CHEMICAL REVIEWS

REVIEW

pubs.acs.org/CR

Bioinorganic Chemistry of Titanium

Katherine M. Buettner[†] and Ann M. Valentine[*,‡]

[†]Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, United States

[‡]Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, United States

CONTENTS

1. INTRODUCTION

Louis-Camille Maillard is best remembered for his namesake organic reaction, one between an amino acid and a reducing sugar.[1] In his final four papers before his death in 1936, however, Maillard reported on the occurrence and possible role of titanium in mammals, and in particular in humans.[2−5] In his last paper,[5] Maillard concluded:

"At the present time, nothing allows us to say whether titanium must be regarded as a constitutional element of the human material, or an accidental one, and we intend for the moment not to take sides, either in one direction or in the other. For this reason, we prefer to declare [that titanium is] not a new element *of* the human body, but more modestly, a new element *in* the human body."

Seventy-five years later, conventional wisdom in bioinorganic chemistry still holds that there is no native role for Ti in the biology of any organism, much less that of humans. Some reports in the literature across several fields suggest that Ti is biologically active, however, and this review attempts to bring together these pieces into a coherent whole, so that the role of Ti as a biological element can better be considered.

Inorganic elements in biology include those with some natural biological effect, whether beneficial or harmful, as well as those used medicinally as probes or drugs.[6,7] The beneficial members of the former group include widely employed elements (such as iron, copper, and zinc) as well as elements that are used by just a few species (such as cadmium and tungsten). When we consider which inorganic elements Nature has selected through evolution,[8] we generally say that Nature employs elements that (1) facilitate useful chemistry and (2) are sufficiently abundant and sufficiently bioavailable for organisms to benefit from their exploitation. Given these selection criteria, it would be surprising if Ti were not a biological element. Humans have found numerous uses for

Received: August 31, 2011
Published: November 11, 2011

dx.doi.org/10.1021/cr1002886 | *Chem. Rev.* 2012, 112, 1863–1881

Ti, including in its complexed form as a catalyst in many important transformations,[9−13] in its oxide form as a pigment and a component of promising solar cells, and in its oxide or alloy forms as useful materials.[14] If Ti has no native role in biology, then humans have found valuable applications for an element for which Nature has never found a use.

Returning to the point about abundance and bioavailability, titanium is certainly abundant; at 5600 ppm, it is the ninth most abundant element in the Earth's crust and is the second most abundant transition metal, after iron (Figure 1).[15,16] Most of that Ti is present as insoluble oxides; the main impediment to Nature's wide use of Ti would be low bioavailability. Titanium(IV) (the predominant oxidation state in an aerobic environment) is a very hydrolysis-prone ion, and Ti(IV) is not very soluble in aerobic aqueous solutions near neutral pH (see below). Geologists generally regard Ti as an immobile element, although some work suggests that it may be more soluble than is generally recognized, even under nonextreme conditions.[17,18] From the point of view of a chemist, though, even if only a small fraction of that environmental Ti is soluble or mobile, it is a small fraction of a large total and may represent a large amount of material on a mole basis.

Still, as Maillard noted, whether or not Ti is a required element for humans or any other species (an element *of* the body), it is a relatively abundant and little-examined component of biological systems (an element *in* the body). Compared to Maillard's human subjects in 1936, we are increasingly exposed to Ti through its growing use in paints and pigments, pharmaceuticals and sunscreens, orthopedic implants, nanomaterials, and so on. If only for this reason, the interactions of Ti with biomolecules are of interest. Some complexes of Ti are demonstrably bioactive; that group includes two once-promising anticancer medicines that stalled in clinical trials. A few reviews over the last 50 years have addressed the occurrence of Ti in biological samples (human tissues, foodstuffs, etc.) and Ti toxicity.[19−27] The current review will cover the aqueous coordination chemistry of Ti most relevant to its bioinorganic chemistry, address the abundance and reported effects of Ti in various organisms, and discuss the molecular interactions of Ti and biomolecules, with special attention to its potential in medicinal or toxic agents.

2. INORGANIC AND COORDINATION CHEMISTRY OF TITANIUM RELEVANT TO BIOINORGANIC CHEMISTRY

2.1. Hydrolysis and Speciation in Aqueous Environments

Titanium(III) and titanium(IV) are the most common oxidation states of Ti;[28] the potential at low pH, formulated for reduction of the titanyl $(Ti(IV)=O)^{2+}$ species,[29] is as follows:

$$TiO^{2+} + 2H^{+} + e^{-} \rightarrow Ti^{3+} + H_2O \quad 0.09\ V\ (vs\ NHE) \qquad (1)$$

In an aerobic atmosphere, particularly near neutral pH, Ti(IV) is favored, and most of the Ti in the environment is oxidized. This discussion of hydrolysis and complex formation will thus focus on Ti(IV), although in reducing environments, including ones that may have occurred during the evolution of the Earth,[8] Ti(III) can be favored. Titanium(III) citrate notably finds an important modern use as a biocompatible reductant, for example, as an agent to maintain anaerobic cell culture.[30,31] Its aqueous speciation is unclear.

Titanium(IV) is a very strong Lewis acid, and water molecules bound to Ti(IV) are prone to hydrolysis. Iron(III) and aluminum(III) are also hydrolysis-prone, but the unhydrolyzed species $Fe^{3+}(aq)$ and $Al^{3+}(aq)$ exist at low pH values.[32] The

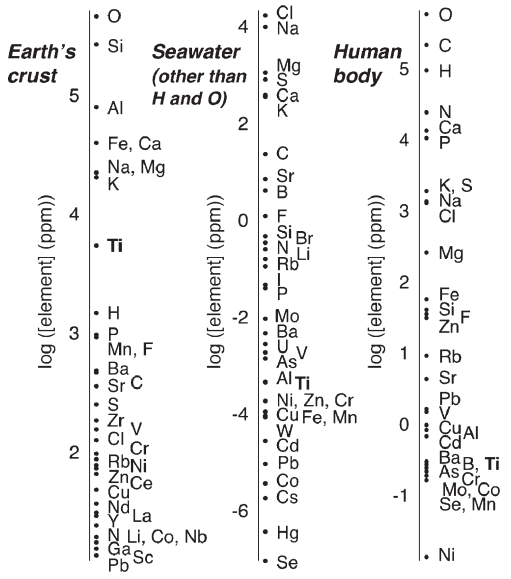


Figure 1. Abundances of the elements in several environments, modeled on the presentation of Kaim and Schwederski (ref 15), according to the data of Emsley (ref 16).

first deprotonation of Fe(III)- and Al(III)-bound water occurs around pH 2 and pH 5, respectively.[32,33] By contrast, the doubly hydrolyzed species $Ti(OH)_2^{2+}$ (often formulated as $TiO^{2+}\cdot H_2O$; see below) predominates even below pH 2.[32] Speciation studies in chloride media between pH −1 and 0.5 revealed the following values for the first and second deprotonation equilibria of Ti(IV)-bound water:[34]

$$Ti^{4+} + H_2O \leftrightarrows Ti(OH)^{3+} + H^{+} \quad \log K_{a1} = 0.3 \qquad (2)$$

$$Ti(OH)^{3+} + H_2O \leftrightarrows Ti(OH)_2^{2+} + H^{+} \quad \log K_{a2} = 1.08 \qquad (3)$$

Further hydrolysis of $Ti(OH)_2^{2+}$ occurs to give $Ti(OH)_3^{+}$ and $Ti(OH)_4$.[32,35] $Ti(OH)_5^{-}$ has also been invoked.[18] These species are written as monomeric and without a titanyl unit ($[Ti{=}O]^{2+}$). Important work by Comba and Merbach investigated the prevalence of titanyls and oligomeric clusters in aqueous solutions of Ti(IV) at low pH.[36] Such polynuclear clusters are well precedented for other Lewis acidic metal ions like Fe(III).[37] The Comba and Merbach work demonstrated oligomers (modeled as trimers and tetramers), in addition to monomers, with oligomers favored at low $[H^+]$, high $[Ti(IV)]_{total}$ ($\geq 0.05m$), and high ionic strength.[36] These species exchanged ligands quite rapidly, with $k_{ex} = 100 \pm 50\ s^{-1}$ for bridging oxo and hydroxo oxygen atoms, $k_{ex} = 3\,400 \pm 200\ s^{-1}$ for oxygen atoms of terminal waters and hydroxo ligands, and $k_{ex} = 16\,000 \pm 5\,000\ s^{-1}$ for titanyl oxygen atoms (with the latter value measured in 68% aqueous methanol). The surprisingly fast exchange of the titanyl oxygen, orders of magnitude faster than that of the vanadyl, was ascribed at least partly to its ease of protonation. The authors argued that these fast exchange rates suggest caution for speciation results based on ion-exchange experiments (which includes much of the early work). This work provided evidence for a titanyl species, but because of its ease of protonation, also argued against models that feature titanyl as the only species in solution (as does the typical formulation for the reduction reaction, eq 1).

dx.doi.org/10.1021/cr1002886 |*Chem. Rev.* 2012, 112, 1863–1881

"Hydrolysis-prone" and "insoluble" are related but not interchangeable terms. Ti(IV) is a stronger Lewis acid than Fe(III) or Al(III), as evidenced by its first hydrolysis constant. If we consider the pH-dependent aqueous species of these ions and their solubilities, however, an interesting result emerges. Near neutral pH, the neutral hydroxide species of all three ions dominate ($Fe(OH)_3$, $Al(OH)_3$, and $Ti(OH)_4$ or $TiO(OH)_2$),[32] each probably further forming polynuclear clusters.[37] The Fe(III) species is soluble on the order of 10^{-12} M (or less) near pH 7.[32,38] The corresponding Al(III) species is soluble on the order of 10^{-6} or 10^{-7} M near pH 7.[32,39] The solubility of Ti(IV) aqueous species as a function of pH, from two different studies, is given in Figure 2.

A few features of these data are worthy of note. Although the soluble species are written as mononuclear, polynuclear clusters are likely.[36] As expected, the total solubility of all Ti(IV) species is greater when in equilibrium with the less stable amorphous ("hydrous" or "freshly hydrolyzed") TiO_2, often formulated as $TiO_2 \cdot nH_2O$ or $Ti(OH)_4(s)$ (Figure 2A).[32,35] These data agree well with data compiled from the older literature.[32,40−42] Although Ti(IV) is certainly only sparingly soluble, Figure 2A illustrates why the insolubility of Ti(IV) is sometimes overstated: estimates of the aqueous solubility of Ti(IV) are sometimes erroneously made by using the K_{sp} of $Ti(OH)_2^{2+}$ and calculating solubility at, for example, pH 7. This calculation effectively extrapolates the steep solubility line at low pH to its value at pH 7. With thermodynamically more stable crystalline rutile as the solid phase, the solubility is several orders of magnitude lower (Figure 2B).[18] For rutile, the lowest temperature at which data are available is 100 °C, although the solubility is relatively constant between 100 and 300 °C. For either amorphous or crystalline TiO_2, however, $[Ti(IV)]_{aq,total}$ is much greater at pH 7 than $[Fe(III)]_{aq,total}$. In other words, Ti(IV) is a stronger Lewis acid than is Fe(III), but the hydrolyzed products are more soluble at neutral pH. Even so, due to difficulties with several older analytical methodologies, measurement of Ti concentrations below 1 μM was historically challenging.[24]

These data in Figure 2A were modeled by stepwise hydrolysis constants:

$$Ti(OH)_2^{2+} + H_2O \leftrightarrows Ti(OH)_3^{+} + H^{+} \quad \log K_{a3} \leq -2.1 \qquad (4)$$

$$Ti(OH)_3^{+} + H_2O \leftrightarrows Ti(OH)_4 + H^{+} \quad \log K_{a4} \geq -3.7 \qquad (5)$$

In the rutile solubility experiments (Figure 2B), the concentration increase above pH 10 was taken as evidence for further hydrolysis to form a more soluble complex, and $Ti(OH)_5^-$ was invoked. In that work, the value for K_{a4} corresponding to eq 5 (determined from the data in Figure 2A for amorphous TiO_2) was comparable ($\log K_{a4} = -2.3$ at 100 °C), but the further hydrolysis was modeled as

$$Ti(OH)_4 + H_2O \leftrightarrows Ti(OH)_5^{-} + H^{+} \quad \log K_{a5} = -10.1 \qquad (6)$$

It is not clear why no comparable increase in concentration of soluble species was observed above pH 10 over freshly precipitated TiO_2 (Figure 2A).

2.2. Aqueous Titanium(IV) Coordination Chemistry with Biological Ligands

The rich coordination chemistry of titanium in its common oxidation states has been reviewed.[13] Because of its propensity for hydrolysis, well-characterized compounds of Ti(IV) that are prepared and/or stable in aqueous solution are somewhat rare. Most commercially available Ti(IV) reagents are not water compatible, and most syntheses of Ti complexes are performed in organic solvent with more or less rigorous exclusion of water. Often, hydrolysis leads to difficult-to-characterize mixtures of products. Most of the ligands that stabilize Ti toward hydrolysis are hard Lewis basic ligands having charged oxygen donors. Ideally one would like to know the pH-dependent speciation of a complex, as protons compete with Ti(IV) for ligand binding at low pH and hydroxide (or oxo) ligands compete with ligand for Ti(IV) binding at higher pH. One would also like to know something about the structure under the conditions of interest.

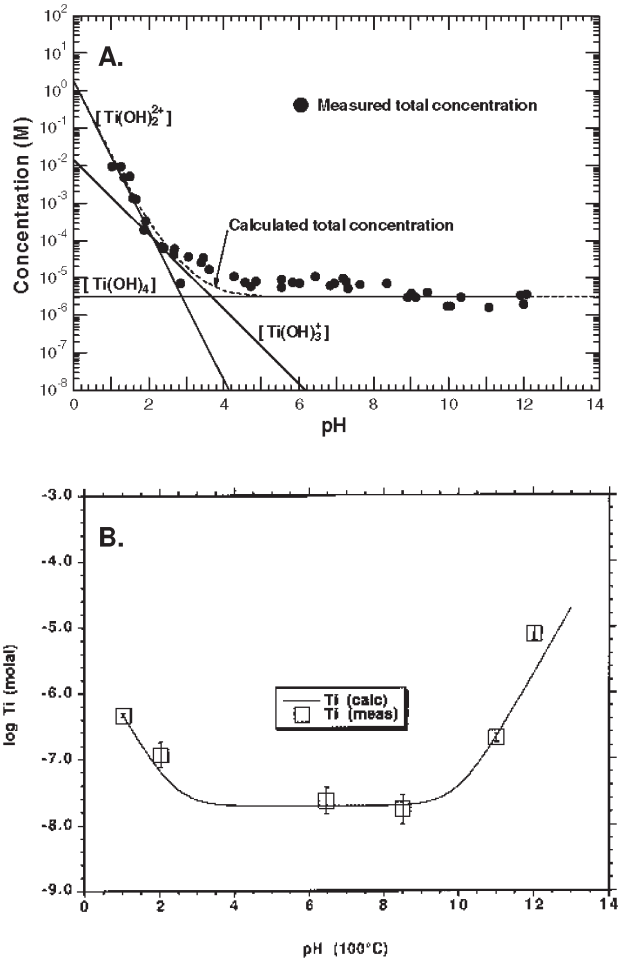


Figure 2. Concentration of soluble Ti(IV) species as a function of pH (A) in equilibrium with freshly hydrolyzed titanium oxide at 25 °C and (B) in equilibrium with crystalline rutile at 100 °C. Figure 2A was reprinted with permission from ref 35. Copyright 2002 Elsevier. Figure 2B was reprinted with permission from ref 18. Copyright 2001 Elsevier.

2.2.1. Macrocycles. Porphyrin complexes (Figure 3A) of Ti(IV) are known but are not generally water-soluble.[43] Substituted porphyrins (Figure 3B) like oxotitanium(IV) *meso*-tetrakis (1-methylpyridinium-4-yl)porphyrin ($OTi(TMPyP)^{4+}$) are water-soluble and commercially available; they have been used, for example, in DNA-binding studies.[44] Phthalocyanine complexes (Figure 3C) of Ti(IV) are known[45,46] but are also not very water-soluble, although substitutions can render them soluble.[47] Titanyl moieties are common in these complexes.

dx.doi.org/10.1021/cr1002886 |*Chem. Rev.* 2012, 112, 1863–1881

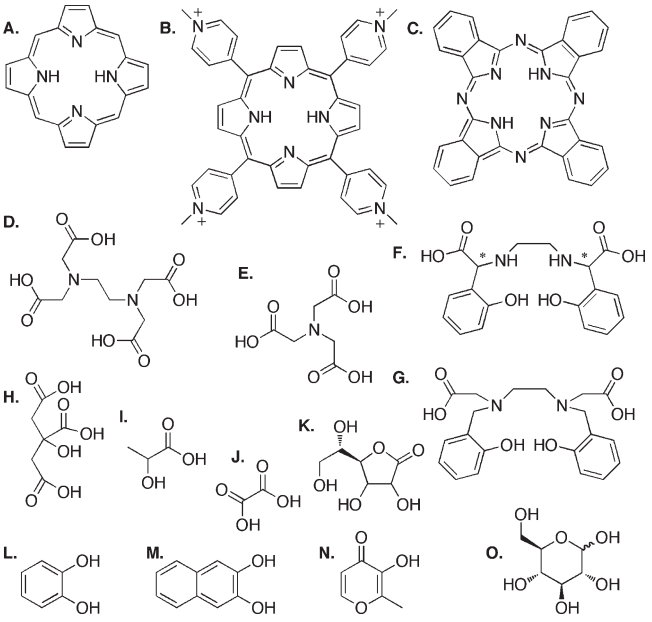


Figure 3. Ligands discussed here include (A) porphyrin, (B) *meso*-tetrakis (1-methyl pyridium-4-yl)porphyrin (TMPyP), (C) phthalocyanine, (D) ethylenediamine tetraacetic acid (EDTA), (E) nitrilotriacetic acid (NTA), (F) *N,N′*-ethylenebis(*o*-hydroxyphenylglycine) (EHPG), (G) *N,N′*-di(*o*-hydroxybenzyl)ethylenediamine-*N,N′*-diacetic acid (HBED), (H) citric acid, (I) lactic acid, (J) oxalic acid, (K) ascorbic acid, (L) catechol, (M) 2,3-naphthalenediol, (N) maltol, and (O) D-glucose.

