Week 8

Amine Reactions and Carbohydrate Structure

8.1 Amines 2

5/17:

- Midterm 2.
  - Scores back after class.
  - Request a regrade (of your whole exam) ASAP if needed.
  - Raw score: 56 ± 24 (median 59).
  - Range: 0-99.
  - Adjusted: 70 ± 10.
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 20.4, 20.12, and 20.6-20.7.
  - Next time: Sections 22.1-22.2, 22.9A.
  - Practice problems: 20.19-20.24, 20.26, 20.34-20.36.
- Review of last lecture.
  - Basicity of amines.
  - Higher $pK_a(RNH_3{}^+)$ means more basic RNH_2.
  - Key: How willing is N to share its lone pair.
- Today, we will cover the following.

I. Properties of amines.
   B. Acid-base properties (cotd.).

II. Preparation of amines.
   A. Alkylation.
   B. Reduction.
   C. Hofmann rearrangement.
   D. Curtius rearrangement (review).

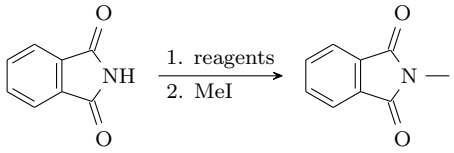
III. Reactions of amines.
   A. Hofmann elimination.
   B. Cope elimination.

- Acid-base properties (cotd.).
- Additional example amine pK_a's.
  - Py has $pK_a(PyH^+) = 5.3$.
    - Its basicity is intermediate between NH_3 and $PhNH_2$ due to its sp^2 hybridization.
  - Pyrrole has $pK_a(RH^+) = 0.4$.
    - Since nitrogen's lone pair here is fully incorporated into the aromatic system, it is not basic.
    - In fact, pyrrole has $pK_a(R) = 16.5$.
    - This means that its amine hydrogen is actually mildly acidic (about equivalent to ethanol's hydroxyl hydrogen).
  - Indole (left to us).
    - Indole is like pyrrole: To have $4n + 2$ aromatic electrons, it needs nitrogen's lone pair.
  - See the Aromaticity 2 lecture from Labalme (2022b) for more on aromatic pK_a's.
  - Amides.
    - An amide will coordinate a proton at its oxygen, not its nitrogen.
    - This protonated species will have $pK_a = 0$.
    - The reason for coordination at oxygen is that the resonance structure with a negative charge on oxygen makes a significant contribution to the overall molecule (oxygen is more electronegative than nitrogen). In fact, this resonance structure implies that the C–N bond in an amide is not rotatable, and thus the six atoms C–C(=O)–NH_2 are coplanar.
    - Additionally, the nitrogen protons are slightly acidic with $pK_a(RNH_2) = 18$.
    - Hence, if we react an amide with a Grignard, we will deprotonate the NH_2 portion.
- A note on how protonation can be used to isolate amines (and other basic species) when synthesizing them in the lab.
  - Begin by protonating the amines and performing an extraction.
  - The protonated amines will be attracted to the polar aqueous layer and all other organic compounds can be separated out with the organic layer.
  - Then we can deprotonate to recover our desired amines.
- Preparation of amines.
- Alkylation (direct).
- General form.

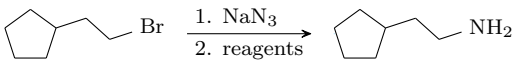
$$NH_3 \xrightarrow[2.\ NaOH]{1.\ MeI} MeNH_2$$

- Mechanism.
  - The first step proceeds via an S_N2 mechanism to yield a quaternary ammonium salt.
  - The second step (a basic workup) removes one of the three nitrogen protons, yielding $H_2O + NaI$ as side products.
- Problems with direct alkylation:
  - Even before the basic workup, we have base in solution (NH_3). This base can accomplish the second-step deprotonation, introducing $MeNH_2$ into our initial reaction mixture.
  - But adding alkyl groups (EDGs) creates more reactive amines, so $MeNH_2$ will preferentially attack CH_3I compared with NH_3.
  - Thus, with direct alkylation, we cannot stop at one particular stage; we will always get a mixture of NH_3, $MeNH_2$, Me_2NH, Me_3N, and Me_4NI.

- One potential solution.
  - In some cases, we can use excess amine and a bulky alkyl halide.
  - For example, mixing approx. 20 equivalents of $MeNH_2$ with BnCl yields fairly pure BnNMeH.
- Alkylation (Gabriel synthesis).
- General form.

