Terahertz Spectroscopy for Pharmaceutical and Biomedical Applications

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***Abstract*—Terahertz (THz) spectroscopy can detect molecular interactions in compounds formed by hydrogen bonds and hydration reactions. Although improvements are required in many respects, we are seeing encouraging progress in quantitative analyses based on THz spectra, and promising directions in the application of THz imaging to pharmaceuticals, the life sciences, and medical diagnostics.**

***Index Terms*—Cocrystal, crystal polymorphism, medical diagnostic, molecular interaction, THz spectroscopy.**

I. Introduction

TERAHERTZ (THz=10^{12} Hz) waves lie in the frequency range between radio waves and light, and convey molecular-level information about phenomena such as crystalline phonon modes, low-frequency molecular vibration modes, and gas rotation modes in the frequency range of 0.1–10 THz. Fig. 1(a) shows the absorption and vibration frequency characteristics of compounds in the microwave, THz, and infrared domains [1]. Middle-infrared/near-infrared spectroscopy and Raman spectroscopy capture higher vibrational modes attributable to the functional groups of molecules. On the other hand, THz spectroscopy can measure lower modes of molecular vibration that are associated with intermolecular bonds such as hydrogen bonds or Van Der Waals interactions. The advantage of THz spectroscopy is that it can obtain molecular network information based on hydrogen bonds between various sorts of biological molecules, including amino acids [2]–[7], sugars [8], [9], pharmaceuticals [10], [11], polypeptides [12], [13], DNAs [14], and proteins [14], [15]. As shown in Fig. 1(b), biological molecules tend to form clusters in water [16]. These clusters bond with other clusters in their vicinity to form large molecular networks. The nature of these molecular networks is related to protein conformations and drug efficacy, and is therefore of great importance in the life sciences and biotechnology fields. However, since the size of a cluster is on the order of nanometers and there are no techniques that can directly observe molecular interactions at this level, these interactions

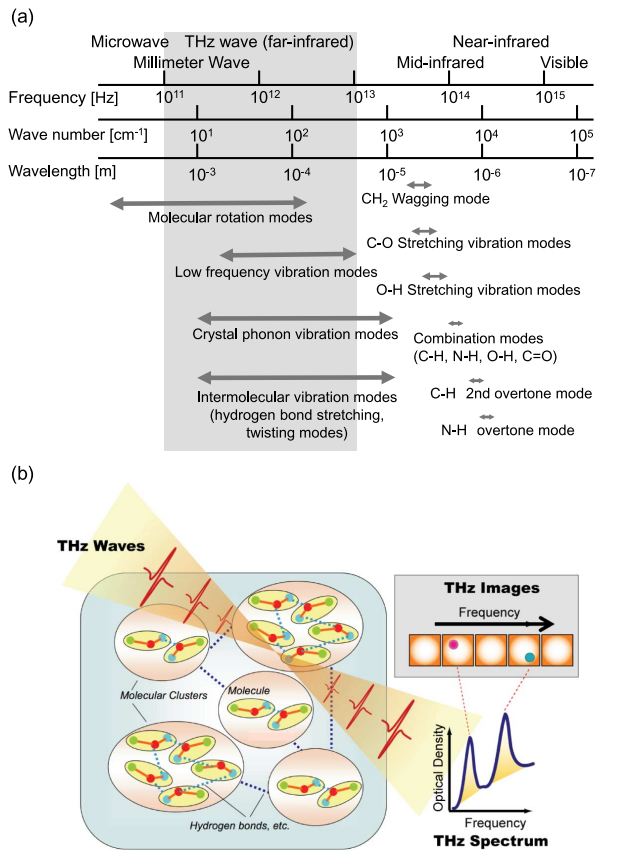

Fig. 1. Molecular information that can be obtained from THz waves. (a) Characteristic absorption frequencies of molecules and crystals in the microwave, THz-wave, and infrared domains [1] (2008 *The Japan Society of Analytical Chemistry*, with alterations). (b) Schematic illustration of the relationship between molecular networks, THz spectra, and THz images corresponding to each peak [16] (2011 IEEE TRANSACTIONS ON TERAHERTZ SCIENCE AND TECHNOLOGY, with alterations).

are not yet fully understood. Nevertheless, their resonant frequencies are known to lie in the THz frequency range, so THz spectroscopy and THz imaging techniques can play a key role in our understanding of these molecular networks.

