OPLS3 - Recent developments in the OPLS force field

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We report the parameterization and validation of the new small molecule and protein force field OPLS3, a significant enhancement with respect to the previous version (OPLS2.1). OPLS3 includes off-center charge sites to better represent halogen bonding and heteroatom lone pairs as well as a complete refit of peptide dihedral parameters to high-level QM data to improve protein structure modeling.

To adequately cover medicinal chemical space, OPLS3 employs over an order of magnitude more reference data and associated parameter types relative to other commonly used small molecule force fields (eg. MMFF and OPLS_2005). We show that a high level of accuracy is achieved in describing small molecule conformational and solvation properties. The newly fitted peptide dihedrals, lead to significant improvements in the representation of secondary structure elements in simulated peptides and native structure stability over a number of proteins.

In a first practical application of the new force field, we show that protein-ligand binding affinities from MD-based free energy calculations are significantly more accurate over a wide range of targets and ligands (less than 1 kcal/mol RMS error) for OPLS3 representing a 30% improvement over earlier variants of the OPLS force field.