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Controlled photonic manipulation of proteins and other nanomaterials

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Abstract

The ability to controllably handle the smallest materials is a fundamental enabling technology for nanoscience. Conventional optical tweezers have proven useful for manipulating microscale objects but cannot exert enough force to manipulate dielectric materials smaller than about 100 nm. Recently, several near-field optical trapping techniques have been developed that can provide higher trapping stiffness, but they tend to be limited in their ability to reversibly trap and release smaller materials due to a combination of the extremely high electromagnetic fields and the resulting local temperature rise. Here, we have developed a new form of photonic crystal “nanotweezer” that can trap and release on-command Wilson disease proteins, quantum dots, and 22-nm polymer particles with a temperature rise less than ~0.3 K, below the point where unwanted fluid mechanical effects will prevent trapping or damage biological targets.

Keywords

Optical trapping; photonic crystal; resonator; nanomanipulation

Conventional optical tweezers have been used for nearly three decades¹⁻⁵, but they are practically limited to trapping dielectric particles larger than about 100 nm in diameter². Trapping dielectric particles smaller than this limit is extremely difficult since the gradient force for a Rayleigh particle ($F_{grad} = (n_m^2 r^3 / 2) [(m^2 - 1) / (m^2 + 2)] \nabla |E|^2$, where r is the radius of the particle, n_m is the refractive index of the medium, m is ratio of the refractive index of the particle to the refractive index of the medium (n_p / n_m), and E is the amplitude of the

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SUPPORTING INFORMATION: Experimental methods and additional details regarding the calculation of the thermophoretic free energy of a 22-nm polymer particle are provided. Movie 1 illustrates the trapping of 48 and 62 nm polystyrene nanoparticles, and movie 2 demonstrates the ability to perform advanced handling operations on 500 nm nanoparticles. Experimental methods, experimental results, and the calculation of the thermophoretic free energy of a 22-nm polymer particle. Movies showing trapping and release of 22-nm polymer particles, QDs, and Wilson disease proteins. This material is available free of charge via the Internet at <http://pubs.acs.org>.

electric field) is proportional to the third power of the particle size. Despite this limitation, optical tweezers have enabled a wide variety of biophysical studies⁵, ranging from the nanomechanical properties of nucleic acids⁶ and proteins⁷ to the mechanochemistry of molecular motors⁸, primarily through the manipulation of larger objects which are tethered to the molecule of interest.

Overcoming this size limitation would enable the direct manipulation of individual nanomaterials and individual biomolecules, without the need for a larger tethering object. The ability to directly handle these extremely small materials could be incredibly enabling for nanoscience allowing for nanoscopic directed assembly or new ways of performing single molecule analysis. Towards this end, researchers have recently demonstrated near-field optical trapping devices that are capable of providing higher trapping forces. Some of these devices, such as plasmonic optical tweezers⁹⁻¹¹, slot waveguides¹², whispering-gallery mode (WGM) resonators¹³, and PhC resonators¹⁴, can trap and release nanoparticles of a few tens of nanometers in size, and some of them, such as self-induced back-action (SIBA) optical traps¹⁵ and double-nanohole optical traps¹⁶, can bias the motion of smaller nanoparticles. Among these different kinds of near-field optical trapping devices, PhC resonators are especially promising for the manipulation of even smaller nanoparticles and biomolecules since they can be easily used in conjunction with other photonic elements and provide unique functions such as sorting and storing¹⁴.

Trapping biomolecules using current near-field optical trapping techniques, however, is limited by the heat arising from the optical absorption of aqueous solution as in the case of silicon devices, or of metallic structures as in the case of plasmonic devices¹⁷. The absorbed optical energy results in an elevated temperature at the location where the electric fields are the strongest and therefore where the particles are most likely to be trapped. Thermophoresis, the migration of particles in response to temperature gradients¹⁸, tends to repel target particles away from the warmest regions, thus limiting the efficiency of the trap. In addition, the temperature increase can affect or even damage biomolecules in biophysical studies, which practically limits the use of these devices to non-biological particles.

