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THEORETICAL STUDY OF THE MECHANISM GENERATING AZOMETHINE YLIDE FROM FORMALDEHYDE AND GLYCINE

P. Wu

Department of Chemistry, Dezhou College, Shandong; Key Laboratory of Coordination Chemistry and Functional Materials at Universities of Shandong, P. R. China
E-mail: Pingwu.dzu@gmail.com

The mechanism to generate azomethine ylide from formaldehyde and glycine is systematically investigated. The density functional theory at the B3LYP/6-311++G(d,p) level is employed for both geometry optimization and single point energy calculation. Our results indicate that two possible pathways can lead to the generation of the carbinolamine intermediate with a favorable step-wise pathway. However, as for the step to form azomethine ylide, a concerted elimination of water and carbon dioxide is preferred. This calculation result is totally different from the widely accepted revised Rizzi mechanism.

Azomethine ylides have been widely applied to synthesize nitrogen-containing pyrrolidines or pyrrolines for organometallic catalysis and natural product synthesis [1—3]. Due to their instability, azomethine ylides are usually generated *in situ* by thermolysis or photolysis of aziridines [4], desilylation [5], tautomerization of imines [6], deprotonation of iminium salts [7], decarboxylation from the corresponding aldehydes and amino acids [8], etc. As for the decarboxylation route, the widely accepted mechanism, also known as the revised Rizzi mechanism, is shown in Scheme 1 [8]. A carbinolamine intermediate is formed, followed by the elimination of a water molecule to give a zwitterion that cyclizes into a thermally labile 5-oxazolidinone intermediate before the thermal decarboxylation to generate final azomethine ylide. While most theoretical investigations focused on the stereoselectivity of azomethine ylides with olefins [9], the mechanism of the generation of azomethine ylides from aldehydes and amino acids has not been investigated so far.

A related study on the zwitterion formation was reported in 2002 by Boyd′s group in a proline-catalyzed enantioselective aldol reaction [10]. The carboxylic group was considered to facilitate either the carbinolamine formation or the zwitterions generation step, but it was not considered important in both steps. As a continuation of our work [11], a systematic study of the azomethine ylide formation from formaldehyde and glycine was investigated in this paper and was calculated at the B3LYP/6-311++G(d,p) level.
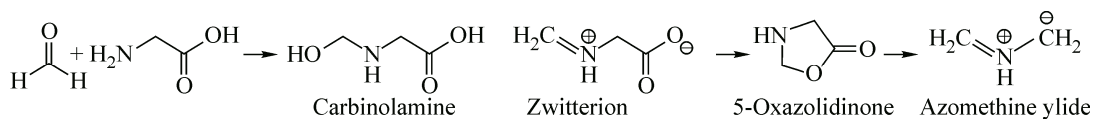

Scheme 1. Revised Rizzi′s mechanism for the azomethine ylide formation from formaldehyde and glycine

CALCULATION PROCEDURE

The computations were carried out using the Gaussian 03 (Reversion D.02) program package at the B3LYP/6-31++G(d,p) level [12]. All zero-gradient structures were characterized by a vibrational analysis with no imaginary frequency. All of the transition state structures were confirmed to have only one imaginary frequency, which was interpreted as a negative vibrational mode, and the intrinsic reaction coordinate (IRC) [13,14] was followed to make sure that each transition state connected the expected two minima.

RESULTS AND DISCUSSION

Our calculation results show that in addition to the revised Rizzi mechanism, a step-wise pathway for the carbinolamine formation (path 1) and a concerted elimination of water and carbon dioxide (path 5) must be taken into account, as is summarized in Scheme 2.

