The Kirkwood–Buff Theory of Solutions and the Local Composition of Liquid Mixtures

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The present paper is devoted to the local composition of liquid mixtures calculated in the framework of the Kirkwood–Buff theory of solutions. A new method is suggested to calculate the excess (or deficit) number of various molecules around a selected (central) molecule in binary and multicomponent liquid mixtures in terms of measurable macroscopic thermodynamic quantities, such as the derivatives of the chemical potentials with respect to concentrations, the isothermal compressibility, and the partial molar volumes. This method accounts for an inaccessible volume due to the presence of a central molecule and is applied to binary and ternary mixtures. For the ideal binary mixture it is shown that because of the difference in the volumes of the pure components there is an excess (or deficit) number of different molecules around a central molecule. The excess (or deficit) becomes zero when the components of the ideal binary mixture have the same volume. The new method is also applied to methanol + water and 2-propanol + water mixtures. In the case of the 2-propanol + water mixture, the new method, in contrast to the other ones, indicates that clusters dominated by 2-propanol disappear at high alcohol mole fractions, in agreement with experimental observations. Finally, it is shown that the application of the new procedure to the ternary mixture water/protein/cosolvent at infinite dilution of the protein led to almost the same results as the methods involving a reference state.

1. Introduction

The Kirkwood–Buff (KB) theory of solution[1] (often called fluctuation theory) employs the grand canonical ensemble to relate macroscopic properties, such as the derivatives of the chemical potentials with respect to concentrations, the isothermal compressibility, and the partial molar volumes, to microscopic properties in the form of spatial integrals involving the radial distribution function. This theory allows one to obtain information regarding some microscopic characteristics of multicomponent mixtures from measurable macroscopic thermodynamic quantities. However, despite its attractiveness, the KB theory was rarely used[2–4] in the first three decades after its publication for two main reasons: (1) the lack of precise data (in particular regarding the composition dependence of the chemical potentials) and (2) the difficulty to interpret the results obtained. Only after Ben-Naim indicated how to calculate numerically the Kirkwood–Buff integrals (KBIs) for binary systems[5] was this theory used more frequently.

So far the KBIs have been calculated for numerous binary systems,[6–17] and the results were used to examine the solution behavior with regard to (1) local composition, (2) various models for phase equilibrium, (3) preferential solvation, and others.[6–22] One should also mention the use of the KB theory for supercritical fluids and mixtures containing supercritical components[23–27] and for biochemical issues such as the behavior of a protein in aqueous mixed solvents.[28–38]

The present paper is focused on the application of the KB theory to the local composition. The key quantity related to the local composition in the KB theory is the excess (or deficit) number of molecules around a central molecule. The conventional method of calculating the excess (or deficit) number of molecules around a central molecule was developed by Ben-Naim.[3,5,18–19,39–40] Let us consider a binary mixture 1–2. The excess (or deficit) number of molecules i ($i = 1, 2$) around a central molecule j ($j = 1, 2$) was defined by Ben-Naim as[3,5,18–19,39–40]

$$\Delta n_{ij}^{\text{BN}} = c_i G_{ij} \tag{1}$$

where c_i is the molar concentration of species i in the mixture and G_{ij} is the Kirkwood–Buff integral defined as (analytical expressions for the KBIs in a binary mixture are given in the Appendix)

$$G_{ij} = \int_0^\infty (g_{ij} - 1)4\pi r^2 \, dr \qquad i, j = 1, 2 \tag{2}$$

where g_{ij} is the radial distribution function between species i and j and r is the distance between the centers of molecules i and j.

However, the following objections can be brought to the use of eq 1 for calculating the excess (or deficit) number of molecules around a central molecule. A first objection (1) is that there are many systems for which all the KBIs (G_{11}, G_{12}, and G_{22}) are negative at least in certain ranges of composition.[22,41] As a result, in such cases all $\Delta n_{ij}^{\text{BN}}$ calculated with eq 1 ($\Delta n_{11}^{\text{BN}}$ and $\Delta n_{21}^{\text{BN}}$ around the central molecule 1 and $\Delta n_{12}^{\text{BN}}$ and $\Delta n_{22}^{\text{BN}}$ around the central molecule 2) would be negative, and this is not plausible because then the density around any molecule in liquid will become lower than that in the bulk. A second objection examined in detail in the next section is that (2) eq 1 does not provide the true excess.

Two other methods to calculate the excess (or deficit) number of molecules around a central molecule have been suggested

