Proteins

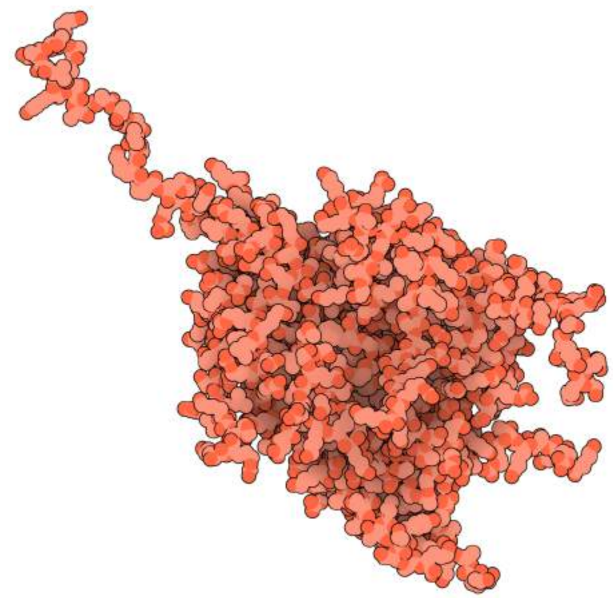
Major workhorses of the cell and most abundant macromolecules

PROTEINS

- CHANNELS & PUMPS (e.g. Na^+K^+ ATPase)
- STRUCTURE & MECHANICS (e.g. actin, myosin)
- TRANSPORT (e.g. rhodopsin)
- ENZYMES (e.g. trypsin, kinase, DNA polymerase)
- ACID-BASE BALANCE (e.g. plasma proteins)
- HORMONES (e.g. insulin, glucagon)
- ANTIBODIES (e.g.Immunoglobulins IgA, IgG)
- SIGNALING MOLECULES (e.g. adenylyl cyclase)
- FLUID BALANCE (e.g. albumin, vasopressin)

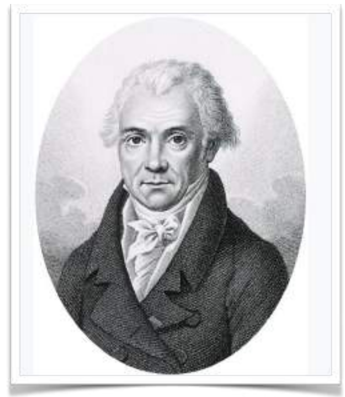
A diverse array of proteins perform a range of cellular functions.
Proteins are polymers of amino acids.

Amino acids: building blocks of Proteins



Discovery of amino acids

- The first few amino acids were discovered in the early 19th century
- First amino acid was discovered in 1806
- Proteins were found to yield amino acids after digestion or acid hydrolysis



Louis-Nicolas Vauquelin

Pierre Jean Robiquet

French chemists that isolated a compound in asparagus eventually named as **asparagine** (the first amino acid to be discovered)

Emil Fischer

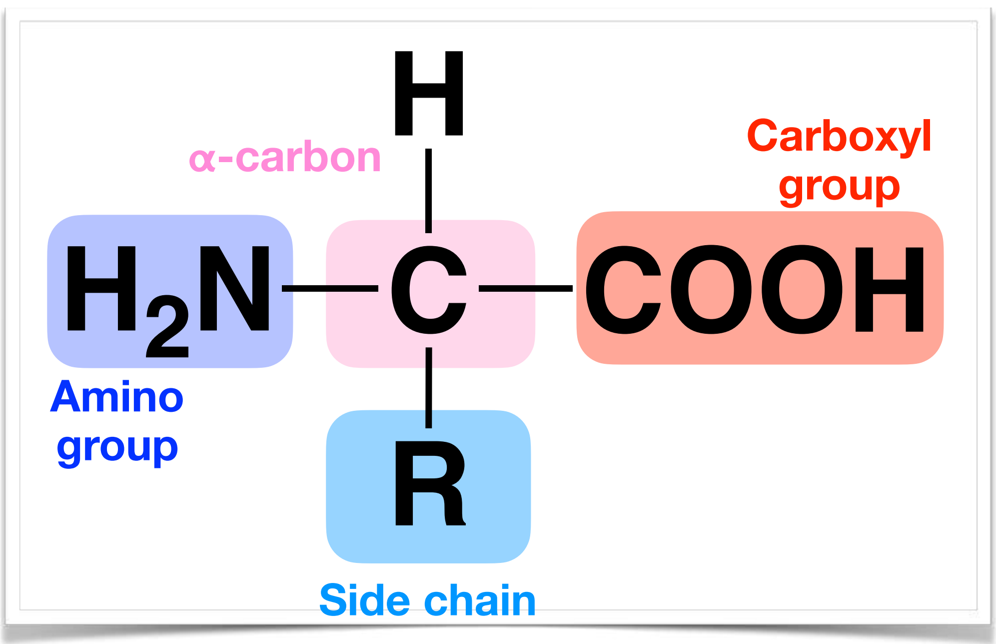
Franz Hofmeister

In 1902, two scientists independently proposed that proteins are formed from many amino acids.

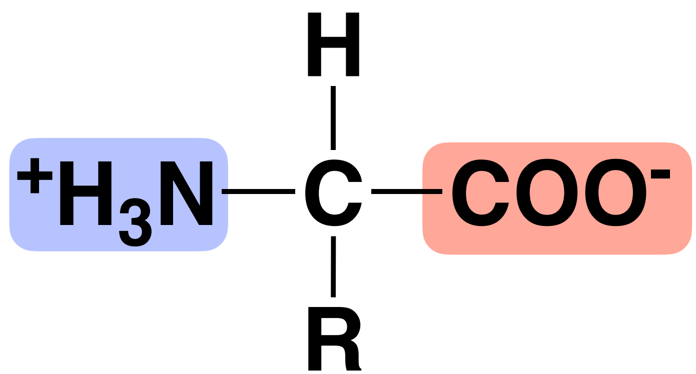
Fischer termed the resulting linear structure that "peptide".

