Cys	8	6.5
Gln	7	4.9
Glu	8	6.5
Gly	6	9.8
His	2	11.4
Ile	12	9.8
Leu	14	11.4
Lys	12	9.8
Met	2	1.6
Phe	4	3.3
Pro	2	1.6
Ser	8	6.5
Thr	7	5.7
Trp	3	2.4
Tyr	4	3.3
Val	2	1.6

27.11 DETERMINATION OF THE AMINO ACID SEQUENCE OF PROTEINS

The Edman Degradation

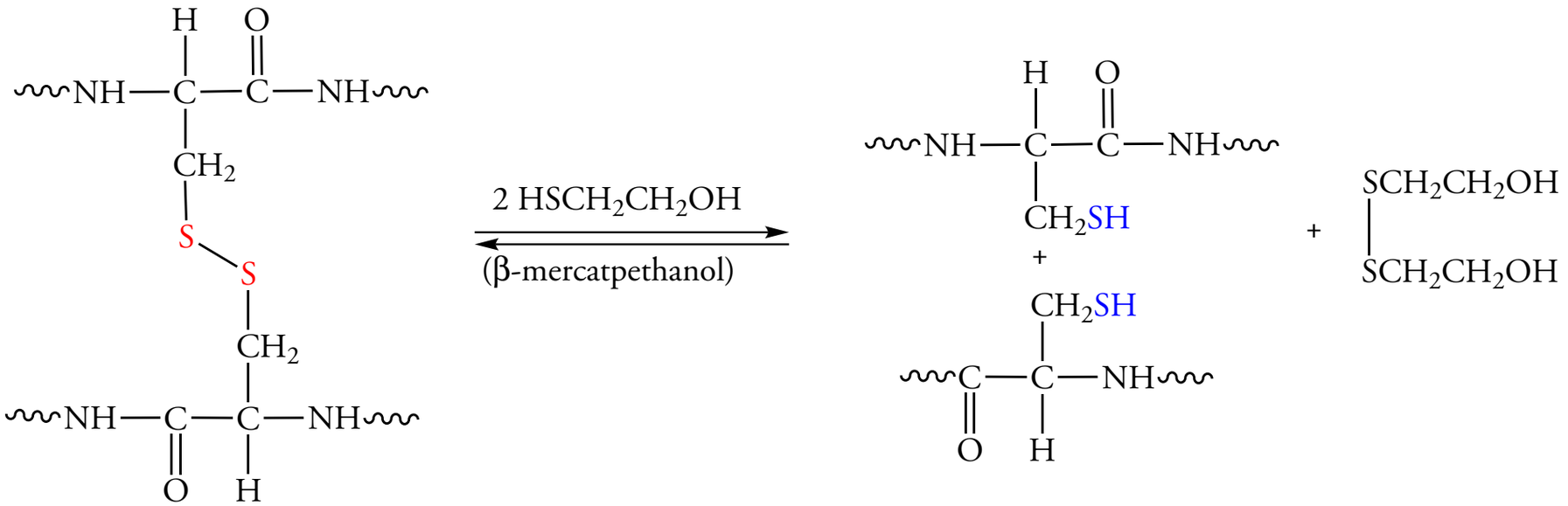
Figure 27.6 Edman Degradation

First, the peptide is converted to its N-terminal PCT derivative by treatment with phenylisothiocyanate. Next, the PCT protein is treated with trifluoroacetic acid, then with water to give the phenylthiohydantoin derivative. The N-terminal amino acid is released in this step. The other peptide bonds are not affected.



