Tellurium: an element with great biological potency and potential

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Tellurium has long appeared as a nearly 'forgotten' element in Biology, with most studies focusing on tellurite, tellurate and a handful of organic tellurides. During the last decade, several discoveries have fuelled a renewed interest in this element. Bioincorporation of telluromethionine provides a new approach to add heavy atoms to selected sites in proteins. Cadmium telluride (CdTe) nanoparticles are fluorescent and may be used as quantum dots in imaging and diagnosis. The antibiotic properties of tellurite, long known yet almost forgotten, have attracted renewed interest, especially since the biochemical mechanisms of tellurium cytotoxicity are beginning to emerge. The close chemical relationship between tellurium and sulfur also transcends into *in vitro* and *in vivo* situations and provides new impetus for the development of enzyme inhibitors and redox modulators, some of which may be of interest in the field of antibiotics and anticancer drug design.

1. Introduction

Tellurium belongs to the group of chalcogens, which also includes the elements oxygen, sulfur, selenium and polonium. It was discovered rather early in History, in 1782, by the Transylvanian chemist Franz-Joseph Mueller von Reichenstein (1742–1825), who was studying gold-containing ores. The name tellurium derives from the Latin word *tellus*, which means "Earth". Despite its early discovery, prominent name and abundance in the Earth's crust (around 0.027 ppm, on par with elements such as silver and gold), tellurium in many respects is a rather shadowy element, with apparently little importance in daily life (see Box for an overview). This virtual 'non-existence' of tellurium in daily life is particularly pronounced in the field of Biology, where tellurium is a truly alien element, with no apparent role in either pro- or eukaryotic organisms. Unlike its relative selenium, which was discovered in 1817 by Joens Jacob Berzelius (1779–1848), tellurium is not an essential biological trace element. This may be one of the reasons why tellurium and its compounds—in sharp contrast to selenium—have so far escaped wider consideration in Medicine and drug development. Little is also known about the toxicity of tellurium in humans, probably because contact with tellurium and its compounds, or indeed tellurium poisoning, is extremely rare. Ultimately, tellurium is among the very few elements in the Periodic Table that has been almost entirely ignored by biochemists. In fact, we probably know more about the biological or medicinal roles of ruthenium or osmium than the ones of tellurium.

In many ways, this is rather surprising. Close relatives of tellurium in the Periodic Table, such as oxygen, sulfur and selenium, occupy pivotal roles in biochemistry. Oxygen is omnipresent and no life on Earth would be possible without it. Similarly, sulfur occurs in virtually all organisms, where it fulfils a range of crucial roles in cellular redox processes, biocatalysis and metal binding. A typical human adult contains around 175 g of sulfur, which is comparable to the amount of sodium or

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potassium, and the sulfur-containing tripeptide glutathione (γ-glutamyl-cysteinyl-glycine, GSH) is present in millimolar concentrations in the cytosol of (most) human cells. While selenium is considerably less abundant (4.9 mg in a typical human adult), its presence in a range of key human proteins and enzymes, such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR), thyroxine deiodinase and the selenium-rich selenoprotein P, means that its role in human biochemistry should not be underestimated.[1]

With oxygen, sulfur and selenium occupying prominent roles in Biology and Medicine, the apparent lack of any such function for tellurium is rather disappointing from a chemist's point of view. Tellurium is not particularly toxic, radioactive or otherwise 'exotic'. Quite on the opposite: the chemistry of tellurium is rich in inorganic and organic substances, including various inorganic salts (*e.g.* tellurides Te^{2-}, tellurites TeO_3^{2-} and tellurates TeO_4^{2-}) and a wide range of diverse organotellurium compounds. From a pharmacological perspective, tellurium and its compounds may therefore rather be considered as 'forgotten' than as 'exotic'. As part of this Emerging Area article, we will argue that organotellurium agents possess a range of unique properties, which, albeit hardly explored to date, may provide the basis for innovative drug development in the future. The respective chemistries of oxygen, sulfur, selenium *and* tellurium are closely intertwined *in vitro* and *in vivo*, and as one consequence, many of the few organotellurides studied to date are clearly potent agents: they inhibit proteins and enzymes, kill various microorganisms, including bacteria and plasmodia, and induce apoptosis in certain cancer cells.

Some of these compounds and their activities will be discussed in the following sections. We should emphasize from the outset that these discussions will be based on a selection of compounds and activities suitable to highlight key aspects of this Emerging Area. This should not be confused with a comprehensive or ultimate overview of tellurium compounds, their chemistry and biological activities.

2. Basic chemical features of tellurium

Before we turn our attention to our present knowledge of tellurium and its compounds in Biology, Medicine and drug development, we will briefly consider some of the basic aspects of tellurium chemistry. Tellurium is a metalloid ('semi-metal') located in the p-block of the Periodic Table (electron configuration [Kr] $4d^{10}$ $5s^2$ $5p^4$) and as such exhibits certain metallic and non-metallic properties. It occurs in two elemental modifications, one of them metallic, silver-shiny and one of them brownish-black. Its primary industrial use is as a metal, for instance as part of alloys to improve the properties of various steels and in solar panels. Because of their excellent thermal, optical and electrical properties, tellurite (TeO_3^{2-}) glasses can be used as a material for photonic switches.[2] Further applications of tellurium in form of polychalcogenides appear possible in the field of solid state materials, *e.g.* for rechargeable batteries.[3] During the last ten years, tellurium has also featured in the development of innovative new materials, such as fluorescent CdTe quantum dots with high quantum yields, which may ultimately serve as novel probes in biological detection.[4] At the same time, a range of telluride clusters,[5] nanoparticles[6] and nanotubes[7] have emerged as part of a fairly new field of nanotechnology research, which may find potential applications in electronics and medicine. It should be pointed out that many of these developments are still in their very early stages, yet in the medium term may result in a more widespread industrial use of tellurium. Ultimately, this will also raise certain wider issues, such as tellurium toxicity, which will be discussed later on.

Apart from its apparent optical features, which are increasingly explored in the area of new materials, tellurium also exhibits interesting spectroscopic properties, which are particularly useful for the characterisation of organotellurium agents. Naturally occurring tellurium is a mixture of several isotopes, namely ^{120}Te (natural abundance 0.09%), ^{122}Te (2.55%), ^{123}Te (0.89%), ^{124}Te (4.74%), ^{125}Te (7.07%), ^{126}Te (18.84%), ^{128}Te (31.74%) and ^{130}Te (34.08%).[8] This distribution of natural isotopes results in

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Claus Jacob

Claus is Junior-Professor of Bioorganic Chemistry at the School of Pharmacy, University of Saarland, Germany. Claus obtained his B.Sc. in Chemistry from the University of Leicester in 1993 and his D.Phil. from Oxford in 1997 working with Allen Hill FRS. From 1996 to 1999, he spent time as a Postdoc with Bert Vallee at Harvard Medical School. After holding the position of lecturer/senior lecturer in inorganic chemistry and EPSRC Advanced Research Fellow at the University of Exeter, he moved to Saarbruecken in 2005. Claus has a particular interest in the chemistry underlying biochemical redox events, with a focus on chalcogen-based redox systems. He is currently coordinator of the EU Marie Curie Initial Training Network "RedCat".

Key facts about Te Te

Discovery
1782, by Franz-Joseph Mueller von Reichenstein (1742-1825)
Natural Sources and abundance
Te is present in copper, gold and silver ores, average content in soil is 0.027 ppm (27 ppb)
Uses
In metallurgy as an alloying element in various types of steel
In chemistry as a secondary vulcanizing agent for rubber
In electronics as an alloy in selenium photoreceptors for printers and in DVDs
Possible future uses
Te-methionine as heavy-atom label for X-ray studies in proteins and enzymes
Fluorescent CdTe particles as biomarkers
Te nanoparticles in Medicine
Te-agents as (selective) antibiotics
Te-agents in cancer drug development
Natural isotopes (relative abundance)
^{120}Te (0.09%), ^{122}Te (2.55%), ^{123}Te (0.89%), ^{124}Te (4.74%), ^{125}Te (7.07%), ^{126}Te (18.84%), ^{128}Te (31.74%), ^{130}Te (34.08%)

a characteristic isotope splitting in mass spectrometry with an isotopic pattern consisting of signals for ^{120}Te (relative signal intensity 0.3%), ^{122}Te (7.5%), ^{123}Te (2.6%), ^{124}Te (13.9%), ^{125}Te (20.7%), ^{126}Te (55.3%), ^{128}Te (93.1%) and ^{130}Te (100%). At the same time, the presence of ^{125}Te, which is a diamagnetic nucleus (spin $\frac{1}{2}$), enables specific Te-NMR studies. Indeed, a 7% natural abundance of ^{125}Te compares favourably to an abundance of just 1% for ^{13}C, which forms the basis for ^{13}C-NMR. Besides its good natural abundance, the wide chemical shifts associated with ^{125}Te are advantageous for distinguishing Te atoms in different chemical environments.[9] The span of shifts observed ranges from $\delta \sim 2600$–3300 ppm in highly deshielded Te–Se dications to $\delta \sim 0$–700 ppm in the much more shielded dialkyl tellurides and dialkyl ditellurides.[10] Diphenyl ditelluride, a compound commonly used in chemical synthesis, for instance, exhibits a chemical shift of 422 ppm (in CH_2Cl_2, relative to the dimethyl telluride as reference at δ 0 ppm).[9] It should be pointed out that many aspects of ^{125}Te-NMR are still being explored, and over the years, different groups have applied quite a range of measuring frequencies, ranging from 31.59 MHz[11] to 63.01 MHz[12] and, more recently, to 94.75 MHz.[13,14]

