CHEM 191
Module 4
Structures and reactions of biological molecules

Lecture 7
Peptides – structure and function

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Module 4 Lecture 7
Learning objectives

Learning Objectives:

- Plan the synthesis of a target dipeptide from two amino acids, including use of 'protecting groups'
- Recognise that amino acids and peptides are drawn/represented with the N-terminus at the lefthand side of the page
- Understand why amide bonds have restricted rotation and the implications of this on peptide shape
- Recognise that hydrogen bonds and disulfide bridges both influence peptide shape. (+ recap thiol oxidation from Lecture 1)

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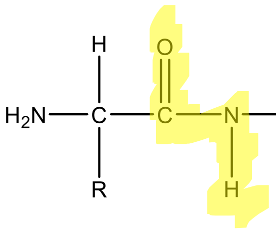
Amide bonds

- In lecture 6 we learnt all about amino acids
- Amino acids join together to make **peptides**, via **amide bonds** (called **peptide bonds** in a peptide)

N-terminus



C-terminus

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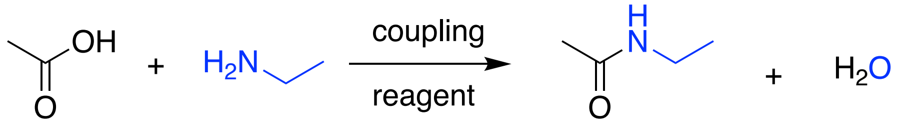
Formation of amide bonds

- A carboxylic acid reacts with an amine

Amide bond formation



- This is a type of **nucleophilic acyl substitution** (Lecture 5) but a ‘coupling reagent’ is required.

..... *Why do we need a coupling reagent?* ....

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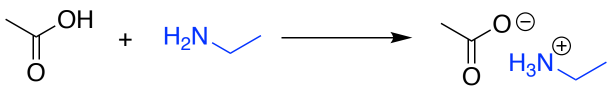
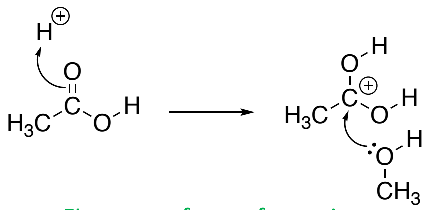
Formation of amide bonds

- Why do we need a peptide coupling reagent to make an amide?
  - 1. the carboxylic acid is not a great electrophile (Lecture 5), and
  - 2. if 'just' an amine and carboxylic acid are combined this happens -



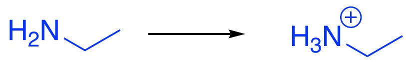
Acid-base reaction

- Why won't adding an acid (H^+) help like we saw with ester formation?



First step of ester formation

Because with an amine, this will happen



And there is no longer an amine nucleophile

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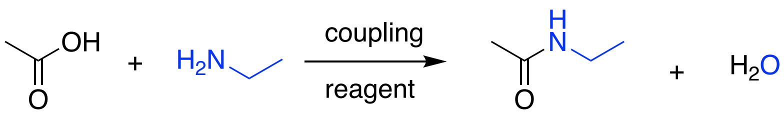
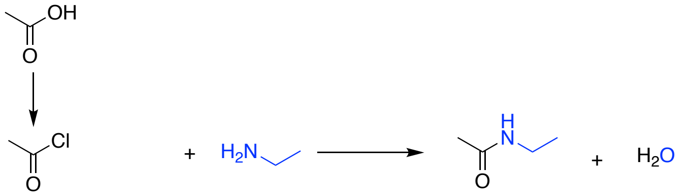
Formation of amide bonds

- We are not covering the details of what 'coupling reagents' are used for peptide synthesis in CHEM 191, just recognizing that a 'coupling reagent' is required



- The coupling reagents essentially do similar chemistry that we have already learnt in Lecture 5 – if we turn the carboxylic acid into something more reactive, e.g.



