JÜLICH
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Halogen bonds, σ-holes

and molecular mechanics of modern drug candidates

November 4, 2014 | Michal H. Kolář

People involved, funding

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Unterstützt von / Supported by

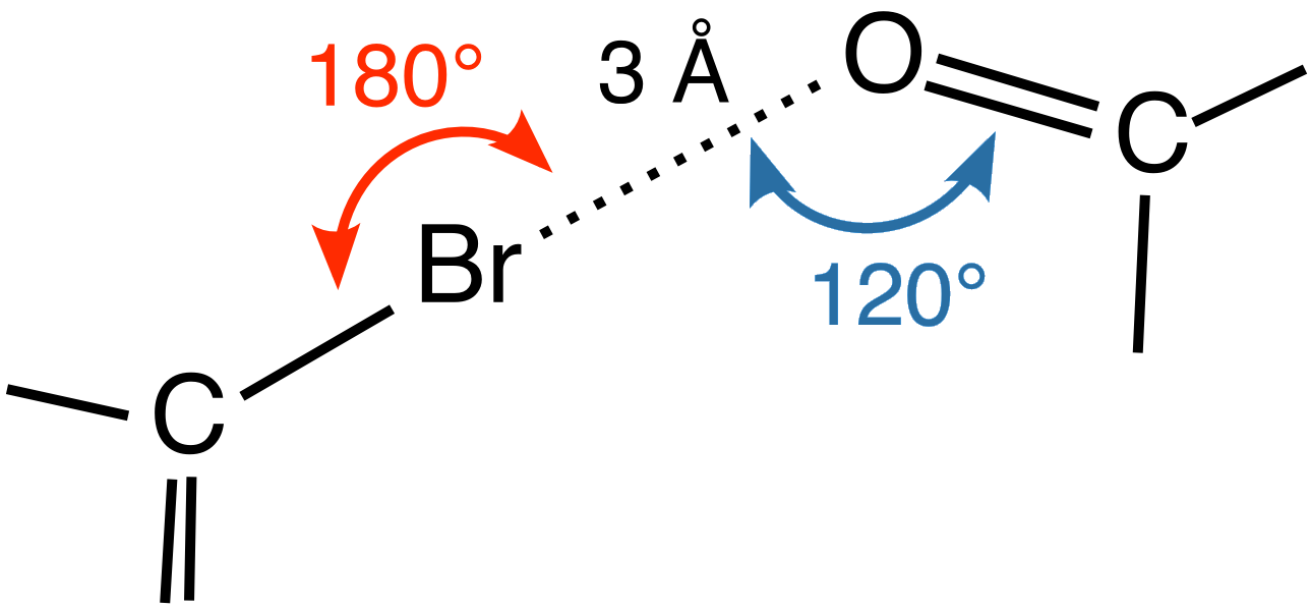
Alexander von Humboldt
Stiftung/Foundation

Outline

1. Background
   - Properties of halogen bonding
   - Applications of halogen bonding
2. Computer Modeling
   - Sigma-holes
   - Molecular mechanics
   - Parametrization
3. Concluding remarks

