DOI: 10.1002/ejic.201001100

Modification of Nanocrystalline TiO_2 with Phosphonate- and Bis(phosphonate)-Bearing Macrocyclic Complexes: Sorption and Stability Studies

Ivan Řehoř,[a] Vojtěch Kubíček,*[a] Jan Kotek,[a] Petr Hermann,[a] Jiřina Száková,[b] and Ivan Lukeš[a]

Keywords: Titanium dioxide / Adsorption / Phosphonates / Surface analysis / Nanostructures

The first systematic study of chemical adsorption/desorption of phosphonic acid and geminal bis(phosphonic acid) on/from the surface of anatase nanoparticles is reported. Stable TiO_2 colloidal nanodispersions were used in the study. The colloidal stability is preserved upon nanoparticle modification. A macrocyclic lanthanide(III) complex, attached through a phosphonic/bis(phosphonic) group to the TiO_2 surface allowed precise quantification of sorption parameters by means of inductively coupled plasma atomic emission spectroscopy (ICP-AES). Results show different behavior of phosphonate and bis(phosphonate) groups. For phosphonate, a monomolecular layer formation was observed, and the desorption rate depends on the sorption conditions. It is probably caused by different phosphonate binding modes on the surface. Excess amounts of phosphate in the washing media accelerates the desorption rate of the phosphonate. The bis(phosphonate) is adsorbed on the surface in large quantities forming multilayers that resist desorption even in the presence of phosphate ions and, thus, the bis(phosphonate) moiety is a suitable group for anchoring other molecules on the TiO_2 particle surface.

Introduction

Surface modification of inorganic materials by organic molecules is widely used in many fields of research and industry as it can improve their performance in a wide range of applications. The modification proceeds through noncovalent or covalent interaction of the adsorbate with the surface. The noncovalent surface coatings are based mainly on van der Waals and electrostatic interactions and are typical for coatings of polymers. Grafting of low-molecular-weight molecules is usually carried out through interaction of the inorganic surface with specific chemical group that serves as a chemical anchor. These interactions are mostly based on the formation of covalent bonds between the anchoring group and substrate, and the sorption is called chemisorption in this case. The most typical example of chemisorption is a surface modification of oxidic materials such as SiO_2[1] or SnO_2[2] with organosilanes/organostannanes or metals such as gold[3,4] with thiol-containing molecules.

Phosphonates have been intensively studied as chemical anchors[5] and have been used for the modification of a wide variety of surfaces like iron oxides,[6] zirconium dioxide,[7] aluminum oxide,[7,8] oxides of rare earths,[9] and other oxidic[10,11] and metallic[12] substrates. Presence of more than one phosphonate group in the molecule can further improve sorption properties.[13] The most studied arrangement of two phosphonate groups, geminal bis(phosphonate), is used in clinical practice for the treatment of osteoporosis and other bone diseases[14] due to its extremely stable sorption onto the surface of bone tissue. The interaction of geminal bis(phosphonates) with various inorganic surfaces has also been studied to prepare new materials applicable, for example, as medical implants,[15] drug-delivery systems,[16] or medical-imaging probes.[17,18]

Titanium dioxide is a highly stable, nontoxic, and chemically inert material. Phosphonate affinity towards the TiO_2 surface is high, and the adsorption proceeds under a wide variety of conditions in terms of reaction temperature, solvent, and pH. The grafting of bis(phosphonates) and phosphonates[19] onto the TiO_2 surface has been studied, and the resulting modified materials have been used for numerous applications. Tuning of the hydrophilicity/hydrophobicity of the surface by organophosphonate coating may improve the TiO_2 properties as a chromatographic material[20] or desirably change the properties of the pores in TiO_2 membranes.[21] Titanium alloys are always covered with a thin layer of TiO_2 and, thus, can also be modified with organic layers to inhibit corrosion[22] or improve biocompatibility

---

[a] Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague,
Hlavova 2030, 12840 Prague 2, Czech Republic
Fax: +420-221951253
E-mail: kubicek@natur.cuni.cz
[b] Department of Agroenvironmental Chemistry and Plant Nutrition, Faculty of Agrobiology, Food and Natural Resources, Czech University of Life Sciences Prague,
Kamýcká 129, 16521 Prague, Czech Republic

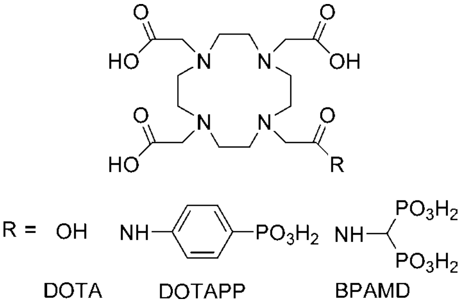
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejic.201001100.

of bone implants.[23,24] TiO_2 particles have been extensively studied for their photochemical properties, and phosphonates were successfully utilized for connecting photosensing dyes to the TiO_2 surface in solar cells.[25] The low toxicity also makes TiO_2 a suitable candidate as an inert inorganic support for functional nanoparticles used in biomedical applications. In addition, the use of photocatalytic TiO_2 as a selective cell killer has been reported.[26,27]

The description of the interaction between a phosphonic acid group and the surface of TiO_2 on a molecular level involves several possible modes of adsorption.[28] Tridentate, bidentate, and monodentate adsorption modes may be present depending on the number of Ti–O–P bonds formed by one phosphonate group. In the case of di- and monodentate adsorption modes, the remaining phosphonate oxygen atom(s) may form hydrogen bond(s) with either surface hydroxy groups or with other phosphonate groups. Interpretation of experimental data and identification of participating binding modes is complicated, and the results reported in the literature may appear contradictory.[21,28–33] Although considerable effort has been devoted to the description of the sorption on a molecular level (i.e., mechanism of absorption and modes of binding), limited attention has been paid to the description of the adsorption from a macroscopic point of view in terms of adsorption capacity,[34] hydrolytic stability (i.e., desorption),[22,25,35–39] and their relation to the reaction conditions used during the sorption process.[33] Whereas the mode of adsorption is important for theoretical studies, the macroscopic behavior of sorbates (in terms of adsorbed amounts and stability of the adsorbed layer against degrading/washing) is of crucial importance for practical applications of such surface-modified materials.

