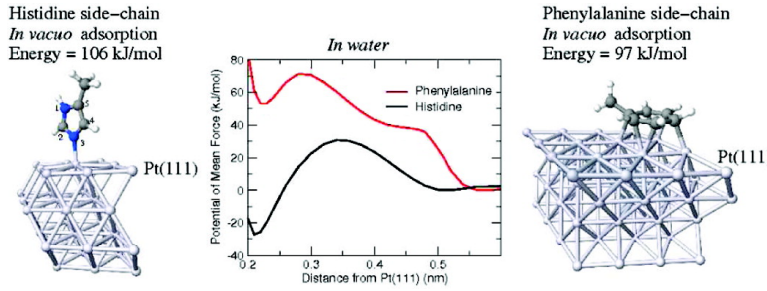
Article

Competing Adsorption between Hydrated Peptides and Water onto Metal Surfaces: From Electronic to Conformational Properties

Luca M. Ghiringhelli, Berk Hess, Nico F. A. van der Vegt, and Luigi Delle Site

J. Am. Chem. Soc., **2008**, 130 (40), 13460-13464 • DOI: 10.1021/ja804350v • Publication Date (Web): 13 September 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES

Published on Web 09/13/2008

Competing Adsorption between Hydrated Peptides and Water onto Metal Surfaces: From Electronic to Conformational Properties

Luca M. Ghiringhelli, Berk Hess, Nico F. A. van der Vegt, and Luigi Delle Site*

Max-Planck-Institute for Polymer Research, Ackermannweg 10, 55128 Mainz, Germany

Received June 9, 2008; E-mail: dellsite@mpip-mainz.mpg.de

Abstract: Inorganic−(bio)organic interfaces are of central importance in many fields of current research. Theoretical and computational tools face the difficult problem of the different time and length scales that are involved and linked in a nontrivial way. In this work, a recently proposed hierarchical quantum-classical scale-bridging approach is further developed to study large flexible molecules. The approach is then applied to study the adsorption of oligopeptides on a hydrophilic Pt(111) surface under complete wetting conditions. We examine histidine sequences, which are well known for their binding affinity to metal surfaces. Based on a comparison with phenylalanine, which binds as strong as histidine under high vacuum conditions but, as we show, has no surface affinity under wet conditions, we illustrate the mediating effects of near-surface water molecules. These contribute significantly to the mechanism and strength of peptide binding. In addition to providing physical−chemical insights in the mechanism of surface binding, our computational approach provides future opportunities for surface-specific sequence design.

I. Introduction

In recent years, a rapidly growing activity has developed in identifying peptide sequences (aptamers) that can specifically recognize and bind to an inorganic surface.[1−5] Peptide−inorganic interfaces provide new routes for materials synthesis and nanoscale fabrication[6] with already proven applications such as linkers for controlled protein immobilization[7] and promoters to control nanoparticle growth.[8] However, the design of such systems is largely done on the basis of empirical knowledge rather than on that of rational systematic design based on the physical and chemical ground of the adsorption process. Theoretical modeling of biomolecule-surface affinities has progressed in the area of atomistic[9] and coarse-grained[10] simulations, but a systematic approach for bridging the various scales, explicitly asked by the community of experimentalists[6,11] is still missing.

An exhaustive explanation of the binding to close-packed metal surfaces of hydrated peptides must include several ingredients and scales. (a) The molecule−surface (and water−surface) interactions are determined by subtle electronic effects and therefore must be treated at the electronic (ab initio) level. (b) The conformational space (orientation and internal degrees of freedom) of a large flexible molecule can in principle be studied at the ab initio level;[12] however, this approach becomes computationally infeasible with even modest molecular sizes. Classical molecular dynamics (MD) simulations represent, in this case, a robust tool to explore the molecular conformational space. A third fundamental aspect emerges when the molecule is solvated: (c) solvation forces, which are determined by the hydration of the individual amino acid residues and the properties of the interfacial water, must be taken into account. Due to the necessity of a large number of solvent molecules, also this aspect needs to be treated at the classical MD level.

