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A Statistical Thermodynamic Supermolecule-Continuum Study of Ion Hydration: Cell and Shell Methods

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A theoretical study of ion hydration using the statistical thermodynamic supermolecule-continuum method is described. The cell and shell methods are used for configurational averaging. Enthalpies, free energies and entropies are calculated for Li^+, Na^+, K^+, F^- and Cl^- each four coordinated with water. The results are in reasonable accord with experiment. A comparison of the site method, cell method and shell method results is presented. The supermolecule-continuum approach to solvent effects seems to be capable of accommodating essential features for the calculation of solvation energy and solvent effects on structure and properties.

Key words: Ion hydration – Statistical thermodynamic supermolecule-continuum method for ion hydration

1. Introduction

This series of papers [1] describes a statistical thermodynamic supermolecule-continuum (STSMC) study of ion hydration. This system is investigated as a prototype solvation problem in order to document the level of agreement to be expected between numerical supermolecule-continuum calculations and experiment and to investigate alternative methodological strategies designed to make STSMC calculations computationally tractable for larger systems of general chemical and biochemical interest.

The basic idea of STSMC theory is to treat solvation phenomena in terms of a partition function obtained from a Monte Carlo calculation considering the solute and first solvation shell explicitly and the remainder of solvent as a polarizable dielectric continuum [2]. There are two basic aspects of STSMC calculations: configurational energy and configurational averaging. For configurational energy

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evaluation we are using pairwise additive analytical intermolecular potential functions representative of large basis set *ab initio* quantum mechanical calculations for solute–solvent and solute–solute interactions for the supermolecular contribution and a generalized reaction potential for polarization energy. For configurational averaging there are various alternatives, defined and described previously as the site method, cell method and shell method [2].

Determination of the capabilities and limitations of STSMC theory and the various methodological alternatives therein requires detailed numerical studies on prototype problems. The ion hydration problem has been extensively studied and is well characterized experimentally and is thus well suited for our present purposes. Paper I of this series contains background details on ion hydration and the results of STSMC calculations on ion hydration energy using the site method for configurational averaging. Here we extend this study by describing results based on the cell method and shell method.

The following section recounts the general theory in expanded detail in order to give a rigorous formulation of the cell method and shell method. Section 3 contains computational details and results of cell method and shell method calculations on ion hydration, a comparison with the results of site method calculations from Paper I, and a quantification of communal errors. Section 4 contains a discussion of results and Sect. 5 a summary of conclusions drawn from Papers I and II.

2. Theory

Statistical thermodynamic supermolecule-continuum theory was previously described in the context of solvent effects on conformational stability and a conformational partition function [2]. The formulation of STSMC theory for solvation energy requires considering explicitly certain terms which cancel out in the conformational problem, and a more rigorous development of the formalism is required. In this section we formulate the theory from first principles, interfacing with the solvation energy and the conformational stability problems at the appropriate juncture. Subsequently, the theoretical apparatus for comparing the site method, cell method and shell method for configurational averaging is developed.

The system under consideration consists of a dissolved particle and a large number of solvent molecules. The classical canonical ensemble partition function Z for the system is

$$Z=\frac{1}{(N-1)!h^{3N}}\int\int e^{-H(P,Q)/kT}\,dP\,dQ \qquad (1)$$

where N is the total number of particles in the system $N-1$ of which are indistinguishable solvent molecules, h is Planck's constant, k is Boltzman's constant and T is the absolute temperature. The quantity $H(P, Q)$ is the classical Hamiltonian for the N particle system, developed in terms of momenta $P=\{p_1, p_2 \ldots p_N\}$

and configurational coordinates $Q=\{q_1, q_2 \ldots q_N\}$ and given by the expression

$$H(P, Q)=T(P)+E(Q) \tag{2}$$

where T is the kinetic energy and E is the potential energy. The complete canonical ensemble partition function can be factored into momentum and configurational terms,

$$Z=Z'Z_Q \tag{3}$$

where in the usual manner [3] [1]

$$Z'=q_W^{N-1}/[(8\pi^2)^{N-1}\,\Lambda^{3N}(N-1)!] \tag{4}$$

with q_W representing the internal partition function of a water molecule, Λ is a one-dimensional translational partition function, and

$$Z_Q=\int e^{-E(Q)/kT}\,dQ \tag{5}$$

The momentum term depends only on the number and type of particles in the system. This is invariant in all applications presently taken up with STSMC theory. The momentum terms will thus always cancel in any difference of thermodynamic quantities and need not be considered further.

