Gaussian fluctuation formula for electrostatic free-energy changes in solution

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Linear-response theory is used to derive a microscopic formula for the free-energy change of a solute-solvent system in response to a change in the charge distribution of the solutes. The formula expresses the change in the solvent polarization energy as a quadratic function of the changes in the partial charges at the atomic centers of the solute atoms. The average electrostatic potential at the sites of the solute charges and the second moment of the fluctuations in the electrostatic potential at these sites enter as parameters in the formula. These parameters can be obtained from computer simulations of a reference system with fixed solute charges and the results then compared with explicit free-energy simulations of the corresponding processes or with experiment. The formula provides a microscopic definition of the dielectric response function for the combined solute plus solvent system which can be related to standard formulas for the dielectric response. A simple numerical example involving a simulation of the charging free energy of two ions in aqueous solution is discussed. The change in the solvent polarization with solute charge predicted using the molecular dielectric response function agrees remarkably well with the results of corresponding free-energy simulations for large changes in the solvent polarization energy. Some applications of the molecular dielectric response formula are discussed.

I. INTRODUCTION

In linear-response theory, as applied to solvation thermodynamics, there is a quadratic relation between the free energy and the solvent polarization coordinate.[1] This relation is one of the assumptions of classical Marcus electron transfer theory.[2] Recent computer simulations of charge transfer in solution have demonstrated the broad range of validity of linear-response theory for such processes,[3-8] although exceptions have also been noted.[9,10] The theory is based on the assumption that the solvent response to a perturbation is linear in the perturbation. While linear-response relations are usually derived by assuming that the perturbation is a small parameter, for systems described by Gaussian distribution functions the linear-response relations are exact. We use this fact to derive a formula for the free-energy change of a solute–solvent system in response to a change in the charge distribution of the solute(s). The formula expresses the change in the solvent polarization energy as a quadratic function of the changes in the partial charges at the atomic centers of the solute atoms. The average electrostatic potential at the sites of the solute charges and the second moment of the fluctuations at these sites enter as parameters in the formula. The parameters can be obtained from computer simulations of a reference system with fixed solute charges and the results then compared with explicit free-energy simulations of the corresponding processes or with experiment. The formula provides a microscopic definition of the dielectric function for the combined solute plus solvent taken as the reference system which can be related to standard formulas for the dielectric response. In Sec. II, we derive the microscopic formula for the electrostatic free-energy change due to a change in the charge distribution of the solute atomic sites. In Sec. III we apply the formula to a

simple model problem, calculation of the solvent polarization energy when two ions at fixed separation are charged up in aqueous solution. The free-energy change predicted using the linear-response formula is compared with the results of explicit free-energy simulations. The sensitivity of the results to the choice of reference system used to evaluate the dielectric function is discussed. As discussed in Sec. III, the variation of the dielectric function parameters with reference system is a manifestation of a (small) nonlinear dielectric effect. Finally, we suggest some possible applications of the molecular dielectric-response formula.

II. THEORY

We consider a set of solute atoms with charges immersed in a solvent. The fluctuations of the solvent molecules lead to fluctuations in the electrostatic potential at the solute sites and to fluctuations in the total electrostatic interaction energy between the solute and the solvent. The electrostatic interaction energy U between the solute and the solvent and the fluctuations ΔU can be written as the following sums over the atomic sites of the solute(s):

$$U = \sum_i V_i q_i, \tag{1a}$$

$$\Delta U = \sum_i \Delta V_i q_i, \tag{1b}$$

$$\Delta V_i = V_i - \overline{V}_i, \tag{1c}$$

where V_i is the instantaneous electrostatic potential due to the solvent at the ith solute site, and ΔV_i is the fluctuation of V_i from the equilibrium average $\overline{V}_i$. If a Gaussian form is assumed for the probability distribution function $p(\Delta U)$, this leads to the parabolic behavior of the free-energy curve

as a function of ΔU (the "polarization coordinate") characteristic of the linear-response model. Simulations have demonstrated that $p(\Delta U)$ does indeed have a Gaussian form for model systems corresponding for example, to aqueous ferrous-ferric ions at internuclear separations (ca. 6 Å),[3] as well as for a contact ion pair in a model dipolar solvent.[4] To derive the formula for the free-energy change corresponding to a change in the charges on the solute sites, we assume that the probability function for the electrostatic potentials at the solute sites due to the solvent is also a multivariate Gaussian,

