Transformations and Tautomeric Equilibrium among Different Intermediates in Proline-Catalyzed Reactions of Aldehydes or Ketones

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The enamines, iminium ions, and oxazolidinones are thought to be the key intermediates in the proline-catalyzed reactions of aldehydes or ketones, but there is an extensive controversy about their roles. Here, the corresponding transition states connecting any two of the three kinds of species are located at the ωB97XD/6-311+G** level of theory. The calculations demonstrate that the oxazolidinones are the predominant species in both the gas phase and solvents; there exists tautomeric equilibrium among these species and the equilibriums are controlled by the employed solvents and temperature in the reaction. These results demonstrate that the concentration and role of the mentioned species are controlled by the employed solvent and temperature. A new reaction pathway is presented herein for the transformation between iminium ions and oxazolidinones through iminium ion-water complex and oxazolidinone-water complex. The calculations demonstrate that the rate-limiting step in proline-catalyzed Mannich reaction between acetaldehyde/ketones and N-Boc imines is the formation of the C−C bond rather than the intermediates tautomerization. These calculations rationalize the available experimental observations and can be valuable in optimizing the experimental conditions of asymmetric organic-catalyzed reactions of aldehydes or ketones.

Key words: Asymmetric organocatalysis, Tautomerism, Transition state, Intermediate, Density functional theory

I. INTRODUCTION

The general mechanism of the proline-mediated reactions of aldehydes or ketones involves iminium/enamine intermediates [1−11]. List et al. reported a series of crystal structures of the stabilized enamines of proline and some of its analogues [12]. Gschwind et al. provided the detailed characterization of intermediates in the proline-mediated self-aldol reaction of propanal in DMSO [13]. Recently Gschwind et al. found the rapid cyclization of the enamine to the oxazolidine in prolinol catalysts [14].

However, what has been detected in the proline-catalyzed asymmetric reactions of carbonyl compounds are oxazolidinones, instead of the enamines, in a number of experimental situations [15−20]. In 2007, Seebach and Eschenmoser presented a model including the oxazolidinone species [21], with stereoinduction in the same sense as in the Houk-List model [4, 5, 7, 9, 16]. The detailed experimental investigation showed that the oxazolidinones were subject to tautomerizing into the zwitterionic iminium ion upon addition of protic solvents and could be the precursors of the asymmetric addition reactions. In recent years, Armstrong et al. [22] and Blackmond et al. [23] highlighted the role of enamine carboxylate species, which can interchange with oxazolidinones depending on the quantity of additives.

The experiments by Pihko et al. demonstrated that the additive water had a highly beneficial effect on proline-catalyzed intermolecular aldol reactions [18, 24]. The experiment by Gschwind et al. indicated that the relative ratios of the intermediates were not affected by added water [13]. Ajitha and Suresh found an iminium ion-water complex can benefit the formation of an enamine by its release of one water molecule [25, 26]. Evidently, the additives play different roles under different conditions.

Proline-derived enamines and prolinol enamines had never been detected in MeOH, MeCN, CHCl3, or PhMe but had been detected in the dipolar aprotic solvent DMSO and DMF [13, 14]. Recently, the experiments by Gschwind et al. [27] demonstrated that the overall amount of enamines decreases gradually when reaction proceed in DMSO, MeCN, CHCl3, and PhMe one by one. Obviously, the properties of the solvents are critical for the detection of proline-derived intermediates.