Focussing now on the configurational partition function, the basic assumption of supermolecule continuum theory (Eq. 20 of Ref. [2]) is that

$$E(q_1, q_2, \ldots q_M \ldots q_N)=E^{\text{eff}}(q_1, q_2, \ldots q_M)+E_{\text{solv}} \tag{6}$$

where $E^{\text{eff}}(q_1, q_2 \ldots q_M \ldots q_N)$ is the effective energy of the solute (particle #1) and $M-1$ vicinal solvent molecules in a cavity embedded in a polarizable dielectric continuum and E_{solv} is essentially the cohesive energy of solvent. This decomposition will be most accurate when we are considering the effects of solvation on an isolated solute molecule. The term E^{eff} will include an accurate treatment of solute interactions with the first solvation shell, and an approximate treatment of the interactions between the supermolecule assembly and the bulk solvent. We are thus concentrating our efforts on the most important interactions in a very dilute solute solution.

The configurational partition function can then be written

$$Z_Q=Z_Q^{\text{smc}}Z_Q^{\text{solv}} \tag{7}$$

where

$$Z_Q^{\text{smc}}=\int\int\cdots\int e^{-E^{\text{eff}}(q_1, q_2 \ldots q_M)/kT}\,dq_1, dq_2 \ldots dq_M \tag{8}$$

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[1] See also: Go, N., Scheraga, H. A.: J. Chem. Phys. **51**, 4751 (1969). These authors point out that when internal coordinates are used, as we will do later, the integration over momenta contributes a term to the total partition function which we are implicitly treating as a constant. Our approximation here neglects the effect of the "kinetic entropy", which is in the order of 0.5 kcal/mole for polymers and is expected to be still smaller for solute molecules amenable to the present treatment.

and

$$Z_Q^{\text{solv}} = \int \cdots \int e^{-E_{\text{solv}}/kT} \, dq_{M+1} \ldots dq_N = V^{N-M} e^{-E_{\text{solv}}/kT} \tag{9}$$

As with Z_p, Z_Q^{solv} will cancel upon a thermodynamic difference and need not be considered further. The quantity of basic interest here is the supermolecule-continuum configurational partition function, Z_Q^{smc} involving as configurational coordinates q_i the sets of quantities specifying the position v_i, orientation ω_i, and internal coordinates x_i for each of the particles of the system. The internal coordinates can be further decomposed into bond lengths r_i, bond angles θ_i and dihedral angles τ_i.

Going over now to specific applications, our previous formal considerations of solvent effects on conformational stability dealt with the reduced partition function

$$Z_Q^{\text{smc}}(\tau_1) = \int \int \cdots \int e^{-E^{\text{eff}}(q_1, q_2, \ldots q_M)/kT} \, dq'_1, dq_2 \ldots dq_M \tag{10}$$

where $dq'_1 = dq_1/d\tau_1$.

Neglecting the hard variables r_i and θ_i and carrying out the calculation with respect to the center of mass and principle orientation of the solute particle leads to

$$Z_Q^{\text{smc}}(\tau_1) = 4\pi^3 V \int \ldots \int e^{-E^{\text{eff}}(\tau_1, q_2, \ldots q_M)/kT} \, dq_2 \ldots dq_M \tag{11}$$

Solvent effects on conformational stability follow from a study of the quantity $(4\pi^3 V)^{-1} Z_Q^{\text{smc}}(\tau_1)$. Eq. (11) is a rigorous formulation of Eq. (22) of Ref. [2]. For the calculation of ion hydration energy, there are no conformational coordinates for the solute, and

$$Z_Q^{\text{smc}} = V_1 \int \cdots \int e^{-E^{\text{eff}}(q_2 \ldots q_M)/kT} \, dq_2 \ldots dq_M \tag{12}$$

We consider now the alternative means proposed for evaluating the configurational integrals on the right hand side of Eqs. (11) and (12). In the following development, we will neglect any changes in the internal variables of the solvent molecules, both bond lengths and bond angles. Therefore the only degrees of freedom remaining to the solvent molecules will be the location of the center of mass, represented by dV_i, and the orientation about the center of mass, represented by $d\omega_i$. For the ions to be studied here, changes in the internal coordinates of a water molecule due to the presence of a neighboring ion have been shown to be negligible [5].

