JCTC Journal of Chemical Theory and Computation

Letter

pubs.acs.org/JCTC

Improving the Prediction of Absolute Solvation Free Energies Using the Next Generation OPLS Force Field

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Supporting Information

ABSTRACT: Explicit solvent molecular dynamics free energy perturbation simulations were performed to predict absolute solvation free energies of 239 diverse small molecules. We use OPLS2.0, the next generation OPLS force field, and compare the results with popular small molecule force fields—OPLS_2005, GAFF, and CHARMm-MSI. OPLS2.0 produces the best correlation with experimental data (R^2 = 0.95, slope = 0.96) and the lowest average unsigned errors (0.7 kcal/mol). Important classes of compounds that performed suboptimally with OPLS_2005 show significant improvements.

INTRODUCTION

Water plays an essential role in biological systems, and the proper treatment of small molecules in water is an integral part of *in silico* drug discovery. For example, to predict protein−ligand binding energies, it is necessary to accurately calculate the desolvation penalty associated with the transfer of ligands from bulk solvent to the binding site. The transfer of a small molecule from the gas phase to water can be precisely measured experimentally and serves as a surrogate for the desolvation process upon ligand binding to a protein. Therefore, the accurate prediction of absolute solvation free energies (ASFEs) is an essential part of any methodology that can reliably predict binding free energies. Furthermore, ASFE predictions provide a direct way of validating force fields and solvent models. Several groups, including ours, have published work on ASFE predictions using a variety of methods and force fields.[1−10] In addition, promising new methods to reduce simulation times and improve accuracy have been proposed in recent years.[10−15] A number of excellent review articles describe free energy simulation methods and highlight the potential implications in drug discovery.[16−18]

Here, we report ASFE predictions on a benchmark set of neutral small molecules using molecular dynamics and free energy perturbation (MD/FEP) with explicit solvent and the next generation OPLS force field, OPLS2.0.[19] The benchmark set, previously published by Shivakumar et al., spans diverse chemical functional groups commonly encountered in drug design, including saturated hydrocarbons, unsaturated hydrocarbons, conjugated systems, aromatic rings, heterocyclic rings, and many polar functional groups.[3] The original work on this set by Shivakumar et al. compared multiple force fields and charge assignment methods and found that the general Amber force field (GAFF)[20] with AM1-BCC[21,22] charges performed better than several other force fields in ASFE calculations.[3] More recently, Shivakumar et al. compared the accuracy of the OPLS_2005 force field with two of the previously published force fields, GAFF[23] and CHARMm-MSI,[24] and found that ASFE predictions using OPLS_2005 had the highest correlation with experimental results and the lowest average unsigned errors.[3,6] However, certain classes of polar compounds had errors greater than 1.0 kcal/mol with OPLS_2005. That work also showed that ASFE predictions on the polar compound classes could be improved by combining a charge assignment method with the noncharge parameters of OPLS_2005. While these results were encouraging, it was suggested that further improvements are likely to be achieved with a systematic parametrization of the force field.[6]

In this work, we present the results of ASFE predictions using the next generation OPLS force field, OPLS2.0, which combines a semiempirical charge assignment method (CM1A-BCC; see the Theory section below) with a parametrization based on a substantially larger training set of *ab initio* and experimental data. We observe significant overall improvements in the ASFE predictions using the OPLS2.0 force field, primarily resulting from better treatment of several classes of polar functional groups, although improvements were consistently seen across the whole data set. The most notable improvements included nitrogen-containing compounds (amides and amines) and other polar compounds (esters, aldehydes, and alkynes). The compounds containing single- and polyhalogenated functional groups also showed marked improvements. Here, we provide a brief description of the OPLS2.0 force field and present results for ASFE predictions. A detailed description of the OPLS2.0 force field methodology and parametrization will be discussed in subsequent publications.

