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A Study on Conformational Similarity of the (R)- and (S)-Enantiomers of Rivastigmine and the Binding Features with AChE by MO Calculations

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Rivastigmine is a carbamate inhibitor of acetylcholinesterase(AChE) in use for treatment of Alzheimer's disease(AD). The (S)-enantiomer has a 10-fold affinity for brain G1 AChE and better stability than the (R)-enantiomer. The nitrogen in the trimethylamine moiety of rivastigmine was assumed to be protonated in the physiological pH range. Nevertheless, the nitrogen in the carbamate seems unprotonated. Both rivastigmine and acetylcholine were found to be a monocationic ligand in an aqueous solution and organic solvents, suggested by the proton affinities calculated using the solvent PCM model. This study is concentrated on the conformation analyses by the potential energy surfaces (PES) using ab initio MO calculations at a B3LYP/6-31G** level of theory. The lowest-energy conformation of each enantiomer of rivastigmine was calculated at B3LYP/6-31G** and the two similar conformations were folded with the C-H...O=C weak hydrogen bond, for example 2.37 angstroms for the (S)-enantiomer. The methyl group attached on the asymmetric carbon might effect on the pharmacological reactivity. For the complex with NAP and the carbamyl moiety group, bound to the OG of SER 200 of AChE, modeled based on the X-ray structure previously analyzed, the interaction energy was decomposed by Kitaura-Morokuma method at HF/6-31G. In the complex, the intermolecular C-H...O=C weak hydrogen bonds were observed (2.16 and 2.82 angstroms) and contribute to its stability. PT and CT energies were compared with the data previously reported for a H-bond complex.