

Polarizable force fields

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Standard force fields used in biomolecular computing describe electrostatic interactions in terms of fixed, usually atom-centered, charges. Real physical systems, however, polarize substantially when placed in a high-dielectric medium such as water — or even when a strongly charged system approaches a neutral body in the gas phase. Such polarization strongly affects the geometry and energetics of molecular recognition. First introduced more than 20 years ago, polarizable force fields seek to account for appropriate variations in charge distribution with dielectric environment. Over the past five years, an accelerated pace of development of such force fields has taken place on systems ranging from liquid water to metalloenzymes. Noteworthy progress has been made in better understanding the capabilities and limitations of polarizable models for water and in the formulation and utilization of complete specifically parameterized polarizable force fields for peptides and proteins.

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Abbreviations

FQ	fluctuating charge
PD	point dipole
RDF	radial distribution function
SDFF	spectroscopically derived force field
SIBFA	sum of interactions between fragments <i>ab initio</i> computed
SPC	simple point charge
TIP	transferable intermolecular potential

Introduction

Computational studies of biomolecular systems routinely make use of empirical potential energy functions or force fields. In such studies, success often depends in a substantial part upon the quality of the molecular force field. Current-generation force fields, such as OPLS [1,2], CHARMM [3], AMBER [4], MMFF [5] and GROMOS [6], however, all have serious theoretical and practical limitations. In particular, all are pairwise additive force fields that describe the electrostatic interactions that dominate molecular recognition events solely in terms of fixed charges, usually centered on atoms. In this article, we will review progress made in developing polarizable molecular force fields that seek to overcome limitations inherent in such approaches and will focus on studies that show why these limitations are important.

A main cause of these limitations is that the high-dielectric medium in a condensed-phase simulation (e.g. water)

polarizes the molecular charge distribution. Current biomolecular force fields, however, describe this polarization only in an averaged way — typically by increasing the atomic charges in order to obtain molecular or fragment dipole moments that are about 10–20% larger than those observed in the gas phase. Such enhanced charges are needed to properly describe the bulk properties of liquid water and (given that the widely employed nonpolarizable water models use such charges) to obtain a proper balance between solvent–solvent, solute–solvent and solute–solute interactions. The mean field approximation they embody, however, limits their accuracy because the dielectric environment, and the resultant polarization response, can vary widely across a biomolecular system — which, for example, may extend from the nearly gas-phase environment of a non-polar pocket in the protein interior to a nearly bulk-water environment at the protein surface. Moreover, even in a gas-phase environment, inclusion of polarizability can strongly affect intermolecular interaction energetics, as Caldwell and Kollman [7] showed in a seminal study on aromatic–cation interactions.

In such situations, ‘one size’, in atomic charge, definitely does not ‘fit all’ and yet every widely used force field makes this approximation. Polarizable force fields, in contrast, allow the charge distribution to vary with the demands of the dielectric environment. In this article, we review methods that have been used to account for polarization and summarize the progress made to date in treating systems ranging from pure water to biomacromolecules in aqueous solution. Such methods have been explored at least since the studies by Vesely [8], Stillinger and David [9], Barnes *et al.* [10], and Warshel [11] more than 20 years ago (the earliest we are aware of), but never as intensively as during the past five years, the time period covered by this first review of polarizable force fields for *Current Opinion in Structural Biology*.

Methods used to account for polarization

Inducible point dipole model

In this method, a point dipole (PD) \mathbf{p}_{ind} is induced at each contributing center in response to the total electric field according to:

$$\mathbf{p}_{ind} = \alpha(\mathbf{E}^o + \mathbf{E}^p) \quad (1)$$

where \mathbf{E}^o is the field due to the permanent atomic charges and \mathbf{E}^p is the field due to the (other) induced dipoles. The total field is determined self-consistently via an iterative procedure that minimizes the polarization energy or by means of the extended Lagrangian method [12]. The contribution of the polarization energy to the total nonbonded energy is then given by:

$$E_{pol} = -1/2 \sum \mathbf{p}_i \cdot \mathbf{E}_i^0 \quad (2)$$

where the summation is over polarizable centers, i .

