

ARTICLE

Computational Exploration of Conformations of Glycine-Arginine and a Deduced Model on Global Minimum Configurations of Dipeptides in Gas Phase

Kai-yi Yang, Bing Yang, Zi-jing Lin*

Hefei National Laboratory for Physical Sciences at the Microscale and Collaborative Innovation Center of Suzhou Nano Science and Technology, Department of Physics, University of Science and Technology of China, Hefei 230026, China

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An extensive computational study on the conformations of gaseous dipeptide glycine-arginine, GlyArg, has been performed. A large number of trial structures were generated by systematically sampling the potential energy surface (PES) of GlyArg. The trial structures were successively optimized with the methods of PM3, HF/3-21G*, BHandHLYP/6-31G* and BHandHLYP/6-311++G** in order to reliably find the low energy conformations. The conformational energies were finally determined with the methods of BHandHLYP, cam-B3LYP, B97D, and MP2 using the basis set of 6-311++G(3df,3pd). The results establish firmly that gaseous GlyArg exists primarily in its canonical form, in sharp contrast with ArgGly that adopts the zwitterionic form. Important data such as the rotational constants, dipole moments, vertical ionization energies, temperature distributions and IR spectra of the low energy conformers are represented for the understanding of the future experiments. Moreover, considering the global minima of all amino acids and many dipeptides, combined with the hydrophobicities of amino acids, a model predicting whether the global minimum configuration of a dipeptide is canonical or zwitterionic is developed.

Key words: Potential energy surface, Amino acid, Oligopeptide, Conformation data, IR spectrum, Structural model

I. INTRODUCTION

The functions of a biological molecule are closely related to the conformations adopted by the molecule and the determinations of protein structures are of huge importance in life sciences. Due to the limitations of the available experimental techniques, computational predictions of protein structures are highly desirable. However, despite of significant progress, producing accurate models remains a challenge for proteins and polypeptides because of the complexity of the systems [1]. The existing results strongly suggest that the knowledge or information based method is the most promising approach to develop an accurate protein structure prediction technique [2–4]. In fact, the knowledge based method seems to be the only reliable method that provides consistent quality predictions for protein structures [5]. As such, detailed information about the structures of protein building blocks is highly desirable and may be very helpful for developing an improved protein structure prediction method.

Dipeptides are the smallest molecules that contain the peptide bond units of protein. Determining the stable dipeptide structures is therefore of fundamental significance for analyzing the structures of proteins and large peptides. A recent study shows that the most stable conformer of gaseous arginyl glycine dipeptide, ArgGly, is a zwitterion [6]. The result is interesting as it shows that ArgGly possess the necessary intramolecular bonding flexibilities to stabilize the zwitterionic structure as the global minimum as observed in large peptides or amino acids in solution or solid [7–9]. The result is also intriguing as zwitterions in gas phase were thought to be possible only for much larger oligopeptides with back bond chains much longer than that of ArgGly. For example, the stable conformations for many tri- and tetra-peptides are known to take the canonical form [10, 11]. These results indicate that the side chain of arginine (Arg) has a strong influence on the stability of zwitterions in the gas phase.

Arg is the most basic amino acid [12–14]. The side chain of Arg has a unique property that the proton affinity of its guanidine is higher than the amino group in the back bond [14, 15]. In fact, only Arg and histidine (His) possess the zwitterions as the local minimum in the potential energy surfaces (PESs) of all amino acids in gas phase. The lowest energy zwitterion of Arg is

* Author to whom correspondence should be addressed. E-mail: zjlin@ustc.edu.cn

protonated on the side chain and is about 15 kJ/mol less stable than the global minimum [15]. The lowest energy zwitterion of His, however, is protonated on the amino group and is about 50 kJ/mol higher in energy than the global minimum [16]. Based on these observations, the stabilizing effect of Arg side chain on the zwitterionic structures is quite understandable.

