

Stability Study of Hypervalent Tellurium Compounds in Aqueous Solutions

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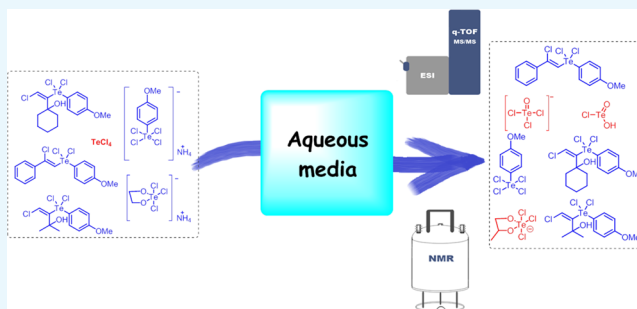
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Supporting Information

ABSTRACT: Hypervalent tellurium compounds (telluranes) are promising therapeutical agents with negligible toxicities for some diseases in animal models. The C–Te bond of organotellurium compounds is commonly considered unstable, disfavoring their applicability in biological studies. In this study, the stability of a set of telluranes composed of an inorganic derivative and noncharged and charged organic derivatives was monitored in aqueous media with ¹H, ¹³C, and ¹²⁵Te NMR spectroscopy and high-resolution mass spectrometry. Organic telluranes were found to be remarkably resistant and stable to hydrolysis, whereas the inorganic tellurane AS101 is totally converted to the hydrolysis product, trichlorooxytellurate, [TeOCl₃][−], which was also observed in the hydrolysis of TeCl₄. The noteworthy stability of organotelluranes in aqueous media makes them prone to further structure–activity relationship studies and to be considered for broad biological investigations.



INTRODUCTION

Tellurium is a rare element narrowly studied in a biological context. A general belief that all its compounds are toxic impairs interest in further exploring their biological activities and applications in therapy. Although toxicity data of elemental tellurium, tellurite, and tellurate are known,¹ only a few organic tellurides and ditellurides were studied in this context.² In contrast to this, there are therapeutically promising examples of inorganic and organic tellurium compounds showing reduced toxicity and potent activities in both *in vitro* and *in vivo* models.^{2–4} The most studied tellurium-containing compound is the inorganic tellurane named AS101, an ammonium tellurate, which presents immunomodulatory action³ and was found to be active in preclinical and clinical studies.⁴ In addition to the known cellular pathways modulated by AS101, the high affinity of the hypervalent tellurium atom with thiols consists the molecular basis of its effects. This affinity was demonstrated by NMR studies of AS101 with cysteine and in the inhibition of cysteine-based proteases (papain and pig spleen cathepsin B) by Albeck and co-workers in 1998.⁵ In the following, we have shown that organic derivatives of tellurium(IV), having ligands prone to exchange-type reactions, were very potent inhibitors of recombinant human cathepsin B, up to 40-fold in the relative second-order Cat.B inhibition rate constants (k_i/K_i) compared to AS101.⁶ After that, the inhibitions of recombinant human

cathepsins B, L, S, and K were determined for an expanded set of diverse organotelluranes, including the inorganic derivatives AS101, a brominated AS101 derivative, and benzyltriethylammonium hexachlorotellurate.⁷ These studies have shown that the inhibition potency is modulated by the organic moieties and by the exchangeable ligands bonded to the tellurium atom. The influence of halides (chloride and bromide) on the inhibition of cathepsins V and S for a structurally related set of organotelluranes showed that the bromides were always more reactive than the chlorides because they led to higher k_i/K_i values, and the corresponding selenuranes were less reactive than the tellurium homologues but showed the same trend as the halides.⁸ It was found that organotelluranes are able to inhibit tyrosine phosphatases,⁹ the β_2 site of proteasome (*trypsin*-like activity),¹⁰ to promote the intracellular proteolysis in *Plasmodium falciparum* trophozoites,¹¹ to impair the bioenergetics of mitochondria elicited by thiol consumption, and to induce the assembly and opening of mitochondrial permeability transition pore¹² and, like AS101, have shown negligible toxicity for animal models so far. Additional activities include *in vitro* antiviral,¹³ antitumoral,¹⁴ and the *in vivo*

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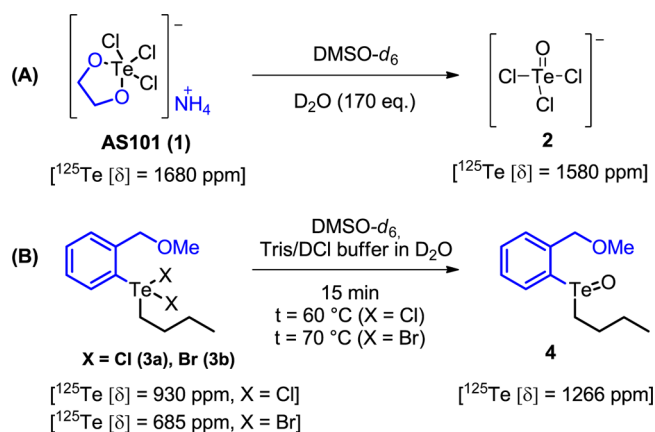
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protection of rats in pilocarpine-induced epilepsy,¹⁵ as well as antileishmanial action in animal models of cutaneous¹⁶ and visceral leishmaniasis.¹⁷

The particular reactivity of telluranes with thiols was previously studied for a few examples of both inorganic and organic derivatives in model reactions. Thiol consumption in such reactions was followed by colorimetric assays^{5–7} and by ¹²⁵Te NMR spectroscopy,^{6,10,18} as changes in chromophores or in the observed tellurium species involved giving insights about ongoing processes. As telluranes have been shown to be promising potential therapeutic agents,^{2–4,11–17} a primary concern consists in their behavior, including stability in aqueous media because hydrolytic products can exhibit distinct reactivity profiles for bionucleophiles. Recently, it has been shown that **AS101** (**1**) is hydrolyzed forming a trichlorooxytellurate (**2**), which is suggested to be the actual inorganic tellurane involved in **AS101** bioactivities (Scheme 1).¹⁹ The stabilities of two

Scheme 1. Reported Conversion of the Inorganic Tellurane AS101 (A) and Organic Telluranes (B) in Aqueous Media to Hydrolysis Products and Their ¹²⁵Te Chemical Shifts



organotelluranes in a buffered medium were monitored by NMR spectroscopy, and both dichloride **3a** and dibromide **3b** were converted to the corresponding telluroxide **4** above 60 and 70 °C, respectively, suggesting that those derivatives are very stable in an aqueous environment (Scheme 1).²⁰

These reports stimulated us to share our results on the stabilities of a set of telluranes depicted in Chart 1. This collection has two telluranes (**8a** and **8b**) with a hydroxyl group, which is coordinated to tellurium, another tellurane **8c**

that lacks a strong intramolecular n-donor group, the ammonium(oxo)trichlorotellurate **AS101** (**1**) and the ammonium tetrachloroaryl tellurate **7**. A systematic study was performed varying the tellurane, the nature of the solvent, and reaction temperature. All experiments were monitored by ¹H, ¹³C, and ¹²⁵Te NMR spectroscopy and mass spectrometry.

