A Theoretical Investigation of Kinetics and Mechanism of Aza-Cope Rearrangement


ABSTRACT
A theoretical study of the kinetic and mechanism of 3-aza-Cope rearrangement in gas phase was performed using DFT methods at B3LYP levels of theory with 6-311++G(d,p) basis set at 298.15K. Equilibrium molecular geometries and harmonic vibrational frequencies of the reactant, transition state and product were calculated. Then, rate constant and activation thermodynamics parameters were calculated and the results showed a fairly good agreement with experimental results that cited in the reference [25]. These calculations indicated that the reaction proceeds through an asynchronous concerted mechanism.

INTRODUCTION
Organic reactions usually end up with products that are in agreement with accepted mechanisms. Consequently the products are often called normal products. In some cases, reactions do not lead to exclusively and solely the expected products, but may give other ones that come from mechanistically different pathways. These unexpected products are called, abnormal products, or rearranged products. The rearranged product is sometimes not only the abnormal but also the major one. This may result from an expectable rearrangement occurring during the reaction to fulfill the principle of the minimum energy state of the whole system. A certain energetic relief or a certain case of the system must manifest to yield the stable product, the rearrangement product. This can be supplied through several phenomena: a) a delocalization of the generated radical, cation or anion species over the atoms of the molecules with the mostly probable localization on the thermodynamically favored site, which is called resonance; this final stage of the intermediate; that is, postulate, b) a shift or a migration of one atom or a the activated complex, would resemble the resulted product in accord with the Hammond group of atoms (radical) from one site to another via a breaking-forming bond rule. Probably all of these mechanistic phenomena occur intramolecularly. In some situations, the rearrangement gives products of an isomerization, coupled with some stereochemical changes. An energetic requirement should be provided in order for a rearrangement to take place; because of this fact, the rearrangement usually involves a heat evolution to be able to produce a more stable compound.

The aza-Cope rearrangement is a sigmatropic process which has been extensively utilized in synthesis. The 3-aza-Cope rearrangement (Scheme 1) first appeared in the chemical literature during the early 1960's [1], even though its oxygen analogue, the Claisen rearrangement, had been known since 1912. This was undoubtedly due to the high kinetic barrier of the 3-aza-Cope rearrangement [2].
In general, allyl enamine structures require heating to 100-150 °C in excess of the temperature for the analogous rearrangement with allyl enol ethers [3]. This corresponds to a ΔG° = 8 kcal mol⁻¹.

Charge on the nitrogen atom kinetically facilitates the 3-aza-Cope rearrangement considerably. In fact, the first reports of 3-aza-Cope rearrangements were those of iminium [4] and ammonium salts [5]. Since then, the effect of charge on the kinetics of these rearrangements has been extensively exploited [6]. The aza-Cope rearrangement is known to be catalyzed by acids and bases. There have been a few attempts to decrease the energy of activation of the 3-aza-Cope rearrangement other than by the generation of ammonium salts [7-10]. Because of the synthetic importance of such reactions, in this work we have performed a kinetic study on the following reaction.

\[ E_a = \Delta H^\circ + RT \]  
\[ A = (ekT/k) \exp(\Delta S^\circ(T)/R) \]

**RESULTS AND DISCUSSION**

Scheme (2) shows the optimized structures of reactant, TS, and product with the selected geometrical parameters at the B3LYP/6-311+G** level (shown in Table 1). Throughout this paper, all inter nuclear distances and angles are in angstroms and degrees, respectively.
The concerted mechanism is initiated with the Cl-N12 bond cleavage and C13-C18 bond formation. The calculation shows that the Cl-N12 bond is elongated and the C19-N12 bond shortened to form the TS. According to Table 1, the transition structure of the aza-Cope rearrangement has a breaking Cl-N12 bond distance of 2.31 angstrom and a forming C13-C18 bond distance of 2.64 angstrom. The Pauling relation [24] was used to determine the related partial bond orders and the values of 0.079 and 0.029 were obtained for Cl-N12, and C13-C18, respectively. The obtained partial bond orders indicate that 92.1% of Cl-N12 bond is broken, whereas C13-C18 has only 2.9% reaching to the transition state. The extent of broken and formed bonds in transition state shows that an asynchronous concerted mechanism has occurred for the aza-Cope rearrangement. 

Table 1. Key geometrical parameters (bond lengths in Å) of the reactant, TS and product at the B3LYP/6-311++G** level of theory for aza-Cope rearrangement (the numbering of atoms is like that in scheme 2). 

