Bioactive Ag$_3$PO$_4$/Polypropylene Composites for Inactivation of SARS-CoV-2 and Other Important Public Health Pathogens

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1. INTRODUCTION

Currently, human beings have been facing a critical problem with the pandemic caused by the emergence of the SARS-CoV-2 virus.\(^1\) Microorganisms (including bacteria, fungi, and viruses) pose serious threats to public health. Particularly, viruses are one of the main causes of diseases worldwide, being responsible for infecting and killing a large part of the population in a given area.\(^2\) Coronaviruses, a class of viruses, are constituted of positive single-stranded RNAs and belong to the Coronavirus family.\(^3\) The establishment of viral tropism depends on the susceptibility and permissiveness of a particular host cell. These types of viruses usually infect animals and humans due to their incredible ability to adapt to their current host, causing respiratory problems and some flu-like symptoms.\(^4\)

SARS-CoV-2 is transmitted by human body fluids and the virion can gain entry through nasopharyngeal and/or oropharyngeal tissues.\(^5\) Recent studies have reported that these viruses can survive for several days on different surfaces.\(^6\) In view of this scenario, efforts in research, development, and manufacture of materials with anti-SARS-CoV-2 activity are increasing, generating potentially safe alternatives to prevent virus contamination and transmission in humans.\(^7\)

Innovations often play an essential role in the acceleration of the discovery of new functional materials.\(^8\) However, their success and applicability largely depend on previous experiences. Our research group has been developing potent biocidal materials based on complex silver-based oxides, such as Ag$_2$CrO$_4$, three polymorphs of Ag$_3$WO$_4$, Ag$_3$PO$_4$, Ag$_2$VO$_3$, and Ag$_2$MoO$_4$ with enhanced antifungal activity. Additionally, to provide a deeper understanding of the atomic and electronic structure and to establish a correlation between the morphology and the biocidal activity, we conducted first-principles calculations at the DFT level to complement and rationalize the experimental findings.\(^9\)

Silver orthophosphate, Ag$_3$PO$_4$ (AP), is an n-type semiconductor with a band gap energy value of 2.4 eV, having high quantum efficiency until 90% for O$_2$ evolution from H$_2$O splitting.\(^10\) Despite its high photocatalytic activities, notable drawbacks have emerged in relation to this material, that is, it invariably displays poor stability when forming metallic Ag$^{3+}$ or dissolved in water,\(^11\) possibly leading to partial dissociation of AP into Ag$^+$ and PO$_4$$^{3-}$. All of these drawbacks have weakened its activity, thus reducing its broad application as a biocidal agent. Very recently, Li et al.\(^12\) discussed and summarized the progress to improve its stability.
and performance, as well as the barriers that should be overcome prior to practical application.

Polypropylene (PP) is a chemically and thermally stable polymer with a wide range of applications, from textile to automotive industries, and one of the most used plastics worldwide since the mid-20th century. PP is used as an immobilization matrix and a substrate for biocompatibility and biocide activity tests in devices of the hospital-medical field, such as masks, aprons, and food trays, among other applications. Based on that, the strategy adopted in this work was to produce a bioactive AP/PP composite to stabilize AP, and the inactivation of bacteria (Staphylococcus aureus and Escherichia coli), fungus (Candida albicans), and virus (SARS-CoV-2) has been investigated. The present composites have the potential for a variety of technological applications, such as the manufacture of packaging, fabrics, and protective equipment, as well as for surface treatment. The underlying technology based on this composite can be considered as an innovation to protect man and avoid the contamination, transmission, and proliferation of SARS-CoV-2 worldwide.

2. METHODS

Synthesis of AP. AP was synthesized by the coprecipitation method in aqueous medium. Separate solutions of NaH$_2$PO$_4$·H$_2$O (98%, Sigma-Aldrich) and AgNO$_3$ (99.8%, Cennabras) were prepared with molar ratios of 1:1. The 100 mL solution of 1 × 10$^{-3}$ mol of NaH$_2$PO$_4$ was added to the 100 mL solution of 1 × 10$^{-3}$ mol of AgNO$_3$ under constant stirring. After the addition, the suspension was stirred for 20 min. The precipitates were washed with deionized water and centrifuged, and this process was repeated until pH neutrality (≅7) was reached. After the washing procedure, this powder was dried at 60 °C for 10 h. The samples were labeled as AP.

