# A Simple QM/MM Approach for Capturing Polarization Effects in Protein-Ligand Binding Free Energy Calculations

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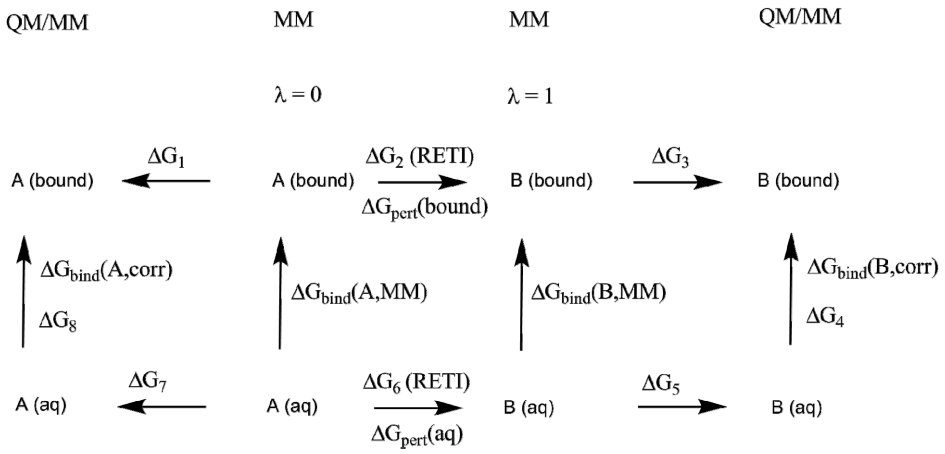
We present a molecular simulation protocol to compute free energies of binding, which combines a QM/MM correction term with rigorous classical free energy techniques, thereby accounting for electronic polarization effects. Relative free energies of binding are first computed using classical force fields, Monte Carlo sampling and replica exchange thermodynamic integration. Snapshots of the configurations at the endpoints of the perturbation are then subjected to DFT-QM/MM single-point calculations using the B3LYP functional and a range of basis sets. The resulting quantum mechanical energies are then processed using the Zwanzig equation to give free energies incorporating electronic polarization. Our approach is conceptually simple and does not require tightly coupled QM and MM software. The method has been validated by calculating the relative free energies of hydration of methane and water and the relative free energy of binding of two inhibitors of cyclooxygenase-2. Closed thermodynamic cycles are obtained across different pathways, demonstrating the correctness of the technique, although significantly more sampling is required for the protein-ligand system. Our method offers a simple and effective way to incorporate quantum mechanical effects into computed free energies of binding. [1]




**Scheme 1.** Thermodynamic cycle with QM/MM corrections used for the calculation of relative free binding energies of protein-ligand complexes.

[1] F. R. Beierlein, J. Michel, J. W. Essex, *J. Phys. Chem. B* **2011**, in the press.