

Chapter 24

Amino Acids and Proteins

Biopolymers

The three most important classes of biopolymers are the:

polysaccharides
proteins
nucleic acids

[Others are the polyisoprenes (like natural rubber) and the lignins.]

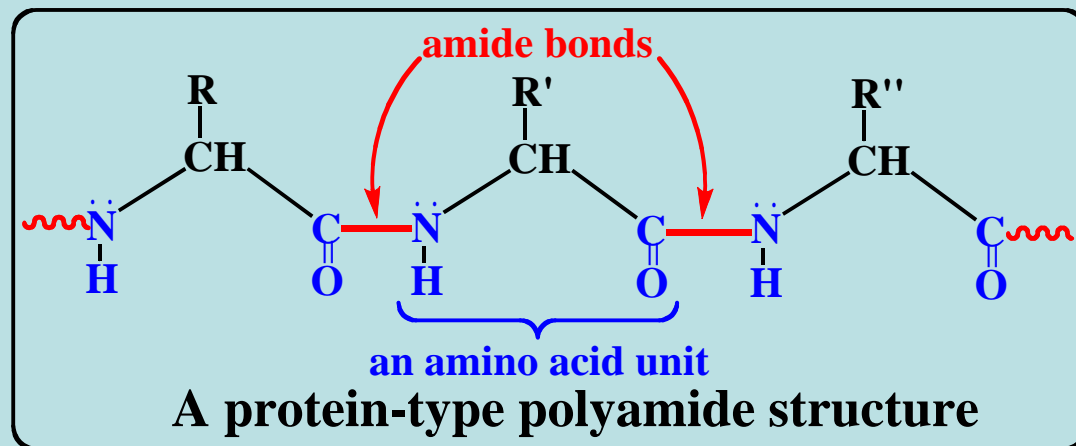
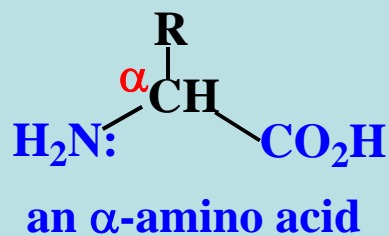
Polysaccharides (see Chapter 22) store energy (glycogen), serve as sites for interaction on the surface of the cell (glycolipids and glycoproteins), and provide the structural materials in plants (cellulose).

Proteins (this Chapter) catalyze and regulate chemical reactions at the cellular level, control body movement as muscles and tendons, provide protection to life forms as skin and hair, transport oxygen as hemoglobin, and protect against diseases as antibodies.

Nucleic acids (see Chapter 25) encode the genetic information that distinguishes organisms (and individuals) and that directs protein synthesis.

Proteins Are Polyamides

Proteins come in a wide variety of shapes and sizes. They all are **polymers of α -amino acids**. The amino acid units are held together by **amide bonds**, so proteins are **polyamides**.

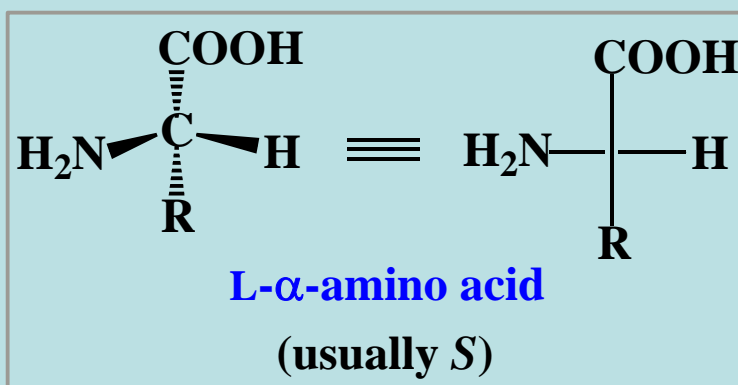
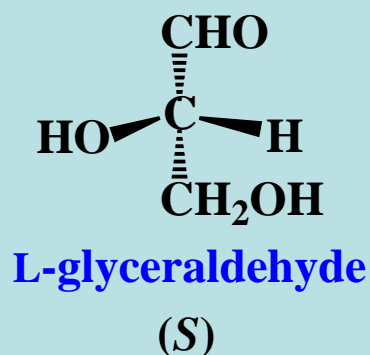


The α -amino acids differ in the structure of their R groups. There are **22 different important amino acids** in nature. In a protein, the sequence of amino acids along the polyamide chain is called the **primary structure**. The intrachain attractive interactions and intrinsic folding of the polyamide chain are responsible for the **secondary** and **tertiary** structures, which will be discussed later.

Stereochemistry

Glycine (2-aminoacetic acid), the simplest of the α -amino acids has two hydrogens on its α C, which is therefore not a chiral center.