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which are based on a reference state. Matteoli and Lepori[10,11] observed that the excesses (or deficits) calculated with eq 1 provide nonzero values for ideal binary mixtures and expressed the opinion that they (the excesses (or deficits)) should be in that case equal to zero. For this reason they proposed that the excess (or deficit) number of molecules around a central molecule should be calculated with respect to a reference state (the ideal binary mixture)

$$\Delta n_{ij}^{ML} = c_i(G_{ij} - G_{ij}^{id}) \tag{3}$$

where G_{ij}^{id} is the Kirkwood–Buff integral for an ideal binary mixture (expressions for G_{ij}^{id} are given in the Appendix). In addition, Matteoli and Lepori[10,11] introduced what could be called the volume conservation condition, which for a binary mixture can be formulated as follows: "the volume occupied by the excess of i molecules around a j molecule must be equal to the volume left free by the j molecules around the same j molecule". One can show that the excesses and deficits calculated using the ideal mixture as reference state do not satisfy the above volume conservation condition. For this reason, a new reference state was suggested by Shulgin and Ruckenstein[12] in which all the activity coefficients were taken as equal to unity and no constraints on the partial molar volumes of the components were imposed. This reference state satisfies the volume conservation condition and provides as that of Matteoli and Lepori[10,11] zero excesses for ideal mixtures for both binary and ternary mixtures.[12,42] The excess (or deficit) number of molecules around a central molecule can be obtained using the expression

$$\Delta n_{ij}^{SR} = c_i(G_{ij} - G_{ij}^{SR}) \tag{4}$$

where G_{ij}^{SR} is the KBI calculated for the reference state suggested by Shulgin and Ruckenstein[12] (expressions for G_{ij}^{SR} can also be found in the Appendix).

However, there is a basic issue regarding the suggested reference states (Matteoli–Lepori and Shulgin–Ruckenstein): Is the excess (or deficit) number of molecules around a central molecule equal to zero in ideal mixtures? The considerations of the above authors imply that the distribution of components in an ideal mixture is random and therefore all excess (or deficit) number of molecules around a central molecule should be zero. However, because the volumes of the components are different, there is no absolute randomness. A new treatment is suggested below, which accounts for a volume which is not accessible to the molecules surrounding a central molecule and which reveals that for ideal mixtures the excesses (or deficits) are not zero. The inaccessible volume thus introduced could be considered a kind of reference state which, however, does not correspond to an ideal mixture.

2. A New Procedure to Calculate the Excess (Or Deficit) Number of Molecules around a Central Molecule

The average number of molecules i (n_{ij}) in a sphere of radius R around central molecules j can be calculated using the expression[40,43]

$$n_{ij} = c_i\int_o^R g_{ij} 4\pi r^2 \, dr \qquad i, j = 1, 2 \tag{5}$$

which can be recast in the form

$$n_{ij} = c_i\int_0^R (g_{ij} - 1)4\pi r^2 \, dr + c_i\int_0^R 4\pi r^2 \, dr \tag{6}$$

As soon as R becomes large enough for $g_{ij} \approx 1$, eq 6 can be rewritten as[18–19,40]

$$n_{ij} = c_i\int_0^\infty (g_{ij} - 1)4\pi r^2 \, dr + c_i\int_0^R 4\pi r^2 \, dr =$$
$$c_i G_{ij} + \frac{c_i 4\pi R^3}{3} \tag{7}$$

The difference between n_{ij} and $c_i 4\pi R^3/3$ was considered as the average excess (or deficit) number of molecules i ($i = 1, 2$) around a central molecule j ($j = 1, 2$), and eq 1 was thus obtained.[3,5,18–19,39–40]

However, the term $c_i 4\pi R^3/3$ includes molecules i assumed to be located in a volume inaccessible to them because of the presence of the central molecule j. Therefore, when the average excess (or deficit) number of molecules i ($i = 1, 2$) around a central molecule j is calculated, those i molecules should be subtracted from $c_i 4\pi R^3/3$, and the second integral in the right-hand side of eq 6 should be subdivided into two parts

$$n_{ij} = c_i\int_0^R (g_{ij} - 1)4\pi r^2 \, dr + c_i\int_{R_j}^R 4\pi r^2 \, dr + c_i\int_0^{R_j} 4\pi r^2 \, dr \tag{8}$$

where R_j is the radius of a volume around the center of molecule j which is inaccessible to molecules i due to the presence of the central molecule j. The first integral in the right-hand side is the Kirkwood–Buff integral when R is sufficiently large, the second integral provides the number of molecules of species i in a bulk liquid between the radii R_j and R, and the third integral provides the number of molecules of species i in a bulk liquid from zero to the radius R_j. The true excess is given by the difference between n_{ij} and the number of molecules of species i in a bulk liquid between the radii R_j and R. Hence

$$\Delta n_{ij} = n_{ij} - c_i\int_{R_j}^R 4\pi r^2 \, dr \tag{9}$$

The third integral $\int_0^{R_j} 4\pi r^2 \, dr$ in eq 8 represents a bulk volume V^j which is not accessible to the molecules of species i.

Consequently, the expression for calculating the average excess (or deficit) number of molecules i ($i = 1, 2$) around a central molecule j ($j = 1, 2$) has the form

$$\Delta n_{ij} = c_i G_{ij} + c_i V^j \tag{10}$$

To estimate the volume V^j, eq 10 is applied to a pure component j ($i = j$, $c_j = c_j^0$). In this case, because of complete randomness one expects Δn_{jj} to be zero. Therefore combining eq 10 and the equation for G_{jj} of a pure substance (eq A-11 in the Appendix) one obtains the following expression for the volume V^j

$$(V^j)_{x_j=1} = V_j^0 - RTk_{T,j}^0 \tag{11}$$

where T is the temperature, x_j is the molar fraction of component j, V_j^0 is the molar volume of the pure component j, $k_{T,j}^0$ is the isothermal compressibility of the pure component j, and R is the universal gas constant. Hence, far from the critical point, the excluded volume V^j is equal to the molar volume of the pure component j because $V_j^0 \gg RTk_{T,j}^0$.[6]

On the basis of the above result, the following expression is suggested for the volume V^j in the entire composition range

$$V^j = V_j - RTk_T \tag{12}$$

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where V_j is the partial molar volume of component j and k_T is the isothermal compressibility of the mixture. Of course, other forms for V^j compatible with eq 11 can be suggested.

