Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS

J. Serb. Chem. Soc. 75 (5) 649–657 (2010) UDC 547.15+547.235'512:541.124
JSCS–3995 *Original scientific paper*

A theoretical study of the mechanism of the addition reaction between carbene and azacyclopropane

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(Received 3 March, revised 15 December 2009)

Abstract: The mechanism of the addition reaction between carbene and azacyclopropane was investigated using the second-order Moller–Plesset perturbation theory (MP2). By using the 6-311+G* basis set, geometry optimization, vibrational analysis and the energy properties of the involved stationary points on the potential energy surface were calculated. From the surface energy profile, it can be predicted that there are two reaction mechanisms. The first one (1) is carbene attack at the N atom of azacyclopropane to form an intermediate, **1a** (IM1a), which is a barrier-free exothermic reaction. Then, IM1a can isomerize to IM1b *via* a transition state **1a** (TS1a), in which the potential barrier is 30.0 kJ/mol. Subsequently, IM1b isomerizes to a product (Pro1) *via* TS1b with a potential barrier of 39.3 kJ/mol. The other one (2) is carbene attack at the C atom of azacyclopropane, firstly to form IM2 *via* TS2a, the potential barrier is 35.4 kJ/mol. Then IM2 isomerizes to a product (Pro2) *via* TS2b with a potential barrier of 35.1 kJ/mol. Correspondingly, the reaction energy for the reactions (1) and (2) is –478.3 and –509.9 kJ/mol, respectively. Additionally, the orbital interactions are also discussed for the leading intermediate.

Keywords: carbene; azacyclopropane; addition reaction.

INTRODUCTION

Carbenes can be defined as divalent carbon intermediates, in which the carbene carbon is linked to two adjacent groups by covalent bonds and possesses two nonbonding electrons. Carbenes play an important role in organic chemistry, especially for the addition reaction between a carbene and a C=O double bond.[1–4] Therefore, they have attracted much attention not only from theoretical but also

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doi: 10.2298/JSC090303031T

applied chemists. For example, the study of carbene has provided simple and direct synthesis of small-ring, highly strained compounds, as well as those that can hardly be synthesized through conventional ways.[5] Lu *et al*. reported systematically the reactions between carbene or substituted carbenes with some small molecules using theoretical calculations.[6–8] Apeloig *et al*. extensively studied the mechanisms and stereoselectivity of carbene addition to olefins using experimental as well as theoretical methods.[9,10] However, the reaction between carbene and small-ring strained molecules, such as azacyclopropane, has not, to the best of our knowledge, been hitherto reported. As a representative small-ring molecule, azacyclopropane also plays an important role in organic and medical chemistry. Therefore, it is very important to study the addition reaction between carbene and azacyclopropane.

In the present study, the addition reaction between carbene and azacyclopropane was systematically investigated employing the MP2/6-311+G* level of theory. Intermediates (IM), transition states (TS) and products (Pro) were located on the potential energy surface. Possible reaction mechanisms have been proposed. Hopefully, the present results will be helpful for further experimental and theoretical studies on the similar addition reactions associated with carbene.

Calculation method

The second-order Moller–Plesset perturbation theory (MP2) method[11] combined with the 6-311+G* basis set was employed to locate all the stationary points along the reaction pathways. Frequency analyses were also performed to confirm the nature of the minima and transition states. Moreover, intrinsic reaction coordinate (IRC) calculations were performed to further validate the calculated transition states connecting the reactants and products. Additionally, relevant energy quantities, such as reaction energies and barrier energies, were rectified with zero-point vibrational energy (ZPVE) corrections.

