Vibrational spectra of ketamine hydrochloride and 3, 4-methylenedioxymethamphetamine in terahertz range

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The terahertz spectrum of ketamine hydrochloride at room temperature, in the range of 0.2–2.6 THz, has been measured by terahertz time-domain spectroscopy (TDS). Full-geometry optimizations and frequency calculations using the density functional theory (DFT) are also applied to predict the absorption spectra of ketamine hydrochloride and 3, 4-methylenedioxymethamphetamine (MDMA). The results of the simulation show qualitative agreement with the experimental data especially for MDMA, and the observed spectra features are assigned based on the DFT calculation. The results suggest that use of the terahertz TDS technique can be an effective method for the detection and inspection of illicit drugs. © *2007 American Institute of Physics*. [DOI: 10.1063/1.2752139]

INTRODUCTION

As an attractive and unique spectroscopic technique in the far-IR range, terahertz time-domain spectroscopy (TDS) has been utilized in a wide range of research fields in the past ten years, including chemical and biological detections and identifications.[1,2] Terahertz TDS, compared with conventional spectroscopic techniques, can provide both the absorption coefficient and the refractive index of a sample with a high signal-to-noise ratio (SNR) and without using the Kramers-Kroning relation.

In regard to border security, the inspection and detection of illicit drugs are among the more demanding problems. Consequently, the inspection and identification of contraband drugs using terahertz TDS could be an additional tool of great significance. To date, in the field of terahertz spectroscopic studies on prohibited drugs, the terahertz spectra of methamphetamine (MA), methylenedioxyamphetamine (MDA), and MDMA have been investigated experimentally by Sun *et al.*[3] Kawase *et al.* and Kawase studied the identification of MDMA and MA by terahertz imaging using a terahertz parametric oscillator.[4,5] Li *et al.* investigated the terahertz spectra of MA using terahertz TDS experimentally and theoretically with the density functional theory (DFT).[6] Furthermore, DFT has proven to be a reliable theoretical method to predict accurate vibrational frequencies for medium size molecules.[7,8] It has been further shown that the combination of terahertz TDS and DFT is an effective way to investigate the characteristic spectra of illegal drugs. Here we present simulations of terahertz spectra for ketamine hydrochloride and MDMA. It would be important to investigate the characteristic spectra of illicit drugs in the terahertz range experimentally and theoretically for applications in the field of security detection as well as for the increase of the knowledge of characteristics of the chemicals. In this work, the terahertz absorption and refractive index of ketamine hydrochloride are presented experimentally using terahertz TDS in the range of 0.2–2.6 THz. DFT was employed to investigate the geometric structures and vibrational frequencies of ketamine hydrochloride and MDMA in this region. Comparisons of theoretical predictions using DFT with the experimental results show satisfactory agreement and the identification of the vibrational modes of two drugs is presented.

EXPERIMENTAL AND THEORETICAL METHODS

Pure ketamine hydrochloride (one of the most widely consumed illicit drugs in the world) was provided by the First Research Institute of the Ministry of Public Security of China. It was compressed into a slice of thickness of 1.3 mm and diameter of 13 mm. The terahertz spectrum of the sample was then measured and agreed with that obtained in Ref. 9. The experimental data were obtained using a pulsed terahertz system.[3,9] The full terahertz beam path was enclosed within a box, purged with dry nitrogen for at least 30 min prior to undertaking the experiments to keep the relative humidity below 4.0%. Terahertz pulses were generated by an 810 nm femtosecond laser (Mai-tai, Spectra Physics) with a pulse duration of 100 fs, a repetition rate of 82 MHz, and an average power of 980 mW. The terahertz TDS system has a dynamic range of 6000:1 and a signal-to-noise ratio of 1000. The temperature was kept at 294 K during the experiment.

