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Electronic Polarizability and the Effective Pair Potentials of Water

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Abstract: Employing the continuum dielectric model for electronic polarizability, we have developed a new consistent procedure for parametrization of the effective nonpolarizable potential of liquid water. The model explains the striking difference between the value of water dipole moment $\mu \approx 3D$ reported in recent ab initio and experimental studies with the value $\mu^{\text{eff}} \approx 2.3D$ typically used in the empirical potentials, such as TIP3P or SPC/E. It is shown that the consistency of the parametrization scheme can be achieved if the magnitude of the effective dipole of water is understood as a scaled value $\mu^{\text{eff}} = \mu/\sqrt{\varepsilon_{\text{el}}}$, where $\varepsilon_{\text{el}} = 1.78$ is the electronic (high-frequency) dielectric constant of water, and a new electronic polarization energy term, missing in the previous theories, is included. The new term is evaluated by using Kirkwood−Onsager theory. The new scheme is fully consistent with experimental data on enthalpy of vaporization, density, diffusion coefficient, and static dielectric constant. The new theoretical framework provides important insights into the nature of the effective parameters, which is crucial when the computational models of liquid water are used for simulations in different environments, such as proteins, or for interaction with solutes.

1. Introduction

Simple nonpolarizable models of water, such as SPC[1] (simple point charge), TIP3P[2] (transferable intermolecular potential with 3 points), TIP4P[2] (transferable intermolecular potential with 4 points), and their modifications, have been in use in computer simulations for over forty years. More recently, a number of more sophisticated models, including flexible and polarizable ones, have also been developed;[3] however, the majority of current simulations, in particular biological ones, still rely upon those simple empirical models.

An important conceptual step in the development of empirical potentials was made in 1987 by Berendsen and co-workers,[4] who recognized that, for a correct comparison between a model and experimental vaporization enthalpy, one of the experimental data points typically used to calibrate the empirical parameters, an additional energy term, a constant, should be added in the effective potential (or equivalently experimental enthalpy should be corrected) to

reflect the energy of repolarization of water upon the transfer from the liquid to gas phase. Indeed, the experimental enthalpy of vaporization involves two different states of the molecule: the liquid, and the gas, and the dipole moment of a gas molecule (1.855D[5]) is much different from that in the liquid state.

This new energy term, which was missing in the previous models, is known as self-polarization energy and is given by

$$E_{\text{pol}} = (\mu_l - \mu_g)^2/2\alpha \tag{1.1}$$

where μ_l and μ_g are liquid- and gas-phase dipole moments of water, respectively, and α is electronic polarizability of water. Most of the conventional nonpolarizable models of liquid water have the dipole moment around 2.3D: TIP3P (2.35), SPC (2.27), TIP4P (2.18); the difference between 2.3D in liquid and 1.85D in gas amount to approximately to 1.25 kcal/mol of self-polarization energy, or about ten percent of the total vaporization enthalpy (10.5 kcal/mol[6]). The self-

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polarization energy accounted for in a modified SPC/E model has been shown to produce significant improvements in the model.[4]

It should be noticed, however, that the dipole moment used in the above estimate is the effective dipole moment of the model, which can be different from the value of actual dipole of liquid water molecule.[7,8] In fact, it is the value of actual dipole of liquid water that should be used in the analysis of experimental vaporization enthalpy.

The exact value of the actual dipole moment of liquid water, surprisingly, is still a matter of debate. Recent estimates deduced from experiments (these are not however direct measurements of the dipole moment) suggest a value around 2.7–2.9D.[9,10] There are no direct measurements of the liquid dipole moment, unfortunately, and the estimates in ref 10 have significant uncertainty of ±0.6D. The ab initio calculations and first principles simulations do not agree on the actual value but mostly point to a much greater value than the effective 2.35D of TIP3P and SPC/E: 2.43D in ref 11, 2.65D in ref 12, 2.70D in ref 13, 2.95D in refs 14 and 15, and 3.09 in ref 16. We argued recently[17] that on the basis of a simple Kirkwood-Onsager model the actual dipole moment should be around 3.0D; moreover our MDEC model[17−19] predicts that the value of actual dipole of water is related to the value of effective dipole of the model as $\mu_l = \sqrt{\varepsilon_{el}} \cdot \mu^{eff}$ where $\varepsilon_{el} = 1.78$ is the electronic (high-frequency) dielectric constant of water; thus if $\mu^{eff} = 2.3D$, the value of actual dipole of liquid water should be about 3.0D; these estimates are in agreement with first principles simulations of liquid water.[14,16]

If indeed the actual dipole moment is much greater than 2.3D, then the self-polarization term is much greater than the previously estimated 1.25 kcal/mol. Assuming for the actual dipole of liquid water a value 3.0D, the self-polarization term amounts in fact to 6−7 kcal/mol, which is more than half of the vaporization enthalpy 10.5 kcal/mol, dramatically changing the vaporization energy data relevant for model building. Therefore the high value of the dipole moment of liquid water appears to be in striking contradiction with the existing parametrization schemes of the effective potentials. [Needless to say that such problems would not appear in the fully polarizable models and only specific for nonpolarizable effective models discussed in this paper.]

In this paper, we show that the disagreement between the existing models and the actual vaporization energy data is due to an important missing term in theory, which is related to electronic polarization of the medium. The missing term is the energy of solvation of water molecule in the electronic continuum representing polarization of bulk water, which needs to be accounted for in an accurate analysis of the vaporization process. This energy also amounts to about 6−7 kcal/mol, of opposite sign to the increase in the self-polarization term, when a water molecule is transferred from the liquid state (which involves polarization of the electronic continuum) to a gas state (no electronic polarization at all).

