Biochemistry

Unit 5 · Lesson 4 · Pentose shunt, glyoxylate and polysaccharides

The notes for Lesson 4 of Unit 5: chapters 5.7 to 5.8 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 4 of 4 | 2 chapters | Chapters 5.7 to 5.8

About these notes

These are the notes for **Lesson 4 · Pentose shunt, glyoxylate and polysaccharides** of the University free n easy video lessons on Biochemistry Unit 5, Bioenergetics and Carbohydrate Metabolism. They are chapters 5.7 to 5.8 of the unit book, unchanged, so a page here is the same page in the full book.

5.7 Pentose phosphate pathway and glyoxylate cycle

Two side roads of glucose and acetyl-CoA metabolism. The **pentose phosphate pathway** oxidises glucose 6-phosphate in the cytosol not for ATP but for two products: NADPH, the reducing power for biosynthesis and antioxidant defence, and ribose 5-phosphate for nucleotides. The **glyoxylate cycle**, found in plants, bacteria and fungi but not in vertebrates, skips the two CO_2-releasing steps of the TCA cycle so that acetyl-CoA from fat can become glucose.

You need: glycolysis intermediates from chapter 5.3; the TCA cycle from chapter 5.4; the reason animals cannot make glucose from fat in chapter 5.6.

Pentose phosphate pathway: the two phases

The pathway is also called the hexose monophosphate (HMP) shunt or phosphogluconate pathway. It is most active in tissues that make fatty acids or steroids (liver, adipose tissue, mammary gland, adrenal cortex) and in red blood cells and the lens, which need NADPH to keep glutathione reduced.

Oxidative phase (irreversible), three steps:

1. **Glucose 6-phosphate dehydrogenase (G6PD)**: glucose 6-phosphate + $NADP^+$ → 6-phosphoglucono-δ-lactone + NADPH. The rate-limiting, committed step.
2. **Lactonase**: the lactone is hydrolysed to 6-phosphogluconate.
3. **6-Phosphogluconate dehydrogenase**: 6-phosphogluconate + $NADP^+$ → ribulose 5-phosphate + CO_2 + NADPH (oxidative decarboxylation).

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Glucose 6-P + 2 NADP⁺ + H₂O → ribulose 5-P + CO₂ + 2 NADPH + 2 H⁺
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Non-oxidative phase (all reversible). Ribulose 5-phosphate is converted to ribose 5-phosphate by an **isomerase**, or to xylulose 5-phosphate by an **epimerase**. Then two enzymes shuffle carbons between sugars: **transketolase** (coenzyme thiamine pyrophosphate) moves a two-carbon unit, and **transaldolase** moves a three-carbon unit. The net effect turns three pentoses into two hexoses and one triose:

