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Group Polarizability Model for Molecular Mechanics Energy Functions

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Abstract: A polarization model for molecular mechanics energy functions is developed that is based on a local group paradigm, namely the polarizability of a rigid substructure of covalently connected atoms. Axes at a "diffuse" site within the group define an anisotropic local group polarizability as well as hyperpolarizability. The theoretical basis for this model is presented, and its performance is described through applications to water, alkanes, and *N*-methylacetamide. The excellent agreement with quantum mechanical electric potentials and molecular polarizabilities indicates that this model must be considered an important candidate for the inclusion of polarization into such force fields. The ab initio-based spectroscopically determined force field (SDFF) protocol for the calculation of parameters assures that, in addition to structures and energies, forces will be accurately modeled.

1. Introduction

Current standard force fields for computer simulation of macromolecular properties are mostly based on pairwise-additive interatomic interactions whose electrostatic component utilizes fixed atomic charges. Recent efforts to improve the quality of such force fields have focused on the need to include many-body, i.e., polarizability, effects in providing a more physical description of electrostatic interactions.[1] Although it is well-known that polarization is not an atomic but rather a group property[2,3] (i.e., that it is the overall electron cloud that is being deformed by the electric field at a site), various atom-based models for introducing polarizablity have been proposed.[4] Induced atomic dipoles, iterated to self-consistency, are perhaps the most commonly used method. This model has reached a high level of sophistication, notably also with respect to the difficult issue of intramolecular polarization.[5] Other methods, too, are currently being evaluated and further developed. Particular effort is devoted to a model based on the classical Drude oscillator.[6] The fluctuating charge model, which is based on electronegativity equalization, has received a lot of attention as well.[7]

In the context of our spectroscopically determined force field (SDFF) methodology for developing molecular mechanics (MM) energy functions,[8] we described polarization using an iterative model consisting of induced atomic charges and anisotropically induced atomic dipoles.[9] However, such detailed approaches may be less than optimal from an efficiency point of view.

Efficiency is also an issue in another connection. In a previous paper,[10] we showed that the induction energy of a molecular system can be accurately computed by a non-iterative procedure suitable for MM calculations. Using waterlike test molecules, it was concluded that well over 90% (and always less than 100%) of the fully iterated induction energy will be retained at densities up to and beyond that of liquid water. This has also been confirmed in later tests. For example, using snapshots from a molecular dynamics (MD) simulation of a droplet of 216 water molecules, the one-step model yielded ∼95% of the fully iterated induction energy. However, even with such a one-step model, inclusion of polarization is still very expensive because the electric field has to be calculated (once) at each polarizable site, and the induced quantities interact with each other. Reducing the number of polarizable sites is another way to increase efficiency, and since polarization is a group property, we

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explore here the possibility of representing the polarizability of a relatively rigid substructure by only a few polarizable sites.

Before doing so, it is important to note that, although undoubtedly relevant, inclusion of polarization in the traditional manner may not be enough if the goal is to realistically reproduce variable charge distributions for intramolecular as well as intermolecular interactions. Although it has been speculated[7] that the fluctuating charge model may be able to account for geometry dependent charge variations, this may not be the case because of the atom-based approximations to the full electronic charge clouds in current MM force fields. Our studies indicate that the inclusion of geometry-dependent charges, implemented through properly balanced[11] charge fluxes,[12] may be even more important than polarizability in providing needed physical accuracy: such inclusion reproduced the opening of the water angle on going from the isolated molecule to the liquid, reproduced the ψ peptide torsion angle with only a single threefold (almost zero barrier) Fourier term, and reproduced the quantum mechanical (QM) MD φ,ψ map of a dipeptide analog.[13] We therefore believe that it is more useful to treat conventional polarization (through the electric field) separately from geometry induced readjustments in the electronic structure. (The latter effect can be very accurately accounted for in our SDFF because the valence charge flux terms can include contributions from all internal coordinates.)

Based on the induced dipole model, a scheme for defining group polarizabilities has been implemented in our modeling package (SPEAR, to be published), and parameters have been determined for a few test compounds. In this paper, we describe the methodology used, discuss some computational considerations, and apply the model to water, alkanes, and *N*-methylacetamide (NMA). In accordance with the SDFF optimization protocol[8] and generally accepted procedure,[2] the reproduction of QM electric potentials and molecular polarizabilities is used to provide a reliable test of the accuracy of the polarizability model.

