Halogen bonds, $\sigma$-holes
and molecular mechanics of modern drug candidates

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People involved, funding

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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

Drug development


## Electronegativity

<table>
<thead>
<tr>
<th>Element</th>
<th>Electronegativity</th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorine</td>
<td>3.2</td>
</tr>
<tr>
<td>bromine</td>
<td>3.0</td>
</tr>
<tr>
<td>iodine</td>
<td>2.7</td>
</tr>
<tr>
<td>carbon</td>
<td>2.6</td>
</tr>
<tr>
<td>oxygen</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Violation of Coulomb’s law
Sigma-hole ($\sigma$-hole)
Computer modeling
Sigma-hole properties

- magnitude
- size
- position
- range

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

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Analysis of ZINC database

- $\sigma$-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

E [kcal/mol]

R [Å]

CCSD(T)
without ESH
with ESH
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
Other ff-based methods

- Off-center point charge models with minor differences
  - 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