Terahertz chemical imaging (TCI) is a technique that extends THz spectroscopy into two or three dimensions, enabling recognition of molecules based on the spectrum of their molecular networks. [1] TCI is expected to lead to new techniques for drug evaluation and medical diagnostics. THz waves can pass through pharmaceutical tablets, allowing the uniformity of their coatings and their crystal polymorphism to be examined from the resulting spectra. Crystal polymorphism refers to the crystal structures formed by different types of hydrogen bonds between crystalline molecules. In pharmaceutical crystalline molecules,

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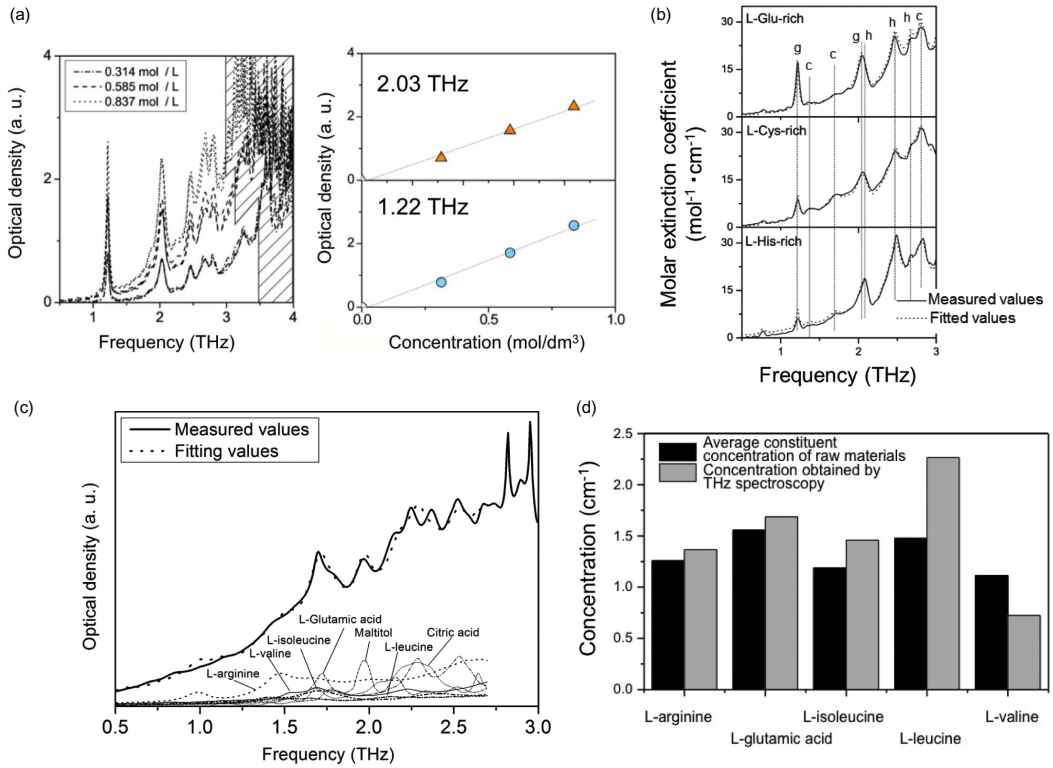

Fig. 2. Quantitative analysis of amino acids using THz spectroscopy (a) THz absorption spectra, each obtained from three measurements of L-Glu tablets with different concentrations, and calibration curves based on the peak intensities at 2.03 THz and 1.22 THz. The THz absorption spectra show the optical density on the vertical axis, and the hatched region on the right shows where the signal to noise ratio was insufficient for obtaining measurements. (b) THz absorption spectra of mixture samples of L-Glu, L-Cys and L-His with different mixing ratios. The real measurements (solid lines) are compared with fitting curves calculated from ε using coefficients k_g, k_c and k_h that best reproduce these measurements (dotted lines). The peaks for L-Glu, L-Cys and L-His are labeled g, c and h, respectively. [17] (2006 American Chemical Society, with alterations). (c) Comparison of the room-temperature THz spectrum in (a) (solid line) and the calculated spectrum obtained from a database (dashed line). The constituent spectra of the values used for fitting are shown at the bottom. (d) Comparison of constituents obtained from the list of ingredients (black) and the concentrations obtained from a database by quantitative analysis for each constituent (gray). [18] (2011 The Japan Society for Analytical Chemistry, with alterations).

these different structures can exhibit different chemical properties such as solubility, melting point, and bioavailability (the rate at which a drug is absorbed). This paper describes quantitative analysis based on THz spectra, and covers the direction of valuable THz application research fields including pharmaceuticals and medical diagnostics.