On the basis of this observation and assuming that neither the exact value of the dipole moment of liquid water nor its polarizability are known, we developed three closely related new self-consistent models that fit accurately experimental data for density, diffusion coefficient, radial distribution functions, as well as the static dielectric constant and vaporization energy. It is shown that the consistency of the parametrization scheme can be achieved if magnitude of the effective dipole of water is understood as a scaled value $\mu^{eff} = \mu_l/\sqrt{\varepsilon_{el}}$, and the new electronic polarization energy term is included. The new term is evaluated by using Kirkwood−Onsager theory.

The effective parameters (charges and Lennard-Jones parameters) of the models derived from the new principles are slightly different from those of the known models; more importantly, however, the new theory provides important insights into their actual nature, which is of significant interest for applications of the effective water models in simulations of biological environments, or for simulation of solute−solvent interactions. We show that self-consistency of the whole theory, and reconciliation of experimental evaporation data with other data (diffusion coefficient, radial distributions, density) is only possible if the value of the actual dipole of liquid water is around 3.0 (±0.1) D.

2. Theory

2.1. Electronic Screening. MDEC Model. There are two effects caused by the electronic polarizability of water molecules important for the following discussion: the enhancement of the dipole in the liquid state, and the screening of electrostatic interactions. As commonly described in the literature,[3] the dipole enhancement is reflected in the partial atomic charges q_i^{eff} of nonpolarizable models, so that the effective dipole in the liquid state is greater than that in the gas phase 1.855D: for example, TIP3P, SPC and TIP4P models have an effective dipole moments of 2.35D, 2.27D, and 2.18D, respectively; there is less clarity in the literature on the screening effect, however.

A simple way to account for the electronic screening effect is to consider all nuclear charges q_i as moving in polarizable electronic continuum with dielectric constant ε_{el}. In this case, all electrostatic interactions are scaled by a factor $1/\varepsilon_{el}$. The empirical parameter ε_{el} is known from experiment as the high-frequency dielectric permittivity ($\varepsilon_{el} = n^2$, where n is a refraction index of the medium). Such a model, which combines a nonpolarizable (fixed-charge) force field for nuclear dynamics (MD) and a phenomenological electronic continuum (EC) for the electronic effects, is referred to as MDEC.[19]

Since electrostatic interactions are quadratic in charges, the effects of electronic dielectric screening can be taken into account implicitly by using scaled partial charges, $q_i^{eff} = q_i/\sqrt{\varepsilon_{el}}$; in this case the Coulomb interactions automatically have the correct form $q_i^{eff} q_j^{eff}/r_{ij} = q_i q_j/\varepsilon_{el} r_{ij}$ without explicitly introducing the factor $1/\varepsilon_{el}$.

The scaling of charges has a direct consequence for the effective dipole moment of liquid water. As we argued earlier,[17−19] the effective dipole of liquid water should be also understood as a scaled value, $\mu^{eff} = \mu_l/\sqrt{\varepsilon_{el}}$. Thus, if the effective dipole value of a model is $\mu^{eff} \approx 2.3D$, as in TIP3P or SPC/E, the actual dipole is $\mu_l = \sqrt{\varepsilon_{el}} \cdot \mu^{eff}$; for water $n = 1.33336^6$ results in $\varepsilon_{el} = n^2 = 1.78$, $\mu_l \approx 3.0D$, which

is in agreement with recent first principles simulations of liquid water[14,16] and within the uncertainty of experimental data.[9,10] As we already pointed out in the Introduction, the high value of the actual dipole moment of liquid water gives rise to a significant problem for the existing parametrization schemes in interpretation of the vaporization experimental data, which is considered next.

2.2. Vaporization Energy and Self-Polarization Term. One of the main benchmark tests characterizing the quality of the effective potential of water $U^{eff}(r)$ is a comparison of the average energy of molecular configurations $\langle U^{eff} \rangle_{bulk}$ with the heat of vaporization given by the relation:[3]

$$\Delta H_{vap} = -\langle U^{eff}(r) \rangle_{bulk} + E^{intra} + RT \qquad (2.1)$$

Here, the total potential energy difference between phases ($\langle U \rangle_{gas} - \langle U \rangle_{bulk}$) was partitioned into intermolecular ($\langle U^{inter} \rangle_{gas} - \langle U^{inter} \rangle_{bulk}$) $= -\langle U^{eff}(r) \rangle_{bulk}$ and intramolecular ($\langle U^{intra} \rangle_{gas} - \langle U^{intra} \rangle_{bulk}$) $= E^{intra}$ components; the first term is directly described by the effective nonpolarizable potential, while the second term E^{intra} is not explicitly present in the nonpolarizable model. As pointed out by Berendsen and co-workers,[4] for a correct comparison with the experiment[6] ($\Delta U_{vap} \equiv \Delta H_{vap} - RT = 9.92$ kcal/mol) both terms, the simulated energy $\langle U^{eff}(r) \rangle_{bulk}$ and E^{intra}, should be taken into account.

The physical meaning of the correction E^{intra} can be understood by partitioning the vaporization process onto two steps illustrated in Figure 1a: fist, a polarized water molecule (i.e., polarized as in liquid state) is moved from the bulk to gas phase (keeping its dipole frozen), then the molecule is relaxed to its equilibrium configuration in the gas phase. The work required for the first step is given by the effective potential energy $-\langle U^{eff}(r) \rangle_{bulk}$, while the energy of the second step is not explicitly present in the nonpolarizable models and therefore should be added separately. Berendsen at el.[4] argued that the main contribution to E^{intra} is because of the difference of the dipole moment of a water molecule in gas and in liquid state and the repolarization self-energy correction, $E^{intra} = -E_{pol}$, where E_{pol} is given by eq 1.1.

