Quasidegeneracy of Zwitterionic and Canonical Tautomers of Arginine Solvated by an Excess Electron

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The zwitterionic tautomers of isolated amino acids have not been identified in the gas-phase despite serious experimental efforts.[1,2] The main reason is that a typical OH bond is stronger than a NH bond by ca. 17 kcal/mol,[3] and thus the canonical tautomer is lower in energy. Indeed, numerous ab initio calculations have confirmed the energy preference for canonical tautomers $H_2N-CHR-COOH$ in the gas phase.[4−6] Because zwitterion formation is important for the structure and function of peptides and proteins, and zwitterions are encountered in the structure of turns and bends of RNA,[7] it is important to know when such species can be more stable than their canonical tautomers. In the present communication, we suggest a new means of preferentially stabilizing zwitterion structures, and we illustrate it for arginine.

New experimental efforts have concentrated on complexes of amino acids with neutral or ionic species.[8−11] Recently we suggested an alternative pathway to stabilize a zwitterion structure through "solvation" of an amino acid by an excess electron.[12] For example, we demonstrated that the instability of the zwitterion structure of glycine relative to its canonical structure is reduced by 8 kcal/mol upon attachment of an excess electron, and we found that a local minimum develops on the anionic potential energy surface. However, the energy at this minimum was still higher than that of the anion derived from the canonical isomer of glycine. We also studied electron attachment to betaine, which is a permanent zwitterion, and we found that the excess electron provides an extra stabilization of 6 kcal/mol relative to its nonionic structure.[13]

In this contribution we focus on arginine, which has the largest proton affinity among all 20 common naturally occurring amino acids.[8] The question of which tautomeric form of *neutral* arginine is dominant in the gas phase has recently been addressed in experimental[1,2] and computational studies.[4−6] These theoretical results favor the canonical form, which was found to be more stable by ca. 3 kcal/mol than the zwitterion. Here, we demonstrate that the *anions* based on the zwitterionic and canonical tautomers of arginine are quasidegenerate, as a result of which we speculate that tautomerization may be facilitated by excess electron attachment. We intend to extend these studies to other biologically important molecules, such as nucleic acid bases and sugars, which also may be involved in damage of cells by high-energy radiation that produces low-energy electrons.[14]

The equilibrium geometries of the neutral and anionic arginine have been optimized at the second-order Møller−Plesset (MP2) perturbation theory level as well as by applying the DFT method with a hybrid B3LYP[15] functional. The latter method was also used to calculate harmonic vibrational frequencies that were used in zero-point vibrational energy corrections. Final energies were determined at the coupled-cluster level with single and double excitations[16] (CCSD) at the MP2 minimum geometries. We used 6-31++G**[15] orbital basis sets supplemented with diffuse functions having low exponents suitable to describe the diffuse charge distribution of the excess electron.[5] All calculations were performed with the GAUSSIAN 98[15] and MOLPRO[17] codes, and three-dimensional plots of molecular orbitals were generated with the MOLDEN program.[18]

The vertical electron detachment energy (D) for the excess electron was first determined at the Koopmans' theorem level (D^{KT}) and then supplemented with orbital relaxation ΔD_{ind}^{SCF} and electron correlation effects determined at the CCSD level. The electron correlation contribution to D was split into the second-order dispersion interaction ΔD_{disp}^{MP2} between the loosely bound electron and the neutral molecule[19] and the remaining higher-order correlation term ΔD^{HO}.

We have examined the anionic states that result from electron attachment to five canonical and three zwitterionic structures of the neutral. These low-energy structures of the neutral were described in our earlier paper.[6] The two most stable anionic species proved to be those resulting from the most stable canonical structure of the neutral (**C5**) and the most stable neutral zwitterion

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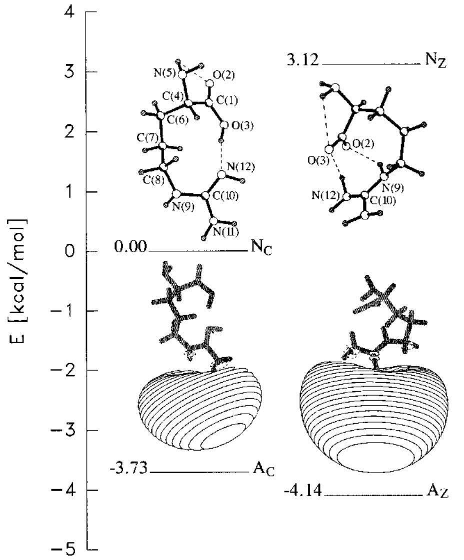

Figure 1. The relative CCSD energies (corrected for zero-point vibrational energies) for the neutral and anionic forms of arginine based on canonical (C) and zwitterionic (Z) structures. Singly occupied orbitals of anionic arginine plotted with a contour spacing of 0.009 Bohr$^{-3/2}$.

(**Z3**) in ref 6. Only these two systems, here labeled **C** and **Z**, respectively, are described in this communication.

The neutral **Z** and **C** structures are able to support a few dipole-bound anionic states because their dipole moments, 9.2 and 7.6 D, respectively, significantly exceed the critical dipole of ~2.5 D required to bind an excess electron.[19] The neutral **C** is characterized by a strong N(12)···HO(3) hydrogen bond with a N(12)···H distance of 1.775 Å, see Figure 1. The neutral **Z** is characterized by two strong hydrogen bonds: O(2)···HN(9) and O(3)···HN(12) with hydrogen−oxygen distances of 1.678 and 1.642 Å, respectively, see Figure 1.