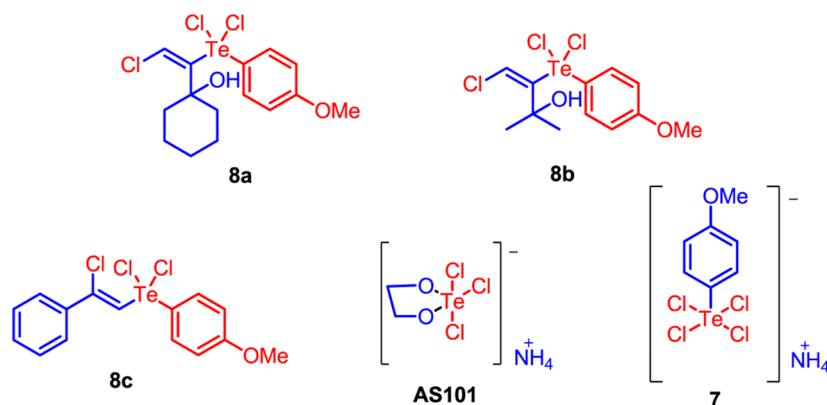
RESULTS AND DISCUSSION

The organotelluranes were prepared by electrophilic addition reactions of tellurium tetrachloride **5**, under microwave irradiation, to the corresponding alkynes or anisole.²¹ Tellurium tetrachloride was prepared by an improved reaction under microwave irradiation using elemental tellurium and sulfuric chloride.²² **AS101** (**1**) was prepared by refluxing a suspension of tellurium tetrachloride and an equimolar amount of ethylene glycol in acetonitrile.²³ Tellurium tetrachloride was submitted to reaction with anisole under microwave irradiation to furnish *p*-methoxyphenyltellurium trichloride (**6**),²⁴ the starting material of the organic telluranes. The trichloride **6** was treated with aqueous hydrogen chloride solution (6 mol/L) followed by reaction with aqueous ammonium chloride to provide ammonium (*p*-methoxyphenyl)tetrachlorotellurate (**7**) in 93% yield.²⁵ Finally, the remaining organotelluranes were prepared by the electrophilic addition reactions of trichloride **6** to the appropriated alkynes under microwave irradiation (Scheme 2).²¹

With compounds **5–8** and **AS101** in hand, we performed a systematic study of their stabilities in organic solvents in the absence and the presence of water. Initially, **AS101** was evaluated in aqueous and alcoholic solutions, as previously described by Silberman and co-workers.¹⁹ A 0.44 mol/L dimethyl sulfoxide (DMSO)-*d*₆ solution of **AS101** was treated with successive additions of D₂O, and 5 min after each addition, the corresponding ¹²⁵Te NMR spectra were recorded. Thus, as 2 equiv of D₂O were added, two species were detected resonating at 1680 and 1520 ppm, relative to **AS101** and a hydrolysis product, [TeOCl₃][−], respectively. After this, 10 equiv of D₂O were added to the same tube and the signals at 1680 and 1520 ppm were attenuated, whereas a new specie resonating at 1650 ppm appeared. In a control experiment, a DMSO-*d*₆ solution of TeCl₄ (0.44 mol/L) treated with 1 equiv of deuterated water led to a tellurium specie, which resonated at 1520 ppm, similarly to what was observed for **AS101** solution strongly supporting the presence of [TeOCl₃][−] (Figure 1).

The characterization of these species was further done by high-resolution mass spectrometry-electrospray ionization

Chart 1. Structures of Studied Telluranes



Scheme 2. Synthesis of Telluranes 8a–c, Tellurate 7, and AS101

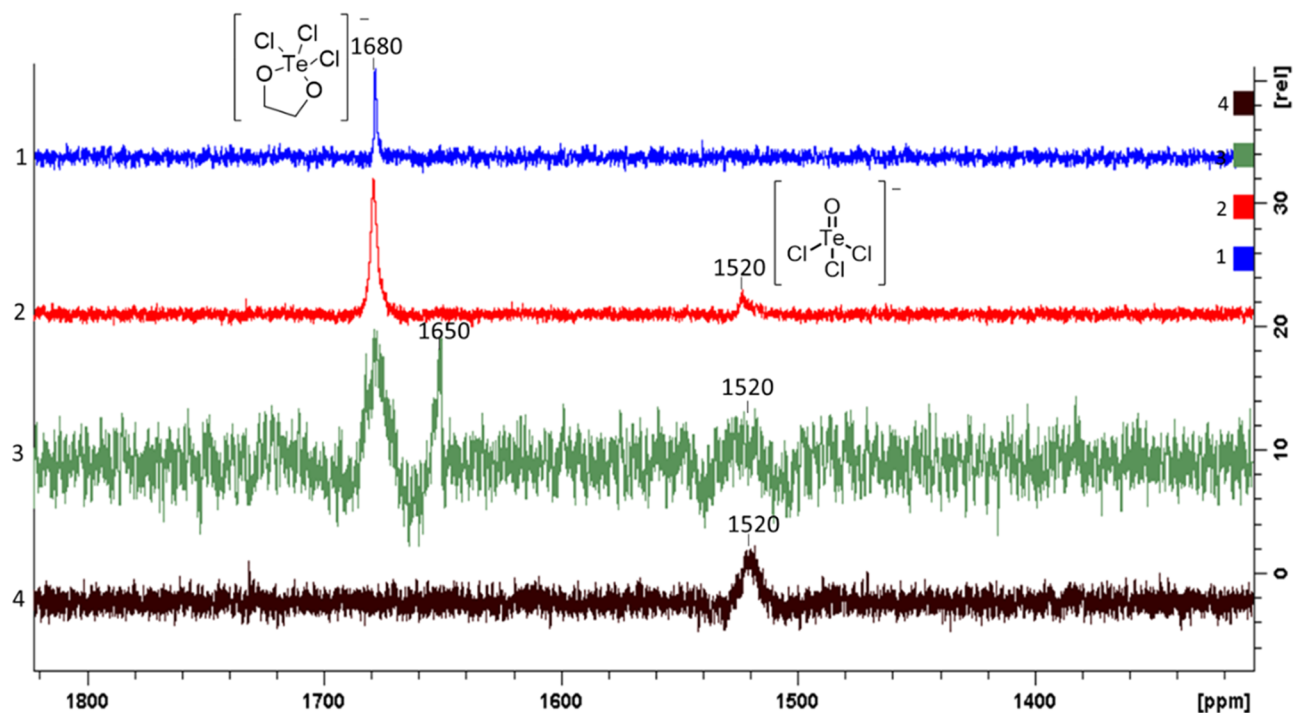
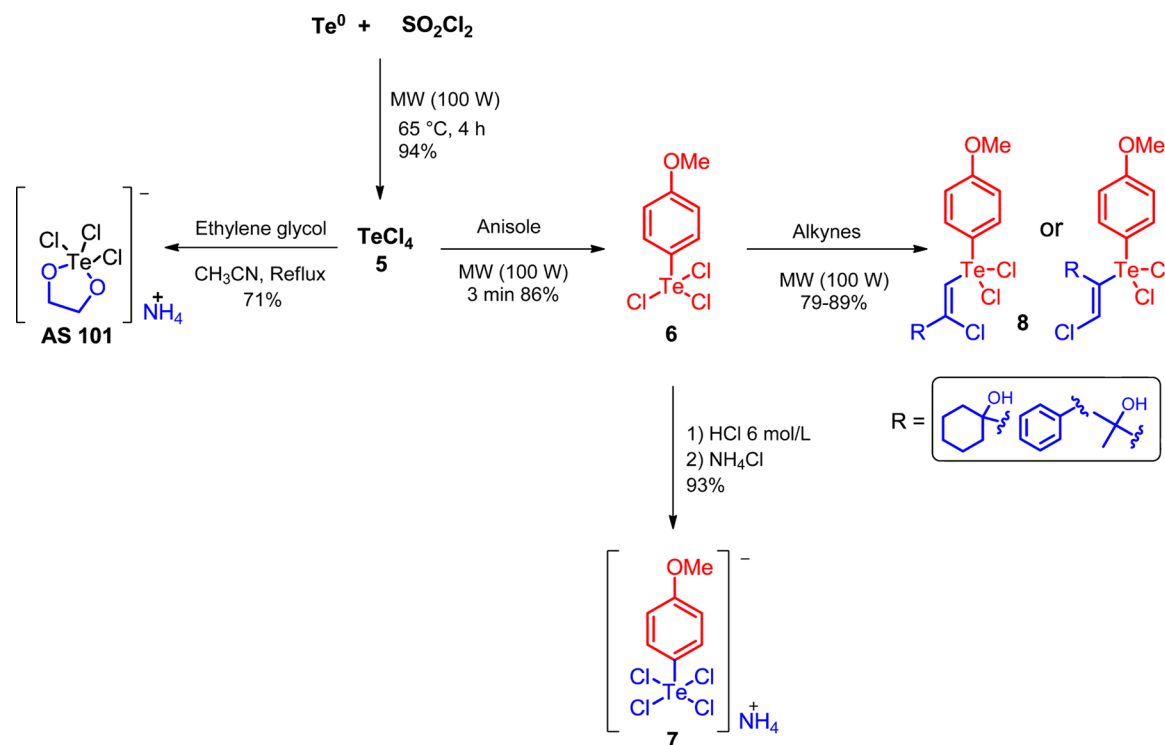