Thus the average excess (or deficit) number of molecules i ($i = 1, 2$) around a central molecule j ($j = 1, 2$) can be calculated using the expression

$$\Delta n_{ij} = c_i G_{ij} + c_i V^j = c_i G_{ij} + c_i(V_j - RTk_T) \qquad (13)$$

Similar relations can be written for the excess (or deficit) number of molecules i ($i = 1, 2, ...$) around a central molecule j ($j = 1, 2, ...$) for ternary and multicomponent mixtures. The new simple expression (13) will be now applied to various systems.

3. The Excess (Or Deficit) Number of Molecules around a Central Molecule Calculated Using the New Expression (13)

3.1. Ideal Binary Mixture. Using eq 13 and relations (A-4 and A-5) from the Appendix, one can write the following expressions for the excesses Δn_{ij} values of ideal binary mixtures around a central molecule 1

$$\Delta n_{11}^{id} = \frac{x_1 x_2 V_2^0 (V_2^0 - V_1^0)}{(x_1 V_1^0 + x_2 V_2^0)^2} \qquad (14)$$

and

$$\Delta n_{21}^{id} = \frac{x_1 x_2 V_1^0 (V_1^0 - V_2^0)}{(x_1 V_1^0 + x_2 V_2^0)^2} \qquad (15)$$

These equations show that the Δn_{ij} values for an ideal binary mixture become zero only when the molar volumes of the pure components are the same, otherwise the excesses and deficits have nonzero values and can be calculated with eqs 14 and 15.

One can also demonstrate that the volume conservation conditions ($V_i \Delta n_{ij} + V_j \Delta n_{jj} = 0$; $i, j = 1, 2$, and $i \neq j$) are satisfied by an ideal mixture when the excesses (or deficits) are calculated with eqs 14 and 15. We calculated the Δn_{ij} around a central molecule 1 with eqs 14 and 15 for $V_1^0 = 30$ cm^3/mol and $V_2^0 = 60$ cm^3/mol. A comparison between the Δn_{ij} calculated with eq 1 and eqs 14 and 15 is presented in Figure 1. Figure 1 shows that both Δn_{11} and Δn_{21} calculated with the conventional eq 1 are negative, whereas those calculated with eqs 14 and 15 provide $\Delta n_{11} > 0$ and $\Delta n_{21} < 0$ in the entire composition range. One should note that the species with lower molar volume (component 1) is in excess. (A similar result was obtained when molecule 2 was the central molecule).

3.2. Binary System Methanol (1)−Water (2). The KBIs for this system ($T = 313$ K)[42] are presented in Figure 2a which shows that, in the composition range ($0 < x_{MeOH} \leq 0.25$), all three KBIs (G_{11}, G_{12}, and G_{22}) are negative. As a result, in this composition range (Figure 2, parts b and c) all four Δn_{ij}^{BN} (excesses or deficits calculated with eq 1) (Δn_{11}^{BN} and Δn_{21}^{BN} around a central methanol molecule and Δn_{12}^{BN} and Δn_{22}^{BN} around a central water molecule) are negative. This means that the densities around any central molecule (methanol or water) are less than those in the bulk. However, the calculations based on eq 13 (Figure 2, parts d and e) provide more reasonable values regarding the excess (or deficit) number of molecules around a central molecule:

(1) Around a central methanol molecule, $\Delta n_{11} > 0$ and $\Delta n_{21} < 0$ for $0 < x_{MeOH} \leq 0.35$, and $\Delta n_{11} < 0$ and $\Delta n_{21} > 0$ for $x_{MeOH} > 0.35$. Therefore, in the composition range $0 < x_{MeOH}$
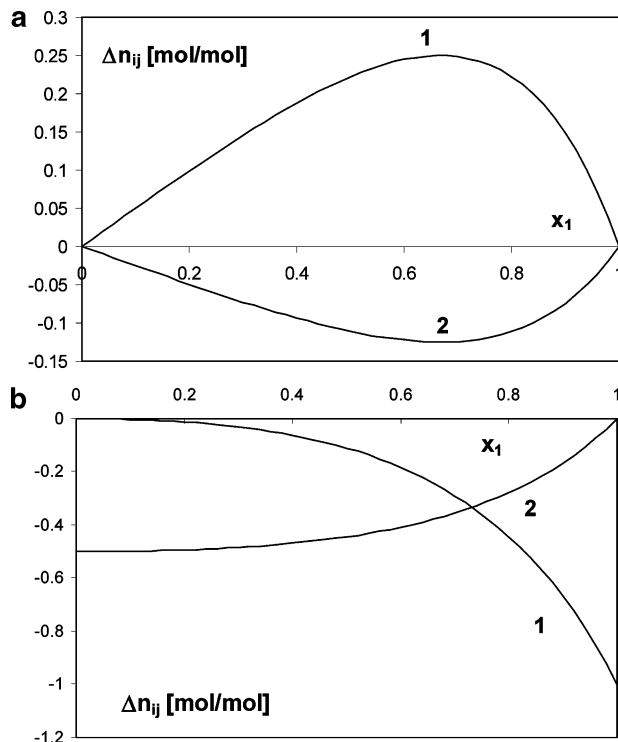

