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Scientific paper

The Role of Nitrogen-Rich Moieties in the Selection of Arginine's Tautomeric Form at Different Temperatures

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Abstract

It is well known that the guanidinium group in Arginine plays an important role in noncovalent interactions. However, its role is not well documented since the selection of its global minimum structure is still controversial. The main difficulties on obtaining accurate results lie on: neutral Arginine can occur in 3 forms, two of which are canonical and one is zwitterion; each form has degenerate enantiomers D- and L-; its numerous degrees of freedom make it challenging to perform a thorough study; the short-range interactions require higher levels of theory to correctly describe them. Thus, we have performed a meticulous global minimum search. We performed optimizations of the systems at the PBE0 / Def2TZVP level of theory and single point calculations at the DLPNO-CCSD(T)/Def2TZVP level with zero-point corrections at PBE0 /Def2TZVP. We also analyzed Thermal Populations and IR Spectra of the systems to fully understand Arginine's behavior. The results show the energy minima structures strongly rely on its internal nitrogen-rich groups.

Keywords: Arginine, canonical forms, zwitterion, theoretical study

1. Introduction

L-amino acids are naturally occurring molecules that are essential in several biofunctions[1–4]. D-amino acids are also important in biological systems such as memory and growth[5–10]. D-serine (D-Ser) is an indicator for early-stage tumor growth. Atypical levels of D-serine can induce schizophrenia, Alzheimer's disease, amyotropic lateral sclerosis[11,12]; low levels of D-aspartic acid (D-Asp) can lead to sexual disfunction[13]; D-arginine (D-Arg) has a high toxicity for bacteria[14–16]. Unfortunately, the understanding of D-amino acids is still incomplete due to technical limitations for their detection[17]

Amino acids exist as zwitterions in aqueous solution at a specific pH window[18–22]. The structure of amino acids is specially sensitive to protic solvents[23–26] since they release H^+ in the solution, forming hydrogen-bonded networks with them. In the absence of solvent, it has been reported experimentally that not all amino acids exist as zwitterions[27–30]. In the case of Arg in aqueous solution, the formation of zwitterions is led by a protonation of the guanidine side chain[31]. Similarly, in the gas phase, the guanidine side chain acts as a competitive site of protonation compared to the carboxylate group[32]. Whether or not the most stable structure in the gas phase is a zwitterion is still under debate[28, 31–36]. Its extremely basic guanidine side

chain makes arginine perhaps one of the common naturally occurring amino acid most likely to form a stable zwitterion[25]. Arg can form stable charged aggregates intermolecularly bound by salt bridges[29,37–39]. In addition, several studies have shown that zwitterionic states can be induced through different mechanisms such as: adding diffuse proximal charges[40–45], electrons[46], noncovalent clustering[29,39] or a few solvent molecules[47–49].

The determination of the dominant tautomeric form of neutral Arg in the gas phase has been studied experimentally[32,35,29,39–42]. According to the work of Price and coworkers, protonated dimers of arginine are bound in a salt bridge[32]. Their study at BLYP/6-31G* and MP2/6-31G* levels of theory implied that the global minimum of arginine is a zwitterion lower by 1 kcal/mol than the lowest canonical tautomer. Anyhow, Maksic and Kovacevic performed MP2 and density functional theory (DFT) calculations[50], where they reported that the most stable structure was canonical with a energy difference between the lowest zwitterion and canonical structures within 1-3 kcal/mol depending on the level of theory. Skurski and coworkers have extended this work at CCSD/6-31++G(d,p)+5(sp)//MP2/6-31++G(d,p)+5(sp) levels of theory[36] and found the canonical form to be 2.8 kcal/mol lower in energy than the lowest zwitterion. This group performed a more extensive global minimum search at CCSD/6-31++G** level of theory, obtaining the minimum canonical structure was 3.2 kcal/mol lower than the lowest zwitterion. Ling and coworkers have similar results at CCSD/6-31++G(d,p) level of theory, where the most stable canonical conformer is 3.4 kcal/mol lower than the lowest zwitterion[51].

