ELSEVIER

Biophysical Chemistry 51 (1994) 263–269

Biophysical
Chemistry

Relation between volume correction and the standard state

B. Lee

Laboratory of Molecular Biology, Division of Cancer Biology, Diagnosis and Centers, National Cancer Institute,
National Institutes of Health, Bldg. 37, Rm. 4B15, Bethesda, MD 20892, USA

Received 18 December 1993; accepted 31 January 1994

Abstract

The suggestion by Sharp et al. (Biochemistry 30 (1991) 9686) that a volume correction should be made to the standard chemical potential of a non-polar solute molecule in water is examined by re-deriving their results using an exact statistical mechanical procedure and comparing them with those of a couple of other similar schemes. It is shown that their suggestion is equivalent to choosing a standard state based on the ideal gas behavior.

Key words: Volume correction; Standard state; Hydrophobicity

1. Introduction

In a recent article, Sharp et al. [1] argued that the expression for the 'unitary' free energy of transfer of a solute molecule into a dilute solution should include a volume correction term r, which is the ratio of the volume of the solute molecule to that of the solvent molecule. The same term appears in the Flory–Huggins theory of the entropy of polymer chain configurations [2–4] and in Hildebrand's free volume theory [5,6]. More recently, Lazaridis and Paulaitis [7] found that the same term appears in their expression for the partial molar entropy of a non-polar solute in water, which was derived entirely independently from the development of Sharp et al. or the other earlier theories.

Although the suggestion by Sharp et al. is controversial [8,9], the occurrence of the same term in these diverse theories requires an explanation. In this article, I suggest that the appearance of this term is related to the choice of the ideal gas as the reference.

2. Theory and results

Neglecting the internal and the orientational degrees of freedom for simplicity, write the canonical partition function of a binary mixture of N_1 and N_2 molecules in volume V at temperature T as

$$Q = \prod_i \frac{V^{N_i}}{N_i! \Lambda_i^{3N_i}} Z, \tag{1}$$

where

$$\Lambda_i = \frac{h}{\sqrt{2\pi m_i kT}} \tag{2}$$

SSDI 0301-4622(94)00047-N

and

$$Z = \left(1/V^{N_1+N_2}\right)\int e^{-U/kT}\,dX_1\,dX_2. \tag{3}$$

In these expressions, h and k are the Planck's and the Boltzmann's constants, respectively, U is the total potential energy of the system, and m_i and X_i are, respectively, the molecular weight and the position vector of all N_i molecules of species i. The Helmholtz free energy, A, can be written as a sum of two terms,

$$A = -kT\,\ln Q = A^{\bullet} + A', \tag{4}$$

where

$$A^{\bullet} \equiv -kT\,\ln Z, \tag{5}$$

which we will refer to as the 'standard' free energy and

$$A' \equiv -kT\,\ln(Q/Z), \tag{6}$$

which is the remainder. Using Sterling's approximation, this term becomes

$$A' = kT\sum N_i\left[\ln\left(\rho_i\Lambda_i^3\right) - 1\right], \tag{7}$$

where $\rho_i = N_i/V$ is the number density of species i. The 'standard' free energy $A^{\bullet}$ is the non-ideal part that goes to zero when U goes to zero. The ideal part A' is equal to the Helmholtz free energy of the system after the interaction U has been turned off under the constant volume condition.

The entropy can also be written as a sum of two terms,

$$S = -(\partial A/\partial T)_V = S^{\bullet} + S', \tag{8}$$

where

$$S^{\bullet} \equiv -(\partial A^{\bullet}/\partial T)_V \tag{9}$$

and

$$S' \equiv -(\partial A'/\partial T)_V = -k\sum N_i\left[\ln\left(\rho_i\Lambda_i^3\right) - 5/2\right]. \tag{10}$$

