Published in final edited form as:

J Comput Chem. 2010 September ; 31(12): 2330–2341. doi:10.1002/jcc.21527.

Polarizable Empirical Force Field for Sulfur-Containing Compounds Based on the Classical Drude Oscillator Model

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Abstract

Condensed-phase computational studies of molecules using molecular mechanics approaches require the use of force fields to describe the energetics of the systems as a function of structure. The advantage of polarizable force fields over non-polarizable (or additive) models lies in their ability to vary their electronic distribution as a function of the environment. Towards development of a polarizable force field for biological molecules, parameters for a series of sulfur-containing molecules are presented. Parameter optimization was performed to reproduce quantum mechanical and experimental data for gas phase properties including geometries, conformational energies, vibrational spectra, and dipole moments as well as for condensed phase properties such as heats of vaporization, molecular volumes, and free energies of hydration. Compounds in the training set include methanethiol, ethanethiol, propanethiol, ethyl methyl sulfide, and dimethyl disulfide. The molecular volumes and heats of vaporization are in good accordance with experimental values, with the polarizable model performing better than the CHARMM22 non-polarizable force field. Improvements with the polarizable model were also obtained for molecular dipole moments and in the treatment of intermolecular interactions as a function of orientation, in part due to the presence of lone pairs and anisotropic atomic polarizability on the sulfur atoms. Significant advantage of the polarizable model was reflected in calculation of the dielectric constants, a property that CHARMM22 systematically underestimates. The ability of this polarizable model to accurately describe a range of gas and condensed phase properties paves the way for more accurate simulation studies of sulfur-containing molecules including cysteine and methionine residues in proteins.

Introduction

There exists a wide array of naturally occurring and synthetic sulfur-containing chemical entities (mercaptans) of industrial and medicinal interests. For example, carbon disulfide is used in the manufacturing of cellophane whereas sulfide moieties are seen in several pharmaceutical products including the anti-inflammatory drug Rofecoxib¹. The importance of sulfur is further emphasized by sulfur-containing amino acids cysteine and methionine. In addition, it is not uncommon for medicinal chemists to substitute benzene rings by five-membered thiophene rings in an effort to ameliorate potency or selectivity while conserving biological activities of the parent compound². This is because, despite the polar nature of the sulfur atom, its electron pair is readily delocalized into the pi-orbital system of the ring.

Computational chemistry approaches using empirical force fields have been employed to study a range of properties of sulfur-containing small molecules and proteins. In molecular mechanics (MM), the majority of the currently available force fields employ all-atom non-

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polarizable (or additive) models with fixed partial charges that deliberately overestimate molecular dipole moments in order to accurately describe the condensed-phase properties, thereby compensating for these models' intrinsic lack of electronic polarizability^{3,4}. Albeit computationally advantageous, additive force fields are significantly limited in their ability to simultaneously describe the electronic response of atoms and molecules in both polar and non-polar environments, a key property for the highly polarizable sulfur atom. To overcome this limitation, polarizable force fields are being developed by implementing concepts of inducible point dipoles^{5,6}, fluctuating charges^{7,8}, and Drude oscillators^{9,10}. To date, only one study of a polarizable model of thiols, based on the fluctuating charge model, has been published⁷, although such models are presumably available as part of the polarizable protein force fields developed by Ponder and coworkers (i.e. AMOEBA) and by Berne, Friesner and coworkers.^{5,11} As part of an ongoing effort to develop polarizable models for small molecules and, ultimately, proteins and other biological models, in the present manuscript we report on the optimization of a polarizable force field based on the classical Drude oscillator for a series of sulfur containing compounds representative of amino acid side chains. The present study uses both *ab initio* and experimental target data for the optimization with emphasis on the overall accuracy and transferability of the parameters across molecules of the targeted chemical classes.

To allow for the explicit treatment of inducible polarization on each molecule, we introduce classical Drude oscillators coupled to the remainder of the terms in the potential energy function, including the bonds, angles, improper angles, dihedrals angles and Lennard Jones (LJ) parameters. In the Drude model, massless charge-carrying auxiliary 'Drude' particles are linked to each non-hydrogen atom via a harmonic bond thereby creating distinct local electronic polarizability. This approach, which is also referred as the "charge-on-spring" or "shell" model¹², has been successfully applied to develop polarizable water^{13,14}, alkanes¹⁵, alcohols¹⁶, amides¹⁷, ethers^{18,19}, aromatics²⁰ and nitrogen-containing heterocycles²¹. In the present work, these efforts are extended to sulfur containing species (Figure 1), with emphasis on model compounds representative of amino acids, thereby moving closer to a polarizable protein force field based on the classical Drude oscillator.

METHODS

Empirical force field calculations were performed using the program CHARMM while quantum mechanical (QM) calculations used the programs Gaussian03²² and QChem²³. Optimized QM geometries for each compound were obtained with the MP2/aug-cc-pVDZ level of theory^{24,25}. This level of theory was also used for vibrational analysis, along with a scaling factor of 0.9017 on the frequencies and assignment of vibrational modes as previously described²⁶. Dihedral angle potential energy scans were performed at the same level of theory by only constraining the target dihedral and allowing all other degrees of freedom to relax. Final energy surfaces were based on RIMP2/cc-pVQZ single point calculations on the MP2/aug-cc-pVDZ optimized geometries.

Partial charges and atomic polarizabilities were determined by fitting to the QM electrostatic potential (ESP) maps and experimental dipole moments as previously described³ and subsequently applied to a number of systems^{9,15,16,20,21,27}. Initial guess charges were obtained from the CHARMM22 additive force field. With the sulfur atoms two virtual particles were used to approximate the sulfur lone pairs (LP). The LPs were displaced from the sulfur atom, with the partial atomic charge distributed between the sulfur and LPs, being equally distributed on the two LPs. Initial values for the polarizabilities were adapted from the Miller polarizabilities²⁸ with a value of $3.4 \text{ \AA}^{-3}$ for the sulfur atom. Polarizability scaling factors of 0.7¹⁶ and 0.85²¹ were applied to thiols and sulfides, respectively. Electrostatic parameter fitting was initiated by placing an ESP grid on concentric non-

intersecting Connolly surfaces around the molecules. A two-part calculation was necessary to determine the ESP perturbation maps required for fitting both the charges and polarizabilities: first, the ESP for the molecule alone was calculated. Then the molecule's electronic structure was "perturbed" by placing individual point charges of +0.5e on the Connolly surfaces to generate perturbed ESP maps around the molecule. The QM ESP maps were calculated using the B3LYP functional^{29–31} with the aug-cc-pVDZ basis set³². ESP fitting also included optimization of atom based Thole scaling terms, as previously shown to be required to accurately reproduce the molecular polarizability tensor^{33,34}. In addition, terminal alkyl groups more than one bond away from the sulfur atom were excluded from fitting, being assigned standard charges and polarizabilities determined for alkanes¹⁵. LP positions were optimized by varying the angle, dihedral, and distances defining their positions relative to their parent sulfur to minimize the root-mean-squared error (RMSE) between empirical and QM calculated ESPs as well as between empirical and QM calculated interactions with water. Once the LP positions were determined, the ESP fitting is repeated to yield the initial electrostatic parameters.

