PHOTONICS Research

Lamellar hafnium ditelluride as an ultrasensitive surface-enhanced Raman scattering platform for label-free detection of uric acid

Yang Li,^{1,†} Haolin Chen,^{2,†} Yanxian Guo,¹ Kangkang Wang,¹ Yue Zhang,¹ Peilin Lan,¹ Jinhao Guo,¹ Wen Zhang,³ Huiqing Zhong,¹ Zhouyi Guo,^{1,4} Zhengfei Zhuang,^{1,5} and Zhiming Liu^{1,*}

¹MOE Key Laboratory of Laser Life Science & SATCM Third Grade Laboratory of Chinese Medicine and Photonics Technology, College of Biophotonics, South China Normal University, Guangzhou 510631, China

²Department of Hematology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen 518107, China

³Department of Medical Biotechnology, School of Basic Medical Sciences, Guangzhou University of Chinese Medicine, Guangzhou 510006, China ⁴e-mail: ann@scnu.edu.cn

⁵e-mail: zhuangzf@scnu.edu.cn

*Corresponding author: liuzm021@126.com

Received 4 February 2021; revised 15 March 2021; accepted 20 March 2021; posted 23 March 2021 (Doc. ID 421415); published 25 May 2021

The development of two-dimensional (2D) transition metal dichalcogenides has been in a rapid growth phase for the utilization in surface-enhanced Raman scattering (SERS) analysis. Here, we report a promising 2D transition metal tellurides (TMTs) material, hafnium ditelluride (HfTe₂), as an ultrasensitive platform for Raman identification of trace molecules, which demonstrates extraordinary SERS activity in sensitivity, uniformity, and reproducibility. The highest Raman enhancement factor of 2.32×10^6 is attained for a rhodamine 6G molecule through the highly efficient charge transfer process at the interface between the HfTe₂ layered structure and the adsorbed molecules. At the same time, we provide an effective route for large-scale preparation of SERS substrates in practical applications via a facile stripping strategy. Further application of the nanosheets for reliable, rapid, and label-free SERS fingerprint analysis of uric acid molecules, one of the biomarkers associated with gout disease, is performed, which indicates arresting SERS signals with the limits of detection as low as 0.1 mmol/L. The study based on this type of 2D SERS substrate not only reveals the feasibility of applying TMTs to SERS analysis, but also paves the way for nanodiagnostics, especially early marker detection. © 2021 Chinese Laser Press

https://doi.org/10.1364/PRJ.421415

1. INTRODUCTION

Surface-enhanced Raman scattering (SERS) can perform labelfree detection of analyte at trace or even single molecule levels, with high sensitivity and selectivity [1]. As a nondestructive vibration testing model, SERS can provide the molecular fingerprint that has been widely used in a variety of scientific fields such as environmental monitoring, food safety testing, drug inspection, and disease diagnosis [2-6]. Noble metal SERS substrates such as gold and silver nanostructures with rough surfaces have been extensively studied by means of surface plasmon resonance excited local electromagnetic field amplification [7-12]. However, the noble metal-based SERS substrates lack repeatability and controllability due to the elaborate and complex synthesis processes. With the development of nanotechnology, SERS research has recently shifted from noble metals mainly based on the electromagnetic mechanism (EM) to novel two-dimensional (2D) nanomaterials based on the chemical mechanism (CM) due to the cheap sources and

simple preparation methods [13-16]. However, since CM is a short-range process that relies on the charge transfer (CT) during the resonance electron transition at the interface between the substrate and the adsorption molecule, its enhancement effect in the entire SERS is still limited to some extent [17,18]. In addition, the limits of detection (LODs) and the enhancement factors (EFs) are still much lower than that of metal nanostructures. Therefore, exploring promising 2D materials suitable for SERS analysis becomes more attractive. 1T-phase transition metal tellurides (TMTs) have recently been investigated as plasmon-free 2D SERS substrates for their brilliant physicochemical properties, which have a flat surface where probe molecules can be uniformly chemisorbed and abundant energy states near the Fermi energy level [19,20]. In addition, telluride nanosheets can also be prepared by facile ultrasonic peeling and hydrothermal reaction.

Uric acid (UA), the final product of purine metabolism, is one of the most important biomarkers in body fluid. The



Fig. 1. Schematic illustration of the SERS detection of uric acid based on $HfTe_2$ nanosheets.

equilibrium concentration of UA in urine is determined to be 0.952 to 5.948 mM (1 M = 1 mol/L) per 24 h and normouricemia is 0.208 to 0.416 mM (male) or 0.149 to 0.357 mM (female) [21–23]. Abnormal UA content is closely related to many diseases such as gout, kidney stones, hypertension, and cardiovascular disease [24-26]. Various methods such as highperformance liquid chromatography, isotope dilution mass spectrometry, colorimetric chemosensors, capillary electrophoresis, and electrochemical biosensors have been applied to detect UA. These techniques, however, are often hindered by complicated sample pretreatment, expensive instruments, and sophisticated instrumentation and equipment, and often lack sensitivity [27-30]. The SERS technique can provide a fast, ultrasensitive, and conventional diagnostic test method for real-time detection of UA. The SERS technique that uses various metal-based SERS substrates such as Au nanofibers, ZnO/Fe₃O₄ composites, Ag-paper, and Ag-modified graphene oxide nanosheets, has been reported for the detection of UArelated diseases, which shows good detection sensitivity [31-34]. However, these types of SERS substrates have certain practical limitations, including sophisticated preparation procedures, high cost due to the use of noble metals, and relatively poor SERS reproducibility caused by the complex nanostructural components.

In this work, a 2D SERS platform based on hafnium ditelluride (HfTe₂) nanosheets is proposed to fabricate an effective SERS detection system for the quantitative analysis of uric acid (Fig. 1). Few-layered HfTe₂ nanosheets are prepared by a facile liquid exfoliation plus a hydrothermal method. The obtained HfTe₂ nanosheets exhibit outstanding SERS activity to analytes with low LODs and high EFs, which can be ascribed to the electronic transition between the 1T-phase layered structure and the detection molecule after theoretical study. The SERS performance based on the HfTe₂ substrate also exhibits superior reproducibility and uniformity, which is further utilized as a new label-free SERS platform to detect trace UA at different conditions.

