

A Polarizable Force Field and Continuum Solvation Methodology for Modeling of Protein–Ligand Interactions

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Abstract: A polarizable force field, and associated continuum solvation model, have been developed for the explicit purpose of computing and studying the energetics and structural features of protein binding to the wide range of ligands with potential for medicinal applications. Parameters for the polarizable force field (PFF) are derived from gas-phase ab initio calculations and then utilized for applications in which the protein binding to ligands occurs in aqueous solvents, wherein the charge distributions of proteins and ligands can be dramatically altered. The continuum solvation model is based on a self-consistent reaction field description of solvation, incorporating an analytical gradient, that allows energy minimizations (and, potentially, molecular dynamics simulations) of protein/ligand systems in continuum solvent. This technology includes a nonpolar model describing the cost of cavity formation, and van der Waals interactions, between the continuum solvent and protein/ligand solutes. Tests of the structural accuracy and computational stability of the methodology, and timings for energy minimizations of proteins and protein/ligand systems in the condensed phase, are reported. In addition, the derivation of polarizability, electrostatic, exchange repulsion, and torsion parameters from ab initio data is described, along with the use of experimental solvation energies for determining parameters for the solvation model.

I. Introduction

The explicit incorporation of polarization into molecular mechanics force fields is a long standing objective of force field development efforts. Early work was focused primarily on development of polarizable force field models for liquid water;^{1–9} a number of water models have now been produced, many of which display very good properties as compared to experiment. A few publications have addressed small organic molecules other than water^{10–13} or small ions;^{14–15}

in these papers few such molecules has been considered, and parameters have typically been fit to condensed phase experimental data, which is not systematically available for many compounds, including the great majority of pharmaceutically interesting ligands. More recently, a number of efforts have been made to develop a polarizable protein force field^{16–18} and to approach the problem of inclusion of polarization in a more systematic fashion.^{19–22} However, many of these models are relatively new and untested; it is clear that the problems of achieving accuracy, reliability, and broad coverage, while explicitly incorporating polarization, are substantial and far from solved at the present time.

In a series of previous publications, we have described the development of automated methods for the construction of a polarizable force field for an arbitrary molecule directly

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from *ab initio* quantum chemical data.^{3,9,16,20–22} The primary goal is to produce a polarizable model that yields accurate results in condensed phase simulations; as we²⁰ and others^{23–25} have discussed previously (this issue is also briefly reviewed below), it appears as though one has to use different polarizability parameters in the gas phase and condensed phase in order to reproduce experimental data reliably. We have developed an approach which has successfully matched experimental heats of vaporization and density for a number of small molecule pure liquid simulations, without explicit fitting to experimental condensed phase data.²⁰ At the same time, we have shown that our methodology is capable of accurately fitting quantum chemical gas-phase conformational data for dipeptides, thus enabling the creation of a polarizable protein force field.¹⁶

However, to deploy a polarizable force field for practical problems in drug design, it is necessary to have the ability to represent an arbitrary medicinal compound by a set of polarizable force field parameters. Furthermore, molecular dynamics simulations, employing explicit solvent, require large amounts of computer time and in addition necessitate the use of expensive sampling algorithms, such as replica exchange methods,²⁶ if free energies of binding are to be determined; for these reasons, this type of approach is currently used very infrequently in modeling projects in the pharmaceutical industry. Instead, a continuum treatment of aqueous solvation, based on for example solution of the Poisson–Boltzmann equation,²⁷ is utilized, along with approximate sampling algorithms (in many cases, simple minimization). Thus, a continuum solvation model that is complementary to the polarizable force field is required if realistic drug discovery problems, as opposed to a small number of carefully chosen model systems, are to be addressed.

In the present paper, we describe a complete integrated software system and associated parametrization for carrying out polarizable force field calculations in continuum solvent for arbitrary protein–ligand complexes. The key components of the system are as follows:

(1) A package for assigning polarizable force field parameters to an arbitrary medicinal compound. The package includes an atom typing algorithm, default polarizability, and van der Waals parameters for a wide range of atom types, and an extensive set of stretching, bending, and torsional parameters (the former are borrowed from our most recent fixed charge force field development effort, the latter are fit to minimize the deviation with gas-phase quantum chemical data for a ~600 compound small molecule data set). Atomic point charges, lone pair charges, and permanent dipoles are determined by fitting high level quantum chemical data, using an automated protocol.

(2) A polarizable protein force field that has been extensively fit to quantum chemical data on dipeptides and tested in a variety of simulations. This work is described in more detail in other publications but is summarized here because of its relevance to the computation of protein–ligand interactions, the principal focus of this paper.

(3) A simulation package for carrying out gas-phase polarizable simulations. The polarization equations are solved

self-consistently at each geometry. In the present paper we focus on minimization; however, methods for molecular dynamics simulation are in place. These will be discussed elsewhere.

(4) A self-consistent reaction field (SCRF) methodology²⁸ in which solution of the Poisson–Boltzmann equation is coupled with determination of the polarization response of the protein and ligand, using the package discussed in (3) above. We have extended our previously developed analytical gradient methodology^{29,30} to handle the polarizable SCRF model; infrequent evaluation of the PB solver significantly improves computational performance without loss of accuracy. Dielectric radius parameters for a wide range of atom types, suitable for this methodology and the underlying force field, have been developed from a database of 147 small molecules, with an average error in the solvation free energy of 0.35 kcal/mol for neutral molecules and 0.5 kcal/mol for charged species.

With these components in hand, it is possible to carry out optimization of a protein–ligand complex and the ligand in continuum solvent and to calculate the total energy difference (such a difference includes the solvation free energy difference but does not include the conformational entropy difference between the protein–ligand complex and the protein and ligand independently in solution). The simplest application of this type of computation would be to correlate the resulting energy difference directly with binding affinity. However, this capability may also be useful, for example, as a component of MM/PBSA type approaches^{31–33} or in continuum solvation based extended linear response calculations.³⁴ It is an interesting and important question as to whether the use of a more accurate force field and solvation models which incorporate polarization explicitly (and, based on our results to date, reasonably accurately) will improve the performance of approaches of this type. Our present software package enables, for the first time, this question to be addressed with a reasonable amount of effort by the user.

Ultimately, highly accurate binding affinity predictions will be achieved by combining an accurate force field and solvation model with equally accurate phase space sampling. In the context of continuum models, methods for computing absolute free energies via direct phase space integration have been proposed, and successfully employed, for example by Gilson and co-workers.³⁵ The polarizable model described here could be employed as a component of this methodology, for example to correct the energies of low-lying minima (using a fixed charge force field to do the extensive sampling required to locate the minima and to evaluate entropic terms). It may also be the case that retention of a crucial subset of explicit waters is required to accurately evaluate protein–ligand interactions. The treatment of explicit waters presents no problem in principle to the present approach, and a very simple test case was recently successfully completed.³⁶ However, robust algorithms for determining the placement of such waters are nontrivial and remain to be rigorously developed and validated.

The present paper is focused on describing the computational methodology associated with the four components enumerated above and providing a demonstration that the

implementation performs properly for a test suite of protein–ligand complexes. The paper is organized as follows. Section II describes the development of the parameters for the medicinal chemistry force field (item (1) above), reviewing our computational methodology and presenting PFF results for hydrogen bond energies and structures of 182 small molecule dimers. Section III discusses the SCRF solvation methodology and presents results for solvation free energies of 147 small molecules which constitute the training set for determining dielectric radii. Section IV presents the full protein–ligand simulation methodology (including a brief overview of the protein polarizable force field), followed by results for a suite of test cases taken from the PDB. In this paper we simply demonstrate that minimizations in gas phase and in solution can be carried out unproblematically and in reasonable CPU time (nontrivial given the possibility of polarization catastrophes and the difficulty of converging solvated large protein minimizations using SCRF methods) and compare the RMSD of the resulting structure with the experimental data; future publications will explore the use of these methods for binding affinity prediction.

II. Development of Polarizable Force Field Parameters for Arbitrary Medicinal Compounds

A. Functional Form of the Polarizable Force Field. We can summarize our conclusions, based on a substantial number of computational experiments,^{3,9,16,20–22} with regard to the functional form of the polarizable force field, as follows:

(1) The underlying permanent charge model can be made reasonably accurate via the use of atomic point charges and dipoles. Others have advocated the use of atomic quadrupoles or other more complex charge distributions;³⁷ our experience is that, while quadrupoles can on occasion make a nontrivial contribution to the electric field, the energy error associated with truncating the electrostatic “basis set” at dipoles is in the vast majority of cases less than 0.5 kcal/mol, which is our overall target accuracy for the force field in the gas phase. On this basis, we judged the additional coding complexity and computational expense of quadrupoles as marginal for the current generation of polarizable models, particularly as the goal is to achieve coverage of medicinal chemistry space, requiring a large scale parametrization effort.

(2) We experimented with the use of both fluctuating charges and polarizable dipoles, individually and in combination. Our conclusions are that fluctuating charges alone are seriously inadequate in describing intermolecular interactions in a significant number of relevant cases; dipoles alone provide reasonable results, and the combination of fluctuating charges and dipoles does not provide a sufficient improvement to dipoles alone (again, in the overall context of the achievable accuracy of current models) to justify the added complexity and difficulties in fitting due to the increased overcompleteness of the model. The use of dipoles only also provides a simpler physical picture of the polarization response. Therefore, we have chosen to employ atomic polarizabilities in the present force field.

(3) It is possible to define new atomic polarizabilities for every atom in each new molecule. At the other extreme, one

can simply have a single polarization parameter for each element (i.e. one for oxygen, one for nitrogen, etc.). Our experience has been that the latter approach (at least in our hands) leads to gross inaccuracies in, for example, hydrogen bonding interactions, whereas the former, while technically feasible, is rather expensive both computationally and in terms of human effort. Therefore, we have adopted an intermediate approach in which polarization parameters are defined for various atom types and fit using a suite of model molecules. This approach provides a good compromise between computational efficiency, convenience, and accuracy; results validating our choice of atom types (by demonstrating good ability to reproduce hydrogen bond energies across a wide range of test cases) are presented below.

(4) Long-range dispersion forces are notoriously difficult to compute via *ab initio* quantum chemistry; on the other hand, liquid-state simulations are very sensitive to these interactions, so arguably they can be obtained by fitting condensed phase experimental data. We hypothesized²⁰ that one could define a single long-range dispersion parameter (the coefficient of the atomic $1/r^6$ term used to construct the corresponding term in the atom–atom pair potential via the usual combining rules) for each atom and that it would be transferable across a wide range of organic systems. This strategy was highly successful,²⁰ and a small number of liquids were used to fit parameters for H, C, O, N, and S, while others were then tested using these parameters without adjustment. No doubt greater accuracy could be achieved by allowing the dispersion parameters to vary with atom type; however, the accuracy achieved using the single parameter ansatz appears to be acceptable at present.

(5) For the remainder of the nonpolar atom–atom pair potential, we investigated the use of both the Lennard-Jones $1/r^{12}$ term and the exponential term in the exp-6 pair function. Because we wanted to fit both hydrogen bond energies and bond lengths, while keeping the dispersive term fixed, we decided to employ a combined function in which both types of terms are present; this is discussed in more detail elsewhere. One could in fact use a numerical pair function defined by a look-up table; the key is having sufficient functional flexibility to fit the quantum chemical data adequately. Nonbonded parameters of these types are defined for a list of atom types as presented below.

(6) As is usual in fixed charge force fields, we eliminated 1–2 and 1–3 interactions from the energy calculations; however, 1–4 interactions are included with no scaling.

(7) Stretches and bends were taken from our fixed charge force field (e.g., from the OPLS-AA protein force field³⁸). This is a reasonable approximation but will be reexamined in the next generation PFF. Torsions are fit to *ab initio* calculations on small model molecules; for the present version of the PFF, we used the same training set of ~600 molecules as has been employed for our fixed charge force field. Future versions of PFF will utilize much larger training sets, so as to eliminate missing torsion parameters for the great majority of medicinal compounds.

Given these choices, the total energy of the PFF force field is defined as

$$E_{\text{PFF}} = E_{\text{str}} + E_{\text{bend}} + E_{\text{tor}} + E_{\text{nb}} + E_{\text{q/q}} + E_{\text{q/u}} + E_{\text{u/u}} + E_{\text{pol}} \quad (1)$$

The stretch, bend, and torsion energy functions in eq 1 are given by

$$E_{\text{str}} = \Sigma K_b (b - b_o)^2 \quad (2)$$

$$E_{\text{bend}} = \Sigma K_\theta (\theta - \theta_o)^2 \quad (3)$$

$$E_{\text{tor}} = \frac{1}{2} \Sigma \{ V_1 [1 + \cos(\varphi)] + V_2 [1 - \cos(2\varphi)] + V_3 [1 + \cos(3\varphi)] + V_4 [1 - \cos(4\varphi)] \} \quad (4)$$

where the K_b , K_θ , V_1 , V_2 , V_3 , and V_4 are force constants, b_o and θ_o are reference values, and where b and θ are bond lengths and bend angles. The V_4 term in eq 4 is normally set to a value of 0. Equation 4 gives the deformation energy for twisting about a bond and for out-of-plane deformations (at trigonal centers), so φ represents both dihedral angles and improper torsion angles.

