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Letter

Inactivation of Coronaviruses and Phage Phi6 from Irradiation across UVC Wavelengths

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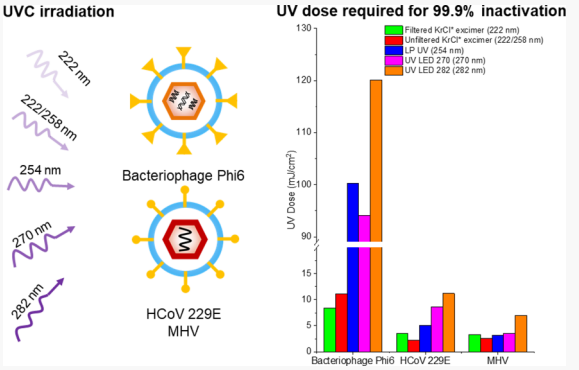
ABSTRACT: Ultraviolet (UV) devices emitting UVC irradiation (200−280 nm) have proven to be effective for virus disinfection, especially on surfaces and in air, due to their rapid effectiveness and limited to no material corrosion. Numerous studies of UV-induced inactivation focused on nonenveloped viruses. Little is known about UVC action on enveloped viruses across UVC wavelengths. In this study, we determined inactivation efficiencies of two coronaviruses (ssRNA) and an enveloped dsRNA bacteriophage surrogate in buffered aqueous solution (pH 7.4) using five commonly available UVC devices that uniquely emit light at different wavelengths spanning 222 nm emitting krypton chloride (KrCl*) excimers to 282 nm emitting UVC LEDs. Our results show that enveloped viruses can be effectively inactivated using UVC devices, among which the KrCl* excimer had the best disinfection performance (i.e., highest inactivation rate) for all three enveloped viruses. The coronaviruses exhibited similar sensitivities to UV irradiation across the UVC range, whereas the bacteriophage surrogate was much more resistant and exhibited significantly higher sensitivity to the Far UVC (<230 nm) irradiation. This study provides necessary information and guidance for using UVC devices for enveloped virus disinfection, which may help control virus transmission in public spaces during the ongoing COVID-19 pandemic and beyond.



INTRODUCTION

Enveloped viruses, such as coronaviruses (e.g., SARS-CoV-1, MERS-CoV, and SARS-CoV-2), have caused several global pandemics of respiratory diseases in the 21st century,[1] including SARS, MERS, and the ongoing COVID-19 pandemic. Respiratory viruses are transmitted primarily via person-to-person pathways through respiratory secretions and airborne droplets.[2] In addition, indirect transmission through contact with contaminated surfaces followed by touching facial areas may also occur,[3] especially considering some enveloped viruses, such as SARS-CoV-2, can stay viable on some common surfaces up to several days.[4,5] Effective disinfection procedures can help reduce viral transmissions, especially in high risk places, such as hospitals, other healthcare facilities, and public transportation systems.

Ultraviolet (UV) devices emitting UVC irradiation (200−280 nm) have proven to be effective for virus disinfection.[6−9] Compared to other disinfection methods (e.g., heating and using chemical oxidants), UVC disinfection has several advantages, including rapid effectiveness, no chemical residual, and limited to no material degradation.[8] UVC devices such as low-pressure (LP) and medium-pressure mercury lamps have been widely used for disinfection of water, air, and surfaces since the early 20th century.[10] These devices, however, are not safe for human exposures due to adverse effects on human skin and eyes.[11,12] Recently, far UVC devices (emitting UVC irradiation in the wavelength range of 200−230 nm) like krypton chloride (KrCl*) excimer have been proposed to disinfect occupied public spaces based on their limited human health exposure risks.[13−15]

UVC irradiation inactivates viruses by damaging nucleic acids (DNA or RNA) and proteins. Previous studies of UV action on nonenveloped viruses, such as adenovirus and MS2 coliphage, suggested that nucleic acid damage tends to dominate virus inactivation with a peak efficacy around 260−265 nm, whereas protein damage is important at wavelengths ∼280 and <240 nm corresponding to protein absorbance peaks.[6,7,16,17] Enveloped viruses, however, may respond to UVC irradiation differently due to their unique structure, which contains a lipid bilayer external to a nucleocapsid that is studded with an outer layer of virus envelop glycoproteins.[18] Little is known about UVC action on enveloped viruses across UVC wavelengths.

