

Generalized Born implicit solvent models for small molecule hydration free energies†

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Hydration free energy estimation of small molecules from all-atom simulations was widely investigated in recent years, as it provides an essential test of molecular force fields and our understanding of solvation effects. While explicit solvent representations result in highly accurate models, they also require extensive sampling due to the high number of solvent degrees of freedom. Implicit solvent models, such as those based on the generalized Born model for electrostatic solvation effects and a solvent accessible surface area term for nonpolar contributions (GBSA), significantly reduce the number of degrees of freedom and the computational cost to estimate hydration free energies. However, a recent survey revealed a gap in the accuracy between explicit TIP3P solvent estimates and those computed with many common GBSA models. Here we address this shortcoming by providing a thorough comparison of the performance of three implicit solvent models with different nonpolar contributions and a generalized Born term to estimate experimental hydration free energies. Starting with a minimal set of only ten atom types, we demonstrate that a nonpolar term with atom type dependent surface tension coefficients in combination with an accurate generalized Born term and fully optimized parameters performs best in estimating hydration free energies, even yielding comparable results to the explicit TIP3P water model. Analysis of our results provides evidence that the asymmetric behavior of water around oppositely charged atoms is one of the main sources of error for two of the three implicit solvent models. Explicitly accounting for this effect in the parameterization reduces the corresponding errors, suggesting this as a general strategy for improving implicit solvent models. The findings presented here will help to improve the existing generalized Born based implicit solvent models implemented in state-of-the-art molecular simulation packages.

Introduction

The estimation of hydration free energies (HFEs) from all-atom molecular simulations has been widely investigated in recent years.¹⁻⁷ Improvements in methods and computational resources allow precise computation of these values in explicit solvent models with statistical errors of the same order of magnitude as experimental errors. This accuracy allows validation and identification of systematic force field errors for molecular simulations *via* the

comparison of computed HFEs to experimental values.^{8,9} The accuracy of these force fields is of interest to pharmaceutical research, where prediction of bioavailability and binding affinity of small organic molecules to target proteins has become an important goal in the process of drug discovery.¹⁰⁻¹²

Based on sampling of the phase space in vacuum and solution, the free energy difference of hydration may be computed using methods such as free energy perturbation,¹³ thermodynamic integration,¹⁴ the Bennett and multistate Bennett acceptance ratio,^{15,16} or the weighted histogram analysis.¹⁷ Unfortunately, the high number of degrees of freedom of an explicit solvent representation requires extensive sampling, and depending on the phase space overlap, sampling of additional intermediate states, to yield well-converged results.¹⁸ In addition to methods based on MD-simulations, a wide variety of QM-based methods^{19,20} or classical models²¹ have been used to model solvation effects.

Implicit solvent models integrate out the solvent degrees of freedom and therefore significantly reduce the amount of sampling required for the computation of HFEs. One common approach is to treat the solvent as a continuous dielectric

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medium that is described *via* Poisson–Boltzmann theory (see for example Grochowski *et al.* for a recent review of Poisson–Boltzmann methods²²). Approximations based on the generalized Born (GB) model are even more popular due to their low computational cost.^{23–38} The polarization of the solvent induced by the charges of the solute is modeled by atomic Born radii, which describe the burial of atoms within the solute and therefore the degree of polarization an atomic charge can induce. The free energy change due to the polarization can be computed using a simple analytic formula.

Nonpolar solvation effects are often modeled by a solvent accessible surface area (SASA) term, that describes the work required to form a cavity for the solute inside the solvent and the dispersion interactions between solvent and solute.²⁴ Other studies have pointed out that this model may be insufficient to capture the behavior of real solvent and have proposed extensions, *e.g.* by using atom type dependent surface tension coefficients,^{39,40} or including the volume of the cavity and explicit modeling of dispersion interactions between solvent and solute.^{5,41–46}

Unfortunately, there is a tradeoff for the reduced computational cost. Recent studies with several commonly used implicit solvent models on a large database of small neutral organic molecules showed that all these models lack accuracy of their estimated HFEs in comparison to explicit solvent results using the TIP3P water model.^{3,7} As pointed out in these studies, improving the estimated HFEs may involve reparameterization or the inclusion of more elaborate models for nonpolar interactions, while polar solvation seems to be modeled sufficiently well by any GB model that agrees well with Poisson–Boltzmann calculations.¹ In the past, several studies focused on the parameterization of one^{29,47–50} or two¹ specific models. However, there is no study that assesses all three models. Furthermore, the use of different molecule sets and atom type definitions in previous studies makes it difficult to compare the performance of the underlying nonpolar models.