As the global minimum of ArgGly is confirmed to be a zwitterion, a natural question arises if the most stable conformation of GlyArg is also a zwitterion. Prell *et al.* have performed a conformational search on the PES of GlyArg [17]. Their result shows that the global minimum structure of GlyArg takes the canonical form. However, the result is obtained through a molecular mechanics force field based Monte Carlo screening search and may miss many important conformations [11, 15]. For example, the ArgGly conformations are also searched in the same work, yielding a canonical form as the global minimum that is later shown to be inaccurate. Clearly, a thorough conformational search is required to provide a reliable description of the PES of GlyArg.

In this work, we report the results of a thorough computational study of the gas phase conformations of GlyArg. The conformational search is conducted by optimizing trial structures generated by considering all possible combinations of the bond rotational degrees of freedom. The thorough investigation is undertaken with the goal to locate all low energy conformers of gaseous GlyArg and to obtain knowledge about their structural features and relative stabilities on the PES. Essential theoretical data such as rotational constants, IR spectra, dipole moments, vertical ionization energies (VIEs) as well as conformational distributions at characteristic temperatures are presented for possible verification of future experiments. Based on the analysis of all the known global minima of amino acids and small peptides, a model about the structural characteristics of the global minimal conformations of all dipeptides is then proposed.

II. COMPUTATIONAL METHODS

Figure 1 illustrates the structural characteristics of two canonical, c1 and c2, and one zwitterionic, z, tautomers of neutral ArgGly. The conformations of the three GlyArg tautomers are investigated respectively and the lowest energy conformers are then determined by comparing the low energy conformers of the three tautomers. The other two tautomers of GlyArg that are zwitterions with protonated α -amino group are not fully investigated as the test calculations show that the resulting structures are of very high energies and are ignored in the ensuing discussion. Similarly, conformations with *cis* peptide bond structures are known to have high energies and are ignored in the conformational searches.

To ensure a reliable finding of all the low energy con-

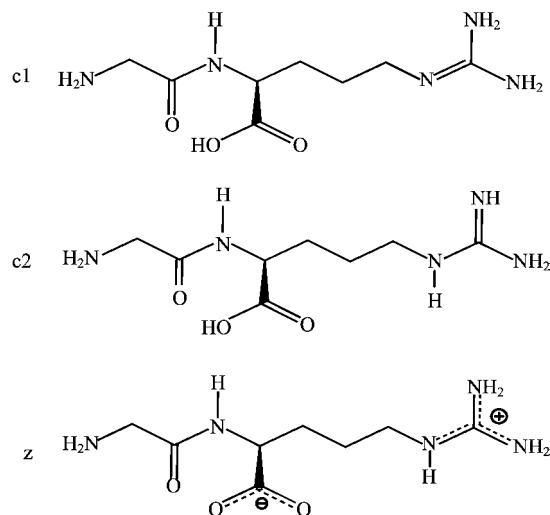


FIG. 1 Sketches of the three tautomers of GlyArg dipeptide.

formers, the conformational spaces of the three GlyArg tautomers with *trans* peptide bond configuration are fully searched. The trial structures for the conformational research are generated through a systematic variation of rotational degrees of freedom for all internal single-bonds, as described in detail in Refs.[18, 19]. As a result, a total of 169236, 314856, and 165024 trial structures were generated for the isomers of c1, c2, and z, respectively.

To confine the computational burden to a manageable level, a hierarchical computational approach combining the semi-empirical and first-principle calculations is adopted. All the trial structures were initially optimized by the semi-empirical method of PM3. The unique structures thus obtained were sorted by their HF/3-21G* energies. There are 2546 conformers for c1, 2411 conformers for c2, and 1751 conformers for z that are within the range of 13 kcal/mol from their respective global minima. These low energy conformers were then optimized using the HF/3-21G* method. The unique conformers obtained at the HF/3-21G* level that were within 5 kcal/mol of the global minimum were further optimized at the BHandHLYP/6-31G* level. Finally, the conformers were optimized at the BHandHLYP/6-311++G(d,p) level so that the obtained structures are essentially basis set convergent.

