Phenylalanine near Inorganic Surfaces: Conformational Statistics vs Specific Chemistry

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Abstract: We present a first principle density functional study of phenylalanine interacting with three different classes of surfaces, namely a purely repulsive hard wall, mildly interacting close packed surfaces of group 11 metals (Cu(111), Ag(111), and Au(111)), and strongly interacting close packed surfaces of group 10 metals (Ni(111), Pd(111), and Pt(111)). In particular, we characterize, by changing the substrate, the passage from the statistical behavior of a flexible molecule in the presence of the topological confinement of a hard wall to a purely chemical behavior where the molecule, highly deformed compared to the free state, strongly binds to the surface and statistical conformations play no longer a role. Such a comparative study allows for characterization of some of the key aspects of the adsorption process for a prototype of flexible amino acids on experimentally and technologically relevant metal surfaces.

1. Introduction

The behavior of large molecules near inorganic substrates is becoming a field of rapidly growing interest due to its relevance in many problems of condensed matter and chemistry, from catalysis,[1-3] through the understanding of chirality,[4-12] to the design of materials properties.[13-16] Of particular interest is the case of biomolecules; this is extremely important for several emerging fields of biophysics and biochemistry, such as the design of biomedical devices[17-20] and of biocompatible materials.[21,22] The above-mentioned interaction between biomolecules and inorganic surfaces is a rather complex problem. As the size of the molecule increases, the number of conformational states accessible becomes larger and the specific chemical structure becomes less relevant; thus statistical generic models are computationally convenient and theoretically well founded for describing the large scale conformational properties. On the other hand the specific chemical structure of each moiety (functional group) of the molecule can react differently in the presence of a surface. The overall result of the balance between the two aspects is that the intrinsic conformational preferences of the free molecule are altered in a different way when it is in the presence of different surfaces, depending on the strength of the attractive interaction between the two systems. This means that a computationally feasible study can be accomplished only via a multiscale approach. Here, for multiscale approach we mean the description of the two different aspects (functional group reactivity and sampling of conformations), each done with the most appropriate method in terms of physical soundness and computational feasibility, but the crucial point is that they must be linked to each other in a sequential and consistent way.[13,14] In particular, from a computational point of view, the first principles treatment of all the relevant molecular conformations on a surface, especially the metal one, is in general a prohibitive task, and thus for large molecules a hierarchical sequence of computational methods, as mentioned above, is required.[13,14,23,24] However, in order to understand the problem in detail, without any *a priori* modeling approximation (instead required by multiscale approaches), one needs to consider a prototype of biomolecule that clearly displays the relevant aspects of the conformational properties (molecular flexibility) and whose study of adsorption on a metal surface is computationally feasible at the quantum level. This study is useful to understand whether or not the flexibility for a large class of

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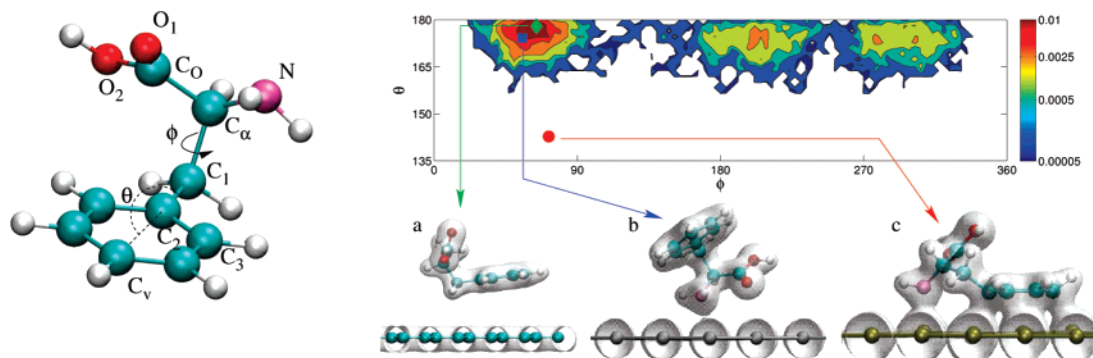
Figure 1. Left: perspective view of the ground state geometry for gas phase Phe. Top Right: the (top) graph displays the contour plot of the probability distribution of the dihedral ϕ and the "out-of-plane" angle θ, derived from the confined trajectory of the molecule (i.e., the molecule near the hard wall). Bottom right row: (a) one of the statistically more visited *internal* conformations of Phe near graphene (the rigid rotation wrt the surface being practically free; the particular orientation we display was chosen for convenience and we label it Ring↓): this conformation of the molecule (diamond in the plot) is basically the same as the gas-phase ground state. (b) Energetically most favorable adsorption of Phe onto Ag(111); in this N# orientation, the conformation of the molecule (square) is close to the gas-phase ground state. (c) Most favorable adsorption of Phe onto Pt(111), with both the ring and the N atom bonded (Ring↓N↓) to the surface; the conformation of the molecule (circle) is never visited during the confined evolution. The bottom panels show also the total electron density; the isosurface level is 0.37 e/Å^3 for all the panels.