A conformational search for arginine is the most challenging of the 20 amino acids due to its great number of degrees of freedom[28,33]. Arginine has two kinds of proton donor groups (OH and NH), six proton acceptor sites (N's and O's) and six/seven (depending on the tautomer) bonds that can be rotated. Thus, a meticulous conformational search is required. If not done carefully, it could lead to mistaking local with global minima. Several conformational searches on arginine have been performed in the gas phase[31, 35, 36, 50–53]. Theoretical studies in the presence of water have also been conducted[24,54–58]. Gu et al. performed a theoretical study on the thermal dissociation of singly protonated Arginine[59]. They reported that backbone dissociations and side-chain fragmentations compete during dissociation. The guanidine loss occurred as a consequence of the side-chain dissociation; while CO and H_2O loss were part of the backbone breakage. The effect of temperature on neutral Arg has been taken into account in the past. However, only a few representative temperatures have been reported[51].

In this paper, we performed a thorough energy minima search for both D- and L- enantiomers, which has only been done to the best of our knowledge for L-arginine in the gas phase[36,51]. Before the study of the solvation of arginine, it is of primordial importance to understand its electronic interactions in the gas phase and use them as a reference point for further investigations. The results could help predict its behavior upon solvation in different media. This search was performed at DLPNO-CCSD(T)/Def2-TZVP level of energy. This wider basis set is a correction to those used in previous papers[36,51] to take into account the dispersion forces involved in these systems more accurately.

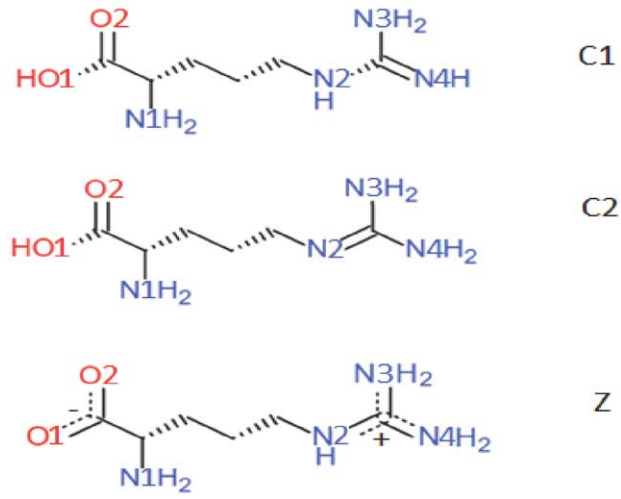

Fig. 1. Structures of canonical 1 (C1), 2 (C2) and zwitterionic arginine considered in this work.

Several works have shown that energy minima structures are temperature-dependent,[60–66]. Thus, we performed a temperature-dependent relative populations analysis in the range of 0–1800 K since enantioselectivity is a function of temperature[60,67]. It is our intention to elucidate if nitrogen-rich moieties such as the guanidinium and amino groups participate in minimizing the energy of Arginine structures, based on reports[22,32] that have affirmed that the guanidine side chain is a competitive site of protonation.

Photodissociation spectra for cationized Arg with Li^+, K^+, Na^+ have been experimentally observed in[68]. In this work, we calculate the gas phase temperature dependent Boltzmann weighted IR spectra. These two spectra are not comparable. To the best of our knowledge, Arginine's IR spectra is not reported.

2. Theoretical Methods

2. 1 Computational Details

We employed the ensemble DFT methodology in order to emulate experimental conditions[69]. It has been proven to be valid for finite temperatures[70]. The global minimum search for Arg is complicated due to the amount of degrees of freedom, as mentioned in the Introduction section. To explore the potential free energy surface, we