All the calculations were realized using Gaussian 98 programs.[12]

RESULTS AND DISCUSSION

The following two pathways are possible for the addition reaction between carbene and azacyclopropane:

$$\mathrm{H_2C{:}} + \text{azacyclopropane} \rightarrow \text{IM1a} \rightarrow \text{TS1a} \rightarrow \text{IM1b} \rightarrow \text{TS1b} \rightarrow \text{Pro1} \qquad (1)$$

$$\mathrm{H_2C{:}} + \text{azacyclopropane} \rightarrow \text{TS2a} \rightarrow \text{IM2} \rightarrow \text{TS2b} \rightarrow \text{Pro2} \qquad (2)$$

Here, reaction (1) is carbene attack of the N atom of azacyclopropane to form an intermediate **1a** (IM1a), which is a barrier-free exothermic reaction. IM1a then isomerizes to IM1b *via* a transition state **1a** (TS1a). Subsequently, IM1b isomerizes to a product Pro1 *via* TS1b. Reaction (2) is carbene attack of a C atom of azacyclopropane, firstly to form IM2 *via* TS2a and then IM2 isomerizes to a product Pro2 *via* TS2b.

Reaction (1) between carbene and azacyclopropane

The selected geometrical parameters for the intermediates (IM1a, IM1b), transition states (TS1a, Ts1b), and product (Pro1) in reaction (1) are given in Fig. 1. Correspondingly, the relevant energy quantities are summarized in Table I. The potential energy profile of the reaction based on Table I is illustrated in Fig. 2. As can be seen in Fig. 2, reaction (1) consists of three steps: the first one is a barrier-free exothermic reaction of 204.2 kJ/mol, resulting in the intermediate IM1a; the second step is the isomerization of IM1a to intermediate IM1b *via* TS1a with a barrier of 30.0 kJ/mol. Subsequently, IM1b isomerizes to product Pro1 *via* TS1b with 39.3 kJ/mol barrier.

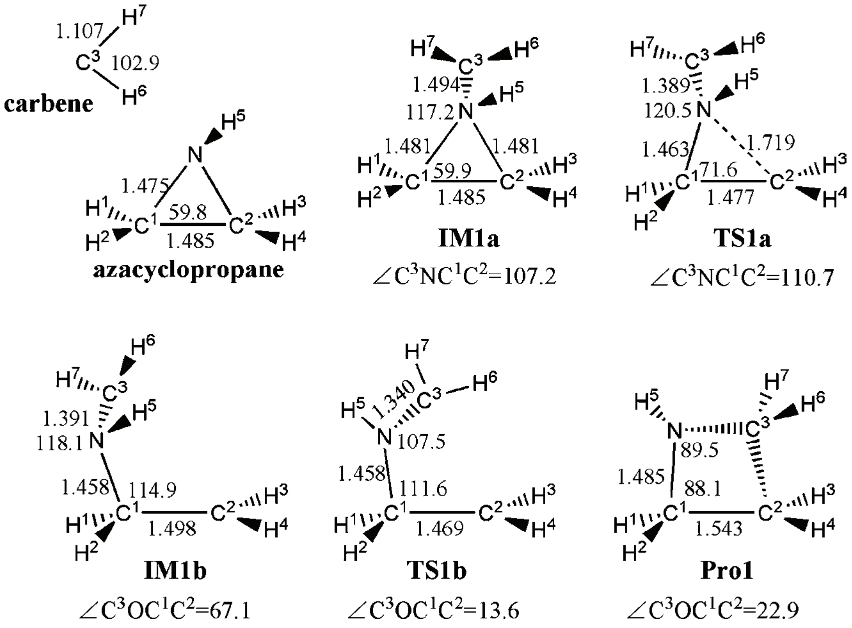

Fig. 1. Optimized structures of the reactants, intermediates (IM), transition states (TS), and product (Pro) of reaction (1) at the MP2/6-311+G* level of theory, where the bond lengths and bond angles are in angstroms and degrees, respectively.

