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Vibrational frequencies of anti-diabetic drug studied by terahertz time-domain spectroscopy

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By using terahertz time-domain spectroscopy, the absorption spectra of seven anti-diabetic pills have been investigated. For gliquidone, glipizide, gliclazide, and glimepiride, an obvious resonance peak is found at 1.37 THz. Furthermore, to overcome the limit of density functional theory that can analyze the normal mode frequencies of the ground state of organic material, we also present a method that relies on pharmacophore recognition, from which we can obtain the resonance peak at 1.37 THz can be attributed to the vibration of sulfonylurea group. The results indicate that the veracity of density functional theory can be increased by combining pharmacophore recognition. © *2012 American Institute of Physics*. [http://dx.doi.org/10.1063/1.3700808]

With the aid of ultrafast laser pulses, terahertz (THz) technology has been developed with great progress, particularly in generating and detecting THz radiation and, therefore, many applications become realizable such as molecular recognition and material characterization.[1,2] THz radiations provide a non-invasive method with much less Rayleigh scattering (due to their long wavelengths) comparing with optical waves. Furthermore, THz wave also can transmit through nonmetals such as plastics, paper-products, and various powders but is strongly absorbed by polar liquids such as water. These characteristics make THz wave have great potential and practical applications of biology, medicine detection, food packaging inspection, quality control, and chemical composition analysis.[3,4] Many large proteins and deoxyribonucleic acid (DNA) molecules have collective vibrational and rotational modes in the THz range, which may provide characteristic fingerprints to identify the type of bio-molecules in biological tissues with the help of density functional theory (DFT).[5] However, a deviation between the calculated and measured collective vibrational and rotational spectra is always the case because the hydrogen bonding is ignored in the theoretical calculation process by using DFT. Although some researchers have owed this deviation to inter- and intra-molecular motions, this error is still far from being solved.[6]

In this article, we present the THz absorption spectra of five insulin secretagogues, alpha-glucosidase inhibitor, and insulin sensitizer from Fourier transformation of time domain THz traces interacting with these drugs. Various absorption peaks for each drug at different frequencies are observed clearly, i.e., all the sulfonylureas have a strong absorption peak located at ~1.37 THz. Furthermore, the vibration frequency of the seven oral anti-diabetic drugs has been studied by DFT at B3LYP/6-31 + G(d, p) level, which is a hybrid function including the exchange energy from Becke's exchange function, combining with the exact energy from Hartree-Fock theory. The deviation between the calculated vibrational frequencies with B3LYP/6-31 + G(d, p) and the experimental data is larger than 0.3 THz, which suggests the limit of DFT in describing intermolecular interactions. In particular, a method is proposed to make up the shortcoming of DFT by combining THz spectra and pharmacophore analysis. Then, the common sulfonylurea group found by HipHop algorithm is calculated and the result agrees well with the experimental value, which shows THz technique is highly sensitive to the molecular structures including the subtle difference of functional groups and chemical bonds, and THz time-domain spectroscopy (THz-TDS) is also a powerful tool for molecular structure and pharmacophore study.

The experimental setup used in this work is THz-TDS. A mode-locked Ti: sapphire laser with the central wavelength at 800 nm, the full width at half maximum (FWHM) of spectral bandwidth at ~20 meV, pulse duration around 80 fs, repeat frequency at 76 MHz, and output power around 1.3 W, was applied. The laser was split to pump beam and probe beam by beam splitter. Pump beam modulated by optical chopper was focused on Gallium Arsenide (GaAs) crystal. The photoexcited electrons were accelerated by the applied electrical field and THz wave emitted out from GaAs crystal.[7,8] THz was focused on sample by off-axis parabolic mirrors. After passing the sample, the THz wave with the information of samples was focused on Zinc Telluride electro-optic crystal, together with probe beam. The free space electro-optics (EO) sampling technique was used to record temporal waveforms of THz electric fields transmitted from the samples.[9,10] The EO sensor used in this experiment was a 700 μm-thick $\langle 110 \rangle$-oriented ZnTe crystal. The high cutoff frequency (~3 THz) was determined by the thickness of the EO crystal and the pulse duration of the femtosecond laser.[11]

The THz spectroscopy system was enclosed in dry-nitrogen-purged boxes to diminish the absorption of far infra-red

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(FIR) wave due to the vibration water vapor molecule. The humidity of covered box was kept less than 8% and temperature was about 295 K.

In order to accurately control the thickness of sample, as well as the absorption coefficient, anti-diabetic drug powders provided by Shanghai YangPu Geriatric Hospital were placed between two 2 mm-thick polyethylene slabs, and the thickness of powders was 0.6 mm. $E_{ref}(t)$ and $E_{sam}(t)$ represent the THz signals from sample box without and with anti-diabetic drugs, respectively.

