Unit 4

Carboxylic Acids and Derivatives

4.23 Carboxylic Acids Intro

10/30:

- Lecture 22 recap.
  - A. Amine synthesis by direct S_N2 (of, for example, NH_3) leads to mixtures unless you use a very large excess of ammonia (Figure 3.13).
    - Alternative: Gabriel synthesis (Figure 3.14).
    - Alternative: Conversion of a primary or secondary alkyl halide to an azide and subsequent reduction (Figure 3.15).
  - B. Reductive amination is an incredibly powerful technique (Figures 3.16, 3.17, & 3.18).
    - It can build primary, secondary, and tertiary amines.
    - Be intimately familiar with this process for Exam 3!!
  - C. Acylation/reduction is also a great method (Figure 3.19).
    - Acylate the amine to give an amide intermediate, reduce with LAH, and quench with water.
  - D. Primary and secondary alkyl bromides, iodides, and tosylates can be substituted to the nitrile and reduced to an amine (Figure 3.21).
    - This is a 1-carbon homologation.
  - E. HONO (generated from $NaNO_2 + HCl$) converts aniline to an aryl diazonium salt (Figure 3.24).
- Announcement: The notes taken by the TFs are posted on Canvas (that's these!).
  - Consider referring to these even over the ones that Prof. Buchwald provides.
- Lecture 22 continued.
- Using the sequence of reaction in Figure 3.25, you can form an aryl diazonium salt.
  - Treating it with KI yields an aryl iodide.
  - Treating it with H_2O yields a phenol.
  - Treating it with hypophosphorus acid (H_3PO_2) yields benzene again.
    - Once again, you are not responsible for the name "hypophosphorus acid."
  - Treating it with CuX (where $X = Cl, Br, CN$) yields PhX.
- This is a great example of what we do with synthesis!
  - Synthesis is all about connecting compounds with transformations.
  - Breaking down the example in such a way is called **retrosynthetic analysis**.

- Recall from last time that azides are reduced to amines by $LiAlH_4$ and a subsequent water workup (Figure 3.15). Here's a further note on this.

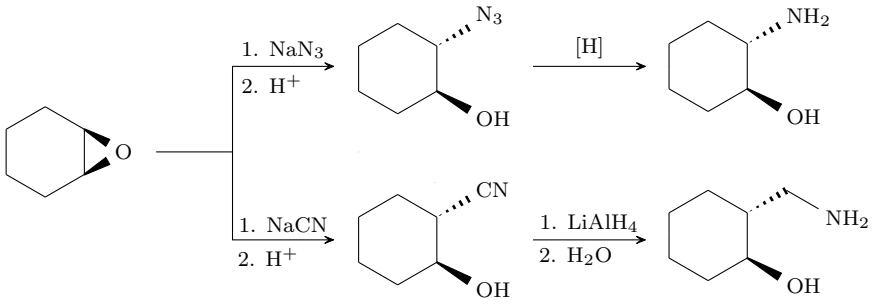


Figure 4.1: Aminoalcohol synthesis from epoxides.

  - Recall from 5.12 that **epoxides** are essentialy just reactive ethers, due to their ring strain.
  - Therefore, if we treat an epoxide with NaN_3, we'll get a backside attack that yields a certain intermediate.
  - Then upon reduction, we get a *trans*-1,2-aminoalcohol.
    - This is an important functional group for β-blockers in biology!
  - Alternatively, we can treat epoxides with CN^-, yielding the cyanoalcohol.
    - We can then reduce this to the 1,3-aminoalcohol.

- This concludes our discussion of amines.
- Today: Introduction to carboxylic acids and their derivatives.
  - Reading: Chapter 10 of Clayden et al. (2012).
- Lecture outline.
  1. Introduction.
  2. Synthesis of carboxylic acids.
     a. Oxidation of alcohols and aldehydes.
     b. Carboxylation of Grignard reagents.
     c. Hydrolysis of nitriles.
     d. Types of carboxylic acid derivatives.
  3. Acyl transfer reactions.
     a. Background.
- We'll begin with Topic 1: Introduction.
- **Carboxylic acid derivative**: A compound of the following form, where $X \neq H, R$. *Structure*

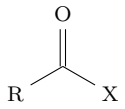


Figure 4.2: Carboxylic acid derivative.

  - Since X is *not* equal to H or R, we're not considering aldehydes or ketones.

- **Carboxylic acid**: A carboxylic acid derivative for which X = OH. *Structure*

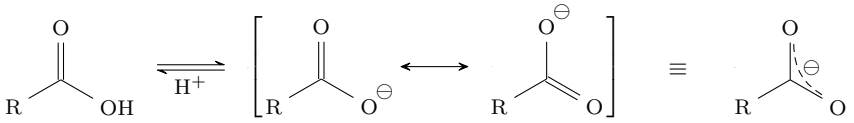


Figure 4.3: Carboxylic acid.

  - $pK_a \approx 5$.
    - By comparison, $pK_a \approx 16$ for an alcohol.
    - Therefore, carboylic acids are *eleven orders of magnitude* more acidic than alcohols.
  - Deprotonation gives us a resonance-stabilized **carboxylate**, which can be drawn either as resonance forms or as a delocalized anion.

- One of the simplest carboxylic acids is **acetic acid**.

- **Acetic acid**: The carboxylic acid for which R = Me. *Structure*

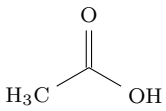


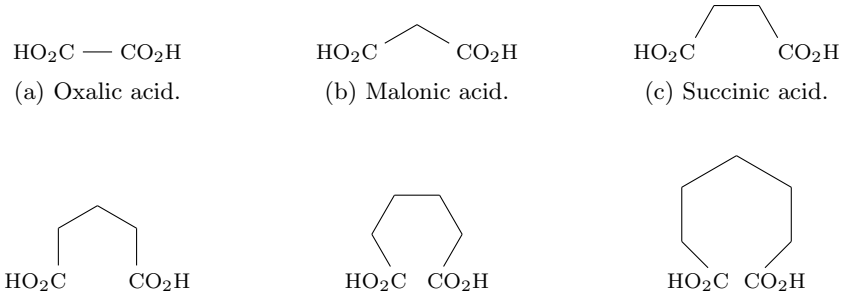
Figure 4.4: Acetic acid.