DFT analysis of the low-frequency vibrational modes was undertaken using the software package GAUSSIAN03 (Ref. 10) to elucidate the origin of the absorption features observed in the experimental results. Full-geometry optimization and frequency analysis of optimized structures were performed at B3LYP/6-311+G* and B3LYP/6-31G* levels for ketamine hydrochloride and MDMA, respectively. The optimized geometry was confirmed by the fact that no negative frequency was found when analyzing the vibrational

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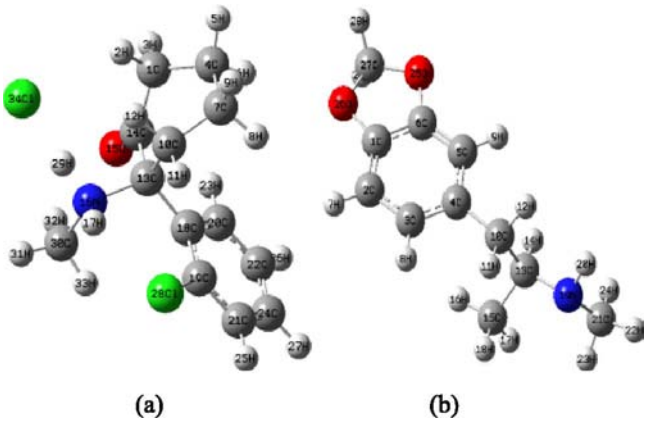

FIG. 1. (Color online) Predicted molecular structure of ketamine hydrochloride (a) and MDMA (b) after geometry.

spectrum. Figure 1 shows their predicted molecular structures after the geometry optimization.

RESULTS AND DISCUSSIONS

The time-domain spectra of both the reference, i.e., the laser beam passing through nitrogen only, and the sample are shown in the insert of Fig. 2. It is clear that the sample both attenuated and delayed the terahertz pulse due to the difference in the refractive index between the sample and nitrogen. A distinct temporal shift of 2.32 ps is observed, implying a sample average refractive index of 1.5388. The corresponding frequency-domain spectra, obtained using the fast Fourier transform, are also shown in Fig. 2. From this spectrum the frequency-dependent absorption coefficient and refractive index may also be determined. The small dips in the frequency-domain reference spectrum are caused by the residual water vapor in the parth of the terahertz beam. The five dips in the frequency-domain spectrum of the sample correspond to the absorption peaks of the material. While, the coincidence of the dips in the refractive index and the peaks in the absorption spectrum can be seen clearly in Fig. 3. It can be easily seen from the absorption spectrum that there are five absorption peaks located at the frequencies of 1.16, 1.35, 1.52, 1.93, and 2.40 THz, respectively, and from

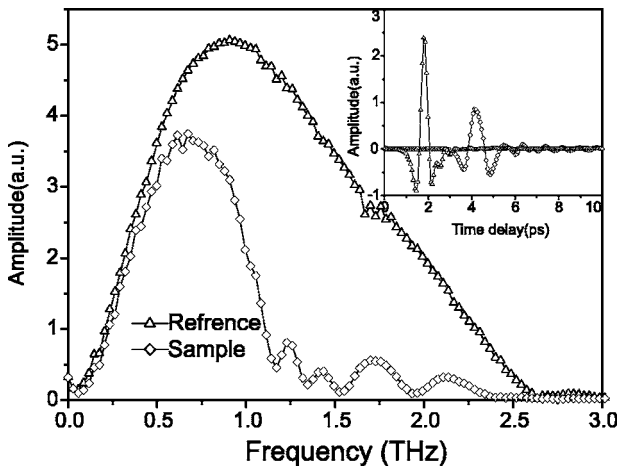

FIG. 2. The Fourier transform frequency spectra. Inset: the time-domain spectra.

