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Cysteine on TiO₂(110): A Theoretical Study by Reactive Dynamics and Photoemission Spectra Simulation

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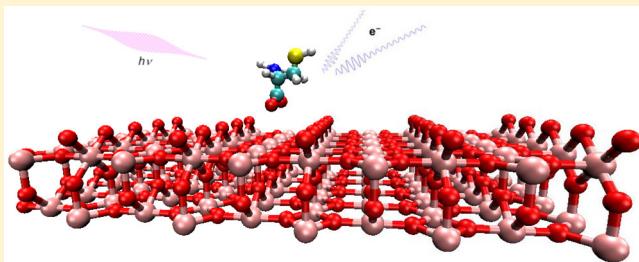
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Supporting Information

ABSTRACT: Owing to the importance of bioinorganic interface properties for the biocompatibility of implants and for biosensing technology, it has become indispensable to gain understanding of their crucial structure–property relations at the atomistic level. Motivated by this fact, we use cysteine amino acid on perfect and defective TiO₂(110) surfaces as model systems and study adsorption by means of classical all-atom reactive molecular dynamics and ab initio O 1s, N 1s, and S 2p photoemission spectra (XPS) simulations of the most relevant adsorbate structures. By analysis of the dynamics results and a detailed comparison with spectra recently collected for this adsorbate, we obtain conclusions of both general and particular character. It is shown that the interaction of cysteine with the TiO₂(110) surface has multipoint character involving the carboxylic group as well as the amino and sulfur groups. The proton-transfer reactivity of cysteine is enhanced by the presence of the surface, and different forms of cysteines are confirmed to be present in the adsorbate. A general conclusion is that reactive force field dynamics combined with selected spectroscopy provides a viable path to understanding bioinorganic surfaces with ramifications for the design of such surfaces for future technological applications.



INTRODUCTION

The design and development of definite bioinorganic interfaces with specific properties have gained importance in modern technology because of their effective use in various sectors from implantology to biosensors and bioelectronics. In order to better understand such hybrid materials at the atomic level and to disclose local features which could be fundamental in more targeted applications, much recent experimental and theoretical efforts have focused on amino acids. These small molecules, which are the main constituents of peptides and proteins, have been chosen as model systems for surface decoration essentially because their conformation, binding interactions, and dynamics can be studied more comprehensively in relation to complex biomolecular structures.

The adsorption of some natural amino acids on titanium, or rather, on titanium dioxide (TiO₂), which is the layer naturally formed at the interface with any environment containing water, has been studied in detail from both experimental and theoretical points of view; see ref 1 and references therein. This is because, for instance, a possible way of improving the testified biocompatibility of this inorganic layer, due to its low corrosion rate and solubility, is through the addition of molecular entities which could be recognized by regenerative agents. However, in addition to its presence as a natural coating layer in titanium-based materials, TiO₂ can also be added to paint, plastics, artificial fibers, paper, rubber, dye-sensitized solar

cells, and even certain food to enhance their white color and brightness (dairy products, candies, etc.).²

Most of the studies regarding the adsorption of amino acids on TiO₂ have been focused on those residues which are part of recognizable motifs of large macromolecular structures. Cysteine (Cys) belongs to this class of residues. Indeed, as already observed by other authors,^{3–5} stable functional monolayers of biomolecules containing Cys can be formed on different types of inorganic supports thanks to the high affinity that sulfur manifests for these substrates. As a consequence, the adsorption behavior of Cys on TiO₂ is particularly interesting not only because of its three functional groups that can act as multiple anchor points to the surface but also because of the different protonation states of the molecule at the interface. The relative abundance of various cysteine species is essentially dependent on the pH in an aqueous solution but can be also related to particular intermolecular interactions in the gas phase. For the aforementioned reasons, the characterization of the mechanisms which regulate cysteine adsorption on TiO₂ is challenging and the limited number of investigations on this interface has left several open questions. For example, whether the thiol group takes part in the adsorption process remains a matter of debate.

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As far as theoretical investigations are concerned, a very interesting and complete computational study of the adsorption of L-cysteine on $\text{TiO}_2(110)$ in an aqueous environment was performed by Langel and coworkers.⁶ The authors employed quantum molecular dynamics simulations to disclose the behavior of the molecule on partially hydroxylated rutile (100) and (110) surfaces. Perfect and defective (oxygen vacancy) interfaces were considered as well. From the results of these calculations it was estimated that the molecule had weak direct interactions of the carboxyl and amino groups with the surface but a strong bonding interaction between the deprotonated thiol moiety and a Ti atom of the substrate. This occurred more easily in the case of the perfect surface, whereas the insertion of the S atom into the oxygen vacancies of the defective layer was seldom detected. Starting from the oxygen zwitterion, namely, the form with COO^- and NH_3^+ groups, the authors observed a very quick conversion to the neutral species followed by the formation of the sulfur zwitterion. This took place through a proton transfer from the thiol to the amino group, which in turn was followed by another proton transfer from the carboxyl group to a bridging O atom of the surface. The S–Ti distance was found to be in the range of 2.6–2.9 Å, suggesting that the insertion of the sulfur atom in the defect point was hindered by the mismatch of Ti–O and Ti–S bond lengths. In a more recent study,⁷ where Car–Parrinello dynamics simulations were carried out for the aqueous solution of cysteine on rutile, the same research group confirmed that the weak adsorption of cysteine on TiO_2 is strongly enhanced by the insertion of the sulfur atom into an oxygen vacancy of the defective layer. The authors also noted that while on the perfect surface the weak Ti–S bond (2.4 Å, 40 kJ/mol) was realized only by a previous proton transfer from SH to a bridge oxygen O_{br} , the insertion of S in the defect point could occur for both the deprotonated and protonated thiol groups. In the latter case, the H atom was positioned between S and Ti. According to their simulations, the stability of the adsorbate was mostly due to the S–Ti interaction, which in the case of the defective surface was about 300 kJ/mol, but it was also supported by hydrogen bonding of the amino group to the surface oxygen atoms. However, they concluded that the adsorption on nonhydroxylated surfaces was very weak.

An interesting theoretical study on the adsorption of cysteine on rutile has been very recently published by Muir and Idriss.⁸ The authors used DFT geometry optimization to characterize a number of cysteine binding modes and to evaluate the adsorption energy, finding that many stable structures within a relatively small energy range are feasible. Geometry optimization is a valid and largely adopted approach for studying adsorbates but provides a static picture of the system at $T = 0$. Most of the time, only a small number of adsorption geometries, suggested by physical intuition and often limited by symmetry constraints, can be investigated, and the model system generally includes a single molecule per surface. Such limitations do not allow us to represent the effects of the temperature and of intermolecular interactions, which can be very relevant in modeling the adsorption process. Molecular dynamics simulations at realistic temperatures are, according to our experience,⁹ more powerful for understanding surface adsorption and reactivity. They let the system evolve from a generic, possibly random, configuration, exploring a very large set of configurations by thermal motion without constraints. Our present molecular dynamics calculations confirm this point of view, showing, in agreement with the static calculations,⁸ that

at room temperature the possible adsorption geometries of a small but complex molecule such as cysteine are several and of comparable stability in the sense that they are equally represented in the dynamics trajectory.

