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Conformational Analysis of Molecules: Combined Vibrational Spectroscopy and Density Functional Theory Study

Partha P. Kundu and Chandrabhas Narayana

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Abstract

Vibrational spectroscopy can be broadly classified into Raman and infrared (IR). These two techniques are complementary to each other as the mechanisms behind these are different. Vibrational spectroscopy provides detail information about the structure of molecules. The advantage of this technique over X-ray diffraction is that it can be used to probe molecules in solid, liquid or gas phase. This is especially helpful for studying biomolecules as those molecules can be probed in their physiological environment. Over the last few decades, quantum mechanical calculation has become important tool to assign bands from vibrational spectra. Combination of these two techniques has been used widely in the field of chemistry and biochemistry. In this chapter, we review some of the works that combine both of these techniques. A brief theoretical background is given for understanding the principle of these two techniques.

Keywords: Raman, infrared (IR), density functional theory (DFT), conformation

1. Introduction

Spectroscopy is a subject that is related to the interaction of electromagnetic radiation with the atoms or molecules. It provides rich information about the structures, physical and chemical properties of the materials. Energy of a stationary molecule can be written as a sum of three parts: electronic, vibrational and rotational. In vibrational spectroscopy, the vibrational levels of a molecule are probed. Vibrational spectroscopy can be broadly classified into two: infrared (IR) and Raman. Even though both techniques probe the vibrational energy

levels, physical processes leading to these spectra are different. Thus, these two techniques offer different information about the molecule and regarded as complementary to each other. To get the structural information from a vibrational spectrum, the first task is to assign the bands. Band assignments can be performed by comparing the modes of similar molecule already existing in literature. However, vibrational frequencies are sensitive to the small difference in the structure and also to the environment. Moreover, it is difficult to assign the large number of closely spaced bands arising from even a medium size molecule. Hence, for reliable assignments of these bands, it is essential to calculate the normal modes theoretically and compare those with the experimental spectra. Over the last few decades, calculation of molecular spectra using quantum mechanics has become a common practice. There are many quantum mechanical-based methods for calculation, of which density functional theory (DFT) is most popular as its computational cost is less without compromising significantly with the accuracy.

Here, we will introduce the basic theory behind these vibrational techniques. Also, the principle of DFT will be discussed in brief. We will provide references so that the interested readers can gain insights about these topics.

2. Theoretical background

2.1. Raman scattering

When a molecule is irradiated with a monochromatic light of wave number $\tilde{v}_0$, a small fraction of the incident light will be scattered. In the scattered radiation, major portion of the light will have the same wave number as the incident light; however, a tiny fraction of light will have the wave number $\tilde{v}' = \tilde{v}_0 \pm v_M$. The first kind of scattering is called Rayleigh scattering while the latter is called Raman scattering. Classically, the phenomenon of Raman scattering can be explained in the following paragraphs.

When a molecule is in an oscillating electric field $E(t)$ with angular frequency ω_L, an induced dipole will be created, Which in the linear approximation can be written (in complex notation) as,

$$\underline{p}(\omega_L) = \hat{\alpha}_L(\omega_L).\underline{E}(\omega_L) \tag{1}$$

where $\hat{\alpha}_L$ is the *polarizability tensor* and $E(t) = \mathrm{Re}(\underline{E} \times e^{-i\omega_L t})$. Here, it is to be mentioned that as the molecule vibrates, the polarizability tensor gets modulated. Polarizability thus not only depends on frequency but also on the atomic positions. To describe the vibrational pattern, *normal coordinates* (Q_k) are introduced. For a specific normal mode k (k = 1, 2, …, 3N-6, where N is the total number of atoms in the molecule), all the atoms in the molecule will oscillate with

the same frequency ω_k. If the polarizability tensor is expanded in Taylor series around the equilibrium position, it can be shown [1] that the induced dipole (real) can be expressed as

$$\boldsymbol{p}(t) = \boldsymbol{p}_L(t) + \boldsymbol{p}_S(t) + \boldsymbol{p}_{aS}(t), \tag{2}$$

where

$$\boldsymbol{p}_L(t) = \mathrm{Re}[\hat{\alpha}_L(\omega_L, 0)\underline{\boldsymbol{E}}(\omega_L)e^{-i\omega_L t}] \tag{3}$$

is the oscillating dipole with frequency ω_L representing Rayleigh scattering,

$$\boldsymbol{p}_S(t) = \frac{Q_k^0}{2}\mathrm{Re}[\hat{R}_k(\omega_L)\underline{\boldsymbol{E}}(\omega_L)e^{-i(\omega_L - \omega_k)t + i\phi}] \tag{4}$$

is oscillating with a frequency $\omega_S = \omega_L - \omega_k$ and produce Stokes Raman scattering,

$$\boldsymbol{p}_{aS}(t) = \frac{Q_k^0}{2}\mathrm{Re}[\hat{R}_k(\omega_L)\underline{\boldsymbol{E}}(\omega_L)e^{-i(\omega_L + \omega_k)t - i\phi}] \tag{5}$$

represents oscillating dipole with frequency $\omega_S = \omega_L + \omega_k$ and gives rise to anti-Stokes Raman scattering. Here, $\hat{R}_k(\omega_L)$ is called Raman tensor, Q_k^0 is the amplitude of oscillation of mode k and ϕ is an arbitrary phase.

