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AB INITIO MO AND MONTE CARLO SIMULATION STUDY ON THE CONFORMATION OF L-ALANINE ZWITTERION IN AQUEOUS SOLUTION

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The conformation of the L-alanine zwitterion (ALAZ) in aqueous solution was examined by an *ab initio* MO method including the solvent effect with the generalized Born (GB) equation. The geometry optimization with the 6–31++G* basis set gave the (ϕ, θ) = (80, 8) conformation as the most stable conformation of ALAZ in aqueous solution, where ϕ is the HNC$^{\alpha}$C torsional angle and θ is the NC$^{\alpha}$CO torsional angle. Stabilization by the solvent is larger in the $\theta = 90°$ conformation than in the $\theta = 0°$ conformation. However, the differential solvation is small and the conformation with a nearly planar NC$^{\alpha}$CO skeleton is the most stable conformation in aqueous solution. The barrier to rotation of the CO_2 group (θ rotation) was calculated to be 6·7 (6–31++G*) and 5·9 (MP2/6–31++G*) kcal mol^{-1}, while that to rotation of the NH_3 group (ϕ rotation) was very small (<1 kcal mol^{-1}). The relative free energy of solvation and relative stability among the representative conformations of ALAZ were calculated by Monte Carlo (MC) simulation with the statistical perturbation method. The energy variation along the θ rotation indicated that the value of $\theta = 5–10°$ is favorable for ALAZ in aqueous solution. The MC simulation supports the *ab initio* GB results for the conformational properties of ALAZ in aqueous solution. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Knowledge of the conformational flexibility of amino acids in aqueous solution is important for understanding the molecular structure and interactions of proteins in biological systems. Glycine is found as a zwitterion in aqueous solution,[1] and the hydration structure of glycine zwitterion (GLYZ) has been studied by Monte Carlo (MC) simulation for a specific conformation.[2] The conformational properties of GLYZ in aqueous solution have been studied by MC simulation with the statistical perturbation theory (SPT) and by the molecular orbital (MO) method in which solvent effect is included by a continuum model; the dihedral angle θ between the NC$^{\alpha}$C and CO_2 planes is 0° in the most stable conformation, and the barrier to the rotation of the CO_2 group is fairly high, 6–8 kcal/mol^{-1} (1 kcal = 4·184 kJ).[3–5]

The alanine zwitterion (ALAZ) has a molecular structure similar to that of GLYZ and its conformational properties may be estimated safely from those of GLYZ. However, alanine is the simplest chiral amino acid and an important species for understanding chirality in biological molecules. Several theoretical studies have shown that the parity-violating weak neutral current interaction between an electron and a nucleus causes an energy difference between the L- and D-forms of an amino acid and ALAZ changes the sign of this energy near $\theta = 0°$.[6] Hence it is very important to estimate correctly the most stable conformation of ALAZ in aqueous solution, even if the ALAZ conformation is expected to be similar to that of GLYZ.

Although there have been many theoretical studies of neutral alanine in the gas phase,[7–9] only a few theoretical studies have been reported on the conformation of ALAZ.[4, 5, 10] In a previous study,[5] we examined the ALAZ conformation in solution by the 6–31G/GB method, in which the solvent effect is included by the continuum model based on the generalized Born (GB) equation. In the present study, two methodologies were employed to determine the most stable conformation of ALAZ in aqueous solution. In the *ab initio* MO/GB method, the 6–31++G* basis set,[11] which is more flexible than that employed in our previous study, was employed and geometry optimization in aqueous solution was carried out. An MC simulation with SPT was

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also carried out to clarify the conformational energy change of ALAZ in aqueous solution.

