Arginine Zwitterion is More Stable than the Canonical Form when Solvated by a Water Molecule

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We present calculations for the Arg–H_2O system and predict that the zwitterionic Arg is thermodynamically more stable than the canonical form in the gas phase under the influence of a single water molecule because of the strongly basic guanidine side chain. Canonical conformers of Arg–H_2O are found to isomerize to the zwitterionic forms via a small barrier (~6 kcal/mol).

I. Introduction

Solvation of amino acids[1–8] has been under intensive study, because the structures and relative stability of canonical[9–12] and zwitterionic[10,13–19] forms are tremendously affected by solvent both in the gas phase and in solution. Amino acids exist in canonical (nonzwitterionic) form in the gas phase, whereas zwitterionic conformer is the predominant form in aqueous solution.[18–21] One of the central questions concerning the biochemical properties of the amino acids is how many water molecules are required to stabilize the zwitterionic form. Examining the relative stability of these two forms as a function of the number of microsolvating water molecules[1–19] has proved quite useful in this regard, and it seems that the transition from the canonical to zwitterionic form gradually starts with three–five water molecules,[1,21,22] and the zwitterion is clearly preferable with more than seven water molecules.[23]

Although arginine (Arg)[24–29] is identical to other amino acids in that the canonical form is only observed in the gas phase, the relative stability of the zwitterionic form seems to be quite sensitive to the environment. Gutowski and co-workers[30] predicted, and Bowen and co-workers[31] recently observed experimentally, that the zwitterionic form of Arg is stabilized by an excess electron. Williams and co-workers[27,28] found that a cation may stabilize the Arg zwitterion. Presence of the strongly basic guanidine side chain in Arg, on the other hand, may also give properties that are distinct from those of the other amino acid. For example, the guanidine side chain may render the proton transfer from the carboxyl group much more facile under the influence of solvent, stabilizing the zwitterionic form of Arg. Solvation of Arg has, however, not been studied yet probably because of the large number of rotational degrees of freedom in the complex. In the present work, we examine the Arg–H_2O system to ask how the strongly basic guanidine side chain in Arg affects the relative stability of zwitterionic versus canonical form in solvated environment. We predict that the zwitterionic Arg is thermodynamically more stable than the canonical form in the gas phase under the influence of a single water molecule, thus

TABLE 1: Energy *E* (Hartree), ZPE (kcal/mol), Relative Energy Δ*E* (kcal/mol), and Relative Gibbs Function at 5 K Δ*G*₅ₖ (kcal/mol) of Arg–(H_2O) with Zwitterionic and Canonical Arg[a]

	E	ZPE	ΔE	ΔG_{5K}
		Zwitterionic		
Z22-1	−683.22550 (−681.26117)	156.3 (156.6)	0[b] (0)[c]	0[b] (0)[c]
Z21-2	−683.22471 (−681.26007)	156.4 (156.5)	0.57 (0.61)	0.64 (0.53)
		Canonical		
C4-1	−683.21962 (−681.24993)	154.6 (154.8)	1.95 (5.30)	0.21 (3.54)
C4-7	−683.21968 (−681.24990)	154.5 (154.8)	1.88 (5.27)	0.11 (3.47)
C5-1	−683.21998 (−681.25012)	154.5 (154.8)	1.68 (5.20)	−0.10 (3.46)

[a] Relative energies of canonical C1, C2, C3, C4, C5, and C6 and zwitterionic Arg Z21 and Z22 are 3.03, 3.42, 4.01, 0.06, 0, 3.16, 3.72, and 3.33 kcal/mol, respectively (B3LYP/6-311++G**); For their structures, see ref 35. [b] Relative energy and Gibbs function with respect to (Z22-1), B3LYP/6-311++G**. [c] MP2/aug-cc-pvdz.
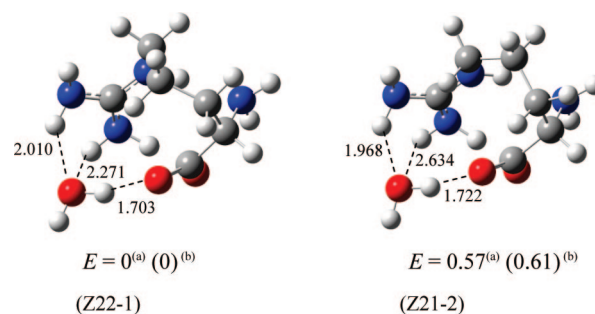

Figure 1. Structures of the lowest-energy conformers of zwitterionic Arg–H_2O (relative energy in kcal/mol and bond lengths in Angstroms). (a) B3LYP/6311++G** and (b) MP2/aug-cc-pvdz.

providing an exceptional example of the effects of microsolvation. We also show that the transformation from the low-energy canonical conformers of Arg–H_2O to the zwitterionic forms readily occurs via a very small (~2 kcal/mol) barrier, thus predicting that the zwitterionic forms would predominantly be observed in the gas phase.