Figure 1. (1) ^{125}Te NMR spectrum of AS101 in $\text{DMSO-}d_6$. (2) ^{125}Te NMR spectrum of AS101 in $\text{DMSO-}d_6$ and 2 equiv of D_2O . (3) ^{125}Te NMR spectrum of AS101 in $\text{DMSO-}d_6$ and 10 equiv of D_2O . (4) ^{125}Te NMR spectrum of TeCl_4 in $\text{DMSO-}d_6$ and 1 equiv of D_2O .

(HRMS-ESI(-)) analyses, where AS101, $[\text{TeOCl}_3]^-$, and a chlorotellurinic acid, $[\text{HTeClO}_2]^-$, were detected in the solution treated with 2 equiv of water (Figure 2A). Other hydrolysis products were detected when the amount of added water reached 100 equiv, which led to the formation of $[\text{HTeO}_2]^-$ as a majority specie (Figure 2B).

The hydrolytic profile of AS101 observed by us is in accordance with that reported by Silberman and co-workers.¹⁹ The ligand-exchange processes of AS101 were further studied using propylene glycol and ethanol. The reaction of AS101 with propylene glycol led to a rapid formation of a major specie, resonating at 1690 ppm, resulting from the transacetalization of

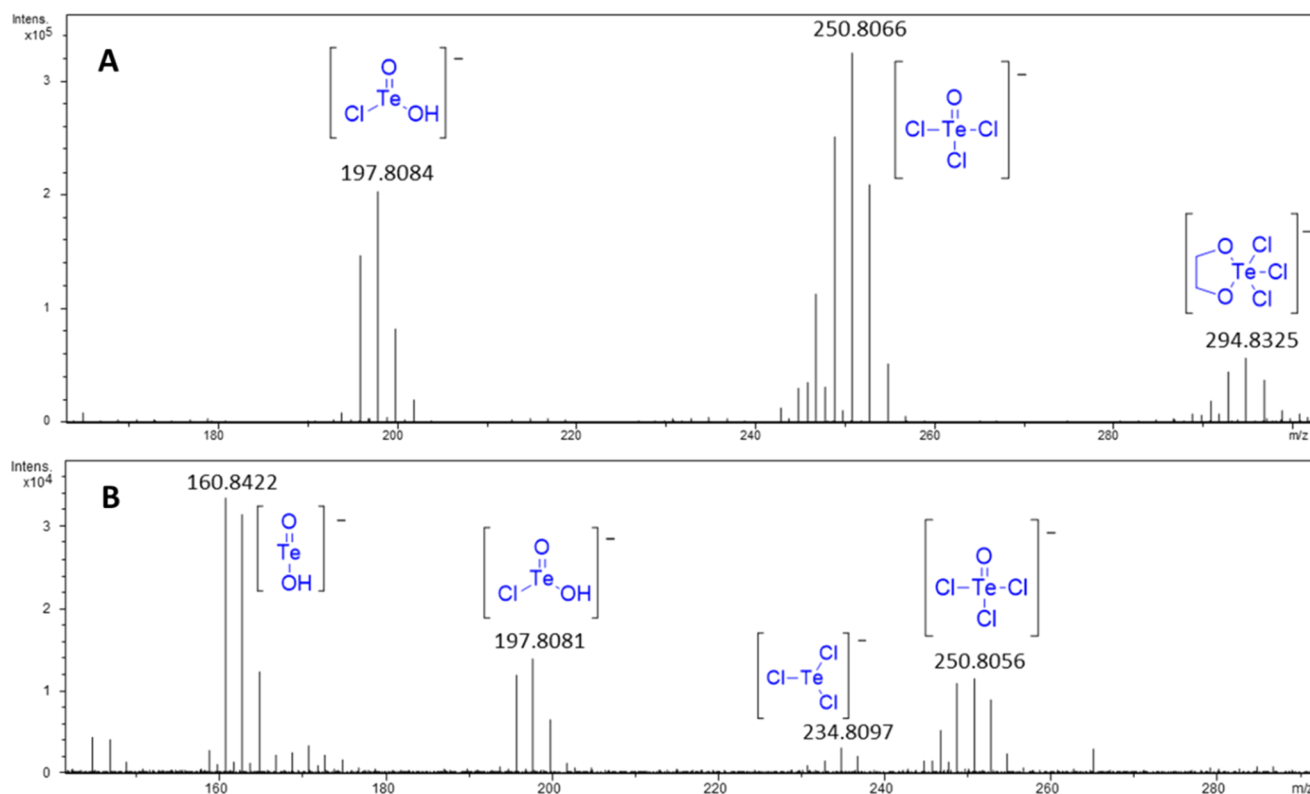


Figure 2. HRMS-ESI(-) spectra of AS101 after treated with (A) 2 equiv and (B) 100 equiv of water.

AS101 to the propylene glycol analogue, as confirmed by the HSMS-ESI(-) spectrum (Figure S1).

The reaction of AS101 with ethanol was checked by HRMS-ESI(-), where a mixture of AS101 hydrolysis products, $[\text{HTeClO}_2]^-$ and $[\text{TeOCl}_3]^-$, AS101, and ethoxytetrachlorotellurate, $[\text{EtOTeCl}_4]^-$, were observed (Figure S2).

To this solution, after the addition of 100 equiv of water, the total consumption of AS101 as the monoethoxylated tellurate was suppressed, leading to the same mixture observed by AS101 hydrolysis (Figure S6). Although this set of experiments supports the instability of inorganic telluranes, which are prone to rapid hydrolysis and ligand-exchange reactions, the biological effects of AS101 and the reactivity of tellurium toward thiols and related processes are still devoid of clarification.

At this point, we moved our attention to the stability of the organotelluranes starting with the ammonium tetrachloroaryl tellurate (7) that exhibited a surprising stability in comparison to AS101 under identical conditions. The ^{125}Te NMR spectrum of 4 in DMSO-*d*₆ shows a signal at 1241 ppm relative to the reference signal of PhTeTePh. The successive addition of 25% in volume of phosphate-buffered saline (PBS) solution did not change the HRMS-ESI(-) and ^{125}Te NMR spectra even after 30 days at 25 °C (Figure 3). The successive addition of D₂O to the DMSO-*d*₆ solution of 7 in a separate experiment also did not furnish any new specie. These results evidence the higher stability of the tellurate 7 toward hydrolysis relative to AS101.

