AMIDES AND RELATED FUNCTIONAL GROUPS

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I. Introduction

Recall that nitrogen has five valence electrons and therefore requires three electrons or bonds to complete its octet (see Amine Tutorial). Based on this valence and bonding order, nitrogen forms three bonds in its neutral state and maintains one pair of non-bonded electrons (NBEs). In amides one of the three bonds is a carbonyl carbon. Thus amides may be viewed as "acylated amines" or as derivatives of carboxylic acids in which the -OH of the acid has been replaced by -NR₂ where R= H, alkyl, aryl, etc.):

Like amines, amides can be classified as "primary", "secondary" or "tertiary" depending on the degree of carbon substitution on nitrogen:

Amides may also be sub-classified as aliphatic, aromatic (i.e. anilides or benzamides) or cyclic (lactams), based on the nature of the nitrogen substituents and overall structure. Aliphatic amides have simple hydrocarbon substituents (alkyl groups) while aromatic amides have at least aromatic ring substituent as shown in the example below. Lactams contain an amide group as part of a cyclic structure:
A variety of methods have been developed for the preparation of amides (similar to esters). Most of these methods involve reaction of an amine with an "activated carbonyl" compound (i.e. acid chloride), very similar to the method used to prepare esters:

The amide is an important functional group present in a number of types of drugs molecules (local anesthetics, antiarrhythmics, etc). It is also the key linking moiety in proteins and peptide drug products:

II. Amide Solubility

Amides contain carbonyl (C=O) and ether (N-C) dipoles arising from covalent bonding between electronegative oxygen and nitrogen atoms and electro-neutral carbon atoms. Primary and secondary amides also contain two- and one N-H dipoles, respectively. Because of the π-bonding arrangement of the carbonyl and the greater electronegativity of oxygen, the carbonyl (C=O) is a stronger dipole than the N-C dipole. The presence of a C=O dipole and, to a lesser extent a N-C dipole, allows amides to act as H-bond acceptors. In primary and secondary amides, the presence of N-H dipoles allows amides to function as H-bond donors as well. Thus amides can participate in hydrogen bonding with water and other protic solvents; the oxygen and nitrogen atoms can accept hydrogen bonds from water and the N-H hydrogen atoms can donate H-bonds. As a result of interactions such as these, the water solubility of amides is greater than that of corresponding
hydrocarbons as illustrated below:
While hydrogen bonding may enhance the water solubility of amides relative to hydrocarbons (alkanes, alkenes, alkynes and aromatic compounds), amides typically are regarded as compounds with low water solubility. They are significantly less water soluble than comparable acids or alcohols due to: 1). their non-ionic character (see acid-base section below), 2). the presence of non-polar hydrocarbon functionality, and 3). the inability of tertiary amides to donate hydrogen bonds to water (they can only be H-bond acceptors). Thus amides have water solubilities roughly comparable to esters (See Ester Tutorial). Typically amides are less soluble than comparable amines and carboxylic acids since these compounds can both donate and accept hydrogen bonds, and can ionize at appropriate pHs to further enhance solubility (See Carboxylic Acid and Amine Tutorial).

III. Reactivity of Amides

As discussed in the introductory section, amides may be viewed as amine derivatives where one nitrogen substituent is a carbonyl moiety. This structural modification produces a significant change in physicochemical properties of amides versus amines. Most importantly, amides are characterized by a "conjugated system" in which the NBEs of nitrogen can delocalized into the adjacent carbonyl (C=O) group. The strongly electron withdrawing nature of the carbonyl group by resonance (due to the presence of the double bond involving an electronegative oxygen atom) allows for delocalization of the NBEs of nitrogen as shown below:

The electron withdrawal created by this conjugated system limits the ability of the nitrogen atoms NBEs to coordinate with electrophiles. This delocalization also reduces the electrophilic nature of the carbonyl present in amides relative to carbonyl groups in compounds such as aldehydes and ketones. As a result of these electronic effects, amides have reactivity profiles that differ significantly from amines as discussed in more detail below.