THEORY AND CALCULATION

In the continuum model with the GB equation, the solvation energy of a molecule is expressed by

$$\Delta G_{\mathrm{sol}} = -\frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\sum_{\mathrm{A}}\sum_{\mathrm{B}} Q_{\mathrm{A}} Q_{\mathrm{B}} \Gamma_{\mathrm{AB}} \tag{1}$$

where ε is the dielectric constant of the solvent, A and B are atoms in the solute molecule and Q_{A} and Q_{B} are fractional charges. The energy of a molecule in solution is expressed as the sum of the energy in its isolated state and solvation energy:

$$E_{\mathrm{sol}} = E_0 + \Delta G_{\mathrm{sol}} \tag{2}$$

By applying variational theorem to this energy functional, Tapia[12] derived correct Fock matrix elements including solvent effects for semiempirical MO calculations. Kozaki *et al.*[13] combined this model with the MNDO theory and applied it to several chemical reactions. Cramer and Truhlar[14] extended it to the AM1 and PM3 versions, including the cavitation energy. We have described the incorporation of the *ab initio* SCF method with the GB model[5] and parametrization.[15] In the *ab initio* GB model, Γ_{AA} is expressed by

$$\Gamma_{\mathrm{AA}} = \frac{f_{\mathrm{A}}}{r_{\mathrm{A}}} \tag{3}$$

where f_{A} is a steric factor and the atomic radius r_{A} is a function of the fractional charge, Q_{A}:

$$r_{\mathrm{A}} = \alpha_{\mathrm{A}} \mathrm{e}^{-\beta_{\mathrm{A}} Q_{\mathrm{A}}} \tag{4}$$

Γ_{AB} is the two-center repulsion energy between unit charges on atoms A and B, and is evaluated by using an Ohno–Klopman type equation:

$$\Gamma_{\mathrm{AB}} = \frac{1}{\sqrt{R_{\mathrm{AB}}^2 + \left[\frac{1}{2}\left(\frac{r_{\mathrm{A}}}{f_{\mathrm{A}}} + \frac{r_{\mathrm{B}}}{f_{\mathrm{B}}}\right)\right]^2}} \tag{5}$$

where R_{AB} is the distance between atoms A and B.

The atomic charge Q_{A} is expressed as

$$Q_{\mathrm{A}} = Z_{\mathrm{A}} - P_{\mathrm{A}} \tag{6}$$

where Z_{A} is the nuclear charge and P_{A} is the atomic population evaluated by Löwdin population analysis:

$$P_{\mathrm{A}} = \sum_{\mu \in \mathrm{A}} (\boldsymbol{S}^{1/2}\boldsymbol{P}\boldsymbol{S}^{1/2})_{\mu\mu} \tag{7}$$

where $\boldsymbol{P}$ is the density matrix and $\boldsymbol{S}$ is the overlap-integral matrix.

The application of variational theorem to equation (2) gives the following Fock matrix elements including the solvent effect for a closed-shell molecule:

$$F_{\mu\nu} = F^0_{\mu\nu} + F^{\mathrm{sol}}_{\mu\nu} \tag{8}$$

$$F^{\mathrm{sol}}_{\mu\nu} = -\sum_{\lambda} \frac{\partial \Delta G_{\mathrm{sol}}}{\partial Q_{\mathrm{A}}} (\boldsymbol{S}^{1/2})_{\mu\lambda} (\boldsymbol{S}^{1/2})_{\nu\lambda} \tag{9}$$

where $F^0_{\mu\nu}$ is the Fock matrix element for an isolated molecule and $F^{\mathrm{sol}}_{\mu\nu}$ describes the contribution of the solvent; A is the atom to which λ belongs. The partial derivative in equation (9) is expressed as

$$\frac{\partial \Delta G_{\mathrm{sol}}}{\partial Q_{\mathrm{A}}} = -\left(1-\frac{1}{\varepsilon}\right)\left[Q_{\mathrm{A}}\Gamma_{\mathrm{AA}} + \frac{1}{2} Q_{\mathrm{A}}^2 \frac{\partial \Gamma_{\mathrm{AA}}}{\partial Q_{\mathrm{A}}} + \sum_{\mathrm{B} \neq \mathrm{A}} \left(Q_{\mathrm{B}}\Gamma_{\mathrm{AB}} + Q_{\mathrm{A}} Q_{\mathrm{B}} \frac{\partial \Gamma_{\mathrm{AB}}}{\partial Q_{\mathrm{A}}}\right)\right] \tag{10}$$

