Theoretical Study of the Nature of S-π Interactions, Their Role in Activation Process of Dopamine D_2 Receptor and Comparison with Se-π Systems

M. Senćanski[1*] and S. Grubišić[2]

[1]*Center for Multidisciplinary Research and Engineering, Institute of Nuclear Sciences Vinča, University of Belgrade, Mike Petrovića Alasa 12-14, 11001 Belgrade, Serbia*
[2]*Center for Chemistry, Institute for Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia*
[*]*Corresponding author:* sencanski@vin.bg.ac.rs

Amino acids Cysteine (Cys) and Methionine (Met) are frequent in proteins and responsible for their stability (e.g. cysteine disulphide bridges) and activity. They play major roles in catalytic sites of the enzymes, and form SH-π (or S-π) interactions with aromatic amino acid residues in protein which also highly contribute to the stability of structure. Although SH-π and S-π interactions were widely described [1-3], there is still much unknown about the nature of their interactions if substituents are present on aromatic ring. This research of the nature of S-π interactions in case of substituted aromatic systems has been stimulated by the recent experiments with fluorine substitution in phenylalanine and tryptophan of D_2 receptor [4]. Analogously to the research of CH-π interactions [5], DFT calculations were used to study substituted benzenes in complex with H_2S, CH_3SH, and CH_3SCH_3, as models for Cys and Met. The results of calculations showed that SH-π interactions had lower energy than S-π interactions. Opposite trends in changes of interaction energies between SH-π and S-π cases were observed with increasing electronegativity of the substituent on benzene ring. We also investigated the model system of Cys⋯Trp interaction in D_2 receptor, as well as adjacent cluster of aromatic amino acids in its active site by constructing the ideal model system of adjacent benzene rings. The results showed that fluorination of benzenes in aromatic cluster transmits electrostatics influence through space and enhances the Cys⋯Trp interaction. This effect is enhanced when transmission occurs through the rest of benzene rings, which suggests possible explanation in mechanism of D_2 receptor activation. [6] In order to interpret difference in nature of S-π and Se-π interactions, we also report extensive DFT calculations of dispersive and electrostatic contributions in Se-π interactions and comparison with S-π calculations. The results show larger contribution of dispersive interactions in case of Se-π systems rather than S-π, which mainly originate from the interaction of Se and substituent groups.

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