Terahertz Spectroscopy and Molecular Dynamics Simulation of Five Citrates

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This research investigation employs a terahertz (THz) time-domain spectroscopy system to study the terahertz spectral characteristics of five different citrates in both solution and solid state. The citrates under examination are lithium citrate, monosodium citrate, disodium citrate, trisodium citrate, and potassium citrate. The results show that the THz absorption coefficients of the first four citrate solutions exhibit a decreasing trend with increasing concentration. However, the potassium citrate solution shows an opposite phenomenon. At the same time, the absorption coefficients of lithium citrate, trisodium citrate, and potassium citrate solutions are compared at the same concentration. The results indicate that the absorption coefficient of citrate solution increases in proportion to the increase of metal cation radius, which is explained from the perspective of the influence of metal cations on hydrogen bonds. In addition, we also study the absorption peaks of solid citrates, and characterize the formation mechanism of the absorption peaks by molecular dynamics simulations. This methodology can be further extended to the study of multitudinous salts, presenting theoretical foundations for the detection in food and medicine industries.

Keywords: Absorption coefficient, Citrate, Microfluidic chip, Molecular dynamics simulations, Terahertz

OCIS codes: (120.4630) Optical constants; (300.1030) Absorption; (300.6170) Spectra

I. INTRODUCTION

In recent decades, the advancement of THz sources and detectors has led to a rapid development of THz detection technology [1]. Currently, THz spectral technology outperforms infrared and Raman spectral technology in analyzing the distinctive vibration modes of biological macromolecules and numerous saccharides [2, 3]. In the realm of THz detection, the solution detection has been restricted by the strong absorption of THz waves by water [4]. Accordingly, effectively examining the internal molecular movement of solution samples using THz technology was a challenge, in contrast to the maturity of THz solid detection technology.

Therefore, we usually increase the THz intensity by improving the transmittance properties of the sample container [5–9]. Among various devices for detecting liquid samples, microfluidic chips can effectively reduce the absorption of THz waves by water, and have the advantages of simple manufacturing, low cost, and reusability, gradually being accepted and widely used by people.

This article uses microfluidic technology to study the THz spectral characteristics of five citrate salts which have...
extensive applications in the food and pharmaceutical industries. Among them, lithium citrate has the potential to function as both a food additive and an antidepressant [10]; Monosodium citrate can serve as an antioxidant and buffer; Disodium citrate can function as an oxidant and buffer; Trisodium citrate can be utilized as a food additive buffer and has anticoagulant and diuretic properties; Potassium citrate can act as a buffer and preservative [11].

This article adopts a simple manufacturing sandwich microfluidic chip, which effectively reduces the absorption of THz waves by water and improves detection sensitivity. The results indicated that the THz spectral intensity of the citrate solutions varies with the concentration and species of solute. In addition, we measured the absorption coefficients of five solid citrates, and conducted MD simulations to identify the reasons for some absorption peaks. Through this work, we can clearly foresee the application of THz spectroscopy in the detection and identification of citrates.

II. MATERIAL AND EXPERIMENTAL DEVICE

2.1. Material Preparation

Lithium citrate, monosodium citrate, trisodium citrate, and potassium citrate were procured from Macklin and disodium citrate was procured from Sigma-Aldrich, as shown in Table 1.

2.2. THz-TDS System

The THz-TDS system used in solution detection is shown in Fig. 1. In this system, the spectral effective frequency range is 0.10–2.00 THz, and the spectral resolution is about 30 GHz. The laser in this system has a central wavelength of 800 nm, a pulse width of 100 fs and a repetition frequency of 82 MHz. After the laser beam passes through a half-wave plate (HWP) and a polarization beam splitter, it is divided into two beams: A pump pulse and a detection pulse. Firstly, the pump pulse excites the InAs crystal and generates THz waves. After passing through the sample solution, THz waves will carry the sample information, then be reflected by indium tin oxide (ITO) mirror and incident into ZnTe crystals. The detection pulse passes through the delay device and ITO mirror, and finally converges on the ZnTe crystal. Then, the THz electric field changes the refractive index distribution of the ZnTe crystal and the polarization state of the detection pulse in the crystal. Subsequently, the quarter-wave plate (QWP) changes the linear polarization into circular polarization, and the photodetector outputs the difference in optical current intensity of two orthogonal linearly polarized lights generated by the Wollastom prism. Finally, the variation of the output signal with time delay is measured to obtain a THz time domain signal, and the frequency spectrum of the THz signal is obtained through a fast Fourier transform.

In order to avoid the influence of moisture in the air, we use another system that has a 0.10–2.60 THz spectral frequency range and can be filled with nitrogen to detect solids. The system uses a photoconductive antenna for THz generation and detection, and the humidity of the system during the detection process does not exceed 2%.

