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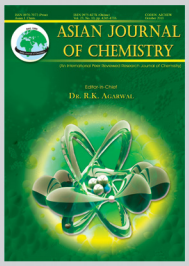

Vibrational Spectra and *ab initio* Studies of L-Prolyl L-Isoleucine

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Quantum mechanical calculation of energies, geometries and vibrational wave numbers of L-prolyl L-isoleucine has been carried out by using density functional theory (DFT/B3LYP) method with 6.31G (d,p) as basic set. The optimized geometrical parameters obtained by DFT calculations are found to be good agreement with experimental X-ray data. The best level of theory in order to reproduce the experimental wave numbers is B3LYP method with the 6.31G(d,p) basis set. The difference between the observed and scaled wave number values of most of the fundamentals is very small. An interpretation of the infrared and Raman spectra has also been reported. The entropy of the compound under study is also performed.

Key Words: Normal coordinates analysis, IR spectrum, L-Prolyl L-isoleucine.

INTRODUCTION

Amino acids and related compounds of biological interest have been studied by many investigators using X-ray, NMR, infrared and Raman spectroscopic techniques. The dipeptide L-prolyl L-isoleucine [LPLI] having the molecular formula $C_{11}H_2N_2O_4$ of considerable importance because of its structural and ligational properties. This molecule belongs to the monoclinic system having space group $P2_1$.

Proline, an amino acid is an important constituent of many proteins. The pyrolidine ring system of proline, whose side chain imposes certain restrictions on the conformation of proteins. This causes a rigid side chain in proline. Also it fixes the dihedral angle between C_α and the peptide nitrogen to a small range[1]. The conformational aspects of pyrolidine ring system are of interest as they reveal different modes of puckering[1]. The conformation of proline ring based on least squares planes is only an approximate way of defining the conformations. A more rigorous approach is to use the concept of pseudo rotation of the five membered ring system and these amino acid residues impose certain restrictions on the conformation of proteins due to the pyrolidine ring system.

The five membered proline and ring is generally nonplanar. The best plane with four atoms N, C_α, C_β, C_δ and the fifth atom C_γ deviates 0.5 Å. The conformation of the pyrolidine ring corresponds to the envelope type.

The occurrence of proline and hydroxy proline in collagen imposes certain steric interactions on the conformation of the individual helices in collagen[1]. The conformational analysis of pyrolidine ring system in crystal structures were studied by Balasubramaniam *et al.*[2].

Pease *et al.*[3], observed the conformation of distinct proline residues in two cyclic peptides by solid state IR and Raman studies. The solid state IR and Raman spectra have individual 13C resonances at their isotropic chemical shift positions[2]. Both intramolecular (conformational) and intermolecular (crystal packing) effects can play important roles in determining the actual environmental of nuclei in solid samples which is reflected in isotropic chemical shift[2].

In constrast solution samples have chemical shifts dominated by intramolecular factors, since most intermolecular interactions are averaged out by rapid molecular motions. It is of interest to find examples of molecules where the solid state IR and Raman shift data can be interpreted in terms of conformational and packing effects separately. The chemical shift correlation for the solid state and solution spectra indicates that the predominant factors leading to the isotropic chemical shifts of the crystalline cyclic pentapeptide are conformational and packing effects play only secondary role; this is in contrast to the situation for amino acid linear peptides[4]. Inspection of arrangement of peptide molecules in the crystal lattice[4], suggests that the packing constraints do not contribute strongly to the molecular environment in solids.

L-Isoleucine was assumed to belong to a rather unusual type in which the molecules have two kinds of conformations[5,6], crystallized L-isoleucine in $P2_1$ symmetry and have given the

bond lengths and bond angles of gauche-I and *trans* L-isolecine. There were no much variation in the bond lengths and bond angles between the two forms. Iitaka *et al*.[5-7] have analyzed the related molecules L-valine.

The crystallographically independent molecules have different rotational angles about the C_α-C_β bond. The crystal structure is formed by the hydrogen bonded double layers of molecules stacked in such a way that the terminal groups of the side chain C(2)-C(3) bond length of the two types N-H…0 hydrogen bonding is similar to α-glycine[8] and β-glycine[9].