Recently, we have reported several Gd^{III} macrocyclic complexes bearing phosphonate or bis(phosphonate) groups in the side chain. The phosphonate/bis(phosphonate) group was used for anchoring the complexes on the surface of TiO_2 or other inorganic materials for application in magnetic resonance imaging (MRI).[40–42] In the complexes, the metal ion is bound in the macrocyclic cavity, whereas phosphonate groups are not involved in the coordination[43,44] and remain freely available for interaction with other metal ions or the particle surface. So, in contrast to most phosphonate/bis(phosphonate) complexes that have a direct coordination bond between the metal ion and the phosphonate groups, in this case, the metal complex is an "inert" component that does not influence the phosphonate sorption properties.

As the described hybrid systems appeared to have promising properties as contrast agents in MRI, we report here a sorption study of phosphonate/bis(phosphonate) molecules bearing DOTA-like (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) lanthanide(III) complexes (Scheme 1) to bring a better insight into the topic of adsorption and to optimize the preparation of this type of probe. The evaluation of the sorption properties of phosphonate and bis(phosphonate) provides information about relations between adsorption conditions and adsorption capacity. In addition, we thoroughly studied the hydrolytic stability of the adsorbed layer formed with both grafting groups and compared their adsorption properties. To the best of our knowledge, this is the first systematic study of this kind. There is limited information about the mentioned properties in the literature, and available data is mainly related to the surfaces of macroscopic particles, whereas our study was performed on the stable nanocolloids.



Scheme 1. Structures of discussed ligands.

Results

Sample Preparation and Stability

We studied the sorption of macrocyclic complexes bearing a phosphonate (Ln–DOTAPP, further denoted simply as "phosphonate") or geminal bis(phosphonate) [Ln–BPAMD, further denoted as "bis(phosphonate)"] pendant arm on TiO_2. Presence of the strongly chelating macrocyclic part of the molecule insures a stable complexation of the lanthanide(III) ion inside the macrocycle cavity (for the complex structure, see the Supporting Information) and, consequently, enables the opportunity to use microelemental analysis (inductively coupled plasma atomic emission spectroscopy, ICP-AES) for a precise quantification of the lanthanide (Gd or Eu) and titanium contents. The phosphonate/bis(phoshonate) group is not involved in the coordination of the metal ion and remains free for sorption.[40–42] Both macrocyclic complexes exhibit a high stability, and, thus, no decomplexation has been observed under experimental conditions used here for the sorption/desorption study according to the NMR and fluorescence experiments as given in the Supporting Information.

In this work, acid-stabilized colloidal nanoparticles of TiO_2 were used as the substrate, and the adsorption reactions also proceeded under acidic conditions. As the study was focused on the preparation of bioapplicable materials, colloidal stability of the prepared samples at physiological pH is essential. The procedure, involving several dialysis cycles and addition of polyvinylalcohol (PVA), was developed to remove the excess amount of sorbate and to obtain the modified material as a colloid, stable at neutral pH. The procedure led to completely transparent colloidal solutions that had a pH of approximately 6.5 (depending on the CO_2

content). The prepared colloids were stable in aqueous or in the physiological (aq. 0.9% NaCl, pH = 7.4) solutions. As the amount of TiO_2 in the samples decreases during processing, the results are presented as Gd/Ti ratio found by using ICP-AES in the final PVA-stabilized colloidal samples. The dialysis times during processing of the samples were chosen with respect to the membrane permeability towards the sorbate. The concentration of macrocycle outside the membrane (i.e., in the washing solution) reached approximately 90% of the equilibrium value after 12 h; after 24 h, the value was around 97% (for more information, see the Supporting Information).

The procedure of the sample preparation is discussed frequently in this text and, thus, here we will introduce a standard notation for the distinct parts of the preparation process. The adsorption reaction, that is, stirring of TiO_2 with phosphonate/bis(phosphonate), is called "incubation". The following process, including three dialysis steps against acidified water, stabilization with PVA polymer, and three dialysis steps against pure water, is called "processing".

The particle morphology in the TEM and HR-TEM microphotographs (Figure 1) as well as the electron-diffraction pattern remain unchanged during the incubation and processing of the samples, which indicates negligible recrystallization of the bulk oxide particles. This is also supported by the measurement of the light scattering. The results show a narrow particle-size distribution that does not change upon modification with phosphonates (average particle diameter 12 nm, for a plot see the Supporting Information). So, the oxide core of the final nanoparticles obtained after processing did not undergo any change, and interaction with the sorbate occurs mainly on the oxide particle surface. These facts raise the question: What is the reason for the above-mentioned decrease of the Ti content in the samples during the dialysis steps? As the loss of material could not be ascribed to the phosphonate-assisted dissolution/recrystallization of the nanocrystalline core, it may be attributed mainly to the dissolving of an amorphous fraction of the original oxide phase in the presence of the strongly complexing phosphonate/bis(phosphonate) group in the solution. Similarly, we did not observe any difference in adsorbed amounts between samples stored and manipulated in the dark or in daylight or under fluorescent tube light, which indicates negligible photodegradation of the organic matter in the presence of the photoactive anatase phase.

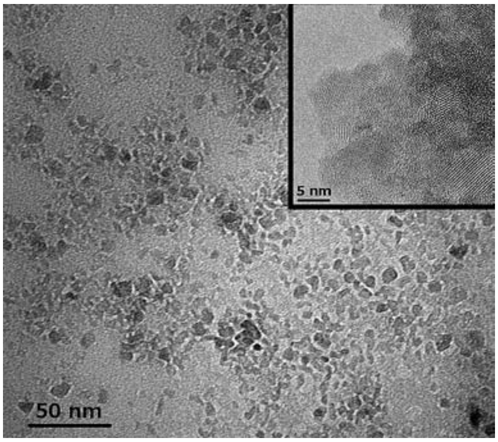


Figure 1. TEM and HR-TEM (inset) microphotography of the studied material after incubation with bis(phosphonate) [1 mL of colloidal solution was treated with Gd–BPAMD (12.4 µmol) at 70 °C; corresponds to the last point of the adsorption capacity estimation plot]. Microphotography was obtained after the first part of processing just before PVA addition as the presence of polymer negatively influences the image quality. The morphology of the sample is identical to the morphology of the starting unmodified TiO_2.