In the conventional picture, following Berendsen at el., the molecular electric moment μ in the liquid state is identified with the effective dipole μ^{eff} of the model; for example for SPC/E $\mu^{eff} = 2.35$D, and the correction E_{pol} is only 1.25 kcal/mol. However, if one assumes that the actual dipole of liquid water is not 2.35D, but rather closer to 3.0D, as recent data indicate, the correction is much greater. For example, using MDEC model, the SPC/E actual dipole moment in the bulk is $\mu_l = \sqrt{\varepsilon_{el}} \cdot \mu^{eff} = 3.14$D, which produces the correction $E_{pol} \approx 8$ kcal/mol, that is, more than half of the total vaporization energy ΔU_{vap}.

It is obvious that if the parameter calibration is done in the standard way, that is, as in ref 4 or 8, the resulting model will be completely at odds with the experimental data for density, structural properties, diffusion coefficients etc. To reconcile the high value of the actual dipole moment of liquid water, and the vaporization data, one needs to consider an additional polarization term.

2.3. Missing Term. According to MDEC model, the actual charges of the effective model should be understood
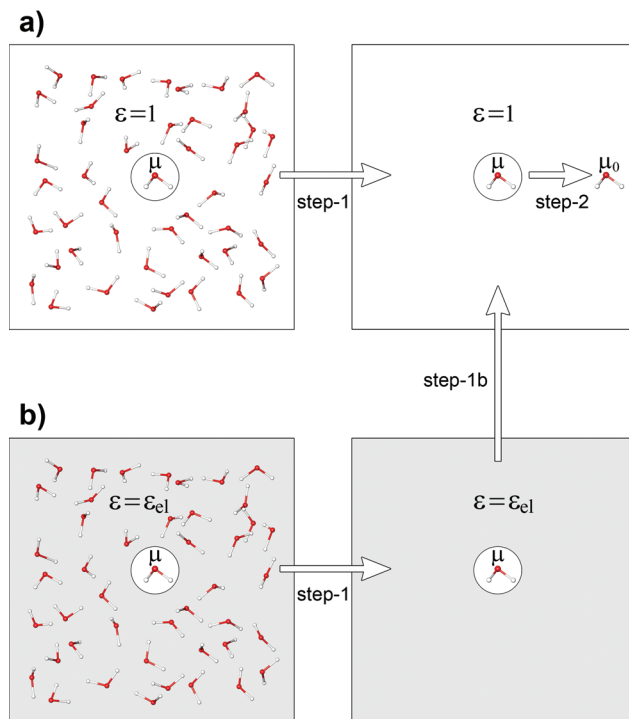

Figure 1. Partitioning the vaporization process onto steps. (a) Standard nonpolarizable model of the medium: on the step 1, the polarized water molecule is moved from the bulk to infinity (keeping its dipole μ frozen), and on the step 2, the molecule relaxes and equilibrates its polarization to the gas-phase value in the absence of polar environment μ_0. (b) MDEC model, charges are moving in the electronic continuum: on the step 1, the polarized water molecule is moved from the bulk to infinity (keeping its dipole μ frozen and remaining in the electronic continuum); on the step 1b, the molecule is moved from the electronic continuum to vacuum (still keeping its dipole μ frozen), and on the step 2, the molecule relaxes and equilibrates its polarization to the gas-phase value in the absence of polar environment μ_0.

as immersed in the electronic dielectric continuum; the vaporization process then is represented by the steps shown in Figure 1b: (1) a polarized water molecule is moved from the bulk to infinity (i.e., is separated from other water molecules), keeping its dipole frozen and remaining in the electronic continuum; (1b) the molecule is moved from the electronic continuum to vacuum (keeping its dipole frozen); and finally (2) the molecule is relaxed to its equilibrium gas-phase state, in the absence of polar environment. As in SPC/E model,[4] the energy associated with step (1) is calculated by the nonpolarizable effective potential as $-\langle U^{eff}(r) \rangle_{bulk}$, and the energy of step (2) is given by the negative self-polarization energy, eq 1.1, while the energy of step 1b is a new energy term, $-E_{sol}$. This new term is the solvation energy of a water molecule, polarized as it is in the liquid state, in the electronic continuum. Therefore, a new expression for E^{intra} in the relation of the vaporization enthalpy and model parameters, eq 2.1, is

$$E^{intra} = -E_{pol} - E_{sol} \qquad (2.2)$$

2.4. Kirkwood−Onsager Model for Electronic Solvation Energy. To estimate the missing term, E_{sol}, that is, interaction of a single molecule with the polarizable environ-

ment, we employ the Kirkwood−Onsager model,[20,21] in which the medium is represented by a continuum dielectric of ε and the solvent molecule is modeled by a point polarizable dipole, placed in a spherical cavity of radius R; the permanent dipole is μ_0 and the polarizability is α.

The reaction field (rf) due to polarization of the environment induces additional polarization of the dipole. Suppose the resulting dipole is μ, the polarization energy of the medium then is[20]

$$\Delta F_{\text{rf}}(\mu) = -\frac{2(\varepsilon - 1)}{(2\varepsilon + 1)} \frac{\mu^2}{2R^3} \qquad (2.3)$$

Combining this term with the self-polarization energy we obtain the total electrostatic (solvation) free energy ΔF_{elec} of the dipole in the polarizable environment

$$\Delta F_{\text{elec}}(\mu) = -\frac{2(\varepsilon - 1)}{(2\varepsilon + 1)} \frac{\mu^2}{2R^3} + \frac{(\mu - \mu_0)^2}{2\alpha} \qquad (2.4)$$

The correction term to vaporization energy (contributions from steps 1b and 2 of the Figure 1b) E^{intra} is given by eq 2.4 with $\varepsilon = \varepsilon_{\text{el}}$, μ_0 being the gas dipole value, and μ being the actual dipole moment of liquid water molecule. It is seen that the two terms in the above expression have different signs.

