Using Ab-Initio Simulations and Experimental ^{31}P NMR Chemical Shifts for the Development of Improved Nucleic Acid – Metal Ion Force Fields

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Electrostatic interactions of nucleic acids and metal ions critically affect the structure and functionality of DNA and RNA in solution. [1–3] It has therefore been a constant effort of molecular dynamics (MD) simulations of aqueous nucleic acid systems to improve the parameterization of non-bonded interactions between metal ions and the biomolecular surface, in particular for doubly charged ions, like Mg^{2+}. However, state of the art, non-polarizable force fields overestimate contact ion pair (CIP) formation in nucleic acids [4,5] and it is therefore an open question to derive adequate non-bonded force field parameters for the simulation of nucleic acids in solution.

We investigate dimethyl phosphate (DMP) in presence of Mg^{2+} as a model system to gain a deeper understanding of the ion-phosphate interaction motif. The analysis of experimental ^{31}P chemical shifts for varying Mg^{2+} content and ab initio (GIAO-DF-LMP2) simulated NMR chemical shifts indicate a preference for solvent separated ion pairs (SSIP) over contact ion pair (CIP) formation, [6] in agreement with previous experimental data. [7] We propose an approach that unifies preceding approaches for the parameterization of a novel force field by fitting to ab initio data from the DMP-metal-ion model system. Missing polarization effects and mismatched surface-ion interactions can be accounted for within the 12-6-4 Lennard-Jones model, which introduces an additional induced dipole term into the 12-6 Lennard-Jones interaction model. [8] An alternative approach relies on the screening of charges in condensed liquid phase, which can be effectively accounted for in a mean field way via a rescaling of charges. [9] We show that the use of non-integer ion charges and a 12-6-4 Lennard-Jones potential can be used to develop new nucleic acid-ion parameter sets. Extensive benchmark MD simulations show that the novel parametrization approach yields an improved 12-6-4 metal ion parameter set with scaled charges that has broad applicability for atomistic force field simulations of nucleic acids in solution.

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