  - Acetic acid is in vinegar! In fact, vinegar is about 4-5% acetic acid in water.
  - Acetic acid is also used as an industrial solvent (in the 100% pure form, which is quite caustic).
  - How is acetic acid made?

$$\mathrm{MeOH} \xrightarrow[\mathrm{cat}]{\mathrm{CO}} \mathrm{CH_3COOH}$$

    - Acetic acid is produced industrially via the Monsanto acetic acid process, which carries out the carbonylation of methanol using a rhodium catalyst.

- The first several biscarboxylic acids.



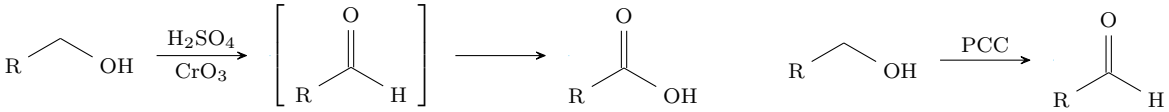
(a) Oxalic acid. (b) Malonic acid. (c) Succinic acid.

(d) Glutaric acid. (e) Adipic acid. (f) Pimelic acid.

Figure 4.5: Biscarboxylic acids.

  - **Oxalic**, **malonic**, **succinic**, **glutaric**, **adipic**, and **pimelic** acids.
  - Aside: Adipic acid is really important because it's involved in the manufacture of nylon.
  - How do you remember all these names? There's a neumonic: OMSGAP or "Oh My, Such Good Apple Pie."

- We now move onto Topic 2: Synthesis of carboxylic acids.
- Aside: A new definition of **oxidation** and **reduction**.
  - Notice that in a carboxylic acid (e.g., see Figure 4.4), the central carbon has 3 bonds to oxygen.
  - In contrast, a primary alcohol's central carbon has 1 bond to oxygen.
    - Thus, we need to do a 4-electron oxidation to turn an alcohol into a carboxylic acid.
  - An aldehyde's central carbon has 2 bonds to oxygen.
    - Thus, we need to do a 2-electron oxidation to turn an aldehyde into a carboxylic acid.
  - CO_2's central carbon has 4 bonds to oxygen.
    - Thus, we need to do a 2-electron reduction to turn CO_2 into a carboxylic acid.
  - This array of related compounds motivates the following two definitions.
- **Oxidation**: A chemical reaction that increases the number of carbon-oxygen bonds.
- **Reduction**: A chemical reaction that decreases the number of carbon-oxygen bonds.
- We now discuss Subtopic 2.a: Oxidation of alcohols and aldehydes.



(a) Primary alcohol or aldehyde to carboxylic acid. (b) Primary alcohol to aldehyde.

Figure 4.6: Oxidation of alcohols and aldehydes.

  - Suppose you have a primary alcohol.
    - To convert it into a carboxylic acid, treat it with **Jones reagent**.
      - ➢ The mechanism proceeds through the aldehyde.
      - ➢ However, it can't stop, so it goes all the way to carboylic acid.
    - To stop the oxidation at the aldehyde, use PCC!
  - Now suppose you're starting at the aldehyde.
    - To convert it to the carboxylic acid, just subject it to Jones reagent conditions! This is like picking up in the middle of the Figure 4.6a mechanism.
  - Relevant reading: Clayden et al. (2012, pp. 194–196).
- **Jones reagent**: The combination of excess H_2SO_4 and CrO_3.
- We now discuss Subtopic 2.b: Carboxylation of Grignard[1] reagents.

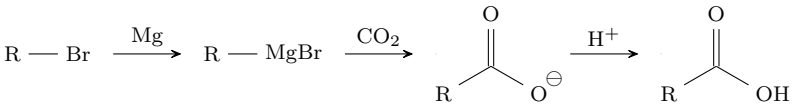


Figure 4.7: Carboxylation of Grignard reagents.

[1] "GRIN-yurd"

  - To make a Grignard reagent, react an alkyl bromide with magnesium.
    - Aside (chemis-tea): Victor Grignard won the Nobel Prize for Grignard reagents, even though his mentor invented them!
    - Note that Grignard reagents are very reactive! They are strong bases and strong nucleophiles, so if there's an acidic hydrogen in solution, it will get deprotonated.
      - ➢ Essentially, we have to consider the functional group tolerance of a method.
    - These reactions are fun to do in the lab!
  - Once you make the Grignard reagent, just throw dry ice (a source of CO_2) into the flask. There will be a bunch of bubbling, and we'll get our carboxylic acid.

- We now discuss Subtopic 2.c: Hydrolysis of nitriles.

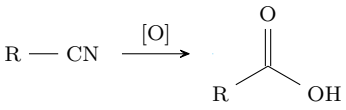


Figure 4.8: Nitrile hydrolysis.

  - Two ways to do this.
    - Acid (H_3O^+) and heat (Δ).
    - Base (HO^-), water (H_2O), and heat (Δ) followed by subsequent quenching with acid and heat.
  - Nitriles are *really, really, really* good intermediates (hint for Exam 3!!).

- We'll now look at how nitriles may come up in a typical test question.
- Typical test question (TTQ): Provide two ways to convert benzyl bromide into phenylacetic acid.

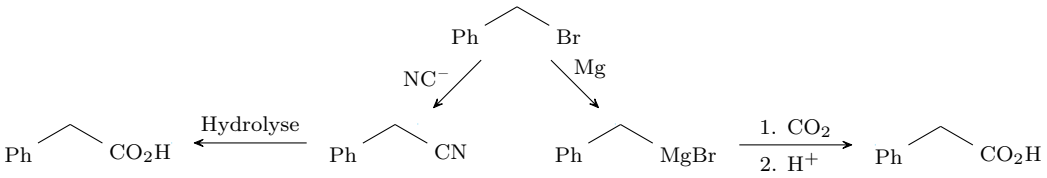


Figure 4.9: Typical test question: Multiple synthetic paths.

  - First way: Make the Grignard and add CO_2.
  - Second way: Do an S_N2 with CN^-, and then hydrolyze the nitrile.
  - Note that Prof. Buchwald uses checkmarks to denote the product on the board.

