



Stabilization of the transition structures of organocatalytic asymmetric direct aldol reaction in wet solvent free condition by the formation of water assisted supramolecular network: A DFT study



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ABSTRACT

Organocatalytic asymmetric direct aldol reaction in wet solvent free medium has been studied by DFT quantum mechanical (QM) method, using L-proline hydrazide as catalyst. Present study has revealed for the first time, the direct involvement of two water molecules in the aldol transition structures (TSs). 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 $-NH_2$ group in the L-proline hydrazide moiety, which is responsible for the favorable entropic 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 (*ee*) in wet solvent free condition by reducing the activation barrier of this reaction.

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1. Introduction

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 [1–3]. In this context, L-proline was found to be an effective organocatalyst in asymmetric aldol additions. It is a well known fact that, intramolecular aldol reaction is entropically more favorable than their intermolecular counterpart. As a consequence, the first example of L-proline catalyzed asymmetric aldol reaction is an intramolecular one, reported by Hajos and Parrish [4–6], and independently by Eder, Sauer, and Wiechert in the early seventies [7,8]. During this period they published a series of papers on the L-proline-catalyzed intramolecular aldol cyclization of triketones (Scheme 1). Later, L-proline was also found to be an effective

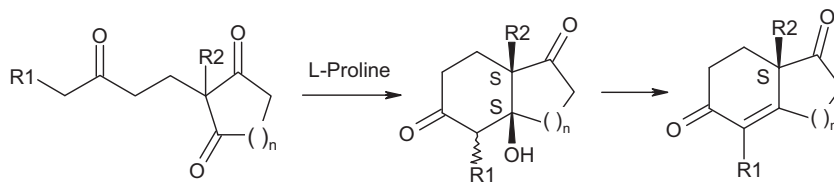
catalyst in the first examples of intermolecular organocatalyzed aldol reactions [9,10].

Two mechanisms were proposed by Hajos and Parrish, one of which involves the formation of carbinolamine intermediate, followed by the displacement of the proline moiety by nucleophilic attacks of the enol from the side chain ketone (Scheme 2A). The other one involves an enaminium intermediate acting as a nucleophile in the C–C bond formation with concomitant N–H--O hydrogen transfer (Scheme 2C).

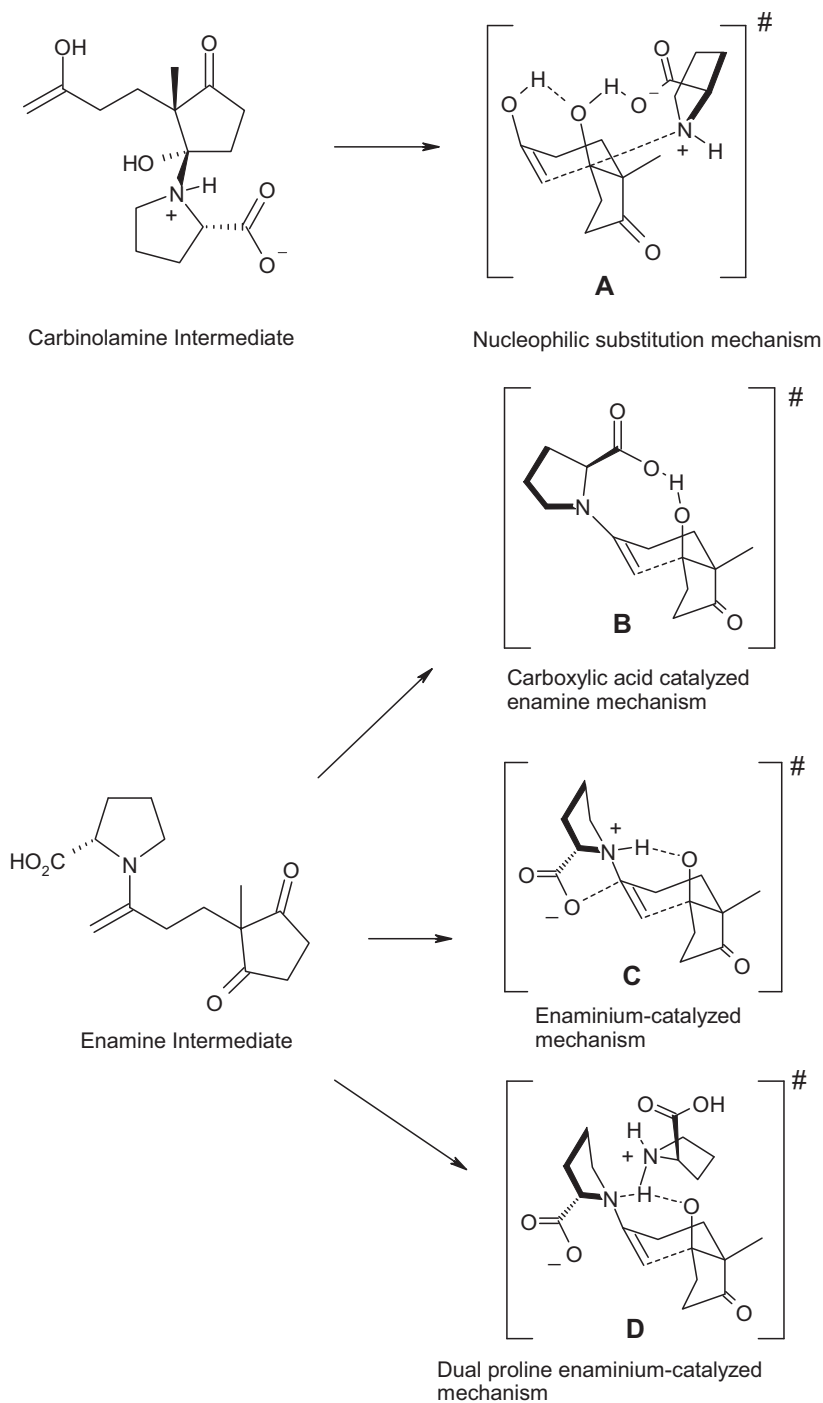
Of late, experimental evidences provided by Spencer, Wakselman, and Eschenmoser supported the formation of enamine intermediates in amine and amino acid catalyzed aldolizations [11–13]. Later studies by Agami et al. proposed the involvement of two proline molecules in the catalytic pathway (Scheme 2D) [14,15]. However, several theoretical studies as well as, recent experimental reports by List's group support one-proline mechanism [16]. The TS model proposed by this group is being named after the two principal authors; Houk and List. Of late, DFT studies on the mechanism of proline catalyzed aldol cyclization by Houk and his group have revealed that this reaction is best described by the nucleophilic addition of the neutral enamine to the carbonyl group of the acceptor together with hydrogen transfer from the proline carboxylic acid moiety to the developing alkoxide [17] (Scheme 2B). It has been observed that the enaminium TS is

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Scheme 1. L-Proline catalyzed intramolecular asymmetric aldolization of a triketone.



Scheme 2. Proposed TSs of L-proline catalyzed intramolecular aldolization of triketones.

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