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Molecular Interactions between Glycine and H_2O Affording the Zwitterion

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Isomerization reactions of glycine were studied computationally. Three water molecules were found to cause the reaction of glycine with the anti carboxyl group. For the glycine with the syn carboxyl group, three and one molecules are concerned with the reaction; one acts as a catalyst to prevent the local proton transfer. A reaction model composed of glycine and eleven water molecules was examined. An “out-of-plane” path was found to be a favorable stepwise channel with two small activation energies. In the path, an ion-pair intermediate was obtained. From the intermediate, a proton may be relayed outward from the hydrogen-bond network. The possibility of this proton dispersal was discussed in relation to experimental evidence of isoelectric points of zwitterions.

1. Introduction

An α-amino acid has an amino group and a carboxyl group on the same carbon, $H_2N-CHR-COOH$. R is a substituent, and the parent (R = H) α-amino acid is glycine. Neutral amino acids are known to have similar values, 6.0, of isoelectric points (pH values of the largest concentration of zwitterions). Scheme 1 exhibits the similarity,[1] which is in contrast to the change of acidity constants of carboxylic acids with respect to the alkyl-group variation (Scheme 2).[2]

This variation is natural, and the constant values in Scheme 1 are hard to understand. Another question in Scheme 1 is in the values (6.0, not 7.0) of the isoelectric points of “neutral” amino acids. It is a question why the weak-acid condition is required to attain the maximum concentration of zwitterions.

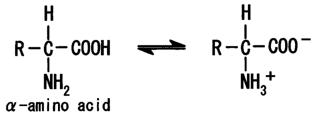
Molecular interactions between α-amino acids and water molecules need to be investigated to rationalize the constant values (= 6.0) of isoelectric points in Scheme 1.

Zwitterions ($^+H_3N-CHR-COO^-$) are generated formally by an isomerization in eq 1:

$$H_2N-CHR-COOH + (H_2O)_n \rightarrow {}^+H_3N-CHR-COO^- + (H_2O)_n \quad (1)$$

Obviously, the ions are stabilized by hydrogen bonds with the surrounding water molecules. When the neutral glycine is dissolved into water, it is transformed exclusively to the zwitterion. This process is ready. It has not been clarified why the isomerization reaction takes place readily. The small activation energy of the isomerization should be explained in terms of molecular interactions (Scheme 3).

SCHEME 1: Isoelectric Points of Alkyl-Substituted α-Amino Acids



$$R-\overset{H}{\underset{NH_2}{C}}-COOH \rightleftharpoons R-\overset{H}{\underset{NH_3^+}{C}}-COO^-$$

α-amino acid

R−	amino acid	isoelectric point at 25℃
H−	glycine	5.97
H_3C-	alanine	6.00
$H_3C-\overset{H}{\underset{H_3C}{C}}-$	valine	5.96
$H_3C-\overset{H}{\underset{H_3C}{C}}-\overset{H}{\underset{H}{C}}-$	leucine	5.98
$H_3C-\overset{H}{\underset{\underset{CH_3}{H-C-H}}{C}}-$	isoleucine	6.02

same values, 6.0.

SCHEME 2: Acidity Constants of Alkyl-Substituted Aliphatic Acids

$$R-COOH \rightleftharpoons RCOO^- + H^+$$

carboxylic acid

R−	aliphatic acid	acidity constant at 25℃ (pKa)
H_3C-	acetic acid	4.76
H_3CCH_2-	propionic acid	4.88
$H_3C-CH_2-CH_2-$	butyric acid	4.82
$H_3C-\overset{H}{\underset{CH_3}{C}}-$	isobutyric acid	4.86
$H_3C-CH_2-CH_2-CH_2-$	valeric acid	4.86
$H_3C-\overset{CH_3}{\underset{CH_3}{C}}-$	pivalic acid	5.05

enlarged.

Many ab initio calculations have been reported as to the stability, structure, and solvent effect on the glycine zwitterion.[3−15] Thirteen conformers of gaseous neutral glycine were precisely examined, and the lowest-energy form has a planar heavy-atom structure and two equal N−H···O hydrogen bonds.[16] By inclusion of a solvent continuum model, a geometry of the in-plane N···H−O hydrogen bond becomes the best one.[17] As for the reaction in eq 1, there are various computational studies. The direct proton shift under the field of water clusters shown in Scheme 3 was extensively studied.[18−20] A free-energy barrier for the (neutral glycine → zwitterions) conversion is only 0.65 kcal/mol. However, the shift involves a geometric strain from the standpoint of hydrogen bond directionality. When one or two ($n = 1$ or 2) H_2O molecule is included, $N\cdots(H_2O)_n\cdots H-$

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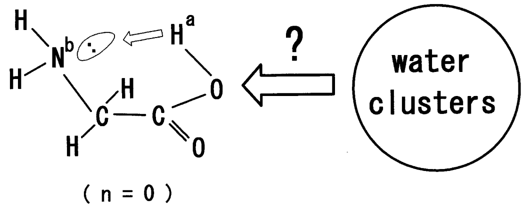
SCHEME 3: Participation of Water Molecules in Isomerization of the Glycine Molecule



Formally, migration of H^a to lone-pair densities of N^b leads to formation of a zwitterion

O, the strain is relaxed and the activation energies become smaller.[21,22] For $n \geq 3$, there seem to be no computational studies. A systematic analysis of the water participation in eq 1 would be necessary. Ready isomerizations are thought to be associated with reasonable hydrogen bond directionality. In this work, we attempted to scrutinize the molecular interactions and reaction paths by the use of density functional theory calculations. Models composed of glycine and water molecules have been adopted. A substituent effect on the hydrogen-bond network in zwitterions was examined by the use of threonine ($R{=}H_3C{-}CH(OH)$). It will be shown that strainless hydrogen-bond networks correspond to ready isomerization paths. Also, an ion-pair intermediate ($H_2N{-}CH_2{-}COO^-$ and H_3O^+) intervenes during the isomerization to cause potentially the proton dispersal toward the outside of networks.