Although classical approach could successfully explained the change in the frequency observed in the scattered radiation, it failed to account for the difference in the intensity observed in Stokes and anti-Stokes Raman. Also, it could not give reasons for the *resonant Raman scattering* phenomenon. Thus, quantum mechanics is required to understand the Raman scattering. According to the quantum picture, when a molecule makes a transition from one state to another with different discrete energies, radiation is absorbed or emitted. To describe the scattering process, it is necessary to treat both the molecule and radiation quantum mechanically. Such a rigorous treatment can be avoided by considering *semi-classical* approach, where the molecule is considered to be a quantum mechanical system, whereas the incident light can be considered as a perturbation to the energy level of the molecule. In this treatment, scattering is viewed as transition probabilities between initial state $|i\rangle$ of the molecule to the final state $|f\rangle$ in the presence of perturbing incident light. It can be shown that for such a transition, a Raman polatizability component is given by [1, 2],

$$\alpha_{kl} = \frac{1}{h} \sum_{r \neq i,f} \left\{ \frac{\langle f | p_k | r \rangle \langle r | p_l | i \rangle}{\omega_r - \omega_i - \omega_L - i\Gamma_r} + \frac{\langle f | p_l | r \rangle \langle r | p_k | i \rangle}{\omega_r - \omega_f + \omega_L + i\Gamma_r} \right\} \tag{6}$$

where the sum is over all possible states $| r \rangle$ of the molecule (except for the initial and final states), p_k and p_l called quantum dipole moment operators, $\hbar(\omega_r - \omega_i)$ is the energy difference between state $| i \rangle$ and $| r \rangle$, and Γ_r is inversely proportional to the lifetime of the state $| r \rangle$. As it can be seen from the expression, polarizability depends on the excitation frequency ω_L. Thus by choosing ω_L close to the frequency corresponding to the transition between two states, transition polarizability can be enormously increased, which is essentially the resonance Raman scattering. Quantum mechanics also successfully explained the difference observed in the intensity of Stokes and anti-Stokes Raman.

Let us now consider the vibrational motion of a molecule consisting of N atoms. Since the motion of the electrons moves much faster than the nucleus, we can consider the motion of the nucleus separately. It can be shown [1] that potential energy of the nucleus can be approximately expressed by,

$$V^n = \frac{1}{2} \sum_{i,j=1}^{3N} f_{i,j} q_i q_j$$
$$f_{i,j} = \left(\frac{\partial^2 V^n}{\partial q_i \partial q_j} \right)_{q_i, q_j = 0} \tag{7}$$

where q_is are called *reduced mass coordinates*. The scalar terms $f_{i,j}$ are called *force constants* represented as a real symmetric matrix called Hessian matrix $\hat{F}$. The dynamics of a molecule can be written as [1],

$$\hat{F}.A = \omega^2 A \tag{8}$$

where $A = (A_i)_{i=1,2,\dots 3N}$. For a particular mode, these quantities completely describe the dynamics of the system. These 3N normal modes form a complete system, any arbitrary pattern of the motion of the atoms can be expressed as a combination of these modes. In a molecule, there are 3N-6 (3N-5, for linear molecule) eigenvectors correspond to the *normal vibrational modes*. The atomic displacement can also be described by set of coordinates Q_k, called *normal coordinates*, defined as $Q_k = A_k . q$. For a single vibrational mode k, a single scalar Q_k can describe the atomic displacements.

2.2. Infrared (IR) spectroscopy

Like Raman spectroscopy, IR spectroscopy also involves the interaction of electromagnetic radiation with the molecule, but the nature of interaction is different. Here, the transition from a state *n* to *m* takes place as a result of absorption of photon. The process is mediated through the electric dipole moment operator $\mu_{q'}$ given by,

$$\hat{\mu}_q = \sum_\alpha e_\alpha . q_\alpha \tag{9}$$

where e_α is the effective charge on the atom α and q_α is the distance from the centre of gravity. It can be shown [3] that the transition probability is given by,

$$\left[\hat{\mu}_q\right] = \sum_{k=1}^{3N-6} \hat{\mu}_q^k \left\langle \psi_m^* \left| Q_k \right| \psi_n \right\rangle \tag{10}$$

where

$$\hat{\mu}_q^k = \left(\frac{\partial \mu_k}{\partial Q_k} \right)_0 \tag{11}$$

A particular mode *k* is IR active if both $\hat{\mu}_q^k$ and $\left\langle \psi_m^* | Q_k | \psi_n \right\rangle$ are non-zero.

