Theoretical Investigation of the Reaction Mechanism for a Type of N-heterocyclic Compound Involving Mono-N-aryl-3-aminodihydropyrrol

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The kinetics of reaction between 4-methylaniline (1), dimethyl acetylenedicarboxylate (2) and formaldehyde (4) has been theoretically investigated to gain further insight into the reaction mechanism. The results of theoretical calculations were achieved using the ab initio method at the HF/6-311G(d,p) level of theory in gas phase. The mechanism of this reaction had 5 steps. Theoretical kinetic data (k and Ea), activation parameters (\(\Delta G^\ddagger\), \(\Delta S^\ddagger\) and \(\Delta H^\ddagger\)) and thermodynamic parameters (\(\Delta G^\circ\), \(\Delta S^\circ\) and \(\Delta H^\circ\)) were calculated for each step and overall reaction. Step 2 of the mechanism was identified as the rate determining step. Also, the method of calculations was improved to B3LYP/6-311G(d,p) level of theory and the reaction mechanism was investigated for all steps of this reaction, again kinetic data and thermodynamic parameters were recalculated at this level of the theory. Improved data at this level was in a good agreement with the HF/6-311G(d,p) level of theory. Theoretical results, altogether were compatible with the literature's reports. As expected, step 2, and step 3 were recognized as the fast and fastest steps among the other steps. The overall reaction was enthalpy-controlled and proceeded chemically-controlled. In addition, step1 was recognized relatively slow, because the five-membered ring formation in this step was inherently an energetically unfavorable process.

Keywords: N-heterocycles, Density functional theory, Aniline, Formaldehyde

INTRODUCTION

A reaction in which three or more reactants are reacted together to produce a product in a single reaction vessel is a multi-component reaction [1,2]. Multi-component reaction is an ideal basic synthesis for some organic methodology such as convergence, atom and step economy, synthetic versatility, selectivity, etc. [3-7]. Multi-component reactions (MCRs) especially with N-heterocycles products are becoming increasingly valuable in organic and medicinal chemistry [8]. N-heterocycles have various biological, medicinal and pharmaceutical applications, and in recent years the synthesis of these compounds have been found a considerable attention [8-10]. There are several bioactive natural molecules with a part of pyrrol-2-one [13,14] such as holomycin and thiolutin [14], thiomarinol A4 [15], oteromycin [16], pyrrocidine A [17], quinolactacinC [18], and ypaoamide [19]. In other words, dihydropyrrol-2-ones have been successfully used as peptidomimetic [20], HIV integrase [21], herbicidals [22], DNA polymerase inhibitors [23], caspase-3 inhibitors [24] cytotoxicandantitumor agents [25], antibiotics [26] and also inhibitor softeannexin A2-S100A10 protein interaction [27]. Previously, kinetics of N-heterocycle compound and some organic reactants have been theoretically investigated [28-38]. A typical organic reaction proceeds using a special mechanism. There may be many proposed mechanisms for a typical organic reaction. Experimental methods have many instrumental limitations such as trapping the intermediates or transition states (TSS) in confirming the mechanism from which the reactions proceed. Computational methods can make confirming the mechanism easier, cheaper and more precise. Because the
UV-Vis spectrophotometry method was not able to follow experimentally kinetics and the reaction mechanism of recent work, theoretical calculations were employed. The purpose of this study is to elucidate the mechanistic details related to the formation of mono-N-aryl-3-aminodihydropyrrrol-2-one-4-carboxylate from the reaction between aniline (1), dimethyl acetylenedicarboxylate (2) and formaldehyde (4). Synthesis of the reaction has been previously reported [39].

THEORETICAL SECTION

Computational Methods

All geometries of the reactants (1, 2 and 3, 4), product, intermediates (5, 6, 7, 8), and transition states (TS1, TS2, TS3, TS4, TS5) involved in the reaction (Scheme 1) were optimized at the HF/6-311G(d,p) level of theory in the gas phase [40]. The stationary points were classified as true minima if there was no imaginary vibrational frequency. The transition states were characterized by the first imaginary vibrational frequency. The activation energies (E_a), the Arrhenius factors, and the rate constants were computed using Eqs. (1), (2) and (3), respectively on page 9, which were derived from the transition state theory [41]. Calculation were performed with the Gaussian 09 program [42].

