

Supporting Information:

Small Molecule Hydration Free Energies: Closing the Gap between Explicit and Implicit Solvent Models

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Comparison of Hydration Free Energies and Solvation Free Energies

Here is a comparison of the computed hydration free energies (HFE) and the corresponding single conformation solvation free energies (SFE). Their agreement indicates that no large errors are present in the computed HFEs due to not having computed new trajectories with the parameterized implicit solvent models. The error analysis presented in Table S1 shows that for all models the average errors

$$E_{avg} = \frac{1}{N_{mol}} \sum_{i=1}^{N_{mol}} (\Delta G_{HFE}^i - \Delta G_{SFE}^i) \quad (1)$$

range from -0.14 kcal/mol to -0.15 kcal/mol and are all slightly negative. One reason for this is that the maximum errors with up to $E_{max} = 0.73$ kcal/mol are rather small in comparison to the minimum errors, which can be as large as $E_{min} = -4.06$ kcal/mol for the GBNP2 model.

However the number of molecules with large errors between SFEs and HFEs is small compared to the total database size of 499 molecules. Only 8, 18 and 11 molecules for GBNP1, GBNP2 and GBNP3 respectively have absolute errors larger than 1.0 kcal/mol. This is also reflected in the average unsigned errors, which are smaller than 0.25 kcal/mol for all models. The corresponding root mean square errors, which are more sensitive to large outliers, are larger than the averaged unsigned errors, but at least for GBNP1 and GBNP3 in the expected range of 0.3 to 0.4 kcal/mol found by Mobley et al.¹ The value of GBNP2 is just slightly above that range. All squared Pearson correlation coefficients are larger than 0.992, demonstrating the good agreement between SFEs and HFEs. Therefore, we think that conclusions drawn from comparisons between our computed HFEs and experimental data are unlikely to be affected by not having produced new implicit solvent trajectories with our models and the optimized parameters.

Table S1. Error analysis for the comparison between the hydration free energies (HFEs) derived from the sampling MD trajectories in vacuum and implicit solvent and the solvation free energies (SFEs) computed for the lowest energy snapshots of the vacuum simulations.

	GBNP1	GBNP2	GBNP3
E_{avg} [kcal/mol]	-0.14	-0.15	-0.14
compounds with $ \Delta G_{HFE} - \Delta G_{SFE} > 1.0$ kcal/mol	8	18	11
E_{max} [kcal/mol]	0.67	0.64	0.73
E_{min}	-2.83	-4.06	-3.39

[kcal/mol]			
average unsigned error [kcal/mol]	0.19	0.22	0.22
root mean square error [kcal/mol]	0.34	0.42	0.37
squared Pearson correlation coefficient	0.995	0.992	0.994

Error Analysis by Atom Types

In order to optimize the parameter sets we have carefully analyzed the data in Table 3. 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. Molecules containing fluorine have the second largest root mean square error for GBNP1 and GBNP3, and by far the largest error for GBNP2. The reason for these errors is due to hexafluoropropene, where the experimental value in the database is given by $\Delta G_{exp} = 3.76 \text{ kcal/mol}$, but computed HFEs range from $\Delta G_{GBNP2} = 0.43 \text{ kcal/mol}$ to $\Delta G_{GBNP3} = 2.28 \text{ kcal/mol}$. Interestingly, explicit TIP3P's estimate $\Delta G_{TIP3P} = 2.29 \text{ kcal/mol}$ for this molecule is also off by a very large amount and positive, in agreement with our implicit solvent model estimates.² During the review process of our work it became apparent that the experimental value for the HFE of hexafluoropropene in the database was incorrect, and that the correct value is $\Delta G_{exp} = 2.31 \text{ kcal/mol}$.³ This value is in very good agreement with the explicit TIP3P water result and also agrees very well with our GBNP3 result. The corresponding GBNP1 and GBNP2 value show less agreement. In addition, the root mean square error of fluorine excluding hexafluoropropene in **Fehler! Verweisquelle konnte nicht gefunden werden.** is larger for GBNP1 or GBNP2 than for GBNP3. This

suggests that the parameterization procedure adapted better to the erroneous value of hexafluoropropene for the GBNP1 or GBNP2 models than for the GBNP3 model. This would result in larger observed errors of fluorine for the GBNP1 and GBNP2 models even after excluding hexafluoropropene.

