**Ionic Strength**

In dilute solutions of nonelectrolytes, activities and concentrations are considered to be practically identical because electrostatic forces do not bring about deviations from ideal behavior in these solutions.

- **weak electrolytes** that are present alone in solution, the differences between the ionic concentration terms and activities are usually disregarded in ordinary calculations because the number of ions present is small and the electrostatic forces are negligible.
- **strong electrolytes** and for solutions of weak electrolytes together with salts and other electrolytes, such as exist in buffer systems, it is important to use activities instead of concentrations.

The activity coefficient, and hence the activity, can be obtained by using one of the forms of the Debye-Hückel equation. The concept of ionic strength, \( \mu \), to relate interionic attractions and activity coefficients. The ionic strength is defined on the molar scale as

\[
\mu = \frac{1}{2} (c_1 z_1^2 + c_2 z_2^2 + c_3 z_3^2 + \cdots + c_j z_j^2) \quad (6-55)
\]

or, in abbreviated notation,

\[
\mu = \frac{1}{2} \sum_{i} c_i z_i^2 \quad (6-56)
\]

where the summation symbol indicates that the product of \( c_i z_i^2 \) terms for all the ionic species in the solution, from the first one to the \( j \)th species, is to be added together.

- \( c_i \) is the concentration in moles/liter of any of the ions
- \( z_i \) is its valence. Ionic strengths represent the contribution to the electrostatic forces of the ions of all types. It depends on the total number of ionic charges and not on the specific properties of the salts present in the solution.

The mean ionic activity coefficients of electrolytes should be expressed at various ionic strengths instead of concentrations. Lewis showed the uniformity in activity coefficients when they are related to ionic strength:

a. The activity coefficient of a strong electrolyte is roughly constant in all dilute solutions of the same ionic strength, irrespective of the type of salts that are used to provide the additional ionic strength.
b. The activity coefficients of all strong electrolytes of a single class, for example, all uni-univalent electrolytes, are approximately the same at a definite ionic strength, provided the solutions are dilute.

The importance of the principle of ionic strength in biochemistry.
1- In the study of the influence of pH on biologic action, 2-the effect of the variable salt concentration in the buffer may obscure the results unless the buffer is adjusted to a constant ionic strength in each experiment.

The Debye-Hückel Theory

Debye and Hückel derived an equation based on the principles
1- strong electrolytes are completely ionized in dilute solution and that the deviations of electrolytic solutions from ideal behavior are due to the electrostatic effects of the oppositely charged ions.
2- The equation relates the activity coefficient of a particular ion or the mean ionic activity coefficient of an electrolyte to the valence of the ions, the ionic strength of the solution, and the characteristics of the solvent.

The equation can be used to calculate the activity coefficients of drugs whose values have not been obtained experimentally and are not available in the literature.

According to the theory of Debye and Hückel, the activity coefficient, \( \gamma_i \), of an ion of valence \( z_i \) is given by the expression

\[
\log \gamma_i = -Az_i^2 \sqrt{\mu} \quad (6-57)
\]

Equation (6-57) yields a satisfactory measure of the activity coefficient of an ion species up to an ionic strength, \( \mu \), of about 0.02. For water at 25°C, \( A \), a factor that depends only on the temperature and the dielectric constant of the medium, is approximately equal to 0.51. The values of \( A \) for various solvents of pharmaceutical importance are found in Tables.

The form of the Debye-Hückel equation for a binary electrolyte consisting of ions with valences of \( z_+ \) and \( z_- \) and present in a dilute solution (\( \mu < 0.02 \)) is

\[
\log \gamma_\pm = -Az_+z_- \sqrt{\mu} \quad (6-58)
\]
The symbols \( z_+ \) and \( z_- \) stand for the valences or charges, ignoring algebraic signs, on the ions of the electrolyte whose mean ionic activity coefficient is sought.

The coefficient in equation (6-58) should actually be \( \gamma_x \), the rational activity coefficient (i.e., \( \gamma^\pm \) on the mole fraction scale), but in dilute solutions for which the Debye-Hückel equation is applicable, \( \gamma_x \) can be assumed without serious error to be equal also to the practical coefficients, \( \gamma_m \) and \( \Lambda_c \), on the molal and molar scales.

