Relationship between Osmolality and Osmolarity

W. H. STRENG ˣ, H. E. HUBER, and J. T. CARSTENSEN *

Received November 10, 1976, from *Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, OH 45215.* Accepted for publication June 23, 1977. *Present address: School of Pharmacy, University of Wisconsin, Madison, WI 53706.

Abstract □ Since the compendia require the osmolarity of certain parenterals to be labeled and since experimentally only the osmolality can be measured, it is necessary to obtain the relationship between these two quantities. This relationship was determined by considering fundamental physical-chemical definitions. The osmolality of a solution was found to be simply related to the osmotic coefficient. The conversion to osmolarity requires the use of the partial molal volume(s) of the solute(s). A single conversion factor is required for a particular solute system; *i.e.*, the conversion factor is independent of the solution concentration.

Keyphrases □ Osmolality—converted to osmolarity using partial molal volume of solute at infinite dilution □ Osmolarity—converted from osmolality using partial molal volume of solute at infinite dilution □ Physicochemical properties—solutions, osmolality converted to osmolarity using partial molal volume of solute at infinite dilution

According to USP XIX (1), labeling on sodium chloride injection must include the osmolarity of the solution. This requirement presents some difficulty since the quantity measured experimentally is the osmolality. Therefore, it is necessary to determine the relationship between osmolality and osmolarity to make the conversion. Clear and concise definitions showing the relationship between these two quantities are not readily available. However, common usage and consistency with the well-established definitions for molality and molarity require that the definition for osmolality be "that mass of solute which, when dissolved in 1 kg of water, will exert an osmotic pressure equal to that exerted by a gram-molecular weight of an ideal unionized substance dissolved in 1 kg of water," and that the definition for osmolarity be "that mass of solute which, when dissolved in 1 liter of solution, will exert an osmotic pressure equal to that exerted by a gram-molecular weight of an ideal unionized substance dissolved in 1 liter of solution."

Murty *et al.* (2) recently found that the conversion necessitated the measurement of the solution density. It will be shown in this paper that, instead, the partial molal volume of the solute at infinite dilution is needed.

DISCUSSION

Single-Solute System—The relationship between the osmotic pressure and solvent activity can be found in many texts (3–5). It is assumed in the derivation that the vapor pressure of the solvent behaves as an ideal gas and that the solution is incompressible. This relationship is:

$$\Pi\bar{v}_1 = RT\ln\frac{p_1^0}{p_1} = -RT\ln\frac{p_1}{p_1^0} = -RT\ln a_1 \qquad \text{(Eq. 1)}$$

where Π is the osmotic pressure; $\bar{v}_1$ is the partial molal volume of the solvent; R is the gas law constant; T is temperature in degrees Kelvin; p_1^0 and p_1 are the vapor pressure of the pure solvent and the solution, respectively; and a_1 is the solvent activity.

Solving for Π yields:

$$\Pi = -\frac{RT}{\bar{v}_1}\ln a_1 \qquad \text{(Eq. 2)}$$

Since, by definition (5):

$$\ln a_1 \equiv -\frac{\nu m W_1}{1000}\varphi \qquad \text{(Eq. 3)}$$

where m is the molality of the solution, W_1 is the molecular weight of the solvent, ν is the number of ions into which the solute dissociates, and φ is the osmotic coefficient, the osmotic pressure is related to the osmotic coefficient according to:

$$\Pi = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{\nu m W_1}{1000}\right\}\varphi \qquad \text{(Eq. 4)}$$

According to the definition, osmolality can be expressed as:

$$\xi_m = \frac{\Pi}{\epsilon_m} \qquad \text{(Eq. 5)}$$

where ξ_m is the osmolality and ϵ_m is the osmotic pressure exerted by a gram-molecular weight of an ideal unionized substance dissolved in 1 kg of water.

The value of ϵ_m can be calculated by substituting the following into Eq. 4:

$$m = \nu = \varphi = 1 \qquad \text{(Eq. 6)}$$

These substitutions can be made since the reference state is, by necessity, ideal and the substance is unionized.

Therefore:

$$\epsilon_m = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{W_1}{1000}\right\} \qquad \text{(Eq. 7)}$$

Inserting Eqs. 7 and 4 into Eq. 5 results in[1]:

$$\xi_m = \nu m\varphi \qquad \text{(Eq. 8)}$$

Similar to osmolality, osmolarity can be expressed as:

$$\xi_c = \frac{\Pi}{\epsilon_c} \qquad \text{(Eq. 9)}$$

where ξ_c is the osmolarity and ϵ_c is the osmotic pressure exerted by a gram-molecular weight of an ideal unionized substance dissolved in a total solution volume of 1 liter.