In this paper, we will address the question of biomolecule−surface specificity by analyzing the adsorption of oligopeptides with phenylalanine (Phe) and histidine (His) as constituent amino acids, onto a Pt(111) surface. Despite the comparable (in vacuo) adsorption energy of the two amino acids onto group 10 metal close packed surfaces (Table 1 and ref 12), we show that they exhibit dramatically different adsorption behavior under wet conditions with interfacial water playing an important role. The computational methodology described here is a first step toward an in silico method guiding molecular design of inorganic−(bio)organic interfaces.

II. Methods

The interdependence between the quantum scale of the chemistry specific adsorption and the larger scale of the molecular conformations (in solution) is the most relevant aspect of the overall adsorption process. The accurate description of such an interplay

(1) Brown, S. *Nat. Biotechnol.* **1997**, *15*, 269.
(2) Weiner, S.; Addadi, L. *J. Mater. Chem.* **1997**, *7*, 689.
(3) Nakanishi, K.; Sakiyama, T.; Imamura, K. *J. Biosci. Bioeng.* **2001**, *3*, 233.
(4) Patwardhan, S. V.; Patwardhan, G.; Perry, C. C. *J. Mater. Chem.* **2007**, *17*, 2875.
(5) Evans, J.; Samudrala, R.; Walsh, T.; Oren, E.; Tamerler, C. *MRS Bull.* **2008**, *33*, 514.
(6) Schiffrin, A.; Riemann, A.; Auwarter, W.; Pennec, Y.; Weber-Bargioni, A.; Cvetko, D.; Cossaro, A.; Morgante, A.; Barth, J. V. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 5279–5284.
(7) Chen, R. J.; Zhang, Y.; Wang, D.; Dai, H. *J. Am. Chem. Soc.* **2001**, *123*, 3838.
(8) Haruyama, T.; Sakai, T.; Matsuno, K. *Biomaterials* **2005**, *26*, 4944.
(9) Harding, J. H.; Duffy, D. M. *J. Mater. Chem.* **2006**, *16*, 1105.
(10) Bachmann, M.; Janke, W. *Phys. Rev. Lett.* **2005**, *95*, 058102.
(11) Lingenfelder, M.; Tomba, G.; Costantini, G.; Colombi Ciacchi, L.; De Vita, A.; Kern, K. *Angew. Chem.* **2007**, *46*, 4492.
(12) Ghiringhelli, L. M.; Delle Site, L. *J. Am. Chem. Soc.* **2008**, *130*, 2634.

10.1021/ja804350v CCC: $40.75

Table 1. Adsorption Energies (in kJ/mol) and Bonding Perpendicular Distances, i.e., the Distance between the Average Top Layer Plane and the Atom (or Fictitious Point Representative of a Functional Group) Specified in the Column Labelled by "X", in nm[a]

molecule	orient.	X	Δz^{X}_{ave} (nm)	E_{ads} (kJ/mol)
NMA	vertical	O	0.24	−18
NMA	flat	O	0.27	−18
NMA	45°	O	0.27	−18
NMA	flat	N	0.24	−18
His	vertical	N	0.21	−106
Phe[12]	fat	ring CoM	0.21	−97
H_2O[28]	∼flat	O	0.24	−29

[a] The estimated uncertainty for E_{ads} is 4 kJ/mol.

requires the employment of a theoretical/computational framework which can suitably combine in a consistent hierarchical procedure the electronic properties of molecular adsorption on the surface and the statistical sampling of the molecular conformations. However, such a procedure must allow to control the underlying approximations and quantify their effects. This latter point is of crucial importance in building a reliable model (for the interaction of both solute and solvent with the surface) where the electronic properties of adsorption are properly translated into a classical force field. Once this is done, then classical MD simulations can be performed for large systems of statistical relevance. We have recently developed a building block procedure that uses quantum calculations of small submolecular moieties at the surface to parametrize in classical terms the interaction of large molecules with metal surfaces.[13] At first (ab initio modeling), quantum calculations of the adsorption of a moiety are performed for a set of representative conformations[12−14] at the surface; such conformations are chosen to be consistent with topologically allowed conformations of the large molecule confined by the surface.[13,15] By using data from the quantum calculations, all the electronic effects are translated into an effective moiety-surface interaction potential; such potential mimics the interaction with the surface that the fragment would have when part of the large molecule. Technically, this is done by assigning virtual interaction sites to the moiety (not necessarily in correspondence of the atom sites), such that its ab initio energies and geometries of adsorption are reproduced within a certain predefined tolerance.[13] The intramolecular interactions of the large molecule are described via an existing and reliable force field. However, the description of the properties of a molecule as the sum of the properties of its individual submolecule might be a rather crude approximation. In fact, some of us have recently shown[12] that the interplay between chemical affinity to the surface and molecular flexibility may play a crucial role for the overall adsorption properties. For this reason, a crucial aspect of this procedure is a consistency check step. This consists of classical simulations of the large molecule or a large representative submolecule, performed on the surface in vacuo. A certain number of conformations are then selected from this simulation and used as an input for quantum calculations. If the output (geometry of the molecule at the surface and the order of energies among the different configurations) of the quantum calculations does not deviate significantly from the classical one, then the model is accepted otherwise is refined and the procedure is repeated until a satisfying consistency is reached (refs 13 and 16 and references therein).

