

CHAPTER 4

THE THREE- DIMENSIONAL STRUCTURE OF PROTEINS

Four Levels of Protein Structure

- **Primary structure** - amino acid linear sequence
- **Secondary structure** - regions of regularly repeating conformations of the peptide chain, such as **α -helices** and **β -sheets**
- **Tertiary structure** - describes the overall three-dimensional arrangement of all atoms in a protein and the shape of the fully folded polypeptide chain
- **Quaternary structure** - arrangement of two or more polypeptide chains, which may be identical or different, into multisubunit molecule

Fibrous proteins

Fibrous proteins

Fibrous proteins

Globular proteins

Globular proteins

Globular proteins

Fibrous proteins

- **with polypeptide chains arranged in long strands or sheets**
- **provide support, shape, strength, flexibility, and external protection**
- **insoluble in water**
- **usually consist largely of a single type of secondary structure**

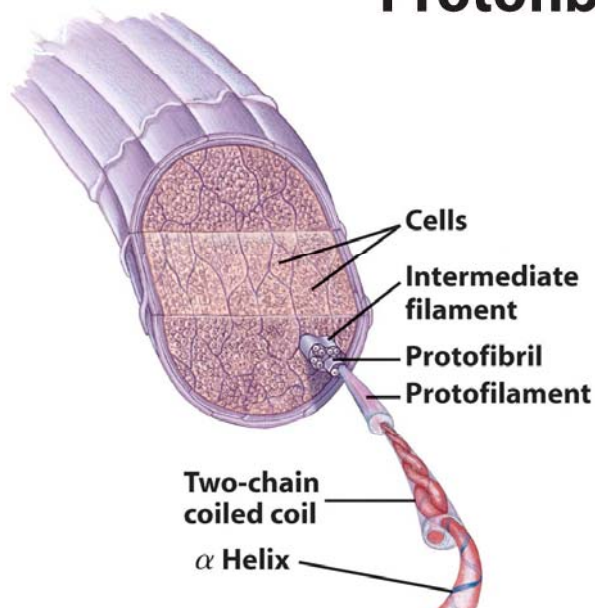
Globular proteins

- **with polypeptide chains folded into a spherical or globular shape**
- **often contain several types of secondary structure**
- **with hydrophilic surface for interacting with water or other molecules**
- **most enzymes and regulatory proteins are globular proteins**

