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Density Functional Theory Study of Conformation-Dependent Properties of Neutral and Radical Cationic L-Tyrosine and L-Tryptophan

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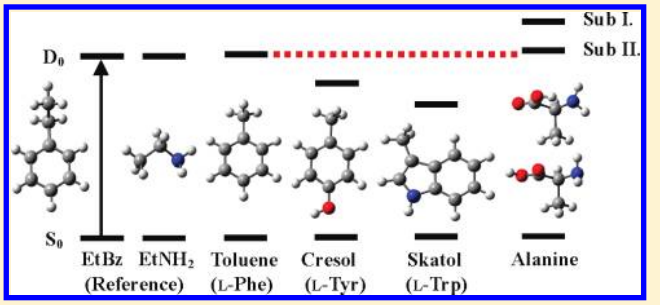
Supporting Information

ABSTRACT: Conformation-dependent properties of L-tyrosine and L-tryptophan in neutral and radical cations were studied by using the density functional theory (DFT) with a new density functional M05-2X. The results are compared with those obtained by using the conventional DFT (B3LYP). Results obtained by both types of DFT were in qualitative accord, including the existence of two conformational subgroups and their subgroup-dependent adiabatic ionization energy and hydrogen bonding. On the other hand, quantitative differences were found between the two DFT methods as well: the M05-2X method successfully reproduced experimental adiabatic ionization energy, whereas the B3LYP functional consistently yielded significantly lower values by 0.2−0.3 eV. More importantly, natural bond orbital (NBO) analysis for cationic conformers showed that all conformers of L-tyrosine and L-tryptophan undergo charge localization upon ionization regardless of the presence of intramolecular hydrogen bonding, unlike the case of L-phenylalanine that was treated earlier by other studies. Different degrees of charge localization among all three aromatic amino acids are explained by employing a simple model in which the aromatic amino acid is assumed to consist of two submoieties of distinct cationic core: the backbone and aromatic side chain. The difference in adiabatic ionization energy between these two submoieties is found to govern the degree of charge localization.



INTRODUCTION

The three aromatic amino acids, L-phenylalanine, L-tyrosine, and L-tryptophan (Figure 1), not only are building blocks of proteins but also play important roles in biochemistry and molecular physiology.[1−7] L-Tyrosine[3,4] and L-tryptophan[5−7] are known to be precursors to neurotransmitters dopamine and serotonin, respectively.

Since aromatic amino acids have high optical absorption cross sections at 250−285 nm in the ultraviolet region,[8] spectroscopic studies of these amino acids have been used as optical probes for structures and dynamics of proteins.[9] Aromatic amino acids have also been utilized as a trigger to charge transfer dynamics of polypeptides.[10−12]

Since the pioneering work by Levy's group,[13−16] a considerable number of studies have been carried out on neutral aromatic amino acids and their radical cations under isolated conditions by experiment (mostly using laser spectroscopy)[4,17−31] and theory.[19,21−26,28−38]

Unlike the radical cation of L-phenylalanine,[33,34,38] those of L-tyrosine and L-tryptophan remain largely unexplored. Theoretical investigation of the cationic structures and properties of these two aromatic amino acids and their conformational dependency is the main goal of this work, which will address the following issues.

First, we propose conformational classification for the neutral as well as cationic form of L-tyrosine and L-tryptophan with a new density functional, M05-2X, which was employed in our previous work for L-phenylalanine.[33] The validity of the new density functional has been discussed by Zhao and Truhlar.[39−42]

By comparison, all conformers of L-phenylalanine belong to one of the two distinct subgroups depending on the directionality of their intramolecular hydrogen bonding in the backbone: subgroup I characterized by $-COOH \rightarrow -NH_2$ vs subgroup II by $-NH_2 \rightarrow -OCOH$.[19] Conformers that belong to a given subgroup share the same characteristic features in the *cationic*

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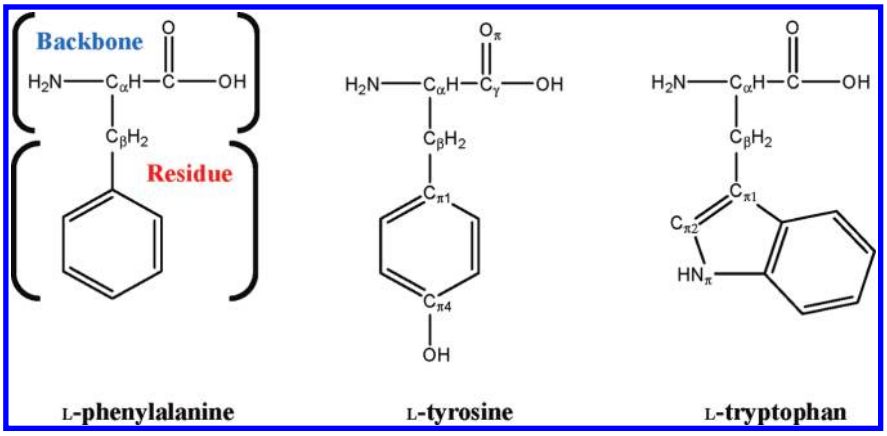

Figure 1. Three aromatic amino acids for L-phenylalanine, L-tyrosine, and L-tryptophan. They can be divided into two substructures, backbone of α-amino acid like alanine and aromatic residue like toluene, cresol, and skatol.

ground state, such as the amino group geometry being pyramidal or planar, the $C_\alpha-C_\beta$ bond length being normal or elongated, and the cationic charge localized in one region or doubly localized at two sites, all depending on the subgroup designation of a given conformer. A theoretical support for these findings has been recently given on the basis of DFT (M05-2X) calculations.[33]

Second, we investigate the differences in structure and charge distribution between the subgroups of L-tyrosine and L-tryptophan. We also attempt to explain theoretically the different trend of charge distribution among the three aromatic amino acids by using the ab initio MO method[43] and DFT method at the M05-2X level of theory[40,42] taking into account the effect of noncovalent, long-range potential. The latter proved to yield significantly more reliable results for the conformational structure and ionization energy of the radical cation than the conventional DFT (B3LYP)[44−46] parametrization.

COMPUTATIONAL DETAIL

All of the calculations in this work were carried out using Gaussian 09 Rev. A02 software package[47] to employ the DFT (M05-2X)[40,42] and DFT (B3LYP)[44−46] methods.

The geometries of neutral conformers of L-tyrosine and L-tryptophan in the ground state were optimized at the M05-2X level with the 6-311+G* basis set, based on the similar conformations of the backbone (alanine) in L-phenylalanine.[33]

The 18 most stable neutral conformers were obtained for both L-tyrosine and L-tryptophan by considering the orientation of the phenolic −OH group for L-tyrosine and the asymmetry of the indole ring for L-tryptophan.

We also carried out geometry optimization for each conformer of L-tyrosine and L-tryptophan radical cation in the ground state at unrestricted M05-2X level with the 6-311+G* basis set by setting the charge and the spin multiplicity to +1 and 2, respectively. We have examined the expectation values of the square of the total electron spin $\langle S^2\rangle$ in order to check the spin contamination of cationic wave functions. The values of $\langle S^2\rangle$ calculated by unrestricted M05-2X (B3LYP) were approximately 0.750 (0.750) for all cationic L-tyrosine and L-tryptophan conformers. The detailed values of $\langle S^2\rangle$ are listed in the Supporting Information. The results confirm the validity of the doublet wave function used in this paper. Charge distributions of cations were obtained using DHDS NBO procedure, in which α and β spin density matrices are separately treated according to the method of "different hybrids for different spins".

