Size Dependence of Transfer Free Energies. 1. A Flory–Huggins Approach

6 **AUTHORS**, INCLUDING:

Sanat K. Kumar
Columbia University
288 PUBLICATIONS **7,249** CITATIONS

Kim A Sharp
University of Pennsylvania
177 PUBLICATIONS **18,414** CITATIONS

Size Dependence of Transfer Free Energies. 1. A Flory–Huggins Approach

Sanat K. Kumar*

*Department of Materials Science and Engineering, Pennsylvania State University,
University Park, Pennsylvania 16802*

Igal Szleifer

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Kim Sharp

*Department of Biochemistry and Biophysics, University of Pennsylvania,
Philadelphia, Pennsylvania 19104*

Peter J. Rossky

Department of Chemistry and Biochemistry, University of Texas, Austin, Texas 78712

Richard Friedman and Barry Honig

*Department of Biochemistry and Molecular Biophysics, Columbia University,
630 West 168 Street, New York, New York 10032*

It has been recently proposed that Flory–Huggins theory (FH), which finds widespread use in the polymer community, be applied to understand the partitioning of relatively short alkane chains between an organic phase and water. Use of this theory, which predicts that the molar volumes of the different species play an important role in determining solubility, results in a significant increase in the hydrophobic surface tension estimated from transfer experiments. However, the application of FH theory to the analysis of alkane solubility has been widely criticized. Here, we derive this theory accounting specifically for the pressure of the lattice system, and show that it is appropriate for transfers from a condensed polymer solvent phase to either a gas phase or a monomer solvent. The sweeping criticisms of the applicability of FH theory to partition experiments that have appeared in the recent literature are therefore not valid. A new result is that FH theory is valid for treating partition data for solutes of arbitrary shape, as long as the solvent is chain-like. On the other hand, Monte Carlo simulations using the chain increment method indicate that Flory–Huggins theory overestimates molecular size effects by 25% even in the case of athermal lattice systems, indicating that the predictions of this theory should be viewed as first-order estimates of true size effects. The physical origins of Flory–Huggins theory are discussed, and connections are made to Hildebrand's free volume theory and also to Sharp et al.'s ideal gas derivation of volume effects. The role of molar volume effects in transfers of solutes from a gas phase to monomer solution are also considered.

1. Introduction

Partition coefficients between nonpolar solvents and water have been widely used to derive information on the magnitude of the hydrophobic effect, which is defined here as the free energy per unit area of a nonpolar surface in contact with water. Free energies are usually obtained from solute transfer experiments using the familiar expression,[1]

$$\Delta G° = -RT \ln\left(\frac{\varrho^{(2)}}{\varrho^{(1)}}\right) \qquad (1)$$

where ϱ is the molar concentration, or number density, of the solute at equilibrium and the superscripts denote the two phases (gas, nonpolar solvent, water, etc.) between which the solute is being transferred.

It has been generally assumed in studies of partitioning that $\Delta G°$ given by eq 1 is a function of solute surface area alone. Dividing $\Delta G°$ by the solute surface area then yields a "surface

tension coefficient", γ, which when extracted from alkane/water systems, provides a measure of the hydrophobic effect. Values of γ determined in this way are often used in biochemical applications, for example, in estimating nonpolar contributions to the free energy of protein folding. The validity of this procedure relies in part on the assumption that transfer free energies are independent of solute size (volume), in which case $\Delta G°$ is a true contact term depending only on solute/solvent interactions. However, polymer theories, such as the Flory–Huggins model, predict that chemical potentials are dependent on molecular size. Consequently, the general expectation for chain-like molecules, such as alkanes, is that $\Delta G°$ contains a molecular volume dependence, as well as a surface area dependence. If we identify $\Delta G°_{int}$ as the component of $\Delta G°$ that is dependent only on contact solute/solvent interactions (sometimes termed the unitary free energy) we may write the general expression

$$\Delta G°_{int} = -RT \ln\left(\frac{\varrho^{(2)}}{\varrho^{(1)}}\right) + f(v_1, v_2, v_p) \qquad (2a)$$

Size Dependence of Transfer Free Energies

J. Phys. Chem., Vol. 99, No. 20, 1995 **8383**

where v_1, v_2, and v_p are the molar volumes of the two solvents and the solute, respectively. If Flory–Huggins theory[2,3] is used to define the volume dependence then eq 2a takes the form

$$\Delta G^{\circ}{}_{fh} = -RT \ln\left(\frac{\varrho^{(2)}}{\varrho^{(1)}}\right) - RT\left(\frac{v_p}{v_1} - \frac{v_p}{v_2}\right) \qquad (2b)$$

Throughout this paper we will refer to the second term on the right-hand side of eq 2b as the Flory–Huggins (FH) term. The explicit consideration of the volume-dependent contribution using eq 2b has the effect of substantially increasing the estimate of γ from ≈25 cal/mole·$Å^2$ (from eq 1) to about 45–50 cal/mole·$Å^2$.[4,5,6,7]

Although the utility of the FH expression in the study of polymeric systems has been well-established, the work of deYoung and Dill,[4] which involved the partitioning of benzene between an n-alkane of variable length [$8 < n < 16$] and water, is the only direct experimental evidence which suggests that molecular size affects transfer free energies between relatively short chain hydrocarbons and water. They found that ΔG° defined following eq 1 depended on the length of the alkane molecules, while $\Delta G^{\circ}{}_{fh}$ was found to be essentially independent of chain length, which is the desired result for a surface term.

Until recently there have been few theoretical studies that dealt with the applicability of polymer theories to the solubility properties of relatively small molecules. A question that has been a concern for some time is whether size effects are only important for chain-like molecules. Hildebrand[8,9] derived an expression for the entropy of mixing hard spheres using free volume considerations. This expression reduces to the FH form when it is assumed that free volume is proportional to molar volume. More recently Sharp et al.[6] demonstrated that the FH term could be recovered exactly from the entropy of mixing of ideal gases under additive volume conditions. Sharp et al.[6] also found that a FH-like term was present in the transfer of solutes from the gas phase to solution, whereas the original FH derivation pertained only to polymer–monomer transfer processes. They argued that since ideal gas mixing terms should not be included in the definition of solute/solvent interactions, $\Delta G^{\circ}{}_{fh}$ was the correct free energy to be used in extracting the magnitude of the hydrophobic effect from partition experiments.

The work of Sharp et al.[5,6] has generated considerable controversy.[10-13] The issue that has raised perhaps the greatest disagreement is the proposed use of eq 2b, rather than eq 1, to define transfer free energies. Ben Naim and Mazo[10] have stressed that the separation of terms described by eq 1 is an exact thermodynamic result, so that ΔG° contains all the information relevant to the transfer process. Consequently, these authors argue that the use of eq 2a is incorrect. Further, Holtzer[14] has argued that Flory–Huggins theory has "no role to play in analyzing data on partition equilibria", while Giesen et al.[15] and Abraham and Sakellariou[16] have raised concerns regarding the applicability of FH theory to the relatively insoluble linear alkanes in dilute aqueous solution.

In our view the most substantive issue under consideration is not how one chooses to define transfer free energy but whether there are significant size-dependent contributions to solubility and how they can best be described. Consequently, while eq 1 is thermodynamically correct, we will emphasize below, in agreement with the suggestion of de Young and Dill[4] and Sharp et al.,[5,6] that it is necessary to introduce size-dependent contributions to solubility, as done in eq 2a, so as to obtain transfer free energies that depend only on solute/solvent contact area. We begin by presenting a generalized derivation of FH theory and show that the FH term in eq 2b, which is a

manifestation of the volume occupied by the molecules, arises even in the limit of zero free volume if one or both of the liquid solvents, between which a solute is being transferred, has chain-like characteristics. As a result of this finding we assert that the FH term is relevant to both gas-to-polymer liquid and liquid-to-liquid transfers if a first estimate of a size-independent transfer free energy is required. This, however, does not hold for gas-to-monomer solution transfer. It is further stressed that other free volume-dependent terms, such as those originally described by Hildebrand,[8] could contribute additionally to the transfer free energy in all cases.