Figures 1(a) and 1(b) show, respectively, the THz time-domain waveforms, $E_{sam}(t)$, of gliquidone, glipizide, gliclazide, glimepiride, acarbose, repaglinide, and metformin, together with their spectra, $E_{sam}(\omega)$, from the Fourier transformation of $E_{sam}(t)$. The observed reference signal and transmitted THz signals from samples were around 2 ps as a single cycle electric field. Furthermore, as a result of the difference of refractive index between the samples and air, the time delay between the samples and the reference signal was about 1.1 ps as shown in Fig. 1(a).

For the THz-TDS system mentioned above, the effective bandwidth for the measured signals is from 0.3 to 2.8 THz and signal noise ratio (S/N) is larger than 1000:1, as the reference signal shown in Fig. 1. Furthermore, the transmission spectra of seven kinds of medicinal powders, $E_{sam}(\omega)$, plotted in Fig. 1(b) show narrow bandwidth (0.3–2.0 THz), indicating that these anti-diabetic drugs with thickness about 0.6 mm are nearly opaque for THz wave when the frequency is above 2.0 THz.

The absorbance of the samples $\alpha(\omega)$ can be calculated by using the following equations:

$$\alpha(\omega) = -\ln[I_{sam}(\omega)/I_{ref}(\omega)]/d, \quad (1)$$

where $d = 0.6$ mm is the thickness of sample, $I_{sam}(\omega) = E_{sam}(\omega) \times E_{sam}(\omega)^*$ are the power spectra of samples, and $I_{ref}(\omega) = E_{ref}(\omega) \times E_{ref}(\omega)^*$ is the power spectrum of reference signal.

By using Eq. (1), the absorption spectra of all samples can be obtained and are shown in Fig. 2(a). The experimental results show two important messages for gli- series drugs. First, for gliquidone, glipizide, gliclazide, and glimepiride, they have the same strong absorption peak at ~1.37 THz. This is because the gli- series drugs belong to same class, sulfonylureas, which have the same resonance peak at 1.37 THz. However, this absorption peak does not appear in the others. Then, we can conclude that the sulfonylurea should have a strong resonant absorption peak at 1.37 THz. Second, the seven samples have the different resonant absorption peaks from 0.3 to 2.0 THz: Gliquidone has another two weak peaks at about 1.68 THz and 1.84 THz, while glimepiride has two weak similar absorption peaks that lie around 1.65 THz and 1.89 THz. Besides, glipizide has another two weak peaks at 1.86 THz and 1.99 THz and the weak peaks for gliclazide are located at 1.84 THz and 1.97 THz. The positions of these weak peaks are very close with a few nuances, which indicate that these gli- series drugs should have similar but slightly different functions for

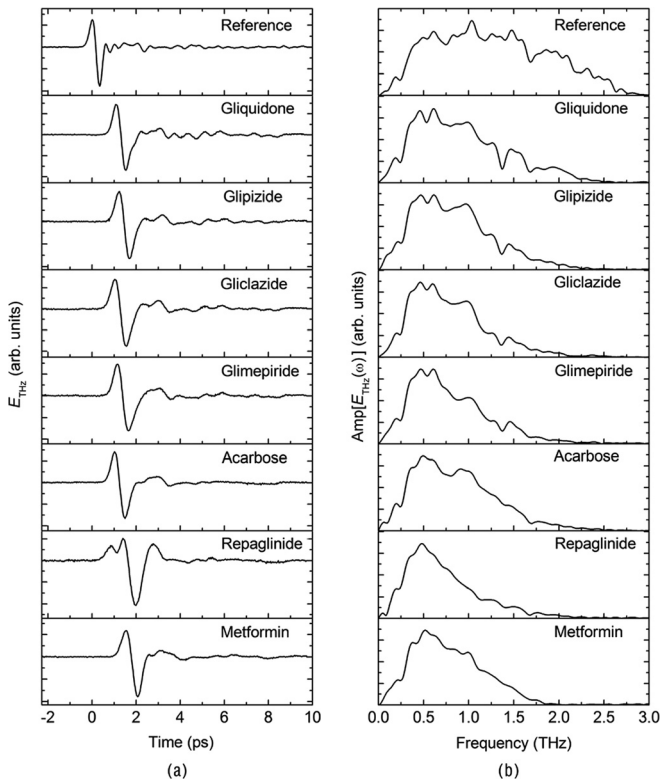

FIG. 1. (a) Time-domain THz waveforms of reference and seven kinds of anti-diabetic drugs. (b) THz spectra of reference and seven kinds of anti-diabetic drugs obtained from the Fourier transformation of $E_{sam}(t)$.

