Ab Initio Study of the Formation of Glycine via Amino Acetonitrile and Amino-Cyano-Acetic Acid

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Ab initio theoretical calculations were carried out to study the hydrolysis of amino acetonitrile (NH_2CH_2CN) and amino-cyano-acetic acid ($NH_2(CN)CHCOOH$). Each of the proposed schemes was considered to be one of the possible reaction paths by which the simplest amino acid, glycine, may be synthesized by nature. The optimized structures of the species on the potential energy surfaces were calculated at both the HF and MP2 levels. We found that the direct hydrolysis of the nitrile group of amino acetonitrile required a higher energy barrier (52.38 kcal/mol) compared to the barrier for the hydrolysis of amino-cyano-acetic acid (46.11 kcal/mol). Our calculated potential energy profiles revealed that this glycine evolution would not occur as easily in an anhydrous atmosphere as in moist surroundings. (The difference in the barriers may be more than 30 kcal/mol.) Molecular orbital interaction between H_2O and the amino acetonitrile was also studied, and we found that the crucial part of this hydrolysis process was the transfer of the hydrogen atom of H_2O to the N atom of the nitrile group rather than the formation of the C−O bond between the O atom of H_2O and the C atom of the nitrile group. The schematic processes with calculated lower energy barriers in the proposed schemes might be considered to be possible mechanisms in the prebiotic chemical evolution on the primitive earth.

Introduction

In 1850, an α-amino acid formed by the treatment of an aldehyde with hydrogen cyanide in the presence of aqueous ammonia[1] made people think seriously about the possibilities and meanings of chemical evolution.[2] In 1953, Miller[3] simulated electric discharges in a reducing atmosphere of CH_4, NH_3, and H_2O and obtained an aqueous solution of simple carboxylic and amino acids, which has long been considered to be one of the pillars of the theory of the heterotrophic origin of life in a prebiotic broth.[4] Many people have repeated the Miller experiments with many variations, using thermal energy,[5−12] ultraviolet light,[13−20] or ionizing radiation[21−25] as the energy source instead of an electric spark. The results were always consistent. A variety of methods of synthesizing chiral amino acids have been developed,[26] and many theoretical studies[27] were focused on the catalyzed mechanisms from methanimine to the amino acetonitrile.

There are several reasons that amino acid syntheses have become such an attractive area of chemical evolution. First, they are the constituent units (monomers) of the proteins. Second, present data indicate that they form more readily (from CH_4, NH_3, and H_2O mixtures) than any of other biomonomers. Finally, very powerful and sensitive techniques exist for amino acid detection and analysis.

Several mechanisms have been proposed to account for the appearance of amino acids in primitive earth experiments.

(a) The cyanohydrin mechanism was invoked by Miller[28] to explain his amino acid products.

$$RCHO \xrightarrow{NH_3,\ HCN} RCH(NH_2)CN \xrightarrow{H_2O} RCH(NH_2)CO_2H$$

(b) The electric discharges in anhydrous methane−ammonia mixtures cause the formation of α-aminonitriles,[29] followed by hydrolysis to form amino acids.

$$CH_4 + NH_3 \rightarrow H_2NCHCN,\ H_3CCH(NH_2)CN \xrightarrow{H_2O} H_2NCH_2CO_2H,\ H_3CCH(NH_2)CO_2H$$

(c) Sanchez et al.[30] have suggested a possibly important role for cyanoacetylene (a product of CH_4-N_2 irradiations) in amino acid synthesis.

$$NCC{\equiv}CH + NH_3 \rightarrow NCCH{=}CHNH_2 \xrightarrow{HCN} NCCH_2CH(NH_2)CN \xrightarrow{H_2O} HO_2CCH_2CH(NH_2)CONH_2 \xrightarrow{H_2O}$$

asparagine

$$HO_2CCH_2CH(NH_2)CO_2H$$

aspartic acid

(d) Abelson,[29] Matthews, Claggett, and Moser,[32−35] and Harada[36] have emphasized a possible key role of HCN oligomers, produced by the base-catalyzed polymerization of HCN. The HCN trimer—amino acetonitrile—and the HCN tetramer—diaminomaleonitrile—give, on heating in water for 24 h at 100°C, as many as 12 of the 20 α-amino acids commonly found in proteins.[34,35]

(e) Akabori proposed a laconic mechanism for glycine.[37] Amino acetonitrile would be formed from the beginning with amino malononitrile, and it could either hydrolyze to glycine or polymerize to polyglycinimide.

In this study, we extended our past research[38] to evaluate the potential energy for every step of the proposed mechanisms starting from amino acetonitrile, as well as via amino-cyano-

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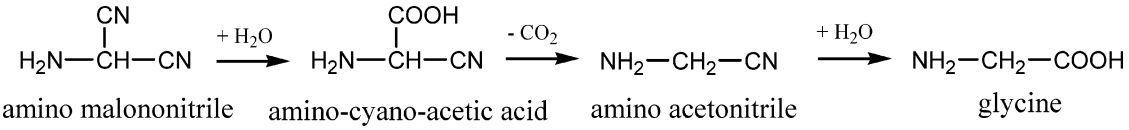


acetic acid to form glycine, which include hydrolysis, decarboxylation, deaminoation, decyanation, and so forth. Knowing that the water-assisted reaction can lower the barrier in the proton-transfer process, we further investigated the catalytic effect by the second H_2O molecule.

