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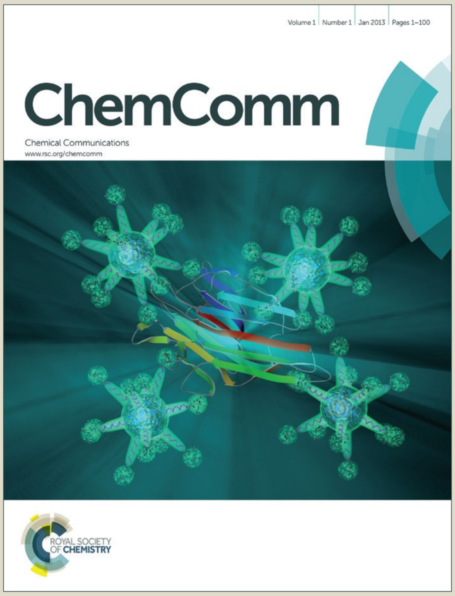

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Manipulating pH using near-infrared light assisted by upconverting nanoparticles

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Zhijun Chen,[a] Yubing Xiong,[a] Roberto Etchenique,[b] and Si Wu*[a]

Near-infrared light can be used to manipulate the pH of aqueous solutions by using upconverting nanoparticle-assisted photocleavage of a ruthenium complex photobase. Upconverting nanoparticles and the photobase were also introduced into a pH-responsive hydrogel, in which near-infrared irradiation induced swelling of the hydrogel.

pH is an important parameter in many chemical, physical and biological processes.[1,2] Photoacids/bases, which can decrease/increase pH upon light irradiation, enable remote control of pH with high spatiotemporal resolution.[3] Light-induced pH change can further control deformation of hydrogels,[4] conductivity,[5] polymerization,[6] and host-guest interactions.[7] pH manipulation has been proposed as a powerful technique to achieve control over relevant paths related to several diseases such as cancer, cardiovascular disease, Alzheimer's disease, etc.[8] However, most photoacids/bases are sensitive to only UV light which can damage biological systems.[9-11] Recently, Liao et al. reported visible-light-responsive photoacids.[4,8,12,13] Further, one of their photoacids can be used in PBS buffer,[8] which is desirable for biomedical applications. Nevertheless, visible light is still not able to deeply penetrate into tissue.[14] Compared to UV and visible light, near-infrared (NIR) light is better suited for biomedical applications because NIR light causes less photodamage to biological systems and can penetrate much deeper into tissue.[15] Therefore, developing NIR-manipulated pH represents significant progress for the biomedical field.

A promising approach to NIR-manipulated pH is based on photochemistry assisted by lanthanide-doped upconverting nanoparticles (UCNPs). UCNPs can convert NIR light into UV/visible light.[16, 17] The upconverted UV/visible light can then induce photoreactions of conventional UV-/visible-light-sensitive compounds. This process is called UCNP-assisted photochemistry.[18-21] UCNP-assisted photoisomerization,[22,23] photocleavage,[24-26] photopolymerization[27,28], and photo coupling reaction[29] have already been studied in the context of various applications.[30-37] Additionally, a new type of UCNP-assisted photochemical process "UCNP-assisted photoinduced protonation/deprotonation" was proposed in the outlook of a recent review.[33] These previous works inspired us to use NIR light to control pH assisted by UCNPs.