Another molecule which shows a large error between computed and experimental HFEs is triacetyl glycerol, where explicit² and our implicit computations estimate HFEs between 13.1 *kcal/mol* and 14.6 *kcal/mol*, but the experimentally determined value is 8.84 *kcal/mol*. Since we use the same protonation states as provided by the mol2 files of the molecule database, changes of the protonation state are not captured by our estimates, and were also not taken into account in the explicit TIP3P water estimates by Mobley et al.² However, Mobley et al.¹ pointed out that several molecules might have more than one relevant protonation state that contributes to the estimates of the HFEs. Such molecules are likely to have good agreement between explicit and implicit HFE estimates, but less agreement to experimental data. Therefore, protonation effects are a common source of errors for implicit and explicit solvent models.

The error analysis in **Fehler! Verweisquelle konnte nicht gefunden werden.** (see Supporting Information) suggests that one reason for the moderate performance of GBNP3 and GBNP1 is the parameterization of nitrogen atoms. They have the highest root mean square error and a relatively high abundance in the database. We will investigate this issue for the GBNP3 model more closely now. Therefore, we group all nitrogen atoms into the AMBER GAFF atom types and compare the HFEs for these groups. We observe in **Fehler! Verweisquelle konnte nicht gefunden werden.**A that the computed HFEs for molecules with the “no” and “nh” atom types are systematically more negative than experimental values, while HFEs for most molecules with “n3” atoms are systematically overestimated.

Closer inspection reveals that “no” nitrogen atoms always carry a positive partial charge, since they are bound to two oxygen atoms, which have a higher electronegativity. All other nitrogen atoms carry negative partial charge. This difference has a large impact on the solvation properties. The corresponding effect is known as the asymmetry of water. Since water molecules are no perfect dipoles, their local distribution and orientation around opposite charged ions varies significantly, causing a large impact on the HFE.⁴⁻¹¹ Because all nitrogen atoms are assigned the same parameters in our investigated implicit solvent models, this effect is not taken into account by our current parameterization. However, the low root mean square error of the GBNP2 model for molecules containing nitrogen (**Fehler! Verweisquelle konnte nicht gefunden werden.**) suggests that the models good performance is partly due to its ability to cope well with the asymmetry of water, despite the effect not being accounted for in the parameterization explicitly.

Analysis of Model Performance

Nevertheless, it is interesting to observe that GBNP2* still performs better than its two competitors, although GBNP3* comes very close to its performance with the new parameterization. Comparing the root mean square errors of the computed to the experimental HFEs reveals that now all three implicit models have a lower $RMSE_{HFE}$ than the explicit TIP3P water model. However, the correlation coefficient for the GBNP1* model is still worse than that of TIP3P. This data highlights the importance of accounting for the asymmetry of water to estimate HFEs accurately. This can be achieved by either using the GBNP2 model or by choosing different parameters for opposite charged atoms in the GBNP1 or GBNP3 models. Although the latter approach is known to not capture the complete asymmetric behavior of water as shown by Mobley et al.,¹¹ it does significantly improve the accuracy of estimated HFEs.

While parameterization of our models is based on the elements contained in the molecule database, the membership of an atom to a chemical group may also be the basis for the definition of atom types. Due to the much larger number of chemical groups than elements, such a procedure would result in a much higher number of free parameters. Nevertheless, it is worthwhile to examine the $RMSE_{HFE}$ for these chemical groups. This may provide further insights how to improve the models, as suggested by Knight et al.,¹² from whom we have taken the classification of the molecules into chemical groups.

As shown in Figure 1A, the nitro group (number 26) has by far the largest error for the GBNP1 and GBNP3 models, while the GBNP2 shows reasonable agreement with experimental data. Noting that the AMBER GAFF “no” atom type corresponds to nitrogen atoms in nitro groups; the reason for the large errors in the two former models is the previously discussed asymmetry of water. After introducing the additional nitrogen atom type (Figure 1B), the error for the nitro group is reduced significantly for all three implicit models.

