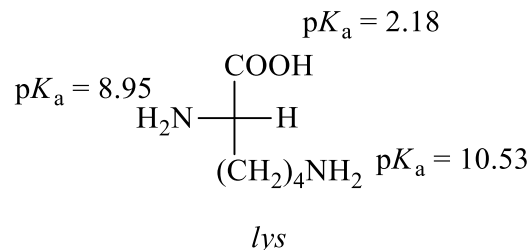
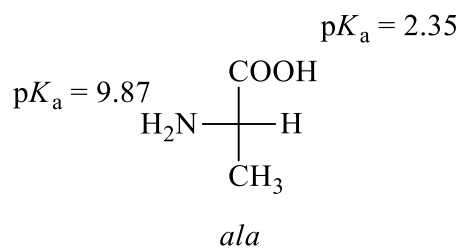


Marks
5

- Alanine (*ala*) and lysine (*lys*) are two amino acids with the structures given below as Fischer projections. The pK_a values of the conjugate acid forms of the different functional groups are indicated.



Draw the structure of the dipeptide *ala-lys* in its zwitterionic form.

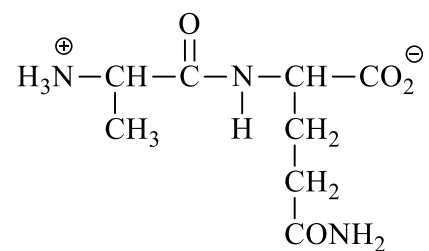
Would you expect the dipeptide to be acidic, neutral or basic? Give a brief reason for your choice.

Estimate the isoelectric point of the dipeptide.

Answer:

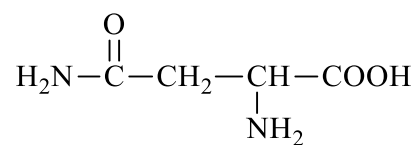
Marks
3

- Draw all products from the acid hydrolysis of the following dipeptide, indicating the correct charge state under these conditions.



THE REMAINDER OF THIS PAGE IS FOR ROUGH WORKING ONLY.

- The amino acid, asparagine, was isolated from asparagus juice in 1806. The uncharged form, **Y**, is given below.



Draw the constitutional formula of the product(s) formed in the reaction of **Y** with the following reagents.

Marks
6

| | |
|--------------------------------|-------------------------------|
| Cold, dilute hydrochloric acid | Cold, dilute sodium hydroxide |
| Hot, 6 M hydrochloric acid | Hot, 6 M sodium hydroxide |

THE REMAINDER OF THIS PAGE IS FOR ROUGH WORKING ONLY.

Marks
6

- Alanine ($R = \text{CH}_3$) and lysine ($R = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$) are two common amino acids. Using *ala* and *lys* to represent the two amino acids, represent all constitutional isomers of the tripeptide formed from one *ala* and two *lys* units.

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Comment, giving your reason(s), on whether the tripeptide(s) will be acidic, neutral or basic in character.

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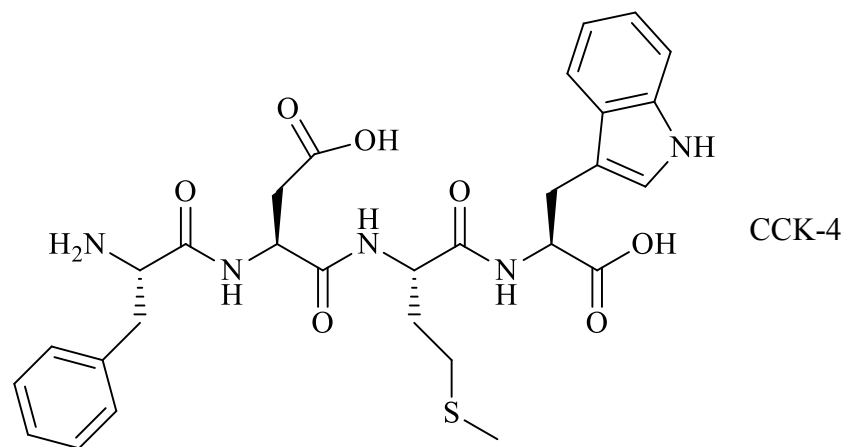
The pK_a values of lysine are 1.82 ($\alpha\text{-COOH}$), 8.95 ($\alpha\text{-NH}_3^+$) and 10.53 (side chain). What is the value of the isoelectric point of lysine?

