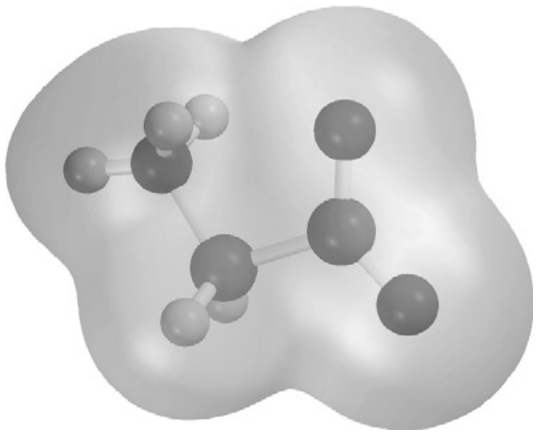
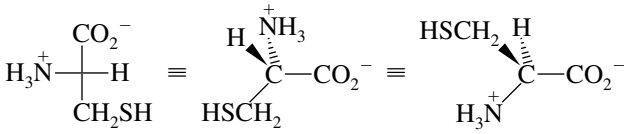


CHAPTER 27

AMINO ACIDS, PEPTIDES, AND PROTEINS. NUCLEIC ACIDS

SOLUTIONS TO TEXT PROBLEMS

27.1 (*b*) L-Cysteine is the only amino acid in Table 27.1 that has the *R* configuration at its stereogenic center.

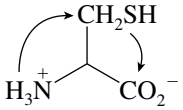


L-Cysteine

The order of decreasing sequence rule precedence is

$$H_3\overset{+}{N}— > HSCH_2— > —CO_2^- > H—$$

When the molecule is oriented so that the lowest ranked substituent (H) is held away from us, the order of decreasing precedence traces a clockwise path.



Clockwise; therefore *R*

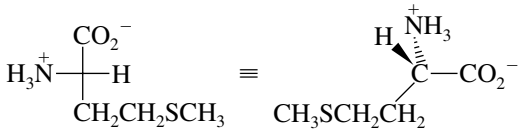
The reason why L-cysteine has the *R* configuration while all the other L-amino acids have the *S* configuration lies in the fact that the $—CH_2SH$ substituent is the only side chain that outranks $—CO_2^-$ according to the sequence rule. Remember, rank order is determined by

atomic number at the first point of difference, and —C—S outranks —C—O. In all the other amino acids $—CO_2^-$ outranks the substituent at the stereogenic center. The reversal in the Cahn–Ingold–Prelog descriptor comes not from any change in the spatial arrangement of substituents at the stereogenic center but rather from a reversal in the relative ranks of the carboxylate group and the side chain.

(*c*) The order of decreasing sequence rule precedence in L-methionine is

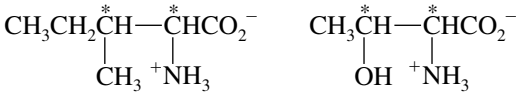
$$H_3\overset{+}{N}— > —CO_2^- > —CH_2CH_2SCH_3 > H—$$

Sulfur is one atom further removed from the stereogenic center, and so C—O outranks C—C—S.



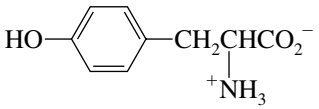
The absolute configuration is *S*.

27.2 The amino acids in Table 27.1 that have more than one stereogenic center are isoleucine and threonine. The stereogenic centers are marked with an asterisk in the structural formulas shown.

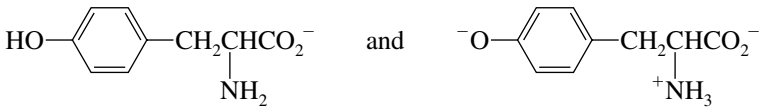


Isoleucine Threonine

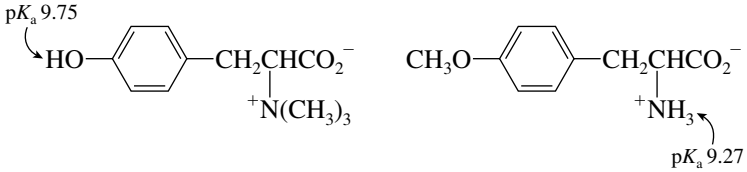
27.3 (*b*) The zwitterionic form of tyrosine is the one shown in Table 27.1.



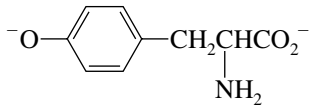
(*c*) As base is added to the zwitterion, a proton is removed from either of two positions, the ammonium group or the phenolic hydroxyl. The acidities of the two sites are so close that it is not possible to predict with certainty which one is deprotonated preferentially. Thus two structures are plausible for the monoanion:



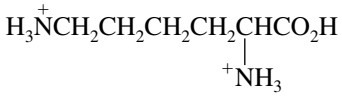
In fact, the proton on nitrogen is slightly more acidic than the phenolic hydroxyl, as measured by the pK_a values of the following model compounds:



(*d*) On further treatment with base, both the monoanions in part (*c*) yield the same dianion.



27.4 At pH 1 the carboxylate oxygen and both nitrogens of lysine are protonated.

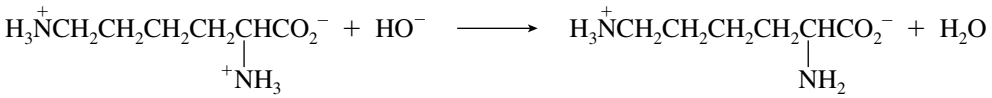


(Principal form at pH 1)

As the pH is raised, the carboxyl proton is removed first.

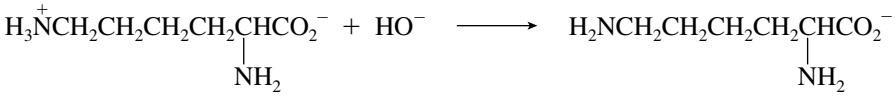
The pK_a value for the first ionization of lysine is 2.18 (from Table 27.3), and so this process is virtually complete when the pH is greater than this value.

The second pK_a value for lysine is 8.95. This is a fairly typical value for the second pK_a of amino acids and likely corresponds to proton removal from the nitrogen on the α carbon. The species that results is the predominant one at pH 9.



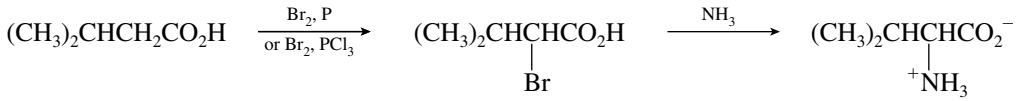
(Principal form at pH 9)

The pK_a value for the third ionization of lysine is 10.53. This value is fairly high compared with those of most of the amino acids in Tables 27.1 to 27.3 and suggests that this proton is removed from the nitrogen of the side chain. The species that results is the major species present at pH values greater than 10.53.



(Principal form at pH 13)

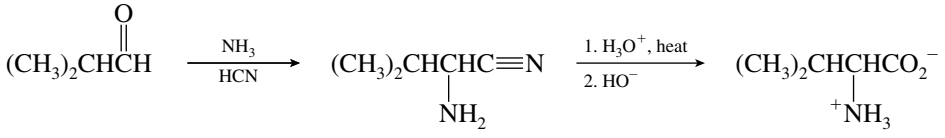
27.5 To convert 3-methylbutanoic acid to valine, a leaving group must be introduced at the α carbon prior to displacement by ammonia. This is best accomplished by bromination under the conditions of the Hell–Volhard–Zelinsky reaction.



3-Methylbutanoic acid | 2-Bromo-3-methylbutanoic acid | Valine

Valine has been prepared by this method. The Hell–Volhard–Zelinsky reaction was carried out in 88% yield, but reaction of the α-bromo acid with ammonia was not very efficient, valine being isolated in only 48% yield in this step.

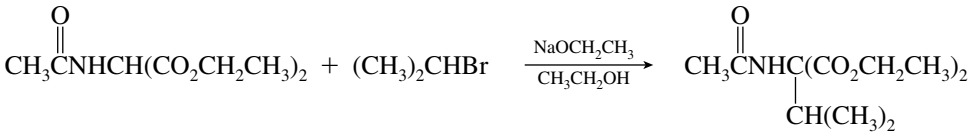
27.6 In the Strecker synthesis an aldehyde is treated with ammonia and a source of cyanide ion. The resulting amino nitrile is hydrolyzed to an amino acid.



2-Methylpropanal — 2-Amino-3-methylbutanenitrile — Valine

As actually carried out, the aldehyde was converted to the amino nitrile by treatment with an aqueous solution containing ammonium chloride and potassium cyanide. Hydrolysis was achieved in aqueous hydrochloric acid and gave valine as its hydrochloride salt in 65% overall yield.