2. EXPERIMENT

A. Materials

Hafnium ditelluride was purchased from SixCarbon Technology Co., Ltd. (Shenzhen, China). Uric acid, urea, rhodamine 6G (Rh6G), crystal violet (CV), malachite green (MG), and methylene blue (MB) were purchased from Sigma-Aldrich (now MilliporeSigma, St. Louis, MO, USA). All reagents were of analytical grade and used directly without further purification. Deionized water was used throughout the study (Milli-Q System, MilliporeSigma).

B. Synthesis of HfTe₂ Nanosheets

A liquid exfoliation method including probe sonication and bath sonication was combined with hydrothermal reaction to prepare $HfTe_2$ nanosheets. The stripped procedures were as follows.

1. 30 mg of the bulk $HfTe_2$ powder was dispersed in 30 mL of ethyl alcohol and sonicated with an ultrasonic probe (600 W, 2 s duration and 4 s interval) for 8 h on ice.

2. The solution was sonicated in an ice bath for 10 h (400 W).

3. The mixture was centrifuged for 20 min at 2000 r/min to remove unexfoliated $HfTe_2$.

4. The exfoliated multilayer $HfTe_2$ was collected by centrifugation at 5000 r/min for 20 min and resuspended in water.

5. The solution was moved to a 50 mL Teflon lined autoclave and heated to 180° C for 8 h.

6. After cooling down to room temperature, $HfTe_2$ nanosheets were dispersed in ultrapure water through a 5-h liquid exfoliation and the same centrifugation process.

7. The nanosheets were stored at 4°C for further use.

C. Characterization

The surface morphology of HfTe2 nanosheets was characterized by a 200 kV transmission electron microscope (TEM, JEM-2010HR, JEOL Ltd., Tokyo, Japan), equipped with an energy-dispersive X-ray (EDX) spectrum. A scanning electron microscope (SEM, SU8010, Hitachi, Ltd., Tokyo, Japan) was used to observe the morphology and size of materials. The height of the nanomaterials was measured by an atomic force microscope (AFM, FSM-Nanoview, Fishman, Suzhou, China). X-ray diffraction (XRD) spectrum was measured by a D8 focus X-ray diffractometer (Bruker Corp., Billerica, MA, USA) by Cu Ka radiation ($\lambda = 1.54051$ Å, 1 Å = 0.1 nm). X-ray photoelectron spectroscopy (XPS) profile of HfTe2 nanosheets was measured by a photoelectron spectrometer (Escalab 250 Xi, Thermo Fisher Scientific Inc., Waltham, MA, USA). The ultraviolet-visible-near infrared (UV-Vis-NIR) absorbance spectrum of the nanosheets was recorded on an absorption spectrometer (UV-6100S, Shanghai Mapada Instruments Co., Ltd., Shanghai, China). Raman spectra were collected using a microspectrometer (inVia, Renishaw plc, Wottonunder-Edge, UK) under a 785 nm diode laser excitation.

D. SERS Experiments

Rh6G, CV, MB, and MG were chosen as the Raman reporters for the SERS study. 4 μ L of the HfTe₂ nanosheets solution was firstly deposited on the Si substrate by the spin-coating method, followed by dropping of 4 μ L of dye molecules. Then the samples were placed under a Renishaw inVia Raman microspectrometer for SERS detection equipped with a 785 nm laser. The laser power on the sample was 1 mW. Raman spectra were recorded in the static mode for a 5 s laser exposure (10 accumulations) in the range of 613–1725 cm⁻¹. All experiments were independently conducted six times. To study the repro**Research Article**

ducibility, the SERS test was repeated for 20 times. For practical application, we finally performed the SERS detection of uric acid based on $HfTe_2$ substrate (using urea as the interfering material).

3. RESULTS AND DISCUSSION

A. Characterization of Nanostructures

Figure 2(a) shows the schematic diagram of the synthetic process of lamellar $HfTe_2$ nanosheets. The morphological characteristics of the as-prepared 2D $HfTe_2$ nanosheets were studied by TEM, SEM, and AFM analysis, respectively. The TEM image reveals the transparency of the flakes to the electron beam of $HfTe_2$, confirming the obvious multilayer morphology after liquid peeling, as shown in Fig. 2(b). The high-resolution TEM (HRTEM) image shows the crystalline structure of HfTe₂ nanosheets with a lattice spacing of 0.33 nm [Fig. 2(b) inset]. As displayed in Fig. 2(c), the sizes and thicknesses of HfTe₂ nanosheets become significantly smaller after 180°C hydrothermal reaction, and the selected-area electron diffraction (SAED) pattern reveals the crystalline nature of HfTe₂ [Fig. 2(c) inset]. Moreover, the SEM image in Fig. 2(d) further demonstrates the layered structure of HfTe₂. The elemental maps of Te and Hf elements are well overlapped with the high-angle annular dark field (HAADF) image of HfTe₂ nanosheets, as shown in Fig. 2(e), indicating the element composition of HfTe₂ nanosheets that is also discerned by EDX spectroscopy [Fig. 2(f)].



Fig. 2. Synthesis and characterization of $HfTe_2$ nanosheets. (a) Schematic representation of the preparation process of $HfTe_2$ nanosheets. (b)–(c) TEM images of multilayer and few-layered hafnium ditelluride nanomaterials. The inset shows the HRTEM image and SAED pattern, respectively. (d) SEM image of $HfTe_2$ nanosheets. (e) HAADF image and corresponding elemental mapping (Te and Hf) of $HfTe_2$ nanosheets. (f) EDX pattern of $HfTe_2$ nanosheets. (g) AFM image with the corresponding size distribution (inset) and (h) height analysis of $HfTe_2$ nanosheets. (i) Raman spectra of bulk and few-layered $HfTe_2$.

