Using nonlocal electrostatics for solvation free energy computations: ions and small molecules

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Abstract

Solvation free energy is an important quantity in Computational Chemistry with a variety of applications, especially in drug discovery and design. The accurate prediction of solvation free energies of small molecules in water is still a largely unsolved problem, which is mainly due to the complex nature of the water-solute interactions. In this letter we develop a scheme for the determination of the electrostatic contribution to the solvation free energy of charged molecules based on nonlocal electrostatics involving a minimal parameter set which in particular allows to introduce atomic radii in a consistent way. We test our approach on simple ions and small molecules for which both experimental results and other theoretical descriptions are available for quantitative comparison. We conclude that our approach is both physically transparent and quantitatively reliable.

Key words: solvation free energy, nonlocal electrostatics

1 Introduction

The unique properties of water, namely its polar nature, high dielectric constant, and its ability to form hydrogen bonds \([\text{I}]\), are responsible for the existence of life as we know it. At the same time, these very properties are the main obstacle in modelling hydration effects. An accurate model of ion and small molecule hydration will therefore have important applications in computational chemistry, chemical engineering, and drug design.

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In the latter, the interest stems from the fact that drug-like small molecules are usually moderately polar to achieve the required bioavailability. Therefore their solvation free energy is generally dominated by the electrostatic contribution, while the nonpolar contribution is more or less negligible. One of the most successful models for predicting solvation free energies of small molecules (and proteins) therefore employs the Poisson or Poisson-Boltzmann equations \(^{2, 3}\). Within this approach, the solvent is typically treated as a structureless medium of a given dielectric constant \(\varepsilon\) (for water, \(\varepsilon \sim 80\)). The solute itself is treated as a low-\(\varepsilon\) “cavity” \(^{4}\).

Clearly, this approach fails to take into account many relevant details of the solvent structure. The presence of long-ranged electrostatic fields induces static correlations among the polar molecules that may vary considerably in space depending on the molecular build-up of the solute. These can be taken into account by performing Molecular Dynamics simulations, thus leaving the continuum description at the expense of high computational cost even for small molecules \(^{5}\).

Including more structural detail into the continuum description on the one hand without increasing computational complexity on the other is therefore highly desirable. At the same time, however, also the avoidance of additional parameter sets, which is common practice in the use of continuum electrostatics in computational chemistry, is a key requirement.

In this work, we follow one particular route to achieve this goal. We develop an approach for the computation of the electrostatic (polar) contribution to the free energy of solvation based on nonlocal electrostatics \(^{7, 8, 9, 10, 11, 12}\). This continuum approach, originating in the physics literature as a generalization of classical electrostatics to account for media with spatial dispersion, is developed here within a physically transparent minimal parameter set and applied to the simplest systems of single ions and small molecules for which experimental and theoretical results are available for quantitative comparison. In particular we address the issue of a systematic choice of ion radii which most commonly is based on essentially empirical parametrizations \(^{13}\). We conclude with an outlook on extensions of our approach for more complex, and biologically relevant, molecules.

2 Nonlocal electrostatics of the solvent

The electrostatic potential \(\phi\) of a charged molecule in solution is, within classical (local) electrostatics, given by the Poisson equation \(^{6}\)

\[
\nabla \left[ \varepsilon(r) \varepsilon_0 \nabla \phi(r) \right] = -\rho(r)
\]

\(1\)
where \( \varepsilon_0 \) denotes the dielectric constant of vacuum, and \( \varepsilon(\mathbf{r}) \) is a local dielectric function which is taken as the constants \( \varepsilon_{\text{water}} \approx 78 \) of the solution (water), and a much smaller value within a solute molecule (for proteins, e.g., a typical value taken is \( \varepsilon \approx 2 - 5 \)). The rhs of eq.(1) is the charge density giving rise to the potential.

This arguably simple description is prone to complications: first, the transition region between solute and solution is ill-described and needs a further (rather delicate) modeling. Second, very little is said about structural effects due to the orientation of the polar water molecules near highly charged regions of a given solute molecule.