Amino acids

General structure and properties



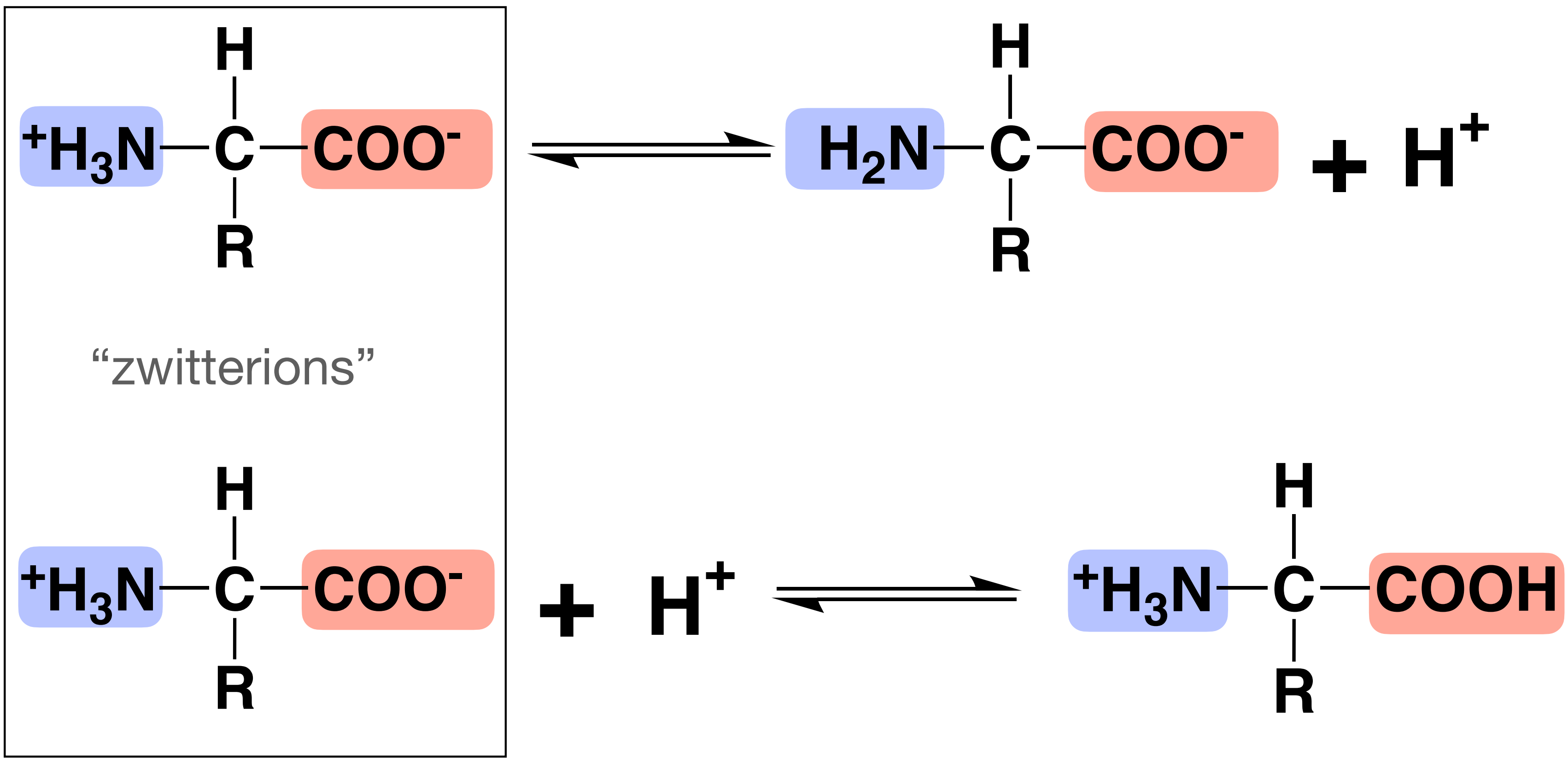
Zwitterionic form



- When dissolved in water an amino acid exists as the dipolar ionic form or as a "zwitterion"

Amino acids

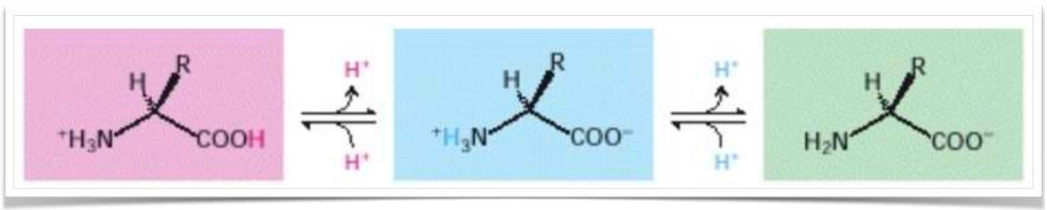
Acid or base?

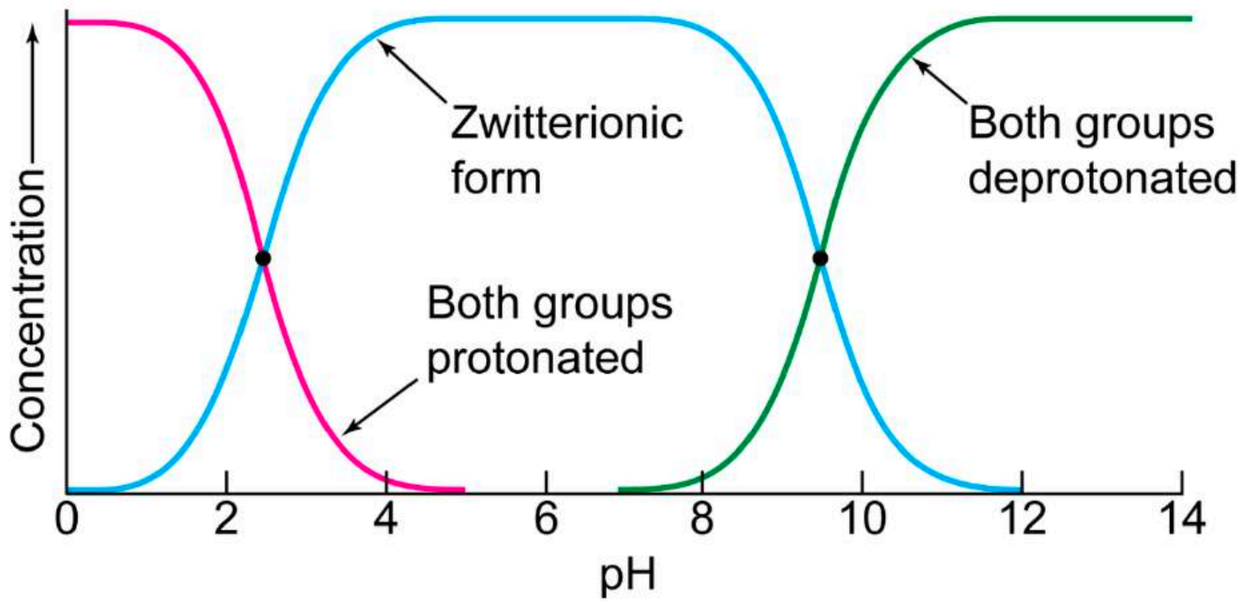


Proton donor
i.e. “acid”

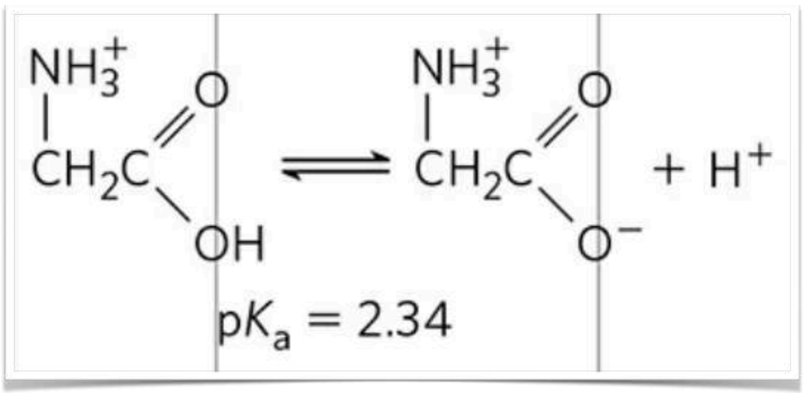
Proton
acceptor
i.e.“base”