- If we're answering a test question like this, will you want two separate arrows, or is one arrow with "1. *reagent*" above and "2. *reagent*" below?
  - Either is good.

- We now discuss Subtopic 2.d: Types of carboxylic acid derivatives.
- **Acid chloride**: A carboxylic acid derivative for which X = Cl. *Structure*

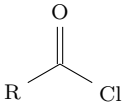


Figure 4.10: Acid chloride.

  - These are far more common than acid bromides or acid iodides.[2]
  - To convert a carboxylic acid into an acid chloride, use $SOCl_2$ and pyridine.[3]
  - Mechanism: Clayden et al. (2012, pp. 214–215).

- **Acid anhydride**: A carboxylic acid derivative for which $X = RCO_2$. *Structure*

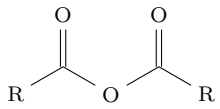


Figure 4.11: Acid anhydride.

  - Synthesize these from two carboylic acids that combine and release water.

- Example of an acid anhydride: Phthalic anhydride.

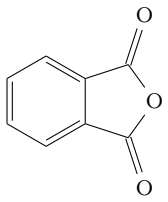


Figure 4.12: Phthalic anhydride.

- **Ester**: A carboxylic acid derivative for which $X = OR'$. *Structure*

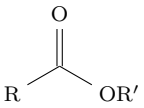


Figure 4.13: Ester.

  - Esters are common in scents and smells.

- Example of an ester: Isoamyl acetate.

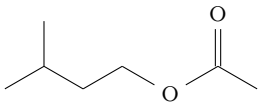


Figure 4.14: Isoamyl acetate.

  - This is the odor of banana oil! The infinite corridor smells like this because of the Banana Lounge.
  - There are easy ways to make this chemical that can legally be described as natural, even if it did not come from a banana.

[2] Coincidentally, acid iodides are used in the Monsanto acetic acid process!
[3] See the 5.12 equation review sheet!!

- **Lactone**: A cyclic ester. *Example*

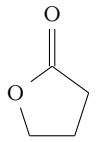


Figure 4.15: γ-butyrolactone.

- **Amide**: A carboxylic acid derivative for which X = NR′R″. *Structure*

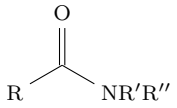


Figure 4.16: Amide.

- Example of a (poly)amide: Nylon.

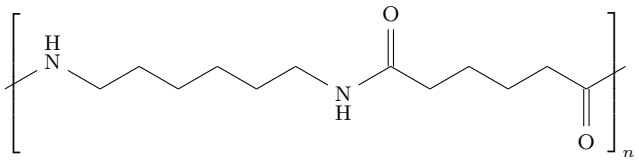


Figure 4.17: Nylon.

- **Lactam**: A cyclic amide. *Example*

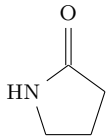


Figure 4.18: 2-Pyrrolidone.

  - Lactams are incredibly imporant; many of us are only alive because of lactams.

- Examples of lactams: The penicillins, a class of molecules that changed the world.

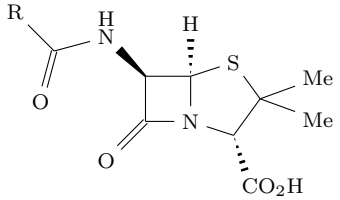


Figure 4.19: Penicillin core structure.

  - Varying R yields different penicillins; all penicillins share the core motif above, though.
  - Penicillins were discovered by Alexander Flemming and changed the course of the world wars.
  - Penicillin and amoxycillin are both β-lactam antibiotics.

- We now move onto Topic 3: Acyl transfer reactions.
- Subtopic 3.a: Background.
- For each X group in a carboxylic acid derivatives, let's see how good of a leaving group it is.

X	Cl	RCO_2	OR	NR_2	O^-
pK_a (HX)	-7	5	16	≈ 35	VERY HIGH

Table 4.1: Leaving groups in carboxylic acid derivatives.

  - To be clear, we're measuring the pK_a's of the following reactions.

$$HX + H_2O \rightleftharpoons X^- + H_3O^+ \qquad K_a = ?$$

    - Example: $HCl + H_2O \rightleftharpoons Cl^- + H_3O^+$.
    - Example: $HO^- + H_2O \rightleftharpoons O^{2-} + H_3O^+$.
  - pK_a — a theromodynamic parameter — is a good measure of how good of a leaving group something is.
    - Important because acyl transfer reactions involve an X group from Table 4.1 departing.
    - Thus, knowing how stable the X group is after leaving as a conjugate base in an acid reaction can help us predict how stable it will be as a departed nucleophile in an acyl transfer reaction, and hence how likely a proposed acyl transfer reaction is to proceed.
- Let's now investigate the resonance stabilization of each of our carboxylic acid derivatives.

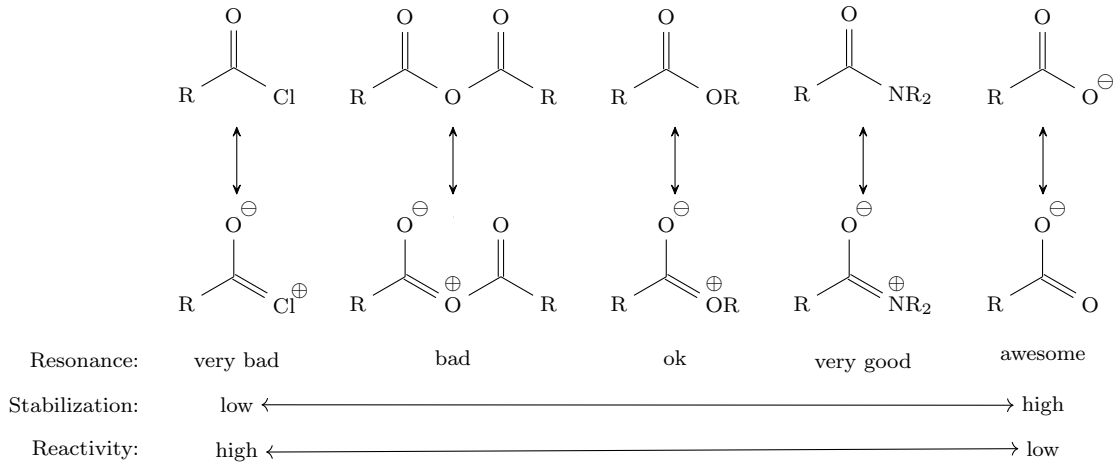


Figure 4.20: Resonance stabilization of carboxylic acid derivatives.