THEORY

OPLS Overview. The OPLS family of force fields[25−29] adopts a functional form that represents the potential energy of the system as the sum of bond, angle, torsion, and nonbonded terms. Details regarding the functional form can be found in the associated references. Parameters for the bond and angle terms aim to reproduce molecular geometries and vibrational frequencies, while the torsion term aims to reproduce the

Received: March 9, 2012
Published: June 24, 2012

   dx.doi.org/10.1021/ct300203w | J. Chem. Theory Comput. 2012, 8, 2553−2558

energetics of conformational rearrangement. The nonbonded terms include electrostatic interactions using atom-centered partial charges and a Lennard-Jones potential representing dispersion and electronic repulsion. Nonbonded parameters are developed against a combination of *ab initio* gas phase properties and experimental condensed phase properties that sensitively probe these intermolecular interactions.

OPLS2.0. The objective in developing the present iteration of OPLS is to improve the accuracy of drug-like molecules, which should improve the general quality of physics-based approaches including the prediction of binding free energies, docking poses, conformational preferences, and energy landscapes. To do so, the OPLS2.0 force field has substantially expanded the data sets used in its parametrization. The present set contains *ab initio* data on more than 11 000 molecules, including their optimized geometries, rotational profiles, and electrostatic potentials with the aim of more thoroughly covering the diversity of chemical functionalities that comprise drug-like molecules. In comparison, the data sets used to parametrize the torsional terms in MMFF[30] and OPLS_2005[31] are based on 140 and 631 rotational profiles, respectively (see Table 1).

Table 1. Comparison of the Number of Rotational Profiles Used to Parameterize the Torsion Term of MMFF, OPLS_2005, and OPLS2.0 Force Fields[a]

	MMFF	OPLS_2005	OPLS2.0
number of rotational profiles	140	631	11 190

[a]The number of profiles in MMFF is calculated on the basis of Halgren and Nachbar.[30] The publication cites ~1450 structures used for parameterization, which would amount to ~140 profiles.

In addition to the expanded parametrical coverage, OPLS2.0 uses semiempirical charges with bond-charge corrections (CM1A-BCC) to help account for changes in charge distributions that result from variations in functional group substitutions. The charges are obtained from a combination of the Cramer–Truhlar CM1A charge model[32] and specifically fit bond charge correction terms (BCC)[22] that are parametrized against the OPLS-AA charges for a core set of 112 molecules and the electrostatic potential at the HF/6-31G* level of theory for the OPLS2.0 training set. In a subsequent refinement step, the BCC terms are adapted to minimize the errors with regard to the ASFE using a training set of 153 molecules. All structures used to perform the CM1A calculations are prepared via a conformational search and subsequent minimization without the electrostatic term and only repulsive vdW parameters for interactions between atoms to prevent collapse of the molecules from intramolecular interactions.

METHODS

The total free energy module implemented in the Desmond molecular dynamics (MD) program[33−35] was used to calculate the absolute solvation free energy (ASFE) for the set of 239 small molecules as described previously by Shivakumar et al.[3,6] The calculations presented in this work were performed using the new OPLS2.0 all-atom force field, available as an add-on module in the Schrödinger 2011 software suite. Comparisons to OPLS_2005 and other force fields were made on the basis of previous calculations from Shivakumar et al.[3,6] The initial 239 neutral small molecules were solvated in an orthorhombic water box using a 10 Å buffer on all sides and no ions. All simulations were run with explicit waters using the SPC model. Previous work showed that there is little difference in overall performance of ASFE predictions between the SPC, TIP3P, and TIP4P water models.[6]

The MD simulation workflow was run with the default parameters in the Maestro interface to Desmond.[36] We define the potential of the system as a function of two-order parameters, λ_{vdw} and λ_{coul}, to scale the vdW and electrostatic potentials, respectively, between the solute and the solvent using a "pseudo" double annihilation protocol wherein only a single annihilation is simulated and the vacuum reference state is recovered by turning off the interactions between the solute and the other molecules. The default 12-window λ schedule with 600 ps of simulation for each λ was used to predict the ASFE for each molecule. A correction term that accounts for the missing long-range dispersion energy due to the cutoff of the vdW potentials is included by default. All numbers reported herein for OPLS_2005 and OPLS2.0 include this long-range correction (LRC) term. We use the Bennett acceptance ratio (BAR)[37] method to estimate the free energy difference from the simulations. The detailed description of the simulation methodology and theory is presented in Shivakumar, 2010.[6]

