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Proline- and thioproline-derived enamines: The theoretical study of torsional and ring-puckering conformations

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ABSTRACT

Proline and its derivatives catalyze Mannich and aldol reactions by forming enamine with ketone substrates. The conformations of such enamine play an important role in stereochemistry of the final products. In this study, the conformational features of proline- and thioproline-derived enamine which are derived from the reaction of cyclohexanone with (S)-proline and (R)-thioproline, respectively, are investigated theoretically using B3LYP and MP2. For proline-derived enamine, two ring-puckering conformations *i.e. up* (*u*) and *down* (*d*) puckered of pyrrolidine ring were located as minima. The conversion from *d* to *u* puckered conformation occurs via an envelop transition state requires 1.7 and 4.0 kcal/mol for *syn* and *anti* forms at MP2 level. The barriers of the rotation of C^{sp2}—N bond leading to *syn* and *anti* conformations are 3.8 and 4.3 kcal/mol for *d* and *u* ring-puckered forms, respectively. For thioproline-derived enamine, apart from the *u* and *d* puckered conformations of thiazolidine ring, a *down* and *envelop* (*de*) ring conformation was found as the global minimum. The barriers of the C^{sp2}—N bond rotation of *d* and *u* puckered ring are 3.5 and 4.3 kcal/mol, similar to the corresponding conformations of proline-derived enamine. The barriers of the ring puckering change from *d* to *u* are 0.7 and 4.1 kcal/mol for *syn* and *anti* form, respectively. An interesting characteristic of the *de* ring conformation is its small C^{sp2}—N bond rotation barrier of 2.3 kcal/mol.

1. Introduction

Proline and derivatives have been widely used as organocatalysts especially for stereoselective organic reactions such as the Mannich reaction [1]. However, the stereoselectivity of organocatalysts depends on their molecular structures. For example, when using proline as the catalyst the Mannich reaction is highly stereoselective with 99%ee as compared to 5%ee when using thioproline. The proposed mechanism for proline-catalyzed Mannich reaction was displayed in Scheme 1. It has been identified that conformations of the proline-derived enamine, *i.e. syn* and *anti*, are crucial for determining the stereochemistry of products [2–4]. The reaction between cyclohexanone and proline could not directly generate *anti* enamine which in later step produces the major product of the Mannich reaction [4]. However, the formation of *anti* enamine is proceeded through the rotation of C^{sp2}—N(pyrrolidine) bond of *syn* enamine. Since proline and thioproline differ by only one position on the five-membered ring (pyrolidine/thiazolidine ring), the S atom substitution in thioproline might cause the different *syn*/*anti* rotational potential which could explain the distinct stereoselectivity between proline and thioproline catalyzed reactions. In addition, the ring-puckering potential of the five-membered ring in proline and thioproline should as well be explored. The interplay between the *syn-anti* and the ring puckering isomerization of enamine might also be important for stereoselectivity of proline and derivatives in the Mannich reaction as has been found in the cases of peptide bond orientation [5–11]. So far there has been no report on *syn-anti* and ring puckering isomerization of proline-derived and thioproline-derived enamines. In this work, the puckering of the pyrrolidine and thiazolidine ring of enamine **1** and **2** as well as the relationship of their *syn* and *anti* conformations will be determined.

2. Computational details

Chemical structures and definitions of dihedral angles *i.e.* around C^{sp2}—N bond (τ) and those of the pyrrolidine and thiazolidine endocyclic (χ^i, $i = 0, 1, \ldots, 4$) of the enamine **1** and **2** are displayed in Fig. 1a. Since the carboxylic acid group of enamine **1** and **2** can form a hydrogen bond with the nitrogen atom of the pyrrolidine and the thiazolidine rings and this hydrogen-bonded structure is crucial for the further stereocontrol step reaction with imine [4], thus only the hydrogen bonded conformations were considered in this study. For enamine **2**, the S atom, another possible hydrogen bond acceptor, is also presented in the thiazolidine ring

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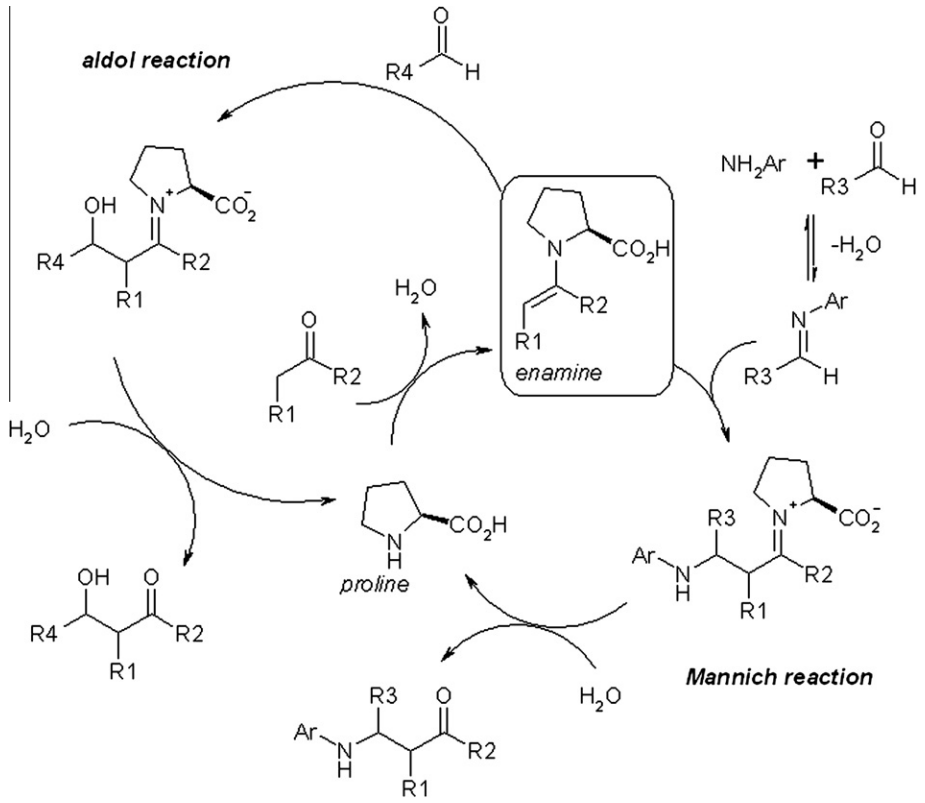