If we restrict the range of the integrals to the first solvation shell S_1, Eq. (12) becomes

$$Z_Q^{\text{smc}} = V_1 \int_{V_2}^{S_1} \int_{\omega_2} \ldots \int_{V_M}^{S_1} \int_{\omega_M} e^{-E^{\text{eff}}(V_2 \omega_2 \ldots V_M \omega_M)/kT} \, dV_2 \, d\omega_2 \ldots dV_M \, d\omega_M \tag{13}$$

and defines the shell method for configurational averaging in STSMC calculations. Alternatively it has been suggested that a cell method, where the solvation shell is partitioned into $M-1$ nonoverlapping cells each with one solvent molecule may provide an adequate approximation to Z_Q^{smc} to be of practical computational value. The partition function for the cell method is then

$$Z_Q^{\mathrm{smc}} = V_1 \int_{V_2}^{c_1} \int_{\omega} \cdots \int_{V_M}^{c_{M-1}} \int_{\omega_M} e^{-E^{\mathrm{eff}}(V_2\omega_2 \ldots V_M\omega_M)/kT} \, dV_2 \, d\omega_2 \ldots dV_M \, d\omega_M \quad . \tag{14}$$

where the positional integrations extend over the domains of the individual solvation cells of each solvent molecule. The extreme case of the cell method is the site method, with total restriction of positional degrees of freedom. Here the $M-1$ solvent molecules are deployed on specific solvation sites in the solvation shell, and only orientational averaging is considered. The site method partition function is simply

$$Z_Q^{\mathrm{smc}} = V_1 \int_{\omega_2} \cdots \int_{\omega_M} e^{-E^{\mathrm{eff}}(\omega_2 \ldots \omega_M)/kT} \, d\omega_2 \ldots d\omega_M \tag{15}$$

The analogous equations for the conformational stability problem are given in Eqs. (23–24) of Ref. [2].

In the previous paper in this series, calculations on ion hydration using the site method were reported. In the following section analogous calculations using the cell and shell method are described, and results on ion hydration using all three methods are compared and critically considered.

3. Calculations and Results

Numerical calculations based on Eqs. (13), (14) and (15) are carried out using Monte Carlo techniques. The expressions for Z_Q^{smc} are first cast into a form suitable for numerical integration, and a coordination number and appropriate geometrical factors assumed. Here we first briefly review the computational aspects of the site method study on ion hydration described in detail in Paper I and give the expressions and specifications for the cell and shell method calculations described herein. Then the relevant details for comparing ion hydration theory and experiment are given, followed by a presentation of results and a comparison of the site, cell and shell methods.

The Monte Carlo calculation of Z_Q^{smc} based on the site method follows from the expression

$$Z_Q^{\mathrm{smc}} = V_1 (4\pi^3)^{M-1} \frac{1}{n} \sum_i^n e^{-E^{\mathrm{eff}}(\omega_{2i}, \ldots \omega_{Mi})/kT} \tag{16}$$

Each term in the summation corresponds to a distinct configuration of the system and n is the total number of configurations considered. Three random numbers are generated to fix the orientation of each solvent molecule, and thus each configuration requires 3 $(M-1)$ random numbers for a complete specification. The factor $(4\pi^3)^{M-1}$ arises when the ranges of integration over orientation angles are transformed to the interval (0, 1) appropriate for the Monte Carlo procedure [4].

The corresponding expression for the cell method is

$$Z_Q^{\text{smc}} = V_1 C_1 C_2 \ldots C_{M-1} (4\pi^3)^{M-1} \frac{1}{n} \sum_i e^{-E^{\text{eff}}(V_{2i}\omega_{2i}, \ldots V_{Mi})/kT} \tag{17}$$

where for each configuration 3 $(M-1)$ random numbers are required to fix the orientation angles ω_i and an additional 3 $(M-1)$ random numbers are required to specify the center of mass of solvent molecules within their respective cells. The cell volume factors $C_1, C_2, \ldots C_{M-1}$ arise from integrations over $dq_2, dq_3, \ldots dq_M$. For the shell method,

$$Z_Q^{\text{smc}} = V_1 S_1^{M-1} (4\pi^3)^{M-1} \frac{1}{n} \sum_i^n e^{-E^{\text{eff}}(V_{2i}\omega_{2i}, \ldots V_{Mi}\omega_{Mi})/kT} \tag{18}$$

where S_1 is the total volume of the first solvation shell.

