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THEORIES OF HYDROPHOBIC EFFECTS AND THE DESCRIPTION OF FREE VOLUME IN COMPLEX LIQUIDS

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Abstract. Recent progress on molecular theories of hydration of nonpolar solutes in liquid aqueous solution has led to new ways to thinking about the old issue of free volume in liquids. This article surveys the principal new results with particular attention to the context of general issues of packing in liquids.

1. Introduction

Aqueous solutions of colloidal solutes are preeminent examples of complex liquids. In such settings, attention is often directed towards the issues of macromolecular structure, including aggregation, and dynamics. However, one aspect of these problems is stubbornly associated with the small molecule size scale, the size scale of a water molecule. That problem is the molecular understanding and description of hydration effects – hydrophobic effects – that stabilize membranes, micelles, folded conformations of globular proteins, and supermolecular aggregates of such structures. This presentation will focus on that basic, molecular scale issue underlying aqueous solutions of interest both to biophysics and colloidal materials science.

Because hydrophobic effects are so broadly discussed, you may be surprised to notice that workers on molecular theories of hydrophobic effects have not achieved good agreement on that molecular theory, at least when we proceed beyond the primitive stage of the principles of statistical mechanics and specification of the intermolecular interactions involved. The empirical fact is that different researchers hold different opinions on the correctness of several available theories, each of which agree with a set of experimental data at least roughly. A sampling of different perspectives is

available from the references [1-33]; this collection, however, is not intended to be complete.

Furthermore, the simplest extensions of our experimental information can spark new debates about our understanding of hydrophobic effects. A current example, the effect of pressure on hydrophobic stabilization of folded, globular proteins, is discussed below.

In consequence of such observations, the theory surveyed here was designed for maximal simplicity on the fundamentals of statistical mechanics and on the physical assumptions applied to the particular problems. The theory that was developed has relevance for the traditional packing problems of theories of liquids and that topic will be an emphasis of this discussion.

A central problem for the theory of hydrophobic effects is the old, but imperfectly solved, theoretical problem of finding space for a solute in liquid solvents. As is well recognized, liquids are dense, disordered materials and it is this combination of attributes that makes these problems difficult. The description of free volume in hard core model liquids is central to the modern understanding of the van der Waals equation of state and is basic to the ordering phase transitions such as the hard sphere and disk freezing and the liquid crystal phase transitions [34]. In the specific motivating case here, the particular molecular structuring characteristic of liquid water is expected to be important. So we must preserve the fidelity of the description of the structure of liquid water, in addition to tackling the problem of packing in dense, disordered materials.

This lecture develops a new conceptualization of this old problem and new techniques for predicting the fractional free volume accessible to hard core molecules in condensed phases. This new approach is based upon an information theory perspective that has general applicability but was initially explicitly heuristic. Information was sought on a condensed medium of interest and on that basis a prediction of the fractional free volume accessible to a hard model solute was made. For some important cases considered so far, the basic information required for accurate, interesting predictions has been surprisingly modest.

2. Free Volume Statistics Sought

Let's begin by consideration of the solubility of inert gases in aqueous solutions. The medium is liquid water and the solute is idealized as a hard object, perfectly repelling the center (oxygen atom) of each water molecule. For such models the interaction part of the chemical potential of the solute is obtained as

$$\beta\Delta\mu = -\ln p_0, \quad (1)$$

with p_0 the probability that the hard solute could be inserted into the system without overlap of van der Waals volume of the solvent; $1/\beta = k_B T$. This is a specialization of Widom's formula [35, 36]

$$\exp\{-\beta\Delta\mu\} = \langle \exp\{-\beta\Delta U\} \rangle_0. \quad (2)$$

ΔU is the change in the solute-solvent interaction potential energy upon placement of the solute in an arbitrary position in the solvent and the average indicated by $\langle \dots \rangle_0$ is over the thermal motion of the solvent unaffected by the solute. The solute is a test particle for this calculation. For the hard core model being considered, ΔU is either *zero* or *infinity*, so the average sought involves a random variable with value either *one* or *zero*; the averaging collects the fraction of solute placements that would be allowed. If presented with a thermal configuration of a sufficiently large volume of solvent, you might estimate these quantities by performing many trial placements of the solute throughout the solvent and determining the fraction of those trial placements that would be allowed. This estimates V_{free}/V , the fractional free volume accessible to the solute. Thus, Eq. (1) is a free volume formula [37], exact for the model being considered.