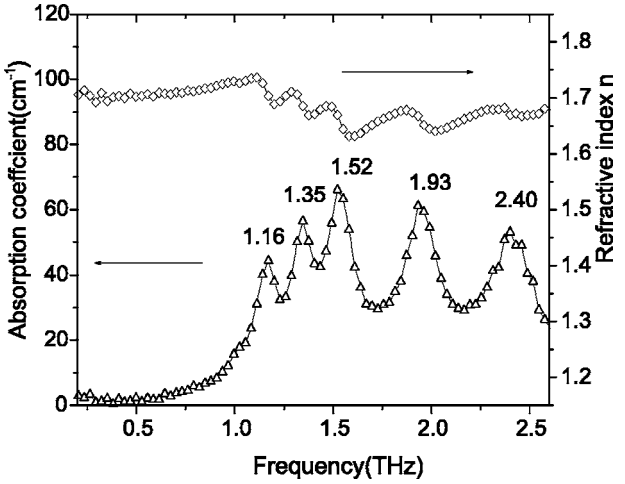

FIG. 3. Absorption coefficient and refractive index of ketamine hydrochloride.

the refractive index spectrum the refractive index varies between the magnitude of 1.48 and 1.57, verifying that an index decreases with frequency corresponds to an absorption peak, that is, abnormal dispersion is always accompanied by obvious absorption. These results are identical to the experimental results in Ref. 9. The absorption spectrum and refractive index spectrum of MDMA, although similar to that of ketamine hydrochloride, have absorption peaks located at different frequencies reflecting the differing molecular structure.

To find the relationship between the absorption spectrum and the corresponding molecular structure, we calculated the vibrational modes and present them in Fig. 1 with the aid of the visualization software "GAUSSIAN VIEW 3.08." All the calculated frequencies are not scaled with the scale factor. Comparisons of experimental and theoretical results for ketamine hydrochloride and MDMA were shown in Figs. 4 and 5, respectively. For ketamine hydrochloride, theoretical calcu-

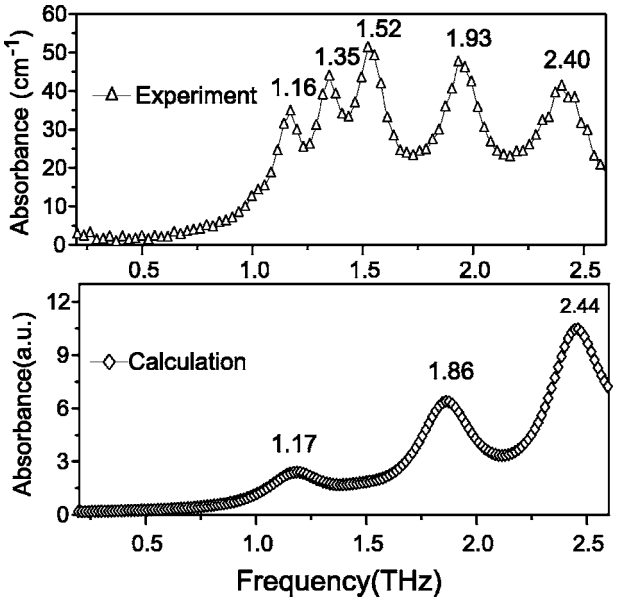

FIG. 4. Comparison of experimental and theoretical results for ketamine hydrochloride.

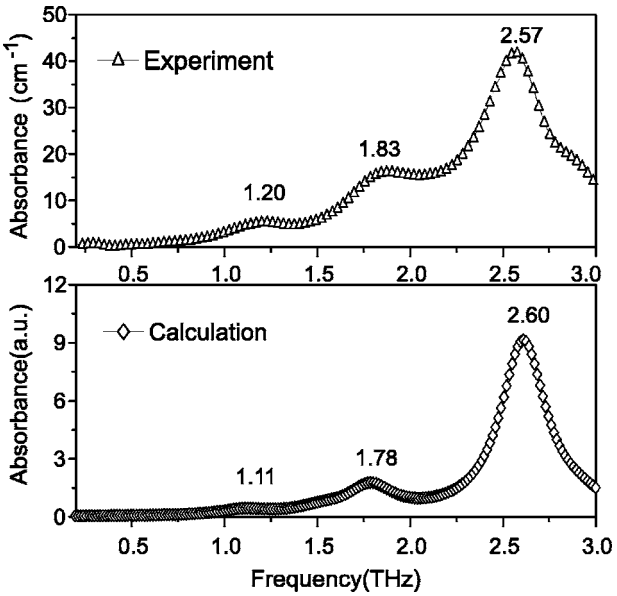

FIG. 5. Comparison of experimental and calculated results for MDMA.