II. Quantitative Chemical Analysis of Intermolecular Hydrogen Bonds by THz Spectroscopy

Since THz frequencies resonate with low vibration modes, such as hydrogen bonds and weak intermolecular interactions, THz spectroscopy is a unique tool for examining molecules or crystalline structures that undergo these sorts of weak interactions. To work with various sample forms, THz spectroscopy supports a number of different measurement methods, including transmission, reflection, attenuated total reflection (ATR), and polarization measurements. Transmission measurements are the simplest and easiest to perform, but ATR is more effective when working with samples in water and other highly polar solvents that absorb strongly at THz frequencies. The ATR method involves bringing the sample material into close contact with a crystalline medium that has a high refractive index. THz waves are incident at an angle greater than the critical angle, resulting in total reflection at the interface between the sample and the crystalline medium. When this total reflection occurs, it is possible to measure the small amount of THz radiation that is reflected on the sample side. In areas of absorption on the sample, the energy of the reflected light diminishes according to the strength of the absorption, so a spectrum can be obtained by measuring this reflected light.

Amino acid crystals have a stable crystalline structure due to intermolecular hydrogen bonding between pairs of amino acid molecules and between amino acids and hydrated water molecules. We are using THz spectroscopy to perform measurements on amino acid crystals. As shown in Fig. 2(a), we have confirmed experimentally for the first time that THz spectral intensity is proportional to their concentration. Next, to perform quantitative analysis, we prepared a spectrum database by obtaining molar absorption coefficients over the frequency range from 0.5 to 3.0 THz for over 30 substances including major amino acids [17].

The molar extinction coefficient (α) is the absorbance (or optical density) measured when a 1-mol/L solution of a substance is placed in a 1-cm cell. As a specific example, we will discuss the quantitative analysis results of samples containing a mixture of three amino acids—L-glutamic acid (L-Glu), L-cysteine (L-Cys), and L-histidine (L-His). The α spectral data for L-Glu, L-Cys, and L-His at 0.5–3 THz are defined as G, C, and H, respectively. Here, the THz absorption spectrum S of a mixed

sample of L-Glu, L-Cys, and L-His can be expressed as follows in terms of the coefficients k_g, k_c, and k_h (corresponding to the concentration of each constituent)

$$S = k_g \bullet G + k_c \bullet C + k_h \bullet H \tag{1}$$

The best combinations of the coefficients k_g, k_c, and k_h that reproduce the experimental spectrum S from 0.5 to 3.0 THz are obtained by least-squares fitting calculations. The resulting coefficients are considered to represent the most likely concentrations of L-Glu, L-Cys, and L-His in the mixed sample. The mixed samples of L-Glu, L-Cys, and L-His were prepared by mixing microcrystalline powders of each amino acid with polyethylene at their respective prescribed concentrations, and pelletizing the resulting mixture. A THz spectrometer was then used to perform measurements under the same conditions as the α spectral data. The resulting measured spectra were adjusted to compensate for the absorption components of polyethylene and the pellet thickness, and the net quantity of amino acids in the sample were calculated. Fig. 2(b) compares S with the spectra reproduced according to the right-hand side of (1). In this figure, g, c, and h correspond to the L-Glu, L-Cys, and L-His peaks, respectively. The respective measured spectra of the mixed sample are well reproduced by fitting calculations. In addition, the ratio of the calculated concentration of each amino acid component to the concentration of mixed reagents in an actual sample was 0.98 for L-Glu, 0.89 for L-Cys, and 0.93 for L-His, indicating that the results were in agreement to within roughly 10%. These results show that molar absorption coefficients obtained from THz spectroscopy can be used for quantitative analysis.

