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Mechanistic Insights into L-Proline-Catalyzed Transamidation of Carboxamide with Benzylamine from the Density Functional Calculations

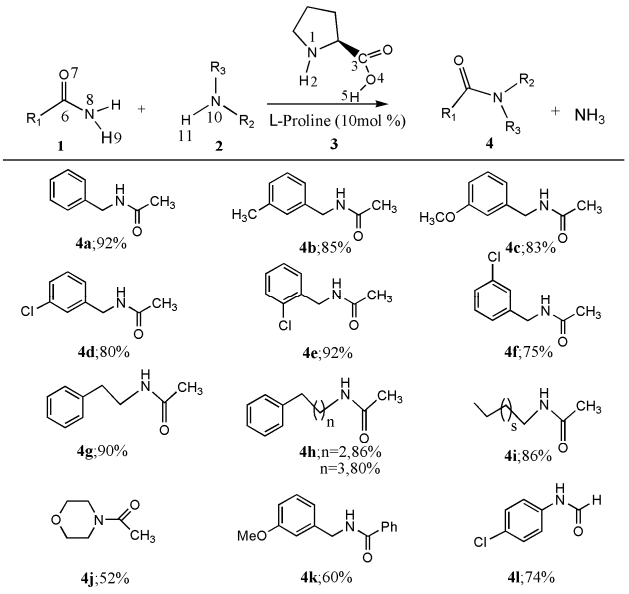
Xin Yang, Linlin Fan, and Ying Xue*[a]

Abstract: The mechanism of the transamidation reaction between carboxamides and benzylamine catalysed by L-Proline in toluene was investigated using the density functional theory (DFT) at the M06/SMD/6-311+G(2d,p)//M06/6-31+G(d,p) level. The calculations reveal that the reaction proceeds through a stepwise mechanism, in which the L-proline acts as Lewis base to activate acetamide. The hydrolysis step is predicted to be the rate-determining step (RDS) in the reaction with an energy barrier of 26.0 kcal/mol. The comparison of the catalytic effect between the acetamide with benzylamine in three different solvents including toluene, EtOH, and H_2O, suggests that toluene exhibits higher catalytic efficiency for the transamidation, and the less polar is in favour of the reaction, which is in good agreement with the experimental observations.

Introduction

The amide bond is one of the most important linkages in nature due to its presence in peptide and protein structures.[1] It is increasingly important in pharmaceutical chemistry, being present in 25% of available drugs, with amidation reactions being among the most commonly used in medicinal chemistry. Amides are also potential precursors for the synthesis of numerous natural products, bio-active polymers, and therapeutic molecules.[2] There is considerable interest in the development of new approaches to direct amidation,[2c,3] and organizations such as the ACS Green Chemistry Institute Pharmaceutical Roundtable have indicated that amide bond formation is one of the most important reactions.[4] Traditionally amides have been prepared by the reaction of amines with carboxylic acid derivatives,[5] alcohols,[6] or aldehydes,[7] hydroamination of alkynes,[8] and hydration of nitriles.[9] Alternatively, transamidation presents one of the most convenient and straightforward methods for exchanging the constituents of two different amide groups and has been emphasized and projected to become a valuable tool in protein engineering or in the preparation of bio-inspired materials. The search for general and efficient methods for the transamidations remains an intensively investigated topic. Transamidation processes catalyzed by transition metal[5b,10] or lanthanide metal[11] have come to the forefront. Although these methods have their own advantages, nonetheless they suffer from the separation of the metal catalyst from products.

In view of the above perceptions, the benign and metal-free transamidation procedures with high yield and selectivity were developed.[12] Particularly, Adimurthy et al. recently has reported a novel L-proline-catalyzed transamidation process which can be general for a wide range of amines and gives good yields, without the need for any specialized experimental setup.[12d] They found that in the presence of L-proline as catalyst, various amides react with a variety of amines, including benzylamines with electron-rich and –deficient (p/m/o) substituents, and alkyl aromatic,



Sheme 1. L-proline-catalyzed transamidation of amides with various amines.

a *Dr. X. Yang, L.L. Fan, Prof. Dr. Y. Xue*
Key Laboratory of Green Chemistry and Technology in Ministry of Education, College of Chemistry
Sichuan University, Chengdu 610064 (P.R. China)
Tel: (+86)28-85418330
E-mail: yxue@scu.edu.cn

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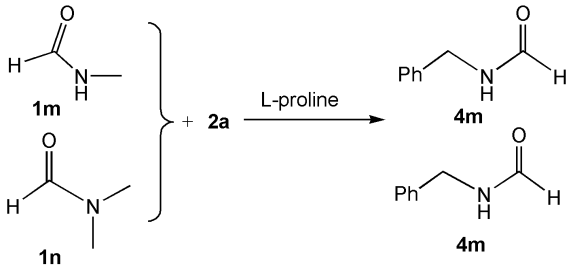
aliphatic, and secondary amines, with remarkable ease (Scheme 1). The reactions demonstrated in Scheme 1 had a high degree of functional group tolerance. The transamidation of **2a** with the secondary and tertiary amides resulted in low to moderate yields compared to primary amides (Scheme 2). Based on the experimental observations and literature reports[12d,13], a possible reaction mechanism was proposed (Scheme 3). The proline functions as a "micro-aldolase" that provides both the nucleophilic amino group and an acid/base cocatalyst in the form of the carboxylate. The catalytic cycle involves the following steps: (1) activation of the acetamide, (2) nucleophilic addition to form C-N bond, (3) elimination of ammonia, (4) hydrolysis to provide the product. (Note that every step may take more than one transition state.)

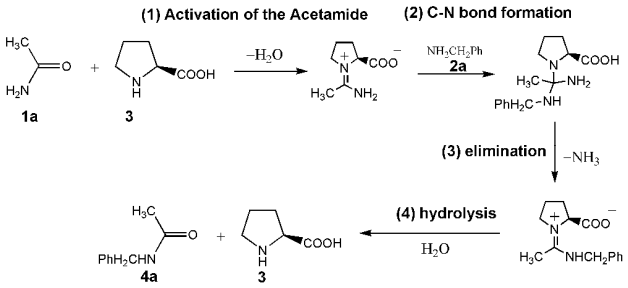


Scheme 2. Transamidation of acetamide with secondary and tertiary amides catalyzed by L-proline.