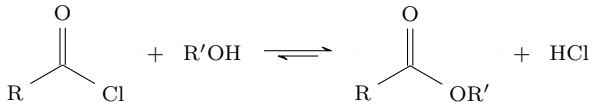
  - The lone pairs on chlorine are high energy, so we can get some degree of resonance, but the resonance structure is very bad.[4]
  - Keep in mind that we have "awesome" resonance *only* for the deprotonated, carboxylate form of a carboxylic acid; carboxylic acids, themselves, aren't nearly as stabilized.
  - Stability and reactivity are clearly inversely related; it should make sense that the less stable something is, the more reactive it is!
- From Table 4.1 and Figure 4.20, we can see that the better leaving groups tend to form more reactive carboxylic acid derivatives, and vice versa!

[4] Think about MOs! Big energy difference means bad mixing and hence poor conjugation

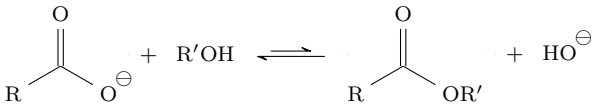
4.24 Acyl Transfer Reactions - 1

11/1:

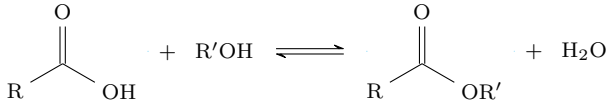
- Lecture 23 recap.
  1. Carboxyic acid derivatives.
     - Substances of the form in Figure 4.2, where $X \neq H, R$.
  2. Synthesis of RCO_2H.
     - Carboxylic acids (Figure 4.3): $pK_a \approx 5$.
     - Oxidation of (primary) alcohols and aldehydes (Figure 4.6).
     - Carboxylation of Grignard reagents (Figure 4.7).
     - Hydrolysis of nitriles (Figure 4.8).
  3. Acyl transfer reaction.
     - Reactivity decreases from acid chlorides > acid anhydrides > esters > amides > carboxylates.
       - Remember that carboxylates are anions.
       - See Table 4.1 and Figure 4.20.
- Before we begin in earnest, let's build a bit more off of this idea of reactivity differences in carboxylic acid derivatives.



(a) Reactivity of an acid chloride.



(b) Reactivity of a carboxylate.



(c) Reactivity of a carboxylic acid.

Figure 4.21: Reactivity of carboxylic acid derivatives toward esterification.

- Measures of reactivity tell us if a given acyl transfer reactions will be thermodynamically favorable, thermodynamically unfavorable, or thermoneutral.
  - Like any thermodynamically favorable reaction, thermodynamically favorable acyl transfer reactions are characterized by high energy reactants becoming low energy products and vice versa for a thermodynamically unfavorable reaction.
  - In a thermoneutral reaction ($K_{eq} \approx 1$), the reactants and products have similar energies.
- Examples.
  - Figure 4.21a: Very favorable because acid chlorides are much more reactive than esters.
  - Figure 4.21b: Very unfavorable because carboxylates are much more stable.
  - Figure 4.21c: Thermoneutral because carboxylic acids and esters have similar reactivity.
- Today: Types of acyl transfer reactions.

- Lecture outline.
  3. Acyl transfer reactions.
     a. Background.
     b. Reactions of acid chlorides.
     c. Reactions of esters.
        i. Hydrolysis.
        ii. Transesterification.
        iii. Amide formation.
     d. Reactions of carboxylic acids.
        i. Fischer esterification.
        ii. Basic esterification (not possible).
        iii. Formation of acid chlorides.
     e. Reactions of amides.
        i. Acid-catalyzed hydrolysis.
        ii. Base-catalyzed hydrolysis.
- We begin by resuming Subtopic 3.a: Background.
- The mechanism of an acyl transfer reaction.

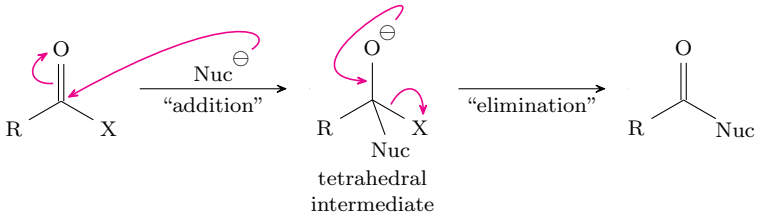


Figure 4.22: Mechanism of a (neutral) acyl transfer reaction.

  - Almost always addition-elimination, not direct displacement.[5]
  - First step: Addition.
    - The nucleophile adds in to the electrophylic site.
    - This gives us a **tetrahedral intermediate**, so named because of its tetrahedral carbon.
  - Second step: Elimination.
    - The best leaving group leaves.
    - There can be equilibriums between which group leaves, but we won't consider those details right now.

- We now move onto subtopic 3.b: Reactions of acid chlorides.

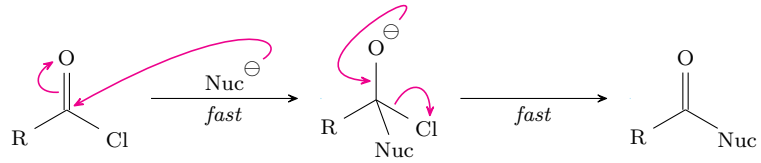


Figure 4.23: Mechanism of an acyl transfer reaction with an acid chloride.

[5]Think about the molecular orbital reasons for why! Nucleophile donation into the C=O π^*-orbital (at the Bürgi-Dunitz angle) *forces* the C=O π-bond to break as the new C−Nuc σ-bond is formed, with the former C=O π-electrons migrating to become a lone pair on the more electronegative atom (oxygen).