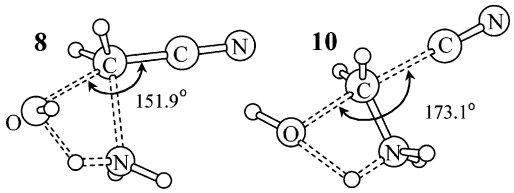
Method of Calculation

The ab initio calculation was performed for complete geometry optimization at both the Hartree−Fock (HF) and second-order Møller−Plesset (MP2) levels by using the Gaussian 98[39] suite of programs. Optimizations of minima as well as transition structures were carried out with triple-ζ-type basis sets including polarization functions (TZP), 6-311G (d,p). At the same level of theory, frequency calculations were performed to identify the stationary points as local minima, transition structures, or higher-order saddle points on the PES. Intrinsic reaction coordinate (IRC) calculations[40] were also performed to ensure that all of the transition states had the desired reaction coordinates at HF/6-311G (d,p) and some at MP2/6-311G (d,p). The HF method was performed at first, and the accuracy of the data was expected to be promoted at the MP2 level with the consideration of electron correlation in the calculation. The calculated energies were corrected for zero-point vibrational energy (ZPVE) with the scaling factor of HF being 0.9248 and that of MP2 being 0.9748.[39] We also performed a natural population analysis (NPA) of charge by using the NBO program[42,43] at the MP2 level. Because the activation energies for the rotational conformations are always not high, we will present only the most stable conformation of MP2 calculations here. All atomic charges and standard orientation coordinates for some transition structures are summarized in Table SI (Supporting Information). Molecular orbital interactions along the potential energy surfaces were also investigated, and the shape of the molecular orbital obtained from the MP2/6-31G** result was plotted using the Molden v3.6 program written by G. Schaftenaar.[44]

Result and Discussion

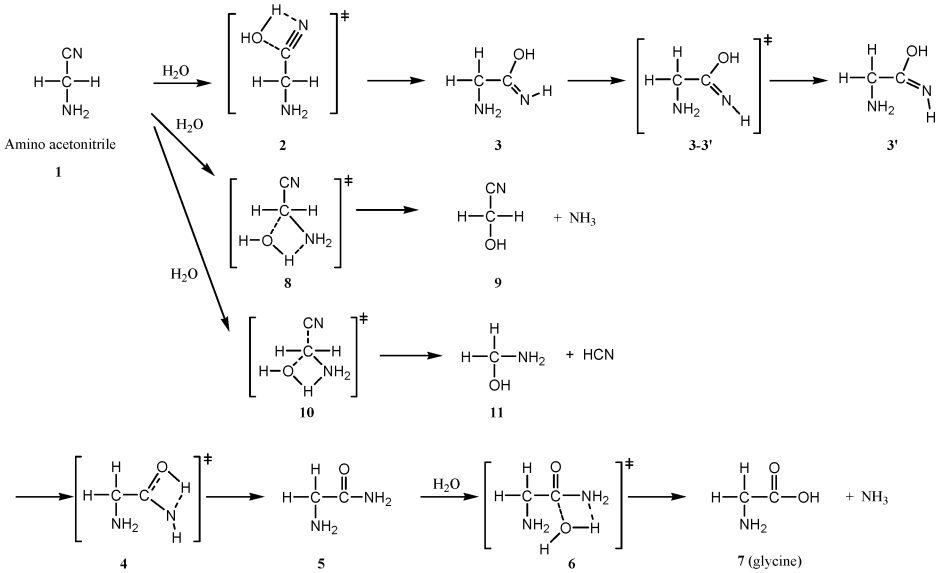
A. Glycine Formation via Amino Acetonitrile, NH_2CH_2CN. The proposed reaction mechanism for the formation of glycine via amino acetonitrile was drawn in Scheme 1.

A number is assigned underneath each structure as a notation of the species. Species **2**−**7** construct the main mechanism of glycine formation via amino acetonitrile, and **8**−**11** are species from branched processes in the first hydrolysis step. There are two potential reaction sites (CN and the central carbon atom) in amino acetonitrile where the added water molecule could attack. If the added H_2O attacks the central carbon atom of **1** by the O atom and shifts a proton to the amino group, then it may form either **9** or **11** depending on the insertion angle of H_2O. If the angle of incoming H_2O with respect to the CN group is significantly smaller than 180° (such as $\angle O_9C_1C_3 = 151.9°$ in **8**), then it would cause the leaving amino group to form **9** plus NH_3 (see the following drawings). On the contrary, if the angle is close to 180° (such as $\angle O_9C_1C_3 = 173.1°$ in **10**), then the CN group could leave (similar to an S_N2 reaction) and form **11** plus HCN.



