# Biochemistry

**Unit 2 · Lesson 1 · Amino acids: structure and properties**

The notes for Lesson 1 of Unit 2: chapters 2.1 to 2.2 of the unit book, with their figures, worked examples, exam traps and quizzes, in one file. The full unit book, with every chapter, the exam question bank and the glossary, is linked at the end.

Lesson 1 of 4 | 2 chapters | Chapters 2.1 to 2.2

## About these notes

These are the notes for **Lesson 1 · Amino acids: structure and properties** of the University free n easy video lessons on Biochemistry Unit 2, Amino Acids and Proteins. They are chapters 2.1 to 2.2 of the unit book, unchanged, so a page here is the same page in the full book.

## 2.1 Amino acids: structure and classification

An amino acid is a small molecule with an amino group and a carboxyl group on the same carbon. Twenty of them, the standard amino acids, are coded by DNA and joined into proteins. They all share one backbone and differ only in one side chain, called R. The side chain decides whether the amino acid likes water, carries a charge or can form a cross-link, so learning the 20 side chains in five groups is the key to everything later in this unit: folding, protein properties and purification all follow from it.

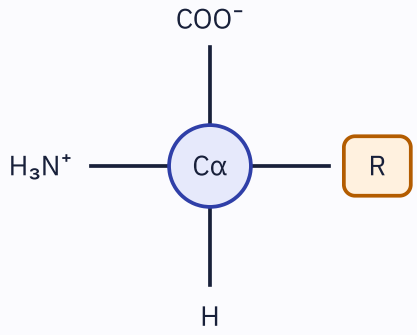
> You need: pH, pKa and weak interactions from Unit 1 (Water, weak interactions, pH and biological buffers).

### The common structure

Every standard amino acid is an α-amino acid. The central carbon is the α-carbon (Cα). Four groups hang on it: a carboxyl group (–COOH), an amino group ($–NH_2$), a hydrogen atom and the side chain R. In water at pH 7, the carboxyl group has lost its proton ($–COO^-$) and the amino group has gained one ($–NH_3^+$). A molecule with both a positive and a negative charge but no net charge is a **zwitterion** (German for "hybrid ion"). Chapter 2.2 uses this to explain the isoelectric point.

Proline is the exception in shape. Its side chain loops back and bonds to its own amino nitrogen, making a five-membered ring. Its nitrogen is therefore a secondary amine, and older books call proline an **imino acid**. The ring makes proline rigid, which matters for the α-helix (Chapter 2.4).

**Common structure at pH 7**




Same backbone in all 20;
only the side chain R differs.

**Grouped by side chain (R)**

**Nonpolar, aliphatic**
Gly, Ala, Pro, Val, Leu, Ile, Met

**Aromatic**
Phe, Tyr, Trp

**Polar, uncharged**
Ser, Thr, Cys, Asn, Gln

**Positively charged (basic)**
Lys, Arg, His

**Negatively charged (acidic)**
Asp, Glu

Top two groups: hydrophobic. Bottom three: hydrophilic.

**Figure 2.1.1** Left: every standard amino acid has the same four groups on its α-carbon; at pH 7 it is a zwitterion. Right: the five side-chain groups used by Lehninger and most syllabi. Notice that Gly (R = H) has no chiral centre and that Tyr and Trp are aromatic but still slightly polar.

## Classification by side chain

The table gives the three-letter and one-letter codes, which you must know for sequences.

| GROUP | AMINO ACIDS (3-LETTER, 1-LETTER) | WHAT THE SIDE CHAIN DOES |
|---|---|---|
| Nonpolar, aliphatic | `Gly G, Ala A, Pro P, Val V, Leu L, Ile I, Met M` | Hydrocarbon chains; pack together in the core of a protein. Met carries a thioether sulfur. |
| Aromatic | `Phe F, Tyr Y, Trp W` | Ring side chains; absorb UV light near 280 nm (Tyr, Trp). Tyr has an –OH, Trp an indole N–H. |
| Polar, uncharged | `Ser S, Thr T, Cys C, Asn N, Gln Q` | Form hydrogen bonds with water. Cys has a thiol (–SH) that forms disulfide bridges. Asn and Gln are the amides of Asp and Glu. |
| Positively charged | `Lys K, Arg R, His H` | Extra amino (Lys), guanidino (Arg) or imidazole (His) group; His side chain has pKa near 6, so it can gain or lose a proton near pH 7. |
| Negatively charged | `Asp D, Glu E` | Extra carboxyl group, ionised (–$COO^-$) at pH 7. |

Older Indian textbooks also group amino acids by the number of amino and carboxyl groups: **neutral** (one of each, such as Gly, Ala), **acidic** (an extra carboxyl: Asp, Glu), and **basic** (an extra basic group: Lys, Arg, His). Some add structural groups: sulfur-containing (Cys, Met), hydroxy (Ser, Thr), branched-chain (Val, Leu, Ile). These are the same 20 sorted a different way; learn the five-group table and derive the rest.