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In this study, UVC inactivation of three enveloped viruses was determined using five UVC devices with different emission spectra emitting across the UVC range. The device performances were compared to evaluate the relative sensitivities of enveloped viruses to different wavelengths of UVC irradiation. Finally, recommendations are made for using UVC devices for enveloped virus disinfection in public and other high risk spaces.

MATERIALS AND METHODS

Virus Stock Preparation and Enumeration. Three enveloped viruses with different genome organizations were used for this investigation: Bacteriophage Phi6 and two coronaviruses: Human coronavirus (HCoV) 229E and murine hepatitis virus (MHV) (Table S1). The detailed methods for virus propagation, purification, and enumeration are included in the Supporting Information.

UV Exposure Experiments. The UV lamps were set up in a bench-scale collimated beam apparatus (Figure 1A) as described by Bolton and Linden.[19] Normalized emission spectra for these UV lamps as used in the experiments (Figure 1B) were measured using a calibrated Maya 2000 Pro spectrometer (Ocean Insight, Dunedin, FL). Four UV sources were used in this investigation: a KrCl* excimer lamp emitting primarily at 222 nm (USHIO, Cypress, CA, USA), a conventional LP mercury lamp emitting at 254 nm, and two benchtop UV LED systems with peak emission wavelengths of 270 and 282 nm (AquiSense Technologies, Earlanger, KY, USA). The KrCl* excimer emissions were primarily at 222 nm with a small peak at 258 nm (Figure 1B). To isolate the irradiation around 222 nm, a 220 nm bandpass filter (Andover Corporation, Salem, NH, USA) was applied just below the excimer lamp. The excimer source exposures were examined with both filtered and unfiltered emissions.

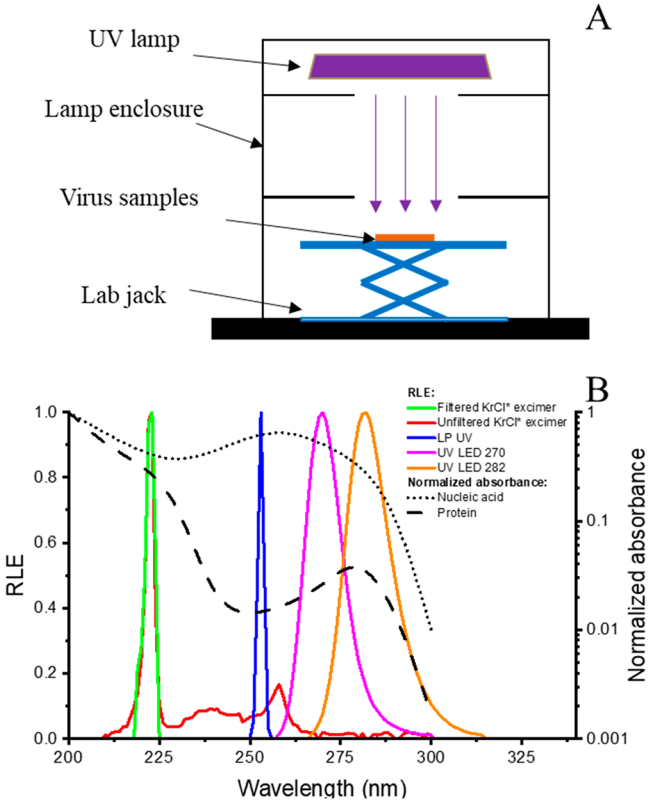

Figure 1. Schematic diagram of bench-scale collimated beam apparatus (A) and absorbance of nucleic acid (DNA/RNA) and protein (normalized to maximum value at 200 nm) and relative lamp emission (RLE) for the UV devices used in this investigation (B), including a filtered KrCl* excimer (with a 220 nm bandpass filter), an unfiltered KrCl* excimer, a LP mercury lamp, and two UV LED lamps with peak emission wavelengths of 270 and 282 nm. The nucleic acid and protein absorbance data were reproduced from Setlow and Doyle[20] and Voet et al.[21]

UV exposure experiments were performed according to a standard protocol by Bolton and Linden.[19] Briefly, aqueous virus samples were placed in 60 mm diameter Petri dishes for UV exposure tests. The UV incident irradiance at the sample surface was measured using a calibrated radiometer (ILT-2400, International Light Technologies, Inc., Peabody, MA, USA). UV exposure time for each sample was calculated using the target UV fluences for unweighted emissions between 200 and 300 nm according to a protocol by Linden and Darby[22] and Bolton and Linden.[19] The infectivity of virus samples without and after UV exposure was measured, and the infectivity reduction in $\log_{10}$ scale was determined. Detailed methods for UV exposure experiments are included in the Supporting Information.

