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Intermolecular and low-frequency intramolecular Raman scattering study of racemic ibuprofen

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J.J. Lazarević [a],*, S. Uskoković-Marković [b], M. Jelikić-Stankov [b], M. Radonjić [c], D. Tanasković [c], N. Lazarević [d], Z.V. Popović [d]

[a] Innovation center, Faculty of Technology and Metallurgy, University of Belgrade, Serbia
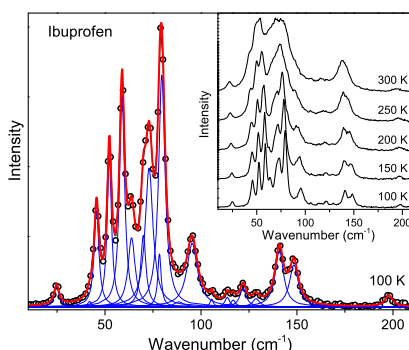[b] Faculty of Pharmacy, University of Belgrade, Serbia
[c] Scientific Computing Laboratory, Institute of Physics Belgrade, University of Belgrade, Pregrevica 118, 11080 Belgrade, Serbia
[d] Center for Solid State Physics and New Materials, Institute of Physics Belgrade, University of Belgrade, Pregrevica 118, 11080 Belgrade, Serbia

HIGHLIGHTS

- Racemic ibuprofen Raman scattering spectra was measured at room and low temperatures.
- First principle calculations of the ibubrofen molecule dynamics properties were performed.
- Correlations between the molecule and crystal vibrations were established.

GRAPHICAL ABSTRACT

ABSTRACT

We report the low-temperature Raman scattering study of racemic ibuprofen. Detailed analysis of the racemic ibuprofen crystal symmetry, related to the vibrational properties of the system, has been presented. The first principle calculations of a single ibuprofen molecule dynamical properties are compered with experimental data. Nineteen, out of 26 modes expected for the spectral region below $200\ cm^{-1}$, have been observed.

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Introduction

Organic molecular crystals are characterized by a pronounced contrast between the strong covalent intramolecular interactions and the weak van der Waals intermolecular attractions or the hydrogen bonding association. Whereas the intermolecular interactions are responsible for specific physical properties of the molecular compounds, the strong covalent bonds maintain the internal molecular structure. The vibrations within the molecular crystals can be of two types: internal vibrations (within the molecule) and external vibrations (between the molecules). Raman spectroscopy allows us to analyze these different kinds of motions. Consequently, external vibrations are closely related to the specific

* Corresponding author.
 E-mail address: jasmina.lazarevic@hotmail.com (J.J. Lazarević).

physical properties of the molecular compounds, providing information on the stability of the physical state at molecular levels, and the nature of solid state transformations. Raman spectroscopy provides direct information on the phase transition from *in situ* investigations on molecular compounds exposed to a wide variety of environmental stress, since no special sample preparation is required. Thereby, Raman spectroscopy has important applications in the field of pharmaceutical sciences.

Ibuprofen (IBP), 2-(4-isobutylphenyl)propanoic acid, is a widely used non-steroidal anti-inflammatory drug having analgesic and antipyretic activities. It can be found in two enantiomeric forms: S(+)-IBP and R(−)-IBP, where the S-IBP is the pharmacologically active form. In fact, the commercial drug is the racemic mixture of these two forms and it appears at ambient temperature as a white crystalline powder. The ibuprofen racemic mixture in its crystalline phase I ((RS)-IBP) is stable up to the melting point $T_{mI} = 349$ K [1]. Recently, the existence of the second solid state phase of the racemic ibuprofen has been reported [2,3].

Although the information about the low-energy external vibrations is crucial for the identification of different solid state phases, previous Raman scattering and theoretical studies on (RS)-IBP vibration properties have been focused mainly on the internal (molecular) vibrations at energies larger than 200 cm^{-1} [4–7]. To the best of our knowledge, the low energy region of the (RS)-IBP Raman spectra has been reported only by Hédoux et al. [3]. The authors reported only three peak structures at about 20 cm^{-1}, 50 cm^{-1} and 80 cm^{-1} and assigned them as the phonon modes, whereas symmetry properties of the (RS)-IBP crystal structure suggest a large number of the external vibrations. No detailed analysis of the spectra in terms of the specific symmetry properties of (RS)-IBP has been performed. In this paper, detailed study of the low energy region of the (RS)-IBP Raman scattering spectra at various temperatures is presented. Vibrational properties of the (RS)-IBP is discussed in terms of the peculiarities of the (RS)-IBP crystal structure. Temperature dependent spectra are analysed by means of the anharmonicity model.