## Stereochemistry: L and D

Because Cα carries four different groups, it is a chiral centre and the amino acid has two mirror-image forms, called enantiomers. Glycine is the only standard amino acid that is not chiral, since its R is a second hydrogen. Proteins use only the **L** form. In a Fischer projection drawn with $-COO^-$ at the top and R at the bottom, the L form has the amino group on the left. L and D describe relation to L-glyceraldehyde, not the direction a solution rotates light; L-alanine is dextrorotatory, for example. D-amino acids do occur in nature: D-alanine and D-glutamate in the peptidoglycan of bacterial cell walls (Unit 5) and in some peptide antibiotics.

Threonine and isoleucine each have a second chiral carbon in the side chain, so each has four stereoisomers. Only one of the four is used in proteins.

## Nutritional, metabolic and other groupings

**Nutritional.** Humans cannot make nine amino acids fast enough and must eat them: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val. These are the **essential** (indispensable) amino acids. Many Indian textbooks call Arg and His semi-essential, because a growing child needs more than the body makes. Cereals such as rice and wheat are low in lysine, and pulses such as dal are low in methionine; that is why rice with dal gives better protein than either alone.

**Metabolic.** When the carbon skeleton is broken down, it can feed glucose synthesis (glucogenic), ketone body synthesis (ketogenic) or both. Leu and Lys are purely ketogenic; Ile, Phe, Trp and Tyr are both; the rest are glucogenic. The pathways are in Unit 6 (Amino acid catabolism).

**Beyond the 20.** Selenocysteine (coded by a UGA codon with a special signal) and pyrrolysine (UAG, in some archaea and bacteria) are sometimes called the 21st and 22nd amino acids. Other residues are made by changing a standard one after the protein is built: 4-hydroxyproline and 5-hydroxylysine in collagen, phosphoserine in signalling proteins. Some amino acids are never in proteins at all: ornithine and citrulline (urea cycle, Unit 6) and GABA, a brain neurotransmitter.

## WORKED EXAMPLE

**Question (6 marks).** For Val, Ser, Lys, Glu, Tyr and His: (a) give the side-chain group, (b) state the charge on the side chain at pH 7.4, (c) mark which are essential in humans. (d) How many stereoisomers does threonine have?

1. **Val**: nonpolar aliphatic (branched chain); side chain uncharged; essential.
2. **Ser**: polar uncharged ($-CH_2OH$); uncharged; not essential (made from a glycolysis intermediate).
3. **Lys**: positively charged; side-chain amino group (pKa about 10.5) is protonated at pH 7.4, so +1; essential.
4. **Glu**: negatively charged; side-chain carboxyl (pKa about 4.3) is ionised, so −1; not essential.
5. **Tyr**: aromatic; phenol –OH (pKa about 10) stays protonated, so uncharged; not essential (made from Phe).
6. **His**: positively charged group, but its imidazole pKa is about 6.0. At pH 7.4, which is 1.4 units above the pKa, only about 1 in 26 molecules carries the proton (ratio $10^{1.4} \approx 25$ to 1). So the side chain is mostly neutral, with a small positive fraction. Essential.
7. **Threonine** has two chiral centres (Cα and Cβ), so $2^2 = 4$ stereoisomers; proteins use only L-threonine.

## EXAM TRAPS

- Glycine is not chiral; do not draw L- and D-glycine.
- L does not mean levorotatory. The L/D label is about configuration, not the sign of optical rotation.
- Histidine is grouped as "basic", but at pH 7 its side chain is mostly uncharged. Examiners like asking why His is common in enzyme active sites: because it can both give and take a proton near pH 7.
- Asn and Gln are polar but not acidic. They are amides, not carboxylic acids.
- Write "essential" as nutritionally essential. All 20 are needed in proteins; "essential" only means the diet must supply it.

## CHECK YOURSELF

– REMEMBER **List the nine essential amino acids for adults.** 2 marks

His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val. (Arg is called semi-essential in many Indian textbooks.)