To evaluate Eq. 9, the osmotic pressure as given according to Eq. 4 must be expressed in terms of molarities:

$$\Pi = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{\nu W_1}{1000}\varphi\right\}\left\{\frac{c}{d - 0.001cW_2}\right\} \qquad \text{(Eq. 10)}$$

where c is the molarity of the solution, d is the density of the solution, and W_2 is the molecular weight of the solute.

The value for ϵ_c can then be determined by substituting the following into Eq. 10:

$$c = \nu = \varphi = 1 \qquad \text{(Eq. 11)}$$

These substitutions can be made since the reference state is ideal and the substance is unionized.

Therefore:

$$\epsilon_c = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{W_1}{1000}\right\}\left\{\frac{1}{d - 0.001cW_2}\right\} \qquad \text{(Eq. 12)}$$

The last term on the right in Eq. 12 can be simplified since the total volume, V_T, is:

$$V_T = n_1\bar{v}_1 + n_2\bar{v}_2 \qquad \text{(Eq. 13)}$$

where n_1 and n_2 are the numbers of moles of the solvent and the solute, respectively, and $\bar{v}_2$ is the partial molal volume of the solute. Then:

$$d - 0.001cW_2 = \frac{n_1W_1 + n_2W_2}{n_1\bar{v}_1 + n_2\bar{v}_2} - \frac{n_2W_2}{n_1\bar{v}_1 + n_2\bar{v}_2} \qquad \text{(Eq. 14)}$$

$$d - 0.001cW_2 = \frac{n_1W_1}{V_T} = \frac{wt_1}{V_T} = d_1 \qquad \text{(Eq. 15)}$$

[1] The osmolality should be expressed as $\xi_m = (\nu m\varphi)(\bar{v}_1^0/\bar{v}_1)$, where $\bar{v}_1^0/\bar{v}_1$ is the ratio of the partial molal volumes for the solvent at infinite dilution and in the solution. This ratio usually has a value close to one for the concentration ranges normally considered.

where wt_1 is the weight of the solvent in the reference solution and d_1 is the density of the solvent in the reference solution.

The determination of the solvent density in the reference solution can be made by utilizing the partial molal volumes at infinite dilution. Since the reference solution is ideal, the total volume in Eq. 13 can be expressed as (6):

$$V_T = n_1\bar{v}_1{}^0 + n_2\bar{v}_2{}^0 \qquad \text{(Eq. 16)}$$

where $\bar{v}_i{}^0$ is the partial molal volume at infinite dilution.

The densities of the solvent for the reference solution and at infinite dilution are given by Eqs. 17a and 17b, respectively:

$$d_1 = \frac{wt_1}{V_T} = \frac{n_1 W_1}{V_T} \qquad \text{(Eq. 17a)}$$

$$d_1{}^0 = \frac{wt_1{}^0}{V_T} = \frac{n_1{}^0 W_1}{V_T} \qquad \text{(Eq. 17b)}$$

With the same volume, V_T, the ratio of the densities equals:

$$\frac{d_1}{d_1{}^0} = \frac{wt_1}{wt_1{}^0} = \frac{n_1}{n_1{}^0} \qquad \text{(Eq. 18a)}$$

or:

$$d_1 = d_1{}^0 \frac{n_1}{n_1{}^0} \qquad \text{(Eq. 18b)}$$

It is possible to determine the value of n_1 in the reference state by rearranging Eq. 16 and realizing that n_2 is equal to one:

$$n_1 = \frac{V_T - \bar{v}_2{}^0}{\bar{v}_1{}^0} \qquad \text{(Eq. 19)}$$

Furthermore, at infinite dilution, n_2 equals zero and, therefore:

$$n_1{}^0 = \frac{V_T}{\bar{v}_1{}^0} \qquad \text{(Eq. 20)}$$

Combining Eqs. 19 and 20 with Eq. 18b results in:

$$d_1 = d_1{}^0 \left\{\frac{V_T - \bar{v}_2{}^0}{V_T}\right\} = d_1{}^0 \left\{1 - \frac{\bar{v}_2{}^0}{V_T}\right\} \qquad \text{(Eq. 21)}$$

