Dynamical Fluctuating Charge Force Fields: The Aqueous Solvation of Amides

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Abstract: The fluctuating charge (FQ) force field, a polarizable potential model in which point charges on atomic sites fluctuate in response to the environment, is applied to the aqueous solvation of acetamide and *trans-* and *cis-N*-methylacetamide (NMA). Two parameters are assigned to each kind of atom, corresponding to an electronegativity and a hardness. The FQ model accurately reproduces both the gas-phase and aqueous-phase charge distributions of these molecules and is therefore effective in treating the influence of functional group substitutions, conformation changes, and solvent on the charge distribution. The FQ model does this in a way that is computationally efficient by propagating the charges in time using an extended Lagrangian method. Solvation free energy calculations are done using both an explicit (FQ) solvent and a dielectric continuum solvent. Both solvent models predict a negligible free energy difference between *trans-* and *cis*-NMA, in agreement with experimental estimates. The explicit solvent calculations find that the free energy difference between NMA and acetamide is 0.5 ± 0.8 kcal/mol, in good agreement, but of opposite sign, with the measured value of -0.3 ± 0.4 kcal/mol. The FQ/dielectric continuum calculations find that this free energy difference is sensitive to the details of the solute cavity, varying from 0.4 to 1.5 kcal/mol.

1. Introduction

The electronic charge distribution in a molecule changes upon isomerization and in response to interactions with solvent molecules. Such changes lead to non-additive effects in the molecular interactions. Both of these effects are important for the solvation of the *cis* and *trans* conformers of *N*-methylacetamide (NMA). The NMA molecule has properties which make it similar to the peptide backbone of proteins. It has a carbonyl oxygen and amide hydrogen which form hydrogen bonds and the C−N bond has partial double bond character, similar to the peptide bond. The *cis* and *trans* conformers are separated by rotations about this bond. In addition, NMA provides a convenient prototype for the study of non-additive collective stabilization of hydrogen bonds. Hartree−Fock calculations of NMA complexed with water and other hydrogen bonding molecules show that the presence of other molecules strengthens the hydrogen bond energies, by 1 to 2 kcal/mol.[1] An additional requirement for molecular force fields is to account for how the charge distribution changes as functional groups are substituted. A comparison of NMA and acetamide, in which a polar hydrogen is substituted for the methyl group, presents a convenient case for studying these substitutional effects. The fluctuating charge model, in which the partial charges on atomic sites are treated as variables dependent on the environment, is a convenient model for treating all of these effects: conformational changes, functional group substitutions, and the influence of solvent molecules.[2]

The solvation free energy of NMA is -10.1 ± 0.2 kcal/mol.[3] The free energy difference between the two conformers in water,[4,5] given by nuclear magnetic resonance measurements, is -2.5 kcal/mol. This free energy difference is insensitive to

the solvent; similar free energy differences are found for NMA in 1,2-dichloroethane,[4] chloroform,[5] and cyclohexane.[5] The gas phase free energy difference has not been measured experimentally, but an estimate of the gas phase enthalpy difference from infrared experiments gives -2.3 kcal/mol,[6] in good agreement with the *ab initio* calculation of Jorgensen and Gao which finds $\Delta H \approx -2.1$ kcal/mol.[7] The solvation free energy of both conformers is therefore the same, within a few tenths of a kcal/mol. The solvation free energy does not change much upon substitution of a hydrogen atom for the *N*-methyl group; the solvation free energy for acetamide is about the same as for NMA, -9.8 ± 0.2 kcal/mol.

The Boltzmann weighted average of the dipole moments of the *cis* and *trans* conformers (which consist mainly of the *trans* form) of NMA in the gas phase is 3.73 D.[8] In electronic structure calculations of the two conformers, it is found that the *cis* conformer has a slightly higher dipole moment that the *trans* conformer.[5,7,9,10] Radzicka *et al*.[5] and Jorgensen and Gao[7] both find 4.03 D for *trans* and 4.21 D for *cis*, whereas Tannor *et al*. find 3.78 D for *trans* and 3.96 D for *cis*. These studies show that the dipole moment changes with conformation for two reasons: the location of the atomic charges changes, and the atomic charges change in magnitude (and possibly sign) because of electronic charge redistribution. For example, the charge of the oxygen atom changes from $-0.55e$ in the *trans* conformer to $-0.60e$ for the *cis* conformer.[10] Electronic structure calculations of solute molecules in a dielectric continuum[10] show that the aqueous dipole moments are enhanced relative to the gas phase values and are 5.33 (*trans*)

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and 5.27 D (*cis*). A Hartree−Fock study which treated the solvent explicitly using the TIP3P water potential reported a dipole moment for *trans*-NMA of 5.18 D, compared to the correspondingly calculated gas phase value of 3.51 D.[11]

Subtle shifts in the charge distribution on going from *trans* to *cis* NMA are reflected in the thermodynamic properties of solution. It is known from experiment that, as discussed above, the solvation free energy for both conformers is approximately the same, or $\Delta\Delta G \equiv \Delta G_{trans} - \Delta G_{cis} \approx 0$. In two interesting free energy calculations using molecular simulations[7,12] it is found that when the same set of atomic charges is used in both conformers $\Delta\Delta G = -2.2 \pm 0.3$ kcal/mol[7] and $\Delta\Delta G = -0.88 \pm 0.12$ kcal/mol.[12] However, if a different set of charges—based on gas phase Hartree−Fock values—is used for each conformer then $\Delta\Delta G \approx 0$.[7,12] These studies do not treat solvent-induced polarization effects, but they demonstrate the importance of conformationally dependent charges on the potential energy. The electronic structure/dielectric continuum, or self-consistent reaction field (SCRF), studies of Tannor *et al.*, which include solute polarization, find that for *cis*-NMA $\Delta G \approx 0.0$.[10] However, not all studies which include solute polarizability find $\Delta\Delta G = 0$; the SCRF studies of Chen *et al.* find $\Delta\Delta G \approx -1.5$ kcal/mol[13] and the point inducible dipole/dielectric continuum studies of Sharp *et al.* find $\Delta\Delta G$ ranging from -4.3 to -1.4 kcal/mol depending on the atomic charges and cavity radii used.[14]

The difference in the solvation free energies of NMA and acetamide is less well understood. Wolfenden's experimental data give $\Delta\Delta G \equiv \Delta G_{NMA} - \Delta G_{acetamide} = -0.3 \pm 0.4$ kcal/mol.[3] The free energy calculations that have been done to date have found that $\Delta\Delta G$ is greater than zero. The SCRF results of Tannor *et al.* find $\Delta\Delta G$ of about 2 kcal/mol[10] and, as discussed in ref 15, there are a number of recent simulations using nonpolarizable potentials which all find $\Delta\Delta G = 2$ to 3 kcal/mol.