RESULTS AND DISCUSSION

A. Geometrical Structures for Neutral and Cationic Conformers of L-Tyrosine and L-Tryptophan. Of the nine most stable conformers predicted for neutral L-phenylalanine,[19,26,28,33−36] six of them (A−E and X) were experimentally identified under a jet-cooled condition.[19,26,28] For L-tyrosine, eight band origins (4−7, 14−17) were observed,[30] while for L-tryptophan, six conformers (A−F) have been experimentally identified.[22]

A-1. L-Tyrosine. Figure 2 shows only the eight valid neutral conformers of L-tyrosine and their corresponding cations among the 18 optimized structures obtained by DFT (M05-2X). The others are listed in the Supporting Information. For subgroup II conformers, the cationic structures obtained by the popular DFT (B3LYP) are different from those from DFT (M05-2X) and shown in parentheses.

A comparison of DFT (M05-2X) and DFT (B3LYP) calculations is shown in Table 1, which lists the dihedral angles $C_{\pi1}-C_\beta-C_\alpha-N$, $C_\alpha-NH_2$, and $O_\pi-C_\gamma-C_\alpha-N$ and the bond lengths $C_\alpha-C_\beta$, $C_\beta-C_{\pi1}$, $C_\alpha-N$, and $C_{\pi4}-O$. The two functionals, M05-2X and B3LYP, yielded nearly the same results with regard to the neutral structure, but the radical cations of subgroup II obtain different conformational structures depending on the functional used. This is mainly due to the effect of long-range noncovalent interactions, which is properly accounted for in the M05-2X functional but not in the B3LYP results.[39−42] It should be noted in Table 1 that L-tyrosine conformers of subgroup II show no drastic change in geometry upon ionization, such as $C_\alpha-C_\beta$ elongation and planarity of the $C_\alpha-NH_2$ as seen in the subgroup II conformers of L-phenylalanine.[33,38]

The neutral species shown in Figure2 are identical to those reported by Ebata and co-workers.[30] The subgroup classification for L-tyrosine in Figure 2 is based on the directionality of the intramolecular hydrogen bonding, as in the case of L-phenylalanine: $-COOH\rightarrow-NH_2$ for subgroup I and $-NH_2\rightarrow-OCOH$ for subgroup II. For L-tyrosine, however, there are two different, nearly iso energetic, orientations of the phenolic −OH group, which are denoted by subscript r (right) or l (left) in Figure 2. Roman numerals (I, II, III, and VII) were adopted from L-phenylalanine labels[33]

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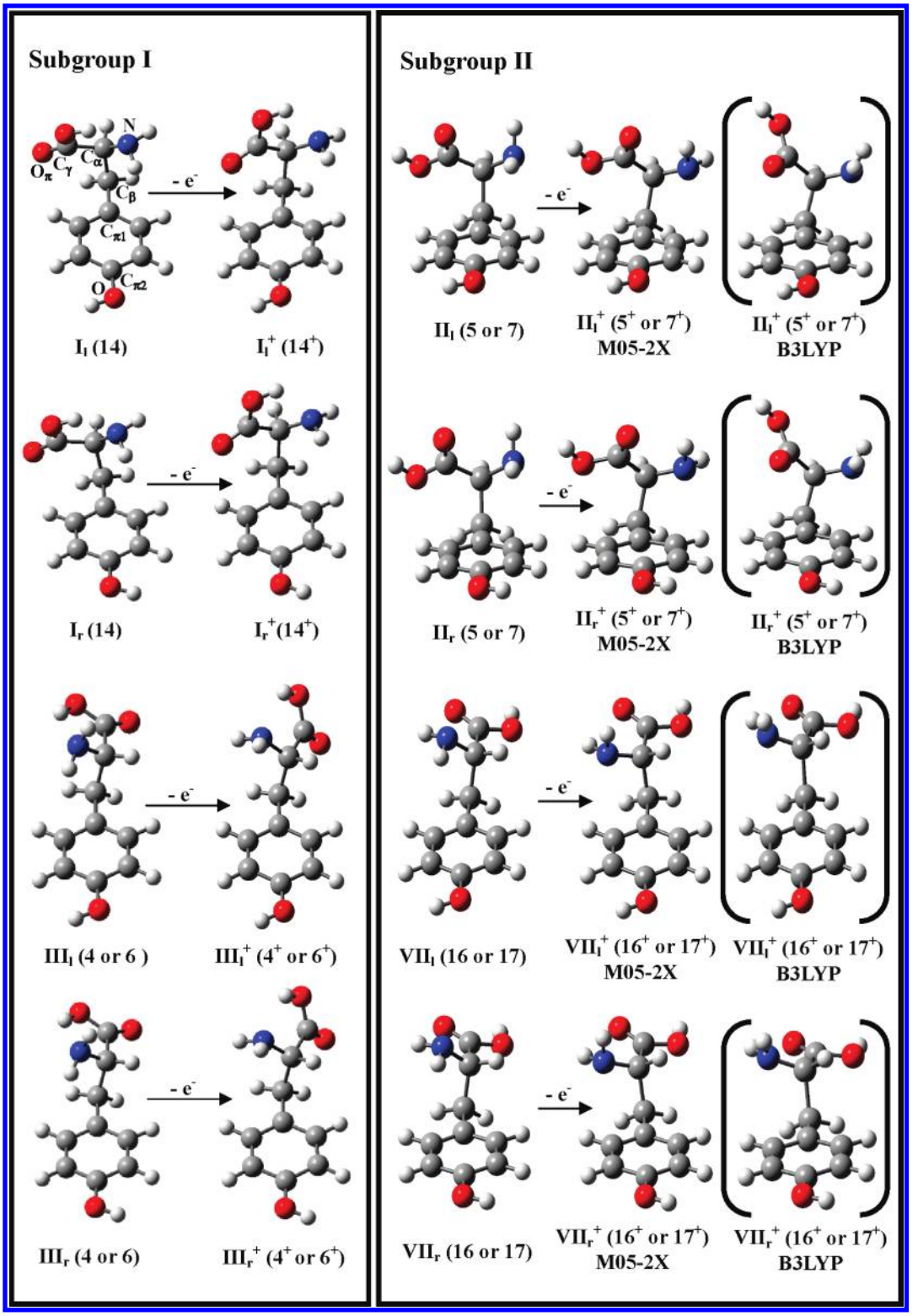

Figure 2. The eight stable structures of representative L-tyrosine conformers in neutrals and cations. All structures were determined at the M05-2X/6-311+G* level of theory. Roman numerals represent the conformers and subscripts l, r indicate orientation of phenolic −OH group. The Numerals in parentheses represent the order of band origins observed by Ebata's group.[30] The cationic conformers are listed on the right-hand side. Conformers belonging subgroup II (II_l, II_r, VII_l, and VII_r) in cations gave different structures between M05-2X and B3LYP. They are marked as M05-2X and B3LYP, respectively. The others lead to almost the same conformers regardless of the methods used.

because of the similarity between L-tyrosine and L-phenylalanine, with the −OH group in L-tyrosine being the major difference.

Ebata and co-workers observed eight origin bands (4, 5, 6, 7, 14, 15, 16, and 17) in their fluorescence excitation spectra[30] and