Structure of hair

角蛋白

頭髮、羊毛、
豪豬的棘刺、
指甲、爪、角
、蹄、皮膚最
外層等



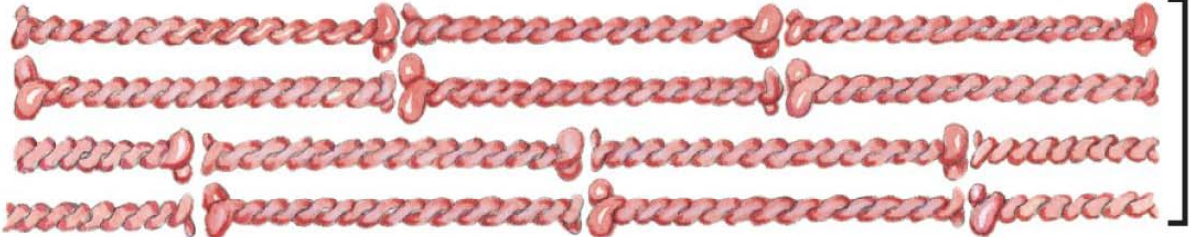
Keratin α helix —  Right-handed

Two-chain coiled coil —  Left-handed

Reported by Crick and Pauling in 1950s

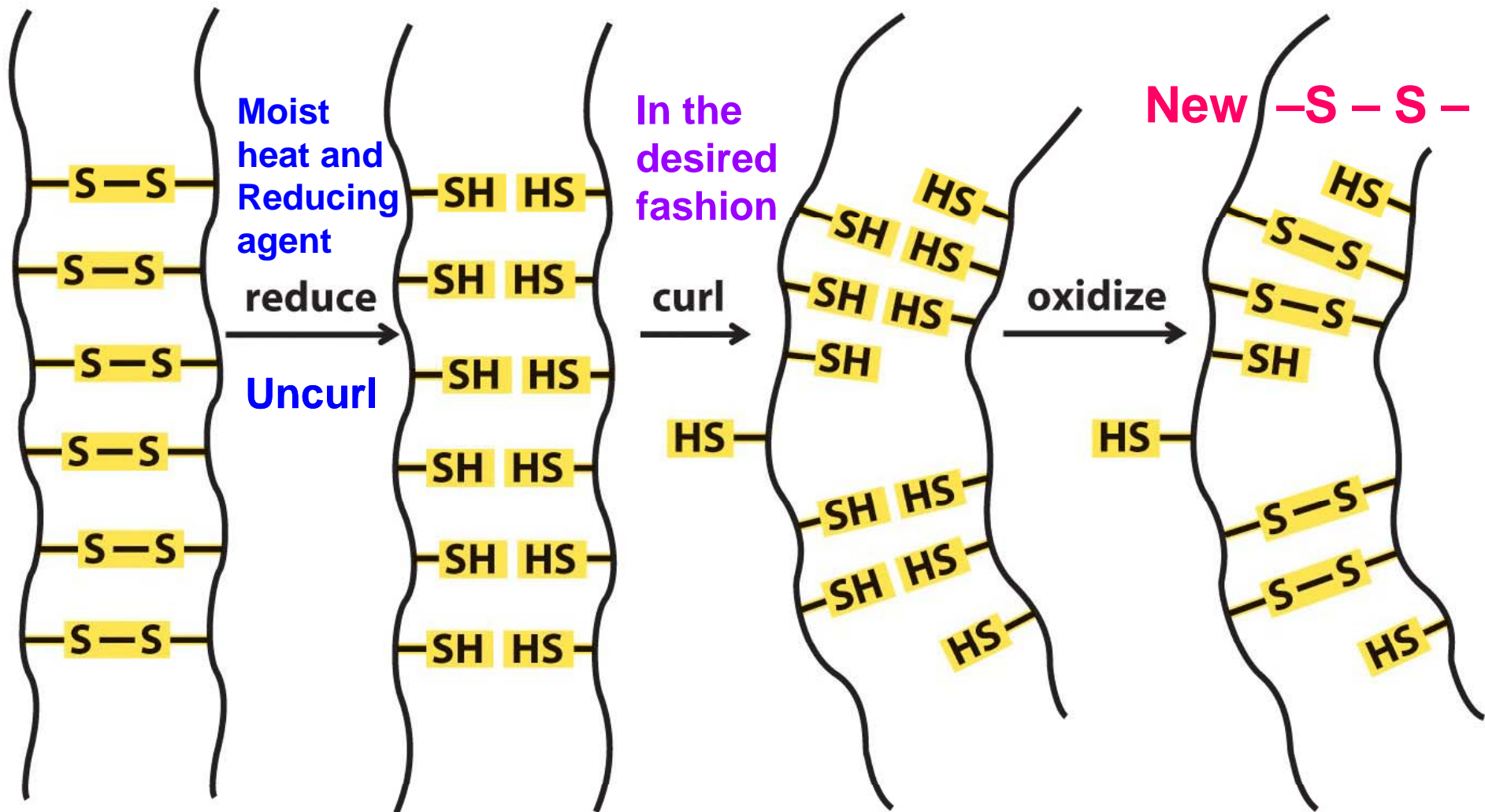
Protofilament {  } 20–30 Å

Rich in the hydrophobic residues Ala, Val, Leu, Ile, Met, and Phe

Protofibril {  }

The cross-links stabilizing quaternary structure are disulfide bonds

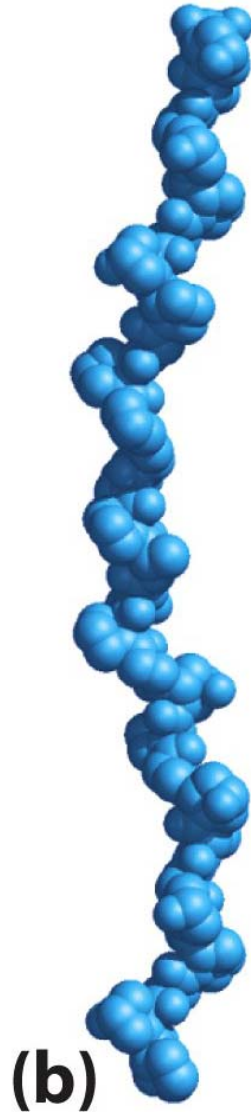
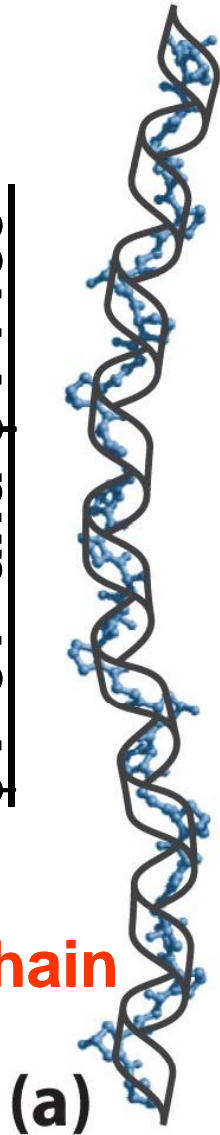
Perm is biochemical engineering



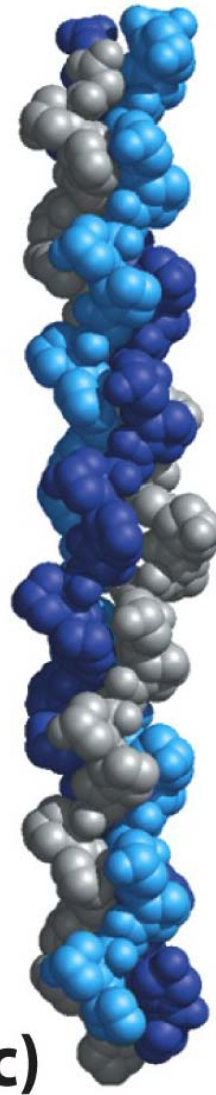
Left-handed,
3 a.a per turn

$\phi : -51^\circ$ and $\psi : +153^\circ$

α chain

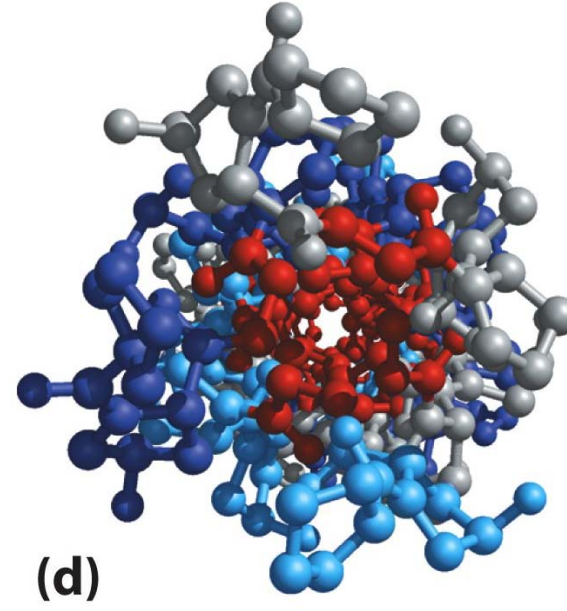


Right-handed,
composed of
Three α chains



Gly-X-Pro
Gly-X-4-HyP
Gly-Pro-4-HyP

Gly: 35%,
Pro or 4-HyP: 21%



Structure
of
collagen

膠原蛋白

韌帶、
軟骨、
角膜、
皮膚等

4-HyP (4-hydroxyproline)  Generated by Prolyl 4-hydroxylase

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Collagen, a triple-helix fibrous protein