$$p\{\Delta V_i\} = \left(\frac{1}{2\pi}\right)^{n/2} (\det \sigma^{-1})^{1/2}$$

$$\times \exp(-\tfrac{1}{2}\Delta V^\dagger \cdot \sigma^{-1}\Delta V), \qquad (2a)$$

$$\sigma = \begin{pmatrix} <(\Delta V_1)^2> & <\Delta V_1\Delta V_2> & & <\Delta V_1\Delta V_n> \\ \cdot & & & \cdot \\ & \cdot & & \cdot \\ & & \cdot & \cdot \\ & & & <\Delta V_n\Delta V_n> \end{pmatrix}.$$

$$(2b)$$

In Eqs. 2(a) and 2(b), σ is the covariance matrix of the fluctuations in the electrostatic potentials at the solute sites with fixed charges on the solutes, σ^{-1} is the inverse matrix, $\Delta V^\dagger$ is the row vector of the fluctuations in the electrostatic potential at the solute sites, $\Delta V^\dagger = (\Delta V_1, \Delta V_2,...,\Delta V_n)$, and the indices run from 1 through n, the total number of solute sites.

The free-energy change in going from a reference state described by a potential function V to a "primed" state with potential function V' can be written as a configurational integral over the partition function of the reference state with potential V,[11]

$$\Delta F = -k_B T \ln \langle e^{-\beta(V'-V)} \rangle_V \qquad (3a)$$

$$= -k_B T \ln\left(\int e^{-\beta(V'-V)}\rho_{eq}(V)d\{x\}\right), \qquad (3b)$$

where $\beta = (k_B T)^{-1}$, $\rho_{eq}(V)$ is the normalized Boltzmann factor for a configuration of the reference state (which depends on all the solute plus solvent coordinates), and the integral is over all the coordinates of the system. If the reference state and primed state differ only by the charge distribution (partial charges) of the solute atoms, then the integral [Eq. 3(b)] may be converted to the following integral over the fluctuations in the electrostatic potential due to the solvent at the solute sites:

$$I_1 = \int e^{-\beta(V'-V)}\rho_{eq}(V)d\{x\}$$

$$= \int \exp\left[-\beta\left(\sum_i (\Delta V_i + \overline{V}_i)\Delta q_i\right)\right]p\{\Delta V_i\}$$

$$\times d\Delta V_1\, d\Delta V_2,...,d\Delta V_n. \qquad (4)$$

In Eq. (4), Δq_i is the difference in the partial charge at the ith solute atom between the primed state and the reference state. If the Gaussian form given by Eq. (2) for $p\{\Delta V_i\}$ is assumed, then the integral in Eq. (4) may be explicitly evaluated,

$$I_1 = \exp\left(-\beta\sum_i \overline{V}_i\Delta q_i\right)\left(\frac{1}{2\pi}\right)^{n/2} (\det \sigma^{-1})^{1/2}$$

$$\times \int \exp(\alpha^T \cdot \Delta V - \tfrac{1}{2}\Delta V^T \cdot \sigma^{-1}\cdot \Delta V)$$

$$\times d\Delta V_1\Delta V_2,...,d\Delta V_n$$

$$= \exp\left(-\beta\sum_i \overline{V}_i\Delta q_i\right)\exp(\tfrac{1}{2}\alpha^T\cdot\sigma\cdot\alpha), \qquad (5)$$

where α^T is the row vector formed from the changes in the partial charges between the reference and primed states multiplied by $-\beta$,

$$\alpha^T = -\beta(\Delta q_1,\Delta q_2,...,\Delta q_n). \qquad (6)$$

Substituting Eq. (5) into the expression for the free-energy change, Eq. (3), we derive an explicit expression for the free-energy change in terms of the changes in the partial charges at the solute sites $\{\Delta q_i\}$, the average values of the electrostatic potential from the solvent at each solute site in the reference system $\overline{V}_i$, and the correlation functions for the joint fluctuations in the electrostatic potentials at sites i and j averaged over the reference system, $\{\langle\Delta V_i\Delta V_j\rangle\}$,

$$\Delta F = \sum_i \overline{V}_i\Delta q_i - \frac{\beta}{2}\sum_{i,j}\langle\Delta V_i\Delta V_j\rangle\Delta q_i\Delta q_j. \qquad (7)$$

