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Discovery of Most Stable Structures of Neutral and Anionic Phenylalanine through Automated Scanning of Tautomeric and Conformational Spaces

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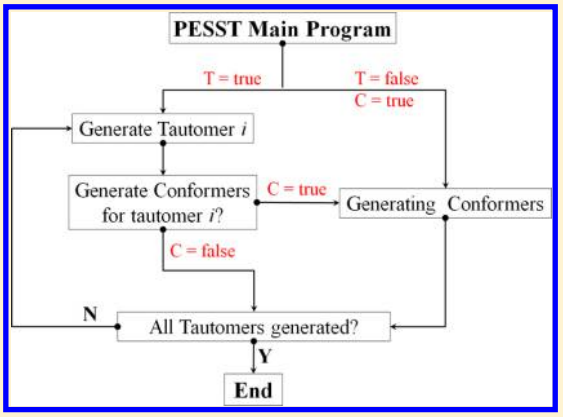
Supporting Information

ABSTRACT: We have developed a software tool for combinatorial generation of tautomers and conformers of small molecules. We have demonstrated it by performing a systematic search for the most stable structures of neutral and anionic phenylalanine (Phe) using electronic structure methods. For the neutral canonical tautomer we found out that the conformers *with* and *without* the intramolecular (O)H···NH_2 hydrogen bond are similarly stable, within the error bars of our method. A unique IR signature of the conformer without the hydrogen bond has been identified. We also considered anions of Phe, both valence type and dipole-bound. We have found out that tautomers resulting from proton transfer from the carboxylic OH to the phenyl ring do support valence anions that are vertically strongly bound, with electron vertical detachment energies (VDE) in a range of 3.2−3.5 eV. The most stable conformer of these valence anions remains adiabatically unbound with respect to the canonical neutral by only 2.17 kcal/mol at the CCSD(T)/aug-cc-pVDZ level. On the basis of our past experience with valence anions of nucleic acid bases, we suggest that the valence anions of Phe identified in this report can be observed experimentally. The most stable conformer of canonical Phe is characterized by an adiabatic electron affinity of 53 meV (a dipole-bound state).



1. INTRODUCTION

Recent years brought significant advances in the nondestructive transfer of low vapor pressure compounds to the gas phase.[1−4] The resulting intact molecules are probed with different spectroscopic methods, and an interpretation of these experimental results frequently invokes comparisons with computed spectroscopic characteristics.[5] These characteristics can be routinely determined for molecules with a few tens of atoms at density functional or second-order Møller−Plesset (MP2) theory levels. The only caveat is that the gas phase molecular structure has to be known.

Information about gas phase structure is frequently limited even for neutral molecules. Computational chemists are tempted to use condensed-phase structures (primarily from crystallographic databases), but these structures might be incorrect under gas phase conditions. The reason is that intermolecular interactions in crystalline lattices might favor conformers, or even tautomers, different from the most stable gas phase structures.[6−9] It has also been recognized that solute−solvent interaction can favor specific conformers[10] and tautomers, e.g., zwitterionic amino acids in polar solutions.[11] Charged molecular systems, e.g., ions of nucleic acid bases, bring additional challenges as they might favor unexpected tautomers.[12−14]

Many ingenious theoretical methods and algorithms aiming to determine the most stable molecular structures have been developed.[15,16] The most common methods are finite temperature Monte Carlo,[17] molecular dynamics,[18] basin-hopping[19] methods, as well as genetic algorithms.[20] In addition, there are brute force methods based on systematically scanning the potential energy surface (PES). Some of them specialize in molecular tautomers[21−23] and others in conformers,[8,24,25] but there is no tool that would deal with tautomers and conformers on equal footing. In the past, we developed a tool that performs a combinatorial/computational search for the most stable tautomers,[22] and we applied this tool to the anions of nucleic acid bases.[26] More recently, we developed a tool for a combinatorial/computational search of the most stable conformers, and we applied it to nucleosides.[8] Here, we discuss the capabilities of our newly developed Potential Energy Surface Scanning Tool (PESST) that searches *simultaneously* for the

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most stable tautomers and conformers,[27] and we demonstrates its usefulness on the neutral and anionic phenylalanine, see Figure 1.

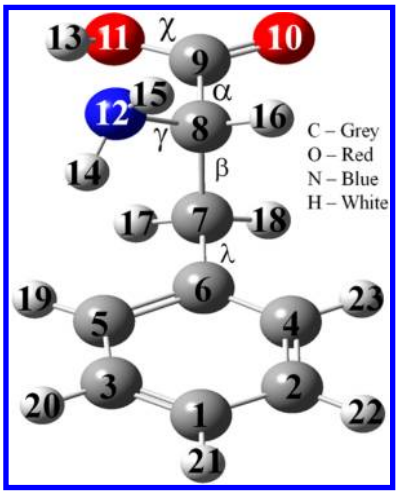

Figure 1. Molecular structure of phenylalanine with labeled atoms and rotatable bonds.

