Comparison of Charge Models for Fixed-Charge Force Fields: Small Molecule Hydration Free Energies in Explicit Solvent

[*The Journal of Physical Chemistry B* 2007, *111B*]. David L. Mobley,* Élise Dumont, John D. Chodera, and Ken A. Dill

Page 2242. Our previously published work[1] suffered from two problems that affected some of the reported results. These problems, described in detail below, resulted in incorrect hydration free energies for the TIP4P-Ew water model and incorrect properties computed from quantum chemical calculations at the MP2 level. Therefore, we have here repeated many of these calculations, leading to a new set of computed hydration free energies, which we provide here. The main changes of consequence are that our present results in TIP3P are in closer agreement with those in TIP4P-Ew, and the MP2/cc-pVTZ SCRF (RESP) charge model does in fact perform quite well for hydration free energies, contrary to what our original study had suggested.

Our first main problem was that hydration free energies computed in TIP4P-Ew[2] were incorrect due to a bug in the version of GROMACS[3] (3.3.1) used for that study that omitted some water−water charge interactions when four-site water models were used. From examination of the GROMACS revision history, it appears this bug was introduced by a developer on December 27, 2004, in the creation of an optimized force calculation loop for four-site waters, and persisted until another developer fixed the bug on January 29, 2009. As such, this bug is expected to affect *all* public release versions of GROMACS from version 3.3 (released October 10, 2005) through 4.0.3 (released January 18, 2009). While we carried out extensive validation tests leading up to our original study to ensure our results matched published values, our testing was confined to three-site waters; we had not realized four-site waters used a different force kernel. Notably, the related work of Hess and van der Vegt[4] did not suffer from this issue because the perturbed atoms were placed in a separate energy group, which works around this problem. We used this workaround here.

Second, due to an error in preparing the Gaussian 98[5] input files for the MP2/cc-pVTZ calculations, properties (such as the electrostatic potential and dipole moment) were computed with the SCF density rather than the MP2 density; hence the reported dipole moments, polarization energy estimates, fitted charges, and corresponding computed hydration free energies reflected only the SCF contribution, rather than the MP2 contribution as originally claimed.

To correct these problems, we repeated the MP2/cc-pVTZ calculations with and without SCRF, in both TIP3P[6] and TIP4P-Ew,[2] and we provide new results for those calculations here. Additionally, we repeated the AM1-BCC TIP4P-Ew calculations and provide new results for those as well. Here, we used GROMACS 3.3.4 (avoiding the bug using the workaround of Hess and van der Vegt). To verify that computed TIP4P-Ew hydration free energies were correct (using the workaround noted above), we (a) verified that computed free energies were substantially different with the workaround, and (b) compared our computed hydration free energy for propionamide with and without the workaround with preliminary results from the research group at IBM Almaden[7] and found agreement within calculated uncertainties after the workaround was applied. These

corrections also bring our TIP4P-Ew results into much closer agreement with the results from Hess and van der Vegt.[4]

Because of a forthcoming study from the research group at IBM Almaden,[7] we have chosen to not repeat the TIP4P-Ew hydration free energy calculations with the remaining charge models, and we hereby *retract* those results from our original paper. A full revised table of our results (clearly showing which are retracted) is available in the Supporting Information for this erratum.

Figures 1 and 2 provide a graphical representation of our computed hydration free energies in TIP3P. Updated deviations from experiment for each charge and solvent model are summarized in terms of average unsigned error (AUE), root-mean-square error (RMSE), correlation coefficient (R^2), and slope of linear fit in Table 1. A full table of computed free energies and experimental values is shown in the Supporting Information, as in our previous study. None of these free energies include a polarization correction, shown recently to be important in making comparisons with experimental hydration free energy data.[8,9] Recomputed free energies are listed in Supporting Information Table 1 side-by-side with their originally reported values.