The initial electrostatic model was further adjusted to reproduce intermolecular interactions of the model compounds with water obtained by QM calculations. Water monomers were independently placed at orientations around the sulfur atom as shown in Figure 2. The water and mercaptan monomers in each of the complexes are constrained to the corresponding SWM4-NDP model¹⁴ and MP2/aug-cc-pVDZ optimized geometries, respectively. The interaction distance between each of the hydrogen acceptor-donor pairs was optimized at the MP2/aug-cc-pVDZ level of theory while all other geometrical features were held fixed. Single point RIMP2/cc-pVQZ calculations were then performed on each of the minimum energy geometries to obtain water-mercaptan interaction energies. Interaction energies were the difference between the dimer and sum of monomer energies; correction for basis set superposition error (BSSE) was included.

Interactions with rare gas atoms were calculated using the QM optimized geometries of mercaptans with the rare gas-model compound orientations corresponding to those of the water-mercaptan orientations (Figure 2). A rare gas atom was placed at the coordinates corresponding to the hydrogen atom of the water molecule at the 120, 180, and BIS orientations and to the proton of the water molecule at the PR orientation. In order to obtain minimum interaction energy distances, a scan in 0.01 Å increments was performed at the MP3/6-311++G(3d,3p) level of theory for each rare gas atom orientation.³⁵ The resulting interactions were used without BSSE correction.

Internal equilibrium parameters such as bonds and angles and associated force constants were optimized targeting values from crystallographic surveys of the Cambridge Structural Database³⁶ of molecules with similar chemical connectivity supplemented with QM optimized geometries for the hydrogen atoms. Internal parameter force constant optimization targeted QM vibrational spectra. Assignment of internal coordinates to vibrational frequencies was performed as presented by Pulay and coworkers²⁶ using the Molvib module in CHARMM. Empirical geometries were optimized to an RMS gradients of 10^{-5} kcal/(mol * Å). In these calculations, as well as those for the dihedral parameter optimization, no truncation of the nonbond interactions was performed.

Dihedral parameters containing only non-hydrogen atoms or the thiol hydrogen were optimized by reproducing QM potential energy surfaces (PES). Each dihedral angle was scanned at increments of 10 degrees. The CHARMM PES was calculated using the QM optimized geometries as the starting point and subsequently minimized with 500 steps of steepest decent (SD) followed by 500 steps of adapted-basis Newton-Raphson (ABNR) method to RMS gradients of 10^{-5} kcal/(mol * Å) while keeping the dihedral of interest at

the target values using harmonic restraints of 10,000 kcal/mol/radian. Torsion parameters were optimized to minimize the difference between the empirical and QM PES profiles.

Simulations of the pure solvents were carried out in the constant pressure/temperature (NPT) ensemble using cubic periodic boundary conditions. A cubic box of 128 molecules was subjected to a MD simulation at a constant pressure of 1 atm and a constant temperature of 298 K (278.9 K for methanethiol) using the velocity Verlet integrator that includes treatment of Drude particles via an extended Lagrangian.^{9,37} Long-range electrostatic interactions were treated with the Particle-Mesh Ewald (PME) method using a real-space cutoff of 12 Å, a kappa value of 0.34 and a 6-order spline and LJ interactions were truncated via a switching function over 10 to 12 Å with an isotropic long range LJ correction³⁸. Gas-phase simulations required to calculate the heats of vaporization were performed using Langevin dynamics with a friction coefficient of 5 ps⁻¹ on each of 10 monomers extracted from respective equilibrated boxes of mercaptans. The gas-phase simulations were run for 100 ps without truncation of nonbond interactions, with the first 50 ps considered as equilibration. Heats of vaporization (ΔH_{vap}) and molecular volume (V_m) were determined following a procedure described elsewhere¹⁵.

During parameter optimization, short MD simulations were performed to facilitate sampling over ranges of LJ parameters: well-depth (ϵ) and minimum energy distance ($R_{min}/2$). To assure that adequately converged results were obtained for each LJ set tested, 10 independent pure solvent MD simulations were each initiated with different initial velocities and run for 100 ps, with the initial 50 ps considered as equilibration. Final results for the calculated molecular volume for the selected set of LJ parameters, however, were based on 5 independent 5 ns MD simulation runs each with different initial velocities. For each run, the first nanosecond was considered as equilibration with the final 4 ns used for analysis. In addition, static dielectric constants of the neat mercaptans were calculated based on methods as previously presented¹⁶. Analysis of the simulations was based on coordinate sets from the trajectories saved at 1 ps intervals.

Free energies of aqueous solvation (ΔG_{sol}) were calculated based on the free energy perturbation approach³⁹ as a sum of nonpolar and electrostatic contributions according to the protocol developed by Deng and Roux⁴⁰. Gas-phase simulations were carried out using Langevin dynamics while aqueous-phase calculations were performed on a single molecule of mercaptan harmonically restrained in the center of a cubic box of 250 SWM4-NDP polarizable water molecules by a force constant of 0.5 kcal/(mol Å²) on all solute atoms except the Drude particles. A NPT simulation of 150 ps at 298 K (278.9 K for methanethiol) and 1 atm pressure was performed for each of the coupling/staging steps as previously described¹⁶. Free energy perturbation calculations were performed on the final 100 ps of these simulations using coordinates saved every 0.1 ps. Weighted histogram analysis method⁴¹ was used to calculate the dispersive and repulsive components of the free energy of solvation. The resulting free energy value was averaged over five independent runs initiated with different initial velocities. Free energies of solvation reported for the additive force field were calculated using the TIP3 water model⁴². Long-range corrections (LRC) for dispersion forces were determined as the difference between the LJ energy terms calculated using 10 and 48 Å nonbond cutoff values and averaged over the last 30 ps of the 50 ps MD simulations of the solvent-solute box system at 1 ps intervals.

RESULTS AND DISCUSSION

Model compounds subject to parameter development include both thiols and sulfides (Figure 1). Parameters for this series of sulfur-containing compounds were optimized using a combination of experimental and *ab initio* target data. These parameters include atomic

charges, atomic polarizabilities and LJ parameters for the nonbond portion of the force field and internal parameter equilibrium geometries, force constants and torsion multiplicities and phases. In order to assure future compatibility of the force field with analogs of interest such as the amino acid cysteine, emphasis was placed on obtaining parameters that accurately reproduced the target data for a series of compounds, with focus on those most relevant with respect to the amino acids. For example, with the thiols, emphasis was placed on ethanethiol parameters that also accurately treated propanethiol. This was done through additional adjustment of the torsion parameters for propanethiol while conserving both electrostatic and LJ parameters inherited from ethanethiol. Of equal biological relevance, dimethyl disulfide, a model for disulfide bridges, and ethyl methyl sulfide, representative of the amino acid methionine, were also subjects of the present development efforts. Furthermore, parameters for aliphatic carbons and hydrogens previously developed in our group^{15,16} were directly applied to the model compounds with the exception of aliphatic moieties immediately adjacent to the sulfur, which were optimized as part of the present study.