The first term corresponds to the free-energy change due to the difference between the initial- and final-state charge distributions of the solute interacting with the electrostatic potential of the reference system, while the second term contains the induction effects related to the change in the polarization of the solvent by the change in the solute charge distribution. This simple formula will have a number of applications to problems involving charge transfer in solution. It provides an estimate, based on simulations of a reference state, of the electrostatic free-energy change due to the creation or redistribution of charge on the solute atoms. By simulations of the appropriate reference systems, it is possible to use the formula to estimate free-energy changes which are currently calculated using the conventional thermodynamic perturbation and integration techniques such as the solvation free energies of ions and molecules,[12-18] solvent induced stokes shifts for optical spectra,[19] or the reorganization energy in electron transfer reactions.[3,20] The formula can be related to the thermodynamic perturbation formulas for ΔF calculated by carrying out a number of simulations in "windows" corresponding to intermediate charge states between the initial and final states.[12] The formula corresponds to a "one window" thermodynamic perturbation calculation in a simulation with a Gaussian distribution for the fluctuations in the electrostatic potential at the solute sites. From this perspective, it is easy to see that the formula could also be used in thermodynamic perturbation simulations and that it should provide increased accuracy and efficiency for such calculations. For example, when the differences between the initial- and final-state charge distributions are sufficiently large that Eq. (7) is no longer accurate, a formula for the free-energy change corresponding to the use of both the initial and final states as references is given by

$$\Delta F = \sum_i \left(\overline{V}'_i q'_i - \overline{V}_i q_i \right) - \frac{\beta}{2} \sum_{i,j} \langle \Delta V'_i \Delta V'_j \rangle q'^2_i q'^2_j$$

$$+ \frac{\beta}{2} \sum_{i,j} \langle \Delta V_i \Delta V_j \rangle q^2_i q^2_j. \tag{8}$$

In Eq. (8) the unprimed variables correspond to the initial state, while the primed variables are those of the final state. Correlation functions from simulations of both the initial and final states are used in the formula. The nonlinear effects in the medium response to a charge perturbation at the solute sites are therefore approximated by averaging over the different linear-response dielectric functions at the initial and final states. It should be noted that if Eq. (2) were really exact, then the covariance matrix of the fluctuations in the electrostatic potentials at the solute sites would be independent of the reference system. There are several possible ways to incorporate higher-order moments of the distribution which give rise to the nonlinearities. However, based on the results of the numerical example presented in Sec. III, we expect that for many problems of interest the nonlinear effects will be small.

An advantage of using the quadratic free-energy formulas over the standard thermodynamic perturbation formulas is related to the importance of the tails of the distribution functions for the fluctuations in the electrostatic potential in evaluating the free-energy change. The $\exp[-\beta(V'-V)]$ weights fluctuations from the mean value of V heavily. Since the tails of the distribution are poorly sampled, errors in the estimates of the tails of the distribution contribute more to the free-energy change calculated by Eq. 3(a) since the tails of the distribution enter explicitly, than by Eqs. (7) or (8). In other words, if the multivariate distribution of fluctuations in the electrostatic potential for a reference state have a Gaussian form for some range of fluctuations about the mean, it is advantageous numerically to replace the actual distribution calculated from a finite simulation with a Gaussian analytical form based on the covariance matrix σ calculated from the simulation. This *ansatz* is conceptually similar to that used in the calculation of free-energy changes for macromolecules using simulations based on the "quasiharmonic" approximation.[21,22] However, for the electrostatic problem, the Gaussian form for the multivariate distribution of fluctuations in the electrostatic potential appears to be a better approximation than the corresponding approximation for the configurational integrals over the macromolecular fluctuations.[23,24]