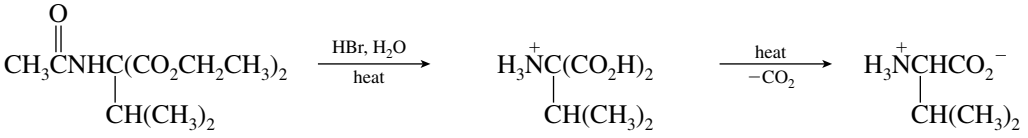
27.7 The alkyl halide with which the anion of diethyl acetamidomalonate is treated is 2-bromopropane.



Diethyl acetamidomalonate — 2-Bromopropane — Diethyl acetamidoisopropylmalonate

This is the difficult step in the synthesis; it requires a nucleophilic substitution of the S_N2 type involving a secondary alkyl halide. Competition of elimination with substitution results in only a 37% observed yield of alkylated diethyl acetamidomalonate.

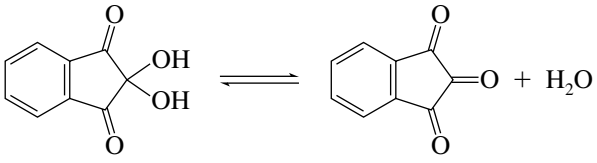
Hydrolysis and decarboxylation of the alkylated derivative are straightforward and proceed in 85% yield to give valine.



Diethyl acetamidoisopropylmalonate — 2-Aminoisopropylmalonic acid — Valine

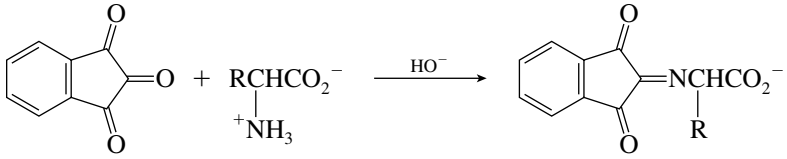
The overall yield of valine (31%) is the product of 37% × 85%.

27.8 Ninhydrin is the hydrate of a triketone and is in equilibrium with it.



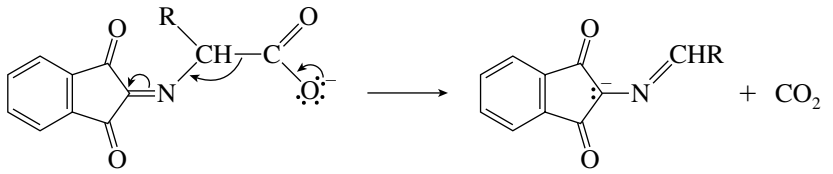
Hydrated form of ninhydrin — Triketo form of ninhydrin

An amino acid reacts with this triketone to form an imine.

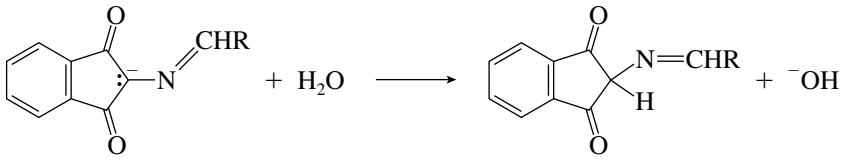


Triketo form of ninhydrin — α-Amino acid — Imine

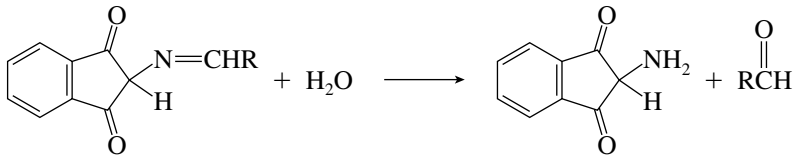
This imine then undergoes decarboxylation.



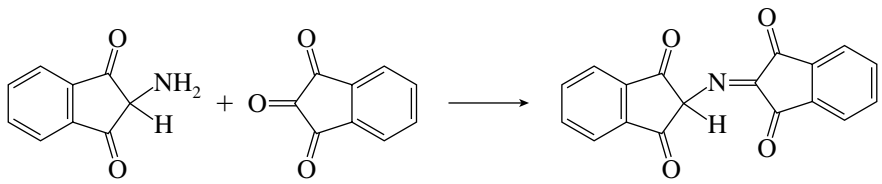
The anion that results from the decarboxylation step is then protonated. The product is shown as its diketo form but probably exists as an enol.



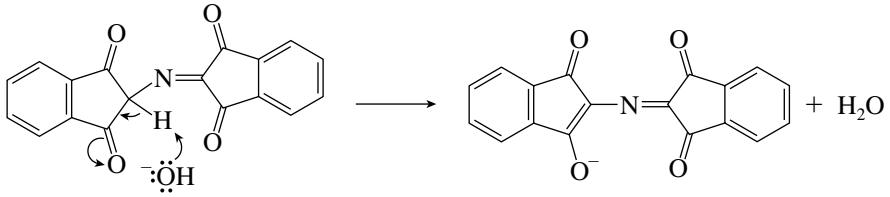
Hydrolysis of the imine function gives an aldehyde and a compound having a free amino group.



This amine then reacts with a second molecule of the triketo form of ninhydrin to give an imine.

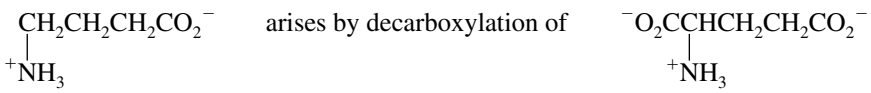


Proton abstraction from the neutral imine gives its conjugate base, which is a violet dye.



Violet dye

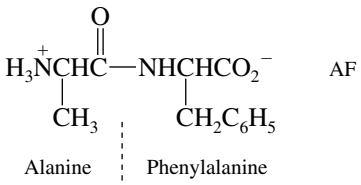
27.9 The carbon that bears the amino group of 4-aminobutanoic acid corresponds to the α carbon of an α-amino acid.



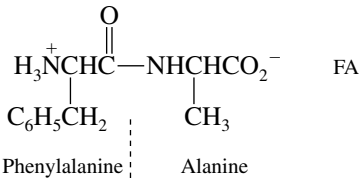
4-Aminobutanoic acid

Glutamic acid

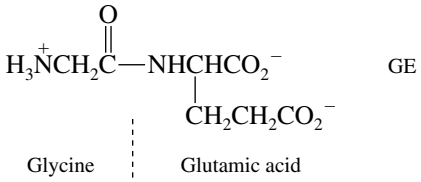
27.10 (*b*) Alanine is the N-terminal amino acid in Ala-Phe. Its carboxyl group is joined to the nitrogen of phenylalanine by a peptide bond.



(*c*) The positions of the amino acids are reversed in Phe-Ala. Phenylalanine is the N terminus and alanine is the C terminus.

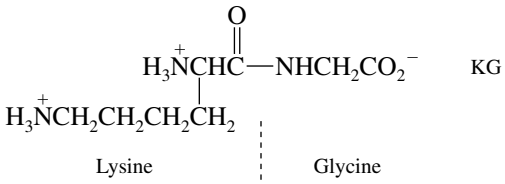


(*d*) The carboxyl group of glycine is joined by a peptide bond to the amino group of glutamic acid.



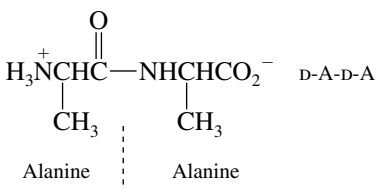
The dipeptide is written in its anionic form because the carboxyl group of the side chain is ionized at pH 7. Alternatively, it could have been written as a neutral zwitterion with a $CH_2CH_2CO_2H$ side chain.

(*e*) The peptide bond in Lys-Gly is between the carboxyl group of lysine and the amino group of glycine.

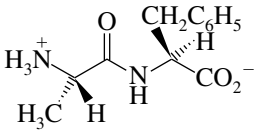


The amino group of the lysine side chain is protonated at pH 7, and so the dipeptide is written here in its cationic form. It could have also been written as a neutral zwitterion with the side chain $H_2NCH_2CH_2CH_2CH_2$.

(*f*) Both amino acids are alanine in D-Ala-D-Ala. The fact that they have the D configuration has no effect on the constitution of the dipeptide.

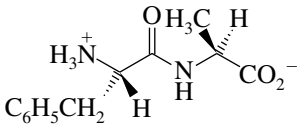


27.11 (*b*) When amino acid residues in a dipeptide are indicated without a prefix, it is assumed that the configuration at the α carbon atom is L. For all amino acids except cysteine, the L configuration corresponds to *S*. The stereochemistry of Ala-Phe may therefore be indicated for the zigzag conformation as shown.