It is apparent from these previous studies that nonpolarizable models do not give good estimates for the relative solvation free energies of these amide molecules. What can we learn about these systems using polarizable models? The purpose of this paper is twofold: first to develop a computationally efficient polarizable force field which can accurately model the coupling of the molecular charge distribution to torsional bond rotation, to functional group substitution, and to the aqueous environment; and second to apply this model to the solvation of acetamide and *cis*- and *trans*-NMA. Other models treat polarizability using point inducible dipoles; these models, since they introduce a new $1/r^3$ dipole−dipole interaction and they require solving for the induced dipole moments, increase the CPU time by a factor of 2 to 4 relative to nonpolarizable models.[16−18] The fluctuating charge model has no intermolecular interactions not present in nonpolarizable models and only increases computational costs by a small amount. For simulations of liquid water, it was found that the fluctuating charge model was only a factor of 1.1 slower than fixed-charge simulations.[2] The next section describes the fluctuating charge model and applies the model to the calculation of solvation free energies using both an explicit molecular solvent—which is in

itself polarizable—and a dielectric continuum solvent. Section 3 reports the results and Section 4 gives the conclusions.

2. Methods

1. Dynamical Fluctuating Charge Models. The fluctuating charge (FQ) model has been defined in a recent publication.[2] Standard force fields assign partial charges to atomic sites which have values that are fixed for the duration of a simulation. The idea of the FQ model is to treat these partial charges as variables which respond to their environments in a way similar to the polarization response of real molecules. The charge on a site will depend on its electronegativity and electronic hardness and charge will redistribute on a molecule so that the electronegativity of each site is equal.[19,20] The charges are propagated in time using extended Lagrangian dynamics. There have been many applications of different versions of the electronegativity equalization idea to estimate charges for molecules in the gas phase, often to be used as input for simulations.[21−25] The unique feature of the fluctuating charge model is that it enforces electronegativity equalization at each time step during a molecular dynamics simulation.

In an isolated atom the energy of creating a partial charge, Q_α, can be expanded to second order as

$$E(Q_\alpha) = \tilde{\chi}_\alpha^0 Q_\alpha + {}^1\!/_2 J_{\alpha\alpha}^0 Q_\alpha^2 \tag{2.1}$$

where $\tilde{\chi}_\alpha^0$ and $J_{\alpha\alpha}^0$ are parameters dependent on the atom type. The parameter $\tilde{\chi}_\alpha^0$ is the Mulliken electronegativity of the isolated atom (per electronic charge $|e|$) and $J_{\alpha\alpha}^0$ is twice the atom's hardness. For a molecule, each charge site will have a charging energy like eq 2.1 plus intramolecular Coulomb interactions, $J_{\alpha\beta}(r)$, or

$$E = \sum_\alpha \tilde{\chi}_\alpha^0 Q_\alpha + {}^1\!/_2 \sum_\alpha \sum_\beta Q_\alpha Q_\beta J_{\alpha\beta}(r_{\alpha,\beta}) \tag{2.2}$$

where $r_{\alpha,\beta}$ is $|r_\alpha - r_\beta|$ and $J_{\alpha\alpha}(0) = J_{\alpha\alpha}^0$. By minimizing this energy with respect to the charges and subject to a charge conservation constraint, one can determine the gas-phase energy, E^{gp}, and the ground state charges. The total energy for N_{molec} molecules includes this molecular energy plus the usual Lennard-Jones and intermolecular Coulomb terms,

$$U(\{Q\},\{r\}) = \sum_{j<i} \sum_\alpha \sum_\beta \left(4\epsilon_{\alpha\beta} \left[\left(\frac{\sigma_{\alpha\beta}}{r_{i\alpha,j\beta}}\right)^{12} - \left(\frac{\sigma_{\alpha\beta}}{r_{i\alpha,j\beta}}\right)^6 \right] + Q_{i\alpha} Q_{j\beta}/r_{i\alpha,j\beta} \right) +$$
$$\sum_i \left(\sum_\alpha \tilde{\chi}_\alpha^0 Q_{i\alpha} + {}^1\!/_2 \sum_\alpha \sum_\beta Q_{i\alpha} Q_{i\beta} J_{\alpha\beta}(r_{i\alpha,i\beta}) - E_i^{gp} \right) \tag{2.3}$$

The usual Lorentz−Berthelot combining rules for the Lennard-Jones parameters are used: the arithmetic mean for σ_{ij} and geometric for ϵ_{ij}. The amount of energy required to change the charges from the gas phase values to the aqueous values is the polarization energy,

$$U_i^{pol} = \sum_\alpha \tilde{\chi}_\alpha^0 Q_{i\alpha} + \frac{1}{2}\sum_\alpha \sum_\beta Q_{i\alpha} Q_{i\beta} J_{\alpha\beta}(r_{i\alpha,i\beta}) - E_i^{gp} \tag{2.4}$$

The electronegativity per unit charge of atom A is given by $\tilde{\chi}_A = (\partial U/\partial Q_A)$. The minimum energy charges are those for which the electronegativities are equal. Since the potential is quadratic in the charges, the minimization will lead to a set of coupled linear equations for the charge. The charges are not independent variables since there is a charge conservation constraint. In the following we constrain each

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molecule to be neutral, $\sum_\alpha Q_{i\alpha} = 0$. We treat the charges as independent and use the method of undetermined multipliers to enforce the constraint.

The charges, as well as the positions, are treated as dynamical variables. The Lagrangian of the system is

$$L = \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{atom}} \frac{1}{2} m_\alpha \dot{r}_{i\alpha}^2 + \sum_{i=1}^{N_{molec}} \sum_{\alpha=1}^{N_{atom}} \frac{1}{2} M_{i\alpha} \dot{Q}_{i\alpha}^2 - U(\{Q\},\{r\}) -$$
$$\sum_{i=1}^{N_{molec}} \lambda_i \sum_{\alpha=1}^{N_{atom}} Q_{i\alpha} \quad (2.5)$$

where m_α is the mass of atom α and $M_{i\alpha}$ is a fictitious charge "mass", with units of energy $\times$ time^2/charge^2, and the λ_i are Lagrange multipliers. The nuclear degrees of freedom evolve according to Newton's equation and the set of charges evolve in time according to

$$M_{i\alpha}\ddot{Q}_{i\alpha} = -\frac{\partial U(\{Q\},\{r\})}{\partial Q_{i\alpha}} - \lambda_i = -\tilde{\chi}_{i\alpha} - \lambda_i \quad (2.6)$$

If the total charge of molecule i is a constant of the motion, then it can be shown that λ_i is the negative of the mass-weighted average electronegativity on molecule i,

$$\lambda_i = -\sum_{\alpha=1}^{N_{atom}} (\tilde{\chi}_{i\alpha}/M_{i\alpha})/\sum_\alpha 1/M_{i\alpha} \quad (2.7)$$

The force on the charge is simply the difference between the average electronegativity and the instantaneous electronegativity at that site.