Background

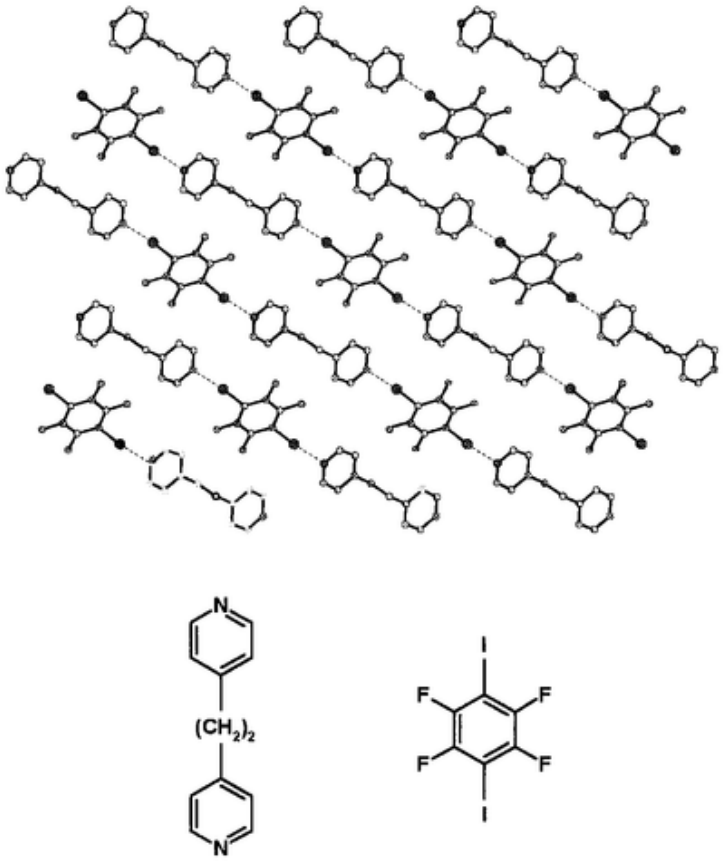
Halogen bond



$$(F) < Cl < Br < I$$

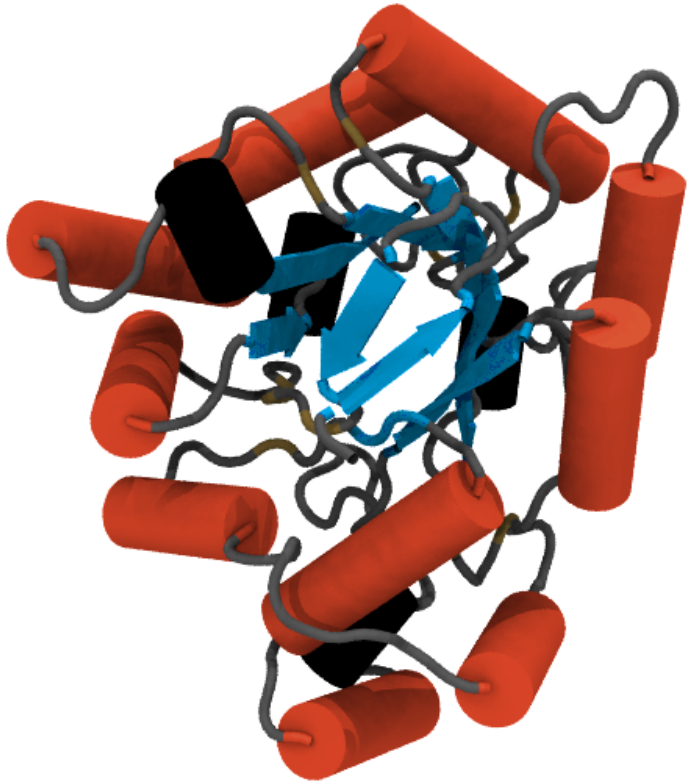
10 kJ/mol

Crystal engineering



Corradi et al. *Angew. Chem. Int. Ed.* 2000, 39, 1782.

Drug development

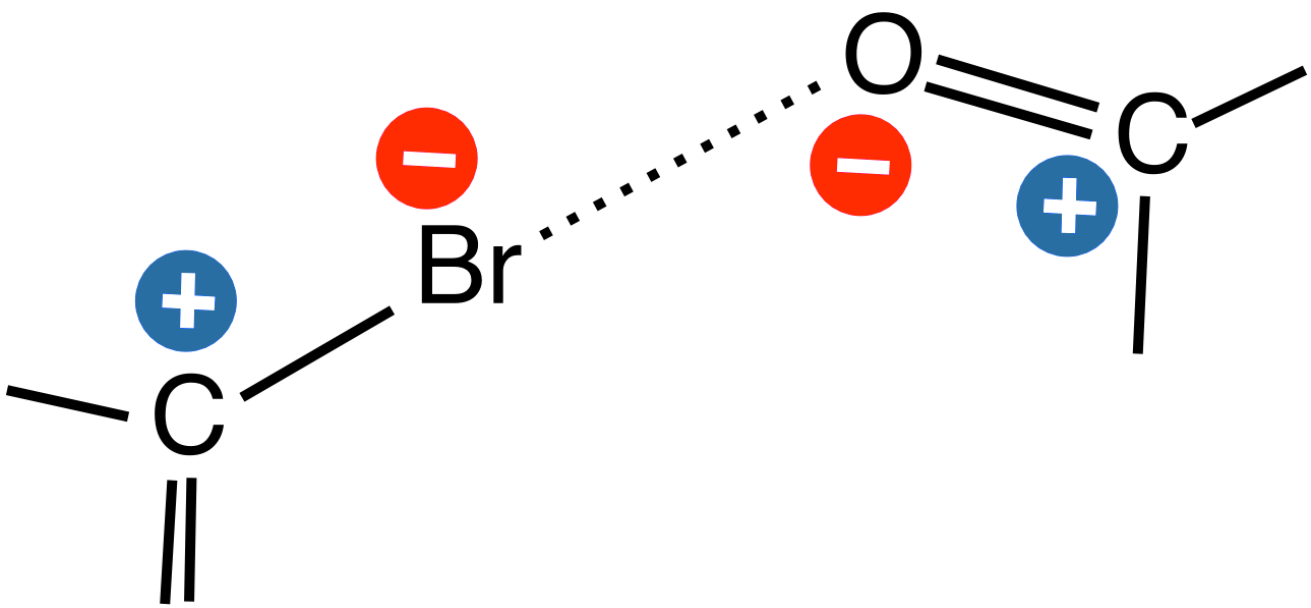


Steuber et al. *J. Mol. Biol.* 2007, 368, 618.