- Collagen is a major protein in connective tissue of vertebrates (**25-35% of total protein in mammals**)
- Collagen consists of **three left-handed helical chains** coiled around each other **in a right-handed supercoil**
- **Three amino acids per turn**, rise 0.31 nm per residue (collagen is more extended than an α helix)
- **Multiple repeats of -Gly-X-Y- where X is often proline and Y is often 4-hydroxyproline**
- Glycine residues are located along central axis of a triple helix (other residues cannot fit)
- For each -Gly-X-Y- triplet, **one interchain H-bond** forms between amide H of Gly in one chain and -C=O of residue X in an adjacent chain
- **No intrachain H-bonds** exist in the collagen helix

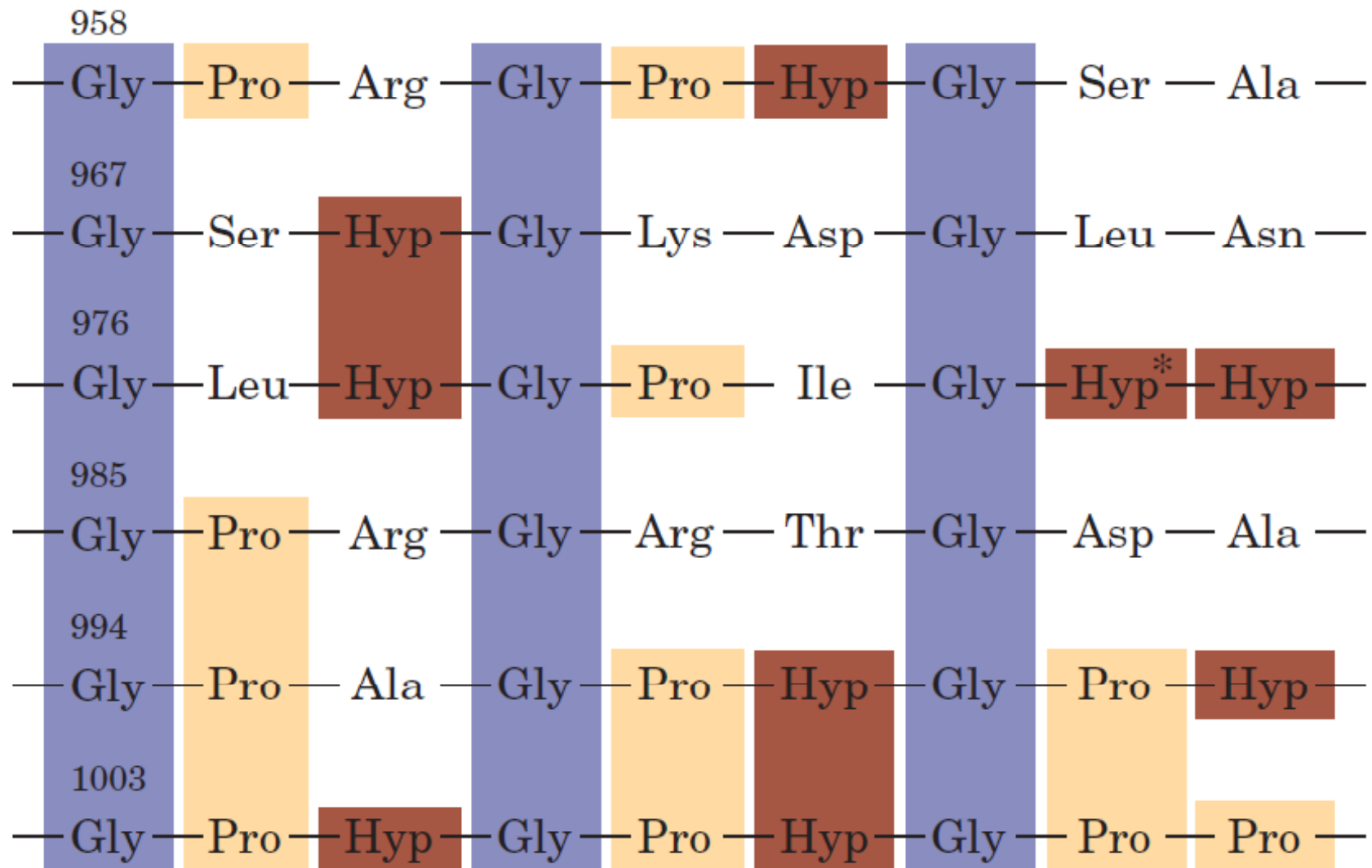


FIGURE 8-28 The amino acid sequence at the C-terminal end of the triple helical region of the bovine $\alpha 1(I)$ collagen chain.