As a result of the above optimization process, a total of 158 geometries were acquired. All these structures were verified to be the true local minima by the vibrational frequency analysis. The vibrational frequencies were calculated at the BHandHLYP/6-311++G** level of theory. The scaling factors for the wavenumbers below and above 2000 cm^{-1} are 0.9608 and 0.9335, respectively [20]. The scaling factors of 0.9540 and 0.9335 were used respectively for the zero point vibrational energy (ZPVE) and the vibrational contribution to the Gibbs free energy [20]. The rotational

TABLE I Relative electronic energies determined by four methods, relative ZPVEs (Δ VE), rotational constants, dipole moments (dipole) and VIEs for 20 canonical and 3 zwitterionic low energy conformers of ArgGly.

Conformer	Relative energy/eV				Δ VE/(kJ/mol)	Rotational constant/GHz			Dipole/Debye	VIE/eV
	E^{BH}	E^{cam}	E^{B97D}	E^{MP2}		X	Y	Z		
c1	0.00	0.00	0.00	0.00	0.00	0.769	0.284	0.259	5.21	8.84
c2	0.55	0.41	0.83	0.94	-0.07	0.789	0.277	0.253	5.22	9.00
c3	0.66	0.62	0.77	0.68	-0.01	0.778	0.283	0.258	5.12	8.98
c4	2.33	2.62	1.37	4.40	-0.24	0.704	0.283	0.249	6.99	9.05
c5	2.80	2.96	2.09	5.12	-0.33	0.721	0.276	0.244	7.00	9.06
c6	3.84	4.74	3.50	4.77	0.49	0.874	0.295	0.243	5.79	8.92
c7	5.02	4.81	2.08	5.80	-0.15	0.777	0.280	0.257	6.25	8.72
c8	6.59	7.42	9.23	10.46	0.35	0.940	0.257	0.228	5.14	9.08
c9	7.21	8.49	6.26	10.21	0.28	0.795	0.293	0.236	7.97	9.05
c10	9.08	10.23	10.71	15.00	0.21	0.849	0.254	0.222	7.49	9.11
c11	9.83	10.18	7.35	11.09	0.44	0.598	0.357	0.275	9.16	9.08
c12	10.84	11.41	4.47	8.43	0.32	0.596	0.390	0.311	5.32	8.87
c13	12.50	16.43	22.55	15.43	0.11	0.680	0.308	0.231	4.16	7.88
c14	13.25	17.57	23.02	19.28	0.10	0.627	0.335	0.271	5.57	7.80
c15	13.29	17.17	23.50	16.28	0.10	0.671	0.309	0.232	4.09	7.89
c16	13.51	17.64	24.75	17.17	0.14	0.675	0.307	0.231	3.79	7.80
c17	14.29	18.38	25.74	18.01	0.09	0.667	0.309	0.233	3.64	7.81
c18	15.24	19.34	23.26	21.26	0.22	0.627	0.332	0.266	7.06	7.87
c19	15.74	18.05	9.99	5.85	0.59	0.688	0.410	0.324	2.52	8.48
c20	16.30	16.15	14.77	14.38	0.25	0.969	0.273	0.260	5.35	8.87
z35	19.27	13.78	15.98	18.81	-0.21	0.907	0.285	0.256	10.60	8.49
z37	19.43	14.33	15.14	20.73	-0.21	0.935	0.266	0.262	11.57	8.68
z40	19.50	13.96	15.51	18.52	-0.14	0.827	0.307	0.287	11.31	8.47

constants were determined at the highest geometry optimization level, *i.e.*, at the level of BHandHLYP/6-311++G(3df,3pd). The dipole moments were calculated with MP2/6-311++G(3df,3pd) as the MP2 dipole moments were known to agree well with the experiment [21]. The relative energies of ArgGly conformations were found to be strongly dependent on the method used [6]. To avoid biased claims, the electronic energies of GlyArg conformations were calculated by the approaches of BHandHLYP, B97D [22], B97D [23, 24], Cam-B3LYP [25], and MP2 [26] with the basis set of 6-311++G(3df, 3pd). The vertical ionization energies (VIEs) of the conformers were calculated at the level of BHandHLYP/6-311++G(3df,3pd).