RESULTS AND DISCUSSION

The reaction between dimethyl acetylenedicarboxylate (DMAD) 2, aniline 1 and formaldehyde 4 were performed in the presence of p-TsOH.H_2O at room temperature for the generation of mono-N-aryl-3-aminodihydropyrrrol-2-one-4-carboxylates as shown in Scheme 1.

Speculative reaction mechanism has been shown in Fig. 1 according to the literature's report [39]. How reliable is the proposed mechanism for the title reaction? (Fig. 1). This is the main question that we attempt to find an appropriate explanation by the following theoretical calculations.

The first step of the reaction starts with C≡C bond cleavage and N-C_2 bond formation (Fig. 2). In the stationary point (compound 2), the C_1=C_2, C_2=C_3 and C_3=C_4 bond lengths, C_1=C_2=C_3, C_2=C_3=C_4 bond angles and the dihedral angle of C_1-C_2-C_3-C_4 are 1.44, 1.2 and 1.45 Å, 135.44° and also 121.568° and also 2.99°, respectively. The N and C_2 atoms are getting close, leading to the N-C_2 bond formation at intermediate 5(I_1). The first transition state has a breaking C≡C bond distance of 1.32 Å, which is 0.12 Å longer than that in DMAD, and also forming N=C_2 bond distance of 1.47 Å. In the transition state (TS_1), the C_1=C_2, C_2=C_3 and C_3=C_4 bond lengths are 1.47, 1.32 and 1.43 Å, respectively. The C_1=C_2=C_3 and N=C_2=C_3 angles are 136.6° and 104.255°. Also, the C_1=C_2=C_3=C_4 dihedral angle is 2.94°. Corresponding bonds in the intermediate 5(I_1), namely the


C1-C2, C2=C3 and C2-C3 bond lengths, are 1.50, 1.33 and 1.47 Å. The C1-C2=C3 and N...C2=C3 angles are 124.95° and 125.89°, respectively. Also, the C1-C2=C3-C4 dihedral angle is 2.85°. These changes are summarized in Table 1.

As can be seen, three significant changes would be prospect:
1) C2=C3 cleavage increase from compound 2 to intermediate 5
2) C1-C2 bond length increase in this order: intermediate 5 > TS1 > compound 1+2
3) N-C2=C3 angles take significant increasing from TS1 to intermediate 5

For the generation of the TS1 structure, it was required to proceed this procedure; the N10 and H3 atoms of aniline

![Diagram](attachment:image.png)

**Fig. 1.** The proposed mechanism between dimethyl acetylenedicarboxylate (DMAD) 2, aniline 1 and formaldehyde 4 in the presence of ρ-TsOH.H2O for the generation of mono-N-aryl-3-aminodihydropyrrrol-2-one-4-carboxylate [39]. In this particular reaction, compounds 1 and 3 are the same.
Table 1. The Major Geometrical Parameters Containing Bond Lengths, Bond Angles and Dihedral Angles for Compounds 1+2, TS1 and Intermediate 5(I1) in the First Step (Step 1) of Mechanism

<table>
<thead>
<tr>
<th>Species</th>
<th>Bond length (Å)</th>
<th>Bond angle (Degree)</th>
<th>Dihedral angle (Degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1-C2</td>
<td>C2≡C3</td>
<td>C1-C2=C3</td>
</tr>
<tr>
<td>Compound 1+2</td>
<td>1.44</td>
<td>1.2</td>
<td>1.45</td>
</tr>
<tr>
<td>TS1</td>
<td>1.47</td>
<td>1.32</td>
<td>1.43</td>
</tr>
<tr>
<td>Intermediate 5</td>
<td>1.5</td>
<td>1.33</td>
<td>1.47</td>
</tr>
</tbody>
</table>

As can be seen, three significant changes would be prospect: 1) C2≡C3 cleavage increase from compound 2 to intermediate 5; 2) C1-C2 bond length increase in this order: intermediate 5 > TS1 > compound 1+2; 3) N-C2≡C3 angles take significant increasing from TS1 to intermediate 5.

