Computational Study of Proline – Water Cluster

Kyung-Min Lee, Sung-Woo Park, In-Sun Jeon, Bo-Ra Lee, Doo-Sik Ahn, and Sungyul Lee[*]

College of Environmental Science and Applied Chemistry (BK21), Kyunghee University, Kyungki-do 449-701, Korea
[*]*E-mail: sylee@khu.ac.kr*

Calculations are presented for the structures of various conformers of the bare proline and proline – (H_2O) cluster. The effects of hydrogen bonding with a water molecule on the relative stability of the low energy conformers of proline are examined. Microsolvation by a water molecule is predicted to affect the relative stability, structures and the infrared frequencies of the conformers to a large degree.

Key Words : Proline, Water, Cluster

Introduction

The effects of solvation on amino acids may be easily appreciated when it is noted that the canonical forms are much more stable in the gas phase, while the zwitterionic (that is, charge-separated) forms are only observed in the aqueous solution phase. One very interesting question concerned is: How many water molecules are needed to stabilize the zwitterionic conformers? Although the PCM[1] type methods were able to elucidate some features of the property of amino acid in aqueous solution phase (for example, the relative stability of the neutral and the zwitterion amino acid in the solution phase), other more important physicochemical properties depend on the nature of the solute – solvent interactions on the molecular level. One example is the solvent-mediated chemical reaction, and in this case the cluster model would be much more helpful. In this latter approach, the solvent molecules are treated by quantum chemical methods explicitly as molecules, and one examines the effects of "microsolvation"[2-19] as a function of the number of solvent molecules by analyzing the detailed interactions between the solute and the solvent molecule(s) affecting the structure and reaction of the solute.

Proline is somewhat different in the structure and reactivity from the other amino acids. Due to the pyrrolidine ring embedded, proline plays an important role in determining the *β*-turn structure in polypeptides and proteins.[20,21] Studies on proline have largely been focused on this structural aspect. Proline is also unique among the amino acids in that the N-terminus is a secondary amine with quite large basicity. This latter characteristics makes the chemistry of proline quite interesting. For example, it was very recently confirmed that metal cation (Li^+ or Na^+) stabilizes the zwitterionic form of proline[22] and *α*-methlyproline[23] to be experimentally detected. Effects of water or organic solvents on proline have not been quite rare, and therefore, a careful study of the effects of solvation on the structure and reaction of this amino acid may reveal interesting features. As the first step toward a systematic study, we calculate the structures of proline and proline – H_2O clusters and examine the effects of hydrogen bonding with water on the relative

stability of conformers in this work. All calculations are carried out using the GAUSSIAN 98W and GAUSSIAN 03 suite of programs.[24] The stationary structures are found by verifying that all the harmonic frequencies are real. The density functional theory (B3LYP/6-311++G**) is employed. Default criteria are employed for all the optimization processes.

Results

Table 1 and Figure 1 present the energies and the

Table 1. Calculated electronic energies (E), zero-point energies (ZPE), relative energies (ΔE) and dipole moments (μ) of four lowest-energy conformers of proline

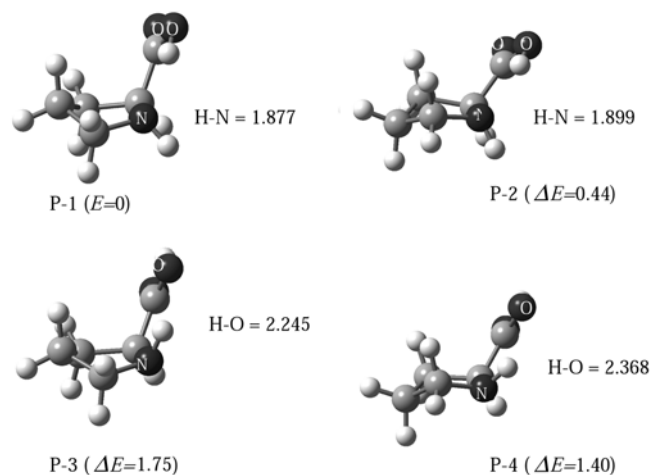| Conformer	E (Hartree)	ZPE (kcal/mol)	ΔE (kcal/mol)	μ (Debye)
(P-1)	-401.28475^a	90.9^a	0^a	5.9
(P-2)	-401.28399	90.8	0.44	6.0
(P-3)	-401.28149	90.6	1.75	2.0
(P-4)	-401.28183	90.4	1.40	1.8

^{a}B3LYP/6-311++G**

Figure 1. Calculated structures and relative energies (kcal/mol) of low energy proline conformers (hydrogen bond lengths in Å).