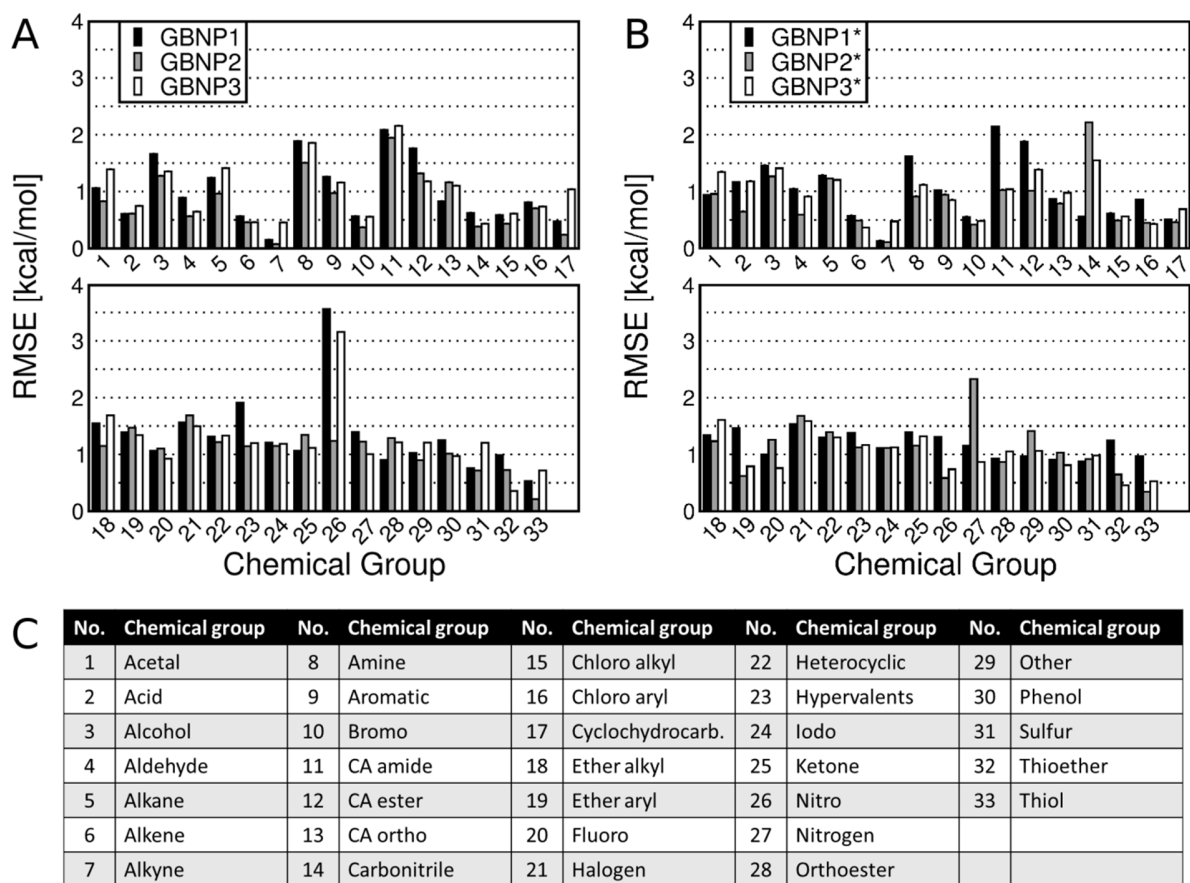


Figure 1. Root mean square errors (RMSE) for each chemical group contained in the database of 499 molecules as classified by Knight et al.¹² The figure shows the errors for the three implicit solvent models GBNP1, GBNP2, and GBNP3 (A) and the errors for the three models GBNP1*, GBNP2*, and GBNP3* that use an additional atom type for nitrogen atoms with positive partial charge (B). The names corresponding to the number of the chemical group are listed in the table below the histograms (C). CA denotes carboxylic acid.

Interestingly, the GBNP2* errors for the nitrogen group (number 27) and carbonitrile group (number 14) increase after introducing the new atom type. Closer inspection of the former group reveals that it contains only two molecules, ammonia, and hydrazine. Due to the small group size, the rather large error of hydrazine with $\Delta\Delta G_{HFE} = 3.03 \text{ kcal/mol}$ is not

averaged out. The carbonitrile group is larger and consists of eleven molecules. Although partial charges of carbonitrile nitrogen atoms are negative, they are less negative than most other nitrogen atoms excluding the positive charged nitrogen atoms in nitro groups. The two nitrogen parameters of the GBNP2 model fit nitrogen atoms with all partial charges reasonably well. But the GBNP2* parameters for nitrogen atoms with negative partial charge fit only nitrogen atoms with large negative partial charge well, because the parameterization procedure does not have to account for the nitrogen atoms in nitro groups with positive partial charge and carbonitrile nitrogen atoms with small negative partial charge are rather rare. Since the $RMSE_{SFE}$ improvement of GBNP2* over GBNP2 is negligible, we suppose that this is an overfitting problem. The parameterization procedure finds a set of parameters, which leads to a slightly smaller overall $RMSE_{SFE}$ at the expense of having much larger errors for specific chemical groups such as carbonitrile, which consists only of a few molecules in comparison to the whole molecule database size. To avoid overfitting, future parameterization procedures should not only optimize the overall root mean square error, but also be aware that no large errors for any chemical groups are introduced.