Statistical Analysis. The UV dose response using different UVC devices were evaluated based on a pseudo-first-order inactivation kinetics model in $\log_{10}$-scale

$$\log_{10} I = \log_{10}\left(\frac{N_0}{N}\right) = k \times D$$

where $\log_{10} I$ is infectivity reduction in the $\log_{10}$ scale, N_0 and N are the virus sample infectivity before and after UV exposure, D is the UV fluence in mJ/cm^2, and k is the pseudo-first-order inactivation rate constant in cm^2/mJ computed from a $\log_{10}$-scale kinetic model. The $\log_{10}$-scale inactivation rate constant was used so that it is easy to calculate the log inactivation from the rate constant.

The mean and standard error (SE) of the inactivation rate constants were calculated using the "linear regression" function in OriginPro 2021 (intercept was fixed at zero). Samples with infectivity equal to or less than the detection limits were excluded from the regression analyses. Analysis of covariance (ANCOVA) was used to determine if there was a statistically significant difference in the inactivation rate constants for different viruses or between different UVC devices.

RESULTS AND DISCUSSION

Comparing Three Enveloped Viruses. Dose response of bacteriophage Phi6, HCoV 229E, and MHV to UV irradiation from all tested UVC devices are shown in Figure 2, and the pseudo-first-order inactivation rate constants (±S.E.) are listed in Table 1. The rate constant (computed from a $\log_{10}$-scale kinetic model) for bacteriophage Phi6 using the LP UV lamp was measured as 0.030 ± 0.002 cm^2/mJ, which is similar to the value from a previous study by Ye et al.[23] (0.029 cm^2/mJ; converted to values based on $\log_{10}$-scale kinetic model) and more than 19 times lower (i.e., it was more UV resistant) than those for HCoV 229E and MHV (0.59 ± 0.04 and 0.93 ± 0.04 cm^2/mJ, respectively). Similar trends between viruses were also observed for other tested UVC devices (Table 1), suggesting that such relatively high resistance of bacteriophage Phi6 against UVC irradiation was not dependent on the UVC device or emission wavelength. The unique sensitivity to UVC

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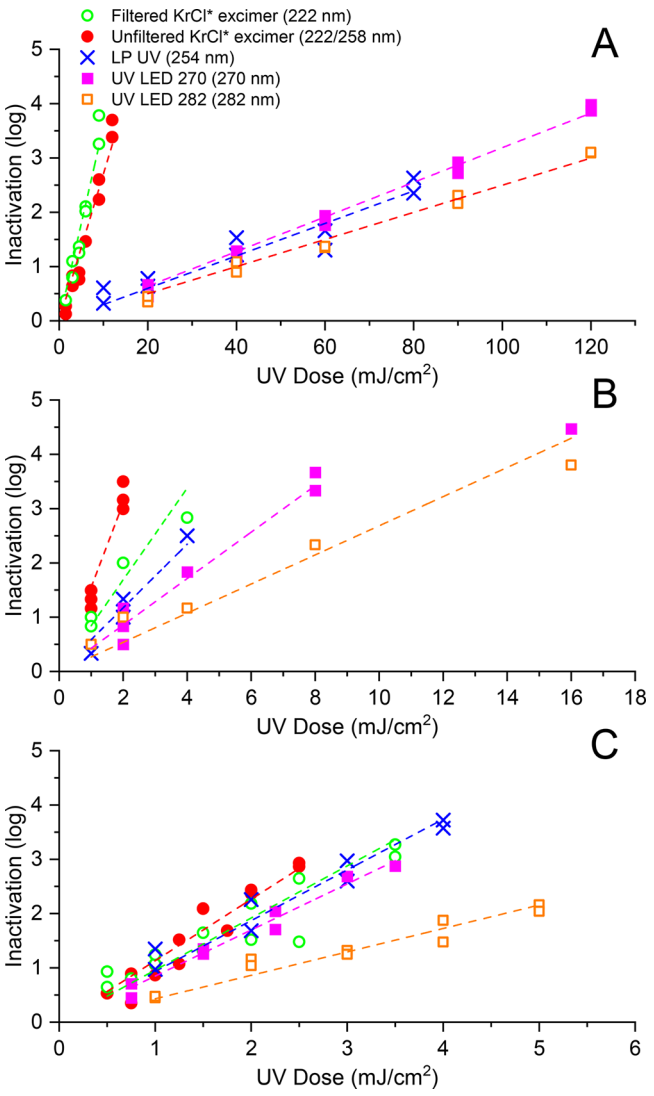