![Fig. 2. Step1 of the theoretical mechanism for the reaction between dimethyl acetylenedicarboxylate (DMAD) 2 and Aniline 1 for the generation of intermediate 5(I1).](image)

The compound should bind C2 and C3 atoms of DMAD 2, instantaneously. To do so, we put DMAD 2 and the aniline 1 structures in a far enough distance from each other, then in each step of scanning, N10 is approaching to C2 (in 0.1 Å distance), through which H3 is getting close to C3 step by step until a peak is obtained (two dimensional scanning). After each scan, the result was represented in a diagram. This is the first generation of TS1 when N10 and C2 atoms were kept in a constant distance.

Then, in the second scan, N10 approaches to C2 again (just in a 0.1 Å distance), at the same time, with respect to the new distance between N10 and C2 (second scan), H3 is getting close to C3 again step by step until a second peak of TS1 is generated. This behavior repeated for obtaining some other TS1 (third, fourth, fifth and final scan) while in each scan, N10 and C2 atoms were kept in a new constant distance. These results are shown in a separate diagram in accordance with the energy of all TS points in each scan versus the changes in N10-C2 bond length, Fig. 4. Each point on this diagram is an exhibition of the possible TS for at least seven scans in this procedure (two dimensional scanning).

This diagram has a point with the lowest energy value that obtains the TS structure. The calculated stretching frequencies at HF/6-311G(d,p) and B3LYP/6-311G(d,p) levels, listed in Table 11, show that aniline, DMAD and intermediate 5(I1) are true minimum points. The TS1 energy
at the HF/6-311G(d,p) level in the gas phase is 68.62 and 23.53 kcal mol\(^{-1}\) higher than the energy of intermediate 5(I\(_1\)) and compound 1+2, respectively (Fig. 4). Hence, this process is exothermic (\(\Delta r = -45.27\) kcal mol\(^{-1}\)) compared to the reactants. The energies of participating species in step\(_1\) at both HF/6-311G(d,p) and B3LYP/6-311G(d,p) levels are shown in Table 2.

In the second step of this mechanism, two components of the reaction, aniline (3) and formaldehyde (4) react together.

The second step of the reaction occurs with the N\(_{12}\)-C\(_{14}\) bond formation between aniline and formaldehyde for the generation of another intermediate 6(I\(_2\)). Herein, N\(_{12}\) is getting close to carbon C\(_{14}\). For the generation of the TS\(_2\) structure it was necessary to conduct the following procedure: we optimized B compound at the HF/6-311G(d,p) level and then in each step of scanning, the N\(_{12}\)-C\(_{14}\) bond length is increased (0.1 Å), H\(_{18}\) approaches to N\(_{12}\) step by step until a peak is obtained (inverse two dimensional scanning). After each scan, the result was represented in a diagram. A same procedure with step\(_1\) was employed for step\(_2\), while the N\(_{12}\)-C\(_{14}\) bond length was increased in each step (just 0.1 Å) of the process. The results are shown in Fig. 6.
Table 2. Energies of the Participating Species in Step1 at Both HF/6-311G(d,p) and B3LYP/6-311G(d,p) Levels

<table>
<thead>
<tr>
<th>Step1</th>
<th>B3LYP/6-311G(d,p) (kcal mol⁻¹)</th>
<th>HF/6-311G(d,p) (kcal mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1+2</td>
<td>-515115.42</td>
<td>-512051.54</td>
</tr>
<tr>
<td>Ts</td>
<td>-515098.48</td>
<td>-512028.07</td>
</tr>
<tr>
<td>Intermediate 5(I₂)</td>
<td>-515163.74</td>
<td>-512102.43</td>
</tr>
</tbody>
</table>

In the second step of this mechanism, two components of the reaction, aniline (3) and formaldehyde (4) react together.

![Diagram](image)

**Fig. 5.** Step2 of the theoretical mechanism for the reaction between formaldehyde 4 and aniline 3 for the generation of intermediate 6(I₂).

This diagram has a point with the lowest energy value that establishes the TS₂ structure (Fig. 6). The TS₂ energy at the HF/6-311G(d,p) level in the gas phase is 17.20 kcal mol⁻¹ which is 28.51 kcal mol⁻¹ higher than the energy of the stationary point compound (3+4) and intermediate 6(I₂), respectively (Fig. 7). Hence, this process is exothermic (Δr = -11.31 kcal mol⁻¹) compared to the reactants.