For other commonly used implicit solvent models, hypervalent sulfurs (group 23) was one group with a very large average unsigned error.¹² While GBNP1 also has a large error for this group close to 2.0 *kcal/mol*, all other implicit solvent models including GBNP1* have a much smaller error ranging from 1.12 *kcal/mol* to 1.37 *kcal/mol*. Therefore, it is possible to achieve relatively accurate estimates of HFEs for hypervalent sulfurs by reparameterization of implicit solvent models without having to change other force field parameters such as Lennard-Jones values. This contrasts the findings of Knight et al.¹² and Mobley et al.,¹³ who argued that the GAFF Lennard-Jones parameters might be the predominant source of error for this chemical group.

For GBNP1* there are still some chemical groups that show significant errors ranging from 1.5 *kcal/mol* to more than 2.0 *kcal/mol*. These are amines, carbon amides, and carbon esters. For these groups we observe the same issue as for nitrogen atoms. Carbon atoms in these groups carry positive partial charge, while carbon atoms for example in alkanes carry small negative partial charges. Because of the smaller charge differences, the induced errors are smaller than those of the nitro group are, but we expect an additional carbon atom type to reduce these errors further. This again underlines the importance of incorporating the asymmetric behavior of water around opposite charged groups into implicit GB based solvent models to achieve an accurate estimation of HFEs.

Best Fit Free Model Parameters

This section lists the best parameter set of each model that resulted from the fit procedure.

GBNP1 and GBNP1* parameters:

Table S2. Atomic radii in Angstrom for the GBNP1 and GBNP1 models. The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all other nitrogen atoms.*

	GBNP1	GBNP1*
atom type	r_i [Å]	r_i [Å]
H	0.831008	0.822679
C	2.087200	2.163286
N+	1.644502	3.290414
N-	1.644502	1.690109
O	1.737180	1.744935
S	2.386663	2.665700
Br	1.848793	1.946602
Cl	1.964041	2.009674

F	2.825541	2.841192
I	2.653648	2.594468
P	2.375304	2.564436

GBNP1: $\gamma = 3.611126 \text{ cal}/(\text{mol } \text{Å}^2)$, $p_r = 1.684932 \text{ Å}$

GBNP1*: $\gamma = 5.401394 \text{ cal}/(\text{mol } \text{Å}^2)$, $p_r = 0.6137033 \text{ Å}$

GBNP2 and GBNP2* parameters:

Table S3. Atomic radii in Angstrom for the GBNP2 and GBNP2 models. The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all other nitrogen atoms.*

atom type	GBNP2		GBNP2*	
	r_i [Å]	γ_i [cal/(mol Å ²)]	r_i [Å]	γ_i [cal/(mol Å ²)]
H	0.887931	-128.312	1.071515	-277.736
C	2.024920	7.065	2.163795	5.471
N+	1.719399	22.721	3.665930	-1.744
N-	1.719399	22.721	3.745685	-21.030
O	1.415210	145.920	1.576668	74.954
S	2.489602	-1.658	2.892409	-6.344
Br	2.722475	-1.887	2.921200	-2.677
Cl	2.504729	1.884	2.352292	1.180
F	4.075766	1.151	4.226569	0.759
I	4.548763	-1.909	2.354108	9.119
P	2.950902	-1.978	0.585610	2404.527

GBNP2: $p_r = 0.6966583 \text{ Å}$

GBNP2*: $p_r = 0.6958299 \text{ Å}$

GBNP3 and GBNP3* parameters:

Table S4. Atomic radii in Angstrom for the GBNP3 and GBNP3 models. The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all other nitrogen atoms.*