2.1. Inorganic tellurium chemistry

The chemistry of tellurium as a metalloid is very diverse and tellurium compounds can be divided roughly into three groups, *i.e.* inorganic tellurides, tellurium-containing complex-like structures and organotellurides. Although this distinction is not sharp and not always applicable, it allows us to rationalize and better understand some basic features of tellurium compounds, such as their stability and reactivity, which becomes particularly important in a biological context.

We will begin our overview with the more traditional inorganic tellurium chemistry. Similar to sulfur and selenium, tellurium is able to occur in numerous oxidation states ranging from –2 (H_2Te) to +6 (TeO_4^{2-}). In Nature, tellurium is found in various forms, for instance as TeO_2 (oxidation state +4) and TeO_3 (oxidation state +6). These oxides form acids, namely tellurious acid (H_2TeO_3) and telluric acid (H_2TeO_4). The corresponding salts are known as tellurites TeO_3^{2-} and tellurates TeO_4^{2-}. Tellurates are generally more stable than tellurites. In addition, the anion TeO_2^{2-} (with tellurium in the oxidation state of +2) also exists. Furthermore tellurium is found as reduced Te^{2-} (telluride anion, oxidation state –2), for instance in Ag_2Te, and as ditelluride dianion Te_2^{2-} (formal oxidation state –1), for instance in Na_2Te_2. As far as applications are concerned, the telluride CdTe is of particular interest due to its unique fluorescent properties.

While the 'inorganic' chemistry of tellurium resembles the one of sulfur and selenium, there are also notable differences. In the case of tellurium, the +4 and +6 oxidation states have comparable stability, and this has a range of implications: in contrast to sulfite,

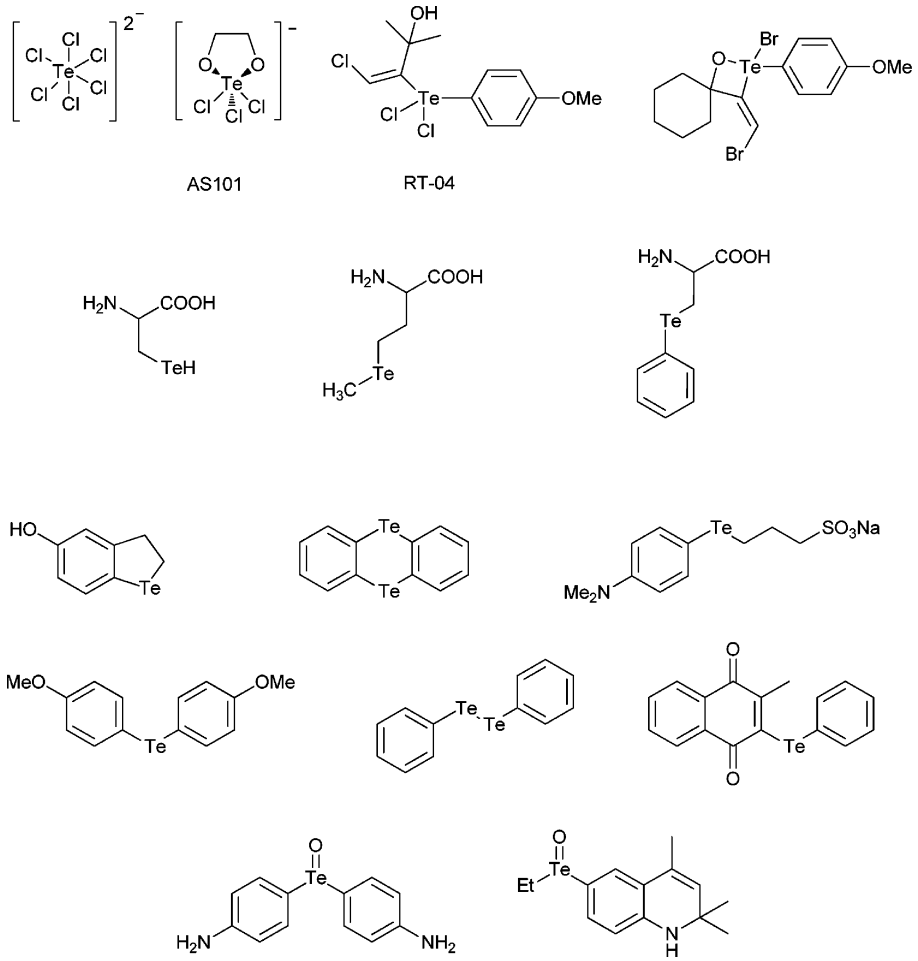

Fig. 1 A selection of tellurium compounds which illustrates the chemical diversity of these agents. The figure shows complex-like tellurium compounds, such as AS101 and RT-04, which inhibit cysteine enzymes *via* ligand exchange and have been studied extensively in biological systems. It also highlights several tellurium-containing amino acid analogues (Te-cysteine, Te-methionine, Te-phenyl-L-tellurocysteine), heterocyclic agents, and a range of chemically rather stable, catalytically active organotellurides. The tellurium atom in most of these compounds is redox active, and telluroxides form a specific group of organotellurides. (See text for discussion and literature)

tellurite is not easily oxidized to tellurate, as reflected in the redox potentials ($E^0(SO_3^{2-}/SO_4^{2-}) = -0.936$ V and $E^0(TeO_3^{2-}/TeO_4^{2-}) = +0.07$ V in alkaline solution). This difference in stability of oxidation states and redox behaviour will become important later on. Overall, the field of inorganic tellurium chemistry is rather extensive and cannot be covered here in full. Fortunately, several excellent reviews on this topic exist which may be consulted for more detailed information.[15,16]

2.2. Tellurium complex chemistry

Tellurium is somewhat more 'metallic' when compared to sulfur and selenium. This leads to the rather curious situation that a group of tellurium compounds exist which, because of bonding, structure and reactivity, may be best described as 'tellurium complexes' (Fig. 1). The latter include (3*E*)-4-chloro-3-[dichloro(4-methoxyphenyl)tellanyl]-2-methylbut-3-en-2-ol (often referred to as RT-04) and trichloro(dioxoethylene-*O*,*O*′)-tellurate (often referred to as AS101), two tellurium compounds which have been studied quite extensively in a biological context. We will therefore briefly discuss these complex-like structures.

The compounds belonging to this group generally contain a central tellurium atom, which is bound to a range of—often multidentate—ligands. The latter regularly coordinate to tellurium *via* an oxygen atom. Coordination numbers vary, but tend to be either 4, 5 or 6, which results in mostly square-planar, trigonal bipyramidal or octahedral structures. The chemical behaviour of these complexes is distinctively different from the one of inorganic tellurium salts or organic tellurides (where tellurium is bound covalently to carbon atoms). The rather weak 'coordinative bond' between the tellurium central atom and the ligands enables ligand-exchange reactions, as observed in Te-containing macrocycles, where iodide is exchanged for chloride.[17,18]

This kind of ligand exchange is also responsible for the majority of biological activities associated with molecules such as AS101.[19] The inhibitory action found against various cysteine proteases, for instance, is due to ligand exchange at the tellurium atom, whereby one of the original chloride ligands is exchanged for the thiol(ate) group of the active site cysteine residue of the protease (as observed for cathepsin B). The resulting, more stable Te–S complex leads to the inactivation of the protease, a process which has a range

of important implications in the context of tumour invasion (see later on).

