11.S: Nucleophilic Acyl Substitution Reactions (Summary)

Before moving forward you should be able to:

- Recognize and draw examples of carboxylic acid derivative functional groups:
  - carboxylic acids/carboxylates
  - acyl phosphates (both acyl monophosphate and acyl-AMP)
  - thioesters
  - esters
  - amides
  - acid chlorides
  - carboxylic acid anhydrides
- Know the meaning of the terms 'acyl', 'acetyl', 'formyl', 'lactone', and 'lactam'.
- You need not memorize the structure of coenzyme A, but you should recognize that it contains a key thiol group and often forms thioester linkages, particularly in fatty acid metabolism.
- Understand what happens in a nucleophilic acyl substitution (also called acyl transfer reaction), and be able to draw mechanistic arrows for a generalized example.
- Know the trends in relative reactivity for the carboxylic acid derivatives:
  - in a biological context (acyl phosphates and thioesters as activated acyl groups)
  - in a laboratory context (acid chlorides and carboxylic acid anhydrides as activated acyl groups)
- Recognize and understand the most important types of nucleophilic acyl substitution reactions in biology:
  - How a carboxylate group, which is unreactive to nucleophilic acyl substitution reactions, is activated in the cell by ATP-dependent phosphorylation to either acyl monophosphate or acyl-AMP.
  - Conversion of an acyl phosphate to a thioester, a (carboxylic) ester, or an amide.
  - Transthioesterification, esterification, and transesterification reactions.
  - Conversion of a thioester or ester to an amide
  - Hydrolysis of a thioester, a (carboxylic) ester, or an amide to a carboxylate.
- Understand the energetics of the above reactions:
  - Carboxylate to acyl phosphate is 'uphill' energetically, paid for by coupling to hydrolysis of one ATP
  - Other conversions above are 'downhill': it is unlikely, for example, to see a direct conversion of an amide to an ester. (Notable exception: the lactam (cyclic amide) group in penicillin is very reactive due to ring strain, and forms an ester with an active site serine residue in the target protein)
- You need not memorize all of the details of peptide bond formation on the ribosome, but you should be able to follow the description in section 7 and recognize the nucleophilic acyl substitution reactions that are occuring.
- Be able to draw complete mechanisms for the following lab reactions:
  - acid-catalyzed esterification of a carboxylic acid
  - saponification (base-catalyzed hydrolysis of an ester), application to soap-making
  - base-catalyzed transesterification, application to biodiesel production
- Understand how acid chlorides and carboxylic acid anhydrides serve as activated acyl groups in laboratory synthesis. Be able to describe how an amide to ester conversion could be carried out in the laboratory.
- Understand how polyesters and polyamides are formed. Given the structure of a polymer be able to identify monomer(s), and vice-versa.
- Be able to recognize, predict products of, and draw mechanisms for the Gabriel synthesis of primary amines, using either hydroxide ion or hydrazine to release the amine product.