One can also use the above expression for an estimate of the liquid molecule dipole itself. In this case $\varepsilon = \varepsilon_0$, where ε_0 is the static dielectric constant of the solvent, and μ is unknown. At equilibrium, the dipole of the solvent molecule in the bulk satisfies the condition $(\delta\Delta F_{\text{elec}}(\mu))/(\delta\mu) = 0$. This condition results in

$$\mu_l = \frac{\mu_0}{1 - \dfrac{2(\varepsilon_0 - 1)}{(2\varepsilon_0 + 1)}\dfrac{\alpha}{R^3}} \qquad (2.5)$$

If one assumes the above value of the equilibrium dipole of liquid water, the total solvation free energy is

$$\Delta F_{\text{elec}}(\mu_l) = -\frac{1}{\dfrac{(2\varepsilon_0 + 1)}{2(\varepsilon_0 - 1)}\dfrac{R^3}{\alpha} - 1} \frac{\mu_0{}^2}{2\alpha} \qquad (2.6)$$

Equations 2.3−2.6 represent a complete set of relations needed to describe polarization effects in a transition of a molecule from gas-phase to dielectric medium of ε. Equation 2.5, derived by Kirkwood[20] in 1939, expresses the magnitude of the molecular dipole enhancement in a polarizable environment, and eq 2.3 with $\varepsilon = \varepsilon_{\text{el}} = 1.78$ expresses the energy correction E_{sol} of step 1b (see Figure 1b), while eq 2.4 gives the total correction E^{intra} to the vaporization energy.

The theory would be complete if one knew the value of the radius R of the molecular cavity. This is obviously a phenomenological parameter, which needs to be fixed in comparison with experimental data, or derived from a suitable theoretical model. In addition to R, we recall that the polarizability α can in principle be different from the gas polarizability of water. [Recently, molecular polarizability of liquid water has been examined in ab initio studies; the

calculations[12,22] show a reduction of polarizability in liquid state in the range of 10−15%; however, in ref 13 a slight increase was observed.] In this case α can also be considered as an unknown phenomenological parameter to be fixed together with R.

In the next section, we describe three related computational models that are based on the above relations, and in which the phenomenological parameters R and α are self-consistently found together with other parameters of the effective potential of water (charges and Lennard-Jones parameters) using the complete experimental data set: density, radial distributions, diffusion coefficient, static dielectric constant, and vaporization energy.

We close this section with an estimate of the polarization term using a simple model for R, and assuming a gas value for polarizability α.

One reasonable estimate of the radius of molecular sphere R is to assume that $2R$ is the average distance between the liquid water molecules, $a = 2R$. The distance between the molecules is related to their number density, N_α, as $N_\alpha = a^{-3} = 1/8R^3$. Employing now the Clausius-Massotti relation between N_α and ε_{el}:

$$\frac{4\pi}{3}\alpha N_\alpha = \frac{\varepsilon_{\text{el}} - 1}{\varepsilon_{\text{el}} + 2} \qquad (2.7)$$

the radius R is expressed as

$$R^3 = \frac{\pi}{6}\frac{(\varepsilon_{\text{el}} + 2)}{(\varepsilon_{\text{el}} - 1)}\alpha \qquad (2.8)$$

and the solvation free energy of the dipole μ in electronic continuum, eq 2.3, that is, the new energy correction term in eq 2.2, becomes:

$$E_{\text{sol}}(\mu) = -\frac{6}{\pi}\frac{(\varepsilon_{\text{el}} - 1)^2}{(2\varepsilon_{\text{el}} + 1)(\varepsilon_{\text{el}} + 2)}\frac{\mu^2}{\alpha} \qquad (2.9)$$

If we take now the dipole value corresponding to SPC/E model $\mu = \sqrt{\varepsilon_{\text{el}}}\cdot\mu^{\text{eff}} = 3.14$ D, and $\alpha = 1.47$ Å^3, the electronic solvation energy E_{sol} is about −6.5 kcal/mol, which almost completely cancels the self-polarization term E_{pol} of 8.0 kcal/mol in eq 2.2, and the total correction E^{intra} in eq 2.2 is only −1.5 kcal/mol. Thus, the electronic term E_{sol}, which was missing in the standard nonpolarizable models, resolves the problem of extremely large correction to vaporization energy.

With the radius R given by eq 2.8, the equilibrium dipole moment in the liquid phase is expressed by eq 2.5 as

$$\mu_l = \frac{\mu_0}{1 - \dfrac{6}{\pi}\dfrac{(\varepsilon_{\text{el}} - 1)}{(\varepsilon_{\text{el}} + 2)}\dfrac{2(\varepsilon_0 - 1)}{(2\varepsilon_0 + 1)}} \qquad (2.10)$$

which gives the value 3.0 D for the bulk water ($\varepsilon_{\text{el}} = 1.78$, $\varepsilon_0 = 78$, $\mu_0 = 1.85$D). This value is in good agreement with the recent experimental estimations; however, it is slightly different from the empirical SPC/E MDEC value, $2.35D\sqrt{1.78} = 3.14$D. This slight inconsistency will be corrected in our computational model I, in the next section.

Potentials of Water

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The approximations involved in the above model are evident: for example, the charge distribution in the actual water molecule is not the same as that of a point dipole located at the center of the van-der-Waals sphere; also, the polarization of the electronic environment might not be perfectly described by the continuum model. Moreover, the parameter R, and to some extent α, are not well-defined for the bulk water. The cavity radius R is in fact completely phenomenological. Yet, despite a number of approximations involved in the Kirkwood−Onsager model, this theory captures qualitatively all the effects of molecular polarization, while quantitative accuracy can be achieved by an appropriate adjustment of the model parameters by fitting experimental data.

In the following section, a computational procedure based on relations 2.3−2.10 is described to develop a new microscopic effective potential of liquid water. Three possible strategies to achieve complete self-consistency of a model are considered.