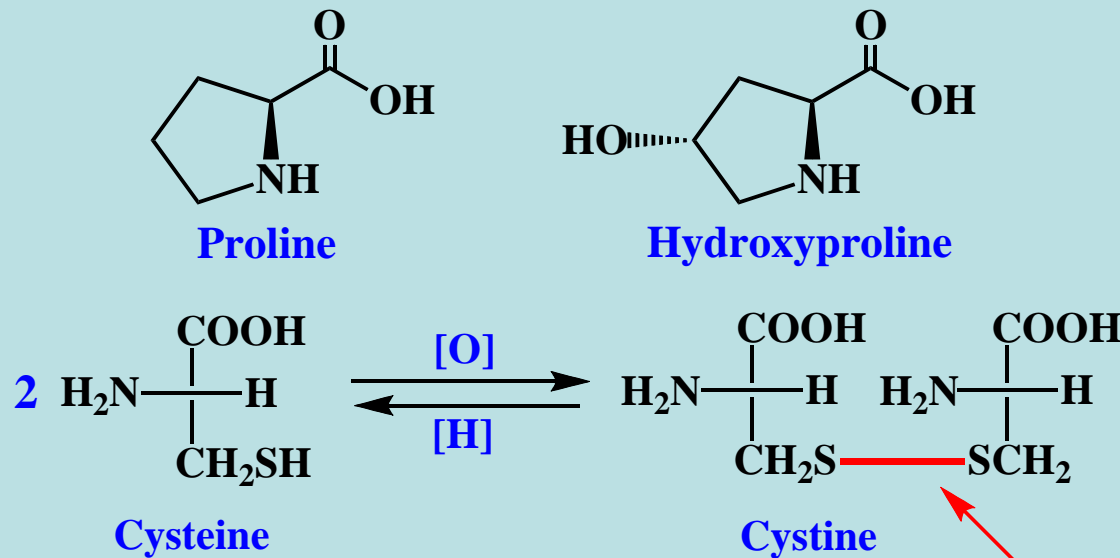
All of the other natural amino acids have a chiral α C of **L configuration** (using the Fischer notation). Drawing the carbon chain vertically, Fischer fashion, shows the amino acids having a chiral α C are analogous with the L-enantiomer of glyceraldehyde, the reference compound for D vs. L designations.



Just as an occasional sugar, e. g., arabinose, is found to have an L-configuration, a very few amino acids have a D-configuration. And three of the 22 common α -amino acids have a second chiral center. They are isoleucine, threonine, and 4-hydroxyproline.

Structures and Names

Of the 22 common α -amino acids, only 20 are actually used to synthesize proteins by the cellular mechanisms. **Hydroxyproline** is synthesized from **proline** after the polyamide chain is formed, and **cystine** is synthesized from **cysteine** by oxidative coupling.



In proteins, even mild oxidants lead to formation of these **disulfide bonds** that create inter- or intrachain bridges that change the shape of the protein.

Essential Amino Acids

Some higher animals cannot synthesize all the amino acids required for proteins. The ones that must be obtained through the diet are called **essential amino acids**. In adult humans, **eight** amino acids are essential.

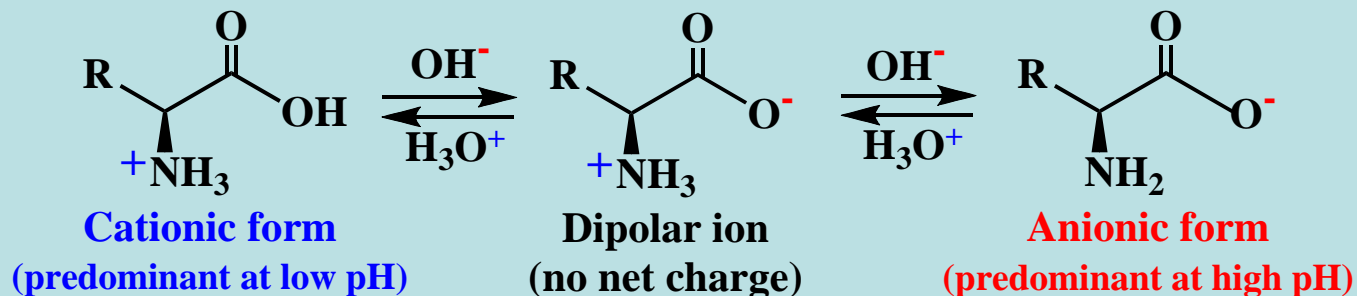
Amino Acids as Dipolar Ions

The properties of amino acids indicate they exist as **dipolar ions (zwitterions)** in the solid state and in solution in water.

- 1) Amino acids are nonvolatile, crystalline solids with high melting points.
- 2) They are soluble in water and insoluble in nonpolar solvents.
- 3) Aqueous solutions of amino acids behave like solutions of high ionic strength.
- 4) Acidity and basicity constants (K_a and K_b) are consistent with zwitterionic structures.

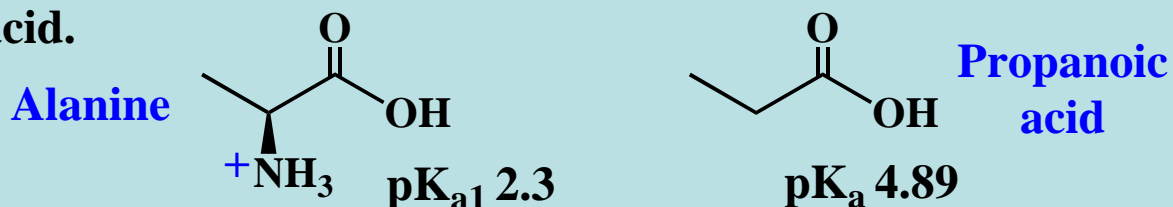
Amino Acids as Dipolar Ions, Continued

The structure of the species in solution depends on the pH:



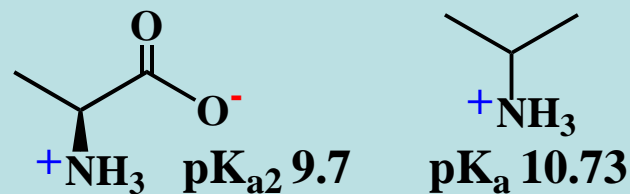
At some intermediate pH, called the **isoelectric point (pI)**, the concentration of the dipolar form is at a maximum and the concentrations of the cationic and anionic forms are equal.