To rationalize the different, even contradictory experimental observations about the three kinds of mentioned intermediates and to provide insight into the
TABLE I The relative energies between different tautomers at the \( \omega \text{B97XD}/6-311++G^{**} \) level of theory, \( \varepsilon \) is the dielectric constant of the solvent.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( \varepsilon )</th>
<th>1a Relative energy/(kcal/mol)</th>
<th>2a Relative energy/(kcal/mol)</th>
<th>3a Relative energy/(kcal/mol)</th>
<th>1s Relative energy/(kcal/mol)</th>
<th>2s Relative energy/(kcal/mol)</th>
<th>3s Relative energy/(kcal/mol)</th>
</tr>
</thead>
<tbody>
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<td>Gas</td>
<td>0.00</td>
<td>-16.61</td>
<td>-10.88</td>
<td>0.67</td>
<td>-17.99</td>
<td>-10.78</td>
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<tr>
<td>CHCl(_3)</td>
<td>4.71</td>
<td>-5.57</td>
<td>-0.69</td>
<td>0.70</td>
<td>-6.91</td>
<td>-0.43</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>7.43</td>
<td>-3.69</td>
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<td>0.56</td>
<td>-5.03</td>
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</tr>
<tr>
<td>CH(_2)Cl(_2)</td>
<td>8.93</td>
<td>-3.08</td>
<td>1.63</td>
<td>0.82</td>
<td>-4.40</td>
<td>1.84</td>
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</tr>
<tr>
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<td>-2.44</td>
<td>2.21</td>
<td>0.68</td>
<td>-3.77</td>
<td>2.55</td>
<td></td>
</tr>
<tr>
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<td>-2.36</td>
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<td>0.69</td>
<td>-3.70</td>
<td>2.63</td>
<td></td>
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<tr>
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<td>0.99</td>
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</tr>
<tr>
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<td>3.53</td>
<td>0.50</td>
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<td>3.85</td>
<td>0.38</td>
<td>-2.02</td>
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<td></td>
</tr>
<tr>
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<td>3.92</td>
<td>0.34</td>
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<td>4.24</td>
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</tr>
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</tr>
<tr>
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<td>4.11</td>
<td>0.34</td>
<td>-1.73</td>
<td>4.43</td>
<td></td>
</tr>
</tbody>
</table>

role of additives and solvents, we here selected proline-catalyzed reaction of acetaldehyde as model system and performed a systematic density functional theory (DFT) study on them. The calculations demonstrate that there exists tautomeric equilibrium among these species depicted in Fig.1, which rationalize the available observations. In addition, the study provides a clue on how to stabilize these intermediates.

II. COMPUTATIONAL DETAILS

In this study, the \( \omega \text{B97XD} \) functional [28] with the 6-311++G\(^{**}\) basis set was used. The \( \omega \text{B97XD} \) functional includes dispersion corrections and can treat hydrogen bonding and van der Waals interactions better than conventional functional, such as BLYP and B3LYP. All geometries were fully optimized without constraint at the \( \text{B97XD}/6-311++G^{**} \) level of theory. The transition states were located at the same level of theory, and have been confirmed by frequency analysis. In some cases, the intrinsic reaction coordinate (IRC) were followed to verify the transition structure connecting the two desired minima of the proposed mechanism. Solvent effects were examined by the polarizable continuum model (PCM). Gibbs free energies of all the stationary points were obtained by frequency calculations at 298.15 K. For the reactions involving water, the activation energies were obtained from the revised energy by the additional water molecule, to insure that the related structures contain the same number of atoms. All calculations were carried out by the use of the Gaussian 09 program [29].

III. RESULTS AND DISCUSSION

A. Stability of the tautomers

In the proline-catalyzed asymmetric reactions, the reaction of aldehydes or ketones with proline leads to the generation of carbinolamine intermediates firstly [12, 25, 30–33] which dehydrate and form the tautomers mentioned above (Fig.1). Tautomeric transformations are subject to solvent effect. The relative energies among different tautomers at the \( \omega \text{B97XD}/6-311++G^{**} \) level of theory is provided in Table I. As seen in Table I, oxazolidinones 2a/2s are the two ones with the lowest energy among all the isomers both in the gas phase and in solvents, indicating that they are the two predominating isomers in the gas phase as well as in the solvents. These results are in good agreement with the experimental observations that the oxazolidinones can be easily detected [15–20]. Sorted by relative energy, the order is 2s<2a<3a<3s<1a<1s in gas phase and CHCl\(_3\); while in other solvents, it is 2s<2a<1a<1s<3a<3s. Obviously, it indicates that the most unstable tautomer is in iminium ion form 1a/1s in
gas phase and CHCl₃, whereas enamine forms 3a/3s in other solvents. The different order of relative energy in gas phase and solvents may be ascribed to the higher screen-effects of polar solvent to the zwitterionics.

Table I shows that the relative energies of 1a and 1s are higher than those of 2a, 2s, 3a, and 3s in gas phase. In addition, the energy differences between species 1(1a/1s) and species 2(2a/2s) or 3(3a/3s) decrease with the increase of dielectric constants of the solvents. This may ascribe to the stronger interaction between the zwitterionic iminium ion 1a/1s and the solvents. This may ascribe to the stronger interaction between the zwitterionic iminium ion 1a/1s and the solvents, suggesting that all the three species may be detected in solvents with higher dielectric constants.

