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STRUCTURE AND VIBRATIONAL SPECTRUM OF L-LEUCINE: A DFT-PCM INVESTIGATION

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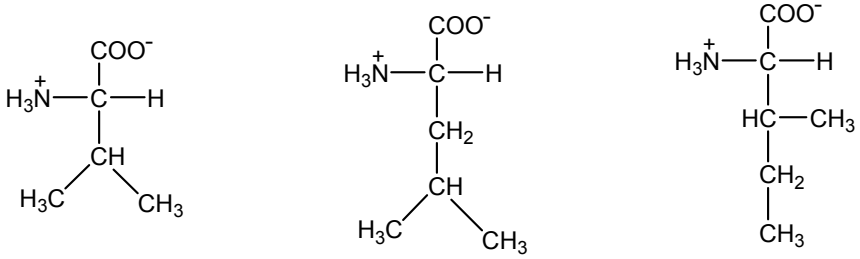
ABSTRACT. The structure of L-Leucine in solution was examined using Density Functional Theory coupled with the Polarized Continuum Model (DFT-PCM). The geometry of L-Leucine zwitterion was studied with the B3LYP/6-311++G(d,p)-PCM method and the results were compared with those previously reported in the literature for X-ray diffraction of L-Leucine. The vibrational frequencies calculated on the most stable zwitterionic conformer of L-Leucine at B3LYP/6-311++G(d,p) were unscaled and in good agreement with the experimental data.

Keywords: *L-Leucine, zwitterions, DFT-PCM, vibrational spectroscopy*

INTRODUCTION

L-Leucine ((2*S*)-2-Amino-4-methylpentanoic acid) is an essential Branched-Chain Amino Acid (BCAA) like L-Isoleucine and L-Valine.



L-Valine L-Leucine L-Isoleucine

Scheme 1.

It is a non-polar and hydrophobic amino acid occurring in proteins about 9.1 % [1]. It is synthesized in living systems being involved in regulations of blood sugar levels and muscular tissue repairing process. Leucine also has a significant contribution in the binding of hydrophobic ligands (lipids) playing an important role in the substrate recognition [2].

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According to [1, 3] in solution at neutral pH, L-Leucine has a predominant zwitterionic form when the amino group is protonated ($-NH_3^+$) and the carboxyl group is deprotonated ($-COO^-$) while the occurance of the nonionic form with amine ($-NH_2$) and carboxyl (-COOH) groups is insignificant.

On the other hand, it is know that vibrational spectroscopy is able as well to provide information on the general aspects of proteins i.e. structure and dynamics [4]. Thus, due to the protein sensitivity to infrared irradiation (*e.g.* vibrational spectroscopic measurements are responsive to pH, phase, solvent polarity and temperature), the use of a model substrate, such as an amino acid, is essential. In addition, a theoretical study is usually required in order to facilitate the interpretation of infrared spectra.

To the best of our knowledge, but a few theoretical (conformational and vibrational) studies focused on L-Leucine were published [2, 5-7].

Recently, Rai *et al.* [2] proposed for L-Leucine fifteen stable conformers in the gas phase, obtained by geometry optimization at the B3LYP/6-311++G(d,p) level. Thus, they analyzed the predicted vibrational infrared spectra of various nonionic L-Leucine conformers. Next, they realized a systematic search on the existence of zwitterionic form of L-Leucine in gas phase and found that the zwitterionic structures revert spontaneously into the canonical form on optimization.

Linder *et al.* [5] investigated, by experimental and theoretical methods, the gas-phase IR spectra of some natural amino acid including L-Leucine. Since they used high temperature (570 K), their study considered limited conformational states and non-hydrogen bonded structures to assume that different conformations would have similar spectra.

In 2010, Dokmaisrijan *et al.* [7] proposed the eight minimum energy conformers of L-Leucine obtained at MP2/6-311++G(2d,2p) level in the gas phase. Their results, relative stability order and some conformational properties of the most stable conformer, were significantly different from the above ones of Rai *et al.* [2]. They also analyzed the effects of intermolecular H-bond and side-chain orientations on the relative stability of L-Leucine.

It is worth to emphasize that these studies [2, 5, 7] considered but the gas-phase state of L-Leucine. This approach may be insufficient as inadequate for the complete description of biological molecules in their natural medium, aqueous solution.