Scheme 2. Possible pathways to generate azomethine ylide from formaldehyde and glycine
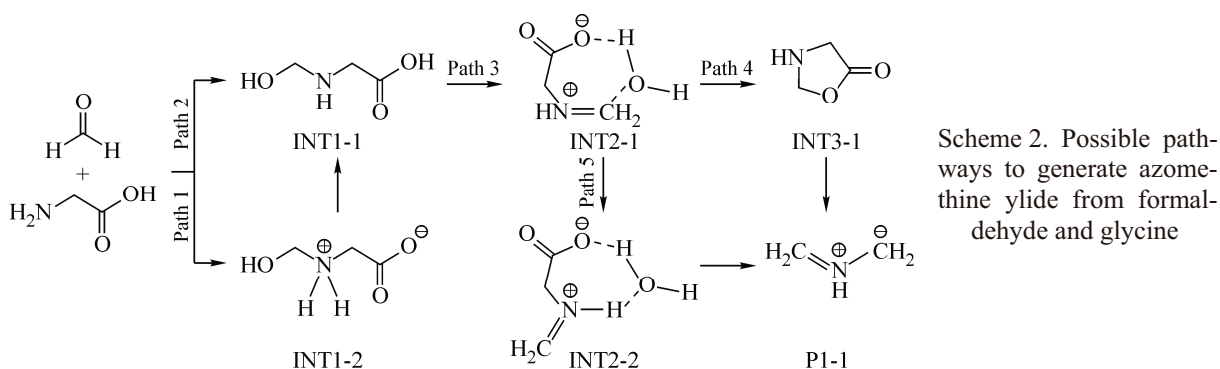
Structures of the transition states, intermediates, and products are shown in Scheme 3 with selected bond lengths included, while the B3LYP/6-311++G(d,p) calculated total Gibbs free energies (G), together with the relative reaction energies are listed in Table 1.

Carbinolamine formation. Similarly to the previously reported imine formation calculations [15], the carbinolamine formation from formaldehyde and glycine proceeds through a concerted proton transfer reaction from the glycine nitrogen atom to the formaldehyde oxygen atom *via* a four-membered ring transition state (TS1-1) which lies 41.59 kcal·mol^{-1} above the reactants. The C1—N1 bond (1.574 Å) is well formed in TS1-1 and the N1—H1 and O1—H1 distances are 1.198 Å and 1.405 Å, respectively. Moreover, as implied by the Boyd group [10], a self-catalyzed pathway, involving the carboxylic group, is found to facilitate the carbinolamine formation through a seven-membered ring transition state (TS1-2) which is only 23.06 kcal·mol^{-1} higher than the reactants. The

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B3LYP/6-31++G(d,p) *calculated Gibbs free energies* (au) *and relative reaction energies* (kcal·mol^{-1}) *for the azomethine ylide formation from formaldehyde and glycine* [a]

Label	G	$\Delta G^{\ddagger a}$	Label	G	$\Delta G^{\ddagger a}$	Label	G	$\Delta G^{\ddagger a}$
Formaldehyde	−114.536334		TS1-3	−398.978800	23.06	TS4-1	−322.525379	22.15 [c]
Glycine	−284.479221		TS2-1	−398.977453	23.91	P1-1	−133.893738	6.91 [d]
TS1-1	−398.949271	41.59	INT2-1	−398.980488	22.00	TS3-2	−398.982691	20.62
INT1-1	−399.011157	2.76	INT2-2	−398.988482	16.99	H$_2$O	−76.454884	
TS1-2	−398.978819	23.05	TS3-1	−398.979977	22.33	CO$_2$	−188.65592	
INT1-2	−398.979124	22.86	INT3-1	−322.561355	−0.43 [b]			