In light of the experimental results, we felt it important to explore the interactions between amides and catalyst on the molecular scale. This research is particularly essential because transamidation process embodies an exciting unconventional route for the functionalization of a given carboxamides. To obtain an insight into the reaction mechanism of transamidation of carboxamides with amines, we here selected L-proline-catalyzed transamidations of acetamide **1a** with benzylamine **2a** as a model system (Scheme 1) and performed a density functional theory (DFT) study on it. Furthermore, the catalytic effect of L-proline **3** for secondary and tertiary amides was also compared based on the theoretical results. The calculations explain how the transamidation happens, the role of L-proline, and disclose the reason why the transamidation can be efficiently catalyzed by L-proline. It is worthwhile to mention that this is the first report on reaction mechanism for an L-proline catalyzed transamidation in detail. The studies and mechanistic insights obtained herein can ultimately prove valuable in accelerating the design and optimization of catalytic processes of metal-free transamidation procedures.

Computational methods

The calculations were performed with Gaussian 09.[14] The density functional theory (DFT) hybrid model M06[15] was used together with the 6-31+G(d,p) basis set for optimizing the geometry of all the minima and transition states (TS) in solution. Truhlar's M06 functional was developed for computations involving main-group thermochemistry, kinetics, and noncovalent interactions.[15-16] The



Scheme 3. Proposed mechanism of the trasamidation catalyzed by L-proline.

vibrational frequencies were computed at the same level of theory to check whether every optimized structure was an energy minimum (no imaginary frequency) or a transition state (unique imaginary frequency). IRC calculations[17] were carried out to confirm that each transition state was connected with its corresponding reactant and product. Solvent effects were considered with the PCM[18] model in toluene (ε = 7.58) at 373.15K (experiment temperature). To obtain further insight into the electronic property of the present system, natural bond orbital (NBO)[19] analysis was performed on the optimized structures. Single point energy calculations including radii and non-electrostatic terms for the SMD solvation model[20] were performed at the M06/6-311+G(2d,p) level with the M06/6-31+G(d,p)(PCM) structure. Note that those single-point energies in solvent at higher level were corrected by the thermodynamic quantities at M06/PCM/6-31+G(d,p) level to free enengies. All energetics reported throughout the text are based on free energies in kcal/mol, and the bond lengths are in angstroms (Å).

Results and Discussion

L-proline-catalyzed reaction: As described before, the transamidation of acetamide **1a** with benzylamine **2a** is considered to consist of four main steps. These studies are described in detail in the sections below.

Activation of the acetamide: L-proline can exists as two species in equilibrium (Figure 1); Calculations indicate that the zwitterionic structure **3-z** is more stable than **3** by about 3.0 kcal/mol with the inclusion of solvent effects (toluene), due to the intramolecular hydrogen-bonding between the H5 and O4 atoms (the O⋯H distance is 1.651Å and the large stabilization energy [LP O4→ BD* N1-H5] is 29.52 kcal/mol). However, it has been shown that only structure **3** can yield the corresponding imine by nucleophilic attack of N atom of **3** to the carboxyl C atom of **1a**.[21]

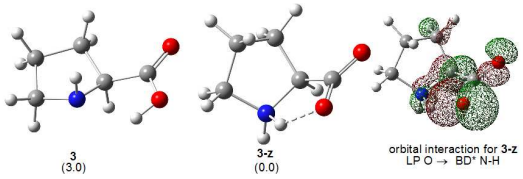


Figure 1. Figure Caption. Optimized geometries of the two conformers (**3-z** and **3**) and their relative free energies in parenthese (kcal/mol), as well as visualization orbital interaction of **3-z**.

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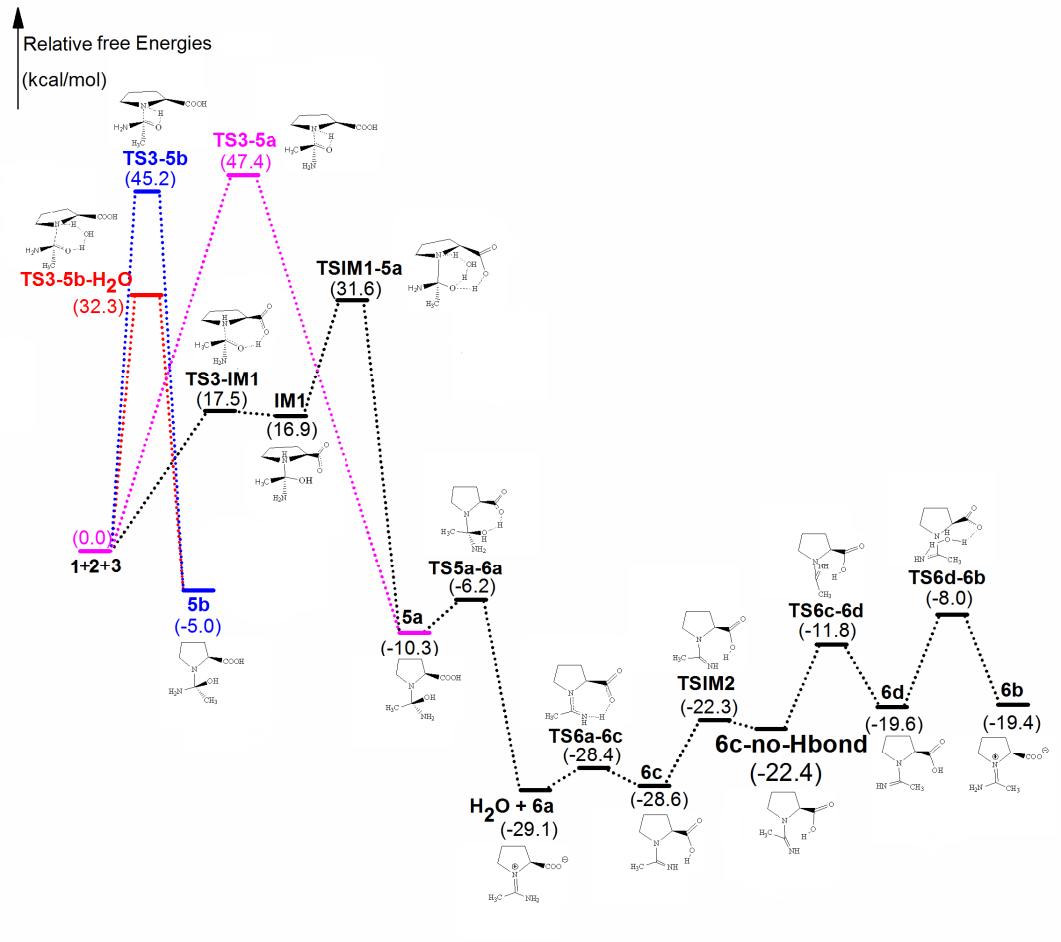

