Terahertz identification and quantification of penicillamine enantiomers postprint

Authors: Ji Te, ZHAO Hongwei, HAN Pengyu, CHEN Min, XIAO Tiqiao

Date: 2023-06-18T00:00:00+00:00

Abstract

Identification and characterization of L-, D-, and DL-penicillamine were demonstrated using Terahertz time-domain spectroscopy (THz-TDS). To understand the physical origins of the low-frequency resonant modes, density functional theory (DFT) was employed for theoretical calculations. The study revealed that collective THz frequency vibrations are determined by intramolecular and intermolecular hydrogen-bonding interactions. Furthermore, quantification of penicillamine enantiomer mixtures was achieved through a THz spectral fitting method with a relative error of less than 3.5%. This technique can serve as a valuable tool for discrimination and quantification of chiral drugs in the pharmaceutical industry.

Full Text

Preamble

Terahertz identification and quantification of penicillamine enantiomers

JI Te[1], ZHAO Hongwei[1], HAN Pengyu[2], CHEN Min[1],*, XIAO Tiqiao[1]

[1]Shanghai Institute of Applied Physics, Chinese Academy of Sciences, Jiading Campus, Shanghai 201800, China
[2]Center for Terahertz Research, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, USA

Abstract

Identification and characterization of L-, D- and DL-penicillamine were demonstrated by Terahertz time-domain spectroscopy (THz-TDS). To understand the physical origins of the low frequency resonant modes, density functional theory (DFT) was adopted for theoretical calculation. It was found that the collective THz frequency motions were determined by intramolecular and intermolecular

hydrogen bond interactions. Moreover, quantification of penicillamine enantiomers mixture was demonstrated by a THz spectra fitting method with a relative error of less than 3.5%. This technique can be a valuable tool for the discrimination and quantification of chiral drugs in pharmaceutical industry.

Key words: Terahertz spectroscopy, Vibration modes, Quantitative analysis

Introduction

Terahertz (THz) time-domain spectroscopy (TDS) is an extremely promising technique for chemical and biomedical applications since rotational and vibrational transitions of molecules and low frequency vibrations of crystal lattices lie within the far- and mid-infrared spectral range [1]. At present, a wide range of applications of THz-TDS technology have been reported [2-7]. Numerous structural biomolecules and chemicals have been investigated, and results indicate that absorption characteristics in the THz range are directly related to the composition and structure of molecules. This highly-sensitive THz spectroscopy provides a particular fingerprint method to discriminate molecules.

There is increasing interest in studying low frequency vibration modes in chiral drugs because these modes can be used to identify isomers. For some drugs, one kind of isomer is biologically active and effective for therapy, while another has no effect or even toxicity. Different chiral forms of a drug may have different biological properties and clinical effects [8]. Hydrogen bonding and van der Waals forces play important roles in the interaction between drugs and organism systems. The corresponding vibrational modes of these weak interaction forces usually lie in the THz range, which provides the theoretical basis for using THz technology to achieve molecular discrimination and study their interactions.

Penicillamine is a thiol drug used in the treatment of rheumatoid arthritis. Only pure D-penicillamine is used clinically since the L-form and DL-racemate are much more toxic, as shown by severe adverse reactions such as neuritis in patients treated with DL-penicillamine [9]. A high degree of purification of D-penicillamine is essential for drug products. The X-ray crystal structure and IR spectra of a racemic mixture of D- and L-penicillamine have been studied; however, there is a lack of study on their vibrational modes [10].

In this paper, the low frequency absorption spectra of L-, D- and DL-penicillamine were measured and characterized by THz-TDS. DFT theoretical calculations were carried out at the B3LYP/6-311G** level using Gaussian 03 packages and GaussView visualization program [11]. Excellent agreement with experiments was achieved in the values of calculated vibrational mode frequencies. In addition, quantification of penicillamine enantiomers in mixtures was determined by fitting the obtained THz absorption spectra.

Supported by National Natural Science Foundation of China (No.60907044), the Major State Basic Research Development Program in China (No.2010CB834301), Chinese Academy of Sciences Key Project of International Co-operation

(No.GJHZ09058) and Science Foundation of the Chinese Academy of Sciences

Corresponding author. E-mail address: chenmin@sinap.ac.cn

Received date: 2012-12-05

2.1 Setup

The setup for the THz-TDS system is the same as the one described in detail in Ref. [12]. The whole system is placed in a closed box purged with dry nitrogen gas to minimize absorption by water vapor. The setup allows spectroscopic data to be recorded in the frequency range from 200 GHz to 2.2 THz with a dynamic range of about 1000 and a spectral resolution better than 40 GHz. The measurements are considered accurate between 0.2 and 1.9 THz because of excessive attenuation caused by the samples at higher frequencies.