The operation of these formulae can be alternatively viewed as follows: Imagine identifying a molecular scale volume at an arbitrary position in the liquid system by (1) hypothetical placement of the solute and (2) determination of those positions of water oxygen atoms that would be excluded due to solute-solvent interactions. Below we will call this volume the observation volume. With such a molecular scale volume defined we could keep track, say during a simulation calculation, of the probabilities p_n that the $n = 0, 1, \dots$ oxygen atom occupants are observed. As the notation suggests, p_0 is the probability that no occupants are observed in the molecular volume. It is clear from this description that our strategy for theoretical prediction of p_0 will be to model the distribution p_n and to extract the extreme value p_0 .

This will be a primitive approach to theories of $\beta\Delta\mu$ and solubilities of inert gases water. Both more and less subtle theoretical works on these topics have been long available. "Less subtle" here means simulation calculations, techniques more straightforwardly useful than many "more subtle" approaches. The "more subtle" means here that further statistical quantities have been introduced for spherical solutes with the intention that they might facilitate more expansive approximate theories. These include

$$d_1(\lambda) = -\frac{dp_0(\lambda)}{d\lambda}, \quad (3)$$

$$G(\lambda) = \left(\frac{-1}{4\pi\lambda^2\rho}\right) \frac{d \ln p_0(\lambda)}{d\lambda}. \quad (4)$$

λ is the radius of a center-to-center exclusion sphere. These quantities have been useful in suggesting physical theories because they have interpretations that are appreciated physically. $d_1(\lambda)$, is the distribution function of distances λ from an arbitrary point in the liquid to the *nearest* solvent center. $4\pi\lambda^2\rho G(\lambda)$ [Eq. (4)] is, in view of Eq. (1), the derivative with respect to exclusion radius of the hydration free energy due to intermolecular interactions, in thermal energy units $k_B T$. It gives the compressive force exerted by the solvent on the hard spherical solute. In addition, $4\pi\lambda^2\rho G(\lambda)d\lambda$ is the expected number of solvent centers in a shell of radius λ and width $d\lambda$ outside a hard sphere that excludes solvent centers from a ball of radius λ .

3. Simulation Results for Liquid Water

Some of the simulation work has determined the quantities of Eqs. (3) and (4) for molecular liquids represented realistically at the current state-of-the-art [14, 16]. Thus we know that $d_1(\lambda)$ for liquid water and for liquid n-hexane are both unimodal with maximum displaced by a distance less than 0.1 Å; the maximum occurs at slightly smaller distances for liquid n-hexane than for liquid water [14, 16]. This difference between liquid n-hexane and liquid water in most probable cavity size is not large. The difference in the most probable cavity size between liquid water and a reference random medium, with sites of the same radius and distributed randomly at the same density, is greater than the difference between n-hexane and water. So the differences observed between the two molecular liquids considered are *not* purely reflections of molecular size and density. This comparison addresses the idea that the low solubility of inert gases in liquid water might be due to the small size of the water molecule and the possibility that "interstitial" cavities will, on this basis, be smaller in water than in coexisting organic liquids of common interest [3, 38]. The fact that the differences between these realistically described molecular liquids are slight is associated with the fact that the basic units considered in n-hexane are the methyl and methylene groups. These are not so different in size from a water molecule. It should be noted also that on a packing fraction basis, typical organic liquids are denser than liquid water [6].

The notable distinction between the results for liquid water and liquid n-hexane is the distribution $d_1(\lambda)$ is significantly narrower for liquid water. This suggests that water is less flexible than n-hexane in opening cavities of substantial size.

Simulation calculations have also produced $G(\lambda)$ for $0 < \lambda < 3.0 \text{ \AA}$, approximately. This size range covers the simplest atomic solutes He and Ne but not much more. This does, however, permit comparison between water and organic solvents, and it permits comparison of available theories with

the simulation data. Thus for the range $2.0\text{\AA} < \lambda < 3.0\text{\AA}$, $G(\lambda)$ for liquid water is approximately two-times larger than for n-hexane. Water exerts a higher compressive force on the surface of an inert solute than do typical organic liquids; water squeezes-out hydrophobic solutes [39].