employed the kick methodology[71]. The global minima search is computationally expensive for medium to large systems. Especially, for Arg with several dihedral angles, the possible configurations rise significantly. We studied it at a higher level of theory than past studies[31,35,36,50–53], at the domain based local pair natural orbital coupled cluster single, double and perturbative triples DLPNO-CCSD(T)[72,73] level of theory. We employed a two-step approach. The first step was to perform a thorough exploration of the potential energy surface at the PBE0 / Def2TZVP[74,75] level in conjunction with the Grimme dispersion correction GD3[76] coupled to the conformational search code (CSC). It generated 800 conformers with the random variation of dihedral angles of Arg, similarly to other conformational search algorithms[77] applied in Python as a part of global search of the GALGOSON code[60,61]. The second step was to obtain single point calculations of the lowest energy systems at the DLPNO-CCSD(T)/ Def2TZVP level with zero-point corrections at the PBE0 / Def2TZVP. The optimizations and single point calculations were all performed using the ORCA software[78].

2. 1. Thermochemical Properties

We used the following equations to calculate thermochemical properties. The partition function Q assuming ideal gas, a particle in a box, rigid rotor harmonic oscillator (RRHO), and Born Oppenheimer approximation (BOA)[79] is stated on equation (1)

$$Q(T) = \sum_I g_i e^{\Delta E_i / k_B T}, \quad (1)$$

Where q_i is the degeneracy factor, k_B is the Boltzmann factor, T is temperature and ΔE_i is the total energy. It should be noted that in order for an accurate comparison between theoretical and experimental results, anharmonicity must be contemplated.

Employing BOA and RRHO approximations, Q can be expressed by equation (2)

$$Q = q_{trans} q_{rot} q_{vib} q_{elec}. \quad (2)$$

The equations for each component to the canonical ensemble are reported in[80]. The equations for free energy, entropy, enthalpy and internal energy (U) depend on the partition function since they can be expressed either in terms of it or its derivatives[80–82].

2. 2. IR Spectra

The IR spectra and vibrational spectra of each isomer were computed employing DFT as implemented in ORCA code[78] under the harmonic approximation. Anharmonic effects are not considered. We scaled harmonic frequencies by a factor of 0.97 and convoluted with a Gaussian line shape of 20 cm^{-1} full width at half maximum (FWHM).

At thermal equilibrium all arginine-rotamers are populated according to the Boltzmann distribution. Consequently, the observed properties in a molecule are statistical Boltzmann-averages over the ensemble of geometrical conformations. We employed the thermal population to compute the IR spectra of arginine at temperature T, we weighted the IR spectrum of each isomer according to the thermal populations and summed them up.

3. Results and DiscUSSION

3. 1. Energy Minima Structures

Qualitatively, the energy values of all reported geometries at PBE0/def2-TZVP and DLPNO-CCSD(T)/ def2-TZVP levels showed the same trend. It is interesting to note that C2 D- geometries where not obtained on previous theoretical studies and therefore we only compare L- geometries. Our results listed in Table 1, confirm L- and D- Arg structures' degeneracy.

Fig. 2 shows the lowest energy structures of arginine for D- and L- enantiomers of C1, C2 and Z at 0K. The global energy minima structures are D- and L- C2. References[36,51] have a very similar L- C2 structure (named C3 and C4 in their papers, respectively) with mild differences. The main hydrogen (H-) bonds are a) between N2 and HO1 and b) two H-bonds form between O2 and the amino group $N1H_2$.

Structures 3 and 4 are only at 0.07 kcal/mol higher than geometries 1 and 2. Most noncovalent interactions in arginine are due to the guanidinium group, as Schug and Linder wrote on their Review[8386]. This has incredible variations on entropy and thus on thermal percent shares, which will be discussed further on.

Table 1. Relative energies in kcal mol^{-1}. DLPNO-CCSD(T) and PBE0 with zero-point energy correction at 0K for structures 1–12.