3. Computational Models for the Effective Potentials of Water

Following the above theory, we will now describe the corresponding new parametrization of pairwise effective potential for water, which accounts for the electronic solvation and polarization effects. Three different schemes: model I, II, and III specified below, are used for the evaluation of the new E^{intra} term; the models are summarized by eqs 3.2, 3.3, and 3.5 below. The conventional 3-site form for the water intermolecular potential is considered

$$u_{a,b} = \sum_{i,j} \frac{q_i^{\text{eff}} q_j^{\text{eff}}}{r_{ij}} - 4\varepsilon\left[\left(\frac{\sigma}{r_{OO}}\right)^6 - \left(\frac{\sigma}{r_{OO}}\right)^{12}\right] \quad (3.1)$$

here i and j indices run over all charge sites of the molecule a and b, respectively, while, the last term stands for the Lennard-Jones interaction between the two oxygen (O) atoms separated by the distance r_{OO}. The geometry of rigid SPC water model is adopted, namely, $r(OH) = 1.0$ Å and an H−O−H angle of 109.47°.

The adjustable parameters are: partial atomic charges (which for the fixed SPC geometry of water are uniquely defined by a value of the effective dipole moment μ^{eff}, which is in fact varied), and the Lennard-Jones (LJ) parameters ε and σ; the experimental data sets are: density, self-diffusion coefficient, and vaporization energy ($T = 298$ K and $P = 1$ atm).

Model I. In this model, we assume the relation ($N_\alpha = a^{-3} = 1/8R^3$) resulting in eqs 2.7−2.9. The corresponding expression for the correction term E^{intra} in this model is

$$E^{\text{intra}}(\mu) = -\frac{(\mu - \mu_0)^2}{2\alpha} + \frac{6}{\pi}\frac{(\varepsilon_{\text{el}} - 1)^2}{(2\varepsilon_{\text{el}} + 1)(\varepsilon_{\text{el}} + 2)}\frac{\mu^2}{\alpha}$$
$$(3.2)$$

Using the above correction term, LJ parameters of the effective potential, and the value of actual dipole of liquid water μ, related to the effective model dipole as $\mu = \sqrt{\varepsilon_{\text{el}}} \cdot \mu^{\text{eff}}$, are adjusted to reproduce in MD simulations the

liquid water density, self-diffusion coefficient, and vaporization energy. The total number of independently variable parameters in this scheme is 3 (μ^{eff}, ε, and σ), while number of experimental properties to be reproduced is also 3 (density, self-diffusion coefficient and vaporization energy), which provides a nonredundant system of equations to uniquely define these parameters.

Model II. In the above scheme, the dipole moment of liquid water is a free adjustable parameter, and only the electronic solvation is calculated by Kirkwood-Onsager model. To follow the logic of Kirkwood−Onsager model more deeply, we can consider that the actual dipole of liquid water is defined by eq 2.5, which requires the knowledge of R, which itself is unknown. In this scheme, we use the relation 2.5 for *definition* of R, still considering the value of water dipole μ as a free parameter. Then the solvation energy E_{sol} is expressed by eq 2.3, with parameter R taken from eq 2.5 (instead of eq 2.8 for model I). The resulting expressions for R and E^{intra} of model II are

$$R^3 = \frac{2(\varepsilon_0 - 1)}{(2\varepsilon_0 + 1)}\frac{\mu}{(\mu - \mu_0)}\alpha$$

$$E^{\text{intra}}(\mu) = -\frac{(\mu - \mu_0)^2}{2\alpha} + \frac{(\varepsilon_{\text{el}} - 1)}{(2\varepsilon_{\text{el}} + 1)}\frac{(2\varepsilon_0 + 1)}{(\varepsilon_0 - 1)}\left(1 - \frac{\mu_0}{\mu}\right)\frac{\mu^2}{2\alpha}$$
$$(3.3)$$

where value of the polarizability α is still identified with its gas phase value ($\alpha = 1.47^{23}$ Å³). The self-consistent values of R and the correction E^{intra} are obtained by adjusting $\mu = \sqrt{\varepsilon_{\text{el}}} \cdot \mu^{\text{eff}}$ and LJ parameters of the effective potential to reproduce the liquid water density, self-diffusion coefficient, and vaporization energy, as in the first model.

In this scheme, there are same 3 variable parameters (μ^{eff}, ε, and σ); the number of experimental data to be reproduced is also 3, which provides a nonredundant system of equations to uniquely define the unknown parameters.

Model III. The use of the Kirkwood−Onsager model can be extended even further to allow for a possibility that the molecular polarizability α of bulk water is not equal to its gas-phase value ($\alpha = 1.47$ Å³), as is assumed in the previous two models. Here the polarizability α is treated as an adjustable parameter. This is achieved as follows.

Here, we still keep eq 3.3 for E^{intra}, but consider α in that expression as unknown. We then use eq 2.6 for total electrostatic solvation energy and assume it to be equal the corresponding energy of the microscopic effective potential: $\Delta F_{\text{elec}}(\mu_l) = \langle U^{\text{eff}}_{\text{elec}}\rangle_{\text{bulk}} - E^{\text{intra}}$, where $U^{\text{eff}}_{\text{elec}}$ is the electrostatic part of the effective potential: $U^{\text{eff}} = U^{\text{eff}}_{\text{elec}} + U^{\text{eff}}_{\text{vdW}}$. In this case, the microscopic vaporization energy $\Delta U_{\text{vap}} \equiv \Delta H_{\text{vap}} - RT = 9.92$ kcal/mol is expressed (employing eqs 2.1 and 2.6 as

$$\Delta U_{\text{vap}} = -\langle U^{\text{eff}}_{\text{vdW}}(r)\rangle_{\text{bulk}} + \frac{1}{\frac{(2\varepsilon_0 + 1)}{2(\varepsilon_0 - 1)}\frac{R^3}{\alpha} - 1}\frac{\mu_0^2}{2\alpha} \quad (3.4)$$

