Molecular and macroscopic aspects of cavity formation in the hydrophobic effect

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The formation of a cavity in water is a conceptual preliminary to the dissolution of a nonpolar solute. The process is of biophysical importance because of its assumed primitive relation to hydrophobic factors affecting biological structure and function. In this paper, cavity formation by the isochoric deformation of a fluid specimen is investigated. Using both molecular and macroscopic descriptions of this process, the volume occupied by the fluid is held constant while the spherical specimen is reversibly deformed in differential steps until it surrounds a spherical cavity. The work of cavity formation results from the integration of energy changes generated directly from the forced, differential deformations of the equilibrium fluid structure; the heat of cavity formation is the integrated result of energy changes that accompany the nonforced, differential adjustments in the distribution of matter which modulate the average fluid structure during the process. This reversible isochoric deformation procedure for introducing the nonpolar system into the polar fluid is compared with the more familiar method that uses a reversible coupling parameter. Simple calculations based on the isochoric deformation method provide estimates of the free energy, internal energy, heat and entropy of cavity formation that agree with values from the scaled particle method.

1. Introduction

One of the most interesting problems in biophysical chemistry today concerns the origin and implications of the hydrophobic effect [1–3]. In descriptive terms, this effect refers to the tendency for nonpolar groups to associate in water. Most of the biologically important issues were raised in Kauzmann's paper [4] and the period since its publication has produced an increasing variety of methods and approaches directed at various features of hydrophobicity [5]. An assumption in much of this work is that some fundamental fea-

tures of hydrophobic processes are reflected in the low solubility of nonpolar solutes in water [6–11]. It has, nevertheless, remained a matter of controversy how the relative insolubility of nonpolar molecules in water is correlated, for example, with free energy constraints on peptide chain folding in proteins or aggregation of lipid molecules in membranes [5,12,13].

Of the concepts which have evolved regarding hydrophobicity, we state three propositions which seem to have special significance. These are (i) the large unfavorable free energy of dissolving a nonpolar solute in water can be attributed to a large entropy decrease associated with rather special structural changes within water [14–16], (ii) the unfavorable free energy is not due to structural changes but is directly dependent on the structure of water [17], and (iii) it may be useful to study

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these processes in water from the general perspective of intermolecular force and energy as in other physical systems [18]. The third statement is essentially a recommendation regarding the other two. In pursuing this recommendation here, we do not suggest that it has not also been used in the approaches to the problems referred to in (i) and (ii). Further, we do not attempt to resolve the points of view expressed in (i) and (ii); these have been thoroughly investigated and defended by their proponents. Instead, our purpose is to study the energetic features of a particular process that is important in hydrophobicity. The process is that of creating a spherical cavity within a condensed phase. Cavity formation is not the only component of dissolving a nonpolar solute in water, but it is a highly significant part in which important features of water as a solvent are found and is therefore worthy of special attention [19–22]. Several computational approaches to the thermodynamic quantities in this process have been given; we mention here (a) the use of scaled particle theory [19,20,23–25], (b) the introduction of the cavity by reversible coupling of an appropriate hard sphere [26,27] and (c) surface free energy relations [28–30]. In the present paper we will use, and assume as well established, these earlier theoretical estimates of positive free energy and negative entropy of cavity formation in water; it is not our aim here to present alternative calculations. Our objective is instead to develop a description of the energetics of cavity formation through which the physical quantities involved in statements (i) and (ii) above may be explored. This is done in two stages. First, to introduce in preliminary form some concepts relevant to reversible processes, we discuss briefly the procedure of placing a nonpolar solute in water. Next, employing these general concepts, the creation of a cavity by the procedure of isochoric deformation is investigated, using both molecular and macroscopic approaches.

The approaches to solvent behavior used here are stated in fairly general terms; the specific systems of biophysical interest are of course aqueous. As is well known, the physical chemistry of these systems is very complex, and we offer here only a brief summary [31]. The properties of liquid water and aqueous systems containing nonpolar groups are primarily determined by the strong, highly directional hydrogen bonds among water molecules. Each molecule interacts through hydrogen bonding with up to four other molecules that tend to be tetrahedrally distributed. A dominant feature is for the water molecules to seek the maximum number of such bonds, even if some bonds are not perfectly formed, i.e., 'strained.' The tendency to maximize hydrogen bonding places enhanced motional constraints on molecules in solvent layers directly adjacent to a nonpolar solute and is related to the strongly negative entropy of solution. The energy of such a system is not given rigorously by summing interaction energies over pairs of molecules; i.e., the hydrogen bonding interactions are cooperative [32]. Thus, the assumption of pairwise additivity of intermolecular energies, which is made in most discussions (including the present one), can be only an approximation. We mention, however, that methods have been given for obtaining 'effective' pair potentials that incorporate cooperative many-body effects [33,34].

2. The reversible coupling method

As a preliminary to our later discussion, we examine here a basic and familiar hydrophobic process, the introduction of a small nonpolar solute, such as argon, into liquid water. The method developed here is used because it introduces and illustrates certain points which are important for the later presentation. The issues raised in statements (i) and (ii) above are fundamentally of an energetic nature. We therefore focus on the energy terms generated when a single nonpolar solute is placed at a fixed, central location in a macroscopic system of N water molecules in constant volume v at constant temperature T. In this section, subscript k denotes the solute molecule fixed at the coordinate origin; subscript j refers to any solvent molecule with position r_j and Euler orientation $\omega_j(\theta_j, \phi_j, \Psi_j)$. The configuration $X_j(r_j, \omega_j)$ combines the spatial and orientational coordinates [35]. With k fixed at the origin, the intermolecular potential energy shared between k and any j depends on X_j and is expressed as $u_{kj}(X_j)$; the

potential between two solvent molecules, j and j', is dependent on their configurations and is given by $u_{jj'}(X_j, X_{j'})$. The contributions to the internal energy of the system made by intramolecular vibrations, and by translational and rotational kinetic energy, are considered to remain constant throughout the constant-temperature procedure. For simplicity, we assume pairwise additivity of intermolecular potentials. The method given by Kirkwood [36], employing a coupling parameter κ, is used to introduce the solute. The interaction between k and all molecules j is increased in reversible, differential steps $d\kappa$, between $\kappa = 0$ and $\kappa = 1$. At the coupling level κ the intermolecular potential between k and any j is $\kappa u_{kj}(X_j)$; the potential between any two solvent molecules, $u_{jj'}(X_j, X_{j'})$, does not vary with κ. However, the potentials of mean force $w_{kj}(X_j, \kappa)$ and $w_{jj'}(X_j, X_{j'}, \kappa)$, which determine the probabilities of occurrence of specific configurations in the system, are functions of both κ and configuration. Thus, the energy of the system for a specified κ, exclusive of the vibrational and kinetic energies discussed above, with $\beta = 1/kT$ (kT: Boltzmann's constant times temperature), is given by [37]

$$E(\kappa) = \frac{N}{8\pi^2 v} \int^{\omega_j v} \kappa u_{kj} e^{-\beta w_{kj}(\kappa)} \, dX_j + \frac{N^2}{2(8\pi^2 v)^2}$$

$$\times \int^{\omega_j v} \int^{\omega_{j'} v} u_{jj'} e^{-\beta w_{jj'}(\kappa)} \, dX_{j'} \, dX_j \qquad (1)$$

