Review of Organic Functional Groups

Introduction to Medicinal Organic Chemistry

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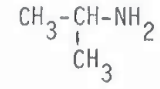
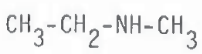
Amines

Two major functional groups still remain to be considered. These two groups, the carboxylic acids and the amines, are extremely important to medicinal chemistry and especially to the solubility nature of organic medicinals. In addition, the functional derivatives of these groups will be considered. In many instances the carboxylic acid or amine functional group is added to organic molecules with the specific purpose of promoting water solubility, since it is generally found that compounds showing little or no water solubility also are devoid of biologic activity.

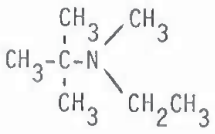
-Common (Alkylamine)



Isopropylamine (Primary amine)

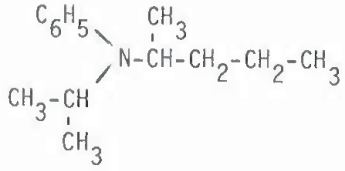


Ethylmethylamine (Secondary amine)



t-Butylethylmethylamine (Tertiary amine)

-IUPAC



N-Phenyl-N-(2-propyl)-2-aminopentane

N= substituent on the Nitrogen

A. Nomenclature. The common nomenclature for amines is illustrated on page 43. Inspection of this nomenclature reveals that the common names consist of the name of the alkyl or aryl radical, followed by the word amine. The examples given also show the different types of amines. The primary amine, isopropylamine, has a single substituent attached to the nitrogen; the secondary amine, methylethylamine, has two substituents attached to the nitrogen. The tertiary amine, t-butylmethylethylamine, has three groups attached directly to the nitrogen. As with all common nomenclatures, the system becomes nearly impossible to use as the branching of the alkyl groups increases, and the official nomenclature becomes necessary. In the IUPAC system, the amines are considered as substituted alkanes. The longest continuous alkyl chain containing the amine is identified and serves as the base name. The alkane chain is numbered in such a manner as to give the lowest possible number to the amine functional group, while the other substituents on the amine group are designated by use of a capital N before the name of the substituents. An example is given on page 43.

B. Physical-Chemical Properties. The amine functional group is probably one of the most common functional groups found in medicinal agents, and its value in the drug is twofold. One role is in solubilizing the drug either as the free base or as a water-soluble salt of the amine. The second role of the amine is to act as a binding site that holds the drug to a specific site in the body to produce the biologic activity. This latter role is beyond the scope of this book, but the former role contributes to an important physical property of the amine. First, let us again pose a question. What influence will the amine functional group have on solubility properties? While amines are polar compounds, they may not show high boiling points or good water solubility. One reason for this is that, in the tertiary amine, one does not find an electropositive group attached to the nitrogen. In the primary and secondary amines, one does have an electropositive hydrogen connected to the nitrogen, but the nitrogen is not as electronegative as oxygen, and the dipole is therefore weak. What all this means is that the amount of the intermolecular hydrogen bonding is minimal in primary and secondary amines and nonexistent in tertiary amines. This leads to relatively low-boiling liquids.

In considering water solubility, a different factor must be taken into account. The amine has an unshared pair of electrons, which leads to high electron density around the nitrogen. This high electron density promotes water solubility because hydrogen bonding between the hydrogen of water and the electron-dense nitrogen occurs. This is similar to the situation with low-molecular-weight

Table 10–1.
Boiling Points and Water Solubility of Common Amines

R_1	R_2	R_3	Boiling Point °C	Solubility (g/100g H_2O)
CH_3	H	H	-7.5	very soluble
CH_3	CH_3	H	7.5	very soluble
CH_3	CH_3	CH_3	3.0	91
C_2H_5	H	H	17.0	
C_2H_5	C_2H_5	H	55.0	very soluble
C_2H_5	C_2H_5	C_2H_5	89.0	14
C_6H_5	H	H	184.0	3.7
C_6H_5	CH_3	H	196.0	slightly soluble
C_6H_5	CH_3	CH_3	194	1.4

points and the solubility effects are shown in Table 10–1. Also illustrated in Table 10–1 is the effect on solubility of increasing the hydrocarbon portion. Primary amines tend to be more soluble than secondary amines, which are more soluble than tertiary amines. The amine can solubilize up to five or six methylenes, which, from a solubility standpoint, makes the amines equivalent to an alcohol.

An extremely important property of the amines is their basicity and ability to form salts. The Brønsted definition of a base is the ability of a compound to donate or share a pair of electrons. Amines have an unshared pair of electrons, which is more or less available for sharing. The statement "more or less" has to do with the strength of a base, and this is considered in Figure 10–1. The strength of a base is defined by its relative ability to donate its unshared pair of electrons. The more readily the electrons are donated, the stronger the base. Two factors influence the availability of the electrons. One of the factors is electronic, while the other is steric. To consider the former, if electron-donating groups are attached to the basic nitrogen, electrons are pushed into the nitrogen. Since a negative repels a negative, the electron pair on the nitrogen will be pushed out from the nitrogen, thus making them more readily available for donating.

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