Determination of the Influence of Various Factors on the Character of Surface Functionalization of Copper(I) and Copper(II) Oxide Nanosensors with Phenylboronic Acid Derivatives

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ABSTRACT: In this work, we attempt to determine the influence of the oxidation state of copper [Cu(I) vs Cu(II)], the nature of the interface (solid/aqueous vs solid/air), the incubation time, and the structure of N-substituted phenylboronic acids (PBAs) functionalizing the surface of copper oxide nanostructures (NSs) on the mode of adsorption. For this purpose, 4-[N-anilino]-[phosphono]-S-methylphenylboronic acid (1-PBA) and its two analogues (2-PBA and bis(1-PBA)) and the copper oxide NSs were synthesized in a surfactant-/ion-free solution via a synthetic route that allows controlling the size and morphology of NSs. The NSs were characterized by scanning electron microscopy, ultraviolet–visible spectroscopy, Raman spectroscopy, and X-ray diffraction, which confirmed the formation of spherical Cu$_2$O nanoparticles (Cu$_2$ONPs) with a size of 1.5 μm to 600 nm crystallized in a cubic cuprite structure and leaf-like CuO nanostructures (CuONSs) with dimensions of 80–180 nm in width and 400–700 nm in length and crystallized in a monoclinic structure. PBA analogues were deposited on the surface of the copper oxide NSs, and adsorption was investigated using surface-enhanced Raman spectroscopy (SERS). The changes in the orientation of the molecule relative to the substrate surface caused by the abovementioned factors were described, and the signal enhancement on the copper oxide NSs was determined. This is the first study using vibrational spectroscopy for these compounds.

1. INTRODUCTION

Arylboronic acids are a class of chemical compounds commonly used in modern synthesis to form C−C and C−heteroatom bonds.1 These acids exhibit a reversible coordination profile that is used as a tool for the construction of stimulus-dependent biconjugates used in pharmaceuticals (e.g., antibiotics2), polymers,3 organic synthesis, electrochemistry, catalysis,4 materials chemistry (e.g., to obtain predictably organized crystalline materials5), or separation processes.6,7 Derivatives of phenylboronic acid (PBA) are used in medicine, for example, in selective drug delivery,8 live cell imaging,9 cancer treatment (e.g., in the boron neutron capture therapy10 and for efficient tumor-targeted chemotherapy with doxorubicin–PBA nanocomplexes11 and low-molecular-weight gels based on PBA derivatives12), in enzyme and HIV inhibition.13,14 PBA are also used in the development of new fluorophores and chemical sensors for glucose in blood14,15 or other body fluids.16

The use of PBA in the treatment of diabetes is based on their specific binding to 1,2-diols or polyols and the formation of reversible covalent PBA/diol complexes.17 The formation of boronic acid esters is favored near or above the $pK_a$ of boronic acid. In order to modify the $pK_a$ of PBA and their efficiency in ester formation, many attempts have been made to synthesize various substituted PBA derivatives.18 For example, it was found that the addition of electron-withdrawing groups to the aromatic ring can lower the $pK_a$ by inductive effects, while the addition of electron-donating substituents can increase the $pK_a$.18 Wulff et al. found that the addition of a nitrogen atom can facilitate the formation of boronate esters.19 On the other hand, the placement of the carbonyl group facilitates the formation of the boronate ester over almost the entire pH range due to the interaction between boron and carbonyl oxygen.20–22 However, compounds containing a carbonyl group have a two-dimensional structure, and the lone pair of electrons of the atoms adjacent to the carbonyl group interacts quite strongly with this group. A similar conjugation is not as

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pronounced in phosphates with a tetrahedral configuration. Therefore, (amino)phosphonic groups are increasingly used in place of carboxyl groups in the rapidly developing field of biochemistry,23–25 although, much work remains to be done in this area. For the abovementioned reasons, we have synthesized N-substituted 4-[(N-H-R)(phosphono)-S-methyl]-phenylboronic acids for our research.

The description of metallic nanostructures (NSs), such as Ag, Au, and Zn nanoparticles (NPs) and semiconductor quantum dots surface modified with PBA derivatives also contributed to the exploration of the use of the NSs for the dynamic quantification of glucose in a physiologically important concentration range of 0–20 mM and pH 7.4,26,27 for the self-regulatory delivery of insulin at a physiological pH,28 and for the detection of sialic acid as a diagnostic and therapeutic agent in cancer.29–33 Despite many studies, both the description of the adsorption mode of PBA derivatives and the change of adsorption under the influence of different environmental conditions and the use of copper NPs have been rather neglected, although Cu has a greater biological significance than Ag or Au.34,35 Accurate adsorption characteristics of PBA derivatives on the surface of NSs is crucial because changes in the intensity of PBA modes can be misinterpreted. That is, changes in the intensity of PBA signals are interpreted quantitatively (e.g., low-intensity signal—low compound concentration, high-intensity signal—high compound concentration) without taking into account the fact that the intensity changes can be associated with a change in the orientation of PBA on the metal surface. Such errors may lead to decreased medical relevance of surface-modified NPs with PBA.

