Determination of the Proton Transfer Energies of Glycine and Alanine and the Influence of Water Molecules

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The proton transfer energies of gas phase glycine and alanine and those of hydrated glycine and alanine were calculated both with Hartree-Fock and Møller-Plesset *ab initio* molecular orbital (MO) calculations with 6-31G** basis set. The transition states of the proton transfer of gas phase glycine was also investigated. For zwitterions, both for glycine and alanine, the water bound to -NH$_3^+$ site stabilize the complex more compared with the water bound to -CO$_2^-$. The proton transfer energy, ΔE_{pt}, of glycine, alanine, mono-hydrated glycine, mono-hydrated alanine, di-hydrated glycine and di-hydrated alanine were obtained as 30.78 (MP2: 22.57), 31.43, 23.99 (MP2: 17.00), 24.98, 22.87, and 25.63 kcal/mol, respectively. The activation energy for proton transfer from neutral (Nt) glycine to zwitterion (Zw) glycine, E_a, was obtained as 16.13 kcal/mol and that for reverse process, E_a', was obtained as 0.85 kcal/mol. Since the transition state of the proton transfer of gas phase glycine locate near the glycine zwitterion on the potential energy surface and the shape of the potential well of the zwitterion is shallow, the zwitterion easily changed to neutral glycine through the proton transfer.

Introduction

Proton transfers are in some way involved in almost every biological mechanism. Therefore the determination of the thermodynamic properties and the mechanism of the proton transfer of amino acids are very important for the understanding of the activity of biological molecules.[1~7] However the proton transfer enthalpies of gas phase amino acids are not known from experiment. Therefore a number of quantum mechanical calculations results have been reported for the proton transfer *in vacuo*,[8~12] in water cluster environments, and in aqueous solution.[13~20]

Most amino acids exist as zwitterionic form (Zw) in aqueous solution and in crystals and as neutral form (Nt) in gas phase. The neutral gas phase amino acids are changed to zwitterions upon solvation in aqueous solution. Since the neutral form does not exist significantly in solution and the zwitterion predominates at neutral pH, the investigation of the physical and chemical properties of the amino acid zwitterions is very important for the understanding of the biological activities of amino acids and peptides. The amino acid zwitterions in molecular crystals transform to neutral amino acid upon sublimation. For this reason, the heat of sublimation of amino acid molecular crystal could not simply be converted into the lattice energy through the correction of the difference in energy partitioned to molecular motions between the gas phase molecule and the molecule in a crystal. Therefore the proton transfer energy of amino acid is necessary for the estimation of the lattice energy of amino acid molecular crystals.

Voogd, Derissen, and Duijneveldt[8] performed extensive computational works on the proton transfer of several amino acids and on the contribution of electrostatic energies to the lattice energies of amino acid molecular crystals. The molecular orbital calculations were made with CNDO/2 and *ab*

initio methods with several basis sets including minimal, split, double-zeta, and polarized double-zeta. Rzepa and Yi[20] calculate the proton transfer energies of some amino acids with semi-empirical molecular orbital calculation and introduce a self-consistent reaction-field (SCRF) model for the calculation of the proton transfer energy in solution.

The purpose of this work is to calculate the proton transfer energy of glycine and alanine both for gas phase and amino acid-water clusters. The transition state of the proton transfer of glycine will be investigated also.

Calculation

STO-3G, 6-31G, and 6-31G** basis sets were used for geometry optimizations and 6-31G** basis set was used for single point (sp) MO calculations through out this work and the calculation were performed at Hartree-Fock (HF) level. All the geometry optimizations were initially performed with STO-3G basis set and subsequently performed with 6-31G or 6-31G** basis set with the STO-3G optimized geometries. MO calculations were made for both glycine and alanine, and their mono- and di-hydrated states. The models are described in Figures 1 and 2. For taking into account the electron correlation, MP2 calculations were performed for the Nt glycine and Zw glycine and their mono-hydrated complexes.

For neutral form (Nt) glycine, three conformations were taken from the several conformations which are possible in the gas phase; minimum energy conformation (Figure 1-a, conformer NtI), another conformer with the -COOH group rotated 180° from that of NtI (Figure 1-b, conformer NtII) and the local minimum energy structure which is believed to located on the minimum energy reaction path (MERP) between the transition state and Nt glycine of the proton transfer reactions (Figure 1-c, conformer NtIII). For zwitterionic form (Zw) glycine, two conformations were investigated; the most stable conformer which is believed to located

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Proton Transfer Enthalpy of Some Amino Acids