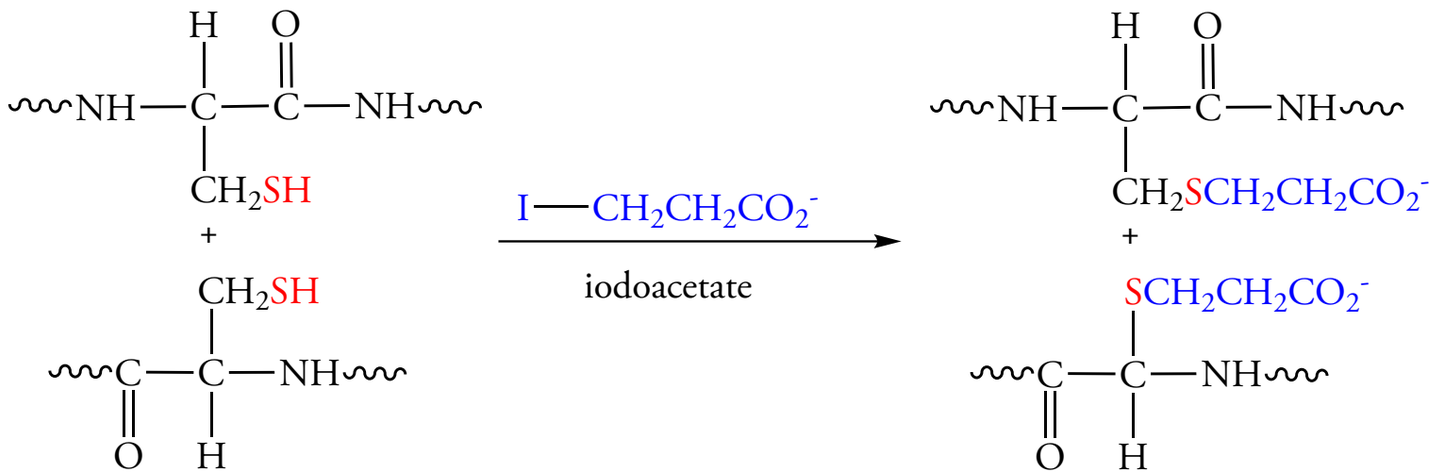
27.11 DETERMINATION OF THE AMINO ACID SEQUENCE OF PROTEINS

Blocking Cystine Residues



cystine residue

2 cysteine residues

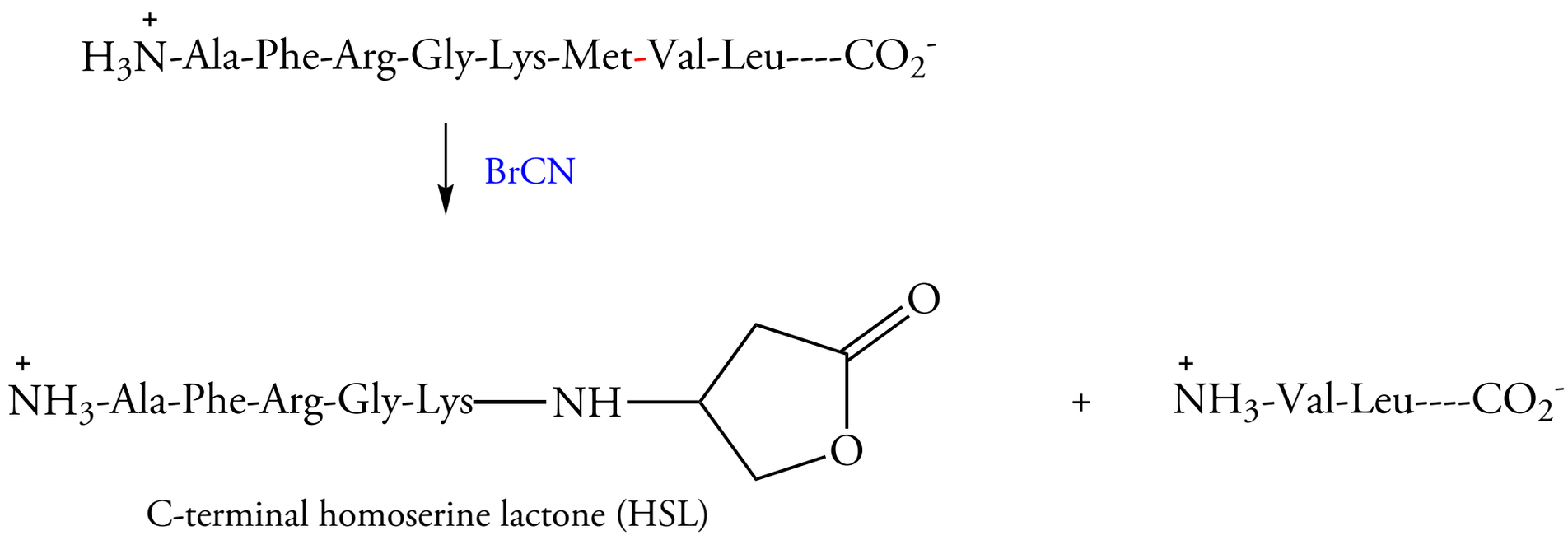


cysteine residues

S-Carboxymethylcysteine residues

27.11 DETERMINATION OF THE AMINO ACID SEQUENCE OF PROTEINS

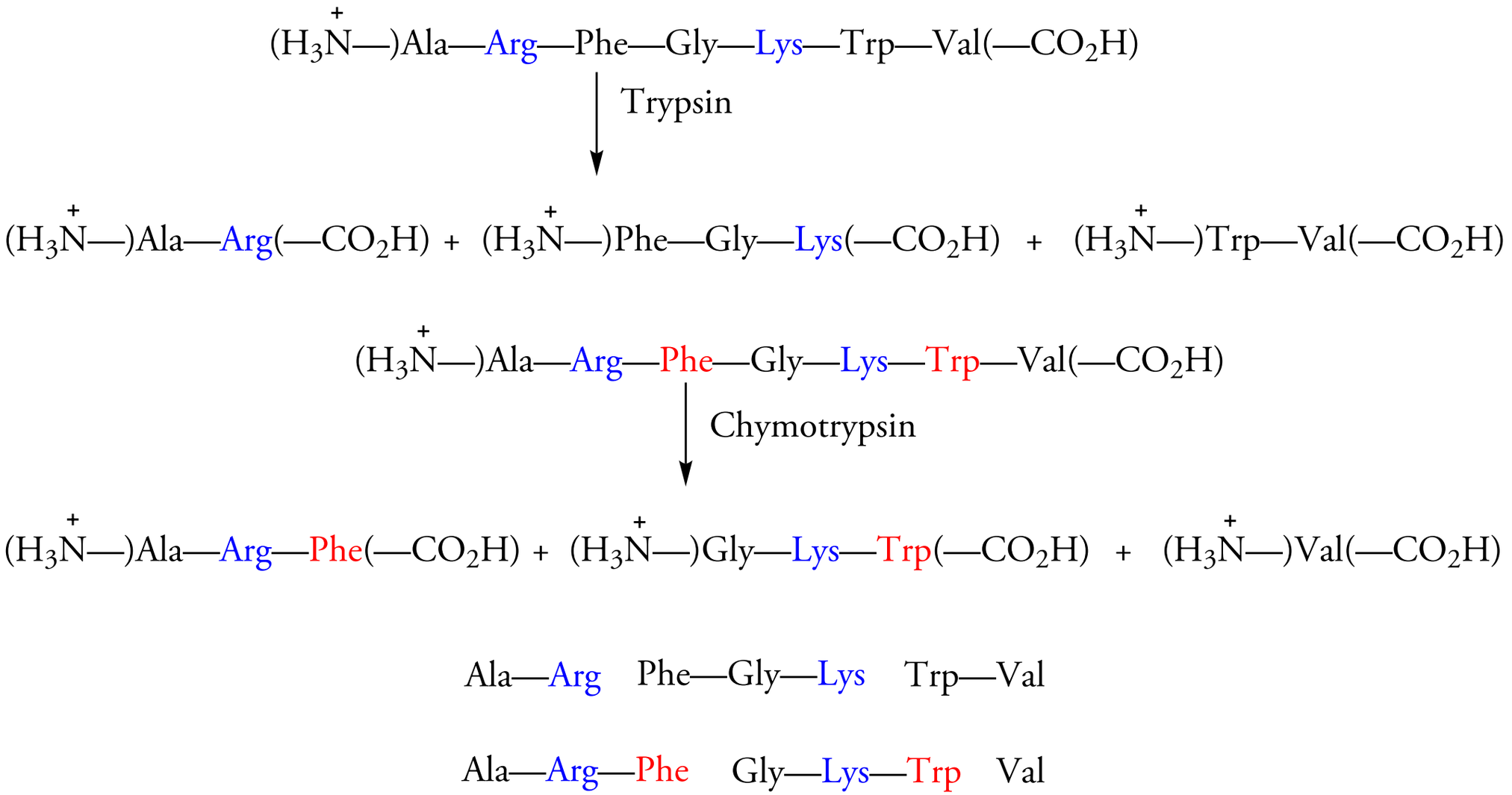
Peptide Cleavage at Methionine Residues



C-terminal homoserine lactone (HSL)

27.11 DETERMINATION OF THE AMINO ACID SEQUENCE OF PROTEINS

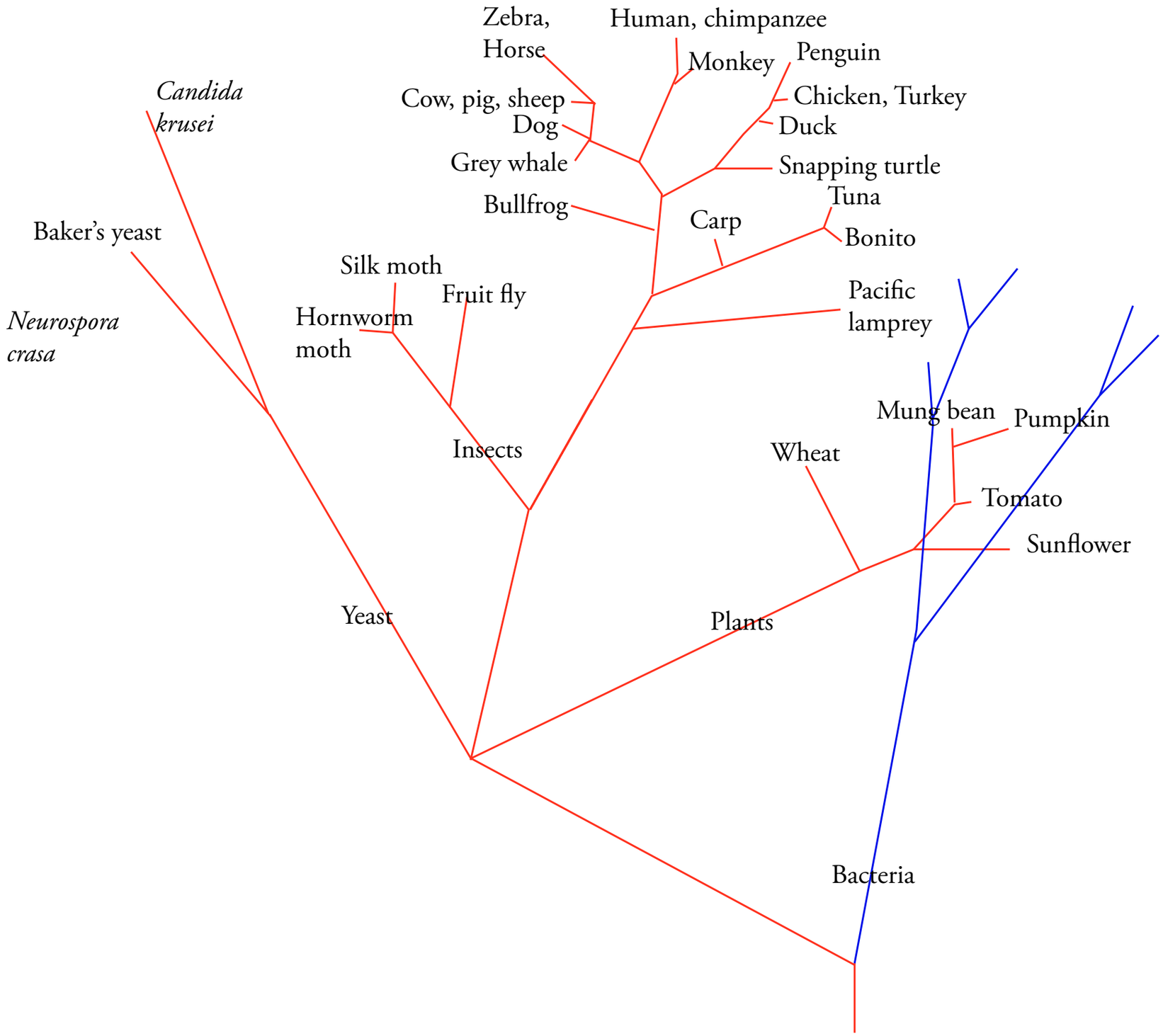
Enzymatic Cleavage of Polypeptide Chains