Next, we introduce an example of the application of this technique to the analysis of a commercial dietary supplement containing amino acids [18]. A commercial supplement (supplement X) containing several amino acids was crushed and formed into a cylindrical tablet, and was then measured using THz spectroscopy. The database used for quantitative measurements includes standard spectra for the amino acids contained in X (L-arginine, L-glutamic acid, L-isoleucine, L-leucine, and L-valine) and for its primary constituents (maltitol and citric acid). After compensating for multiple reflection components in the spectrum of supplement X, we calculated the content of amino acid contained in it from the ratio of the spectral values to the database values, taking the tablet thickness and mass into consideration. The results were then compared with the quantities specified in the table of ingredients. The THz spectrum of supplement X obtained by THz-TDS was shown to have been satisfactorily reproduced by the calculated spectrum obtained by fitting from the database, as shown in Fig. 2(c). As shown in Fig. 2(d), by comparing the concentrations obtained from the table of constituents with concentrations obtained by calculation, we found that a quantitative precision of roughly 8%–20% is achieved for L-arginine, L-glutamine, and L-isoleucine, and that this precision is higher for constituents with more characteristic spectral profiles. In the future, we hope to achieve even higher quantitative precision by improving the database and using more effective fitting techniques.

III. Application to the Pharmaceutical Field

TCI is a technique that provides the two-dimensional or three-dimensional distribution of molecules based on the THz absorption spectrum of a sample. This technique is useful when analyzing the distribution and concentration of chemical substances in a sample. THz imaging makes it possible to distinguish substances by detecting absorption that occurs due to weak intermolecular and intramolecular vibration modes. Furthermore, since THz waves are able to pass through a variety of non-polar materials such as the plastics and paper that are often used as packaging materials, the TCI technique can be used for imaging and analysis of pharmaceuticals hidden behind materials that are transparent to THz waves [19]–[23].

Fig. 3(a) shows an example where a TCI analysis system is used to distinguish between crystal polymorphism and excipients (inactive constituents) in a pharmaceutical product [22]. Crystal polymorphism is the phenomenon whereby crystals formed by the same kinds of molecules can take different forms depending on how those molecules are joined together. This can result in large variations in the effectiveness of medicines due to differences in chemical properties such as solubility. To hold medical crystals together when preparing tablets, they are sometimes mixed with excipients (additives such as cellulose or sugar that have no pharmaceutical effect). However, since these excipients often have their own THz absorption spectra, identifying them is an important issue. Famotidine, a constituent of some stomach medicines, exhibits crystal polymorphism between a low-solubility type A and a high-solubility type B. It is said that only type B is medically effective. Since these two crystal polymorphs have completely different THz spectra, they can easily be distinguished from each other. However, it is often difficult to distinguish them from excipients. For these test tablets, the D-mannitol and famotidine-B peaks are so close to each other they are indistinguishable in room-temperature images. However, we found that if the temperature is reduced inside an environmental control chamber, it is possible to separate the three substances—famotidine-A, famotidine-B, and D-mannitol. This is probably because of differences in the structural changes (e.g., intermolecular distance) that occur in each type of crystal when the temperature changes. Thus, although the peaks in the THz spectrum are relatively broad, they can sometimes be separated and correctly assigned by varying the temperature.

Fig. 3(b) shows an example of the analysis of the distribution of cocrystals in a pharmaceutical product [23]. A cocrystal is a complex molecular crystal that consists of a pharmaceutical molecular crystal (a drug that forms the main constituent of a medicine) and one or more additive crystals (coformers). The merit of cocrystals is that they can exhibit functions and properties that are unobtainable with crystals of single compounds. In particular, improved solubility is very important in formulation development because it allows the limitations on the pharmaceutical molecule to be relaxed with regard to oral absorption or the choice of formulation. The TCI analysis method can distinguish very clearly between additives and cocrystals and their constituent drugs (active constituents), and can do so