2.2 Data Analysis

The method detailed in the paper by Duvillaret et al. [13] is used to extract the complex refractive index from the THz-TDS data. In short, the extraction of parameters is performed in two steps. Firstly, a reference spectrum is obtained in the absence of the sample, and then a spectrum in the presence of the sample is measured. The ratio of the sample data to the reference data gives the complex transmission coefficient, which is a function of frequency. As noted in Ref. [13], the error function is gradually minimized using a standard algorithm, which yields the desired values for the complex refractive index.

2.3 Sample Preparation

All samples were crystalline powder with purity higher than 98%, purchased from Sigma-Aldrich. [Figure 1: see original paper] shows the molecular structures of L-, D- and DL-penicillamine. All samples were carefully mixed with polyethylene (PE) powder with a weight ratio of 1:1 and a total weight of 200 mg, and then pressed into 1.554–1.642 mm thick pellets. PE was chosen because of its low absorption coefficient (<5 cm^{-1} below 4 THz).

2.4 Computational Methods

Theoretical calculations were performed using density functional theory (DFT). The DFT method is widely used in molecular spectra calculations. Its computational requirements are considerably smaller than HF (Hartree-Fock) and MP2 (Møller-Plesset) methods under the same conditions, and its demands are relatively low for computer system performance. Moreover, the DFT method can obtain more accurate calculation results relative to the HF method because it considers electron correlation energy [14].

Geometry optimization and frequency analysis of the title compounds were performed using DFT B3LYP with the 6-311++G** basis set [15,16]. Chiral peni-

cillamine and racemate exist with a zwitterion structure in the solid state. The two C–O bond lengths in the carboxylate group are equal and three hydrogen atoms are attached to a nitrogen atom [10]. The X-ray structure of racemate DL-penicillamine provides useful information about the interaction between the enantiomers. The isolated molecule and dimer models of L- and D-penicillamine were also investigated.

3 Results and Discussion

The absorption spectra of L-, D- and DL-penicillamine measured at room temperature are shown in [Figure 2: see original paper]. The experimental results show significant differences in the absorption spectra between enantiomers (L- and D-penicillamine) and racemate (DL-penicillamine). The absorption spectra of L- and D-penicillamine also show some differences in the THz range. L-penicillamine has two absorption peaks located at 1.52 and 1.88 THz, while the peaks lie at 1.58 and 1.87 THz for D-penicillamine. This is in good agreement with the Raman spectrum of D-penicillamine measured by Howard-Lock H E, et al. [10]. In addition, two weak absorption peaks appear at 1.00 and 1.32 THz for D-penicillamine. The crystal structures of enantiomers (L- and D-penicillamine) are orthorhombic with the space group P2$*{2}*2{1}, *and* *DL* − *penicillamine* *is* *monoclinic* *with* *the* *space* *group* *P*2_{1}$/c [10]. This indicates that THz-TDS is sensitive to changes in crystal structure and can be used for identification applications.

The vibrational frequencies were calculated by quantum chemical theory using the packages of Gaussian 03. The molecular structures of L-, D- and DL-penicillamine were obtained through geometrical optimization. No negative frequency mode was found in the calculation results. shows the experimental modes and the calculated mode values at the B3LYP/6-311++G** level for L-, D-, and DL-penicillamine in the 0.2–2.0 THz range. Fewer frequency modes were obtained from single molecule and racemic models compared with dimer models. It suggests that molecular interactions need to be considered when calculating low frequency vibrations.

According to calculations using the GaussView visualization program, approximate structural and low frequency vibrational modes were identified. Two hydrogen atoms of the protonated amine take part in the formation of intra- and intermolecular hydrogen bonds. Two strong intermolecular hydrogen bonds N-H $\cdots$ O=C (0.152 nm) with N $\cdots$ O distance equal to 0.259 nm exist in a pair of racemate DL-penicillamine molecules. These interactions play an important role in maintaining the molecular structure in the solid state. The corresponding modes of racemate DL-penicillamine are shown in [Figure 3: see original paper]. The DFT calculation predicts four bands at 0.63, 1.29, 1.41 and 1.67 THz for DL-penicillamine. The vibrational mode at 0.63 THz is assigned as a butterfly mode with face-to-face orientation of D- and L-molecules of penicillamine. The modes at 1.29, 1.41 and 1.67 THz are regarded as torsions which cause weak deformation vibrations of whole molecules. Therefore, the intra- and intermolec-

ular hydrogen bonds are involved in the molecular motion. The low frequency theoretical calculation modes obtained from the dimer model indicate that the vibration modes are not localized atomic motions but whole molecular motions.