pH titration vs zwitterion formation



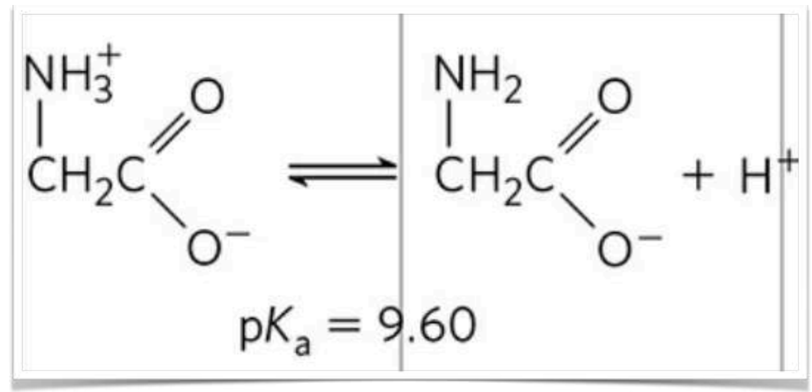


pH

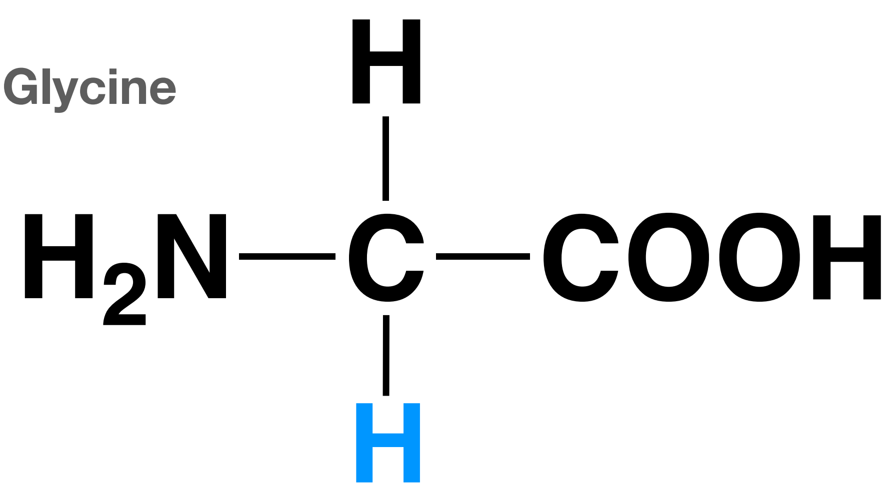


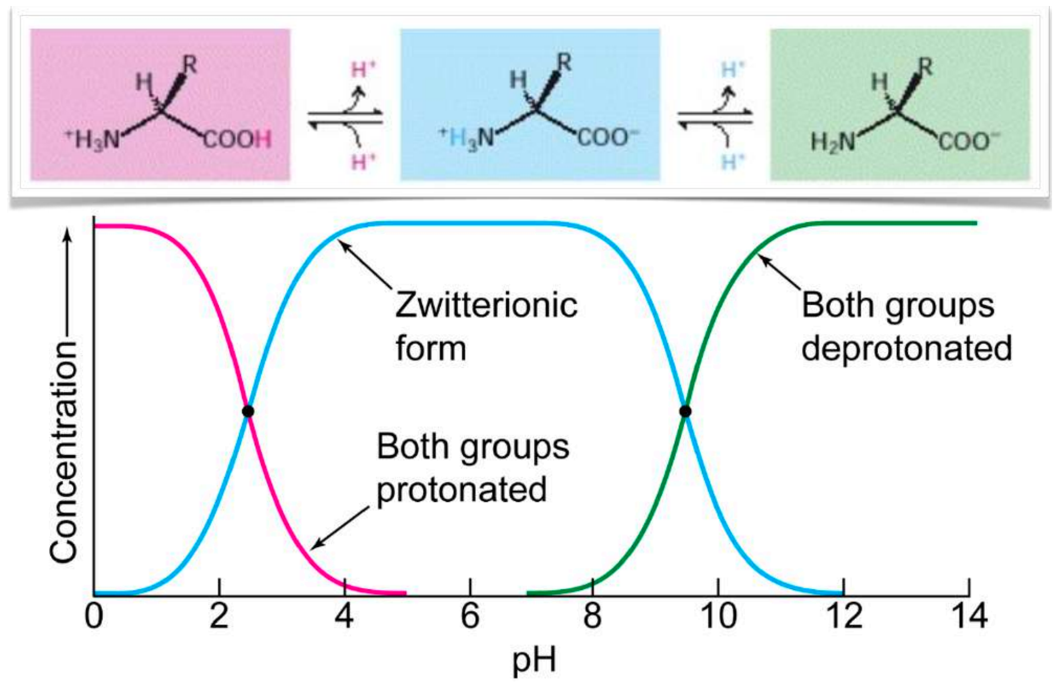
Glycine, carboxyl
($K_a = 4.57 \times 10^{-3}$ M);

Glycine, amino
($K_a = 2.51 \times 10^{-10}$ M)



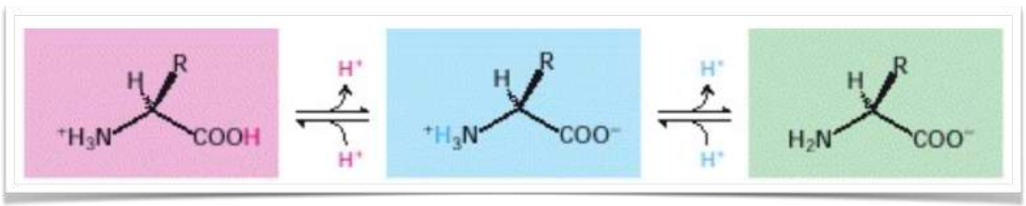
Glycine

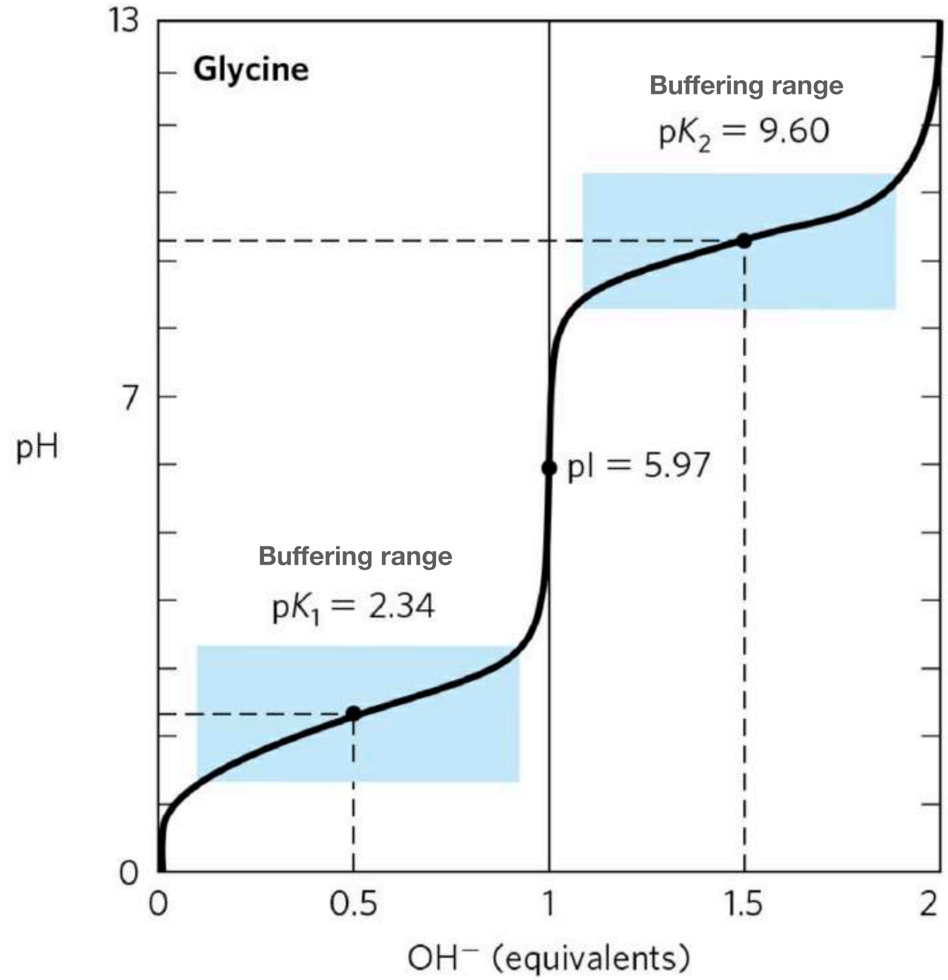




Isolectric point (pI)