Figure 2. Dose response of bacteriophage Phi6 (A), HCoV 229E (B), and MHV (C) to UV irradiation from all tested UVC devices. Dashed lines represent linear regression results computed from experimental data. The adjusted R^2 values for all linear regression analyses are greater than 0.96. Primary emission wavelengths for UVC devices are listed in the legend.

irradiation between viruses is likely attributable to the differences in their genome organization despite the fact that they are all enveloped. Previous literature suggested that dsRNA viruses (e.g., bacteriophage Phi6) were generally more resistant to UV_{254} irradiation than ssRNA viruses (e.g., HCoV 229E and MHV).[24] The shorter genome size of bacteriophage Phi6 (Table S1) compared to the coronaviruses tested also likely contributed to its higher UV resistance as previous studies have concluded that viruses with large genomes are more susceptible to UV inactivation than viruses with small genomes.[25,26] The nucleic acid sequence composition in the genome (Table S1) also affects the viral UV sensitivity in which adjacent pyrimidines are photoreactive under UVC irradiation, forming pyrimidine dimers.[27,28] Thus, fewer adjacent pyrimidines in bacteriophage Phi6 genome (Table S1) may also contribute to its higher UV resistance. Other than these factors, genome segmentation in bacteriophage Phi6 may also play an important role in its high UV resistance, but the precise role needs to be investigated in future research.

Minor differences in inactivation rate constants were also observed between HCoV 229E and MHV. The inactivation rate constants for MHV were significantly higher than those for HCoV 229E ($P < 0.05$) using LP UV lamps and two tested UV LEDs, which is likely attributed to the larger genome of MHV compared to HCoV 229E (approximately 31 vs 27 kb; Table S1). Surprisingly, a significantly lower rate constant ($P < 0.05$) was observed for MHV compared to HCoV 229E using the unfiltered KrCl* excimer, and no significant difference ($P > 0.05$) was observed using the filtered KrCl* excimer. One possible explanation for such different trends is that MHV may be less susceptible to protein damage than HCoV 229E, and the filtered and unfiltered KrCl* excimers are capable of producing much more protein damage than the LP UV lamp and UV LEDs due to their irradiation around 222 nm.[16,17]

Comparing Different UVC devices. The performance of the UVC devices (i.e., inactivation rate constant; Table 1) tested for bacteriophage Phi6 was ranked as filtered KrCl* excimer > unfiltered KrCl* excimer > LED 270 ≈ ($P > 0.05$) LP UV lamp > LED 282. For HCoV 229E and MHV, the performance was ranked as unfiltered KrCl* excimer > filtered KrCl* excimer > LP UV lamp > LED 270 > LED 282. The relative device-specific sensitivities of all three selected enveloped viruses, reported as the ratio of the inactivation rate constant for a specific UVC device to the values for the LP UV lamp, were also calculated and shown in Figure 3.

The greater inactivation performance of KrCl* excimers (unfiltered and filtered) compared to other UVC devices was observed for all selected enveloped viruses, which is similar to nonenveloped viruses (e.g., MS2 coliphage and adenovirus) in previous studies.[6,7,29] This is likely because KrCl* excimers were capable of dealing greater protein damage than other devices due to the higher protein absorbance at far UVC wavelengths around 222 nm emitted by these devices (Figure 1B and Figure S2). Comparing the unfiltered and filtered KrCl* excimer, the unfiltered KrCl* excimers, including the 222 and 258 nm peaks, performed better for HCoV 229E and MHV ($P < 0.05$). This could be attributed to some combined effects of irradiance at 222 and 258 nm, targeting both protein