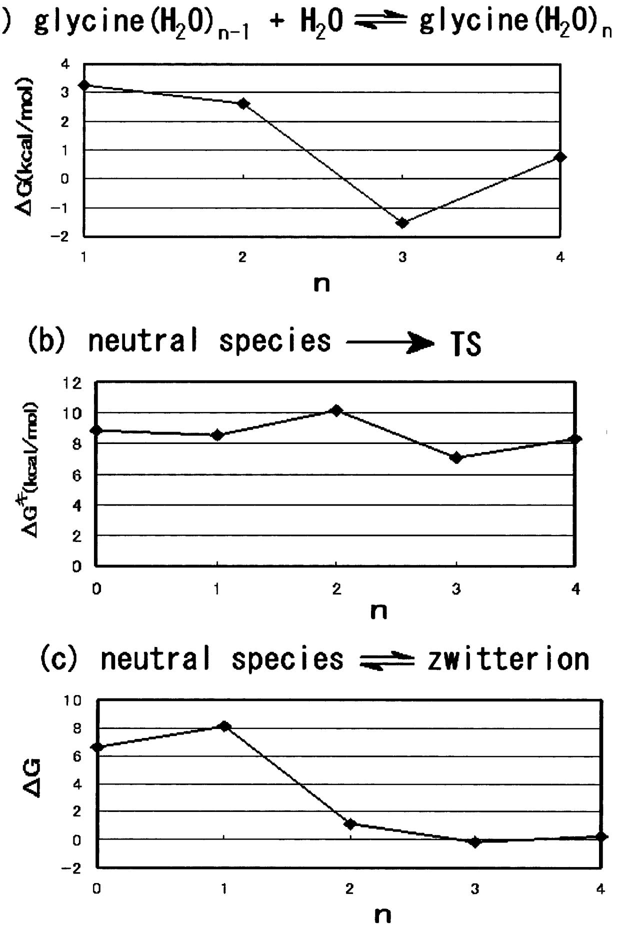


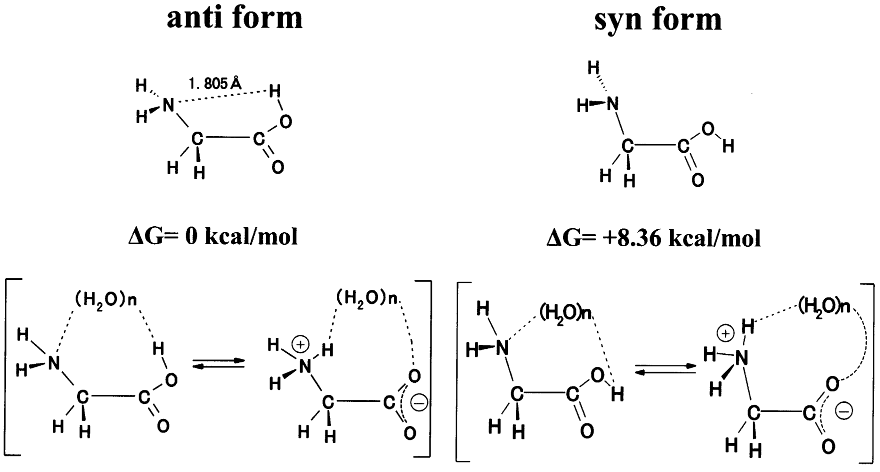
Figure 1. (a) Dependence of the number (= n) of water molecules on three energy changes. The change of Gibbs free energies ($T = 298.15$ K, $P = 1$ atm) on the stepwise H_2O additions to the anti glycine molecule. (b) The change of free activation energies of isomerization reactions shown in Figures S2, S3, S4, S5, and S6. (c) The relative free energies. Positive values mean that the neutral species is more stable than the zwitterion.

2. Computational Methods

The geometries of glycine, glycine$(H_2O)_n$ ($n = 2-4$, 11, and 17) and threonine$(H_2O)_{11}$ were determined by density functional theory calculations. B3LYP/6-31G* methods[23] were used for geometry optimizations. The solvent effect was taken into account by Onsager's Self-Consistent Field[24] with the dielectric constant = 78.39 (water). B3LYP seems to be a suitable method, because it includes the electron correlation effect to some extent. MP2 calculations are slightly of higher quality than B3LYP. But, MP2 requires much more computation time than B3LYP for the present large systems and is not practical. The SCRF effect is indispensable to describe zwitterions of amino acids. The MP2/SCRF combination does not work for geometry optimizations. For neutral and zwitterions of $n = 11$, RB3LYP/6-31+G** SCRF calculations were also carried out to check the reliability of RB3LYP/6-31G* SCRF data. The RB3LYP/6-31+G** method was used in ref 20.