The procedure for parameter optimization followed that used previously for optimization of the Drude polarizable force field for a number of classes of small molecules^{15,16,20,21}, which was adapted from the CHARMM additive force field development protocol⁴³. A flow diagram of the parameter optimization process is depicted in Figure 3. We begin with initial guesses on the electrostatic model derived from the CHARMM22 force field and Miller's polarizabilities and initial geometries determined from QM optimization. With the geometry fixed at the QM values, the electrostatic parameters, including the partial atomic charges and polarizabilities, were optimized to fit the unperturbed and perturbed QM ESP maps. Internal parameters were then adjusted to reproduce experimental and QM geometries and QM vibrational spectra. The electrostatic model was then put to a second round of optimization with the new internal parameters in place. The partial atomic charges were further adjusted to reproduce QM intermolecular interaction energies with water. Next, the LJ parameters were optimized to reproduce experimental condensed phase properties supplemented with rare gas-mercaptan interactions. Selection of LJ parameters also took account of intermolecular interactions with water and, it should be emphasized, the optimization of the electrostatic and LJ parameters was performed in an iterative fashion as it is the combination of the two that dictates the interactions of the model compounds with their environment, including the reproduction of experimental condensed phase properties. In addition, to proper balance the LJ parameters for the different atom types in the molecule, we probed for rare gas interactions by placing helium and neon atoms at positions corresponding to the water-mercaptan orientations (Figure 3). The final models were further tested through extended pure solvent simulations to check the dielectric and diffusion constants. This latter step was of particular importance to confirm the appropriate scaling of the atomic polarizabilities¹⁷. In addition, the ability of the molecule to reproduce the anisotropy of polarizability was verified. The aforementioned steps for parameter optimization were repeated until convergence is observed. Results presented below, except where noted, are based on the final set of optimized parameters.

Internal Parameter Optimization

Target data for the equilibrium bond distances and angles were obtained from surveys of the Cambridge Structural Database (CSD)³⁶. Because of the limitations in X-ray crystallography, angles involving hydrogens were optimized to target values from MP2/aug-cc-pVDZ gas-phase optimized geometries. Optimized equilibrium values for the bonds and distances are summarized in Table 1. Our empirical model shows good overall agreement with target data with a maximum deviation of 0.4° for the H-C-H angle, with parameters transferred directly from corresponding polarizable alkanes, and 0.01 Å for the C-S bond (C-SH).

Vibrational spectra and torsional potential energy surfaces were used to optimize bond, angle, and dihedral force constants. Internal parameter force constants were optimized by comparing the empirical vibrational spectra with the QM target data. Results shown in Table S1 indicate an excellent agreement in the magnitude and assignment of each vibrational mode. The largest discrepancies between the empirical and QM torsion frequencies occurred in the lowest frequency modes associated with torsional rotations; these differences were largely due to optimization of the corresponding dihedral parameters being performed to reproduce QM PES. As shown in Figure 4, the final Drude model yields torsional energy landscapes that correspond well with the QM energy surfaces. The Drude energy profile is a significant improvement over additive CHARMM22 surfaces; such improvement is expected as the additive model was fit to a different QM level of theory. Accurate reproduction of vibrational spectra and dihedral surfaces is necessary for correct sampling of intramolecular conformations during MD simulations.

Electrostatic Model

The initial electrostatic model was optimized through ESP fitting. This is achieved by placing point charges on grids around the molecule thereby probing for orientation-dependent electrostatic perturbations of the model compound allowing for fitting of both the partial atomic charges and atomic polarizabilities. In order to account for reduced polarization expected for the condensed phase, as previously discussed³, polarizability scaling is applied during ESP fitting. Scaling factors of 0.7 and 0.85, which originate from the polarizable water and alcohol models^{13,16} and nitrogen-containing heteroaromatic compounds²¹, were applied to thiols and sulfides, respectively. Justification for the selection of these scale factors is presented below. The ESP fitted partial atomic charges were then manually adjusted to better reproduce gas-phase water interactions.

Previously, polarizability scaling was found to be necessary in order to compensate for the issue of overpolarization of molecules in solution. Two scaling factors, 70% and 85%, were previously applied to alcohols and heteroaromatic compounds^{16,20} and were tested in this study (Table 2). In the case of thiols, the use of 70% scaling yielded dielectric constants in better agreement with experimental values. For sulfides, data was only available for dimethyl disulfide, where implementation of 85% scaling factor improved the calculated results by nearly 9%. Therefore, we initially applied 70% polarizability scaling for the thiols and 85% for ethyl methyl sulfide and dimethyl disulfide. However, we later discovered that the use of 60% scaling on the sulfur atom in ethyl methyl sulfide improves its pure solvent properties, as discussed below.

Electron distributions are typically not symmetric about atoms in molecules thereby contributing to asymmetric interactions with the environment. Accordingly, a lack of electronic anisotropy at the atom level in the force field can limit its ability to achieve the proper balance of interactions with the environment as a function of orientation. In the Drude force field, such anisotropy is accounted for by the presence of LPs and by anisotropic atomic polarizabilities⁴⁴, typically placed on hydrogen bond acceptors. As previously discussed, inclusion of LPs is particularly important to accurately reproduce the angular dependence of electrostatic response^{44,45}. Initially, LP positions on the sulfurs were optimized to reduce RMSE between the empirical and QM ESP maps. The resulting electrostatic model was then used to calculate interaction energies with water as a function of orientation (see below) using LJ parameters obtained from the pure solvent optimization and LP positions were further adjusted to improve the anisotropy of such interactions. This procedure was performed for methanethiol (MESH) with the resulting LP positions transferred to ethanethiol (ETSH) and propanethiol (PRSH) with additional optimizations to the LP distance only. In the case of dimethyl disulfide (DMDS) and ethyl methyl sulfide (EMS), the LP positions were further adjusted to improve agreement with QM water-

interactions. The final sulfur LP positions were as follows: distance between the sulfur atomic centers and LPs = 0.80 Å for MESH and EMS, 0.75 Å for ETSH/PRSH, and 0.90 Å for DMDS; C-S-LP angle = 95.0° for MESH/ETSH/PRSH/EMS and 110.0° for DMDS; virtual torsion angle H(S)-C-S-LP = $\pm 100^\circ$ for MESH/ETSH/PRSH/EMS and $\pm 90^\circ$ for DMDS.

