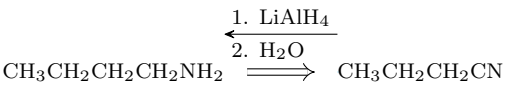
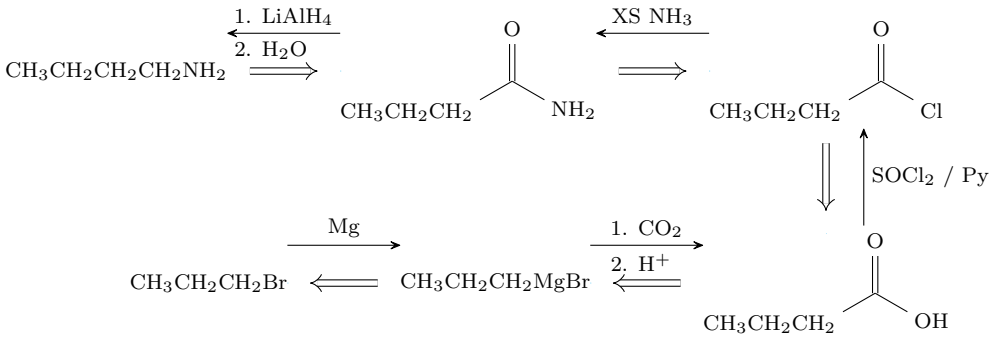
4.25 Acyl Transfer Reactions - 2

11/4:

- Lecture 24 recap.
  1. Mechanism of acyl transfer (Figure 4.22).
     - Proceeds via a two-step addition-elimination process and a tetrahedral intermediate.
  2. Acid chlorides (Figure 4.10) and acid anhydrides (Figure 4.11) are very reactive, so no catalyst is needed for their acyl transfer reactions.
  3. Esters have three important reactions: Hydrolysis (Figure 4.26), transesterification (Figure 4.29), and amide formation (Figure 4.33).
     - Esters are *not* great electrophiles, so we need an acid or base catalyst to promote their reactions.
     - We can make an amide from an ester by heating the amine and ester. The amine acts as both the nucleophile and the base in this case.
  4. Acid catalyzed esterification: Fischer esterification (Figure 4.34).
     - Driven by excess alcohol or removal of water.
     - Under basic conditions, we form an unreactive carboxylate (Figure 4.35).
  5. Amide hydrolysis (Figure 4.37).
     - Driving force under acidic conditions: The formation of a (very stable) salt.
     - Driving force under basic conditions (Figure 4.39): The formation of a (very stable) carboxylate.
- Feedback: Prof. Buchwald has heard that there's a lot of anxiety about synthesis questions, so he'll go over one example problem today, another on Wednesday, and many on Friday!
  - Source of anxiety around synthesis: There's no one right answer.
  - Positive outlook: There is more than one thing you can write down for 100% credit!
- Example: How can we make *n*-butyl amine (^{n}BuNH$_2$) from *n*-propyl bromide (^{n}PrBr) and any 1-carbon compound?



(a) Pathway through the nitrile.



(b) Pathway through the amide.

Figure 4.42: TTQ: Synthesis of *n*-butyl amine from *n*-propyl bromide.

  - This is a medium-difficulty question.
  - We'll start with a retrosynthetic analysis.[8]
    - You may want to start by identifying the number of carbons in the starting material and product.
    - This tells us that we need to attach a CH_2NH_2 to the starting material. How can we do this?
  - We don't know too many reactions yet, but here are two possibilities.
    - Transform ^{n}BuNH$_2$ to butyronitrile (^{n}PrCN).[9]
      - ➢ In the forward direction, we'd use $LiAlH_4$ and then H_2O (a water workup).
    - Transform ^{n}BuNH$_2$ to butyramide (^{n}PrCONH$_2$).
      - ➢ In the forward direction, we'd use $LiAlH_4$ and then H_2O, as well.
      - ➢ Next step: Transform butyramide to the acid chloride via excess (XS) ammonia.
      - ➢ Next step: Transform the acid chloride to the carboxylic acid via $SOCl_2$ / Py.
      - ➢ Next step: The carboxylic acid could have come from the primary alcohol via Jones reagent. However, this route would require a 4-carbon primary alcohol starting material, which would be difficult to access from *n*-propyl bromide. More simply, transform the carboxylic acid to a Grignard reagent via carboxylation with CO_2.
      - ➢ Final step: Transform the Grignard reagent to the original *n*-propyl bromide via magnesium metal.