biomolecules must be considered as a primary aspect when predicting adsorption affinities with metal surfaces. This, in turn, provides a valid tool for the interpretation of experimental data and of course becomes at a later stage of high importance in the development of simplified models of molecule/metal interface which can then access simulation times and sizes farther beyond those of the standard quantum approaches. For this reason we have chosen phenylalanine (Phe) as the molecule to study; it is large enough to display relevant flexibility and at the same time is small enough to be studied near metal surfaces by first principles methods at a reasonable computational cost. Previous studies of a relatively large biomolecules at a metal surface[4–12,25–27] could not take the flexibility of the molecule into account since they do consider molecules whose flexibility is rather limited. In particular, most of those studies[4–12] are mainly focused on the important aspect of the chirality of the adsorbate and explore the effect of the lateral interactions between molecules at relatively high coverages.

In light of what was stated above, in this work we present a density functional (DFT) study of the interaction of (isolated) phenylalanine with various substrates, namely a purely repulsive surface, and closed packed surface of group 10 (Ni(111), Pd-(111), and Pt(111)) and group 11 (Cu(111), Ag(111), and Au-(111)) metals. Despite the limitations of DFT, this approach still represents an extremely powerful theoretical tool to gain insights into the electronic properties of matter, and it is particularly suited for the systems under consideration. It must also be noticed that the metals we selected are among those commonly used in experiments of organic molecules on metals and in technological applications. In this study we neglect the role of the solvent because (a) the size of the calculations would become prohibitive and (b) experiments of gas phase adsorption of organic molecules, such as amino acids, onto metal surfaces are nowadays performed,[28,16] although the comparison between experiments and numerical simulations is still at the qualitative level. Because of point (b), there is currently an urging demand

for theoretical studies in the field in order to allow for a clearer interpretation of experimental data and design of new experiments.[16] Besides the reasoning given above, the amino acid we have chosen allows also for some generalization of the results to the adsorption behavior of other molecules which display similar properties. In fact, this study, on one hand, provides the adsorption energies and geometries related to the interaction of the amino and carboxylic functional groups (common to all amino acids) with the specific surface and, on the other hand, due to the high flexibility at the C_1–C_α and C_2–C_1 bonds (as displayed in Figure 1) common to other amino acids, predicts a trend of the molecular distortion as a function of the substrate. For this reason the results found in this work are expected to approximately hold for similar flexible amino acids such as tyrosine (with phenol as side group), tryptophan (with indole), and histidine (with imidazole). In all these cases the amino acid can also be thought of as part of a polypeptide, with the side group still flexible in the chain. Next we proceed to describe the approach used. In order to explore the space of molecular conformations in an exhaustive and computational efficient way, we adopt two complementary approaches. On one side we analyze the statistics of preferred conformations of the molecule in the presence of a purely confining surface; the most probable conformations (named in the following "statistical conformations") are then located on the particular metal surface and adsorbed. From the other side, one can consider the molecule as a composition of submolecules (in our case alanine and a phenyl ring, and alanine can be in turn subdivided into amino, carboxylic, and methyl groups); thus, "non-statistical conformations" are designed following a building-blocks criterion.[29] In brief, for a building-blocks approach we mean that when the interaction of moieties with the selected surface are known, topologically allowed conformations of the complete molecule near the surface, obtained from the composition of the interacting moieties, are tested.

We found that the two classes of metals clearly split into two interacting behaviors. Noble metals of group 11 only allow for adsorption in "statistical conformations" (i.e., the conformations determined first by the topological confinement due to

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the surface), whereas group 10 metals prefer "non-statistical conformations" (i.e., the conformations which are highly deformed wrt the free state due to the interaction with the surface). The reason for the different behavior, which we will show, is in the competition between surface response and internal strain of the molecule.