Valence anions of molecular systems are more challenging for structural determination than their neutral counterparts. They might favor tautomers that would be quite unstable for the neutral system. For example, our past studies of valence anions of nucleic acid bases demonstrated that the most stable anionic tautomers result from proton transfer from a typical proton donor (e.g., NH) to carbon sites, rather than to conventional proton acceptors involving highly electronegative atoms (O or N).[12−14] The valence anions observed experimentally were characterized by significant electron vertical detachment energies (VDE) of 1−3 eV, though computational results demonstrated that these anionic tautomers might be adiabatically unbound by a few kilocalories per mole with respect to the most stable conventional neutral tautomers.[26] Apparently, the anionic tautomers are separated by sufficiently high barriers from these regions of PES where the valence anion is weakly bound or even unbound. Notice that the six-member ring of phenylalanine might support unusual tautomers of its valence anion, which would result from proton transfer from the carboxylic group to the phenyl ring. Identification of these tautomers and their most stable conformers is the main goal of this project.

Amino acids typically take the canonical HOOC−CHR−NH_2 form in the gas phase.[28] However, an excess electron bound by the dipolar potential of a neutral amino acid can promote intramolecular proton transfer and is responsible for the development of a zwitterionic minimum, which remains local in the case of the anion of glycine[29] but becomes global in the case of the anion of arginine.[30,31] Further stabilization of these anions by water molecules has also been considered.[32,33] In this report, we will search for dipole-bound anions of phenylalanine associated with its canonical and zwitterionic forms.

L-Phenylalanine (Phe) is one of the 20 standard amino acids found in nature. It is an essential, nonpolar, α-amino acid and is a precursor for another amino acid, tyrosine. Previous studies on Phe focused on electronic spectra using flourescence spectroscopy in a supersonic jet, and five conformers of Phe were stabilized at low temperatures.[34] The study was extended by Meijer and co-workers,[35] using mid- and far-infrared spectra, who reported six conformers in the gas phase. Their work showed good agreement between the experimental spectrum and the one computed at the B3LYP/6-311++G(2d,p) and MP2/6-311+G(2df,2p) levels of theory, with vibrational frequencies scaled uniformly by 0.98. Fausto and co-workers[36] reported a matrix-isolation IR spectrum and concluded that entropic effects play a major role in the relative abundance of conformers. On the basis of their B3LYP/6-311++G(d,p) results, they confirmed that only six structures contribute to the spectrum of Phe.

Many computational studies addressed the structural preference of Phe. Purushotham et al.[37] used the M052X functional[38] and extended basis sets to characterize the conformational space and noncovalent interactions in the neutral canonical Phe, as well as in ions resulting from its protonation and deprotonation. Lin and co-workers[39] performed a conformational search on neutral Phe at the B3LYP/6-311++G(d,p) level and characterized the intramolecular hydrogen bonding using the Atoms in Molecules approach.[40] Lee et al. reported relative energies of the six most stable neutrals and cations of Phe at the B3LYP and MP2 levels of theory with 6-31+G* basis sets.[41] They paid particular attention to the dependence of vertical ionization energies on intramolecular hydrogen bonding. The neutral structures were similar to those from refs 37 and 39. Other studies were focused on the cations resulting from protonation of Phe.[42]

In the current study, we use the neutral and anionic Phe to demonstrate how the PESST tool can be used to identify stable molecular structures. The anions we have considered result from the attachment of an excess electron, not from the deprotonation of Phe. We consider both valence- and dipole-bound anions. The latter might be supported by polar canonical or zwittterionic structures of the neutral.

2. COMPUTATIONAL APPROACH

The libraries involving tautomers and conformers of Phe were generated with PESST.[27] An overview of PESST is shown in Figure 2. It creates conformers for each tautomer resulting in a double-loop structure of the program. The code builds on our past efforts to construct libraries of tautomers[22] and

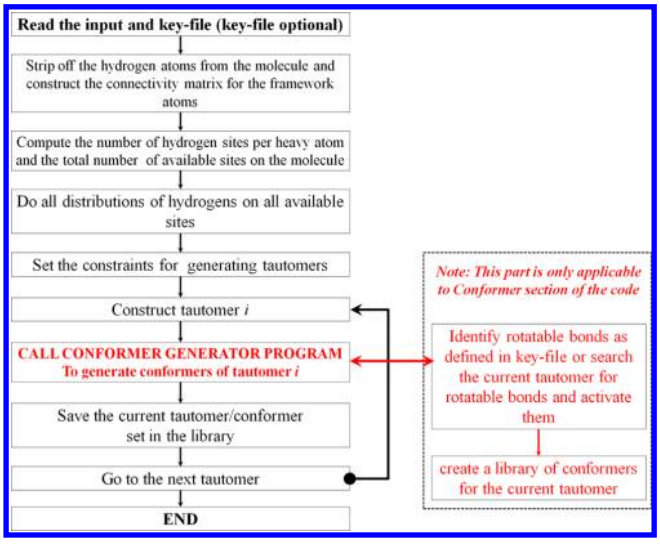

Figure 2. The working procedure of PESST. The generation of conformers for each tautomer is marked in red.