In the particular case of the interaction between (liquid) water and the metal surface, the moieties are replaced by small water clusters which reproduce possible local tetrahedral structures when confined by a surface.[17,18] As for the large molecule, consistency tests are then performed to check whether the classical parametrization reproduces larger structures, as for example thin films, obtained from quantum calculations.[13,19] Interestingly, we have proven that our model of interaction with the surface is basically independent of the classical water model considered and leads to the same liquid structure at the surface and free energy barrier for the case of benzene in water adsorbed on the metal surface, for each tested classical water model.[13]

III. Ab Initio Modeling

For the present work, we modeled an oligopeptide, i.e., a sequence of different amino acids, as a backbone, i.e., a repetition of the monomer [(HC$_\alpha$)−(C═O)−NH−], where to each C$_\alpha$ is attached a side group, specific to the particular amino acid. The building blocks we address here are *N*-methylacetamide (NMA, mimicking the backbone monomeric unit), and the side chains of Phe and His. For the ab initio calculations we used Alavi's finite temperature density functional method,[20] as implemented in the plane-waves based code CPMD.[21] We used the PBE functional;[22] all of the pseudopotentials were already tested for former publications of some of us.[12,14,23] The cutoff for the plane-wave expansion is set at 60 Ry and a 3 × 3 × 1 k-point mesh. We used a 3 × 3 hexagonal supercell containing four metal 111 layers and one molecule. The vacuum above the molecule was at least 1 nm and the lateral size of the super cell is such that lateral interactions between molecules's replicas can be neglected. Convergency with respect to plane wave cutoff and number of planes was thoroughly tested for previous works.[12,14,15,23,24]

A. NMA. NMA is the smallest molecule containing the CONH peptide unit, yet displaying the same steric constraints as if the peptide bond were embedded in the backbone. In particular, the presence of the methyl groups, which are known theoretically[12,14] and experimentally[25,26] to be repelled by metal surfaces, mimics the steric hindrance given by the C$_\alpha$ in the peptide chain. By analogy with former studies of ours,[14] the only possible adsorbing sites of NMA can be the N and O atoms. In Figure 1, right panel, we show one of the strongest adsorbing geometry of NMA, i.e., through O and in a "vertical" orientation. In Table 1, we report also other adsorbing geometries of NMA that have practically the same adsorption energy. All of the orientations are referred to the angle between the surface plan

