Organic Functional Groups

Introduction to Medicinal Organic Chemistry

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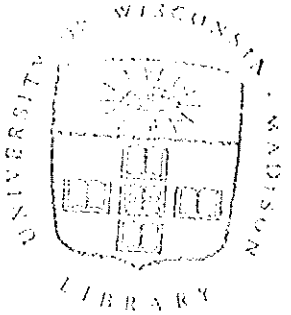

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16

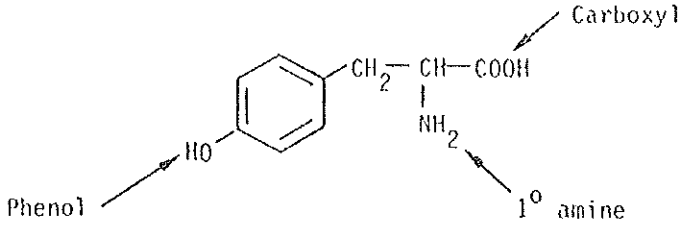
Predicting Water Solubility

1. EMPIRIC METHOD

We have now reviewed the major functional groups that might be expected in drug molecules. It will soon become obvious to you that the majority of the drugs discussed are not simple monofunctional molecules but instead are polyfunctional molecules. Most drugs will be found to contain two, three, four, or more of the organic functional groups within a single chemical entity. How then does one predict physical and chemical properties of these more complex molecules? As mentioned throughout the book, one must recognize the individual functional groups within the more complex structures. Once this is done, the chemical properties, namely, in vitro stability and in vivo stability, are easily predicted. The chemical properties of a functional group are usually not affected by the presence of another functional group within the molecule. Therefore, each functional group can be treated independently of the other functional groups present.

If we consider the important physical property of water solubility, it is found that polyfunctional molecules behave somewhat differently than monofunctional molecules. A simple summation of the water-solubilizing properties of each functional group will usually not lead to a successful prediction of water solubility for the more complex systems. When one looks at the water-solubilizing property of a single functional group, there is no possibility of intramolecular bonding, that is, bonding within the molecule, because no second functional group is present. On the other hand, with polyfunctional molecules, intramolecular bonding may become a significant interaction. With the individual functional groups, the solubilizing potential of the groups took into consideration intermolecular bonding. As an example, an alcohol functional group in a molecule such as hexanol binds to a second molecule of hexanol through dipole-

dipole bonding. This bonding must be broken in order to dissolve the hexanol in water. When one states that an alcohol functional group solubilizes approximately six carbon atoms, this statement took into consideration intermolecular bonding of this type. But what about the polyfunctional molecules? The intermolecular bonding between like functional groups can still occur, but now a new type of bonding is possible, the intramolecular bond. Bonding may occur between dissimilar functional groups, and these types of intermolecular and intramolecular bonding may be quite strong. In order for a molecule to dissolve in water, the intramolecular and intermolecular bonding must first be broken so that the water molecules can bond to the functional groups.



Tyrosine

Solubility in water 0.45 g/1000 ml @ 25°C

An excellent example of the importance of intramolecular bonding is seen with the amino acid tyrosine. This molecule has three functional groups present, a phenol, an amine, and a carboxylic acid. By a simple summation of the water-solubilizing potential of each functional group, one would predict that the phenol would solubilize 6 to 7 carbon atoms, the amine 6 to 7 carbon atoms, and the carboxyl 5 to 6 carbon atoms, giving a total solubilizing potential of 17 to 20 carbon atoms. Tyrosine contains 9 carbons, yet the molecule is soluble to the extent of 0.5%. The explanation for this lack of water solubility can be understood if one recognizes the possibility of intramolecular bonding. The amino acid can exist as a zwitterion (Fig. 16–1). The charged molecule exhibits intramolecular ion-ion bonding. As a result, this destroys the ability of these two functional groups to bond to water. The phenol is not capable by itself of dissolving the molecule. If the intramolecular bonding is destroyed by either adding sodium hydroxide or hydrochloric acid to the amino acid, the resulting compound becomes quite water soluble.

Although less dramatic, most functional groups are capable of showing some intra- and intermolecular hydrogen bonding, which decreases the potential for promoting water solubility. How much

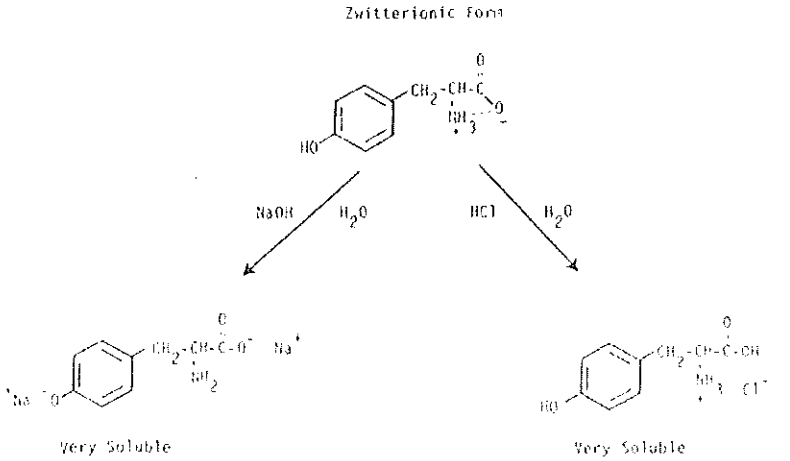


Fig. 16–1. Solubilization of tyrosine in aqueous base or aqueous acid

weight should be given to each such interaction for individual functional groups? This is a difficult question to answer, but as a general rule, if one is conservative in the amount of solubilizing potential that is given to each functional group, one will find that fairly accurate predictions can be made for polyfunctional molecules.

In Table 16–1, the various functional groups that have been discussed are listed with the solubilizing potential of each group when present in a monofunctional molecule and the solubilizing potential when present in a polyfunctional molecule. This latter value will be the more useful value, since most of the molecules that we discuss will be polyfunctional.

Several examples will help demonstrate this method of predicting water solubility. In the first molecule (Fig. 16–2), one should recognize the presence of two tertiary amines. If the more liberal solubilizing potential for an amine is used, it might be expected that each amine would have the capability of solubilizing up to 7 carbon atoms, leading to a total potential of dissolving 14 carbon atoms in the molecule. Since the molecule contains 13 carbon atoms, one would predict that the molecule would be soluble. Using the more conservative estimate and allowing 3 carbons worth of solubility to each amine, a prediction of insoluble would result. It turns out that the molecule is water soluble. The use of the more liberal estimate in order to obtain the correct results is acceptable in this case since the molecule contains only amines that act alike, not creating any new inter- and intramolecular bonds.

With *para*-dimethylaminobenzaldehyde (Fig. 16–2), a nine-carbon molecule, the liberal estimate would predict solubility, since

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