Although these expressions were derived using the canonical ensemble, the final expressions are true for any system in thermodynamic equilibrium, including those that are represented by an N–p–T ensemble, provided that the volume is now the equilibrium, average volume rather than the precise volume of the canonical ensemble. As clearly spelled out by, for example, Hill [10], this is because fluctuations about the mean value are so small for a macroscopic system that there is never any practical difference between the precise and the average values of a macroscopic variable. For example, Eq. (10) is the well-known Sackur–Tetrode equation for the translational entropy of an ideal gas [11] as applied to the mixture. The chemical potential of species 2, which we will consider to be the solute, is given by

$$\mu_2 = (\partial G/\partial N_2)_{T,p} = (\partial A/\partial N_2)_{T,V} = \mu_2^{\bullet} + \mu_2', \tag{11}$$

where

$$\mu_2^{\bullet} \equiv (\partial A^{\bullet}/\partial N_2)_{T,V} \tag{12}$$

and

$$\mu_2' \equiv (\partial A'/\partial N_2)_{T,V} = kT\,\ln\left(\rho_2\Lambda_2^3\right). \tag{13}$$

In these and most other partial derivatives in the rest of this paper, the number of solvent molecule, N_1, is kept constant, but the subscript N_1 on the partial derivatives is suppressed for the sake of notational simplicity. $\mu_2^{\bullet}$ is Ben-Naim's [12] pseudo-chemical potential and is equal to the work of inserting a single solute molecule at a fixed position in the liquid. μ_2' is what Ben-Naim [12] called the 'liberation' free energy and is equal to the free energy change when the solute molecule is released from the fixed position in the liquid.

Now consider the change in entropy upon addition of a solute molecule under the constant pressure. This entropy change can be derived in either of two ways: one could (a) first calculate the entropy and then take its derivative with respect to the number of solute molecules or (b) first calculate the chemical potential of the solute and then take its temperature derivative, i.e.

$$s_2 = \left(\frac{\partial S}{\partial N_2}\right)_{T,p} = -\left[\frac{\partial}{\partial N_2}\left(\frac{\partial G}{\partial T}\right)_{N_2,p}\right]_{T,p}$$
$$= -\left[\frac{\partial}{\partial T}\left(\frac{\partial G}{\partial N_2}\right)_{T,p}\right]_{N_2,p} = -\left(\frac{\partial \mu_2}{\partial T}\right)_{N_2,p}. \tag{14}$$

Using Eqs. (8), (9), and (10), procedure (a) gives

$$s_2 = s_2^{\bullet a} + s_2'^{a}, \tag{15}$$

where

$$S_2^{\bullet a} \equiv \left(\frac{\partial S^\bullet}{\partial N_2}\right)_{T,p} \tag{16}$$

and

$$s_2'^{a} \equiv \left(\frac{\partial S'}{\partial N_2}\right)_{T,p} = -k\left(\ln(\rho_2 \Lambda_2^3) - \frac{3}{2} - \frac{v_2}{v}\right) \tag{17}$$

where

$$v_2 \equiv \left(\frac{\partial V}{\partial N_2}\right)_{T,p} \tag{18}$$

is the partial molar volume of the solute species and

$$v \equiv \frac{V}{N_1 + N_2} \tag{19}$$

is the molar volume of the system. The v_2/v term in Eq. (17) arises from the differentiation of the system volume, V, which is in the denominator of ρ_i in Eq. (10). This term measures the entropy change due to the change in the volume of the system that occurs when a solute molecule is added under the constant pressure condition. Similarly, using Eqs. (11), (12), and (13), procedure (b) gives

$$s_2 = s_2^{\bullet b} + s_2'^{b}, \tag{20}$$

where

$$s_2^{\bullet b} \equiv -\left(\frac{\partial \mu_2^\bullet}{\partial T}\right)_{N_2,p} \tag{21}$$

and

$$s_2'^{b} \equiv -\left(\frac{\partial \mu_2'}{\partial T}\right)_{N_2,p} = -k\left[\ln(\rho_2 \Lambda_2^3) - \tfrac{3}{2} - \alpha T\right], \tag{22}$$

where

$$\alpha \equiv \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_p$$

is the thermal expansion coefficient of the system. The αT term in Eq. (22) is analogous to the v_2/v term in Eq. (17) in that it arises from the differentiation of V which is in the denominator of ρ_2 in Eq. (13). Unlike the v_2/v term, however, this term measures the entropic component of the 'liberation' free energy that is due to the non-zero *temperature*-dependence of the volume of the system.