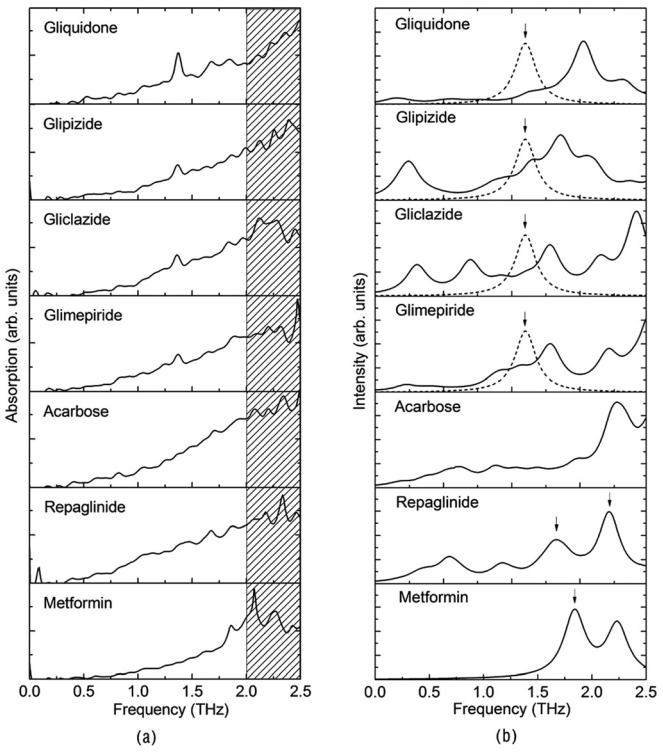

FIG. 2. (a) THz absorption spectra of gliquidone, glipizide, gliclazide, glimepiride, acarbose, repaglinide, and metformin. The hatched sector from 2 to 2.5 THz is the low signal noise ratio range due to the strong absorption of THz waves by the samples. (b) The predicted vibrational frequencies of sulfonylurea group (dashed line) and 7 samples (solid line) by DFT at B3LYP/6–31 + G(d, p) level.

treating diabetes mellitus (DM) in pharmacology. In addition, it is clearly observed that the repaglinide has noticeable absorption peaks at 1.68 THz and 1.87 THz, and a strong peak of metformin shows at 1.86 THz. The absorption spectra of acarbose are smooth, which indicate that it has no obvious absorption peaks in THz frequency range.

In order to analyze the resonant absorption peaks due to the vibration of chemical bonds and functional groups, we performed a vibrational analysis based on DFT, by using B3LYP theory with 6–31 + G(d, p) basis set. The popular B3LYP (Becke, three-parameter, Lee-Yang-Parr)[12] exchange-correlation function can be expressed as

$$E_{xc}^{B3LYP} = E_{xc}^{LDA} + a_0(E_x^{HF} - E_x^{LDA}) + a_x(E_x^{GGA} - E_x^{LDA}) + a_c(E_c^{GGA} - E_c^{LDA}), \quad (2)$$

where $a_0 = 0.20$, $a_x = 0.72$, and $a_c = 0.81$ are the three empirical parameters determined by fitting the predicted values to a set of atomization energies, ionization potentials, proton affinities, and total atomic energies;[13] E_x^{GGA} and E_c^{GGA} are generalized gradient approximations: the Becke 88 exchange function[14] and the correlation function calculated by Lee, Yang, and Parr,[15] and E_c^{LDA} is the correlation function obtained by using Vosko-Wilk-Nusair (VWN) local-density approximation.[16]

Figure 2(b) shows the theoretical calculated results of the seven anti-diabetic drugs, which are obtained at the basis set of 6–31 + G(d, p). The simulation results of metformin and repaglinide agree well with the experimental data at 1.68 THz and 1.84 THz, which is only a slight difference (~0.02 THz). For acarbose, simulation and experimental results are also consistent.