Transition states (TSs) were characterized by vibrational analyses, which checked whether the obtained geometries have single imaginary frequencies ($\nu^{\ddagger}$). All the calculations were carried out using the GAUSSIAN 98[25] program package

SCHEME 4: Two Isomers of the Glycine Molecule and Their Tautomerization Reactions. Geometries of the Isomers Are Shown in Figure S1 (Supporting Information)



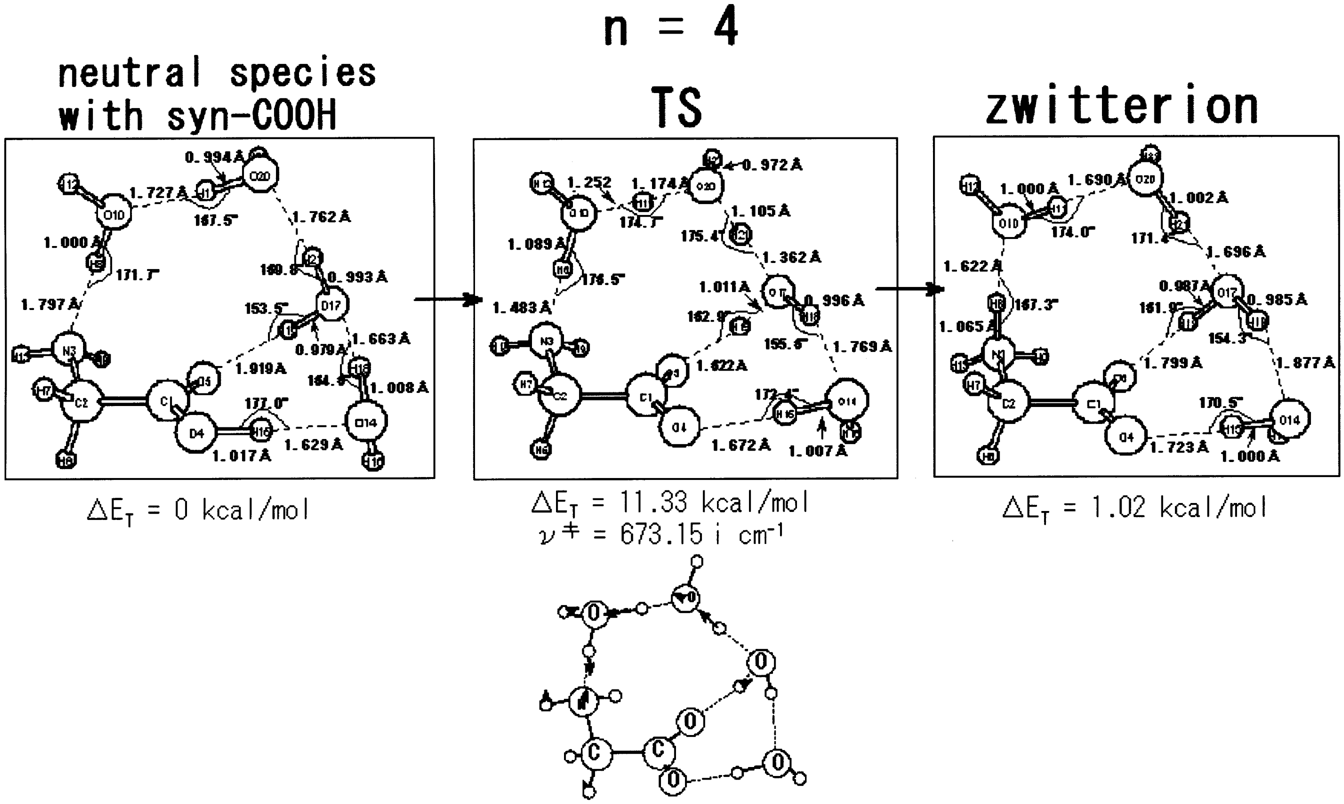


Figure 2. An isomerization reaction of the glycine molecule of the syn carboxyl group with four water molecules ($n = 4$).

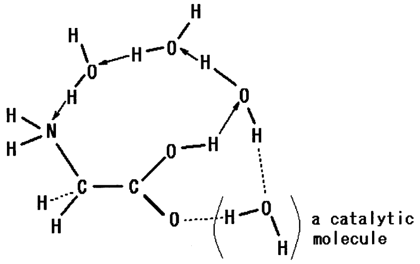
installed on Compaq ES 40 at the Information Processing Center (Nara University of Education).

3. Results and Discussion

(1) Isomerization Paths of Glycine. Geometries of syn and anti isomers in the gas phase were examined as a starting point. They are shown in Scheme 4 and Figure S1 (Supporting Information). ΔE_T is the B3LYP/6-31G* energy difference, and the positive value corresponds to the less stable system. The anti form is 8.36 kcal/mol more stable than the syn form. The former form has an intramolecular (N···H−O) hydrogen bond (1.805 Å). In glycine···H_2O interacting systems, intermolecular hydrogen bonds are involved. Therefore, for a fair comparison of the stability of anti and syn isomeric forms, the (N···H−O) hydrogen bond energy was estimated separately. A model system of acetic acid and ammonia, $H_3C-COOH\cdots NH_3$ was employed. This hydrogen-bond energy was calculated to be 13.21 kcal/mol. Thus, if it were not for the N···H−O intramolecular hydrogen bond in the anti form, the syn form in Scheme 4 would be more stable than the anti form. For reactions in eq 1, both forms were considered as reactants.