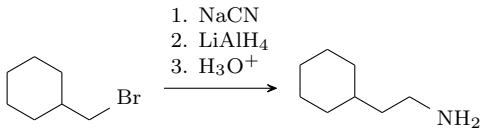


  - The Gabriel synthesis prepares primary amines.
  - The starting material is called **phthalimide**.
  - Reagents is either NaH (nice because it liberates $H_{2(g)}$ as an additional driving force) or K_2CO_3 (nice because it's not as strong as NaH).
- **Phthalimide**: A 2° amine, the lone hydrogen of which has has $pK_a = 8.3$ since it is subject to *two* EWG carbonyls and additional resonance with the aromatic ring. *Structure* see above left.
- Mechanism.
  - The first step is a deprotonation.
  - The second step proceeds via an S_N2 mechanism.
    - Thus, we preferentially use it in conjunction with primary alkyl halides.
    - Secondary, allylic, and benzylic alkyl halides will work.
    - An attempt to run this reaction with a tertiary alkyl halide will lead to elimination.
  - Notice that the product is a 3° amide and thus cannot react any further.
- There are three ways to recover the primary amine from the product above.
  1. Use H_2SO_4, H_2O, and heat.
     - This amide hydrolysis proceeds analogously to the last several steps of Figure 2.12.
     - A subsequent deprotonation of $MeNH_3^+$ will be required.
  2. Use NaOH, H_2O, and heat.
     - This amide hydrolysis proceeds analogous to the saponification mechanism.
  3. Use H_2NNH_2 and reflux.
     - See Solomons et al. (2016) for the mechanism.
- Reduction.
  - This method of preparation can proceed from a number of starting materials.
- From azides.



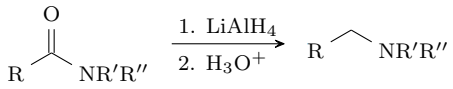
  - Begin with the desired alkyl group as an alkyl halide.
  - React it with an azide nucleophile via an S_N2 mechanism.
    - Azide is one of the few nucleophiles that is a very poor base, so it is very good for S_N2.
  - Reagents is either $LiAlH_4$ followed by an acidic workup or hydrogenation ($H_2 + Pd/C$).

- From nitriles.



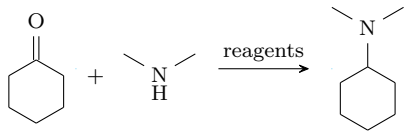
  - Take the desired alkyl group, S_N2 it with a cyanide nucleophile, and then reduce with $LiAlH_4$ as in Chapter 17.
  - Notice that this reaction adds an extra carbon before the amide, unlike with azides.

- From amides.



  - This is a review reaction; see the discussion associated with Figure 3.4.

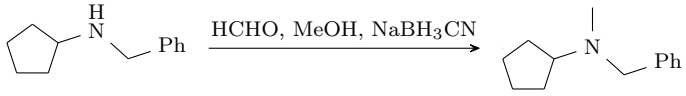
- From iminium ions (reductive amination).



  - This is a very useful reaction in the pharmaceutical industry.
  - Depending on the reagents, we can accomplish this reaction in a stepwise fashion or all at once.
  - Stepwise reagents.
    - Use mild H^+ followed by a mild hydride source, such as $NaBH_4$.
    - In the first step, we create an enamine in equilibrium with the corresponding iminium ion.
    - In the second step, hydride attacks the iminium ion's carbon, leading to the final product.
  - This set of reagents explains the name of the reaction: It is *amination* because we are replacing an oxygen with a nitrogen and *reductive* because we are reducing the iminium ion's double bond.
  - If we use these reagents, we must (in theory) perform the reaction stepwise because $NaBH_4$ can reduce any unreacted ketone.
    - In reality, there is a trick we can use to do this reaction all at once with these reagents.
  - One-step reagents.
    - Use sodium cyanoborohydride ($NaBH_3CN$) in alcoholic solvent (EtOH or MeOH).
  - $NaBH_3CN$ is a weaker hydride source (cyano groups are EWGs), so it can't react with the ketone because it's not electrophilic enough (the charged iminium ion is much more electrophilic).

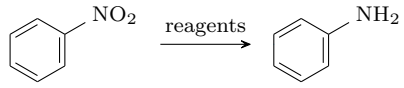
- Reductive amination describes the above reaction of a relatively complicated ketone with a relatively simple amine. If we use, instead, a relatively simple ketone and a relatively complicated amine, the reaction is called...

- Reductive alkylation.

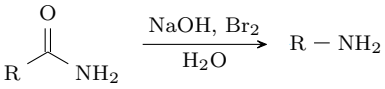


  - Remember that HCHO is formaldehyde, which is our carbon source here.

- Reductive amination/alkylation can be more controlled than alkylation.
  - This is because with alkylation, our final 3° amine could still form a quaternary ammonium salt in the presence of excess MeI.
  - However, a 3° amine can never form another iminium ion.
- From nitro groups.



  - Reagents is $H_2 + Pd/C$, $Fe + HCl$, or $Zn(Hg) + HCl$.
- Hofmann rearrangement.
- General form.



  - Whereas with azides and amides kept the number of carbons constant and nitriles added a carbon, here we lose a carbon.
  - This reaction is similar to the Curtius rearrangement.
  - The conditions are identical to those used in the haloform reaction, and we will see that there are homologies in the mechanisms, too.
- Mechanism.

