Continuum Polarizable Force Field within the Poisson-Boltzmann Framework

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Abstract

We have developed and tested a complete set of nonbonded parameters for a continuum polarizable force field. Our analysis shows that the new continuum polarizable model is consistent with B3LYP/cc-pVTZ in modeling electronic response upon variation of dielectric environment. Comparison with experiment also shows that the new continuum polarizable model is reasonable, with similar accuracy as B3LYP/cc-pVTZ in reproduction of dipole moments of selected organic molecules in the gas phase. We have further tested the validity to interchange the Amber van der Waals parameters between the explicit and continuum polarizable force fields with a series of dimers. It can be found that the continuum polarizable model agrees well with MP2/cc-pVTZ, with deviations in dimer binding energies less than 0.9 kcal/mol in the aqueous dielectric environment. Finally we have optimized atomic cavity radii with respect to experimental solvation free energies of 177 training molecules. To validate the optimized cavity radii, we have tested these parameters against 176 test molecules. It is found that the optimized PB atomic cavity radii transfer well from the training set to the test set, with an overall root-mean-squared deviation of 1.30 kcal/mol, unsigned average error of 1.07 kacl/mol, and correlation coefficient of 92% for all 353 molecules in both the training and test sets. Given the development documented here, the next natural step is the construction of a full protein/nucleic acid force field within the new continuum polarization framework.

Introduction

Most commonly used force fields are additive or nonpolarizable in computational simulations of structures, dynamics, and functions of biomolecules. They incorporate a relatively simple potential energy function:

$$V(r) = \sum_{\text{bonds}} k_b(b-b_0)^2 + \sum_{\text{angles}} k_\theta(\theta-\theta_0)^2 + \sum_{\text{torsions}} k_\varphi \left[\cos(n\varphi+\delta)+1\right]$$
$$+ \sum_{\text{nonbond pairs}} \left[\frac{q_i q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6}\right] \tag{1}$$

The first three summations are over bonds (1-2 interactions), angles (1-3 interactions), and proper/improper torsions (1-4 interactions). The final summation (over pairs of atoms *i* and *j*) excludes 1-2 and 1-3 interactions and often uses different parameters for atoms separated by three covalent bonds (i.e. the 1-4 interactions) from those for atoms separated by more than three covalent bonds. It describes electrostatics interactions that are represented by a Coulombic potential, and dispersion and exchange repulsion interactions that are represented by a Lennard-Jones 6-12 potential. Many such force fields have been developed for biomolecular simulations, such as Amber,[1-6] CHARMM,[7,8] GROMOS,[9] and OPLS.[10-12]

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In force field applications, the covalent bonding terms are not that critical in biomolecular simulations, as long as bond and angle parameters are taken from small molecule structures and vibrational frequencies, and torsion terms are fitted to high level quantum mechanical potential energy surfaces. The van der Waals parameters are not very different among various force fields either, mostly derived from Jorgensen's OPLS parameter set.[10] The most important differences among various force fields are the treatments of electrostatics.

To develop parameters for electrostatics, all force fields face the problem of how to effectively wrap polarization into the total potential energy as physically and cleanly as possible. Amber based its parameter development on a set of HF/6-31G* calculations to effectively increase molecular dipole moments,[3] to a similar amount observed in the TIP3P and SPC water models. [13,14] In CHARMM charges were derived primarily from fits to solute-water dimer energetics. In addition to fitting the dimer interaction energies, charges for model compounds were adjusted to obtain dipole moments somewhat larger than experimental or gas-phase *ab initio* values. OPLS placed a strong emphasis on deriving nonbonded interactions by comparison to liquid-phase thermodynamics.[11,12] Although the OPLS parameters were principally derived with reference to condensed phase simulations, comparisons to gas-phase peptide energetics also show good results.[15]

A cornerstone for accurate biomolecular simulations is the molecular mechanical force field. Accuracy of the force field parameters ultimately determines that of the simulations. Arguably, polarizable force fields of various forms offer more consistent and balanced treatment of solute-solute and solute-solvent interactions for biomolecular simulations, at least for the environment-sensitive electrostatic components. Indeed, it is widely recognized that the use of an electrostatic model based on fixed charges as in nonpolarizable force fields has a significant shortcoming: the model is unable to respond directly to the molecular environment. Nevertheless, it should be pointed out that the need for explicit inclusion of polarization effects in force fields is still a matter of current discussion in the literature.[16,17]

Three basic methods for including polarization have been studied: fluctuating charge, Drude oscillator, and induced dipole models. Fluctuating charge models use the principle of electronegativity equalization to produce a set of point charges that optimize the total electrostatic energy. In theory, intermolecular charge transfer is then handled by requiring conservation of charge for the whole system. In applications, charge conservation is often enforced for each individual molecule.[18-21] Drude oscillator methods, also referred to as shell models, use a harmonic restraint potential to tether a mobile point charge to an interaction site. In a general Drude oscillator model, an atom carries a charge fixed at the nucleus and a second restrained charge of variable position. The charge magnitudes and harmonic force constants are fit to atomic and molecular polarizability data and experimental energies. As with fluctuating charge model, the Drude oscillator model is most often used with an extended Lagrangian treatment of the variable charges during a molecular dynamics simulation.[22] Probably the best-studied method for handling polarization is use of induced multipole moments. While higher-order multipole polarization and hyperpolarization can be included in force fields,[23] only induced dipoles are usually considered.

To date, most polarizable force fields are still under developments with a few published applications limited to those from the development groups. The Amber *ff02* potential represents an initial polarizable member in the Amber force fields with most of its components retained from nonpolarizable force fields.[24,25] The Amoeba force field is a fully polarizable force field with its own polarizable water potential.[26,27] The CHARMM fluctuating charge force field is another fully polarizable force field.[28,29] This force field has been tested with 7 representative globular proteins in explicit polarizable solvent represented by the TIP4P-FQ potential.[28,29] Drude polarizable CHARMM force field incorporates induced polarization into

the potential function on the basis of the classical Drude oscillator model.[30-34] The early versions of PROSA force fields were first based on a fluctuating charge formalism.[35] This model was later extended via the addition of induced dipoles on some sites.[36] The SIBFA force field has been applied to a series of protein structure and molecular recognition problems. [37-39] The energy function is based on a rather direct decomposition of *ab initio* SCF computations, including multipole electrostatics, repulsion, and dispersion-like terms.[37-39] Notably, separate terms are used for polarization and charge transfer.[37-39] Very recently, the NEMO potential for a capped glycine residue has been reported.[40] This study devoted considerable attention to the intramolecular potential.[40] The SDFF force field is unique among current polarizable protein force-field efforts in its extensive use of cross-terms and emphasis on valence potential functions.[41]

With ever improving accuracy in implicit solvents,[42-45] an interesting question in the development of polarizable force fields is how to incorporate electronic polarization in implicit solvents. Maple *et al* directly incorporated an explicit polarizable force field in their generalized Born implicit solvent.[46] Schneiders *et al* combined a Poisson-Boltzmann solvent and the explicit polarizable Amoeba force field successfully.[47] Alternatively, it is also reasonable to treat electronic polarization in a continuum manner since implicit solvents have treated solvent polarization in a continuum manner. However, adoption of such a strategy does not argue for its capability to handle atomic-detailed polarization effects within a molecular environment. Instead, it is intended to offer an efficient and self-consistent approach in treating polar interactions in biomolecular simulations more satisfactory than existing additive force fields with implicit solvents. Continuum treatment of electronic polarization was often used in many calculations related to solvation free energies.[48,49] Typical implicit solvents, such as numerical Poisson-Boltzmann approaches[50,51] and generalized Born approaches[52,53] were developed to deal with non-vacuum solute interior. However, a molecular mechanics force field that is designed to be consistent with such a treatment of electronic polarization just began to emerge.[54] In a previous study we explored the feasibility to treat electronic polarization in a continuum manner.[54] We found that an electrostatic model with a single set of parameters can be used in different environments and conformations with such a continuum treatment of electrostatic polarization.[54] In this work we want to investigate the highly important nonbonded components for such a force field.

Method

Continuum Polarizable Force Field

In our proposed continuum polarizable model a continuum dipole moment density within the solute interior is used to represent electronic polarization. The dipole moment density, termed polarization (**P**) in classical electrostatics, is related to electric filed (**E**) as

$$\mathbf{P} = \frac{\varepsilon - 1}{4\pi} \mathbf{E},$$

(2)

where ε is the solute dielectric constant, a value of 4 was found to be optimal for tested molecules.[54]

Note that this is different from the commonly used high protein dielectric constants > 20 or the widely accepted low protein dielectric constant of 2. This discrepancy can be better understood after a brief review of protein dielectric constants as discussed by Warshel and co-workers.[55] Warshel and co-workers have pointed out that the protein dielectric constant is 1 when all electrostatic details, such as permanent dipoles and induced dipoles, are represented and sampled explicitly. This is the case for explicit polarizable force fields. Incidentally, this also argues for why existing additive force fields that are designed with a protein dielectric constant of 1 are already fundamentally flawed. They have also pointed out that the protein

dielectric constant is 2 or higher when all except induced dipoles are represented and sampled. This is the case for continuum polarizable force fields. In other words, the solute dielectric in the continuum polarizable force fields should be similar to its dielectric at high frequency limit, ε_∞, as in the Debye equation for frequency dependent complex dielectric constant: $\varepsilon = \varepsilon' + \varepsilon''$,

with $\varepsilon' = \varepsilon_\infty + \dfrac{\varepsilon_s - \varepsilon_\infty}{1 + \omega^2 \tau^2}$ and $\varepsilon'' = \dfrac{(\varepsilon_s - \varepsilon_\infty)\omega\tau}{1 + \omega^2 \tau^2}$. Here ε_s is static dielectric value at zero frequency and ω is angular frequency, τ is the relaxation time for molecular orientation. It should be pointed out that ε_∞ are different for different molecules, ranging from about 2.0 for cyclohexane, to 4.0 for N-methyl acetamide (NMA) and 5.2 for liquid water at room temperature. Thus, this value is very different from measured or simulated protein *macroscopic* dielectric constant, which can be as high as 20 and above. The much higher value is to account for rotational polarization, exchange of protein and water in the solvent-exposed region of protein, and also average over ionization states of acids and bases. This in part explains why a value as high as 20 has to be used in many previous applications of implicit solvents in protein stability and pK a predictions where no explicit representation or sampling of any polarization details presents.[55-57] The current model adopts an empirically optimized "average" solute dielectric constant of 4 in all molecular mechanics calculations. This value was shown to give the best agreement in included dipole moments between the continuum electronic polarizable model and the B3LYP/cc-pVTZ theory for tested model compounds in tested continuum solvents.[54]

