

Theoretical Investigation of the Gas Phase Cu⁺-Activated Fragmentation of D-Alanine

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The gas phase Cu⁺-activated fragmentation of D-alanine was theoretically investigated at B3LYP and MP2 levels. The experimentally observed products can be rationalized by the mechanism as: Cu⁺+D-alanine → η²(NH₂, C=O) complex → C_α-COOH bond insertion → O=C-OH bond insertion → H migration from -NH₂ to -OH → [CH₃CHNH-(H₂O)Cu(CO)]⁺. Dissociations of the final intermediate in different forms produce the products corresponding to loss of H₂O, CO and H₂O + CO, respectively. Another product channel leading to elimination of HCOOH was also identified but it is energetically less favourable than the first one. By comparing the Cu⁺ + alanine reaction with previously studied Cu⁺ + phenylalanine reaction, it was concluded that different α-amino acids may share common reaction mechanisms for the same product channels. Different side chains change the reactivity but do not change the mechanisms significantly.

Key Words: Cu⁺, D-Alanine, Insertion, Fragmentation, Theoretical.

INTRODUCTION

Gas phase reactions between transition metal cations and biomolecules may result in fragmentation of the biomolecules. Based on the produced products, the structural details of the biomolecules, such as amino acids or peptides, can be obtained. Lei and Amster investigated the gas phase reactions between ground-state Cu⁺ and Fe⁺ with 20 natural α-amino acids by using Fourier transform mass spectrometer¹. It was found that 15 of the amino acids are reactive toward Cu⁺ and collisions with Cu⁺ resulted in the fragmentation of the amino acids. For most of these amino acids, the products corresponding to the mass loss of 18 μ were observed. The products of 28 μ loss were detected for 6 of them and 46 μ loss were observed for 8 of them. For alanine, valine and phenylalanine, all of these products were observed. Amster *et al.*¹ proposed that the 18, 28 and 46 μ loss products corresponding to the elimination of H₂O, CO and HCOOH, respectively. Recently, we performed theoretical calculations on the Cu⁺-D-phenylalanine reaction². The identified energetically most favourable reaction pathway starting from a -NH₂ and -C=O coordinated complex suggests that the loss of H₂O + CO (46 μ) favours over the loss of HCOOH. Whether similar mechanisms and energetics can also be applied to other amino acids? To answer this question, in this work, theoretical calculations were carried out on the reaction between ground state Cu⁺ (¹S₀, 3d¹⁰) and D-alanine.

Based on the theoretical results of this work and our previous study, comparisons can be made. D-alanine has two conformations like D-phenylalanine due to the C-C bond rotation: the C=O and -NH₂ groups are in the same side or different sides of the C-C bond. According to our calculations, the initial collision complex formed between Cu⁺ and the former conformation has the higher binding energy. Therefore, in this work, only the pathways related to this conformation were considered.

COMPUTATIONAL METHOD

As our previous studies²⁻⁵ on Cu⁺ and other transition metal-containing systems show that the DFT method B3LYP^{6,7} can provide reasonable accuracy with affordable computational cost. All the geometries of the stationary points were fully optimized at the B3LYP/6-31G⁸ theoretical level. Harmonic vibrational analysis was carried out at the same level to characterize the nature of the stationary points. Zero-point vibrational energies have been used to correct all the relative energies. To ensure that the lowest-energy electronic states were found, the Stable calculation method was used to test the stability of DFT density function. All connectivities of minima and transition states were verified by intrinsic reaction coordinate (IRC) calculations. To obtain improved energies, single point calculations were performed at MP2/6-311+G^{**9,10}. All the calculations were carried out with GAUSSIAN 03 program package¹¹.

RESULTS AND DISCUSSION

According to our calculations, the observed products corresponding to the loss of 16 and 28 μ can be produced through elimination of H₂O and CO, respectively. The identified reaction pathways are demonstrated in Fig. 1. The potential energy profiles obtained at MP2/6-311+G** (ZPE included) level is shown in Fig. 2.