Table 1. Device-Specific Inactivation Rate Constants (Computed from a Log_{10}-Scale Kinetic Model) for Bacteriophage Phi6, HCoV 229E, and MHV

	k (mean ± SE; cm^2/mJ)		
UVC devices	Phi 6	HCoV 229E	MHV
Filtered KrCl* excimer (222 nm)	0.36 ± 0.01	0.84 ± 0.06	1.03 ± 0.06
Unfiltered KrCl* excimer (222/258 nm)	0.27 ± 0.01	1.33 ± 0.10	1.22 ± 0.04
LP UV (254 nm)	0.030 ± 0.002	0.59 ± 0.04	0.93 ± 0.04
LED 270 (270 nm)	0.032 ± 0.001	0.35 ± 0.03	0.85 ± 0.02
LED 282 (282 nm)	0.025 ± 0.000	0.27 ± 0.02	0.43 ± 0.02

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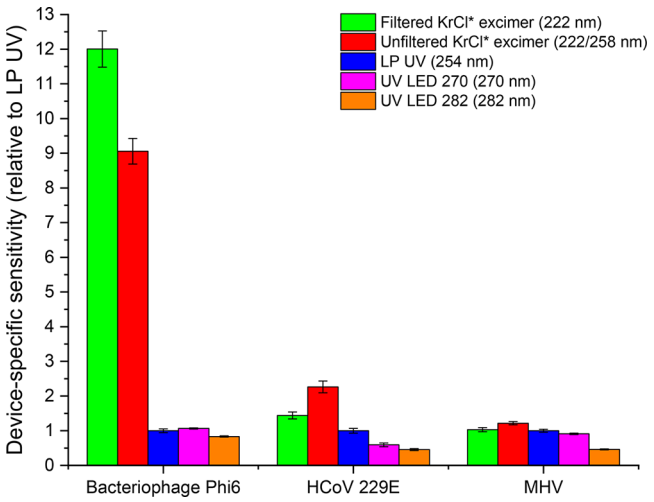

Figure 3. Relative device-specific sensitivity (relative to LP UV lamp) of bacteriophage Phi6, HCoV 229E, and MHV. Primary emission wavelengths for UVC devices are listed in the legend.

and nucleic acid damage on viruses. Similar combined effect for 222 and 254 nm in UVC inactivation was also observed on other viruses, such as MS2 coliphage and adenovirus.[9,30] Interestingly, the filtered KrCl* excimer performed better for inactivating bacteriophage Phi6 than the unfiltered KrCl* excimer. Bacteriophage Phi6 was much more susceptible to UV 222 nm irradiation than HCoV 229E and MHV (Figure 2). The additional protein damage provided by the pure 222 nm filtered KrCl* excimer may outweigh any synergistic effect of the induced protein and nucleic acid damage from the unfiltered KrCl* excimer for Phi6. The fluence attributed to Far UVC around 222 nm (200−230 nm) in the unfiltered UV source was proportionally about 55.1% percent of the fluence attributed to 222 nm for the filtered source (which was 100% emission around 222 nm).

The LP UV lamp performed marginally better than LED 270. Nucleic acid damage is the primary inactivation mechanism for both devices based on their emission spectrum (Figure 1B and Figure S2), and it is likely that the average spectral sensitivity of the viral genome to the LP UV lamp is slightly higher than that for LED 270. LED 282 provided the lowest inactivation rate constants for all selected viruses, despite the potential synergistic effect of wavelengths affecting both protein and nucleic acid damage due to its emission spectrum (267−314 nm with a peak emission wavelength at 282 nm; Figure 1B) overlapping both nucleic acid absorbance and the secondary peak of protein absorbance (Figure 1B and Figure S2).[20,21] This smaller effect is plausible because both viral nucleic acids and proteins absorb less UV irradiation in the wavelength range emitted from LED 282 compared to the other sources. A previous study on adenovirus reported that viral proteins are less sensitive to damage at high wavelengths (>280 nm) compared to low wavelengths (<240 nm)[17] supporting this hypothesis. Spectral sensitivity of nucleic acids at greater than 280 nm is much lower than at 250−270 nm.[6,31] Similarly, the protein absorbance at 280 nm is much lower compared to below 230 nm (Figure 1B and Figure S2).[20] Finally, a portion of the irradiation from LED 282 came from greater than 300 nm (3.8% of the total irradiation), which, while contributing to the overall UV irradiance, is not considered germicidal.[32]