Recent X-ray spectroscopic investigations were able to provide evidence of the presence of different chemical forms of the adsorbate even though they were conducted on films deposited from the gas phase under dry conditions.^{10–12} Surprisingly, these studies showed that the thiol group of cysteine was more acidic than the carboxylic group and that the thiolate anion could be present even in the gas phase. In aqueous solution both the anionic and zwitterionic forms of cysteine are, of course, stabilized by the interaction with water. Some experimental IR spectroscopy studies were found in favor of the thiolate group,¹³ whereas other similar measurements¹⁴ supported the presence of the carboxylic anion. The XPS measurements on a thick film of cysteines deposited on TiO_2 at low temperature (100 K) focused mostly on the S 2p spectrum, where two doublets are clearly visible, and led to an estimation that the thiol group is deprotonated in about half of the cysteines in the sample while only 13% of the carboxylic groups are deprotonated. Considering that DFT calculations for the geometry optimization of cysteine in a small cluster of water molecules¹⁵ predicted that both the neutral and the oxygen zwitterionic forms were energetically more favorable than the sulfur zwitterion, the dominance of this last species in thick films was attributed to the unusual growth procedure adopted for this sample. On the contrary, XPS spectra collected from submonolayer to multilayer films grown at room temperature¹⁶ on perfect and defective rutile surfaces showed a very complex adsorption scenario with different cysteine species bound to the surface. The suggested interpretation of the data was that the main binding arrangement is the one where the deprotonated carboxylic groups of the molecules interact with the 5-fold-coordinated Ti atoms. A second binding mechanism was tentatively attributed to the dissociative interaction between the thiol groups of the cysteines and the bridging oxygen vacancies of the defective surface. It was assumed that the amino group remains neutral in the submonolayer regime¹⁶ but able to receive a proton when the coverage is increased. However, regarding the bonding mode of the amino group to the surface, calculations gave controversial descriptions. Some of them predicted that adsorption geometries with protonated amino groups are more stable than those with neutral amino groups,¹⁷ but others opposed this picture.¹⁸

The aim of the present investigation is to describe at the atomic level the reactive adsorption of cysteine on the TiO_2 rutile (110) interface by simulating both the adsorption process and the X-ray photoemission spectra (XPS). The study will provide useful information on the mechanisms connected to cysteine–surface binding and on the different chemical species present on the interface. A modeling approach recently developed and applied to several bioinorganic interfaces,^{19–23} will be used to characterize the adsorption of the molecule on perfect and defective $\text{TiO}_2(110)$ surfaces by taking into account its reactivity (intra- and intermolecular proton transfer as well as hydrogen release to the surface) and dynamics. The simulations are based on reactive molecular dynamics calculations²⁴ (RMD) at room temperature using force fields developed by quantum chemical calculations on model systems.²⁵ As a support for the assignment of the measured XPS spectra, calculations of the core binding energies of O 1s, N 1s, and S 2p for a number of adsorbate geometries, extracted

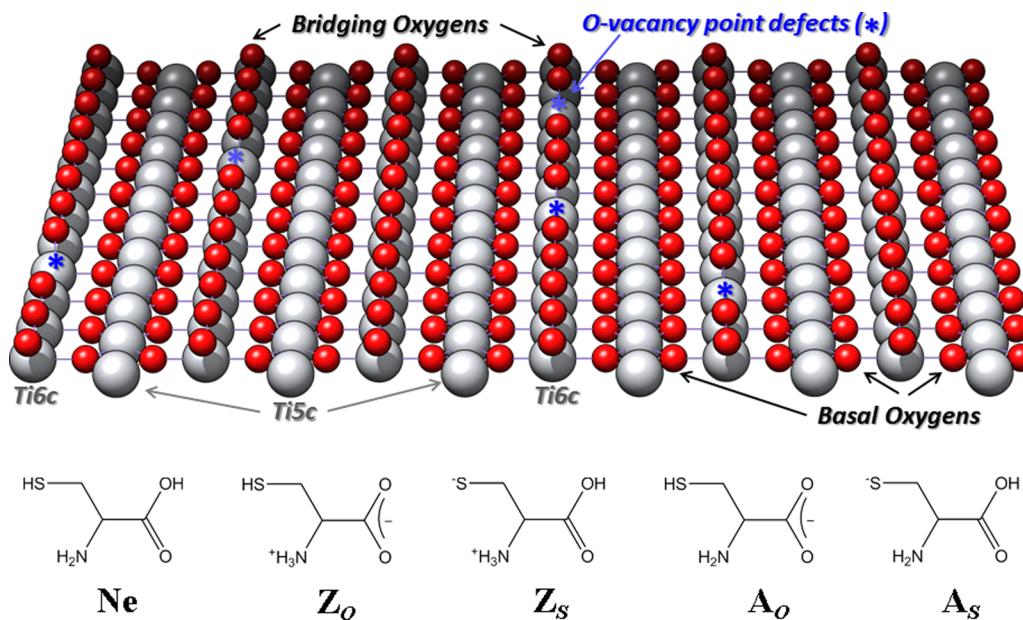


Figure 1. (Top) Rutile (110) defective surface model. Perspective view of the surface showing the various sites available for cysteine adsorption: 5-fold-coordinated Ti, bridging oxygens and defects (missing bridging oxygens). In the perfect surface no vacancies are present. (Bottom) Cysteine species: neutral (Ne), oxygen zwitterion (Z_O), sulfur zwitterion (Z_S), oxygen anion (A_O), and sulfur anion (A_S).

from the molecular dynamics, were carried out by means of Δ SCF (self-consistent field) calculations.