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3 Pentose 5-P (15 C) ⇌ 2 fructose 6-P (12 C) + glyceraldehyde 3-P (3 C)
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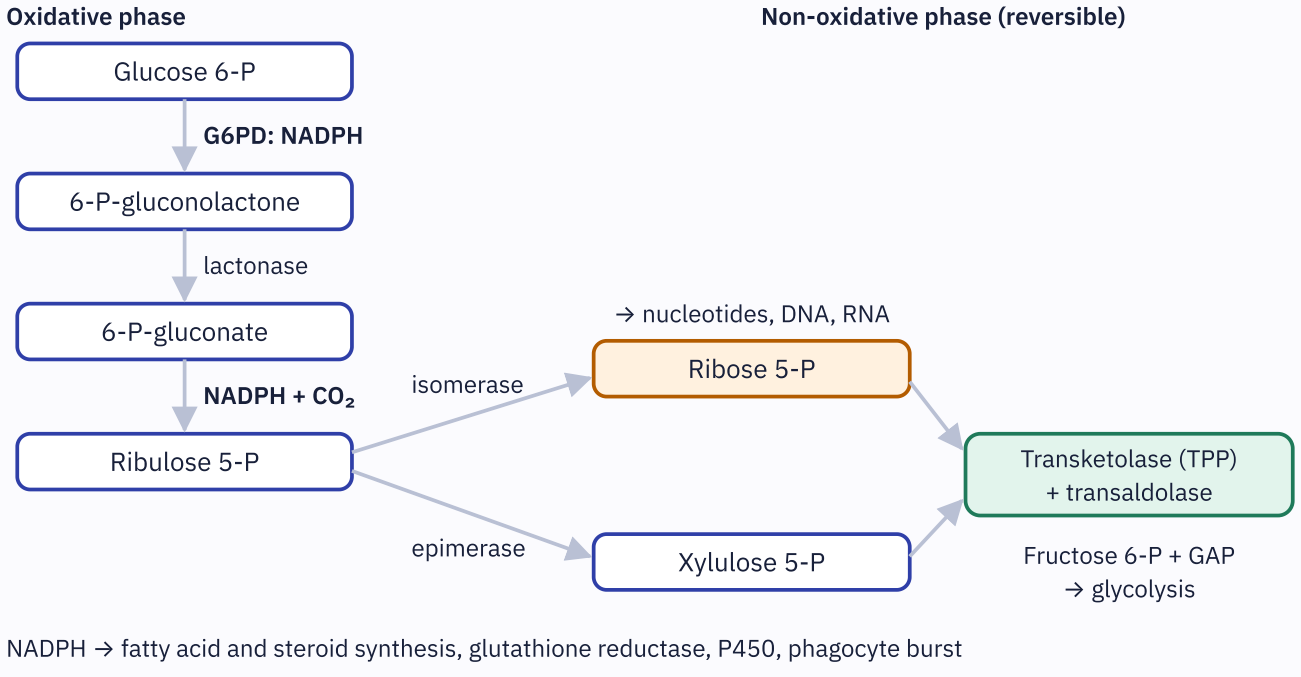


Figure 5.7.1 The pentose phosphate pathway. The oxidative phase makes 2 NADPH and 1 CO_2 per glucose 6-phosphate; the reversible non-oxidative phase either supplies ribose 5-phosphate or recycles extra pentoses back into glycolysis. Notice that no ATP is made or used anywhere.

Modes of operation and regulation

Because the non-oxidative phase is reversible, the cell can run the pathway to match its needs. If it needs **ribose more than NADPH** (dividing cells), fructose 6-phosphate and GAP from glycolysis run backwards through transketolase and transaldolase to make ribose 5-phosphate

without the oxidative phase. If it needs **both equally**, the oxidative phase alone suffices. If it needs **NADPH more than ribose** (adipose tissue), the pentoses are converted back to fructose 6-phosphate and GAP, which are recycled to glucose 6-phosphate, so the glucose is completely oxidised to CO_2 in effect. The flux through G6PD is set mainly by the $NADP^+$/NADPH ratio: NADPH inhibits the enzyme, so the pathway speeds up when NADPH is used.

Clinical links. G6PD deficiency is an X-linked disorder, common in several Indian communities and in malaria regions. Red cells with low G6PD cannot make enough NADPH to keep glutathione reduced, so oxidant drugs (primaquine, some sulphonamides) or fava beans cause haemolysis. The trait gives some protection against falciparum malaria. Red-cell **transketolase activity** is used as a test of thiamine status, since thiamine pyrophosphate is its coenzyme (see Unit 4, Water-soluble vitamins).