2.3. Density functional theory

Over the past few decades, *density functional theory* has gain its popularity as computational tool in quantum chemistry because of its computational cost comparable to that of Hartree-Fock (HF) theory [4], yet accuracy similar to the computationally demanding post-Hartree-Fock methods. Earlier attempts were made to express energy in terms of electron density alone [5–7]. The most successful attempt, suggested by Kohn and Sham [8], was to divide the kinetic energy into two parts. The major contribution is analogous to the HF kinetic energy, which can be calculated precisely, with a small contribution due to correlation. The main idea of Kohn-Sham theory is to calculate the kinetic energy by assuming a non-interacting system. The missing kinetic energy term, existing in real system, is absorbed in a term called *exchange-correlation.* According to the Kohn-Sham approach, the DFT energy can be written as

$$E_{DFT}[\rho] = T_S[\rho] + E_{ne}[\rho] + J[\rho] + E_{xc}[\rho] \tag{12}$$

In the above equation, the first term corresponds to kinetic energy of non-interacting electrons, the second term denotes the nuclear-electron attraction, the third represents Coulomb electron-electron repulsion, and the last term is called the exchange-correlation. In Kohn-Sham theory, the only approximation to be made is for the exchange-correlation functional. Different DFT methods vary in the functional form of this exchange-correlation energy. Kohn-Sham approach is an independent particle model, similar to the HF theory, but simpler than many-particle (correlation) wave function methods. Once proper exchange-correlation functional has been chosen, the next job is to determine a set of orthogonal orbitals corresponding to the minimum energy. There are different types of exchange-correlation functionals. *Local density approximation* (LDA) [9–13] is the simplest exchange-correlation functional, where the density is treated as a uniform electron gas, or slowly varying function at a given point. A better approximation is the *generalized gradient approximation* (GGA) [14–16] that apart from the density itself includes the first derivative of the density as a variable. Another popular type is hybrid functional that is a combination of DFT correlation and DFT and HF exchange [17, 18].

Molecular orbitals (MOs) are generally expressed in terms of basis set. Although it requires infinite functions to represent a MO, the basis sets used are finite for practical purpose. Two common types of orbitals used to form basis set are Slater type orbitals (STOs) [19] and Gaussian type orbitals (GTOs) [20]. Another computationally less costly basis set is contracted basis set [4]. Some examples are 3-21G, 6-31G, 6-311G, etc. Polarization [21] and diffuse [22] functions can be added to each of these basis sets.

2.4. Geometry optimization

The first step of any quantum chemical calculation is the geometry optimization of the molecule. In general, optimization is performed on an isolated molecule, considering non-interacting system in the gas phase. Initial structure is either taken from the literature or obtained from *empirical force field model*. Geometry optimization starts with solving the Kohn-Sham equation self-consistently on the initial geometry. Energy and force on the molecule are calculated from the solution. If the force on the molecule is not zero, a different geometry is assumed. The process of finding a local minimum in the *potential energy surface* is achieved through the *conjugate gradient* [23] method.

2.5. Frequency calculations

Once the equilibrium atomic positions of the atoms are known, the electronic structure can be calculated on the optimized structure. The interaction of the atoms is now known, which enables to calculate force constants. Force constants can be calculated by displacing each atom from their equilibrium positions and recalculating the total energy of the deformed configuration. By numerical differentiation of the total energy, force constants on each atom can be calculated. This enables to construct Hessian matrix for the vibrational modes as described earlier. The frequency needs to be calculated at the same theoretical model and with same basis set as that used in the optimization procedure.

3. Applications of the combined study of vibrational spectroscopy and DFT for conformational analysis

Conformational analysis of molecules is very important in chemistry, biochemistry and structural biology as it determines their functions. Intra- and inter-molecular interactions play important role in determining structure of a molecule. Solvent has significant effect on the structure. The effect of solvent on structure of protein was studied by Zhu et al. [24] on a model tripeptide upon micro-solvation. Doubly terminated tripeptide Z-Aib-Pro-NHMe (Z = benzyloxycarbonyl), an important structure for many natural and synthetic peptides, was studied in solvent-free gas phase and complexed with one- and two-methanol molecules. There are two competing secondary structures present in the peptide as found in the literature. In the condensed phase, it prefers β-turn structure, whereas in gas phase, γ-turn structure is found. In this work, authors carried out IR study combined with the theoretical study of the peptide in the gas phase and in solvent. IR absorption of amide bands [25] and fingerprint region (<1500 cm^{-1}) was recorded. The DFT calculation was carried out at B3LYP/6-311++G(d, p) level for different conformers. Amide bands are sensitive to the secondary structure of the protein and can be used as marker bands. The three amide bands namely amide I, II and III were used to determine the secondary structures of the peptides. It was shown that the model tripeptide in the unsolvated form and one-methanol cluster prefers to form γ-turn structure, whereas in the two-methanol cluster, because of more H-bonding interaction with the methanol, γ-turn structure is favourable that is similar to the condensed phase. From the shift observed in the amide bands and the comparison of experimental spectrum with the theoretical one, it was also concluded that the methanol binding sites are the head and tail part of the tripeptide (see **Figure 1**).