2. Polarizability Model

2.1. Anisotropic Local Group Polarizability. In the new model, polarization groups are formed by sets of covalently connected atoms in molecular fragments. The location of a group is the weighted average of the positions of the atoms of the group, and the local polarizability axes are given by vectors between subsets of atoms in the group. The weighting factors and the axis vectors, and of course the polarizability parameters themselves, are specified for each group template in the electrostatic parameter file. Most other MM polarizability models are based on some implementation of isotropic atomic-level polarizability. Anisotropy in the molecular polarizability is then only produced in actual calculations by letting the induced charges or dipoles iteratively polarize one another to self-consistency. In our model, on the other hand, any anisotropy is explicitly included from the start. Up to three principal polarizability directions may be defined for a site. If the polarizability elements of a site i are α_{i1}, α_{i2}, α_{i3}, then the polarizability tensor for the site can be written as

$$\boldsymbol{\alpha}_i = \text{diag}(\alpha_{i1}, \alpha_{i2}, \alpha_{i3}) \tag{1}$$

Under the influence of an electric field, $\mathbf{E}_i$, a dipole is then induced at the site according to

$$\boldsymbol{\mu}_i = \boldsymbol{\alpha}_i \mathbf{E}_i = \sum_{n=1}^{3} \alpha_{in}(\mathbf{e}_{in} \cdot \mathbf{E}_i)\mathbf{e}_{in} \tag{2}$$

where the $\mathbf{e}_{in}$ are unit vectors in the chosen directions. In practice, at most two such vectors need to be explicitly defined, the third direction being perpendicular to the plane formed by the first two vectors. The field includes balanced contributions from all permanent charges (and multipoles, if any) outside the group and any external electric field but not the field from induced quantities. Since SDFF atomic charges consist of bond charge increments (BCIs),[8] and charges inside a group are not allowed to contribute to the field at that site, charge balance is accomplished by excluding from the electric field calculation all BCIs that have at least one end inside the group.

Simplifications are often possible and should be utilized. In the case of cylindrical polarizability, only one vector $\mathbf{e}_i$ needs to be defined, since the polarizability is the same in all directions perpendicular to that vector. For totally isotropic polarizability, of course, no vectors need to be defined. Thus, in the general case, there are N_i vectors and N_i+1 polarizabilities given for a site i, with $N_i = 0$, 1, or 2. This notation can be used to establish a compact algorithm for calculating $\boldsymbol{\mu}_i$, applicable in all cases, as seen in the following way.

If $N_i = 0$ (isotropic polarizability), $\boldsymbol{\mu}_i$ is parallel to the field, i.e.,

$$\boldsymbol{\mu}_i = \alpha_{i1}\mathbf{E}_i \tag{3}$$

If $N_i = 1$ (cylindrical polarizability), the electric field component perpendicular to the given vector is obtained by subtracting the field component in the direction of the vector from the total field, giving the induced dipole as

$$\boldsymbol{\mu}_i = \alpha_{i1}(\mathbf{e}_{i1} \cdot \mathbf{E}_i)\mathbf{e}_{i1} + \alpha_{i2}[\mathbf{E}_i - (\mathbf{e}_{i1} \cdot \mathbf{E}_i)\mathbf{e}_{i1}] \tag{4}$$

Similarly, if $N_i = 2$ (totally anisotropic polarizability), then the field component in the direction of the third unit vector is obtained by subtracting the field components in the first two directions from the total field, i.e.,

$$\boldsymbol{\mu}_i = \alpha_{i1}(\mathbf{e}_{i1} \cdot \mathbf{E}_i)\mathbf{e}_{i1} + \alpha_{i2}(\mathbf{e}_{i2} \cdot \mathbf{E}_i)\mathbf{e}_{i2} + \alpha_{i3}[\mathbf{E}_i - (\mathbf{e}_{i1} \cdot \mathbf{E}_i)\mathbf{e}_{i1} - (\mathbf{e}_{i2} \cdot \mathbf{E}_i)\mathbf{e}_{i2}] \tag{5}$$

This can also be written as

$$\boldsymbol{\mu}_i = \sum_{n=1}^{N_i} \alpha_{in}(\mathbf{e}_{in} \cdot \mathbf{E}_i)\mathbf{e}_{in} + \alpha_{i,N_i+1}[\mathbf{E}_i - \sum_{n=1}^{N_i} (\mathbf{e}_{in} \cdot \mathbf{E}_i)\mathbf{e}_{in}] \tag{6}$$

and, rearranging the terms, we finally get

$$\boldsymbol{\mu}_i = \alpha_{i,N_i+1}\mathbf{E}_i + \sum_{n=1}^{N_i} (\alpha_{in} - \alpha_{i,N_i+1})(\mathbf{e}_{in} \cdot \mathbf{E}_i)\mathbf{e}_{in} \tag{7}$$

Although eq 7 was derived assuming totally anisotropic polarizability, it also holds in the other cases since setting

$N_i = 0$ yields eq 3 and setting $N_i = 1$ yields eq 4. Thus, eq 7 can be used to compute the induced dipole at any polarizable site.