This relation is then used for a consistent definition of α (assuming R defined by eq 2.5). The self-consistent set of equations for α, R, and E^{intra} in this model are

$$\alpha = \frac{(\mu - \mu_0)\mu_0}{2} \frac{1}{(\Delta U_{vap} + \langle U_{vdW}^{eff} \rangle)}$$

$$R^3 = \frac{2(\varepsilon_0 - 1)\mu_0 \mu}{(2\varepsilon_0 + 1)} \frac{1}{2} \frac{1}{(\Delta U_{vap} + \langle U_{vdW}^{eff} \rangle)}$$

$$E^{intra}(\mu) = -(\Delta U_{vap} + \langle U_{vdW}^{eff} \rangle)\frac{\mu}{\mu_0}\left(1 - \frac{\mu_0}{\mu} - \frac{(\varepsilon_{el} - 1)}{(2\varepsilon_{el} + 1)}\frac{(2\varepsilon_0 + 1)}{(\varepsilon_0 - 1)}\right)$$

$$(3.5)$$

The consistent values of the parameters α, R, and correction E^{intra} are obtained in this parametrization procedure adjusting $\mu = \sqrt{\varepsilon_{el}} \cdot \mu^{eff}$ and LJ parameters of the effective potential to reproduce the liquid water density, self-diffusion coefficient, and vaporization energy, as in the previous two models.

The number of independently variable parameters in this scheme is still 3 (μ^{eff}, ε, and σ) the same as for models I and II because the value of α depends on these 3 parameters as given by eq 3.5, where the value of $\langle U_{vdW}^{eff} \rangle_{bulk}$ extracted from MD is also function of the effective potential parameters. The number of experimental properties to be reproduced is also 3, this provides a nonredundant system of equations to uniquely define all 3 adjustable parameters of the effective potential.

4. Results

The parameters of the effective potentials obtained by using models I, II, III are summarized in Table 1; for reference, the parameters of TIP4P[2] and SPC/E[4] models are also shown. The optimized parameters of the models, cavity radius R and polarizability α, obtained in the fitting procedures, are given in the Table 2. The quality of fitting of the experimental

data for liquid state properties of water by different effective potentials is shown in Table 2. The comparison of radial distribution functions for different models with experiment is shown in Figure 2. Details of the simulations are given in the Appendix.

It is seen that for all models the electronic solvation term E_{sol} essentially cancels the significant (7−8 kcal/mol) self-polarization term E_{pol}, so that the total energy correction E^{intra} becomes approximately 1 kcal/mol. It is remarkable that in the new scheme, the overall vaporization energy correction E^{intra} is essentially the same as in the original SPC/E model because of a cancellation of the corrected self-polarization term, E_{pol}, and the new electronic solvation energy term E_{sol}. Indeed, for example, eq 3.5 of model III yields a correction 1.21 kcal/mol for SPC/E potential, while in the original SPC/E model[4] the correction is 1.25 kcal/mol. The almost complete cancellation of the two terms perhaps is not fortuitous, since both the electronic solvation term E_{sol} and the polarization term E_{pol} are of the same origin, namely due to electronic polarizability of water molecules.

As a result of the effective cancellations of the two correction terms E_{pol} and E_{sol} the obtained parameters of the effective potentials are not much different from those of the SPC/E or TIP4P, which means that these models are consistent with the concepts of electronic continuum model MDEC,[17] on which the present theory is entirely based. In other words, SPC/E and similar effective potentials, which were developed purely empirically and have no reference to electronic polarizability, in fact are

Table 1. Parameters for Water Model Potentials

parameter	experiment[a]	TIP4P	SPC/E	model I	model II	model III
r(OH), Å	0.9572[24]	0.9572	1.0000	1.0000	1.0000	1.0000
$\angle$HOH, deg	104.52[24]	104.52	109.47	109.47	109.47	109.47
r(OM), Å		0.15				
q(O), e		0	−0.8476	−0.7894	−0.8384	−0.8456
q(H), e		0.52	0.4238	0.3947	0.4192	0.4228
q(M), e		−1.04				
μ^{eff}, D	1.855[5]	2.177	2.351	2.189	2.325	2.345
ε, kcal/mol		0.155	0.155	0.0818	0.146	0.155
σ, Å		3.1536	3.1656	3.2227	3.1689	3.1659

[a] The experimental data[5,24] correspond to the gas phase.

Table 2. Liquid State Properties of Different Water Models at 1 atm and 298.15 K

property	experiment	TIP4P[e]	SPC/E[e]	model I[a]	model II[b]	model III[c]
ρ, g/cm^3	0.997[6]	0.995	1.000	0.998	0.999	0.999
D_{self}, 10^{-5} cm^2/s	2.3[25]	3.2	2.4	2.6	2.4	2.4
U_{vap}, kcal/mol	9.92[d]	9.70	9.99	9.94	9.95	9.93
$\langle U^{eff} \rangle$, kcal/mol		−9.92	−11.20	−9.87	−10.96	−11.11
E_{pol}, kcal/mol		6.60	8.32	5.56	7.62	8.25
E_{sol}, kcal/mol		−6.38[c]	−7.11[c]	−5.62	−6.61	−7.07
$\langle U_{vdW}^{eff} \rangle$, kcal/mol		1.77	2.13	2.56	2.15	2.10
μ, D	2.9[10]	2.904	3.137	2.920	3.102	3.129
R, Å		1.482[c]	1.505[c]	1.551	1.531	1.505
α, Å^3	1.47[23]	1.20[c]	1.42[c]	1.47[23]	1.47[23]	1.42
ε (dielectric constant)	78.4	51	71	60	71	71