structures of lower-lying conformers ((P-1)-(P-4)) of proline. The conformers depicted in Figure 1 are the four lowest-lying conformers of proline. We find that the other conformers lie more than 3 kcal/mol higher in energy above the lowest energy conformer (P-1). Thus, it seems that the proline conformers "split" into four low-lying and a large number of higher lying ones, probably due to the stiffness of the ring system, as also noticed by Czinki and Csaszar.[25] This interesting pattern may render the experimental assignment of proline in the gas phase to be simpler than other amino acids. The energies of the conformers (P-1)-(P-4) are, however, quite close (within 2 kcal/mol). Differ-

ences in the structures among these low-lying conformers are to be noted: The two conformers (P-1) and (P-2) (and also (P-3) and (P-4) differ in the conformation of the five-membered ring with respect to the carboxyl group: in (P-1) and (P-3) the ring is puckered "down", while it is in the "up" position in (P-2) and (P-4). The difference in energy is quite small, less than 1 kcal/mol. In the conformers (P-1) and (P-2), the carboxyl OH forms an intramolecular hydrogen bonding by donating a proton to the N atom, while it is the NH group donating a proton to the oxygen atom in (P-3) and (P-4). The slightly lower energies of (P-1) and (P-2) relative to (P-3) and (P-4) seem to indicate that the OH···N
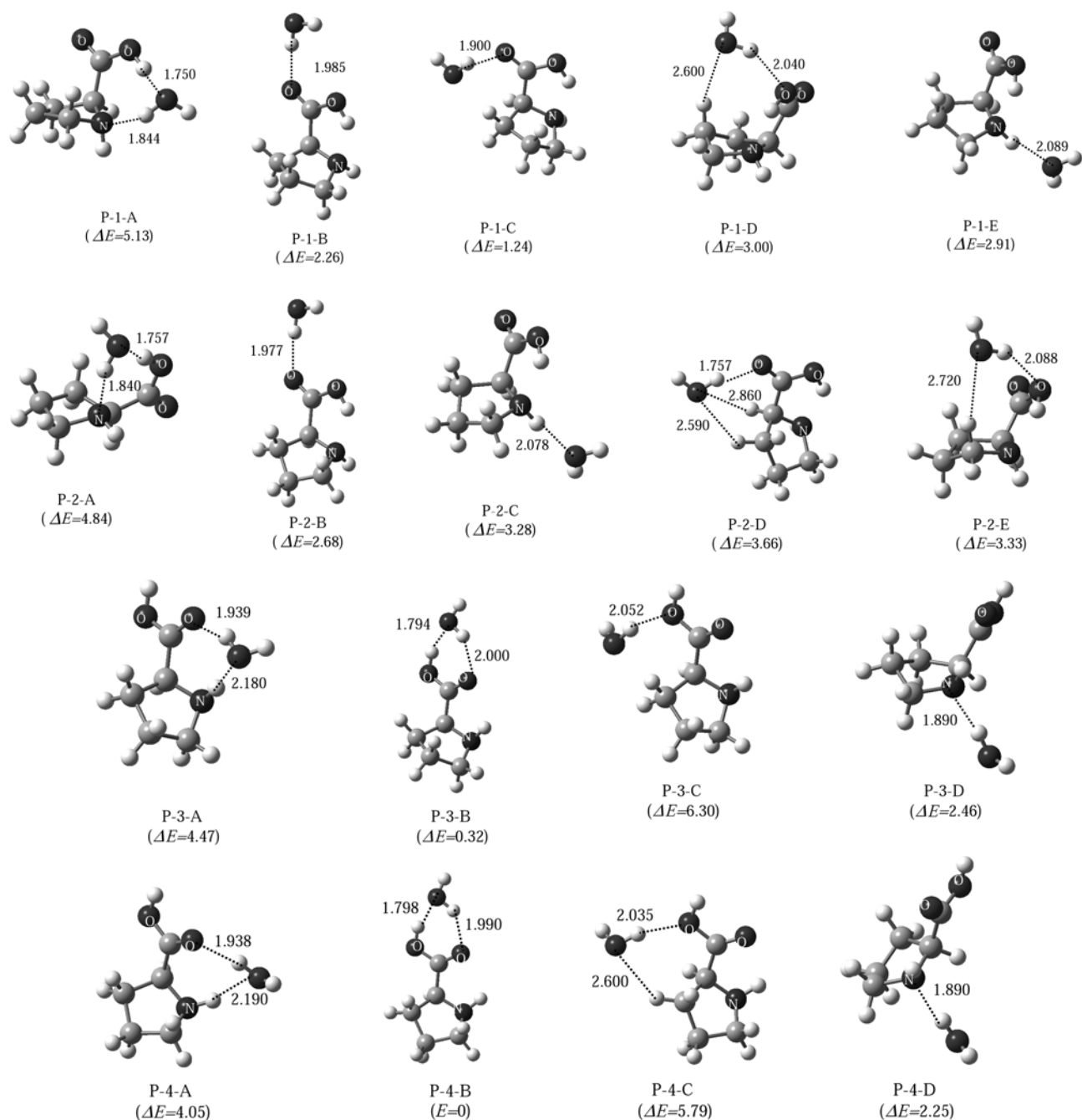

Figure 2. Calculated structures and relative energies (kcal/mol) of proline − (H₂O) cluster (hydrogen bond lengths in Å).