With obvious notation, eq. 1 may be expressed as

$$E(\kappa) = \bar{E}_{kj}(\kappa) + \bar{E}_{jj'}(\kappa) \qquad (2)$$

Formally, each term on the right-hand side of eq. 2 has the form [38]

$$\bar{E} = \sum_i P_i E_i \qquad (3)$$

where P_i describes the probability distribution in the system, over the manifold of all possible pair-configuration energies E_i. Thus, E_i corresponds to κu_{kj} in the first term of eq. 1 and to $u_{jj'}$ in the second term. Then, since both terms on the right-hand side of eq. 2 are functions of the coupling level, they may each separately be expressed in

differential form according to

$$d\bar{E} = \left(\sum_i P_i \, \partial E_i/\partial \kappa\right) d\kappa + \left(\sum_i E_i \, \partial P_i/\partial \kappa\right) d\kappa \qquad (4)$$

As discussed elsewhere [38], the first term on the right-hand side of eq. 4 corresponds formally to work; infinitesimal change in energies with constant probabilities produces differential work ($-dW$). The second term on the right-hand side of eq. 4 corresponds formally to heat; infinitesimal change in probabilities with constant energies produces differential heat (dQ). We apply eq. 4 to each of the terms on the right-hand side of eq. 1 and note that

$$\frac{\partial(\kappa u_{kj})}{\partial \kappa} = u_{kj} \quad \text{and} \quad \frac{\partial u_{jj'}}{\partial \kappa} = 0 \qquad (5)$$

Collecting work and heat terms, we have

$$-dW = \left\{ \frac{N}{8\pi^2 v} \int^{\omega_j v} u_{kj} e^{-\beta w_{kj}(\kappa)} \, dX_j \right\} d\kappa \qquad (6)$$

$$dQ = \left\{ \frac{N}{8\pi^2 v} \int^{\omega_j v} \kappa u_{kj} \frac{\partial}{\partial \kappa} \left(e^{-\beta w_{kj}(\kappa)} \right) dX_j \right\} d\kappa$$

$$+ \left\{ \frac{N^2}{2(8\pi^2 v)^2} \int^{\omega_j v} \int^{\omega_{j'} v} u_{jj'} \right.$$

$$\left. \times \frac{\partial}{\partial \kappa} \left(e^{-\beta w_{jj'}(\kappa)} \right) dX_{j'} \, dX_j \right\} d\kappa \qquad (7)$$

Integration of eq. 6 over κ yields the usual definition for the work of coupling [36]. This approach to eqs. 6 and 7 has been used in order to bring out certain general points regarding the coupling procedure. First, we see that the work in eq. 6 derives solely from a summation of properly weighted solute-solvent interactions, and that the heat in eq. 7 is a combination of contributions from both solute-solvent and solvent-solvent interactions. Second, we note that this coupling procedure is one example of a hypothetical, reversible mechanism that can use an infinitesimal change in free energy of a system to perform a numerically equal amount of work on the surroundings of that system. Finally, we point out that for a step $d\kappa$ to be reversible, both energy transactions, the work in eq. 6 and the heat in eq. 7, are required; i.e., each isothermal, reversible step $d\kappa$ generates two kinds

of energy changes that are conceptually separable and have formally distinguishable origins. All of these general considerations appear in another method, described in the following sections, for introducing the nonpolar system. Some of these points can be simplified by division of the interaction between the nonpolar solute and polar solvent into repulsive (hard sphere) and attractive (soft central) parts; the simplification occurs when the attractive part is omitted. Indeed, it has been shown that the coupling of a hard sphere is equivalent to the formation of a cavity of an appropriate size in the solvent [26,27]. Because of its conceptual simplicity, the process of cavity formation has been considered to be a primitive model for hydrophobic phenomena [20,27]. We describe in the following sections an additional method for introducing the cavity.

3. Cavity formation by isochoric deformation

Our main objective in this paper is to examine the energy changes associated with cavity formation from the perspective of the Gibbs equation, which is the general expression for the differential change in internal energy in any thermodynamic system [39,40].

$$dE = -dW - p\, dv + T\, dS + \mu\, dn + \psi\, de \qquad (8)$$

The notation here is standard and, in the present and subsequent sections, the terms on the right-hand side are, in order, (1) non-pv mechanical work, (2) pv mechanical work, (3) reversible heat dQ, (4) chemical work and (5) electrical work. The systems of interest here are closed, electrically neutral and have constant volume, so terms 2, 4 and 5 do not contribute.

$$dE = -dW + T\, dS \qquad (9)$$

Depending on the context, $-dW$ and $T\, dS$ can assume various forms. In the present and following sections we are particularly interested in the case where $-dW$ has its primitive physical meaning and, for a total system, is given by summation of the force-displacement terms from each part of the system, i.e., where the external force f_i displaces the internal part i through the vector dis-

tance ds_i, and [39,40]

$$-dW = \sum_i f_i \cdot ds_i \qquad (10)$$

Preliminarily to describing the procedure in detail, we need to mention some simple points regarding cavity formation in general. First, it is an experimental observation that stable cavities, even of molecular size, do not form spontaneously in water. Thus, work (free energy increase) must be done on a macroscopic specimen of water in order to create a cavity of some radius λ. Next we note that a cavity of radius λ, having been formed by intervention of an external, work-performing agency, has no tendency to increase spontaneously its radius. Thus, in summary, the free energy required to introduce a cavity is an increasing function of its radius λ. Therefore, since there is a functional quantity $W(\lambda)$, there are also, by thermodynamic manipulation, the functions $E(\lambda)$ and $Q(\lambda)$ for energy and heat of cavity formation, respectively.

