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Electronic Supplementary Information

Ultra-sensitive ROS-responsive tellurium-containing polymers

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1 EXPERIMENTAL SECTION

1.1 Materials. Sodium borohydride, deuterium chloride were purchased from Alfa-aesar. 11-bromoundecanol, 8-bromooctanoic acid was the products of TCI. Tellurium powder was obtained from Aladdin chemical company. Hydrogen peroxide, other organic solvents and chemicals used in this paper were analytical grade products from Beijing Chemical Reagent Company. The tetrahydrofuran (THF) was dried by Sodium Type A (4A) molecular sieves to remove moisture. All the chemicals and solvents were used as received unless otherwise stated.

1.2 Methods.

Cyclic voltammetry measurements were performed in a conventional three-electrode glass electrochemical cell at ambient temperature. Sodium tetraborate buffer was utilized to increase the solubility and ensure sufficient conductivity. The working electrode was a glassy carbon electrode, while the auxiliary electrode was a carbon electrode to ensure no reaction would happen with the bulk solution, and the reference electrode was an Ag/AgCl (3M KCl) electrode. The solution of 2 mM $K_3[Fe(CN)_6]$ and 0.1 M KCl was utilized as the negative indicator. Prior to the measurements, the electrolyte solutions were purged with nitrogen for 30 min, and a constant flow of nitrogen was applied above the liquid phase during the whole measurements. The potential sweep rate was 100 mV s^{-1}.

The micelle samples were irradiated with γ rays at Department of Applied Chemistry, Peking University, with a ^{60}Co radiation source at a dose rate of 0.2 Gy min^{-1}. The unit Gy refers to the radiation energy absorbed by objects of a certain mass: 1 Gy=1 J kg^{-1}.

TEM images were obtained on a JEM-2010 Microscope with an accelerating voltage of 80 kV. Samples were prepared by drop-coating the water solution on the carbon-coated copper grids for 15 min and then observed without staining. Dynamic light scattering (DLS) tests were performed on a Malvern ZEN3690 Zetasizer at 25 ℃. ESI-mass spectra were measured on a LTQ LC/MS apparatus. The ^{1}H NMR spectra and ^{13}C NMR spectra were measured on a JEOL JNM-ECA 400 (400 MHz). While ^{1}H NMR spectra for the polymer samples were recorded by a JEOL JNM-ECA 600 (600 MHz) spectrometer.

Synthesis of 8,8'-tellurodioctanoic acid. The telluride containing monomer was synthesized with the preparation steps reported before.[1] Disodium telluride was prepared by the reaction of Te powder and excess amount of sodium borohydride and 8-bromooctanoic acid in THF was added under Ar flow at 50 ^oC for 6 h. Products were purified by filtration and recrystallization.

Oxidation of 8,8'-tellurodioctanoic acid. The 8,8'-tellurodioctanoic acid was add into water and deprotonated by sodium carbonate. Different amounts of H_2O_2 were added to the samples and placed in the dark to avoid the decomposition of the H_2O_2 under light. The water was freeze dried and the solute was directly transferred into deuterium oxide for NMR measurements. For the NMR measurements in chloroform-d, the samples were pretreated with deuterium chloride to ensure enough solubility in chloroform before being transferred to chloroform-d. 8,8'-tellurodioctanoic acid ^1H NMR (400 MHz, D_2O, 298 K) δ (ppm): 2.70(4H, t, TeCH_2), 2. 19(4H, t, CH_2COOH), 1.82-1.25(20H, m, $HOOCCH_2(CH_2)_5CH_2Te$). ^{13}C NMR (400MHz, D_2O, 298 K), δ (ppm): 184.2 (1C, s, *C*OOH), 38.4 (1C, s, CH_2COOH), 29.0-32.5 (1C, s, $TeCH_2$ $(CH_2)_4CH_2CH_2COOH$), 26.7 (1C, s, CH_2CH_2COOH), 3.9 (1C, s, TeCH_2), 161 (Na_2CO_3, which is added to deprotonate the –COOH groups).