2. Methods and Model Systems

2.1. Hard Wall (Graphene). In order to closely mimic a simple repulsive wall in the DFT framework, we adopted a graphene-like sheet. For this purpose, we used Car–Parrinello molecular dynamics as implemented in the CPMD code.[30] During the molecular dynamics (MD) run, all the atoms of graphene were kept fixed (with the C–C distance at the optimal value for our setting) and the other degrees of freedom were thermostatted via a Nose–Hoover algorithm[31,32] at 300 K. For all the DFT calculations, the wavefunctions are expanded in a plane-wave basis set, with a cutoff at 60 Ry, which we find to yield well converged bonding energies. We employed norm conserving Troullier–Martins pseudopotentials[33] extensively tested before.[13,27] We use the PBE generalized gradient approximation (GGA).[34] For modeling the graphene sheet, we adopted a rectangular supercell of edges 12.3 × 12.8 × 12.3 Å^3; in correspondence to the $x-y$ face we placed a graphene sheet consisting of a 5 × 3 supercell (60 atoms). In this way, the evolution of the molecule is confined between two hard walls, due to periodic replicas. The perpendicular distance between the replicas of the graphene sheets, i.e., 12.3 Å, is such that the molecule, when temporarily in the center of the slab, does not feel the presence of the walls and thus is still free to display rigid body rotations. In nature Phe would interact with graphene via dispersion interactions (see the similar case of phenol on graphene[1]). However, to our advantage, the latter are not accounted for in the DFT scheme we adopted, and thus our modeled graphene behaves approximately as a hard wall: for atom–surface (perpendicular) distances below 2 Å the interaction energy quickly rises to several times the average thermal energy of the molecule at 300 K.

2.2. Metals. For studying the adsorption of Phe onto metal surfaces, we used the DFT based finite-electronic temperature method of Alavi et al.[35] (FEMD), as implemented in the CPMD code.[30] The metallic surfaces were represented by four close-packed layers of Ni(111), Pd-(111), Pt(111), Cu(111), Ag(111), and Au(111), with the two top layers allowed to relax. We use a 4 × 4 lateral supercell in a hexagonal symmetry and a 2 × 2 × 1 k-point mesh. The two lattice vectors in the xy-plane have the following lengths: 10.12 (Ni), 11.24 (Pd), 11.28 (Pt), 10.48 (Cu), 11.72 (Ag), and 11.68 Å (Au). The cell dimension in the z-direction is two times the x lattice vector, so that the vacuum thickness between the bottom layer of the image slab of the metallic surface and the atom in Phe with the highest z-coordinate (its identity depends on the orientation of the molecule) is at least 10 Å. The Troullier–Martins pseudopotentials for the metals were extensively tested for previous studies.[19] The structures studied here were considered fully relaxed when the ionic forces fell below 2×10^{-3} atomic units and the change of total energy between two subsequent geometry optimization steps was below 1×10^{-4} atomic units. We geometrically optimized systems consisting of one Phe molecule and a metal (111) surface.

3. Results and Discussion

3.1. Hard Wall (Graphene). For the statistical analysis of the confined molecule, we monitored during the MD runs the trajectory of the most representative variables of the molecular

Table 1. Adsorption Energies (in eV) and Bonding Perpendicular Distances (i.e., the Distance between N or the Ring and the Average First Layer Plane, in Å) for Selected Conformations of Phe onto Metal (111) Surfaces^a

metal	conformation	E_{ads}	z_{ave}^{ring}	z_{ave}^{N}	E_{resp}	E_{strain}^{mol}	E_{strain}^{surf}
Pt	Ring↓	−1.0	2.15	−	−3.0	1.7	0.3
	N↓	−1.1		2.19	−1.2	0.1	0.0
	O↓	−0.4		2.22*	−0.6	0.2	0.0
	Ring↓N↓ (c)	**−1.3**	2.11	2.28	−4.0	2.4	0.3
	Ring↓N↓ (d)	**−1.3**	2.13	2.35	−4.5	2.7	0.5
Ni	Ring↓	−0.9	2.08		−1.9	0.8	0.2
	N↓	−0.6		2.20	−0.8	0.1	0.1
	Ring↓N↓ (c)	**−1.1**	2.07	2.19	−2.8	1.5	0.2
	Ring↓N↓ (d)	**−1.1**	2.05	2.23	−3.3	1.9	0.3
Pd	Ring↓	−0.9	2.17		−2.1	1.0	0.2
	N↓	−0.7		2.12	−0.9	0.2	0.0
	Ring↓N↓ (d)	**−1.0**	2.12	2.32	−3.2	2.0	0.2
Cu	Ring↓	−0.1	2.89		−0.1	0.0	0.0
	N↓	**−0.5**		2.22	−0.6	0.1	0.0
	Ring↓N↓			unstable			
Au	Ring↓	−0.0	3.25		−0.0	0.0	0.0
	N↓	**−0.4**		2.30	−0.6	0.1	0.1
	Ring↓N↓			unstable			
Ag	Ring↓	−0.1	3.09		−0.1	0.0	0.0
	N↓	−0.3		2.31	−0.4	0.1	0.0
	Ring↓N↓			unstable			

