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Improved QM Methods and Their Application in QM/MM Studies of Enzymatic Reactions[1]

WILLIAM L. JORGENSEN, Dept. of Chemistry, Yale University

Quantum mechanics (QM) and Monte Carlo statistical mechanics (MC) simulations have been used by us since the early 1980s to study reaction mechanisms and the origin of solvent effects on reaction rates. A goal was always to perform the QM and MC/MM calculations simultaneously in order to obtain free-energy surfaces in solution with no geometrical restrictions. This was achieved by 2002 and complete free-energy profiles and surfaces with full sampling of solute and solvent coordinates can now be obtained through one job submission using BOSS [JCC 2005, 26, 1689]. Speed and accuracy demands also led to development of the improved semiempirical QM method, PDDG-PM3 [JCC 1601 (2002); JCTC 817 (2005)]. The combined PDDG-PM3/MC/FEP methodology has provided excellent results for free energies of activation for many reactions in numerous solvents. Recent examples include Cope, Kemp and E1cb eliminations [JACS 8829 (2005), 6141 (2006); JOC 4896 (2006)], as well as enzymatic reactions catalyzed by the putative Diels-Alderase, macrophomate synthase, and fatty-acid amide hydrolase [JACS 3577 (2005); JACS (2006)]. The presentation will focus on the accuracy that is currently achievable in such QM/MM studies and the accuracy of the underlying QM methodology including extensive comparisons of results from PDDG-PM3 and ab initio DFT methods.

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