Hyp*: 3-Hydroxyprolyl

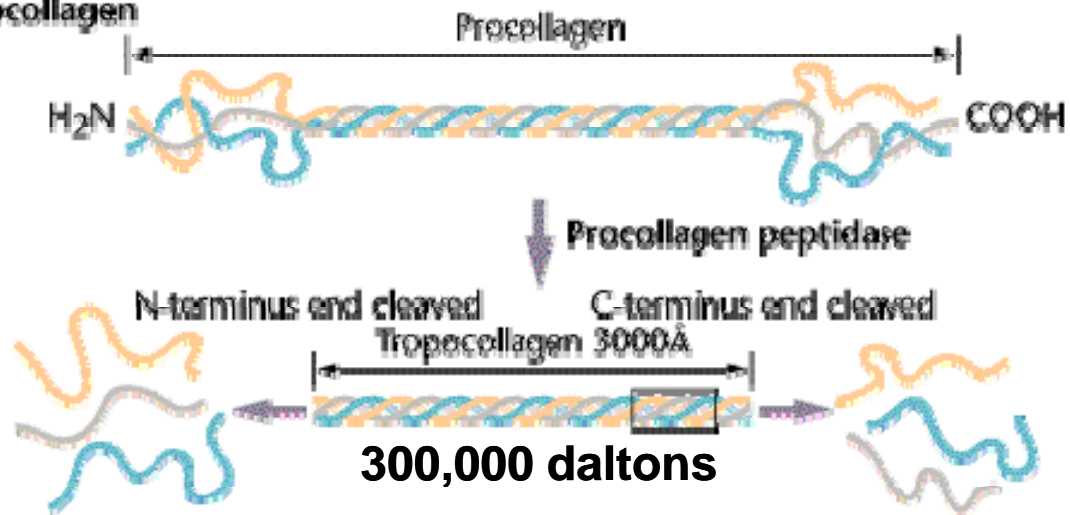
Formation of collagen

TABLE 8-2 The Most Abundant Types of Collagen

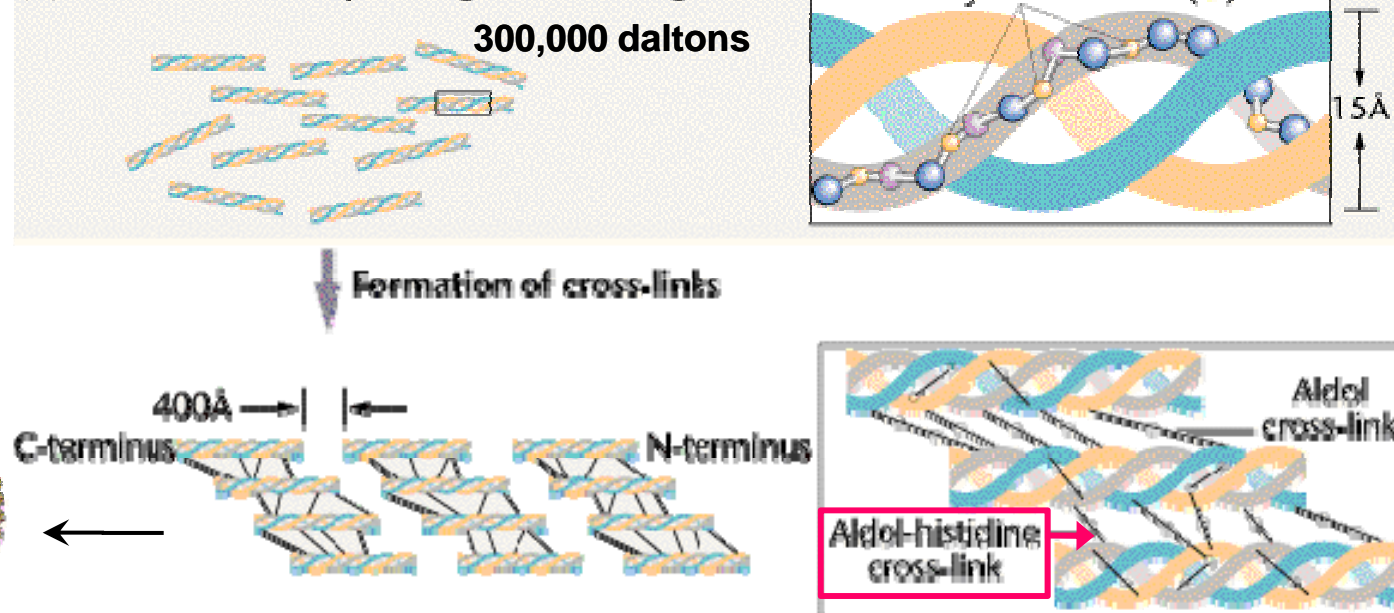
Type	Chain Composition	Distribution
I	$[\alpha 1(I)]_2\alpha 2(I)$	Skin, bone, tendon, blood vessels, cornea
II	$[\alpha 1(II)]_3$	Cartilage, intervertebral disk
III	$[\alpha 1(III)]_3$	Blood vessels, fetal skin

Source: Eyre, D.R., *Science* **207**, 1316 (1980).

