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# The effects of conformation and intermolecular hydrogen bonding on the structural and vibrational spectral data of *naproxen* molecule

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ABSTRACT

The structural and vibrational properties of *naproxen*, an inhibitor of cyclooxygenase (*COX*) enzyme, were investigated by molecular modeling and experimental IR and Raman spectroscopic techniques. Possible conformers of the molecule were searched *via* a molecular dynamics simulation carried out with *MM2* force field. The total energies, equilibrium geometries, force fields, IR and Raman spectral data of the found stable conformers were determined by means of *geometry optimization* and *harmonic frequency* calculations carried out using the *B3LYP* method and *Pople-style* basis sets of different size. The stability order obtained for the lowest-energy conformers was confirmed by high-accuracy thermochemistry calculations performed with *G3MP2B3* composite method. Some electronic structure parameters of naproxen and the anharmonicity characters of its vibrational modes were determined by means of *natural population analysis* (*NPA*) and *anharmonic frequency* calculations at *B3LYP/6-31++G(d,p)* and *B3LYP/6-311++G(d,p)* levels of theory. A part of these calculations carried out for free naproxen molecule were repeated also for its energetically most favored dimer forms. Two different scaling procedures ((1) "*SQM-FF* methodology" and (2) "*Dual scale factors*") were independently applied to the obtained harmonic vibrational spectral data to fit them to the corresponding experimental data. In the light of the obtained calculation results, which confirm the remarkable effects of conformation and intermolecular hydrogen bonding on the structural and vibrational spectral data, in particular, on those associated with the functional groups in the propanoic acid chain, a reliable assignment of the fundamental bands observed in the experimental IR and Raman spectra of the molecule was achieved.



## 1. Introduction

*Naproxen*, [S(+)-2-(6-methoxy-2-naphthyl) propionic acid], has become one of the most popular and widely used Non-Steroidal Anti Inflammatory Drugs (*NSAIDs*) since approved by *U.S. FDA* in December 1991. Unlike the synthetically produced steroid drugs which work by suppressing the immune system, *naproxen* and other *NSAIDs* work by preventing the formation of the prostaglandins, which are a cluster of bioactive lipids generated in the human and animal tissues through the activities of cyclooxygenase isozymes (*COX-1* and *COX-2*), and play important role in many cellular responses and pathophysiologic processes [1]. Today, *naproxen* is known as a *NSAID* compound widely used in the treatment of many diseases such as rheumatoid arthritis, osteoarthritis, degenerative joint disease, ankylosing spondylitis, acute gout and primary dismenorrea [2]. It has been also reported that the compound is effective in the treatment of traditional and nontraditional migraine-associated symptoms [3], and it is used in the prevention and treatment of adolescent migraine [4,5] and menstrual migraine [6,7]. According to various epidemiological studies, *naproxen* and some other *NSAIDs* are promising candidates for chemoprevention against colon cancer, and some experimental data suggest that *NSAIDs* might provide protection against cancers of mammary gland, skin, liver and urinary bladder [8–11]. Besides these, it has been reported that long-term prophylactic use of *naproxen* can reduce the risk of Alzheimer disease [12–14].

The first structural analysis on *naproxen* molecule was performed by Ravikumar et al. [15], and then this was followed by a series of structure and conformation studies performed by Wenzel and Buss [16], Bednarek et al. [17], Bachechi et al. [18], Lahmani et al. [19], King et al. [20], Okulik et al. [21] and Alvarez et al. [22]. Nevertheless, one can reach only three published papers on the analysis of the vibrational motions of *naproxen* and associated experimental spectral data. The first of them, based on IR and Raman spectroscopic measurements and molecular modeling, was reported by Jubert et al. [23]. This was followed by the other two valuable papers of Luber et al. [24] and Liu et al. [25]. Besides this, the effects of solvent–solute interactions, intermolecular hydrogen bonding and recrystallization on the morphology of *naproxen* were discussed by Tomasko and Timko [26]. Although

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each of the studies mentioned above provides significant contributions to the current literature, none of them has focused on the effects of conformation and intermolecular hydrogen bonding on the structural and vibrational spectral data of the molecule, specifically. Considering this situation and also some wrong or suspicious band assignments given in the previous papers, a comprehensive analysis, the main purpose of which is to reveal the effects of conformation and intermolecular hydrogen bonding on the structural and vibrational spectral properties of *naproxen* as well as on its IR and Raman spectra recorded at room temperature, has been first given in this study.

## 2. Methods and calculations

### 2.1. Experimental measurements

*Naproxen* (CAS number: 22204-53-1; chemical formula: $C_{14}H_{14}O_3$; molecular weight: 230.27 g mol$^{-1}$; purity: 98%, physical form: a powder of white color) was provided by *FLUKA* and used without performing any further purification. The FT-IR spectrum (400–4000 cm$^{-1}$) of the transparent disk sample prepared from potassium bromide (100 mg) and *naproxen* (2–3 mg), was recorded on a Jasco 300E model FT-IR spectrometer with resolution of 2 cm$^{-1}$ by 160 scanning. In addition, the FT-IR spectra of the dilute solutions of *naproxen* prepared with ethanol and methanol solvents (at the concentrations of 0.01–0.1 M) were recorded by using the same spectrometer in the same experimental conditions. On the other hand, the corresponding Raman spectra for the pure compound (in solid phase) and for its ethanol suspension, were recorded by using a *Jasco NRS 3100* model dispersive micro-Raman spectrometer (equipped with a laser source of 532 nm wavelength, a cooled CCD detector of high-sensitivity and a grating of 1200 lines/mm) and also using a *Bruker* "*Multi Ram*" model FT-Raman spectrometer (source: Nd:YAG Laser of 1064 nm wavelength, power: 1000 mW; detector: germanium detector cooled by liquid nitrogen). The FT-Raman spectrum (resolution: 1 cm$^{-1}$) for the spectral region 4000–50 cm$^{-1}$, and the dispersive micro-Raman spectrum for the spectral regions 1800–150 cm$^{-1}$ (resolution: 3.78 cm$^{-1}$) and 3400–2700 cm$^{-1}$ (resolution: 2.89 cm$^{-1}$) were obtained over 250 and 100 scanning, respectively. After carefully applied baseline and background corrections, the resultant experimental IR and Raman spectra reported in this study were obtained.