Normal coordinate analysis: Based on the result obtained by the density functional theory the molecules belonging to C1 point group, with 102 degree of freedom. The Gaussian molecular structure adopted for L-prolyl L-isolecine [LPLI] is shown in Fig. 1. The structural parameters, bond angle and bond distance are shown in Table-1. All the 102 fundamental vibrations are found to be IR actives for DFT. The potential constants are calculated using Urey-Bradley force field is given in Table-2.

EXPERIMENTAL

The sample, L-prolyl L-isoleucine [LPLI], (reagent grade) was obtained from sigma chemicals company, USA by Chacko *et al*.[9], for their structural analysis by X-ray methods. We have recorded the infrared spectra of this solid sample on a Hitachi 270-50 model spectrophotometer using KBr pellet form in the range 4000-250 cm^{-1}. The molecular arrangement has been shown in Fig. 1 . The observed frequencies were calibrated with the usual standards. There were no peaks observed in Laser Raman spectra.

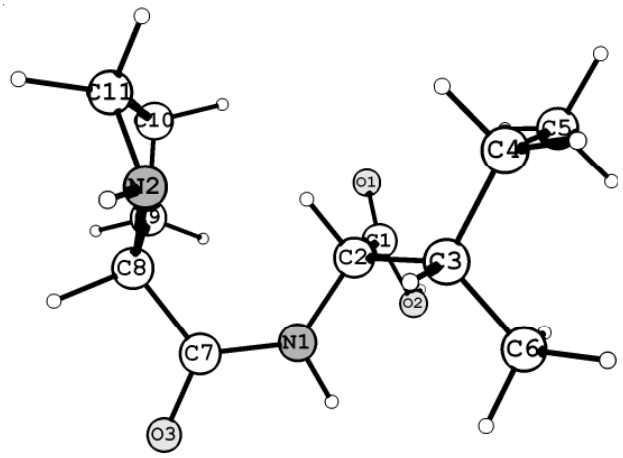

Fig. 1. Molecular structure and labeling of atoms in L-propyl L-isoleucine

One might expect that a high molecular weight polymer with large number of atoms would yield the spectrum which is too complex for interpretation. The frequency of an absorption is governed by the bond strength and bond length and by the masses of the atoms present in the absorption group. If bond strength decreases as the consequence of molecular interactions, bond length will increase and absorption frequency decreases. The decreased frequency can therefore be accompanied by an increase in the optical density of the band.

While band assignments can be made mathematical calculations based on atomic masses, force constants *etc*., the majority of peaks in large molecules are assigned from experimental observations. Certain classes of compounds exhibit absorptions for specific groups that occur within a narrow

TABLE-1
STRUCTURE PARAMETER [BOND DISTANCE (Å) AND BOND ANGLE (º)]