A recent theoretical study focused on the oxotitanium complexes of porphyrin, octamethylporphyrin, porphyrazine, and phthalocyanine.[48]

2.2.2. Carboxylate-Bearing Chelating Ligands. Reported stability constants[33] for complexes with some common chelators such as EDTA (Figure 3D) invoke titanyl complexes,[36,49] although the crystallized $[Ti(EDTA)(H_2O)]$ complex exhibits no such metal-oxo moiety,[50] and polarography was successful only below pH 5.[51] Above that pH, the EDTA complex and those of similar carboxylate-bearing chelating ligands precipitate. Complexes with NTA (Figure 3E) were prepared and studied in aqueous solution at pH ≤ 2; an oxo-bridged tetranuclear species was crystallographically characterized.[52]

Chelating ligands that model coordination environments found in metal-binding proteins like transferrins afford moderately aqueous-stable Ti(IV) complexes. One of these, *N,N′*-ethylenebis-(*o*-hydroxyphenylglycine) (EHPG) (Figure 3F), forms monomer $(Ti(EHPG)\cdot H_2O)$ and oxo-bridged dimer $([Ti(H(EHPG))(H_2O)]_2O)$ Ti(IV) complexes for the racemic and meso ligand, respectively,[53] in which the metal is seven-coordinate. The monomer is stable from pH 1−7 whereas the dimer is stable only from pH 2.5 to 5.5. A mononuclear Ti(IV) complex of *N,N′*-di(*o*-hydroxybenzyl)ethylenediamine-*N,N′*-diacetic acid (HBED) (Figure 3G) was also characterized.[54]

2.2.3. α-Hydroxy Acids. A family of mononuclear Ti(IV) complexes having only citric acid ligands (Figure 3H) has been prepared and isolated from aqueous solutions. The fully protonated citric acid is designated H_4cit here because the ligand can lose as many as four protons from its three carboxylic acids and hydroxyl functionality. In each mononuclear complex, Ti(IV) coordinates three citrate ligands though the α-hydroxy acid moiety (Figure 4), leaving a total of six dangling carboxylates,

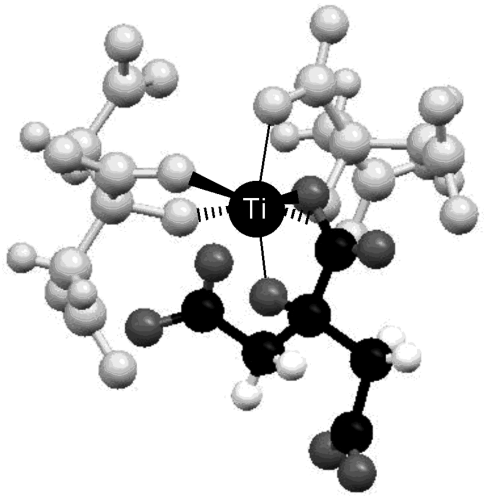


Figure 4. Structure of the anion $[Ti(IV)(cit)_3]^{8-}$ (ref 57), highlighting the coordination by one of the three citrate ligands. Each citrate binds with the central α(hydroxy) acid, leaving two carboxylic acids per ligand not coordinated to the metal ion.

which are protonated to varying degrees depending on pH between pH ≈ 2 and pH ≈ 9.[55−57] Thus, at pH ≈ 2, the peripheral carboxylates are fully protonated to form $[Ti(H_2cit)_3]^{2-}$,[55] whereas by pH ≈ 7, the carboxylates are deprotonated to form $[Ti(cit)_3]^{8-}$.[57] The pH dependent speciation and properties of these complexes have been investigated.[57−60] When dissolved in water in the absence of an excess of free citrate to promote the formation of the mononuclear tris-citrate complex, citrate ligands are released, presumably with concomitant formation of multinuclear complexes, as is well precedented for Fe(III).[61,62] These Ti(IV) citrate complexes demonstrate interesting photoreactivity, generating Ti(III).[63] Citric acid has also been shown to adsorb to the surface of TiO_2 nanoparticles.[64]

Titanium citrate complexes of higher nuclearity are known. Dinuclear Ti complexes having only citrate ligands include $(NH_4)_5[Fe(H_2O)_6][Ti(H_2cit)_3(Hcit)_3Ti]$ (from solution at pH 2.5−3.5) and $Ba_3(NH_4)_7[Ti(cit)_3H_3(cit)_3Ti]$ (from solution at pH 5−6).[56] Other Ti(IV) citrate complexes include an oxotitanium complex with a Ti_8O_{10} structural core.[65] Tetranuclear[66] and dinuclear[67] complexes of Ti with both peroxo and citrate ligands have been prepared.

A complex of lactic acid (Figure 3I), formulated as the ammonium salt of Ti(IV) bis(lactato)dihydroxide (DuPont Tyzor-LA), is a commercially available reagent supplied as a 50 wt % solution in water. The tris(lactato) complex $(NH_4)_2[Ti(lactato)_3]$ was prepared in and crystallized from aqueous solution.[68]

The complexes of Ti and oxalic acid have been studied for many applications, including peroxide determinations,[69] and are commonly used in materials chemistry.[70−73] Early work studying Ti oxalate complexes probed the polarography of the compounds in aqueous solution. Below pH 3, a reversible wave is seen for the reduction of Ti(IV) to Ti(III). The potential is independent of Ti concentration but did show a dependence on oxalate concentrations. Above pH 4, the wave became irreversible, but the Ti oxalate complex remained in solution.[74] Crystal structures of Ti oxalate complexes have been determined and feature dimeric Ti(III) structures with a bridging oxalate and distorted trigonal bipyramidal Ti ions with a second bidentate oxalate and three bound waters.[58,75] Monomeric bis- and trisoxalate Ti complexes

dx.doi.org/10.1021/cr1002886 |*Chem. Rev.* 2012, 112, 1863–1881

have also been crystallographically characterized, and the oxalate acts as a bidentate ligand for Ti(III) in both.[76,77] Mononuclear Ti(IV) oxalate species, of the form $Ti(OH)_2(C_2O_4)_2^{2-}$, have been characterized in solution[78] and can be precipitated with lead to form lead titanyl oxalates.[79] Many polynuclear Ti oxalate species are of the form $M_2[TiO(ox)_2]\cdot nH_2O$, where M includes a number of alkali metals[80] or ammonium,[81] some of which are commercially available. Oxalic acid has also been shown to facilitate the dissolution of TiO_2 under conditions that mimic mineral weathering.[82]

2.2.4. Ascorbic Acid. Because of their low Ti(IV)/Ti(III) reduction potential, complexes of ascorbic acid (Figure 3K), H_2asc, with Ti(IV) are not prone to the metal-induced ligand oxidation that renders many other metal ascorbate complexes very reactive.[83−85] The Ti complexes of ascorbic acid, first reported in 1936,[86] have been used for detection and quantitation of Ti(IV).[87] The early work was reviewed by Sommer.[88] The data supported the predominant species $Ti(Hasc)^{3+}$ (pH < 1), $TiO(Hasc)^{+}$ (1 < pH < 1.6), $TiO(Hasc)_2$ (1.6 < pH < 2.2), and $Ti(asc)_3^{2-}$ (2.5 < pH < 4.8). Minority species $TiO(Hasc)_2^{2-}$ and $Ti(asc)_2$ were also detected. Above pH 4.8, the color bleached and hydroxo complexes were suspected.[88] This quantitative work agreed well with the original qualitative titrations.[86] Another study invoked $TiO(Hasc)^{+}$ and a second anionic complex that formed at lower ascorbate concentration and higher pH.[89] Complexes formulated as $TiO(Hasc)_2$ and $TiO(OH)(Hasc)$ were prepared and characterized by elemental analysis and IR and ^{1}H NMR spectroscopies.[90,91] The former complex is one predicted by Sommer to occur at low pH; the latter complex, a presumed hydrolysis product prepared by methanol extraction of the former, was not one of the species believed to predominate in aqueous solution.[88] The IR spectra were not reported below 1500 cm^{-1},[91] so the presence or absence of a Ti=O stretch could not be ascertained. A complex formulated as $K_2Ti(asc)_3$ was isolated from EtOH and characterized by elemental analysis, but the ligand dianion was thought to be too basic to form in aqueous solution.[92]

2.2.5. Aromatic 1,2-Diols. Catechols (Figure 3L) and substituted catechols, occurring in biology as 3,4-dihydroxyphenylalanine (DOPA) or in siderophore- or tunichrome-like ligand environments, are notably good ligands for Ti(IV).[93−98] The Ti(IV) triscatecholate, $[Ti(catechol)_3]^{2-}$, has a formation constant of 10^{60}.[94] This complex is stable to hydrolysis up to pH 11, and its X-ray crystal structure, UV/vis and IR spectra, and redox potential are known.[95] At high pH, the dimeric anion $[TiO(catechol)_2]_2^{4-}$ forms; its structure is also known.[95] The 3,5-disulfonate substituted catechol, tiron, was so named because it is a useful reagent for the analytical determination of Ti and iron.[99,100] Multidentate ligands providing catechol moieties to the metal are also excellent ligands.[101] A $[Ti(L)_3]^{2-}$ species having 2,3-naphthalenediolate ligands (Figure 3M) has been described.[102] The catecholate and 2,3-naphthalenediolate ligands powerfully stabilize the Ti(IV) oxidation state, lowering the redox potential to below −1 V vs NHE.[95,102]

2.2.6. Other Ligands. Additional aqueous-stable Ti(IV) complexes have been reported, but their pH-dependent speciation is not well characterized. The Ti(IV) complex with maltol (Figure 3N) was formulated as $Ti(maltolato)_2(OH)_2$ in aqueous solution, but it crystallized as the multinuclear complex $[Ti_4(maltolato)_8(\mu\text{-}O_4)]$.[103] An orange−red water-soluble complex of Ti(IV) with D-glucose (Figure 3O) was reported[104] but eluded satisfactory elemental analysis and characterization. Peroxide is an excellent ligand for Ti(IV), particularly in combination with other ligands: there are many Ti(IV) peroxo compounds, and Ti(IV) reagents have been used as peroxo sensors.[105]

Because of their potential as anticancer medicines (see below), the aqueous stability and hydrolytic reactions of certain other Ti(IV) complexes have been investigated. The hydrolysis of Cp_2TiCl_2, the complex that progressed farthest in human clinical trials, was studied in detail.[106] Under a renewed focus on the relationship between hydrolytic stability and efficacy,[107] some of the new medicinally active compounds (see below) have been demonstrated to be stable toward hydrolysis for many hours in THF/water or acetone/water solutions.[108−113]

3. PREVALENCE OF TITANIUM IN THE ENVIRONMENT

Several reviews on the occurrence of titanium in a variety of natural environments are available.[19−27] Key points relevant to the exposure of organisms to Ti are highlighted here.

3.1. Titanium in Soil

Titanium is the ninth most abundant element in the Earth's crust (Figure 1). Most of the Ti in the environment is present in the Ti(IV) oxidation state in common mineral forms, notably in rutile (one of several crystal forms of TiO_2) and ilmenite ($FeTiO_3$).[27,82] An excellent review of Ti solubility and speciation in the environment is available.[17] The weathering rate of Ti is very slow, and it is considered an immobile element for mass-balance weathering rate studies.[114] Some studies do suggest, however, that Ti can be mobile in soils.[82,115] One process that may enable this mobility is dissolution of minerals by both organic and inorganic acids.[116] Dissolution of nanoparticulate TiO_2 has shown interesting kinetic effects with particle size.[117]

Titanium dioxide mineral in the environment has been associated with origin-of-life chemical processes. Under low-intensity UV light, the C_1 compound formamide is converted to high molecular weight compounds including nucleoside bases on the (001) surface of a TiO_2 crystal.[118]

3.2. Titanium in Natural Waters

The data on the titanium concentrations in natural waters have been reviewed.[17,27] Soluble Ti concentrations range between 4 pM in the surface ocean[119] to 100 μM in the waters of a hot spring.[17]

The dominant form of dissolved Ti in both fresh water and seawater is formulated from thermodynamic models as $TiO(OH)_2$.[120] In that widely cited work, it is important to note that sulfate (SO_4^{2-}) was the only complexing ligand considered; sulfate was calculated not to contribute to complex formation. Stability constants were not available for Ti complexes with chloride, fluoride, carbonate, or other ligands, and so they were not included in the speciation model. Furthermore, in studies of Ti concentrations in natural waters, "dissolved" Ti has an operational definition, most often meaning material that will pass through a 0.2 μm filter. This definition is consistent with the operational definitions used in laboratory solubility studies.[18,32,35] The soluble species is often assumed to be a monomer, and metal ion clusters[36] are typically not considered.

3.2.1. Freshwater. Titanium concentrations in rivers and near coastal waters vary between 1 pM and >100 nM.[121−125] Where rivers meet the ocean, much of the dissolved or fine colloidal Ti moves to the particulate phase during processes of coagulation, precipitation, or adsorption onto larger particles.[124−127]

dx.doi.org/10.1021/cr1002886 |Chem. Rev. 2012, 112, 1863–1881

The dissolved Ti concentrations decrease with increasing salinity until they reach open ocean values (see below).

Titanium solubility is enhanced in some natural waters, including alkaline fluoride- and carbonate-containing mine waters. Oxalic acid and citric acid notably increase the solubility of Ti from mineral sources.[82]

3.2.2. Seawater. Early work on dissolved Ti in seawater was difficult due to low concentrations and inadequate analytical methodologies.[128,129] Several studies improved on early techniques and probed the Ti concentration with depth distribution in the open ocean.[119,127,130] The characteristics of these vertical profiles can suggest biological involvement of the element. For example, nutrient elements tend to be depleted near the surface of the ocean, where there is photosynthetic life, and enriched in deeper waters.[131]

In a study focusing on the northern Pacific and Atlantic oceans, Ti was depleted near the surface (4−8 pM) and enriched in deep water (200−300 pM) (Figure 5).[119] Scavenging (either biotic or abiotic) could explain such a distribution. The residence time of Ti in the ocean was determined to be a rather short 100−200 years.[119] A vertical profile of Ti from a region near the Sargasso Sea in the North Atlantic revealed a complex concentration with depth profile,[127] but was roughly in agreement with the earlier study.[119] In contrast, a study in the Mediterranean Sea determined the concentration with depth profile of Ti to be relatively constant throughout the water column (100−150 pM).[130]

In each of these studies, the Ti was far undersaturated with respect to the concentrations that the laboratory solubility data predict. One would expect >1 μM if the solid phase were amorphous[32,35] and >10 nM if the solid phase were crystalline rutile.[18] Instead, pM concentrations were detected.

The study in the Mediterranean Sea found that a large fraction of the Ti was not released by treatment with acid but instead was released upon UV irradiation, suggesting complexation by organic ligands.[130] In biogenic ocean sediments, Ti is also highly bound by organic ligands.[132] Titanium thus may be preferentially removed from the water column by binding to such ligands (as opposed to by oxide particle reactivity). Taken together, these data support, at least in some places in the ocean, a hybrid distribution for Ti reflecting a recycled-type profile but with indications of scavenging behavior.[133]

4. OCCURRENCE OF TITANIUM IN ORGANISMS

Attributable at least partly to its abundance in the environment, titanium occurs in the tissues of most organisms.[21,22,27,134] Some organisms have displayed a particular affinity for Ti, however, and those cases will be addressed here.

4.1. The Question of Essentiality of Titanium

Essentiality of trace elements is usually identified by distributional studies, by a purified or special diet approach, and/or by identification of naturally occurring deficiencies.[135] Titanium has never been demonstrated to be essential for any organism, nor to occur natively in any metalloenzyme. However, the essentiality of Ti for organism(s) would be quite easy to miss. As described above, Ti is very abundant in the environment. It is diamagnetic in its common oxidation state (Ti(IV)), and its complexes tend to be colorless or show nondistinctive metal-to-ligand charge transfer transitions, often in the UV. Because its analytical detection has been challenging and because Ti is not already understood to have a biological role, most investigators tend not to analyze for it in elemental surveys. More recent work using

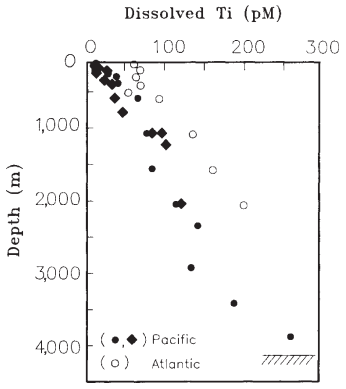


Figure 5. Dissolved titanium concentration as a function of water column depth in the North Pacific and North Atlantic. Reprinted with permission from ref 119. Copyright 1990 Macmillan Publishers Ltd.

modern mass spectrometry has begun to include Ti among the elements analyzed for in the characterization of metalloproteomes, and high Ti levels in some cells were detected.[136]

For many of the same reasons, demonstrating that Ti is *not* required is quite difficult and has never been done. Between 10 and 20 mg are found in the body of the Standard Man,[16,19,24,26,137−139] making Ti the 14th most abundant element there, more common than cobalt, an essential element required by vitamin B12. Titanium is not invariably detected in newborns, but in adults it is concentrated in the lung, liver, spleen, and kidney.[19] Its concentration has been reported as 116.7 ppb (~2 μM) in human blood serum and 250 ppb (~5 μM) in milk.[140] (Contradicting these results, lower Ti concentrations (mid-nM concentrations in serum) are reported as normal baseline levels in negative controls in Ti toxicity studies (see below).)

