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AN ASPARTATE-AMINE SALT BRIDGE – THE ETS-NOCV STUDY

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The human G-protein-coupled receptors (GPCRs) represent the most important set of potential therapeutic targets.[1] It is well known that the ligand binding site of aminergic GPCRs is located within the transmembrane (TM) region of the receptor and $D^{3.32}$ is common as an anchoring point throughout the entire biogenic amine family.[1-3] Aspartic acid acting as the counterion for the charged amine, forming the interaction responsible for a correct ligand orientation.[4] Theoretical study indicated that $D^{3.32}$ is directly involved in agonist and antagonist binding for the aminergic GPCRs.[5] Considering the above, it was reasonable to undertake advanced theoretical study on the nature of salt bridge, which are exactly the double charge-assisted hydrogen bond (+/-CAHB). For this purpose, the ETS-NOCV (the natural orbitals for chemical valence (NOCV) combined with extended-transition-state method (ETS), [6]) calculations were performed for the model systems representing the all possible scenarios in biological interactions.

E_1^{σ}=-27.3 kcal/mol E_2^{σ}=-3.6 kcal/mol E_3^{σ}=-2.8 kcal/mol

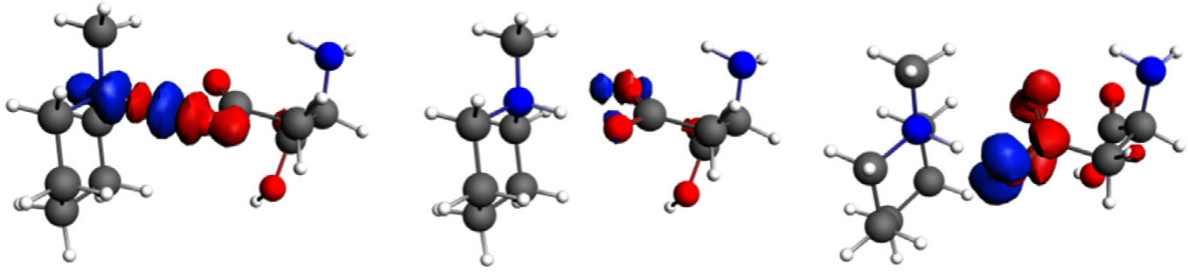

Figure: *N*-methyl-piperidinum – aspartate.

The results indicated that the main force of +/-CAHB is the charge transfer from an oxygen atom of aspartic acid. The binding is enhanced by the flow of electron density between the oxygen atoms of D, as illustrated by the third π-type orbital NOCV.

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