Our calculation showed no energy barrier for the migration of a proton from NH_3^+ to CN^-. However, the energy barriers for these two substitution reactions are considerably high: 86.27 kcal/mol for the former (**9** + NH_3) and 84.11 kcal/mol for the latter. The calculated potential energy profile is presented in Figure 1. In contrast, the energy barrier for the hydrolysis on the CN group is much smaller, only 52.38 kcal/mol. Therefore, the added H_2O prefers to undergo a hydrolysis reaction with

SCHEME 1



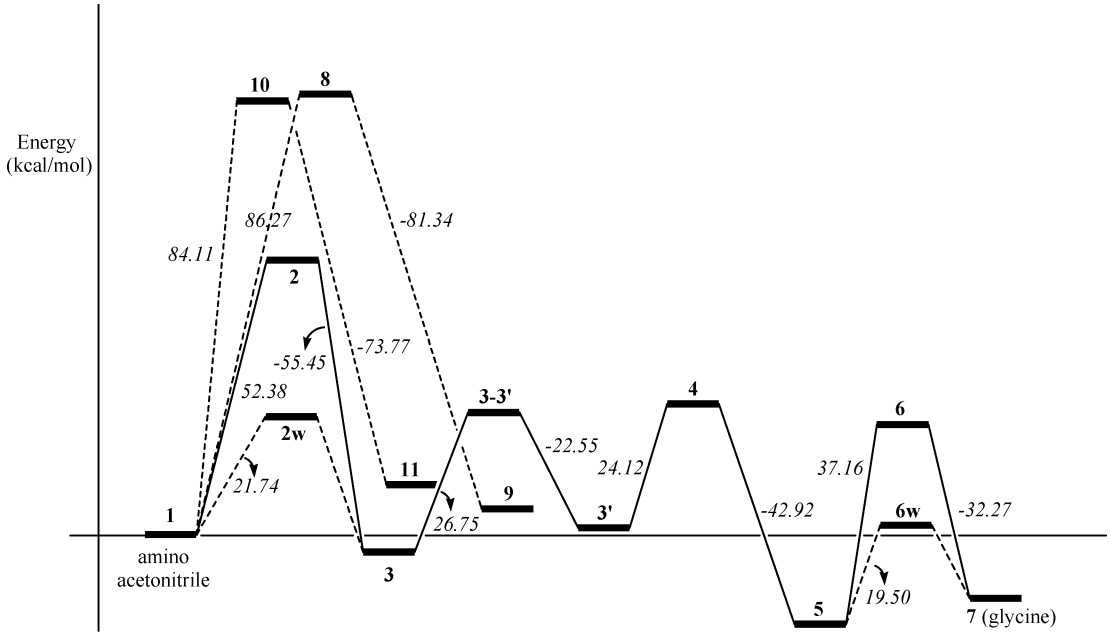
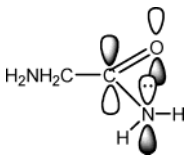
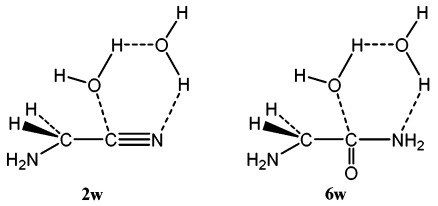


Figure 1. Potential energy diagram for the formation of glycine from amino acetonitrile, calculated at the MP2(FC)/6-311G** level of theory.

the nitrile group of amino acetonitrile thermodynamically. In addition, the hydrolysis of the CN group is exothermic by 3.07 kcal/mol (from **1** to **3**), but the other two substitution reactions are endothermic by 4.93 and 10.34 kcal/mol for the formation of **9** and **11**, respectively. Thus, the addition of the H_2O molecule onto the CN group to produce the hydroxyl imine was a major pathway to be considered. Because there was a lone-pair electron in the imine group, it was possible to proceed via intramolecular hydrogen transfer. Transition state **3**−**3′** was obtained (with an energy barrier of 26.75 kcal/mol) by rotating the lone-pair electrons facing the hydrogen group, **3′**, followed by hydrogen transfer passing transition state **4**. The energy barrier was 24.12 kcal/mol, and then it slid into a quite stable amide structure, **5**. From the NBO calculation, we found that there was a strong back-donation interaction between the lone-pair p orbital of the N atom and the antibonding π_{CO} orbital (LP N $\rightarrow \pi^*_{C=O}$). These two orbitals are parallel to each other (as shown in the following drawing)