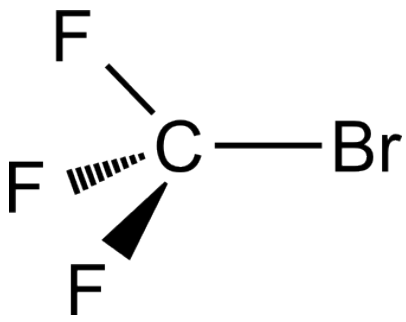
Electronegativity

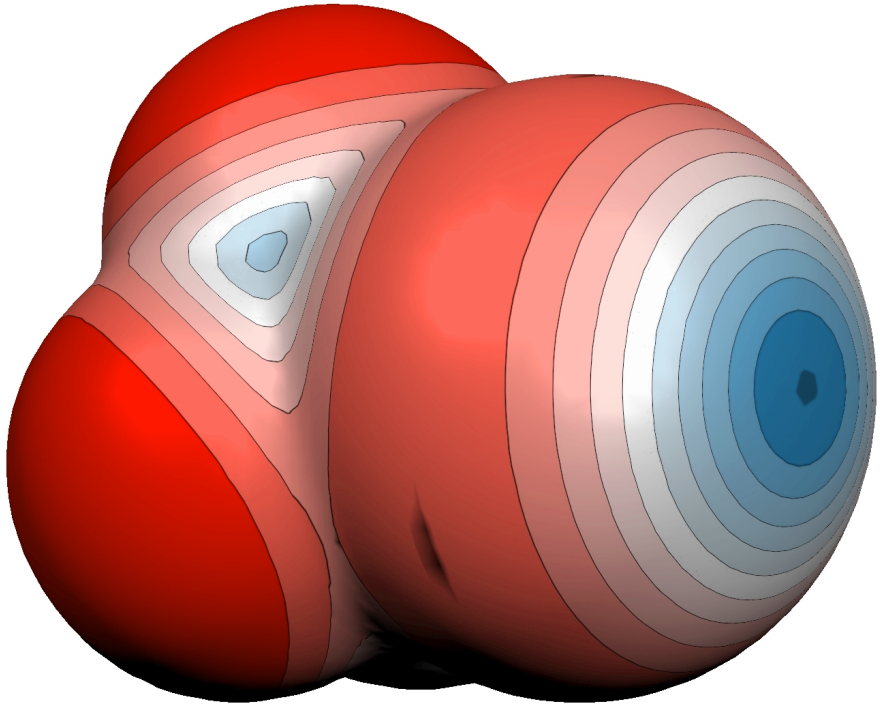
chlorine	3.2
bromine	3.0
iodine	2.7
carbon	2.6
oxygen	3.0

Violation of Coulomb's law



Sigma-hole (σ-hole)





Computer modeling

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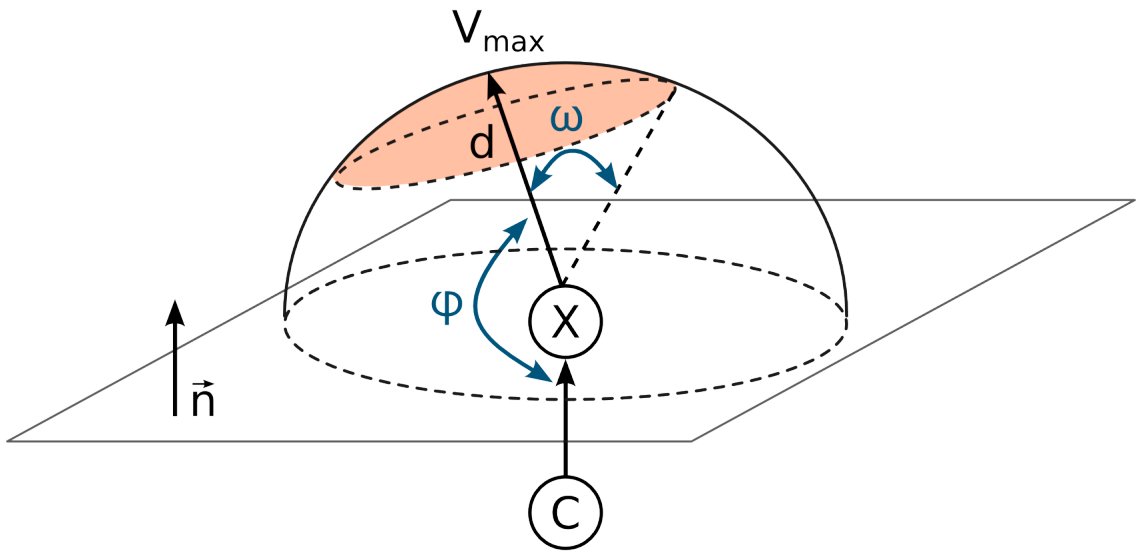
Sigma-hole properties