In the one-step model, the first derivatives of the induced dipoles with respect to the atomic coordinates are explicitly needed to compute atomic forces. The derivatives are given by

$$\frac{\partial \boldsymbol{\mu}_i}{\partial x_{km}} = \alpha_{i,N_i+1}\frac{\partial \mathbf{E}_i}{\partial x_{km}} + \sum_{n=1}^{N_i}(\alpha_{in} - \alpha_{i,N_i+1})\left[\left(\frac{\partial \mathbf{E}_i}{\partial x_{km}}\cdot\mathbf{e}_{in}\right)\mathbf{e}_{in} + \left(\mathbf{E}_i\cdot\frac{\partial \mathbf{e}_i}{\partial x_{km}}\right)\mathbf{e}_{in} + (\mathbf{E}_i\cdot\mathbf{e}_{in})\frac{\partial \mathbf{e}_i}{\partial x_{km}}\right] \quad (8)$$

where x_{km}, $m = 1, 2, 3$, are the Cartesian coordinates of atom k. The major computational effort involved here is to calculate the electric field and its derivatives at each site.

2.2. Hyperpolarizability. With anisotropy in the polarizability explicitly taken into account, it is easy to include (limited) hyperpolarizability in the calculation of the induced dipoles. The most visible effect of hyperpolarizability is that an induced dipole may change significantly in magnitude when the electric field is reversed. In a water molecule, for example (using ab initio MP2/6-31++G**), the induced dipole moment is 0.65 D with an electric field of 0.04 au (~2V/Å) pointing along the bisector from the oxygen toward the hydrogens but 0.69 D if the field is reversed. For compatibility with the linear polarizability of eq 2, and for convenient inclusion in eq 7, the following simplified forms can be used for the induced dipoles due to hyperpolarizability

$$\boldsymbol{\mu}_i^\beta = \sum_{n=1}^{N_i}\beta_{in}(\mathbf{e}_{in}\cdot\mathbf{E}_i)^2\mathbf{e}_{in}, \quad \text{quadratic} \quad (9)$$

$$\boldsymbol{\mu}_i^\gamma = \sum_{n=1}^{N_i}\gamma_{in}(\mathbf{e}_{in}\cdot\mathbf{E}_i)^3\mathbf{e}_{in}, \quad \text{cubic} \quad (10)$$

etc.

where β_{in} and γ_{in} are (scalar) quadratic and cubic polarizability parameters, respectively. Thus, hyperpolarizability is here limited to diagonal terms in the directions explicitly defined by the given N_i vectors, but inclusion of these nonlinear terms requires very little additional computational effort. For example, adding quadratic hyperpolarizability to the induced dipoles of eq 7 yields

$$\boldsymbol{\mu}_i + \boldsymbol{\mu}_i^\beta = \alpha_{i,Ni+1}\mathbf{E}_i + \sum_{n=1}^{N_i}[\alpha_{in} - \alpha_{i,N_i+1} + \beta_{in}(\mathbf{e}_{in}\cdot\mathbf{E}_i)]$$

$$(\mathbf{e}_{in}\cdot\mathbf{E}_i)\mathbf{e}_{in} \quad (11)$$

Inclusion of hyperpolarizability in the first derivatives of the induced dipoles is likewise straightforward, with the addition of a few simple terms to the derivatives of the linearly induced dipoles.

2.3. One-Step vs Iterated Dipoles. Induced dipoles have somewhat nonintuitive properties and are not directly comparable to permanent dipoles. Similarly, one-step induced dipoles are not directly comparable to iterated ones. Iterated

dipoles yield the induction energy by interactions with the electric field from permanent quantities only.[4,10] This is because the dipole−dipole interaction energy is implicitly included through the iterative calculation of the dipoles. In the one-step model, however, the induced dipoles behave more like the permanent ones, and the induction energy depends on the dipole−dipole interactions.

Using the electric field from the permanent quantities only, eqs 7 or 11 yields the induced dipoles needed in our noniterative polarization scheme to calculate the induction energy of a system. However, these dipoles cannot be directly used for nonpotential-energy calculations or comparisons. For such procedures, the $\boldsymbol{\mu}_i$ must be replaced by the *energy equivalent* (ee) induced dipoles

$$\boldsymbol{\mu}_i^{\text{ee}} = \boldsymbol{\mu}_i + \alpha_i\mathbf{E}_i^{(1)} \quad (12)$$

As indicated in eq 12, these are obtained by adding to the $\boldsymbol{\mu}_i$ at each site the incremental dipoles induced by the electric field, $\mathbf{E}_i^{(1)}$, from the primarily induced dipoles. This corrects the induced dipoles for their mutual interactions (which are explicitly included in the calculation of the potential energy) and is equivalent to making one iteration cycle (after the zeroth one). An important example of a nonpotential-energy property that depends directly on the induced dipoles, and where eq 12 has to be used, is the electric potential.