After oxidation by 1 equiv. H_2O_2 ^1H NMR (400 MHz, D_2O, 298 K) δ (ppm): 2.85(4H, t, TeCH_2), 2. 19(4H, t, CH_2COOH), 1.88(4H, t, Te CH_2CH_2), 1.82-1.25(16H, m, $HOOCCH_2(CH_2)_5CH_2Te$). ^{13}C NMR (400MHz, D_2O, 298 K), δ (ppm): 184.2 (1C, s, *C*OOH), 38.4 (1C, s, CH_2COOH), 29.0-32.5 (1C, s, $TeCH_2$ $(CH_2)_4CH_2CH_2COOH$), 26.7 (1C, s, CH_2CH_2COOH), 23.7 (1C, s, TeCH_2). ^1H NMR (400 MHz, $CDCl_3$, 298 K): 3.49(4H, t, TeCH_2), 2. 36(4H, t, CH_2COOH), 2.15(4H, t, Te CH_2CH_2), 1.69-1.38(16H, m, $HOOCCH_2(CH_2)_5CH_2CH_2Te$). ESI-MS: *m/z* Calcd. $C_{16}H_{29}O_5Te^-$, 433.11, $(C_{16}H_{28}O_5Na_2Te)^{2-}$, 238.04, found $(M+O)^-$ 433.11, $(M+ O+2Na)^{2-}$ 238.07.

After oxidation by 10 equiv. H_2O_2 ^1H NMR (400 MHz, D_2O, 298 K) δ (ppm): 2.98(4H, t, TeCH_2), 2. 19(4H, t, CH_2COOH), 1.88(4H, t, Te CH_2CH_2), 1.82-1.25(16H, m, $HOOCCH_2(CH_2)_5CH_2Te$). ^{13}C NMR (400MHz, D_2O, 298 K), δ (ppm): 184.2 (1C, s, *C*OOH), 38.4 (1C, s, CH_2COOH), 29.0-32.5 (1C, s, $TeCH_2$ $(CH_2)_4CH_2CH_2COOH$), 26.7 (1C, s, CH_2CH_2COOH), 25.0 (1C, s, TeCH_2), ^1H NMR (400 MHz, $CDCl_3$, 298 K) 3.53(4H, t, TeCH_2), 2. 36 (4H, t, CH_2COOH), 1.88(4H, t, Te CH_2CH_2), 1.80-1.32(16H, m, $HOOCCH_2(CH_2)_5CH_2Te$). ESI-MS*: m/z* Calcd. $C_{16}H_{29}O_6Te^-$, 447.10, found $[M+2O]^-$ 447.10.

Preparation of the PEG-PUTe-PEG micelles. The polymer micelles were prepared by dialysis methods as reported before. The polymers were dissolved in DMF first and then added dropwise in to deionized water. The suspension were then sealed in dialysis bag (MWCO 3500) and dialyzed against deionized water for 24 h.

Oxidation of the PEG-PUTe-PEG micelles. The micelle suspension was sealed in dialysis bag with MWCO of 7000 and then immersed in H_2O_2 of different concentrations, 0.1 mM and 3 mM. The whole vial was stored in shaking table at 37 ^oC. For DLS measurements, the samples were taken out at desired time intervals to perform the tests and then returned to the dialysis bags. For the ^1H NMR analysis, the micelle suspension was freeze dried and dissolved in chloroform-d.

Before oxidation, ^1H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm): 4.15(4H, b, NHCOOCH_2), 3.66(4H, b, OCH_2CH_2 of PEG), 2.62(4H, b, TeCH_2), 2.18(4H, b, $TeCH_2CH_2$), 1.80-1.21 (32H, b, $NHCOOCH_2(CH_2)_8$ CH_2CH_2Te).

After oxidation for 16 h, ^1H NMR (600 MHz, $CDCl_3$, 298 K) δ (ppm): 4.15(4H, b, NHCOOCH_2), 3.66(4H, b, OCH_2CH_2 of PEG), 3.50(4H, b, TeCH_2), 2.18(4H, b,

$TeCH_2$*CH_2*), 1.80-1.21 (32H, b, $NHCOOCH_2$*$(CH_2)_8$* CH_2CH_2Te).

2 DETAILED CHARACTERIZATION.

2.1 Morphological change of the PEG-PUTe-PEG micelles after treated with 100 μM H_2O_2 for 60 h.

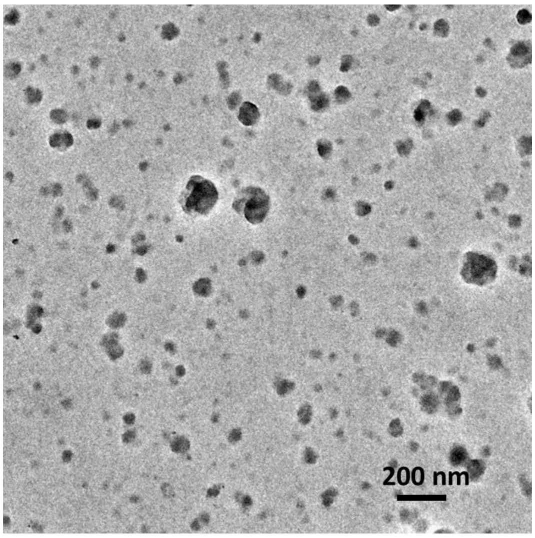

Figure S1. The TEM image of the PEG-PUTe-PEG micelles after treated with 100 μM H_2O_2 for 60 h.