A similar coordinative bond also plays a significant role in the catalytic activity of certain tellurium (and selenium) agents. Here, a kind of internal chelation between the tellurium atom and specific heteroatoms present in the molecule (such as nitrogen or oxygen) results in an internal stabilisation of the different tellurium oxidation states. The latter leads to an improved catalytic activity when compared to similar molecules lacking the heteroatom stabilisation.[20,21]

2.3. Organotellurium compounds

The field of organotellurium chemistry includes a vast and diverse range of different organotellurides with characteristic tellurium–carbon bonds. Fig. 1 shows a selection of tellurium compounds which represent various aspects of organotellurium chemistry. The tellurium atom is mostly di- or tetravalent, which in some instances is also a reflection of its oxidation state. It may be bound to alkyl or aryl residues, but also to other atoms, such as halides, oxygen or hydrogen. The tellurium–carbon bond is not particularly stable. Although exact numbers are difficult to obtain, the trend within Group 16, which proceeds from 358 kJ mol^{-1} for the C–O-bond to 272 kJ mol^{-1} for the C–S-bond and 234 kJ mol^{-1} for the C–Se-bond places the C–Te-bond at around 200 kJ mol^{-1} (or even lower).[22] Te-aryl or Te-alkylaryl compounds are generally more stable when compared to Te-alkyl compounds.[23,24] Halide ions bound to the tellurium are easily exchangeable, for instance for oxygen and sulfur (see above).

Tellurium is also redox active, and compounds which contain a Te═O bond, so-called telluroxides (RTe(O)R, R ≠ H) are formed from tellurides (RTeR) by oxidation. The telluride/telluroxide redox pair plays an important role as far as the catalytic properties of tellurium are concerned, which will be discussed at length in section 2.4. Similarly, compounds with a tellurium–hydrogen bond, so-called tellurols (RTeH), are also redox active. These compounds are reasonably acidic (the pK_a of H_2Te is 2.6, compared to 3.8 for H_2Se and 7.0 for H_2S),[25] and the presence of the tellurolate (RTe^-) anion at a pH of 7.4 provides in a highly reducing tellurium species under physiological conditions. The latter is readily oxidized to a ditelluride (RTeTeR). Despite the weakness of the Te–Te bond, tellurium, like sulfur, has a tendency to catenate, and Te_x chains as well as 'mixed' polychalcogenides have been found in a range of compounds.[3]

One particular and frequently recurring issue concerning organotellurium compounds is their chemical stability. Many of the compounds containing Te–Hal, Te–O, Te–H or Te–Te bonds are chemically unstable. These compounds are often coloured, light-sensitive and tend to hydrolyse and to decompose, forming telluroxides, tellurite, tellurate or indeed elemental tellurium, in the process. Diaryl tellurides and alkylaryl tellurides appear to be more stable and during the last two decades have been studied increasingly in a biological context. Similarly stable, yet less explored are heterocyclic tellurium compounds where the Te atom is incorporated into (aromatic) ring systems.[26] These compounds appear to be particularly stable, yet have hardly been studied in biological *in vitro* assays or indeed *in vivo*.

Organic tellurium chemistry embraces a wide and diverse arsenal of chemical reactions, including reductions and oxidations, ring closure reactions and transmetallation reactions. This chemistry can be exploited for catalysis (see later on), but also for functionality transformations, protection/deprotection of functional groups and in radical chemistry. Details of the more 'organic' aspects of tellurium chemistry may be found in the book entitled "Tellurium in Organic Synthesis" by Nicola Petragnani and Hélio Stefani,[27] and in recent authoritative reviews by Petragnani *et al.* and by Zeni *et al.*[28,29] Since we will primarily focus on the biological aspects of tellurium chemistry, we will finally turn our attention to one specific aspect of tellurium chemistry, namely tellurium-based catalysis, which will feature prominently in the following sections.

2.4. Tellurium-based redox-activity and catalysis

Among the various chemical aspects of organotellurium agents, redox-activity and catalysis are perhaps the most exciting. Many tellurium-based substances are redox-active, with formal oxidation states of tellurium in these compounds ranging from −2 to +6. Fig. 2 outlines a selection of commonly observed redox-transformations centred around the Te atom. While this illustration is far from complete, it still provides a closer look at the more common tellurium chemotypes involved in redox catalysis, including tellurides (RTeR), telluroxides (RTe(O)R), tellurols (RTeH) and ditellurides (RTeTeR). One of the most important aspects of this redox-chemistry is its close relationship with the other chalcogen elements, in particular with oxygen and sulfur. Reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), for instance, are able to oxidize tellurides to telluroxides and tellurols to ditellurides. In contrast, thiols often act as reducing agents, transforming telluroxides to tellurides and ditellurides to tellurols.

This particularly close connection between the redox chemistries of oxygen, sulfur and tellurium also forms the basis for highly specific redox interactions within the group of chalcogen compounds. For instance, it provides the platform for a powerful, tellurium-centred redox catalysis which involves oxygen and sulfur compounds. Such a catalytic cycle is illustrated in Fig. 2. The cycle starts with a reduced tellurol (RTeH) or telluride (RTeR), which is oxidized by a ROS to a ditelluride (RTeTeR) or telluroxide (RTe(O)R), respectively. The latter are subsequently reduced back to RTeH or RTeR by the attack of two thiol equivalents. Overall, this catalytic cycle reduces H_2O_2 to H_2O and consumes two RSH equivalents to form RSSR. It resembles the cycle of the human antioxidant selenium enzyme glutathione peroxidase (GPx), which is the reason why many organotellurides have been tested *in vitro* and in cell culture as antioxidant 'GPx mimics'. While the exact mechanism of Te-based catalysis is not yet fully understood, it probably proceeds *via* a tellurosulfide intermediate. A similar redox mechanism is also found in the case of selenium compounds, yet many studies show that Te-based catalysis is considerably more powerful, with Te-analogues often ten or more times catalytically more active compared to their Se-analogues (sulfur analogues are usually catalytically inactive in this context). Recently, a fairly good correlation between the (first) electrochemical oxidation potential Epa_1 of these tellurides and catalytic and/or biological activity has been postulated.[30,31]

The GPx-like activity of organic tellurium agents has stimulated research into the wider antioxidant properties of tellurium and its

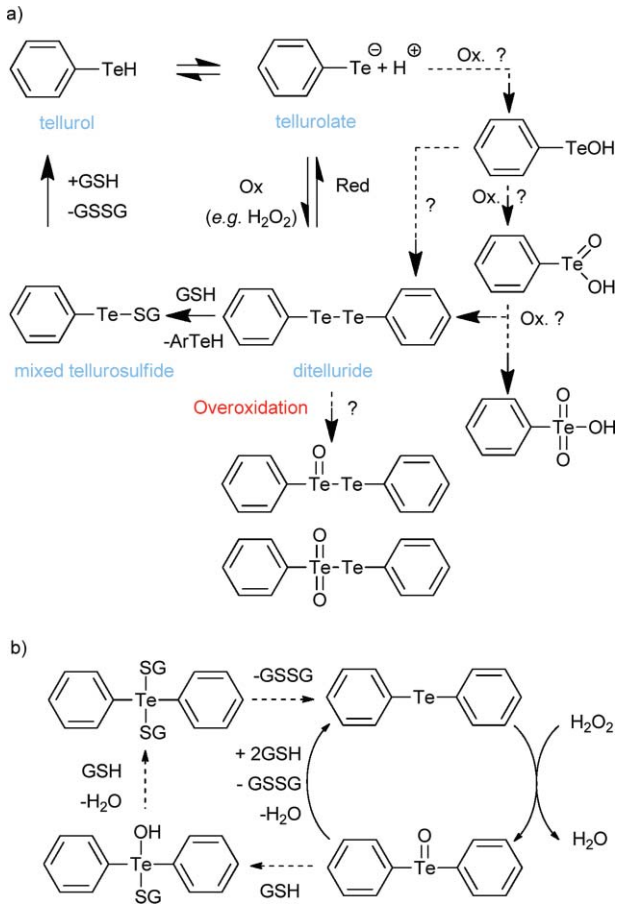

Fig. 2 Tellurium-based oxidation states and associated redox transformations. The scheme, albeit incomplete, indicates the various redox processes which also form the basis for catalysis. It should be noted that there are two distinct tellurium-based redox networks of interest in biological chemistry, one based on tellurols (RTeH) and ditellurides (RTeTeR), the other on tellurides (RTeR) and telluroxides (RTe(O)R). The latter appears to be the chemically more stable and catalytically more reliable one of the two. Several of the reactive intermediates, such as the tellurium based acids (RTeOH, RTe(O)OH and $RTe(O)_2OH$) and the tetra-coordinated, reduced forms of the telluroxides, are still speculative at this time.

compounds. Certain organotellurides have been tested as chain-breaking antioxidants, whose (biochemical) activity resembles the one of vitamin E. Such 'vitamin E mimics' appear to reduce peroxyl radicals more efficiently compared to α-tocopherol and are also able to decompose hydroperoxides in the presence of stoichiometric amounts of thiol reducing agents.[32,33] Nonetheless, it should be pointed out that the redox behaviour of organotellurium compounds is often rather complicated, and that unexpected side reactions may also need to be accounted for. This complex behaviour is reflected in particular in studies which have evaluated tellurium compounds in biological systems.