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conformers[8] and brings further extensions and improvements. We refer readers to the Supporting Information (SI) for a detailed discussion of PESST. In short, the tautomer part of the code creates sites for hydrogen atoms associated with each framework atom, and then different tautomers result from various occupations of these sites by the available hydrogen atoms. When creating conformers, the program identifies rotatable bonds, splits the molecule across each rotatable bond into disconnected fragments, and rotates the smaller fragment with increments of $360°/n_{rot}$, where n_{rot} is an integer defined for each rotatable bond. The prescreening of the resulting structures is automated, starting from the construction of input files, running calculations, and analyzing output files using Gaussian Output Tools (GOT) to extract converged geometries, corresponding energies, dipole moments, etc.[43]

The prescreening of initial structures for the neutral and valence anions of Phe was conducted through geometry optimizations with the B3LYP exchange-correlation functional[44−47] and standard Pople's basis sets.[48] This selection of methodology for the prescreening step was validated and used in our previous studies focused on the identification of most stable tautomers of small biomolecules such as nucleosides.[12−14] However, these basis sets and electronic structure models are not sufficient for dipole-bound states.[49] Electronic structure calculations for dipole-bound anions require basis sets with very diffuse basis functions.[50,51] Here, we have used Dunning's aug-cc-pVDZ basis set (ADZ)[52] supplemented with extra seven s and seven p functions centered on the nitrogen atom. The exponents of these functions form an even-tempered series initiated from the lowest exponent in the standard basis set and advance with the geometric progression constant of 3.2^{-1}.[53] We will use a label DF for these additional diffuse functions and ADZ+DF for the combined basis set. Prescreening for dipole-bound anions was performed at the Hartree−Fock/ADZ+DF level.

For the neutral Phe, we identified only canonical tautomers; the zwitterions did not support local minima. The conformational search was performed activating dihedral angles χ, α, β, γ, and λ illustrated in Figure 1. The n_{rot} values were $n_\chi = 2$, $n_\alpha = 12$, $n_\beta = 12$, and $n_\gamma = 3$, and last λ was probed at 0° and 90°. PESST created 1728 initial structures which were fully optimized at the B3LYP/6-311G* level, and the resulting optimized structures converged into 45 local minima. The three most stable conformers were then subjected to further MP2/ADZ+DF reoptimization and frequency calculations and single-point coupled cluster calculations with single, double, and noniterative triple excitations (CCSD(T)).[54]

In the case of valence anions, we engaged PESST to construct a library of tautomers and conformers. The constraints set on the program are shown in Table SI1. It created 50 tautomers that were subjected to the B3LYP/6-31G* conformational search based on all rotatable bonds and the default settings for n_{rot}'s. The most stable tautomers/conformers within the energy range of 5 kcal/mol were reoptimized, and frequencies were determined at the MP2/ADZ level. Three families of valence anions have been identified. The single point CCSD(T)/ADZ calculations have been performed for the most stable conformer from each family.

A search for the most stable dipole-bound (**DB**) anionic conformers was performed for the canonical (**CDB**) and zwitterionic tautomers (**ZDB**). The confromational search for **CDB**s was performed with the following values of n_{rot}: $n_\chi = 2$, $n_\alpha = 6$, $n_\beta = 6$, and $n_\gamma = 3$, and λ was probed at 0° and 90°. These constraints resulted in 432 initial structures. The conformational search for **ZDB**s was performed with $n_\beta = 6$ and probing γ at 0° and 90°, and α at 0° and 90° and γ at 0° and 60°. These constraints led to 48 initial structures. The most stable structures (three **CDB**s and two **ZDB**s) were subjected to the MP2/ADZ+DF optimizations and frequency calculations, and vertical and adiabatic electron binding energies were determined at the CCSD(T)/ADZ+DF level.

To summarize, our final results are based on CCSD(T) energies determined at the optimal MP2 geometries. The basis set is ADZ for valence anions and ADZ+DF for neutrals and dipole-bound anions. The zero-point vibrational corrections and thermal contributions to energy and entropy are determined in the rigid rotor−harmonic oscillator approximation, assuming $T = 298$ K and $p = 1$ atm, based on the MP2 geometries and harmonic frequencies. The calculations were performed using the Gaussian 09 suite of programs.[55] The singly occupied molecular obitals of the anions of Phe were visualized using the Visual Molecular Dynamics (VMD) package,[56] and the orbital contour values were determined with the OpenCubMan[57] package. These countour values were obtained for 80% of the orbital electron density.