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| pI = |

Draw the Fischer projection of the zwitterionic form of lysine.

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- Cholecystikin tetrapeptide (CCK-4), (Phe-Asp-Met-Trp) is a peptide fragment derived from the larger peptide hormone cholecystikin. Unlike cholecystikin, which has a variety of roles in the gastrointestinal and central nervous systems, CCK-4 acts primarily in the brain as an anxiogenic.



Draw the Fischer projections of the four L-amino acids that result from the acid hydrolysis of CCK-4.

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Marks
4

What is the major species present when aspartic acid (Asp) is dissolved in water at pH 12 and pH 1? The pK_a values of aspartic acid are 1.88 (α -COOH), 9.60 (α -NH₃⁺) and 3.65 (side chain).

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|-------|------|
| pH 12 | pH 1 |
|-------|------|

Give the constitutional formulas for the following dipeptides in their zwitterionic states.

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| Trp-Asp |
| Met-Phe |

THE REMAINDER OF THIS PAGE IS FOR ROUGH WORKING ONLY.

Marks
4

What is the major species present when lysine (Lys) is dissolved in water at pH 12 and pH 5.6. The pK_a values of lysine are 1.82 (α -COOH), 8.95 (α -NH₃[⊕]) and 10.53 (side chain).

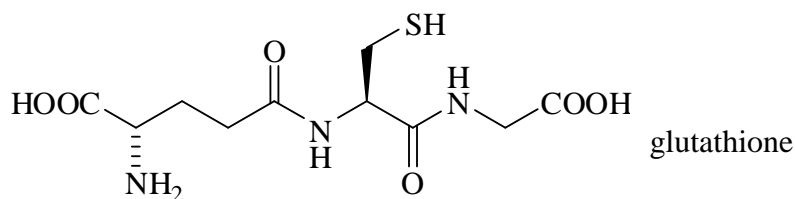
| | |
|-------|--------|
| pH 12 | pH 5.6 |
|-------|--------|

Give the constitutional formulas for the following dipeptides in their zwitterionic states. The pK_a values of proline (Pro) are 1.95 and 10.64.

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|---------|
| Lys-Thr |
| Pro-Lys |

- Glutathione is an important tripeptide (Glu-Cys-Gly) which acts as an antioxidant, protecting cells from toxins such as free radicals. It is an unusual peptide in that the peptidic linkage with glutamic acid (Glu) involves the carboxylic acid group in the side chain.

Marks
10



Give the product when glutathione undergoes oxidation.

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Draw the Fischer projections of the three amino acids (in their natural absolute configurations, where applicable) that result from the vigorous acid hydrolysis (with 6 M HCl) of glutathione.

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Draw the major species present when glutamic acid (Glu) is dissolved in water at pH 1 and pH 12. The pK_a values of glutamic acid are 2.1 (α -COOH), 9.5 (α -NH₃[⊕]) and 4.0 (side chain).

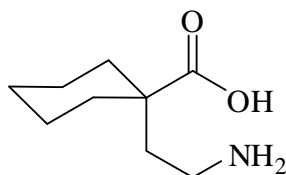
| | |
|------|-------|
| pH 1 | pH 12 |
|------|-------|

Give the constitutional formula for the dipeptide Cys-Gly in its zwitterionic state.

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Marks
4

- Neurontin[®] is a pharmaceutical now widely used for the treatment of nerve pain. The structure of the active ingredient in Neurontin, gabapentin, is shown below. The pK_a value for the carboxyl group is 3.68, whilst the pK_b value for the amine group is 3.30.



gabapentin

Explain whether gabapentin can reasonably be described as an amino acid.

Orally-delivered pharmaceutical agents that contain amine functional groups are often prepared as hydrochloride salts, rather than as free amines. Suggest a reason why gabapentin is not delivered as a hydrochloride salt, illustrating your answer with a suitable diagram.

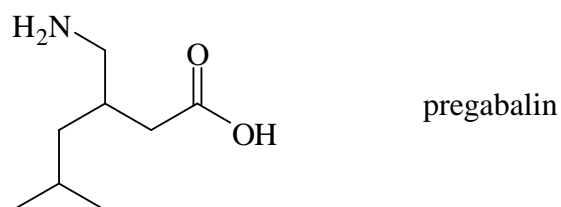
Gabapentin was originally synthesised as it was anticipated that it would bind to the same receptors as the neurotransmitter GABA (4-aminobutanoic acid). Draw the structure of GABA. Suggest a reason why it might have been anticipated that gabapentin would interact with GABA receptors, and what form such interactions might take.