The charge mass, $M_{i\alpha}$, a fictitious quantity, is chosen to be small enough to guarantee that the charges readjust rapidly to changes in the nuclear degrees of freedom.[2] For heterogeneous systems which have fluctuating charge sites on atoms with different degrees of polarizabilities, it is most convenient to use a charge mass dependent on atom type and to couple the charge degrees-of-freedom to a Nosé–Hoover thermostat.[26–28] The charge masses used are 0.6 for the water charges, 2.0 for the methyl carbons and the nitrogen, 2.6 for the amide hydrogen, 5.0 for the methyl hydrogens, and 1.2 for the carboxyl carbon and oxygen (all in units of $10^{-4}(ps/e)^2$). The Nosé–Hoover thermostat was given a temperature of 1 K and a mass of 50. The charge mass and thermostat parameters were chosen to give the best possible agreement with the charge values found by exactly solving the matrix equations for a shoft trajectory.

The Coulomb interaction, $J_{ij}(r)$, for intramolecular pairs is taken to be the Coulomb overlap integral between Slater orbitals centered on each atomic site,

$$J_{ij}(r) = \int d\mathbf{r}_i d\mathbf{r}_j |\phi_{n_i}(r_i)|^2 \frac{1}{|\mathbf{r}_i - \mathbf{r}_j - \mathbf{r}|} |\phi_{n_j}(r_j)|^2 \quad (2.8)$$

The Slater orbitals are given by

$$\phi_{n_i}(r) = A_i r^{n_i-1} e^{-\zeta_i r} \quad (2.9)$$

and are characterized by a principal quantum number, n_i, and an exponent ζ_i. A_i is a normalization factor. The value of $J_{ii}(r)$ for $r = 0$ is J_{ii}^0 and therefore the value of ζ_i uniquely determines J_{ii}^0. For hydrogen, $n_H = 1$ and $J_{HH}^0 = 5\zeta_H/8$, and for second-row elements, $n = 2$ and $J_{AA}^0 = 93\zeta_A/256$. Notice that in the FQ model, unlike other molecular force fields, all charges on the same molecule interact, with the charges screened by $J_{ij}(r)$. Beyond a distance of about 2.5 Å $J_{ij}(r)$ becomes equal to $1/r$.

The electrostatic parameters for NMA and acetamide are chosen to accurately reproduce the molecules' electronic charge distribution relative to *ab initio* results using the Pseudo-Spectral Gaussian Valence

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Table 1. Potential Parameters for the Fluctuating Charge Model[a]

		ϵ (kcal/mol)	σ (Å)	$\tilde{\chi}$ (kcal/(mol e))	ζ (Å^{-1})
water	H	0	0	0	1.70
	O	0.2862	3.159	68.49	3.08
amides	H(amide)	0	0	0	3.21
	H(methyl)	0	0	55.34	3.21
	C(carbonyl)	0.109	3.40	83.02	2.83
	C(methyl)	0.109	3.40	108.38	2.65
	N	0.139	3.35	124.52	3.02
	O	0.169	3.28	166.03	2.89

[a] For each molecule, it is only the difference in the electronegativities that influences the charges, so one of the $\tilde{\chi}$'s is arbitrary.

Bond (PSGVB) program.[29] The PSGVB calculations were done with a 6-31G** basis set, correlating heteroatom pairs (all but C−C and C−H bonds). In order to accurately find the charges, it was found that it was necessary to use a different set of parameters on the amide and methyl hydrogens and the methyl and carboxyl carbons. The FQ parameters were chosen to minimize the function $X^2 = \sum_i ((Q_i^{FQ} - Q_i^{PSGVB})/Q_i^{PSGVB})^2$, where Q_i^{FQ} is the FQ charge and Q_i^{PSGVB} is the PSGVB electrostatic potential (ESP) fitted charge for center i, and the sum is over all atoms of the two NMA conformers and acetamide. Since they give accurate charges for these three molecules, the parameters contain information about conformational and functional group changes. The electrostatic parameters, so obtained, also predict accurate charges for similar molecules. For example, these parameters give a dipole moment of 3.36 D for formamide (the experimental value is 3.73 D[8]) and 2.59 D for formaldehyde (the experimental value is 2.33 D[8]). Thus these parameters are a first step toward transferable interaction parameters.

The Lennard-Jones parameters were taken from Cieplak and Kollman.[12] However, some modifications of these parameters were necessary since the charges are different (the solvated FQ charges are larger) and the Lennard-Jones parameters are different for FQ water and TIP4P water. The σ and ϵ for the oxygen and nitrogen atoms are adjusted so that the hydrogen bonded water−NMA dimer has an energy and geometry which is comparable to *ab initio* estimates. Various hydrogen bond energies can be calculated from the FQ model. The energy of the hydrogen bond between the carbonyl oxygen and the water hydrogen is −7.4 kcal/mol for the *trans* conformer and −6.5 kcal/mol for the *cis* conformer, with an OH bond distance of 1.9 Å. The energy of the hydrogen bond between the amide hydrogen and the water oxygen is −4.3 (*trans*) and −4.9 kcal/mol (*cis*), with an OH bond length of 2.0 Å. The difference in the hydrogen bond energies between the two conformers is due to the presence of the methyl group. Estimates of these energies from Hartree−Fock calculations (with 6-31G* basis sets) are about −7 kcal/mol (OH bond length 2.0 Å) for the carboxyl oxygen/water hydrogen bond, and −5 and −6 kcal/mol (OH bond length 2.1 Å) for the amide hydrogen/water oxygen bond, and are very sensitive to the level of accuracy of the electronic structure calculation used.[7,30,31] The carbon Lennard-Jones parameters were unchanged from the Cieplak−Kollman values. A careful examination of the strength of the methyl/water interaction would make for an interesting future study. The parameters are given in Table 1.

2. Free Energy Calculations. The solvation free energies were calculated using free energy perturbation theory by integrating along the thermodynamic path in two steps, first the Lennard-Jones then the Coulombic interactions between the water and solute are turned on. This two-step path is chosen because it allows for comparison with dielectric continuum theory for the electrostatic part of the free energy. Also, it turns out to be an efficient means for calculating the total free energy since the most difficult part of the free energy integration—where the solute−solvent coupling goes to zero—is treated without using the most expensive interactions—the Coulombic interactions. For the