Once polarization is known from Eqn (2), the polarization energy (V_{pol}) can then be calculated from induced charges (ρ^{ind}) due to polarization and potential generated by solute point charges (ϕ^{perm}):

$$V_{pol} = -\frac{1}{2}\int \rho^{ind}\varphi^{perm} d\upsilon, \tag{3}$$

$$\rho^{ind} = -\frac{1}{4\pi}\nabla \cdot \mathbf{P} \tag{4}$$

Note that the use of Eqns (2) - (4) requires electrostatic field, **E**. In the proposed continuum polarizable force field, **E** ($= -\nabla\phi$) can be obtained by solving the Poisson's equation with a given set of solute point charges (ρ^{perm}, permanent charges):[54]

$$\nabla \cdot (\varepsilon\nabla\varphi) = -4\pi\rho^{perm}. \tag{5}$$

In the continuum polarizable force field, atomic charges of each molecule are fitted with respect to the quantum mechanical electrostatic potential (ESP) simultaneously *in vacuo*, a low dielectric environment ($\varepsilon = 4$), and a high-dielectric aqueous environment ($\varepsilon = 78.39$) with a modified RESP methodology that was developed to accommodate the proposed continuum electronic polarization treatment.[54] The modified RESP was based on a least square fit between the molecular mechanical (MM) electrostatic potential and the quantum mechanical (QM) electrostatic potential as in the original RESP.[58,59] The procedure can be summarized in the following steps:

1. Atomic charges Q are initialized by fitting $\mathbf{E}^{QM}$, i.e. the electrostatic potential from QM, without considering electronic polarization.

2. Induced electronic dipole moment density (**P**) is calculated by Eqn. (2) and Poisson's equation ($\nabla\cdot\varepsilon\mathbf{E} = 4\pi\rho^{perm}$) with given ρ^{perm}, i.e. atomic charges Q.

3. $\mathbf{E}^{ind}$, electrostatic potential from induced electronic dipole moment density (**P**), is computed.

4. New atomic charges Q are refitted to the difference between electrostatic potential from QM and that from induced electronic dipole moment density ($\mathbf{E}^{QM}$-$\mathbf{E}^{ind}$).

5. Go to Step 2) until convergence is achieved.

As discussed in our previous study, when the environment is not *in vacuo*, there are two contributions to polarization, the first is electronic and the second is solvent. What complicates the picture is that there is, in general, a coupling between the two polarization effects. Thus it is not straight forward to separate the final polarization effect into two isolated components: solvent and electronic polarization effects. The MM electrostatic field from solving Poisson's equation includes all the effects. However, the QM electrostatic field does not include the contribution of solvent polarization due to the way that ESP is computed in the Gaussian program.[60] Therefore the contribution of solvent polarization has to be subtracted from the included electrostatic field to achieve a consistency between QM and MM as discussed in our previous study.[54]

In this study, the quantum mechanical electrostatic potential was obtained in B3LYP/cc-pVTZ with the Gaussian03 program.[60] The PCM solvent[61,62] was used to model polarization responses to different dielectric environments. The charge fitting calculations were performed with a revised Amber9 package.[63] The electrostatic field was calculated with a numerical Poisson-Boltzmann (PB) solver[64,65] (igb=10) in the SANDER module. Atomic radii were set to be consistent with those in the PCM solvent[61,62] in Gaussian03.[60] The probe radius was set to be 0.6 Å.[44] Solvent excluded surface was used to assign dielectric constant in the solute interior. Dielectric constant for the solute region was set to be 4 as discussed above, and that for the solvent region was set to be 1 for vacuum, 4 for a low dielectric environment, and 78.39 for a high-dielectric aqueous environment to be consistent with the PCM solvent in Gaussian03.[60] The ionic strength was set to 0 mM. A grid spacing of 0.2 Å was used in the finite-difference PB solver. To ensure accurate boundary potential on the finite-difference grid, the longest dimension of the finite-difference grid was set to be 4 times that of solute. The relative convergence criterion was 0.0001 for the finite-difference solver. No cutoff for electrostatic interactions was used.

Parameter Development Strategy

Since covalent components vary little upon treatments of non-covalent components, it is safe to retain these parameters from previous generations of force fields, at least at this stage of the development. However, the two non-covalent components, namely, electrostatics and van der Waals interactions need careful refinement. Accurate treatment of non-covalent interactions were pioneered by OPLS developers in their efforts to pursuing accurate reproduction of the thermodynamic properties of pure organic liquids.[11,66] Indeed, the OPLS non-covalent parameters have become the basis for all other modern force fields.

The accuracy of non-covalent parameters is also crucial for the development of any polarizable force fields. In this study we assumed that there is an overall consistency between implicit and explicit polarizable models, at least for intramolecular electrostatic interactions, because both models are designed to be consistent with the same benchmark ab initio training data, the B3LYP/cc-pVTZ electrostatics.[54] Due to the consistency in electrostatics, intramolecular non-covalent parameters can be made interchangeable, at least approximately, between implicit and explicit polarizable models in Amber. Any future update of van der Waals parameters for the explicit polarizable model can be plugged into the continuum polarizable force field without further changes. This strategy apparently simplifies future refinements of all force fields based on the same benchmark *ab initio* quantum mechanical theory.

The only issue left in the development of non-covalent terms in the continuum polarizable force field is reproduction of solvation free energies of model compounds in a given solvent. In this study, we adopted the widely used thermodynamic cycle shown in Fig. 1 to compute solvation free energies of small organic compounds.[49] In the thermodynamic cycle,

electrostatic free energy, $\Delta G_1^{V,pol}$, is evaluated by discharging the solute in the first solvent (here in vacuum). The solute, now completely nonpolar, is transferred between the two solvents. This step gives the nonpolar, or repulsive/attractive contributions to the solvation energy, ΔG_2^{np}. The solute is then recharged in the second solvent (here in water), and the associated electrostatic interaction energy, $\Delta G_3^{W,pol}$, is calculated. The total solvation free energy, ΔG_4^{sol}, is obtained from the sum of the free energies of the three separate steps:

$$\Delta G_4^{sol} = \Delta G_1^{V,pol} + \Delta G_2^{np} + \Delta G_3^{W,pol}$$

The total electrostatic solvation free energy at steps 1 and 3 is usually termed polar solvation free energy and the nonelectrostatic solvation free energy at step 2 is usually termed nonpolar solvation free energy. Thus, the total solvation free energy of a molecule can be expressed as a sum of polar (electrostatic) and nonpolar (van der Waals) solvation free energies. Both polar and nonpolar components need to be optimized for the continuum polarizable force field. Our previous study of nonpolar solvation free energy, however, shows that the nonpolar solvation free energy model does not contain any compound specific parameters that can be adjusted for optimal accuracy.[45] Thus only polar solvation free energy needs to be optimized. In doing so the accuracy of the nonpolar solvation free energy model is on the order of ~1.0 kcal/mol when it is compared with the TIP3P solvent even if an exhaustive optimization was utilized.[45] Thus the lack of compound specific parameters does limit the overall accuracy of the calculated total solvation free energy.

Since only atomic cavity radii are the freely adjustable parameters in the polar component, the optimization of the polar component becomes rather straightforward. Here we have used a large and diversified set of generic organic molecules to optimize the atomic cavity radii. Following our previous effort in the calibration of atomic cavity radii for the nonpolarizable Amber force field,[44] the atomic cavity radii can first be grouped by Amber atom types and the net charges of functional groups to increase the ratio between parameters and fitting data constraints. To further increase the ratio between parameters and fitting data constraints, we have removed a few rare atom types that cover less than 10 training molecules. Finally, a total of 20 parameters are used for the 39 Amber atom types against 353 experimental data constraints.

Computational Details

Polar solvation free energy is calculated by the PB solvent with the continuum polarizable solute force field. The boundary between solute and solvent is the solvent excluded surface with a probe radius of 0.6 Å[44] and atomic cavity radii to be optimized. The solute and solvent, with associated charges and dielectric boundaries, are mapped onto a finite-difference grid. Electrostatic potentials are calculated by solving the PB equation with the finite-difference solver.[64,65] The total polar solvation energy is the sum of steps 1 and 3 of Fig. 1,

$$\Delta G^{pol} = 1/2 \sum_i q_i \left(\varphi_i^W - \varphi_i^V \right),$$

where q_i and ϕ_i are the charge and calculated potential at the ith gridpoint, for the case of transfer from vacuum (V) to water (W).

