



Research paper

Fine-tuning of atomic point charges: Classical simulations of pyridine in different environments



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ABSTRACT

A correct description of electrostatic contributions in force fields for classical simulations is mandatory for an accurate modeling of molecular interactions in pure liquids or solutions. Here, we propose a new protocol for point charge fitting, aimed to take into the proper account different polarization effects due to the environment employing virtual sites and tuning the point charge within the polarizable continuum model framework. The protocol has been validated by means of molecular dynamics simulations on pure pyridine liquid and on pyridine aqueous solution, reproducing a series of experimental observables and providing the information for their correct interpretation at atomic level.

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1. Introduction

Classical Molecular Dynamics (MD) is a powerful tool, which allows to estimate macroscopic properties from microscopic models [1]. This computational approach has demonstrated to be effective in investigating the structure of organic liquids used as solvents in chemical, biological and technological applications. The reliability of simulations in these studies is related to the availability of an accurate *force field* (FF), which describes the interaction at the atomic and molecular level using a set of functional forms [2] based on a limited number of parameters. These are usually derived from quantum mechanical (QM) calculations of isolated molecules for a selected set of molecular targets and/or tuned in order to reproduce some of physical observables used as references. Despite its key role in describing the solvation ability of a substance, the static dielectric constant remains one of the most difficult bulk properties for classical simulations [3] and is especially sensitive to the electrostatic part of the force field. Since the most widely used FFs still rely on partial atomic charges,

several strategies have been employed to determine effective values for these quantities; one of the most adopted approaches relies in optimize their values to reproduce the QM derived electrostatic potential of a molecule [4]. The atomic charges depend strongly on the level of theory used in QM calculations and on the description of solvation effects. In this present study, the electrostatic parameters have been obtained through the Charge Model 5 (CM5) [5] taking into account the bulk solvent effects by means of Conductor-like Polarizable Continuum Model (C-PCM) [6]. This allows one to take into account the different polarization effect of various solvents (here pyridine or water) in tuning the effective atomic charges (as explained in Methods and by Fig. 1).

Furthermore, since the presence of hydrogen bonds (HB) has a remarkable effect on magnitude of the static dielectric constant (ϵ) [7], a thorough description of intermolecular interactions is necessary. One of the problems in the HB description is its directionality. A possible solution is the use of off-site charges (so-called virtual sites or dummy atoms, VS hereafter) with a fixed position with respect to the generating atom that is meant to model the presence of lone pairs [8,9]. In fact, an improved HB description of pyridine in aqueous solution has been obtained employing VS and adjusting the charges on the carbon atoms directly bound to nitrogen to preserve the molecular dipole moment [9]. However, to develop a model for pyridine able to describe the interactions both in aqueous solution and in pure liquid, the atomic charges

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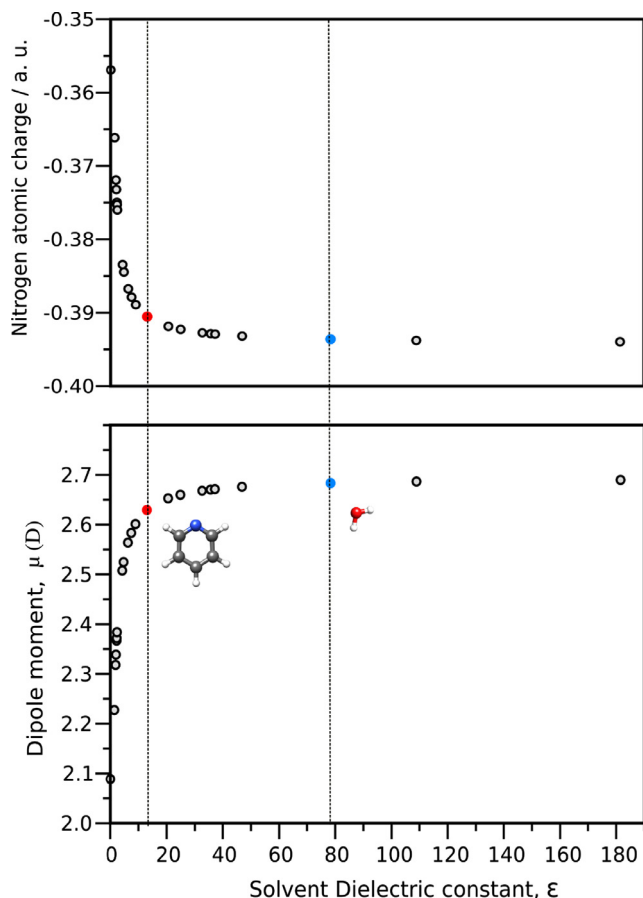


Fig. 1. Above: the trend of nitrogen atom partial charge changing the solvent dielectric constant value used in C-PCM. Below: the trend of pyridine molecular dipole moment changing the solvent dielectric constant value used in C-PCM. In red and blue the values obtained imposing pyridine and water as solvents respectively. The nitrogen atomic charges (red and blue circles in the above picture) have been used in our simulations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

on the whole molecule have been determined with a fitting procedure using as reference parameters both the molecular dipole and quadrupole moments. Therefore, we propose a method for the derivation of partial atomic charges and VS, which completely depends on properties determined at the QM level without any additional empirical parameters. We show that the same strategy works for both pure (liquid) pyridine and its aqueous solution.