The neutral organotelluranes 8a–c were then studied to check their stability toward an aqueous environment. A control experiment consisting in a DMSO-*d*₆ (0.26 mol/L) solution of 8a and D₂O solution of 8a (90:10 v/v) has been maintained on the lab bench, and ^1H , ^{13}C , and ^{125}Te NMR spectra were recorded for over 2 years, showing no extent of decomposition and hydrolysis. This astounding result encouraged us to carry

out further experiments with organotelluranes 8a–c monitoring possible hydrolysis reactions. All experiments were performed in NMR tubes containing 0.25 mol/L solutions of compounds 8a–c in a DMSO-*d*₆/D₂O (90:10) mixture using diphenylditelluride as an external reference. NMR spectra were recorded in the course of 30 days (initially on a daily basis for 1 week and on a weekly basis for 1 month). As shown in the ^{125}Te NMR spectra, the telluranes 8a–c were remarkably stable toward hydrolysis in these solutions (Figures 4–6).

In addition to that, the organotellurane 8a was held in a DMSO-*d*₆/PBS buffer (pH 7.4) mixture and monitored over the course of 4 days varying the incubation temperatures in three independent experiments. In the first experiment, the solution was maintained at 25 °C for 2 h (Figure 7A); in the second experiment, the solution was incubated at 40 °C for 48 h (Figure 7B). Finally, the solution was incubated at 40 °C for 96 h (Figure 7C). In all cases, the organotellurane 8a remained intact.

In a further experiment, the stability of compound 8a was checked in acidic media. In a 5 mm NMR tube, 50 mg of compound 8a was diluted in a mixture of DMSO-*d*₆ (300 μL) and HCl (30 μL, 6 mol/L), the solution was maintained at 25 °C for 24 h, and after that time, compound 8a did not show any transformation. The same behavior was observed in a less acidic medium composed of a mixture of DMSO-*d*₆ and buffered acetate solution (pH 5.5). As telluranes react with bases in known reactions of diorganyl tellurium dichlorides, which are converted into dihydroxides²⁶ or oxides,²⁷ their stability in basic media is therefore worrying. Nevertheless, organotellurane 8a did not resist when challenged in concentrated basic media using sodium hydroxide (pH 12) it showed a remarkable persistence at pH 8.0 (sodium phosphate buffer) that was monitored for 6 days at room temperature.

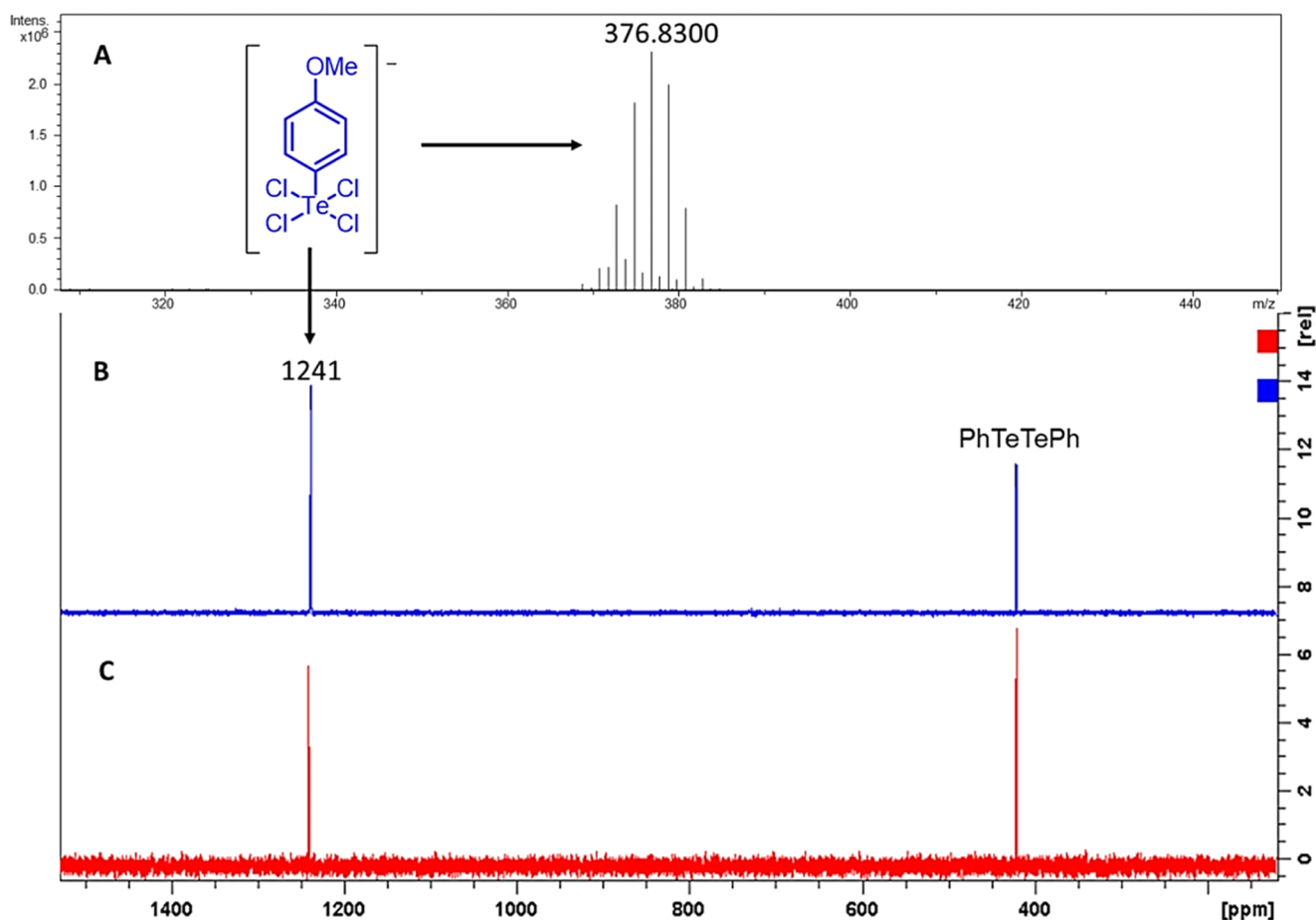


Figure 3. (A) HRMS-ESI(-) spectrum of compound **7** after 30 days in aqueous solution. (B) ^{125}Te NMR spectrum of compound **7** in $\text{DMSO-}d_6$. (C) ^{125}Te NMR spectrum of compound **7** after 30 days in $\text{DMSO-}d_6$ (300 μL) and PBS (100 μL , 1 mol/L).

Taken together, our data demonstrate a striking difference in the stabilities of inorganic and organic telluranes. As inorganic telluranes are promptly converted to other species eliminating their ligands, the organic moieties of organotelluranes are remarkably persistent in aqueous environments. In an attempt to gain insight into these differences, we performed density functional theory calculations. The Gibbs free energies, collected in Scheme S1 (see Supporting Information), were used to evaluate the relative stability of the compounds **AS101**, **7**, and **8b** against hydrolysis. The computed thermochemistry indicates that **AS101** undergoes hydrolysis more easily than compounds **7** and **8b** because it showed to be less stable than the other compounds by ~ 4 kcal/mol. Also, the charge distributions in these molecules were obtained using the Natural Population Analysis (NPA) model (Table S1). In agreement with the behavior observed in the thermochemistry results, the NPA charges indicate that the higher negative charges were observed on the ethylene glycol's oxygen atoms in **AS101**. The NPA showed that tellurium atom presents the larger positive charges of +1.894 for **AS101** and +1.450 and +1.565 for telluranes **7** and **8b**, respectively. These differences point to a more electrophilic character of **AS101**'s tellurium atom than in the organic derivatives that suffer a nucleophilic attack of water followed by the protonation of alkoxide in a stepwise mechanism yielding the $[\text{TeOCl}_3]^-$ specie.