(13) Schravendijk, P.; Ghiringhelli, L. M.; Delle Site, L.; van der Vegt, N. F. A. *J. Phys. Chem. C* **2007**, *111*, 2631.
(14) Ghiringhelli, L. M.; Schravendijk, P.; Delle Site, L. *Phys. Rev. B* **2006**, *74*, 035437.
(15) Delle Site, L.; Abrams, C. F.; Alavi, A.; Kremer, K. *Phys. Rev. Lett.* **2002**, *89*, 156103.
(16) Delle Site, L.; Kremer, K *Int. J. Quantum Chem.* **2005**, *101*, 733–739.
(17) Sebastiani, D.; Delle Site, L. *J. Chem. Theory Comput.* **2005**, *1*, 78–82.
(18) Schravendijk, P.; van der Vegt, N.; Delle Site, L.; Kremer, K. *ChemPhysChem* **2005**, *6*, 1866–1871.
(19) Delle Site, L.; Ghiringhelli, L. M.; Andreussi, O.; Donadio, D.; Parrinello, M. *J. Phys.: Condens. Matter* **2007**, *19*, 242101; fast track communication.
(20) Alavi, A.; Kohanoff, J.; Parrinello, M.; Frenkel, D. *Phys. Rev. Lett.* **1994**, *73*, 2599.
(21) CPMD, version 3.10, developed by J. Hutter, A. Alavi, T. Deutsch, and W. Silvestri, copyright MPI für Festkörperforschung Stuttgart (1995−2001) and IBM Zurich Research Laboratory (1990−2006).
(22) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.
(23) Ghiringhelli, L. M.; Caputo, R.; Delle Site, L. *J. Phys.: Condens. Matter* **2007**, *19*, 176004.
(24) Delle Site, L.; Alavi, A.; Abrams, C. F. *Phys. Rev. B* **2003**, *67*, 193406.
(25) Barlow, S.; Louafi, S.; Le Roux, D.; Williams, J.; Muryn, C.; Haq, S.; Raval, R. *Langmuir* **2004**, *20*, 7171.
(26) Terborg, R. H. J. K. M.; Polcik, M; Pascal, M.; Kang, J.; Lamont, C.; Bradshaw, A.; Woodruff, D *Surf. Sci.* **2000**, *457*, 1.
(27) Preuss, M.; Schmidt, W. G.; Bechstedt, F. *Phys. Rev. Lett.* **2005**, *94*, 236102.
(28) Michaelides, A. *Appl. Phys.* **2006**, *85*, 415.

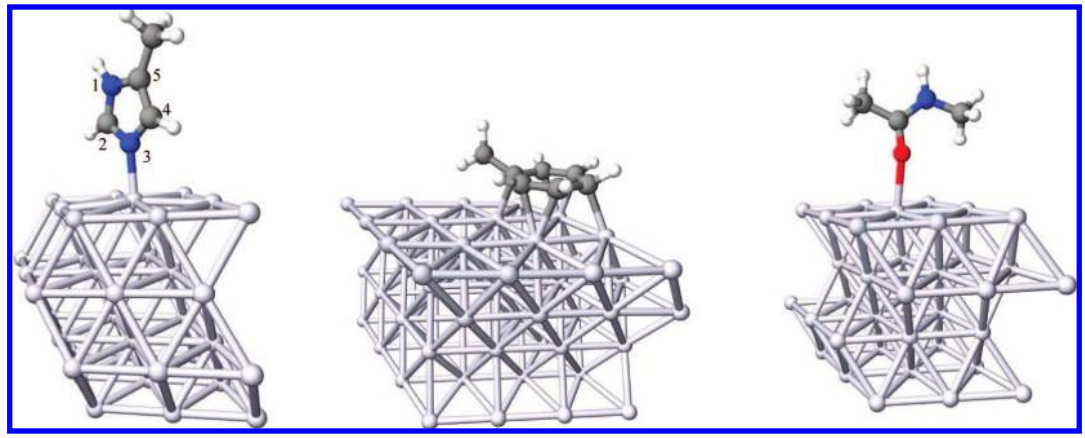


Figure 1. Favored adsorptions, compatible with the chain constraints, for (from left to right) His and Phe side chains and NMA.

Table 2. Distance r_{min} and Value at the Minimum V_{min} of the 10−4 Potential for Peptide−Pt Interactions[a]

group	atom	r_{min} (nm)	V_{min} (kJ/mol)
SPC/E	O	0.24	−35
SPC/E	H	0	0
backbone	O	0.24	−18
backbone	N_H	0.24	−18
backbone	H	0.24	+5
phenyl	C	0.21	−30
phenyl	H	0.21	+5
imidazole	N	0.21	−150
	rest	0.24	+5

[a] A positive V_{min} indicates that only the repulsive 10th power is used with a coefficient corresponding to that of 10−4 potential with a minimum of $-V_{min}$.