In this study, we provide a systematic assessment of the performance of three GB based implicit solvent models with different nonpolar terms to estimate HFEs for a large database of small neutral organic molecules accurately. We use fully optimized polar and nonpolar model parameters that enable a fair comparison between these three models without bias due to imperfect parameterization. The HFEs computed with our models will also answer the question if they are in principle able to reproduce experimental HFEs with the same or higher accuracy as explicit solvent models such as TIP3P for the large database of 504 molecules provided by Mobley *et al.*⁴ In addition, the analysis of the computed HFEs and their errors to experimental data enables us to draw general conclusions that will also help to improve other existing GB based implicit solvent models.

Methods

Implicit solvent models

Implicit solvation models integrate out the solvent degrees of freedom, yielding an additional contribution to the Hamiltonian

of the molecular force field for each conformation of the solute.⁵¹ We will refer to this additional contribution as the solvation free energy ΔG_{SFE} . Since it is defined for a single conformation, it does not account for the entropy of the solute. We separate the solvation free energy according to Roux and Simonson^{51–54} in an electrostatic contribution and a nonpolar contribution

$$\Delta G_{\text{SFE}} = \Delta G_{\text{elec}} + \Delta G_{\text{NP}} \quad (1)$$

In this study, we will investigate three different implicit solvent models. Each of these models contains the same GB term to model electrostatic solvation effects and one of three different nonpolar solvation terms. We will refer to the models as GBNP1, GBNP2, and GBNP3.

For the electrostatic contribution in eqn (1) we use the GB model based on the proposal by Still.²⁷ The electrostatic solvation free energy is approximated by a pairwise analytical formula

$$\begin{aligned} \Delta G_{\text{elec}} &\approx \Delta G_{\text{GB}} \\ &= \frac{1}{2} \left(1 - \frac{1}{\epsilon_w} \right) \sum_{i,j}^{N_{\text{atoms}}} \frac{q_i q_j}{\sqrt{d_{ij}^2 + R_i R_j} \exp\left(\frac{d_{ij}^2}{4R_i R_j}\right)} \end{aligned} \quad (2)$$

where $\alpha = 331.84 \text{ kcal } \text{Å} \text{ mol}^{-1}$ is a constant, $\epsilon_w = 78.5$ is the dielectric constant of water, d_{ij} the distance between two atoms i and j , q_i the partial charge of an atom in atomic units and R_i the atomic Born radius describing the amount of polarization induced in the solvent. The Born radius can be approximated by solving the R6 integral proposed by Grycuk⁵⁵

$$\frac{1}{R_i^3} = \frac{3}{4\pi} \int_{\text{water}} \frac{d^3x}{|x - x_i|^6} \quad (3)$$

where the atom is located at position x_i and the integration is carried out over the whole water region. We use the solvent excluded surface^{56–58} to define the boundary of the water region, because it yields electrostatic solvation free energies in good agreement to hybrid⁵⁹ or explicit⁶⁰ solvent simulations. To construct the solvent excluded surface, atomic radii r_i and the probe radius p_r are required. Thus, these are the free parameters of the electrostatic contribution to the solvation free energy. We note that these radii r_i are empirical parameters and not necessarily equal to the sigma parameter of Lennard–Jones potential.¹⁹ Such empiric radii were shown to provide more accurate solvation free energies.^{61–63}

The simplest model for the nonpolar contribution in eqn (1) considered in this work consists of only one SASA term to penalize cavity formation in water. The penalty depends on the number of water molecules in the first solvation shell, which is assumed to be proportional *via* the surface tension γ to the surface area of the cavity.⁴⁵

$$\Delta G_{\text{NP1}} = \gamma \sum_{i=1}^{N_{\text{atoms}}} A_i \quad (4)$$

The cavity area is given by summing the SASA A_i of each atom. Thus, this nonpolar contribution has only one free parameter. Implicit solvent models based on a GB term and such a

nonpolar contribution are commonly referred to as GBSA models in the literature.

Following the suggestion of Knight *et al.*⁷ we also investigate how the model of Eisenberg and McLachlan³⁹ or Ooi *et al.*⁴⁰ is able to improve the accuracy of computed HFES.

$$\Delta G_{\text{NP2}} = \sum_{i=1}^{N_{\text{atoms}}} \gamma_i A_i \quad (5)$$

Within this model, the global surface tension γ is replaced with one surface tension γ_i for each atom type.

The last extension of the nonpolar model investigated here uses not only a SASA based term as in eqn (4). In addition, the solvent accessible volumes (SAV) V_i of the atoms buried inside the solvent accessible surface are subject to a pressure p to model repulsive solute-solvent interactions.⁴² The Born radii R_i together with an offset B describe attractive dispersion interactions between solvent and solute *via* the factor α_i as proposed in the literature.^{5,41-46}

$$\Delta G_{\text{NP3}} = \gamma \sum_{i=1}^{N_{\text{atoms}}} A_i + p \sum_{i=1}^{N_{\text{atoms}}} V_i - \sum_{i=1}^{N_{\text{atoms}}} \frac{\alpha_i}{(R_i + B)^3} \quad (6)$$

There are two new global parameters p and B , and one additional parameter α_i for each atom type. Table 1 summarizes the free parameters, the models to which they belong, and the number of these free parameters.