Of particular importance is the fact that the parameters of the formula for the electrostatic free-energy change [Eq. (7)] depend only on the reference state. Equation (7) constitutes a dielectric-response function for the combined solute plus solvent system. This differs from the usual construction of a dielectric-response function which is defined in terms of the dielectric properties of the pure solvent. On a molecular level, the solvent dielectric function has a wave-vector dependence which reflects the nonlocal nature of the solvent dielectric response on a molecular length scale. There has been considerable recent interest in the construction of wave-vector dependent dielectric functions for li-

quids.[25-28] We have used simulations to construct the wave-vector dependent dielectric function $\epsilon(k)$ for water and calculated free-energy changes for ion charging based on $\epsilon(k)$.[28] Our results suggest that the perturbation of the solvent by the solute needs to be accounted for in the construction of dielectric-response functions. The Gaussian fluctuation formula for the electrostatic free-energy change presented in this paper, Eq. (7), provides a useful approach to the analysis of the dielectric response of a polar medium which includes the effects of the solutes on the solvent structure.

The assumption that the solvent bath obeys Gaussian fluctuation statistics has been used previously within the context of liquid state integral equation theory to derive a formula for the solvent polarization due to its interactions with a solute which bears a close resemblance to the free-energy formula we have derived.[29] To make the analogy, we suppose the charge density ρ_s of a solvent bath is characterized by a Gaussian distribution functional with variance $\chi_{ss}(r - r') = \langle \delta \rho_s(r) \delta \rho_s(r') \rangle$, the density–density correlation function for the pure solvent. We further assume that the solute sites i are linearly coupled to the solvent density with strength $c_{is}(r^\alpha - r)$ in units of $-\beta^{-1}$. Then the canonical partition function for the solute-solvent system can be evaluated and the excess chemical potential in the Gaussian fluctuation approximation is given by[29]

$$\Delta \mu^{GF} = \frac{-\rho_s}{\beta} \sum_i \int d\mathbf{r} \, c_{is}(\mathbf{r}^i - \mathbf{r})$$

$$- \frac{1}{2\beta} \sum_{i,j} \int d\mathbf{r} \, d\mathbf{r}' c_{is}(\mathbf{r}^i - \mathbf{r}) \chi_{ss}(\mathbf{r} - \mathbf{r}') c_{sj}(\mathbf{r}' - \mathbf{r}^j). \tag{9}$$

The coupling parameter c_{is} can be identified with the direct correlation function in the RISM integral equation theory.[29] As for Eq. (7), the first term of Eq. (9) corresponds to the solute charges interacting with the potential field of the reference system—which vanishes for a pure solvent reference state—while the second term contains the induction effects. We note that in the context of the integral equation approach to the solvation of polar systems, the Gaussian fluctuation approximation has been found to give better solvation thermodynamics than alternative closure equations (e.g., the hypernetted chain approximation).[30] It is instructive to make the following identification between Eqs. (7) and (9):

$$\int d\mathbf{r} \, d\mathbf{r}' c_{is}(\mathbf{r}^i - \mathbf{r}) \chi_{ss}(\mathbf{r} - \mathbf{r}') c_{sj}(\mathbf{r}' - \mathbf{r}^j)$$

$$\rightarrow \beta^2 \langle \Delta V_i \Delta V_j \rangle q_i q_j. \tag{10}$$

The perturbing effects of the solute's extended structure and charge on the polarization response of the solvent are accounted for in the integral equation theory through their influence on the direct correlation functions. These depend on the approximations inherent in the closure relation used to solve the integral equation. It would be interesting to attempt to construct a theory for the solvent density fluctuations in the presence of the solutes $\chi(\mathbf{r}^i - \mathbf{r}, \mathbf{r}^j - \mathbf{r}')$, but the loss of the symmetry properties inherent in the pure solvent makes the problem of constructing such a response function rather complicated. Of course $\chi(\mathbf{r}^i - \mathbf{r}, \mathbf{r}^j - \mathbf{r}')$, can always be evaluated numerically from a simulation, and that is what

is done implicitly when we apply Eq. (7). In Sec. III we provide a simple numerical application of the dielectric function formula, Eq. (7).