COMPUTATIONAL DETAILS

Simulation of the Adsorption Process by Reactive Molecular Dynamics. In order to model the adsorption of cysteine molecules on TiO_2 , two kinds of surfaces were considered: the most stable perfect $TiO_2(110)$ surface and a defective $TiO_2(110)$ surface that, in agreement with the experimental study,¹⁶ contains approximately 7% bridging oxygen defects. The structure of the $TiO_2(110)$ surface is shown in Figure 1 (Ti atoms are gray and oxygen atoms in red), where the characteristic sites of this surface are pointed out, namely, the 5-fold-coordinated Ti atoms (Ti5c) that together with the basal oxygens form the basal plane and the bridging oxygens that are above this plane and join a couple of Ti atoms (Ti6c) that then become 6-fold coordinated. The defective surface is characterized by missing (stars) bridging oxygens. Different forms of cysteine were taken as starting structures of the dynamics simulations: the neutral form (Ne) and two zwitterionic forms (Z_O , Z_S) where the positive charge is on the NH_3^+ group while the negative charge is, alternatively, on the COO^- or S^- group. For each zwitterionic–Cys–surface system, different conformers of cysteines have been selected as starting points according to previous investigations.²⁶

The geometry of neutral and zwitterionic forms of cysteines, shown in Figure 1, has been optimized at the DFT-B3LYP/6-31G(d) level of theory using the GAMESS²⁷ package. The optimized conformations were used to build three different clusters made of 50 cysteines each, where all the molecules adopted one of the three forms mentioned above. These aggregates were put on top of the perfect (S_p) and defective (S_d) rutile (110) surfaces, in random orientation, at an average distance of about 7 Å. We adopted this procedure, already successfully employed in our previous similar investigations, because bringing cysteines onto the surface molecule by molecule could be unphysical in the case of vapor deposition of molecules that can easily form a hydrogen-bonding network. It is quite often observed that this kind of deposition can form second or even third layers of adsorbate before the monolayer is completed. In the nanodroplet procedure, the molecules are initially bound to each other, but when they come under the influence of the surface, their interconnecting hydrogen-bond network is partially disrupted and adsorption takes place. The surfaces were modeled by a five-layer slab with a size of about 37 and 35 Å in

the x and y directions, respectively. The height of the simulation box was fixed at 75 Å. Periodic boundary conditions were applied in all directions during the dynamics.

Reactive molecular dynamics (RMD) of the built models was performed by means of the ReaxFF code implemented in the Amsterdam density functional (ADF) package.²⁴ The rutile slab and the cysteine droplet were equilibrated separately by slowly heating both of the systems from 10 to 300 K in about 25 ps. Then, the equilibrated configurations were combined by placing the relaxed droplet close to the relaxed titanium dioxide slab. The important role of surface distortion in the electron-transfer process between TiO_2 surfaces and adsorbates, as pointed out by very recent studies in the field of photocatalysis, should be stressed.^{28,29} The dynamics of the resulting configuration was finally simulated at 300 K in order to allow the adsorption of the cysteines. After 10 ps most of the molecules had established contacts with the surface. Then configurations were sampled for about 1 ns. All RMD production simulations were performed at $T = 300$ K in the NVT ensemble using the Berendsen thermostat³⁰ with a relaxation constant of 0.1 ps. The equations of motion were solved with the Verlet leapfrog algorithm³¹ using a time step of 0.25 fs. System configurations were saved every 0.5 ps of the total simulation.

Calculations of Core Electron Binding Energies. N 1s, O 1s, and S 2p core binding energies were calculated as the difference between the total electronic energy of the ground state and that of the relaxed core-ionized state obtained by all electron calculations on a cluster containing one adsorbed molecule and a fragment of the slab containing the Ti and O atoms more directly interacting with the cysteine. In order to sample a relatively small number of adsorbate structures, the geometry of the system was analyzed during the last 900–1000 ps interval of the simulation by the g_cluster code (a GROMACS tool³²). The most relevant structures were then chosen by considering both the conformation and the adsorption mode, and a cluster model was extracted from each of such adsorbate structures, as specified above. With a cutoff value of 5 Å for the distance of slab atoms from the ionization site, each final model cluster for the core binding energy calculations includes 1 cysteine and 10 TiO_2 units to represent the surface. The ionization potentials were calculated using the DALTON code³³ with the AhlrichsVTZ basis set in the Δ SCF approximation. In the following figures, each BE is presented as a bar (intensity 1 in arbitrary units) that is convoluted (full line in the figures), with a Gaussian function of $fwhm = 1$ eV to simulate both the

