Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 188 (2018) 189–196

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

The nature of hydrogen-bonding interactions in nonsteroidal anti-inflammatory drugs revealed by polarized IR spectroscopy

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ARTICLE INFO

Article history:
Received 27 May 2017
Received in revised form 5 July 2017
Accepted 8 July 2017
Available online 09 July 2017

Keywords:
Nonsteroidal anti-inflammatory drugs
Hydrogen bond
Polarized IR spectra
Isotopic effects

ABSTRACT

The influence of hydrogen-bonding interactions in the solid phase on the IR spectroscopic pattern of the ν_{O-H} band of nonsteroidal anti-inflammatory drugs (NSAIDs) was studied experimentally by IR spectroscopy with the use of polarized light at two temperatures (293 K and 77 K) and in isotopic dilution. The neat and deuterated crystals of (*S*)-naproxen ((*S*)-NPX), (*R*)-flurbiprofen ((*R*)-FBP), (*RS*)-flurbiprofen ((*RS*)-FBP) and (*RS*)-ketoprofen ((*RS*)-KTP) were obtained by melt crystallization between the two squeezed CaF_2 plates. The vibrational spectra of selected α-aryl propionic acid derivatives (2APAs) reflected the characteristics of their hydrogen-bond networks, i.e., 2APAs were characterized by the chain ((*S*)-NPX, (*R*)-FBP) and by dimeric ((*RS*)-FBP, (*RS*)-KTP) arrangement of hydrogen bonds in the crystal lattice. Spectroscopic results showed that the interchain (*through-space*) exciton coupling, between two laterally-spaced hydrogen bonds, dominates in the crystals of four NSAIDs. The same exciton coupled hydrogen bonds were also responsible for the H/D isotopic recognition mechanism in the crystalline spectra of deuterated 2APAs. The presented spectral results may help to predict the hydrogen bond motifs in the crystalline NSAIDs, which structures are not yet known, based on their IR spectra of hydrogen bond in the crystals.

1. Introduction

Profens (2-Arylpropionic acids; 2APAs) belong to the most crowded family of nonsteroidal anti-inflammatory drugs (NSAIDs) due to their demonstrated efficacy in reducing pain and the inflammation associated with a variety of human disorders, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout, dysmenorrhea, dental pain and headache [1,2]. All NSAIDs act through inhibiting prostaglandin synthesis, a catalytic activity possessed by two distinct cyclooxygenase (COX) isozymes encoded by separate genes [3]. 2APAs are probably the most frequently cited drugs exhibiting the chiral inversion phenomenon, i.e., one enantiomer of drug is converted into its antipode either in the presence of a solvent or more often in inner environment of an organism [4–6]. Sajewicz et al. discovered a striking ability of NSAIDs from the group of 2-APAs, i.e., ibuprofen, naproxen, flurbiprofen and ketoprofen, to undergo, in vitro, a repeated structural conversion from one chiral configuration to the opposite one (labelled as 'oscillatory transenantiomerization') [7–11]. They formulated a hypothesis that all the 2-APAs can behave in a similar manner when dissolved in certain low-molecular-weight (aqueous or non-aqueous) solvents and assumed that structural differences among the various 2-APAs can result in differentiated dynamics of oscillatory transenantiomerization, which is omnipresent with this class of compounds [7–11].

Profens are commercially available drugs widely used in medicine as racemates as well as pure enantiomers. The inflammatory activity of certain examples from group of 2APAs, i.e., ketoprofen, flurbiprofen, ibuprofen, and naproxen, is mainly due to their (*S*)-enantiomer [12]. In many cases the (*R*)-enantiomers of these drugs exhibit lower pharmacological activity in COX inhibition [12]. Recent studies have shown that (*R*)-flurbiprofen (tarenflurbil, TFB) has antinociceptive and antitumorigenic properties both in vitro and in vivo in various animal models of colon and prostate cancer, as well as it demonstrates marked antiproliferative activity [12,13]. Additionally, TFB demonstrates encouraging results on cognitive and functional outcomes among patients with mild Alzheimer disease [14–16]. The application of (*R*)-ketoprofen in current medicine as an additive to toothpaste is used to prevent periodontal disease [12]. Besides the chiral inversion, many pharmaceuticals also exhibit polymorphic behaviour in which the substance has several crystalline forms, with different arrangements or conformations of the constituents in the crystal lattice, depending on processing conditions [17]. Different polymorphs of a drug can display different physicochemical properties like dissolution and solubility, chemical and physical stability, flowability and hygroscopicity. These forms also differ in various important drug outcomes like drug efficacy, bioavailability, and even toxicity [18].