The simplest way to introduce structural effects into a continuum description of the solvent is to account for correlations due to polarization effects between solution molecules characterized by a correlation length \( \lambda \). This gives rise to a nonlocal generalization of eq.(1) given by (7)

\[
\nabla_r \int dV' \varepsilon(|\mathbf{r} - \mathbf{r}'|)\varepsilon_0 \nabla_{r'}\phi(\mathbf{r'}) = -\varrho(\mathbf{r})
\]

where isotropy of the liquid medium is supposed. Eq.(2) needs to be accompanied by suitable boundary conditions (see (11)). These conditions can be simplified considerably by assuming the atomic constituents as conducting spheres, which is exact for the case of ions, and approximate for the case of small molecules. The solution of the nonlocal solvation problem with a treatment of the full boundary conditions is beyond the scope of this work and will be reported elsewhere (14).

The rationale behind eq.(2) is the following. Since the electrostatic fields are long-ranged, the solvent molecules will feel the presence of the fields of other molecules over characteristic distances (that will be of particular relevance below). Maintaining locality of the physical fields (i.e., electrostatic potentials and electric fields), it is the response functions into which this purely static correlation effect needs to be embedded. We note that the dielectric function is related to the dielectric response function via \( \varepsilon = 1 + \chi \), irrespective of the local or nonlocal character of the theoretical description.

Due to the assumption of spatial isotropy, eq.(2) lends itself to a treatment in Fourier space, reducing the linear integro-differential equation eq.(2) to an algebraic equation involving the Fourier-transformed function \( \varepsilon(|\mathbf{k}|) \) with wavevector \( \mathbf{k} \). Explicit functional dependences of either \( \varepsilon(|\mathbf{r} - \mathbf{r}'|) \) or \( \varepsilon(|\mathbf{k}|) \) have been derived from various approaches, e.g. within a Ginzburg-Landau theory for the polarization fields (10).

Motivated by these works we have formulated a family of nonlocal dielectric functions fulfilling the following minimal requirements (15)
i) for high \( k \)-values (equivalently, on small spatial scales) the solvent molecules cannot follow the polarization forces.

Thus, a limiting value for the macroscopic dielectric function has to be reached in this limit. Typical choices in the literature are \( \lim_{k \to \infty} \varepsilon(k) \sim \varepsilon_{\infty} \approx 1.8 \) (10, 16), or \( \varepsilon_{\infty} = 1 \) (17). We have considered both cases and do not find a significant dependence on this choice;

ii) in the opposite limit, \( k \to 0 \), the value for \( \varepsilon \) should equal the macroscopic value;

iii) the physical length scale of the polarization fluctuations is characterized by a correlation length \( \lambda \). The local electrostatic limit is given by \( \lim_{\lambda \to 0} \varepsilon(|r - r'|) = \varepsilon_{\text{loc}} \delta(r - r') \);

iv) causality conditions (Kramers-Kronig relations) need to be fulfilled (17).

While the conditions i)-iv) are clearly not sufficient to determine the dielectric function unambiguously, we find that the following class of functions in Fourier space fulfill these criteria sufficiently well (18)

\[
\varepsilon(k) = \frac{1}{(2\pi)^{3/2}} \left[ \varepsilon_{\infty} - \frac{\varepsilon_{\infty} - \varepsilon_{\text{loc}}}{(1 + \lambda^2 k^2)^n} \right],
\]

which depend on only two parameters, \( n \), and \( \lambda \). For \( n = 2 \), the dielectric function decays exponentially in real-space, while \( \varepsilon(k) \) is a Lorentzian for \( n = 1 \), decaying in real-space as \( \exp(-r/\lambda)/r \). Note that formally the case \( n = 1 \) was discussed previously in (18-19), based, however, on a different physical interpretation (see also (19) for a similar approach in the context of nuclear physics). We have also tested alternative choices, e.g. a Gaussian model and a nonlocal model derived from a Ginzburg-Landau theory for polarization fields (10).

The comparison of our nonlocal models with other approaches and experimental data is made possible by using the concept of an effective local dielectric function \( \tilde{\varepsilon}(r) \). It is usually defined for the potential of a point charge \( q \),

\[
\phi(r) = \frac{1}{4\pi \varepsilon_0} \frac{q}{\tilde{\varepsilon}(r)r}.
\]
where
\[ \hat{\varepsilon}(r) \equiv \left[ \int \frac{dk}{(2\pi)^{3/2}} \frac{\sin(kr)}{kr} \frac{1}{\varepsilon(k)} \right]^{-1}. \]

For a general charge distribution \( \hat{\varepsilon}(r) \) can be defined as well (14). We note that our determination of the effective dielectric constant is consistently performed within the nonlocal continuum theory and does not rely on data-based fits (20, 21).