– REMEMBER **Which standard amino acid is not optically active, and why?** 2 marks

Glycine; its α-carbon carries two hydrogen atoms, so it has no four different groups and no chiral centre.

– UNDERSTAND **Why is proline called an imino acid?** 2 marks

Its side chain is bonded to the α-amino nitrogen, forming a ring, so the nitrogen carries only one hydrogen (a secondary amine, –NH–) instead of a free $–NH_2$.

– UNDERSTAND **Explain the difference between glucogenic and ketogenic amino acids with one example of each.** 4 marks

Glucogenic amino acids give pyruvate or citric acid cycle intermediates that can be turned into glucose (Ala, Ser). Ketogenic ones give acetyl-CoA or acetoacetate, which form ketone bodies but not glucose (Leu, Lys).

– APPLY **Write the one-letter sequence for Met-Lys-Trp-Glu-Asn-Gln.** 2 marks

M K W E N Q, written MKWENQ.

– APPLY **At pH 7, what is the net charge of free lysine and of free aspartate?** 3 marks

Lysine: α-$COO^-$ (–1), α-$NH_3^+$ (+1), side-chain $NH_3^+$ (+1), net +1. Aspartate: α-$COO^-$ (–1), α-$NH_3^+$ (+1), side-chain $COO^-$ (–1), net –1.

– ANALYZE **A protein has many Leu, Val and Phe residues inside and many Lys and Glu on its surface. Explain this pattern.** 4 marks

Nonpolar side chains (Leu, Val, Phe) avoid water and cluster in the core (the hydrophobic effect). Charged side chains (Lys, Glu) interact with water and with ions, so they sit on the surface, where they also keep the protein soluble.

BEYOND THE SYLLABUS

Chemists can now add amino acids that nature does not use. In genetic code expansion, a cell is given an extra tRNA and enzyme pair that puts a chosen unnatural amino acid at a stop codon, for example to attach a fluorescent label or a drug to an antibody. D-amino acids are used to make peptide drugs that the body's proteases cannot easily cut. Search "genetic code expansion" and "noncanonical amino acids". This is not for the exam.

## 2.2 Physical, chemical and biological properties of amino acids

Amino acids behave the way they do because they are zwitterions: each carries a positive and a negative charge at once. That explains their high melting points, water solubility and acid–base behaviour. Their amino and carboxyl groups also react with lab reagents in ways used to detect and sequence them, and inside the body they are raw material for hormones, neurotransmitters and haem.

You need: the side-chain groups from Chapter 2.1 and the Henderson–Hasselbalch equation from Unit 1.

### Physical properties

- **State and melting point.** Colourless crystalline solids that melt (usually with decomposition) above 200 °C, because the crystal is held by ionic attraction between zwitterions, like a salt.
- **Solubility.** Soluble in water, poorly soluble in nonpolar solvents such as ether. Least soluble at the isoelectric point.
- **Optical activity.** All except glycine rotate plane-polarised light (Chapter 2.1).
- **UV absorption.** Tryptophan and tyrosine absorb strongly near 280 nm; this is why protein solutions are measured at 280 nm (Chapter 2.8).

### Amphoteric behaviour and the isoelectric point

An amino acid can give a proton (from $-NH_3^+$) or take one (on $-COO^-$), so it is **amphoteric**. Titrating glycine with NaOH shows two buffering plateaus. Near $pKa_1 = 2.34$ the carboxyl loses its proton; near $pKa_2 = 9.60$ the amino group does. Between them sits the **isoelectric point (pI)**, the pH at which the average net charge is zero and the molecule does not move in an electric field.