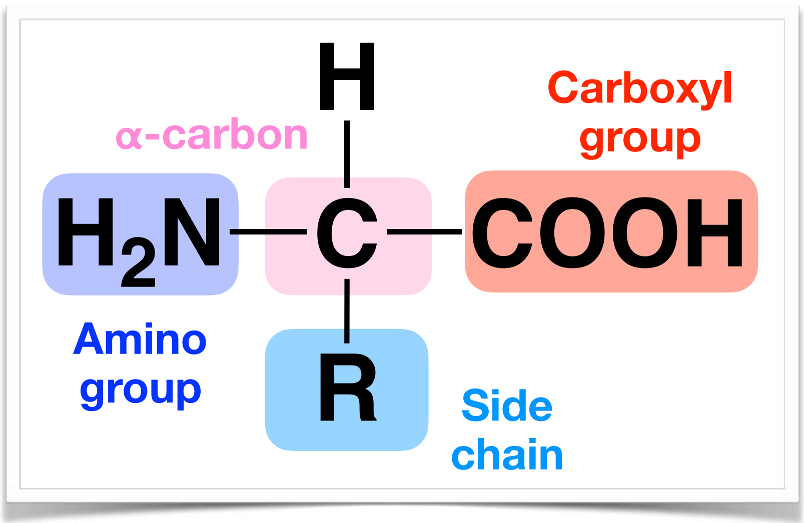
Isoelectric point (pI) of an **amino acid** is the **pH at which the amino acid has a neutral charge**.

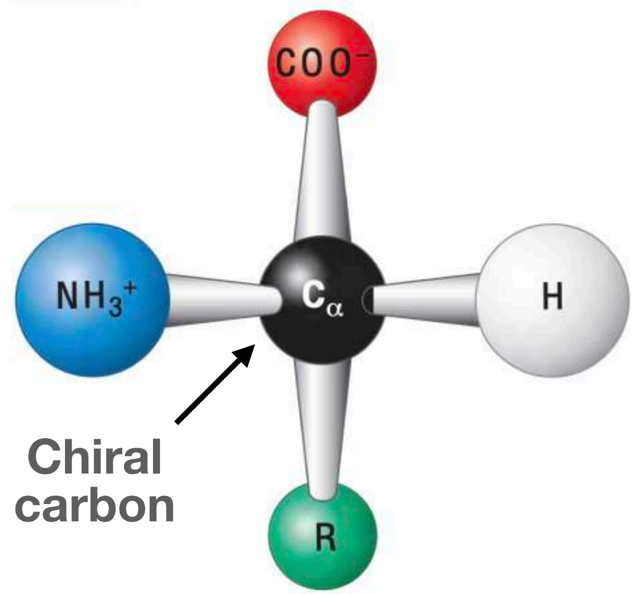




Amino acid stereochemistry

Chirality

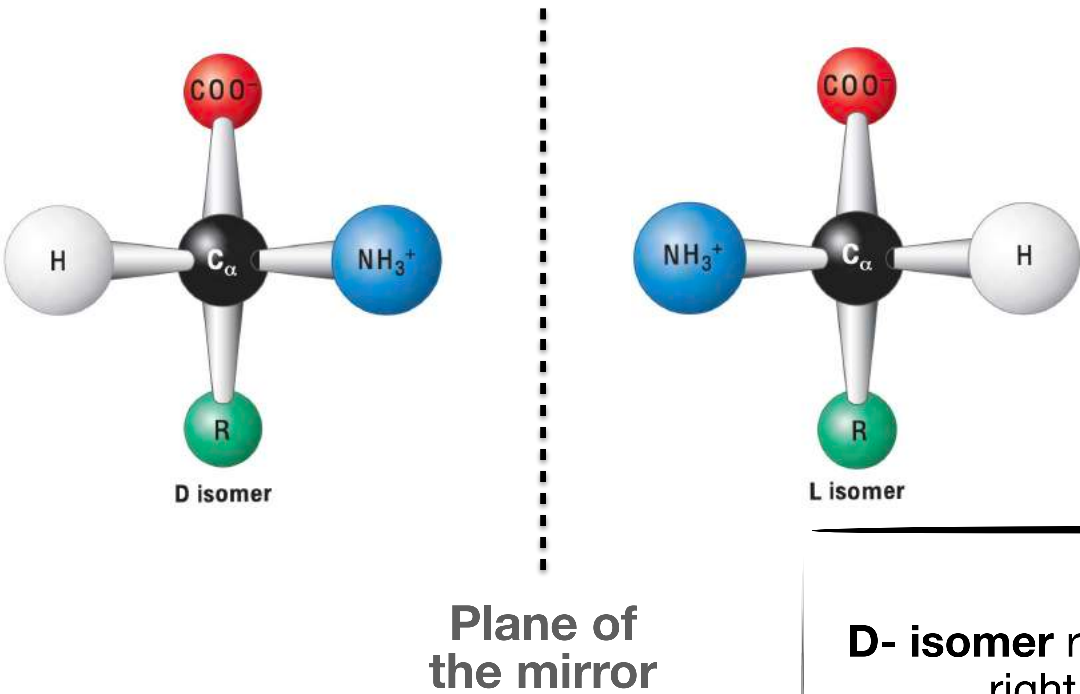




- The central alpha-carbon of an amino acid asymmetric since it is surrounded by 4 different substituent groups and is known as a **"chiral center"**. In **achiral** carbons this asymmetry does not exist.
- In 3D these four substituents can adopt two different configurations, also known as **stereoisomers**

Amino acid stereochemistry

D- and L-isomers



- Both D- and L- stereoisomers exist in nature and are mirror images of each other.
- Such non-superimposable, mirror images are called **enantiomers**.
- **Amino acids in proteins are all L-isomers.**

Generally:

D- isomer rotates the plane of plane polarized light to the right, where "D" stands for "dextrorotatory"

L-isomer rotates the plane of plane polarized light to the left, where "L" stands for "levorotatory"

AMINO ACIDS ARE AN EXCEPTION TO THIS RULE

Life as we know it has a "handedness"

But scientists don't care…

Cell Chemical Biology

Article

Copying Life: Synthesis of an Enzymatically Active Mirror-Image DNA-Ligase Made of D-Amino Acids

Joachim Weidmann,[1,2] Martina Schnölzer,[3] Philip E. Dawson,[2,4] and Jörg D. Hoheisel[1,4,5,*]

[1]Functional Genome Analysis, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany

[2]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

[3]Functional Proteome Analysis, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 581, 69120 Heidelberg, Germany

[4]These authors contributed equally

[5]Lead Contact

*Correspondence: j.hoheisel@dkfz.de

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"Our objective is the creation of an enantiomeric, self- replicating molecular system
Toward this end, a DNA-ligase in D-enantiomeric protein conformation was synthesized
This mirror-image to the natural enzyme exhibits activity on chirally inverted DNA…"

But scientists don’t care…

Cell Chemical Biology

Article

Interactions between biological molecules are almost invariably stereospecific: they require a close fit between complementary structures in the interacting molecules.