In order to accomplish such a theoretical simulation, it is possible to take into account the solvent effect in two ways i) a certain number of solvent molecules are placed around the solute and ii) the solvent is considered as a continuum medium (with specific physical properties) and the solute molecule is placed in a cavity within the solvent [8].

Vibrational analysis of L-Leucine in hydrated media was previously reported by Derbel *et al.* [6]. They found that if the amino acid was surrounded by twelve water molecules, a good correlation between theoretical calculation at B3LYP/6-31++G(d) level of theory and experimental data occurred.

Hence, in order to study the stability of L-Leucine zwitterions in aqueous solution, for the present exploration we applied a density functional method (DFT/B3LYP) in conjunction with a continuum solvation model, Polarized Continuum Model (PCM). This model uses a cavity of overlapping spheres centered on the solute atoms and apparent surface charges that depend on the dielectric constant ε of the solvent.

We also reporte herein the calculated I.R. spectrum of L-Leucine zwitterion at the B3LYP/6-311++G(d,p) level together with a tentative assignment of its vibrational modes. Thus, all our calculations were carried out using Gaussian03 Package [9]. To display the molecular structure and the simulated I.R. spectra, the Program we used for visualization was Gabedit 2.3.0 [10]. The Avogadro 1.0.1 Program provided information on vibrational modes [11].

RESULTS AND DISCUSSION

1. Molecular geometry

The atom numbering and the most stable zwitterionic conformer of L-Leucine optimized at B3LYP/6-311++G(d,p) in aqueous solution employing PCM model (DFT-PCM) are shown in Figure 1.

The calculations were realized on two geometries i) the X-ray zwitterionic L-Leucine from leucin01 [12] and ii) the zwitterionic structure obtained by transferring the proton from the carboxyl group to the amino group in the lowest-energy gas-phase conformer reported by Rai *et al* [2].

Starting from structures i) and ii), two optimized geometries were obtained. For these geometries, we performed frequency calculations in order to assess which one represents the global minima. The results revealed that the geometry of X-ray zwitterionic L-Leucine optimized using PCM, to include the effect of water, at the B3LYP/6-311+G(d,p) level is not a global minimum because we found three imaginary frequencies.

Next, no imaginary frequency was found for the second zwitterionic structure optimized at the DFT-PCM (water) level; that is, the geometry depicted in Figure 1 is a true minimum on the Potential Energy Surface (PES).

Table 1 lists the selected optimized geometrical parameters of the structure studied in aqueous solution by DFT-PCM. Our results are compared with the DFT data previously reported for L-leucine + 12H_2O (*DFT in hydrated media*) [6] and the corresponding experimental X-ray values [12].

The *intramolecular N-H...O interaction* is a characteristic feature for several α-amino acids both in crystal state and in solution. The two or three-center *intermolecular N-H...O hydrogen bonds* are met in crystal structures of non-polar amino acids (L-Leucine crystallizes as hydrogen-bonded dimmers) [13]. In solution, our theoretical study revealed a value of 1.87 Å for the

intramolecular hydrogen bond between one ammonium hydrogen and one carboxylic oxygen atom (H-9-O-2, Figure 1). Following this intramolecular hydrogen bond interaction, in our model, the atoms N-6, C-4, C-1, O-2 were close to planarity, with a N-6-C-4-C-1-O-2 dihedral angle of -9.3 degree meanwhile in the X-ray structure the N-6-C-4-C-1-O-2 dihedral angle is about -31.7 degree.

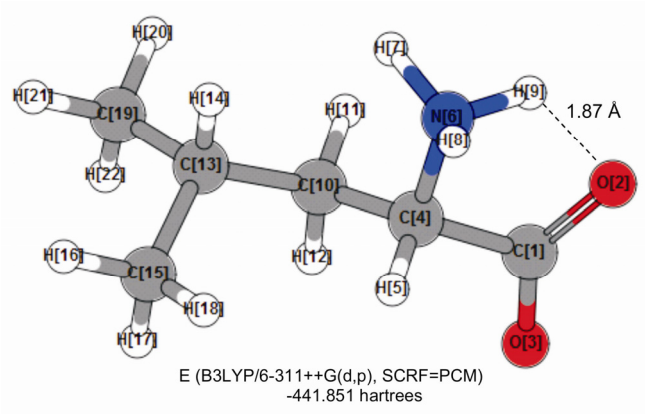

Figure 1. Optimized molecular structure of L-Leucine using PCM (water) model at B3LYP/6-311++G(d,p) level of theory.