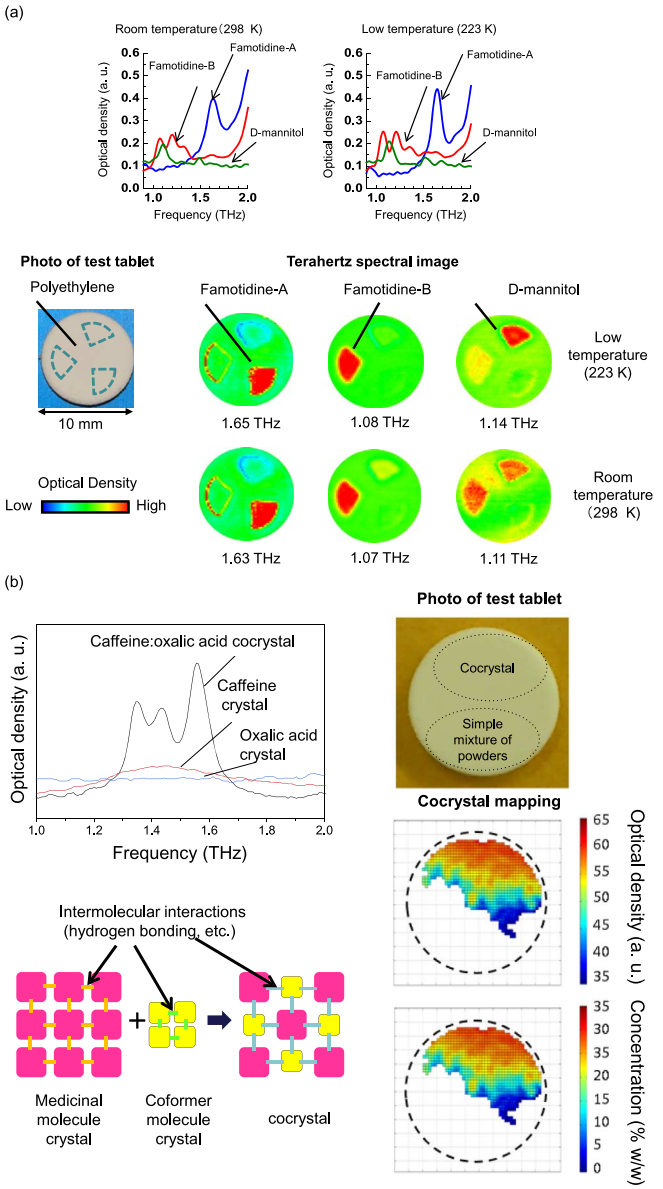

Fig. 3. Example of TCI applied to pharmaceutical analysis. (a) Distinguishing between pharmaceutical crystal polymorphs and excipients. THz spectra of famotidine-A, famotidine-B and the excipient D-mannitol at room temperature (298 K) and low temperature (223 K), and THz images corresponding to their corresponding peaks in a test tablet. [22] (2014 The Electrochemical Society, with alterations). (b) Example of cocrystal identification in a pharmaceutical product. THz spectra and THz images of cocrystals consisting of caffeine (crystallized drug molecule) and oxalic acid (coformer molecule). The top part of the tablet used for THz imaging consisted of the caffeine:oxalic acid cocrystal, and the bottom parts were obtained by simply mixing powders of caffeine and oxalic acid. [23] (2013 American Chemical Society, with alterations).