27.11 DETERMINATION OF THE AMINO ACID SEQUENCE OF PROTEINS

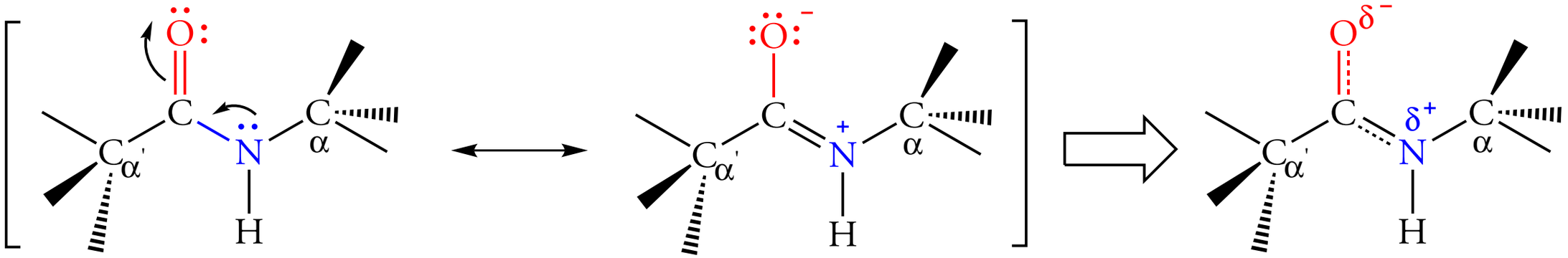
Primary Structures and Evolutionary Relationships

Figure 27.7 Evolutionary Family Tree for Cytcochrome c



27.12 BONDING IN PROTEINS

Structure of the Peptide Bond



contributing structure 1 | contributing structure 2 | resonance hybrid

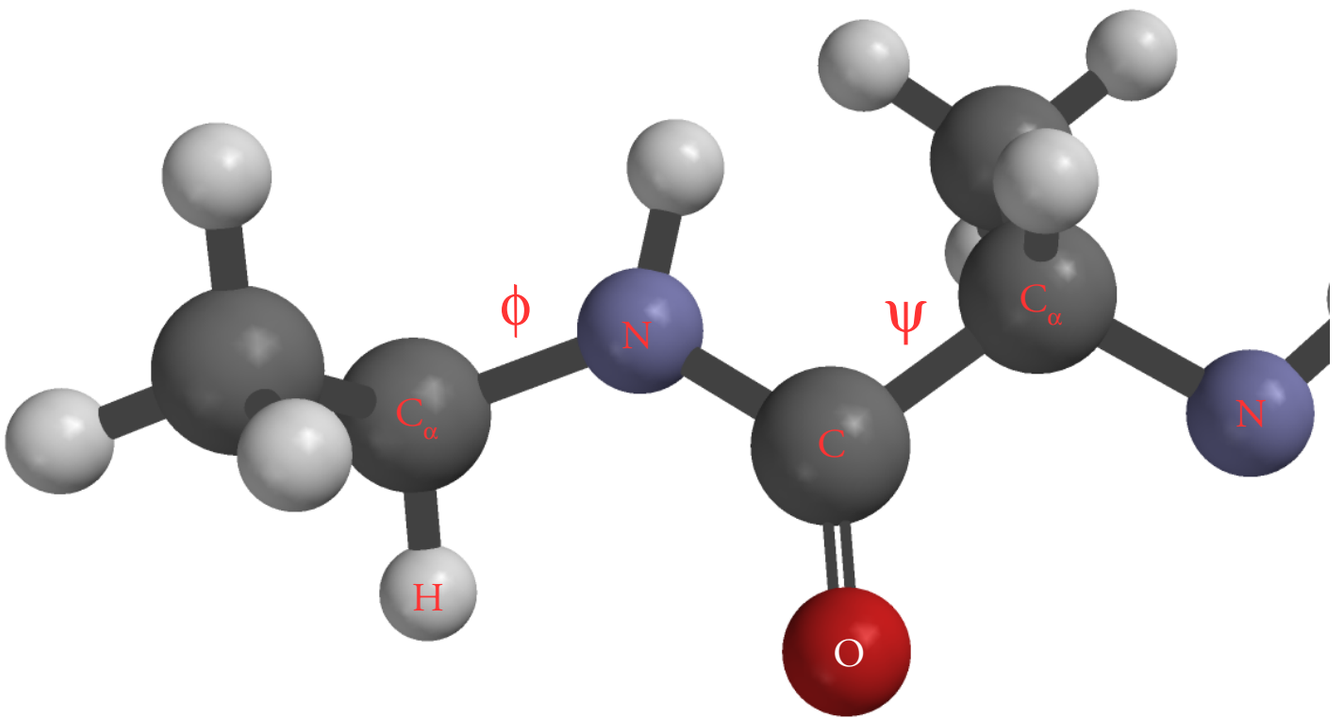
27.12 BONDING IN PROTEINS

Structure of the Peptide Bond

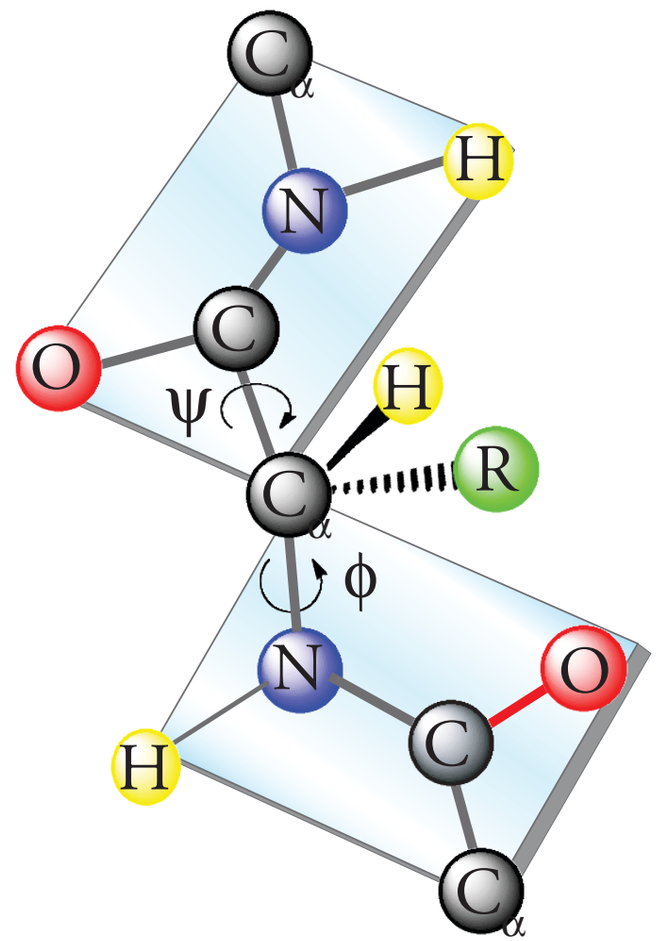
Figure 27.8 Structure of the Peptide Bond

(a) Rotation around the C—N bond, which has 50% double bond character, does not occur at room temperature. However, rotation around the N—C_a bond (ϕ) and the C—C_a bond (ψ) is possible, and many conformations are possible in peptides and proteins.
(b) we can think of the α-carbon as a "hinge" between two planar peptide bonds. If one takes two note cards, and links them with a swivel, it is easy to see that many arrangements are possible. However, some ϕ and ψ are not possible because of steric interference of the side chain R group. Glycine, for example, can assume many more conformations than amino acids like proline and tryptophan.

(a)



(b)