2.1 Characterization for the model compounds for cyclic voltammetry.

2.1.1 The tellurium-containing molecule.

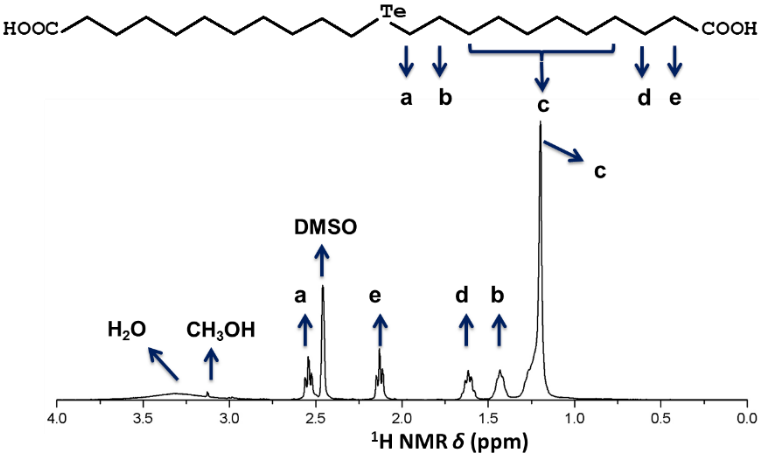

Figure S2. ^1H NMR spectrum of the tellurium-containing molecule (400MHz, DMSO).

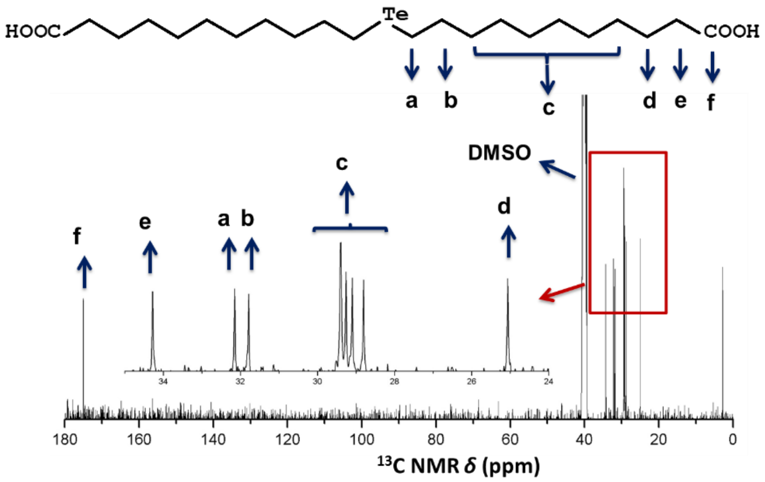

Figure S3. ^{13}C NMR spectrum of the tellurium-containing molecule (400MHz, DMSO).

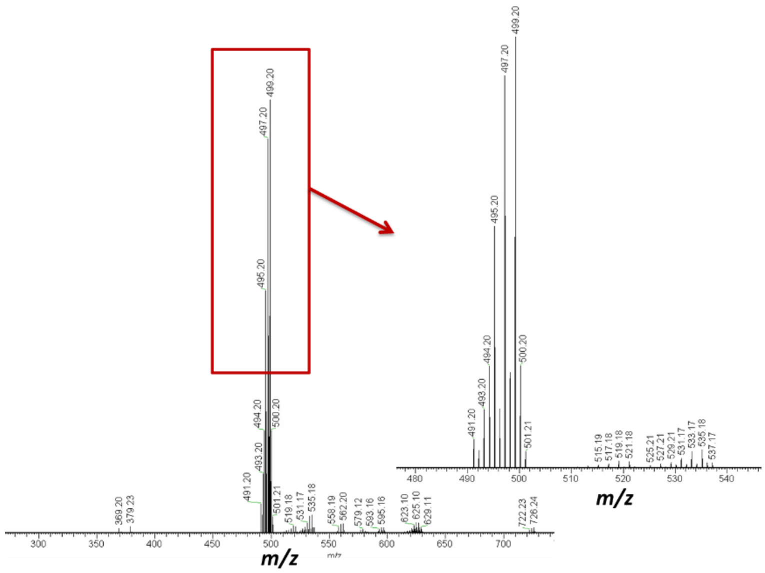

Figure S4. ESI-MS spectrum of the tellurium-containing molecule.

