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Investigation of chemical stability of dihalogenated organotelluranes in organic-aqueous media: the protagonism of water

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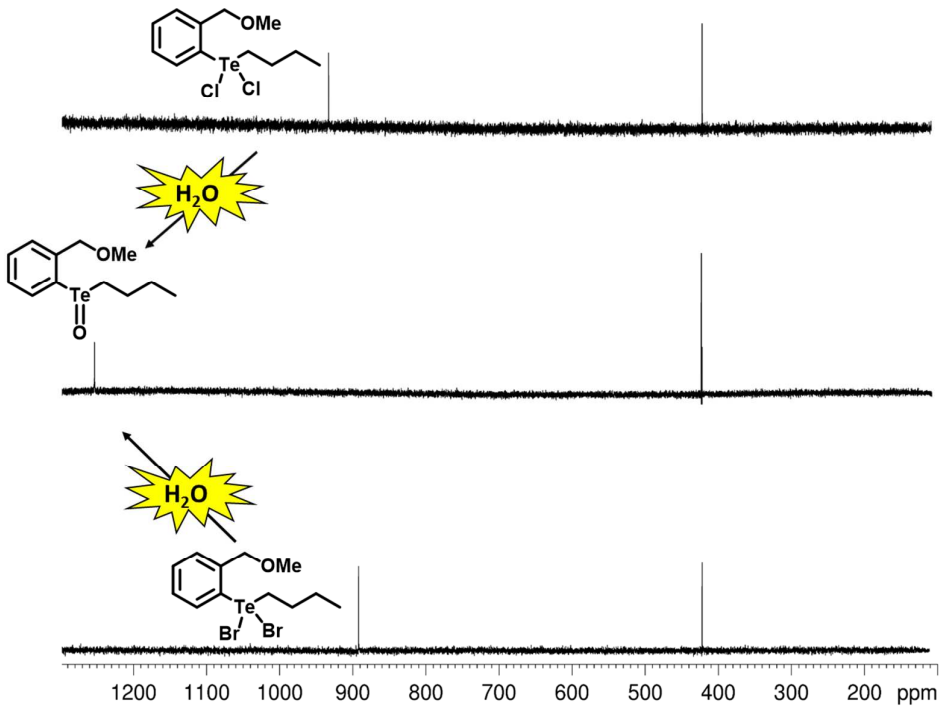


Abstract: The biological activity of tellurium compounds is closely related to the tellurium oxidation state or some of their structural features. Hypervalent dihalogenated organotelluranes 1-[butyl(dichloro)-λ^4-tellanyl]-2-(methoxymethyl)benzene (**1a**) and 1-[butyl(dibromide)-λ^4-tellanyl]-2-(methoxymethyl)benzene (**1b**) have been described as inhibitors of proteases (cysteine and threonine) and tyrosine phosphatases. However, poor attention has been given to their physicochemical properties. Here, a detailed investigation of the stability in water of these organotelluranes is reported, using ^{125}Te NMR analysis. Dihalogenated organotelluranes **1a** and **1b** were both stable in DMSO-d_6 (from 25 to 75 ºC), demonstrating their thermal stability. However, the addition of a phosphate buffer solution (pH 2-8) to **1a** or **1b** resulted in an immediate conversion to a new Te-species, assumed to be the corresponding telluroxide. Similar behavior was observed in pure water, demonstrating the low chemical stability of these dihalogenated species in the presence of water. These results allow concluding that previous biological activity reported for dihalogenated organotelluranes **1a** and **1b** could be attributed to the corresponding derivatives from the reaction with water. In the same way as supposed to AS-101, we demonstrated that organotelluranes **1a** and **1b** are not stable in aqueous solution. It suggests a proactive role of these organotelluranes in previously reported biological activity.

Introduction

Tellurium is an important element from group 16 of the periodic table and its chemical properties allow broad applications in both organic and inorganic chemistry[1], such as materials[2,3] and pharmacological science[4] and medicinal chemistry[5]. An intrinsic characteristic of this element is its wide range of oxidation states (-2 to +6), which allows the expansion of the Lewis octet rule[6,7], giving the possibility of hypervalent species[8-10.] These compounds have potential applications in enzymatic inhibition[11-17] and some therapeutic applications[18].

Albeck et al. described for the first time the behavior of inorganic hypervalent Te(IV) compounds as inhibitors of cysteine proteases (papain and cathepsin B), in contrast to the complete absence of activity for Te(VI) pertelluranes[12]. From inorganic telluranes (Te(IV) compounds), AS-101 was identified as the most powerful inhibitor of those proteases. Since then, AS-101 has been described as an immunomodulator against certain microorganisms[18-21], and as having anticancer[22-24], antimicrobial[25], anti-inflammatory[26], bactericidal[27] and antiviral[28,29] activity, as well as being a preventive agent against Type-2 diabetes[30].