Expression (5) allows to test our approach against previous results. We took empirical models for the radial dependence of \( \varepsilon \) derived for experimental results from Mehler and Eichele (ME) (20) and Conway (CO) (22). The CO-model is reproduced best by the Lorentzian \((n = 1)\) for \( \lambda = 15\text{Å} \), while the ME-model is reproduced best for \( \lambda = 24.13\text{Å} \). The purely exponential model \((n = 2)\) displays unphysical singularities in \( \hat{\varepsilon}(r) \) at small \( r \), while with a choice of \( \lambda = 5\text{Å} \), the CO-model is reproduced for larger distances, \( r > 15\text{Å} \). Figure 1 shows \( \hat{\varepsilon}(r) \), as computed by eq.(5) for a single sodium ion, using the Lorentzian model with \( \lambda = 15\text{Å} \). The computation of \( \hat{\varepsilon}(r) \) performed here makes use of a specifically adapted FFT applicable also to molecules (14).

A Gaussian choice for \( \varepsilon(k) \), however, leads to strong oscillations in the effective dielectric function, although its overall shape resembles the CO-model for \( \lambda = 5\text{Å} \). Checking our approach against the nonlocal model by Sutmann et al. (10), we find that their theory fails to comply with our requirement iii), i.e., it does not reproduce the correct limiting value at large distances.

3 Single ions and the choice of their radii

We now turn to the application of our approach to small ions. We treat these ions as Born spheres. A standard problem in the definition of Born-type ions is the definition of the ion radius (13). Starting from the accepted interpretation that a solvated ion is surrounded by solvation shells, the first of these shells will be “as close as possible” to the ion. We can therefore identify the position of the centers of the oxygen in the first solvation shell with the first peak in the radial distribution function (rdf) which can be obtained either from scattering experiments or from molecular dynamics simulations.

We defined the radius of the water oxygen as half the position of the first peak in the oxygen-oxygen radial distribution function (rdf) of bulk water. The ion radii were then derived by subtracting this radius from the position of the first peak of the ion-oxygen rdf derived from a molecular dynamics simulation.
As a specific input for our calculations we take the values for the ion radii determined by Åqvist (23), obtained from a combined free energy perturbation/force field approach based on the GROMOS force field (24), employing several different water models (flexible SPC, rigid SPC, and TIP3P). Based on this input, we have determined the solvation free energy from nonlocal electrostatics, which is given by

\[
\Delta G^{\text{polar}} = -\frac{1}{2\varepsilon_0} \int dk \left\{ 1 - \frac{1}{(2\pi)^{3/2}\varepsilon(k)} \right\} D^2(k) \quad (6)
\]

where \(D(k)\) is the dielectric flux density.

The result of the calculation is shown in Figs. 2 for monovalent ions and in Fig. 3 for divalent ions, for all models to be compared here. Note that we chose the parameter \(\lambda\) based on its fit to the effective dielectric function. The CO-model was reproduced by \(\lambda = 5\,\text{Å}\) for \(n = 2\) (exponential model), by \(\lambda = 15\,\text{Å}\) for \(n = 1\) (Lorentzian) and by \(\lambda = 5\,\text{Å}\) for the Gaussian model. The ME-model could only be reproduced by \(n = 1\) with \(\lambda = 24.13\,\text{Å}\). The value for the exponential model is in accord with the findings in Ref. (11). Also note, as shown in Table 1, that the values we obtain are only marginally corrected (if at all) by effects due to nonlinear saturation, which contributes in principle as well to a reduction of the dielectric constant near the ion.

The model by Sutmann was used with two different limiting values (Sutmann 1 with \(\varepsilon_\infty = 1\), and Sutmann 2 with \(\varepsilon_\infty = 1.8\)). As the figures show, our results are consistently better than all the other theoretical curves.

The computation of electrostatic solvation free energies is also possible by employing eq.(5) in a standard (local) Poisson solver. We have implemented this in an available library (BALL) (25; 14). Fig. 4 compares the results of our computations for the monovalent ions with the nonlocal theory based on eq.(6) and from the effective local dielectric function, eq.(5), demonstrating the consistency of both approaches. Fig. 5 finally compares the theoretical results of the local and nonlocal approaches, obtained with the Poisson solver, with the experiment values. Evidently, the nonlocal approach yields results consistently superior to those obtained from the standard local theory.