Consider the case of **alanine**, the simplest chiral amino acid. The **pK_a of its cationic form** is appreciably lower than that of the simpler analog propanoic acid.



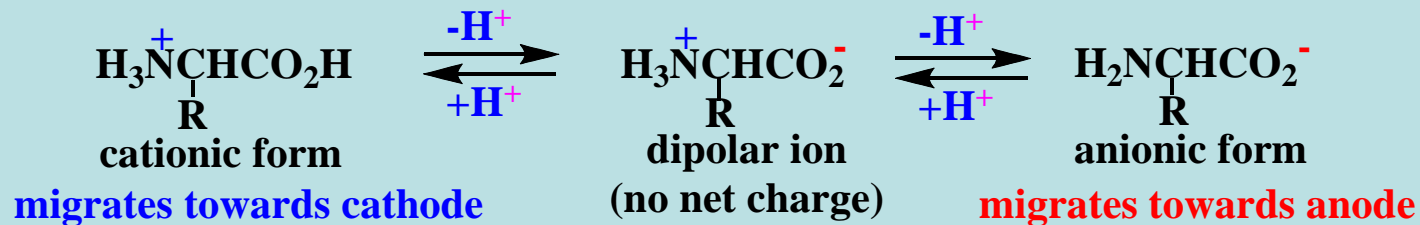
The inductive effect of the aminium ion makes alanine more acidic.

The pK_a of the dipolar ion shows that it is more acidic than its analog isopropylaminium ion. This is contrary to expectation and is likely due to a difference in the effectiveness of stabilization by solvation.



Isoelectric Point, pI

In the presence of an **electric field**, chemical species with a **net charge** migrate towards the pole of the electric field with opposite charge. This is the basis of a separation procedure called **electrophoresis** that is applicable to both amino acids and proteins.



At some pH unique to the amino acid or protein being studied, it will have no net ionic charge and will not migrate under the influence of an electric field. **This pH is that defined as the pI** for the compound studied.

When applying electrophoresis to a mixture of dipolar species, at any given pH some will be present with an excess of cationic forms, some with an excess of anionic forms, and if the pH is equal to the pI of some component it will not migrate.

The Henderson-Hasselbalch Equation

This is a variant of the more familiar equation $K_a = \frac{[H^+][A^-]}{[HA]}$ and can be derived from it when needed.

1) Solve for $[H^+]$ $[H^+] = K_a \frac{[HA]}{[A^-]}$

2) Invert $\frac{1}{[H^+]} = \frac{1}{K_a} \cdot \frac{[A^-]}{[HA]}$

3) Write in log form

$$\log \frac{1}{[H^+]} = \log \frac{1}{K_a} + \log \frac{[A^-]}{[HA]}$$

4) Recall that $\log x = -\log \frac{1}{x}$

Therefore $\log \frac{1}{[H^+]} = \text{pH}$, and $\log \frac{1}{K_a} = \text{p}K_a$

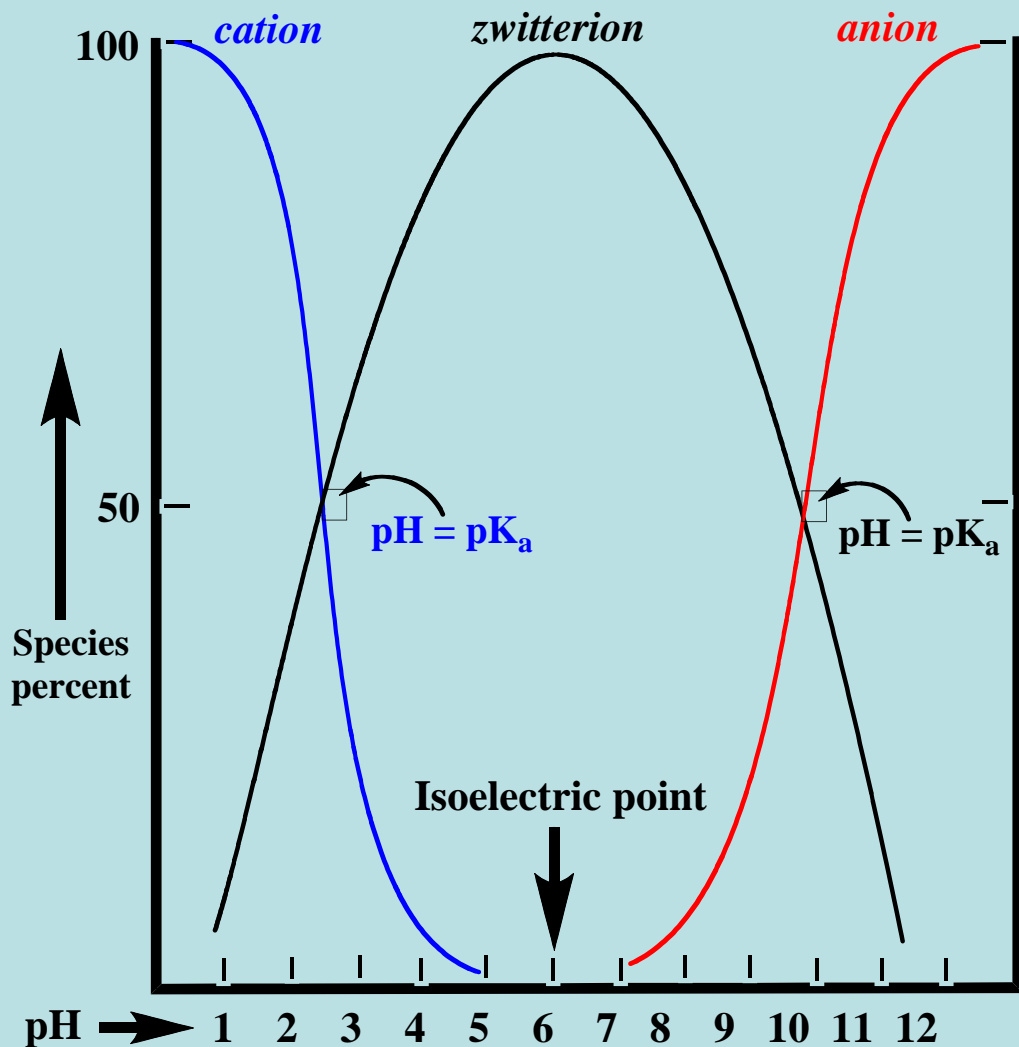
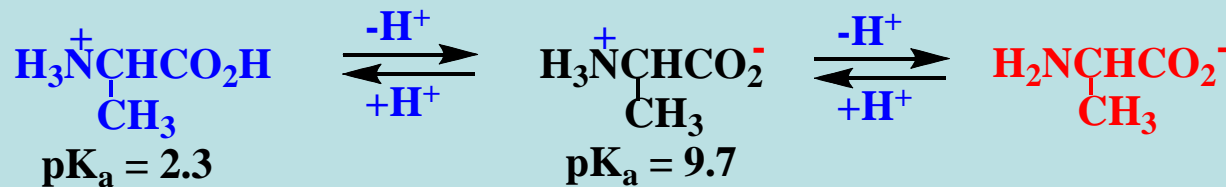
5) Rewriting gives the **Henderson-Hasselbalch equation**:

$$\text{pH} = \text{p}K_a + \log \frac{[A^-]}{[HA]}$$

6) From this, it is seen that when $[A^-] = [HA]$ the last term becomes the log of 1, which is 0, and thus at this condition

$$\text{pH} = \text{p}K_a$$

The concentrations of the three species of the alanine system vary according to the pH of the solution, as shown below.



As learned from the Henderson-Hasselbalch equation, at the **half neutralization point** of an acid

$$\text{pK}_a = \text{pH} + \log \frac{[\text{HA}]}{[\text{A}^-]}$$

So when $[\text{HA}] = [\text{A}^-] = x$,

$$\text{pK}_a = \text{pH} + \log \frac{x}{x}$$

$$\text{pK}_a = \text{pH} + \log 1$$

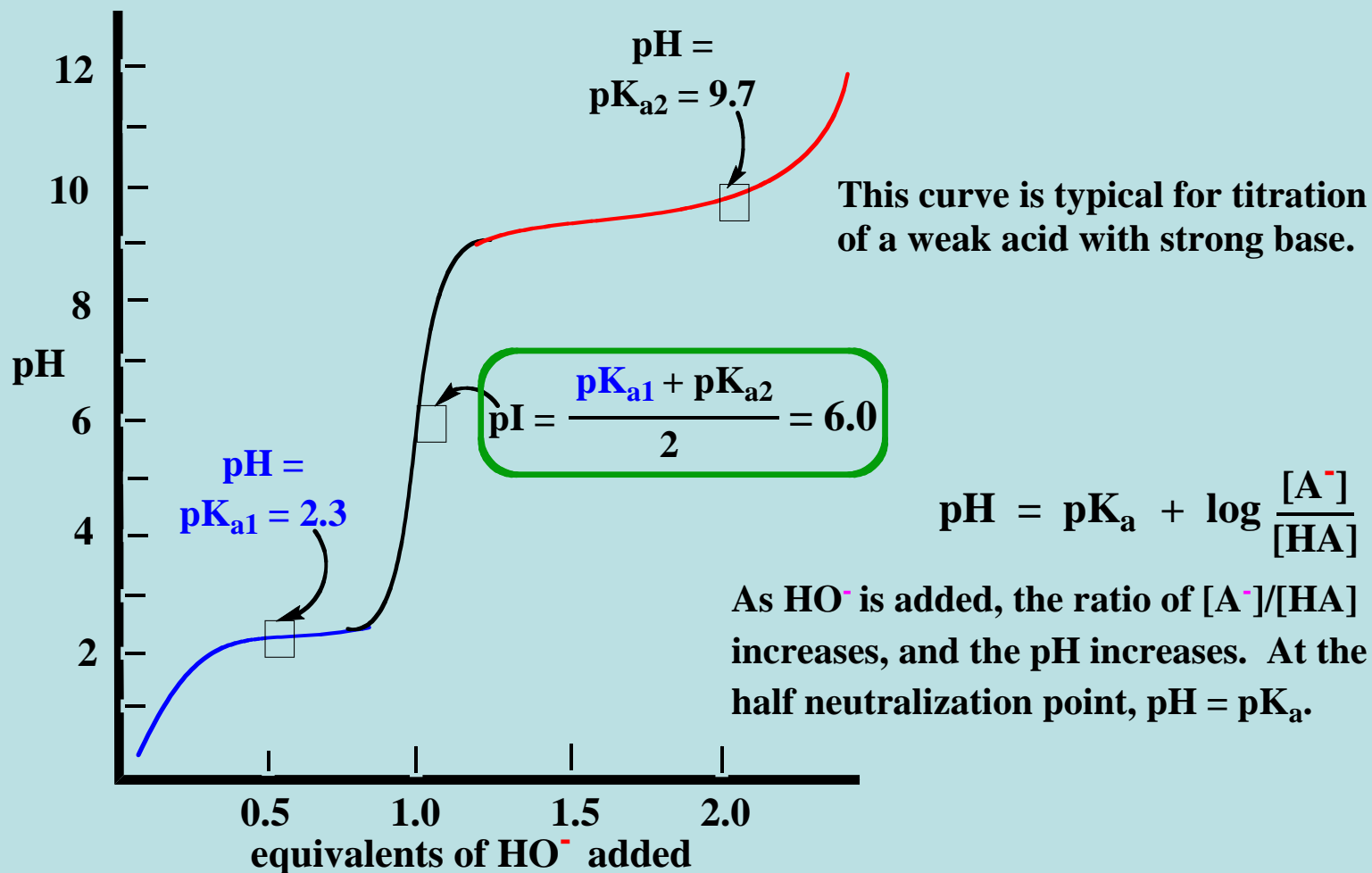
$$\text{pK}_a = \text{pH} + 0$$

OR

$$\text{pK}_a = \text{pH}$$

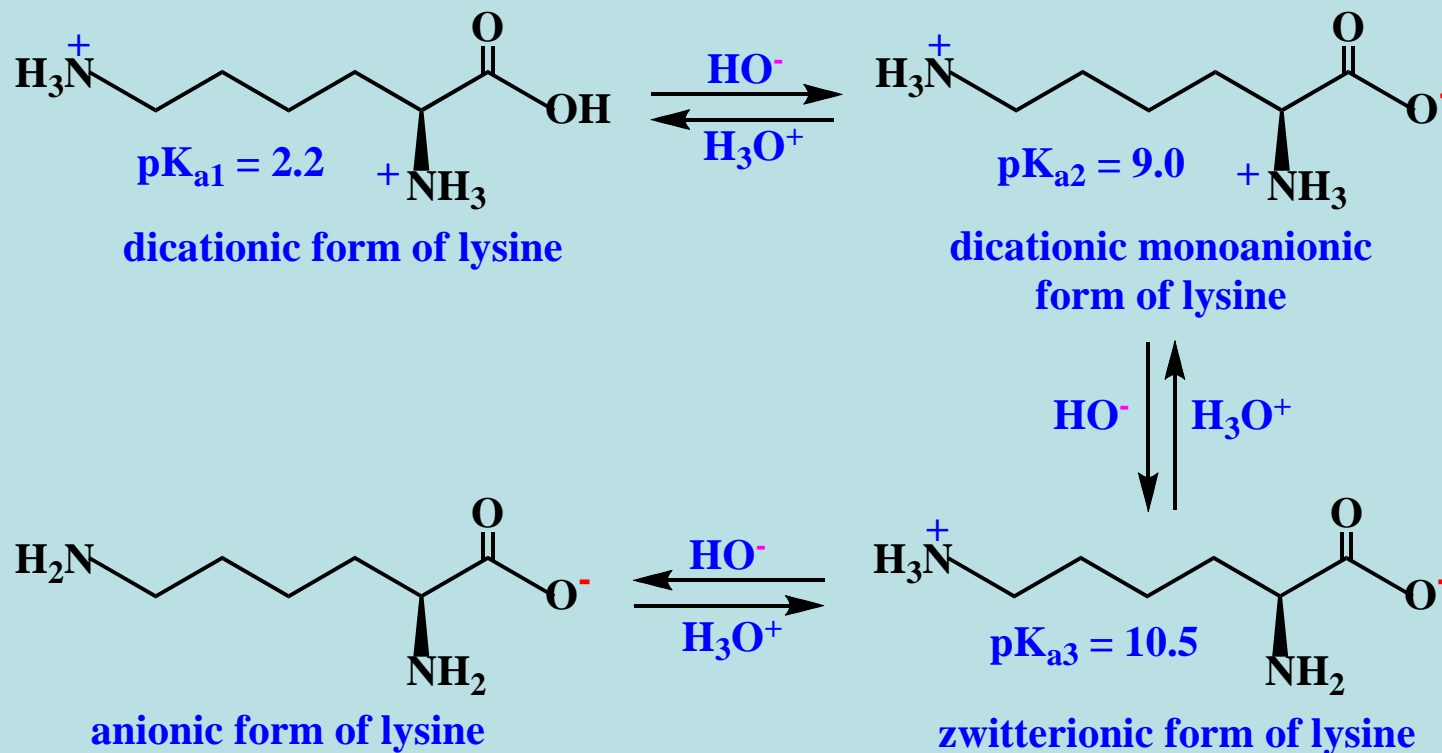
Titration Curve for Alanine

As hydroxide ion is added to an acidic solution of alanine, the pH of the solution changes as shown in the titration curve below.



Additional Observations on Isoelectric Points

Lysine has one carboxyl and two amino functions. At low pH, it has three acidic functions that deprotonate in order of their acid strengths as HO^- is added.