Nonpolar solvation free energy is decomposed into two terms: ΔG_{rep}, repulsive (cavity) free energy, and ΔG_{att}, attractive (dispersion) free energy.[45] Free energy simulations of spherical cavities have shown that for small cavities, ΔG_{rep} correlates with the cavity volume, while for large cavities, ΔG_{rep} correlates with the cavity surface.[67-69] The crossover occurs around the cavity radius of 10 Å.[70,71] Interestingly, a surprising conclusion from our previous analysis is that both molecular surfaces and volumes can be used as estimators of repulsive solvation

free energies with very similar high accuracies even if the tested monomer molecules are all within the previously reported switching region (spherical radii around 10 Å) from volume-dependence to surface-dependence.[45] A probable reason for the apparent discrepancy between our previous conclusion[45] and the literature is that our simulations were on "realistic" molecules,[45] while the literature simulations were performed on ideal spherical cavities. Our additional tests of both molecular surfaces and volumes on larger biomolecules show that molecular volumes transfer better from small molecules to large biomolecules (Tan and Luo, in preparation). Thus the molecular volumes were used to estimate ΔG_{rep}. Specifically, the solvent accessible volume (SAV, i.e. the molecular volume enclosed by the solvent accessible surface) was used:[45]

$$\Delta G_{rep} = p \cdot \text{SAV} + c \tag{6}$$

where $p = 0.0378$ kcal/mol-Å^3 is a solvent pressure parameter and $c = -0.5692$ kcal/mol.[45] These parameters were optimized with respect to the TIP3P solvent, and the SAV was computed with the atomic van der Waals *rmin* radius definition and an optimized solvent probe of 1.30 Å.[45]

ΔG_{att} is approximated by the van der Waals attractive interaction potential energy between solute (u) and solvent (v) as[72-74]

$$\Delta G_{att} \approx \langle U_{att}^{uv} \rangle \tag{7}$$

In general, the solute-solvent van der Waals interaction energy can be analytically expressed as the following volume integral

$$U_{att}^{uv} = \sum_{a=1}^{N_s} \int \rho_{aw}(\mathbf{r}_{aw}) V_{att}(\mathbf{r}_{aw}) d\mathbf{r}_{aw} \tag{8}$$

Here the sum is over all solute atoms (N_s) and the integration is over the solvent occupied volume. $\rho_{aw}(\mathbf{r}_{aw})$ is a solvent distribution function around solute atom a at a given solute-solvent distance $\mathbf{r}_{aw}$. $V_{att}(\mathbf{r}_{aw})$ is the attractive van der Waals potential in the σ decomposition scheme: [45]

$$V_{rep}(r) = \begin{cases} u_{LJ}(r) & r \leq \sigma \\ 0 & r > \sigma \end{cases} \tag{9}$$

$$V_{att}(r) = \begin{cases} 0 & r \leq \sigma \\ u_{LJ}(r) & r > \sigma \end{cases} \tag{10}$$

where $u_{LJ}(r) = \dfrac{A}{r^{12}} - \dfrac{B}{r^6}$ is the Lennard-Jones 6-12 potential. Here, $A = 4\varepsilon\sigma^{12}$ and $B = 4\varepsilon\sigma^6$, ε and σ are the well-depth and radius parameters of the Lennard-Jones potential, respectively. The Amber *ff02* nonbonded parameters were used in this study for all molecules.

As a first approximation, a uniform distribution (i.e. constant density) can be used in Eqn (8). Under the constant water density approximation the volume integral in Eqn (8) can be transformed into an integral over the solute accessible surface (SAS) with a simple application of the divergence theorem:[75]

$$U_{att}^{uv} = \rho_w \sum_{a=1}^{N_s} \sum_{b=1}^{N_s} \int_{s_b} \Theta_{att}(\mathbf{r}_{as}) \mathbf{r}_{as} \cdot n_s d\sigma_s, \tag{11}$$

where indexes a and b run over all solute atoms. The surface integration is over the SAS of atom b (S_b). $\Theta_{att}(\mathbf{r}_{as})$ is a function defined on the SAS of atom b, and τ is the outward normal vector associated with the SAS element, $d\sigma_s$. In the σ decomposition scheme, the corresponding Θ_{att} in Eqn (11) can be shown to be

$$\Theta_{att} = \frac{1}{3|\mathbf{r}_{as}|^3}\left[\frac{A_{aw}}{3\sigma^9} - \frac{B_{aw}}{\sigma^3}\right] \text{if} \quad r_{as} \leq \sigma$$

(12)

$$\Theta_{att} = \frac{A_{aw}}{9|\mathbf{r}_{as}|^{12}} - \frac{B_{aw}}{3|\mathbf{r}_{as}|^6}\text{if} \quad r_{as} > \sigma$$

(13)

Here A_{aw}, B_{aw} are the van der Waal coefficients for interactions between solute atom a and water oxygen atoms (w).[45]

Empirical parameter optimization was conducted with a genetic algorithm (GA) based optimizer.[76] GA is an efficient stochastic optimization method that has been widely applied to minimization problems because it is ideally suited for multiple-dimensional global search problems where the search space contains multiple local minima and the search variables may or may not be correlated. The GA begins with the generation of an initial population of a given number of solutions. The fitness of each solution, here the root mean squared deviations between the computed and experimental solvation free energies, is first evaluated. Then a new population is generated via selection, crossover, and mutation based on their fitness. This process is repeated until a desired fitness is reached or the maximum number of generations exceeded.

Molecular Systems

A set of 353 organic molecules[77] was used in the parameterization of the polar component of the continuum polarizable force field. The complete 353-molecule set is further divided into two sets for the optimization and validation of PB cavity radii: 1) training set, which consists of odd sequence-numbered molecules; and 2) test set, which consist of even sequence-numbered molecules. Only the solvation free energies in water were used in the parameterization.[78-81] All molecules were built with the SYBYL software package of Tripos Inc.[82] and optimized using the MMFF94 force field.[83-87] For each molecule, only the global minimum conformation was used. Simple conformational searches were performed for some molecules in cases where the global minimum conformations were not apparent. The geometry of each molecule was further optimized in HF/6-31G* using the Gaussian03 program.[60]

Results and Discussion

Quality of Atomic Charges

The agreement between theoretical and experimental solvation free energies strongly depends on the quality of atomic charges for tested molecules. As shown in our previous study, in principle it is possible to use one set of atomic charges to describe different solvent dielectric environments with the continuum polarizable model.[54] However, it is impossible to do so when a traditional nonpolarizable model is used.[54] This turns out to be the case in the current study with a much larger set of test molecules. Figure 2 shows the correlations of total molecular dipole moments between the continuum polarizable model and B3LYP/cc-pVTZ for the three dielectric environments used, *in vacuo, $\varepsilon=4$*, and *$\varepsilon=78.39$*. It should be pointed out that the total molecular dipole moment from the continuum polarizable model is the sum of the permanent dipole moment from the atomic point charges and the induced dipole moment computed from Eqn (4) after solving the PB equation. It can be found that the continuum polarizable model is consistent with B3LYP/cc-pVTZ as far as molecular dipole moments are concerned with correlation coefficients higher than 99% for all three different dielectric

environments. It should also be emphasized again that it is impossible to use a single set of charges in the nonpolarizable model to achieve the same agreement with B3LYP/cc-pVTZ in all three environments simultaneously, as pointed out in our previous study for a smaller set of molecules.[54]

Comparison with experimental dipole moments also shows that the continuum polarizable model is reasonable as shown in Table 1. The root mean square deviation (RMSD), unsigned average error (UAVG), correlation coefficient is 0.50 Debye, 0.22 Debye, 90%, respectively, between the continuum polarizable model and experiment. This agreement should be viewed in the context that the same set of charges has to be used for all three different dielectric environments. Thus, the agreement with experiment in the gas phase alone is not trivial. The dipole moments with B3LYP/cc-pVTZ are also given. Given that B3LYP/cc-pVTZ and the continuum polarizable model are highly correlated, its agreement with experiment should be similar to that of the continuum polarizable model with RMSD of 0.52 Debye, UAVG of 0.20 Debye, and correlation coefficient of 90%. It should be pointed out that noticeable deviations exist between the continuum polarizable model and experiment for formates. However, similar deviations also exist for the same compounds with B3LYP/cc-pVTZ. This is not a surprise because the continuum polarizable model is trained to be consistent with B3LYP/cc-pVTZ. Finally the atomic charges for all molecules are given in the Amber *prepin* format in the Supplementary Material.

Quality of van der Waals Parameters

The second important component in the continuum polarizable model that has to be properly calibrated is the van der Waals interaction. As discussed in Methods, the van der Waals parameters are assumed to be interchangeable between explicit and implicit polarizable force fields if an overall consistent electrostatic treatment can be maintained as the case between the *ff02* explicit polarizable force field and the newly proposed continuum polarizable force field in Amber.

We have used dimer binding energies at the MP2/cc-pVTZ level of theory in the PCM solvent to test the compatibility between the continuum polarizable model and the existing van der Waals treatment in the Amber force fields. Table 2 lists the binding energies of four tested dimers in water, the intended environment to use the continuum polarizable model. It can be found that overall the continuum polarizable model agrees with MP2/cc-pVTZ very well, with deviations less than 0.9 kcal/mol. This can be compared with the agreement between the *ff02* explicit polarizable force field and MP2/cc-pVTZ, which is also shown in Table 2. Note that the deviations between *ff02* and MP2/cc-pVTZ are much larger in the gas phase, as high as 3.0 kcal/mol. However, it should be pointed that all binding energies are also uniformly larger in the gas phase. The electrostatic screening in water in general brings down the deviation in the aqueous phase as in the case for the continuum polarizable model. Thus, whether implicit or explicit polarizable treatment is used, reasonable agreement with MP2/cc-pVTZ can be achieved in the molecular mechanics approaches.

Calibration of PB Cavity Radii

The third important issue in the development of the continuum polarizable force field is the accuracy of solvation treatment. Note that this is very different from any polarizable or nonpolarizable force field that is intended for explicit solvent simulations, where the solvent interactions have been incorporated within the calibration of the van der Waals parameters of both solute and solvent molecules. As discussed in Methods, a total of 20 parameters are used for the 39 Amber atom types in the optimization against 353 experimental data constraints.

