Adsorption of Native Amino Acids on Nanocrystalline TiO2: Physical Chemistry, QSPR, and Theoretical Modeling

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ABSTRACT

The affinity of biomolecules, such as peptides and proteins, with inorganic surfaces, is a fundamental topic in biotechnology and bionanotechnology. Amino acids are often used as “model” bits of peptides or proteins for studying their properties in different environments, and/or developing functional surfaces. Despite great demand for knowledge about amino acid interactions with metal oxide surfaces, studies on the issue represent a fragmentary picture. In this paper, we describe amino acids adsorption on nanocrystalline anatase systematically at uniform conditions. Analysis of the Gibbs free adsorption energy indicated how the aliphatic, aromatic, polar and charged side chain groups affect the binding affinity of the amino acids. Thermodynamic features of the *L*-amino acids adsorption receive thorough interpretation with calculated molecular descriptors. Theoretical modeling shows amino acids complex with TiO2 nanoparticles as zwitterions via ammonium group.

KEYWORDS titanium dioxide, anatase, nanoparticles, *L*-amino acid, adsorption, BET-model, MERA-model.

INTRODUCTION

TiO2 is a wide band gap semiconductor, which can be synthesized on the nanometer scale exhibiting unique photoelectronic and photochemical properties.1 It is utilized for photodynamic therapy,2 in generating superhydrophilic surfaces,3 as well as in a new generation of transistors and biosensors.4,5 Functional biomolecular coatings such as proteins and peptides that are strongly and specifically adsorbed to the oxide may further advance the development of TiO2-based nanobiotechnological applications.

In the field of biotechnology immobilization of biomolecules onto solid supports, such as TiO2, is mandatory to obtain a biologically functional material. The production of stable, functional and high surface density molecular films to improve *in situ* performance is strongly required for all biotechnological applications, ranging from biosensors to tissue engineering.6 For medical implants in the human body, titanium is a very important inorganic implant material.7

The interplay of titanium dioxide surfaces and biomolecules is of great interest in biomineralization, where composite materials are formed, which have mechanical properties superior to the inorganics.8 Single amino acids may determine the surface orientations of titanium dioxide nanocrystals.9,10 Small peptides with 10 to 20 amino acids control the nucleation11 and structural formation of minerals and provide molecular scaffolds in the formation of hard tissue.12

Fundamental studies of the adsorption of protein building blocks to TiO2 may provide useful insights into biomaterial/biomolecule surface interactions and hence a better understanding of interaction on the molecular level.13 Recent classical molecular dynamics calculations of collagen on rutile indicate that proteins are attached to the surface via a small number of contact points.10,14 For peptides, it is likely to be the side groups of the amino acids which control the overall adsorption mechanism, because the terminal carboxyl and amine groups form a small proportion of the overall molecule.10 Therefore, to better understand the impact of the adsorption on protein structure, a comprehensive understanding of amino acid-nanoparticle interactions is required.

The first thermodynamic data on the amino acids adsorption on titanium oxide under biocompatible conditions were obtained by S. Okazaki for *L*-lysine.15 Using the Langmuir model the Gibbs free energy was calculated for the adsorption in deionized water (2.3 kJ/mol). Three decades later similar data were obtained for histidine at different temperatures (293.15÷320.15 K).16

Meanwhile, the spectroscopic methods are most utilized for studying affinity of the amino acids to TiO2. Despite their descriptive character, they became useful in revealing meaningful insights of amino acids adsorption. For example, *in situ* IR-spectroscopic study showed that Lys adsorption behavior is indifferent towards TiO2 crystallinity or lysine chirality.13 Later, the same group revealed that Glu adsorption to TiO2 involves at least two structures, while Asp gave a single surface species.17 A detailed IR-spectroscopic study of Asp and Glu on TiO2 pointed out both carboxylic groups of the molecules are coordinated to the surface, wherein one of them is bonded monodentally to a surface Ti ion, while the other is stabilized by a hydrogen bond. Amino acids with the amide (glutamine) or aromatic (phenylalanine) side chains were shown to interact rather weakly with TiO2.18

IR-spectroscopic study of histidine adsorption on nanocrystalline anatase proposed that the adsorption is somewhat more complex than a single conﬁguration and that there are diﬀerent modes of adsorption for heteroaromatic amino acid on the NPs surface.15

X-ray photoelectron spectroscopy analysis of cysteine and homocysteine adsorption on the amorphous TiO2 film concluded the amino acids adsorb onto TiO2 surfaces by their carboxyl groups replacing a basic hydroxyl on a Ti site in acidic media.19 The similar type of the cysteine binding to titanium dioxide was subsequently supported elsewhere.20 XPS analysis of aspartic acid adsorption onto TiO2 revealed amino acid binding via the amino groups.21

An important description approach to the amino acids adsorption is the calculation methods (theoretical models). Theoretical studies dealing with the solid-liquid evolved tremendously in recent years. In particular, molecular dynamics calculations based on density functional theory (DFT-MD) now allow description of both the oxide surface and the liquid phase with the same level of theory, i.e., including bond breaking and formation.22

*Ab initio* consideration of the amino acid adsorption by density functional methods showed Asp, Lys, and Arg interact with the surface mainly through the side chain groups.23 DFT analysis of the arginine adsorption on anatase (101) surface showed that preferred carboxylate binding occurs in bidentate configuration.24 DFT study of adsorption of 11 amino acids on anatase (101) showed that three types of interaction determine the amino acid adsorption: (i) dative bonds between O and N atoms (of the backbone and the lateral chains) and surface Ti atoms, (ii) H-bonds between the amino acids and the surface and (iii) dispersion interaction.25

The MD simulations of amino acid side chain analogues adsorption at the aqueous rutile (110)done by the Brandt and Lyubartsev26 emphasize that tightly bound surface waters play a key role for peptide and protein structures when bound to inorganic surfaces in biological environments. Similar studies indicated that serine side chain analogue (methanol) featured a hydrogen bonding to the surface.27,28

Adsorption of glycine, methionine, serine, and cysteine on rutile (100) and (110) simulated by MD methods show week surface binding of both the carboxyl groups and ammonium groups. Also, authors first indicated the equivalence of sorbate-sorbent and sorbate-sorbate interactions.29 MD investigation of the twenty standard amino acids interacting with TiO2 NPs showed charged amino acid – Arg, Lys, Glu, and Asp – adsorb significantly stronger than non-charged amino acids, which is in good agreement with recent experimental findings13,18 and with atomistic MD simulations of amino acid side chain analogues.27,28 Within the charged group, the basic residues (Arg and Lys) are favored over the acidic residues (Glu and Asp) when adsorbing onto the TiO2 NPs due to the dominant number of oxygen atoms at the TiO2 surface.30

Majority of reports describe amino acid interactions with titanium dioxide surface in a qualitative manner. That is related to the prevalence of spectroscopic and computer-based methods in the adsorption studies. Only two papers provide substantial data on thermodynamics, although it were obtained for different sorbates at surfaces with different crystallinity, which makes comparative analysis impossible.15,16 Despite the extensive utilization of the biomolecule-TiO2 interfaces, interactions at the aqueous titanium dioxide interface remain far from being fully understood. Without such an understanding, it will be challenging to design, predict, and/or optimize peptide adsorption and the concomitant properties of the resulting biointerface, amenable to utilization. Here we present the bulk adsorption study of major (19) *L*-amino acids on nanocrystalline anatase at uniform conditions mimicking biological medium. Discovered adsorption features are interpreted in terms of molecular descriptors, and binding geometries are disclosed by theoretical modeling of TiO2-amino acid complexes.

