際整合性確保に関する研究（研究代表者　四方田千佳子）
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Analysis of terahertz absorptions of structural isomers of tyrosine using a molecular orbital simulation and mid-infrared absorptions

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Abstract— **Differences in the terahertz spectral features and the assignment of terahertz absorptions and hydrogen bond networking of tyrosines were examined. The inter- and intra-molecular absorptions in a terahertz region were calculated by the structural optimization simulation "Gaussian 03" at B3LYP/6-31G (d) level using the mid-IR absorptions.**

I. Introduction And Background

The properties of terahertz waves have been expected to be useful for scrutinizing the properties of pharmaceuticals, the *in vivo* function of proteins and so on. However, fundamental spectroscopy of a terahertz electro-magnetic wave, for example the assigning of terahertz absorption, is still not sufficiently understood, although there is one report concerning the assignment of terahertz absorption using a deuterium-substituted amino acid. A terahertz spectrum would be especially influenced by physical properties such as polymorphs rather than the chemical properties of the samples. Thus, submitting these physical properties such as polymorphs to a spectral evaluation using samples obtained from different resources is very important. Although the spectroscopic nature of a terahertz electro-magnetic wave has advantages for sensitively detecting changes of crystal structure, an interpretation of spectral information based on a correspondence between the spectral features would often be inaccurate. Therefore, the establishment of a suitable assignment procedure is highly desired. The authors tried to assign the peak positions of the absorptions observed in the terahertz spectra of tyrosine (*p*-tyrosine) and its structural isomers (*o*-tyrosine and *m*-tyrosine).

Tyrosine (*p*-tyrosine), which is synthesized from phenylalanine in the human body by an enzymatic reaction, was used. Tyrosine is transformed to dopa or other various physiologically active substances by an enzymatic reaction. Thus, tyrosine is a very important substance in the neurotransmission and endocrine systems. A Gaussian function can provide information regarding intra-molecular vibrations based on optimization of the molecule structural positions. In order to estimate the intra-molecular absorptions of tyrosines in a terahertz electromagnetic wave region, these absorptions were compared with the calculated values obtained with Gaussian03 using the mid-infrared absorptions of these tyrosines. It was found that discrimination between intra- and inter-molecular vibrations was possible, and the terahertz absorptions were successfully assigned through a comparison of spectral features among substances that have a position isomerism of the aromatic hydroxyl group.

II. Results

The vibration analysis results that were obtained by the chemical structural optimization using the B3LYP/6-31G (d) level of the Gaussian function are shown in Table 1. The nine intra-molecule vibrations were calculated in all compounds in the far-infrared/ terahertz region below 12 THz (approx. 400 cm^{-1}). In the measurement range (from 1 THz to 5 THz) of this study, the three intra-molecular vibrations of each compound were calculated. Moreover, one vibration of each compound was calculated in the region below 1 THz (from 0.62 to 0.79 THz). These calculation results suggest that a total of 4 intra-molecular vibrations would exist in the terahertz region. Table 2 summarizes the terahertz measurements that were obtained from phenylalanine and tyrosines. The absorption at 1.13 THz that is observed in all positional isomers of tyrosine, the absorptions at 2.41 THz and 3.01 THz that are observed in *o*- and *m*-tyrosine, and the absorptions around 2.8 THz and 3.25 THz that are observed in all compounds including phenylalanine, corresponded to the calculated values. Therefore, these absorptions are predicted to be intra-molecule vibrations. Furthermore, the strong absorption at 1.79 THz that was observed in *m*-tyrosine would suggest a strong inter-molecular hydrogen bond with the neighboring molecule, because this absorption was characteristic of *m*-tyrosine and predicted to be an inter-molecular vibration (Figure 1). The very strong absorption at 2.43 THz in *p*-tyrosine was predicted to be an inter-molecular vibration because no intra-molecular vibration was calculated. The absorptions at 2.30 THz and 2.38 THz observed in *m*- and *o*-tyrosine, respectively, were estimated to be intra-molecular vibrations.

Based on the chemical structure of phenylalanine, which did not have a hydroxyl function, the observed small peak in the second derivative spectrum of phenylalanine was presumed to be the intra-molecular hydrogen bond between the aromatic ring and [$-NH_3^+$] or [$-COO^-$]. This hypothesis would suggest that the absorption at 2.41 THz would be derived from the intra-molecule hydrogen bond in the common phenylalanine-based structure.