2.4. Diffuse Size. Because each polarizable site in the group polarizability model represents a substructure of some finite size, the induced dipoles may be defined to be 'diffuse' instead of singular points. This is done using a technique originating from fluid dynamics:[14,15] the distance r from the induced dipole to a point is replaced by the buffered distance

$$r_s = \sqrt{r^2 + s^2} \quad (13)$$

where s is the buffer size. This makes the dipole behave like a charge distribution[16] at close distances, with almost no computational overhead. Other models[17,18] are more expensive.

The electric potential U, generated by a dipole $\boldsymbol{\mu}$, is then calculated as

$$U = \frac{1}{4\pi\epsilon_0}\frac{\boldsymbol{\mu}\cdot\mathbf{r}}{r_s^3} \quad (14)$$

where $\mathbf{r}$ is an ordinary vector from the dipole to the point. The electric field from the dipole is determined by

$$\mathbf{E} = -\nabla U \quad (15)$$

in the usual way. The case of two interacting dipoles is equivalent to having one dipole interact with the field from the other. If the dipoles have sizes s_1 and s_2, then the square of the combined buffer size is taken as $s^2 = s_1^2 + s_2^2$.

2.5. Group−Group Vector. A vector from a polarization group X to a group Y can be written as

$$\mathbf{r}_{xy} = \sum_{i=1}^{n_y}b_i\,\mathbf{y}_i - \sum_{i=1}^{n_x}a_i\mathbf{x}_i \quad (16)$$

where n_x and n_y are the number of atoms in each group, a_i and b_i are atomic weighting factors, and $\mathbf{x}_i = (x_{i1}, x_{i2}, x_{i3})$

and $\mathbf{y}_i = (y_{i1}, y_{i2}, y_{i3})$ are the Cartesian coordinates of the atoms in X and Y, respectively. Accordingly, the true distance between the sites is

$$r_{xy} = \sqrt{\mathbf{r}_{xy} \cdot \mathbf{r}_{xy}} \qquad (17)$$

and the buffered distance is

$$r_{xy,s} = \sqrt{r_{xy}^2 + s_x^2 + s_y^2} \qquad (18)$$

where s_x and s_y are the diffuse sizes of X and Y, respectively. The derivatives of eqs 16−18 are easily shown to be

$$\frac{\partial \mathbf{r}_{xy}}{\partial x_{km}} = -a_k \mathbf{e}_m, \quad \frac{\partial \mathbf{r}_{xy}}{\partial y_{km}} = b_k \mathbf{e}_m \qquad (19)$$

$$\frac{\partial r_{xy}}{\partial x_{km}} = \frac{\mathbf{r}_{xy}}{r_{xy}} \cdot \frac{\partial \mathbf{r}_{xy}}{\partial x_{km}}, \quad \frac{\partial r_{xy}}{\partial y_{km}} = \frac{\mathbf{r}_{xy}}{r_{xy}} \cdot \frac{\partial \mathbf{r}_{xy}}{\partial y_{km}} \qquad (20)$$

$$\frac{\partial r_{xy,s}}{\partial x_{km}} = \frac{\mathbf{r}_{xy}}{r_{xy,s}} \cdot \frac{\partial \mathbf{r}_{xy}}{\partial x_{km}}, \quad \frac{\partial r_{xy,s}}{\partial y_{km}} = \frac{\mathbf{r}_{xy}}{r_{xy,s}} \cdot \frac{\partial \mathbf{r}_{xy}}{\partial y_{km}} \qquad (21)$$

where $\mathbf{e}_m$ is a unit vector along the Cartesian axis m. Note that the use of a buffered distance does not add any terms to the derivatives.

Group−group vectors are also used to define the polarization directions inside a group. In this case, subgroups of atoms are formed as needed, and the polarization axes are given by unit vectors $\mathbf{e}_{xy} = \mathbf{r}_{xy}/r_{xy}$ (with no buffering). The derivatives of such a unit vector are

$$\frac{\partial \mathbf{e}_{xy}}{\partial x_{km}} = \left(r_{xy} \frac{\partial \mathbf{r}_{xy}}{\partial x_{km}} - \mathbf{r}_{xy} \frac{\partial r_{xy}}{\partial x_{km}} \right) \frac{1}{r_{xy}^2} \qquad (22)$$

for atoms belonging to group X (and similarly for atoms of group Y).