We consider a spherical fluid specimen, whose volume v has a fixed value, with constant mass M and temperature T. Any point within v is associated with a radius vector r, with origin at the center of the system. In our molecular description (section 4.1), the mass M is divided among N identical fluid molecules with explicit translational and rotational degrees of freedom and mutual distance-orientation dependent interactions. In our macroscopic description (section 4.2), molecular properties are not specified and the system is assumed to consist of a continuous spatial distribution of matter. A spherical cavity is introduced into the center of the specimen by a reversible process done in a particular way. Initially, the volume v has the outer radius $r_0 = (3v/4\pi)^{1/3}$ and surrounds a central spherical cavity of radius $\lambda = 0$. The radius of the cavity is changed, by reversible increments $d\lambda$, from $\lambda = 0$ to $\lambda = \tau$ while the outer radius $r_0(\lambda)$ varies from $(3v/4\pi)^{1/3}$ to $(\tau^3 + 3v/4\pi)^{1/3}$. The full process is carried out in differential steps in a manner such that, at any intermediate stage, the constant volume v is confined between spherical surfaces with radii λ and $(\lambda^3 + 3v/4\pi)^{1/3}$. During the process, only the matter and space between the spherical surfaces

constitute the system proper. That is, for any value of λ, the extensive thermodynamic properties of the fluid specimen are obtained by integration only within the volume v contained between the spherical surfaces defined by λ and $r_0(\lambda)$. The surfaces at λ and $r_0(\lambda)$ are variable external constraints on the closed, constant T, v system and the process is thus the reversible deformation of the system from the initial to the final constraints. Although for any λ the volume occupied by the cavity is not part of the system, forces between fluid particles must be considered as being transmitted undisturbed across this volume. This isochoric deformation requires for the increase $d\lambda$, when the cavity radius is λ, that the fluid matter located at any point with radius vector r be displaced a vector distance dl, where

$$dl = \lambda^2 \, d\lambda i / r^2 \tag{11}$$

and i is a unit vector, located at r, that is directed outward along r.

Forces originating external to the system are required to act at all points within the system in order to produce the prescribed deformations. It is not necessary for the present purpose to specify the properties of this force field imposed from the exterior, other than to describe its effects and the strength, duration and direction of application. The field acts simultaneously at all points in the system along radial directions and, at any point, has only the strength and acts only over the distance required to produce, in a reversible manner, the above-prescribed differential deformation dl. Finally, the external force field acts on the system only during the actual physical displacements involved in each deformation step. That is, with the constant T, v system at equilibrium surrounding a cavity of some radius λ, the force field is applied in the prescribed fashion to produce the differential displacement dl required at each point; as a result of this differential deformation of the entire specimen, the external constraints are moved from λ and $r_0(\lambda)$ to $\lambda + d\lambda$ and $r_0(\lambda) + \lambda^2 \, d\lambda / r_0^2(\lambda)$. The application of the field is then stopped and, with the external constraints held stationary in the minutely displaced condition, the interior of the system (still at constant T) adjusts passively to maintain equilibrium with the new values of the external constraints. These procedures are then repeated for each succeeding step $d\lambda$; the two parts of each step are needed in order that the full process, $\int d\lambda$, be thermodynamically reversible. For a step $d\lambda$, the reversible work $-dW$ is generated in the first part (deformation) and the reversible heat dQ arises in the next part (adjustment). The two parts together yield the internal energy change dE in the constant T, v system for the reversible step $d\lambda$. We note here as an essential point of comparison between the coupling parameter method in section 2 and the isochoric deformation in this section that both isothermal reversible processes generate distinguishable work and heat parts. As discussed earlier, because the free energy of cavity formation is positive, the forces operating within the equilibrium system will, on average, act to oppose the spontaneous appearance of a stable cavity. The function of the external force field described above is to provide an external agency which, operating only during the deformation part of each step $d\lambda$, will reversibly override these average internal forces and result in the creation of a cavity.

4. Molecular and macroscopic features of cavity formation

In this section, we use two alternative approaches to describe the energetic features of cavity formation by isochoric deformation, (1) a statistical-molecular method (section 4.1) and (2) a macroscopic-phenomenological method (section 4.2).

4.1. Molecular aspects

In this subsection we are interested generally in polar liquids with definable molecular structures and interactions, particularly water. The system consists of N identical, fully coupled molecules in the spherical volume v at temperature T. The molecules are assumed to interact in pairwise additive fashion through hard exchange repulsion, relatively soft dispersion attraction and powerful orientation-dependent forces. They have effective radius r_w. For descriptive purposes we use a

Cartesian coordinate frame with origin at the center of v. For the fluid to surround a molecular-sized cavity of final radius $\lambda = \tau$, molecular centers must be excluded from a central spherical region with radius $\tau = 2r_w$ [27], so in the initial state all molecular centers are confined within $r_0 = (3v/4\pi)^{1/3}$ and in the final state the molecular centers are confined between $\lambda = 2r_w$ and $r_0 = (8r_w^3 + 3v/4\pi)^{1/3}$.

The configuration of a molecule i is denoted by X_i and consists of the radius vector r_i from the origin to the molecular center and the Euler angles θ_i, ϕ_i, Ψ_i defining the orientation of i in space [35]. The Euler angles $\omega_i(\theta_i, \phi_i, \Psi_i)$ are measured relative to local orthogonal axes which, at any spatial location for the center of i, have X, Y, Z axes parallel, respectively, to X, Y, Z axes fixed at the origin. For convenience of notation in the present section, we denote a representative pair of solvent molecules by i and j (rather than j and j' as in section 2). The intermolecular potential energy shared between i and j, $u_{ij}(X_i, X_j)$, is a function of the two-molecule configuration X_i, X_j. The probability of occurrence of the pair configuration X_i, X_j in the system with cavity radius λ is a function of the potential of mean force between i and j, which depends on X_i, X_j as well as on λ; this potential is denoted by $w_{ij}(\lambda)$ [36,37,41].

The cavity is introduced at the center of the specimen according to the procedures given in the preceding section. With the system at equilibrium and λ of any value between zero and τ, the force field is applied that is required to displace in isochoric fashion the molecular centers of all pairs i and j from the state where they are confined between λ and $r_0(\lambda)$ to the state where they are confined between $\lambda + d\lambda$ and $r_0(\lambda) + \lambda^2 \, d\lambda/r_0^2$ (λ). The essential features of this force field, which acts on the system from the exterior, were discussed previously. This differential deformation requires that the centers of any pair i and j, located with equilibrium pair probability in any configuration X_i, X_j within v, be simultaneously displaced in a radially outward direction by dl_i and dl_j.