In this work we demonstrate a new approach to near field optical trapping that produces a near neutral thermal background. Using specially designed silicon nitride photonic crystal resonators, we demonstrate the controlled trapping and release of 22-nm polymer particles, quantum dots (QDs), and proteins with a temperature increase of less than 0.3 K. A small hole was added to the center of the cavity, which was proposed theoretically but never tested experimentally¹⁹, to confine the electric fields more tightly. In addition, to reduce the temperature rise and the unwanted fluid mechanical effects that prevent trapping, silicon nitride instead of silicon was used to fabricate the device to enable operating the PhC resonators at 1064 nm, here the optical absorption of water is two orders of magnitude lower than that at 1550 nm, the wavelength commonly used in silicon-based nanophotonic devices. Photodamage to biomolecules is also minimized since many biomolecules are transparent in the wavelengths ranging from 750 to 1200 nm³. Silicon nitride was chosen over silicon as the material of the resonators because of its low optical absorption at 1064 nm and other properties suitable for optical resonators^{20, 21}. The fact that the refractive index of silicon nitride (refractive index $n_{Si_3N_4} = 2$) is smaller than silicon ($n_{Si} = 3.56$) also suggests that the difficulty of fabrication is reduced because the structures do not need to be as small as with silicon. Moreover, the smaller refractive index contrast between the resonator and the surrounding medium (refractive index $n_{SiO_2} = 1.45$, $n_{H_2O} = 1.33$) leads to an increase in the extension of the evanescent field (penetration depth ~ 160 nm), which increases the chance that the biomolecules in the flow chamber move into the potential well.

As shown in Figure 1a, our one-dimensional PhC resonator consists of 53 holes on both sides of a resonator cavity and a central hole. The holes were etched in a silicon nitride waveguide lying on a silicon dioxide substrate. Following the design principles proposed by Quan *et al.*²², the periodicity of the PhC structure was kept constant, and the hole sizes were chosen so as to have a Gaussian-shaped field attenuation inside the Bragg mirror and have a desired resonant wavelength. By adding a small hole at the center of the cavity¹⁹, the superposition of evanescent fields leads to an increase in the field intensity, as shown in Figure 1b, and thus the trapping stiffness is also significantly increased. The resonant wavelength of the device was found to be ~1064 nm in a three-dimensional finite-difference time-domain (FDTD) simulation. The Q-factor is ~5000, which could be increased by optimizing the design of the resonator, and the mode volume is $\sim 4.4 (\lambda/n)^3$. It should be noted that, to have the same amount of optical power coupled into the device, the linewidth of the laser needs to be narrower as the Q-factor of the resonator increases, which increases the difficulty of exciting the resonator exactly at the resonant wavelength. Figure 1c is a schematic illustrating trapping of a nanoparticle on a silicon nitride PhC resonator, the upper surface of which was exposed to the aqueous solution in a flow chamber made by placing parafilm spacers between a coverslip and a fabricated chip, as shown in Figure 1d.

Figure 2a-e (see also Supplementary Movies 1, 2) illustrate on-command trapping and release of 22-nm fluorescent polymer particles (refractive index $n = 1.57$). As shown in the figures (and Supplementary Movies 1, 2), a 22-nm polymer particles was trapped on the PhC resonator when the TE-polarized 1064-nm laser light was coupled into the waveguides connected to the resonator. The laser power coupled in to the resonator was ~11 mW. As can be seen, the particle trapped upstream of the cavity gradually moved towards the cavity, where the gradient force was the strongest, because of the propelling force from optical scattering along the waveguide on the surface of the resonator. In addition, as a result of the fact that the electric fields were much stronger between two adjacent holes than in the holes except at the center of the cavity, as shown in Figure 1b, the trapped particle jumped from one hotspot to another in the direction of the light propagation, as will be shown in Figure 3c. When the laser was turned off, the trapped particle was released from the PhC resonator, which demonstrates that the trapping of the polymer particles was caused by optical forces rather than non-specific binding.

Similar optical trapping experiments were performed with streptavidin-coated CdSe/ZnS QDs, the core of which is ~10-15 nm in diameter. Because of the intrinsic fluorescence of silicon nitride²¹, we found it difficult to resolve QDs in the close vicinity of the resonators through fluorescence microscopy. Instead, the images presented in Figure 2f-j (and Supplementary Movie 3) are the results of mixed fluorescence/near-infrared imaging that allowed simultaneous observation of both the fluorescence signal of the flowing QDs in solution and of the intense scattered laser light from the trapped QDs on the surface of the resonator. With the ability to trap QDs, as demonstrated in Figure 2g-j (and Supplementary Movie 3), micron-sized polymer particles can be advantageously replaced by QDs as handles for optical manipulation in biophysical experiments.