As Cu⁺ can bind with D-alanine in several sites, some different initial collision complexes may be formed. The complex IM1 shown in Fig. 1 is the most stable one in which the Cu⁺ interacts strongly with both -NH₂ and the C=O groups with high binding energy of 271.8 kJ/mol. The counterpart complex for Cu⁺-D-phenylalanine was also located in our previous study² and it is more stable than IM1 by 20.8 kJ/mol. Via the transition state TS1 which has the unique imaginary

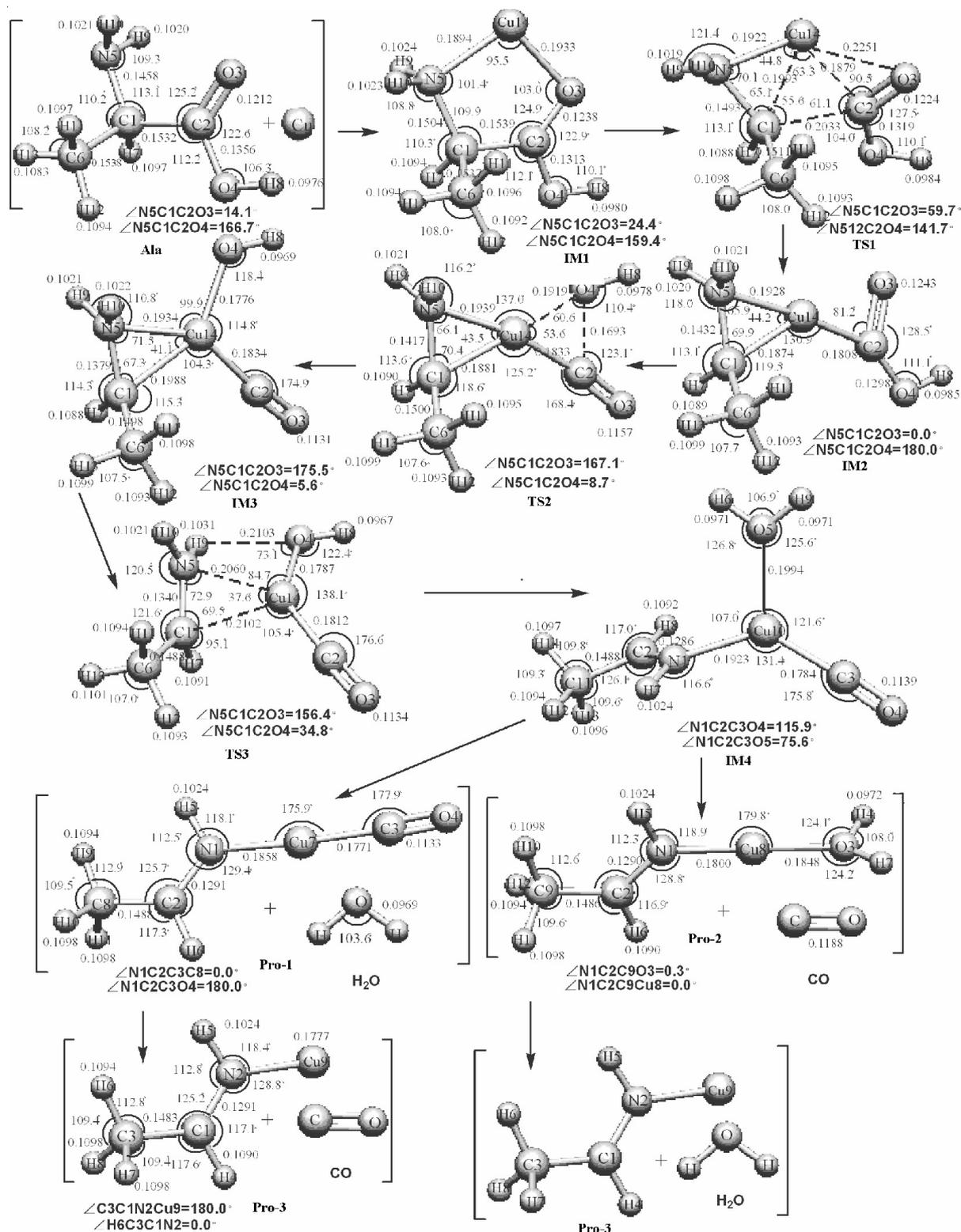


Fig. 1. Optimized geometries for the reaction pathways of H₂O and CO elimination at B3LYP/6-31G*

