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Structures and isomerization of serine in aqueous solution: Computational study

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Abstract

Calculations are presented for the structure and the isomerization reaction of serine in aqueous solution. Polarizable continuum model (PCM) is employed to determine the effects of solvent on the stability of serine zwitterion relative to the canonical form and the proton transfer paths for the zwitterion/canonical isomerization reaction in the solution phase. The discrete/continuum model is also adopted to analyze the solute–solvent interactions. We find that the latter model gives much more accurate relative stability of canonical and zwitterion forms of serine than PCM in the aqueous solution.

1. Introduction

Solvation is one of the fundamental issues of chemistry, because the structure and reactivity of molecules may change significantly due to the interactions with the solvent. Since most biochemical reactions of interest occur in the solution phase, the effects of solvation will be very important for determining the properties of biomolecules. The solute–solvent interactions are of molecular nature, and thus, they must be treated on molecular level. Detailed interactions between the functional groups both in the biomolecule and in the solvent molecules may efficiently be probed by systematically examining the structures of the clusters consisting of the biomolecule and a number of solvent molecules (cluster approach) [1–8]. If one is interested in obtaining more realistic descriptions for the biomolecule in the solution phase, one may also employ the continuum model [9,10] for the other infinite number of solvent molecules around the cluster (supramolecule/continuum model). Since the difference in energy between the conformers is usually rather small (usually at most 5 kcal/mol), many biomolecules may exist in solution as a number of conformers, and thermal energies of the molecules may easily transform from one conformer to another in room temperature solution phase. On the other hand, in clusters formed by cooling in the supersonic expansion experiments at very low temperature the magnitude of activation barrier for isomerization between the conformers is very important, because they determine the kinetic stability (that is, the rate constant of isomerization) of the conformers. Amino acid, which is the building block of protein, is an ideal system to study the effects of solvation on the biochemical activity due to their moderate size. Systematic study was carried out recently on the amino acid–water clusters, notably by Tomasi and co-workers [11], and by Silla and co-workers [12–14] theoretically, and experimentally by Simons and co-workers [16], and by Kim's group [7]. Both the structures of canonical amino acids [15–18] and the corresponding zwitterions [11,19–21] in clusters

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and in solution are of fundamental interest. It is well-known that amino acids exist in the canonical form in the gas phase, while in aqueous solution the zwitterion is the predominant form [12,22–24]. Serine is the smallest amino acid containing an 'active' side chain functional group (OH), and may be very different from the smaller amino acids such as glycine or alanine that may be more important as structural units in proteins for forming peptide links with other amino acids. This hydroxyl group in serine may actively be involved in biochemical reaction of enzyme, for example, as a nucleophile in the critical step of the hydrolysis of proteins by serine protease.

In this Letter, we present calculations for serine in the aqueous solution employing the PCM and the discrete/continuum model. Various zwitterion conformers are obtained, and their relative Gibbs energies are compared to estimate their relative stability. Systematic analysis is presented for isomerization between the canonical serine and the corresponding serine zwitterion (SerZW).

2. Methods of calculation

In this study all of the calculations are carried out using the GAUSSIAN 98W and the GAUSSIAN 03 set of programs [25]. The stationary structures are found by ascertaining that all the harmonic frequencies be real. The structures of the transition states are obtained by verifying that one of the harmonic frequencies be imaginary and also by carrying out the intrinsic reaction coordinate (IRC) analysis for the reaction pathways. The density functional theory method (B3PW91/6-31 + G**) [26–28] is employed for the discrete, and the integral equation version of the polarized continuum model (IEFPCM) [29–31] is employed to account for the effects of the solvent continuum. Barrier heights are computed by subtracting the energies of the reactants and products from those of the transition states, correcting for the zero-point energies (ZPE). Default criteria are employed for all the optimization processes.