RESULTS AND DISCUSSION

We used the MD/FEP protocol described above with the OPLS2.0 force field to predict the absolute solvation free energies (ASFEs) for a test set containing 239 small molecules with diverse functional groups. Figure 1 shows the correlation

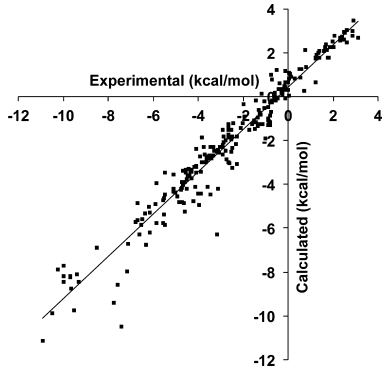

Figure 1. Correlation plot showing calculated (y-axis) and experimental (x-axis) absolute solvation free energies (kcal/mol) for the test set, with slope (0.97), intercept (0.43), and coefficient of determination (R^2 = 0.95).

plot of experimental versus calculated ASFEs, with a coefficient of determination (R^2) of 0.95 for OPLS2.0. The correlation reported previously for the same set of molecules using the force fields OPLS_2005, AM1-BCC/GAFF, and CHelpG/CHARMm-MSI is 0.94, 0.87, and 0.72, respectively. While the correlation did not increase substantially compared with OPLS_2005, the y-intercept (0.42) and slope (0.96) show a significant improvement in comparison with OPLS_2005 (0.68 and 0.86 for the y-intercept and the slope, respectively). This suggests that the OPLS2.0 force field is doing a superior job at reproducing the underlying physics of the molecules.

In Figure 2, we compare the average unsigned error (AUE) for different functional classes with OPLS2.0, OPLS_2005, GAFF, and CHARMm-MSI. As reported previously, the OPLS_2005 force field produced better ASFE predictions compared with GAFF and CHARMm. While the CHARMm

