Molecular theory for the effects of solute attractive forces on hydrophobic interactions

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We consider the local molecular field (LMF) theory for the effects of solute attractive forces on hydrophobic interactions. The principal result of LMF theory is outlined, then tested by obtaining radial distribution functions (rdfs) for Ar atoms in water, with and without attractive interactions distinguished by the Weeks-Chandler-Andersen (WCA) separation. Change from purely repulsive atomic solute interactions to include realistic attractive interactions substantially diminishes the strength of hydrophobic bonds. Since attractions make a big contribution to hydrophobic interactions, Pratt-Chandler theory, which did not include attractions, should not be simply comparable to computer simulation results with general physical interactions, including attractions. The rdfs permit evaluation of osmotic second virial coefficients $B_2$. Those $B_2$ are consistent with the conclusion that incorporation of attractive interactions leads to more positive (repulsive) values. In all cases here, $B_2$ becomes more attractive with increasing temperature below $T = 360K$. Ultimately, LMF theory does not accurately describe the numerical results for the effects of solute attractive forces on hydrophobic interactions in this case. This is due to the incomplete evaluation within LMF theory of the mean hydration energy of the second Ar atom joining the Ar pair.

I. INTRODUCTION

The original, specifically statistical mechanical theory of hydrophobic interactions[1] was formulated for hard sphere hydrophobic solutes in water. In view of the surprising ingredients of the theory[2] and the apparent disagreement with some experiments[3–6] that do involve attractive forces, questions were raised promptly about the consequences of solute attractive forces associated with simple hydrophobic solutes [7].

That issue has been broadly discussed several times over the intervening years [5, 7–11] without achieving a definitive solution. That situation may now change due to numerically exact results for hydrophobic correlations for precisely the hard-sphere solutes that were treated by the original theory [12]. For the first time, those results unambiguously identified limitations of the hard-sphere theory. Independently, new results for broader solute models arrived at the physically consistent conclusions for those cases [13].

The now-expected [14] distinctions deriving from inclusion of solute attractive forces are exemplified in FIG. 1 and FIG. 2. Inclusion of solute attractive forces diminishes the strength of hydrophobic bonding: solute attraction to the solvent tends to push the solute species apart. Still, though this behavior is expected from previous speculation and simulations [7, 11], a definitive molecular theory has not been established. The local molecular field theory (LMF) discussed below is presently the most specifically proposed theory [15]. Clarifying and testing that theory is the goal of this research.

In the next section we outline the LMF theory. Numerical results, and conclusions are identified in Sec. [III] Methods for the several computational steps are collected in Sec. [V]
II. LOCAL MOLECULAR FIELD THEORY

The LMF idea is to study the inhomogeneous density of a fluid subject to an external field. We focus on the density structure resulting from the placement of an Ar atom at a specific location. That distinguished atom exerts an external field on the surrounding fluid and distorts the density. With \( U \) the intermolecular potential energy function for the system and \( \Phi \) the external field exerted at position \( r \) of \( \alpha \) atoms of a molecule of type M. The goal of the LMF theory is to analyze \( \rho_{\alpha M}(r; U, \Phi) \) on the basis of the characteristics of the interactions \( U \) and \( \Phi \).

We assume that a reference potential energy, denoted by \( U^{(0)} \), has been identified with the goal that this case should help in analyzing \( \rho_{\alpha M}(r; U, \Phi) \). Specifically, our goal is the match

\[
\rho_{\alpha M}(r; U, \Phi) = \rho_{\alpha M}(r; U^{(0)}, \Phi^{(0)}) ,
\]

achieved for the reference system with interactions \( U^{(0)} \), and an effective external field \( \Phi^{(0)} \). Determination of that effective field is the goal of the analysis below. A successful match Eq. (1) establishes aspects of \( U \) that can be treated as molecular mean-fields, thus offering a molecular mechanism for \( \rho_{\alpha M}(r; U, \Phi) \).