A. Acid-Base Chemistry

Amides are considered to "non-basic" and "non-acidic" under physiologic conditions. As discussed above, the reduction in basicity observed for amides versus amines results from electron withdrawal by the amide carbonyl via resonance. Thus the NBEs of amides are not as readily shared with a proton as the NBEs of an amine and therefore amides are not considered to be basic:
Recall that in order for the resonance phenomenon to occur, the atoms involved in "sharing" electrons (the atoms over which the electrons are delocalized) must be able to adopt a coplanar conformation. In the case of amides this means that the N-C=O atoms must be capable of existing in the same plane so their $\pi$-orbitals can overlap to "share" electrons by delocalization:

Therefore, in amides where coplanarity is not possible, as in the beta-lactam antibiotics (penicillins), resonance stabilization cannot occur. In these compounds the bicyclic ring structure does not allow the amide N-C=O atoms to exist in the same plane. Thus resonance delocalization of nitrogens NBEs is not possible and these amides are more basic (and more reactive toward nucleophiles as discussed below) than 'typical' amides where coplanarity allows for resonance stabilization:
Amides are also considered to be "non-acidic". Secondary and tertiary amides are similar to carboxylic acids in that they have a proton attached to a "heteroatom", and the charge formed from loss of this proton (ionization to yield the conjugate base formation) could be stabilized by resonance as shown in the figure below. However, in spite of this common resonance stabilization, acids are substantially more acidic than amides. This difference is due to a difference in the electronic nature of the atoms over which the charge is formed and distributed. In the base form of acids, the charge is formed on oxygen and is delocalized over two oxygen atoms and the central carbon atom. In amides the charge is formed on nitrogen and it is distributed over an oxygen, a nitrogen and the central carbon atom. Since oxygen is significantly more electronegative than nitrogen, it is better able to stabilize negative charge. Thus, the greater number of oxygen atoms in carboxylic acids allows for greater stabilization of the conjugate base in acids versus amides. Naturally tertiary amides do not have a proton attached to the amide nitrogen and thus are not capable of ionization such as shown in the figure below:

It should be noted that while amides are considered to be non-acidic and non-basic under physiologic conditions, this functional group can be "protonated" (act as a base) or unprotonated (act as an acid) under more extreme chemical conditions. For example, in the presence of very
strong acid, amides may be at least partially protonated and, in the presence of very strong bases, an amide hydrogen may be removed. This reactivity under more extreme conditions is taken advantage of in reactions such as chemical hydrolysis and N-alkylation reactions:
B. Nucleophilic-Electrophilic Reactions and Hydrolysis

Because of the resonance delocalization of the NBEs in these compounds, amides are significantly less nucleophilic than amines, and generally less electrophilic than esters. Again, the low nucleophilicity of amides relative to amines is a result of the reduced availability of NBEs to coordinate with an electrophile. In the laboratory the nucleophilicity of primary and secondary amides can be enhanced by first promoting ionization with strong base as shown below. In its ionized form, amides are significantly more nucleophilic and can participate in displacement reactions:

The relatively low electrophilicity of amide carbonyl groups is reflected by their resistance to hydrolysis relative to functional groups such as esters. Recall that the presence of a carbonyl (C=O) and ether (O-C) dipole renders the "central" carbonyl carbon of an ester electron deficient; it is an electrophilic carbon atom. Thus the esters carbonyl carbon is susceptible to "attack" by electron rich atoms (nucleophiles) including the oxygen of water and the nucleophilic residues at the active sites of esterase enzymes. When in the presence of a nucleophile, an ester may undergo reaction leading to cleavage of the carbonyl carbon-ether bond as shown below and discussed in more detail in the Ester Tutorial.