Biological molecules remain in zwitterionic form naturally. Conformational analysis of these molecules is important as they are highly flexible, and their conformations determine H-bonding networks leading to the hydrophobic and hydrophilic interactions. Moreno et al. [26] have studied two amino acids, L-Phenylalanine (L-Phe) and L-Tyrosine (L-Tyr), by IR and Raman spectroscopy in the zwitterionic form to investigate their conformational preferences. For conformational analysis study, different conformers of zwitterionic forms were found by force field method. The DFT calculation was carried out with B3LYP and MO62X functionals together with 6-31+G(d) and 6-311++G(d,p) basis sets. The MO62X functional was found to be better for agreement with the experiment as it describes the non-covalent interactions present in the zwitterionic form well. It was found that the low-frequency region (30–500 cm^{-1} region) contained rich information about different conformers. Comparing the calculated spectra of different conformers and the experimental spectra, contribution on spectra from different conformers could be identified. This study might help in understanding the folding mechanism of proteins.

Conformational preferences of two tripeptides, *N*-acetyl-Phe-Pro-NH$_2$ and *N*-acetyl-Pro-Phe-NH$_2$, were studied by Chin et al. [27] in the gas phase with the help of IR spectroscopy and DFT. Modification of *N* and *C* termini helps in investigating the conformational preference of each residue isolated from the neighbouring residues. Initially, the lowest energy conforma-

tions were found out by exploring the potential energy surface. Further, geometry optimization and vibrational frequency were carried out by DFT calculation at B3LYP/6-31+G (d) level. The NH stretch region was found to be sensitive to the conformations and used as marker bands. Together with the DFT calculation, it was concluded that most of the conformation assumed repeated γ-turn structure; however, only one conformation of N-Ac-Phe-Pro-NH$_2$ took up β-turn structure. It was also observed that the conformation is dependent on the neighbouring residues of the Phe. In case of N-acetyl-Phe-NH$_2$ or N-acetyl-Phe-Pro-NH$_2$, Phe favours β conformation while in case of N-acetyl-Pro- Phe-NH$_2$, it prefers γ$_L$ conformation.
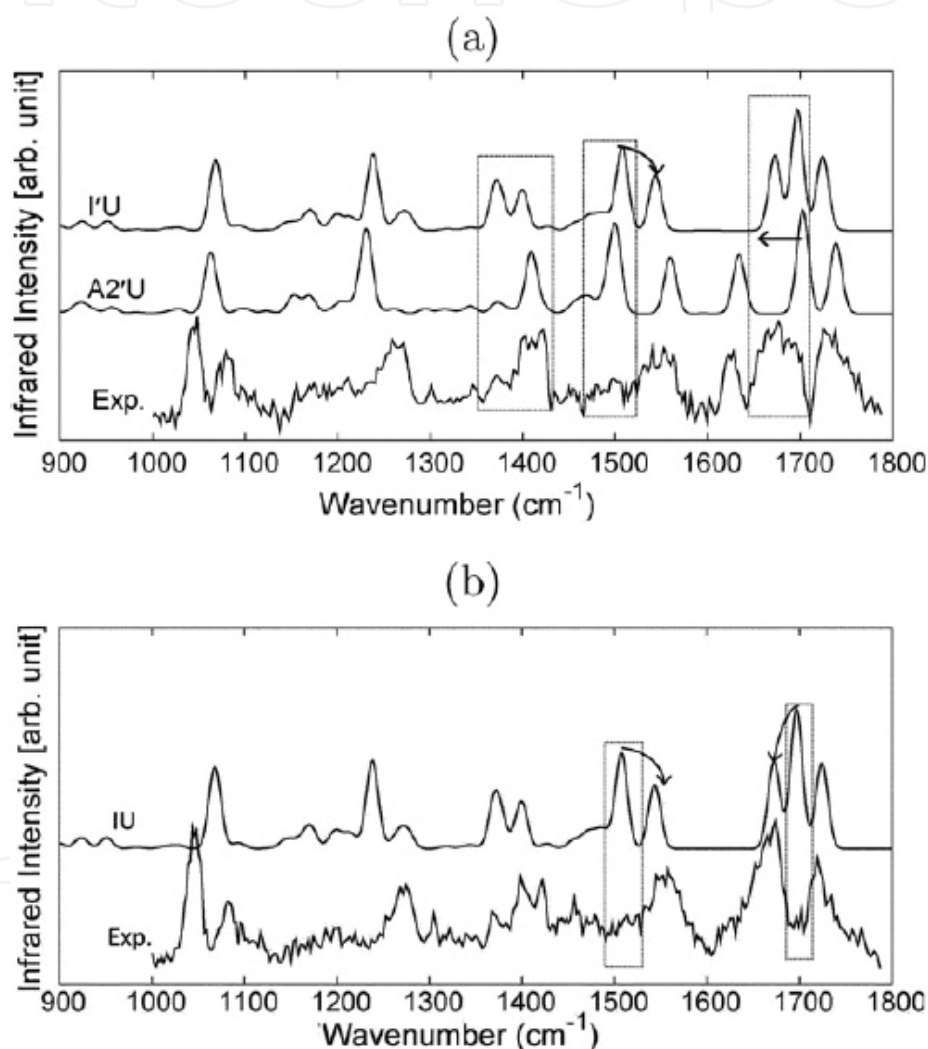
Figure 1. Comparison between theoretical and experimental mid-IR spectra for peptide with (a) one or (b) two methanol. Reproduced from Ref 24 with permission of The Royal Society of Chemistry.