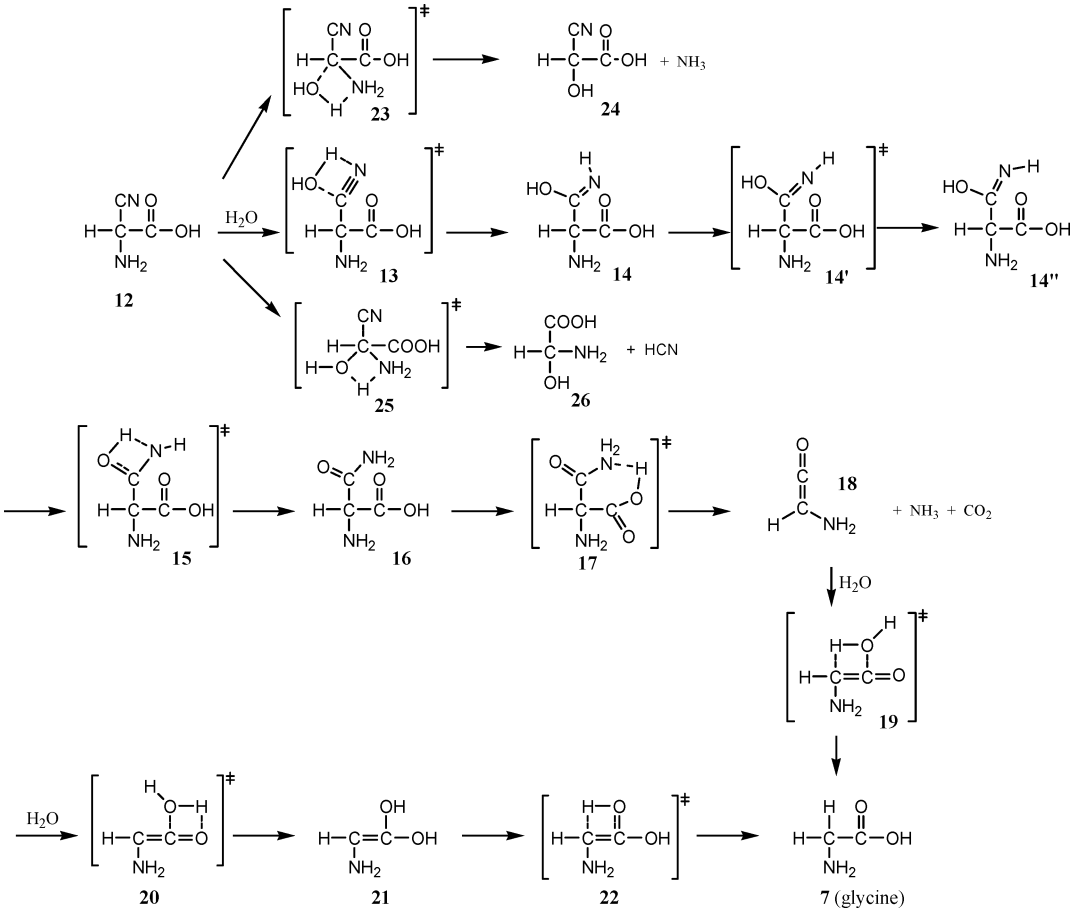
and the hydride character of the N atom is close to sp^2 instead of sp^3. The effect of this strong interaction made structure **5** the most stable species on the potential profiles (19.67 kcal/mol lower than amino acetonitrile). Another H_2O molecule was added to continue the glycine-formation process. It was also possible to have some branching reactions not leading to glycine formation if H_2O attacked on positions other than the carbonyl carbon atom. However, here we focused only on the process leading to glycine formation. A substitution reaction took place, and glycine was found via transition structure **6** with an energy barrier of 37.16 kcal/mol. From Figure 1, it is clear that the overall energy barrier for the addition of one H_2O molecule onto the CN group of amino acetonitrile to form glycine is 52.38 kcal/mol, which is rather high compared to the hydrolysis of the nitrile group in the aqueous solvent. To understand the water-assisted effect, we added an additional H_2O molecule to the system, and the resultant transition structures **2w** and **6w** were drawn as



Surprisingly, the net barriers were 21.74 and 19.50 kcal/mol, respectively, which were much smaller than those in the previous non-water-assisted case (52.38 and 37.16 kcal/mol). Therefore, the catalytic effect of the additional H_2O molecule in the system is enormous, and this may facilitate the rate of reaction considerably.

B. Glycine Formation via Amino-cyano-acetic Acid, $NH_2CH(CN)COOH$. In our previous study,[38] amino-cyano-acetic acid (labeled **12** in Scheme 2) was an intermediate in the production of amino acetonitrile from amino malononitrile NH_2-$CH(CN)_2$. The energy barrier of decarboxylation from **12** to produce amino acetonitrile was 61.08 kcal/mol, high enough to become a rate-determining step in the whole prebiotic synthesis. This barrier did not decrease too much even with the additional H_2O molecule added as a catalyst (42.86 kcal/mol, water-assisted decarboxylation). Therefore, we were curious to determine whether glycine could be formed via amino-cyano-acetic acid directly, so we considered the reaction in Scheme 2 by using **12** as a starting material. If the added H_2O molecule attacks the central carbon atom of structure **12,** it then may pass through either transition structure **23** or **25**, depending on the insertion angle of the H_2O, and then each produced **24** or **26,** respectively. If the added H_2O attacks the CN group (**13**), it may produce intermediate structure **14**. The latter process is more preferable energetically, with a barrier of only 46.11 kcal/mol, which is much smaller than the direct decarboxylation (61.08 kcal/mol) to form amino acetonitrile. In addition, it is more exothermic ($\Delta H = -20.60$ kcal/mol) than decarboxylation ($\Delta H = -14.24$ kcal/mol). Obviously, structure **12** is more likely