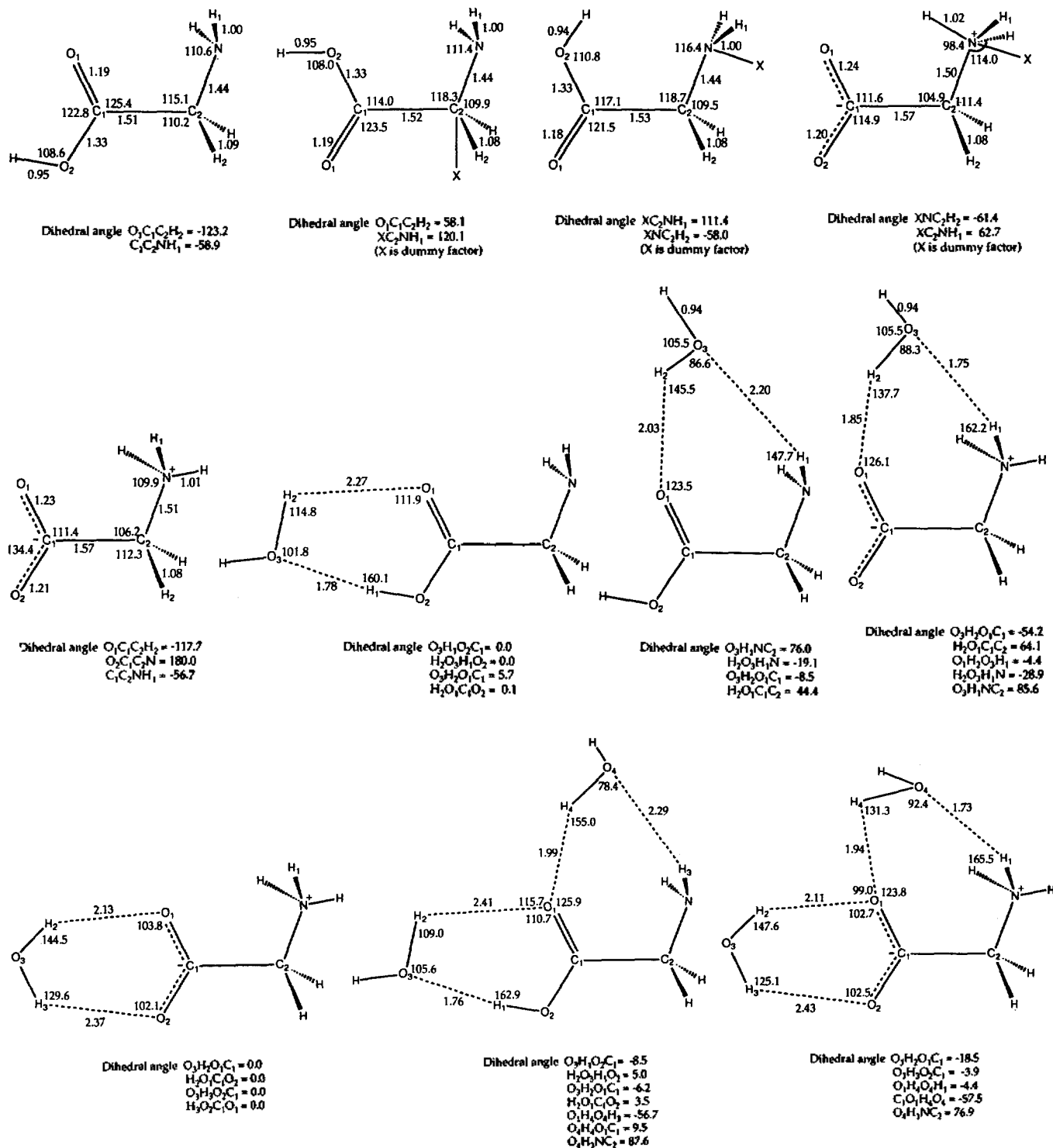*Bull. Korean Chem. Soc.* **1995,** *Vol. 16, No. 5* **411**

Figure 1. The several conformations of neutral and zwitterionic, and mono-and di-hydrated neutral and zwitterionic glycine which are possible in the gas phase. a) conformer NtI, b) conformer NtII, c) conformer NtIII, d) conformer ZwI, e) conformer ZwII, f) NtI···water (O), g) NtI···water (N), h) ZwII···water (N⁺), i) ZwII···water (O⁻), j) NtI···water (N) (O), k) ZwII···water (N⁺) (O⁻).

on the MERP of the proton transfer (PT) reaction (Figure 1-d, conformer ZwI) and one local minimum conformation (Figure 1-e, conformer ZwII). Since, for both Nt and Zw glycine, the conformations which belong to Cs point group are energetically favorable compared with the conformations be-

long to C₁ point group, the mirror plane formed with N-C-C-O was introduced. Except the mirror plane, no additional constraints on geometries were introduced.