[a] The values of R and E_{sol} are calculated according to eqs 2.8 and 2.9, respectively. [b] The values of R and E_{sol} are calculated according to eq 3.3. [c] The values of R, α, and E_{sol} are calculated according to eq 3.5. [d] The value ΔH_{vap} from ref 6 corrected by RT term. [e] TIP4P and SPC/E liquid state properties were recalculated according to the modern simulation protocol, for example, using PME treatment of electrostatic interactions and long-range dispersion correction for pressure and energy (see Appendix). Accordingly, some data shown for TIP4P and SPC/E models are slightly different from those reported in the original papers.[2,4]
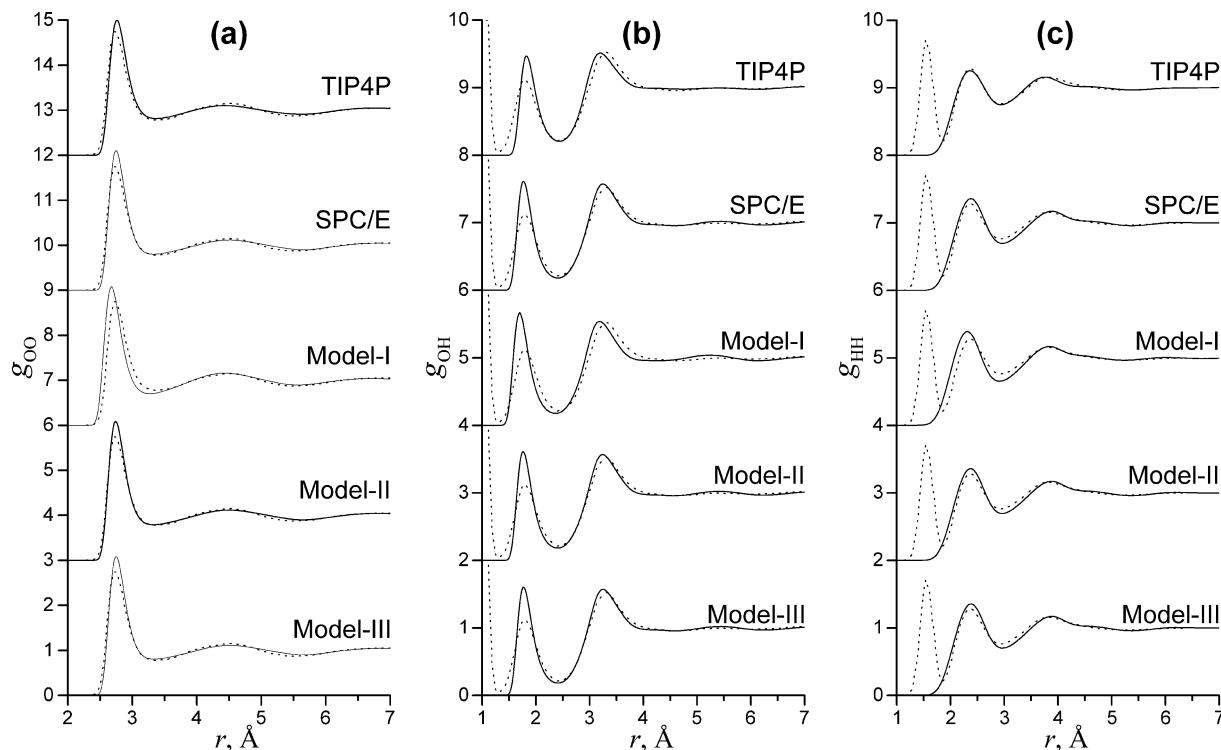
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Figure 2. Radial distribution functions of water: (a) oxygen−oxygen; (b) oxygen−hydrogen and (c) hydrogen−hydrogen. The simulated curves (solid lines, this work) are compared with the re-evaluated[26] Soper neutron diffraction data[27] (dotted lines).

MDEC-type models, in the sense that they use the effective, scaled charges.

This equivalence to MDEC model sheds new light on the physical meaning of the effective charges of standard nonpolarizable models such as SPC/E, providing their interpretation as *scaled* actual charges. It also helps to reconcile those models with the data on the larger than previously thought dipole moment of liquid water. Namely, the apparent inconsistency of the value of water dipole ∼2.3D of TIP3P, SPC or SPC/E, and the value ∼3D observed in the recent ab initio simulations[14,16] and experimental study,[10] is eliminated once the dipole, that is, charges, of effective potential are considered as the real charges scaled by the factor of $1/\sqrt{\varepsilon_{el}}$ (0.75 for $\varepsilon_{el} = 1.78$).

5. Discussion

The majority of current simulations, in particular biological ones, still rely upon simple nonpolarizable models of water, such as TIP3P, SPC/E, TIP4P and their modifications. Since these models describe the properties of pure liquid water reasonably well, it is often tacitly assumed that they will work equally well for solutions or in different environments, such as proteins, channels, or membranes. In fact, the transferability of such models often is an open question, and their use in conditions different from those in a pure liquid state, for which the empirical parameters of the models were optimized, requires great care. In general, a clear understanding of the physical nature of the empirical parameters involved is a key issue. This paper provides important insights into the nature of the effective parameters of liquid water.

The much discussed, but still unsettled issue is that of water electronic polarizability and its role in the effective

potentials of water. The empirical models are typically developed so as to match the experimental data for density, radial distribution functions, diffusion coefficient, static dielectric constant, and the enthalpy of vaporization. It should be noticed that the first three types of data require only a correct description of the nuclear dynamics of water in simulations, thus an empirical choice of the appropriate effective internuclear potentials of increasing complexity (i.e., using more adjustable parameters) can, in principle, produce a model ideally matching the experimental data. The last two data types are more subtle, however, since the experimental observables involve the behavior of the electronic degrees of freedom, i.e. polarization, which is not explicitly present in the model.

In case of the dielectric constant, the electronic polarizability is directly involved. Typically it is expected that a good nonpolarizable model should reproduce the total dielectric response of the bulk water, despite the fact that only nuclear motions are involved in the model. We have recently argued[19] that in fact a consistent model can (and should) reproduce only the nuclear part of dielectric response of the real system, $\varepsilon_{MD} = \varepsilon_0/\varepsilon_{el}$, where ε_{MD} is the dielectric constant of the effective model, $\varepsilon_0 = 78.4$ is the actual static dielectric constant of liquid water, and ε_{el} is the electronic part of the dielectric constant. In that case the effective charges of the model should be understood as real charges "scaled" by the factor $1/\sqrt{\varepsilon_{el}}$. The results of this paper fully support this picture.