EXPERIMENTAL SECTION

**Materials.** Titanium (IV) isopropoxide (TIP, >98%), *L*-amino acids (АА, 99%) (Ala, Val, Leu, Ile, His, Phe, Trp, Gly, Pro, Met, Asn, Gln, Ser, Thr, Lys, Arg, Asp, Glu, Tyr) and phenylisothiocyanate (PITC, 98%) were purchased from Acros Organics. Trifluoroacetic acid (TFA, 99%) and acetonitrile (HPLC grade) were received from Panreac AppliChem and were used without purification. 2-(*N*-morpholino)ethanesulfonic acid (MES, >98%) was purchased from TCI Chemicals and was used as received. Isopropanol (99.7%) and triethylamine (TEA) (99%) were obtained from Sigma-Aldrich (Merck) and used without purification. Double-distilled water (DDW) was obtained on spot.

**Nanocrystalline titanium (IV) oxide.** Nanocrystalline titanium dioxide (TiO2) particles were prepared via sol-gel method, using Titanium (IV) isopropoxide as the precursor. The preparation was accomplished in isopropanol with water as the hydrolyzing agent. Water addition was followed by heating under a reflux condenser for 60 h. The obtained particles of TiO2 were washed with distilled water 3 times and centrifuged after each wash, dried and calcined by heating up to 400 °C, with the heating rate of 6.25 °С/min.

Transmission electron microscopy (TEM) analysis was carried out by a JEOL JEM-2100 instrument operating at an accelerating voltage of 200 kV, equipped with a field emission gun (FEG) and an ultra-high resolution pole-piece that provided a point-resolution better than 0.19 nm. The samples for TEM were dispersed in ethanol, sonicated and sprayed on a holey carbon film coated copper grid and then allowed to air-dry; finally, Gatan SOLARUS 950 was used before carrying out observations with the microscope. The crystal size distribution from the TEM observation was plotted considering the data obtained for 150 particles. The crystalline phase of TiO2 nanoparticles was characterized by powder X-ray diffraction (PXRD) using RIGAKU ULTIMA IV device operating on Cu Kα radiation at λ = 0.154 nm which corresponds to 8.04 keV. The amount of amorphous phase in the titanium dioxide sample was determined by the internal standard method. The PXRD data, collected from the samples mixed with 20 wt% of CaF2, were refined using MAUD software.

Fourier-transform infrared spectrum (FTIR) was recorded on a Shimadzu IRAffinity-1S FTIR spectrometer. The specific surface area of the titanium dioxide particles was determined by the Brunauer-Emmett-Teller (BET) method using nitrogen adsorption at 77 K. The size and the volume of mesopores were determined by the BJH method.

**Stock solutions and buffer.** Ten stock solutions of each amino acid with concentrations between 0.4÷16.0 mM were prepared by dissolving dry amino acids in DDW. In case of Tyrosine (Tyr) five stock solutions were prepared with a concentration between 0.4÷2.0 mM due to limited solubility of the amino acid. All stock solutions were pH-adjusted to pH = 7.4 using 50 mM MES-solution or sodium hydroxide. MES buffer with a concentration of 10 mM was prepared from dry 2-(*N-*morpholino)ethanesulfonic acid and pH was adjusted to 7.4 with dry sodium hydroxide.

**Adsorption of amino acids on TiO2.** Dispersions of TiO2 nanoparticles (2 mg/mL, 1 mL) in double-distilled water and MES-buffer (10 mM, pH 7.4) were added to a series of *L*-amino acid solutions (1 mL). Resulting series of samples were stored in thermostat (Julabo F25) at 0.00, 10.00, 20.00, 30.00 and 40.00 °C for 24 h to achieve the adsorption equilibrium. Afterward, the samples were filtered through the syringe filter (Vladfilter, 0.2 µm pore) to remove any nanoparticles and used for analysis.

**Derivatization and high performance liquid chromatography (HPLC) analysis.** Prior to analysis samples were derivatized with the Edman reagent.31 Briefly, 400 µL of sample mixed with 400 µL of triethylamine and phenyl isothiocyanate solution in acetonitrile (50 mM each). The mixture was thermostated at 60 °C for 15 min, neutralized with of 225 µL TFA.

20 µL of the resulting solution were analyzed by HPLC (Shimadzu, LC-20 Prominence) equipped with UV-Vis detector (λ = 254 nm). The analysis was done using reversed phase Zorbax column (150 × 2.5  mm i.d. with a mean particle size of 5 µm). Mobile phase consisted of 0.1% TFA in deionized water and pure acetonitrile, with acetonitrile gradient from 20% to 90% at 286 nm for Glu, Asp, Arg, Lys, Ala, Phe, Val, Gly, Pro, Gln, Met, Asp, Ser, Thr, Asn, Tyr and Trp (280 nm) in 13 min, and from 10% to 90% at 286 nm for His, Leu, Ile in 30 min. Each sample was analyzed in triplicate (see Figure S1).

**Theoretical study of the "amino acid-titanium dioxide" complexes.** Theoretical study of the “amino acid-titanium dioxide” complexes was carried out within the MOPS algorithm framework32 in the combined force field MM3/MERA with a continual account of the medium influence within the MERA model.33 The calculation of the difference between the LUMO and HOMO energies was carried out on the basis of DFT B3LYP 6/311G(d,p) for the zwitterionic forms of amino acids.

RESULTS AND DISCUSSION

**Nanomaterial Characterization.** TEM images of TiO2 particles in **Figure 1A** and **1B** clearly show a high degree of crystallinity of the synthesized material. The electron diffraction pattern in **Figure 1C** shows lattice fringes corresponding to (101) faces of anatase. The TiO2 nanocrystals are anisotropic with dimensions varying in the range of 5 to 20 nm (**Figure 1A**) and being 10.6 ± 3.3 nm an average crystal size calculated from the Gaussian fit of the size distribution (See Figure S2).

|  |  |  |
| --- | --- | --- |
|  | TEM TiO2 10 nm.tif | SAED TiO2.tif |
| A | B | С |

**Figure 1.** TEM images (A, B) and corresponding the selected-area electron diffraction (SAED) patterns (C) of TiO2 nanostructures.