Our corrected TIP4P-Ew calculations generally improve the agreement of the TIP4P-Ew results with experiment. The deviation from experimental hydration free energies in TIP3P (AUE 0.92 kcal/mol, RMSE 1.10 kcal/mol) is still smaller than for TIP4P-Ew (AUE 1.13 kcal/mol, RMSE 1.34 kcal/mol), though the difference between the two is now reduced. Differences between computed and experimental hydration free energies still do not significantly improve with increasing level of quantum theory when SCRF is employed, except that, now, RESP[10] partial charges computed from the MP2/cc-pVTZ SCRF calculations give the smallest overall deviation (in terms of RMSE, AUE, and R^2, but not slope) for both TIP3P and TIP4P-Ew water models. This was not the case previously, where *all* results with higher levels of quantum theory were worse. While this is a relatively limited data set, these results suggest that RESP MP2/cc-pVTZ SCRF partial charges ought to be considered as a viable choice when high-quality partial charges are needed, provided the computational expense of computing charges at this level of theory can be spared.

Because of the problem with our MP2/cc-pVTZ calculations, polarization-corrected hydration free energies with this model were not the correct MP2/cc-pVTZ polarization-corrected results, so we provide the updated results in the Supporting Information. As before, this approach did not result in the best agreement with experiment (rms errors 1.84 kcal/mol (TIP3P) and 1.91 kcal/mol (TIP4P-Ew); R^2 0.81 and 0.83; AUE 1.04 and 1.31, and slope 0.85 and 0.90), but there are a variety of reasons it may be important to include these corrections anyway.[1,8,9,11]