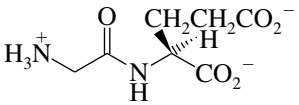


The L configuration corresponds to *S* for each of the stereogenic centers in Ala-Phe.

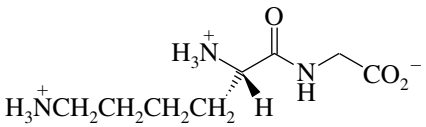
(*c*) Similarly, Phe-Ala has its substituent at the N-terminal amino acid directed away from us, whereas the C-terminal side chain is pointing toward us, and the L configuration corresponds to *S* for each stereogenic center.



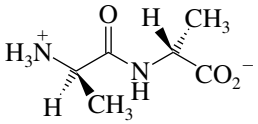
(*d*) There is only one stereogenic center in Gly-Glu. It has the L (or *S*) configuration.



(*e*) In order for the N-terminal amino acid in Lys-Gly to have the L (or *S*) configuration, its side chain must be directed away from us in the conformation indicated.



(*f*) The configuration at both α-carbon atoms in D-Ala-D-Ala is exactly the reverse of the configuration of the stereogenic centers in parts (*a*) through (*e*). Both stereogenic centers have the D (or *R*) configuration.



27.12 Figure 27.7 in the text gives the structure of leucine enkephalin. Methionine enkephalin differs from it only with respect to the C-terminal amino acid. The amino acid sequences of the two pentapeptides are

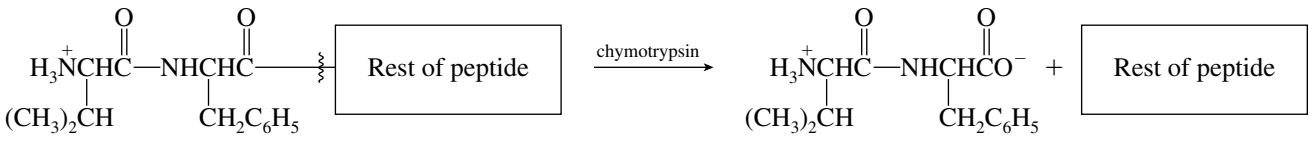
Tyr-Gly-Gly-Phe-Leu	Tyr-Gly-Gly-Phe-Met
Leucine enkephalin	Methionine enkephalin

The peptide sequence of a polypeptide can also be expressed using the one-letter abbreviations listed in text Table 27.1. Methionine enkephalin becomes YGGFM.

27.13 Twenty-four tetrapeptide combinations are possible for the four amino acids alanine (A), glycine (G), phenylalanine (F), and valine (V). Remember that the order is important; AG is not the same peptide as GA. Using the one-letter abbreviations for each amino acid the possibilities are

AGFV	AGVF	AFGV	AFVG	AVGF	AVFG
GAFV	GAVF	GFAV	GFVA	GVFA	GVAF
FAGV	FAVG	FVAG	FVGA	FGAF	FGFA
VAGF	VAFG	VGAF	VGFA	VFAG	VFGA

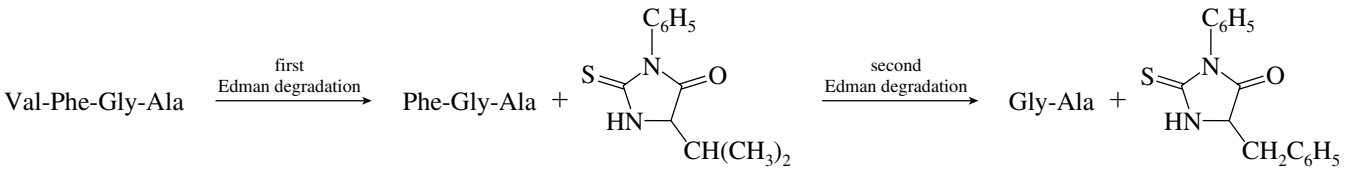
27.14 Chymotrypsin cleaves a peptide selectively at the carboxyl group of amino acids that have aromatic side chains. The side chain of phenylalanine is a benzyl group, $C_6H_5CH_2$—. If the dipeptide isolated after treatment with chymotrypsin contains valine (V) and phenylalanine (F), its sequence must be VF.



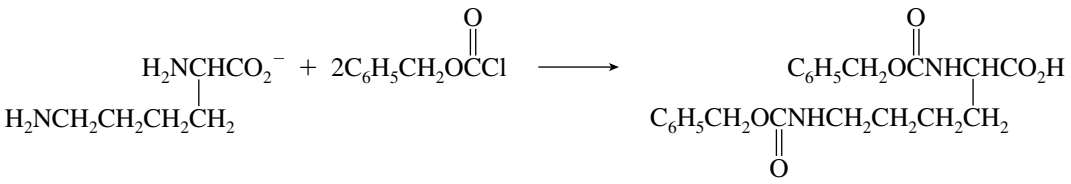
Valine Phenylalanine Valinylphenylalanine (VF)

The possible sequences for the unknown tetrapeptide are VFAG and VFGA.

27.15 The Edman degradation removes the N-terminal amino acid, which is identified as a phenylthiohydantoin derivative. The first Edman degradation of Val-Phe-Gly-Ala gives the phenylthiohydantoin derived from valine; the second gives the phenylthiohydantoin derived from phenylalanine.

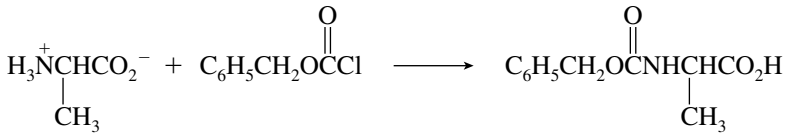


27.16 Lysine has two amino groups. Both amino functions are converted to amides on reaction with benzyloxycarbonyl chloride.



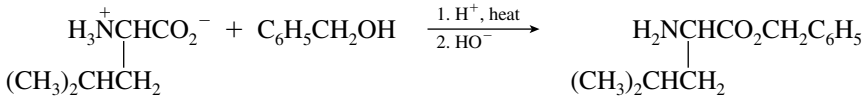
27.17 The peptide bond of Ala-Leu connects the carboxyl group of alanine and the amino group of leucine. We therefore need to protect the amino group of alanine and the carboxyl group of leucine.

Protect the amino group of alanine as its benzyloxycarbonyl derivative.



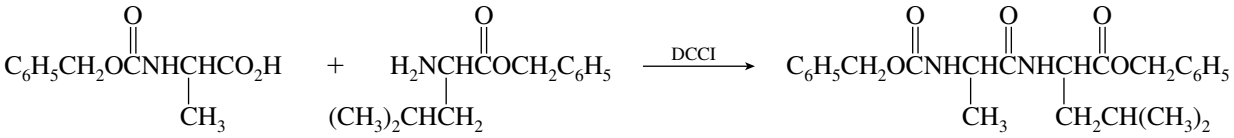
Alanine Benzyloxycarbonyl chloride Z-Protected alanine

Protect the carboxyl group of leucine as its benzyl ester.



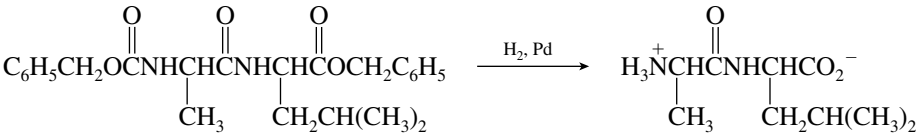
Leucine | Benzyl alcohol | Leucine benzyl ester

Coupling of the two amino acids is achieved by *N*,*N*′-dicyclohexylcarbodiimide (DCCI)-promoted amide bond formation between the free amino group of leucine benzyl ester and the free carboxyl group of Z-protected alanine.



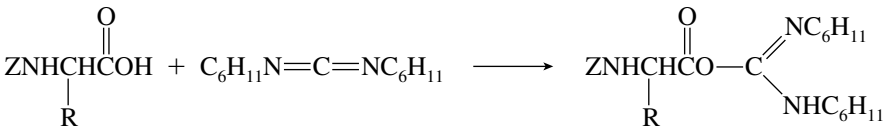
Z-Protected alanine | Leucine benzyl ester | Protected dipeptide

Both the benzyloxycarbonyl protecting group and the benzyl ester protecting group may be removed by hydrogenolysis over palladium. This step completes the synthesis of Ala-Leu.