Table 2. Calculated electronic energies (E), zero-point energies (ZPE), relative energies (ΔE) and dipole moments (μ) of low energy proline – H_2O

	E (Hartree)	ZPE (kcal/mol)	ΔE (kcal/mol)	μ (Debye)	Corresponding bare proline
(P-1-C)	-477.75480^a	106.0^a	1.24^a	4.3^a	(P-1)
(P-2-B)	-477.75203	105.8	2.68	8.9	(P-2)
(P-3-B)	-477.75666	106.3	0.32	0.7	(P-3)
(P-4-B)	-477.75682	106.1	0	0.6	(P-4)

[a]B3LYP/6-311++G**

interaction is a bit stronger than O···HN. In other conformers of proline, such an intramolecular hydrogen bonding is not feasible. Table 1 also lists the dipole moments of the conformers, which may be an important property in the formation of dipole-bound anions. It is interesting to note that the dipole moments of the two conformers (P-1) and (P-2) are quite large (close to 6 Debye), whereas those for the other two lower energy conformers (P-3) and (P-4) are too small for experimental observation by dipole binding technique. The zwitterionic conformer of amino acids has never been observed experimentally in the gas phase without the influence of solvent molecules, and we also could not obtain any stable proline zwitterion in the present calculations.

Based on the four lowest energy conformers of bare proline in Figure 1, we calculate the structures of the proline – H_2O clusters by employing the B3LYP/6-311++G** method. We obtain numerous stationary structures as depicted in Figure 2, of which the lowest energy conformers are presented in Table 2. The conformers are labeled in such a way to indicate from which bare proline the conformer is formed (for example, (P-1-A) to (P-1-E) result from adding a water molecule to (P-1)). The water molecule may combine with proline in a number of ways in proline – H_2O clusters. It may interact with the carboxyl OH, carbonyl, amino group, or even with CH in the pyrrolidine ring, acting either as a proton – donor or proton – acceptor. In some conformers, H_2O may bridge the two functional groups as in (P-1-A) or (P-1-D). (P-1-C) is calculated to be of lowest energy of the conformers of proline – H_2O clusters deriving from the bare proline (P-1). In these conformers the H···NH intramolecular bonding remains more or less intact except for (P-1-A) of relatively higher energy, in which the water molecule bridges the OH and NH groups. Similarly, the conformer (P-2-A) with the bridging water molecule is calculated to be higher in energy among the proline – H_2O clusters corresponding to (P-2). No conformers deriving from (P-1) and (P-2) are obtained with the water molecule bridging the carboxyl group (that is, CO and OH). In the proline – H_2O clusters resulting from the interaction of H_2O with the proline conformer (P-3) and (P-4), the water molecule is predicted to bridge the carboxyl group, and these conformers (P-3-B) and (P-4-B) are found to be lower energy conformers.

It is interesting to note that the lowest energy conformer (P-4-B) of the proline – H_2O cluster corresponds to the fourth low-lying conformer of proline (P-4), although it is

Table 3. Calculated stretching frequencies[a] (cm^{-1}) of low energy conformers of proline and proline – H_2O

Conformer	Carbonyl C=O	Carboxyl OH	NH
(P-1)	1832	3394	3563
(P-2)	1834	3424	3558
(P-3)	1801	3758	3524
(P-4)	1801	3757	3548
(P-1-C)	1803	3329	3560
(P-2-C)	1829	3351	3520
(P-3-B)	1756	3401	3520
(P-4-B)	1756	3406	3548

[a]B3LYP/6-311++G**

only 0.32 kcal/mol higher in energy than (P-3-B). This indicates that the energy difference of 1.40 kcal/mol in the bare proline may be easily overcome by interacting with a water molecule in the proline – H_2O cluster. Microsolvation of the proline conformer (P-2) of second lowest energy by a water molecule is predicted to make it quite higher (more than 2.68 kcal/mol) in energy than the lowest energy conformer (P-4-B), again suggesting the significant influence of microsolvation. In the two lowest energy conformers (P-3-B) and (P-4-B), the water molecule bridges the carboxyl group of proline, interacting in a six-membered cyclic fashion. In (P-2-B) and (P-1-C), on the other hand, the water molecule interacts with the carbonyl group. Two conformers (P-3-B) and (P-4-B) are of very similar energy, somewhat distinguished from the other two conformers. Thus it seems that the binding of a water molecule further "splits" the energy of the conformers. The large difference in the dipole moments of (P-1) and (P-2), and of (P-3) and (P-4) are still seen in their complexes with a water molecule. No proline – H_2O cluster is obtained with the zwitterionic proline, indicating that hydrogen bonding with a water molecule is not sufficient to give stable proline zwitterion, as also predicted for other amino acids.[15,18,19]