Preparation of PP/AP Composites. The composites were compounded using an internal mixer (Thermo Scientific—Polylab OS model) with a counter-rotating rotor connected to the Rheomix 600 OS Lab mixing chamber. The conditions employed within the closed and locked chamber were a temperature of 200 °C and a rotor speed of 50 rpm for 4 min, which operated with 70% of its capacity. AP was added to the polymer (PP) in proportions of 0.5, 1.0, and 3.0% wt.

The processing conditions, especially those concerning the thread profile and temperatures, were outlined to ensure an adequate dispersive and distributive mixture. The samples were named according to the AP content as follows: PP/0.5AP, PP/1AP, and PP/3AP. The experimental characterizations, biological tests, and theoretical calculations are described in Supporting Information.

3. RESULTS AND DISCUSSION

From the XRD patterns of the PP/AP composites, it is possible to observe that the alpha structure of PP was maintained, as well as the structure of the crystals of AP, suggesting the successful formation of the PP/AP composites (see Figure S4 in Supporting Information). These results corroborate with FTIR spectroscopy, micro-Raman, UV–vis, and atomic force microscopy (AFM) analyses, showing that at long and short ranges, the structure of AP is maintained within the polymeric matrix (Figures S5–S8). The interactions between the matrix and the AP particles, as well as their dispersion state, were evaluated by rheological measurements in the dynamic state, and SEM was conducted on cryogenically fractured samples (see Figure 1).

PP presents a pseudoplastic flow behavior with viscosity decrease as a function of frequency. A gradual increase in the viscosity of the Newtonian plateau region can be observed with the increase of the filler content. The low-frequency region named terminal zone is in the $G' \propto \omega$ and $G'' \propto \omega^2$ regions. When the degree of dispersion increases, powers 1 and 2 change to lower values. Figure 1B presents the same inclination values, which means low dispersion exists between the filler and the polymer matrix because a percolation network to observe that the alpha structure of PP was maintained, as well as the structure of the crystals of AP, suggesting the successful formation of the PP/AP composites (see Figure S4 in Supporting Information). These results corroborate with FTIR spectroscopy, micro-Raman, UV–vis, and atomic force microscopy (AFM) analyses, showing that at long and short ranges, the structure of AP is maintained within the polymeric matrix (Figures S5–S8). The interactions between the matrix and the AP particles, as well as their dispersion state, were evaluated by rheological measurements in the dynamic state, and SEM was conducted on cryogenically fractured samples (see Figure 1).

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Figure 2. Contact angle results of pristine PP, PP/05AP, PP/1AP, and PP/3AP.

PP/3AP samples (Figure 1E,F), some micron-sized agglomerates of AP are formed, corroborating the structural data.

Figure 2 displays the contact angle results of the pristine PP and PP/AP composites. It is observed that for the PP sample, the contact angle value is 86° and it significantly increases to 98, 94, and 95° for the PP/05AP, PP/1AP, and PP/3AP samples, showing statistically significant differences between samples (p < 0.05). Because PP is an apolar polymer with hydrophobic properties,47 by increasing the AP semiconductor content, there is a consequent increase in hydrophobicity. Kasraei and Azarsina48 observed the same behavior in Ag-based nanocomposites in polymeric matrices. The formation of a composite with a more hydrophobic surface may inhibit and/or decrease the activities of pathogenic microorganisms as a result of the lower interaction between the composite surface and the microorganism.

Once AP was successfully incorporated into the polymeric PP matrix, contact microbicidal inhibition tests were performed for S. aureus (Gram +), E. coli (Gram -), and C. albicans (fungi). The time-kill tests (Figure 3) were carried out following the microbicidal evolution of the obtained materials to corroborate the halo of inhibition tests (Figure S9). The analyses were performed using time variations [2, 4, 8, 16, 32, 64, 128, 256, 512, 1440 (1 day), 2880 (2 days), and 4320 min (3 days)]. For S. aureus (Figure 3A), it was possible to note a reduction of 99.999% in colony-forming units (CFU) at the maximum time (3 days) for the PP/3AP sample. In contrast, for E. coli (Figure 3B), there was a reduction of 99.999% at 256 min (~4.5 h) for all composites. This difference between the elimination capacities of these tested bacteria was due to the fact that the composition of their membranes is very different, conferring greater resistance to the Gram + S. aureus.49−58 For the elimination of C. albicans, that is, a more complex cellular constitution, the PP/3AP composite had contact elimination of 99% at the maximum time (3 days). For all microorganisms, it is observed that the PP/3AP sample was more effective, inactivating at least 99% of all microorganisms (bacteria and fungus) tested.