If it were required, titanium is so abundant that an organism would be unlikely to experience a dietary deficiency. Americans consume on the order of 300 μg/day.[19−27] Even patients receiving sustenance through total parenteral nutrition (TPN) are exposed to relatively high amounts of Ti (up to 200 μg/day).[141,142] Large amounts of Ti occur in processed foods, which are consumed in increasing amounts in developed countries.[19] Small children, who tend to put nonfood items in their mouths, may ingest quite high concentrations, on the order of 1−10 mg/day.[143]

Intentionally inducing a dietary deficiency has been unsuccessful. The essentiality (or not) of several trace metals was established in classic "metal-free" experiments in mice and rats, but attempts by Schroeder and his group to expose mice to a titanium-free environment failed. Experimenters were unable to prevent the accumulation of Ti even in animals receiving very little of the metal in their diet. They suspected that the mice were getting Ti from their bedding of wood chips.[144,145] The evidence for the essentiality of Ti to mammals was judged to be inconclusive.

4.2. Avid Marine Sequesterers of Titanium

Several broad surveys of marine organisms have found widespread but low (generally <100 ppm) levels of Ti in a variety of marine organisms.[134,146−148] Higher Ti levels have been associated with several types of marine organisms, although its essentiality has not been investigated. Mussels bioaccumulate Ti when exposed to high levels through industrial pollution, and these organisms may serve as pollution indicators;[149] however, the focus in the following section is on organisms that sequester Ti when exposed to natural concentrations (Figure 6).

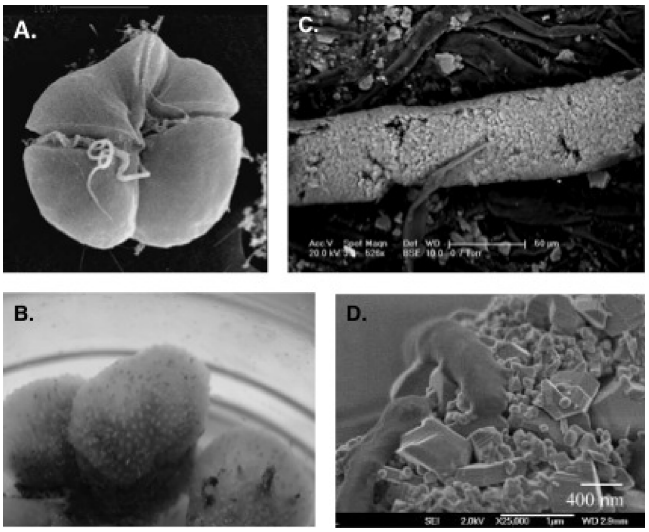


Figure 6. Some marine organisms associated with titanium. (A) Dinoflagellate *Karenia brevis* (Davis) (photo courtesy of the Florida Fish and Wildlife Conservation Commission, copyright 2011). Organisms are 20−40 μm in diameter. (B) Ascidian *Eudistoma ritteri* (photo courtesy of Jarrett Byrnes/Stachowicz Lab, UC Davis, copyright 2011). Each yellow lobe is up to 5 cm long and 3 cm in diameter. (C) Foraminiferan *Bathysiphon argenteus* (photo courtesy of Kathryn Cole/Valentine Lab, Yale, copyright 2011). Scale bar 50 μm. (D) Bacterium *Rhodococcus ruber* GIN-1. Rodlike bacteria (smooth) are shown adhering to TiO_2 particles. Scale bar 400 nm. Reprinted with permission from ref 194. Copyright 2003 Wiley-VCH Verlag GmbH & Co. KGaA.

4.2.1. Diatoms. In laboratory culture, diatoms take up Ti from the media to levels of 940 ppm in the whole organism.[150] In natural samples, Ti occurs at up to 1254 ppm in the acid-resistant siliceous frustules of diatoms.[151] This phenomeneon may explain why dissolved Ti is depleted along with silicon during a spring diatom bloom[124] and may contribute to the surface-depleted profile of Ti in the ocean, when such a profile is observed.[119] It could be due to simple precipitation of Ti onto the siliceous frustule. Alternatively, the incorporation of Ti could be facilitated by biomolecules in the organism. The enzymes directing biomineralization of silica in diatoms are called silaffins;[152] synthetic peptides derived from silaffins[153,154] and recombinant silaffins themselves[155] direct TiO_2 mineralization given an otherwise soluble source of Ti.[152,156]

4.2.2. Dinoflagellates. Extremely high Ti concentrations (33 700 ppm) have been linked with the "red tide" bloom of the marine dinoflagellate *Gymnodinium brevis* (now called *Karenia brevis*).[157] Added Ti impedes the growth of that species in laboratory culture,[158] but the link has not been explored further.

4.2.3. Sponges. Though most species have Ti levels below 100 ppm,[159,160] several species collected from the coast of Madeira exhibited Ti levels above 1 500 ppm, with one species, *Ircinia fasciculata*, having 3 500 ppm.[160] The authors suggested that high Ti content of the basic basalt lava coast was responsible, although other species collected from the same area had levels as low as 117 ppm. Silicatein, the enzyme responsible for silica biomineralization in the sponge, also directs the mineralization of Ti dioxide from a soluble Ti(IV) precursor.[156,161,162]

4.2.4. Ascidians. Ascidians are a group of marine invertebrates, many species of which sequester remarkably high concentrations of metal ions, most famously vanadium.[163−165] Several species accumulate Ti. *Eudistoma ritteri* is the most avid of these and sequesters up to 1 500 ppm (dry weight) Ti in the whole organisms.[166−168] Assuming ∼80% water weight, this value corresponds to ∼100 mM Ti, a surprisingly high concentration even given that the blood pH of this species is reported to be 1.5.[167] Titanium was below detection limits in the nearby water, but if present at concentrations near the ones discussed above for natural waters, this concentration implies a very high bioconcentration factor (up to 10^{10}). Somewhat lower amounts of Ti (∼100 ppm) were found in other ascidian species *Pyura chilensis* and *Ascidia dispar*; in the latter case most of the Ti was located in the blood cells, where it occurred at >1 500 ppm.[169] The chemical form of Ti was unclear, although at least a portion of it was associated with a high molecular weight apparently organic fraction. Intriguingly, in addition to their avid sequestration of metal ions, ascidians are noted for their production of secondary metabolites, known as tunichromes,[164,170] and proteins, such as ferreascidin,[171] that feature DOPA and catechol moieties that would make them excellent binders of Lewis acidic metal ions including Ti(IV). No complex of these molecules with Ti has been isolated.

4.3. Organisms Associated with Titanium Minerals

Many organisms employ inorganic minerals for mechanical support or protection, for metal ion storage or detoxification, or as sensors, instruments, or weapons.[172−175] There are relatively few examples of the association of organisms with Ti minerals, even though those minerals are abundant.[82] As described above, Ti has been found in the acid-resistant amorphous silica comprising the siliceous frustules of diatoms, implying that it is present in mineral form there along with the silica.[151] One text alludes to an unpublished observation of biomineralization of amorphous ilmenite ($FeTiO_3$) by an undetermined bacterial species.[172] The full report has not appeared.

Organisms may produce mineral materials by active biomineralization with varying degrees of control or they may collect them as detrital materials from their environment. In the case of Ti minerals, either origin raises intriguing issues. The former suggests some mechanism for sequestering Ti from the environment and actively directing mineralization (albeit to produce an extremely thermodynamically stable phase). The latter suggests a strong and specific interaction between cell-surface biomolecules on the cell or organism with the surfaces of Ti minerals.

Some suggestions about how this recognition might work at the molecular level are provided by peptides evolved through phage display to bind strongly and specifically to TiO_2 surfaces,[176,177] and by the observation from the field of proteomics that glycopeptides, phosphopeptides, and phosphoproteins exhibit a notably high affinity for TiO_2.[178,179] This affinity has been utilized to purify glycopeptides and phosphopeptides by binding to titania microspheres.[179] Specific amino acid sequences, perhaps similar to the ones that have been discovered by phage display, may help cells and organisms bind Ti minerals, and phosphorylated or glycosylated biomolecules may contribute to adhesion.

4.3.1. Titanium Teeth in Fossils. The teeth on the radula (similar to a tongue) of a cephalopod fossil were originally reported to feature ordered ilmenite grains.[180] A lively ensuing controversy centered around whether the fossils were not actually teeth but instead were individuals of *Volborthella* (members of an extinct wormlike group),[181,182] or perhaps were horns on a worm or mollusklike animal.[183] The point that the grains were ilmenite attracted little notice and has not been followed up.

4.3.2. Ilmenite and Insects. The hornet *Vespa orientalis* attaches a grain of a Ti-containing mineral, possibly ilmenite, in each cell of its honeycomb-shaped nest.[184,185] It is unclear whether the mineral material is collected (detrital) or secreted (actively biomineralized), or what function it might serve. The grain may be a gravity indicator, indicating direction in the nest.[185]

4.3.3. Foraminifera. Two modern species of foraminifera have been linked with Ti in two different mineral forms. Foraminifera are eukaryotic, unicellular organisms, some of which have agglutinated shells with embedded mineral material.[186,187]

Bathysiphon argenteus is a species of agglutinated foraminifera collected from the Irish coast.[188] The species is characterized by the presence of rod-shaped needles in its shell. The original authors noted that the needles were resistant to boiling in nitric acid, and they concluded that their small size and uniform shape suggested that the needles were secreted by the organism.[188] A later investigation found the needles to be less uniform than in the earlier report, and the authors argued that they were detrital and embedded in the shell.[189] Because of an abundance of rutile near the collection site, it was suggested that they might be TiO_2 in the rutile form.[189] A recent reinvestigation found that the needles were indeed TiO_2, consistent with rutile, and also supported a detrital origin.[190]

Another foraminifera species, *Ammobaculites balkwilli*, selectively collects TiO_2 in the anatase form. Although anatase is a minor component of the local environment of that species, it occurs at up to 10% of the shell material.[191] Taken together, these two examples suggest that certain foraminifera can select specific TiO_2 mineral grains at the expense of others, which implies a specific interaction between the secreted biomolecules in the agglutinated shell walls and the inorganic (grain surface) materials.

4.3.4. TiO_2-Adhesive Bacteria. Bacteria from the Mediterranean Sea were selected for their ability to adhere very tightly to TiO_2 particles.[192,193] One isolated Gram positive species, *Rhodococcus ruber* GIN-1, adhered selectively to TiO_2 over other metal oxides within 1 min, at pH values between 1 and 9, and at temperatures from 4 to 80 °C.[192] Adhesion was robust when challenged with dilute acids, alcohols, and cationic or nonionic detergents. A cell surface homologue of the normally cytosolic protein dihydrolipoamide dehydrogenase was among the proteins implicated in the cell adhesion.[194,195]

Biosorption of nanoparticulate TiO_2 has also been observed.[196−201] This adsorption has been seen with *E. coli* and *Pseudomonas aeruginosa* and has been hypothesized to occur more broadly. Adsorption has been observed for the bacteria to the particle surfaces, and agglomeration of the particles has been observed on the bacteria. These interactions have been facilitated by both siderophores and polysaccharides on cell surfaces.

5. EFFECTS OF TITANIUM ON ORGANISMS

5.1. Effects of Titanium on Bacteria

In literature going back at least to the first World War, the antibacterial effect of titanium complexes and TiO_2 has been investigated. Much of that early medicinal use has been reviewed.[202] More recent work reported differential sensitivity to titanium of six bacterial strains and implicated a plasmid-encoded resistance, at least for one strain of *Pseudomonas aeruginosa*.[203]

5.2. Effects of Titanium on Yeast

Although the application of Ti(IV) ascorbate to growing *Saccharomyces cerevisiae* did not significantly affect growth rate, the yeast did incorporate Ti at up to 1500−2000 ppm dry weight.[204]

5.3. Effects of Titanium on Plants

The concentration of Ti in plants varies up to 100 mg/kg (100 ppm), with the range in common food plants being 0.1 to 10 mg/kg.[19,21,26,27,205,206] Several groups, notably that of Pais, reported a favorable effect of Ti treatment on various plant species, most often measured by higher growth and chlorophyll and sugar content. Much of the early work was reviewed.[206,207] Titanium ascorbate received further attention[208,209] and was patented as a plant growth promoter.[210] In wheat plants sprayed with a titanium/ascorbic acid formulation (TITAVIT), the Ti accumulated in roots and specifically in the cell nuclei.[211] Research continues into quantitating and explaining the apparent beneficial effects of Ti on plants.[212−218]

5.4. Effects of Titanium on Mammals

As described above, Ti is naturally present at appreciable concentrations in the human body.[19,21,24,27,134,137,138] Several groups have investigated the effects of intentional Ti treatment on mammals. As part of his wide-ranging studies in the 1960s on the role of trace elements on health, Schroeder addressed the occurrence and possible bioeffects of Ti.[19] Although there was little demonstrable long-term toxicity to an individual animal,[144,145] the metal was toxic to reproduction in rats.[219] In that study, fewer animals given Ti in their water survived to the third generation than in controls, and the male−female ratio decreased progressively in each generation. Mortality increased slightly for male but not female mice.[145] Mice given Ti(IV) oxalate in their water gained more weight and developed fewer tumors than control animals. Favorable effects of Ti have been reported on other mammals, including on goats[220] and infant and young mice.[221,222] Complexes of Ti are patented as fodder additives and claimed in the patent literature to improve weight gain in domestic animals.[223]

Titanium deliberately administered to animals accumulates in organs. In the mouse study above, the metal concentrated in the heart, lung, and spleen.[145] When injected into hamsters, Ti accumulated in the blood, kidney, liver, and spleen.[224] Hamsters injected with still higher concentrations also accumulated Ti in the mineral and matrix phases of bone.[225] When the ^{45}Ti radioisotope was injected into rats as $^{45}TiOCl_2$ or in combination with phytate, metal accumulated in the liver and spleen. Titanium injected with other complexing agents (human serum albumin, diethylenetriaminepentaacetic acid, ascorbic acid, or citric acid) also accumulated there, but in addition, high Ti levels in the blood persisted for hours.[226] When ^{45}Ti was administered in complex with ^{14}C-labeled ascorbic acid, images of the two radioisotopes did not coincide, with the ^{45}Ti signal being concentrated in the heart, lung, spleen, liver, and blood and the ^{14}C signal mainly concentrated in the adrenal glands, gut, and liver.[227]

In anticipation of human clinical trials of the titanium anticancer compounds (see below), limiting toxicities were established in a series of studies in mice. Treatment with titanocene dichloride (Cp_2TiCl_2), either at therapeutic or toxic doses, caused no significant changes to renal morphology or renal function.[228] Chemical changes in blood and urine suggested reversible liver damage.[229] Titanocene dichloride (Cp_2TiCl_2) was toxic to mouse embryos, lowering the number of live fetuses per litter, decreasing mean fetal body weight and skeletal ossification, and inducing cleft palate.[230]

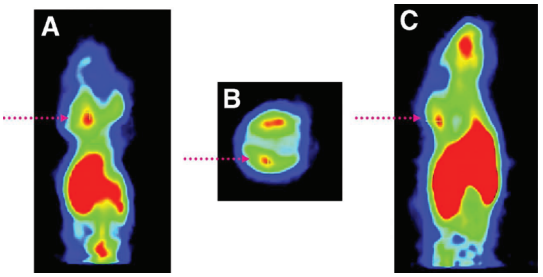


Figure 7. Image slices showing (A) coronal, (B) transaxial, and (C) sagittal views of a female BALB/c mouse bearing EMT-6 murine mammary carcinoma tumor (denoted by arrow) in the nape of the neck injected with 7.59 MBq (205 μCi) ^{45}Ti-citrate, 2 h after injection. Reprinted with permission from ref 234. Copyright 2005 Society of Nuclear Medicine.

The activity of titanocene dichloride was also monitored in renal cell tumors xenografted onto athymic mice and grown in vitro, and activity was seen to be greatest when titanocene dichloride was delivered in fractionated doses.[231]

6. MEDICINAL CHEMISTRY OF TITANIUM

Complexes of Ti(IV) are bioactive in various ways. The anticancer, antibacterial, and anti-inflammatory properties of Ti compounds reported in the older literature have been reviewed,[202] and some key features and recent developments will be covered here.

6.1. ^{45}Ti as an Imaging Agent

The ^{45}Ti isotope offers potential for positron emission tomography (PET) and micro-PET imaging, including imaging of solid tumors.[227,232−234] It has a half-life of 3.1 h and decays 15% by electron capture and 85% by positron emission with an $E_{\beta+\max}$ = 1.04 MeV. The isotope can be prepared in good yield in biomedical cyclotrons by the bombardment of scandium with protons.[233] In one application, uptake of ^{45}Ti-transferrin by an EMT-6 murine mammary carcinoma tumor was visualized by microPET. Administration of citrate-complexed ^{45}Ti afforded similar images (Figure 7), perhaps because the Ti may have been bound by transferrin in vivo before imaging (see below).[234]

6.2. Titanium Anticancer Complexes

The best-studied bioactivity of titanium relates to the antitumor activity of titanocene dichloride (Cp_2TiCl_2) and β-diketonato complexes of Ti such as budotitane (Figure 8). Original work by Köpf and Köpf-Maier for Cp_2TiCl_2 and related metallocenes beginning in 1979[235] and Keppler et al. for budotitane in the 1980s[236] led both of these compounds into human clinical trials as anticancer drugs. Early reviews by those pioneering workers remain very valuable.[237,238] More recent excellent reviews cover the work on Ti anticancer drugs to within the last five years, with several having particular focus on metallocenes.[239−247] The reader is directed to those reviews; only a few points will be emphasized here.