The nonbonded energy function, which includes both dispersion and exchange repulsion terms, is

$$E_{\text{nb}} = \frac{1}{2} \Sigma \{ A_{ij}/R_{ij}^{12} - B_{ij}/R_{ij}^6 + C_{ij} \exp [-R_{ij}/\sigma_{ij}] \} \quad (5)$$

Here R_{ij} is the distance between atoms i and j , and A_{ij} , B_{ij} , C_{ij} , and σ_{ij} are adjustable parameters. The factor of $1/2$ is introduced to exclude double counting of interactions.

The interaction energies between all pairs of interacting charges is indicated in eq 6, where q_j is the charge at atomic or virtual (i.e., lone pair) site j and where the factor of $1/2$ again excludes double counting.

$$E_{\text{q/q}} = \frac{1}{2} \Sigma q_i q_j / R_{ij} \quad (6)$$

PFF employs permanent dipoles at atomic sites, to model the anisotropy in the charge distribution surrounding each atom. This anisotropy is an inherent result of bonding (in both polar and covalent bonds) and causes the interaction energy of a point charge with an atom to depend on whether the charge (or field due to a distribution of charges) is located parallel or perpendicular to a bond. The permanent dipole (μ_i) on atom i interacts with the total field (\mathbf{F}^q_i) due to all interacting charges. The interaction energy between the dipole on atom i and the charges is given by $-\mu_i \mathbf{F}^q_i$, where both the dipole and field are vector quantities. Consequently, the total interaction energy between all interacting charges and permanent dipoles is determined by summing over all dipoles, as indicated in eq 7.

$$E_{\text{q/u}} = -\Sigma \mu_i \mathbf{F}^q_i \quad (7)$$

Similarly, permanent dipoles on other atoms create a field (\mathbf{F}^u_i) that also interacts with the dipole on atom i , and the total energy of interaction between all permanent dipoles is given by eq 8. The PFF electrostatic interaction energy is the total energy of interaction between all charges and permanent dipoles and is the sum of eqs 6–8.

$$E_{\text{u/u}} = -\frac{1}{2} \Sigma \mu_i \mathbf{F}^u_i \quad (8)$$

With PFF all ligand atoms are polarizable, which means that an induced dipole (μ'_i) is created on each atom. As shown by eq 9, the magnitude of the induced dipole (at atom i) is proportional to the polarizability (α_i) of atom i and to the total field exerted at this atom.

$$\mu'_i = \alpha_i (\mathbf{F}^q_i + \mathbf{F}^u_i + \mathbf{F}^{u'}_i) \quad (9)$$

The last term in eq 9 is the field (at atom i) due to all induced dipoles that interact with the atom. Initially, this field and the induced dipoles are not known, so guess values for the induced dipoles are assumed, and μ'_i and $\mathbf{F}^{u'}_i$ are then iteratively refined until the value of each induced dipole has converged. For continuum solvent simulations there is an additional field source that is added to eq 9. This is the self-consistent reaction field due to the solvent.

Energy is required to create the induced dipoles, and this energy, which is often called the self-polarization energy,³⁹ is given in eq 10.

$$E_{\text{self}} = \frac{1}{2} \Sigma \mu'_i (\mathbf{F}^q_i + \mathbf{F}^u_i + \mathbf{F}^{u'}_i) \quad (10)$$

The net change in interaction energy (that is caused by polarization of each atom) is the sum of the self-polarization energy and the energy of interaction of the induced dipoles with the charges, permanent dipoles, and (all other) induced dipoles, as indicated in eq 11. Due to cancellation of terms, eq 11 reduces to eq 12, which is the PFF polarization energy.

$$E_{\text{pol}} = E_{\text{self}} - \Sigma \mu'_i (\mathbf{F}^q_i + \mathbf{F}^u_i + \frac{1}{2} \mathbf{F}^{u'}_i) \quad (11)$$

$$E_{\text{pol}} = -\frac{1}{2} \Sigma \mu'_i (\mathbf{F}^q_i + \mathbf{F}^u_i) \quad (12)$$

B. Development of Default PFF Parameters. The first step in the parametrization of the PFF is the development of polarizability and atomic nonbonded parameters for a set of specified atom types, using a test suite of model molecules. Permanent electrostatic parameters for each model molecule (atomic point charges and dipoles) are obtained by standard electrostatic potential (ESP) fitting methods to high level quantum chemical wave functions. In previous work, we used DFT wave functions to obtain permanent charge distributions.^{3,16,20–22} In the course of the more extensive investigation of chemical space carried out for this paper, we have concluded that local second-order Moller–Plesset perturbation theory (LMP2) calculations with large basis sets provide more accurate and reliable results, although the DFT approach is still quite reasonable. An important target for the dimer binding energies was to reproduce results obtained from LMP2 extrapolated to the basis set limit. On the whole using LMP2/cc-pVTZ(-f) derived charge distributions leads to better agreement of the model with the target quantum chemical dimer extrapolated binding energies than does the use of B3LYP/cc-pVTZ(-f) derived charge distributions. As a result of this, it was possible to derive exchange repulsion parameters which gave somewhat better agreement with the extrapolated binding energies when LMP2, rather than DFT, was employed for calculating the permanent charge distributions. Consequently, charge distributions should be derived from LMP2 in order to maintain maximum consistency with

the derived exchange repulsion parameters. Nevertheless, geometry optimizations can be performed at the DFT level, so only single point LMP2/cc-pVTZ(-f) calculations are required, leading to reasonable computational expense as compared with other aspects of the overall modeling protocol. The LMP2 charge distributions are expected to be close to the results one would obtain with fully converged high level quantum chemical calculations. Pseudospectral LMP2 methods in the Jaguar program⁴⁰ were used to carry out the LMP2 calculations.

Because of the accuracy of the LMP2 charge distributions, charges and dipoles (both permanent and induced) were allowed to interact without scaling for interactions in which atoms were separated by three (or more) bonds (e.g., 1–4 interactions). As usual for force field calculations, interactions between charges (and dipoles) were not included for atom pairs separated by one or two bonds.

Charges and permanent dipoles were determined from fits of the LMP2/cc-pVTZ(-f) esp, as discussed above, with appropriate constraints and restraints. Eigenvalues calculated by singular value decomposition were consistently very small for the permanent dipoles on buried atoms that were surrounded by other atoms. This is an indication that the permanent dipoles for these atoms are small. These atoms could not be sampled well enough to distinguish the esp due to the charges and dipoles. Consequently, the permanent dipoles on tetrahedrally bonded atoms, such as the carbon and phosphorus atoms in alkyl and phosphate groups, were constrained to a value of 0 (i.e., permanent dipoles were not placed on these atoms). To prevent the occurrence of large (physically unrealistic) charges and dipoles, a penalty function ($0.2p^2$) was also used as a restraint, where p is the charge or dipole parameter value. This penalty function was applied to each charge and (permanent) dipole parameter and was added to the total sum of squared deviations (for the fit of the esp), which was then minimized.

Once the procedure for determining the permanent charge distribution is obtained, the next step is to fit polarizability parameters to reproduce the response of the model molecules to applied electric fields. Dipole probes were used to apply an electric field to the molecule, and these probes consisted of two point charges (0.7815 and -0.7815 e) separated by 0.5774 Å, so that the molecules were exposed to fields which are similar to those that occur in an aqueous solvent. These point charges were used to probe the polarization response of an atom by placing a probe near the atom and then using quantum mechanics to determine the energy of interaction between the molecule and probe, as described below. All atoms, except for those in alkyl groups, were similarly probed.

Dipole probe positioning depended on each atom's bonding and hybridization. Whenever possible, probes were placed in hydrogen bonding positions. For oxygen and sulfur with sp^2 or sp^3 hybridization, the two point charges were oriented along the axis through the atom and lone pair position, and two probes were utilized in these cases (i.e., one probe for each lone pair). Probes for terminal atoms were placed along the bond axis (e.g., along the N–H bonds in formamide) for H, F, Cl, N (e.g., nitriles) and O and S atoms

(without sp^2 or sp^3 hybridization, as in methoxide anion, phosphates, and sulfates). For pyramidal atoms, the probes were placed along the pyramidal axis, so that in the case of amine nitrogen, the probe was placed along the axis from the nitrogen to the lone pair. In all of these cases the probes were placed at a distance of 1.8 Å from H, N, O, and F and at a distance of 1.9 Å from P, S, and Cl. For planar atoms, such as sp^2 C and N in amides or C in aromatic rings, the probe was placed along the axis through the atom and perpendicular to the plane (at a distance of 2.0 Å from the plane). For tetrahedral N, P, and S a line was drawn through a bond, and a probe was placed on the other side of the tetrahedral atom (at a distance of 1.8 Å from N and 1.9 Å from P and S). Four of these probes (corresponding to the four bonds) were created for each tetrahedral atom, and then those probes with the closest contacts (to the atoms bonded to the tetrahedral atom) were discarded. Although the polarizability model used here is isotropic, while polarization is inherently anisotropic, the parametrization procedure employed here is optimized to reproduce the polarization response in the direction of greatest importance for intermolecular interactions. For example, oxygens and sulfur are probed in the lone pair direction, arenes are probed perpendicular to the plane of the aromatic ring, and terminal bonds are probed along the bond axis.

When point charges are placed near a molecule, the quantum mechanical interaction energy is given by

$$E = E(\text{molecule} + \text{point charges}) - E(\text{isolated molecule}) - E(\text{point charges}) \quad (13)$$

and

$$E = E_{\text{elec}} + E_{\text{pol}} \quad (14)$$

where E_{elec} and E_{pol} are the electrostatic and polarization components of the interaction energy. Other high intensity field terms (i.e., hyperpolarization) can be neglected at field strengths typical of biomolecular systems, and all other interaction terms (e.g., exchange repulsion and dispersion) are nonexistent in this case. As demonstrated in the Appendix, the electrostatic and polarization components of the interaction energy vary linearly and quadratically, respectively, with the field strength, and this variance in the field strength dependence allows these two energy components to be separately determined. For example, the Appendix demonstrates that for the case of two point charges (q_1 and q_2) the electrostatic and polarization energy components of the interaction energy are given by

$$E_{\text{elec}} = C_1 q_1 + D_1 q_2 \quad (15)$$

$$E_{\text{pol}} = C_2 q_1^2 + D_2 q_2^2 + C_{11} q_1 q_2 \quad (16)$$

In eq 15 C_1 and D_1 are the molecule's electrostatic potential evaluated at the location of the two charges, while C_2 , D_2 , and C_{11} are coefficients that are determined from derivatives of the interaction energy with respect to the point charges (evaluated at point charge values of 0). Since these derivatives can be readily evaluated by the method of finite differences, the polarization energy component of the

Table 1. PFF and LMP2/cc-pVTZ(-f) Polarization Energies Are Compared for Formamide Interacting with Dipole Probes for Each Atom

atom	polarizability (Å ³)	polarization energy (kcal/mol)			% difference
		QM	PFF	difference	
H	0.207	-0.636	-0.633	0.003	-0.43
H	0.207	-0.639	-0.640	-0.001	0.18
HC	0.346	-0.940	-0.945	-0.005	0.53
C	0.766	-1.699	-1.698	0.001	-0.04
N	1.291	-1.839	-1.838	0.001	-0.06
O	0.891	-1.883	-1.884	0.000	0.02
O	0.891	-1.825	-1.821	0.004	-0.21

interaction energy can be calculated from quantum mechanics and also from PFF. Thus, the PFF atomic polarizabilities can be parametrized to reproduce polarization energies calculated from quantum mechanics, and this can be done prior to determining the charges and permanent dipoles for the molecule.

The example in Table 1 demonstrates the procedure for deriving atomic polarizabilities for formamide. As previously described, the hydrogens were probed along the N–H and C–HC bonds, and the C and N were probed perpendicular to the plane of the atom, while O was probed along the line between the O and the two lone pairs. Thus, there were two dipole probes for the oxygen and one each for all other atoms. For each system, which consisted of the formamide molecule with one dipole probe, the LMP2/cc-pVTZ(-f) polarization energy was calculated from eq 16, and the resulting polarization energies are given in the third column of Table 1. LMP2/cc-pVTZ(-f) calculations were used for maximum compatibility of the polarizability parameters with the charge and permanent dipoles, which were also determined at this level of theory.