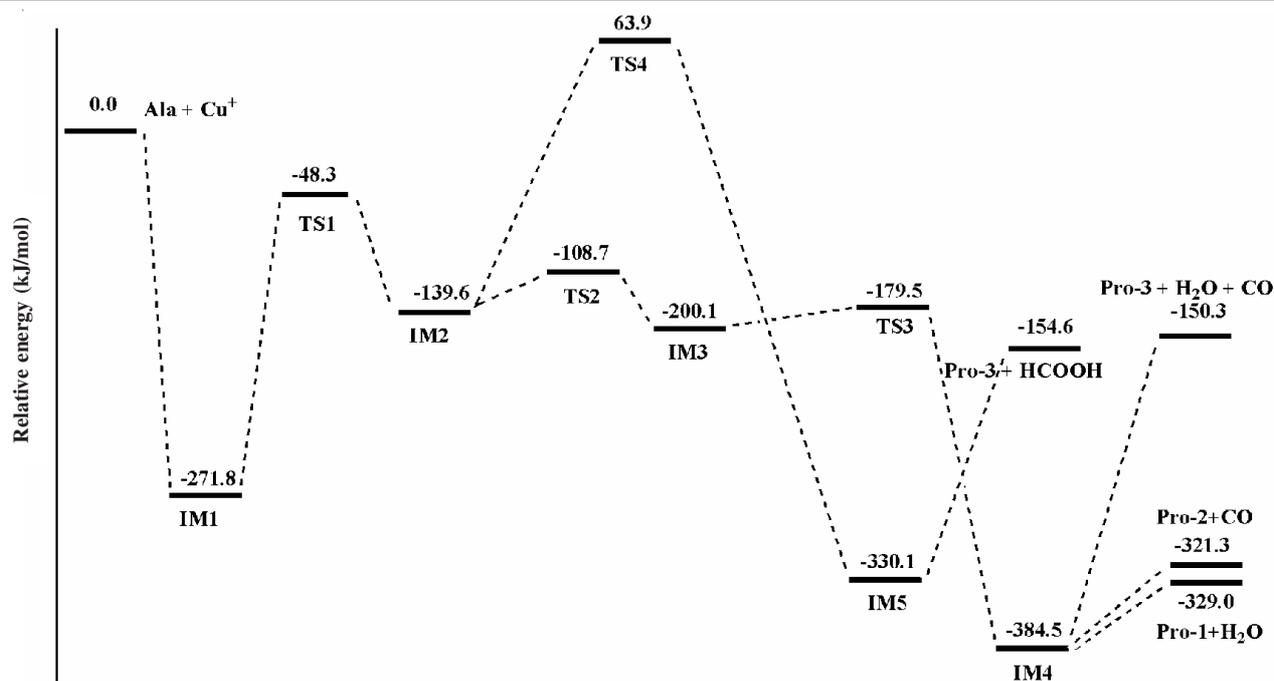


Fig. 2. Calculated potential energy profiles at MP2/6-311+G**

frequency of 369i, the Cu inserts into the C1-C2 bond. TS1 lies above IM1 by 223.5 kJ/mol, but lower in energy than the reactants by 48.3 kJ/mol. The insertion intermediate IM2 has a relative energy of -139.6 kJ/mol, less stable than IM1 by 83.9 kJ/mol.

With insertion of Cu into to the C2-O4 bond, the IM2 evolves to IM3 *via* TS2 (224i). This step has an energy barrier of 30.9 kJ/mol with respect to IM2. After IM3, one of the hydrogen atoms on -NH₂ is abstracted by the -OH group on Cu. TS3 which has a barrier of 20.6 kJ/mol relative to IM3 is the transition state of this step. The vibrational mode of the small imaginary frequency (119i) of TS3 corresponds to the swing of the H9 atom to the -OH group. As the water molecule binding to Cu is formed, the energy of this system decreases dramatically, leading to the product-like intermediate IM4 which has the lowest relative energy of -384.5 kJ/mol. Dissociations of IM4 can produce the H₂O and CO elimination products, Pro-1 and Pro-2, respectively. The breakages of Cu-O5 and Cu-C3 bonds cost energy of 55.5 and 63.2 kJ/mol, respectively. The two product channels are exothermic by 329.0 and 321.3 kJ/mol, respectively. Apparently, one of the possible products that lost 46 μ from alanine in the experiment would also be produced *via* simultaneous loss of H₂O + CO from IM4. As it can be seen in Fig. 2, this channel is exothermic by 150.3 kJ/mol. Of course, consecutive loss of H₂O and CO from IM4 produces the same product and theoretically, it should be more favourable than simultaneous loss.

Another reaction pathway that also leads to the product of loss of 46 μ was identified. As shown in Fig. 3, this pathway is branched from IM2. *Via* the multi-center transition state TS4 with an imaginary frequency of 205i, a H atom on -NH₂ group shifts to C3, forming the intermediate IM5. Dissociation of Cu-O bond in IM5 produces the product of Pro-3 + HCOOH (46 μ). However, as shown in Fig. 2, TS4 has an activation barrier of 63.9 kJ/mol relative to the reactants and lies 112.2

kJ/mol above TS1. Therefore, this product channel is energetically less favourable than the channel of losing H₂O + CO. But under energetically allowed condition, it can be a competitive process. For Cu⁺-D-phenylalanine reaction, this pathway has lower activation energy² of 49.5 kJ/mol.