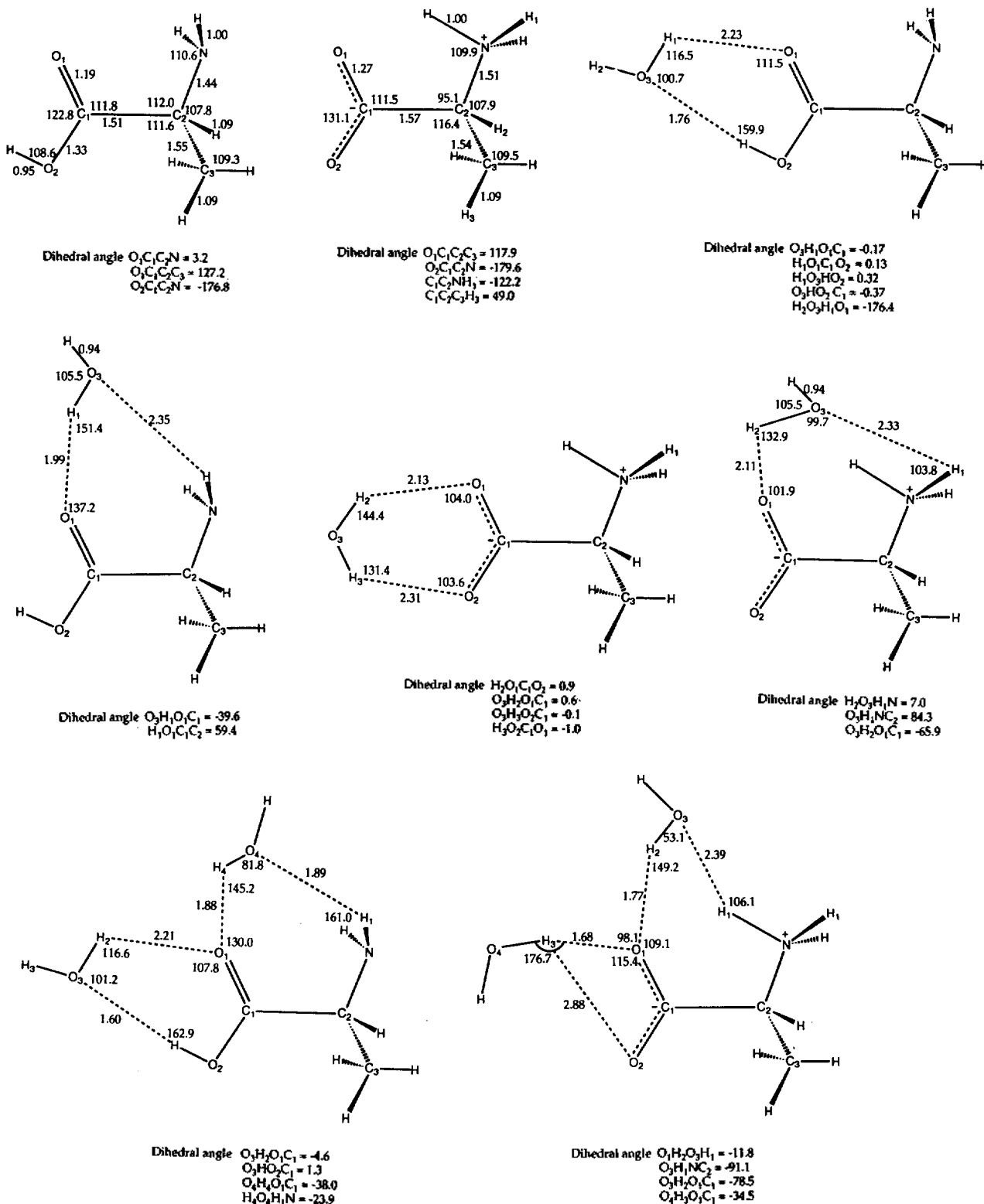For mono-hydrated Nt glycine, two mono-hydrated complexes were considered; the most stable hydrated conformer

Figure 2. The several conformations of neutral and zwitterionic, and mono- and di-hydrated neutral and zwitterionic alanine which are possible in the gas phase. a) conformer Nt, b) conformer Zw, c) Nt···water (O), d) Nt···water (N), e) Zw···water (O⁻), f) Zw···water (N⁺), g) Nt···water (N) (O), h) Zw···water (N⁺) (O⁻).