- Aside (connection to real-world chemistry): In real-life synthesis problems, chemists work to make compounds as inexpensively as possible.
  - However, cost is not a consideration in 5.13.
- Prof. Buchwald's advice on 5.13-level synthesis problems: The more practice problems you do, the more you'll see how things work retrosynthetically.
- This concludes today's synthesis example; we now return to acyl transfer reactions.
- Lecture outline.

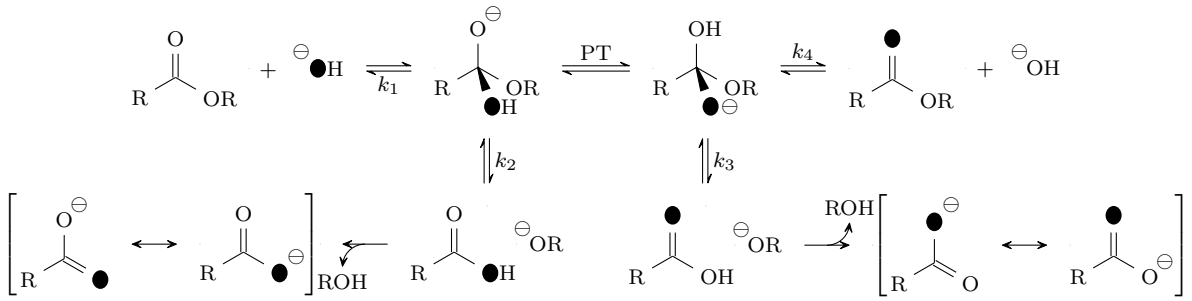
4. Evidence for a tetrahedral intermediate.
   a. Ester hydrolysis.
   b. Amide hydrolysis (basic).
   c. Amide hydrolysis (acidic) — deferred to recitation.
5. Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.

- We'll begin with Topic 4: Evidence for a tetrahedral intermediate.
- According to Prof. Buchwald, every acyl transfer reaction goes through a tetrahedral intermediate.
  - But Prof. Buchwald just told us this; why should we believe it's true?
  - Here's some evidence that this happens.
- Recall the general addition-elimination mechanism from last lecture (Figure 4.22).
  - Why couldn't we have the S_N2-like mechanism instead?

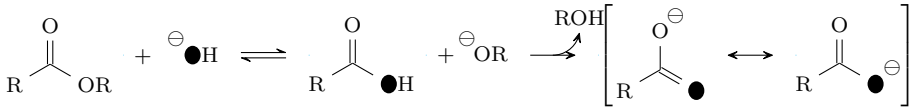
[8] Note that the double-lined arrows are called "retrosynthetic arrows." It is common nomenclature to see retrosynthetic arrows in the reverse direction, overset by forward arrows and conditions.

[9] Although it was not covered in class, we could then transform butyronitrile to *n*-propyl bromide with CN^- (see Figure 3.21). This would be a highly efficient synthesis!

- We can differentiate these two mechanisms via an isotopic labeling study.
  - Most naturally occurring oxygen is ^{16}O.[10] However, we can also use molecules containing heavy oxygen, which is interchangeably denoted as ^{18}O, ^{18}●, or just ●.[11]
  - In particular, we could run an ester hydrolysis reaction using H●$^-$ as the nucleophile and H$_2{}^{18}$● as the solvent!
    - Such a reaction would yield RCO●H as the product instead of RCOOH.
    - We can then use mass spec to measure how much ^{18}O has been incorporated, for example by looking at the ratio of the heights of the parent peak (RCOOH) and the $[M+2]^{+\cdot}$ peak (RCO●H).
  - In this particular experimental setup, we will stop the ester hydrolysis process at partial conversion for reasons that will become clear shortly.
    - We can then look for ^{18}● in the acid *and* in the starting material.
- We now discuss Subtopic 4.a: Evidence for a tetrahedral intermediate in the ester hydrolysis reaction.



