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Peptide Interactions with Metal and Oxide Surfaces

ANNE VALLEE, VINCENT HUMBLOT, AND
CLAIRE-MARIE PRADIER*

Laboratoire de Réactivité de Surface, UMR CNRS 7197, Université Pierre et Marie Curie Paris 6, 4 place Jussieu, Case 178, 75252 Paris Cedex 05, France

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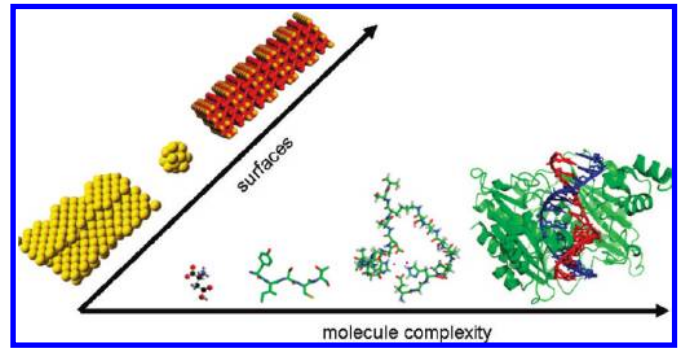
CONSPECTUS

Increasing interest in bio-interfaces for medical, diagnostic, or biotechnology applications has highlighted the critical scientific challenge behind both the understanding and control of protein−solid surface interactions. In this context, this Account focuses on the molecular-level characterization of the interactions of peptides, ranging in size from a few amino acids to long sequences, with metal and oxide surfaces. In this Account, we attempt to fill the gap between the well-known basic studies of the interaction of a single amino acid with well-defined metal surfaces and the investigations aimed at controlling biocompatibility or biofilm growth processes. We gather studies performed with surface science tools and macroscopic characterization techniques along with those that use modeling methods, and note the trends that emerge. Sulfur drives the interaction of cysteine-containing peptides with metal surfaces, particularly gold. Moreover, intermolecular interactions, such as hydrogen bonds may induce surface self assembly and chiral arrangements of the peptide layer. Depending on the solvent pH and composition, carboxylates or amino groups may also interact with the surface, which could involve conformational changes in the adsorbed peptide.



On oxide surfaces such as titania or silica, researchers have identified carboxylate groups as the preferential peptide binding groups because of their strong electrostatic interactions with the charged surface. In high molecular weight peptides, systematic studies of their interaction with various oxide surfaces point to the preferential interaction of certain peptide sequences: basic residues such as arginine assume a special role. Researchers have successfully used these observations to synthesize adhesive sequences and initiate biomineralization. Studies of the interaction of peptides with nanoparticles have revealed similar binding trends. Sulfur-containing peptides adhere preferentially to gold nanoparticles. Peptides containing aromatic nitrogen also display a high affinity for various inorganic nanoparticles.

Finally, we describe a novel class of peptides, genetically engineered peptides for inorganics (GEPIs), which are selected from a phage display protocol for their high binding affinity for inorganic surfaces. Extended investigations have focused on the mechanisms of the molecular binding of these peptides to solid surfaces, in particular the high binding affinity of some sulfur-free sequences of GEPIs to gold or platinum surfaces. We expect that this clearer view of the possible preferential interactions between peptides and inorganic surfaces will facilitate the development of new, more focused research in various fields of biotechnology, such as biocompatibility, biomimetics, or tissue engineering.

Introduction

A biomimetic approach based on the immobilization of peptides is often applied to optimize the properties of implant surfaces or to elaborate biosensing devices on inorganic materials, for instance. Peptides are the already complex building blocks of proteins and thus are relevant partners when studying the factors governing biocompatibility or biofilm growth on solid surfaces. The interaction of proteins or peptides with oxide solid surfaces is still not fully

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understood, especially at a molecular level.[1] One reason for that is the high mass and ternary/secondary structure complexity of biomolecules. To unravel some bases of the chemistry that governs protein/metal or protein/oxide interactions, attention was paid, in this Account, to the interactions of synthetic or natural small peptides with rather well-defined surfaces, like gold, silica, or titania. Di- or tripeptides, and in some cases higher mass oligopeptides, gave rise to the most fundamental studies; these rather small biomolecules are exciting because they bear well-identified and easily quantifiable chemical functions and also peptide bonds, like real proteins; for larger peptides, the influence of the amino acid sequence and of the conformation may be significant like in natural proteins.

In this research area, one may distinguish two types of investigations, those involving di- or tripeptides, ending with a description of the peptide−metal or peptide−oxide interaction at a molecular scale, and those considering fragments of proteins, sufficiently big to mimic proteins with their conformation and possible denaturation upon adsorption. In the latter case, interactions between peptides and solid surfaces is most often investigated by nonlocal spectroscopies; special attention is paid to the peptide composition or sequence that appears to have a determining role in the adsorption process.

The goal of such an Account is to contribute to fill the gap between the numerous studies of amino acid adsorption[2,3] and the questions addressed by the direct interaction of proteins and cells with inorganic materials.[4,5] We will not consider the grafting of peptides via cross-linking agents, self-assembled monolayers, or polymers.

This Account gathers and discusses the results of some recent investigations of the interaction of small or larger peptides with some common metals and oxides; some clear tendencies arise from this ensemble of studies, which will help to better understand and foresee the type of interactions that may be reasonably expected in various biointerfacial systems. The still open questions are the existence and strength of the interaction as well as the nature of the chemical groups preferentially interacting with such and such surface and, of course, the degree of denaturation or destructuration of a peptide when interacting with a surface.