The AFM image clearly shows the thickness of HfTe₂ nanosheets in Fig. 2(g), which displays the desirable monodispersity and fairly well-defined dimensions with the average thickness concentrated at 1-2 nm, as shown in the inset of Fig. 2(g). Figure 2(h) demonstrates two representative topographic plots of HfTe₂ nanosheets in Fig. 2(g), proving the ultrathin layer. The Raman features of $HfTe_2$ are shown in Fig. 2(i). It can be noted that the main Raman peaks of HfTe₂ are located at 100–200 cm⁻¹, which is far from the Raman fingerprint region of ordinary analytes (600-1800 cm⁻¹); thus, unnecessary Raman interference can be largely avoided. The Raman bands of few-layered HfTe2 nanosheets experienced a slight blue shift compared to that of bluk HfTe2, which may be ascribed to the layer-dependent band structure of the 2D material nanostructures [20,35,36].

HfTe2 crystal possesses a stable 1T-phase layered structure with weak interlayer interactions, corresponding to the CaI₂ type triangular structure with a P-3m1 space group [37,38]. In each layer, Hf atoms are sandwiched by Te atom layers with reverse symmetry at the top and bottom, as shown in Figs. 3(a)and 3(b). In the unit cell, Hf atoms are distributed at eight apex angles, and Te atoms are distributed in a regular trigonal column composed of three upper and lower Hf atoms, spaced at the center of the upper half and the center of the lower half, as shown in Fig. 3(c). The XRD pattern of the synthesized $HfTe_2$ is shown in Fig. 3(d), and the positions of the diffraction peaks found in the XRD pattern are consistent with the results of HfTe2 in the standard JCPDS card No. 26-0736, with standard lattice parameters (a = b = 3.95 Å, c = 6.67 Å) [39].

XPS analysis was used to validate the stoichiometry of 2D $HfTe_2$ nanosheets. Figure 4(a) illustrates the XPS spectra of the HfTe2 bulk and nanosheets, which can discern the variation of

(b)

(d)

Intensity (a.u.)

002)

20

Top view

40 60 2θ (deg)

60

HfTe₂

PDF#26-0736

80

(a)

(c)

Left view

Fig. 3. Atomic structure of monolayer HfTe2 nanosheet. (a) Left and (b) top views of lattice structures. (c) Unit cell structure of the nanostructures. Green spheres, tellurium atoms; and yellow spheres, hafnium atoms. (d) XRD pattern of HfTe2 nanosheets.

the surface chemical composition during the peeling process. Comparing the peak positions of HfTe₂ before and after the exfoliation, the results remain consistent across the basic, which proves that the chemical state of the material remained in a stable state during the preparation process. The highresolution XPS spectra of Hf 4f are illustrated in Figs. 4(b) and 4(c), where the peaks in the spectral line of few-layered HfTe₂ sheets are slightly wider than that of HfTe₂ bulk, indicating mild oxidation occurred during the preparation process [40,41]. In addition, an absorption band at around 587 nm with decreasing absorption intensity is mainly observed in the UV-Vis-NIR absorption spectrum of the prepared HfTe2 nanosheets, as shown in Fig. 4(d). The optical bandgap of HfTe2 was evaluated by its absorption spectrum, and its band gap was estimated by

$$\alpha = \frac{2.303A}{d},\tag{1}$$

$$\alpha h\nu = \alpha_0 (h\nu - E_g)^{1/2},$$
 (2)

where a, A, d, hv, and E_{g} were the absorption constant, the absorbance, the thickness of colorimetric ware, the photon energy, and the direct energy bandgap, respectively [42].



Fig. 4. (a) XPS analysis of $HfTe_2$ nanosheets. The high resolution XPS spectra of Hf 4f in (b) bulk and (c) few-layered HfTe2 sheets. (d) UV-Vis-NIR absorbance spectrum. (e) Typical optical absorption curve of HfTe₂ nanosheets, where E_g is estimated to be 4.93 eV. (f) Valence band spectrum of HfTe₂ nanosheets, where E_{vb} is calculated to be -4.98 eV.

Therefore, E_g can be obtained by drawing the curve of $(\alpha h\nu)^2 - h\nu$, and then extending the linear part to α_0 , as shown in Fig. 4(e). The E_g value of HfTe₂ is then calculated to be 4.93 eV. The valence band spectrum can directly reflect the external electronic structure of the compound. Figure 4(f) shows the valence band spectrum of HfTe₂ nanosheets, and the valence band (VB) energy (E_{vb}) of HfTe₂ is obtained from the fitting curve of the linear part, which is determined to be -4.98 eV. Finally, the conduction band (CB) energy (E_{cb}) of HfTe₂ nanosheets is counted from $E_{vb} + E_g$ (i.e., -0.05 eV).

B. SERS Activity of Hafnium Telluride

To study the SERS properties of the transition metal hafnium telluride, we first measured the SERS spectra of a typical dye Rh6G on HfTe₂ substrate under the excitation wavelength at 785 nm. As clearly displayed in Fig. 5(a), the normal Raman spectrum of Rh6G molecules is seriously interfered by the autofluorescence background. However, the fluorescence signals of Rh6G are greatly suppressed by nearly 30-fold after depositing the dye molecules onto HfTe₂ nanosheets, indicating the obvious fluorescence quenching effect of this kind of 2D nanomaterial. Moreover, remarkable enhancement in intensity of the typical Raman bands of Rh6G molecules is also observed in the spectral line, such as 774 cm⁻¹, 1182 cm⁻¹, 1313 cm⁻¹, 1365 cm⁻¹, 1514 cm⁻¹, and 1652 cm⁻¹, which can be attributed to C-C-C ring out-of-plane bending, C-C stretching vibrations, C = C stretching vibration, and the last three belonging to aromatic C-C stretching vibrations, respectively [43,44]. We then investigated the SERS detection of Rh6G with gradually decreasing concentrations from 10⁻³ to 10⁻⁹ M using HfTe₂ as the SERS substrate. Figure 5(b) displays the concentration-dependent SERS signals of Rh6G molecules, and the LOD value is noticed to be as low as $10^{-9}\ \text{M}.$ The quantitative intensity values of five typical Raman peaks of



Fig. 5. (a) Raw Raman spectra of Rh6G (10^{-3} M) dye on Si wafer with or without HfTe₂ substrate. (b) SERS spectra of different concentrations of Rh6G on HfTe₂ substrate. (c) Intensity values of typical Raman peaks in (b). Fitting curve of the inset is the SERS intensity-concentration plot for 1313 cm⁻¹ (R₂) band of Rh6G. (d) EF values of five typical Raman peaks of Rh6G at different concentration levels.