Glyoxylate cycle

Germinating oil seeds (groundnut, castor, sunflower) have stored fat but no photosynthesis yet, so they must turn fat into sugar. They do it in **glyoxysomes**, specialised peroxisomes. The cycle uses three TCA enzymes (citrate synthase, aconitase, malate dehydrogenase) and two of its own:

1. **Isocitrate lyase** splits isocitrate (6C) into succinate (4C) and glyoxylate (2C), instead of decarboxylating it.
2. **Malate synthase** joins glyoxylate with a second acetyl-CoA to make malate (4C).

$$2\ \text{Acetyl-CoA} + \text{NAD}^+ + 2\ \text{H}_2\text{O} \rightarrow \text{succinate} + 2\ \text{CoA} + \text{NADH} + 2\ \text{H}^+$$

Both CO_2-releasing steps of the TCA cycle are skipped, so two acetyl-CoA give one net four-carbon molecule. The succinate goes to the mitochondrion, becomes oxaloacetate through the TCA cycle, and oxaloacetate becomes glucose by PEPCK and gluconeogenesis. Vertebrates lack isocitrate lyase and malate synthase, which is the exact reason they cannot make net glucose from fatty acids.

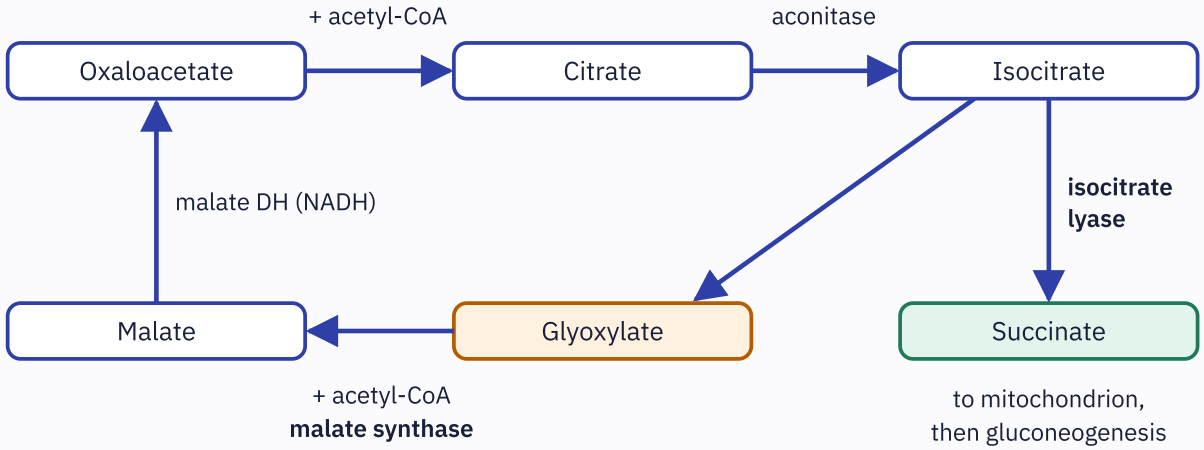


Figure 5.7.2 The glyoxylate cycle in a glyoxysome. Isocitrate lyase and malate synthase (bold) replace the two decarboxylation steps of the TCA cycle, so carbon from two acetyl-CoA leaves as succinate instead of CO_2. Notice that two acetyl-CoA enter per turn.

WORKED EXAMPLE

Question. An adipose cell needs 12 NADPH for fatty acid synthesis and no ribose. Show how the pentose phosphate pathway can supply this from glucose 6-phosphate and write the net equation.

1. Each glucose 6-phosphate through the oxidative phase gives 2 NADPH, so 6 G6P are needed: 6 G6P → 6 ribulose 5-P + 6 CO_2 + 12 NADPH.
2. Non-oxidative phase: 6 pentoses (30 C) → 4 fructose 6-P (24 C) + 2 GAP (6 C).
3. Recycling by the gluconeogenic enzymes: 4 fructose 6-P → 4 G6P; 2 GAP → 1 fructose 1,6-bisphosphate → 1 fructose 6-P (FBPase-1 releases Pi) → 1 G6P. Total 5 G6P regenerated.
4. Net: 6 G6P used, 5 regenerated, so 1 G6P is consumed.

Answer. G6P + 12 $NADP^+$ + 7 H_2O → 6 CO_2 + 12 NADPH + 12 H^+ + Pi. In effect one glucose 6-phosphate is completely oxidised to CO_2, with all its electrons going to NADPH instead of to oxygen.