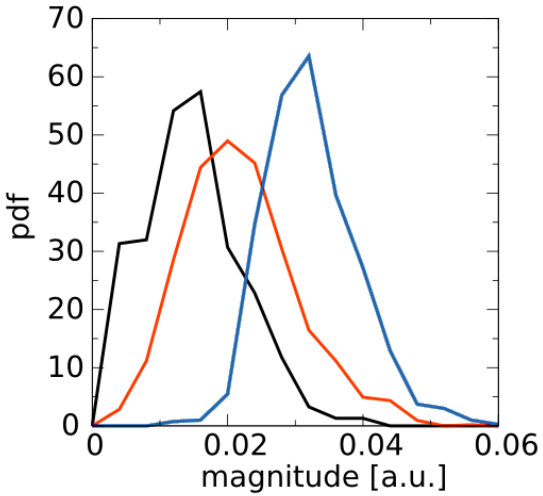


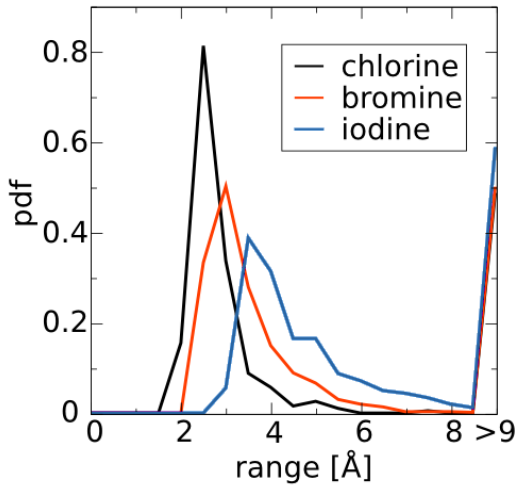
- magnitude
- size
- position
- range

Kolář, Carloni, Hobza, PCCP 2014, 16, 19111.

Analysis of ZINC database

- σ-holes of 2400 drug-like molecules analyzed
- size and magnitude correlate
- intramolecular polarization plays a minor role in positioning



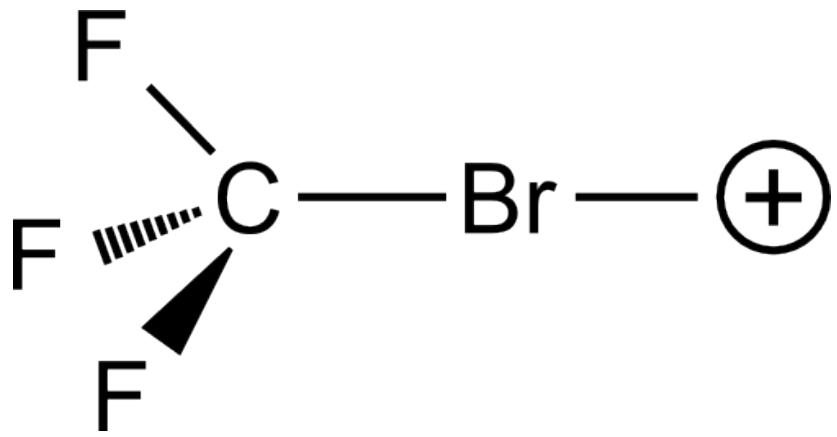


Biomolecular/halogen force fields

State-of-the-art

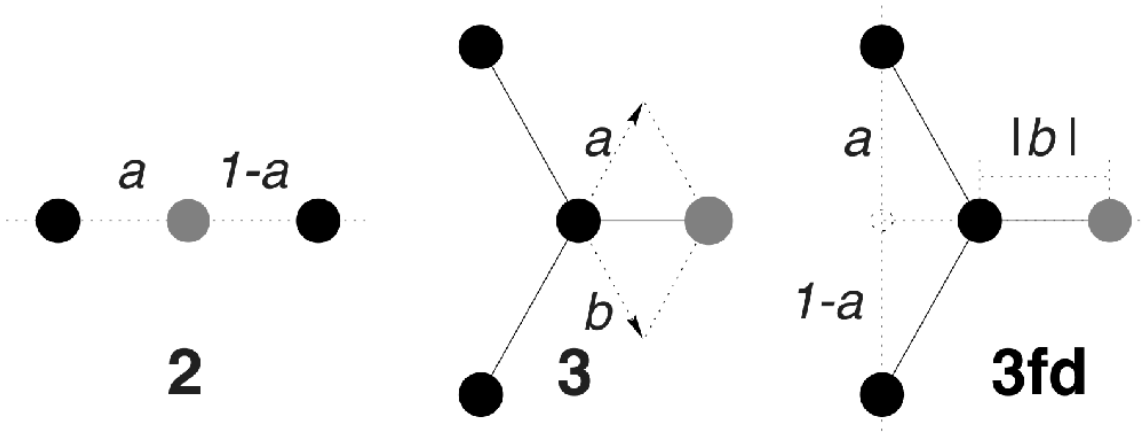
- pairwise non-bonded part
- partial atom-centered point charges (fixed)
- 12-6 Lennard-Jones potential
- transferable parameter sets
- overall effective potentials