(Figure 1-f) and the local energy minimum conformer where the water molecule is bound to the NH₂ group (Figure 1-g). For mono-hydrated Zw glycine, the most stable conformer

(Figure 1-h) and a local energy minimum conformer (Figure 1-i) were investigated. Di-hydrated Nt (Figure 1-j) and Zw (Figure 1-k) glycines were also investigated. In di-hydrated
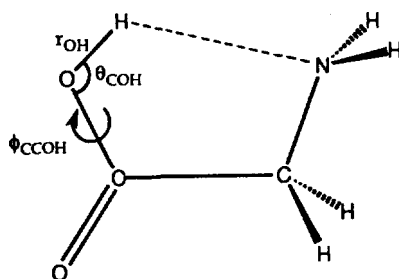
Figure 3. Three geometrical parameters, θ_{COH}, r_{OH}, ϕ_{CCOH}, which mainly contribute to the reaction coordinate.

Nt (or Zw) glycine, one water is bound to -NH$_2$ (or -NH$_3^+$) and another water is bound to -CO$_2$H (or -CO$_2^-$). All the symmetry constraints were removed during the geometry optimization of the hydrated glycine.

For alanine, the geometry optimizations were performed for the Nt (Figure 2-a) and Zw (Figure 2-b) alanine, mono-hydrated Nt (Figure 2-c, 2-d) and Zw alanine (Figure 2-e, 2-f), and di-hydrated Nt (Figure 2-g) and Zw (Figure 2-h) alanine. No symmetry constraints were introduced in all the conformational calculations of alanine.

The transition state (TS) of the PT of the gas phase glycine was investigated. Since it was difficult to locate the TS of the PT reaction on the potential energy surface, usually, the TSs of internal rotations were found, when the "TS" option was used in Gaussian program. Therefore the TS was obtained through grid search with the SCAN option in Gaussian program. Since the grid search is quite time consuming procedure, only three degrees of freedoms which mainly contribute to the reaction coordinate along MERP, θ_{COH}, r_{OH}, and ϕ_{CCOH}, were introduced, Figure 3. All the *ab initio* calculations were performed with the Gaussian 92 program.[21]

Results and Discussions

The optimized geometries are described in Figure 1 for glycine and Figure 2 for alanine and the energy of each compound is summarized in Table 1 for glycine and in Table 2 for alanine. Figure 1-a shows the minimum energy conformation (MEC) of Nt glycine. The energy difference between this MEC (NtI) and the conformer with its -CO$_2$H group is rotated 180° from that of MEC (NtII) is 1.91 kcal/mol. The energy increase 7.06 kcal/mol as the hydrogen in -CO$_2$H is rotated 180° from that of NtII (NtIII). Both in conformers NtI and NtII, there are intra hydrogen bonds between carboxylic oxygen and the hydrogens in amines. In conformer NtIII, the interatomic distance between the hydroxyl H and the nitrogen, $r_{NH(O)}$, is 2.28 Å. This conformation is believed to be located on the MERP of the PT reaction occured in gas phase glycine.

The MEC of gas phase Zw glycine was obtained as in Figure 1-d, ZwI. The energy difference between conformer ZwI and NtI, which is correspond to the PT energy at 0°K, ΔE_{pt}, of gas phase glycine, was obtained as 30.78 and 22.57 kcal/mol with HF and MP2 calculations, respectively. For mono-hydrated Nt glycine, the water bound to -COOH group, W(O), stabilize the complex more than the water bound to -NH$_2$, W(N), by 3.00 kcal/mol (3.33 kcal/mol with MP2). For

Table 1. The Proton Transfer Energies Calculated with 6-31G** basis set for Mono-, Di-hydrated Glycine, and in aqueous solution both with HF and beyond HF methods (MP2 and MP4) and those calculated with AM1 and PM3 for 7, 15 hydrated and in aqueous solution

Amino Acid	*ab initio* (in Hartree)		E_{pt}
	Neutral	Zwitterion	(in kcal/mol)
Glycine	NtI: −282.84834	ZwI: −282.79931	30.78
	NtI: −283.64316[a]	ZwI: −283.60720[a]	22.57[a]
	NtI: −283.70010[b]	ZwI: −283.66342[b]	23.02[b]
			(NtI→ZwI)
	NtII: −282.84530	ZwII: −282.79469	
	NtIII: −282.83405		
Glycine···W(N)	−358.88140	−358.84318	23.99
	(−359.87447[a])	(−359.84740[a])	(17.00[a])
Glycine···W(O)	−358.88616	−358.83383	32.85
	(−359.87978[a])	(−359.83531[a])	(27.92[a])
Glycine···W(N) W(O)	−434.91882	−434.88238	22.87
Glycine (aq.)[c]	−282.84932	−282.86476	−9.69
	−	−	−11.2[c] (−11.5[d])
Solvation energy[d]	−0.00103	−0.06936	
	(−0.65 kcal/mol)	(−43.52 kcal/mol)	
Glycine·7H$_2$O	−	−	4.0[e](13.2[f])
Glycine·15H$_2$O	−	−	−0.4[e](5.0[f])