The new PB atomic cavity radii are optimized by reproducing the solvation free energies of 177 molecules in the training set, and are tested against the test set of 176 molecules. Genetic algorithm (GA) was used to optimize the cavity radii. The optimized cavity radii along with the corresponding Amber atom types in the continuum polarizable model are given in Table 3. The statistics for the training set, the test set, and the complete 353-molecule set are shown in Table 4. It can be found that the optimized PB atomic cavity radii transfer well from the training set to the test set. RMSD, UAVG, correlation coefficient are 1.27 kcal/mol, 1.06 kcal/mol, 93% for the training set, and 1.34 kcal/mol, 1.08 kcal/mol, 91% for the test set, respectively. Overall an RMSD of 1.30kcal/mol, UAVG of 1.07 kcal/mol, and correlation coefficient of 92% are achieved for the 353-molecule set. Correlation between theoretical and experimental solvation free energies for the 353-molecule set is also given in Fig. 3. Table 5 lists the solvation free energies for all molecules by both theory and experiment. The polar components, the nonpolar cavity components, and the nonpolar attractive components of solvation free energies are also given for all 353 molecules.

A detailed analysis of agreement between theory and experiment for each functional group is shown in Table 6. It can be found that the agreements for the first five classes of compounds (alkanes, alkenes, alkynes, aromatic hydrocarbons, and fluorides) are very well, with RMSD's less than 1.0 kcal/mol. The performance for aromatic groups is particularly excellent with RMSD of 0.54 kcal/mol only. However, agreements for nitro compounds and compounds with nitrogen on hetero rings are much worse with RMSD higher than 2.0 kcal/mol. Note that we have use a uniform PB cavity radius value for all nitrogen atom types. This may be an over-simplification of highly diversified chemical environments of different nitrogen atoms. A similar discrepancy between theoretical and experimental solvation free energies for amines and amides was also reported before for free energy simulations in explicit solvent in both the Amber and OPLS force fields.[88-90] As shown in Table 1, theoretical dipole moments for nitrogen containing compounds generally agree well with experiment. Therefore the poor agreement for solvation free energies are mostly likely related to either the continuum solvation approximation or the classical electrostatic approximation of solute solvent interactions.

Conclusions

In this work we have developed and tested a complete set of nonbonded parameters for a continuum polarizable force field. Our analysis shows that the new continuum polarizable model is consistent with B3LYP/cc-pVTZ in modeling electronic response upon variation of dielectric environment. Comparison with experiment also shows that the new continuum polarizable PB model is reasonable, with similar accuracy as B3LYP/cc-pVTZ in reproduction of dipole moments of selected organic molecules in the gas phase. However, it should be pointed out that the proposed continuum polarization scheme is not intended to describe the atomic-detailed polarization within molecular environment. For example, the response of the continuum polarizable model under an external electric field is left unstudied. Incidentally, such studies have never been conducted for published explicit polarizable models either. It is likely that none of the existing classical polarizable models can properly reproduce experiment in such studies. Instead we intend to offer an efficient and self-consistent approach in treating polar interactions in biomolecular simulations more satisfactory than existing additive force fields with implicit solvents.

The modest goal is justified because implicit solvents have been developed for their efficiency. Apparently there are limitations in these simplified solvation treatments, for example the limitations of atom-centered dielectric models[91] and the related issue in the use of solvent excluded surface in molecular dynamics simulations.[65] Further improvements in the nonpolar components are also needed.[45] Interestingly, efforts to address these limitations have emerged, such as in the treatment of coupling between polar and nonpolar components.[92,93]

We have further tested the validity to interchange the Amber van der Waals parameters between the explicit and continuum polarizable force fields with a series of dimers. It can be found that the continuum polarizable model agrees well with MP2/cc-pVTZ, with deviations in dimer binding energies less than 0.9 kcal/mol in the aqueous dielectric environment.

Finally we have optimized atomic cavity radii with respect to experimental solvation free energies of 177 training molecules. To validate the optimized cavity radii, we have tested these parameters against 176 test molecules. It is interesting to note that the optimized PB atomic cavity radii transfer well from the training set to the test set. Overall an RMSD of 1.30 kcal/mol, UAVG of 1.07 kacl/mol, and correlation coefficient of 92% are achieved for all 353 molecules in both sets. In addition, a detailed analysis of the agreement between theoretical and experimental solvation free energies for each functional group shows that the new polarizable model works excellently for alkanes, alkenes, alkynes, aromatic hydrocarbons, and fluorides. However, agreements for nitro compounds and compounds with nitrogen on hetero rings are much worse. Because theoretical dipole moments for nitrogen containing compounds agree very well with experimental values, a likely reason for the discrepancy between theory and experiment may be the over-simplification in using a single PB cavity radius value for all nitrogen atom types in the highly diversified chemical environments. The poor agreement in solvation free energies may also be related to the lack of modeling electron transfer between the solute and solvent molecules in the continuum solvation treatments, which has been argued for the particular difficult modeling of solvation free energies of amines by classical force fields.[88-90]

Based on the development documented here, our next natural step is the construction of a full protein/nucleic acid force field within the new continuum polarization framework. Given implicit solvents that are based on the Poisson-Boltzmann theory, for example either numerical Poisson-Boltzmann approaches[50,51] and generalized Born approaches[52,53] that were developed to deal with non-vacuum solute interiors, the dielectric forces can be computed on-the-fly in molecular dynamics simulations. Therefore, such a polarizable force field can be applied in implicit-solvent molecular dynamics simulations with virtually no additional cost over a nonpolarizable force field. Nevertheless, more detailed refinement efforts in both the covalent terms and the van der Waals terms in the Amber polarizable force fields, which have left untouched, should also be addressed in future publications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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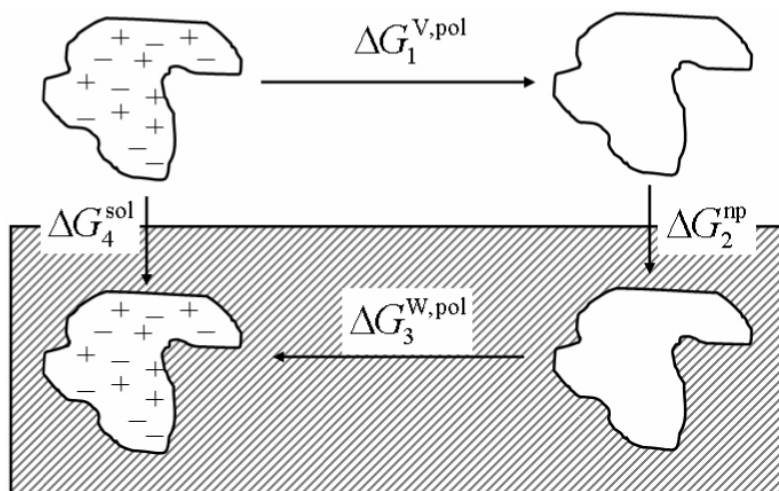
Fig. 1.
Thermodynamic cycle for solvation free energy calculation.
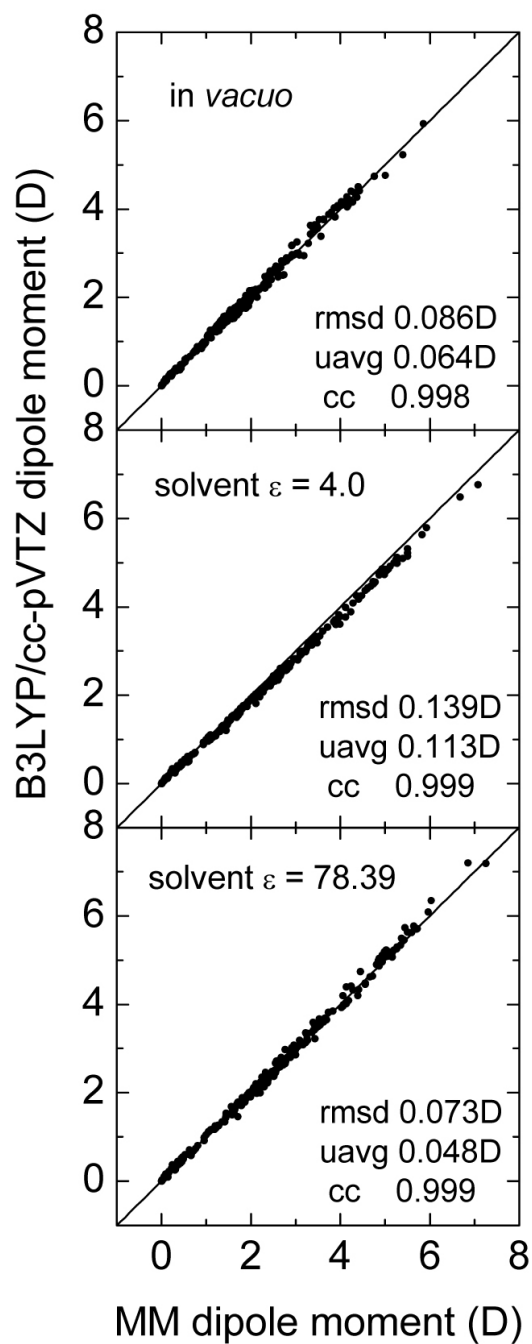
Fig. 2.
Dipole moments *in vacuo*, *ε = 4*, and *ε = 78.39* for the 353-molecule set.
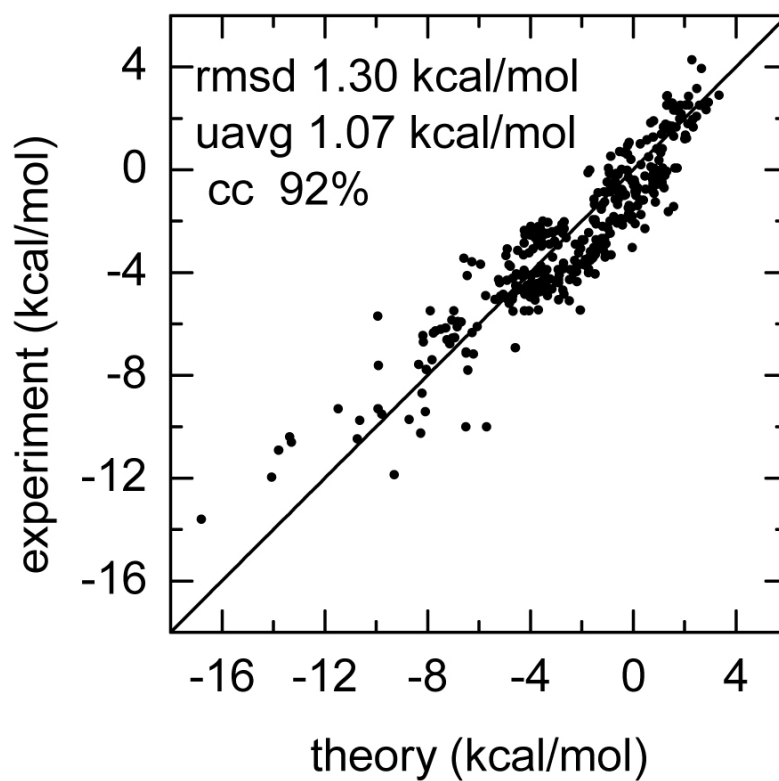
Fig. 3.
Calculated and experimental solvation free energies for the 353-molecule set.