Figure 1. The excess (or deficit) number of molecules i ($i = 1, 2$) around a central molecule 1 for a binary ideal mixture with $V_1^0 = 30$ cm^3/mol and $V_2^0 = 60$ cm^3/mol. Line 1 is Δn_{11}, and line 2 is Δn_{21}. Shown are (a) Δn_{ij} values of an ideal binary mixture calculated with the new eq 13, and (b) Δn_{ij} values of an ideal binary mixture calculated with eq 1 (the KBIs were provided by eqs A-4 and A-5 in which k_T^{id} was taken as zero).

≤ 0.35, methanol is in excess in the vicinity of a central methanol molecule. However, at sufficiently high methanol mole fractions ($x_{MeOH} > 0.35$) the water molecules become in excess in the vicinity of a central methanol molecule. This result differs somewhat from the previous findings based on a reference state,[12,14] where methanol was found to be in excess in the vicinity of a central methanol molecule over the entire composition range.

(2) Around a central water molecule, $\Delta n_{22} > 0$ and $\Delta n_{12} < 0$ for $0 \leq x_{MeOH} \leq 1$. This means that the water molecules are in excess around a central water molecule over the entire composition range.

3.3. Binary System 2-Propanol (1)−Water (2). The KBIs for this system ($T = 298.15$ K)[12] are presented in Figure 3a. In the composition range ($0.33-0.35 < x_{i-PrOH} \leq 1$), Δn_{11}^{BN} and Δn_{21}^{BN} around a central 2-propanol molecule are negative (Figure 3b). This means that in the above composition range the density around a 2-propanol molecule is less than in the bulk. The calculations based on eq 13 (Figure 3, parts d and e) provide more reasonable values regarding the excess (or deficit) number of molecules around a central molecule: around the 2-propanol molecule $\Delta n_{11} > 0$ and $\Delta n_{21} < 0$ for $0 < x_{i-PrOH} \leq 0.55-0.57$, and $\Delta n_{11} < 0$ and $\Delta n_{21} > 0$ for $0.55-0.57 < x_{i-PrOH} \leq 1$. Therefore, in the composition range $0 < x_{i-PrOH} \leq 0.55-0.57$ the 2-propanol is in excess in the vicinity of a central 2-propanol molecule. However, at higher 2-propanol mole fractions ($0.55-0.57 < x_{i-PrOH} \leq 1$) the water molecules are in slight excess in the vicinity of a 2-propanol molecule. These results differ somewhat from the previous findings based on a reference state,[12,14] where 2-propanol was found to be in excess in the vicinity of a central 2-propanol molecule over the entire
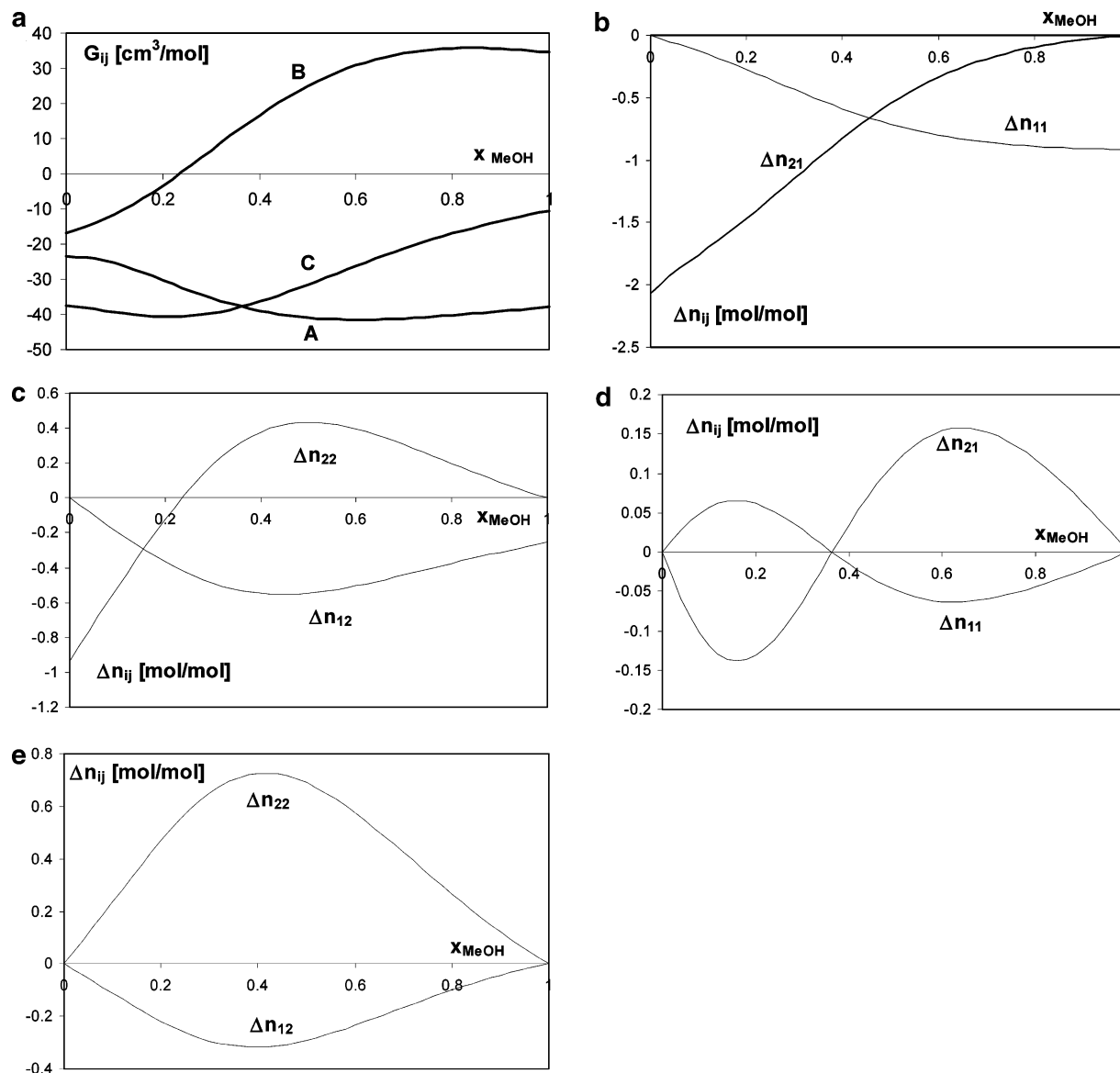
Figure 2. The KBIs and excesses (or deficits) for methanol (1)/water (2) mixtures ($T = 313.15$ K). (a) The KBIs[42]: G_{11} (A), G_{22} (B), and G_{12}(C); (b) excesses (or deficits) around a central methanol molecule calculated with eq 1; (c) excesses (or deficits) around a central water molecule calculated with eq 1; (2) excesses (or deficits) around a central methanol molecule calculated with eq 13; (e) excesses (or deficits) around a central water molecule calculated with eq 13.