2.6. Induction Energy. In the one-step polarization model, the induction energy, V^{ind}, consists of two terms

$$V^{\text{ind}} = -\frac{1}{2} \sum_i V_i + \frac{1}{4\pi\epsilon_0} \sum_{i<j} V_{ij} \qquad (23a)$$

where i and j run over the polarizable sites, and

$$V_i = \boldsymbol{\mu}_i \cdot \mathbf{E}_i \qquad (23b)$$

accounts for the interactions between the electric field and the induced dipoles as well as for the self-energy of the induced dipoles, and

$$V_{ij} = \frac{\boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j}{r_{ij}^3} - \frac{3(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_i)(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_j)}{r_{ij}^5} \qquad (23c)$$

gives the dipole−dipole interaction energy. The induction energy can be efficiently computed in two stages. At each site i, the electric field $\mathbf{E}_i$ is first determined and used to compute $\boldsymbol{\mu}_i$ and V_i.

The $\boldsymbol{\mu}_i$ need to be stored, but the field can be discarded. In the second stage the V_{ij} are computed using the stored $\boldsymbol{\mu}_i$. Summing the V_i and V_{ij} according to eq 23a then yields the global induction energy V^{ind}.

2.7. First Derivatives. In molecular dynamics simulations, the first derivatives of the potential energy with respect to the Cartesian coordinates are needed for the calculation of atomic forces. Below we evaluate the derivatives of the two parts of V^{ind} and briefly indicate how the different terms that arise are processed.

The derivatives of V_i with respect to the atomic Cartesian coordinates are

$$\frac{\partial V_i}{\partial x_{km}} = \frac{\partial \boldsymbol{\mu}_i}{\partial x_{km}} \cdot \mathbf{E}_i + \boldsymbol{\mu}_i \cdot \frac{\partial \mathbf{E}_i}{\partial x_{km}} \qquad (24)$$

The electric field $\mathbf{E}_i$ (from permanent quantities only) and its derivatives at each site are first calculated, from which the induced dipole and its derivatives as well as V_i and V_{ij} are obtained.

The electric field quantities can be discarded after use, but the $\boldsymbol{\mu}_i$ and $\partial\boldsymbol{\mu}_i/\partial x_{km}$ need to be stored to streamline the calculation of the $\partial V_{ij}/\partial x_{km}$ in the next step.

By writing eq 23c in the form

$$r_{ij}^5 V_{ij} = r_{ij}^2 \boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j - 3(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_i)(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_j) \qquad (25)$$

the derivatives of V_{ij} are readily shown to be

$$\frac{\partial V_{ij}}{\partial x_{km}} = \frac{\partial r_{ij}}{\partial x_{km}}(-5r_{ij}^4 V_{ij} + 2r_{ij}\boldsymbol{\mu}_i \cdot \boldsymbol{\mu}_j)\frac{1}{r_{ij}^5} - \frac{\partial \mathbf{r}_{ij}}{\partial x_{km}} \cdot [\boldsymbol{\mu}_i(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_j) +$$

$$\boldsymbol{\mu}_j(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_i)]\frac{3}{r_{ij}^5} + \frac{\partial \boldsymbol{\mu}_i}{\partial x_{km}} \cdot [r_{ij}^2 \boldsymbol{\mu}_j - 3\mathbf{r}_{ij}(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_j)]\frac{1}{r_{ij}^5} + \frac{\partial \boldsymbol{\mu}_j}{\partial x_{km}} \cdot$$

$$[r_{ij}^2 \boldsymbol{\mu}_i - 3\mathbf{r}_{ij}(\mathbf{r}_{ij} \cdot \boldsymbol{\mu}_i)]\frac{1}{r_{ij}^5} \qquad (26)$$

which are now straightforward to compute since all the quantities involved are known or can easily be determined. We have not implemented analytical second derivatives of the induction energy, but numerical differentiation of eqs 24 and 26 is used to derive very accurate Hessians for the calculation of vibrational frequencies and SDFF valence parameters.

3. Computational Considerations

In MD simulations, the most efficient way to incorporate polarizability is through the extended Lagrangian procedure,[4] which can be used with virtually any polarization model. However, in cases where the potential energy has to be explicitly calculated, inclusion of polarization requires nontrivial computational resources for large systems. In iterative models, the major drawback is that the electric field from the induced dipoles has to be calculated many times at each site for a single configuration while the dipoles converge toward self-consistency.