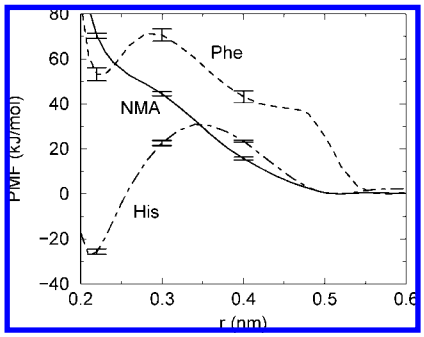


Figure 2. Potential of mean force of hydrated amino acids the and peptide backbone (NMA) as a function of the distance to the Pt surface. Error bars are shown for selected points.

and the plane defined by the peptide bond, which is a flat and rather rigid structure. The adsorption energy of NMA via oxygen seems to be rather independent of the tilting of the molecule. We find that NMA can bind flat also via nitrogen atom, with N in an atop position. From previous studies of ours,[12,14] we know that nitrogen in amino acids is generally a strong binder to metal surfaces; on Pt(111) it normally binds with an adsorption energy on the order of 100 kJ/mol, if molecular deformations do not diminish this value. In the case of NMA, the binding via nitrogen is achieved by means of a buckling of the plane defined by the peptide unit, similar to the case of adenine as seen in ref 27. This buckling has a rather high energetical cost, bringing the adsorption energy down to 18 kJ/mol, by coincidence similar to the binding energy of the molecule via oxygen.

B. Side Groups. The side chain of His is 5-methylimidazole (see Figure 1, left panel). Imidazole is one of the strongest bases that can exist at neutral pH; it contains a very nucleophilic tertiary amine, with the unusual property of having little steric hindrance.[29] We consider the neutral form of this molecule, as it is the case for the molecule solvated in water at physiological pH. Here we consider only the case where the nonprotonated N is in position 3 (see Figure 1). In fact, when the nonprotonated N is in position 4 (or 1), its adsorption is hindered by the presence of the methyl group. It is known that both species are found in proteins, and it is believed that the precise form depend on the local environment of the side chain.[29] It is worth noting that His-chain tags are commonly used as chemically active handles (they bind to metal surfaces in water) to achieve precise control over the orientation of biomolecules (enzymes, motors) on metal surfaces.[8,30] The geometry shown in Figure 1, left panel, is the most adsorbing onto Pt(111). The ab initio adsorption study of Phe was already the subject of a recent publication by some of us.[12] In Table 1, the values useful for the present discussion are reported, i.e., those corresponding to the adsorption via the side group (toluene) (see Figure 1, center panel). Phe adsorbs also via the amino nitrogen or via the ring and nitrogen simultaneously. Though, for the present modeling, we have in mind Phe as a residue and the nitrogen would be involved in the peptide bond as part of the backbone. For this reason, the parametrization of the binding via nitrogen must be done using the information coming from NMA, not from Phe.

One important observation regarding this modeling procedure is that, for the cases treated so far, molecular adsorption on close packed transition metal surfaces modifies the structure of the surface only of a negligible amount. Typically the modification of the surface upon adsorption may lead to a different reactivity toward the adsorbing molecules (or chemical moieties within the same molecule), but capturing this aspect is the very reason for our building block iterative modeling procedure. Obviously, if major reconstruction of the surface happened, the modeling procedure should be modified in order to include the new surface patterning. Regarding the kind of systems we have treated here (adsorption on close packed transition metal surfaces), no significant modification of the surface is observed (this is true even for the extreme case of thiolate, see experiments in refs 31 and 32 and theory in ref 23). Furthermore, for a more open

(29) Creighton, T. E. *Proteins: structures and molecular properties*; Freeman: New York, 2002.
(30) Montemagno, C.; Bachand, G. *Nanotechnology* **1999**, *10*, 225.
(31) Li, Z.; Chang, R.; Williams, S. C. *Langmuir* **2003**, *19*, 6744.
(32) Laiho, T.; Lukkari, J.; Meretoja, M.; Laajalehto, K. J. K; Leiro, J. A. *Surf. Sci.* **2005**, *584*, 83.