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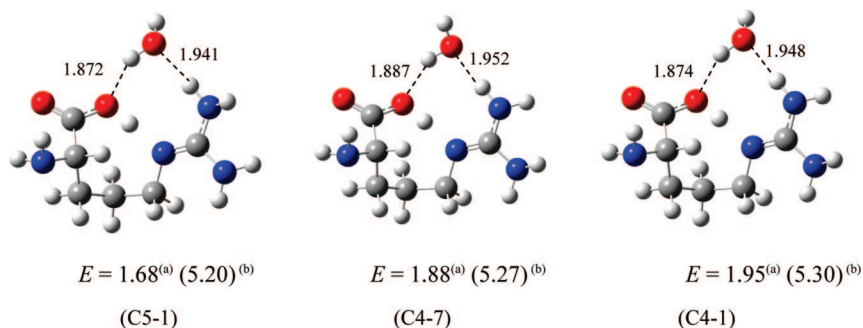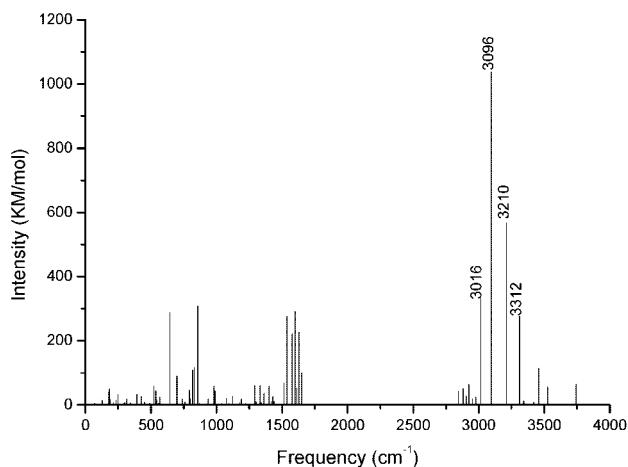[§] Korea Advanced Institute of Science and Technology.

$E = 1.68^{(a)} (5.20)^{(b)}$ $E = 1.88^{(a)} (5.27)^{(b)}$ $E = 1.95^{(a)} (5.30)^{(b)}$

(C5-1)   (C4-7)   (C4-1)

Figure 2. Structures of the low-energy conformers of canonical Arg−H$_2$O (relative energy with respect to (Z22-1) in kcal/mol). (a) B3LYP/6-311++G** and (b) MP2/aug-cc-pvdz.
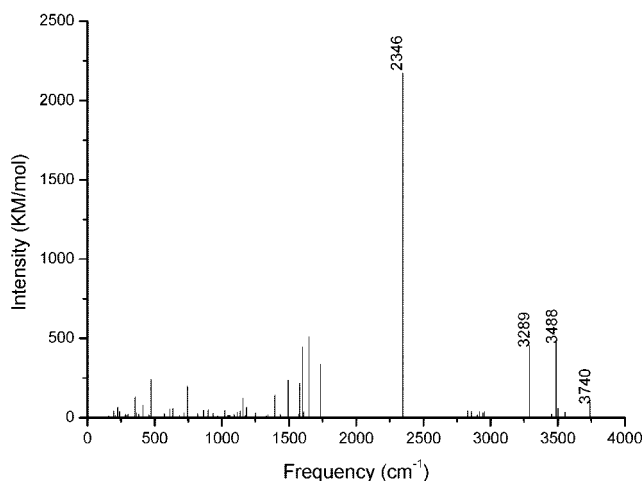

Figure 3. IR spectra of low-energy conformers ((Z22-1) and (C5-1)) of Arg−(H$_2$O) (a scaling factor of 0.9613 is employed).

II. Computational Methods

We employ the density functional theory (B3LYP[32,33]) with 6-311++G** and the MP2 method with the aug-cc-pvdz and 6-311+G* basis sets, as implemented in the GAUSSIAN 03 set of programs.[34] Structures of Arg−H$_2$O cluster are calculated by allowing a water molecule to interact over extensive configuration space with the functional groups (hydroxyl, amino, carbonyl, and guanidine) in Arg conformers that were exhaustively reported by Gutowski and co-workers.[35] We find that various initial configurations lead to water molecule bridging the two functional group in the complex, as described below.