Concerning the elimination of more complex microorganisms, tests were carried out to verify the elimination of the SARS-CoV-2 virus by placing it on the surface of contact with the composite materials obtained for 5 min (see Figure 4). The result of viricidal efficacy is negative when the cytopathic effects are visualized and positive when there is no cytopathic effect detected. To determine the viral inhibition index, the logarithmic difference between the control group and the group in contact with the composite samples (percentage of viral elimination compared to viral control, viral solution, and DMEN) was calculated. An analysis of the results renders that the PP and PP/05 AP samples (Figure 4A,B) do not show viral elimination, whereas the PP/1AP and PP/3AP samples (Figure 4C,D) reveal 90% viral elimination. The results regarding the increasing elimination as a function of the increase in the concentration of AP in PP are consistent with the detections expected because the microbicidal action comes from the semiconductor.59−64 In addition, the semiconductor/polymer interaction impairs the surface fixation of pathogens in the composite, according to the contact angle results.

It is well established that the photocatalytic and biocide activities of a given semiconductor are dependent on the efficient formation and separation of electrons (e−) and holes (h+) and the low recombination ratio of the e−−h+ pair. It has potent antimicrobial activity, which is typically associated with the contact-induced membrane stress and is associated with the presence of reactive oxygen species (ROS), thus having potential for a variety of biomedical applications.17−19 20−26

The activation of both molecular oxygen, O2, and water, H2O, is a fundamental step in almost all photocatalytic oxidation/reduction reactions and then the generation of ROS. At this point, it is important to note that the possible mechanism of the biocide activity is very dependent not only on the oxidation/reduction capacity of the different ROS but also on the nature of the radical chain reactions. Located in the valence band of the semiconductor, h+ reacts with H2O to form a hydroxyl radical (·OH) and a proton (H+), while the e−, which is excited in the conduction band, interacts with O2 to form O2·−. Parallel reactions involving the formation of hydrogen peroxide (H2O2), which is developed during the disproportionation of O2·−, can also occur, further transforming it into ·OH and forming singlet oxygen (1O2). In summary, ·OH, H2O2, ·O2·−, and 1O2 are generated by the stepwise oxidation of H2O, while the stepwise reduction of O2 generates ·O2·−, H2O2, and ·OH. These free radicals and reactive species are capable of killing microorganisms by the
oxidation and breaking of cellular constituents and membranes of bacteria, fungi, and viruses.\(^{69-74}\) The ability to generate ROS has been explored by analyzing the adsorption processes of \(\text{H}_2\text{O}\) and \(\text{O}_2\) molecules on the AP (110) surface. This surface has been selected because several experimental\(^{75-79}\) and theoretical studies\(^{80}\) report that this surface is responsible for the high catalytic activity of AP.

The Ag cations on the first two layers of the clean (110) surface are low twofold coordinated in comparison with fourfold coordinated Ag cations in the bulk (see Figure 5A). This low coordination has already been reported as having a direct correspondence with increased biocide activity, consequently activating molecules that interact with an n-type semiconductor.\(^{81-83}\) Bader analysis of the electron density distribution\(^{84}\) reveals that these Ag cations are more reduced than the innermost ones. Thus, the effective charge of the AP (110) surface from the topmost layer is \(+0.50-0.52\) \(\text{e}^+\), whereas those of the Ag bulk cations are \(+0.41-0.44\) \(\text{e}^+\). This fact suggests that Ag superficial cations would be preferential sites for molecular adsorption, promoting electron transfer processes to account for their lack of electron density.

Different superficial Ag cations were considered as potential sites for the \(\text{H}_2\text{O}\) molecule adsorption. The most favorable site with a calculated adsorption energy of \(-1.410\) eV is depicted in Figure 5B. This adsorption process also distorts the surface with concomitant breaking bond processes between the Ag cation and the farthest O anion. The analysis of the bond critical points demonstrates a significant weakening of the covalent bond between the O atom of \(\text{H}_2\text{O}\) and the H atom closer to the surface with concomitant enlargement of the bond distance from 0.97 to 1.10 Å. It is also shown that the \(\text{H}_2\text{O}\) molecule establishes a second bond with the surface in the form of a weak covalent bond between its H atom and the nearest surface O atom. The emerging Ag–O interaction between the \(\text{H}_2\text{O}\) molecule and the surface is characterized as van der Waals-type according to the Bader analysis. These results demonstrate that the n-type semiconductor surface activates the \(\text{H}_2\text{O}\) molecule, leading to the formation of the \(^*\)OH and H\(^+\) species.