SCHEME 2



to carry out the addition reaction of H_2O onto the nitrile group instead of the decarboxylation reaction to form amino acetonitrile. This conclusion is quite different from Calvin's[37b] predictions in the process of chemical evolution; he stated that a direct decarboxylation to form amino acetonitrile was considered first. The formation of the hydroxyl imine, **14**, was followed by intramolecular hydrogen transfer via **14′** → **14″** → **15** → **16** (drawn in Scheme 2) to form an amide intermediate, with the transition energies being 29.75 kcal/mol (**14** → **14′**) and 23.28 kcal/mol (**14″** → **15**), respectively. The potential energy profiles for this scheme are drawn in Figure 2. Structure **16** simultaneously possesses amino, amide, and carboxyl functional groups, which may easily carry out the intramolecular hydrogen transfer (via a six-membered construction, **17**) to decarboxylate and deaminate to form an amino ketene (**18**). The ketene is very reactive and can easily form carboxylic acid by the addition of an H_2O molecule. From the NPA calculation, the atomic charge of carbon atom C_α in the amino ketene is +0.84, and those of C_β and O atoms are −0.35 and −0.55, respectively.

Therefore, it is more likely that the C_α atom receives the O atom of H_2O via transition structure **19** to form glycine directly,

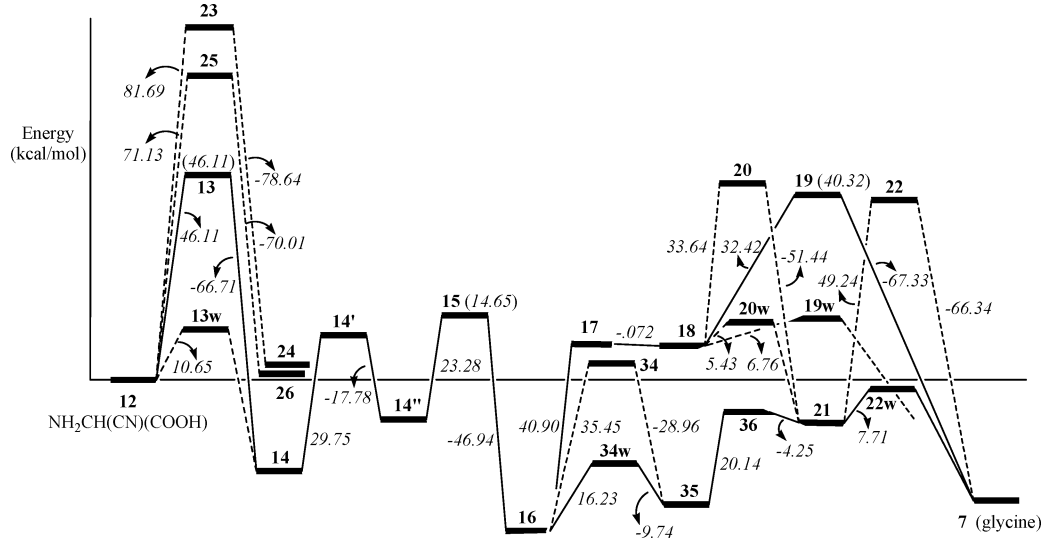
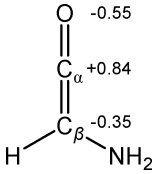
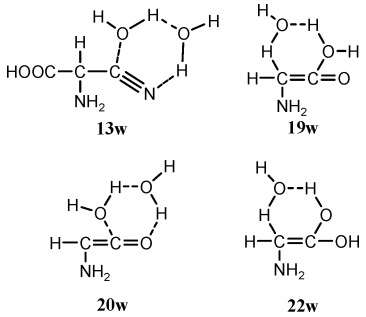


Figure 2. Potential energy diagram for the formation of glycine via amino-cyano-acetic acid, calculated at theMP2(FC)/6-311G** level of theory.



with an energy barrier of 32.42 kcal/mol. The H_2O molecule may alternatively react with the C_α═O portion of the amino ketene (via transition structure **20**) to form an enediol (**21**, energy barrier = 33.64 kcal/mol) and then via **22** to form glycine (energy barrier = 49.24 kcal/mol). Obviously, this process is less probable. At this point, we were curious about how well the water-assisted catalytic effect could bring down the energy barriers in the proposed reaction scheme (Scheme 2). As shown in the following drawings