  - The addition step is fast in this case because the acid chloride is the least resonance stabilized of the carboxylic acid derivatives we've considered.
    - This is because the chlorine atom is a really bad π-donor; there is a large energy mismatch between the n_{Cl} and π^*_{CO} MOs.
  - The elimination step is also fast because Cl^- is a great leaving group.
    - We know that Cl^- is a great leaving group because $\mathrm{p}K_{\mathrm{a}}(\mathrm{HCl}) = -7$ (see Table 4.1), meaning that the conjugate base (Cl^-) is weak.
    - When the conjugate base is weaker, it's a better leaving group.
  - Thus, overall, acid chlorides are very reactive and no catalyst is needed for their acyl transfer reactions.

- Aside: Like acid chlorides, acid anhydrides are very reactive and also don't need a catalyst to participate in an acyl transfer reaction.

- Example acyl transfer reaction of an acid chloride: Forming an ester.

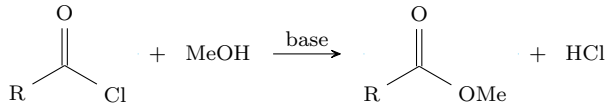


Figure 4.24: Acyl transfer: Acid chloride to ester.

  - This is a very vigorous reaction: Lots of bubbling, flask gets really hot, releases a white cloud of caustic gas (HCl).
  - As such, you usually add a base to solution.
    - The base is not necessary for the reaction to work, but rather for us to be alive.
    - Indeed, the base neutralizes the acid as it's formed, making a salt: $\mathrm{B} + \mathrm{HCl} \longrightarrow \mathrm{HB}^+\,\mathrm{Cl}^-$.
  - Typical bases: $\mathrm{Et_3N}$ or pyridine.

- Example acyl transfer reaction of an acid chloride: Forming an amide.

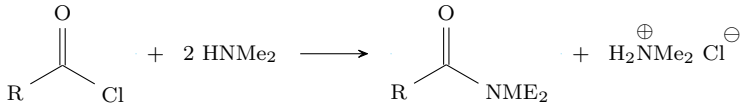


Figure 4.25: Acyl transfer: Acid chloride to amide.

  - This reaction forms an amide.
    - Recall from Figure 4.20 that amides are very stable.
  - We do not need an additional base this time because the amine already acts as one!
    - Indeed, a *second* equivalent of the amine forms a salt at the end of the reaction, again preventing us from dying.

- Do we need two equivalents of $\mathrm{HNMe_2}$?
  - If you have a valuable amine, maybe add in $\mathrm{Et_3N}$ as a second base because it will do basically the same thing.

- We now move onto Subtopic 3.c: Reactions of esters.
  - Three ester reactions to consider: **Hydrolysis**, **transesterification**, and **amide formation**.

- We now discuss Subtopic 3.c.i: Hydrolysis of esters.
- Let's first consider the energetics of the overall reaction.

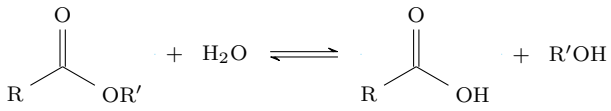


Figure 4.26: Acyl transfer: Ester hydrolysis.

  - Esters are not great electrophiles, and water is not a great nucleophile.
    - Thus, the general addition-elimination mechanism (Figure 4.22) will proceed very slowly here.
  - Additionally, the reaction is thermoneutral overall ($K_{eq} \approx 1$), so we'll get a 50 : 50 mixture of reactants and products under many experimental setups.
- So how do we get the reaction to proceed? Two ways:
  - Use an acid to make the ester a better electrophile.
  - Use a base to make water a better nucleophile.
- Acid-catalyzed mechanism.

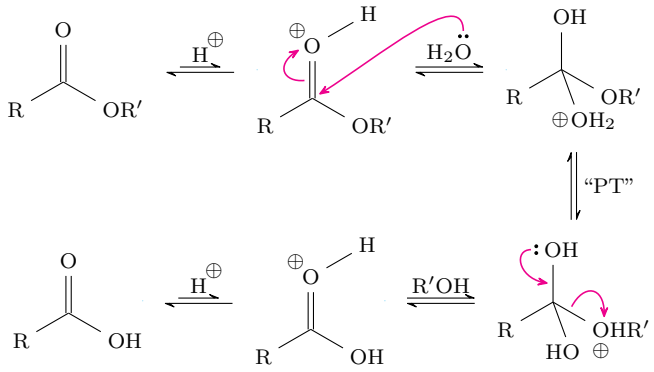


Figure 4.27: Ester hydrolysis mechanism (acid-catalyzed).

  - First step: We get a small quantity of protonated, activated ester that is a much better electrophile.
  - Second step: Now that we have a much better electrophile, water can add in.
  - Third step: Proton transfer (PT), likely intermolecular and possibly stepwise.
  - Fourth step: Elimination.
  - Fifth step: Deprotonation.
  - Observe that we have only drawn positively charged intermediates.
    - If we're in acidic solution, we should not draw any anionic intermediates!
    - This is because anions will immediately be protonated, stopping the reaction there.
  - Since acid adds in at the beginning and leaves at the end, this mechanism is *catalytic* in acid.
- Basic mechanism.

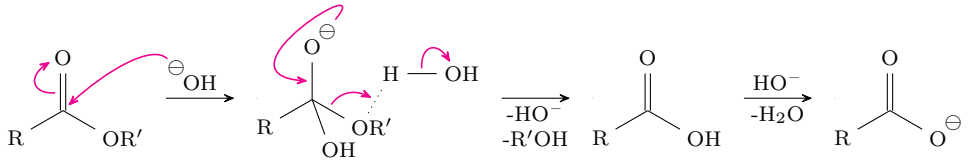


Figure 4.28: Ester hydrolysis mechanism (basic).

- This is much more similar to the general mechanism (Figure 4.22): The starting material undergoes addition by hydroxide, followed by subsequent elimination.[6]
  - However, a final deprotonation step will make the *carboxylate* the major product, not the carboxylic acid.
  - If we want the carboxylic acid, we can recover that with a water workup.
- Problem: RO^- is a bad leaving group (see Table 4.1).
  - Solution: In aqueous media, RO^- will be a slightly better leaving group due to hydrogen bonding with water.
  - This spreads out and stabilizes its negative charge, and also provides a nearby proton donor.
- Since carboxylates are the most stable carboxylic acid derivative we've considered (see Figure 4.20), this *is* a thermodynamically favorable pathway.
- Observe that analogously to Figure 4.27, we have only drawn *negatively* charged intermediates.
  - This is again because cations should not be formed in basic solution.
- Since one equivalent of base is used in this mechanism, it is *not* catalytic in base.
  - We may think of this pathway as base-*accelerated* if we prefer.

