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Upconverting Nanoparticles

Upconverting Nanoparticles for Nanoscale Thermometry

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lanthanoids · luminescence · nanoparticles · sensors · temperature determination

Upconverting materials are capable of absorbing near-infrared light and converting it into short-wavelength luminescence. The efficiency of this remarkable effect is highly temperature dependent and thus can be used for temperature determination (thermometry) on a nanometer scale. All the upconverting materials discovered so far display several (mainly two) narrow emission bands, each of which has its own temperature dependence. The ratio of the intensity of two of these bands provides a referenced signal for optical sensing of temperature, for example inside cells.

1. Introduction

Temperature is a fundamental parameter whose knowledge is essential in various kinds of industrial processes and scientific research. Among the methods for its determination, one may distinguish between contact methods and noncontact methods. The contact methods (e.g. thermistors and thermoelements) require electrical wiring, can produce strong electromagnetic noise along with possibly perilous sparks, and cannot be applied in corrosive environments. Because of these limitations, noncontact methods have been developed.[1] The most widespread method is based on the use of infrared light and allows fast imaging of temperature,[2] but requires the kind of material investigated (and its emissivity) to be known. In addition, water vapor and common glass materials absorb the wavelengths typically used in IR thermometry, thus often preventing measurements through optical windows. Most notably, the spatial resolution of IR thermometry is in the micrometer range and also is limited by the size of the sensor pixels.[3]

Luminescence thermometry in the visible and near-infrared (NIR) range can circumvent many of these limitations. The strong effect of temperature T on the luminescence intenxity of lanthanoid ions has been known for quite some time and has led to various sensing schemes, most based on the use of molecular probes,[4] sometimes in combination with optical fibers.[5] The work of Grattan et al. is particularly significant.[6] Recently, lanthanoid-based probes,[7] in the forms of microparticles[4b] and nanoparticles,[8] have been described that serve the purpose of sensing temperature in solution and in sensor paints. However, these particles suffer from the disadvantage of requiring UV or short-wavelength visible excitation, which can cause substantial background luminescence and Raman scattering unless signals are separated by means of temporal discrimination.

2. Materials Displaying Luminescence Upconversion

Upconverting nanoparticles (UCNPs) most often are composed of a host crystal (usually fluorides, oxides, phosphates, or sulfides of metal ions) doped with up to three trivalent lanthanoid ions.[9] The dopants display regular photoluminescence if excited in the UV/Vis range. The most remarkable property, though, is their capability of emitting visible luminescence when excited with NIR light. Figure 1 shows a typical emission spectrum of UCNPs that were prepared by the coprecipitation method,[10] along with the effect of temperature on the emission. Most notably, UCNPs are known to display luminescence that varies strongly in the physiological temperature range (20–50 °C), thus suggesting their use in biomedical studies.

Luminescence upconversion is the result of nonlinear photoexcitation processes where two or more photons are sequentially absorbed, followed by emission from low-lying electronic states of the dopant(s). Reviews on materials, syntheses, and spectral properties of UCNPs were given by Wang et al.[11] and Auzel.[12] Table 1 lists examples of typical materials. Among the many methods reported[12,13] for the synthesis of UCNPs, we find[14] the so-called oleic acid

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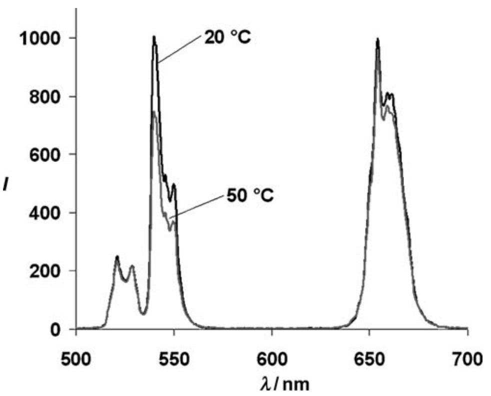

Figure 1. Emission spectra of a colloidal solution of UCNPs of the type $NaYF_4$:Yb,Er in 95 % ethanol at 20 °C and 50 °C, respectively. Excitation wavelength 980 nm; particle size ≈100 nm.