	GBNP3	GBNP3*
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atom type	r_i [Å]	α_i [(kcal Å ³)/mol]	r_i [Å]	α_i [(kcal Å ³)/mol]
H	0.816137	-2.524530	0.772943	-4.284599
C	2.133091	-21.050510	2.181877	-27.947199
N+	1.716055	-12.762645	3.144805	-241.118002
N-	1.716055	-12.762645	2.044383	-189.160701
O	1.673299	-0.000060	1.633465	-0.000001
S	2.801938	-166.328461	2.828581	-259.174124
Br	2.535302	-111.014188	2.347882	-126.354113
Cl	2.223324	-51.322217	2.055575	-56.367841
F	2.268272	-30.823847	2.021757	-1.748481
I	2.703671	-136.896710	2.572762	-134.051851
P	4.055450	-1528.802976	2.277134	-101.064951

GBNP3: $\gamma = 3.819235$ cal/(mol Å²), $p = 21.27358$ cal/(mol Å³), $p_r = 0.8616802$ Å, $B = 0.8265109$ Å

GBNP3*: $\gamma = 4.202191$ cal/(mol Å²), $p = 7.932126$ cal/(mol Å³), $p_r = 1.198619$ Å, $B = 2.005747$ Å

Variation of Free Model Parameters

The following tables show the average parameter values and their standard deviation for the best ten parameter sets of each model that resulted from the parameter optimization procedure. In addition, the range of fit result $RMSE_{SFE}$ is also given.

GBNP1 and GBNP1*:

GBNP1:

- $RMSE_{SFE}$: 1.316 kcal/mol to 1.317 kcal/mol
- $\gamma = (0.0031 \pm 0.0004)$ kcal/(mol Å²)
- $p_r = (2.1 \pm 0.4)$ Å

GBNP1*:

- $RMSE_{SFE}$: 1.172 kcal/mol to 1.174 kcal/mol
- $\gamma = (0.0056 \pm 0.0004)$ kcal/(mol \AA^2)
- $p_r = (0.8 \pm 0.2)$ \AA

Table S5. Average free model parameters and their standard deviation for the GBNP1 and GBNP1* models. The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all other nitrogen atoms.

Element	GBNP1		GBNP1*	
	avg. r_i [\AA]	std. dev. r_i [\AA]	avg. r_i [\AA]	std. dev. r_i [\AA]
H	0.84	0.01	0.83	0.01
C	2.07	0.03	2.12	0.02
N+	1.64	0.01	3.27	0.01
N-	1.64	0.01	1.67	0.01
O	1.73	0.01	1.72	0.02
S	2.43	0.06	2.56	0.06
Br	1.86	0.02	1.88	0.03
Cl	1.94	0.02	1.99	0.03
F	2.83	0.03	2.83	0.01
I	2.63	0.04	2.54	0.03
P	1.38	0.78	2.57	0.01

GBNP2:

- $RMSE_{SFE}$: 1.00 kcal/mol to 1.03 kcal/mol
- $p_r = (0.70 \pm 0.09)$ \AA

Table S6. Average free model parameters and their standard deviation for the GBNP2 model. The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all other nitrogen atoms.

Element	avg. γ_i [kcal/(mol \AA^2)]	std. dev. γ_i [kcal/(mol \AA^2)]	avg. r_i [\AA]	std. dev. r_i [\AA]
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H	-9.05E-02	5.09E-02	0.84	0.09
C	6.43E-03	4.08E-04	2.07	0.04
N+	2.33E-02	2.50E-02	1.71	0.07
N-	2.33E-02	2.50E-02	1.71	0.07
O	1.38E-01	9.84E-03	1.44	0.03
S	-2.77E-03	8.10E-04	2.57	0.08
Br	-2.00E-03	1.54E-04	2.80	0.05
Cl	1.57E-03	3.23E-04	2.55	0.07
F	3.12E-03	4.02E-03	3.75	0.66
I	3.59E-03	8.11E-03	3.69	1.13
P	9.15E-01	2.67E+00	2.49	0.42

GBNP2*:

- $RMSE_{SFE}$: 1.00 kcal/mol to 1.03 kcal/mol
- $p_r = (1.2 \pm 0.5) \text{ \AA}$

Table S7. Average free model parameters and their standard deviation for the GBNP2 model.*

The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all other nitrogen atoms.