The checking of theories against the available simulation data for $G(\lambda)$ has also been revealing [14, 16]. We now know that the scaled particle model (SPM) [40, 41] significantly underestimates the numerically exact results for $G(\lambda)$. The Pratt-Chandler (PC) integral equation theory [42-44] predicts results for $G(\lambda)$ that are significantly too large. The more pragmatic revised scaled particle model due to Stillinger [2] typically predicts $G(\lambda)$ between those two theories and with some empiricism about interpolation junctions can describe the available simulation data satisfactorily [14, 16]. For sizes $\lambda \gg 3.0\text{\AA}$ that available computer simulation data are less detailed, the theories less convincing, and the checking has been pursued less vigorously. See, however, the recent results of Reference [45].

4. Information Model

We now return to the theoretical program of predicting p_0 . What are the standard theoretical tools for this? The most immediate guiding theory is the 'inclusion-exclusion' development [46] of Eq. (2) [47, 48]:

$$p_0 = 1 + \sum_{m=1}^{\infty} \frac{(-1)^m}{m!} \int_v d\mathbf{r}_1 \int_v d\mathbf{r}_2 \cdots \int_v d\mathbf{r}_m \rho^{(m)}(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_m), \quad (5)$$

where $\rho^{(m)}$ is the m -body joint density for solvent centers. This is depicted in a standard way in Figure 1. These are standard combinatorial results, more frequently seen in forms such as [46]

$$p_0 = 1 - \langle n \rangle_0 + \sum_{m=2}^{\infty} \frac{(-1)^m}{m!} \langle n(n-1) \cdots (n-m+1) \rangle_0. \quad (6)$$

Here the random variable n is the number of solvent centers within the observation volume and, *e.g.* $\langle n \rangle_0$ is the expected number of centers within the observation volume. Several important points that can be made from Figure 1. The first is that the van der Waals approximation, the primordial free volume model, is obtained from the first two terms shown $\beta\Delta\mu \approx \ln[1 - \langle n \rangle_0]$. The second point is direct and basic: p_0 is naturally expressed in terms of occupancy moments, indeed binomial moments here. The sum truncates sharply for cases where a finite maximum number of particles can be present in the observation volume. The sum can be of practical value in the van der Waals case that only the first nontrivial term must be retained. For large solute volumes or solvent densities, this sum is not directly useful;

we seek a way to exploit the same information but in a more broadly useful form.

$$\begin{aligned}
 p_0 &= \text{○} + \text{○} \text{---} \text{●} \quad \rho^{(1)} + \text{○} \text{---} \text{●} \text{---} \text{●} \quad \rho^{(2)} + \dots \\
 &= 1 - \langle n \rangle_0 + (1/2) \langle n(n-1) \rangle_0 + \dots
 \end{aligned}$$

Figure 1. Mayer-Montroll expansion for the insertion probability p_0 . The standard notation follows [49, 50], e.g., the solid bonds indicate Mayer f-functions. The second line gives the evaluations for the diagrams shown in the case of a hard core solute. n is the number of solvent centers in the observation volume.

The next most immediate theoretical guidance comes from the virial expansion depicted in Figure 2. This can be considered a resummation of the series Figure 1 and is better in the sense that such a truncation cannot produce a negative probability as truncation of Figure 1 can do. However, when that trouble is avoided Figure 2 is not necessarily more accurate. In fact the van der Waals free volume approximation is often satisfactory and then Figure 2 is likely to be less so.

$$\begin{aligned}
 -\beta\Delta\mu &= \text{○} \text{---} \text{●} \quad \rho^{(1)} + \text{○} \text{---} \text{●} \text{---} \text{●} \quad \delta\rho^{(2)} + \dots \\
 &= - \langle n \rangle_0 + (1/2) \{ \langle n(n-1) \rangle_0 - \langle n \rangle_0^2 \} + \dots
 \end{aligned}$$

Figure 2. Virial expansion, notation as in Figure 1. Note that 'virial' often connotes a low density expansion but here we are assuming full knowledge of the medium correlation functions in the absence of the solute; $\delta\rho^{(2)}(1,2) = \rho^{(2)}(1,2) - \rho^{(2)}(1)\rho^{(1)}(2)$. Thus from the perspective of a density expansion is organization shuffles the contributions to the virial coefficients. In fact, here contributions are ordered according to the number of bonds attached to the root point. Successive contributions have a structure that may be derived from that of familiar cumulants with the formal replacement $\langle n^k \rangle_0 \rightarrow \langle n(n-1)\dots(n-k+1) \rangle_0$. See [51, 52]. Table 1 gives formulae for contributions through 5th order. It is helpful to realize that these successive contributions can be directly observed in simulations and those observations can assist the theoretical analysis.