<table>
<thead>
<tr>
<th></th>
<th>Reaction</th>
<th>TS</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl-C16</td>
<td>1.496</td>
<td>1.388</td>
<td>1.332</td>
</tr>
<tr>
<td>C13-C16</td>
<td>1.331</td>
<td>1.375</td>
<td>1.505</td>
</tr>
<tr>
<td>C13-C18</td>
<td>1.375</td>
<td>1.573</td>
<td>1.502</td>
</tr>
<tr>
<td>C16-C19</td>
<td>1.336</td>
<td>1.375</td>
<td>1.502</td>
</tr>
<tr>
<td>Cl-N12</td>
<td>1.548</td>
<td>2.306</td>
<td>1.290</td>
</tr>
<tr>
<td>C19-N12</td>
<td>1.506</td>
<td>1.379</td>
<td>1.255</td>
</tr>
</tbody>
</table>

Fig. 1. Schematic energy profile of the potential energy surface for the studied reaction at B3LYP/6-311++G** level of theory (Reaction coordinate in Å).

Table 2. Distributed NBO charges on the reactant and TS at the B3LYP/6-311++G** level of theory for the studied reaction (the numbering of atoms is like that in scheme 2).

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C13</th>
<th>C16</th>
<th>C18</th>
<th>C19</th>
<th>N12</th>
</tr>
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<tbody>
<tr>
<td>Reactant</td>
<td>-0.1762</td>
<td>-0.3865</td>
<td>-0.2539</td>
<td>0.0440</td>
<td>-0.0635</td>
<td>-0.3581</td>
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<tr>
<td>TS</td>
<td>-0.1841</td>
<td>-0.3023</td>
<td>-0.2696</td>
<td>0.0413</td>
<td>0.0324</td>
<td>-0.3900</td>
</tr>
<tr>
<td>ΔCharge</td>
<td>0.0079</td>
<td>0.0037</td>
<td>0.0035</td>
<td>0.0036</td>
<td>-0.0079</td>
<td>0.0319</td>
</tr>
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</table>
The imaginary frequency for the transition structure was calculated to confirm the TS (-234.37 cm⁻¹ at B3LYP/6-311++G**). Table 3 presents, ΔG°, ΔH°, ΔS°, E_a, and rate constants for the reaction. The Gibbs free energy barrier is 19.69 kcal mol⁻¹ at B3LYP/6-311++G**, for the TS formation. The experimental value of ΔH° for this rearrangement is 19.17 kcal mol⁻¹ (see Table 3). Using the energy barrier for this reaction calculated by the B3LYP/6-311++G (d, p) method, it is possible to estimate a TST rate coefficient of 2.27 x 10¹⁰ S⁻¹ at 298.15 K in gas phase. The calculated rate constant indicates that the reaction is not too slow and can be done at room temperature. There was no experimental data about the reaction in gas phase but there were some, in liquid solutions and at the presence of suitable catalyst [25]. As can be seen there is a fairly good agreement between experimental and theoretical results.

**CONCLUSION**

A typical aza-Cope rearrangement was studied by the Density Functional theory using 6-311+G** basis set. The calculated E_a in the gas phase by the B3LYP/6-311++G** is 19.76 kcal mol⁻¹ meaning the TS formation is energetically feasible to occur. This formation is endothermic and the reaction rate increases with temperature.

The extent of broken and formed bonds in transition state shows that an asynchronous concerted mechanism has occurred for the aza-Cope rearrangement. The charge analysis shows that electron donor groups at C16 and C19 accelerate the reaction. However, at C1, C13, and C18 positions, opposite result is observed.

Table 3. Theoretical kinetic and activation parameters for aza-Cope rearrangement in gas phase at 293.15K. ΔG°, ΔH°, and E_a are in kcal mol⁻¹ and ΔS° is in cal mol⁻¹ K⁻¹.

<table>
<thead>
<tr>
<th>Method</th>
<th>ΔG°</th>
<th>ΔH°</th>
<th>ΔS°</th>
<th>E_a</th>
<th>log A (s⁻¹)</th>
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<tbody>
<tr>
<td>B3LYP</td>
<td>19.69</td>
<td>19.17</td>
<td>-1.76</td>
<td>19.76</td>
<td>12.84</td>
</tr>
<tr>
<td>6-311++G**</td>
<td></td>
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</tr>
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</table>

**REFERENCES**