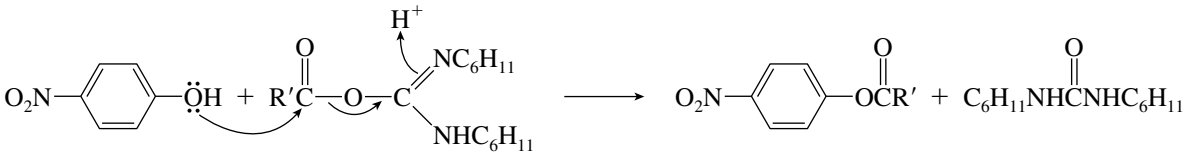
Protected dipeptide | Ala-Leu

27.18 As in the DCCI-promoted coupling of amino acids, the first step is the addition of the Z-protected amino acid to DCCI to give an *O*-acylisourea.

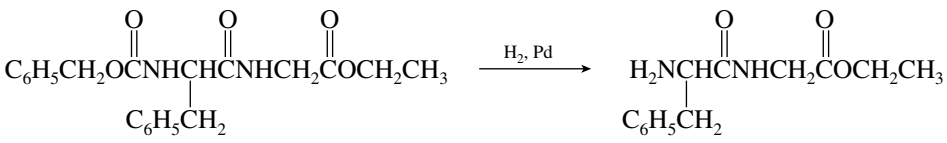


Z-Protected amino acid | DCCI | *O*-Acylisourea

This *O*-acylisourea is attacked by *p*-nitrophenol to give the *p*-nitrophenyl ester of the Z-protected amino acid.



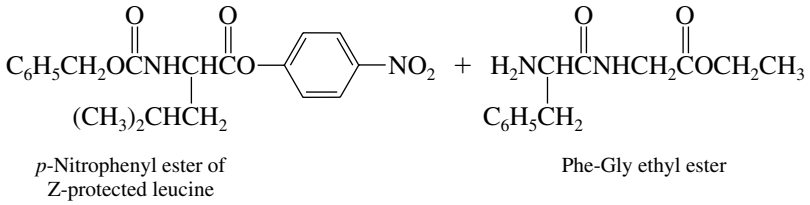
27.19 To add a leucine residue to the N terminus of the ethyl ester of Z-Phe-Gly, the benzyloxycarbonyl protecting group must first be removed. This can be accomplished by hydrogenolysis.



Z-Protected ethyl ester of Phe-Gly | Phe-Gly ethyl ester

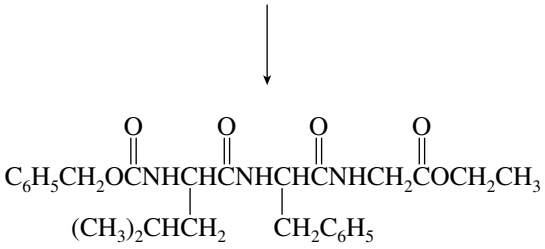
The reaction shown has been carried out in 100% yield. Alternatively, the benzyloxycarbonyl protecting group may be removed by treatment with hydrogen bromide in acetic acid. This latter route has also been reported in the chemical literature and gives the hydrobromide salt of Phe-Gly ethyl ester in 82% yield.

Once the protecting group has been removed, the ethyl ester of Phe-Gly is allowed to react with the *p*-nitrophenyl ester of Z-protected leucine to form the protected tripeptide. Hydrogenolysis of the Z-protected tripeptide gives Leu-Phe-Gly as its ethyl ester.

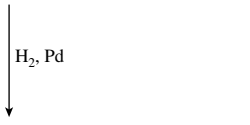


p-Nitrophenyl ester of Z-protected leucine

Phe-Gly ethyl ester

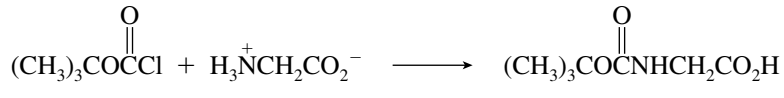


Z-protected Leu-Phe-Gly ethyl ester



Leu-Phe-Gly ethyl ester

27.20 Amino acid residues are added by beginning at the C terminus in the Merrifield solid-phase approach to peptide synthesis. Thus the synthesis of Phe-Gly requires glycine to be anchored to the solid support. Begin by protecting glycine as its *tert*-butoxycarbonyl (Boc) derivative.

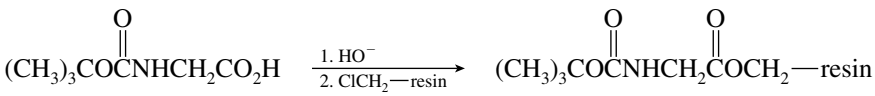


tert-Butoxycarbonyl chloride

Glycine

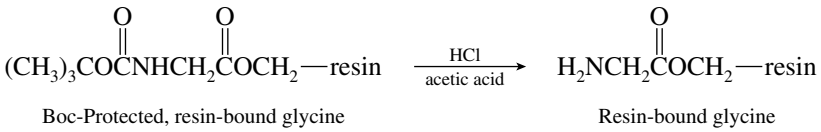
Boc-Protected glycine

The protected glycine is attached via its carboxylate anion to the solid support.



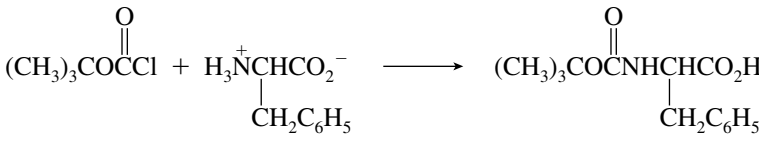
Boc-Protected glycine

The amino group of glycine is then exposed by removal of the protecting group. Typical conditions for this step involve treatment with hydrogen chloride in acetic acid.



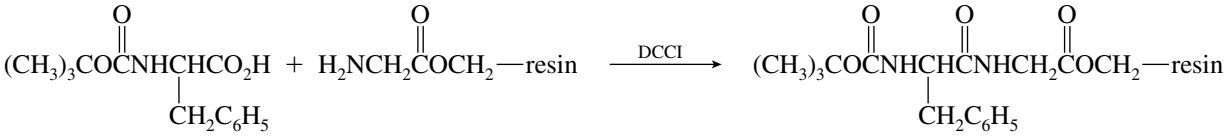
Boc-Protected, resin-bound glycine — Resin-bound glycine

To attach phenylalanine to resin-bound glycine, we must first protect the amino group of phenylalanine. A Boc protecting group is appropriate.



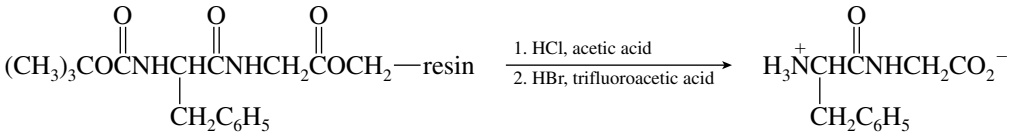
tert-Butoxycarbonyl chloride — Phenylalanine — Boc-Protected phenylalanine

Peptide bond formation occurs when the resin-bound glycine and Boc-protected phenylalanine are combined in the presence of DCCI.



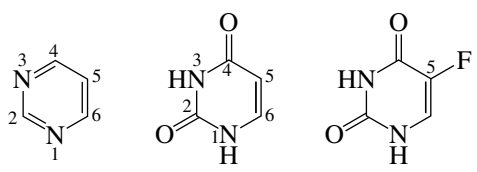
Boc-Protected phenylalanine — Resin-bound glycine — Boc-Protected, resin-bound Phe-Gly

Remove the Boc group with HCl and then treat with HBr in trifluoroacetic acid to cleave Phe-Gly from the solid support.



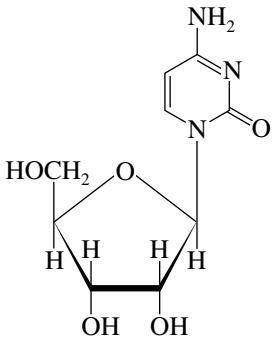
Boc-Protected, resin-bound Phe-Gly — Phe-Gly

27.21 The numbering of the ring in uracil and its derivatives parallels that in pyrimidine.

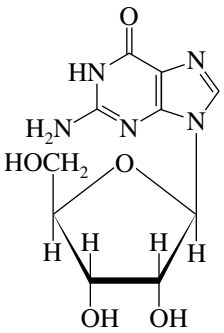


Pyrimidine — Uracil — 5-Fluorouracil

27.22 (*b*) Cytidine is present in RNA and so is a nucleoside of D-ribose. The base is cytosine.



(*c*) Guanosine is present in RNA and so is a guanine nucleoside of D-ribose.