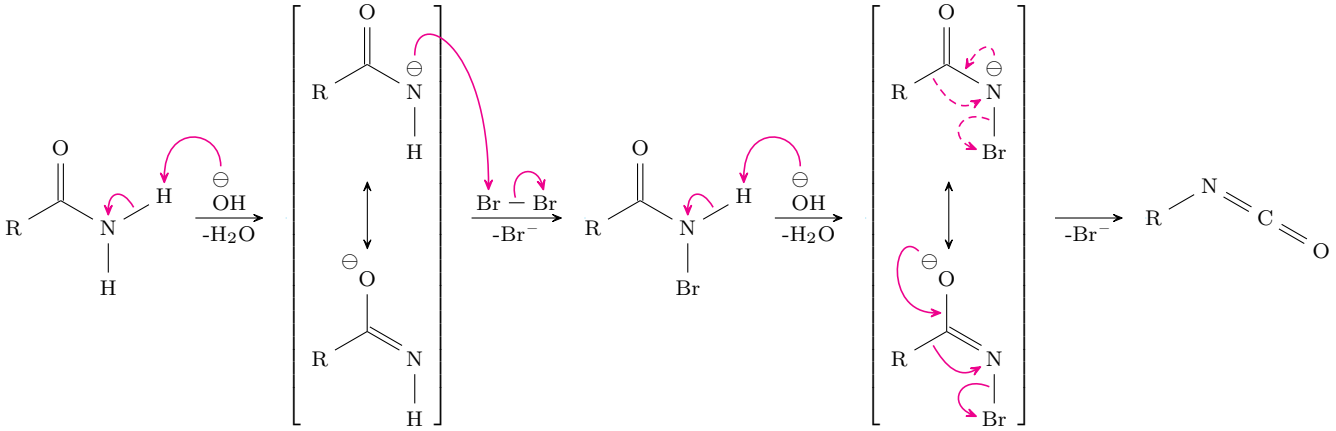


Figure 8.1: Hofmann rearrangement mechanism (isocyanate formation).

  - Many of these reactions are reversible, but the equilibria are not that important here.
  - The first two brominations proceed analogously to those in Figure 4.8.
    - Recall that the second bromination happens more readily because having bromine (an EWG) on the nitrogen makes the remaining hydrogen more acidic.
  - There are two possible rearrangement mechanisms after this for forming the isocyanate.
    - The two proceed from different resonance structures.
    - The one drawn in dashed lines is advocated for by Solomons et al. (2016). In it, the *nitrogen* lone pair kicks in, the alkyl group migrates to the nitrogen, and bromine leaves.

    - The one drawn in solid lines is advocated for by Tang. In it, the *oxygen* lone pair kicks in, the alkyl group migrates to the nitrogen, and bromine leaves.
    - Tang will accept either on a test despite her preference for the latter.
  - Once we have an isocyanate, we remove it exactly as in Figure 3.13b.
    - The NHCOOH intermediate (intermediate 2 in Figure 3.13b) is a **carbamic acid**.
    - A possible intermediate between intermediate 1 and the carbamic acid is a resonance form of the former wherein we have kicked the oxygen lone pair in and used the double bond to create a lone pair on nitrogen, negatively charging it.
    - Note that Solomons et al. (2016) uses a simplified mechanism for these first two steps (isocyanate to carbamic acid). Therein the hydroxide attacks the isocyanate carbon and kicks the N=C electrons back onto nitrogen, forming the negatively charged nitrogen intermediate described above in one go. From here, the negative nitrogen can attack water to form the carbamic acid.
    - The mechanism of Solomons et al. (2016) is inaccurate, though, because when displaced the electrons will preferentially move toward the more electronegative oxygen.
    - Regardless, both mechanisms will be accepted as correct in this course.
  - Other comments.
    - Whereas we can isolate the isocyanate intermediate in the Curtius rearrangement, the conditions of the Hofmann rearrangement are such that it will continue reacting immediately upon being formed.
    - Even though CO_2 is released by this mechanism, we will not observe bubbling in the reaction mixture because the gas is absorbed by the basic media.
    - Overall, we form isocyanate and then perform two consecutive types of nucleophilic acyl substitution.

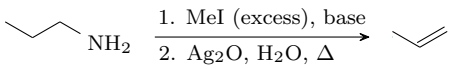
- An advantage of the Hofmann rearrangement is that it maintains the chirality in the R group.
  - In particular, we preserve the chirality at the carbon that ends up being α to the amine.
  - This differs from any of the reductive pathways that use S_N2, for instance.

- Comments on the Curtius rearrangement.
  - In the first step, heat is used to transform the (relatively stable) acyl azide into the isocyanate and liberate N_2 gas.
  - This detail was not mentioned in Lecture 6 and is not shown in Figure 3.13a.
  - You can hydrolyze the isocyanate with alcohol instead of water, leading to different products. We will explore this in PSet 5.

- Reactions of amines.

- Hofmann elimination.

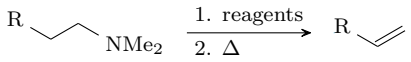
- General form.