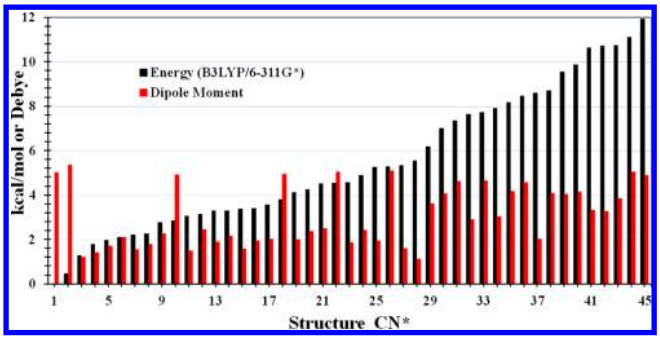
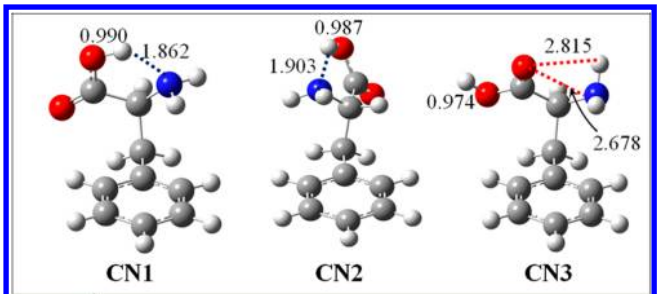


Figure 3. Relative energies and dipole moments of Phe calculated at the B3LYP/6-311G* level of theory. The energy of **CN1** is set to zero.

Table 1. The MP2/ADZ+DF Structures of the Three Most Stable Conformers of the Neutral Canonical Phe with Distances in Å and Dipole Moments in D[a]



System	Relative Stability					
	MP2		CCSD(T)			
	μ	E_{el}	E_{el}	$E_{el}+E_0^{vib}$	H	G
CN1	4.95	0.00	0.00	0.00	0.00	0.00
CN2	5.28	2.02	1.49	1.24	1.42	0.65
CN3	1.16	0.73	0.60	0.19	0.42	-0.14

[a]The intramolecular hydrogen bonds marked with dashed lines with the color of the proton acceptor atom. The relative stability (kcal/mol) determined at the MP2 and CCSD(T) levels (E_{el}, E_0^{vib}, H, and G for electronic energy, zero-point vibrational correction, enthalpy, and Gibbs free energy, respectively). The CCSD(T) energies determined at the optimal MP2 geometries. The zero-point and thermal corrections determined at the MP2/ADZ+DF level.

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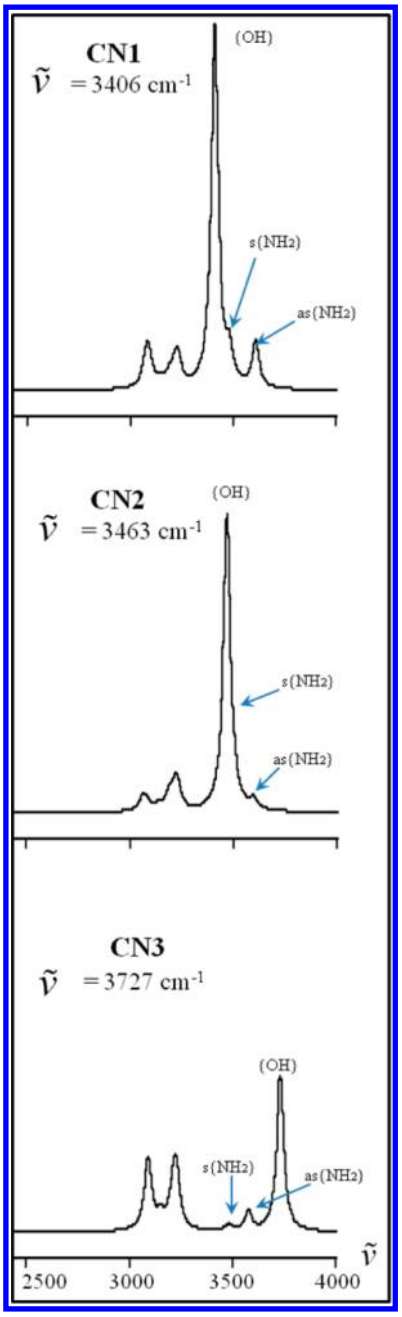
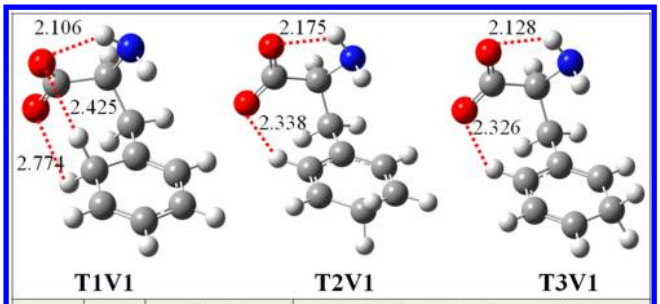


Figure 4. The stretching modes of **CN1**, **CN2**, and **CN3** calculated at the MP2/ADZ+DF level of theory. Keywords: s, symmetric; as, asymmetric. Lonrentzian vibrational spectra with scaling factor of 1.0 and half-width of 20.0 cm^{-1}.