^{31}P NMR spectroscopy can provide information about the binding modes of the phosphonic acid group attached to the oxide surface, and, therefore, diamagnetic La^{III} complexes were prepared. ^{31}P NMR spectra of TiO_2 modified with phosphonate complex in colloidal solution showed one broad signal at $\delta \approx 13$ ppm (Figure S7A in the Supporting Information). The low quality of the spectra is mainly due to an extremely low concentration of phosphorus in the colloidal sample. On the contrary, for bis(phosphonate), two sharp signals at $\delta = 13.2$ and 8.4 ppm were found (Figure S7B in the Supporting Information). IR spectra of Gd complexes of both ligands (freeze-dried material mixed with KBr) are rather complicated, both in the free as well as in the adsorbed forms (Figure S8 in the Supporting Information). This prevented identification of the P–O stretching bands, and, consequently, no information on the type of interaction could be obtained from the spectra.

Adsorption Capacity

A set of experiments was performed to estimate adsorption capacities of the material for phosphonate and bis(phosphonate) molecules. The Gd/Ti ratio found in the final samples after processing was plotted against the initial Gd/Ti ratio used for incubation (Figure 2). The resulting curves exhibit a typical saturation shape. For phosphonate, the curve reaches a plateau of 27 mmol of the complex per 1 mol of TiO_2 (0.337 mmol per 1 g of TiO_2). For bis(phosphonate), the adsorption capacity is significantly higher as the curve reaches a plateau of 115 mmol of the complex per 1 mol of TiO_2 (1.43 mmol per 1 g of TiO_2). Based on the BET measurements, the TiO_2 particles show a surface area of 178 $m^2 g^{-1}$ and negligible porosity. From the obtained Gd/Ti ratios and the TiO_2 specific surface area, the estimated area occupied by one molecule of phosphonate and bis(phosphonate) is around 90 and 20 Å^2, respectively.

Phosphonate/Bis(phosphonate) Coadsorption

Macrocyclic complexes of lanthanide(III) ions show similar physicochemical properties along the whole lanthanide series. Thus, complexes with different metal ions should exhibit the same sorption behavior. This allows a parallel

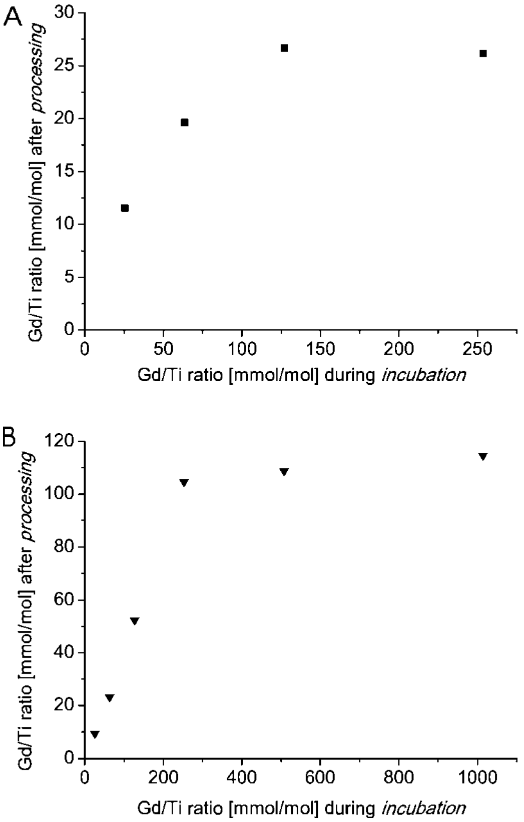


Figure 2. Estimation of the adsorption capacity of (A) phosphonate and (B) bis(phosphonate). The Gd/Ti ratio during incubation (70 °C, pH = 2.5) is on the *x* axis, the ratio found in samples after processing is on the *y* axis.

quantification of two or more complexes, each containing a different lanthanide.

We studied the sorption ability of the Gd–BPAMD [the bis(phosphonate)] and Eu–DOTAPP (the phosphonate) complexes during cosorption from a solution containing an equimolar mixture of the complexes. The Ln/Ti ratios found in the cosorbed samples are summarized in Table 1. The values are compared with those found for the single sorption (estimation of the adsorption capacity experiment above). The amount of adsorbed phosphonate is somewhat decreased due to the presence of bis(phosphonate). But the decrease was significantly lower than that expected for a simple competition of two sorbates on the surface. On the contrary, the adsorbed amount of bis(phosphonate) was not affected much by the presence of phosphonate.

Desorption Experiments

To determine the hydrolytic stability of the materials, they were incubated at various temperatures, and the decrease of the Gd/Ti ratio as a function of the dialysis time (with regular exchange of the dialysis solution) was monitored. Furthermore, as our research is focused on bioapplicable materials, we also studied the desorption in the presence of phosphate anions as they are present in physiological fluids; a phosphate concentration of 1.5 mM and pH = 7.4 as found in human blood plasma were used.[45] The presence of phosphate was expected to accelerate the desorption rate as it may compete with the adsorbed phosphonate or bis(phosphonate) groups. The results of the desorption experiments are shown in Figure 3.

For phosphonate, a significant desorption occurred during washing. The extent of the desorption was lower for the samples incubated at elevated temperature. After three weeks of washing with water, the remaining amount of the sorbate varied from 34% of the adsorbed amount found after the processing (sample incubated at 30 °C) up to 50% (sample incubated at 90 °C). If the dialysis was performed against phosphate buffer the desorption was accelerated (for a direct comparison of washing curves, see the Supporting Information). Surprisingly, the adsorbed complex was not washed out completely, and its amount on the oxide surface converges towards the constant value of around 30 and 15% for the samples incubated at 90 and 30 °C, respectively.

