Chapter 25. Amines.

1. Amines are widely found in organisms. Many have the distinct odor of rotten fish. Important biological properties such as neurotransmitters and other messenger molecules.

2. Nomenclature.
   a) The simplest amine is ammonia, NH$_3$. By replacing each of the H atoms on NH$_3$ successively with alkyl groups, one obtains primary (1°), secondary (2°), and tertiary (3°) amines, respectively, i.e. RNH$_2$, R$_2$NH, and R$_3$N. Note that the definitions of 1°, 2°, and 3° amines are different from the definitions of 1°, 2°, and 3° alcohols or carbons.
   b) A 1° amine RNH$_2$ is named as an alkylamine, e.g. ethylamine, isopropylamine, etc. Phenylamine is called aniline.
   c) The 2° and 3° amines in which the two or three alkyl groups are the same are called dialkylamine or trialkylamine, e.g. dibenzylamine, triethylamine.
   d) The 2° and 3° amines in which the three groups are not all the same have the root name of the 1° amine with the longest alkyl group. Then the compound is named as the 1° amine substituted on N by adding the prefix N-alkyl or N,N-dialkyl or N-alkyl-N-alkyl. E.g., N,N-dimethylcyclohexylamine.
   e) When amines also have carbonyl groups, the carbonyl group is used to name the compound, and the amine group is indicated by the prefix amino- or alkylamino. E.g., 2-aminopropionic acid.
   f) Amines are widely found in organisms, and many of these compounds have trivial names, e.g. putrescine, spermidine, and spermine. Amino acids and amino sugars have widely used trivial names.
   g) Cyclic amines have their own system of names. Piperidine, pyrrolidine. Aromatic amines have their own names still. Pyrrole, pyridine, indole, quinoline, imidazole, pyrimidine, etc.

3. Chirality.
   a) An amine with three different groups attached is chiral. The three groups and the lone pair point to the four corners of a tetrahedron. Ignoring the lone pair, the amine is said to be pyramidal. However, inversion of an amine through a planar transition state occurs very readily, and most amines can't be isolated in one or the other configuration. Amines therefore consist of pairs of rapidly equilibrating stereoisomers.
   b) A N atom with four different groups attached has a formal positive charge, and is called an ammonium salt. Ammonium salts are stereogenic at N if four different groups are attached, just like C. Since there is no lone pair, inversion can't occur, and quaternary ammonium salts can be isolated in stereochemically pure form.

4. Reactivity.
   a) Ammonia and 1° and 2° amines are very weak acids, with pK$_a$'s of about 35-37. (Cf. ethyl acetate, pK$_a$ = 25). Conversely, deprotonated amines, called amides, are very strong bases. E.g., LDA.
   b) The lone pair of amines is very reactive, and amines are both good nucleophiles and good bases.
More alkyl substitution makes an amine more basic and nucleophilic due to the inductive donating effect of alkyl groups. So 3° amines are more basic and nucleophilic than 1° amines, as long as the alkyl groups are not branched where they are attached to N. However, increasing steric hindrance around an amine can reduce its nucleophilicity drastically, at the same time increasing the basicity.

c) Protonation of amines gives ammonium ions. Ammonium ions are weak acids, with pKₐ's of about 10. They are less acidic than acetic acid (pKₐ = 4.7), but more acidic than diethyl malonate (pKₐ = 13). Amines are protonated at physiological pH, just like acids are deprotonated.

d) Carboxamides RCONH₂ are non-basic. The lone pair on N is tied up by resonance with the carbonyl.

5. Preparation.

a) S_N₂ reaction of alkyl halides with N nucleophiles.
   i) Ammonia and amines react with alkyl halides R’X to give 1°, 2°, 3°, or 4° ammonium salts; the first three can be deprotonated to give 1°, 2°, or 3° amines. This synthesis can be inefficient, because the products are more nucleophilic than the starting materials, although ratio of products can be controlled by use of large excess of starting amine.
   ii) 1° Amines can be efficiently prepared from alkyl halides by S_N₂ substitution with azide N₃⁻. The product, an alkyl azide RN₃, can be reduced to the 1° amine RNH₂ by hydrogenation over Pd/C or by LiAlH₄.
   iii) 1° Amines can also be efficiently prepared from alkyl halides by S_N₂ substitution with potassium phthalide, PhthN⁻K⁺ (Gabriel synthesis), to give PhthNR. The N⁻ anion is stabilized by the two flanking carbonyls. The Phth group is removed with hydrazine N₂H₄ to give the free amine H₂NR.