A second issue relevant to the analysis of partition experiments concerns the validity of the FH expression, which is based on a mean-field approximation and only accounts for chain connectivity at the most rudimentary level. We evaluate the applicability of this mean-field model to lattice polymer systems by performing Monte Carlo simulations and calculating chain chemical potentials using a novel technique termed the chain increment method.[17] We find that the FH expression (eq 2b) is a reasonable first approximation to the more general eq 2a, even for mixtures containing short athermal chains. The implications of our results for the magnitude of the hydrophobic effect are considered in the Discussion.

2. Lattice Theory

In this section a lattice model is utilized to derive analytical expressions, in the framework of FH statistics, for the chemical potential of a polymeric solute in the gas phase, as an infinitely dilute solution in a small monomeric liquid solvent, and in a condensed polymer phase. Note that, although we shall use the same lattice to describe all of the equilibrium phases, this restriction could be relaxed to incorporate solvents with arbitrarily varying monomer volumes in the different phases. In addition to the usual excluded volume effects in FH theory, it should be recognized that experimentally accessible situations, involving condensed phases, cannot be considered unless attractive interactions are included. A further key point in connecting lattice models to experimental systems is that the pressure must be defined and be equal across phases in equilibrium. This is done by including holes in the lattice as suggested earlier by Sanchez.[18] Once this is done it becomes possible to define chemical potentials in terms of solute insertion, and also to obtain the free energy of solute transfer between different phases under constant pressure conditions. Specific attention will be paid to identifying the role of molecular sizes in the calculated chemical potential expressions. Although eq 1 will give a thermodynamically consistent value of the free energy of transfer, this value will depend explicitly on the size of the molecules in question when one or more of the solvents involved has a polymeric nature. This leads to a justification for use of the FH model, eq 2b, as a first-order method to obtain transfer free energies which only depend on the alkane–water contact interactions.

2.1. Polymer Chains in a Dilute Gas Phase. We begin by deriving the chemical potentials of chain molecules of length s at very low density in the gas phase following a procedure recommended earlier by Widom.[19] Note that the enumeration of the canonical partition function, Ω, for the many chain system in this case of a dilute gas phase is equivalent to the calculation of the internal partition function of an isolated chain since interchain interactions can be ignored in the zero density limit,[20]

$$\Omega = \exp[-\beta A] = \frac{(Vq^{int})^{N_p}}{N_p!} \qquad (3)$$

8384 *J. Phys. Chem., Vol. 99, No. 20, 1995*

Kumar et al.

Here N_p is the number of polymer chains in the system, q^{int} is the internal partition function, which may also include intramolecular attractive interactions, β is the thermodynamic temperature, and A is the Helmholtz energy of the system of interest. In the athermal limit q^{int} denotes the number of self-avoiding walks that a chain of length s can assume on this lattice. Consequently, the chemical potential of a chain in this gas phase state can be expressed as[21]

$$\beta\mu_p^g = \frac{\beta A}{N_p} = -\ln q^{int} + \ln \varrho_p^g \equiv \beta\mu^{int} + \ln \varrho_p^g \qquad (4)$$

To make contact with eq 1.9 of Ben-Naim[1] it should be noted that the second term after the final equality in eq 4 is the translational contribution to the chemical potential, and the term involving Λ, the deBroglie wavelength, does not appear since it describes kinetic energy effects which are ignored in this development. This term can also be included implicitly as part of μ^{int}, since it will cancel out and therefore play no role in the energetics of transfer between different phases.

2.2. A Single Polymer Chain Dissolved in a Monomeric Solvent. Consider N_s monomeric solvent molecules on a lattice of N_0 sites each of volume v_0 in the athermal limit. The configurational partition function of the pure solvent can be derived exactly to be[20]

$$\Omega_0 = \frac{N_0!}{N_s!(N_0 - N_s)!} \qquad (5)$$

As above we have only considered the contribution of the system potential energy to the partition function and assumed that the contributions from the kinetic energy, which will not play a role in the transfer process, are not included. We now follow a procedure recommended by Sanchez[18] to determine the pressure of the pure solvent phase,[21]

$$\beta P_s = \frac{\partial(\beta A)}{\partial V}\bigg|_{T,N_s} = \frac{1}{v_0}\frac{\partial \ln \Omega_0}{\partial N_0}\bigg|_{T,N_s} \qquad (6)$$

Using eq 5 in eq 6, combined with Stirling's approximation, results in

$$\beta P_s v_0 = -\ln(1 - \phi_s) \qquad (7)$$

where $\phi_s = N_s/N_0$ is the volume fraction of solvent molecules on the lattice. The chemical potential of a solute molecule occupying s lattice sites in a monomeric solvent is obtained following the expression, $\beta\mu_p^s = -\ln(\Omega_1/\Omega_0)$. The partition function of the system comprised of solvent molecules and a single chain of length s, Ω_1, is exactly equal to

$$\Omega_1 = \frac{N_0!}{N_s!(N_0 - N_s)!}q_{int}N_0\left(1 - \frac{N_s}{N_0}\right)^s \qquad (8)$$

This equation was obtained by first quantifying the number of different ways of placing the solvent molecules on the lattice. This quantity is the first factor on the right-hand side of this equation, which follows directly from eq 5. Now quantify the number of different ways of placing a self-avoiding chain of length s on this partially filled lattice. Since the monomeric solvent is uncorrelated, this quantity is equal to the last term in this equation. The q_{int} factor then accounts for the number of different self-avoiding walks that can be realized by the chain. Note that this separation of the conformations of the solvent molecules and the polymer chain only occurs because the solvent

molecules, which are athermal, form an uncorrelated medium. The chemical potential of a chain of length s in an athermal, monomeric solvent is therefore

$$\beta\mu_p^s = \beta\mu^{int} - s \ln(1 - \phi_s) + \ln \varrho_p^s \qquad (9)$$

It is important, at this juncture, to stress that the chemical potential of a single chain in a solvent does not have a FH-like term as in eq 2b.

Next, we introduce cohesive interactions into our development to treat transfer processes between a condensed phase and a gas phase under atmospheric pressure conditions. The energy of interaction between two solvent molecules immediately adjacent to each other is denoted by $-\epsilon_{ss}$ (where $\epsilon_{ss} > 0$). Similarly, the energy of interaction between a solvent molecule and an immediately adjacent polymer segment is $-\epsilon_{sp}$. All interactions involving a vacant site are considered to be athermal as is usual practice.[18] For a lattice of coordination number z, the mean number of solvent–solvent interactions in a pure solvent is given by $zN_s\phi_s/2$. Consequently, the interaction energy contribution to the solvent free energy is $-\epsilon_{ss}zN_0\phi_s^2/2$. Using eq 6 it can be shown that the pressure of the monomeric solvent is now

$$\beta P_s v_0 = -\ln(1 - \phi_s) - \frac{\beta\epsilon_{ss}z\phi_s^2}{2} \qquad (10)$$

Note that the configurational entropy, or excluded volume, makes a positive contribution to the pressure, which we denote as $\beta P_s^{hs}v_0 = -\ln(1 - \phi_s)$ (see eq 7). For water at atmospheric pressure, $v_0 = 30$ Å^3/molecule, and $\phi_s = 0.7$.[22] This yields $P^{hs} = 4.0 \times 10^{-2}$ $k_BT/$Å^3, where k_B is the Boltzmann constant. The pressure of 1 atm corresponds to about 2.5×10^{-5} $kT/$Å^3, which is about 1500 times smaller. Consequently, it is clear that the cohesive interactions make a negative contribution to the net pressure which largely cancels the excluded volume (or "hard sphere") term in this case.