Cunha et al. demonstrated that organotelluranes were more potent than AS-101 in the inhibition of cysteine proteases[13,14]. Piovan et al. reported a structure-activity relationship of dihalogenated organochalcogenanes in inhibition of cathepsins V and S and that organotelluranes were superior to organoselenuranes[15]. The same behavior was observed for inhibition of thiol-dependent protein tyrosine phosphatases (PTP1B and the YopH)[16] and 20S proteasome, in this case a threonine protease[17]. Recently, several species of tellurium have been described, not only as inhibitors, but also as having other important applications such as antimicrobial[25], anti-inflammatory[26] or anticancer activity[31,32].

Despite the advances in the discovery of potential therapeutic properties of tellurium compounds, research and development of new drugs (R&D) is a complex, long and costly process[33]. In recent years, physicochemical, metabolic and pharmacokinetic properties have emerged as important factors in the success of the drug discovery and development process. Hence, the coupling of physicochemical properties and the structure of the bioactive molecules, or structure-properties relationship (SPR), increases the chances of success in the development of biologically active compounds[34].

In the case of bioactive telluranes, only a few reports about their physicochemical properties are available[17,35-37]. Silva and Andrade reported that organotelluranes **1a** and **1b** (Figure 1) were not thermally stable and suggested the formation of a telluroxide derivative based exclusively on the ^{125}Te NMR chemical shifts[36]. However, the identity of Te-derivative in water remains inconclusive, since this telluroxide had never been isolated. Another interesting point about organotelluranes' reactivity is the stoichiometry of reactions: in reaction with cysteine, the substitution of a single chlorine atom is proposed[36]. On the other hand, two halogen atoms are substituted when organotelluranes are exposed to water, explaining the telluroxide formation as proposed in the literature[36]. Silberman et al. demonstrated that AS-101 (Figure 1) is not stable in aqueous or alcoholic solutions, indicating that this tellurane is sensitive to ligand-substitution reactions[35]. In the case of AS-101, those authors also proposed telluroxide formation, but here by ethylene glycol moiety substitution and maintenance of halogens[35]. However, prior works by the same authors described that AS-101 reacts with 4 equivalents of cysteine to originate $Te(Cys)_4$[12] instead of 1 equivalent as previously observed for organotelluranes.

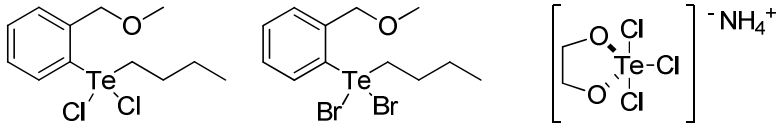


Figure 1. Chemical structures of organotelluranes **1a** and **1b** and inorganic tellurane AS-101.

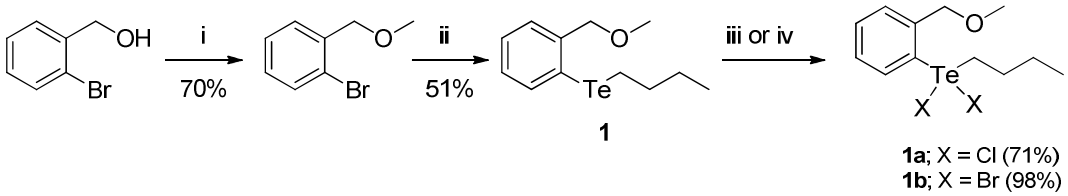
In order to supply more data for this discussion, here we report an extensive study of the chemical stability of bioactive dihalogenated organotelluranes (1-[butyl(dichloro)-λ^4-tellanyl]-2-(methoxymethyl)benzene (**1a**) and 1-[butyl(dibromide)-λ^4-tellanyl]-2-(methoxymethyl)benzene (**1b**). Organotelluranes **1a** and **1b** have been described as inhibitors of cysteine proteases[15], protein tyrosine phosphatases[16] and 20S proteasome[17]. In our design, we assumed possible oral administration for them. The oral route is most commonly used. Besides being safe and economical, it is comfortable and painless in patients who are not prone to nausea, vomiting or difficulties to swallow pills[38]. There is a precedent in clinical studies using AS-101 where it was administered in aqueous physiological solutions (usually as phosphate-buffered saline (PBS) or as propylene glycol/water mixtures)[35]. The investigation of **1a** and **1b** stabilities was carried out by ^{125}Te NMR analysis using different solvent mixes (organic and aqueous

solutions), pH screening (2.5 to 8.0) and temperature variation (25 to 75 ºC). Also, ^{81}Br, ^{1}H and ^{13}C NMR analyses were used to obtain complementary data.