Ultimately these considerations avoid the issue that we have only limited information and we want to make the best prediction of p_0 that we can. When the problem is stated this way what to do next is clear: we model the probabilities p_n on an information theory basis. We consider a relative

TABLE 1. Successive contributions to the series Figure 2. $\binom{j}{k} \equiv j!/[(j-k)!k!]$ is a binomial coefficient.

Order	Formula
1	$\langle \binom{n}{1} \rangle_0$
2	$-[\langle \binom{n}{2} \rangle_0 - \langle \binom{n}{1} \rangle_0^2/2]$
3	$\langle \binom{n}{3} \rangle_0 - \langle \binom{n}{2} \rangle_0 \langle \binom{n}{1} \rangle_0 + \langle \binom{n}{1} \rangle_0^3/3$
4	$-[\langle \binom{n}{4} \rangle_0 - \langle \binom{n}{3} \rangle_0 \langle \binom{n}{1} \rangle_0 - \langle \binom{n}{2} \rangle_0^2/2 + \langle \binom{n}{2} \rangle_0 \langle \binom{n}{1} \rangle_0^2 - \langle \binom{n}{1} \rangle_0^4/4]$
5	$\langle \binom{n}{5} \rangle_0 - \langle \binom{n}{4} \rangle_0 \langle \binom{n}{1} \rangle_0 - \langle \binom{n}{3} \rangle_0 \langle \binom{n}{2} \rangle_0 + \langle \binom{n}{3} \rangle_0 \langle \binom{n}{1} \rangle_0^2 + \langle \binom{n}{2} \rangle_0^2 \langle \binom{n}{2} \rangle_0 \dots$ $-\langle \binom{n}{2} \rangle_0 \langle \binom{n}{1} \rangle_0^3 + \langle \binom{n}{1} \rangle_0^5/5$

or cross information entropy [53],

$$\eta(\{p_n\}) = - \sum_{n=0}^{\infty} p_n \ln \left(\frac{p_n}{\hat{p}_n} \right), \quad (7)$$

where \hat{p}_n represents a "default model" chosen heuristically. The information typically considered are moments of the p_n . We then maximize this information entropy subject to the constraints that the probabilities reproduce the available information. The information typically used is exactly the moments that enter into the series Figure 2, obtained from simulation calculations if necessary. The formal maximization of such this entropy gives probabilities

$$p_j \propto \hat{p}_j \exp \left(- \sum_{k=1}^{\max} \zeta_k \binom{j}{k} \right). \quad (8)$$

where the ζ_k are Lagrange multipliers to be adjusted so that the probabilities finally reproduce the information given initially. The machinery for doing this can be developed straightforwardly. For example, the normalization of the probabilities can be deferred at an intermediate stages of the calculation. Then the final thermodynamic result can be given in terms of the required normalization factor

$$\beta \Delta \mu = \ln \sum_{n=0}^{\max} \frac{\hat{p}_n}{\hat{p}_0} \exp \left(- \sum_{k=1}^{\max} \zeta_k \binom{n}{k} \right). \quad (9)$$

This is suggestive of the calculation of a partition function for a modest-sized set of states with effective interactions. The interesting questions then involve the predictions extracted from the p_j for properties other than the given information. In our case, the property of first interest is $\beta \Delta \mu$.

We can make the comforting observation that use of only $\langle n \rangle_0$ and the natural default model $\hat{p}_j \propto 1/j!$ produces the Poisson distribution as expected; $\zeta_1 = -\ln \langle n \rangle_0$ and $\beta \Delta \mu = \langle n \rangle_0$ as would be found by retaining only

the first term shown in Figure 2. Note that evaluation of the second term there with the Poisson distribution gives zero as it should [52]; $\langle \delta n^2 \rangle_0 = \langle n \rangle_0$ for a Poisson distribution.