Due to their electronic similarity to esters, amides can also undergo hydrolysis, but they are less susceptible to nucleophilic attack such as that involved in hydrolysis reactions, again due to resonance stabilization and the donating of nitrogen's NBEs to the carbonyl carbon. This delocalization has the effect of reducing the electrophilicity (reduce the partial positive charge) of the carbonyl carbon, and thereby reducing its ability to undergo attack by nucleophiles such as water or hydroxide in hydrolysis reactions:
Note the basic structural difference between an ester and amide at the site of reaction is a single atom! Amides have a nitrogen atom where esters have an (ether) oxygen. The difference in electrophilic and hydrolytic reactivity between amides and esters is directly related to the different electronic character of these atoms. Oxygen is more electronegative than nitrogen, thus it is less likely to donate its NBEs to the adjacent carbonyl. As a result, there is a lower degree of resonance delocalization through the ester carbonyl than there is in the amide carbonyl. This results in ester carbonyl carbons being relatively more electron deficient, or more electrophilic, than amide carbonyl carbons. This difference in carbonyl electrophilicity accounts for the difference in reactivity between esters and amides.

It is important to understand that amides do undergo hydrolysis! The difference is the "ease" or rate at which hydrolysis occurs. Amides undergo hydrolysis at a slower rate than structurally related esters under comparable reaction conditions. Consider the general example below. When placed in an aqueous alcohol solvent in the presence of base, the hydrolysis of the ester shown below may be complete in several hours. Under the same reaction conditions, it may take days (or longer) for the structurally similar amide to hydrolyzed!

Also, note the similarity in the reaction and reaction products. Both esters and amides yield an acid upon hydrolysis. The other hydrolytic product for an ester is an alcohol, and an amine for an amide.

Amide hydrolysis is also similar to ester hydrolysis in that the rates of hydrolysis reactions are influenced by electronic and steric factors. For example, amides in which the nitrogen atom is linked to an electron withdrawing group (by resonance or induction) undergo hydrolysis more readily than those that do not. This is due to destabilization of the C-N bond AND stabilization of the "amine" leaving group by the electron withdrawing functionality as illustrated below. Note that in the case of the "anilide" the nitrogen is linked to an aromatic ring which can "pull" electron electron density from this atom, weakening the amide C-N bond. This ring can also stabilize the leaving group be delocalization of electron pairs on nitrogen. As a result, the anilide is hydrolyzed more rapidly than the alkyl amide:
Also, sterically hindered amides may be hydrolyzed more slowly than unhindered amines, due to limited access by nucleophiles, particularly on the surfaces of enzymes. A more complete discussion of how electron and steric effects influence the rate of hydrolysis reactions is provided in the ester tutorial.

IV. The Chemistry of Functional Groups Related to Amides

There are a number of functional groups structurally related to amides (and esters) that are important constituents of drug molecules and biomacromolecules. Perhaps the most important of these are the carbamates, ureas, imides and sulfonamides. The structures and properties of each of these, relative to amides and other functional groups are summarized briefly below:

A. Carbamates

Carbamates may be viewed as "ester-amide" hybrid structures and they display chemical reactivity which is, at least, comparable to these functional groups. As amide-like structures, they do not behave as acids or bases over the normal pH range (1-14). This again, is due to delocalization of nitrogens NBEs into the carbonyl moiety. Carbamates, however, are more electrophilic than amides as a result of the presence of an additional electron-attracting "ether" oxygen atom. Thus carbamates undergo reactions such as hydrolysis more readily than amides. It is important to realize that the initial step of carbamate hydrolysis yields a carbonic acid derivative that can "decarboxylate". Therefore complete hydrolysis of a carbamate yields an alcohol product, an amine product and CO2:

\[
R-O-C-N^{\prime}\text{H}^+H_2O\longrightarrow R-O-H + CO_2 + H-N^{\prime}\text{R}^\text{''}
\]