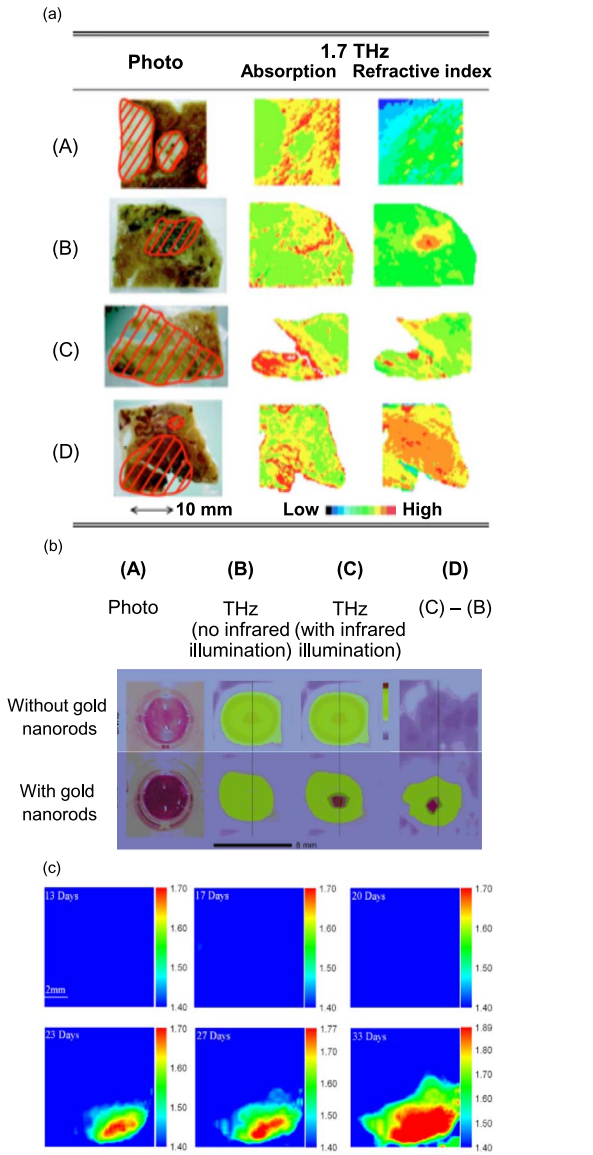

Fig. 4. Detection of cancer cells by TCI. (a) Four sample photos and THz images of cancer imaging. Areas with red hatching represent the extent of cancer cells in each sample [27]. (2009 AIP Publishing, with alterations). (b) THz images of cancer cells with and without gold nanorods [28]. (2009 The Optical Society, with alterations) (c) THz images from *in vivo* THz transmission imaging of early human breast cancer in a subcutaneous xenograft mouse model. THz images of the mouse are 10 mm × 10 mm in size and are taken from the 13th day to 33th day after cancer cell implantation. [30]. (2009 The Optical Society, with alterations).

even in pharmaceutical cocrystals where the structure is stabilized by intermolecular and intramolecular interactions such as hydrogen bonds. In this example, a cocrystal was synthesized from caffeine (crystallized drug molecule) and the readily soluble additive oxalic acid (conformer), after which a tablet model with a uniform distribution of constituents was prepared and the cocrystal distribution was analyzed by a TCI system. When mixed with powdered polyethylene and formed into a test tablet, a comparison of THz spectra showed hardly any absorption for crystals of the individual compounds of caffeine or oxalic acid. On the other hand, the caffeine:oxalic acid cocrystal showed a strong absorption peak, especially at low temperature. These results indicate that a cocrystal and its constituent medicinal ingredients and additives can be clearly distinguished. We also showed that TCI analysis using absorption peaks that are characteristic of a cocrystal makes it possible to observe a two-dimensional image depicting the cocrystal distribution in a tablet model with a uniform distribution of constituents. Since cocrystals have intermolecular hydrogen bonds, their THz spectra exhibit strong absorption peaks that are very useful for analysis.

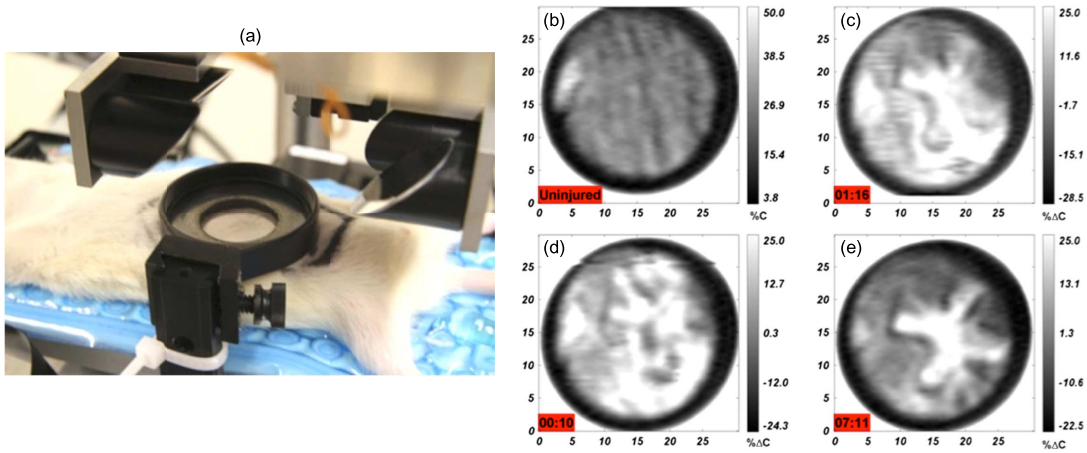

Fig. 5. Burn diagnosis technique using TCI (a) Photo of rat fixed to the THz spectrometer, and (b)–(e) a temporal series of THz images of the burn. The burn is seen through a round observation window. (b) Appearance before receiving the burn. (c) Immediately after receiving a cross-shaped burn. (d) After one hour. (e) After seven hours [31]. (2012 SPIE, with alterations).