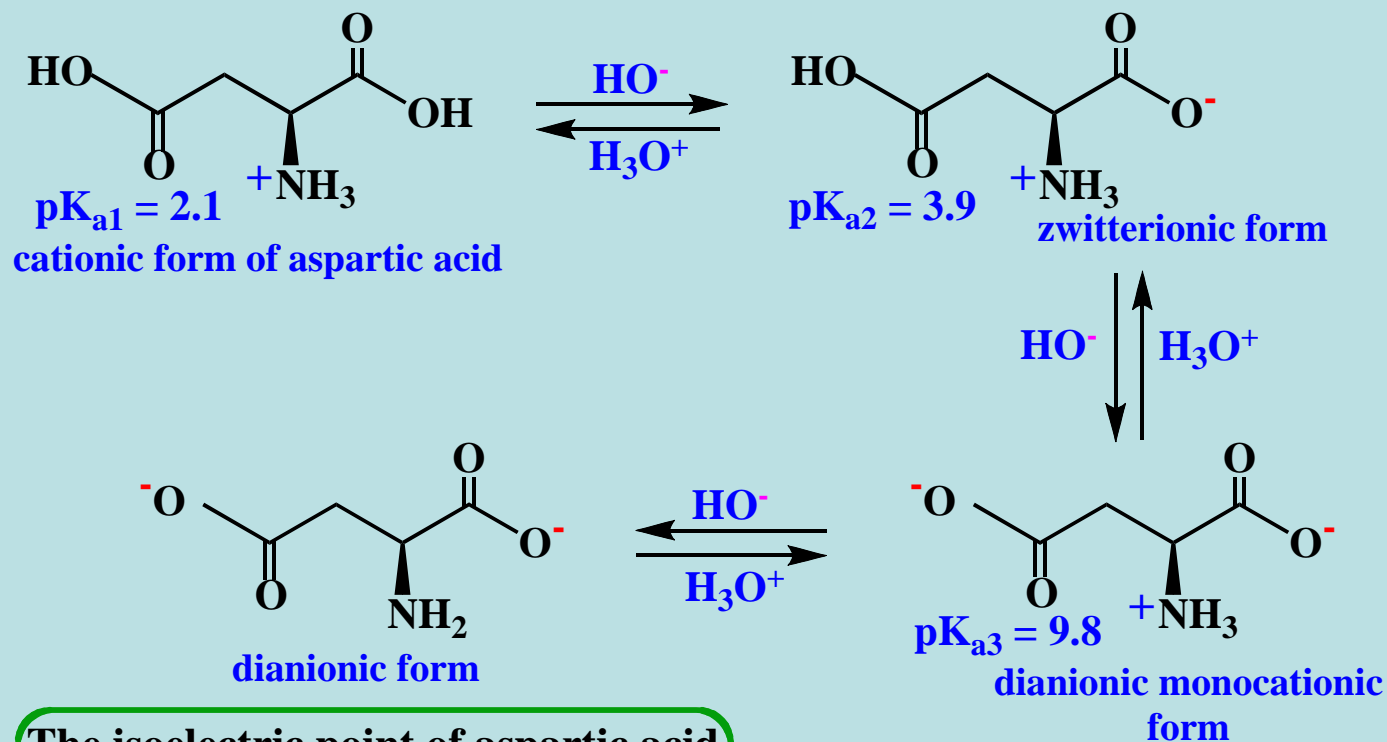


The isoelectric point of lysine is the average of pK_{a2} and pK_{a3} :

$$\text{pI} = \frac{9.0 + 10.5}{2} = 9.8$$

At $\text{pH} = 9.8$, the dominant lysine species in solution is the zwitterionic form just above.

Aspartic acid has one amino and two carboxyl functions. At low pH, it has three acidic functions that deprotonate in the order of their acid strengths as HO^- is added.



The isoelectric point of aspartic acid is the average of pK_{a1} and pK_{a2} :

$$\text{pI} = \frac{2.1 + 3.9}{2} = 3.0$$

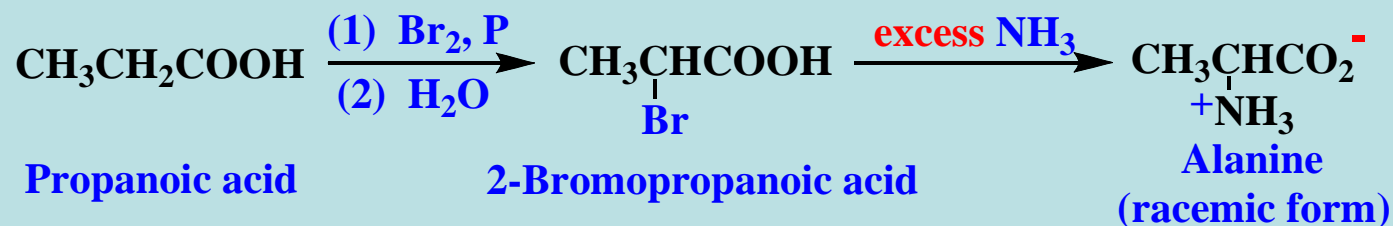
At $\text{pH} = 3.0$, the dominant form of aspartic acid is the neutral zwitterion.