In the stationary point, the comparison of molecular geometries in reactants, TS₂ and intermediate 6(I₂) at HF/6-311G(d,p) level show that the N₁₂-C bond length changes from 1.38 to 1.43 and 1.39 Å, the C₁₄-N₁₂ bond length changes from 3.57 to 1.55, and 1.42 Å and O₁₇-C₁₄ from 1.2 to 1.39 and 1.43 Å, and the O₁₇-C₁₄-N₁₂ angles change from 60.61° to 94.47° and 114.55° and also the dihedral angle is 111.59° and 80.05° in the TS₂ and intermediate I₂. These changes are summarized in Table 3.

As can be seen, three significant changes would be prospect:
1) N₁₂-C₃ cleavage increase from reactant to TS₂
2) C₁₄-N₁₂ bond length decrease in this order: intermediate 5 > TS₂ > compound 3+4
3) C₃-N-C₁₄ angles take significant increase from TS₁ to intermediate 6

The Energies of participating species in step2 at the both

HF/6-311G(d,p) and B3LYP/6-311G(d,p) levels are shown in Table 4.

The same procedure was employed for step 3, step 4 and step 5. All the relevant Figs. (1-7) and Tables (1-6) have been reported in the supplemental materials file (SMF). The first stretching frequencies for all steps of the mechanism at the HF/6-311G(d,p) and B3LYP/6-311G(d,p) levels of theory at 298.15 K are shown in Table 5 with respect to the sum of the result obtained from all the figures and tables mentioned in SMF. Activation parameters including $\Delta H^\ddagger$, $\Delta G^\ddagger$ and $\Delta S^\ddagger$ for each step of the speculative mechanisms at the HF/6-311G(d,p) and B3LYP/6-311G(d,p) levels at 298.15 K, are reported in Table 6.

As can be seen, the activation enthalpy ($\Delta H^\ddagger$) and the activation Gibbs free energy ($\Delta G^\ddagger$) for step 2 at higher level of theory (B3LYP/6-311G(d,p)) are larger than the other steps which suggest that the energy required for step 2 is relatively high and it is an energetically unfavorable

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**Fig. 6.** The two dimensional scan of the obtained TS$_2$ structure.

**Fig. 7.** The potential energy profile for step 2 of the proposed mechanism at the HF/6-311G(d,p) level.
The parameters including hydrogenative membered ring formation between two intermediates 5(I) and 6(I) are reported in Tables 7 and 8, respectively. As can be seen, at both levels of the theory, step 2 is the rate determining step and step 1 is the fastest step. The step 1 is relatively fast, this is true, because in this step two intermediates, 5(I) and 6(I), react with each other. It seems that at higher level (B3LYP/6-311G(d,p)) the results are much more reliable than the HF/6-311G(d,p) level, because, step 3, which is a fast reaction between two intermediates 5(I) and 6(I), is kinetically more favorable at this level. Also the step 5 is relatively fast, because this step involves [1,3] hydrogen proton transfer which is usually fast process. The step 4, is relatively slow, because the five membered ring formation is inherently an energetically unfavorable process.

As can be seen, three significant changes would be prospect: 1) N12-C3 cleavage increase from reactant to TS2; 2) C14-N12 bond length decrease in this order: intermediate 5 > TS2 > compound 3+4; 3) C3-N-C14 angles take significant inceas from TS1 to intermediate 6.

Table 3. Some of the Bond Lengths, Bond Angles and Dihedral Angles of Step 2 of the Proposed Mechanism

<table>
<thead>
<tr>
<th>Species</th>
<th>Bond length (Å)</th>
<th>Bond angle (Degree)</th>
<th>Dihedral angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N12-C3</td>
<td>1.38</td>
<td>3.57</td>
<td>1.2</td>
</tr>
<tr>
<td>C14-N12</td>
<td>1.39</td>
<td>1.55</td>
<td>1.39</td>
</tr>
<tr>
<td>O17-C14</td>
<td>60.61</td>
<td>109.12</td>
<td>109.68</td>
</tr>
<tr>
<td>O17-C14-N12</td>
<td>114.55</td>
<td>114.03</td>
<td>125.03</td>
</tr>
<tr>
<td>H12=O-C14</td>
<td>119.88</td>
<td>115.59</td>
<td></td>
</tr>
<tr>
<td>C3-N-C14</td>
<td>80.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O17-C14-N12-C3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As can be seen, intermediate 5 > TS2 > compound 3+4; 3) C3-N-C14 angles take significant increments from TS1 to intermediate 6.