**Figure 2A** shows the XRD pattern of the calcined sample of TiO2 nanoparticles. The determined characteristics, 2Ѳ values and [hkl] planes are 25.36° [101], 38.01° [004], 48.10° [200], 54.11° [105], 54.98° [211], 62.76° [204], 68.96° [116], 70.30° [220], 75.25° [215] and 82.77° [303] respectively, which refer to the anatase crystal structure.34 Rutile and brookite most intensive peaks at 27° and 30° respectively are not detected, meaning the crystalline phase is a 100% anatase. Average crystal size calculated with Scherrer equation using FWHM (full width at half maximum) of the most intensive anatase peak at 25.36° corresponds to 8.2 nm. Average crystallite size calculated by Scherrer equation agree with estimations made by TEM observation when the error is taken into account. The weight percentage of the amorphous phase is 1.1 ± 0.5% (see Figure S3).

FTIR pattern of nanocrystalline anatase sample is depicted in **Figure 2B**. The most intensive and wide band at 400÷900 cm‑1 is attributed to the titanium dioxide lattice vibrations. Adsorption band at 3000÷3700 cm‑1 corresponds to the surface hydroxyl group stretching vibrations, while the small band at 1650 cm‑1 corresponds to the O‑H bonds deformation mode.

|  |  |
| --- | --- |
| XRD TiO2.tif | IR.tif |
| A | B |

**Figure 2.** XRD pattern of the TiO2 sample (A) and FTIR spectrum of TiO2 nanoparticles (B).

Specific surface area calculated based on BET method is 131.9 m2/g (see Figure S4).

**Adsorption of amino acids on nanocrystalline TiO2.** Adsorption studies of amino acids at uniform conditions require pH stability. pH strongly influences charges of the surface and the sorbate.16,18,22 This is why we employed MES buffer with pH of 7.4, relating to physiological medium. We refrained from using conventional phosphate buffer as phosphate ions are known to suppress amino acid adsorption.15 We chose to use the non-coordinating MES-buffer, as it is incapable of forming even weak complexes with metal ions, and thus would not coordinate surface titanium.35

Adsorption of amino acids on nanocrystalline titanium dioxide was measured within the temperature range of 0÷40 °C (273.15÷313.15 K) corresponding to biocompatible conditions. Properties of the mineral sorbent change insignificantly within this range, meaning the fluctuation of the adsorption parameters is caused by changes in the physicochemical properties of the adsorbed amino acids. The dependences of the adsorption from the equilibrium amino acid concentration after adsorption (adsorption isotherms) were plotted according to the obtained experimental data. The value of the amino acids adsorption (A, mmol/g) on the surface of a solid sorbent was calculated from equation (*1*).

(*1*),

where А is the adsorbed amino acid, mmol/g; С0 и Се are initial and equilibrium concentrations of amino acids, mM; V is the volume of an initial solution of amino acids, L; m is the mass of the sample adsorbent, g.

The study of Tyr adsorption on nanocrystalline TiO2 in the range of concentrations from 0.4÷2.0 mM did not show any detectable change in the amino acid initial concentration for all considered temperatures. Similarly, Ile and Trp did not adsorb on TiO2 at 40 °C.

The measurements of the amino acids adsorption were data processed using the Langmuir model. Satisfactory compliance with the experimental points was observed only for the low concentrations. However, an extension of the Langmuir model on the full range of the experimental data, lead to the incorrect determination of the adsorption constant and the Gibbs energy (see Table S1).

Adsorption from a solution to a solid sorbent may proceed in multilayered mode.36 Following this consideration, we used the Brunauer, Emmett, and Teller model (BET) which assumes a Langmuir adsorption for each of the layers (Eq. *2*).37

(*2*),

where А is the equilibrium adsorption, mmol/g; Am is the adsorption capacity of the adsorbent at saturation, mmol/g; К is the equilibrium binding constant; Се is the equilibrium concentration of amino acid in solution after adsorption, mM; Сs is the limiting concentration (its solubility at a given temperature) of substance in solution, mM.38–40 The calculated correlation coefficients R2 fall into 0.93÷0.99 range for all obtained BET model isotherms (see Figure S5).

We used the linear form of the BET equation (*3*) for identification of the adsorption constant.

(*3*)

The equilibrium binding constant and the adsorption capacity of the adsorbent at saturation (Am, mmol/g) was calculated from the slope and the intersection at of the linear form of the BET equation in the corresponding coordinates .

The Van't Hoff equation (*4*) was used for determining the Gibbs free energy (ΔG, kJ/mol) for each temperature (see Table S2).

(*4*),

where R is the ideal gas constant, J/mol K; Т is the temperature of the adsorption process, К.

Plotting a graph of ΔG versus T, we determined ΔH as interception of the linear graph with the ∆G axis for each *L*-amino acid. Change in entropy for each temperature was determined from the fundamental relation (*5*).

(*5*)

The adsorption thermodynamic parameters of 18 amino acid calculated by the BET model, are presented in **Table 1**.