6-31G** optimized energy of water molecule is −76.02360 Hartree, and the optimized r_{OH} is 0.941 Å and the bond angle is 105.49°. [a]MP2 calculation. [b]MP4 calculation. [c]*ab initio* self-consistent reaction-field (SCRF) calculation with 6-31G** basis set. The radius of the sphere of solute was taken as 6.822 a$_o$. [d]The stabilization energy of the solutes, glycine and glycine zwitterion, by the solvent arround the solutes, expressed by reaction fields. [e]PM3 calculation. [f]AM1 calculation. [g]self-consistent reaction-field (SCRF) model calculation. [e,f,g]are taken from reference 20.

Table 2. The Proton Transfer Energies Calculated with 6-31G** basis set for Mono-, Di-hydrated Alanine and those calculated with AM1 and PM3 for 7, 15 hydrated and in aqueous solution

Amino Acid	*ab initio* (in Hartree)		E_{pt}
	Neutral	Zwitterion	(in kcal/mol)
Alanine	−321.88808	−321.83801	31.43
Alanine···W(N)	−397.92035	−397.88055	24.98
Alanine···W(O)	−397.92678	−397.87749	30.94
Alanine···W(N) W(O)	−473.95137	−473.91055	25.63
Alanine·7H$_2$O	−	−	9.1[a](14.8[b])
Alanine·15H$_2$O	−	−	5.6[a](1.0[b])
Alanine (aq.)	−	−	−7.4[a,c](−2.9[b,c])

[a]PM3 calculation. [b]AM1 calculation. [c]self-consistent reaction-field (SCRF) model calculation. [a,b,c]are taken from reference 20.

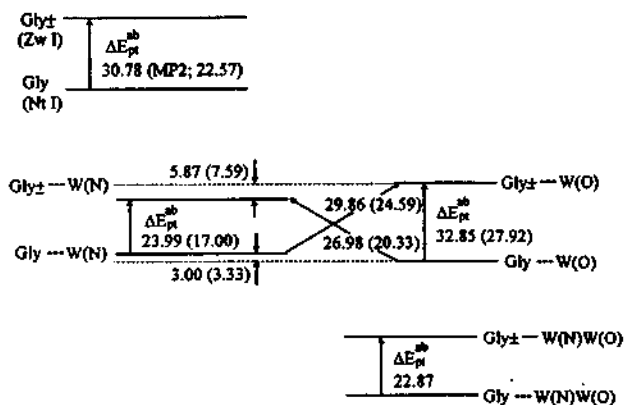414 *Bull. Korean Chem. Soc.* 1995, Vol. 16, No. 5

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Figure 4. The energy states of glycine model compounds, calculated with 6-31G** HF and 6-31G** MP2. MP2 results are listed in parenthesis.

Gly± (Zw I)
ΔE_{pt}^{ab} 30.78 (MP2; 22.57)
Gly (Nt I)

Gly±—W(N) — 5.87 (7.59) — Gly±—W(O)
ΔE_{pt}^{ab} 23.99 (17.00) — 29.86 (24.59) — ΔE_{pt}^{ab} 32.85 (27.92)
Gly···W(N) — 26.98 (20.33) — Gly···W(O)
3.00 (3.33)

Gly±—W(N)W(O)
ΔE_{pt}^{ab} 22.87
Gly···W(N)W(O)

Figure 5. The energy states of alanine model compounds.

Ala± (Zw I)
ΔE_{pt}^{ab} 31.43
Ala (Nt I)

Ala±—W(N) — 1.92 — Ala±—W(O)
ΔE_{pt}^{ab} 24.98 — 26.91 — ΔE_{pt}^{ab} 30.94
Ala···W(N) — 29.02 — Ala—W(O)
4.04

Ala±···W(N)W(O)
ΔE_{pt}^{ab} 25.63
Ala···W(N)W(O)

mono-hydrated Zw glycine, the water bound to -NH$_3^+$, W (N$^+$), stabilize the complex molecule more than the water bound to -CO$_2^-$, W(O$^-$), by 5.87 kcal/mol (7.59 kcal/mol with MP2).

The energy state of each glycine model compound is depicted in Figure 4.

