

Microsolvation of Lysine by Water: Computational Study of Stabilized Zwitterion

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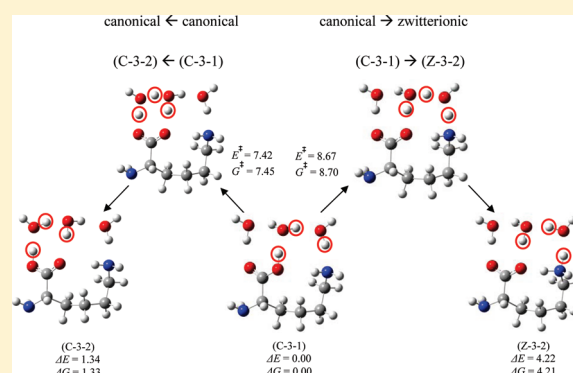
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ABSTRACT: We present calculations for $\text{Lys}-(\text{H}_2\text{O})_n$ ($n = 2, 3$) to examine the effects of microsolvating water on the relative stability of the zwitterionic vs canonical forms of Lys. We calculate the structures, energies, and Gibbs free energies of the conformers at the B3LYP/6-311++G(d,p), wB97XD/6-311++G(d,p), and MP2/aug-cc-pvdz levels of theory, finding that three water molecules are required to stabilize the Lys zwitterion. By calculating the barriers of the canonical \leftrightarrow zwitterionic pathways of $\text{Lys}-(\text{H}_2\text{O})_3$ conformers, we suggest that both forms of $\text{Lys}-(\text{H}_2\text{O})_3$ may be observed in low temperature gas phase.



I. INTRODUCTION

Effects of solvation on the structures and reactivity of amino acids, both canonical^{1–12} and zwitterionic,^{10,13–20} have been under intensive study. One of the most intriguing questions concerning the solvation is: What are the effects of solvation on the relative stability of canonical and zwitterionic conformers? This has been addressed for a number of amino acids by examining the relative stability of these two forms as a function of the number of microsolvating water molecules.^{1–20} It is now agreed that the transition from a canonical conformer to a zwitterionic conformer starts with four to five water molecules^{1,21,22} and the zwitterion is clearly preferable with more than seven water molecules.²³

Lysine (Lys) is the amino acid with a very basic side chain, which is second only to arginine. Although the canonical form of Lys is only observed in the gas phase, the presence of the strongly basic side chain may render different structural features of Lys. For example, a single cation may stabilize the Lys zwitterion, as it was observed that the stability of the zwitterionic form relative to the nonzwitterionic form of aliphatic amino acids is directly related to proton affinity.^{24,25} The presence of the amino group in the side chain may also give distinct effects of solvation on the relative stability of canonical vs zwitterionic conformers of Lys. Microsolvating water molecules, for example, may interact with this basic amino group,

influencing the proton transfer process from the carboxyl group. This structural feature may also allow the zwitterionic conformers of Lys to be stabilized under the influence of fewer water molecules than are ordinarily observed in other amino acids.

In the present work, we examine $\text{Lys}-(\text{H}_2\text{O})_n$ ($n = 2, 3$), predicting that the zwitterionic Lys becomes quasidegenerate with the canonical forms as a result of the solvating effects of three water molecules. We also study the canonical \leftrightarrow zwitterion pathways to show that the two lowest energy zwitterionic and canonical conformers of $\text{Lys}-(\text{H}_2\text{O})_3$ are not interconnected by direct routes. Because each of the two forms is kinetically correlated with other higher energy conformers of $\text{Lys}-(\text{H}_2\text{O})_3$, we suggest that both of them may be observed in jet-cooled low temperature gas phase.