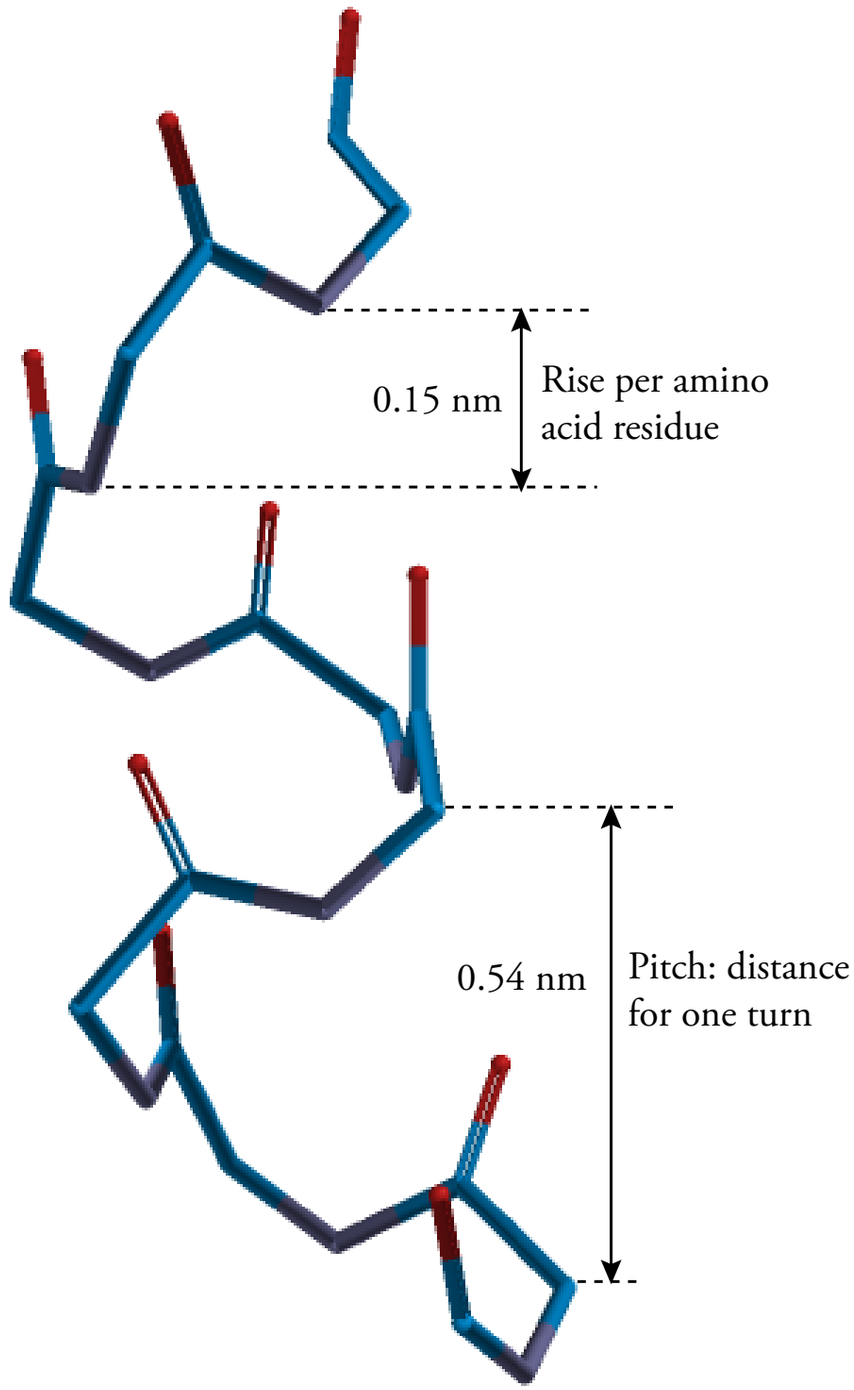


27.12 BONDING IN PROTEINS

The α-Helix

Figure 27.8 Dimensions of an α-Helix

The distance between amino acid residues in an α-helix is 0.15 nm. The distance required for one turn of the helix, its pitch, is 5.4 nm.

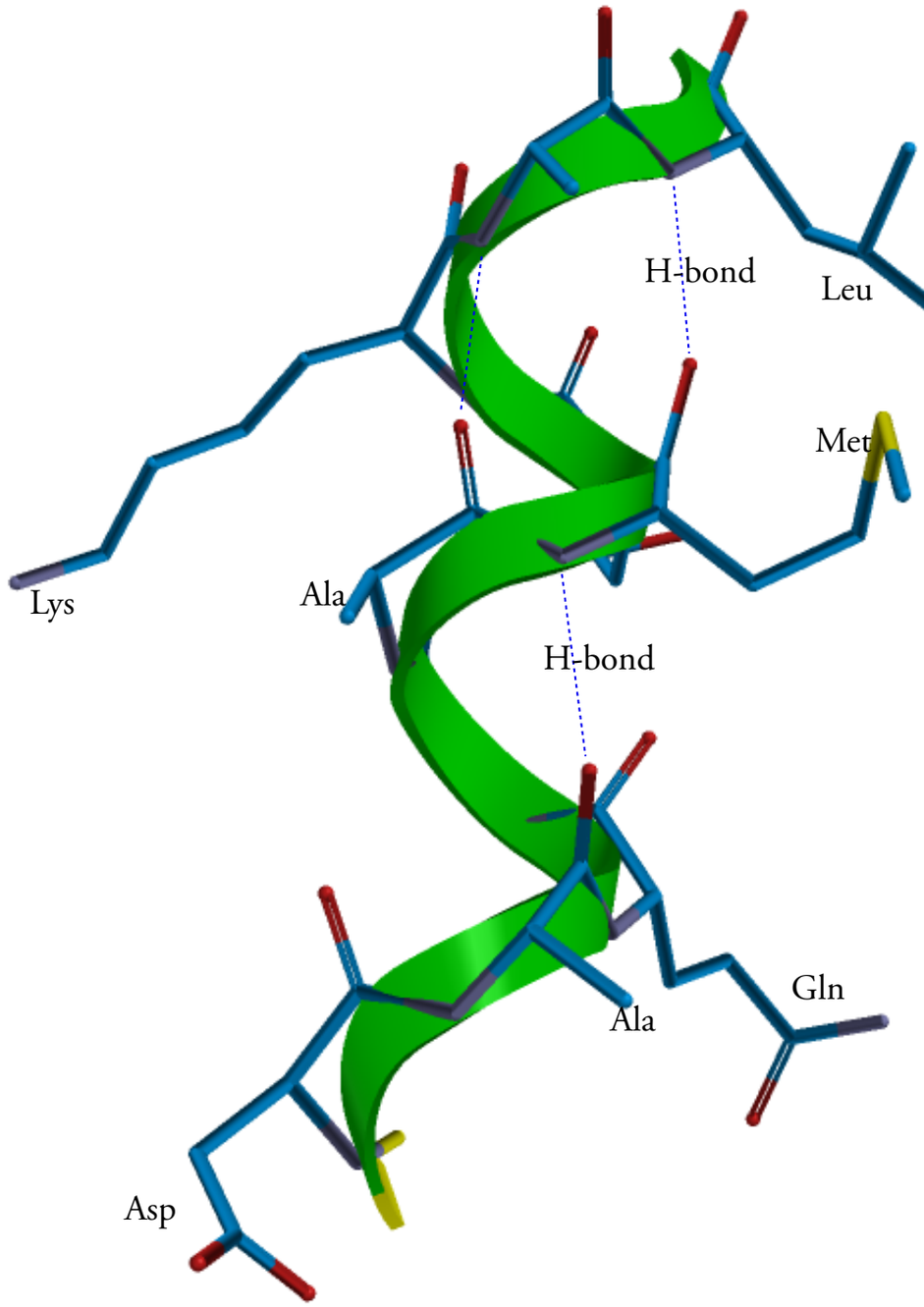


27.12 BONDING IN PROTEINS

The α-Helix

Figure 27.9 Ribbon Diagram of an α-Helix

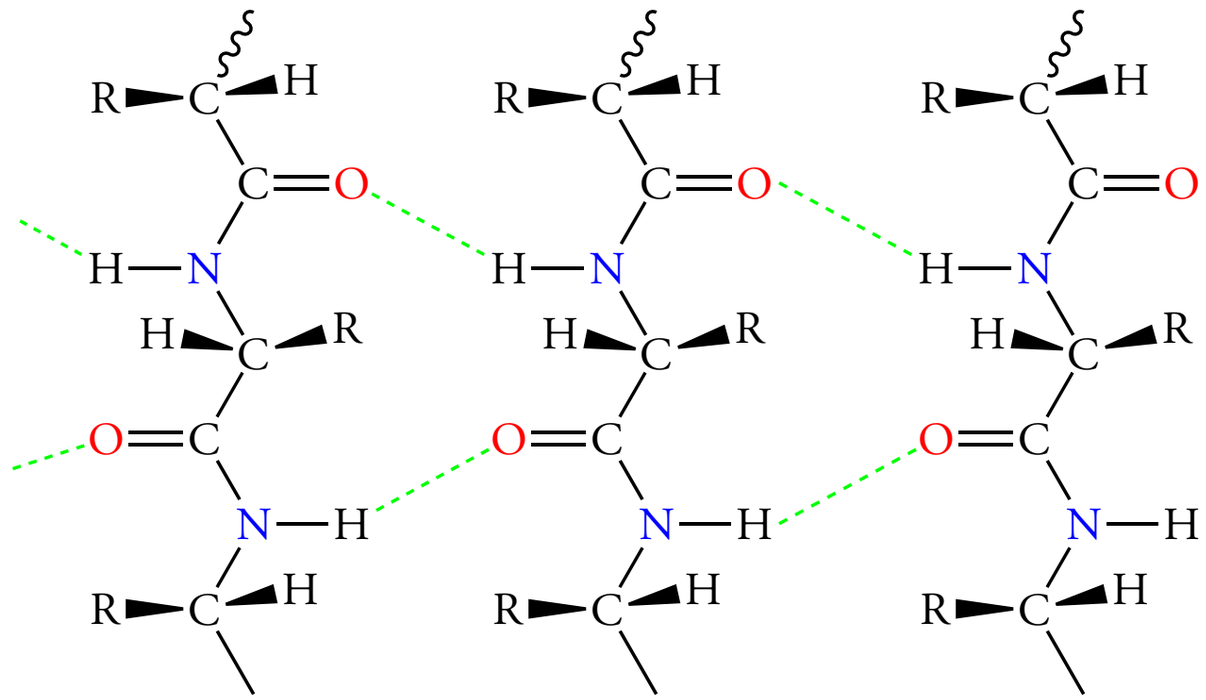
Hydrogen bonds in an α-helix are approximately parallel to long axis of the helix. They from between carbonyl oxygen and amide hydrogens separated by 3.6 residues. Side chains radiate outward from the helix. The α-helix is right-handed.