The atomic radius r_{A} is expressed as a function of Q_{A} and the steric factor f_{A} is evaluated from the excluded volume of the solvent shell of atom A whose thickness is 3·5 Å. The determination of the parameters α and β parameters in equation (4) and the evaluation of steric factors f_{A} were described in a previous paper.[15]

In the present study, the method was extended to include diffuse basis functions, which will be important for the calculation of anionic species. Diffuse functions have small orbital exponents and the radius used in the Born equation was modified. The one-center solvation energy due to the electron population in diffuse functions was estimated separately from that due to other electrons. Thus, in the calculation of one-center term Γ_{AA}, another sphere of atom A, $r^{\mathrm{d}}_{\mathrm{A}}$, and a fractional charge

$$Q^{\mathrm{d}}_{\mathrm{A}} = -P^{\mathrm{d}}_{\mathrm{A}} \tag{11}$$

where $P^{\mathrm{d}}_{\mathrm{A}}$ is the electron population due to the diffuse functions in the A atom, were considered for the diffuse function of atom A. The atomic fractional charge, equation (6), is thus modified to

$$Q^0_{\mathrm{A}} = Q_{\mathrm{A}} - Q^{\mathrm{d}}_{\mathrm{A}} \tag{12}$$

Γ_{AA} depends on the basis function of the A atom and equation (10) is replaced by

$$\frac{\partial \Delta G_{\text{sol}}}{\partial Q_{\text{A}}^{0}} = -\left(1-\frac{1}{\varepsilon}\right)\Bigg[(Q_{\text{A}}^{0}\Gamma_{\text{AA}}^{00}+Q_{\text{A}}^{\text{d}}\Gamma_{\text{AA}}^{0\text{d}}) + \frac{1}{2}\left(Q_{\text{A}}^{0}Q_{\text{A}}^{0}\frac{\partial \Gamma_{\text{AA}}^{00}}{\partial Q_{\text{A}}^{0}}+2Q_{\text{A}}^{0}Q_{\text{A}}^{\text{d}}\frac{\partial \Gamma_{\text{AA}}^{0\text{d}}}{\partial Q_{\text{A}}^{0}}\right) + \sum_{\text{B}\neq\text{A}}\left(Q_{\text{B}}\Gamma_{\text{AB}}+Q_{\text{A}}Q_{\text{B}}\frac{\partial \Gamma_{\text{AB}}}{\partial Q_{\text{A}}}\right)\Bigg] \tag{13}$$

when λ in equation (9) is a core or valence basis function, and by

$$\frac{\partial \Delta G_{\text{sol}}}{\partial Q_{\text{A}}^{\text{d}}} = -\left(1-\frac{1}{\varepsilon}\right)\Bigg[(Q_{\text{A}}^{0}\Gamma_{\text{AA}}^{0\text{d}}+Q_{\text{A}}^{\text{d}}\Gamma_{\text{AA}}^{\text{dd}}) + \sum_{\text{B}\neq\text{A}}\left(Q_{\text{B}}\Gamma_{\text{AB}}+Q_{\text{A}}Q_{\text{B}}\frac{\partial \Gamma_{\text{AB}}}{\partial Q_{\text{A}}}\right)\Bigg] \tag{14}$$

when λ in equation (9) is a diffuse function. One-center terms in equations (13) and (14) are

$$\Gamma_{\text{AA}}^{00} = \frac{f_{\text{A}}}{r_{\text{A}}^{0}} \tag{15}$$

$$\Gamma_{\text{AA}}^{\text{dd}} = \frac{f_{\text{A}}}{r_{\text{A}}^{\text{d}}} \tag{16}$$

$$\Gamma_{\text{AA}}^{0\text{d}} = \frac{f_{\text{A}}}{\frac{1}{2}(r_{\text{A}}^{0}+r_{\text{A}}^{\text{d}})} \tag{17}$$