In our PCM model, the optimized values for the N-H bond lengths were shorter than the corresponding ones issued from the DFT calculation in hydrated media or from experimental X-ray data, see Table 1. However, the N-H bond lengths values obtained by us were in good agreement with those obtained by [6], the difference being less than 2.28%.

In our model, the N-6-H-9 bond length value (1.044 Å) was longer than the other two N-H bonds (Table 1) and we supposed that happened because the hydrogen atom, H-9, is involved in the intramolecular hydrogen-bonding H-9-O-2 (Figure 1).

As shown in Table 1, the bond length N-6-C-4 (1.515 Å) obtained using our model was longer than the standard C-N bonds (1.47 Å) [14], this situation being characteristic for the C-NH_3^+ bond from amino acids [15]. In the two theoretical models, our DFT-PCM model and the DFT in hydrated media model, the C-N bond lengths (1.515 Å and 1.508 Å) were longer than the experimental value (1.497 Å), but the theoretical and experimental values were in a good agreement.

The COO^- bond lengths are stretched, but our theoretical values were more closer to the experimental ones than the values reported by [6] for DFT in hydrated media model.

Table 1. Selected parameters of zwitterionic L-Leucine. Comparison between our results obtained with DFT-PCM model and the results reported by [6] and [12].

Energies	Zwitterionic structure		
	L-Leucine B3LYP/ 6-311++G(d,p) PCM	Leucine+12H_2O B3LYP/ 6-31++G(d) [6]	L-Leucine Experimental X-ray [12]
E_e (Hartrees)	-441.851	-1359.009	-
Bond Lengths (Å)			
N-6-H-7	1.029	1.040	1.080
N-6-H-8	1.029	1.053	1.081
N-6-H-9	1.044	1.046	1.080
N-6-C-4	1.515	1.508	1.497
C-4-H-5	1.092	1.094	1.080
C-4-C-1	1.561	1.560	1.539
C-1-O-2	1.261	1.270	1.254
C-1-O-3	1.247	1.254	1.237
C-4-C-10	1.531	1.528	1.550
C-10-C13	1.543	1.546	1.508
C-13-C-15	1.535	1.538	1.539
C-13-C-19	1.536	1.538	1.481
Valence Angles (°)			
H-7-N-6-H-8	107.7	105.6	109.4
H-7-N-6-H-9	109.9	106.97	109.4
H-8-N-6-H-9	108.3	105.9	109.4
H-7-N-6-C-4	114.1	116.4	119.4
H-8-N-6-C-4	112.4	111.8	107.1
H-9-N-6-C-4	104.2	109.6	101.5
N-6-C-4-H-5	107.2	106.3	111.5
N-6-C-4-C-1	106.5	105.0	109.9
H-5-C-4-C-1	108.3	107.3	107.5
C-4-C-1-O-2	115.7	114.5	115.7
C-4-C-1-O-3	116.0	119.96	116.5
O-2-C-1-O-3	128.3	125.5	127.7
C-4-C-10-C-13	116.2	116.1	114.9
C-10-C-13-C-15	112.2	112.4	113.7
C-10-C-13-C-19	109.6	109.5	108.4
Torsion Angles (°)			
N-6-C-4-C-1-O-2	-9.3	-	-31.7
N-6-C-4-C-1-O-3	171.2	-	148.8
O-2-C-1-C-4-C-10	112.2	-	85.7
O-3-C-1-C-4-C-10	-67.4	-	-93.7

The C-4-C-1 bond was stretched whereas the C-4-C-10 was shortened compared to the experimental values (Table 1); this situation was encountered in the model reported by Derbel too [6], but our values were more closer to the experimental data. The other bond lengths and angles computed by us showed satisfactory agreement with experiment.

2. *Vibrational data*

The Leucine contains 22 atoms and according to the 3*N*-6 rule (*N*-the number of atoms), it exhibits 60 normal modes of vibration.

In Figure 2, the theoretical vibrational spectrum at B3LYP/6-311++G(d,p) level for zwitterionic L-Leucine previously optimized at PCM (water)-B3LYP/6-311++G(d,p) is presented. The I.R. spectrum was simulated on the region 0-4000 cm^{-1}.