3. Tellurium in biology

Despite the diversity and reactivity of tellurium compounds, Biology does not appear to take any major advantage of tellurium and its associated chemistry. There are very few examples where the element actually occurs in living organisms.

Table 1 Natural abundance and man-made enrichment of tellurium in soil, water and certain gaseous emissions. Please note that the samples studied were obtained from selected sites and values may differ significantly depending on location. It should also be pointed out that some of these concentrations are close to the detection limit for tellurium.

Soil content		
San Joaquin soil (CA, USA)	90	ppb
Average of Guangxi area (China)	70	ppb
Deposition from atmosphere (Norway)	5.2	ppb
Water content		
River and harbor sediments	<0.001	ppb
Geothermal waters (New Zealand)	<0.001	ppb
Gaseous emissions		
Soil gases near ore deposits (near Mainz, Germany)	0.000003	ppb
Gaseous emissions from mechanical/biological waste treatment	0.0001	ppb
Gaseous emissions from industrial sludge fermenter	0.1	ppb
Sewage gas (near Dortmund, Germany)	0.001	ppb
Gas from domestic waste deposits (Asslar, Germany)	0.001	ppb

3.1. Tellurium in plants, fungi and bacteria

The level of tellurium in plants depends on the plant species and the level of tellurium in the soil or the surrounding environment. An average abundance of 0.027 ppm tellurium in the soil has been estimated based on samples from Australia, China, Europe, New Zealand and North America. Nonetheless, the global distribution of tellurium varies widely. The tellurium content in Chinese soils, for instance, may range from 0.007 to 0.113 ppm.[34] Varying concentrations of tellurium in Nature are also found in certain geothermal waters, such as in the New Zealand geothermal water, or at polluted sites, such as in waste water, sewage sludge and in landfills (Table 1).[35–37]

These natural (and man-made) differences in abundance in the soil and water are reflected in the tellurium content of plants. In the late 1980s, Cowgill and colleagues carried out an extensive study of the tellurium content of plants, examining over 1,000 samples from trees, shrubs and flowering plants from the Ely mining region in Nevada, US and from western Colorado.[38] They noticed that plants known to accumulate selenium were also able to accumulate tellurium up to levels of approximately 1 ppm.

While tellurium does not seem to be a particularly beneficial element for plants, accumulation, probably *via* selenium pathways, may be used for tellurium detoxification of polluted areas, known as phytoremediation. The latter may proceed *via* several mechanisms, including phytoextraction, rhizofiltration, phytodegradation, phytostabilisation or phytovolatisation.[39] In the case of tellurium bioremediation by plants, the two first processes, *i.e.* accumulation of Te from soil in plants that can be harvested, and decontamination of polluted water (*e.g.* sewage) by absorbing Te *via* the roots of plants, are preferred. Such processes may also be integrated into the human food chain, for instance to lower Te levels in milk.[40] In the case of fungi, biovolatisation may also play a role in the removal of tellurium: Certain fungi are able to process tellurium compounds by biomethylation (in analogy to selenium compounds), which results in dimethyltelluride $(CH_3)_2Te$. Although $(CH_3)_2Te$ is toxic, it is also volatile and is continuously removed from the system *via* 'evaporation'.[41]

In rare cases, when fungi are grown without a sulfur source but in the presence of sodium tellurite, tellurium-containing amino

acids (tellurocysteine, tellurocystine and telluromethionine) and even tellurium-containing proteins are formed.[41] This more or less random incorporation of heavier chalcogen analogues instead of sulfur is well known for selenium, which substitutes for sulfur in the amino acid methionine, for instance in yeast. It is therefore not too surprising that similar processes also occur in the case of tellurium, at least in fungi. If such tellurium-incorporation also plays a role in plants and higher organisms, such as animals, is unclear. In any case, it would be highly interesting to extract such Te-containing proteins and enzymes from their organisms of origin and to study their properties, in particular their redox-behaviour and catalytic activities. The latter should differ significantly from the ones associated with the normal, sulfur-containing proteins and enzymes.

Many tellurates and tellurites are reasonably soluble and bioassimilation of tellurium is usually based on these anions. Unfortunately, both anions appear to be rather toxic to most living organisms. Microbiological studies related to tellurium have therefore focused on biochemical detoxification and resistance mechanisms rather than on (beneficial) tellurium metabolism. Nonetheless, these studies have also shed some light on the possible metabolic processes surrounding this element and its compounds. Resistance against tellurate and tellurite appears to rely mostly on reductive processes. Many microorganisms able to grow in the presence of tellurate and tellurite reduce these anions to elemental, insoluble Te^0, which does no longer pose any danger. Alternatively, reduction proceeds further to H_2Te which is methylated to volatile $(CH_3)_2Te$ or to ionic $(CH_3)_3Te^+$, both of which are subsequently excreted (see section 3.2).[42] These metabolic transformations seem to rely on pathways which exist for the metabolism of selenium, whereby H_2Se is generated from SeO_3^{2-} *via* selenodiglutathione (GSSeSG). H_2Se is a key intermediate in the synthesis of selenocysteine, yet is also methylated and excreted in situations where an excess of selenium is present. It is possible that tellurium 'highjacks' the metabolic machinery associated with selenium, and hence ends up as H_2Te, $(CH_3)_2Te$, $(CH_3)_3Te^+$ and also as part of certain amino acids. This implies that tellurodiglutathione (GSTeSG) may also be present, which so far—to the best of our knowledge—has not been reported in Te metabolism. The presence of GSTeSG in cells could result in a rather intricate biological activity, including selective toxicity associated with catalytic ROS generation, as has been shown previously for GSSeSG.[43]

Interestingly, recent studies have revealed yet another side to tellurate and tellurite metabolism: these anions can serve as electron acceptors in the respiratory chain and hence sustain anaerobic growth of certain bacteria. Bacteria able to employ tellurate and tellurite in this manner are rather exotic, though, and include *Bacillus selenitireducens*, *Sulfurospirillum barnesii*,[44] and *Bacillus beveridgei* sp. nov., which have been isolated from deep ocean hydrothermal vent worms.[45,46] When grown with tellurate or tellurite as terminal electron acceptors, these microbes produce uniformly sized nanoparticles of Te(0). In the case of *Bacillus selenitireducens*, these particles appear as nano-rods of 10 nm × 200 nm in size, while *Sulfurospirillum barnesii* forms irregular spheres of less than 50 nm in diameter. There are several possible applications for such tellurium nanoparticles, and a *biological* source for such materials would be most welcome.

3.2. Tellurium toxicity and currently known metabolism in humans

Besides the rather complex chemistry of many tellurium compounds, one of the reasons why tellurium has not been considered in drug development may be due to its early association with toxic and otherwise 'disagreeable' effects on humans. Indeed, it has known since the 19th century that humans or animals ingesting tellurium compounds, such as TeO_2 or tellurite, breathe out a "disagreeable garlic-like odour". Apart from this rather unpleasant side effect, more severe clinical manifestations of acute tellurium toxicity in patients include a metallic taste, nausea and vomiting.[47]

Nonetheless, one must emphasize that there is no generalized toxicity of 'tellurium', like there is also no general toxicity of 'oxygen'. The toxic effects associated with specific tellurium compounds depend on the chemical form of tellurium, such as inorganic *versus* organic tellurium compounds, and often also on the oxidation state. As will be discussed in more detail in the following section, organotellurium compounds with reasonably stable tellurium–carbon bonds are generally considered as less toxic compared to inorganic tellurium compounds, such as tellurate and tellurite. This may in part be due to different pharmacological and pharmacokinetic profiles, and different metabolic conversions inside the human body. Chasteen *et al.* have recently published a rough ranking of (inorganic) tellurium toxicity in *Pseudomonas fluorescens* K27, where tellurite is more toxic than tellurate which in turn is more toxic than elemental tellurium.[48] This ranking also appears to apply to humans.