2.3. Microfluidic Chip

In this study, the substrate and cover of the THz microfluidic chip are made of Zeonor 1420R (Zeonor, CA, USA). Zeonor 1420R was selected for fabricating microfluidic chips due to the following reasons: Refractive index dispersion in the THz waves can be ignored, the absorption of the THz waves is weak, and raw materials are cheap and easy to obtain [12]. In the microfluidic chip, the substrate and cover plate are bonded with double-sided adhesive with a thickness of 50 μm, and the middle of the double-sided adhesive is hollowed out for storing the solution to be tested, as shown in Fig. 2.

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**TABLE 1. Information of five different citrate powder samples**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Formula</th>
<th>Molecular Weight (g/mol)</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium Citrate</td>
<td>C₆H₅Li₃O₇</td>
<td>281.98</td>
<td>&gt;99.5</td>
</tr>
<tr>
<td>Monosodium Citrate</td>
<td>C₆H₇NaO₇</td>
<td>214.11</td>
<td>99.0</td>
</tr>
<tr>
<td>Disodium Citrate</td>
<td>C₆H₆Na₂O₇</td>
<td>236.09</td>
<td>98.0</td>
</tr>
<tr>
<td>Trisodium Citrate</td>
<td>C₆H₅Na₃O₇</td>
<td>258.07</td>
<td>99.0</td>
</tr>
<tr>
<td>Potassium Citrate</td>
<td>C₆H₅K₃O₇</td>
<td>306.39</td>
<td>&gt;98.0</td>
</tr>
</tbody>
</table>

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**FIG. 1.** Schematic of THz-TDS system for solution sample detection.

**FIG. 2.** Schematic of microfluidic chip manufacturing process.
III. EXPERIMENTAL RESULTS

3.1. Data Processing Method

The absorption coefficients of citrate solutions and solid citrates were measured using empty chip and air as control groups, respectively. The absorption coefficient is influenced by various factors, including but not limited to the hydration state, temperature, and conformational alterations [13–15]. Therefore, we measured solid citrates in a constant temperature and nitrogen-filled environment to minimize the effects of temperature and humidity. The sample’s refractive index n and absorption coefficient can be obtained separately using Eqs. (1) and (2).

\[
n(\omega) = \frac{c}{\omega d} \left[ \phi_{\text{sam}}(\omega) - \phi_{\text{ref}}(\omega) \right] + 1,
\]

\[
\alpha(\omega) = \frac{2}{\omega d} \ln \left[ \frac{n(\omega) + 1}{4n(\omega)} \right] \rho(\omega),
\]

where \(c\) is light speed in vacuum, \(\omega\) is circular frequency of THz waves, \(d\) is the thickness of microfluidic chip sample cell or the thickness of solid sample tablet, \(\phi_{\text{sam}}(\omega) - \phi_{\text{ref}}(\omega)\) is the phase difference, \(\rho(\omega)\) is the ratio of sample signal to reference signal after Fourier transform.

3.2. Experiments of Citrate Solutions

We measured the THz spectra of five citrate salts at different concentrations, and due to the limitation of the solubility of sodium citrate, the concentration gradient was different from other citrates. The concentrations of 0.05, 0.10, and 0.15 g/mL have been set for monosodium citrate solution, while the remaining concentrations have been set to 0.10, 0.20, and 0.30 g/mL. The time domain resolution of the experimental system is 30 GHz, and the frequency domain resolution is 66 fs. The THz time-domain spectrum of each sample takes about three minutes to obtain, and each sample is measured three times. The absorption coefficients of lithium citrate solutions, monosodium citrate solutions, disodium citrate solutions, and trisodium citrate solutions exhibit a decreasing trend with increasing concentration, as shown in Figs. 3–6. Because the distinction between curves is best when the spectral amplitude is maximum [16], we illustrate the relationship between solution concentration, spectral amplitude, and absorption coefficient through Figs. 3(c)–6(c). The results show that except for disodium citrate, the other citrates have a good linear relationship, the frequency domain amplitude increases linearly with the

FIG. 3. The spectra of lithium citrate solution at different concentrations: (a) THz frequency domain spectra, (b) absorption coefficient spectra, (c) THz frequency domain amplitude and absorption coefficient versus the concentration at 0.37 THz, and (d) error analysis.
FIG. 4. The spectra of monosodium citrate solution at different concentrations: (a) THz frequency domain spectra, (b) absorption coefficient spectra, (c) THz frequency domain amplitude and absorption coefficient versus the concentration at 0.37 THz, and (d) error analysis.