The trial structures were generated by our in-house developed software. All the quantum chemistry calculations were performed with the Gaussian 09 [27] suit of programs on our PC clusters and at the Supercomputer Center of the University of Science and Technology of China.

III. RESULTS AND DISCUSSION

A. Conformations of GlyArg

For convenience, the conformations of GlyArg are denoted as *cn* and *zn* in the following discussion. Here

c and *z* are letters indicating the conformations to be the canonical and zwitterionic structures, respectively. The numeral suffix *n* is used to indicate the stability of the conformation ordered according to the ascending BHandHLYP/6-311++G(3df,2pd) energy. A total of 53 conformers are found in the range of 5 kcal/mol from the global electronic energy minimum. Table I shows the relative electronic energies, relative ZPVEs, dipole moments, rotational constants, vertical ionization energies, VIEs, for the 20 lowest energy canonical and 3 lowest energy zwitterionic conformers. The relative electronic energies calculated by the approaches of BHandHLYP, Cam-B3LYP, B97D, and MP2 are denoted as E^{BH} , E^{cam} , E^{B97D} , and E^{MP2} , respectively.

As shown in Table I, the results of BHandHLYP and cam-B3LYP are similar, and the results of B97D and MP2 are alike, while notable differences are observed between the results of BHandHLYP/cam-B3LYP and B97D/MP2. The results indicate that B97D is better than cam-B3LYP for representing the long-range dispersion interaction in GlyArg. Nevertheless, all methods agree on the set of four lowest energy conformers and that the energy of the most stable zwitterionic conformer is about 4 kcal/mol above the global minimum. Though a number of low energy conformers found here

TABLE II Equilibrium distributions (%) of important GlyArg conformers at various temperatures as calculated by four different methods. Equilibrium content below 1% is ignored.

Conformer	98 K				298 K				498 K			
	BH	Cam	B97D	MP2	BH	Cam	B97D	MP2	BH	Cam	B97D	MP2
c1	37.49	37.22	28.33	52.42	19.64	20.29	16.11	27.90	12.83	13.74	12.15	18.63
c2	25.39	29.81	13.62	21.98	16.63	18.16	12.19	20.18	11.53	12.76	10.21	15.23
c3	17.36	18.10	11.42	23.61	15.52	16.30	12.17	21.85	11.29	12.21	10.41	16.31
c4	10.31	7.09	25.03	1.14	20.37	18.65	24.52	12.55	18.09	18.02	21.56	15.93
c5	9.25	7.56	16.73		20.95	20.30	22.89	11.66	19.43	20.03	21.86	16.12
c6									1.31	1.13	1.34	1.51
c7			4.84		3.22	3.63	8.67	3.35	4.37	4.92	8.43	5.26
c8									1.12			
c9									1.51	1.19	1.80	1.06
c10									1.32	1.07		
c12											1.48	
c14									1.13			