Table 1: Examples of upconversion nanoparticles with blue, green, red, or near-IR luminescence following photo-excitation at around 980 nm, with data emission peak wavelengths (λ_{em}), and typical particle diameters (Ø).

Material	λ_{em} [nm]	Ø [nm]	Ref.
$NaYF_4$:Yb,Er	521, 539, 651	30–120	[16]
$NaYF_4$:Yb,Er,Gd	538, 667	20–30	[17]
$NaYF_4$:Yb,Tm	449, 474, 644, 693, 800	ca. 14	[18]
$BaYF_4$:Yb,Tm	475, 650, 800	ca. 15	[19]
Y_2O_3:Yb,Er	550, 660	ca. 200	[20]
YPO_4:Er	526, 550, 657, 667	ca. 7	[21]
Lu_2O_3:Yb,Er	662	40	[22]
YVO_4:Yb,Er	525, 550	39	[23]

method[15] to be quite useful because it is comparably simple and yields UCNPs of rather small (15–25 nm) and uniform size.

Strong light sources (usually mW diode lasers) are required for NIR excitation. Such lasers are rather small (like laser pointers) and affordable, yet can be operated over a wide range of modulation or pulse frequencies and pulse widths. Moreover, they are available in numerous wavelengths.

Little information is available on the luminescence efficiency (quantum yield, QY) of UCNPs. Because of the nonlinearity of the upconversion process, QYs often are given as a function of the excitation power density rather than a classical percentage value.[24] Values on the order of 1 % have been reported[24b] for erbium-doped nanoparticles of the type $RE_{10}Pb_{25}F_{65}$ (where RE stands for a rare-earth or lanthanoid ion) with an average size of 8 nm. The same host material, when co-doped with $Yb^{3+}$and Er^{3+}, is said to display a quantum yield of as much as 15 %. Such high QYs are interpreted in terms of low phonon energy and short interdopant distance in the fluoride compounds.[24,25] Very recently, Boyer and van Veggel[26] have described a technique for measuring the absolute QYs of such nanomaterials. Lanthanoid-doped UCNPs gave rather low QYs (0.005 % to 0.3 %) at particle sizes between 10 and 100 nm, while QYs of up to 3 % were measured for bulk samples.

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Gregory S. Harms completed his PhD studies at the University of Kansas. As a Fulbright scholar in Europe at the Swiss Federal Institute of Technology in Zürich, in Austria (Linz), and in the Netherlands (Leiden), he pioneered the detection of single fluorescent proteins and single-ion channels by current and fluorescence. He was then a scientist at the Pacific Northwest National Laboratory in the USA. Professor Harms currently leads the microscopy facilities of the Bio-Imaging Center and Rudolf Virchow Center and holds a professorship in Microscopy and Biophysics in Würzburg (Germany) and in Physics, Engineering, Biology and Chemistry at Wilkes University in the USA.

Lorenz H. Fischer, born in 1983, graduated from the University of Regensburg in 2008. He is currently pursuing his PhD at the Institute of Analytical Chemistry, Chemo- and Biosensors under the supervision of Prof. Wolfbeis. His research is focused on dually sensitive thin films and coatings for measuring oxygen (i.e. air pressure) and temperature.

Luminescence upconversion from glasses and bulk materials has been utilized for temperature measurement since the early 1990s.[27] Usually, the object (such as the surface of a reactor) whose temperature is to be determined (or imaged) is coated with the upconverting crystalline compound incorporated in a binder material such as glass[28] or an organic polymer. Alternatively, the material may be placed at the tip of an optical fiber (for remote temperature measurements, for example in strong electromagnetic fields),[29] on silica-on-silicon waveguides,[30] or at the tungsten tip of a scanning thermal microscope.[31]

These approaches are not suitable for either resolution on the nanometer scale or for intracellular sensing. In addition, the size of crystals typically used is on the order of micrometers, which also entails a drawback in that the material may act as a thermal insulator. In terms of imaging temperature, the spatial resolution also is governed by the light diffraction of both the excitation and emission. Large particles

(>0.4 μm) usually have rough surfaces and cause strong light scattering, and this greatly compromises resolution.