II. COMPUTATIONAL METHODS

We employ the density functional theories (B3LYP^{26,27} and wB97XD²⁸) with the 6-311++G* and the MP2/aug-cc-pvdz methods, as implemented in the GAUSSIAN 03 set of programs.²⁹

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Table 1. Relative Energy ΔE (kcal/mol), Relative Gibbs Free Energy ΔG_{SK} (kcal/mol) at 5 K, and Dipole Moment μ (Debye) of Lys-(H₂O)₂ with Zwitterionic and Canonical Lys

	ΔE	ΔG_{SK}	μ
(zwitterion)			
Z-2-1	2.81 ^a (2.64) ^b (3.36) ^c (-1.97) ^e	2.81 ^a (2.63) ^b (3.36) ^c	5.7704
Z-2-2	2.90 ^a (3.00) ^b (3.55) ^c (-1.87) ^e	2.90 ^a (2.99) ^b (3.55) ^c	5.6428
Z-2-3	4.91 ^a (5.50) ^c (1.34) ^e	4.91 ^a (5.51) ^c	4.4559
(canonical)			
C-2-1	0.00 ^a (0.00) ^b (0.00) ^c (0.00) ^d (0.00) ^e	0.00 ^a (0.00) ^b (0.00) ^c	2.7926
C-2-2	1.60 ^a (3.05) ^c (3.86) ^d	1.59 ^a (3.05) ^c	3.8282
C-2-3	1.75 ^a (4.07) ^c (2.61) ^d	1.75 ^a (4.07) ^c	9.2979
C-2-4	3.55 ^a (2.31) ^c (3.14) ^d	3.56 ^a (2.31) ^c	4.0033
C-2-5	2.98 ^a (4.74) ^c (3.09) ^d	2.98 ^a (4.74) ^c	7.6082
C-2-6	3.65 ^a (3.86) ^c (2.61) ^d	3.65 ^a (3.86) ^c	5.0205
C-2-7	3.59 ^a (4.68) ^c (3.99) ^d	3.59 ^a (4.68) ^c	8.5281
C-2-8	3.49 ^a (3.57) ^c (3.15) ^d	3.48 ^a (3.57) ^c	9.1126
C-2-9	3.47 ^a (3.55) ^c (3.15) ^d	3.47 ^a (3.55) ^c	9.1216
C-2-10	4.36 ^a (4.65) ^c (4.75) ^d	4.36 ^a (4.65) ^c	6.7787
C-2-11	3.24 ^a (5.54) ^c (4.02) ^d	3.24 ^a (5.54) ^c	9.3448
C-2-12	4.22 ^a (3.85) ^c (3.53) ^d	4.22 ^a (3.85) ^c	6.7231

^a B3LYP/6-311++G(d,p) (BSSE corrected). ^b MP2/aug-cc-pvdz. ^c wB97XD/6-311++G(d,p). ^d MP2/aug-cc-pvdz//wB97XD/6-311++G(d,p). ^e IEFPCM/B3LYP/6-311++G(d,p).

We also use the IEFPCM³⁰ method to calculate the influence of bulk water on the relative energies and Gibbs free energies of canonical and zwitterionic Lys. Structures of the Lys-(H₂O)₂ clusters are calculated by allowing an additional water molecule to interact over an extensive configuration space with the Lys-H₂O that were exhaustively investigated by Lin and co-workers.³¹ We find that various initial configurations lead to a water molecule bridging the two functional groups, as described below. Stationary structures are confirmed by ascertaining that all the harmonic frequencies are real. The structure of the transition state 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 pathways. Zero point energies (ZPE) are taken into account, and default criteria are used for all optimizations.

III. RESULTS

III-1. Lys-(H₂O)₂. Table 1 and Figures 1 and 2 present the calculated structures and relative energies of the zwitterionic and canonical conformers of Lys-(H₂O)₂. We have extensively searched for conformers over the potential energy surface, using the Monte Carlo technique for adding a water molecule to the six lowest energy structures of Lys-H₂O reported by Lin and co-workers.³¹ At both the B3LYP/6-311++G(d,p) and MP2/aug-cc-pvdz levels of theory, we find that the energies (electronic energy + ZPE) and Gibbs free energies of the three zwitterionic conformers Z-2-1, Z-2-2, and Z-2-3 are higher than those of the lowest energy (corrected for the basis set superposition error (BSSE)) canonical form

Table 2. Relative Energy ΔE (kcal/mol), Relative Gibbs Free Energy ΔG_{SK} (kcal/mol) at 5 K, and Dipole Moment μ (Debye) of Lys-(H₂O)₃ with Zwitterionic and Canonical Lys