### B. Transformations between different Intermediates

Obviously, the different intermediates play different roles in the reaction; however the experimental observations are discrepant from different research group. We think that there exists possible interconversion among iminium ions 1a/1s, oxazolidinones 2a/2s, and enamines 3a/3s, and the transition state structures for their conversion are located (Fig.2). Actually, Parasuk et al. have examined the transformation between iminium ion 1a/1s and enamine 3a/3s, but oxazolidinones 2a/2s were not considered [34]. We here focus on the intertransformations among these intermediates and highlight the role of water in the process of tautomerism. The proposed transformations are presented in Fig.2 and the calculated activation energies are reported in Table II.

The rotation of the C–N bond from syn-enamine 3s to anti-enamine 3a was studied by Parasuk et al. and was found to be an easy process [34]. The energy barrier for the rotation of C–N bond between 3a and 3s calculated herein are only 5.47 and 5.70 kcal/mol, which demonstrates that the rotation of C–N bond is indeed a good bridge to connect the syn- and anti-enamine configurations.

As seen in Table II, \( \Delta G_{12a} \) are lower than \( \Delta G_{21a} \) in various solvents. It indicates the iminium ion 1a is easier to transform into oxazolidinone 2a. Moreover, with the increase of dielectric constant of the solvents, \( \Delta G_{12a} \) increases while \( \Delta G_{21a} \) decreases. According to this result, it becomes easier to generate the iminium ion 1a from the thermodynamically more stable oxazolidinone 2a in the solvents with higher dielectric constant. The calculated result agrees with the results in Table I that the energy differences between iminium ion 1a and oxazolidinone 2a decrease with the increase of the dielectric constant of the solvents. \( \Delta G_{13a}^{\text{w}} \) and \( \Delta G_{23a}^{\text{w}} \) increase and decrease respectively with the increasing of dielectric constant of solvents. This tendency is similar to the case of \( \Delta G_{12a} \) and \( \Delta G_{21a} \). Obviously it is conducive to generate iminium ion 1a from enamine 3a in solvent with high dielectric constant. As both the \( \Delta G_{23a} \) and \( \Delta G_{32a} \) decrease with the increase of the dielectric constant of solvents, it suggests that the solvents with higher dielectric constant are conducive to the transformation between oxazolidinone 2a and enamine 3a.

For the transformation between syn-configurations, the same conclusions can be obtained. To verify that the transition states are to connect the two minima, we performed the intrinsic reaction coordinate (IRC) calculations. The calculations show that TS₁₂a, TS₁₂s, TS₁₃s, and TS₁₃a connect iminium ion 1a/1s and oxazolidinone 2a/2s intermediates; and that the TS₂₃a is the transition state between oxazolidinone 2a and enamine 3a; and that the TS₁₃s, TS₁₃a, and TS₂₃s are the transition states between iminium ion 1a/1s and enamine 3a/3s. In addition, both \( \Delta G_{13s} \) and \( \Delta G_{23s} \), i.e., the activation energies of TS₁₃s without water’s participation are lower than \( \Delta G_{13a}^{\text{w}} \) and \( \Delta G_{23a}^{\text{w}} \), i.e., the activation energies of TS₁₃s with water’s participation in various solvents, respectively. As a result, the transformation between iminium ion 1s and enamine 3s is more likely to conduct through TS₁₃s. These results suggest that additives do not always accelerate the reaction.