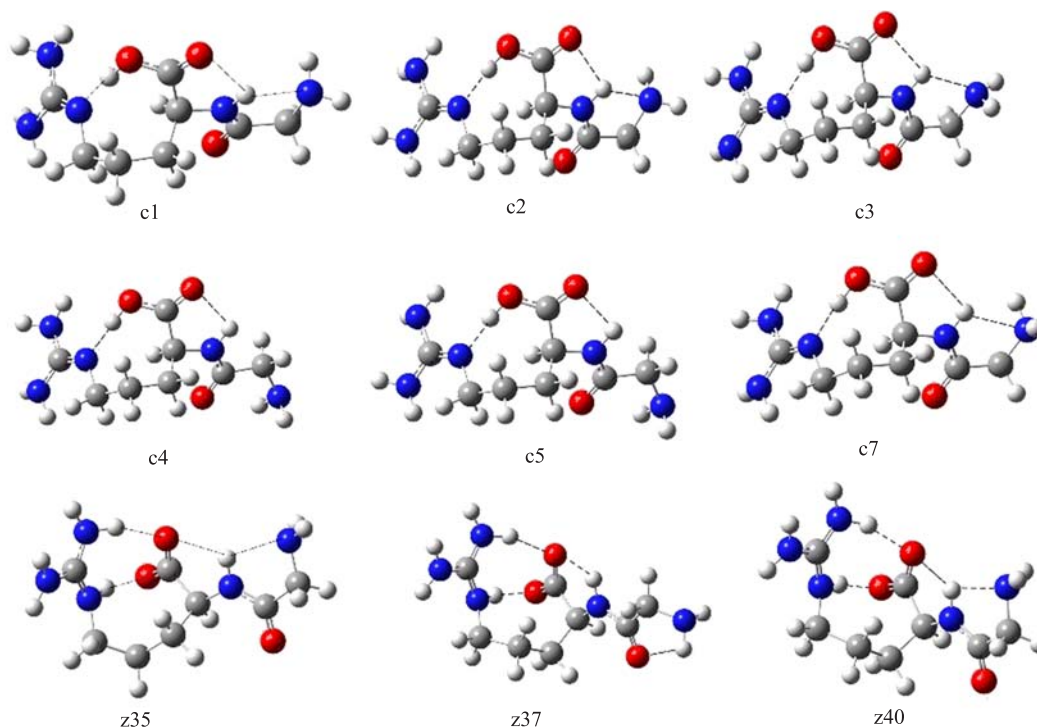


FIG. 2 Structures of representative low energy conformers of GlyArg.

are reported before, the global minimum identified here, c1, is the same as the previous one [17].

Table II shows the equilibrium distributions of significant conformers at three characteristic temperature of 98, 298, and 498 K. A significant conformer is loosely defined here as any conformer that has an equilibrium content larger than 1% at any examined characteristic temperature, as calculated by any one of the methods of BHandHLYP, Cam-B3LYP, B97D and MP2. As shown in Table II, all significant conformers are canonical. Moreover, the four methods provide similar re-

sults for the conformational distributions of GlyArg. The results are characteristically different from that of ArgGly [6]. In addition, it is noted that GlyArg is a genuine multi-conformational ensemble as there are five conformers with populations over 10% at room temperature. In fact, even at the low temperature of 98 K, there are at least 3 coexisting conformers with populations over 10% (Table II). Besides, the entropic effect on the conformational distribution of GlyArg is less significant than that of Arg and ArgGly [6, 15] due to the relatively high similarity among the low energy confor-

TABLE III Characteristic vibrational modes of canonical and zwitterionic conformations of gaseous GlyArg.

Frequency/cm ⁻¹	c1	z35
1451.02		Stretching of C=O in COO
1497.96	Wagging of O–H in COOH	
1826.87	Stretching of C=O in COOH	
2868.17		Antisymmetric stretching of N–H in guanidine plane
2925.65	Stretching vibration of O–H in COOH	
2969.70		Symmetric stretching of N–H in guanidine plane

mations of GlyArg, as shown in Fig.2.

The dipole moments, rotational constants and vertical ionization energies of molecules may be measured directly by experiments [21, 28, 29]. The data reported in Table I and Table II may be verified by and/or used to explain the future experiments. The IR spectra are also informative on revealing internal structural characteristics and are measured routinely [30, 31]. To provide more possibilities for the verification of the above reported conformational results by the future experiments, Fig.3 shows the IR spectra for the representative conformations, c1, c2, c3, c4, c5 and z35, and the ensemble average of GlyArg conformations at various temperatures. Figure 3 may be used to identify the IR modes that distinguish the canonical conformations and zwitterions. For clarity, it is noted that all the important canonical conformers are c1 conformers, as seen from Fig.2 and Table II. Therefore, the vibrations concerning the neutral or deprotonated carboxyl group and the N–H group in the guanidine plane are the candidates for differentiating the canonical and zwitterionic conformations. Using c1 and z35 as the representatives of the canonical structure and zwitterions, the relevant IR modes are shown in Table III. As may be seen in Fig.3, an IR peak at around 1830 cm⁻¹ can be seen for all canonical conformers, but is absent for the zwitterionic conformer. The peak corresponds to the stretching vibration of carboxyl O=C that should be present for all conformers. For all low energy zwitterions, however, the vibrational mode is dramatically red shifted due to the strong electrostatic interaction between the deprotonated carboxyl group and the protonated guanidine group. For example, the vibrational frequency is 1451 cm⁻¹ for z35, as shown in Table III. As a result, the presence of IR peak at ~1830 cm⁻¹ is an evidence for the presence of canonical structure in the conformational ensemble. Though GlyArg is a genuine multi-conformation ensemble for most temperature, only the global minimum may be observed at very low temperature, say, around 10 K or below. Therefore, the global minimum of GlyArg may be verified to be a canonical conformer if the peak at ~1830 cm⁻¹ is observed at very low temperature. On the other hand, the vibrational frequency at ~2970 cm⁻¹ is due to the stretching vibration of guanidine H and is characteristic of the zwitterions structure. The frequency of the stretching vibration