(a) The kinetic network for the addition-elimination mechanism.



(b) The kinetic network for the S_N2 mechanism.

Figure 4.43: Isotopic labeling to prove a tetrahedral intermediate: Ester hydrolysis.

  - Figure 4.43a displays the full kinetic network of the addition-elimination mechanism.
    - All of the little k's indicate kinetic rate constants.
    - This is the ugliness of reality: It's a very complicated kinetic network.
  - Here's a rough explanation of the network.
    - We begin in the upper-left corner, with our ester and isotopically labeled H●$^-$ nucleophile.
    - H●$^-$ can add into the ester, yielding the tetrahedral intermediate.
    - Now we have three options: Go backwards and eliminate H●$^-$, go down and eliminate RO$^-$, go right and do proton transfer followed by eliminating HO$^-$.
      - ➢ Going backwards occurs with rate constant k_1 from the tetrahedral intermediate.
      - ➢ Going down occurs with rate constant k_2 from the tetrahedral intermediate.
      - ➢ Going right occurs with rate constant k_4 from the tetrahedral intermediate.

[10] "oh sixteen."

[11] All pronounced "oh eighteen;" these notes will use these symbols interchangeably, as well, so that you get practice looking at all of the forms.

- The last option is that we could do proton transfer, and then eliminate RO^-. This process occurs with rate constant k_3.
- Note that any time we eliminate RO^- (k_2 or k_3), the resultant carboxylic acid will be irreversibly deprotonated under the present basic conditions.

– HO^- and RO^- are comparable leaving groups (i.e., comparably good at leaving).
- Thus, we should have $k_1 \approx k_2 \approx k_3 \approx k_4$.
- So if this scheme is correct, we expect to get some ^{18}O in the recovered ester, via the k_4 pathway!

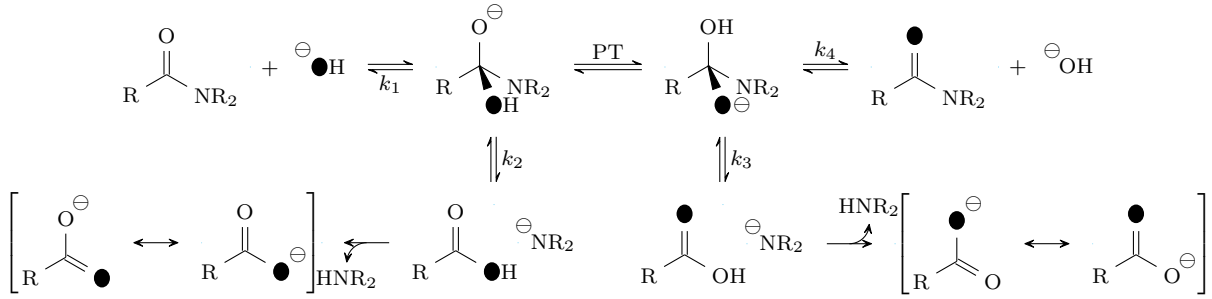
– Now let's consider the other possibility: Figure 4.43b displays the full kinetic network for the S_N2 mechanism.

– If we do an S_N2 reaction, we should get a stable carboxylate that does not participate in a back reaction.
- Therefore, we should see no ^{18}O in the recovered ester SM at 50% conversion.

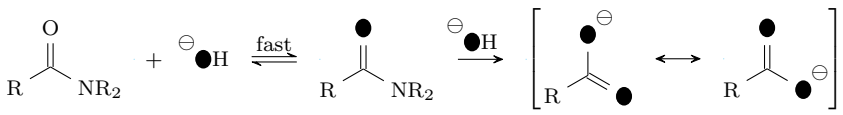
– Experimentally, what we find is that there *is* ^{18}O in the recovered ester.
- Therefore, the tetrahedral intermediate does exist!

– If this experimental setup isn't making sense right now, go home, meditate, relax, and then look at this again under calmer circumstances.