Rh6G at various concentrations are shown in Fig. 5(c), which confirms the decreasing Raman signal as the concentration decreases. Furthermore, the EFs of Rh6G on $HfTe_2$ nanosheets are calculated using

$$EF = (I_{SERS}/I_{Raman})(C_{Raman}/C_{SERS}),$$
 (3)

where I_{SERS} and I_{Raman} are the SERS and Raman intensities of the dye molecules, respectively. C_{Raman} and C_{SERS} denote the concentrations of probe molecules used for Raman and SERS experiments, respectively. As demonstrated in Fig. 5(d), the EF value of Rh6G ascends with the declining molecule concentration, and the maximum EF can reach 2.32×10^6 at the concentration of 10⁻⁹ M, which is significantly higher than that induced by graphene- or phosphorene-based 2D SERS substrates [35,45]. To the best of our knowledge, the calculated LOD at 10⁻⁹ M is one of the lowest reported so far in the detection of dye molecules using transition metal tellurides materials (such as WTe₂, MoTe₂, NbTe₂, and NiTe₂) as a SERS substrate [20,46–48]. A chemical selectivity of 2D nanomaterials to dye molecules due to the CT mechanism has been reported [49]. To study the universal applicability of HfTe₂ nanosheets, we further performed the SERS detection of MB, CV, and MG dyes on HfTe₂ substrate. The corresponding EFs of these molecules at different concentrations $(10^{-3}-10^{-9} \text{ M})$ are listed in Table 1, which illustrates comparable Raman enhancement, indicating the availability of HfTe₂ nanosheets for SERS analysis.

The ultrathin 2D nanosheets have smooth surfaces and can produce uniform SERS signals better than rough surfaces [50]. For SERS reproducibility study, we randomly acquired 20 SERS spectral lines of 10^{-5} M Rh6G on HfTe₂ substrate. It is strikingly apparent that the Raman signals of Rh6G can be clearly displayed on the HfTe₂ substrate with predominant reproducibility, as shown in Fig. 6(a). Then the relative standard deviations of the Raman characteristic peaks at 1514 cm⁻¹, 1365 cm⁻¹, and 1313 cm⁻¹ are calculated to be 4.201%, 4.459%, and 7.198%, respectively, as shown in Figs. 6(b)–6(d), indicating better SERS uniformity than that of other telluride SERS substrates [46,48]. Similar data are also discerned in the SERS analysis of MB and CV. These results obviously demonstrate that HfTe₂ nanosheets can be used as excellent SERS substrate with uniform SERS signals.

Raman mapping was further carried out in a randomly selected region (10 μ m × 17 μ m, step size 1 μ m) to evaluate the SERS reproducibility and uniformity of HfTe₂ nanosheets. The laser exposure time on the sample was 3 s under

 Table 1. Calculated Maximum EFs of Typical SERS

 Peaks of Different Dyes on HfTe2 Substrate

Analyte	Raman Shift (cm ⁻¹)	EF
Rh6G	1313	1.73×10^{6}
	1652	2.32×10^{6}
MB	1302	1.95×10^{6}
	1624	9.62×10^5
CV	825	1.35×10^{6}
	1303	1.0×10^{6}
MG	1176	3.98×10^{5}
	1622	3.95×10^5



Fig. 6. (a) Cluster of SERS spectra of Rh6G samples randomly collected at 20 sites on the HfTe₂ substrate. (b)–(d) SERS intensities of three typical peaks at 1514 cm⁻¹, 1365 cm⁻¹, and 1313 cm⁻¹ in the 20 SERS spectra.

785 nm laser excitation. Figure 7(a) shows the SERS image of Rh6G molecules on $HfTe_2$ nanosheets using the Raman peak at 1514 cm⁻¹, which indicates a relatively uniform distribution of SERS signals. Then 170 Raman spectral lines were collected from the SERS image, and the contour map is plotted in Fig. 7(b). It can be seen that the characteristic Raman peaks of Rh6G (1182 cm⁻¹, 1313 cm⁻¹, 1365 cm⁻¹, and 1514 cm⁻¹) have favorable continuity and uniformity. Moreover, we reconstructed a Raman spectrum along the green diagonal line in Fig. 7(b), which exhibited almost identical spectral pattern compared to the average SERS spectrum, as shown in Fig. 7(c), corroborating the good SERS uniformity of HfTe₂ nanosheets. The same scenario also emerges in the SERS mapping of CV molecules.



Fig. 7. (a) SERS image of Rh6G molecules (1514 cm⁻¹) on HfTe₂ nanosheets. (b) Contour map of 170 SERS spectra collected from the Raman mapping. (c) Average spectrum (blue line) of the 170 spectral data and the reconstructed spectrum (green line) along the green diagonal line in (b).