The degree of adsorbed phosphonate varied among the samples even before the washing experiment started: the amount of adsorbed material increased with increasing incubation temperature (Figure 3A and C). This phenomenon could be explained by an enhancement of the absorption capacity with higher incubation temperature or by a hypothesis that the fraction of the sorbate being washed out during the processing is proportional to the incubation temperature. Therefore, the Gd and Ti contents were measured during processing just after the first dialysis step (12 h) for the samples incubated at 30 or 90 °C; the adsorbed amounts were 40 mmol Gd per mol Ti and 37 mmol Gd per mol Ti, respectively. So, the differences in the amounts of bound sorbate found in the samples after the whole washing procedure are due to the different degree of processing desorption, which is dependent on the incubation temperature. The amount of the bound complex during incubation is probably similar at any temperature used.

Table 1. Comparison of the phosphonate/bis(phosphonate) single sorption and cosorption (70 °C, pH = 2.5).

Experiment	Ln/Ti ratio used in incubation [mmol/mol]		Ln/Ti ratio found after processing [mmol/mol]	
	Phosphonate	Bis(phosphonate)	Phosphonate	Bis(phosphonate)
Single sorption	63	–	19.6	–
	–	63	–	23.1
Coadsorption	63	63	14.5	27.0
Single sorption	254	–	26.2	–
	–	254	–	104.5
Coadsorption	254	254	19.5	93.5

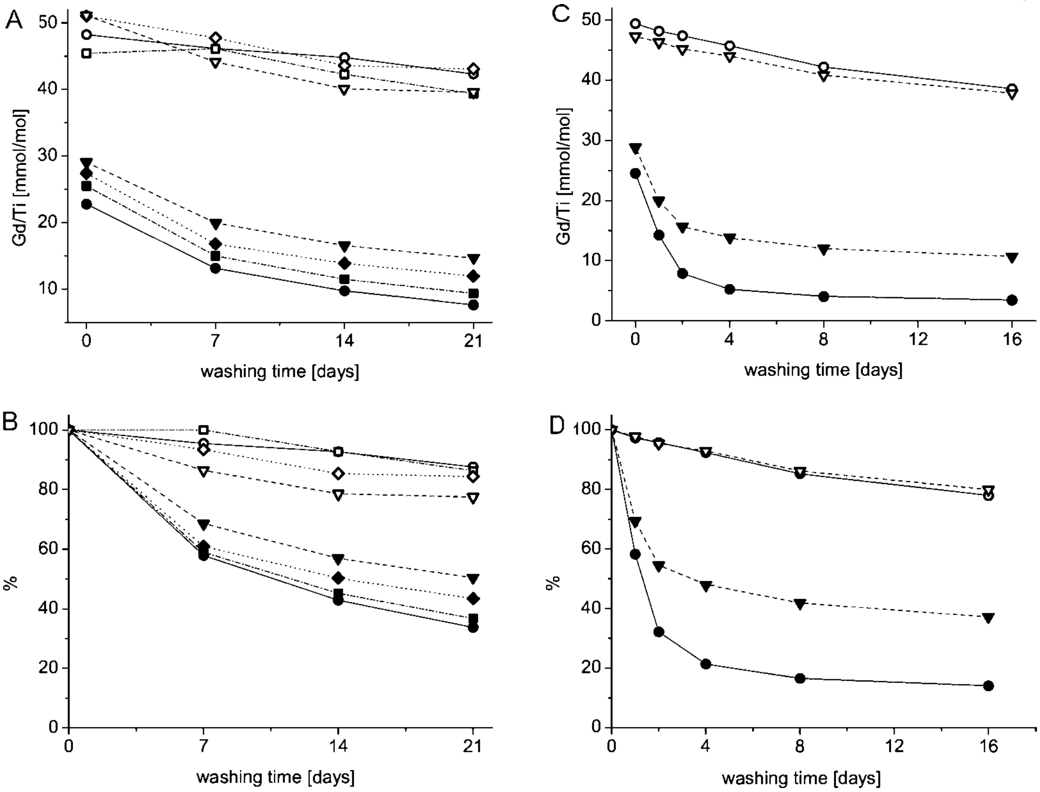


Figure 3. Decrease of the Gd/Ti ratio as a function of dialysis time for the samples containing adsorbed phosphonate (full symbols) and bis(phosphonate) (empty symbols) incubated at 30 °C (circles, solid line), 50 °C (squares, dash-dotted line), 70 °C (diamonds, dotted line), and 90 °C (triangles, dashed line). Dialysis solution: pure water [(A) absolute values; (B) relative values]; phosphate buffer [1.5 mM, pH = 7.4; (C) absolute values, (D) relative values]. The initial point refers to the Gd/Ti ratio in the samples after the processing cycle.

In the case of the bis(phosphonate) system, the desorption was significantly slower. After three weeks of washing, around 80% of bis(phosphonate) remained bound to the oxide surface in each sample. Furthermore, no dependence of the desorption rate on the incubation temperature was observed. Desorption rates were uniform for all bis(phosphonate) samples within statistical significance. The presence of phosphate in the washing solution had a negligible effect on the desorption rate.

Discussion

It is well known that lanthanide(III) complexes of DOTA-like ligands are thermodynamically extremely stable ($\log K_{\mathrm{ML}} > 20$) and, mainly, kinetically inert (no ligand/metal ion exchange is expected even in the presence of an excess amount of other ligands or metal ions).[46–48] For the studied ligands, it has been shown that the lanthanide(III) ion is located inside the macrocyclic cavity binding to four nitrogen atoms of the ring and four carboxylate oxygen atoms, and there is no interaction with phosphonate/bis(phosphonate) moieties in the side arm; the phosphorus(V) groups are freely available for interactions with other ions or substrates.[40,41,43,44] However, the amine and carboxylate groups are involved in the coordination, and, thus, they cannot interact with the sorbent. Nevertheless, the sorption of the carboxylate groups is very weak and could be considered negligible in comparison with phosphonates as it has been shown previously.[32,49] So, complexes of the ligands employed in this study provide a unique opportunity for quantification of the sorption ability of the phosphorus-containing side chains by means of measurement (by ICP) of the concentration of the rare-earth metal atom bound in the macrocyclic cavity.