Carbamate

Carbamates containing an "alkoxy" group which is a good leaving group (i.e., an electron withdrawing aromatic ring) are sufficiently reactive to spontaneously react with nucleophiles. Such is the case with the carbamate acetylcholinesterase (AChE) inhibitors that are capable of reacting with a nucleophile on AChE and "carbamylating" the enzyme (see Acetylcholine Chapters).
B. Ureas

The urea functionality may be viewed as "diamides" and has physico-chemical properties similar to amides. There are two nitrogen atoms in these structures, but the NBEs of each nitrogen atom are in conjugation with the adjacent carbonyl group. Thus ureas are regarded to be non-acids and non-bases. Their reactivity as electrophilic species in reactions such as hydrolysis is similar to that of amides. Ureas can hydrolyzed under more extreme conditions, to yield two amine components and CO₂ analogous to the products formed from carbamate hydrolysis:

\[
\text{Urea} \quad \xrightarrow{\text{H}^+} \quad \text{R} - \text{N} - \text{C} - \text{N} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{R} - \text{N} - \text{H} + \text{CO}_2 + \text{H} - \text{N} - \text{R}' - \text{R}''
\]

Acylated urea derivatives (acylureides) are found in a number of important drug compounds including the barbiturates and hydantoins, as well as the acylureidopenicillins. The acylureide group displays chemical reactivity very similar to that of ureas and amides:

C. Imides

Imides are "acylated" amide derivatives. The presence of the imide group increases water solubility due to its ability to act as both a H-bond donor, and acceptor if the imide nitrogen is unsubstituted (is an N-H). Unsubstituted imides (N-H) are significantly more acidic than amides (pKa 10), due largely to the ability of the charge in the conjugate being be stabilized over the entire O-C-N-C-O system by resonance as shown below. Of course, acidity is a property only of N-unsubstituted imides (those imides with an N-H)!

\[
\text{Imide} \quad \xrightarrow{\text{Base}} \quad \text{Imide conjugate base: Stabilized by resonance}
\]
Imides are similar to amides in their susceptibility to hydrolysis under acidic conditions. Under basic conditions, the susceptibility to hydrolysis depends upon whether the imide possesses and acidic proton. If an acidic proton is present the initial reaction with base would be proton abstraction which would produce an anion which is not susceptible to hydrolysis. If no acidic imide proton is present the imide is similar to the amide in its susceptibility to hydrolysis.

\[
\begin{align*}
\text{CH}_3\text{C} & \text{O} \\
\text{N} & \text{CH}_3 \\
\text{CH}_3\text{C} & \text{O} \\
\text{H}^+ & \text{H}_2\text{O} \\
\text{CH}_3\text{C} & \text{OH} \\
\text{H} & \text{N} & \text{CH}_3 \\
\text{CH}_3 & \text{C} & \text{O}
\end{align*}
\]

N-Substituted Imide

D. Sulfonamides

Sulfonamides are amide analogs in which the carbonyl moiety is replaced with an isosteric SO\(_2\) group. Like amides, sulfonamides may be classified as primary, secondary or tertiary depending on the degree of substitution on the sulfonamide nitrogen:

Primary Sulfonamide  Secondary Sulfonamide  Tertiary Sulfonamide

There are a number of drug classes containing the sulfonamide group including the sulfonamide antibacterials, some diuretics and the sulfonylurea hypoglycemics (more on these below and in the Antidiabetic Drug Tutorial).

Primary sulfonamides contain two hydrogen atoms on the sulfonyl group and secondary sulfonamides contain one hydrogen atom. These hydrogens are relatively acidic (pKa 10), again because the charge formed in the conjugate base can be stabilized by resonance. Sulfonamides display greater acidity than amides because the negative charge formed in the conjugate base can be stabilized over more electronegative atoms as shown by the following resonance structures:

\[
\begin{align*}
\text{CH}_3\text{C} & \text{O} \\
\text{N} & \text{CH}_3 \\
\text{CH}_3\text{C} & \text{O} \\
\text{H} \rightarrow \text{H} & \text{N} \leftarrow \text{H} \\
\text{CH}_3 & \text{C} & \text{O} \\
\end{align*}
\]

Also, sulfonamides with electron withdrawing groups on nitrogen, particularly electron withdrawing by resonance, can be significantly more acidic than the simple sulfonamide shown above, as illustrated by the sulfonamide antibacterial drugs:
Also, it is important to realize that tertiary sulfonamides are NOT acidic because they do not contain an "ionizable" proton (see structures on previous page).