Nicotinic acid and its derivatives are subjects of intense study because of their biological activity and versatile bonding capability. The conformational and vibrational studies (Fourier transform (FT) IR and FT-Raman) of two derivatives of nicotinic acids, 2-bromonicotinic acid and 6-bromonicotinic acids, were reported by Karabacak et al. [28]. The geometrical optimi-

zation and vibrational wave numbers were calculated by DFT method using B3LYP as a functional and the 6-311++G(d,p) as basis set. By varying the dihedral angle, energy of different conformations was calculated, and most stable conformation was found. Vibrational assignments were made based on the total energy distribution (TED) [29]. Raman activities calculated by Gaussian program [30] were converted to relative intensity [31]. The calculated and experimental vibrational spectra were compared. Disagreement between experimental and calculated spectra was ascribed to the neglect of inter-molecular interaction present in solid samples as well as the neglect of anharmonicity present in real system. After applying proper scaling factor, calculated spectra resembled well with the experimentally obtained spectra. Dimer structures of the two derivatives and the presence of inter-molecular H-bonding between the pyridine N atom and O-H group were also determined.

The room temperature ionic liquids (ILs) have gained interest over last decade due to their potential applications. They are environment friendly because of their non-volatility. Their high thermal stability and tuneable solvent property make them ideal candidates to use as reaction media for organic synthesis or as electrolytes in solar cell. To understand the relation between structure and function of these ILs, details structural and bonding data are required. In the absence of X-ray structural data for the liquids, vibrational spectroscopic data can be helpful in gaining insights into their structures. Several imidazolium-based ILs were studied by Katsyuba et al. [32] by vibrational spectroscopy along with the DFT calculations. The functional chosen for calculation was B3LYP with 6-31G* basis set. Multiple stable structures were found placing anions at different positions. It was shown that halide anions were able to occupy all the positions around the imidazolium ring, whereas perfluorinated anions prefer forward position. Vibrations of the cations depend upon the conformation as well as the interaction with the counterions. In the complex, only imidazolium C-H group vibrations (stretching and out-of-plane vibrations) and perfluoroanions stretching vibrations are affected. Thus, the study could shed some light on the relationship between the structure, vibrations and melting point of ILs.

In another study by the same group [33], combination of vibrational spectroscopy with theoretical calculation was used to quantitatively characterize the strength of H-bonding in ILs. DFT calculation was carried out by B3LYP functional with 6-31G** basis set. Since B3LYP functional does not take into account the van der Waals dispersion forces, dispersion-corrected energy was calculated using DFT-D3 [34] along with Becke-Johnson damping function [35]. It was found that various interactions affect the structure and vibrational spectra. These interactions led to the blue shift of the CH group stretching vibration. This study could help in understanding the role of H-bonding in ILs, which would help in synthesis of ILs of desired physical and chemical properties.

The spectroscopic distinction of bis(trifluoromethanesulphonyl)imide anion (TFSI⁻) was carried out by Herstedt et al. [36]. The TFSI⁻ anion can exist in two conformational states, a tronsoid form of C_2 symmetry and a cisoid form of C_1 symmetry. In this work, the effect on Raman and IR spectroscopy due to conformation was investigated with the help of theoretical calculation. DFT calculations were performed at B3LYP/6-31G** level. It was shown that even the effect of conformation on the vibrational spectra was subtle, still it was possible to

distinguish TFSI⁻ conformational isomerism. In IR spectroscopy, the regions 130–1380 and 480–60 cm^{-1} were found to be sensitive to the conformational state. It was also possible to distinguish the change due to conformational state from that due to ionic interactions. The ratio of the two conformers in solution was found by measuring IR bands at 602 or 656 (for cisoid, C_1) and 618 cm^{-1} (for transoid, C_2). In Raman spectra, the marker bands were found at 629 (for transoid) and 653 cm^{-1} (for cisoid).
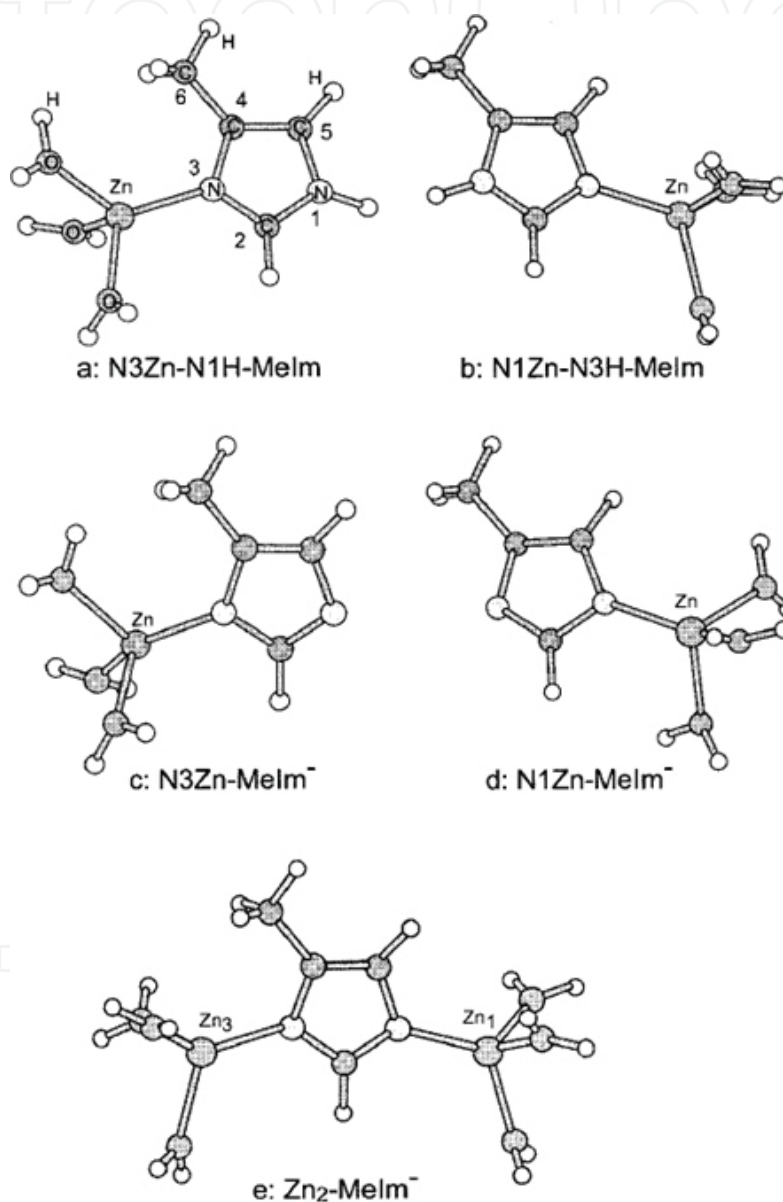