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Lennard-Jones path, the separation-shifted scaling method of Zacharias *et al.* was used.[32] This method provides a much smoother path between the pure water and fully interacting system than the commonly used linear scaling. The method consists of shifting the interactions by adding a term $\delta(1 - \lambda)$, where δ, λ_1, and λ_2 are "charging" parameters. The potential is then scaled in two steps as

$$U(\lambda_1,\lambda_2) = U_{\text{water,water}} + \lambda_1 \sum_i^N \sum_{\beta=1}^{N_{\text{solute}}^{\text{atoms}}} 4\epsilon_{\text{O}\beta} \left[\left(\frac{\sigma_{\text{O}\beta}^2}{r_{i\text{O},\beta}^2 + \delta(1 - \lambda_1)} \right)^6 - \right.$$
$$\left. \left(\frac{\sigma_{\text{O}\beta}^2}{r_{i\text{O},\beta}^2 + \delta(1 - \lambda_1)} \right)^3 \right] + \lambda_2 \left[\sum_\alpha \tilde{\chi}_\alpha^0 Q_\alpha + \frac{1}{2}\sum_\alpha \sum_\beta Q_\alpha Q_\beta J_{\alpha\beta}(r_{\alpha,\beta}) - \right.$$
$$\left. E_{\text{solute}}^{\text{gp}} + \sum_{i=1}^N \sum_\alpha^3 \sum_{\beta=1}^{N_{\text{solute}}^{\text{atoms}}} Q_{i\alpha} Q_\beta / r_{i\alpha,\beta} \right] \quad (2.10)$$

where $U_{\text{water,water}}$ contains all the non-solute interactions, $r_{i\alpha,\beta}$ is the distance between the atom α on water molecule i and the atom β on the solute, and O labels the water oxygen site. First, λ_1 is increased from 0 to 1 with $\lambda_2 = 0$, then λ_2 is increased from 0 to 1, with $\lambda_1 = 1$. The free energy can be calculated by thermodynamic integration

$$\Delta A = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda_2} \right\rangle_{\lambda_1,\lambda_2=0} \mathrm{d}\lambda_1 + \int_0^1 \left\langle \frac{\partial U}{\partial \lambda_2} \right\rangle_{\lambda_1=1,\lambda_2} \mathrm{d}\lambda_2 \quad (2.11)$$

where $\langle\cdots\rangle_{\lambda_1,\lambda_2}$ corresponds to canonical ensemble averages using $U(\lambda_1,\lambda_2)$. The two parts of the free energy will be labeled ΔA_1 and ΔA_2. The polarization component of ΔA_2 is

$$\Delta A_{\text{pol}} = \int_0^1 \langle U_{\text{solute}}^{\text{pol}} \rangle_{\lambda_1=1,\lambda_2} \mathrm{d}\lambda_2 \quad (2.12)$$

with $U_{\text{solute}}^{\text{pol}}$ defined in eq 2.4. The parameter δ is chosen for convenience. The optimal choice for δ will be the one that makes the shortest path between the $\lambda_1 = 0$ and 1 states. This is simply the path which is linear in λ_1. One method for finding a good choice of δ is to run a few short (20 ps) simulations to find the δ value which gives a second derivative for the free energy,

$$\frac{\partial^2 \langle A \rangle_{\lambda_2}}{\partial \lambda_1^2} = \beta \left[\left(\left\langle \frac{\partial U}{\partial \lambda_1} \right\rangle_{\lambda_1} \right)^2 - \left\langle \left(\frac{\partial U}{\partial \lambda_1} \right)^2 \right\rangle_{\lambda_1} \right] + \left\langle \frac{\partial^2 U}{\partial \lambda_1^2} \right\rangle_{\lambda_1} \quad (2.13)$$

which is close to zero, thus making the dependence on λ_1 approximately linear. For the present simulations, a value of 7 Å^2 was used.

The potential parameters used are given in Table 1. The water potential used is the fluctuating charge model using a TIP4P geometry.[33] The properties of the TIP4P-FQ model have been described in ref 2. The simulation of 256 TIP4P-FQ water molecules plus the solute was done in the canonical (constant *T*, *V*, *N*) ensemble, by coupling to a Nosé−Hoover thermostat at a temperature of 300 K.[26,27] The thermostat variable had a mass of 1000. The solute was given a volume of 3 water molecules and geometries of the solute molecules were obtained by optimization at the Hartree−Fock level using a 6-31G** basis set using the PSGVB program.[29] The simulations were performed on the Connection Machine CM-5, using a 1 fs time step and the Ewald sum for the long-ranged electrostatic interactions, and bond constraints were enforced using the SHAKE algorithm.[34] For each path along the integration coordinates, the system was allowed to equilibrate for 2 ps. Averages were taken over 4.2 ns for the NMA conformers and 2.4 ns for acetamide along the λ_1 path with integration points at $\lambda_1 = 0.001$ and ten other values equally spaced from 0.1 to 1.0. Along the λ_2 path, shorter simulation lengths of 0.8 ns were used, with integration points at $\lambda_2 = 0.2, 0.4, 0.6, 0.8, 0.9,$ and 1.0. Error estimates are made

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Table 2. Fluctuating Charge (FQ) Results for *cis*- and *trans*-*N*-Methylacetamide (NMA) and Acetamide for the Gas Phase, μ_{gp}, and Aqueous μ_{aq}, Dipole Moments (in Debyes), and the Various Components of the Solvation Free Energy (in kcal/mol) Calculated from Thermodynamic Integration as well as the Experimental Values

	FQ						experiment	
	μ_{gp}	μ_{aq}	ΔA_1	ΔA_2	ΔA_2^{pol}	ΔA_{tot}	μ_{gp}	ΔA
trans-NMA	3.58	5.8(1)	1.5(2)	−9.3(2)	1.4(1)	−7.8(4)	3.73	−10.1(2)
cis-NMA	3.77	6.1(1)	1.5(2)	−9.0(2)	1.3(1)	−7.5(4)		
acetamide	3.67	5.6(1)	1.3(2)	−9.6(2)	1.2(1)	−8.3(4)	3.76	−9.8(2)

by calculating the variances of averages of blocks of 10 ps of data at each integration point. The error bars reported represent two standard deviations.

3. Dielectric Continuum Methods. An alternative to the explicit solvent free energy calculations described in the preceding section is to treat the solvent as a dielectric continuum. Such approaches—based on the numerical solution of the Poisson equation—are much faster than molecular dynamics simulations and have been applied to a wide variety of systems.[35] The interaction of solute site *i* with the solvent is given by the electrostatic reaction field potential, ϕ_i. In order to combine the dielectric continuum and the FQ model of the solute, the solute−solvent (reaction field) interaction is added to eq 2.2 to give

$$\Delta G_2 = \sum_\alpha \tilde{\chi}_\alpha^0 Q_\alpha + {}^1\!/_2 \sum_\alpha \sum_\beta Q_\alpha Q_\beta J_{\alpha\beta}(r_{\alpha,\beta}) - E_{\text{solute}}^{\text{gp}} + {}^1\!/_2 \sum_\alpha Q_\alpha \phi_\alpha \quad (2.14)$$

The charges can then be found by the electronegativity equalization principle. The electrostatic reaction field ϕ_α will depend on the charges, so once the new set of charges is found, new values of ϕ_i need to be computed. Equation 2.14 is then interated to convergence and typically takes about 5 iterations starting from the gas phase charges.

The Poisson equation is solved using the DelPhi program, which discretizes space on a cubic grid (with 65 × 65 × 65 points).[36] The calculations reported here use a box for which 50% of the grid points are inside the solute cavity, corresponding to a grid spacing of about 0.2 Å. The interface between the solute and solvent is defined by the contact (Conway) surface between solute and a probe solvent molecule, given a radius of 1.4 Å.[37] In addition to the solute charges, other input is the internal and external dielectric constants (1 and 80, respectively) and the cavity radii, which will be discussed below.