EXAM TRAPS

- The pentose phosphate pathway makes NADPH, not NADH, and makes no ATP. Do not add it to an ATP count.
- Transketolase transfers 2 carbons and needs TPP; transaldolase transfers 3 carbons and needs no coenzyme.
- The oxidative phase is irreversible; the non-oxidative phase is reversible. Questions on "modes" depend on this.
- The glyoxylate cycle is absent in humans; isocitrate lyase and malate synthase are its marker enzymes.

CHECK YOURSELF

– REMEMBER **Name the enzyme of the committed step of the pentose phosphate pathway and its coenzyme.** 2 marks

Glucose 6-phosphate dehydrogenase; $NADP^+$.

– REMEMBER **Name the two enzymes unique to the glyoxylate cycle.** 2 marks

Isocitrate lyase and malate synthase.

– UNDERSTAND **Why do red blood cells depend on the pentose phosphate pathway though they make no fatty acids?** 3 marks

It is their only source of NADPH, needed by glutathione reductase to keep glutathione reduced. Reduced glutathione removes hydrogen peroxide and protects haemoglobin and the membrane from oxidation.

– UNDERSTAND **How does the glyoxylate cycle let seeds convert fat to sugar?** 4 marks

Isocitrate lyase and malate synthase bypass the two decarboxylations of the TCA cycle, so two acetyl-CoA give a net succinate instead of two CO_2. Succinate becomes oxaloacetate, then PEP and glucose by gluconeogenesis.

– APPLY **How many acetyl-CoA are needed to make one glucose through the glyoxylate cycle and gluconeogenesis?** 3 marks

Two acetyl-CoA give one succinate, then one oxaloacetate, then one PEP (one CO_2 lost at PEPCK). Glucose needs two PEP, so 4 acetyl-CoA.

– APPLY **A dividing cell needs ribose 5-phosphate but little NADPH. Which route supplies it?** 2 marks

The reversed non-oxidative phase: 2 fructose 6-P + 1 GAP from glycolysis → 3 ribose 5-P by transketolase, transaldolase, epimerase and isomerase, without the oxidative phase.

– ANALYZE **Why does a G6PD-deficient person stay healthy until exposed to primaquine or fava beans?** 4 marks

Normal oxidant load is handled even by low NADPH supply. Oxidant drugs and fava-bean compounds raise peroxide production sharply; older red cells, whose remaining G6PD is lowest, cannot regenerate enough reduced glutathione, so haemoglobin and membranes are damaged and the cells lyse.

BEYOND THE SYLLABUS

Fast-growing tumour cells push glucose through the pentose phosphate pathway to supply both nucleotides and NADPH against oxidative stress, so its enzymes are studied as cancer targets. Isocitrate lyase is essential for *Mycobacterium tuberculosis* to survive on host lipids during chronic infection, making it a long-studied TB drug target. Engineers also add glyoxylate-cycle genes to industrial microbes so they can grow on acetate. Search "isocitrate lyase tuberculosis persistence". This is not for the exam.

5.8 Biosynthesis of starch, sucrose, cellulose and peptidoglycan

Cells build polysaccharides from sugars that have first been "activated" by joining a nucleotide: ADP-glucose for starch, UDP-glucose for sucrose and cellulose, and UDP-N-acetylglucosamine for the bacterial wall. The nucleotide makes the glycosidic bond easy to form, and the release and hydrolysis of pyrophosphate drives the reaction forward. The peptidoglycan part matters for anyone heading to microbiology or antibiotic work.

You need: glucose 1-phosphate and the structures of starch, cellulose and the glycosidic bond from Unit 1, Polysaccharides and Disaccharides; ATP and pyrophosphate from chapter 5.2.