$$dl_i = \lambda^2 \, d\lambda \, i_i / r_i^2 \qquad (12)$$

$$dl_j = \lambda^2 \, d\lambda \, i_j / r_j^2 \qquad (13)$$

where i_i and i_j are unit vectors pointing radially outward from X_i and X_j, respectively. During the deformation part of $d\lambda$, the action of the external force field thus ensures well-defined functional relations between (a) the cavity radius λ and cavity displacement $d\lambda$ and (b) the physical displacements of the molecular centers of any pair ij with specified X_i, X_j. These displacements of molecular centers are done in a manner that preserves the individual orientations of i and j in Cartesian space; however, their orientation relative to one another will in general change. That is, differential displacement of the molecular centers of i and j along their outward radial directions, while maintaining constant orientation of each molecule in the space of the Cartesian frame, will cause differential changes both in relative orientation and in relative separation of molecular centers. The reversible work, performed during this deformation part of the step $d\lambda$, is generated because these changes in relative configuration are done against the forces and torques operating between i and j. We note then that the potential energy of the pair ij changes during the deformation part of a step $d\lambda$ from $u_{ij}(r_i, \omega_i; r_j, \omega_j)$ to $u_{ij}(r_i + dl_i, \omega_i; r_j + dl_j, \omega_j)$ with dl_i and dl_j given by eqs. 12 and 13. The application of the field is then stopped and the reversible heat is obtained when, in the adjustment part of the step $d\lambda$, the distribution of molecules throughout the specimen adjusts passively to the new values of the constraints.

The discussion above focused on a single pair ij in a single pair configuration X_i, X_j. The properties of the system of N molecules are determined by $N(N-1)/2$ pairs, with each pair distributed statistically over all pair configurations consistent with the external constraints. We develop here the statistical expressions for the work and heat contributions to internal energy change. As in section 2, intramolecular vibrational energies and average kinetic energies of molecular translation and rotation remain constant; changes in internal energy are then equivalent to changes in average potential energy E in the system. For any cavity radius λ this will be [37]

$$E(\lambda) = \frac{N^2}{2(8\pi^2 v)^2} \int^{\omega, v_\lambda} \int^{\omega_j v_\lambda} u_{ij}(X_i, X_j)$$

$$\times e^{-\beta w_{ij}(\lambda)} \, dX_j \, dX_i \qquad (14)$$

The term multiplying the integral arises from the value at large N of $N(N-1)/2$ (the number of molecular pairs) and the normalizing factors for the differentials dX_j and dX_i. The coordinate integrations are over the rotational space $\omega(\theta,\phi,\Psi)$ and Cartesian v_λ of the molecules. The volume symbol v_λ denotes that the possible positions of molecular centers r, while always within a volume of magnitude v, must be integrated between the radial limits λ and $(\lambda^3 + 3v/4\pi)^{1/3}$ for a specified λ. The Boltzmann factor containing the potential of mean force determines the probability of the configuration X_i, X_j with potential energy $u_{ij}(X_i, X_j)$.

In principle, eq. 14 could be evaluated for any λ. With regard to this equation, a useful property of the isochoric deformation is that any selected pair configuration in the specimen with cavity radius λ is derived uniquely from a specific pair configuration in the specimen with cavity radius zero. That is, let $(r_i(0),\omega_i; r_j(0),\omega_j)$ be any specific configuration contributing the pair energy u_{ij} $(r_i(0),\omega_i; r_j(0),\omega_j)$ to the integration for $E(0)$. As the cavity radius increases from zero to λ, we may regard the isochoric deformation as acting to transform the locations of i and j from $r_i(0)$ and $r_j(0)$ to $r_i(\lambda)$ and $r_j(\lambda)$ where

$$r_i(\lambda) = \left(\lambda^3 + r_i(0)^3\right)^{1/3} i(r_i) \qquad (15)$$

$$r_j(\lambda) = \left(\lambda^3 + r_j(0)^3\right)^{1/3} i(r_j) \qquad (16)$$

and $i(r_i)$ and $i(r_j)$ are unit vectors at the origin that point in the directions of $r_i(0)$ and $r_j(0)$, respectively. We thus have the transformations

$$\left(r_i(0),\omega_i; r_j(0),\omega_j\right) \rightarrow \left(r_i(\lambda),\omega_i; r_j(\lambda),\omega_j\right) \quad (17a)$$

$$u_{ij}\left(r_i(0),\omega_i; r_j(0),\omega_j\right) \rightarrow u_{ij}\left(r_i(\lambda),\omega_i; r_j(\lambda),\omega_j\right) \qquad (17b)$$

$$E(0) \rightarrow E(\lambda) \qquad (17c)$$

As can be verified from eqs. 15 and 16, an important property of this transformation is that

$$dr(\lambda)/d\lambda = (\lambda/r(\lambda))^2, \qquad (18)$$

which gives the displacements in eqs. 12 and 13. This one-to-one correspondence between any

specific u_{ij} contributing to $E(0)$ and a unique u_{ij} contributing to $E(\lambda)$ means (a) all possible pair configurations are accounted for in the integrations for both $E(0)$ and $E(\lambda)$ and (b) all pair configuration energies u_{ij} contributing to any $E(\lambda)$ are functions of λ. The latter point implies that eq. 14 may, similar to the case in section 2, be expressed formally as a probability-weighted (P_i) sum over all pair energies (E_i); we note that the i subscript, in this context, is an index of summation for pair energies and pair probabilities in [38]

$$\bar{E}(\lambda) = \sum_i P_i(\lambda) E_i(\lambda) \qquad (19)$$

and the work $-dW$ and heat dQ may be obtained from

$$d\bar{E} = \left(\sum_i P_i \, \partial E_i/\partial\lambda\right) d\lambda + \left(\sum_i E_i \, \partial P_i/\partial\lambda\right) d\lambda \qquad (20)$$

In summary, the deformation procedure may be regarded as a reversible displacement of all pairs of molecules from the initial manifold of ij configurations (belonging to the specimen of cavity radius zero) to the final manifold of ij configurations (belonging to the specimen of cavity radius λ); reversibility is achieved by providing a 'pause' after each differential displacement of pair configurations, in order to permit a differential adjustment in pair configuration probabilities. These points are pursued below, where the work is expressed in the form given in eq. 10.