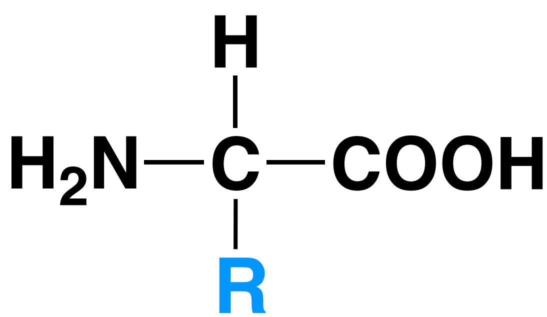
https://doi.org/10.1016/j.chembiol.2019.02.008

Our objective is the creation of an enantiomeric, self- replicating molecular system

Toward this end, a DNA-ligase in D-enantiomeric protein conformation was synthesized

This mirror-image to the natural enzyme exhibits activity on chirally inverted DNA

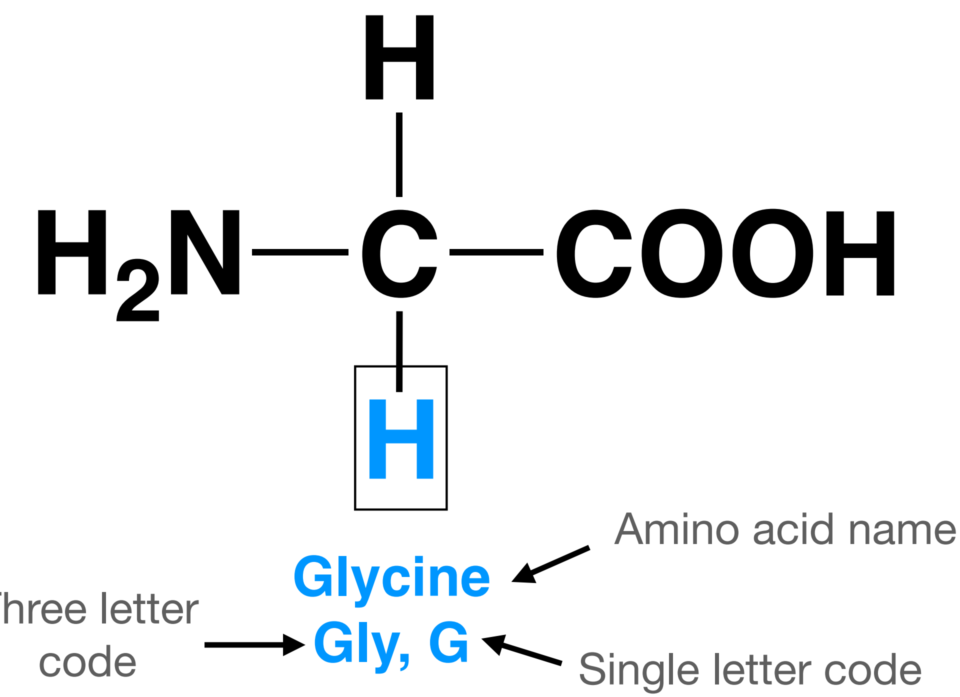
Amino acids: side chains determine identity



- 20 amino acids that are "proteinogenic" amino acids form proteins.
- This fundamental alphabet of proteins is several billion years old.
- Contain an alpha-carboxyl group, an alpha amino group, and a distinctive R group substituted on the alpha carbon atom.
- The side chains vary in size, shape, charge, hydrogen-bonding capacity, hydrophobic character, and chemical reactivity.
- All proteins in all species—bacterial, archaeal, and eukaryotic—are constructed from the same set of 20 amino acids.

Proteinogenic amino acids

Glycine: the simplest amino acid



Glycine

Gly, G

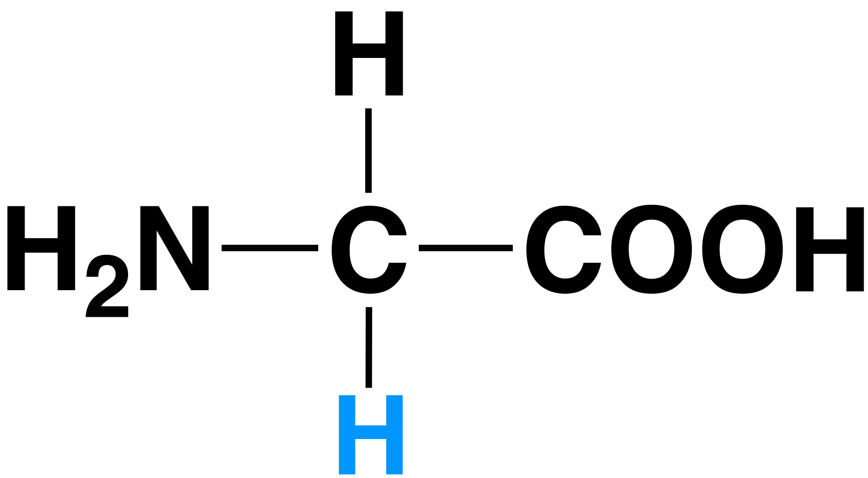
Margaret Oakley Dayhoff

1925-1983

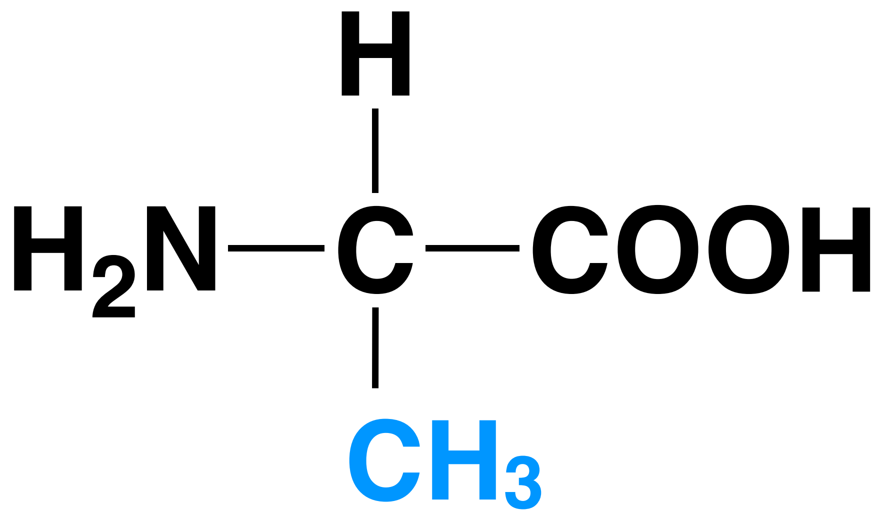
- Early pioneer “bioinformatician”
- In 1965, first published her collection of the 65 known proteins in the *Atlas of Protein Sequence and Structure*
- Developed the concept of phylogenetic tree
- The one- letter code was devised by her in an attempt to reduce the size of the data files (in an era of punch-card computing) used to describe amino acid sequences.