The radius r_{A}^{0} is calculated by equation (4) for Q_{A}^{0}, while r_{A}^{d} is fixed at constant value determined empirically; $r_{\text{A}}^{\text{d}} = 1{\cdot}95$, 2·10, 1·85 and 1·70 Å for H, C, N and O atoms, respectively. As will be pointed out below, the relative solvation energies among different conformations do not depend greatly on the basis function. It is noted that the procedure given here becomes the original procedure when the diffuse functions are not included or when the population in the diffuse function becomes zero.

In the present model, the thickness of the solvent shell affects the magnitude of solvation energy through the steric factor, f_{A}, although its effect on the relative solvation energies among different conformations is very small. The value of 2·8 Å is more popular for the thickness of the water solvent shell,[16] and this value was adopted in this study. For *ab initio* GB calculations, the 6–31++G* basis set was used. The MIDI-4(d) basis set,[17] which was used in the MC simulations, was also used. The MP2 calculations were carried out to examine the effect of electron correlation. The value of $\varepsilon = 79$ was used for aqueous solution. Conformation of ALAZ was expressed by two torsional angles, θ and ϕ, defined in Figure 1.

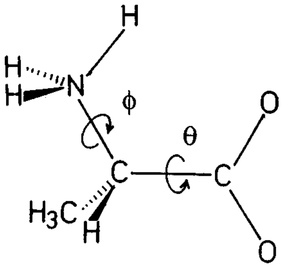

Figure 1. Definition of two torsional angles of the L-alanine zwitterion. θ is the rotation of the CO_2 group and ϕ is the rotation of the NH_3 group in the directions indicated

In the MC simulation, the three-point model of potential functions was used for water molecules, which has been determined previously by *ab initio* MIDI-4(d) calculations.[18] It was shown that this model and the more popular TIP4P model[19] gave similar results for glycine conformational energies.[4] The intermolecular potential functions between ALAZ and H_2O were newly determined. In this procedure, the four conformations $(\phi,\theta) = (0,0)$, (60,0), (0,90) and (60,90) were used for ALAZ fixing bond lengths and angles at the standard values:[3, 20] bond lengths C—C = 1·53 Å, C—O = 1·25 Å, C—N = 1·48 Å, C—H = 1·09 Å, N—H = 1·03 Å; bond angles OCO = 125°, CCN=CCH=CNH = 109·47°. The methyl group was set as a staggered conformation. The MIDI-4(d) calculations were carried out for the 490 orientations for the ALAZ–H_2O dimer, which were selected in the vicinity of several energy-minimum geometries, and for those selected randomly. On the basis of the calculated interaction energies for the dimers, the potential function between ALAZ and H_2O, which is constructed by Lennard–Jones (12–6) terms and the coulombic term,

$$E_{ij} = \sum_{r\text{ on }i}\sum_{s\text{ on }j}\left(\frac{A_rA_s}{R_{rs}^{12}} - \frac{C_rC_s}{R_{rs}^{6}} + \frac{q_rq_se^2}{R_{rs}}\right) \tag{18}$$

was determined. The parameters determined are listed in Table 1. The MC simulation was carried out by NVT ensemble according to the standard Metropolis method[21] for one ALAZ solute and 212 water molecules in a cubic cell. The volume of the cell was determined from the density of 1 g cm^{-3} for pure water. The temperature of the system was set at 298 K. The Owicki–Scheraga–Jorgensen preferential sampling technique[22] was employed. The changes in free

Table 1. Parameters of the L-alanine zwitterion in the potential functions with the three-point model of water

	A	*C*	*q*
Alanine:			
C^{α}	1720	29·6	0·107
Me	1860	42·3	0·040
$H(C^{\alpha})$			0·018
C(O)	1123	48·2	0·842
N	387	11·1	−0·179
O	690	21·0	−0·825
H(N)			0·274
Water[a]*:*			
O	850	38·7	−0·702
H			0·351

[a] Ref. 18.

energy of solvation were calculated along the rotation of ϕ and θ in steps of 5° using SPT with the double wide sampling technique.[23]

All MO calculations were carried out using our ABINIT program and MC simulations using our SIMPLS program on HP-735 workstations and GAIA-300 personal supercomputers.