Fluctuating charge model

In this method, the atomic charges fluctuate in response to the environment according to the principle of electronegativity equalization, which states that charge flows between atoms until the instantaneous electronegativities of the atoms are equal. In this approach, the fluctuating charges (FQs) are assigned fictitious masses and are treated as additional degrees of freedom in the equations of motion. In the context of molecular dynamics, the equations that result are efficiently solved using the extended Lagrangian method [13] at a computational cost little greater than that required for a fixed-charge, pairwise-additive force field. This model has also been implemented, though less efficiently, for use in Monte Carlo simulations [14].

Water models

Most efforts to develop polarizable force fields have focused on liquid water because its elaborate network of cooperative interactions provides fruitful grounds for testing methods and because it plays such a central role in biological processes. In the PD model, the additional empirical parameters are the polarizabilities, α , of Equation 1. Some approaches include isotropic point polarizabilities on all atoms. These approaches subdivide into cases in which the molecular polarizability is taken to be a simple additive sum of the atomic polarizabilities [15] and others in which the point polarizabilities interact intramolecularly with those on neighboring atoms (1,2- and 1,3-bonded) [16]. Other force fields place a single point polarizability, often set to the experimental value of 1.444 \AA^3 , at the oxygen atom or positioned along the H–O–H bisector [17–19].

In the FQ approach, the parameters that determine the atomic charges and the polarization response can be adjusted empirically [13], but have also been fit to reproduce quantum mechanical two-body and three-body (i.e. nonadditive) interaction energies for water dimers and trimers [20]. As applied to water, this model, though highly efficient, has the disadvantage that the polarizability is confined to the molecular plane, whereas experimentally the polarizability is nearly isotropic.

The PD models cited above were parameterized to reproduce the experimental value of the dipole moment of the water monomer in the gas phase and the heat of vaporization and density of bulk water at ambient temperatures. These water models use either the experimentally based transferable intermolecular potential (TIP) TIP3P [21]/TIP4P [22] geometry or the idealized tetrahedral simple point charge (SPC) [23] geometry (which has an H–O–H bond angle of 109.5°). From results obtained to date, it is not yet clear which is to be preferred; however, as force-field parameterization usually involves fitting to

quantum mechanical data, the TIP geometry is often a better choice for a polarizable force field.

Jedlovsky and Richardi [24••] have compared the performance of the Chialvo–Cummings (CC) [17], Brodholt–Samplioi–Vallauri (BSV) [18] and Dang–Chang (DC) [19] models under ambient conditions and at higher temperatures. In relation to the nonpolarizable TIP4P and SPC models, the polarizable models obtain a diffusion constant that is in much better agreement with experiment. Recently, Sorensen *et al.* [25•] completed new measurements of the radial distribution functions (RDFs) for water and compared them with predictions made for both polarizable and nonpolarizable water models. They found that the calculated RDFs for the polarizable models (CC, TIP4P-FQ [13]) were generally in better agreement with experiment than those for the pairwise-additive TIP3P and SPC three-site models. The RDFs for the polarizable force fields, however, were not significantly better than those for the four-site TIP4P model and not as good as those for the new nonpolarizable five-site TIP5P model [26•]. This suggests that improved force fields for general molecules need to include some representation of anisotropic charge distributions (e.g. off-center charges or ‘lone pairs’ on heteroatoms), as well as polarizability.

The only critical bulk property that is not satisfactorily reproduced by these PD models is the dielectric constant, which generally is too large [27,28]. This appears to result from the fact that these models predict an average dipole moment for bulk-phase water monomers of 2.8–3.2 Debye, whereas empirical evidence indicates that only an average dipole moment of about 2.6 Debye can reproduce the experimental dielectric constant of approximately 80 [28,29].

