

- Predicting reaction outcomes or yields can be hit or miss.
- There have been maybe 1 000 000 chemical reactions ever catalogued, but most of them are not that useful.
- The low-data regime of predictive modeling is the final frontier, and the especially important one for chemistry.
- Taking high-level expertise and making it algorithmically applicable can be really difficult.
- “High accuracies are achieved only if the machine is provided some chemical ‘insight’ about the reaction (in particular, information about the reaction’s core and key substituents).”
- While ML models cannot provide the generality of quantum mechanics, they work much faster.
- They trained the model with inverse electron-demand Diels-Alder reactions, Diels-Alder reactions that need to be site-selective, etc.
- The website to help you predict Diels-Alders is historical at this point, so don’t worry if you can’t access it in the paper.
- There are several classes on computational chemistry in both Course 5 and Course 10 if you’re interested!
- A problem with Reaxys: All of the reactions in the database are data-scraped from old papers, so a significant number of them are wrong or incomplete (20-30%, and worse in other databases).
- Predictive modeling really reveals how difficult it is to predict reaction outcomes: Prof. Elkin has published papers where their model can predict yield far better than even chemistry experts.
- Conclusion: ML can be useful in predicting outcomes and can generalize to unseen reactions when descriptors carrying physically relevant information are used, and the machine gets appropriately formatted information.
- Note: None of this is testable material!

3.21 Amines - 1

10/25:

- New lecturer for the second half of the course: Prof. Steve Buchwald.
 - Born in Bloomington, Indiana.
 - Undergrad at Brown, PhD at Harvard, Postdoc at Caltech (with Bob Grubbs, a Nobel laureate).
 - At MIT for 40 years (since 1984).
 - Has two cats :)
 - Researches **organometallic chemistry**, with a focus on the synthesis of fine chemicals like pharmaceuticals.
 - Most organometallic chemistry is predicated on the development of ligands.
 - Many of Prof. Buchwald’s ligands are named after his former cats!
 - Example: The RuPhos ligand is named after Prof. Buchwald’s since-passed cat, Rufus.
- **Organometallic** (chemistry): A hybrid of organic and inorganic chemistry.
- Prof. Elkin is in Washington, D.C. today advising the federal government!

- Announcements.
 - The first half of this semester covered analytical techniques and physical chemistry; this half is more synthesis-focused.
 - Review your 5.12 reactions!! A list of what you need to know for PSet 5 will be posted on Canvas.
 - The teaching team will also keep a running list of reactions from this half of the course.
 - This will tell you what to know for the exams and PSets.
 - Prof. Buchwald will post “study guides” for each unit, containing all the unit’s content.
 - Clayden et al. (2012) doesn’t have a specific section on amines. Thus, the study guide lists all the pages spread throughout Clayden et al. (2012) where the different reactions can be found.
 - If you still have Smith (2023) — your 5.12 textbook — it’s Chapter 23.
 - Plan: This lecture and the following one will cover amines.
 - Amines have a special place in Prof. Buchwald’s heart because they’re connected to a lot of his research!
 - Like Prof. Elkin, Prof. Buchwald will continue giving fun facts that relate these topics to the real world.
- Outline for the next two lectures.
 - A. Intro.
 - B. Chirality (or “handedness;” recall from 5.12).
 - C. Brønsted basicity.
 - D. Synthesis and reactivity (we’ll spend the majority of our time on this topic).
 1. Alkylation of ammonia and alternatives.
 2. Reductive amination.
 3. Acylation and reduction.
 4. Reduction of nitriles (i.e., $R-C\equiv N$ functional groups).
 5. Other miscellaneous methods.
- Today: We’ll cover Topic A through most of Topic C.
- We now begin with Topic A: Introduction.
- **Amine:** An R_3N compound, where each R may be distinct and R is an H, alkyl, or aryl group.
- The simplest amine is ammonia (NH_3).
 - Notice that ammonia *is* an amine by the definition: All of its R groups are identically equal to H!
 - Fun fact: Ammonia is a necessary ingredient in fertilizer.
 - It is prepared industrially from N_2 using the Haber-Bosch process.
 - One could make a reasonable argument that the industrial production of ammonia is the most important technological advance in the history of the world.
 - This is because it enabled us to produce far more fertilizer, so that we could produce more food, so that we can feed a population of seven billion people.
 - Before Haber-Bosch, fertilizer came from an island covered in bird feces.
 - Two Nobel prizes were awarded in connection with the development of this process.
 - Haber won the Nobel Prize for his work on this process in 1918 (for the process).
 - Bosch won the Nobel Prize for his work on this process in 1931 (for high-pressure chemistry).