Activated sugars

Glucose 1-phosphate reacts with a nucleoside triphosphate:

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Glucose 1-P + UTP → UDP-glucose + PPi      (UDP-glucose pyrophosphorylase)
Glucose 1-P + ATP → ADP-glucose + PPi      (ADP-glucose pyrophosphorylase)
PPi + H₂O → 2 Pi                            (inorganic pyrophosphatase)
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The first reaction alone is near equilibrium; hydrolysis of PPi ($\Delta G^{\circ\prime} \approx -19$ kJ/mol) makes the pair irreversible. Different nucleotides label sugars for different pathways, so the cell can control each one separately. Animals use UDP-glucose to make glycogen; plants use ADP-glucose for starch.

Starch and sucrose in the plant leaf

Starch is made inside the chloroplast during the day (and in amyloplasts of storage tissues). **Starch synthase** transfers glucose from ADP-glucose to the non-reducing end of a growing chain, forming an α(1→4) bond. A **branching enzyme** moves a short piece of chain to make α(1→6) branches, giving amylopectin. ADP-glucose pyrophosphorylase is the control point: 3-phosphoglycerate (abundant when photosynthesis is fast) activates it and Pi inhibits it.

Sucrose is made in the cytosol, from triose phosphates exported from the chloroplast in exchange for Pi. They become fructose 6-phosphate and UDP-glucose, then two steps follow:

1. **Sucrose 6-phosphate synthase**: UDP-glucose + fructose 6-phosphate → sucrose 6-phosphate + UDP.
2. **Sucrose 6-phosphate phosphatase**: sucrose 6-phosphate + H_2O → sucrose + Pi.

Sucrose is the form in which the plant moves carbon through the phloem; starch is the form in which it stores carbon. The Pi released by sucrose synthesis returns to the chloroplast, and a shortage of it shifts carbon into starch.

Cellulose

Cellulose synthase sits in the plasma membrane as large rosette-shaped complexes. It takes glucose from UDP-glucose on the cytosolic side and adds it with a β(1→4) bond, pushing the growing chain out through the membrane. Many chains made side by side hydrogen-bond into a microfibril. Cortical microtubules under the membrane guide the direction the complexes move, so they set the orientation of the microfibrils in the wall.

Peptidoglycan of the bacterial wall

Peptidoglycan (murein) is a mesh of glycan chains of alternating N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), joined β(1→4), with a short peptide on each NAM that cross-links neighbouring chains. It is made in three places (Figure 5.8.1):

1. **Cytoplasm.** UDP-NAG gains a lactyl group from PEP (enzyme MurA, target of fosfomycin) and is reduced to UDP-NAM. Amino acids are added one by one, ending with the dipeptide D-Ala-D-Ala, to give UDP-NAM-pentapeptide (in *E. coli*: L-Ala, D-Glu, meso-diaminopimelic acid, D-Ala, D-Ala). D-Alanine is made by alanine racemase and joined by D-Ala-D-Ala ligase, both blocked by cycloserine.
2. **Membrane.** NAM-pentapeptide is transferred to the lipid carrier **bactoprenol** (undecaprenyl phosphate) to form lipid I; adding NAG gives lipid II, which is flipped to the outer face.
3. **Outside. Transglycosylases** join the disaccharide units into chains; **transpeptidases**, the penicillin-binding proteins, cross-link the peptides, cutting off the last D-Ala. The carrier returns as bactoprenol pyrophosphate and must be dephosphorylated; bacitracin blocks this step.