Results and Discussion

Organotelluranes 1-[butyl(dichloride)-λ^4-tellanyl]-2-(methoxymethyl)benzene (**1a**) and 1-[butyl(dibromide)-λ^4-tellanyl]-2-(methoxymethyl)benzene (**1b**) were both prepared according to the procedures described in the literature[16] (Scheme 1).

Scheme 1. Reagents and conditions: (**i**) a: NaH, THF (0 °C, 30 min.); b: MeI (r.t., 3 h); (**ii**) a: *t*-BuLi, THF (−78 °C, 30 min.); b: (*n*-BuTe)$_2$, THF (r.t., 3 h); (**iii**) SO_2Cl_2, THF, (0 °C, 20 min.); (**iv**) Br_2, THF, (0 °C, 20 min.).



Organotelluranes **1a** and **1b** were first evaluated in pure DMSO-d_6 and then in a mixture of DMSO-d_6/phosphate buffered solution (pH 2-8) at 25 ^{o}C. All assays were monitored by ^{125}Te-NMR. As can be seen in Figure 2, when pure DMSO-d_6 was used as solvent, the typical chemical shifts[36] were observed for organotelluranes **1a** (δ = 937) and **1b** (δ = 887) in the ^{125}Te NMR spectrum. However, addition of phosphate buffered solution (PBS) at pH = 7.5 (in the same tube containing DMSO-d_6) caused the complete disappearance of the prior signals for **1a** and **1b**, and the appearance of one signal around δ = 1255, from both compounds, indicating the formation of a new and common tellurium species. To enhance the knowledge about their stability at different pH levels, experiments employing PBS with pH = 2.0, 6.5 and 8.0 were performed and the same behavior was observed. Acidic (pH = 2.0) or basic (pH = 8) solutions presented similar results and a single signal at $\delta_{DMSO/PBS}$ =1260 was observed in the ^{125}Te NMR spectra for both **1a** and **1b,** demonstrating that a new Te-species was formed independent of the pH value.

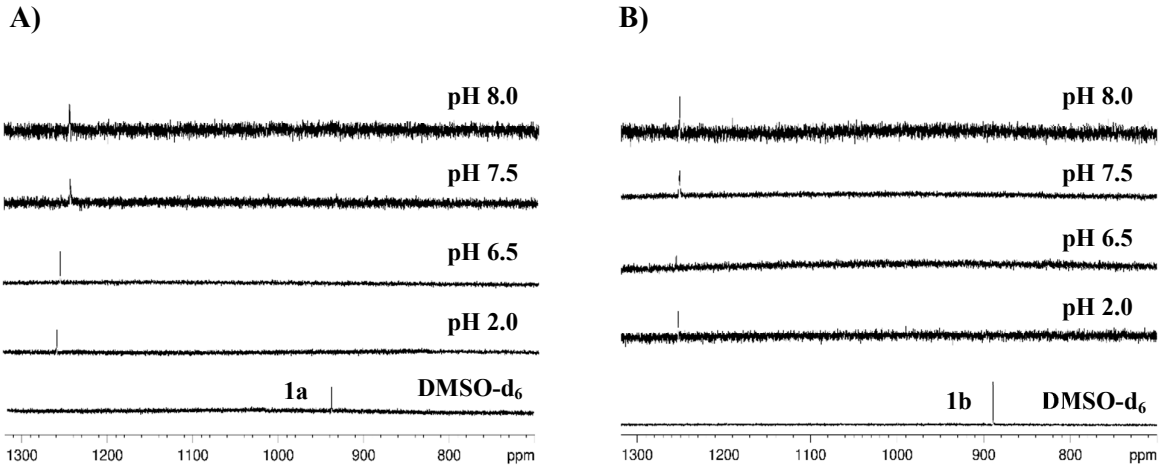


Figure 2. ^{125}Te NMR spectra (126.2 MHz) of A) organotellurane **1a** and B) organotellurane **1b** in pure DMSO-d_6 and DMSO-d_6/~phosphate buffered solutions (pH 2-8) at 25 ºC.

