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Tetrahedron: Asymmetry

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

# Enantiomer discrimination using terahertz spectroscopy via formation of a diastereomer salt

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## ARTICLE INFO

Article history: Received 29 January 2010 Accepted 19 February 2010 Available online 9 April 2010

## ABSTRACT

This paper presents a new recognition method using terahertz (THz) spectroscopy. By forming a guesthost diastereomer with an optically active compound (host) as a chiral recogniser, the chirality of the enantiomer (guest) can be clearly discriminated according to its absorption spectra. In this proof-of-concept study, we examined a pair of host–guest (h–g) complexes made of (R)- or (S)- $\alpha$ -methylbenzylamine (guest) and cholic acid (host).

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## 1. Introduction

Terahertz (THz) spectrometry is an excellent tool to investigate the properties of molecules. Because of the rapid development of THz-band light sources and detectors in the past two decades, their applications have been generating considerable interest. It has been shown that THz spectra can provide information about the structure of molecular crystals and the supramolecular behaviour of materials.<sup>1–3</sup> For example, there are obvious differences in the THz absorption spectra between individual molecular crystals and their co-crystals or complexes.<sup>4,5</sup> This phenomenon implies that the differences in supramolecular structure appear as changes in the THz absorption spectra.

A pair of enantiomers, in principle and actuality, shows identical transmission spectra,<sup>6</sup> it is impossible to determine the absolute configuration of a chiral molecule with only a measurement of the transmission spectra. However, if the enantiomer combines with a chiral compound to form a diastereomer, it should be possible to judge its configuration. Thus, in this study, we demonstrated the enantiomer discrimination of an amine using THz spectrometry. We synthesised a pair of supramolecular diastereomer salts using  $\alpha$ -methylbenzylamine enantiomers **1** ( $\alpha$ -MBA) as guests and the optically active cholic acid **2** (CA) as a host molecule through a published protocol.<sup>7</sup> We then measured the THz spectra of the crystalline salts and distinguished the chirality of the guests.



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## 2. Results and discussion

Figure 1 shows the terahertz transmission spectra of the  $\alpha$ -MBA–CA diastereomer salts. The (R)- $\alpha$ -MBA–CA salt has absorption peaks at 2.42 and 3.80 THz, while the (S)- $\alpha$ -MBA–CA salt has peaks at 2.35 and 3.16 THz. In addition, broad peaks were observed at 1.8 and 3.0 THz for the (R)- $\alpha$ -MBA–CA. As shown in the figure, these compounds are clearly distinct from each other. These peaks may account for intra- and intermolecular vibration modes and phonons. At present, reliably assigning each peak to a definite vibrational mode is a challenging task and is beyond the scope of this study.

Figure 2 displays the atomic configuration of the salts obtained by X-ray analysis. Both salts have the same space group,  $P_{2_1}$ , and similar lattice constants, which are summarised in Table 1. They are essentially identical to those previously reported by Sada et al.<sup>7</sup>





**Figure 1.** Terahertz transmission spectra of the diastereomer salts. The spectra were measured at  $24 \pm 1$  °C. A frequency range of 1.0–5.0 THz, where data with enough signal-to-noise ratios were achieved, were displayed.

We think that the differences between these spectra mainly result from the differences in molecular conformation. This conformational difference directly affects molecular skeletal vibrations and intramolecular local vibrations. A secondary factor responsible for these differences is the stacking manner of the molecules in the crystal, which changes the phonon frequency.

In this experiment, we formed a diastereomer salt, but we believe that this method is also applicable to supramolecular diastereomers composed of neutral molecules. The difference in the interaction between the target guest molecule and its environment allows slight changes caused by switching enantiomers to be detected with high sensitivity using THz spectrometry.

## 3. Conclusion

We have demonstrated a new technique to discriminate between two enantiomers with terahertz spectroscopy via formation of diastereomer complexes. The advantage of this technique is that the THz spectrum reflects the entire molecular environment, in contrast with chromatography and capillary electrophoresis methods, which only measure the thermodynamic parameters.



Figure 2. Crystal structures of the diastereomer salts viewed from the *b* axis. (a) (*R*)- $\alpha$ -MBA–CA. (b) (*S*)- $\alpha$ -MBA–CA.