The pyridine aqueous solution, as well as the pure liquid, have been studied by means of classical simulations employing several models [9,10,12,13]. Although some of the tested FFs provide reasonable results, here we want to highlight the transferability of our model, able to simulate both pure pyridine and its aqueous solution, overcoming the limitations on these FFs and delivering accurate structural and thermodynamic properties together with the static dielectric constant.

2. Methods

Classical MD simulations of both pure liquid and aqueous solution of pyridine were carried out using GROMACS v. 4.6.5 [11] and the OPLS/AA force field [12,13] to describe intramolecular and intermolecular potential with the exception of the pyridine atomic charges, which were estimated using the CM5 population analysis [5]. Density Functional Theory (DFT) calculations were performed at the B3LYP/6-31+G(d) level of theory using GAUSSIAN-09 [14]

package and taking into account bulk solvent effects by means of the Conductor-like Polarizable Continuum Model (C-PCM) [6] setting the reference solvent (pyridine or water) and imposing the value of the scaling factor for the sphere radius (α) to 1.05. In Fig. 1, the nitrogen atom charge, and the pyridine dipole moment, are reported to show the polarization effects induced by several solvents with increasing dielectric constant (from 1.43 to 181.96) and implicitly described by the C-PCM. A virtual site (VS) was located at the position of the centroid of the localized molecular orbital describing the sp^2 lone-pair of the nitrogen atom using the Pipek-Mezey localization procedure [15] (the centroid distance from the nitrogen atom has been constrained during the simulation). The charge on the VS has been obtained adjusting the atomic charges of pyridine through a fitting procedure to reproduce the calculated dipole and quadrupole moments, as indicated in Table 1 (for atom labeling Table 1).

The simulation for the pyridine pure liquid was performed on a system containing 500 molecules, whereas the simulation of the aqueous solutions was performed on one pyridine and 512 TIP3P-FB [16] water molecules. In both cases, we employed a cubic box with periodic boundary conditions. After a steepest descent energy minimization the systems were heated up to 298.15 K for 200 ps (using the velocity-rescale [17] thermostat and $\tau = 0.1$ ps) and then the time step and temperature coupling constant were increased to 2.0 fs and 0.2 ps respectively, and systems were let to converge to uniform density in a NPT ensemble (using the Parrinello-Rahman barostat [18] and $\tau = 0.1$ ps).

Afterward production runs were run in the NVT ensemble [17], fixing the fastest degrees of freedom with LINCS algorithm ($\delta t = 2.0$ fs) [19]. The total sampling time was 50 ns for both the pure liquid and the aqueous solution. Electrostatic interactions were evaluated using the particle-mesh Ewald (PME) [20] method with a grid spacing of 1.2 Å and a spline interpolation of order 4.

Harder et al. [21] have proposed an OPLS3 pyridine model, which also has an off-site charge on the nitrogen atom and reproduces well the hydration free energy (-4.3 kcal/mol). We performed a MD simulation using this force field, to determine structural information on pure liquid and compare the obtained results with our model. The main difference between OPLS3 and our model is the charge on nitrogen atom, which is not null in OPLS3 (+0.179 e) and the procedure employed to define the virtual site position [8]. An *ab initio* molecular dynamics (AIMD) simulation of a pyridine aqueous solution at ambient temperature was carried out using the CP2K program [22,23] to further assess the reliability of our procedure to describe the hydrogen bond interactions and their directional character. We considered a cubic box of size 11.77 Å containing 1 pyridine and 50 water molecules and subjected to periodic boundary conditions. We performed a simulation of 20 ps in the NVE ensemble with a time step of 0.1 fs. The electronic structure was calculated with DFT, utilizing the BLYP functional [24,25]. The TZV2P basis set was used in conjunction with the GTH pseudopotentials [26,27]. A plane wave cutoff of 340 Ry was adopted for electron density. Van der Waals interactions have been described by the method proposed by Grimme [28].

Dielectric constant and density have been evaluated using standard tools provided with GROMACS. To calculate the heat of vaporization, ΔH_{vap} , gas-phase simulations of 2 ns ($\delta t = 0.2$ fs) have been added for both systems. The ΔG_{hyd} were calculated using Bennett acceptance ratio (BAR), [29] a free energy perturbation (FEP) method, performing the simulations with GROMACS v. 4.6.5. Structural analysis was performed with TRAVIS package [30]. Spatial distribution function (sdf) graphs were prepared using the Caffeine [31] molecular viewer.

The relative orientation of first neighbour pyridine molecules was also investigated by means of the KMeans clustering algorithm

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