Explicit sigma-hole



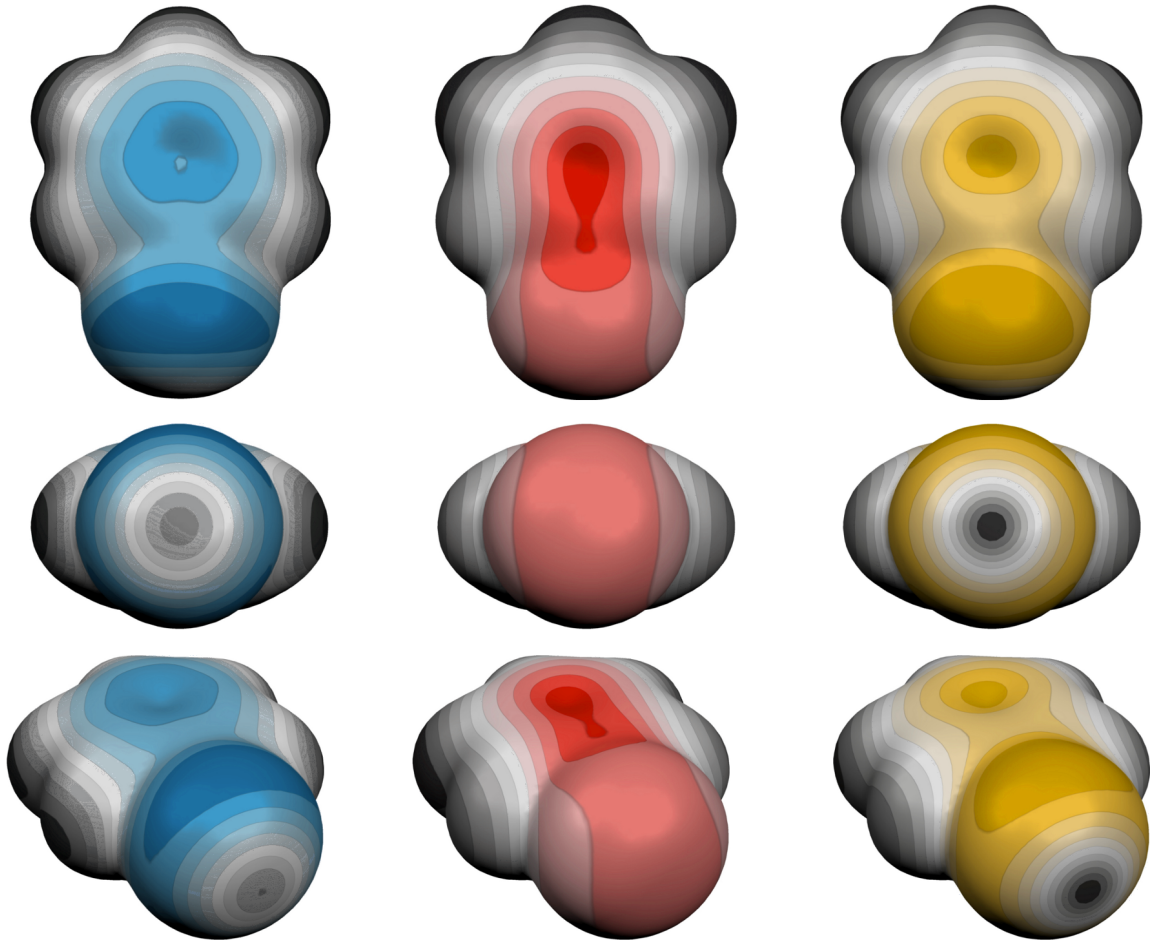
Kolář, Hobza, JCTC 2012, 8, 1325.