Table 4. Energies of Participating Species in Step 2 at the both HF/6-311G(d,p) and B3LYP/6-311G(d,p) Levels

<table>
<thead>
<tr>
<th>Step 2</th>
<th>B3LYP/6-311G(d,p) (kcal mol(^{-1}))</th>
<th>HF/6-311G(d,p) (kcal mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1+2</td>
<td>-252400.96</td>
<td>-250714.03</td>
</tr>
<tr>
<td>TS</td>
<td>-252408.55</td>
<td>-250724.51</td>
</tr>
<tr>
<td>Intermediate 5</td>
<td>-252362.81</td>
<td>-250667.65</td>
</tr>
</tbody>
</table>

Table 5. The First Stretching Frequency for all Steps of the Mechanism at HF/6-311G(d,p) and B3LYP/6-311G (d,p) Levels of Theory

<table>
<thead>
<tr>
<th>Species</th>
<th>First stretching frequency (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF/6-311G(d,p)</td>
</tr>
<tr>
<td>Ground state of the reactants (1 and 2) in the step 1</td>
<td>23.3</td>
</tr>
<tr>
<td>TS1</td>
<td>2138.7i</td>
</tr>
<tr>
<td>Ground state of the product (I₁) in the step 1</td>
<td>25.2</td>
</tr>
<tr>
<td>Ground state of reactants (3 and 4) in the step 2</td>
<td>20.7</td>
</tr>
<tr>
<td>TS₂</td>
<td>1941.9i</td>
</tr>
<tr>
<td>Ground state of the product (I₂) in the step 2</td>
<td>48.7</td>
</tr>
<tr>
<td>Ground state of the reactants (I₁ and I₂) in the step 3</td>
<td>14.1</td>
</tr>
<tr>
<td>TS₃</td>
<td>400.5i</td>
</tr>
<tr>
<td>Ground state of the products (I₃) in the step 3</td>
<td>16.5</td>
</tr>
<tr>
<td>Ground state of the reactants (I₁) in the step 4</td>
<td>11.9</td>
</tr>
<tr>
<td>TS₄</td>
<td>1667.6i</td>
</tr>
<tr>
<td>Ground state of the products (I₄) in the step 4</td>
<td>14.6</td>
</tr>
<tr>
<td>Ground state of the reactants (I₃) in the step 5</td>
<td>19.7</td>
</tr>
<tr>
<td>TS₅</td>
<td>2396.0i</td>
</tr>
<tr>
<td>Ground state of the final product in the step 5</td>
<td>19.8</td>
</tr>
</tbody>
</table>

\[
E_a = \Delta H^\ddagger(T) + nRT \tag{1}
\]
\[
A = (ekBT/h) \exp(\Delta S^\ddagger/R) \tag{2}
\]
\[
k = \frac{k_e T}{h} \times (R \times T)^{\alpha^\ddagger} \times e^{-\Delta H^\ddagger/k_b T} \times e^{\Delta S^\ddagger/k_b T} \tag{3}
\]

In addition, the overall thermodynamic reaction parameters for this mechanism are listed in Table 8. It was found that the reaction is thermodynamically favorable and spontaneous. The free Gibbs energy analysis shows that the mechanism is exothermic and values of \(\Delta_r H^\circ_{\text{total}}\) and \(\Delta_r G^\circ_{\text{total}}\) are large negative which implies that the reaction is exothermic and spontaneous and these features makes the reaction thermodynamically favorable. In addition the reaction is enthalpy controlled because the activation enthalpy (\(\Delta H^\ddagger\)) is much greater than \(T\Delta S^\ddagger\) (Table 6).

Kinetic Calculations

Based on the results presented, the simplified scheme for the proposed mechanism (Fig. 1) is shown in Fig. 8.