Figure 3 shows how this prediction scheme work-outs when the solvent is computer simulated liquid water and the solute is a hard sphere of a size appropriate for comparison with a Ne atom. The immediate point is that a model based upon the two moments that can be readily obtained from experiment, $\langle n \rangle_0$ and $\langle n(n-1) \rangle_0$, fortuitously provides the most satisfactory simple prediction of p_0 . In contrast the Poisson model that uses only a single moment and is the primitive free volume theory is not satisfactory. Further, inclusion of moments higher than the second is not advantageous unless several higher moments are available. The behavior of the information entropy η suggests that the initial two moments do a good job of describing the distribution and the subsequent higher moments are 'uninformative.'

These points are remarkable also because recent analyses [54, 55] have underscored the fact that Percus-Yevick approximate integral equations can be derived on the assumption that solvent density fluctuations are distributed according to a Gaussian probability functional. The results of the present investigations, including particularly [56-59], give further insight and support to those ideas. The Pratt-Chandler approximate integral equation theory of hydrophobic effects [42], at its inception merely a Percus-Yevick analogue, can be given a similar basis [54]. The PC theory is thereby given a better foundation than was available at its genesis.

Note that present modeling even if limited to two moments only is not merely an assumption of a Gaussian probability functional for a density field. The occupancies are also required be nonnegative integers. That this be true of all subvolumes of the observation volume is also a nontrivial restriction that we have found can be important.

That specifically binomial moments are involved in the series above emphasizes the point that the occupancies must be nonnegative integers. Further perspective on the convergence issue is obtained by examination of successive contributions to the series Figure 2. Numerical results are shown in Table 2. The first and second order terms make a significant contribution but by themselves are not close to the full answer. The values of the additional terms do not establish rapid or monotonic convergence to the known full answer. It is suggestive that the average occupancy in this case is 3.77 and that problematic convergence is evident only upon examination of contributions of order 4 and larger. In any case, we can view the information theory model as a technique for reorganization of the series.

TABLE 2. Approximate evaluation of contributions to the series Figure 2 for the circumstances of Figure 3, $\lambda=3.0\text{\AA}$. The column 'Order Contribution' gives approximate values for the formulae of Table 1.

j	$\langle \binom{n}{j} \rangle_0$	Order Contribution	Cumulative Result
1	3.77	3.77	3.77
2	5.75	1.36	5.13
3	4.71	0.89	6.02
4	2.04	1.03	7.05
5	0.51	1.55	8.60
∞	-	-	7.93

4.1. ENTROPY CONVERGENCE

When the typical occupation numbers n are large the granularity of the distribution p_n is expected to be less significant, at least near the center of the distribution and when viewed on a coarse enough scale. In such circumstances the predictions of two-moment information theory models are not significantly different than those of the PC theory. It is remarkable that a simple calculation along these lines gives a convincing explanation of the puzzling and contentious issue of "entropy convergence" in hydrophobic hydration [58].

The phenomenon to be explained is the following: entropies of transfer of non-polar molecules from gas phase or a non-polar solvent into water converge at a temperature of about 400 K to approximately zero entropy change. Similar behavior was also seen in the microcalorimetry experiments on unfolding of several globular proteins. This behavior is insensitive to the particular hydrophobic solute molecule. Since the entropy is a temperature derivative of a hydration free energy, the convergence temperature identifies a region where graphs of hydration free energy versus temperature are extremal, in fact, maximal. Below that region the hydrophobic hydration free energy is increases with temperature but above that region the hydrophobic hydration free energy decreases as the temperature is raised.