Figure 2. Energy profile of L-proline–catalyzed trasamidation of **1a** with **2a** in step "the activation of the acetamide". The relative free energies in toluene at M06/6-311+G(2d,p)//M06/6-31+G(d,p) level are given in kcal/mol.

The schematic structures along the reaction pathways are illustrated in Figure S1 in the Supporting Information. As shown in Figure 2, in the absence of water molecule, the reaction takes place via two possible attack directions, which are concerted mechanism through four-membered-ring transition states (**TS3-5a** and **TS3-5b**) with high activation energy barriers. The nitrogen center of **3** acts as a Lewis base to activate acetamide **1a**. On the other hand, the reaction can alternatively take place in the presence of water. The electrophilic attack of **1a** to **3** via a concerted six-membered ring transition state **TS3-5b-H_2O** requires a lower free energy of activation of 32.3 kcal/mol, which is 12.9 kcal/mol lower than that through **TS3-5b**. However, the reaction goes through a stepwise pathway to **5a** in the presence of water. Starting from the reactant complex, the attack of C6 in **1a** occurs via seven-membered ring transition state **TS3-IM1** which only needs to surmount an energy barrier of 17.5 kcal/mol in free energy. The intermediate **IM1** is a zwitterion, and the hydrogen bonds of O(H_2O)-H2 (the O...H2 distance is 1.842 Å) and H(H_2O)-O7 (the H...O7 distance is 2.056Å) are formed, which can increase the stability of the zwitterionic intermediate. NBO analysis shows the remarkably interreaction of O(H_2O) and H2 [LP O → BD*N1-H2 (21.2 kcal/mol)]. From **IM1**, the cleavage of N1-H2 bond with the water-assisted proton transfer can easily occurs via **TSIM1-5a** with an energy barrier of 14.7 kcal/mol.

Both the intermediates **5a** and **5b** can go through dehydration reaction in the next step. However, the energy barrier for the addition of **1a** to **5b** via **TS3-5b-H_2O** is as high as 32.3 kcal/mol (the free energy barrier without the participation of water is up to 45.2 kcal/mol). Through further analysis, it can be seen that the energy barriers of the preferable pathway (from **1a** via **IM1** to **5a**) do not exceed 30 kcal/mol. So, in the next calculation, **5a** is used as a further reaction rather than **5b**. As shown in Figure 2, the direct formation of **6a** from **5a** undergoes the departure of a water molecule. **6a** is a zwitterion, and can yield **6c** via the hydrogen transfer from N8 to O4. In accord with **3-z**, there is a intramolecular hydrogen-bond in **6a** (the O4…H9 distance is 1.643 Å and the Wiberg bond indice is 0.1128). As a result, the relative free energy of **6a** is -29.1 kcal/mol, slightly lower than that of **6c**. From the resulting intermediate **6c**, the rotation of N1-C6 bond occurs via a stepwise pathway, which involves: 1) the remove of hydrogen bond in **6c** through **TSIM2**, 2) the rotation of N1-C6 to generate the intermediate **6d**. Like the transformation

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between **6a** and **6c**, the transfer of H9 from N8 in **6c** to O4 can form the zwitterion **6b**. Due to the lack of intramolecular hydrogen bond, the free energies of **6b** and **6d** are ca. 9 kcal/mol higher than those of **6a** and **6c**.

According to the calculations, the preferable energy surface in this step does not include any high energetic transition states (the highest energy barrier of free energy is 17.5 kcal/mol[22]) or any highly stable intermediates indicating that the "Activation of acetamide" can proceed readily via the C-N addition and dehydration reactions.

Nucleophilic addition to form C-N bond: In this step, the addition of **2a** into imine to form C6-N10 bond is considered to proceed via eleven different mechanisms. They are related to the nucleophilic attack of the four intermediates, **6a**-**6d**. In addition, we also take the water-assisted nucleophilic addition into consideration. The energy profile of the reaction pathways is shown in Figure 3. The schematic structures along the reaction pathways are illustrated in Figure S2 in the Supporting Information. The details of reactions with different intermediates **6a**-**6d** are discussed below.