When carbene approaches the N atom of azacyclopropane, it can form an intermediate (IM1a) with azacyclopropane, which is a barrier-free process. In IM1a, the conformation of azacyclopropane is changed slightly compared with that in the isolated azacyclopropane. For example, the bond length of C^1–C^2 and the bond angle of N–C^1–C^2 in IM1a and in isolated azacyclopropane are almost equal to each, whereas the bond length of N–C^1 is slightly prolonged by 0.006 Å, denoting a weakening of the N–C^1 bond. Based on population analyses, some electrons on atom N in isolated azacyclopropane have been transferred to atom C^3 in IM1a; *i.e.*, the Mulliken charges on N (C^3) are –0.291 (–0.392) and –0.039

(–0.962) for the isolated reactants and IM1a, respectively. To investigate this combined process of carbene and azacyclopropane interaction, the potential energy curve for IM1a was constructed along the distance between the two fragments. As shown in Fig. 3, the energy of the system decreases continuously before combination. Actually, to the best our ability, no transition state could be located for this combined process.

TABLE 1. The electronic structure energies (E_{SE}), zero-point energies (E_{ZP}), total energies (E_T) and relative energies (E_R) for the species of the addition reaction between carbene and azacyclopropane at the MP2/6-311+G* level of theory

Species	E_{SE} / a.u.	E_{ZP} / a.u.	E_T[a] / a.u.	E_R / kJ mol^{-1}
CH_2 + azacyclopropane	–192.3657253	0.075571	–172.416767	0.0
IM1a	–172.5933031	0.098745	–172.494559	–204.2
TS1a	–172.5790342	0.095911	–172.483123	–174.2
IM1b	–172.6006735	0.094209	–172.506464	–235.5
TS1b	–172.5846392	0.093144	–172.491495	–196.2
Pro1	–172.7004242	0.101444	–172.598980	–478.3
TS2a	–172.4950407	0.091775	–172.403266	35.4
IM2	–172.5979765	0.093005	–172.504972	–231.5
TS2b	–172.5844913	0.092897	–172.491594	–196.4
Pro2	–172.7101680	0.099146	–172.611022	–509.9

[a] $E_T = E_{SE} + E_{ZP}$

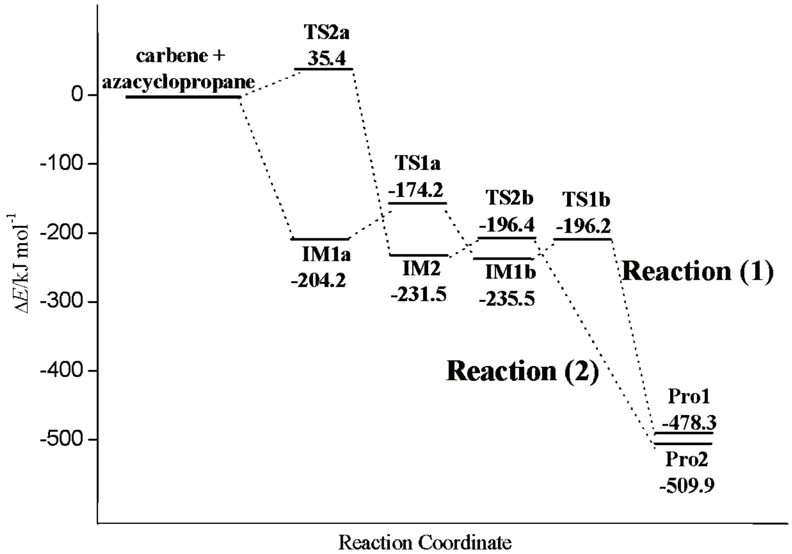

Fig. 2. Potential energy surface for the addition reaction between carbene and azacyclopropane at the MP2/6-311+G* level of theory.

As illustrated in Fig. 4, the formation mechanism of IM1a can be explained by frontier molecular orbital (MO) analysis. The unoccupied p orbital (main component of the LUMO) of C^3 of carbene overlaps with the *p* electron at the N of azacyclopropane, consequently forming a p → p interaction in the N–C^3 donor–acceptor bond, which changed the two reactants into IM1a.