The calculations described herein all involve four solvent molecules in the first solvation shell of hydrated ions. In Paper I both tetrahedral and octahedral site method studies were reported, and from this and other sources it is likely that six coordination is more appropriate for the larger ions, especially Cl^-. In view of the increased dimensionality of the Monte Carlo calculation using the cell and shell method, we restrict our comparison here to four coordination.

In the site method study, the centers of mass of solvent molecules were disposed on a sphere of radius $r_i + r_w$ where r_i is the ionic radius and r_w is an effective radius for the water molecule, taken as 1.38 Å. The cavity radius for the calculation of polarization energy was taken as $r_i + 2r_w$. In the cell method calculations, the center of each cell was taken to coincide with the tetrahedrally disposed sites in the previous study. The center of gravity of a solvent molecule was permitted a maximum radial displacement of 0.4 Å from the center of the cell; this is the largest displacement possible which maintains the solvent molecules within the cavity. For the shell method, the centers of gravity of solvent molecules were maintained within concentric spheres of radii $r_i + r_w \pm 0.4$, corresponding to simply removing the lateral walls of the solvation cells. The cavity radius for the calculation of polarization energy in the cell and shell method is retained as $r_i + 2r_w$.

All other details of the calculation are exactly as described in Ref. [1]. The configurational energy is a sum of supermolecular and polarization contributions. The supermolecular energy is calculated from a pairwise additive analytical potential function developed by Clementi and co-workers from *ab initio* quantum mechanical molecular orbital calculations on ion–water [5] and water–water interactions [6]. The polarization energy is calculated from Kirkwood's expression [7] for the generalized reaction potential of a charge distribution in a spherical cavity.

The last quantity to specify in Z_Q^{smc} is V_1, the volume in which the center of mass of the ion is free to move. In many applications (e.g. conformational studies) V_1 is constant for the process and does not contribute to relative thermodynamic quantities. In the ion hydration process, the ion goes from the gas phase to the liquid, and V_1 changes significantly. To estimate the changes in the thermodynamic properties resulting from the change in V_1 we follow the procedure suggested by Eley and Evans [8]. In the gas phase, V_1 equals V_g, the molar volume of a perfect gas at 298°K. In the liquid, the free volume of the ion is approximated by V_f, the free volume of the solvent, taken to be 4×10^{-2} e/mol. The temperature dependence of V_f is taken from the estimate of Eyring and Stearn [9], $V_f=bT^m$ where m is 5.02. The resulting changes in the thermodynamic functions from this contribution are then

$$\Delta A_{V_1}=RT\ln(V_g/V_f)=7.9\text{ kcal/mol} \tag{19}$$

$$\Delta U_{V_1}=5.02\,RT=3.0\text{ kcal/mol} \tag{20}$$

and

$$\Delta S_{V_1}=R[5.02-\ln(V_g/V_f)]=-16.5\text{ kcal/deg mol} \tag{21}$$

all at 298°K. The estimates of these quantities are not especially sensitive to the model used for determining V_1. An additional term of RT or 0.6 kcal/mol must be added to ΔA and ΔU in order to obtain the corresponding values for ΔG and ΔH. All these corrections to ΔG, ΔH and ΔS are the same as those used in the results already reported for the site method [1].

To compare the calculated results with experiment, we refer to the thermocycle described in detail in Paper I. If X is any thermodynamic function, G, H or S, we use the equation

$$\Delta X_{\text{el}}^{i-w}=\Delta X_{\text{smc}}^{i-w}-\Delta X_{\text{hyd}}^{n}+\Delta X_{\text{cav}}+\Delta X_{\text{rel}}^{i-w} \tag{22}$$

to obtain calculated values of the electrostatic thermodynamic quantity $\Delta X_{\text{el}}^{i-w}$ to compare with experiment [10]. As described in Paper I, $\Delta X_{\text{smc}}^{i-w}$ is the result of a supermolecule-continuum calculation of the ion–water system, including the corrections described in the preceding paragraph, $\Delta X_{\text{hyd}}^{n}$ is interpolated from experimental results on hydration of rare gas atoms, and ΔX_{cav} is the result of a supermolecule continuum calculation on cavitated water without the ion. Note that the multiplicative preintegration factors in the STSMC partition function occur in $\Delta X_{\text{smc}}^{i-w}$ and then in ΔX_{cav} with opposite sign and thus cancel. The term $\Delta X_{\text{rel}}^{i-w}$ represents the structuration of bulk water in the vicinity of the supermolecular assembly, and is not known with any degree of accuracy. Neglect of this term is part of the methodological error in a single shell STSMC calculation.