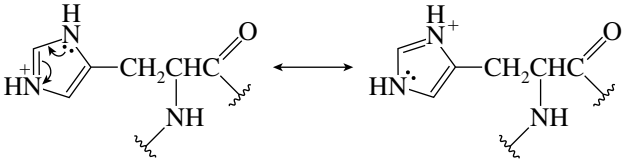


27.23 Table 27.4 in the text lists the messenger RNA codons for the various amino acids. The codons for valine and for glutamic acid are:

Valine:	GUU	GUA	GUC	GUG
Glutamic acid:		GAA		GAG

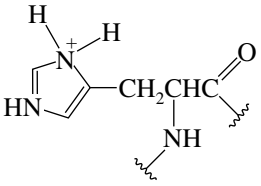
As can be seen, the codons for glutamic acid (GAA and GAG) are very similar to two of the codons (GUA and GUG) for valine. Replacement of adenine in the glutamic acid codons by uracil causes valine to be incorporated into hemoglobin instead of glutamic acid and is responsible for the sickle cell trait.

27.24 The protonated form of imidazole represented by structure A is stabilized by delocalization of the lone pair of one of the nitrogens. The positive charge is shared by both nitrogens.



A

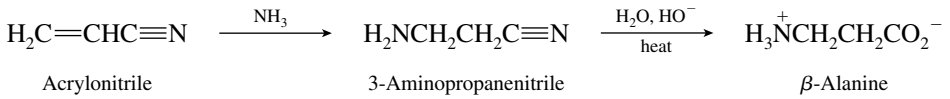
The positive charge in structure B is localized on a single nitrogen. Resonance stabilization of the type shown in structure A is not possible.



B

Structure A is the more stable protonated form.

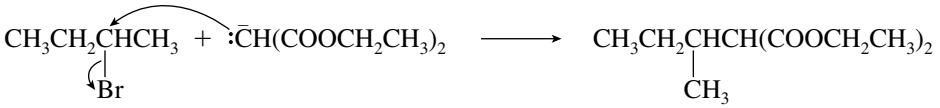
27.25 The following outlines a synthesis of β-alanine in which conjugate addition to acrylonitrile plays a key role.



Acrylonitrile — 3-Aminopropanenitrile — β-Alanine

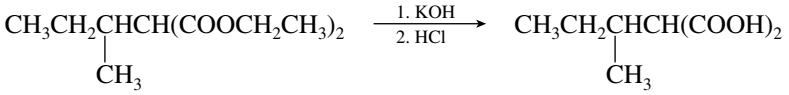
Addition of ammonia to acrylonitrile has been carried out in modest yield (31–33%). Hydrolysis of the nitrile group can be accomplished in the presence of either acids or bases. Hydrolysis in the presence of $Ba(OH)_2$ has been reported in the literature to give β-alanine in 85–90% yield.

27.26 (*a*) The first step involves alkylation of diethyl malonate by 2-bromobutane.



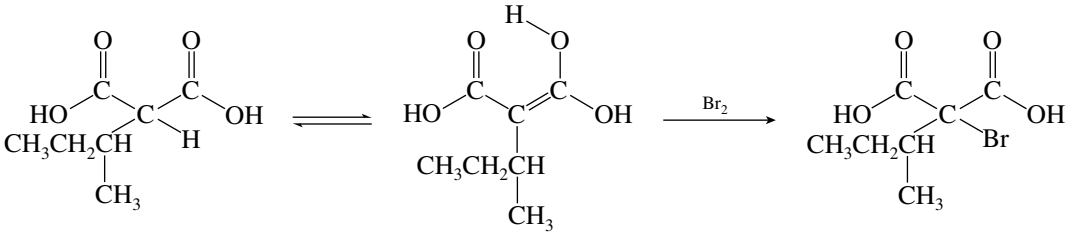
2-Bromobutane — Anion of diethyl malonate — Compound A

In the second step of the synthesis, compound A is subjected to ester saponification. Following acidification, the corresponding diacid (compound B) is isolated.



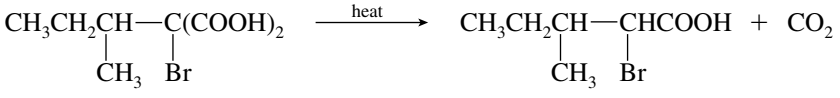
Compound A — Compound B ($C_7H_{12}O_4$)

Compound B is readily brominated at its α-carbon atom by way of the corresponding enol form.



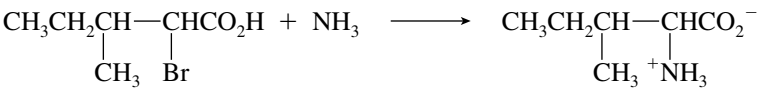
Compound B — Enol form — Compound C ($C_7H_{11}BrO_4$)

When compound C is heated, it undergoes decarboxylation to give an α-bromo carboxylic acid.



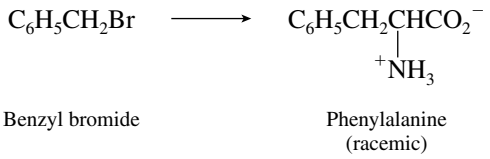
Compound C — Compound D — Carbon dioxide

Treatment of compound D with ammonia converts it to isoleucine by nucleophilic substitution.

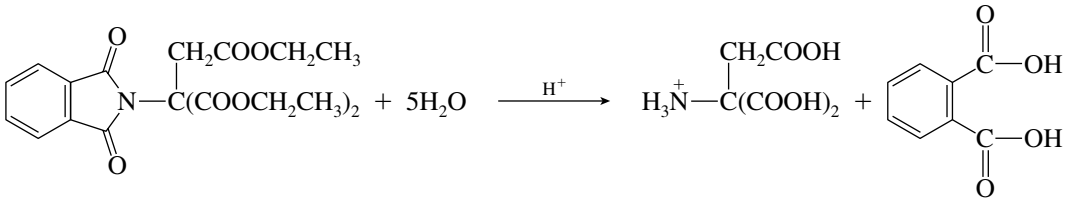


Compound D — Isoleucine (racemic)

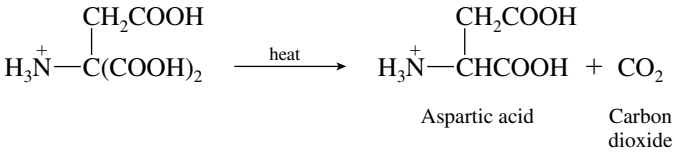
(*b*) The procedure just described can be adapted to the synthesis of other amino acids. The group attached to the α-carbon atom is derived from the alkyl halide used to alkylate diethyl malonate. Benzyl bromide (or chloride or iodide) would be appropriate for the preparation of phenylalanine.



27.27 Acid hydrolysis of the triester converts all its ester functions to free carboxyl groups and cleaves both amide bonds.

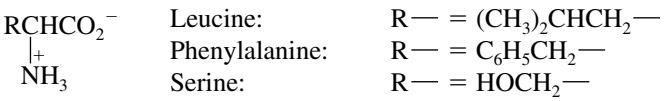


The hydrolysis product is a substituted derivative of malonic acid and undergoes decarboxylation on being heated. The product of this decarboxylation is aspartic acid (in its protonated form under conditions of acid hydrolysis).

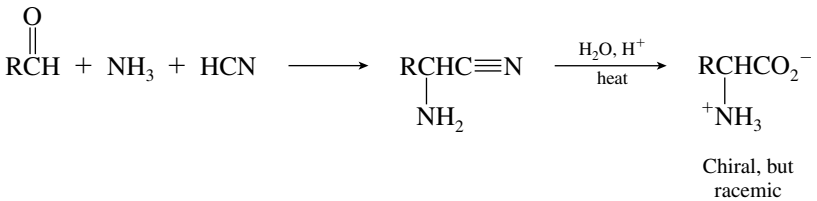


Aspartic acid is chiral, but is formed as a racemic mixture, so the product of this reaction is not optically active. The starting triester is achiral and cannot give an optically active product when it reacts with optically inactive reagents.

27.28 The amino acids leucine, phenylalanine, and serine each have one stereogenic center.



When prepared by the Strecker synthesis, each of these amino acids is obtained as a racemic mixture containing 50% of the D enantiomer and 50% of the L enantiomer.



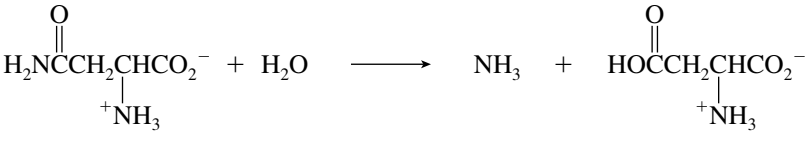
Thus, preparation of the tripeptide Leu-Phe-Ser will yield a mixture of 2^3 (eight) stereoisomers.