Uptake routes of tellurium compounds from the environment into the organism differ. Cases of acute or chronic tellurium poisoning can occur due to oral ingestion. Alternatively, tellurium-containing dust may be inhaled and hence enter the body *via* the lungs. Once inside the human body, the tellurium compound in question may exert its toxicity *via* several avenues, most of which involve a strong interaction with (cysteine-containing) proteins and enzymes.

Several *in vivo* studies with tellurite performed in rats and mice, for instance, indicate that ingestion of TeO_3^{2-} causes a transient demyelination of peripheral nerves due to inhibition of squalene epoxidase (squalene monooxygenase). This enzyme contains active site Cys-490 and Cys-557 residues[49,50] and converts squalene to squalene-2,3-oxide as part of the first oxygen-dependent step in the biosynthesis of cholesterol, which in turn is a prominent component of myelin.[51,52] The underlying mechanism of squalene epoxidase inhibition has been studied in more detail, and appears to be due to binding of methyltellurium compounds to the thiol groups of the vicinal cysteine residues at the active site. While tellurite itself also binds to these cysteine residues, it does so with less affinity since the reactive cysteine residues in question are located in a hydrophobic pocket.[52] This may also explain the findings by Goodrum and colleagues, which found no effect for tellurite on squalene epoxidase *in vitro* as well as *in vivo*, whereas organic tellurium compounds, such as dimethyl- and trimethyltellurium, did inhibit squalene epoxidase in Schwann cells.[53,54]

Squalene epoxidase, however, may not be the only target for tellurium agents able to interact with cysteine residues. Nogueira and colleagues have recently performed a wide range

of toxicological studies with organotellurium compounds in mice and rats. They noticed that diphenyl ditelluride is neurotoxic in mice, teratogen in rat foetuses and also induces alterations to the glutamatergic system. This toxicity is, at least in part, due to the interaction of diphenyl ditelluride with the thiol groups of cysteine-containing proteins and enzymes, such as δ-ALA-D and Na^+, K^+-ATPase.[55–60] Future studies need to explore further the underlying chemistry, extent and possible specificity of such tellurium-sulfur-interactions. It is possible that the tellurium-sulfur chemistry at work here prefers a high(er) sulfur-coordination number around tellurium, which in turn would imply a strong preference for vicinal thiol groups.

While tellurium–sulfur chemistry may explain certain biological effects associated with tellurium compounds, one should not ignore the high affinity of tellurium to selenium, either. Another possible cause of tellurium toxicity may therefore be the adventitious binding of tellurium compounds to selenium present in certain selenium proteins and enzymes. Such a process may be equally detrimental to protein function and enzyme activity, and hence may cause significant damage to the (human) cell. In fact, it may even be possible that tellurium compounds prefer selenium over sulfur, *i.e.* exhibit a certain specificity for cellular selenium proteins. Prominent selenium-containing targets may include selenoprotein P and various GPx enzymes.[61] The activity of the human selenoenzyme thioredoxin reductase (TrxR) is also affected by tellurium compounds, possibly as a result of such tellurium–selenium interactions.[62]

Interactions between tellurium compounds on the one hand, and sulfur- and selenium-containing biomolecules on the other, may have severe consequences (Fig. 3). The hepatotoxicity of tellurium, for instance, has been linked to tellurite-binding to selenoprotein P and/or GPx.[61] Direct or indirect inhibition of GPx-activity would ultimately cause a loss of antioxidant defence, a build-up of H_2O_2 and widespread oxidative damage. A similar oxidative process may also occur in the central nervous system and especially in the brain. Employing a rat model, Widy-Tyszkiewicz *et al.* have shown that acute exposure of such animals to tellurite disturbs learning and spatial memory. These cognitive disorders may be attributed to an impairment and possible damage of hippocampal and prefrontal cortex neurons.[63]

Interestingly, tellurium compounds may not only weaken the cell's antioxidant defence, but also actively generate ROS, as has been observed for related selenium compounds. It has been known for several decades that the reduction of selenate and in particular selenite leads to a range of (mostly undefined) selenium intermediates which are able to redox cycle in the presence of dioxygen. These selenium-species, which may include molecules such as $GSSe^-$ or protein-bound selenols, reduce O_2 to the superoxide radical anion ($O_2^{\bullet -}$), which in the cell is processed further to H_2O_2 and the hydroxyl radical ($^{\bullet}OH$). These processes, which also involve superoxide dismutase enzymes, result in a cascade of rather potent ROS-based oxidative stressors and trigger a highly damaging oxidative burst. The selenium species oxidized in the process can be re-cycled in the presence of cellular reducing agents, such as GSH, and hence re-enter the vicious catalytic process of ROS generation. A similar, tellurium-centred chemistry, although speculative at this time, would also result in a severe oxidative burst, and may explain some of the toxic effects associated with tellurium, including radical generation, mutagenesis, neurotoxicity and interference with DNA repair.

Despite the various possible mode(s) of toxic tellurium action, the human body is also able to metabolize and ultimately excrete tellurium. Although the exact metabolic pathway or pathways are still not fully known, once more there appears to be a close resemblance with the pathways of selenium - even if there are differences in terms of absorption. As mentioned above, tellurium may in a sense 'highjack' the metabolic processes normally dealing with (an excess of) selenium. After ingestion of tellurite and tellurate, both are reduced to telluride, probably *via* GSTeSG and Te(0), and possibly in large parts by chemical rather than enzymatic processes. In the liver, telluride is then methylated, leading to the formation of dimethyltellurium ($(CH_3)_2Te$) and ultimately trimethyltellurium ($(CH_3)_3Te^+$). These methylated species are likely to be the most abundant forms of tellurium in circulation, which is primarily found in the kidney and is distributed to the spleen and the lungs. Ultimately, tellurium is excreted *via* the urine (mostly as

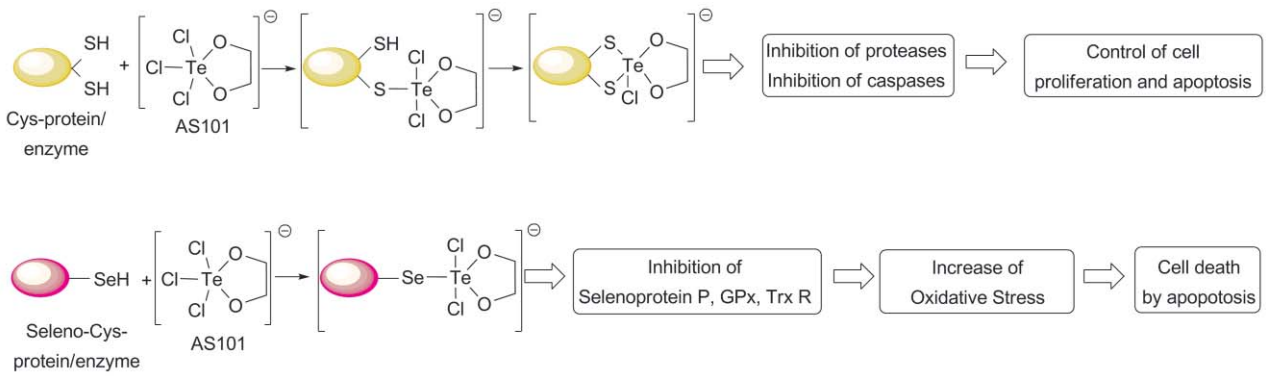

Fig. 3 Modification and inhibition of cysteine and selenocysteine-containing proteins and enzymes. Compounds such as AS101 to some extent behave like complexes and hence are able to undergo ligand-exchange reactions. Since the tellurium atom appears to have a certain preference for sulfur-ligands, cysteine-containing proteins and enzymes are attacked preferably, which results in change of function and loss of activity of these biomolecules. Attack on cysteine-proteases, such as cathepsin B and caspases, for instance, causes widespread changes to cellular metabolism and may ultimately result in cell death (*via* apoptosis). Although selenocysteine-containing proteins and enzymes are less abundant, proteins such as selenoprotein P, glutathione peroxidases (GPx) and thioredoxin reductase (TrxR) are also possible targets. The resulting tellurium–selenium bond in these proteins abolishes normal activity, which in the case of GPx and TrxR may subsequently trigger OS and ultimately lead to cell death.