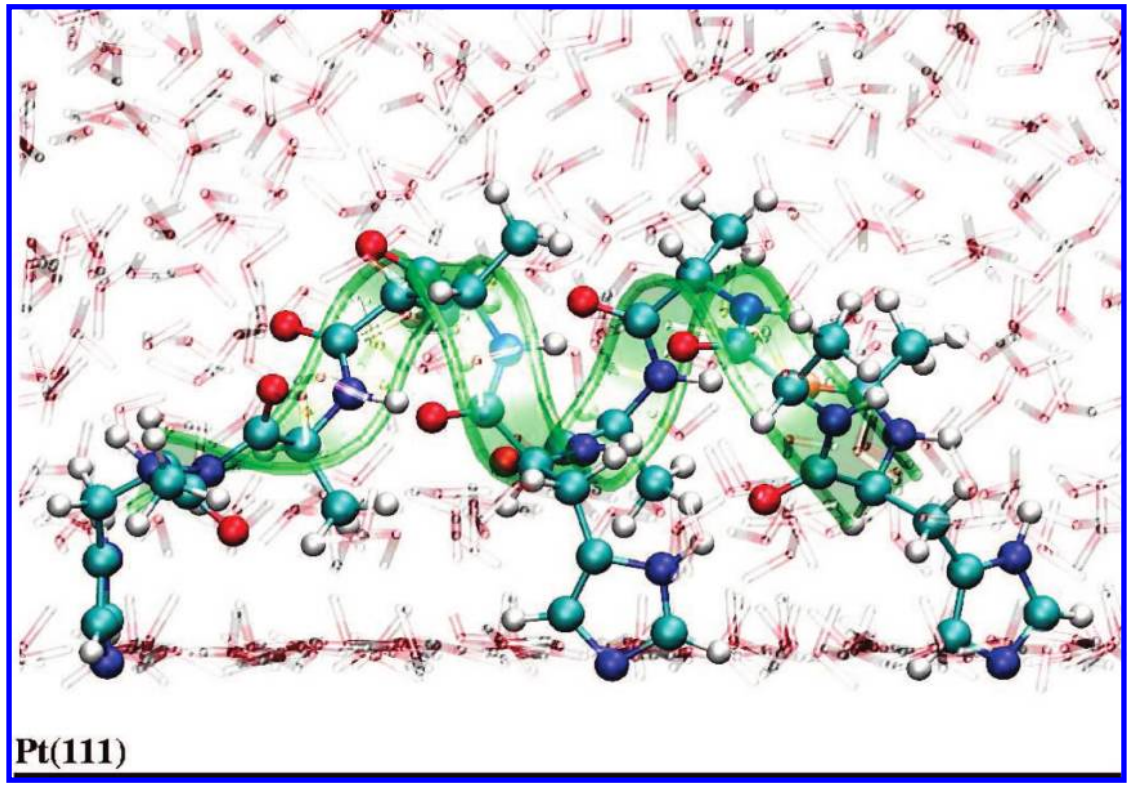


Figure 3. Three point adsorption (3 imidazoles) of solvated His−Ala_3−His−Ala_3−His. Water molecules are shown via a "ghostly" texture, in order to highlight the structure of the solvated and adsorbed molecule.

surface like Cu(110), it has been shown experimentally that the structure of the surface is not modified upon diphenylalanine adsorption.[11] For the most delicate case of water films, both experimental and theoretical work did not show evidence of any reconstruction.[19,33,34]

IV. Classical Parametrization

For the classical parametrization, we used as peptide−peptide force field the OPLS-AA (all-atom) force field.[35] The water model used is SPC/E.[36] For the peptide−surface and water−surface interactions, we define suitable interacting sites on the molecules, as they are suggested by the ab initio modeling. We use a flat, uniform surface, such that the interaction depends only on the perpendicular distance between the surface plane and suitable sites on the molecule. The C and H atoms (and, in general, the nonadsorbing groups, like the methyl group of alanine[14]) have a small repulsive (r^{-10}) potential, to prevent them from getting close to the surface. To the adsorbing sites (amide N, carbonyl O, center of mass of the phenyl ring) was attached an attractive 10−4 potential, whose depth and range were fit to the DFT data. The parameters are given in Table 2.