The activity coefficient of a strong electrolyte in dilute solution depends on
1. the total ionic strength of the solution.
2. the valence of the ions of the drug involved.
3. the nature of the solvent,
4. the temperature of the solution.

The \( z_1 ; z_2 \) terms apply only to the drug whose activity coefficient is being determined.

**Extension of the Debye-Hückel Equation to Higher Concentrations**

The limiting expressions (6-57) and (6-58) are not satisfactory above an ionic strength of about 0.02, A formula that applies up to an ionic strength of perhaps 0.1 is

\[
\log \gamma^\pm = -\frac{Az_+z_-\sqrt{\mu}}{1 + a_iB\sqrt{\mu}} \quad (6-59)
\]

\( a_i \) is the mean distance of approach of the ions and is called the *mean effective ionic diameter* or the *ion size parameter*.

\( B \), like \( A \), is a constant influenced only by the nature of the solvent and the temperature.

Because \( a_i \) for most electrolytes equals 3 to 4 \( \times \) 10\(^{-8} \) and \( B \) for water at 25°C equals 0.33 \( \times \) 10\(^8 \), the product of \( a_i \) and \( B \) is approximately unity. Equation (6-59) then simplifies to

\[
\log \gamma^\pm = -\frac{Az_+z_-\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (6-60)
\]

In aqueous solution

Sodium chloride. Use equations (6-58) through (6-60) and compare the results. To account for the increase in \( \gamma^\pm \) at higher concentrations, an empirical term \( C\mu \) can be added to the Debye-Hückel equation, resulting in the expression

\[
\log \gamma^\pm = -\frac{Az_+z_-\sqrt{\mu}}{1 + a_iB\sqrt{\mu}} + C\mu \quad (6-61)
\]

Concentrations as high as 1 M

This equation gives satisfactory results in solutions of concentrations as high as 1 M. The mean ionic activity coefficient obtained from equation (6-61) is \( \gamma_x \); however, it is not significantly different from \( \gamma_m \) and \( \gamma_c \) even at this concentration.
**Coefficients for Expressing Colligative Properties**

**The L Value**

The van’t Hoff expression $\Delta T_f = iK_fm$ probably provides the best single equation for computing the colligative properties of nonelectrolytes, weak electrolytes, and strong electrolytes. It can be modified slightly for convenience in dilute solutions by substituting molar concentration $c$ and by writing $iK_f$ as $L$, so that

$$\Delta T_f = Lc$$

$L$ from experimental data for a number of drugs. It varies with the concentration of the solution. At a concentration of drug that is isotonic with body fluids, $L = iK_f$ is designated here as

- $L_{iso}$. It has a value equal to about 1.9 (actually 1.86) for nonelectrolytes.
- 2.0 for weak electrolytes, 3.4 for uni-univalent electrolytes, and larger values for electrolytes of high valences.

![Fig. 6-7. Liso values of various ionic classes.](image)

A plot of $iK_f$ against the concentration of some drugs is presented in Figure 6-7, where each curve is represented as a band to show the variability of the $L$ values within each ionic class. The approximate $L_{iso}$ for each of the ionic classes can be obtained from the dashed line running through the figure.
**Osmotic Coefficient**

Other methods of correcting for the deviations of electrolytes from ideal colligative behavior have been suggested. One of these is based on the fact that as the solution becomes more dilute, \( i \) approaches \( \nu \), the number of ions into which an electrolyte dissociates,

- at infinite dilution, \( i = \nu \), or \( i/\nu = 1 \).
- at more concentrated solutions, \( i/\nu \) becomes less (and sometimes greater) than unity.

The ratio \( i/\nu \) is designated as \( g \) and is known as the *practical osmotic coefficient* when expressed on a molal basis. In the case of a weak electrolyte, it provides a measure of the degree of dissociation.

