Modeling Organic and Biomolecular Systems in Solution

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Research highlights are provided from our work including development of the TIPnP water models and OPLS-AA force field, free energy calculations, QM/MM studies of reactions in solution, and computationally guided drug discovery.

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 readily using *BOSS* or *MCPRO* [1]. Speed and accuracy demands also led to development of the improved semiempirical QM method, PDDG-PM3. The combined PDDG-PM3/MC/FEP methodology has provided excellent results for free energies of activation and mechanistic insights for many reactions in numerous solvents. Examples include Cope, Kemp and E1cb eliminations, S_N2, Henry and Diels-Alder reactions, as well as enzymatic reactions catalyzed by the putative Diels-Alderase, macrophomate synthase, and fatty-acid amide hydrolase [2].

Drug discovery is being pursued through computer-aided structure-based design [3]. For *de novo* lead generation, the *BOMB* program builds combinatorial libraries in a protein binding site using a selected core and substituents, and *QikProp* is applied to filter all designed molecules to ensure that they have drug-like properties. Monte Carlo/free-energy perturbation simulations are then executed to refine the predictions for the best scoring leads including ca. 1000 explicit water molecules and extensive sampling for the protein and ligand. FEP calculations for optimization of substituents on an aromatic ring and for choice of heterocycles are now common. Alternatively, docking with *Glide* is performed with the ZINC database to provide leads, which are then optimized via the FEP-guided route. Successful application is illustrated for HIV reverse transcriptase and macrophage migration inhibitory factor (MIF); micromolar leads have been rapidly advanced to extraordinarily potent inhibitors.

References

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[2] Acevedo, O.; Jorgensen, W. L. Advances in QM/MM Simulations for Organic and Enzymatic Reactions *Acc. Chem. Res.* **2010**, *43*, 142-151.

[3] Jorgensen, W. L, Efficient Drug Lead Discovery and Optimization. *Acc. Chem. Res.* **2009**, *42*, 724-733.