The Born radii in eqn (2), (3) and (6) are computed with the PowerBorn method by Brieg *et al.*, which results in errors of ΔG_{GB} of about one percent in comparison to Poisson-Boltzmann calculations.³³ Since ΔG_{elec} is of the order 10 kcal mol^{-1} for the molecules discussed in this work, the errors by approximating ΔG_{elec} by ΔG_{GB} are negligible. This approximation is also supported by the findings of Rizzo *et al.* that computing HFES with Poisson-Boltzmann methods or GB models leads to highly correlated results.¹ SASA and SAV are computed with the analytical PowerSasa method by Klenin *et al.*⁶⁴ The evaluation of the energy terms in eqn (2) and (4)-(6) for a given structure or trajectory is then straightforward. We have coded a small C++ program that reads a parameter file, the molecule files of the data set in PQR format and the corresponding AMBER trajectories. It assigns the atom types and parameters to the corresponding molecules and can compute the solvation free energies for each investigated model according to

eqn (1), (2) and (4)-(6). The PQR input files of the data set were generated from the mol2 files contained in the database using the AMBER Tools package of AMBER 10.

Database and model parameterization

We use the database of small organic molecules published by Mobley *et al.*⁴ using AM1-BCC charges^{65,66} and GAFF^{67,68} parameters. The duplicates pointed out by Knight *et al.*⁷ in the 2009 version of the dataset were removed, resulting in a database size of 499 molecules, which was used for parameterization of the model. The 144 molecules added subsequently to the dataset⁶⁹ were used to validate the transferability of the models (for 22 molecules the GAFF forcefield parameterization failed, so that only 122 molecules were considered). The molecular dynamics (MD) trajectories used in this work were also provided by David Mobley (Mobley Lab Resources: <http://mobleylab.org/resources.html>)³

The computation of HFES requires the computation of ΔG_{SFE} in eqn (1) for all snapshots in the vacuum and implicit solvent trajectories and for each molecule. To save computation time, we only fit single conformation solvation free energy (SFE) to the corresponding experimental values. According to Mobley *et al.*,³ the lowest energy snapshot from the vacuum trajectories should yield single conformation SFEs in close agreement with the HFES for most molecules in the database. To extract the lowest energy snapshot from the vacuum trajectory for each molecule, we recomputed their energies with AMBER 10. However, we caution that while this approach may be justified for the particular set of molecules discussed here, the equivalence of SFE and HFE is far from trivial as discussed in ref. 20 and 70.

The model parameterization is carried out in two stages. At first, we use a particle swarm algorithm implemented in the ArFlock library⁷¹ for global optimization to reduce the root mean square error between the single conformation SFEs and the experimental HFES (RMSE_{SFE}). This optimization is run using different sets of swarm parameters to ensure proper sampling of the free parameter space. In the second step, the results are subject to local minimization using Powell’s method as implemented in the SciPy package⁷² due to the faster convergence to local minima of this method.

Table 2 gives an overview of valid ranges for the free parameters. Running the particle swarm optimization requires all free model parameters to be of the same order of magnitude for good convergence. The parameters r_i , p_r , and B are of the order of $O(1)$. However, the model parameters γ , γ_i , α_i and p are not of order $O(1)$ according to.

Table 2, wherefore they are chosen *via* an exponential mapping

$$x = 10^{\tilde{x}} \quad (7)$$

where x is the absolute value of the model parameter and \tilde{x} is of the order $O(1)$.

As a starting point for the parameterization of the models, we have chosen atom types according to the identity of the chemical elements, which we consider the minimal set of reasonable parameters. The molecules in the database consist

Table 1 This table gives an overview over the free model parameters contained in the three different investigated implicit solvent models GBNP1, GBNP2, and GBNP3. An “X” in column three to five shows that this parameter is present in the corresponding model. The number of free parameters is also given

Free model parameter	Relevant equations	GBNP1	GBNP2	GBNP3	Number of parameters
r_i	(2), (3) and (6)	X	X	X	10
p_r	(2), (3) and (6)	X	X	X	1
γ	(4) and (6)	X		X	1
γ_i	(5)		X		10
p	(6)			X	1
α_i	(6)			X	10
B	(6)			X	1

Table 2 Free parameters of the implicit solvent models investigated in this work, their units, and valid parameter ranges for the model parameterization procedure. Atom type specific parameters are marked with an index i

