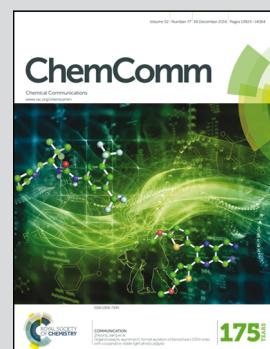


Showcasing research from Max Planck Institute for Polymer Research, Germany and Departamento de Química Inorgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina

Manipulating pH using near-infrared light assisted by upconverting nanoparticles

Upconverting nanoparticles convert near-infrared (NIR) light to UV or visible light, which can activate photoresponsive Ru complexes. Because NIR light can penetrate deeply into tissue, the NIR photoactivation approach shows deep-tissue biomedical applications.

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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 light-induced pH manipulation represents significant progress for the biomedical field.

A promising approach to NIR light-induced pH manipulation 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 photo-reactions of conventional UV-/visible-light-sensitive compounds. This process is called UCNPs-assisted photochemistry.^{18–21}

UCNP-assisted photoisomerization,^{22,23} photocleavage,^{24–26} photopolymerization,^{27,28} and photocoupling reaction²⁹ have already been studied in the context of various applications.^{30–37} Additionally, a new type of UCNPs-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.

Here, we experimentally demonstrate that the combination of UCNPs and a photobase enables the control of pH by NIR light (Fig. 1a). We refer to this new combination as a photon upconversion pH manipulation. The complex $[\text{Ru}(\text{bpy})_2(\text{PPh}_3)(\text{BuNH}_2)]^{2+}$

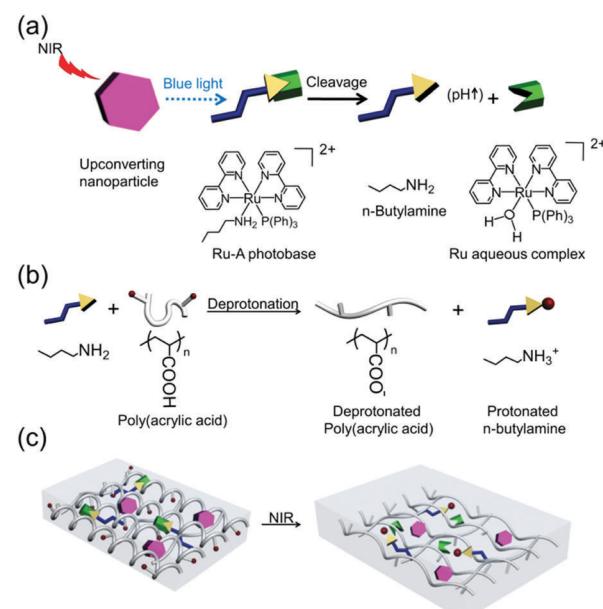


Fig. 1 Schematic illustration of photon upconversion pH manipulation and NIR light-induced swelling of the nanocomposite hydrogel. (a) The blue emission from UCNPs triggers the cleavage of the Ru photobase (Ru-A) and induces pH change. (b) The butylamine released from Ru-A results in the deprotonation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

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(bpy = 2,2' bipyridine, PPh₃ = triphenylphosphine, BuNH₂ = *n*-butylamine), hereafter Ru-A (Fig. 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 UCNPs 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 light irradiation. On these bases, Ru-A was combined with UCNPs, which would convert NIR light into blue light to enable the release of *n*-butylamine from Ru-A (Fig. 1a). The released butylamine 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 (Fig. 1b). Thus, to demonstrate the potential application of NIR light-manipulated pH, we introduced UCNPs and Ru-A into a PAA hydrogel (Fig. 1c).

NaYF₄:TmYb@NaYF₄ UCNPs (core = NaYF₄: 0.5 mol% Tm³⁺: 30 mol% Yb³⁺; shell = NaYF₄) with a diameter of 50 nm were synthesized as the upconverters (Fig. 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 (Fig. 2a). To demonstrate absorption of upconverted blue light by Ru-A, we compared the upconversion luminescence spectra of UCNPs 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 (Fig. 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 (Fig. 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 (Fig. 2c). This spectral change was identical to that observed for Ru-A which was directly photocleaved using blue light (Fig. S1, ESI[†]). Thus, Ru-A was photocleaved through NIR light irradiation. The exposure of Ru-A to NIR light in the absence of UCNPs did not change the absorption spectrum (Fig. S2, ESI[†]), proving that the photocleavage of Ru-A was induced by the photon upconversion process.