An important application of eq. 14 would be to derive the quantity $\Delta E = E(\lambda_2) - E(\lambda_1)$ when $\lambda_2 = \tau$ and $\lambda_1 = 0$. Of more general interest here is the case where the state described by $E(\lambda_2)$ is, by process of isochoric deformation, only infinitesimally removed from the state described by $E(\lambda_1)$. Then with $\lambda_2 = \lambda_1 + d\lambda$,

$$E(\lambda_1 + d\lambda) - E(\lambda_1) = dE = -dW + dQ \qquad (21)$$

Like the terms in eq. 1, eq. 14 is the summation over the probability-weighted potential energy manifold of a representative pair. The infinitesimal deformation procedure, that forces the specimen from $E(\lambda_1)$ to $E(\lambda_1 + d\lambda)$, will generate differential changes in both (1) the possible poten-

tial energies of the representative pair and (2) the probabilities of occurrence of specified configurations of the pair. Thus,

$$dE = \frac{N^2}{2(8\pi^2 v)^2} \int^{\omega_i v_\lambda} \int^{\omega_j v_\lambda} (\delta u_{ij}) e^{-\beta w_{ij}(\lambda)} \, dX_j \, dX_i$$

$$+ \frac{N^2}{2(8\pi^2 v)^2}$$

$$\times \int^{\omega_i v_\lambda} \int^{\omega_j v_\lambda} u_{ij} \, \delta(e^{-\beta w_{ij}(\lambda)}) \, dX_j \, dX_i \quad (22)$$

and the expression would be evaluated at $\lambda = \lambda_1$.

The differential quantities $\delta(e^{-\beta w_{ij}(\lambda)})$ and δu_{ij} are defined as follows:

$$\delta(e^{-\beta w_{ij}(\lambda)}) = \{\partial(e^{-\beta w_{ij}(\lambda)})/\partial\lambda\} \, d\lambda \quad (23)$$

$$\delta u_{ij}(r_i, \omega_i; r_j, \omega_j) = \left\{ \frac{\partial u_{ij}}{\partial r_i} \frac{\partial r_i}{\partial\lambda} + \frac{\partial u_{ij}}{\partial \omega_i} \frac{\partial \omega_i}{\partial\lambda} \right.$$

$$\left. + \frac{\partial u_{ij}}{\partial r_j} \frac{\partial r_j}{\partial\lambda} + \frac{\partial u_{ij}}{\partial \omega_j} \frac{\partial \omega_j}{\partial\lambda} \right\} \, d\lambda$$

$$(24)$$

As discussed above, the displacements in eqs. 12 and 13 are not accompanied by changes in the individual orientations of i and j:

$$\frac{\partial \omega_i}{\partial\lambda} = 0 \quad \text{and} \quad \frac{\partial \omega_j}{\partial\lambda} = 0 \quad (25)$$

The gradients of the intermolecular potentials, along the radial directions, give the magnitudes of the intermolecular force in these directions when molecules i and j are in the configuration $(r_i, \omega_i; r_j, \omega_j)$.

$$\frac{\partial u_{ij}}{\partial r_i} = -f_{ji} \quad \text{and} \quad \frac{\partial u_{ij}}{\partial r_j} = -f_{ij}, \quad (26)$$

where f_{ji} is the magnitude of the force from molecule j, acting at the center of i, in the direction of r_i; f_{ij} has the complementary meaning for the force from i acting at the center of j. An individual force, e.g., f_{ji}, will be positive or negative depending on whether it is directed radially outward or inward, respectively; this direction will, of course, depend on the specific X_i, X_j. The changes in radial coordinates are given by the

requirements of the isochoric deformation, eqs. 12 and 13.

$$\frac{\partial r_i}{\partial\lambda} = \frac{dl_i}{d\lambda} = (\lambda/r_i)^2 \quad \text{and} \quad \frac{\partial r_j}{\partial\lambda} = \frac{dl_j}{d\lambda} = (\lambda/r_j)^2$$

$$(27)$$

We see for dE in eq. 22 that the first term is the summation of contributions from changes in pair energies under constant probabilities and gives the reversible work; the second term is the summation of contributions from changes in probabilities under constant pair energies and gives the reversible heat.

Summarizing these relations,

$$-dW = \left\{ \frac{N^2}{2(8\pi^2 v)^2} \int^{\omega_i v_\lambda} \int^{\omega_j v_\lambda} - \left[f_{ji}(\lambda/r_i)^2 \right. \right.$$

$$\left. \left. + f_{ij}(\lambda/r_j)^2 \right] e^{-\beta w_{ij}(\lambda)} \, dX_j \, dX_i \right\} \, d\lambda$$

$$(28)$$

$$dQ = \left\{ \frac{N^2}{2(8\pi^2 v)^2} \int^{\omega_i v_\lambda} \int^{\omega_j v_\lambda} u_{ij}(X_i, X_j) \right.$$

$$\left. \times \frac{\partial}{\partial\lambda} (e^{-\beta w_{ij}(\lambda)}) \, dX_j \, dX_i \right\} \, d\lambda \quad (29)$$

The quantities $dX_j \, dX_i$ in these equations are simply the usual differential elements of configuration which must be integrated over all configurations consistent with a specified λ; these $dX_j \, dX_i$, which are essentially indices of summation, should not be confused with the infinitesimal changes in molecular coordinates, eq. 27, generated during the deformation part of each $d\lambda$ step. We see then that ΔE above can, in principle, be obtained by two methods: (1) eq. 14 can be evaluated for λ_2 and λ_1 separately and the difference calculated or (2) eqs. 28 and 29 can each be integrated over λ between λ_1 and λ_2 and the results added to give $\Delta E = -\Delta W + \Delta Q$. In the latter case, $-\Delta W$ and ΔQ are each obtained as the limit of the sum of infinitesimal isothermal contributions, generated while the isochoric deformation procedure is performed reversibly.

4.2. Macroscopic aspects

We derive in this subsection some energetic implications of the isochoric deformation when the fluid specimen surrounding a cavity of radius λ is regarded as a continuous, macroscopic distribution of matter. Our objective is to present briefly certain phenomenological points that are relevant to the molecular discussion above. We are again interested in the fluid of total mass M, constant temperature T, confined in the constant volume v between the spherical surfaces with radii λ and $(\lambda^3 + 3v/4\pi)^{1/3}$; when a specific value of λ is of interest, this constant volume will again be denoted v_λ. A spherical polar coordinate system is convenient in this case and the fluid matter located at a point with radius vector r within v_λ then has specified (r, θ, ϕ). A volume element within v_λ is $dv_\lambda = r^2 \sin\theta \, dr \, d\theta \, d\phi$.