3. Results

1. Explicit Solvent. The results for the solvation of acetamide and the two NMA conformers, using the FQ model for both the water and the solute, are listed in Table 2. The dipole moment induced by the solvent, $\mu_{\text{aq}} - \mu_{\text{gp}}$, is large (62% larger for NMA and 53% larger for acetamide). The solvation free energies are about 2 kcal/mol larger than the experimental values. The relative free energies of the molecules are more accurate. The difference in the solvation free energies between *trans*- and *cis*-NMA is -0.3 ± 0.8 kcal/mol, in good agreement with the estimate of ≈0 based on both NMR measurements in solvent[4,5] and *ab initio* calculations in the gas phase.[7] The FQ calculations find that $\Delta\Delta A = \Delta A_{trans-NMA} - \Delta A_{acetamide} = 0.5 \pm 0.8$ kcal/mol. Experimentally, this free energy difference is -0.3 ± 0.4 kcal/mol, favoring *trans*-NMA.[3] As noted in the introduction, there have been a number of recent SCRF calculations and molecular simulations with nonpolarizable potentials which report $\Delta\Delta G$ values between 2 and 3 kcal/mol (see ref 15 and references therein). The polarizable FQ model brings this solvation energy different much closer to the experimental value.

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(36) Nicholls, A.; Honig, B. *J. Comp. Chem.* **1991**, *12*, 435.

(37) Lee, B.; Richards, F. M. *J. Mol. Biol.* **1992**, *55*, 379.
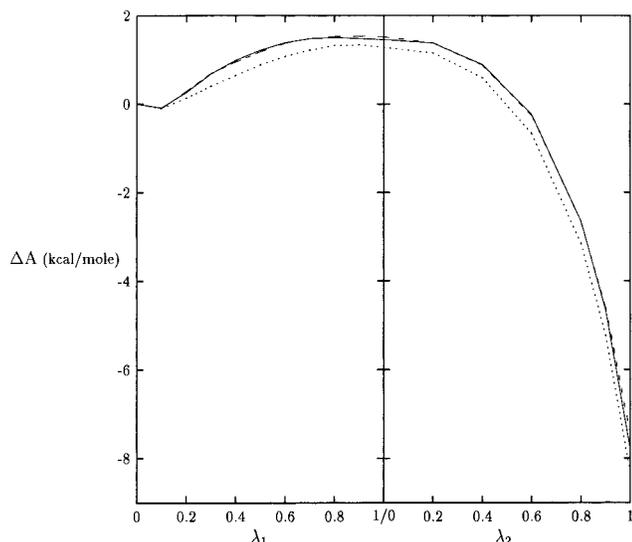
Figure 1. Solvation free energy of *trans-* (solid line) and *cis-* (dashed line) *N*-methylacetamide and acetamide (dotted line) as a function of the thermodynamic integration variables, λ_1 and λ_2.

The free energy was calculated in two steps. The nonpolar contribution to the free energy is ΔA_1. This is the free energy involved in turning on the solute−solvent Lennard-Jones interactions with the Coulombic interactions not present (see eq 2.11). Since it measures the energy to create a nonpolar solute cavity, ΔA_1 is sometimes referred to as the cavity or hydrophobic free energy. For NMA, ΔA_1 is 1.5 kcal/mol, and for acetamide, which is smaller in size than NMA, ΔA_1 is 1.3 kcal/mol. The major contribution to the free energy is the electrostatic contribution, ΔA_2. ΔA_2 can be subdivided into the polarization free energy ΔA_2^{pol}, which by definition is the free energy to change the charges from the gas phase to the aqueous phase values (see eq 2.12), and the rest of the electrostatic energy. The polarization free energy, ΔA_2^{pol}, is found to be slightly larger than 1 kcal/mol for the three solutes.

The free energy as a function of the integration path is plotted in Figure 1. For the path ($0 \leq \lambda_1 \leq 1$), corresponding to scaling the Lennard-Jones interactions, it is apparent that separation-shifted scaling provides a smooth path. At small values of λ_1 (≤ 0.1), the path behaves differently than at higher values and the free energy becomes negative. This different behavior at small λ_1 is due to the fact that water can pass through the solute at $\lambda_1 \leq 0.1$ but not at greater values. The potential at zero separation is given by

$$U(r = 0) = \lambda_1 4\epsilon \left[\left(\frac{\sigma^2}{\delta(1 - \lambda_1)} \right)^6 - \left(\frac{\sigma^2}{\delta(1 - \lambda_1)} \right)^3 \right] \quad (3.1)$$

which, using the Lennard-Jones parameters for the oxygen−water interaction, is 1.4 kcal/mol at $\lambda_1 = 0.1$ and 6.0 kcal/mol at $\lambda_1 = 0.2$, and the corresponding Boltzmann factor, $e^{-\beta U}$, is 0.1 and 10^{-5}, respectively. Therefore, at $\lambda_1 \leq 0.1$ there is a fair probability that a water molecule will occupy the same space as the solute, but at greater λ_1 values there will be a solvent-excluded cavity.

The solvent structure around an NMA molecule is characterized by the radical distribution functions. Figure 2 shows the correlation function, $g_{yx}(r)$, between and atom y on *trans*-NMA and an atom x—either the oxygen, O_W (solid line), or the hydrogen, H_W (dotted line)—on the water molecule for (a) y = the methyl carbon bonded to the nitrogen, (b) y = the amide hydrogen, and (c) y = the oxygen atom. The three functional groups exhibit a range of structures for aqueous solvation. The
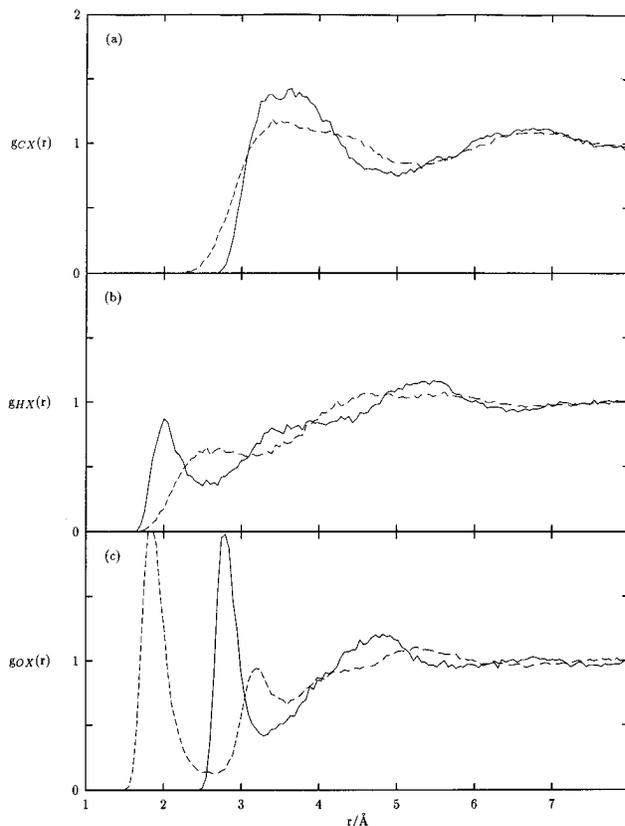
Figure 2. Radial distribution functions between *trans N*-methylacetamide and the oxygen (solid line) and hydrogen (dotted line) atoms of water: (a) methyl carbon bonded to the nitrogen, (b) amide hydrogen, and (c) oxygen.