To determine the stiffness of the optical trap, the reduced Brownian motion of a 22-nm fluorescent polymer particle trapped at the center of the cavity was analyzed^{14, 23}. Figure 3a,b illustrates the histograms of the displacement of the trapped particle in the X and Y direction when the laser power coupled into the resonator was ~11 mW. We determined the standard deviation of the Brownian motion in the X and Y direction to be 53.2 nm and 66.0 nm, respectively. The power-normalized stiffness of the optical trap in the X and Y direction are $\sim 0.14 \text{ pN nm}^{-1} \text{ W}^{-1}$ and $\sim 0.09 \text{ pN nm}^{-1} \text{ W}^{-1}$, respectively. A trapped particle can remain trapped for a long period of time until the polarization of the laser is changed or the laser input power is decreased. Figure 3c shows the motion of the trapped 22-nm particle

shown in Figure 2a-e (and Supplementary Movies 1, 2). The particle was trapped on some of the hotspots for a period of time before it moved to the next hotspot towards the center of the cavity because of the radiation pressure, as shown in Figure 3c.

To determine the temperature rise in the solution, the PhC resonator was also modeled with the finite element method. As shown in Figure 3d, under our experimental conditions, the temperature rise at the resonator cavity was found to be lower than 0.3 K, which is small enough not to affect biological activities. As a comparison, a silicon PhC resonator operating at 1550 nm with a Q-factor of ~3000 was modeled in the same way²⁴. The simulation result shows that the temperature rise at the cavity was on the order of 57 K for the same power coupled into the cavity (Figure 3e shows the temperature increase at mid resonator height and along the X direction). Using finite element modeling the free energy profile associated with the thermophoretic barrier that prevents a particle from entering into the trap was computed assuming a Boltzmann distribution and local equilibrium (see Supporting Information). As shown in Figure 3f, the thermophoretic energy barrier to trapping almost vanishes in our novel design when compared to the Si devices operating at 1550nm²⁴.

Figure 4a-e (see also Supplementary Movies 4, 5) show that Wilson disease proteins with a molecular weight of ~46 kDa (see Methods) were also trapped using our silicon nitride PhC resonators. In human cells, Wilson disease proteins interact dynamically with the copper chaperone Hah1 for transporting copper ions, which can be toxic if it is not trafficked properly^{25, 26}. Here we show that Cy5-labelled Wilson disease proteins were trapped by an optically excited resonator, as shown in Figure 4a-e,g, and were released from the resonator when the laser was switched off, as shown in Figure 4f. Figure 4h illustrates that the Cy5 dyes conjugated with the target proteins shown in Figure 4a-g were gradually photobleached in ~25 seconds. Since only one or two Cy5 dyes were conjugated with each protein, the gradual decay of the fluorescence intensity shown in Figure 4h indicates that more than one protein was trapped²⁷. Anti-Brownian electrokinetic (ABEL) traps that uses an elaborate tracking and feedback system to suppress Brownian motion have also been employed to trap proteins recently²⁸. Compared with ABEL traps, the silicon nitride PhC resonators demonstrated in this Letter are not limited to trapping one particle at a time and do not require fluorescent labeling of the target. We believe that our device can be used to trap proteins such as Wilson disease proteins for the study of weak, transient protein-protein interactions.