**Table 1.** Thermodynamic parameters of the amino acids adsorption.[[1]](#footnote-1)

| **Т, *К*** | **R‒** | **АA** | **ΔG, *kJ/mol*** | **ΔH, *kJ/mol*** | **ΔS, *kJ/mol K*** | |
| --- | --- | --- | --- | --- | --- | --- |
| *aliphatic АA* | | | | | | |
| 273.15 |  | Ala | ‑15.5 ± 0.2 | 13 ± 6 | 0.10 ± 0.03 |  | |
| 283.15 | ‑16.2 ± 0.5 |  | |
| 293.15 | ‑16.7 ± 0.4 |  | |
| 303.15 | ‑17.9 ± 0.2 |  | |
| 313.15 | ‑19.7 ± 0.6 |  | |
| 273.15 |  | Val | ‑14.5 ± 0.2 | ‑10 ± 10 | 0.00 ± 0.04 |  | |
| 283.15 | ‑15.1 ± 0.3 |  | |
| 293.15 | ‑13.3 ± 0.5 |  | |
| 303.15 | ‑14.1 ± 0.6 |  | |
| 313.15 | ‑15.2 ± 0.4 |  | |
| 273.15 |  | Leu | ‑7.9 ± 0.3 | 0 ± 10 | 0.05 ± 0.03 |  | |
| 283.15 | ‑9.8 ± 0.4 |  |
| 293.15 | ‑8.8 ± 0.4 |  |
| 303.15 | ‑10.3 ± 0.3 |  |
| 313.15 | ‑10.0 ± 0.2 |  |
| 273.15 |  | Ile | ‑11.4 ± 0.4 | 10 ± 20 | 0.06 ± 0.07 |  |
| 283.15 | ‑10.0 ± 0.2 |  |
| 293.15 | ‑11.6 ± 0.2 |  |
| 303.15 | ‑12.8 ± 0.2 |  |
| 313.15 | - |  |
| *aromatic АA* | | | | | | |
| 273.15 |  | His | ‑4.0 ± 0.3 | 49 ± 9 | 0.19 ± 0.03 |  |
| 283.15 | ‑6.0 ± 0.3 |  |
| 293.15 | ‑9.0 ± 0.2 |  |
| 303.15 | ‑9.4 ± 0.3 |  |
| 313.15 | ‑11.9 ± 0.3 |  |
| 273.15 |  | Phe | ‑8.5 ± 0.3 | 8 ± 3 | 0.06 ± 0.01 |  |
| 283.15 | ‑8.7 ± 0.4 |  |
| 293.15 | ‑9.6 ± 0.4 |  |
| 303.15 | ‑10.4 ± 0.4 |  |
| 313.15 | ‑10.7 ± 0.5 |  |
| 273.15 |  | Trp | ‑4.0 ± 0.2 | 30 ± 30 | 0.2 ± 0.1 |  |
| 283.15 | ‑6.4 ± 0.2 |  |
| 293.15 | ‑9.9 ± 0.3 |  |
| 303.15 | ‑8.0 ± 0.3 |  |
| 313.15 | - |  |
| *nonpolar АA* | | | | | | |
| 273.15 |  | Gly | ‑15.8 ± 0.2 | ‑3 ± 6 | 0.05 ± 0.01 |  | |
| 283.15 | ‑15.9 ± 0.2 |  | |
| 293.15 | ‑17.1 ± 0.3 |  | |
| 303.15 | ‑16.6 ± 0.5 |  | |
| 313.15 | ‑17.8 ± 0.4 |  | |
| 273.15 |  | Pro | ‑14.4 ± 0.3 | 70 ± 40 | 0.3 ± 0.1 |  | |
| 283.15 | ‑13.4 ± 0.4 |  | |
| 293.15 | ‑14.8 ± 0.2 |  | |
| 303.15 | ‑21.2 ± 0.3 |  | |
| 313.15 | ‑26.0 ± 0.5 |  | |
| 273.15 |  | Met | ‑7.5 ± 0.4 | 34 ± 3 | 0.15 ± 0.01 |  | |
| 283.15 | ‑9.5 ± 0.3 |  | |
| 293.15 | ‑11.0 ± 0.3 |  | |
| 303.15 | ‑12.5 ± 0.3 |  | |
| 313.15 | ‑13.7 ± 0.3 |  | |
| *polar АA* | | | | | | |
| 273.15 |  | Asn | ‑7.3 ± 0.4 | 50 ± 10 | 0.21 ± 0.04 |  | |
| 283.15 | ‑7.7 ± 0.5 |  |
| 293.15 | ‑10.0 ± 0.5 |  |
| 303.15 | ‑12.4 ± 0.3 |  |
| 313.15 | ‑15.4 ± 0.2 |  |
| 273.15 |  | Gln | ‑8.9 ± 0.3 | 20 ± 30 | 0.10 ± 0.09 |  |
| 283.15 | ‑11.2 ± 0.3 |  |
| 293.15 | ‑7.9 ± 0.3 |  |
| 303.15 | ‑12.5 ± 0.2 |  |
| 313.15 | ‑13.4 ± 0.3 |  |
| 273.15 |  | Ser | ‑16.8 ± 0.1 | 20 ± 10 | 0.14 ± 0.03 |  |
| 283.15 | ‑16.7 ± 0.2 |  |
| 293.15 | ‑18.1 ± 0.2 |  |
| 303.15 | ‑20.3 ± 0.2 |  |
| 313.15 | ‑21.8 ± 0.3 |  |
| 273.15 |  | Thr | ‑11.8 ± 0.1 | 26 ± 9 | 0.14 ± 0.03 |  |
| 283.15 | ‑12.4 ± 0.3 |  |
| 293.15 | ‑14.3 ± 0.2 |  |
| 303.15 | ‑14.7 ± 0.3 |  |
| 313.15 | ‑17.4 ± 0.3 |  |
| *charged АA* | | | | | | |
| 273.15 |  | Lys | ‑15.7 ± 0.4 | 20 ± 20 | 0.13 ± 0.06 |  | |
| 283.15 | ‑16.2 ± 0.3 |  | |
| 293.15 | ‑16.4 ± 0.6 |  | |
| 303.15 | ‑17.6 ± 0.3 |  | |
| 313.15 | ‑21.5 ± 0.6 |  | |
| 273.15 |  | Arg | ‑16.0 ± 0.5 | 19 ± 8 | 0.13 ± 0.03 |  | |
| 283.15 | ‑16.6 ± 0.5 |  | |
| 293.15 | ‑18.5 ± 0.5 |  | |
| 303.15 | ‑20.3 ± 0.4 |  | |
| 313.15 | ‑20.4 ± 0.3 |  | |
| 273.15 |  | Asp | ‑4.4 ± 0.5 | 20 ± 10 | 0.08 ± 0.04 |  | |
| 283.15 | ‑6.7 ± 0.3 |  | |
| 293.15 | ‑8.0 ± 0.3 |  | |
| 303.15 | ‑8.1 ± 0.4 |  | |
| 313.15 | ‑7.9 ± 0.4 |  | |
| 273.15 |  | Glu | ‑5.7 ± 0.2 | 2 ± 3 | 0.03 ± 0.01 |  | |
| 283.15 | ‑5.8 ± 0.2 |  | |
| 293.15 | ‑5.8 ± 0.2 |  | |
| 303.15 | ‑6.5 ± 0.2 |  | |
| 313.15 | ‑6.7 ± 0.2 |  | |

Data shows that the amino acid adsorption on nanocrystalline TiO2 is a spontaneous process (ΔG < 0). The calculated value of the Gibbs energy for His was ‑11.9 kJ/mol at a temperature of 313.15 K, which is nearby to the previously disclosed value of ‑13.5 kJ/mol at 310.15 K.16 The values of calculated ΔG for all investigated amino acids were <80 kJ/mol, which confirms the previous assumption of physical adsorption.41,42

The direction of the spontaneous process is determined by two factors: enthalpic (ΔH) and entropic (ΔS).43 For Gly, and Val the calculated enthalpy values are negative and are equal to ‑3.0 kJ/mol and ‑13.6 kJ/mol respectively, which indicates the exothermic nature of the adsorption of these amino acids and corresponds to the classical concept of the adsorption thermodynamics. Moreover, the calculated value of ΔH for Gly is close to the value of the enthalpy change of ‑2.2 kJ/mol, which was measured for the adsorption of Gly on silica.43 The calculated values of ΔH for all other observed amino acids indicate the endothermic nature of the adsorption (ΔH > 0), meaning that the process is entropy driven, and is likely related to the conformational changes of amino acids or the hydrate layer substitution on the sorbent surface.44–46

Uncertainties of some calculated enthalpies and entropies were found to be larger than the values themselves, especially for the cases of Trp, Gln, Val, Leu, and Ile. Mathematically, such errors are associated with imperfect linear trend of the G change. Thermodynamic reason of big uncertainties is a simultaneous monolayer and multilayer adsorptions with different enthalpic and entropic contributions to the adsorption.

Calculated Gibbs free energy of adsorption tends to increase within a row of aliphatic amino acids: Ala, Val, Ile, Leu (**Figure 3**), meaning higher homologue of the amino acid is less prone to binding to TiO2. Considering the trend, one may suggest the energy of adsorption of the highest homologues to stabilize nearby Leu. The fact that Leu has higher binding free energy than Ile suggest that the branching structure of the aliphatic side chain has the as strong influence on adsorption as the number of carbons in the homologous series.

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**Figure 3.** Dependences of the Gibbs free energy of the aliphatic amino acids adsorption on temperatures.