THIS QUESTION CONTINUES ON THE NEXT PAGE.

This expectation has proven to be incorrect, as gabapentin does not interact well with GABA receptors. Suggest a reason why this might be the case.

Marks
4

Pregabalin (marketed under the trade name Lyrica) has been developed as a successor to gabapentin as it is more potent. Its structure is shown below.



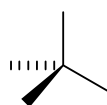
The pharmaceutical formulation contains only the (*S*) enantiomer of pregabalin. Rank the substituents around the stereocentre in decreasing order of priority.

highest priority

lowest priority

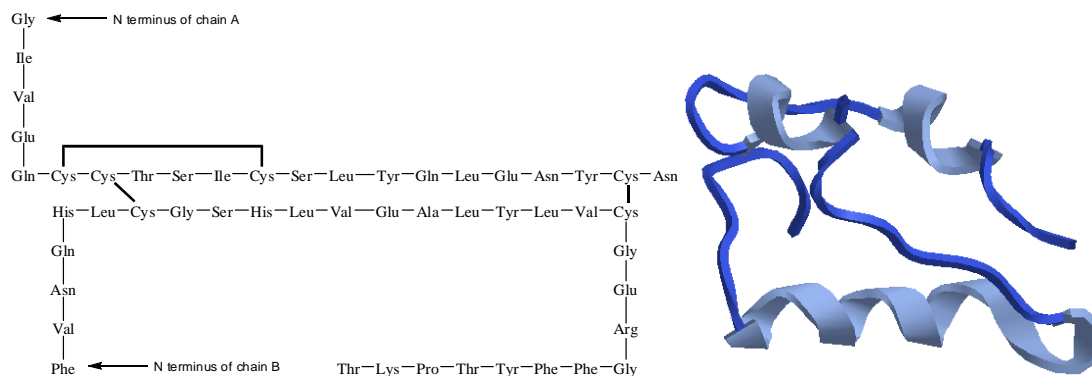
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Draw the (*S*) enantiomer of pregabalin.



Marks
4

- Insulin is an important hormone involved in the regulation of glucose availability in the body. It consists of two peptide chains, one consisting of 21 amino acids (the "A" chain) and one of 30 amino acids (the "B" chain). Below are two representations of insulin, one showing the amino acid sequence and the other a stylised ribbon diagram.



Define the terms *primary structure*, *secondary structure* and *tertiary structure* in relation to proteins. Illustrate your answer with appropriate diagram(s) and by making reference to the representations shown above.

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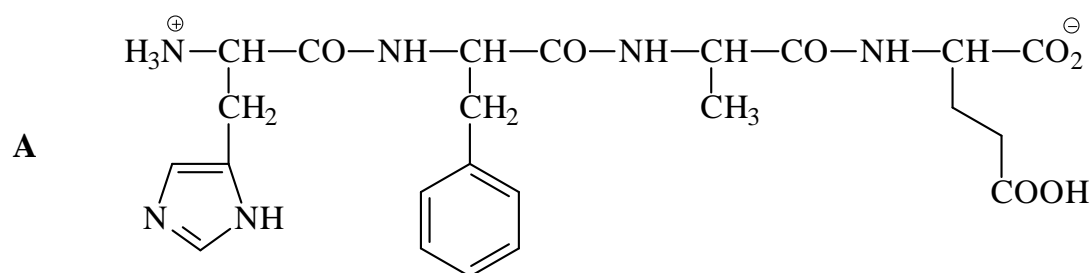
The peptide links in a protein chain are said to be *resonance stabilised*. Use a diagram to explain what is meant by this term, and indicate one important consequence relating to protein structure and one important consequence relating to the chemistry of proteins.

Marks
4

Modern medicine now uses insulin analogues (where one or more of the amino acid residues has been changed) in the treatment of diabetes. In one such analogue, glargine insulin, the changes have increased the isoelectric point of the enzyme from 5.4 to 6.7, thereby reducing its solubility at physiological pH. Explain how changes in the primary amino acid sequence can alter the pI and solubility of the analogue without altering its interaction with blood-glucose.

Marks
10

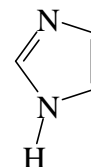
- The structure of the naturally occurring tetrapeptide His-Phe-Ala-Glu, **A**, is shown below as the zwitterion.