acid chloride
easily reacts with amines

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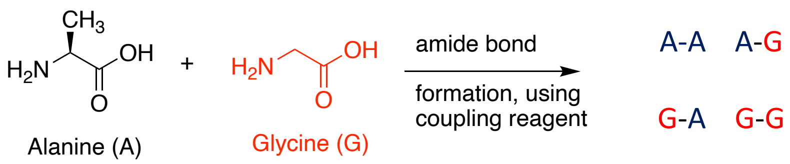
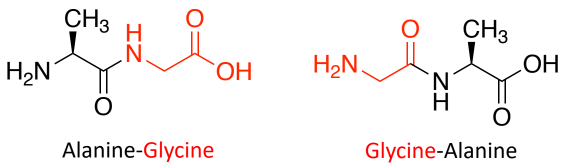
Synthesis of peptides

- Since an amino acid contains an amine and a carboxylic acid, if two unprotected amino acids are reacted, then four **dipeptide** products are possible



- Peptides are always written with the N-terminus at the LHS of the page
  - A-G is a different compound to G-A



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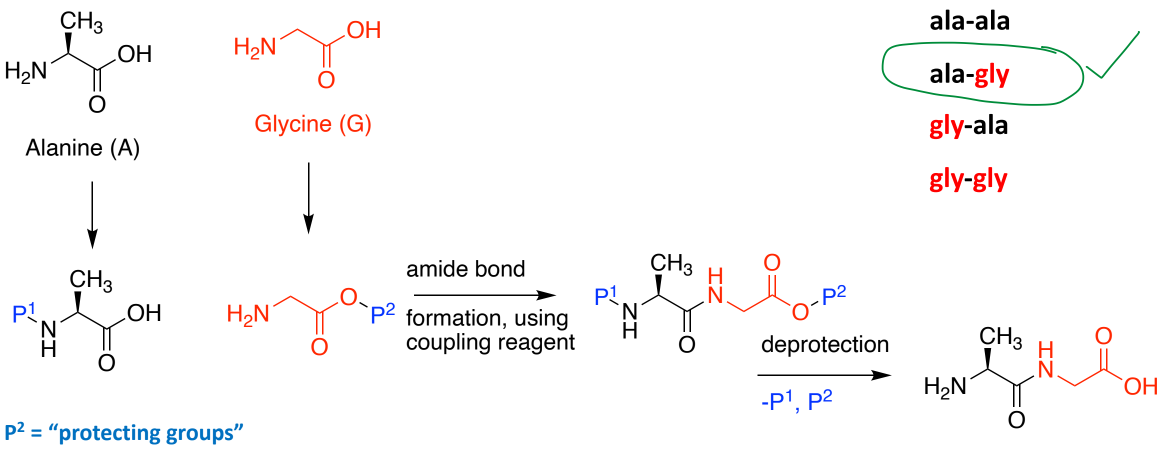
Synthesis of peptides

- Solution to making only 1 target product – protect the functional groups that you don't want to react. (i.e. temporarily block the reactivity in that position).
  E.g. if the target peptide is ala-gly



ala-ala

ala-gly

gly-ala

gly-gly

P^1, P^2 = "protecting groups"

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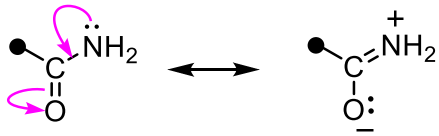
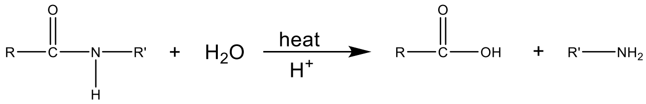
Peptide bond structure

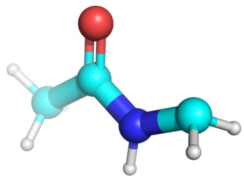
- The lone pair of electrons of the amide nitrogen is in resonance / the nitrogen lone pair of electrons is delocalised towards the carbonyl group oxygen



- This means that peptide bonds in peptides are
  1. Relatively unreactive towards nucleophiles so are **chemically quite stable** (recap from Lecture 5)



  2. **Rigid and planar**, due to the delocalised electrons and restricted rotation of the **O-C-N** bonds.