3. Results

We carried out extensive calculations for SerZW in the aqueous solution, and find that there may exist numerous stationary structures for SerZW. This is in high contrast with the gas-phase SerZW, for which no stationary structures were obtained [32] (no zwitterionic amino acids have been predicted or experimentally observed in the gas phase in the absence of solvent). Moreover, these zwitterionic conformers are calculated to be kinetically stable, indicating that SerZW may isomerize to the canonical form in the solution phase with small but finite activation barrier. Fig. 1 and Table 1 present the relative Gibbs energies and the structures of the most stable conformers of zwitterionic serine (Z1–Z4) in the aqueous solution phase. The conformers Z1, Z2 and Z4 are calculated to be of very similar Gibbs energy, the difference in the Gibbs function being only within 0.5 kcal/mol at 298 K. Therefore, these conformers may be considered to co-exist in room temperature aqueous solution phase. The other conformer Z3 lies much higher in the Gibbs function, by 3.14 kcal/mol above Z2. It is interesting to compare the present results for SerZW in the aqueous solution with the *gas-phase* SerZW–$(H_2O)_2$ cluster, which is the smallest serine–water cluster producing kinetically stable species [32]. In the present work, Z2 is predicted to be the most stable in solution, whereas the SerZW–$(H_2O)_2$ cluster corresponding to Z4 is found to be the most kinetically stable conformer in the gas phase. The difference in the Gibbs

Table 1
Electronic energy E, zero-point energy (ZPE) and Gibbs function G of the calculated structures

	E (Hartee)	ZPE (kcal/mol)	G (kcal/mol)
Z1	−398.86470	70.50	−250238.46
Z2	−398.86513	70.68	−250238.80
Z3	−398.86182	71.26	−250235.66
Z4	−398.68441	70.44	−250238.69
N1	−398.86314	69.75	−250238.06
N2	−398.86301	69.86	−250237.96
N3	−398.86051	69.93	−250236.44
N4	−398.86208	69.57	−250237.98
N5	−398.86235	69.28	−250238.74
Z4-1	−475.28578	85.94	−298180.36
N5-1	−475.28187	84.16	−298180.05
Z4-2	−551.71109	101.27	−346123.40
N2-2	−551.70268	101.05	−346118.27

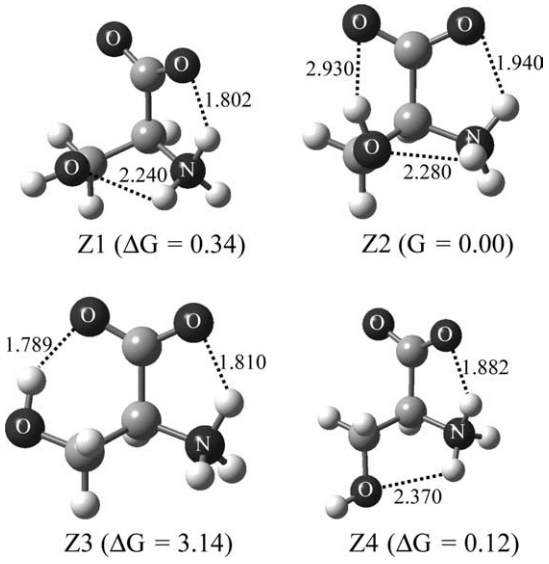

Fig. 1. Structures and relative Gibbs function (kcal/mol) of SerZW in aqueous solution (bond lengths in Å).

function of Z2 and Z4 depicted in Fig. 1 is, however, very small as noted above.

It is very intriguing to observe that the kinetically unstable (that is, stationary but spontaneously transforms to the canonical form without reaction barrier) lowest energy conformer of the SerZW–$(H_2O)_2$ gas-phase cluster ((Z2-0) in Fig. 5 of [32]) now becomes kinetically stable (that is, isomerizes to the canonical form with finite barrier) in the solution phase. This finding may indicate the effectiveness of PCM over the cluster model to predict the stability of the zwitterionic forms of amino acid in the presence of solvent.

Fig. 2 presents the relative Gibbs energies and the structures of the most stable conformers of canonical (N1–N5) serine. The conformer N5 is calculated to be the most stable, but N1, N2 and N4 are within 1 kcal/mol in Gibbs function. The effects of solvation on the stability of the canonical serine are found to be quite interesting. For example, the most stable canonical conformer N5 in the solution phase corresponds to the serine conformer predicted to be of the lowest Gibbs function in the gas phase. On the other hand, the most stable gas-phase canonical serine–$(H_2O)_2$ cluster corresponds to N2 [32], which is calculated to be 0.78 kcal/mol higher than N5 in Gibbs function in Fig. 2. Thus, it seems that the relative stability predicted by the cluster model may be different from that obtained by the PCM approximations, and that the amino acids in the gas-phase microsolvated environment may not be in the intermediate states between the isolated molecule and the condensed phase [33]. The SerZW Z2 is calculated to be lower in Gibbs function than the canonical serine by 0.07 kcal/mol, which may be regarded as being too small considering that the corresponding difference for glycine is 7.27 kcal/mol [33].