Stationary structures are confirmed by ascertaining that all the harmonic frequencies are real. Structure of the TS is obtained by verifying that one and only one of the harmonic frequencies is imaginary and also by carrying out the intrinsic reaction coordinate analysis along the reaction pathway. Zero-point energies (ZPE) are taken into account, and default criteria are used for all optimizations.

III. Results and Discussion

Table 1, Figure 1, and Figure 2 present the calculated structures and relative energy of the zwitterionic and canonical conformers of Arg−H$_2$O. We find that the energy of the conformer (Z22-1) with the zwitterionic Arg core is lower than those of the lowest energy canonical form (C5-1) by ∼2 (∼5) kcal/mol, whereas its Gibbs energy at 5 K are very similar to (lower by ∼3.5 kcal/mol than) the canonical forms by B3LYP/6-311++G** (MP2/aug-cc-pvdz) method, respectively. This observation is quite striking when considering that the zwitterionic Arg is at least 3 kcal/mol higher in energy than the canonical Arg.[35] It is also remarkable to note that a single microsolvating water molecule can stabilize the zwitterionic form of the amino acid with respect to the canonical form, because it is now well agreed that at least three[21](for phenylalanine), four (for tryptophan),[1,22] and five (for glycine)[1] molecules of water are necessary to make the zwitterionic form energetically competitive with the canonical conformer, although the proton is transferred from the carboxyl to the side-chain guanidine group in Arg in contrast with other amino acids. The two zwitterionic conformers (Z22-1) and (Z21-2) depicted in Figure 1 are almost of the same energy (within 0.5 kcal/mol), and their structures are also quite similar. In both conformers, the water molecule bridges the carboxylate and the protonated guanidine side chain, with the difference being in the interactions between the water molecule and the guanidine side chain. In (Z22-1), the oxygen atom in water interacts with a proton in the guanidine side chain much more strongly ($R_{O-H} = 2.271$ Å) than in (Z21-2) ($R_{O-H} = 2.634$ Å). It is useful to note that the energy differences between the canonical and the zwitterionic forms of the bare Arg are much smaller than those of other amino acids such as Gly or Ala because of the strong basicity of the guanidine side chain in Arg. It seems that the water molecule solvates the zwitterion forms better than the canonical forms, making the two forms of Arg more or less equally stable.

Figure 2 depicts the structures and relative energies of the canonical Arg−H$_2$O. We find that the low-energy conformers of Arg−H$_2$O with canonical Arg core are produced mainly from the lowest-energy canonical Arg, (C4) and (C5) see ref 35). The three lowest-energy canonical conformers (C4-1), (C4-7), and (C5-1) are very similar in energy, within 0.3 kcal/mol. The relative energy of the canonical Arg−H$_2$O is more or less in

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$E^{\ddagger} = 4.46^{(a)} (4.62)^{(b)}$
$G^{\ddagger} = 2.29^{(a)} (2.19)^{(b)}$

(C22-1)

$E = 6.86^{(a)} (8.46)^{(b)}$
$G = 6.29^{(a)} (7.58)^{(b)}$
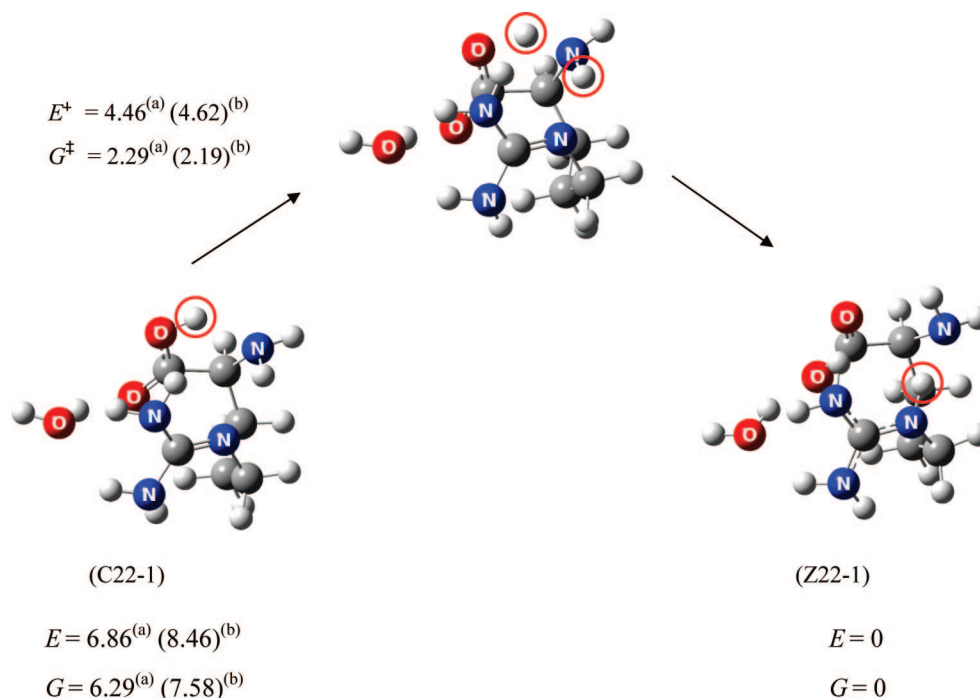
(Z22-1)