Proteinogenic amino acids

Non-polar side chains



Glycine
Gly, G

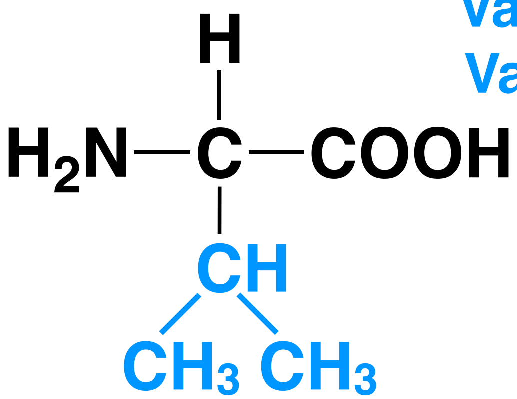


Alanine
Ala, A

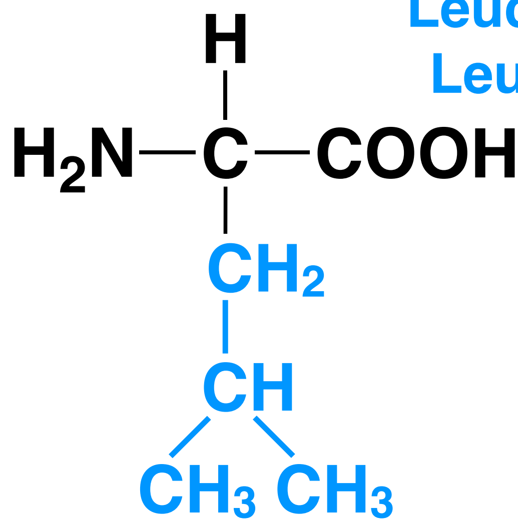
Proteinogenic amino acids

Nonpolar side chains contd.