The interaction energy contribution to the chemical potential of the polymer chain is obtained using the same nearest neighbor bond counting scheme, also termed as the Flory counting procedure.[23] This results in the chemical potential of a single polymer chain in the interacting solution,

$$\beta\mu_p^s = \beta\mu^{int} - s \ln(1 - \phi_s) + \ln \varrho_p^s - \beta zs\phi_s\epsilon_{sp} \qquad (11)$$

2.3. The Condensed Polymer Phase. The chemical potential of a chain in a polymeric condensed phase is now derived to understand the origin of the FH term in eq 2b. We consider the most general case where a solute of length s is inserted into a polymeric solvent of length r. Consider an athermal system comprised of N_p chains of length r on a lattice of size N_0 sites. We do not present a derivation of the canonical partition function of this system, which was enumerated originally by Sanchez and Lacombe,[18]

$$\Omega_0 = \frac{N_0!}{N_p!(N_0 - rN_p)!}\left(\frac{z - 1}{N_0}\right)^{(r-1)N_p} \qquad (12)$$

It should be noted here that eq 12 is approximate, in contrast to the corresponding exact expression for solvent systems (eq 5), since the connectivity of chain molecules is incorporated in this calculation only at the (mean-field) level of Flory-like counting. Further, the term $[z - 1]^{(r-1)}$ is the Flory approximation to the internal partition function for each of these athermal chains,

q^{int}. The pressure of this system can be derived following eq 6 as

$$\beta P_p^{hs} v_0 = -\ln(1 - \phi_p) + \phi_p\left(\frac{1}{r} - 1\right) \tag{13}$$

where the volume fraction of the pure polymer phase is $\phi_p = rN_p/N_0$. The chemical potential of a chain of length s when it is in this sea of N_p chains can be derived in analogy to the development presented above for a chain in an athermal solvent,

$$\beta\mu_p^p = \beta\mu_{int} - s \ln(1 - \phi_p) + \ln \varrho_p^p \tag{14}$$

It is important, at this juncture, to note that the expression for the chemical potential of a chain molecule in a polymeric solvent (eq 14) is identical to that for a chain in an athermal monomeric solvent (eq 9) at the same filling. This result, which is a manifestation of the Flory counting adopted in this development, can be understood by studying the insertion probability of a self-avoiding polymer chain of length s into the appropriate athermal solvent[24]

$$p_{ins}(s) = \exp(-\beta\mu_r) = \frac{\Omega_1}{q^{int}\Omega_0 N_0} = (1 - \phi)^s \tag{15}$$

where μ_r is the residual part of the chemical potential of the chain molecule. It is clear that the insertion probability of a chain of length s in the athermal limit is *not* dependent on the architecture of the solvent molecules and only depends on the volume fraction filling of the lattice.

Energetic interactions are now introduced, and it is assumed that the energy of interaction between any two nearest neighbor polymer segments is $-\epsilon_{pp}$. All other interactions are athermal. Following the procedure used for the solvent molecules we can derive the equation of state (EOS) and the chemical potential in this case

$$\beta P_p v_0 = -\ln(1 - \phi_p) + \phi_p\left(\frac{1}{r} - 1\right) - \frac{\beta z\epsilon_{pp}\phi_p^2}{2} \tag{16}$$

$$\beta\mu_p^p = \beta\mu_{int} - s \ln(1 - \phi_p) + \ln \varrho_p^p - \beta zs\phi_p\epsilon_{pp} \tag{17}$$

Note again that eq 17 does not contain the FH term. These results stress, as we shall show below, that the FH term, which is not present in the chemical potential expressions derived for a polymer chain in a monomer or polymeric solvent, must appear when the pressures of the two phases are equalized as required for chemical equilibrium.

2.4. Gas-to-Liquid Transfer for Pure Polymeric Systems.

The transfer of a chain molecule of length s from a pure gas phase to the polymer phase comprised of chains of length r is now considered under the constraint that the two phases must be at the same pressure. The requirement of the equality of pressure across the two phases relates the volume fraction filling of the two phases following eq 16,

$$\ln\left(\frac{1 - \phi_p^p}{1 - \phi_p^g}\right) = \phi_p^p\left(\frac{1}{r} - 1\right) - \phi_p^g\left(\frac{1}{s} - 1\right) - \frac{\beta z\epsilon_{pp}}{2}[(\phi_p^p)^2 - (\phi_p^g)^2] \tag{18}$$

Equating the chemical potential of the chain molecule across

the two phases (eq 17) and using eq 18 then yields

$$\ln\left(\frac{\varrho_p^p}{\varrho_p^g}\right) = \beta zs\epsilon_{pp}\phi_p^p\left(1 - \frac{\phi_p^p}{2}\right) + s\phi_p^p\left(\frac{1}{r} - 1\right) \tag{19}$$

where we have assumed that $\phi_p^g = 0$. Assuming, additionally, that the liquid phase is completely filled with segments then results in

$$\ln\left(\frac{\varrho_p^p}{\varrho_p^g}\right) = \frac{\beta zs\epsilon_{pp}}{2} + s\left(\frac{1}{r} - 1\right) \tag{20}$$

In the special case where $s = r$, this equation simplifies to

$$\ln\left(\frac{\varrho_p^p}{\varrho_p^g}\right) = \frac{\beta zr\epsilon_{pp}}{2} - (r - 1) \tag{21}$$

clearly displaying the Flory–Huggins term separately from energetic effects. We thus have shown that contributions from molar volume play a role in the gas-to-liquid transfer process for a pure polymer.

2.5. Transfer of a Polymer Chain from a Gas Phase to a Monomeric Solvent.

The equilibrium transfer of a polymer chain from a pure vapor phase to a monomeric liquid solvent is now examined. Proceeding as for the gas-to-polymer transfer and equating the chemical potentials of the polymer chains in the two phases under constant pressure results, under the same limiting conditions for ϕ, in

$$\ln\left(\frac{\varrho_p^s}{\varrho_p^g}\right) = \beta zs\left(\epsilon_{sp} - \frac{\epsilon_{ss}}{2}\right) \tag{22}$$

In this case we find that no Flory–Huggins term appears in the free energy of transfer, in distinct contrast to eq 20.

2.6. Transfer of a Polymer Chain from a Polymer Liquid to a Monomeric Solvent.

The development presented in the last two sections allows us to consider the final case of interest to us, the transfer of a chain of length s from a polymer phase comprised of chains of length r to a monomeric solvent. Using eqs 20 and 22 gives

$$\ln\left(\frac{\varrho_p^p}{\varrho_p^s}\right) = s\chi + s\left(\frac{1}{r} - 1\right) \tag{23}$$

where χ is the Flory interchange energy parameter[23]

$$\chi = \beta z\left(\frac{\epsilon_{pp} + \epsilon_{ss}}{2} - \epsilon_{sp}\right) \tag{24}$$

Again the FH term is explicit and appears in the conventional form for the case $r = s$. The essential conclusion of this analysis is that the Flory–Huggins term that was found in eq 2b appears in the transfer of a polymer chain between either a gas or a monomeric solvent phase and a condensed polymeric phase. A simple extension of these ideas to the transfer from one condensed polymer phase to another would result in a term of the type $(s/r_1 - s/r_2)$ in eq 23, which suggests that the specific details of the lattice, such as the cell volume, v_0, do not play a role in determining the free energy of transfer in this context.