Overall, from our original manuscript, we have provided updates here to Figures 1 and 2, Table 1, and the data in one column of Table 5. Additionally, a small amount of the data in Figures 3, 4, 6, and 7 and Table 3 are incorrect and are replaced by the data presented in this erratum, but since the majority of the data in those figures/tables are correct we are not providing revised versions, as our full data set is presented here in the
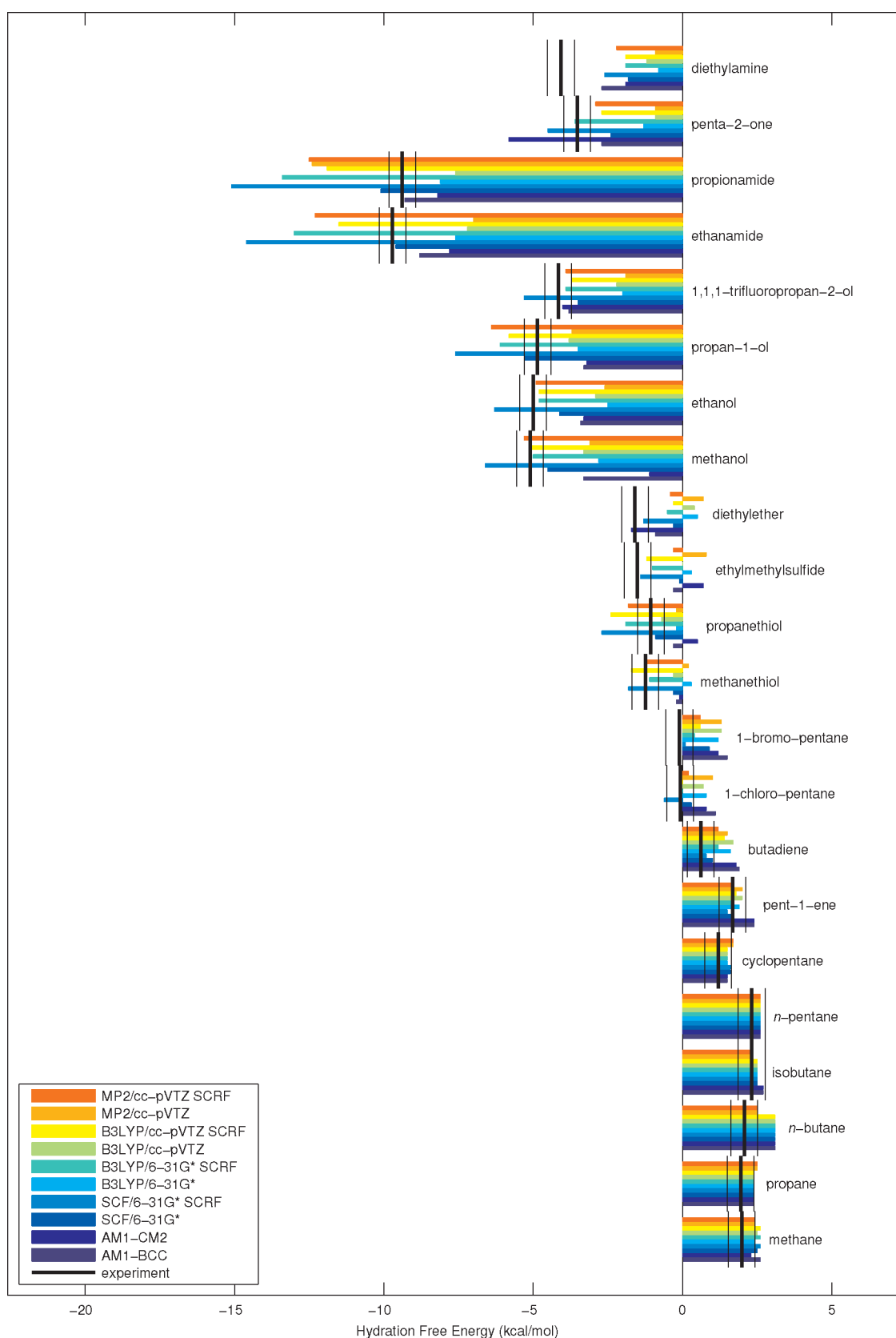
Figure 1. Experimental and corrected calculated free energies in TIP3P, part 1. Experimental values are shown as a thick black vertical line; estimated experimental uncertainties are shown as thin vertical lines. Estimated uncertainties in calculated free energies are comparable to the experimental uncertainties.
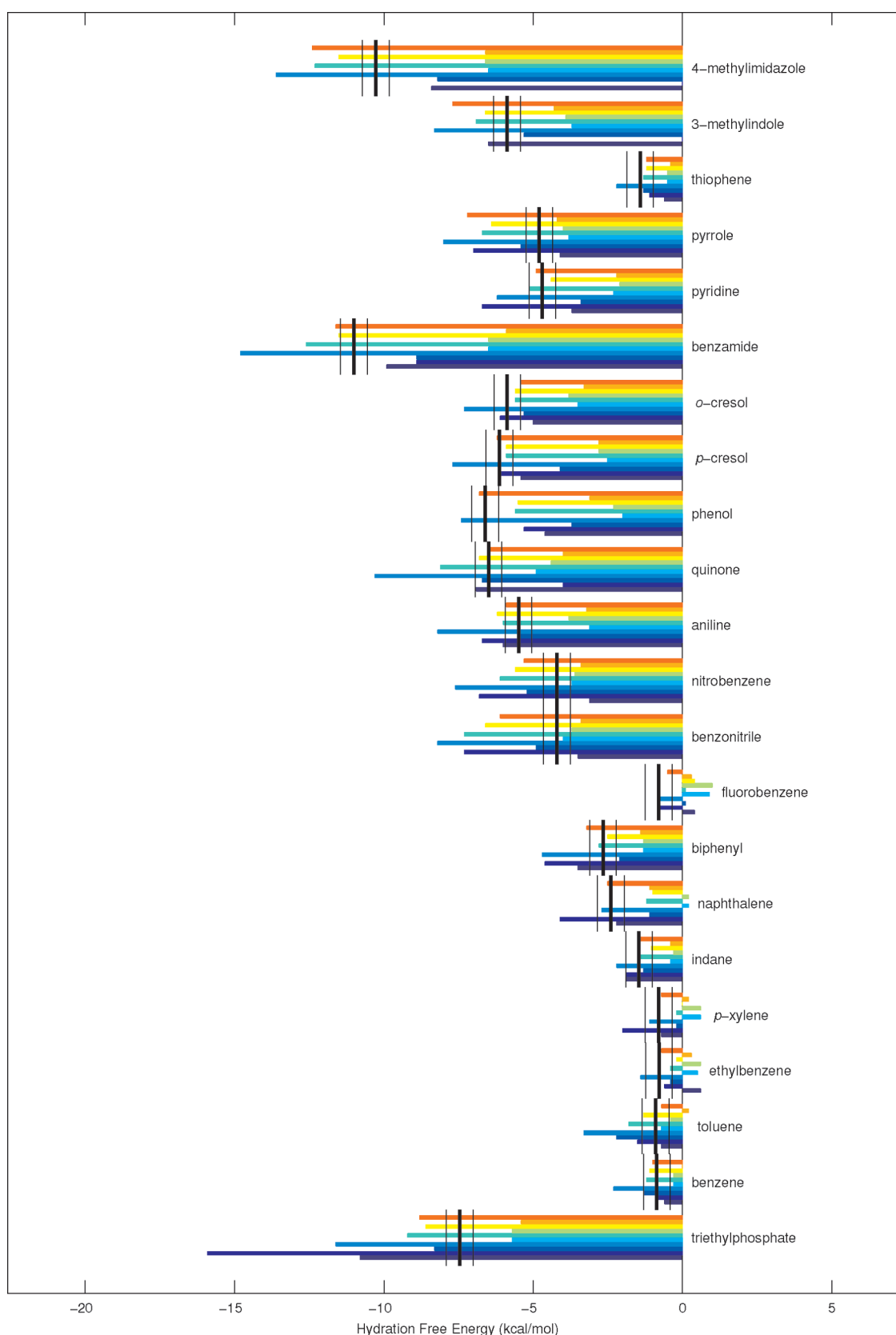
Figure 2. Experimental and corrected calculated free energies in TIP3P, part 2. Experimental values are shown as a thick black vertical line; estimated experimental uncertainties are shown as thin vertical lines. Estimated uncertainties in calculated free energies are comparable to the experimental uncertainties.