This Account will be divided into two main sections. One deals with small peptides, consisting of two or three amino acids and mostly studied by applying surface science techniques, as well as by modeling methods. Some data deduced from amino acid adsorption studies will be recalled to help understand the behavior of peptides. The second one will report on the interaction of high mass peptides with solid surfaces. Relevant information was most often obtained thanks to a macroscopic characterization of the surfaces after interaction with the peptides or by statistical analysis of the most often encountered peptide sequences on the solid surfaces.

Adsorption of Small Peptides (Di- or Tripeptides)

This section deals with the adsorption of small peptides on metal surfaces. In the past 15 years, adsorption of amino acids, which are the building blocks of peptides, on metal surfaces has given rise to a number of successful studies that shed light on the various modes of adsorption, their 2D surface organization, and the most favorable points of interactions with a surface. They are the starting point toward the comprehensive description of peptide−surface interaction. After the pioneer works of Raval[2] and Liedberg's team,[6] we made clear that the way histidine, an amino acid bearing an aromatic imidazole ring, interacts with a surface is substrate-specific. On gold, the molecule forms strong bonds via the carboxylate group, whereas on copper two interaction points were evident, COO^- and the ring NH_2 group, inducing a novel geometry of the adsorbed molecule.[7] The role of oxygen on the surface may also dramatically change the mode of interaction. This was observed for histidine, as well as for lysine, whose interactions were investigated on metallic and on partially oxidized copper.[8,9] The conditions of interaction, gas or liquid phase, for instance, will also have a significant influence; this was demonstrated for cysteine and lysine on Cu(110).[8,10] These few examples stress the importance of considering the nature of the substrate, metal or oxide in particular, as well as the conditions of adsorption when investigating the interaction of biomolecules with solid surfaces.

The first studies involving slightly more complex molecules than amino acids dealt with homopeptide adsorption on copper surfaces. The scanning tunneling microscopy (STM) characterization under vacuum of dialanine on Cu(110) has highlighted the formation of chain-like structures with intermolecular connections between carboxylic acid and amine, with a temperature-dependent organization in islands.[11] Moreover, the racemic mixture deposition of diphenylalanine in the gas phase has shown homochiral chain formation (Figure 1).[12] This result may be correlated to the observation of chiral domains made of a regular arrangement of chains upon adsorption of lysine on Cu(110).[13,14]

An infrared study of the tri(L-alanine) and tri(L-leucine) adsorbed in gas phase on Cu(110)[15] suggested that the two peptides are adsorbed intact, in their anionic form, via the terminal carboxylic ions (COO^-), the amino groups, and the C=O

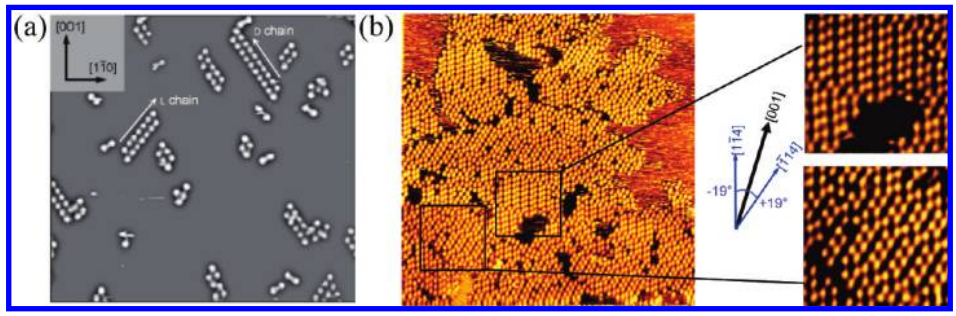

FIGURE 1. (a) STM image (36 × 34 nm^2) of coadsorbed L-Phe-L-Phe and D-Phe-D-Phe, under low pressure, on Cu(110) at 300 K. The arrows indicate the growth direction of the homochiral chains (adapted with permission from ref 12, copyright 2007 Wiley). (b) STM image (350 × 350 Å^2; insets 110 × 110 Å^2) of the low-coverage phase of L-lysine adsorbed on Cu(110) at 300 K showing pairs of lysine molecules growing in two directions (reproduced with permission from ref 13, copyright 2007 Elsevier).