The adsorption suppression within homologous series is also clear for the hydroxyl-containing amino acids where the methyl bearing Thr is a weaker adsorbate than the Ser. It is hard to conclude whether this tendency is true for amide-containing Gln and Asn, as they show a somewhat similar adsorption activity (**Figure 4**). Another conclusion that comes from the analysis of the polar amino acids is hydroxyl-group makes amino acids to bind stronger to TiO2, than does the amide function (**Figure 4**). A possible explanation comes from the previous ﬁrst principles MD simulations, which proposed a strong bonding between a deprotonated hydroxyl group of serine and the TiO2 surface.29

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**Figure 4.** Dependences of the Gibbs free energy of the polar amino acids adsorption on temperatures.

Interaction patterns exhibited by aromatic and heteroaromatic cycles comprise hydrophobic, polar, hydrogen bonding, cation-π, amide-π, halogen-π, and π-stacking interactions47 which gives the rise of functionality and diverse adsorption activity, as recently was demonstrated for the case of Histidine.16 Hence, one would expect the larger variance of adsorption Gibbs free energies among aromatic amino acids. However, aromatic cycles: benzene, indole, made Phe and Trp behave as relatively weak adsorbates. This is especially surprising as most of their aliphatic analogues behave rather differently: they have lower free energy of adsorption (**Figure 5**). We suggest that stabilization of possible aromatic amino acid aggregates via π-π stacking compete with the adsorption.48 In contrast, weak dispersion interactions between aliphatic side chain make corresponding amino acids rather good binders compared to aromatic analogues.

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**Figure 5.** Dependences of the Gibbs free energy of the aliphatic (blue) and aromatic (red) amino acids adsorption on temperatures.

According to the recent spectroscopic studies13,18 and previous simulations27,28,30 charged amino acids – Arg, Lys, Glu, and Asp – are more prone to be adsorbed onto the TiO2 NP surface than non-charged amino acids. Our data show that these are true only for basic amino acids Lysine and Arginine, which exhibit the strongest affinity, while Aspartic and Glutamic acids show the weakest affinity (except for Trp and His at 273÷283 °C). Based on the previously determined values of the isoelectric points of the nanocrystalline anatase,49 the surface of the TiO2 is negatively charged under the experimental conditions, thus the antipodal activity of amino acids with charged side functions is explained with predominantly electrostatic nature of the adsorption (**Figure 6**).

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**Figure 6.** Dependences of the Gibbs free energy of the charged amino acids adsorption on temperatures.

Although majority of amino acids have a smooth linear trend of Gibbs free energy decrease upon heating, some exhibit complex behavior including formation of local maxima (Gln, Val) or minima (Trp) (**Figure 7A**), interestingly coinciding at 20 °C, or sharp change of the trend (Pro) (**Figure 7B**). Complex behavior makes extraction of the enthalpy and entropy challenging, creating deviations in the series of enthalpies. Such abnormalities are likely associated with the change in the adsorption mechanism and demand additional studies.

|  |  |
| --- | --- |
| C:\Users\Лена\Desktop\trpglnval141218.tif | C:\Users\Лена\Desktop\pro141218.tif |
| A | B |

**Figure 7.** Dependences of the Gibbs free energy of the Trp, Gln, Val (A) and Pro (B) adsorption on temperatures.

Comparing the saturation Am values for the observed 18 amino acids, calculated from the BET model, we established the affinity sequences (**Table 2**).

**Table 2.** The adsorption capacity of *L*-amino acids at nanocrystalline titanium dioxide at different temperatures (the amino acids are ordered according to their affinity to TiO2 which decreases from left to right).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| T, *K* | *Amino acids* | | | | | | | | | | | | | | | | | | |
| 273.15 | **His**40 | **Met**39 | **Pro**38 | **Lys**38 | **Asp**38 | **Leu**38 | **Phe**38 | **Val**39 | **Glu**38 | **Thr**38 | **Gln**38 | **Ser**38 | **Trp**38 | **Ile**38 | **Asn**38 | **Arg**40 | **Gly**38 | **Ala**38 |
| *Am* | *20.33* | *2.76* | *1.96* | *1.95* | *1.79* | *1.61* | *1.46* | *1.04* | *0.83* | *0.74* | *0.67* | *0.62* | *0.58* | *0.56* | *0.55* | *0.52* | *0.45* | *0.41* |
| *soly* | *194* | *122* | *7712* | *3001* | *17* | *169* | *117* | *712* | *23* | *445* | *118* | *2570* | *40* | *230* | *65* | *545* | *1656* | *1460* |
| 283.15 | **His** | **Pro** | **Lys** | **Met** | **Phe** | **Asp** | **Glu** | **Val** | **Asn** | **Ser** | **Leu** | **Arg** | **Trp** | **Gly** | **Thr** | **Gln** | **Ala** | **Ile** |
| *Am* | *9.35* | *3.76* | *2.04* | *1.86* | *1.55* | *1.34* | *1.03* | *0.93* | *0.89* | *0.77* | *0.76* | *0.67* | *0.65* | *0.54* | *0.54* | *0.41* | *0.33* | *0.32* |
| *soly* | *258* | *8557* | *3400* | *227* | *145* | *22* | *33* | *726* | *113* | *2850* | *172* | *656* | *51* | *2032* | *581* | *178* | *1510* | *252* |
| 293.15 | **His** | **Pro** | **Met** | **Lys** | **Gln** | **Asp** | **Leu** | **Phe** | **Glu** | **Val** | **Asn** | **Ser** | **Arg** | **Gly** | **Thr** | **Ala** | **Ile** | **Trp** |
| *Am* | *4.04* | *3.28* | *2.24* | *2.00* | *1.66* | *1.57* | *1.43* | *1.31* | *1.25* | *1.03* | *0.77* | *0.65* | *0.64* | *0.60* | *0.53* | *0.39* | *0.32* | *0.30* |
| *soly* | *322* | *9221* | *350* | *3673* | *244* | *32* | *180* | *152* | *49* | *743* | *176* | *3405* | *859* | *2447* | *761* | *1535* | *253* | *60* |
| 303.15 | **His** | **Lys** | **Met** | **Asp** | **Phe** | **Leu** | **Val** | **Glu** | **Gln** | **Thr** | **Gly** | **Asn** | **Trp** | **Ser** | **Arg** | **Ala** | **Pro** | **Ile** |
| *Am* | *2.70* | *1.83* | *1.81* | *1.56* | *1.22* | *1.01* | *1.00* | *0.94* | *0.70* | *0.69* | *0.62* | *0.58* | *0.49* | *0.46* | *0.45* | *0.30* | *0.28* | *0.08* |
| *soly* | *386* | *4000* | *409* | *46* | *179* | *190* | *751* | *67* | *329* | *870* | *2832* | *278* | *81* | *4690* | *1241* | *1657* | *10362* | *269* |
| 313.15 | **Asp** | **His** | **Met** | **Glu** | **Phe** | **Lys** | **Arg** | **Leu** | **Gln** | **Gly** | **Val** | **Ser** | **Asn** | **Thr** | **Ala** | **Pro** |  |  |
| *Am* | *2.01* | *1.71* | *1.01* | *0.97* | *0.93* | *0.86* | *0.80* | *0.77* | *0.61* | *0.49* | *0.39* | *0.38* | *0.33* | *0.26* | *0.25* | *0.03* |  |  |
| *soly* | *64* | *450* | *523* | *100* | *219* | *4289* | *2586* | *200* | *392* | *3305* | *768* | *5633* | *449* | *945* | *1816* | *11438* |  |  |

*Am* is the saturation, mmol/g. *soly* is the limiting solubility of an amino acid at given temperature, mM.