	ΔE	ΔG_{SK}	μ
zwitterion			
Z-3-1	2.30 ^a (-0.98) ^b (-1.30) ^c	2.29 ^a (-0.98) ^b (-1.30) ^c	4.6330
Z-3-2	4.22 ^a (3.38) ^c	4.21 ^a (3.38) ^c	7.1919
Z-3-3	4.54 ^a (1.27) ^c	4.53 ^a (1.27) ^c	4.5317
Z-3-4	4.71 ^a (4.91) ^c	4.71 ^a (4.91) ^c	5.7169
Z-3-5	5.33 ^a (2.91) ^c	5.33 ^a (2.91) ^c	5.2003
Z-3-6	5.96 ^a (4.67) ^c	5.96 ^a (4.67) ^c	6.9226
Z-3-7	7.84 ^a (7.58) ^c	7.84 ^a (7.58) ^c	9.9325
(canonical)			
C-3-1	0.00 ^a (0.00) ^b (0.00) ^c	0.00 ^a (0.00) ^b (0.00) ^c	3.0582
C-3-2	1.34 ^a (1.20) ^b (1.10) ^c	1.33 ^a (1.11) ^b (1.10) ^c	2.6962
C-3-3	1.54 ^a (1.68) ^c	1.54 ^a (1.68) ^c	3.9294
C-3-4	3.56 ^a (1.78) ^c	3.56 ^a (1.78) ^c	1.8358
C-3-5	3.74 ^a (1.69) ^c	3.74 ^a (1.69) ^c	2.0892
C-3-6	4.63 ^a (2.23) ^c	4.63 ^a (2.23) ^c	2.0868
C-3-7	4.52 ^a (2.99) ^c	4.53 ^a (2.99) ^c	2.6420
C-3-8	5.04 ^a (5.25) ^c	5.04 ^a (5.25) ^c	4.0073

^a B3LYP/6-311++G(d,p) (BSSE corrected). ^b MP2/aug-cc-pvdz. ^c wB97XD/6-311++G(d,p).

(C-2-1) by 3.6–6.7 (>2.6, >3.4) kcal/mol by B3LYP/6-311++G(d,p) (MP2/aug-cc-pvdz, wB97XD/6-311++G(d,p)) level of theory. Although the B3LYP/6-311++G(d,p) method may give an uncertainty of energies of <2 kcal, calculations by the more accurate MP2/aug-cc-pvdz indicate that the zwitterionic Lys-(H₂O)₂ is thermodynamically much less stable than the canonical forms and that two microsolvating water molecules are not sufficient to stabilize the Lys zwitterion. In all canonical structures, the two water molecules bridge the side chain amino group and either the carboxyl or the amino group bonding to the α -carbon. The energies of canonical conformers C-2-2, C-2-3, C-2-4, and C-2-5 are quite close to each other, within \sim 2 kcal/mol. The relative energies of canonical Lys-(H₂O)₂ obtained by single energy calculations MP2/aug-cc-pvdz//wB97XD/6-311++G(d,p) are more or less in line with those obtained by B3LYP/6-311++G(d,p), MP2/aug-cc-pvdz, and wB97XD/6-311++G(d,p) methods. The two zwitterionic conformers (Z-2-1 and Z-2-2) depicted in Figure 2, originating from the lowest energy zwitterionic Lys-(H₂O)₂ (ϵ -Z-1),³⁰ are also of very similar energy. In both conformers, the water molecules bridge the carboxylate and the ammonium in side chain, with the difference being in the orientations of the solvating water molecules with respect to the Lys moiety. One of the interesting questions will be: How will the continuum water affect the relative thermodynamic stability of the zwitterionic vs canonical Lys-(H₂O)₂ in aqueous solution? We adopt a discrete/continuum approach employing the IEFPCM³⁰ method, adding the water continuum to the lowest energy zwitterionic (Z-2-1 and Z-2-2) and canonical (C-2-1) conformers of Lys-(H₂O)₂. As expected, the energies of zwitterionic conformers Z-2-1 and Z-2-2 are calculated to be \sim 2 kcal/mol lower than that of C-2-1. It may be worth noting that, in all the zwitterionic