By comparing the Cu⁺-D-alanine reaction with Cu⁺-D-phenylalanine reaction², it can be found that the identified mechanisms corresponding to the same product channels are basically similar. The difference is that the energy barriers represented by the key transition states in Cu⁺-D-phenylalanine reaction are lower than those in Cu⁺-D-alanine reaction by about 20 kJ/mol. Further, the initial collision complex and intermediates in Cu⁺-D-phenylalanine reaction are also more stable. Thus, it is concluded that the similar mechanisms may also be applied to other α -amino acids. This conclusion is likely to be safe since these reactions mainly involve the activations of C α -COOH, C-OH and N-H bonds. The existences of different side chains may change the reactivity of the amino acids but do not change the mechanisms significantly.

Conclusion

The fragmentation of D-alanine by Cu⁺ was theoretically investigated. The eliminations of H₂O, CO and H₂O + CO, are initiated by coordination of Cu⁺ with alanine and the following steps involve C-C bond insertion, C-O bond insertion, H-migration and bond dissociations of the final intermediate. The calculated potential energies indicate that all the reaction steps have no activation energy barriers above the reactants and the product channels are significantly exothermic. The elimination of HCOOH is also a possible pathway which involves simultaneously C-C bond insertion and H-migration. This pathway has a positive activation energy of 63.9 kJ/mol relative to the reactants, suggesting this channel is allowed only under high-energy condition.

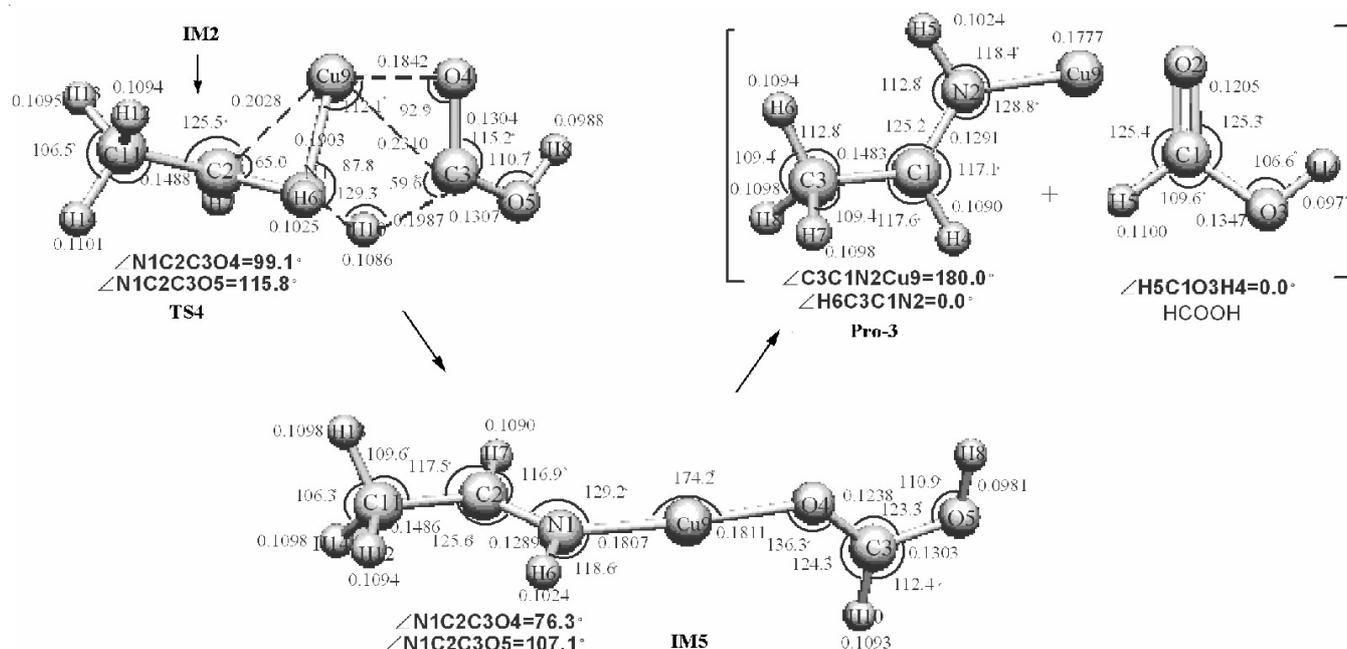


Fig. 3. Optimized geometries for the reaction pathway of HCOOH elimination at B3LYP/6-31G*

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