These limitations have been overcome by decreasing the crystal size to the nanometer scale to end up with UCNPs. The most attractive feature of nanoscale thermometry is the option of measuring the temperature inside cells. The group of Uchiyama[32] has presented the first method to sense temperature in cells by applying a highly hydrophilic fluorescent organic nanohydrogel that readily internalizes into the cytoplasm and emits stronger fluorescence at a higher temperature. Tikhomirov et al.[33] have suggested the use of UCNPs as nanoheaters for hyperthermal treatment of cells in combination with simultaneous monitoring of temperature by exploiting the temperature dependence of the intensity ratio of two bands. The use of UCNPs for optical chemical sensing (where the temperature must usually be known to obtain reliable data) has been reviewed recently.[34] Nanosized materials also pave the way to possible biological and biomedical applications[35,32] including bioconjugation and imaging.[14] Among the advantages of UCNP application is that NIR light can easily penetrate tissue and does not cause any background luminescence in the visible; in this way (ratiometric) measurements can be made against virtually zero background. The ratio of the intensities also is independent of fluctuations in excitation intensity.[36]

3. Temperature Dependence of the Luminescence of UCNPs

The temperature dependence of the luminescence upconversion of UCNPs is rather complex and highly individual. Chen et al.[37e] report that the fluorescence upconversion of the Mn^{2+} ion in $ZnS:Mn^{2+}$ is more sensitive to temperature than the respective Stokes luminescence where the particles are excited with UV light. The determination of temperature is based on the measurement of the ratio of the intensity of two transitions that have different temperature dependencies.[36,38] Figure 2 shows a diagram of the energy levels governing the ratio of the luminescence intensities.

Equation (1) describes the temperature dependency of the ratio R of the two intensities (I_{20}/I_{10}). Here, A is a constant, ΔE_{21} is the energy gap separating the upper levels, k is the Boltzmann constant, and T is temperature. A temperature resolution of ±0.1 °C is desirable for the physiological range (e.g. in hyperthermal cancer therapy), while it can be much smaller (±2 °C) for applications at temperatures above 200 °C (as often encountered in industry). Figure 3 shows representative upconversion spectra at various temperatures along with the corresponding calibration plot.

$$R = \frac{I_{20}}{I_{10}} = A\exp\left(-\frac{\Delta E_{21}}{kT}\right) \tag{1}$$

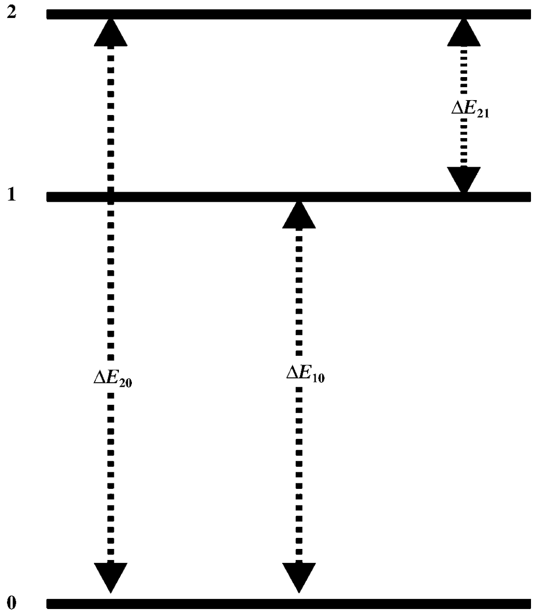

Figure 2. Energy level diagram of two closely spaced excited levels and one ground state in a rare-earth ion (the "dopant"). Also see Ref. [30a].