- Examples of amines.

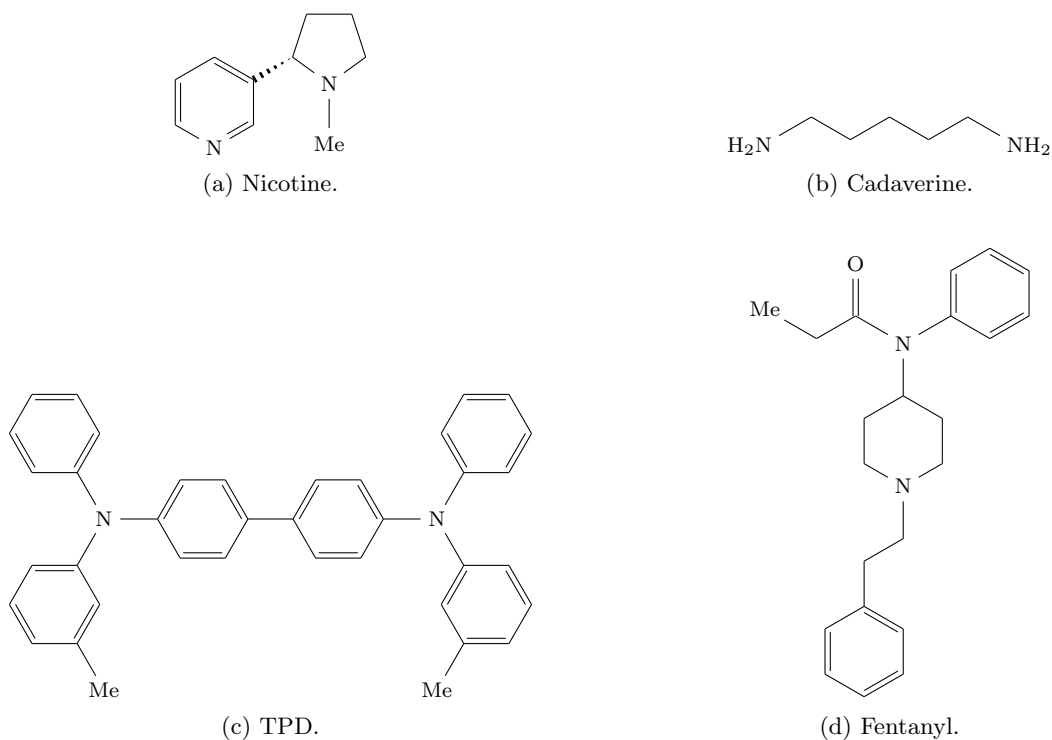


Figure 3.1: Amine examples.

- The top-selling pharmaceuticals in the world are all amines, at least in part.
 - Not all of these “pharmaceuticals” are fun, though! Some are illicit drugs.
- Example: Nicotine (Figure 3.1a).
 - It’s one of the most difficult habits to break.
 - There are drugs that mimic the structure of nicotine but bind to the receptor better and block nicotine from doing its job.
- Example: Cadaverine (Figure 3.1b).
 - Does not smell good.
 - When animals die, their flesh putrifies/rots and this is what causes the smell.
- Example: TPD (Figure 3.1c).
 - This is a hole transport agent commonly found in the toner cartridges of laser printers.
- Example: Fentanyl (Figure 3.1d).
 - A synthetic opioid that has caused unbelievable amounts of societal problems.
- Classes of amines.
 - Ammonia (NH₃).
 - Good because it helps feed the world.
 - Bad because it’s a toxic gas and smells horrible.
 - **Primary amines.**
 - **Secondary amines.**
 - **Tertiary amines.**
 - **Quaternary ammonium salts:** A related family of compounds.

- **Primary** (amine): An amine in which we've replaced one of the H's in ammonia with an (alkyl or aryl) R group. Denoted by 1° . General form RNH_2 .