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Peptides

- Peptides are polymers of amino acids
- Can be named according to the number of monomers in the peptide -

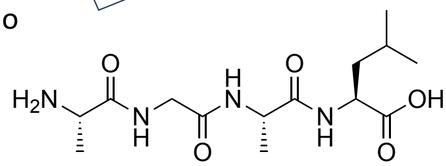
2 amino acids	**di**peptide
3 amino acids	**tri**peptide
many amino acids	**poly**peptide

?

Is it a peptide or protein??

The word 'protein' is generally used to describe peptides than are greater than 50 amino acids long

- Peptides have a directional sense, like amino acids do
  - As for amino acids, always write peptides with the N terminus on the left



Ala-Gly-Ala-Leu

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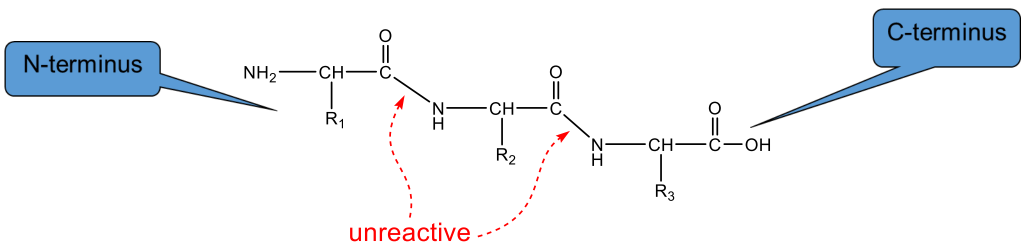
Peptide properties

- Peptide properties are governed by the sequence of amino acid units, this is called the **primary structure**
    - Different amino acids have different **side chains**, the properties of these **side chain** groups (e.g. ionisation at certain pHs, hydrogen-bonding) influence peptide properties.



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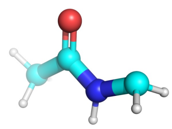
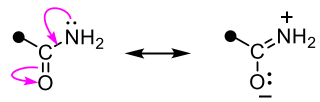
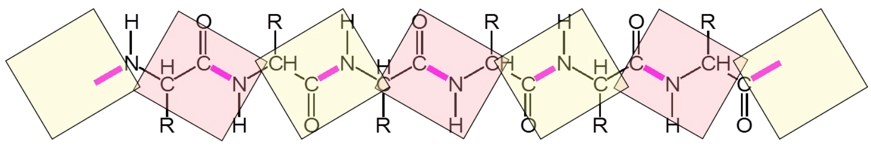
Peptide properties

- Because of the restricted rotation of the **O**-**C**-**N** bonds







Bond rotation is not easily possible about the amide bonds

Sequential α-carbons are usually in a *trans* relationship

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Peptide, protein shape and structure

primary structure - sequence of amino acids

secondary structure - segments of structure along the peptide chain , e.g. α-helix, turns, β-sheet