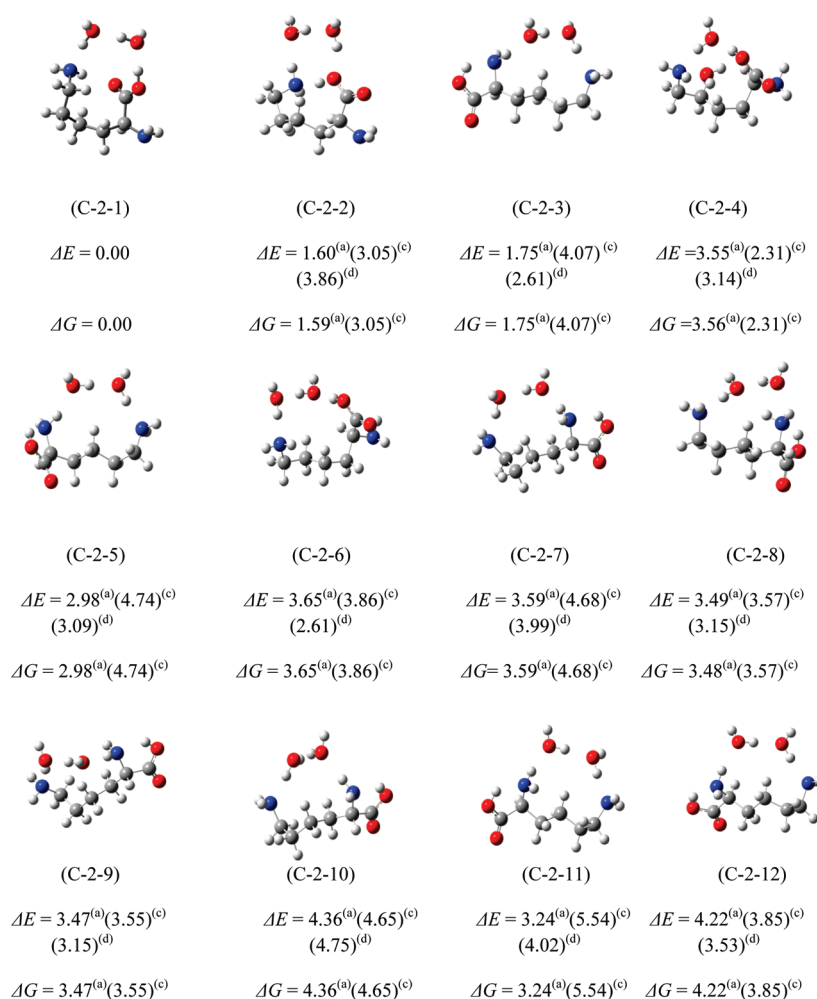


Figure 1. Structures of the low energy conformers of canonical Lys–(H₂O)₂ (relative energies and Gibbs free energies at 5 K with respect to C-2-1 in kcal/mol): (a) B3LYP/6-311++G(d,p) (BSSE corrected); (b) MP2/aug-cc-pvdz; (c) wB97XD/6-311++G(d,p); and (d) MP2/aug-cc-pvdz//wB97XD/6-311++G(d,p).

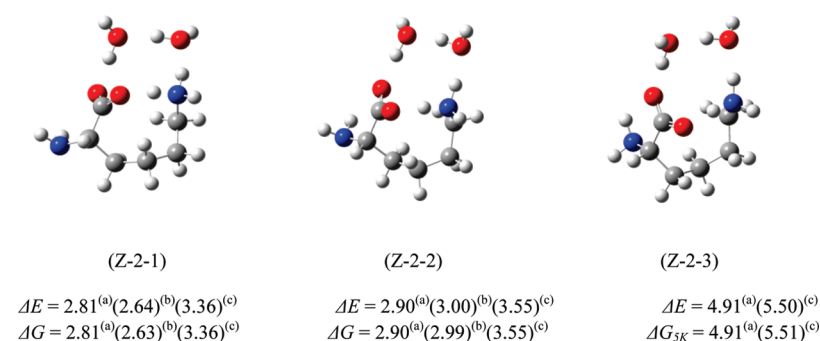


Figure 2. Structures of the lowest energy conformers of zwitterionic Lys–(H₂O)₂ (energies and Gibbs free energies at 5 K relative to C-2-1 Lys–(H₂O)₂ in kcal/mol): (a) B3LYP/6-311++G(d,p) (BSSE corrected); (b) MP2/aug-cc-pvdz; and (c) wB97XD/6-311++G(d,p).

conformers given in Figure 2, the acidic proton is binding not to the amino on the α -carbon but to the side chain amino group.

