

Week 7

Intro to Amines

7.1 Amines 1

- 5/10:
- Today's lecture content in Solomons et al. (2016).
 - Today: More examples for Chapter 19 and Sections 20.1-20.3.
 - Next time: Sections 20.4, 20.12, and 20.6-20.7.(review).
 - Practice problems: None.
 - The exam format will be the same as Midterm 1; the difficulty will be decreased.
 - Tang thinks that Chapter 19 is the hardest chapter in Organic Chemistry III.
 - Problem set 4 incorporates real reactions from the literature!
 - Review of Chapter 19 content.
 - Many good examples/tables/charts/summaries.
 - Carbonyl condensation calling cards.
 - A 1,3-dioxygen setup comes from a condensation reaction (aldol or Claisen).
 - Similarly, the Mannich reaction yields a 1,3-diheteroatom setup.
 - A 1,5-dioxygen setup comes from conjugate addition.
 - A cyclohexenone group comes from Robinson annulation.
 - The only alkoxide bases we will ever see for the Chapter 19 reactions are ethoxide or methoxide.
 - NaOH / EtOH and NaOEt / EtOH are equivalent conditions.
 - A trick for drawing cyclized molecules from linear molecules: The enolate side does not change.
 - For an aldol reaction, the enolate side will be the one that kept the carbonyl.
 - For a Claisen condensation, the enolate side will be the one that kept the ester.
 - Mechanics of the retro-Claisen.
 - The lack of a middle α -hydrogen implies that the ketone carbonyl carbon is much more reactive. In other words, if the ethoxide base is not attracted to an electrophilic, acidic proton, it is more likely to be attracted to the electrophilic carbonyl carbon.
 - Once ethoxide adds in, it can definitely be kicked back out again. However, we will only draw the productive route, i.e., that in which the next step is breaking the C–C bond.
 - Always look out for forward Claisens after performing a retro-Claisen (we are still under Claisen condensation conditions)!
 - As a particular example, if we subject the leftmost molecule in Figure 6.5 to NaOEt / EtOH, the final product will not be the middle molecule but the rightmost molecule.

- Claisen condensation special/tricky cases.
 - A Claisen condensation will proceed with most any *single* R group on the α -carbon of the ester; in particular, we need not just have a methyl group there, but can also have bigger things, like isopropyl groups. Issues only arise when we have *two* R groups on the ester's α -carbon.
 - Ethyl cyclohexanecarboxylate cleverly disguises double R groups on the α -carbon as a ring. Regardless, if we can correctly identify it, we will see that it will only react via protonation/deprotonation under Claisen condensation conditions.
 - Claisen condensation products that can perform a retro-Claisen can sometimes continue to react in another forward Claisen. However, in such cases, we find that the retro-Claisen is preferred. There will always be a bunch of background reactions, but what determines the major product is still thermodynamics (i.e., what the most stable product is).
- Motivating Chapter 20.
 - Amines are very important in chemistry, biochemistry, and pharmaceuticals.
 - We have simple 1°, 2°, and 3° amines in chemistry.
 - In biology, amines appear in nucleotide base pairs, peptides, amphetamines, etc.
 - Amides are the least reactive (neutral) carboxylic acid derivative.
- Acid/base properties of amines.
 - Amines are our first basic functional group.
- Tang is dividing this chapter into three parts.
 - I. Properties of amines.
 - II. Preparation of amines.
 - III. Reactions of amines.
- Today, we will cover the following.
 - I. Properties of amines.
 - A. Structure.
 - B. Acid-base properties.
- Draws a 3D hybridized amine structure and discusses the stereochemical inversion of amines about the nitrogen center.
 - Chirality cannot be stably maintained.
 - For the umbrella flip, $E_a = 6 \text{ kcal mol}^{-1}$.
 - Recall that this is very much on the same order of magnitude as rotation from eclipsed to staggered to eclipsed in ethane (that transformation has an activation barrier of about 3 kcal mol^{-1}).
 - Note that any reaction with $E_a < 25 \text{ kcal mol}^{-1}$ can proceed at room temp.
 - This reaction is far below that barrier, so it proceeds readily. Perhaps we could isolate amines in one conformation at lower temperatures, though?
 - With all four substitutions different, nitrogen behaves like a carbon and does not stereoinvert.
- Acid-base properties.
- Amines are not that strong but *tend* to be good bases.
 - We say “tend” because there are cases where amines are not basic.

- Quantifying the basicity of amines.
 - We use the pK_a of the protonated amine.
 - This is so that we can consider RNH_2 species picking up a new proton (as desired). If we were to consider $pK_a(RNH_2)$, we would be discussing that species losing a proton (or RHN^- picking up a proton).
- Simple amines have $pK_a \approx 9-10$.
 - HCl has $pK_a = -7$.
 - BuH has $pK_a = 50$.
- Example amine pK_a 's.
 - NH_3 has $pK_a(NH_4^+) = 9.24$.
 - $MeNH_2$ has $pK_a(MeNH_3^+) = 10.62$.
 - This pK_a is higher because methyl groups are electron donating, so they make the nitrogen more nucleophilic.
 - $PhNH_2$ has $pK_a(PhNH_3^+) = 4.6$.
 - The nitrogen lone pair participates in resonance with the phenyl group.
 - Thus, it is sp^2 hybridized.
 - Another consequence of this resonance/hybridization is that the whole molecule will be planar. From an orbital perspective, this promotes facile resonance among all seven p orbitals. This also presents an activation barrier to free rotation about the C–N bond.
 - The overall effect is that since the nitrogen's lone pair is delocalized into the π system and held closer to the nucleus via the sp^2 hybridization, it is less basic.
 - Substituted anilines.
 - EWGs on the ring lower pK_a .
 - EDGs on the ring raise pK_a .