The two-moment information theory model above was applied to this problem for hard sphere solutes in water with the heuristic modification that a flat default model was used; $\hat{p}_j \propto \text{constant}$ for $j \leq j_{max}$ and zero otherwise. This latter adjustment was found empirically to give slightly better hydration free energies. The results of the model and simulation calculations accurately agreed on the temperature dependence of the hydration free energies. To analyze this agreement the information theory model was

simplified to a continuous Gaussian distribution that then gives

$$\Delta\mu \approx \frac{k_B T}{2} \left\{ \frac{\langle n \rangle_0^2}{\langle \delta n^2 \rangle_0} + \ln[2\pi \langle \delta n^2 \rangle_0] \right\} \quad (10)$$

$$= T \rho_{sat}(T)^2 \{ k_B v^2 / 2 \langle \delta n^2 \rangle_0 \} + T \{ k_B \ln(2\pi \langle \delta n^2 \rangle_0) / 2 \}. \quad (11)$$

v is the observation volume and $\rho_{sat}(T)$ is the liquid density along the vapor saturation curve so that $\langle n \rangle_0 = \rho_{sat}(T)v$. $\langle \delta n^2 \rangle_0$ is found to be insensitive to temperature for the relevant conditions. Further, the first term of Eq. (11) is larger than the second. Thus the non-monotonic behavior of the free energy with temperature and the entropy convergence is largely a consequence of the non-monotonic variation of $T\rho_{sat}(T)^2$ with temperature. The only molecular parameter to complicate matters is the volume v and with this formula v does not affect the entropy convergence temperature [58]. Thus the temperature of entropy convergence is about the same for a wide family of solutes.

The physical point is: the entropy convergence phenomenon occurs for water because of the low and temperature insensitive values of $\langle \delta n^2 \rangle_0$. In fact, the isothermal compressibility of water at low pressure has a minimum value at $T=319$ K. That temperature differs substantially from the observed entropy convergence temperatures but it is not necessary that these temperatures be approximately equal, just that $\langle \delta n^2 \rangle_0$ be insensitive to temperature in the region $d[T\rho_{sat}(T)^2]/dT \approx 0$.

The technical point of Eq. (10) is: this formula is simple and effective but how it is obtained from the series Figure 2 is not simple. Part of the complication is that two additional twists have been interjected, the flat default model and the continuous approximation.

4.2. PRESSURE DENATURATION OF PROTEINS

It is a common view, based upon our current understanding, that hydrophobic effects provide a nonspecific, cohesive stabilization of compact protein structures. However, it has been argued [60] that our current understanding of hydrophobic effects is not consistent with the experimental facts of pressure denaturation of globular proteins. The information theory model of the previous section was applied also to study hydration free energies and potentials of mean force (pmfs) for two and three hydrophobic spherical solutes in water as a function of pressure [61]. As is well known, those pmfs exhibit contact and solvent-separated minima corresponding, respectively, to cases where the hydrophobic spheres contact each other or where a water molecule intervenes. It was found that increasing pressure shifted the free energy balance of those two cases towards the solvent-separated

circumstance. This suggested an intercalation mechanism for pressure denaturation: as the pressure of the liquid is raised, water molecules are forced into protein structure. A similar point of view can be taken of the formation of clathrate hydrates at elevated pressures: a low pressure hydrophobic effects lead to close contacts and to clustering of hydrocarbon gases dissolved in water. But sufficiently high pressure stabilizes the crystalline phase that eliminates close solute contacts. If attention is focused in the hydrocarbon material this behavior might seem counter-intuitive because the hydrocarbon material seems to expand. But, in view of the thermodynamic principle that increasing pressure stabilizes the phase of lower volume, we conclude that the system may be packed more efficiently and have a lower total volume when water molecules are intercalated into the hydrocarbon clusters. These topics will be the subject of subsequent research.

5. Concluding Comments

Identification of some generalizations and future directions for these theories will provide concluding comments. Firstly, we note that the generalization of these ideas to treat continuous, rather than only hard core repulsive, solute-solvent interactions is known [62].

Secondly, in the context of the aqueous solution problems we note the importance of our restriction here to small molecule solutes. It is by now well recognized that treatment of larger solutes requires consideration of the multiphase character of these solutions on large length scales [2, 56, 61]. For large enough hard sphere solutes dissolved in water close to phase coexistence, the possibility that the solvent will pull away from the solute surface requires specific attention. Further subtleties arise when the solute-solvent interactions are not strictly repulsive but include attractive interactions too [63, 64]. These issues will surely be the subject of further research in the area of hydrophobic effects. It seems likely that an appropriately designed default model should be able to describe such effects in a physical manner.