Also, the superior stability of organotelluranes combined with a higher reactivity for biological thiols⁷ may explain in part the high biological activities but might raise concerns about

their clearance from the body. The mechanisms of organotellurium metabolism are not yet clear as for elemental tellurium and tellurite in plants and some microorganisms. In this direction, further pharmacokinetics studies are currently under way to clarify this point. On the other hand, the higher stability of tellurium organic derivatives prompts their structure–activity relationship studies due to the persistence of the organic moieties bonded to tellurium.

EXPERIMENTAL SECTION

General Information. Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Co., Matthews, NC), with a continuous focused microwave power delivery system in a glass vessel (10 or 35 mL) sealed with Teflon cap, under magnetic stirring. Analytical thin-layer chromatography for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al plates. NMR spectra were recorded on a Bruker AC 200 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Baden-Württemberg, Germany) operating at 200, 50, and 63 MHz for ^1H , ^{13}C , and ^{125}Te NMR spectroscopies, respectively. $\text{DMSO-}d_6$ was used as solvent and internal reference, tetramethylsilane for ^1H and ^{13}C NMR spectroscopies, and diphenylditelluride for ^{125}Te NMR spectroscopy, chemical shifts (δ) are given in parts per million, and coupling constants (J) are given in hertz (Hz). All reagents are of commercial grade and were pretreated whenever required (all reagents were purchased from Sigma-Aldrich

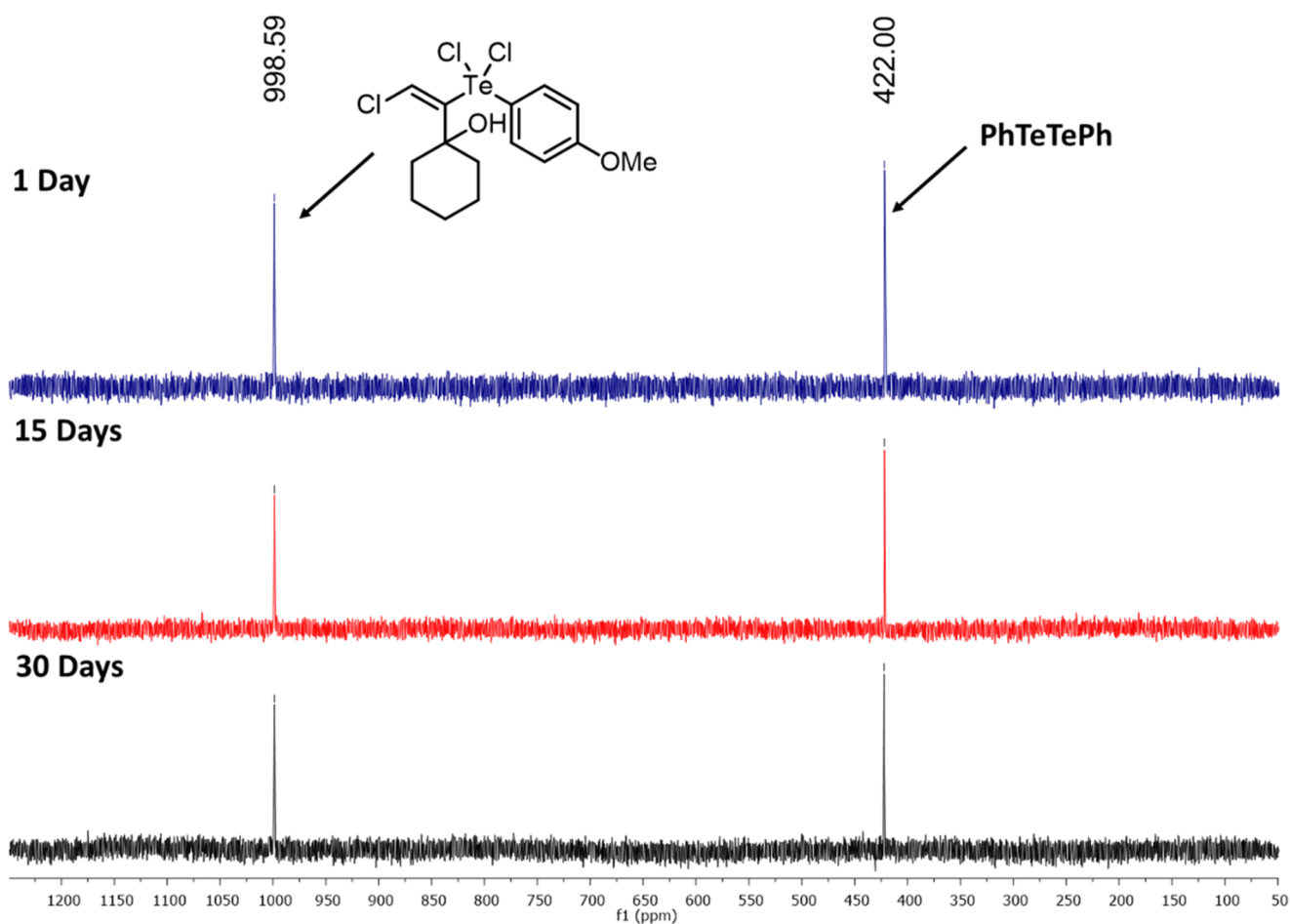


Figure 4. ^{125}Te NMR spectrum of **8a** in a DMSO- d_6 /D $_2$ O (90:10) mixture.

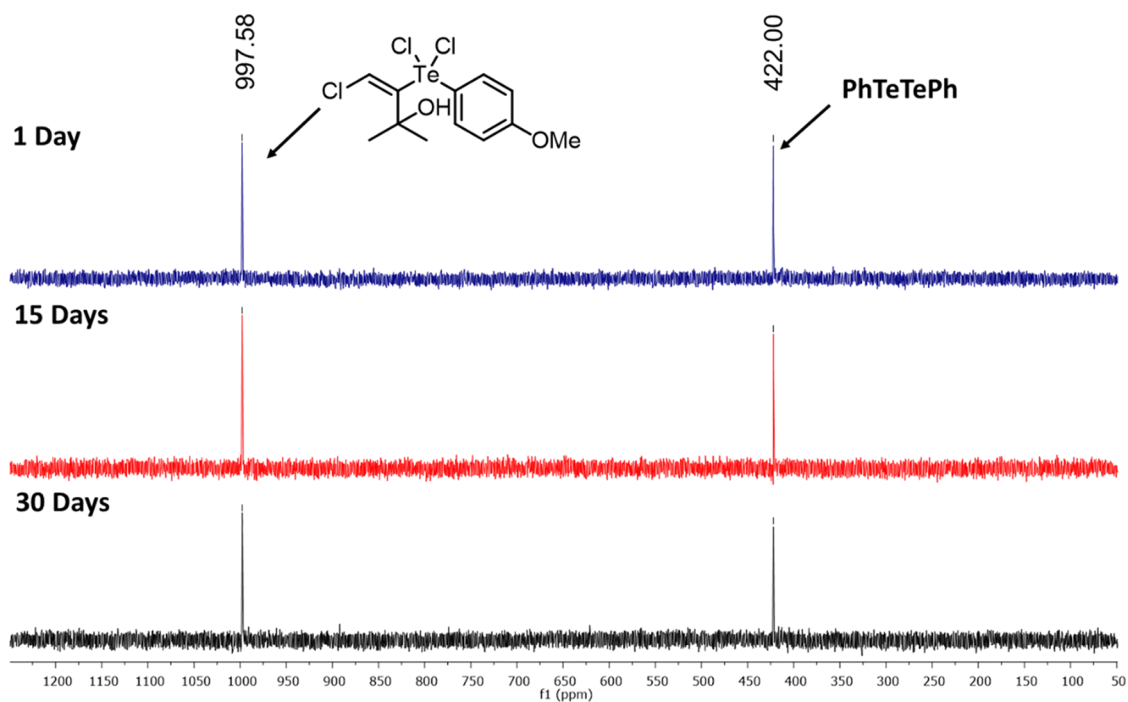


Figure 5. ^{125}Te NMR spectrum of **8b** in a DMSO- d_6 /D $_2$ O (90:10) mixture.