III-2. Lys–(H₂O)₃. Table 2 and Figures 3 and 4 present the calculated structures, energies, and Gibbs free energies of Lys–(H₂O)₃. We have also used the Monte Carlo technique

to add a water molecule to the structures of Lys–(H₂O)₂ presented above. We find that the thermodynamic stability of zwitterionic Lys–(H₂O)₃ relative to canonical forms depends on the method employed. Using the B3LYP/6-311++G(d,p) level of theory, the lowest energy zwitterionic conformer (Z-3-1) lies ~ 2.5 kcal/mol higher in energy and Gibbs free

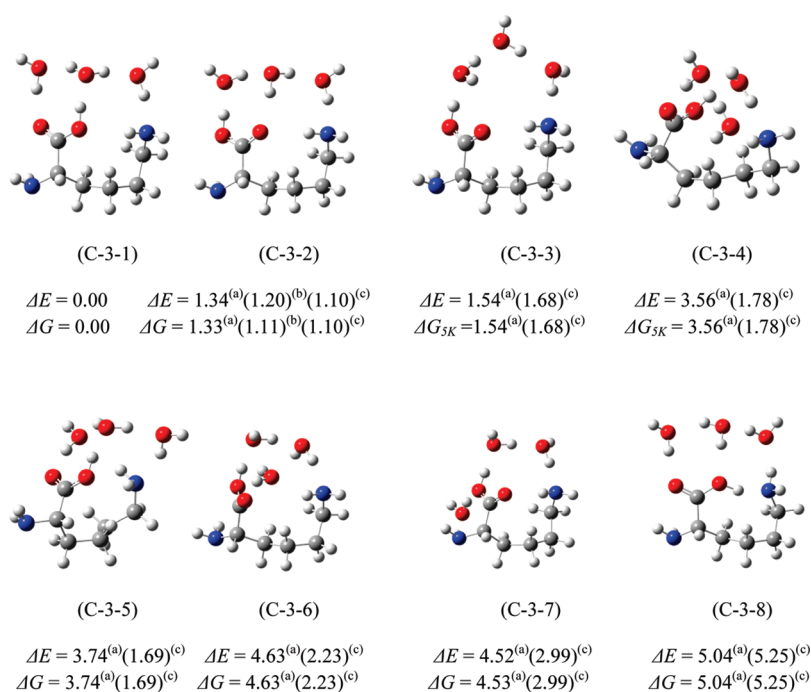


Figure 3. Structures of the low energy conformers of canonical Lys-(H₂O)₃ (relative energy and Gibbs free energy in kcal/mol): (a) B3LYP/6-311++G(d,p) (BSSE corrected); (b) MP2/aug-cc-pvdz; and (c) wB97XD/6-311++G(d,p).