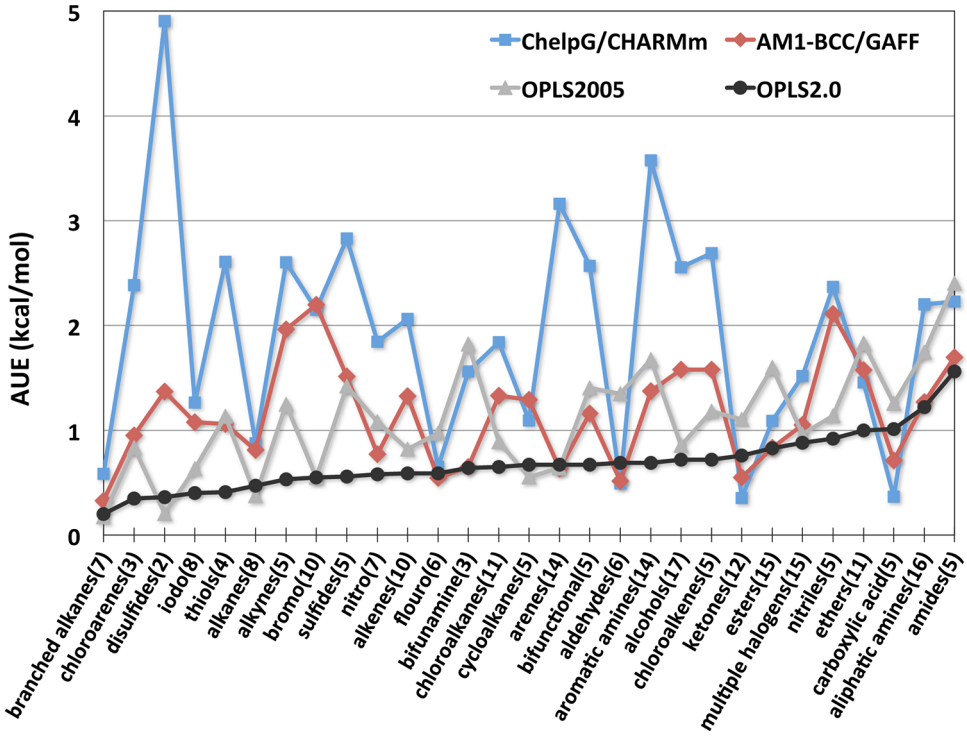

Figure 2. Comparison of the average unsigned error (AUE, kcal/mol) for the different functional classes of compounds using CHARMm/ChelpG (blue squares), GAFF/AM1-BCC (red diamonds), OPLS_2005 (gray triangles), and OPLS2.0 (black circles). The number of compounds for each class is in parentheses. Compound classes are sorted in order of increasing OPLS2.0 AUE.

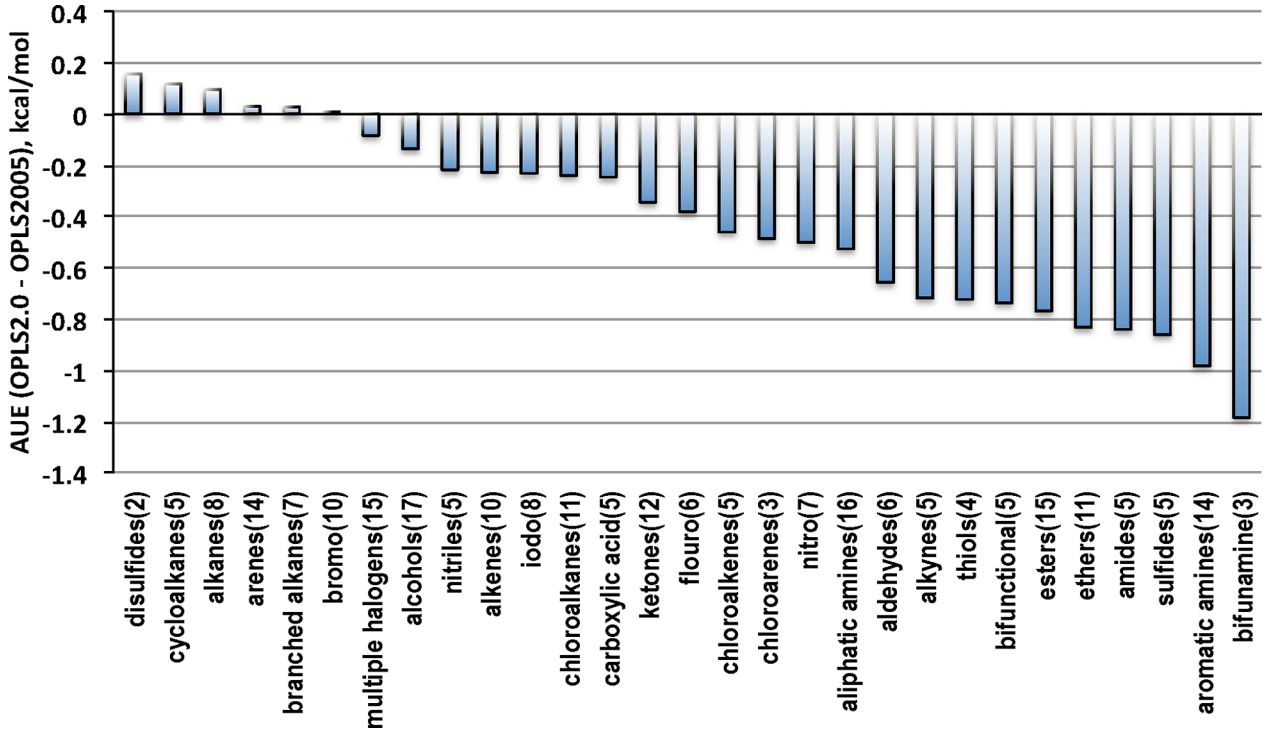

Figure 3. Differences in absolute solvation free energy predictions for each compound class using the OPLS2.0 and OPLS_2005 force field. Negative values represent an improved (i.e., lower) AUE using OPLS2.0 compared with OPLS_2005. Compound classes are sorted in order of the difference between OPLS2.0 and OPLS_2005 energies.