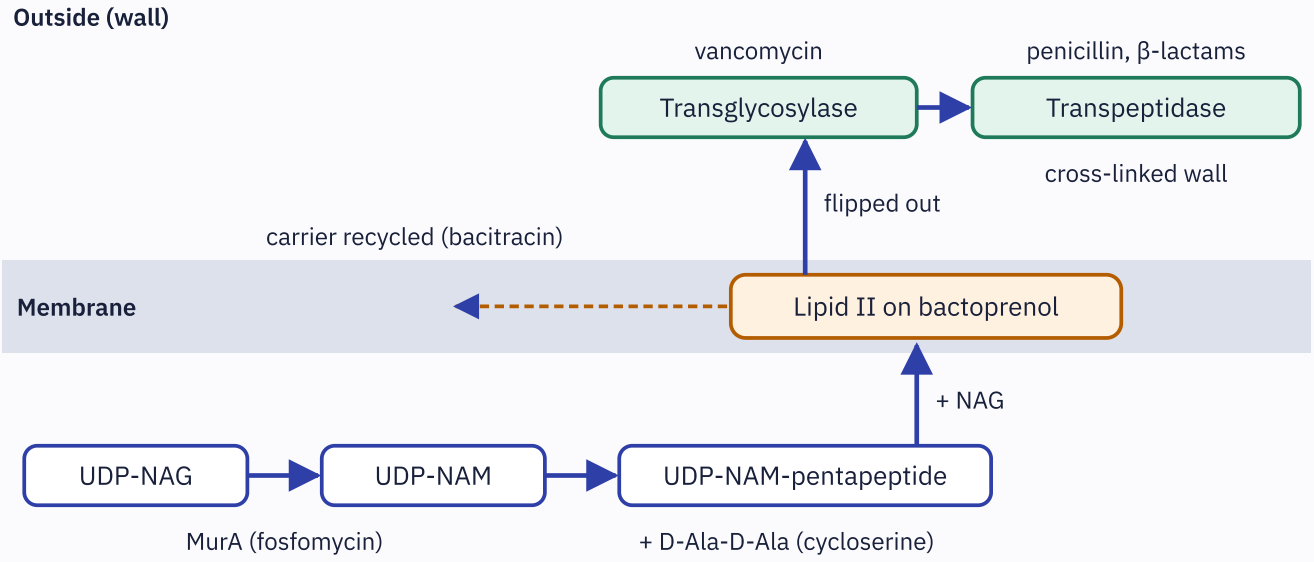


Figure 5.8.1 Peptidoglycan synthesis runs across three compartments, carried through the membrane on bactoprenol. Antibiotic names mark the step each one blocks; vancomycin acts by binding the D-Ala-D-Ala end of the substrate, not the enzyme. Notice that the final cross-linking happens outside the cell, where no ATP is available, so it is driven by cutting off the terminal D-Ala.

WORKED EXAMPLE

Question. How many high-energy phosphate bonds are spent to add one glucose from glucose 6-phosphate to a starch chain?

1. Glucose 6-P → glucose 1-P by phosphoglucomutase: no ATP.
2. Glucose 1-P + ATP → ADP-glucose + PPi: one phosphoanhydride bond of ATP is used.
3. PPi → 2 Pi: a second phosphoanhydride bond is hydrolysed.
4. Starch synthase transfers glucose and releases ADP: no further cost.

Answer. Two high-energy bonds per glucose added (one ATP becomes ADP, plus PPi hydrolysis). The same count applies to glycogen synthesis in animals with UTP.

EXAM TRAPS

- Plants make starch from ADP-glucose but sucrose and cellulose from UDP-glucose; do not mix them.
- Starch is made in the chloroplast; sucrose in the cytosol.
- Penicillin inhibits transpeptidation, the last step outside the cell, not the cytoplasmic steps; animal cells have no peptidoglycan, which is why it is selective.
- Lysozyme breaks the β(1→4) bond between NAM and NAG; it does not stop synthesis.

CHECK YOURSELF

– REMEMBER **Which activated sugar donates glucose for starch, sucrose and cellulose?** 3 marks

ADP-glucose for starch; UDP-glucose for sucrose and for cellulose.

– REMEMBER **Name the lipid carrier of peptidoglycan synthesis.** 1 mark

Bactoprenol (undecaprenyl phosphate).

– UNDERSTAND **Why does pyrophosphate hydrolysis matter in sugar activation?** 3 marks

The pyrophosphorylase reaction is near equilibrium. Removing PPi by hydrolysis (about –19 kJ/mol) pulls it forward and makes activation effectively irreversible.

