Stereoselectivity of Proline-catalyzed Mannich Reaction: a Density Functional Study

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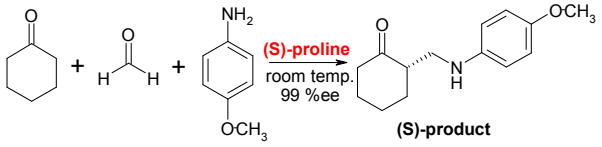
Abstract: The stereoselective step of (S)-proline catalyzed Mannich reaction of cyclohexanone, formaldehyde, and aniline were theoretically investigated using density functional theory, B3LYP, with 6-31++g(d,p) basis set. From the proposed mechanism, cyclohexane and (S)-proline generate enamine and formaldehyde and aniline generate imine. The activation energies of the reaction between the enamine and imine which yield (S)- and (R)-intermediate are 8.5 and 12.4 kcal/mol, respectively. This is in agreement with experimental result that (S)-intermediate upon hydrolyzed yields major (S)-Mannich base product.

Keywords: proline, organocatalyst, Mannich reaction, DFT

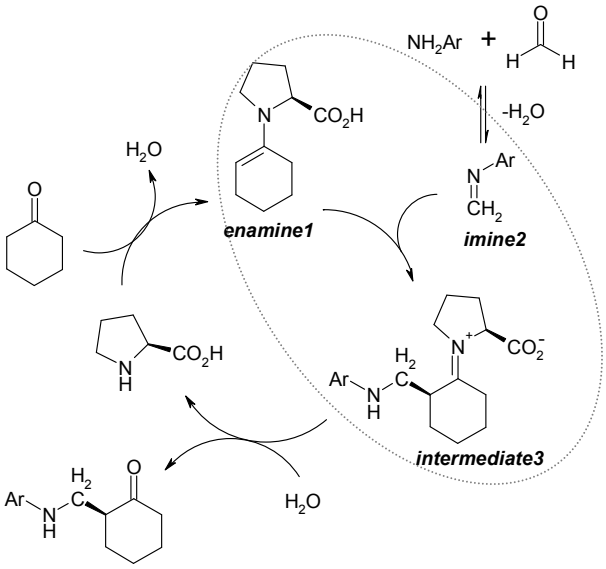
1 Introduction

Mannich reaction is a multi-component reaction of an aldehyde, a primary or secondary amine, and a carbonyl compound. The final product of this reaction is Mannich base, a β-amino carbonyl compound, which can be applied in the syntheses of several classes of compounds. The stereochemistry of Mannich base is of interest for organic chemists. Thus, stereoselective procedures of Mannich-type reaction have been investigated by several research groups utilizing different classes of catalysts i.e. organometallic complexes, amino acids and their derivatives.[1] Recently, Ibrahem *et al*. reported the enantioselectivity and limitations of one-pot Mannich reaction catalyzed by S-proline and its derivatives as shown in scheme 1.[2]



Scheme 1 Proline catalyzed one-pot Mannich reaction of cyclohexanone, formaldehyde, and methoxyaniline

The proposed mechanism of proline catalyzed Mannich reaction is presented in scheme 2.[3]



Scheme 2 Proposed mechanism for proline catalyzed Mannich reaction. The stereocontrol step is circled.

Proline reacts with cyclohexanone yields an enamine1 and formaldehyde reacts with aniline yields an imine2. Then the enamine reacts with imine gives an iminium ion intermediate3 in which a chiral center is introduced at the α-position. The corresponding final product can be obtained upon hydrolysis of the intermediate. The

enantiomer control step is the step of iminium ion intermediate formation. In this work, we determine the enantioselective step of this reaction using density functional theory.