^{a} The metals are ordered from the strongest to the weakest binding (and the strongest adsorption energy for each metal is in bold). In the case of the O↓ conformation on Pt, the * distance is between the carbonyl O and the surface. The other columns show the decomposition of the adsorption energies into partial contributions (see text). The estimated uncertainty for E_{ads} is 0.05 eV.

flexibility. In Figure 1 we show the probability density of two such variables, namely the dihedral ϕ (described by the 4 atoms $C_2-C_1-C_\alpha-N$) and the "out-of-plane" angle θ (referred to atoms $C_v-C_2-C_1$). It turned out that the torsion around the C_1-C_α bond (dihedral ϕ) is limited to three well separated basins, while Phe is almost free to rotate around the C_2-C_1 bond (not shown in Figure 1). This behavior is similar to that occurring for the gas-phase Phe (we tested also this case) and is consistent with what it is generally known about aliphatic systems.

In Figure 1a we show one of the statistically more visited conformations of Phe on graphene, taken from the trajectory at 300 K. Analysis of the frozen configuration taken from the snapshot reveals that there is a negligible (i.e., below the accuracy of our setup) attraction between the molecule and the surface, independently of the molecule orientation (i.e., the rotation of the molecule keeping the distance of closest approach to the surface always gave a negligible attractive interaction). When dispersions are properly described, and thus graphene does not have the role of a hard wall anymore (as already underlined above), the adsorption energy is much higher.

3.2. Metals. In Table 1 we report the adsorption energies on the metals for a selection of the conformation we studied. Adsorption energies are usually defined as $E_{ads} = E_{mol+surf} - E_{mol}^{relax} - E_{surf}^{relax}$; i.e., the total energy of the relaxed fragments, viz. the molecule and the surface, is subtracted from the total energy of the adsorbed system. All metals allow for the adsorption via the amino group, with the phenyl ring away from

(30) *CPMD*, version 3.4.1, developed by Hutter, J.; Alavi, A.; Deutsch, T.; Silvestri, W. copyright MPI für Festkörperforschung Stuttgart and IBM Zurich Research Laboratory (1995−1999).
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the surface (conformation N↓, labeled with b in Figure 1). The molecule adsorbs N↓ on all surfaces basically in its gas-phase ground state geometry, with a small distortion localized at the amino group. The first striking difference between the two classes of closed packed surfaces concerns the interaction with the phenyl ring: benzene scarcely adsorbs on Cu, Ag, and Au[36] while it strongly does on Ni,[37] Pd, and Pt.[38] Consistently, the Ring↓ conformation strongly adsorbs on group 10 metals and almost negligibly on group 11 metals. This conformation is similar to the one labeled as in Figure 1, but with the ring parallel to the surface. A new important aspect, with respect to the hard wall-like surface, is the possibility that, due to the interaction with the surface, the molecule can be highly deformed with subsequent massive internal strain. In fact, as evidence of the fact that chemistry starts to play a clear role, we note that the strong adsorption on Ni, Pd, and Pt is accompanied by a relevant bending up of the ring's hydrogens. In contrast, Phe on Cu, Ag, and Au is not deformed, and the equilibrium distance is much higher than that on Pt.