Once optimization of the LP positions was complete, anisotropic polarizability was assigned to the sulfur atoms by treating its Drude force constant (k_D) as a tensor, as previously described⁴⁴. The polarizability tensors were optimized to reproduce the QM polarization response as determined by calculating the electrostatic field around the molecule as a function of orientation in the absence and the presence of a perturbing ion⁴⁴. The difference between the electric field in the presence and absence of the ion determines the polarization response. To model this property, two perpendicular arcs of +0.5e point charges were placed around each sulfur atom of the model compounds presented in this study. Ethanethiol, ethyl methyl sulfide, and dimethyl disulfide are shown in Figure 5 and additional molecules are shown in Figure S1 of the supporting information. To produce reference data, QM calculations were performed using the B3LYP/aug-cc-pVDZ level of theory. The polarizability tensor on each sulfur atom was then adjusted to maximize the agreement of polarization response with the QM data. Comparison of the QM and polarizable model profiles shows the latter to satisfactorily reproduce the change in the polarization response as a function of orientation. As expected, electronic polarization peaks at the anticipated LP positions on the sulfur atoms in both profiles. The overall decrease in magnitude of polarization calculated by our model is expected given the scaling of polarizabilities applied to the compounds. In addition, optimized values for ethanethiol were directly applied to and shown to be valid for propanethiol (Figure S1 of the Supporting Information). This indicates potential parameter transferability across analogous molecules, a key property that would alleviate future parameter development.

QM and experimental gas phase dipole moments along with those calculated using the final electrostatic models are shown in Table 3. Compared to the non-polarizable CHARMM22 force field, where an average underestimation of 12% is observed, the Drude polarizable model showed improvement with an average 5% overestimation of the experimental dipole moments. Worth noting is the 28% underestimation of the gas-phase dipole moment of ethyl methyl sulfide in the additive model compared to the 6% overestimation by the polarizable force field. However, the dipole moment for ethanethiol was overestimated by 13% compared to an underestimation of 9% by the additive force field. This disagreement may arise from systematic overestimation of the dipole moment by QM methods due to inadequate treatment of electron correlation⁴⁶. As these QM values were also considered as target data during optimization of the electrostatic model, this may have contributed to the observed pattern. The systematic underestimation by the non-polarizable CHARMM22 model is surprising since the partial atomic charges in that model were typically optimized to yield dipole moments larger than gas phase experimental or QM values. That underestimation may be due to the use of different QM theory as the target data as well as the relatively larger contribution of the LJ energy to the pure solvent properties in the mercaptans as compared to, for example, alcohols, making the exact treatment of the dipole moment less critical. Nevertheless, our polarizable model presents an overall improvement in terms of prediction of molecular dipole moments as compared to the non-polarizable CHARMM22.

Interactions with water

Hydrogen bonding depends largely on electrostatic interactions, namely those involving permanent dipoles. Therefore, intermolecular interactions with water represent an essential target for the nonbond model. To perform additional optimization of the electrostatic

parameters beyond those obtained from ESP fitting, the QM minimum interaction energies and distances for water molecules placed around the thiol or sulfide groups were used as target data. Reproduction of this target data required minor adjustments to the partial atomic charges of the sulfur, their LPs, and adjacent alkyl group as well as the LP positions. The level of agreement between the polarizable model and the QM data is shown in Table 4. Because our focus was to assure that the model reflects the anisotropy of the interactions with the environment, we aimed to maximize the overall balance by minimizing the both the energy differences and the standard deviation of energy differences. In general, minimum interaction distances and energies were in good agreement with QM values with the 120 orientations being in the worst agreement for all molecules. This is especially pronounced in EMS, resulting in a standard deviation of 0.57. However, the order of the interaction energies is conserved between the two orientations indicating reproduction of the anisotropy of the interactions. Importantly, as discussed below, experimental condensed phase properties were also well behaved. Sacrifice of certain elements in order to achieve better agreement of more important properties is often required during force field optimization because of the simplified energy function being applied to model a range of physical aspects of molecules.

Results from the CHARMM22 additive force field calculations for the interactions with water are provided in Table S2 of the supplemental data. Analysis of the additive CHARMM22 force field results shows them to be significantly more favorable than the QM target data. This overestimation of interaction energies is expected as the partial charges in the additive model need to be overpolarized in order to compensate for the lack of explicit polarizability and allow for reproduction of condensed phase properties. Furthermore, the additive force field systematically underestimates the interaction energy at the 120 orientation. This discrepancy is characteristic of a system that lacks electrostatic anisotropy. In contrast, the two anisotropic elements introduced in our Drude polarizable force field (e.g.: LPs and polarizability tensors on hydrogen bond acceptors) allowed our model to produce more accurate energies and geometries for the interactions with water. This is clearly evident for ethanethiol, where the SD for the interaction energies using the polarizable model is 0.05 kcal/mol, a clear improvement over 0.63 kcal/mol for the CHARMM22 non-polarizable force field (Table S2).

Of particular challenge was optimization of the LJ parameters to obtain MM interaction distances that are both in satisfactory agreement with QM calculated values and are able to reproduce experimental condensed phase properties. In the optimized model, the MM distances for the interactions with water were significantly shorter than the QM values (Table 4). This difference may be due to sulfur being a “softer,” more polarizable atom than, for example, oxygen, as evidenced by the changes in the interaction energy for the water-sulfur dimers with respect to distance being relatively small at regions near the minima (Figure 6). These results also indicate that interaction distances relatively far from the QM minimum value are thermodynamically accessible in the condensed phase.

Pure Solvent Properties

Accurate treatment of intermolecular interactions in force fields relies on the correct combination of the electrostatic and LJ parameters. As noted above, the optimization of the LJ parameters is performed iteratively along side with optimization of the electrostatic parameters. This step proved to be especially challenging since ionic and hydrogen bond interactions as well as dispersion types of interactions stem from these attributes of the force field. Optimal LJ parameters for the sulfur atoms were determined by identifying LJ parameters that best reproduce condensed phase properties of the molecule defined by experimental enthalpy of vaporization (H_v) and molecular volume (V_m) as well as the relative interaction of the model compounds with rare gases as a function of orientation⁴⁷.

