DFT STUDY ON THE MECHANISM OF THE ADDITION REACTION BETWEEN CARBENE AND GLYCINE

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ABSTRACT

The mechanism of addition reaction between the singlet carbene and glycine has been investigated at the B3LYP/6-311+G* level of theory, including geometry optimization and vibrational analysis for the involved stationary points on the potential energy surface. Computational results suggest that there are two reaction pathways (1) and (2) during the addition process. In the pathway (1), carbene attacks the C=O bond from the H¹C² side of glycine to form an intermediate (IM1), which is a barrier-free exothermic reaction. Then, IM1 isomerizes to a product (Pro1) via a transition state (TS1) with a potential barrier of 25.7 kJ/mol. Similarly, in the pathway (2), carbene attacks the C=O bond from the H²C¹ side of glycine to form an intermediate IM2. Subsequently, IM2 isomerizes to Pro2 via TS2, where the Pro2 and Pro1 are enantiomers actually. The calculated potential barrier of 51.3 kJ/mol is higher than that of the pathway (1). Correspondingly, the reaction energy for the both pathways is -258.5 kJ/mol. Additionally, the atoms in molecules (AIM) theory has also been performed to characterize the bonding interaction and structural features for the addition reaction.

Key words: Carbene, Glycine, Addition reaction, Density functional theory (DFT).

1. INTRODUCTION

Carbene can be defined as a divalent carbon intermediate, where the carbene carbon is linked to two adjacent groups by covalent bonds and possesses two nonbonding electrons¹. As well known, carbene plays an important role in organic chemistry, especially for the addition reaction between carbene and C=O double bond²⁻⁷. Therefore, much attention has been paid on them not only from applied but also theoretical chemists. For example, they can provide simple and direct synthesis for small-ring, highly strained compounds, as well as those that are hard to synthesize through conventional ways⁸. At present, as an important catalyzer, metal-carbene complexes are applied widely in the organic synthesis⁹⁻¹¹. Lu et al. reported reaction between carbene or substituted carbene and some small molecules using theoretical calculation¹²⁻¹⁴. Apeloig et al. extensively studied the mechanisms and stereoselectivity of carbene addition to olefin using experimental as well as theoretical methods^{15,16}. On the other hand, some extrinsic substance can produce carbene in the human body. For example, carbon tetrachloride (CCl₄) is a hepatotoxic molecule and a two-step reduction of it would liberate a chloride ion to yield the highly reactive dichlorocarbene.¹⁷ Dacarbazine (DTIC) is clinically effective in the treatment of several malignant disorders, including metastatic malignant melanoma, melanoma, Hodgkin's disease, and soft tissue sarcomas, in combination with other anticancer drugs¹⁸. Photoactivated DTIC generates the carbene and aryl radicals, which may induce DNA adduct, resulting in the photogenotoxicity¹⁹. As the simplest amino acid, glycine plays central roles both as building blocks of proteins and as intermediates in metabolism. Due to the existence of the carboxyl group in glycine, it is probable that the active carbene can react with the glycine. To our best knowledge, this kind of reaction has not been reported so far. Therefore, it is necessary to study the reaction between carbene and glycine to further understand the potential role of carbene in the life fields.

In the present study, the reaction between carbene and glycine has been systematically investigated employing the B3LYP/6-311+G* level of theory. The possible intermediates (IM), transition states (TS), and products (Pro) have been located on the potential energy surface. The possible reaction mechanisms have been proposed. Hopefully, the present results would be helpful to better understand the potential reaction between carbene and life molecules.

2. Calculation method

The density functional theory (DFT^{20,21}) B3LYP method (Becke's three-parameter hybrid function²² with the non-local correlation of Lee-Yang-Parr²³) combined with the 6-311+G* basis set are employed to locate all the stationary points along the reaction pathways. Frequency analyses have also been carried

out to confirm the nature of the minima and transition states. Moreover, intrinsic reaction coordinate (IRC) calculations have also been performed to further validate the calculated transition states connecting the reactants and products. Additionally, relevant energy quantities, such as reaction energies and barrier energies, have been corrected with zero-point vibrational energy (ZPVE) corrections.

To characterize the structural and bonding features, the atoms in molecules (AIM) theory²⁴ has been performed on the basis of the calculated geometries. According to the AIM theory, the existence of a bond is indicated by the presence of a so-called bond critical point (BCP). Similarly, the ring structures are characterized by the existence of a ring critical point (RCP). Additionally, the nature of the chemical bond can be assessed from the calculated Laplacian of electron density at the critical point.

All the calculations have been performed using Gaussian 98 program²⁵.