composition range. There is some experimental evidence that clusters dominated by 2-propanol molecules disappear at high 2-propanol concentrations. Hayashi, et al.[44] using small-angle X-ray scattering found clusters dominated by 2-propanol molecules, with sizes from 1.5 to 6.5 Å, in the range of alcohol mole fractions from 0.1 to 0.3 that disappeared at higher mole fractions. Around a central water molecule, $\Delta n_{22} > 0$ and $\Delta n_{12} < 0$ for $0 \leq x_{i-\text{PrOH}} \leq 1$. This means that the water molecules are in excess around a central water molecule over the entire composition range.

3.4. Comparison between Equation 13 and Equations 3 and 4 for Binary Mixtures. The results obtained on the basis of eq 13 are comparable numerically to those obtained with eqs 3 and 4 when the molar volumes of the pure components or the partial molar volumes become comparable. Indeed, in this case ($V_1^0 \approx V_2^0$ or $V_1 \approx V_2$) and hence one can write, using eqs (A-4 to A-7) from the Appendix, that

$$\Delta n_{ij}^{\text{ML}} = c_i(G_{ij} - G_{ij}^{\text{id}}) \approx c_i G_{ij} + c_i(V_j^0 - RTk_T^{\text{id}}) \approx \Delta n_{ij} \quad (16)$$

and

$$\Delta n_{ij}^{\text{SR}} = c_i(G_{ij} - G_{ij}^{\text{SR}}) \approx c_i G_{ij} + c_i(V_j - RTk_T) = \Delta n_{ij} \quad (17)$$

To compare the present method with the Matteoli−Lepori and Shulgin−Ruckenstein methods based on reference states, a hypothetical binary mixture (We are indebted to one of the referees for the suggestion to use such an hypothetical binary mixture for analyzing the new method) with the volumes of the pure components $V_1^0 = 30$, $V_2^0 = 70$ and the volumes at infinite dilution $V_1^\infty = 26$ and $V_2^\infty = 66$ (all volumes in [cm³/mol]) will be considered. In addition, the contribution of the isothermal compressibility will be neglected, and the partial molar volumes will be assumed to be linear functions of the mole fractions. Let us first observe that eqs 3, 4, and 13 can be formally written in the following unified form