Bond distance	Values (Å)	Bond angles	Values (º)	Bond angles	Values (º)
R(C1-C2)	1.518	A(C2-C1-O1)	125.6	A(H9-C6-H10)	107.1
R(C1-01)	1.236	A(C2-C1-O2)	112.9	A(H9-C6-H11)	108.2
R(C1-02)	1.380	A(C1-C2-N1)	109.3	A(H10-C6-H11)	107.6
R(C2-N1)	1.468	A(C1-C2-C3)	115.7	A(C8-C7-O3)	119.0
R(C7-N1)	1.376	A(C1-C2-H2)	107.1	A(C7-C8-N2)	115.1
R(N1-H1)	1.013	A(O1-C1-O2)	121.5	A(C7-C8-C9)	113.7
R(C2-C3)	1.566	A(C1-O2-H12)	110.5	A(C7-C8-H14)	103.4
R(C2-H2)	1.090	A(C2-N1-C7)	129.3	A(C8-N2-C11)	108.4
R(C3-C4)	1.554	A(C2-N1-H1)	117.1	A(C8-N2-H13)	114.5
R(C3-C6)	1.540	A(N1-C2-C3)	111.1	A(N2-C8-C9)	103.7
R(C3-H3)	1.100	A(N1-C2-H2)	106.6	A(N2-C8-H14)	112.2
R(C4-C5)	1.540	A(C7-N1-H1)	113.4	A(C11-N2-H13)	115.6
R(C4-H4)	1.099	A(N1-C7-C8)	121.2	A(N2-C11-C10)	102.1
R(C4-H5)	1.099	A(N1-C7-O3)	119.8	A(N2-C11-H19)	112.7
R(C5-H6)	1.096	A(C3-C2-H2)	106.6	A(N2-C11-H20)	110.5
R(C5-H7)	1.094	A(C2-C3-C4)	113.1	A(C9-C8-H14)	108.8
R(C5-H8)	1.096	A(C2-C3-C6)	114.7	A(C8-C9-C10)	105.6
R(C6-H9)	1.097	A(C2-C3-H3)	102.1	A(C8-C9-H15)	109.4
R(C6-H10)	1.096	A(C4-C3-C6)	112.6	A(C8-C9-H16)	111.8
R(C6-H11)	1.093	A(C4-C3-H3)	105.8	A(C10-C9-H15)	111.9
R(O2-H12)	0.983	A(C3-C4-C5)	117.5	A(C10-C9-H16)	111.0
R(C7-C8)	1.530	A(C3-C4-H4)	106.7	A(C9-C10-C11)	104.4
R(C7-O3)	1.254	A(C3-C4-H5)	108.4	A(C9-C10-H17)	109.9
R(N2-C8)	1.480	A(C6-C3-H3)	107.3	A(C9-C10-H18)	112.2
R(N2-C11)	1.478	A(C3-C6-H9)	109.6	A(C9-C9-H16)	107.2
R(N2-H13)	1.016	A(C3-C6-H10)	111.6	A(C11-C10-H17)	110.2
R(C8-C9)	1.570	A(C3-C6-H11)	112.4	A(C11-C10-H18)	112.1
R(C8-H14)	1.100	A(C5-C4-H4)	108.4	A(C10-C11-H19)	110.4
R(C9-C10)	1.556	A(C5-C4-H5)	109.2	A(C10-C11-H20)	113.1
R(C9-H15)	1.094	A(C5-C5-H6)	109.8	A(H17-C10-H18)	108.0

TABLE-2
EXPERIMENTAL AND B3LYP LEVELS COMPUTED VIBRATIONAL (cm^{-1}) OBTAINED FOR L-PROPYL L-ISOLEUCINE

Frequency		Reduced mass	Force constant	IR Intensity	Assignment
Exp. frequency	Scaled				
3601	3457	1.064	8.128	36.45	OH Sym stretching
3596	3452	1.075	8.186	17.25	N_1H_1 Sym stretching
3546	3404	1.075	7.968	0.52	N_2H_{13} Sym stretching
3152	3026	1.098	6.424	19.46	CH_3 Asym stretching
3089	2965	1.064	5.980	35.47	CH Sym stretching
3017	2896	1.084	5.811	45.12	CH Sym stretching
2955	2837	1.072	5.517	117.44	CH Sym stretching
1727	1658	8.656	15.215	187.52	CO Sym stretching
1690	1622	4.873	8.201	344.74	CO Sym stretching
1567	1504	1.094	1.582	1.90	CH Bending
1503	1443	1.480	1.971	2.13	NH Bending
1383	1328	1.622	1.829	45.41	CH_2 Bending,CH_3 bending
1343	1289	1.227	1.303	2.97	CC Bending,CH_2 bending
1312	1260	1.459	1.479	15.23	CH_2 Bending, CO bending
1234	1185	1.309	1.175	2.88	CH_2 Bending, CNH bending
1168	1121	2.160	1.735	11.43	CH_3 Out of plane bending
1080	1037	2.387	1.641	20.72	CH_2 Bending, CNH bending.
1045	1003	1.858	1.194	4.13	HCC Bending,CH_2 bending
979	940	2.892	1.632	4.17	CNC Bending, CNH bending
939	901	2.039	1.060	31.28	CH_2 Out of plane bending
927	890	3.026	1.531	0.19	CC Sym stretching
887	852	1.971	0.914	10.34	CH_2 Torsion
871	836	3.254	1.454	44.27	HCC Out of plane bending
833	800	2.415	0.988	37.63	NH Out of plane ending.
813	781	1.810	0.705	0.13	CH_2 Torsion
794	762	1.938	0.720	14.92	NH Torsion
729	700	3.057	0.958	3.09	CCO Out of plane bending
677	650	2.209	0.596	53.67	CNH Out of plane bending
555	533	2.633	0.477	29.67	CH_3 Wagging