A strong absorption at 2.74 THz or 2.84 THz was observed in the spectrum of *o*-tyrosine or phenylalanine, respectively. These absorptions exist near the position of the calculated intra-molecular vibration at 2.98 THz. However, the absorption at 3.02 THz observed in the spectra of *o*-tyrosine and *m*-tyrosine is located more closely to the calculated vibration. These observations suggest that the absorption at 3.02 THz was predicted to be an intra-molecular vibration. This prediction

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introduces a hypothesis that the two strong absorptions at 2.74 THz and 2.84 THz, which are predicted to be an inter-molecular hydrogen bond network, would be derived from the common molecular structures of these compounds, and they form a hydrogen bond network with the neighboring molecule. Furthermore, the functional group which forms this hydrogen bond network would be located far from the aromatic hydroxyl group. This hypothesis suggests that a functional group such as [$-NH_3^+$], [$-COO^-$] would form the main hydrogen bond network in their crystalline structure. Further study is necessary to provide evidence for this hypothesis. The authors believe that the melting points of these compounds will provide an important hint to consider the hypothesis. For example, the melting points of *p*-tyrosine, *m*-tyrosine, and *o*-tyrosine, which have a hydroxyl group in their molecule structures, are reported to be 343 °C, 280-285 °C and 256 °C, respectively. *p*-Tyrosine and *m*-tyrosine, which are predicted to form a hydrogen bond network with the aromatic hydroxyl group, have strong absorptions. The intensity of absorption would be correlated not only with the strength of the inter-molecular hydrogen bond network but also with the melting points of these compounds. Moreover, *o*-tyrosine, which would form the hydrogen bond network without the aromatic hydroxyl group, has the lowest melting point. This fact suggests that a stronger inter-molecular hydrogen bond network formed by the aromatic hydroxyl group contributes the stable crystalline structure. On the other hand, the authors believe that phenylalanine (mp: 283 °C), which has a symmetric molecule structure, is more stable than *o*-tyrosine (mp: 256 °C). The authors presume that *p*-tyrosine forms a very stable crystalline structure based not only on the strong domination of the inter-molecule hydrogen bond derived from the aromatic hydroxyl group at 2.43 THz but also on the strong domination of the hydrogen bond that is detected at 2.14 THz. For example, the order of the melting points of the three compounds corresponds to that of the THz absorbance intensities derived from the strongest absorptions, which are assumed to form the inter-molecular hydrogen bond network with the adjacent molecules. This observation suggests that the intensities of terahertz absorptions may become one of the indicators of crystalline stability formed from a single molecule. Further study concerning the relationship between THz absorption and physical properties is necessary and requires the accumulation of data obtained from various compounds.

The absorption at about 2.4 THz was observed in all of the structural isomers of tyrosine that were used in this study. The terahertz electromagnetic region can detect not only intra-molecular vibrations but also inter-molecular vibrations such as hydrogen bonds. Therefore, distinguishing between intra- and inter-molecular vibrations using only terahertz absorptions would be quite difficult. The authors examined the prediction of intra-molecular vibrations in the terahertz region with the combination of a structural optimization simulation using the Gaussian function and mid-infrared absorptions. The distinguishability of absorptions between the intra- and inter-molecular vibrations was shown. This combination prediction procedure would provide useful information for assigning terahertz absorptions.

Table 1 Predicted frequency of intra-molecular vibration in terahertz electro-magnetic region
(Simulated by Gaussian 03 with B3LYP/6-31G(d))

Phenylalanine	o-Tyrosine	*m*-Tyrosine	*p*-Tyrosine
1.08 THz	1.03 THz	1.10THz	1.07 THz
2.43 THz	2.38 THz	2.30 THz	1.87 THz
2.98 THz	2.94 THz	2.98 THz	2.97 THz

Table 2 Frequencies of absorptions observed in the terahertz spectra of 4 kinds of compounds

Phenylalanine	0.94		1.56	1.82	2.03					2.84 (s)		3.26*
o-Tyrosine		1.13*	1.64		1.98		2.22	2.41*		2.74 (s)	3.02*	3.24* (s)
m-Tyrosine		1.13*	1.59	1.79 (s)			2.22	2.41*	2.65	2.83	3.02*	3.24* (s)
p-Tyrosine		1.12*				2.14 (s)		2.43 (vs)		2.85		3.23*

- The underlined frequencies represent commonly observed absorptions.
- The frequencies marked with a star (*) correspond to the simulated intra-molecular vibrations.

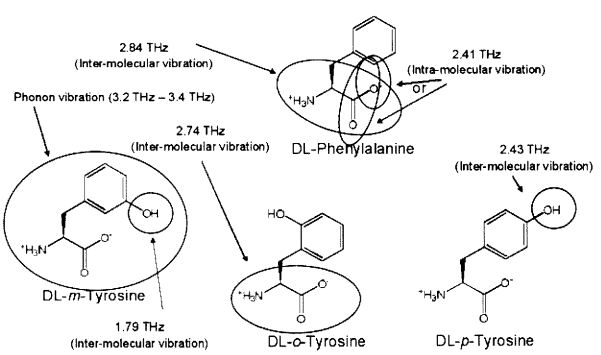

Fig. 1 Predicted intra- and inter-molecular vibrations based on the comparison of terahertz absorptions among four compounds and on Gaussian 03 simulation

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