Comparing Eqs. (17) and (22), it can be seen that the two procedures do not yield an identical result. If the system is an ideal gas mixture, $\alpha T = v_2/v = 1$ and the two results are the same. However, α of a dilute aqueous solution will be practically equal to that of the pure water, in which case $\alpha = 0.257$ per 1000°C [13] and $\alpha T \approx 0.077$ at room temperature, whereas v_2/v is much larger than unity for common non-polar molecules [1]. Since Eq. (14) holds, the total entropy change is the same whichever procedure is followed. This means that $s_2^{\bullet a}$ and $s_2^{\bullet b}$ are generally different also. Thus, the same total entropy is divided differently into the 'standard' part and the remainder by procedures (a) and (b).

The enthalpy change upon addition of a solute molecule under constant pressure can be obtained by the relation

$$h_2 = \mu_2 + Ts_2. \tag{23}$$

From (13), (17), and (22), one obtains

$$h_2'^{a} = kT\left(\frac{3}{2} + \frac{v_2}{v}\right) \tag{24}$$

and

$$h_2'^{b} = kT\left(\tfrac{3}{2} + \alpha T\right). \tag{25}$$

Since the αT and v_2/v terms appear in both the entropy and the enthalpy expressions, these are 'compensation' terms, i.e., they affect the standard state values of the entropy and enthalpy, but not that of the free energy.

The dissection scheme proposed by Sharp et al. [1] is similar, but not identical, to the procedure (a) above. In effect, they consider the process of inserting a solute molecule under constant pressure in three steps as follows (Fig. 1): (I) The solution with N_1 molecules of solvent and N_2 molecules of solute is converted into the ideal gas mixture by turning off the intermolecular poten-

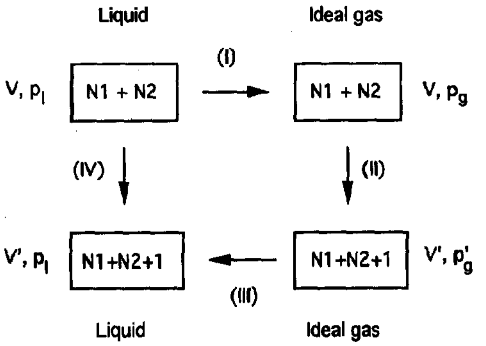

Fig. 1. The three-step decomposition of the solute insertion process according to Sharp et al. [1]. The original process (IV) is insertion of one solute molecule in a solution that consists of N_1 molecules of the solvent and N_2 molecules of the solute species (upper left box) under the constant pressure, p_l, resulting in a solution with N_1 and N_2+1 solvent and solute molecules, respectively (lower left box). The volume has increased from V to $V' = V + v_2$, where v_2 is the partial molar volume of the solute. The same process can be accomplished in three steps, (I), (II), and (III). In step (I) the interaction potential among all molecules is turned off under the constant volume condition. The resulting system (upper right box) is an ideal gas at a pressure p_g, which will be more than 1000 times p_l. Step (III) is defined as a reverse of step (I), except that it applies to the final solution of $N_1 + N_2 + 1$ molecule system. The pressure, $p_{g'}$, of the ideal gas system with $N_1 + N_2 + 1$ molecules (lower right box) is generally different from that with $N_1 + N_2$ molecules (upper right box). For example, if the solute is of larger size than the solvent, addition of a solute molecule reduces the number density of the system and the pressure drops. Step (II) is defined as the process of conversion between these two ideal gas systems.

tial under constant volume, V. (II) The number of molecules N_2 is increased by one and the volume of the system is increased to that of the final real solution, V'. Generally, the pressure of the system also changes by this operation since the composition of the mixture is changed. If the solute molecules are larger in size than the solvent molecules, the number density, and the pressure, will decrease. (III) Finally, the intermolecular potential is turned back on, again under the constant volume condition. The chemical potential and the partial molar entropy, enthalpy, and other thermodynamics quantities of the solute are again written as a sum of two terms; the 'standard' part which is the sum of the changes associated with steps (I) and (III) and the non-standard part which consists of the change in step (II).