At first, the rate law is written using the final step for the formation of the product.

\[
\text{Rate} = k_5[I_4] \tag{4}
\]
**Table 6.** Activation Parameters ($\Delta G^\ddagger$ and $\Delta H^\ddagger$) and $\Delta S^\ddagger$, in kcal mol$^{-1}$, at 298.15 K, for each Step of the Mechanism for both Levels

<table>
<thead>
<tr>
<th>Step $i$</th>
<th>$\Delta G^\ddagger$</th>
<th>$\Delta H^\ddagger$</th>
<th>$\Delta S^\ddagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF</td>
<td>B3LYP</td>
<td>HF</td>
</tr>
<tr>
<td>Step 1</td>
<td>19.333</td>
<td>10.35</td>
<td>19.59</td>
</tr>
<tr>
<td></td>
<td>71.38</td>
<td>61.45</td>
<td>71.18</td>
</tr>
<tr>
<td>Step 2</td>
<td>50.7</td>
<td>40.48</td>
<td>45.31</td>
</tr>
<tr>
<td>Step 3</td>
<td>19.3</td>
<td>7.94</td>
<td>15.96</td>
</tr>
<tr>
<td>Step 4</td>
<td>46.14</td>
<td>25.11</td>
<td>44.43</td>
</tr>
<tr>
<td>Step 5</td>
<td>42.56</td>
<td>23.48</td>
<td>38.92</td>
</tr>
</tbody>
</table>

**Table 7.** The Thermodynamic Parameters Including $\Delta H^o$, $\Delta G^o$ (kcal mol$^{-1}$) and $\Delta S^o$ (cal K$^{-1}$ mol$^{-1}$) for each Step of the Mechanism at 298.15 K, at both Levels of the Theory

<table>
<thead>
<tr>
<th>Step</th>
<th>$\Delta H^o$</th>
<th>$\Delta G^o$</th>
<th>$\Delta S^o$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF</td>
<td>B3LYP</td>
<td>HF</td>
</tr>
<tr>
<td>1</td>
<td>-51.58</td>
<td>-51.78</td>
<td>-52.043</td>
</tr>
<tr>
<td>2</td>
<td>-8.283</td>
<td>-5.517</td>
<td>-3.419</td>
</tr>
<tr>
<td>3</td>
<td>0.1619</td>
<td>-1.714</td>
<td>2.915</td>
</tr>
<tr>
<td>4</td>
<td>6.68</td>
<td>5.68</td>
<td>5.0195</td>
</tr>
<tr>
<td>5</td>
<td>-7.605</td>
<td>-6.344</td>
<td>-3.018</td>
</tr>
</tbody>
</table>

**Table 8.** Overall Reaction Parameters Including $\Delta H^o_{\text{total}}$, $\Delta G^o_{\text{total}}$ and $\Delta S^o_{\text{total}}$ at 298.15 K, at both Levels of the Theory

<table>
<thead>
<tr>
<th>$\Delta S^o$</th>
<th>$\Delta H^o_{\text{total}}$</th>
<th>$\Delta G^o_{\text{total}}$</th>
<th>$\Delta S^o_{\text{total}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF</td>
<td>B3LYP</td>
<td>HF</td>
</tr>
<tr>
<td></td>
<td>-60.4</td>
<td>-59.7</td>
<td>-53.5</td>
</tr>
</tbody>
</table>

$^a$kcal mol$^{-1}$. $^b$cal mol$^{-1}$ K$^{-1}$.
We can apply the steady-state approximation to $[I_4]$, $[I_3]$, $[I_2]$ and $[I_1]$. To obtain a suitable expression for $[I_4]$, $[I_3]$, $[I_2]$ and $[I_1]$, we can assume that after an initial brief period the concentration of $[I_4]$, $[I_3]$, $[I_2]$ and $[I_1]$ achieve a steady state while their rates of formation and disappearance are balanced. Therefore, $\frac{d[I_4]}{dt}$, $\frac{d[I_3]}{dt}$, $\frac{d[I_2]}{dt}$ and $\frac{d[I_1]}{dt}$ are zero and we can obtain expressions for the intermediates as follows:

$$\frac{d[I_4]}{dt} = k_4[I_3] - k_1[I_4] = 0$$

$$[I_4] = \frac{k_4[I_3]}{k_1}$$

(5)

$$\frac{d[I_3]}{dt} = k_3[I_2] - k_2[I_3] = 0$$

$$[I_3] = \frac{k_3[I_2]}{k_2}$$

$$\frac{d[I_2]}{dt} = k_2[I_1] - k_1[I_2] = 0$$

$$[I_2] = \frac{k_2[I_1]}{k_1}$$

(6)

$$\frac{d[I_1]}{dt} = k_1[I_1] - k_3[I_2] = 0$$

$$[I_1] = \frac{k_1[I_1]}{k_3}$$

Table 9. Rate Constant and Activation Energies for all Steps of the Mechanism at the B3LYP/6-311G(d,p) Level