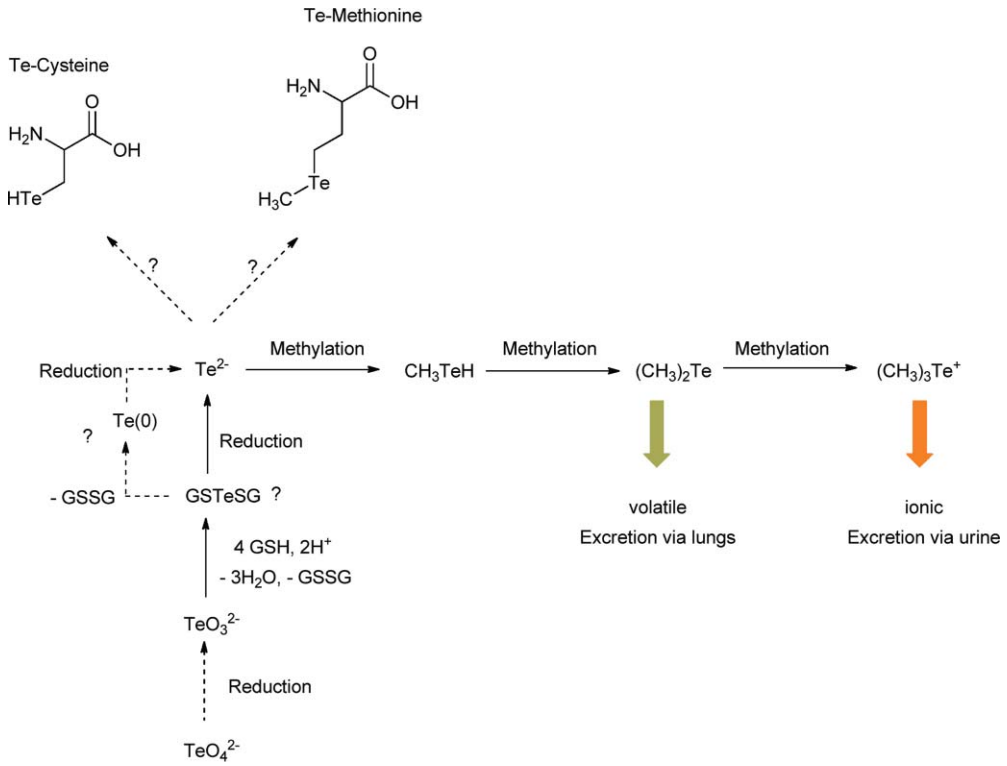

Fig. 4 Aspects of (human) tellurium metabolism. The scheme is still speculative at this time, and in part based on our knowledge of selenium metabolism, which to a certain extent appears to be 'highjacked' by the tellurium analogues. It should also be pointed out that the scheme contains a certain 'patchwork' of metabolic conversions taken from various organisms. Nonetheless, data available to date confirms the basic features of this scheme, such as an uptake of tellurite and tellurate, the formation of methylated forms of H_2Te (resulting in 'garlic breath') and, in some organisms, the presence of telluromethionine. In order to avoid any confusion, the most speculative parts of the scheme have been labelled clearly with question marks.

ionic, polar $(CH_3)_3Te^+$) and also *via* the breath, mostly as volatile $(CH_3)_2Te$, which has a boiling point of 82°C at atmospheric pressure[64]). The latter causes the garlic-like odour characteristic of metabolised, exhaled tellurium. (Fig. 4)

Dimethyltellurium species can also accumulate in red blood cells. This phenomenon has been studied in rats, where $(CH_3)_2Te$ bound to haemoglobin has been observed. The interaction of this tellurium compound with haemoglobin resembles the action of arsenic (in form of dimethylarsenious acid(III), $(CH_3)_2AsOH$), and may explain some of the toxic effects associated with tellurium.[22,42,65–67] Accumulation of such tellurium compounds in red blood cells ultimately also results in raised levels of tellurium in the spleen.

It must be pointed out, however, that the metabolic pathways of different tellurium compounds may vary considerably. Our considerations so far have mainly focused on 'inorganic' tellurium species. It is likely that organotellurium compounds with more or less stable tellurium–carbon bonds follow different metabolic avenues.

To date, issues surrounding the metabolism and toxicity of tellurium and its compounds in humans have only been studied superficially. Since tellurium has hardly been used on an industrial scale in the past, matters concerning its toxicity may indeed have been more or less academic. Nonetheless, this situation is changing rapidly. Since tellurium is increasingly present in daily goods—either intentionally or as a contamination—humans become more and more exposed to this element. Recent or new sources of tellurium in our environment include, for instance, vulcanized rubbers, alloys, glasses and DVDs. More thorough studies on tellurium toxicity and the associated metabolic and pathologic processes are therefore required in the near future. Such studies may also consider possible applications of tellurium in diagnostics and in therapy.

4. Potential applications of tellurium in diagnostics and in therapy

4.1. Tellurium as a biological marker

Although the biological chemistry of tellurium and its compounds is only just emerging, there have already been a range of interesting attempts to exploit the unique properties associated with this element in diagnostics and drug development. Here, we will discuss briefly a selection of some of the more stimulating approaches which employ tellurium in this context.

The various physical, chemical and in particular spectroscopic properties of tellurium have raised the possibility that tellurium-containing substances may serve as effective biological markers. Since the chemistry of tellurium somewhat resembles that of sulfur, tellurium may be incorporated into amino acids such as cysteine and methionine.[68–70] Interestingly, the incorporation of tellurium into methionine—and subsequently into proteins and enzymes—may not require a complicated tellurium-sulfur exchange chemistry or peptide synthesis. It may occur 'naturally'

via bioincorporation, as long as tellurium agents, such as synthetic telluromethionine, are present in the medium. Such a formal exchange of sulfur for the heavy atom tellurium (average atomic mass of 127.60 Da) is of considerable advantage, for instance in the context of protein structural studies by X-ray crystallography. Here, bioincorporation of selenium (as selenomethionine) has a longer tradition, yet can only provide certain protein structure highlights by the multi-wavelength anomalous dispersion (MAD) method. In contrast, tellurium is a true heavy atom and provides clear signals in both isomorphous and anomalous difference Patterson maps at the commonly used Cu-K_α wavelengths.[71] Ultimately, telluromethionine-labelled proteins allow X-ray imaging without the need of synchrotron radiation and the technically demanding MAD experiments. The apparent advantages of the tellurium-labelling method include convenience of the labelling procedure, selective labelling at the methionine sites, stability of telluromethionine, high isomorphism with the parent molecule, and—from a crystallographic point of view—high phasing power, relative abundance and mobility of target sites. A more widespread future use of this labelling method would therefore be hardly surprising.

The potential uses of tellurium as a biomarker are not limited to telluromethionine. In the early 1980s, Knapp, Kirsch and colleagues synthesized a range of fatty acids containing tellurium, including the radioactive ^{123m}Te isotope (single gamma photon emitter, half-life 120 d). These fatty acids were studied extensively in rats and dogs. The Te-containing fatty acids were hardly metabolised, but apparently 'trapped' in the myocardium (heart muscle). Because of the enrichment of the Te-containing fatty acids in specific organs, a possible application in nuclear imaging, for instance as part of the diagnosis of heart and pancreatic diseases, or in nuclear medicine, was proposed.[72–74] Although the underlying causes of this selective enrichment remained speculative at the time, a 'redox switch' was suggested, whereby the fatty acid telluride (RTeR) was oxidized *in vivo* to an insoluble telluroxide form, which was subsequently 'trapped' at sites with an oxidizing redox environment.[72] Apart from being biologically active themselves, such Te-containing fatty acids may therefore also serve as organ-specific carrier systems, for instance for radioactive bromine or iodine atoms.