IV. Application to Life Sciences and Medical Diagnostics

THz waves cause practically no damage to materials, and can therefore be used for non-invasive detection of biological materials. These features make TCI a particularly promising tool for the analysis of living material or medical samples, such as teeth, skin, and cancer tissue [26]. The application of THz technology to pathological diagnosis is of great importance. Although not yet at a practical stage, a variety of studies have been performed. Some examples are presented below.

Fig. 4 (a) shows a THz image of cancer tissue embedded in paraffin for the purpose of removing its internal moisture [27]. There is a correlation between the optical image and the THz absorption image at 1.7 THz, and this result is supported by principal component and clustering analyses. Fig. 4(b) shows how TCI technology can be combined with the infrared absorption of gold nanorods by surface plasmon resonance [28]. Gold nanorods are spherical gold nanoparticles that have been stretched into rods to give them a surface plasmon resonance peak that can be varied between visible and near-infrared (NIR) wavelengths (roughly 550–1,400 nm). With the addition of modifying groups on the surface, they are able to be taken up by cancer cells and can be used as contrast agents for THz imaging of cancer cells. Gold nanorods inside cancer cells cause a change in temperature during NIR irradiation, which increases THz absorption, as can be clearly seen in THz images. As another example of gold nanorods for THz cancer imaging, it has been reported that cancer cells can be distinguished from normal cells by using two types of THz image—one showing absorbance, and the other showing the refractive index [29]. This result shows that there is a large difference of nearly 0.5 THz between healthy and cancer cells, which is thought to be related to water content, although the detailed principles of discrimination are not yet known. In addition, the development of THz imaging techniques for the early detection of breast cancer began in mice inoculated with subcutaneous xenografts [30]. The mice were successfully monitored continuously for growth of human breast cancer based on the intrinsic contrast between the dense tumour and the surrounding adipose tissue, which has a higher water content Fig. 4(c).

In a new application, studies related to the diagnosis of burns have also been reported [31]. It is difficult to determine the depth of burn wounds, and in particular it is very challenging to make instantaneous judgments on the severity of burns when large numbers of people have been injured in a major disaster. Fig. 5(a) shows a photograph of a rat fixed in THz analysis equipment. The rat was subjected to a burn injury inside a circular observation window, and the changes in the state of the skin in the affected area over time were monitored by THz imaging. Fig. 5(b) shows the state prior to receiving the burn, Fig. 5(c) shows the state immediately after receiving a burn in the shape of a cross, Fig. 5(d) shows the state after one hour, and Fig. 5(e) shows the state after seven hours. It can be seen that the contrast of the cross shape becomes more apparent as time passes. This intensity is related to the state of water molecules, and is thought to be correlated to the depth of the burn. Although a few examples have been shown here, the key to using THz waves for medical diagnostic applications lies in clarifying the relationship between the molecular state of a disease or injury, such as hydrogen bonding and hydration, and its severity.

V. Summary

In this article we introduced the development of THz spectroscopy in the pharmaceutical, life science, and medical diagnostics fields. This is a new analytical chemistry technique whose strength lies in its ability to observe molecular networks or the distribution of intermolecular interactions in compounds (e.g. hydration reactions) or non-covalent bonding (e.g. hydrogen bonding). Although many aspects of the analysis of THz spectra and THz spectral images are not yet fully understood, research is ongoing and is spreading widely among researchers who previously had little or no experience with THz imaging.

To develop THz spectroscopy and imaging for practical applications, it will be necessary to understand intermolecular interactions and the basic properties of molecular networks, and to clarify their basic principles and theories. For this purpose, a greater understanding could be achieved by combining THz

spectroscopy with other widely used spectroscopy methods such as Fourier transform infrared, Raman, NMR (nuclear magnetic resonance), microwave, and dielectric spectroscopy, and further useful information could be obtained by comparing THz imaging with other imaging modalities such as MRI (magnetic resonance imaging).

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