3. Computer Simulations: Test of the FH Approach

This section of the paper is devoted to utilizing computer simulations to examine the applicability of Flory theory[23] to

8386 *J. Phys. Chem., Vol. 99, No. 20, 1995*

Kumar et al.

lattice polymer systems. The derivation of the theory involved the use of the mean-field approximation, and the partition functions for the many chain systems were evaluated through a counting procedure where the chain connectivity is maintained to only a first-order level. Thus, although we have established above that terms involving the disparity in size of the constituent molecules are required to properly capture the size dependence of transfer free energies, it is not clear if Flory theory is even adequate to model the systems for which it was developed.

Here we shall use a relatively new technique, termed the chain increment method,[17] to enumerate the chemical potentials of chain molecules in a variety of environments. These results will then be compared to the predictions of Flory theory to examine the range of applicability of this mean-field model to lattice polymer systems.

3.1. The Chain Increment Method. The calculation of the free energies of macromolecular systems, especially condensed phases, is a difficult problem since this involves the determination of the complete partition function for the system. Previously, Widom[19] had suggested that this difficulty could be circumvented through the use of the "test particle method" which involved the random insertion of a ghost particle into a frozen snapshot of the system, which contains N particles in a volume V, and the evaluation of the energy experienced by this test particle. The chemical potential of the particles in the system, μ, could then be obtained through the relationship,

$$\beta\mu = -\ln\langle\exp(-\beta U)\rangle - \ln\left(\frac{V}{N\Lambda^3}\right) \equiv \beta\mu_r + \ln(\varrho\Lambda^3) \quad (25)$$

where U is the energy experienced by the ghost particle, and $\langle\rangle$ represents a canonical ensemble average. While the second term is the "ideal" gas contribution, μ_r is the residual chemical potential, which is the quantity that is evaluated in the simulations. It has been shown that this method is very useful for small spherical particles at all densities, except those corresponding to solid-like phases.

The direct extension of this test particle method for the calculation of the chemical potentials of the components of a macromolecular phase would involve the random insertion of a polymer chain into a frozen snapshot of the medium of interest. Frenkel and co-workers[25] and dePablo et al.[26] have shown that this procedure will encounter sampling problems for chains longer than ≈ 5 at liquid-like densities since the randomly inserted chain will, in almost all cases, overlap either itself or one of the other molecules in the system. Consequently, there is a need for a new procedure to evaluate the chemical potentials of truly long polymer chains and the one we shall use, termed the chain increment method,[17] allows for this calculation. This method utilizes the fact that, although the insertion of a whole chain as a test particle into a system encounters difficulties, the corresponding insertion of a single monomer encounters very little difficulty until one approaches solid-like densities. Therefore the method splits the calculation of the chemical potential of a chain of length s into a sequence of s separate calculations, where the chain is incrementally grown to its full length a unit at a time in each of the simulations. Each simulation therefore results in the evaluation of the *"incremental chemical potential"* of a chain of length x ($0 < x \leq s$) a quantity which is formally defined as

$$\mu_{inc}(x) = \mu_{r,chain}(x+1) - \mu_{r,chain}(x) \quad (26)$$

Here $\mu_{inc}(x)$ is the incremental chemical potential of a chain of length x, which is defined as the difference in residual chemical potential of a chain of length $x + 1$, $\mu_{r,chain}(x + 1)$, and the
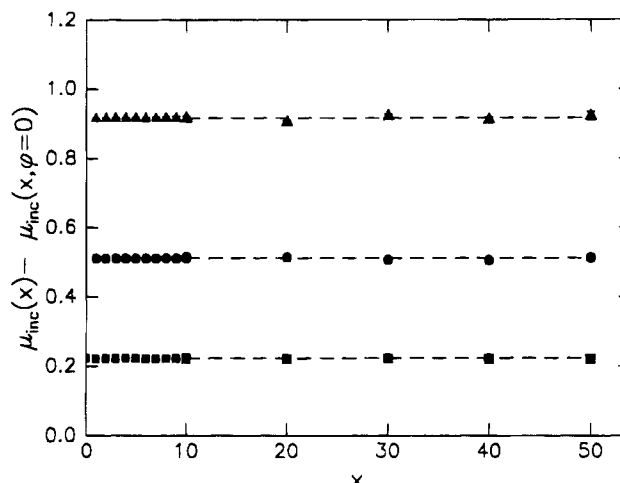
Figure 1. Incremental chemical potentials for a chain of length x in an athermal monomer solvent. The symbols are results from simulation for $\phi = $ (■) 0.2, (●) 0.4, and (▲) 0.6. Lines are the exact result.

corresponding quantity for a chain of length x. The residual chemical potential of a chain of length s can then be obtained by summing the incremental chemical potentials of all chains shorter than s,

$$\mu_{r,chain}(s) = \sum_{x=0}^{s-1} \mu_{inc}(x) \quad (27)$$

The systems simulated in this work were considered in a space that was discretized into a cubic lattice filled with either a monomeric ($r = 1$) or polymeric ($r = 50$) solvent to a volume fraction of ϕ. Typical lattices were $30 \times 30 \times 30$ in size, and periodic boundary conditions were assumed in all three directions. The systems only included excluded volume interactions.

A single chain of length x ($0 \leq x \leq 50$) was placed in the system which was simulated at equilibrium with standard moves such as reptation and crank-shaft moves.[17] The moves were accepted using the Monte Carlo method with Metropolis importance sampling. The system was then frozen at random times, and a test bead was added to a randomly selected end of the chain of length x. The energy of interaction experienced by this test bead, U_x, was tabulated and the incremental chemical potential obtained through the relationship,[17]

$$\beta\mu_{inc}(x) = -\ln\langle\exp(-\beta U_x)\rangle \quad (28)$$

The results obtained from these simulations are discussed below.
3.2. Results. We begin by considering the chemical potentials of chain molecules inserted into a monomeric solvent (see ref 27 for more details). The exact analytical expression for the incremental chemical potential in this case is (see eq 9)

$$\beta[\mu_{inc}(x) - \mu_{inc}(x,\phi = 0)] = -\ln(1 - \phi) \quad (29)$$

Here $\mu_{inc}(x,\phi = 0)$, which is the incremental chemical potential at zero monomer concentration, is the contribution of intramolecular interactions which we have denoted as q^{int}. In Figure 1 we compare this analytical prediction with results from computer simulations for monomer solvent volume fraction fillings, ϕ, of 0.2, 0.4, and 0.6, respectively. It can be seen that the results from the computer simulations agree quantitatively with analytical theory in these cases. Further, the incremental chemical potentials are independent of chain length, again in agreement with theory. These results confirm that the simulation procedure allows for an exact enumeration of the thermodynamics of the polymer—monomeric solvent system at infinite dilution.