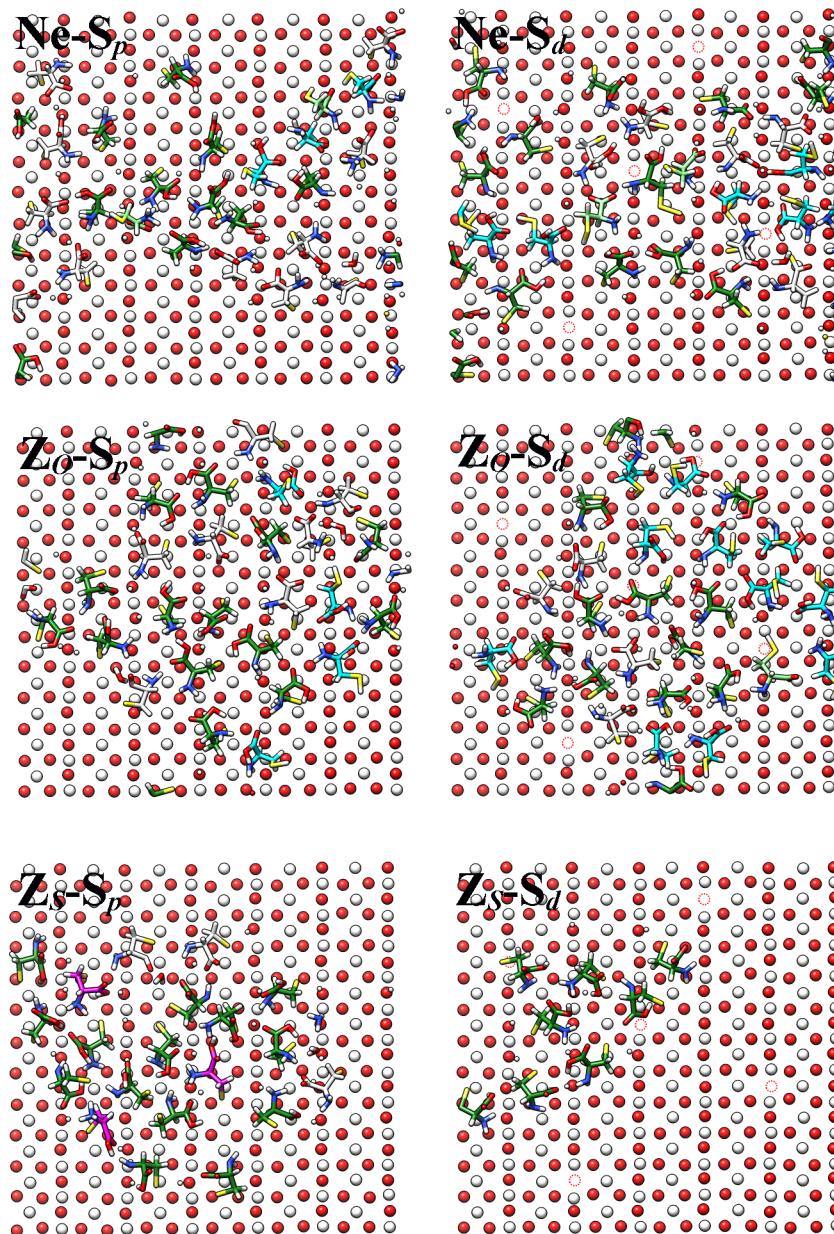


Figure 2. Top view of the final configurations of cysteines in the first layer over the surface from different dynamics simulations. Balls represent atoms of the rutile surface: red for O and white for Ti; red dashed balls represents missing bridge oxygens of the defective surface. A stick representation is used for cysteine atoms: red for O, blue for N, and yellow for S. The color of C atoms also shows the form of the cysteine molecule: A_S in dark green, A_O in light green, Ne in cyan, Z_S in magenta, and other (Table 1) in white. The number of cysteines of each species can be found in Table 1.

finite experimental resolution and the vibrational envelope. In the case of the S 2p spectrum, each bar, before the convolution procedure, was empirically split in two contributions with intensities of $\frac{1}{3}$ and $\frac{2}{3}$ and an empirical energy splitting of 1.2 eV in order to reproduce the effect of the spin-orbit splitting not explicitly included in our calculations.

RESULTS AND DISCUSSION

Simulations Analysis. The examination of the data sampled during the reactive simulations is essentially focused on two different aspects of the adsorption process, namely, the kinetics and the reactivity of the molecules at the surface. As already described in the previous section, the cysteine molecules were initially set in ordered layers far from the surface so that, in principle, all of them had the same probability of interacting with each other and approaching the

surface during the first 25 ps of the simulation time. Considering earlier studies on other amino acids,³⁴ this time period is sufficient to allow the molecules to interact with each other reactively, that is, to exchange protons between the terminus regions as well as their side chains before interacting with the surface. The influence of the interface is weakened by self-interactions of the molecular species, making the adsorption process appear quite slow. Indeed, the molecules remain tightly interconnected through a dense network of hydrogen bonds and by frequent hydrogen exchanges. The final coverage obtained after 1 ns is in the range of 50–60% in Ne-S_p, Ne-S_d, Z_O-S_p, and Z_O-S_d models (Figure 2). The coverage is defined here as the ratio between the number of occupied O_{br} and Ti atoms and their total number in the first layer of the

surface. It can be noted that the main molecular species in the adsorbed layers are basically the same, independent of the initial chemical composition of the model system: As and Ne cysteines, as shown in Table 1 and Figure 3. For the simulations

Table 1. Chemical Composition of the Adsorbed Layer in Different Model Simulation by RMD^a

model	Ne	Z _S	Z _O	A _S	A _O	CA	other ^b	total
Ne-S _p	3			12	2		11	28
Ne-S _d	6			16	2		6	30
Z _O -S _p	4			15			8	27
Z _O -S _d	11			13	1		3	28
Z _S -S _p		3		14			3	18
Z _S -S _d				8				8

^aSee the text for labelling. ^bOther species including double anions and cysteines with strong hydrogen bonds and stretched C–O bonds.

starting from samples of either neutral cysteines or oxygen zwitterions, we obtain rather similar chemical compositions after 1 ns. In the case of the Z_S dynamics, after the same time,

the main differences with the other simulations are a much lower concentration of neutral cysteine and a higher concentration of sulfur anions. This can be ascribed to the peculiar stability of the S[–] group that does not easily accept a proton, in agreement with the experimental evidence that the acidity of the thiol group is much higher than that of the carboxylic group³⁵ even in the gas phase. This result suggests that only longer simulation times would have allowed us to obtain fully convergent values of the percentage of the different cysteine species independently of their starting orientations and geometries. However, after 1 ns of simulation, the percentages of the deposited species show a clear tendency to remain constant, and this was considered sufficient for the aim of the present investigation where the dynamics calculations are mainly intended to guide in the selection of highly probable adsorbate configurations for the simulation of the XPS spectra.

Proton Transfer. In order to quantify the chemical activity among the cysteines and among the cysteines and the rutile surface, we present in Table 2 the results of an analysis of the dynamics trajectories pointing out the proton transfers occurring in the different samples.