For mono-hydrated glycine, the minimum PT energy was obtained as 23.99 kcal/mol (17.00 kcal/mol with MP2), the energy difference between Zw gly···W(N$^+$) and Nt gly···W (N). The ΔE_{pt} of the mono-hydrated glycine is 6.8 kcal/mol (5.6 kcal/mol with MP2) less compared with that of glycine. However the ΔE_{pt} between Zw gly···W(O$^-$) and Nt gly···W (O) was obtained 32.85 kcal/mol (27.92 kcal/mol with MP2) which is comparable to the ΔE_{pt} of gas phase glycine. The water bound to N$^+$ plays an important role in stabilizing the zwitterionic form. The water molecule bound to -NH$_3^+$ site stabilizes glycine zwitterion much, 12.73 kcal/mol, and that bound to -CO$_2^-$ site stabilizes only 6.86 kcal/mol, in the mono-hydrated case. For the di-hydrated Gly zwitterion, the stabilization energy is only 1 kcal lower than -NH$_3^+$ site mono-hydrated Gly zwitterion. Nt form is less stabilized than the zwitterion form by mono- and di-hydration. ΔE_{pt} of di-hydrated glycine was obtained as 22.87 kcal/mol which is only 1.12 kcal/mol lower than mono-hydrated case. The energy difference in PT of gas phase glycine between HF and MP2 calculation is about 8.21 kcal/mol. The MP2 ΔE_{pt} of mono-hydrated glycine was obtained 7 kcal/mol less compared with that obtained HF calculation. Therefore one must use beyond HF calculation method for obtaining reliable ΔE_{pt}, especially for complex molecules.

The trend of the stabilization energies in Nt and Zw of alanine upon hydrations is quite similar to that of glycine (Figure 5). ΔE_{pt} of gas phase alanine is 31.43 kcal/mol, the smallest ΔE_{pt} of mono-hydrated alanine is 24.98 kcal/mol and the largest ΔE_{pt} of mono-hydrated alanine is 30.94 kcal/mol. ΔE_{pt} of di-hydrated alanine is 25.63 kcal/mol. ΔE_{pt} is decreased about 6.5 kcal/mol upon mono-hydration which is comparable to the glycine case, 6.8 kcal/mol.

The enthalpy difference between neutral and zwitterion glycine aqueous solution is well-established experimentally as −9.9 kcal/mol. Extensive study of the energy differences
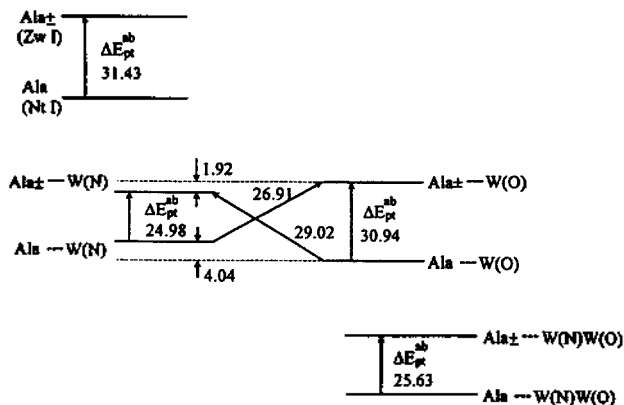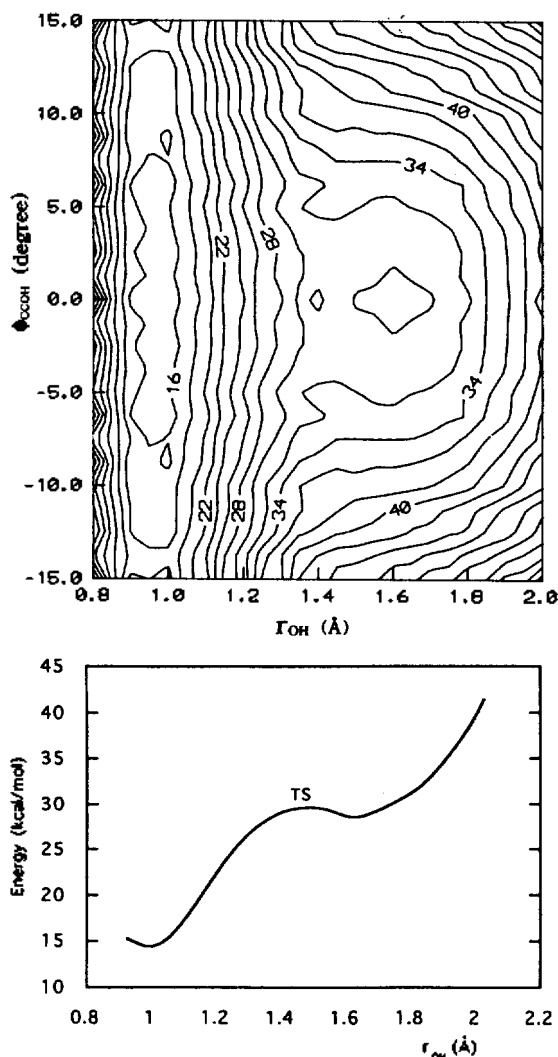
Figure 6. The 6-31G** HF potential energy surfaces for the proton transfer of gas phase glycine a) the potential energy surface was calculated at the grid points, r_{OH}, ϕ_{CCOH}. b) the potential curve is plotted along the MERP.