Organotelluranes **1a** and **1b** have already been described as stable compounds in DMSO-d_6/Tris-buffered solution[17,36] and this prior observation clearly conflicts with our results employing DMSO-d_6/phosphate-buffered solution. Since the experimental differences involved the nature of buffer solution, we decided to carry out an assay in pure D_2O to compare the results under the same conditions. To our pleasure, only one signal was observed in δ_{D2O} = 1271 (Figure 3), so now our results converged to that

reported by Silva and Andrade (Figure S2 of Support information of reference 36). Other mixtures of solvents were also evaluated (DMSO-d_6/distilled water, DMSO-d_6/D_2O) and same result was obtained as from the previous assays, with the disappearance of the signals for organotelluranes and the appearance of one signal at $\delta_{DMSO/H2O\ dist.} = \delta_{DMSO/D2O}$ 1254 (Figure 3). These results allow the conclusion that a new species of tellurium is derived from the reaction with water, with the pH parameter (values or buffer nature) being irrelevant.

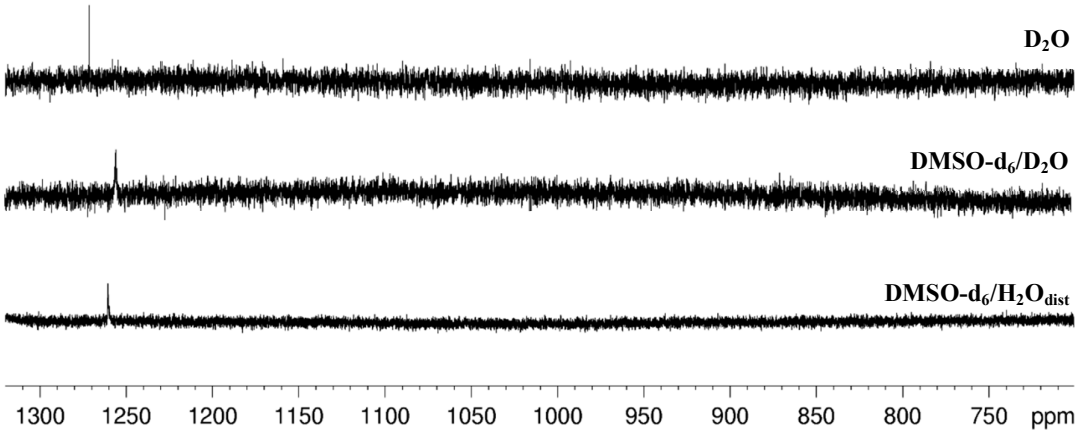


Figure 3. ^{125}Te NMR spectra (126.2 MHz, 25°C) of organotellurane **1b** in D_2O, DMSO-d_6/D_2O and DMSO-d_6/distilled water.

After that, organotelluranes **1a** and **1b** were mixed and solubilized together in DMSO-d_6. The corresponding signals were observed (932 ppm for **1a** and 887 ppm for **1b** in DMSO-d_6**)** in the ^{125}Te NMR spectra. Besides these two signals, a third one at 914 ppm was observed, but although its identity was not explored (Figure 4), it is possibly a compound with one chloride/one bromide bonded to the tellurium atom, showing the lability of these ligands. When PBS or deuterated water was added to the tube, only one signal in the ^{125}Te-NMR spectrum at 1251 ppm was observed (Figure 4).