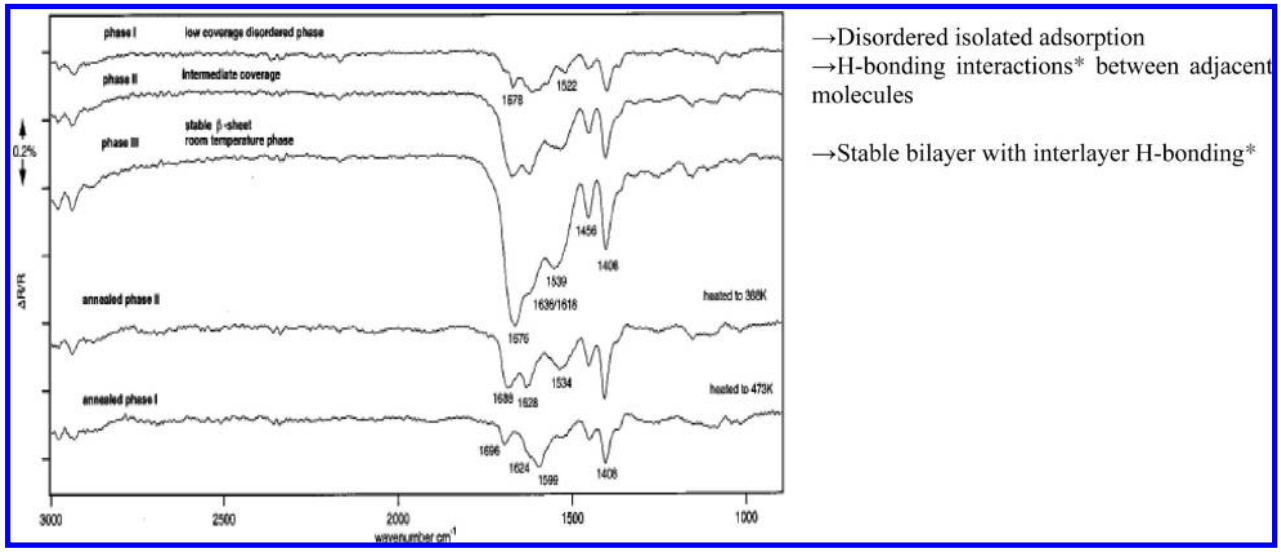

FIGURE 2. RAIRS spectra of tri(L-alanine) deposited on Cu(110) at 300 K. Reproduced with permission from ref 15. Copyright 2001 American Chemical Society.

functionality of the amide groups. Three adsorption phases, corresponding to different reflection absorption infrared spectroscopy (RAIRS) spectra, have been identified for tri(L-alanine) at high flux and room temperature. Intermolecular hydrogen bonds have an important role in the formation of phase II and III adsorbed layers (Figure 2).

Tri(L-leucine) adsorbs in the same way as the tri(L-alanine) at low coverage but does not form double layers. The longer side chains of the tri(L-leucine) could cause a steric inhibition to the growth of bilayers.

Following these studies involving homopeptides, we started investigating the adsorption of more complex peptides, constituted of various amino acid fragments. As an immediate consequence, the reactive groups have multiple possible surroundings that may influence the conformation and orientation of the adsorbed peptides.

Two tripeptides, the peptide of the insulin-like growth factor (IGF(1−3), Gly-Pro-Glu) and gluthatione (GSH, Glu-Cys-Gly), mainly differing by their central fragment, as well as one dipeptide, Gly-Pro, consisting of two of the three amino acids of IGF, were adsorbed on Au(110) and Au(111) surfaces under ultrahigh vacuum (UHV) conditions.[16−18]

Adsorption kinetics, as well as the chemical and structural characterization of the adlayers, were obtained by combining *in situ* polarization modulation-reflection absorption infrared spectroscopy (PM-RAIRS) and low-temperature (100 K) X-ray photoelectron spectroscopy (LT-XPS) techniques. Low-energy electron diffraction (LEED) and scanning tunneling microscopy (STM) observations are also reported. The main results are the following: under low pressure, GSH, IGF, and Gly-Pro molecules adsorb intact on Au(110) and Au(111) in two different ionic forms, the zwitterionic one, $COOH/NH_3^+/COO^-$, and the neutral one, $COOH/NH_2/COOH$ (COO^-/NH_3^+ and $COOH/NH_2$ for Gly-Pro). GSH adsorbs via the S atom of the cysteine fragment; however, even at very low coverage (after 5 min of exposure at $P = 1 \times 10^{-9}$ Torr), XPS data show the coexistence of unbound and Au-bound sulfur. Moreover, when the gold samples are warmed from 100 K to room tem-

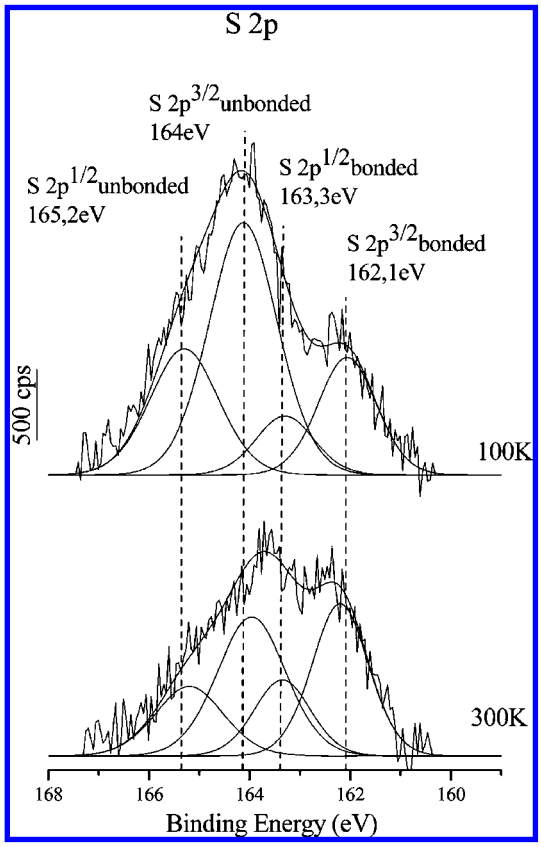

FIGURE 3. S 2p XPS high-resolution spectra recorded after adsorption of GSH for the high coverage on Au(111) (adapted with permission from ref 16, copyright 2008 Elsevier).