Besides telluromethionine and Te-containing fatty acids, CdTe nanoparticles have recently been considered as biomarkers for fluorescent imaging. Such 'quantum dots' may well provide the basis for a highly sensitive imaging method. Future studies may investigate in more detail how such particles are distributed within the organism, if they enrich at sites of particular diagnostic interest (such as tumours) and if the resulting combination of distribution on the one hand and image-giving on the other is sufficient to provide a reliable diagnostic tool. Here, the arsenal of fluorescent tellurium particles is not limited to CdTe, but also includes CdSeTe, CdHgTe and CdTe/ZnTe, each of them exhibiting its own biological profile.[75–78]

4.2. Tellurium-based antibiotics

While the field of tellurium-based protein-labelling and fluorescent quantum dot imaging is still in its infancy, the area of tellurium-based cytotoxins, including antibiotics, has a longer tradition. Indeed, toxic tellurium agents experienced a very early, yet temporary, prominence at the beginning of the 20th century. A hundred years ago, in the pre-penicillin era, tellurite was used to inhibit the growth of many microorganisms, yet its action on bacteria was highly variable.[79] While tellurite was not employed to treat infections in humans, it was used in research, for instance as a 'benchmark antibiotic'. In 1932, Sir Alexander Fleming compared the antibacterial activities of penicillin and tellurite, and in nearly all cases, penicillin-insensitive bacteria were tellurite-sensitive and *vice versa*.[80]

At the time, however, the causes of tellurium toxicity, possible selectivity (as observed in passing by Fleming) and the underlying biochemical mechanisms were not considered. In hindsight, this may have been rather unfortunate, since the 'chemistry' associated with such compounds and their cytotoxicity is more complicated - and also more interesting - than initially thought. If deployed properly, such a chemistry may indeed enable a selective attack against certain microorganisms, including bacteria, and also against specific cancer cells. It is obvious that within this context of antibiotic drugs, tellurite may not be the most promising candidate, yet chemistry has moved on and there are numerous tellurium compounds available now, each with its very own activity and pharmacological profile. Many synthetic tellurides have turned out to be toxic when tested in cell culture or animal models. Apart from a pronounced cytotoxicity against certain cancer cells, which will be discussed later on, some of these compounds have also shown an interesting activity against microorganisms. One such organism, *Plasmodium falciparum*—which causes malaria—appears to be particularly sensitive against certain tellurium and selenium compounds.[81] The rather selective toxicity against plasmodia may be due to the fact many tellurium agents are redox active and increase levels of oxidative stress (OS), while plasmodia lack certain antioxidant defence systems and hence are particularly sensitive to this condition.

4.3. Organotellurium agents as redox modulators

As already mentioned, a number of organotellurium compounds exhibit rather promising, GPx-like catalytic properties, which are often superior to those of their selenium analogues (see section 2.4). At the same time, organotellurium compounds are able to sequester radicals, reduce peroxynitrite ($ONOO^-$) in the presence of RSH and protect metallothionein proteins against certain ROS.[24,82,83] These *in vitro* findings have fuelled a number of investigations into possible antioxidant properties of tellurium compounds. Indeed, some tellurium-containing agents have shown promising antioxidant activity in cell culture, such as 4,4′-dihydroxydiphenyltelluride, which has turned out to be considerably more protective in an (OS)-related model of Alzheimer's disease when compared to the benchmark selenium antioxidant ebselen.

There is, however, a serious caveat associated with these findings: while 4,4′-dihydroxydiphenyltelluride is catalytically quite active, it is non-specific with regard to its substrates. Rather than just consuming sacrificial GSH (which can be recycled in the presence of NADPH with the help of the enzyme glutathione disulfide reductase), it also oxidizes other thiols, in particular redox-sensitive cysteine residues in proteins and enzymes (Fig. 5). Ironically, the most reactive and sensitive cysteine residues are essential residues at the active site of enzymes, and those enzymes

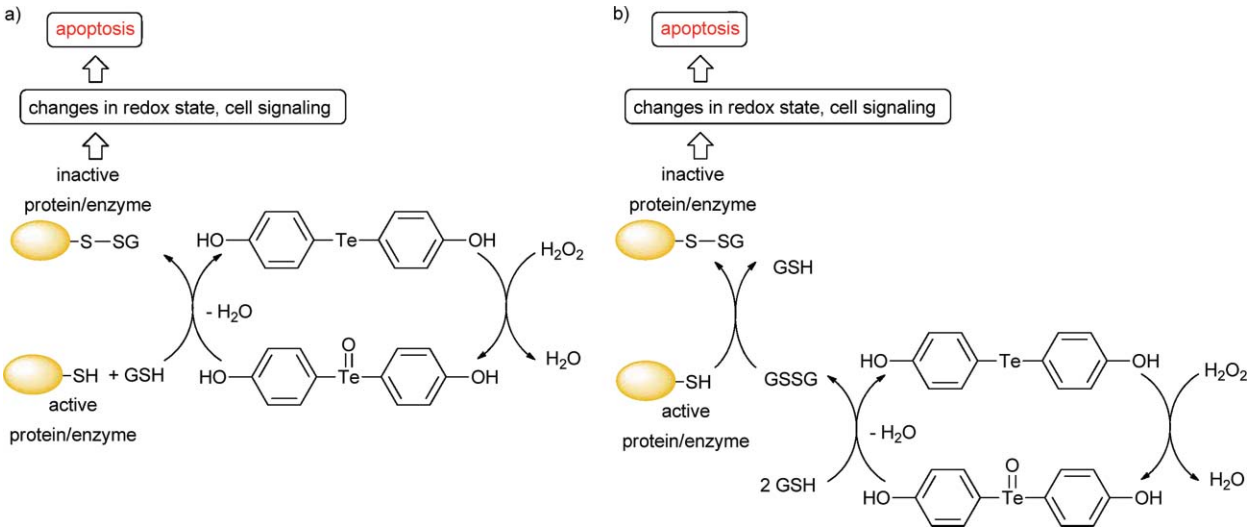

Fig. 5 Tellurium-based agents are able to sense the presence of ROS and subsequently oxidize key cysteine-containing proteins and enzymes. This process is often catalytic and results in the formation of S-thiolated biomolecules. The latter are either formed directly as part of the catalytic cycle itself **(a)**, or indirectly in a follow-on process caused by increased levels of GSSG **(b)**.

are affected severely by tellurium agents even in the presence of a large excess of (less reactive) GSH.

While oxidation and subsequent inhibition of cysteine proteins and enzymes may be considered as highly undesirable at first glance, it may also have considerable benefits. The oxidation of cysteine residues in proteins is an effective, yet also selective process, whereby the most reactive residues are targeted preferentially. This forms the basis for a rather interesting approach in anticancer research. Redox modulators, so-called 'sensor/effector' agents,[84] rely on this combination of high activity and (chemical) selectivity in order to recognize cancer cells under OS and kill these cells selectively, whilst leaving normal cells vastly unaffected. The underlying biological 'chemistry' is surprisingly straightforward. Research during the last two decades has shown that numerous cancer cells proliferate under OS, *i.e.* in the presence of elevated levels of ROS and an impaired antioxidant defence. By modulating this disturbed redox balance even further, it is possible to push such cells over a critical 'redox threshold', which triggers a cascade of apoptotic processes ultimately resulting in cancer cell death. Since normal cells are naturally lower in ROS (and other stressors), they are less affected by these processes. It therefore appears that the catalysts in question 'recognize' or 'sense' a particular 'biochemical signature' of OS in cancer cells and develop their effects accordingly.

Within this context, tellurium-based catalysts with GPx-like activity are of particular importance. For instance, a fairly selective activity of 2,3-bis(phenyltellanyl)naphthoquinone has been observed in various cancer cell lines, such as HT29 and CT26 human colon cancer cells, which are more affected by this tellurium compound when compared to normal cultured NIH 3T3 fibroblast cells. Similar results have been found in a model of human chronic lymphocytic leukemia (CLL). When CLL B-cells isolated from patient blood where treated with 2,3-bis(phenyltellanyl)naphthoquinone, a clear reduction in cell numbers was observed. In contrast, healthy B-cells from the same patients and control peripheral blood mononuclear cells (PBMC) cells were considerably less affected.[85] More detailed studies have revealed that the effects observed are due to redox modulation. Compounds such as 2,3-bis(phenyltellanyl)naphthoquinone are able to increase OS, either by generating ROS, converting less reactive ROS (such as $O_2^{\bullet -}$ radicals) into more reactive species (such as H_2O_2, $HO^{\bullet}$ radicals) or by catalyzing the ROS-driven oxidation of proteins and enzymes.[30,83,86] Some of these compounds may act *via* their tellurium site, but also *via* other sites, such as the redox-active quinone.