27.12 BONDING IN PROTEINS

β-Pleated Sheets

Figure 27.10 Hydrogen Bonding In Parallel β-Pleated Sheet



27.12 BONDING IN PROTEINS

Disulfide Bonds

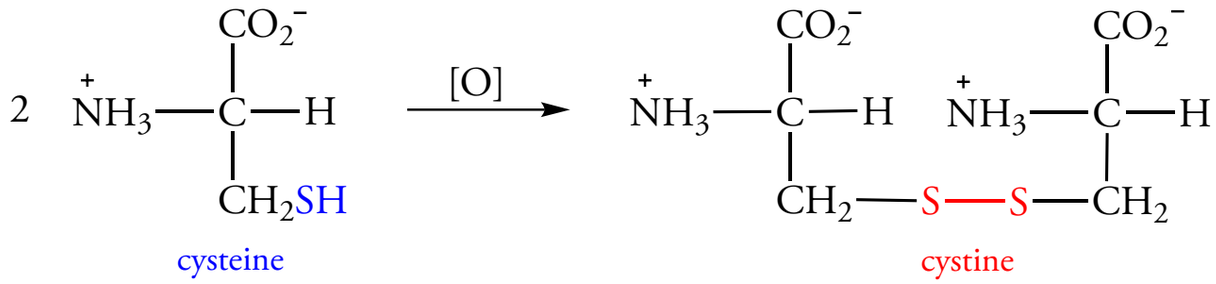
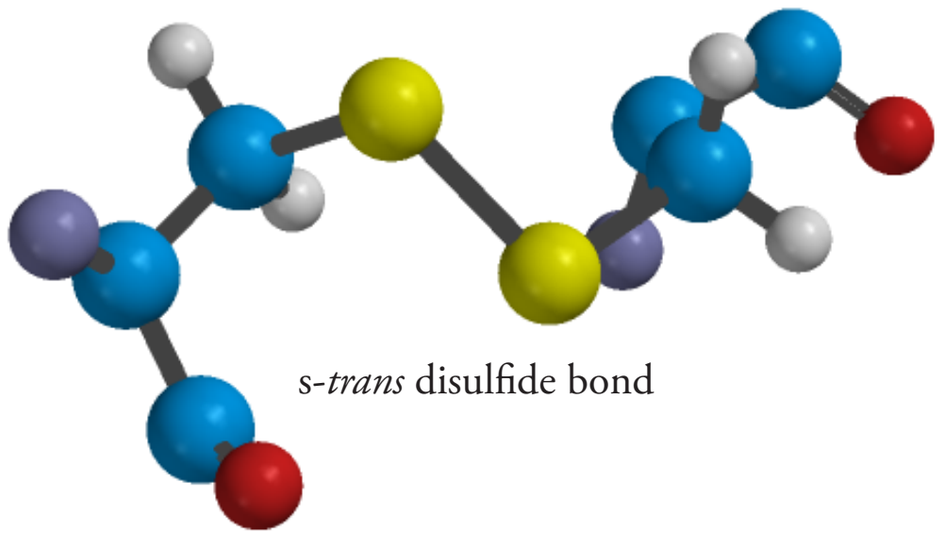


Figure 27.12 Conformation of an s-trans Disulfide Bond



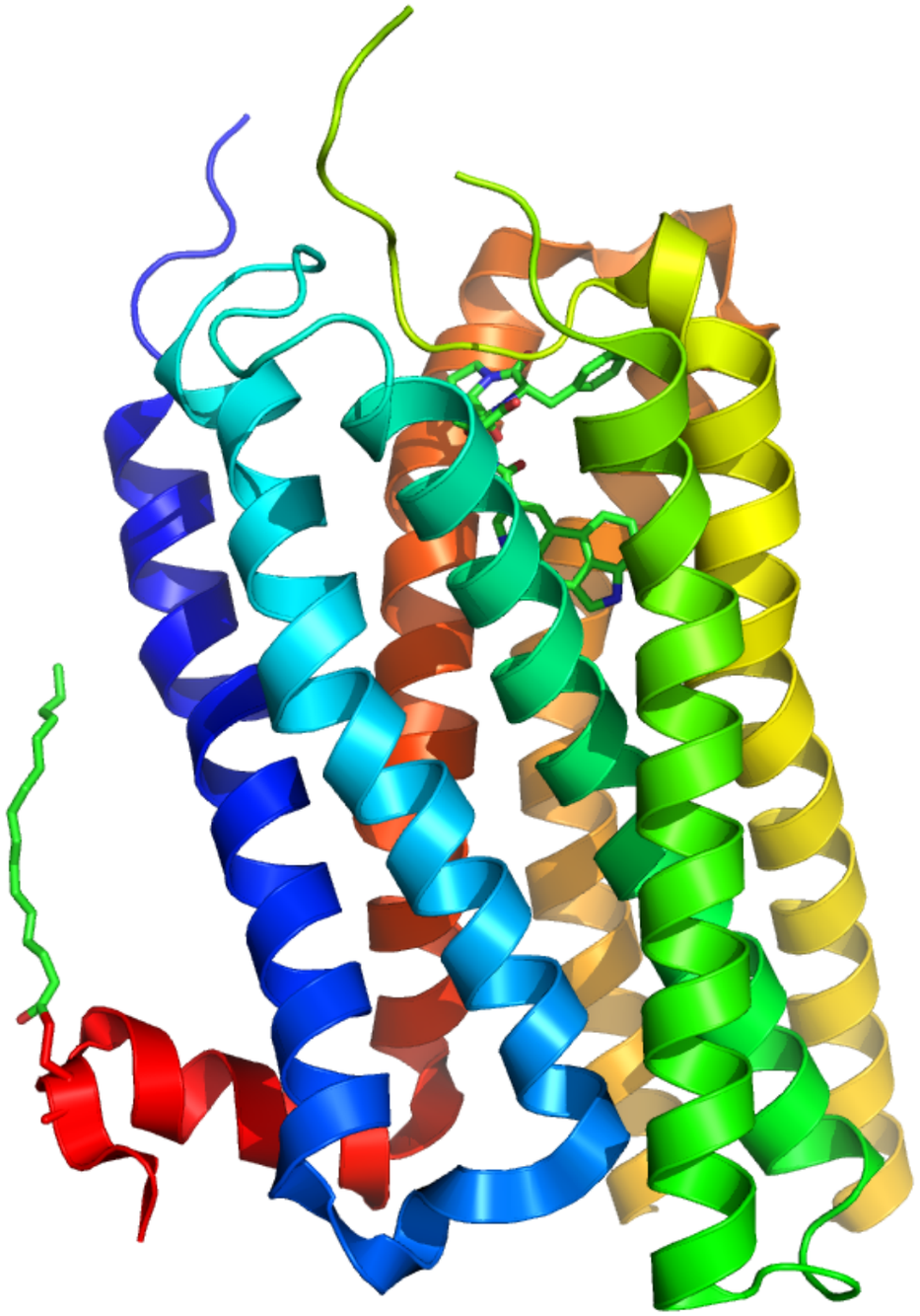
s-*trans* disulfide bond

Table 27.5
Examples of Proteins Having Quatenary Structure

Protein	Molecular Weight	Number of Subunits	Function
alcohol dehydrogenase	80,000	4	enzymatic reaction in fermentation
aldolase	150,000	4	enzymatic reaction in glycolysis
fumarase	194,000	4	enzymatic reaction in citric acid cycle
hemoglobin	65,000	4	oxygen transport in blood
insulin	11,500	2	hormone that regulates metabolism of glucose

27.13 PROTEIN STRUCTURE

Figure 27.13 Ribbon Diagram of the Membrane Region of the Serotonin Receptor
The seven helix region of the serotonin receptor is the site of serotonin binding. The serotonin receptor is a member of the G-coupled receptor protein family. These proteins have similar structures. Their different specificities depend upon differences in primary structure at the ligand bindings site.