When **6a** reacts with benzylamine **2a**, two possible mechanisms are located, respectively. As shown in Figure S2, one corresponds to the pericyclic reaction to give the intermediates **7** and **8**, and the other corresponds to the amino auxiliary proton transfer to give the intermediates **9**-**12**. As shown in Figure 3, the pericyclic reaction of **2a** with **6a** undergoes concerted nucleophilic addition, and the proton transfer from **2a** to carboxyl group of **6a**. Two possible transition stats **TS6a-7** and **TS6a-8** are located owing to different offensive orientation. Among these two transition states, the free energy barrier of **TS6a-7** is 18.7 kcal/mol and lower than that of **TS6a-8**. In **TS6a-8**, the two forming bonds are weakened, verified by the longer C6…N10 and H11…O4 distances (1.917 Å and 1.848 Å vs. 1.840 Å and 1.703 Å in **TS6a-7**). On the other hand, the reaction can occur via amino of auxiliary proton transfer pathway, and two directions (above or below the plane of C-N=C of **6a**) have been considered. The proton transfer from N10 atom of **2a** to N8 atom and from N8 to carboxyl group of **6a** happens via a concerted mechanism. Two possible transition states **TS6a-9** and **TS6a-10** are located with much higher energy barriers of 47.3 and 44.6 kcal/mol in free energy, respectively. Moreover, the water molecule can also assist the proton transfer together with amino group via a stepwise mechanism. For the first step, **2a** reacts with **6a** to afford zwitterionic intermediate **11** through transition state **TS6a-11**. The second step is the proton transfer via concerted transition state **TS11-12**. The energy barriers for the two steps are calculated to be 27.6 and 10.1 kcal/mol in free energies, respectively, which suggests that the addition reaction of **2a** and **6a** through this pathway is also facile.

When considering the interaction between **6c** and **2a**, both the direct addition and water-assisted addition are taken into account. However, only one possible pathway is found, which is water-assisted addition from the opposite plane of N-C=N. The other three reactive channels are finally found to be the same with reaction pathways through **TS6a-9**-**TS11-12**, and the reactants have been proved to be **6a**. This is possibly due to the very similar energy and the low energy barrier between **6c** and **6a**. As shown in Figure 3, the reaction between **6c** and **2a** takes place via a concerted mechanism with six-membered-ring transition state (**TS6c-13**), which needs to surmount a little high free energy barrier 35.3 kcal/mol. This energy barrier is much higher than the lowest free energy barrier for **6a** ($\Delta G^{\ddagger}$=18.7 kcalmol), which suggests that zwitterion **6c** exhibits poor Lewis acid characteristics than **6a** in reaction with **2a**.

As shown in Figure 3, the nucleophilic addition between **6d** and **2a** undergoes concerted mechanism. For this step, four possible pathways have been taken into consideration (the direct addition and water-assisted addition). In the directed addition, the reaction can occur via two different four-membered-ring transition states, **TS6d-14** and **TS6d-15**, which need to surmount an energy barrier of 63.9 kcal/mol and 51.0 kcal/mol in free energy respectively. On the other hand, in water-assisted addition, the energy barriers are significantly reduced by 15.3-26.2 kcal/mol via six-membered-ring transition states **TS6a-16** and **TS6a-17**. This might be due to the fact that four-membered-ring suffers larger ring strain than six-membered-ring. Unfortunately, the lowest free energy barrier of the reaction between **6d** and **2a** is still as high as 35.7 kcal/mol.

Considering **6b** reacting with **2a**, only one possible pathway has been taken into considering, due to the configuration of **6b**. Calculation has shown that the carboxyl is above the plane of N=C-CH3, the transition state structure cannot be formed when benzylamine attacks **6b** from the bottom of N=C-CH3 plane. Compared with **6a**, there is no intramolecular hydrogen bond in the zwitterion **6b**. Starting from the high reactivity complex, the nucleophilic addition of **2a** to **6b** easily happens via the seven-membered ring transition state **TS6b-18** with much lower energy barrier of 14.2 kcal/mol in free energy. In **TS6b-18**, the large stabilization energy [LP O4 → BD* N10-H11 (39.7 kcal/mol vs. 34.82 kcal/mol in **TS6a-7**)] indicates that the dominate promotion occurs from carboxyl group to N-H bond. As a result, the free energy barrier of **TS6b-18** is lower than that of **TS6a-7**, which suggests that the proton transfer from N atom of **2a** to carboxyl group mediated by the intermediate **6b** is energetically favorable.

According to our further calculations, the largest energy barrier in the preferable pathway doesn't exceed 30 kcal/mol. Therefore, only intermediates **7**, **8**, **12**, and **18**, which own energy barriers below 30 kcal/mol, can further participate in the next reactions.

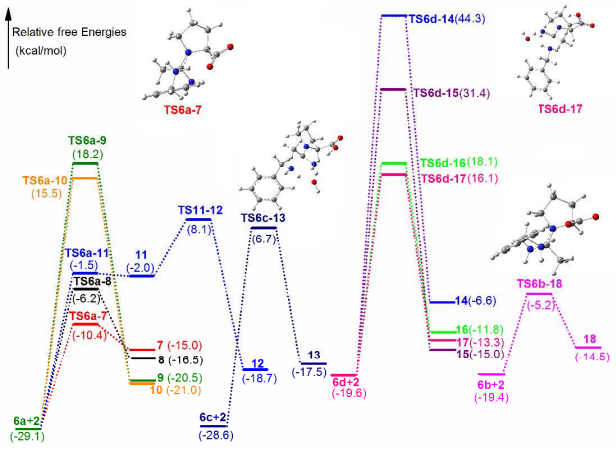

Figure 3. Energy profile of L-proline–catalyzed trasamidation of **1a** with **2a** in step "C-N bond formation". The relative free energies in toluene at M06/6-311+G(2d,p)//M06/6-31+G(d,p) level are given in kcal/mol.