Arg	CCSD(T)	PBE0
1	0.00	0.00
2	0.00	0.00
3	0.07	0.02
4	0.07	0.02
5	1.47	1.07
6	1.47	1.07
7	1.53	1.14
8	1.53	1.14
9	1.51	1.37
10	1.51	1.37
11	5.04	2.13
12	5.04	2.13

Structures 5 and 6, at a relative energy of 1.47 kcal/mol, differ from the last structures mainly on the loss of a H-bond between O2 and N1H2. Structures 7 and 8 have a

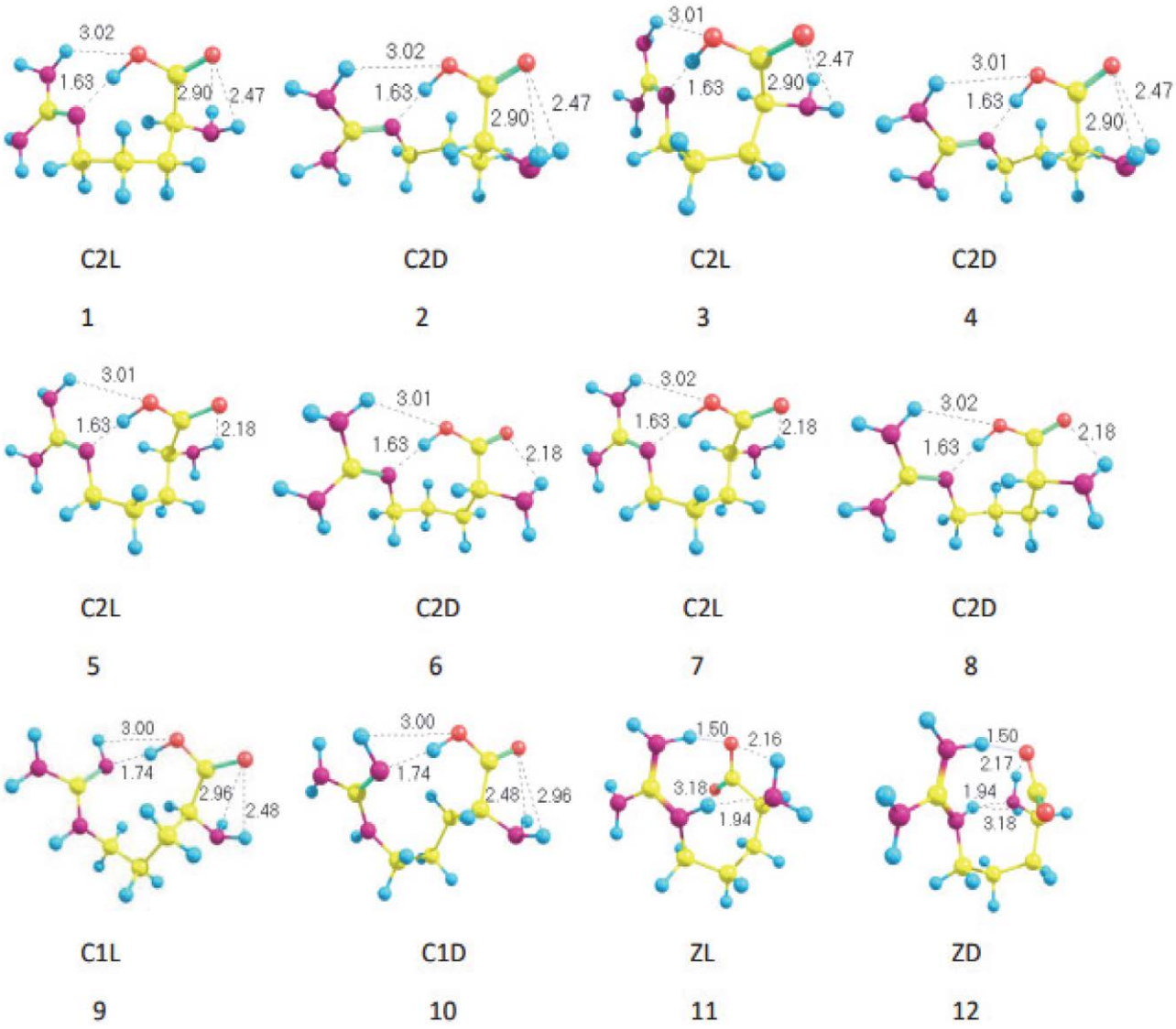

Fig. 2. Selected geometrical parameters in Å for geometries 1–12, where C1, C2 and Z stand for canonical 1, 2 or zwitterion, respectively according to Fig. 1. L or D stand for Levorotatory or Dextrorotatory enantiomers, respectively.