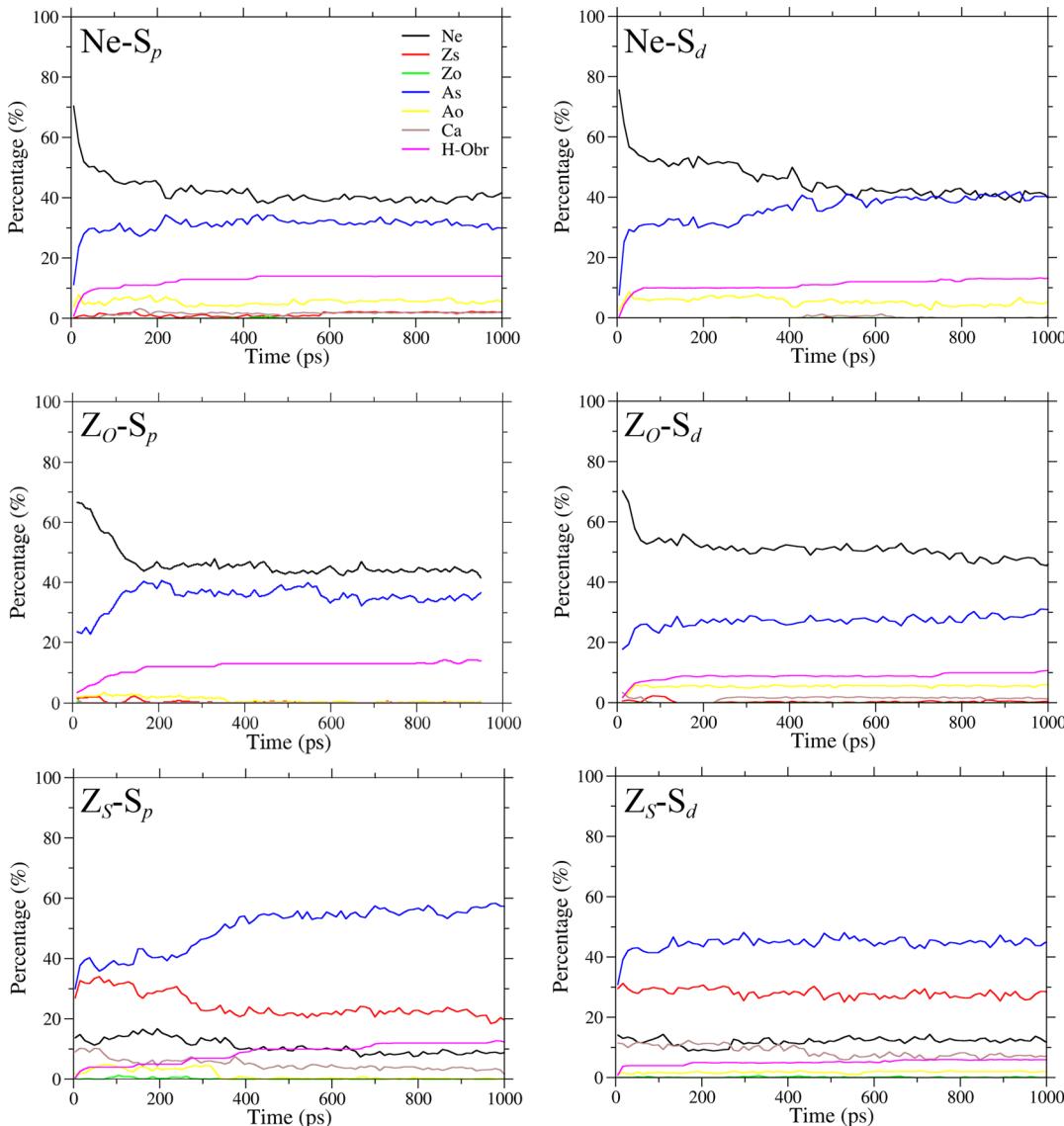


Figure 3. Percentage of cysteine species and of H adsorbed on bridge oxygens in different simulations vs time.

Table 2. Proton Transfer in RMD Simulations of 50 Cysteines during the Simulations^a

in the gas phase						
transfer\	Ne	Z _O	Z _S			
N → N			1			
N → O		47	15			
N → S			2			
O → N						
O → O	1		1			
O → S	1		15			
S → N						
S → O	1	2				
S → S						
on the rutile surface						
transfer\	Ne-S _p	Ne-S _d	Z _O -S _p	Z _O -S _d	Z _S -S _p	Z _S -S _d
N → N	2		1	1	1	1
N → O				1	4	2
N → S						
O → N	3	1	1	2	3	
O → O	4		1			1
O → S			1			
S → N			1	1		
S → O	2	6	2	2	1	
S → S				1		
N → surf			3	4	13	6
O → surf	7	10	3	3		
S → surf	21	17	20	13	9	5

^aSee the text for labelling.

As shown in Table 2, different initial forms of cysteine and different chemical compositions of the sample lead to quite different patterns for the proton transfer during the reactive dynamics.

In the first part of the dynamics, when cysteines in the gas phase get clustered before interacting with the surface, an intense proton transfer occurs in the case of the Z_O and Z_S samples; this is pointed out in the top part of Table 2. We observe in 49 Z_O cysteines intramolecular proton transfer to the COO⁻ group from the NH₃⁺ group (42 times) or the SH group (2 times). In the case of the Z_S sample there is a more complex proton transfer with, mainly, 15 O → S transfers followed by 15 N → O transfers, with the final result of having the conversion of 15 Z_S cysteine in 15 Ne cysteines. In the simulation starting from neutral cysteines Ne, the proton transfer within cysteines is much less evident than in the simulations starting from the zwitterions. This is in line with the fact that the neutral form is the most stable one in the gas phase, which is also confirmed by the large conversion from the Z_O to Ne form (top of Table 2) observed in the Z_O dynamics. However, it should also be noted that in the time range of the present Z_S dynamics the proton transfer to the S⁻ group is only partial, supporting the recent finding¹¹ that such an unconventional zwitterionic state of cysteine can also be stable in the gas phase.

In the following part of the dynamics when the cysteines come in closer contact with the surface (bottom part of Table 2), the multistep character of proton transfer is even more emphasized and hydrogens are also transferred from the cysteine active sites to the surface. This is essentially a transfer to the bridge oxygen atoms of the slab, and in the time range of our simulations, it is an irreversible step. For instance, in the simulation starting with Z_O cysteines on the S_p surface, 26

protons are donated to the surface. Twenty of them are coming directly from the SH group and 6 from the NH₃⁺ group, while 3 protons (2 coming from S and 1 coming from an O of a second cysteine) are first passed to an oxygen atom and then transferred to the surface. Apart from the Z_S-S_d case we see that at least 20 protons move to the surface in any simulation, mostly from the SH group that apparently shows more acidic character than the COOH group. It should also be observed that the interaction with the substrate strongly affects the proton redistribution inside the cysteine cluster. For instance, at equilibrium in the gas-phase Z_S cysteine sample, the number of protons passed from nitrogen to oxygen and from oxygen to sulfur is the same, while in the Z_S-S_p and Z_S-S_d simulations, where the surface and the deposited cysteines interact, most of the protons adsorbed onto the top TiO₂ layer originate from the breaking of N-H and S-H bonds.

It should be stressed that the data presented in Tables 1 and 2 as well as the snapshots in Figure 2 refer to the last frame of the 1 ns trajectory obtained from each dynamic. They are not intended to represent the composition of the different samples but provide only a picture of the intense proton-transfer activity.

Computed Core Binding Energies. The present theoretical study is aimed at supporting the rationalization of the observed XPS spectra of cysteine on titanium dioxide¹⁶ in terms of the geometrical and electronic structure of the adsorbed species. From the ReaxFF simulations, a few adsorbate structures have been extracted and classified according to the connections of the cysteine molecules to the surface. The most representative structures are shown in Figure 4. These model clusters extracted from the adsorption simulations, formed by 1

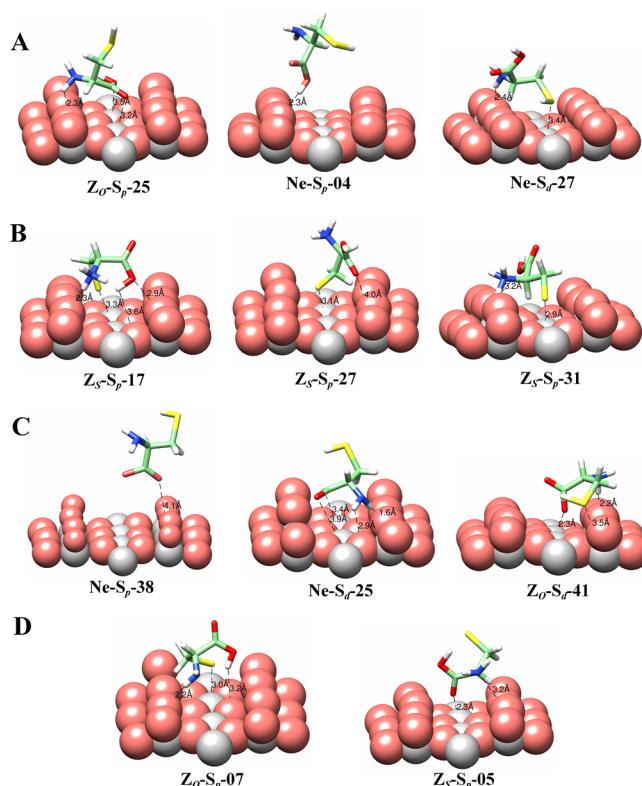


Figure 4. Most representative structures for cysteine adsorbed on a perfect (S_p) or defective (S_d) rutile surface. (A) Ne, (B) Z_S, (C) A_O, and (D) A_S.

cysteine molecule and 10 TiO₂ units, have been employed in the all-electron calculations for O 1s, N 1s, and S 2p core binding energies (BE) of the adsorbed cysteine.