Figure 2. Optimized geometries of the zinc complexes of 4-MeIm in different protonation states. Reprinted with permission from The Journal of Physical Chemistry A, vol. 106, pp.3377–3390. Copyright 2012 American Chemical Society [39].

The alkaloids that are mainly found in plants, and to a lesser quantity in animals, have been studied by ATR-IR and FT-Raman spectroscopy for fast, reliable detection in pharmaceutical

products. One such candidate in the group, morphine, was studied by Baranska and Kaczor [37]. For theoretical study, potential energy scanning (PES) was performed to find the minimum energy conformations. Subsequently, geometry optimizations and frequency calculations were carried out on these conformers. It was found that IR spectroscopy could help in monitoring the arrangement of hydroxyl group of the morphine molecule while Raman is not very sensitive to these changes. Chemical modifications of perfluoropolymers were studied using spectroscopic method and quantum calculation by Radice et al. [38]. In the IR absorption spectra, carbonyl stretching region was found to be sensitive to the different polymer degradation pathways.

Metal plays an important role in determining the structure and properties of molecules. Several authors investigated metal-molecule interactions using vibrational spectroscopy. When metal binds to the molecule, few peaks change considerably and those peaks can be used as marker bands to determine its coordination and protonation state. Hasegawa et al. [39] studied different protonated and metal-bound forms of 4-methylimidazole (4-MeIm) vibrational spectroscopy in conjunction with theoretical calculations. The N-H stretching frequencies were seen to be downshifted by ~50 cm^{-1} on complexation with Zn while CH stretching vibration showed upshifts. The CC and CN stretching showed complicated behaviour in the Zn-bound form as these vibrations are coupled with other vibrations, and upon metal binding, some of the coupling changed. From these changes, together with theoretical study, the different metal-bound forms of the histidine could be identified (see **Figure 2**).
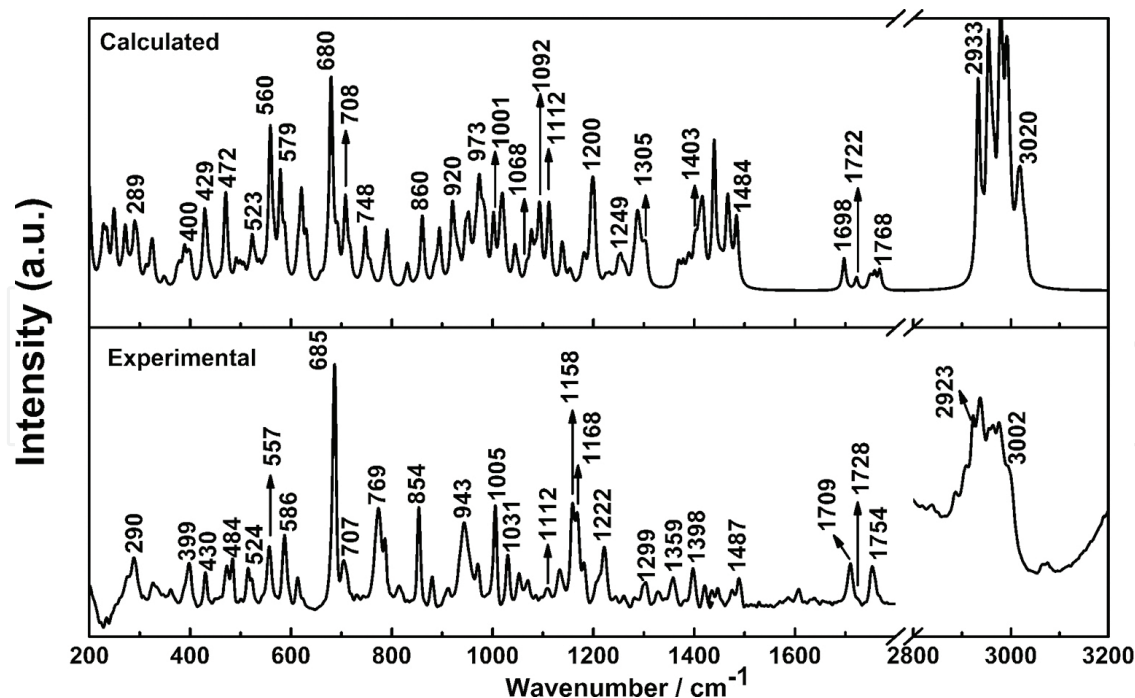
Figure 3. A comparison between experimental and calculated Raman spectrum. Reprinted from Journal of Molecular Structure, vol. 1102, Kundu *et al.*, Raman, IR and DFT studies of mechanism of sodium binding to urea catalyst, pp 267-274, Copyright (2015), with permission from Elsevier [41].