Experiment

Raman scattering measurements were performed using the Jobin Yvon T64000 Raman systems in backscattering micro-Raman configuration with 1800/1800/1800 grooves/mm gratings in subtractive regime. The external and second intermediate slits were set to 100 μm, whereas lateral slits were adjusted so the minimum noise is achieved. The 514.5 nm line of a mixed Ar$^+$/Kr$^+$ gas laser was used as an excitation source. The corresponding excitation power density was less than 0.3 kW/cm^2. Temperature dependent measurements were performed using LINKAM THMS 600 heating/cooling stage. All the Raman scattering spectra are corrected by the corresponding Bose factor $n(T)$.

Results and discussion

The structure of a single IBP molecule is presented in Fig. 1. Due to the low symmetry, all 93 A modes representing the vibrations of a single IBP molecule, are both infrared and Raman active. Commercially, IBP is found as a racemate in the form of the molecular crystals. (RS)-IBP crystalizes in the monoclinic type of structure with four ($Z = 4$) molecular units per unit cell [8–12]. The (RS)-IBP, R(−)- and S(+)-IBP enantiomers form a cyclic dimer across hydrogen bonds of their carboxylic groups through the center of inversion. This leads to an increase of a symmetry from the $P2_1$ for the S-IBP to $P2_1/c$ (C_{2h}^5) in the case of (RS)-IBP. The main implication of the inversion symmetry presence in the crystal is the separation of the Raman and infrared active modes.

In general, for the molecular crystals, two types of vibrations could be distinguished: external vibrations (vibrations between the molecules) and internal vibrations (vibrations within the molecules). Depending on the type of the motion, external vibrations could be translations (representing the translational motions of the molecules) or librations (representing the rotational motions of the molecules).

In order to determine the vibrational structure of the (RS)-IBP, the correlation method was applied [13]. By correlating the translational and the rotational modes of a single molecule to the site symmetry and the crystal symmetry (see Fig. 2), the external vibrational mode distribution at the Brillouin zone center (Γ point) was obtained:

$$\Gamma_{Raman} = 6A_g + 6B_g,$$
$$\Gamma_{infrared} = 5A_u + 4B_u,$$
$$\Gamma_{acoustic} = A_u + 2B_u$$

Thus one can expect 12 external modes to be observed in the Raman scattering experiment.

In the same manner, by establishing the correlation between the symmetry of the molecular vibrations, the site symmetry and the symmetry of the crystal through the peculiarities of the (RS)-IBP crystal structure (see Fig. 2), 186 internal modes ($93A_g + 93B_g$) are expected to be observed in the Raman scattering experiment. This substantial increase in the number of the observable vibrational modes for the molecular crystal in comparison to an isolated molecule is a consequence of the interactions between the molecules. Having in mind that the molecules are connected with very weak van der Waals interactions, the internal modes will usually appear as a $A_g - B_g$ doublets around the energies that correspond to the energies of the single molecule vibrations. Furthermore, the splitting within the doublets is rather small and thus they are typically observed as a single feature in the Raman scattering spectra.

Nature of the intermolecular bonds suggests that all external vibrations are expected to be found in the low energy part of the Raman spectra. However, ibuprofen is a highly flexible molecule, and thus one can also expect a number of low-lying internal doublets, each arising from a mode of the isolated molecule (see Fig. 2).