We stress the significant advantage of our computations to work with first-principle radii without arbitrary adjustments. In Figs. 2-5, the Åqvist-radii were used (23). In addition, we have also tested the Shannon-radii derived from X-ray crystal data (27; 28), without significant effect on our results. Our result thus give a basis to the general belief that the need to introduce effective radii is in fact a consequence of the local water structure around the ions (26). We believe that our nonlocal approach demonstrates that it is therefore preferable conceptually to introduce the length-scale governing the
structural effects in the solvent rather than introducing necessarily artificial procedures to adjust the Born radii.

4 Small molecules

As a second application we apply our approach to determine the solvation free energy for small alcohols for which we can assume that the polar contribution exceeds the nonpolar one. Fortunately, accurate measurements of the solvation free energies of these molecules are available. We write the charge distribution of these molecules as a linear superposition of radially symmetric partial distributions translated by a vector \( \mathbf{R}_i \), \( \rho_i = \rho(|\mathbf{r} + \mathbf{R}_i|) \), i.e.

\[
\rho(r) = \sum_{i=1}^{N} \rho_i(|\mathbf{r} + \mathbf{R}_i|).
\]

Its Fourier transform is then given by the expression

\[
\rho(k) = \sum_{i=1}^{N} \rho_i(k) \exp(-i\mathbf{R}_i \cdot \mathbf{k}).
\]

Again we have to define the radii of the atoms. For this we chose to classify the atoms into classes depending on their chemical environment in the molecule (e.g., like the hydrogen atom in an OH-group), expecting that the radii of all atoms in a certain class are more or less similar. For methanol (\( \text{CH}_3\text{OH} \)), e.g., we defined four classes of atoms and used their rdf’s with the oxygen of water to find the following set of radii: Methyl C: 2.135 Å, hydroxyl O: 2.014 Å, hydroxyl H: 1.115 Å, methyl H: 1.394 Å.

Compared to the calculation of the free energies for the ions this computation is slightly more involved as it requires a three-dimensional integration instead of a one-dimensional one. Within the framework of the simplified boundary conditions, the unperturbed fields of the atomic constituents are simply superimposed. To ensure short computation times, in our implementation we have used the VEGAS-Monte-Carlo integration scheme \(^{(29)}\) that is supplied with the GNU scientific library GSL \(^{(30)}\). Details of these computations will again be given elsewhere \(^{(14)}\).

The results for some small alcohols are shown in Table 1. For the comparison we have used the exponential with \( \lambda = 5 \) Å, the Lorentzian with \( \lambda = 15 \) Å, and the Lorentzian with \( \lambda = 24.13 \) Å. All values in these tables are given in kJ/mol.

The interpretation of the results is more complicated than in the Born ion case. While there we could assume that the contribution of the nonpolar part of the free energy of solvation could be neglected (for the Born ions it can be estimated to be of the order of 10 − 20 kJ/mol), this is not the case for the alcohols. The electrostatic contribution is still the dominant part, but not the only significant one. We therefore applied a very simple model for the nonpolar contribution \(^{(31)}\) in order to be able to compare our results to experimental
data. The results given for the polar contribution can also be optimized by considering improved charge distributions \[14\].

5 Conclusions and outlook

We have demonstrated that the approach to the computation of solvation free energies based on nonlocal electrostatics is able to reproduce experimental data for ions and small molecules with reasonable accuracy. The approach we put forward has the basic advantage to rely on essentially one parameter which has a transparent physical interpretation as the correlation length of the polarization fluctuations. While within the present paper this parameter is used as a fitting parameter, it should be clear that it might be also determined by experiment or simulation. A further significant advantage is that our approach does not make use of the commonly used adjustments of atomic or ionic radii. A challenge for the future will be the extension of our approach to determine electrostatic solvation free energies for more complex and biologically relevant molecules. Work in this direction is in progress \[14\].

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Fig. 1. $\tilde{\varepsilon}(r)$ for a single sodium ion
Fig. 2. Free energy of solvation for monovalent ions

Fig. 3. Free energy of solvation for divalent ions
Fig. 4. Free energy of solvation for monovalent ions, from the nonlocal expression, eq.(6), and from the solution of the local Poisson equation with the effective dielectric constant, eq.(5).