Both complexes are prone to hydrolysis. The hydrolysis of Cp_2TiCl_2 has been studied in detail.[106,248] Below pH 5.5, both chlorides were lost quickly, followed by loss of the Cp rings within hours. At neutral pH, the Cp rings were also lost rapidly,[106] which is consistent with the lack of evidence for intact titanocene in vivo.[249] A recent computational study has revisited this work and modeled the hydrolysis.[250] Budotitane is similarly hydrolysis-prone and furthermore can exist in several interconverting isomeric forms;[251] its pharmaceutical formulation

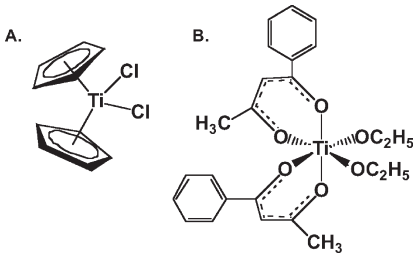


Figure 8. Two Ti anticancer drugs used in human clinical trials. (A) Titanocene dichloride, Cp_2TiCl_2. (B) Bis(β-diketonato) complex known as budotitane. Other isomers are possible.

remains quite challenging. The cis−cis−trans isomer of budotitane was recently characterized by X-ray crystallography.[252]

The compounds are most active against gastrointestinal and head and neck carcinomas and show no cross resistance with the platinum drug cisplatin, suggesting a distinct mechanism of action.[253] A clustering analysis of tumor cell cytotoxicity profiles for compounds in the National Cancer Institute's compound repository identified membrane function or "unexplored" as the likely response categories for Ti(IV) compounds.[254] Budotitane derivatives made up 76% of the test compounds in that study. In contrast to the prevailing models about their mode of action (see below), nucleic acid metabolism was not identified as a major response category. In vitro, the Ti compounds are more effective than equitoxic doses of cisplatin. Preclinical studies on both Cp_2TiCl_2 and budotitane were promising.[239−247]

6.2.1. Human Clinical Trials. Human clinical trials of Cp_2TiCl_2 used water-soluble formulations developed by Medac GmbH in Germany.[255] Phase I trials identified the maximum tolerated dose, identified dose-limiting toxicities (cumulative reversible damage to the liver and kidney), defined pharmacokinetics, and guided a recommended dosing schedule.[256,257] Phase II trials, however, were not encouraging. In a 6-week study of 14 patients with advanced renal cell carcinoma, no partial or complete response was observed.[258] In a study of 12 patients with metastatic breast cancer, no objective remission was observed, although 2 patients exhibited a minor positive response.[259]

Phase I and pharmacokinetic trials of budotitane identified maximum tolerated doses, with cardiac toxicity as the dose-limiting toxicity.[260] Difficulties in formulation have impeded the development of budotitane as a drug.

6.2.2. Effects on Gene Expression. Recently, changes in global gene expression of lung cancer cells were reported in response to treatment with the Cp_2TiCl_2 analog Titanocene C (bis-*N*,*N*-dimethylamino-2-(*N*-methylpyrrolyl)methyl cyclopentadienyl Ti(IV). The authors concluded that direct DNA damage and perturbation of Zn^{2+} homeostasis were responsible for the cytotoxic effects of the compound.[246]

6.2.3. Interactions with Biomolecules. Proteins. Similar activity and toxicity patterns of Cp_2TiCl_2 and budotitane suggested that they may be converted to the same active species, and that metal-serum protein interactions may be key to their activity. Sadler and co-workers proposed that the ligands are lost, and Ti(IV) is carried into the tumor cell by the serum iron transport protein transferrin.[261] This hypothesis is consistent with the observed serum complexation of Ti[226] as well as Sadler's in vitro and in vivo results.[261] Tumor cells express more transferrin receptors than do normal cells, which would account for the compounds' specificity. The interactions of Ti with transferrin

dx.doi.org/10.1021/cr1002886 |*Chem. Rev.* 2012, 112, 1863–1881

have been an active focus of investigation by a number of groups.[261−266] Titanium binds tightly to transferrin, and Ti-bound transferrin binds to the transferrin receptor.[54,266] Different Ti starting materials bind differently to transferrin.[267] The tight binding of Ti to transferrin raises questions about how it could be released, presumably in the acidic endosome.[261] Metal reduction probably does not contribute; the reduction potential of Ti(IV) to Ti(III) is apparently beyond the range of biological reductants,[268] although a conflicting report was recently published.[269] Administration of transferrin together with Ti anticancer agents had a variable effect on their efficacy against tumor cell lines; transferrin increased the efficacy of Cp_2TiCl_2 but had no effect or a slightly negative effect for other agents.[107]

Association of Ti complexes including Cp_2TiCl_2 with serum albumin has also been investigated, both experimentally[102,266,270] and computationally.[271] When Ti was administered as a diethylenetriamine pentaacetic acid (DTPA) complex, there was some binding to albumin,[226] although in an in vitro study with rat plasma, the metal bound mostly to serum transferrin and not to albumin.[272] These serum Ti-protein complexes react with blood lymphocytes.[273]

It remains to be seen whether Ti interacts strongly with many iron proteins, or whether the transferrin case is unusual. In one recent study, Ti biomineralization inside ferritin was achieved, albeit by a photochemical route that is not likely to operate in vivo.[274]

Although DNA binding is thought to be the most important mode of activity for these Ti(IV) complexes, inhibition of enzymes including protein kinase C and DNA topoisomerase II may contribute to the compounds' activity.[248,275] An alternative theory holds that Cp_2TiCl_2 acts by inhibiting tumor gelatinases and other proteolytic enzymes such as trypsin.[276] Cp_2TiCl_2 may inhibit in a competitive manner by binding to the substrate collagen, a result that harks back to older work on Ti inhibition of tyrosinase,[277] in which Ti was also believed to act by competitive substrate complexation.

6.2.4. Interactions with Biomolecules. Nucleic Acids. DNA has long been invoked as the probable target for Ti anticancer drugs, partly because of the superficial similarity to cisplatin of both Cp_2TiCl_2 and budotitane, with their labile ligands in cis-configuration. This notion was supported by early work, which found that Ti localizes to the chromatin and inhibits DNA synthesis.[237] An X-ray fluorescence intracellular mapping study of Cp_2TiCl_2-treated hamster lung cells revealed Ti distributed throughout the cell, but somewhat concentrated in the nucleus.[278]

Titanocene interactions with DNA have been studied in vitro by using a variety of physical methods.[248,270,279−286] Below pH 5, Ti complexes such as Cp_2TiCl_2 bind to nucleotides, notably to the phosphate moieties, but binding is generally very weak near pH 7. Binding to nucleotide triphosphates is stronger, and Ti binding promotes ATP and GTP hydrolysis.[284]

6.2.5. Next-Generation Anticancer Complexes. New Ti complexes are being synthesized and evaluated as potential next-generation anticancer drugs in several laboratories. The complexes in Table 1 represent some currently promising strategies. A more extensive discussion appears in a recent review.[243] It is difficult to compare directly the efficacy of the compounds, because their cytotoxicity is frequently measured in different assays or against different cell lines. In general, though, most of the compounds in the table are benchmarked against and are more active than Cp_2TiCl_2.

6.3. Titanium in Implants

Commercially pure Ti and Ti alloys are widely used in orthopedic, dental, and other implants, including in fractural fixation devices (plates and screws) and spinal, hip, and knee replacements. They are well tolerated by most patients, have a superior ability to integrate with bone, and are excellent materials for many applications.[332−334] They can, however, degrade by mechanical wear to produce wear particles[335] or by physiochemical or cell-mediated corrosion to produce Ti(IV) ions.[336−338] The result, in some patients, is inflammatory reactivity and metal hypersensitivity. Key questions are how much Ti is released from the implant, what chemical form the released metal takes, where and in what quantity the metal is transported, and whether that release has any biological significance.[337]

The metal release from these materials in vitro in the absence or presence of human serum, as well as protein binding to these materials in the latter case, has been investigated. In vitro, the release of Ti ions was fairly low ($0.01-0.1\ \mu g\cdot cm^{-2}\cdot day^{-1}$) except under acidic conditions, where as much as $2\ \mu g\cdot cm^{-2}$ was released over 7 days.[339,340] Serum became saturated with Ti at ~3500 ng/mL (~73 μM), and Ti bound to both small (<32 kD) and large (180−250 kD) serum proteins.[341] Small biomolecules may also contribute to Ti complexation: the chemical form of Ti in synovial fluid in one study was identified as Ti citrate,[342] a complex that induces shape changes that damage human erythrocytes and may do the same to other cell types.[343] One in vivo study saw release of TiO_2 from maxillofacial plates into the soft tissue surrounding the implants but did not see any detrimental effects from the increase in Ti concentrations;[344] another in vivo study saw significant damage to tissues surrounding TiO_2 maxillofacial plates and recommended their removal from patients upon healing.[345]

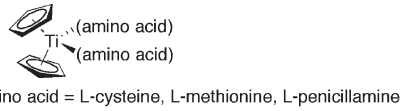
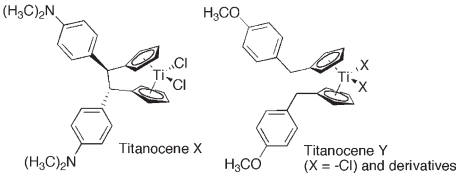
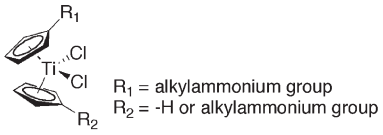
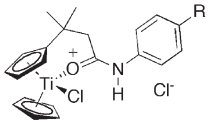
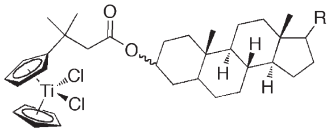
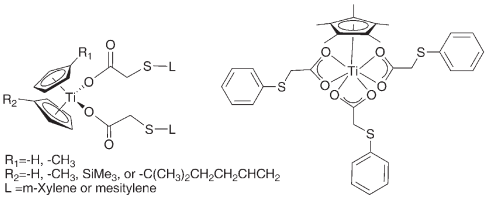
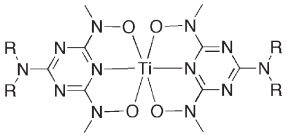
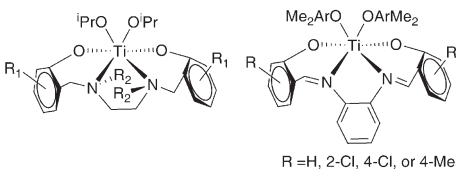
A number of studies have reported increased Ti levels in serum, urine, and even hair in experimental animals and patients with Ti implants, even with well-functioning implants in the absence of wear.[265,346−350] The serum Ti levels detected in mammals with implants vary, ranging from ~50 nM to ~3 μM. In an influential study by Jacobs and co-workers,[347] control serum levels of Ti were ~1.5 ng/mL (31 nM). After 36 months, patients with well-functioning Ti alloy implants averaged 4.13 ng/mL (86 nM), with levels up to 11.7 ng/mL (244 nM).[347] Analysis of serum protein fractions from such patients revealed that a single molecular weight range (~70 kD) bound the Ti released.[351] This range would be consistent with albumin and/or transferrin. This result contrasts with the in vitro study above, in which smaller and larger serum proteins bound Ti released from Ti alloys.[341] In other work, both particles and ions migrated to distant tissues.[225,337,352] Reports suggest that Ti metal accumulates in the lungs and lymph nodes,[353] and chronic exposure may cause pulmonary granulomatous disease.[354]

Possible bioeffects of Ti biomaterials and their released Ti have been investigated, often by using cells in culture. Many studies focus on inflammation, immunosuppression, function of osteoblasts (the cells from which bones develop), or hemostasis (the arrest of bleeding). Exposure of osteoblasts to ultrafine Ti particles like the ones released from implants stimulated protein tyrosine phosphorylation and activated the proinflammatory transcription factor NF-κB and various cytokines.[355−358] Particle size was shown to affect the cytotoxicity of Ti released. Ti particles smaller than cells were determined to be toxic, whereas particles larger than cells were

not; macroscopic implants were concluded to be safe because of the passivating oxide layer.[359] Particles of different sizes also exerted different detrimental effects on osteoblasts.[360] Growth of osteoblasts on Ti surfaces induced significant up- and downregulation of genes with a variety of functions;[361] the genes affected changed when grown on pure anatase surfaces.[362] Titanium ions also induced cytokines in various cell types and induced cellular effects that can also lead to inflammation and/or implant loosening.[363−365] The Ti released through corrosion may induce cell differentiation toward bone-resorbing osteoclasts, which would further exacerbate implant loosening.[366] Titanium biomaterials are highly thrombogenic (clot-producing),[367,368] a property that can be attenuated by surface modification, for example, with apatite.[369] Surface modifications with PEGylated peptides have shown promise toward creating more infection-resistant Ti surfaces.[370]

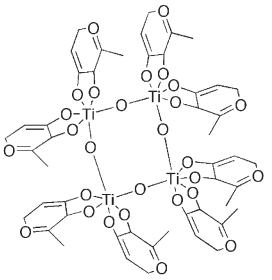
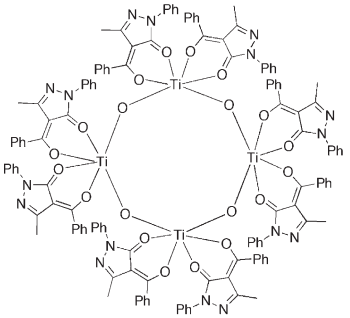
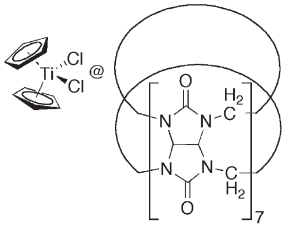
The fate of Ti ions released from implants may be related to the fate of Ti ions released by hydrolysis of the Ti-containing anticancer drugs, particularly because both bind to serum proteins, and perhaps both to transferrin. This possible relationship raises the question of whether Ti implants might suppress cancer. Little information is available on this point: one study

Table 1. Molecules Representing Some Current Strategies in Development of Titanium Anticancer Drugs

Description	Representative structure	Notes	Refs
Cp_2Ti(amino acid) complexes		IC_{50} values ≥ 600 μM against several cancer cell lines	287,288
Substituted titanocenes, such as titanocenes X and Y and derivatives with alkyl, boryl, and indolyl substitutions on the Cp rings		Broad class of compounds are active in cell lines and xenografted tumors	289-309
Cp_2TiCl_2 derivatives with alkylammonium substitutions on the Cp rings		IC_{50} values as low as 10 μM against several cancer cell lines	310-314
Amide-functionalized titanocenyls		IC_{50} values as low as 10 μM against HT-29 (colon cancer) cells	315
Steroid-functionalized titanocenes		IC_{50} values as low as 10 μM against HT-29 (colon cancer) and MCF-7 (breast cancer) cells	316
Carboxylate complexes of substituted Cp_2Ti or ansa-titanocene		IC_{50} values ~ 80 μM against K562 (human myelogenous leukemia) cells	308,317,318
Hydroxyamino-1,3,5-triazines		Inhibition of growth (30-40% inhibition at ~100 mg/mL) of OVCAR-1 and HT-29 cells	108,109
Salan and salen complexes		IC_{50} values as low as 1-10 μM against several cancer cell lines	107,111,113,319-323

dx.doi.org/10.1021/cr1002886 |*Chem. Rev.* 2012, 112, 1863–1881

Table 1. Continued

Description	Representative structure	Notes	Refs
Maltol complex		IC_{50} values as low as 200 μM against several cancer cell lines	103,287,288
Ti(IV) complexes of 4-acyl-5-pyrazones		T/C values[a] ~ 300% for mice bearing TA-3 mouse mammary adenocarcinoma	324-327
Inclusion complexes of Cp_2TiCl_2 in cucurbit[n]urils		Host-guest complex exhibits reduced hydrolysis rate, but precipitation precluded preparation of a formulation for cell testing	328
Titanocene-functionalized mesoporous materials	MCM-41/[$TiCp_2\{SCH_2CH_2CH_2Si(OCH_3)_3\}_2$] or MCM-41/[$TiCp_2\{SCH_2CH_2CH_2Si(O\,CH_2CH_3)_3\}_2$] or MCM-41 or SBA-15 /[$Ti(\eta^5\text{-}C_5H_4Me)_2Cl_2$] or MCM-41 or SBA-15/[$Ti\{Me_2Si(\eta^5\text{-}C_5Me_4)\,(\eta^5\text{-}C_5H_4)\}Cl_2$] or MCM-41/[$Ti(\eta^5\text{-}C_5H_5)_2Cl_2$] or MCM-41/[$Ti(\eta^5\text{-}C_5H_5)(\,\eta^5\text{-}C_5H_4{}^{i}Pr)Cl_2$] or MCM-41/[$Ti(\eta^5\text{-}C_5H_5)(\,\eta^5\text{-}C_5H_4{}^{t}Bu)Cl_2$] or MCM-41/[$Ti(\eta^5\text{-}C_5H_5)\{\,\eta^5\text{-}C_5H_3(SiMe_3)_2\}Cl_2$]	M_{50}[b] = 200-1000 μg against HeLa or K562 cells	329-331