frequency range, however, the range can be so modified by molecular interactions, for example, hydrogen bonding. And the effects of crystalline, that may be difficult in practice to differentiate between hydrogen bonded groups and hydrogen bonded NH groups as a consequence of differences in hydrogen bond strength. While the majority of characteristic vibrational modes arise from side groups or end groups, absorption in the 1400-1000 cm^{-1} region arise from skeletal modes which appear sufficiently unique to be termed as 'finger print'.

In a hydrogen bond, C=O···H-N the reduced effective restoring force to the stretching of the N-H bond decreases its frequency of vibration and consequently, the deformation frequency is introduced. Since the change in frequency of a stretching vibration is proportional to the strength of the hydrogen bond formed, the presence of different structural conformation in a natural material, such as protein, will be indicated by the number and frequency of hydrogen bonded groups showing absortions in a given region of the spectrum.

The X-ray structure studies of LPLI, done by Chacko and Panneerselvam[9], indicates the $P2_1$ symmetry for the molecule. A complete normal coordinate analysis (NCA) is made to give a tentative assignment for the observed infrared frequencies. The peak values are given in Table-2.

RESULTS AND DISCUSSION

In the infrared spectrum L-proline L-leucine, 87 peaks were observed. But only 37 of them could be assigned due to the above inadequacies. The rest of the peaks have very low intensity and they are of less significance. The frequency values are compared with the values reported for related molecules.

The two bands observed at 3478 and 3442 cm^{-1} are assigned to the two NH_2 asymmetric stretching modes since in L-alanine the 3455 cm^{-1} band is assigned to the NH_2 asymmetric stretching mode. The region of C-H and N-H stretching modes. The band due to NH_2 stretching for the related compounds.

The two strong bands observed at 3076 and 2968 cm^{-1} are assigned to the CH_3, CH_2 asymmetric stretching modes, respectively. But there are differences in the peak values of the related compounds. For D-isoleucine the CH_3 asymmetric stretching mode was observed at 2907 cm^{-1}, for L-proline at 2933 cm^{-1} and for d-N-phenacetyl isoleucine and d1-N-phenacetyl alanine the peak values were observed at the same wave number 3030 cm^{-1}. The C-H stretching modes are observed at 3316, 2968 and 2878 cm^{-1} for L-proline L-isoleucine.

It is observed that the bands due to the C=O stretching modes are very strong because of its position in the peptides. The oxygen atom in the C=O does not make any bonding with other atoms in the chain. The very intense bands at 1683, 1650 and 1614 cm^{-1} of L-proline L-isoleucine correspond to the carbonyl stretching mode. The related band of (Ala) occurs at 1650 cm^{-1}, for dl-valine at 1736 cm^{-1}, for d-N-phenacetyl isolecine at 1727 cm^{-1} and for phenacetyl proline at 1700 cm^{-1}.