Vibrational proposed spectral assignments for zwitterionic L-Leucine are presented in Table 2, together with its computed unscaled frequencies at B3LYP/6-311++G(d,p) level of theory and the experimental I.R. spectrum. The vibrational assignments were achieved by combining i) the motions observed using Avogadro Program, ii) the infrared band intensities with iii) L-Leucine experimental I.R spectra [16, 17] and iv) previously tentative assignments [6, 16, 17]. Thus, for the experimental values, we were interested only in L-Leucine I.R. spectra measured in aqueous solution (500-1800 cm^{-1}) [16] or film sample obtained from aqueous solutions at different pH (0-700 cm^{-1}) [17].

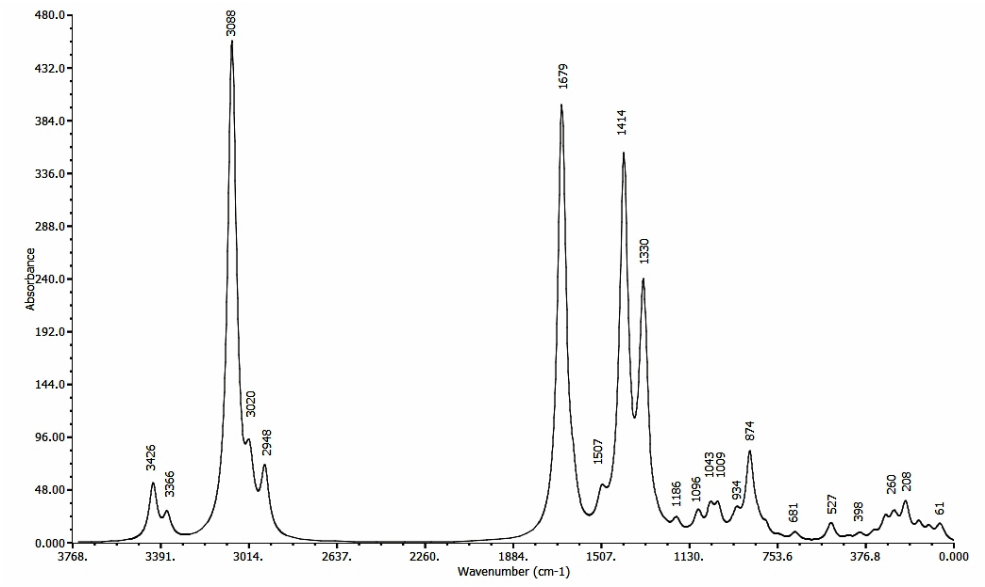

Figure 2. Simulated infrared spectrum of zwitterionic L-Leucine at B3LYP/6-311++G(d,p) level.

The I.R. spectra of the amino acid are characterized by the absorption due to the carbonyl asymmetric and symmetric vibration (ν COO^-) and the stretches and bends of ammonium group (NH_3^+).

Carbonyl (COO^-) vibrations

Wolpert *et al.* [16] assigned for the group COO^- of the amino acids the following arbitrary positions (cm^{-1}): 1530 (antisymmetric stretching, ν_{as}), 1410 (symmetric stretching, ν_s) for most significant modes and ~ 800 (β COO^- scissoring), ~ 650 (w COO^- wagging) and ~ 650-600 (r COO^- rocking) for other modes.

In our exploration, by B3LYP/6-311++G(d,p) level of theory, the three bending vibrations of COO^- group were predicted at 681 (δ COO^-, w COO^-), 527 (δ COO^-, w COO^-) and 398 (r COO^-) cm^{-1}. These values were in good agreement with the experimental frequencies (670, 535, 343 cm^{-1}). We did not find the other deformation modes (629, 586, 579, 364 cm^{-1}) assigned in the literature [16, 17] for the COO^-group (Table 2). For asymmetric COO^- stretch (ν_{as}) we found the absorption at 1679 cm^{-1} while the symmetric COO^-stretches (ν_s) occur at 1414 (strong), 1401 (weak), 1376 (weak), and 1354 (weak) cm^{-1}. These bands are in agreement with the values reported in the literature for the strong COO^- stretching (near 1600 cm^{-1} for asymmetric and near 1400 cm^{-1} for symmetric vibration [18]) and with the values reported by Wolpert for L-Leucine in aqueous solution at pH= 3 (Table 2) [16].