Table 1. Molecular Constants for Eight L-Tyrosine Conformers in Neutrals and Those for Cations in Parentheses[a]

			dihedral angle (deg)			bond length (Å)			
subgroup	origin bands[b]	conformer	$C_{\pi 1}-C_\beta-C_\alpha-N$	$C_\alpha-NH_2$	$O_\pi-C_\gamma-C_\alpha-N$	$C_\alpha-C_\beta$	$C_\beta-C_{\pi 1}$	$C_\alpha-N$	$C_{\pi 4}-O$
			(a) M05-2X, neutral (cation)						
I	14	I_l	52 (70)	123 (132)	−169 (−150)	1.54 (1.56)	1.51 (1.48)	1.46 (1.44)	1.36 (1.31)
I	14	I_r	51 (68)	123 (132)	−169 (−151)	1.54 (1.56)	1.51 (1.48)	1.46 (1.44)	1.36 (1.31)
I	4 or 6	III_l	−63 (−80)	122 (132)	163 (−161)	1.54 (1.56)	1.51 (1.47)	1.46 (1.44)	1.36 (1.31)
I	4 or 6	III_r	−63 (−82)	122 (132)	163 (−162)	1.54 (1.56)	1.51 (1.47)	1.46 (1.44)	1.36 (1.31)
II	5 or 7	II_l	62 (66)	119 (125)	−1 (**0**)	1.54 (1.57)	1.51 (1.48)	1.45 (1.44)	1.36 (1.31)
II	5 or 7	II_r	62 (67)	119 (124)	0 (**0**)	1.54 (1.57)	1.51 (1.48)	1.45 (1.44)	1.36 (1.31)
II	16 or 17	VII_l	−60 (−63)	122 (**120**)	−30 (−12)	1.55 (**1.56**)	1.50 (1.48)	1.45 (1.45)	1.36 (1.31)
II	16 or 17	VII_r	−60 (−65)	122 (**121**)	−30 (−12)	1.55 (**1.56**)	1.50 (1.48)	1.45 (1.44)	1.36 (1.31)
			(b)B3LYP, neutral (cation)						
I	14	I_l	53 (75)	123 (135)	−170 (−150)	1.55 (1.59)	1.51 (1.49)	1.47 (1.44)	1.37 (1.32)
I	14	I_r	52 (69)	123 (135)	−170 (−154)	1.55 (1.59)	1.51 (1.48)	1.47 (1.44)	1.37 (1.32)
I	4 or 6	III_l	−64 (−84)	122 (136)	165 (−162)	1.55 (1.58)	1.51 (1.48)	1.47 (1.43)	1.37 (1.32)
I	4 or 6	III_r	−64 (−85)	122 (136)	165 (−162)	1.55 (1.58)	1.51 (1.48)	1.47 (1.43)	1.37 (1.32)
II	5 or 7	II_l	62 (62)	120 (131)	−4 (**−86**)	1.55 (1.57)	1.51 (1.49)	1.45 (1.44)	1.37 (1.32)
II	5 or 7	II_r	62 (63)	120 (130)	−4 (**−81**)	1.55 (1.57)	1.51 (1.49)	1.45 (1.44)	1.37 (1.32)
II	16 or 17	VII_l	−61 (−73)	122 (**140**)	−32 (−17)	1.57 (**1.64**)	1.51 (1.47)	1.45 (1.41)	1.37 (1.32)
II	16 or 17	VII_r	−61 (−72)	122 (**143**)	−32 (−18)	1.57 (**1.64**)	1.51 (1.47)	1.45 (1.41)	1.37 (1.33)

[a] These were evaluated at the optimized geometries shown in Figure 2. (a) Results obtained by M05-2X; (b) results obtained by B3LYP. Values that are considerably different between these two funcionals are written in boldface. [b] The numbers display ordering of band origin (S_0-S_1) in experiment (ref 30).

Table 2. Relative Energies (in kcal/mol) of Eight Stable L-Tyrosine Conformers in the Neutral (Cationic) Ground State Calculated by M05-2X and B3LYP with a 6-311+G* Basis Set Including Zero-Point Energy Correction

			neutral[b]		cation	
subgroup	origin bands[a]	conformer	M05-2X	B3LYP	M052X	B3LYP
I	14	I_l	0.00 (1)	0.00 (1)	4.60	4.69
I	14	I_r	0.32 (2)	0.35 (4)	5.53	5.51
I	4 or 6	III_l	1.05 (6)	0.13 (3)	8.70	5.56
I	4 or 6	III_r	0.82 (5)	0.11 (2)	8.45	5.37
II	5 or 7	II_l	0.56 (3)	0.91 (8)	0.18	0.00
II	5 or 7	II_r	0.66 (4)	0.90 (7)	0.00	0.38
II	16 or 17	VII_l	1.86 (13)	1.15 (9)	0.98	0.18
II	16 or 17	VII_r	1.65 (11)	1.15 (10)	1.30	0.04

[a] The numbers display ordering of band origin (S_0-S_1) in experiment from ref 30. [b] The numbers in parentheses indicate the relative energy ordering, which depends on respective theoretical methods.

proposed that pairs of 4 and 6, 5 and 7, 16, and 17 correspond to two rotational isomers arising from the different orientations of phenolic −OH. Table 2 shows relative energies of L-tyrosine conformers in neutrals (cations), which were calculated by using M05-2X and conventional B3LYP methods. Here, zero point energy corrections (ZPE_{corr}) were taken into account. According to the results in Table 2, these sets of rotational conformers are no different energetically.

A-2. L-tryptophan. Figure 3 shows the geometrical structures of L-tryptophan for the most six valid neutral conformers and five cationic ones in their ground states. The others are listed in the Supporting Information. The structures were calculated by using M05-2X optimization with the 6-311+G* basis set and they were tentatively classified into two subgroups, I (I, III) and II (II, V), as for L-phenylalanine.[33]

It has already been understood qualitatively that each subgroup for L-phenylalanine has two different types of intramolecular hydrogen bonding.[19] The two functionals, M05-2X and B3LYP, gave almost the same results regarding geometrical structures for L-tryptophan in neutral and cation.

The neutral conformers of six alphabetic capital letters, A, B, C, D, E, and F in Figure 3 were quoted from ref 22 in which their assignment was carried out using mass-selected resonant two-photon ionization (MS-R2PI) spectra, UV−UV hole-burn spectra, and IR−UV ion dip spectra together with predictions by ab initio MO calculations employing B3LYP.

The four Roman numerals, I, II, III, and V, were adopted from our previous work[33] on L-phenylalanine for similarity of the backbone, that is, orientation of backbone (alanine) in L-tryptophan and L-phenylalanine are almost the same. Subscripts a and b represent different orientations of the residue (indole ring) because of asymmetry in L-tryptophan.

In Figure 3, M05-2X results show that cationic structures of conformer I_a belonging to subgroup I are similar to that of L-phenylalanine, in other words, geometry of the backbone (alanine) in L-tryptophan is almost same as that of L-phenylalanine, while conformer III_a in radical cations is quite different from that of L-phenylalanine.

Table 3 shows the molecular constants for six conformers of L-tryptophan in the neutral and radical cationic ground states. Both the M05-2X and B3LYP results have the similar tendency in their molecular constants. Furthermore, there exist no significant differences in the molecular constants between subgroups I and II.