relative energy of 1.53 kcal/mol. They share most H-bond values. Anyhow, positions of the hydrogens on both, the guanidinium and amino groups differ. Structures 5–7 are most similar to structure C5 on ref,[51] There are no similar structures for ref.[36]

At a relative energy of 1.51 kcal/mol the D- and L-enantiomers of C1 Arg were found. These structures also form H-bonds similar to those of Ref[36]. As for Ref.[51], the most stable C1 geometry is totally different, with a relative energy of 0.65 kcal/mol.

At 5.038 kcal/mol, we found the first zwitterionic arginine enantiomers. The DFT relative energy for the zwitterionic enantiomers was of 2.13 kcal/mol. This notable difference can be accounted for the importance of the methodology used on systems with short-range interactions. The results of[36,51] show that the first zwitterion was 3.2 and 3.4 kcal/mol away from the most stable canonical structure, respectively. The wider basis set we used (def2-TZVP) models dispersion forces better, which increase on zwitterionic structures. The most stable zwitterion at 0K we found shows half structure facing toward the other half, which increases the van der Waals interactions and even adds a H-bond between N1 and N4H of 1.94 Å (1.96 Å for Ref[51]) in addition to a H-bond between O2 and N3Hthe carboxylate group and the guanidinium group of 1.50 Å (1.59 Å for Ref[51]). The first zwitterion found on Ref[36] does form this last H-bond at 1.64 Å, yet the amino group lies far apart from the guanidinium group and does not form a H-bond.

3. 1. Thermal Populations

At 0K, thermal populations of C2-Arg structures 1 and 2 are immensely different from those of 3 and 4. It is

interesting to note that the main difference between these pairs of structures relies on the position of hydrogen atoms on amino and guanidinium groups.

At low temperatures, the degrees of freedom of the system are minimum. However, at higher temperatures, kinetic energy allows movement. Thus, this implies higher degrees of freedom, positively influencing entropy. At around 335 K, which is a healthy body temperature, structures 1–4 are equiprobable.

Fig.3 depicts the importance of nitrogen-rich groups in arginine on thermal populations. These groups are responsible for not only the gap at 0K between structures 1–4, but also with the rest of the geometries, which is confirmed by Shug and Linder's review[8386], where they state that the guanidinium group is accountable for most non-covalent interactions of arginine, as mentioned in the above Results and Discussion section. Structures 5–8 are also C2-Arg, with an important difference, the loss of a hydrogen bond between O2 and HN1. Structures 9 and 10 correspond to C1-Arg, where the main difference with C2-Arg lies on a double bond in the guanidinium group.

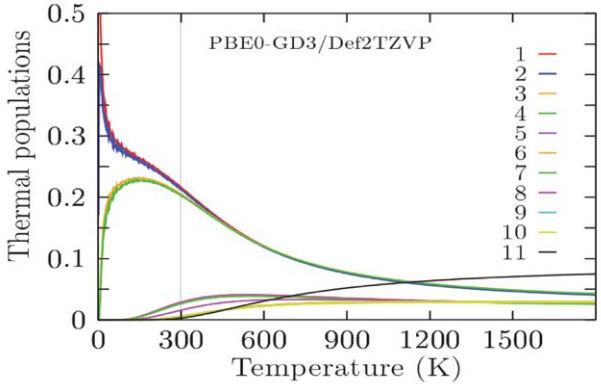

Fig. 3. Relative population for temperature 0–1800 K at the CCS-D(T)/Def2-TZVP.

Geometries 11 and 12 pertain to Z D- and L- enantiomers. By around 750 K, their curve has crossed those of structures 5–10 and by around 1100 K, their thermal population is the highest. At higher temperatures, increased kinetic energy could contribute to the migration of a hydrogen from the carboxyl group to the guanidinium one.