<table>
<thead>
<tr>
<th>Step</th>
<th>Rate constant</th>
<th>Pre-exponential factor (frequency factor)</th>
<th>$E_a$ forward</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steps 1, 2 and 3 (mol$^{-1}$ l$^{-1}$ s$^{-1}$)</td>
<td>(mol$^{-1}$ l$^{-1}$ s$^{-1}$)</td>
<td>(kcal mol$^{-1}$)</td>
</tr>
<tr>
<td>1</td>
<td>$k_1 = 1.5 \times 10^5$</td>
<td>$A_1 = 8.46 \times 10^{10}$</td>
<td>10.54</td>
</tr>
<tr>
<td>2</td>
<td>$k_2 = 1.3 \times 10^{-17}$</td>
<td>$A_2 = 1.5 \times 10^{10}$</td>
<td>36.92</td>
</tr>
<tr>
<td>3</td>
<td>$k_3 = 9.3 \times 10^{-6}$</td>
<td>$A_3 = 3.5 \times 10^{11}$</td>
<td>6.25</td>
</tr>
<tr>
<td>4</td>
<td>$k_4 = 2.4 \times 10^{-9}$</td>
<td>$A_4 = 2.27 \times 10^{6}$</td>
<td>23.24</td>
</tr>
<tr>
<td>5</td>
<td>$k_5 = 3.77 \times 10^{-5}$</td>
<td>$A_5 = 2.62 \times 10^{10}$</td>
<td>20.15</td>
</tr>
</tbody>
</table>

Table 10. Rate Constant and Activation Energies for all Steps of the Mechanisms at HF/6-311G(d,p)

<table>
<thead>
<tr>
<th>Step</th>
<th>Rate constant</th>
<th>Pre-exponential factor (frequency factor)</th>
<th>$E_a$ forward</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steps 1, 2 and 3 (mol$^{-1}$ l$^{-1}$ s$^{-1}$)</td>
<td>(mol$^{-1}$ l$^{-1}$ s$^{-1}$)</td>
<td>(kcal mol$^{-1}$)</td>
</tr>
<tr>
<td>1</td>
<td>$k_1 = 4.5 \times 10^{-2}$</td>
<td>$A_1 = 2.6 \times 10^{13}$</td>
<td>20.19</td>
</tr>
<tr>
<td>2</td>
<td>$k_2 = 4.38 \times 10^{-25}$</td>
<td>$A_2 = 1.96 \times 10^{9}$</td>
<td>45.90</td>
</tr>
<tr>
<td>3</td>
<td>$k_3 = 5.91 \times 10^{-2}$</td>
<td>$A_3 = 8.07 \times 10^{10}$</td>
<td>16.55</td>
</tr>
<tr>
<td>4</td>
<td>$k_4 = 4.42 \times 10^{-18}$</td>
<td>$A_4 = 9.42 \times 10^{11}$</td>
<td>39.51</td>
</tr>
<tr>
<td>5</td>
<td>$k_5 = 9.8 \times 10^{-16}$</td>
<td>$A_5 = 3.6 \times 10^{10}$</td>
<td>36.37</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
(1) & \quad 1 + 2 \xrightleftharpoons[k_{-1}]{k_1} I_1 \quad \text{or} \quad \text{cis}(I_1) \\
(2) & \quad 3 + 4 \xrightleftharpoons[k_{-1}]{k_{3\text{slow}}} \text{CAT} \quad I_2 \quad \text{or} \quad \text{cis}(I_2) \\
(3) & \quad I_1(\text{cis}(I_1)) + I_2(\text{cis}(I_2)) \xrightarrow[k_{3\text{relatively fast}}]{k_3} I_3 \quad \text{or} \quad \text{cis}(I_3) \\
(4) & \quad I_3(\text{cis}(I_3)) \xrightarrow[k_{4\text{fast}}]{k_4} \text{product} \\
(5) & \quad \text{I}_4(\text{cis}(I_4)) \xrightarrow[k_{5\text{fast}}]{k_5} \text{product}
\end{align*}
\]