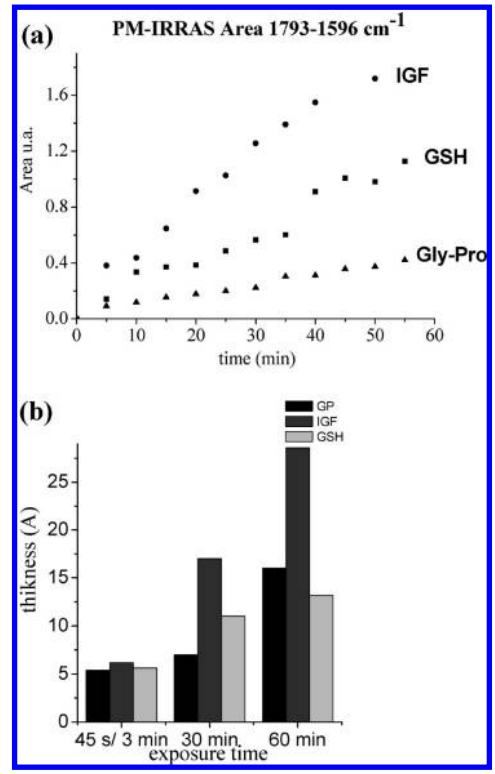

FIGURE 4. (a) Evolution of the PM-RAIRS area in the 1793−1596 cm^{-1} region of GSH, IGF, and Gly-Pro on Au(110) under exposure. (b) Evolution of the GSH, IGF, and Gly-Pro thickness, calculated from the XPS data at various exposure times. Reproduced with permission from ref 18. Copyright 2009 American Chemical Society.

perature under vacuum, XPS shows the desorption of part of the molecules that were not bound to the surface via their S atoms[16] (Figure 3).

Moreover, GSH and IGF layers grow in different ways. At very low exposure, GSH molecules adsorb via the S atoms; when the exposure increases, the contributions from unbound sulfur suggest the formation of dimers or small GSH clusters on the surface. Conversely, IGF and Gly-Pro, having no thiol group, interact strongly with the gold surface leading to an organized 2D structure as witnessed by LEED patterns at very low coverage. Further on, charge effects, observed on the IGF and Gly-Pro XPS spectra, indicate the formation of 3D aggregates. In the case of IGF, an additional differential charge effect is observed, highlighting the formation of heterogeneous layers, likely made of aggregates of various sizes on the surface. Note eventually that the average thickness of the IGF layer increases much faster than that of GSH for identical exposures (Figure 4).

Small di- and tripeptides, all containing a cysteine fragment, have also been adsorbed on gold surfaces from liquid phase[19] and characterized by XPS and RAIRS. The Arg-Cys peptide adsorbs intact in its zwitterionic form via the sulfur atom. A large set of studies has then been focused on the adsorption of GSH[17,20−22] because it is the most abundant nonprotein thiol in mammalian cells and has a central role in metabolic pathways.[23] GSH is also adsorbed on gold via the thiol group of the cysteine. Moreover, the PM-RAIRS and XPS spectra highlight different ionic forms of GSH when adsorbed from solutions at various pH.[16]

From DFT calculations,[20] the molecule geometry depends on its charge, and from XPS data recorded after adsorption under liquid phase, charges and orientations of the molecules are retained upon adsorption on gold.[16]

A protonation−deprotonation process, accompanied by a reorientation of the molecules, is observed when an ethanol solution, containing or lacking hydrochloric acid, is passed over the substrate. The transition from one ionic form to another is identified by changes in the ATR spectra (Figure 5). It takes place in two stages, a rapid deprotonation of the carboxylic group of glutamic acid moiety followed by a slow deprotonation of the carboxylic group of the glycine moiety, assisted by the adsorption of carboxylate groups on the surface. During protonation−deprotonation, a rearrangement of the hydrogen-bonding network (inter- and intramolecular) takes place[20] (see Figure 6).

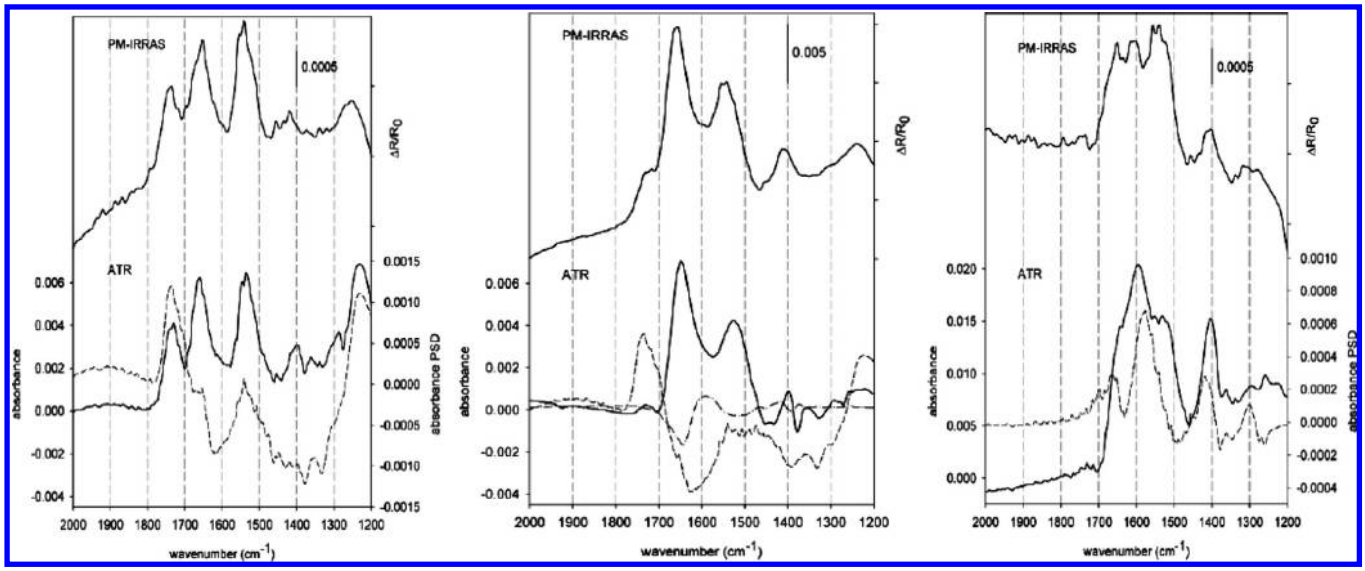

FIGURE 5. IR spectra of the GSH adsorbed on gold from solution at different pH values: (a) cationic, (b) zwitterionic, and (c) anionic forms. Adapted with permission from ref 20. Copyright 2005 American Chemical Society.

