where the subscript, d, denotes the dissolution process, 2 represents the solute as the second component in the solution system, $\Delta\bar{H}_{\mathrm{d},2}$ is the partial molal enthalpy change for the solute, T denotes the absolute temperature at which dissolution occurs, and $\Delta\bar{S}_{\mathrm{d},2}$ is the partial molal entropy change for the solute. A negative free-energy change is the driving force for the dissolution process. Thus, an exothermic process promotes dissolution, and an endothermic process inhibits dissolution.

On the basis of the thermodynamic expression, the Gibb's free-energy change for mixing in solution can in turn be related to the activity of a solute at equilibrium as described by Equations 3.7 through 3.10 in Chapter 2 of this book, namely,

$$\Delta\bar{G}_{\mathrm{mix},2} = RT\ln a_2 \tag{3.2}$$

where a_2 is the activity of the solute in the solution.

It is clear from Equations 3.1 and 3.2 that the activity of the solute at equilibrium can be calculated if the free-energy change can be determined. Indeed, this approach has been taken by Hildebrand to develop regular solution theory (Hildebrand et al., 1970). In regular solution theory, the enthalpy of mixing was approximated using a geometric rule, while the entropy of mixing was simplified using the entropy of mixing in an ideal solution. These approximations limit the theory to solutions in which no specific interactions occur. When hydrogen bonding occurs in molecular interactions, the enthalpy of mixing will deviate from the geometric rule, and the entropy of mixing will be smaller than the random mixing in an ideal solution. Therefore, new methods accounting the effects of specific molecular interactions in a solution will be useful for the study of solubility.

Alternatively, the structure–solubility relationship estimates solubility using equations that relate solubility to the molecular structures of solutes. The structure–solubility relationship is generally regarded as an empirical method. There is no doubt that an exact theoretical method is preferred over an empirical method for the study of solubility phenomena. However, owing to the very complicated nature of molecular interactions and the various simplifications used in the development of mathematical models, exact thermodynamic approaches may not always provide accurate results without an extensive study of the compound of interest. At the present time, both theoretical and empirical approaches result in similar accuracy, and can be used equally well in the estimation of solubility.

In this chapter, new approaches developed in recent years for the prediction of solubility of organic compounds in solutions, both theoretical and empirical, will be discussed. It is intended to update readers on the methods for prediction of solubility and to provide tools for the design and study of new molecules in pharmaceutical research and development.

MOBILE ORDER THEORY

Taking the specific interactions in solution into consideration, Ruelle et al. (1991) have developed a comprehensive equation for the calculation of solubility of nonelectrolytes. This equation was called the mobile order theory. The equation was developed partly on the basis of the perpetual moving nature of molecules. According to this theory, each molecule of a particular species in a solution is presented the same mobile environment. Spatial orientations of molecules in solution change constantly. Molecular movement in the solution is random, and the entropy of mixing is the same as that of an ideal solution if there is no preferential molecular interaction in the system. When preferential interactions such as hydrogen bonding occur, molecular orientation and movement in the solution are not random. Consequently, the entropy of solution decreases as compared to that of an ideal solution. The change in entropy as a result of preferential intermolecular interaction is then used to account for solubility. In this approach, solubility in a nonpolar solution system is predicted in a way similar to regular solution theory, while solubility in solutions with polar interactions is treated with specific interaction constants. Thus, this approach provides more accurate results for the estimation of solubility.