Size Dependence of Transfer Free Energies

J. Phys. Chem., Vol. 99, No. 20, 1995 **8387**
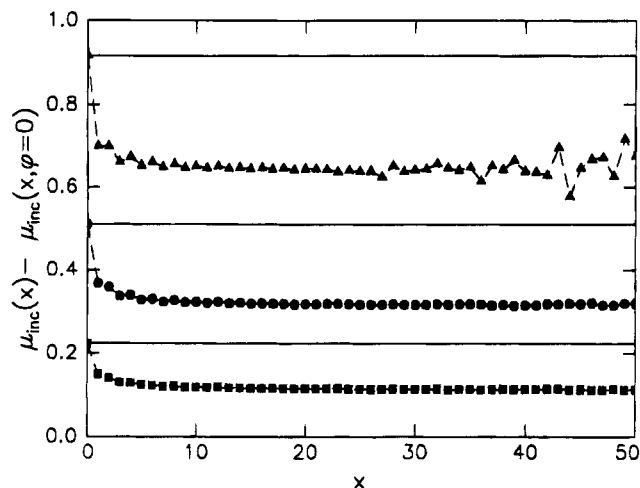
Figure 2. Incremental chemical potentials for a chain of length x in an athermal polymer solvent of length 50. The symbols are results from simulation for $\phi = $ (■) 0.2, (●) 0.4, and (▲) 0.6. Dark lines are the Flory—Huggins result with density decreasing from top to bottom.

Having examined the situation of a single chain dissolved in a monomeric solvent, we now examine the other phase involved in the development presented above, *i.e.*, a chain dissolved in a sea of chains of length 50. Again, we have considered an athermal system. The results of the simulations are plotted in Figure 2, and the first point we note is that the incremental chemical potentials are not chain length independent. Instead they are strongly dependent on chain length for short chains, $x < 10$, after which they assume their asymptotic, chain length independent value.

Examination of the theory developed in section 2 suggests that the incremental chemical potentials, in the Flory approximation, are expected to also follow eq 29 in this case, independent of chain length. A comparison of this prediction with the simulation results at three different filling fractions, ϕ, of 0.2, 0.4, and 0.6, respectively, suggests that the number predicted by the theory is in exact agreement with the simulation result corresponding to the insertion of a monomer into the chain fluid, $\mu_{inc}(0)$. The analytical result, however, overpredicts the simulation result for the incremental chemical potentials associated with all other chain lengths by about 25%.

In summary, the computer simulations have shown that Flory theory is only able to approximate the effects of chain connectivity on the calculated chemical potentials, except when one considers an athermal monomeric solvent, where it is exact. Thus we stress that, although Flory theory does represent a first-order method to incorporate the effects of connectivity on free energies of transfer, the results obtained are clearly an approximate, model-dependent estimate of this important quantity.

4. Discussion

4.1. Defining Transfer Free Energies. The definition of transfer free energies and the relative merits in using eqs 1 or 2 to analyze partition experiments are examined in this section. It is emphasized that, at equilibrium, the free energy change associated with the transfer of a solute between any two phases must be zero. While there is no thermodynamic restriction on the manner this "zero" may be split, a particularly useful procedure is to place solute—solvent interaction terms on the left side of the equation and combinatorial/translational entropy terms on the right. (The phrase "unitary" free energy is often associated with interaction terms and "cratic" to the entropic terms, but there are ambiguities associated with their definitions).

The merit of defining free energies in terms of eq 1 is, as emphasized by Giesen et al.,[15] that all experimental quantities appear on the right-hand side of the equation. However, the use of eq 1 implies that other size effects are being mixed with solute/solvent interaction terms in the definition of the transfer free energy, which severly limits its value as an interesting physical quantity. In contrast, the use of eq 2a will include the effects of molecular size explicitly in the combinatorial part of the transfer free energy so that a size-independent unitary quantity can be extracted from experiments. However, since no exact analytical expression is available for $f(\nu_1, \nu_2, \nu_p)$ (eq 2a) its approximation with the FH term (eq 2b), or any other expression, implies that a model-dependent approximation for size effects is being added to the ln ϱ term, which is model independent. Once one understands the underlying issues, it is of little consequence whether one uses eq 1 or 2b. In this light the emphatic negative response of Ben-Naim and Mazo[10] and Holtzer[14,28] to the use of eq 2b thus seems somewhat extreme.

It should be pointed out in this regard that Sharp et al.[6] have advocated the universal use of eq 2b to model partition phenomena, irrespective of the size and shape of the solute and the solvent. The basis of their argument is the demonstration that an expression, identical in form to the FH term, corresponds to the ideal contribution to the entropy of mixing under additive volume conditions. The validity of their derivation has been questioned by Ben-Naim and Mazo,[10] but these workers failed to consider the experimental condition of additive volumes, from which this term arises. In fact, this term is quite general and has been derived by a number of different treatments.[11-13] It does not, however, capture the physics of chain connectivity effects which, as shown in this work, are properties only of the polymer phase. As will be shown in a forthcoming publication,[29] even for spherical solvent molecules, the favorable contribution to the entropy due to ideal gas expansion is clearly present, but this effect may be thought of as being largely cancelled by nonideal excluded volume effects of opposing sign. Thus the partition of free energy advocated by Sharp et al.,[6] though formally valid, need not provide a generally useful approach to the analysis of partition data.

4.2. Entropy Changes on Solvation. Here we consider in more detail the conformational and translational entropy changes involved in moving a chain molecule from a gas phase to a monomeric solvent when the transfer is done at constant volume or at constant pressure. The former process, which is natural in the development presented to this point, from eqs 5 and 8 yields

$$\frac{\Delta S_{NVT}}{k_B} = s \ln(1 - \phi_s) \qquad (30)$$

where we have denoted the entropy change with a subscript of NVT to denote mixing under "constant volume" conditions.[30] It can be seen immediately that the entropy change in this process is *negative* suggesting that the process of dissolving a chain into a solvent under constant volume conditions is an unfavorable process. From an examination of the equation of state of the pure solvent (eq 7) we can immediately write

$$\frac{\Delta S_{NVT}}{k_B} = -s\beta v_0 P_s^{hs} = -\beta v_p^{hs} P_s^{hs} \qquad (31)$$

where v_p^{hs} ($=sv_0$) is the "hard sphere" volume of the polymer chain. The corresponding result for transfers under constant pressure conditions, which are most relevant to the experimental situations of interest, can be derived following the thermody-

namic relationship

$$\frac{\partial S}{\partial N_{\mathrm{P}}}\bigg|_{T,P,N_s} = \frac{\partial S}{\partial N_{\mathrm{P}}}\bigg|_{T,V,N_s} + \frac{\partial P}{\partial T}\bigg|_{V,N_s,N_\mathrm{p}} \bar{V}_\mathrm{p} \qquad (32)$$

where N_p is the number of polymer chains in the system. Evaluating the derivatives and assuming the partial molar volume of the polymer, $\bar{v}_\mathrm{p}$ is approximately equal to $(s/\phi_s)v_0$ immediately results in

$$\frac{\Delta S_{NPT}}{k_\mathrm{B}} = \beta v_\mathrm{p}^{\mathrm{free}} P_\mathrm{s}^{\mathrm{hs}} \qquad (33)$$

where $v_\mathrm{p}^{\mathrm{free}} = sv_0((1/\phi_s) - 1)$ is the "free volume" associated with the polymer chain that is inserted into the fluid. In contrast to the *NVT* ensemble it is clear that solvation under constant pressure conditions is entropically favored. In spite of this difference in entropy changes on mixing, the corresponding chemical potentials in the two ensembles cannot be different. Consequently, it is clear that the unfavorable entropy reduction in the *NVT* ensemble can be offset, in the presence of attractive interactions, by stronger interactions due to compression of the solvent,[31] combined with any work terms present in the *NPT* case (see also discussion in reference 32). This difference in entropy change on solvation in these two ensembles was previously assumed to be very small,[33] but it is in fact significant, as pointed out by Laziridis and Paulaitis.[11] We have derived these differences within the framework of the lattice model to reemphasize this point.