For the BSV model, Alfredsson *et al.* [27] found that the dipole moment calculated for the dimer is too large only for H···O separations of less than 1.8 \AA . As such distances are rarely observed in simulations of bulk water, the authors concluded that the overestimation of the bulk-phase dipole moment does not arise from the inherent inaccuracy of using PDs instead of finite charge distributions (PDs in principle could, and in practice sometimes do, lead to a ‘polarization catastrophe’, in which the magnitude of the induced dipole increases rapidly, without bound, as the internuclear separation decreases). Rather, they suggest that it may not be appropriate to use the full experimentally derived polarizability of the isolated water molecule for calculation in the dense fluid phase. The Friesner group came to a similar conclusion in the course of developing a PD model for water almost entirely from *ab initio* quantum mechanics. They found that the reference quantum mechanical polarizabilities need to be based on large, but not limiting, basis sets (thereby leading to smaller calculated values) and argue that Pauli exclusion effects should reduce the effective polarizability of the water molecule in the condensed phase (RA Friesner, personal communication). In contrast, many of the FQ models yield

reasonable values for the dielectric constant [13,20], but in this approach, the polarizabilities are fitted, rather than preassigned quantities, and yield average bulk-phase dipole moments of approximately 2.6 Debye when the dielectric constant is obtained accurately.

Aqueous solution and aqueous interfaces

Recent studies by Dang and co-workers have demonstrated the importance of polarizability in modeling aqueous phenomena. For example, the paper that introduced the DC model [19] also characterized the manner in which the average water molecule dipole moment falls off from the bulk value (2.75 Debye for the DC model) toward the gas-phase value (1.85 Debye) as the water/vapor interface is approached and crossed. Interestingly, the transition is smooth and takes place over a distance of several angstroms, such that even water molecules a few angstroms deep into the water layer have noticeably reduced polarity. A second study examined the water/CH₂Cl₂ interface and found that the average dipole moment of water falls by about 30% as the interface is approached from the aqueous side and individual water molecules begin to penetrate into the organic phase. Similarly, the approach to the interface and penetration into the aqueous phase of CH₂Cl₂ molecules raises their dipole moment by about 10% [30]. Similar results had previously been reported for the water/CCl₄ interface using an earlier version of the polarizable potential [31]. Of course, no variation in dipole moment is permitted in a nonpolarizable model.

A third study characterized the structure of iodide ion complexed to water clusters containing 2–10 water monomers [32]. A main finding was that the iodide ion prefers to sit at the surface of the cluster, rather than at an interior position, where it would be surrounded to a greater degree ('solvated') by water monomers. Interestingly, this attribute is lost if the iodide ion is taken to be nonpolarizable; energetic analysis indicates that the origin of the seemingly counterintuitive preference for a surface position is the enhancement by iodide polarization of the strength of the favorable interactions within the attached water clusters. A fourth study examined the free energy of transport of chloride and cesium ions across a water/CCl₄ liquid/liquid interface [33]. In contrast to an earlier report on a related system that used nonpolarizable potentials, this study found no free energy minimum for Cl⁻ (or for Cs⁺) at the interface, indicating that these ions are not surface active with the DC potential. On the other hand, transport of benzene across the water liquid/vapor interface encounters a substantial free energy minimum of -4 kcal/mol [34], indicating that benzene is surface active.

An intriguing free energy perturbation study by Soetens *et al.* [35] examined the potential of mean force for the approach of a pair of coplanar guanidinium ions in fixed-charge SPC/E (extended SPC) water and in PSPC (polarizable SPC) water. Surprisingly (at least to us), this study found free energy minima of -4.7 and -2.7 kcal/mol,

respectively, for a contact like-ion pair. This is contrary to simple effective-dielectric-constant thinking, which would hold that water would greatly reduce the repulsion between the like ions — but that repulsion there would be, nonetheless. Especially for the polarizable force field, however, the computed free energy minimum was substantially smaller in magnitude than the minimum of -10 kcal/mol calculated for the guanidinium contact ion pair in TIP4P water, also cited in the paper. Thus, inclusion of polarizability markedly reduces the stability of the contact ion pair; we are tempted to say that this is a more 'physical' result, but perhaps this is just our prejudice talking. Further studies are clearly warranted.

Polarizable force fields for small molecules

Polarizable force fields for small molecules — for example, CCl₄, CH₂Cl₂, benzene and the guanidinium ion — were employed in the studies reviewed above. Others have been reported recently by Hermida-Ramon and Rios [36], and by Krimm and co-workers [37] for formaldehyde; by Levy and co-workers [38] for small aliphatic amines and small amides; by Kollman and co-workers [39] for small amines; and by Krimm for *N*-methylacetamide (S Krimm, personal communication). These force fields all utilize inducible PDs, though Krimm's formulation [37] — a more complex, polarizable analog of his SDFP (spectroscopically derived force field) model — also uses FQs in part. For both their polarizable and nonpolarizable SDFP models, Krimm and co-workers (in the references cited) computed dipole moments and molecular electrostatic potentials for small-molecule dimers as a function of orientation. Their results are noteworthy because they demonstrate that inclusion of polarizability markedly improves the agreement with *ab initio* quantum mechanics for these measures of the charge distribution. Thus, we see that neglect of polarizability will cause other parts of a system to experience erroneous electrostatic interactions with hydrogen-bonded moieties contained within it.