(a) Formation of tropocollagen

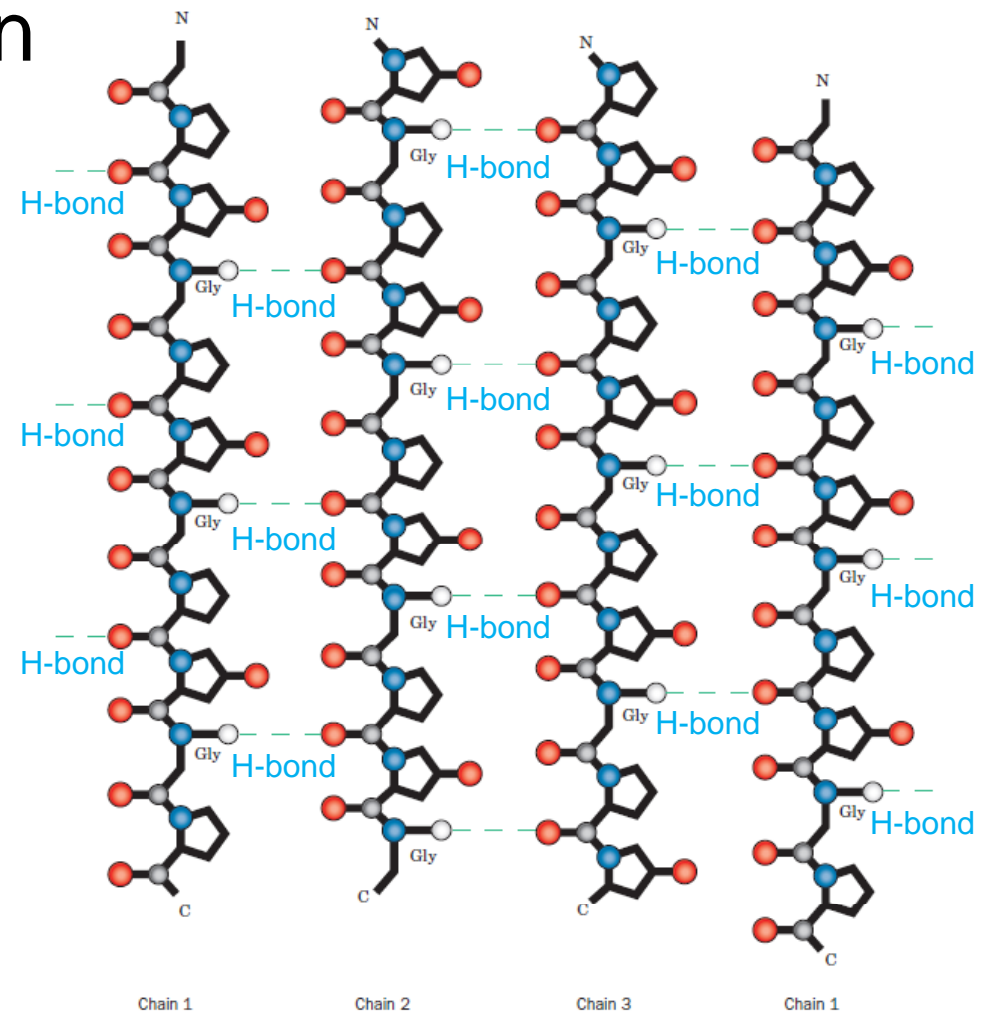
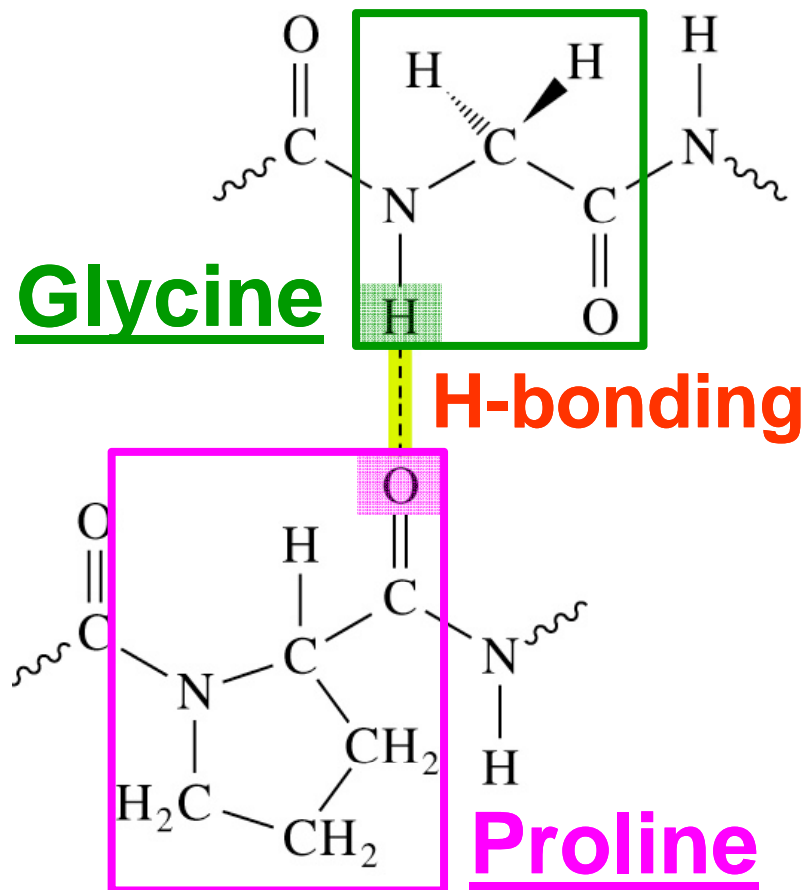