Synthesis of α -Amino Acids

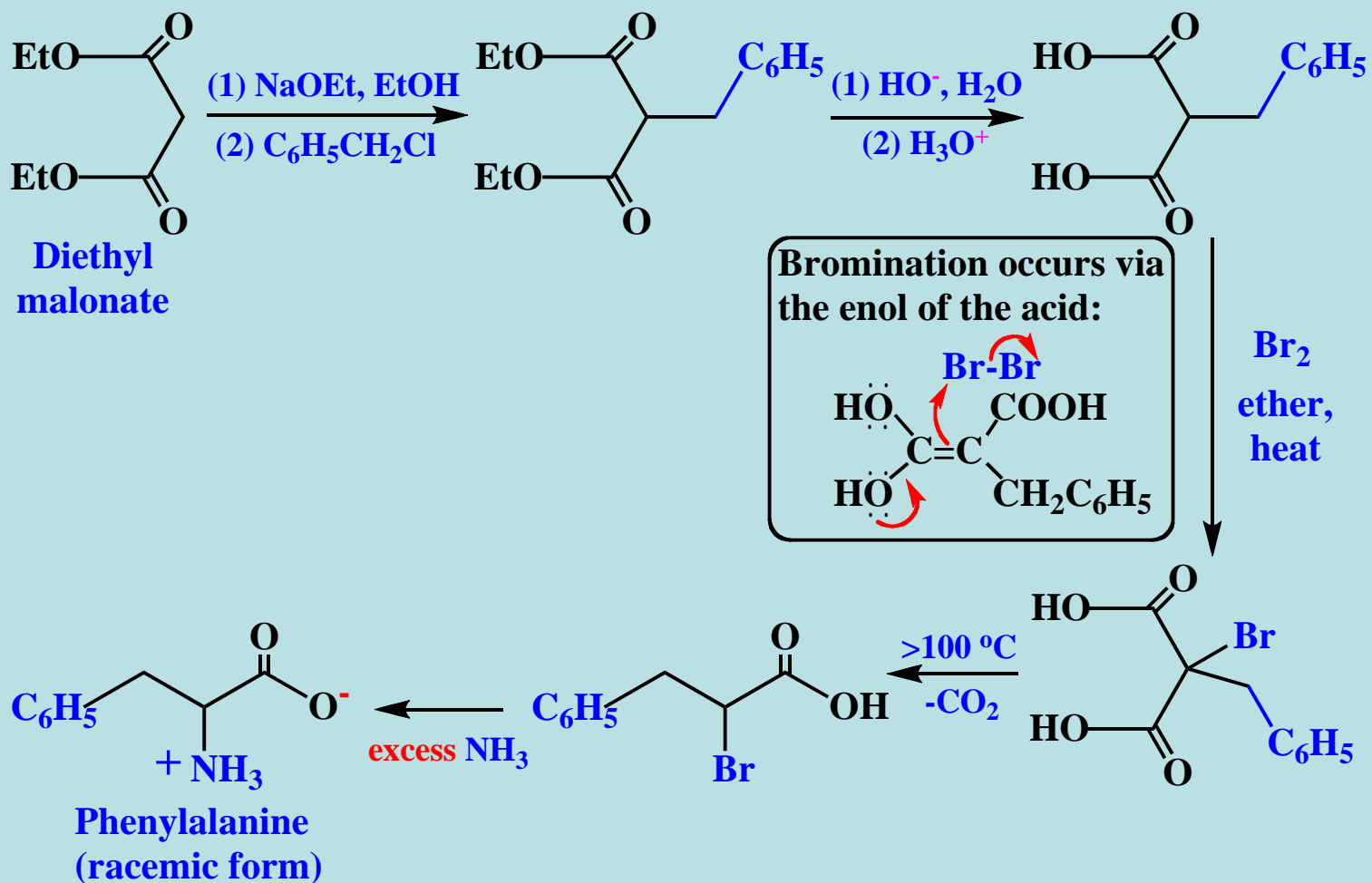
There are several standard syntheses of α -amino acids.