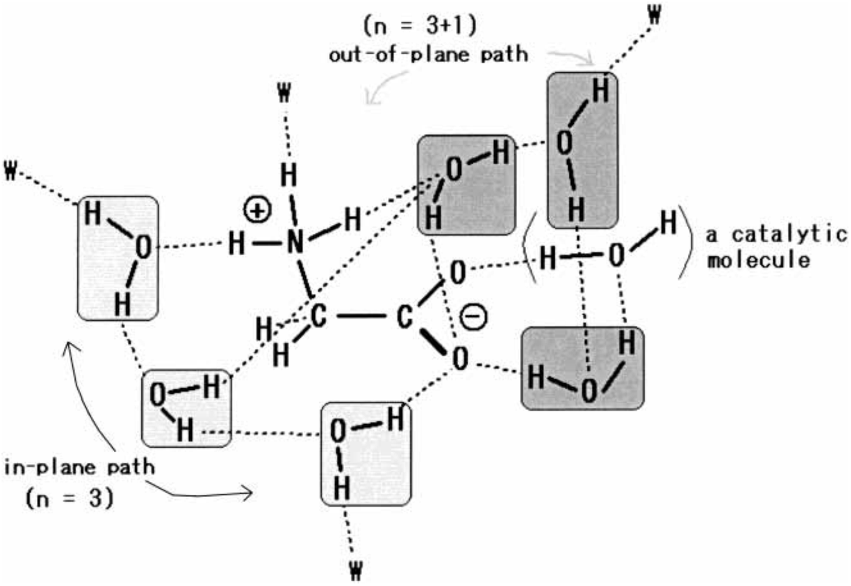
Reactions for the anti-form glycine (in the left of Scheme 4) were examined in Figure S2 ($n = 0$), Figure S3 ($n = 1$), Figure S4 ($n = 2$), Figure S5 ($n = 3$) and Figure S6 ($n = 4$). (Figure numbers beginning with "S" are in Supporting Information.) As $n = 0 \rightarrow 1 \rightarrow 2 \rightarrow 3 \rightarrow 4$, proton relays become more facile due to the less strained hydrogen-bond networks. At TSs, hydrogen-bond angles are 137.2° ($n = 0$), 161.8° and 166.1° ($n = 1$), and ca. 170° ($n \geq 2$). The $n = 3$ reaction model in Figure S5 is the best one, which is shown by three energy changes in Figure 1. Figure 1a shows the change of Gibbs free energies for the stepwise H_2O additions to the neutral glycine. The glycine$(H_2O)_3$ cluster attains the largest stability. Figure 1b presents the change of Gibbs free activation energies. The $n = 3$ system has the smallest energy. Figure 1c exhibits the energy difference between a neutral glycine$(H_2O)_n$ and the zwitterion isomer $^+H_3N-CH_2-COO^-(H_2O)_n$. Only, the $n = 3$ model has a negative $\Delta G°$ value ($= -0.13$ kcal/mol). The zwitterion is stabilized effectively by the water trimer. As three results of Figure 1, the $n = 3$ model is the best one. However, it does not mean that the model is realistic. One shortcoming is the small negative $\Delta G°$ value of $n = 3$ in Figure 1c, which is inconsistent with the exclusive presence in the glycine zwitterion form in aqueous media. Aside from the reality or reliability of the $n = 3$ model, the anti-carboxyl group is linked best with the amino group via a water trimer.

SCHEME 5: A Proton Relay Leading to the Zwitterion

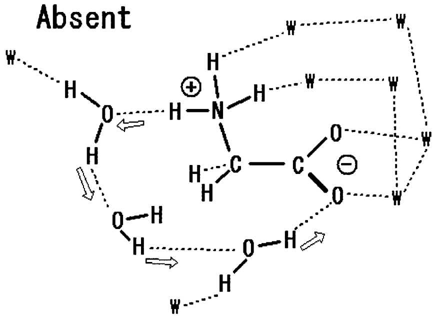


Reactions for the syn-form glycine (in the right of Scheme 4) were examined. For $n = 0$ and 1, they could not be obtained; the carboxyl proton is too distant from the lone-pair electrons of the amino group to form a hydrogen-bond network. For $n = 2$, a reaction path was obtained and is shown in Figure S7 (Supporting Information). However, the network involves the ring strain in TS, and the activation energy is relatively large (=14.76 kcal/mol). Figure S8 (Supporting Information) exhibits an $n = 3$ model. The network in TS is less strained than that of $n = 2$. However, as the reaction-coordinate vectors show, TS

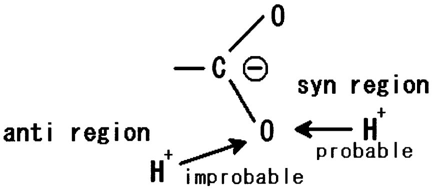
SCHEME 6: A Zwitterion Model of Glycine(H_2O)$_{11}$. W Stands for an outer Water Molecule



SCHEME 7: The Second Proton-Relay via the In-Plane Path from the Zwitterion to the Neutral Species with Anti Carboxyl Group



SCHEME 8: Region Restriction for the Proton Capture of the Carboxylate Group



is not for the correct proton-relay between the neutral form and the zwitterion one. To make the matter worse, the reaction energy is large ($\Delta E_T = 10.73$ kcal/mol, endothermic). Figure 2 shows a $n = 4$ model. The four water molecules are not involved in the linear-type network but constitute a different network (Scheme 5).

One water molecule is a catalyst to prevent a local proton relay, e.g., $-C(=O)-OH \rightarrow -C(OH)=O$. At TS of Figure 2, there in no ring strain. Various $n = 5$ models are present. However, one of these models is a ($n = 4 + 1$) model and others involve the mere local proton relay. The syn-form glycine has a large spatial distance between NH_2 and COOH groups and tends to involve a local proton exchange in COOH via in-plane two water molecules. Scheme 5 seems to present a minimum model of the proton transfer from the syn-form glycine. Four water molecules have respective roles; a proton donor adjacent to the H_2N group, a mediator, a proton acceptor adjacent to the $-COOH$ group, and a catalyst.

For the anti-form glycine, three water molecules have been fit for the concerted proton transfer (Figure 1). Hereafter, the path is called "in-plane path". For the syn-form glycine, four water molecules are needed. The path is "out-of-plane path". An integrated model is shown by the use of the glycine zwitterion in Scheme 6.