  - This reaction solves the problem of how to turn NH_2 into a good leaving group so that we can eliminate it.
  - Example bases are NEt_3 or a NaOH pellet (it doesn't even have to be dissolved).
  - Yields the non-Zaitsev product[1] (less substituted alkene).

[1] This is why Mrs. Meer introduced the Zaitsev v. Hofmann product!

- Mechanism.
  - The first step makes the amide NH_2^- into a good leaving group by transforming it into a quaternary ammonium salt.
  - The second step causes the elimination. How it works centers around the dual role Ag_2O serves.
    - First, it relinquishes a silver cation to precipitate the iodide anion of the ammonium salt[2].
    - Second, the remaining AgO^- species acts as a strong bulky base.
- If we use a non-Hofmann elimination base (e.g., NaOEt) after forming the quaternary ammonium salt, then we get a mix of products with the Zaitsev product as the major product.
- Cope elimination.
- General form.



  - Reagents is mCPBA or H_2O_2.
  - We need heat around 150 °C in the second step.
- Mechanism.

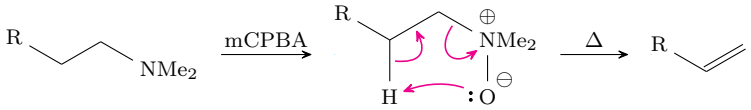


Figure 8.2: Cope elimination mechanism.

  - A concerted second step; hence, this is syn elimination.
- The Cope elimination is regioselective.

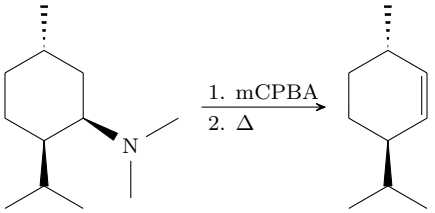


Figure 8.3: Cope elimination regioselectivity.

  - The hydrogen and oxygen need to be able to align (i.e., in the transition state). Thus, if they cannot, we will not get elimination there.
  - Guiding principle: The proton that you pull off has to point in the same direction as the nitrogen.

8.2 Carbohydrates 1

5/19:
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 22.1-22.2 and 22.9A.
  - Next time: Sections 22.3-22.4, 22.6-22.7, and 22.9B. Read Sections 22.10-22.11.

[2]Silver and iodide ions preferentially bond because of the HSAB principle from Labalme (2022a).

  - Practice problems: 22.21, 22.24, 22.28, 22.30.

- At this point, we have learned 98% of all of the reactions we'll learn for Organic Chemistry III.
  - We'll see some new reactions in this chapter, but they're all fairly obvious mechanistic analogues of previous reactions.
- Review of last lecture.
  - You don't need to be able to identify major and minor Cope elimination products for this course, just which ones can form and which ones cannot form.
- **Hydrolysis**: The addition of a water molecule to the starting material and subsequent breaking of some bond.
- **Alcoholysis**: The addition of an alcohol molecule to the starting material and subsequent breaking of some bond.
  - Note that neither hydrolysis nor alcoholysis has to involve the formation of two products from one SM (i.e., they don't need the bond broken to have been the only one holding two molecular fragments together).
- Tang is dividing this chapter into two parts.

  I. Names, structures, and properties.

  II. Reactions.
- Today, we will cover the following.

  I. Names, structures, and properties.

    A. Definitions.

    B. Structures.

  II. Reactions.

    A. Kiliani-Fischer synthesis.
- The following, up until stated otherwise, is not testable material.
- **Carbohydrate**: Sugar molecules, both simple and complicated.
- The etymology of the term, "carbohydrate."
  - Before NMR and other characterization methods, chemists determined the molecular formulas of compounds by burning them and measuring how much O_2 is consumed, how much CO_2 is formed, and how much H_2O is formed.
  - For a certain class of compounds, they determined that the formulas are of the form $(CH_2O)_n$.
  - Since these compounds all have a $1:1$ ratio of carbon to water, i.e., their unit structure is a carbon hydrate, chemists chose the name *carbohydrate*.
- The number of degrees of unsaturation of a simple sugar.
  - We can discount oxygen from the empirical formula, learning that the simple sugar $(CH_2O)_n$ has the same number of degrees of unsaturation as the hydrocarbon C_nH_{2n}.
  - Thus, since a fully saturated hydrocarbon has empirical formula C_nH_{2n+2}, we know that a simple sugar has *one* degree of unsaturation.
- Photosynthesis and cellular respiration.
  - Plants can synthesize glucose from carbon dioxide and water.

        - They us an additional special organelle with chlorophyll.
        - The energy source is sunlight.
        - Plants can also burn glucose for energy.
    - Humans cannot synthesize glucose from simpler molecules.
        - We can synthesize more complicated carbohydrates from glucose, however.
        - We solely burn glucose for energy, producing ATP and heat.

- Function of carbohydrates.