The deformation is a bending type of vibration which produces changes in the angles between the atoms in the structure group itself. The high and low NH_2 deformations

TABLE-3
HOMO ENERGY (a.u.), LUMO ENERGY (a.u.), HOMO-LUMO ENERGY GAP (a.u.), CHEMICAL HARDNESS (a.u.), SCF (a.u.) FOR L-PROLYL L-ISOLEUCINE

Parameters	HOMO energy	LUMO energy	HOMO – LUMO energy gap	Chemical hardness	Ionization potential	SCF
DFT	-0.22114	-0.00242	-0.21872	-0.10936	-0.11178	-766.17

TABLE-4
THEORETICALLY COMPUTED ENERGIES (a.u.), ZERO-POINT VIBRATIONAL ENERGIES (kcal mol^{-1}), ROTATIONAL CONSTANTS (GHz), ENTROPIES (cal $mol\ K^{-1}$) AND DIPOLE MOMENT (D) for L-PROLYL L-ISOLEUCINE

Parameters	Total energy	Zero-point vibrational energy	Rotational constants	Total	Translational	Rotational	Vibrational	Dipole moment
DFT	-765.85	198.46	0691 0.881 0.342	209.224	0.889	0.889	207.446	1.9556

corresponding to symmetric and asymmetric modes are assignable at 1614 and 1587 cm^{-1} which compare reasonably with those of L-isolecine observed at 1610 and 1585 cm^{-1}, respectively. The CH_3 deformation and asymmetric deformation are assigned to the bands observed at 1506 and 1323 cm^{-1}, respectively for LPLI. The CH_3 deformation reported in the case of phenacetyl proline is 1425 cm^{-1}, slightly lower than that of L-proline L-isoleucine and for CH_3 asymmetric deformation is 1447 cm^{-1} moderately higher than that of L-proline L-isoleucine.

The medium intensity bands observed at 672 cm^{-1} is assigned to the CH wagging and in d-N-phenacetyl isoleucine this mode is assigned to the CH wagging and in d-N-phenacetyl isoleucine this mode is assigned at a much higher value 1145 cm^{-1}. For β-alanine the CH wagging is observed at 1127 cm^{-1} comparable with that of d-N-phenacetyl isoleucine. The CH_2 wagging is assigned to the 948 cm^{-1} band which is lower than 1167 cm^{-1} observed in d1-N-phenacetyl alanine.

The band observed at 1044 cm^{-1} assigned to the various CH_2 rocking vibrations which is comparable with that of d-N-phenacetyl isoleucine observed at 1053 cm^{-1}, dN-phenalacetyl alanine at 1031 cm^{-1}, phenacetyl proline at 1031 cm^{-1}, L-proline at 1171 cm^{-1}.

The band observed at 750 cm^{-1} is assigned to the ring twisting which agrees exactly with that of phenacetyl proline at 750 cm^{-1}.

The HOMO-LUMO energy gaps of L-prolyl L-isoleucine calculated at the B3LYP/6.31G(d,p) levels, reveals that the energy gap reflect the chemical activity of the molecule. LUMO as an electron acceptor represents the ability to an electron, HOMO represents the ability to donate an electron. Moreover the lower in the HOMO and LUMO energy gap explains the eventual charge transfer interaction taking place within the molecule (Table-3).

Other molecular properties: Several calculated thermodynamics parameters are presented in Table-4. Scale factors have been recommended for an accurate prediction in determining the zero-point vibration energies (ZPVE) and the entropy, $S_{vib}(T)$. The variations in the ZPVE seem to be insignificant. The total energies and the change in the total entropy of L-prolyl L-isoleucine at room temperature at different methods are also presented.

Conclusion

Density functional theory calculation have been carried out on the structure and vibrational spectra of L-prolyl L-isoleucine. The equilibrium geometry computed by DFT level for both the bond lengths angle bond angles are performed better. The vibrational frequencies analysis by B3LYP/6.31G(d,p) method agree satisfactorily with experimental results. On the basis of agreement between the calculated and experimental results, assignments of all the fundamental vibrational modes of -L-prolyl L-isoleucine were examined and proposed. Therefore, the assignments made at higher level of theory with higher basis set with only reasonable deviations from the experimental values, seems to be correct. HOMO and LUMO energy gap explains the eventual charge transfer interaction taking place within the molecule. This study demonstrates that scaled DFT/B3LYP calculations are powerful approach for understanding the Vibrational spectra of medium sized organic compounds.

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