[a] Relative reaction energies ($\Delta G^{\ddagger}$) are referred to the sum of formaldehyde and glycine.
[b] Sum values of INT3-1 and water referred to formaldehyde and glycine.
[c] Sum values of TS4-1 and water referred to formaldehyde and glycine.
[d] Sum values of P1-1, water, and carbon dioxide referred to formaldehyde and glycine.
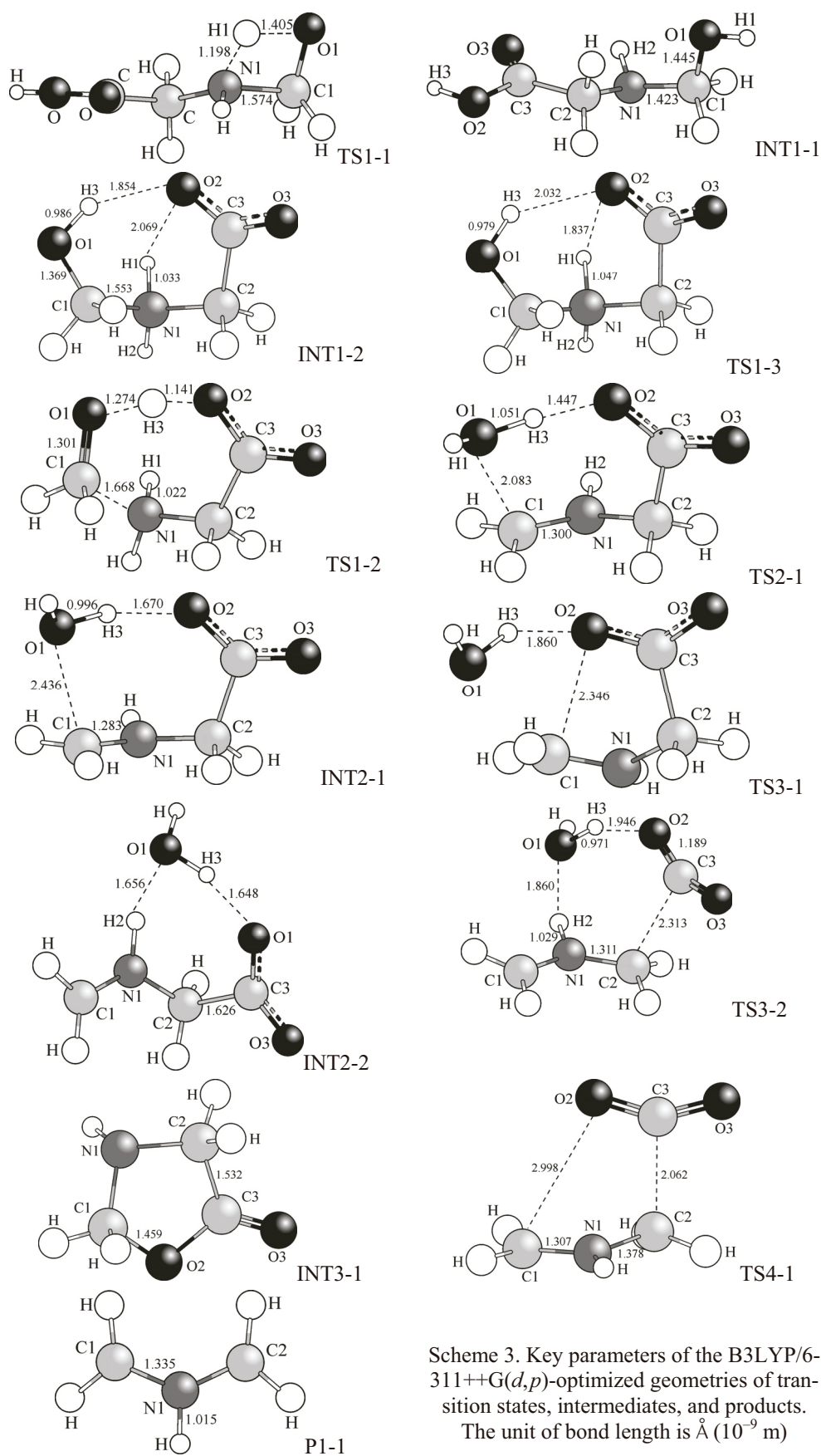
Scheme 3. Key parameters of the B3LYP/6-311++G(*d,p*)-optimized geometries of transition states, intermediates, and products. The unit of bond length is Å (10^{-9} m)
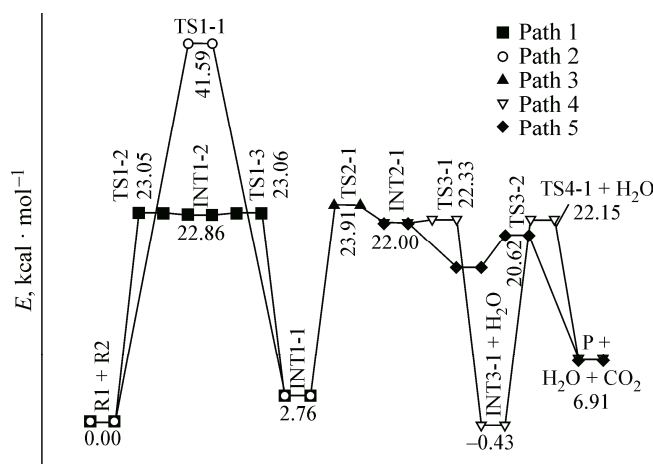
Fig. 1. Energy profile for the generation of azomethine ylide from formaldehyde and glycine at the B3LYP/6-311++G(*d,p*) level