(b) Association of tropocollagen into collagen fiber

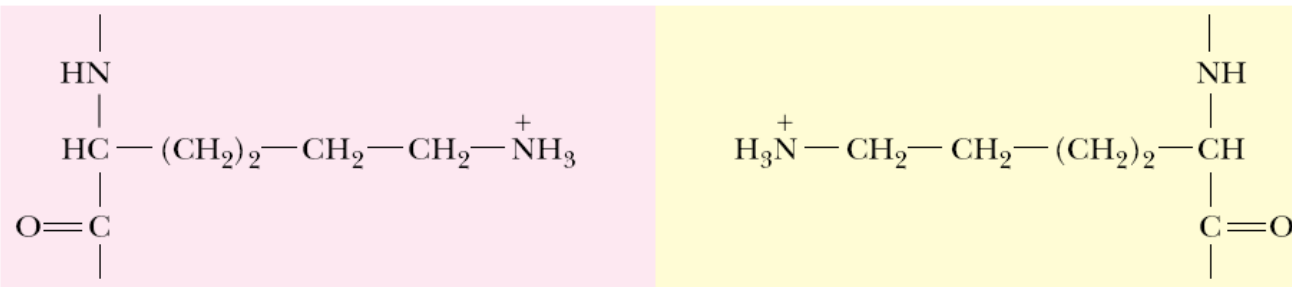


Interchain H-bonding in collagen

- Amide H of Gly in one chain is H-bonded to C=O in another chain

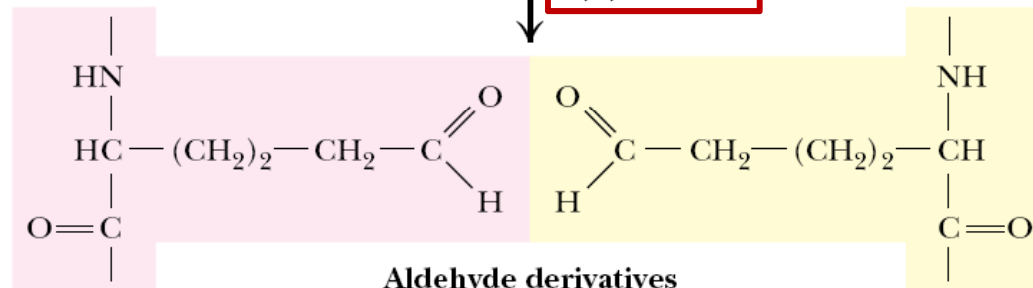


Collagen fibers are stabilized and strengthened by Lys–Lys cross-links



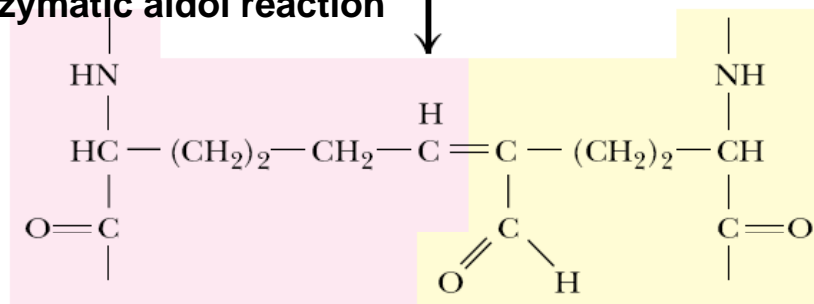
Lysine residues

Lysyl oxidase



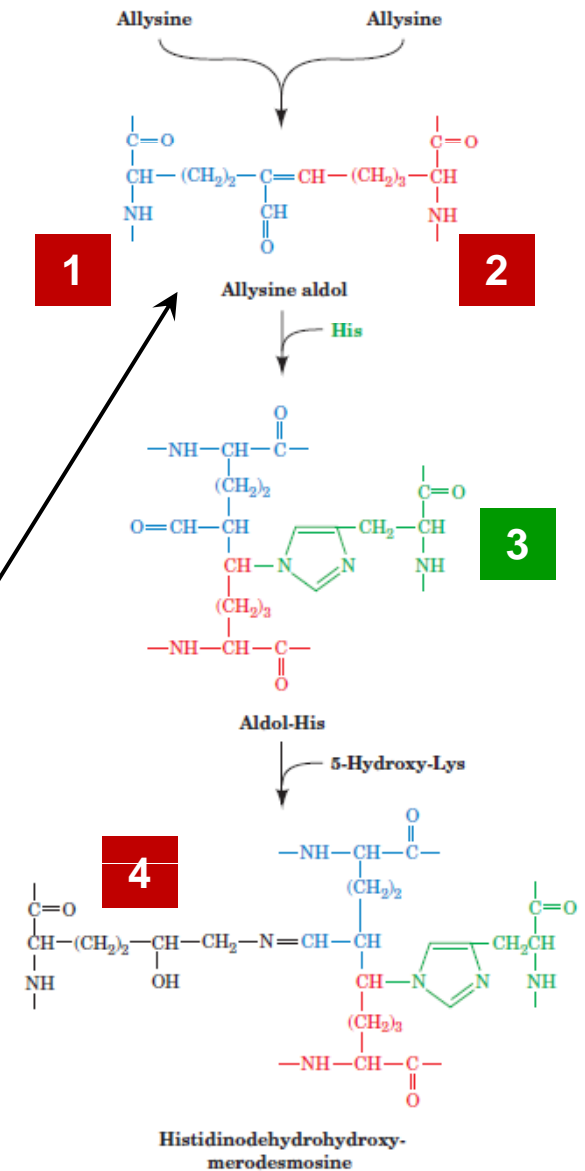
Aldehyde derivatives
(allysine)

A spontaneous
nonenzymatic aldol reaction



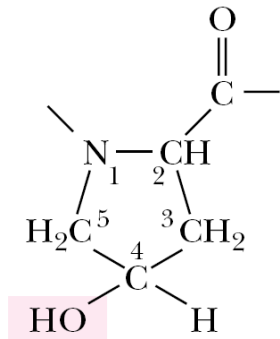
Aldol cross-link

Allysine aldol



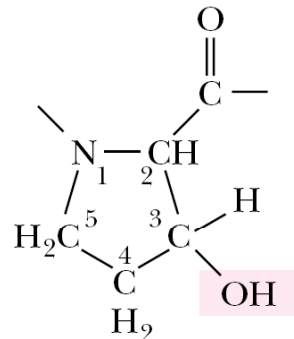
The hydroxylated residues typically found in collagen

4-Hydroxyproline



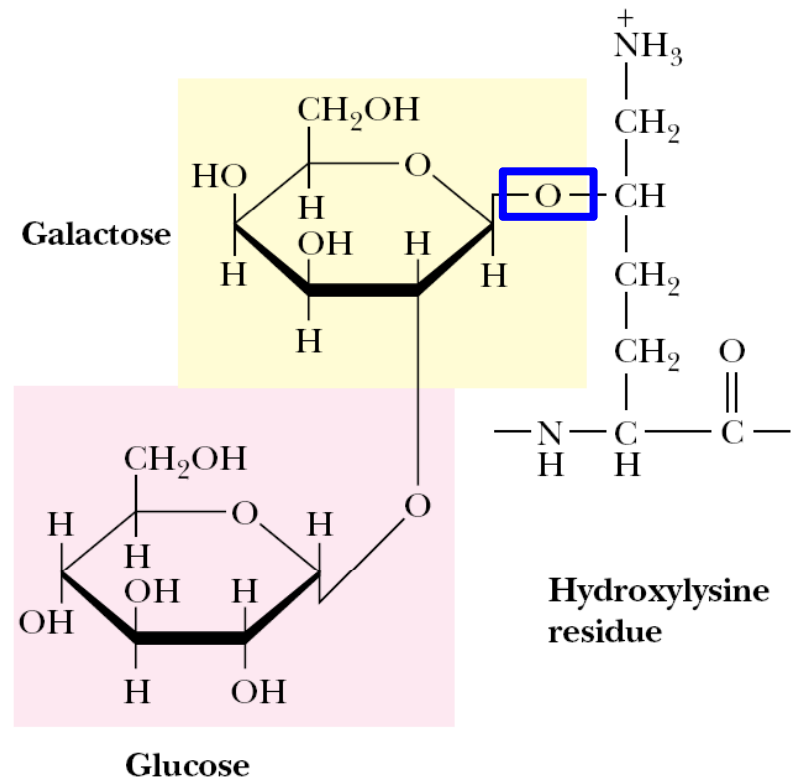
4-Hydroxyprolyl residue (Hyp)