The **Table 2** shows that the amino acids His, Met, Lys, Asp, Leu and Phe exhibit the highest adsorption capacity to the surface of the nanocrystalline TiO2 in the entire range from 273.15 K to 313.15 K, while the worst sorbates are Ile and Ala. However, relative position in the row is not static. As temperature changes, all amino acids shift within affinity series, and Pro, Gln, Asn, and Arg may shift dramatically. Such behavior is caused by various and competing factors such as the ionization degree, hydrophobic, hydrophilic, structural properties of amino acids, etc.22 Complex character of the adsorption capacity is explained with molecular descriptors further in the text.

**OSPR of amino acid thermodynamic parameters.** Earlier studies devoted to amino acid adsorption on TiO2 indicated that adsorbate-adsorbent interaction depends on the fraction of unbound electrons in the molecules, molecular size, and spatial structure, the polarity of the chemical bond in molecular adsorption sites. In addition, the adsorption process is affected by solvation of adsorbate molecules and hydrogen intermolecular and intramolecular bond.29,50

We analyzed some of the amino acids molecular characteristics with respect to their adsorption thermodynamic parameters and discovered the dependence of the adsorption Gibbs free energy at low temperatures (273.15÷303.15 K) from the fraction of unbound electrons *Ре* (calculated by the MERA model51):

(6),

where *a* and *b* are the parameters; *Pe* is the fraction of unbound electrons.

The values of the *a* and *b* parameters, the correlation coefficients R and the standard deviations S (**Table 3**) indicate that the dependence decreases upon heating up to 313.15 K, where it ceases. At this point, a weak dependence of *ΔG* on the linear molecular dimensions appears, which could refer to a predominantly Van der Waals character of adsorption. The *a* and *b* coefficients have the largest absolute values at 273.15 K, while at temperatures of 283.15÷303.15 K they decrease and differ insignificantly.

**Table 3.** The values of the parameters *a* and *b* for different temperatures, the correlation coefficients R and the standard deviations S.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Т, *K*** | **a** | **b** | **R** | **S, *kJ/mol*** |
| 273.15 | 99 | ‑409 | 0.867 | 2.3 |
| 283.15 | 84 | ‑356 | 0.844 | 2.2 |
| 293.15 | 75 | ‑328 | 0.795 | 2.4 |
| 303.15 | 82 | ‑355 | 0.694 | 3.6 |

The larger the fraction of unbound electrons in the system, the greater the probability of binding unshared electron pairs to titanium atoms. The *Pe* values are presented in **Table 4**.

The adsorption enthalpy depends on the *α*-nitrogen partial charge *QN* and on the energy gap between the HOMO and LUMO ∆ (all quantum characteristics are calculated at the DFT B3LYP 6/311G(d,p) level of theory for the zwitterionic forms of amino acids). The dependence is the following:

(*7*),

where Δ is the HOMO and LUMO gap, Hartree; *QN* – *α*-nitrogen partial charge, a.u. The correlation coefficient is 0.838, the standard deviation is 13 kJ/mol. The values of Δ and *QN* are given in **Table 4**.

Amino acids adsorb predominantly with endothermal effect. A simultaneous increase in *QN* and decrease in ∆ lead to a higher enthalpy of the process, which argues for a significant role of the “head-to-tail” interactions between amino acid in water solutions. Adsorption of amino acids is a multistage process, which includes:

-disruption of the “head-to-tail” amino acid agglomerates in amino acid solution;

-solvation of the free amino acid;

-interaction of the amino acid with the TiO2 surface;

where only the first stage is endothermal. Interestingly, *ΔH* correlates with the energy of ‑COO–...H3N+ hydrogen bond.

**Table 4.** The values of the fraction of unbound electrons (*Pe*), the energy gap between the HOMO and LUMO (Δ), *α*-nitrogen partial charge (*QN*), the nitrogen atom fraction of unbound electrons (*PNe*) and the minimum moment of inertia (*I*).

| **AA** | **Pe** | **Δ, *Ha*** | **QN, *u*** | **PNe** | **I, *Da Å2*** |
| --- | --- | --- | --- | --- | --- |
| *aliphatic* | | | | | |
| Ala | 0.2799 | 0.2582 | ‑0.502 | 0.5574 | 103.85 |
| Val | 0.2729 | 0.2664 | ‑0.503 | 0.5707 | 249.92 |
| Leu | 0.2729 | 0.2678 | ‑0.503 | 0.5741 | 208.47 |
| Ile | 0.2717 | 0.2662 | ‑0.504 | 0.574 | 201.70 |
| *aromatic* | | | | | |
| His | 0.259 | 0.2128 | ‑0.498 | 0.7381 | 648.42 |
| Phe | 0.265 | 0.2348 | ‑0.502 | 0.5734 | 283.40 |
| Trp | 0.2788 | 0.1918 | ‑0.503 | 0.5588 | 178.15 |
| *nonpolar* | | | | | |
| Gly | 0.2858 | 0.2672 | ‑0.524 | 0.5424 | 93.22 |
| Pro | 0.2695 | 0.2545 | ‑0.444 | 0.7039 | 115.60 |
| Met | 0.2583 | 0.2171 | ‑0.504 | 0.5684 | 177.68 |
| *polar* | | | | | |
| Asn | 0.261 | 0.2328 | ‑0.503 | 0.5447 | 177.56 |
| Gln | 0.2583 | 0.2510 | ‑0.503 | 0.5588 | 218.58 |
| Ser | 0.2738 | 0.2523 | ‑0.504 | 0.5576 | 177.50 |
| Thr | 0.2687 | 0.2599 | ‑0.501 | 0.5679 | 219.64 |
| *charged* | | | | | |
| Lys | 0.2814 | 0.2461 | ‑0.503 | 0.5646 | 166.13 |
| Arg | 0.2748 | 0.2315 | ‑0.505 | 0.6311 | 192.08 |
| Asp | 0.2542 | 0.2587 | ‑0.499 | 0.5606 | 226.53 |
| Glu | 0.2572 | 0.2553 | ‑0.503 | 0.5683 | 193.69 |

The amino acid adsorption entropy insignificantly depends on nitrogen partial charge in the *α*-position according to the equation (*8*). The values of parameters *a1* and *b1* at different temperatures, correlation coefficients R and standard deviations S are presented in **Table 5**.