The entropy change associated with dissolving a polymer chain of length s in a polymeric condensed phase comprised of chains of length r can also be derived in the *NVT* ensemble,

$$\frac{\Delta S_{NVT}}{k_\mathrm{B}} = s \ln(1 - \phi_\mathrm{p}) = -v_\mathrm{p}^{\mathrm{hs}}(\beta P_\mathrm{s}^{\mathrm{hs}}) \qquad (34)$$

where the pressure utilized here is that of the *pure hard sphere solvent system* at the same filling fraction as the polymer phase. The rationale for using the hard sphere pressure, and not the pressure corresponding to the polymeric solvent, can be visualized by studying the insertion probability of a self-avoiding polymer chain of length s into the solvent at constant volume in the Flory approximation (see eq 15).[24] It is clear that the insertion probability of a chain of length s is *not* dependent on the architecture of the solvent molecules and only depends on the volume fraction filling of the lattice, thus explaining the use of the hard sphere pressure. Similarly for transfers at constant pressure we have

$$\frac{\Delta S_{NPT}}{k_\mathrm{B}} = v_\mathrm{p}^{\mathrm{free}}(\beta P_\mathrm{s}^{\mathrm{hs}}) + s\left(\frac{1}{r} - 1\right) \qquad (35)$$

which should be contrasted with eq 33. The difference in entropy of an insertion at constant pressure into a monomeric solvent vs a polymeric solvent directly yields the FH term in the free energy of transfer, showing that this term is a manifestation of the connectivity of the chain molecules which form one phase involved in the transfer process.

4.3. The Origin of Flory–Huggins Theory. Equations 20, 22, and 23 are the major results of our theoretical development. These results demonstrate that, within the mean-field approximation with Flory counting, the FH term (eq 2b) necessarily arises in the transfer of a polymer from a condensed polymer phase to a solvent phase. Similar terms also appear for the transfer of a polymer chain from a gas phase to a polymer liquid, but not for a polymer solute transferred from a gas phase

to a monomeric solvent. Several implications of these results for determining unitary transfer free energy information from partition coefficient data are discussed below.

To understand the molecular origin of the FH $(r - 1)$ term in gas-to-polymer phase or polymer-to-solution phase transfer, consider the physical interpretation of the entropy changes of the solute on dissolution under constant pressure conditions, eqs 33 and 35, respectively. In each case there is a favorable configurational entropy contribution to the dissolution of the polymer which arises from the "solvent" being able to explore the "free volume" accompanying the solute. However, when the "solvent" is polymeric there is also an unfavorable contribution that arises because the number of configurations available to the solvent is reduced due to chain connectivity effects. Note that there are two distinctly different contributions to the chemical potential: the free volume associated with the chain, and the $s(1/r - 1)$ term which is only driven by chain connectivity effects for the solvent molecules. Further, the $s(1/r - 1)$ term will continue to be present even in the limit of zero free volume. These aspects serve to differentiate the Flory–Huggins theory from the Hildebrand free volume model as will be discussed further in section 4.5.

The previous discussion establishes a relationship between Flory–Huggins theory and *PV* terms. The expression of chain connectivity effects in terms of *PV* contributions can be further illustrated by the following argument. Consider a phase comprised of monomeric solvent alone and one comprised of polymer chains of length r both being at the same filling fraction, ϕ, in the athermal limit. Using the equations of state for the two systems derived above (eqs 7 and 13) it is easy to show that

$$\beta r v_0 (P_\mathrm{p}^{\mathrm{hs}} - P_\mathrm{s}^{\mathrm{hs}}) = r\left[-\ln(1 - \phi) + \phi\left(\frac{1}{r} - 1\right) + \ln(1 - \phi)\right] = -\phi(r - 1) \qquad (36)$$

Equation 36 clearly shows that the pure polymer phase would be at a lower hard sphere pressure than a corresponding monomer solvent at a given filling fraction, with the difference in pressures being directly related to the FH term appearing in the transfer expression. Indeed, if a "Maxwell demon" were introduced into a pure polymer system and it snipped $N_\mathrm{p} - 1$ of the chains into their monomers keeping the volume of the system constant, then the pressure would immediately increase by an amount given by eq 36. The system would then expand so as to reduce its pressure to its original value, and the chemical potential of the chain would change by $(r - 1)$. This clearly establishes that the FH term in the transfer free energy between a polymer and monomer phase is associated with *PV*-like work of a hard sphere solvent. This point is also clear from comparing eqs 11 and 17 or from eq 15, which demonstrates that, within the mean-field approximation, the hard sphere contribution to the chemical potential of a solute molecule is a function of solute size and solvent packing fraction, independent of the solvent size or shape. The FH term arises only when the condition of equal pressure is applied, as pointed out in the discussion following eq 15.

It should be recognized that the Flory–Huggins term occurs in all cases where the constituents of the two solvent media involved in the transfer process are chains of different size. The only apparent violation of this "rule" is the transfer of a polymer chain from a pure gas phase to a monomeric solvent. By recognizing that the primary constituent in a gas phase is unoccupied lattice sites, or holes, we can reconcile all of our theoretical findings. Another important conclusion we draw from this analysis is that the $(r - 1)$ term is a manifestation not

Size Dependence of Transfer Free Energies

J. Phys. Chem., Vol. 99, No. 20, 1995 **8389**

just of the molecule being transferred but also of the molecules which constitute the condensed phase solvent.

4.4. The Applicability of Flory–Huggins Theory to Partition Data.

The major objections that have been raised to the use of Flory–Huggins theory to analyze alkane partition data is that the theory is not appropriate for dilute solutions and short chains.[15,16,28] This is indeed the standard perception, but the results of the analysis presented above lead to a very different conclusion. First, as shown in Figure 1, Flory statistics are exact for a single self-avoiding polymer chain on an athermal monomer lattice. However, this issue is in any case irrelevant to the analysis of partition data since we have seen that the source of the FH term lies in the alkane phase, which is hardly dilute. Indeed, the term even arises in transfers to the gas phase, which is a new and quite unexpected result.

The most relevant criticism of the use of the FH term is based on its performance in the polymer phase, and here Figure 2 suggests that it overestimates the chemical potentials of short chains by about 10% (1 < x < 4), and by about 25% for longer chains. Thus, FH theory would appear to provide a reasonable first approximation to be used in the analysis of partition data. However, it is stressed that the molecules considered in these simulations are very simple lattice chains, and the connection of these entities to free space alkane chains, which include bond and torsional angle restrictions, is not direct. Indeed, recent work of Hall and co-workers[24] has shown that the FH theory itself fails when extended to hard sphere chains in free space. While there is therefore a need for better theories for modeling realistic alkane chains, it is clear that the Flory–Huggins theory provides a reasonable estimate of size effects and hence its use in analyzing small molecule partitioning data following eq 2b is expected to provide an improved estimate of hydrophobic surface terms as compared to classical approaches.

4.5. Volume Contributions to Solubility.

We have seen that Flory–Huggins theory results in volume effects that are specific to chain-like molecules. However, there are other possible sources of volume effects. As shown in eq 33, the entropy change associated with adding a polymer to a monomer solvent under constant pressure conditions is given by the product of the hard sphere pressure and the free volume introduced. This result is quite general and for example, as will be shown in a forthcoming publication,[29] can be obtained explicitly from a hard sphere equation of state. This is essentially a generalization of Hildebrand's derivation[8] and argues that there will always be size-dependent contributions to the entropy, independent of the shapes of the molecules involved.