Table 3 presents the (unscaled) frequencies of the carboxyl OH, carbonyl C=O and NH stretching modes of proline and proline – H_2O that may be useful for assigning the conformers. The C=O stretching frequencies of (P-3) and (P-4) are about 30 cm^{-1} smaller than those of (P-1) and (P-2), and similar trend is also seen for the proline – H_2O cluster. Interactions with a water molecule are predicted to lower the absorbed frequency for this mode. It seems that the carboxyl OH stretching mode is the most useful for distinguishing the conformers of proline and proline – H_2O. The OH frequency

in (P-1) is about 30 cm^{-1} smaller than that in (P-2), whereas those for (P-3) and (P-4) are calculated to be significantly larger. The frequency of (P-1) and (P-2) decrease by about 70 cm^{-1} as the result of microsolvation by H_2O, while those for (P-3) and (P-4) are predicted to decrease by as much as 350 cm^{-1}.

In conclusion, our present results have clearly shown that the water molecule interacting with proline may profoundly affect the relative energies of proline, providing an excellent example of the influence of microsolvation on biomolecules. We hope that the present work would stimulate experimental studies on this interesting system.

References

1. Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161, and references therein.
2. Zwier, T. S. *J. Phys. Chem. A* **2001**, *105*, 8827.
3. Shishkin, O. V.; Sukhanov, O. S.; Gorb, L.; Leszczynski, J. *Phys. Chem. Chem. Phys.* **2002**, *4*, 5359.
4. Robertson, E. G.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1.
5. Scheiner, S.; Kar, T.; Pattanayak, J. *J. Am. Chem. Soc.* **2002**, *124*, 13257.
6. Schutz, M.; Burgi, T.; Leutwyler, S.; Fischer, T. *J. Chem. Phys.* **1993**, *98*, 3763.
7. Ahn, D.-S.; Park, S.-W.; Jeon, I.-S.; Lee, M.-K.; Kim, N.-H.; Han, Y.-H.; Lee, S. *J. Phys. Chem. B* **2003**, *107*, 14109.
8. Bandyopadhyay, P.; Gordon, M. S.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **2002**, *116*, 5023.
9. Tortonda, F. R.; Pascual-Ahuir, J. L.; Silla, E.; Tunon, I. *J. Chem. Phys.* **1998**, *109*, 592.
10. Lee, K. T.; Sung, J.; Lee, K. J.; Kim, S. K., Park, Y. D. *Chem. Phys. Lett.* **2003**, *368*, 262.
11. Xu, S.; Niles, J. M.; Bowen, K. H. *J. Chem. Phys.* **2003**, *119*, 10696.
12. Snoek, L. C.; Kroemer, R. T.; Hockridge, M. R.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1819.
13. Spinor, J.; Sulkes, M. *J. Chem. Phys.* **1993**, *98*, 9389.
14. Park, S.-W.; Ahn, D.-S.; Lee, S. *Chem. Phys. Lett.* **2003**, *371*, 74.
15. Bonaccorsi, R.; Palla, P.; Tomasi, J. *J. Am. Chem. Soc.* **1984**, *106*, 1945.
16. Kassab, E.; Langlet, J.; Evieth, E.; Akacem, Y. *J. Mol. Struct. Theochem.* **2000**, *531*, 267.
17. Jensen, J. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 8159.
18. Ahn, D.-S.; Lee, S. *Bull. Korean Chem. Soc.* **2003**, *24*, 545.
19. Ahn, D.-S.; Lee, S.; Cheong, W. J. *Bull. Korean Chem. Soc.* **2004**, *25*, 1161.
20. Kang, Y. K. *J. Phys. Chem. B* **2004**, *108*, 5463.
21. Momany, F. A.; McGuire, R. F.; Burgess, A. W.; Scheraga, H. A. *J. Phys. Chem.* **1975**, *79*, 2361.
22. Kapota, C.; Lemaire, J.; Maitre, P.; Ohanessian, G. *J. Am. Chem. Soc.* **2004**, *126*, 1836.
23. Lemoff, A. S.; Bush, M. F.; Williams, E. R. *J. Phys. Chem. A* **2005**, *109*, 1903.
24. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 2003.
25. Czinki, E.; Csaszar, A. G. *Chem. Eur. J.* **2003**, *9*, 1008.