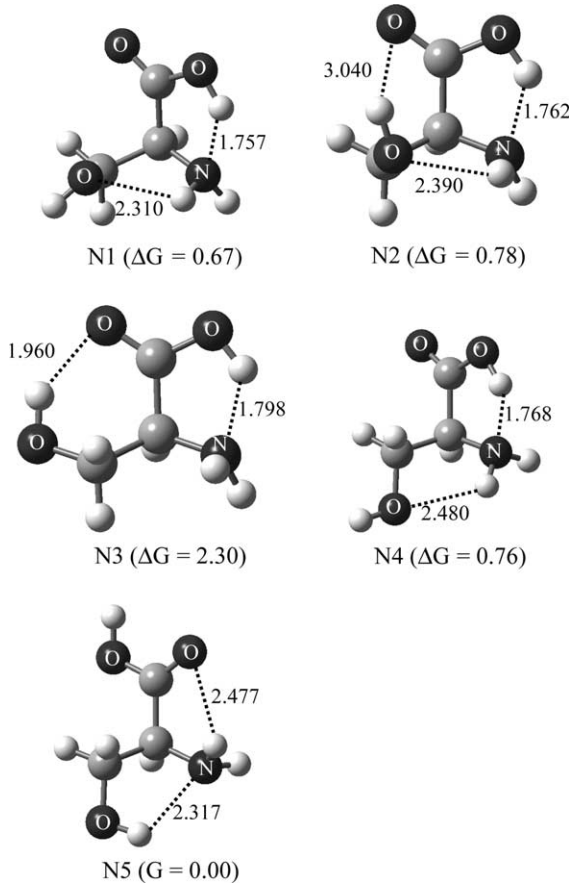

Fig. 2. Structures and relative Gibbs function (kcal/mol) of canonical serine in aqueous solution (bond lengths in Å).

We have demonstrated in our previous works [19,24] that the conformers of amino acids may by observed experimentally only when they are thermodynamically stable (of low Gibbs energy) and when they are kinetically stable (that is, may transform to other conformers with finite barrier). The relative energy or the Gibbs function is the key thermodynamic property, while the kinetic stability depends on the barrier to the canonical ↔ zwitterion isomerization reaction. This kinetic stability of the conformers may only be studied by carrying out calculations for the entire pathway for isomerization to obtain the transition state and the reaction barrier. The detailed mechanism of the isomerization (proton transfer) processes would also be elucidated this way. Several groups have extensively studied the proton transfer process of glycine, taking advantage of the PCM type approximations. For example, Tunon et al. [14] employed B3LYP/6-31G** and the self-consistent reaction field (SCRF) method to study the proton transfer in the canonical/zwitterion isomerization of glycine. For the case of alanine, Tortonda et al. [13] employed the ellipsoidal cavity model for the water continuum, and calculated that the alanine zwitterion is of lower energy (by 1.15 kcal/mol) than canonical alanine in aqueous solution.

The process of the proton transfer for isomerization from the most stable SerZW Z2 to the canonical form N2 in the aqueous solution is depicted in Fig. 3. The SerZW is calculated to be lower in Gibbs function than the canonical species produced by isomerization by 5.17 kcal/mol. The barrier to zwitterion → canonical isomerization, which is a very important parameter determining the kinetic stability of the zwitterion, is predicted to be 8.84 kcal/mol, significantly increasing from the corresponding value of 5.60 kcal/mol for similar process in the presence of two microsolvating water molecules in low temperature gas-phase environment. This finding seems to suggest that solvation by increasing number of water molecules tends to widen the gap between the stability of zwitterion vs. canonical serine. The magnitude of the barrier to zwitterion/canonical isomerization of serine is larger than that (5.26 kcal/mol) of alanine [24], also indicating that the effects of solvation on the relative stability of zwitterion/canonical serine in aqueous solution may be larger than the case of