Direct Ammonolysis of α -Halo Acids

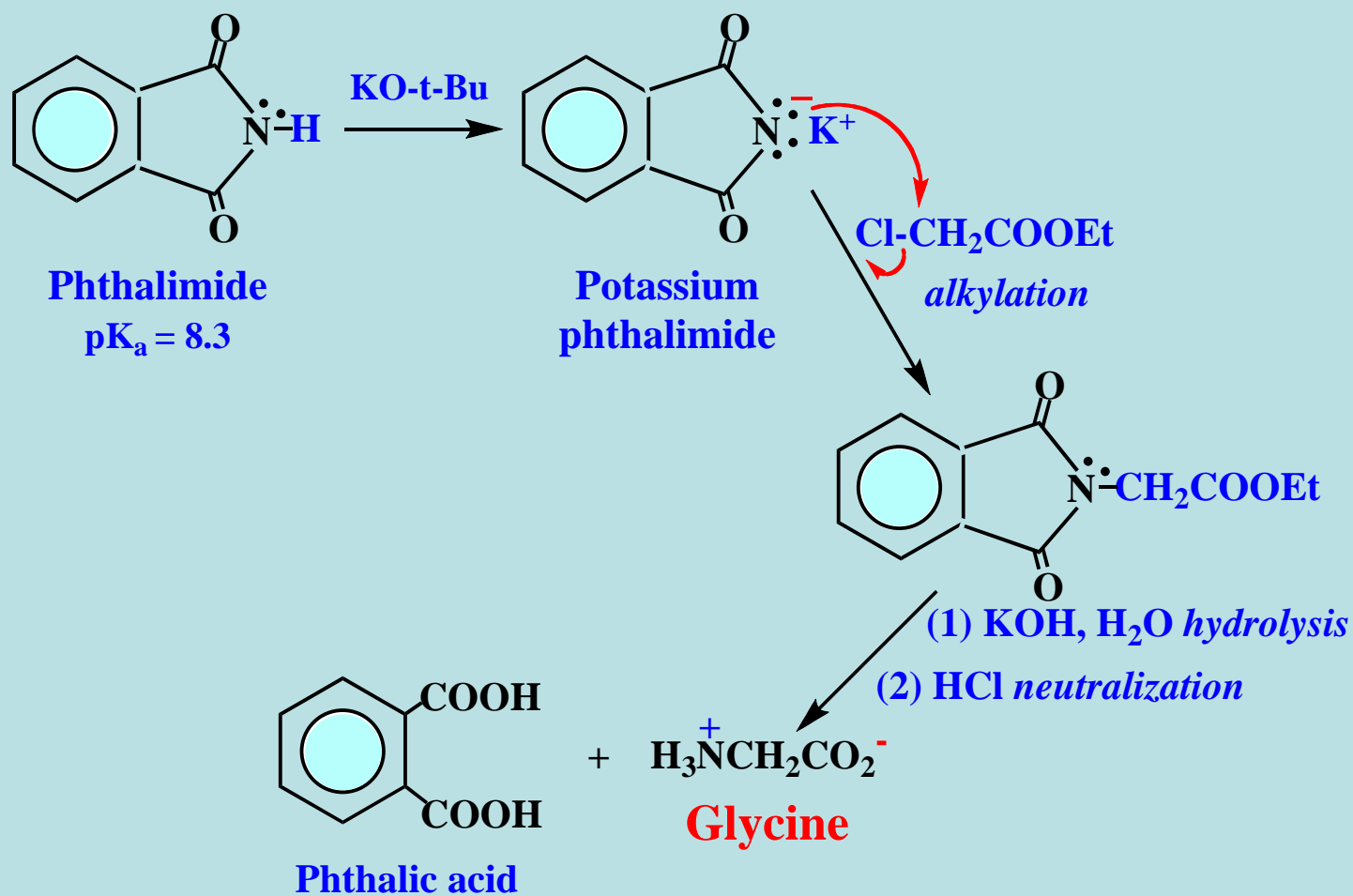


This is the method of amine or, as here, ammonia alkylation that is difficult to limit to monoalkylation, which is why an excess of ammonia is used.

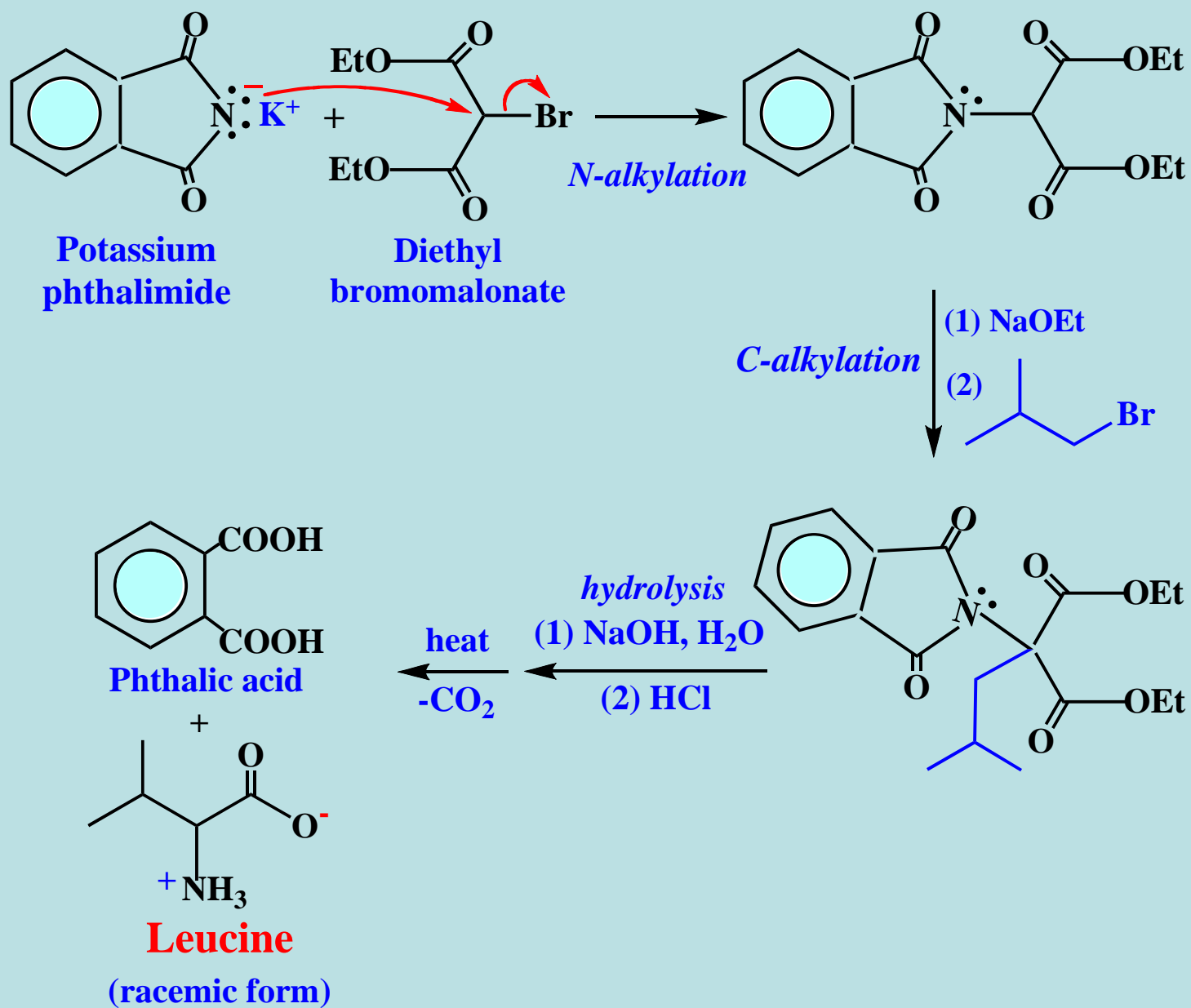
The Malonic Ester Synthetic Route



The Gabriel Synthesis: Potassium Phthalimide



The Malonic Ester Variation of the Gabriel Synthesis



The Strecker Synthesis

α -Amino acids may be prepared by reaction of an aldehyde, ammonia and hydrogen cyanide, followed by hydrolysis of the α -aminonitrile produced. This procedure is called the **Strecker synthesis** in recognition of Adolph Strecker (1822-71), who discovered the reaction in the laboratory of Justus von Liebig in 1850.



A Mechanism for the Strecker Synthesis