The PFF polarization energy was also computed from eq 16, and the atomic polarizability parameters (in eq 9) were adjusted to reproduce the LMP2 polarization energy. This was done with a sequential and iterative procedure. The polarizability parameter for the first atom, which is a polar hydrogen, was adjusted to reproduce the LMP2 polarization energy (-0.636 kcal/mol) for the system in which this hydrogen was probed. Then, the polarizability parameter for the second atom, which was also a polar hydrogen, was similarly adjusted to fit the -0.639 kcal/mol polarization energy for the system in which this hydrogen was probed. This process was repeated for each system, but only one probe was used during the fitting procedure for the oxygen. This procedure then was repeated several times until convergence was reached. The end result is that 6 atomic polarizability parameters were fitted to 6 LMP2 polarization energies. In the case of the oxygen atom there were two systems in which the oxygen was probed from different directions (corresponding to probing the two lone pairs). The system with the -1.883 kcal/mol LMP2 polarization energy was fitted, but the resulting 6 atomic polarizabilities also reproduced the -1.825 kcal/mol LMP2 polarization energy for the other system in which the oxygen atom was probed. The percentage error in this latter case was -0.21%, which was less than the 1.0% convergence criteria. If the error had

exceeded the 1.0% convergence criteria, the target polarization energy would have been adjusted somewhat so that the polarization energy for both systems with the oxygen probe were fitted equally well. Thus, even when there are two probes for a single atom, there will still be only a single target function (i.e., polarization energy) per atom. Therefore, the 6 optimized polarizability parameters (given in column 2) are the nearly exact solution to 6 nonlinear equations for the ab initio polarization energies (given in column 3), as seen by the close agreement (in column 4) of the resulting PFF polarization energies.

Note that the polarization energy for the carbon atom probe (-1.699 kcal/mol) is almost as large as the energy for the nitrogen atom probe (-1.839 kcal/mol), even though the carbon polarizability (0.766 Å³) is much smaller than for the nitrogen (1.291 Å³). The reason for this is that the carbon is in close proximity to two much more polarizable atoms (i.e., oxygen and nitrogen). As a result the dipole probe for the carbon atom also substantially polarizes the oxygen and nitrogen, and the net polarization energy results from the polarization of all atoms. The effect of these overlapping polarizations (i.e., each probe polarizes all atoms and not just the closest atom) is sorted out by the simultaneous solution to the system of N equations (for the polarization energy) with N unknowns (i.e., atomic polarizability parameters).

This procedure was used to optimize polarizability parameters for each atom (except for alkyl carbons and hydrogens) in 153 molecules representing a wide variety of functional groups. Alkyl carbon and hydrogen atoms, which were assigned atomic polarizability parameter values of 1.223 and 0.25 Å³, were the only atoms that were not probed (and parametrized). A common value for the polarizability of various types of atoms, such as the hydroxyl oxygen in alcohols, was obtained by averaging the polarizability found for all atoms of this type. For cases in which there were large variations within a group, than averages were performed over smaller groups with consistent polarizability values. For example, the polarizabilities for nitrogen in primary (1.36 Å³), secondary (1.15 Å³), and tertiary (0.97 Å³) amides were distinguished, due to large variations. The latter variations were caused by resonance effects, wherein nitrogen alkylation stabilizes resonance structures with delocalization of the lone pair on the nitrogen. The resulting delocalization reduces the lone pair electron density in the vicinity of the nitrogen atom, which in turn reduces the nitrogen polarizability.

After classifying the polarizability parameters, they were placed into parameter files and atom typing algorithms are used to identify which atomic polarizability parameter to assign to each atom in ligands outside the 153 molecule training set.

In computing the polarizabilities, we deliberately do not employ extended basis sets; the smallest exponents in the basis set have values for which the basis function would not strongly overlap a neighboring molecule in the condensed phase. As is discussed in detail elsewhere,²⁰ the use of extended (diffuse) basis functions in computation of the polarizability in the gas phase is of course correct but leads to serious overpolarization in the condensed phase (as has

been observed by us and others empirically). We hypothesize that the reason for this is that in the condensed phase, diffuse functions have high energy due to the Pauli exclusion principle and Coulomb repulsion; they overlap with occupied orbitals of neighboring molecules, which generate matrix elements leading to higher energies. Simply removing these functions from the basis set is a heuristic approach to correcting the problem but appears to work well in our small molecule liquid-state simulations, which have been described in detail.²⁰

Given a complete set of polarizability parameters, we next determine the nonbonded atomic parameters by fitting hydrogen bond energies and geometries of a large set of molecular dimers. Hydrogen bond energies are computed quantum mechanically, using an LMP2 based extrapolation procedure (described in detail elsewhere⁴¹), which has been benchmarked to yield an accuracy of better than ~ 0.5 kcal/mol in comparison with high level correlated quantum chemical calculations. Results for a suite of 140 dimers are presented in detail below.

The model compounds used in the dimer calculations are typically small molecules with little conformational flexibility. Nevertheless, geometry optimization of the FF structures is required to compute the hydrogen bond energies. This process therefore has to be performed iteratively in parameter space; for the initial development of the nonbonded parameters, initial guesses for torsions are employed; after torsions are fitted, the dimers are reexamined, and the nonbonded parameters are reoptimized if necessary.

Once a complete set of nonbonded parameters are available, the next step is the development of torsional parameters. As was mentioned above, stretches and bends are taken from our fixed charge parametrization. Torsions are fit to quantum chemical data computed at the LMP2/cc-pVTZ(-f)//B3LYP/6-31G* level. Using the almost identical set of model compounds as have been employed in developing the OPLS_2003 fixed charge force field, 975 new torsional parameters have been fit, which leads to a total of 2281 torsion types and which includes protein specific types and torsion types of nonrotatable bonds. The average RMSD of the PFF and quantum chemical conformational energy differences defining our test suite is 1.02 kcal/mol which is comparable in size to the RMSD when a fixed charge functional form is employed (RMSD=0.77 kcal/mol). Additional torsions will be added as new model compounds are added to the database, something that we expect will be an ongoing process.

The final set of parameters for amides, amines, alcohols, carboxylate anions, and ammonium cations are listed in Tables 2–9. Table 2 lists the symbolic atom types for atoms in molecules with these functional groups, and these are used to define the stretch, bend, torsion, and out-of-plane parameters in Tables 3–6. The Lennard-Jones parameters are listed in Table 7, and the exponential repulsion and polarizability parameters are in Table 8. Equations 1–12 define these parameters. Table 9 lists solvation parameters, which are defined in section III.

The most complex aspect of the parametrization process is the fitting of the nonbonded parameters to agree with the

Table 2. Symbolic Atom Types Used To Define Stretch, Bend, Torsion, and Out-of-Plane Parameters for Alcohols, Amides, Amines, Ammonium Cations, and Carboxylate Anions

C	amide carbon
CA	arene carbon
CO3	carboxylate carbon
CT	alkyl carbon
H	polar hydrogen in amines/amides
HC	alkyl and nonpolar amide hydrogen
HNP	ammonium hydrogen
HO	alcohol hydrogen
N	amide nitrogen
NE	arylamine nitrogen
NP	ammonium nitrogen
NT	aliphatic amine nitrogen
O	amide oxygen
OH	alcohol oxygen
O2Z	carboxylate oxygen

Table 3. Stretch Parameters^a

K_b	b_o	type
340.000	1.090	HC–CT
268.000	1.529	CT–CT
317.000	1.510	CT–CA
469.000	1.400	CA–CA
367.000	1.080	HA–CA
334.643	1.101	HC–C
570.000	1.229	O–C
490.000	1.335	N–C
434.000	1.010	N–H
317.000	1.522	CT–C
337.000	1.449	N–CT
434.000	1.010	NT–H
434.000	1.010	H–NE
434.000	1.010	NP–HNP
382.000	1.448	NT–CT
481.000	1.340	NE–CA
367.000	1.471	NP–CT
320.000	1.410	OH–CT
553.000	0.945	OH–HO
450.000	1.364	OH–CA
317.000	1.522	CT–CO3
400.000	1.490	CA–CO3
656.000	1.250	O2Z–CO3

^a Units for K_b and b_o are kcal/mol/Å² and Å.

quantum chemical hydrogen bond energies and geometries. Our work on parametrizing small molecules for liquid-state simulations has demonstrated (admittedly for a relatively small set of test cases) that properly fitting accurate quantum chemical data for these quantities in the gas phase leads to good thermodynamic properties in the condensed phase, an average error less than 0.5 kcal/mol for the heat of vaporization and less than 5% for the density, comparable to what is obtained when a fixed charge force field is fit directly to experimental data. However, obtaining agreement with the quantum chemical results and having that agreement be transferable to a significant number of heterodimer complexes (as well as the homodimers employed in our liquid-state parametrization work) is a highly challenging task, and

Table 4. Bend Parameters^a

K_θ	θ_0	type
80.000	120.400	O–C–CT
48.218	123.439	O–C–HC
62.898	111.761	N–C–HC
70.000	116.600	N–C–CT
80.000	122.900	O–C–N
63.000	120.000	CA–CA–CA
35.000	120.000	HA–CA–CA
70.000	120.000	CA–CA–OH
70.000	120.000	CT–CA–CA
70.000	120.100	NE–CA–CA
85.000	120.000	CA–CA–CO3
70.000	117.000	O2Z–CO3–CT
80.000	126.000	O2Z–CO3–O2Z
80.000	120.400	CA–CO3–O2Z
33.000	107.800	HC–CT–HC
37.500	110.700	HC–CT–CT
58.350	112.700	CT–CT–CT
35.000	109.500	HC–CT–C
35.000	109.500	N–CT–HC
35.000	109.500	HC–CT–OH
50.000	109.500	OH–CT–CT
63.187	113.715	OH–CT–CA
35.000	109.500	NT–CT–HC
56.200	109.470	NT–CT–CT
35.000	109.500	NP–CT–HC
35.000	109.500	HC–CT–CO3
23.749	111.033	CT–CT–CO3
80.000	111.200	CT–CT–NP
35.000	119.800	H–N–C
35.000	120.000	H–N–H
50.000	121.900	CT–N–C
38.000	118.400	H–N–CT
50.000	118.000	CT–N–CT
35.000	113.500	H–NE–CA
35.000	109.500	HNP–NP–CT
35.000	109.500	HNP–NP–HNP
62.035	112.251	CT–NP–CT
35.000	109.500	H–NT–CT
43.600	106.400	H–NT–H
51.800	107.200	CT–NT–CT
55.000	108.500	HO–OH–CT
35.000	113.000	HO–OH–CA

^a Units for K_θ and θ_0 are kcal/mol/rad² and degrees.

one which also tests the adequacy of the nonbonded functional form.

Table 10 presents results for 140 dimers representing a large variety of functional groups. An attempt was made to include functional groups bonded to aliphatic, vinyl, and aromatic groups as well as neutral and charged forms of functionalities that are acidic or basic. In addition, for functional groups that can act as both hydrogen donors and acceptors (e.g., alcohols and amines), dimers with both types of interactions (i.e., hydrogen donating and accepting) were included. In some cases a relatively small number of molecules were used to represent various functionalities, such as those with sulfur, including thioacetone, thiazole, thiols, sulfides, sulfide anions, thioacetate anions, sulfonic acids, sulfamides, sulfoxides, sulfones, and other related functionalities. In other cases (e.g., alcohols, amines, nitro groups,

Table 5. Torsion Parameters^a

V_1	V_2	V_3	type
0.000	0.000	0.300	HC–CT–CT–HC
0.000	0.000	0.300	CT–CT–CT–HC
0.713	0.008	0.574	CT–CT–CT–CT
0.000	0.000	0.934	HC–CT–CT–OH
−0.675	−0.226	0.000	CT–CT–CT–OH
−4.034	0.000	0.000	OH–CT–CT–OH
−1.013	−0.709	0.473	HC–CT–CT–NT
6.439	−3.041	2.285	CT–CT–CT–NP
0.000	7.250	0.000	CA–CA–CA–CA
0.000	7.250	0.000	CA–CA–CA–HA
0.000	7.250	0.000	CT–CA–CA–HA
0.000	7.250	0.000	CA–CA–CA–CT
0.000	7.250	0.000	CA–CA–CA–OH
0.000	7.250	0.000	NE–CA–CA–CA
0.000	7.250	0.000	NE–CA–CA–HA
0.000	0.000	0.000	CA–CA–CT–HC
0.615	1.248	0.680	CA–CA–CT–OH
0.000	0.000	0.000	HC–CT–C–O
0.000	0.000	0.000	HC–CT–C–N
0.000	9.917	0.000	H–N–C–HC
0.000	4.900	0.000	H–N–C–O
0.000	6.089	0.000	CT–N–C–O
2.300	6.089	0.000	CT–C–N–CT
0.000	4.900	0.000	CT–C–N–H
2.834	−0.673	−0.488	CT–N–C–HC
0.000	0.000	−0.139	C–N–CT–HC
0.000	0.000	0.000	H–N–CT–HC
0.000	0.000	0.000	CT–N–CT–HC
0.000	0.000	0.400	H–NT–CT–HC
0.000	0.000	−0.271	CT–NT–CT–HC
−0.190	−0.417	0.418	CT–CT–NT–H
0.000	3.138	0.000	CA–CA–NE–H
0.000	0.000	0.261	HNP–NP–CT–HC
0.000	0.000	0.189	CT–NP–CT–HC
0.895	−0.212	0.454	CT–CT–NP–CT
0.000	0.000	0.347	CT–CT–NP–HNP
0.000	0.000	0.416	HC–CT–OH–HO
1.107	−0.243	0.471	CT–CT–OH–HO
−0.104	0.042	2.066	CA–CT–OH–HO
0.000	1.682	0.000	CA–CA–OH–HO
0.000	0.000	0.000	HC–CT–CO3–O2Z
2.858	1.055	0.000	CT–CT–CO3–O2Z
0.000	2.444	0.000	CA–CA–CO3–O2Z
0.000	7.250	0.000	CA–CA–CA–CO3

^a Units are kcal/mol.

and phosphates) many members of a functional group were included, to get an understanding of how transferable the exchange repulsion parameters were. It can be seen that the average errors in hydrogen bond energies are on the order of 0.6 kcal/mol, with a very small number of outliers displaying individual errors greater than 1 kcal/mol. The ability to adequately reproduce the binding energies of the heterodimers for a significant number of functional group classes is particularly noteworthy.