Generally sulfonamides are relatively unreactive compounds. They can be hydrolyzed under relatively extreme conditions to the corresponding sulfonic acid and amine as shown below:

Also, although relatively unreactive as nucleophiles, similar to amides, primary and secondary sulfonamides can be converted to more nucleophilic anions upon treatment with strong bases, and these nucleophiles can participate in displacement reactions similar to ionized amides as shown below:
**Principles of Drug Action 1, Spring 2005, Amides**

**ESTERS AND AMIDES**

*What you should know*

**Basic Structures:**

- Ester: \( \text{O} \)
- Amide: \( \text{N} - \text{C} - \)

**Water Solubility**

- Generally esters and amides are H-bond acceptors (primary and secondary amides can also donate) and thus have water solubilities comparable to aldehydes and ketones, BUT lower than amines and acids (which can ionize and donate/accept H-bonds) or even alcohols (which can donate/accept H-bonds).

**Acidity/Basicity:** Amides and Esters are "non-acidic" and "non-basic" at physiologic pH. The nitrogen atom of amides is non-basic because its non-bonded electrons are withdrawn by resonance by the carbonyl (see chapter). Amides and esters, like all carbonyl compounds may have protons on the carbon alpha to the carbonyl that are weakly acidic (only removed by strong base), but these are LESS acidic than the acidic protons of sulfonic acids, carboxylic acids, phenols, etc:

- Alpha-protons weakly acidic, but less than other organic acids.

**Ester and Amide Hydrolysis:** Both esters and amides may hydrolyze in aqueous acid or aqueous basic, or in the surface of hydrolytic enzymes (esterases, amidases). Esters are hydrolyzed more readily than amides because the nitrogen atom of amides is a better electron donor by resonance and this decreases the reactivity of amide carbonyl to hydrolytic attack (see notes for details). Hydrolysis of esters yields the corresponding acid and alcohol fragments as shown below. Hydrolysis of amides yields the corresponding acid and amine fragment as shown below:

- Ester: \( \text{C} - \text{O} - \text{C} \) → \( \text{C} - \text{O} - \text{H} + \text{HO} - \text{C} \)
- Amide: \( \text{N} - \text{C} - \text{C} - \text{H} \) → \( \text{C} - \text{O} - \text{H} + \text{HN} - \text{C} - \text{H} \)

**The relative rates of hydrolysis of different esters or different amides is dependent on steric and electronic factors (over)**
**RELATIVE RATES OF HYDROLYSIS OF ESTERS AND AMIDES**

*Esters (less resonance stabilization of carbonyl by more electronegative oxygen) hydrolyze more readily than amides (more resonance stabilization of carbonyl by amide nitrogen which is less electronegative)*

**Electronic Effects:** Esters and amides with electron withdrawing group (by -I or -R) on the heteroatom (O or N) hydrolyze more readily (better leaving group)

**Steric Effects:** Steric bulk alpha to the carbonyl (example A) and to a lesser extent on the carbonyl next to the heterocatom (example B) slow the rate of hydrolysis of esters and amides by steric mechanisms!
V. Problems

1. Rank the compounds below in terms of their relative rates of hydrolysis in vivo (1 = most rapidly hydrolyzed, 4= most slowly hydrolyzed):

2. Which compound below is most water soluble? Why?

3. Show the products formed in the following reactions:
4. Show the products of the following acid/base reactions.

![Chemical structure 1]

5. Show all the products which result from carbamate hydrolysis of the following molecule.

![Chemical structure 2]