Identification of a reference potential energy function \( U^{(0)} \) thus requires physical insight. One serious suggestion for the inter-atomic force fields of current simulation calculations corresponds to Gaussian-truncated electrostatic interactions associated with the partial charges of simulation models [15]. In that case, the crucial difference

\[
U - U^{(0)} = \sum_{\alpha M, \gamma M'} u_{\alpha M \gamma M'}^{(1)} (|r_{\alpha M} - r_{\gamma M'}|) ,
\]

is atom-pair decomposable since the summation runs over atom-pairs. For the case of interest here, \( u_{\alpha M \gamma M'}^{(1)} (|r_{\alpha M} - r_{\gamma M'}|) \) is the WCA-attractive part of the Lennard-Jones interactions associated with the Ar atoms.

In seeking the match Eq. (1), we follow an atom-based perspective, and focus on the chemical potential,

\[
\mu_{\alpha M} = \beta^{-1} \ln \left[ \rho_{\alpha M}(r; U, \Phi) \Lambda_{\alpha M}^3 \right] + \varphi_{\alpha M}(r) + \mu_{\alpha M}^{(ex)}(r; \rho, \beta U) ,
\]

of \( \alpha \) atoms, which decomposes

\[
\Phi = \sum_{\alpha M} \varphi_{\alpha M}(r_{\alpha M}) .
\]

Here the temperature is \( T = (k_B \beta)^{-1} \); the thermal de-Broglie wavelength \( \Lambda_{\alpha M} \) depends only on \( T \) and on fundamental parameters associated with \( \alpha \) atoms. As indicated, the excess contribution \( \mu_{\alpha M}^{(ex)}(r; \rho, \beta U) \) depends functionally on \( (\rho, \beta U) \), not on the external field.

For some simulation models, the atom-based perspective we follow in considering \( \mu_{\alpha M} \) (Eq. (3)) may raise questions regarding the operational status of atom chemical potentials. But this perspective would be satisfactory for \( ab \) initio descriptions of the solution, and is sufficiently basic that we do not further side-track this discussion. Similarly for the reference case

\[
\mu_{\alpha M}^{(0)} = \beta^{-1} \ln \left[ \rho_{\alpha M}^{(0)}(r; \rho^{(0)}, \beta U^{(0)}) \Lambda_{\alpha M}^3 \right] + \varphi_{\alpha M}^{(0)}(r) + \mu_{\alpha M}^{(ex)}^{(0)}(r; \rho^{(0)}, \beta U^{(0)}) ,
\]

with

\[
\Phi^{(0)} = \sum_{j} \varphi_{\alpha M}^{(0)}(r_{\alpha M}) .
\]

The forms Eqs. (3) and (5) allows us to express the match Eq. (1) as

\[
\varphi_{\alpha M}^{(0)}(r) = \varphi_{\alpha M}(r) + \left[ \mu_{\alpha M}^{(ex)}(r; \rho, \beta U) - \mu_{\alpha M}^{(ex)}^{(0)}(r; \rho^{(0)}, \beta U^{(0)}) \right] + \text{constant} .
\]

The bracketed terms in Eq. (7) depend functionally on the densities, not on the external fields. The constant in Eq. (7) involves the chemical potentials of the two systems.

The approximation of interest here is then

\[
\beta \varphi_{\alpha M}^{(0)}(r) \approx \beta \varphi_{\alpha M}(r) + \sum_{\gamma M'} \int p_{\gamma M'}(r') \beta u_{\gamma M' \alpha M}^{(1)} (|r' - r|) dr' + \text{constant} .
\]
In view of Eq. (7), this approximation is transparently analogous to van der Waals theory [16]. Transcribing to the case of Ar(aq) at infinite dilution produces

\[
\beta \varphi_{Ar}^{(0)}(r) \approx \beta \varphi_{Ar}(r) + \int [\rho_{O}(r') - \rho_{O}] \beta u_{OAr}^{(1)}(|r' - r|) \, dr'.
\]  

(9)

The fields vanish far from their source, and the constant contribution of Eq. (8) is accommodated explicitly in Eq. (9). This argument does indeed match the results of Rodgers and Weeks [17] in the several instances they considered. The outline here is frankly heuristic with the advantage of concision. Available derivations already provide more basic considerations and higher detail [18–20].