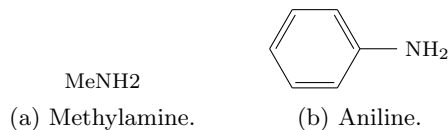


Figure 3.2: Primary amine examples.

- Example: Methylamine (Figure 3.2a).
 - A gas like ammonia, but a liquid under pressure.
 - It's a controlled substance.
 - In *Breaking Bad*, this is what Walt, Jessie, and Todd heisted from the train!
- Example: Aniline (Figure 3.2b).
 - Very important historically: Modern chemistry began in the 1800's with aniline-based dyes.
 - These companies are the precursor to modern-day pharmaceutical companies!
- **Secondary** (amine): An amine in which we've replaced two of the H's in ammonia with (alkyl or aryl) R groups. Denoted by 2° . General form $\text{RR}'\text{NH}$.

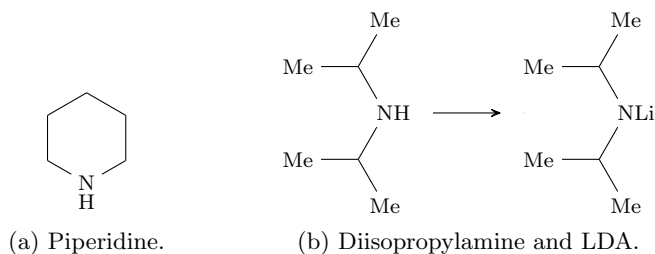


Figure 3.3: Secondary amine examples.

- The R groups can be separate, or they can be linked together.
- Example of a cyclic secondary amine: Piperidine (Figure 3.3a).
 - Piperidine is important in a number of applications, including sequencing DNA.
- Example of an acyclic secondary amine: Diisopropylamine (Figure 3.3b).
 - If you replace the amine hydrogen with lithium, you get lithium diisopropylamide (LDA).
 - This is a very strong base that we'll talk more about later in this course.
- **Tertiary** (amine): An amine in which we've replaced all three of the H's in ammonia with (alkyl or aryl) R groups. Denoted by 3° . General form $\text{RR}'\text{R}''\text{N}$.
- **Quaternary ammonium salt**: A nitrogen covalently bonded to four R groups (and hence having a positive formal charge), coordinated to a negative counterion. General form $\text{R}_4\text{N}^+ \text{X}^-$.

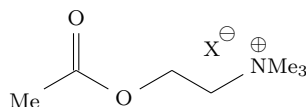


Figure 3.4: Quaternary ammonium salt example.

- Example: Acetylcholine, an important neurotransmitter (Figure 3.4).

- This concludes our introduction to amines.
- Aside: Prof. Buchwald *strongly* recommends you show up for lecture the day before Halloween :)
- We now move onto Topic B: Chirality.
- Recall from 5.12 that some compounds are *chiral*, i.e., they can have enantiomers.

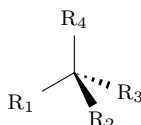


Figure 3.5: A chiral compound.

- These enantiomers can often be separated.
- They can also have different biological activities.
 - Fun fact: The FDA now requires all chiral molecules to be prepared in both enantiomers and independently tested, in part because of the thalidomide scandal.
- The structure of amines.

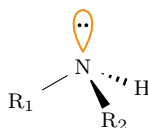


Figure 3.6: Amine structure.

- Amines are sp^3 -hybridized with a tetrahedral electron pair arrangement.
 - 3 bonding orbitals and 1 lone pair (lp).
- The lp is responsible for the Brønsted basicity of amines.
- If one of the R groups is hydrogen, then the amine can participate in hydrogen bonding (a very important interaction you should recall from Gen Chem).
- Is pyridine a tertiary amine?
 - Technically, yes; we'll discuss pyridine next lecture.
- Amines have two enantiomers as well.

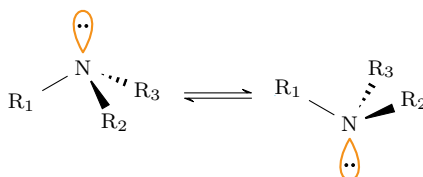


Figure 3.7: Amine enantiomer interconversion.