A bis-camphorsulphonyl was synthesized as a hydrogen-bonding catalyst [40]. It was found that the enantioselectivity capability of the catalyst is poor. However, when it was complexed with sodium ion, the selectivity of the catalyst increased significantly. The X-ray crystallographic structure showed that the native conformation of the catalyst is unfavourable for enantioselectivity. The X-ray data for the complex form could not be obtained as it was not soluble in most of the organic solvents, and thus crystal could not be formed. Since vibrational spectroscopy does not require crystalline samples, we were interested to probe the structure of the catalyst in its free and sodium-bound form by vibrational spectroscopy, both experimentally and theoretically [41]. For DFT calculations, we have chosen B3LYP/6-31G (d,p) level. To include the inter-molecular interaction present in the solid form, we considered dimer structure of the catalyst for frequency calculation. A comparison between calculated Raman spectrum and experimentally obtained one is shown in **Figure 3**. To study the effect of sodium
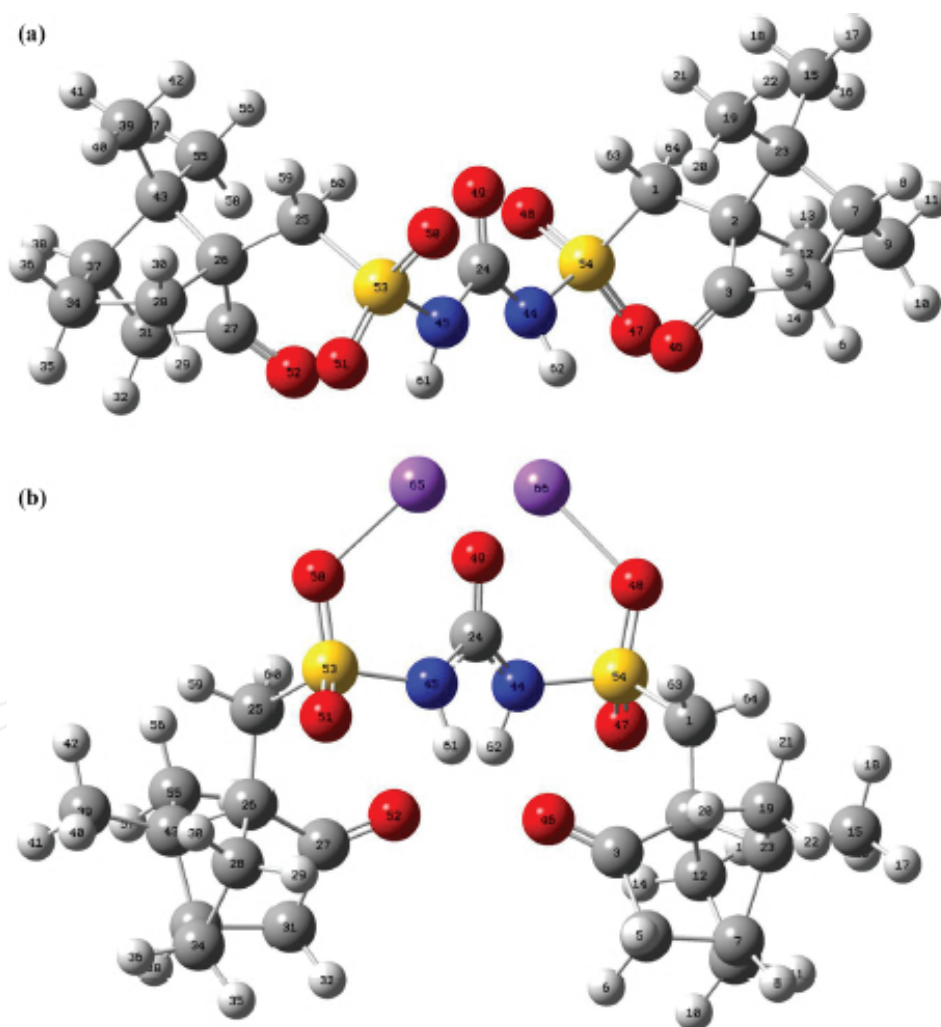
Figure 4. Optimized structure of urea catalyst in (a) free and (b) Na-bound form. Colour representation: white–hydrogen, red–oxygen, grey–carbon, blue–nitrogen, violet–sodium, yellow–sulphur. Reprinted from Journal of Molecular Structure, vol. 1102, Kundu *et al.*, Raman, IR and DFT studies of mechanism of sodium binding to urea catalyst, pp 267-274, Copyright (2015), with permission from Elsevier [41].