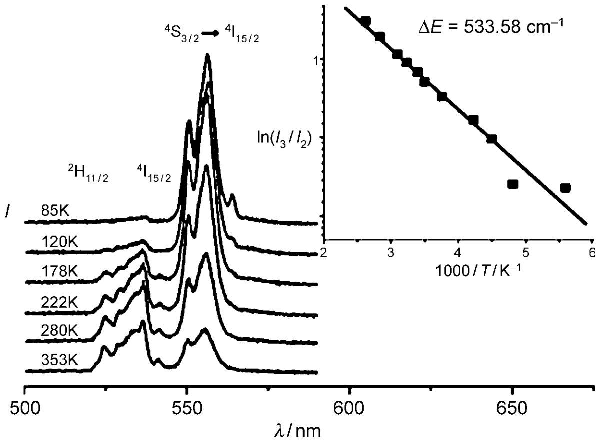

Figure 3. Temperature dependence of the upconversion spectra of $ZnO:Er^{3+}$ nanoparticles. Inset: Temperature dependence of the logarithm of the integrated intensity ratio of the $^2H_{11/2}\rightarrow{}^4I_{15/2}$ transition (referred to as I_3) to the $^4S_{3/2}\rightarrow{}^4I_{15/2}$ (referred to as I_2) transition. From Ref. [37a] with permission.

The logarithm of R usually is plotted versus reciprocal temperature. Table 2 gives parameters for three typical UCNPs along with the slopes of the response towards temperature. Sensitivity (S) also is temperature-dependent and defined by Equation (2). The data on sensitivity in Table 2 refer to the maximum sensitivities. As can be seen, they cover a wide range of temperatures.

$$S = \frac{dR}{dT} = R\left(\frac{\Delta E_{21}}{kT^2}\right) \tag{2}$$

Figures 1 and 2 shows that the intensity of the luminescence upconversion of all transitions decreases with increasing temperature. The effect can be described by an Arrhenius type of equation [Eq. (3)], where $N(T)$ is the population in the level at a given temperature T, and τ is the lifetime of the

Table 2: Composition and properties of representative kinds of upconverting nanoparticles (UCNPs) for use in optical thermometry. All data for photo-excitation at around 980 nm.

Host material	Dopant ion	Particle size [nm]	Excitation density [$kW\,cm^{-2}$]	λ_{em} [nm]	$S^{[a]}$	Temperature range [K]	Ref.
ZnO	Er^{3+}	80	27.5–51	536, 553	6.2 at 443 K	273–573	[37a]
Gd_2O_3	Er^{3+},Yb^{3+}	17–50	–	523, 548	3.9 at 300 K	300–900	[37b]
$BaTiO_3$	Er^{3+}	26	2	526, 547	5.2	310–500	[39]
$NaYF_4$	Yb^{3+},Tm^{3+}	50–100		475, 800			[49]

[a] Sensitivity (S) expressed as $10^{-3}\,dR/dT$, where $R = (I_{20}/I_{10})$ and T is given in K [see Eq. (2)].

excited state. The reciprocal value of τ is the sum of the radiative and nonradiative relaxation rates.

$$N_T = N_0 \exp\left(\frac{-T}{\tau}\right) \tag{3}$$

The rate of nonradiative relaxation increases with temperature. As a result, the luminescence intensities and lifetimes of the various transitions decrease.[37b] Obviously, not all transitions have the same temperature dependence. Wang et al.[37a] and Singh et al.[37b] report that the luminescence intensity of the $S_1 \rightarrow S_0$ transition is higher than that of the $S_2 \rightarrow S_0$ transition at low temperatures but that this is inverted at higher temperatures. Effects of the crystal lattice may further complicate the situation. When UCNPs are prepared by the co-precipitation method, the initial, cubic form has to be converted into the hexagonal form (by thermal annealing) in order to obtain UCNPs with high upconversion efficiency. This conversion to the hexagonal form often remains incomplete.