Finally, since the molar concentration scale is being used, the total volume equals 1000 ml and Eq. 21 becomes:

$$d_1 = d_1{}^0(1 - 0.001\bar{v}_2{}^0) \qquad \text{(Eq. 22)}$$

Therefore, the ideal reference state osmotic pressure is equal to:

$$\epsilon_c = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{W_1}{1000}\right\}\left\{\frac{1}{d_1{}^0(1 - 0.001\bar{v}_2{}^0)}\right\} \qquad \text{(Eq. 23)}$$

Inserting Eqs. 23 and 10 into Eq. 9 results in:

$$\xi_c = \nu\varphi\left\{\frac{c}{d - 0.001cW_2}\right\}\{d_1{}^0(1 - 0.001\bar{v}_2{}^0)\} \qquad \text{(Eq. 24)}$$

or:

$$\xi_c = \nu m\varphi\{d_1{}^0(1 - 0.001\bar{v}_2{}^0)\} \qquad \text{(Eq. 25)}$$

Combining Eq. 8 with Eq. 25 results in the relationship between osmolarity and osmolality[2]:

$$\xi_c = \xi_m\{d_1{}^0(1 - 0.001\bar{v}_2{}^0)\} \qquad \text{(Eq. 26)}$$

The fact that the partial molal volume of the solute is included in Eq. 23 implies that the reference state is dependent on the compound. The conversion from osmolality to osmolarity does not require knowing the density of the solution but rather the density of the pure solvent and the partial molal volume of the solute at infinite dilution.

Multisolute System—Equation 26 is only applicable to two-component systems, *i.e.*, a solvent and one solute. If there is more than one solute, then the concentrations need to be replaced by summations over all solute species. The osmotic pressure expressed according to Eq. 4 then becomes:

$$\Pi = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{W_1\varphi}{1000}\right\}\left\{\sum_i \nu_i m_i\right\} \qquad \text{(Eq. 27)}$$

The osmolality is still expressed as given in Eq. 5, and the evaluation of ϵ_m remains the same since the conditions given in Eq. 6 are changed to:

$$\sum_i m_i = \nu_i = \varphi = 1 \qquad \text{(Eq. 28)}$$

Inserting Eqs. 7 and 27 into Eq. 5 results in[3]:

$$\xi_m = \sum_i \nu_i m_i \varphi \qquad \text{(Eq. 29)}$$

A similar approach to the osmolarity results in:

$$\Pi = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{W_1\varphi}{1000}\right\}\left\{\sum_i \frac{\nu_i c_i}{d - 0.001\sum_n c_n W_n}\right\} \qquad \text{(Eq. 30)}$$

In Eq. 30, the summation $\Sigma_n c_n W_n$ is the sum of the weights of all solute species per unit volume.

For multisolute systems, the reference state needs to be defined as having 1 mole of particles dissolved in 1 liter of solution. Expressing the reference state this way is identical to saying a gram-molecular weight of solute for the two-component system. Evaluation of the osmotic pressure for the reference state, ϵ_c, utilizes the condition:

$$\sum_i c_i = \nu_i = \varphi = 1 \qquad \text{(Eq. 31)}$$

for which Eq. 12 becomes:

$$\epsilon_c = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{W_1}{1000}\right\}\left\{\sum_i \frac{c_i}{d - 0.001\sum_n c_n W_n}\right\} \qquad \text{(Eq. 32)}$$

The last term on the right in Eq. 32 can be simplified since the total volume is:

$$V_T = n_1\bar{v}_1 + \sum_i n_i\bar{v}_i \qquad \text{(Eq. 33)}$$

where the summation is over all solute species; then:

$$d - 0.001\sum_n c_n W_n = \frac{n_1 W + \sum_i n_i W_i}{n_1\bar{v}_1 + \sum_i n_i\bar{v}_i} - \frac{\sum_i n_i W_i}{n_1\bar{v}_1 + \sum_i n_i\bar{v}_i} \qquad \text{(Eq. 34)}$$

$$d - 0.001\sum_n c_n W_n = \frac{n_1 W_1}{V_T} = \frac{wt_1}{V_T} = d_1 \qquad \text{(Eq. 35)}$$