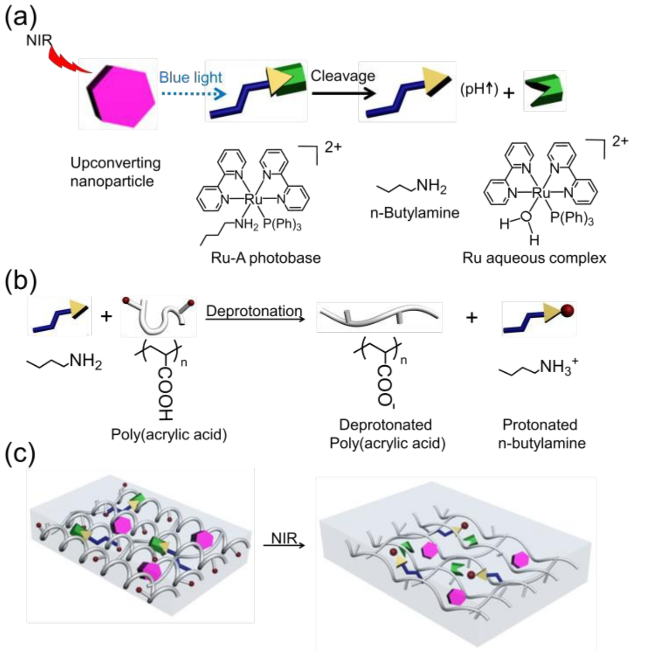

Fig. 1 Schematic illustration of photon upconversion pH manipulation and NIR light-induced swelling of the nanocomposite hydrogel. (a) The blue emission from UCNPs triggers the cleavage of the Ru photobase (Ru-A) and induces pH change; (b) The released butyl amine from Ru-A results in the deprotonation of poly(acrylic acid) (PAA); (c) NIR light-induced swelling of the nanocomposite hydrogel, which was prepared by inducing UCNPs and Ru-A into crosslinked PAA. All the symbols are shown in (a) and (b).

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[a] *Max Planck Institute for Polymer Research, Ackermannweg 10, 55128, Mainz, Germany. Email: wusi@mpip-mainz.mpg.de*

[b] *Departamento de Química Inorgánica, Analítica y Química Física, INQUIMAE, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria Pabellón 2, AR1428EHA Buenos Aires, Argentina.*

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Here, we experimentally demonstrate that the combination of UCNPs and a photobase enables the control of pH by NIR light (Figure 1a). We refer to this new combination as a photon upconversion pH manipulation. The complex $[Ru(bpy)_2(PPh_3)(BuNH_2)]^{2+}$ (bpy=2,2' bipyridine; PPh_3 = triphenylphosphine, $BuNH_2$ = n-butylamine), hereafter Ru-A (Figure 1a), was used as the photobase because blue light irradiation on Ru-A can cause a pH change within nano to microseconds.[38] Moreover, we found that UCNPs can efficiently assist photocleavage of Ru complexes because of spectral overlap of Ru complex absorption[39-41] and UCNP emission.[19, 42] Further, we have recently demonstrated the true sectioning power of the upconversion excitation,[17] allowing precise z-axis manipulation of the downstream effects of NIR irradiation. On these bases, Ru-A was combined with UCNPs which would convert NIR light to blue light to enable the release of n-butylamine from Ru-A (Figure 1a). The released butyl amine would then increase the pH of an aqueous solution. When NIR light-induced release of n-butylamine occurs in the presence of poly(acrylic acid) (PAA), PAA can become more hydrophilic via deprotonation and thus swell due to electrostatic repulsion (Figure 1b). Thus, to demonstrate the potential application of NIR light-manipulated pH, we introduced UCNPs and Ru-A into a PAA hydrogel (Figure 1c).

$NaYF_4$:TmYb@$NaYF_4$ nanoparticles UCNPs (core = $NaYF_4$: 0.5 mol% Tm^{3+}: 30 mol% Yb^{3+}; shell = $NaYF_4$) with a diameter of 50 nm were synthesized as the upconverters (Figure 2a). These UCNPs emitted blue light under 974 nm NIR light excitation. The absorption band of the photobase Ru-A in the blue light region overlapped with the blue emission of the UCNPs (Figure 2a). To demonstrate absorption of upconverted blue light by the Ru-A, we compared upconversion luminescence spectra of UCNP in the presence and absence of Ru-A. The intensity of upconversion luminescence of UCNPs at 440 nm and 470 nm decreased significantly in the presence of Ru-A (Figure 2b). Additionally, Ru-A with higher concentration absorbed more upconverted blue light and resulted in lower emission intensity. In contrast, the emission at 800 nm, a spectral region where Ru-A has no absorption, still remained. (Figure 2b). This result proved efficient absorption of the upconverted blue light by Ru-A. When irradiating a dispersion of UCNPs and Ru-A with NIR light, the absorption band of Ru-A decreased and red shifted (Figure 2c). This spectral change was identical to that observed for Ru-A which was directly photocleaved using blue light (Figure S1, ESI). Thus, Ru-A was photocleaved by NIR light irradiation. The exposure of Ru-A to NIR light in the absence of UCNPs did not change the absorption spectrum (Figure S2, ESI), proving the photocleavage of Ru-A was induced by the photon upconversion process.