between neutral and zwitterionic form of glycine and alanine at several hydration level was performed with some semi-empirical molecular orbital calculations by Rzepa and Yi.[20]
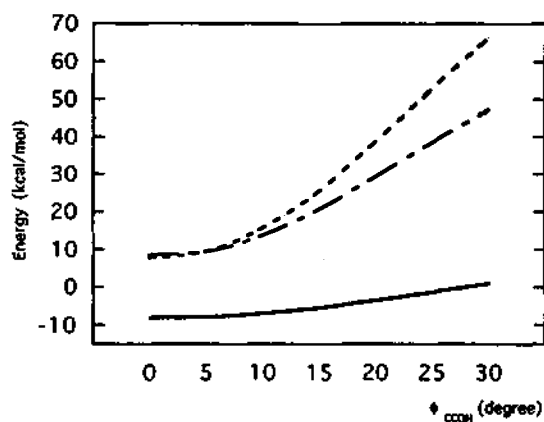
Figure 7. The potential energy curves which pass through PC (—), TS (---), RC (---). These curves are perpendicular to MERP, Figure 6-b.
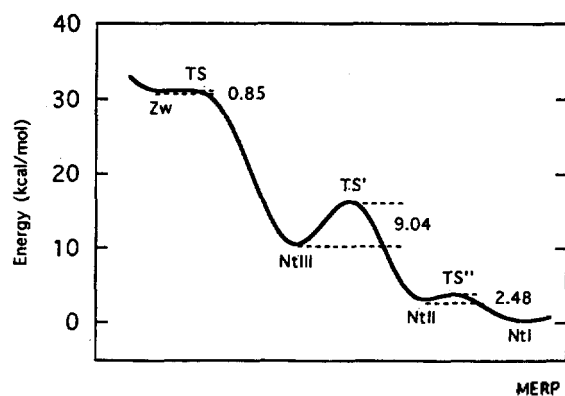

Figure 8. The energy curve for the proton transfer from the zwitterionic form to the most stable neutral form glycine.

With PM3 and AM1 methods, they calculate the proton transfer energy of the hydrated glycine and alanine supermolecules. Seven or fifteen water molecules are included for hydration. The ΔE_μ obtained from SCRF calculation for glycine, -11.2 kcal/mol (PM3 calculation), is comparable to the experimentally obtained value, -9.9 kcal/mol. The SCRF calculation with 6-31G** basis set at HF level gives almost same with experimental data.

The potential energy surface (PES) for the proton transfer of gas phase was calculated. In the PES calculation, only three geometrical variable, r_{OH}, θ_{COH}, and ϕ_{CCOH} were introduced, Figure 3. The energies of the points on the PES, Figure 6-a, were calculated at the grid points, (r_{OH}, ϕ_{CCOH}), and θ_{COH} was optimized at each grid point. The potential energy curve, Figure 6-b, is plotted along MERP which correspond to the section of Figure 6-a when ϕ_{CCOH} equal to zero. Since the energy difference between reactant complex, RC, (Zwitterionic form), and TS is very small, 0.85 kcal/mol, and the conformation of TS is quite similar to that of RC. The location of RC is quite near to TS in the geometric parameter space. For this reason, the zwitterionic form is quite unstable in gas phase and easily change to product complex, PC, (Neutral form) through the proton transfer. In Figure 7, the potential energy curves which pass through PC, TS, and RC

are plotted which correspond to the sections of Figure 6-a at fixed r_{OH}, 0.975, 1.425, and 1.626 Å. From the curves it is evident that ϕ_{CCOH} must take value arround 0 for the proton transfer, especially at TS. In Figure 8, the minimum energy path for the proton transfer from the zwitterionic glycine to the most stable neutral form is plotted. Each local minimum energy and its conformation were obtained through the energy minimization procedure. The energy barrier, the activation energy which connect two minimum energy configurations, was also obtained. The activation energy from NtI to NtII is 4.39 kcal/mol and that from NtII to NtIII is 16.10 kcal/mol.