(*8*)

**Table 5.** The values of parameters *a1* and *b1* at different temperatures, correlation coefficients R and standard deviations S.

| **T, *K*** | **a1** | **b1** | **R** | **S, *kJ/mol*** |
| --- | --- | --- | --- | --- |
| 273.15 | 1.93 | 3.64 | 0.681 | 0.063 |
| 283.15 | 1.83 | 3.44 | 0.678 | 0.060 |
| 293.15 | 1.79 | 3.37 | 0.653 | 0.062 |
| 303.15 | 1.83 | 3.43 | 0.673 | 0.062 |
| 313.15 | 1.85 | 3.48 | 0.682 | 0.062 |

Like in the case of the Gibbs free energy, the equation parameters have the highest absolute values at 273.15 K, while at temperatures of 283.15÷303.15 K they decrease and differ insignificantly. Dependence of the entropy on the molecular characteristics is very weak and the correlation coefficients do not exceed the value of 0.7.

At temperatures, 273.15 K (Eq. *9*) and 303.15 K (Eq. *10*) the saturation Am depends on the carbonyl oxygen partial charge and on the energy difference between the LUMO and HOMO. Since the first layer is adsorbed via ammonium groups, as described earlier,16,21 free carboxylate groups act as the second adsorption layer sites. Equations (*9*) and (*10*) describe multilayer amino acid adsorption at low temperatures as the process governed by COO‑ groups, through the formation of a hydrogen bond with ammonium groups of the second layer. Second layer formation comes with a transfer of the electron density from the HOMO localized at negatively charged carboxylate group to the LUMO localized at positively charged hydrogens of the second layer ammonium group.

, R = 0.707, S = 3.60 (*9*)

, R = 0.709, S = 0.51 (*10*)

For the temperatures at 273.15 and 283.15 K (Eq. *11*) Am depends on the nitrogen atom fraction of unbound electrons *PNe* (calculated by the MERA model51) and the minimum moment of inertia *I*. At 293.15 K (Eq. *12*) the minimum moment of inertia ceases to be an important factor (**Table 6**). Starting with the 303.15 K this dependence is lost, probably because for the number of amino acids, the second layer is not formed (indeed, in many cases, the saturation significantly decreases). At the temperature of 313.15 K, saturation starts being dependent on the carbonyl oxygen *QO* and *α*-hydrogen *QH* charges (Eq. *13*).

(*11*)

(*12*)

**Table 6.** The values of the parameters *a2*, *b2* and *c2* for different temperatures, the correlation coefficients R and the standard deviations S.

| **T, *K*** | **a2** | **b2** | **c2** | **R** | **S, *mmol/g*** |
| --- | --- | --- | --- | --- | --- |
| 273.15 | ‑18.8 | 25.5 | 0.0282 | 0.942 | 1.7 |
| 283.15 | ‑13.4 | 22.5 | 0.0084 | 0.931 | 0.85 |
| 293.15 | ‑7.2 | 14.6 | - | 0.776 | 0.67 |

, R = 0.788, S = 0.35 (*13*)

**Theoretical study of the amino acid complexation with TiO2 nanoparticles.** The intermolecular co-relation of titanium dioxide nanoparticles and amino acids were simulated using model particles with the composition Ti1028O2056. Size of the modeled particles corresponded to the size of the synthesized TiO2 nanocrystals, calculated with Sherrer equation, and fit the mode of the TEM-observed size distribution. Modeling of titanium dioxide complexes with amino acid zwitterions and energy minimization by geometrical parameters were carried out within the MOPS algorithm32 in the combined force field MM3/MERA with a continual account the solvent influence according to the MERA model.33 The applicability of this approach for studying organic, inorganic and combined systems was previously shown elsewhere.52,53,62–69,54–61 The MOPS algorithm was used for the modeling of oxyhydrate gels formation,51,57,61 for the modeling of crystal structures of triosmium clusters,53,55,56,60,62,65,67 for the study of organic molecules complexation during chemical reactions,32,33,54,59,63,64,68 for the modeling of proteins affinity,66 for the modeling of crystal structures and interaction energies of gas hydrates.58,69 The calculated energies, thermodynamic characteristics (such as enthalpies, entropies, Gibbs free energies); modeled structures of complexes, crystals, and clusters; predicted yields, rates, regio- and stereospecificity of reactions were in a good agreement with the experimental ones that shown enough in the above-listed publications.

The total energy of a system TiO2 – solvent – amino acid (*ET*) was calculated using the equation *(14)* according to 52-69

 *(14)*

where *K* is the number of system componentsn; *Nn* and *Nl* are the numbers of atoms of *n*th and *l*th components, correspondingly; *Eij* is the interaction energy between *i*th and *j*th atoms of *n*th and *l*th components correspondingly (sum of Coulomb and Van der Waals energies); *k* is the Boltzmann constant; *T* is the absolute temperature; *Rij* is the distance; between *i*th and *j*th atoms; *χn* and *χl* are concentrations (mole doles) of *n*th and *l*th components correspondingly. Thus, concentrations of all components of the solution, including the solvent, were taken into account.

The analysis of the total energy for titanium dioxide complexes with amino acids and their zwitterions revealed that complexation of an amino acid is more favorable in its zwitterionic form (**Table 7**). Although XPS studies of Pro adsorption on TiO2 (110),70 *ab inito* study of the Gly on the anatase (101),71 and computational study of Cys adsorption to rutile (110)72 concluded that zwitterions are less stable at surface than neutral structures, majority of the reports considers amino acid adsorbed species as zwitterions. Predominant adsorption mode of the amino acid zwitterion on TiO2 surface is yet under discussion and varies depending on the conditions and method applied. Some reports suggest amino acid undergo ligand exchange or stabilization at Ti-atom via carboxylic group,17–20,73–78 others describe mixed adsorption modes involving side chain groups.13,25,29 Only two studies reported amino acids to bind at negatively charged oxygens of TiO2 with **ammonium group.16,21

**Table 7.** The total energy of the “amino acid-titanium dioxide” complex in molecular (E1) and in the zwitterionic form (Е2).

| **AA** | **E1, *kJ/mol*** | **E2, *kJ/mol*** |
| --- | --- | --- |
| *aliphatic* | | |
| Ala | ‑738.1 | ‑859.7 |
| Val | ‑720.2 | ‑819.7 |
| Leu | ‑716.9 | ‑827.0 |
| Ile | ‑714.3 | ‑849.7 |
| *aromatic* | | |
| His | ‑634.5 | ‑779.1 |
| Phe | ‑723.0 | ‑825.7 |
| Trp | ‑687.3 | ‑791.7 |
| *nonpolar* | | |
| Gly | ‑741.1 | ‑860.8 |
| Pro | ‑676.8 | ‑727.7 |
| Met | ‑730.8 | ‑845.4 |
| *polar* | | |
| Asn | ‑749.5 | ‑829.1 |
| Gln | ‑754.7 | ‑868.4 |
| Ser | ‑749.4 | ‑850.9 |
| Thr | ‑729.4 | ‑833.4 |
| *charged* | | |
| Lys | ‑727.3 | ‑851.8 |
| Arg | ‑712.5 | ‑806.9 |
| Asp | ‑735.8 | ‑886.5 |
| Glu | ‑735.8 | ‑871.7 |

Structure modeling of the “amino acid-TiO2” complexes for Gly, Asn, Arg, Ala, and Asp showed that the ammonium group of the amino acid is embedded in the nanoparticle defect with the formation of two types of reduced contacts: two-center hydrogen bond and bifurcated hydrogen bond with titanium dioxide.