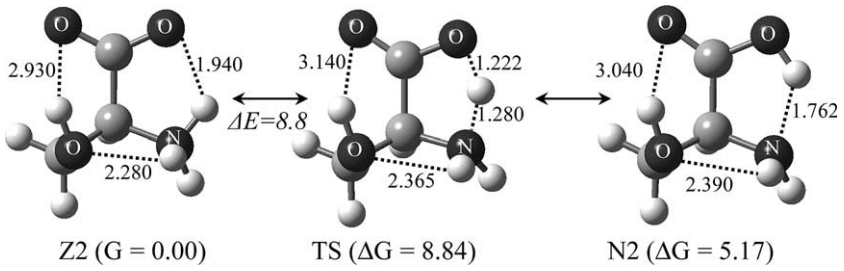

Fig. 3. Isomerization between the lowest energy zwitterion and canonical serine in aqueous solution (relative Gibbs function in kcal/mol and bond lengths in Å).

alanine. The mechanism of the canonical → zwitterion isomerization is the direct transfer of a proton form the carboxyl to the amino group, as depicted in Fig. 3.

Finally, we present in Fig. 4 the structures of the most stable canonical and zwitterion serine–$(H_2O)_n$ (n = 1,2) *clusters* in the presence of water continuum (discrete/continuum model) [24] to treat the solute–solvent interactions more explicitly on the molecular level. We find that the structures for the canonical and zwitterion serine of the lowest Gibbs function correspond to N5 and Z4 (N2 and Z4), respectively, when one (two) water molecule interacts in the cluster in the presence of the water continuum. It may be noted that N2-2 and Z4-1, Z4-2 correspond to the canonical conformers N2 and Z4, respectively, that are not of the lowest Gibbs function in the PCM approximation (see Figs. 1 and 2). Thus, the effects of solvation are calculated to be quite intricate depending on the methods employed, since many conformers are of comparable stability in the room temperature aqueous solution phase. It would be rather difficult to determine which conformers predicted by the two models are the most stable before the experimental observations are made for this system. On the other hand, the relative Gibbs function of the zwitterion vs. canonical serine is calculated to be −0.31 and −5.13 kcal/mol for the most stable serine–$(H_2O)_n$ (n = 1,2) *clusters* in the presence of water continuum. Although, no experimental results are available for comparison, this calculated difference in the Gibbs function for the discrete/continuum model of serine–(H_2O) cluster plus water continuum does not seem to be accurate, considering that it has been experimentally estimated to be 7.27 kcal/mol for glycine in aqueous solution [34]. We find, however, that the calculated ΔG (5.13 kcal/mol) between the canonical and zwitterion serine–$(H_2O)_2$ plus water continuum seems to be much more reasonable. Therefore, the discrete/continuum model seems to allow better prediction than PCM for the relative stability of canonical and zwitterion forms of serine in the aqueous solution, when at least *two* water molecules are treated explicitly on the molecular basis and the others are approximated as continuum.

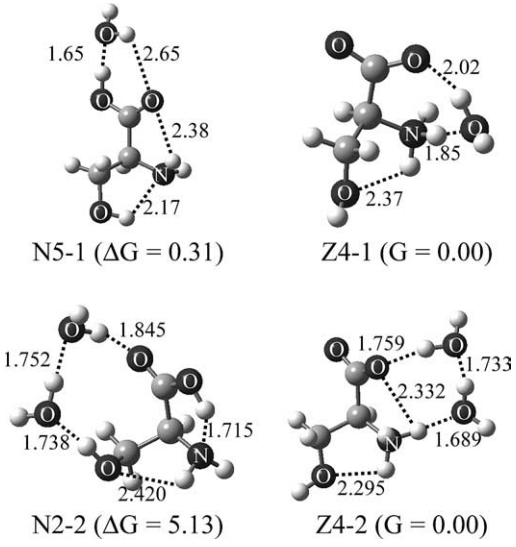

Fig. 4. Lowest energy zwitterion and canonical serine–$(H_2O)_n$ (n = 1,2) *clusters* in aqueous solution (relative Gibbs function in kcal/mol bond lengths in Å).

In conclusion, we treated the effects of solvent on the stability of serine zwitterion relative to the canonical form and the proton transfer path for the zwitterion/canonical isomerization reaction in the solution phase by employing the PCM and the discrete/continuum model. We find that the solvent continuum may yield notable differences in the aqueous solution phase from the gas-phase cluster environment. Experiments on these findings would be highly desirable.

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