Ab initio Studies on Synthetic Routes of Glycine from Simple Molecules via Ammonolysis of Acetolactone: Applications of the Scaled Hypersphere Search Method

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New synthetic routes of glycine, the simplest amino acid molecule, have been discovered by theoretical search of ab initio potential energy surfaces. One step reaction of an acetolactone molecule with an ammonia molecule can produce a glycine molecule without byproducts, and its activation energy is only 1.6 kcal·mol^{-1}. Acetolactone can be produced from either carbon dioxide and singlet methylene ($CO_2 + CH_2$) or carbon monoxide and formaldehyde ($CO + HCHO$) with respective activation energies of 3.2 and 36.3 kcal·mol^{-1}.

Synthetic reactions of amino acid from simple molecules are important for understanding generations of amino acid in interstellar space, some planets, or the early earth in connection with origin of life. In 1953, Miller demonstrated a synthetic experiment producing some amino acids including glycine by electric discharges in mixture of methane, ammonia, water, and hydrogen molecules.[1] Hoyle and Wickramasinghe suggested another possibility of synthetic reaction of glycine in interstellar molecular clouds from simple organic molecules, methyleneimine and formic acid.[2] Very recently Nakahara et al. developed a way of synthesis yielding glycolic acid ($HOCH_2COOH$) in hot water from formaldehyde and formic acid,[3,4] and they suggested a new synthetic route of glycine by amination of glycolic acid generated in hot water.[4]

Reaction routes can be studied theoretically by searching for equilibriums (EQ) and transition states (TS) on potential energy surfaces (PES). Although ab initio and density functional theory (DFT) calculations have been made for reactions yielding glycine[5] and its precursors,[6–9] there have been difficulties to get global survey of reaction paths on PES.

Recently, we developed the scaled hypersphere search (SHS) method for global mapping of reaction paths on PES.[10] The SHS method enables us to follow reaction pathways from EQ to neighboring TS, noting that the potential energy along a reaction path becomes lower than the respective harmonic potential. The SHS method detects such anharmonic downward distortions of PES as energy minima on a hyper surface which would have a constant energy if the potentials are harmonic. The SHS method can be used to find out all reaction paths leading to anharmonic downward distortions. By searching for decomposition paths from a product, the SHS method can reveal synthetic paths to the product without byproducts.

In this study, we applied the SHS method[10] to glycine (H_2NCH_2COOH) and we wish to report two new reaction pathways yielding glycine from simple molecules of (CO_2, CH_2, NH_3) and (CO, HCHO, NH_3) with no byproducts.

Decomposition pathways releasing an ammonia (NH_3) molecule from an isomer of glycine were searched on the PES of ab initio HF/6-31G calculations. The structures were refined by B3LYP/6-311++G(d,p) calculations and shown in Figure 1. Ab initio calculations were made by GAUSSIAN 94 programs.[11]

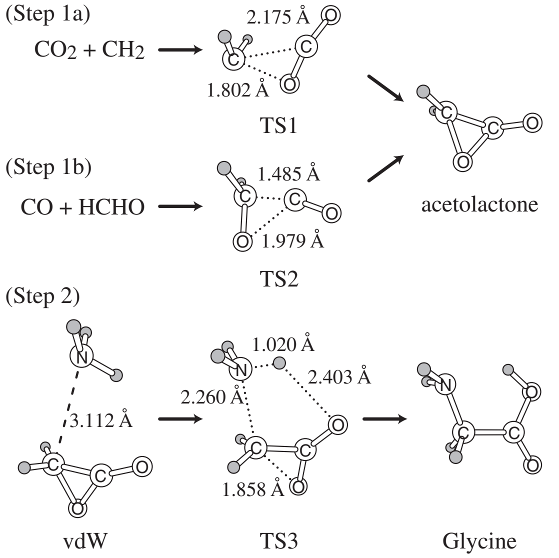

Figure 1. Reaction schemes and corresponding structures of EQ and TS by B3LYP/6-311++G(d,p) calculations. Chemical bonds are written by double solid lines, and weak bonds are denoted by dashed lines. A set of bonds rearranging around TS are indicated by dotted lines.

In both of the new reaction pathways yielding glycine, a three membered cyclic compound of acetolactone (H_2COCO) plays the dominant role as an intermediate. Although this α-lactone had long been experimentally unknown, its generation has been demonstrated in mass spectrometric experiments.[12]

In Step 1a, a reaction of CO_2 and singlet CH_2 (^{1}:CH_2) yields acetolactone.

$$CO_2 + {}^1{:}CH_2 \rightarrow H_2COCO. \qquad \text{(Step 1a)}$$

In Step 1b, a reaction of CO and HCHO yields acetolactone.

$$CO + HCHO \rightarrow H_2COCO. \qquad \text{(Step 1b)}$$

Step 1a or 1b can be followed by Step 2, a reaction with ammonia, to yield glycine.

$$H_2COCO + NH_3 \rightarrow H_2NCH_2COOH. \qquad \text{(Step 2)}$$

In Figure 1, optimized structures by B3LYP/6-311++G(d,p) calculations are shown. Chemical bonds are written by double solid lines, and weak bonds are denoted by dashed lines. A set of bonds rearranging around transition states (TS1, TS2, TS3) are indicated by dotted lines. In Step 2, the initial stage starts from a weekly bound van der Waals (vdW) complex.