The selenium-containing molecule.

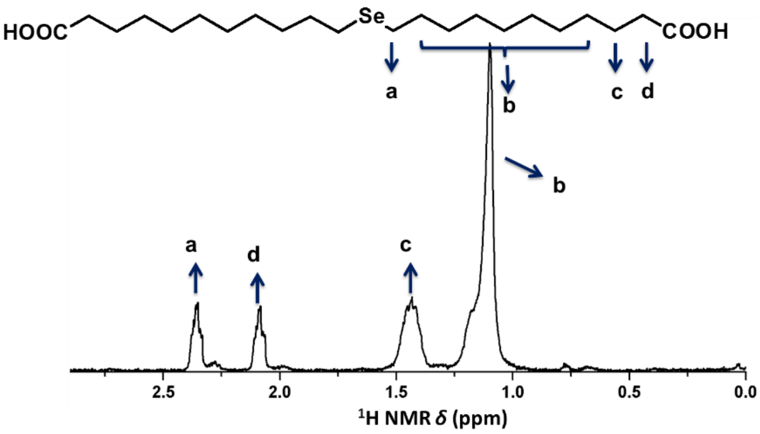

Figure S5. ^{1}H NMR spectrum of the selenium-containing molecule (400MHz, $CDCl_3/CD_3OD$).

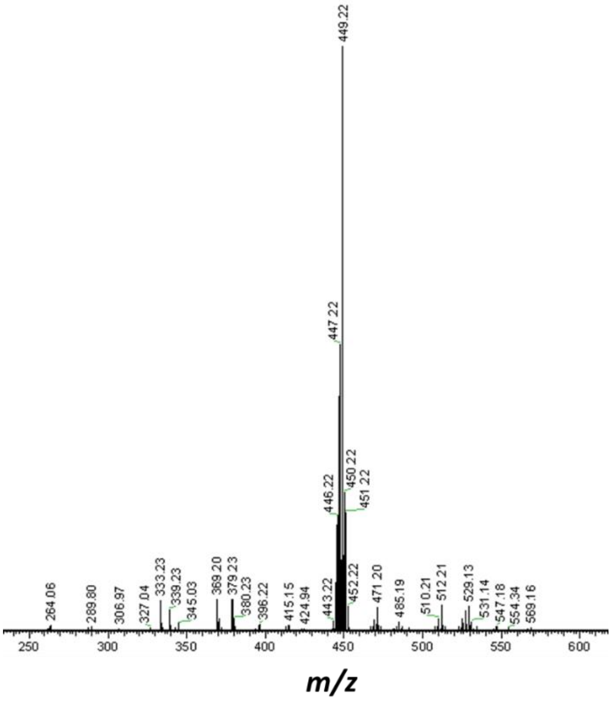

Figure S6. ESI-MS spectrum of the selenium-containing molecule.

The sulfur-containing molecule.

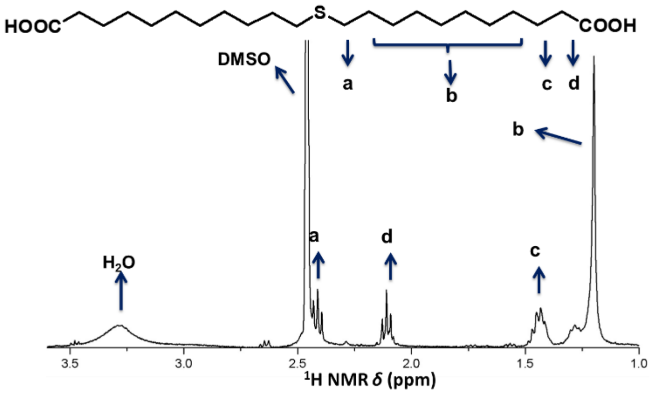

Figure S7. ^{1}H NMR spectrum of the sulfur-containing molecule (400MHz, DMSO).