In order to calculate the thermodynamic quantities associated with step (II), we proceed as follows. The Helmholtz free energy of the ideal gas species involved is given by Eq. (7). Since this system obeys the ideal gas law, $pV = kT\Sigma N_i$, the Gibbs free energy is given by

$$G' = A' + pV = kT \sum N_i \ln\left(\rho_i \Lambda_i^3\right). \tag{26}$$

The change in this free energy upon step (II) is

$$\begin{aligned} \mu_2'^{\mathrm{c}} &\equiv G'(N_1,\ N_2+1,\ V') - G'(N_1,N_2,V) \\ &= kT\left[(N_1+N_2)\ \ln\left(\frac{V}{V'}\right) + N_2\ \ln\left(\frac{N_2+1}{N_2}\right) \right. \\ &\quad \left. + \ln\left(\frac{N_2+1}{V'}\Lambda_2^3\right)\right] \\ &\approx kT\left(-\frac{v_2}{v} + 1 + \ln\left(\rho_2\Lambda_2^3\right)\right), \end{aligned} \tag{27}$$

where the superscript c indicates the dissection scheme of Sharp et al. In the last step of this derivation, we used the fact that $V' = V + v_2$ and assumed that $\ln(1 + v_2/V) \approx v_2/V$ and that $\ln(1 + 1/N_2) \approx 1/N_2$. Also, although $(N_2+1)/V'$ is the number density of the solute after the insertion, which is not identical to that before the insertion, we assume that the system is so large that addition of one solute molecule does not appreciably change the bulk property of the solution. The entropy of the ideal gas species in this scheme is still given by Eq. (10). The change in entropy upon step (II) is, therefore,

$$\begin{aligned} s_2'^{\mathrm{c}} &\equiv S'(N_1,N_2+1,V') - S'(N_1,N_2,V) \\ &= -k\left[(N_1+N_2)\ln\left(\frac{V}{V'}\right) + N_2\ \ln\left(\frac{N_2+1}{N_2}\right) \right. \\ &\quad \left. + \ln\left(\frac{N_2+1}{V'}\Lambda_2^3\right) - \frac{5}{2}\right] \\ &\approx -k\left(-\frac{v_2}{v} + 1 + \ln\left(\rho_2\Lambda_2^3\right) - \frac{5}{2}\right). \end{aligned} \tag{28}$$

The enthalpy change is then given by

$$h_2'^{\mathrm{c}} \equiv \mu_2'^{\mathrm{c}} + Ts_2'^{\mathrm{c}} = (5/2)kT. \tag{29}$$

The expression for the entropy change, Eq. (28), is identical to that for procedure (a) given in Eq. (17). However, the v_2/v term is not a compensation term in this dissection scheme since it appears in the expression for the free energy change.

3. Discussion

In the previous section, three similar but different ways of defining the standard state quantities were described. Scheme (a) is theoretically the most straightforward. The v_2/v term appears in the entropy expression, Eq. (17), of this scheme for the same reason as it does in the partial molar entropy expression of Lazaridis and Paulaitis [7]. Scheme (b) is the one advocated by Ben-Naim [12]. Scheme (c) is that proposed by Sharp et al. [1] and has the v_2/v term appear in the free energy expression, Eq. (27), as well as in the entropy.

Which of these schemes should one use? In considering this question, we note first that the volume correction term v_2/v, or the analogous αkT term in scheme (b), does not affect the total entropy or the total free energy – it only affects the dissection scheme by which the same total is divided into the 'standard' part and the rest. Therefore, to the extent that the choice of the standard state is equivocal and ultimately a matter of convention and standardization, the debate as to whether the volume correction term should be included in the standard thermodynamic quantities must be settled, not in terms of being correct or incorrect, but in terms of the convenience and usefulness of the 'standard' quantities that result from a particular dissection scheme.

The dissection scheme given by the Eqs. (4) to (7) is natural from the theoretical point of view since it separates out the part that depends on the interaction energy U, and therefore difficult to compute, from the remainder, which is easy to compute. The part that is easy to compute happens to be the free energy of the ideal gas since it lacks the interaction energy term. Thus, a more physical interpretation for the dissection scheme defined by the Eqs. (4) to (7) is that the non-standard part represents the free energy of the associated ideal gas system and that the standard part is the difference between the real and ideal free energies. The dissection of entropy given by Eqs. (8) to (10) is consistent with the free energy dissection and can be given similar ideal gas interpretation. It can be noted that the volume correction term v_2/v appears explicitly in the partial molar entropy expression in schemes (a) and (c), because both of these procedures start from the ideal gas entropy expression, Eq. (10).