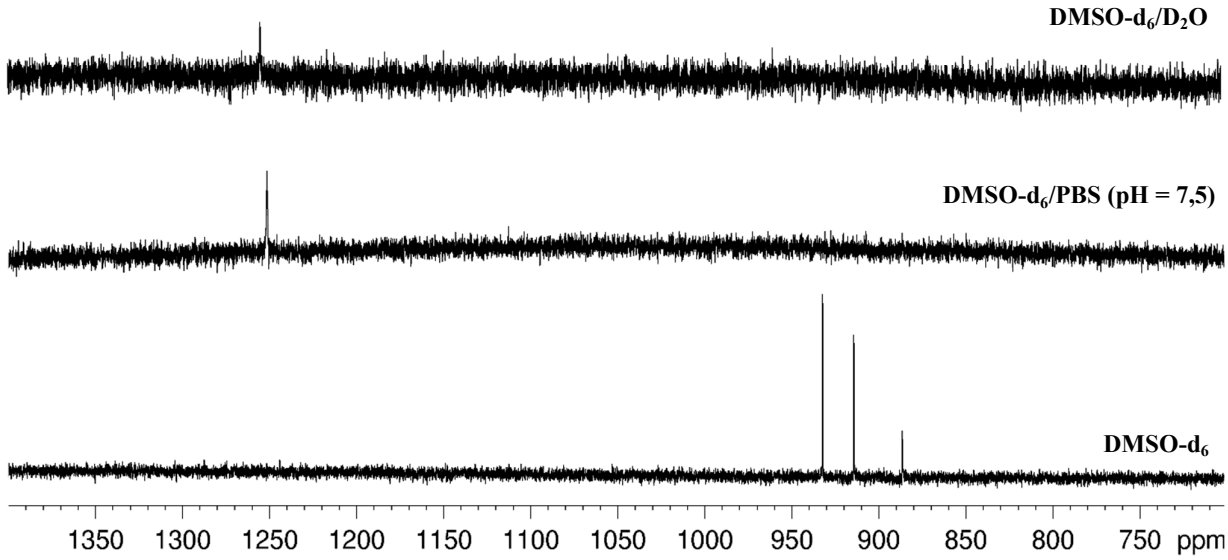


Figure 4. ^{125}Te NMR spectra (126.2 MHz, 25 ^{o}C) of the mixture of organotelluranes **1a** + **1b** in DMSO-d_6/D_2O, DMSO-d_6/PBS (pH 7.5) and DMSO-d_6 (25 ºC).

It is important to highlight that the new Te-species must originate from a displacement of halogens in **1a** and **1b**. To confirm the halogen release, a ^{81}Br NMR spectrum was recorded using organotellurane **1b** solubilized in D_2O. After recording ^{81}Br NMR of KBr spectra in D_2O (δ_{KBr} = 0.00 ppm), the spectrum of **1b** was recorded, and only a signal at δ = 0 was observed, indicating the presence of bromide ions in solution (Figure 5). Thus, it can be concluded that in the presence of water, bromide ions were released from tellurane **1b**, leading to the formation of a new product with chemical shift in δ_{D2O} = 1274 in the ^{125}Te-NMR spectrum (Figure 5).

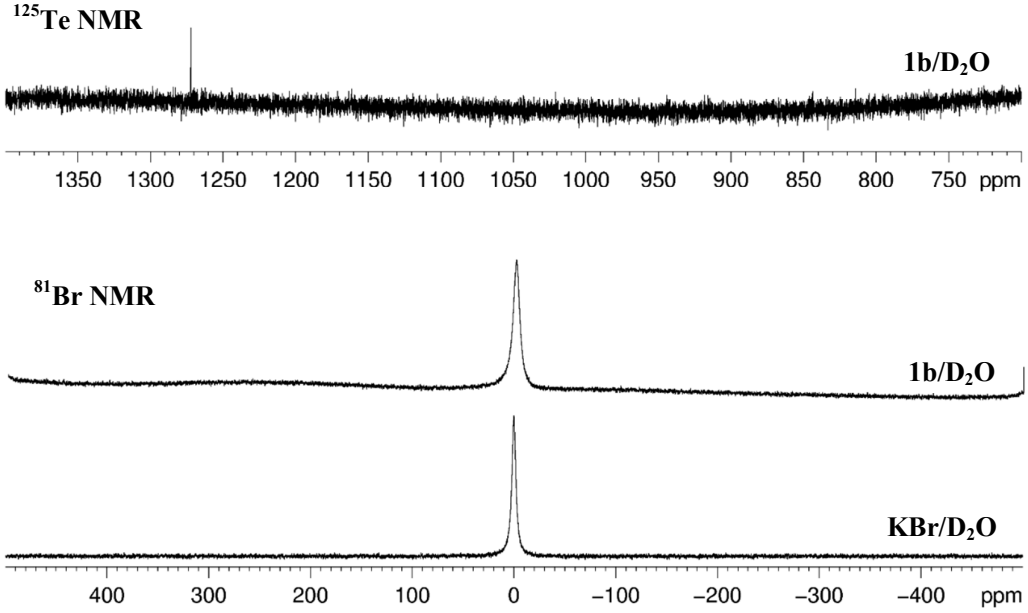


Figure 5. ^{125}Te NMR spectrum (126.2 MHz, 25 ^{o}C) of organotellurane **1b** in D_2O and ^{81}Br NMR spectra (108.06 MHz, 25 ^{o}C) of **1b** and KBr in D_2O.

Finally, the thermal stability of organotellurane **1b** in anhydrous DMSO-d_6 was evaluated. The intention of this experiment was to analyze the behavior of dibromide tellurane in DMSO-d_6 at 35, 45, 55, 65 and 75 ºC, in the absence of water at high temperatures for 15 min in each (Figure 6).