Though the statistical mechanical theory of Eqs. (7) and (9) is simple, the fields sought depend on the densities, which themselves depend on the fields. So a linear statistical mechanical approximation Eq. (8) produces the non-linear Eq. (7) to solve. The non-linearity is not an obstacle here because the densities on the right of Eq. (9) are straightforwardly obtained from routine simulation (FIG. 3 see also [21]). Notice (FIG. 3) that the effects of attractive AO interactions on AO correlations are modest, as was argued long ago [7].

Now consider \( \rho_{Ar}(r; U^{(0)}, \Phi^{(0)}) \), the density of Ar atoms without attractive interactions \( \beta u_{OAr}^{(1)}(r) \) but experiencing the effective field \( \beta \varphi_{Ar}^{(0)}(r) \). We approximate

\[
- \ln \rho_{Ar}(r; U^{(0)}, \Phi^{(0)})/\rho_{Ar} \approx \beta \varphi_{Ar}^{(0)}(r) - \ln HS(r)
\]

(10)

adapting the repulsive-force solute results of FIG. 1. The field \( \varphi_{Ar}^{(0)}(r) \) incorporates aspects of the intermolecular attractions as mean-field effects according to Eq. (9).

With the match Eq. (1), the approximation Eq. (9) produces

\[
\beta \left( \varphi_{Ar}(r) - u_{ArAr}^{(0)}(r) \right) + \int [\rho_{O}(r') - \rho_{O}] \beta u_{OAr}^{(1)}(|r' - r|) \, dr' - \ln g_{ArAr}^{(0)}(r) = - \ln g_{ArAr}^{(0)}(r),
\]

(11)

and finally

\[
- \ln \left[ \frac{g_{ArAr}^{(0)}(r)}{g_{ArAr}^{(0)}(r)} \right] \approx \beta u_{ArAr}^{(1)}(r) + \int h_{ArO}(r') \rho_{O} \beta u_{OAr}^{(1)}(|r' - r|) \, dr'.
\]

(12)

Though the right-side of Eq. (12) can be evaluated for ArAr overlapping configurations, it is intended for application to Ar2 configurations actually observed, e.g. in simulation calculations.

Theories of years ago [5, 7, 11, 24, 25] supply perspective on Eq. (12). Previously [7, 25], a theory of ArO correlations with just the structure of Eq. (12) was assumed without detailed justification. The Pratt-Chandler work for ArAr correlations took explicit account of the Ar2 diatom structure [1], but assumed that corrections due to attractive interactions would contribute linearly in \( \beta u_{ArAr}^{(1)}(r) \), as in Eq. (12). That Pratt-Chandler model seemed successful in describing the effects of attractive interactions for the unusually strong case considered [10].

By calculating the correction associated with a Gaussian statistical model, Asthagiri, et al. [11] justified that linear dependence on \( \beta u_{OAr}^{(1)}(r) \). Quasi-chemical theory (QCT) does assist in understanding this LMF theory. Since QCT is designed to evaluate interaction contributions to chemical potentials, Eq. (7) is particularly helpful. From the QCT point of view [11, 26], the packing contributions to those two chemical potentials cancel each other exactly. Next to be considered is the mean hydration energy of the Ar whose appearance at \( r \) is being characterized; that mean hydration energy may be [11] denoted by \( \langle \varepsilon | r, n_A = 0 \rangle \). Indeed, previous QCT effort suggests that \( \langle \varepsilon | r, n_A = 0 \rangle \) is the most important factor in describing the effect of attractive interactions being included [7, 11]. Returning to the LMF theory, the second term on the right of Eq. (8) suggests this most important QCT contribution, \( \langle \varepsilon | r, n_A = 0 \rangle \), but does not calculate it fully. This incomplete evaluation is the most important concern for this LMF theory.
III. RESULTS AND CONCLUSIONS

Changing purely repulsive atomic interactions to include realistic attractions diminishes the strength of hydrophobic bonds (FIGs. 1 and 2). Influential previous work on hydrophobic interactions compared Pratt-Chandler theory results which did not include attractions to computer simulation results with general physical interactions, including attractions. Since attractions make a big contribution, those results should not be simply comparable [11].