2 Computational details

The kinetics of the formation of both enantiomers of intermediate3, i.e. ***int3*** and ***int3a*** refer to (S)- and (R)-enantiomers, from the reactant complexes of enamine1 and imine2, i.e. ***cpx12*** and ***cpx12a*** were investigated. Fig. 1 shows the diagram of this step. S-path and R-path refer to the reaction yielding (S)- and (R)-intermedaite, respectively. Geometries of all species were optimized using B3LYP functional with 6-31++g(d,p) basis set. The geometries and energies of the corresponding transition states i.e. ***TS1*** and ***TS1a***, of the reaction were located by QST2. All the calculations were performed using GUASSIAN03 package.[4]

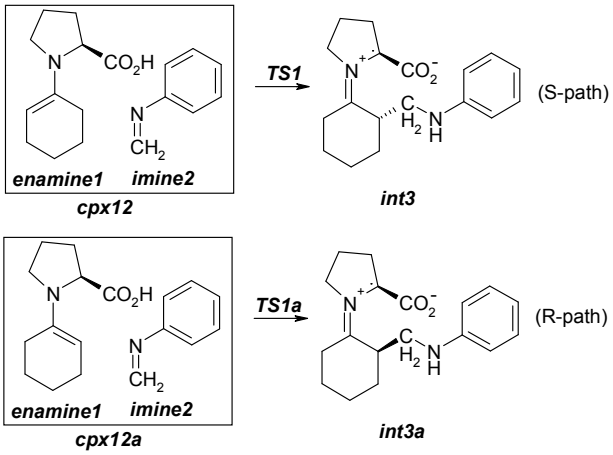


Fig. 1 Model of the enantiocontrol step

3 Results and Discussion

3.1 Geometries

Fig. 2 displays the geometry of reactant complex, ***cpx12***, between enamine1 and imine2 which is the starting point of the enantioselective step leading to (S)-intermediate, ***int3***. Distances between atoms directly involved in this reaction step are collected in Table 1. During the reaction progress, the acidic proton of the carboxylic group of proline (H1) is transferred to nitrogen atom of imine2 (N2) as the distance H1-O1 becomes longer (from 0.994 Å in ***cpx12*** to 1.325 Å in ***TS12*** and finally 1.903 Å in ***int3)*** and the distance N2-H1 becomes shorter. The double bond character between C2 and N2 of the imine2 is also altered as evident by the elongation C2-N2 distance. The carbon-carbon bond formation is indicated by the shortening of C1-C2 distance of ***int3***. These evidences are similarly observed in the formation of (R)-intermediate, ***int3a***. It is worth to note that the distance C1-C2 of 5.146 Å for ***cpx12a*** is much longer than 3.798 Å for ***cpx12***. Thus, the late transition state is observed for the R-path which makes the process of the S-path being preferred.

Table 1 Geometric parameters of reactant complexes, transition states, and intermediates; distances in Angstrom

species	distance			
	N2-C2	N2-H1	C1-C2	H1-O1
Cpx12	1.309	1.883	3.798	0.994
TS12	1.309	1.170	2.429	1.325
Int3	1.450	1.026	1.564	1.903
Cpx12a	1.308	2.104	5.146	0.985
TS12a	1.308	1.084	2.567	1.520
Int3a	1.438	1.022	1.590	1.958

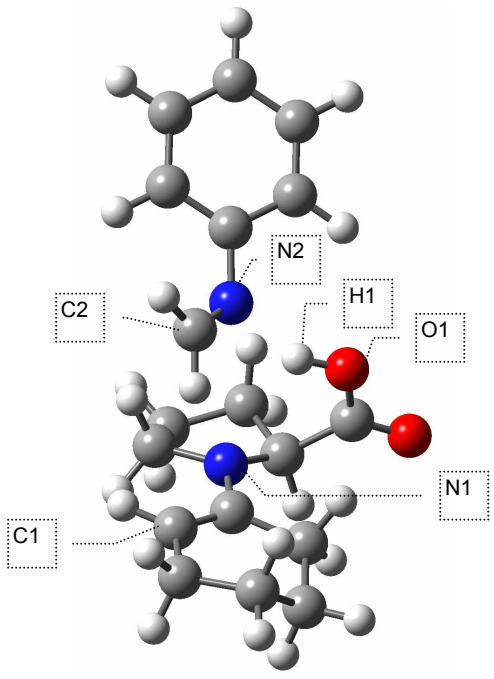
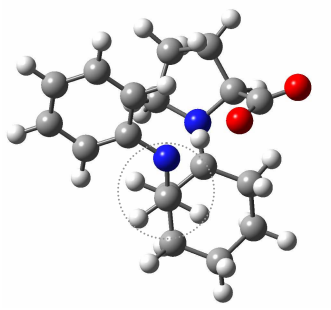


