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PHYSICS OF SOLID STATE AND CONDENSED MATTER

Structure and Dynamics Investigation of Ibuprofen Dimers by DFT Method

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Abstract—Ibuprofen is a representative of a group of nonsteroidal anti-inflammatory drugs widely used in modern medicine. This article presents the results of the ibuprofen structure and dynamics investigations using IR- and Raman-spectroscopy in combination with quantum chemical calculations in the DFT approximation. Ibuprofen R-S dimer cluster model was used for calculations. Discussion is focused on the key parameters of the molecular geometry of the cyclic R-S dimer and vibrations of the H-bonded carboxylic COOH group of ibuprofen.

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INTRODUCTION

Many medicinal substances are a racemic mixture of enantiomers, in which only one is biologically active. An example is ibuprofen, a drug from the Vital, Essential, and Necessary Drug Listing (Fig. 1a). Its inactive R-enantiomer in vivo undergoes metabolic inversion and turns into an active S-enantiomer [1]. That is why most pharmaceutical formulations of ibuprofen contain the racemic mixture of enantiomers, and there is no need to separate them. In modern research practice, ibuprofen is widely used as a model compound to study the various effects on their biological properties as well as to develop new methodologies for the identification of compounds of this class by various methods [2–5]. Combination of the complementary experimental and computational methods for drugs characterization becomes a common research practice. Thus, the pros and cons of structural model for computational investigations can be crucial for correct interpretation of results. Molecular dynamics of ibuprofen is well characterized by IR- and Raman-spectroscopy and DFT calculations were used [6] for the full assignment of experimental bands in vibrational spectra of ibuprofen. Nevertheless, some assignments within 1500–2800 cm^{-1} are contradictory due to limitations of structure models used in calculations (single molecule) because all intermolecular interactions are ignored in this case.

This article presents the results of the ibuprofen structure and dynamics investigations using IR- and Raman-spectroscopy in combination with quantum chemical calculations in the DFT approximation. Ibuprofen R-S dimer cluster was used for calculations. We focus on the key parameters of the molecular geometry of the cyclic R-S dimer and vibrations of the H-bonded carboxylic COOH group of ibuprofen.

EXPERIMENTAL

The ibuprofen (Ibu) sample used in experimental investigations was of NMR spectroscopic grade. The differential scanning calorimetry experiments were carried out with Netzsch differential scanning calorimeter; model DSC-204 F1 Phoenix with a heating rate of 10°C/min up to 120°C in an argon atmosphere. Experimentally determined melting point of Ibu (m.p. = 76.8°C) corresponds to the known one for racemic Ibu [8]. Infrared spectrum of the Ibu in 7 mm KBr pellets (ca. 0.3% (w/w)) was recorded at room temperature on Nicolet iS50 FTIR spectrometer. Raman spectrum of the Ibu was measured at room temperature on Confotec MR200 microspectrometer combined with NIKON Ni upright microscope at an excitation wavelength of $\lambda = 473$ nm.

All DFT calculations were performed using the software package ORCA 5.0.3 [9]. Structures of S- and R-enantiomers of Ibu known from X-ray diffraction experiment [7] were used as starting models for calculations. Molecular geometry optimization of the Ibu enantiomers and their dimer followed by vibrational frequencies calculations were carried out using the