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Table 1. Statistics for Corrected Hydration Free Energies from this Study, Relative to Experiment (in kcal/mol)[a]

solute		AM1-BCC	AM1-CM2	SCF/6-31G*	SCF/6-31G* SCRF	B3LYP/6-31G*	B3LYP/6-31G* SCRF	B3LYP/I TZ	B3LYP/TZ SCRF	MP2/TZ	MP2/TZSCRF
							RESP ab initio charges				
TIP4P-Ew	AUE	1.13	n/d	n/d	n/d	n/d	n/d	n/d	n/d	2.04	0.90
	RMSE	1.34	n/d	n/d	n/d	n/d	n/d	n/d	n/d	2.32	1.19
	R^2	0.96	n/d	n/d	n/d	n/d	n/d	n/d	n/d	0.85	0.96
	Slope	1.05	n/d	n/d	n/d	n/d	n/d	n/d	n/d	0.84	1.22
TIP3P	AUE	0.92	1.38	0.82	1.62	1.62	0.921	1.58	0.78	1.66	0.71
	RMSE	1.10	1.97	1.04	2.17	1.97	1.9	1.0	1.00	1.99	1.06
	R^2	0.94	0.75	0.94	0.96	0.92	0.95	0.94	0.95	0.87	0.96
	Slope	1.03	1.04	0.98	1.39	0.79	1.1	0.79	1.13	0.81	1.18

[a] n/d: not done.

Supporting Information. Table 2 and Figure 5 were correct as published.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Table comparing our original computed free energies with the corrected values here; a corrected table of calculated hydration free energies for each molecule, method, and water model in the test set; a table of polarization-corrected results for the MP2/cc-pVTZ calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ ACKNOWLEDGMENT

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