I. Phenylalanine and Tyrosine Biosynthesis

Sec. 22.2.4 Chorismate is a key Intermediate in the Synthesis of Tryptophan, Phenylalanine, and Tyrosine

This section appears identical in editions 4 and 5 except for page numbers.

In this section, ignore the information on the synthesis of tryptophan from chorismate (Figs. 22-17 and 22-18). Focus only on synthesis of phenylalanine and tyrosine (Figs. 22-16 and 22-19).

General Principles

- Amino acids are typically synthesized in "Families" from central metabolites
- The stereospecific reaction for synthesis of L-amino acids is usually transamination of an α-keto acid.
- The benzene ring is synthesized from a linear poly-hydroxy chain by ring closure, followed by introduction of double bonds (aromaticity) by dehydration reactions.

Step 6 in Fig. 22-16 (EPSP Synthase) is the target of GLYPHOSATE, the active ingredient in the herbicide widely marketed under the name "ROUNDUP". Glyphosate is thought to act as an inhibitor of EPSP because it is a transition state analog of the PEP substrate.

The protonated nitrogen in glyphosate is analogous to the carbocation on the transition state.
Those of you who have a better recollection of O-Chem than I may recognize that the conversion of Chorismate to Prephenate (Step 1 in Fig. 22-19) is an electrocyclic Diels-Alder Reaction. These are very unusual in biochemistry.

STUDY QUESTIONS

The bacterium *Klebsiella pneumoniae* is capable of growing in a mineral salts medium in which glucose is the only organic compound available. Furthermore, *K. pneumoniae* is sensitive to inhibition by glyphosate. What does this suggest about the metabolism of *K. pneumoniae*?

Mutants of *K. pneumoniae* that are resistant to glyphosate inhibition can be readily isolated. These mutants have an altered gene for EPSP Synthase. The mutated, glyphosate-resistant EPSP gene has been inserted into the genome of soybeans. What is the commercial incentive for doing this?

Trace origin of the -OH group in the Tyr ring back to its origin in the precursors for the biosynthetic pathway.

What exactly happen to this -OH in Phe biosynthesis?

Describe the reactions that introduce the chiral carbon atoms in Phe and Tyr biosynthesis.

Describe the reactions that introduce the nitrogen atoms in Phe and Tyr biosynthesis.

What is a transition state analog (TSA)? Give an example of a TSA that is an important drug.
II. **Catabolism of Aromatic Amino Acids**

Sec. 18.3.4  Seven Amino Acids Are Degraded To Acetyl-CoA  p. 677^/p. 695^  
Again, focus only on Phe and Tyr.

Sec. 18.3.5  Phenylalanine Catabolism Is Genetically Defective In Some People  p. 679^/p. 696^  

**General Principles**

Nearly all aromatic ring modification and cleavage in biochemistry requires oxygenases.

Oxygenases are extremely important in "xenometabolism".

**OXYGENASES**

Oxygenases are enzymes that catalyze reactions in which molecular oxygen is a substrate. The \( \text{O}_2 \) is reduced in the reaction by 4 electrons derived from one or more donor substrates, and one or both oxygen atoms are incorporated in a product. All oxygenases are classified as oxidoreductases.

**Monooxygenases** ("Mixed Function" Oxygenases)

\[
C + \text{O}_2 + \text{reduced cofactor} \rightarrow C-\text{OH} + \text{H}_2\text{O} + \text{oxidized cofactor}
\]

2 of the necessary electrons are derived from a carbon atom in the principal substrate; the other 2 electrons are derived from one of several standard redox cofactors. The redox cofactor for many monooxygenases is \( \text{FMNH}_2 \), but the monooxygenases that participate in aromatic amino acid metabolism the cofactor tetrahydrobioprerin (THBT) based on the pterin ring (Fig. 18-24). Note that several of the monooxygenases involved in aromatic amino acid biosynthesis are referred to as "hydroxylases".

