

The hpCADD NDDO-based Polarizable Force Field: Classical Force-Field Potentials and Parameterization

Christof M. Jäger, Ahmed El Kerdawy, Heike B. Thomas, Matthias Hennemann,
Timothy Clark

*Computer-Chemie-Centrum, Department Chemie und Pharmazie, Friedrich-Alexander-Universität
Erlangen-Nürnberg; Nögelsbachstraße 25, 91052 Erlangen, Germany*

We present the second part of the parameterization of the new **hpCADD** polarizable force field. Since the electrostatic interaction between drug-molecule and its target plays a crucial role in Computer-Aided-Drug-Design (CADD), the quality of a force field is linked to its ability to represent such interactions as accurately as possible. In many cases, atom-centered monopole charges are not able to represent the molecular electrostatic potential (MEP) accurately enough. A far better way to describe the MEP is to use atom-centered multipoles derived from semiempirical molecular-orbital (MO)-theory. [1,2]

The new **hpCADD** force field now combines electrostatics (Coulomb and exchange) taken from a specially parameterized NDDO wavefunction directly with classical force field potentials for an accurate representation of structures and relative energies.

In the first step, the semiempirical NDDO-Hamiltonian was parameterized in order to represent the *ab initio* (MP2/aug-cc-pVDZ) molecular electrostatic potential (MEP) at the 0.01 a.u. electronic isodensity surface of the molecule accurately. [3]

We now describe the second step, in which the classical force field potentials were parameterized while keeping the NDDO-based Coulomb and exchange interactions fixed. Classical harmonic bond-stretch and angle-bend potentials were used with Fourier series torsional potentials, a correction potential for electronic interpenetration (i.e. a short-range correction to the multipole approximation) and an undamped dispersion term.

The performance of the new force field for hydrocarbons will be demonstrated.

[1] A. H. C. Horn, J.-H. Lin and T. Clark, *Theor. Chem. Acc.*, **2005**, *114*, 159–168; Erratum: *Theor. Chem. Acc.*, **2007**, *117*, 461–465.

[2] M. J. S. Dewar, W. Thiel, Ground states of molecules. 38. The MNDO method. Approximations and parameters. *J. Am. Chem. Soc.* **1977**, *99*, 4899-4907.

[3] H. B. Thomas, M. Hennemann, T. Clark, *J. Mol. Model.*, to be submitted.