Molecular Informatics 2016 vol.35 N11-12, pages 629-638

Predictive Models for the Free Energy of Hydrogen Bonded Complexes with Single and Cooperative Hydrogen Bonds

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Abstract

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, WeinheimIn this work, we report QSPR modeling of the free energy ΔG of 1 : 1 hydrogen bond complexes of different H-bond acceptors and donors. The modeling was performed on a large and structurally diverse set of 3373 complexes featuring a single hydrogen bond, for which ΔG was measured at 298 K in CCl4. The models were prepared using Support Vector Machine and Multiple Linear Regression, with ISIDA fragment descriptors. The marked atoms strategy was applied at fragmentation stage, in order to capture the location of H-bond donor and acceptor centers. Different strategies of model validation have been suggested, including the targeted omission of individual H-bond acceptors and donors from the training set, in order to check whether the predictive ability of the model is not limited to the interpolation of H-bond strength between two already encountered partners. Successfully cross-validating individual models were combined into a consensus model, and challenged to predict external test sets of 629 and 12 complexes, in which donor and acceptor formed single and cooperative H-bonds, respectively. In all cases, SVM models outperform MLR. The SVM consensus model performs well both in 3-fold cross-validation (RMSE=1.50 kJ/mol), and on the external test sets containing complexes with single (RMSE=3.20 kJ/mol) and cooperative H-bonds (RMSE=1.63 kJ/mol).

http://dx.doi.org/10.1002/minf.201600070

Keywords

free energies of single and cooperative hydrogen bonds, hydrogen bonding strength, QSPR