results were relatively poor across the entire data set, AM1-BCC/GAFF performed on par with OPLS_2005 for some functional groups, such as branched alkanes, cycloalkanes, alkynes, some polar groups, and most of the halogenated molecules.[6] In that work, OPLS_2005 exhibited more than 1.0 kcal/mol error for certain functional groups, such as some N-containing classes (amides, aliphatic amines, aromatic amines, and nitro). Using the CM1A-BCC charge method with the

dx.doi.org/10.1021/ct300203w | J. Chem. Theory Comput. 2012, 8, 2553−2558

OPLS_2005 force field improved the absolute solvation free energies for some of the polar compound classes,[6] indicating that the improved CM1A-BCC charges were beneficial. Figure 2 shows that the AUE decreases further for most functional classes using the OPLS2.0 force field. The AUE is less than 1.0 kcal/mol for all functional groups except amides and aliphatic amines. While amides were the biggest outlier using OPLS_2005 (AUE of 2.4 kcal/mol), this class was also challenging for the other force fields, with GAFF and CHARMm having an AUE of 1.6 and 2.3 kcal/mol, respectively. Using OPLS2.0, we observe an improvement in AUE to 1.5 kcal/mol, and the trend in solvation free energy changes on going from acetamide to methylacetamide and dimethylacetamide is improved (data not shown).

Figure 3 shows the difference in the AUE for each compound class between OPLS_2005 and OPLS2.0. Improvements in absolute solvation free energy predictions are observed for most compound classes, as seen by the negative bars in Figure 3. The most notable improvements in AUE between OPLS_2005 and OPLS2.0 (ΔAUE $\geq$ 0.5 kcal/mol) are observed for alkyne, aldehydes, esters, ethers, aromatic amines, aliphatic amines, amides, nitro, thiols, and sulfides. Moderate improvements (0.1−0.5 kcal/mol) are observed for alkenes, alcohols, ketones, carboxylic acids, halogenated compounds (fluoro, chloroalkenes, chloroarenes, iodo, and multiple halogens), and nitriles. Alkanes, cycloalkanes, branched alkanes, and arenes show minor changes in AUE (AUE changed by less than 0.1 kcal/mol).

Due to the very large number of molecules in the OPLS2.0 training set (see the Methods section), it was necessary to look separately at molecules that were not part of the training set, especially for the charge model where solvation free energies were explicitly part of the fitting function for the BCCs. Of the 239 molecules, 82 were members of the BCC training set. In Table 2, we show the error in the ASFE predictions for the BCC training set molecules and the non-BCC test set molecules. For both OPLS_2005 and OPLS2.0, we observe a small drop in the correlation with experimental results when the training molecules are removed, although the results are still favorable as compared with the other force fields. The slope and intercept also do not change significantly between the BCC training set molecules and the molecules not in the training set. In fact, the slope using OPLS2.0 on the non-BCC training molecules improves over the BCC training set molecules and is nearly unity. Therefore, the improvements in predicting the absolute solvation free energies are not limited to the training set of molecules used for force field parametrization but are also transferable to the nontraining set molecules, which is a crucial criterion for a force field to be transferable and generalized across diverse compound space.

Table 2. ASFE Prediction Statistics for the Molecules in the BCC Training Set and Those Not in the Training Set (non-BCC) Set Using OPLS_2005 and OPLS2.0

		R^2	slope	intercept
OPLS_2005	non-BCC	0.93	0.85	0.62
	BCC	0.94	0.84	0.72
OPLS2.0	non-BCC	0.94	0.98	0.42
	BCC	0.96	0.93	0.44