The changes with inclusion of attractive interatomic interactions noted here are directly reflected in the values of osmotic $B_2$ (FIGs. 4 and 5). In all cases here, however, $B_2$ becomes more attractive with increasing temperature below $T = 360K$.

The LMF theory does not capture this behavior accurately (FIG. 6). Viewed from perspective of quasichemical theory, this is due to the incomplete evaluation within LMF theory of the mean hydration energy of the second Ar atom joining the ArAr pair.

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V. METHODS

A. Simulations

The simulations were carried out with the GROMACS package [29], the SPC/E model of the water molecules [30], and the OPLS force field. GROMACS selects SETTLE [31] constraint algorithm for rigid SPC/E water molecules. Same constraint algorithm was used in previous simulations involving water. [12] [32] Standard pe-
periodic boundary conditions were employed, with particle mesh Ewald utilizing a cutoff of 1 nm and long-range dispersion corrections applied to energy and pressure. The Parrinello-Rahman barostat controlled the pressure at 1 atm, and the Nose-Hoover thermostat was used to maintain the temperature. The simulation cell for the Ar(aq) system consisted of two (2) argon molecules and 1000 water molecules. Initial configurations were constructed with PACKMOL \cite{33} to construct a system close to the density of interest. The solute-solute separation spanning 0.33 nm to 1.23 nm was stratified using standard window concepts and the results combined using the weighted histogram analysis method (WHAM) \cite{34}. This involved 19 windows (and simulations) for window separations \( r \) ranging from 0.33 nm to 1.23 nm.

**B. Osmotic \( B_2 \)**

The distribution function \( g_{\text{ArAr}}(r) = h_{\text{ArAr}}(r) + 1 \) provides access to the osmotic second virial coefficient,

\[
B_2 = -\frac{1}{2} \lim_{\rho_{\text{Ar}} \to 0} \int h_{\text{ArAr}}(r) \, d^3 r . \tag{13}
\]

We utilize the extrapolation procedure of Krüger, et al. \cite{32} \cite{30}

\[
-2B_2 = \lim_{R \to \infty} 4\pi \int_{0}^{2R} h_{\text{ArAr}}(r) \, w(r/2R) r^2 \, dr , \tag{14}
\]

with

\[
w(x) = 1 - \left( \frac{3}{2} \right) x + \left( \frac{1}{2} \right) x^3 . \tag{15}
\]

Computed values for \( 1/2R > 0 \) were least-squares fitted with a polynomial quadratic order in \( 1/2R \). The results above present the extrapolated \( 1/2R = 0 \) value. Chaudhari, et al. \cite{32} showed that this can be an accurate procedure.

**C. LMF theory**

With the information FIG. 3 the LMF approximation Eq. (12) further depends linearly on the attractive interactions. We evaluated Eq. (12) in a standard way by introducing the spatial Fourier transforms

\[
\hat{u}_{\text{OAr}}^{(1)}(k) = \int u_{\text{OAr}}^{(1)}(r) \left( \frac{\sin kr}{kr} \right) \, dr , \tag{16}
\]

and

\[
\hat{h}_{\text{OAr}}(k) = \int h_{\text{OAr}}(r) \left( \frac{\sin kr}{kr} \right) \, dr . \tag{17}
\]

Then

\[
\int \hat{h}_{\text{ArO}}(k) \rho_O \beta \hat{u}_{\text{OAr}}^{(1)}(k) \left( \frac{\sin kr}{kr} \right) \frac{dk}{(2\pi)^3} \equiv \beta \Delta \varphi_{\text{Ar}}^{(0)}(r) . \tag{18}
\]

The parameters for this application are \( \rho_O = 33.8/\text{nm}^3 \), \( \varepsilon_{\text{OAr}} = 0.798 \text{ kJ/mol} \), \( \sigma_{\text{OAr}} = 0.328 \text{ nm} \), \( \varepsilon_{\text{ArAr}} = 0.978 \text{ kJ/mol} \), and \( \sigma_{\text{ArAr}} = 0.340 \text{ nm} \).