Eleven water molecules are coordinated around the zwitterion. The left-side three boxed ones are in accord with those in Figure S5. The right-side three boxed and a catalytic one are in accord with those in Figure 2. Four water molecules denoted Ws are concerned not with proton relays of the isomerization but with stabilization of the system. By the use of the model in Scheme 6, we may judge which is more likely for proton relays, the in-plane path or the out-of-plane path.

Figure 3 exhibits geometries in the out-of-plane path. The first step is a proton relay from the syn-carboxyl group (TS1). The relay is not concerted up to the zwitterion. After TS1, an ion-pair intermediate is formed; a hydronium ion (H_3O^+) is involved.[26] The intermediate was not obtained in Figure 2. From it, the second proton relays take place leftward (TS2) to arrive at the zwitterion. The reaction-coordinate vectors of TS1 and TS2 are shown in Figure S9 (Supporting Information). Noteworthy is a small geometric change (except the transferred protons) during the isomerization in Figure 3. The relative energy $\Delta E_T = -7.30$ kcal/mol of the zwitterion reflects reasonably its stability. The energy is somewhat smaller than the reaction enthalpy ($= -9.9$ kcal/mol) measured from the acidity constant.[27] Through the out-of-plane path, the isomerization has been found to be of two steps with two small activation energies. An ion-pair intermediate intervenes.

The in-plane path defined in Scheme 6 was examined in a reverse reaction, the zwitterion → the neutral species. Figure 4 shows the reaction. As a proton H(19) in the zwitterion is removed for relay, the second ion pair is arrived at via TS3. A hydronium ion O(14)H_3^+ is yielded. When a proton H(16) is shifted downward from the second ion pair, the third ion-pair intermediate is formed via TS4. Reaction-coordinate vectors of TS3 and TS4 are shown in Figure S10 (Supporting Information). TS4 is peculiar in that it contains movement of only one proton, H(15). Also, the third ion pair is peculiar in that a hydronium ion O(32)H_3^+ is in contact with the carboxylate group, $-COO^-$.

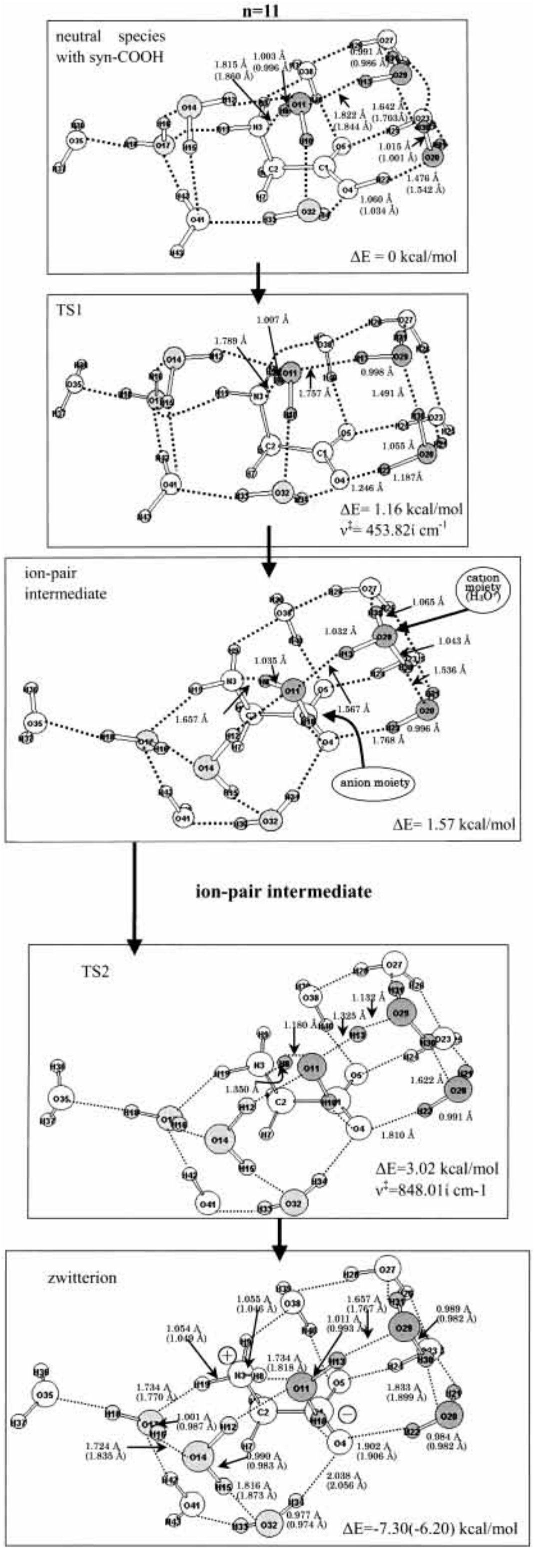


Figure 3. An isomerization reaction of glycine$(H_2O)_{11}$ along the out-of-plane path in Scheme 6. Numbers without and with parentheses are those obtained by RB3LYP/6-31G* SCRF and RB3LYP/6-31+G** SCRF, respectively. The reaction-coordinate vectors of TS1 and TS2 are shown in Figure S9 (Supporting Information). In series of the optimized geometries, the starting one is of the zwitterions. The model construction is in accord with Scheme 6. After the geometry of zwitterions was optimized, the proton position is varied successively. The ion-pair intermediate ($\Delta E = 1.57$ kcal/mol) is very slightly less stable than TS1($\Delta E = 1.16$ kcal/mol). The apparent problem comes probably from the small inconsistency of many hydrogen bonds involved and the SCRF solvent effect. In any event, the ion-pair intermediate is a very transient species.