tertiary structure - how secondary structural elements fit together

quaternary structure - how proteins or independent peptide chains come together

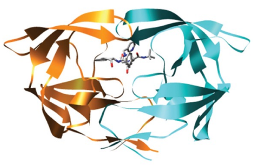

Figure 31.23, page 1432, example of quaternary structure

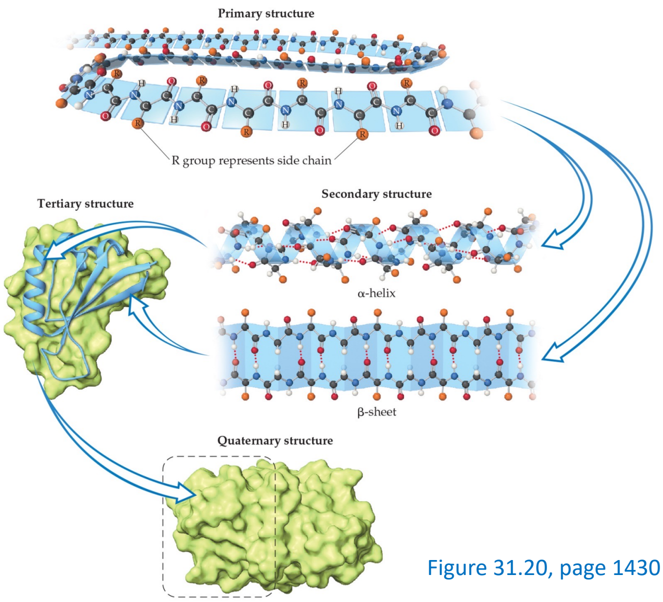

Figure 31.20, page 1430

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Why to peptides adopt secondary structures?

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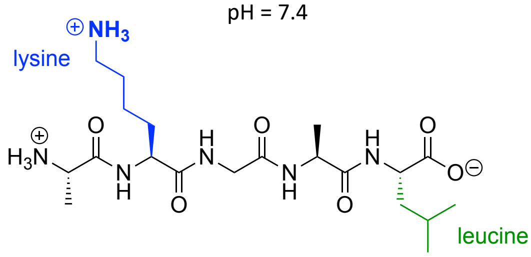
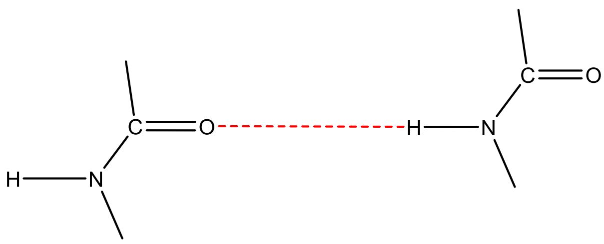
- In an aqueous environment, the chain will adopt a conformation to **expose the polar side chains (hydrophilic groups)** and **bury the non polar side chains (hydrophobic groups)** i.e. maximise favourable non-covalent interactions



- Hydrogen bonding between different amide bonds also stabilises secondary structural structures



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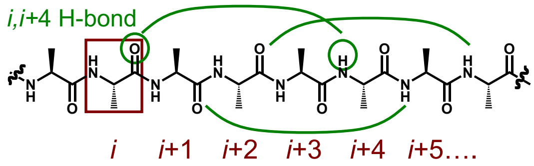
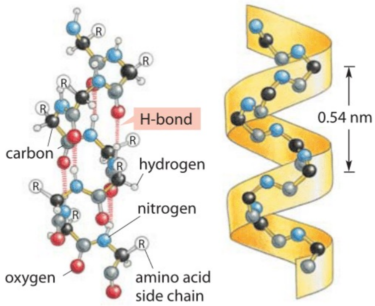
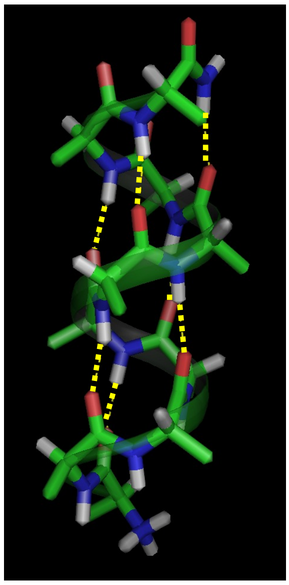
Secondary structure example – alpha helix

- The NH from an amide **hydrogens bonds** with the CO of a different amide 4 amino acids along the chain
- This same pattern of hydrogen bonds repeated along the peptide gives the stabilised helical secondary structure







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Even one amino acid change can change the shape of a protein

- Sickle-cell anaemia is a genetic disease where one glutamic acid in the protein haemoglobin is replaced with the amino acid valine.