$E = 0$

$G = 0$

Figure 4. Isomerization from the canonical form of Arg−H₂O to the zwitterionic form (relative energy in kcal/mol, ZPE included). (a) B3LYP/6-311++G** and (b) MP2/6-311+G*.

parallel to those of the bare Arg (see footnote to Table 1), indicating that the effects of microsolvation by a water molecule on the relative stability within the canonical Arg are much smaller than those for stabilizing the Arg zwitterion over the canonical form. In most of these canonical conformers, the water molecule bridges the carboxyl and the guanidine group as in the low-energy zwitterionic complexes depicted in Figure 1, with the OH moiety in the carboxyl group orienting toward the guanidine side chain and away from the water molecule. Other zwitterionic complexes derived from the bare Arg (C1), (C2), (C3), and (C6) listed in ref 35 are much higher (by more than 5 kcal/mol) in energy than the lowest-energy Arg−(H₂O) complexes.

Figure 3 presents the calculated infrared (IR) spectra (the frequencies calculated by the B3LYP/6-311++G** method are scaled by a factor of 0.9613) of the lowest-energy conformers with zwitterionic and canonical Arg core. The IR spectrum of (Z22-1) is characterized by the wide window in the 1700−2800 cm⁻¹ region and four strong bands in 3000−3300 cm⁻¹ describing the proton-transfer modes between the functional groups in the complex (guanidine ↔ CO_2^- ↔ H_2O, CO_2^- ↔ H_2O, guanidine ↔ CO_2^-, and H_2O ↔ guanidine, in increasing frequency). On the other hand, the IR absorption of (C5-1) is featured by an intense band at 2346 cm⁻¹ for the guanidine ↔ CO_2H proton-transfer mode.

When the Arg−(H₂O) complex is produced from Arg and water vapor in low-temperature environment, one important issue would be the mechanism and the barrier of formation of the zwitterionic complex, because the canonical Arg must be transformed to a zwitterion in the course of combining with a water molecule to produce the zwitterionic Arg−(H₂O). If the Arg−(H₂O) complex initially produced with canonical Arg core is kinetically very stable (that is, if the barrier to zwitterionic Arg−(H₂O) is high), the latter form of Arg−(H₂O) complex core could hardly be formed. We find that a single kinetic pathway does not connect the lowest-energy canonical conformers (C4-1), (C4-7), and (C5−1) to the most stable zwitterionic form (Z22,1). The processes seem to involve many transition

states and intermediates along the path, which we could not follow. Figure 4 depicts that the lowest energy zwitterionic form (Z22-1) connects via a double-proton-transfer process to the canonical form (C22-1), the Gibbs free energy of which is ∼4 kcal/mol higher than that of (C4-1), (C4-7), and (C5-1). Thus, by assuming that (C22-1) is formed from the lower-energy canonical conformers before transforming to the zwitterion (Z22-1), we may estimate that the magnitude of barrier to (Z22-1) is low ($G^{\ddagger}$= ∼6 kcal/mol).

The formation of the zwitterionic Arg−H₂O from Arg and H₂O in gas phase is exothermic ($\Delta G_{5K} \approx -14$ kcal/mol), and thus, it will be a spontaneous process at low temperature. On the other hand, the decrease in entropy in the process will eventually make ΔG positive at a higher temperature, and we find (by MP2/aug-cc-PVDZ method) that the zwitterionic Arg−H₂O would not be stable at $T > 415$ K. The zwitterionic Arg−H₂O may also be produced by photodetaching the Arg−H₂O anion with the zwitterionic Arg core, which would be formed by combining a water molecule with zwitterionic Arg anion that was found to be quasidegenerate with the canonical Arg.[30]

In summary, we have shown that Arg zwitterion is stabilized by a water molecule and that the canonical Arg−H₂O complex is not stable, both thermodynamically and kinetically, to be observed in the gas phase. Experimental studies for our predictions would be highly desirable.

Supporting Information Available: Energy, ZPE, and Gibbs function for the structures of zwitterionic and canonical Arg−H₂O and IR spectra. This material is available free of charge via Internet at http://pubs.acs.org.

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