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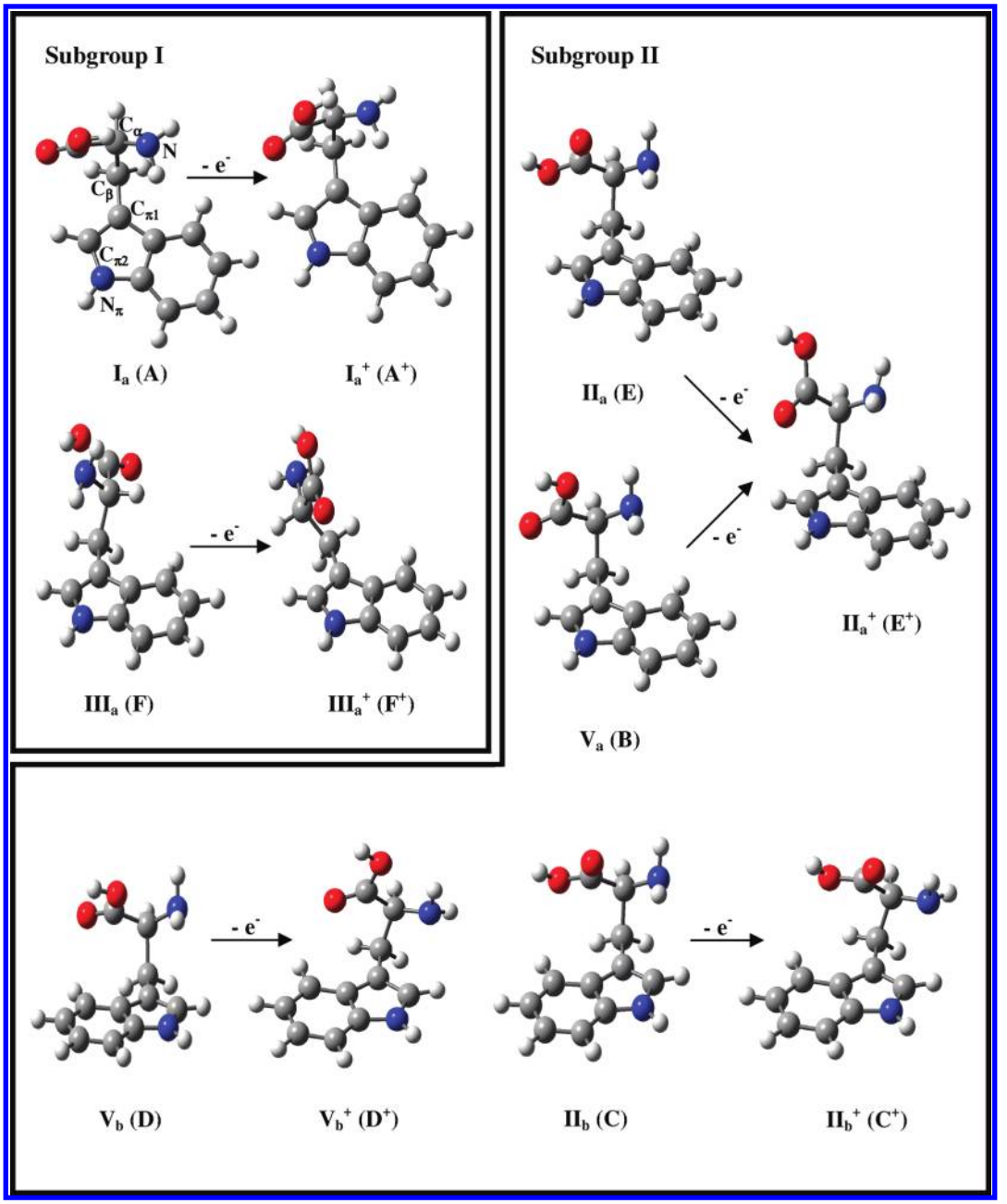

Figure 3. The six stable structures of representative L-tryptophan conformers in neutrals and cations. All structures were determined at M05-2X/6-311+G* level of theory. Alphabetic capital letters in parentheses represent the conformers observed experimentally and subscripts a, b were adopted from ref 22. Roman numerals represent the structure of the stable conformers. The six neutral conformers converged at five optimized cationic structures on the right-hand side.

Cationic L-tryptophan conformers belonging to subgroup II have neither $C_\alpha-C_\beta$ elongation nor planarity of $C_\alpha-NH_2$, which is different from cationic conformers belonging to subgroup II of L-phenylalanine.

Table 4 shows relative energies of L-tryptophan conformers in neutrals (cations), which were calculated by using M05-2X and conventional B3LYP method. Here, zero point energy corrections (ZPE_{corr}) were taken into account. The M05-2X functional gave more reasonable candidates corresponding to observed conformers in L-tryptophan than the B3LYP based on order of relative energies. As mentioned above, there exist two types of hydrogen bonding in L-tryptophan based on their structures and frequency analysis and then conformer I_a and III_a, which belong to subgroup I and which have intramolecular hydrogen bonding ($-COOH \rightarrow -NH_2$), should be candidates for observed conformers A and F, conformer II_a, II_b, V_a, and V_b, which belong to subgroup II and which have free $-OH$, should correspond to conformers E, C, B, and D, which were observed by Simons and co-workers in ref 22. In this work, results from newly employed M05-2X for L-tryptophan in neutral provides the validity to show good agreement with assignments by Simon and co-workers.

B. Comparison of Ionization Energies and Charge Distributions between Aromatic Amino Acids. In this subsection, the calculated results of adiabatic ionization energies and charge

Table 3. Molecular Constants for Six L-Tryptophan Conformers in Neutrals and Those for Cations in Parentheses[a]

			dihedral angle (deg)		bond length (Å)			
subgroup	experiment assignment[b]	conformer	$C_{\pi 1}-C_\beta-C_\alpha-N$	$C_\alpha-NH_2$	$C_\alpha-C_\beta$	$C_{\pi 1}-C_{\pi 2}$	$C_\alpha-N$	$C_{\pi 2}-N_\pi$
			(a) M05-2X, neutral (cation)					
I	A	I_a	55 (68)	122 (130)	1.53 (1.56)	1.37 (1.44)	1.46 (1.45)	1.37 (1.32)
I	F	III_a	−62 (172)	121 (128)	1.54 (1.54)	1.37 (1.43)	1.46 (1.45)	1.38 (1.32)
II	E	II_a	65 (58)	119 (123)	1.54 (1.54)	1.37 (1.43)	1.45 (1.45)	1.38 (1.32)
II	C	II_b	63 (63)	119 (122)	1.54 (1.55)	1.37 (1.43)	1.45 (1.45)	1.38 (1.32)
II	B	V_a	63 (58)	121 (123)	1.54 (1.54)	1.37 (1.43)	1.45 (1.45)	1.38 (1.32)
II	D	V_b	60 (59)	120 (120)	1.54 (1.54)	1.37 (1.43)	1.45 (1.46)	1.38 (1.32)
			(b) B3LYP, neutral (cation)					
I	A	I_a	55 (72)	123 (131)	1.55 (1.57)	1.37 (1.43)	1.47 (1.45)	1.38 (1.33)
I	F	III_a	−62 (171)	121 (129)	1.55 (1.55)	1.37 (1.43)	1.47 (1.45)	1.38 (1.33)
II	E	II_a	65 (58)	120 (126)	1.55 (1.56)	1.37 (1.43)	1.45 (1.45)	1.38 (1.33)
II	C	II_b	64 (63)	119 (122)	1.55 (1.56)	1.37 (1.43)	1.45 (1.46)	1.38 (1.33)
II	B	V_a	64 (58)	121 (126)	1.55 (1.56)	1.37 (1.43)	1.46 (1.45)	1.38 (1.33)
II	D	V_b	60 (59)	121 (120)	1.55 (1.55)	1.37 (1.43)	1.45 (1.47)	1.38 (1.33)

[a] These were evaluated at the optimized geometries shown in Figure 3. (a) Results obtained by M05−2X; (b) results obtained by B3LYP. There is no considerably difference between these two functionals. [b] These experimental assignments are cited from ref 22.

Table 4. Relative Energies (in kcal/mol) of Six Stable L-Tryptophan Conformers in the Neutral (Cationic) Ground State Calculated by M05-2X and B3LYP with a 6-311+G* Basis Set Including Zero-Point Energy Correction

			neutral[b]		cation	
subgroup	experiment assignments[a]	conformers	M05-2X	B3LYP	M052X	B3LYP
I	A	I_a	0.00 (1)	0.00 (1)	4.14	4.12
I	F	III_a	1.39 (3)	0.13 (2)	4.36	2.55
II	E	II_a	1.32 (2)	0.91 (7)	0.00	0.00
II	C	II_b	1.66 (4)	0.90 (10)	0.26	0.98
II	B	V_a	1.83 (5)	1.15 (13)	0.00	0.00
II	D	V_b	2.11 (9)	1.15 (14)	0.23	0.94

[a] These experimental assignments are cited from ref 22. [b] The numbers in parentheses indicate the relative energy ordering. It should be noted that the ordering depends on the theoretical methods used.

distributions in radical cations for both L-tyrosine and L-tryptophan are presented. An important role of their aromatic residue on ionization energy and charge distribution is discussed.

B-1. Adiabatic Ionization Energies. Figure 4 shows the calculated adiabatic ionization energies for L-tyrosine in the middle and those for L-tryptophan at the bottom. For comparison, in the upper part, adiabatic ionization energies for L-phenylalanine are also shown from ref 33. Here, zero-point energy corrections were taken into account. The adiabatic ionization energies calculated by DFT (M05-2X) are higher than those calculated by DFT (B3LYP) for all of the conformers by nearly 0.4 eV.