In order to determine the vibrational spectra of a single molecule, we perform first principle calculations of the IBP molecule dynamics properties, within density functional perturbation theory [14] as implemented in the QUANTUM ESPRESSO package [15]. We used scalar relativistic ultra-soft pseudopotentials, generated within general gradient approximations with Perdew–Burke–Ernzerhof exchange correlation functional. Structural parameters are relaxed so that total force acting on each atom is less than 10^{-4} Ry/a.u. In order to study the isolated molecule, the unit cell is made to be several times larger than the size of the molecule itself and all calculations are performed at the center of the Brillouin zone. Energy cut-offs for the wave functions and the electron densities are 60 Ry and 800 Ry respectively, determined to ensure a stable convergence. Calculated vibrational mode energies of a single S-IBP molecule in the low energy region are summarized in Table 1. Corresponding displacement patterns are presented in Fig. 1. We have also performed calculations on R-IBP and there are no significant changes in phonon energies between these two forms. Obtained energies of the vibrational modes at energies larger than 200 cm^{-1} are in good agreement with previously published data [4–7] and with our Raman (RS)-IBP measurements presented in Fig. 3(a).

According to the symmetry considerations for the (RS)-IBP crystal structure, 12 Raman active modes originating from the external vibrations are expected. From the single IBP molecule numerical calculations, we have found that in the spectral region under
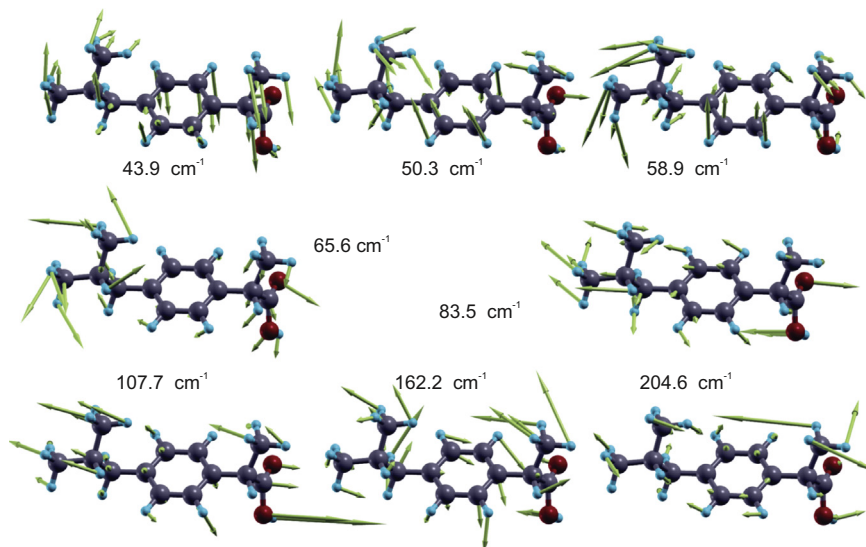
Fig. 1. Displacement patterns of the low energy Raman active vibrational modes of (RS)-IBP. The lengths of the arrows are proportional to the vibration amplitudes.
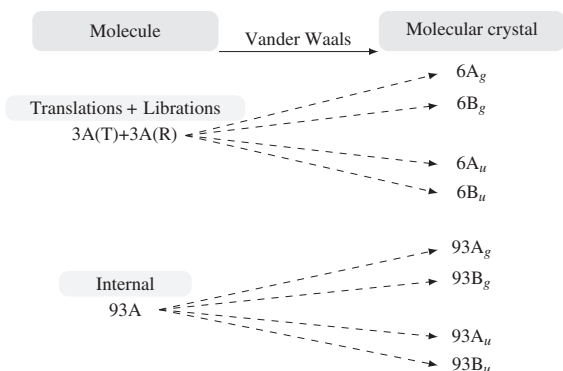