 Table 1

 Crystal data for MBA-CA diastereomers

	(R)-a-MBA-CA	(S)-a-MBA-CA
Crystal colour, habit Crystal system	Colourless, needle Monoclinic	Colourless, platelet Monoclinic
Space group	P21	P21
Lattice parameters		
a (Å)	11.0289(9)	11.7780(3)
b (Å)	7.6653(6)	7.68927(16)
c (Å)	18.0608(15)	16.4165(4)
β (°)	97.876(4)	103.8203(11)
Ζ	2	2
V (Å <sup>3</sup> )	1512.4(2)	1443.70(6)

The data were collected at  $0 \pm 1$  °C. (*R*)- $\alpha$ -MBA–CA: Of the 13,153 collected reflections, 2963 were unique; 344 variables;  $R_1[I > 2\sigma(I)] = 0.0582$ . (*S*)- $\alpha$ -MBA–CA: of the 16,513 collected reflections, 5050 were unique; 346 variables;  $R_1[I > 2\sigma(I)] = 0.0410$ .

When binding energies and equilibrium constants are similar for two enantiomers, it is difficult to distinguish their chiralities with enough sensitivity and resolution using chromatography and capillary electrophoresis. In addition, fine crystalline powder may also be examined through this THz spectroscopy method, whereas a larger specimen would be required for X-ray single-crystal diffraction.

## 4. Methods

## 4.1. Material preparations

The (*R*)- $\alpha$ -methylbenzylamine (Fluka, Germany) and (*S*)- $\alpha$ methylbenzylamine (Aldrich, USA) were poured into a cholic acid (Wako, Japan) solution in tetrahydrofuran (Wako). The crystals were obtained and dried overnight at room temperature under ambient pressure. The diastereomer salts were mixed with the polyethylene powder, a diluent that is transparent in the THz range, at a concentration of 10 wt % and pressed into a 330 mg disk of diameter 20 mm and thickness of approximately 1 mm. As a reference, a pure polyethylene disk (300 mg) was also prepared and measured. The present transmission values were divided by the data obtained for the pure polyethylene disk to estimate the net transmissions. Colourless crystals of (R)- $\alpha$ -MBA-CA (0.27  $\times$  $0.04 \times 0.03~mm^3)$  and of (S)- $\alpha$ -MBA–CA (0.17  $\times$  0.11  $\times$  0.04  $mm^3)$ were examined by X-ray analysis using a Rigaku RAXIS RAPID imaging plate area detector with filtered Cu Ka radiation. The structure solution was made using the direct method. All calculations were performed using the CrystalStructure crystallographic software package,<sup>8</sup> except for the refinement, which was performed using SHELXL-97.<sup>9</sup> Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary

publication numbers CCDC 763674 and 763675 for (S)- and (R)- $\alpha$ -MBA–CA, respectively.

#### 4.2. THz spectrometry

A wide-range THz spectrometer TSS-I (Terahertz Laboratory, Yuzawa, Japan) with a coherent THz electromagnetic wave source was used to measure the transmission spectra. The wave source was based on the principle of difference-frequency generation in a gallium phosphide crystal through the Raman effect of the phonon–polariton mode.<sup>10–13</sup> Two Cr:Forsterite lasers operated in a 1.2  $\mu$ m band were used as the pump sources. This spectrometer could sweep the frequency from 0.5 to 6.5 THz (17–217 cm<sup>-1</sup>). The line width of the generated THz wave was approximately 3 GHz (0.1 cm<sup>-1</sup>), and the measurements were conducted using a 15-GHz (0.5-cm<sup>-1</sup>) step. A pair of deuterated triglycine sulfate pyroelectric sensors was used to detect the transmission and reference intensities. Further details about the THz wave generator and the spectrometer have been provided in the literature.<sup>14</sup>

## Acknowledgements

We thank Professor M. Watanabe and Professor T. Kurabayashi (Iwate Prefectural University) for giving us the opportunity to start this study, and Dr. K. Aburaya (Rigaku) for X-ray analyses, a part of sample preparation, and valuable advice. This study was supported by the Dreamland Iwate Strategic Research Promotions Project of Iwate Prefecture and by the Project Research Fund of Iwate Prefectural University.

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