$$\Delta n_{ij} = c_i(G_{ij} - \Gamma) \quad (18)$$

where $\Gamma = -V_j + RTk_T$ for the new method, $\Gamma = G_{ij}^{\text{id}}$ for
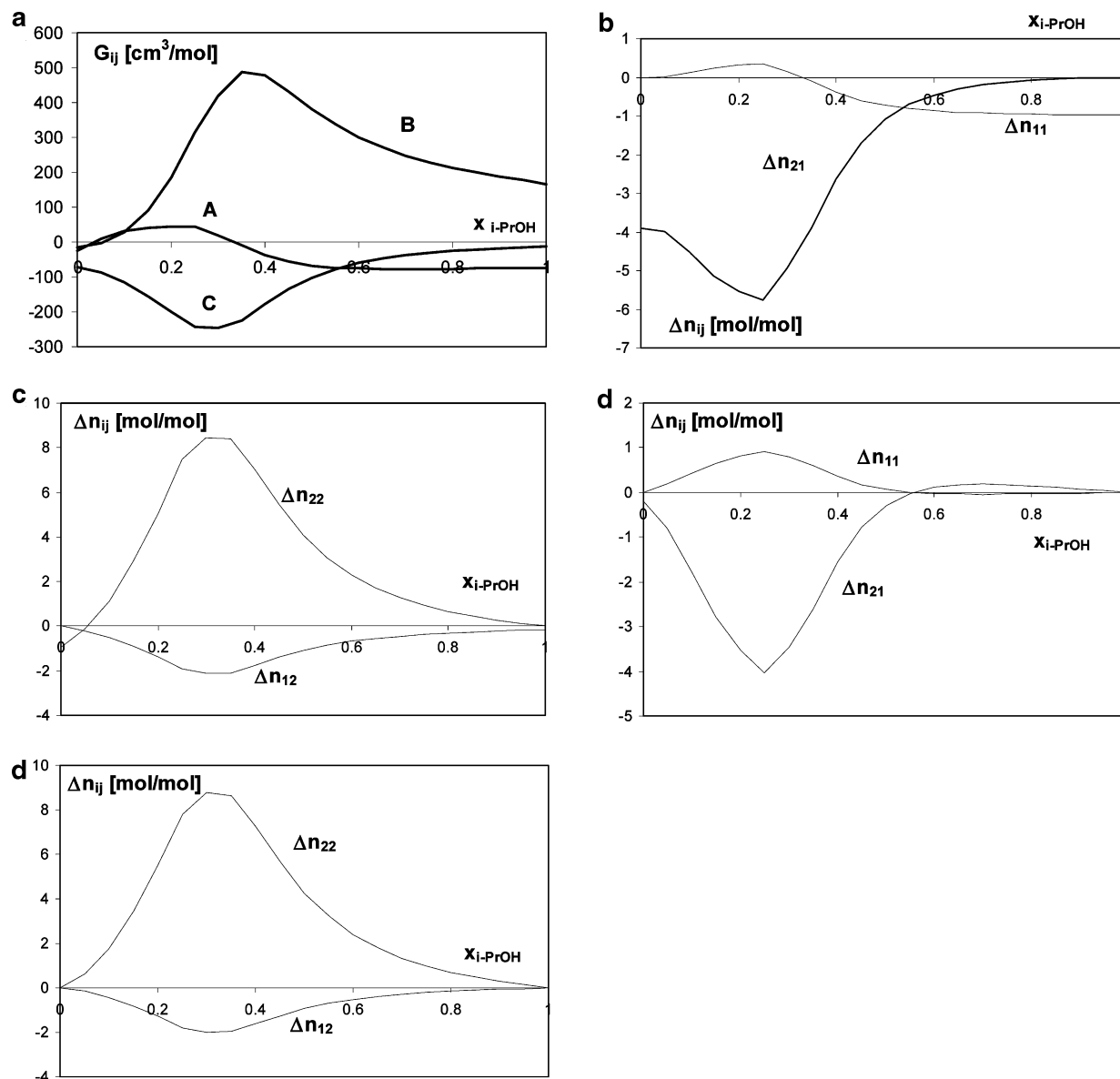
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Figure 3. The KBIs and excesses (or deficits) for 2-propanol (1)/water (2) mixtures ($T = 298.15$ K). (a) The KBIs[12]: G_{11} (A), G_{22} (B), and G_{12} (C); (b) excesses (or deficits) around a central 2-propanol molecule calculated with eq 1; (c) excesses (or deficits) around a central water molecule calculated with eq 1; (3) excesses (or deficits) around a central 2-propanol molecule calculated with eq 13; (e) excesses (or deficits) around a central water molecule calculated with eq 13.