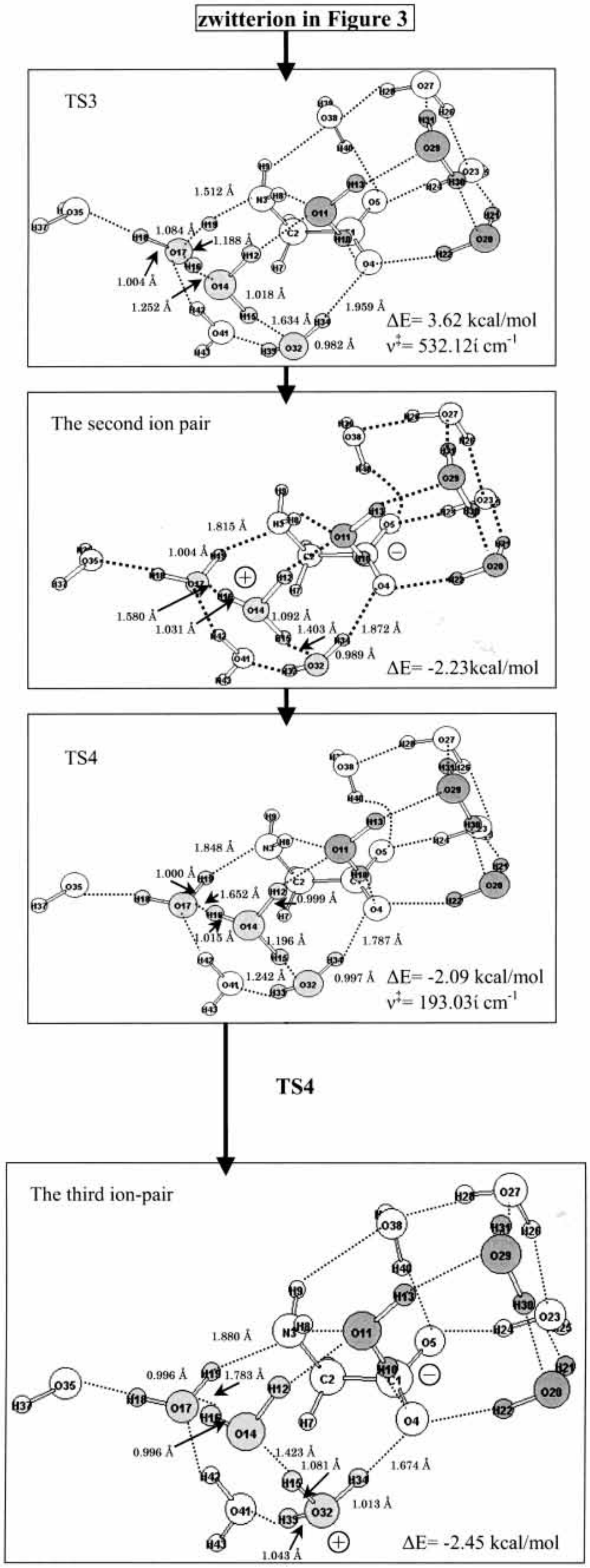


Figure 4. A reverse reaction of glycine$(H_2O)_{11}$ along the in-plane path in Scheme 6. Note that H_3O^+ is in contact with $-COO^-$ in the third in-pair, which demonstrates that the carboxyl group with anti form is not attained via the in-plane route. Reaction coordinate vectors of TS3 and TS4 are shown in Figure S10 (Supporting Information).

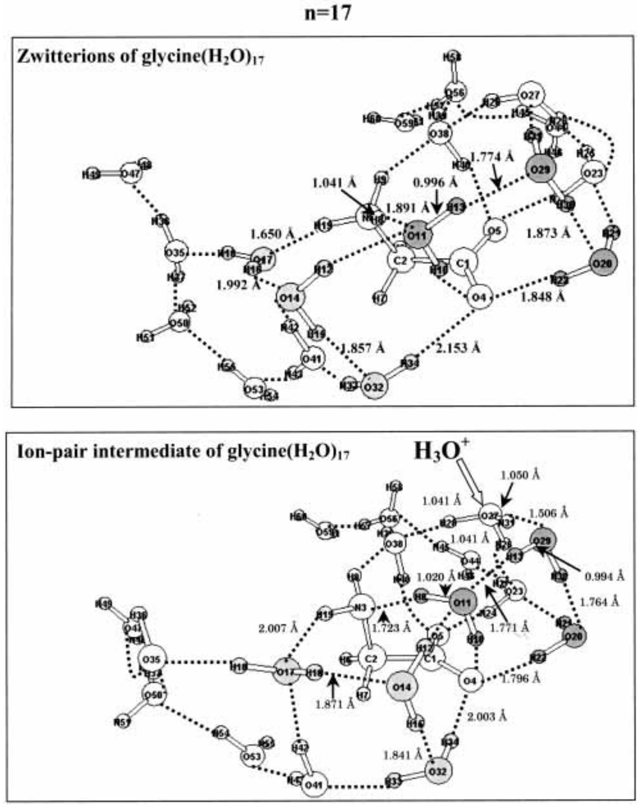


Figure 5. Geometries of the zwitterion and the ion-pair intermediate of glycine$(H_2O)_{17}$. The glycine$(H_2O)_{11}$ moieties are almost the same as those in Figure 3.

Formation of the anti carboxyl group (i.e., the anti neutral glycine) has been resisted. Thus, when networks of in-plane and out-of-plane paths coexist, the in-plane channel is blocked. The in-plane path plays a role merely as a catalytic network (Scheme 7).