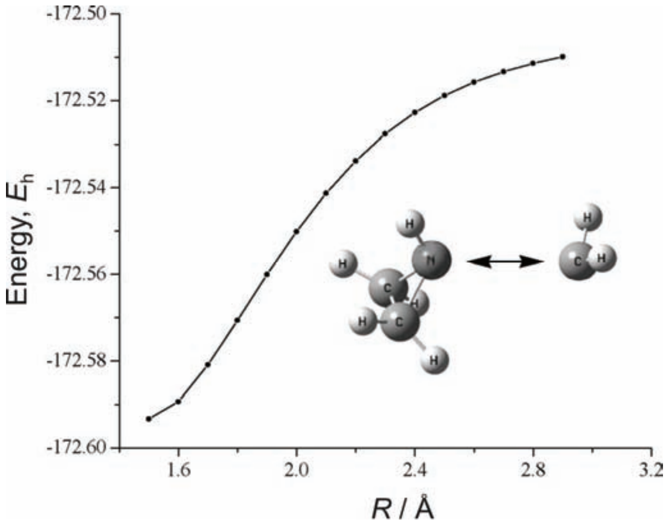

Fig. 3. Energy changes in the combined process of IM1a, together with the distance between two fragments at the MP2/6-311+G* level of theory.

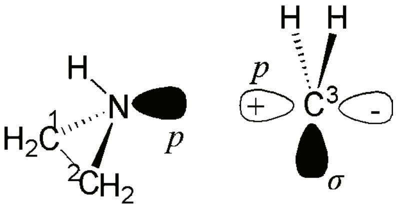

Fig. 4. Frontier molecular orbital (MO) symmetry-adoption of carbene and azacyclopropane.

The unique imaginary frequency of the transition state TS1a is 776.928i cm^{-1}, and the transition state can, therefore, be affirmed as real. According to the calculation of the IRC of TS1a and further optimization for the primary IRC results, TS1a connects IM1a and IM1b. In TS1a, the distance of N–C^1 and N–C^2 reached 1.463 and 1.719 Å, respectively. Compared with the IM1a, the N–C^1 and N–C^2 distances in TS1a are shortened slightly by 0.018 Å and elongated by 0.238 Å, respectively, which denote rupturing of the N–C^2 bond and destruction of the three-membered azacyclopropane ring. Simultaneously, the N–C^1–C^2 angle in TS1a is changed to 71.6°, which can decrease the angle tensility of N–C^1–C^2. Furthermore, the distance between C^3 and N is 1.389 Å, which is shortened by 0.105 Å compared with the corresponding distance in IM1a, suggesting that a new C^3–N bond is to be formed.

In intermediate IM1b, the N–C^1 distance is 1.458 Å, which is approximately the normal length of an N–C single bond. The distance between C^3 and N decreased to 1.391 Å, which is shortened by 0.103 Å compared with the corresponding distance in IM1a, suggesting the formation of a new C^3–N bond. Simultaneously, because of the release of the restriction of the small ring, the C^1–C^2 bond length is elongated to 1.498 Å, *i.e.*, by 0.013 Å compared with the corresponding distance in IM1a. The N–C^1–C^2 angle is 114.9°, meaning that the C^1 atom had adopted a normal sp^3 hybridization state. There is an unconjugated electron in C^2 and C^3, respectively. The dihedral angles of $H^3C^2C^1H^4$ and $H^6C^3NH^7$ are 166.0° and 144.2°, respectively. In contrast, the dihedral angle of H^1–C^1–C^2–H^2 is only 116.7°. Therefore, C^2 and C^3 adopt a sp^2 hybridization state. Since C^2 and C^3 has an unconjugated electron, the energy of IM1b is higher; therefore, it can transfer to the more stable conformer Pro1.

The unique imaginary frequency of the transition state TS1b, which connects IM1b and Pro1, is 730.712i cm^{-1}. In TS1b, the N–C^1–C^2 angle is 111.6°, which is reduced compared with the corresponding angle in IM1b (114.9°). Simultaneously, the dihedral angle of C^3–N–C^1–C^2 is 13.6°, which is significantly decreased compared with the corresponding dihedral angle in IM1b (67.1°), suggesting the planar structure Pro1 is to be formed.