[a] T/C is a measure of survival time increase; T/C is 100% for untreated tumor-bearing mice. [b] M_{50} is the quantity of material necessary to inhibit cell survival by 50%.

reported a small but statistically significant decrease in gastric cancer in patients having hip replacement with metal implants.[371]

7. NANOTOXICOLOGY OF TITANIUM MATERIALS

Nanomaterials (with at least one dimension <100 nm) are used for applications in imaging, diagnosis, drug delivery, pharmaceuticals, cosmetics, paints, pigments, and textiles. Increasing concerns about the potential dangers to human health associated with these nanoscale materials have led to the emerging field of nanotoxicology.[372−374]

Metal oxide nanoparticles, and nano-TiO_2 in particular, have found broad applications. TiO_2 is used widely as a white pigment and food colorant, in sunscreens and cosmetic creams, as a photocatalyst and wastewater disinfectant,[375,376] and as a photosensitizer for photodynamic anticancer therapy. The important expected routes of human exposure are through the skin or by inhalation. Uptake of TiO_2 particles near the nanoscale (160−500 nm) after oral administration has, however, been demonstrated in mammals.[377,378] A "passivating" layer of TiO_2 (some of it nanoscale in nature) also forms on Ti metal and alloy implants, and particles including micro- and nanosized particles

dx.doi.org/10.1021/cr1002886 |*Chem. Rev.* 2012, 112, 1863–1881

are sloughed off to the surrounding tissue during implant wearing. Considering the photoactivity of TiO_2,[379] special attention has been paid to the possibility of nanoparticle photoreactivity, possibly resulting in the production of damaging reactive oxygen species. The photo-Kolbe reaction has been shown to be active on TiO_2 surfaces.[380−382] This photoreactivity has been exploited for its possible anticancer activity, when the nanoparticles have been coated with a rhodamine gadolinium complex, which can also be used as an imaging agent.[383]

The preponderance of evidence suggests that TiO_2 nanoparticles are benign except when inhaled at very high levels.[21,374,384] A 2006 World Health Organization working group concluded that the epidemiological studies on TiO_2 as an inhalation hazard in humans did not provide compelling evidence of carcinogenicity, although experiments in rodents suggested some evidence of carcinogenicity.[385] In sunscreens, these nanoparticles do not penetrate the skin deeply,[386] although further study under UV irradiation and on broken skin was urged. In keeping with the generally increasing profile of nanotoxicology and concern over nanomaterials, a group of recent papers do raise concerns, including the finding that nano-TiO_2 can convert benign tumor cells to malignant ones in mice through the generation of reactive oxygen species.[387] TiO_2 nanoparticles also caused an inflammatory response in a human modular immune in vitro construct[388] and were cytotoxic in mouse fibroblast cells,[389] human bronchial epithelial cells,[390,391] and human monoblastid cells.[392] Protein adsorption to TiO_2 particles in serum inhibited the growth of human keratinocyte and carcinoma cells.[393] Exposure to TiO_2 nanoparticles also modified gene expression in human keratinocytes, particularly genes involved in the inflammatory response and cell adhesion, but not those involved in oxidative stress or apoptosis.[394] Another study observed changes in levels of gene expression upon exposure to anatase TiO_2 particles. Differences were primarily observed for genes relating to drug response, detoxification, DNA damage, and protein stress.[395] The specific morphology of the TiO_2 nanoparticles may be important for predicting their toxicity when irradiated.[396] Polyoxometalates of Ti, such as the dodecatitanates,[397] have been prepared; there are no data on their effects on humans.

8. CONCLUSION

Titanium has never been demonstrated to be essential for any organism, and no Ti-requiring biomolecule such as a titanium enzyme has been identified. Nonetheless, titanium is an abundant and bioactive element, and human exposure to titanium is increasing. Contrary to its reputation as a completely inert and insoluble metal, a good deal of information is available about the bio- and environmentally relevant aqueous coordination chemistry of titanium, about its abundance in various organisms (including its sequestration by some organisms), and about its bioeffects both positive and negative. It is hoped that this review will help chemists better evaluate whether Ti may be involved in biological processes, perhaps not broadly but in some selected environments. Further, it is hoped that, by better understanding the bioinorganic chemistry of titanium, we can learn to exploit fully the medicinal potential of Ti, whether as an anticancer medicine or in implants, while objectively evaluating the possibility of its ill effects, including nanotoxicity.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ann.valentine@temple.edu.

BIOGRAPHIES

Katherine Buettner was raised outside Cleveland, OH. She earned a B.S. in chemistry from Lafayette College in 2007 where she performed research with Steven Mylon to determine the Hamaker constant of cerium oxide nanoparticles. She also studied drinking water disinfection byproducts at the U.S. EPA under the direction of Susan Richardson. She is currently a fifth-year graduate student at Yale University. Her current research is focused on the interactions of titanocene dichloride derivatives with human serum proteins.

Ann Valentine earned a B.S. in chemistry at the University of Virginia in 1993 and a Ph.D. in 1998 at MIT, where she worked with Stephen J. Lippard. After a postdoctoral fellowship with Stephen J. Benkovic at Penn State University, she joined the faculty at Yale in 2001. In 2011 she moved to Temple University. Her research group focuses on how nature manages hydrolysis-prone elements, including titanium. She is the recipient of a Research Corporation Research Innovation Award, an American Cancer Society Research Scholar Award, and the 2009 Paul Saltman Award for Metals in Biology.

ACKNOWLEDGMENT

Support from the American Cancer Society (Research Scholar Grant #RSG-06-246-01-CDD) for titanium research in the author's laboratory is gratefully acknowledged. The authors thank Kathy Batchler for her careful reading of this manuscript, and helpful suggestions. The authors would like to dedicate this review to Dr. Estees Potter Levine, a fascinating scientist whose 1961 paper on Ti in *Eudisotma ritteri* was an inspiration.

ABBREVIATIONS

TMPyP	tetrakis (1-methylpyridinium-4-yl)porphyrin
DOPA	dihydroxyphenylalanine
EHPG	*N,N′*-ethylenebis(*o*-hydroxyphenylglycine)
HBED	*N,N′*-di(*o*-hydroxybenzyl)ethylenediamine-*N,N′*-diacetic acid
ICP	inductively coupled plasma
ICP-MS	inductively coupled plasma mass spectrometry
MCM-41	Mobil composition of matter-41
SBA-15	Santa Barbara amorphous-15
PET	positron emission tomography

REFERENCES

(1) Baynes, J. W. *The Maillard Reaction: Chemistry at the Interface of Nutrition, Aging, and Disease*; New York Academy of Sciences: New York, 2005.

(2) Maillard, L. C.; Ettori, J. C. R. *Hebd. Seances Acad. Sci.* **1936**, *202*, 1459.

(3) Maillard, L. C.; Ettori, J. C. R. *Hebd. Seances Acad. Sci.* **1936**, *202*, 1621.

(4) Maillard, L. C.; Ettori, J. C. R. *Seances Soc. Biol. Fil.* **1936**, *122*, 951.

(5) Maillard, L. C.; Ettori, J. *Bull. Acad. Natl. Med.* **1936**, *115*, 631.

(6) Lippard, S. J.; Berg, J. M. *Principles of Bioinorganic Chemistry*; University Science Books: Mill Valley, CA, 1994.

(7) Bertini, I.; Gray, H. B.; Stiefel, E. I.; Valentine, J. S. *Biological Inorganic Chemistry: Structure and Reactivity*; University Science Books: Sausalito, CA, 2007.

(8) Williams, R. J. P.; Frausto da Silva, J. J. R. *Natural Selection of the Chemical Elements*; Clarendon Press: Oxford, U.K., 1996.

(9) Horváth, I. T. *Encyclopedia of Catalysis*; Wiley: Hoboken, NJ, 2003.

(10) Chirik, P. J.; Boukamp, M. W. In *Comprehensive Coordination Chemistry II: From biology to nanotechnology*; McCleverty, J. A., Meyer, T. J., Eds.; Elsevier Pergamon: Amsterdam, The Netherlands, 2004; Vol. 4.

(11) Mountford, P.; Hazari, N. In *Comprehensive Coordination Chemistry II: From biology to nanotechnology*; McCleverty, J. A., Meyer, T. J., Eds.; Elsevier Pergamon: Amsterdam, The Netherlands, 2004; Vol. 4.

(12) Cuenca, T. In *Comprehensive Coordination Chemistry II: From biology to nanotechnology*; McCleverty, J. A., Meyer, T. J., Eds.; Elsevier Pergamon: Amsterdam, The Netherlands, 2004; Vol. 4.

(13) Smith, S. B.; Stephan, D. W. In *Comprehensive Coordination Chemistry II*; McCleverty, J. A., Meyer, T. J., Eds.; Elsevier: New York, 2003; Vol. 4.

(14) Lütjering, G.; Williams, J. C. *Titanium*; Springer: Berlin/New York, 2003.

(15) Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life: An Introduction and Guide*; Wiley: Chichester/New York, 1994.

(16) Emsley, J. *The Elements*, 3rd ed.; Clarendon Press: Oxford, U.K., 1998.

(17) Van Baalen, M. R. *Chem. Geol.* **1993**, *110*, 233.

(18) Knauss, K. G.; Dibley, M. J.; Bourcier, W. L.; Shaw, H. F. *Appl. Geochem.* **2001**, *16*, 1115.

(19) Schroeder, H. A.; Balassa, J. J.; Tipton, I. H. *J. Chronic Dis.* **1963**, *16*, 55.

(20) Williams, D. F. In *Systematic Aspects of Biocompatibility*; Williams, D. F., Ed.; CRC Press, Inc.: Boca Raton, FL, 1981; Vol. 1.

(21) World Health Organization International Programme on Chemical Safety Environmental Health Criteria 24: Titanium, 1982; http://www.inchem.org/documents/ehc/ehc/ehc24.htm.

(22) Nielsen, F. H. In *Trace Elements in Human and Animal Nutrition*, 5th ed.; Mertz, W., Ed.; Academic Press: San Diego, 1986.

(23) Whitehead, J. In *Metals and Their Compounds in the Environment*; Merian, E., Ed.; VCH: Weinheim, Germany, 1991.

(24) Templeton, D. M. In *Handbook on Metals in Clinical and Analytical Chemistry*; Seiler, H. G., Sigel, A., Sigel, H., Eds.; Marcel Dekker, Inc.: New York, 1994.

(25) Pais, I.; Jones, J. B. In *The Handbook of Trace Elements*; St. Lucie Press: Boca Raton, FL, 1997.

(26) Anke, M.; Seifert, M. In *Elements and Their Compounds in the Environment*; Ernest, M., Anke, M., Ihnat, M., Stoeppler, M., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2.

(27) Kabata-Pendias, A.; Mukherjee, A. B. *Trace Elements from Soil to Human*; Springer: Berlin, 2007.

(28) Valentine, A. M. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; John Wiley and Sons: Chichester, U.K., 2005.

(29) Schmets, J.; Van Muyleder, J.; Pourbaix, M. In *Atlas of Electrochemical Equilibria in Aqueous Solutions*; Pourbaix, M., Ed.; Pergamon Press: Oxford, U.K., 1966.

(30) Zehnder, A. J.; Wuhrmann, K. *Science* **1976**, *194*, 1165.

(31) Seefeldt, L. C.; Ensign, S. A. *Anal. Biochem.* **1994**, *221*, 379.

(32) Baes, C. F.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley: New York, 1976.

(33) Martell, A. E.; M., S. R. *Critical Stability Constants*; Plenum Press: New York, 1974−1977.

(34) Ciavatta, L.; Ferri, D.; Riccio, G. *Polyhedron* **1985**, *4*, 15.

(35) Sugimoto, T.; Zhou, X. P.; Muramatsu, A. *J. Colloid Interface Sci.* **2002**, *252*, 339.

(36) Comba, P.; Merbach, A. *Inorg. Chem.* **1987**, *26*, 1315.

(37) Spiro, T. G.; Saltman, P. *Struct. Bonding (Berlin)* **1969**, *6*, 116.

(38) Stefansson, A. *Environ. Sci. Technol.* **2007**, *41*, 6117.

(39) Martell, A. E.; Hancock, R. D.; Smith, R. M.; Motekaitis, R. J. *Coord. Chem. Rev.* **1996**, *149*, 311.

(40) Babko, A. K.; Gridchina, G. I.; Nabivanets, B. I. *Russ. J. Inorg. Chem.* **1962**, *7*, 66.

(41) Liberti, A.; Chiantella, V.; Corigliano, F. *J. Inorg. Nucl. Chem.* **1963**, *25*, 415.

(42) Nabivanets, B. I.; Lukachina, V. V. *Ukranskii Khimicheskii Zhurnal* **1964**, *30*, 1123.

(43) Fournari, P.; Guilard, R.; Fontesse, M.; Latour, J. M.; Marchon, J. C. *J. Organomet. Chem.* **1976**, *110*, 205.

(44) Jeon, K. S.; Park, J. S.; Suh, Y. D.; Yoon, M. *J. Photochem. Photobiol., A* **2009**, *207*, 20.

(45) Taube, R. *Z. Chem.* **1963**, *3*, 194.

(46) Block, B. P.; Meloni, E. G. *Inorg. Chem.* **1965**, *4*, 111.

(47) Masilela, N.; Idowu, M.; Nyokong, T. *J. Photochem. Photobiol., A* **2009**, *201*, 91.

(48) Zakharov, A. V.; Girichev, G. V. *J. Mol. Struct. (Theochem.)* **2008**, *851*, 183.

(49) Hseu, T. M.; Wu, S. T.; Lin, Z. F. *J. Chin. Chem. Soc.* **1985**, *32*, 417.

(50) Fackler, J. P.; Kristine, F. J.; Mazany, A. M.; Moyer, T. J.; Shepherd, R. E. *Inorg. Chem.* **1985**, *24*, 1857.

(51) Pecsok, R. L.; Maverick, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 358.

(52) Wieghardt, K.; Quilitzsch, U.; Weiss, J.; Nuber, B. *Inorg. Chem.* **1980**, *19*, 2514.

(53) Guo, M. L.; Sun, H. Z.; Bihari, S.; Parkinson, J. A.; Gould, R. O.; Parsons, S.; Sadler, P. J. *Inorg. Chem.* **2000**, *39*, 206.

(54) Tinoco, A. D.; Incarvito, C. D.; Valentine, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 3444.

(55) Zhou, Z.-H.; Deng, Y.-F.; Jiang, Y.-Q.; Wan, H.-L.; Ng, S.-W. *J. Chem. Soc., Dalton Trans.* **2003**, *2003*, 2636.

(56) Deng, Y. F.; Zhou, Z. H.; Wan, H. L. *Inorg. Chem.* **2004**, *43*, 6266.

(57) Collins, J. M.; Uppal, R.; Incarvito, C. D.; Valentine, A. M. *Inorg. Chem.* **2005**, *44*, 3431.

(58) Uppal, R.; Incarvito, C. D.; Lakshmi, K. V.; Valentine, A. M. *Inorg. Chem.* **2006**, *45*, 1795.

(59) Deng, Y. F.; Jiang, Y. Q.; Hong, Q. M.; Zhou, Z. H. *Polyhedron* **2007**, *26*, 1561.

(60) Panagiotidis, P.; Kefalas, E. T.; Raptopoulou, C. P.; Terzis, A.; Mavromoustakos, T.; Salifoglou, A. *Inorg. Chim. Acta* **2008**, *361*, 2210.