C. Chemical Mechanism of $HfTe_2$ -induced Raman Enhancement

Chemical enhancement mechanism plays a leading role in SERS of transition metal dichalcogenides [51]. The possible Raman enhancement mechanism of HfTe2 substrate to Rh6G probe is represented in Fig. 8. There are four possible types of CT resonances in this SERS system: (i) exciton resonance of HfTe₂ from VB to CB state; (ii) molecular resonance in dye from the highest occupied molecular orbit (HOMO) to the lowest unoccupied molecular orbit (LUMO) level; (iii) exciton electron transfers from molecule ground state to surface transition detection state, followed by photon-induced electron transition that occurs from the surface transition detection state to CB state; and (iv) light-induced electron transfer occurs from VB state to molecular excited state [52-54]. Rh6G is a traditional SERS probe with HOMO and LUMO levels of -5.70 eV and -3.40 eV, respectively [55], while the VB and CB of HfTe2 are calculated as -4.98 eV and -0.05 eV, respectively [Figs. 4(e) and 4(f)]. Therefore, among the possible CT resonances mentioned above, when exciton resonance (i) and molecular resonance (ii) occur, the required excitation energies are 4.93 eV and 2.30 eV, respectively. However, the excitation energy of a 785 nm laser is only 1.58 eV [56]. Consequently, since the energy provided is much smaller than the energy required, these two processes of CT resonance can be excluded [55,57]. Similarly, photon energy of 5.65 eV is needed to directly transfer electron from the HOMO energy level of Rh6G molecule to the CB state of HfTe2. Even in the presence of a surface transition detection state, photon-induced CT resonance cannot occur. In type (iv), the energy required for the excitation transition of the electron is 1.58 eV between the LUMO and VB state, which matches the laser excitation energy. A similar result is also provided after mechanism deduction in the HfTe₂-based SERS analysis of MB and CV dyes. Therefore, the CT resonance process between the VB state of 2D nanosheet and the LUMO level of dye molecule probably dominates the Raman enhancement of HfTe2 nanosheets.



Fig. 8. Schematic diagram of the photo-induced charge transfer process between $HfTe_2$ and Rh6G under 785 nm laser excitation.

D. SERS Screening of Uric Acid

The excessive UA level is prone to cause gout and even uremia. The detection of UA content in urine has momentous predictive significance for the onset of gout disease. For clinical practice, urea is the biggest interference factor for the SERS detection of UA. We first measured the SERS signals of pure uric acid, urea, and their mixture on HfTe₂ substrate. As shown in Fig. 9, the SERS spectral patterns of UA and urea are in remarkable agreement with what was reported in the literature [22,58]. The characteristic SERS peaks of UA at 999 cm⁻¹, 1039 cm⁻¹, and 1122 cm⁻¹ can be attributed to ring vibrations, skeletal ring deformation, and C-N vibrations, respectively [31]. In the SERS spectrum of the mixture of UA and urea, the typical SERS peaks of UA and urea can be obviously distinguished with little mutual interference. Then we performed SERS analysis of UA at concentrations ranging from 100 μ M to 1 mM to study the limit of detection. Figure 10(a) shows a concentration-dependent SERS effect that the intensity of the SERS signal increases when the concentration of UA improves. The fitting curve of the peak at 1039 cm⁻¹ indicates that the SERS intensity is directly proportional to the amount of UA adsorbed on the HfTe2 nanosheets [Fig. 10(b)], and the LOD of HfTe2-based SERS analysis to UA is 100 µM. It has been reported that the lowest normal uric acid level is of 149 µM in vivo [21]. So, this 2D SERS system based on HfTe₂ nanomaterials is sufficient for the monitoring of UArelated diseases. To simulate the in vivo environment, UA with different concentrations was mixed with 4 mM urea. Figure 10(c) illustrates the concentration-relevant SERS spectra of UA in the presence of urea, where both the fingerprint information of UA and urea can be observed. Decreasing SERS signals of UA along with signals of UA in the mixture is still noticed with concentrations as low as 100 μ M. The Raman intensity of 1039 cm⁻¹ band (UA) relative to 1012 cm⁻¹



Fig. 9. Mean SERS spectra of pure uric acid, urea, and their mixture on $HfTe_2$ nanosheets.



Fig. 10. (a) SERS detection of UA at different concentrations on HfTe₂ nanosheets. Curves a to j: SERS spectra of UA at 1000, 600, 500, 400, 350, 300, 250, 200, 150, and 100 μ M, respectively. Curve k: normal Raman spectrum of UA at 1 mM. (b) Fitting curve of SERS intensity-logarithmic concentration for 1039 cm⁻¹ band of UA. (c) SERS spectra of UA (0.1–0.5 mM) on HfTe₂ nanosheets in the presence of 4 mM urea. (d) Calibration curve by plotting the peak intensity ratio (I_{1039}/I_{1012}) as a function of UA concentration. Enlargements of the typical Raman peaks (urea 1012 cm⁻¹, uric acid 1039 cm⁻¹) are shown as insets.

peak (urea) as a function of UA concentration is displayed in Fig. 10(d). The I_{1039}/I_{1012} value illustrates an exponential change with the UA concentration increase, indicating a promising potential of HfTe₂ nanosheets for clinical diagnosis of the diseases related to UA abnormality.

4. CONCLUSIONS

In summary, we have prepared few-layered $HfTe_2$ nanosheets via a facile liquid exfoliation combined with hydrothermal reaction. We believe $HfTe_2$ nanosheets can serve as a novel 2D TMT SERS substrate due to the outstanding SERS activity and reproducibility. Compared to some existing SERS platforms, the SERS analysis based on $HfTe_2$ does not suffer from the background interference from the substrate. The charge transfer from the VB state of $HfTe_2$ to the LUMO level of dye molecule may contribute to the enhancement mechanism in a $HfTe_2$ -based SERS system, which leads to the maximum EF of 2.32×10^6 . For practical application, $HfTe_2$ nanosheets have successfully been used for the SERS detection of UA, the important biomarker for gout disease, which demonstrated a reliable LOD of 100 μ M. The study of the $HfTe_2$ -based SERS platform opens up bright prospects for nanodiagnostics.

Funding. National Natural Science Foundation of China (11874021, 32071399, 61675072); Science and Technology Program of Guangzhou (201904010323, 2019050001);

Natural Science Foundation of Guangdong Province (2021A1515011988); Science and Technology Project of Guangdong Province of China (2017A020215059); Open Foundation of Key Laboratory of Optoelectronic Science and Technology for Medicine (Fujian Normal University), Ministry of Education, China (JYG2009); Natural Science Research Project of Guangdong Food and Drug Vocational College (2019ZR01).

Disclosures. The authors declare no conflicts of interest.

[†]These authors contributed equally to the paper.