Parameter	r_i [Å]	p_r [Å]	γ [kcal mol ⁻¹]	$ \gamma_i $ [kcal (mol Å ²) ⁻¹]	p [kcal (mol Å ³) ⁻¹]	α_i [(kcal Å ³) mol ⁻¹]	B [Å]
Description	Atomic radius	Probe radius	Global SASA tension	Atomic SASA tension	Global SAV pressure	Atomic dispersion coefficient	Born radii offset
Minimum	0.5	0.5	10.0 ⁶	10.0 ⁶	10.0 ⁶	10.0 ⁶	0.0
Maximum	5.0	3.0	10.0 ¹	10.0 ¹	10.0 ¹	10.0 ⁶	5.0

of ten different elements, thus the number of atom types in our implicit solvent models is ten, unless specified otherwise.

Computation of hydration free energies

The hydration free energy (HFE), also referred to as the solvation free energy of water, is the free energy difference between the vacuum state and the solvated state. It does not require the solute to be in a fixed conformation. In contrast to the SFE, it also accounts for conformational and entropic changes of the solute upon solvation. We use the multistate Bennett acceptance ratio as implemented in pyMBAR¹⁶ to compute HFEs. As phase space samples, we use the vacuum and implicit solvent trajectories provided by David Mobley.^{3,69} We recomputed bonded and non-bonded energies for all trajectories using AMBER 10. SFEs for all trajectory snapshots were computed as described in the sections ‘‘Implicit Solvent Models’’ and ‘‘Database and Model Parameterization’’.

Different implicit solvent models may result in different trajectories and therefore different HFEs. The generation of new trajectories would require a molecular simulation package that contains all three investigated models. While the GBNP1 model is common in simulation packages such as AMBER or CHARMM,⁷³ these packages do not provide the GBNP2 and GBNP3 models to our knowledge. To generate new trajectories, it would be necessary to implement, test, and validate the GBNP2 and GBNP3 models into a molecular simulation package, which is beyond the scope of this work. Since the change of the HFEs by using a different implicit solvent model to generate the trajectory was shown to be very small for the majority of molecules in the considered database,⁷ we will neglect that change for this work. To validate if that is indeed the case, we can compare the single conformation SFEs to the HFEs computed from the whole trajectories. This comparison should show good agreement if the neglected change is small. The reason is that the single conformations were taken from the vacuum trajectories, which do not depend on the implicit solvent model.

Results and discussion

In the following section, we first report the results of the parameterization procedure, followed by an in-depth analysis of the performance of the three different models, which has led to a refinement of the atom types used in the parameterization of the nonpolar terms. Finally, we tested the performance of the model using an independent set of molecules to assess the transferability of the results.

We have performed the parameterization procedure as described in the methods section. The ESI† contains the best

parameter set for each model. In addition, it contains average values and standard deviations of all free model parameters for the ten best parameter sets of each investigated model that were generated by the parameterization procedure.

With the best parameter set of each model, we have computed hydration free energies (HFEs) for all molecules in the database, which is also explained in the methods section. Our chosen approach relies on the fact that reusing existing implicit solvent trajectories introduces no large errors in our computed HFEs. This is the case if the single conformation solvation free energies (SFEs) agree well with our computed HFEs. We tested this assertion and find good agreement for the majority of the database with only few exceptions. The detailed analysis can be found in the ESI†

To assess the performance of the investigated implicit GB based solvent models in estimating experimentally measured HFEs, we computed the root mean square errors $RMSE_{HFE}$ and squared Pearson correlation coefficients R^2 of the computed HFEs in relation to experimental data. The GBNP1 model, whose nonpolar term is likely the most-widely used in GB based implicit solvent models, yielded a $RMSE_{HFE} = 1.30$ kcal mol⁻¹ and $R^2 = 0.826$. For GBNP2 the results are $RMSE_{HFE} = 0.99$ kcal mol⁻¹ and $R^2 = 0.900$, and for GBNP3 $RMSE_{HFE} = 1.19$ kcal mol⁻¹ and $R^2 = 0.853$. The corresponding data is shown in Fig. 1. As indicated by the much lower $RMSE_{HFE}$ and the higher correlation coefficient, the GBNP2 model outperforms its two competitors significantly, suggesting that the NP2 nonpolar model of eqn (5) in combination with a GB model is best suited for accurate estimation of small molecule HFEs.