This process is difficult to parallelize efficiently because, in every iteration, the field at each polarizable site is influenced by the field from the induced dipoles at all other sites, which increases the need for communication and synchronization among the processors. Also, if a cutoff distance for nonbonded interactions is used, then the cutoff is not absolute for iterative polarization interactions, since

the induced dipoles at all sites j within the cutoff sphere of a particular site i depend on the induced dipoles within the j (or secondary) cutoff spheres, the dipoles in which depend on the dipoles within the tertiary cutoffs, and so on. This may lead to slow convergence. If the induced dipoles are updated on the fly, iterative polarization also does not result in uniform quality of the induced dipoles across the system, unless a very large number of iterations are made. The first sites to be updated in, say, the second iteration, will only be subject to the field from the dipoles of the zeroth and first iterations, while the last sites to be updated will be subject to the zeroth, first, and second iteration fields from most other sites. The detailed result then also depends on the particular order in which the polarizable sites are processed.

In our one-step model, on the other hand, only the field from the permanent quantities is used, so no communication between the processors is needed to compute the induced dipoles. The calculation of the induction energy can also be very efficiently parallelized in this model. And if a cutoff distance is used, the one-step induced dipole at a site is only affected by the permanent charges inside its own cutoff sphere. In fact, the induced dipole at a site can be calculated without computing any other induced dipoles in the system, although the induction energy of course involves all induced dipole−induced dipole interactions. This makes the non-iterative model ideal for Monte Carlo calculations or for other computations that do not require forces such as the calculation of solvation energies.

However, when forces have to be computed, the use of the derivatives of the induced dipoles requires memory and CPU resources not needed in iterative models. Efficient parallelization is still possible by dividing the polarizable sites evenly among the nodes so that each one calculates, stores, and uses only its share of the $\partial \boldsymbol{\mu}_i / \partial x_{km}$. But the calculation of the force in eq 26 is an $O(N^2)$ operation because every $\partial \boldsymbol{\mu}_i / \partial x_{km}$ consists of $3N$ vectors interacting with vectors at M polarizable sites (and $M \sim N/3$). The corresponding operation in an iterative model is $O(N)$, although a large number of iterations may be required in order to obtain near-analytical quality of the forces. Using analytically exact forces as given by the noniterative procedure provides many advantages, such as complete absence of the polarization catastrophe (or any spurious overpolarization), excellent accuracy and stability, and, therefore, unbeatable energy conservation, but such forces come at a price.

4. Applications

To illustrate the group polarization methodology described above, we present its application to a few important model systems, viz., water, alkanes, and NMA. For all of these systems, the electrostatic parameters (atomic and off-atom charges and polarizability) were optimized by least-squares fitting to the quantum mechanical (QM) electric potential outside the molecules. Using the GAMESS[19] software package, the potentials were calculated on CHELPG grids and on planes through the molecules, while applying electric fields ranging from -0.04 to $+0.04$ au in three mutually perpendicular directions. The MM parameter optimization was then done with SPEAR. Only very high-level QM

Table 1. Water Group Polarizability Parameters

location:	on HOH bisector 0.19 Å from oxygen toward hydrogens	
buffer size:	0.45 Å	
polarizability elements:	α_1 0.982 Å³	along bisector
	α_2 1.188 Å³	perpendicular to bisector, in plane
	α_3 0.976 Å³	perpendicular to molecular plane
	β_1 -0.180^a	along bisector, positive direction from oxygen to hydrogens

^{a} The unit of $\beta_1 E$ is Å³.

methods yield close to experimental values for the geometry, dipole moment, and molecular polarizability of water. In order to maintain compatibility with our QM data on protein and other units, however, we have used the same method (MP2/6-31++G**) to calculate the electric potentials of all compounds.

4.1. Water. Not surprisingly, one polarization group located near the oxygen was found to be sufficient for water. Our newly developed electrostatic model for water (to be published) was used as a basis to which polarization was simply added. However, for water at least, the optimized polarizability parameters are not very sensitive to the details of the basic electrostatic model.

The group polarizability properties are listed in Table 1. The linear polarizability tensor is almost cylindrical with the axis being parallel to a line through the H atoms. A small quadratic hyperpolarizability ($\beta_1 = -0.18$) was determined for the direction along the bisector. With this hyperpolarizability included, the previously mentioned QM calculated change in magnitude of the induced dipole moment on reversal of the electric field is now accurately reproduced: the group polarizability model gives 0.656D and 0.691D compared to the QM values 0.652D and 0.687D, respectively. The fit to the electric potential is also excellent, the weighted relative root-mean-square (wrrms) deviation[20] of the MM electrostatic potential from the QM one being 1.14% (1.16% without β_1). Even with a totally isotropic and linear model, the fit to the electric potential is quite good, i.e., 1.28% (yielding $\alpha = 0.991$ Å³).