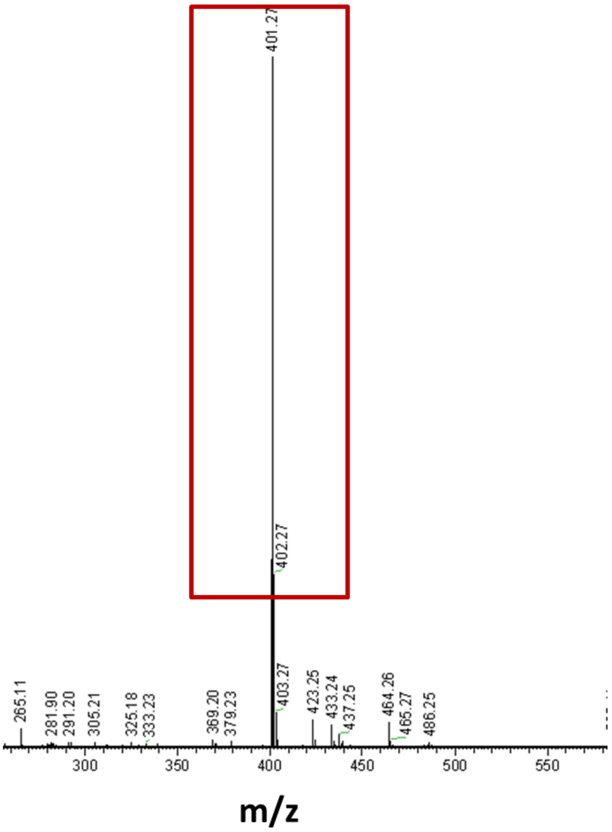

Figure S8. ESI-MS spectrum of the sulfur-containing molecule.

2.3 Cyclic voltammetry characterization of the sulfur-containing compound.

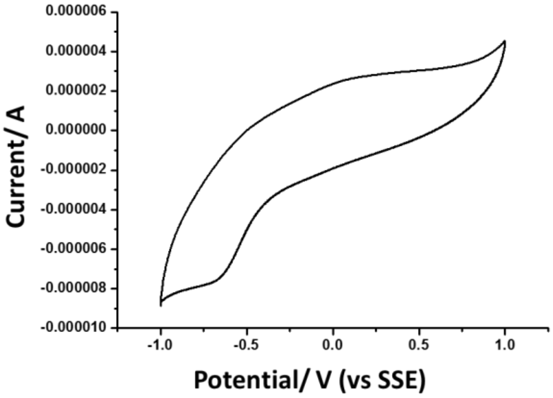

Figure S9. Cyclic voltammetry curves of the sulfur-containing model compounds in pH 9.2 buffer (0.4 mM).

2.4 Detailed analysis of the oxidation products of m-Te7COOH.

2.4.1 ESI-MS spectra of the product of m-Te7COOH and 1 equivalent H_2O_2.

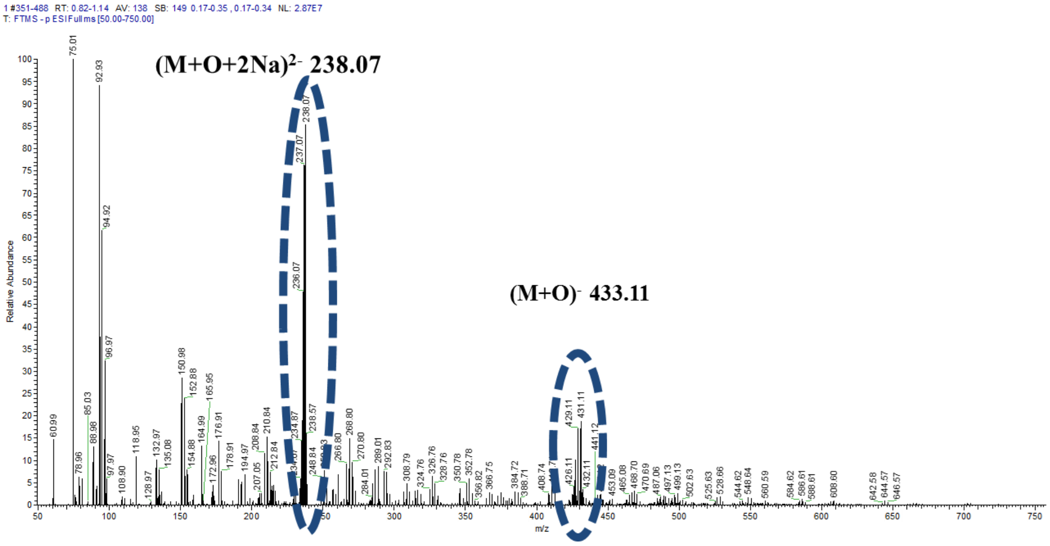

Figure S10. Negative ESI-MS spectra of the product of m-Te7COOH and 1 equivalent H_2O_2. ESI-MS*: m/z* Calcd. $C_{16}H_{29}O_5Te^-$, 433.11, $(C_{16}H_{28}O_5Na_2Te)^{2-}$, 238.04, found $(M+O)^-$ 433.11, $(M+O+2Na)^{2-}$ 238.07.