It can be seen from Figure 4 that adiabatic ionization energies for all of the conformers of both L-tyrosine and L-tryptophan can be classified into two groups depending on subgroups I and II as those for L-phenylalanine: adiabatic ionization energies for the subgroup I conformers are higher than those for the subgroup II conformers. The energy difference between subgroup I and subgroup II becomes small, i.e., 0.29, 0.21, and 0.19 eV, as aromatic amino acid is replaced from L-phenylalanine to L-tyrosine and L-tryptophan. Experimental values of adiabatic ionization energy are also shown in Figure 4. The adiabatic ionization energies of subgroup II (II and VII) conformers of L-tyrosine, which were calculated by DFT (M05-2X), reproduces those observed by photoelectron spectroscopy on L-tyrosine,[48] whereas for conformer I and III belonging to subgroup I, their adiabatic ionization energies reproduce the experimental value of cresol.[49]

For L-tryptophan, the M05-2X adiabatic ionization energies of the subgroup I conformers, I_a (A) and III_a (F), are close to that of skatol at the bottom of Figure 4. The adiabatic ionization energies of the subgroup II conformers, II_a (E), II_b (C), V_a (B), and V_b (D), are close to that of L-tryptophan and their energy differences are within 0.1 eV.[27]

In Figure 5, toluene, cresol, and skatol are employed as representative aromatic residue chromophores for L-phenylalanine, L-tyrosine, and L-tryptophan, respectively. Alanine is the backbone common to all of the three aromatic amino acids, and the experimental values of their ionization energies were 8.88, 8.82, 8.35, and 7.51 eV for alanine,[48] toluene,[49] cresol,[50] and skatol,[51] respectively. The ionization energies predicted by M05-2X (B3LYP) with the 6-311+G* basis set are 8.74 (8.59), 8.12 (7.95), and 7.53 (7.31) eV for toluene, cresol, and skatol, and 9.36 (9.07), 8.94 (8.70) eV for alanine belonging to subgroups

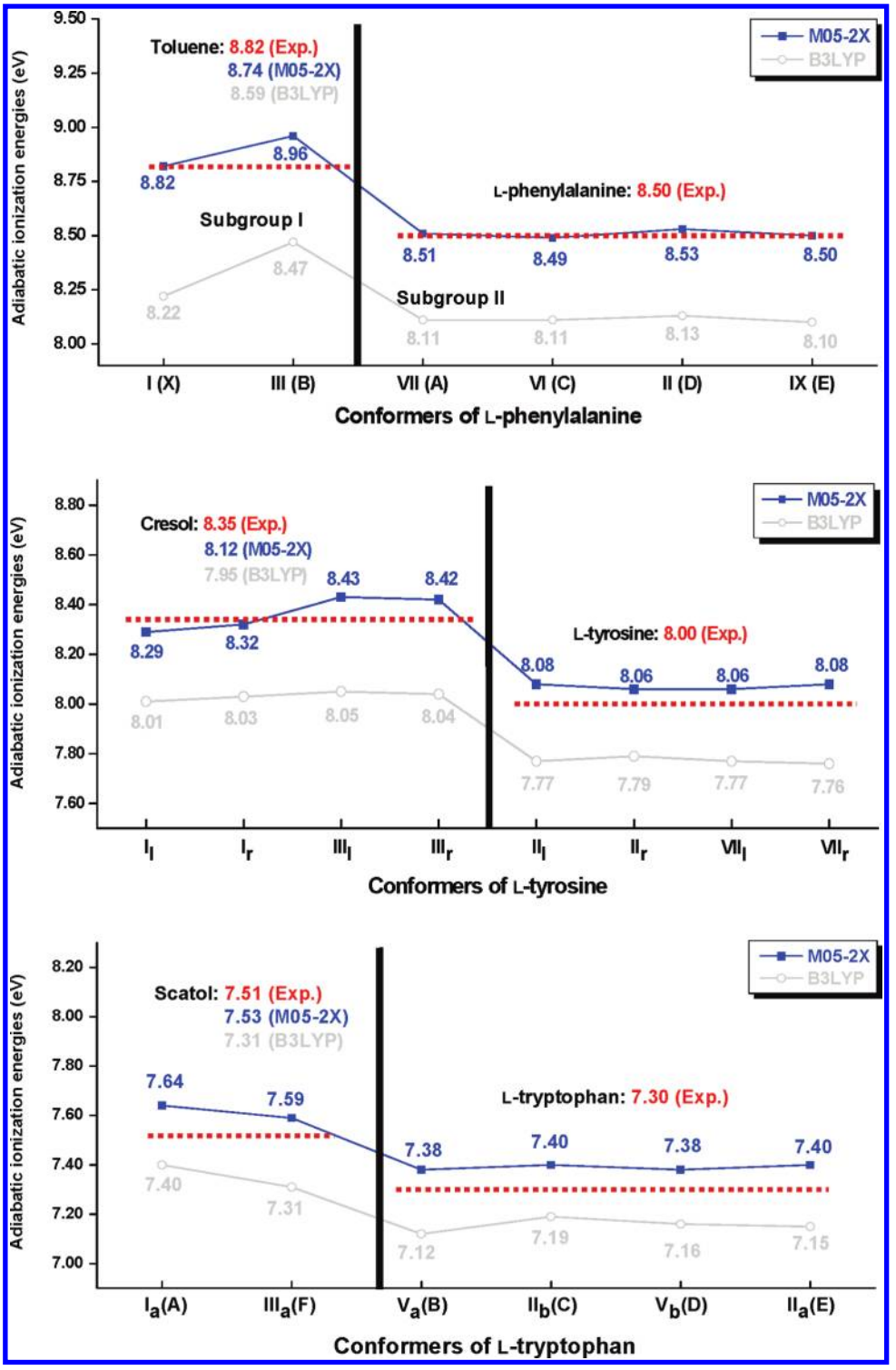

Figure 4. M05-2X and B3LYP results for adiabatic ionization energies of the six stable conformers in L-phenylalanine (upper), eight stable conformers in L-trysosine (middle), and six stable conformers in L-tryptophan (lower). Zero-point energy corrections are included. Experimental values are also shown for comparison. Adiabatic ionization energies of aromatic residues are shown. The dotted lines in subgroup II denote adiabatic ionization values obtained by phtoionization mass spectroscopic measurement of mixed conformers for L-phenylalanine and L-tryptophan,[27] respectively. For L-tyrosine, they were obtained by using photoelectron spectroscopy.[52] The other dotted lines in subgroup I correspond to photoelectron spectroscopic adiabatic ones of aromatic residues (toluene,[49] cresol,[50] and skatol[51]) of L-phenylalanine, L-tyrosine, and L-tryptophan, respectively.

I and II, respectively. A typical molecule for charge doubly localization (division) upon ionization is 2-phenylethylamine, analogue of phenylalanine, which is supposed to be formed by ethylbenzene as a residue and ethylamine as a backbone in Figure 5. They have almost the same ionization energy (8.77 eV for ethylbenzene, 8.80 eV for ethylamine) in experiment according to ref 52.