Fig. 8. A simplified proposed scheme for the reaction mechanism.

\[
\frac{d[I_2]}{dt} = k_2[I_1][I_4] - k_4[I_2] \quad \Rightarrow \quad 0 = k_2[I_1][I_4] - k_3[I_2] 
\]

\[
\frac{d[I_3]}{dt} = k_3[I_3][I_2] - k_3[I_3][I_4] = 0 \quad \Rightarrow \quad \frac{k_3[I_3][I_2]}{k_3 + k_4[I_4]} = [I_3]
\]

The value of (6) can be replaced in Eq. (5) to yield Eq. (9)

\[
[I_4] = \frac{k_3[I_3][I_2]}{k_4}
\]

and with the replacement of Eqs. (7) and (8) in (9), the following equation is obtained:

\[
[I_4] = \frac{k_3[I_3][I_2]}{k_4}
\]

With the replacement of Eqs. (10) in (4), the rate equation becomes:

\[
\text{Rate} = k_5 [I_4]
\]

The final equation indicates that the overall order of the reaction is two. In addition, according to this equation, partial orders with respect to each reactant of step 2, namely aniline (3) and formaldehyde (4), are 1 and 1, respectively. In addition, the rate constants such as \( k_1, k_3, k_4 \), and \( k_5 \) could not be seen in the rate law (11), so these steps are not rate determining steps. Step 2 is the only RDS and this is in agreement with the theoretical results.

CONCLUSIONS

In this work, detailed kinetics and mechanism of the reaction between dimethyl acetylenedicarboxylate (DMAD) 2 and aniline 1 and formaldehyde 4 were theoretically studied in the presence of \( \rho \)-TsOH.H2O for the generation of mono-N-aryl-3-aminohydropyrrol-2-one-4-carboxylates.

By considering the kinetic data and thermodynamic parameters of the mechanism, the following results can be asserted:

1. At both levels of theory, the second step of the mechanism (step 2) was recognized as a rate-determining step among the competition steps involved the reaction mechanism with \( E_a \), forward \( = 45.90 \text{ kcal mol}^{-1} \) and \( k_2 = 4.38 \times 10^{-25} \text{ (M s}^{-1}) \) at HF/6-311G(d,p) and also \( E_a \), forward \( = 36.2 \text{ kcal mol}^{-1} \) and \( k_2 = 1.31 \times 10^{-17} \text{ (M s}^{-1}) \) at B3LYP/6-311G(d,p) level of theory.
2. The third step (step 3) of the mechanism was recognized as a fast step with \( Ea \), forward \( = 16.55 \text{ kcal mol}^{-1} \) and \( k_3 = 5.91 \times 10^{-2} \text{ (M s}^{-1}) \) at HF/6-311G(d,p) and \( Ea \), forward \( = 6.25 \text{ kcal mol}^{-1} \) and \( k_3 = 9.3 \times 10^{-4} \text{ (M s}^{-1}) \) at B3LYP/6-311G(d,p). This is a logical fact because in this step both the intermediates 5(I1) and 6(I2) react together.
3. The step 3 is relatively slow because the five membered ring formation is inherently an energetically unfavorable process.
4. Also, step 4 is considerably fast because of the \([1,3]\) H-shift which is usually a fast process.
5. $\Delta H^\circ_{\text{total}}$ and $\Delta G^\circ_{\text{total}}$ of the overall reaction were 59.6768 kcal mol$^{-1}$ and -50.54 kcal mol$^{-1}$, respectively, at B3LYP/6-311G(d,p) level, indicating that the reaction is exothermic and spontaneous process and it is thermodynamically favorable.

6. The theoretical kinetic studies show that the overall order of reaction is two, which is overall order of the reaction with respect to each reactant that participate in step 2 namely aniline (3) and formaldehyde (4).

7. The reaction is enthalpy-controlled because the value of ($\Delta H^\circ$) is much greater than $T\Delta S^\circ$.

8. Activation enthalpy ($\Delta H^\circ$) and Gibbs free energy ($\Delta G^\circ$) for step2 at higher level (B3LYP/6-311G(d,p)) are larger than the other steps involved the reaction mechanism, suggesting that the reaction is chemically-controlled.

9. The results at higher level (B3LYP/6-311G(d,p)) were are in better agreement with the experimental results.

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