Adsorption Capacity

Based on the X-ray data, on average, the geometry of the DOTA-like complex was a sphere with a diameter of 8 Å[50] (for the complex structure, see the Supporting Information). Using a simple geometrical model and considering such spheres and the most dense hexagonal packing, leads to a monolayer with an area of 55 Å^2 occupied by one molecule of the complex. By taking into account thermal movement around the phosphonate pendant arm, the experimental value of the surface occupation obtained for phosphonate (ca. 90 Å^2) is in the range expected for the formation of a monomolecular layer. Our previously published results obtained for adsorption of the same phosphonate-containing complex onto a different TiO_2 matrix (Degussa P25) gave the area occupied by one molecule of the complex as approximately 160 Å^2.[40]

The experimental value for the surface occupied by one bis(phosphonate)-containing molecule (20 Å^2) is extremely small for the bulky macrocyclic complex and cannot be realistic considering the monomolecular layer formation. Several layers of the complex are more likely present on the oxide surface; one can speculate that the molecules are connected through Ti^{IV} ions as a cross-linking agent into a 3D coordination polymer. As the core of nanoparticles remains intact during incubation and processing, one can conclude that the Ti^{IV} ions present in the multilayer originate from an amorphous fraction present in the starting material. This is also supported by the saturation shape of the curve (Figure 2B) that excludes a bulk recrystallization of the oxidic material. The multilayer structure could resemble structures of some Ti^{IV} phosphonates reported previously as products of the reaction of TiO_2 with phosphonates under hydrothermal conditions.[51–56] Such a Ti^{IV}–bis(phosphonate) 3D coordination polymer present on the oxide particle surface is more likely stabilized due to extensive cross-linking through Ti^{4+} ions and due to the presence of two tetrahedral phosphonate moieties in one molecule. Each bis(phosphonate) moiety can form a six-membered chelate ring with a single titanium(IV) ion (chelating motif). Independently, each phosphonate group itself can participate in binding to another titanium(IV) ion, thereby resulting in the 3D polymer network in which oxygen atoms can be bound to different metal ions (phosphonate bridge, Ti–O–P–O–Ti motif) or even simply bridge two metal ions (oxygen bridge, Ti–O–Ti motif). All these binding motifs have been observed in metal–phosphonate complexes.[55,57,58] Despite variable conditions being tested (sorption at room temperature, with pre-dialyzed starting material, etc.), an excess amount of bis(phosphonate) always led to multilayer formation. So, one can conclude that the formation of multilayers is a general trend in the bis(phosphonate) sorption.

This hypothesis is also supported by the ^{31}P NMR spectroscopy measurements of the modified colloids. In the case of phosphonate, the spectra show a broad signal at $\delta \approx$ 13 ppm that indicates tridentate phosphonate binding to the surface.[33] In the case of bis(phosphonate), two sharp signals in the ^{31}P NMR spectrum indicate two different environments of the phosphonate groups. In the literature, there are no data correlating chemical shift of the titanium–bis(phosphonates) to a particular sorption mode. So, we can only speculate that one of the signals is related to phosphonate groups directly coordinated to the TiO_2 surface, whereas the other one is related to groups included in the multilayer. Unfortunately, this cannot be supported by IR spectroscopy measurements as both complexes exhibit complicated spectra that prevent identification of the P–O stretching bands.

The formation of the multilayer could also explain the results of cosorption experiments employing phosphonate and bis(phosphonate). The amount of adsorbed bis(phosphonate) remains almost unaffected by the presence of phosphonate, whereas the adsorbed amount of phosphonate is only slightly lowered (by approximately 25%) compared with that from the single-sorption experiment. The sum of the adsorbed bis(phosphonate) and phosphonate molecules exceeds the adsorbed amounts from the single-sorption experiments. This excludes monomolecular-layer formation as it would lead to the competition of both sorbates on the surface.[42] Thus, it is more likely that the phosphonate is efficiently involved in the multilayers formed by bis(phosphonates) during the surface reaction.

Stability of the Sorbent–Sorbate Interaction

The amount of adsorbed complex decreases with an increase in the washing time in all samples, but the absolute amount of the desorbed complexes is significantly lower for bis(phosphonate) than for phosphonate. This could be explained by the higher denticity of the bis(phosphonate), which leads to the formation of more stable structures. The stronger interaction of bis(phosphonates) than that of simple phosphonates is pronounced in many types of interactions, for example, in surface adsorption to other materials[14] or in coordination to metal ions.[59]

The higher stability of the bis(phosphonate) multilayers is also reflected in the phosphate-assisted desorption. The desorption is not affected – even in the presence of a large excess amount of phosphate anions in the washing solutions. This could be explained by the fact that the interaction of bis(phosphonates) with Ti^{4+} ions is several orders of magnitude stronger than that of phosphates.

The lower stability of the phosphonate-containing complex on the oxide surface results in faster desorption that is even accelerated in the presence of competing phosphate anions. The desorption rates of phosphonate are dependent on the incubation temperature; the samples incubated at an elevated temperature exhibit a slower desorption rate. The relationship between incubation temperature and stability of the sorbate on the oxide surface could be explained by the existence of several modes of interaction between the sorbate and sorbent surface that are energetically nonequivalent. This nonequivalency could originate from different hapticity of the sorbate; mono-,[29] di-,[30] and tridentate[21] adsorption modes of phosphonate on the TiO_2 surface have been described in the literature as well as their coexistence in one material.[28] The slow energy-demanding transition between the mentioned binding modes leads to stronger sorbate–sorbent interactions. It could explain the slower desorption of phosphonate incubated at higher temperatures. A similar observation has been reported by Kim et al.[10]

The parallel existence of two or more phosphonate binding modes could also explain the "convergence" of the desorption found for the phosphonate samples dialyzed against phosphate buffer. It is evident that a part of the sorbed complexes is washed out swiftly, but the remaining sorbate resists washing. The remaining amount of sorbed complex is higher for the samples incubated at elevated temperature. This observation is in good agreement with the presumption that slow conversion tends towards stronger binding modes (di/tridentate binding of the phosphonates) and, thus, leads to the higher stability of surface-bound complexes; it is accelerated if the samples are treated at elevated temperature during incubation.