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Elimination of ammonia: In this process, the elimination of ammonia from the intermediates produced in the previous step leads to the formation of the zwitterionic intermediates. The energy profile of the four reaction pathways from intermediates **7**, **8**, **12**, and **18** is presented in Figure 4, and the optimized structures involved in this step are illustrated in Figure S3. Before

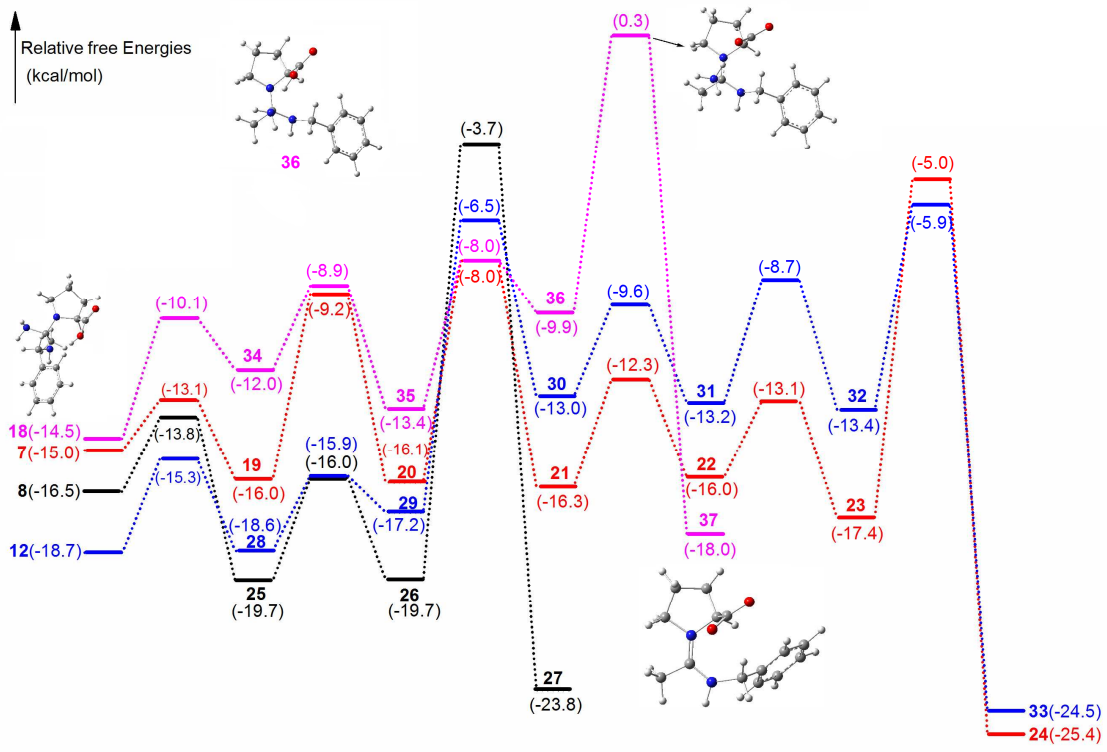

Figure 4. Energy profile of L-proline–catalyzed trasamidation of **1a** with **2a** in step "elimination". The relative free energies in toluene at M06/6-311+G(2d,p)//M06/6-31+G(d,p) level are given in kcal/mol.

the elimaination of ammonia takes place, all the intermediates have to go through a serious of transition states including the removal of hydrogen bond from the previous intermediates, rotating the groups on C6 atom through one or more transition state in order to form the hydrogen bond of N8 - H atom of carboxyl group, and the formation of hydrogen bond between amino group -NH_2 and carboxyl group to facilitate the leave of ammonia molecule. The energy barrier summits are about 10-12 kcal/mol except that the largest energy barrier starting from the intermediate **8** is 16.0 kcal/mol.

Hydrolysis: Strating from the intermediates **24**, **27**, **33**, and **37** produced by the elimination of ammonia, the insertion of H_2O into those intermediates to produce the transamidation product is considered to proceed via a stepwise mechanism. As shown in Figure 5, the hydrolysis undergoes two steps, which includes the formation of C6-O in H_2O, and the leaving of catalytic agent **3** to form the final product. This mechanism is similar to the mechanism of the step "Activation of the acetamide". For the C-O bond formation step, four possible transition states **TS24-38**, **TS27-40**, **TS33-42**, and **TS37-44** are located, respectively. All these four transition states have almost the same activation energy barrier ca. 20 kcal/mol. The leaving of **2a** molecular takes place *via* the four-membered-ring transition state, **TS38-39**, **TS40-41**, **TS42-43**, and **TS44-45**, respectively. Downhill from those four transition states, the final product is yielded with the release of one catalyst molecule with an energy barrier of 26-29 kcal/mol in free energy.

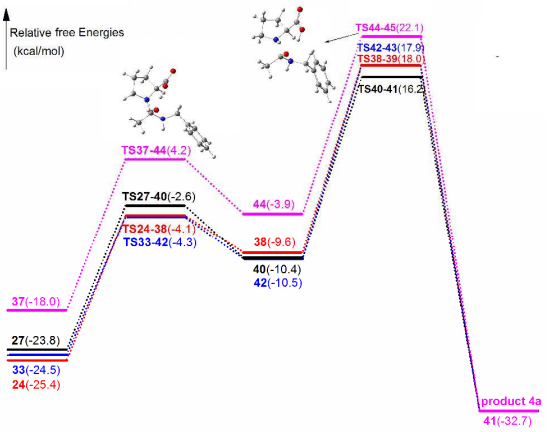

Figure 5. Energy profile of L-proline–catalyzed trasamidation of **1a** with **2a** in step "hydrolysis". The relative free energies in toluene at M06/6-311+G(2d,p)//M06/6-31+G(d,p) level are given in kcal/mol.

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In summary, the hydrolysis to form transamidation product possesses the largest energy barrier (ca. 27 kcal/mol) along the potential energy surface (PES). Therefore, this step can be regarded as the rate-determining step (RDS) along the stepwise pathway. Among all possible pathways, the active energy barrier through intermediate **6b** is lowest, indicating that the transamidation of **1a** with **2a** catalyzed by L-proline prefers to undergo the formation of zwitterion without intramolecular hydrogen bond.

Role of solvent in the reaction: Since the transamidation of **1a** with **2a** catalyzed by a combination of L-proline and solvents with different polarity was found to give different conversion and the lower polarity of the solvent was more effective in the experiment, the catalytic mechanisms of this reaction under different solvents (H_2O (ε=78.35) and EtOH (ε=24.85), together with toluene (ε=2.37)) were studied to clarify the role of low polarity solvent for accelerating the reaction rate. The energy profile along the reaction pathway catalyzed by L-proline and different solvents (EtOH and H_2O) are illustrated in Figure S5-S8 and Figure S9-12 in the Supporting Information. The preferable energy profiles of the reaction pathway in three different solvents are shown in Figure 6.