Co., St. Louis, MO). Compounds **8a–c**, AS101, and organotellurate **7** were prepared as previously described.^{5,21,25}

Exposure Stability Study of Tellurium Tetrachloride in Water. In a 5 mm NMR tube, 50 mg of 0.37 mmol tellurium

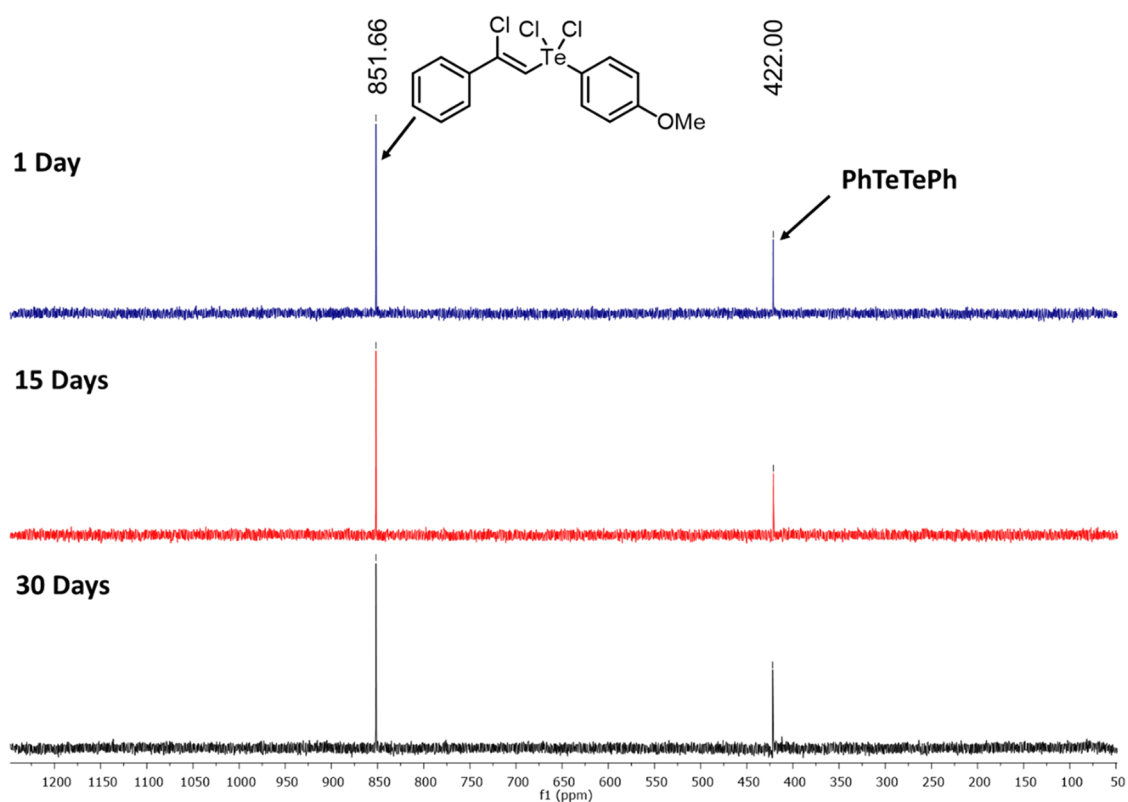


Figure 6. ^{125}Te NMR spectrum of **8b** in a DMSO- d_6 /D $_2$ O (90:10) mixture.

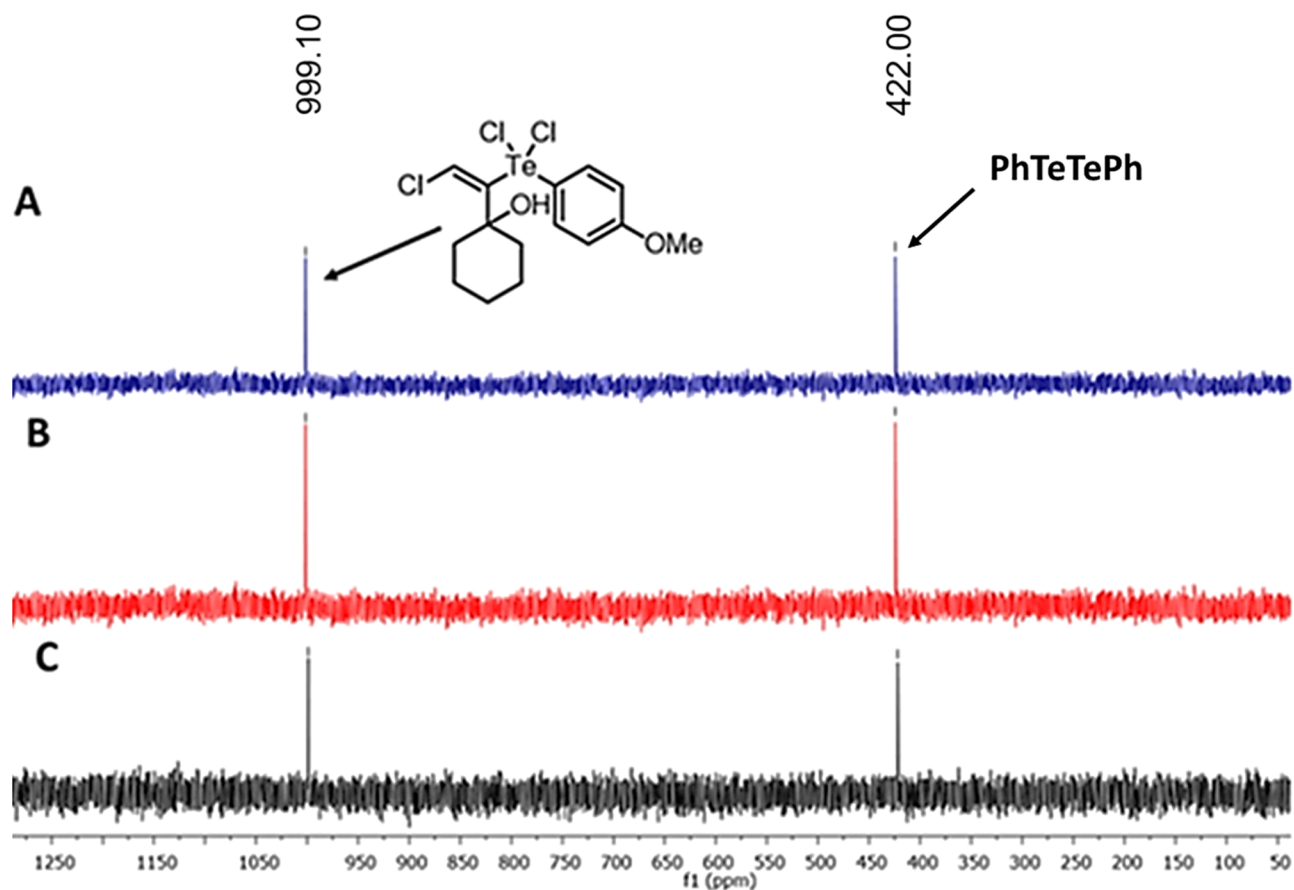


Figure 7. ^{125}Te NMR spectrum of **8a** in a DMSO- d_6 /PBS buffer (pH 7.4) mixture at (A) 25 °C after 2 h, (B) 40 °C after 48 h, and (C) 40 °C after 96 h.

tetrachloride was diluted in a 300 μL of $\text{DMSO-}d_6$ and then 1 equiv of deuterated water (7.5 μL) was added. A capillary tube of diphenylditelluride was used as a chemical shift standard. After 1 h, ^{125}Te NMR spectrum was recorded at 25 $^\circ\text{C}$.