REFERENCES

- S. M. Nie and S. R. Emery, "Probing single molecules and single nanoparticles by surface-enhanced Raman scattering," Science 275, 1102–1106 (1997).
- E. Garcia-Rico, R. A. Alvarez-Puebla, and L. Guerrini, "Direct surfaceenhanced Raman scattering (SERS) spectroscopy of nucleic acids: from fundamental studies to real-life applications," Chem. Soc. Rev. 47, 4909–4923 (2018).
- S. Hussain, H. Chen, Z. Zhang, and H. Zheng, "Vibrational spectra and chemical imaging of cyclo[18]carbon by tip enhanced Raman spectroscopy," Chem. Commun. 56, 2336–2339 (2020).
- J. Yu, M. Yang, Z. Li, C. Liu, Y. Wei, C. Zhang, B. Man, and F. Lei, "Hierarchical particle-in-quasicavity architecture for ultratrace *in situ* Raman sensing and its application in real-time monitoring of toxic pollutants," Anal. Chem. 92, 14754–14761 (2020).
- W. Zhang, F. Lin, Y. Liu, H. Zhang, T. A. Gilbertson, and A. Zhou, "Spatiotemporal dynamic monitoring of fatty acid-receptor interaction on single living cells by multiplexed Raman imaging," Proc. Natl. Acad. Sci. USA 117, 3518–3527 (2020).
- C. Zong, M. Xu, L. J. Xu, T. Wei, X. Ma, X. S. Zheng, R. Hu, and B. Ren, "Surface-enhanced Raman spectroscopy for bioanalysis: reliability and challenges," Chem. Rev. **118**, 4946–4980 (2018).
- S. Y. Ding, J. Yi, J. F. Li, B. Ren, D. Y. Wu, R. Panneerselvam, and Z. Q. Tian, "Nanostructure-based plasmon-enhanced Raman spectroscopy for surface analysis of materials," Nat. Rev. Mater. 1, 16021 (2016).
- S. Y. Ding, E. M. You, Z. Q. Tian, and M. Moskovits, "Electromagnetic theories of surface-enhanced Raman spectroscopy," Chem. Soc. Rev. 46, 4042–4076 (2017).
- C. Li, S. Xu, J. Yu, Z. Li, W. Li, J. Wang, A. Liu, B. Man, S. Yang, and C. Zhang, "Local hot charge density regulation: vibration-free pyroelectric nanogenerator for effectively enhancing catalysis and *in-situ* surface enhanced Raman scattering monitoring," Nano Energy **81**, 105585 (2021).
- H. S. Su, H. S. Feng, Q. Q. Zhao, X. G. Zhang, J. J. Sun, Y. H. He, S. C. Huang, T. X. Huang, J. H. Zhong, D. Y. Wu, and B. Ren, "Probing the local generation and diffusion of active oxygen species on a Pd/Au bimetallic surface by tip-enhanced Raman spectroscopy," J. Am. Chem. Soc. **142**, 1341–1347 (2020).
- H. Zhang, S. Duan, P. M. Radjenovic, Z. Q. Tian, and J. F. Li, "Coreshell nanostructure-enhanced Raman spectroscopy for surface catalysis," Acc. Chem. Res. 53, 729–739 (2020).
- X. Zhao, C. Liu, J. Yu, Z. Li, L. Liu, C. Li, S. Xu, W. Li, B. Man, and C. Zhang, "Hydrophobic multiscale cavities for high-performance and self-cleaning surface-enhanced Raman spectroscopy (SERS) sensing," Nanophotonics 9, 4761–4773 (2020).
- X. H. Li, S. H. Guo, J. Su, X. G. Ren, and Z. Y. Fang, "Efficient Raman enhancement in molybdenum disulfide by tuning the interlayer spacing," ACS Appl. Mater. Interfaces 12, 28474–28483 (2020).
- X. Ling, W. J. Fang, Y. H. Lee, P. T. Araujo, X. Zhang, J. F. Rodriguez-Nieva, Y. X. Lin, J. Zhang, J. Kong, and M. S. Dresselhaus, "Raman enhancement effect on two-dimensional layered materials: graphene, h-BN and MoS₂," Nano Lett. **14**, 3033–3040 (2014).