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http://dx.doi.org/10.1016/j.saa.2017.07.005
1386-1425/

Infrared spectroscopy can be used to identify a pure crystal form and to quantify a mixture of two forms. Different polymorphs have different IR spectra including changes in their frequencies, relative intensities, band contours and the number of bands [19]. The polymorphic formation of a given substance lies in a compromise between inter- and intramolecular interactions which can be affected by crystallization conditions [20]. Thus, hydrogen bonding is considered to be the major factor contributing to increased propensity toward polymorphism in molecular solids. Infrared spectroscopy also provides valuable information about the enantiomeric purity of chiral drugs as a pure epimer can crystallize in one crystal structure frequently, while a racemic form in a different one. The differences in the IR spectra of the racemic and enantiomeric forms of chiral drugs can describe in relation to the structural features, including crystal symmetry, the geometric parameter distinctions and the intermolecular interactions [21]. Polarized IR spectra can yield deep insights into hydrogen bonding being the source of the information about the vibrational coupling mechanism of the proton stretching vibrations, ν_{O-H}, in the excited state. The nature of the temperature dependence of IR spectral properties of the ν_{O-H} bands is important in explaining many of the physical properties of the organic compound. From our spectroscopic studies it results that the character of the inter hydrogen bond vibrational exciton coupling mechanisms in crystals is sensitive to temperature [22a–g]. Moreover, the temperature dependence of the IR spectral properties is closely related with the electronic structure of hydrogen-bonded systems [22a–g]. Thus, the IR spectrum of organic compound originates from the competing of two exciton coupling mechanisms, the intrachain (*through-bond*) and the interchain (*through-space*), in a given temperature. The temperature-induced changes in the coupling mechanisms can be responsible for noticeable changes in the intensity distribution in the branch of the ν_{X-H} band characterizing the crystalline polarized IR spectra [22a–g].

Selective replacement of hydrogen atoms with deuterium has the unique benefit of retaining the pharmacologic profile of physiologically active compounds, in certain instances, improving the safety, efficacy, and/or tolerability of a therapeutic agent [23,24]. Using DECS (deuterium-enabled chiral switching, i.e. the substitution of the proton at the chiral center by a deuterium to facilitate chiral switching), DeWitt et al. have recently stabilized and begun to differentiate in vitro and in vivo properties of monodeuterated enantiomers of several thalidomide analogs, including reduced degradation, improved pharmacokinetics and separation of in vitro anti-inflammatory effects [25]. Lowenson et al. reported that the replacement of the hydrogen atom on the *alpha* carbon with a deuterium can markedly reduce the degree of spontaneous racemization in a model asparagine-containing peptide [26]. The H/D exchange technique also allows to understanding of the generation mechanism of the vibrational shift in the infrared spectroscopy. The new H/D isotopic recognition phenomenon, depending on a non-random distribution of protons and deuterons in the lattices of isotopically diluted crystals, deserves special attention [27]. The new kind of co-operative interactions involving hydrogen bonds (i.e., the dynamical cooperative interactions) is responsible for the anomalous arrangement of protons and deuterons between the hydrogen bonds [27].

Efforts to understand and interpret the characteristic spectroscopic features of hydrogen bonds in selected NSAIDs have been taken due to the importance of NSAIDs in pharmacology. The investigated compounds, (*S*)-naproxen, (*R*)-flurbiprofen, (*RS*)-flurbiprofen and (*RS*)-ketoprofen, are carboxylic acid derivatives so their IR spectra exhibit the well-developed ν_{O-H} band fine structure patterns being sensitive to small variations in the molecular geometry and in hydrogen bonding patterns. Thus, the IR spectra of four crystalline carboxylic acids were measured at two temperatures with the use of polarized light and in isotopic dilution what allowed to characterize the inter hydrogen bond interaction nature in selected NSAIDs.