ion, we have compared the monomer form of the catalyst and its complex (see **Figure 4**). In our predicted structure, we considered two sodium forming bond with the oxygen atoms of the urea carbonyl and sulphonyl groups. The shift of stretching frequency of carbonyl, sulphonyl, C-N and N-H frequencies observed experimentally could be qualitatively reproduced in the theoretical calculation. The study showed how in the absence of any X-ray data, vibrational spectroscopy together with theoretical study was helpful in predicting the conformation of the catalyst in complex form (see **Figure 5**).
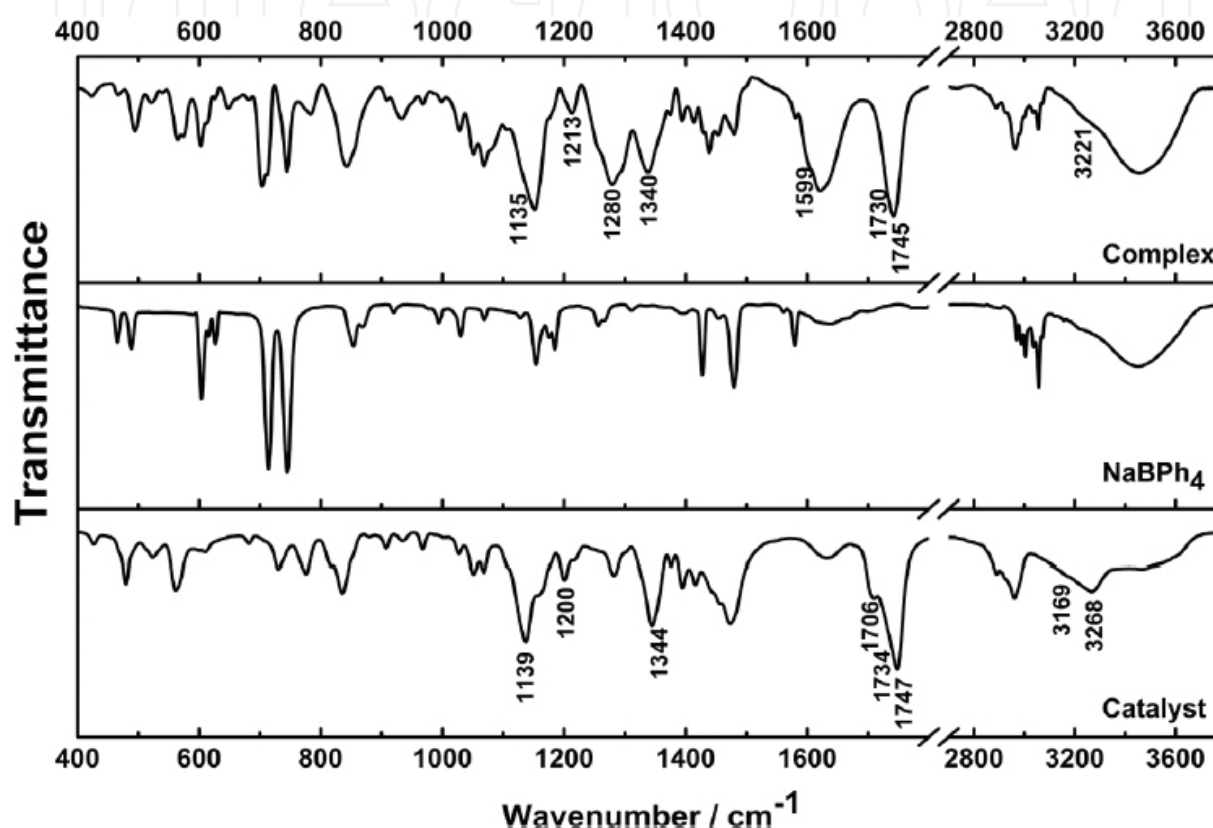
Figure 5. Experimental IR spectra of urea catalyst, NaBPh4 and complex showing the changes in the spectrum of catalyst upon sodium binding. Reprinted from Journal of Molecular Structure, vol. 1102, Kundu *et al.*, Raman, IR and DFT studies of mechanism of sodium binding to urea catalyst, pp 267–274, Copyright (2015), with permission from Elsevier [41].

4. Conclusions

In conclusion, in this chapter, we discuss two complementary vibrational techniques, Raman and IR. We give brief theoretical background for this technique. We also discuss about density functional theory, widely used to predict the spectrum of a molecule and help in assigning the bands. Then, we discuss the use of the combination of these two techniques in different molecular systems. We hope this will give the readers an idea of the potential of these techniques for various conformational analyses.

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