A related issue concerns the vaporization data matching by an empirical model. Namely, the actual experimental enthalpy of vaporization involves two different states of the molecule: the liquid, and the gas. The dipole moment of a

gas molecule is much different from that in the liquid state, because in the liquid state water is additionally polarized by the reaction field of the environment of other water molecules. The problem is that the effective model deals only with the liquid state molecule, thus the direct comparison with experiment is not possible. Moreover, the exact value of the dipole moment of liquid water molecule is still unknown.

In this and the previous papers of this series, we have shown that on the basis of a simple Kirkwood−Onsager model, the actual dipole moment should be around 3.0D; MDEC model predicts that the value of actual dipole of water is related to the value of effective dipole of the model as $\mu_l = \mu^{\text{eff}}\sqrt{\varepsilon_{\text{el}}}$; thus if $\mu^{\text{eff}} = 2.3\text{D}$, the actual dipole of liquid water should be about 3.0D; these estimates are in agreement with first principles simulations of liquid water.[14,16]

The self-polarization energy correction term of Berendsen and co-workers accounts for the energy of repolarization of water upon transfer from liquid- to gas-phase. If one identifies the effective dipole moment of the model, which is about 2.3 D or less, with the value of actual dipole of liquid model the correction is only about 1.25 kcal/mol, or about 10% of the total vaporization enthalpy. However, the use of the actual dipole moment results in much higher values (6−8 kcal/mol) and gives rise to an apparent problem for theory. We have shown that the problem can be resolved by including the effects of electronic polarization, which are only implicitly present in the effective models. The new correction term introduced in this paper, E_{sol}, is the electronic solvation energy which, in addition to the Berendsen term,[4] E_{pol}, is also an inherent part of the vaporization energy. The new term is the energy of repolarization of the electronic continuum of liquid water upon transfer of a molecule from the liquid to the gas phase.

MDEC model is based on a simple idea of describing the effects of electronic polarization by considering a system of point charges immersed in polarizable electronic continuum. The combination of the MDEC model and Kirkwood-Onsager theory allowed us to develop a self-consistent model that naturally incorporates the effects of electronic polarization into the effective potential of liquid water. The effective parameters of the models derived from the new principles, turns out to be not much different from those of known models; more importantly, however, is that the theory sheds new light onto their actual nature, which is of significant interest for applications of the effective water models in simulations of biological environments, or for simulation of solute−solvent interactions. We showed that self-consistency of the whole theory, and reconciliation of experimental evaporation data with other data (diffusion coefficient, radial distributions, density) is only possible if the value of the actual dipole of liquid water is around 3.0 (±0.1) D.

6. Conclusions

Concluding, the paper can be summarized as follows:

(1) A new set of parameters for the effective potential of liquid water consistent with the idea of dynamics in polarizable electronic continuum has been developed; the theory

illuminates the nature of the effective charges and the dipole moment of standard nonpolarizable models as scaled values.

(2) The average dipole moment of water molecule in the liquid μ_l is about 3.0(±0.1) D. This high value is fully consistent with the value of effective dipole $\mu^{\text{eff}} = 2.35\text{D}$ of SPC/E and TIP3P models, or smaller values of other models, for example, TIP4P. The reason for the discrepancy is that the effective dipole moment is a scaled value: $\mu^{\text{eff}} = \mu_l/\sqrt{\varepsilon_{\text{el}}}$.

(3) The apparent contradiction of the high dipole moment of a liquid water molecule and the vaporization data is resolved by including the new electronic solvation energy term, E_{sol}. The effects of electronic polarization and screening are present in the effective empirical models in the form of scaled charges.

(4) A combination of MDEC model and Kirkwood−Onsager theory can satisfactory account for the effects of electronic polarization, including the difference between the gas phase dipole of water (1.85D) and the liquid state dipole, around 3.0D.

(5) The effective charges of SPC/E or TIP3P models are scaled values of the actual charges by a factor of $1/\sqrt{\varepsilon_{\text{el}}}$. The scaled nature of these charges should be taken into account in developing the effective potentials of interactions with solutes, or using these models in different (e.g., biological) environments. For example, the charges of ionized groups (±1) in the aqueous solutions, or in a protein, should be also scaled by the same factor $1/\sqrt{\varepsilon_{\text{el}}}$.

Appendix

Computational Details. The properties of liquid water were obtained in molecular dynamics simulations by Gromacs[28] package. The cubic MD box was formed by 512 water molecules. The electrostatic interactions were treated by the PME technique with a real space cutoff of 12 Å and sixth order spline for mesh interpolation. van der Waals interactions were switched at 10 Å to vanish at 12 Å. The long-range dispersion correction was accounted for pressure and energy. Nonbonded pair list was updated each 5 fs.

The new Berendsen thermostat with a stochastic term and coupling constant 0.5 ps and Berendsen barostat with coupling constant 0.4 ps were applied to keep the temperature at 298 K and pressure 1 atm. For each parameter set, the system was equilibrated first during a 1 ns run, followed by 10 ns data collection run with the MD time step 1 fs. The trajectory was saved each 0.1 ps resulting in total to 100000 configurations.

The self-diffusion coefficient was calculated from mass weighted mean square displacements of atoms from their initial positions using the Einstein relation as implemented in the g_msd program.[28] The dielectric constant was obtained from fluctuations of the total dipole moment of the MD box as implemented in g_dipoles program.[28] The vaporization energy was calculated according to the theory described in the manuscript.

The calculated liquid water properties are summarized in the Table 2.

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