lations predict three absorption peaks at 1.17, 1.86, and 2.44 THz. The peak of 1.16 THz is tentatively assigned as the wagging of C4–C7 and the peak of 1.93 THz as the scissoring of chlorphenyl and ring (C1C4C7), while the peak of 2.40 THz is the wagging of C4–C7 and the torsion of chlorphenyl. The absorption peaks located at 1.35 and 1.52 THz are absent in the calculation, which can possibly be attributed to the intermolecular vibration or phonon modes other than an isolated-molecular vibration. For MDMA, the calculated and experimental results agree more closely. The calculated absorption peaks located at 1.11, 1.78, and 2.60 THz correspond to the experimental absorption bands that peaked at 1.20, 1.83, and 2.57 THz, respectively. The small frequency shift between the calculated and measured spectra can be attributed to the packing force and steric effect in the crystalline.[11] This indicates that the spectrum of MDMA in the 0.2–2.6 THz region is mainly due to the intramolecule vibrations and the normal modes of the single molecule are adequate to identify this drug. We can easily see that the mode at 1.20 THz can be assigned to the torsion of C4–C10 out of the plane, the mode at 1.83 is assigned to the bending of C4–C10 out of the plane, and the mode at 2.57 is assigned to the rocking CH_2. To sum up, the identification of the two molecules' vibrational modes is shown in Table I. The calculated results also indicate that the whole vibration modes are accompanied by the torsion of the whole structure, and the magnitude of vibration increases with the increase of frequency.

The small frequency differences between experiment and simulation may be due to the fact that the theoretical calculation models the dynamics of a single molecule in the gas phase at a temperature of 0 K, while experimental results of the crystal samples were obtained at 294 K. Moreover, several approximations such as in the model potential, the assumed molecular geometry, the rigid molecule approximation, and the harmonic approximation in the lattice dynamics may lead to inaccuracies in the calculated results.

TABLE I. Assignments of observed vibrational frequencies (THz).

Experiment frequency (THz)	Calculation frequency (THz)	Assignments
		Ketamine hydrochloride
1.16	1.17	Wagging of C4–C7
1.35		
1.52		
1.93	1.86	Scissoring of chlorphenyl and ring (C1C4C7)
2.40	2.44	Wagging of C4–C7 and torsion of chlorphenyl
		MDMA
1.20	1.11	Torsion of C4–C10 out of plane
1.83	1.78	Bending of C4–C10 out of plane
2.57	2.60	Rocking of CH_2[a]

[a]27 CH_2 groups.

CONCLUSIONS

In summary, the terahertz spectrum of ketamine hydrochloride has been studied experimentally using terahertz TDS in the region of 0.2–2.6 THz. DFT calculations are applied to study the geometric structures and vibrational frequencies of ketamine hydrochloride and MDMA. Calculated vibrational frequencies of ketamine hydrochloride are in agreement with the experimental results except for the absence of the absorption peaks at 1.35 and 1.52 THz. Excellent agreement for MDMA between the calculated and the experimental results has been achieved in the terahertz region. The assignments of vibrational frequencies are proposed based on DFT computational results. Although the agreement between calculated and observed spectra does not allow a definitive characterization of the spectra, it is possible to make tentative assignments of many of the observed features in the terahertz region for the samples. For calculated results that will fit experimental data more closely, a more suitable theoretical analysis should be undertaken. Anyway, the combination of terahertz TDS and DFT has been proved to be an effective method to identify the highly characteristic spectra of the molecular vibrational modes of ketamine hydrochloride and MDMA. This opens up the possibility of employing the terahertz TDS technique for drug inspection and detection.

ACKNOWLEDGMENTS

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