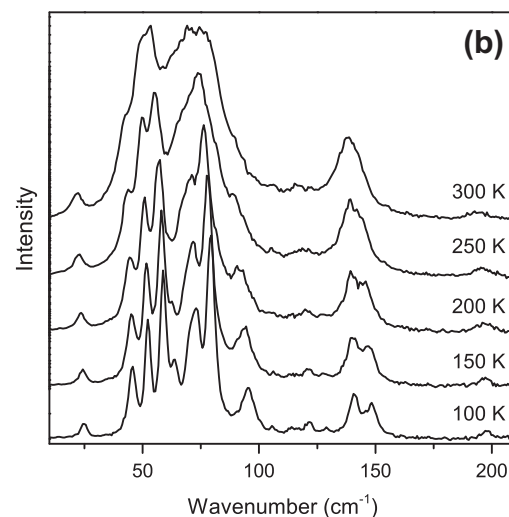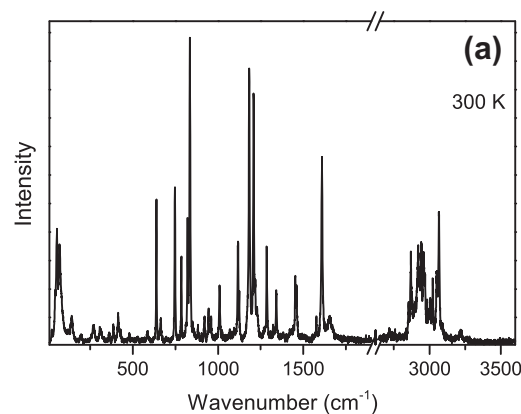**Fig. 2.** Correlation diagram betwen the molecular and crystal vibrations.

Fig. 3. (a) Wide range Raman scattering spectra of the (RS)-Ibuprofen. (b) The low energy region Raman scattering spectra of (RS)-Ibuprofen measured at various temperatures.

Table 1
Calculated vibrational mode energies, symmetry and activity for a single S-IBP molecule in the low energy region.

Symmetry	Calculated energy (cm^{-1})	Activity
A	43.9	IR + R
A	50.3	IR + R
A	58.9	IR + R
A	65.6	IR + R
A	83.5	IR + R
A	107.7	IR + R
A	162.2	IR + R

$200\ cm^{-1}$ 7 intramolecular doublets are expected, each arising from a mode of the isolated molecule. This give rise to the total of 26 Raman active modes to be observed in the spectral region under $200\ cm^{-1}$. The presence of both the internal and the external vibrational modes in the same spectral region indicates the strong mixing between the two types of vibrational modes [16–18].

Fig. 3(b) shows the low energy region Raman scattering spectra of (RS)-IBP measured at various temperatures. As one can see, at room temperature only four structures at about $21\ cm^{-1}$, $52\ cm^{-1}$, $74\ cm^{-1}$ and $138\ cm^{-1}$ can be clearly distinguished. This is in agreement with the findings of Hédoux et al. [3], where the authors observed three peaks at around $20\ cm^{-1}$, $50\ cm^{-1}$ and $80\ cm^{-1}$ and assigned them as phonon peaks. However, as already mentioned, symmetry of the system predicts a much larger number of peaks and thus we should consider these structure to be multi-peak structures. In order to analyse these multi-peaks structure, we performed the low temperature measurements. In

general, with decreasing temperature linewidth of each mode decreases due to the anharmonicity effects [19]. Consequently, a large number of modes become observable at 100 K (see Fig. 3(b)).

Fig. 4 shows unpolarized Raman scattering spectra of (RS)-Ibuprofen measured at 100 K. Solid lines represent deconvoluted spectra obtained by least-squares fitting with multiple Lorentzian line shapes. We were able to observe 19 out of 26 modes predicted by structural considerations. Energies of the observed modes are summarized in Fig. 4. Whereas all the modes below 140 cm^{-1} are expected to have mixed character to some extent, all additional modes above 140 cm^{-1} can be safely assigned as an intramolecular doublets.

Fig. 5(a) shows Raman scattering spectra of the peak structure around 145 cm^{-1} of (RS)-IBP measured at various temperatures. Although, only a single mode is predicted by the numerical calculation for the IBP molecule in this spectral region (see Table 1), two modes are clearly observed at low temperatures. Thus, this structure can be assigned as an $A_g - B_g$ doublet, as suggested by symmetry analysis (see Fig. 2). Energy separation within the doublet is related to the interaction between the molecules and the crystal structure of the sample. With increasing temperature the modes are shifted toward the lower wavenumbers and become progressively broader in accordance with anharmonicity effects (see Fig. 5(b)).