(61) Spiro, T. G.; Pape, L.; Saltman, P. *J. Am. Chem. Soc.* **1967**, *89*, 5555.
(62) Spiro, T. G.; Bates, G.; Saltman, P. *J. Am. Chem. Soc.* **1967**, *89*, 5559.
(63) Paradies, J.; Crudass, J.; MacKay, F.; Yellowlees, L. J.; Montgomery, J.; Parsons, S.; Oswald, L.; Robertson, N.; Sadler, P. J. *J. Inorg. Biochem.* **2006**, *100*, 1260.
(64) Mudunkotuwa, I. A.; Grassian, V. H. *J. Am. Chem. Soc.* **2010**, *132*, 14986.
(65) Kemmitt, T.; Al-Salim, N. I.; Gainsford, G. J.; Bubendorfer, A.; Waterland, M. *Inorg. Chem.* **2004**, *43*, 6300.
(66) Kakihana, M.; Tada, M.; Shiro, M.; Petrykin, V.; Osada, M.; Nakamura, Y. *Inorg. Chem.* **2001**, *40*, 891.
(67) Dakanali, M.; Kefalas, E. T.; Raptopoulou, C. P.; Terzis, A.; Voyiatzis, G.; Kyrikou, I.; Mavromoustakos, T.; Salifoglou, A. *Inorg. Chem.* **2003**, *42*, 4632.
(68) Kakihana, M.; Tomita, K.; Petrykin, V.; Tada, M.; Sasaki, S.; Nakamura, Y. *Inorg. Chem.* **2004**, *43*, 4546.
(69) Sellers, R. M. *Analyst* **1980**, *105*, 950.
(70) Bassaid, S.; Robert, D.; Chaib, M. *Appl. Catal., B* **2009**, *86*, 93.
(71) Gao, L.; Xu, H. R. *J. Am. Ceram. Soc.* **2004**, *87*, 830.
(72) Liu, F. H.; Xu, G. J.; Wu, J. H.; Cheng, Y. C.; Guo, J. J.; Cui, P. *Colloid Polym. Sci.* **2010**, *288*, 1739.
(73) Peill, N. J.; Hoffmann, M. R. *Environ. Sci. Technol.* **1996**, *30*, 2806.
(74) Pecsok, R. L. *J. Am. Chem. Soc.* **1951**, *73*, 1304.
(75) Drew, M. G. B.; Fowles, G. W. A.; Lewis, D. F. *J. Chem. Soc., D: Chem. Commun.* **1969**, 876b.
(76) Drew, M. G. B.; Eve, D. J. *Acta Crystallogr.* **1977**, *B33*, 2919.
(77) Eve, D. J.; Niven, M. L. *Inorg. Chim. Acta* **1990**, *174*, 205.
(78) Vandevelde, G. M. H. *J. Inorg. Nucl. Chem.* **1977**, *39*, 1357.
(79) Vandevelde, G. M. H.; Venselaar, J. *J. Inorg. Nucl. Chem.* **1977**, *39*, 1363.
(80) Brisse, F.; Haddad, M. *Inorg. Chim. Acta* **1977**, *24*, 173.
(81) Vandevel, Gm; Harkema, S.; Gellings, P. J. *Inorg. Chim. Acta* **1974**, *11*, 243.
(82) Correns, C. W. In *Handbook of Geochemistry*; Wedepohl, K. H., Ed.; Springer: Berlin, 1969−1978; Vol. 2.
(83) Martell, A. E. In *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seib, P. A., Tolbert, B. M., Eds.; American Chemical Society: Washington, DC, 1982; Vol. 200.
(84) Davies, M. B. *Polyhedron* **1992**, *11*, 285.
(85) Zümreoglu-Karan, B. *Coord. Chem. Rev.* **2006**, *250*, 2295.
(86) Ettori, J. C. *R. Hebd. Séances Acad. Sci.* **1936**, *202*, 852.
(87) Hines, E.; Boltz, D. F. *Anal. Chem.* **1952**, *24*, 947.
(88) Sommer, L. *Collect. Czech. Chem. Commun.* **1963**, *28*, 449.
(89) Susic, M. V. *Bull. Boris Kidric Inst. Nucl. Sci.* **1963**, *14*, 125.
(90) Jabs, W.; Gaube, W. Z. *Anorg. Allg. Chem.* **1984**, *514*, 179.
(91) Jabs, W.; Gaube, W. Z. *Anorg. Allg. Chem.* **1984**, *514*, 185.
(92) Jabs, W.; Gaube, W.; Fehl, C.; Lukowski, R. *Inorg. Chim. Acta* **1990**, *175*, 273.
(93) Rosenheim, A.; Sorge, O. *Chem. Ber.* **1920**, *53*, 932.
(94) Sommer, L. *Collect. Czech. Chem. Commun.* **1963**, *28*, 2102.
(95) Borgias, B. A.; Cooper, S. R.; Koh, Y. B.; Raymond, K. N. *Inorg. Chem.* **1984**, *23*, 1009.
(96) Davis, A. V.; Firman, T. K.; Hay, B. P.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 9484.
(97) Creutz, C.; Chou, M. H. *Inorg. Chem.* **2008**, *47*, 3509.
(98) Uppal, R.; Israel, H. P.; Incarvito, C. D.; Valentine, A. M. *Inorg. Chem.* **2009**, *48*, 10769.
(99) Yoe, J. H.; Armstrong, A. R. *Science* **1945**, *102*, 207.
(100) Yoe, J. H.; Armstrong, A. R. *Anal. Chem.* **1947**, *19*, 100.
(101) Albrecht, M.; Burk, S.; Stoffel, R.; Luchow, A.; Frohlich, R.; Kogej, M.; Schalley, C. A. *Eur. J. Inorg. Chem.* **2007**, 1361.
(102) Tinoco, A. D.; Eames, E. V.; Incarvito, C. D.; Valentine, A. M. *Inorg. Chem.* **2008**, *47*, 8380.
(103) Lamboy, J. L.; Pasquale, A.; Rheingold, A. L.; Melendez, E. *Inorg. Chim. Acta* **2007**, *360*, 2115.
(104) Kaiwar, S. P.; Rao, C. P. *Carbohydr. Res.* **1992**, *237*, 203.
(105) Mühlebach, J.; Müller, K.; Schwarzenbach, G. *Inorg. Chem.* **1970**, *9*, 2381.
(106) Toney, J. H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 947.
(107) Tshuva, E. Y.; Peri, D. *Coord. Chem. Rev.* **2009**, *253*, 2098.
(108) Peri, D.; Alexander, J. S.; Tshuva, E. Y.; Melman, A. *Dalton Trans.* **2006**, 4169.
(109) Shavit, M.; Peri, D.; Melman, A.; Tshuva, E. Y. J. *Biol. Inorg. Chem.* **2007**, *12*, 825.
(110) Hermon, T.; Tshuva, E. Y. *J. Org. Chem.* **2008**, *73*, 5953.
(111) Peri, D.; Meker, S.; Shavit, M.; Tshuva, E. Y. *Chem.—Eur. J.* **2009**, *15*, 2403.
(112) Immel, T. A.; Debiak, M.; Groth, U.; Burkle, A.; Huhn, T. *ChemMedChem* **2009**, *4*, 738.
(113) Immel, T. A.; Groth, U.; Huhn, T. *Chem.—Eur. J.* **2010**, *16*, 2775.
(114) Hutton, J. T. In *Minerals in Soil Environment*; Dixon, J. B., Weed, S. B., Eds.; Soil Science Society of America: Madison, WI, 1977.
(115) Cornu, S.; Lucas, Y.; Lebon, E.; Ambrosi, J. P.; Luizao, F.; Rouiller, J.; Bonnay, M.; Neal, C. *Geoderma* **1999**, *91*, 281.
(116) Welch, S. A.; Christy, A. G.; Kirste, D.; Beavis, S. G.; Beavis, F. *Chem. Geol.* **2007**, *245*, 183.
(117) Schmidt, J.; Vogelsberger, W. *J. Phys. Chem. B* **2006**, *110*, 3955.
(118) Senanayake, S. D.; Idriss, H. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 1194.
(119) Orians, K. J.; Boyle, E.; Bruland, K. W. *Nature* **1990**, *348*, 322.
(120) Turner, D. R.; Whitfield, M.; Dickson, A. G. *Geochim. Cosmochim. Acta* **1981**, *45*, 855.
(121) Kennedy, V. C.; Zellweger, R.; Jones, B. F. *Water Res. Research* **1974**, *10*, 785.
(122) Yan, L. S.; Stallard, R. F.; Key, R. M.; Crerar, D. A. *Geochim. Cosmochim. Acta* **1991**, *55*, 3647.
(123) Yokoi, K.; Vandenberg, C. M. G. *Anal. Chim. Acta* **1991**, *245*, 167.
(124) Skrabal, S. A.; Ullman, W. J.; Luther, G. W. *Marine Chem.* **1992**, *37*, 83.
(125) Skrabal, S. A. *Geochim. Cosmochim. Acta* **1995**, *59*, 2449.
(126) Skrabal, S. A. In *Changes in Fluxes in Estuaries: Implications from Science to Management*; Dyer, K., Orth, R., Eds.; Olsen & Olsen Press: Friedensborg, Denmark, 1994.
(127) Skrabal, S. A. *Marine Chem.* **2006**, *102*, 218.
(128) Griel, J. V.; Robinson, R. J. *J. Mar. Res.* **1952**, *11*, 173.
(129) Goldberg, E. D. *Mem.—Geol. Soc. Am.* **1957**, *67*, 345.
(130) van den Berg, C. M. G.; Boussemart, M.; Yokoi, K.; Prartono, T.; Campos, M. L. A. M. *Mar. Chem.* **1994**, *45*, 267.
(131) Butler, A. *Science* **1998**, *281*, 207.
(132) Kryc, K. A.; Murray, R. W.; Murray, D. W. *Earth Planet. Sci. Lett.* **2003**, *211*, 125.
(133) Donat, J. R.; Bruland, K. W. In *Trace Elements in Natural Waters*; Salbu, B., Steinnes, E., Eds.; CRC Press LLC: Boca Raton, FL, 1995.
(134) Bowen, H. J. M. *Trace Elements in Biochemistry*; Academic Press: New York, 1966.
(135) Mertz, W.; Cornatzer, W. E. *Newer Trace Elements in Nutrition*; M. Dekker: New York, 1971.
(136) Cvetkovic, A.; Menon, A. L.; Thorgersen, M. P.; Scott, J. W.; Poole, F. L., 2nd; Jenney, F. E., Jr.; Lancaster, W. A.; Praissman, J. L.; Shanmukh, S.; Vaccaro, B. J.; Trauger, S. A.; Kalisiak, E.; Apon, J. V.; Siuzdak, G.; Yannone, S. M.; Tainer, J. A.; Adams, M. W. *Nature* **2010**, *466*, 779.
(137) Tipton, I. H.; Cook, M. J.; Steiner, R. L.; Boye, C. A.; Perry, H. M., Jr.; Schroeder, H. A. *Health Phys.* **1963**, *9*, 89.
(138) Tipton, I. H.; Cook, M. J. *Health Phys.* **1963**, *9*, 103.
(139) Tipton, I. H.; Schroeder, H. A.; Perry, H. M., Jr.; Cook, M. J. *Health Phys.* **1965**, *11*, 403.
(140) Lavi, N.; Alfassi, Z. B. *Analyst* **1990**, *115*, 817.
(141) Pluhator-Murton, M. M.; Fedorak, R. N.; Audette, R. J.; Marriage, B. J.; Yatscoff, R. W.; Grarulich, L. M. *J. Parenter. Enter. Nutr.* **1999**, *23*, 222.
(142) Pluhator-Murton, M. M.; Fedorak, R. N.; Audette, R. J.; Marriage, B. J.; Yatscoff, R. W.; Gramlich, L. M. *J. Parenter. Enter. Nutr.* **1999**, *23*, 228.

(143) Davis, S.; Waller, P.; Buschbom, R.; Ballou, J.; White, P. *Arch. Environ. Health* **1990**, *45*, 112.
(144) Schroeder, H. A.; Vinton, W. H.; Balassa, J. J. *J. Nutr.* **1963**, *80*, 39.
(145) Schroeder, H. A.; Balassa, J. J.; Vinton, W. H. *J. Nutr.* **1964**, *83*, 239.
(146) Noddack, I.; Noddack, W. *Ark. Zool.* **1939**, *32A*, 1.
(147) Vinogradov, A. P. *The Elementary Chemical Composition of Marine Organisms*; Sears Foundation for Marine Research: New Haven, CT, 1953.
(148) Eisler, R. *Trace Metal Concentrations in Marine Organisms*; Pergamon Press: New York, 1981.
(149) Coulon, J.; Truchet, M.; Martoja, R. *Ann. Inst. Oceanogr., Paris* **1987**, *63*, 89.
(150) Riley, J. P.; Roth, I. *J. Mar. Biol. Assn. U. K.* **1971**, *51*, 63.
(151) Martin, J. H.; Knauer, G. A. *Geochim. Cosmochim. Acta* **1973**, *37*, 1639.
(152) Kroger, N.; Sandhage, K. H. *MRS Bull.* **2010**, *35*, 122.
(153) Sewell, S. L.; Wright, D. W. *Chem. Mater.* **2006**, *18*, 3108.
(154) Cole, K. E.; Ortiz, A. N.; Schoonen, M. A.; Valentine, A. M. *Chem. Mater.* **2006**, *18*, 4592.
(155) Kroger, N.; Dickerson, M. B.; Ahmad, G.; Cai, Y.; Haluska, M. S.; Sandhage, K. H.; Poulsen, N.; Sheppard, V. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7239.
(156) Dickerson, M. B.; Sandhage, K. H.; Naik, R. R. *Chem. Rev.* **2008**, *108*, 4935.
(157) Collier, A. *Science* **1953**, *118*, 329.
(158) Martin, D. F.; Olander, W. K. *Environ. Lett.* **1971**, *2*, 135.
(159) Bowen, V. T.; Sutton, D. *J. Mar. Res.* **1951**, *10*, 153.
(160) Araujo, M. F.; Cruz, A.; Humanes, M.; Lopes, M. T.; da Silva, J. A. L.; da Silva, J. *Chem. Speciation Bioavailability* **1999**, *11*, 25.
(161) Sumerel, J. L.; Yang, W. J.; Kisailus, D.; Weaver, J. C.; Choi, J. H.; Morse, D. E. *Chem. Mater.* **2003**, *15*, 4804.
(162) Brutchey, R. L.; Morse, D. E. *Chem. Rev.* **2008**, *108*, 4915.
(163) Carlisle, D. B. In *Proceedings of the Royal Society B*; Pirie, N. W., Ed.; The Royal Society: London, 1968; Vol. 171.
(164) Smith, M. J.; Ryan, D. E.; Nakanishi, K.; Frank, P.; Hodgson, K. O. In *Metal Ions in Biological Systems*; Sigel, H., Sigel, A., Eds.; M. Dekker: New York, 1995; Vol. 31.
(165) Gaffney, J. P.; Valentine, A. M. *Dalton Trans.* **2011**, *40*, 5827.
(166) Levine, E. P. *Science* **1961**, *133*, 1352.
(167) Levine, E. P. *J. Morph.* **1962**, *111*, 105.
(168) Swinehart, J. H.; Biggs, W. R.; Halko, D. J.; Schroeder, N. C. *Biol. Bull.* **1974**, *146*, 302.
(169) Roman, D. A.; Molina, J.; Rivera, L. *Biol. Bull.* **1988**, *175*, 154.
(170) Taylor, S. W.; Kammerer, B.; Bayer, E. *Chem. Rev.* **1997**, *97*, 333.
(171) Dorsett, L. C.; Hawkins, C. J.; Grice, J. A.; Lavin, M. F.; Merefield, P. M.; Parry, D. L.; Ross, I. L. *Biochemistry* **1987**, *26*, 8078.
(172) Lowenstam, H. A.; Weiner, S. *On Biomineralization*; Oxford University Press: New York, 1989.
(173) Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*; Oxford University Press: New York, 2001.
(174) Addadi, L.; Politi, Y.; Nudelman, F.; Weiner, S. *Eng. Cryst. Mater. Prop.* **2008**, 1.
(175) Weiner, S. *J. Struct. Biol.* **2008**, *163*, 229.
(176) Sano, K. I.; Shiba, K. *J. Am. Chem. Soc.* **2003**, *125*, 14234.
(177) Meyers, S. R.; Hamilton, P. T.; Walsh, E. B.; Kenan, D. J.; Grinstaff, M. W. *Adv. Mater.* **2007**, *19*, 2492.
(178) Thingholm, T. E.; Jorgensen, T. J. D.; Jensen, O. N.; Larsen, M. R. *Nat. Protoc.* **2006**, *1*, 1929.
(179) Yan, J. Y.; Li, X. L.; Yu, L.; Jin, Y.; Zhang, X. L.; Xue, X. Y.; Ke, Y. X.; Liang, X. M. *Chem. Commun.* **2010**, *46*, 5488.
(180) Firby, J. B.; Durham, J. W. J. *Paleontology* **1974**, *48*, 1109.
(181) Glaessner, M. F. *J. Geol. Soc. London* **1976**, *132*, 259.
(182) Yochelson, E. L.; Kisselev, G. N. *Lethaia* **2003**, *36*, 8.
(183) Signor, P. W.; Ryan, D. A. *Geology* **1993**, *21*, 805.
(184) Stokroos, I.; Litinetsky, L.; van der Want, J. J.; Ishay, J. S. *Nature* **2001**, *411*, 654.
(185) Ishay, J. S.; Riabinin, K.; Kozhevnikov, M.; van der Want, H.; Stokroos, I. *Biomacromolecules* **2003**, *4*, 649.
(186) Sen Gupta, B. K. *Modern Foraminifera*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1999.
(187) Lipps, J. H. *Annu. Rev. Microbiol.* **1973**, *27*, 471.
(188) Heron-Allen, E.; Earland, A. *Proc. R. Irish Acad.* **1913**, *31* (Section 3 Part 64), 1.
(189) Dick, A. B. *Trans. Edin. Geol. Soc.* **1925**, *12*, 19.
(190) Cole, K. E.; Valentine, A. M. *Dalton Trans.* **2006**, 430.
(191) Allen, K.; Roberts, S.; Murray, J. W. J. *Micropalaeontol.* **1999**, *18*, 183.
(192) Shabtai, Y.; Fleminger, G. *Appl. Environ. Microbiol.* **1994**, *60*, 3079.
(193) Shabtai, J.; Hasharon, R.; Fleminger, G.; Fleming, J.; The Israel Electric Corporation, Ltd. U. S. Patent 5,290,697, 1994.
(194) Gertler, G.; Brudo, I.; Kenig, R.; Fleminger, G. *Mat.-wiss. u. Werkstofftech.* **2003**, *34*, 1138.
(195) Siegmann, A.; Komarska, A.; Betzalel, Y.; Brudo, I.; Jindou, S.; Mor, G.; Fleminger, G. *J. Mol. Recognit.* **2009**, *22*, 138.
(196) Horst, A. M.; Neal, A. C.; Mielke, R. E.; Sislian, P. R.; Suh, W. H.; Maedler, L.; Stucky, G. D.; Holden, P. A. *Appl. Environ. Microbiol.* **2010**, *76*, 7292.
(197) Kiser, M. A.; Westerhoff, P.; Benn, T.; Wang, Y.; Perez-Rivera, J.; Hristovski, K. *Environ. Sci. Technol.* **2009**, *43*, 6757.
(198) Kiser, M. A.; Ryu, H.; Jang, H. Y.; Hristovski, K.; Westerhoff, P. *Water Res.* **2010**, *44*, 4105.
(199) Li, B. K.; Logan, B. E. *Colloids Surf., B* **2004**, *36*, 81.
(200) McWhirter, M. J.; Bremer, P. J.; Lamont, I. L.; McQuillan, A. J. *Langmuir* **2003**, *19*, 3575.
(201) McWhirter, M. J.; McQuillan, A. J.; Bremer, P. J. *Colloids Surf., B* **2002**, *26*, 365.
(202) Schwietert, C. W.; McCue, J. P. *Coord. Chem. Rev.* **1999**, *184*, 67.
(203) Park, S. M.; Kim, H. S.; Yu, T. S. *J. Microbiol.* **2006**, *44*, 255.
(204) Hegoczki, J.; Janzso, B.; Suhajda, A. *Acta Aliment.* **1995**, *24*, 181.
(205) Tipton, I. H.; Stewart, P. L.; Martin, P. G. *Health Phys.* **1966**, *12*, 1683.
(206) Dumon, J. C.; Ernst, W. H. O. *J. Plant Physiol.* **1988**, *133*, 203.
(207) Carvajal, M.; Alcaraz, C. F. *J. Plant Nutr.* **1998**, *21*, 655.
(208) Pais, I.; Feher, M.; Farkas, E.; Szabo, Z.; Cornides, I. *Commun. Soil Sci. Plant Anal.* **1977**, *8*, 407.
(209) Pais, I.; Feher, M.; Bokori, J.; Nagy, B. *Water, Air, Soil Pollut.* **1991**, *57*−*58*, 675.
(210) Pais, I.; Nagy, B.; Feher, M.; Szabo, Z.; Palfalvi, A.; Reibling, J.; Merei, L.; Kimura, S. Patent AU-B-76051/87-592211 Australia, 1990.
(211) Kelemen, G.; Keresztes, A.; Bacsy, E.; Feher, M.; Fodor, P.; Pais, I. *Food Struct.* **1993**, *12*, 67.
(212) Lesko, K.; Stefanovits-Banyai, E.; Pais, I.; Simon-Sarkadi, L. *J. Plant Nutr.* **2002**, *25*, 2571.
(213) Hruby, M.; Cigler, P.; Kuzel, S. *J. Plant Nutr.* **2002**, *25*, 577.
(214) Kuzel, S.; Hruby, M.; Cigler, P.; Tlustos, P.; Van, P. N. *Biol. Trace Elem. Res.* **2003**, *91*, 179.
(215) Kuzel, S.; Cigler, P.; Hruby, M.; Vydra, J.; Pavlikova, D.; Tlustos, P. *Plant, Soil Environ.* **2007**, *53*, 16.
(216) Alcaraz-Lopez, C.; Botia, M.; Alcaraz, C. F.; Riquelme, F. *J. Plant Physiol.* **2003**, *160*, 1441.
(217) Alcaraz-Lopez, C.; Botia, M.; Alcaraz, C. F.; Riquelme, F. *J. Sci. Food Agric.* **2004**, *84*, 949.
(218) Alcaraz-Lopez, C.; Botia, M.; Alcaraz, C. F.; Riquelme, F. *J. Plant Nutr.* **2004**, *27*, 713.
(219) Schroeder, H. A. *Arch. Environ. Health* **1971**, *23*, 102.
(220) Anke, M. K. In *Elements and Their Compounds in the Environment*; Ernest, M., Anke, M., Ihnat, M., Stoeppler, M., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1.
(221) Yaghoubi, S.; Schwietert, C. W.; McCue, J. P. *Biol. Trace Elem. Res.* **2000**, *78*, 205.
(222) Schwietert, C. W.; Yaghoubi, S.; Gerber, N. C.; McSharry, J. J.; McCue, J. P. *Biol. Trace Elem. Res.* **2001**, *83*, 149.

