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

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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.

Keywords: DFT; Kinetics; Aza-Cope rearrangement; Activation parameters

INTRODUCTION

Organic reactions usually end up with products that are in agree 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 ease 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].

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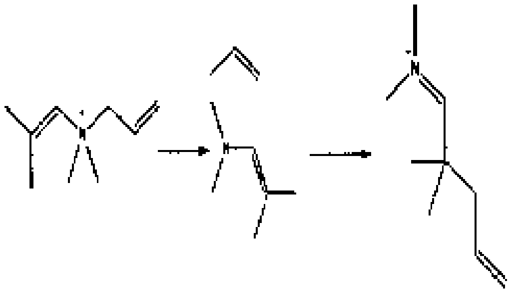
In general, allyl enamine structures require heating to 100-150 °C in excess of the temperature far the analogous rearrangement with allyl enol ethers [3]. This corresponds to a $\Delta G^{\ddagger} \geq 8$ kcal mol^{-1}.

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-Cape 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.



Scheme 1. 3-aza-Cope rearrangement.

COMPUTATIONAL DETAILS

The structures corresponding to the reactant, TS, and product were optimized and the electronic structures and harmonic vibrational frequencies of all stationary points along the reaction pathway were calculated using Gaussian 03 computational package [11] with DFT methods.

Optimization of the geometries of the stationary points on the potential energy surfaces were performed using Beck's there-parameter hybrid exchange functional with the correlation functional of Lee ,Yang, Parr(B3LYP) [12-13] using 6-311++G** basis set [14-15]. The synchronous transit guided quasi Newton (STQN) method [16-17] was used to locate the TS. The intrinsic reaction coordinate (IRC) method [18-19] was also applied in order to check and obtain the profiles connecting the TS to the two associated minima of the proposed mechanism. The natural bond orbital (NBO) analysis [20-21] was also applied to determine the charge changes occurring in the studied process. All minimum and transition state structures are verified by vibrational frequency analysis.

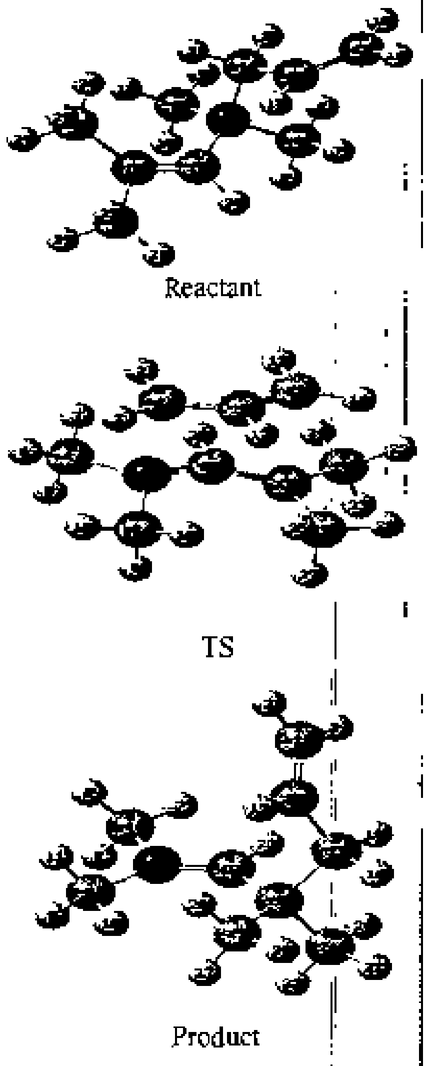
The activation energies and Arrhenius factors were computed using eqns. (1) and (2), respectively, which were derived from the transition state theory [22- 23].

$$E_a = \Delta H^{\neq} + RT \quad (1)$$

$$A = (ek_B T / h)\exp(\Delta S^{\neq}(T) / R) \quad (2)$$

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** (shown in Table 1). Throughout this paper, all inter nuclear distances and angles are in angstroms and degrees, respectively.



Reactant

TS

Product

Scheme 2. Optimized geometries of reactant, TS and product for the studied reaction at the B3LYP/6-311++G** level .

The concerted mechanism is initiated with the C1-N12 bond cleavage and C13-C18 bond formation. The calculation shows that the C1-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 C1-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 0.079and 0.029 were obtained for C1-N12, and C13-C18, respectively. The obtained partial bond orders indicate that 92.1% of C1-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. B3LYP/6-311++G** results for the reaction paths are shown in Fig 1. It demonstrates the energy as a function of the reaction coordinate, C1-N12, and represents the minimum energy paths which connect the reactant to the product through the saddle point.

Table 2 shows the charge distribution in the reactant, TS and the charge difference between TS and reactant (Δcharge) by means of NBO analysis. The results indicate that a small negative charge developed on C1, and N12 at the TS, which demonstrates that C1–N12 bond cleavage is faster than C13-C18 bond formation. In addition, the charge difference shows that electron donor groups at C1, C16, C18 and N12 accelerate the reaction while at C19 and C13 positions opposite results are observed.

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)

	Reactant	*TS*	*Product*
C1-C16	1.496	1.388	1.332
C13-C16	1.331	1.375	1.505
C13-C18	---	2.638	1.573
C18-C19	1.336	1.375	1.502
C1-N12	1.548	2.308	---
C19-N12	1.500	1.379	1.290

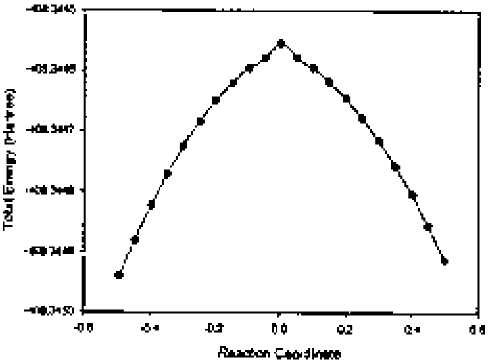


Fig. 1. Schematic energy profile of the potential energy surface for the studied reaction at B3LYP/6-311++G** level of theory (Reaction coordinate in Å).

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)

	C1	*C13*	*C16*	*C18*	*C19*	*N12*
Reactant	-0.1762	-0.2865	-0.2539	0.0449	-0.0655	-0.3581
TS	-0.1841	-0.2023	-0.2896	0.0413	0.0324	-0.3900
ΔCharge	0.0079	-0.0842	0.0357	0.0036	-0.0979	0.0319

The imaginary frequency for the transition structure was calculated to confirm the TS (-234.37 cm^{-1} at B3LYP++G**). Table 3 presents, $\Delta G^{o\#}$, $\Delta H^{o\#}$, $\Delta S^{o\#}$, 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 $\Delta H^{\circ,\#}$ for this rearrangement is 23.1(±0.8) [25] and the calculated value 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 $2.27\times10^{-2}S^{-1}$ 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 B$_3$LYP/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 298.15K. $\Delta G^{\#}$, $\Delta H^{\#}$, and E_a are in kcalmol^{-1} and $\Delta S^{\#}$ is in cal mol $^{-1}$K^{-1}

B3LYP	$\Delta G^{\#}$	$\Delta H^{\#}$	$\Delta S^{\#}$	E_a	log A(s^{-1})
6-311++G**	19.69	19.17	-1.76	19.76	12.84

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