# A QM/SQM embedded cluster RISM approach for predicting EPR parameters of protein-bound nitroxide spin probes

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Spectroscopic methods such as electron paramagnetic resonance (EPR) have become popular tools to study structure and dynamics of biomolecular systems. First principles calculations of spectra can enhance the understanding of these processes at an atomic scale, though the size and complexity of solvated biomolecular systems such as enzymes often require a drastic simplification of the underlying physics, thus decreasing the predictive capabilities of the computational method. [1] Since their first description by Warshel and Levitt [2] multiscale methods have emerged as an effective tool to model chemical processes in a heterogeneous protein environment in a cost-effective way. For instance, a detailed quantum-mechanical (QM) treatment of a region of interest in a complex system such as a solvated protein could be coupled to a force field-based, molecular mechanics (MM) environment including an atomically resolved solvent, giving rise to the class of hybrid QM/MM models [1] that are also applicable to the prediction of spectroscopic parameters. [3] Still, further reduction of system size to include only relevant solvent molecules explicitly could further enhance computational performance as long as quantitative properties are negligibly affected. To this end, realistic implicit solvent models that retain some structural information about the environment could offer a way forward.

We here present a computational method to predict electron paramagnetic resonance (EPR) parameters, such as isotropic hyperfine constants, on the basis of the "embedded cluster reference interaction site model" (EC-RISM) [4,5] and its application to a nitroxide spin probe in free solution and attached to a protein. The methodology combines ideas from multiscale approaches with a 3D RISM-based solvation description that models the background based on distribution functions of a granular solvent model. More specifically, in addition to the statistical solvent background a spin probe can be exposed to a few explicitly QM-modeled protein residues based on the extrapolative ONIOM scheme, [6] thus facilitating mutual polarization of the spin probe and the high-level QM zone of the protein. Additionally, the description of the complete protein system by semi-empirical QM methods (QM/SQM) allows for the polarization of all remaining protein residues by the solvent environment, giving rise to a more realistic description of the system compared to conventional QM/MM approaches. First results are presented and discussed in comparison to experimental evidence.

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