Table 1

Gas-phase dipole moments (D) of selected organic compounds in the 353 molecule set. About two per functional groups are chosen. MM: continuum polarizable model. QM:B3LYP/cc-pVTZ. EXPT: Experimental values from the CRC Handbook of Chemistry and Physics, 87th.

Compound	MM	QM	EXPT
propane	0.06	0.09	0.08
2-methyl-1,3-butadiene	0.23	0.26	0.25
propyne	0.76	0.8	0.78
1-butyne	0.77	0.77	0.78
1-hexyne	0.93	0.93	0.83
toluene	0.32	0.36	0.38
ethylbenzene	0.30	0.35	0.59
fluoromethane	1.54	1.71	1.86
chlorofluoromethane	1.72	1.72	1.82
chloromethane	1.87	1.94	1.9
dichloromethane	1.66	1.67	1.6
bromomethane	1.89	1.92	1.82
dibromomethane	1.58	1.52	1.43
methanol	1.39	1.57	1.7
ethanol	1.35	1.49	1.69
phenol	1.24	1.28	1.22
diethyl ether	0.95	0.99	1.15
diisopropyl ether	1.04	1.11	1.13
acetaldehyde	2.44	2.55	2.75
propanal	2.63	2.69	2.72
acetone	2.68	2.82	2.88
acetic acid	1.67	1.7	1.7
methyl formate	3.94	4.08	1.77
ethyl formate	4.03	4.16	1.93
ethyl acetate	1.95	2.04	1.78
methylamine	1.1	1.26	1.31
ethylamine	1.1	1.22	1.22
propylamine	1.06	1.16	1.17
diethylamine	0.78	0.81	0.92
pyridine	2.14	2.15	2.21
2-methylpyridine	1.88	1.86	1.85
4-methylpyridine	2.61	2.63	2.7
acetonitrile	3.81	3.92	3.92
nitroethane	3.38	3.59	3.23
1-nitropropane	3.62	3.76	3.66
2-nitropropane	3.44	3.64	3.73
N-methylformamide	4.04	4.08	3.83
acetamide	3.63	3.77	3.68
dimethyl sulfide	1.51	1.57	1.55
diethyl sulfide	1.49	1.59	1.54

Table 2

Dimer binding potential energies (kcal/mol). NMA: n-methylamine. ASH: acetate. SER: methanol. A: adenine. T: thymine. C: cytosine. G: guanine. ff02: explicit polarizable ff02 model. MP2: MP2/cc-pVTZ. MM: continuum polarizable model. Note that ff02 and associated MP2 calculations were performed in gas phase.

Dimers	MM	MP2	ff02	MP2
NMA/NMA	-3.85	-3.01	-7.16	-7.47
ASH/SER	-3.24	-2.64	-8.93	-11.95
AT	-6.41	-6.50	-13.25	-15.29
CG	-12.53	-11.71	-28.65	-28.04

Table 3

PB atomic cavity radii (Å) and atom types.

Atom type	PB radius	Description
h1	0.421	H bonded to aliphatic carbon with 1 electrwd. group
h2	0.327	H bonded to aliphatic carbon with 2 electrwd. group
h4	0.577	H bonded to non-sp3 carbon with 1 electrwd. group
h5	2.021	H bonded to non-sp3 carbon with 2 electrwd. group
ha	0.735	H bonded to aromatic carbon
hc	0.753	H bonded to aliphatic carbon without electrwd. group
hn	0.681	H bonded to nitrogen atoms
ho	0.000	Hydroxyl group
o	1.117	Oxygen with one connected atom
oh	1.293	Oxygen in hydroxyl group
os	1.094	Ether and ester oxygen
c	1.200	Sp2 C carbonyl group
c1	1.139	Sp C
c2	1.200	Sp2 C
c3	1.181	Sp3 C
ca	1.139	Sp2 C in pure aromatic systems
cc	1.139	Sp2 carbons in non-pure aromatic systems
cd	1.139	Sp2 carbons in non-pure aromatic systems, identical to cc
ce	1.139	Inner Sp2 carbons in conjugated systems
cf	1.139	Inner Sp2 carbons in conjugated systems, identical to ce
cp	1.139	Head Sp2 C that connect two rings in biphenyl sys.
n	1.114	Sp2 nitrogen in amide groups
n1	1.114	Sp N
n2	1.114	Aliphatic Sp2 N with two connected atoms
n3	1.114	Sp3 N with three connected atoms
na	1.114	Sp2 N with three connected atoms
nb	1.114	Sp2 N in pure aromatic systems
nc	1.114	Sp2 N in non-pure aromatic systems
nd	1.114	Sp2 N in non-pure aromatic systems, identical to nc
nh	1.114	Amine N connected one or more aromatic rings
no	1.114	Nitro N
s	2.210	S with one connected atom
sh	2.210	Sp3 S connected with hydrogen
ss	2.210	S with one connected atom
p5	1.514	Phosphate with four connected atoms, such as O P(OH)3
py	1.514	Special p5 in conjugated system
f	1.612	Fluorine
cl	2.488	Chlorine
br	2.616	Bromine

Table 4

Statistics for the training set (177), the test set (176), and the 353-molecule set. RMSD: root-mean-squared deviation (in kcal/mol). UAVG: unsigned average error (in kcal/mol). CC: correlation coefficient.

	training	test	all
RMSD	1.27	1.34	1.30
UAVG	1.06	1.08	1.07
CC	93%	91%	92%

Table 5

Solvation free energies (in kcal/mol) of all 353 organic compounds. POL: the polar/electrostatic component; NP_{rep}: the repulsive nonpolar component; NP_{att}: the attractive nonpolar component; TOT: total theoretical values; EXP: experimental values.

No.	Compound	POL	NP_{rep}	NP_{att}	TOT	EXP
1	methane	-0.75	6.35	-3.78	1.82	1.98
2	propane	-0.39	11.18	-8.46	2.33	1.96
3	2-methyl propane	-1.19	13.17	-10.40	1.58	2.32
4	2,2-dimethyl propane	-1.44	14.97	-12.23	1.31	2.50
5	n-butane	-0.61	13.44	-10.36	2.47	2.08
6	2,2-dimethylbutane	-1.48	16.82	-13.80	1.54	2.59
7	cyclopentane	-0.05	13.83	-11.77	2.01	1.20
8	n-pentane	-0.33	15.68	-12.50	2.85	2.33
9	2-methylpentane	-1.08	17.48	-14.23	2.17	2.52
10	3-methyl pentane	-0.53	17.26	-14.14	2.58	2.51
11	2,4-dimethyl pentane	-1.89	19.22	-15.99	1.34	2.88
12	2,2,4-trimethyl pentane	-2.09	20.75	-17.35	1.31	2.85
13	methylcyclopentane	-0.90	15.93	-13.52	1.52	1.60
14	n-hexane	-0.57	17.94	-14.66	2.71	2.49
15	cyclohexane	-0.02	15.62	-13.52	2.08	1.23
16	methylcyclohexane	-0.76	17.63	-15.46	1.41	1.71
17	cis-1,2-dimethylcyclohexane	-1.24	19.36	-16.80	1.32	1.58
18	n-heptane	-0.72	20.20	-16.56	2.92	2.62
19	n-octane	-0.58	22.49	-18.57	3.34	2.89
20	ethylene	-1.99	7.72	-4.95	0.77	1.27
21	propylene	-2.03	10.20	-7.38	0.79	1.27
22	2-methyl propene	-2.37	12.44	-9.54	0.53	1.16
23	1-butene	-1.92	12.54	-9.52	1.10	1.38
24	2-methyl-2-butene	-1.35	14.56	-11.63	1.58	1.31
25	3-methyl-1-butene	-2.66	14.61	-11.26	0.69	1.83
26	1-pentene	-1.99	14.79	-11.61	1.18	1.66
27	trans-2-pentene	-1.27	15.02	-11.70	2.05	1.34
28	4-methyl-1-pentene	-2.54	16.62	-13.27	0.80	1.91
29	1-hexene	-1.92	17.07	-13.47	1.68	1.66
30	cyclohexene	-1.07	14.86	-12.78	1.01	0.37
31	trans-2-heptene	-1.44	19.54	-15.77	2.33	1.66
32	1-methylcyclohexene	-1.41	17.05	-14.57	1.07	0.67
33	1-octene	-2.13	21.59	-17.58	1.87	2.17
34	1,3-butadiene	-3.29	11.44	-8.37	-0.22	0.61
35	2-methyl-1,3-butadiene	-3.23	13.44	-10.58	-0.37	0.68
36	2,3-dimethyl-1,3-butadiene	-2.93	15.35	-12.50	-0.09	0.40
37	1,4-pentadiene	-3.56	13.84	-10.49	-0.21	0.94
38	1,5-hexadiene	-3.38	16.18	-12.51	0.29	1.01
39	acetylene	-4.28	6.80	-4.20	-1.68	-0.01
40	propyne	-3.75	9.40	-6.66	-1.01	-0.48
41	1-butyne	-3.71	11.85	-8.78	-0.65	-0.15
42	1-pentyne	-3.94	14.08	-11.00	-0.86	-0.16
43	1-hexyne	-3.85	16.37	-12.98	-0.45	0.01
44	1-heptyne	-3.89	18.62	-14.97	-0.25	0.60
45	1-octyne	-4.07	20.87	-17.32	-0.52	0.71
46	1-nonyne	-3.98	23.14	-19.30	-0.15	1.05
47	benzene	-2.56	12.95	-10.93	-0.54	-0.89
48	toluene	-3.10	15.25	-12.97	-0.82	-0.76
49	1,2,4-trimethylbenzene	-3.50	19.40	-16.81	-0.91	-0.86
50	ethylbenzene	-2.57	17.49	-14.91	0.01	-0.61
51	m-xylene	-3.49	17.51	-14.92	-0.90	-0.80