Give the product(s) obtained when **A** is treated with cold 1 M NaOH solution.

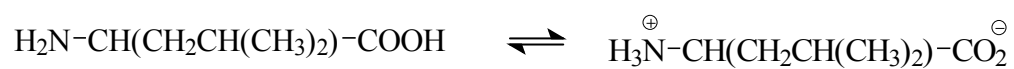
Give the Fischer projections of the four L-amino acids in their correct ionic states obtained from the vigorous basic hydrolysis (6 M KOH) of **A**.

The heterocycle present in the sidechain of histidine is imidazole, whose structure is shown on the right. Give the structure of the product formed when imidazole is treated with HCl. State, giving reasons, whether the product is aromatic.

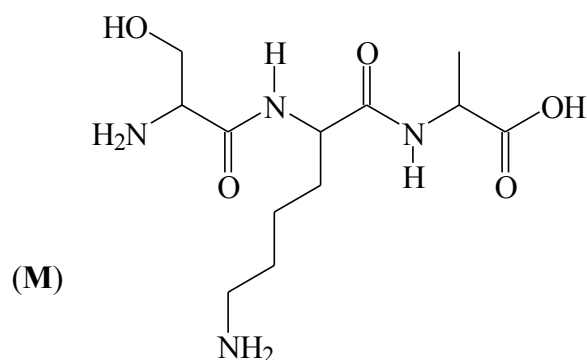


What is the major species present when histidine is dissolved in water at pH 1. The pK_a values of histidine are 1.82 (-COOH), 9.17 (-NH₃[⊕]) and 6.04 (sidechain).

Given that the pK_a of the carboxylic acid group of leucine is 2.32 and the pK_b of the amine group is 4.24, do you expect the classical or the zwitterionic form to predominate when leucine is dissolved in water? In other words, does the following equilibrium lie to the right or left? Show your reasoning.



- The constitutional formula of the tripeptide seryllysylalanine (Ser-Lys-Ala), **M**, is shown below.



Draw the Fischer projections for the L-configurations of the amino acids formed when compound **M** is hydrolysed with hot 6 M hydrochloric acid.

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The pK_a values of lysine are $pK_{a1} = 1.82$ (α -COOH), $pK_{a2} = 8.95$ (α -NH₃[⊕]) and $pK_{a3} = 10.53$ ($-(CH_2)_4NH_3^{\oplus}$). Give the structures of the predominant species present in a solution of lysine at pH 12 and at pH 5.6.

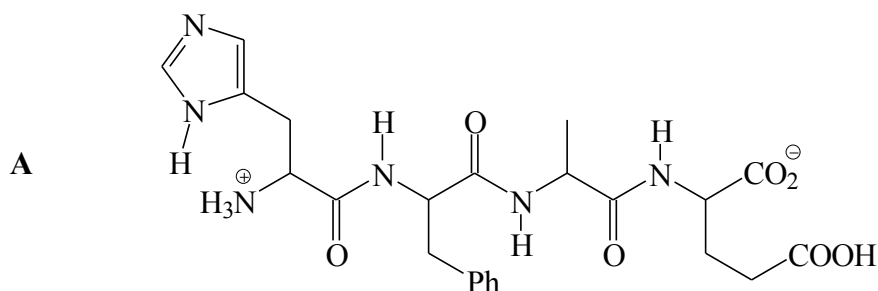
| | |
|---------|--------|
| pH 12.0 | pH 5.6 |
|---------|--------|

Give the constitutional formulas for the following dipeptides in their zwitterionic states.

| | |
|---------|---------|
| Lys-Ser | Ser-Ala |
|---------|---------|

Marks
9

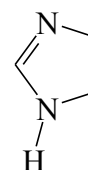
- The structure of the naturally occurring tetrapeptide His-Phe-Ala-Glu, **A**, is shown below as the zwitterion.



Give the product(s) obtained when **A** is treated with cold 1 M NaOH.

Vigorous acid hydrolysis of **A** gives four products. Give the structures of these four products in their correct ionic states as Fischer projections.

The heterocycle present in the sidechain of histidine is imidazole, whose structure is shown on the right. Give the structure of a tautomer of imidazole and state, giving reasons, whether your tautomer is aromatic.



What is the major species present when histidine is dissolved in water at pH 12. The pK_a values of histidine are 1.82 ($-\text{COOH}$), 9.17 ($-\text{NH}_3^+$) and 6.04 (sidechain).