Ammonium (NH_3^+) vibrations

The amino acids exhibit NH_3^+ stretching and deformation vibrations that appear in the region 3200-3000 cm^{-1} (asymmetric stretch), near 2700 and 2100 cm^{-1} (symmetric stretch, these bands are not always present), 1660-1590 cm^{-1} (asymmetric deformation, δ_{as}), 1550-1485 cm^{-1} (symmetric deformation, δ_{as}) and 1295-1090 cm^{-1} (rocking vibration, r), [19].

In our study, the NH_3^+ asymmetric stretching vibrations appeared in the range 3426-3078 cm^{-1}, while for the symmetric stretching we did not find any band. The bands due to the NH_3^+ asymmetric deformation were observed at 1679, 1660 and 1632 cm^{-1} as the NH_3^+ symmetric deformations occur at 1428 and 1414 cm^{-1}. In the region 1238-1009 cm^{-1}, rocking vibrations of NH_3^+ group were observed. These frequencies are in agreement with the previous literature data [19] and the infrared spectra reported for L-Leucine in aqueous solution (Table 2) [16].

C-N, C-C, C-H vibrations

The C-N stretching absorptions of L-Leucine at B3LYP/6-311++G(d,p) occur at 874, 842, 746 cm^{-1}. These vibrations were coupled with CH or COO^- deformations or C-C stretching vibrations (Table 2).

Tabel 2. Vibrational wave numbers obtained at B3LYP/6-311++G(d,p) level, experimental FTIR Spectra for zwitterionic L-Leucine and vibrational assignments

Vibrational mode number obtained from DFT simulation	Unscaled wavenumbers (cm^{-1}) B3LYP/6-311++G(d,p)	Experimental (cm^{-1}) [16, 17]	Vibrational assignments
1	55	53	τ NH_3, τ CH_3, δ CH
2	61	73	τ NH_3, τ CH_3, τ COO^-
3	108	107	τ NH_3, τ CH_3, τCH_2, τ COO^-
-	-	122	τ COO^-, τ CC, rotational
4	151	138	τ COO^-, τ CC
-	-	170	τ COO^-
5	208	203	r NH_3, δ CCN, τ CH_3
6	232	223	δ CH_2, w CH_3
7	254	-	δ $CH(CH_3)_2$
8	260	-	r CH_3, w CH_3, w NH_3, δ CH_2
9	295	-	w NH_3, δ CCC
-	-	330	δ CCN, δ CCC
10	344	-	δ CH, δ CCN
11	398	343	r COO^-, δ CCN, δ CCC
-	-	364	r COO^-, δ CCN
-	-	402	δ CCC
12	411	442	δ CCC
13	454	456	δ $CH(CH_3)_2$
14	527	535	δ COO^-, w COO^-, δ CCN
-	-	579	γ OCO^-
-	-	586	δ COO^-
-	-	629	w COO^-
15	681	670	δ COO^-, w COO^-, δ CCN
-	-	716	-
16	746	736	δ CH, ν CN
17	806	834	ν CC, r CH_2, w NH_3
18	842	848	δ COO^-, ν CC, ν CN
19	874	-	δ CH, ν CC, ν CN
20	924	907	r CH_3, ν CC
21	934	943	ν CCN, ν CC
22	953	-	δ CH
23	969	973	ν CC, r CH_3
24	1009	1003	r NH_3, r CH_3, ν CC
-	-	1031	ν CN

Vibrational mode number obtained from DFT simulation	Unscaled wavenumbers (cm^{-1}) B3LYP/6-311++G(d,p)	Experimental (cm^{-1}) [16, 17]	Vibrational assignments
25	1043	-	δ CH, r NH_3
26	1096	-	δ CCN, r NH_3, ν CC
27	1137	1135	r CH_3, ν CC, δ CCN
28	1186	1174	r NH_3^+, δ CH
29	1198	1185	r NH_3^+, r CH_3, ν CC
30	1238	1239	r NH_3^+, t CH_2, r CH_3, ν C-COO^-
-	-	1295	t CH_2
31	1279	1316	δ CH
32	1322	-	ν CC, t CH_2
33	1330	1340	ν CC, t CH_2
34	1354	1353	ν_s COO^-, δ CH
35	1376	1372	ν_s COO^-, δ_s CH_3
36	1401	1392	ν_s COO^-, ν CC, δ COO^-
37	1406	-	δ $CH(CH_3)_2$
-	-	1412	ν_s COO^-
38	1414	-	ν_s COO^-, δ_s NH_3^+
39	1428	-	δ_s NH_3^+, δ CH_2, δ_{as} CH_3
-	-	1440	δ CH_2
-	-	1455	-
-	-	1471	δ_{as} CH_3
40	1480	-	δ CH, δ CH_2, δ_{as} CH_3
41	1488		δ CH (C-4), δ CH_2, δ_{as} CH_3
42	1496	-	δ CH (C-4), δ CH_2, δ_{as} CH_3
43	1507	-	δ CH_2, δ_{as} CH_3
44	1512	-	δ CH_2, δ_{as} CH_3
-	-	1520	-
-	-	1538	δ_{as} NH_3^+
5	1632	1625	δ_{as} NH_3^+
46	1660	-	δ_{as} NH_3^++ δ CH
47	1679	1598	ν_{as} COO^-, δ_{as} NH_3^+
48	2948	-	ν CH_3
49	3007	-	ν CH
50	3016	-	ν CH_3, ν CH2
51	3020	-	ν CH_3, ν CH2
52	3075	-	ν CH
53	3078	-	ν NH_3^+/ ν CH
54	3082	-	ν NH_3^+/ ν CH