2.4.2 ESI-MS spectra of the product of m-Te7COOH and 10 equivalent H_2O_2.

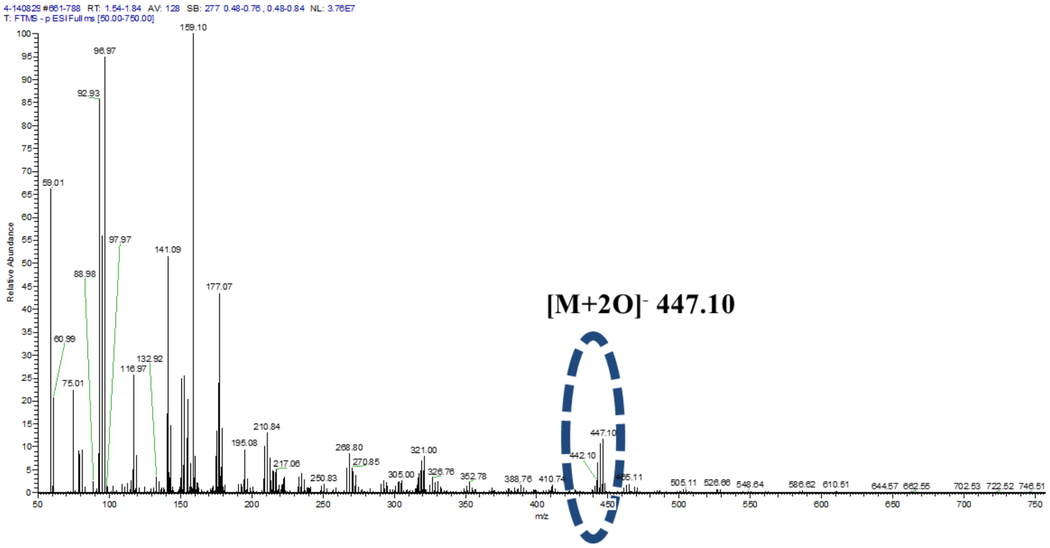

Figure S11. Negative ESI-MS spectra of the product of m-Te7COOH and 10 equivalent H_2O_2. ESI-MS: *m/z* Calcd. $C_{16}H_{29}O_6Te^-$, 447.10, found $[M+2O]^-$ 447.10.

2.4.2 NMR spectra in D_2O of the oxidation reaction with different amount of H_2O_2 added.

To study the exact oxidation chemistry, systematic investigations were carried out on another tellurium-containing model small molecule, m-Te7COOH. Compared with the model for the electrochemical measurement, the molecules m-Te7COOH were slightly modified by shortening the alkyl chains so as to increase the water solubility. The molecules could dissolve well in neutralized water with concentration as high as 10 mM, which makes it ideal for the further characterization. The oxidation reaction of m-Te7COOH could be monitored by ^{1}H NMR to see the exact structural changes in molecules. With 1 equivalent H_2O_2 added into the D_2O solution of m-Te7COOH, the peak for the α protons of Te atoms in reduced states at 2.70 ppm downshifted to 2.85 ppm in Fig S12. It should be highlighted that this reaction is quite fast and could complete within 1 h. With increasing amount of H_2O_2, the 2.85 ppm signals gradually disappeared while new peaks at 2.98 ppm arised, which was anticipated to be the result of the higher oxidation state of tellurium atoms. Tellurium can be oxidized to IV or further to VI states in the presence of oxidants. Secondly, corresponding to the ^{1}H NMR results, ^{13}C NMR also supported the oxidation reaction. As shown in Fig S13, in the reduced state, the chemical shift of the α carbon of Te atom was 3.7 ppm, which is the typical position for alkane telluride compounds. It downshifted to 23.7 ppm after treatment with 1 equivalent H_2O_2, and further downshifted to about 25.0 ppm with the addition of 10 equivalent H_2O_2. The dramatic downshifts should be due to the deshielding effects of the oxygen atoms. Additionally, to acquire more information on the constitution of organotelluride species involved in these reactions, ESI-MS measurements were carried out to determine their molecular weight. When treated with 1 equivalent H_2O_2, ionic peaks at 431.11 was found with typical isotopic peaks, and corresponded to m-Te7COOH with one oxygen atom added (see supporting information Fig S10). While with 10 times more H_2O_2, the molecules with 2 oxygen atoms added was identified (see supporting information Fig S11). Therefore, we can conclude that the telluride compound could react with hydrogen peroxide easily and that it could be oxidized into different states with increasing amount of H_2O_2. The first step of oxidation was rapid, which may account for the quick response to ROS of the polymer micelles. While the second step took longer time, thus the decrease in size happened after almost a whole day when incubated in 100 μM H_2O_2. Further decomposition of the telluride molecules could be observed after treated with H_2O_2 for even longer time, around one week.