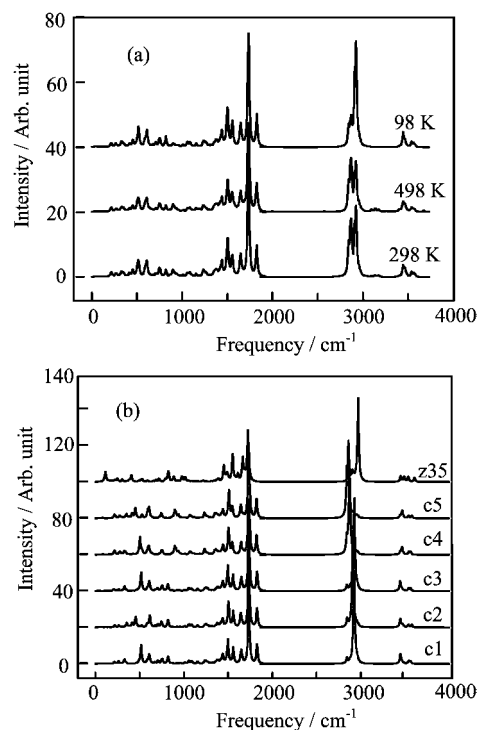


FIG. 3 IR spectra of GlyArg conformers. (a) Ensemble average at three temperatures, (b) by the individual conformer of c1, c2, c3, c4, c5 or z35. The IR bands are Lorentzians with the full width at half maximum of 20 cm⁻¹.

of guanidine H in zwitterions is higher than that of the carboxyl O–H stretching vibration in canonical conformers by more than 40 cm⁻¹ and the two modes are easily distinguishable experimentally. If the vibrational mode at the vicinity of 2970 cm⁻¹ is observed in the IR measurement of well equilibrated GlyArg ensemble, the presence of stable zwitterions is established, which would invalidate our theoretical predictions.

B. Model about the global minimum configuration of dipeptide

Based on the conformations of dipeptides that have been investigated thoroughly and considering the hydrophobicity/hydrophilicity of the amino acid residues, a model about the configurations of the global minima

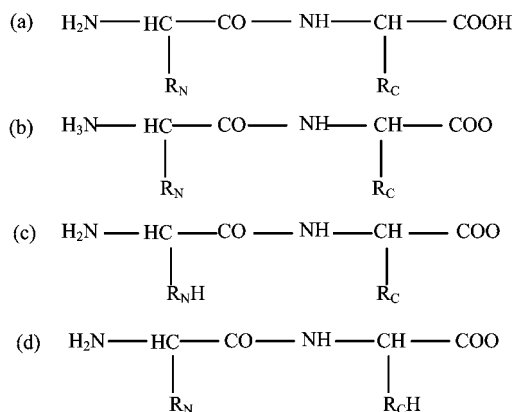


FIG. 4 Structure sketch for the possible conformational types of dipeptides.

of gaseous dipeptides may be proposed.

Figure 4 illustrates the possible conformational types of dipeptides. R_N and R_C in Fig.4 represent the side chains of N-terminal and C-terminal, respectively. R_N and R_C are also used to represent the residues of N- and C-terminal in the following discussion. Figure 4(a) shows a canonical configuration, referred as type C structure below. As the deprotonation propensity of backbone carboxyl is higher than that of any amino acid side chain [32–35], there are three possible configurations for zwitterions, as illustrated in Fig.4 (b), (c), and (d). Figure 4 (b), (c) and (d) indicate that the protonation sites are the backbone amino group, R_N and R_C , and are referred below as Z_b , Z_n and Z_c , respectively.