The sensitivity to temperature also depends on the annealing temperature[37a] as it affects the energy gap between the two excited levels (as shown for the case of Er^{3+} ion in a ZnO host). The UCNPs are more sensitive to temperature when annealed at higher temperatures. In general, temperature has a larger effect on nanosized crystals than on the respective bulk material, probably because surface defects become increasingly important. Consequently, the temperature dependence of the intensity ratio is enhanced due to stronger electron–phonon interaction.[37b,39] One also has to take into account that the heating of the UCNPs by NIR light is more pronounced for the nanosized crystals than for the micrometer-sized materials or the bulk phase.[33] This effect of extra heating is supposed to result from the quantum confinement of phonons resulting in an enhanced electron–phonon interaction in the nanoparticles.

One particularly attractive application of responsive nanomaterials is in intracellular sensing of parameters such as temperature[32,40] or pH value.[41] Recently, Vetrone et al.[40] have demonstrated that $NaYF_4$:Er^{3+},Yb^{3+} UCNPs can be used as nanoprobes for sensing temperature in HeLa cervical cancer cells. UCNPs of the type $NaYF_4$:Er^{3+},Yb^{3+} with a mean size of 18 nm are efficiently internalized by such cells. When excited with a 920 nm laser (with an excitation intensity of below 0.5 $kW\,cm^{-2}$ to avoid pump-induced heating), they displayed fairly strong green fluorescence which was collected using a confocal microscope connected to a high-resolution spectrometer. The cells were externally heated, and the internal temperature of an illuminated cell was measured by determining the temperature-dependent ratio of the fluorescence intensities of the UCNPs at 525 and 545 nm. Intracellular changes in temperature resulting from external heating were easily detectable, and cells were simultaneously imaged. Figure 4 shows a typical result.

Figure 5 shows data from our groups that were obtained with UCNPs of the type $NaYF_4$:Yb,Er which were prepared according to literature methods[10] to sense temperature in human embryo kidney cells (of type HEK 293). The cells were transfected with UCNPs and then spectrally imaged separately by recording their green and red images (I_{539}/I_{651}) at temperatures of 18 and 33 °C, respectively, by confocal fluorescence microscopy. Images were acquired with a Leica TCS SP5 MP confocal laser scanning microscope. Luminescence was excited with a Ti:sapphire femtosecond-pulsed laser operated at 980 nm, with excitation powers of 50 mW at the objective. Spectrally selective photon-counting detectors were set at 520–540 nm for the green emission of the UCNPs and at 630–660 nm for the red emission. The intensity of the green emission (510–530 nm) remains virtually constant. Its change with temperature is rather small compared to that of

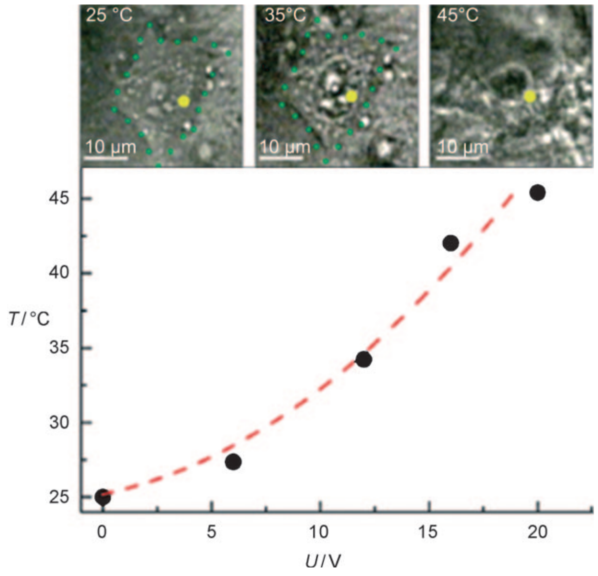

Figure 4. Top: Optical transmission images of an individual HeLa cell at three inner temperatures. Cell death is observed at 45 °C. Bottom: Temperature of the HeLa cell determined by the fluorescence of the Er^{III} ion in the NaYF4:Er,Yb UCNPs as a function of the applied voltage of the heater. From Ref. [40] with permission.