Ab initio molecular dynamics (AIMD) simulations at low temperatures (see Videos S1 and S2 in Supporting Information) starting from the described adsorption arrangement reveal the spontaneous breakage of the weakened O–H bond of the adsorbed \(\text{H}_2\text{O}\) molecule, corresponding to the early events associated to the formation of \(^*\)OH and H\(^+\), which remain adsorbed on the surface. There is a O–H bond involving the nearest O atom on the second layer, whereas the \(^*\)OH is linked to the Ag cation on the first layer. At a higher temperature (50 K), this process occurs more rapidly, with more intense vibrational frequencies of both newly formed H–O and Ag–O bonds (Figure 5).

Similarly, an \(\text{O}_2\) molecule is adsorbed on the surface at the same site with a calculated adsorption energy of \(-1.458\) eV, as shown in Figure 6A. After the relaxation process, the molecule displays an increased bond length from 1.23 Å (for the free molecule) to 1.30 Å, a clear indication of bond weakening caused by the interaction with the surface (Figure 6B). Furthermore, the total spin calculated after adsorption corresponds to doublet oxygen \((S = 1/2)\), differently from the triplet \((S = 1)\) for the free \(\text{O}_2\) molecule. These results can be associated with the initial events resulting from the formation of \(^*\)O\(_2^-\) in the AP (110) surface.

4. CONCLUSIONS

Pathogenic microorganisms (bacteria, fungi, and viruses) represent a severe problem in public health. Therefore, there is great interest in developing advanced materials and new technologies capable of inactivating opportunistic pathogens, thus reducing the risk of infection and transmission. In this
work, a AP/PP composite was developed and optimized for the first time. This composite has the physicochemical property of oxidizing bacteria (S. aureus and E. coli), fungi (C. albicans), and SARS-COV-2 viruses by surface contact. The adsorption processes of H$_2$O and O$_2$ molecules on the most active AP (110) surface were modeled through ab initio calculations to explain the early events of the formation of both the hydroxyl radical $^\cdot$OH and superoxide radical anion $^\cdot$O$_2$$^-\$ as reactive species in the biocide activity.

Figure 4. Microscopic images of cell cultures incubated with viral dilutions in contact with (A) PP, (B) PP/0.5AP, (C) PP/1AP, and (D) PP/3AP samples.

Figure 5. (A) Side views of the relaxed clean AP (110) surface. The Ag cation where H$_2$O and O$_2$ molecules adsorb is highlighted in black color. (B) Side and top views of the H$_2$O adsorption system. O, P, and Ag atoms on the surface are represented by red, violet, and gray balls, respectively. For clarity, the O and H atoms of the H$_2$O molecule are indicated in blue and white colors, respectively.
Figure 6. Side (A) and top (B) views of one O$_2$ molecule adsorbed on the AP (110) surface. O, P, and Ag atoms on the surface are represented by red, violet, and gray balls, respectively. For clarity, the Ag adsorption site and the O$_2$ molecule are colored in black and blue, respectively.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcb.1c05225.

Video of the AIMD simulations of the activation of a water molecule on the AP (110) surface at 10 K during 900 fs (MPG)

Detailed experimental and theoretical procedures, structure analyses, DRX, micro-Raman, FTIR, DRS, and AFM, and halo of inhibition tests (PDF) (PDF)

Video of the AIMD simulations of the activation of a water molecule on the AP (110) surface at 50 K during 900 fs (MPG)

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L.K.R. and M.A.: Data curation, formal analysis, investigation, methodology, writing—original draft, review and editing, and visualization. L.R.L., D.C., R.S.P., F.L., M.O.G., L.N.M., and L.F.A.: Data curation, formal analysis, methodology, original draft, review and editing, and visualization. L.H.M., R.M.T.G., M.A.S.-M., C.P.S., I.L.V.R., and E.L.: Funding acquisition, resources, supervision, writing—original draft, writing—review and editing, and visualization.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AP silver phosphate, Ag₃PO₄
PP Polypropylene
XRD X-ray diffraction
FTIR Fourier transform infrared spectroscopy
AFM atomic force microscopy
UV–vis ultraviolet–visible
SEM scanning electron microscopy
SARS severe acute respiratory syndrome
MERS Middle East respiratory syndrome
DFT density functional theory
ICSD Inorganic Crystal Structure Database
G’ storage modulus
G” loss modulus
e− electron
h+ hole
Eg band gap energy

CFU colony-forming unit

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