The importance of PBA, the enhanced catalytic activity of copper oxides (as Cu is rapidly oxidized under physiological conditions) in the destruction of cancer cells36–38 and the advantages of surface-enhanced Raman spectroscopy (SERS)—a technique used in a variety of fields,39–45 which allows us to describe the behavior of a selected molecule at the solid/liquid and solid/air interfaces—led us to study the adsorption of N-substituted 4-[(N-H-R)(phosphono)-S-methyl]phenylboronic acid and the changes in adsorption due to changes in the chemical structure of the substituent R (see Figure 1), oxidation state of Cu (copper(I) (Cu2O) and copper(II) (CuO)), and interface type (solid/liquid vs solid/air).

2. MATERIALS AND METHODS

2.1. Synthesis of N-Substituted 4-[(N-H-R)(phosphono)-S-methyl]phenylboronic Acids. 4-[(N-Anilino)(phosphono)-S-methyl]phenylboronic acid (1-PBA), 4-[(N-benzylamino) (phospho-
no)-S-methyl]phenylboronic acid (2-PBA), and bis{4-[(N-anilino)-(phosphono)-S-methyl]phenylboronic acid} (bis{1-PBA}) (Table 1) were synthesized according to the procedure described previously.50 The purity and chemical structure of the compounds were verified by 1H, 13C, 31P, and 11B NMR (Bruker Avance DRX 300 MHz spectrometer, Bruker Polska, Poznań) and ESI-MS spectroscopy (Bruker MicrOTOF-Q spectrometer, Bruker Polska, Poznań).

2.2. Synthesis of Colloidal Cu2ONPs and CuONSs. Copper(I) oxide (cuprous oxide, Cu2ONPs) and copper(II) oxide (cupric oxide, CuONSs) nanostructures (NPs) were prepared by chronoamperometry (at room temperature using a VoltaLab potentiostat PGZ301 and at a constant electrode potential of 0.8 V for 4 h).34,35 0.1 M aqueous solution of lithium chloride (LiCl) from Sigma-Aldrich was freshly prepared and used for CuONS synthesis, while an ethanolic LiCl solution with 10% water was freshly prepared and used for the synthesis of Cu2ONPs. The electrochemical treatment was carried out under an inert atmosphere by slowly bubbling the solution with argon gas in a conventional three-electrode cell with a platinum wire as a counter electrode and an Ag/AgCl (1 M KCl) electrode as a reference electrode (the potential is indicated against this electrode). A copper rod served as the working electrode. Before electrochemical treatment, metallic copper (99.99% Cu) was polished with sandpaper to reduce the grain size and then purified in anhydrous ethanol (99.95% from Sigma-Aldrich). The precipitated product was in the form of orange Cu2ONPs and brown CuONSs.

2.3. Ultraviolet–Visible Spectrum Measurements. The ultraviolet–visible spectra (UV–vis) spectra of an aqueous sol and a sample/sol system, measured after 180 min of mixing, were recorded using a LAMBDA 25 UV–vis spectrometer.

2.4. Scanning Electron Microscopy Measurements. The scanning electron microscopy (SEM) images of an aqueous sol were acquired using a SEM instrument, model S-5000 (Hitachi Ltd., Japan), operated at 20 kV.

2.5. X-ray Diffraction Measurements. X-ray diffraction (XRD) patterns were recorded using a Rigaku UltimaIV X-ray diffractometer (Rigaku Co., Japan) with Cu Kα ( λ = 1.54 Å) radiation at 40 kV and 40 mA in the range of 20–80° (2θ) with a step of 0.02.

2.6. Raman and SERS Measurements. Aqueous solutions of the studied compounds were prepared by dissolving each compound in deionized water (18 Ω cm–1; sample concentration 10–4 M). 10 μL of the sample solution was mixed with 20 μL of aqueous sol solution. The 20 μL of the sample/sol mixture was applied to a glass plate, and the SERS spectra were recorded (no measurements were made for the dried droplet). The spectra were recorded three times at three different locations on each surface. The Raman and SERS spectra were recorded using a HoloSpec f/1.80 Focal Plane Imaging Spectrometer (Kaiser Optical Systems Inc.) equipped with a liquid-nitrogen-cooled CCD detector (Princeton Instruments). The 785.0 nm line of a NIR diode laser (Invictus) was used as the excitation source. The laser power at the sample position was set to ~15 mW. The typical exposure time for each SERS measurement was 40 s with four accumulations. The spectral resolution was set to 4 cm–1. The SERS spectra of a given adsorbate on a given substrate were almost identical, except for small differences (up to 5%) in some band intensities. No spectral changes that could be associated with the decomposition of the sample were observed in these measurements.