Conclusion

This is the first systematic adsorption and desorption study dealing with the interaction between phosphonate- and/or bis(phosphonate)-containing molecules and the surface of TiO_2. A new methodology for the evaluation of sorption was developed allowing the precise quantification of the adsorbed amount. Titanium dioxide nanocolloids were treated with in-cage complexes of phosphonate- and/or bis(phosphonate)-modified macrocyclic ligands to study the relationship between the reaction conditions during absorption to the oxide matrix, post-reaction treatment of the materials, the resulting abundance of complex on the surface, and the stability of the modified materials against desorption. After stabilization with polyvinylalcohol, the obtained colloids were stable in water at neutral pH and in physiological solution. ICP-AES is a convenient method for quantification of the sorption/desorption of the lanthanide(III) macrocyclic complexes. For the phosphonate-containing complex, monomolecular layer formation was confirmed. The results indicate formation of Ti–O–P bonds. The bis(phosphonate)-containing complex shows a significantly higher stability and formation of a 3D coordination polymer on the TiO_2 surface. The desorption rate of the complex with a phosphonate side arm is dependent on the conditions used during the preparation of the samples as more phosphonate binding modes are possible; the more stable ones are formed to a greater extent at elevated temperatures. Bis(phosphonate) is a better anchoring group than phosphonate for modification of the TiO_2 surface as bis(phoshonate) interacts significantly stronger with Ti^{4+} ions. The different TiO_2 coating that is obtained with phosphonates and with bis(phosphonates) assigns the two anchoring groups for different applications. The hydrolytically stable bis(phosphonate) coating could be used for applications requiring stable materials (implants, imaging probes, etc.). In contrast, phosphonate coatings, which undergo faster hydrolysis, can be extremely useful for drug delivery and release systems. Furthermore, both types of anchors can be combined in advanced materials with multimodal functions.

In general, our study is an important step to a better understanding of the interaction between phosphonic acids and TiO_2 on a macroscopic level as well as the stability of the sorbed phosphorus-containing molecules on the oxide surface. It should help in the design of new molecules for the stable oxide modification and for the inorganic–organic hybrid material synthesis. Furthermore, the outcome of the study can serve as preparation of coated materials with tunable hydrolytical stability.

Experimental Section

Materials: Ligands DOTAPP and BPAMD and their complexes were prepared according to published procedures.[40,41] Nanocrystalline anatase (average particle diameter 12 nm) was used as the sorbent.[60] The material was used in the form of a stable transparent colloidal solution (pH ≈ 2.5, TiO_2 concentration 1.8 g L^{-1} according to ICP-AES). The surface area of TiO_2 was 178 m^2 g^{-1} (estimated by BET); a decrease of the surface area was observed upon heating of dry material at high temperature (300–400 °C). Polyvinylalcohol (M_r = 80 kDa, 86–89 % hydr., Wacker) was used for colloid stabilization. Standard-grade chemicals and deionized water were used for adsorption and desorption experiments; for the preparation of the ICP samples, high-purity grade sulfuric acid, nitric acid, hydrogen peroxide, and reverse-osmosis purified water were used.

Dialysis: An Ultrapor membrane with 6–8 kDa cutoff was used for dialysis. The ratio between volumes inside the membrane and the washing media was 1:250 for all experiments. One dialysis step was performed at room temperature for 12 or 24 h as noted for the particular experiments. During the dialysis, the washing solution was stirred.

ICP-AES: The concentrations/amounts of Gd and Ti were determined with an ICP-AES spectrometer VistaPro (Varian) in axial plasma configuration, equipped with an autosampler SPS-5, an inert parallel flow nebulizer, an inert spray chamber and a demountable torch with an inert injector tube. The samples (200 µL) were digested in concentrated H_2SO_4 (300 µL) and concentrated H_2O_2 (100 µL) at 170 °C for 24 h. For the measurements, the solutions were diluted with 1 % HNO_3 to a volume of 10 mL. All ratios of Ln/Ti in the text are molar ratios.

TEM and HR-TEM: The morphology and size of the particles were investigated by means of TEM (TecnaiG2 SpiritTwin 12; 120 kV) and HRTEM (Jeol JEM 3010; 300 kV). To prepare the samples, a drop of diluted colloidal solution was placed on a carbon-coated copper grid (SPI 3630C-MB) and was left to dry freely.

NMR Spectroscopy: ^{31}P (161.9 MHz) NMR spectra of the colloidal samples were recorded with a Varian Unity Inova-400 spectrometer at 25 °C, using 5 mm sample tubes. 1 % H_3PO_4 in D_2O was used as an external reference.

IR Spectroscopy: Infrared spectra were recorded with a Thermo Nicolet 6700 FTIR spectrometer by using the DRIFTS (diffuse reflectance infrared Fourier transform spectroscopy) method with a Pike Technologies EasiDiff accessory (128 scans, 4 cm^{-1} resolution, 4000–400 cm^{-1} range, Happ-Genzel apodization). Freeze-dried samples were mixed and grinded with KBr (ratio approximately 1:50) in an agate mortar.

Dynamic Light Scattering: The light scattering setup (ALV, Langen, Germany) consisted of a 633 nm He/Ne laser, an ALV CGS/8F goniometer, an ALV High QE APD detector, and an ALV 5000/EPP multibit, multitau autocorrelator.

Adsorption Capacity Estimation: An appropriate amount of Gd–DOTAPP (0.32–3.2 µmol) or Gd–BPAMD (0.32–12.8 µmol) in solution (75 mM, pH = 2.5) was mixed with the TiO_2 colloidal solution (1 mL). The reaction mixture was stirred at 70 °C for 3 d. The reaction mixture was dialyzed three times against HCl solution (250 mL, pH = 2.5) for 12 h to remove excess sorbate. Then, PVA solution (0.33 mL, 50 mg PVA per mL) was added, and mixture was stirred in the vial for 12 h. Then, the reaction mixture was dialyzed three times against pure water (250 mL) for 12 h. The resulting pH was around 6.5.