Fig. 2 Optimized structure of reactant complex, ***cpx12***, some important atoms are labeled.


a)

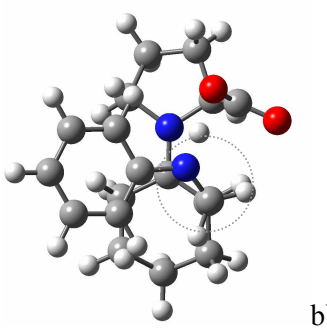

b)

Fig. 3 Transition state structures, a) ***TS12*** and b) ***TS12a***

Geometries of the transition state for both S- and R-paths, ***TS12*** and ***TS12a***, are shown in Fig. 3. The major difference between ***TS12*** and ***TS12a*** is the orientation of the atoms bonded to C1 of enamine and C2 of imine, as circled in Fig. 3. In ***TS12*** the staggered conformation about C1 and C2 is arranged. But this is not the case for ***TS12a***, in which the staggered conformation could not be arranged, and results in the higher energy for ***TS12a***.

3.2 Energy profile

Energies of the investigated species are listed in Table 2. Relative energies are the energies relative to reactant complex, ***cpx12***. Reactant complex of the S-path, ***cpx12***, is slightly (0.55 kcal/mol) lower in energy than the reactant complex of the R-path, ***cpx12a***. While S-intermediate, ***int3***, is 6.77 kcal/mol more stable than R-intermediate, ***int3a***. The S-path reaction is 6.39 kcal/mol exothermic, whereas it is 0.17 kcal/mol endothermic for the R-path. Therefore, as reactant complexes of both paths are comparably stable, the S-path reaction is favored by the more stable intermediate formation. From the transition state point of view, the ***TS12*** of the S-path is 4.48 kcal/mol more favored than the ***TS12a*** of the R-path. This energy difference is in the range of 2-10 kcal/mol as suggested in the work of Allemann *et al*, [5] and comparable with that reported by Clemente and Houk for a stereoselective proline catalyzed aldol cyclization (3.3 kcal/mol).[6]

Table 2 Energies of the studied species, total energy in Hartree and energy relative to ***cpx12*** in kcal/mol

	Total energy	Relative energy
Cpx12	-960.3719927	0.00
TS12	-960.3584494	8.50
Int3	-960.3821723	-6.39
Cpx12a	-960.3711158	0.55
TS12a	-960.3513143	12.98
Int3a	-960.3713881	0.38

In Fig. 4, the energy profiles of the enantioselective step, both S- and R-path, are plotted and compared. The energies plotted are relative to their corresponding reactant complexes. The activation energies of the S- and R-path are 8.50 and 12.43 kcal/mol, respectively. This supports the preference of S-path reaction which leading to the S- major product.

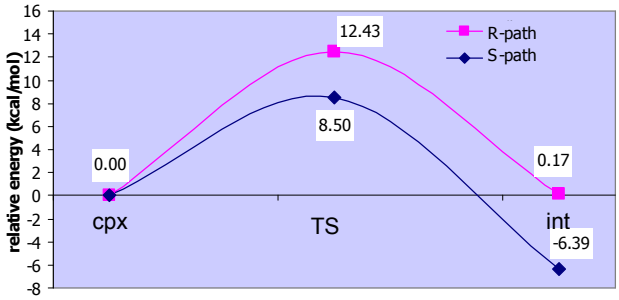


Fig. 4 Compared energy profile of the S- and R-path reation

4 Conclusions

In the stereocontrol step, the formation of S-intermediate, ***int3***, in the S-path is favored both kinetically and thermodynamically in agreement with experiment. However, the effects of solvent and electron correlation have not been considered. Further investigations on these effects on the enantioselectivity of the proline catalyzed mannich reaction should be carried out. We are also interested in other steps involved in the stereocontrol such as the formation and conformation of the enamine2, formed between the catalyst and cyclohexanone.

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