2.7. Spectral Analysis. Spectral analysis was performed using a GRAMS/AI program (Galactic Industries Co., Salem, NH).

Several unseparated bands were fitted using the GRAMS/AI program (Galactic Industries Co., Salem, NH). A 50/50 Lorentzian/Gaussian band shape was assumed and fixed for all bands.

3. RESULTS AND DISCUSSION

3.1. Properties of Cu2ONPs. SEM analysis of the bare copper(I) oxide NPs (Cu2ONPs) in Figure 2 (A—scale bar 10 μm and B—scale bar 1.5 μm) shows that the NPs have a spherical shape with a size of 1.5 μm to 600 nm. The UV–vis spectrum of Cu2ONPs confirms these observations, as two small plasma resonances are observed at 330 and 590 nm.
Table 1. Wavenumbers (the Position of the Bands Differ Slightly between the Spectra of the Studied Compounds) and Band Assignment for N-Substituted 4-[(NH-R)(Phosphono)-S-methyl]phenylboronic Acids Adsorbed on the Surfaces of CuONSs and Cu2ONPs

| Wavenumber (cm⁻¹) | Band assignment | Wavenumber (cm⁻¹) | Band assignment |
|-------------------|-----------------|-------------------|-----------------|
| 422               | υ₁(B(=O)₂)      | 881               | υ₁(P–O/C) + υ₂(P(OH) + δ(CPN) |
| 525               | γ(HOBC) + (HOBO)/υ₁ab | 930               | υ₁(P–O)/υ₂(C–P/C/N)/υ₂ab [B₁] |
| 551               | υ₁ab [B₁]/(HOBC)/HOBO/[HOBO] | 989               | υ₁52 |
| 584               | υ₁(NC(H)₂C) + δ(CC(P)N) | 1005              | υ₁52 |
| 622               | δ₁ab [B₁]      | 1012              | δ(BOH) |
| 632               | δ(CBO₂) + δ(CC(P)N) | 1034              | υ₁56 |
| 665               | ωw(CPO)/δ(CC(P)N) | 1045              | υ₁56 + υ₁(C–B) |
| 711               | δoop(CC(B)C) + υ(C–B) | 1075              | υ₁(B–OH) |
| 721               | δoop(CC(B)C) ₂ | 1096              | δ(BOH) + υ₁(B–O) |
| 760               | δ(C=C)          | 1127              | υ₁(C–N) + δ(NH) |
| 789               | υ(C–B) + υ(B–O)/υ₁ | 1178              | υ₁5/ν₈a |
| 807               | δ(CN(H)C)       | 1203              | υ₁7a |

![Figure 2](image_url)

Figure 2. (A,B) SEM images of Cu₂ONPs (measurement conditions: (A) 20.0 kV, ×3.00 K, scale 10.0 μm; and (B) 20.0 kV, ×20.0 K, scale 1.5 μm), (C) excitation spectra (UV−vis) of aqueous solution of Cu₂ONPs (dashed red trace) and a sample/Cu₂ONPs mixture (solid red trace), (D) Raman spectrum of Cu₂ONPs, and (E) XRD pattern of Cu₂ONPs.

(Figure 2C, red dashed line). The first maximum belongs to the band-to-band transition in nanocrystalline Cu₂O [O²⁻:Cu¹⁺ charge-transfer band (O 2p → Cu 3d)], while the second absorption is due to the band gap transition of the CuO layer at the surface of Cu₂O nanocrystals.

3.2. Properties of CuONSs. SEM images of CuONSs obtained by the anodic dissolution of Cu are shown in Figure 3 at different magnifications (A—scale bar 2 μm and B—scale bar 300 nm). These images show that the monodisperse CuONSs have a leaf-like structure with average dimensions of 80–180 nm in width and 400–750 nm in length. Moreover, image B shows that these structures are composed of small spherical particles that are self-aligned, which is consistent with previous data on the directional growth of CuO nanocrystals along the axis. Monodisperse CuONSs form a honeycomb-like skeleton consisting of interconnected networks of sub-micrometer pores 2–3 μm in diameter and 1–1.5 μm thick (Figure 3A).