    1. An energy source for humans.
        - We can digest glucose.
        - We can also digest a number more types of sugar, e.g., sucrose (table sugar), starch (from bread), and maltose.
        - There are types of sugar that we cannot digest, e.g., cellulose.
            - Cows and sheep can digest cellulose, however, thanks to specialized bacteria in their gut.
        - The reason for the difference in digestibility between starch and cellulose hails from the type of linkage used between the sugar monomers.
    2. Other roles.
        - Structure materials (cellulose is structural in cell walls).
        - Components of nucleic acids (think ATP, as well as the sugar-phosphate backbone of DNA).
        - Many others (the following are a few specific examples).
            - The core structure of vitamin C.
            - Mediation of antibody-antigen recognition.

- Linus Pauling and vitamin C.

    - A great chemist who won (solo) the Nobel Prizes for both chemistry and peace.
    - Every day, he consumed multiple grams of vitamin C — he believed it would slow the aging process.
    - Pauling did live to 93, but one wonders if he would have lived a lot longer without such a surplus of vitamin C.
    - Modern-day vitamin doses.
        - We slightly overdose to compensate for the fact that only part of the dose will be absorbed.
        - As a particular example, shortly after taking a dose of vitamin B, your urine will become bright yellow and have a special smell. This is the excess being flushed out of your body.

- Antibody-antigen recognition.

    - This is the most important role of sugars in our body.
    - Most of the mediation is actually done by sugars instead of the primary amino-acid sequence of the antigens and antibodies.
    - Specific examples.
        - The COVID-19 vaccine gives us spike protein antibodies; having the disease gives us more. Discusses how glycoxylation of the COVID-19 spike protein allows our antibodies to recognize it and thus neutralize the virus.
        - HIV is similar.
        - A/B/O blood types also work much the same way. These work via modification of lipids. O-type blood has galactose connected to fructose as the terminal of the lipid glycin (this does not generate antibodies). A-type is the same as O-type, except with an additional galactosamine on the galactose. B-type is the same as O-type, except with an additional galactose. AB-type has both the A-type and B-type modifications to O-type.

- **Monosaccharide**: A single sugar monomer.
- **Disaccharide**: Two sugar monomers connected together.
- **Trisaccharide**: A molecule with a three sugar monomers.
- We can continue this pattern.
- **Oligosaccharide**: A chain of monosaccharides that is not too long.
  - The definition is very vague.
- **Polysaccharide**: A (longer) chain of monosaccharides.
- We now begin listing testable material.
- Structure.
- Fischer projections.

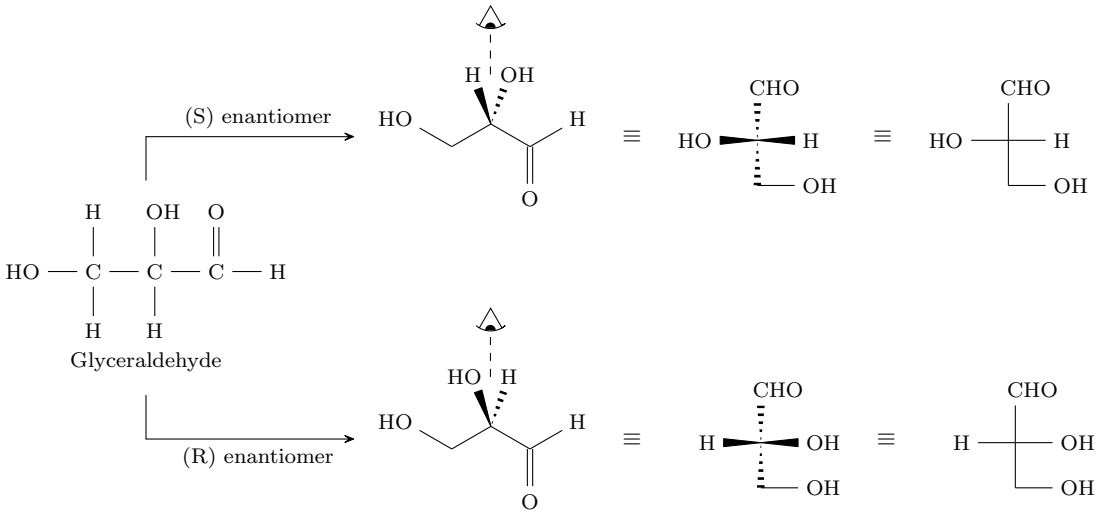


Figure 8.4: Interpreting the Fischer projections of glyceraldehyde.

  - We may have learned Fischer projections first quarter, but we've never used them up until now.
    - This makes sense because Fischer projections are only used for sugars nowadays.
  - The elements of Figure 8.4.
    - The leftmost molecule is **glyceraldehyde**. It has one chiral carbon (the central one) and thus two enantiomers.
    - The (S) enantiomer of glyceraldehyde is drawn in line-angle, in a top-view, and as a Fischer projection along the top row. The same is true of the (R) enantiomer along the bottom row.
    - The line angle drawings are fairly self-explanatory.
    - The top view is simply a redrawing of the line-angle but from the perspective of the eyes, with right being out of the page and left being into the page.
    - The Fischer projection then takes this view and simplifies all of the wedges and dashes to straight lines.
  - We canonically place the carbonyl group at the top of a Fischer projection.
  - The backbone of the hydrocarbon always curves into the page in a Fischer projection.
- **Absolute configuration** (of a molecule): The stereochemistry as denoted by R/S nomenclature.