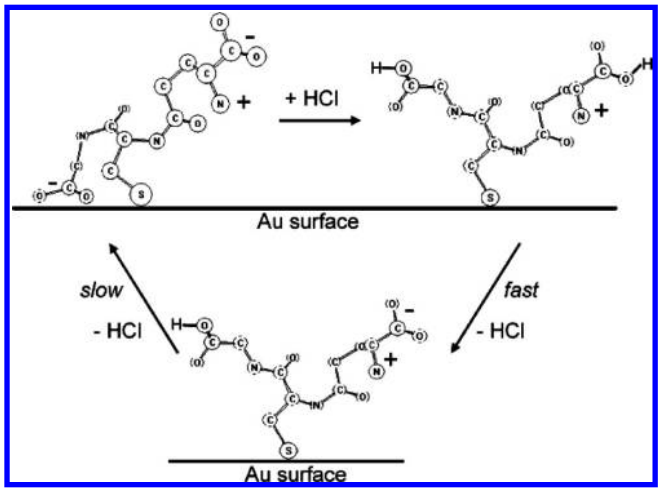

FIGURE 6. Pictorial representation of the processes occurring during protonation/deprotonation of L-glutathione on gold. Reproduced with permission from ref 20. Copyright 2005 American Chemical Society.

Other works have shown similar conformational and chemical changes, when proline, instead of HCl, was added into the ethanol flow,[21] proving the influence of the molecules surrounding the peptide in solution.

Finally, polylysine peptides (PLL_n-SH, $n = 4-10$) modified by a terminal thiol group have been adsorbed on a gold surface.[24] AFM and FT-RAIRS analyses have identified various modes of adsorption depending on the peptide length and conformation in solution. The polypeptide secondary structures, characterized in solution by circular dichroism, strongly depend on the degree of polymerization, leading to different structures on the gold surface.

The following section gathers recent results concerning the adsorption of small peptides on oxide surfaces. As a first example, adsorption on TiO_2 of two dipeptides, AE (L-alanine−L-glutamic acid) and AK (L-alanine−L-lysine), which are the repeating units of self-assembled EAK oligopeptides, was investigated by a combined theoretical and experimental approach.[25] Molecular dynamics simulations revealed that the major fraction of AE molecules interact via the glutamate carbonyl oxygen coordinated to a Ti center, the structure being stabilized by hydrogen bonding between the NH_2 groups and surface oxygens. Note that, to mimic adsorption from aqueous solution, the authors considered that the peptides were solvated by water molecules. In the case of AK, a conformer bound via two carbonyl oxygen atoms and one NH_2 is most likely, as shown in Figure 7.

The zwitterionic peptide adsorbs in a bidentate coordination with the COO^- group bound to two Ti atoms. This result is in direct continuation with the studies of amino acid adsorption on TiO_2, which showed the preferential interaction of the carboxyl groups with the surface Ti^{4+} cations.[26,27]

The same authors had previously studied by molecular calculation the mechanism of adsorption of the same AK and AE peptides in the presence of water molecules on a rutile TiO_2 surface. They came to two important results: (i) carbonyl oxygen and nitrogen atoms are possible coordination sites, and (ii) intermolecular interactions are responsible for changes in the molecule conformation.[28]

Another small peptide, the RGD (Arg-Gly-Asp) peptide, has been the subject of a considerable number of studies because of its role as a cell adhesion promoter.[29−31] RGD adsorption on titanium surfaces was investigated by molecular dynamics simulation.[32] On either anatase (001) or rutile (010), the

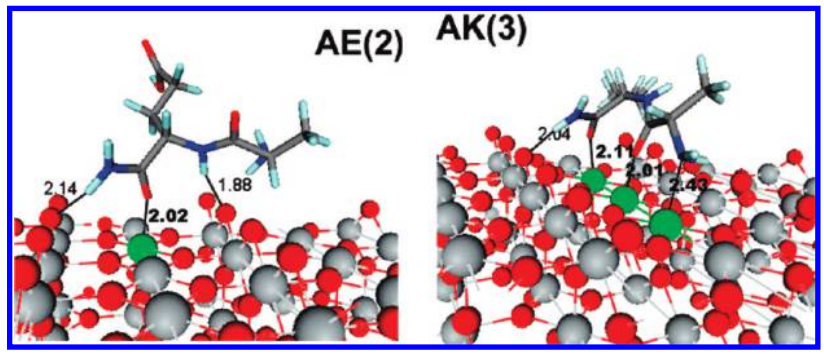

FIGURE 7. Stable structures of Ala-Glu (a) and Ala-Gly dipeptides (b) on rutile TiO_2(110) surface (from molecular dynamics simulation and XPS measurements after deposition of peptides in solution). Carbon, oxygen, nitrogen, and hydrogen atoms are in gray, red, blue, and cyan, respectively. Adapted with permission from ref 25. Copyright 2008 American Chemical Society.