The values used for $\Delta G_{\text{hyd}}^{n}$, ΔG_{cav} and corresponding enthalpies and entropies are given in Table 1. The calculated results for electrostatic free energy, enthalpy and entropy for ion hydration using the cell method and shell method are collected in Table 2. The final results of the site method calculations from Paper I are also listed in Table 2 for comparative purposes.

Table 1. Values used for ΔG^n_{hyd} and ΔG_{cav} and corresponding enthalpies and entropies in comparing theory and experiment, units of kcal/mol

Ion	r_i	ΔG^n_{hyd}	ΔG_{cav}	ΔH^n_{hyd}	ΔH_{cav}	ΔS^n_{hyd}	ΔS_{cav}
Li^+	0.6	1.1	-1.4^a	1.0	-2.6^a	-6.9	-3.9^a
			4.5^b		6.6^b		6.8^b
Na^+	0.95	1.7	2.2^a	-1.6	2.1^a	-11.0	-0.2^a
			7.3^b		10.6^b		11.1^b
K^+	1.33	2.4	4.8^a	-2.2	6.9^a	-15.4	6.9^a
			9.9^b		14.8^b		16.4^b
			2.0^c		3.6^c		5.9^c
F^-	1.36	2.4	4.9^a	-2.3	7.1^a	-15.7	7.3^a
			10.0^b		15.0^b		16.7^b
			2.0^c		2.3^c		5.6^c
Cl^-	1.81	3.2	6.3^a	-3.0	9.6^a	-20.9	11.0^a
			11.4^b		17.2^b		19.2^b

[a] Site method, 20*K* configurations.
[b] Cell method, 50*K* configurations.
[c] Shell method, 200*K* configurations.

Table 2. Calculated and observed thermodynamic functions for ion hydration, units of kcal/mol

		$\Delta G^{i-w}_{\text{el}}$		$\Delta H^{i-w}_{\text{el}}$		$\Delta S^{i-w}_{\text{el}}$	
Ion	r_i	calc.	obs.	calc.	obs.	calc.	obs.
Li^+	0.6	-148.4^a	-122.1	-158.3^a	-129.7	-33.3^a	-25.4
		-142.7^b		-149.8^b		-24.3^b	
Na^+	0.95	-114.0^a	-98.4	-121.5^a	-103.6	-25.2^a	-17.5
		-109.2^b		-113.9^b		-15.9^b	
K^+	1.33	-82.7^a	-80.6	-86.5^a	-83.4	-13.0^a	-9.4
		-77.9^b		-79.7^b		-6.2^b	
		-89.6^c		-90.3^c		-19.3^c	
F^-	1.36	-98.8^a	-89.5	-97.2^a	-97.8	-11.5^a	-27.8
		-88.5^b		-89.8^b		-5.6^b	
		-90.2^c		-97.1^c		-18.6^c	
Cl^-	1.81	-61.0^a	-76.1	-61.4^a	-80.3	-1.3^a	-14.0
		-56.2^b		-54.9^b		$+2.1^b$	

[a] Site method, 20*K* configurations.
[b] Cell method, 50*K* configurations.
[c] Shell method, 200*K* configurations.

4. Discussion

The level of agreement between theory and experiment reported in the STSMC site method is generally maintained in the cell and shell method results. The difference between the calculated and observed thermodynamic quantities is partly due to neglect of the relaxation terms $\Delta X_{\rm rel}^{i-w}$. For ΔG and ΔH, the discrepancy between calculated and observed values is between $+10$ and $+25$ cal/mole for Li^+ and Na^+, near zero for K^+ and F^-, and negative for Cl^-. This is well within the range estimated for $\Delta H_{\rm el}^{i-w}$ in previous studies.

The results indicate that relative size of the ion is of prime importance in determining the effect of an ion on structuration beyond the first solvation shell. The K^+ and F^- ions have radii very close to that of a water molecule; this may allow them to become solvated without causing a disruption of the average number of hydrogen bonds in solvations shells beyond the first. With Li^+ and Na^+, the first shell of water molecules is collapsed slightly in solvating the ions, and the second shell hydrogen bond network is affected. The Cl^- ion is larger than a water molecule, and here even the assumption of tetrahedral coordination is likely inadequate.