the Matteoli−Lepori reference state, and $\Gamma = G_{ij}^{SR}$ for the Shulgin−Ruckenstein reference state. The calculated values of V_1, V_2, $-G_{ij}^{id}$, and $-G_{ij}^{SR}$ are plotted in Figure 4. Several observations can be made regarding Figure 4 and eqs 3, 4, and 13: (1) All three methods provide almost the same values of Γ when the molar volumes of the pure components become comparable. (2) In the new method, $\Gamma = -V_j + RTk_T$ is the same for both Δn_{ij} ($i \neq j$) and Δn_{jj} excesses, whereas for the methods involving reference states, $\Gamma = G_{ij}^{ref}$ for Δn_{ij} ($i \neq j$) and $\Gamma = G_{jj}^{ref}$ for Δn_{jj} (where ref = id or SR). As well known and as shown in Figure 4, G_{ij}^{ref} ($i \neq j$) $\neq G_{jj}^{ref}$ for both reference states. (3) The values Δn_{jj} for pure components are zero in all three methods. (4) The differences between G_{ij}^{id} and G_{ij}^{SR} are small but not negligible, and this proves the observation[12,15] that far from critical conditions, where the differences are large, the two reference states methods provide similar results. In addition, Figure 4 indicates that the excesses calculated using the two reference states are close to each other. (5) The volume conservation conditions[10,11] ($V_i \Delta n_{ij} + V_j \Delta n_{jj} =$
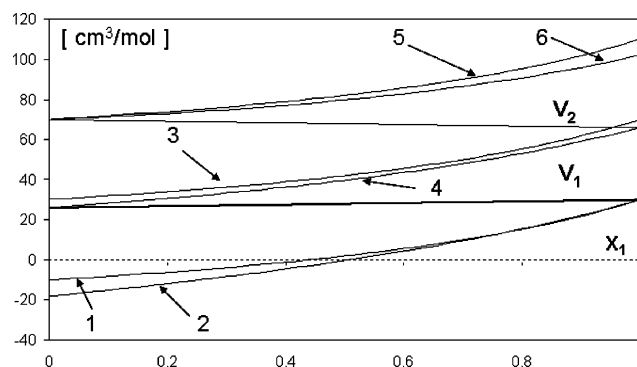

Figure 4. The partial molar volumes V_1 and V_2 for the artificial mixture (see text), and their comparison with the KBIs for Matteoli−Lepori and Shulgin−Ruckenstein reference states: $-G_{11}^{id}$ (1), $-G_{11}^{SR}$ (2), $-G_{12}^{id}$ (3), $-G_{12}^{SR}$ (4), $-G_{22}^{id}$ (5), and $-G_{22}^{SR}$ (6).

0; $i, j = 1, 2$ and $i \neq j$) are satisfied by the present method and by the method involving the reference state introduced by Shulgin and Ruckenstein.[12] For the present method, this can be

demonstrated using eq 13 for Δn_{jj} and Δn_{ij} together with expressions (A-1 to A-3) for the corresponding KBIs from the Appendix.

3.5. Ternary Mixture: a Biomolecule in a Mixed Solvent. In the last several years the KB theory was applied to the systems water (1)/protein (2)/cosolvent (or salt) (3) mixtures.[28−38] Experimental information regarding the partial molar volumes and the preferential binding parameters were used to calculate G_{12} and G_{23} at infinite dilution of the protein. Further the calculated KBIs were used to obtain the excesses (or deficits) of the constituents of the mixed solvent near a protein molecule (with respect to the bulk concentrations of a protein-free mixed solvent).[34−35,38] The use of the conventional eq 1 provided unreasonable results. For example,[34] for an infinitely dilute ribonuclease A (2) in water (1) + glycerol (3) mixtures, one obtains that for a volume fraction of glycerol of 30%: $c_1 G_{12} = -341.8$ mol of water which has a volume of -6.18 L, and $c_3 G_{23} = -48.1$ mol of water which has a volume of -3.52 L. Therefore, the use of the conventional eq 1 provided large deficits of water and glycerol in the vicinity of ribonuclease A. In contrast, many experiments confirmed that in this mixture water is in excess and glycerol is in deficit in the vicinity of a protein molecule.[45−47] The use of the reference state G_{ij}^{SR} (eq 4) led to the following excesses (or deficits): $\Delta n_{12} \cong 33.3$ mol of water which has a volume of 0.602 L, and $\Delta n_{23} \cong -8.2$ mol of glycerol which has a volume of 0.602 L.

It is worth noting that the application of the new method based on eq 13 to the mixture water (1)/protein (2)/cosolvent (or salt) (3) provides the same results as those based on a reference state (eqs 3 and 4). This occurs, because the protein molecule is much larger than the water molecule and typical cosolvents molecules, $V_2^{\infty} \gg V_i$, $i = 1, 3$. For this reason one can write the following expressions for G_{12} and G_{23} at infinite dilution of the protein[34]

$$G_{12}^{SR} = RTk_T - V_3 c_3 (V_1 - V_3) - V_2^{\infty} \approx RTk_T - V_2^{\infty} \quad (19)$$

and

$$G_{23}^{SR} = RTk_T - V_1 c_1 (V_1 - V_3) - V_2^{\infty} \approx RTk_T - V_2^{\infty} \quad (20)$$

Hence, one can write for the excesses (or deficits) of water and cosolvent around a protein molecule

$$\Delta n_{12}^{SR} = c_1 (G_{12} - G_{12}^{SR}) \approx c_1 G_{12} + c_1 (RTk_T - V_2^{\infty}) = \Delta n_{12} \quad (21)$$

and

$$\Delta n_{23}^{SR} = c_3 (G_{23} - G_{23}^{SR}) \approx c_3 G_{23} + c_3 (RTk_T - V_2^{\infty}) = \Delta n_{23} \quad (22)$$

Therefore, for the system water (1)/protein (2)/cosolvent (or salt) (3), the new method for calculating the excesses (or deficits) around a biomolecule at its infinite dilution (eq 13) leads to the same results as those based on a reference state (eqs 3 and 4). The method based on eq 1 leads to erroneous results because it does not reflect the true excesses (deficits) of water and cosolvent around an infinitely dilute biomolecule.