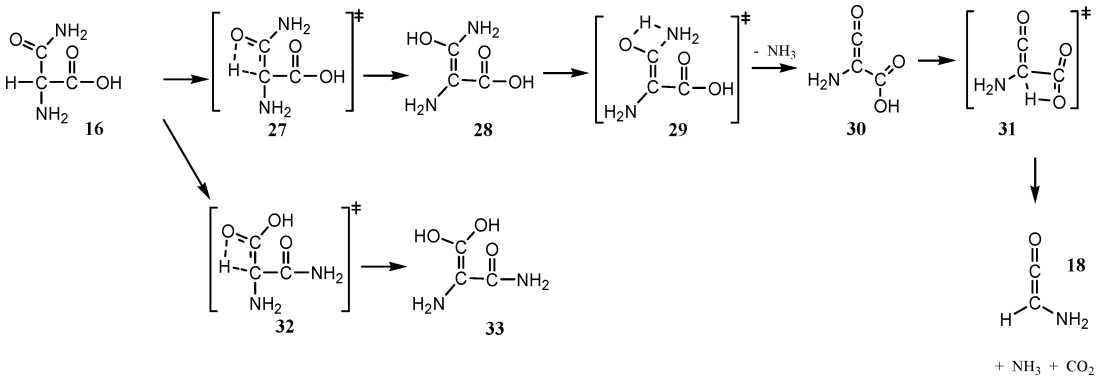
transition structures **13w**, **19w**, **20w**, and **22w** all have one more H_2O molecule added to assist the process of the reactions. Surprisingly, the energy barriers are largely reduced to 10.65, 6.76, 5.43, and 16.23 kcal/mol, and the decreased amounts are 35.5, 25.7, 28.2, and 41.5 kcal/mol, respectively, compared to non-water-assisted counterparts. This catalytic effect is greatly enhanced in amino ketene systems, showing the intense reaction of ketene toward H_2O. Our calculation reveals that when there is water assistance it is favorable for the $(H_2O)_2$ to add onto the C_α═O portion of the ketene, which agrees well with others' results.[45] Nevertheless, in the non-water-assisted case, H_2O prefers to add onto the C_α═C_β portion of the ketene.



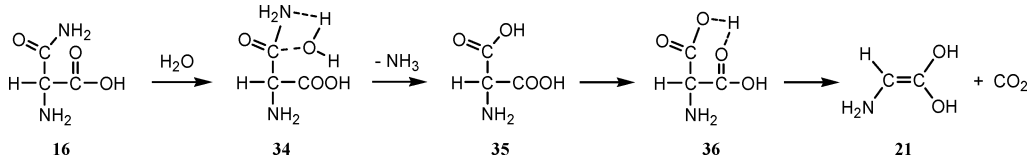
There is an alternative pathway to form the amino ketene, designed in Scheme 3.

Because the hydrogen atom of C_α−H in structure **16** is flanked by amide and carboxyl groups, its acidity is enhanced even more. The breakage of the C_α−H bond would be simpler, and the following intramolecular proton transfer could lead to amino ketene (**18**) formation. However, the calculated energy barrier for process **16** → **27** was extremely high, 64.02 kcal/mol, indicating that this process was not significant. Also, it was endothermic by 14.06 kcal/mol. The other two energy barriers (deamination and decarboxylation) in this amino ketene-formation scheme were not low: 53.07 kcal/mol for **28** → **29** and 51.87 kcal/mol for **30** → **31**, respectively, as compared to that of **16** → **17** → **18** in Scheme 2. Incidentally, the other C_α−H abstraction process from **16** → **32** to form **33** also has a high barrier, 71.39 kcal/mol. There is another possibility that structure