Vibrational mode number obtained from DFT simulation	Unscaled wavenumbers (cm^{-1}) B3LYP/6-311++G(d,p)	Experimental (cm^{-1}) [16, 17]	Vibrational assignments
55	3084	-	ν CH
56	3087		ν NH_3^+/ ν CH
57	3088		ν NH_3^+/ ν CH
58	3094		ν NH_3^+/ ν CH
59	3366		ν NH_3^+
60	3426		ν NH_3^+

ν: streching, δ: deformation, γ: out of plane deformation, τ: torsion, w: wagging, r: rocking, t: twisting; a: antisymmetric, s: symmetric.

According to Barth [20], the aliphatic side chain of amino acids gives several characteristic absorbance bands of medium to weak intensity. In solid phase, the characteristic vibrations δ_{as} CH_3, δ CH_2, δ_s CH_3 appear near 1465, 1450, 1475 cm^{-1} and are not coupled to other vibrational modes while the δ CH and γ CH_2 are often coupled to other modes. In solution, Wolpert [16] assigned the δ_{as} CH_3, δ CH_2, δ_s CH_3 vibrations at 1471, 1440, 1372 cm^{-1} respectively; the latter is coupled with ν COO^-. Our finding consists of the δ_{as} CH_3 to be coupled with δ CH_2, δ CH vibrations and appeared in the range 1512-1428 cm^{-1} while δ_s CH_3 appeared at 1376 cm^{-1} together with ν_s COO^- vibration. Our theoretical I.R. spectrum revealed bands in the region 3094-2948 cm^{-1} for the CH stretching (ν CH) that it is in good agreement with the experimental data (3000-2850 cm^{-1}) [19].

The band below 500 cm^{-1} was mainly assigned to the CCN and CCC skeletal deformation and torsional vibrations.

CONCLUSIONS

The present work described a theoretical study of the structure and I.R. spectrum of zwitterionic L-Leucine. In order to obtain reasonable information about this amino acid at physiological conditions, we optimized the zwitterionic structure of L-Leucine using a density functional method [DFT/B3LYP/6-311++G(d,p)] in conjunction with a continuum solvation model, Polarized Continuum Model (PCM). The comparison between our theoretical results and experimental structural parameters indicates that our data are in good agreement with the experimental values.

Vibrational frequencies, calculated by B3LYP/6-311++G(d,p), agree very well with the I.R. spectra of L-Leucine in aqueous solution. Thus, tentative assignments of this zwitterionic amino acid normal modes of vibrations were performed.

Our study demonstrates the performance of DFT-PCM methods in calculating molecular structure and frequencies of L-Leucine in aqueous solution.

EXPERIMENTAL SECTION

The calculations were carried out using Gaussian03 package [9]. The programs used for visualization were: Gabedit 2.3.0 to display molecular structure and simulated infrared spectra [10] and Avogadro 1.0.1 to obtain information on vibrational modes [11].

The zwitterionic L-Leucine was optimized using a density functional method (DFT/B3LYP/6-311++G(d,p)) in conjunction with a continuum solvation model, Polarized Continuum Model (PCM).

Vibrational frequencies were simulated at B3LYP/6-311++G(d,p) level of theory. An approximate assignment of vibrational frequencies was realized by analysis of normal modes motion using Avogadro program. Our results were compared with the previously tentative assignments for L-Leucine [6, 16, 17].

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