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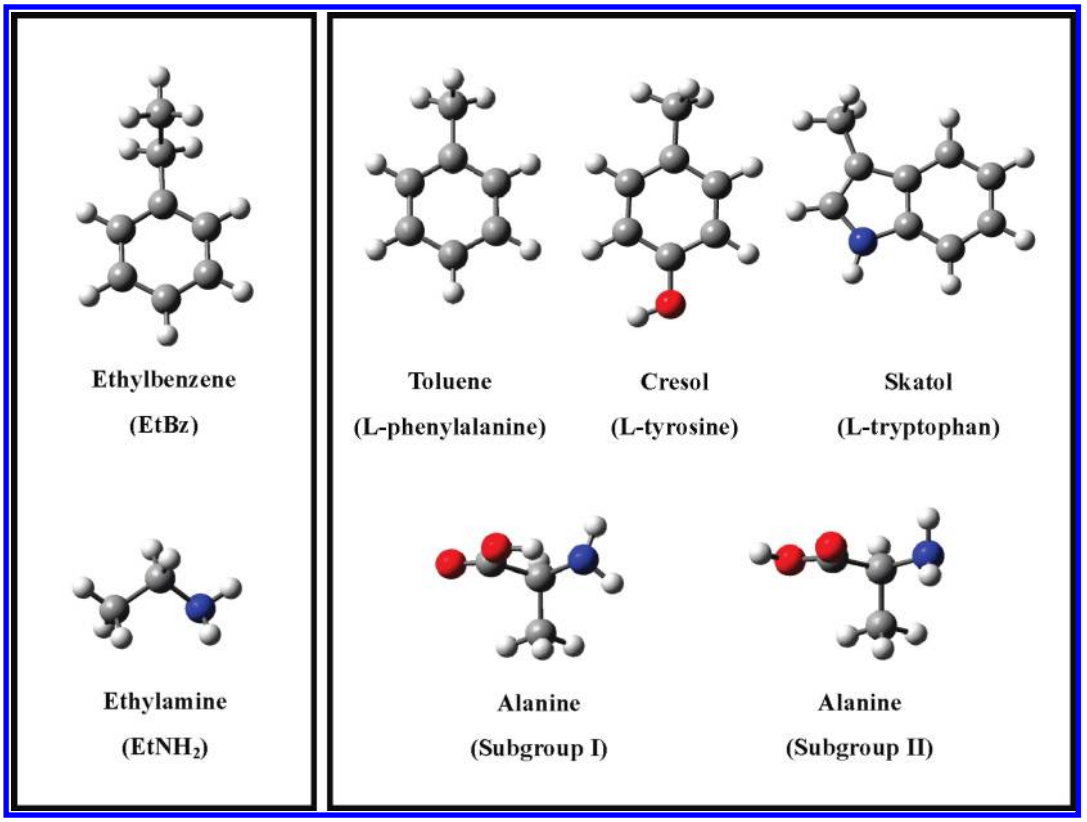

Figure 5. Several chromphores for explanation of charge distribution of aromatic amino acids. Ethylbenzene and ethylamine were adopted from ref 52 as reference molecules having chromophore whose ionization energies are the same. Toluene, cresol, and skatol take the place of aromatic residues for L-phenylalanine, L-tyrosine, and L-tryptophan, respectively. Subgroups (I and II) for alanine correspond to the backbone for the three aromatic amino acids.

Only both toluene and alanine have almost same observed ionization energy. Photoelectron spectroscopic values of skatol (7.51 eV)[51] and L-tryptophan (7.30 eV)[27] are plotted in the bottom of Figure 4. Both the M05-2X and B3LYP values of adiabatic ionization energy for skatol are also plotted to estimate a possible error in their calculations.

Figure 6 shows a qualitative explanation for the calculated adiabatic ionization energies of each aromatic amino acid based on a simple molecular orbital picture. Figure 6a shows the ionization of three aromatic amino acids belonging to subgroup I. In this case, ionization takes place from the π-HOMO of the aromatic residue of each amino acid because nonbonding MO of the residue is stabilized by formation of intramolecular hydrogen bonding. Figure 6b shows the ionization of the aromatic amino acids belonging to subgroup II. In this case, on the other hand, ionization takes place from the HOMO of aromatic amino acids.

B-2. Charge Distribution in Radical Cations. Results of charge distribution obtained by NBO analysis are given in parts a and b of Table 5 for L-tyrosine and L-tryptophan, respectively. It can be seen from the M05-2X results in Table 5 that their charge of 90% is localized on the residue (phenol and indole) for all of the L-tyrosine and L-tryptophan subgroup II conformers. This makes clear contrast with L-phenylalanine conformers belonging to subgroup II, in which charge is doubly localized (divided) in each phenyl group and amino group with equal weight.[33]

Let us now make a semiquantitative discussion about the charge distribution shown in Table 5 by using a simple two-state model. In Figure 6, the model consists of the HOMO of aromatic residue, ϕ_π, and nitrogen nonbonding MO of the backbone, ϕ_{nN}. The HOMO (MO from which electron is released) of the aromatic amino acid Φ can be expressed by a linear combination of these two MO's as $\Phi = \beta\phi_\pi - \alpha\phi_{nN}$. Here, α and β are coefficients given as

$$\alpha = \{(\Delta\varepsilon^2 + 4\gamma^2)^{1/2} - \Delta\varepsilon\}/[\{(\Delta\varepsilon^2 + 4\gamma^2)^{1/2} - \Delta\varepsilon\}^2 + 4\gamma^2]^{1/2}$$

and

$$\beta = 2|\gamma|/[\{(\Delta\varepsilon^2 + 4\gamma^2)^{1/2} - \Delta\varepsilon\}^2 + 4\gamma^2]^{1/2}$$

Here, $\Delta\varepsilon = \varepsilon_\pi - \varepsilon_{nN}$ and $\gamma = \langle\phi_\pi|\hat{H}|\phi_{nN}\rangle$; γ is the interaction energy between ϕ_π and ϕ_{nN}. $\hat{H}$ is the electonic Hamiltonian of aromatic amino acid at the ground state geometrical structure.

For L-phenylalanine belonging to subgroup II, $|\alpha| = |\beta|$ since both ϕ_π and ϕ_{nN} have the same value of orbital energy and $\Delta\varepsilon = 0$. This means that charge is doubly localized (divided) between the backbone and aromatic residue with equal weight, i.e., $|\alpha|^2 = |\beta|^2$. In this case, γ can be estimated as the ionization energy difference between phenyl (or amino) group and L-phenylalanine. γ was estimated to be 0.32 eV from the experimental ionization energies.

Let us consider charge distribution of L-tyrosine by using the two-state model in Figure 6. We obtained $|\alpha|^2 = 0.11$ and $|\beta|^2 = 0.89$. Here, we adopted $\gamma = 0.32$ eV, which was estimated from L-phenylalanine since the aromatic ring of L-tyrosine has the similar aromatic ring as that of L-phenylalanine. We note from comparison of geometrical structures between L-tyrosine and L-phenylalanine