Although the comparison between SFEs and HFEs in the ESI† resulted in root mean square errors of up to 0.42 kcal mol⁻¹, these differences are not reflected in the comparison of SFEs or HFEs to experimental data. The corresponding root mean square errors $RMSE_{SFE}$ and $RMSE_{HFE}$ are nearly identical (see Fig. 1). Mobley *et al.* found that differences between SFEs and HFEs for implicit solvent models with a moderate performance of $RMSE_{HFE} \approx 2$ kcal mol⁻¹ were not reflected in the comparison of SFEs or HFEs to experimental data.³ Our results demonstrate that this statement also holds for implicit solvent models with $RMSE_{HFE}$ as low as 1.0 kcal mol⁻¹.

Knight *et al.*⁷ found in their survey of computing HFEs using common GB based implicit solvent models on the same molecule database, that the GBSW model⁷⁴ has the lowest $RMSE_{HFE} = 1.52$ kcal mol⁻¹, and the GMBV²³ model had the best correlation coefficient with $R^2 = 0.809$. All these results were achieved with the nonpolar model NP1 of eqn (4) and an optimized value of γ . Comparison to our results shows that all three of our investigated models using optimized parameters outperform the models considered in that survey. Even our worst performing

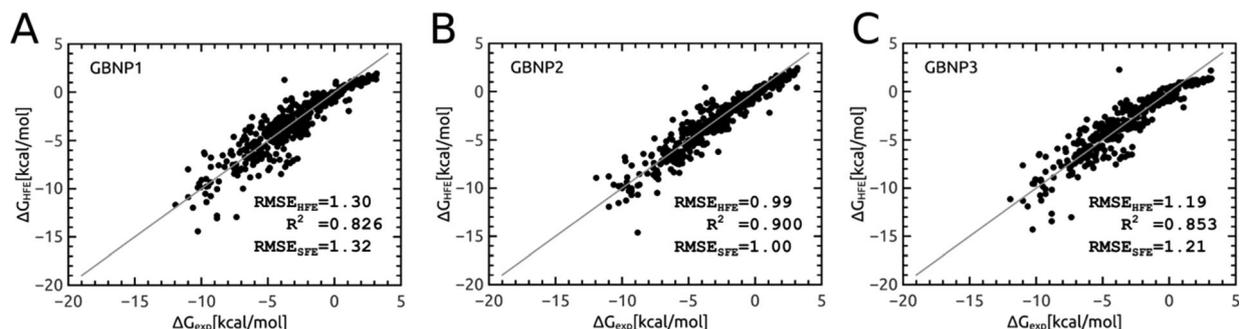


Fig. 1 Comparison of computed hydration free energies (HFEs) to experimental HFEs for the small molecule database using optimized parameters for the GBNP1 model (A), GBNP2 model (B), and GBNP3 model (C). The root mean square error for the data shown in the graphs is denoted as $RMSE_{HFE}$ and the corresponding squared Pearson correlation coefficient is R^2 . The root mean square error between the single conformation solvation free energies and the experimental HFEs that resulted from the parameter optimization procedure is denoted as $RMSE_{SFE}$.

GBNP1 model's $RMSE_{HFE}$ is at least $0.2 \text{ kcal mol}^{-1}$ lower than that of GBSW or any other implicit solvent model considered in that survey. Therefore, we conclude that optimization of atomic radii and GB parameters together with nonpolar parameters such as γ in eqn (4) is one key to success for improving small molecule HFE estimates of commonly used GB based implicit solvent models. Exchanging the nonpolar term to the NP2 model in eqn (5), based on the proposals of Eisenberg *et al.*³⁹ and Ooi *et al.*,⁴⁰ provides further significant improvements in accurately estimating HFEs of small molecules.

Comparison of computed HFEs using the explicit TIP3P water model resulted in an $RMSE_{HFE} = 1.26 \text{ kcal mol}^{-1}$ and $R^2 = 0.888$ as reported by Mobley *et al.*,⁴ and accounting for the duplicates in the database as pointed out by Knight *et al.*⁷ The GBNP1 model with optimized parameters is unable to close the accuracy gap to the explicit TIP3P water model with the given number of atom types and free parameters. Although the GBNP3 model has a slightly smaller $RMSE_{HFE}$ than TIP3P, the squared Pearson correlation coefficient R^2 is still smaller than that of TIP3P, despite having 12 more free parameters than GBNP1. However, the GBNP2 model's $RMSE_{HFE}$ is $0.27 \text{ kcal mol}^{-1}$ smaller than that of TIP3P and the correlation between computed and experimental data is also higher. This demonstrates that with a minimal reasonable set of optimized parameters, the combination of the NP2 nonpolar model (eqn (5)) with an accurate GB term (eqn (2)) is able to estimate HFEs as accurately as models with explicit TIP3P solvent for the given database.