Fig. 5. Free energy of solvation for monovalent ions, from the nonlocal expression, eq.(6), (circles) and from the solution of the local Poisson equation (squares), i.e. the Born energies. (The experimental values corresponding to the ions are on the diagonal.)
Table 1
Comparison of different models for the hydration free energy of different mono- and divalent cations. All energies are in kJ/mol. \( \Delta G_B \) is the hydration free energy computed for a Born ion of radius \( r \). \( \Delta G_{nloc} \) is the electrostatic hydration free energy computed with our nonlocal Lorentzian model (\( \lambda = 24.13 \)). \( \Delta G_{npol} \) is the nonpolar contribution to the hydration free energy as computed with the model of Uhlig (31). \( \Delta G_{corr} \) is the nonlinear correction to the hydration free energy for the corresponding ion (taken from (26)). \( \Delta G_{exp} \) is the experimental hydration free energy (taken from (32)). \( \Delta G_{calc} = \Delta G_{nloc} + \Delta G_{npol} \). \( \Delta G_{calc}^{corr} = \Delta G_{calc} + \Delta G_{corr} \).

| Ion | \( r \) [Å] | \( \Delta G_B \) | \( \Delta G_{nloc} \) | \( \Delta G_{npol} \) | \( \Delta G_{corr} \) | \( \Delta G_{calc} \) | \( \Delta G_{calc}^{corr} \) | \( \Delta G_{exp} \) |
|-----|------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Li\(^+\) | 0.645 | -1063.08 | -568.9 | 5.03 | 0 | -563.87 | -563.87 | -481 |
| Na\(^+\) | 1.005 | -682.30 | -392.51 | 5.48 | 0 | -387.03 | -387.03 | -375 |
| K\(^+\) | 1.365 | -502.36 | -306.79 | 6.01 | 0 | -300.78 | -300.78 | -304 |
| Rb\(^+\) | 1.505 | -455.63 | -284.02 | 6.23 | 0 | -277.79 | -277.79 | -281 |
| Cs\(^+\) | 1.715 | -399.84 | -256.39 | 6.59 | 0 | -249.8 | -249.8 | -258 |
| Mg\(^{2+}\) | 0.615 | -4459.74 | -2370.66 | 4.99 | 110 | -2365.67 | -2255.67 | -1838 |
| Ca\(^{2+}\) | 1.015 | -2707.32 | -1557.41 | 5.49 | 45 | -1551.92 | -1506.92 | -1515 |
| Sr\(^{2+}\) | 1.195 | -2295.29 | -1364.6 | 5.75 | 30 | -1358.85 | -1328.85 | -1386 |
| Ba\(^{2+}\) | 1.385 | -1980.43 | -1213.12 | 6.04 | 24 | -1207.08 | -1183.08 | -1259 |
| Substance     | Exponential $\lambda = 5 \text{ Å}$ | Nonpolar | $\sum$ | Experiment |
|---------------|--------------------------------------|----------|--------|------------|
| Ethanol       | -32.84                               | 8.89     | -23.95 | -20.51     |
| Methanol      | -25.64                               | 8.10     | -17.54 | -21.26     |
| 1-Butanol     | -29.79                               | 10.31    | -19.48 | -19.76     |
| 1-Hexanol     | -37.41                               | 11.83    | -25.58 | -18.25     |
| Octanol       | -33.63                               | 13.28    | -20.35 | -17.12     |
| Cyclopentanol | -28.90                               | 10.31    | -18.59 | -22.98     |
| Lorentzian    |                                      |          |        |            |
| Ethanol       | -34.17                               | 8.89     | -25.28 | -20.51     |
| Methanol      | -29.49                               | 8.10     | -21.39 | -21.26     |
| 1-Butanol     | -31.13                               | 10.31    | -20.82 | -19.76     |
| 1-Hexanol     | -38.88                               | 11.83    | -27.05 | -18.25     |
| Octanol       | -35.08                               | 13.28    | -21.79 | -17.12     |
| Cyclopentanol | -30.16                               | 10.31    | -19.85 | -22.98     |
| Lorentzian    |                                      |          |        |            |
| Ethanol       | -32.89                               | 8.89     | -24.0  | -20.51     |
| Methanol      | -27.88                               | 8.10     | -19.78 | -21.26     |
| 1-Butanol     | -29.94                               | 10.31    | -19.63 | -19.76     |
| 1-Hexanol     | -37.65                               | 11.83    | -25.82 | -18.25     |
| Octanol       | -33.77                               | 13.28    | -20.49 | -17.12     |
| Cyclopentanol | -29.06                               | 10.31    | -18.75 | -22.98     |

Table 2

Results for the free energy of solvation for small alcohols. All free energies are given in kJ/mol.