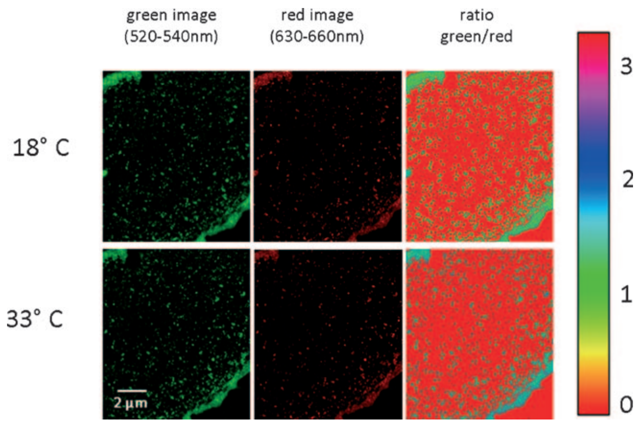

Figure 5. Temperature-dependent images of human embryo kidney cells transfected with UCNPs of the type $NaYF_4$:Yb,Er (see Table 1 and Ref. [10]) showing sub-micometer resolution. The differences in the luminescence intensities of the green channel (left) and the red channel (center) are quite evident. The right panel gives the green/red ratio in pseudo colors. The far-right bar reflects the green-to-red ratio, also in pseudo colors.

the yellow–green (530–560 nm) and the red emission (see Figure 1). The ratio of red and green intensities is somewhat more easily determined than the ratio of the intensities of two adjacent bands.

Ratiometric sensing is a particularly reliable method as shown, for example, for temperature determination with Eu,Tb-based and dually emitting conventional nanoparticles.[8b] In the case of UCNP-based sensors, ratiometric sensing also becomes possible because of the presence of two (if not more) emission bands, one of which is more strongly affected by the parameter to be sensed than the other.[14,34,41,42] Figure 6 gives a plot of the ratio of the averaged intensities of the green and the red channels, respectively, of the data in Figure 5. Resolution still is moderate, probably because data were obtained from microscope pictures. Subsequent images of pure UCNPs recorded within the same temperature range (picture not shown) revealed the same trend.

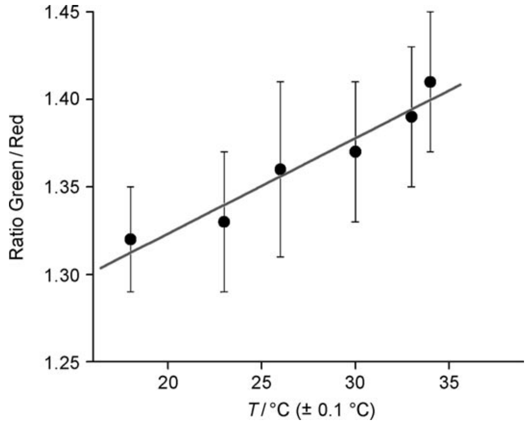

Figure 6. Calibration plot for the temperature-sensitive nanoparticles inside HEK cells. The particles were synthesized according to Ref. [10].

4. Outlook

UCNPs enable, for the first time, ratiometric (i.e. self-referenced) fluorescent sensing of temperature in nanometer resolution and with zero background arising from NIR photoexcitation. The latter also allows for photo-excitation in the biological window of tissue (700–1000 nm). Typical fields of applications include sensing of temperature inside cells, in synthetic nanometer-sized structures and machines. Other conceivable applications include temperature measurements in micro- and nanofluidic systems,[4g,43] in micro/nano/femto-volume (bio)chemistry,[44] in thermally induced drug release,[45] in microdroplets used for chemical synthesis,[46] and wherever exothermal chemical[47] or enzymatic reactions[48] occur on a micro- or nanoscale. Despite such promising perspectives, major challenges remain. These include the need for a) UCNPs possessing higher quantum yields and that be accessible with better control of particle size, b) an optimization of the kind, relative concentration, and ratio of the dopants, and c) an optimization of the host material in general, so to reach the ultimate goal of UCNPs capable of resolving temperature with a precision of ± 0.1 °C if not better.

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