A UV−vis spectrum of the bare leaf-like CuONSs (black dashed line) and that of the sample adsorbed on their surface (sample/CuONSs; black solid line) are also shown in Figure 3. No optical absorption band at ~290 nm is seen in the UV−vis spectrum of the bare, large-area, self-assembled CuONSs. However, a weak absorption at 219 nm is observed in this spectrum (Figure 3C, black dashed line), which is attributed to...
the direct transfer of electrons. The spectrum of the sample/CuONSs (Figure 3C, black solid line) shows a broad plasmon resonance with a maximum at about 237 nm. This band is probably due to the $\pi-\pi^*$ electronic transition of the aromatic C=C groups of the molecule and/or the electrostatic interaction between the CuONS surface and the molecule deposited on this surface.

The Raman spectrum of CuONSs in Figure 3D shows the formation of the pure monoclinic CuO structure (space group C2/c). For the monoclinic structure with two CuO molecules in the unit cell, the group theory predicts six IR-
active (of $3A_u + 3B_u$ symmetry) and three Raman-active ($A_g + 2B_g$ of oxygen vibrations) optical modes.\(^7\) The three Raman-active modes are observed at 295 ($A_g$), 340 ($B_g$), and 604 cm\(^{-1}\) ($B_g$) (Figure 3D).

The XRD pattern used to characterize the size and size distribution of the crystalline CuO domains is shown in Figure 3E. The diffraction peaks at $2\theta = 32.29, 35.32, 38.54, 48.54, 53.40, 58.07, 61.37, 65.96,$ and $67.81^\circ$ are indexed as [110], [111]/[002], [111]/[200], [202], [020], [202], [113], [311], and [220] planes of the pure CuO nanophase with a monoclinic structure (JCPDS no. 48-1548).\(^7\) The pronounced intensity of the diffraction peaks indicates the highly crystalline nature of the CuONSs.

### 3.3. Influence of the Oxidation State of Copper on Surface Functionalization: CuONSs versus Cu\(_2\)ONPs

The Raman (Figures 4A–6A, blue traces) and SERS spectra at an excitation wavelength 785.0 nm of 1-PBA, 2-PBA, and bis{1-PBA} adsorbed at the surface of CuONSs (Figures 4B–6B, black traces) and Cu\(_2\)ONPs (Figures 4C–6C, red traces) in aqueous solution at pH = 7 are shown in Figures 4–6. The assignment of bands in these spectra (mainly based on the density functional calculation for PBA derivatives\(^7\)) is given in Table 1.

As can be seen in Figure 4B, the SERS spectrum of 1-PBA adsorbed from aqueous solution on the surface of CuONSs is dominated by two broad bands at 584 (full width at half maximum, fwhm = 58 cm\(^{-1}\)) and 670 cm\(^{-1}\) (fwhm = 33 cm\(^{-1}\)) (see Table 1 for the assignment of these bands). These bands are not visible in the corresponding Raman spectrum (Figure 4A). Therefore, it can be assumed that the 1-PBA molecule binds to the CuONSs surface via the fragment $-C(N)PO-$. This implies that the free electron pair on the oxygen (of the phosphonic acid group) and the nitrogen atoms are in direct contact with the substrate surface. Considering the sp\(^2\) and sp\(^3\)
hybridization of boron and oxygen and nitrogen, respectively, it is expected that the phenyl ring (Ph) adopts an inclined orientation with respect to the surface of the substrate. This arrangement confirms a shift of $-5$ cm$^{-1}$ in the wavenumber and a broadening of 3 cm$^{-1}$ in the bandwidth of the SERS signal at 998 cm$^{-1}$ (compared to the values in the corresponding Raman spectrum (Figure 4A)). This statement can be supported by the enhancement of the other bands due to the aromatic ring modes (at 1034, 1183, 1214, 1587, and 1607 cm$^{-1}$). However, there is no evidence of interaction of the boronophenyl ring (PhB(OH)$_2$) with the CuONS surface (weak or no bands due to the vibrations of the boronic acid group).

Together with the change in the oxidation state of copper (CuO vs Cu$_2$O), a change in the character of the 1-PBA interaction with the substrate surface is observed. For 1-PBA adsorbed on Cu$_2$ONPs (Figure 4C), the enhancement of two groups of $\nu_{12}$, $\nu_{15a}$, $\nu_{16a}$, and $\nu_{16b}$ modes is observed (at 1003', 1038', 1593, and 1611 cm$^{-1}$ and at 992', 1029', 1582, and 1605 cm$^{-1}$; where c represents the curve-fitted bands), indicating the contact of two aromatic rings with the Cu$_2$ONP surface. The strong intensity of the SERS signal at 1003 cm$^{-1}$ combined with the absence of a shift in its wavenumber and a broadening of its width indicates the perpendicular arrangement of a ring with respect to the Cu$_2$ONP surface. On the other hand, the weak intensity, downward shift in the wavenumber ($\Delta$ $\nu_{12} = -8$ cm$^{-1}$), and broadening of the width ($\Delta$ $\nu_{12}$, $\nu_{16a}$ = 4 cm$^{-1}$) of the spectral feature at 992 cm$^{-1}$ indicate a nearly horizontal orientation of the second ring.