- We now discuss Subtopic 3.c.ii: Transesterification.
- Let's first consider the energetics of the overall reaction.

Figure 4.29: Acyl transfer: Transesterification.

- This reaction involves taking one ester and going to another ester.
- Usually, $K_{eq} \approx 1$ and the reaction is not very fast, so we use catalysis again.

- Acid-catalyzed mechanism.

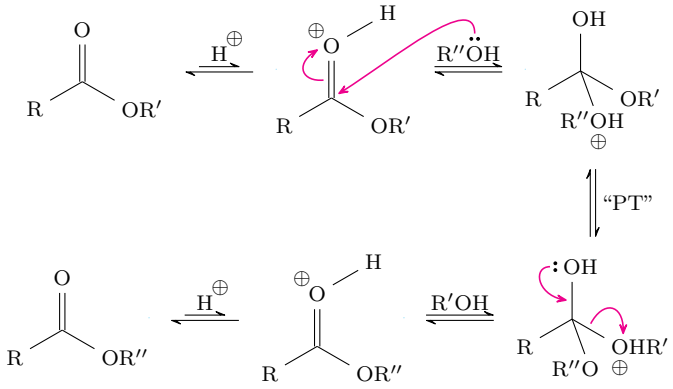
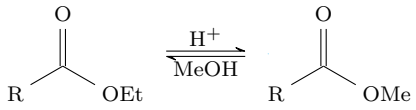


Figure 4.30: Transesterification mechanism (acid-catalyzed).

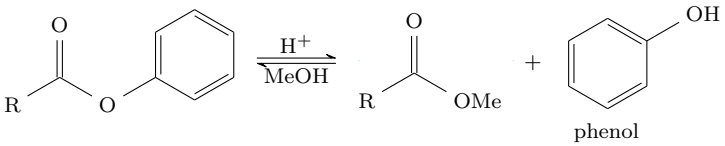
- Mostly the same as Figure 4.27.
- Proton transfer is thermoneutral, so we'll get a mixture of the final product and the pre-PT intermediate.

[6] A good way of introducting hydroxide base is with NaOH.

- Two methods to drive the acid-catalyzed mechanism in the forward direction.



(a) Excess nucleophile.



(b) Ground state destabilization and product stabilization.

Figure 4.31: Driving the transesterification equilibrium.

  - Use R″OH as the solvent.
    - Example: If we want to change an ethyl ester into a methyl ester, use methanol (MeOH) as the solvent instead of just as the nucleophile (Figure 4.31a).
  - Destabilize the reactants and stabilize the products.
    - Example: Use a phenyl ester (Figure 4.31b).
      - ➢ The phenyl ester is more electrophilic than, for example, a methyl ester. This is because the n_O lone pair can now donate into the aromatic ring as well, lowering its electron density near the carbonyl carbon.
      - ➢ Additionally, phenol is a very stable byproduct (again, due to resonance delocalization of its lone pair).
    - Phenol was the horrible smell of paste used in nursery schools.

- Base-accelerated conditions.

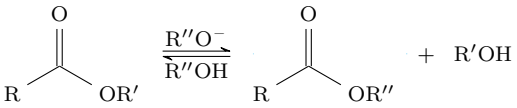


Figure 4.32: Transesterification (basic).

  - The mechanism is analogous to Figure 4.28.[7]

- We now discuss Subtopic 3.c.iii: Amide formation from esters.

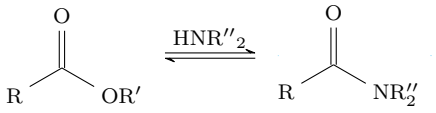


Figure 4.33: Acyl transfer: Ester to amide.

  - The mechanism is also analogous to Figure 4.28, and we don't need base because HNR_2 is one!
  - This reaction is driven forward by the greater resonance stabilization of amides relative to esters (see Figure 4.20).

[7] A good way of introducing alkoxide base is with NaOR.

- We now move onto Subtopic 3.d: Reactions of carboxylic acids.
- We'll begin with Subtopic 3.d.i: The Fischer esterification.

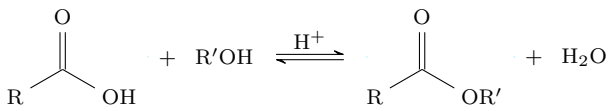


Figure 4.34: Fischer esterification.

  - Combine a carboxylic acid and an alcohol under acidic conditions.
  - Again, $K_{eq} \approx 1$.
  - However, we can drive the reaction forward by removal of water (either by distillation or drying agents).
- We now discuss Subtopic 3.d.ii: Why basic esterification isn't possible.
- Under basic conditions, the first thing that happens will be an acid-base reaction between the carboxylic acid and whatever base we've added to solution.

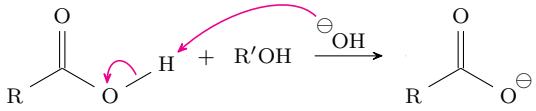


Figure 4.35: Side reaction under "basic esterification" conditions.

  - This will produce a carboxylate, which (recall from Figure 4.20) is a *terrible* electrophile with a *terrible* leaving group.
- As such, we *cannot* do basic esterification of carboxlic acids!
- So what do we do if we want to convert a carboxylic acid into an ester but can't use acidic conditions, perhaps because there are other functional groups in our molecule that would react with acid?
- The answer lies in Subtopic 3.d.iii: Formation of acid chlorides.

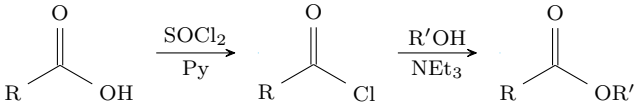


Figure 4.36: Acyl transfer: Carboxylic acid to ester.