Exposure Stability Study in Water. In a 5 mm NMR tube, 50 mg of the compound under investigation was diluted in a mixture of 360 μL of $\text{DMSO-}d_6$ and 40 μL of D_2O . A capillary glass tube containing diphenylditelluride was used as a chemical shift standard. The same sample was maintained for a period of 30 days in solution in this mixture. The ^{125}Te NMR spectrum was recorded daily for 7 days and weekly for up to 30 days.

Exposure Stability Study in PBS. In a 5 mm NMR tube, 50 mg of the compound under investigation was diluted in a mixture of 300 μL of $\text{DMSO-}d_6$ and 30 μL of D_2O . A capillary glass tube containing diphenylditelluride was used as a chemical shift standard. The same sample was maintained for a period of 30 days in this solution and then the ^{125}Te NMR spectrum was recorded.

Thermal Stability Study. In a 5 mm NMR tube, 50 mg of the compound under study was diluted in a mixture of 360 μL of $\text{DMSO-}d_6$ and 40 μL of D_2O or PBS. A capillary glass tube containing diphenylditelluride was used as a chemical shift standard. An initial ^{125}Te NMR spectrum was recorded at 25 $^\circ\text{C}$. The same sample was heated (40 $^\circ\text{C}$) for 24–96 h, and ^{125}Te NMR spectra were recorded.

Exposure Stability Study in Acid Media. In a 5 mm NMR tube, 50 mg of the compound under study was diluted in a mixture of 300 μL of $\text{DMSO-}d_6$ and 30 μL of HCl (6 mol/L) or 200 mmol/L sodium acetate buffer (pH 5.5). A capillary glass tube containing diphenylditelluride was used as a chemical shift standard. After 24 h, a ^{125}Te NMR spectrum was recorded at 25 $^\circ\text{C}$.

Theoretical Calculations. All calculations were performed with the Gaussian 09²⁸ suite of program. The M06L functional,²⁹ which includes dispersion effects, was used in this study. The SDD pseudopotential and its associated double zeta basis set were used for Te, whereas 6-31+G(d,p) basis set was used for the rest of atoms.^{30–37} The optimized geometries were calculated including the solvent effect (water) using the SMD continuum solvation model.³⁸ All energies reported herein are Gibbs free energies at 273.15 K and 1 atm. The NPA model³⁹ was used to determine the charges distributed on the molecule atoms.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00628.

Detailed experimental procedures, NMR spectra (^1H , ^{13}C , and ^{125}Te), HRMS spectra, theoretical calculation details, and supplemental references (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Gerhardsson, L. Tellurium. *Handbook on the Toxicology of Metals*; Nordberg, G., Fowler, B. A., Nordberg, M., Friberg, L. T., Eds.; Academic Press: Amsterdam, 2015; Chapter 40, pp 815–825.
- (2) (a) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. Organoselenium and Organotellurium Compounds: Toxicology and Pharmacology. *Chem. Rev.* **2004**, *104*, 6255–6285. (b) Cunha, R. L. O. R.; Gouveia, I. E.; Juliano, L. A glimpse on biological activities of organotellurium compounds. *An. Acad. Bras. Cienc.* **2009**, *81*, 393–407.
- (3) (a) Sredni, B. Immunomodulating tellurium compounds as anti-cancer agents. *Semin. Cancer Biol.* **2012**, *22*, 60–69. (b) Halpert, G.; Sredni, B. The effect of the novel tellurium compound AS101 on autoimmune diseases. *Autoimmun. Rev.* **2014**, *13*, 1230–1235.
- (4) (a) Tiekink, E. R. T. Therapeutic potential of selenium and tellurium compounds: Opportunities yet unrealized. *Dalton Trans.* **2012**, *41*, 6390–6395. (b) Ba, L. A.; Döring, M.; Jamier, V.; Jacob, C. Tellurium: an element with great biological potency and potential. *Org. Biomol. Chem.* **2010**, *8*, 4203–4216.
- (5) Albeck, A.; Weitman, H.; Sredni, B.; Albeck, M. Tellurium compounds: selective inhibition of cysteine proteases and model reaction with thiols. *Inorg. Chem.* **1998**, *37*, 1704–1712.
- (6) Cunha, R. L. O. R.; Urano, M. E.; Chagas, J. R.; Almeida, P. C.; Trindade, C. B.; Tersariol, I. L. S.; Comasseto, J. V. Tellurium-based cysteine protease inhibitors: evaluation of novel organotellurium(IV) compounds as inhibitors of human cathepsin B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 755–760.
- (7) Cunha, R. L. O. R.; Gouveia, I. E.; Feitosa, G. V. P.; Alves, M. F.; Bromme, D.; Comasseto, J. V.; Tersariol, I. L. S.; Juliano, L. Irreversible inhibition of human cathepsins B, L, S and K by hypervalent tellurium compounds. *Biol. Chem.* **2009**, *390*, 1205–1212.
- (8) Piovan, L.; Alves, M. F. M.; Juliano, L.; Brömme, D.; Cunha, R. L. O. R.; Andrade, L. H. Structure–activity relationships of hypervalent organochalcogenanes as inhibitors of cysteine cathepsins V and S. *Bioorg. Med. Chem.* **2011**, *19*, 2009–2014.
- (9) Piovan, L.; Wu, L.; Zhang, Z. Y.; Andrade, L. H. Hypervalent organochalcogenanes as inhibitors of protein tyrosine phosphatases. *Org. Biomol. Chem.* **2011**, *9*, 1347–1351.
- (10) Piovan, L.; Milani, P.; Silva, M. S.; Moraes, P. G.; Demasi, M.; Andrade, L. H. 20S proteasome as novel biological target for organochalcogenanes. *Eur. J. Med. Chem.* **2014**, *73*, 280–285.
- (11) Maluf, S. E. C.; Melo, P. M. S.; Varotti, F. P.; Gazarini, M. L.; Cunha, R. L. O. R.; Carmona, A. K. Hypervalent organotellurium compounds as inhibitors of *P. falciparum* calcium-dependent cysteine proteases. *Parasitol. Int.* **2016**, *65*, 20–22.
- (12) (a) Pessoto, F. S.; Faria, P. A.; Cunha, R. L. O. R.; Comasseto, J. V.; Rodrigues, T.; Nantes, I. L. Organotellurane-promoted mitochondrial permeability transition concomitant with membrane lipid protection against oxidation. *Chem. Res. Toxicol.* **2007**, *20*, 1453–1461. (b) Yokomizo, C. H.; Pessoto, F. S.; Prieto, T.; Cunha, R. L. O. R.; Nantes, I. L. Effects of Trichlorotelluro-dypnone on Mitochondrial Bioenergetics and Their Relationship to the Reactivity with Protein Thiols. *Chem. Res. Toxicol.* **2015**, *28*, 1167–1175.