We recall that the internal energy of this system, $E(\lambda)$, can be changed by application of an external force field from $E(\lambda_1)$ to $E(\lambda_2)$, in a large number of successive, reversible, infinitesimal steps. As before, each reversible step consists of two parts, (1) a deformation part in which the matter at all points, in every volume element dv_λ, is forced radially outward, resulting in a displacement of the matter from any r to $r + \lambda^2 \, d\lambda/r^2$ and (2) an adjustment part in which passive redistribution of the fluid among the volume elements will maintain equilibrium against the minutely changed external constraints. In order to examine the differential change $dE = E(\lambda + d\lambda) - E(\lambda)$ from the macroscopic perspective, we focus on the internal energy associated with a single dv_λ. Due to the nature of the isochoric deformation procedure, an individual volume element dv_λ may be regarded as maintaining its magnitude throughout both parts of a differential step $d\lambda$. That is, considering any particular dv_λ, the geometric effect of the deformation part is to compress the element minutely along the radial direction and to expand it minutely around the tangential directions, while the matter in dv_λ and the magnitude of dv_λ are each conserved; thus, the local density (mass per unit volume) in dv_λ as well as the magnitude of dv_λ remain constant during the deformation part of $d\lambda$. However, dur-

ing the adjustment part of $d\lambda$, while the redistribution of fluid causes no change in the magnitude of any dv_λ, the local density within any dv_λ may change. We thus find as an essential phenomenological point relevant to both molecular and macroscopic methods that, not only is the overall procedure isochoric, it is also locally isopycnic during the deformation part of any $d\lambda$. The internal energy of the fluid [42] within any dv_λ surrounding a location r is $u_r(\lambda) D_r(\lambda) \, dv_\lambda$, where $u_r(\lambda)$ and $D_r(\lambda)$ are, respectively, the internal energy per unit of mass and the local density (mass per unit volume) at the location r when the cavity radius is λ.

The internal energy of the specimen is then [42]

$$E(\lambda) = \int^{v_\lambda} u_r(\lambda) D_r(\lambda) \, dv_\lambda \qquad (30)$$

The reversible isochoric change from λ to $\lambda + d\lambda$ produces the energy change $dE = E(\lambda + d\lambda) - E(\lambda)$.

$$dE = \int^{v_\lambda} \delta u_r(\lambda) D_r(\lambda) \, dv_\lambda$$
$$+ \int^{v_\lambda} u_r(\lambda) \delta D_r(\lambda) \, dv_\lambda \qquad (31)$$

$$\delta u_r(\lambda) = (\partial u_r(\lambda)/\partial\lambda) \, d\lambda \qquad (32)$$

$$\delta D_r(\lambda) = (\partial D_r(\lambda)/\partial\lambda) \, d\lambda \qquad (33)$$

The quantity $\delta u_r(\lambda) D_r(\lambda) \, dv_\lambda$ is the work performed, under isopycnic conditions, by the external field on the fluid in dv_λ during the deformation part of $d\lambda$; $u_r(\lambda) \delta D_r(\lambda) \, dv_\lambda$ is the energy change within dv_λ due to the change in local density during the adjustment part, and represents the heat contribution from dv_λ in the step $d\lambda$. We define

$$(\partial u_r(\lambda)/\partial\lambda) \, d\lambda = (f_r(\lambda) \, dl_r(\lambda)/d\lambda) \, d\lambda \quad (34)$$

where $f_r(\lambda)$ is the total force exerted by the external field on all the matter in dv_λ, divided by the total mass in dv_λ; it is the external force, per unit of mass, that is required to produce, in a reversible manner, the isopycnic displacement of the fluid in dv_λ at r, when the cavity radius is λ. From eq. 11, $dl_r(\lambda)$ is the prescribed displacement of the fluid located at r when the cavity has radius λ and

$$dl_r(\lambda)/d\lambda = (\lambda/r)^2 \qquad (35)$$

From the foregoing discussion, the macroscopic counterparts of eqs. 28 and 29 are

$$-dW = \left\{ \int^{v_\lambda} f_r(\lambda)(\lambda/r)^2 D_r(\lambda)\, dv_\lambda \right\} d\lambda \qquad (36)$$

$$dQ = \left\{ \int^{v_\lambda} u_r(\lambda)\, \partial D_r(\lambda)/\partial\lambda\, dv_\lambda \right\} d\lambda \qquad (37)$$

5. Work and heat of cavity formation in water

We examine here some quantitative implications of section 4. We restate the work and heat components in eq. 22 in the following forms.

$$-dW = \frac{N^2}{2(8\pi^2 v)^2}$$
$$\times \int^{\omega_i v_\lambda} \int^{\omega_j v_\lambda} \left\{ \delta u_{ij} \right\} e^{-\beta w_{ij}(\lambda)}\, dX_j\, dX_i$$
$$(38)$$

$$dQ = \frac{N^2}{2(8\pi^2 v)^2} \int^{\omega_i v_\lambda} \int^{\omega_j v_\lambda} \left\{ -\beta u_{ij}\delta w_{ij}(\lambda) \right\}$$
$$\times e^{-\beta w_{ij}(\lambda)}\, dX_j\, dX_i \qquad (39)$$

Where δu_{ij} is defined by eq. 24 and 25, and $\delta w_{ij}(\lambda)$ is given by

$$\delta w_{ij}(\lambda) = \left(\partial w_{ij}(\lambda)/\partial\lambda \right) d\lambda \qquad (40)$$

The probability distribution factors are identical in eqs. 38 and 39; during any $d\lambda$, the relative contributions from a specific configuration (X_i, X_j) to the work and heat, respectively, are then determined by the signs and magnitudes of the factors in brackets. While we indicate here these relations between work and heat during a small change in size of the cavity, we shall not attempt a rigorous integration over λ of eqs. 38 and 39. We will instead assume greatly simplified approximations to these expressions in order to describe some of the contributing effects. These approximations are as follows:

(1) rather than a summation of many infinitesimal steps (with each step having deformation and adjustments parts), the cavity of radius r will be formed in one finite step consisting of (a) one

deformation of an assumed initial structure in order to open the cavity, followed by (b) one adjustment of an assumed final structure around the cavity; thus, the work part emphasizes the deformation of the bulk liquid structure and the heat part stresses the structural adjustment to accommodate the cavity.

(2) Simple molecular distributions will be assumed to represent essential structural features of the initial [43] and final [24,44] states; thus, the relevant initial and final distribution functions in eqs. 38 and 39, respectively, are not explicitly given, but are assumed to produce pre-selected structures characteristic of water near $4°C$ (277 K).

(3) Only the energy changes among nearest-neighbor molecules in the first and second shells surrounding the cavity are included; we thus assume in the one-step integrations of eqs. 38 and 39 that δu_{ij} and δw_{ij} vanish except in the immediate vicinity of the cavity and are negligible between non-nearest neighbors.

(4) Only dipolar electrostatic energies are considered.

(5) $\delta w_{ij}(\lambda)$ will be approximated by an expression [45] derived from application of liquid-state theory to interactions of polar molecules in a dielectric medium.