  - Essentially, we back off and run the reaction in two steps: A review reaction from 5.12 followed by Figure 4.24.
  - Note that Py stands for pyridine.
- We now move onto Subtopic 3.e: Reactions of amides.
- Recall that amide-bond formation is an incredibly useful driving force in other reactions (e.g., see Figures 4.25 & 4.33).
  - As such, amides are very stable, and we might not expect them to do much.
  - Regardless, however, they hydrolyse to the carboxylic acid under acidic conditions.

- Let's first consider the energetics of the overall reaction.

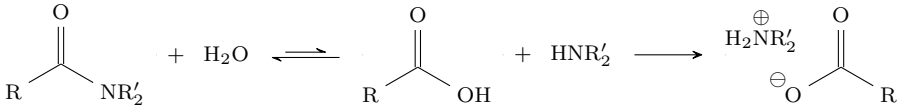


Figure 4.37: Acyl transfer: Amide hydrolysis.

  - As stated above, it seems unlikely that a stable SM would become a less stable product.
    - Indeed, the first step has $K_{eq} < 1$.
  - However, we get a subsequent acid-base reaction between the carboxylic acid and amine base.
    - This forms $H_2NR_2^+$ $RCOO^-$ (a salt), taking the reaction to near completion.
  - This process is called **linking** steps!

- **Linked** (steps): A phenomena in which a disfavored reaction step is coupled to an irreversible reaction step to drive product formation.

- We now discuss Subtopic 3.e.i: Acid-catalyzed hydrolysis.

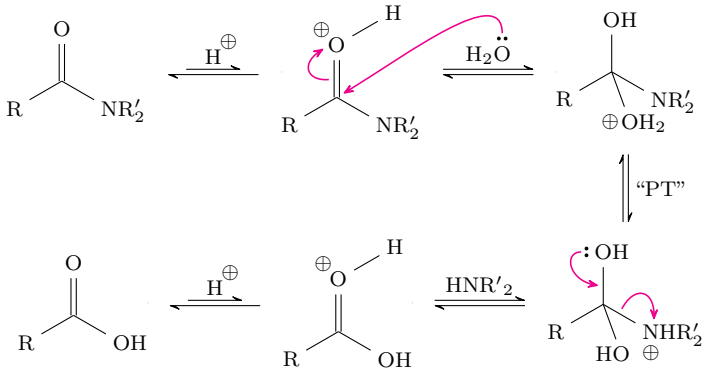


Figure 4.38: Amide hydrolysis mechanism (acid-catalyzed).

  - Acid catalyis is needed because, per Figure 4.20, amides are very poor electrophiles.
    - Indeed, there is excellent $n_N \rightarrow \pi^*_{CO}$ resonance.
  - We protonate the carbonyl instead of the amide because the carbonyl has lone pairs not currently in resonance; if we protonate the amide nitrogen, the result no longer has resonance stabilization.
  - Once we protonate/activate the carbonyl, the rest of the mechanism is analogous to Figure 4.27.

- We now discuss Subtopic 3.e.ii: Basic hydrolysis.

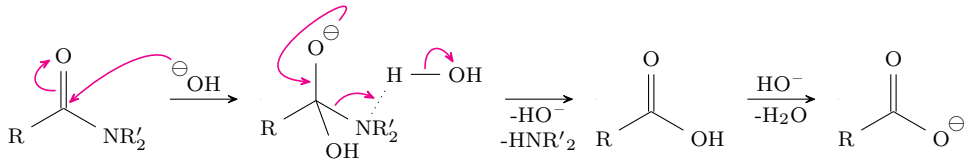
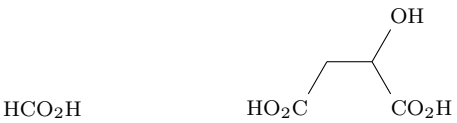


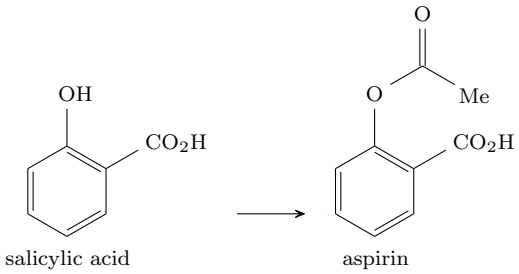
Figure 4.39: Amide hydrolysis mechanism (basic).

  - Conundrum: Like with basic ester hydrolysis (see Figure 4.28), NR_2^- is a poor leaving group.
    - However, we can once again solve this issue with a hydrogen bond to water
  - Under basic conditions, we can't form the salt in Figure 4.37, but we are still thermodynamically driven toward the more stable carboxylate (see Figure 4.20).

- Application to real-world cheimstry: Wine.
- Carboxylic acids in wine.



(a) Formic acid. (b) Malic acid. (c) Butyric acid. (d) Tartaric acid.



(e) Salicyclic acid can be made into aspirin.

Figure 4.40: Wine contains carboxylic acids.

  - Formic acid (Figure 4.40a): Used in the leather tanning industry.
  - Malic acid (Figure 4.40b): An ingredient in dermatology products; a skin exfoliating agent.
  - Butyric acid (Figure 4.40c): The smell in dirty gym socks.
  - Salicylic acid (Figure 4.40e): No real connection to taste or smell, but it's a precursor in the synthesis of the pain medication, aspirin.
  - You ever notice the crystalline material at the bottom of a wine glass?
    - It's just (2*R*,3*R*)-(+)-tartaric acid (Figure 4.40d)!
    - The potassium salt of tartaric acid (which contains the carboxylate, tartarate!) is more commonly known as cream of tartar and used in many baking recipes.
- Bonus: What does it mean to say that a bad-tasting wine is "corked?"

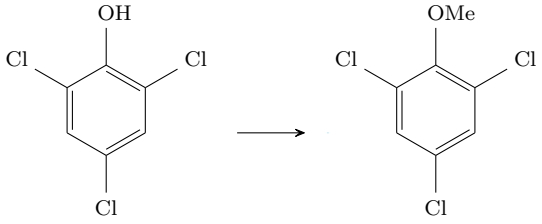


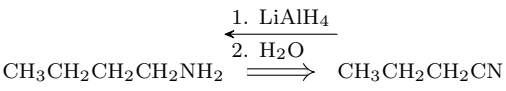
Figure 4.41: Wine can be "corked."