In Pro1, three carbon atoms adopt sp^3 hybridization and the bond lengths of C–C and C–N are 1.543 and 1.485 Å, respectively. The angle tensility in a four-membered ring is smaller than that in a three-membered ring. Therefore, Pro1 is more stable than IM1b. Based on the calculated results, the energy of Pro1 is lower by 242.8 kJ/mol than IM1b.

Reaction (2) between carbene and azacyclopropane

When carbene approaches the carbon atom of azacyclopropane, it can form an intermediate (IM2) with azacyclopropane *via* TS2a, then IM2 can isomerize to Pro2 *via* TS2b. The geometrical parameters for the intermediate (IM2), transition state (TS2a, TS2b), and product (Pro2) in reaction (2) are given in Fig. 5. Correspondingly, the relevant energy quantities are summarized in Table I. The potential energy profile of reaction (2) based on Table 1 is illustrated in Fig. 2, from which, it can be directly seen that reaction (2) consists of two steps: the first one is carbene and azacyclopropane form IM2 *via* TS2a, for which the potential barrier is 35.4 kJ/mol; then, IM2 isomerizes to product Pro2 with a barrier of 35.1 kJ/mol.

The unique imaginary frequency of the transition state TS2a is 1286.34i cm^{-1}, therefore the transition state can be affirmed as real. According to the calculation of the IRC of TS2a, and further optimization for the primary IRC results, TS2a connects reactants and IM2. In TS2a, the distance of N–C^2 reached 1.696 Å, compared with isolated azacyclopropane, this distance is elongated by 0.221 Å.

Simultaneously, the N–C^1–C^2 angle reached to 70.7°, which is increased by 10.9° compared with that in isolated azacyclopropane. Therefore, the N–C^2 bond is to be ruptured and the three-membered azacyclopropane ring to be destroyed. In TS2a, the N–C^3 distance is 1.980 Å, which denotes an N-C^3 bond is to be formed.

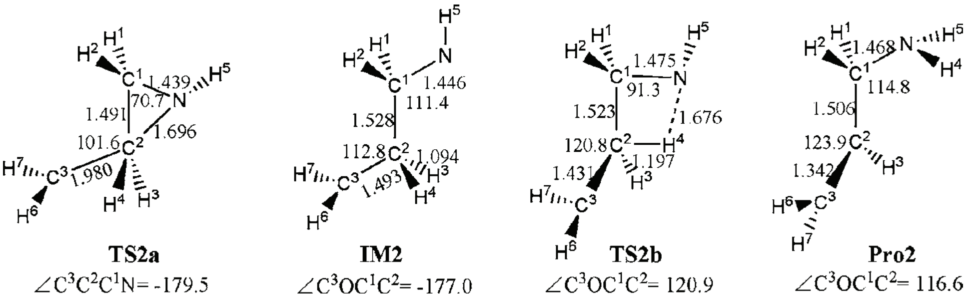

Fig. 5. Optimized structures of the intermediates (IM), transition states (TS), and product (Pro) of reaction (2) at the MP2/6-311+G* level of theory, where the bond lengths and bond angles are in angstrom and degree, respectively.

In IM2, both C^1 and C^2 adopt the sp^3 hybridized state. The N–C^1–C^2 angle is 111.4°, which denotes that the three-membered ring of azacyclopropane is unfolded. Simultaneously, there is an unconjugated electron in N and C^3, respectively. Therefore, IM2 has a higher energy and it can transfer to the more stable conformer Pro2.

The unique imaginary frequency of the transition state TS2b, which connects IM2 and Pro2, is 778.737i cm^{-1}. In TS2b, the C^2–C^3 distance is shortened to 1.431 Å, denoting a double C^2–C^3 bond is to be formed. The C^2–H^4 distance is about 1.197 Å, which is prolonged by 0.103 Å compared with that in IM2. Simultaneously, the N–H^4 distance attains 1.676 Å, which is shortened largely compared with that in IM2. Thus, in the TS2b, a new N–H^4 bond is to be formed and the C^2–H^4 bond is to be broken simultaneously.