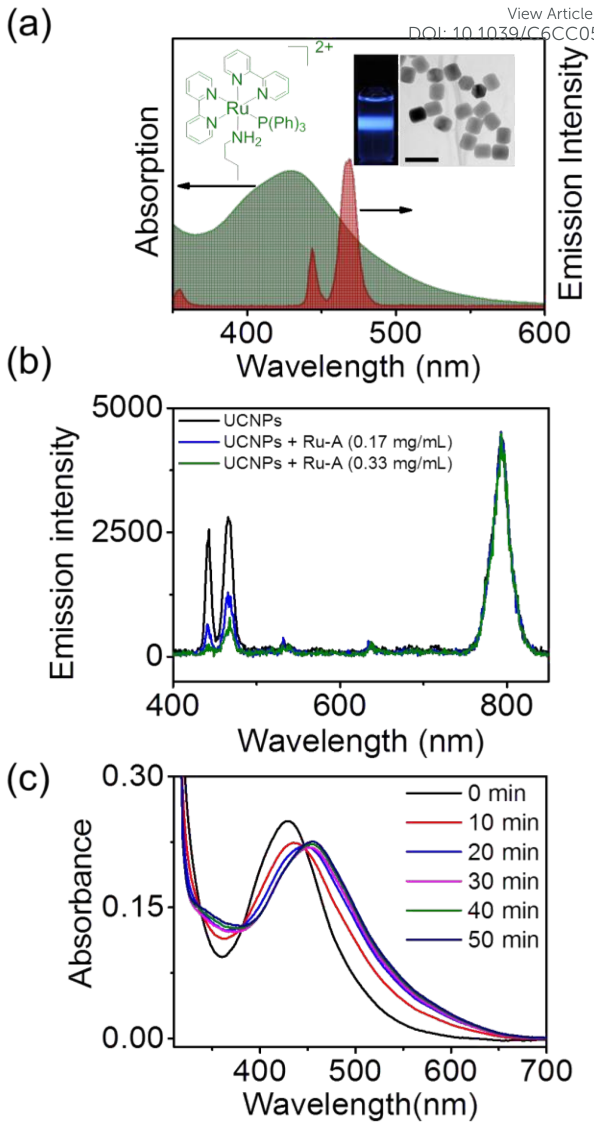

Fig. 2 (a) Absorption spectrum of Ru-A and emission spectrum of UCNPs under excitation by 974 nm light (5.5 W/cm^2). Insets: TEM image of UCNPs (scale bar 100 nm) and photograph of UCNPs under 974 nm light exposure; (b) Upconversion luminescence spectra of UCNPs (1 mg/mL) and UCNPs/Ru-A excited by 974 nm light. The concentrations of Ru-A were 0.17 (blue line) and 0.33 mg/mL (green line), respectively; (c) UV/Vis absorption spectra of the dispersion of UCNPs (0.15 mg/mL) and Ru-A (0.05 mg/mL) in acetone/water mixture (0.5/99.5, V/V) upon 974 nm light exposure (5.5 W/cm^2).

To demonstrate a NIR-induced pH increase, an aqueous dispersion of UCNPs was prepared by ultrasonic treatment of UCNPs in water (Figure S3 and Video S1, ESI). Afterword, Ru-A was introduced into the UCNPs dispersion. The UCNP/Ru-A dispersion was placed into an ice bath and irradiated with NIR light. The NIR light-induced pH change of the UCNP/Ru-A dispersion was measured (Figure 3a). The initial pH of the UCNP/Ru-A dispersion was 5.2, which did not change in the dark. However, exposure to NIR light (5.5 W cm^{-2}) changed the pH from 5.23 to 6.80 (Figure 3a). NIR light irradiation can induce the release of n-butylamine from Ru-A (Figure 2). The coordinated n-butylamine in Ru-A does not act as a base because its electron pair is strongly coordinated with Ru^{2+}. However, the released free n-butylamine is a relatively strong base with pK_a 10.77.[38] Thus, the NIR light-induced pH change was attributed to the released n-butylamine from Ru-A. As a control experiment, exposure of Ru-A in the absence of UCNPs to NIR light in an ice bath showed no pH change (Figure S4, ESI), which further confirmed the pH change was due to the photon upconversion process. In addition, NIR light irradiation also changed the color of the