### 2.2. Molecular modeling calculations

The minimum-energy conformers of *naproxen* molecule, which is a naphthalene derivative including the methoxy and propanoic acid substituents (see Fig. 1), were searched by means of a molecular dynamics simulation carried out by "*Chem3D*" software [27] using *Allingers'MM2 force field* [28]. The input geometrical data used in the simulation, where the temperature parameter was gradually increased from 0 K to 500 K, were formed from the optimized geometrical parameters reported for monomeric *naproxen* by Okulik and Jubert [21]. For each trajectory determined through the simulation, the corresponding geometrical parameters were reached *via* energy minimization calculations performed by using the same software and force field. These calculations were followed by successive geometry optimization and harmonic frequency calculations carried out by *Gaussian03* software [29] using *B3LYP* method based on the density functional theory (*DFT*) [30,31] and various *Pople-style* basis sets {*6-31G(d)*, *6-31++G(d,p)* and *6-311++G(d,p)*}. In order to examine the stability order for the determined stable conformers, additional high-accuracy thermochemistry calculations were carried out using *G3MP2B3* method, which includes some empirical spin–orbit and higher-level energy corrections [32–34]; this composite method, which employs the equilibrium geometrical parameters and zero point energies calculated at *B3LYP/6-31G(d)* level as well as the energy correction terms calculated at *CCSD(T,FC)/6-31G(d)* and *MP2(FC)/G3MP2(Large)* levels, is known as the most economic and efficient one among all the methods based on *Gaussian-3 theory* (*G3*). For each of the stable conformers, the energies of the frontier molecular orbitals were calculated at *B3LYP/6-31++G(d,p)* and *B3LYP/6-311++G(d,p)* levels of theory and then these calculation data were used in the definition of the ionization potential ($I$), electron affinity ($A$), absolute electronegativity ($\chi$) and chemical hardness ($\eta$) as well as the electrophilicity index ($w$) values within the validity of Koopmans' theorem [35], where the energies of the highest occupied molecular orbital (*HOMO*) and the lowest unoccupied molecular orbital (*LUMO*) are assumed to equal $I$ and $A$, respectively. In these definitions realized by using the empirical equations given by Yang, Pearson and Parr [36–42], the absolute electronegativity values were taken as −1/2 times the sum of the energies of the frontier orbitals (*HOMO* and *LUMO*), while chemical hardness parameters were equaled to the absolute value of the *HOMO–LUMO* energy gap. On the other hand, for the conformers estimated to have the largest populations in the molecular medium at room temperature, the corresponding *natural population analysis* (*NPA*) data {the natural atomic charges, the occupancies and energies of the natural bonding orbitals (*NBO*s), the polarization coefficients for natural hybrid orbitals (*NHO*s), the electron delocalization energies as well as the Canonical Molecular Orbital (*CMO*) coefficients showing the contributions of the *NBO*s to the frontier orbitals} were calculated at the *B3LYP/6-311++G(d,p)* level of theory by utilizing the software *NBO 5.9* [43]. In addition, the *Fukui function* values, which show the local reactivity and selectivity of the conformers in electrophilic, nucleophlic and radical attacks, were derived from the calculated natural atomic charges using the approach proposed by Parr and Ayers [44,45]. In order to reveal the anharmonicity characters of the vibrational modes of *naproxen*, the frequency calculations were repeated for each stable conformer dominating the room-temperature experimental spectra of the molecule at *B3LYP/6-311++G(d,p)* level in the *anharmonic oscillator* approach which includes the cubic and quartic force constant correction terms. On the other hand, the overestimations at the calculated harmonic wavenumbers were corrected by the aid of two different types of scaling procedures called "*Dual scale factors*" [46] and "Scaled quantum mechanical force field (*SQM-FF*)" methodology [47–49]. In the former procedure, where two different empirical scale factors are employed to improve the calculated harmonic wavenumbers, one scale factor {"0.977" for *B3LYP/6-31++G(d,p)* and "0.980" for *B3LYP/6-311++G(d,p)*} is employed for the wavenumbers below 1800 cm$^{-1}$ while another one {"0.962" for *B3LYP/6-31++G(d,p)* and "0.967" for *B3LYP/6-311++G(d,p)*} for the wavenumbers higher than 1800 cm$^{-1}$; the scale factors used in this study were derived from those proposed by Frosch et al. for *B3LYP/6-31++G(d,p)* level of theory [50] by optimizing them so as to reach the smallest root-mean-square (*r.m.s.*) error values. Differently, in the *SQM-FF* methodology, the scaled wavenumbers are reproduced over the optimized geometry and force field parameters obtained from ab initio or DFT calculations. This second scaling procedure was applied to naproxen molecule by utilizing Collier's software ("*Fcart*", *version-06* [51–53]); in the scaling of the force constants of the described internal coordinates (see Table S1, supporting data), which were derived from the force constants (in Cartesian coordinate terms) obtained through the harmonic frequency calculations at *B3LYP/6-31G(d)* level of theory, the original scale factors proposed by Baker et al. [54] for the same level of theory (see Table S2, supporting material) were employed without any modification. The potential energy distribution (*PED*) values calculated in the *SQM-FF* methodology constituted the primary data set