For each molecule, a broad range of LJ parameters were scanned followed by more rigorous local scans in order to obtain sets that reproduce condensed phase properties within 3% of the respective experimental values. As a result, these scans involved generation of a range of well-depth and $R_{\min}/2$ values and then performing pure solvent simulations for each pair, with the set yielding the best agreement with experiment selected for re-evaluation of the electrostatic parameters. During optimization, the following assumptions were made. The LJ parameters for ethanethiol and propanethiol were restrained to be identical, while those of methanethiol were allowed to differ due to the inability to obtain parameters that treated all three molecules with sufficient accuracy. Facilitation of the LJ parameter optimization with respect to the relative values of the individual LJ parameters was obtained by monitoring interactions with rare gases. The RMS fluctuations about the average difference for the minimum interaction energies and distances are indicators for the balance in dispersion interactions across different atom types and orientations.³⁵ The results from this analysis are included in Table S3 of the supplemental material with the pure solvent enthalpies and molecular volumes shown in Table 5. Overall, the agreement is satisfactory. Results for the methanethiol, dimethyl disulfide and ethyl methyl sulfide all fall within 3% of experimental values. With ethanethiol and propanethiol it was not possible to attain this level of agreement with the constraint that the LJ parameters be identical for these two molecules. However, the extent of agreement, 3.7% or better, was deemed acceptable. It is encouraging to note that parameters directly transferred from ethanethiol to propylthiol were able to reproduce condensed phase properties within 1% of experimental data and well within the targeted error (Table 5). Also worth noting is that LJ parameters differ across our model compounds. This lack of LJ parameter transferability stems from the high sensitivity of mercaptan pure solvent properties to LJ parameters, as exemplified based on calculations of the pure solvent properties of ethanethiol and ethyl methyl sulfide for a range of LJ parameters as shown in Table S4 of the supplementary material.

Free energy of aqueous solvation

As an additional test of the model, the hydration free energy for each of the model compounds was calculated and compared to experimental data. Although more emphasis was attributed to the pure solvent properties, free energies of solvation were considered during the optimization process since they reflect the overall behavior of molecules in water and are especially important for MD simulations of biological entities in explicit water systems. The results for the non-polarizable CHARMM22, polarizable Drude, and experimental values are shown in Table 6. The table also includes the LJ long-range correction to the free energies due to the truncation of the long-range LJ interactions. Comparisons of the Drude and experimental data show that the polarizable model, with the exception of propanethiol and ethyl methyl sulfide, systematically overestimates hydration free energies (Table S5 of the supplementary material) in contrast to CHARMM22 that produces less favorable values than experiment, consistent with previously reported results^{40,48,49}. This overestimation has also been observed in other polarizable force field development efforts in our group including alkanes¹⁵, alcohols¹⁶, aromatic compounds²⁰, and nitrogen-containing heteroaromatic compounds²¹, as well as in work based on a fluctuating charge model of alkanes⁵⁰. One way to modulate solvation free energy is to adjust the LJ parameters of the sulfur atom. However, this would disrupt the already well-reproduced pure solvent properties. An alternate approach to circumvent this problem is to derive specific atom LJ parameters for interactions of specific atom pairs^{51,52}. Implementing this approach, we used LJ terms (i.e. NBFIX option in CHARMM) specific for the individual S---O_{water} atom pairs. The strategy was to increase the well-depth and $R_{\min}$ simultaneously while capping the variation of each at 0.05 kcal/mol and 0.05 Å, respectively, so to not disturb the overall anisotropy of interactions with water molecules. As

depicted in Table 6, inclusion of this extra degree of freedom yields solvation free energies that are in good agreements with experimental values.

Pure solvent dielectric constants

Dielectric constant is an important property that reflects the degree of polarization of individual solvent molecules, their reorientation behavior in pure solvents, as well as contributing to the energetics of dissolution of solutes in that liquid. Thus, the ability of a force field to reproduce experimental dielectric constant is an efficient marker for the quality of our parameters. In addition, as discussed above, our optimization strategy uses the dielectric constant as an indicator for the scaling of polarizability in our models. Presented in Table 2 are the Drude model, non-polarizable model, and experimentally determined dielectric constants. In general, the Drude model is in satisfactory agreement with the available experimental values with an average overestimation of +2%. The results using the 0.7 versus 0.85 scaling in the table justify the selection of the former for the thiols and the latter for the sulfides, with the exception of ethyl methyl sulfide in which 0.60 scaling is applied to the sulfur atom (see following paragraph). Another observation is the consistent underestimation of the dielectrics by CHARMM22, being as much as 68% for ethyl methyl sulfide. Such disagreement represents the inherent limitation of the model associated with the additive approximation, an issue previously discussed for alkanes¹⁵.

The lack of an experimental dielectric constant for ethyl methyl sulfide led us to generate dimethylsulfide (DMS) using parameters from both dimethyl disulfide and ethyl methyl sulfide. Direct transfer of the electrostatic parameters through analogy leads to an overestimation of the computed dielectric constant ($\epsilon = 9.65$) versus the experimental value ($\epsilon = 6.51$) (Table 7). Closer analysis of that dimethyl disulfide model showed the dipole moment to significantly overestimate both the experimental and calculated QM gas-phase values. To determine if the overestimation of the dipole led to the overestimation of the dielectric, partial atomic charge was manually transferred from the LPs to terminal the carbon atoms, yielding two additional models where the dipole moment was in agreement with the QM (Model 2) and experimental (Model 3) gas phase values. As may be seen, the decrease in the dipole leads to lower dielectric constants, with the charge distribution yielding the experimental gas phase values giving a dielectric constant for the pure solvent in satisfactory agreement with experiment (Table 7). As the ethyl methyl sulfide model also reproduces the experimental gas phase dipole moment it may be assumed that the dielectric constant for that model is representative of the experimental regimen, validating the use of 0.6 scaling of the polarizabilities for the sulfides.

Conclusion

The classical Drude oscillator model provides a means to explicitly include electronic polarization in a force field. In this study we have developed a polarizable force field for a series of sulfur-containing compounds using this model. Because fluctuations in electron densities are made possible by oscillation of virtual charges on harmonic springs attached to the core of each non-hydrogen atom, variations in intermolecular interactions arising from transitions between environments of varying electric fields are more accurately described as compared to additive force fields. To support this hypothesis, we compared various properties calculated by both additive and polarizable force fields. These properties include heats of vaporization, molecular volumes, molecular interactions with water, solvation free energies, as well as dielectric constants. Our results demonstrate that explicit inclusion of electronic polarization raises the accuracy of the force field in describing these various properties, leading to significant improvement over the CHARMM22 additive force field. Accordingly, the presented model for mercaptans provides a building block towards a more

accurate computational representation of biomolecules and will be valuable for *in silico* studies of various sulfur-containing molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge financial support from the NIH (GM051501 and GM072558) and computational support from the DoD High Performance Computing, the Pittsburgh Supercomputing Center and the NSF/TeraGrid computational resources.