RESULTS AND DISCUSSION

The (ϕ,θ) potential energy map of ALAZ in aqueous solution was created by 6–31++G*/GB calculations. The ϕ and θ angles were changed in steps of 10°, the other molecular parameters being fixed at the standard values. The calculated energy map is shown in Figure 2. The values cited in Figure 2 are energies in kcal mol^{-1} relative to the global minimum. In the standard geometry, the NH_3 and CO_2 groups have C_3 and C_2 local symmetry axes, respectively, and the (ϕ,θ) potential energy map shows 120° and 180° periodicity for ϕ and θ, respectively. The conformation with a nearly planar $NC^{\alpha}CO$ skeleton ($\theta \approx 0°$) is stable and the θ rotation requires an appreciable activation energy irrespective of the ϕ value. On the other hand, the potential energy surface is very flat for the $-10° < \theta < 10°$ region and the ϕ rotational barrier is very small. These qualitative features for the potential energy map are similar to the 6–31G/GB results.[5]

Table 2 shows the relative energies of four representative conformations of ALAZ which were calculated using the standard geometry. *In vacuo* ($\epsilon = 1$), the (0,0) conformation is the most stable among the four and the (60,0) conformation lies within 1 kcal mol^{-1} above the global minimum. The $\theta = 90°$ conformations are more unstable than the

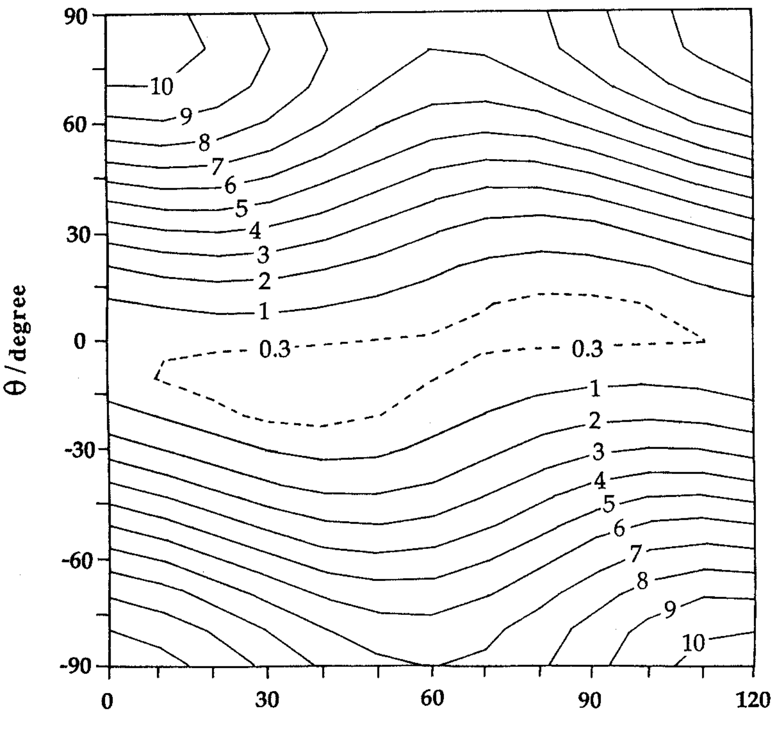

Figure 2. The (ϕ,θ) energy map of the L-alanine zwitterion in aqueous solution. The values cited are energies in kcal mol^{-1} which are relative to the most stable conformation. The map was calculated by the 6–31++G*/GB method using the standard geometry