While attributing improvements in ASFE predictions to specific parts of the force field can be difficult due to the coupling of the force field parameters, insights can be attained through inspection of the charges in OPLS2005 and OPLS2.0. Figure 4 shows some of the molecules with the greatest improvement in ASFE predictions with OPLS2.0. In all cases, the predicted free energy with OPLS_2005 was not negative enough, whereas OPLS2.0 approached the experimental solvation free energy. For N-methylacetamide (Figure 4A), the negative charge is more strongly localized on the N and O atoms, resulting in a more negative solvation free energy. This is also the case with 1,4-dioxane (Figure 4D), although that change is coupled with systematically more charge on the H atoms with OPLS2.0. For 4-hydroxybenzaldehyde (Figure 4C), most of the differences come from an increased positive charge on the aromatic hydrogens. Also, charge changes on H have a larger effect on solvation free energies compared with C, N, and O because the charge center is closer to the solvent. Similarly, 2-methylpyrazine (Figure 4B) improves through increased charge magnitude on the hydrogens even though the charge magnitude on the N atoms is reduced considerably. Overall, the increase in charge magnitude on H atoms is a common trend in many of the molecules with improved solvation free energy predictions. While these charge changes are subtle, they have a significant impact on the solvation free energy because charge changes on H atoms have more influence than those on non-H atoms, which can be attributed to the fact that the smaller van der Waals radius of the hydrogen puts its charge closer to the solvent, thereby making the solvation free energy more negative. The charge distributions for all atoms from the 10 molecules with the greatest improvement going from OPLS_2005 to OPLS2.0 are shown in the Supporting Information S1. In addition, OPLS2.0 parameters for all 239 molecules studied in this work are available. Finally, it should be noted that acenaphthylene (compound m78) should likely be acenaphthene, since the reported solvation free energy matches the experimental value for acenaphthene. Indeed, the ASFE error for acenaphthene with OPLS2.0 reduces from 3.1 to 1.1 kcal/mol, and the average error for the 15 arenes improves from 0.7 to 0.5 kcal/mol. However, for the results presented in this work, we have retained the compound as acenaphthylene, so the results could be directly compared with the previous results on this data set using other force fields, which were run on acenaphthylene. Additionally, we have provided the structure and parameters labeled as m78 for acenaphthylene and m78_new for acenaphthene (see Supporting Information for details).

CONCLUSION

We reported absolute solvation free energy (ASFE) predictions for a diverse set of 239 neutral small molecules using the next generation OPLS force field, called OPLS2.0, and an MD/FEP protocol with explicit solvent. The accuracy was compared with predictions on the same set of molecules using commonly used small molecule force fields—OPLS_2005, GAFF, and CHARMm-MSI. OPLS2.0 performed well compared with the above-mentioned force fields. The coefficient of determination between the calculated and experimental absolute solvation free energies with OPLS2.0 was high (R^2 = 0.95). The y-intercept and slope between the calculated and experimental ASFE improved considerably over OPLS_2005, which itself was previously shown to perform better than GAFF and CHARMm-MSI. Classes of polar compounds that performed suboptimally previously with OPLS_2005 showed significant improvements with the new force field. The most notable