N K-Edge. The computed XPS spectra of N 1s in neutral cysteine adsorbed in different geometries are displayed in Table S1 (in Supporting Information) and Figure 5 together with that

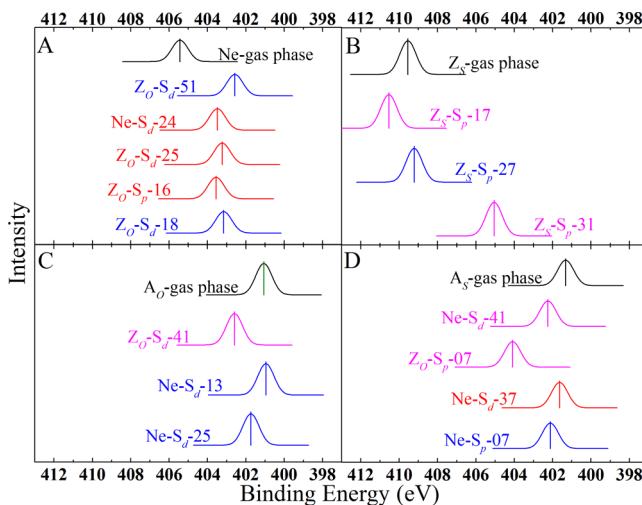


Figure 5. Computed N 1s spectrum of cysteine in the gas phase compared to that for different adsorption structures (Figure 4) and different cysteine species: A (Ne), B(Z_S), C(A_O), and D(A_S). The line color of the spectra represents the number of contact points between the cysteines and rutile surface: red for 1, blue for 2, and magenta for 3.

of the isolated molecule (gas phase). In the Ne as well as in the A_S and A_O forms of cysteine, the hydrogen bonding of the NH₂ group to the bridge oxygen of the surface (Z_O-S_d-16, Z_O-S_d-25, Ne-S_d-24, Z_O-S_p-35, Ne-S_d-13, Ne-S_d-04, Z_O-S_p-25, Z_O-S_d-21, Z_O-S_d-51, Z_O-S_d-18, Ne-S_d-23, Ne-S_d-27) provides electron charge for a more effective screening of the core hole; therefore, the N 1s BE decreases in the adsorbate with respect to that of the molecule in the gas phase. Depending on the adsorption mode, the energy shift (Figure 5A) is estimated to be in the range of -1.5 to -3 eV with an average value of the BE of about 403.3 eV. The cysteines directly bound to the surface by an NH₃⁺ group (Z_S-S_p-31) instead show values of the N 1s BE that are more differentiated, depending on the adsorption mode. When the protonated amino group is away from the surface (Z_S-S_p-17, Z_S-S_p-27), the value (about 410 eV) is, as could be expected, very close to the one estimated for zwitterions Z_O and Z_S in the gas phase, as shown in Figure 5B. A strong interaction of cysteine by a proton of the NH₃⁺ group with two bridge oxygens, as observed in the adsorption structure (Z_S-S_p-31), leads instead to a large negative chemical shift (Figure 5B) with an estimated value for the N 1s BE of about 405 eV. In this adsorbate geometry the H bond between H in NH₃⁺ and O_{br} is as short as 1.08 Å, while the N–H bond length for the adsorbed hydrogen is stretched to 1.42 Å, which means that one proton is almost transferred to the surface. Our present calculations then predict that the difference in the core IP between the amino group and the protonated amino group is reduced when the molecule interacts with the rutile surface. The N 1s chemical shift that for cysteine in gas phase is as large as +5 eV is largely reduced to about +1.7 eV when the molecule is adsorbed. This is due to a hydrogen-bonding mechanism that almost realizes a proton transfer from the NH₃⁺ group to the

surface. This prediction agrees with the experimental chemical shift of +2 eV measured by Ataman and coworkers¹⁶ for submonolayer films of cysteine on rutile. Let us remind the reader that the theoretical values of ionization potentials cannot be directly compared to the experimental ones for adsorbates because of the missing work function that makes the theoretical results more directly comparable to gas-phase experimental measurements. A comparison of the chemical shifts is evidently not affected by this drawback.

When the cysteine is adsorbed in anionic forms A_O and A_S, our calculations (Figures 5C,D respectively) predict in general a positive chemical shift for the N 1s BE of the adsorbed molecules compared to that of the same forms in the gas phase. This can be rationalized as due to an electron relaxation from the charged molecule to the surface. This effect is strongly dependent on the adsorption mode and essentially reflects the efficiency of such charge transfer as a function of the number of contact points and the involvement of the amino group; the largest positive chemical shift is observed in Figure 5D for A_S cysteine in the Z_S-S_p-07 structure where the molecule interacts with the surface with all its chemical groups (Figure 4D). The values of the N 1s BE for the anionic forms cover a large range with an average value of about 402.5 eV that is lower than that predicted for the cysteine adsorbed in the neutral form.

O K-Edge. Also for the computed O 1s XPS spectra in Figure 6 the presence of the slab brings more electrons to the

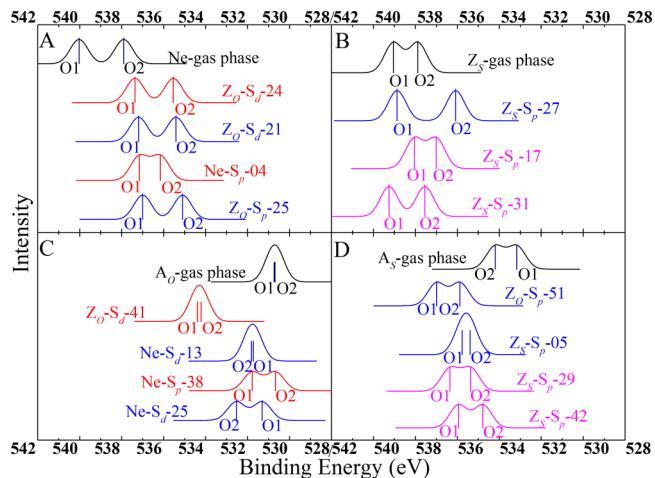


Figure 6. Computed O 1s spectrum of cysteine in the gas phase compared to that for different adsorption structures (Figure 4) and different cysteine species: (A) Ne, (B) Z_S, (C) A_O, and (D) A_S. The line color of the spectra represents the number of contact points between the cysteines and the rutile surface: red for 1, blue for 2, and magenta for 3.