Hydrogen bonding among tetrahedrally distributed nearest-neighbor molecules is assumed in both the initial and final states, with center-to-center distance $\tau = 2.76$ Å and dipole moment $m = 2.18$ Debye; m consists of a permanent moment 1.88 Debye plus a 16% polarization component [43]. The dipolar energy u between two nearest-neighbors in these structures is [43]

$$u = \frac{-2m^2(\cos\gamma)_{av}}{\tau^3} \qquad (41)$$

where $(\cos\gamma)_{av}$ is the average cosine of the angle between the dipole vectors of the two molecules; $(\cos\gamma)_{av}$ is 0.33 in the tetrahedral configuration [43]. With these conventions and the procedures given below, the calculations of δu_{ij} and $-\beta u_{ij}\delta w_{ij}$ for the initial and final structures, respectively, are straightforward; we shall omit the numerical details and only briefly outline our estimates of work and heat.

5.1. Initial structure

We represent the initial structure of the bulk fluid by a configuration of eight water molecules. Two of the eight molecules, referred to as 'central', are hydrogen-bonded to one another, and each of these central molecules is hydrogen-bonded to three 'outer' molecules. Geometrically, the molecular centers in this structure correspond roughly to atomic centers in an ethane molecule. The midpoint of the bond between the central molecules is chosen as the site of origin for the cavity; the inital position vectors $r(0)$ of the eight molecules relative to this origin are determined by the assumed geometry, and the initial electrostatic energy of this structure is the sum of seven equal pair energies of the form given by eq. 41. In the one-step isochoric deformation, the introduction of the cavity of radius τ then displaces all eight molecules to deformed positions $r(\tau)$ which are computed from the inital positions $r(0)$, using eqs. 15 and 16. The factor $(\cos \gamma)_{av}$ in eq. 41 is already rotationally averaged, and we assume in our simple calculation that this factor, as well as m, remains constant for each pair in the one-step deformation. Equations of the form eq. 41, but with intermolecular distances appropriate to the displaced configuration, then give the electrostatic pair energies in the deformed state. The intermolecular distances after displacement are readily derived from the assumed initial geometry and the results of the isochoric deformation, eqs. 15 and 16. Six of the pair energies in the deformed state, between the central and outer molecules, are equal; the pair energy between the central molecules is more positive because the displaced distance is larger. We may then represent the change in total dipolar energy by Δu_t and express this as

$$\Delta u_t = \Delta u(c,c) + 6\Delta u(c,o) \qquad (42)$$

where $\Delta u(c,c)$ is the change in electrostatic interaction between the central molecules as a result of the deformation, and $\Delta u(c,o)$ is the change between a central and an outer molecule. With this expression we estimate Δu_t to be 4830 cal/mol; this is thus our estimate of the work of cavity formation in the present single-step approximation to the integration of eq. 38. For order of

magnitude, this figure may be compared to the scaled particle method [20] where 5200 cal/mol is required to make the cavity in water for solutes the size of argon or nitrogen. In the present method, we find that 40% of the 4.8 kcal derives from the interaction between the central molecules and 60% is from the six equivalent central-outer interactions. We stress as a concluding point in this subsection that the distribution of molecules resulting from the one-step deformation of the assumed initial structure should not be identified with the assumed final structure described below; in principle, however, if the cavity were formed in small steps, with reversible deformation-adjustment in each step, the final deformed structure and the final adjustment structure would be the same.

5.2. Final structure

Hydrogen-bonded networks of water molecules, with intermolecular distance τ, form cages around cavities in the liquid [24,44]. In cold water $(T = 277$ K), a closed, nonplanar chain of eight nearest water molecules forms the cage for a cavity whose center is approximately a distance τ from the center of each molecule [24,44]. In this assumed final structure, the center of the cavity, and the centers of any two cage waters which are hydrogen-bonded to one another, then form an equilateral triangle of side length τ. There are in this cage structure eight equivalent pair energies, with each assumed given by eq. 41; for our simple calculation, the assumption will be that only these eight pair energies contribute significantly to the adjustment. Physically, this is equivalent to the assumption that in the process of cavity formation, eight pair interactions are transferred from the bulk-water environment to the cavity-cage environment. In addition to these pair energies and the assumed final structure just described, we also need a finite Δw_{ij} in order to approximate the integration of eq. 39 in one finite step. For a polar liquid, the effect on the w_{ij} of two adjacent dipoles i and j, caused by the electric moments in the surrounding dielectric environment, was examined in a recent paper [45]. In the notation of the present method and with some geometric terms

expressed numerically, the effect on the w_{ij} of two equal, parallel, end-to-end dipoles p_i and p_j, caused by removing a molecular electric moment from a molecule-sized volume Δv of the medium directly adjacent to i and j, is given by [45]

$$\Delta w_{ij} = (-5.76)\frac{3p^2}{2\pi}\frac{(3\cos^2 60° + 1)^{\frac{1}{2}}}{16\tau^6}\Delta v \qquad (43)$$

where $\Delta v = 4\pi/3\,(\tau/2)^3$, $p = m\cos(109°/2)$ and $p^2 = m^2\cos^2 54.5° = m^2(\cos\gamma)_{av}$. We note that this equation has components which depend on both the tetrahedral geometry (109°) of the water cage and the equilateral geometry (60°) of the cage-cavity structure. With the final structure given above, u_{ij} from eq. 41 and Δw_{ij} from eq. 43, we estimate the heat of cavity formation q at 277 K.

$$q = -8\beta u_{ij}\Delta w_{ij} \qquad (44)$$

At 277 K, the heat is -4015 cal/mol and this is our single-step approximation to the integration of eq. 39; the corresponding entropy of cavity formation is -14.5 e.u. These values may be compared to the results of the scaled particle method for 298 K, where the figures are -4400 cal/mol and -14.7 e.u. [20]. Our estimate for the change in internal energy (which would be the integrated form of eq. 22) is 815 cal/mol, which may be compared to 800 cal/mol derived from the scaled particle method.