D-Leu-D-Phe-D-Ser	L-Leu-L-Phe-L-Ser
D-Leu-D-Phe-L-Ser	L-Leu-L-Phe-D-Ser
D-Leu-L-Phe-D-Ser	L-Leu-D-Phe-L-Ser
D-Leu-L-Phe-L-Ser	L-Leu-D-Phe-D-Ser

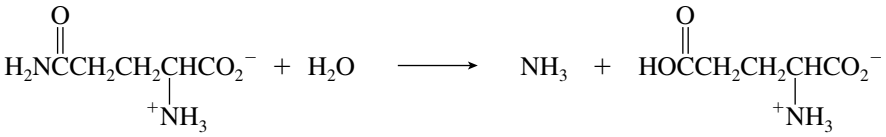
27.29 Bradykinin is a nonapeptide but contains only five different amino acids. Three of the amino acid residues are proline, two are arginine, and two are phenylalanine. Five peaks will appear on the strip chart after amino acid analysis of bradykinin.

$$\text{Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg} \longrightarrow 2\text{Arg} + 3\text{Pro} + \text{Gly} + 2\text{Phe} + \text{Ser}$$

27.30 Asparagine and glutamine each contain an amide function in their side chain. Under the conditions of peptide bond hydrolysis that characterize amino acid analysis, the side-chain amide is also hydrolyzed, giving ammonia.

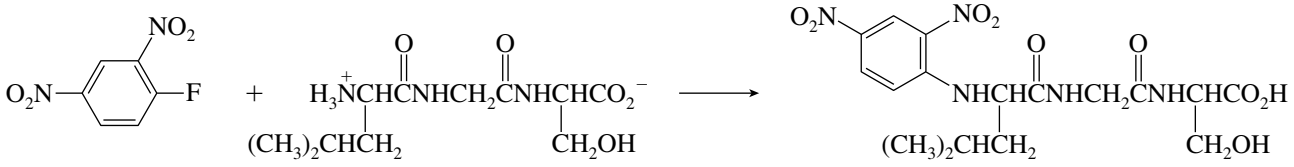


Asparagine Water Ammonia Aspartic acid



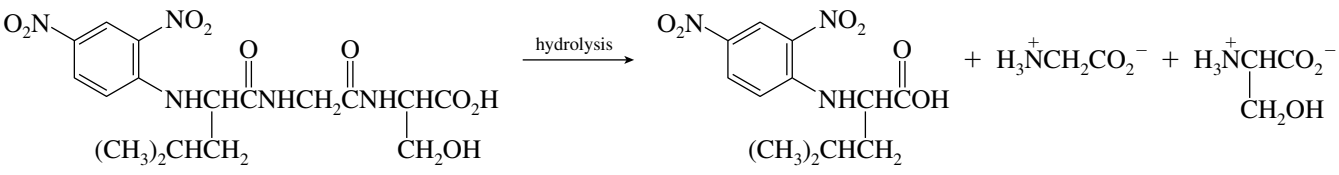
Glutamine Water Ammonia Glutamic acid

27.31 (*a*) 1-Fluoro-2,4-dinitrobenzene reacts with the amino group of the N-terminal amino acid in a nucleophilic aromatic substitution reaction of the addition–elimination type.



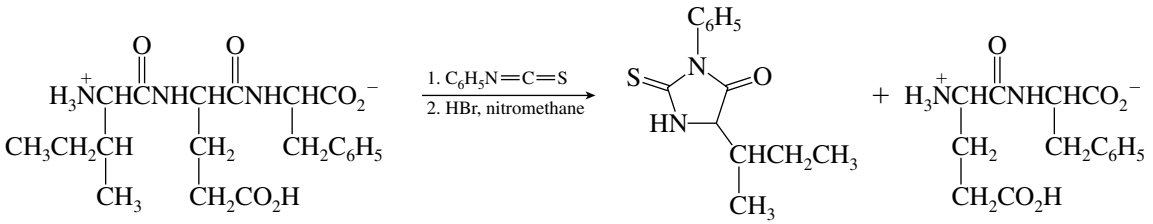
1-Fluoro-2,4-dinitrobenzene Leu-Gly-Ser DNP-Leu-Gly-Ser

(*b*) Hydrolysis of the product in part (*a*) cleaves the peptide bonds. Leucine is isolated as its 2,4-dinitrophenyl (DNP) derivative, but glycine and serine are isolated as the free amino acids.



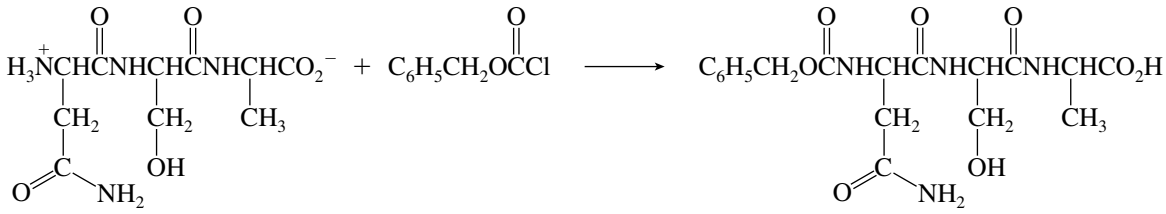
DNP-Leu-Gly-Ser DNP-Leu Gly Ser

(*c*) Phenyl isothiocyanate is a reagent used to identify the N-terminal amino acid of a peptide by the Edman degradation. The N-terminal amino acid is cleaved as a phenylthiohydantoin (PTH) derivative, the remainder of the peptide remaining intact.



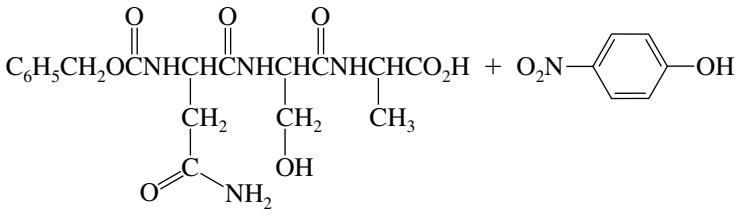
Ile-Glu-Phe | PTH derivative of isoleucine | Glu-Phe

(*d*) Benzyloxycarbonyl chloride reacts with amino groups to convert them to amides. The only free amino group in Asn-Ser-Ala is the N terminus. The amide function of asparagine does not react with benzyloxycarbonyl chloride.

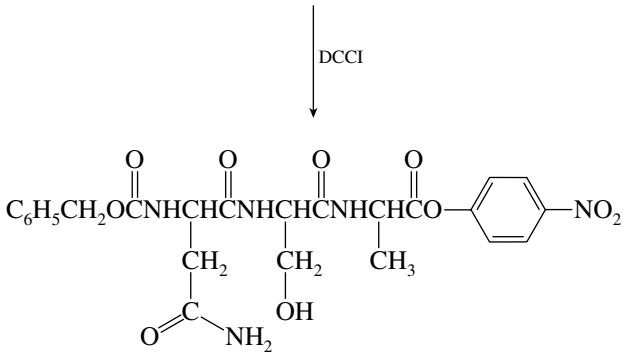


Asn-Ser-Ala | Benzyloxycarbonyl chloride | Z-Asn-Ser-Ala

(*e*) The Z-protected tripeptide formed in part (*d*) is converted to its C-terminal *p*-nitrophenyl ester on reaction with *p*-nitrophenol and *N*,*N*′-dicyclohexylcarbodiimide (DCCI).

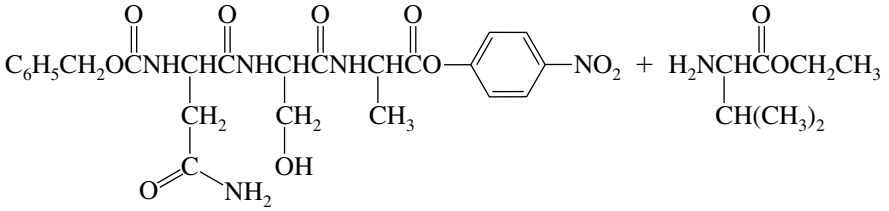


Z-Asn-Ser-Ala | *p*-Nitrophenol

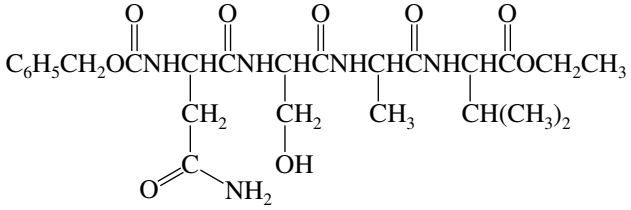


Z-Asn-Ser-Ala *p*-nitrophenyl ester

(*f*) The *p*-nitrophenyl ester prepared in part (*e*) is an "active" ester. The *p*-nitrophenyl group is a good leaving group and can be displaced by the amino nitrogen of valine ethyl ester to form a new peptide bond.