The determination of the solvent density in the reference solution can be made by utilizing the partial molal volumes at infinite dilution. Since the reference solution is ideal, the total volume in Eq. 33 can be expressed as:

$$V_T = n_1\bar{v}_1{}^0 + \sum_i n_i\bar{v}_i{}^0 \qquad \text{(Eq. 36)}$$

As before, the densities of the solvent in the reference solution and at infinite dilution are related according to Eq. 18b. Evaluation of n_1 is somewhat more complex, giving:

$$n_1 = \frac{V_T - \sum_i n_i\bar{v}_i{}^0}{\bar{v}_1{}^0} \qquad \text{(Eq. 37)}$$

The infinite dilution value is expressed according to Eq. 20, and Eq. 21 becomes:

$$d_1 = d_1{}^0\left\{\frac{V_T - \sum_i n_i\bar{v}_i{}^0}{V_T}\right\} = d_1{}^0\left\{1 - \frac{\sum_i n_i\bar{v}_i{}^0}{V_T}\right\} \qquad \text{(Eq. 38)}$$

and since V_T = 1000 ml:

$$d_1 = d_1{}^0\left(1 - 0.001\sum_i n_i\bar{v}_i{}^0\right) \qquad \text{(Eq. 39)}$$

Therefore, the ideal reference state osmotic pressure is:

$$\epsilon_c = \left\{\frac{RT}{\bar{v}_1}\right\}\left\{\frac{W_1}{1000}\right\}\left\{\frac{1}{d_1{}^0\left(1 - 0.001\sum_i n_i\bar{v}_i{}^0\right)}\right\} \qquad \text{(Eq. 40)}$$

[2] As mentioned, the ratio $\bar{v}_1{}^0/\bar{v}_1$ has not been included in Eq. 8. This same ratio should be in Eqs. 24 and 25. Equation 26 is correct as written.

[3] The osmolality should be expressed as $\xi_m = \Sigma_i \nu_i m_i \varphi(\bar{v}_1{}^0/\bar{v}_1)$, in accordance with footnote 1.

Table I—Relationship between Osmolality and Osmolarity of Sodium Chloride Solutions

Weight-Volume Percent	Weight Percent	Molarity	Molality	φ	Π, atm	ξ_m, mOsm/kg	ξ_c, mOsm/liter
0.04	0.04	0.0064	0.0064	0.974	0.30	12.5	12.2
0.15	0.15	0.026	0.026	0.955	1.19	48.9	47.9
0.34	0.34	0.058	0.058	0.941	2.65	108	106
0.50	0.50	0.086	0.086	0.942	3.95	162	159
0.59	0.59	0.102	0.102	0.932	4.66	191	187
0.9	0.9	0.15	0.15	0.928	6.97	286	280
1.01	1.00	0.172	0.173	0.928	7.83	321	315
1.51	1.50	0.259	0.261	0.923	11.8	482	473
2.02	2.00	0.346	0.349	0.921	15.7	643	630
2.54	2.50	0.435	0.439	0.920	19.7	808	792
3.06	3.00	0.523	0.529	0.922	23.8	975	956
3.58	3.50	0.613	0.621	0.924	28.0	1150	1130
4.11	4.00	0.703	0.713	0.926	32.2	1320	1290
4.64	4.50	0.793	0.806	0.929	36.5	1500	1470
5.17	5.00	0.885	0.901	0.932	41.0	1680	1650
5.71	5.50	0.976	0.995	0.936	45.4	1860	1820

Substituting Eqs. 40 and 30 into Eq. 9 results in:

$$\xi_c = \varphi \left\{ \sum_i \frac{\nu_i c_i}{d - 0.001 \sum_n c_n W_n} \right\} \left\{ d_1{}^0 \left(1 - 0.001 \sum_i n_i \bar{v}_i{}^0 \right) \right\} \qquad \text{(Eq. 41)}$$

or:

$$\xi_c = \sum_i \nu_i m_i \varphi \left\{ d_1{}^0 \left(1 - 0.001 \sum_i n_i \bar{v}_i{}^0 \right) \right\} \qquad \text{(Eq. 42)}$$

Combining Eq. 29 with Eq. 42 results in the relationship between the osmolarity and osmolality of solutions having any number of solutes[4]:

$$\xi_c = \xi_m \left\{ d_1{}^0 \left(1 - 0.001 \sum_i n_i \bar{v}_i{}^0 \right) \right\} \qquad \text{(Eq. 43)}$$

The fact that the partial molal volumes of the solutes are included in Eq. 40 implies that the reference state using a molarity concentration scale is dependent on the composition of the solution. Equation 43 reduces to Eq. 26 when there is one solute since n_i then equals one. It should be reemphasized that the values for n_i used in Eq. 43 are the reference state values and not those for the actual solution being measured.