C1—N1 bond is slightly longer (1.668 Å), and the O2—H3 and O1—H3 bonds are 1.141 Å and 1.274 Å respectively, indicating that the H3 proton leaves O2 to combine with O1. The IRC analysis reveals that TS1-2 leads to the INT1-2 intermediate which is only 0.19 kcal·mol^{-1} more stable than TS1-2. INT1-2 has a 1.553 Å C1—N1 bond and the O1—H3 bond is 0.986 Å. A pass through TS1-3, INT1-2 will lead to INT1-1 by the proton transfer from the iminium nitrogen atom to the carboxylate group. Although TS1-3 has a very similar structure to INT1-2, the IRC analysis does connect INT1-2 and INT1-1 through TS1-3. In TS1-3, while the N1—H1 distance is lengthened by 0.014 Å (1.033 *vs*. 1.047 Å), the O2—H1 bond is shortened to 1.837 Å from 2.069 Å. Meanwhile, the separation between O2 and H3 atoms increases from 1.854 Å to 2.032 Å. The energy barrier for TS1-3 differs by only 0.2 kcal·mol^{-1} from that of INT1-2. The final INT1-1 intermediate is 2.76 kcal·mol^{-1} more endothermic, as compared to the reactants.

The energy profile for the azomethine ylide generation from formaldehyde and glycine is depicted in Fig. 1, which clearly indicates that the carboxylic group participation in seven-membered transition states is favored by at least 18.53 kcal·mol^{-1}.

Zwitterion formation. The elimination of a water molecule from INT1-1 was also found to pass through a seven-membered ring transition state (TS2-1) which has an energy barrier of 21.15 kcal·mol^{-1}. In TS2-1, the C1—N1 bond is shortened to 1.300 Å, indicating a double bond formation, while the C1—O1 bond is broken (C…O is 2.083 Å). Meanwhile, the H3 proton combines with the hydroxyl group to generate a water molecule. The IRC analysis of TS2-1 ends up with the INT2-1 complex as a local minimum with the C1—O1 and O2—H3 bonds of 2.436 Å and 1.670 Å respectively. Furthermore, we tried to locate a transition state for the generation of a water molecule from INT1-2 to produce INT2-1 directly, but failed. Only TS2-1 is found to form a water molecule from INT1-1 to the INT2-1 complex.

Azomethine ylide formation. INT2-1 has two ways to reach P1-1. One is the formation of a 5-oxazolidinone intermediate, then thermally decarboxylate to P1-1 (Path 4); the other one starts with a geometry transformation to INT2-2, followed by a concerted elimination of water and carbon dioxide (Path 5). For the first pathway, INT3-1 was obtained from INT2-1 *via* a TS3-1 transition state, which differs only by 0.33 kcal·mol^{-1} from INT2-1. In TS3-1, the C1—O2 bond is 2.346 Å, while the H3—O2 hydrogen bond is found to be 1.860 Å. INT3-1 is a very stable intermediate which is 22.76 kcal·mol^{-1} more exothermic than TS3-1. TS4-1 is nearly at the same energy level as TS3-1 (22.15 *vs*. 22.33 kcal·mol^{-1}). While the C2—C3 bond is 2.062 Å, the C1—O2 distance is 2.998 Å, indicating that C1 and O2 are completely dissociated and carbon dioxide is ready to leave. The final product (azomethine ylide) is 6.91 kcal·mol^{-1} above the reactants, thus being an unstable product, which also explains why azomethine ylides were always generated *in situ*.

As for path 5, INT2-1 first converts to INT2-2 by changing its conformation from the C1…O1 weak interaction (2.436 Å) to the O1—H2 hydrogen bond (1.656 Å). Meanwhile, another O2—H3 hydrogen bond is also slightly lengthened from 1.670 Å to 1.648 Å. The total energy is lowered by 5.01 kcal·mol^{-1}. The elongation of the C2—C3 distance from 1.626 Å to 2.313 Å, together with the increased O1—H2 (1.860 Å) and O2—H3 (1.946 Å) hydrogen bonds, make TS3-2 be 3.63 kcal·mol^{-1} higher than INT2-2. The simultaneous elimination of water and carbon dioxide finishes the azomethine ylide formation as P1-1, which is preferred by at least 18.95 kcal·mol^{-1} as compared with path 4.

CONCLUSIONS

In this paper, a detailed mechanistic study of the azomethine ylide formation from formaldehyde and glycine has been carried out. Out of five possible pathways, the most favorable route would be the through the carboxylic group, involving seven-membered ring transition states, to carbinolamine and the following concerted elimination of water and carbon dioxide, i.e. path 1 → path 3 → path 5.

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