However, the above conformations are still among those obtained from the statistical analysis of a confined molecule (see square and diamond in the graph of Figure 1), and it would suggest that bonding geometries have to be searched among conformations with high probability (though upon some local optimization, as in this case of the hydrogens). This argument, we show now, is not sufficient. Following our building-blocks idea,[39] several "non-statistical conformations" with N and the ring (Ring↓N↓); or carbonyl O and the ring; or N, O, and the ring near the surface were considered. We find the second striking difference between the two classes of surfaces: only on (all) group 10 metals the Ring↓N↓ conformations adsorb. We find that the Ring↓N↓ conformations are typically characterized by a high molecular strain and, consistently, statistically never sampled near the hard wall. None of them are stable on Cu, Ag, and Au, since even a small strain overcomes the mild binding of the ring, leaving the N−metal binding as the only possibility. In contrast, we find four nonequivalent Ring↓N↓ on Pt (on Ni only two of those were considered and on Pd only one). Here we have shown the one with the strongest E_{ads} (labeled with c in Figure 1 and in Table 1, with the angle θ distorted up to 140°). Another one, with the same adsorption energy, not shown in Figure 1 and labeled with d in Table 1, results from a significant deformation which decreases the angle θ, from the equilibrium value of 178°, up to 133°, and the molecule is oriented with the two C_1 hydrogens pointing away from the surface. Here we note that a small molecular distortion has been already observed for adsorption of, e.g., glycine[2] and adenine[26] on metallic surfaces; however, the relevant angular distortions we have found cause strains that are 1 order of magnitude stronger than previously found and are, above all, widely unpredictable, if considering typical angles for aliphatic systems. Within the building-blocks framework, only this combination of chemical intuition, based on the knowledge regarding the affinity of the moiety to the surface, and the conformational analysis brought to the extreme case of large and counterintuitive deformations, could reveal those adsorbing

conformations. We conclude that on group 10 metals the adsorption ground state is one of the Ring↓N↓ conformations, where the molecule is highly strained, contrary to the case of group 11 metals where only nonstrained conformations adsorb. Referring to surface reactivity, we find a trend along the groups and rows of the periodic table consistent with the *d*-band model of Hammer and Nørskov.[40] We quantify the balance between adsorption and internal strain, by decomposing the adsorption energy into three contributions, the "response" of the surface E_{resp}, and the strain energies of molecule and surface, E_{strain}^{mol} and E_{strain}^{surf}: $E_{ads} = E_{resp} + E_{strain}^{mol} + E_{strain}^{surf}$. $E_{resp} = E_{mol+surf} - E_{mol}^{ads} - E_{surf}^{ads}$; i.e., the total energies of the isolated molecule and surface frozen in their adsorbed geometries are subtracted from the total energy of the adsorbed system. $E_{strain}^{mol} = E_{mol}^{ads} - E_{mol}^{relax}$, i.e., the energy needed to strain the molecule into its adsorbed conformation. A similar definition holds for E_{strain}^{surf}. In Table 1 we report the values for those quantities. In Figure 1, we show, for three adsorption conformations, also the total electron densities, whose comparison summarizes the results described above. Keeping in mind that the isosurface level we chose is the same for the three cases, we see that no distortion of the electron density is associated with the graphene−Phe interaction, a small polarization accompanies the adsorption of the molecule onto Ag, while a significant overlap of the surface and molecular electron density is seen in correspondence to the adsorption onto Pt. The latter is a clear signature of a strong chemical bond between the molecule and the surface, and the corresponding molecular geometry is located rather far away from the region of sampled conformations. Regarding this point, it has to be noted that the molecule maximizes the electronic overlapping with the surface thanks to its large flexibility which allows for a strong structure deformation.

Besides the adsorbing conformations discussed above, we find that Phe adsorbs on all metals also via the carbonyl O, but always with lower adsorption energy than the adsorption via N (see in Table 1 the case of Pt, but compare also to how Ala adsorbs on Ni(111)[27]). In a previous work concerning Ala on Ni(111),[24] and confirmed on Pt(111) for the present study, we found that the simultaneous adsorption of N and the carbonyl O (a conformation that is found for the adsorption of Ala on open metal surfaces[4,7−12]) is not bonding. In our case the internal strain (the molecule has to bend in order to allow for the concomitant adsorption through both atoms) made this conformation energetically not favored. Furthermore we find that even on the more reactive group 10 metals the conformation with both the ring and the carbonyl O adsorbed is not stable, nor is a conformation with the ring, N, and O adsorbed. In all these cases the internal strain overcomes the response of the surface. Still a question remains open, that is, if a deprotonation process occurs, specifically, the deprotonation of the carboxylic group and thus the formation of a carboxylate group. In some experimental as well as theoretical work, the bonding of the carboxylate group is claimed to be a bonding motif of interest for similar molecules on metals (see, e.g., refs 10 and 11 and references therein) although according to a recent experimental work this seems to not be important for alanine (and thus most likely for phenylalanine).[28] However, in this case the main issue is the determination of the deprotonation path. This in general can happen in two ways: via the internal transfer of the proton