In the case of glycine (**Figure 8A** and **B**), two hydrogens of the ammonium group form bifurcated hydrogen bonds N‑H...O with oxygens of titanium dioxide with intermolecular distances of 1.69 Å, 1.97 Å and 2.03 Å, 1.73 Å, respectively. Also, the ammonium group of glycine forms one two-centered hydrogen bond with titanium dioxide oxygen N‑H...O, with an intermolecular distance of 1.71 Å.

In the asparagine and arginine complexes with TiO2-nanoparticle (**Figure 8C**, **D**, and **E**, **F**) amino acid molecules are arranged in such a way that two hydrogens of the ammonium group form a hydrogen bond with the nanoparticle surface. Similarly, two hydrogens of amide and guanidine side functions form close two-centered contacts in asparagine and arginine, respectively.

The ammonium group of alanine (**Figure 8G** and **H**) and aspartic acid (**Figure 8I** and **J**) is oriented to oxygens of titanium dioxide, forming three two-centered hydrogen bonds. Aspartic acid forms four hydrogen bonds with oxygen atoms of nanoparticle through its ammonium group and side carboxylic groups with an intermolecular distance of 1.66 Å, 1.66 Å, 1.72 Å, and 2.40 Å, respectively. Ammonium group acts as a major binding site in agreement with previous XPS spectroscopic study.21 Its side carboxylic group forms intramolecular hydrogen bond (1.78 Å) stabilizing the complex, and weak bond with surface oxygen, as previously was reported by Pászti et al.18 The *α*-carboxyl group remains open for interaction with the second layer of amino acids (**Figure 8I** and **J**).

|  |  |
| --- | --- |
| **Gly** | |
| C:\Users\7\Desktop\Figures for pub Lagmuir\Figure 6\Gly-A.tif | C:\Users\7\Desktop\Figures for pub Lagmuir\Figure 6\Gly-B.tif |
| A | B |
| **Asn** | |
| Asn-A.tif | Asn-B.tif |
| C | D |
| **Arg** | |
| Arg-A.tif | Arg-B.tif |
| E | F |
| **Ala** | |
| Ala-A.tif | Ala-B.tif |
| G | H |
| **Asp** | |
| Asp-A.tif | Asp-B.tif |
| I | J |

**Figure 8.** Simulated structure of amino acid-TiO2 nanoparticle complexes: glycine (A, B), asparagine (C, D), arginine (E, F), alanine (G, H) and aspartic acid (I, J). C – cyan, О – red, Н – white, N – dark blue, Ti – grey.

CONCLUSIONS

In this study, we present the investigation of the amino acids adsorption on nanocrystalline TiO2 at pH = 7.4 and temperatures of 0÷40 °C (273.15÷313.15 K) corresponding to biocompatible conditions. For the first time, it was shown the adsorption of all native amino acids is adequately described by the BET model on the entire studied range of concentrations. The calculated thermodynamic parameters confirm the adsorption is physical and for most amino acids proceeds endothermically, indicating the process is entropy driven.

Analysis of adsorption among aliphatic amino acids reveals a gradual increase in Gibbs free energy in homologues series. Branching of the aliphatic chain affects adsorption among isomeric aliphatic amino acids as was shown on examples of Leu and Ile. Binding suppression trend is also clear for hydroxyl-bearing amino acids, where additional methyl group significantly increases the adsorption energy of Thr compared to Ser.

Among polar amino acids, hydroxyl function serves as a better binder to TiO2 than amide group, due to a possible strong bonding between the deprotonated hydroxyl group with surface Ti cations. Aromatic side chain has a lower or similar affinity toward TiO2 compared to aliphatic analogues. This is especially surprising as aromatic and heteroaromatic structures should exhibit diverse absorption bands, as was recently demonstrated on the example of His.16 In the series of charged amino acids basic and acidic species lie on the polar sides of the adsorption scale with Lys and Arg having the strongest affinity and Asp and Glu showing the lowest affinity. This behavior towards negatively charged TiO2 surface speaks for predominantly electrostatic interactions of the charged amino acids.

Although majority of amino acids have a smooth linear trend of Gibbs free energy decrease upon heating, some exhibit complex behavior including formation of local maxima (Gln, Val) or minima (Trp) (**Figure 7A**) coinciding at 20 °C, or sharp change of the trend (Pro) (**Figure 7B**). Such abnormalities are likely associated with a change in the adsorption mechanism within the studied temperature range, which requires additional investigation.

Dependences of ΔH, and Am on HOMO-LUMO band gap Δ, carbonyl oxygen atom charge *QO* and the *α*-nitrogen atom charge *QN* speak for significant influence of carboxylate-ammonium interactions between amino acids in adsorption process, whether it is an amino acid associate disruption or second amino acid layer formation onto TiO2. The amino acid fraction of unbound electrons *Pe* correlates with the Gibbs free energy at 273.15÷303.15°K. The *α*-nitrogen fraction of unbound electrons at 273.15 and 283.15°K significantly affects the saturation, which supports the assumption of *α*-nitrogen as a major adsorption site.

Computational modeling confirms the physical nature of amino acids adsorption towards nanocrystalline TiO2. Each amino acid forms two or three hydrogen bonds via *α*-ammonium group with oxygens located at the surface defect of titanium dioxide nanocluster, which coincides with the assumptions made elsewhere.15,21,23 For acidic and basic amino acids, a formation of additional hydrogen bonds is possible via side functional groups.

The available literature data about the interaction of amino acids with titanium dioxide largely describe the process qualitatively and are difficult to compare because of the variety of descriptive approaches: from the canonical construction of adsorption isotherms to computer modeling. It is also necessary to note the fragmented nature of the data, the narrowness of the research problems without a comprehensive survey of the adsorption properties of a whole range of native amino acids. In our next paper, we plan to disclose a complete theoretical study of the *L*-amino acid-titanium dioxide complexes: structure modeling and establishing relationship between energy characteristics and the experimentally determined values of the enthalpy and entropy of the amino acids adsorption.

ASSOCIATED CONTENT

**Supporting Information**

Chromatograms and the detection limits of analytical techniques. Particle size distribution according to TEM observation of 150 TiO2 nanoparticles. PXRD pattern of the TiO2 sample. The TiO2 sample N2 adsorption-desorption isotherm at 77 K. The Gibbs free energies (ΔG) and equilibrium constants (K) of the amino acids adsorption on nanocrystalline TiO2 at different temperatures, calculated from the Langmuir model. The amino acids adsorption isotherms calculated by the BET equation for each temperature. The Gibbs free energies (ΔG) and equilibrium constants (K) of the amino acids adsorption on nanocrystalline TiO2 at different temperatures, calculated from the BET model.

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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1. See protocols S1 and S2 for calculation of the confidence intervals for G, H, S [↑](#footnote-ref-1)