Considering that the GBNP3 model has the largest number of free parameters and the supposedly most elaborate nonpolar model investigated in this study, its surprisingly moderate performance requires further investigations. Therefore, we group

the molecule database into ten sets corresponding to the ten atom types. Each set only contains molecules that have at least one atom of the corresponding atom type. We can then investigate for which atom type subsets the current parameterization exhibits the largest error. Table 3 lists the number of molecules containing at least one atom of the specified atom type as well as the root mean square errors for the atom type subsets. Only eight out of the ten subsets are shown in Table 3. Carbon and hydrogen are excluded from this analysis, as they are contained in nearly every molecule in the database. Therefore, the root mean square errors for these two elements are unlikely to show any significant differences compared to those for the full database.

Next to carbon and hydrogen, oxygen is the most abundant atom type followed by nitrogen. All other atom types are rather rare in the database, thus one should be careful when drawing conclusions from these small subsets. For GBNP1 and GBNP3, molecules containing nitrogen have the largest root mean square error, molecules containing fluorine the second largest error and molecules containing oxygen have only the third largest. In contrast, the corresponding errors for GBNP2 are significantly lower. The discussion of the root mean square errors in Table 3 (see ESI[†]) suggests that one reason for the moderate performance of GBNP3 and GBNP1 is the parameterization of nitrogen atoms. This group shows the highest root mean square error and a relatively high abundance in the database.

The results of this analysis suggested that the errors could be significantly reduced by introducing a new atom type for nitrogen atoms with positive partial charge. We have again carried out the parameterization procedure for the three GBNP models with the additional atom type. We will refer to these models as GBNP1*, GBNP2*, and GBNP3* respectively. Fig. 2 shows that the

Table 3 Root mean square errors in kcal mol^{-1} for each implicit model and atom type except carbon and hydrogen. The values in parentheses for fluorine exclude hexafluoropropene, which shows a significant error between computed implicit as well as explicit hydration free energies and the corresponding experimental value, because of an wrong experimental value in the database⁷⁶

Atom type	All	O	N	F	Br	S	I	Cl	P
Subset size [#]	499	227	86	26	23	21	11	8	2
GBNP1 [kcal mol^{-1}]	1.30	1.65	1.93	1.67 (1.37)	0.69	1.08	1.21	0.66	0.74
GBNP2 [kcal mol^{-1}]	0.99	1.13	1.14	1.70 (1.51)	0.50	0.71	1.15	0.40	0.96
GBNP3 [kcal mol^{-1}]	1.19	1.41	1.76	1.56 (1.04)	0.56	0.84	1.18	0.24	0.82

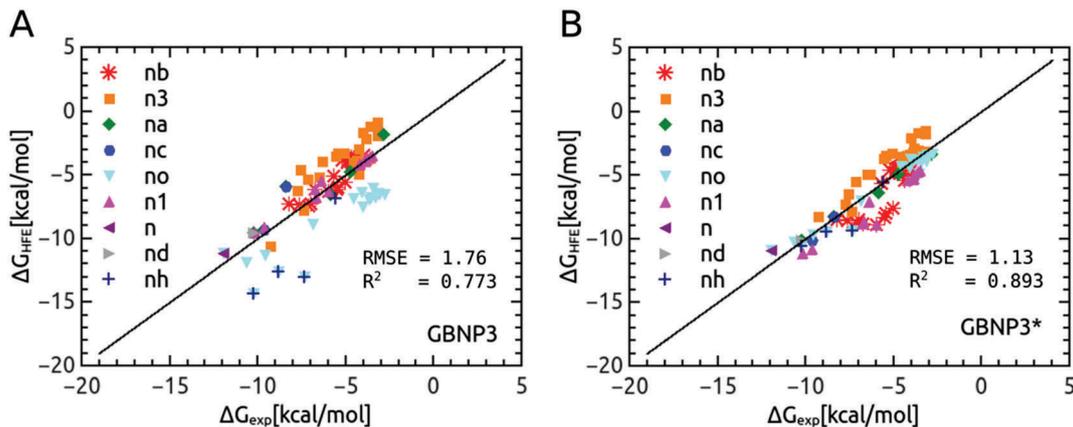


Fig. 2 Comparison of experimental hydration free energies to hydration free energies computed with the GBNP3 model using only one nitrogen atom type (A), and the GBNP3* model with two nitrogen atom types for either positive or negative partial charged nitrogen atoms (B). Only molecules containing nitrogen are considered. Their colors and symbols correspond to the Amber GAFF atom types^{67,68} listed in the figure legend. The panels also show the respective root mean square errors (RMSE) and squared Pearson correlation coefficients (R^2).