2. Experimental

2.1. Materials and Methods

(*S*)-NPX ((*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid; 98%), (*R*)-FBP (tarenflurbil; (*R*)-(−)-2-(2-fluoro-4-biphenylyl)propionic acid; 97%), (*RS*)-KTP ((*RS*)-(±)-2-(3-benzoylphenyl) propionic acid; 98%) and deuterium oxide (99.9% D) were purchased from Sigma-Aldrich. The purchased samples of (*S*)-NPX, (*R*)-FBP and (*RS*)-KTP used as such to record IR spectra. The crystals of (*RS*)-FBP were obtained by re-crystallization of the commercial (*R*)-FBP from an ethanol-acetone (1:1 v/v) mixture and the crystal structure of (*RS*)-FBP was further confirmed by single-crystal X-ray diffraction.

To obtain the deuterated compounds, 2APAs were dissolved in deuterium oxide. The liquid was then removed by the evaporation at room temperature and at reduced pressure and KBr pellets of the solid were prepared. According to the spectroscopic data about 60%, 70%, and 30% of the solid (*S*)-NPX, (*R*)-FBP and (*RS*)-KTP were deuterated, respectively. When this procedure was applied to (*RS*)-FBP, a significantly lower degree of deuteration (20%) was obtained. Moreover, a rapid D/H exchange in partially deuterated (*RS*)-FBP was observed during the melt crystallization.

The solutions of (*S*)-NPX, (*R*)-FBP and (*RS*)-KTP in carbon tetrachloride were used to obtain the IR spectra of the isolated molecules under study.

The Nicolet Magna-IR 560 spectrometer was used to record the IR spectra of the samples with the KBr pellet technique (4000–400 cm^{-1}, 4 cm^{-1} resolution) and the polarized IR spectra (4000–1000 cm^{-1}, 4 cm^{-1} resolution) of selected drugs. The spectra were measured at room temperature (RT = 293 K) and at temperature of liquid nitrogen (LNT = 77 K), using a standard cryostat system.

The IR spectra of polycrystalline sample of partially deuterated (*RS*)-FBP were collected on IRT-5200 FT-IR Microscope (JASCO) and FT-IR-6700 spectrometer (JASCO) in the range of 4000–600 cm^{-1} (4 cm^{-1} resolution). In order to record the low-temperature IR spectra (77 K), a small amount of polycrystalline sample of partially deuterated (*RS*)-FBP was kept in a sample holder, which was placed onto a freezing stage (FDCS196, Linkam Scientific Instruments Ltd., Surrey, UK). A cryo-stage with sample was placed on a platform which has a manual X-Y stage below the microscope objective. A thermal cycle in two stages was used, i.e. cooling the sample to − 196 °C and then heating to 20 °C. Tests were run at constant rates of heating and cooling of 20 °C min^{-1}.

Monocrystalline films of (*S*)-NPX, (*R*)-FBP, (*RS*)-FBP and (*RS*)-KTP, used in IR spectroscopy measurements, were prepared by the melt crystallization between the two squeezed CaF_2 windows under a suitable temperature gradient. The selection and the orientation of investigated monocrystalline fragments from the crystalline mosaics were performed with the help of a polarization microscope (Nikon Eclipse E200). The oriented monocrystalline samples were separated for the experiment by placing them on a metal plate diaphragm with a 1.5 mm diameter hole. Measurements of the polarized IR spectra of the compounds were performed for two different orientations of the electric field vector "*E*" with respect to an individual crystal lattice, i.e., for parallel polarized light (P) and for perpendicular polarized light (S), and were repeated for ca. ten different single crystals of a given compound.

2.2. X-ray Crystallography

The crystal structure of (*S*)-NPX was determined at RT in 1984, 1985, 1987, 2015 and at 102 K in 2011 [28–32]. To correctly analyze the IR spectra of (*S*)-NPX with the temperature variation, the crystal structure was re-determined at 100 K [28]. (*S*)-NPX crystallizes in the $P2_1$ space group with $a = 7.7162(15)$ Å, $b = 5.7022(11)$ Å, $c = 13.371(3)$ Å, $\beta = 93.73(3)°$, $Z = 2$ [33]. An asymmetric unit of (*S*)-NPX contains one molecule. (*S*)-NPX molecules are linked together by O—H···O hydrogen