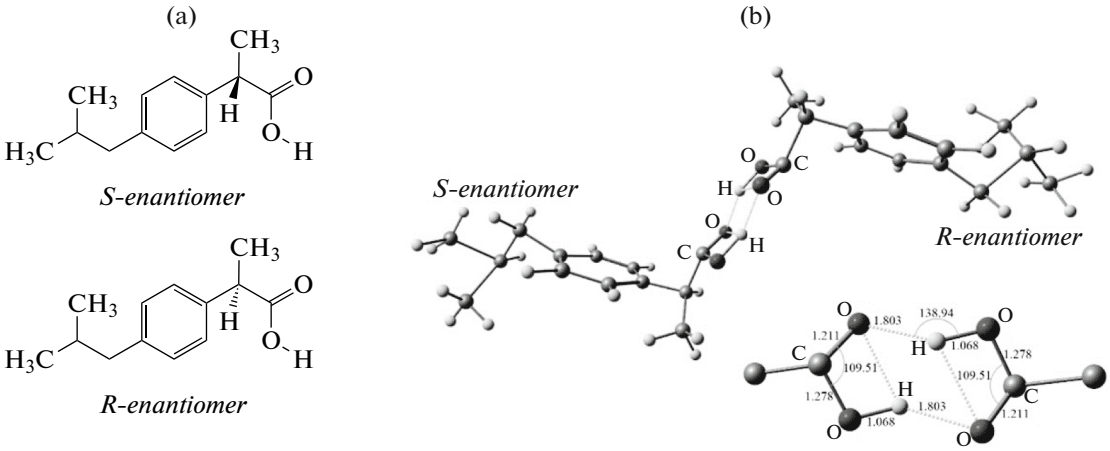

Fig. 1. 2D structural models of ibuprofen enantiomers (a) and R-S dimer cluster fragment from the crystal lattice of racemic ibuprofen [7] (b).

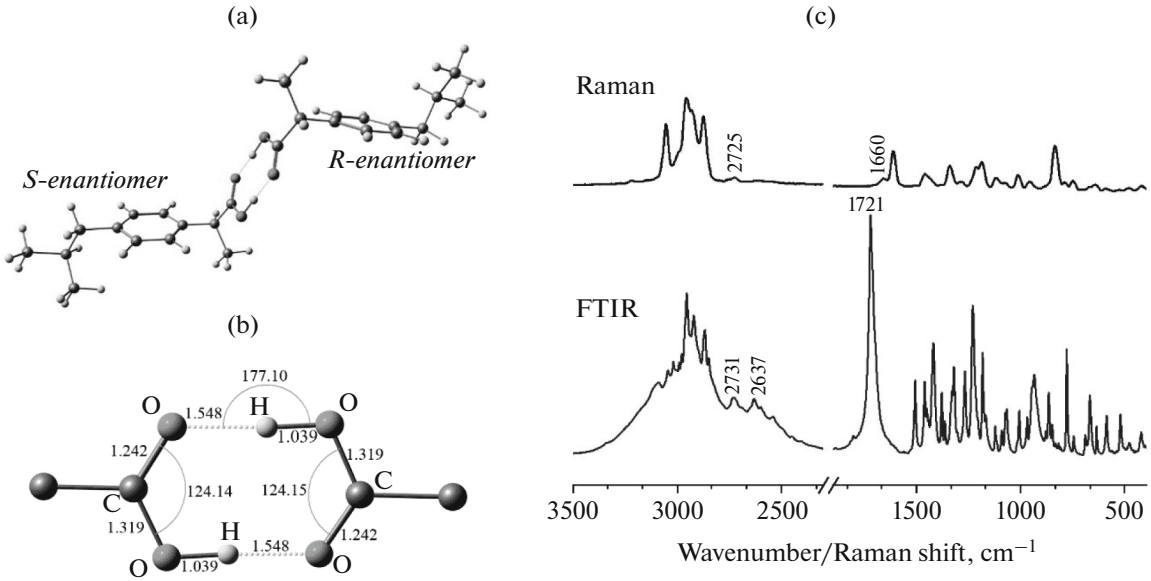

Fig. 2. Equilibrium configuration of the cyclic R-S dimer of Ibu at the BP86/def2-TZVP level of theory (a); some key parameters of the molecular geometry of the cyclic S-R dimer (b); experimental FTIR and Raman spectra of racemic Ibu (c).

BP86 functional [10, 11] in combination with the def2-TZVP basis set. The binding enthalpy ($\Delta_{bind}H^0$) for dimer considered was calculated as $\Delta_{bind}H^0 = H_{dimer} - (H_R + H_S)$, were H_{dimer} – enthalpy of dimer, H_R and H_S are enthalpies of corresponding Ibu enantiomers. Stability of the dimers was estimated using binding Gibbs free energy ($\Delta_{bind}G^0$) calculated as $\Delta_{bind}G^0 = G_{dimer} - (G_R + G_S)$, were G_{dimer} is the Gibbs free energy of dimer, G_R and G_S are the Gibbs free energies of the corresponding Ibu enantiomers.