Table 4 Performance comparison of the three implicit solvent models before and after introducing a new atom type for nitrogen atoms with positive partial charges to account for the asymmetric behavior of water around opposite charged ions. The number of atom types is denoted as N . Values for the explicit TIP3P water model⁷ are also given as a reference

Parameterization	Implicit ($N = 10$)			Implicit ($N = 11$)			Explicit TIP3P ⁷
	GBNP1	GBNP2	GBNP3	GBNP1*	GBNP2*	GBNP3*	
RMSE _{SFE} [kcal mol ⁻¹]	1.32	1.00	1.21	1.17	1.00	1.04	
RMSE _{HFE} [kcal mol ⁻¹]	1.30	0.99	1.19	1.16	0.96	1.01	1.26
R^2	0.826	0.900	0.853	0.860	0.903	0.894	0.888

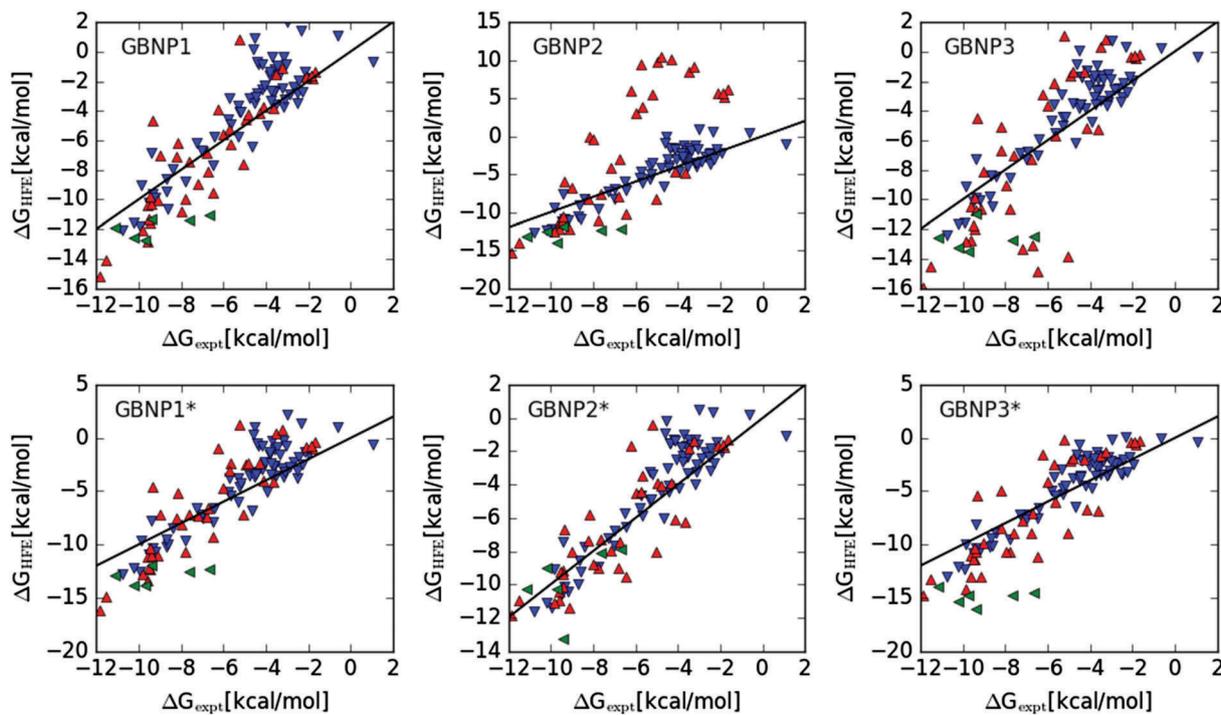


Fig. 3 Comparison of implicit solvent model hydration free energies vs. experimental hydration free energies for the test set of 122 molecules, which were not used to parameterize the models. Molecules containing nitrogen atoms with a partial charge larger than $0.3e$ are indicated in red, molecules containing carbon atoms with a partial charge larger than $0.8e$ are indicated in green, respectively. All data is detailed in the ESI.†

Table 5 Model performance for the test set of 122 molecules, divided into two subsets, covering the range of HFE over which the models were parameterized and all models, respectively. All data is detailed in the ESI

Model	Parameterization range		All molecules	
	RMSD in kcal mol ⁻¹	R ²	RMSD in kcal mol ⁻¹	R ²
GBNP1	2.05	0.801	2.59	0.765
GBNP2	4.65	0.513	4.52	0.647
GBNP3	2.57	0.718	2.83	0.749
GBNP1*	2.41	0.791	2.76	0.786
GBNP2*	1.68	0.815	2.23	0.803
GBNP3*	2.39	0.779	2.53	0.803
TIP3P	1.74	0.829	2.05	0.824

errors for the different AMBER nitrogen types with the GBNP3* model have improved in comparison to GBNP3. The HFEs of molecules containing “n3”, “no” and “nh” atom types agree much better with the experimental HFEs. The root mean square error for the molecules containing nitrogen drops from 1.76 kcal mol⁻¹ to 1.13 kcal mol⁻¹ for GBNP3* due to the enhanced parameterization with the additional atom type.