5.3. Dependence of work on cavity radius

In order to examine the dependence of the work $-\Delta W$ on cavity size, we compare some formal and practical results between scaled particle theory and the present method. The fundamental expression for $-\Delta W$ in the scaled particle method is [20]

$$-\Delta W(\tau) = \int_0^\tau \{\rho G(\lambda)kT\}4\pi\lambda^2\,d\lambda \qquad (45)$$

where ρ is the particle number density and $G(\lambda)$ the conditional singlet probability function that a particle is located between λ and $\lambda + d\lambda$ when the cavity radius is λ; kT has the usual meaning. The following substitutions may be made in eq. 36: $D_r(\lambda) = (\text{mass}/\text{particle})\rho G(r,\lambda)$, $dv_\lambda =$

$r^2\,dr\sin\theta\,d\theta\,d\phi$, and we note that $G(r,\lambda)$ is the conditional singlet probability function that a particle will be found at r when the cavity radius is λ. If the resulting equation for fixed λ is integrated over angular variables, then expressed as an integral over λ, the equation is then

$$-\Delta W(\tau)$$
$$= \int_0^\tau \left\{\int_\lambda^{r_0(\lambda)} \rho G(r,\lambda)f(r,\lambda)\,dr\right\}4\pi\lambda^2\,d\lambda \qquad (46)$$

where $f(r,\lambda)$ now has the meaning of radial force per particle required to produce isopycnic displacement at r when the cavity radius is λ, and it will be recalled that the outer radius $r_0(\lambda) = (\lambda^3 + 3v/4\pi)^{1/3}$. With the volume of the cavity $v_c = 4\pi/3\lambda^3$ and $dv_c = 4\pi\lambda^2\,d\lambda$, eqs. 45 and 46 may be transformed

$$d(-\Delta W)/dv_c = \rho G(\lambda)kT \qquad (47)$$

$$d(-\Delta W)/dv_c = \int_\lambda^{r_0(\lambda)} \rho G(r,\lambda)f(r,\lambda)\,dr \qquad (48)$$

The similarity of eqs. 47 and 48 is readily apparent, particularly when it is noted that kT in eq. 47 is the work done per particle at the surface of the cavity, and $f(r,\lambda)\,dr$ in eq. 48 is the work done per particle in the spherical layer of thickness dr at r. If it is supposed, as in the discussion above, that most of the contributions to the integral in eq. 48 are concentrated in the nearest one to two molecular layers around the cavity, then we can use the approximate calculations to make rough comparisons between the predictions of eqs. 47 and 48. It was found above that, at 277 K, the total work of cavity formation performed on the eight molecules in the assumed initital structure was 4830 cal/mol, or an average of 600 cal/mol per molecule. For 277 K, the value of kT is 550 cal/mol. As a further comparison, we see in eq. 47 from scaled particle theory that the integral over v_c of $\rho G(\lambda)\,dv_c$, which gives the total number of particles displaced in making the cavity, is $-\Delta W(\tau)/kT$. At 298 K, the quantity $-\Delta W(\tau)/kT$ is 8.7 [20], in rough agreement with the assumed initial and final structures in our simple approximations for 277 K.

6. Summary and conclusions

Our purposes here are (a) to compare the features of the coupling parameter method for introducing the nonpolar group (section 2) with those of the method of isochoric deformation (section 4.1) and (b) to compare the conclusions of the molecular (section 4.1) and macroscopic (section 4.2) descriptions with one another and with the energetic concerns of statements (i) and (ii) in section 1.

For convenience in the discussion, the coupling procedure will be referred to as the 'κ-process,' and the deformation procedure as the 'λ-process.' Both reversible procedures are, of course, strictly hypothetical; κ is an abstract, dimensionless parameter varying between zero and unity, while λ, varying between zero and τ, is an actual physical dimension of the system, the cavity radius. When $\kappa = 1$, the fluid specimen surrounds a fixed nonpolar solute; when $\lambda = \tau$, the specimen surrounds a fixed cavity. Reversibility is achieved in each elementary $d\kappa$ or $d\lambda$ by the provision of distinct, infinitesimal work and heat components. The constant-temperature surroundings provide for the heat components, eq. 7 in the κ-process and eq. 29 in the λ-process. There are interesting contrasts between the work components in the two cases. In the κ-process, $-dW$ in eq. 6 results from an infinitesimal change in coupling under conditions of fixed configuration, summed over all configurations; in the λ-process, $-dW$ in eq. 28 results from an infinitesimal change in configuration under conditions of fixed (full) coupling, summed over all configurations. In each procedure, the infinitesimal work is performed on the system by an appropriate external agency that can operate reversibly; i.e., the work performed on the system by the hypothetical external agency exactly equals the increase in free energy of the system.

We have investigated, by parallel development of molecular and macroscopic approaches, how the concepts of force, energy, structure and structural change enter the description of the work and heat of cavity formation by isochoric deformation. The unifying principle for the two methods is the Gibbs relation, eq. 8. We note the similarity of eqs. 14 and 30 and the descriptive correspondence

between eqs. 22 and 31, between eqs. 28 and 36 and between eqs. 29 and 37. For the work $-dW$, we see that eqs. 28 and 36 have the form given in eq. 10. The forces specified in the force-displacement terms of eq. 28 are internal in the sense discussed at the end of section 3; the negative sign multiplying these molecular force displacements indicates the energetic effect of the external force field.

In section 4.1 the fluid 'structure' prevailing for a value λ is governed by $e^{-\beta w_{ij}(\lambda)}$ and 'structural change' in the fluid is determined by the behavior of $\partial(e^{-\beta w_{ij}(\lambda)})/\partial\lambda$. The work of cavity formation, the integral over λ of eq. 28, is derived cumulatively from minute, forced deformations of a statistical structure, with the work of each deformation step dependent on the static, average structure present at that step. The heat, which is the integrated form of eq. 29, is derived cumulatively from minute, nonforced statistical adjustments, against stationary constraints, as the isochoric system of molecules accommodates the expanding cavity. We see that the physical events in which potential energy changes appear as work or heat, respectively, are distinguishable and separable.

In general, constant p,T systems are preferred in thermodynamic descriptions because they reflect the most common laboratory situations. Nevertheless, constant v,T conditions have frequently been used in theoretical discussions of condensed macroscopic systems under moderate pressure because the pressure-dependent contributions to changes in thermodynamic variables are small in such systems [27,36,37,43,46]. In section 5, we discussed some formal and numerical similarities between the isochoric deformation (constant v,T) and the scaled particle method (constant p,T). Further, it has been shown by detailed calculations in the scaled particle approach [20] that the pressure-dependent term contributes a negligible quantity to the free energy of cavity formation and that this free energy is determined only by the temperature, the particle diameter and the number density. It has also been pointed out [24,44] in the scaled particle method that the volume available to the solvent molecular centers is the same before and after the introduction of the cavity; this is of course identical to the situation in the present

isochoric deformation method. In both cases then, the entropy change accompanying cavity formation is determined only by the restructuring of solvent around the cavity [24,44]. Thus, if applications of the present (constant v,T) methods are confined to number densities appropriate to the liquids near 1 atm, thermodynamic conclusions will be the same as in constant p,T methods. Finally we mention that, although pv work is rigorously zero in both the κ-process of section 2 and the λ-process of section 4, the reasons are different in the two cases. In the κ-process, no pv work is done because there is no displacement of external constraints; in the λ-process, for any increase $d\lambda$ in cavity radius, the pv work done on the system at the inner surface (radius λ) is exactly cancelled by the pv work done by the system at the outer surface (radius $r_0(\lambda)$).

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