With the change of the substrate from CuONSs to Cu$_2$ONPs, the bands originating from the vibrations of the P=O fragment lose intensity or disappear (at 1286 and 670 cm$^{-1}$) (Figure 4C). The disappearance of the band at 584 cm$^{-1}$ (on CuONSs) and the increase of intensity at 524, $-600$, and 1383 cm$^{-1}$ in Figure 4C (on Cu$_2$ONPs) are also observed. On the other hand, the wavenumber of the SERS signal at 789 cm$^{-1}$ ($\nu$(B=O) + $\nu$(B–O)) shifts to 781 cm$^{-1}$, and the intensity increases. To explain these observations, it can be assumed that the phosphonic acid fragment is away from the Cu$_2$ONP surface and the sp$^3$ orbital of the boron oxygen atom occupied by the free electron pair has a vertical orientation with respect to this surface. In this orientation, the Ph$_{B(OH)_2}$ ring is tilted by about 70° with respect to the surface normal, that is, it adopts a nearly horizontal orientation on the surface of the substrate, while the Ph ring adopts a nearly vertical orientation.

In the case of 2-PBA adsorbed on CuONSs and Cu$_2$ONPs, the change in the oxidation state of copper also leads to changes in the adsorption mode. For this molecule immobilized on Cu$_2$ONPs (Figure 5C), a strong enhancement of the bands attributed to the vibrations of the aromatic ring (in particular, the 1005 cm$^{-1}$ band), together with the absence of the wavenumber shift and band broadening compared to the SERS spectrum on CuONSs, is evidence of the vertical arrangement of the aromatic ring on the Cu$_2$ONP surface. Also, the absence of spectral features at 937, 789, and 551 cm$^{-1}$ for 2-PBA on Cu$_2$ONPs (Figure 5C), which are the most intense bands in the SERS spectrum of this molecule on CuONSs (Figure 5A), indicates the absence of C–N–Cu$_2$ONP, P–O–Cu$_2$ONP, and B(OH)$_2$–Cu$_2$ONP interactions.

The SERS spectrum recorded immediately after the addition of bis{1-PBA} to the CuONSs sol (Figure 6B) is dominated by the Ph$_{B(OH)_2}$ ring modes ($\nu_{18a}$, $\nu_{19a}$, $\nu_{2a}$, $\nu_{12}$, $\nu_1$, $\nu_{16b}$, and $\nu_{16b}$ (see Table 1)),$^{73}$ of which $\nu_{12}$ is the most intense. Again, the changes in the intensity (Raman vs SERS) of these bands indicate the presence of the ring in the perpendicular orientation on the CuONS surface. Moreover, the absence of the characteristic $\delta$(BOH) mode (at about 1075 cm$^{-1}$) indicates that the $-B(OH)_2$ group is not involved in the interaction with the substrate, so that the 786 and 523 cm$^{-1}$ bands are due to ring vibrations. When the substrate is changed from CuONSs (Figure 6B) to Cu$_2$ONPs (Figure 6C), there is a strong enhancement of the band at 1045 cm$^{-1}$ accompanied by SERS signals of the intermediate intensity at 1015, 881, 797, and 672 cm$^{-1}$ (see Table 1 for band assignments). These bands indicate the adsorption of bis{1-PBA} by the Ph$_{B(OH)_2}$ ring, which is arranged more or less

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**Figure 7.** Time-dependent SERS spectra of bis{4-[(N-anilino)(phosphono)-S-methyl]phenylboronic acid} (bis{1-PBA}) adsorbed at the water/Cu$_2$ONP interface in the spectral range of 1700–300 cm$^{-1}$. 

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horizontally with respect to the Cu2ONP surface, allowing the observation of a strongly enhanced band at 1045 cm\(^{-1}\) (containing a contribution from the C–B vibration) and a weakly enhanced spectral feature at 1005 cm\(^{-1}\). In addition, the \(-\text{C(N)PO}\cdots\text{Cu2ONP}\) interactions are possible with this ring arrangement.