We have shown that silicon nitride PhC resonators operating at near infrared wavelength allow for trapping of Wilson disease proteins, QDs and 22-nm polymer particles for long periods of time. Unlike plasmonic trapping devices^{9, 10, 29, 30}, in which the heat generation is always present due to light absorption in metal (although there has been some progress in improving the heat transfer through creative nanostructuring transfer¹⁰), our device can trap 22-nm polymer particles with a temperature increase of less than 0.3 K. The significantly reduced heat generation ensures that the trapped biomolecules can function normally and that the transport of biomolecules in the flow chamber will not be affected by thermal effects. Silicon nitride PhC resonators such as the one used in this work can be used to trap biomolecules that are too small to be trapped using other optical trapping techniques for single-molecule studies. We expect that these “molecular nanotweezers”, and others of the same type, will provide a platform for conducting single-molecule experiments in lab-on-a-chip systems or enabling the directed assembly of nanomaterials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Scanning electron microscope image of a silicon nitride PhC resonator. (b) FDTD simulation showing the electric field distribution near the resonator cavity (indicated by the red dashed lines in (a)). The colors indicate the relative field intensity (arbitrary unit). Strong field enhancement can be seen within the small hole at the center of the cavity. (c) Schematic showing trapping of a nanoparticle on a silicon nitride PhC resonator. (d) Schematic showing the relative locations of the resonator and the flow chamber. The resonator and the waveguides connected to the resonator are on the top of a silicon dioxide layer. The upper part of the resonator is exposed to the aqueous solution in the flow chamber, while the waveguides connected to the resonator are surrounded by silicon dioxide. Scale bars in (a) and (b), 1 μm .

Figure 2.

Trapping and release of fluorescent 22-nm polymer particles and QDs on silicon nitride PhC resonators. Movies showing the capture and release of the 22-nm particles (Supplementary Movies 1, 2) and the QDs (Supplementary Movie 3) are included in the Supporting Information. The flow in the chamber is from the left to the right. A 1064-nm laser is used to excite the resonator in all of the images except (e) and (f). (a–d) A 22-nm polymer particle (indicated by arrows) is propelled by the optical scattering force towards the center of the cavity while it is trapped on the resonator surface. (e) The 22-nm polymer particle is released from the resonator when the laser is switched off. (f) QDs flowing in the channel are observed under the mixed fluorescence/near-infrared imaging mode. Since the laser is off in (f), there is no laser light scattering from the resonator. (g–j) As time increases, more QDs are trapped on the optically excited resonator, and the scattered 1064-nm light increases with the number of the trapped QDs. The intense light in the location of the resonator is the scattered laser light.

Figure 3.

Analysis of the Brownian motion and thermophoretic energy of a 22-nm polymer particle trapped on PhC resonators and the temperature profile around the resonators. The laser power coupled into the silicon nitride PhC resonator was ~ 11 mW. The images used for the particle tracking were taken with an exposure time of 30 ms. For (a) and (b) the particle was tracked for ~ 8 seconds. (a, b) Histograms of the displacement of the trapped particle from the trap center in the X and Y direction. The direction of the laser is the positive Y direction. (c) The Y-position of the trapped 22-nm particle shown in Figure 2a-e (Supplementary Movies 1, 2). The positions were measured relative to the position of the particle at the beginning of Supplementary Movie 1. (d) Temperature profile as numerically calculated under the experimental conditions. The maximum temperature increase is 0.3 K at mid resonator height. (e) Line plots of the temperature increase at mid resonator height in the X direction at $y = 0$ for the silicon nitride device operating at 1064 nm (same as the device shown in (d)) and a similar silicon device operating at 1550 nm²⁴. Solid line: silicon nitride device; dashed line: silicon device. The power coupled into the cavity was assumed to be 6 mW in both simulations. The arrow represents the direction of the flow. (f) Calculation of the thermophoretic free energy of a 22-nm polymer particle under our experimental conditions for the silicon nitride device operating at 1064 nm and the silicon device operating at 1550 nm²⁴. Solid line: silicon nitride device; dashed line: silicon device. The free energy was deduced from the concentration profile calculated numerically. Scale bar in (d), 5 μm .

Figure 4.

Trapping of Wilson disease proteins on a silicon nitride PhC resonator. Movies (Supplementary Movies 4, 5) showing the capture of Wilson disease proteins are included in the Supporting Information. (a-d) Cy5-labeled Wilson disease proteins (indicated by arrows) are trapped when they arrive at the vicinity of an optically excited resonator. The fluorescence intensity of the Cy5-labeled proteins decreases over time because of photobleaching. (e, f) The proteins are released from the resonator when the laser is switched off. (g) A picture of the trapped proteins. (h) Plot illustrating the decay of the fluorescence intensity (0-255, arbitrary unit) of the target proteins. The fluorescence decays to background levels within ~25 seconds because of photobleaching. The images were taken using a Hamamatsu CCD camera with contrast and brightness adjustments to the entire image.