uncharged molecule. In the case of cysteine adsorbed in the neutral and zwitterion forms, this feature leads to a lowering of the core BE in comparison to the molecular species in the gas phase. In the case of the adsorbed anionic form, a general shift to higher energy is instead observed, for the same reason as previously discussed for the N 1s spectra. The carboxyl group of an amino acid in the neutral form contains two oxygen atoms (C=O, OH) that are not chemically equivalent; this is reflected in two well resolved peaks in the O 1s photoemission spectrum. The chemical shift observed in the XPS measurements in the gas phase, where the most stable form of an amino acid is the neutral one, is about 1.8 eV.³⁶ In the carboxylate

group, obtained by deprotonation, the two oxygen atoms are basically equivalent and the chemical shift is reduced to almost zero, leading to a single unresolved band. This effect is easily reproduced by the calculation, as can be seen from a comparison of the gas-phase spectra shown in Figure 6A,C. Apart from the contribution of the surface oxygens (≈ 530.5 eV) that fades relatively with increasing coverage, the O 1s spectrum measured for cysteine on rutile shows¹⁶ an unresolved band (≈ 532.0 eV) with a width from 1.61 to 1.97 eV (Table 1¹⁶) that is attributed to the carboxylate group. In a pioneering XPS investigation on several amino acids adsorbed in solution on the rutile surface,³⁷ Schmidt and Steinemann estimated a large chemical shift (≈ 3 eV) between the substrate peak and that due to the COO^- group. It should also be observed that the presence of the substrate and the different modes of interaction of the carboxylate group with the surface can remove the substantial equivalence of the two oxygen atoms assumed for the species in the gas phase. Our calculations (Figure 6C) predict that because of the monodentate bonding of the COO^- group, what is achieved in the adsorption geometry $\text{Ne-S}_\text{p}-38$ (Figure 4C) or because of a defect of the surface as in the case of the adsorbate $\text{Ne-S}_\text{d}-25$ (Figure 4C), a relative chemical shift for the two oxygen atoms of the carboxylate group of about 1 eV can be obtained. On the other hand, the formation of a hydrogen bond between the intact carboxyl group and O_{br} , as observed in the structures $\text{Ne-S}_\text{p}-04$ (Figure 4A) and $\text{Z}_\text{s}-\text{S}_\text{p}-17$ (Figure 4B), gives origin to an electronic transfer from the surface to the molecule with a consequent decrease in the chemical shift of the two nonequivalent oxygen atoms that may be reduced to about 1 eV and then becomes compatible with the width of the experimentally unresolved band. A similar decrease is also predicted in the case of the COOH group of adsorbate $\text{Z}_\text{s}-\text{S}_\text{p}-05$ (Figure 4D) due to the strong interaction of the C=O oxygen atom with a titanium atom. The comparison between experiment and theory then leads to an assignment of the broad band in the O 1s spectrum as mainly due to the presence of the carboxylate group in the adsorbate, but the presence of the carboxyl group, intact but strongly interacting with the surface, cannot be completely excluded. This has also been suggested for cysteine adsorbed on Cu(110)³⁸ as an explanation of the higher BE tail of the O 1s spectrum.

S K-Edge. Because of the spin-orbit coupling, the S 2p photoemission spectrum presents two generally resolved peaks of intensity in a ratio of 1:2 and a split in energy of about 1.2 eV. In the case of cysteine on rutile,¹⁶ the measured S 2p spectral profile has been deconvoluted with two bands separated by a chemical shift of about 2 eV. While the band at high BE is easily assigned to the ionization of the sulfur in the thiol group (SH), the interpretation of the lower-energy contribution is not unambiguous. Its intensity is comparable to that of the SH band to very low coverage but decreases rapidly when the coverage tends to a nominal monolayer; this is compatible with a spectral signal corresponding to a species present mainly on the surface. The nature of this chemical form of cysteine and its interaction with the surface is not clear, however. It could not even be excluded¹⁶ that it may be due to atomic S obtained by the breakage of the C–S bond, despite the cleavage of a strong covalent bond at room temperature being quite unlikely. The results of our calculations of the S 2p BE for different chemical forms of cysteine and different geometries of adsorption on rutile are shown in Figure 7. The values obtained for the two forms (Ne, A_o) shown in Figure

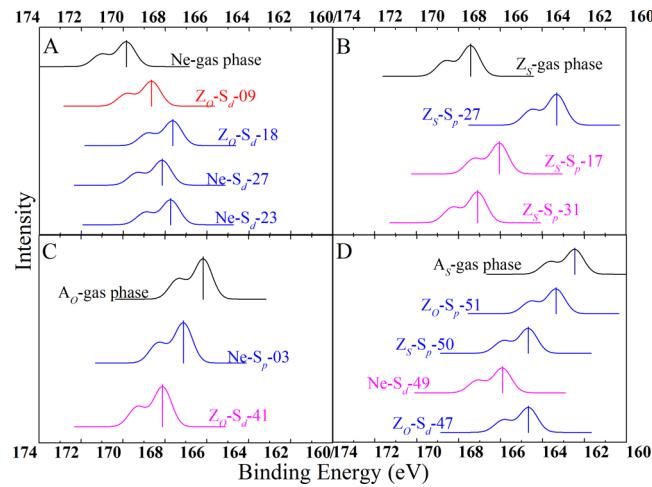


Figure 7. Computed S 2p spectrum of cysteine in the gas phase compared to the one for different adsorption structures (Figure 4) and different cysteine species: (A) Ne, (B) Z_s , (C) A_o , (D) A_s . The line color of the spectra represents the number of contact points between the cysteines and rutile surface: red for 1, blue for 2, and magenta for 3.

7A,C, respectively, are collected in a relatively small energy range with an average value of about 168 eV. In the case of species (Z_s , A_s) in which the thiol group is deprotonated, (Figure 7B,D), the BE shows a larger dependence on the adsorption geometry with a mean value of 164.5 eV. All of these adsorbates show a direct interaction of S^- with an atom of Ti ($R_{\text{Ti}-\text{S}} \approx 3$ Å). Two of them, namely, $\text{Z}_\text{s}-\text{S}_\text{p}-17$ and $\text{Z}_\text{s}-\text{S}_\text{p}-31$ (Figure 4B), bind to the surface also with the other functional groups of cysteine, in particular, by a strong interaction between NH_3^+ and the bridge oxygens. This leads to a sensibly higher N 1s BE ≈ 166.5 eV, corresponding to a chemical shift of ≈ 1.5 eV. The calculations therefore appear to predict a large spread of the chemical shift between SH and S^- , with values depending on the interaction mode, in agreement with the large width of the low-energy band obtained by the deconvolution of the experimental spectrum. The maximum of this broad band corresponds, according to calculations, to cysteine in Z_s form and a multipoint interaction with the surface.