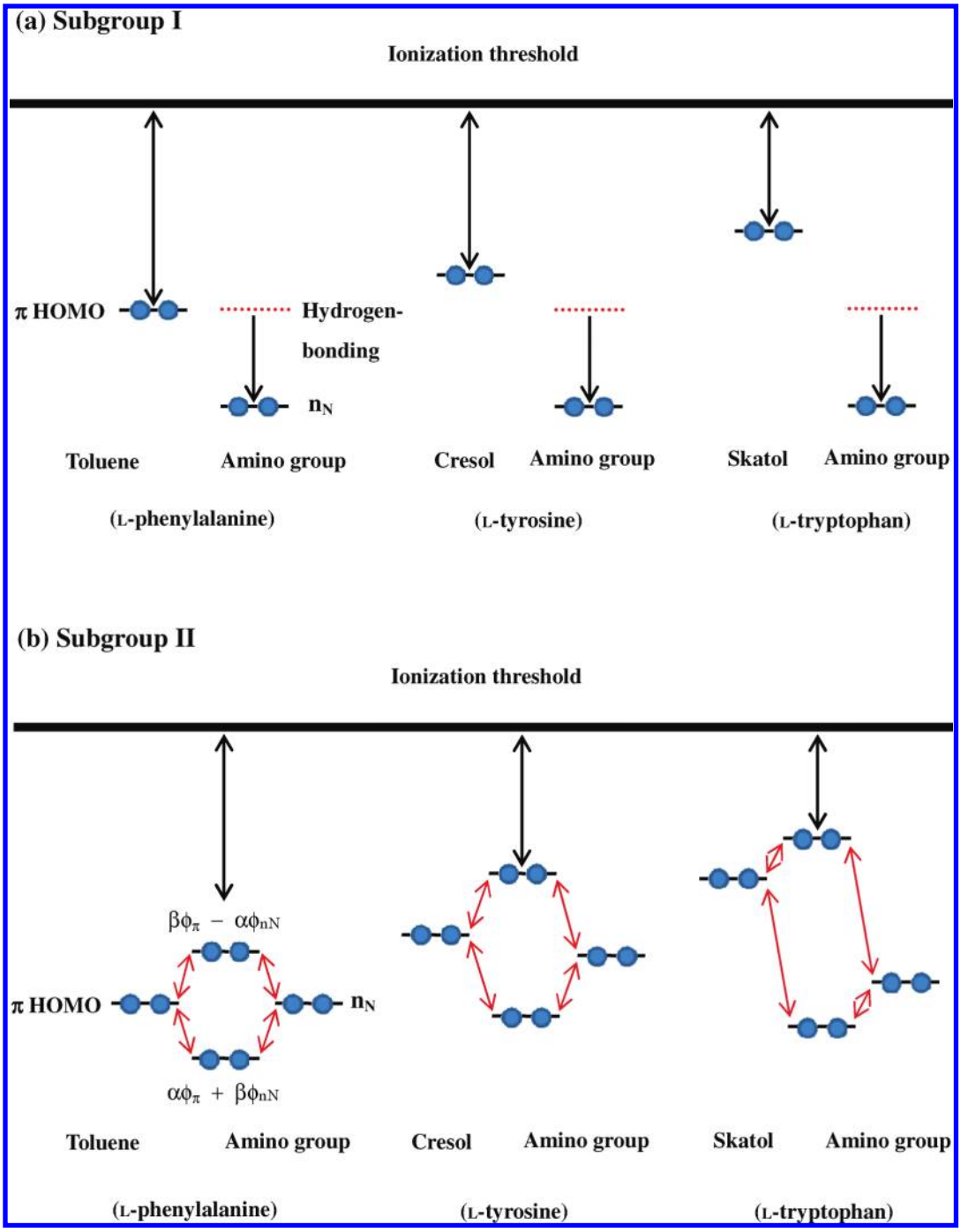

Figure 6. An MO picture showing the differences in ionization energies between conformers belonging to subgroup I and those belonging to subgroup II for the three aromatic amino acids: L-phenylalanine, L-tyrosine, and L-tryptophan. (a) For subgroup I, intramolecular hydrogen bonding between the carboxylic hydrogen and the nitrogen of amino group induces stabilization for the nonbonding orbital of nitrogen. (b) For subgroup II, the nonbonding orbital of the amino group and the π-HOMO of the aromatic residue interact to form new bonding and antibonding MO's. The antibonding MO is destabilized. This results in lower ionization energy than those of the π-HOMO and nonbonding MO in noninteracting systems.

that their conformers have one-to-one correspondence with respect to their conformation.[33] Furthermore, the angle between the directions of two orbitals (ϕ_π and ϕ_{nN}) of each L-tyrosine conformer is almost equal to that of the corresponding L-phenylalanine conformer. We used $\Delta\varepsilon = 0.82$ eV which was taken from the theoretical ionization energies of two substructures, cresol and alanine belonging to subgroup II. The values of the charge distribution obtained by using the simple model explain semiquantitatively those shown in Table 5a. In the similar way, we obtained $|\alpha|^2 = 0.04$ and $|\beta|^2 = 0.96$ for L-tryptophan with $\Delta\varepsilon = 1.41$ eV. It can be seen that there is significant difference in the charge distribution between the ab initio calculation and the simple two-state model. The main difference originates from use of the same interaction energy $\gamma = 0.32$ eV as that used in L-phenylalanine for evaluation of L-tryptophan charge distribution in the simple model even though there is a large discrepancy in aromatic rings between L-tryptophan

Table 5. Partial Charge Distributions of L-Tyrosine and L-Tryptophan Conformers in Cations[a]

(a) L-Tyrosine

	experiment		M05-2X (B3LYP)			
subgroup	assignments[b]	conformer	phenol group		amino group	
I	14	I_l	0.89	(0.78)	0.03	(0.07)
I	14	I_r	0.89	(0.78)	0.03	(0.08)
I	4 or 6	III_l	0.85	(0.69)	0.04	(0.10)
I	4 or 6	III_r	0.85	(0.69)	0.04	(0.10)
II	5 or 7	II_l	0.90	(0.75)	0.02	(0.10)
II	5 or 7	II_r	0.90	(0.75)	0.02	(0.09)
II	16 or 17	VII_l	0.91	(0.67)	0.01	(0.17)
II	16 or 17	VII_r	0.91	(0.65)	0.01	(0.18)

(b) L-Tryptophan

	experiment		M05-2X (B3LYP)			
subgroup	assignments[c]	conformers	indole group		amino group	
I	A	I_a	0.90	(0.85)	0.02	(0.04)
I	F	III_a	0.87	(0.81)	0.04	(0.05)
II	E	II_a	0.89	(0.84)	0.03	(0.06)
II	C	II_b	0.92	(0.90)	0.01	(0.01)
II	B	V_a	0.90	(0.84)	0.03	(0.06)
II	D	V_b	0.93	(0.92)	0.01	(0.01)

(c) L-Phenylalanine

	experiment		M05-2X (B3LYP)			
subgroup	assignments[d]	conformer	phenyl group		amino group	
I	X	I	0.79	(0.62)	0.04	(0.09)
I	B	III	0.73	(0.53)	0.09	(0.17)
II	A	VII	0.34	(0.41)	0.34	(0.35)
II	C	VI	0.38	(0.44)	0.33	(0.34)
II	D	II	0.39	(0.44)	0.31	(0.34)
II	E	IX	0.34	(0.41)	0.34	(0.35)

[a] These were obtained by NBO analysis of the M05-2X and B3LYP (in parentheses) results. [b] These experimental assignments are cited from ref 30. [c] These experimental assignments are cited from ref 22. [d] These experimental assignments are cited from ref 19.

and L-phenylalanine. Actually, $\gamma = 0.53$ eV was obtained from the expression for α (β) with ab initio values of the charge distribution for L-tryptophan in Table 5b. On the other hand, $\gamma = 0.31$ eV was obtained from the expression for α (β) with ab initio values of the charge distribution for L-tyrosine in Table 5a and there is almost no discrepancy of γ between L-phenylalanine and L-tyrosine.

In summary, charge doubly localization (division) for the subgroup II conformers of L-phenylalanine can be considered as a special case. The tendency of no $C_\alpha-C_\beta$ elongation and nonplanarity of the $C_\alpha-NH_2$ for all of the L-tyrosine and L-tryptophan conformers in radical cations, as shown in Tables 1 and 3, can be qualitatively explained using the same model. Charge localization of aromatic residue in aromatic amino acids means that ionization takes place from the HOMO of aromatic residue. Therefore, the degree of contribution of molecular orbital character like n_N and π plays an important role in determining whether the charge is localized or doubly localized (divided).

CONCLUSION

Conformation-dependent properties of the aromatic amino acids L-tyrosine and L-tryptophan for L-phenylalanine in radical cations have been studied by using new density functional theory, DFT (M05-2X). The DFT (M05-2X) results showed that all of the conformers of both L-tyrosine and L-tryptophan undergo charge localization irrespective of formation of intramolecular hydrogen bonding. Such localization behavior originates from the existence of HOMO energy difference between the backbone and residue of the aromatic amino acid. Among three aromatic amino acids, L-phenylalanine, L-tyrosine, and L-tryptophan, only subgroup II conformers of L-phenylalanine without intramolecular hydrogen bonding ($-COOH \rightarrow -NH_2$) in the backbone undergo charge doubly localization (division). This is due to nearly the same energy values of HOMO's between the backbone, alanine, and aromatic residue, toluene. The analysis given here provides clues to analyze the dynamics of charges in peptides and amino acids.