- Z. M. Liu, H. L. Chen, Y. L. Jia, W. Zhang, H. N. Zhao, W. D. Fan, W. L. Zhang, H. Q. Zhong, Y. R. Ni, and Z. Y. Guo, "A two-dimensional fingerprint nanoprobe based on black phosphorus for bio-SERS analysis and chemo-photothermal therapy," Nanoscale **10**, 18795– 18804 (2018).
- Y. Tan, L. N. Ma, Z. B. Gao, M. Chen, and F. Chen, "Two-dimensional heterostructure as a platform for surface-enhanced Raman scattering," Nano Lett. 17, 2621–2626 (2017).
- J. A. Dieringer, A. D. McFarland, N. C. Shah, D. A. Stuart, A. V. Whitney, C. R. Yonzon, M. A. Young, X. Y. Zhang, and R. P. Van Duyne, "Surface enhanced Raman spectroscopy: new materials, concepts, characterization tools, and applications," Faraday Discuss. 132, 9–26 (2006).
- B. N. J. Persson, K. Zhao, and Z. Y. Zhang, "Chemical contribution to surface-enhanced Raman scattering," Phys. Rev. Lett. 96, 207401 (2006).
- P. Q. Lu, Y. Wang, H. L. Xu, X. Y. Wang, N. Ali, J. Q. Zhu, and H. Z. Wu, "Surface-enhanced Raman scattering on sandwiched structures with gallium telluride," J. Mater. Sci. 55, 10047–10055 (2020).
- L. Tao, K. Chen, Z. Chen, C. Cong, C. Qiu, J. Chen, X. Wang, H. Chen, T. Yu, W. Xie, S. Deng, and J. B. Xu, "1T' transition metal telluride atomic layers for plasmon-free SERS at femtomolar levels," J. Am. Chem. Soc. 140, 8696–8704 (2018).
- A. L. Wang, C. Guan, G. Y. Shan, Y. W. Chen, C. L. Wang, and Y. C. Liu, "A nanocomposite prepared from silver nanoparticles and carbon dots with peroxidase mimicking activity for colorimetric and SERSbased determination of uric acid," Microchim. Acta 186, 644 (2019).
- C. Westley, Y. Xu, B. Thilaganathan, A. J. Carnell, N. J. Turner, and R. Goodacre, "Absolute quantification of uric acid in human urine using surface enhanced Raman scattering with the standard addition method," Anal. Chem. 89, 2472–2477 (2017).
- F. Yang, P. Sun, H. Zhao, C. Zhao, N. Zhang, and Y. Dai, "Genetic association and functional analysis of rs7903456 in *FAM35A* gene and hyperuricemia: a population based study," Sci. Rep. 8, 9579 (2018).
- K. M. Black, H. Law, A. Aldoukhi, J. Deng, and K. R. Ghani, "Deep learning computer vision algorithm for detecting kidney stone composition," BJU Int. **125**, 920–924 (2020).
- C. C. Chang, C. H. Wu, L. K. Liu, R. H. Chou, C. S. Kuo, P. H. Huang, L. K. Chen, and S. J. Lin, "Association between serum uric acid and cardiovascular risk in nonhypertensive and nondiabetic individuals: the Taiwan I-Lan longitudinal aging study," Sci. Rep. 8, 5234 (2018).
- P. Richette, M. Doherty, E. Pascual, V. Barskova, F. Becce, J. Castaneda, M. Coyfish, S. Guillo, T. Jansen, H. Janssens, F. Liote, C. D. Mallen, G. Nuki, F. Perez-Ruiz, J. Pimentao, L. Punzi, A. Pywell, A. K. So, A. K. Tausche, T. Uhlig, J. Zavada, W. Y. Zhang, F. Tubach, and T. Bardin, "2018 updated European league against rheumatism evidence-based recommendations for the diagnosis of gout," Ann. Rheum. Dis. **79**, 31–38 (2020).
- X. H. Dai, X. Fang, C. M. Zhang, R. F. Xu, and B. Xu, "Determination of serum uric acid using high-performance liquid chromatography (HPLC)/isotope dilution mass spectrometry (ID-MS) as a candidate reference method," J. Chromatogr. B 857, 287–295 (2007).
- D. Habibi, A. R. Faraji, and A. Gil, "A highly sensitive supported manganese-based voltammetric sensor for the electrocatalytic determination of captopril," Sens. Actuators B 182, 80–86 (2013).
- Y. W. Tao, X. J. Zhang, J. W. Wang, X. X. Wang, and N. J. Yang, "Simultaneous determination of cysteine, ascorbic acid and uric acid by capillary electrophoresis with electrochemiluminescence," J. Electroanal. Chem. 674, 65–70 (2012).
- Q. H. Yan, N. Zhi, L. Yang, G. R. Xu, Q. G. Feng, Q. Q. Zhang, and S. J. Sun, "A highly sensitive uric acid electrochemical biosensor based on a nano-cube cuprous oxide/ferrocene/uricase modified glassy carbon electrode," Sci. Rep. **10**, 10607 (2020).
- M. T. Alula, P. Lemmens, L. Bo, D. Wulferding, J. Yang, and H. Spende, "Preparation of silver nanoparticles coated ZnO/Fe₃O₄ composites using chemical reduction method for sensitive detection of uric acid via surface-enhanced Raman spectroscopy," Anal. Chim. Acta **1073**, 62–71 (2019).
- E. Gurian, P. Giraudi, N. Rosso, C. Tiribelli, D. Bonazza, F. Zanconati, M. Giuricin, S. Palmisano, N. de Manzini, V. Sergo, and A. Bonifacio,

"Differentiation between stages of non-alcoholic fatty liver diseases using surface-enhanced Raman spectroscopy," Anal. Chim. Acta **1110**, 190–198 (2020).

- 33. R. S. Juang, Y. W. Cheng, W. T. Chen, K. S. Wang, C. C. Fu, S. H. Liu, R. J. Jeng, C. C. Chen, M. C. Yang, and T. Y. Liu, "Silver nanoparticles embedded on mesoporous-silica modified reduced graphene-oxide nanosheets for SERS detection of uremic toxins and parathyroid hormone," Appl. Surf. Sci. **521**, 146372 (2020).
- R. K. Saravanan, T. K. Naqvi, S. Patil, P. K. Dwivedi, and S. Verma, "Purine-blended nanofiber woven flexible nanomats for SERS-based analyte detection," Chem. Commun. 56, 5795–5798 (2020).
- X. Ling, L. M. Xie, Y. Fang, H. Xu, H. Zhang, J. Kong, M. S. Dresselhaus, J. Zhang, and Z. Liu, "Can graphene be used as a substrate for Raman enhancement?" Nano Lett. **10**, 553–561 (2010).
- C. Qiu, H. Zhou, H. Yang, M. Chen, Y. Guo, and L. Sun, "Investigation of *n*-layer graphenes as substrates for Raman enhancement of crystal violet," J. Phys. Chem. C **115**, 10019–10025 (2011).
- C. Cheng, J. T. Sun, X. R. Chen, and S. Meng, "Hidden spin polarization in the 1T-phase layered transition-metal dichalcogenides MX₂ (M = Zr, Hf; X = S, Se, Te)," Sci. Bull. 63, 85–91 (2018).
- B. Harbrecht, M. Conrad, T. Degen, and R. Herbertz, "Synthesis and crystal structure of Hf₂Te," J. Alloy. Compd. 255, 178–182 (1997).
- S. Aminalragia-Giamini, J. Marquez-Velasco, P. Tsipas, D. Tsoutsou, G. Renaud, and A. Dimoulas, "Molecular beam epitaxy of thin HfTe₂ semimetal films," 2D Mater. 4, 015001 (2017).
- M. Chennabasappa, M. Lahaye, B. Chevalier, C. Labrugere, and O. Toulemonde, "A successful process to prevent corrosion of rich Gdbased room temperature magnetocaloric material during ageing," J. Alloy. Compd. 850, 156554 (2021).
- R. Lai, M. Wei, J. Wang, K. Zhou, and X. Qiu, "Temperature dependence of resistive switching characteristics in NiO(111) films on metal layer," J. Phys. D 54, 015101 (2021).
- H. Hichem, A. Djamila, and A. Hania, "Optical, electrical and photoelectrochemical characterization of electropolymerized poly methylene blue on fluorine doped tin oxide conducting glass," Electrochim. Acta 106, 69–74 (2013).
- S. Lin, W. Hasi, X. Lin, S. Han, T. Xiang, S. Liang, and L. Wang, "Labon-capillary platform for on-site quantitative SERS analysis of surface contaminants based on Au@4-MBA@Ag core-shell nanorods," ACS Sens. 5, 1465–1473 (2020).
- 44. D. Pristinski, S. L. Tan, M. Erol, H. Du, and S. Sukhishvili, "*In situ* SERS study of Rhodamine 6G adsorbed on individually immobilized Ag nanoparticles," J. Raman Spectrosc. **37**, 762–770 (2006).
- J. Lin, L. Liang, X. Ling, S. Zhang, N. Mao, N. Zhang, B. G. Sumpter, V. Meunier, L. Tong, and J. Zhang, "Enhanced Raman scattering on in-plane anisotropic layered materials," J. Am. Chem. Soc. 137, 15511–15517 (2015).
- J. P. Fraser, P. Postnikov, E. Miliutina, Z. Kolska, R. Valiev, V. Svorcik, O. Lyutakov, A. Y. Ganin, and O. Guselnikova, "Application of a 2D molybdenum telluride in SERS detection of biorelevant molecules," ACS Appl. Mater. Interfaces 12, 47774–47783 (2020).
- 47. C. Jiang, Y. Wei, P. Zhao, P. Wang, Y. Fang, and L. Zhang, "Investigation of surface-enhanced Raman spectroscopy on the