References

1. Schnitzer TJ, Truitt K, Fleischmann R, Dalgin P, Block J, Zeng Q, Bolognese J, Seidenberg B, Ehrich EW. *Clinical Therapeutics*. 1999; 21(10):1688–1702. [PubMed: 10566565]
2. Sperry JB, Wright DL. *Curr Opin Drug Discov Devel*. 2005; 8(6):723–740.
3. Anisimov VM, Lamoureux G, Vorobyov IV, Huang N, Roux B, MacKerell AD. *J Chem Theory Comput*. 2005; 1(1):153–168.
4. MacKerell AD Jr. *J Comput Chem*. 2004; 25(13):1584–1604. [PubMed: 15264253]
5. Kaminski GA, Stern HA, Berne BJ, Friesner RA. *J Phys Chem A*. 2004; 108(4):621–627.
6. Warshel A, Levitt M. *J Mol Biol*. 1976; 103(2):227–249. [PubMed: 985660]
7. Patel S, Brooks CL III. *J Comput Chem*. 2004; 25:1–15. [PubMed: 14634989]
8. Rappé AKG, WA. *J Phys Chem A*. 1991; (95):6.
9. Lamoureux G, Roux B. *The Journal of Chemical Physics*. 2003; 119(6):3025–3039.
10. Drude, P. *The Theory of Optics*. Longmans, Green, and Co; New York: 1902.
11. Ponder JW, Case DA. *Adv Protein Chem*. 2003; 66:27–85. [PubMed: 14631816]
12. Rick SW, Stuart SJ. *Rev Comp Chem*. 2002; 18:89–146.
13. Lamoureux G, Harder E, Vorobyov IV, Roux B, MacKerell AD Jr. *Chem Phys Lett*. 2006; 418:245–249.
14. Lamoureux G, MacKerell AD Jr, Roux B. *J Chem Phys*. 2003; 119:5185–5197.
15. Vorobyov IV, Anisimov VM, MacKerell AD Jr. *J Phys Chem B*. 2005; 109(40):18988–18999. [PubMed: 16853445]
16. Anisimov VM, Vorobyov IV, Roux B, MacKerell AD Jr. *J Chem Theory Comp*. 2007; 3:1927–1946.
17. Harder E, Anisimov VM, Whitfield T, MacKerell AD Jr, Roux B. *J Phys Chem B*. 2008; 112(11):3509–3521. [PubMed: 18302362]
18. Vorobyov I, Anisimov VM, Greene S, Venable RM, Moser A, Pastor RW, MacKerell AD Jr. *Journal of Chemical Theory and Computation*. 2007 In Press.
19. Baker CM, Mackerell AD Jr. *J Mol Model*. 2009
20. Lopes PE, Lamoureux G, Roux B, Mackerell AD Jr. *J Phys Chem B*. 2007; 111(11):2873–2885. [PubMed: 17388420]
21. Lopes PEM, Lamoureux G, MacKerell AD Jr. *Journal of Computational Chemistry*. 2008
22. Frisch, MJT.; GW; Schlegel, HB.; Scuseria, GE.; Robb, MA.; Cheeseman, JR.; Montgomery, JA., Jr; Vreven, T.; Kudin, KN.; Burant, JC.; Millam, JM.; Iyengar, SS.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, GA.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, JE.; Hratchian, HP.; Cross, JB.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, RE.; Yazyev, O.; Austin, AJ.; Cammi, R.; Pomelli, C.; Ochterski, JW.; Ayala, PY.; Morokuma, K.; Voth, GA.; Salvador, P.; Dannenberg, JJ.; Zakrzewski, VG.; Dapprich, S.; Daniels, AD.; Strain, MC.; Farkas, O.; Malick, DK.; Rabuck, AD.; Raghavachari, K.; Foresman, JB.; Ortiz, JV.; Cui, Q.; Baboul, AG.; Clifford, S.; Cioslowski, J.; Stefanov, BB.;

- Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, RL.; Fox, DJ.; Keith, T.; Al-Laham, MA.; Peng, CY.; Nanayakkara, A.; Challacombe, M.; Gill, PMW.; Johnson, B.; Chen, W.; Wong, MW.; Gonzalez, C.; Pople, JA. Gaussian 03, Revision C.02. Gaussian, Inc; Wallingford CT: 2004.
23. Shao Y, Molnar LF, Jung Y, Kussmann J, Ochsenfeld C, Brown ST, Gilbert AT, Slipchenko LV, Levchenko SV, O'Neill DP, DiStasio RA Jr, Lochan RC, Wang T, Beran GJ, Besley NA, Herbert JM, Lin CY, Van Voorhis T, Chien SH, Sodt A, Steele RP, Rassolov VA, Maslen PE, Korambath PP, Adamson RD, Austin B, Baker J, Byrd EF, Dachsel H, Doerksen RJ, Dreuw A, Dunietz BD, Dutoi AD, Furlani TR, Gwaltney SR, Heyden A, Hirata S, Hsu CP, Kedziora G, Khalliulin RZ, Klunzinger P, Lee AM, Lee MS, Liang W, Lotan I, Nair N, Peters B, Proynov EI, Pieniazek PA, Rhee YM, Ritchie J, Rosta E, Sherrill CD, Simmonett AC, Subotnik JE, Woodcock HL 3rd, Zhang W, Bell AT, Chakraborty AK, Chipman DM, Keil FJ, Warshel A, Hehre WJ, Schaefer HF 3rd, Kong J, Krylov AI, Gill PM, Head-Gordon M. *Phys Chem Chem Phys*. 2006; 8(27):3172–3191. [PubMed: 16902710]
24. Kendall RA, Dunning JTH, Harrison RJ. *The Journal of Chemical Physics*. 1992; 96(9):6796–6806.
25. Woon DE, Dunning TH Jr. *J Chem Phys*. 1993; 98:1358–1371.
26. Pulay P, Fogarasi G, Pang F, Boggs JE. *J Am Chem Soc*. 1979; 101:2550–2560.
27. Vorobyov I, Anisimov VM, Greene S, Venable RM, Moser A, Pastor RW, MacKerell AD Jr. *Journal of Chemical Theory and Computation*. 2007; 3:1120–1133.
28. Miller KJ. *J Am Chem Soc*. 1990; 112(23):8533–8542.
29. Becke AD. *Phys Rev A*. 1988; 38:3098–3100. [PubMed: 9900728]
30. Becke AD. *J Chem Phys*. 1993; 98:5648–5652.
31. Lee C, Yang W, Parr RG. *Phys Rev B*. 1988; 37:785–789.
32. Kendall RA, Dunning Thom H Jr, Robert JH. *The Journal of Chemical Physics*. 1992; 96(9):6796–6806.
33. Thole BT. *Chem Phys*. 1981; 59:341–350.
34. van Duijnen PT, Swart M. *The Journal of Physical Chemistry A*. 1998; 102(14):2399–2407.
35. Yin D, MacKerell AD Jr. *J Comp Chem*. 1998; 19:334–348.
36. Allen FH. *Acta Crystallogr, Sect B*. 2002; B58:380–388. [PubMed: 12037359]
37. Iftimie R, Minari P, Tuckerman ME. *Proc Natl Acad Sci U S A*. 2005; 102(19):6654–6659. [PubMed: 15870204]
38. Allen, MP.; Tildesley, DJ. *Computer Simulation of Liquids*. Oxford University Press; New York: 1989.
39. Simonson, T. *Computational Biochemistry and Biophysics*. Becker, Oren M.; ADMJ; Boux, Benoit; Watanabe, Masakatsu, editors. New York: 2001. p. 169
40. Deng Y, Roux B. *J Phys Chem B*. 2004; 108(42):16567–16576.
41. Kumar S, Bouzida D, Swendsen RH, Kollman PA, Rosenberg JM. *J Comput Chem*. 1992; 13:1011.
42. Jorgensen WL, Chandrasekhar J, Madura JD, Impey RW, Klein ML. *Journal of Chemical Physics*. 1983; 79:926–935.
43. MacKerell AD, Bashford D, Bellott M, Dunbrack RL, Evanseck JD, Field MJ, Fischer S, Gao J, Guo H, Ha S, Joseph-McCarthy D, Kuchnir L, Kuczera K, Lau FTK, Mattos C, Michnick S, Ngo T, Nguyen DT, Prodhom B, Reiher WE, Roux B, Schlenkrich M, Smith JC, Stote R, Straub J, Watanabe M, Wiorkiewicz-Kuczera J, Yin D, Karplus M. *J Phys Chem B*. 1998; 102(18):3586–3616.
44. Harder E, Anisimov VM, Vorobyov IV, Lopes PEM, Noskov SY, MacKerell AD, Roux B. *Journal of Chemical Theory and Computation*. 2006; 2(6):1587–1597.
45. Dixon RW, Kollman PS. *Journal of Computational Chemistry*. 1997; 18:1632–1646.
46. Noga J, Pluta T. *Chemical Physics Letters*. 1997; 264(1–2):101–108.
47. Yin D, MacKerell AD Jr. *J Phys Chem*. 1996; 100:2588–2596.
48. Shishkin OV, Gorb L, Zhikol OA, Leszczynski J. *J Biomol Struct Dyn*. 2004; 21:537–553. [PubMed: 14692798]