ASSOCIATED CONTENT

Supporting Information. Figures showing energetically stable structures of L-tyrosine and L-tryptophan and tables of molecular constants and relative energies in L-tyrosine and L-tryptophan conformers. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Nett, M.; Gulder, T. A. M.; Kale, A. J.; Hughes, C. C.; Moore, B. S. *J. Med. Chem.* **2009**, *52*, 6163.
(2) Mutatu, W.; Klettke, K. L.; Foster, C.; Walker, K. D. *Biochemistry* **2007**, *46*, 9785.
(3) Han, X.; Civiello, R. L.; Fang, H.; Wu, D.; Gao, Q.; Chaturvedula, P. V.; Macor, J. E.; Dubowchik, G. M. *J. Org. Chem.* **2008**, *73*, 8502.
(4) Grace, L. I.; Cohen, R.; Dunn, T. M.; Lubman, D. M.; de Vries, M. S. *J. Mol. Spectrosc.* **2002**, *215*, 204.
(5) Bell, C.; Abrams, J.; Nutt, D. *Brit. J. Psychiatry* **2001**, *178*, 399.
(6) Lima, S.; Kumar, S.; Gawandi, V.; Momany, C.; Phillips, R. S. *J. Med. Chem.* **2009**, *52*, 389.
(7) Shi, Z.; Devasagayaraj, A.; Gu, K.; Jin, H.; Marinelli, B.; Samala, L.; Scott, S.; Stouch, T.; Tunoori, A.; Wang, Y.; Zang, Y.; Zhang, C.; Kimball, S. D.; Main, A. J.; Yu, X.; Buxton, E.; Patel, S.; Nguyen, N.;

Swaffield, J.; Powell, D. R.; Wilson, A.; Liu, Q. *J. Med. Chem.* **2008**, *51*, 3684.
(8) Steiner, R. F.; Weinryb, I. *Excited States of Proteins and Nucleic Acids*; Macmillan: London, 1971.
(9) Beechem, J. M.; Brand, L. *Annu. Rev. Biochem.* **1985**, *54*, 43.
(10) Weinkauf, R.; Schanen, P.; Yang, D.; Soukara, S.; Schlag, E. W. *J. Phys. Chem.* **1995**, *99*, 11255.
(11) Weinkauf, R.; Schanen, P.; Metsala, A.; Schlag, E. W.; Burgle, M.; Kessler, H. *J. Phys. Chem.* **1996**, *100*, 18567.
(12) Lehr, L.; Horneff, T.; Weinkauf, R.; Schlag, E. W. *J. Phys. Chem. A* **2005**, *109*, 8074.
(13) Rizzo, T. R.; Park, Y. D.; Peteanu, L.; Levy, D. H. *J. Chem. Phys.* **1985**, *83*, 4819.
(14) Cable, J. R.; Tubergen, M. J.; Levy, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 6198.
(15) Philips, L. A.; Webb, S. P.; Martinez, S. J., III; Fleming, G. R.; Levy, D. H. *J. Am. Chem. Soc.* **1988**, *110*, 1352.
(16) Martinez, S. J., III; Alfano, J. C.; Levy, D. H. *J. Mol. Spectrosc.* **1992**, *156*, 421.
(17) Lindinger, A.; Toennies, J. P.; Vilesov, A. F. *J. Chem. Phys.* **1999**, *110*, 1429.
(18) Cohen, R.; Brauer, B.; Nir, E.; Grace, L.; de Vries, M. S. *J. Phys. Chem. A* **2000**, *104*, 6351.
(19) Snoek, L. C.; Robertson, E. G.; Kroemer, R. T.; Simons, J. P. *Chem. Phys. Lett.* **2000**, *321*, 49.
(20) Piuzzi, F.; Dimicoli, I.; Mons, M.; Tardivel, B.; Zhao, Q. *Chem. Phys. Lett.* **2000**, *320*, 282.
(21) Robertson, E. G.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1.
(22) Snoek, L. C.; Kroemer, R. T.; Hockrige, M. R.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1819.
(23) Snoek, L. C.; Kroemer, R. T.; Simons, J. P. *Phys. Chem. Chem. Phys.* **2002**, *4*, 2130.
(24) Lee, K. T.; Sung, J.; Lee, K. J.; Park, Y. D.; Kim, S. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4114.
(25) Lee, K. T.; Sung, J.; Lee, K. J.; Kim, S. K.; Park, Y. D. *J. Chem. Phys.* **2002**, *116*, 8251.
(26) Lee, Y.; Jung, J.; Kim, B.; Butz, P.; Snoek, L. C.; Kroemer, R. T.; Simons, J. P. *J. Phys. Chem. A* **2004**, *108*, 69.
(27) Wilson, K. R.; Jimenez-Cruz, M.; Nicolas, C.; Belau, L.; Leone, S. R.; Ahmed, M. *J. Phys. Chem. A* **2006**, *110*, 2106.
(28) Hashimoto, T.; Takasu, Y.; Yamada, Y.; Ebata, T. *Chem. Phys. Lett.* **2006**, *421*, 227.
(29) Ebata, T.; Hashimoto, T.; Ito, T.; Inokuchi, Y.; Altunsu, F.; Brutschy, B.; Tarakeshwar, P. *Phys. Chem. Chem. Phys.* **2006**, *8*, 4783.
(30) Inokuchi, Y.; Cobayashi, Y.; Ito, T.; Ebata, T. *J. Phys. Chem. A* **2007**, *111*, 3209.
(31) Hernandez, B.; Pfluger, F.; Adenier, A.; Kruglik, S. G.; Ghomi, M. *J. Phys. Chem. B* **2010**, *114*, 15319.
(32) Suresh, C. H.; Mohan, N.; Vijayalakshmi, K. P.; George, R.; Mathew, J. M. *J. Comput. Chem.* **2008**, *30*, 1392.
(33) Baek, K. Y.; Hayashi, M.; Fujimura, Y.; Lin, S. H.; Kim, S. K. *J. Phys. Chem. A* **2010**, *114*, 7583.
(34) Lee, K. T.; Sung, J.; Lee, K. J.; Kim, S. K.; Park, Y. D. *Chem. Phys. Lett.* **2003**, *368*, 262.
(35) Huang, Z.; Yu, W.; Lin, Z. *J. Mol. Struct.: THEOCHEM* **2006**, *758*, 195.
(36) Bouchoux, G.; Bourcier, S.; Blanc, V.; Desaphy, S. *J. Phys. Chem. B* **2009**, *113*, 5549.
(37) Zhang, M.; Huang, Z.; Lin, Z. *J. Chem. Phys.* **2005**, *122*, 134313.
(38) Lee, K. T.; Kim, H. M.; Han, K. Y.; Sung, J.; Lee, K. J.; Kim, S. K. *J. Am. Chem. Soc.* **2007**, *129*, 2588.
(39) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.
(40) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364.
(41) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Phys.* **2005**, *123*, 161103.
(42) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
(43) Sahnoun, R.; Fujimura, Y.; Kabuto, K.; Takeuchi, Y.; Noyori, R. *J. Org. Chem.* **2007**, *72*, 7923.
(44) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133.
(45) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(46) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 785.
(47) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.1*; Gaussian, Inc.: Wallingford, CT, 2009.
(48) Campbell, S.; Beauchamp, J. L.; Rempe, M.; Lichtenberger, D. L. *Int. J. Mass Spectrom. Ion Processes* **1992**, *117*, 83.
(49) Lu, Kuelh-Tzu; Eiden, G. C.; Weisshaar, J. C. *J. Phys. Chem.* **1992**, *96*, 9742.
(50) Palmer, M. H.; Moyes, W.; Speirs, M.; Ridyard, J. N. A. *J. Mol. Struct.* **1979**, *52*, 293.
(51) Hager, J. W.; Wallace, S. C. *Anal. Chem.* **1988**, *60*, 5.
(52) Weinkauf, R.; Lehrer, F.; Schlag, E. W.; Metsala, A. *Faraday Discuss.* **2000**, *115*, 363.