- For strong electrolytes, \( g \) is equal to unity for complete dissociation, and the departure of \( g \) from unity, that is, \( 1 - g \),
- moderately concentrated solutions is an indication of the interionic attraction. Osmotic coefficients, \( g \)
- for electrolytes and nonelectrolytes are plotted against ionic concentration, \( \nu m \), in Figure 6-8. Because \( g = 1/\nu \) or \( i = g\nu \) in a dilute solution, the cryoscopic equation can be written as

\[
\Delta T_f = g\nu K_f m \quad (6-63)
\]

![Fig. 6-8. Osmotic coefficient, \( g \), for some common solutes.](image)

**Osmolality**

5
Osmotic pressure classically is given in atmospheres, in clinical practice it is expressed in terms of osmols (Osm) or milliosmols (mOsm).

A solution containing 1 mole (1 g molecular weight) of a nonionizable substance in 1 kg of water (a 1 m solution) is referred to as a 1-osmolal solution. It contains 1 osmol (Osm) or 1000 milliosmols (mOsm) of solute per kilogram of solvent.

Osmolality measures the total number of particles dissolved in 1 kg of water, that is, the osmols per kilogram of water, and depends on the electrolytic nature of the solute.

For an electrolyte that dissociates into ions in a dilute solution, osmolality or milliosmolality can be calculated from

\[
\text{Milliosmolality (mOsm/kg)} = i \cdot mm
\]

where \(i\) is approximately the number of ions formed per molecule and \(mm\) is the millimolal concentration.

If no ionic interactions occurred in a solution of sodium chloride, \(i\) would equal 2.0.

In a typical case, for a 1:1 electrolyte in dilute solution, \(i\) is approximately 1.86 rather than 2.0, owing to ionic interaction between the positively and negatively charged ions.

Osmolarity is used more frequently than osmolality in labeling parenteral solutions in the hospital. Yet, osmolarity cannot be measured and must be calculated from the experimentally determined osmolality of a solution.

\[
\text{Osmolarity} = (\text{Measured osmolality}) \times (\text{solution density in (g/ml-anhydrous solute conc.in g/ml)})
\]

Osmolality is converted to osmolarity using the equation

\[
\text{mOsm/liter solution} = \frac{\text{mOsm/(kg H}_2\text{O)}}{d_1^\circ (1 - 0.001 \bar{v}_2^\circ)}
\]

where \(d_1^\circ\) is the density of the solvent and \([\bar{v} \text{ with bar above}]^\circ\) is the partial molal volume of the solute at infinite dilution.

Osmolarity differs from osmolality by only 1% or 2%.

Whole blood, plasma, and serum are complex liquids consisting of proteins, glucose, nonproteins, nitrogenous materials, sodium, potassium, calcium, magnesium, chloride, and bicarbonate ions. The serum electrolytes, constituting less than 1% of the blood’s weight, determine the osmolality of the blood.
Sodium chloride contributes a milliosmolality of 275, whereas glucose and the other constituents together provide about 10 mOsm/kg to the blood.

Colligative properties such as freezing point depression are related to osmolality through equations (6-27) and (6-63):

\[ \Delta T_f \approx K_f i m \]  

(6-67)

where \( i = gv \) and \( im = gvm \) is osmolality.

Glucose is a nonelectrolyte, producing only one particle for each of its molecules in solution, and for a nonelectrolyte, \( i = \nu = 1\) and \( g = i/\nu = 1 \). Therefore, the freezing point depression of a 0.154 m solution of glucose is approximately

\[ \Delta T_f \approx K_f i m \]

The osmolality of a nonelectrolyte such as glucose is identical to its molal concentration because osmolality = \( i \times \) molality, and \( i \) for a nonelectrolyte is 1.00. The milliosmolality of a solution is 1000 times its osmolality or, in this case, 154 mOsm/kg.

Although the osmolality of blood and other body fluids is contributed mainly by the content of sodium chloride, the osmolality and milliosmolality of these complex solutions by convention are calculated on the basis of \( i \) for nonelectrolytes, that is, \( i \) is taken as unity, and osmolality becomes equal to molality.