3.4. Effect of Incubation Time on Surface Functionalization. The spectra of bis[1-PBA] adsorbed at the Cu2ONPs/water interface show spectral changes as a function of incubation time (Figure 7). In the spectrum measured immediately after the adsorption of the compound on the substrate surface (\(t = 0\) min), the band at 1045 cm\(^{-1}\) is the most intense, and the band at 1015 cm\(^{-1}\) has an intensity of 30\% of the band at 1045 cm\(^{-1}\). When the incubation time is \(t = 5\) min, the SERS signal at 1045 cm\(^{-1}\) decreases, while the band at 1015 cm\(^{-1}\) increases in intensity (\(I_{1015}/I_{1045} = 0.6\)). Further extension of the incubation time to 10 min leads to a further increase in both the \(I_{1015}/I_{1045}\) intensity ratio to 0.7 and the intensity of the spectral feature at 1005 cm\(^{-1}\), which becomes the strongest band in the spectrum (4 times stronger than the 1045 cm\(^{-1}\) band). Another important change over time in the SERS spectra of bis[1-PBA] adsorbed at the Cu2ONP/water interface is the decrease in the intensity of the 881, 797, 672, and 523 cm\(^{-1}\) bands. Extending the incubation time beyond 10 min has no effect on the SERS spectrum profile, suggesting that only in the first 10 min of adsorption is there a reorientation of the molecule at the Cu2ONP/water interface. This reorientation is the adsorption of an upright position of the molecule, where only one of the PhB(OH)\(_2\) rings is in direct contact with Cu2ONPs versus the flat position, where the PhB(OH)\(_3\) rings are arranged horizontally on the substrate surface and the P–O fragment interacts with Cu2ONPs.

3.5. Effect of Changes in the Chemical Structure on Surface Functionalization. The 2-PBA differs from the 1-PBA by the –CH\(_2\) group (Figure 1). In 1-PBA, the amino group is substituted by a phenyl group, whereas in 2-PBA it is substituted by a benzyl group. Along with this structural change, a change in the adsorption mode is observed. In contrast to 1-PBA on CuONNs (Figure 4B), in the SERS spectrum of 2-PBA on CuONNs (Figure 5B): (1) the 1005 cm\(^{-1}\) band shows very low intensity, and 1032, 632, and 551 cm\(^{-1}\) spectral features are the most intense bands of the phenyl ring, (2) the 937 cm\(^{-1}\) SERS signal \([\nu(\text{C–C/N}) + \nu(\text{P–O})]\) is the strongest band of the spectrum, (3) the 670 and 584 cm\(^{-1}\) bands disappear, and (4) the 789 cm\(^{-1}\) SERS signal is enhanced and has an intensity comparable to that of the 632 cm\(^{-1}\) SERS signal. It can be concluded that after the substitution of the phenyl group (1-PBA) by the benzyl group (2-PBA), the Ph ring is either flat on the surface of the CuONNs or is not in direct contact with this surface. To determine which of these two situations is most likely and which of the two aromatic rings interacts with the CuONNs, one must consider the absence of changes in the wavenumber and bandwidth of the 1005 cm\(^{-1}\) band and the presence of bands associated with the vibrations of the –B(OH)\(_3\) fragment (at 789, 632, and 551 cm\(^{-1}\)). The fact that the SERS signal at 1005 cm\(^{-1}\) has a low intensity, with no broadening in width and no shift in frequency, indicates a vertical orientation of the ring at some distance from the substrate surface. On the other hand, the enhancement of the bands of the boronic acid vibrations indicates that the ring interacting with the CuONNs is PhB(OH)_3.

For the further modification of the molecular structure by doubling the fragment of \(-[\text{N-anilino}(\text{phosphono})-S\text{-methyl}]\text{phenylboronic acid (bis[1-PBA])}, a closer contact between the molecule and the CuONS surface can be proposed, maintaining the orientation of the PhB(OH)\(_3\) ring and limiting the contact between the –C(N)PO– fragment and the CuONNs. This conclusion is based on the intense PhB(OH)\(_3\) modes (see the Results and Discussion section above) and a slight broadening of the bandwidth for these modes.

In the SERS spectra of the studied analogues adsorbed on the Cu2ONP surface, the following changes were observed under the influence of the structural modifications. The two aromatic rings of 1-PBA interact with the substrate surface, which is accompanied by P=O, B–C, and B–O···Cu2ONP interactions. The extension of the chain with the –CH\(_2\) group (in the case of 2-PBA) moves the PhB(OH)\(_3\) ring away from the surface and reduces other types of interactions. Substitution of the Ph ring by a fragment of \(-[\text{N-anilino}(\text{phosphono})-S\text{-methyl}]\text{phenylboronic acid (the bis[1-PBA] case}) forces the molecule to bind to the substrate surface with strong P–O···CuONPs interactions.