In such an ideal gas-based dissection scheme, it is obviously important to precisely specify the procedure by which the associated ideal gas system is obtained. According to Eqs. (4) to (7), the associated ideal gas is defined for each system as that which results when the interaction energy U is turned off under the constant volume condition. This definition makes this ideal gas system to behave slightly differently from an ordinary ideal gas, particularly with respect to an increase in N_2. For example, when N_2 is increased by one under the constant temperature and pressure, the Gibbs free energy of an ordinary ideal gas mixture increases by μ' given by Eq. (13). However, the change in N_2 of the ideal gas associated with a real system generally does not occur under the constant pressure; it occurs according to Fig. 1, which requires that the pressure (as well as the volume) of the gas change unless it is associated with a pure liquid. Therefore, the free energy change under constant pressure is not relevant for this system. The relevant free energy change, one that is consistent with the definition of the associated ideal gas as implied by the dissection scheme of Eqs. (4) to (7), is in fact given by Eq. (27). Thus, if the standard state is to be chosen on the basis of the ideal gas behavior, one must chose the procedure of Sharp et al. [1] and include the volume correction term in the chemical potential as in Eq. (27).

On the other hand, Ben-Naim [12] showed that the dissection scheme of Eqs. (11) to (13) can be interpreted in a totally different way, without using the notion of the ideal gas at all. Thus, Ben-Naim considers dissolving a solute molecule in two actual, non-ideal steps. In the first step, the solute molecule is inserted at a fixed point in the solution. The second step consists of releasing this solute molecule into the bulk of the solution. He then demonstrated that the work of the first step is given exactly by $\mu_2^\bullet$ of Eq. (12) and the work of the second step by μ'_2 of Eq. (13). Thus, Ben-Naim's dissection scheme corresponds to the dissection of the insertion process into two real (non-ideal) processes. Since what is dissected is the insertion process, the first quantity dissected is the *change* in free energy upon the insertion process. Total quantities are not dissected and quantities such as $A^\bullet$, A', $S^\bullet$, and S' do not have much physical meaning in this dissection scheme. The enthalpy and entropy changes associated with each of these two steps must be obtained by the temperature-dependence of the respective μ_2's.

Although procedure (a) appears to be the most straightforward, above analysis indicates that it is in fact the least physically meaningful. We therefore compare only the procedures (b) and (c) in the following. Comparing Eqs. (22) and (28), since v_2/v is larger than αT (see the previous section), procedure (c) assigns larger values to the non-standard part of the entropy than procedure (b). This is understandable since entropy should increase more when a new particle is released into an ideal gas system than into the real (crowded) liquid. The standard entropy change is correspondingly smaller when the dissection scheme (c) is used than when (b) is used. Comparison of the enthalpy changes is also illuminating. The $(3/2)kT$ portion of the enthalpy changes given in Eqs. (25) and (29) is the translational energy of the newly released particle. The remainder is the pV change, which is equal to αTkT in both procedures. The difference is that α is the thermal expansion coefficient of the real solution in (b) whereas it is for the ideal gas in (c), in which case $\alpha = 1/T$. Again, since $\alpha T \approx 0.076$ for the dilute aqueous solutions at room temperature, the non-standard part is larger in (c) than in (b) and the standard part is correspondingly smaller in (c) than in (b). The difference in the free energies, as given by Eqs. (13) and (27), is given by the difference between these two effects (enthalpy minus entropy). Since v_2/v is larger than unity for most solute species of interest, the non-standard part is smaller, and the standard part larger, when procedure (c) is used than when (b) is used. Thus the increased hydrophobicity in the case of the dissection scheme (c), as indicated by the larger value of $\mu^\bullet$, is due to the v_2/v term, which in turn originates from the fact that the reference procedure in this dissection scheme is the insertion of the solute into an ideal gas, rather than into the (crowded) real solution.

Because of the large differences that exist between an ideal gas and a real liquid, use of the ideal gas behavior as the reference can be misleading, except in certain special situations such as the polymer theory of Flory–Huggins. For example, it is easy to assume that the ideal gas entropy given by Eq. (17), with or without the v_2/v term, represents the translational entropy of a species in the system. However, the translational entropy of a real system clearly depends on the interaction energy among the molecules and is not given by a formula that applies to the ideal gas. In the case of the pure hard sphere liquid that obeys the equation of state by Carnahan and Starling [14], it can be shown (unpublished result) that the molar entropy of the real system is less than that of the ideal gas of the same molar density and temperature by

$$\Delta S = R\left[\xi(4-3\xi)/(1-\xi)^2\right], \tag{30}$$

where R is the gas constant and ξ is the volume packing density defined as $(\pi/6)d^3\rho$ where d is the diameter of the hard spheres and ρ is the number density of the liquid. The value of the term in the square brackets in Eq. (30) is 5.4 when ξ is 0.517, which is the estimated volume packing density for cyclohexane [15], and 2.6 when ξ is 0.363, the corresponding value for water [15].