- The energy barrier (ΔG^\ddagger) between the two enantiomers is 5-6 kcal/mol.
- Additionally, note that if $\Delta G^\ddagger \leq 20$ kcal/mol, the process is fast at room temperature.
- Thus, amine enantiomers rapidly interconvert at room temperature, so we (usually) cannot resolve amines into individual enantiomers.
 - One time we can resolve amines into enantiomers is in the case of **aziridines**.

- **Aziridine:** A three-membered ring containing one nitrogen and two carbons. *Structure*

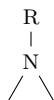


Figure 3.8: Aziridine.

- These are the amine equivalent of an epoxide.
- Like in any other amine, R can still be H, alkyl, or aryl.
- The sp^3 -hybridized atoms all want to have 109° bond angles but are strained to 60° .
- In order for aziridines to undergo **racemization**, the molecules must go through a transition state with an sp^2 -nitrogen.

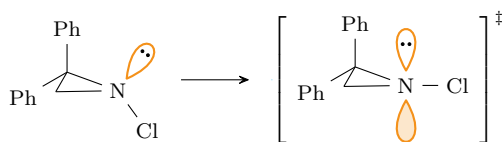


Figure 3.9: Aziridine enantiomer interconversion.

- This sp^2 -nitrogen wants to have 120° bond angles but is still strained down to 60° .
 - This is even worse than the strain in an sp^3 -nitrogen!
- Thus, the energy barrier to aziridine enantiomer interconversion is $\Delta G^\ddagger \approx 24 \text{ kcal/mol}$.
- Therefore, (many) aziridines *do not* interconvert at room temperature because $24 > 20$.
- **Racemization:** The interconversion of enantiomers.
- This concludes our discussion of chirality.
- We now move onto Topic C: Brønsted basicity.
- Consider the following two protonation reactions.



Figure 3.10: Basicity of methanol vs. methylamine.

- For MeOH_2^+ , $\text{p}K_{\text{a}} \approx -2$.
 - This means that MeOH_2^+ is very acidic.
 - It follows that MeOH is only weakly basic.
- For MeNH_3^+ , $\text{p}K_{\text{a}} \approx 9 - 11$.
 - Thus, MeNH_2 is *much* more basic than MeOH.
- Something critical to everyday life: Why do fish smell so bad after they die?



Figure 3.11: Amines explain why fish smell, and how to season them!

- Not all fish smell to the same degree.
 - Ocean fish (like cod) smell worse than river fish (like catfish) after they die.
 - Ocean fish smell worse because of trimethylamine oxide.
 - There's a lot of salt in the ocean, so ocean fish use trimethylamine oxide to balance the salt levels in their cells.
 - This compound does not smell very much, but after they die, enzymes from the fish (and from bacteria in the fish) reduce trimethylamine oxide to trimethylamine (which smells horrible).
 - Second important thing: We put lemon juice on fish because the acidity of the lemon juice (coming from citric acid) protonates the trimethylamine, decreasing the smell (and the taste since smell is connected to taste) so that the fish tastes better.
- Resonance decreases the basicity of amines.

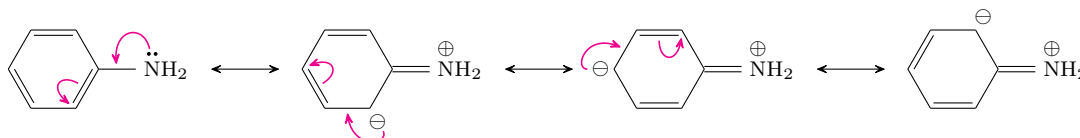


Figure 3.12: Basicity of aniline.

- The conjugate base of aniline (PhNH_3^+) has $\text{p}K_{\text{a}} \approx 5$, indicating that aniline is much less basic than methylamine ($\text{p}K_{\text{a}} \approx 9 - 11$).
- Why? Two reasons:
 1. The sp^2 -carbon adjacent to the nitrogen in aniline is more electron-donating than the sp^3 -carbon adjacent to the nitrogen in methylamine.
 2. Resonance.
 - Just like in a phenol, we can push the heteroatom electrons into the benzene ring to get three other resonance forms (Figure 3.12).
 - Resonance decreases basicity, so aniline is much less basic than any alkylamine.

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