3.6. Influence of Interface Type on Surface Functionalization. The change of the interface from Cu2ONPs/water (Figures 4C, 5C, and 6C) to Cu2ONPs/air (Figures 4D, 5D, and 6D) leads to a change of the spectral profile, that is, the adsorbed geometry. Briefly, for 1-PBA at the Cu2ONP/water interface, the very strong 781 cm\(^{-1}\) SERS signal is significantly broadened (\(\Delta_{\text{rel}}\) = 50 cm\(^{-1}\)) and has an asymmetric shape. The decomposition of this band shows that it contains two principal components at 781 and 760 cm\(^{-1}\) \([\delta(\text{ring})]\). The very intense spectral features at 1003 and 1038 cm\(^{-1}\) decrease significantly in intensity compared to those for 1-PBA at the Cu2ONP/water interface, while the SERS signals at 992 and 1029 cm\(^{-1}\) disappear, which indicates that only one of the rings is in contact with the Cu2ONP/air interface in a tilted orientation. Because the bands at 781 and 1075 cm\(^{-1}\) are enhanced in the spectrum, it can be assumed that this ring is a PhB(OH)\(_3\) ring.

2-PBA is adsorbed at the Cu2ONP/air interface by the vertical Ph ring (see the Results and Discussion section above) (Figure 5C), whereas the ring at the Cu2ONP/air interface is not in contact with the substrate surface, as indicated by a slight enhancement of the 1005 cm\(^{-1}\) band, which does not shift in the wavenumber and increases in the bandwidth. The fragment –C(N)PO– is responsible for the adsorption of 2-PBA at the Cu2ONP/air interface, as confirmed by the pronounced 937 cm\(^{-1}\) SERS signal and the broad band with maxima at 632, 622, and 583 cm\(^{-1}\) (see Table 1 for band assignments).

In the case of bis[1-PBA] at the Cu2ONP/air interface, the intensity of a 1045 cm\(^{-1}\) band decreases and is therefore masked by a 1032 cm\(^{-1}\) band whose intensity increases as does the intensity of the SERS signal at 1005 cm\(^{-1}\). At the same time, the SERS signals at 881 and 797 cm\(^{-1}\) are attenuated and enhanced, respectively, and the spectral feature at 523 cm\(^{-1}\) disappears. Considering the assignment of the above bands to the modes proposed in Table 1, we can conclude that the change of the interface brings the PhB(OH)\(_3\) ring closer to the surface, with simultaneous positioning perpendicular to the
CuONP/air interface. The average intensity of the 797 cm$^{-1}$ band also suggests that the B–O has an angular orientation with respect to this interface. For this to be possible, the Ph$_2$(OH)$_2$ ring must be in contact with the substrate via the C$_3$–C$_3$ atoms of the ring.

3.7. Mechanism of Enhancement. The enhancement factor (EF) quantitatively evaluates the effectiveness of the SERS substrate. The most commonly used definition of EF is $EF = (I_{SERS}/c_{SERS})/(I_{RS}/c_{RS})$, where $I_{SERS}$ and $I_{RS}$ are the Raman intensities of SERS and non-SERS substrates, respectively, while $c_{SERS}$ and $c_{RS}$ are the analyte concentrations used for SERS and non-SERS substrates, respectively. For the same analyte concentrations, EF is equal $I_{SERS}/I_{RS}$. The calculated EF is up to 10$^6$ orders of magnitude for Ag and Au@SiO$_2$, 10$^5$ orders of magnitude for Au, 10$^4$ orders of magnitude for Cu and Ti; 10$^3$ orders of magnitude for ZnO, CuO, Cu$_2$O, TiO$_2$, and γ-Fe$_2$O$_3$; and 10$^2$ orders of magnitude for Zn and Fe.$^{76,77}$

The mechanism of the enhancement can be predicted from the SERS spectra. When the adsorbate is physisorbed on the metal surface (electromagnetic (EM) mechanism), its SERS spectrum resembles the Raman spectrum of the free molecule.$^{78,79}$ When the adsorbate is chemisorbed on the metal surface (charge transfer (CT) mechanism), the formed adsorbate–molecule complex leads to drastic changes in the wavenumbers and intensities of the SERS bands of the adsorbate compared to the corresponding Raman bands.$^{76}$

The results of Otero and colleagues have shown that the CT mechanism is responsible for the enormous SERS intensity of the $\nu_{\text{va}}$ mode, which can be used as a marker band to detect and estimate the enhancement produced by the CT mechanism for an adsorbate with an aromatic ring (e.g., benzene, pyridine, pyridazine, and derivatives).$^{80–82}$ Considering the above information and the fact that (1) the intensity, width, and wavenumber of the adsorbate bands are only slightly changed compared to these values in the Raman spectrum and (2) there is no particular enhancement of the band due to the $\nu_{\text{va}}$ mode, it can be concluded that on the tested substrates the EM mechanism is responsible for the signal enhancement.

4. CONCLUSIONS

Compared to their precursor, boronic acid, PBA derivatives show a stronger and more selective antimigratory response to cancer cells in the short term while decreasing the long-term viability of these cells.$^{85,84}$ These properties make PBA analogues promising compounds for new cancer therapies. This motivates us to search for and develop new PBA analogues that can selectively inhibit the metastatic properties of various cancer cells.