3. RESULTS

3.1. Neutral Phenylalanine. The conformers of the canonical neutral (**CN**) tautomer were labeled **CN*m*** ($1 \leq m \leq 45$), with ordering based on the B3LYP/6-311G* electronic energies of fully optimized structures. Their relative energies and dipole moments are illustrated in Figure 3. The MP2/ADZ+DF optimized structures and relative energies of the three most stable conformers are shown in Table 1. At the MP2 and CCSD(T) levels of theory, the relative energies of **CN1**−**CN3** span ca. 2 kcal mol^{-1}. Thus determination of the most stable conformer becomes a computationally demanding task. Our most accurate CCSD(T) electronic energies corrected for harmonic, zero-point, MP2 vibrational terms indicate that **CN3** is less stable than **CN1** by only 0.19 kcal/mol, and it becomes the most stable conformer in terms of Gibbs free energy. The results presented in Table 1 demonstrate that entropic effects contribute to the relative stability of the most stable conformers, in agreement with earlier observations.[36]

Table 2. The Most Stable Conformers for Three Families of Valence Anions of Phe[a]



System	$\mu_{neutral}$	VDE		Relative Stability *w.r.t* CN1				
	MP2	MP2	CCSD(T)	PMP2	CCSD(T)			
				E_{el}	E_{el}	$E_{el}+E_0^{vib}$	H	G
T1V1	15.13	3.35	3.25	8.63	4.35	2.17	2.41	1.67
T2V1	17.05	3.30	3.22	12.07	7.53	5.28	5.65	4.22
T3V1	18.20	3.52	3.50	11.98	7.64	5.37	5.66	4.64

[a]The dipole moment of neutral Phe at the optimal anionic geometry, $\mu_{neutral}$, in D. The electron vertical detachment energy (VDE) in eV. The relative stability of anions with respect to **CN1** in kcal/mol. The anionic structures (with distances in Å) optimized at the MP2/ADZ level of theory. The remaining quantities are the same as in Table 1.

There is an important structural difference between **CN3** and the two remaining conformers **CN1** and **CN2**, which leads to a unique feature in the IR spectrum of **CN3** (Figure 4). The **CN1** and **CN2** conformers support a hydrogen bond between the OH site of the carboxylic group and the NH_2 site, with (O)H···N distances of 1.862 and 1.903 Å, respectively, but the OH site in the **CN3** conformer is not engaged in any hydrogen bond (see Table 1). As a consequence, the OH stretching mode is strongly red-shifted in the **CN1** and **CN2** conformers, as illustrated by the MP2 harmonic frequency of 3406 and 3463 cm^{-1}, respectively, but its frequency is much higher in the **CN3** conformer, $\tilde{\nu}$ = 3727 cm^{-1} (Figure 4). The OH stretching mode of the carboxylic group routinely carries the largest IR intensity, and the simulated IR spectra in the 2500−4000 cm^{-1} region are presented in Figure 4. The most intense IR peak for the **CN1** and **CN2** conformers, i.e., the OH stretching mode, has a lower frequency than the symmetric and asymmetric stretching NH modes. On the other hand, the most intense IR peak in **CN3**, again the OH stretching mode, has the largest frequency. We believe this difference between **CN3** and the pair **CN1** and **CN2** will help to discriminate contributions from different conformers to the IR spectra of gas phase Phe recorded at different temperatures.

It was counterintuitive for us to find out that the conformer *without* the intramolecular (O)H···N hydrogen bond, i.e., **CN3**, might be the most stable. One reason might be that formation of this hydrogen bond in **CN1** and **CN2** is associated with intramolecular strain (a destabilizing effect). The results obtained with the MM3 force field[58] confirm this hypothesis. The sum of angle bending, torsional, and bond stretching terms is more attractive in **CN3** than in **CN1** by 2.8 kcal/mol.

The stability of tautomers and conformers in polar environments is strongly dependent on the molecular dipole moment.