Amino acid side chain

Glutamic acid

$-CH_2-CH_2-C(=O)-OH$

normal

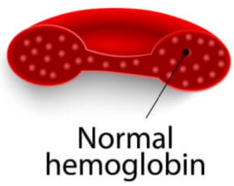
Valine

$-CH(CH_3)-CH_3$

abnormal

The change from the hydrophilic glutamic acid (CO_2^- at pH 7.4) to the non-polar, more hydrophobic valine causes the protein to aggregate

Hemoglobin protein shape inside red blood cells



Resulting shape of red blood cells

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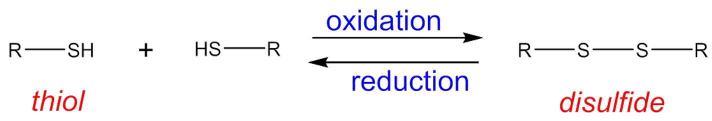
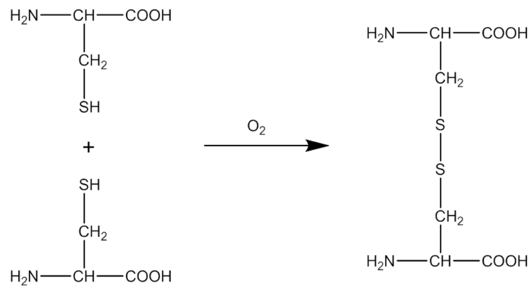
Disulfide bridges

- Depending on the protein, disulfide bond (or bridges) can be defined as stabilising both secondary or tertiary peptide/protein secondary structures.



- The amino acid cysteine contains a thiol functional group on it's side chain.
- Even under just mild air oxidation conditions, two cysteines can react in an oxidation reaction to give a disulfide bond



Two cysteines, each with a thiol

Disulfide bond

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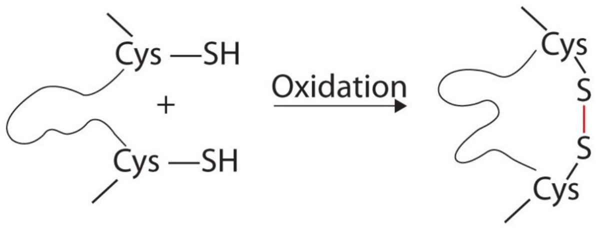
Disulfide bridges

- A peptide may contain the amino acid cysteine in several places.
- If a disulfide bridges forms, this can even link/bring together otherwise remote ends of the peptide.



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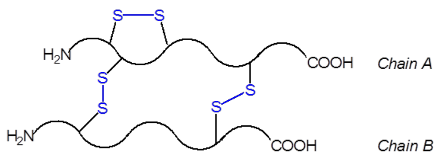
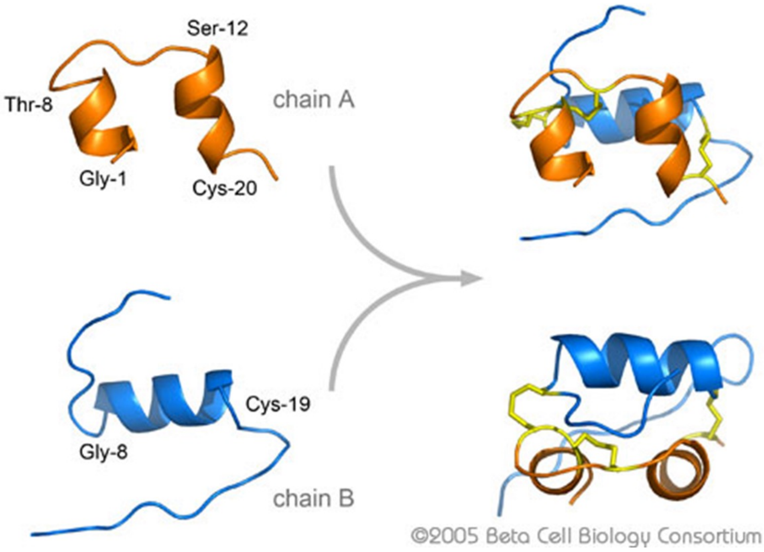
Disulfide bridges – insulin example

- Disulfide bridges can even join together separate peptides into a single molecule



Insulin is two peptide chains connected/stabilised by three disulfide bonds, one intrachain and two interchain



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• Homework *

31.21, 31.23, 31.25, 31.62, 31.63(a), 31.64, 31.67(c, harder)(d)

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