

Formation of the Water Assisted Supramolecular Assembly in the Transition Structure of Organocatalytic Asymmetric Aldol Reaction: A DFT Study

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Abstract : Aldol reaction is an important class of carbon-carbon bond forming reactions. One of the popular ways to impose asymmetry in aldol reaction is the introduction of chiral auxiliary that binds the approaching reactants and create dissymmetry in the reaction environment, which finally evolves to enantiomeric excess in the aldol products. The last decade witnesses the usage of natural amino acids as chiral auxiliary to control the stereoselectivity in various carbon-carbon bond forming processes. In this context, L-proline was found to be an effective organocatalyst in asymmetric aldol additions. In last few decades the use of water as solvent or co-solvent in asymmetric organocatalytic reaction is increased sharply. Simple amino acids like L-proline does not catalyze asymmetric aldol reaction in aqueous medium not only that, In organic solvent medium high catalytic loading (~30 mol%) is required to achieve moderate to high asymmetric induction. In this context, huge efforts have been made to modify L-proline and 4-hydroxy-L-proline to prepare organocatalyst for aqueous medium asymmetric aldol reaction. Here, we report the result of our DFT calculations on asymmetric aldol reaction of benzaldehyde, p-NO₂ benzaldehyde and t-butylaldehyde with a number of ketones using L-proline hydrazide as organocatalyst in wet solvent free condition. Gaussian 09 program package and Gauss View program were used for the present work. Geometry optimizations were performed using B3LYP hybrid functional and 6-31G(d,p) basis set. Transition structures were confirmed by hessian calculation and IRC calculation. As the reactions were carried out in solvent free condition, No solvent effect were studied theoretically. Present study has revealed for the first time, the direct involvement of two water molecules in the aldol transition structures. In the TS, the enamine and the aldehyde is connected through hydrogen bonding by the assistance of two intervening water molecules forming a supramolecular network. Formation of this type of supramolecular assembly is possible due to the presence of protonated -NH₂ group in the L-proline hydrazide moiety, which is responsible for the favorable entropy contribution to the aldol reaction. It is also revealed from the present study that, water assisted TS is energetically more favorable than the TS without involving any water molecule. It can be concluded from this study that, insertion of polar group capable of hydrogen bond formation in the L-proline skeleton can lead to a favorable aldol reaction with significantly high enantiomeric excess in wet solvent free condition by reducing the activation barrier of this reaction.

Keywords : aldol reaction, DFT, organocatalysis, transition structure

Conference Title : ICCCECP 2015 : International Conference on Chemistry, Chemical Engineering and Chemical Process

Conference Location : Venice, Italy

Conference Dates : April 13-14, 2015