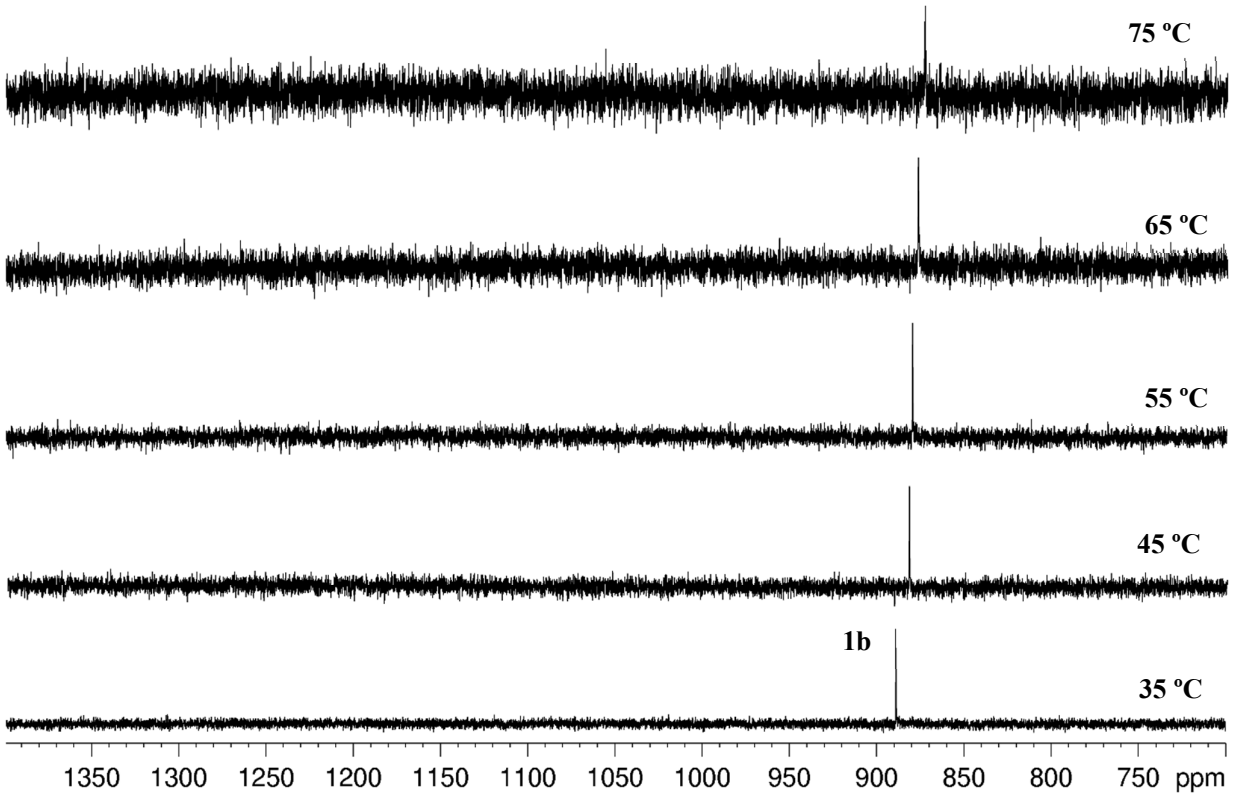


Figure 6. ^{125}Te NMR spectra (126.2 MHz) of organotellurane **1b** in DMSO-d_6 at different temperatures.

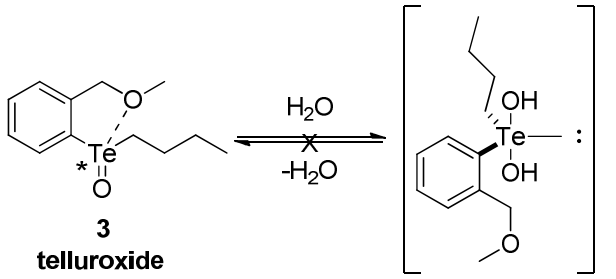
These results show that organotellurane **1b** was thermally stable in DMSO-d_6 reinforcing our observation about the role of water as pivotal for the transformation of dihalogenated organotelluranes **1a** and **1b**.

Based on the ^{125}Te NMR data, we assume that organotelluranes **1a** and **1b** were transformed into corresponding telluroxide. However, telluroxide could occur in equilibrium with corresponding dihydroxytelluride[39], which could imply two types of ^{125}Te NMR signals. In view of the proposed formation of a telluroxide or dihydroxytelluride, from **1a** and **1b**, in aqueous media, we tried to synthesize these compounds via oxidation of telluride **1** (Scheme 1) using hydrogen peroxide[40], sodium hydroxide[41] or *N*-bromosuccinimide[42]. However, the syntheses were not successful, due to the difficulty of isolating the formed species.

On the other hand, it is known that a noncovalent intramolecular interaction involving non-ligand electrons in the oxygen and antibonding molecular orbital of the Te=O bond in **3** can prevent the dihydroxytelluride **4** formation[43]. This non-covalent interaction is responsible for increasing the stability of the telluroxide **3**[43] (Scheme 2)

and avoids the β-elimination reaction in telluroxides[44]. To confirm this hypothesis, tellurane **1b** in D_2O was analyzed via ^{1}H and ^{13}C NMR, and it was possible to observe signals indicating the conversion of dibromide organotellurane into a new species without butyl carbon chain changes (see supporting information).