**Dioxygenases**

\[
C-C + \text{O}_2 \rightarrow \text{HO-C-C-\text{OH}}
\]

Here, all 4 electrons are derived from the principal carbon substrate, so there is no redox cofactor required.

**STUDY QUESTIONS**

What is the difference between a monooxygenase and a dioxygenase?

List all the oxygenase enzymes involved in aromatic amino acid modification and catabolism, and identify each as a mono- or di- oxygenase.

Why is dietary restriction of phenylalanine intake not always a sufficient treatment, by itself, for PKU? What additional dietary measures may be necessary, and why?
In the structure of Phe:

1. identify the carbon atom that is lost as CO2.
2. circle the carbons that enter the TCA Cycle as fumarate.
3. circle the carbons that enter the TCA Cycle as Acetyl-CoA.

List the "Inborn Errors of Metabolism" associated with Phe catabolism, and the defective enzyme responsible for each.

One of the mono-oxygenases involved with aromatic amino acid metabolism uses a redox cofactor other than FMNH₂ or THBT. Draw the structures of the oxidized and reduced forms of this cofactor.

Chapter 18 Problem #4/#11
III. Secondary Products Made From Phe and Tyr

22.3.5 Aromatic Amino Acids are Precursors of Many Plant Substances  p. 859
22.3.6 Biological Amines are Products of Amino Acid Decarboxylation  p. 878

Again, in these sections we are interested in ONLY the information pertaining to Phe and Tyr (i.e. only the LEFT panel of Fig. 22-9).

General Principles

The amino acids, and intermediates in amino acid biosynthesis, are frequently used as precursors for important "secondary metabolites. Synthesis of these secondary metabolites is often restricted to particular phylogenetic groups, and even to specific tissues.

In this diagram, pathways restricted to animals are shown in blue. Green arrows show pathways that may also found in plants and bacteria. Remember that the secondary metabolites in animals must be synthesized from dietary amino acids.
Melanin Pigments

Gr. *melas, melanos* = “black”

**Melanins** are a family of brown, yellow-brown, and red-brown pigments found in many animals. They are high molecular weight polymers whose complexity and insolubility has frustrated attempts to provide definitive structural characterization. They are synthesized from the amino acid tyrosine (or from phenylalanine) via L-DOPA, which is also the precursor for several important neurotransmitters.

Melanins are found in both invertebrates and vertebrates. Examples include industrial melanism in the “peppered Moth” and other insects, the “ink” of squid, and camouflage in flounder.

The functions ascribed to melanin include: cryptic coloration, signaling, and protection from sunlight.

In vertebrates, melanins are synthesized in specialized cells derived from the neural crest called **melanocytes** that invade the epidermis, the hair follicles, and the eye. Melanin is not uniformly distributed throughout melanocytes, but is synthesized in specific sub-cellular granules called **melanosomes**.

Melanosomes are transferred from melanocytes to epidermal cells (keratinocytes) that will eventually die and form the bulk of the epidermis and the hair shaft. Melanocytes are also transferred to cells that form the iris and the retina. Each melanocyte has numerous long processes, or tubular extensions, that allow each melanocyte to deliver melanosomes to as many as several dozen keratinocytes. Ultimately, keratinocytes may have higher melanin content than melanocytes.

Variation in pigmentation is due largely to the concentration of melanosomes in keratinocytes. This is associated with the relative rates of melanosome synthesis and loss, and not to the number of melanocytes, which is essentially uniform in all individuals.

As epidermal cells age, and move outwards, melanosomes may fuse with other organelles called lysosomes, and this fusion brings about the destruction of melanosomes. Accordingly, cells of the upper epidermis have decreased melanin content. Old, dead keratinocytes are eventually shed.
In the initial stages of melanosome synthesis, the melanosome is a fibrillar protein network with tyrosine hydroxylase (and other enzymes?) attached. These unpigmented immature melanosomes are frequently observed in albinos.