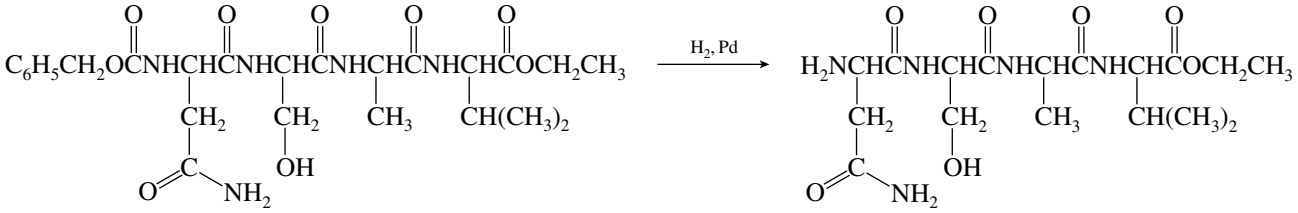


Z-Asn-Ser-Ala *p*-nitrophenyl ester Valine ethyl ester



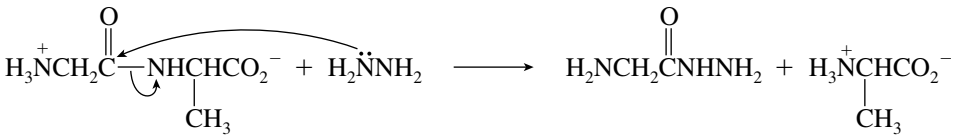
Z-Asn-Ser-Ala-Val ethyl ester

(*g*) Hydrogenolysis of the Z-protected tetrapeptide ester formed in part (*f*) removes the Z protecting group.



Z-Asn-Ser-Ala-Val ethyl ester Asn-Ser-Ala-Val ethyl ester

27.32 Consider, for example, the reaction of hydrazine with a very simple dipeptide such as Gly-Ala. Hydrazine cleaves the peptide by nucleophilic attack on the carbonyl group of glycine.



Gly-Ala Hydrazine Hydrazide of glycine Alanine

It is the C-terminal residue that is cleaved as the free amino acid and identified in the hydrazinolysis of peptides.

27.33 Somatostatin is a tetradecapeptide and so is composed of 14 amino acids. The fact that Edman degradation gave the PTH derivative of alanine identifies this as the N-terminal amino acid. A major piece of information is the amino acid sequence of a hexapeptide obtained by partial hydrolysis:

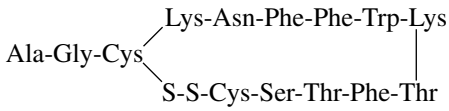
Ala-Gly-Cys-Lys-Asn-Phe

Using this as a starting point and searching for overlaps with the other hydrolysis products gives the entire sequence.

Ala-Gly-Cys-Lys-Asn-Phe
Asn-Phe-Phe-Trp-Lys
Phe-Trp
Lys-Thr-Phe
Thr-Phe-Thr-Ser-Cys
Thr-Ser-Cys

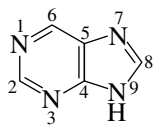
Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys
1 2 3 4 5 6 7 8 9 10 11 12 13 14

The disulfide bridge in somatostatin is between cysteine 3 and cysteine 14. Thus, the primary structure is

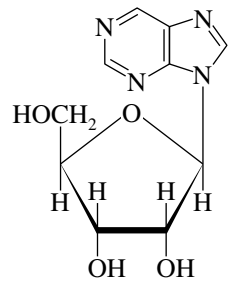


27.34 It is the C-terminal amino acid that is anchored to the solid support in the preparation of peptides by the Merrifield method. Refer to the structure of oxytocin in Figure 27.8 of the text and note that oxytocin, in fact, has no free carboxyl groups; all the acyl groups of oxytocin appear as amide functions. Thus, the carboxyl terminus of oxytocin has been modified by conversion to an amide. There are three amide functions of the type $\overset{O}{\overset{\|}{C}}NH_2$, two of which belong to side chains of asparagine and glutamine, respectively. The third amide belongs to the C-terminal amino acid, glycine, $-NHCH_2\overset{O}{\overset{\|}{C}}OH$, which in oxytocin has been modified so that it appears as $-NHCH_2\overset{O}{\overset{\|}{C}}NH_2$. Therefore, attach glycine to the solid support in the first step of the Merrifield synthesis. The carboxyl group can be modified to the required amide after all the amino acid residues have been added and the completed peptide is removed from the solid support.

27.35 Purine and its numbering system are as shown:

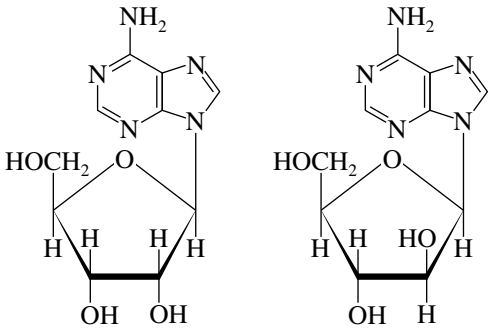


In nebularine, D-ribose in its furanose form is attached to position 9 of purine. The stereochemistry at the anomeric position is β.



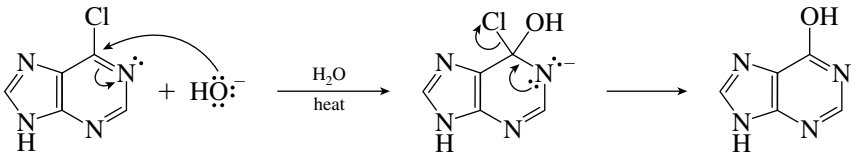
9-β-D-Ribofuranosylpurine
(nebularine)

27.36 The problem states that vidarabine is the arabinose analog of adenosine. Arabinose and ribose differ only in their configuration at C-2.



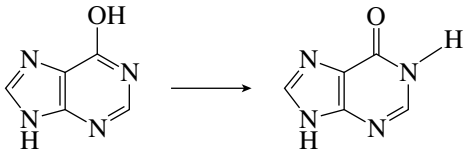
Adenosine Vidarabine

27.37 Nucleophilic aromatic substitution occurs when 6-chloropurine reacts with hydroxide ion by an addition–elimination pathway.



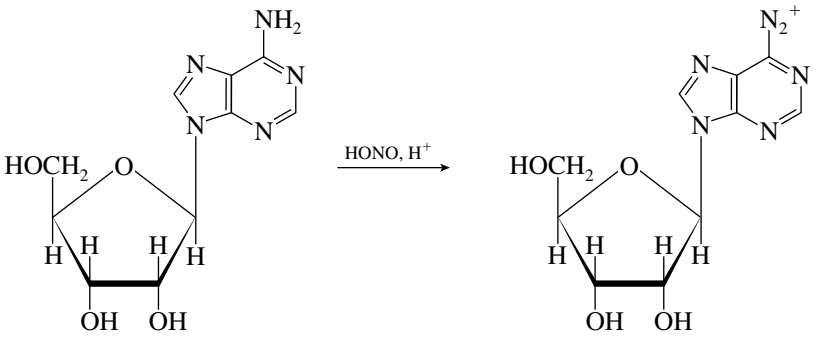
6-Chloropurine

The enol tautomerizes to give hypoxanthine.



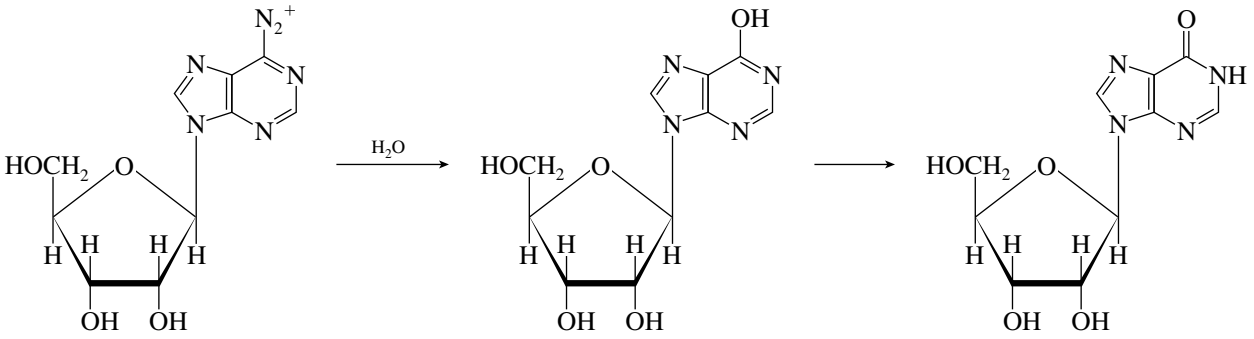
Hypoxanthine

27.38 Nitrous acid reacts with aromatic primary amines to yield diazonium ions.



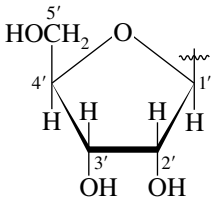
Adenosine

Treatment of the diazonium ion with water yields a phenol. Tautomerization gives inosine.