3. RESULTS AND DISCUSSION

It is reported that there are 13 stable conformers for glycine in the gas phase.²⁶ As displayed in Figure 1, for the most stable conformer, the main skeleton of it, such as N, C¹, C², O¹, and O² atoms, are in the same plane approximately. Obviously, the weak intramolecular H-bonds exist between O¹ and H³, H⁴, and H⁵. For the sake of simplicity, the most stable glycine has been discussed in the following study.

Figure 1. The most stable glycine optimized at the B3LYP/6-311+G* level of theory, where the bond length and bond angle are in angstrom and degree, respectively.

There are two possible pathways for the addition reaction between carbene and glycine as follows:

Here, both pathways (1) and (2) are similar to each other. Namely, in the pathway (1), carbene attacks the C=O bond from the H¹C¹C² side of glycine to form an intermediate (IM1) before isomerizing to a product (Pro1) via a transition state (TS1). Certainly, in the pathway (2), carbene can also attack the C=O bond from the H²C¹C² side of glycine to form an intermediate (IM2), which isomerizes to Pro2 via TS2.

3.1 Reaction pathway (1) between carbene and glycine

When carbene approaches glycine from the H¹C¹C² side, it can form an intermediate (IM1) with the C²=O¹ double bond of glycine, which is a barrier-free process. The geometrical parameters for the intermediate (IM1), transition state (TS1), and product (Pro1) in the pathway (1) are given in Figure 2. Correspondingly, the relevant energy quantities have been summarized in Table 1. The unique imaginary frequency of the transition state TS1 is 288.79i cm⁻¹ and the transition state can therefore be affirmed as real. Moreover, the calculated TS1 connecting IM1 and Pro1 can be further confirmed by the IRC calculations.

Figure 2. Optimized structures of intermediates(IM), TSs, and products(Pro), where the bond length and bond angle are in angstrom and degree, respectively.

Obviously, pathway (1) consists of two steps. Namely, an intermediate IM1 has been spontaneously formed firstly, which is stabilized by about 67.4 kJ/mol relative to the reactants. Then, IM1 isomerizes to product Pro1 with a barrier of 25.7 kJ/mol. The overall reaction energy is about -258.5 kJ/mol, implying that the pathway (1) is an exothermic process.

Table 1: The electronic structure energies (ESE), zero-point energies (EZP), total energies (ET) and relative energies (ER) for the species of the addition reaction between carbene and glycine at the B3LYP/6-311+G* level of theory.

Species	E _{SE} /a.u.	E _{ZP} /a.u.	E _T /a.u.	E _R /(kJ/mol)
H ₂ C: + glycine	-323.6575772	0.096429	-323.561148	0.0
IM1	-323.6916628	0.104836	-323.586827	-67.4
TS1	-323.6817615	0.104717	-323.577045	-41.7
Pro1	-323.7671853	0.107548	-323.659637	-258.5
IM2	-323.6883424	0.104215	-323.584127	-60.3
TS2	-323.6673902	0.102820	-323.564571	-9.0
Pro2	-323.7671853	0.107550	-323.659635	-258.5

$$^a\text{E}_\text{T} = \text{E}_\text{SE} + \text{E}_\text{ZP}$$

Compared with the isolated glycine, the double bond character of the C²=O¹ in IM1 has been weakened. For example, the bond length of it has been prolonged by 0.063 Å than that in isolated glycine. The corresponding electron densities at the BCP has been decreased by about 0.0772. At the same time, the dihedral angle of the O¹C¹C²O² in IM1 has been changed to 173.4°.

As for transition state TS1, the distance of the C²-C³ has been shortened by about 0.213 Å to 2.202 Å compared with that of the IM1 despite of the nonexistence of the corresponding BCP using AIM theory. At the same time, the distance of C²-O¹ has been elongated to 1.279 Å, which is in the intermediate between the normal C-C single bond and C=C double bond. Thus, in the TS1, the new C²-C³ bond is to be formed and the C²-O¹ bond is to be broken simultaneously. On the other hand, the dihedral angle of C³C¹C²O² in TS1 has been changed to -32.8°, which also suggest that it is impossible for C² atom to maintain *sp*² hybridization state.

Compared with TS1, the distance of C²-C³ in product Pro1 has been further shortened to 1.467 Å, which denote the formation of the C²-C³ bond. At the same time, the distance of the C²-O¹ has been elongated to 1.422 Å, suggesting that the initial double bond between C² and O¹ has been transformed to single bond. Additionally, as shown in Table 2, there is a RCP involving the O¹, C², and C³ atom, suggesting the formation of a three-membered ring structure among the O¹, C², and C³ atom.