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For an amino acid with no ionisable side chain:
  pI = (pKa₁ + pKa₂) / 2
For an acidic or basic amino acid:
  pI = average of the two pKa values on either side of the neutral (zwitterion) form
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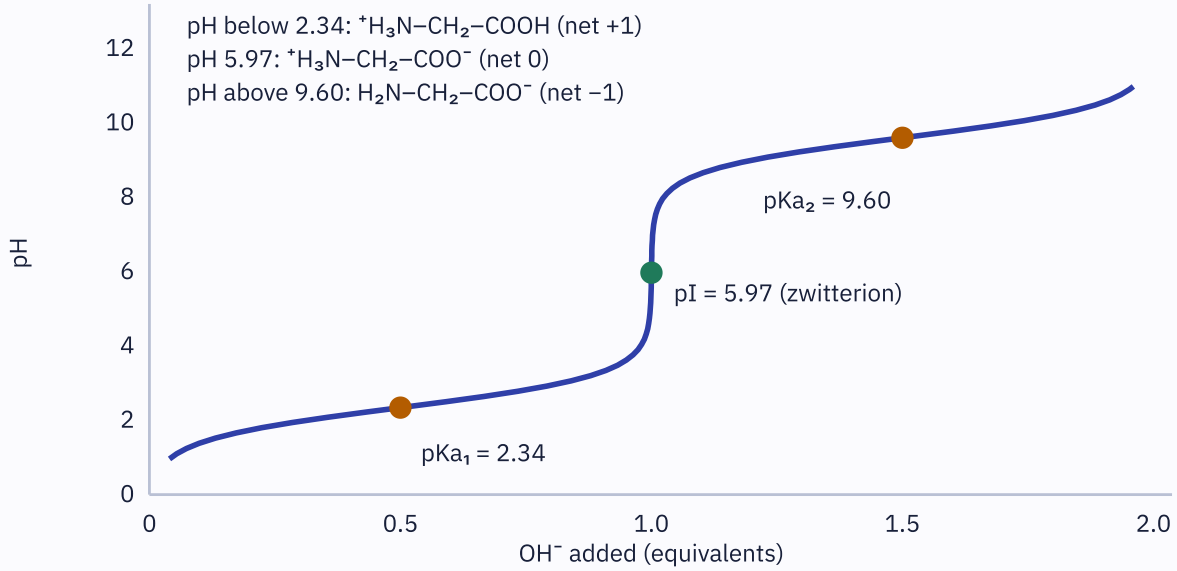



**Figure 2.2.1** Titration curve of glycine, computed from $pKa_1 = 2.34$ and $pKa_2 = 9.60$ with the Henderson–Hasselbalch equation (water's own buffering ignored). The flat parts are where glycine buffers best; the steep part at 1 equivalent is the isoelectric point.

## Chemical properties

- **Ninhydrin.** Heated with ninhydrin, free α-amino acids give a purple colour (Ruhemann's purple). Proline, with its ring nitrogen, gives yellow. Used to detect amino acids on paper chromatograms and in amino acid analysers.
- **Sanger's reagent (FDNB)** and **Edman's reagent (phenyl isothiocyanate)** attach to a free amino group; they identify the N-terminal residue of a peptide (Chapter 2.3).
- **Decarboxylation** removes $CO_2$ and gives an amine: histidine → histamine, tryptophan (via 5-hydroxytryptophan) → serotonin, glutamate → GABA.
- **Thiol oxidation.** Two cysteine molecules oxidise to cystine, joined by a disulfide (–S–S–) bond.

## Biological roles, and glycine and cysteine

Besides building proteins, amino acids are precursors: tyrosine gives adrenaline, thyroxine and melanin; tryptophan gives serotonin and niacin; arginine gives nitric oxide. **Glycine** is the smallest amino acid; it is used to make haem, purines and creatine, conjugates bile acids (glycocholic acid) and is an inhibitory neurotransmitter in the spinal cord. **Cysteine** forms

disulfide bridges that hold proteins such as insulin and keratin together, and supplies the –SH of glutathione (γ-Glu-Cys-Gly), the cell's main antioxidant, and of coenzyme A.

### WORKED EXAMPLE

**Question (5 marks).** (a) Calculate the pI of glycine (pKa 2.34 and 9.60). (b) Aspartate has pKa values 1.88 (α-COOH), 3.65 (side-chain COOH) and 9.60 (α-$NH_3^+$). Find its pI. (c) In electrophoresis at pH 6.0, which way does each move?

1. Glycine: pI = (2.34 + 9.60) / 2 = 11.94 / 2 = **5.97**.
2. Aspartate: list forms from low pH. Net +1 (all protonated) → lose α-COOH proton at 1.88 → net 0 → lose side-chain proton at 3.65 → net −1 → lose amino proton at 9.60 → net −2.
3. The neutral form lies between pKa 1.88 and 3.65, so pI = (1.88 + 3.65) / 2 = **2.77**.
4. At pH 6.0 glycine is very slightly above its pI, so it is almost neutral and hardly moves. Aspartate is far above its pI, so it is negative and moves toward the anode (+).

### EXAM TRAPS

- For acidic and basic amino acids, do not average all three pKa values. Average only the two around the neutral form.
- At the pI, the molecule is not uncharged; it carries + and − charges that cancel.
- Ninhydrin with proline is yellow, not purple. Examiners ask why: proline has a secondary amino group.
- Cystine (two residues, S–S) and cysteine (one residue, SH) are different molecules.