The source to prohibit the in-plane path is a region restriction shown in Scheme 8. The negative charge in the carboxylate group is localized inside the group, and a proton should be captured in the syn region. The restriction was also found in hydrolysis reactions of acetic acid.[28]

A reaction model, glycine$(H_2O)_{11}$, has been investigated. The out-of-plane path starting from the syn-form glycine has been found to be a channel for isomerization to the zwitterion. The model has been constructed on basis of the zwitterion geometry in Scheme 6. There, four outer water molecules denoted Ws have been adopted. To check validity of the reaction model, geometries of a zwitterion$(H_2O)_{17}$ and an ion pair were examined and are shown in Figure 5. Aside from the difference in the number of water molecules, the shape of zwitterion$(H_2O)_{17}$ is almost the same as that of zwitterion$(H_2O)_{11}$ in Figure 3.[29] Noteworthy is a result that H_3O^+ [O(27)H(26)H(28)H(31)]is outside and adjacent to the out-of -plane path. The result will be discussed in relation to the isoelectric points.

Six boxed and a catalytic water molecules in Scheme 6 would be skeletal for the isomerization. The three ones in the in-plane path are needed to support a sterically favorable out-of-plane path.

(2) Substituent Effect on Hydrogen-Bond Networks. Isomerization paths in eq 1 have been investigated by the use of the parent α-amino acid, glycine. Here, generality of in-plane

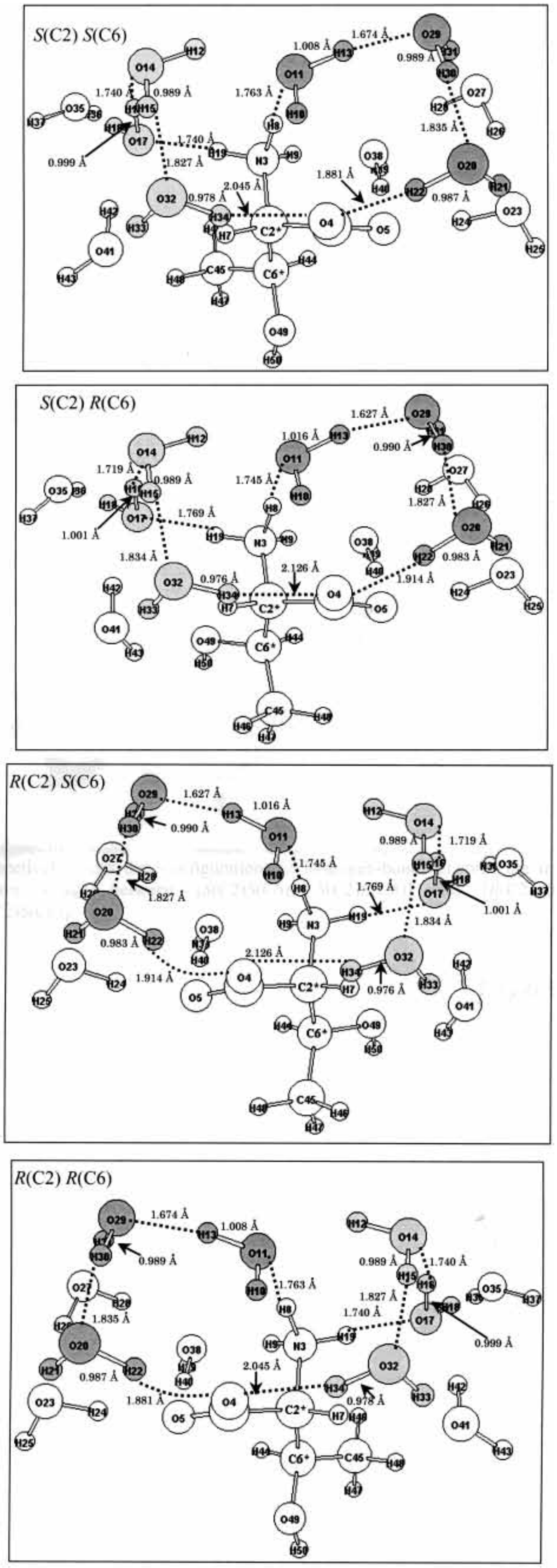
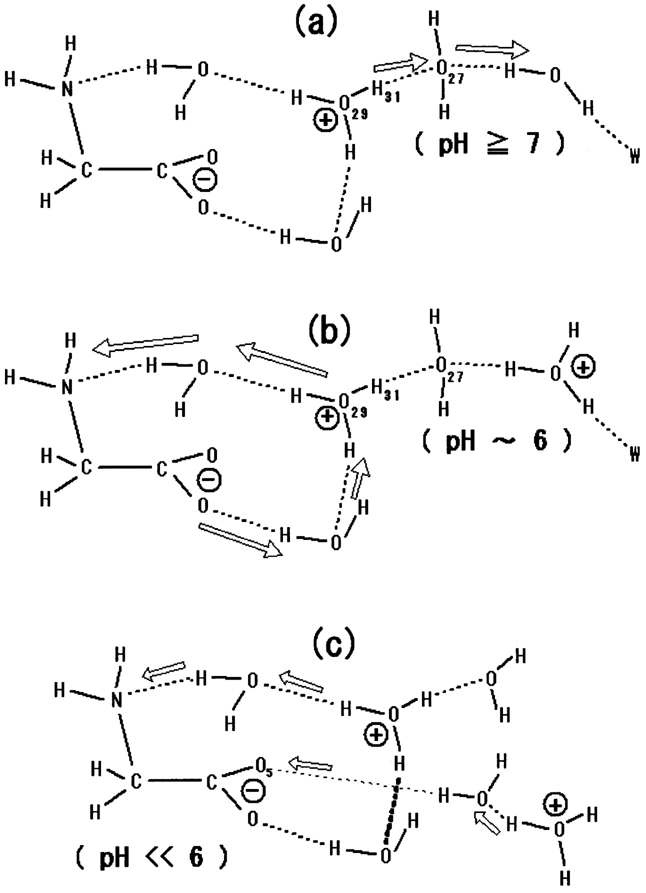