In any case, the chemical and biochemical events surrounding such tellurium compounds and their cytotoxicity are rather complex and considerably more intricate than originally thought. Based on recent studies by us and others, it is feasible that the tellurium-agents in question regulate the activity of specific apoptosis-inducing proteins in cancer cells, yet also trigger an antioxidant response in normal cells. Compound AS101 illustrates the (bio)chemical complexity associated with many tellurium agents. AS101 specifically inactivates cysteine proteases by interacting with and ultimately oxidizing the catalytic thiol to a disulfide. It also inhibits caspases, thereby down-regulating caspase-1 inflammatory products, such as interleukin-18 (IL-18) and IL-1β.[87] Direct inhibition of anti-inflammatory cytokine IL-10 induces the up-regulation of glial cell line-derived neurotrophic factor (GDNF), which in turn induces the activation of Akt and the associated cell survival pathways.[19]

In the last couple of years, various vinyl tellurium agents have been developed for therapeutic uses, which also inhibit cysteine proteases, similar to compound AS101.[88,89] Compound RT-04, for instance, inhibits mainly cathepsin B and therefore is able to induce apoptosis in HL60 cells with no significant toxic effects observed in normal bone marrow cells. A possible biochemical mode of action involves the regulation of Bcl proteins in these cancer cells.[90] Matters surrounding these and similar compounds and their mode(s) of action provide plenty of scope for future

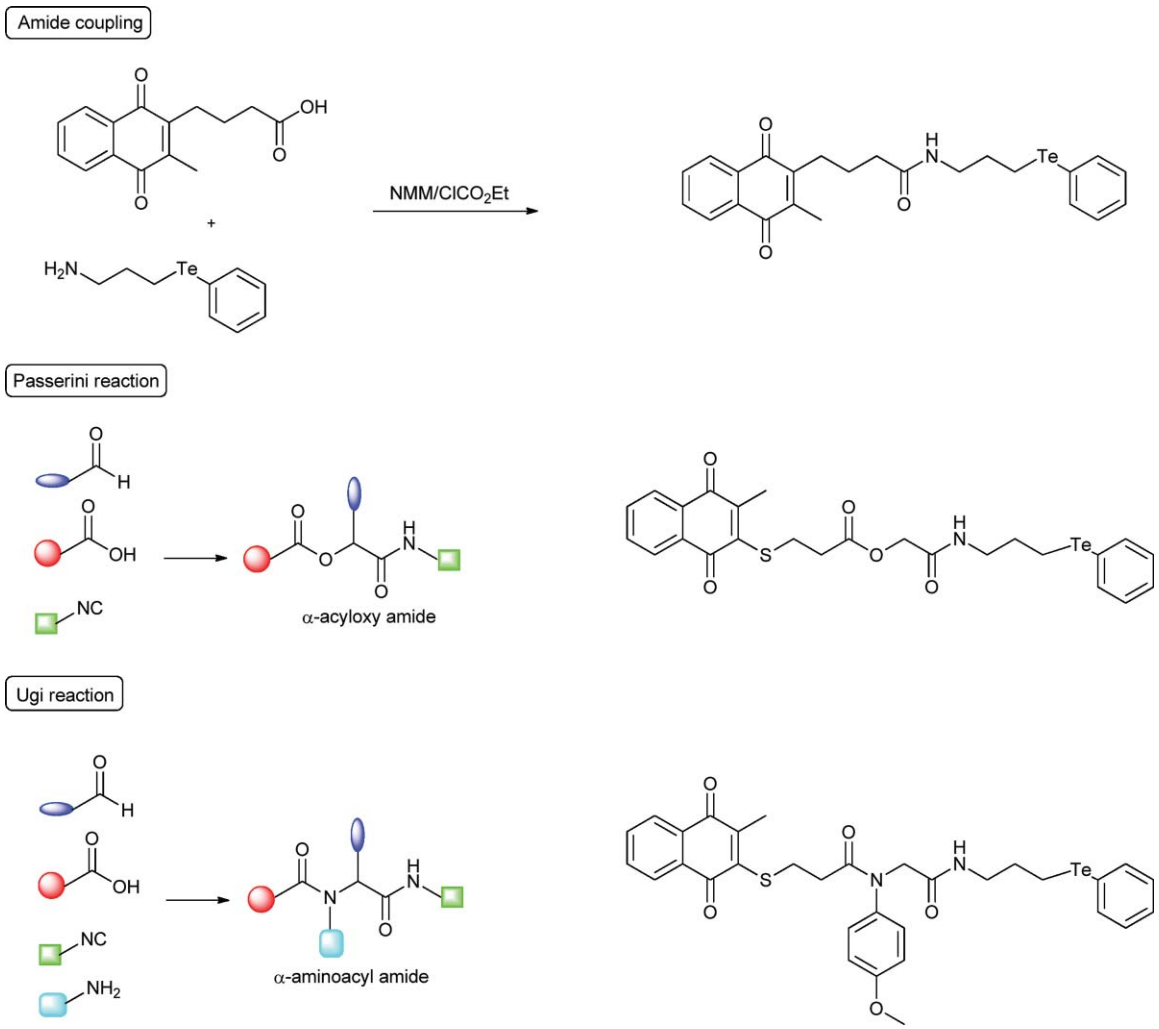

Fig. 6 Recently explored avenues for the synthesis of more complicated, often multifunctional tellurium agents. The use of building blocks which can be assembled in a final, straightforward coupling step is of particular interest, since it allows a 'mix and match' approach and, compared to more traditional methods, the synthesis of 'libraries' of rather large numbers of related tellurium agents within a short period of time.

investigations and, of course, the synthesis of more—and more sophisticated—tellurium agents.

4.4. Tellurium in multicomponent reactions

The issues surrounding the varied activity of tellurium agents in cancer and in normal cells are highly exciting and complicated at the same time. Not surprisingly, an increased interest in tellurium among biological chemists and pharmacists has fuelled the search for more and more diverse tellurium compounds. The design and synthesis of such compounds often has to overcome synthetic obstacles, such as sensitivity of tellurium compounds against water, air and light. As a result, several synthetic strategies have been explored during the last couple of years. Traditionally, simple modifications of certain tellurium-containing starting materials have been employed to 'build up' more complex molecules, for instance by adding groups *via* nucleophilic or electrophilic substitution. Diphenylditelluride, for instance, is easily reduced to the corresponding telluride (ArTeH), which may then act as nucleophile. In contrast, tellurium tetrachloride ($TeCl_4$) is a tellurium-centred electrophile which is also used extensively for the synthesis of organotellurium compounds.

Unfortunately, the subsequent modification of tellurium-containing molecules is often difficult. In order to overcome these chemical problems and to enable the production of highly functionalized tellurium-containing agents, it is often advisable to employ a very different strategy: rather than adding functionalities to a pre-existing tellurium-containing molecule, it may be more sensible to synthesize first a range of 'building blocks', each bearing the desired groups. These blocks can then be combined to a more complex molecule in a final assembly step. Once an arsenal of fairly stable building blocks, for instance compounds bearing a carboxylic acid, amine, aldehyde or isonitrile function, is available, these blocks can be 'assembled' using a variety of straightforward 'assembly reactions'. The latter include coupling reactions between aldehyde and amine, amide coupling (carboxylic acid and amine), the three-component Passerini reaction (carboxylic acid, aldehyde, isonitrile) and the four-component Ugi reaction (carboxylic acid, amine, aldehyde, isonitrile).[81,91] (Fig. 6) These coupling methods allow an extensive 'mix and match' of individual building blocks

in order to generate highly functionalized agents. Several of them have already been used successfully to synthesize a range of compounds combining tellurium with quinone redox centres and metal binding sites.

5. Conclusions and outlook

As the previous sections have illustrated, the field of biological tellurium chemistry is slowly emerging from the shadows with the potential to become a major player in protein chemistry, imaging and diagnostics, as well as in the search for new and more potent antibiotics and anticancer agents. This emerging area is fuelled by two parallel developments. On the one hand, the synthesis of novel and sophisticated tellurium agents with tailor-made properties; on the other, the detailed evaluation of reactivity, biochemical targets and mechanisms associated with these compounds. Both areas provide numerous opportunities for future research. Extensive biochemical studies are required to identify the various targets of the tellurium compounds—which may well differ depending on the individual compound—and to elucidate the chemical and biochemical processes which occur once such a target is being hit.

At the same time, the field of tellurium synthesis requires a certain renaissance. Traditionally, biological studies have employed tellurium compounds which were modelled on their respective selenium analogues. Since the chemical diversity, reactivity, biochemistry, metabolism and hence also biological activity of tellurium and selenium agents differ significantly, simply synthesizing 'analogues' is no longer sufficient. Once appropriate biological targets for tellurium agents have been identified, it will be possible to design more specific, tailor-made tellurium agents. In the medium term, areas such as synthetic tellurium chemistry, tellurium-based spectroscopy and imaging are likely to grow, whilst tellurium biochemistry and a niche area of tellurium-centred pharmacology may emerge and develop depending on the results obtained during the next couple of years.

Abbreviations

δ-ALA-D	δ-aminolevulinate dehydratase
CLL	chronic lymphocytic leukemia
DVD	digital versatile disc
GDNF	glial cell line-derived neurotrophic factor
GSH	glutathione
GPx	glutathione peroxidase
IL	interleukin
MAD	multi-wavelength anomalous dispersion
OS	oxidative stress
PBMC	peripheral blood mononuclear cells
ROS	reactive oxygen species
GSSeSG	selenodiglutathione
GSTeSG	tellurodiglutathione
TrxR	thioredoxin reductase

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