III. NUMERICAL EXAMPLE

We have been interested in analyzing the factors which contribute to the apparent dielectric response in computer simulations of aqueous solutions.[28,31] Towards this end, we have recently been carrying out free-energy simulations of simple systems which involve charging up one or two ions in water, treating the long-range interactions in different ways. In this section we use one of these simulations to test the accuracy of Eq. (7). The free-energy change obtained by explicitly discharging the charge on two ions in water is compared with the predicted free-energy change using the Gaussian fluctuation dielectric formula, Eq. (7). The model system consists of two spheres in water (341 molecules) separated by 10 Å in a cubic box, the length of each side is 21.7 Å. The Lennard-Jones parameters of the spheres correspond to those appropriate for a chloride ion, $\sigma/2 = 2.2$ Å and $\epsilon = 0.118$ kcal/mol.[32] The SPC water model is used for the solvent.[33] In the numerical example reported here, the nonbonded interactions were truncated with a spherical cutoff at 10.85 Å; the results of extensive studies with different truncation schemes are reported elsewhere.[31(d)] In our first study, we have used the fully charged system with a $+1$ charge on one ion and a -1 charge on the other as the reference state. The average potential $\bar{V}_i$ and the fluctuations in the average potential $\langle \Delta V_i \Delta V_j \rangle$ obtained from a 16 ps molecular dynamics simulation of the reference state (fixed charges on the ions) are listed in Table I(a). The more favorable electrostatic potential at the anion is a manifestation of the difference in the solvation shell structures of the two ions; this is the basis for the need to adjust the cation and anion crystallographic radii differently when fitting the classical Born ion solvation energy formula to experiment.[31(b)] At the large ion internuclear separation (10 Å) chosen in

this numerical example, the off-diagonal term of the fluctuation matrix σ_{+-} is much smaller (ca. 5–10 %) than the diagonal terms, although dielectric coupling between the two sites can affect both the diagonal and the off-diagonal terms.

The free-energy change for discharging the ions from the reference state was calculated using the thermodynamic integration simulation method,[11,12]

$$\Delta F = \int_0^1 \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_\lambda d\lambda \cong \sum_{i=1}^{N-1} \langle U(\lambda_{i+1}) - U(\lambda_i) \rangle_{\lambda_i}. \quad (11)$$

The initial state contains the fully charged ions in water, while the final state contains the fully discharged ions. We note that the difference between the initial and final states corresponds to the transfer of an electron from the anion to the cation. The charges on the ions in the intermediate states i are given by $(1 - \lambda)$ and $(-1 + \lambda)$. In the "slow growth" approximation[34] to thermodynamic integration which was used to obtain the free-energy simulation results listed in Table I(b), the charges on the ions are varied by a very small amount at each step in a single simulation instead of carrying out many separate simulations with different ionic charges between 1 and 0. For the discharge of the two ions, the changes in the charges on the ions were broken into $N = 16\,000$ steps so that the increment in charge per step is $\Delta q = 6.25 \times 10^{-5}$; the charges on the cation and anion at step i are therefore equal to $[+1 - (i)\Delta q]$ and $[-1 + (i)\Delta q]$, respectively.

In Table I(b) the free-energy change for discharging the ions calculated from the thermodynamic integration simulation is compared with the predictions of the dielectric formula [Eq. (7)] using the parameters from the fully charged reference system. The close agreement between the two calculations over such a large variation in Δq (and very large variation in the free energy) is remarkable. For example, there is less than a 2% difference between the dielectric formula and thermodynamic integration result for $\Delta q = 0.5$,

TABLE I. (a) Fully charged reference system parameters. The reference system parameters correspond to those obtained from a simulation with two ions with charges $+1$ and -1, separated by 10 Å in a box of 341 water molecules. (b) Predicted change in the polarization energy for discharging the ions.

(a)

Average electrostatic potential ($\bar{V}_i$) at the ions
[kcal/mol (charge)]

$+$ Ion	-118.65
$-$ Ion	147.27

Correlation functions for fluctuations in the electrostatic potential at the ions, σ_{ij}
[kcal/mol (charge)]^2

$\langle \Delta V_+ \Delta V_+ \rangle$	72.48
$\langle \Delta V_+ \Delta V_- \rangle$	-6.40
$\langle \Delta V_- \Delta V_- \rangle$	106.10

(b)

Δq	0.10	0.20	0.40	0.50	0.60	0.70	0.90	1.0
Thermodynamic integration[a]	24.63	46.72	82.19	95.90	106.58	114.74	123.68	125.00
Dielectric function [Eq. (7)]	24.74	46.94	81.24	93.65	102.92	109.00	111.77	108.31