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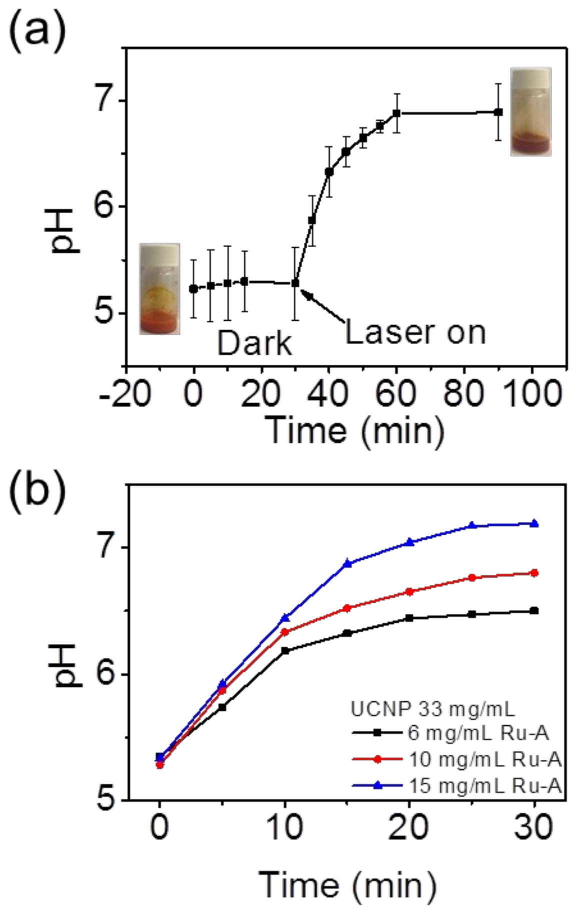

Fig. 3 (a) pH change of a dispersion of UCNPs (33 mg/mL) and Ru-A (10 mg/mL) in acetone/water mixture (6/94, V/V) upon NIR light irradiation (5.5 W cm^{-2}) in an ice bath. Inset: Photos of the dispersion before and after NIR light irradiation; (b) pH change of a dispersion of UCNPs (33 mg/mL) and Ru-A with different concentrations in acetone/water mixture (6/94, V/V) upon NIR light irradiation (5.5W cm^{-2}) in an ice bath.

dispersion because the absorption spectra of Ru-A and Ru-aqua photoproduct (Ru-H_2O, Figure 1a) are different. Moreover, the ratio of UCNPs and Ru-A was tuned to investigate its influence on pH change of the solution. The concentration of UCNPs was fixed. As the concentration of Ru-A increased, pH change was larger (Figure 3b). The larger pH change was because more n-butylamine can be released from Ru-A with a higher concentration. Thus, the ratio of UCNPs and Ru-A can be used to adjust the range of pH change.

Subsequently, the NIR-manipulated pH increase was used to control deformation of a pH-sensitive hydrogel. A nanocomposite hydrogel was prepared by cross-linking PAA in the presence of Ru-A and UCNPs. Upconverted luminescence was observed from the nanocomposite hydrogel upon irradiation with NIR light (Figure 4a), which further confirmed UCNPs were incorporated inside the hydrogel. A nanocomposite hydrogel with the volume of 0.28 cm^3 was immersed in an aqueous solution (pH 3.5) and irradiated with NIR light for 15 min in an ice bath. NIR irradiation was conducted in an ice bath because an ice bath can prevent overheating problems of NIR irradiation and heat-induced side effects (Figure S5, S6).[33, 43] After irradiation, the volume of the hydrogel increased to 0.37 cm^3, which was 32% larger than the hydrogel before irradiation (Figure 4b, left**)**. In addition, the color of the hydrogel changed from orange to brown upon NIR light irradiation, which is identical to the color change observed in the dispersion of UCNPs and Ru-A upon NIR irradiation (Figure 3a). Thus, the swelling was attributed to deprotonation of PAA by the released n-butylamine from Ru-A. In a control experiment, the hydrogel without irradiation did not change size or color (Figure 4b, right**)**. In another two control experiments, hydrogels with only Ru-A or UCNPs were prepared. The hydrogel with Ru-A and without UCNPs did not show any color or volume change upon NIR irradiation in an ice bath (Figure S7, ESI). The hydrogel only incorporating UCNPs also was unresponsive to NIR irradiation (Figure S8, ESI). These results further confirmed the swelling of the hydrogel was due to the released n-butyl amine upon NIR irradiation.