Table 2. Relative energies (kcal mol^{-1}) of four conformations of the L-alanine zwitterion in the gas phase and in aqueous solution[a]

Method	(0,0)	(60,0)	(60,90)	(0,90)
In vacuo:				
MIDI-4(d)	0·0	0·6	9·6	14·7
6–31++G*	0·0	0·8	9·5	13·7
MP2/MIDI-4(d)	0·0	1·4	9·6	—
MP2/6–31++G*	0·0	1·3	9·3	—
In water:				
MIDI-4(d)/GB	1·0	0·0	7·4	11·5
6–31++G*/GB	0·1	0·0	6·7	10·4
MP2/MIDI-4(d)/GB	0·5	0·0	6·5	—
MP2/6–31++G*/GB	− 0·3	0·0	5·9	—
Monte Carlo	1·9	0·0	5·1	—

[a] Calculated by rigid rotation of the standard geometry.

Table 3. Solvation energies (kcal mol^{-1}) of four conformations of the L-alanine zwitterion in aqueous solution[a]

Method	(0,0)	(60,0)	(60,90)	(0,90)
MIDI-4(d)	− 43·5	− 45·1	− 46·7	− 47·7
	(0·0)	(− 1·6)	(− 3·2)	(− 4·2)
6–31++G*	− 53·5	− 54·3	− 56·3	− 56·9
	(0·0)	(− 0·8)	(− 2·8)	(− 3·4)
MP2/MIDI-4(d)	− 38·5	− 40·4	− 42·1	—
	(0·0)	(− 1·9)	(− 3·6)	—
MP2/6–31++G*	− 48·6	− 49·6	− 51·8	—
	(0·0)	(− 1·0)	(− 3·2)	—
Monte Carlo	(0·0)	(− 2·5)	(− 3·7)	—

[a] Relative values in parentheses.

corresponding $\theta=0°$ conformations by 9–15 kcal mol^{-1}. These values agree well with the 6–31++G* values for ALAZ in the gas phase.[10] In aqueous solution, the (60,0) conformation is more stable than the (0,0) conformation, although the energy difference is very small. The energy difference between the $\theta=0°$ and $\theta=90°$ conformations is slightly reduced in aqueous solution, and the (ϕ,θ) potential energy map becomes flatter than that in the gas phase. This is due to the differential solvation; stabilization by solvation is larger in the $\theta=90°$ conformation than in the $\theta=0°$ conformation. This is shown in Table 3, which compares the solvation energies of the four conformations.

The magnitude of the solvation energy depends on the basis set, since the electron population and charge density depend significantly on the basis set. Our previous 6–31G/GB calculations indicated that the solvation energies for these four conformations are in the range from − 85 to − 92 kcal mol^{-1},[5] which are much larger than the values in Table 3. This is mainly due to the steric factor, which was not included in the previous calculation.

The energy lowering of ALAZ caused by addition of diffuse functions to the 6–31G* basis set was about 10 kcal mol^{-1} in the gas phase and 16–17 kcal mol^{-1} in aqueous solution; the increase in the solvation energy due to the diffuse functions is 6–7 kcal mol^{-1}. However, the differences among the energy lowerings in the four conformations of ALAZ are less than 1 kcal mol^{-1} and the overall shape of the present 6–31++G* (ϕ, θ) map resembles the previous 6–31G/GB map. The effect of electronic correlation was examined by MP2 calculations for the (0,0), (60,0) and (60,90) conformations. The results are given in Tables 2 and 3, and show that the electron correlation reduces the solvation energies of the three conformations uniformly (4·5–5·0 kcal mol^{-1}) and the relative stabilities among the conformations in the gas phase and in solution are not significantly affected by the electron correlation. The barrier height to the CO_2 rotation in aqueous solution is reduced by only 0·8 kcal mol^{-1}. The exclusion of the diffuse basis functions and electron correlation will not bring a crucial effect into the conformational analysis of ALAZ in aqueous solution.