Acknowledgement

I thank Professor M. Paulaitis for making his article available before publication and for many useful discussions.

References

[1] K.A. Sharp, A. Nicholls, R. Friedman and B. Honig, Biochemistry 30 (1991) 9686.

[2] P.J. Flory, J. Chem. Phys. 9 (1941) 660.
[3] M.L. Huggins, J. Chem. Phys. 9 (1941) 440.
[4] P.J. Flory, Principles of polymer chemistry (Cornell Univ. Press, Ithaca, 1953).
[5] J.H. Hildebrand, J. Chem. Phys. 15 (1947) 225.
[6] J.H. Hildebrand and R.L. Scott, Regular solutions (Prentice-Hall, Englewood Cliffs, 1962).
[7] T. Lazaridis and M.E. Paulaitis, J. Phys. Chem. 97 (1993) 5789.
[8] A. Holtzer, Biopolymers 32 (1992) 711.
[9] A. Ben-Naim and R.M. Mazo, J. Phys. Chem. 97 (1993) 10829.
[10] T.L. Hill, An introduction to statistical thermodynamics (Addison-Wesley, Reading, 1960).
[11] F.T. Wall, Chemical thermodynamics, 3rd Ed. (Freeman, San Francisco, 1974).
[12] A. Ben-Naim, J. Phys. Chem. 82 (1978) 792.
[13] G.S. Kell, in: CRC handbook of chemistry and physics, 50th Ed. (Chemical Rubber Company, Cleveland, 1969) p. F-5.
[14] N.F. Carnahan and K.E. Starling, J. Chem. Phys. 51 (1969) 635.
[15] B. Lee, Biopolymers 24 (1985) 813.

Discussion to the paper by B. Lee

Comments

By A. Ben-Naim

(1) "The debate as to whether the volume correction term should be included in the standard quantities must be settled not in terms of it being correct or incorrect but in terms of the convenience and usefulness…"

In my opinion this is not the issue. One can, of course, chose different standard states for convenience or usefulness. However, the "volume correction" suggested by Sharp et al., was added to a specific definition of the solvation Gibbs energy. As such their "corrected" solvation Gibbs energies are simply incorrect.

By M.E. Paulaitis

If the solute is present at infinite dilution, then the thermal expansion coefficient in Eq. (22) is the thermal expansion coefficient for pure water, and the αT term in this equation will not depend on properties of the solute. In contrast, the infinite-dilution partial molar volume in Eq. (17) depends on both the isothermal compressibility of pure water as well as solute–water pair correlations, as given by the Kirkwood–Buff expression, and therefore does depend on solute properties. However, as you point out, the v_2/v term in Eq. (17) accounts for the entropy change associated with the one particle or "liberation" entropy of the solute (i.e. $-k \ln \rho\Lambda^2$) due to the volume change for solvation. Therefore, I conclude that neither of these terms would correspond to that part of the free energy of solute transfer that Honig and co-workers hypothesize depends on the molar volumes of the solute and solvent, and can be separated from a contribution that depends on the accessible surface area of the solute. In other words, your analysis does not appear to explain the basic, general hypothesis of Honig and co-workers; i.e. that there exists separable volume and surface area contributions to transfer free energies for hydrophobic solutes. Please comment.

Responses by B.K. Lee to Comments

To A. Ben-Naim

I do not believe that Sharp et al. [1] ever defined the term "solvation Gibbs free energy" precisely. But, perhaps the authors of Sharp et al. [1] can better reply to this comment.

To M.E. Paulaitis

I believe that the basis for suggesting that there is a volume term in the expression for the transfer free energy, at least according to ref. [1], is essentially the one given by Eq. (28), i.e. Sharp et al. did not propose anything more or less than the volume term in Eq. (28). It is possible that they implied more than this in other publications, but not in ref. [1]. Perhaps Dr. K. Sharp and/or Dr. B. Honig can comment further on this.