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from the carboxylic group to the ammonium group, i.e., the molecule goes into the zwitterionic state where it becomes polar but conserves the total charge, and that where the proton is adsorbed by the surface, and thus the molecule becomes ionic. In the context of this work the question to address concerns the fact that potentially a strong bond can be formed by the deprotonated carboxylic group, and this could influence the conclusions regarding the importance of chemisorption relative to the conformation. To address this issue one has to keep in mind that the zwitterionic state occurs in water at physiologic conditions while in vacuo the molecule is in its neutral state; thus in principle, for the adsorption study in vacuo the zwitterionic state should not play a relevant role. One can still argue that the internal proton transfer can be activated by the adsorption process; however in our previous work on alanine on Ni(111) and test calculations on Pt(111), after a detailed analysis, we have found no evidence which supports the hypothesis above.[27] Obviously this does not prove that the process cannot occur but certainly suggests that the internal proton transfer may have a rather complicated path with a very high, and perhaps sharp, energy barrier. Regarding the deprotonation of the molecule (ionic state) upon adsorption, this can strongly depend on the chemical nature of the metal and on the topology of the surface. For example for the simple case of water, deprotonation can occur on Rh(111) but does not occur on any of the surfaces considered in this work (see ref 41 and references therein). Furthermore, a detailed study of deprotonation of phenol on Ni(111), Ni(110), and Ni(221) showed that for the more open surfaces the energy barrier to the deprotonation is lower because of their stronger reactivity compared to the (111) surface however, in all cases, is very high and makes the process unlikely to happen.[42] From the discussion above one may tend to conclude that the deprotonation is not likely to occur for the molecule and the surfaces we are currently considering. Of course to properly address the question and go beyond speculations one must carry a detailed study of the deprotonation process in a proper way, probably using some sort of transition path sampling, which given the size of the system and the number of degrees of freedom of the molecule is, at the current state, computationally prohibitive. In any case, already at this stage, based on our previous study of zwitterionic alanine on Ni(111)[27] and test calculations of zwitterionic alanine on Pt(111) we can conclude that, at least for the zwitterionic state, the bonding of the carboxylate group is at best of the same magnitude as the bonding of the amino group. Thus, the balance between the flexibility of the molecule and the chemical affinity to the surface holds the same relationship, since one would have a bonding situation as that occurring for the (Ring↓N↓), where in this case the N↓ is substituted by the COO⁻.

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4. Conclusions

In conclusion, the relevance of our study is manifold; on the one hand we have quantitatively documented the adsorption of a prototype flexible amino acid on several relevant metal surfaces. Our results can be extended to all other amino acids regarding the adsorption via the amino group. Moreover we have considered the molecular flexibility and by that introduced an aspect which we have shown being of high if not dominant relevance. The utility of this work for the theoretical modeling and for the design and (or) interpretation of experimental and technological applications should be now evident. For the latter, one can choose the surface that shows adsorption properties on demand. For modeling purposes, a far from obvious conclusion is that the internal strain of the molecule has to be carefully taken into account, together with the direct interaction of the submolecular fragments. Concerning both the interpretation of experiments and the modeling, one would have been easily lead to assume that a flexible molecule would choose its conformation at the surface among those allowed near a confining (hard wall) surface and only at a later stage the specific chemistry of the surface comes into play, e.g., selecting for adsorption the conformations allowed by the symmetry of the surface. We have shown that this is not always the case, and the flexibility of the molecule and chemical response of the surface cannot be naively decoupled.

The current study focuses on the response of the single molecule to the presence of the surface. Our technical setup was such that the molecule did not experience a molecule−molecule interaction with its periodic images. Of course it would be of high interest to study the effect of additional molecules in the system, but to properly describe cooperative effects among the adsorbed molecules, one needs to include at least two molecules in the simulation supercell. While for smaller molecules this is still doable,[4−11] for our large and flexible molecule the sampling of all the possible conformations, even restricted to few conformations per molecule, would become quickly computationally unfeasible. From this perspective, this study could be used in principle to model the molecule−surface interaction, which then can be plugged into a classical force field, where the molecule−molecule interaction is already well described (see, e.g., ref 24). Finally, a classical MD, which is computationally feasible, could provide a first guess regarding such an effect.

For all the reasons given above, this work could be relevant to fulfilling the lack of theoretical studies and may inspire further theoretical and experimental work.