The studies of amine and amide hydration by Levy and co-workers [38], and of amine hydration by Kollman and co-workers [39] are especially noteworthy because they agree, despite quite different parameterizations, that inclusion of polarizability substantially improves the reproduction of the experimental free energies of aqueous solvation upon successive replacement of amino hydrogens by relatively highly polarizable methyl groups. In particular, their polarizable models gave the change in free energy of hydration on going from ammonia to trimethylamine as about +3 kcal/mol. This is still larger than the experimentally determined difference of +1.1 kcal/mol, but is in much better agreement with experiment than the estimates of +4.4 to +6.6 kcal/mol obtained from their pairwise-additive fixed-charge force fields [38,39]. Inclusion of polarizability, however, did not resolve a key qualitative discrepancy — namely, that the first methylation in each case increases the magnitude of the experimental, but decreases that of the calculated, solvation free energy. The

explanation for these discrepancies may rest in the finding by Friesner, Honig and co-workers [40] that, when used in force-field calculations, atomic charges determined by fitting to quantum mechanical electrostatic potentials (or, equally, to experimental dipole moments, as in [38]) underestimate the binding energy of hydrogen-bonded dimers for the more highly methylated systems; as a result, systems such as trimethylamine are calculated to be too poorly solvated by the force-field model. Evidently, a proper physical resolution will require both the inclusion of polarizability and the assignment of permanent charges that reproduce quantum mechanical dimerization energies. An approach along these lines has been taken by Rizzo and Jorgensen [41[•]], using the nonpolarizable OPLS-AA force field. These workers are able to reproduce the amine hydration series quite accurately, but find that their amine–water dimerization energies need to become increasingly more negative (i.e. larger in magnitude) than the benchmark large basis set localized MP2 *ab initio* calculations as additional methyl groups are added — perhaps to compensate for the lack of polarizability, which favors the hydration of the more highly methylated members of the series.

Peptides and proteins

An approach to polarizability commonly taken by Kollman and co-workers [4,39] builds on AMBER by adding point polarizabilities, usually based on the Applequist model [42], and by compensatingly reducing the permanent charges, typically to 88% of the values used for the pairwise-additive fixed-charge force field. This protocol provides a convenient way of generating polarizable force fields for general organic molecules. However, the practice of keeping all other parameters set at values taken from the additive force field affects the performance of the polarizable force field to some degree, for example, for conformational energies [4].

A major effort to develop polarizable force fields for peptides and proteins has been reported by Friesner, Berne and co-workers [43^{••},44[•]]. Following closely on the heels of the two initial publications [43^{••},44[•]], this work has now led to a complete protein force field covering all 20 naturally occurring amino acids (RA Friesner, personal communication). The first of the cited papers [43^{••}] utilizes the FQ model exclusively. It derived polarizability parameters by fitting to the quantum mechanical response to electric fields generated by charged probe particles placed strategically around the van der Waals envelope of the system. The second paper [44[•]] uses PD polarizabilities in a mixed PD/FQ model for substituted benzenes to overcome limitations of the FQ framework (such as the limitation of the polarizability to the plane of a phenyl ring, analogous to the limitation of the polarizability to the plane of the water molecule in the FQ model for water). This paper also presents a PD model for a limited set of amino acid residues, which the unpublished work has now extended to produce a complete protein force field.