27.13 PROTEIN STRUCTURE

Figure 27.14 Structure of 1GB1

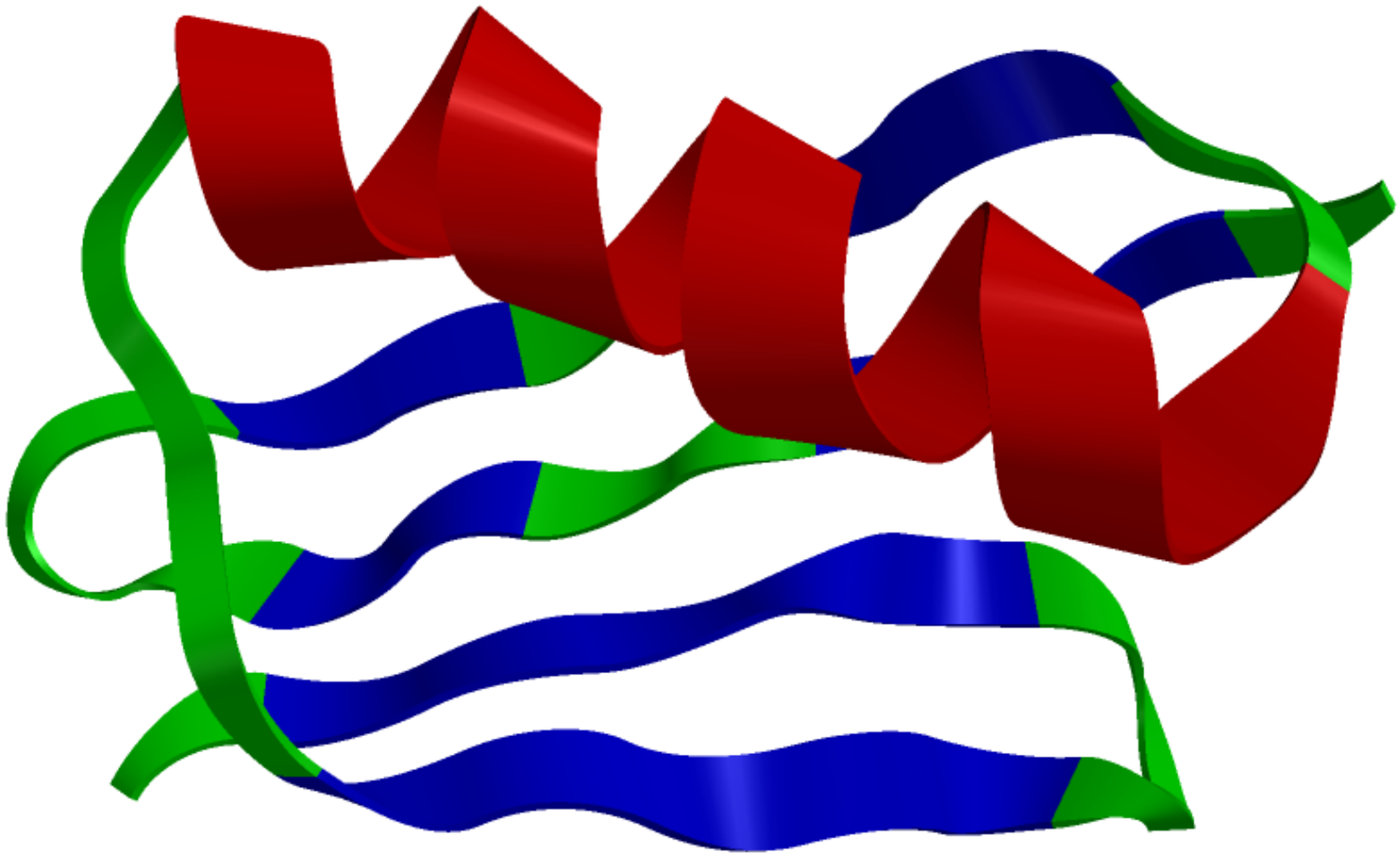


Figure 27.15 Parallel b Strands and an α-Helix in a β-α-β Arrangement

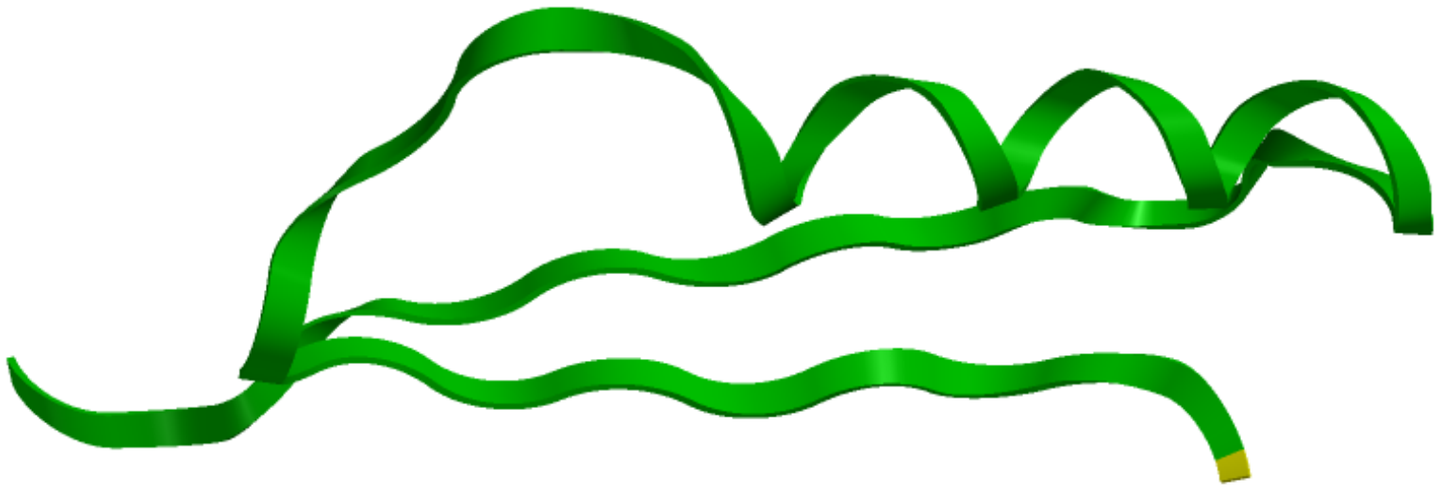
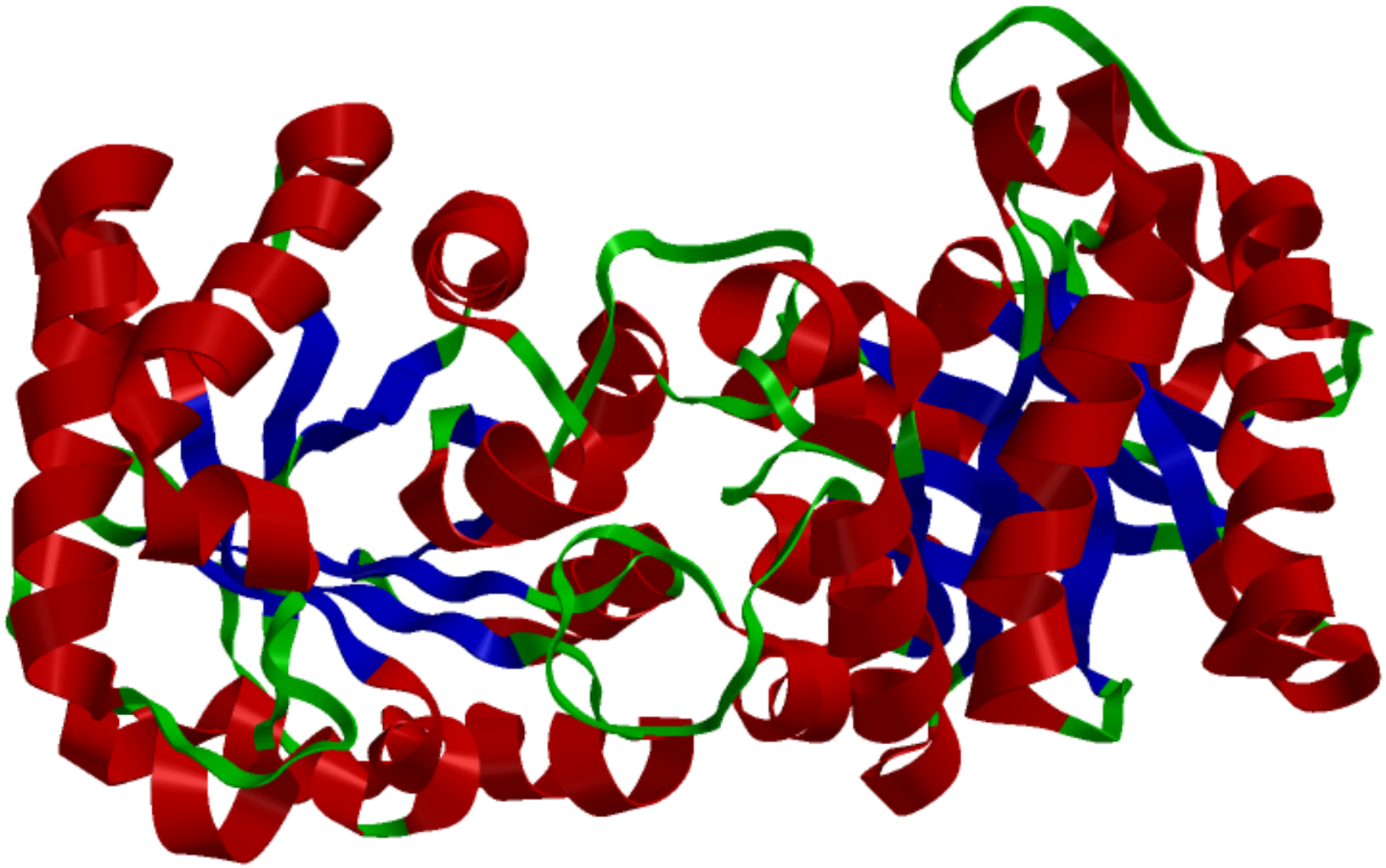