Surrogate for Disinfection Tests of Coronaviruses. HCoV 229E and MHV exhibited greater similarities in inactivation rate constants (Table 1) and relative device-specific sensitivities (Figure 3) across tested UVC devices compared to the enveloped virus bacteriophage Phi6. Biosafety level (BSL) 2 viruses like HCoV 229E and MHV should be considered reliable surrogates for UV disinfection experiments of viruses like SARS-CoV-1 and SARS-CoV-2, which are limited to use only in BSL 3 laboratories. This conclusion is supported by recent investigations on UV inactivation of SARS-CoV-2. The inactivation rate constant of SARS-CoV-2 using LP UV lamps was calculated as 0.81 cm^2/mJ (log_{10} scale), based on the reported data from Bianco et al.,[33] which is similar (within 37% difference) to the values for HCoV 229E and MHV (Table 1). Our results for HCoV 229E and MHV are also comparable to the recent predictive model values by Rockey et al.,[24] which are 0.83 and 0.87 cm^2/mJ (converted to values based on log_{10} scale) for SARS-CoV-1 and SARS-CoV-2, respectively, using a LP UV lamp. Considering that both HCoV 229E and MHV viruses are coronaviruses, it is likely that coronaviruses in general have similar sensitivities to UVC irradiation due to their similar molecular structures. The greater resistance of Phi6 at 254 nm may be too conservative to be useful in LP UV studies, but at 222 nm, Phi6 can serve as a practical and realistic conservative virus surrogate where use of coronaviruses is not feasible (e.g., lack of mammalian cell culture facilities). Use of enveloped viruses like bacteriophage Phi6 is desirable because it may capture potential effects of a viral envelope on virus interaction with its environment, such as on a surface or in aerosol, which may impact UV disinfection performance.[34−36] While not evaluated here, nonenveloped RNA bacteriophages (e.g., MS2 and Q-Beta) and non-RNA bacteriophages (e.g., T1UV and T7) could also be used for UV disinfection performance evaluation and calibration applications. T-phages show sensitivities to UV at both 254 and 222 nm very similar to coronaviruses[31] but lack genomic similarity.

Implication of Using UVC Devices for Virus Disinfection. This investigation documented that UVC devices can be used to effectively disinfect enveloped viruses, especially coronaviruses, which are much more sensitive to UVC irradiation than other enveloped viruses and nonenveloped viruses, such as MS2 coliphage and adenovirus.[6,7] One limitation of UVC device application is that conventional UVC devices, such as LP UV lamps, are not safe for human exposure, because they can cause acute adverse health effects such as erythema and photokeratitis at low doses.[11,12] Far UVC devices like a KrCl* excimer, however, may not have such a limitation as recent studies reported that 222 nm UVC light caused no adverse effects on skin or eyes in mouse studies[13,15] because of its very limited penetration into biological materials.[37] This means that it is likely safe to apply continuous far UVC (200−230 nm) exposure in occupied public spaces, up to the allowable threshold limit values (25 mJ/cm^2 at 220 nm, ACGIH 2018[38]) or perhaps beyond, to disinfect viruses in respiratory secretions and airborne droplets as well as on contaminated surfaces to limit the presence and transmission of infectious virus pathogens like SARS-CoV-2. This is particularly promising because the KrCl* excimer exhibited the best disinfection performance among all tested devices in this study and therefore acts the fastest for disinfection. It is important to note that the inactivation rate constant values were measured in a liquid

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matrix (i.e., virus in PBS). A few studies on aerosol and surface disinfection suggested that viruses in airborne droplets and on surfaces tend to be more susceptible to UVC irradiation,[39,40] but it is still unclear how to convert the inactivation kinetics in an aqueous matrix to other matrices, such as surfaces, aerosols, and droplets. Recent studies by Kitagawa and co-workers showed that 1 and 3 mJ/cm^2 of irradiation from the filtered KrCl* excimer resulted in 88.5% and 99.7% reduction (0.94 and 2.52 $\log_{10}$-scale reduction) of viable SARS-CoV-2 on polystyrene surfaces,[41,42] which is similar to our values for HCoV 229E and MHV in aqueous solution (Figure 2). Further studies are needed to investigate effects of humidity on viral UV susceptibility in aerosol and surface disinfection, UV inactivation of these viruses on porous and nonporous surfaces, and in protective matrices such as in sputum and saliva where they may be protected from UV exposure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.1c00178.

Methods for virus stock preparation and enumeration, methods for UV exposure experiments, mean UVT of virus samples used for UV exposure experiments, absorbance of nucleic acids (DNA/RNA) and protein, and genome organization information for all selected enveloped viruses .(PDF)

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Notes

The authors declare no competing financial interest.

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