3. 2. IR Spectra

A direct comparison between experimental IR data and IR spectra is not possible since in most DFT calculations the temperature is not considered. Differences between experimental and calculated IR spectra can be due mainly to finite temperature, anharmonic effects and the fact that IR experiments are essential of multi-photon nature, whereas IR spectra calculations assume single-photon processes and DFT calculations are at O K.

According to our DFT calclulations, only few low energy structures on the free energy surface strongly dominate the thermal population in temperature range 0 to 900 K and are responsible for the observed IR in Arg. This is displayed in Fig. 3.

Fig. 4 displays the Boltzmann spectrum for Arg. In it there are two main peaks. The first one is located at 1700 cm^{-1} that pertains to the carbonyl-bending of the carboxylate group. The second peak at 491 cm^{-1} represents the bending of the hydrogens attached to N3 and N4.

In Fig.4a we show the IR spectrum of the lowest energy structure of arginine. D-enantiomers at room temperature have a contribution of 21%. We underline the lowest energy conformers of arginine are enantiomers. Fig. 4b portrays the IR spectrum of the lowest energy enantiomers-L. Their contribution to total IR spectrum is similar, with a value of 20.7%. In Fig. 4c,d we show the spectrum of the lowest Arg-enantiomers configurations with just an H with a different orientation in the amine group. Energetically, the isomers located at the same thermal point, but at cold temperature, below 335 K, have a different probability. In summary, the IR spectrum and all molecular properties are strongly dominated by those four structures through the entire temperature range of 20 to 900 K.

4. Conclusion

According to our studies, more than 89% of Arg occurrence is attributed to C2. D- and L- enantiomers showed to be equally likely in all the range of temperatures. At 0K, structures 1 and 2 are global energy minima. The difference with structures 3 and 4 lies only in the orientation of hydrogen atoms bonded to N-rich groups such as the amino and guanidinium groups. As temperature rises, at around 335 K, structures 1–4 are equiprobable. This could be explained by the fact that as temperature increases, so does kinetic energy, enabling the movement from one configuration to another. Structures 5–8 have only form 1 hydrogen bond O2-HN1, whereas for structures 1–4, they form 2 hydrogen bonds between these moieties. The first zwitterion appeared at 5.04 kcal/mol higher in energy than the global energy minimum C2 structure. The relative energy at which the first zwitterion appears has been a very controversial subject. We reported energies at the DLPNO-CCSD(T)/Def2TZVP and the PBE0/Def2TZVP level. The greatest difference in them was with the zwitterion, where the predicted energy was of 2.13 kcal/mol. This is more than twice the energy difference. Zwitterions should be studied at a high theory level, since short range interaction such as dispersion forces play a strong role in their interactions. This could be the reason why previous works36,50,51 differ so much on how far from the most stable canonical structure are they.