Figure 27.16 Tertiary Structure of Triose Phosphate Isomerase

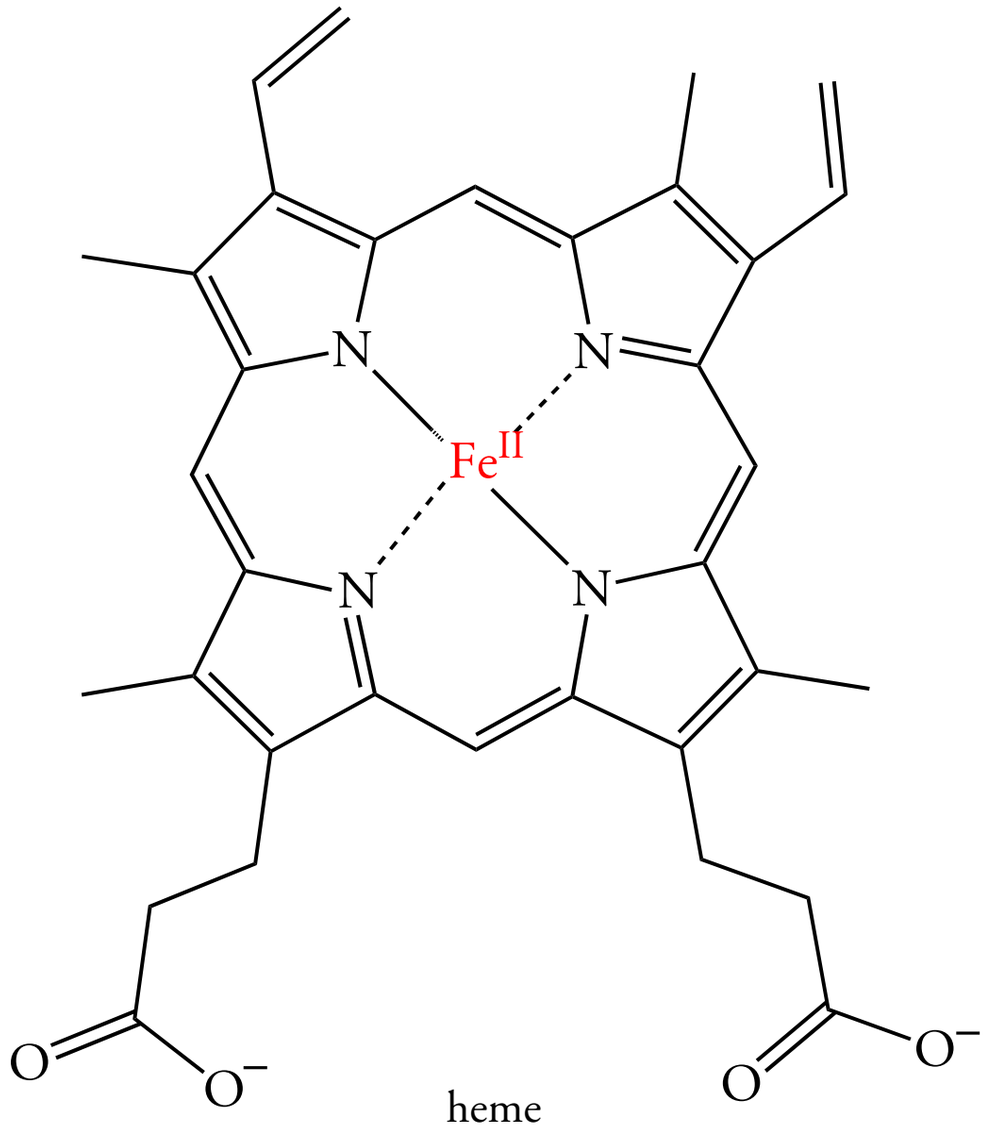
The α-helices are shown in red, β-pleated sheets are blue, and less structured "loops" are shown in green.



27.14 OXYGEN STORAGE AND TRANSPORT: MYOGLOBIN AND HEMOGLOBIN

Myoglobin

Figure 27.18 Heme



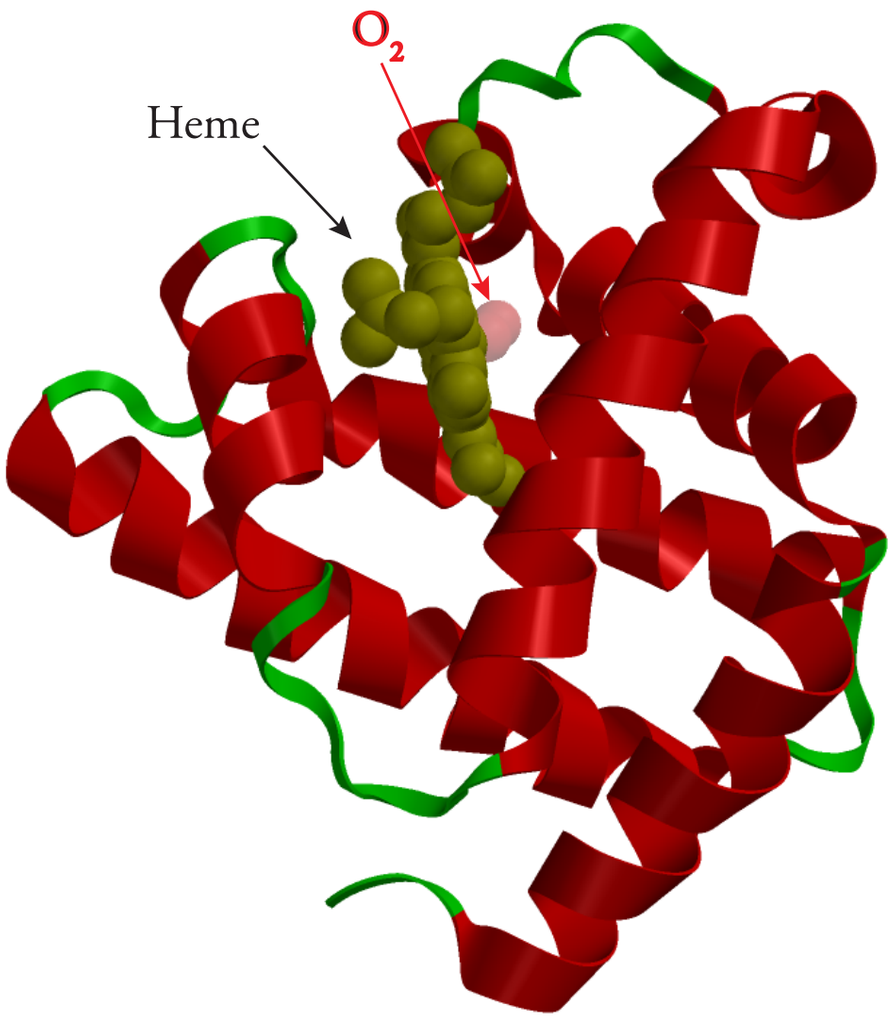
heme

27.14 OXYGEN STORAGE AND TRANSPORT: MYOGLOBIN AND HEMOGLOBIN

Myoglobin

Figure 27.17 Structure of Oxymyoglobin.
(a) The α-helices are shown in red, and less structured "loops" are shown in green. (b) Structure of the heme group bound to myoglobin via a bond from a nitrogen on histidine 93 and the Fe^{II} ion. Oxygen binds on the opposite side of the histidine.