No.	Compound	POL	NP_rep	NP_att	TOT	EXP
52	o-xylene	-3.45	17.11	-15.03	-1.36	-0.90
53	p-xylene	-3.37	17.55	-14.96	-0.78	-0.80
54	propylbenzene	-2.99	19.75	-16.70	0.07	-0.53
55	2-propylbenzene	-3.28	19.37	-16.27	-0.18	-0.30
56	butylbenzene	-3.36	21.99	-18.59	0.04	-0.40
57	2-butylbenzene	-3.09	21.46	-18.41	-0.04	-0.45
58	tert-butylbenzene	-3.60	20.85	-17.95	-0.69	-0.44
59	tert-amylbenzene	-3.59	22.73	-19.72	-0.58	-0.18
60	naphthalene	-4.55	17.89	-16.48	-3.14	-2.41
61	anthracene	-5.85	22.82	-21.67	-4.69	-4.23
62	phenanthrene	-5.48	22.55	-21.61	-4.54	-4.06
63	acenaphthene	-4.43	20.71	-19.41	-3.13	-3.4
64	p-chlorotoluene	-2.40	16.85	-14.82	-0.37	-1.92
65	fluoromethane	-1.16	6.73	-4.32	1.25	-0.22
66	1,1-difluoroethane	-1.54	9.94	-7.38	1.02	-0.11
67	tetrafluoromethane	-0.10	8.94	-6.36	2.48	3.16
68	hexafluoroethane	-0.08	12.27	-9.53	2.67	3.94
69	octafluoropropane	-0.27	15.19	-12.63	2.29	4.28
70	fluorobenzene	-2.83	13.61	-11.44	-0.66	-0.78
71	2-chloro-1,1,1-trifluoroethane	-2.97	11.98	-9.98	-0.96	0.05
72	chlorofluoromethane	-2.19	8.35	-6.60	-0.44	-0.77
73	chlorotrifluoromethane	-0.01	9.90	-7.84	2.05	2.52
74	dichlorodifluoromethane	0.00	10.89	-9.36	1.53	1.69
75	fluorotrichloromethane	-0.01	11.85	-10.70	1.14	0.82
76	1,1,2-trichloro-1,2,2-trifluoroethane	-0.02	14.89	-13.59	1.28	1.77
77	1,1,2,2-tetrachlorodifluoroethane	-0.03	15.76	-14.80	0.92	0.82
78	chloropentafluoroethane	-0.04	13.17	-10.99	2.15	2.86
79	1,1-dichlorotetrafluoroethane	-0.04	14.04	-12.16	1.84	2.50
80	1,2-dichlorotetrafluoroethane	-0.02	14.06	-12.34	1.70	2.31
81	1-bromo-1-chloro-2,2,2-trifluoroethane	-2.67	14.37	-12.61	-0.91	-0.13
82	bromotrifluoromethane	-0.01	10.98	-8.85	2.13	1.79
83	1-bromo-1,2,2,2-tetrafluoroethane	-3.08	13.50	-11.28	-0.86	0.52
84	chloromethane	-1.77	7.74	-5.96	0.02	-0.56
85	dichloromethane	-2.41	9.37	-8.14	-1.19	-1.36
86	tetrachloromethane	-0.03	12.78	-12.05	0.70	0.10
87	chloroethane	-0.85	10.29	-8.29	1.15	-0.63
88	1,1-dichloroethane	-1.41	11.82	-10.28	0.14	-0.85
89	e-1,2-dichloroethane	-1.68	11.72	-10.21	-0.18	-1.73
90	1,1,1-trichloroethane	-0.79	13.39	-12.15	0.46	-0.25
91	1,1,2-trichloroethane	-2.57	13.19	-12.16	-1.54	-1.95
92	1,1,1,2-tetrachloroethane	-2.43	14.69	-13.79	-1.52	-1.15
93	1,1,2,2-tetrachloroethane	-3.65	14.60	-13.89	-2.93	-2.36
94	pentachloroethane	-2.04	16.04	-15.50	-1.50	-1.36
95	hexachloroethane	-0.05	17.40	-17.17	0.17	-1.40
96	1-chloropropane	-1.33	12.61	-10.38	0.90	-0.35
97	2-chloropropane	-1.13	12.54	-10.36	1.05	-0.24
98	1,2-dichloropropane	-2.87	13.91	-12.15	-1.10	-1.25
99	1,3-dichloropropane	-2.18	14.00	-12.29	-0.47	-1.90
100	1-chlorobutane	-1.51	14.86	-12.55	0.80	-0.14
101	2-chlorobutane	-1.25	14.69	-12.28	1.16	0.07
102	1,1-dichlorobutane	-1.84	16.26	-14.24	0.19	-0.70
103	1-chloropentane	-1.31	17.11	-14.49	1.31	-0.07
104	2-chloropentane	-1.10	16.95	-14.14	1.71	0.07
105	3-chloropentane	-1.00	16.80	-14.16	1.64	0.07
106	chloroethylene	-1.60	9.36	-7.17	0.60	0.49
107	cis-1,2-dichloroethylene	-1.44	10.91	-9.21	0.26	-1.17

No.	Compound	POL	NP_{rep}	NP_{att}	TOT	EXP
108	*trans*-1,2-dichloroethylene	-1.16	10.99	-9.33	0.49	-0.76
109	trichloroethylene	-0.50	12.53	-11.23	0.81	-0.44
110	tetrachloroethylene	0.00	14.06	-13.25	0.82	0.05
111	3-chloropropane	-1.30	12.61	-10.40	0.91	-0.57
112	chlorobenzene	-2.02	14.55	-12.87	-0.35	-1.01
113	*o*-chlorotoluene	-2.47	16.60	-14.71	-0.59	-1.15
114	1,2-dichlorobenzene	-1.73	16.02	-14.90	-0.61	-1.36
115	1,3-dichlorobenzene	-1.40	16.14	-15.03	-0.29	-0.98
116	1,4-dichlorobenzene	-1.29	16.17	-14.77	0.11	-1.01
117	2,2'-dichlorobiphenyl	-3.97	24.52	-21.99	-1.45	-2.73
118	2,3-dichlorobiphenyl	-3.64	24.48	-22.57	-1.72	-2.45
119	2,2',3'-trichlorobiphenyl	-3.56	25.93	-23.88	-1.52	-1.99
120	bromotrichloromethane	-0.03	13.75	-12.91	0.81	-0.93
121	1-chloro-2-bromoethane	-1.79	12.78	-11.06	-0.06	-1.95
122	bromomethane	-2.32	8.90	-6.98	-0.41	-0.82
123	dibromomethane	-3.08	11.57	-9.93	-1.44	-2.11
124	bromoethane	-0.96	11.34	-9.17	1.21	-0.70
125	1,2-dibromoethane	-1.85	13.85	-11.92	0.09	-2.10
126	1-bromopropane	-1.61	13.66	-11.27	0.78	-0.56
127	2-bromopropane	-1.13	13.50	-11.25	1.13	-0.48
128	1,2-dibromopropane	-3.48	15.82	-13.82	-1.48	-1.94
129	1,3-dibromopropane	-2.68	16.13	-14.14	-0.70	-1.96
130	1-bromo-2-methylpropane	-2.65	15.46	-13.04	-0.23	-0.03
131	1-bromobutane	-1.85	15.94	-13.33	0.76	-0.41
132	1-bromo-3-methylbutane	-2.47	17.73	-14.96	0.30	0.20
133	1-bromopentane	-1.57	18.19	-15.41	1.21	-0.08
134	3-bromopropene	-3.48	12.70	-10.34	-1.12	-0.86
135	bromobenzene	-1.97	15.60	-13.68	-0.04	-1.46
136	1,4-dibromobenzene	-1.14	18.24	-16.64	0.46	-2.30
137	*p*-bromotoluene	-2.40	17.89	-15.63	-0.14	-1.39
138	1-bromo-2-ethylbenzene	-1.97	19.57	-17.20	0.40	-1.19
139	*o*-bromocumene	-2.49	21.42	-18.85	0.07	-0.85
140	methanol	-5.21	6.71	-5.32	-3.81	-5.07
141	ethanol	-4.98	9.30	-7.64	-3.33	-4.90
142	2,2,2-trifluoroethanol	-6.56	11.02	-9.36	-4.90	-4.30
143	ethylene glycol	-10.63	9.72	-9.01	-9.92	-9.30
144	1-propanol	-5.93	11.60	-9.88	-4.21	-4.85
145	2-propanol	-5.52	11.63	-9.72	-3.61	-4.75
146	1,1,1-trifluoro-2-propanol	-6.18	13.19	-11.28	-4.27	-4.16
147	2,2,3,3-tetraflutoropropanol	-7.53	13.53	-11.74	-5.74	-4.90
148	2,2,3,3,3-pentafluoropropanol	-5.84	14.15	-12.27	-3.96	-4.15
149	hexafluoro-2-propanol	-6.68	14.66	-12.75	-4.77	-3.76
150	2-methyl-1-propanol	-6.44	13.54	-11.67	-4.57	-4.51
151	1-butanol	-5.53	13.86	-11.89	-3.56	-4.72
152	2-butanol	-5.49	13.82	-11.81	-3.48	-4.61
153	*tert*-butyl alcohol	-6.07	13.67	-11.70	-4.09	-4.51
154	2-methyl-1-butanol	-5.78	15.59	-13.49	-3.67	-4.42
155	3-methyl butanol	-6.02	15.70	-13.67	-3.98	-4.42
156	2-methyl-2-butanol	-5.99	15.64	-13.39	-3.74	-4.43
157	2,3-dimethylbutanol	-6.34	17.30	-15.20	-4.25	-3.91
158	1-pentanol	-5.58	16.12	-13.94	-3.39	-4.49
159	2-pentanol	-5.36	16.09	-13.63	-2.90	-4.39
160	3-pentanol	-4.56	16.04	-13.67	-2.18	-4.35
161	2-methyl-1-pentanol	-6.02	17.86	-15.42	-3.58	-3.93
162	2-methyl-2-pentanol	-6.17	17.89	-15.38	-3.66	-3.93
163	2-methyl-3-pentanol	-5.82	17.79	-15.33	-3.36	-3.89