Virtual sites in Gromacs

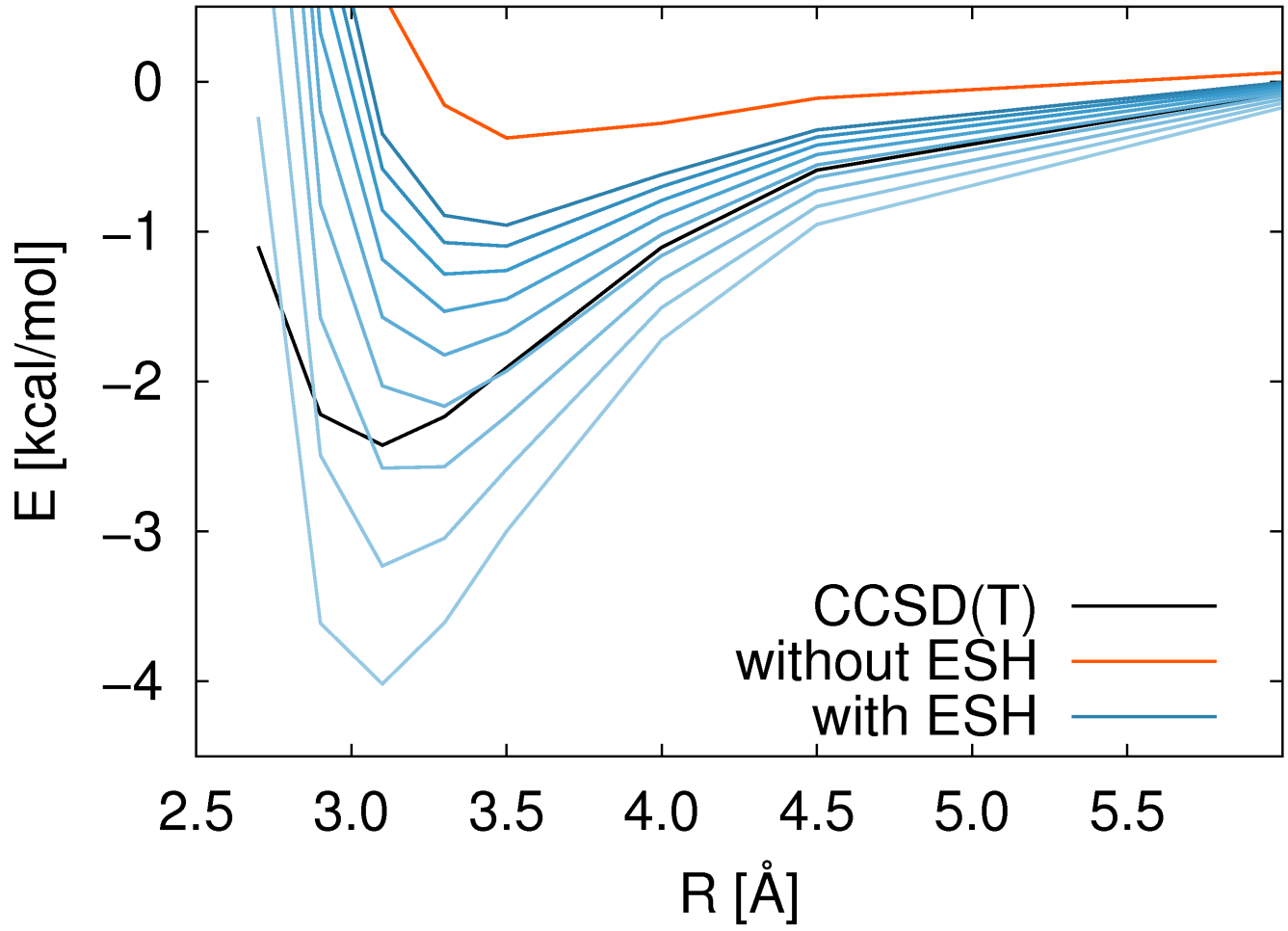


- typically used for speeding up simulations or TIP4P water
- modeling of electron lone pairs (Dixon, Kollman, J. Comput. Chem, 1997, 18, 1632)
- modeling of graphene sheets (Kocman et al. PCCP 2014, 16, 3152)