Despite the relationship between the Hildebrand and Flory–Huggins expressions, there is a fundamental and very important difference between them as alluded to earlier. Hildebrand's expression arises from the first term on the right-hand side of eq 35 while the Flory–Huggins expression corresponds to the second term. The former is a property of any solvent while the latter is an additional effect specific to chain-like molecules. Note, however, that the first term depends on the existence of free volume while the second term does not. In fact in obtaining eqs 20, 22, and 23, we considered the simple limiting condition $\phi \rightarrow 1$ which causes free volume effects to disappear while chain connectivity effects remain. It should also be pointed out that the free volume term will yield a size-dependent contribution to the transfer free energy only if the free volume is proportional to the molar volume. Indeed if the free volume were proportional to the surface area (an equally plausible hypothesis, particularly for large solutes), its contribution to the chemical potential might most appropriately be regarded as a contact free

energy and included as an intrinsic component of the solute/solvent interaction.

Although Ben-Naim and Mazo[10] insist on the use of eq 1, these authors nevertheless argue that volume-dependent terms make an important contribution to transfer free energies. Thus, although they do not point this out, they apparently agree with the central conclusion of Sharp et al.[5,6] However, their criticism based on scaled particle theory is physically irrelevant because the magnitude of the volume-dependent term in this theory depends critically on the pressure. As is well-known[34] the magnitude of this term under atmospheric pressure conditions is extremely small so that scaled particle theory predicts that there will be no volume-dependent contributions to solubility. This illustrates the uncertainty associated with the application of scaled particle theory to other than essentially spherical molecules.

4.6. Arbitrary Shapes.

The relevance of Flory–Huggins theory to molecules that are not linear chain-like molecules has been a problem of interest for some time. Prausnitz and co-workers[35,36] have extended Flory–Huggins theory to consider molecules of different degrees of compactness and concluded that the FH term represents an upper limit for size effects. Given the fact that Flory–Huggins theory is in itself only a first-order approximation, it is likely that the issue can only be resolved through explicit simulations of the type described for the chain increment method.

A second question that has only been indirectly addressed is whether solute or solvent shape is the crucial variable. This issue pertains directly to the experiments of de Young and Dill[4] where benzene was transferred between an alkane phase and water. While we have clearly shown that the origin of the term $s(1/r - 1)$ is a manifestation of not only the size of the solute molecule, s, but also of the alkane solvent molecule, r, nevertheless we argue here that the properties of the solvent are primarily responsible for size effects as embodied in this term. To see this, consider the insertion of a compact, globular solute molecule occupying s lattice sites into a polymeric fluid where each chain is linear with length r in the Flory approximation. In this case the results derived above (eq 9) would continue to hold and the use of Flory–Huggins theory to model the entropic part of the transfer process is appropriate. This result is consistent with the success of the de Young and Dill analysis for the transfer of a benzene molecule between a linear alkane phase and water. The situation where the solvent phase itself is composed of compact molecules, however, is out of the realm of the analysis presented here, and clearly, the explicit treatment of these systems would be of great interest in this regard.

4.7. The Magnitude of the Hydrophobic Effect.

A clear conclusion of our analysis is that linear alkane/water partition coefficients should be affected significantly by size effects. Since the FH term is found to be a reasonable approximation of these effects for chain-like molecules, even in dilute solution, the value of the hydrophobic surface tension, γ, appears to be significantly larger than that derived from eq 1. This result is in agreement with the conclusions of de Young and Dill[4] and Sharp et al.[5,6] Whether the number is as large as predicted by FH theory (approximately 45 cal/mole·Å^2) is difficult to determine, but this value does appear to be a reasonable first approximation.

Let us now reconsider eq 2b in the form which was employed for analyzing the transfer of benzene molecules between an alkane phase and water in ref 4,

$$\Delta G^{\circ}_{\text{fh}} = -RT \ln\left(\frac{\varrho^{(\text{water})}}{\varrho^{(\text{alkane})}}\right) - RT\left(\frac{v_{\text{benzene}}}{v_{\text{alkane}}} - \frac{v_{\text{benzene}}}{v_{\text{water}}}\right) \quad (37)$$

This equation suggests that the molar volume of water explicitly enters the evaluation of the free energy of transfer. Our analysis, following eq 23, can be applied to this situation if we assume that the size of a lattice cell in the polymer phase is defined by the molar volume of a methylene unit. This is a reasonable assumption since alkane chain conformations can be defined through different spatial orientations of these individual groups, a fact that is utilized for example in the rotational isomeric states theory of these molecules.[23] By the same argument, the size of a single water molecule then defines the lattice size of the aqueous phase, which then plays the role of the monomeric solvent in the transfer process. Further, the lattices defining the two solvent phases can be treated as identical since the molar volume of water, v_{water} (=18 cm^3/mol), is very similar to that of methylene, $v_{methylene}$ (=15 cm^3/mol). The operational definitions employed in converting eq 23 so as to be applicable to the transfer of benzene from an alkane phase to water are

$$s = \frac{v_{benzene}}{v_{methylene}}; \quad r = \frac{v_{alkane}}{v_{methylene}} \tag{38}$$

from which it follows that

$$\Delta G^{\circ}_{fh} = -RT \ln\left(\frac{\varrho^{(water)}}{\varrho^{(alkane)}}\right) - RT\left(\frac{v_{benzene}}{v_{alkane}} - \frac{v_{benzene}}{v_{methylene}}\right) \tag{39}$$

which is somewhat different in form from that employed in ref 4. It may be observed that the molar volume of water does not directly enter in the evaluation of transfer free energies following eq 39 and the source of the $(r-1)$ term lies purely in the alkane phase. No contribution is made by the water phase since it is a monomeric solvent. While there is a conceptual difference between eq 37 and eq 39, operationally, the derived values of the free energy of transfer are not altered since the molar volumes of methylene and water are practically identical.

It should be pointed out that the values of γ discussed here are obtained using the "accessible" surface area which is the surface defined by the center of the water molecules surrounding the solute. A number of workers have pointed out that if the smaller "molecular surface" (the solute/solvent contact surface) is used, the value of γ obtained is much closer to the macroscopic value, without invoking curvature effects.[14,37] The theoretical justification for using the accessible surface is that it is proportional to the number of water molecules that can be packed around a solute. It also arises naturally in scaled particle theory.[34] In contrast, there is no physical justification for using the molecular surface, and moreover, it seems unrealistic to invoke a model in which surface tension does not depend on curvature. Thus, the use of the molecular surface appears to be an ad-hoc procedure that has no theoretical basis.

While the value of the microscopic hydrophobic surface tension appears to be much larger than previously believed, the situation for gas phase-to-water transfer is uncertain. As we have seen, FH-like size effects are not relevant to this process, whereas the importance of free volume effects is difficult to determine. This would appear to agree with the study of Giesen et al.[15] who analyzed the solubilities of linear and branched alkanes in water and found that a better fit of transfer free energy to surface area was obtained if eq 1 rather than eq 2b was applied. On the other hand, there are clearly other unaccounted contributions to solubility as is evident from the fact that the gas phase-to-water solubilities of cyclic alkanes obtained from eq 1 are essentially independent of surface area whereas those obtained from eq 2b exhibit a surface area dependence.[38] Thus,

the experimental situation regarding gas phase-to-water transfer appears to remain unresolved.

5. Conclusions

By adding empty lattice sites to our derivation of FH theory, we are able to recover both Hildebrand-like free volume terms as well as the FH term. The former are characteristic of any solute while the latter arises only for chain-like solvent molecules. Both can be related to PV work of expansion for related hard sphere fluids.