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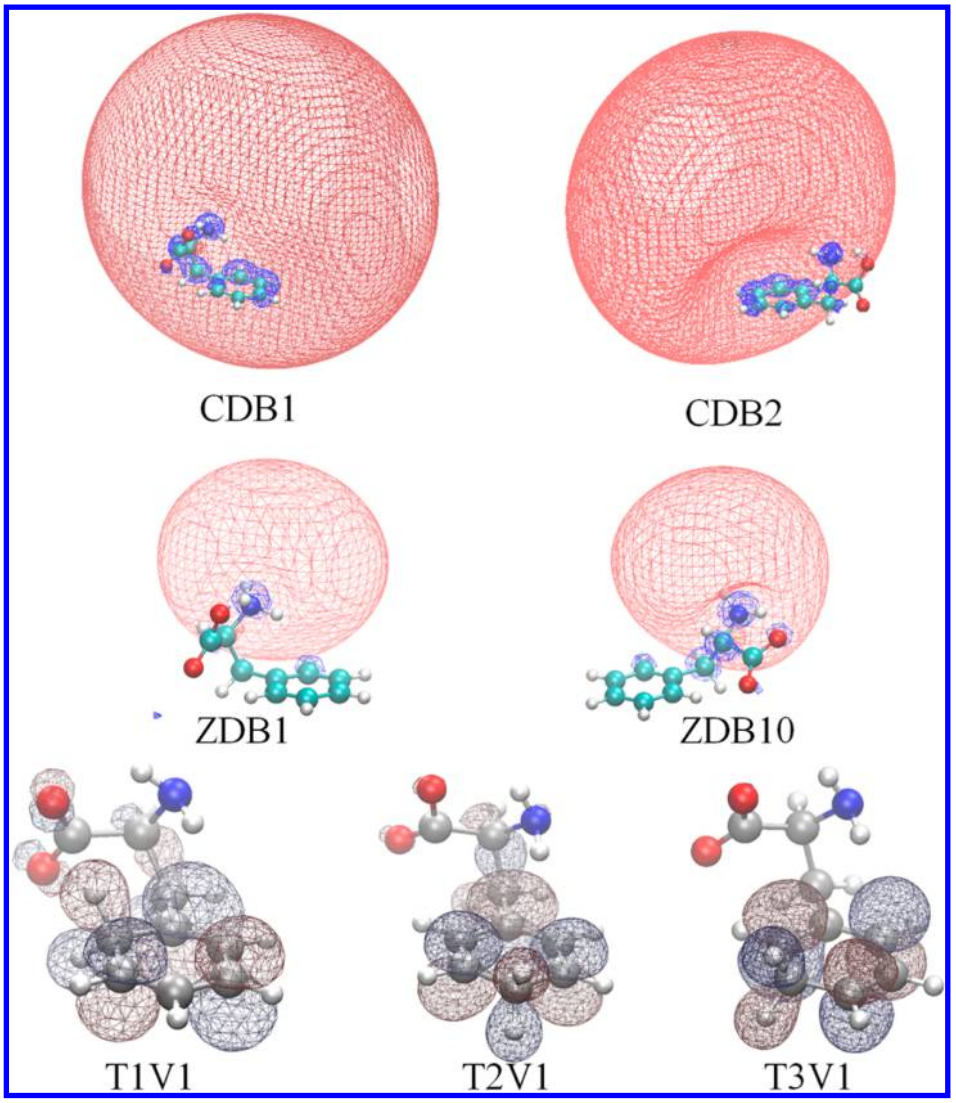

Figure 5. Highest occupied molecular orbital of the dipole- and valence-bound anions of phenylalanine generated with contour values determined with the OpenCubMan program[57] (80% of the orbital electron density).

Moreover, molecules with dipole moments exceeding 1.625 D can bind an excess electron.[50] The dipole moments of 45 neutral conformers of Phe, characterized at the B3LYP/6-311G* level, lie in a wide range from 1.1 to 5.4 D (Figure 3). The five conformers of Phe with the largest dipole moments (in excess of 5 D) follow the order **CN2** > **CN26** > **CN22** > **CN44** > **CN1**. These results suggest that the **CN2** and **CN1** will be more stabilized in polar environments (or by a dipole-bound electron) than the **CN3** conformer, which is characterized by a dipole moment of 1.16 D only.

3.2. Valence Anions of Phenylalanine. We did not identify any bound valence anion when considering the canonical tautomer of Phe. The result was not surprising as bound valence anionic states are not known for either glycine or toluene, which might be considered as building blocks of Phe.[59] Using the PESST tool, we explored noncanonical tautomers and their conformers. In the course of this search, we identified three families of valence anions, which involve proton transfer from COOH to the phenyl ring. The first family, **T1V** (tautomer #1, valence anion) involves proton transfer to either **C4** or **C5**. The second, **T2V**, involves proton transfer to **C1** and the third, **T3V**, to **C2** or **C3**.

The most stable conformers for each family, i.e., **T1V1**, **T2V1**, and **T3V1**, are characterized in Table 2 (see Figures SI9 and SI10 for a more complete set of conformers). The VDE values for these valence anions exceed 3.2 eV at the projected MP2 and CCSD(T) levels. The excess electron is described by a π^* orbital localized primarily on the protonated phenyl ring (Figure 5). One protic H(N) is involved in a hydrogen bond with COO^-, and the second H(N) "solvates" electron density on the phenyl ring (Table 2 and Figure 5).

The **T*n*V1** structures (n = 1−3) do not make much "chemical sense" for the neutral Phe, which is reflected in dipole moments exceeding 15 D and large values of VDE for these valence anions. However, the instability of these anions with respect to the most stable canonical neutral, **CN1**, is surprisingly small. For **T1V1**, it drops from 4.35 kcal/mol in terms of the CCSD/ADZ electronic energy to 2.17 kcal/mol in terms of electronic energy corrected for zero point vibrations, and further to 1.67 kcal/mol in terms of Gibbs free energy. This instability is comparable with error bars of our theoretical model, CCSD(T)/ADZ plus zero-point and thermal corrections.[60] We believe that valence anions of Phe can be formed