One particular class of compounds that has given a great deal of trouble in developing fixed charge force field parameters are the amines.⁴⁷ Initially, virtually all fixed charge force fields were unable to reproduce the trend in solvation free energy as methyl groups were added to

Table 6. Improper Torsion Parameters (kcal/mol)^a

V_2	type
21.0	HC–N–C–O
21.0	CT–N–C–O
2.2	CA–HA–CA–CA
2.2	CA–CA–CA–CT
2.2	CA–OH–CA–CA
2.2	CA–NE–CA–CA
21.0	O2Z–CT–CO3–O2Z
21.0	O2Z–CA–CO3–O2Z
2.0	H–C–N–H
2.0	H–C–N–CT
2.0	CT–C–N–CT
2.0	H–CA–NE–H

^a The third atom in the second column specifies the out-of-plane atom. The V_1 and V_3 terms (see eq 4) are 0.

Table 7. Lennard-Jones Parameters^a

A	B	SMARTS	description
7500.0	740.0	[#6]	all carbon
600.0	20.0	[#1] [#6]	hydrogen bonded to carbon
4000.0	900.0	[#7]	all nitrogen
3500.0	950.0	[#8]	all oxygen

^a Units for A and B are \AA^{12} kcal/mol and \AA^6 kcal/mol (see eq 5). Parameter assignments are made according to the SMARTS pattern.

ammonia; we attributed this problem to gross deviations of force field amine–water binding energies from accurate quantum chemical data.⁴² Subsequently, Jorgensen and co-workers showed that modification of the model (most importantly the charge distributions on primary, secondary, and tertiary amine nitrogens) to achieve better agreement with the quantum chemical hydrogen bonding data results in qualitatively improved hydration free energy trends;⁴³ however, this required ad hoc adjustment of the charge parameters, which were not derivable from for example ESP-fitting data. It is gratifying to note that in Table 10, the binding energies of the various amines with water accurately reproduce quantum chemical data, using the standard fitting protocols that we apply to all of the compounds in our training set. This demonstrates that the functional form and parametrization protocol we are employing is powerful enough to handle a very challenging case, for which fixed charge force fields failed qualitatively in the past.

To further assess the accuracy of PFF interaction energies, a dimer set consisting of various combinations of water, methanol, dimethyl ether, acetone, formamide, acetamide, *N*-methylformamide, and *N*-methylacetamide was constructed, and both the cis and trans conformers of the latter two molecules were included. The PFF and (high level) ab initio binding energies for this set are compared in Table 11, wherein it can be seen that the rms deviation is 0.6 kcal/mol, which is the same as obtained in Table 10. The binding energy results in Table 10 correspond almost exclusively to binding with water, while Table 11 indicates the same level of accuracy for binding to 7 other molecules, including amides, which are the building blocks for proteins. Binding energy comparisons for 182 distinctive dimer structures are presented in Tables 10 and 11.

Agreement for hydrogen bond lengths in some cases appears somewhat problematic, on the order of 0.1 Å. However, errors of this magnitude typically occur when the hydrogen bond is weak and the potential energy surface relatively flat. In such cases, the exact location of the minimum is not critical for obtaining reasonable predictions of key condensed phase properties, as our liquid-state simulation results indicate. Of course, individual cases may still be cause for concern; this can be ascertained, however, only by deploying the relevant parameters in a realistic condensed phase application.

C. Construction of a Complete PFF Gas-Phase Parametrization for a New Molecule. To assemble a PFF parameter set for a new molecule, the following steps must be executed:

(1) Atom typing software is used to assign atom types to each atom of the molecule.

(2) Quantum chemical calculations of the electrostatic potential at the LMP2/cc-pVTZ(-f) level are used to generate the permanent charge parameters (i.e. atomic point charges and dipoles) specific to the particular molecule in question. An automated least-squares fitting procedure is used to generate charges and permanent dipoles that reproduce the ab initio electrostatic potential. Multiple conformations can be used to simultaneously fit permanent charges and dipoles, when desired. Ordinarily, the fit of data from multiple conformations has not been found to be necessary.

(3) Using the atom types, the program assigns parameters for atomic polarizability, nonbonded atom–atom pair interactions, stretches, bends, and torsions.

III. Self-Consistent Reaction Field Continuum Solvation Methodology Based on Solution of the Poisson–Boltzmann Equation

In a continuum solvation model, aqueous solvent is represented as a continuum of dielectric 80. Solution of the Poisson–Boltzmann (PB) equation²⁷ provides the electric field in all of space, including the reaction field of the solvent, for a fixed solute charge distribution and dielectric boundary. In previous publications, we have described our PB solver, PBF, which computes not only solvation free energies but also analytical gradients of the solvation free energy, for an arbitrary solute geometry, using finite element methods.^{28–30,44,45} A Gaussian surface, constructed based on atomic dielectric radii, is employed to describe the dielectric boundary. The present software package utilizes PBF as an integral component of the solvation model.

As is well-known, in a continuum model the reaction field of the solvent can be exactly represented as a distribution of charge on the dielectric surface (surface charge). Furthermore, the surface charge is readily computed from the solution to the PB equation as proportional to the discontinuous jump in the electrostatic potential across the dielectric boundary in the normal direction. These surface charges can then be used to represent the electric field due to the solvent, which induces additional polarization in the solution, which in turn can be computed via the polarizable force field.

In fact, the problem of determining the solute polarization and reaction field for a given solute configuration using a

Table 8. Exponential Repulsion and Polarizability Parameters^a

σ	C	α	SMARTS	description
0.3209	10417.0	1.22	[CX4]	CT alkyl carbon
0.25	1500000.0	1.49	[c]	CA arene carbon
0.25	300000.0	0.83	[CX3H](=O)[#7X3H2]	C formamide
0.25	500000.0	0.83	[CX3](=O)[#7X3]	C amide
0.25	10000.0	0.815	[CX3](=[O])[O-]	CO3 carboxylate anions
0.2385	5563.3	0.25	[#1]C	HC alkyl hydrogen
0.2385	2000.0	0.39	[#1][c]	HA arene hydrogen
0.2385	2000.0	0.25	[#1][CX3;H](=O)[#7]	HC amides
0.20	10.0	0.24	[#1][N]~[*]=O	H amides
0.20	160.0	0.24	[#1][N]	H amines
	0.0	0.22	[#1][OX2]	HO alcohol
0.20	10.0	0.24	[#1][#7X4+]	HNP ammonium cations
0.28	150000.0	1.36	[NX3H2][CX3](=O)[#1]	N formamide
0.28	200000.0	1.36	[NX3][CX3H2]=O	N acetamide
0.28	100000.0	1.085	[NX3H][CX3H]=O	N <i>N</i> -methylformamide
0.28	160000.0	1.15	[NX3H][CX3]=O	N <i>N</i> -methylacetamide
0.28	90000.0	0.97	[NX3H0][CX3]=O	N <i>N,N</i> -dimethylacetamide
0.28	70000.0	1.33	[NX3]	NT aliphatic amine
0.28	70000.0	1.42	[NX3]-[a]	NE arylamine
0.28	49000.0	0.44	[NX4+]	NP ammonium cations
0.253	320000.0	0.91	O=[CX3][#7X3H2]	O primary amide
0.253	450000.0	0.91	O=[CX3][#7X3H]	O secondary amide
0.253	700000.0	0.91	O=[CX3][#7X3]	O tertiary amide
0.233	700000.0	0.77	[OX2H]	OH alcohol
0.253	520000.0	0.97	[OX1]~[CX3]~[OX1]	O2Z carboxylate anions

^a Parameter assignments are made according to the SMARTS pattern. The symbolic atom types in the last column are included only for the purpose of providing an additional aid to understanding the parameter assignments. Units are Å, kcal/mol, and Å³ for σ , C, and α (see eqs 5 and 9).

polarizable force field is isomorphic to the same problem when the solute is represented by a quantum mechanical Hamiltonian. The latter is a problem we have already addressed, and the solution—a self-consistent reaction field (SCRf) methodology—is described in detail in previous publications.^{28,29} Briefly, one first computes the gas-phase charge distribution of the solute, then solves the PB equation using this charge distribution, calculates the surface charge, and then determines the new charges on the solute by solving the solute equations—either quantum mechanical or those of the PFF—in the field of the surface charges. This process is iterated until self-consistency is achieved.

To develop an SCRf methodology for PFF, one simply replaces the quantum chemical Hamiltonian with the PFF Hamiltonian. The principal additional complication in the present case is the presence of dipoles, in addition to point charges, in the PFF functional form, but this is a technical issue that is easily addressed (e.g., by treating each dipole as closely spaced point charges). More challenging is making the methodology efficient for large systems; in the QM case, the SCRf methodology has principally been applied to systems of fewer than 200 atoms, whereas in the present case it must be made to converge for thousands of atoms, with an acceptable level of noise in the gradient. There are similarly performance issues associated with having to solve the PB equation numerous times for a large system, calculate gradients, etc. We have developed a considerable amount of new technology, which will be discussed in more detail elsewhere, to accomplish this task. A key component is that the PB forces are evaluated infrequently, as they vary

relatively slowly with geometry, to reduce the computation time. We have also designed the methodology to enable specifying frozen regions of the protein. This is essential for practical applications in which one wishes to focus on the ligand and nearby active site residues, for reasons of both efficiency and reduction of random noise in the total energy.

To have any hope of achieving accurate results for a dielectric continuum methodology, it is necessary to parametrize the dielectric radii as well as a nonpolar (cavity) term representing the energetics associated with immersing the solute in water in the absence of charge on the solute (but including the van der Waals interaction between solute and solvent).^{46,47} We use the nonpolar functional form developed by Levy and co-workers^{46,47} which has been shown to be significantly more accurate than a simple surface area model for the nonpolar term.

The solvation free energy model we used for the PFF/PBF/NP parametrization can be described by the following equations⁴⁶

$$\Delta G_{\text{solv}} = \Delta G_{\text{elec}} + \Delta G_{\text{NP}} \quad (17)$$

$$\Delta G_{\text{NP}} = \sum_{i=1}^N [\gamma_i A_i + \alpha_i S_i] \quad (18)$$

$$S_i = 1/\{1 + B_i \exp[-12.0 (1.5/B_i - 0.4)]/1.5\} \quad (19)$$

where ΔG_{solv} is the total solvation free energy; ΔG_{elec} is the electrostatic solvation free energy, including the free energy components of both the reaction field of the continuum

Table 9. PFF/PBF/NB Solvation Parameters (See Eqs 18 and 19), Which Are the Reaction Field Radii (R^{RF} in Å), Nonpolar Cavity Radii (R^{C} in Å), Surface Tension Coefficient (γ in kcal/mol/Å²), and vdW Correction Coefficient (α in kcal/mol)

R^{RF}	R^{C}	γ	α	SMARTS	description
2.050	1.750	0.024713	-1.018973	[CX4]	alkyl C
2.250	1.775	0.016117	-0.885767	[c]	arene C
2.050	1.875	0.012244	-0.466651	[CX3](=O)[NX3;H2]	primary amide
2.050	1.875	0.012244	-0.466651	[CX3](=O)[NX3]	amide
1.900	1.650	0.012244	-0.466651	[CX3](=O)[O-]	carboxylate
1.250	1.250	0.001904	0.513867	[#1][#6]	alkyl H
1.555	1.210	0.016117	0.548275	[#1][c]	aryl H
1.250	1.250	0.001904	0.513867	[#1][CX4][NX3]C=O	in amides
1.250	1.250	0.031394	-0.308647	[#1][CX4][NX3]	in amines
1.250	1.000	0.027081	0.206693	[#1][#7]	amide/amine H
1.250	1.000	0.001904	-0.100305	[#1][#8]	alcohol H
1.000	1.000	0.072353	-0.707296	[#1][#7;+]	ammonium H
2.000	1.625	0.020791	-1.020601	[NX3][CX3]=O	amide N
2.000	1.625	0.020791	-1.020601	[NX3;H2][CX3]=O	primary amide
1.955	1.650	0.010187	-1.674489	[NX3;H2][CX4]	primary amine
1.855	1.650	0.010187	-1.674489	[NX3;H]([CX4])[CX4]	secondary amine
1.830	1.650	0.010187	-1.674489	[NX3]([CX4])([CX4])([CX4])	tertiary amine
1.755	1.650	0.010187	-1.674489	[NX3;R]([@CX4])@[CX4]	NT amine N
2.215	1.650	0.010187	-1.674489	[NX3]c	arylamine N
2.115	1.625	0.010187	-1.909777	[#7X4+]	ammonium N
2.025	1.625	0.010187	-1.255859	[NX4+;H1]([CX4])([CX4])[CX4]	ammonium
2.025	1.625	0.010187	-3.749130	[NX4+;H0]([CX4])([CX4])[CX4]	ammonium
2.025	1.625	0.010187	-1.909777	[NX4+][c]	arylammonium
1.685	1.480	0.010211	-0.466651	[OX1]=[CX3][NX3]	amide O
1.855	1.480	0.010211	-0.466651	[OX1]=C[NX3;H2]	primary amide
1.625	1.560	0.024713	-0.827593	[OX2H]	alcohol O
1.725	1.535	0.024713	-0.827593	[OH][CX4][CX4][OH]	diol O
1.625	1.535	0.024713	-0.827593	[OX2H]c	phenol O
1.600	1.480	0.010211	-0.606651	[OX1]~[#6]~[OX1]	carboxylate O
1.550	1.480	0.010211	-0.606651	[OX1]~[#6](~[OX1])c	arylcarboxylate

solvent and the polarization of the solute molecule. ΔG_{NP} is the nonpolar (NP) solvation free energy; γ_i , A_i , α_i , and S_i are the surface tension coefficient, the solvent accessible surface area, the vdW/correction coefficient, and the switching function for atom i , respectively. B_i is the Born radius of atom i , which is defined by our Surface Generalized Born (SGB)⁴⁸ solvent model. The purpose of the switching function is to switch off the van der Waals interaction and hydrogen bond interaction of the solute atom with the solvent as the atom is buried deeper and deeper in the solute molecule.^{46,47} The Born radius is used as a measure of how deeply an atom is buried in a molecule. The advantage of using the Born radius, rather than using the distance from the surface, is that the Born radius takes into account the overall geometry/cavity shape of the whole solute molecule.