b) Reduction of nitriles or carboxamides.
   i) Carboxamides RCONH₂, RCONHR, and RCONRR’ are reduced with LiAlH₄; the C=O group is reduced to CH₂ to give RCH₂NH₂, RCH₂NHR, and RCH₂NRR’. Probably the best way to prepare 2° amines and 3° amines with two or three different groups attached to N, as long as one of the groups is a 1° alkyl group!
   ii) Nitriles RC≡N are reduced to 1° amines RCH₂NH₂ by catalytic hydrogenation or with LiAlH₄. Catalytic hydrogenation proceeds via the imine RCH=NH. Problem: product amine RCH₂NH₂ can react with intermediate imine RCH=NH to give new imine RCH=NCH₂R, which is reduced to 2° amine, not 1° amine. (Imine exchange proceeds by attack of amine on protonated imine.) Prevented by carrying out reduction under strongly acidic conditions, under which product amine is protonated permanently. No such problems with LiAlH₄.

c) Reductive amination or reductive alkylation. Reduction of imines.
   i) Aldehydes RCH=O and ketones R₂C=O react with NH₃ or 1° or 2° amines to give iminium ions RCH=NH₂, R₂C=NH₂, RCH=N⁺R₂, etc. (In the case of NH₃ or 1° amines, the iminium
ions can be deprotonated to give imines, but that's irrelevant.)

ii) When the imines are formed in the presence of H₂ and Pd/C or in the presence of NaBH₃CN (a relative of NaBH₄), the iminium ion π bond is reduced to give the ammonium ion RCH₂N⁺H₃, R₂CHNH₃, RCH₂NHR₂, etc. Deprotonation of N then gives the free amines RCH₂NH₂, R₂CHNH₂, RCH₂NR₂, etc.

iii) Problem: the amines produced in the reaction can react further with starting carbonyl groups to give overalkylated products. E.g., MeNH₂ + i-PrCHO → MeNH-i-Bu + MeNi-Bu₂. Especially a problem with aldehydes, which produce less hindered product amines, which are more prone to form imines again with starting materials.

iv) Especially useful for 2° amines + formaldehyde to give 3° amines with a methyl group.

v) Reductive amination carried out physiologically using pyridoxal phosphate (discussed earlier).

d) Hofmann and Curtius rearrangements.

i) RCONH₂ + Br₂ and NaOH → [RCONHBr] → [RCONBr] → RN=C=O, + H₂O → RNH₂.

ii) RCOCl + NaN₃ → RCON₃ ↔ RCON₂⁺, + Δ → RN=C=O, + H₂O → RNH₂.

iii) Both proceed via intermediates that have a leaving group attached to N. The R group migrates to N, displacing the leaving group Br⁻ or N₂, to give an isocyanate as intermediate, which is hydrolyzed to the free amine.

iv) Best way to prepare 1° amines with a 3° alkyl group attached, e.g. t-BuNH₂. Also useful for arylamines ArNH₂ from benzoic acids ArCO₂H.

6. Partial summary of preparative methods.

a) Sequence RX → RN₃ (or RNPhth) → RNH₂ is way to convert alkyl halides to 1° amines with same number of C's. Sequence RX → RC≡N → RCH₂NH₂ is way to convert alkyl halides to 1° amines with one more C.

b) Sequence RCO₂H → RCOCl → RCON₃ → RNH₂ is way to convert carboxylic acids (which can be prepared from alcohols) to 1° amines with one fewer C. Sequence RCO₂H → RCOCl → RCONH₂ → RCH₂NH₂ is way to convert carboxylic acids to 1° amines with same number of C's.

c) 2° and 3° amines can be prepared by reduction of carboxamides (when one alkyl group is 1°) or reductive amination of aldehydes (when one alkyl group is 1°) or ketones (when one alkyl group is 2°).

7. Phase transfer catalysis. Electrophilic compounds such as alkyl halides are usually soluble only in organic solvents, whereas simple salts of nucleophiles such as NaOH, NaN₃, KCl, etc. are normally soluble only in H₂O. Quaternary ammonium salts R₄N⁺X⁻ are partly soluble both in organic solvents such as CH₂Cl₂ and in H₂O. The ammonium ion can form an ion pair with a nucleophilic counterion in an aqueous layer, transport it into the organic layer to react with the alkyl halide, and then carry the halide ion back to the aqueous layer, where the process can be repeated. Thus quaternary ammonium salts are phase transfer catalysts.