structure around the methyl group shows no hydrogen bonding and the nearest water molecules are on average tangential to the methyl group since the first peaks of $g_{CO_W}(r)$ and $g_{CH_W}(r)$ are in the same place. There is a small peak in $g_{HO_W}(r)$ at 2 Å that represents hydrogen bonding between the amide hydrogen and water. For the $g_{OH_W}(r)$ and $g_{OO_W}(r)$, the hydrogen bond peaks are much higher, illustrating that there is strong hydrogen bonding between the carboxyl oxygen and water. In fact this interaction is stronger than the water−water hydrogen bond since the $g_{OH_W}(r)$ peak is higher than the $g_{O_WH_W}(r)$ peak for pure TIP4P-FQ water.[2] The correlation functions for *cis*-NMA and acetamide are much the same as those for *trans*-NMA; the one difference is that the heights of the first peaks of $g_{OH_W}(r)$ and $g_{OO_W}(r)$ are slightly smaller, about 1.8 but are in the same position. Acetamide, having two amide hydrogens, has a second peak in the $g_{HO_W}(r)$ at 3.5 Å.

Additional information about solvent near the solute can be obtained from examining the dipole moments of the neighboring water molecules. The average dipole moment of TIP4P-FQ water[2] is 2.62 D whereas, on average, the dipole moment of the water molecule nearest to the oxygen atom of the solute is 2.72 D. This enhancement is consistent with the strong hydrogen bonds exhibited by the $g_{OH_W}(r)$. Water forms stronger hydrogen bonds with the oxygen atom of the solute than it does with other water molecules. In contrast, the dipole moments of the water molecules neighboring the other solute atoms are all about 2.58 D, less than the bulk value, indicating that these electrostatic interactions are weak. This is the same dipole moment as that of water molecules neighboring the uncharged ($\lambda_1 = \lambda_2 = 0$) solute.

2. Dielectric Continuum. An alternative to performing explicit solvent simulations of the solution is to treat the solvent

Table 3. Dielectric Continuum Results for the Fluctuating Charge Model (FQ) and the *ab Initio* Results of Tannor *et al.* with Different Sets of Atomic Radii, Showing the Gas Phase, μ_{gp}, and Aqueous Phase, μ_{aq}, Dipole Moments (in Debyes) and the Free Energies (in kcal/mol): The Total Electrostatic Solvation Free Energy, ΔG_2, the Electrostatic Solvation Free Energy Calculated Using Gas-Phase Charges, ΔG_2^{gp}, and the Change in the Solute Self-Energy due to the Polarization of the Charges, ΔG_2^{pol}

		μ_{gp}	μ_{aq}	ΔG_2	ΔG_2^{gp}	ΔG_2^{pol}
FQ + radii A	*trans*-NMA	3.58	5.45	−11.2	−8.1	4.7
	cis-NMA	3.77	6.14	−11.2	−8.0	4.9
	acetamide	3.67	5.53	−12.7	−9.3	5.0
ab initio + radii A	*trans*-NMA	3.77	5.33	−11.3	−8.4	2.6
	cis-NMA	3.96	5.27	−11.0	−8.5	2.2
	acetamide	3.81	5.14	−13.1	−10.4	2.6
FQ + radii B	*trans*-NMA	3.58	5.09	−8.7	−6.4	3.2
	cis-NMA	3.77	5.80	−8.8	−6.4	3.6
	acetamide	3.67	5.14	−9.1	−6.8	3.1

Table 4. Gas-Phase Dipole Moments, μ_{gp}, (in Debyes) and Electrostatic Solvation Free Energies, ΔG_2^{gp}, for the NMA Conformers Using Various Gas-Phase Charge Distributions with Two Different Sets of Atomic Radii

			ΔG_2^{gp}	
conformer	charges	μ_{gp}	radii A	radii B
trans	*trans*	3.58	−8.1	−6.4
cis	*cis*	3.78	−8.0	−6.4
trans	*cis*	4.00	−9.4	−7.4
cis	*trans*	3.98	−7.7	−6.1

as a dielectric continuum surrounding an FQ model of the solute molecules, as described in Section 2.3. We can then examine how successfully our FQ model of the solute molecule (See eq 2.14) compares with combined electronic structure/continuum solvent (SCRF) models.[10,13,38−41] In addition, we can evaluate the adequacy of the dielectric continuum approach by comparing the explicit solvent results of the previous section with the continuum calculations.

A comparison of SCRF and FQ/continuum solvent calculations allows for a clear test of the FQ model in solution. Table 3 lists, for the dielectric continuum calculations, the gas phase and aqueous phase dipole moments, the electrostatic part of the free energy, ΔG_2, the free energy calculated with the gas phase charges, ΔG_2^{gp}, and the polarization component of the free energy, ΔG_2^{pol}, which is simply given by $\Delta G_2^{pol} = U_{solute}^{pol}$ (see eq 2.4). Results are given for the FQ model with two different sets of radii. Also listed are the *ab initio* results of Tannor *et al.*[10] In order to compare with the *ab initio* study, we use the same values for the atomic radii, which define the solute cavity. These values are 1.6, 1.6, 1.9, and 1.15 Å for O, N, C, and H, respectively. This set of radii will be denoted as radii "A". In the *ab initio* calculations, solvation energies are obtained in a self-consistent manner in which the Schrodinger equation is solved in the presence of a solvent reaction field.[10] The FQ parameters are chosen to reproduce gas-phase charges (although not the charges from ref 10) so the properties (μ_{gp}, ΔG_2^{gp}) which depend on these gas phase charges are in close agreement with the electronic structure results by construction. The small differences observed are due in part to the use of different molecular geometries in ref 10 and in the present study. Using the same geometries in both models would allow for a more

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(41) Rashin, A.; Bukatin, M.; Andzelm, J.; Hagler, A. *Biophys. Chem.* **1994**, *51*, 375.