The training set for the solvation parametrization includes 147 small molecules. The molecules were picked to cover all the typical functional groups and chemical varieties for which the experimental solvation free energies can be found in the literature.

The basic protocol of the parametrization is fitting the molecules class by class, starting with the alkanes. The NP solvation energies and the corresponding parameters, which were originally fitted for the fixed charge SGB solvent model with the same set of molecules, were taken as the initial guess of the NP component of the current PFF/PBF/NP param-

etrization. Then, the total computed solvation energies were fitted to the experimental data by varying the PBF dielectric radii. Finally, the NP parameters and PBF radii were further adjusted in an iterative fashion. For the sake of the parametrization convenience, the cavity radii for the NP term have been fixed to be the same as the OPLSAA vdW radii. In this way, the electrostatic and the NP components of the solvation energies can be adjusted independently. Moreover, the same switching function used for the SGB model (as described by eq 19) was applied with no modification. Further optimization of the switching function will be considered in our future development. Table 9 lists the final solvation parameters for amides, amines, alcohols, carboxylate anions, and ammonium cations.

Table 12 presents experimental and calculated solvation free energies for 147 small molecule solutes, as computed by the final optimized SCRf model. Table 13 presents the summary of the error analysis of the fitted solvation energies by functional group classes. The average unsigned error of 0.26 kcal/mol for 126 neutral molecules and 0.35 kcal/mol for the whole training set are comparable to that obtained for a fixed charge model for the same set of solutes. Parameters are assigned based on the atom types classified by SMARTS pattern (e.g., see Table 9) based on chemical functional groups, and these parameters can then be used to describe an arbitrary organic compound using the atom type

Table 10. Comparison of 140 Binding Energies (kcal/mol) Calculated by Quantum Mechanics and by PFF^a

dimer	binding energy (kcal/mol)			hydrogen bonds ^c
	TZ/QZ ^b	PFF	diff	
Alcohols				
methanol homodimer	−5.79	−5.66	0.13	OH–HO..OH
methanol	−4.95	−5.07	−0.12	OH–HO..OW
phenol	−6.85	−6.17	0.69	OH–HO..OW
vinyl alcohol	−6.65	−6.21	0.44	OH–HO..OW
ethanol	−4.90	−4.86	0.04	OH–HO..OW
<i>tert</i> -butyl alcohol	−4.98	−5.46	−0.48	OH–HO..OW
cyclohexanol	−4.78	−5.20	−0.42	OH–HO..OW
benzyl alcohol	−7.09	−5.93	1.16	OH–HO..OW
ethylene glycol	−5.66	−5.99	−0.34	OH–HO..OW
<i>p</i> -nitrophenol	−7.98	−7.70	0.29	OH–HO..OW
<i>m</i> -nitrophenol	−8.02	−7.47	0.55	OH–HO..OW
methanol	−5.49	−5.31	0.18	OW–HW..OH
phenol	−4.16	−4.40	−0.24	OW–HW..OH
vinyl alcohol	−3.98	−3.88	0.10	OW–HW..OH
ethanol	−5.51	−5.32	0.20	OW–HW..OH
<i>tert</i> -butyl alcohol	−5.99	−5.66	0.33	OW–HW..OH
cyclohexanol	−6.10	−5.91	0.18	OW–HW..OH
benzyl alcohol	−4.77	−5.28	−0.50	OW–HW..OH
ethylene glycol	−5.77	−5.67	0.11	OW–HW..OH
<i>p</i> -nitrophenol	−3.21	−3.60	−0.39	OW–HW..OH
rms =0.43				
Ethers and Esters				
dimethyl ether	−5.18	−5.46	−0.28	OW–HW..OS
methylvinyl ether	−4.42	−4.56	−0.14	OW–HW..OS
tetrahydrofuran	−6.54	−7.48	−0.93	OW–HW..OS
methylphenyl ether	−3.98	−4.70	−0.72	OW–HW..OS
methylformate	−2.93	−3.28	−0.35	OW–HW..OS
rms = 0.57				
Aldehydes, Ketones, Esters, and Urea				
methylformate	−5.74	−6.65	−0.91	OW–HW..O
formaldehyde	−5.16	−4.23	0.93	OW–HW..O
acetone	−5.88	−5.60	0.28	OW–HW..O
propiolactone	−6.54	−5.54	1.00	OW–HW..O
acrolein	−5.90	−5.55	0.35	OW–HW..O
acetophenone	−5.43	−5.55	−0.13	OW–HW..O
butanal	−5.39	−5.40	−0.01	OW–HW..O
urea	−9.91	−9.15	0.76	OW–HW..O
rms = 0.66				N–H..OW
Carboxylic Acids				
acetic acid	−9.47	−9.50	−0.03	OW–HW..O
trans,trans-oxalic acid	−10.21	−8.61	1.59	OW–HW..O
cis,cis-oxalic acid	−4.01	−5.13	−1.12	OW–HW..O
benzoic acid	−9.55	−9.45	0.10	OW–HW..O
rms = 0.98				OH–HO..OW
Oxide Anions				
methoxide anion	−21.17	−21.45	−0.28	OW–HW..OM
vinyloxide anion	−13.15	−13.46	−0.31	OW–HW..OM
<i>N</i> -methylhydroxamate anion	−15.62	−15.46	0.16	OW–HW..OM
acetate anion	−18.60	−18.71	−0.11	OW–HW..O2Z
rms = 0.23				OW–HW..N
Nitro and Nitrite Groups				
nitrobenzene	−3.63	−4.23	−0.60	OW–HW..ON
nitrobenzene	−4.35	−4.63	−0.28	OW–HW..ON
<i>p</i> -nitrophenol	−3.65	−4.43	−0.77	OW–HW..ON
<i>m</i> -nitrophenol	−3.73	−4.13	−0.40	OW–HW..ON
<i>m</i> -nitroaniline	−3.69	−4.34	−0.65	OW–HW..ON
nitromethane	−3.28	−3.39	−0.12	OW–HW..ON
methylnitrite	−2.44	−3.03	−0.59	OW–HW..ON
				OW–HW..ON

Table 10 (Continued)

dimer	binding energy (kcal/mol)			hydrogen bonds ^c	
	TZ/QZ ^b	PFF	diff		
Nitro and Nitrite Groups					
nitroethylene	-3.31	-3.75	-0.44	OW-HW..ON	OW-HW..ON
nitrosomethane	-3.68	-3.21	0.47	OW-HW..ON	
nitroethylene	-5.28	-4.15	1.13	OW-HW..ON	CM-HC..OW
rms = 0.61					
Aromatic Heterocycles with N and O					
imidazole	-5.94	-6.55	-0.60	NA5-H..OW	
pyrrole	-5.22	-5.59	-0.37	NA5-H..OW	
pyrazole	-7.83	-6.57	1.26	NA5-H..OW	OW-HW..N5A
imidazole cation	-16.75	-16.94	-0.19	N5P-HNP..OW	
pyridine	-6.26	-6.10	0.16	OW-HW..NA	
pyrimidine	-5.60	-5.77	-0.17	OW-HW..NA	
tetrazole anion	-16.09	-16.26	-0.17	OW-HW..N5M	OW-HW..N5M
imidazole	-5.15	-6.04	-0.90	OW-HW..N5B	
oxazole	-4.55	-4.89	-0.34	OW-HW..N5B	
1,2,4-oxadiazole	-5.12	-4.10	1.02	OW-HW..N5B	
isoxazole	-4.16	-3.91	0.25	OW-HW..N5A	
1,2,4-oxadiazole	-3.14	-3.28	-0.14	OW-HW..N5A	
furan	-2.65	-2.71	-0.05	OW-HW..OA	
rms = 0.57					
Amines					
ammonia	-6.11	-6.10	0.02	OW-HW..N3	
methylamine	-6.62	-7.30	-0.68	OW-HW..NT	
dimethylamine	-6.81	-6.38	0.43	OW-HW..NT	
trimethylamine	-7.31	-6.98	0.33	OW-HW..NT	
tert-butylamine	-7.33	-7.53	-0.20	OW-HW..NT	
aniline	-5.40	-5.21	0.19	OW-HW..NE	
dimethylamine	-2.67	-3.30	-0.63	NT-H..OW	
vinylamine	-3.91	-3.73	0.18	NE-H..OW	
p-nitroaniline	-5.28	-5.08	0.19	NE-H..OW	
m-nitroaniline	-5.68	-5.59	0.09	NE-H..OW	
p-cyanoaniline	-5.20	-4.79	0.41	NE-H..OW	
rms = 0.37					
Imines					
formamidine	-10.32	-9.75	0.57	OW-HW..NI	
formaldehydeimine	-6.16	-5.61	0.55	OW-HW..NI	
guanidine	-7.00	-10.66	-3.66 ^d	OW-HW..NE	NE-H..OW
butadiene Schiff base	-6.43	-7.51	-1.09	OW-HW..NI	
butadiene Schiff base	-3.40	-3.42	-0.02	NI-H..OW	
azomethane	-7.75	-7.55	0.20	OW-HW..NN	
rms = 1.59					
Imine Cations					
guanidinium cation	-17.18	-16.61	0.57	NG-HNP..OW	
formamidine cation	-16.20	-16.22	-0.02	NG-HNP..OW	
formamidine cation	-18.13	-17.92	0.20	NG-HNP..OW	NG-HNP..OW
formaldehydeimine cation	-19.76	-19.86	-0.10	NIP-HNP..OW	
rms = 0.31					
Nitriles					
dimethyldiazomethane	-2.82	-3.41	-0.59	OW-HW..NZT	
methyl azide	-4.01	-3.23	0.78	OW-HW..NZT	
acetonitrile	-4.76	-4.77	-0.01	OW-HW..NZ	
rms = 0.56					
N-Hydroxyl					
methylethylhydroxylamine	-8.37	-8.24	0.13	OH-HO..OW	OW-HW..NT
N-methylhydroxamic acid	-7.29	-7.09	0.20	OH-HO..OW	OW-HW..N
rms = 0.17					