Desorption Experiments: Gd–DOTAPP (3.2 µmol) or Gd–BPAMD (3.2 µmol) in solution (75 mM, pH = 2.5) was mixed with TiO_2 colloidal solution (2 mL). The reaction mixture was stirred at a given temperature (30, 50, 70, or 90 °C) for 3 d. The reaction mixture was dialyzed three times against HCl solution (500 mL, pH = 2.5) for 12 h to remove excess amounts of the sorbate. Then, PVA solution (0.66 mL, 50 mg PVA per mL) was added, and the mixture was stirred in a vial for 12 h. Consequently, the reaction mixture was dialyzed three times against pure water (500 mL) for 12 h. The resulting pH was around 6.5. The resulting colloids were further dialyzed against water or phosphate buffer (1.5 mM, pH = 7.4) at room temperature. The washing solution was exchanged every 24 h. The amount of Gd and Ti in regularly collected samples was determined by ICP.

Coadsorption Experiments: Eu–DOTAPP (0.80 or 3.2 µmol) and Gd–BPAMD (0.80 or 3.2 µmol) solutions (75 mM, pH = 2.5) were mixed with TiO_2 colloidal solution (1 mL). The reaction mixture was stirred at 70 °C for 3 d. The reaction mixture was dialyzed three times against HCl solution (250 mL, pH 2.5) for 12 h to remove excess sorbates. Then PVA solution (0.33 mL, 50 mg PVA per mL) was added, and the mixture was stirred in the vial for 12 h. Then, the reaction mixture was dialyzed three times against pure water (250 mL) for 12 h. The resulting pH was around 6.5.

Supporting Information (see footnote on the first page of this article): Details on the test of membrane permeability, complex stability under acidic and incubation conditions, direct comparison of desorption, visualization of Gd–BPAMD, and ^{31}P NMR and IR spectra of the studied materials.

Acknowledgments

We thank our co-workers from the Heyrovsky Institute of Physical Chemistry (Prague, Czech Republic), Jaromír Jirkovský and Michal Kolář, for providing us with the TiO_2 nanoparticles. Support from the Academy of Science of the Czech Republic (no. KAN201110651) from the Ministry of Education of the Czech Republic (MSM0021620857, MSM6046070901, and SVV261206/2010) and from the Grant Agency of the Czech Republic (no. P207/11/1437) is acknowledged. This work was also supported by the Grant Agency of the Charles University (no. 70208). V. K. thanks RP MSMT 14/63 for support. This work was carried out within the framework of COST D38 (MSMT OC179) and COST CM802 (PhoSciNet) Actions.

---

[1] C. Haensch, S. Hoeppener, U. S. Schubert, *Chem. Soc. Rev.* **2010**, *39*, 2323–2334.
[2] M. Batzill, U. Diebold, *Prog. Surf. Sci.* **2005**, *79*, 47–154.
[3] P. Maksymovych, O. Voznyy, D. B. Dougherty, D. C. Sorescu, J. T. Yates Jr., *Prog. Surf. Sci.* **2010**, *85*, 206–240.
[4] M.-A. Neouze, U. Schubert, *Monatsh. Chem.* **2008**, *139*, 183–195.
[5] P. G. Mingalyov, G. V. Lisichkin, *Russ. Chem. Rev.* **2006**, *75*, 541–547.
[6] C. Yee, G. Kataby, A. Ulman, T. Prozorov, H. White, A. King, M. Rafailovich, J. Sokolov, A. Gedanken, *Langmuir* **1999**, *15*, 7111–7115.
[7] W. Gao, L. Dickinson, C. Grozinger, F. G. Morin, L. Reven, *Langmuir* **1996**, *12*, 6429–6435.
[8] B. Adolphi, E. Jahne, G. Busch, *Anal. Bioanal. Chem.* **2004**, *379*, 646–652.
[9] C. A. Traina, T. J. Dennes, J. Schwartz, *Bioconjugate Chem.* **2009**, *20*, 437–439.
[10] C. S. Kim, R. J. Lad, C. P. Tripp, *Sens. Actuators B* **2001**, *76*, 442–448.
[11] G. P. Holland, R. J. Sharma, O. Agola, S. Amin, V. C. Solomon, P. Singh, D. A. Buttry, J. L. Yarger, *Chem. Mater.* **2007**, *19*, 2519–2526.
[12] X. Marguerettaz, D. Fitzmaurice, *Langmuir* **1997**, *13*, 6769–6779.
[13] D. Portet, B. Denizot, E. Rump, J.-J. Lejeune, P. Jallet, *J. Colloid Interf. Sci.* **2001**, *238*, 37–42.
[14] H. Fleisch, *Bisphosphonates in Bone Disease*, 4th ed., Academic Press London, **2000**.
[15] I. Fishbein, I. S. Alferiev, O. Nyanguile, R. Gaster, J. M. Vohs, G. S. Wong, H. Felderman, I.-W. Chen, H. Choi, R. L. Vilensky, R. J. Levy, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 159–164.
[16] F. Benyettou, Y. Lalatonne, O. Sainte-Catherine, M. Monteil, L. Motte, *Int. J. Pharm.* **2009**, *379*, 324–327.
[17] Y. Lalatonne, C. Paris, J. M. Serfaty, P. Weinmann, M. Lecouvey, L. Motte, *Chem. Commun.* **2008**, 2553–2555.
[18] V. Kubíček, I. Lukeš, *Future Med. Chem.* **2010**, *2*, 521–531.
[19] A. Vioux, J. Le Bideau, P. H. Mutin, D. Leclerq, *Top. Curr. Chem.* **2004**, *232*, 145–174.
[20] D. H. Taffa, M. Kathiresan, L. Walder, *Langmuir* **2009**, *25*, 5371–5379.
[21] J. Randon, P. Blanc, T. Paterson, *J. Membr. Sci.* **1995**, *98*, 119–129.
[22] E. Jaehne, S. Oberoi, H.-J. P. Adler, *Prog. Org. Coat.* **2008**, *61*, 211–223.
[23] J. Schwartz, M. J. Avaltroni, M. P. Danahy, B. M. Silverman, E. L. Hanson, J. E. Schwarzbauer, K. S. Midwood, E. S. Gawalt, *Mater. Sci. Eng. C* **2003**, *23*, 395–400.
[24] J. Beuvelot, D. Portet, G. Lecollinet, M.-F. Moreau, M. F. Basle, *J. Biomed. Mater. Res. B* **2009**, *90B*, 873–881.
[25] E. Bae, W. Choi, J. Park, H. S. Shin, S. B. Kim, J. S. Lee, *J. Phys. Chem. B* **2004**, *108*, 14093–14101.
[26] N. Huang, M. Xu, C. Juan, R. Yu, *J. Photochem. Photobiol. A: Chem.* **1997**, *108*, 229–233.
[27] F. M. Salih, *J. Appl. Microbiol.* **2002**, *92*, 920–926.
[28] F. Brodard-Severac, G. Guerrero, J. Maquet, P. Florian, C. Gervais, P. H. Mutin, *Chem. Mater.* **2008**, *20*, 5191–5196.
[29] P. Raghunath, M. C. Lin, *J. Phys. Chem. C* **2009**, *113*, 8394–8406.
[30] S. Pawsey, M. McCormick, S. De Paul, R. Graf, Y. S. Lee, L. Reven, H. W. Spiess, *J. Am. Chem. Soc.* **2003**, *125*, 4174–4184.
[31] R. Luschtinetz, J. Frenzel, T. Milek, G. Seifert, *J. Phys. Chem. C* **2009**, *113*, 5730–5740.
[32] E.-O. Ganbold, Y. Lee, K. Lee, O. Kwon, S.-W. Joo, *Chem. Asian J.* **2010**, *5*, 852–858.
[33] G. Guerrero, P. H. Mutin, A. Vioux, *Chem. Mater.* **2001**, *13*, 4367–4373.
[34] C. Viornery, *Surface Functionalisation of Titanium with Phosphonated Ligands to Improve Bone Bonding*, PhD Thesis, Ecole Polytechnique Federale de Lausanne, Laussane, Switzerland, **2000**.
[35] J. J. Shephard, S. A. Dickie, A. J. McQuillan, *Langmuir* **2010**, *26*, 4048–4056.
[36] S. Marcinko, A. Y. Fadeev, *Langmuir* **2004**, *20*, 2270–2273.
[37] E. S. Gawalt, M. J. Avaltroni, N. Koch, J. Schwartz, *Langmuir* **2001**, *17*, 5736–5738.
[38] M. P. Danahy, M. J. Avaltroni, K. S. Midwood, J. E. Schwarzbauer, J. Schwartz, *Langmuir* **2004**, *20*, 5333–5337.
[39] C. R. Kaufmann, G. Mani, D. Marton, D. M. Johnson, C. M. Agrawal, *Biomed. Mater.* **2010**, *5*, 025008.
[40] I. Řehoř, V. Kubíček, J. Kotek, P. Hermann, I. Lukeš, J. Száková, L. Vander Elst, R. N. Muller, J. A. Peters, *J. Mater. Chem.* **2009**, *19*, 1494–1500.
[41] V. Kubíček, J. Rudovský, J. Kotek, P. Hermann, L. Vander Elst, R. N. Muller, Z. I. Kolar, H. T. Wolterbeek, J. A. Peters, I. Lukeš, *J. Am. Chem. Soc.* **2005**, *127*, 16477–16485.
[42] T. Vitha, V. Kubíček, P. Hermann, Z. I. Kolar, H. T. Wolterbeek, J. A. Peters, I. Lukeš, *Langmuir* **2008**, *24*, 1952–1958.
[43] T. Vitha, V. Kubíček, P. Hermann, L. Vander Elst, R. N. Muller, Z. I. Kolar, H. T. Wolterbeek, W. A. P. Breeman, I. Lukeš, J. A. Peters, *J. Med. Chem.* **2008**, *51*, 677–683.