(223) Pais, I.; Feher nee Ravasz, M.; Nagy, B.; Bokori, J.; Szabo, Z. U. S. Patent 4,482,550, 1984.
(224) Merritt, K.; Margevicius, R. W.; Brown, S. A. *J. Biomed. Mater. Res.* **1992**, *26*, 1503.
(225) Merritt1, K.; Brown, S. A. *J. Biomed. Mater. Res.* **1995**, *29*, 1175.
(226) Ishiwata, K.; Ido, T.; Monma, M.; Murakami, M.; Fukuda, H.; Kameyama, M.; Yamada, K.; Endo, S.; Yoshioka, S.; Sato, T.; Matsuzawa, T. *Int. J. Radiat. Appl. Instrum., A* **1991**, *42*, 707.
(227) Kawamura, M.; Ido, T.; Ishiwata, K.; Inoue, K.; Kimura, S.; Matsuda, K.; Kawashima, K.; Kameyama, M. *J. Label. Compd. Radiopharm.* **1986**, *23*, 1360.
(228) Köpf-Maier, P.; Funke-Kaiser, P. *Toxicol.* **1986**, *38*, 81.
(229) Köpf-Maier, P.; Gerlach, S. J. *Cancer Res. Clin. Oncol.* **1986**, *111*, 243.
(230) Köpf-Maier, P.; Erkenswick, P. *Toxicol.* **1984**, *33*, 171.
(231) Kopf-Maier, P. *Anticancer Res.* **1999**, *19*, 493.
(232) Ishiwata, K.; Ido, T.; Monma, M.; Murakami, M.; Fukuda, H.; Kameyama, M.; Yamada, K.; Endo, S.; Yoshioka, S.; Sato, T.; Matsuzawa, T. *Appl. Radiat. Isot.* **1991**, *42*, 707.
(233) Vavere, A. L.; Laforest, R.; Welch, M. *J. Nucl. Med. Biol.* **2005**, *32*, 117.
(234) Vavere, A. L.; Welch, M. J. *J. Nucl. Med.* **2005**, *46*, 683.
(235) Köpf, H.; Köpf-Maier, P. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 477.
(236) Keppler, B. K.; Friesen, C.; Moritz, H. G.; Vongerichten, H.; Vogel, E. *Struct. Bonding (Berlin)* **1991**, *78*, 97.
(237) Köpf-Maier, P. In *Metal Complexes in Cancer Chemotherapy*; Keppler, B. K., Ed.; VCH: Weinheim, Germany, 1993.
(238) Keppler, B. K.; Friesen, C.; Vongerichten, H.; Vogel, E. In *Metal Complexes in Cancer Chemotherapy*; Keppler, B. K., Ed.; VCH: Weinheim, Germany, 1993.
(239) Harding, M. M.; Mokdsi, G. *Curr. Med. Chem.* **2000**, *7*, 1289.
(240) Melendez, E. *Crit. Rev. Oncol. Hematol.* **2002**, *42*, 309.
(241) Caruso, F.; Rossi, M. In *Metal Ions in Biological Stystem, Vol. 42: Metal Complexes in Tumor Diagnostics and as Anticancer Agents*; Sigel, A., Sigel, H., Eds.; Marcel Dekker, Inc.: New York, 2004.
(242) Caruso, F.; Rossi, M. *Mini-Rev. Med. Chem.* **2004**, *4*, 49.
(243) Abeysinghe, P. M.; Harding, M. M. *Dalton Trans.* **2007**, 3474.
(244) Dabrowiak, J. C. In *Metals in Medicine*; Wiley: West Sussex, U. K., 2009.
(245) Kostova, I. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 827.
(246) Olszewski, U.; Hamilton, G. *Anti-Cancer Agents Med. Chem.* **2010**, *10*, 302.
(247) Gasser, G.; Ott, I.; Metzler-Nolte, N. *J. Med. Chem.* **2011**, *54*, 3.
(248) Kuo, L. Y.; Liu, A. H.; Marks, T. J. In *Metal Ions in Biological Systems*; Sigel, A., Sigel, H., Eds.; Marcel Dekker, Inc.: New York, 1996; Vol. 33.
(249) Wittrisch, H.; Schroer, H. P.; Vogt, J.; Vogt, C. *Electrophoresis* **1998**, *19*, 3012.
(250) Chen, X.; Zhou, L. X. *J. Mol. Struct. (Theochem.)* **2010**, *940*, 45.
(251) Comba, P.; Jakob, H.; Nuber, B.; Keppler, B. K. *Inorg. Chem.* **1994**, *33*, 3396.
(252) Dubler, E.; Buschmann, R.; Schmalle, H. W. *J. Inorg. Biochem.* **2003**, *95*, 97.
(253) Guo, Z.; Sadler, P. J. In *Advances in Inorganic Chemistry*; Academic Press: New York, 2000; Vol. 49.
(254) Huang, R. L.; Wallqvist, A.; Covell, D. G. *Biochem. Pharmacol.* **2005**, *69*, 1009.
(255) Müller, B. W.; Müller, R.; Lucks, S.; Mohr, W. Medac Gesellschaft für klinische Spezialpräparate mbH: U.S.A., 1994.
(256) Christodoulou, C. V.; Ferry, D. R.; Fyfe, D. W.; Young, A.; Doran, J.; Sheehan, T. M. T.; Eliopoulos, A.; Hale, K.; Baumgart, J.; Sass, G.; Kerr, D. J. *J. Clin. Oncol.* **1998**, *16*, 2761.
(257) Korfel, A.; Scheulen, M. E.; Schmoll, H. J.; Grundel, O.; Harstrick, A.; Knoche, M.; Fels, L. M.; Skorzec, M.; Bach, F.; Baumgart, J.; Sass, G.; Seeber, S.; Thiel, E.; Berdel, W. E. *Clin. Cancer Res.* **1998**, *4*, 2701.
(258) Lümmen, G.; Sperling, H.; Luboldt, H.; Otto, T.; Rübben, H. *Cancer Chemother. Pharmacol.* **1998**, *42*, 415.
(259) Kröger, N.; Kleeberg, U. R.; Mross, K.; Edler, L.; Saß, G.; Hossfeld, D. K. *Onkologie* **2000**, *23*, 60.
(260) Schilling, T.; Keppler, K. B.; Heim, M. E.; Niebch, G.; Dietzfelbinger, H.; Rastetter, J.; Hanauske, A. R. *Invest. New Drugs* **1995**, *13*, 327.
(261) Guo, M.; Sun, H.; McArdle, H. J.; Gambling, L.; Sadler, P. J. *Biochemistry* **2000**, *39*, 10023.
(262) Sun, H.; Li, H.; Weir, R. A.; Sadler, P. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1577.
(263) Messori, L.; Orioli, P.; Banholzer, V.; Pais, I.; Zatta, P. *FEBS Lett.* **1999**, *442*, 157.
(264) Tinoco, A. D.; Valentine, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 11218.
(265) Sarmiento-Gonzalez, A.; Encinar, J. R.; Cantarero-Roldan, A. M.; Marchante-Gayon, J. M.; Sanz-Medel, A. *Anal. Chem.* **2008**, *80*, 8702.
(266) Tinoco, A. D.; Eames, E. V.; Valentine, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 2262.
(267) Buettner, K. M.; Snoeberger, R. C., III; Batista, V. S.; Valentine, A. M. *Dalton Trans.* **2011**, *40*, 9580.
(268) Parker Siburt, C. J.; Lin, E. M.; Brandt, S. J.; Tinoco, A. D.; Valentine, A. M.; Crumbliss, A. L. *J. Inorg. Biochem.* **2010**, *104*, 1006.
(269) Shen, M.; Wang, J.; Yang, M.; Li, G. X. *Electrochem. Commun.* **2011**, *13*, 114.
(270) Ravera, M.; Gabano, E.; Baracco, S.; Osella, D. *Inorg. Chim. Acta* **2009**, *362*, 1303.
(271) Sarsam, S. W.; Nutt, D. R.; Strohfeldt, K.; Watson, K. A. *Metallomics* **2011**, *3*, 152.
(272) Ishiwata, K.; Ido, T.; Monma, M.; Murakami, M.; Kameyama, M.; Fukuda, H.; Matsuzawa, T. J. *Label. Compd. Radiopharm.* **1982**, *19*, 1539.
(273) Hallab, N. J.; Mikecz, K.; Vermes, C.; Skipor, A.; Jacobs, J. J. *J. Biomed. Mater. Res.* **2001**, *56*, 427.
(274) Klem, M. T.; Mosolf, J.; Young, M.; Douglas, T. *Inorg. Chem.* **2009**, *48*, 9041.
(275) Mokdsi, G.; Harding, M. M. *J. Inorg. Biochem.* **2001**, *83*, 205.
(276) Pavlaki, M.; Debeli, K.; Triantaphyllidou, I. E.; Klouras, N.; Giannopoulou, E.; Aletras, A. J. *J. Biol. Inorg. Chem.* **2009**, *14*, 947.
(277) Cavanaugh, D. J.; Harris, J.; Hearon, J. Z. *J. Am. Chem. Soc.* **1955**, *77*, 1531.
(278) Waern, J. B.; Harris, H. H.; Lai, B.; Cai, Z. H.; Harding, M. M.; Dillon, C. T. *J. Biol. Inorg. Chem.* **2005**, *10*, 443.
(279) McLaughlin, M. L.; Cronan, J. M.; Schaller, T. R.; Snelling, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 8949.
(280) Murray, J. H.; Harding, M. M. *J. Med. Chem.* **1994**, *37*, 1936.
(281) Mokdsi, G.; Harding, M. M. *J. Organomet. Chem.* **1998**, *565*, 29.
(282) Yang, P.; Guo, M. L. *Coord. Chem. Rev.* **1999**, *186*, 189.
(283) Melendez, E.; Marrero, M.; Rivera, C.; Hernandez, E.; Segal, A. *Inorg. Chim. Acta* **2000**, *298*, 178.
(284) Guo, M.; Guo, Z.; Sadler, P. J. *J. Biol. Inorg. Chem.* **2001**, *6*, 698.
(285) Vera, J. L.; Roman, F. R.; Melendez, E. *Anal. Bioanal. Chem.* **2004**, *379*, 399.
(286) Mascini, M.; Bagni, G.; Di Pietro, M. L.; Ravera, M.; Baracco, S.; Osella, D. *Biometals* **2006**, *19*, 409.
(287) Hernandez, R.; Lamboy, J.; Gao, L. M.; Matta, J.; Roman, F. R.; Melendez, E. *J. Biol. Inorg. Chem.* **2008**, *13*, 685.
(288) Hernandez, R.; Mendez, J.; Lamboy, J.; Torres, M.; Roman, F. R.; Melendez, E. *Toxicol. in Vitro* **2010**, *24*, 178.
(289) Vessieres, A.; Plamont, M. A.; Cabestaing, C.; Claffey, J.; Dieckmann, S.; Hogan, M.; Muller-Bunz, H.; Strohfeldt, K.; Tacke, M. *J. Organomet. Chem.* **2009**, *694*, 874.
(290) Strohfeldt, K.; Tacke, M. *Chem. Soc. Rev.* **2008**, *37*, 1174.
(291) Sweeney, N. J.; Mendoza, O.; Muller-Bunz, H.; Pampillon, C.; Rehmann, F. J. K.; Strohfeldt, K.; Tacke, M. *J. Organomet. Chem.* **2005**, *690*, 4537.
(292) Kelter, G.; Sweeney, N. J.; Strohfeldt, K.; Fiebig, H. H.; Tacke, M. *Anti-Cancer Drugs* **2005**, *16*, 1091.