FIG. 5. The spectra of disodium citrate solution at different concentrations: (a) THz frequency domain spectra, (b) absorption coefficient spectra, (c) THz frequency domain amplitude and absorption coefficient versus the concentration at 0.37 THz, and (d) error analysis.
FIG. 6. The spectra of trisodium citrate solution at different concentrations: (a) THz frequency domain spectra, (b) absorption coefficient spectra, (c) THz frequency domain amplitude and absorption coefficient versus the concentration at 0.37 THz, and (d) error analysis.

FIG. 7. The spectra of (a) THz frequency domain spectra, (b) absorption coefficient spectra, (c) THz frequency domain amplitude and absorption coefficient versus the concentration at 0.37 THz, and (d) error analysis.
concentration, and the absorption coefficient is opposite. Finally, to verify the accuracy of the results, we conducted an error analysis on each group of data and confirmed that the error was basically within 2%, indicating high reliability, as shown in Figs. 3(d)–6(d).

The absorption coefficients of potassium citrate solution exhibit an opposite trend to the four aforementioned solutions in THz spectra. Specifically, as the solution’s concentration increases, the solution’s absorption coefficients gradually increase as depicted in Figs. 7(a) and 7(b). Figure 7(c) demonstrates the linear relationship between the frequency domain amplitude and concentration, absorption coefficient and concentration at 0.37 THz. Figure 7(d) is the repeatability error analysis.

Figure 8 displays THz spectral characteristics of various citrate solutions with a concentration of 0.10 g/mL arranged in ascending order: lithium citrate solution, monosodium citrate solution, disodium citrate solution, trisodium citrate solution, and potassium citrate solution. By comparing the results of lithium citrate, trisodium citrate, and potassium citrate, we find that the absorption coefficient of the solution increases in proportion to the cation radius. Then the experimental results of sodium citrate, disodium citrate, and trisodium citrate solutions were compared. As a result, we found the concentration of sodium ions and the absorption coefficient gradually increased when the solute concentration in the solution was the same. These phenomena are consistent with the experimental results shown in Figs. 4–6.

### 3.3. Experiments and MD Simulations of Solid Citrates

During the experimental analysis of citrate solutions, THz spectral technology distinguished citrate solutions of different concentrations while obtaining the THz absorption peaks of each sample in the solution state was impossible. Therefore, we measured the THz spectra of solid citrates and verified the causes of absorption peaks by MD simulations, as depicted in Figs. 9–13. In Fig. 9, the THz experimental spectra of lithium citrate are highly consistent with the simulated spectra. The simulated absorption peaks observed at frequencies of 1.71, 2.01, and 2.52 THz correspond to the experimental absorption peaks observed at frequencies of 1.67, 2.02, and 2.51 THz, respectively.

FIG. 8. The spectra of different citrate solutions at 0.1 g/mL: (a) THz frequency domain spectra, (b) absorption coefficient spectra.

FIG. 9. THz spectra of lithium citrate: (a) Experiment, (b) simulation.
The absorption peaks simulated by monosodium citrate at 1.79, 2.00, and 2.42 THz are consistent with those at 1.81, 2.16, and 2.34 THz in the experiment, as shown in Fig. 10.

In Fig. 11, it is shown that the simulation results of disodium citrate at 1.67, 2.21, 2.31, and 2.54 THz are partially consistent with the experimental results at 1.84, 2.07, 2.19,
The simulated absorption peaks of trisodium citrate at 1.82, 2.19, and 2.40 THz are consistent with the experimental results at 1.81, 2.22, and 2.40 THz, as shown in Fig. 12.

Finally, the simulation results of potassium citrate at 1.27, 1.66, 1.89, 2.10, and 2.50 THz are similar to the experimental results at 1.28, 1.69, 1.90, 2.10, 2.40, and 2.51 THz, as shown in Fig. 13.

**IV. DISCUSSION**

The THz absorption is significantly affected by the hydrogen bonds present in water. Matsumura et al. [17] reveals that the absorption of THz waves by liquid water is significantly greater than that by solid ice. Water is composed of an enormous amount of hydrogen and oxygen atoms, directly proportional to the number of hydrogen bonds present. Because hydrogen bonds are a kind of weak interaction and water molecules make molecular thermal motions all the time, the relative positions of molecules are constantly changing. Therefore hydrogen bonds are always broken and produced, and their total number is in a dynamic balance. Water molecules and hydrogen bonds finally constitute the hydrogen bond network in water [18]. Hydrogen bond networks present in liquid water predominantly take the form of five-membered rings, six-membered rings, and pentagonal dodecahedron [19]. Conversely, solid ice primarily exists in the configuration of ice crystals [20]. There is a vast difference in the number of hydrogen bonds between them, which proves the importance of hydrogen bonds in detecting solution samples by THz spectra. Hydrogen bonds in a solution are susceptible to various factors, including temperature, external electromagnetic fields, and solute species [21–23]. Water molecules in an ionic solution are subject to Coulomb force, causing them to alter their behavior. This results in the formation of water shells around the ions. However, the physical properties of water within these shells differ from those of free water. This microscopic change ultimately impacts the macroscopic properties of the solution.