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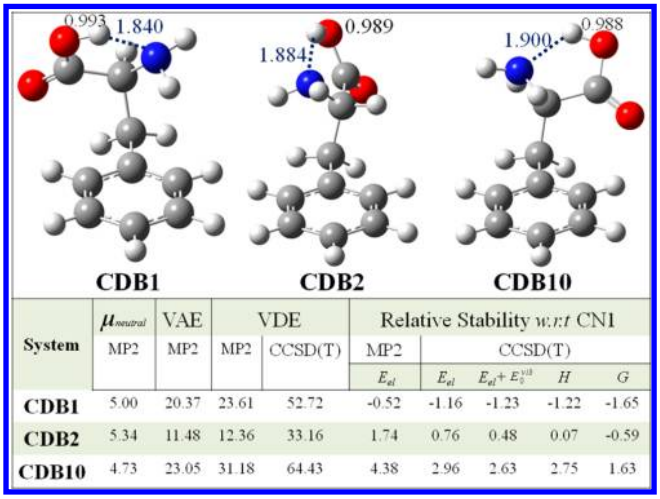
under experimental conditions similar to those used in the past to identify valence anions of nucleic acid bases.[26]

3.3. Dipole-Bound Anions of Phenylalanine. The three most stable conformers of dipole-bound anions of Phe based on the canonical tautomer are characterized in Table 3. They

Table 3. The Three Most Stable Conformers of Dipole-Bound Anions of Phe Based on the Canonical Tautomer[a]



System	$\mu_{neutral}$ MP2	VAE MP2	VDE MP2	VDE CCSD(T)	Relative Stability w.r.t CN1 MP2 E_{el}	CCSD(T) E_{el}	CCSD(T) $E_{el}+E_0^{vib}$	CCSD(T) H	CCSD(T) G
CDB1	5.00	20.37	23.61	52.72	-0.52	-1.16	-1.23	-1.22	-1.65
CDB2	5.34	11.48	12.36	33.16	1.74	0.76	0.48	0.07	-0.59
CDB10	4.73	23.05	31.18	64.43	4.38	2.96	2.63	2.75	1.63

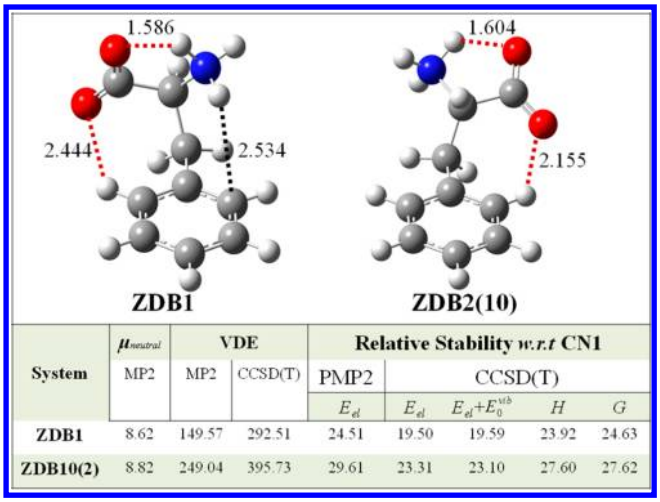
[a]The dipole moment of neutral Phe at the optimal anionic geometry, $\mu_{neutral}$, in D. The electron vertical attachment (VAE) and detachment energy (VDE) in meV. The relative stability of anions with respect to **CN1** in kcal/mol. The anionic structures (with distances in Å) optimized at the MP2/ADZ+DF level of theory. The remaining quantities are the same as in Table 1.

are labeled **CDB1**, **CDB2**, and **CDB10** as they are associated with the neutral canonical conformers **CN1**, **CN2**, and **CN10**. These neutrals are characterized by MP2 dipole moments of 4.95, 5.28, and 4.54 D, respectively. Recall that the dipole moment of **CN3** is only 1.16 D, which is too small to support a dipole-bound state. The molecular frameworks distort only slightly upon binding an excess electron, and the dipole moment of the neutral increases by 0.05, 0.06, and 0.19 D, upon these geometrical distortions (Tables 1 and 3). The geometrical distortions can be viewed as nascent zwitterionization, because the (O)H···N distance shortens by 0.02 Å, and the OH distance elongates by 0.002 Å.

The excess electron binding energies are in the 30−65 meV range and the vertical attachment and detachment energies barely differ (Table 3), which is common for dipole-bound anions.[50] Despite their small values, these electron binding energies are measurable in anion photoelectron spectroscopy and Rydberg electron transfer experiments.[5] On the basis of the $E_{el} + E_0^{vib}$ stability of **CDB1** with respect to **CN1**, we conclude that the gas phase neutral Phe is characterized by an adiabatic electron affinity of 53 meV. Notice the lack of correlation between the electron vertical binding energies and the values of dipole moment of the neutral, with **CDB2** having apparently a too small electron binding energy for its dipole moment. The reason is the relative orientation of its dipole and the phenyl ring. The excess electron in typical dipole-bound anions is localized in the region where the electrostatic potential produced by the dipole of the neutral is the most attractive. The electron still fulfills the Pauli exclusion principle, and the anionic singly occupied molecular orbital (SOMO) remains orthogonal to the occupied orbitals of the neutral, which requires some nodal surfaces in the regions of atoms localized close to the positive pole of the dipole. In the case of **CDB2**, the phenyl ring happens to be in the region where the dipolar electrostatic potential would favor localization of the excess electron. The SOMO needs to develop several nodal surfaces that are preceded by a dent visible in Figure 5. The multitude of nodal surfaces destabilizes the anion, which is reflected in relatively small values of electron vertical binding energies.