According to energy profiles in Figure 6, the PESs of the reaction under various solvents are similar with each other. The proposed mechanisms of the transamidation reaction in H_2O and EtOH also occur through a four main steps cycle. The relative free energies of **TS44-45**s are calculated to be 20.6 and 13.6 kcal/mol in H_2O and EtOH, respectively. Since **TS44-45** bears the largest energy barrier (29.7 and 26.8 kcal/mol in H_2O and EtOH, respectively) on the PES, the "hydrolysis" step of the L-proline catalyst is identified as the RDS of the entire catalytic cycle under water and EtOH solvents. This result is consistent with that in toluene solvent. Furthermore, the energy barriers via **TS44-45** are 29.7 and 26.8 kcal/mol in H_2O and EtOH, ca. 3.7 and 0.8 kcal/mol higher than that *via* **TS44-45** in toluene solvent. This result indicates that the transamidation reaction is more kinetically favored by using less polar solvent. This is compatible with the experimental observation where toluene exhibits higher reactivity and better catalytic performance than H_2O and EtOH.

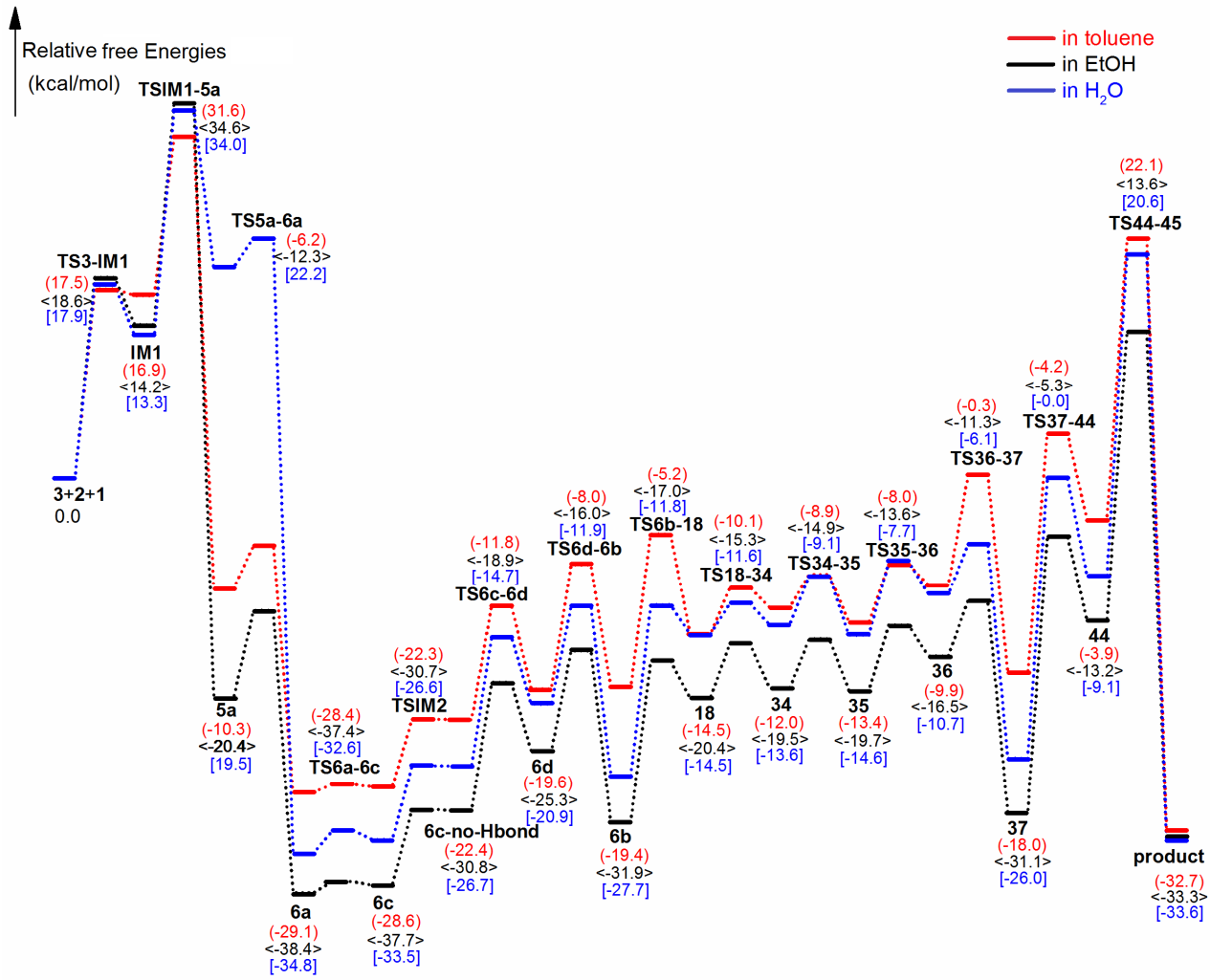

Figure 6. The preferable profile of L-proline–catalyzed trasamidation of **1a** with **2a** in three different solvents. The relative free energies at M06/SMD/6-311+G(2d,p)//M06/PCM/6-31+G(d,p) level are given in kcal/mol.