To demonstrate a NIR light-induced pH increase, an aqueous dispersion of UCNPs was prepared by ultrasonic treatment of UCNPs in water (Fig. S3 and Video 1, ESI[†]). Afterwards, Ru-A was introduced into the UCNPs dispersion. The UCNPs/Ru-A dispersion was placed into an ice bath and irradiated with NIR light. The NIR light-induced pH change of the UCNPs/Ru-A dispersion was measured (Fig. 3a). The initial pH of the UCNPs/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 (Fig. 3a). NIR light irradiation can induce the release of *n*-butylamine from Ru-A (Fig. 2). The coordinated *n*-butylamine in Ru-A does not act as a base because its electron pair is strongly coordinated to Ru²⁺. However, the released free *n*-butylamine is a

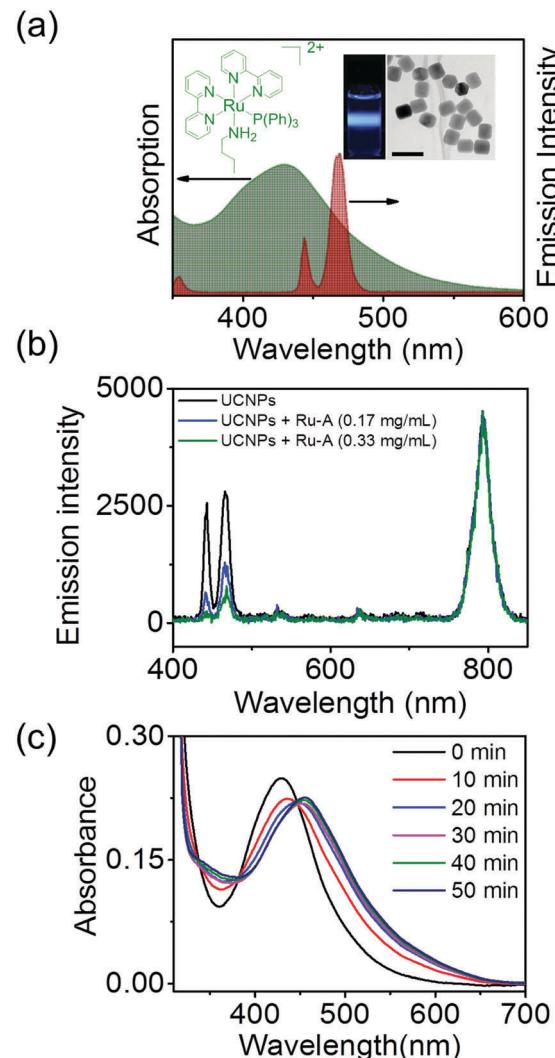


Fig. 2 (a) The absorption spectrum of Ru-A and the emission spectrum of UCNPs under excitation by 974 nm light (5.5 W cm⁻²). Insets: TEM image of UCNPs (scale bar 100 nm) and photograph of UCNPs upon exposure to 974 nm light. (b) Upconversion luminescence spectra of UCNPs (1 mg mL⁻¹) and UCNPs/Ru-A excited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

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 (Fig. S4, ESI[†]), which further confirmed that the pH change was due to the photon upconversion process. In addition, NIR light irradiation also changed the color of the dispersion because the absorption spectra of Ru-A and the Ru-aqua photoproduct (Ru-H₂O, Fig. 1a) are different. Moreover, the ratio of UCNPs to Ru-A was tuned to investigate its influence on the pH change of the solution. The concentration of UCNPs was fixed. As the concentration of Ru-A increased, the pH change was larger (Fig. 3b). The larger pH change was because more