Table 10 (Continued)

dimer	binding energy (kcal/mol)			hydrogen bonds ^c	
	TZ/QZ ^b	PFF	diff		
Quaternary Ammonium Salts					
methylammonium cation	−18.49	−18.77	−0.28	NP–HNP..OW	
dimethylammonium cation	−17.12	−16.83	0.30	NP–HNP..OW	
rms = 0.29					
Fluorides					
fluoromethane	−3.51	−3.17	0.34	OW–HW..F	
1,1,1-trifluoromethane	−2.81	−3.01	−0.20	OW–HW..F	OW–HW..F
vinylfluoride	−2.90	−2.88	0.02	OW–HW..F	
rms = 0.23					
Chlorides					
1-chloropropane	−4.14	−3.67	0.47	OW–HW..Cl	
1,1,1-trichloromethane	−2.72	−3.03	−0.32	OW–HW..Cl	OW–HW..Cl
vinyl chloride	−2.56	−2.73	−0.16	OW–HW..Cl	
rms = 0.34					
Phosphates and Phosphines					
methyl phosphate	−12.60	−13.17	−0.57	OW–HW..O2Z	OS–HO..OW
phosphineoxide	−6.61	−6.86	−0.24	OW–HW..O2Z	
trimethylphosphineoxide	−9.29	−8.84	0.45	OW–HW..O2Z	
CH ₃ –CH ₂ –PO ₂ –CH ₃ anion	−17.89	−17.87	0.02	OW–HW..O2Z	OW–HW..O2Z
CH ₃ –NH–PO ₂ –CH ₃ anion	−17.80	−17.43	0.37	OW–HW..O2Z	OW–HW..O2Z
CH ₃ –NH–PO ₂ –CH ₃ anion	−16.57	−17.30	−0.74	OW–HW..O2Z	OW–HW..NX
CH ₃ –O–PO ₂ –CH ₃ anion	−17.89	−17.25	0.63	OW–HW..O2Z	OW–HW..O2Z
phosphoric acid	−12.80	−12.30	0.50	OW–HW..O2Z	OS–HO..OW
dihydrogenphosphate anion	−15.30	−15.98	−0.68	OW–HW..O2Z	OW–HW..OS
dihydrogenphosphate anion	−16.89	−16.58	0.30	OW–HW..O2Z	OW–HW..O2Z
hydrogenphosphate dianion	−23.48	−23.74	−0.26	OW–HW..O2Z	OW–HW..O2Z
methylphosphine	−3.40	−3.21	0.19	OW–HW..PR	
trimethylphosphine sulfide	−7.75	−7.78	−0.02	OW–HW..ST	
rms = 0.45					
Molecules with Sulfur					
hydrogensulfide homodimer	−1.63	−1.69	−0.06	SH–HS..SH	
hydrogensulfide	−2.84	−2.59	0.25	SH–HS..OW	
thiomethanol	−3.00	−2.55	0.45	SH–HS..OW	
hydrogensulfide	−2.81	−3.22	−0.42	OW–HW..SH	
thiomethanol	−3.79	−4.39	−0.61	OW–HW..SH	
dimethyl sulfide	−5.80	−5.27	0.53	OW–HW..S	
thioacetone	−3.70	−3.56	0.14	OW–HW..S=	
thiophene	−3.46	−3.67	−0.21	OW–HW..SA	
thiazole	−6.99	−6.93	0.06	OW–HW..N5B	
isothiazole	−2.70	−2.86	−0.16	OW–HW..N5A	
methyl sulfide anion	−10.42	−10.53	−0.11	OW–HW..SM	
vinylsulfide anion	−14.48	−14.69	−0.22	OW–HW..SM	OW–HW..CM
thioacetate anion	−14.18	−14.15	0.03	OW–HW..SM2	OW–HW..SM2
CH ₃ –NH–SO ₂ –phenyl	−8.41	−8.40	0.01	OW–HW..OY	
CH ₃ –NH–SO ₂ –CH ₃	−9.86	−9.11	0.76	OW–HW..OY	
CH ₃ –CO–NH–SO ₂ –CH ₃	−10.05	−9.72	0.33	OW–HW..OY	NS–H..OW
methanesulfonic acid	−12.28	−12.80	−0.52	OW–HW..OY	OS–HO..OW
sulfamide	−8.81	−8.71	0.10	OW–HW..OY	NS–H..OW
dimethyl sulfoxide	−9.15	−9.23	−0.08	OW–HW..OZ	
CH ₃ –SO(NH)(CH ₃)	−7.52	−7.48	0.05	OW–HW..OY	NST–H..OW
CH ₃ –SO ₂ –N–CH ₃ anion	−17.04	−17.75	−0.71	OW–HW..OY	OW–HW..NM
methylsulfonate anion	−14.87	−15.21	−0.33	OW–HW..OY	OW–HW..OY
sulfate dianion	−18.14	−18.18	−0.04	OW–HW..OY	OW–HW..OY
dimethyl sulfone	−7.40	−7.92	−0.51	OW–HW..OY	
CH ₃ –NH–SO ₂ –CH ₃	−8.59	−9.56	−0.97	OW–HW..OY	NS–H..OW

Table 10 (Continued)

dimer	binding energy (kcal/mol)			hydrogen bonds ^c	
	TZ/QZ ^b	PFF	diff		
Molecules with Sulfur					
CH ₃ –CO–NH–SO ₂ –CH ₃	–6.75	–7.22	–0.47	OW–HW..OY	OW–HW..O
CH ₃ –SO ₂ –N–CH ₃ anion	–15.34	–15.47	–0.13	OW–HW..OY	OW–HW..OY
rms = 0.40					
overall rms			0.58		

^a All dimers are heterodimers with water, except for the methanol and hydrogen sulfide homodimers. ^b The TZ/QZ results are binding energies extrapolated to the basis set limit from LMP2/cc-pVTZ(-f) and LMP2/cc-pVQZ(-g) calculations at dimer structures optimized by LMP2/cc-pVTZ(-f). ^c Hydrogen bonds are indicated in the last column, using OW and HW to indicate the oxygen and hydrogen in water and using OPLS2003 symbolic atomtypes for all other atoms. As an example, OH–HO..OW indicates an alcohol oxygen donating a hydrogen to an oxygen in water, while for OW–HW..OH water donates a hydrogen to the alcohol oxygen. ^d The amino groups are puckered in the LMP2/cc-pVTZ(-f) optimized structure of guanidine, while they are planar in the PFF structure. As a result, PFF is no longer able to form a OW–HW..NE hydrogen bond, and PFF gives a different optimized structure. If the improper torsion potential is adjusted to allow amino puckering in guanidine, PFF will not have a problem getting the correct dimer structure and binding energy.

assignment algorithms. We do not yet have data that validates the accuracy of the solvation model in protein and other complex applications.

IV. Modeling of Proteins and Protein–Ligand Complexes

A. Protein Force Field. Construction of a protein PFF represents a special case of the general problem of constructing a PFF for a general organic molecule. Thus, the basic technology is similar to that discussed above in section II, although some rules are required for assembling the force field description of a long polymer from parameters for individual amino acids (see ref 16 for details). Blocked dipeptides are used as model molecules for generating torsional parameters. A large database of rotamer states, which are identical to that employed in developing our fixed charge protein force field, is employed to generate the potential energy surfaces for torsional fitting. The set of dipeptide and alanine tetrapeptide conformers in Tables 14 and 15 were described elsewhere.^{16,38} The alanine dipeptide minima were chosen by examination of the complete ϕ/ψ map, and all of the alanine di- and tetrapeptide minima are listed elsewhere.⁴⁹ For all other dipeptides a molecular mechanics conformational search was followed by further HF/6-31G** geometry optimizations with Jaguar. The final values of the quantum mechanical conformational energies were determined with single-point LMP2/cc-pVTZ(-f)//HF/6-31G** Jaguar calculations. These calculations were performed without solvent for all electrostatically neutral peptides (in Table 14).

For the charged residues (Table 15), a somewhat different technique was employed. Gas-phase optimizations could not be used to obtain the structures, since a geometry with a favorable gas-phase energy could have a significantly higher relative energy in aqueous solution for the charged species. This is why liquid-phase SCRF HF/6-31G** optimizations were used to find the solvated minimum energy structures. They were followed by gas-phase, single point LMP2/cc-pVTZ(-f) calculations to find the final target energies. Thus, on one hand, the part of the conformational space relevant in aqueous solutions was sampled, and, on the other hand, the final quantum mechanical energies were determined in gas phase and can be compared with the gas-phase PFF results.

In Tables 14 and 15 we summarize the average RMSDs achieved by PFF for relative conformational energies of the various rotamer states, as compared to quantum chemical data generated at the LMP2/cc-pVTZ(-f) level, for the 20 naturally occurring amino acids. The average RMSD of about 0.6 kcal/mol is comparable to that achieved for our small molecule training set discussed in section II above, and it is similar to what is obtained when a fixed charge model is used. Moreover, the average error for the charged residues is ca. 1.5 times smaller than with the fixed charge OPLS-AA/L force field. This suggests that the polarizable force field does better than OPLS-AA in reproducing energetics of systems with strong electrostatic interactions, such as, for example, charged protein residues. To reduce errors beyond this point, further work likely has to be done to improve the valence part of the force field (new stretch and bend parameters, along with cross terms coupling stretches, bends, and torsions, etc.).

B. Minimization Protocol. As an initial deployment of PFF in studying protein–ligand complexes, we have developed a protocol for minimizing such complexes in both the gas phase and in continuum solvent. Minimization of the protein in solution, ligand in solution, and protein–ligand complex in solution allows a crude estimator, which may correlate with the binding free energy to be obtained; as was discussed above, these energy differences may also be useful as a component of a more sophisticated approach. We do not attempt to use the methodology to address the binding free energy problem in the present paper; rather, the objective is to demonstrate that the minimization protocol is robust with regard to parameter assignment and generation for the ligands (which requires, of course, deploying the full protocol for parameter generation described above), does not undergo polarization catastrophes, and produces reasonable RMSDs for the proteins and protein–ligand complexes. We also are able to present an initial calibration of the required CPU time for these computations, although this should not be regarded as highly optimized.

We have carried out a number of initial tests of the protein PFF, for example minimizing protein structures starting from the crystal structure and computing the RMSD of the final result as compared to experiment. In carrying out such minimizations, we begin by minimizing the protein using a

Table 11. Comparison of Binding Energies Calculated by Quantum Mechanics and PFF

dimer ^a	binding energy ^b (kcal/mol)			hydrogen bonds	
	TZ/QZ	PFF	diff		
Amide/Amide Dimers					
FOR/FOR	−14.23	−14.61	−0.38	N–H..O	N–H..O
ACE/ACE	−13.92	−14.49	−0.57	N–H..O	N–H..O
cNMF/cNMF	−15.55	−15.16	0.39	N–H..O	N–H..O
cNMA/cNMA	−14.97	−13.90	1.07	N–H..O	N–H..O
FOR/FOR	−7.05	−8.26	−1.21	N–H..O	
tNMA/tNMA	−7.95	−8.91	−0.97	N–H..O	
FOR/FOR	−9.62	−8.57	1.05	N–H..O	C–HC..O
FOR/FOR	−5.23	−5.00	0.23	C–HC..O	C–HC..O
FOR/FOR	−3.90	−4.79	−0.89	no H-bond (stacked)	
ACE/ACE	−5.35	−6.13	−0.78	no H-bond (stacked)	
tNMA/tNMA	−5.98	−7.08	−1.10	no H-bond (stacked)	
Water Dimer					
H2O/H2O	−4.83	−4.81	0.02	OW–HW..OW	
Amide/Water Dimers					
FOR/H2O	−4.97	−5.09	−0.13	N–H..OW	
ACE/H2O	−4.96	−4.56	0.40	N–H..OW	
tNMF/H2O	−4.98	−5.52	−0.53	N–H..OW	
tNMA/H2O	−5.20	−5.07	0.12	N–H..OW	
H2O/FOR	−5.82	−5.82	0.00	OW–HW..O	
H2O/ACE	−7.50	−7.47	0.03	OW–HW..O	
H2O/tNMF	−7.45	−7.66	−0.21	OW–HW..O	
H2O/tNMA	−7.42	−8.26	−0.85	OW–HW..O	
H2O/ACE	−6.92	−7.54	−0.63	OW–HW..O	CT–HC..OW
H2O/cNMA	−6.95	−6.89	0.07	OW–HW..O	CT–HC..OW
H2O/FOR	−9.32	−8.30	1.02	N–H..OW	OW–HW..O
H2O/ACE	−9.38	−8.84	0.53	N–H..OW	OW–HW..O
cNMA/H2O	−9.48	−8.33	1.14	N–H..OW	OW–HW..O
Dimers with Methanol					
MEOH/MEOH	−5.79	−5.66	0.13	OH–HO..OH	
H2O/MEOH	−5.50	−5.31	0.19	OW–HW..OH	
MEOH/H2O	−4.95	−5.07	−0.12	OH–HO..OW	
FOR/MEOH	−5.69	−5.92	−0.23	N–H..OH	
ACE/MEOH	−5.64	−5.66	−0.02	N–H..OH	
tNMA/MEOH	−6.11	−6.10	0.01	N–H..OH	
MEOH/tNMA	−7.68	−8.94	−1.27	OH–HO..O	
MEOH/FOR	−9.84	−9.31	0.53	N–H..OH	OH–HO..O
MEOH/ACE	−9.60	−9.70	−0.10	N–H..OH	OH–HO..O
cNMA/MEOH	−9.86	−9.37	0.49	OH–HO..O	N–H..OH
Dimers with Dimethyl Ether					
H2O/DME	−5.18	−5.46	−0.28	OW–HW..OS	
MEOH/DME	−5.59	−6.01	−0.42	OH–HO..OS	
FOR/DME	−7.91	−6.99	0.93	N–H..OS	
ACE/DME	−5.86	−6.35	−0.49	N–H..OS	
tNMA/DME	−6.08	−7.01	−0.94	N–H..OS	
cNMA/DME	−7.49	−6.87	0.62	N–H..OS	
Dimers with Acetone					
H2O/ACETONE	−5.88	−5.60	0.28	OW–HW..O	
MEOH/ACETONE	−6.17	−6.20	−0.03	OH–HO..O	
FOR/ACETONE	−8.29	−8.34	−0.05	N–H..O	
ACE/ACETONE	−5.63	−6.25	−0.62	N–H..O	
tNMA/ACETONE	−5.91	−6.84	−0.93	N–H..O	
cNMA/ACETONE	−8.37	−8.18	0.19	N–H..O	
rms deviation			0.63		

^a This dimer set was constructed from combinations of water (H2O), methanol (MEOH), dimethyl ether (DME), acetone, formamide (FOR), acetamide (ACE), *trans*- and *cis*-*N*-methylformamide (tNMF and cNMF), and *trans*- and *cis*-*N*-methylacetamide (tNMA and cNMA). ^b The QM binding energies were determined from TZ/QZ binding energy extrapolations, as described in Table 10.