Even though the gas phase neutral Phe does not support zwitterionic minima, local minima of this type exist on the anionic potential energy surface, and the two most stable, **ZDB1** and **ZDB2**, are illustrated in Table 4. **ZDB1** might be

Table 4. The Two Most Stable Conformers of Dipole-Bound Anions of Phe Based on the Zwitterionic Tautomer[a]



System	$\mu_{neutral}$ MP2	VDE MP2	VDE CCSD(T)	Relative Stability w.r.t CN1 PMP2 E_{el}	CCSD(T) E_{el}	CCSD(T) $E_{el}+E_0^{vib}$	CCSD(T) H	CCSD(T) G
ZDB1	8.62	149.57	292.51	24.51	19.50	19.59	23.92	24.63
ZDB10(2)	8.82	249.04	395.73	29.61	23.31	23.10	27.60	27.62

[a]The dipole moment of neutral Phe at the optimal anionic geometry, $\mu_{neutral}$, in D. The electron vertical detachment energy (VDE) in meV. The relative stability of anions with respect to **CN1** in kcal/mol. The anionic structures (with distances in Å) optimized at the MP2/ADZ+DF level of theory. The remaining quantities are the same as in Table 1.

viewed as a product of proton transfer from COOH to NH_2 initiated from **CDB1**. The dipole moment of the neutral increases upon this proton transfer by 3.62 D, and the **ZDB1** minimum is characterized be a VDE of 0.293 eV. This is a 5-fold increase in comparison with the VDE of **CDB1**. **ZDB1** is, however, unstable with respect to **CN1** by ca. 19.6 kcal/mol, thus adiabatically more unbound than **T1V1**. Similarly, **ZDB2** results from proton transfer initiated in either **CDB2** or **CDB10**. In fact, geometrically it more resembles **CDB10** than **CDB2** (Tables 3 and 4). The difference in dipole moments of the neutral at the **ZDB2** and **CDB2** geometries is 3.48 D, and the VDE value for **ZDB2** is 0.396 eV. Again, **ZDB2** is unstable with respect to **CN1** by 23.1 kcal/mol. Notice a significant contraction of the SOMO orbital, attached to the nitrogen terminus of the molecular framework, upon proton transfer from COOH to NH_2 (Figure 5).

4. SUMMARY

The Potential Energy Surface Scanning Tool (PESST)[27] allows automated scanning of molecular tautomeric and conformational spaces. Its performance has been tested on the neutral and anionic phenylalanine (Phe). Molecular ions frequently favor structures different from those of the neutral species; thus the anions of Phe have been particularly challenging. The prescreening has been performed with lower level electronic

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structure methods (B3LYP exchange-correlation functional for the neutral and valence anions and Hartree−Fock for dipole-bound anions), while final energies were determined at the CCSD(T) level with basis sets of aug-cc-pVDZ quality.

Three conformers of the neutral canonical Phe have been found differing in stability by less than 1.3 kcal/mol. It was counterintuitive for us to find out that conformers *with* and *without* the intramolecular (O)H···NH_2 hydrogen bond might be similarly stable. It has been interpreted as a manifestation of structural strain, which develops upon formation of the hydrogen bond. We have identified a unique IR signature of the conformer without the intramolecular hydrogen bond.

We have identified three tautomeric families of valence anions of Phe resulting from proton transfer from COOH to the phenyl ring. They are characterized by significant values of VDE, in a range of 3.2−3.5 eV. At 0 K, the most stable tautomer/conformer of valence anions is adiabatically unbound with respect to the most stable canonical neutral by only 2.17 kcal/mol, and its stability further improves at elevated temperatures. On the basis of our past experience with valence anions of nucleic acid bases,[26] we suggest that the valence anions of Phe identified in this report can be observed experimentally.

We characterized dipole-bound anions supported by the canonical and zwitterionic tautomers of Phe. These based on the canonical tautomer are relatively weakly bound, with electron vertical binding energies in a range of 30−65 meV. Still, these might be the lowest anionic states in the system, and we predict an adiabatic electron affinity of 53 meV for the most stable conformer of the neutral. The dipole-bound anions remain vertically bound upon intramolecular proton transfer from COOH to NH_2. Local zwitterionic minima develop for these anions with electron vertical binding energies in a range of 290−400 meV. These minima are adiabatically unbound with respect to the canonical neutral by ca. 19−23 kcal/mol. We observed that the phenyl ring of Phe can interfere with the SOMO orbital of its dipole-bound anion and thus reduce the stability of the anion.

■ ASSOCIATED CONTENT

Supporting Information

(a) Description of the PESST code, (b) characteristics of various conformers of valence anions of Phe, (c) a set of constraints used to construct a library of tautomers for valence anions of Phe. The material is availabe free of charge via the Internet at http://pubs.acs.org

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Notes

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