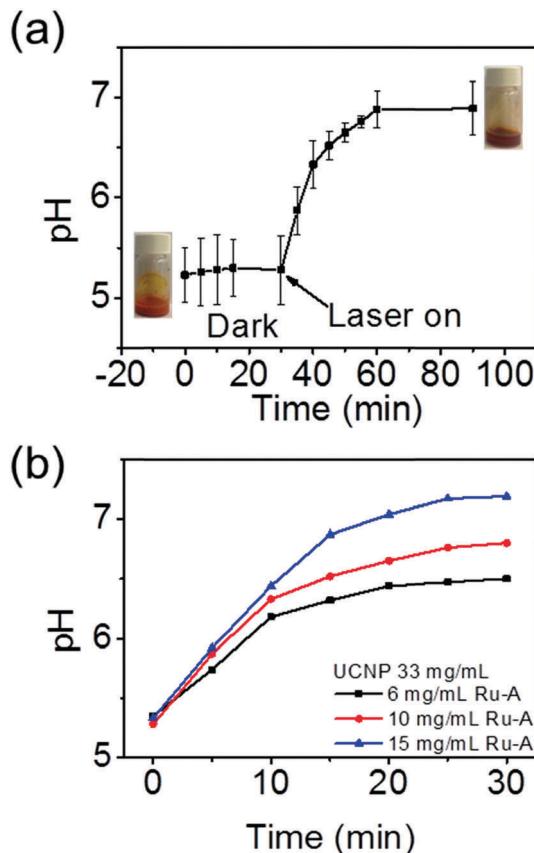


Fig. 3 (a) pH change of a dispersion of UCNPs (33 mg mL^{-1}) and Ru-A (10 mg mL^{-1}) in an acetone/water mixture (6/94, V/V) upon NIR light irradiation (5.5 W cm^{-2}) in an ice bath. Inset: Photos of the dispersion before and after NIR light irradiation. (b) pH change of the dispersion of UCNPs (33 mg mL^{-1}) and Ru-A with different concentrations in the acetone/water mixture (6/94, V/V) upon NIR light irradiation (5.5 W cm^{-2}) in an ice bath.

n-butylamine could be released from Ru-A with a higher concentration. Thus, the ratio of UCNPs to Ru-A can be used to adjust the range of pH change.

Subsequently, the NIR light-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 (Fig. 4a), which further confirmed that UCNPs were incorporated inside the hydrogel. A nanocomposite hydrogel with a 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 light irradiation was conducted in an ice bath because an ice bath can prevent overheating problems of NIR light irradiation and heat-induced side effects (Fig. S5 and S6, ESI†).^{33,43} After irradiation, the volume of the hydrogel increased to 0.37 cm^3 , which was 32% greater than the hydrogel before irradiation (Fig. 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 light irradiation (Fig. 3a). Thus, the swelling was attributed to the deprotonation of PAA by the *n*-butylamine released from Ru-A.

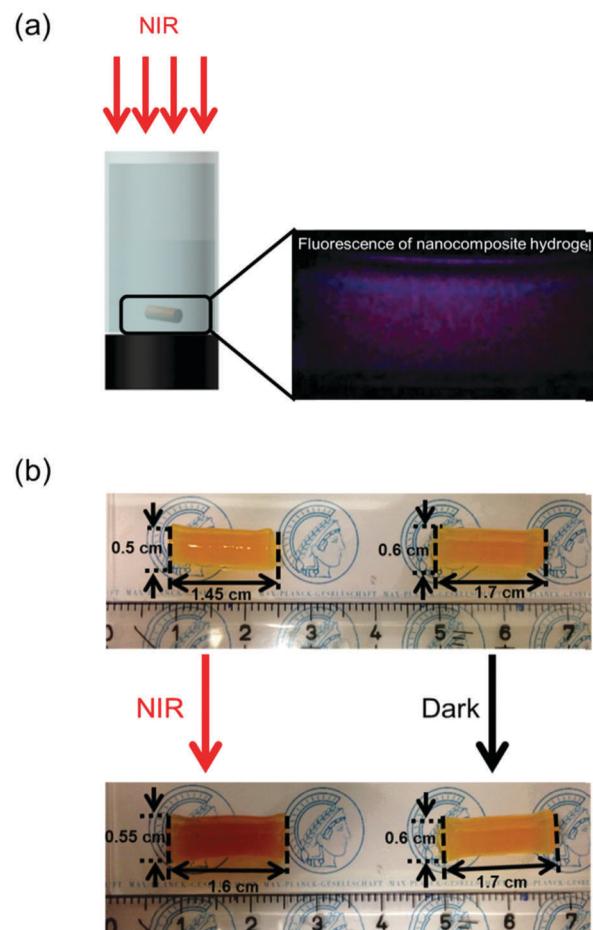


Fig. 4 (a) Schematic illustration of the set up for NIR light-controlled swelling of the nanocomposite hydrogel (with UCNPs, 33 mg mL^{-1} ; and Ru-A, 10 mg mL^{-1}). (b) Nanocomposite hydrogel before and after NIR light irradiation (5.5 W cm^{-2} , 15 min) (left) and in the dark (right). The samples were placed in an ice bath during irradiation.

In a control experiment, the hydrogel without irradiation did not change in size or color (Fig. 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 light irradiation in an ice bath (Fig. S7, ESI†). The hydrogel incorporating only UCNPs was also unresponsive to NIR light irradiation (Fig. S8, ESI†). These results further confirmed that the swelling of the hydrogel was due to the released *n*-butylamine upon NIR light irradiation.

In conclusion, we demonstrated that NIR light could increase the pH with the assistance of UCNPs and the photobase Ru-A. UCNPs converted NIR light into blue light, which triggered the release of *n*-butylamine from Ru-A. The released *n*-butylamine could 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 many other photoacids/photobases can also alter solution pH after light irradiation. Thus, the concept "photon upconversion pH manipulation" reported in this work is a general approach to controlling 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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