A hallmark of the Friesner–Berne effort has been the development of nearly completely automated techniques for deriving electrostatic and polarization parameters from *ab initio* quantum mechanics. The unpublished work also derives Lennard–Jones parameters or, most recently, Buckingham exp-6 van der Waals parameters (in which the repulsive term is described by an exponential function) by fitting to small-molecule hydrogen-bonded dimers computed at very high levels of *ab initio* theory; the approach then adjusts the dispersion parameters that multiply the r^{-6} term in the expression for the interatomic potential to fit the experimental density for organic liquids that relate to fragments of amino acids (e.g. for methanol and formamide). In preliminary work, this approach yielded predicted heats of vaporization in excellent agreement with experiment, even though the heat of vaporization was not a fitted quantity (RA Friesner, personal communication). In addition, good reproduction of high-quality *ab initio* conformational energies for peptides has been demonstrated in both the published [43^{••},44[•]] and unpublished work.

Gresh *et al.* [45[•]] have also developed polarizable models for proteins and peptides. Most of their work is reviewed below, but we include here an application to the energetics of hydrogen bonding by dimers of formamide, *cis-N*-methylacetamide and alanine and glycine dipeptides. This study derived PD models within the framework of the SIBFA (sum of interactions between fragments *ab initio* computed) method described below. It is of particular interest in this context because it supports a conjecture one of us made [46] that more than simple atom-centered charges (e.g. lone pairs or higher multipole moments) are needed to properly account for the directionality and energetics of hydrogen bonding between amide groups. Of course, the influential study by Dixon and Kollman [47], which appeared at about the same time as [46], leaves little room for doubt on this score, though the systems examined are different. This study [47] found, for example, that coordination of pyridine by a hydrogen-bonding water molecule in which the water oxygen lies in the plane of the ring is favored over a coordination by a water molecule displaced vertically over the ring nitrogen by 3–4 kcal/mol quantum mechanically, but by only a few tenths of a kcal/mol for the standard, pairwise-additive AMBER force field. Addition of an off-center charge site in the ‘lone pair’ region proved essential for recovering the proper hydrogen-bond directionality and energetics; polarization alone was ineffective.

Protein metals and metalloenzymes

Gresh and co-workers [48–54] have published more than a dozen papers on the SIBFA method since 1995. Most have defined the force field or have described its parameterization for the binding of prototype ligands to protein metals, usually Zn²⁺. Some, like the paper cited above [45[•]], have pursued complete applications of interest in biomolecular computing. SIBFA uses the PD approach, but places it

within a complex framework in which induced-dipole and other attractive interactions are damped at close range, and in which polarizabilities, together with 'van der Waals bodies', are placed at bond and lone-pair centroids, rather than on atoms. SIBFA also incorporates a complex mechanism for accounting for geometric and some energetic (but not explicitly for charge redistribution) effects of the charge transfer from protein ligands to protein metals that takes place in the course of partial bond formation [48]. In this approach, individual terms are constructed to reproduce *ab initio* supermolecule calculations that have been partitioned into corresponding contributions via the restricted variational space procedure of Stevens and Fink [55]. Because of this attention to detail, we would expect SIBFA calculations to reproduce many facets of the true physics of the system far better than a more standard approach can. A drawback, however, is that analytic gradients are not available, precluding application to molecular dynamics simulations. A second drawback is that all SIBFA calculations reported to date have had to use the 'rigid rotor' approximation — that is, bond angles and bond lengths cannot yet be relaxed during energy minimization. Moreover, despite the good work done here, it remains to be seen whether a complete molecular mechanics approach such as SIBFA or a mixed quantum/classical mechanics (QM/MM) approach [56] will be more successful for metal-containing systems.

The mutation of protonated His231 to alanine in a close relative of thermolysin is an especially interesting application. This mutation almost completely abolishes the binding of phosphoramidate inhibitors, but scarcely affects that of thiolates, such as thiorphan. To probe the physical basis for this difference, Gresh and Roques [57] studied a model system in which torsional flexibility was allowed for key sidechains, but in which the protein coordinates for the 27 amino acid residues were otherwise taken from the crystallographically determined thiorphan–thermolysin complex (again reflecting the current inability to treat internal degrees of freedom other than torsions). On the basis of energy balances computed in continuum solvent, the authors concluded that the difference arises because an unfavorable change upon mutation in the energy for direct interaction (i.e. such as would be found in the gas phase) is compensated for in thiorphan, but not in the phosphoramidate, by a more favorable solvation energy of the mutated site, which bears a larger net ionic charge.