Thirdly and specifically on the topic of hydrophobic effects, we note that these approaches provide some unanticipated answers [62] to the questions such as "How is water different from hydrocarbon liquids as a solvent for nonpolar solutes?" The importance of the low and temperature insensitive values of the isothermal compressibility of liquid water is noteworthy. However, such answers are not in the format that is most often intended when such questions are asked. Most often such a question solicits information about particular patterns of solvent structure in the neighborhood of a hydrophobic solutes. Some groundwork has been laid for consideration of those detailed structural issues in a format consistent with the discussion of this paper [65]. Pursuit of answers about the detailed structural issues and

their relevance to hydrophobic effects will surely be the subject of future research.

Finally, we note again the relevance of these ideas to the classic problems of packing in liquids. The importance of these issues is reflected in the significance of the hard sphere fluid system to our understanding of liquids generally. Such model systems may not be directly realistic. But it continues to surprise that when attention is directed to new physical problems, *e.g.* the thermodynamics and structure of glasses or folded proteins, understanding of basic packing problems is again requested. Such problems turn-up quite broadly [66-72]. It would be interesting to see the ordering phase transitions associated packing problems, crystallization and liquid crystallization transitions, analyzed on these bases. An initial step along such lines for the hard sphere fluid has been taken [73] but more work is deserved.

We hasten to add that the results so far have not superceded previous theoretical results. But this new approach offers the possibility of better, more physical understandings of packing problems in the equilibrium statistical mechanics of non-crystalline materials and the previous theories of them. This approach *has* achieved new understanding for the problems of primitive hydrophobic effects. By exploiting information external to conventional theories, even simulation data, and by proposing a pattern for utilizing that information, these approaches begin to respond to Andersen's [74] request for a 'theory of theories.'

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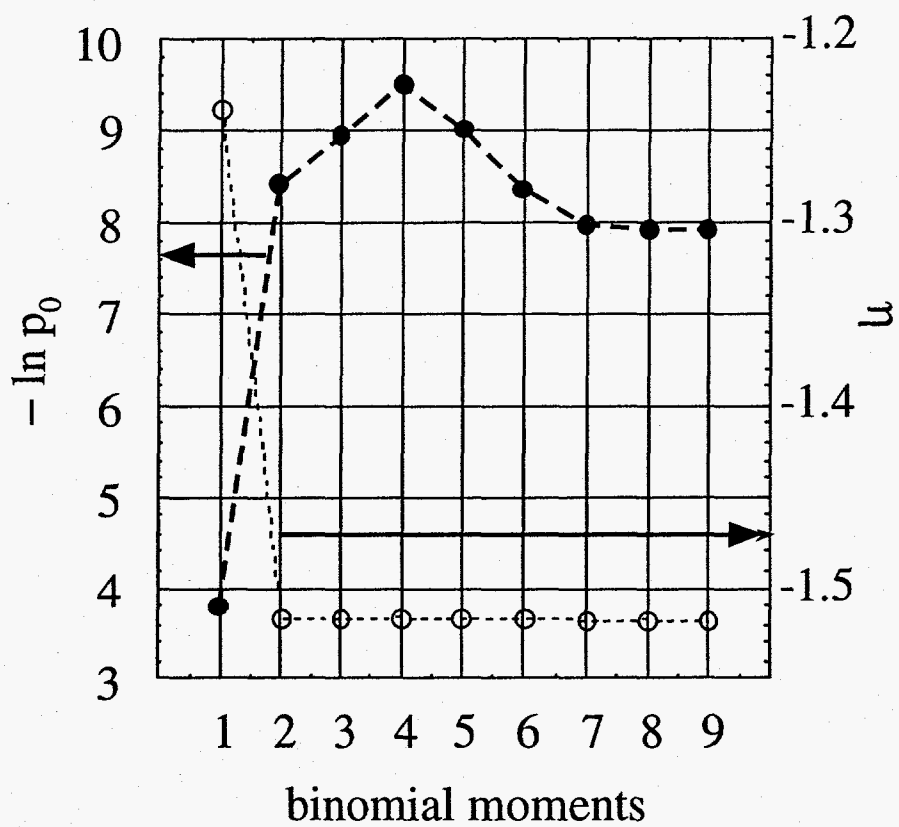


Figure 3. Convergence of predictions for hydration free energy and information entropy with numbers of binomial moments employed. The moment information was obtained from computer simulation of liquid water [56]. $\lambda=3.0\text{\AA}$.