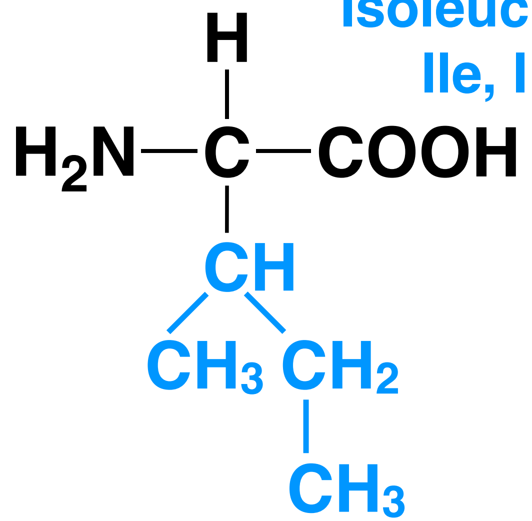
Valine
Val, V



Leucine
Leu, L

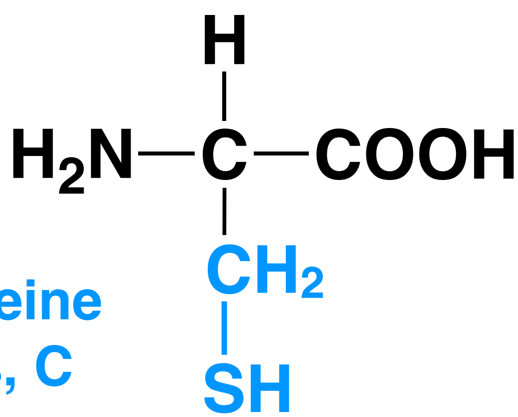


Isoleucine
Ile, I

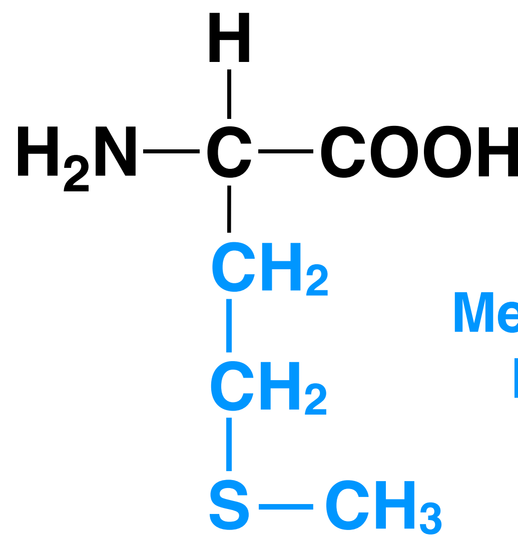


Proteinogenic amino acids

Sulphur containing



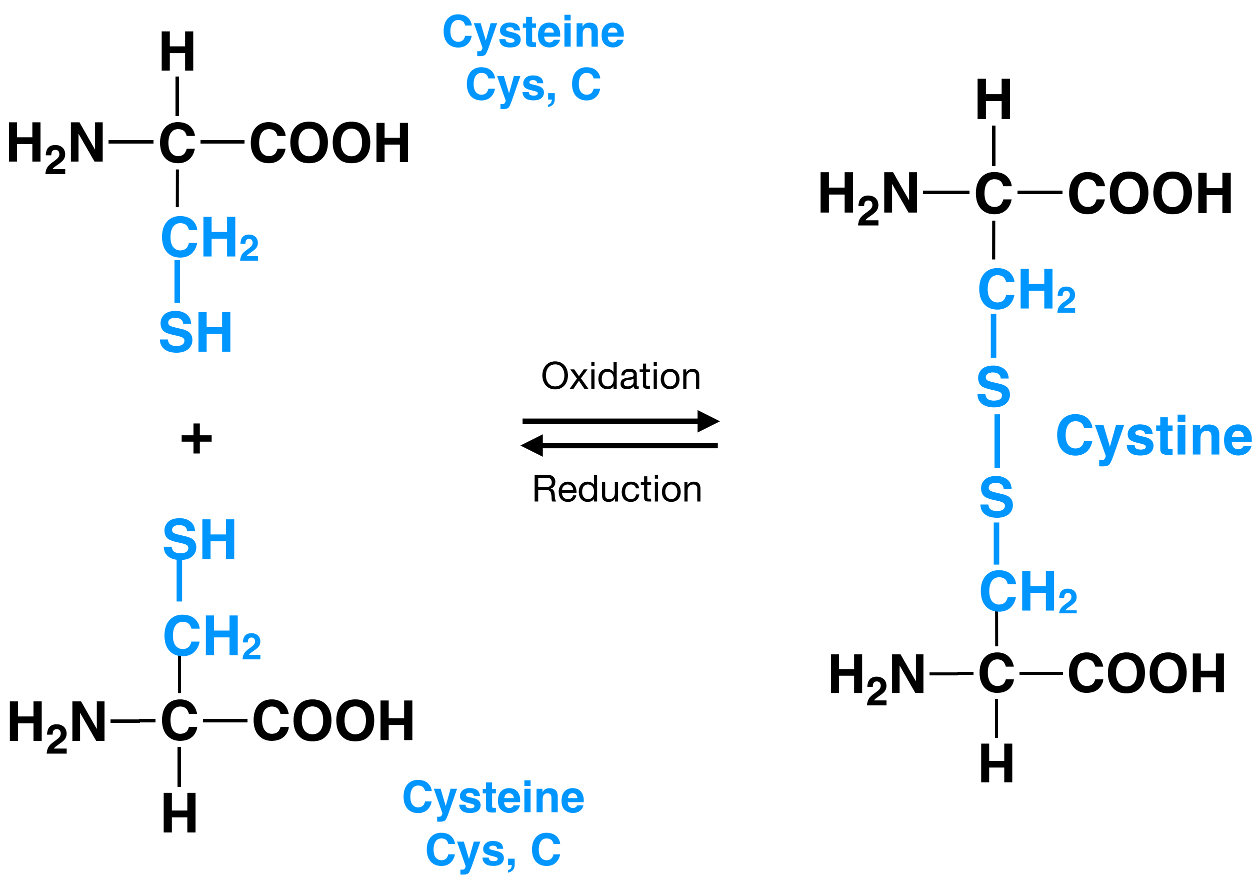
Cysteine
Cys, C



Methionine
Met, M

Cystine

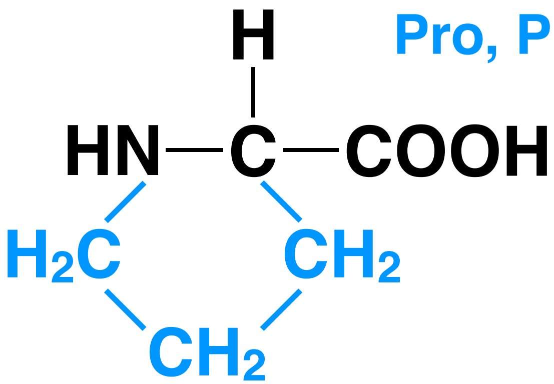
Disulfide bonds



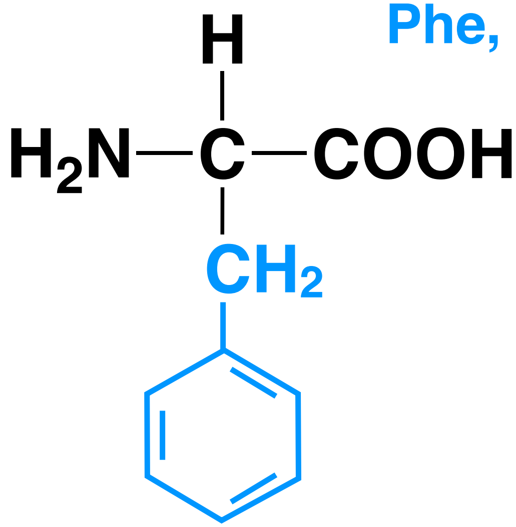
- **Disulfide bridges** (or S-S linkages/bonds) can form between two side chain cysteines and result in a cystine.
- S-S bonds are important for the structural integrity of peptides and proteins and influence protein structure at the secondary and tertiary levels.

Proteinogenic amino acids
Nonpolar side chains contd.

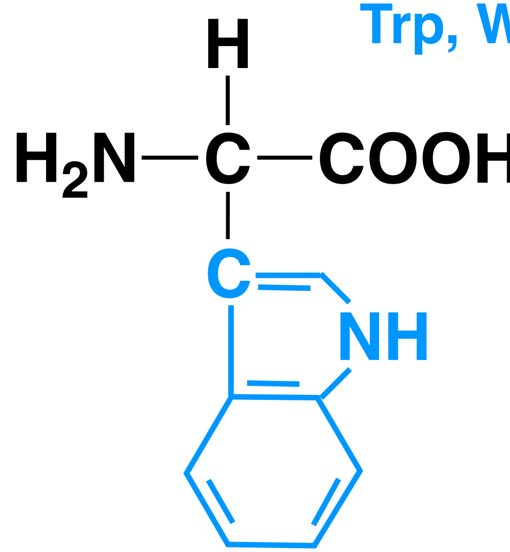
Proline
Pro, P



Phenylalanine
Phe, F



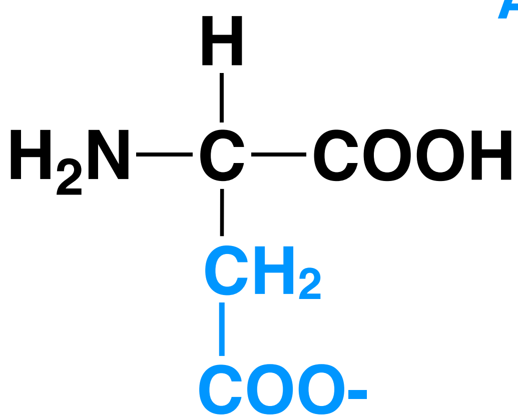
Tryptophan
Trp, W



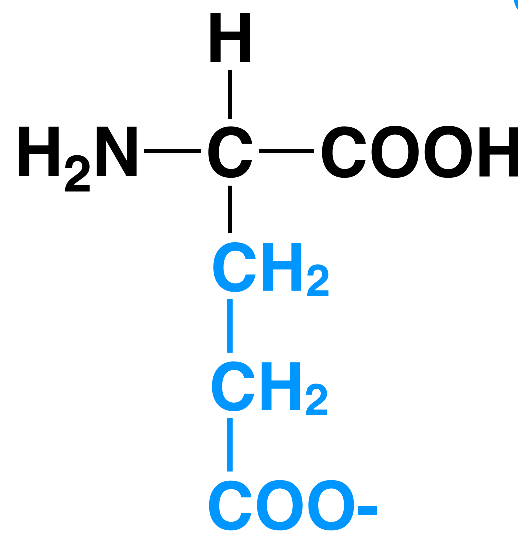
Pro is actually an **imino acid**

Proteinogenic amino acids
Acidic side chains

Aspartic acid
Asp, D



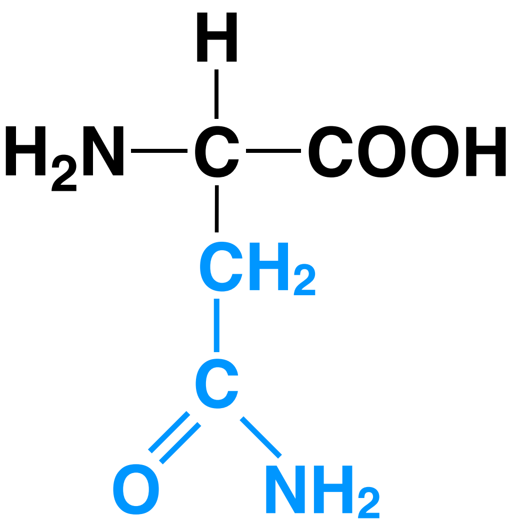
Glutamic acid
Glu, E



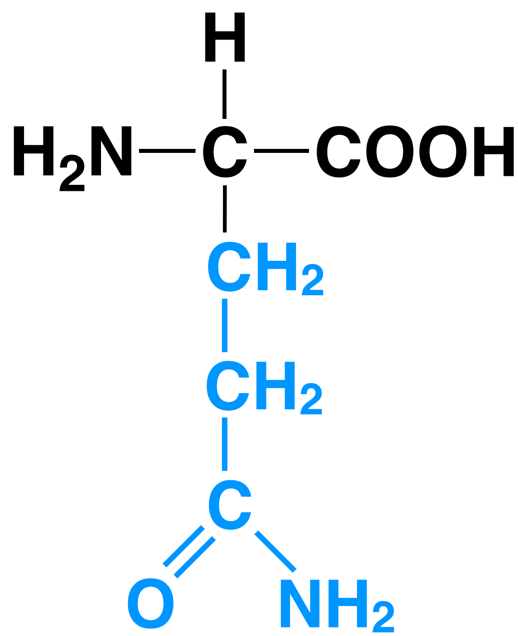
These amino acids are negatively charged at neutral pH