On the other hand, it has been shown that the unique property of PBA analogues is that they can reversibly bind diols in a covalent manner, which allows, for example, the measurement of glucose fluctuations or the recognition of sialic acid (the expression of sialoglycans in neoplastic cells is observed$^{85}$), giving them great potential for therapeutic diagnostics.$^{96–98}$ Non-enzymatic glucose sensors based on copper or copper oxide/hydroxide NPs have also been developed.$^{91,92}$ The presence of copper has been shown to increase the rate of the glucose oxidation reaction and the stability of the sensor itself. It has also been shown that boronic acid groups immobilized on the surface of copper oxide NPs can form reversible covalent bonds with diol groups of glycoproteins on the surface of the microbial cell, which greatly increases the antimicrobial or antifungal activity of these NPs.$^{96,98}$ However, it should be kept in mind that copper oxide NPs need to be strictly regulated due to the toxic effect of Cu(II) ions released into the body, which can cause neurodegenerative diseases.$^{100}$ Therefore, the prepared sensors containing boric acid can be used to detect copper ions.

Therefore, not only are PBA analogues being sought after but techniques are also being developed to enable the detection of these molecules, such as the highly sensitive and selective SERS technique. However, the vast majority of these studies focus mainly on the detection capabilities of SERS and are concerned only with the structure of boronic acid derivatives and the nature of the molecular recognition process, ignoring the immobilization of PBA molecules on metal surfaces. Insights into the behavior of immobilized molecules and the intermolecular interactions between the functional groups during molecular recognition are therefore highly desirable for the proper design of SERS sensors. In the absence of such detailed studies, we have performed and described them in this work for a newly developed potential biosensor combining the properties of copper oxide NPs and PBA.

In Figure 8, we present a summary in terms of the depicted changes caused by various factors, such as the oxidation state of copper (Cu(I) vs Cu(II)), the type of interface (solid/aqueous vs solid/air), the incubation time, and the structure of...
the N-substituted analogues of 4-[(NH-R)-(phosphono)-S-methyl]phenylboronic acid that functionalize the surface of the copper oxide NSs after adsorption. Briefly,

1. 1-PBA interacts with the surface of CuONSSs via only one aromatic ring—the phenyl ring, aligned at an angle to this surface, and lone pairs of electrons on the nitrogen and oxygen atoms of the −C(N)PO− fragment. At the Cu2ONP/water interface, the phosphonic acid group is moved away from the substrate surface and two aromatic rings of 1-PBA participate in the interaction with this substrate; the Ph ring adopts a vertical orientation with respect to the substrate surface, while the PhB(OH)2 ring is almost horizontal. The change of the interface from Cu2ONP/water to CuO2NPs/air forces the molecule to “straighten up” so that the contact between the PhB(OH)2 ring and the substrate surface is maintained while the Ph ring moves away from this surface.

2. By replacing the phenyl group with the benzyl group, the 2-PBA molecule interacts with the CuONS surface via the phosphonic acid group and the Ph ring, which moves away from the substrate surface and assumes a nearly vertical orientation with respect to that surface. 2-PBA adsorbs at the Cu2ONP/water and CuO2NP/air interfaces via the vertical Ph ring and the fragment −C(N)PO−, respectively.

3. Further modification of the 1-PBA structure leads to another change in the bis[1-PBA] adsorption mode. That is, bis[1-PBA] is planar aligned near the CuONS surface, while the more or less vertical PhB(OH)2 rings are preserved. On the other hand, immediately after adsorption at the Cu2ONP/water interface, PhB(OH)2 is in contact with this interface and adopts a vertical orientation. In the following minutes after adsorption (up to 10 min), a reorientation is observed—the molecule lies down on the interface so that its two PhB(OH)2 rings adopt a more or less horizontal orientation with respect to the interface. Unlike at the CuO2NP/water interface, the skeleton of bis[1-PBA] adopts an angular orientation.

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E.P.: research foundation, conception and design of the study, synthesis of copper(II) oxide NSs, spectroscopic measurements, data analysis, preparation of figures, writing of the original manuscript, discussion with reviewers, and final drafting of the manuscript; M.S.: synthesis of copper(I) oxide NPs; Y.O.: suggestions for the final drafting of the manuscript.

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**ABBREVIATIONS**

CuONPs, copper(I) oxide nanoparticles; CuONSSs, copper(II) oxide nanostructures; 1-PBA, 4-[(N-anilino)(phosphono)-S-methyl]phenylboronic acid; 2-PBA, 4-[(N-benzylamino)-(phosphono)-S-methyl]phenylboronic acid; bis[1-PBA], bis-4-[(N-anilino)(phosphono)-S-methyl]phenylboronic acid; SERS, surface-enhanced Raman spectroscopy

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