Figure 6. Geometries of four optical isomers of zwitterions of threonine$(H_2O)_{11}$ designated by absolute configurations, *rectus(R)* and *sinister(S)*, with respect to two asymmetric carbon atoms, C(2) and C(6). *R*(C2)*S*(C6) means, for instance, *rectus* for C(2) and *sinister* for C6, respectively. Note that configurations of hydrogen-bond networks are in the mirror image between [*S*(C2)*S*(C6), *S*(C2)*R*(C6)], and [*R*(C2)-*R*(C6), *R*(C2)*S*(C6)].

SCHEME 9: Proton Relays in Different pH Regions



and out-of-plane networks in Scheme 6 was examined by the use of a substituted α-amino acid, threonine [$H_2N-CH(CH(OH)-CH_3)-COOH$]. There are four diastereomers with respect to two asymmetric carbon atoms of threonine. *R* and *S* optical isomers are present as to the central carbon atom C(2) and the adjacent one C(6). Geometries of zwitterions coordinated by eleven water molecules were optimized. Those ions are susceptible better to hydrogen bonds than neutral species, and the geometry optimizations are feasible more readily. Figure 6 shows four geometries. Three water molecules, $O(20)H_2$, $O(29)H_2$, and $O(11)H_2$, participate in the out-of-plane path for all optical isomers. Similarly, the number of water molecules along the in-plane path is not affected by the substituent, $-CH(OH)CH_3$. Thus, the out-of-plane and in-plane paths are invariant. They are located apart from the substituent R.

(3) Discussions of a Correlation between the Computed Results and Isoelectric Points. In Scheme 1, isoelectric points of neutral α-amino acids have been shown. Those data are discussed in terms of the geometries in Figures 3 and 5. Scheme 9 presents proton relays starting from the ion-pair intermediate. Scheme 9a shows the relay under neutral or basic (alkaline) condition. The proton H(31) may escape from the out-of-plane path. The proton dispersal outward makes the glycine moiety an anion (not a zwitterion). In fact, a H(31)−O(27) covalent bond is formed in the ion-pair intermediate of glycine$(H_2O)_{17}$ (Figure 5). In Scheme 9b, the proton relay is confined to the out-of-plane path by tuning the weak-acid source outside the network. The isomerization reaction in eq 1 is assured. Scheme 9c shows a double proton attachment to the anionic glycine moiety by a strong acid condition. This attachment makes the moiety a cation (not a zwitterion). Of course, the present calculations cannot predict values of the isoelectric points. However, it is explicable by presence of the ion-pair intermediate that they should be slightly smaller than pH = 7. If it were not for the intermediate, the proton dispersal outward would be avoided. In this case, the isoelectric point would be 7.0.

4. Concluding Remarks

Isomerization paths for glycine have been investigated computationally. Three and four water molecules are concerned with in-plane and out-of-plane paths, respectively. A reaction model composed of glycine and eleven water molecules has been examined. The in-plane path is absent and its three water molecules act as a catalyst group to support the out-of-plane path. The following five results have been obtained and are summarized in Scheme 10.

[1] Neutral species of α-amino acids would be isomerized via the out-of-plane path to zwitterions with small activation energies.

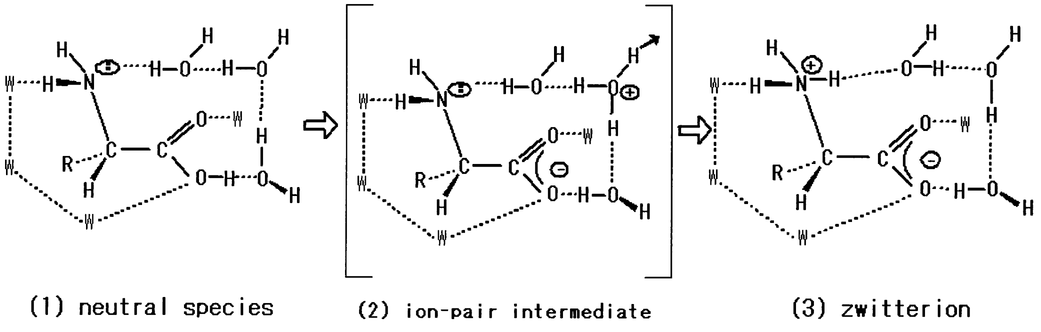
[2] Sizes of the out-of-plane and in-plane paths are not affected by the substituent R.

[3] An ion-pair intermediate, $H_2N-CHR-COO^-$ H_3O^+, intervenes during the isomerization.

[4] In order both to avoid the proton dispersal toward the outside of the out-of-plane hydrogen-bond network, and to ensure the largest concentration of zwitterions, a weak-acid environment is required. This would be a reason isoelectric points are not 7.0 but 6.0 for "neutral" α-amino acids.

[5] Very small differences of those values in Scheme 1 are attributable to the result of [4]; the key factor for the largest concentration of zwitterions is the presence or absence of the proton dispersal. The factor exists apart from the amino acid skeleton.

SCHEME 10: A Minimum Model of the Isomerization of α-Amino Acid. Reactant Water Molecules Are Denoted H_2O, and Others Are Ws. An Arrow in (2) Ion-pair Intermediate Indicates an Access Point of the Proton Dispersal



Supporting Information Available: Figures S1−S10 are auxiliary to the figures and discussions in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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