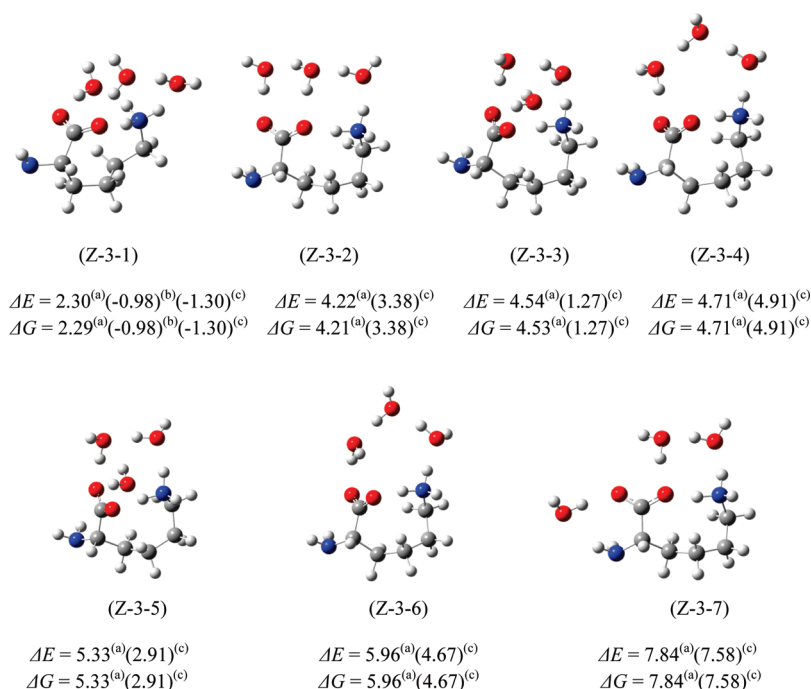


Figure 4. Structures and energies (relative to the lowest energy canonical conformer (C-3-1)) of the low energy conformers of zwitterionic Lys-(H₂O)₃ (relative energy and relative Gibbs free energy in kcal/mol): (a) B3LYP/6-311++G(d,p) (BSSE corrected); (b) MP2/aug-cc-pvdz; and (c) wB97XD/6-311++G(d,p).

energy, whereas they are calculated to be ~ 1 kcal/mol lower than those of the lowest energy canonical form (C-3-1), by the more accurate MP2/aug-cc-pvdz method. It seems that the wB97XD method developed by Head-Gordon and co-workers²⁸ is much better than the B3LYP method for

assessing the relative stability of zwitterionic vs canonical conformers of Lys-(H₂O)₃, rendering the energy of the zwitterion Z-3-1 to be lower than that of canonical form C-3-1 by 1.3 kcal/mol, which is much more in line with the MP2/aug-cc-pvdz result, which is presumably a result of the