V. Adsorption Free-Energy of the Solvated Fragments

Using the classical model, we have calculated the solute-surface potential of mean force in water of NMA, Phe and His. The simulations were done, using the GROMACS 4 package,[37] in a cubic box of edge 4 nm containing 2140 water molecules. Only the bottom surface reacts as the modeled Pt(111); the top surface repels everything. Pressure coupling (in the z-direction only) and temperature coupling were used to 1 bar and 298 K. The neutral amino acids His and Phe were considered. The free-energy was determined by constraining the distance of the amide oxygen, phenyl center of mass, or imidazole nitrogen to the Pt surface. We performed simulations at fixed distances, separated by 0.01 or 0.02 nm. At each distance, the system was equilibrated for 100 ps and the constraint force was averaged over 400 ps. The integral of the negative of the mean constraint force over distance then gives the potential of mean force. The results are shown in Figure 2.

This study allows us get the feeling of the interplay between surface affinity (of the side chains) and steric effects due the flexibility. We find that solvated NMA loses free-energy upon adsorption, because already the energy balance between its adsorption and the desorption of a single water molecule disfavors the process. Albeit Phe and His have almost the same adsorption energy, for the adsorption of toluene (similarly to what was found for phenylalanine onto Ni(111)[13]) there is a large barrier of 30 k_BT. This is because several water molecules need to desorb simultaneously from the surface before the phenyl ring can adsorb flat on the surface. However, even when the phenyl ring adsorbs, it still does not compensate for the water−surface interactions, as the free energy is positive by 20 k_BT, although a small desorption barrier of 8 k_BT is present. In contrast, the free-energy for the adsorption of His (via the N3 atom of the 5-methylimidazole group) is large and negative: −11 k_BT, whereas the barrier of 12 k_BT can be overcome by thermal fluctuations, given enough time. The

(33) Ogasawara, H.; Brena, B.; Nordlund, D.; Nyberg, M.; Pelmenschikov, A.; Pettersson, L. G. M.; Nilsson, A. *Phys. Rev. Lett.* **2002**, *89*, 276102.
(34) Michaelides, A.; Ranea, V. A.; de Andres, P. L.; King, D. A. *Phys. Rev. Lett.* **2003**, *90*, 216102.
(35) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225–11236.
(36) Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269–6271.
(37) Hess, B.; Kutzner, C.; van der Spoel, D.; Lindahl, E. *J. Chem. Theor. Comp.* **2008**, *4*, 435–447.

barrier for the imidazole to approach the surface is lower than for a phenyl group, since 5-methylimidazole binds in the vertical orientation and thus less water molecules have to desorb in the process. Already at the level of the fragments, these results reveal a striking effect due to the presence of solvent: two moieties, toluene and 5-methylimidazole, with similar adsorption energies show two dramatically different adsorption free-energy landscapes when solvated. The results concerning NMA, Phe, and His make us argue that an oligopeptide in water would never adsorb through its backbone, nor it would via toluene as a side group. We did not try to extend the free-energy study to longer chains (bigger flexible molecules) since our all atom model, albeit classical, becomes rapidly computationally infeasible for such a sampling.

VI. Tailoring Adsorption Structures

In order to further underline the fundamental role of the solvent, we studied the adsorption behavior of a chain consiting of 9 alanine (Ala) units. Such a chain is expected to adsorb via the oxygen of the backbone. Adsorption via the nitrogen of the backbone might be also possible (the N−surface attraction is included in the potential), but intuitively less likely due to sterical hindrance. When this $(Ala)_9$ chain is near the surface without solvent, it indeed adsorbs only via (some of) the oxygens. In particular, we find a competion between two adsorbing structures, i.e., a compact one, with (minor) β-sheet character, and an elongated one displaying a perfect α-helix sticking on one end to the surface with three oxygens belonging to three consecutive backbone units. When water is added to the system, the chain irreversibly desorbs in less than 100 ps.

In order to show that our approach can be used for designing specific binding structures, we studied the important case of the adsorption of solvated model polypeptides, consisting of regular sequences of His and Ala. For instance, one would like to know how to design a sequence such that the peptide adsorbs keeping an α-helix structure, but with the maximum possible number of links to the surface. To this aim, we tried different spacings between the histidines, but the chain length was fixed to 9 units and the chains were always capped with CH_3-CO and $NH-CH_3$. Oligo-peptides containing His were placed in the box of water with no group initially penetrating the second water layer. Since a barrier of 12 k_BT, associated with the adsorption of a single His, is not likely to be overcome in an unbiased MD run, we put a harmonic restraint on the nonprotonated N atoms of the imidazole rings. Such a procedure destroys any information about the dynamics of the approach to the surface, yet the binding structures are those that are most likely to occur on an experimentally accessible time-scale. We note that the adsorption proved to be irreversible on our sampled time-scale, after the restraint was switched off.

