3D MOLECULAR FRAGMENT DESCRIPTORS FOR STRUCTURE-PROPERTY MODELING

Vitaly Solov'ev [a], Andrey Solovev [b]

[a] *A.N. Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Leninskiy prosp., 31, 119071 Moscow, Russia*
[b] *School of Software Engineering, Faculty of Computer Science, National Research University Higher School of Economics, Moscow, Russia*
E-mail: solovev-vp@mail.ru

Summary

We report new **3D** fragment descriptors to model parameters and properties of stereoisomeric molecules and conformers. New **3D** fragment descriptors have been applied to discriminate between stereoisomers in predictive QSPR modeling of the standard free energy (ΔG°) for the 1:1 inclusion complexation of enantiomeric pairs of chiral compounds with β-cyclodextrin in water at 298 K.

Problem

2D molecular fragment descriptors are one of the most important types of descriptors used for design of substances with the desired properties by Quantitative Structure Property Relationship (QSPR) modeling [1, 2]. Despite many advantages of 2D fragment descriptors, there is a problem of modeling of molecular properties, which depend on stereochemical molecular structure [1]. In this work for the QSPR modeling of various physical and chemical properties, as well as biological activity, the problem was overcome by developing of new **3D** molecular fragment descriptors taking into account spatial arrangement of fragment atoms.

Method

1 Optimization of the 3D structures of molecules

The preliminary optimization of the 3D structures of molecules was performed using MM+ molecular mechanics force field, then a more precise optimization was carried out with the semi-empirical PM3 method in HyperChem using the Polak–Ribiere algorithm.

2 Generation of 2D subgraphs of molecular graph of 3D molecular structure

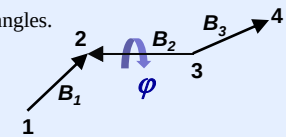
Initially similar to 2D fragment descriptors [2], **3D** fragment descriptors were generated as subgraphs of molecular graph of **3D** molecular structure. For every pair of atoms in molecule, the shortest chains of bonded atoms were chosen as subgraphs.

3 Calculation of bond and dihedral angles of generated fragments of molecule

a). The law of cosines was used for the estimation of the bond angles.

b). The calculation of the dihedral angles:

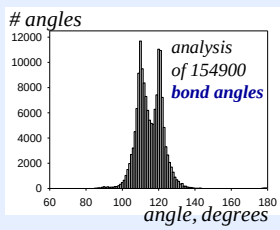
1, 2, 3 and 4 are atoms, B_1, B_2 and B_3 are bonds

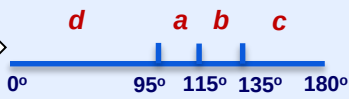


$$\varphi = ArcTan2(y, x)$$
$$x = \mathbf{n}_1 \cdot \mathbf{n}_2,\ y = \mathbf{m} \cdot \mathbf{n}_2$$
$$\mathbf{n}_1 = \mathbf{b}_2 \times \mathbf{b}_1,\ \mathbf{n}_2 = \mathbf{b}_3 \times \mathbf{b}_2,\ \mathbf{m} = \mathbf{b}_2 \times \mathbf{n}_1$$
$$\mathbf{b}_i = \mathbf{B}_i / ||\mathbf{B}_i||,\ \mathbf{B}_i = \mathbf{r}_{i+1} - \mathbf{r}_i,\ i = 1, 2, 3$$

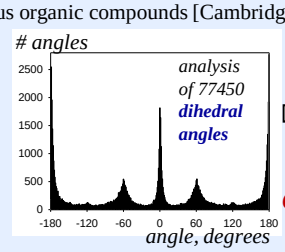
4 Categorization of bond and dihedral angles into basic groups

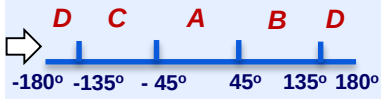
Distributions of bond and dihedral angles of 978 various organic compounds [Cambridge Structural Database]





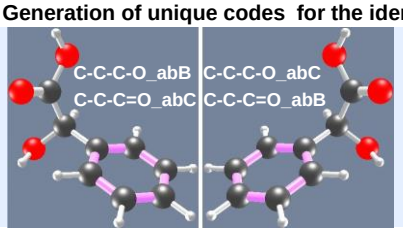
categories of bond angles





CATEGORIES of dihedral angles

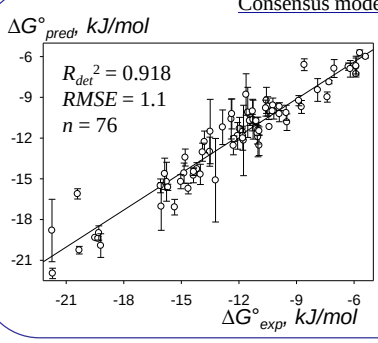
5 Generation of unique codes for the identification of 3D fragment descriptors



Demonstration of similar 3D fragment descriptors for the enantiomers: (*R*)- and (*S*)-mandelic acid

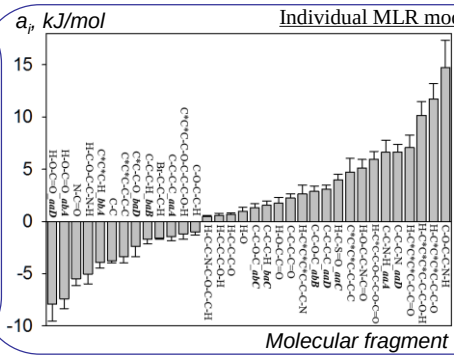
Results

Consensus model



Predicted versus experimental values of the standard free energy for the 1:1 inclusion complexation of chiral compounds with β-cyclodextrin in water. The predicted data represent a combination of the five external test sets of the 5-fold cross-validation.

Individual MLR model



QSPR modeling of standard free energy ΔG° for the 1:1 inclusion complexation of 38 enantiomeric pairs of chiral compounds with β-cyclodextrin:
fragment contributions (a_i) in the individual MLR model
$\Delta G^\circ = \sum_{i=1}^{k} a_i N_i$, where N_i is an occurrence of the ith fragment in chiral compound. The fragment type is a combination of the 2D and **3D** fragments.

Conclusions

New **3D** molecular fragment descriptors recognize quite clearly different stereoisomeric molecular forms and conformers. The models based on the compositions of the 2D and **3D** fragment descriptors discriminate between the two stereoisomers predicting the different free energies for antipodal guests in the 1:1 inclusion complexation of chiral guests with β-cyclodextrins in water.

References

1. Baskin I. and Varnek A. , Fragment Descriptors in SAR/QSAR/QSPR Studies, Molecular Similarity Analysis and in Virtual Screening, in *Chemoinformatics Approaches to Virtual Screening*, A. Varnek, A. Tropsha, Eds. Cambridge: RCS Publishing, 2008, pp. 1 – 43.
2. Solov'ev, V.P., Varnek, A.A., Wipff, G.: Modeling of Ion Complexation and Extraction Using Substructural Molecular Fragments. *J. Chem. Inf. Comput. Sci*. 40(3), 847-858 (2000)