As shown in Figure 3, the mechanism of the reaction (1) could be explained with the knowledge of the frontier molecular orbital. The combination of the unoccupied 2p orbital of the C³ atom in carbene with the π orbital of C²-O¹ in glycine gives a π→p donor-acceptor bond, resulting in the formation of the intermediate IM1 characterized by a three-membered ring structure when carbene initially interacts with glycine. We have done detailed potential energy surface scan for the formation of IM1. Computational results show that the formation of IM1 is a barrier-free exothermic reaction, which is probably due to the strong bonding effect of the 2p unoccupied orbital of C³ atom of carbene with the π-bonded electron cloud of C²-O¹ of glycine. With the reaction going on, carbene will rotate clockwise in the plane of C³C²O¹, and then the lone electron pair of carbene can enter the π* orbital of C²-O¹ of glycine. Accordingly, the addition reaction completes finally.

Figure 3. MO symmetry-adaptation of carbene and the C=O of glycine.

Table 2: Charge Density ρ and its Laplacian $\nabla^2\rho$ as well as its eigenvalues at the bond critical point (BCP) and ring critical point (RCP) for the addition reaction between carbene and glycine (pathway (1)) calculated at the B3LYP/6-311+G* level of theory.

Conformer	Atom Pair	ρ	λ_1	λ_2	λ_3	$\nabla^2\rho$
IM1	O ¹ -C ³	0.2171	-0.3102	-0.1779	0.8120	0.3239
	C ² -O ¹	0.3416	-0.8552	-0.6359	1.6576	0.1665
TS1	O ¹ -C ³	0.1729	-0.1996	-0.1387	0.3376	-0.0007
	C ² -O ¹	0.3598	-0.9171	-0.8164	1.2604	-0.4731
Pro1	O ¹ -C ³	0.2347	-0.4253	-0.2442	0.3872	-0.2823
	C ² -O ¹	0.2589	-0.5100	-0.3342	0.4209	-0.4233
	C ² -C ³	0.2527	-0.5195	-0.4330	0.3666	-0.5859
	O ¹ -C ² -C ³	0.2062	-0.3803	0.2284	0.5160	0.3641

As displayed in Figure 3, due to the existence of the lone electrons in carbene fragment, IM1 possesses high energy relative to the corresponding product. Therefore, the system reduces its own energy by increasing the dihedral angles $\angle\text{C}^3\text{C}^1\text{C}^2\text{O}^1$ (IM1: -1.7° ; TS1: -32.8° ; Pro1: 154.8°), resulting in the formation of the more stable product Pro1 via TS1. As shown in Table 2, there is no BCP between C² and C³ in IM1 and TS1. However, a BCP of this bond exists in Pro1 within the framework of the AIM theory. Moreover, from the calculated negative Laplacian at the BCP, the C²-C³ bond in Pro1 should be covalent in nature.

3.2 Reaction pathway (2) between carbene and glycine

As displayed in Figure 2, the pathway (2) is similar to the reaction pathway (1). Thus, the analyses above for the pathway (1) are also true here. Namely, in the pathway (2), carbene attacks the C=O bond from the H³C¹C² side of glycine to form an intermediate IM2, which isomerizes to Pro2 via TS2. Here, it should be noted that Pro2 and Pro1 are enantiomers actually. The selected geometrical parameters for the intermediate (IM2), transition state (TS2), and product (Pro2) are given in Figure 2. The unique imaginary frequency of the transition state TS2 is 299.38i cm⁻¹, which has been further confirmed by the IRC calculations.

Based on Table 1, IM2 is less stable than IM1 by about 7.1 kJ/mol, suggesting that IM1 is favorable to be generated from reactants thermodynamically. Moreover, the barrier in pathway (1) (25.7 kJ/mol) is lower by about 25.6 kJ/mol than that in pathway (2). Thus, the pathway (1) will be a major reaction pathway for the addition reaction between carbene and glycine.

4. CONCLUSIONS

The mechanism of the addition reaction between the singlet carbene and glycine has been investigated employing the B3LYP/6-311+G* level of theory, including geometry optimization and vibrational analysis for the involved stationary points on the potential energy surface. Overall, there are two reaction pathways (1) and (2) during the addition process. Both the reactions consist of two steps. Namely, carbene and glycine first form an intermediate (IM) through a barrier-free exothermic reaction. Then this intermediate isomerizes to a product (Pro) via a transition state (TS), where both products are enantiomers actually. The barrier heights of the two reactions are 25.7, and 51.3 kJ/mol at the B3LYP/6-311+G* level of theory, respectively. Therefore, from the viewpoint of dynamics, the pathway (1) will be a major reaction path for the addition reaction between carbene and glycine.

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