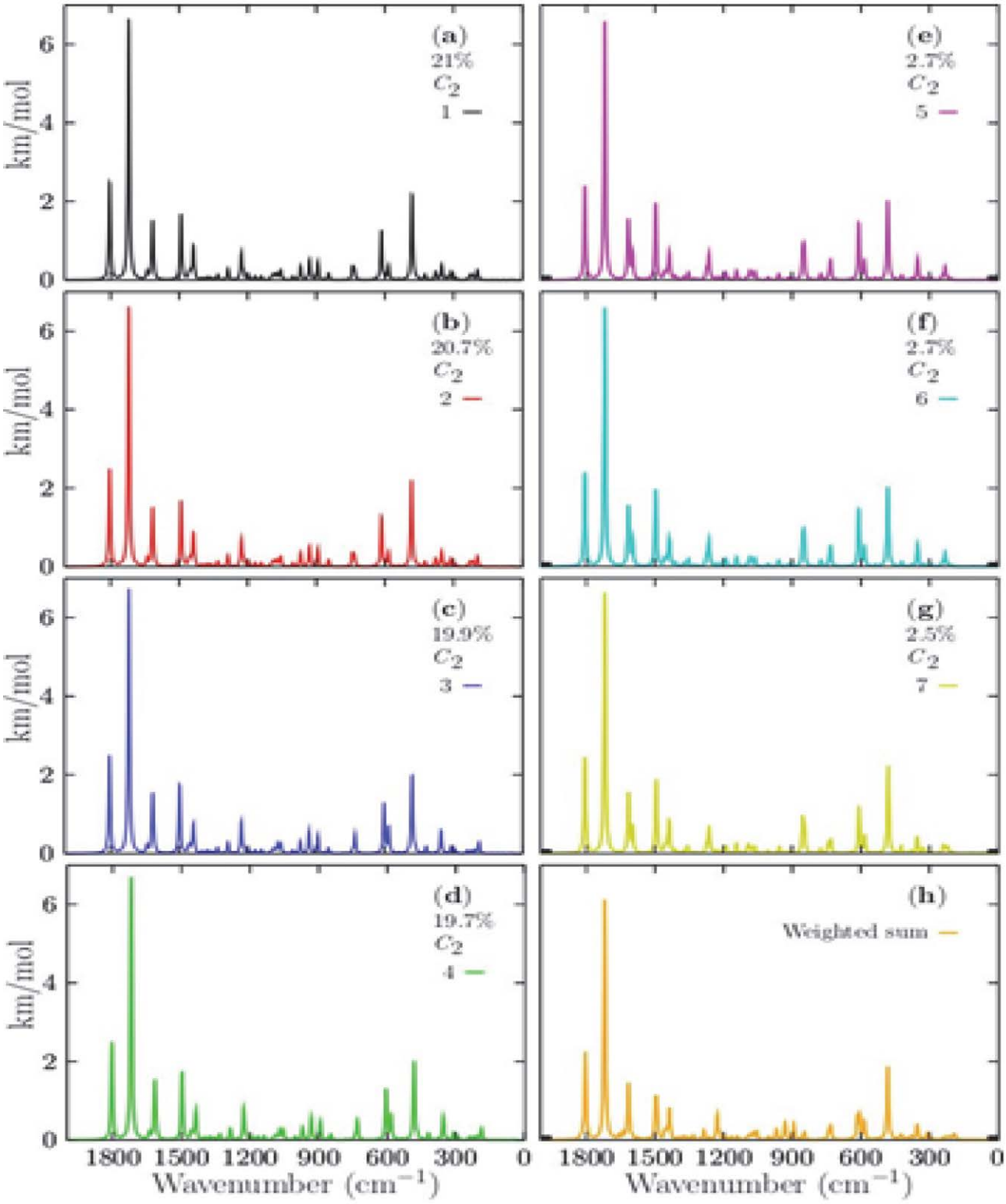

Fig. 4. IR Spectra of most probable structures (1–7). They comprise 89.2% of occurrence.

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Povzetek

Dobro je znano, da ima gvanidinska skupina v argininu pomembno vlogo pri nekovalentnih interakcijah. Kljub temu njena vloga ni dobro dokumentirana, saj je določitev strukture v globalnem minimumu energije težka in nezanesljiva. Glavna težava pri pridobivanju natančnih rezultatov je v tem, da lahko nevtralni arginin obstaja v treh oblikah; vsaka oblika ima degenerirani enantiomeri D- in L-. Številne prostostne stopnje arginina otežujejo temeljito študijo; za pravilno opisovanje kratkosežnih interakcij je potrebno uporabiti visoko raven teorije. Zato smo izvedli natančno iskanje globalnega minimuma. Opravili smo optimizacije sistemov na nivoju PBE0/Def2TZVP, ki jim je sledil izračun energije na nivoju DLPNO-CCSD(T)/Def2TZVP s popravki ničelnega vibracijskega nivoja, izračunanimi po metodi PBE0/Def2TZVP. Prav tako smo analizirali termične populacije vibracijskih stanj in infrardeče spektre sistemov, da bi podrobneje razumeli lastnosti molekule arginina. Rezultati kažejo, da so strukture energijskih minimumov močno odvisne od položaja z dušikom bogatih funkcionalnih skupin arginina.