– APPLY **A bacterium becomes resistant to vancomycin by making D-Ala-D-lactate ends. Explain.** 3 marks

Vancomycin binds D-Ala-D-Ala by hydrogen bonds; D-Ala-D-lactate loses one of them, so binding is much weaker while transpeptidases can still use the substrate.

– ANALYZE **Why do high 3-phosphoglycerate and low Pi in the chloroplast favour starch synthesis?** 4 marks

They signal active photosynthesis with carbon in excess of export. 3-PGA activates and Pi inhibits ADP-glucose pyrophosphorylase; low cytosolic Pi also slows triose phosphate export, so carbon stays in the chloroplast and is stored as starch.

BEYOND THE SYLLABUS

Lipid II is a target of new antibiotics such as teixobactin, found in 2015 in a soil bacterium grown with new culture methods. Cellulose synthase structures solved by cryo-EM are helping engineer biomass for second-generation ethanol, which India's biofuel policy encourages. Search "lipid II antibiotics" and "cellulose synthase structure". This is not for the exam.

Key terms of this lesson

TERM	MEANING OR FORMULA	CHAPTER
Pentose phosphate oxidative phase	G6P + 2 $NADP^+$ → ribulose 5-P + CO_2 + 2 NADPH	5.7
Glyoxylate cycle net	2 acetyl-CoA → succinate + NADH	5.7
Activated sugars	ADP-glucose (starch), UDP-glucose (sucrose, cellulose), UDP-NAG (peptidoglycan)	5.8

Glossary (terms used in this lesson)

Bactoprenol Undecaprenyl phosphate, the lipid carrier that moves peptidoglycan units across the bacterial membrane.

Committed step	The first irreversible step unique to a pathway; usually the main control point.
G6PD deficiency	X-linked lack of glucose 6-phosphate dehydrogenase causing drug- or food-triggered haemolysis.
Glyoxysome	Plant peroxisome that houses the glyoxylate cycle in germinating oil seeds.
NADPH	Reduced nicotinamide adenine dinucleotide phosphate, the electron donor of biosynthesis.
Transketolase	TPP enzyme that transfers two-carbon units between sugars.

The full unit book

Every chapter of Unit 5, the unit summary, the exam question bank with model answers and the full glossary: Biochemistry · Unit 5 · Bioenergetics and Carbohydrate Metabolism (one file, works offline).

Sources and further reading

- D. L. Nelson and M. M. Cox, *Lehninger Principles of Biochemistry*, 8th edition (2021): chapters on bioenergetics, glycolysis and gluconeogenesis, the citric acid cycle, oxidative phosphorylation, and carbohydrate biosynthesis in plants and bacteria (from memory; check).
- J. M. Berg, J. L. Tymoczko, G. J. Gatto and L. Stryer, *Biochemistry* (W. H. Freeman); the 5th edition is on the NCBI Bookshelf (from memory; check the edition you use).
- D. Voet and J. G. Voet, *Biochemistry* (Wiley) (from memory; check).
- U. Satyanarayana and U. Chakrapani, *Biochemistry* (Elsevier India), widely used in Indian colleges (from memory; check).
- J. L. Jain, S. Jain and N. Jain, *Fundamentals of Biochemistry* (S. Chand) (from memory; check).
- ExplorEnz, The Enzyme Database news item on the new EC 7 translocase class (August 2018): enzyme-database.org/news.php?id=5
- U.S. National Library of Medicine technical bulletin on adding Berg, Tymoczko and Stryer's *Biochemistry* (5th edition) to the Bookshelf: nlm.nih.gov technical bulletin

Standard ΔG°' and E°' values in this unit are the commonly tabulated textbook values (Lehninger tables; from memory; check against your prescribed book).

Syllabus: the University free n easy universal syllabus, built from top universities' syllabi.

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