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IS THE MECHANISM OF THE PROLINE-CATALYZED ENANTIOSELECTIVE ALDOL REACTION RELATED TO BIOCHEMICAL PROCESSES ?

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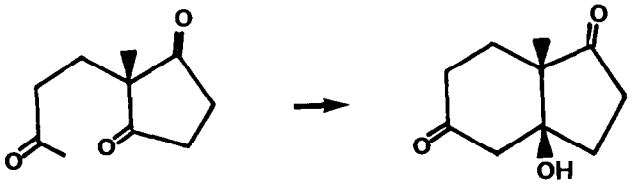
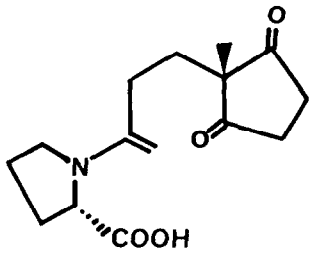
Abstract - The enantioselectivity shown by the title reaction is explained by an intramolecular hydrogen bond in an enamine intermediate resulting from nucleophilic catalysis by one molecule of proline and by a proton transfer mediated by a second molecule of proline.

The amino acid-catalyzed Robinson annulation,[1,2] one of the earliest efficient enantioselective condensations is still a benchmark reaction among asymmetric syntheses. Although the relevant synthetic applications[3] were undertaken without delay, most of the mechanistic features were reported only recently.



We wish to present a mechanistic model which is consistent with the following facts : (i) the stereodifferentiation is based on hydrogen bonding,[1] (ii) replacement of the amino acid carboxylate by a derived function leads to a lowering of the enantioselectivity,[4] (iii) (S)-proline induces a *si*-enantiofacial selectivity,[5] (iv) a non-enantioselective condensation can compete with the asymmetric synthesis,[6,7] (v) two molecules of proline are involved during the enantiodifferentiating step.[7,8]

Proline, the most suitable amino acid, has a secondary amine function and is therefore able to transform the side-chain carbonyl into an enamine moiety Nucleophilic attack of the enamine at a ring carbonyl group gives rise to the cyclization . A closely related condensation occurs during the Stork reaction between methyl vinyl ketone and a pyrrolidine enamine.[9] The selective activation of the side-chain carbonyl results from the known greater reactivity of the less substituted tertiary enamines;[10] an inverse trend has been recently repor-

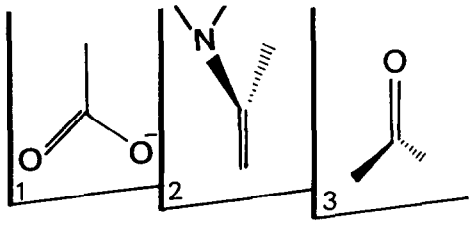


ted[11] with secondary enamines (resulting from primary amines) where alkylation occurs at the most substituted position. This explains why phenylalanine is the most suitable catalyst[6,12] for the enantioselective annulation of triketones whose side-chain carbonyl is bonded to a group other than methyl. No bridged ketol arising from activation of the ring carbonyl groups has been reported during proline (or pyrrolidine) catalyzed annulation,[1,13] whereas such ketols have frequently been described during achiral acid- or base-catalyzed Robinson annulation.[14]

Actually, the dominant problem concerns the stereoselectivity. The cis nature of the ring junction produced is well documented when achiral catalysts are involved,[15] and can be understood as a consequence of the steric hindrance due to the angular methyl which forces nucleophilic attack to occur from the opposite side. On the other hand, the preference for attack at the si face of the pro R carbonyl group versus attack at the re face of the pro S analogue is a crucial matter.

At this stage it is worthy to note that one of the most famous biochemical processes exhibits striking similarities with this reaction : muscle aldolase catalyses the stereospecific condensation of the enzyme bound enamine of dihydroxyacetone phosphate with D-glyceraldehyde.[16] Two of the main features which govern the aldolase-catalyzed condensation are: (i) the occurence of an intramolecular proton transfer from an iminium ion to the incipient hydroxyl group of the ketol,[17] (ii) a multi-layered organization of the reaction centers.[18] The mechanism of this enzymatic reaction obviously pertains to the proline-catalyzed aldol reaction; moreover it should be pointed out that enamines are often invoked in biochemical processes involving Schiff base formation.[19,20]

As regards the Hajos-Parrish condensation, the stereoselectivity stands out from the following spatial prerequisite. Three parts of the enamine intermediate are set into three parallel planes : the carboxylate group of the proline moiety (plane 1), the double bond of the enamine (plane 2) and one of the diastereotopic ring carbonyl groups (plane 3). The relative arrangement of planes 1 and 2 allows an electrostatic stabilization of the incipient iminium cation by the anionic carboxylate group.[21] Such interactions are well-known in biochemical processes[22] and a very similar example has been described in connection with rhodopsin biochemistry.[23] As a result, the proline nitrogen atom is chiral and this is the



starting point for the asymmetric induction. The relative arrangement of planes 2 and 3 is stabilized when a hydrogen bond between the carbonyl group and the protonated nitrogen atom is possible (this structure corresponds to the zwitterionic form of proline). Molecular models show that, with (S)-proline as catalyst, this hydrogen bond is feasible as long as the pro R ring carbonyl is involved (fig. 1). The relative disposition of the chiral nitrogen atom and the prochiral pro S ring carbonyl precludes such an intramolecular hydrogen bond (fig. 2).

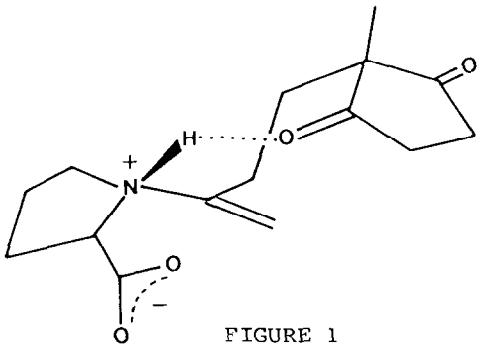


FIGURE 1

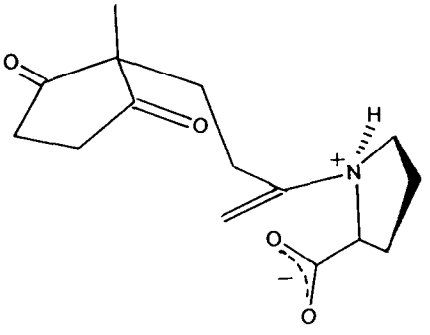
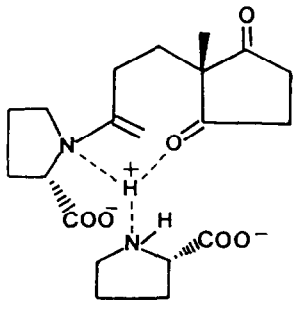


FIGURE 2

Although satisfactory from a stereochemical point of view, the involvement of a protonated enamine moiety suffers from an important drawback. Thus, the nucleophilic property of the enamine should vanish if the nitrogen electron pair is engaged in a bond to hydrogen. The presence of a second proline molecule as an additional site for the hydrogen bond removes this contradiction. The electron pair of the first proline moiety is now available within a dynamic system where the proton shifts among three acceptor sites. Therefore, the proton transfer is mediated by the second molecule of proline.



In conclusion, it appears that the amino acid catalyst (the simplest model of an enzyme !) plays a dual role and this is the main analogy between the biochemical and the nonbiochemical enantioselective aldol reaction processes.

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