Figure 2 shows that the potential energy surface is very flat at the energy minimum region. In order to determine the most stable geometry of ALAZ in water, geometry optimization was carried out starting from several points on the map. In the optimization, the local C_3 symmetry was assumed for the CH_3 group and other molecular parameters were optimized. It is pointed out that the present model is very convenient for determining the molecular structure in solution; the geometry optimization can be carried out as in the gas phase with little extra computation time. The lowest energy structure obtained is shown in Figure 3 and the molecular parameters are given in Table 4. The NC$^{\alpha}$C^1 and O^{1}C^{1}O^2 planes are not coplanar and the most stable conformation has N—C$^{\alpha}$—C^1—O dihedral angles of +9° and − 173°. This slight rotation of the CO_2 group from the $\theta=0°$ conformation permits a favorable interaction between the O atom in CO_2 and the H atoms in CH_3. Three H atoms in the NH_3 group have H—N—C$^{\alpha}$—C^1 angles of 80°, 200° and 321°. It may be stated that the most stable conformation is the $(\phi,\theta)=(80,8)$ conformation.

The relative free energy of solvation and the relative

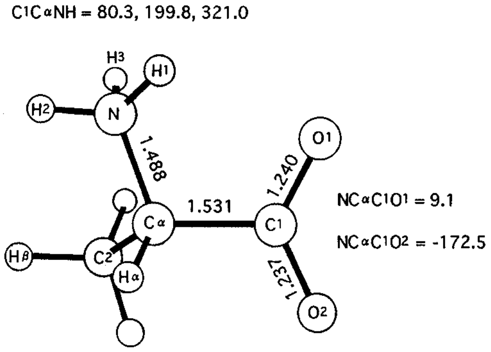

Figure 3. 6–31++G* optimized structure of the L-alanine zwitterion in aqueous solution. Geometrical parameters are listed in Table 4

Table 4. 6–31++G*/GB optimized structure of the L-alanine zwitterion in aqueous solution

Bond lengths (Å)		Bond angles (°)		Dihedral angles (°)	
C^{α}–C^1	1·531	$C^{\alpha}C^1O^1$	116·2	$NC^{\alpha}C^1O^1$	9·1
C^1–O^1	1·240	$C^{\alpha}C^1O^2$	115·4	$NC^{\alpha}C^1O^2$	187·5
C^1–O^2	1·237	$NC^{\alpha}C^1$	109·6	$C^1C^{\alpha}NH^1$	− 39·0
C^{α}–N	1·488	$C^1C^{\alpha}C^2$	114·7	$C^1C^{\alpha}NH^2$	199·8
C^{α}–C^2	1·521	$C^1C^{\alpha}H^{\alpha}$	107·3	$C^1C^{\alpha}NH^3$	80·3
$C^{\alpha} - H^{\alpha}$	1·084	$C^{\alpha}NH^1$	111·2	$C^1C^{\alpha}C^2H^{\beta}$	177·9
N–H^1	1·014	$C^{\alpha}NH^2$	111·5	$O^1C^1C^{\alpha}C^2$	132·8
N–H^2	1·107	$C^{\alpha}NH^3$	112·7	$O^1C^1C^{\alpha}H^{\alpha}$	104·9
N–H^3	1·013	$C^{\alpha}C^2H^{\beta}$	110·7		
C^2–H^{β}	1·084				

conformational energy in aqueous solution were calculated by MC SPT simulation. The variation in the free energy of solvation along the C—C bond rotation (θ rotation) was calculated for the ϕ=60° conformation. The solvation energy change was determined from the mean value of those calculated for two rotations in opposite directions. The results are shown in Figure 4 and Tables 2 and 3. The relative conformational energies in the gas phase shown in Figure 4 were obtained by *ab initio* MIDI-4(d) calculations. Stabilization by the solvent increases as θ increases. However, the destabilization of the isolated molecule is much larger than the stabilization by the solvent, and ALAZ becomes unstable in aqueous solution when the torsional angle of the CO_2 group increases. Figure 5 shows the energy variation along the rotation of the NH_3 group for θ=0°. Stabilzation by the solvent is largest at ϕ=60° and the preferred conformation of the NH_3 group is determined by the solvation energy. The trends observed in the difference in the solvation energies among three conformations and thus the conformation stability of ALAZ in aqueous