We present THz spectroscopy measurement conducted on citrate solutions of varying types and concentrations, and investigate the impacts of ions on the hydrogen bond and the resulting changes in THz spectral characteristics. The absorption coefficients of the solutions are related to the type and concentration of solute. We attribute this relationship to the change in the number of hydrogen bonds, which means that ions will change the arrangement of surrounding water molecules. Comparing the results in Figs. 3–8, it can be inferred that the addition of lithium ions and sodium ions will reduce the amount of hydrogen bonds in the solution, while potassium ions will promote the formation of hydrogen bonds, which will lead to the increase or decrease of the absorption coefficient of the solution. At the same time, the absorption spectra of lithium citrate solutions, trisodium citrate solutions and potassium citrate solutions with the same concentration further verifies our conclusion, as shown in Fig. 9. These phenomena are closely related to the microscopic effects of metal cations on water molecules. According to Anne’s work, the addition of ions has little effect on the water molecules outside the first solvation shell of an ion [24]. Barbara’s research on the first solvation shell shows that cations can indirectly affect hydrogen bonds between water molecules through electrostatic forces. Due to electrostatic force, the redistribution of water molecules in the first hydrated shell ultimately affects the number of hydrogen bonds between water molecules in the shell. As the radius of cations increases, the electrostatic force between ions and water decreases, leading to an increase in water-water hydrogen bonds, thereby changing the absorption coefficient of the solution. In conclusion, for larger cations, such as potassium ions, the electrostatic force they generate is helpful to the formation of hydrogen bonds in the first solvated shell. For smaller cations, such as lithium and sodium ions, the formation of hydrogen bonds will be inhibited, eventually leading to a decrease in the number of hydrogen bonds.
hydrogen bonds [25]. According to our experiment, in the process of metal cations attracting water molecules, sodium ions and lithium ions in the solution destroy the hydrogen bonds and improve the absorption coefficients of the solutions because of their small ion radius; In contrast potassium ions show the opposite phenomenon.

Since the absorption of water for THz waves is much greater than that of citrates, we cannot analyze the absorption characteristics and vibration modes of citrate itself through the absorption spectra of the solution. Therefore, we further analyzed solid citrates through THz spectroscopy and molecular dynamics simulations. Table 2 presents the absorption peaks of five citrates as observed in both experiments and MD simulations. The data indicate that each citrate exhibits unique absorption peaks. The experimental data partially match the simulation results, which can be the foundation for studying the fingerprint of citrates.

There are discrepancies between the experiments and MD simulations, for example, some absorption peaks observed in the experiment cannot be accurately predicted through MD simulations. These may be due to the gap between the theoretical cluster model and experimental molecular structure [26]. Moreover, the molecules of citrates are inorganic compounds, so the molecular interaction in the crystal will also affect the absorption peaks of THz experimental spectra. Secondly, a slight shift to higher frequency is observed in some of the simulated absorption peaks when compared to the absorption peaks of THz experiments. The observed phenomena can be ascribed to the MD simulation technique, which tends to overestimate the overall energy of the present system in a specific characteristic mode [27].

In short, most of the absorption peaks calculated from MD simulation can be mutually verified with experimental results. Moreover, MD simulations can explain the mechanism of some absorption peaks observed in experimental spectra. Therefore, we can better understand the absorption peaks of substances by studying the simulation results and analyzing the vibration modes.

### V. CONCLUSION

In this paper, the THz spectra of five citrates at different concentrations were measured. The results indicate that the absorption coefficients of the solutions exhibited a certain regularity with changes in solute concentration and solute type. At the same time, we find that the number of hydrogen bonds directly affects the THz absorption coefficient. Lithium ion and sodium ion inhibit the formation of hydrogen bonds in the first solvation water shell layer through electrostatic force, while potassium ion has a completely opposite promoting effect. In addition, the solid citrates were studied by THz spectroscopy and MD simulation technology. We emphatically analyzed the molecular vibra-
tation modes represented by different absorption peaks, and identified the factors contributing to the observed discrepancies between the experimental and simulated outcomes. In brief, this research examines the THz spectral properties of citrate solutions, and the influence of metal cation radius on it is analyzed. The findings have significant implications for elucidating the dynamics of water. Furthermore, the absorption spectra of solid citrates in the THz range can provide valuable insights for understanding the vibration characteristics of THz band.

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DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

REFERENCES