[1] Pratt, L. R., and Chandler, D. (1977) Theory of the hydrophobic effect. *J. Chem. Phys.* 67, 3683–3704.
[2] Chan, D. Y. C., Mitchell, D. J., Ninham, B. W., and Pailthorpe, B. A. In *Recent Advances in Water: A Comprehensive Treatise*; Franks, F., Ed.; Plenum: New York, 1979; Vol. 6; pp 239–278.
[3] Tucker, E. E., and Christian, S. D. (1979) A prototype hydrophobic interaction. The dimerization of benzene in water. *J. Phys. Chem.* 83, 426–427.
[4] Rossky, P. J., and Friedman, H. L. (1980) Benzene-benzene interaction in aqueous solution. *J. Phys. Chem.* 84, 587–589.
[5] Pratt, L. R. (1985) Theory of Hydrophobic Effects. *Ann. Rev. Phys. Chem.* 36, 433–449.
[6] Bernal, P. J., Christian, S. D., and Tucker, E. E. (1986) Vapor-pressure studies of hydrophobic association - thermodynamics of fluorobenzene in dilute aqueous-solution. *J. Soln. Chem.* 15, 947–956.
[7] Pratt, L. R., and Chandler, D. (1980) Effects of solute-solvent attractive forces on hydrophobic correlations. *J. Chem. Phys.* 73, 3434 – 41.
[8] Watanabe, K., and Andersen, H. C. (1986) Molecular-dynamics study of the hydrophobic interaction in an aqueous-solution of krypton. *J. Phys. Chem.* 90, 795 – 802.
[9] Smith, D. E., Zhang, L., and Haymet, A. D. J. (1992) Entropy of association of methane in water: a new molecular dynamics computer simulation. *J. Am. Chem. Soc.* 114, 5875–5876.
[10] Smith, D. E., and Haymet, A. D. J. (1993) Free energy, entropy, and internal energy of hydrophobic interactions: computer simulations. *J. Chem. Phys.* 98, 6445–6454.
[11] Asthagiri, D., Merchant, S., and Pratt, L. R. (2008) Role of attractive methane-water interactions in the potential of mean force between methane molecules in water. *J. Chem. Phys.* 128, 244512.
[12] Chaudhari, M. I., Holleran, S. A., Ashbaugh, H. S., and Pratt, L. R. (2013) Molecular-scale hydrophobic interactions between hard-sphere reference solutes are attractive and endothermic. *Proc. Nat. Acad. Sci. USA* 110, 20557–20562.
[13] Koga, K. (2013) Osmotic second virial coefficient of methane in water. *J. Phys. Chem. B* 117, 12619–12624.
[14] Chaudhari, M. I. Molecular Simulations to Study Thermodynamics of Polyethylene Oxide Solutions. Ph.D. thesis, Department of Chemical & Biomolecular Engineering, Tulane University, 2013.

[15] Rodgers, J. M., and Weeks, J. D. (2008) Local molecular field theory for the treatment of electrostatics. J. Phys.: Condens. Matter 20, 494206.

[16] Widom, B. (1967) Intermolecular forces and the nature of the liquid state. Science 157, 375–382.

[17] Rodgers, J. M., and Weeks, J. D. (2008) Local molecular field theory for the treatment of electrostatics. J. Phys.: Condens. Matter 20.

[18] Rodgers, J. M., and Weeks, J. D. (2009) Accurate thermodynamics for short-ranged truncations of Coulomb interactions in site-site molecular models. J. Chem. Phys. 131, 244108.