- This concludes our discussion of how an isotopic labeling study provides evidence for the existence of the tetrahedral intermediate over an S_N2 pathway.
- We now move onto an isotopic labeling study of amide hydrolysis, with the goal of showing how a mechanism that proceeds through a tetrahedral intermediate can explain the following two experimental results.
  – Under basic amide hydrolysis conditions (which we stop at 50% conversion), we get lots of ^{18}O in the recovered amide.
  – Under acidic amide hydrolysis conditions (which we stop at 50% conversion), we get much less ^{18}O in the recovered amide.
- We now dive more deeply into the mechanism under basic conditions, which is Subtopic 4.b.



(a) The kinetic network for the addition-elimination mechanism.



(b) The overall reaction.

Figure 4.44: Isotopic labeling to prove a tetrahedral intermediate: Amide hydrolysis.

  - The overall scheme (Figure 4.44a) bears a great resemblence to Figure 4.43a. However, there is one key difference.
    - H_2O has a much lower pK_a than HNR_2 (see Table 4.1), which means that HO^- (the conjugate base of H_2O) is a *much* better leaving group than R_2N^- (the conjugate base of HNR_2).
    - This means that while $k_1 \approx k_4$ and $k_2 \approx k_3$, we have that $k_1 \gg k_2$.
  - This implies that under basic conditions, the initial amide equilibrates fast with the isotopically labeled amide (Figure 4.44b).
    - It follows that we'll often observe a carboxylate product with two ^{18}O's!
    - To reiterate, this is because the first gets incorporated fast, and the second happens more slowly. So by the time we do amide hydrolysis, some ^{18}O will have already been incorporated!

- A deep dive into the mechanism under acidic conditions will be covered in recitation by the TFs.
- We now move onto Topic 5: Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.
- Per a conversation this morning between Prof. Buchwald and Dr. Wendlandt — the chemistry professor currently teaching 5.12 — this should be review.
- Let's consider how our carboxylic acid derivatives react with the above four reagents.

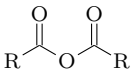
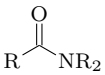
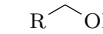
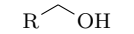
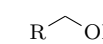
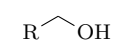
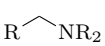
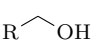
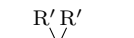
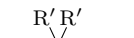
					
$NaBH_4$			NR	NR	NR
$LiAlH_4$					
$R'MgBr$					NR
$R'Li$					

Table 4.2: Reactions of carboxylic acid derivatives with $NaBH_4$, $LiAlH_4$, RMgBr, RLi.

  - Recall from Figure 4.20 that our carboxylic acid derivatives can be partitioned into...
    - More reactive compounds (acid chlorides and acid anhydrides);
    - Mid-range compounds (esters);
    - More stable compounds (amides);
    - By the far least reactive compounds (carboxylates).
  - Our reagents also vary in strength.
    - $NaBH_4$ is weaker. This can be good because it's more selective!
    - $LiAlH_4$, in contrast, is stronger and less selective.
  - It follows that $NaBH_4$ will reduce acid chlorides, acid anhydrides, and ketones to primary alcohols, but it will *not* reduce esters, amides, or carboxylates.
    - Aside: This fact is useful in **chemoselective** syntheses!
    - For example, you could put an ester and acid anhydride in the same molecule and know that only the acid anhydride will react with $NaBH_4$!
    - Chemoselectivity is one of the big trends in modern synthesis.
  - $LiAlH_4$ reduces everything to alcohols.

  - The Grignard reagent adds twice to carboxylic acid derivatives, yielding a tertiary alcohol.
    - This happens to acid chlorides, acid anhydrides, and esters.
    - Amides turn into the ketone (this is a special case!).
    - Carboxylates do not react.
  - Organolithium reagents (more potent than Grignards) react exactly the same as Grignards, except that they will *also* turn carboxylates into ketones!
    - This is a very surprising result, since we've talked about how unreactive carboxylates are.

- Where do ketones and aldehydes fit into the picture?
  - Ketones and aldehydes are between anhyrides and esters, and aldehydes are more reactive than ketones.
  - $NaBH_4$ will reduce ketones and aldehydes to the primary alcohol.
  - We'll talk about this more later.

- Next time: A mechanistic explanation for Table 4.2.