Scheme 1. Proline-catalyzed Mannich reaction.

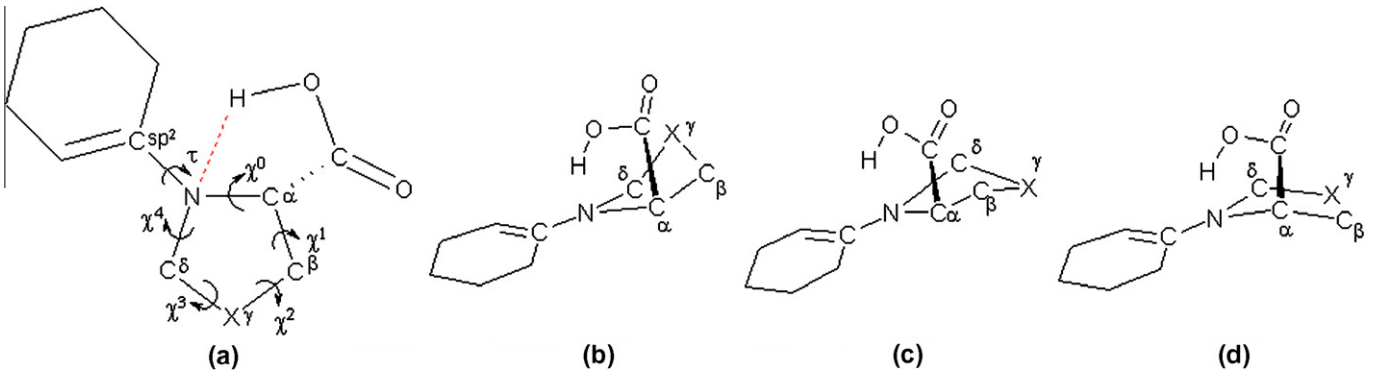

Fig. 1. Structures of enamine derivatives of proline (X = CH_2, enamine **1**) and thioproline (X = S, enamine **2**) (a) with notations for endocyclic (χ^i) and C^{sp2}—N bond dihedral angles (τ), (b) in *down* puckered conformation, (c) in *up* puckered conformation, and (d) in *down-envelop* puckered conformation.

and must be as well examined, However, our preliminary calculations concluded that the conformation with the hydrogen bond between the carboxylic group and the S atom is higher in energy than the one between the carboxylic group and the N atom for the thioproline-derived enamine. The pyrrolidine and thiazolidine ring-puckering conformations are described as *up* and *down* which are denoted by *u* and *d* and their structures are schematically displayed in Fig. 1b and c. For the *u* conformation, X^{γ} atom aligns below the C^{δ}—N—C^{α} plane and on the opposite side to the C=O group while for the *d* conformation, X^{γ} and C=O are on the same side of the C^{δ}—N—C^{α} plane. Another characteristic of the *up* and *down* conformers is the negative (for *u*) and positive (for *d*) values of the endocyclic dihedral angle χ^1. Firstly, we investigated the *syn* to *anti* conversion of the *u* puckered conformation of enamine **1** and **2**. Geometries of the *syn* and *anti* enamine **1** and **2**, of which starting from τ ($C{=}C^{sp2}{-}N{-}C^{\alpha}$) = 0° and 180° respectively, were fully optimized using B3LYP [12] and 6-31++G(d, p) basis set [13]. For enamine **1** and **2**, the dihedral angle τ was scanned from 0° to 360° at the increment of 30° using the optimized rotor model. To better determine the C^{sp2}—N rotation barrier, a transition state between the *syn* and *anti* conformations was searched using a QST3 algorithm [14], where the highest energy structure from the dihedral angle τ scanned surface was used as the guessed transition state structure. The rotational barriers of the torsion angle τ of the *d* puckered enamine **1** and **2** were determined in the same fashion as the *u* puckered conformation. For ring puckering barriers of enamine **1** and **2**, it is quite difficult to obtain the guessed transition state structures in the same fashion as the C—N bond rotation barrier owing to the multidimensionality of the ring torsions, therefore, the transition state structures between the *d* and *u* puckered conformations of both *syn* and *anti* conformations were located using a QST2 approach [14] instead. In this approach, only