  - It means that the wine has too much trichloroanisole, a compound that smells and tastes bad.
  - Trichloroanisole can be transferred to the wine from the cork.
    - Cork comes from a cork tree.
    - Humans spraying synthetic trichlorophenol insecticides onto trees led funghi to evolve and detoxify it by adding a methyl group.
    - Trichloroanisole is then good for the funghi, but tastes bad to us.

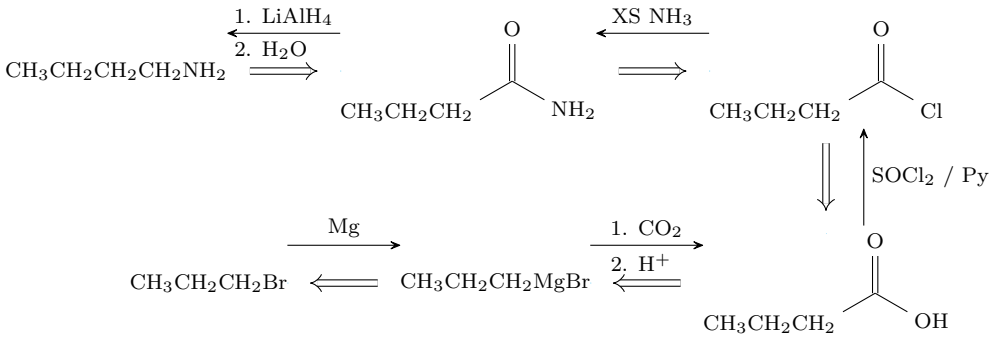
4.25 Acyl Transfer Reactions - 2

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.

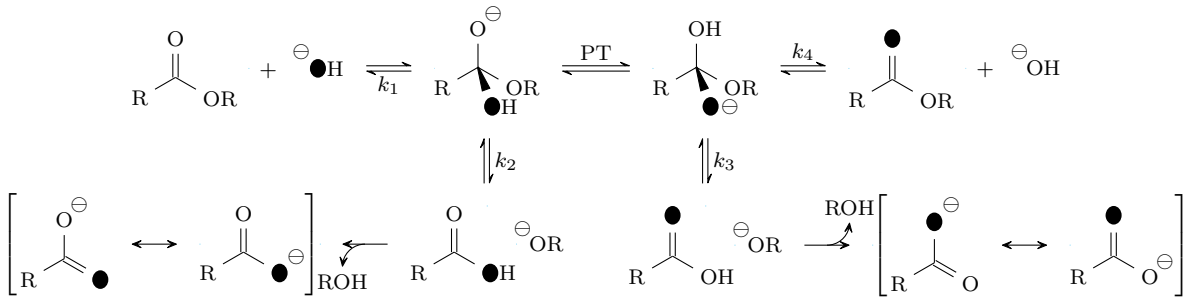
4. Evidence for a tetrahedral intermediate.
   a. Ester hydrolysis.
   b. Amide hydrolysis (basic).
   c. Amide hydrolysis (acidic) — deferred to recitation.
5. Reactions with $NaBH_4$, $LiAlH_4$, RMgBr, and RLi.

- 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?

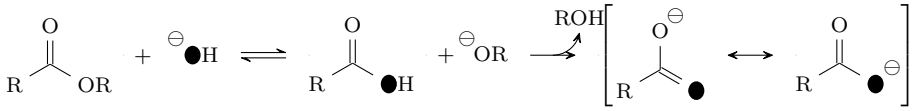
[8] Note that the double-lined arrows are called "retrosynthetic arrows." It is common nomenclature to see retrosynthetic arrows in the reverse direction, overset by forward arrows and conditions.

[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 $[M+2]^+$ 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!

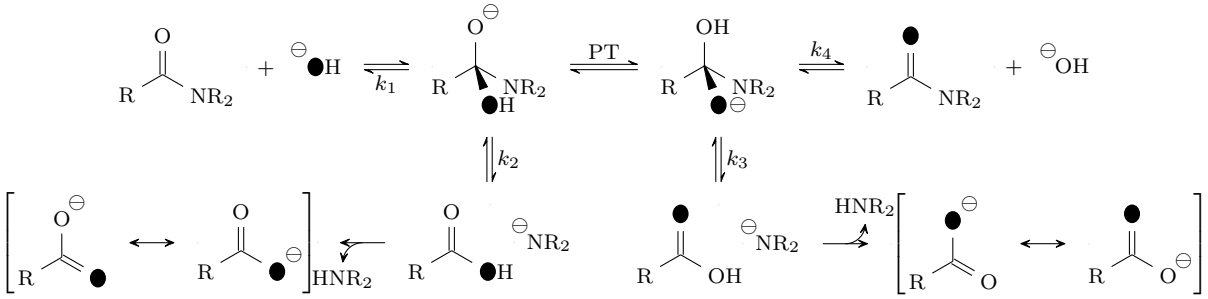
– Now let's consider the other possibility: Figure 4.43b displays the full kinetic network for the S_N2 mechanism.

– 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.

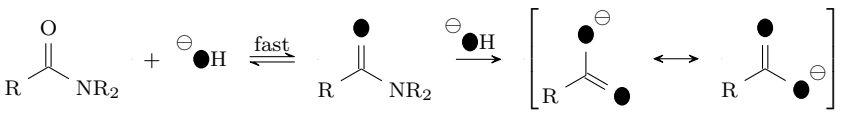
– Experimentally, what we find is that there *is* ^{18}O in the recovered ester.
- Therefore, the tetrahedral intermediate does exist!

– 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.

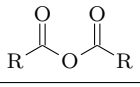
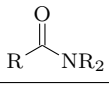
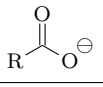
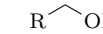
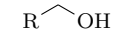
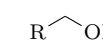
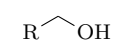
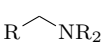
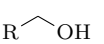
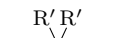
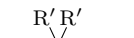
					
$NaBH_4$			NR	NR	NR
$LiAlH_4$					
$R'MgBr$					NR
$R'Li$					

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.