Scheme 2. Preventing the hydration reaction of telluroxide through the intramolecular Te-O interaction.



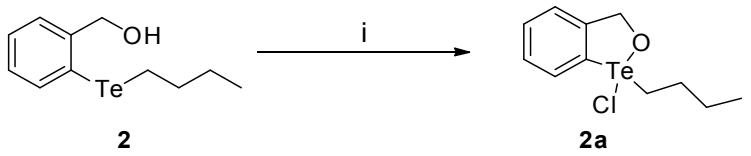
3
telluroxide

4
dihydroxytelluride

In contrast, we succeeded in synthesizing oxatellurole **2a** (Scheme 3), which contains an intramolecular covalent Te-O bond that simulates the change of a Te-halogen bond (halogen release was previously confirmed – Figure 5) with a Te-O bond like one from a water attack on **1a** and **1b.** To our pleasure, a signal at δ_{DMSO} = 1219 was observed, indicating that 2a is structurally similar to the product of **1a** and **1b** after reaction with water (~ 1256 ppm). So, it can be suggested that a Te-O bond was formed in place of at least one Te-Cl or Te-Br bond in the organotelluranes exposed to water. Finally, ^{125}Te NMR analysis showed that **2a** was stable to water exposure (

Figure 7). This observation indicates that organotelluroles are new water-stable hypervalent Te-containing compounds for biological applications.

Scheme 3. Reagents and conditions: (**i**): *N*-chlorosuccinimide, dichloromethane (0 °C, 20 min.)



2 **2a**

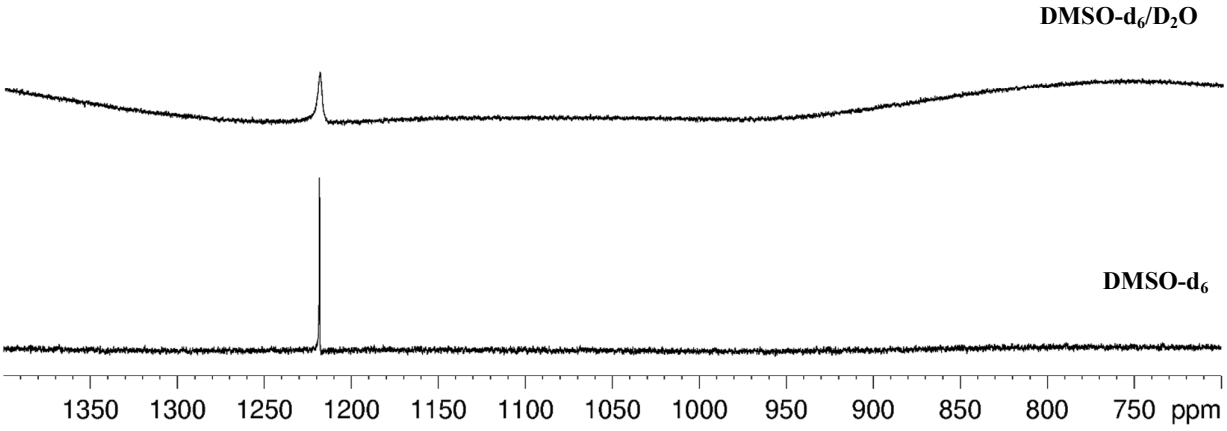


Figure 7. ^{125}Te NMR spectra (126.2 MHz, 25 ^{o}C) of oxatellurole **2a** in DMSO-d_6 and DMSO-d_6/D_2O.

Conclusion

Our observations allowed us to conclude that organotelluranes **1a** and **1b**, when exposed to organic-aqueous or just aqueous solution are immediately converted into new species. This transformation was observed in the presence of D_2O, distillated water or buffered solution, independent of the pH (value or buffer nature). Analysis of ^{81}Br-NMR of **1b** in D_2O demonstrated release of bromide ions, indicating the occurrence of a displacement reaction in dibromide tellurane **1b**. We also assumed the formed Te-species is a telluroxide, but in our opinion this claim needs more investigation. In the same way as supposed to AS-101, we demonstrated that organotelluranes **1a** and **1b** are not stable in aqueous solution. It suggests a proactive role of these organotelluranes in previously reported biological activity, being the named telluroxide the possible active specie.