49. Shirts MR, Pande VS. *J Chem Phys.* 2005; 122(13):134508. [PubMed: 15847482]
50. Davis JE, Warren GL, Patel S. *J Phys Chem B.* 2008; 112(28):8298–8310. [PubMed: 18570394]
51. Halgren TA. *J Am Chem Soc.* 1992; 114:7827–7843.
52. Al-Matar AK, Rockstraw DA. *J Comput Chem.* 2004; 25(5):660–668. [PubMed: 14978709]
53. David, R.; Lide, E. *Handbook of Chemistry and Physics.* 84. CRC Press: Boca Raton, Florida; 2003.
54. Buyong Ma J-HLNL. *Journal of Computational Chemistry.* 2000; 21(10):813–825.
55. Wang M, Wong CF, Liu J, Zhang P. *Chemical Physics Letters.* 2007; 442(4–6):464–467.
56. Chambers CC, Hawkins GD, Cramer CJ, Truhlar DG. *The Journal of Physical Chemistry.* 1996; 100(40):16385–16398.
57. Alessandra Villa AEM. *Journal of Computational Chemistry.* 2002; 23(5):548–553. [PubMed: 11948581]

Figure 1.

Mercaptan series of compounds subject to parameter optimization: primary mercaptans (thiols) (A) methanethiol, (B) ethanethiol, and (C) propanethiol and sulfides (D) dimethyl disulfide and (E) ethyl methyl sulfide.

Figure 2.

Orientations of water molecules around the mercaptan demonstrated using methanethiol (left) and dimethyl disulfide (right). Sulfur lone pairs are shown as cyan spheres. In the “120” orientation, the hydrogen atom of the water molecule points toward one of the lone pairs of the sulfur atom while water at the “BIS” orientation points towards the sulfur atom by cutting between the two lone pairs. Water molecules at the “180” orientation looks toward the sulfur atom in the same axis as the C-S bond. In the “PR” orientation, O_w is directed at the proton atom in the S-H bond axis. For dimethyl disulfide, the water molecule at the “TRI” position is perpendicular to and bisects the S-S bond.

Figure 3. Schematic overview of the process of parameter optimization for the CHARMM polarizable force field.

Figure 4. Potential energy surfaces for rotation of dihedrals in the mercaptan series. Where available, the fitted Drude data (solid line) are compared to both QM (“X”) and non-polarizable CHARMM22 (dotted line). QM energies were computed at the MP2/aug-cc-pVQZ level of theory on MP2/aug-cc-pVDZ optimized geometries

Figure 5. Polarization response as a function of the ion orientation around the sulfur atom. Perturbation ions around the selected molecule are shown as red and blue spheres for ions placed on arcs that are in and out of the C-S-H/S/C plane, respectively, with corresponding polarization profile shown on the right from the QM B3LYP/aug-cc-pVDZ and Drude polarizable models.

Figure 6.

QM/Drude interaction energies for MESH-water dimers as a function of distance between H_w -S for 120, 180, and BIS orientations and between O_w ---H for PR orientation. QM scans on the distances and subsequent energy calculations were both performed at the MP2/aug-cc-pVDZ level of theory.

Table 1

Comparisons of internal geometries using Drude polarizable models with results from a survey of the Cambridge Crystallographic database and in cases involving hydrogens, from MP2/aug-cc-pVDZ optimized geometries.

Bonds	MESH			ETSH			EMS			DMDS			RMSD
	Drude	Target		Drude	Target		Drude	Target		Drude	Target		
bSH	1.35	1.35		1.35	1.35								0.00
bCS	1.81	1.83		1.81	1.81		1.80	1.79		1.81	1.81		0.01
bCS-C							1.81	1.81					0.00
bSS										2.03	2.03		0.00
bHC	1.11	1.10		1.11	1.10		1.11	1.10		1.11	1.10		0.01
bC2H							1.11	1.10					0.01
Angles													
aCSH	96.80	96.60		96.40	96.60								0.20
aHCS	109.60	109.50		106.60	106.60		109.90	109.70		109.30	109.10		0.15
aHCH	109.30	109.40		109.10	108.40		109.10	109.20		109.60	109.80		0.37
aCCS				113.30	113.40		113.40	113.70					0.22
aCSS										103.90	103.90		0.00
aCSC							100.80	100.41					0.39

Bonds in Å and angles in degrees and RMSD is the root-mean-square difference. Drude values were obtained from energy minimized structures.

Table 2

Calculated and experimental dielectric constants.

Molecule	C22	Drude _{0.70}	Δ%	Drude _{0.85}	Δ%	Exp. ε
MESH	5.91 (0.02)	8.60 (0.01)	n/a	9.43 (0.02)	n/a	n/a
ETSH	4.30 (0.00)	7.79 (0.01)	17	8.35 (0.02)	25	6.67
PRSH	n/a	5.94 (0.01)	1	6.38 (0.00)	7	5.94
EMS	4.98 (0.01)	6.91 (0.02) *	n/a	7.09 (0.01)	n/a	n/a
DMDS	3.03 (0.00)	8.15 (0.01)	-15	8.44 (0.03)	-12	9.60

ε_∞ estimation from the Clausius-Mossotti equation using gas-phase polarizabilities of mercaptans. Values in bold represent those for the final polarizable model.

Experimental dielectric constants were extracted from literature ⁵³.