- (13) Gouvea, I. E.; Santos, J. A. N.; Burlandy, F. M.; Tersariol, I. L. S.; da Silva, E. E.; Juliano, M. A.; Juliano, L.; Cunha, R. L. O. R. Poliovirus 3C proteinase inhibition by organotelluranes. *Biol. Chem.* **2011**, *392*, 587–591.
- (14) Abondanza, T. S.; Oliveira, C. R.; Barbosa, C. M. V.; Pereira, F. E. G.; Cunha, R. L. O. R.; Caires, A. C. F.; Comasseto, J. V.; Queiroz, M. L. S.; Valadares, M. C.; Bincoletto, C. Bcl-2 expression and apoptosis induction in human HL60 leukaemic cells treated with a novel organotellurium(IV) compound RT-04. *Food Chem. Toxicol.* **2008**, *46*, 2540–2545.
- (15) Persike, D. S.; Cunha, R. L. O. R.; Juliano, L.; Silva, I. R.; Rosim, F. E.; Vignoli, T.; Dona, F.; Cavalheiro, E. A.; Fernandes, M. J. S. Protective effect of the organotelluroxetane RF-07 in pilocarpine-induced status epilepticus. *Neurobiol. Dis.* **2008**, *31*, 120–126.
- (16) Lima, C. B. C.; Arrais-Silva, W. W.; Cunha, R. L. O. R.; Giorgio, S. A Novel Organotellurium Compound (RT-01) as a New Antileishmanial Agent. *Korean J. Parasitol.* **2009**, *47*, 213–218.
- (17) Pimentel, I. A. S.; Paladi, C. S.; Katz, S.; Judice, W. A. S.; Cunha, R. L. O. R.; Barbiéri, C. L. *In Vitro* and *In Vivo* Activity of an Organic Tellurium Compound on *Leishmania (Leishmania) chagasi*. *PLoS One* **2012**, *7*, No. e48780.
- (18) Silberman, A.; Kalechman, Y.; Hirsch, S.; Erlich, Z.; Sredni, B.; Albeck, A. The Anticancer Activity of Organotelluranes: Potential Role in Integrin Inactivation. *ChemBioChem* **2016**, *17*, 918–927.
- (19) Silberman, A.; Albeck, M.; Sredni, B.; Albeck, A. Ligand-Substitution Reactions of the Tellurium Compound AS-101 in Physiological Aqueous and Alcoholic Solutions. *Inorg. Chem.* **2016**, *55*, 10847–10850.
- (20) Silva, M. S.; Andrade, L. H. 77 Se and 125 Te NMR spectroscopy on a selectivity study of organochalcogenanes with l-amino acids. *Org. Biomol. Chem.* **2015**, *13*, 5924–5929.
- (21) Princival, C. R.; Dos Santos, A. A.; Comasseto, J. V. Solventless and Mild Procedure to Prepare Organotellurium(IV) Compounds under Microwave Irradiation. *J. Braz. Chem. Soc.* **2015**, *26*, 832–836.
- (22) Petragani, N.; Mendes, S. R.; Silveira, C. Tellurium tetrachloride: an improved method of preparation. *Tetrahedron Lett.* **2008**, *49*, 2371–2372.
- (23) Albeck, M.; Tamari, T.; Sredni, B. Synthesis and Properties of Ammonium Trichloro(dioxyethylene-O,O')tellurate (AS-101). A New Immunomodulating Compound. *Synthesis* **1989**, *1989*, 635–636.
- (24) Cunha, R. L. O. R.; Zukerman-Schpector, J.; Caracelli, I.; Comasseto, J. V. Revisiting the addition reaction of TeCl₄ to alkynes: The crystal structure and docking studies of 1-chloro-2-trichlorotelluro-3-phenyl-propen-2-ol. *J. Organomet. Chem.* **2006**, *691*, 4807–4815.
- (25) Petragani, N.; Comasseto, J. V.; Kawano, Y. New anionic species of tellurium(IV). *J. Inorg. Nucl. Chem.* **1976**, *38*, 608–612.
- (26) (a) Uemura, S.; Fukuzawa, S. I. New aspects of the telluroxide elimination: a facile elimination of sec-alkyl phenyl telluroxide leading to olefins, allylic alcohols, and allylic ethers. *J. Am. Chem. Soc.* **1983**, *105*, 2748–2752. (b) Uemura, S.; Fukuzawa, S. I. Oxidation of alkyl phenyl selenides, tellurides, and telluroxides with meta-chloroperbenzoic acid for a facile and novel transformation of C-Se and C-Te bonds to C-O bonds. *J. Chem. Soc., Perkin Trans. 1* **1985**, 471.
- (27) (a) Lederer, K. Zur Kenntnis der *p*-Anisyl-Tellurverbindungen. *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 1076–1082. (b) Morgan, G. T.; Kellett, R. E. CXL. Interactions of tellurium tetrachloride and aryl alkyl ethers. Part II. *J. Chem. Soc.* **1926**, *129*, 1080. (c) Bergman, J. Tellurium in Organic Chemistry. I. Novel synthesis of biaryls. *Tetrahedron* **1972**, *28*, 3323. (d) Ley, S. V.; Meerholz, C. A.; Barton, D. H. R. Diaryl telluroxides as new mild oxidizing reagents. *Tetrahedron* **1981**, *37*, 213–223.
- (28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2016.
- (29) Zhao, Y.; Truhlar, D. G. A new local density functional for main-group thermochemistry, transition metal bonding, thermochemical kinetics, and noncovalent interactions. *J. Chem. Phys.* **2006**, *125*, No. 194101.
- (30) Igel-Mann, G.; Stoll, H.; Preuss, H. Pseudopotentials for main group elements (IIIA through VIIA). *Mol. Phys.* **1988**, *65*, 1321–1328.
- (31) Bergner, A.; Dolg, M.; Kuechle, W.; Stoll, H.; Preuss, H. Ab-initio energy-adjusted pseudopotentials for elements of groups 13–17. *Mol. Phys.* **1993**, *80*, 1431–1441.
- (32) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. Self-consistent molecular-orbital methods. 24. Supplemented small split-valence basis-sets for 2nd-row elements. *J. Chem. Phys.* **1982**, *77*, 3654–3665.
- (33) Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-consistent molecular-orbital methods. 9. Extended Gaussian-type basis for molecular-orbital studies of organic molecules. *J. Chem. Phys.* **1971**, *54*, 724–728.
- (34) Rassolov, V. A.; Pople, J. A.; Ratner, M. A.; Windus, T. L. 6-31G* basis set for atoms K through Zn. *J. Chem. Phys.* **1998**, *109*, 1223–1229.
- (35) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self-consistent molecular-orbital methods. 12. Further extensions of Gaussian-type basis sets for use in molecular-orbital studies of organic molecules. *J. Chem. Phys.* **1972**, *56*, 2257–2261.
- (36) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; DeFrees, D. J.; Pople, J. A.; Gordon, M. S. Self-consistent molecular-orbital methods. 23. A polarization-type basis set for 2nd-row elements. *J. Chem. Phys.* **1982**, *77*, 3654–3665.
- (37) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
- (38) Reed, A. E.; Weinstock, R. B.; Weinhold, F. Natural-population analysis. *J. Chem. Phys.* **1985**, *83*, 735–746.
- (39) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, version 3.1; University of Wisconsin-Madison, 2017.