In Pro2, the N–H^4 distance is shortened to 1.014 Å, denoting that the atom H^4 has been transferred to the N atom and a new N–H^4 bond is formed. Both the C^2 and C^3 atoms adopt an sp^2 hybridized state and the C^1–C^2–C^{3}angle is 123.9°. The C^2–C^3 distance is 1.342 Å, which is the normal C=C double bond length.

A comparison between the two reaction pathways indicates that the two potential barriers along reaction (1) is 30.0 (IM1a → IM1b) and 39.3 (IM1b → Pro1) kJ/mol, respectively, which is similar to that along reaction (2) (reactants → → IM2, 35.4 kJ/mol, and IM2 → Pro2, 35.1 kJ/mol). Hence, it can be predicated that reactions (1) and (2) should be the parallel reactions from the viewpoint of kinetics. However, the energy of reaction (1) is –478.3 kJ/mol, which is lower than that of reaction (2) (–509.9 kJ/mol). Therefore, from the thermodynamic viewpoint, Pro2 should be the dominant product.

CONCLUSIONS

In the present study, the mechanism of the addition reaction between carbene and azacyclopropane was investigated at the MP2/6-311+G* level of theory. Geometry optimization, vibrational analysis, and relevant energy properties for the involved stationary points on the potential energy surface were calculated. Two reactions, (1) and (2), were found. Reaction (1) is carbene attack of the N atom of azacyclopropane to form an intermediate **1a** (IM1a), which is a barrier-free exothermic reaction. IM1a then isomerizes to IM1b *via* a transition state **1a** (TS1a), where the potential barrier is 30.0 kJ/mol. Subsequently, IM1b can isomerize to a product Pro1 *via* TS1b with a potential barrier of 39.3 kJ/mol. The orbital interactions are also discussed to explain the combined process of the leading intermediate. Reaction (2) is carbene attack of the C atom of azacyclopropane, firstly to form IM2 *via* TS2a, the potential barrier of which is 35.4 kJ/mol. Then IM2 isomerizes to a product Pro2 *via* TS2b with a potential barrier of 35.1 kJ/mol. The reaction energies for reactions (1) and (2) are –478.3 and –509.9 kJ/mol, respectively. From the kinetic viewpoint, reactions (1) and (2) should be the parallel reactions. However, from the thermodynamic viewpoint, Pro2 should be the dominant product. Hopefully, the present results will fill a void in the available data in the study of the interactions between carbene and the small-ring strained molecules.

Acknowledgements. This work was supported by the Scientific Research Foundation of Jinan University (XKY0709).

ИЗВОД

ТЕОРИЈСКО ПРОУЧАВАЊЕ МЕХАНИЗМА АДИЦИЈЕ КАРБЕНА НА АЗАЦИКЛОПРОПАН

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Испитиван је механизам адиције карбена на азациклопропан помоћу Moller–Plesset-ове пертурбационе теорије другог реда (MP2). Применом базног сета 6-311+G* извршена је оптимизација геометрије, вибрациона анализа и одређене енергетске особине стационарних тачака на хиперповршини потенцијалне енергије. На основу енергетског профила предвиђено је да постоје два реакциона механизма, (1) и (2). У првом (1), карбен напада N атом азациклопропана и гради интермедијер **1a** (IM1a), што је егзотермна реакција без баријере. Затим се IM1a изомеризује у IM1b преко прелазног стања **1a** (TS1a), где потенцијална баријера износи 30,0 kJ/mol. После тога, IM1b се изомеризује у продукт (Pro1) преко TS1b са потенцијалном баријером од 39,3 kJ/mol. У другом механизму (2), карбен напада C атом азациклопропана, прво градећи IM2 преко TS2a, са потенцијалном баријером од 35,4 kJ/mol. Затим се IM2 изомеризује у продукт (Pro2) преко TS2b са потенцијалном баријером од 35,1 kJ/mol. Доследно томе, енергије реакција (1) и (2) су –478,3 и –509,9 kJ/mol, редом. Осим тога, разматрана је и интеракција између орбитала код главних интермедијера.

(Примљено 3. марта, ревидирано 15. децембра 2009)

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