### CHECK YOURSELF

– REMEMBER **Define isoelectric point.** 1 mark

The pH at which an amino acid or protein has zero net charge and does not move in an electric field.

– UNDERSTAND **Why do amino acids have high melting points compared with organic molecules of similar size?** 2 marks

In the solid they are zwitterions held by strong ionic attractions, like a salt crystal, not by weak van der Waals forces.

– UNDERSTAND **Why does ninhydrin give a yellow colour with proline but purple with other amino acids?** 2 marks

Proline has a secondary amino group in a ring, so it forms a different (yellow) product; primary α-amino groups give Ruhemann's purple.

– APPLY **Lysine has pKa values 2.18, 8.95 and 10.53. Find its pI.** 3 marks

Forms: +2 → +1 (after 2.18) → 0 (after 8.95) → −1 (after 10.53). Neutral form lies between 8.95 and 10.53, so pI = (8.95 + 10.53)/2 = 9.74.

– ANALYZE **A mixture of Asp, Gly and Lys is run in electrophoresis at pH 6. Predict the order of movement.** 4 marks

Asp (pI 2.77) is negative and moves to the anode; Gly (pI 5.97) is about neutral and stays near the start; Lys (pI 9.74) is positive and moves to the cathode.

BEYOND THE SYLLABUS

Modern amino acid analysis hydrolyses a protein in 6 M HCl, separates the free amino acids by HPLC and detects them after a labelling reaction, or by mass spectrometry. Glutamate and lysine for food and animal feed are made on an industrial scale by fermentation with the bacterium Corynebacterium glutamicum. Search "amino acid fermentation" and "pKa shifts in proteins". This is not for the exam.

## Key terms of this lesson

| TERM | MEANING OR FORMULA | CHAPTER |
|---|---|---|
| α-Amino acid | Cα carrying $–COO^-$, $–NH_3^+$, H and side chain R; L form in proteins | 2.1 |
| Essential amino acids | His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val | 2.1 |
| Isoelectric point | $pI = (pKa_1 + pKa_2)/2$, averaging the two pKa values around the neutral form | 2.2 |
| Henderson–Hasselbalch | $pH = pKa + \log([A^-]/[HA])$ | 2.2 |

## Glossary (terms used in this lesson)

| | |
|---|---|
| **Amphoteric** | Able to act as both an acid and a base. |
| **Disulfide bridge** | A covalent –S–S– bond between two cysteine side chains. |
| **Essential amino acid** | One the body cannot make in enough amount; it must come from food. |
| **Hydrophobic effect** | The tendency of nonpolar groups to cluster away from water, which drives folding. |
| **Isoelectric point (pI)** | The pH at which a molecule has zero net charge. |
| **Residue** | An amino acid unit within a peptide chain. |
| **Zwitterion** | A molecule with both positive and negative charges and no net charge. |

## The full unit book

Every chapter of Unit 2, the unit summary, the exam question bank with model answers and the full glossary: Biochemistry · Unit 2 · Amino Acids and Proteins (one file, works offline).

## Sources and further reading

### Textbooks


- David L. Nelson and Michael M. Cox, *Lehninger Principles of Biochemistry*, W. H. Freeman; chapters on amino acids, peptides and proteins, and on protein structure (from memory; check). Source of the pKa values used here.
- Jeremy M. Berg, John L. Tymoczko, Gregory J. Gatto Jr. and Lubert Stryer, *Biochemistry*, W. H. Freeman; chapters on protein composition and structure and on exploring proteins (from memory; check).
- Donald Voet and Judith G. Voet, *Biochemistry*, Wiley (from memory; check).
- U. Satyanarayana and U. Chakrapani, *Biochemistry*, Elsevier India; widely prescribed in Indian universities for the classification of proteins and colour reactions (from memory; check).


### Open resources opened for this book


- G. N. Ramachandran, C. Ramakrishnan and V. Sasisekharan, "Stereochemistry of polypeptide chain configurations", *Journal of Molecular Biology* 7 (1963) 95–99, record at the Indian Academy of Sciences repository: repository.ias.ac.in/49564.

- C. B. Anfinsen, "Principles that govern the folding of protein chains", *Science* 181 (1973) 223–229 (the Nobel lecture): PDF copy. Source of the ribonuclease details in Chapter 2.6.
- Nobel Prize page for Anfinsen's lecture, 1972: nobelprize.org.

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