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Confinement Potential for QM and QM/MM Optimization with Implicit Solvent under Non-Periodic Boundary Conditions

A current limitation in the geometric optimization of solute/solvent clusters containing a large number of solvent molecules, also including an implicit model for the solvent bulk, both at the QM and QM/MM level, concerns the stability of solvent molecules placed within the cavity embedded in the dielectric medium. For example, molecules near the edge of the cavity tend to collapse toward the boundary rather than remain evenly distributed within the cavity itself, leading to unphysical minimum energy structures with overestimated solute-solvent interactions. This behavior arises from the dominance of explicit-explicit interactions over explicit-implicit ones, which leads to geometrically unstable or physically unrealistic structures. Indeed, dispersion-repulsion models currently available to account for non electrostatic explicit-implicit interactions are not adequate for large clusters, being developed to reproduce the solvation free energy of the solute in combination with the electrostatic contribution [1,2,3] rather then average van der Waals potentials for a large number of solvent molecules. Such models prove to be ineffective also in dynamic simulations, where the adoption of non-periodic boundary conditions (non-PBC) is more suitable for a proper description of dispersion and repulsion forces [4,5,6,7].

In this work, we propose the integration of the non-PBC dispersion-repulsion term—also acting as a confinement potential—directly into the classical component of the quantum Hamiltonian. This approach enables a more realistic representation of the minimum energy structure, even for large solute-solvent clusters. We also present several case studies that demonstrate the effectiveness of the method, including structural optimization and the calculation of vibrational frequencies and vibronic spectra.

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