The theoretical results of gliclazide, glimepiride, glipizide, and gliquidone do not agree well with the corresponding experimental data, which comes from the limit of DFT in describing hydrogen bond interaction.[17] In the process of theoretical calculation, single molecule models were used so that intermolecular interactions are negligible and unconsidered, which makes it clear that the frequency shifts from calculated results are not attributed to intermolecular interactions but to intramolecular interactions. At the meantime, it is considered that the same group vibration mode causes the matching frequency at 1.37 THz in these sulfonylureas. Although the different temperatures impact on the match of the experimental results (T = 295 K) and the theoretical results (T = 0 K), these sulfonylurea medicines should coincide well with each other in Bose-Einstein condensate at 0 K and the calculated resonance frequency should have the same shift. In contrast, the theoretical results show different frequency shifts in the THz range, which proves that the error analysis of DFT does not come from the application of wrong temperature condition (T = 0 K) in simulation. To find out the molecular group, we established 3D pharmacophore model of sulfonylurea by using the HipHop algorithm which identifies configurations or three-dimensional spatial arrangements of chemical features that are common for molecules in a training set.[18] The configurations are identified by a pruned exhaustive search, starting with small sets of features and extending them until no larger common configuration is found. Training set members are evaluated on the basis of types of chemical features that they contain. Then they are along with the ability to adopt a conformation that allows those features to be superimposed on a particular configuration. Figure 3 shows the pharmacophore model abstracted from gliquidone, glipizide, gliclazide, and glimepiride. The four green conjoint balls represent hydrogen bond acceptors and the other two blue disjoint balls represent hydrophobic bonds. The latter component comes from different groups: alkyl group (glimepiride), phenyl group (gliquidone and glipizide), and cyclopentene group (gliclazide). These characteristic elements of the pharmacophore do not show obvious absorption peaks in the absorption spectra from 0.3 to 2.8 THz. The blue isolated ball just means a possible common pharmacophoric group which is calculated by HipHop algorithm from all four molecules; however, for the gliclazide case, it is not real existence. Therefore, the hydrogen bond acceptors of the pharmacophore are all from sulfonylurea group, which simultaneously indicates the pharmacodynamic effects of the vibration mode from sulfonylurea group.

Hence, the molecular structures of sulfonylurea are changed to dislodge hydrogen bonds and other unrelated groups as shown in Fig. 3, and only sulfonylurea group is retained to calculate vibrational frequencies with DFT at B3LYP/6–31 + G(d, p) level. Two hydrogen bonds in the sulfonylurea group are kept for the sake of the balance of covalent bond. Figure 3 shows the vibration mode from

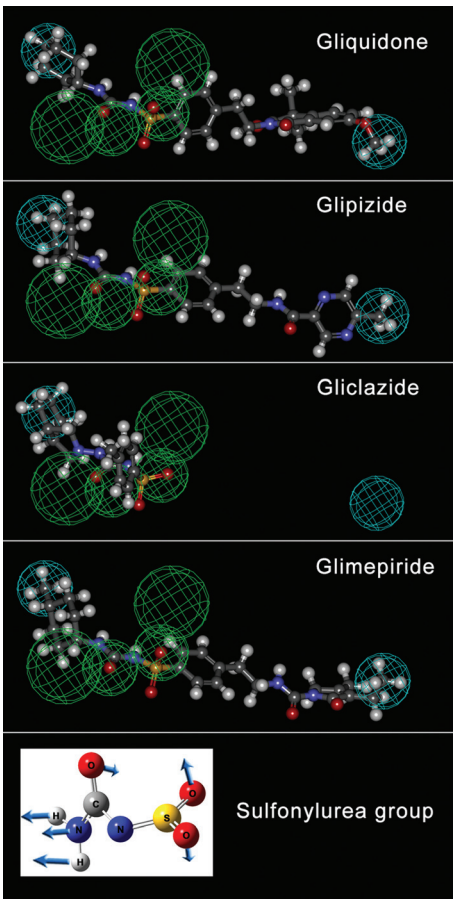

FIG. 3. The 3D pharmacophore model of four sulfonylureas and its matching with gliquidone, glipizide, gliclazide, and glimepiride. The last picture is the structure and the vibration mode of sulfonylurea group calculated by DFT.

sulfonylurea group. Its corresponding theoretical vibrational frequencies located at ~1.38 THz are shown in Fig. 2(b) as marked by black dashed line, which are scaled by 0.9642, a recommended scaling factor for this level of theory taken from the NIST Computational Comparison. The simulated result agrees well with the experimental data with ~0.01 THz deviation, which strongly proves that the absorption peak located at 1.37 THz in all the sulfonylureas comes from the vibration of sulfonylurea group.

We have demonstrated the use of terahertz time-domain spectroscopy for the measuring absorption spectra of gliquidone, glipizide, gliclazide, glimepiride, acarbose, repaglinide, and metformin. For gliquidone, glipizide, gliclazide, and glimepiride, an obvious resonance peak is found at 1.37 THz, which indicates that sulfonylurea should have a strong resonant absorption peak at 1.37 THz. However, this strong resonant absorption peak cannot be obtained by using DFT, which is always employed to examine normal mode frequencies of the ground state of organic material. With the help of the pharmacophore analysis, the shortcoming of DFT can be overcome, which is of extremely important improvement for using THz wave in biological samples inspection. The common sulfonylurea group is calculated and the result agrees well with the experimental result. In conclusion, THz absorption spectra of these drugs are highly sensitive to the molecular structures including the subtle difference of functional groups and chemical bonds, which indicates that THz technique may help for molecular recognition.

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