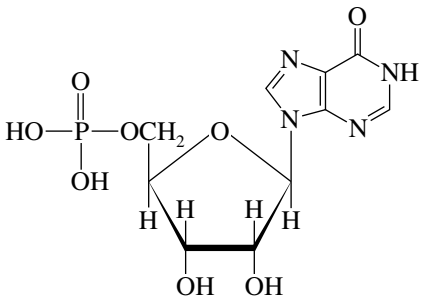


Inosine

27.39 The carbon atoms of the ribose portion of a nucleoside are numbered as follows:

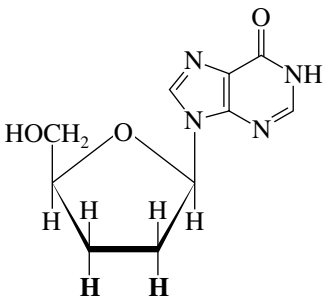


(*a*) A 5′-nucleotide has a phosphate group attached to the C-5′ hydroxyl.



Inosinic acid

(*b*) Deoxy nucleosides have hydrogens in place of hydroxyl groups at the positions indicated with **boldface.**



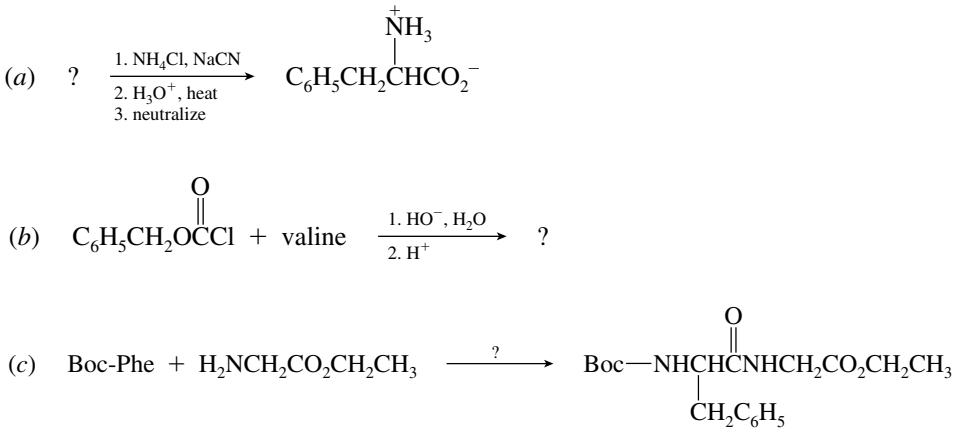
2′,3′-Dideoxyinosine

27.40 All the bases in the synthetic messenger RNA prepared by Nirenberg were U; therefore, the codon is UUU. By referring to the codons in Table 27.4, we see that the UUU codes for phenylalanine. A polypeptide in which all the amino acid residues were phenylalanine was isolated in Nirenberg's experiment.

SELF-TEST

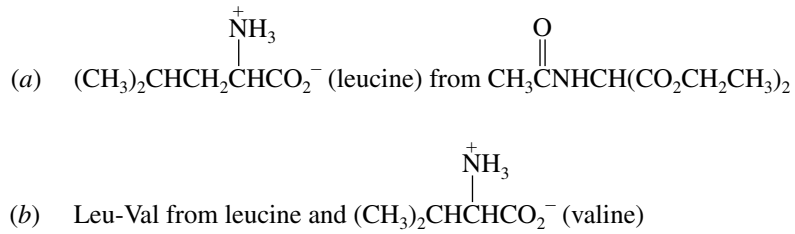
PART A

A-1. Give the structure of the reactant, reagent, or product omitted from each of the following:



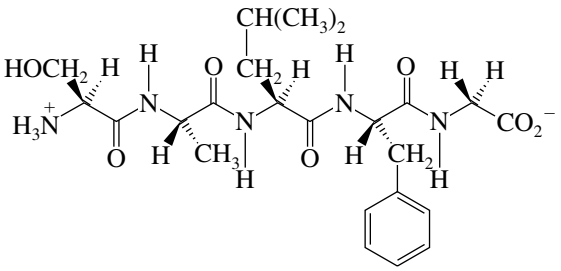
A-2. Give the structure of the derivative that would be obtained by treatment of Phe-Ala with Sanger's reagent followed by hydrolysis.

A-3. Outline a sequence of steps that would allow the following synthetic conversions to be carried out:



A-4. The carboxypeptidase-catalyzed hydrolysis of a pentapeptide yielded phenylalanine (Phe). One cycle of an Edman degradation gave a derivative of leucine (Leu). Partial hydrolysis yielded the fragments Leu-Val-Gly and Gly-Ala among others. Deduce the structure of the peptide.

A-5. Consider the following compound:



(*a*) What kind of peptide does this structure represent? (For example, dipeptide)
(*b*) How many peptide bonds are present?
(*c*) Give the name for the N-terminal amino acid.
(*d*) Give the name for the C-terminal amino acid.
(*e*) Using three-letter abbreviations, write the sequence.

A-6. Consider the tetrapeptide Ala-Gly-Phe-Leu. What are the products obtained from each of the following? Be sure to account for all the amino acids of the peptide.
(*a*) Treatment with 1-fluoro-2,4-dinitrobenzene followed by hydrolysis in concentrated HCl at 100°C.
(*b*) Treatment with chymotrypsin.
(*c*) Treatment with carboxypeptidase
(*d*) Reaction with benzyloxycarbonyl chloride

PART B

B-1. Which phrase correctly completes the statement?
Except for glycine, which is achiral, all the amino acids present in proteins …
(*a*) are chiral, but racemic
(*b*) are meso forms
(*c*) have the L configuration at their α carbon
(*d*) have the *R* configuration at their α carbon
(*e*) have the *S* configuration at their α carbon

B-2. Which statement correctly describes the difference in the otherwise similar chemical constituents of DNA and RNA?
(*a*) DNA contains uracil; RNA contains thymine.
(*b*) DNA contains guanine but not adenine; RNA contains both.
(*c*) DNA contains thymine; RNA contains uracil.
(*d*) None of these applies—the chemical constitution is the same.

B-3. Assume that a particular amino acid has an isoelectric point of 6.0. In a solution of pH 1.0, which of the following species will predominate?

(*a*) $H_3\overset{+}{N}\overset{R}{\overset{|}{C}}HCO_2H$ (*c*) $H_3\overset{+}{N}\overset{R}{\overset{|}{C}}HCO_2^-$

(*b*) $H_2N\overset{R}{\overset{|}{C}}HCO_2H$ (*d*) $H_2N\overset{R}{\overset{|}{C}}HCO_2^-$

B-4. Choose the response which provides the best match of terms.

	Purine	Pyrimidine
(*a*)	Adenine	Guanine
(*b*)	Thymine	Cytosine
(*c*)	Cytosine	Adenine
(*d*)	Guanine	Cytosine

B-5. Which of the following reagents would be combined in the synthesis of Phe-Ala?

[In phenylalanine (Phe), R in the generalized amino acid formula H_2NCHCO_2H is $CH_2C_6H_5$, and in alanine (Ala) it is CH_3.]

1. $ZNHCH(CH_3)CO_2H$
2. $H_2NCH(CH_3)CO_2CH_2C_6H_5$
3. $ZNHCH(CH_2C_6H_5)CO_2H$
4. $H_2NCH(CH_2C_6H_5)CO_2CH_2C_6H_5$

(*a*) 1 and 2 (*b*) 1 and 4 (*c*) 2 and 3 (*d*) 3 and 4

B-6. A nucleoside is a
(*a*) Phosphate ester of a nucleotide
(*b*) Unit having a sugar bonded to a purine or pyrimidine base
(*c*) Chain whose backbone consists of sugar units connected by phosphate groups
(*d*) Phosphate salt of a purine or pyrimidine base

B-7. What are the products obtained following treatment of Ser-Tyr-Val-Ala with chymotrypsin?
(*a*) Serine + Tyr-Val-Ala
(*b*) Ser-Tyr + Valine + Alanine
(*c*) Ser-Tyr + Val-Ala
(*d*) Ser-Tyr-Val + Alanine
(*e*) Serine + Tyrosine + Val-Ala

B-8. The first cycle of the Edman degradation of the tetrapeptide Gly-Ala-Ile-Leu would give a PTH derivative of
(*a*) Glycine
(*b*) Alanine
(*c*) Isoleucine
(*d*) Leucine