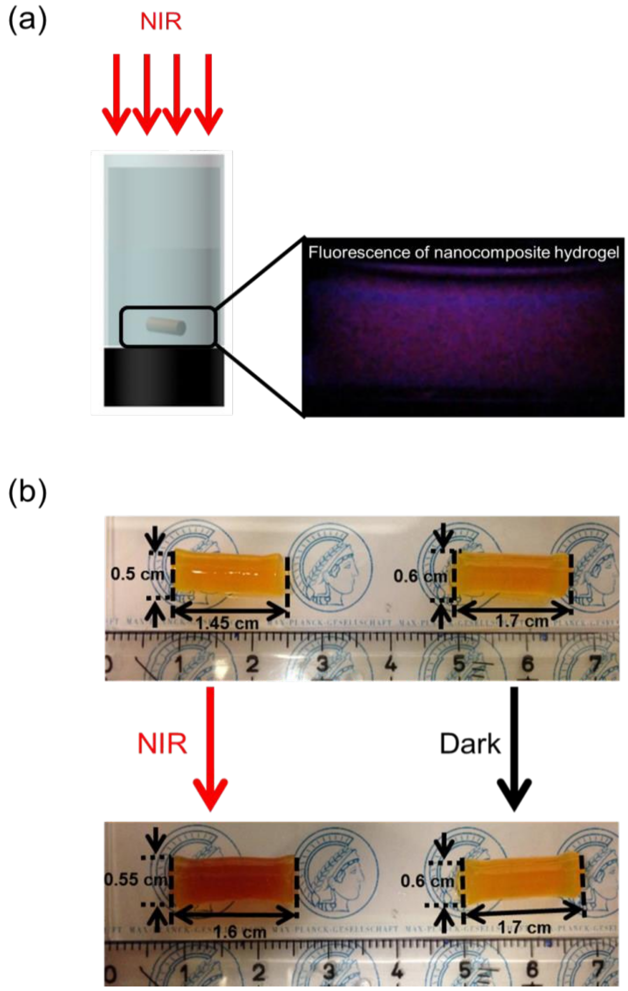

Fig. 4 (a) Schematic illustration of the set up for NIR-controlled swelling of nanocomposite hydrogel (with UCNPs, 33 mg/mL and Ru-A, 10 mg/mL). (b) Nanocomposite hydrogel before and after NIR light irradiation (5.5 W/cm^2, 15 min) (left) and in the dark (right). The samples were placed in an ice bath during irradiation.

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In conclusion, we demonstrated that NIR light can increase the pH under the assistance of UCNPs and the photobase Ru-A. UCNPs converted NIR light to blue light, which triggered the release of n-butylamine from Ru-A. The released n-butylamine can further deprotonate PAA. The strategy of photon upconversion pH manipulation was further developed to control the swelling of pH-sensitive PAA hydrogels. Not only Ru-A but also many other photoacids/photobases can alter solution pH after light irradiation. Thus, the concept “photon upconversion pH manipulation” reported in this work is a general approach to control pH by NIR light. Also, photon upconversion pH manipulation can not only induce swelling of pH-sensitive hydrogels but can also stimulate other pH-responsive materials, such as micelles, capsules, and supramolecules. Thus, photon upconversion pH manipulation is a new and general way to control pH-responsive materials with high spatiotemporal resolution for various applications.

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