3-Hydroxyproline

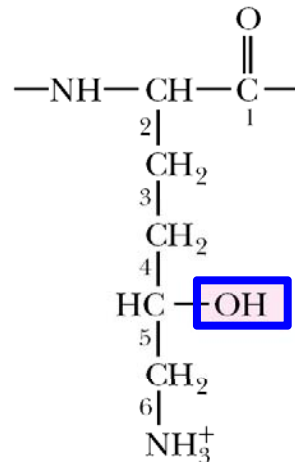


3-Hydroxyprolyl residue

5-Hydroxylysine



5-Hydroxylysine



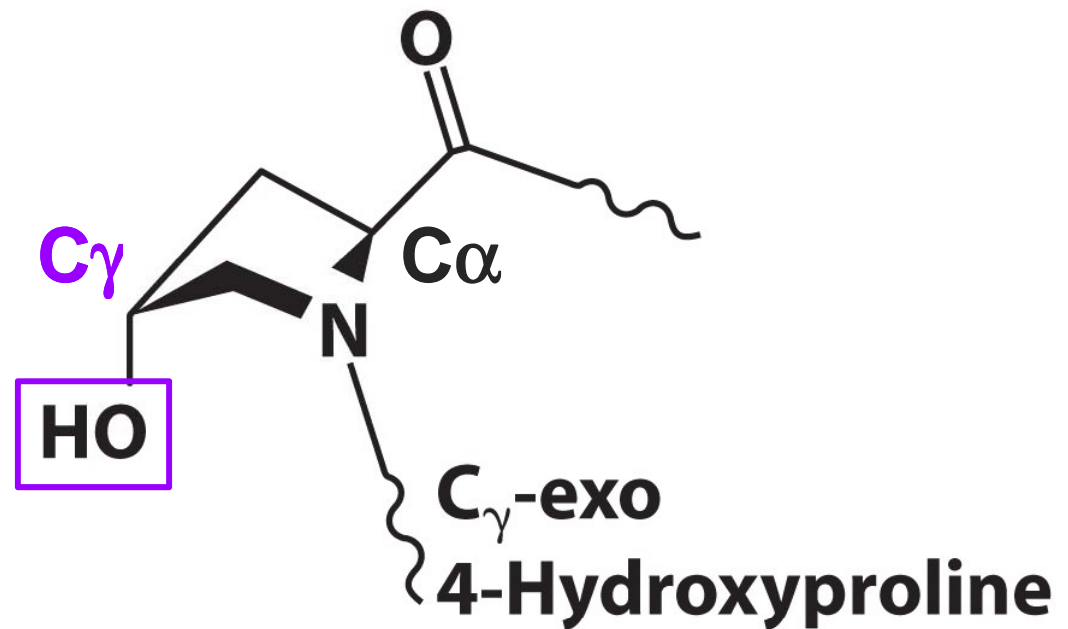
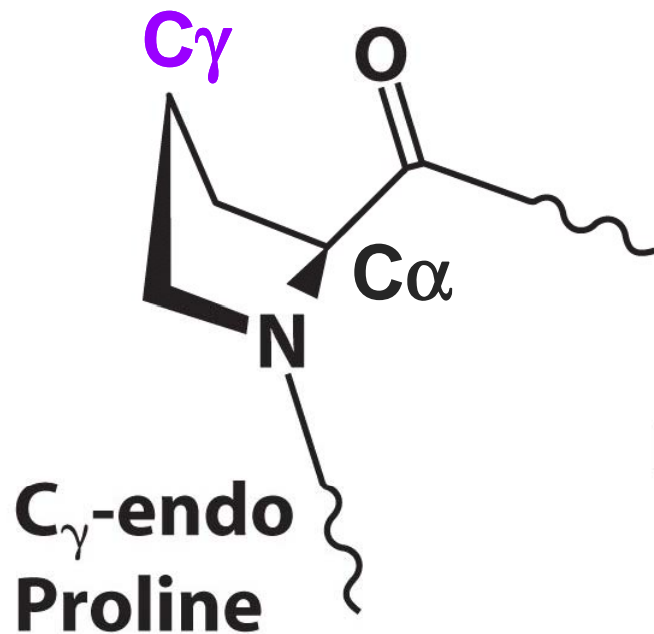
5-Hydroxylysyl residue (Hyl)

3-Hydroxyprolyl and 5-hydroxylysyl (Hyl) residues also occur in collagen but in smaller amounts.