- **D/L nomenclature**: An empirical way of describing the chirality at a carbon in a sugar. *Procedure*
  1. Identify the (bottommost) chiral carbon in the Fischer projection of a sugar.
  2. If the hydroxyl group here points to the left, we insert "L-" before the name of the sugar.
  3. If the hydroxyl group here points to the right, we insert "D-" before the name of the sugar.
- D/L nomenclature in Figure 8.4.
  - The (S) enantiomer is **L-glyceraldehyde**.
  - The (R) enantiomer is **D-glyceraldehyde**.
- All naturally occurring sugars have the D configuration.
- **Aldose**: A sugar in which the one degree of unsaturation comes from an aldehyde.
- **Ketose**: A sugar in which the one degree of unsaturation comes from a ketone.
- **Triose**: A sugar with three carbons.
- **Tetrose**: A sugar with four carbons.
- **Pentose**: A sugar with five carbons.
- **Hexose**: A sugar with six carbons.
- Examples.
  - D-glyceraldehyde is an aldose triose.
  - **D-threose** is an aldose tetrose.
  - **D-fructose** is a ketose hexose.
- **D-threose**: The following sugar. *Structure*

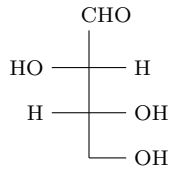


Figure 8.5: D-threose.

- D-threose has two chiral carbons.
  - As we've previously discussed, the "D" tells us the chirality at the bottom carbon.
  - The name "threose" differentiates the the chirality at the top carbon from that of this molecule's diastereomer, **D-erythrose** (see Figure 8.15).
  - Note that there also exist L-threose and L-erythrose (diastereomers of the respective D-versions with inverted chirality at the bottom carbon).
- Conformations of D-threose.
  - If we draw the conformation of D-threose indicated by the Fischer projection, we will notice that a lot of groups are eclipsed and that this is actually a very high energy conformation of the molecule.
  - This is why Fischer projections are not used beyond sugars: because normal molecules would never assume such a conformation.
  - A normal compounds gets drawn in the typical zig-zag/line-angle form.

- **D-fructose**: The following sugar. *Structure*

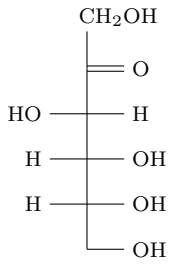


Figure 8.6: D-fructose.

- **D-glucose**: The following sugar. *Also known as* **dextrose**. *Structure*

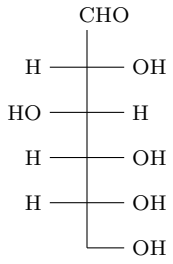
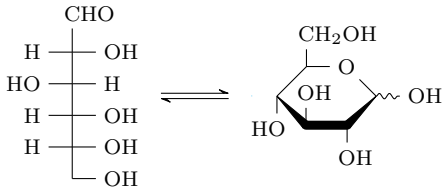


Figure 8.7: D-glucose.

  - This is the only structure Tang expects us to know by heart; every other structure will be given.
- Open and closed structures.
- General form.



  - This is how we transfer the one degree of unsaturation from an aldehyde or ketone to a ring.
  - The open and (multiple) closed forms are always in equilibrium.
    - For instance, D-glucose prefers to exist as a six-membered ring, but we can find trace amounts ($\approx 0.02\%$) of the open form and even smaller amounts of a five-membered ring form.
    - We will still never observe four-membered rings (or smaller) or seven-membered rings (or bigger).
  - The wavy line represents indeterminate chirality.
  - This is very testable material!
- Mechanism.
  - This process is just hemiacetal/hemiketal formation, as we can see by observing the similarities between Figure 8.8 and the first three steps of Figure 1.14.
  - We now know that the indeterminacy in the chirality at the one carbon comes from the fact that chirality is set by the intramolecular attack, not the prior stereochemistry.