(a)



(b)

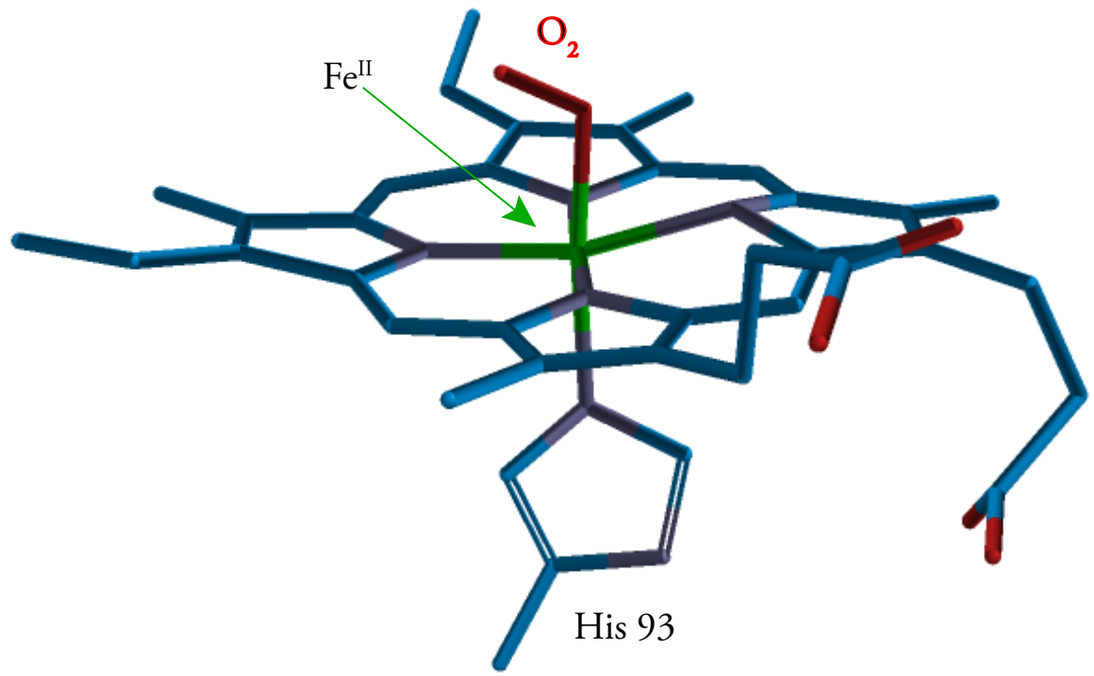
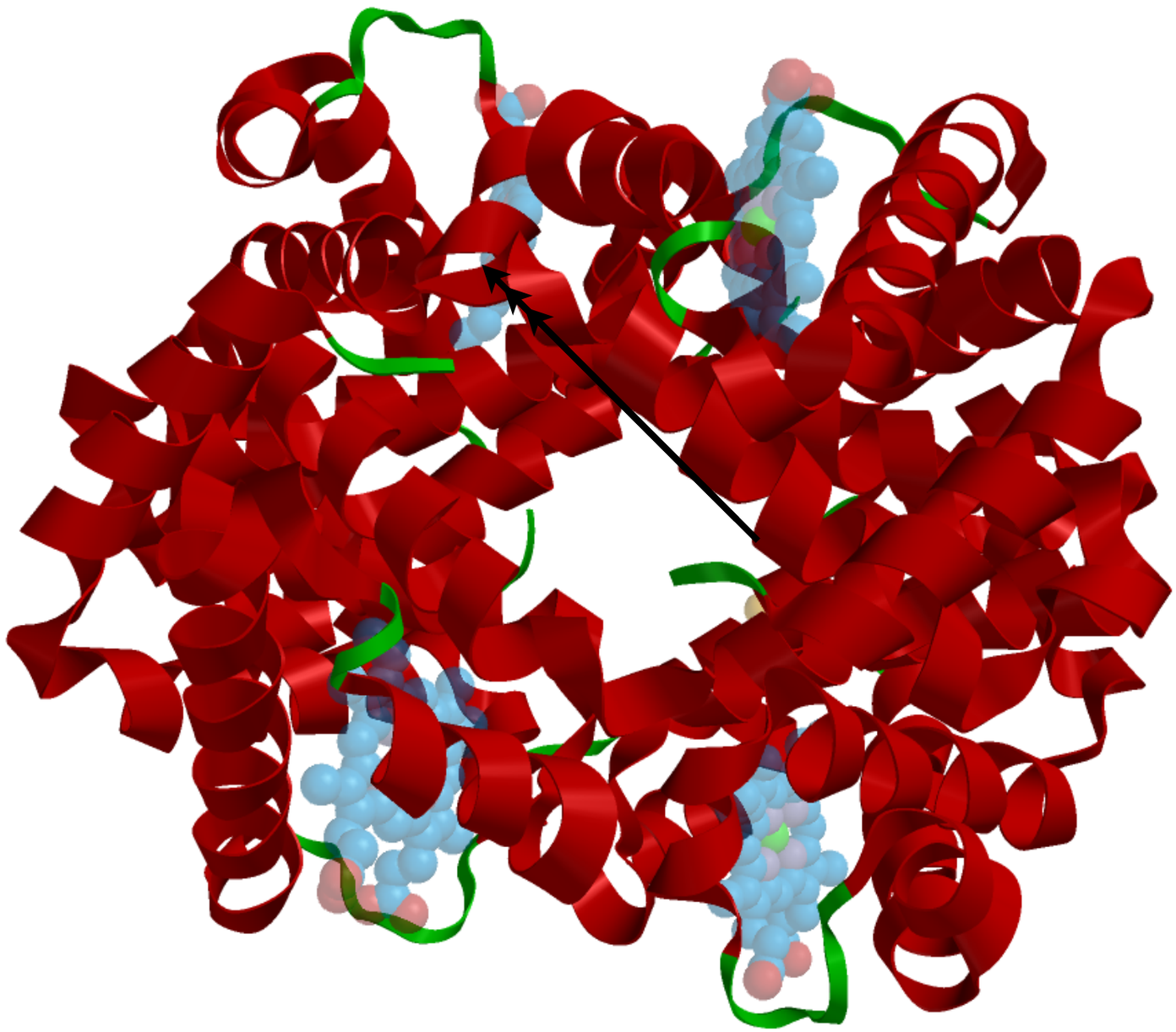


Figure 27.19 Structure of Deoxyhemoglobin.
The α and β subunits of hemoglobin interact cooperatively, and when one heme binds O_2, the each of the others rapidly bind O_2.



27.14 OXYGEN STORAGE AND TRANSPORT: MYOGLOBIN AND HEMOGLOBIN

Sickle Cell Hemoglobin

	1	2	3	4	5	6	7	8
Hemoglobin A	Val-	His-	Leu-	Thr-	Pro-	Glu-	Glu-	Lys-
Hemoglobin S	Val-	His-	Leu-	Thr-	Pro-	Val-	Glu-	Lys-

27.14 OXYGEN STORAGE AND TRANSPORT: MYOGLOBIN AND HEMOGLOBIN

Sickle Cell Hemoglobin

Figure 27.20 Structure of Deoxyhemoglobin Dimer.

The β subunits of hemoglobin interact by van der Waals contact between the isopropyl side chains at residue 6 of sickle cell hemoglobin (HbS). Since each HbS has two β subunits on opposite sides of the tetramer, a fibrous polymer forms. HbS polymerizes when HbS releases O_2, which disorts the red blood cells into the shape of a sickle.