Table 12. Computed PFF/PBF/NP and Experimental Solvation Free Energies (kcal/mol) of 147 Small Molecules

molecule	expt	PFF/PBF/NP	diff	molecule	expt	PFF/PBF/NP	diff
Alkanes							
methane	1.91	1.78	0.13	2-methylbutane	2.38	2.36	0.02
ethane	1.83	1.90	-0.07	2-methylpentane	2.52	2.55	-0.03
propane	1.96	2.06	-0.10	2,2-dimethylbutane	2.59	2.65	-0.06
butane	2.08	2.18	-0.10	cyclopropane	0.75	0.82	-0.07
isobutane	2.32	2.26	0.06	cyclopentane	1.20	1.11	0.09
pentane	2.33	2.32	0.01	cyclohexane	1.23	1.20	0.03
Alkenes							
ethylene	1.27	1.26	0.01	<i>trans</i> -2-pentene	1.34	1.36	-0.02
1-propene	1.27	1.28	-0.01	cyclopentene	0.56	0.51	0.05
1-butene	1.38	1.48	-0.10	acetylene	-0.01	-0.03	0.02
Alkynes							
1-propyne	-0.31	-0.16	-0.15	1-buten-3-yne	0.04	-0.09	0.13
1-butyne	-0.16	-0.13	-0.03				
Arenes							
benzene	-0.87	-0.75	-0.12	1,3-dimethylnaphthalene	-2.47	-2.33	-0.14
toluene	-0.89	-0.48	-0.41	2,7-dimethylnaphthalene	-2.63	-2.30	-0.33
<i>o</i> -xylene	-0.90	-0.50	-0.40	fluorene	-3.44	-3.83	0.39
<i>m</i> -xylene	-0.84	-0.73	-0.11	phenanthrene	-3.95	-4.06	0.11
biphenyl	-2.64	-2.96	0.32	acenaphthalene	-3.15	-3.20	0.05
naphthalene	-2.39	-2.23	-0.16	anthracene	-4.23	-4.06	-0.17
Alcohols							
methanol	-5.11	-5.61	0.50	cyclopentanol	-5.49	-5.53	0.04
ethanol	-5.01	-5.21	0.20	cyclohexanol	-5.48	-5.47	-0.01
1-propanol	-4.83	-4.41	-0.42	phenol	-6.62	-6.29	-0.33
2-propanol	-4.76	-5.11	0.35	ethandiol	-9.60	-9.96	0.36
1-butanol	-4.72	-4.22	-0.50	2-propene-1-ol	-4.80	-5.12	0.32
Ethers							
dimethyl ether	-1.90	-1.85	-0.05	phenyl methyl ether	-1.04	-2.06	1.02
diethyl ether	-1.63	-1.50	-0.13	1,3-dioxalane	-4.10	-5.05	0.95
methyl <i>n</i> -propyl ether	-1.66	-1.23	-0.43	1,4-dioxane	-5.05	-5.04	-0.01
methyl isopropyl ether	-2.01	-1.98	-0.03	tetrahydropyran	-3.12	-2.16	-0.96
tetrahydrofuran	-3.47	-3.24	-0.23	2-methoxy-1-ethanol	-6.80	-7.57	0.77
2,5-dimethyltetrahydrofuran	-2.92	-2.87	-0.05				
Ketones, Aldehydes							
acetone	-3.85	-3.16	-0.69	propanal	-3.44	-3.04	-0.40
2-butanone	-3.64	-3.78	0.14	butanal	-3.18	-2.85	-0.33
2-pentanone	-3.53	-3.77	0.24	benzaldehyde	-4.02	-4.22	0.20
acetophenone	-4.58	-4.53	-0.05	<i>p</i> -hydroxybenzaldehyde	-10.48	-10.32	-0.16
ethanal	-3.50	-3.22	-0.28				
Carboxylic Acid							
acetic acid	-6.70	-6.18	-0.52	butyric acid	-6.36	-6.61	0.25
propionic acid	-6.48	-6.78	0.30				
Esters							
methyl acetate	-3.32	-2.97	-0.35	methylpropanoate	-2.93	-3.13	0.20
ethyl acetate	-3.10	-2.91	-0.19	ethylpropanoate	-2.80	-3.18	0.38
<i>n</i> -propyl acetate	-2.86	-2.64	-0.22	methylbenzoate	-4.28	-3.96	-0.32
isopropyl acetate	-2.65	-2.58	-0.07	ethylformate	-2.65	-2.68	0.03
Amines							
methylamine	-4.56	-4.14	-0.42	triethylamine	-3.02	-2.03	-0.99
ethylamine	-4.50	-4.78	0.28	pyrrolidine	-5.48	-5.68	0.20
<i>n</i> -propylamine	-4.39	-4.32	-0.07	piperidine	-5.11	-5.17	0.06
<i>n</i> -butylamine	-4.29	-4.25	-0.04	ammonia	-4.31	-4.51	0.20
dimethylamine	-4.29	-4.49	0.20	aniline	-4.90	-4.61	-0.29
diethylamine	-4.07	-3.81	-0.26	<i>N</i> -propylguanidine	-10.92	-11.31	0.39
trimethylamine	-3.24	-4.22	0.98				

Table 12 (Continued)

molecule	expt	PFF/PBF/NP	diff	molecule	expt	PFF/PBF/NP	diff
Amides							
acetamide	−9.71	−9.63	−0.08	<i>N</i> -methyl formamide (NMF)	−10.00	−9.94	−0.06
propionamide	−9.41	−9.73	0.32	<i>N,N</i> -dimethylacetamide	−8.50	−8.27	−0.23
NMA(trans)	−10.08	−10.30	0.22				
Nitriles							
acetonitrile	−3.89	−4.31	0.42	butyronitrile	−3.64	−3.13	−0.51
propionitrile	−3.85	−3.50	−0.35	3-hydroxybenzonitrile	−9.67	−9.07	−0.60
Nitros							
nitroethane	−3.71	−3.61	−0.10	nitrobenzene	−4.12	−3.99	−0.13
1-nitropropane	−3.34	−3.54	0.20	3-nitrophenol	−9.63	−9.55	−0.08
2-nitropropane	−3.14	−3.12	−0.02				
N Hetero Aromatic							
pyridine	−4.70	−4.68	−0.02	<i>N</i> -methyl-2-pyridone	−10.00	−9.79	−0.21
2-methylpyridine	−4.63	−4.19	−0.44	methylimidazole	−10.25	−10.81	0.56
2-methylpyrazine	−5.52	−5.28	−0.24	methylindole	−5.91	−5.57	−0.34
Thiols, Sulfides							
methanethiol	−1.24	−1.02	−0.22	dimethyl sulfide	−1.54	−1.23	−0.31
ethanethiol	−1.30	−0.88	−0.42	diethyl sulfide	−1.43	−1.10	−0.33
benzenethiol	−2.55	−2.72	0.17	methyl phenylsulfide	−2.73	−3.02	0.29
Halogen Compounds							
fluoromethane	−0.22	0.23	−0.45	chloroethane	−0.63	−0.54	−0.09
1,1-difluoroethane	−0.11	0.06	−0.17	1-chloropropane	−0.27	−0.28	0.01
trifluoromethane	0.81	0.55	0.26	chlorobenzene	−1.12	−1.00	−0.12
tetrafluoromethane	3.11	2.54	0.57	tetrachloromethane	0.10	−0.80	0.90
tetrafluoroethene	1.38	2.14	−0.76	hexachloroethane	−1.41	−0.93	−0.48
2,2,2-trifluoroethanol	−4.31	−4.57	0.26	tetrachloroethene	0.05	0.24	−0.19
chloromethane	−0.56	−0.70	0.14				
Ionic Compounds							
acetate anion	−79.90	−79.49	−0.41	pyrrolidinium cation	−61.60	−62.88	1.28
propionate anion	−79.10	−79.26	0.16	piperidinium cation	−60.00	−59.70	−0.30
benzoate anion	−76.00	−76.50	0.50	trimethylammonium cation	−56.60	−58.64	2.04
ammonium cation	−86.00	−86.18	0.18	triethylammonium cation	−50.20	−49.01	−1.19
methylammonium cation	−71.30	−71.76	0.46	tetramethylammonium cation	−52.30	−53.18	0.88
ethylammonium cation	−68.40	−68.47	0.07	tetraethylammonium cation	−45.30	−44.30	−1.00
isopropylammonium cation	−66.50	−65.69	−0.81	anilinium cation	−66.00	−65.97	−0.03
<i>tert</i> -butylammonium cation	−63.10	−61.88	−1.22	<i>N,N</i> -dimethylanilinium cation	−52.00	−52.31	0.31
dimethylammonium cation	−63.90	−65.14	1.24	pyridinium cation	−56.10	−57.92	1.82
diethylammonium cation	−58.90	−59.84	0.94	methylimidazolium cation	−64.13	−62.38	−1.75
di- <i>n</i> -propylammonium cation	−57.70	−56.96	−0.74				

fixed charge force field in SGB solvent, then switch to PFF using an SCRF description of solvation for the final stage of minimization; this saves significant amounts of CPU time. We also performed minimizations in the gas phase to make sure the methodology is working correctly and to compare optimized structures in the gas phase and in solution. Results for 18 proteins are listed in Table 16, where it can be seen that the average rms structural deviations are 1.85 Å in the gas phase and that these deviations are reduced to an average of 1.10 Å in the continuum solvent.

Finally, we have studied 33 protein–ligand complexes using technology similar to that described above. For most of these cases, we minimize only a small region of the protein around the active site in addition to the ligand. Ligand parameters were produced in accordance with the protocol described in section II. Table 17 presents a list of the 33 systems that have been studied, along with CPU times and

RMSDs of the ligand as compared to the crystal structure. The quality of the results from the point of view of structural RMSDs is acceptable. The CPU times are long compared to a fixed charge, gas-phase minimization but are clearly short enough to enable a significant number of complexes and structures to be studied in future work.

V. Conclusion

We have developed a comprehensive polarizable force field methodology which can be used to develop parameters, through a mixture of quantum chemical calculations and atom typing parameter assignment, for an arbitrary small organic molecule. A wide range of functional groups has been addressed, and performance of the methodology in the gas phase has been assessed for a substantial training set, examining both conformational energy differences and the binding energy of pairs of small molecules. The average

Table 13. Summary of the Error Analysis of the PFF/PBF/ NP Computed Solvation Free Energies for 147 Small Molecules by Functional Group Classes

functional group	average ^a	rms ^a	molecules ^a
alkanes	0.06	0.07	12
alkenes	0.04	0.05	5
alkynes	0.08	0.10	4
arenes	0.23	0.26	12
alcohols	0.30	0.34	10
ethers	0.42	0.58	11
ketones, aldehydes	0.28	0.33	9
carboxylic acids	0.36	0.38	3
esters	0.22	0.25	8
amines	0.34	0.45	13
amides	0.18	0.21	5
nitrils	0.47	0.48	4
nitro compounds	0.11	0.12	5
N hetero aromatic	0.30	0.35	6
thiols, sulfides	0.29	0.30	6
halogen compounds	0.34	0.43	13
neutral subtotal	0.26	0.35	126
ionic compounds	0.83	1.01	21
grand total	0.34	0.50	147

^a The first two columns are the average unsigned error (kcal/mol) and the rms error (kcal/mol) relative to the experimental data. The number of molecules in each function group class is listed in the last column.

Table 14. rms Energy Deviations (kcal/mol) from LMP2/cc-pVTZ(-f)//HF/6-31G** for Peptides

peptide	PFF	OPLS-AA/L ^a
tetrapeptide: alanine	0.81	0.56
dipeptides: alanine	0.20	0.27
serine	0.16	0.44/0.34
phenylalanine	0.05	0.15
cysteine	0.31	0.35
asparagine	0.19	0.16
glutamine	0.69	0.96
histidine	0.90	0.85
leucine	0.57	0.34/0.38
isoleucine	1.04	0.38
valine	0.14	0.08/0.16
methionine	0.59	0.59
proline	0.76	1.54
tryptophan	0.63	0.50
threonine	0.61	0.87
tyrosine	0.25	0.39
average ^b	0.55	0.47

^a Kaminski, G. A.; Friesner, R. A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Phys. Chem. B* **2001**, 105, 6474. ^b Proline not included.

errors obtained for conformational energy differences are comparable to those obtained for fixed charge force field parametrization. The dimer binding energetics are qualitatively superior, as fixed charge models cannot be rigorously fit to accurate ab initio gas-phase values due to polarization effects in the condensed phase. Similarly, the energy errors observed in the polarization model are relatively small. We have also developed a complementary continuum solvation model, which has been fit to reproduce experimental solvation free energy data for 147 small molecules. Finally, minimization of 18 proteins and 33 protein–ligand com-

Table 15. rms Energy Deviations (kcal/mol) from LMP2/cc-pVTZ(-f)//HF/6-31G** for Charged Dipeptides

peptide	PFF	OPLS-AA/L ^a
aspartic acid	0.41	0.16/1.95
glutamic acid	1.41	1.53
lysine	0.32	0.88
protonated histidine	0.57	0.97
arginine	0.72	1.15
average	0.69	0.94/1.29

^a Kaminski, G. A.; Friesner, R. A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Phys. Chem. B* **2001**, 105, 6474.