No.	Compound	POL	NP$_{rep}$	NP$_{att}$	TOT	EXP
164	4-methyl-2-pentanol	-6.07	17.85	-15.37	-3.59	-3.74
165	cyclopentanol	-5.44	14.32	-13.11	-4.23	-5.49
166	1-hexanol	-6.03	18.40	-15.93	-3.56	-4.36
167	3-hexanol	-4.73	18.32	-15.68	-2.10	-3.68
168	cyclohexanol	-5.22	16.10	-14.89	-4.01	-4.95
169	4-heptanol	-4.64	20.56	-17.66	-1.74	-4.01
170	cycloheptanol	-5.39	17.86	-16.52	-4.05	-5.49
171	1-heptanol	-5.91	20.66	-17.97	-3.22	-4.25
172	1-octanol	-5.81	22.92	-19.98	-2.87	-4.10
173	allyl alcohol	-6.83	10.63	-8.70	-4.90	-5.03
174	cyclopentanol	-5.44	14.32	-13.11	-4.23	-5.49
175	phenol	-8.16	13.61	-12.39	-6.94	-6.53
176	4-bromophenol	-7.69	16.25	-15.06	-6.50	-7.10
177	4-nitrophenol	-12.28	15.95	-16.97	-13.29	-10.6
178	4-tert-butylphenol	-8.95	21.52	-19.26	-6.69	-5.92
179	2-creol	-8.57	15.75	-14.24	-7.06	-5.86
180	3-creol	-8.52	15.88	-14.33	-6.97	-5.49
181	4-creol	-8.38	15.91	-14.38	-6.85	-6.12
182	2,2,2-trifluoroethanol	-6.56	11.02	-9.36	-4.90	-4.31
183	p-bromophenol	-7.69	16.25	-15.06	-6.50	-7.13
184	2-methoxyethanol	-8.09	12.26	-11.30	-7.13	-6.77
185	dimethoxymethane	-4.02	12.45	-11.35	-2.92	-2.93
186	methyl propyl ether	-2.39	14.15	-11.91	-0.15	-1.66
187	methyl iopropyl ether	-3.11	13.90	-11.69	-0.90	-2.00
188	methyl tert-butyl ether	-3.51	15.68	-13.35	-1.18	-2.21
189	diethyl ether	-2.08	14.45	-12.07	0.30	-1.75
190	ethyl propyl ether	-2.66	16.73	-14.10	-0.03	-1.81
191	dipropyl ether	-3.51	19.04	-16.22	-0.69	-1.16
192	diiopropyl ether	-4.12	18.53	-15.24	-0.84	-0.53
193	di-n-butyl ether	-2.42	23.56	-20.38	0.77	-0.83
194	tetrahydrofuran	-2.23	12.28	-11.21	-1.17	-3.12
195	2-methyltetrahydrofuran	-3.04	14.64	-13.06	-1.46	-3.3
196	aniole	-4.45	15.87	-14.53	-3.11	-2.45
197	ethyl phenyl ether	-4.68	18.45	-16.24	-2.46	-4.28
198	1,1-diethoxyethane	-4.17	19.83	-16.73	-1.07	-3.27
199	1,2-dimethoxyethane	-4.19	14.80	-13.30	-2.70	-4.84
200	1,2-diethoxyethane	-4.60	19.98	-17.65	-2.28	-3.53
201	1,3-dioxolane	-3.96	10.69	-10.70	-3.97	-4.09
202	1,4-dioxane	-4.67	12.65	-12.68	-4.70	-5.05
203	2,2,2-trifluoroethyl vinyl ether	-4.47	15.28	-12.56	-1.75	-0.12
204	acetaldehyde	-3.67	8.77	-6.95	-1.85	-3.50
205	propanal	-3.69	11.13	-9.19	-1.74	-3.44
206	butanal	-3.82	13.41	-11.24	-1.66	-3.18
207	pentanal	-3.90	15.67	-13.29	-1.53	-3.03
208	hexanal	-3.83	17.93	-15.36	-1.26	-2.81
209	heptanal	-4.00	20.17	-17.27	-1.10	-2.67
210	octanal	-4.04	22.44	-19.37	-0.97	-2.29
211	nonanal	-3.96	24.71	-21.37	-0.62	-2.07
212	trans-2-butenal	-4.42	12.51	-10.47	-2.38	-4.23
213	trans-2-hexenal	-4.61	17.11	-14.54	-2.05	-3.68
214	trans-2-octenal	-4.48	21.61	-18.70	-1.57	-3.44
215	trans,trans-2,4-hexadienal	-5.65	16.23	-13.74	-3.16	-4.64
216	benzaldehyde	-5.06	15.05	-13.73	-3.74	-4.02
217	m-hydroxybenzaldehyde	-10.33	15.69	-15.14	-9.78	-9.51
218	p-hydroxybenzaldehyde	-11.26	15.70	-15.17	-10.73	-10.47
219	acetone	-4.10	11.15	-9.25	-2.19	-3.80

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No.	Compound	POL	NP$_{rep}$	NP$_{att}$	TOT	EXP
220	2-butanone	-4.04	13.41	-11.26	-1.89	-3.71
221	3-methyl-2-butanone	-4.45	15.37	-13.03	-2.12	-3.24
222	3,3-dimethylbutanone	-4.68	16.88	-14.44	-2.25	-2.89
223	2-pentanone	-4.18	15.69	-13.16	-1.66	-3.52
224	3-pentanone	-3.61	15.67	-13.15	-1.09	-3.41
225	4-methyl-2-pentanone	-4.61	17.53	-14.96	-2.04	-3.06
226	2,4-dimethyl-3-pentanone	-5.02	19.49	-16.39	-1.92	-2.74
227	cyclopentanone	-3.99	13.90	-12.63	-2.73	-4.68
228	2-hexanone	-4.35	17.96	-15.15	-1.55	-3.41
229	2-heptanone	-4.23	20.21	-17.32	-1.34	-3.04
230	4-heptanone	-4.24	20.23	-17.10	-1.12	-2.93
231	2-octanone	-4.31	22.46	-19.20	-1.05	-2.88
232	2-nonanone	-4.45	24.75	-21.20	-0.89	-2.48
233	5-nonanone	-4.86	24.76	-21.11	-1.21	-2.67
234	2-undecanone	-4.46	29.27	-25.22	-0.41	-2.15
235	acetophenone	-5.23	17.23	-15.94	-3.95	-4.58
236	acetic acid	-9.05	9.44	-8.56	-8.17	-6.70
237	propionic acid	-9.33	11.72	-10.57	-8.18	-6.46
238	butyric acid	-9.27	13.99	-12.5	-7.77	-6.35
239	pentanoic acid	-8.94	16.26	-14.61	-7.29	-6.16
240	hexanoic acid	-9.40	18.52	-16.60	-7.48	-6.21
241	4-amino-3,5,6-trichloropyridine-2-carboxylic acid	-12.64	20.39	-21.81	-14.07	-11.96
242	methyl formate	-4.01	9.43	-8.48	-3.06	-2.78
243	ethyl formate	-3.95	12.04	-10.68	-2.60	-2.65
244	propyl formate	-4.23	14.32	-12.82	-2.73	-2.48
245	methyl acetate	-5.64	11.96	-10.59	-4.27	-3.31
246	iopropyl formate	-4.28	14.21	-12.60	-2.67	-2.02
247	iobutyl formate	-4.46	16.29	-14.61	-2.78	-2.22
248	ioamyl formate	-4.62	18.44	-16.59	-2.76	-2.13
249	ethyl acetate	-5.77	14.56	-12.69	-3.89	-3.08
250	propyl acetate	-6.30	16.87	-14.82	-4.24	-2.85
251	iopropyl acetate	-5.99	16.66	-14.48	-3.81	-2.65
252	butyl acetate	-5.84	19.13	-16.90	-3.61	-2.55
253	iobutyl acetate	-6.45	18.77	-16.55	-4.23	-2.36
254	amyl acetate	-6.11	21.40	-18.80	-3.50	-2.45
255	ioamyl acetate	-6.47	20.96	-18.47	-3.98	-2.21
256	hexyl acetate	-6.35	23.64	-20.90	-3.61	-2.26
257	methyl propionae	-5.25	14.25	-12.55	-3.56	-2.97
258	ethyl propionate	-5.82	16.85	-14.60	-3.56	-2.80
259	propyl propionate	-6.63	19.16	-16.73	-4.20	-2.54
260	iopropyl propionate	-6.16	18.95	-16.48	-3.69	-2.22
261	amyl propionate	-6.38	23.69	-20.81	-3.51	-1.99
262	methyl butyrate	-5.70	16.52	-14.54	-3.71	-2.84
263	ethyl butyrate	-5.80	19.11	-16.73	-3.43	-2.50
264	propyl butyrate	-6.47	21.44	-18.75	-3.78	-2.28
265	methyl pentanoate	-6.15	18.78	-16.64	-4.01	-2.54
266	ethyl pentanoate	-6.02	21.40	-18.82	-3.45	-2.52
267	methyl hexanonate	-5.68	21.05	-18.70	-3.32	-2.48
268	ethyl heptanoate	-5.90	25.89	-22.67	-2.68	-2.30
269	methyl octanoate	-6.23	25.57	-22.65	-3.31	-2.05
270	methyl benzoate	-6.54	18.15	-16.84	-5.23	-4.28
271	methylamine	-5.24	7.03	-5.50	-3.70	-4.60
272	ethylamine	-5.34	9.60	-7.90	-3.64	-4.61
273	propylamine	-6.04	11.89	-9.98	-4.12	-4.50
274	butylamine	-5.61	14.16	-11.99	-3.44	-4.38