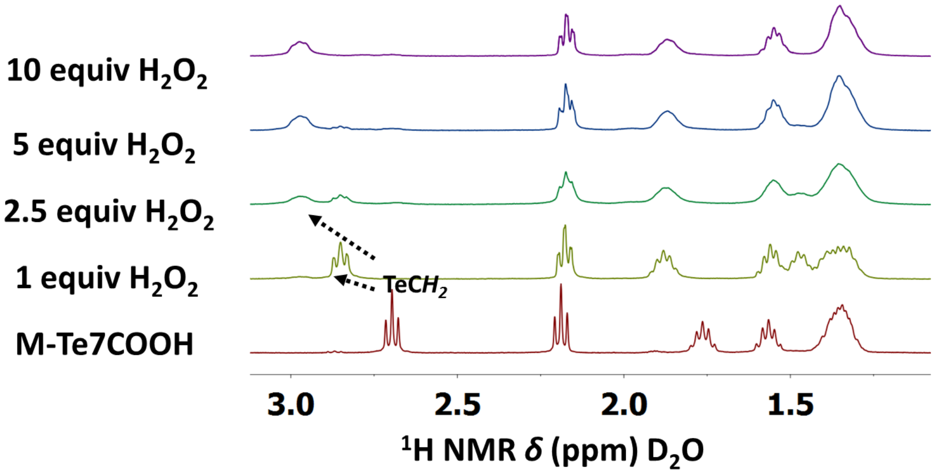

Figure S12. ^{1}H NMR characterizations for the reaction of module compound m-Te7COOH with H_2O_2 of different amounts.

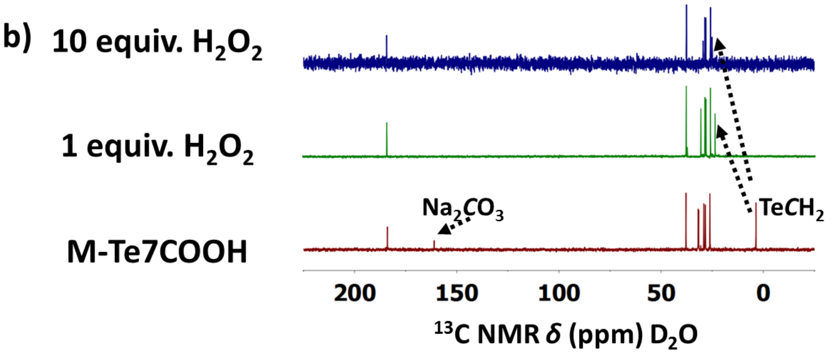

Figure S13. ^{13}C NMR spectra with D_2O as the solvent at 298 K for the reaction of model compound m-Te7COOH with H_2O_2 of different amounts (Na_2CO_3 was added to deprotonate the sample for better solubility).

2.4.3 ^{1}H NMR spectra in chloroform-d of the oxidation reaction.

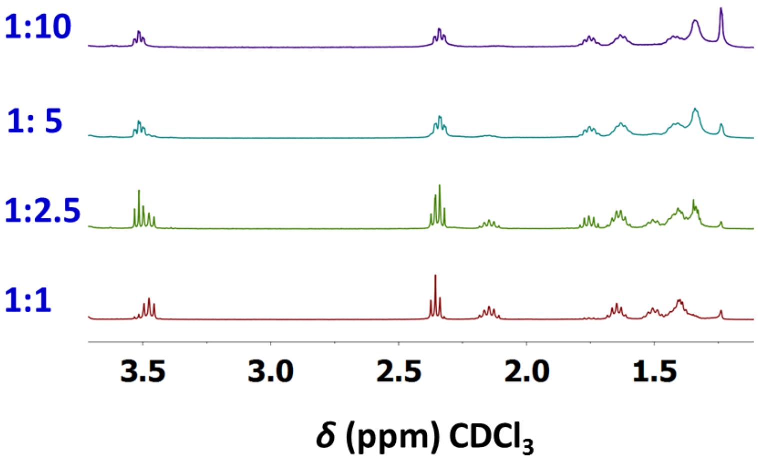

Figure S14. ^{1}H NMR spectra of m-Te7COOH and different amount of H_2O_2 in chloroform-d.