RESULTS AND DISCUSSION

The key feature of the ibuprofen racemate in the crystalline state is the presence of cyclic dimers formed by the S- and R-enantiomers in its structure (Fig. 1b) [7]. The presence of two H-bonds in these dimers affects the molecular dynamics of Ibu and determines some features of its experimental vibrational spectra. We consider the cyclic R–S dimer to be a small cluster model of the Ibu structure in which intermolecular H-bonds are taken into account. Equilibrium configuration of the cyclic R–S dimer of Ibu obtained at BP86/def2-TZVP level of theory is presented in (Fig. 2a). This dimer is stabilized by the two almost equivalent O–H···O hydrogen bonds between each molecule's COOH group (Fig. 2b). The binding energy for the dimer is $\Delta_{bind}H^0 = -70.49$ kJ/mol, and the binding Gibbs free energy is $\Delta_{bind}G^0 = -10.61$ kJ/mol. The two H-bonds between R- and S-enantiomers in the Ibu cluster considered can be classified as moderate according to the criteria listed in [12].

Table 1. Key vibrational modes of carboxylic groups in the DFT-calculated and experimental vibrational spectra of the Ibu

Vibrations	DFT calculation, cm^{-1}*				Experimental, cm^{-1}	
	S- and R-enantiomer		R-S Dimer			
	IR	Raman	IR	Raman	IR	Raman
O–H stretching	3595	3595	2669	2669	2731	2725
	–	–	2504	2504	2637	–
C=O stretching	1743	1743	1671	1671	1721	–
	–	–	1591	1591	–	1660
C–O stretching + O–H bending	–	–	1436	1436	1420	–
	1298	1298	1295	1295	1231	–
O–H out-of-plane bending	–	–	1067	1067	940	936
	–	–	1032	1032	920	–

* Vibrational frequencies are listed without any corrections.

For the purpose of comparative analysis, experimental FTIR- and Raman-spectra of the racemic Ibu sample were obtained (Fig. 2c). They are in good agreement with the known data for this compound [6] as well as with the calculated spectra for the R-S dimer. Key vibrational modes of COOH groups are listed in Table 1.

Stretching modes of the O–H bonds (3595 cm^{-1}) and C=O bonds (1743 cm^{-1}) are of the same value in calculated spectra for the S- and R-enantiomers and correspond to the vibrations of non-bonded molecules (Table 1). For the dimer and racemate Ibu C=O stretching bands are shifted noticeably. A band at 1721 cm^{-1} in the IR-spectrum is assigned to the symmetric C=O stretching, and at 1660 cm^{-1} in the Raman-spectrum is assigned to the antisymmetric one. There are no vibrational bands within 1750–2900 cm^{-1} range in enantiomers' calculated spectra in contrast with the experimental spectra for Ibu racemate. Intensive stretching vibrations of H-bonded O–H groups are observed within the pointed range for R-S dimer. Thus bands in experimental IR (2731 and 2637 cm^{-1}) and Raman (2725 cm^{-1}) spectra may be assigned to the O–H stretching modes of dimers. Bands at 1420 and 1231 cm^{-1} correspond to the combination C–O stretching and O–H in-plane bending modes, whereas cooperative H-bonded O–H out-of-plane bending modes appear in the experimental IR-spectrum at 940 cm^{-1} (in-phase) and 920 cm^{-1} (out-of-phase) and are absent in calculated enantiomers spectra. Good linear correlation ($R = 0.99883$) was obtained between experimental vibrational frequencies of H-bonded carboxylic groups and DFT-calculated ones for R-S dimer.

CONCLUSIONS

Complex experimental and in silico investigations of the vibrational spectra features of ibuprofen in neutral form were performed. As a result of the vibrational frequency calculations for the S-R dimer of ibuprofen, it was demonstrated that this small cluster model can be used as a starting point for the intermolecular interactions investigations by DFT methods. Satisfactory linear correlation between the experimental and DFT-calculated vibrational frequencies of H-bonded carboxylic groups were obtained. These modes will be used as intermolecular interactions markers in further investigations of Ibu dynamics by complementary experimental and computational methods.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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