It is possible to select any number of states that will satisfy the conditions for the reference state in Eqs. 31 and 43 because the sum of the molar concentrations equals one in the reference state and nothing is specified concerning the individual concentrations. One possible reference state would maintain the same mole fractions of all solutes and adjust the weights so that the total concentration is one, as shown in Eq. 44:

$$wt_i = \left[\frac{\dfrac{wt_x}{W_x}}{\sum \dfrac{wt_n}{W_n}} \right] \{W_x \sum c_i\} = \frac{wt_x \sum c_i}{\sum \dfrac{wt_n}{W_n}} = \frac{wt_x}{\sum \dfrac{wt_n}{W_n}} \qquad \text{(Eq. 44)}$$

where:

wt_i = weight of solute in reference state

wt_x = weight of solute in sample solution

W_n, W_x = molecular weight of solute

$\sum \dfrac{wt_n}{W_n}$ = total number of moles in sample solution

$\sum c_i$ = 1 = total concentration in reference state

$\left[\dfrac{\dfrac{wt_x}{W_x}}{\sum \dfrac{wt_n}{W_n}} \right]$ = mole fraction of solute X in sample solution

[4] Similar to the single-solute system, the ratio $\bar{v}_1{}^0/\bar{v}_1$ has not been included in Eqs. 41 and 42. Equation 43 is correct as written.

Table II—Conversion Factors for Several Compounds

Salt	$\bar{v}_2{}^0$, ml/mole	$d_1{}^0(1 - 0.001\bar{v}_2{}^0)^a$
Potassium chloride[b]	26.74	0.97041
Potassium bromide[b]	33.97	0.96320
Potassium sulfate[b]	32.28	0.96488
Sodium chloride[c]	16.63	0.98049

[a] $d_1{}^0$ = 0.99707 g/ml at 25°. [b] Reference 10. [c] Reference 9.

The weights of each solute in the reference state can be calculated according to Eq. 44 and these weights can be inserted into Eq. 45:

$$n_i = \frac{wt_i}{W_i} \qquad \text{(Eq. 45)}$$

to find the number of moles that would then be inserted into Eq. 43. Whether this is the best reference state needs to be investigated.

CALCULATIONS

Table I gives the relationships between osmolality (milliosmoles per kilogram) and osmolarity (milliosmoles per liter) for sodium chloride solutions. This calculation utilized Eq. 26 for which the conversion factor $d_1{}^0(1 - 0.001\bar{v}_2{}^0)$ is equal to 0.9805. The data were obtained from Refs. 7–9, and the partial molal volume, $\bar{v}_2{}^0$, is equal to the apparent molal volume at infinite dilution. Table II lists the conversion factors for several compounds at 25°.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975.

(2) B. S. R. Murty, J. N. Kapoor, and P. P. DeLuca, *Am. J. Hosp. Pharm.*, **33,** 546 (1976).

(3) S. Glasstone and D. Lewis, "Elements of Physical Chemistry," 2nd ed., Van Nostrand, New York, N.Y., 1960, p. 252.

(4) G. N. Lewis, M. Randall, K. S. Pitzer, and L. Brewer, "Thermodynamics," 2nd ed., McGraw-Hill, New York, N.Y., 1961, p. 323.

(5) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd ed. (rev.), Butterworths, London, England, 1970, p. 30.

(6) G. N. Lewis, M. Randall, K. S. Pitzer, and L. Brewer, "Thermodynamics," 2nd ed., McGraw-Hill, New York, N.Y., 1961, p. 226.

(7) "CRC Handbook of Chemistry and Physics," 49th ed., Chemical Rubber Co., Cleveland, Ohio, 1968, p. D-174.

(8) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd ed. (rev.), Butterworths, London, Eng' .id, 1970, p. 483.

(9) G. N. Lewis, M. Randall, K. S ’itzer, and L. Brewer, "Thermodynamics," 2nd ed., McGraw-Hill, New York, N.Y., 1961, p. 205.

(10) H. E. Wirth, *J. Am. Chem. Soc.*, **59,** 2549 (1937).