[44] T. Vitha, V. Kubíček, J. Kotek, P. Hermann, L. Vander Elst, R. N. Muller, I. Lukeš, J. A. Peters, *Dalton Trans.* **2009**, 3201–3214.
[45] G. J. Kemp, A. Btumsohn, B. W. Morris, *Clin. Chem.* **1992**, *38*, 400–402.
[46] P. Hermann, J. Kotek, V. Kubíček, I. Lukeš, *Dalton Trans.* **2008**, 3027–3047.
[47] E. Brücher, *Top. Curr. Chem.* **2002**, *221*, 103–122.
[48] R. Delgado, V. Félix, L. M. P. Lima, D. W. Price, *Dalton Trans.* **2007**, 2734–2745.
[49] S. Pawsey, K. Yach, L. Reven, *Langmuir* **2002**, *18*, 5205–5212.
[50] F. Benetollo, G. Bombieri, L. Calabi, S. Aime, M. Botta, *Inorg. Chem.* **2003**, *42*, 148–157.
[51] C. Ninclaus, C. Serre, D. Riou, G. Ferey, *R. Acad. Sci., Ser. IIc: Chim.* **1998**, *1*, 551–556.
[52] C. Serre, G. Ferey, *Inorg. Chem.* **1999**, *38*, 5370–5373.
[53] X.-J. Zhang, T.-Y. Ma, Z.-Y. Yuan, *Eur. J. Inorg. Chem.* **2008**, 2721–2726.
[54] X.-J. Zhang, T.-Y. Ma, Z.-Y. Yuan, *J. Mater. Chem.* **2008**, *18*, 2003–2010.
[55] E. Matczak-Jon, V. Videnova-Adrabinska, *Coord. Chem. Rev.* **2005**, *249*, 2458–2488.
[56] T.-Y. Ma, X.-Z. Lin, Z.-Y. Yuan, *Chem. Eur. J.* **2010**, *16*, 8487–8494.
[57] G. K. H. Shimizu, R. Vaidhyanathan, J. M. Taylor, *Chem. Soc. Rev.* **2009**, *38*, 1430–1449.
[58] A. Clearfield, *Curr. Opin. Solid State Mater. Sci.* **2002**, *6*, 495–506.
[59] NIST Standard Reference Database 46 (Critically Selected Stability Constants of Metal Complexes), Version 8.0, **2004**.
[60] M. Kolář, H. Měšťánková, J. Jirkovský, M. Heyrovský, J. Šubrt, *Langmuir* **2006**, *22*, 598–604.

Received: October 15, 2010