substrates of telluride 2D material," Eur. Phys. J. Plus 135, 671 (2020).

- K. Wang, Z. Guo, Y. Li, Y. Guo, H. Liu, W. Zhang, Z. Zou, Y. Zhang, and Z. Liu, "Few-layer NbTe₂ nanosheets as substrates for surfaceenhanced Raman scattering analysis," ACS Appl. Nano Mater. 3, 11363–11371 (2020).
- A. Sarycheva, T. Makaryan, K. Maleski, E. Satheeshkumar, A. Melikyan, H. Minassian, M. Yoshimura, and Y. Gogotsi, "Two-dimensional titanium carbide (MXene) as surface-enhanced Raman scattering substrate," J. Phys. Chem. C **121**, 19983–19988 (2017).
- H. Wu, X. Zhou, J. Li, X. Li, B. Li, W. Fei, J. Zhou, J. Yin, and W. Guo, "Ultrathin molybdenum dioxide nanosheets as uniform and reusable surface-enhanced Raman spectroscopy substrates with high sensitivity," Small 14, 1802276 (2018).
- J. Langer, D. J. de Aberasturi, J. Aizpurua, R. A. Alvarez-Puebla, B. Auguie, J. J. Baumberg, G. C. Bazan, S. E. J. Bell, A. Boisen, A. G. Brolo, J. Choo, D. Cialla-May, V. Deckert, L. Fabris, K. Faulds, F. J. G. de Abajo, R. Goodacre, D. Graham, A. J. Haes, C. L. Haynes, C. Huck, T. Itoh, M. Ka, J. Kneipp, N. A. Kotov, H. Kuang, E. C. Le Ru, H. K. Lee, J. F. Li, X. Y. Ling, S. A. Maier, T. Mayerhofer, M. Moskovits, K. Murakoshi, J. M. Nam, S. Nie, Y. Ozaki, I. Pastoriza-Santos, J. Perez-Juste, J. Popp, A. Pucci, S. Reich, B. Ren, G. C. Schatz, T. Shegai, S. Schlucker, L. L. Tay, K. G. Thomas, Z. Q. Tian, R. P. Van Duyne, T. Vo-Dinh, Y. Wang, K. A. Willets, C. Xu, H. Xu, Y. Xu, Y. S. Yamamoto, B. Zhao, and L. M. Liz-Marzan, "Present and future of surface-enhanced Raman scattering," ACS Nano 14, 28–117 (2020).
- W. Ji, L. Li, W. Song, X. Wang, B. Zhao, and Y. Ozaki, "Enhanced Raman scattering by ZnO superstructures: synergistic effect of charge transfer and Mie resonances," Angew. Chem. 58, 14452–14456 (2019).
- E. Kazuma, J. Jung, H. Ueba, M. Trenary, and Y. Kim, "STM studies of photochemistry and plasmon chemistry on metal surfaces," Prog. Surf. Sci. 93, 163–176 (2018).
- N. J. Kim, J. Kim, J. B. Park, H. Kim, G. C. Yi, and S. Yoon, "Direct observation of quantum tunnelling charge transfers between molecules and semiconductors for SERS," Nanoscale 11, 45–49 (2018).
- J. Lin, Y. Shang, X. X. Li, J. Yu, X. T. Wang, and L. Guo, "Ultrasensitive SERS detection by defect engineering on single Cu₂O superstructure particle," Adv. Mater. 29, 1604797 (2016).
- Z. Yu, W. Yu, J. Xing, R. A. Ganeev, W. Xin, J. Cheng, and C. Guo, "Charge transfer effects on resonance-enhanced Raman scattering for molecules adsorbed on single-crystalline perovskite," ACS Photon. 5, 1619–1627 (2018).
- X. Wang, W. Shi, G. She, and L. Mu, "Using Si and Ge nanostructures as substrates for surface-enhanced Raman scattering based on photoinduced charge transfer mechanism," J. Am. Chem. Soc. 133, 16518–16523 (2011).
- K. Chen, X. Y. Zhang, and D. R. MacFarlane, "Ultrasensitive surfaceenhanced Raman scattering detection of urea by highly ordered Au/ Cu hybrid nanostructure arrays," Chem. Commun. 53, 7949–7952 (2017).