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Effect of carboxamides: To investigate the effect of the carboxamides on the reaction, the secondary and tertiary amides **1m** and **1n** were employed as the reagents for the transamidation of **2a** catalyzed by L-proline. The predicted mechanisms and energy profiles are presented in Figure 7, Figure 8 and Figures S13-S15 in Supporting Information. As shown in Figure 7 and Figures S13-S15, the mechanism for the secondary amide **1m** is similar with the primary amide **1a**, and also includes four main steps. Two different imines **S-6a** and **S-6b** are formed via the first step "Activation of the carboxamide", and the largest free energy barrier is 17.0 kcal/mol. Those two imines intermediates can react with benzylamine in the next step. According to the results, as compared to the other three pathways which go through intermediates **S-7**, **S-8**, and **S-12** respectively, the active free energy barrier of RDS which go through intermediate **S-18** is lowered by 1.0 kcal/mol—4.3 kcal/mol, indicating that the reaction of **1m** and **2a** prefers to undergo the stepwise pathway through the intermediate **S-18**, and the steps of "hydrolysis" are RDS for the catalytic cycles. The relative free energy of **S-TS31-38** is calculated to be 20.9 kcal/mol, and the energy barrier for the RDS is 27.6 kcal/mol, which is slightly higher than the free energy barrier for the RDS in the reaction of **1a** and **2a**. As for the reaction of **1n** and **2a**, only two pathways can occur because there is no H atom in amino group in the imine intermediate **T-6a** and **T-6b**, and the carboxyl and amino groups are not in a plane. Among two possible pathways, the active energy barrier through intermediate **T-6a** is lower, indicating that the transamidation of **1a** with **2a** catalyzed by L-proline prefers to undergo the intermediate **T-6a**. The RDS for the reaction of **1n** and **2a** is the first step "activation of the carboxamide ", and the energy barrier for RDS is 33.6 kcal/mol, which is the highest among the three different amides. This indicates that the transamidation between **1n** and **2a** catalyzed by L-proline proceeds more slowly than with primary and secondary amides. This result is in agreement with the experimental observations.

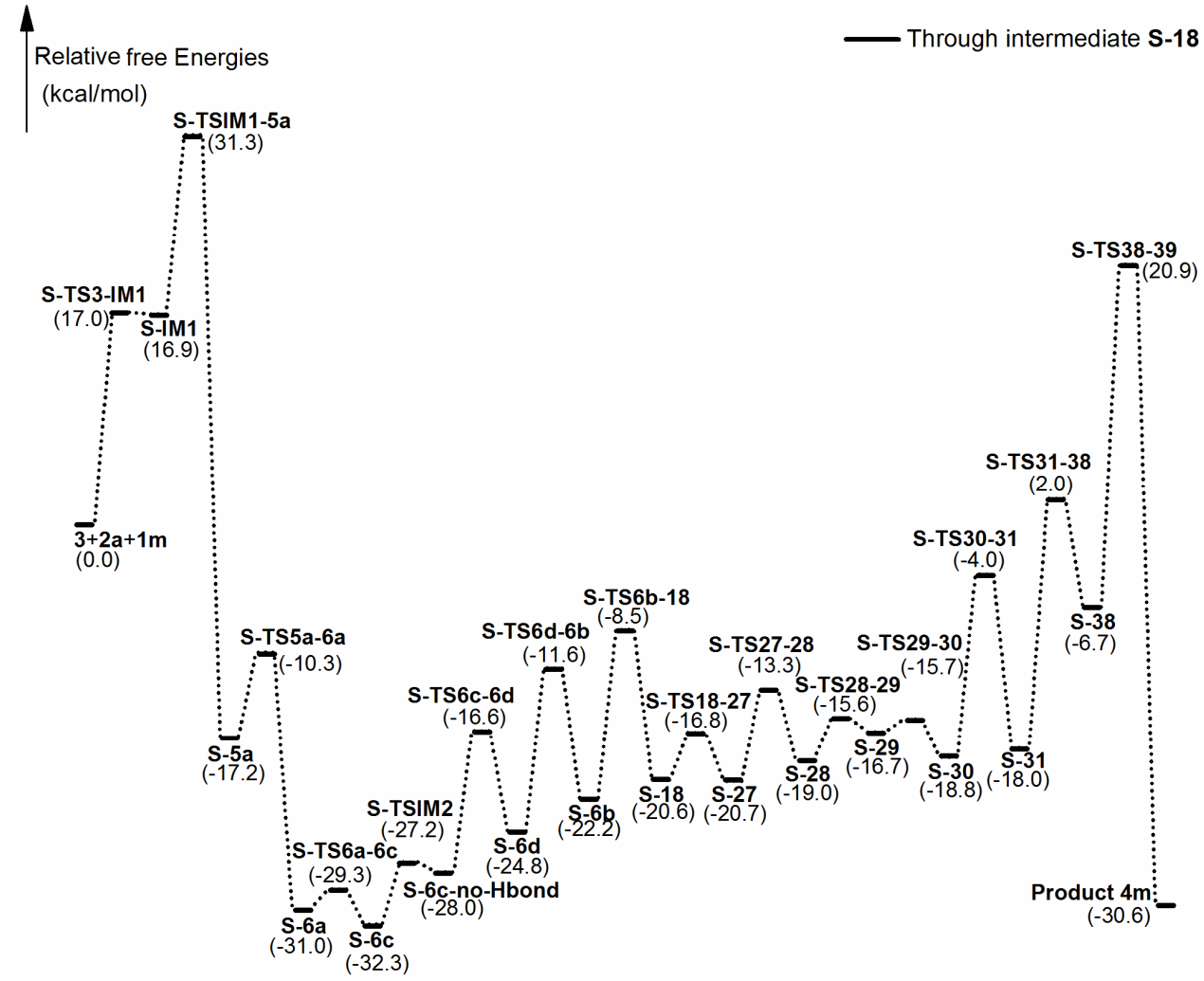

Figure 7. The preferable energy profile of L-proline–catalyzed trasamidation of **1m** with **2a** in toluene. The relative free energies at M06/SMD/6-311+G(2d,p)//M06/PCM/6-31+G(d,p) level are given in kcal/mol.

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Conclusion

The mechanisms for the transamidation of carboxamides with benzylamine catalyzed by L-proline in three different solvents have been theoretically investigated using DFT calculations at the M06/6-311+G(2d,p)//M06/6-31+G(d,p) level of theory. The major conclusions are listed as follows.