Moreover, the reactive dynamic calculations for the sample of 50 cysteines on the surface partially defective for missing O_{br} 's, show that S^- can interact also with the two Ti atoms exposed at the location of the defect. This is realized in adsorbates s1, s2, and s3 in Figure 8. In this case, $R_{\text{Ti}-\text{S}} \approx 2.8$ Å, a distance that is much larger than $R_{\text{Ti}-\text{O}_{\text{br}}} = 1.95$ Å in the perfect surface, as could be expected for the larger size of the S atom compared to that of O. Calculations for this type of adsorbate provide an average S 2p BE of 166.4 eV and a corresponding chemical shift of 1.6 eV compared to the BE of the SH group. The low-energy broad band obtained by deconvolution of the complex experimental spectrum¹⁶ may then be generally assigned to cysteines with the thiol group deprotonated that directly interact with an atom of Ti. It should be added that the reactive dynamics calculations show that in the adsorbed layer (28–30 cysteine molecules in most cases), the percentage of A_s is between 50 and 100% in our six simulations (Table 1), while considering the full set of cysteines, i.e., also for the second and third layers formed in the three-dimensional adsorption process, the percentage reduces to 30–50%. Anionic-sulfur cysteines are mainly present in the first adsorbed layer; this

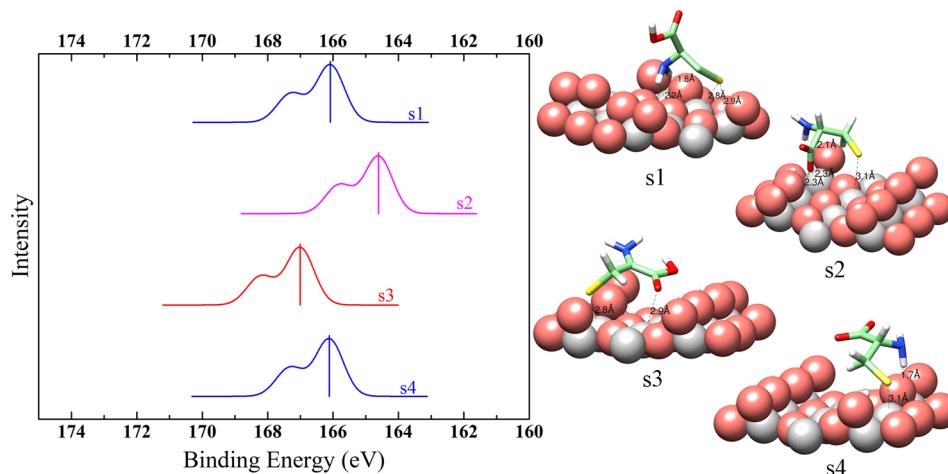


Figure 8. Computed S 2p spectrum of cysteine adsorbed near the defective bridge oxygen and their structures. The line color of the spectra represents the number of contact points between the cysteines and rutile surface: red for 1, blue for 2, and magenta for 3.

results rationalize the experimental finding that the peak of lower BE seems to disappear with the increasing cysteine coverage.

CONCLUSIONS

Motivated by the growing importance and development of bioinorganic interfaces with specific properties and the need to understand the basic structure–property relations of such interfaces, we have in this work explored in depth the binding of a prototype bioinorganic molecular adsorption system, namely, cysteine on perfect and defective $\text{TiO}_2(110)$ surfaces. We have used molecular dynamics with reactive force fields together with analysis of X-ray photoelectron spectra, a combination that has the potential to disclose the important features of this interaction and which is in line with a general philosophy to validate the outcome of structural simulations with computations of observables obtained by spectroscopy.

Regarding the character of the bonding itself, we find in accordance with the experimental work of Ataman et al.¹⁶ that the deprotonated carboxyl group provides the main contact point of cysteine to two Ti atoms. We observe, however, that this is not the only contact and that multisite adsorption is energetically more advantageous. In fact, as previously noted for other amino acids adsorbed on metal and metal oxide surfaces,^{26,39} the energy loss due to the deviation of the COO^- group from the perpendicular orientation with respect to the surface is more than compensated for by the interaction of the amino and sulfur groups that can be realized in a tilted geometry. Moreover, it is found that it is not strictly necessary to assume the deprotonation of the carboxylic group in order to assign the broad band in the O 1s spectrum. The present core electron BE calculations show that the chemical shift for the two oxygens of an intact carboxylic group interacting with two Ti atoms can be too small to be experimentally resolved.

We find that the fact that NH_3^+ is formed by intermolecular proton transfer in the 3D growth of the adsorbate and that it does not interact with the surface is not in agreement with a careful analysis of the N 1s photoelectron spectra. Indeed, our calculations show that the measured chemical shift with NH_2 is too large to be caused by H bonding but also too small for a free NH_3^+ group. The interaction of such a group with the bridging oxygens of the surface, which is observed in our simulation of the adsorption dynamics, is predicted to lead to a

chemical shift of the N 1s BE compatible with the measured one. The molecular dynamics simulation results also show that the NH_3^+ group interacts more easily with the surface as the coverage increases. This is in line with the data found in other amino acids/metal simulations where the molecules move from a standing orientation to a bent arrangement lying flat on the surface.

Regarding the open question on the reactivity of the thiol group and its involvement in the adsorption process, we conclude that the thiol group can also be deprotonated on the perfect surface. The maximum in the experimental low-energy band can be correlated to the interaction of S^- with Ti atoms in the higher layer but also with Ti atoms exposed for the lack of an O_{br} in the defective surface. In this last case the S atom cannot exactly take the place of the missing oxygen due to a different atomic size, and the resulting S–Ti length is predicted to be almost the same in the two cases.

The results of this investigation support the view that a combined approach of state-of-the-art reactive force field molecular dynamics and X-ray photoelectron spectroscopy is promising and effective for studies of molecular hybrid systems made of biomolecules adsorbed on inorganic materials. Our aim is to capitalize on this approach to address problems concerning such hybrid systems that are of scientific interest as well as practical utility.

ASSOCIATED CONTENT

S Supporting Information

N 1s, O 1s, and S 2p computed binding energies and other structures of cysteine/ TiO_2 clusters. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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