No.	Compound	POL	NP$_{rep}$	NP$_{att}$	TOT	EXP
275	pentylamine	-5.81	16.43	-14.06	-3.44	-4.09
276	hexylamine	-6.18	18.68	-16.00	-3.49	-4.04
277	dimethylamine	-4.32	9.52	-8.10	-2.90	-4.28
278	diethylamine	-3.89	14.64	-12.23	-1.48	-4.06
279	dipropylamine	-5.08	19.26	-16.36	-2.18	-3.65
280	dibutylamine	-4.01	23.79	-20.64	-0.86	-3.31
281	trimethylamine	-5.73	11.68	-10.00	-4.05	-3.23
282	triethylamine	-2.87	18.58	-15.74	-0.04	-3.03
283	piperazine	-7.80	13.10	-13.13	-7.83	-7.40
284	N,N'-dimethylpiperazine	-8.69	17.43	-17.09	-8.35	-7.58
285	N-methylpiperazine	-8.19	15.25	-15.11	-8.05	-7.77
286	aniline	-9.22	13.86	-12.53	-7.89	-5.49
287	1,1-dimethyl-3-phenyl urea	-10.22	21.83	-20.90	-9.30	-11.87
288	N,N-dimethyl aniline	-4.470	18.00	-16.78	-3.25	-2.90
289	ethylenediamine	-11.57	10.34	-9.41	-10.64	-9.75
290	hydrazinehydrazine	-12.42	5.90	-4.96	-11.47	-9.30
291	2-methoxyethanamine	-8.15	12.57	-11.45	-7.03	-6.55
292	morpholine	-6.14	12.86	-12.93	-6.20	-7.17
293	N-methylmorpholine	-6.47	15.03	-14.83	-6.26	-6.34
294	N-methylpyrrolidine	-3.44	14.74	-13.49	-2.20	-3.97
295	N-methylpiperidine	-3.80	16.54	-15.18	-2.45	-3.89
296	pyrrolidine	-3.12	12.49	-11.42	-2.05	-5.47
297	piperidine	-3.67	14.36	-13.17	-2.49	-5.10
298	pyridine	-5.70	12.29	-11.11	-4.52	-4.69
299	2-methylpyridine	-6.06	14.70	-13.03	-4.39	-4.62
300	3-methylpyridine	-5.73	14.56	-13.07	-4.24	-4.77
301	4-methylpyridine	-6.68	14.57	-13.04	-5.16	-4.92
302	2-ethylpyridine	-5.09	16.95	-14.88	-3.03	-4.32
303	3-ethylpyridine	-5.67	16.83	-14.96	-3.80	-4.60
304	4-ethylpyridine	-6.04	16.83	-14.98	-4.20	-4.72
305	2,3-dimethylpyridine	-5.64	16.61	-14.95	-3.98	-4.81
306	2,4-dimethylpyridine	-7.00	16.97	-15.02	-5.05	-4.85
307	2,5-dimethylpyridine	-5.91	17.03	-15.09	-3.97	-4.70
308	2,6-dimethylpyridine	-6.31	17.11	-15.00	-4.20	-4.60
309	3,4-dimethylpyridine	-6.47	16.49	-14.83	-4.81	-5.21
310	3,5-dimethylpyridine	-5.63	16.87	-15.03	-3.79	-4.84
311	2-methylpyrazine	-5.46	14.03	-13.23	-4.67	-5.51
312	2-ethylpyrazine	-4.93	16.29	-15.04	-3.68	-5.45
313	2-iobutylpyrazine	-6.95	20.31	-18.73	-5.37	-5.05
314	2-ethyl-3-methoxypyrazine	-6.38	19.22	-18.03	-5.19	-4.39
315	2-iobutyl-3-methoxypyrazine	-7.82	23.25	-21.36	-5.93	-3.68
316	9-methyladenine	-15.43	17.37	-18.74	-16.80	-13.60
317	1-methylthymine	-12.83	17.31	-17.84	-13.36	-10.40
318	methylindole	-8.17	18.48	-17.13	-6.83	-5.91
319	methylimidazole	-9.11	12.68	-11.84	-8.26	-10.25
320	N-propyl guanidine	-14.84	15.92	-14.86	-13.79	-10.92
321	acetonitrile	-4.95	8.75	-6.70	-2.91	-3.89
322	propionitrile	-4.94	11.18	-8.95	-2.71	-3.85
323	butyronitrile	-5.06	13.44	-11.09	-2.71	-3.64
324	nitroethane	-5.09	11.24	-10.98	-4.83	-3.71
325	1-nitropropane	-5.57	13.55	-12.91	-4.94	-3.34
326	2-nitropropane	-5.10	13.40	-12.79	-4.48	-3.14
327	1-nitrobutane	-5.70	15.80	-15.00	-4.90	-3.08
328	nitrobenzene	-6.13	15.31	-15.63	-6.45	-4.12
329	2-nitrotoluene	-6.45	17.30	-17.12	-6.27	-3.59
330	3-nitrotoluene	-6.66	17.60	-17.53	-6.59	-3.45

No.	Compound	POL	NP_{rep}	NP_{att}	TOT	EXP
331	N,N'-dimethyl formamide	-5.58	11.92	-11.02	-4.68	-4.90
332	N-methylformamide	-6.55	9.72	-8.87	-5.70	-10.00
333	acetamide	-9.72	9.72	-8.71	-8.70	-9.72
334	z-N-methylacetamide	-7.78	12.22	-10.95	-6.51	-10.00
335	propionamide	-9.29	12.00	-10.79	-8.08	-9.42
336	thioanisole	-3.73	16.97	-15.22	-1.98	-2.73
337	dimethyl sulfide	-3.09	10.50	-8.64	-1.23	-1.54
338	diethyl sulfide	-1.02	15.53	-12.92	1.58	-1.43
339	methyl ethyl sulfide	-2.43	13.04	-10.80	-0.19	-1.49
340	dipropyl sulfide	-2.12	20.15	-17.15	0.87	-1.27
341	dimethyl disulfide	-2.66	12.80	-10.89	-0.75	-1.83
342	diethyl disulfide	-1.29	17.82	-15.16	1.38	-1.63
343	trimethyl phosphate	-8.96	17.05	-16.31	-8.22	-8.70
344	triethyl phosphate	-8.83	24.77	-22.38	-6.43	-7.80
345	tripropyl phosphate	-9.60	31.69	-28.16	-6.06	-6.10
346	2,2-dichloroethenyl dimethyl phosphate	-7.96	22.01	-21.29	-7.24	-6.61
347	dimethyl 4-bromo-2,5-dichlorophenyl thiophosphate	-10.51	28.50	-27.93	-9.94	-5.70
348	dimethyl 2,4,5-trichlorophenyl thiophosphate	-4.37	28.97	-27.50	-2.89	-5.06
349	dimethyl 4-nitrophenyl thiophosphate	-9.79	27.12	-27.24	-9.91	-7.62
350	diethyl 2,4-dichlorophenyl thiophosphate	-4.91	32.47	-29.28	-1.72	-3.86
351	dimethyl 3-methyl-4-thiomethoxyphenyl thiophosphate	-6.88	31.24	-28.94	-4.58	-6.92
352	diethyl 4-nitrophenyl thiophophosnate	-9.16	30.51	-29.04	-7.68	-6.27
353	O-ethyl O'-4-bromo-2-chlorophenyl S-propyl phosphorothioate	-7.77	35.75	-32.49	-4.50	-4.09

Table 6

Performance by solute functional group. No. of solute: number of solute molecules. The ranges of compound sequence numbers as in Table 5 are also shown for the listed solute groups. RMSD and UAVG are in kcal/mol.

Solute group	No. of solute	RMSD	UAVG
alkanes	19(1 - 19)	0.74	0.59
alkenes	20(20 - 39)	0.78	0.68
alkynes	7(40 - 46)	0.84	0.78
aromatic hydrocarbons	18(47 - 64)	0.54	0.41
fluorides	19(65 - 83)	0.89	0.74
chlorides	38(84 - 121)	1.10	0.98
bromides	18(122 - 139)	1.35	1.16
alcohols	45(140 - 184)	1.07	0.90
ethers	19(185 - 203)	1.44	1.25
aldehydes	15(204 - 218)	1.44	1.33
ketones	17(219 - 235)	1.59	1.52
acids	6(236 - 241)	1.55	1.52
esters	29(242 - 270)	1.10	1.00
amines	27(271 - 297)	1.65	1.36
amides	23(298 - 320)	1.43	1.10
nitriles	4(321 - 324)	1.05	1.05
nitro compounds	6(325 - 330)	2.24	2.15
compounds with N in heterorings	5(331 - 335)	2.59	2.07
compounds with S	7(336 - 342)	1.94	1.66
compounds with P	11(343 - 353)	1.97	1.59