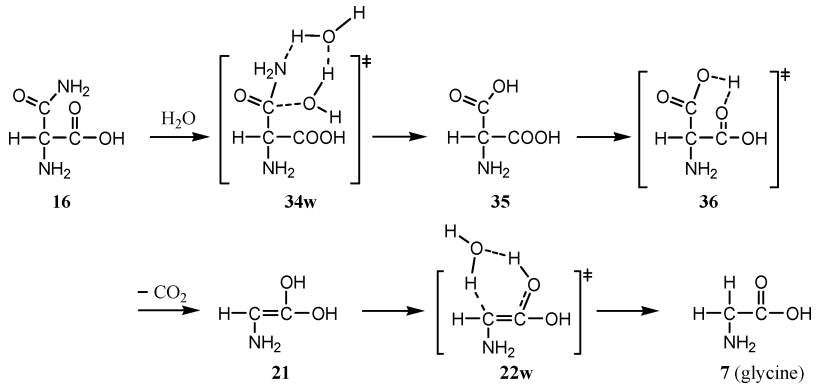
SCHEME 3



SCHEME 4



SCHEME 5



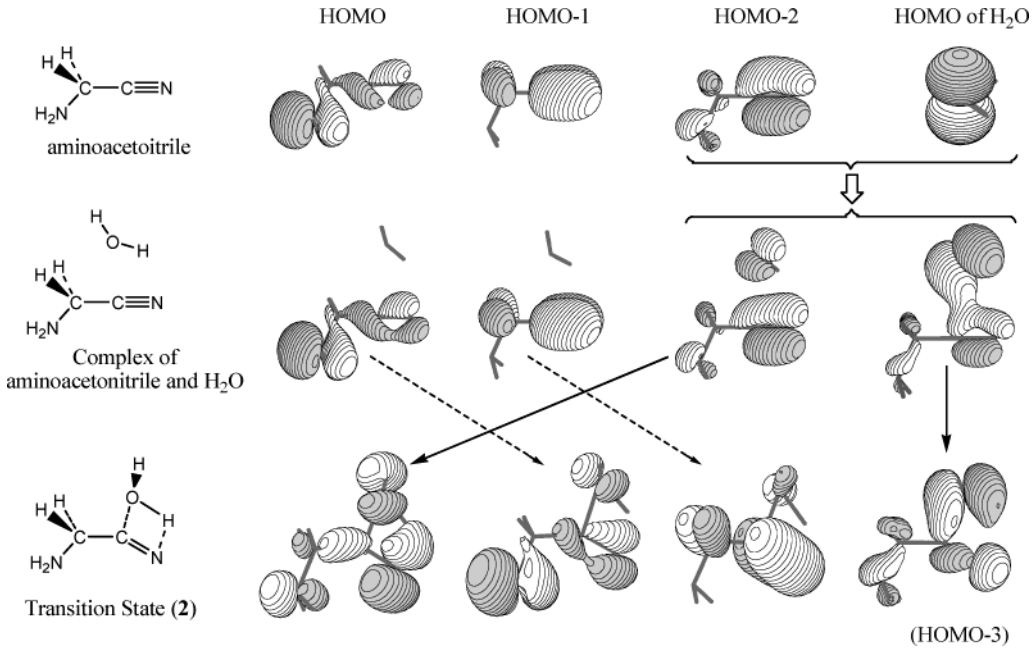


Figure 3. Shape of frontier orbitals (HOMO, HOMO-1, HOMO-2, and HOMO-3) of reactants (amino acetonitrile, complex of H_2O and amino acetonitrile) and transition structure **2**.

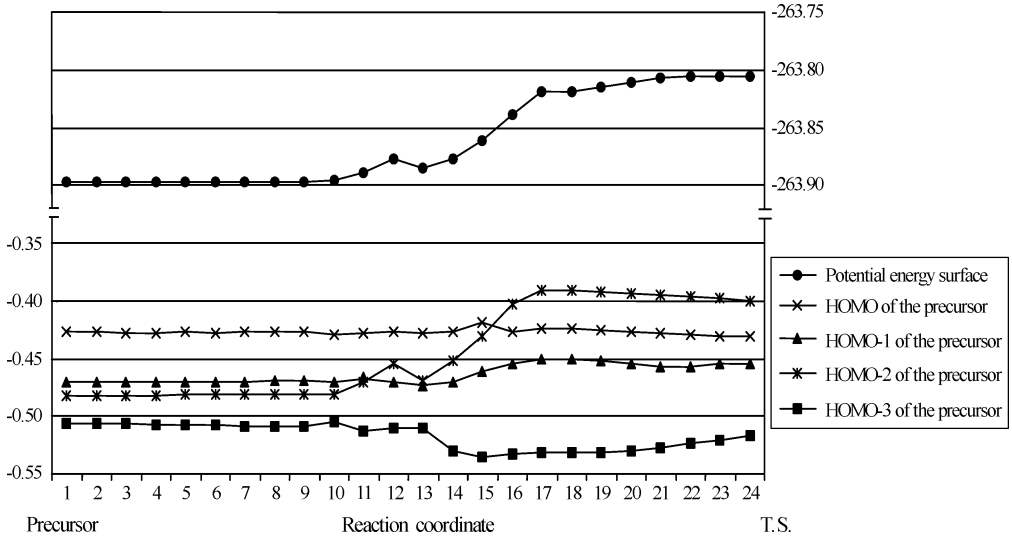


Figure 4. (upper graph) Potential energy surface of transition structure **2** with respect to the change in reaction coordinates. (lower graph) Orbital energies of HOMO, HOMO-1, HOMO-2, and HOMO-3 of the precursor (reaction complex) at different approaching distances between amino acetonitrile and H_2O. As can be seen from the diagram, the trend in HOMO-2 orbital energy is similar to the curve of the potential energy surface of transition structure **2** on the approach of the reactants, indicating the crucial relationship between orbital interaction in HOMO-2 of the precursor and the energy of transition structure **2** on the approach of the reactants.

16 may react with H_2O to deaminate first (through transition state **34**) to form **35** (a dicarboxylate intermediate with a barrier of 35.54 kcal/mol), designed in Scheme 4, and then decarboxylate via **36** to form an enediol (**21**) with an energy barrier of 20.14 kcal/mol, which could be further isomerized to form glycine.