Table 5. Charges for Fluctuating Charge (FQ) Model and Electrostatic Potential (ESP) Fitted Charges from the PSGVB Electronic Structure Calculations in the Gas Phase and in Aqueous Phase Using the DelPhi Poisson Equation Solver, in Units of Electronic Charge, e

molecule	atom	FQ-DelPhi gas phase	FQ-DelPhi aqueous	PSGVB-DelPhi gas phase	PSGVB-DelPhi aqueous	difference gas phase	difference aqueous
trans-NMA	C(C)	−0.702	−0.709	−0.545	−0.569	−0.157	−0.140
	H	0.177	0.200	0.134	0.157	0.043	0.043
	H	0.177	0.200	0.134	0.157	0.043	0.043
	H	0.203	0.208	0.156	0.150	0.047	0.058
	C	0.765	0.820	0.766	0.821	−0.001	−0.001
	O	−0.557	−0.743	−0.545	−0.655	−0.012	−0.088
	N	−0.528	−0.543	−0.523	−0.541	−0.005	−0.002
	H	0.305	0.352	0.316	0.358	−0.011	−0.006
	C(N)	−0.244	−0.231	−0.260	−0.257	0.016	0.026
	H	0.143	0.151	0.123	0.115	0.020	0.036
	H	0.143	0.151	0.123	0.115	0.020	0.036
	H	0.119	0.145	0.156	0.150	−0.037	−0.005
cis-NMA	C(C)	−0.660	−0.675	−0.439	−0.459	−0.221	−0.216
	H	0.179	0.199	0.127	0.150	−0.052	0.049
	H	0.179	0.199	0.127	0.150	0.052	0.049
	H	0.198	0.204	0.124	0.119	0.074	0.085
	C	0.757	0.812	0.758	0.814	−0.001	−0.002
	O	−0.577	−0.765	−0.587	−0.701	0.010	−0.064
	N	−0.512	−0.534	−0.548	−0.568	0.036	0.034
	H	0.324	0.359	0.316	0.347	0.008	0.012
	C(N)	−0.274	−0.249	−0.188	−0.205	−0.086	−0.044
	H	0.130	0.150	0.090	0.101	0.040	0.049
	H	0.130	0.150	0.090	0.101	0.040	0.049
	H	0.126	0.149	0.131	0.150	−0.005	−0.001
acetamide	C	−0.707	−0.708	−0.577	−0.587	−0.130	−0.121
	H	0.183	0.208	0.152	0.173	0.031	0.035
	H	0.183	0.208	0.152	0.173	0.031	0.035
	H	0.205	0.214	0.148	0.140	0.057	0.074
	C	0.877	0.932	0.944	0.990	−0.067	−0.058
	O	−0.586	−0.774	−0.586	−0.696	0.000	−0.078
	N	−0.917	−0.930	−1.108	−1.138	0.191	0.208
	H	0.371	0.423	0.434	0.477	−0.063	−0.054
	H	0.389	0.427	0.440	0.467	−0.051	−0.040

direct comparison. The gas phase charges and those found in the reaction field are listed in Table 5. This table presents a comparison between the PSGVB and FQ results, using the same molecular geometries and cavity radii. The agreement for both the gas-phase and the aqueous charges is very good. The largest difference is for the charges on the methyl groups. In both the gas phase and upon solvation, the charges on the methyl hydrogens are about 0.04 e larger and the charges on the methyl carbons are 0.12 e smaller than the *ab initio* results so that the overall charge on the methyl groups is about the same, but the charge distribution is different. The FQ charges on the other atoms are in very good agreement with the electronic structure values. This indicates that using gas-phase electronic structure information, the FQ model can be constructed to accurately describe aqueous-phase properties as well. The solvation energies, ΔG_2, are also in good agreement. However, the aqueous dipole moments are larger than the *ab initio* results, particularly for *cis*-NMA.

In order to compare the dielectric continuum with the simulations involving explicit solvent molecules, atomic radii need to be chosen for the continuum calculations which are more consistent with the potentials used in the simulation. One simple way to do this is to use liquid structure information in the form of the pair correlation functions, $g(r)$, to define the solute cavity as was pointed out in a previous paper.[42] The radii are defined as the shortest distance at which the pair correlation function between that solute atom and the solvent first reaches a value of 0.01. This gives the following radii: 1.5, 2.4, 2.4, and 1.6 Å

(42) Rick, S. W.; Berne, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 3949.

for O, N, C, and H, respectively. This set of radii is denoted as radii "B". Notice that this set of radii is appreciably different from the minimum of the Lennard-Jones potential, $2^{-5/6}\sigma_{\alpha O}$, which is about 1.8 Å for the Lennard-Jones parameters used here. Using the set B of radii given free energies which are close to the simulation values but the induced dipole moments are slightly smaller than the simulation values. The difference in ΔG_2 of the *trans* and *cis* conformers is ≈0 for both sets of radii, in agreement with experiment. The difference in ΔG_2 of NMA and acetamide is sensitive to the radii used, varying from 1.5 kcal/mol using radii A to 0.4 kcal/mol using radii B. This difference depends most strongly on the size of the cavity around the polar hydrogen. The continuum calculations find that acetamide has a larger solvation energy than NMA, in disagreement with experiment.[3]

It is of interest to investigate the variation in the relative solvation free energy predictions of continuum theory with respect to different charge distributions. Solvent-induced polarization stabilizes both NMA conformers by the same amount, about 3 kcal/mol. The FQ/dielectric continuum calculations with two different sets of radii show that ΔG_2^{gp}—the solvation energy calculated with gas-phase charges and without polarization by the reaction field—is the same for both conformers. The same conclusion follows from the simulation studies of Jorgensen and Gao[7] and Cieplak and Kollman[12] where the charges used for each conformer were taken from gas-phase Hartree−Fock calculations. Both of these studies found that the two conformers have the same solvation free energy. What happens to the solvation energies if the same set of charges is used for both conformers? The results when the gas-phase charges of one conformer are used to calculate the solvation free energy of the other conformer are given in Table 4. Consistently, whether the *cis* or *trans* charges are used and for both sets of atomic radii, the *trans* conformer is found to be more stable by 0.3 to 1.4 kcal/mol than the *cis* isomer. Thus if the same set of charges is used for both conformers, then the solvation free energies will not be the same, a result consistent with the previous simulation studies.[7,12]

4. Conclusions

The results of the previous section demonstrate that the electrostatic interactions in aqueous solutions of amides are well represented by the simple and computationally efficient FQ model, a model in which the partial charges on atomic sites are variables which respond to their environment. In particular, potential parameters can be chosen such that the FQ model accurately reproduces gas-phase charge distributions for acetamide and *cis*- and *trans*-NMA, and can therefore model the effects of conformational and functional group changes. In addition, compared to SCRF *ab initio* calculations in a dielectric continuum[10] the FQ model in a dielectric continuum accurately describes these molecules in aqueous solution (see Table 5). Therefore, the FQ model with parameters determined from gas-phase electronic structure calculations is a simple, accurate polarizable model potential for these amides as well as for water.[2] Parameters for the nonelectrostatic interactions, such as the Lennard-Jones terms, must be determined by a separate procedure and are the most uncertain parameters of the potential. Simply representing hydrogen bonds as originating from the electrostatic interactions plus Lennard-Jones terms, an approximation made in the construction of many force fields including this one, is a questionable assumption. The method used here of choosing the Lennard-Jones parameters so that the water-solute hydrogen-bonded dimer has the energy and geometry close to results from electronic structure calculations

provides a quick method, not requiring full aqueous simulations, and thus does not build in the properties of solvation which one is trying to predict. It is important to note in this connection that hydrogen bond energies are sensitive to the accuracy of the electronic structure used.