The calculations reveal that the reaction catalyzed by L-proline through a stepwise mechanism, which includes four steps:(1) activation of the carboxamides, (2) nucleophilic addition to form C-N bond, (3) elimination of ammonia, (4) hydrolysis to provide the product. The active intermediate imine is initially formed through proton transfer from L-proline to the carbonyl group of carboxamide, followed by the addition of benzylamine to the imine intermediate. Then through one ammonia molecule's leaving, the hydrolysis reaction takes place to produce the final product. The hydrolysis reaction with the largest energy barrier (26.0, 26.8, and 29.7 kcal/mol in toluene, EtOH, and H_2O, respectively) is predicted to be the RDS for the catalysis cycle. As compared with the transamidation reactions with secondary and tertiary amides, the H atom of amino group in amide plays key roles in: 1) lowering the activation free energy(from 33.6 kcal/mol in tertiary amide in step "activation of the carboxamide" to 17.5 kcal/mol in primary amine through reducing the electronic cloud density of C atom in carboxyl group, and increasing the nucleophilic reaction activity, 2) transforming the intermediate imine into high activity specie as a result of the hydrogen bond between H atom in amino group and O atom in carboxyl group.

The comparison of the catalytic effect between acetamide with benzylamine in three different solvents suggests that less polar solvent toluene is in favour of the transamidation reaction. The calculations also indicate that both free N-H and -COOH groups of L-proline involve in the catalytic reaction and are necessary for the formation of product, which strongly suggests they might play an important role in the catalytic cycle.

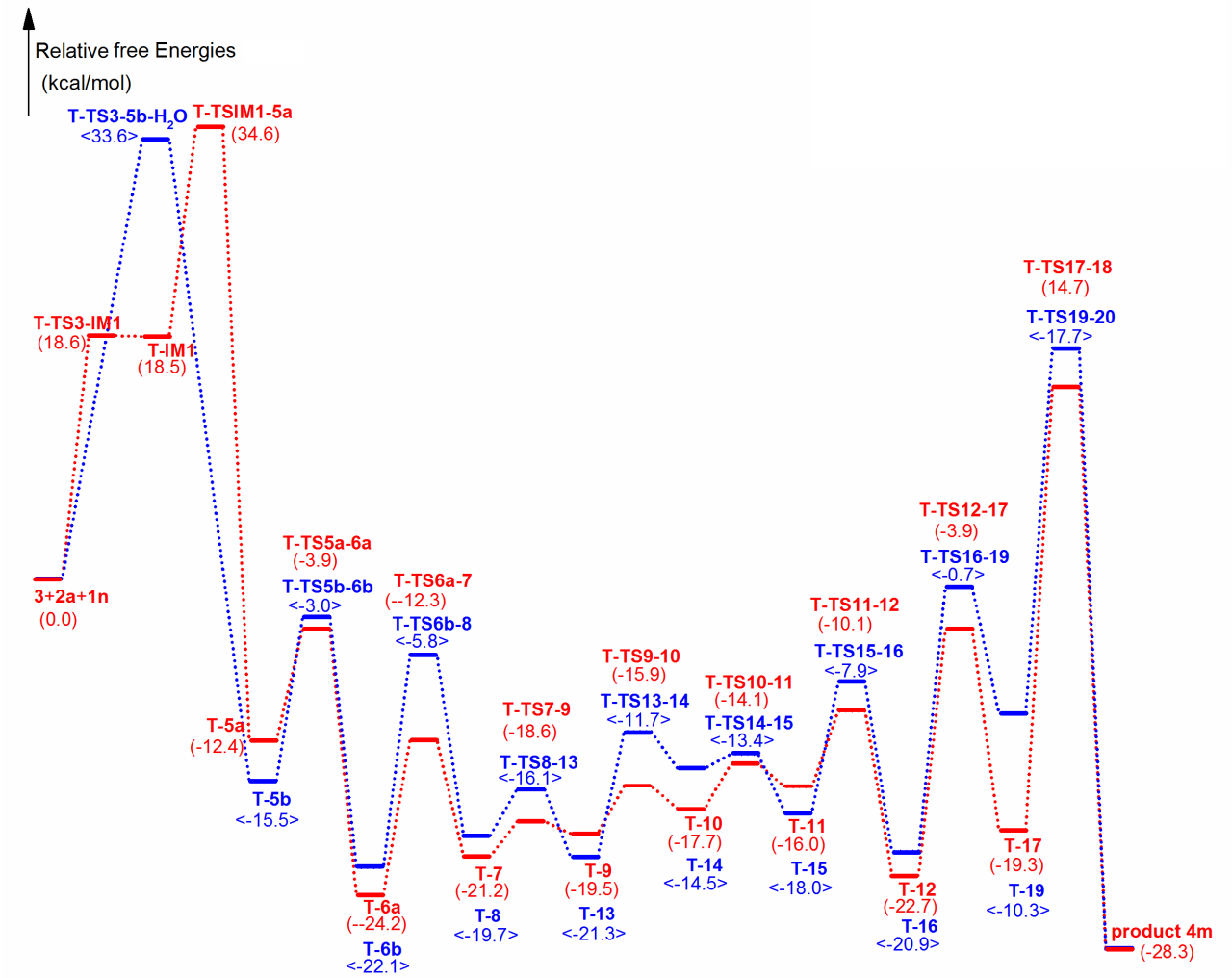

Figure 8. Energy profile of L-proline–catalyzed trasamidation of **1n** with **2a** in toluene. The relative free energies at M06/6-311+G(2d,p)//M06/6-31+G(d,p) level are given in kcal/mol.

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Keywords: L-Proline • trasamidation • density function calculations• solvent effect • reaction mechanisms

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22 In this paper, we have used the free energies that were gotten by the single-point energies at the M06/SMD/6-311+G(2d,p) level plus the thermal correction in M06/PCM/6-31+G(d,p) method.

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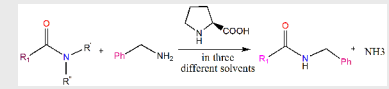

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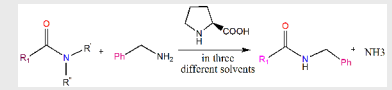

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