* Data for EMS was calculated with 0.60 polarizability scaling on the sulfur atom.

Table 3Dipole moments (Debye) for model compounds in the *gauche* (g) conformation

	Exp.	QM	C22	% diff _{exp}	Drude	% diff _{exp}
MESH (g)	1.52 ⁵⁴	1.71	1.43	-6	1.52	0
ETSH (g)	1.58 ⁵⁴	1.84	1.44	-9	1.78	13
PRSH (g)	1.60 ⁵⁴	1.78	n/a	n/a	1.62	1
DMDS (g)	1.85 ⁵³	2.32	1.73	-6	1.89	2
EMS (g)	1.56 ⁵⁴	1.85	1.13	-28	1.66	6
Avg.				-12		4

Table 4
QM and Drude Mercaptan-Water Minimum Interaction Energies and Distances

MESH	QM	Drude		
Orientation	D _{min}	E _{int}	D _{min}	ΔE _{int}
120	2.52	-3.48	2.26	-0.26
180	2.81	-0.97	2.58	-0.23
BIS	2.69	-1.60	2.55	-0.14
PR	2.26	-2.02	2.07	-0.19
SD				0.05
Avg.				-0.21
RMS				0.21
ETSH (g)	QM	Drude		
Orientation	D _{min}	E _{int}	D _{min}	ΔE _{int}
120	2.51	-3.14	2.24	-0.27
180	2.74	-1.11	2.45	-0.29
BIS	2.66	-1.67	2.45	-0.21
PR	2.22	-2.37	1.99	-0.23
SD				0.04
Avg.				-0.25
RMS				0.25
ETSH (t)	QM	Drude		
Orientation	D _{min}	E _{int}	D _{min}	ΔE _{int}
120	2.49	-3.34	2.20	-0.29
180	2.74	-1.10	2.46	-0.28
BIS	2.65	-1.77	2.41	-0.24
PR	2.22	-2.22	1.97	-0.25
SD				0.02
Avg.				-0.27
RMS				0.27
PRSH (g)	QM	Drude		
Orientation	D _{min}	E _{int}	D _{min}	ΔE _{int}

MESH		QM		Drude	
Orientation	D _{min}	E _{int}	D _{min}	E _{int}	AD
120	2.49	-3.39	2.22	-4.03	-0.27
180	2.72	-1.16	2.43	-1.45	-0.29
BIS	2.61	-1.93	2.40	-2.32	-0.21
PR	2.25	-1.99	2.01	-2.03	-0.24
SD					0.03
Avg.					-0.25
RMS					0.25
PRSH (t)	QM	Drude			
Orientation	D _{min}	E _{int}	D _{min}	E _{int}	AD _{min}
120	2.49	-3.38	2.21	-3.73	-0.28
180	2.74	-1.13	2.45	-1.30	-0.29
BIS	2.65	-1.81	2.42	-2.11	-0.23
PR	2.22	-2.20	2.03	-2.58	-0.19
SD					0.05
Avg.					-0.25
RMS					0.25
DMDS	QM	Drude			
Orientation	D _{min}	E _{int}	D _{min}	E _{int}	AD _{min}
120	2.50	-2.75	2.29	-2.32	-0.21
BIS	2.64	-1.66	2.39	-1.87	-0.25
TRI	3.60	-1.59	3.51	-1.26	-0.09
SD					0.08
Avg.					-0.18
RMS					0.20
EMS (g)	QM	Drude			
Orientation	D _{min}	E _{int}	D _{min}	E _{int}	AD _{min}
120	2.45	-3.82	2.31	-3.07	-0.18
BIS	2.61	-2.07	2.44	-2.12	-0.21
SD					0.02
Avg.					-0.20

MESH	QM		Drude		AD		ΔE_{int}
Orientation	D_{min}	E_{int}	D_{min}	E_{int}	ΔD_{min}	ΔE_{int}	
RMS							0.54
EMS (t)	QM		Drude				
Orientation	D_{min}	E_{int}	D_{min}	E_{int}	ΔD_{min}	ΔE_{int}	
120	2.44	-4.27	2.25	-2.75	-0.23	1.52	
BIS	2.60	-2.26	2.40	-1.44	-0.20	0.82	
SD					0.01	0.49	
Avg.					-0.22	1.17	
RMS					0.22	1.22	

* Calculations were based on gauche (g) and trans (t) conformations. Distances in Å and energies in kcal/mol. D_{min} : minimum interaction distance; E_{int} : minimum interaction energy; SD: standard deviation; Avg.: average; RMS: root-mean-squared value.

Calculated condensed phase properties using the non-polarizable CHARMM22 and polarizable Drude models and compared to experiment.

Table 5

	Exp.			C22			Drude	
	T _m	V _m	ΔH _v	V _m (% err)	ΔH _v (%err)	V _m (% err)	ΔH _v (% err)	
MESH	278.9	90.17	5.87	86.71 (-3.8)	5.99 (+2.0)	90.15 (+0.0)	5.80 (-1.2)	
ETSH	298.0	124.09	6.73	120.21 (-3.1)	6.59 (-2.0)	119.47 (-3.7)	6.74 (+0.1)	
PRSH	298.0	150.04	7.62	n/a	n/a	149.03 (-0.7)	7.61 (-0.1)	
DMDS	298.0	147.22	9.04	148.84 (+1.1)	8.97 (-0.8)	149.64 (+1.6)	8.87 (-1.9)	
EMS	298.0	150.17	7.61	151.88 (+1.1)	7.72 (+1.4)	154.17 (+2.7)	7.39 (-2.8)	

LJ Parameters (well-depth; R_{min}/2): MESH (-0.43; 2.05), ETSH/PRSH (-0.42; 2.02), DMDS (-0.32; 2.00), EMS (-0.31; 2.05). Temperatures are in Kelvin, V_m in Å³ and ΔH_v in kcal/mol.

Table 6

Calculated free energies of solvation using the additive CHARMM22 and polarizable Drude models compared to experiment.

	CHARMM22			Drude		
	Exp.	LRC	C22	% diff	LRC	Drude
MESH	-1.24 ⁵⁵	-0.27	-0.91	27	-0.32	-1.18
ETSH	-1.30 ⁵⁵	-0.36	-0.86	34	-0.40	-1.37
PRSH	-1.05 ⁵⁶	n/a	n/a	n/a	-0.49	-1.14
DMDS	-1.83 ⁵⁶	-0.48	-1.09	39	-0.54	-1.88
EMS	-1.46 ⁵⁷	-0.47	-0.02	99	-0.49	-1.37
Average				50		

Units in kcal/mol

Table 7

Calculated dipole moments and dielectric constants using different dimethyl sulfide charge models.

	μ	ϵ
Experiment/QM	1.50/1.79	6.51
Model 1	2.12	9.65
Model 2	1.76	8.57
Model 3	1.47	6.77

Experimental μ : 1.50; ϵ : 6.51. Model 3 was accepted as the final model.