(293) Fichtner, I.; Pampillon, C.; Sweeney, N. J.; Strohfeldt, K.; Tacke, M. *Anti-Cancer Drugs* **2006**, *17*, 333.
(294) O'Connor, K.; Gill, C.; Tacke, M.; Rebmann, F. J. K.; Strohfeldt, K.; Sweeney, N.; Fitzpatrick, J. M.; Watson, R. W. G. *Apoptosis* **2006**, *11*, 1205.
(295) Bannon, J. H.; Fichtner, I.; O'Neill, A.; Pampillon, C.; Sweeney, N. J.; Strohfeldt, K.; Watson, R. W.; Tacke, M.; Mc Gee, M. M. *Br. J. Cancer* **2007**, *97*, 1234.
(296) Beckhove, P.; Oberschmidt, O.; Hanauske, A. R.; Pampillon, C.; Schirrmacher, V.; Sweeney, N. J.; Strohfeldt, K.; Tacke, M. *Anti-Cancer Drugs* **2007**, *18*, 311.
(297) Oberschmidt, O.; Hanauske, A. R.; Pampillon, C.; Sweeney, N. J.; Strohfeldt, K.; Tacke, M. *Anti-Cancer Drugs* **2007**, *18*, 317.
(298) Claffey, J.; Gleeson, B.; Hogan, M.; Muller-Bunz, H.; Wallis, D.; Tackell, M. *Eur. J. Inorg. Chem.* **2008**, 4074.
(299) Claffey, J.; Hogan, M.; Muller-Bunz, H.; Pampillon, C.; Tacke, M. *ChemMedChem* **2008**, *3*, 729.
(300) Dowling, C. M.; Claffey, J.; Cuffe, S.; Fichtner, I.; Pampillon, C.; Sweeney, N. J.; Strohfeldt, K.; Watson, R. W. G.; Tacke, M. *Lett. Drug Des. Discovery* **2008**, *5*, 141.
(301) Fichtner, I.; Behrens, D.; Claffey, J.; Gleeson, B.; Hogan, M.; Wallis, D.; Weber, H.; Tacke, M. *Lett. Drug Des. Discovery* **2008**, *5*, 489.
(302) Claffey, J.; Deally, A.; Gleeson, B.; Hogan, M.; Mendez, L. M. M.; Muller-Bunz, H.; Patil, S.; Wallis, D.; Tacke, M. *Metallomics* **2009**, *1*, 511.
(303) Eger, S.; Immel, T. A.; Claffey, J.; Muller-Bunz, H.; Tacke, M.; Groth, U.; Huhn, T. *Inorg. Chem.* **2010**, *49*, 1292.
(304) Immel, T. A.; Martin, J. T.; Dürr, C. J.; Groth, U.; Huhn, T. *J. Inorg. Biochem.* **2010**, *104*, 863.
(305) Hogan, M.; Gleeson, B.; Tacke, M. *Lett. Drug Des. Discovery* **2010**, *7*, 310.
(306) Gomez-Ruiz, S.; Kaluderovic, G. N.; Polo-Ceron, D.; Prashar, S.; Fajardo, M.; Zizak, Z.; Juranic, Z. D.; Sabo, T. J. *Inorg. Chem. Commun.* **2007**, *10*, 748.
(307) Gomez-Ruiz, S.; Kaluderovic, G. N.; Zizak, Z.; Besu, I.; Juranic, Z. D.; Prashar, S.; Fajardo, M. *J. Organomet. Chem.* **2009**, *694*, 1981.
(308) Kaluderovic, G. N.; Tayurskaya, V.; Paschke, R.; Prashar, S.; Fajardo, M.; Gomez-Ruiz, S. *Appl. Organomet. Chem.* **2010**, *24*, 656.
(309) Hogan, M.; Gleeson, B.; Tacke, M. *Organometallics* **2010**, *29*, 1032.
(310) Allen, O. R.; Croll, L.; Gott, A. L.; Knox, R. J.; McGowan, P. C. *Organometallics* **2004**, *23*, 288.
(311) Allen, O. R.; Gott, A. L.; Hartley, J. A.; Hartley, J. M.; Knox, R. J.; McGowan, P. C. *Dalton Trans.* **2007**, 5082.
(312) Causey, P. W.; Baird, M. C.; Cole, S. P. C. *Organometallics* **2004**, *23*, 4486.
(313) Potter, G. D.; Baird, M. C.; Chan, M.; Cole, S. P. C. *Inorg. Chem. Commun.* **2006**, *9*, 1114.
(314) Potter, G. D.; Baird, M. C.; Cole, S. P. C. *J. Organomet. Chem.* **2007**, *692*, 3508.
(315) Gao, L. M.; Matta, J.; Rheingold, A. L.; Melendez, E. *J. Organomet. Chem.* **2009**, *694*, 4134.
(316) Gao, L. M.; Vera, J. L.; Matta, J.; Melendez, E. J. *Biol. Inorg. Chem.* **2010**, *15*, 851.
(317) Gomez-Ruiz, S.; Kaluderovic, G. N.; Prashar, S.; Polo-Ceron, D.; Fajardo, M.; Zizak, Z.; Sabo, T. J.; Juranic, Z. D. *J. Inorg. Biochem.* **2008**, *102*, 1558.
(318) Gomez-Ruiz, S.; Gallego, B.; Zizak, Z.; Hey-Hawkins, E.; Juranic, Z. D.; Kaluderovic, G. N. *Polyhedron* **2010**, *29*, 354.
(319) Shavit, M.; Peri, D.; Manna, C. M.; Alexander, J. S.; Tshuva, E. Y. *J. Am. Chem. Soc.* **2007**, *129*, 12098.
(320) Tshuva, E. Y.; Ashenhurst, J. A. *Eur. J. Inorg. Chem.* **2009**, 2203.
(321) Manna, C. M.; Tshuva, E. Y. *Dalton Trans.* **2010**, *39*, 1182.
(322) Tzubery, A.; Tshuva, E. Y. *Inorg. Chem.* **2011**, *50*, 7946.
(323) Meker, S.; Manna, C. M.; Peri, D.; Tshuva, E. Y. *Dalton Trans.* **2011**, DOI: 10.1039/C1DT11108F
(324) Caruso, F.; Rossi, M.; Tanski, J.; Sartori, R.; Sariego, R.; Moya, S.; Diez, S.; Navarrete, E.; Cingolani, A.; Marchetti, F.; Pettinari, C. *J. Med. Chem.* **2000**, *43*, 3665.
(325) Caruso, F.; Pettinari, C.; Marchetti, F.; Natanti, P.; Phillips, C.; Tanski, J.; Rossi, M. *Inorg. Chem.* **2007**, *46*, 7553.
(326) Caruso, F.; Rossi, M. *J. Inorg. Biochem.* **2001**, *86*, 170.
(327) Caruso, F.; Rossi, M.; Opazo, C.; Pettinari, C. *Bioinorg. Chem. Appl.* **2005**, *3*, 317.
(328) Buck, D. P.; Abeysinghe, P. M.; Cullinane, C.; Day, A. I.; Collins, J. G.; Harding, M. M. *Dalton Trans.* **2008**, 2328.
(329) Kaluderovic, G. N.; Perez-Quintanilla, D.; Zizak, Z.; Juranic, Z. D.; Gomez-Ruiz, S. *Dalton Trans.* **2010**, *39*, 2597.
(330) Perez-Quintanilla, D.; Gomez-Ruiz, S.; Zizak, Z.; Sierra, I.; Prashar, S.; del Hierro, I.; Fajardo, M.; Juranic, Z. D.; Kaluderovic, G. N. *Chem.—Eur. J.* **2009**, *15*, 5588.
(331) Kaluderovic, G. N.; Perez-Quintanilla, D.; Sierra, I.; Prashar, S.; del Hierro, I.; Zizak, Z.; Juranic, Z. D.; Fajardo, M.; Gomez-Ruiz, S. *J. Mater. Chem.* **2010**, *20*, 806.
(332) Tengvall, P.; Lundstrom, I. *Clin. Mater.* **1992**, *9*, 115.
(333) Long, M.; Rack, H. J. *Biomaterials* **1998**, *19*, 1621.
(334) Geetha, M.; Singh, A. K.; Asokamani, R.; Gogia, A. K. *Prog. Mater. Sci.* **2009**, *54*, 397.
(335) Urban, R. M.; Jacobs, J. J.; Tomlinson, M. J.; Gavrilovic, J.; Black, J.; Peoc'h, M. *J. Bone Joint Surg. Am.* **2000**, *82A*, 457.
(336) Jacobs, J. J.; Gilbert, J. L.; Urban, R. M. *J. Bone Joint Surg. Am.* **1998**, *80A*, 268.
(337) Hallab, N. J.; Jacobs, J. *J. Corros. Rev.* **2003**, *21*, 183.
(338) Cadosch, D.; Chan, E.; Gautschi, O. P.; Filgueira, L. *J. Biomed. Mater. Res., A* **2009**, *91*, 1252.
(339) Strietzel, R.; Hosch, A.; Kalbfleisch, H.; Buch, D. *Biomaterials* **1998**, *19*, 1495.
(340) Okazaki, Y.; Gotoh, E. *Biomaterials* **2005**, *26*, 11.
(341) Hallab, N. J.; Skipor, A.; Jacobs, J. J. *J. Biomed. Mater. Res., A* **2003**, *65*, 311.
(342) Silwood, C. J.; Grootveld, M. *Biochem. Biophys. Res. Commun.* **2005**, *330*, 784.
(343) Suwalsky, M.; Villena, F.; Norris, B.; Soto, M. A.; Sotomayor, C. P.; Messori, L.; Zatta, P. *J. Inorg. Biochem.* **2005**, *99*, 764.
(344) Rosenberg, A.; Gratz, K. W.; Sailer, H. F. *Int. J. Oral Maxillofac. Surg.* **1993**, *22*, 185.
(345) Kim, Y. K.; Yeo, H. H.; Lim, S. C. *J. Oral Maxillofac. Surg.* **1997**, *55*, 322.
(346) Bianco, P. D.; Ducheyne, P.; Cuckler, J. M. *Biomaterials* **1996**, *17*, 1937.
(347) Jacobs, J. J.; Skipor, A. K.; Patterson, L. M.; Hallab, N. J.; Paprosky, W. G.; Black, J.; Galante, J. O. *J. Bone Joint Surg. Am.* **1998**, *80*, 1447.
(348) Liu, T. K.; Liu, S. H.; Chang, C. H.; Yang, R. S.; Tohoku, J. *Exp. Med.* **1998**, *185*, 253.
(349) Kasai, Y.; Iida, R.; Uchida, A. *Spine* **2003**, *28*, 1320.
(350) Woodman, J. L.; Jacobs, J. J.; Galante, J. O.; Urban, R. M. *J. Orthopaed. Res.* **1984**, *1*, 421.
(351) Hallab, N. J.; Jacobs, J. J.; Skipor, A.; Black, J.; Mikecz, K.; Galante, J. O. *J. Biomed. Mater. Res.* **2000**, *49*, 353.
(352) Olmedo, D. G.; Tasat, D. R.; Guglielmotti, M. B.; Cabrini, R. L. *J. Mater. Sci., Mater. Med.* **2008**, *19*, 3049.
(353) Elo, R.; Uksila, E.; Arstila, A. U.; Maatta, K. *Arch. Pathol.* **1972**, *94*, 417.
(354) Redline, S.; Barna, B. P.; Tomashefski, J. F.; Abraham, J. L. *Br. J. Ind. Med.* **1986**, *43*, 652.
(355) Vermes, C.; Roebuck, K. A.; Chandrasekaran, R.; Dobai, J. G.; Jacobs, J. J.; Glant, T. T. *J. Bone Mineral Res.* **2000**, *15*, 1756.
(356) Vermes, C.; Chandrasekaran, R.; Jacobs, J. J.; Galante, J. O.; Roebuck, K. A.; Glant, T. T. *J. Bone Joint Surg. Am.* **2001**, *83A*, 201.
(357) Roebuck, K. A.; Vermes, C.; Carpenter, L. R.; Fritz, E. A.; Narayanan, R.; Glant, T. T. *J. Bone Miner. Res.* **2001**, *16*, 501.
(358) Fritz, E. A.; Glant, T. T.; Vermes, C.; Jacobs, J. J.; Roebuck, K. A. *J. Orthopaed. Res.* **2002**, *20*, 490.

(359) Kumazawa, R.; Watari, F.; Takashi, N.; Tanimura, Y.; Uo, M.; Totsuka, Y. *Biomaterials* **2002**, *23*, 3757.
(360) Choi, M. G.; Koh, H. S.; Kluess, D.; O'Connor, D.; Mathur, A.; Truskey, G. A.; Rubin, J.; Zhou, D. X. F.; Sung, K. L. P. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 4578.
(361) Carinci, F.; Volinia, S.; Pezzetti, F.; Francioso, F.; Tosi, L.; Piattelli, A. *J. Biomed. Mater. Res., B* **2003**, *66*, 341.
(362) Sollazzo, V.; Palmieri, A.; Pezzetti, F.; Scarano, A.; Martinelli, M.; Scapoli, L.; Massari, L.; Brunelli, G.; Caramelli, E.; Carinci, F. *J. Biomed. Mater. Res., B* **2008**, *85*, 29.
(363) Cadosch, D.; Chan, E.; Gautschi, O. P.; Filgueira, L.; Zellweger, R. *J. Am. Coll. Surgeons* **2008**, *207*, S51.
(364) Cadosch, D.; Gautschi, O. P.; Chan, E.; Simmen, H. P.; Filgueira, L. *J. Biomed. Mater. Res., A* **2010**, *92*, 475.
(365) Cadosch, D.; Sutanto, M.; Chan, E.; Mhawi, A.; Gautschi, O. P.; von Katterfeld, B.; Simmen, H. P.; Filgueira, L. *J. Orthopaed. Res.* **2010**, *28*, 341.
(366) Cadosch, D.; Chan, E.; Gautschi, O. P.; Meagher, J.; Zellweger, R.; Filgueira, L. *J. Biomed. Mater. Res., A* **2009**, *91*, 29.
(367) Hong, J.; Andersson, J.; Ekdahl, K. N.; Elgue, G.; Axen, N.; Larsson, R.; Nilsson, B. *Thromb. Haemostasis* **1999**, *82*, 58.
(368) Hong, J.; Azens, A.; Ekdahl, K. N.; Granqvist, C. G.; Nilsson, B. *Biomaterials* **2005**, *26*, 1397.
(369) Uchida, M.; Ito, A.; Furukawa, K. S.; Nakamura, K.; Onimura, Y.; Oyane, A.; Ushida, T.; Yamane, T.; Tamaki, T.; Tateishi, T. *Biomaterials* **2005**, *26*, 6924.
(370) Khoo, X.; Hamilton, P.; O'Toole, G. A.; Snyder, B. D.; Kenan, D. J.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2009**, *131*, 10992.
(371) Nyren, O.; Mclaughlin, J. K.; Gridley, G.; Ekbom, A.; Johnell, O.; Fraumeni, J. F.; Adami, H. O. *J. Natl. Cancer Inst.* **1995**, *87*, 28.
(372) Oberdorster, G.; Oberdorster, E.; Oberdorster, J. *Environ. Health Perspect.* **2005**, *113*, 823.
(373) Sanvicens, N.; Marco, M. P. *Trends Biotechnol.* **2008**, *26*, 425.
(374) Oberdorster, G. *J. Int. Med.* **2010**, *267*, 89.
(375) McCullagh, C.; Robertson, J. M. C.; Bahnemann, D. W.; Robertson, P. K. J. *Res. Chem. Intermed.* **2007**, *33*, 359.
(376) Robertson, J. M. C.; Robertson, P. K. J.; Lawton, L. A. *J. Photochem. Photobiol., A* **2005**, *175*, 51.
(377) Jani, P. U.; McCarthy, D. E.; Florence, A. T. *Int. J. Pharm.* **1994**, *105*, 157.
(378) Böckmann, J.; Lahl, H.; Eckhert, T.; Unterhalt, B. *Pharmazie* **2000**, *55*, 140.
(379) Hancock-Chen, T.; Scaiano, J. C. *J. Photochem. Photobiol., B* **2000**, *57*, 193.
(380) Sato, S. *J. Phys. Chem.* **1983**, *87*, 3531.
(381) Dey, G. R. *J. Nat. Gas Chem.* **2007**, *16*, 217.
(382) Hoffmann, M. R.; Martin, S. T.; Choi, W. Y.; Bahnemann, D. W. *Chem. Rev.* **1995**, *95*, 69.
(383) Rehor, I.; Vilimova, V.; Jendelovai, P.; Kubicek, V.; Jirak, D.; Herynek, V.; Kapcalovai, M.; Kotek, J.; Cernyi, J.; Hermann, P.; Lukes, I. *J. Med. Chem.* **2011**, *54*, 5185.
(384) Schilling, K.; Bradford, B.; Castelli, D.; Dufour, E.; Nash, J. F.; Pape, W.; Schulte, S.; Tooley, I.; van den Bosch, J.; Schellauf, F. *Photochem. Photobiol. Sci.* **2010**, *9*, 495.
(385) Baan, R.; Straif, K.; Grosse, Y.; Secretan, W.; El Ghissassi, F.; Cogliano, V.; Agency, W. I. *Lancet Oncol.* **2006**, *7*, 295.
(386) Newman, M. D.; Stotland, M.; Ellis, J. I. *J. Am. Acad. Dermatol.* **2009**, *61*, 685.
(387) Onuma, K.; Sato, Y.; Ogawara, S.; Shirasawa, N.; Kobayashi, M.; Yoshitake, J.; Yoshimura, T.; Iigo, M.; Fujii, J.; Okada, F. *Am. J. Pathol.* **2009**, *175*, 2171.
(388) Schanen, B. C.; Karakoti, A. S.; Seal, S.; Drake, D. R.; Warren, W. L.; Self, W. T. *ACS Nano* **2009**, *3*, 2523.
(389) Jin, C. Y.; Zhu, B. S.; Wang, X. F.; Lu, Q. H. *Chem. Res. Toxicol.* **2008**, *21*, 1871.
(390) Gurr, J. R.; Wang, A. S. S.; Chen, C. H.; Jan, K. Y. *Toxicology* **2005**, *213*, 66.
(391) Chen, E.; Ruvalcaba, M.; Araujo, L.; Chapman, R.; Chin, W. C. *J. Exp. Nanosci.* **2008**, *3*, 171.
(392) Vamanu, C. I.; Cimpan, M. R.; Hol, P. J.; Sornes, S.; Lie, S. A.; Gjerdet, N. R. *Toxicol. in Vitro* **2008**, *22*, 1689.
(393) Horie, M.; Nishio, K.; Fujita, K.; Endoh, S.; Miyauchi, A.; Saito, Y.; Iwahashi, H.; Yamamoto, K.; Murayama, H.; Nakano, H.; Nanashima, N.; Niki, E.; Yoshida, Y. *Chem. Res. Toxicol.* **2009**, *22*, 543.
(394) Fujita, K.; Horie, M.; Kato, H.; Endoh, S.; Suzuki, M.; Nakamura, A.; Miyauchi, A.; Yamamoto, K.; Kinugasa, S.; Nishio, K.; Yoshida, Y.; Iwahashi, H.; Nakanishi, J. *Toxicol. Lett.* **2009**, *191*, 109.
(395) Gou, N.; Onnis-Hayden, A.; Gu, A. Z. *Environ. Sci. Technol.* **2010**, *44*, 5964.
(396) Chen, J. Y.; Zhou, H. J.; Santulli, A. C.; Wong, S. S. *Chem. Res. Toxicol.* **2010**, *23*, 871.
(397) Day, V. W.; Eberspacher, T. A.; Klemperer, W. G.; Park, C. W. *J. Am. Chem. Soc.* **1993**, *115*, 8469.