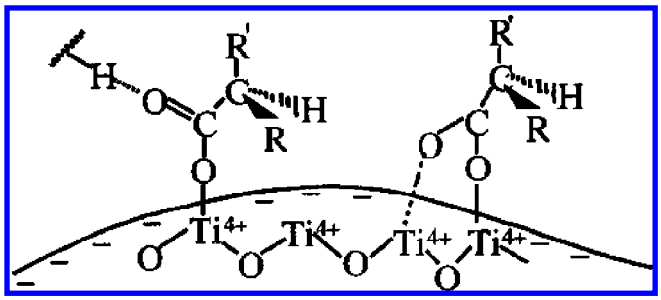

FIGURE 8. Schematic representation of possible carboxylate coordination to TiO_2 (reproduced with permission from ref 35, copyright 1999 Elsevier).

RGD peptide adopts an on-top conformation, resulting from interactions between the O atoms of the aspartate residues and Ti charged atoms of the topmost oxide layer. Note, in agreement with that conclusion, that immobilized peptides may be used as metal ion chelating agents due to the particular affinity of the amino acid side groups toward metal cations; this is the case for poly(L-cysteine), immobilized on magnetic γ-Fe_2O_3 nanoparticles.[33,34]

The characterization of adsorption of lysine peptides (n = 2−5) and of polylysine on hydrous TiO_2 films made clear the role of electrostatic interactions between the positively charged end groups of the peptide and the negatively charged TiO_2 surface (Figure 8).

Adsorption of Higher Molecular Weight Peptides

The fugosenic peptide B18 (LGLLLRHLRHSHSNLLANI) or peptides containing the sulfur-bearing amino acid histidine are often studied on oxide surfaces for their key role in cell adhesion to inorganic materials.

From a macroscopic point of view, physicochemical properties of peptides are determined in their interaction with a solid surface, and the adsorption is the result of an interplay between electrostatic and hydrophobic interactions. As an example, from solution at pH = 7.4, the positively charged peptide B18, even though hydrophobic, adsorbs on negatively charged hydrophilic surfaces; it also adsorbs on strongly hydrophobic surfaces, making clear the determining influence of one or the other type of interaction depending on the environment; in the case of B18, hydrophobic interactions are reinforced by the presence of leucine side chains at both ends of the peptide molecule. Moreover, adsorbed B18 rapidly forms aggregates due to surface diffusion, and to the preferential adsorption of a second molecule on top of an adsorbed one.[36]

Combinatorial biology has been successfully employed to identify the regions of proteins, that is, the preferential peptide sequences, involved in the binding with inorganic solid surfaces; peptide libraries can thus be created and peptide sequences incorporated in any protein. One should note that on Cr_2O_3 and Fe_2O_3, basic amino acids, arginine and lysine, play a particular role in the binding of biomolecules.[37,38]

In an attempt to develop a biological system able to sequester heavy metals, Kjaegaard et al. tested a series of peptide sequences; they identified ZnO-binding sequences enriched in histidine, arginine, aspartate, and methionine; interestingly, these identified sequences were highly specific to the oxide form of zinc and not to Zn^{2+} ions under another form.[39]

Thai et al. tested the interaction of disulfide-constrained dodecapeptides with Cu_2O and ZnO surfaces.[40] By combining statistical analyses of the number of occurrences of binding peptides and molecular dynamics calculation, they pointed out the role of the basic arginine amino acid; geometrical considerations could also explain the discrimination of the two surfaces, Cu_2O and ZnO. These results should be taken with care because a number of other amino acids may also contribute to the peptide−oxide interaction. In a further study, the same authors pointed out the determining role of the peptide conformation when binding to metal oxide surfaces; the

surface specificity may be tuned by changing the amino acid sequence in peptides of similar compositions. Interestingly, a peptide presenting a disulfide-bonded loop bound to Cu_2O, whereas linear peptide of the same composition did not.[41]

By a phage display technique, disulfide-constrained heptapeptides with specific binding affinity for SiO_2 and TiO_2 nanoparticles have been identified; peptides enriched in basic amino acid residues exhibit a pH-dependent affinity toward both oxides, demonstrating the role of electrostatic interactions.[42,43] The authors demonstrated (i) that peptide mutants having one lysine residue replaced by an alanine completely lost the affinity to TiO_2 and (ii) that peptides with a higher number of lysines, or more basic residues, display lower affinity. The peptide geometry, that is, the possibility to align the positively charged residues toward the surface, is also a key point.

Adsorption on Al_2O_3 of two polypeptides, poly(glutamic acid) and polylysine, from solutions containing $CaCl_2$ was investigated by IR spectroscopy. Interestingly, at basic pH, polyglutamic peptides adsorb in the form of aggregates, due to specific interactions between the COO^- groups on the peptide side chain and the surface; such an effect was not observed in the absence of salt in solution or for polylysine whatever the conditions.[44] This could beautifully explain the adsorption of a protein, BSA, on stainless steel surfaces, which is promoted in salt-rich aqueous conditions.[45]

Adsorption of the EAK16 peptide sequence (H-AKAKAEAE-AKAKAEAE-NH_2) on TiO_2, was investigated by NEXAFS, XPS, and IR spectroscopies.[46] Assuming that amino acids bind to TiO_2 surfaces by a reaction between the basic Ti−OH groups and the carboxyl groups, Polzonetti et al.[25] deduced the following model: the EAK16 peptide adsorbs under a β-sheet conformation in an ordered arrangement ensured by a self-assembly process, that is, intermolecular forces, rather than by peptide−surface interactions.

More recently, two other peptides were adsorbed on gold and titanium, PeptA bearing the RGD motif linked to a sequence of EAK16 (H-RGD-AEAEAKAKAEAEAKAK-NH_2) and PeptB bearing the RGD motif linked to a "mixed" sequence from the EAK16 (H-RGD-AAKAEAEAAEKAKAEK-NH_2). Like EAK16, PeptA adopts a β sheet conformation. In the case of PeptB, the IR spectrum shows broader bands, which suggest a less ordered structure than that of PeptA and EAK16, likely due to the absence of intermolecular interactions on the peptide chain (Figure 9).