Conclusions

Polarizable force fields were introduced more than 20 years ago, but most progress on their formulation and application has occurred during the past five years. Such force fields unquestionably provide a far superior physical description of organic and biomolecular systems. Even though the properties of bulk water do not, in general, come out better with current polarizable force fields, studies at interfaces have shown large changes in charge distribution and dipole moment that can only be described by an

approach of this kind. Polarizability has also been found to contribute strongly to the directionality and/or energetics of hydrogen-bond formation and of cation–aromatic interaction, and thus of molecular recognition.

But, despite the clear logical and practical arguments that can be made, the necessity of including polarizability (plus a representation of the permanent charge distribution beyond fixed, atom-centered charges) for accurately predicting, say, ligand–receptor binding affinities has not yet been proven — that is, there is as yet no 'smoking gun'. Simpler nonpolarizable force fields have undeniably had many successes (along with many failures) in predicting relative binding affinities. Given the accelerated progress made in the past five years, however, the next few years bode well to establish the limitations of standard, nonpolarizable fixed-charge force fields and to make the case for routinely including polarizability in biomolecular calculations.

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- This work provides an important service to the community by comparing the ability of the BSV, CC and DC polarizable models, and the SPC/E and TIP4P nonpolarizable models to reproduce thermodynamic properties of water as a function of temperature and pressure. Unfortunately for polarizable force field aficionados, the polarizable models do not always fare best. The authors suggest that better polarizable models may require a different form for the van der Waals repulsion energy or a more realistic description of polarizability than is possible with a single polarizable dipole center. Another possibility is that molecular flexibility may need to be added. We base this conjecture on the fact that studies published elsewhere have shown that introduction of flexible bond angles (and bond lengths) affects the thermodynamic properties of nonpolarizable models fairly considerably. Perhaps, in taking one step forward (inclusion of polarizability) it is necessary to take another (inclusion of flexibility) to yield a balanced representation. Or perhaps not.
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- Of particular interest here is the finding that iodide ion, when coordinated to water clusters of various size, prefers to sit at the apex of the cluster, rather than to be surrounded by solvating water molecules. Dang shows that this behavior occurs, however, only when the iodide ion is polarizable. For confirmation, it would be good to see similar studies using optimized nonpolarizable potentials. The surface-sitting effect, it seems to us, may have a parallel in the energetics of solvation of charged sidechains at the surface of a protein; perhaps apical solvation is optimal, provided that the water model is polarizable, not just what is possible geometrically. If so, a proper account of this effect could have implications for ligand-receptor binding when one partner presents a charged group for coordination to the other.
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 34. Dang LX, Feller D: **Molecular dynamics study of water-benzene interactions at the liquid/vapor interface of water.** *J Phys Chem B* 2000, **104**:4403-4407.
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 36. Hermida-Ramon JM, Rios MA: **A new intermolecular polarizable potential for a formaldehyde dimer. Application to liquid simulations.** *J Phys Chem A* 1998, **102**:10818-10827.
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- Particularly noteworthy is the degree to which mutual polarization alters the charge distribution and electrostatic potential of a hydrogen-bonded pair, whose potential is then 'seen' by other neighboring parts of the composite system. These effects are reproducible only by a polarizable force field and this paper quantifies how large they are.
38. Ding Y, Bernardo DN, Krogh-Jespersen K, Levy RM: **Solvation free energies of small amides and amines from molecular dynamics/free energy perturbation simulations using pairwise additive and many-body polarizable potentials.** *J Phys Chem* 1995, **99**:11575-11583.
 39. Meng EC, Caldwell JW, Kollman PA: **Investigating the anomalous solvation free energies of amines with a polarizable potential.** *J Phys Chem* 1996, **100**:2367-2371.
 40. Marten B, Kim K, Cortis C, Friesner RA, Murphy RB, Ringnalda MN, Sitkoff D, Honig B: **New model for calculation of solvation free energies: correction of self-consistent reaction field continuum dielectric theory for short-range hydrogen-bonding effects.** *J Phys Chem* 1996, **100**:11775-11788.
 41. Rizzo RC, Jorgensen WL: **OPLS all-atom model for amines: resolution of the amine hydration problem.** *J Am Chem Soc* 1999, **121**:4827-4836.
- As discussed in the body of this review, Rizzo and Jorgensen find that charge distributions that better fit quantum mechanically calculated hydrogen-bonding energetics can accurately describe the hydration free energies of ammonia and the monomethyl-, dimethyl-, and trimethyl-substituted amines derived from it. In essence, to circumvent intrinsic limitations, the empirical force-field model is required to falsify the electrostatics (as measured by the computed dipole moment or the calculated electrostatic potential) in the service of a greater good – that is, the quest to account for experiment. It would be nice one day to have a physical model that does not require that such corners be cut, but this paper and the associated commentary on the amide/amine hydration anomaly in this review show that this day is not yet