[a] Thermodynamic integration simulation using the "slow growth" method, see the text for details.

which for two ions separated by 10 Å results in a free-energy change of almost 100 kcal/mol. These results show that the multivariate probability distribution function for the fluctuations in the electrostatic potential at the ionic sites $p(\Delta V_+, \Delta V_-)$ is indeed close to Gaussian over a very large range. In related studies, Kuharski et al.[3] and Carter and Hynes[4] have analyzed the Gaussian nature of the distribution function for the solvent fluctuations by calculating the distribution of fluctuations in the electrostatic potential difference between the two sites. They have shown that this function has a Gaussian form for fluctuations in the electrostatic potential difference corresponding to free energy changes of up to ~20 kcal/mol for two solvent separated ionic sites[3] and ~10 kcal/mol for a contact ion pair.[4]

Small deviations from linear response theory can also be observed in Table I(b). For example, the maximum in the free-energy surface predicted by the linear-response formula occurs at $|\Delta q_i| = 0.9$, which can be determined by taking the derivative of Eq. (7) with respect to Δq_i and setting the result to zero,

$$\Delta q^{max} = \beta^{-1}\sigma^{-1}\overline{V}. \qquad (12)$$

However, the anharmonic free-energy surface must have a maximum at $|\Delta q_i| = 1$, since the solvent remains polarized for smaller changes in the charge. The deviations from the parabolic surface constructed from the fully charged reference state parameters are only apparent at very large changes in the free energy.

Another way to assess the effects of nonlinearities is to compare the predictions of the Gaussian fluctuation approximation free-energy formula using a different reference system to evaluate the parameters which are used in Eq. (7). In Tables II(a) and II(b) we present results corresponding to the use of an uncharged reference state. The average electrostatic potentials and the fluctuations in the potentials at the solute sites were determined from a simulation of two uncharged spheres separated by 10 Å with the same Lennard-Jones parameters as used in the charged simulations. The solute sites are labeled " + " and " − ", although there is no actual charge at the centers of the spheres. Comparing the predicted changes in the solvent polarization, the results using the two different reference systems are very similar. The predicted change in the polarization energy for $\Delta q = 1$ is 106 kcal/mol using the Gaussian fluctuation formula with parameters from the uncharged reference while the corresponding free-energy change predicted using the charged state reference system is 108 kcal/mol. It should be noted that for $\Delta q < 1$, the predicted free-energy change using the charged reference state should be different from that calculated with the same Δq for the uncharged reference state because the processes correspond to different initial and final states. For example, when $\Delta q = 0.1$ in Table II(b), the solvation free-energy change corresponds to the process of charging up neutral spheres to 0.1; while when $\Delta q = 0.1$ in Table I(b), the solvation free-energy change corresponds to discharging two spheres with initial charge 1.0 and final charge 0.9. It is also of interest to examine the way in which the average electrostatic potential and the fluctuations in the potential at the solute sites vary with the reference system. The average electrostatic potential from the solvent at the neutral spheres is slightly negative (~11 kcal/mol) which suggests an ordering of the solvation shell in which the water hydrogens point away from the neutral spheres. If the Gaussian approximation were exact, the fluctuation matrix of second moments in the electrostatic potential would not vary with reference system. However, the fluctuations in the electrostatic potential at the solute sites are larger when a simulation of the charged reference system is used to evaluate these parameters [Table I(a)] as compared with the uncharged reference [Table II(a)]. This nonlinearity is most evident for the change in $\langle \Delta V_- \Delta V_- \rangle$. There is a compensating nonlinear change in the average electrostatic potential at the negative ion which diminishes the effects of nonlinearities on the sensitivity of the Gaussian fluctuation formula to the choice of reference state. In summary, the dielectric for-

TABLE II. (a) Fully uncharged reference system parameters. The reference system parameters correspond to those obtained from a simulation with two neutral spheres, separated by 10 Å in a box of 341 water molecules. (b) Predicted change in the polarization energy for charging the ions.