4. Discussion and Conclusion

One of the most important applications of the KB theory consists of its use to extract some microscopic characteristics of liquid mixtures from measurable macroscopic thermodynamic quantities. The excess (or deficit) number of molecules of

various species around a selected (central) molecule is a key quantity in the analysis of the microscopic characteristics of liquid mixtures. Therefore, the correct estimation of the above excesses (or deficits) is important, and the present paper provides a procedure for calculating the excess (or deficit) number of molecules of various species around a selected (central) molecule in binary and multicomponent mixtures.

The conventional method based on eq 1 provides unreasonable results, such as nonzero excesses (or deficits) for single components, all negative excesses for an ideal binary mixture A−B when all three KBIs are negative, and all negative excesses in some concentration ranges for some real binary mixtures.

It is shown in this paper that the number of bulk molecules in the conventional method based on eq 1 was overestimated because the inaccessible volume due to the presence of the central molecule was not taken into account.

The new method eliminates the above inconsistencies: It provides a zero excess for pure components, and excesses (or deficits) which satisfy the volume conservation condition (for both ideal and real mixtures). The derived eq 13 allows one to calculate the excess (or deficit) for an ideal binary mixture (Figure 1) and shows that they become zero only when the molar volumes of the components are equal.

It is clear (see Figures 1−3) that the excesses (or deficits) calculated with the new eq 13 are always very different from those obtained with eq 1. However, eq 13 and eqs 3 and 4 provide comparable results for binary mixtures when the molar volumes of the components are approximately the same. The results obtained using eq 1 and those obtained from eq 13 for methanol/water and 2-propanol/water mixtures are very different. In contrast to the methods based on a reference state, the new method predicts that the alcohols are preferentially hydrated at high alcohol mole fractions. For the 2-propanol/water mixtures there are experimental observations which support this prediction.

In the application of the KB theory to the system water (1)/protein (2)/cosolvent (or salt) (3), eq 13 provided results, comparable with experiment. Because in such cases the molar volume of the protein is much larger than those of water and cosolvent (salt), eqs 3 and 4 provided almost the same results. In contrast, eq 1 failed to provide plausible values for the excesses (or deficits) of water and cosolvent (salt) in the vicinity of a protein surface.

Appendix

The purpose of this Appendix is to provide expressions for calculating the KBIs for binary mixtures from measurable thermodynamic quantities such as the derivatives of the chemical potentials with respect to concentrations, the isothermal compressibility, and the partial molar volumes.

The main formulas for the KBIs are [6, 10−11]

$$G_{12} = G_{21} = RTk_T - \frac{V_1 V_2}{VD} \quad (A-1)$$

$$G_{ii} = G_{12} + \frac{1}{x_i}\left(\frac{V_j}{D} - V\right) \quad i \neq j \quad (A-2)$$

where

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$$D = \left(\frac{\partial \ln \gamma_i}{\partial x_i}\right)_{P,T} x_i + 1 \tag{A-3}$$

P is the pressure, T is the temperature in K, k_T is the isothermal compressibility, V_i is the partial molar volume of component i, x_i is the molar fraction of component i, V is the molar volume of the mixture, γ_i is the activity coefficient of component i and R is the universal gas constant.

The KBIs for an ideal mixture G_{ij}^{id} are provided by the expressions:[10−11]

$$G_{12}^{id} = RTk_T^{id} - \frac{V_1^0 V_2^0}{V^{id}} \tag{A-4}$$

and

$$G_{ii}^{id} = G_{12}^{id} + V_j^0 - V_i^0 \quad i \neq j \tag{A-5}$$

where V_i^0, k_T^{id}, and V^{id} are the molar volume of the pure component i, the isothermal compressibility, and the molar volume of an ideal solution, respectively.

The KBIs for the Shulgin−Ruckenstein reference state are provided by the expressions[12]

$$G_{12}^{SR} = RTk_T - \frac{V_1 V_2}{V} \tag{A-6}$$

and

$$G_{ii} = G_{12}^{SR} + V_j - V_i \quad i \neq j \tag{A-7}$$

At infinite dilution, or for pure components, the following limiting expressions can be obtained for the KBIs[6,10−11]

$$\lim_{x_i \to 0} G_{12} = RTk_{T,j}^0 - V_i^\infty \quad i \neq j \tag{A-8}$$

$$\lim_{x_i \to 1} G_{12} = RTk_{T,i}^0 - V_j^\infty \quad i \neq j \tag{A-9}$$

$$\lim_{x_i \to 0} G_{ii} = RTk_{T,j}^0 + V_j^0 - 2V_i^\infty - V_j^0 \left(\frac{\partial \ln \gamma_i}{\partial x_i}\right)_{P,T,x_i=0} \quad i \neq j \tag{A-10}$$

and

$$\lim_{x_i \to 1} G_{ii} = RTk_{T,i}^0 - V_i^0 \tag{A-11}$$

where $k_{T,i}^0$ is the isothermal compressibility of the pure com-

ponent i and V_i^∞ is the partial molar volume of component i at infinite dilution.

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