Figure 2a shows relative energies in Step 1a and 1b with respect to the total energy of CO_2 and ^{1}:CH_2 by B3LYP/6-311++G(d,p) calculations. Figure 2b shows relative energies in Step 2 with respect to the total energy of NH_3 and acetolactone. Both CO_2 and CO reactions (Figure 2a) can generate acetolactone with respective activation energies of 3.2 and 36.3 kcal·mol^{-1}. In Figure 2b, glycine is expected to be generated from acetolactone and ammonia by overcoming 1.6 kcal·mol^{-1} barrier, since the second smallest activation barrier from the vdW complex corresponds to the route via TS2. The very small activation barrier of TS3 from the vdW complex can be related with the following two aspects. (1) NH_3 is bonded with the remaining part very weekly both in the vdW complex and TS3. (2) The energy for the CO bond dissociation in the triangle structure is expected to be small, because the triangle has a large constraint. Among the isomers of $C_2H_2O_2$, acetolactone has the lowest energy as has been confirmed previously.[12]

Production of CO and HCHO has been studied by a reaction of CO_2 with (singlet or triplet) CH_2, and acetolactone has been supposed to be the intermediate.[13]

$$CO_2 + CH_2 \rightarrow H_2COCO \rightarrow CO + HCHO.$$

Recent theoretical work[14] revealed that acetolactone is formed as the intermediate on the singlet PES of the reaction, and structures of acetolactone, TS1, and TS2 reported by HF/6-31G(d) and MP2/6-31G(d) calculations[14] correspond well to those in Figure 1.

Reactions of acetolactone with halide anion have been studied by theoretical calculations,[15,16] in connection with the observation of the next reaction.[17]

$$RCH(X)COO^- + Y^- \rightarrow RCH(Y)COO^- + X^-.$$

Step 2 (NH_3 reaction with acetolactone) yielding glycine has not yet been reported, though it is similar to the above anion reaction and also similar to the synthetic process of β-alanine via ammonolysis of the corresponding β-lactone.[18] It follows that once acetolactone is formed in liquid ammonia or in a medium where ammonia molecules are abundant, glycine is expected to be produced easily.

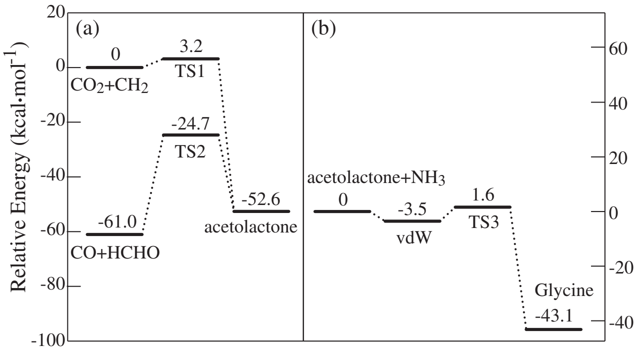

Figure 2. Energy diagrams at B3LYP/6-311++G(d,p) level of theory. (a) shows relative energies for Step 1a and 1b generating acetolactone with respect to the total energy of CO_2 and ^{1}:CH_2. (b) shows relative energies for Step 2 producing glycine with respect to the total energy of NH_3 and acetolactone.

Production of glycine via Step 1a or 1b followed by Step 2 is quite simple without loss of chemical components in reactants in comparison with other reaction paths proposed in some theoretical calculations that undergo many intermediates and precursors with some losses of chemical components.[5–9] All reactants in the present reaction routes, (CO_2, CH_2 in Step 1a), (CO, HCHO in Step 1b), and (NH_3 in Step 2), are simple molecules observed in interstellar molecular cloud.[19] In interstellar media, the present reaction routes will not proceed, since interstellar reactions require barrier free processes.[20] Even if acetolactone could be produced via TS1, its heat of formation will be used to decompose the lactone into CO and HCHO via TS2.

The activation energy for Step 1a is 3.2 kcal·mol^{-1}, which is much lower than the reported lowest energy barrier of 14.6 kcal·mol^{-1} for glycine synthesis from aminocyanoacetic acid in previous studies.[5] Although the activation energy of 36.3 kcal·mol^{-1} for Step 1b is much smaller than the activation energy of 49.0 kcal·mol^{-1} required to produce aminocyanoacetic acid from aminomalononitrile,[8] Step 1b will not proceed at low temperature. The activation energy of 1.6 kcal·mol^{-1} in Step 2 is very small, and this step may easily proceed at room temperature. Thus, the present routes of Step 1a or 1b followed by Step 2 seems to have a great significance for synthetic routes of glycine from simple molecules, although dynamic effects or free energies need to be considered to elucidate experimental conditions for the reactions in detail.

The SHS method has been used to discover many isomerization and synthetic (decomposition) pathways for other systems such as $C_2H_2O_2$, which includes HCHO as an isomer. Reaction paths generating HCHO from inorganic species (H_2 and CO, or H_2O and singlet C atom) have been reported.[10] In the present study, new synthetic routes of glycine from simple species without byproducts could be discovered as minimum energy pathways on PES by use of the SHS method.

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