4.2. Alkanes. Ethane, propane, t-butane, g-butane, and isobutane were chosen as model molecules for alkanes. Methane was also included but does not share any parameters with the other molecules. We first designed an appropriate static charge model for them. In CH_4, a CH BCI of 0.125e was obtained (H positive). However, in the CH_3 and CH_2 groups the atomic charges on the H atoms come out negative in a fit to the QM electric potential. This probably arises from not capturing the asymmetric charge distribution at the carbon atom by a point charge representation. Such a counterintuitive result was accommodated by adding an extra negative charge site near the carbon atom. In both cases the site is optimally located 0.375 Å from the carbon along the symmetry axis toward the hydrogens and carries a charge of -0.211e. No off-atom charge was needed for the CH group. The CH BCIs then came out as 0.0897e for CH_2 and CH_3 and 0.0558e for CH (all H atoms positive). No significant values were obtained for CC BCIs.

Polarizable sites were then placed near the carbon atoms, and parameters were optimized. Cylindrical symmetry was assumed for the CH_3 and CH groups, but full anisotropy was

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Table 2. Alkane Group Polarizability Parameters

CH_4 location: on carbon
    buffer size: 0.50 Å
    polarizability element: α_1 2.036 Å³ isotropic

CH_3 location: on CH_3 symmetry axis, 0.12 Å from carbon toward
    hydrogens
    buffer size: 0.65 Å
    polarizability elements: α_1 2.006 Å³ along CH_3 symmetry axis
                         α_2 1.883 Å³ perpendicular to CH_3
                                  symmetry axis

CH_2 location: on HCH bisector, 0.07 Å from carbon toward
    hydrogens
    buffer size: 0.45 Å
    polarizability elements: α_1 2.125 Å³ along carbon backbone chain
                                   (perpendicular to HCH plane)
                         α_2 1.563 Å³ perpendicular to backbone
                                   chain

CH location: on carbon
    buffer size: 0.80 Å
    polarizability elements: α_1 1.247 Å³ along CH bond
                         α_2 1.957 Å³ perpendicular to CH bond

Table 3. NMA Group Polarizability Parameters

peptide group (OCNH)
    location: mean of O, C, N positions
    buffer size: 1.00 Å
    polarizability elements: α_1 4.216 Å³ along C=O bond
                         α_2 5.292 Å³ in OCN plane, perpendicular to
                                   C=O bond
                         α_3 1.777 Å³ perpendicular to OCN plane

C methyl
    location: on CH_3 carbon
    buffer size: 0.80 Å
    polarizability elements: α_1 1.892 Å³ along CH_3 symmetry axis
                         α_2 1.959 Å³ perpendicular to CH_3 symmetry
                                   axis

N methyl
    location: on CH_3 symmetry axis, 0.11 Å from carbon toward
    hydrogens
    buffer size: 0.40 Å
    polarizability elements: α_1 1.157 Å³ along CH_3 symmetry axis
                         α_2 1.764 Å³ perpendicular to CH_3 symmetry
                                   axis

initially allowed for the CH_2 group, with principal axis 1 along the imagined carbon backbone chain (perpendicular to the HCH plane), axis 2 parallel to a line though the H atoms, and axis 3 along the HCH bisector. However, the last two directions turned out to have equal polarizabilities within the statistical uncertainty limits, and cylindrical symmetry was therefore also imposed on the CH_2 group (axis 3 being the symmetry axis). The optimized polarizabilities are given in Table 2. The group polarizability properties turned out to be very well behaved, with excellent transferability. For example, the parameters of the CH_3 group optimized to ethane only (2.006 and 1.827 Å³) do not differ much from the final values optimized to all of the compounds simultaneously (2.006 and 1.883 Å³). The wrrms deviation from the QM electric potentials was 4.85% for all alkanes except methane, for which it was 11.24%.

A somewhat surprising result was obtained involving the interactions of intramolecular induced dipoles. It turned out, namely, that it is not beneficial for the fit to the electric potential, nor for the induction energy, to have (1,2), (1,3), or even (1,4) dipoles interact. This remains true even if screening is applied. However, for intermolecular interactions over distances similar to (1,4) it is clearly necessary to have the dipoles interact in order to reproduce QM induction energies. Thus, there is a difference between polarization interactions over space and those through covalently bonded structures. A possible reason is that intramolecular electron clouds deformed by an electric field cannot be treated in terms of isolated induced dipoles that interact normally. Rather, we should assume that the covalent interaction in a bond causes two local deformations (such as at the carbon atoms in ethane) to adjust immediately to one another, and when we fit induced dipoles to the electric potential, the coupling then becomes implicitly included in the polarizability parameters. Our results show that the coupling is the same whenever sp^3 carbons are involved. On the other hand, when two separate molecules are in an electric field, the electron clouds are deformed independently. Their interaction has not been implicitly included anywhere and therefore has to be explicitly taken into account.