The solvation free energies for *trans*- and *cis*-NMA were found to be the same, in agreement with experiment,[4,5,7] using the FQ model for the solute with either an explicit (FQ) solvent or a dielectric continuum solvent, indicating the importance of conformationally dependent charges for this molecule (see Tables 2 and 3). Using conformationally independent charges, the *trans* isomer was found to be more stable by 0.3−1.4 kcal/mol (see Table 4). It can be concluded that using conformationally dependent charges gives the correct relative solvation energies, whereas using conformationally independent charges does not. This conclusion agrees with the results of Jorgensen and Gao[7] and Cieplak and Kollman,[12] which, in contrast, are based on nonpolarizable potentials.

The difference in the solvation free energies between NMA and acetamide poses a more difficult problem than the observed insensitivity of the solvation free energy in NMA to conformational states. The present simulations find that $\Delta A_{NMA} - \Delta A_{acetamide} = 0.5 \pm 0.8$ kcal/mol. This behavior is opposite to the trend in the experimental free energies, in which $\Delta G_{NMA} - \Delta G_{acetamide} = -0.3 \pm 0.4$ kcal/mol. It is interesting to note that the measured solvation free energy of *N,N*-dimethylacetamide is 8.6 ± 0.3 kcal/mol, making it *less* soluble than NMA by 1.5 kcal/mol.[3] This same trend (one *N*-methyl group decreases and two *N*-methyl groups increase the solvation free energy) is seen in the *N*-methylated derivatives of amines.[3] Other simulations using nonpolarizable potentials find that $\Delta G_{NMA} - \Delta G_{acetamide} = 2$ to 3 kcal/mol,[15,43] so the polarizable FQ potential brings the relative solvation energy in better agreement with experiment. Calculations of the solvation free energies of *N*-methylated amines using dipole-polarizable potentials also reveal improvements over nonpolarizable models, although this study still finds the opposite sign for the relative solvation free energies: experimentally $\Delta G_{NH_2CH_3} - \Delta G_{NH_3} = -0.3$ kcal/mol,[3] the polarizable model predicts 0.3 ± 0.5 kcal/mol,[43] and nonpolarizable models give 1.1 ± 0.2[43] and 0.62 ± 0.05 kcal/mol.[15]

The FQ solute/dielectric continuum solvent calculations find that the solvation free energy difference between NMA and acetamide, unlike the free energy difference between the *trans*- and *cis*-NMA, is sensitive to the size of the solute cavity (Table 3). These are subtle shifts, representing 5% of the solvation free energies, and are a difficult test of the potential. Nevertheless, these types of effects—substituting one functional group for another—are important for many applications of molecular simulations, especially with respect to its use in rational drug design, and it is therefore important to construct force fields that are successful in this regard. One issue related to the discrepancy in the relative solvation free energies and, in addition, in the absolute free energies is the effects of bond stretches, bond angle bends, and torsional angle bends, all of which were left out of the present calculations, which used rigid geometries. Another is the strength of the amide hydrogen water interaction ($H_2O\cdots H-N$) versus the strength of the methyl group water interaction [$H_2O\cdots H-C(N)$]. The strengths of these interactions can be estimated by calculating the energy between the amide molecule and a single water molecule (although this not only determines the hydrogen bond interaction but also the entire interaction energy between all the atoms on the two

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molecules). Using the FQ potential, the $H_2O\cdots H-N$ interaction energies are -4.3 (*trans*-NMA), -4.9 (*cis*-NMA), and -4.5 kcal/mol (acetamide). This is about the same as the FQ water dimer energy of -4.5 kcal/mol.[2] The $H_2O\cdots H-C(N)$ energies are -2.2 (*trans*-NMA) and -2.1 kcal/mol (*cis*-NMA), which, since there are three methyl hydrogens, means that there is a fairly strong interaction between the solvent and the methyl group. Interactions stronger than typical van der Waals energies for $H_2O\cdots H-C-X$ complexes, where X is an electronegative atom, are evident from calorimetric and crystallographic studies (see ref 44). There is evidence of strong $H_2O\cdots HC$ bonds from *ab initio* calculations as well. For example, the $H_2O\cdots H_3CF$ energy is -1.3 kcal/mol,[45] much stronger than the water–methane energy of 0.59 kcal/mol.[46] This interaction continues to get stronger with each substitution of a hydrogen by a flourine atom. Therefore the $H_2O\cdots HC(N)$ bond energies of -2 kcal/mol from the FQ model are reasonable. In addition, using the parameters from Table 1, the water–methane energy is -0.60 kcal/mol, in agreement with the electronic structure value.[46] Therefore, it is evident that the substitution of a polar hydrogen for a methyl group is not a simple matter, and involves a subtle balance of effects.[10]

In summary, the following points can be made:

1. The FQ model accurately reproduces the effects of conformational change and functional group substitution on the gas-phase charge distributions of acetamide and *trans*- and *cis*-NMA.

2. The FQ model combined with the dielectric continuum solvent model also accurately reproduces the aqueous phase charge distributions and solution free energies for these molecules, as compared with electronic structure/dielectric continuum calculations.[10]

3. Thermodynamic integration calculations were performed with FQ explicit water by scaling the entire solute molecule in two steps: first the Lennard-Jones interactions are scaled, and then the electrostatic interactions are scaled. In this way, not only relative but also absolute solvation free energies are calculated.

4. Both simulations with explicit water molecules and the continuum solvent model (using two different solute cavity sizes) predict that the solvation free energies of *trans*- and *cis*-NMA are essentially equal, in agreement with estimates based on experimental and *ab initio* data.[4,5,7]

5. The simulations with explicit solvent molecules predict

$$\Delta\Delta A \equiv \Delta A_{NMA} - \Delta A_{acetamide} = 0.5 \pm 0.8$$

which, within the error bars, is in agreement (but of opposite sign) with the experimental value of -0.3 ± 0.4 kcal/mol.[3] The FQ/dielectric continuum calculations predict $\Delta\Delta G_2 = 0.4$ and 1.5 kcal/mol, depending on the size of the solute cavity, and are also of opposite sign. These continuum results together with the simulation results of the present study and others[15] indicate that this free energy difference is sensitive to the details of the solute–solvent interactions.

6. The FQ force field treats polarizability in a computationally efficient manner with charge parameters which are transferable to different systems. The model is readily extendible to large-scale biomolecular systems.

7. The success of the FQ force field presented here is due in part to its inclusion of solute and solvent polarizability through the fluctuating charges as well as the parameterization of the short-range interactions to be in compliance with the *ab initio* hydrogen bond energies and geometries between the various molecules and the water solvent.

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