The Flory–Huggins term, which is a manifestation of chain connectivity, is a property of the polymer phase and is present in transfers from a chain solvent phase to either the gas phase or to a monomeric condensed phase but not from the gas phase to the monomer phase. The role of connectivity can be seen in an earlier formal development by Chandler[39] where it is manifest in the ideal translational entropy for n-mers. It is evident that the form given for this contribution is equivalent to the Flory entropy. Since the Flory–Huggins term constitutes a first approximation to size effects that do not reflect contact intermolecular interactions, it is appropriate, within the limitations of this theory, to obtain surface-dependent free energies from eq 2b or, equivalently, to apply an FH "correction" to the free energies defined in eq 1.

Contrary to claims made in the literature, both eq 1 and eq 2a are thermodynamically valid ways of defining transfer free energies. Equation 1 has the advantage that all experimental quantities appear on one side of the equation while eq 2b has the advantage that it approximately separates the solute/solvent size differences from the transfer free energies.

The physical origins of FH theory may be thought of as resulting from the relationship between the hard sphere pressure of a solvent and the packing fraction. Indeed, the FH term only arises when the condition of pressure equalization between the two phases is applied.

The entropic part of FH theory is valid for solutes of arbitrary shape in chain-like solvents. In applying FH theory to a particular phase the essential variable that enters in the calculation of transfer free energies is not the specific values of the chain lengths of the solute and the solvent but rather their ratio s/r. Consequently, the results presented in this work, though derived through the device of a lattice model, do not explicitly depend on this construct.

Within the limitations of lattice theory, the entropy of adding a solute to the solvent under constant pressure conditions is equal to the product of the lattice (hard sphere) pressure and the free volume. Since adding a solute under constant volume conditions results in a decrease in entropy, there must be compensating enthalpic terms due to solvent compression in this case so that the chemical potential change will be the same under constant volume and constant pressure conditions.

Use of the chain increment method to evaluate chemical potentials indicates that FH theory is only a first-order approximation which overestimates the chemical potentials of polymeric chains in macromolecular solvents. The method, however, allows for the estimation of the free energies of polymer chains of arbitrary architecture in solvents and is therefore capable of providing information needed to build more accurate theories to model the condensed polymer state. This represents an obvious area of future research.

An important conclusion of this study is that volume dependent contributions originating in the alkane phase affect partition coefficients of solutes between alkane and water. Indeed, such effects of solvent size can be seen to play an explicit role in alkane to water transfer free energies calculated

Size Dependence of Transfer Free Energies

J. Phys. Chem., Vol. 99, No. 20, 1995 **8391**

by Pratt and Chandler.[40] Equation 2b provides a first-order approximation for obtaining size-independent transfer free energies from linear alkane/water partition coefficients. The large value (45 cal/mole·Å^2) for the hydrophobic surface tension derived in this way is likely to be a better estimate than the value (25 cal/mole·Å^2) obtained from eq 1. On the other hand, since it is uncertain whether size effects contribute to gas phase-to-water transfers, there is no clear justification for using eq 2b to evaluate this process.

References and Notes

(1) Ben-Naim, A. *Solvation Thermodynamics*; Plenum: New York, 1987.

(2) Flory, P. J. *J. Chem. Phys.* **1941**, *9*, 660.

(3) Huggins, M. L. *J. Chem. Phys.* **1941**, *9*, 440.

(4) DeYoung, L. R.; Dill, K. A. *J. Phys. Chem.* **1990**, *94*, 801.

(5) Sharp, K. A.; Nicholls, A.; Fine, R. M.; Honig, B. *Science* **1991**, *252*, 106.

(6) Sharp, K. A.; Nicholls, A.; Friedman, R.; Honig, B. *Biochemistry* **1991**, *30*, 9686.

(7) Nicholls, A.; Sharp, K. A.; Honig, B. *Protein* **1991**, *11*, 281.

(8) Hildebrand, J. H. *J. Chem. Phys.* **1947**, *15*, 225.

(9) Hildebrand, J. L.; Scott, R. L. *Regular Solutions*; Prentice Hall: Engelwood Cliffs, NJ, 1962.

(10) Ben-Naim, A.; Mazo, R. M *J. Phys. Chem.* **1993**, *97*, 10829.

(11) Lazaridis, T.; Paulaitis, M. *J. Phys. Chem.* **1992**, *96*, 3847.

(12) Lee, B. K *Biophys. Chem.* **1994**, *51*, 263.

(13) Tunon, I.; Silla, E.; Pascual-Ahuir, J. L. *J. Phys. Chem.* **1994**, *98*, 377.

(14) Holtzer, A. *Biopolymer* **1994**, *34*, 315.

(15) Giesen, D. J.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem.* **1994**, *98*, 4141.

(16) Abraham, M. A.; Sakellariou, P. *J. Chem. Soc., Perkin. Trans.* **1994**, *2*, 405.

(17) Kumar, S. K.; Szleifer, I.; Panagiotopoulos, A. Z. *Phys Rev. Lett.* **1991**, *66*, 2935.

(18) Sanchez, I. C.; Lacombe, R. H. *J. Phys. Chem.* **1976**, *80*, 2352.

(19) Widom, B. *J. Chem. Phys.* **1963**, *39*, 2808.

(20) Hill, T. L. *Statistical Mechanics*; McGraw-Hill: New York, 1956.

(21) Throughout we shall use subscripts to denote the component, p for polymer solute and s for monomeric solvent, and superscripts to denote the phase, g for gas, p for condensed polymer, and s for monomeric solvent.

(22) Pierotti, R. A. *J. Phys. Chem.* **1965**, *69*, 281.

(23) Flory, P. J. *The principles of polymer chemistry*; Cornell Univeristy Press: Ithaca, 1953.

(24) Dickman, R.; Hall, C. K. *J. Chem. Phys.* **1986**, *85*, 4108.

(25) Frenkel, D.; Smit, B. *Mol. Phys.* **1992**, *75*, 983.

(26) dePablo, J. J.; Laso, M.; Suter, U. W. *J. Chem. Phys.* **1992**, *96*, 6157.

(27) Szleifer, I.; Panagiotopoulos, A. Z. *J. Chem. Phys.* **1992**, *97*, 6666.

(28) Holtzer, A. *Biopolymers* **1992**, *32*, 711.

(29) Sharp, K. A.; *et al.* Manuscript in preperation.

(30) Hansen, J. P.; MacDonald, I. R. *Theory of Simple Liquids*; Academic Press: London, 1986.

(31) Neff, R. O.; McQuarrie, D. **1973**, *77*, 413.

(32) Rashin, A. A.; Bukatin, M. A. *Biophys. Chem.* **1994**, *51*, 167.

(33) Stillinger, F. *J. Solution. Chem.* **1973**, *2*, 141.

(34) Reiss, H. *Adv. Chem. Phys.* **1965**, *IX*, 1.

(35) Donohue, M. D.; Prausnitz, J. M. *Can. J. Chem.* **1973**, *53*, 1586.

(36) Lichenthaler, R. N.; Abrams, D. S.; Prausnitz, J. M. *Can. J. Chem.* **1975**, *51*, 3071.

(37) Jackson, R. M.; Sternberg, M. J. E. *Nature* **1993**, *366*, 638.

(38) Sitkoff, D.; Sharp, K. A.; Honig, B. *Biophys. Chem.* **1994**, *51*, 397.

(39) Chandler, D. Equilibrium theory of polyatomic fluids. In *The Liquid State of Matter: Fluids, Simple and Complex*; Montroll, E. W., Lebonitz, J. L., Eds.; North Holland: New York, 1982.

(40) Pratt, L. R.; Chandler, D. *J. Chem. Phys.* **1977**, *63*, 3683.

(41) Chan, H. S.; Dill, K. A. *J. Chem. Phys.* **1994**, *101*, 7007.