C. Mechanisms to Form Glycine. The mechanism to form glycine via amino acetonitrile is quite simple via the direct hydrolysis of the nitrile group into carboxylic acid, in which the energy barrier is not low (52.38 kcal/mol without water assistance), and it decreases to 21.74 kcal/mol with one additional water molecule added as a catalyst. However, the energy barrier of the decarboxylation of amino-cyano-acetic acid ($NH_2CH(CN)COOH$) to form amino acetonitrile was much higher (61.08 kcal/mol) than that for the production of amino acetonitrile from amino malononitrile ($NH_2CH(CN)_2$) via the decarboxylation of amino-cyano-acetic acid, which may not be practical. In addition, the energy barrier in each step of amino-cyano-acetic acid directly forming glycine is smaller than that for the decarboxylation step of forming amino acetonitrile. Therefore, it would be more effective to follow another alternative, that is, amino-malononitrile to amino-cyano-acetic acid, **12**, and then to glycine, as described in Scheme 2. If an additional H_2O molecule were added as a catalyst, then the reaction pathway would change when it reached to **16**. The pathway would be **16** → **34w** → **35** → **36** → **21** → **22w** → glycine, as described in Scheme 5, with the highest net energy barrier being less than 15 kcal/mol (counted from the base point of structure **12** to the transition state **15**), as compared to 46.11 kcal/mol in the previous noncatalytic scheme.

This low-energy barrier could facilitate the pathway with the feature of no amino ketene formation. Therefore, whether the

formation of amino ketene was detected in the true reaction could help to determine the real reaction pathway. Our calculated potential energy profiles revealed that this glycine evolution would not occur as easily in an anhydrous atmosphere as in moist surroundings. Incidentally, the structural acidic α-hydrogen in **16** does not migrate easily. Both energy barriers of intramolecular hydrogen transfer, **16** → **27** and **16** → **32**, are quite high, 64.02 and 79.20 kcal/mol, respectively, partly because of having a highly strained four-membered ring transition state in each process and also partly because this H migration would distort the well-balanced structure maintained by the three sets of intramolecular hydrogen bonds. Therefore, this hydrogen transfer of **16** in Scheme 3 is not likely to occur. Nevertheless, the hydrolysis of **16** via **34** in Scheme 4 is possible; through this mechanism the three sets of intramolecular hydrogen bonds can still be maintained. The energy barrier is thus much lower, 35.45 kcal/mol, and is similar to the type of process in **5** → **6** (37.16 kcal/mol).

D. Interaction of Molecular Orbitals in the Hydrolysis of Amino Acetonitrile. It is interesting to notice the molecular orbital interaction between the H_2O molecule and amino acetonitrile (**1**). We plotted the frontier orbitals of **1**, the complex (H_2O + **1**, precursor of reactants), and transition state **2** in Figure 3. Assuming that the molecular plane of **1** passes through the central carbon atom, the nitrile group, and the nitrogen atom, we then can distinguish the HOMO-1 as being symmetric to the molecular plane, from HOMO-2, on the molecular plane of **1**. These two MOs feature the two π orientations of the CN group. When H_2O starts to approach **1**, the shapes of these MOs as well as the energy order do not change (as shown in the complex portion of MOs in Figure 3). However, we found that the energy of HOMO-2 of the complex starts to increase as the two approaching moieties get closer and closer, and it became HOMO at the transition state. We can trace these points along the reaction coordinate and plot the change in these MO energies, shown in Figure 4. At point 12 where the C···O distance is 2.53 Å and the H···OH distance is 1.01 Å, the MO energy of the original HOMO-2 jumps over and becomes HOMO-1. This MO energy keeps on rising, and at point 16 where the C...O distance is 1.89 Å and the H···OH distance is 1.02 Å, it becomes HOMO and remains HOMO to the transition state. This MO energy trend is similar to the potential energy profile of the transition state. On the contrary, the energies of the original HOMO and HOMO-1 of the precursor do not follow the trend and become HOMO-1 and HOMO-2, respectively, at the transition state. This result reminds us not to ignore the molecular interaction occurring in HOMO-2 of the precursor, which almost dominates the energy change of the reaction process. We found out that the formation of HOMO-2 and HOMO-3 in the precursor was mainly an MO combination from the HOMO of H_2O and the HOMO-2 of amino acetonitrile, drawn in Figure 3. The positive (or same phase) combination forms HOMO-3, and the negative (or opposite phase) combination forms HOMO-2. Along the reaction coordinate, we inspected the changes in these MOs and assured that HOMO-2 represented the transfer of the hydrogen to the N atom of the nitrile group in amino acetonitrile, whereas that of HOMO-3 represented the formation of the C−O bond of the C atom of the nitrile group with the O atom of H_2O. Because the MO energy of HOMO-3 does not change significantly (in fact, it decreases a little bit in Figure 4) during the whole reaction process, we are convinced that the crucial part of this nitrile hydrolysis process was the transfer of the hydrogen atom of H_2O to the N atom of the nitrile group but not the formation of the C−O bond between H_2O and the nitrile group.

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Supporting Information Available: Atomic charges and standard orientation coordinates for some transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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