When the dimer model is adopted to simulate the low frequency motion of L-, D- and DL- molecules, there are some differences in vibrational frequency between racemate and its enantiomers, which is caused by the different crystal structures of racemate (monoclinic $P2_1/c$) and the enantiomer (orthorhombic P2\$*{2}*2{1}\$). In addition, the vibrational frequencies of the enantiomers in L- and D- molecules are somewhat different. This can be understood from the following discussion. On one hand, the enantiomers have the same crystal configuration but would form different hydrogen bonds or relative motions with adjacent molecules in their respective configurations. It suggests that the frequency difference of penicillamine enantiomers obtained by experiment originates from their different configurations. On the other hand, the theoretical model does not simulate the actual experimental condition perfectly and gives almost the same vibrational frequencies for L- and D-penicillamine. For example, multiple molecular interactions are not considered. This causes some discrepancy between the theoretical prediction and experimental results, such as in the value of peak frequency.

To demonstrate the capability of quantification using THz-TDS, we measured the absorption spectra of solid powder mixtures of L- and D-penicillamine with different weight ratios. The weight content of L-penicillamine in the mixtures was 40%, 60% and 80%, respectively. [Figure 4: see original paper] shows the absorption spectra of L-, D-penicillamine and their mixture (60% L- and 40% D-). According to the Lambert-Beer law, if the absorption spectra of pure samples and their mixture are measured, the relative percentage of pure samples in the mixture can be obtained using the least square fit method. In this work, the absorption spectra of the penicillamine enantiomers and their mixture were fitted in the range from 1.2 to 1.7 THz, and the relative content of penicillamine enantiomers was obtained. A series of mixtures of penicillamine enantiomers with different weight ratios were measured and analyzed. The calculated weight percentage concentrations of L-penicillamine in the mixture are 40.9%, 62.1% and 81.5%, which are quite close to the actual concentrations of 40%, 60% and 80%. The analytic errors are 2.5%, 3.5% and 1.9%, respectively. The concentration of penicillamine enantiomers in their mixture can be quantitatively determined using the THz spectra fitting method. This provides a valuable tool for quantitative analysis of medicine and potential applications in pharmaceutical industry.

4 Conclusion

We have characterized the far infrared absorption properties of L-, D- and DL-penicillamine by THz-TDS in the region of 0.2–1.9 THz. The chiral molecules show distinct THz fingerprints due to their different crystal structures and molecular conformations. DFT theory with the 6-311++G** basis set has been em-

ployed to calculate low frequency resonance. More accurate information has been obtained from the dimer model than from the isolated molecule model, which suggests that weak molecular interaction needs to be taken into account when calculating low frequency vibration. The calculation results indicate that the characteristic vibrational frequencies come from various collective motions and intermolecular hydrogen bond interactions are involved. The quantification of penicillamine enantiomers mixture has been achieved by the THz spectra fitting method with a relative error less than 3.5%. The study shows that THz-TDS is a capable tool for qualitative and quantitative detection of chiral drugs.

References

[1] Ferguson B, Zhang X C. Nat Mater, 2002, 1: 26−33.

[2] Melinger J S, Laman N, Grischkowsky D. Appl Phys Lett, 2008, 93: 011102.

[3] Jameson A D, Kevek J W, Tomaino J L, et al. Appl Phys Lett, 2011, 98: 221111.

[4] Walker G C, Bowen J W, Naftaly M, et al. Meas Sci Technol, 2011, 22: 037003.

[5] Reid C B, Pickwell-Macpherson E, Laufer J G, et al. Phys Med Biol, 2010, 55: 4825−4838.

[6] Kawase K, Shibuya T, Hayashi S, et al. C R Physique, 2010, 11: 510−518.

[7] Wang Weining, Wang Guo, Zhang Yan. Chin Phys B, 2011, 20: 123301.

[8] Kean W F, Lock C J L, Howard-Lock H E. Lancet, 1991, 338: 1565−1568.

[9] Gotti R, Pomponio R, Andrisano V, et al. J Chromatogr A, 1999, 844: 361−369.

[10] Howard-Lock H E, Lock C J L, Smalley P S. J Cryst Spectr Res, 1983, 13: 333−353.

[11] Frisch M J, Trucks G W, Schlegel H B, et al. GAUSSIAN03, Revision C. 02, Gaussian Inc., Pittsburgh, Pa., 2003.

[12] Han J G, Xu H, Zhu Z Y, et al. Chem Phys Lett, 2004, 392: 348−351.

[13] Duvillaret L, Garet F, Coutaz J L. IEEE J Sel Top. Quantum Electron, 1996, 2: 739−746.

[14] Lee C, Yang W, Parr R G. Phys Rev B, 1988, 37: 785−789.

[15] Dewar M J S, Zoebisch E G, Healy E F, et al. J Am Chem Soc, 1985, 107: 3902−3909.

Note: Figure translations are in progress. See original paper for figures.