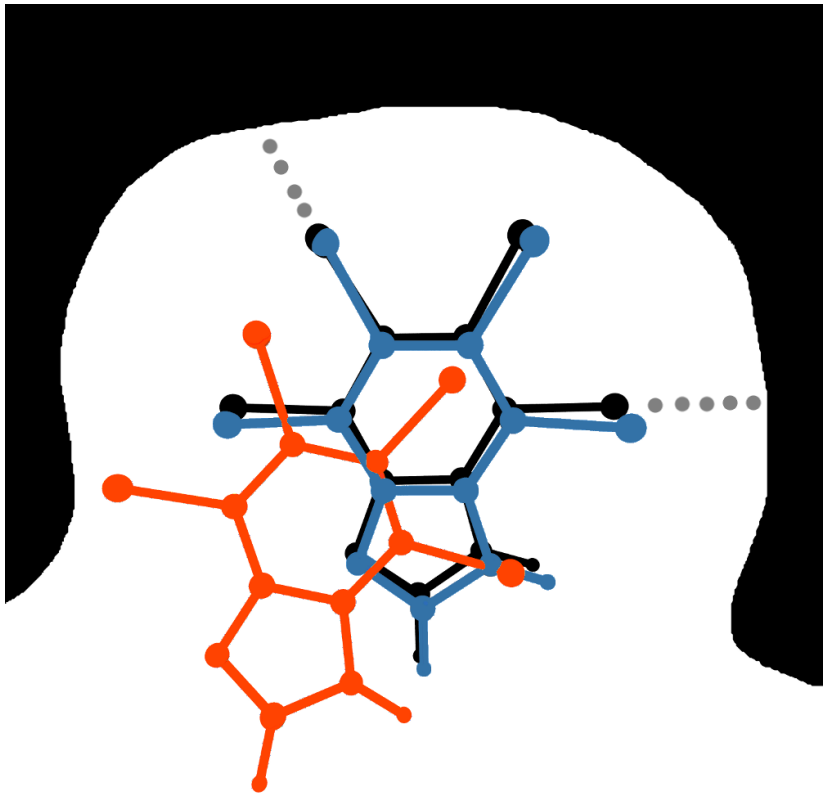
Electrostatic potential of bromobenzene



Disociation of a gas phase complex

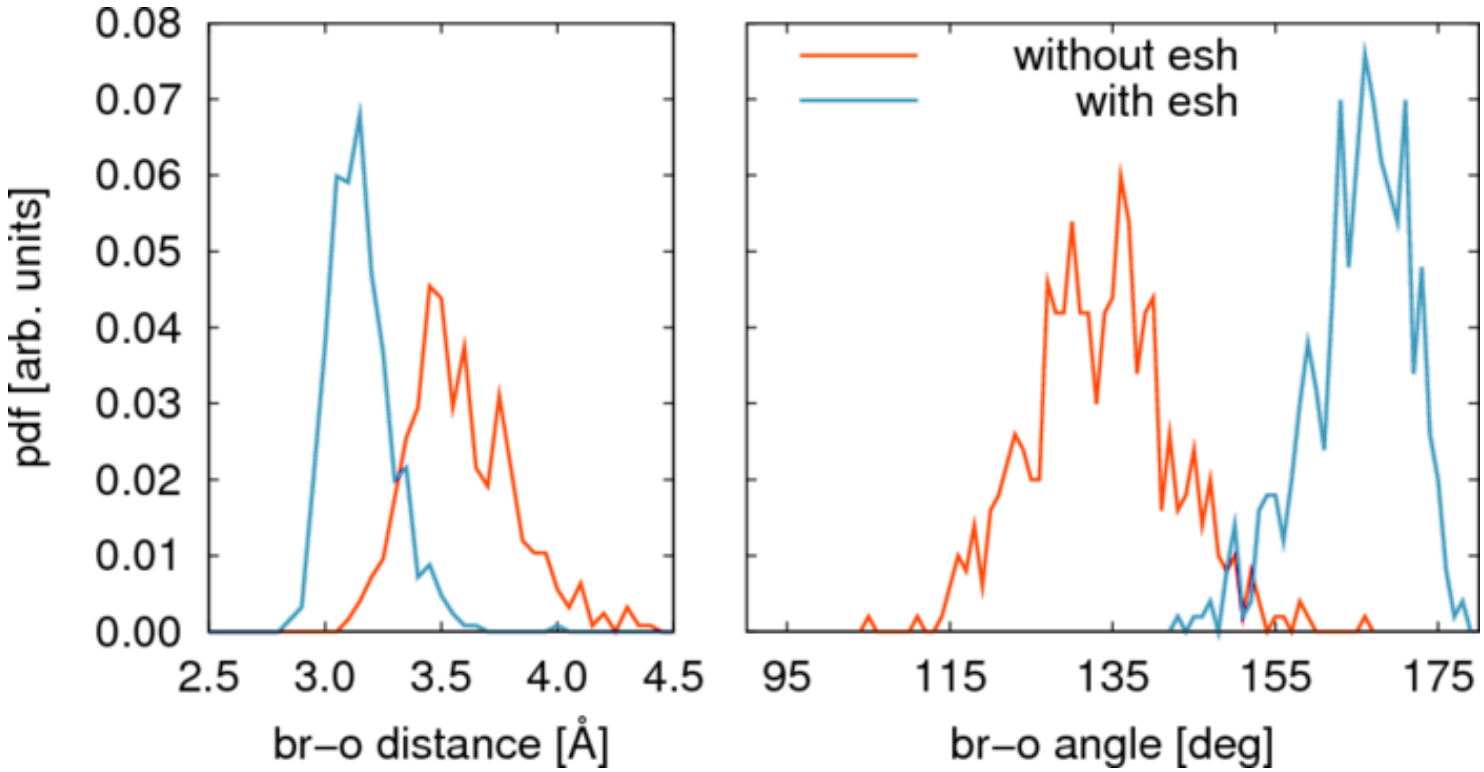


Geometry



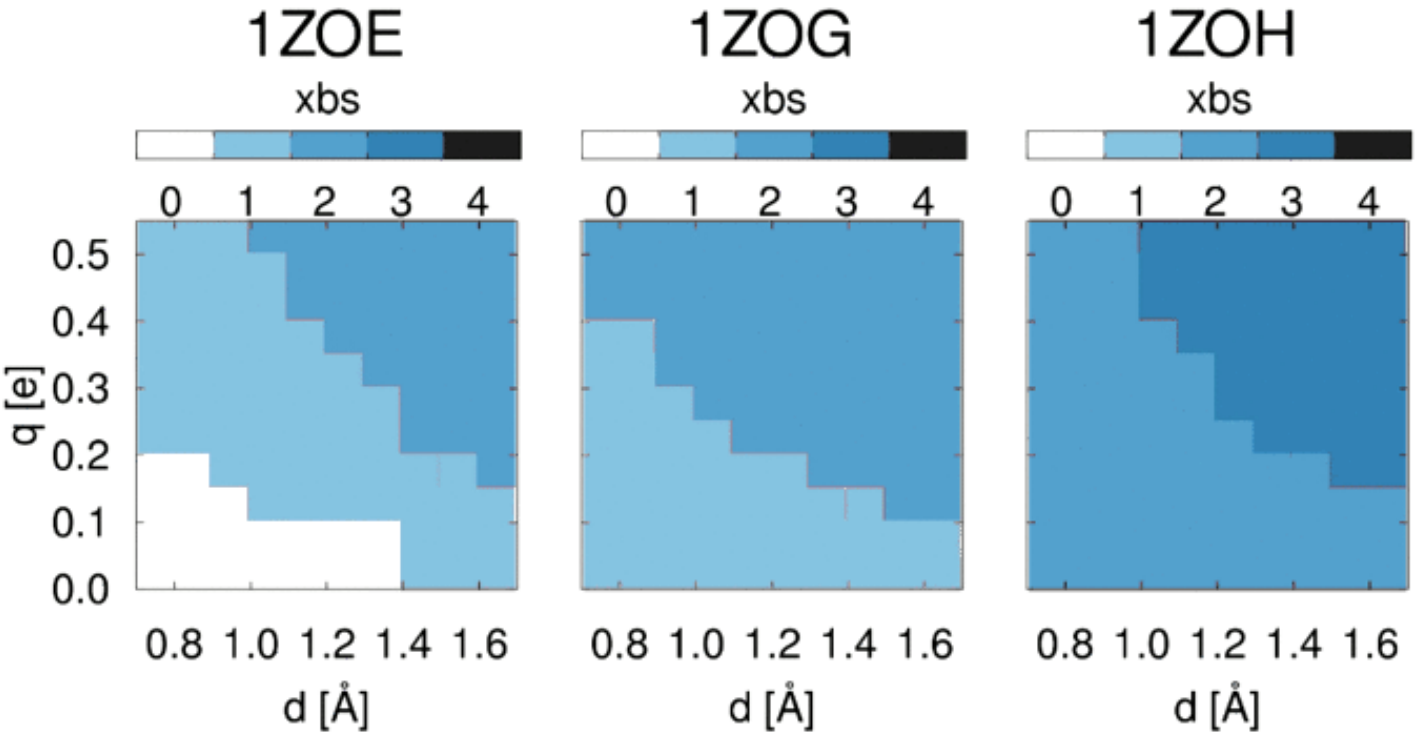
- protein kinase CK2 active site
- two halogen bonds

Dynamics



- aldose reductase molecular dynamics

Parameter dependence



- number of halogen bonds of three CK2 complexes

Molecular docking

- prediction of protein-ligand structure
- even simpler potentials
- 90 of 92 complex structures reproduced with ESH model
- Kolář et al. Chem. Commun. 2013, 49, 981.

Other ff-based methods

off-center point charge models with minor differences

- Ibrahim, J. Comput. Chem. 2011, 23, 2564.
- Rendine et al. PCCP 2011, 43, 19508.
- Jorgensen, Schyman, JCTC 2012, 8, 3895.

angle-dependent Lennard-Jones term

- Carter et al. JCTC 2012, 8, 2461.

Concluding remarks

- atom-centered charge models fail in description of charge anisotropy
- off-center model helps improve electrostatics
- not necessarily related to the overall quality of results
- remains unclear its performance on free energies

Further reading

Kolář, Carloni, Hobza, PCCP 2014, 16, 19111
: 3D sigma-hole characteristics, ZINC analysis

Kolář, Hostaš, Hobza, PCCP 2014, 16, 9987
: 2D sigma-hole characteristics, energy decomposition

Kolář et al. Chem. Commun. 2013, 49, 981
: sigma-holes in molecular docking

Kolář, Hobza, JCTC 2014, 8, 1325
: explicit sigma-holes