Excess electron attachment leads primarily to geometrical modifications of the hydrogen bonds and to a lesser extent to modifications of valence bonds and angles. The driving force of these modifications is to lower the energy of the dipole-bound anion through enhancement of the dipole moment of the neutral. Indeed, the dipole moment of the neutral increases by 1.0 and 0.8 D for **Z** and **C**, respectively, upon electron attachment. For the **Z** structure, the distance between the proton-accepting O's and proton-donating NH groups *increases* by 0.06−0.08 Å. Clearly, this geometrical relaxation increases the separation between the positive and negative poles of the zwitterionic dipole. For the **C** structure, however, the distance between the proton-accepting N(12) atom and proton-donating O(3)H group *decreases* by 0.07 Å upon electron attachment. One can recognize in this mode of relaxation the first stage of "zwitterionization" of the canonical structure.

The relative stabilities of the neutral and anionic structures, estimated from the electronic CCSD energies corrected for zero-point vibrational energies determined at the B3LYP level, are displayed in Figure 1. The instability of the zwitterionic structure of the neutral of 3.12 kcal/mol is counterbalanced by the excess electron binding energy that is much larger for the zwitterionic than for canonical structure. As a result, the anion derived from the zwitterionic structure **Z** becomes quasidegenarate with that supported by the canonical structure **C**. In fact **Z**$^-$ is more stable by 0.4 kcal/mol than **C**$^-$, but this difference is smaller than the uncertainty of our ab initio calculations.

For both structures, the excess electron is localized on the positive side of molecular dipole, in the vicinity of the guanidine group; see Figure 1. The CCSD values of the electron binding energy D for **Z**$^-$ and **C**$^-$ are significant and amount to 7.5 and 3.2 kcal/mol, respectively, see Table 1. This magnitude of D is more typical for weakly bound valence anions than for experimentally characterized model dipole-bound-anions.[19] As we pointed out, however, the magnitude of D should not be used as an indicator whether an anion is a genuine dipole-bound anion.[20] Simply, the values of D will be significant for molecular systems with large dipole moments, and molecular zwitterions of amino acids and peptides provide excellent examples of such species.

Table 1. Incremental Contributions to Vertical Electron Detachment Energies (D in kcal/mol) for the Zwitterionic (**Z**) and Canonical (C) Anions of Arginine

components of D	Z$^-$	C$^-$
D^{KT}	4.04	1.54
$\Delta D_{\mathrm{ind}}^{\mathrm{SCF}}$	0.73	0.24
$\Delta D_{\mathrm{disp}}^{\mathrm{MP2}}$	2.54	1.27
ΔD^{HO}	0.19	0.10
sum = D^{CCSD}	7.50	3.15

The value of D for the **C** structure is 2.4 times smaller than for the **Z** structure. This difference is related to a larger dipole moment of **Z** and also to a different chemical environment for the excess electron in the **C** and **Z** structures. Indeed, the excess electron in **Z**$^-$ is strongly delocalized as it is attached to the N(11)H$_2$, N(12)H$_2$, and C(8)H$_2$ groups. In **C**$^-$ it is more localized and attached only to the N(11)H$_2$ and N(9)H groups. One also recognizes that the C(10) atom is not valence-saturated for the **Z** structure of the neutral. Therefore, the singly occupied orbital (SOMO) that describes the excess electron in **Z**$^-$ has a small amplitude on the C(10) atom, which is in *bonding* relation with the main lobe of this orbital. This admixture of bonding valence character may stabilize **Z**$^-$ relative to **C**$^-$. On the other hand, in typical dipole-bound anions all atoms of the neutral are valence-saturated, and atom-centered amplitudes in anionic SOMOs are in *antibonding* relations with the main lobe. The case of **Z**$^-$ illustrates that there is no clear border between dipole-bound and valence anions.

The incremental contributions to D for the anions of arginine based on **C** and **Z** are collected in Table 1. D^{KT} represents approximately 50% of D^{CCSD} for both systems. The SCF orbital polarization term $\Delta D_{\mathrm{ind}}^{\mathrm{SCF}}$ does not exceed 10% of D^{CCSD}. The $\Delta D_{\mathrm{disp}}^{\mathrm{MP2}}$ term is the second most important after D^{KT} and represents 34 and 41% of D^{CCSD} for **Z**$^-$ and **C**$^-$, respectively. The higher-order electron correlation contribution ΔD^{HO} does not exceed 0.2 kcal/mol.

In summary, we demonstrated that the 3.1 kcal/mol instability of the zwitterion form of neutral arginine in the gas phase relative to the canonical tautomer could be suppressed by attaching an excess electron. This solvation by an excess electron provides and extra stabilization of 7.3 kcal/mol for the zwitterion structure and only 3.7 kcal/mol for the canonical structure. Hence, the anions based on the zwitterionic and canonical structures become quasidegenerate with their electronic energies differing by less than 0.4 kcal/mol. Higher-order treatment of electron correlation effects and more complete one-electron basis sets may be required to identify the global minimum for the anion. Moreover, thermal effects will contribute to the stability of different anionic tautomers and rotamers. The effect of electron attachment/detachment on tautomerization reactions is currently being investigated.

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