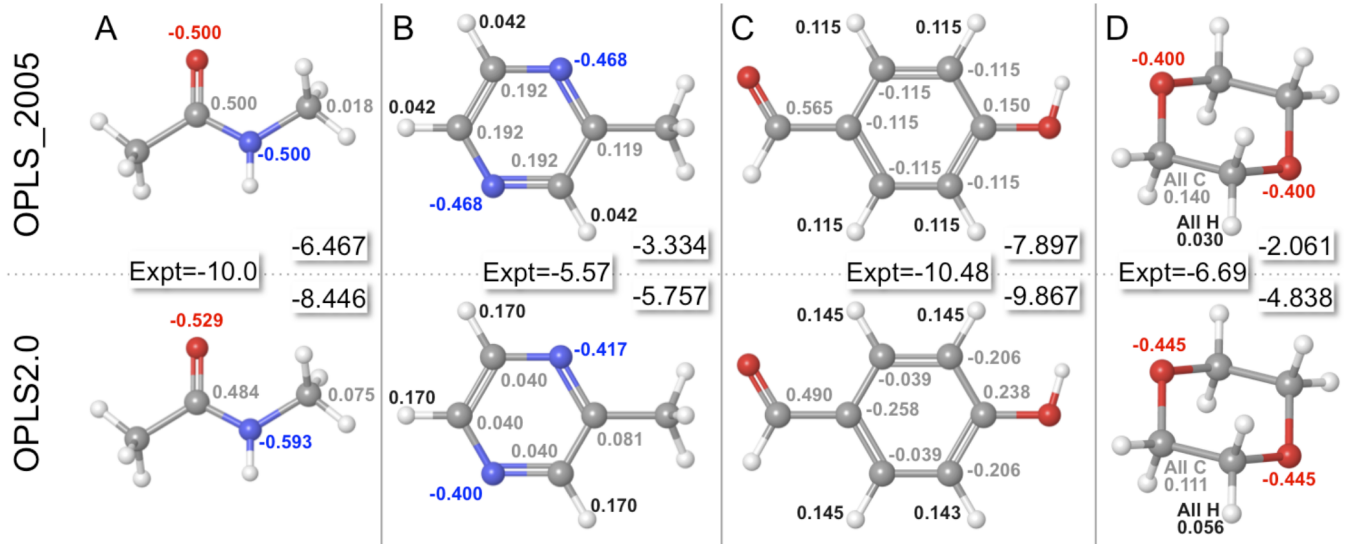

Figure 4. Example charge distributions and associated solvation free energies. OPLS_2005 charges and energies are show in the top row and OPLS2.0 in the bottom row. The experimental energy is denoted with "Expt". All energies in kcal/mol and charges in units of elementary charge (*e*). For clarity, only the charges with the most significant changes between OPLS_2005 and OPLS2.0 are shown for (A) N-methylacetamide, (B) 2-methylpyrazine, (C) 4-hydroxybenaldehyde, and (D) 1,4-dioxane. Charges for all atoms of the molecules with the greatest improvements between OPLS_2005 and OPLS2.0 are provided in the Supporting Information.

improvements between OPLS_2005 and OPLS2.0 were observed for alkyne, aldehydes, esters, ethers, aromatic amines, aliphatic amines, amides, nitro, thiols, and sulfides. We also demonstrated that the improvements in predicting the absolute solvation free energies is not limited to the training set of molecules used for force field parametrization but is also transferable to the nontraining set molecules, which is a crucial criterion for a force field to be transferable and generalized across diverse compound space. The improved performance of the new force field can be attributed in part to the increase in charge magnitude on hydrogen atoms, which seems to be a common trend in many of the molecules with improved solvation free energy predictions. While these changes are subtle, they have a significant impact on the solvation free energy because charges on hydrogen atoms have more influence than non-hydrogen atoms, which can be understood by the fact that the smaller van der Waals radius of the hydrogen puts its charge closer to the solvent, thereby making the solvation free energy more negative.

The accurate characterization of solvation effects is a critical component in the modeling of protein−ligand binding in structure-based drug design. The prediction of solvation free energies provides a surrogate for the biologically relevant process of transferring a small molecule from solution (high dielectric environment) to the binding site of a protein (low dielectric region) and therefore is an important step toward predicting accurate binding free energies. However, solvation free energies alone are insufficient to accurately predict binding energies. Further work is needed to show the impact of the improved OPLS2.0 force field in important applications like strain assessment of bioactive ligand conformations, binding pose prediction, and binding free energy estimation. Improvements in the force field should bring substantial value to computer-aided drug design through the reduction of errors and improved predictive capabilities. A more complete description of the OPLS2.0 force field and validation across a range of applications will be reported elsewhere.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The charge distributions for all atoms from the 10 molecules with the greatest improvement going from OPLS_2005 to OPLS2.0 are shown in the Supporting Information S1. This information is available free of charge via the Internet at http://pubs.acs.org. Additionally, OPLS2.0 parameters for all 239 molecules studied in this work are available. Also available are the structure and parameters labeled as m78 for acenaphthylene and m78_new for acenaphthene. This information is available at http://www.schrodinger.com/productpage/14/3/105/.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank Prof. Bill Jorgensen for helpful discussion and feedback regarding solvation free energy calculations, CM1A-BCC charge development, and force fields in general. The authors would like to acknowledge Dr. Ramy Farid for helpful discussions and suggestions on the manuscript.

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