Element	avg. γ_i [kcal/(mol \AA^2)]	std. dev. γ_i [kcal/(mol \AA^2)]	avg. r_i [\AA]	std. dev. r_i [\AA]
H	-1.55E-01	6.33E-02	1.00	0.15
C	4.75E-03	1.23E-03	2.14	0.10
N+	4.70E-05	2.31E-03	3.61	0.49
N-	-4.52E-03	1.99E-02	3.16	0.94
O	8.60E-02	4.80E-02	1.50	0.08
S	-4.05E-03	1.58E-03	2.72	0.14
Br	-1.85E-03	6.28E-04	2.75	0.18
Cl	9.88E-04	4.43E-04	2.41	0.13
F	3.53E-03	2.80E-03	3.30	0.75
I	3.65E-03	4.42E-03	3.23	1.07

P	5.43E+00	1.51E+01	2.02	0.67
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GBNP3:

- $RMSE_{SFE}$: 1.21 kcal/mol to 1.24 kcal/mol
- $\gamma = (0.005 \pm 0.002)$ kcal/(mol Å²)
- $p = (0.009 \pm 0.006)$ kcal/(mol Å³)
- $p_r = (1.1 \pm 0.3)$ Å
- $B = (1.2 \pm 0.4)$ Å

Table S8. Average free model parameters and their standard deviation for the GBNP3 model.

The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all others.

Element	avg. α_i [(kcal Å ³)/mol]	std. dev. α_i [(kcal Å ³)/mol]	avg. r_i [Å]	std. dev. r_i [Å]
H	-1.45E+00	1.29E+00	0.81	0.04
C	-1.77E+01	6.37E+00	2.20	0.15
N+	-3.11E+02	3.92E+02	2.47	0.98
N-	-3.11E+02	3.92E+02	2.47	0.98
O	-9.80E-05	2.43E-04	1.66	0.05
S	-1.54E+02	3.16E+01	2.83	0.04
Br	-9.00E+01	1.94E+01	2.51	0.15
Cl	-3.18E+01	1.27E+01	2.07	0.11
F	-2.13E+01	2.22E+01	2.41	0.20
I	-8.96E+01	7.05E+01	2.60	0.22
P	-2.17E+02	4.39E+02	1.88	0.96

GBNP3*:

- $RMSE_{SFE}$: 1.04 kcal/mol to 1.05 kcal/mol
- $\gamma = (0.006 \pm 0.001)$ kcal/(mol Å²)
- $p = (0.007 \pm 0.001)$ kcal/(mol Å³)
- $p_r = (1.1 \pm 0.1)$ Å
- $B = (2.8 \pm 0.6)$ Å

Table S9. Average free model parameters and their standard deviation for the GBNP3* model. The atom type N+ is assigned to nitrogen atoms with positive partial charge and N- to all other nitrogen atoms.

Element	avg. α_i [(kcal Å ²)/mol]	std. dev. α_i [(kcal Å ²)/mol]	avg. r_i [Å]	std. dev. r_i [Å]
H	-7.97E+00	2.98E+00	0.78	0.01
C	-4.60E+01	1.41E+01	2.19	0.03
N+	-4.11E+02	1.12E+02	3.21	0.04
N-	-2.42E+02	8.22E+01	1.90	0.05
O	-4.45E-04	5.27E-04	1.63	0.01
S	-4.09E+02	1.37E+02	2.82	0.03
Br	-2.61E+02	8.86E+01	2.49	0.14
Cl	-1.01E+02	3.81E+01	2.08	0.04
F	-6.07E+01	6.46E+01	2.36	0.26
I	-2.03E+02	8.43E+01	2.53	0.09
P	-1.29E+02	4.21E+01	1.58	0.63

Here we note some observations made from the average values and standard deviations. The radii of phosphorus show a high standard deviation for all models except GBNP1*. The reason is likely that only two molecules containing phosphorus are present in the database. Thus, the data set for phosphorus is likely too small to result in an unambiguous value for the fit parameter.

All parameters for fluorine and iodine show large standard deviations except for the GBNP1 and GBNP1* models. The latter models contain only one parameter specific to the atom type fluorine, while the other models contain two parameters for that atom type. Therefore, the reason for the large standard deviation seems to be an ambiguity of the models. For example, in the GBNP2 and GBNP2* model, a larger radius r_i of iodine can be compensated by a different absolute value of the corresponding surface tension coefficient γ_i of iodine. The same holds for the atomic radii r_i , the Born radius offset B and atomic dispersion coefficient α_i in the GBNP3 and GBNP3* models.

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