Conclusions

The ΔE_μ of the glycine and alanine and their hydrated complex were investigated. The water molecule bound to $^+NH_3$ stabilize the zwitterion much compared with that bound to $-CO_2^-$. For the complex molecules, the electron correlation effect must be take into account for reliable value of ΔE_μ. Therefore beyond HF method is recommended for the ΔE_μ calculation of supermolecules. SCRF calculation could well reproduce the experimental ΔE_μ of glycine in aqueous solution. The TS of PT of glycine locate quite near to the zwitterionic form and ΔE_μ from the zwitterion to the neutral form is about 31 kcal/mol. Therefore the Zw form is quite unstable at gas phase. The MERP for PT of glycine was also obtained through grid calculation of the PES.

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Reaction of Lithium Gallium Hydride with Selected Organic Compounds Containing Representative Functional Groups

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The approximate rates and stoichiometry of the reaction of excess lithium gallium hydride with selected organic compounds containing representative functional groups were examined under the standard conditions (diethyl ether, 0 ℃) in order to compare its reducing characteristics with lithium aluminum hydride and lithium borohydride previously reported, and enlarge the scope of its applicability as a reducing agent. Alcohols, phenol, and amines evolve hydrogen rapidly and quantitatively. However lithium gallium hydride reacts with only one active hydrogen of primary amine. Aldehydes and ketones of diverse structure are rapidly reduced to the corresponding alcohols. Conjugated aldehyde and ketone such as cinnamaldehyde and methyl vinyl ketone are rapidly reduced to the corresponding saturated alcohols. *p*-Benzoquinone is mainly reduces to hydroquinone. Caproic acid and benzoic acid liberate hydrogen rapidly and quantitatively, but reduction proceeds slowly. The acid chlorides and esters tested are all rapidly reduced to the corresponding alcohols. Alkyl halides and epoxides are reduced rapidly with an uptake of 1 equiv of hydride. Styrene oxide is reduced to give 1-phenylethanol quantitatively. Primary amides are reduced slowly. Benzonitrile consumes 2.0 equiv of hydride rapidly, whereas capronitrile is reduced slowly. Nitro compounds consumed 2.9 equiv of hydride, of which 1.9 equiv is for reduction, whereas azobenzene, and azoxybenzene are inert toward this reagent. Cyclohexanone oxime is reduced consuming 2.0 equiv of hydride for reduction at a moderate rate. Pyridine is inert toward this reagent. Disulfides and sulfoxides are reduced slowly, whereas sulfide, sulfone, and sulfonate are inert under these reaction conditions. Sulfonic acid evolves 1 equiv of hydrogen instantly, but reduction is not proceeded.

Introduction

The discovery of lithium aluminum hydride[1] and lithium borohydride[2] brought about a revolutionary change in the procedures utilized for the reduction of functional groups in organic chemistry. Of these two reagents, lithium borohydride[3] is relatively mild reducing agent which is practically specific for the carbonyl group in aldehydes, ketones, and esters, whereas lithium aluminum hydride[4] is an exceedingly powerful reagent which attacks almost all reducible groups.

Therefore, lithium di- and trialkoxyaluminum hydride,[5] lithium trialkylaluminum hydride,[6] lithium trichloroaluminum hydride,[7] lithium bis- and tris(dialkylamino)aluminum hydride,[8] lithium mono- and trialkylborohydride,[9] and lithium cyanoborohydride[10] were studied in order to control the reducing abilities of lithium aluminum hydride and lithium borohydride. But, the previous studies were restricted to aluminohydride and borohydride species.

In 1973, Raman and infrared data of various metal hydride salts with monovalent cation were reported by Shirk and

Shriver.[11] They showed that the stretching frequencies of metal hydrides were $AlH_4^- = 1757$ cm^{-1}, $GaH_4^- = 1807$ cm^{-1}, and $BH_4^- = 2294$ cm^{-1}, and the calculated associated force constants of metal-hydrogen were $AlH_4^- = 1.84$ mdyn/Å, $GaH_4^- = 1.94$ mdyn/Å and $BH_4^- = 3.07$ mdyn/Å. From these results, we thought that if the bonded alkali metal is same, the reducing power of metal hydride would be $AlH_4^- > GaH_4^- > BH_4^-$. Indeed it was reported that lithium aluminum hydride had much stronger reducing power than that of lithium borohydride. But the reducing abilities of gallium hydride species were not studied. So we decided to carry out the systematic study for the reduction of organic compounds containing representative functional groups with lithium gallium hydride.

Results and Discussion

Lithium gallium hydride was prepared by the reaction of gallium chloride with lithium hydride in diethyl ether as reported by Shrik and Shriver.[12] The general procedure for reduction was to add 1 mmol of the organic compound to