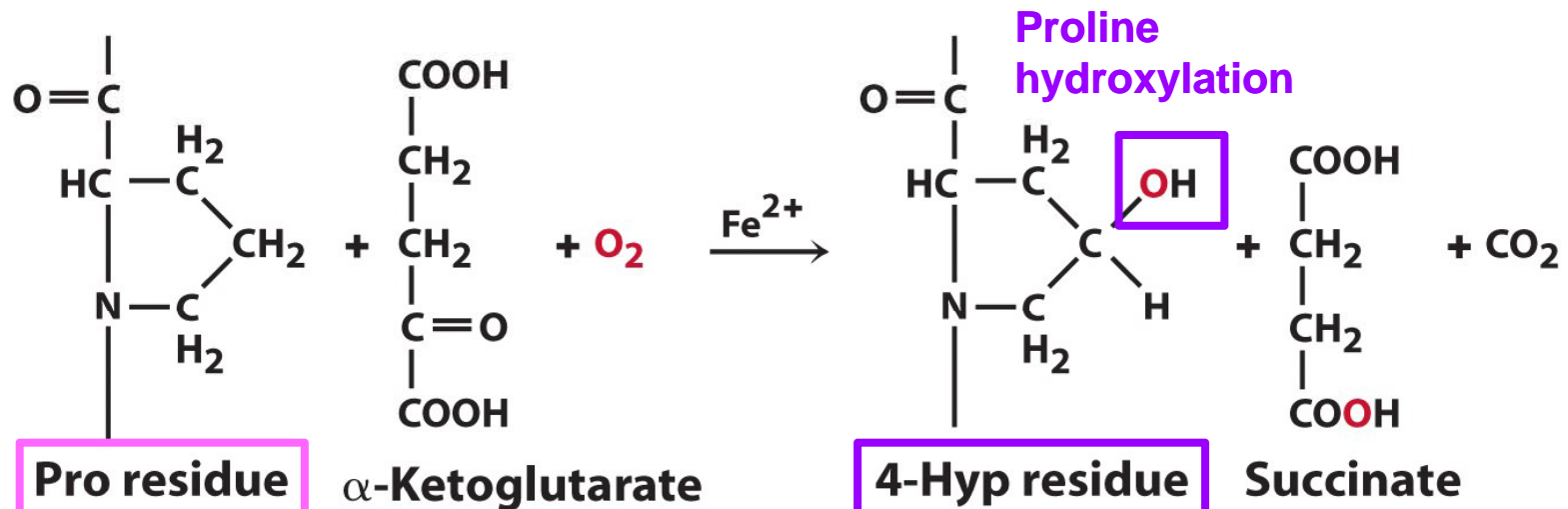
FIGURE 6.20 • A disaccharide of galactose and glucose is covalently linked to the 5-hydroxyl group of hydroxylysines in collagen by the combined action of the enzymes galactosyl transferase and glucosyl transferase.

4-HyP is generated by Prolyl 4-hydroxylase

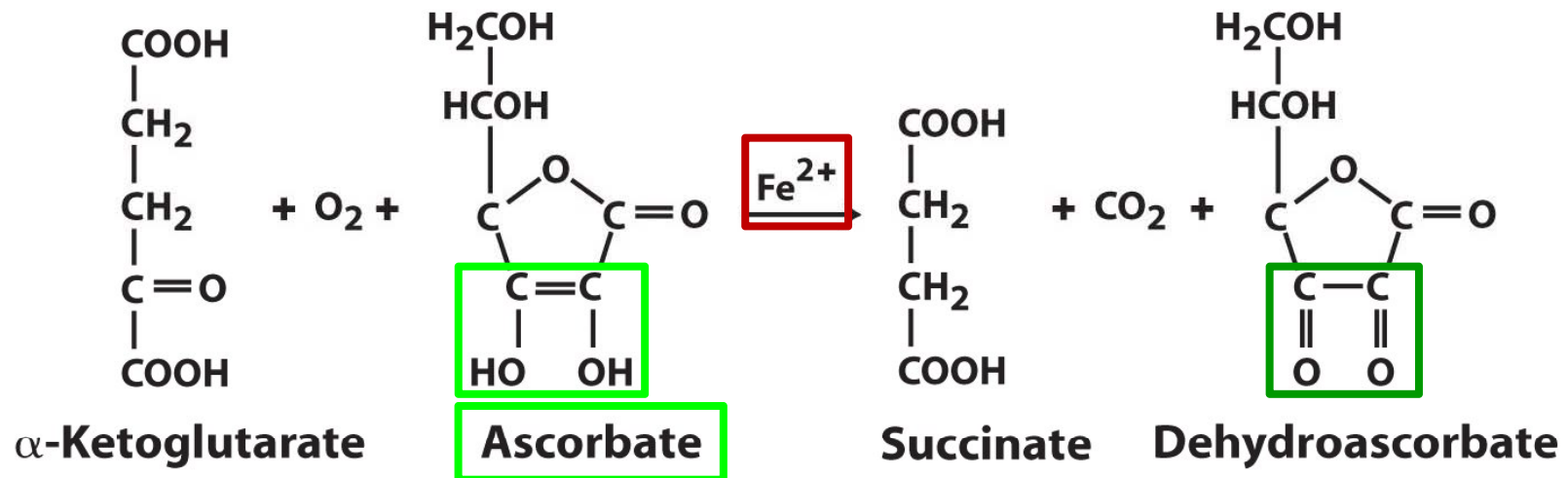
The collagen helix structure requires the Pro residue in the Y positions to be in the C γ -exo conformation, which is enforced by the hydroxyl substitution at C γ in 4-HyP



Reactions catalyzed by **Vitamin C-dependent** **Prolyl 4-hydroxylase**



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Restore enzyme activity by reducing the oxidased iron

Collagen defects are responsible for a variety of human diseases

Scurvy 壞血病

- Vitamin C (ascorbic acid) deficiency leads to lack of proper hydroxylation and defective collagen triple helix, and the connective tissue problems (skin lesions, fragile blood vessels, bleeding gums)

Osteogenesis imperfecta 成骨不全症

- 致病原因為形成第一型膠原蛋白 (collagen type I) 相關的基因 COL1A1 和 COL1A2 產生突變而引起。若基因突變提早形成終止密碼 (premature stop codon) 會影響膠原蛋白的產量；或因突變造成原為 Gly 之位置被具有較大 R group 之胺基酸置換所導致；由於 Gly 為膠原蛋白之結構穩定所必須，所以任何一個 Gly 被置換後，皆會使膠原蛋白的結構產生異常。

Ehlers-Danlos syndrome 鬆皮症

Marfan's syndrome 馬凡氏症候群 (指趾過長症候群)

- 為一先天膠原結締組織異常之遺傳疾病，此症由於體內合成膠原蛋白出現障礙，以致產量不足或品質不好；或因突變造成原為 Gly 之位置被具有較大 R group 之胺基酸置換所導致。患者皮膚與關節具高度延展性，皮膚和血管較為脆弱，傷口癒合比較慢，，所以也被稱為橡皮人症候群 (rubber man syndrome)。

Structure of silk

絲蛋白

蠶絲、蜘蛛絲

Fibroin
in
spider
web

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Fibroin consists of layers of anti-parallel β sheets rich in Ala and Gly residues