Table 4 shows the effects of the new parameterization on the achieved model results and errors of the computed HFEs for the whole molecule database. The GBNP1* and GBNP3* model’s RMSE_{SFE}, RMSE_{HFE} and R² improve significantly, while the parameterization result RMSE_{SFE} for GBNP2* shows practically no improvement. However RMSE_{HFE} and R² improve slightly. This is not surprising, since nitrogen had no large error for GBNP2 without the additional nitrogen atom type (see Table 3), which is related to the fact that the radii for oppositely charged nitrogen atoms are similar. A detailed analysis of the data for the new models is provided in the ESI.†

In order to test the transferability of the models to molecules not contained in the parameterization dataset, we have computed the HFE for the set of 122 molecules which were not in the 2009⁴ version of the database that was used for parameterizing the model (see Fig. 3 and Table 5; data for each molecule in the ESI†). As for the parameterization set, we find significantly better performance for the new models, which distinguish between nitrogen with positive and negative partial charge. This is most apparent for the GBNP2 models where the error drops from 4.65 kcal mol⁻¹ for GBNP2* to 1.68 kcal mol⁻¹ for GNPB2 (for the parameterization range), rivaling that of the explicit water model. This indicates that the additional terms in part compensate for deficiencies in the GB model. This is also illustrated in Fig. 3, where we have highlighted the charged molecules.

Conclusions

A survey by Knight *et al.*⁷ of common GB based implicit solvent models to estimate hydration free energies (HFEs) of small organic molecules revealed an accuracy gap between these models and explicit TIP3P water estimates. We have investigated how to improve the implicit solvent model estimates by assessing the performance of three GB based implicit solvent models with different nonpolar solvation terms using a minimal set of atom

types. All models were parameterized by fitting single conformation solvation free energies (SFEs) to experimental HFEs of a large database of small molecules to enable a fair comparison between the three models.

The most commonly used nonpolar term in combination with a GB model (GBNP1 model, eqn (2) and (4)) and our optimized parameters performs adequately in estimating HFEs for the small molecule database both for the test and the training set. However, comparisons to other common GB based implicit solvent models investigated by Knight *et al.*⁷ demonstrate that optimization of all model parameters together, *e.g.* atomic radii and the surface tension coefficient, can still leads to a significant accuracy improvement of the computed HFEs. Adding the solvent accessible volume to model nonpolar repulsion and Born radii to model solute–solvent dispersion interactions (GBNP3 model, eqn (6)) as proposed in the literature^{5,41–45,77} further improved the accuracy of estimating HFEs, but at the expense of a much larger set of free parameters in the model.

Exchanging the nonpolar term to that proposed by Eisenberg *et al.*³⁹ and Ooi *et al.*⁴⁰ with atom type dependent surface tension coefficients (GBNP2 model, eqn (5)) resulted in the most accurate estimates of HFEs when compared to experimental data. The root mean square error for the training/test sets is RMSE_{HFE} = 0.99/1.68 kcal mol⁻¹ and the squared Pearson correlation coefficient is R² = 0.90/0.81 with our optimized set of parameters for ten different atom types. This model yields results that are comparable to the explicit solvent TIP3P estimates for the given database, which yielded RMSE_{HFE} = 1.26 kcal mol⁻¹ and R² = 0.888.^{4,7}

A detailed error analysis provided evidence that deficiencies of the GB model for oppositely charged atoms is the main source of error for the GBNP1 and GBNP3 models. This effect is not accounted for in the parameterization of the models. The errors in the GBNP2* model are significantly smaller and methods that are able to decompose the contributions to the solvation energy at the QM-level^{61,78} are required to investigate the physical reasons for these deviations. Accounting for this asymmetric behavior in the parameterization *via* a new atom type resulted in better agreement between estimated HFEs and experimental values for all models, suggesting this as a general strategy for improving any GB based implicit solvent model.

It has been argued by Mobley *et al.*, that parameterization of implicit solvent models by fitting single conformation SFEs to experimental HFEs could cause significant problems if errors between computed and experimental HFEs reach those between SFEs and HFEs.³ However this is not the case for the models investigated here and for other commonly available GB based methods investigated by Knight *et al.*⁷ While there are models in the literature that report estimation of HFEs with errors as low as 0.3 kcal mol⁻¹, these errors were derived using either much smaller databases^{48,49,75} or a very large set of over 40 atom types⁴⁷ and are therefore not directly comparable to the results in this work. Thus, we believe that parameterization of implicit models to single conformation SFEs is still viable and an especially cheap method to improve the accurate estimation of HFEs using common GB based implicit solvent models significantly.

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