We find that the sequence $His-Ala_3-His-Ala_3-His$ adsorbs via all the imidazole rings and with the backbone structured in a α-helix (see Figure 2). The same happens for the sequence $Ala-His-Ala_2-His-Ala_2-His-Ala$. In contrast, the sequence $Ala_2-His-Ala-His-Ala-His-Ala_2$ adsorbed with an extended backbone, whereas the backbone of the sequence $Ala-His-Ala_5-His-Ala$ showed only a partial helix. The results are consistent with the (mis)match of the helical pitch of 3.6 residues with the His spacing. It is worth noting that the adsorption of the oligopeptide occurs through the imidazole rings. Each of these groups displaces only few water molecules in the first water layer; the rest of the peptide floats well above this first layer and only slightly perturbs the second water layer which is already far less structured than the first and almost bulk like (see ref 13). This example shows how to design the sequence according to the demanded binding structures.

VII. Conclusions

Currently, the availability of experimental data for the system treated here and similar ones is scarce. This of course makes it difficult to discuss our result in an experimental context and to validate our computational methodology. In particular, we do not make a comparison here because in recent experimental work,[38−40] one of the major difficulties is the determination and control of the surface symmetry and purity. This of course is a crucial point in understanding the fundamental interactions between (bio)molecules and inorganic surfaces and for rational design. In this sense, in the near future, our approach could be also used to interpret experimental results regarding the molecular recognition ability of a given surface structure and composition.

A somewhat indirect validation of our approach is the fact that histidine tags are used for a specific binding and for positioning and orienting large biomolecules in water on metal surfaces,[8,30] in the very same spirit in which we have designed the anchoring and obtained the desired positioning of the polypeptide on the platinum surface.

The work presented here represents a step forward with respect to existing literature regarding the understanding of the effect of the water ad-layer upon adsorption on inorganic surfaces (see, e.g., refs 2 and 41). In our case, two large molecules, with nearly the same adsorption energies in vacuo but with different bonding motif and, above all, different hydration properties, display surprisingly different adsorption properties in aqueous solvent: adsorption vs nonadsorpion. This also implies that the implicit solvent approach, largely used for this kind of study,[10,42] is not sufficient to properly describe the interface properties. This aspect is strictly linked to the capability of the method to explain why His is an optimal molecule for anchoring properties (in solution) and why other, similar, molecules are not. This of course means that the method is predictive and indeed can be used as a guiding tool for a rational design of systems with on demand specific interface properties. An important point to stress is that, in this specific case, the difference in free energy for the adsorption of the different molecules is such that the conclusions are likely to qualitatively hold despite the quantitative limitations of the model. Such results can be obtained only by having an explicit solvent. Cases with similar large differences in free energy are the optimal ones for the application of our model, at this stage. The advantage of this approach is that, without requiring complicated parametrizations, it can describe the relevant physics and chemistry by just linking the different scales and related computational tools in their essential aspects.

Acknowledgment. L.M.G. acknowledges the AvH foundation for financial support. We thank D. Andrienko and S. Iacopini for a critical reading of the manuscript.

JA804350V

(38) Sarikaya, M.; Tamerler, C.; Jen, A. K.-Y.; Schulten, K.; Baneyx, F. *Nat. Mater.* **2003**, *2*, 577.
(39) Willet, R. L.; Baldwin, K. W.; West, K. W.; Pfeiffer, L. N. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 7817–7822.
(40) Tamerler, C.; Sarikaya, M. *MRS Bull.* **2008**, *33*, 504.
(41) Kerisit, S.; Parker, S. C. *J. Am. Chem. Soc.* **2004**, *126*, 10152.
(42) Feig, M.; Brooks, C. L. *Curr. Opin. Struct. Biol.* **2004**, *14*, 217.