Electronic Supplementary Information (ESI) for Chemical Communications

Plugging the explicit σ-holes in molecular docking

Michal Kolář,[a,b] Pavel Hobza[a,c] and Agnieszka K. Bronowska*[d,e]

[a] *Institute of Organic Chemistry and Biochemistry and Gilead Science Research Center, Academy of Sciences of the Czech Republic, Flemingovo nam. 2, 16610 Prague 6, Czech Republic.*
[b] *Department of Physical and Macromolecular Chemistry, Faculty of Science, Charles University in Prague, Albertov 6, 12843 Prague 2, Czech Republic.*
[c] *Department of Physical Chemistry, Palacký University, Olomouc 77146 Olomouc, Czech Republic.*
[d] *Faculty of Chemistry, University of Heidelberg, Im Neuenheimer Feld, D-69115 Heidelberg, Germany.*
[e] *Heidelberg Institute for Theoretical Studies, Schloss-Wolfsbrunnenweg 35, D-69118 Heidelberg, Germany. Fax: +49 6221 533298; Tel: +49 6221 533510; E-mail: agnieszka.bronowska@h-its.org*

Materials and Methods

In this work, the following protein-ligand complexes were studied: 1IEI, 1US0, 1Z89, 1Z8A, 2IKI, 2IKJ, 2PFH, 2R3F, 1H07, 2VU3, 2R3K, 1WCC, 1PXI, 1FVT, 1H1R, 1H08, 1H01, 2R3J , 2J9M, 2V22, 2R3Q, 2I40, 2C68, 1P5E, 3MY5, 2VTJ, 2R3R, 2R3P, 1Y8Y, 1YKR, 3UNK, 2R3L, 2IW6, 2C69, 3LFS, 2VTR, 2B54, 2BHE, 3LE6, 3KXH, 2OXX, 1ZOH, 3PVG, 3KXG, 1ZOG, 3KXN, 1J91, 2PVK, 2OXY, 3KXM, 2QC6, 2OXD, 1ZOE, 3NGA, 3RPS, 1HNV, 1HNI, 3DYA, 3DLE, 3C6U, 2VG6, 1TKZ, 3MEC, 2VG5, 1FK9, 1TL1, 1RT5, 3C6T, 1VRU, 1RT6, 3I0R, 3FFI, 3DI6, 2RKI, 1TL3, 1RT7, 3E01, 2RF2, 1EP4, 3T19, 3DRP, 2VG7, 1TKT, 3I0S, 3DLG, 1DTT, 3R8D, 3QIN, 3HYF, 1JLG, 2YKM, 1IKX.

The charges of the ligands were assigned by the UCSF Chimera program suite[1] at the AM1-BCC level in a standard manner.[2] Then, the ESH was constructed as the nF model[3] as described in Kolář and Hobza:[4] the dummy atom with a desired positive charge was added to the halogen and the charge of the halogen was lowered by the same value. Hence, the net charge of the ESH-halogen pair remained identical as the initial halogen atom charge. None of the other atoms was modified. This model is well suited for high-throughput calculations since it does not require any additional quantum chemical calculation, once the atomic partial charges are known. On the other hand the effect of sigma-hole is reduced only to the vicinity of the halogen. Nevertheless, its performance on interaction energies was proven to be sufficient.[4]

The ESH was added to all halogen atoms except fluorine, which is known not to create halogen bonds in organic drug-like molecules.[5] The ESH parameters (charge, ESH-halogen distance) were chosen as follows and were not subject of any further optimization: (0.1 e, 1.0 Å) for chlorine, (0.2 e, 1.3 Å) for bromine, and (0.3 e, 1.6 Å) for iodine. These parameters follow the recommendation in Ref. 14 and also the known features of halogens, where iodine exhibits the largest σ-hole and chlorine the smallest. The ESH-halogen distance was, however slightly shortened when compared with Ref. 14 (i.e. 1.3 Å vs. 1.5 Å for bromine). Large ESH-halogen distance caused problems with the docking algorithm. Consequently, the change in improved scoring arises mainly from the improved electrostatics and also

from the shape complementarity between ligand and receptor (distances being corrected for the presence of dummy atom mimicking the sigma-hole).

Molecular docking was performed using UCSF DOCK6.5 suite, [6] using a grid scoring, in an implicit solvent. The grid spacing was 0.25 Å, and the grid box included 12 Å beyond the ligand binding site. The energy score has been regarded as a sum of electrostatic and Van der Waals contributions. In the course of the docking procedure, the ligand was subjected to 2500 cycles of molecular-mechanical energy minimization. The number of maximum orientations was 5000.

References:

1 E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng, T. E. Ferrin, *J. Comput. Chem.*, 2004, **25**, 1605.

2 A. Jakalian, D. B. Jack, C. I. Bayly *J. Comput. Chem*., 2002, **23**, 1623.

3 The script used to introduce ESH into MOL2 files is available upon request.

4 M. Kolář, P. Hobza, *J. Chem. Theory Comp*., 2012, **8**, 1325.

5 P. Politzer, K. E. Riley, F. A. Bulat, J. S. Murray, *Comput. Theor. Chem.*, 2012, **998**, 2.

6 P. T. Lang, S. R. Brozell, S. Mukherjee, E. F. Pettersen, E. C. Meng, V. Thomas, R. C. Rizzo, D. A. Case, T. L. James, I. D. Kuntz, *RNA*, 2009, **15**, 1219.