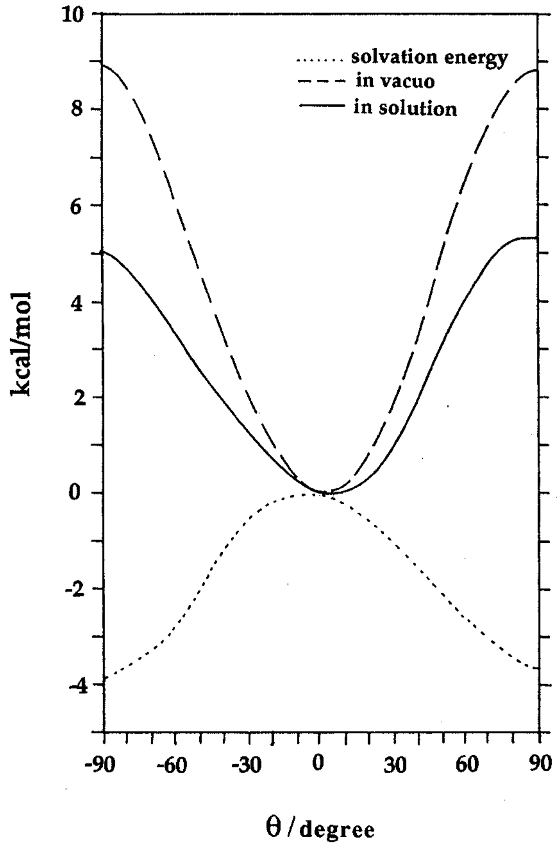

Figure 4. Variations in free energy of solvation (· · ·) and relative conformational energies in the gas phase (- - -) and in aqueous solution (——) along the θ rotation with a fixed value of ϕ=60°. The relative energy of solvation was calculated by MC SPT simulation and the relative conformational energy in the gas phase by MIDI-4(d) calculations

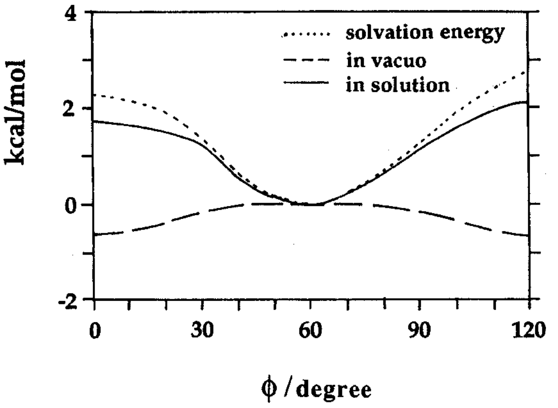

Figure 5. Variations in free energy of solvation (· · ·) and relative conformational energies in the gas phase (- - -) and in aqueous solution (——) along the ϕ rotation with a fixed value of θ=0°. The relative energy of solvation was calculated by MC SPT simulation and the relative conformational energy in the gas phase by MIDI-4(d) calculations

solution, which were obtained using MC SPT, are parallel to those obtained by *ab initio* GB calculations.

CONCLUSION

The 6–31++G*/GB calculations predicted that ALAZ has the conformation with $\theta \approx 10°$ in aqueous solution. The effect of the CH_3 group on the dissymmetry of the molecular structure is evident, although its effect is small. The barrier to the rotation of the CO_2 group of ALAZ in aqueous solution is high, whereas that of the NH_3 group is very low. The MC simulation supports the *ab initio* GB results for the conformational properties of ALAZ in aqueous solution.

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