2.5 DLS analysis of the size change of PEG-PUTe-PEG micelles after treated with 3 mM H_2O_2.

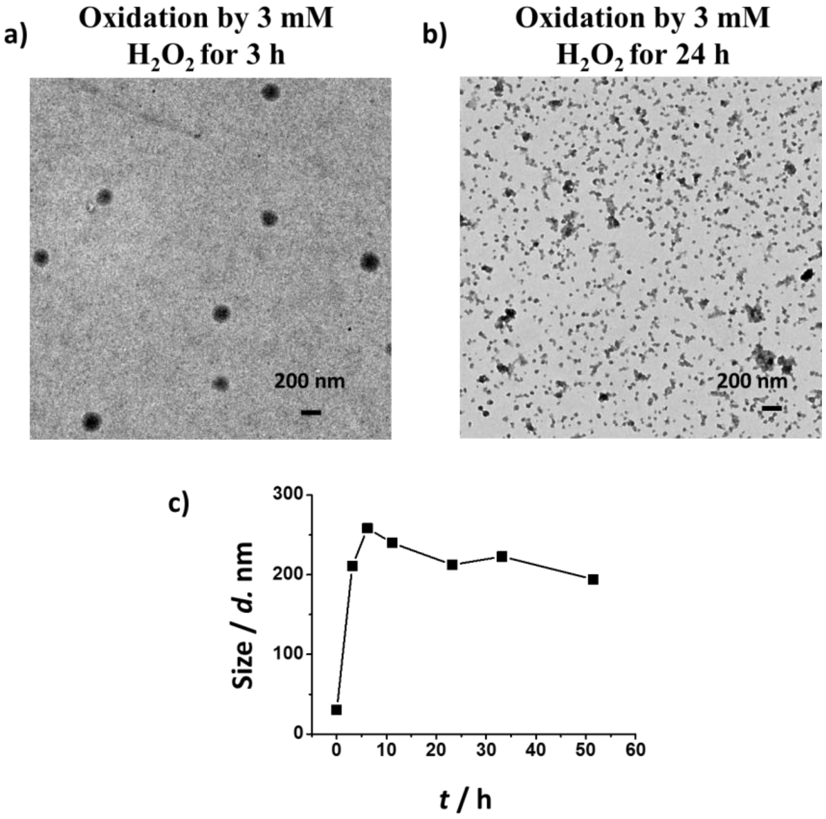

Figure S15. Oxidation responsiveness to 3 mM H_2O_2 of the tellurium-containing polymer micelles. a) TEM images of the tellurium-containing polymer micelles after oxidation by 3 mM H2O2 for 3 h and b) 24 h. c)The size changed a lot after treated with as 3 mM H_2O_2.

2.6 Stability of the PEG-PUTe-PEG micelles under ambient environments.

To further testify the trend in ROS responsive morphological changes of the PEG-PUTe-PEG micelles, the H_2O_2 concentration was elevated to 3 mM and the self-assembly behaviors were studied continuously over time. The hydrodynamic diameter of the micelles also increased a lot from 30 nm to 210 nm in the first 2 hours. The swelling could be observed clearly with TEM. As a result of the higher oxidant concentration, the turning point from swelling state to irregular aggregates was earlier. As shown in Fig S15c, after about 6 h, the micelles began to decrease in size. As shown by TEM images in Fig S15 a and b, the size decrease was ascribed to the oxidation-induced transformation into irregular aggregates. So it could be concluded that with higher oxidant concentration, the tellurium-containing polymer could be oxidized faster, and the variation in morphology, which showed similar trend, also took place in shorter time.

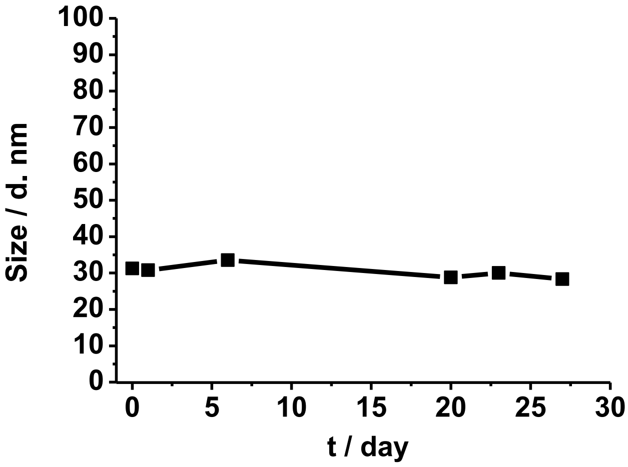

Figure S16. DLS data of the micelles in one month.

References.

1 W. Cao, L. Wang and H. Xu, *Chem. Commun.*, 2015, DOI: 10.1039/C1034CC08588D.