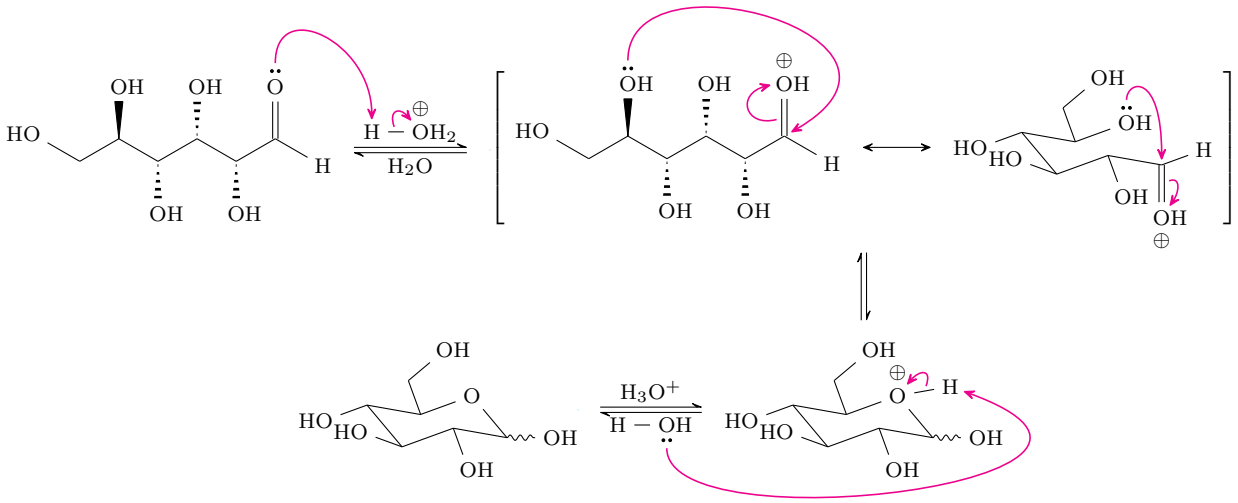


Figure 8.8: Glucose ring-closing mechanism.

  - Note that the six-membered ring of glucose is particularly favored because every substituent is in the equatorial position.

- **Anometic** (carbon): The carbon whose chirality is decided by the attack.
- **β-D-glucose**: The six-membered ring form of D-glucose wherein the hydroxyl group on the anomeric carbon is equatorial. *Also known as* **β-D-glucopyranose**.
- **α-D-glucose**: The six-membered ring form of D-glucose wherein the hydroxyl group on the anomeric carbon is axial. *Also known as* **α-D-glucopyranose**.
- **Pyran**: The following compound. *Structure*

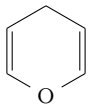


Figure 8.9: Pyran.

  - Pyran is useful in describing the cyclized form of sugars.
  - Indeed, we call six membered rings with five carbons and one oxygen **pyranose**.

- **Furan**: The following compound. *Structure*

Figure 8.10: Furan.

  - Similarly, we call five membered rings with four carbons and one oxygen **furanose**.
  - This is why we have tetrahydrofuran!

- The ratio of β-D-glucose to α-D-glucose in water is 64 : 36, owing to the former's greater stability.
- β- vs. α-linkages play a key role in determining how easy it is to hydrolyze polysaccharaides. For example, starch monomers are connected via α-linkages and thus can be easily hydrolyzed; on the other hand, cellulose monomers are connected via β-linkages and thus cannot be easily hydrolyzed.

- Reducing carbohydrates.
  - Note that the six-membered ring form of D-glucose (see the end product in Figure 8.8) contains a hemiacetal.
  - Thus, since hemiacetal formation is readily reversible, we will have some of the open form in solution with which we can perform aldehyde chemistry.
  - In particular, if we mix a solution of glucose with $NaBH_4$, we can reduce it.
  - Note that if we have a hemiketal instead, we can observe muted reactivity.
- Fun facts.
  - This is not testable content.
  - Draws the structure of **sucrose**.
    - Sucrose contains an acetal in its ring system, and fructose contains a ketal in its ring system.
    - Thus, the formation is not readily reversible, so sucrose cannot be reduced by $NaBH_4$.
    - A **glucometer** (tests blood sugar) determines whether or not the blood is oxidative.
  - Glucose is 0.75 times as sweet as glucose.
  - Fructose is 1.75 times as sweet as fructose.
  - High-fructose corn syrup (industrial synthesis).
    - Start from corn starch (cheap compared to cane sugar; mostly made of glucose).
    - Do hydrolysis to yield glucose.
    - Add an enzyme to convert some of the glucose into fructose, yielding a 55 : 45 ratio of fructose and glucose. We will also have about 20% water in solution.
- **Sucrose**: A disaccharide of glucose and fructose connected by an α-linkage. *Also known as* **table sugar**. *Structure*

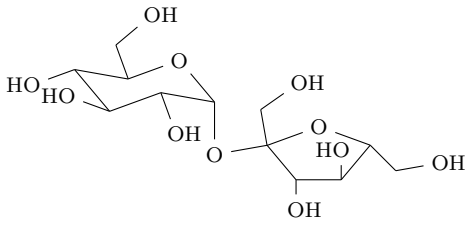


Figure 8.11: Sucrose.

- **Saccharin**: An artificial sweetener that is 350 times sweeter than table sugar. *Structure*

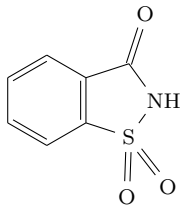


Figure 8.12: Saccharin.

- The discovery of saccharin (according to legend).
  - The chemist who first synthesized it didn't wash his hand very well after lab, went home, touched the dough of a cake that his wife was baking, and commented that it was really sweet. He later figured out that the additional sweetness was coming from saccharin.