Furthermore, we present a new reaction pathway between iminium ion 1a/1s and oxazolidinone 2a/2s intermediates with the participation of water in the ring-opening of oxazolidinones 2a/2s, as shown in Fig.2. Iminium ion 1a/1s and oxazolidinone 2a/2s can transform mutually through the transition states TS₁₂a, and TS₁₂s, by the direct opening or closing of the five-membered ring. However, when there is water in the reaction system, water may play an important role in the mutual transformation of these species. Our calculations demonstrate that iminium ion-water complex 1a/w/1w and oxazolidinone-water complex 2a/w/2s can transform mutually through the transition states TS₁₂a/w, and TS₁₂s/w with water’s participation in the opening or closing of the five-membered ring. And, the iminium ion-water complex 1a/w/1s and oxazolidinone-water complex 2a/w/2s release one water molecule and transform into iminium ion 1a/1s and oxazolidinone 2a/2s respectively. As shown in Table II, in the anti-configuration, \( \Delta G_{21a}^{\text{w}} \) is lower than \( \Delta G_{21a} \) in various solvents. Furthermore, as the energy of 1a/w/2a/w is much lower than that of 1a/2a with additional water, the concentration of 1a/w/2a/w would be higher than that of 1a/2a when water is accessible (see Table S1, in Supplementary material). So the transformation between iminium ion 1a and oxazolidinone 2a is more likely to be conducted through TS₁₂a/w. Although \( \Delta G_{21a}^{\text{w}} \) is a bit higher than \( \Delta G_{12a} \) in the reverse process, the concentration of 1a(w) is much higher than that of 1a, so the transformation from iminium ion to oxazolidinone is still likely through TS₁₂a. For the syn-configuration, similar conclusions can be obtained. As seen in Table II, \( \Delta G_{21a} \) are lower than that of \( \Delta G_{12a} \) in MeOH, MeCN, DMF, and DMSO. The result indicates that it is easy for the oxazolidinone 2a to transform into iminium ion 1a with water’s participation, therefore it can increase the odds of the conversion of iminium ion 1a into enamine 3a. And, the result that \( \Delta G_{21a} \) in DMF and DMSO is
FIG. 2 Transformation of iminium ions 1a/1s, oxazolidinones 2a/2s, enamines 3a/3s, and the transition states of the transformations among tautomers. The superscript "w" represents the participation of water in the transformation. Bond lengths are in Å.
TABLE II Gibbs free energy of activation (in kcal/mol) for the transformations between tautomers at the $\omega$B97XD/6-311++G** level of theory, $\varepsilon$ is the dielectric constant of the solvent.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\varepsilon$</th>
<th>$\Delta G_{12a}$</th>
<th>$\Delta G_{21a}$</th>
<th>$\Delta G_{13a}$</th>
<th>$\Delta G_{31a}$</th>
<th>$\Delta G_{13w}$</th>
<th>$\Delta G_{31w}$</th>
<th>$\Delta G_{w12a}$</th>
<th>$\Delta G_{w31a}$</th>
</tr>
</thead>
<tbody>
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<td>Gas</td>
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<td>17.10</td>
<td>30.65</td>
<td>32.33</td>
<td>10.64</td>
<td>21.52</td>
<td>4.13</td>
<td>12.84</td>
</tr>
<tr>
<td>CHCl$_4$</td>
<td>4.71</td>
<td>5.09</td>
<td>10.66</td>
<td>32.69</td>
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<td>19.24</td>
<td>19.94</td>
<td>7.87</td>
<td>8.24</td>
</tr>
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<td>21.72</td>
<td>19.51</td>
<td>7.74</td>
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<td>23.07</td>
<td>19.46</td>
<td>8.12</td>
<td>6.66</td>
</tr>
</tbody>
</table>

lower than that in MeOH indicates the transformation is easier to proceed in DMF and DMSO. These results are consistent with the experimental observations that the enamine 3a/3s can be detected in DMF and DMSO easily [13, 14, 27].

As a whole, the activation energies of TS$_a$ in the transformations between different anti-configurations are lower than those of the TS$_s$ in the transformations between different syn-configurations (as shown in Fig.3, which excludes the comparison of TS$_{w13a}$ with TS$_{13s}$, as they are the different reaction pathways among the same species). The energy barriers of C-N bond rotation between 3a and 3s are lower than those in the transformation between any two of the three kinds of intermediates, suggesting that both the syn- and anti-enamines may have the same chance to react with the other reactant in the proline-catalyzed reactions of aldehydes or ketones no matter what intermediate is formed firstly.

Compared with our recent study on the proline-catalyzed Mannich reactions between acetaldehyde and N-Boc imines [35], the lowest activation energy of the transition state for the C-C bond formation is 21.66 kcal/mol at the B3LYP/6-31G* level of the-
3a/3s are easy to proceed and their relative concentrations can be shifted by the solvents and/or additives employed. The formation of the C–C bond is the rate-determining step in proline-catalyzed Mannich reaction between acetaldehydes and N-Boc imines. These calculated findings rationalize the available experimental observations and can also be valuable in the optimization of the experimental conditions.

V. ACKNOWLEDGMENTS

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Supplementary material: The relative energy between material and material hydrate and the activation energies of transition states in the transformations between tautomers at the B3LYP/6-31G* level of theory in the gas phase are given.

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