4.3. NMA. Using our previously determined fixed atomic charges for NMA[20] as a starting point, we explored group polarizability models with one, two, and three sites for the peptide group, in addition to the C and N methyl sites. Although the fit to the electric potential was slightly better with more polarizable sites, the differences were not very significant. Additional virtual charge sites on the oxygen and on the methyl groups were also explored, but they did not improve the fit to the electric potentials enough to warrant their presence. The wrrms deviations were typically ~4%, ~3%, and ~2.5% for the best one-, two-, and three-site models, respectively. Because of the simplicity it represented, we therefore chose to pursue the one-site model further. The optimum location of this site is at the mean of the O, C, and N positions. The site is anisotropic with (optimized) principal axis 1 parallel to the C=O bond, axis 2 in the molecular (OCN) plane perpendicular to axis 1, and axis 3 perpendicular to the plane. These directions are not obvious. We initially expected axis 1 to be in the direction of the NMA dipole moment, whose direction is approximately from the O to H(N) and makes an angle of 16° with the C=O bond, but this is not optimal. The optimized polarizability parameters are listed in Table 3.

Similarly to what was found for the alkanes, it is not beneficial to have any of the polarizable sites in NMA interact. This simple model was found to provide an excellent electrical component for the optimization of van der Waals parameters to NMA dimer interaction energies (to be published).

4.4. Molecular Polarizabilities. In Table 4 we compare the molecular polarizabilities given by the group polarizability parameters to those given by QM (calculated with Gaussian 03[21] using the MP2/6-31++G** level and basis set). The group model systematically overestimates the molecular polarizabilities by ~3% on the average. Thus, by scaling the parameters by ~97%, the discrepancies could be significantly reduced. However, we have not done so, mainly for two reasons. First, the parameters were optimized to the electric potentials around the molecules. The values are therefore those that are likely to best reproduce electro-

Table 4. Molecular Polarizability Tensor Elements (in Å³)[a]

		QM	MM
water	xx	0.95	0.98
	yy	1.16	1.19
	zz	0.96	0.98
methane	isotropic	2.00	2.04
ethane	xx	3.61	3.77
	yy	3.61	3.77
	zz	3.90	4.01
propane	xx	5.12	5.33
	yy	5.84	6.06
	zz	5.34	5.41
t-butane	xx	7.03	7.24
	yy	7.84	7.92
	zz	6.57	6.89
	xy	−0.38	−0.52
g-butane	xx	6.88	7.12
	yy	7.43	7.64
	zz	6.94	7.28
	xy	0.40	0.39
isobutane	xx	7.44	7.77
	yy	7.44	7.77
	zz	6.69	6.93
NMA	xx	8.08	8.44
	yy	7.49	7.84
	zz	5.41	5.50
	xy	−0.36	−0.32

[a] Calculated using QM optimized geometries (MP2/6-31++G**) of the molecules in standard orientations as given by Gaussian 03. Only tensor elements whose absolute values are greater than 0.1 Å³ are given.

static interactions with other molecules. The slightly too large molecular polarizabilities may come about in the optimization because the group sites are buried inside the molecules, and are also buffered, so that it takes somewhat larger induced dipoles to reproduce the electric potential when the fields are applied. Second, we combine the group polarizability model with our noniterative polarization protocol and thereby already scale the polarization energy by ~95%. Further reduction of this energy may therefore not be warranted.

Aside from the systematic deviation, the molecular polarizability elements given by the model are quite good. Their magnitudes are always in the same order as the QM values, and even small off-diagonal elements are satisfactorily reproduced.

5. Conclusions

Our SDFF efforts to produce more physically accurate MM energy functions[8] have focused on the need to reproduce maximally correct forces as well as structures and energies.[13] The incorporation of polarizability is a significant component of this goal, although we also have noted that a necessary ingredient in point charge force fields is the contribution, through the nonelectrostatic terms, of conformation-dependent charges through charge fluxes[12,8] and polarizability fluxes.[13] Since the SDFF protocol is completely based on QM data, both the polarization and the fluxes are guaranteed to produce analytically exact forces.

This paper deals with the issue of an optimal polarization model and presents the theoretical foundation of a group polarizability paradigm. The group consists of a rigid substucture of covalently connected atoms, and local axes define an anisotropic local group polarizability, thus including anisotropy explicitly from the start. We also show that a simple form of hyperpolarizability can be incorporated. Provision is made for an equivalent nonsingular-point polarizability through a "diffuse" site. Various properties of the theoretical formulation are developed in detail.

The performance of our model is described through applications to water, alkanes, and NMA. The concurrently optimized charge and polarizability parameters give excellent fits to the QM electric potentials, and the QM molecular polarizabilities are well reproduced. We conclude that such a group polarizability model must be considered a very good candidate for the inclusion of polarization into MM force fields, and we note that the SDFF protocol assures that, in addition to structures and energies, forces will be accurately modeled.

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