The hydrophobicity/hydrophilicity of amino acid side chain may be measured with a hydrophobic index I_pho . I_pho varies from -4.5 to 4.5 for the 20 natural amino acids: Arg(-4.5), Lys(-3.9), Asp(-3.5), Glu(-3.5), Asn(-3.5), Gln(-3.5), His(-3.2), Pro(-1.6), Tyr(-1.3), Trp(-0.9), Ser(-0.8), Thr(-0.7), Gly(-0.4), Ala(1.8), Met(1.9), Cys(2.5), Phe(2.8), Leu(3.8), Val(4.2), Ile(4.5) [36]. A positive value for I_pho means that the side chain is hydrophobic, while a negative value for I_pho shows that the side chain is hydrophilic. $-I_\text{pho}$ is indicative about the degree of energy gain by forming intramolecular hydrogen bond. Since only strong H-bonds may stabilize the zwitterions, and considering a high energy local minimum zwitterions may be formed in histidine with $-I_\text{pho}=3.2$, the AA residues may be classified into two groups, $\text{R}_1(-I_\text{pho}>3)$ and $\text{R}_2(-I_\text{pho}<3)$. As a relatively low energy zwitterions may be formed by Arg, R_1 may be further divided into $\text{R}_{11}(-I_\text{pho}>4)$, *i.e.*, $\text{R}_{11}=\text{Arg}$, and $\text{R}_{12}(3<-I_\text{pho}<4)$.

Based on the results for GlyArg, the global minima of dipeptides belong to the type C structure when $\text{R}_\text{N}=\text{R}_2$ and $\text{R}_\text{C}=\text{R}_1+\text{R}_2$, *i.e.*, R_C can be any amino acid residue. Due to the results for ArgGly [6], the global minima of dipeptides are Z_n for $\text{R}_\text{N}=\text{R}_{11}$ and $\text{R}_\text{C}=\text{R}_{12}+\text{R}_2$. The global minimum for $\text{R}_\text{N}=\text{R}_{11}$ and $\text{R}_\text{C}=\text{R}_{11}$ may be either Z_n or Z_c , though the former is

more likely. In light of the results for LysGly [11], the global minima are type C structures when $\text{R}_\text{N}=\text{R}_{12}$ and $\text{R}_\text{C}=\text{R}_2$. For $\text{R}_\text{N}=\text{R}_{12}$ and $\text{R}_\text{C}=\text{R}_1$, the conclusions are uncertain and require detailed studies. It is very likely that the global minima for $\text{R}_\text{N}=\text{R}_{12}$ and $\text{R}_\text{C}=\text{R}_{11}$ are Z_c . For $\text{R}_\text{N}=\text{R}_{12}$ and $\text{R}_\text{C}=\text{R}_{12}$, the global minima may be Z_b or type C.

IV. CONCLUSION

The conformational space of gaseous GlyArg has been searched extensively through a systematic exploration of the potential energy surfaces of three ArgGly tautomers. A total of 53 conformers are found within a range of 5 kcal/mol of the global minimum. The global minimum is confirmed to be a canonical conformation by all the four methods of BHandHLYP, B3LYP, B97D and MP2 with the basis set of 6-311++G(3df,3pd). Important data such as relative energies, dipole moments, rotational constants, VIEs, equilibrium conformation populations and IR spectra are presented that are helpful for understanding the future experiments. In addition, a model predicting whether the global minimum configuration of a gaseous dipeptide is canonical or zwitterionic is proposed. The model is deduced from the information about the global minima of all amino acids and a substantial number of dipeptides, combined with the hydrophobicity/hydrophilicity of the side chain of amino acid residue. The model may be easily generalized for a large portion of tri- and tetra-peptides.

V. ACKNOWLEDGMENTS

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