Proteinogenic amino acids

Uncharged, polar side chains



Asparagine
Asn, N



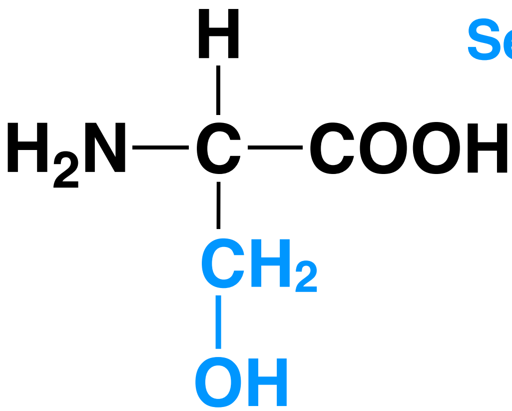
Glutamine
Gln, Q

Although the amide N is not charged at neutral pH, it is polar

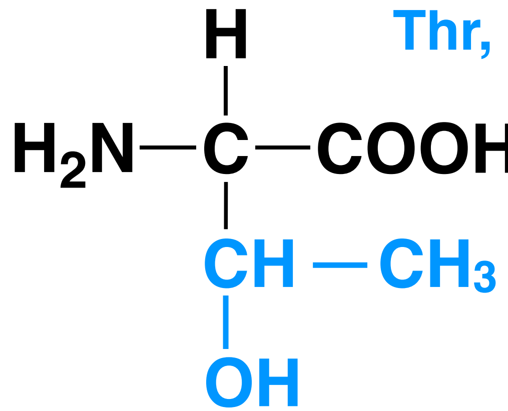
Proteinogenic amino acids

Uncharged, polar side chains contd.

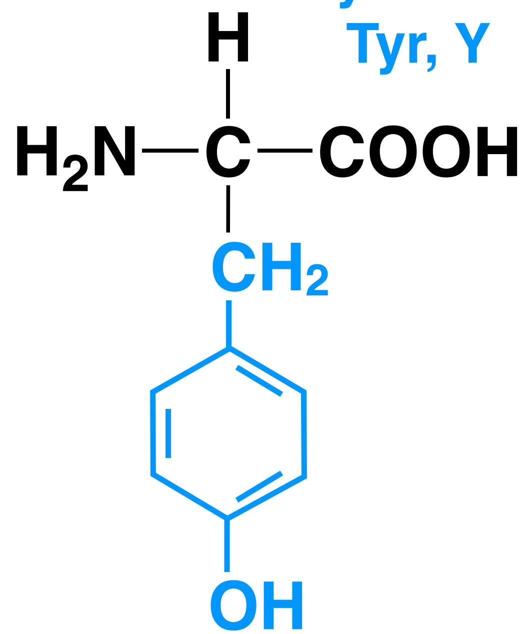
Serine
Ser, S



Threonine
Thr, T



Tyrosine
Tyr, Y

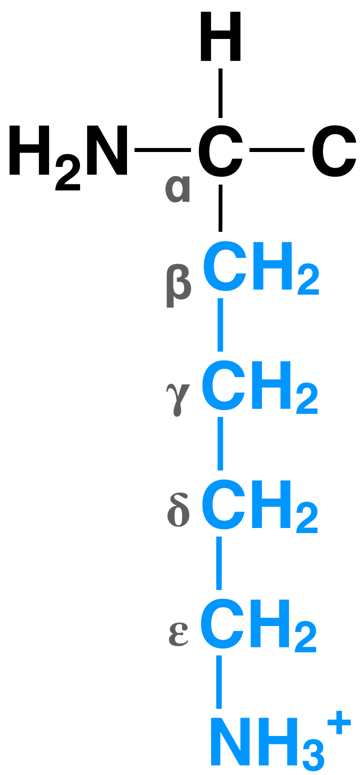


The -OH group is polar

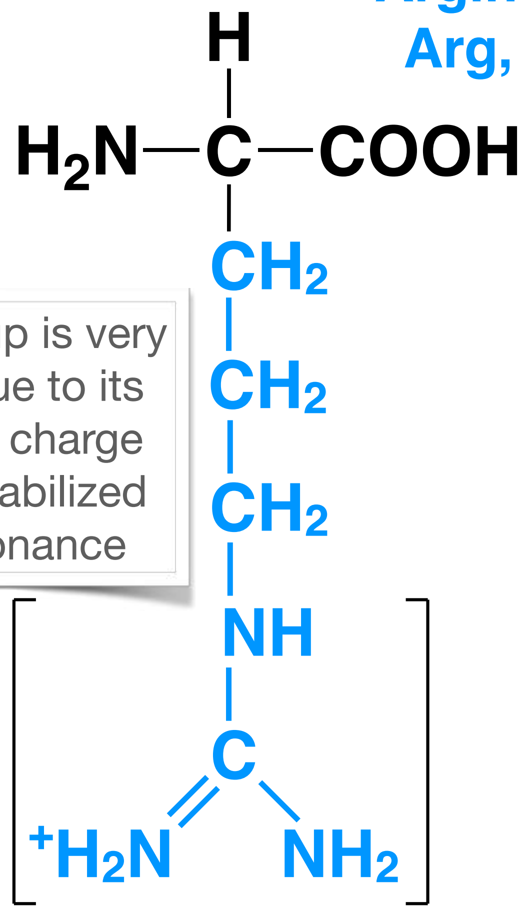
Proteinogenic amino acids

Basic side chains

Lysine
Lys, K

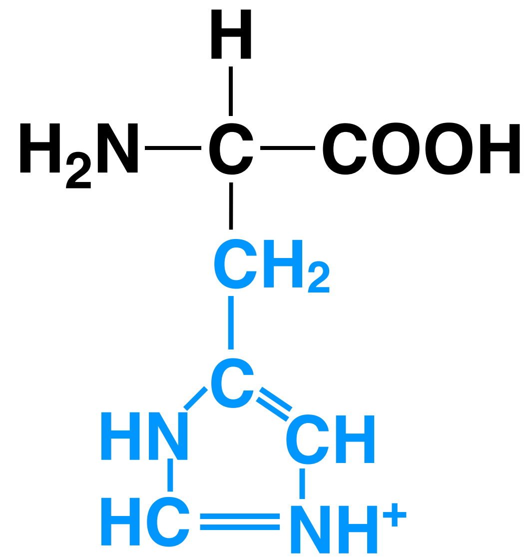


Arginine
Arg, R



This group is very basic due to its positive charge being stabilized by resonance

Histidine
His, H



These nitrogens have a relatively weak affinity for a H+ and are only partly positive at neutral pH

Uncommon amino acids

Non-proteinogenic amino acids

- In addition to the 20 a.as found in proteins, ~300 amino acids have been found in cells. Uncommon amino acids have important functions.
- Often these modifications are incorporated post-synthetically
- 4-hydroxy proline and 5-hydroxylysine (found in collagen, a fibrous protein of connective tissues)
- Ornithine and citrulline, are not found in proteins but are intermediates in the biosynthesis of arginine (and in the urea cycle)
- D-alanine and D-glutamic acid are key constituents of the peptidoglycan of bacterial cell wall
- D-serine plays an important role in mammalian brain neurotransmission