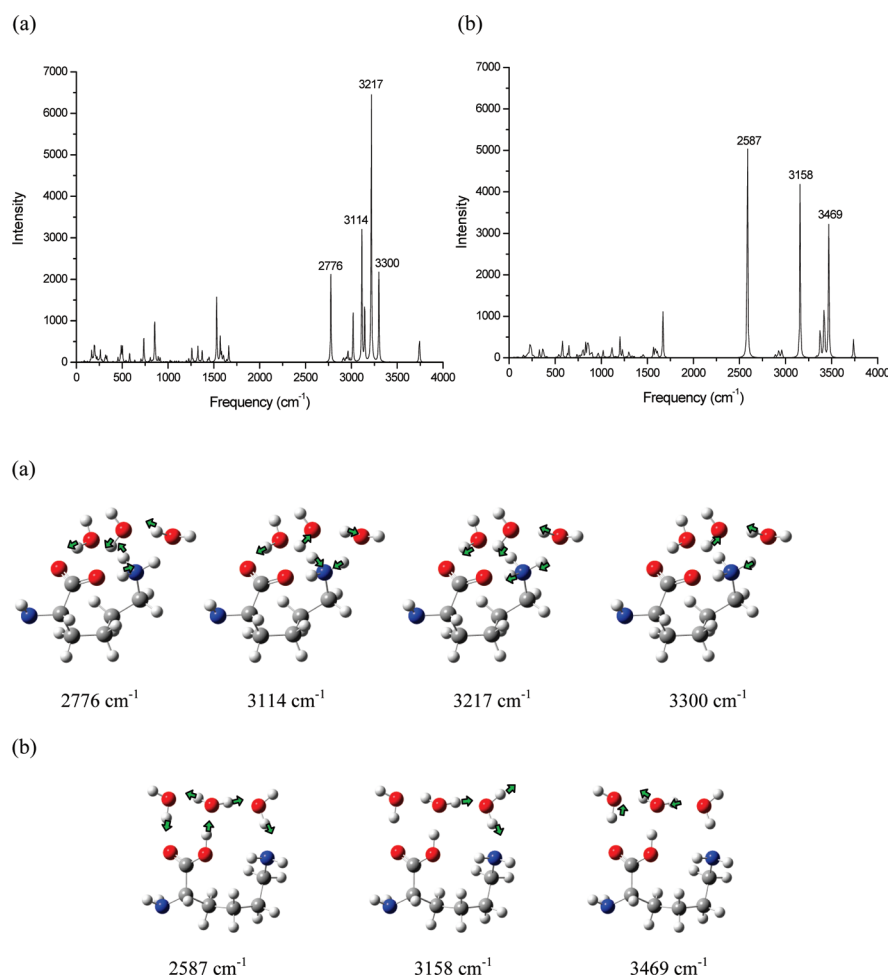


Figure 5. IR spectra of the lowest energy and normal modes of the most intense bands of (a) zwitterionic Z-3-1 and (b) canonical C-3-1 conformers of $\text{Lys}-(\text{H}_2\text{O})_3$ (B3LYP/6-311++G(d,p) with a scaling factor of 0.9613).

superiority of the wB97XD method for treating weak interactions in the present system. Therefore, it seems that the two forms of $\text{Lys}-(\text{H}_2\text{O})_3$ are quite comparable in thermodynamic stability. It can be seen that the lowest energy zwitterionic conformer (Z-3-1) is far more stable than others and that the energies of the three canonical conformers C-3-1, C-3-2, and C-3-3 are quite close (within 1.5 kcal/mol), at both the B3LYP/6-311++G(d,p) and MP2/aug-cc-pvdz levels of theory. In the low energy canonical (zwitterionic) structures depicted in Figure 3 (Figure 4), the three water molecules bridge the amino (ammonium) and carboxyl (carboxylate) in a variety of fashions. This role of microsolvating water molecules influences the transfer of a proton from the acidic group to the basic group in $\text{Lys}-(\text{H}_2\text{O})_3$ and influences the corresponding transformation between the canonical and zwitterionic forms, as discussed below. Because the acidic proton is binding to the side chain amino group in all the zwitterionic conformers of $\text{Lys}-(\text{H}_2\text{O})_3$ depicted in Figure 4, it can be presumed that more than three water molecules are necessary to stabilize the zwitterionic Lys in which the proton is transferred from the carboxyl to the amino group on the α -carbon, just like the cases of the other amino acids.^{1,21–23}

Figure 5 presents the infrared (IR) spectra (the frequencies calculated by the B3LYP/6-311++G(d,p) method are scaled by a

factor of 0.9613) and the normal modes of the lowest energy conformer of $\text{Lys}-(\text{H}_2\text{O})_3$, with zwitterionic and canonical Lys core. The IR spectra of Z-3-1 and C-3-1 exhibit widely different features that may be very helpful for discerning them experimentally: Z-3-1 is characterized by strong bands at 3300, 3217, 3114, and 2776 cm^{-1} with a wide window in the 1500–2750 cm^{-1} region; and C-3-1 is characterized by intense bands at 3469, 3158, and 2587 cm^{-1} . The normal modes of these bands consist of complicated stretches of the solvent OH and ammonium NH bonds in the zwitterionic $\text{Lys}-(\text{H}_2\text{O})_3$ and of the solvent OH and amino side chain NH bonds in the canonical $\text{Lys}-(\text{H}_2\text{O})_3$. Of these, the lower bands at 2776 (Z-3-1) and 2587 (C-3-1) cm^{-1} exhibit the normal modes resembling the multiple proton transfer between the basic and acidic moieties.

Because the two types (zwitterionic and canonical) of $\text{Lys}-(\text{H}_2\text{O})_3$ are of similar energies, they may equally be favorable thermodynamically for detection in gas phase at low temperature. In this case, the barrier of zwitterionic \leftrightarrow canonical isomerization may also be of interest. Figure 6a depicts the dynamic pathways of transformation from the lowest energy canonical (C-3-1) to the other conformers. We find that the canonical conformer C-3-1 may transform either to the canonical conformer C-3-2 via the activation