- **Aspartame**: An artificial sweetener that is 180 times sweeter than table sugar. *Structure*

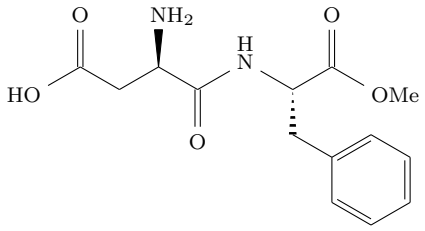


Figure 8.13: Aspartame.

- **Sucralose**: An artificial sweetener that is 600 times sweeter than table sugar. *Also known as* **Splenda**. *Structure*

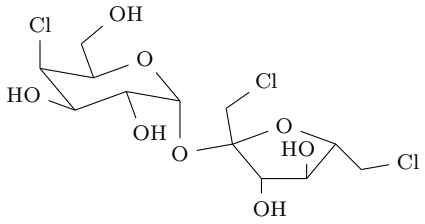
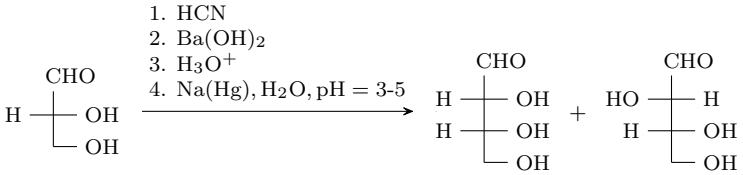


Figure 8.14: Sucralose.

- The discovery of sucralose (according to legend).
  - A PI asks his (Indian) post-doc to synthesize this chlorinated sucrose analogue. The post-doc reports the complete synthesis and the PI ask him to "test it," as in characterize spectroscopically. However, the post-doc hears "taste it," is confused but goes and does so, and reports, "sir, it's very sweet."
- All artificial sweeteners were discovered by accident — there's no reason you'd think they're sweet just by looking at the structure.
- Artificial sweeteners are dangerous in extreme excess, but not in any ordinary amount.
  - Tang goes over an experiment on mice and their kidneys to support this claim.
  - If we use a sugar alcohol, however, (e.g., sorbitol), we can get diarrhea for eating too much.
    - This is because these are not as sweet, so we use more; but since they are not digestible, consuming too much does not bode well for the digestive system.
- Kiliani-Fischer synthesis.
- General form.



  - This is a **chain-elongation reaction**.
- **Chain-elongation reaction**: A reaction that takes a simple sugar and extends it by one carbon.

- Mechanism.

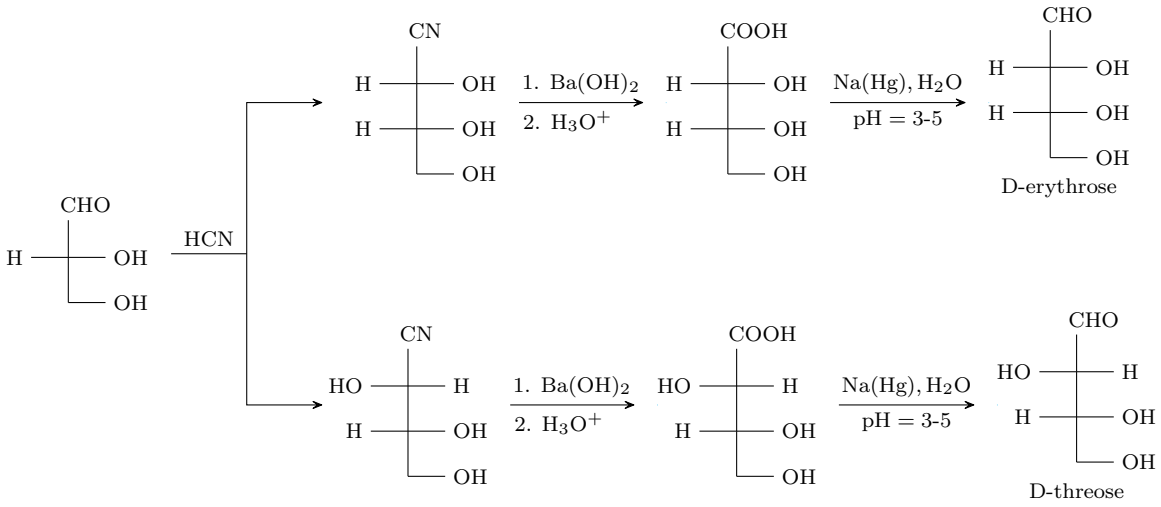


Figure 8.15: Kiliani-Fischer synthesis mechanism.

  - In the first step (cyanohydrin formation), the cyanide ion can attack either face. Thus, the first step leads to the formation of two diastereomers.
  - In the second and third steps, it is an empirical finding that barium hydroxide is a better base source than NaOH or something else of the sort, but it is hard to say that any of these alternatives flat-out would not work. What we are basically accomplishing here, though, is nitrile hydrolysis (see Figure 2.12).
    - Tang indicates that the $Ba(OH)_2$ generates a carboxylate from our nitrile and then the acid protonates it to a carboxylic acid.
  - The last step is a reduction.