here. Conjecturally, the additional terms retained in the SIBFA framework described later in this review [45*,48–54,57] might be enough to do the trick: it will be interesting to see.

42. Appellequist J, Carl JR, Fung K-K: **An atom-dipole interaction model for molecular polarizability. Application to polyatomic molecules and determination of atom polarizabilities.** *J Am Chem Soc* 1972, **94**:2952-2960.

43. Banks JL, Kaminski GA, Zhou R, Mainz DT, Berne BJ, Friesner RA:
 •• **Parameterizing a polarizable force field from *ab initio* data. I. The fluctuating point charge model.** *J Chem Phys* 1999, **110**:741-754.

Although the FQ model employed in this paper has been superseded by PDs, this work is noteworthy because it carefully defines the methodology needed to determine the parameters for a polarizable force field for general molecules in a rigorous, systematic and largely automated fashion, while giving appropriate attention to ensuring the accuracy with which the force field reproduces many-body energetics. Application to the conformational energetics of the alanine tetrapeptide shows that the completed, fully analytic force field indeed performs substantially more accurately relative to high-level quantum mechanics than any of the nonpolarizable force fields examined in [46] and, indeed, better than many of the simpler *ab initio* methods characterized there.

44. Stern HA, Kaminski GA, Banks JL, Zhou R, Berne BJ, Friesner RA:
 • **Fluctuating charge, polarizable dipole, and combined models: Parameterization from *ab initio* quantum chemistry.** *J Phys Chem B* 1999, **103**:4730-4737.

This successor paper to [43**] examines limitations for substituted benzenes of the FQ model that result from confinement of the polarization response to the local plane (e.g. the plane of the benzene ring). The paper also develops PD models for peptides containing alanine, serine and phenylalanine, and shows that the alanine tetrapeptide energetics explored in [46] can be reproduced at least as accurately as had been achieved in [43**] by the FQ model.

45. Gresh N, Guo H, Salahub DR, Roques BP, Kafafi SA: **Critical role of anisotropy for the dimerization energies of two protein-protein recognition motifs: *cis-N*-methylacetamide versus a beta-sheet conformer of alanine dipeptide. A joint *ab initio*, density functional theory, and molecular mechanics investigation.** *J Am Chem Soc* 1999, **121**:7885-7894.

This paper addresses the conjecture one of us made in [46] – that a proper account of hydrogen-bond directionality and, in cases like those examined here, hydrogen-bond energetics requires a representation of the permanent charge distribution that goes beyond the simple framework of atom-centered charges used in traditional force fields. Indeed, the authors find that inclusion of higher terms within the framework of the atom-centered multipole expansions used in the SIBFA approach (e.g. inclusion of atom–dipole and dipole–dipole terms) is needed to correctly predict that *cis-N*-methylacetamide has a larger dimerization energy than the alanine dipeptide. They also find, for their method, that polarization and charge-transfer contributions are needed to correctly reproduce the quantum mechanical differences in dimerization energy. This supports the contention in [46] (as does [47] more directly), but stops short of a complete confirmation, which would require one to also examine the behavior of an otherwise comparable force field derived under the constraint that only fixed, atom-centered charges are used.

46. Beachy MD, Chasman D, Murphy RB, Halgren TA, Friesner RA:
Accurate *ab initio* quantum chemical determination of the relative

energetics of peptide conformations and assessment of empirical force fields. *J Am Chem Soc* 1997, **119**:5908-5920.

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48. Gresh N: **Energetics of Zn²⁺ binding to a series of biologically relevant ligands: A molecular mechanics investigation grounded on *ab initio* self-consistent field supermolecule computations.** *J Comput Chem* 1995, **16**:856-882.
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