[19] Rodgers, J. M., Hu, Z., and Weeks, J. D. (2011) On the efficient and accurate short-ranged simulations of uniform polar molecular liquids. Mol. Phys. 109, 1195–1211.

[20] Archer, A. J., and Evans, R. (2013) Relationship between local molecular field theory and density functional theory for non-uniform liquids. J. Chem. Phys. 138, 014502.

[21] Pratt, L. R., and Pohorille, A. In Proceedings of the EBBA 1992 International Workshop on Water-Biomolecule Interactions; Palma, M. U., Palma-Vittorelli, M. B., and Parak, F., Eds.; Societ`a Italiana di Fisica: Bologna, 1993; pp 261–268.

[22] Asthagiri, D., Ashbaugh, H. S., Piryatinski, A., Paulaitis, M. E., and Pratt, L. R. (2007) Non-van der Waals treatment of the hydrophobic solubilities of CF4. J. Am. Chem. Soc. 129, 10133 – 10140.

[23] Chandler, D., and Weeks, J. D. (1970) Equilibrium structure of simple liquids. Phys. Rev. Letts. 25, 149–152.

[24] Ichiye, T., and Chandler, D. (1988) Hypernetted chain closure reference interaction site method theory of structure and thermodynamics for alkanes in water. J. Phys. Chem. 92, 5257–5261.

[25] Hummer, G., and Garde, S. (1998) Cavity expulsion and weak dewetting of hydrophobic solutes in water. Phys. Rev. Lett. 80, 4193–4196.

[26] Rogers, D. M., Jiao, D., Pratt, L. R., and Rempe, S. B. (2012) Structural Models and Molecular Thermodynamics of Hydration of Ions and Small Molecules. Ann. Rep. Comp. Chem. 8, 71–127.

[27] Pangali, C., Rao, M., and Berne, B. J. (1979) A Monte Carlo simulation of the hydrophobic interaction. J. Chem. Phys. 71, 2975–2981.

[28] Garde, S., Hummer, G., García, A. E., Paulaitis, M. E., and Pratt, L. R. (1996) Origin of entropy convergence in hydrophobic hydration and protein folding. Phys. Rev. Letts. 77, 4966 – 4968.

[29] Hess, B., Kutzner, C., van der Spoel, D., and Lindahl, E. (2008) GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation. J. Chem. Theory. Comput. 4, 435–447.

[30] Berendsen, H. J. C., Grigera, J. R., and Straatsma, T. P. (1987) The missing term in effective pair potentials. J Phys Chem 91, 6269–6271.

[31] Miyamoto, S., and Kollman, P. A. (1992) Settle: An analytical version of the SHAKE and RATTLE algorithm for rigid water models. Journal of Computational Chemistry 13, 952–962.

[32] Chaudhari, M. I., Sabo, D., Pratt, L. R., and Rempe, S. B. (2014) Hydration of Kr (aq) in dilute and concentrated solutions. J. Phys. Chem. B

[33] Martinez, L., Andrade, R., Birgin, E. G., and Martinez, J. M. (2009) PACKMOL: A package for building initial configurations for molecular dynamics simulations. J. Comput. Chem. 30, 2157–2164.

[34] Kumar, S., Rosenberg, J. M., Bouzida, D., Swedsen, R. H., and Kollman, P. A. (1992) The weighted histogram analysis method for free-energy calculation on biomolecules I. The method. J. Comput. Chem. 13, 1011–1021.

[35] Krüger, P., Schnell, S. K., Bedeaux, D., Kjelstrup, S., Vlugt, T. J., and Simon, J.-M. (2012) Kirkwood–Buff integrals for finite volumes. J. Phys. Chem. Letts. 4, 235–238.

[36] Schnell, S. K., Englebienne, P., Simon, J.-M., Krüger, P., Balaji, S. P., Kjelstrup, S., Bedeaux, D., Bardow, A., and Vlugt, T. J. (2013) How to apply the Kirkwood–Buff theory to individual species in salt solutions. Chem. Phys. Letts. 582, 154–157.