The peptide organization seems to only depend on that of the EAK16, not on the RGD. If PeptA adsorbs through the terminal $CONH_2$ of the EAK16, the RGD sequence must be exposed on the top of the surface and thus well oriented to interact with other molecules. In the case of PeptB, disorder of the structure may hide the RGD sequence.

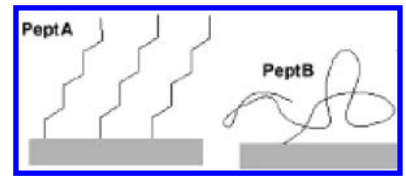

FIGURE 9. Possible configuration of peptides adsorbed on gold or titanium surfaces (adapted with permission from ref 46, copyright 2007 Elsevier).

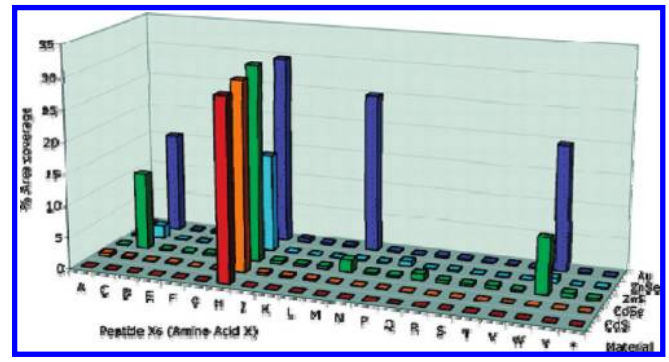

FIGURE 10. Homohexamers (X6) of the 20 natural amino acids (X) tested for binding to five different inorganic materials including gold nanoparticles. Reproduced with permission from ref 54. Copyright 2005 American Chemical Society.

A better understanding of a disulfide bond-constrained peptide −CHKKPSKSC−, or STB1, and TiO_2 surfaces was attained by testing various point mutants of the peptide. Electrostatic forces appeared to be governing the affinity toward the surface, positively charged lysine residues being particularly favorable.[47]

Peptide-based biomaterials were recently investigated to better understand the mechanisms of calcium phosphate mineralization;[48] two hydroxyapatite-binding peptides were selected, exhibiting different affinities for hydroxyapatite. The peptide affinity governs the calcium phosphate crystal size and morphology; a possible explanation is that the histidine residues interact via hydrogen bonds or ionic interactions with the phosphate ions, thus limiting the accessibility of PO_4^{3-} to the active growth sites of the newly formed nuclei. The possible control of biomineralization processes by peptides may find great applications in tissue engineering.

Self-assembling peptides have been identified, and the mechanism of their structuration made clear the importance of the amphiphilic properties of the biomaterial, the hydrophobic and electrostatic interactions between charged residues, as well as the amino acid position in the peptide

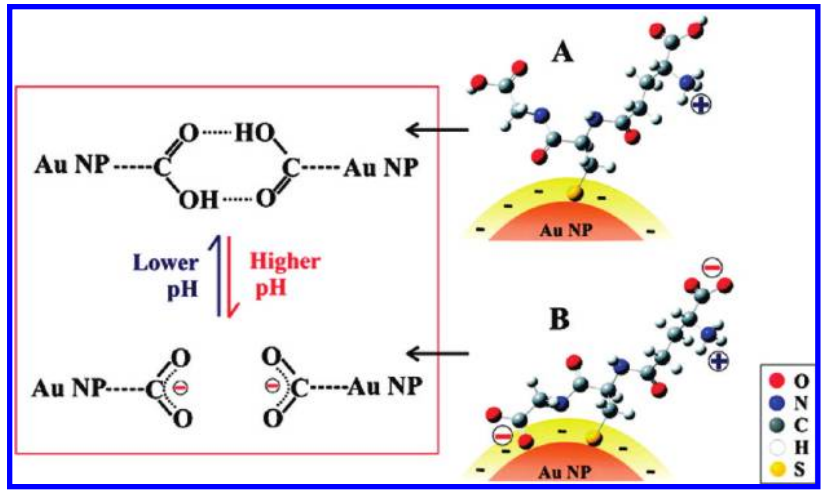

FIGURE 11. Schematic illustration of the possible modes of interaction between gold nanoparticles and GSH molecules, as well as interparticle interactions. Reproduced with permission from ref 56. Copyright 2008 American Chemical Society.

sequence.[49] Despite the importance of these studies for biocompatibility, little is said about the direct peptide−solid interactions.

Interfacial peptide self-assembly was also shown to occur when cationic peptides, like V6K2, react with a hydrophilic silica surface. The adsorption starts with a fast initial step resulting in a dense peptide layer interacting via the cationic head groups; it is followed by the formation of a bilayer resulting from hydrophobic interpeptide interactions.[50]

Similarly to cellular processes for the assembly of inorganic nanostructures, some peptides may be used to precipitate silica from solution, acting as templates in inorganic material synthesis.[51]

Understanding how amino acids, peptides, and proteins interact with inorganic material surfaces is more than relevant in the field of nanotechnologies. Peptides are sometimes anchored to nanoparticles, acting as sensors, heterolinkers, or assembly agents between nanoparticles (NPs). They may also be used to control the shape and size of NPs.[52,53]

Several studies were carried out to determine which amino acid was responsible for the binding of peptides onto inorganic nanoparticles. Figure 10 presents systematic adsorption assays of homohexapeptides of the 20 naturally occurring amino acids.[54] These results clearly show that only homohexamers containing aromatic nitrogen (histidine or tryptophan) or sulfur (cysteine or methionine) were capable of binding to various types of NPs.