In general, temperature dependence of the vibrational mode energy, $\Omega(T)$ is usually governed by anharmonic effects. If, for the sake of simplicity, we assume a symmetric decay of the low lying optical vibration into two acoustic vibrations, the anharmonicity induced energy temperature dependence can be described with [19,20]:

$$\Omega(T) = \Omega_0 - C\left(1 + \frac{2}{e^x - 1}\right), \tag{1}$$

where Ω_0 is the Raman mode energy, C is the anharmonic constant and $x = \hbar\Omega_0/2k_BT$.

Fig. 5(c) shows the highest intensity low lying modes energy temperature dependence. Dashed lines represent calculated spectra by using Eq. (1). The best fit parameters are presented in Table 2. Good agreement between the experimental data and the calculated spectra suggest that the temperature dependence of the low energy (RS)-IBP Raman active modes is mainly driven by the anharmonicity effects. In general, knowledge about the Raman modes energy temperature dependence alone is not sufficient to separate the low lying internal from the external modes [21,22]. More complete approach for determination of the modes type
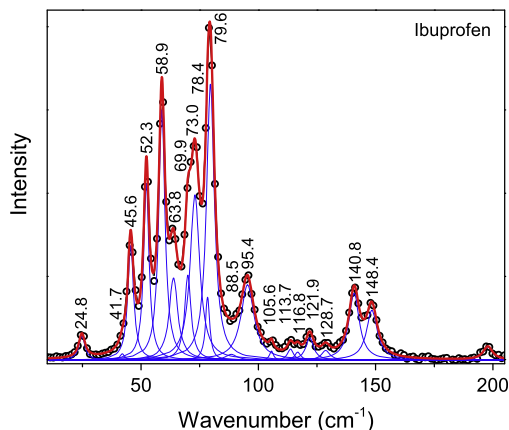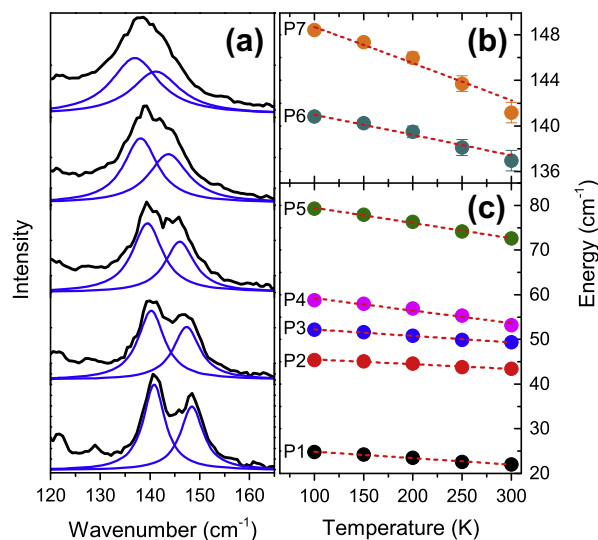

Fig. 5. (a) Raman scattering spectra of the double peak structure around 145 cm^{-1} of (RS)-IBP measured at various temperatures. (b and c) Energy temperature dependance of highest intensity Raman modes.

Table 2
Best-fitting parameters for Raman modes energy temperature dependence using Eq. (1).

	Ω (cm^{-1})	C (cm^{-1})		Ω (cm^{-1})	C (cm^{-1})
P1	26.3	0.13	P5	83.0	1.0
P2	46.6	0.18	P6	143.0	0.9
P3	53.7	0.28	P7	152.3	1.8
P4	62.0	0.6			

would require combination of pressure and temperature dependent measurements [22].

Conclusion

The Raman scattering spectra of the (RS)-IBP measured at various temperatures has been reported. Detailed analysis of the (RS)-IBP crystal symmetry, predicted 12 external modes for this system. According to the numerical calculations, appearance of internal vibrational modes is also expected in the low energy region of the spectra, mostly in terms of $A_g - B_g$ doublets, as in the case of the 141–148 cm^{-1} structure. Total of nineteen Raman active modes have been observed in the region below 200 cm^{-1}. Temperature dependance of the low energy (RS)-IBP Raman active modes is driven by anharmonicity effects.

Acknowledgments

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Fig. 4. Raman scattering spectra of (RS)-IBP measured at 100 K. Solid lines represent calculated spectra by using Lorentz profiles.

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