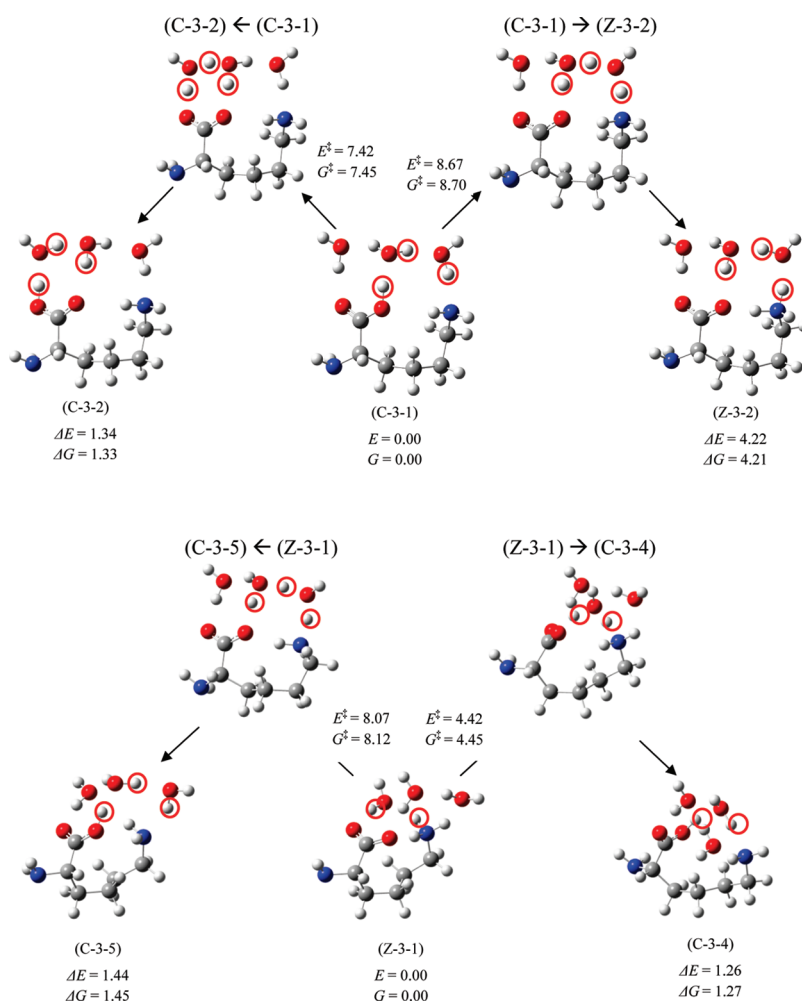


Figure 6. Transformation (a) from the lowest energy canonical conformer of Lys-(H₂O)₃ to zwitterionic form and (b) from the lowest energy zwitterionic conformer to canonical form (relative energy in kcal/mol, ZPE included; B3LYP/6-311++G(d,p)).

barrier of 7.4 kcal/mol or to the zwitterionic form Z-3-2 via $E^\ddagger = 8.7$ kcal/mol, both by triple proton transfer mediated by water molecules. Although these barriers are rather low, the energies of the resulting C-3-2 and Z-3-2 are higher (by 1.3 and 4.2 kcal/mol, respectively) than those of C-3-1. Because there exists no direct pathway from C-3-1 to the lower energy zwitterionic structure (Z-3-1), this indicates that C-3-1, once it is produced (for example, by photodetaching the canonical form with an extra electron), may be observed experimentally at least in low temperature gas phase. Figure 6b shows that the lowest energy zwitterionic conformer (Z-3-1) may transform to the two canonical forms C-3-4 and C-3-5 by double and triple proton transfer mediated by water molecules, via $E^\ddagger = 4.4$ and 8.1 kcal/mol, respectively. These barriers are also low; however, the energies of the two canonical forms are higher (by 1–1.5 kcal/mol) than that of Z-3-1. Therefore, we suggest that both the lowest energy zwitterionic (Z-3-1) and canonical (C-3-1) conformers of Lys-(H₂O)₃ may be observed in low temperature (~ 5 K) gas phase.

IV. CONCLUSION

In contrast to other amino acids for which more water molecules are required to stabilize the zwitterion, we find that,

in this case, three water molecules are enough because of the strongly basic side chain. By studying the kinetic paths and activation barriers of the canonical \leftrightarrow zwitterion transformation, we also suggest that both (canonical and zwitterionic) forms of Lys-(H₂O)₃ may be observed in jet-cooled low temperature gas phase. Experimental studies such as the one carried out by Bowen and co-workers¹ on this intriguing Lys–water system would be highly desirable.

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