Table 16. PFF/PBF/NP Minimizations of 18 Proteins^a

protein	residues	atoms	rmsd (gas)	rmsd (solvent)	cpu times ^b
1aho	64	962	1.30	0.91	87.4
1nps	88	1321	1.17	1.00	154.2
1ew4	106	1659	3.86	1.11	226.2
1dhn	121	1932	2.03	1.30	306.1
1qto	122	1813	3.30	1.97	353.3
1whi	122	1937	1.50	1.00	270.6
1ej8	140	2174	1.54	1.04	318.6
1dvo	152	2482	2.53	1.09	492.5
1bv1	159	2451	1.62	1.02	541.6
1u9a	160	2571	1.98	1.03	520.7
2fcb	173	2686	1.76	1.16	555.8
1bk7	190	2934	1.08	0.94	510.5
1pbv	195	3148	2.40	1.16	677.2
1a8l	226	3622	1.36	0.93	1143.5
1b2p	238	3682	1.23	0.90	1029.5
1qts	247	3913	1.76	1.35	1171.0
1bue	265	4065	1.17	0.83	1339.1
1ako	268	4311	1.64	1.05	1453.6
average			1.85	1.10	

^a Columns 2 and 3 give the number of residues and atoms, while columns 4 and 5 compare gas phase and continuum solvent rms structural deviations (Å) from the experimental structures. The last column specifies the CPU time (minutes) for the optimizations in solvent. ^b The convergence criteria for the polarization energy and PB calculation are 0.001 and 0.05 kcal/mol, respectively. Convergence of the final total energy gradient was set to 0.05 kcal/mol/Å.

plexes in continuum solvent yields reasonable results in terms of RMSDs from experimental data and does not display any major numerical problems (e.g. polarization catastrophes).

As indicated above, the goal of the present work was the creation of a platform enabling testing of the methodology with regard to improving accuracy in the computation of protein–ligand binding affinities. Several possible approaches in which the methodology could be used were discussed, and computational experiments along these lines on realistic pharmaceutical ligands and targets are now feasible with a limited amount of human effort (as opposed to the formidable problem of generating new ligand parameters for each complex medicinal chemistry compound from scratch). Because there are so many factors that contribute to errors in the various alternative types of calculations, it is difficult to predict how much improvement will be realized in early efforts using existing sampling methods and the current continuum solvation model. Ultimately, however, improvements in all aspects of the calculation will enable

Table 17. PFF/PBF/NP Minimizations of the Protein–Ligand Complex Active Sites with the Ligands^a

compound name	protein		ligand atoms	rmsd (Å)	cpu times ^b (min.)
	residues	atoms			
1rds	105	1497	63	0.86	207.9
1fkg	107	1664	68	0.56	104.1
1stp	121	1745	31	0.13	142.4
1rob	124	1855	33	0.68	396.2
1lmo	129	1952	57	0.40	500.8
1icn	131	2107	53	0.65	287.0
2ifb	131	2114	49	0.27	283.8
1cbs	137	2200	49	0.19	160.6
4fxn	138	2133	50	0.43	237.9
1rbp	175	2756	51	0.12	315.7
1fen	176	2773	50	0.11	288.3
1aaq	198	3123	91	0.79	353.0
1hpv	198	3125	66	0.48	324.3
1hpx	198	3125	87	0.39	367.8
1hsg	198	3125	92	0.31	287.4
1htf	198	3124	79	0.79	587.5
1odw	198	3118	84	1.01	351.8
1pro	198	3131	80	0.34	271.1
1sbg	198	3131	81	0.42	314.2
2upj	198	3124	81	0.55	554.5
1sre	235	3408	29	0.45	444.5
1hsl	238	3684	20	0.33	631.4
1lah	238	3599	22	0.03	751.2
1lst	238	3581	25	0.21	890.8
1aha	246	3895	15	0.06	353.5
1mrg	246	3899	15	0.06	469.9
1mrk	247	3840	32	0.60	570.5
1di8	283	4618	37	0.14	1345.6
1g5s	283	4618	62	0.33	1359.4
1ulb	289	4496	16	0.07	676.7
1abe	305	4673	20	0.09	1487.5
8abp	305	4678	24	0.10	772.3
9abp	305	4669	24	0.08	956.2

^a The active site is defined as the residues having any atoms within 5 Å from the ligand atoms. Thirty-three complexes were sorted by the total number of residues in the proteins of the complexes. ^b The convergence criteria for the polarization energy and PB calculation are 0.001 and 0.05 kcal/mol, respectively. Convergence of the final total energy gradient was set to 0.05 kcal/mol/Å.

the polarization model to deliver significant improvements. We believe that the present effort, based on its demonstrated accuracy in test cases and range of coverage, represents a substantial step in this direction.

VI. Appendix

The interaction energy of a molecule with an external field is given by

$$E = E_{\text{elec}} + E_{\text{pol}} + E_{\text{hyp}} \quad (20)$$

where E_{elec} , E_{pol} , and E_{hyp} are the electrostatic, polarization, and hyperpolarization components of the total interaction energy. These energy terms are respectively dependent on the first, second, and higher order powers of the electrostatic potential (ϕ), external field components (F_α , F_β , and F_γ), and the first (F'), second (F''), and higher order derivatives of the field. For example, the electrostatic interaction energy

is

$$E_{\text{elec}} = q_{\text{mol}}\phi - [\mu_\alpha F_\alpha + (1/2)\theta_{\alpha\beta}F_{\alpha\beta}' + (1/15)\Omega_{\alpha\beta\gamma}F_{\alpha\beta\gamma}'' + \dots] \quad (21)$$

In eq 21 implicit summations over the Cartesian coordinate components (α , β , γ) are assumed, and q_{mol} is the net charge of the molecule (e.g., -1 electrons for formate anion). The quantities μ_α , $\theta_{\alpha\beta}$, and $\Omega_{\alpha\beta\gamma}$ are the molecular dipole, quadrupole, and octupole moments components. The polarization energy is given by

$$E_{\text{pol}} = -[(1/2)\alpha_{\alpha\beta}F_\alpha F_\beta + (1/3)A_{\alpha\beta\gamma}F_\alpha F_{\beta\gamma}' + (1/6)C_{\alpha\beta\beta\gamma}F_{\alpha\beta}F_{\beta\gamma}'' + \dots] \quad (22)$$

where $\alpha_{\alpha\beta}$ is a molecular dipole polarizability tensor component and $A_{\alpha\beta\gamma}$ and $C_{\alpha\beta\beta\gamma}$ are molecular quadrupole polarizability tensor components. These energy expressions as well as the higher order hyperpolarization energy terms which depend on the third and higher powers of the field (and field derivatives), have been known for a long time.^{50,51}

A. Calculation of ab Initio Electrostatic and Polarization Energies for a Molecule/Point Charge System. When the field source is a point charge, the electrostatic potential, field, and field derivatives are all proportional to the value of the point charge. Consequently, the interaction energy (E) between a molecule and a point charge (q) can be described by the Taylor series expansion

$$E = C_1 q + C_2 q^2 + C_3 q^3 + C_4 q^4 + \dots \quad (23)$$

where

$$C_1 = d_1 \quad \text{where } d_1 = (\partial E / \partial q)_{q=0} \quad (24)$$

$$C_2 = d_2 / 2 \quad \text{where } d_2 = (\partial^2 E / \partial q^2)_{q=0} \quad (25)$$

$$C_3 = d_3 / 6 \quad \text{where } d_3 = (\partial^3 E / \partial q^3)_{q=0} \quad (26)$$

$$C_4 = d_4 / 12 \quad \text{where } d_4 = (\partial^4 E / \partial q^4)_{q=0} \quad (27)$$

and where all derivatives are evaluated at $q = 0$ from finite differences. Equation 23 is a special case of eq 20. The physical significance of the four terms in eq 23 is shown below, where the constant C_1 is the electrostatic potential at the position of the point charge.

$$E_{\text{elec}} = C_1 q = \text{ab initio electrostatic energy} \quad (28)$$

$$E_{\text{pol}} = C_2 q^2 = \text{ab initio polarization energy} \quad (29)$$

$$E_{1,\text{hyp}} = C_3 q^3 = \text{ab initio first hyperpolarizability energy} \quad (30)$$

$$E_{2,\text{hyp}} = C_4 q^4 = \text{ab initio second hyperpolarizability energy} \quad (31)$$

In principle, numerical differentiation (by finite differences) can be very accurate (to 8 or more significant figures). However, there is an inherent limit to the precision of ab initio energies. Ideally, the smaller the step size used (for

the finite differences) the more accurate the results, but higher order terms (e.g., the fourth derivative) sometimes require larger step sizes. A step size of 0.10 electrons has been found to be sufficient for energy calculations that are accurate to at least (0.01 kcal/mol), though a step size of 0.05 electrons works just as well. Two evaluations of the ab initio energy are needed for the numerical determination of C_1 and the electrostatic energy (eq 28) for a given location of the point charge. One additional energy evaluation is needed to determine the coefficient in eq 29 for the polarization energy.

Equation 23 has been used to determine the total interaction energy as well as the electrostatic, polarization, and hyperpolarization energy components, for a system consisting of water interacting with Mg^{2+} ion, which was replaced by a +2 electron point charge.⁵²

B. Calculation of ab Initio Electrostatic and Polarization Energies in Molecule/Dipole Probe Systems. Because dipole probes can be used to impose electric fields that approximate the fields in aqueous solutions, it would be nice to be able to directly calculate electrostatic and polarization interaction energies for systems in which two point charges interact with the molecule. The third-order expansion in eqs 32–35, which can be used to represent a molecule interacting with two point charges, is a special case of eq 20.

$$E(q_1) = C_1 q_1 + C_2 q_1^2 + C_3 q_1^3 \quad (32)$$

$$E(q_2) = D_1 q_2 + D_2 q_2^2 + D_3 q_2^3 \quad (33)$$

$$E(q_1, q_2) = C_{11} q_1 q_2 + C_{12} q_1 q_2^2 + C_{21} q_1^2 q_2 \quad (34)$$

$$E = E(q_1) + E(q_2) + E(q_1, q_2) \quad (35)$$

Here, $E(q_1)$ and $E(q_2)$ describe the dependence of the ab initio interaction energy (E) on the point charges q_1 and q_2 , and the coefficients C_1 , C_2 , and C_3 have already been described (see eqs 28–30). The D_1 , D_2 , and D_3 coefficients are also determined from eqs 28–30. They are computed at the location of the second point charge (q_2), though. Equation 34 includes three coupling interactions with coefficients calculated as follows:

$$C_{11} = (\partial^2 E / \partial q_1 \partial q_2)_{q=0} - c/r_{12} \quad (36)$$

$$C_{12} = (1/2)(\partial^2 E / \partial q_1 \partial q_2^2)_{q=0} \quad (37)$$

$$C_{21} = (1/2)(\partial^2 E / \partial q_1^2 \partial q_2)_{q=0} \quad (38)$$

The $(\partial^2 E / \partial q_1 \partial q_2)_{q=0}$ derivative from eq 36 is caused in part by polarization of a molecule by the two point charges q_1 and q_2 . However, the interaction energy also includes the Coulombic interaction, which is given by $c q_1 q_2 / r_{12}$, between these two point charges, where r_{12} is the distance between them and $c = 332.06 \text{ Å-kcal}/(\text{mol-e}^2)$ is a units conversion factor. The second derivative of this Coulombic term is subtracted out in eq 36, so that only the polarization component of the second derivative is left.

The electrostatic, polarization, and first hyperpolarization energies for the molecule/dipole probe system are given by eqs 39–41.

$$E_{\text{elec}} = C_1 q_1 + D_1 q_2 \quad (39)$$

$$E_{\text{pol}} = C_2 q_1^2 + D_2 q_2^2 + C_{11} q_1 q_2 \quad (40)$$

$$E_{1,\text{hyp}} = C_3 q_1^3 + D_3 q_2^3 + C_{12} q_1 q_2^2 + C_{21} q_1^2 q_2 \quad (41)$$

Four evaluations of the ab initio energy are needed for the numerical determination of C_1 and D_1 and, therefore, the electrostatic energy for a given location of the two point charges (q_1 and q_2). Five additional energy evaluations are needed to determine the coefficients in eq 40 for the polarization energy.

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