It was suggested in the previous paper that the unphysical negative values for $\Delta G_{\rm cav}$ and $\Delta H_{\rm cav}$ reported there were artifacts of the site method. In view of the results in Table 1, this appears to be the case; those terms all have realistic values in the cell and shell methods. The problem in the site method calculation of these terms was a poor choice of the sites for the water-in-water supermolecule calculation, resulting in artificially high energies for this reference state. When the sites were allowed to "relax" in the cell and shell methods, more nearly optimum dispositions of the water molecules were located.

The entropies of hydration are still in relatively poor agreement with experiment. A major error here is undoubtedly our crude estimate of the $\Delta S_{\rm hyd}^{n}$ terms, which make an important contribution. At present we have no alternative but to use these estimates in our thermocycle. However, the need for such terms will only arise when *absolute* thermodynamic quantities are needed. Thus we will not have to rely on estimates of unknown quantities in a thermocycle when conformational problems are considered.

Comparing the results of the cell method with those previously obtained for the site method, the results in Table 2 show that the cell method gives improved results Li^+, Na^+, K^+ and F^-. The site method results are not improved by the cell method for Cl^-, but here as mentioned above the assumption of four coordination is part of the problem. The cell method gives improved entropies for the positive ions but not for negative ions; in particular the positive calculated entropy of hydration for F^- is probably unphysical.

For the two cases for which STSMC shell method calculations were carried out, both are in reasonable agreement with experiment and the overall results on F^- are improved over the site method and cell method results. The trends in the calculated thermodynamic quantities are not simply monotonically changing since the $\Delta X_{\mathrm{el}}^{i-w}$ involve a balance between both $\Delta X_{\mathrm{smc}}^{i-w}$ and ΔX_{cav}.

We have just recently implemented methodology for carrying out Monte Carlo calculations of internal energy using the Metropolis method [12], and we have now produced shell method results for the ion hydration enthalpies of K^+ and F^-. The results are $^{-}96.2$ kcal/mol for K^+ and -114.3 kcal/mol for F^-, based on 50 K points and a step size chosen to accept $\sim 50\%$ of the points in the stochstic walk. A full description of this work will be provided in a forthcoming paper. Note also that in parallel with our work the gas phase ion hydration problem has been treated by Mruzik, Abraham, Schreiber and Pound [13].

With the overall agreement between calculated and observed thermodynamic quantities using the cell method and shell method commensurate with the results obtained using the site method, the general considerations on the physicochemical basis of ion hydration and the geometry of the ion–water complex carry over intact from paper I. The effect of configurational averaging on ΔG and ΔH remains minimal in the ion hydration problem, and is the main reason why the results for the site, cell and shell methods are so similar. Larger differences can be anticipated for systems involving less polar solutes, where orientation effects are less configurational averaging becomes more important.

5. Summary and Conclusions

The calculated results on hydrated ions show that statistical thermodynamic supermolecule-continuum theory gives reasonable agreement with experiment at a level as good or better than previous theoretical studies, with the added advantage of being more rigorous and straightforwardly extendable to other solvation problems. The use of analytical pairwise potential functions for configurational energy has been successful in rapidly providing accurate energies for Monte Carlo calculations, and the site and cell method are seen to be good approximations to a full shell method configurational averaging in ion hydration to be of considerable practical computational value at least in certain cases. There are obvious limitations to the theory as it falls far short of a detailed theoretical description of the liquid state, but overall the supermolecule-continuum model appears adequate to describe the thermodynamics of the solvation process and the essential features of solvent effects on molecular structure and properties.

We are presently extending STSMC methodology to solvation problems involving polyatomic solutes and prototype conformational stability problems. We are investigating optimum methods for generating analytical potential functions representative of *ab initio* quantum mechanical calculations of solute–solvent and solvent–solvent interactions valid in the region of the first solvation shell. The *heuristic potential function method* [14], whereby the data base of quantum mechanical energies is dynamically evolved to provide an analytical function with prescribed predictive value appears quite promising at present.

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Note added in proof.

Subsequent to this study we have carried out further calculations based on this model, including more solvent particles explicitly and considering electrically neutral as well as charged species. Calculations of the radial distribution function for the supermolecular cluster show clearly incipient surface tension effects at the boundary of the cavity. Also the calculation time for the polarization energy goes up rapidly as the number of discrete particles increases. Rather than extend this type of calculation further, we have taken up fully discrete Monte Carlo–Metropolis computer simulation under periodic boundary conditions, as in S. Swaminathan and D. L. Beveridge, J. Am. Chem. Soc. **99**, 8392 (1977).