(a)							
Average electrostatic potential ($\overline{V}_i$) at the ions [kcal/mol (charge)]							
+ Ion			−11.11				
− Ion			−11.54				

Correlation functions for fluctuations in the electrostatic potential at the ions, σ_{ij} [kcal/mol (charge)]^2	
$\langle \Delta V_+ \Delta V_+ \rangle$	64.95
$\langle \Delta V_+ \Delta V_- \rangle$	3.65
$\langle \Delta V_- \Delta V_- \rangle$	69.20

(b)								
Δq	0.10	0.20	0.40	0.50	0.60	0.70	0.90	1.0
Thermodynamic integration[a]	1.32	2.82	18.42	29.10	42.81	50.68	100.40	125.00
Dielectric function [Eq. (7)]	1.06	4.24	16.97	26.52	38.18	52.00	85.92	106.07

[a] Thermodynamic integration simulation using the "slow growth" method, see the text for details.

mula, Eq. (7), works remarkably well for this model problem when either the charged or uncharged solute plus solvent states are chosen as the reference system.

We can compare the results in Tables I and II to the continuum solvent formula for the free-energy change due to charging up two ions in water. The Born formula for the polarization energy is

$$\Delta F_{\text{Born}} = (\Delta q)^2 \left(1 - \frac{1}{\epsilon}\right)\left(\frac{1}{\sigma_+} + \frac{1}{\sigma_-} - \frac{1}{r}\right). \quad (13)$$

The first two terms account for the polarization of the solvent by the ions at infinite separation, while the third term accounts for the change in the solvent polarization due to the finite separation of the ions. The discharged state is the reference system. Using the Lennard-Jones radii of the ions $\sigma/2 = 2.2$ Å, and the dielectric constant of the SPC water model[31(a)] $\epsilon = 70$, the Born formula predicts a free-energy difference between the fully charged and fully discharged ions of $\Delta F = 117$ kcal/mol. The continuum result is midway between the molecular dielectric prediction (107 kcal/mol) and the anharmonic free-energy difference (125 kcal/mol) calculated explicitly by a thermodynamic integration simulation. We note that the solvent polarization energy in the continuum model is very insensitive to variations in the macrocscopic dielectric constant since it enters in the formula as $(1 - 1/\epsilon)$. It is of interest to ask if it is possible to calculate the dielectric constant as a difference between the solvent polarization energy due to charging up two ions at r and the sum of the polarization energies of the isolated ions. For high dielectric liquids, the difference between the polarization energies must almost exactly cancel the direct Coulomb interaction between the ions at r. We find that the direct calculation of the dielectric constant by this method is unstable as the difference between the two free-energy simulations is very sensitive to the boundary conditions used to treat the long-range interactions.[31(d)] In any case, it is very clear from the present numerical example that for simulations of ions in water, the polarization energy of the water responds to a charge perturbation as a linear dielectric.

IV. CONCLUSIONS

We have used linear-response theory to derive a microscopic formula for the free-energy change of a system composed of one or more solutes plus solvent responding to a change in the charge distribution on the solutes. The formula expresses the change in the solvent polarization energy as a quadratic function of the changes in the partial charges at the atomic centers of the solute atoms. The average electrostatic potential at the sites of the solute charges and the second moment of the fluctuations at these sites enter as parameters in the formula. These parameters can be obtained by simulations of a reference system with fixed solute charges. The formula provides a microscopic definition of the dielectric-response function for the reference system which consists of the combined solute plus solvent. Thus, the formula implicitly includes the perturbing effect of the solutes on the solvent structure and dielectric response. In a simple numerical example, it was demonstrated that the microscopic

dielectric formula provides a remarkably accurate estimate of the free-energy change accompanying the charging of two ions in water calculated by thermodynamic integration free-energy simulations. We expect that the formula will have a number of useful applications. By simulation of a single reference system, it is possible to accurately estimate the effects of redistributing the charges on the solute atoms in different ways. For example, we have used the formula to calculate the adiabatic free-energy change accompanying the simulated excitation of a chromophore in solvent (indole in water).[35] The predicted solvent polarization changes agree to within a few percent with the results of explicit free-energy simulations of this process. As another application, we suggest that the use of the microscopic dielectric formula will simplify the task of analyzing the sensitivity of molecular models used in condensed phase simulations to the parameterization of the partial charges on the solute sites. The variation in the solvation energy with changes in the electrostatic model can be estimated using a molecular dielectric function constructed from the simulation of a single reference system. Work along these lines is in progress.

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