Briñas et al.[53] and Negishi et al.[55] made clear that GSH anchors to gold nanoparticles via the sulfur atom. Lim et al., by controlling the protonation/deprotonation of one of the amine groups, found evidence for several interaction points,[56] depending on the pH, thus inducing changes in the molecule conformation (Figure 11).

Note eventually that, a very recent studies of thiol adsorption on gold Nps made clear the formation of bridges formed by the bonding of each sulfur atom to two gold ones; together with that very new result, the authors explain that, on nanoparticles, the thiol coverage may reach a value twice as much higher than on planar surfaces.[57] The configuration might be similar for cysteine residue-containing peptides.

To finish with the studies of the interaction of peptides with metal or oxide surfaces, let us mention this new class of peptides called "genetically engineered peptides for inorganics" (GEPI), selected by using a bacterial cell surface and phage display protocol for their affinity for various inorganic substrates.[58,59] Several studies have been conducted to better understand the adsorption selectivity and kinetics of the $3rGBP_1$ ($[MHGKTQATSGTIQS]_3$) peptide. Though it does not contain cysteine residues, this peptide exhibits a higher affinity for gold than for platinum.[60] Its adsorption on Au(111) proceeds in two steps with an evolution of the structure observed by AFM.[61] The first step corresponds to monomers adsorbed homogeneously on the surface; it is followed by aggregation and growth in the form of clusters (Figure 12).

A recent AFM study, coupled with molecular simulation,[62] showed the formation of an order at the supramolecular level due to self-assembly of this 3rGBP1 peptide on Au(111).

Conclusion

This Account reports on a number of studies all aiming at characterizing the interaction of peptides with metal or oxide surfaces. A huge amount of information, both at a macro-

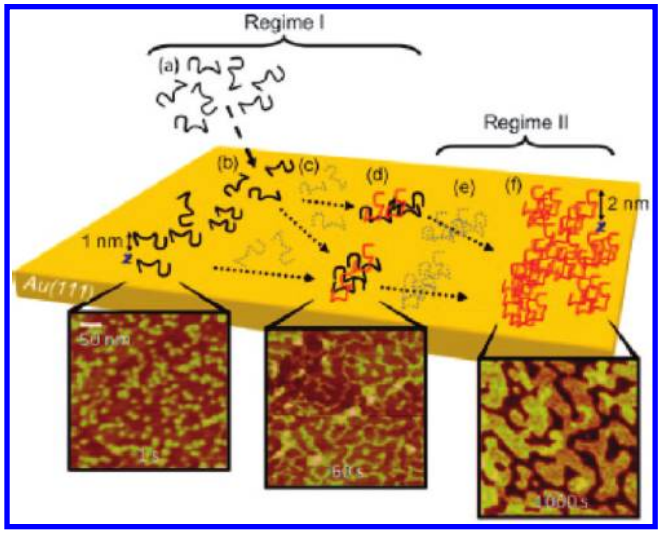

FIGURE 12. Schematic model showing the proposed mechanism of the binding, diffusion, and assembly of 3rGBP1 on Au(111) with corresponding AFM images (reproduced with permission from ref 61, copyright 2009 Wiley).

scopic and at a molecular level, has been drawn thanks to the use of surface science, solid chemistry techniques, and advanced theoretical methods.

The following tendencies may be remembered:

Small and higher mass peptides interact with metal and oxide surfaces, and the preferential affinity of some amino acids was demonstrated. All peptides bearing a thiol group bind to gold via the S atom. Other peptides also bind to metal and oxides surfaces, likely via their carboxylate groups. A combination of H-bonding and electrostatic interactions was shown to exist between peptides and oxide surfaces. Self-assembly of peptides on surfaces, leading to 2D regular arrangements, was made clear, favored by intermolecular interactions within the adsorbed layer.

Adsorption may induce conformation changes in the peptide; moreover, the geometry or conformation of the peptides may be controlled by various types of stimuli, like pH changes or additives in the solvent.

Peptides also bind to inorganic nanoparticles, in similar ways as they do on bulk surfaces. Interestingly, peptides may act as heterolinkers between these solids, contributing to the formation of controlled nanoparticle assemblies.

This Account shows that, thanks to the combination of spectroscopic, structural, and theoretical techniques, a better understanding of peptide−surface interactions has been reached. Some of these tendencies may be of determining importance when considering the interaction of proteins with inorganic surfaces.

It brings new hope in the understanding of biological interfaces. It also opens new directions toward the elaboration of materials whose reactivity in a biological environment needs to be controlled, such as biocompatible or biosensing materials.

BIOGRAPHICAL INFORMATION

Anne Vallee received her Ph.D. in 2009 from the Pierre et Marie Curie University under the direction of Claire-Marie Pradier in the Laboratoire de Réactivité de Surface. Her doctoral work focused on the understanding of biomolecule−metallic surface interfaces. She is now pursuing a postdoctoral period at the University of Torino in the group of G. Martra.

Vincent Humblot received his Ph.D. in 2002 from Liverpool University under the direction of Rasmita Raval in the Department of Chemistry. Since 2004, he has been appointed researcher at the CNRS, where he is working on the modification of metal or oxide surfaces by biomelocules.

Claire-Marie Pradier is senior researcher at the CNRS French institution; she is the director of the Réactivité de Surface Laboratory at the University Pierre et Marie Curie, Paris-6. Her main concern is to apply surface science tools to study biointerfaces, elaborate biosensors, and control biofilm growth on metal and oxide surfaces.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: claire-marie.pradier@upmc.fr.

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