Experimental Section

General Methods:

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III at 9.4 Tesla (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR, 126.2 for ^{125}Te-NMR and 108.06 MHz for ^{81}Br). The chemical shifts of ^{1}H and ^{13}C NMR were registered relative to an internal standard (tetramethylsilane (δ_{TMS} = 0.00)) and ^{125}Te NMR to an external standard (diphenyl ditelluride ($C_6H_5Te_2$ = 422.0)). ^{1}H-NMR data were reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, st = sextet and m = multiplet), coupling constant in Hz and relative intensity (integral). ^{13}C-NMR and ^{125}Te-NMR data were reported as chemical shift in ppm (δ).

Infrared spectra were recorded from KBr discs on a Bomem MB100 (Fourier Transform Infrared – FTIR) spectrometer. Maximum absorption (ν_{max}) is reported in wavenumber (cm^{-1}).

1. Synthesis

2-Butyltellurobenzyl alcohol (2): 1-Bromo-2-(methoxymethyl)benzene (0,372 g, 2 mmol), under argon atmosphere, was dissolved in anhydrous THF (15 mL) at -78 ºC. Then, *terc*-BuLi (2,5 mL, 4 mmol, 1,7 mol L^{-1} in pentane) was carefully added dropwise, thereby resulting a yellow or green clear mixture was stirred at 0 ºC for 30 min. After that, the mixture was cooled to 0 ^{o}C and dibutyl ditelluride (0,740 g, 2 mmol) was added and the mixture was stirred for 3h at room temperature. The reaction was quenched with ammonium chloride (15 mL) and brine (15 mL), the organic phase was diluted with diethyl ether (50 mL) and washed with brine (2x20 mL). The organic phase was separated, dried over anhydrous magnesium sulphate and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using a mixture of hexane and ethyl acetate (80:1) as eluent to afford the purified orange dark oil of the product in 51% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.71 (m, 1H), 7.24 (m, 2H), 7.10 (m, 1H), 4.69 (s, 2H), 4.63 (s, 2H), 2.85 (t, ^{3}J = 7.61, 2H), 1.75 (qt, ^{3}J = 7.59, 2H), 1.39 (st, ^{3}J = 7.24, 2H), 0.89 (t, ^{3}J = 7.39 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 144.6, 140.9, 138.1, 132.5, 128.9, 128.8, 128.5, 128.4, 127.9, 127.8, 127.6, 126.9, 114.9, 68.7, 65.2, 33.7, 25.1, 13.4, 8.3; ^{125}Te (126.24 MHz, $CDCl_3$) δ 354.

1-Butyl-1-chloro-2,1λ^4-benzoxa-tellurole (2a): Hydroxytelluride **2** (100 mg, 0,34 mol) was dissolved in DCM (2 mL) at 0 ºC. Then, *N*-chlorosuccinimide (NCS) (50 mg, 0,34 mol) with excess of 10% was added, thereby resulting a clear mixture was stirred at r.t. for 30 min. After this, the flask was kept in a freezer for 24h, filtered on cotton and the remained NCS was extracted with distilled water (3x10 mL). The organic portions were combined and pre-dried with brine (2x10mL), and dried with anhydrous $MgSO_4$, then the solvent was removed under vacuum without heating. The solid crude was crystallized from distilled water/DMSO (5:1) to afford purified colorless crystals of the product in 40 % yield. ^{1}H NMR (DMSO-d$_6$, 400 MHz, TMS) δ 8.22 (m, 1H), 7,59 (m, 1H), 7.52 (m, 1H), 7.45 (m, 1H), 5.61 (d, ^2J = 14.7 Hz, 1H), 5.30 (d, ^2J = 14.7 Hz, 1H), 2.91 (m, 2H), 1.52 (m, 2H), 1.25 (st, ^3J = 7.24 Hz, 2H), 0.77 (t, ^3J = 7.35 Hz, 3H); ^{13}C (100 MHz, DMSO-d$_6$) δ 148.6, 132.5, 130.8, 128.5, 128.1, 123.4, 73.7, 43.2, 26.7, 23.5, 13.2; ^{125}Te (126.24 MHz, DMSO-d_6) δ 1218.

2. Stability Assays

The chemical stability studies were performed using the ^{125}Te, ^{81}Br, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) technique. In all analyses of ^{125}Te NMR a capillary tube was used, containing the diphenyl ditelluride ($C_6H_5Te_2$), as external standard with chemical shift calibrated to 422 ppm. It is worth mentioning that, in the spectra of ^{125}Te, the spectral window was read from 0 to 3000 ppm, as in though, in the absence of signals above 2000 ppm, the spectral window will be shown between 200 and 2000 ppm (see Supporting Information for details).

Acknowledgments.

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Supporting Information Available:

The Supporting Information is available free of charge on the ACS Publications website at DOI:

General experimental methods and conditions for stability assays, spectral data of ^{1}H, ^{13}C, ^{125}Te and ^{81}Br – NMR and infrared (FTIR).

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