# A Bio-inspired Potassium and pH Responsive Double-gated Nanochannel

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**Bio-inspired nanochannels have emerged as an interface to mimic the functionalities of biological nanochannels. One remaining challenge is to develop double-gated nanochannels with dual response, which can regulate the ion transport direction by alternately opening and closing the two gates. In this work, a bio-inspired potassium and pH responsive double-gated nanosystem is presented, constructed through immobilizing C-quadruplex and G-quadruplex DNA molecules onto the top and bottom tip side of a cigar-shaped nanochannel, respectively. It is demonstrated that the two gates of the nanochannel can be opened and closed alternately/simultaneously. This phenomenon results from the attached DNA conformational transition caused by adjusting the concentrations of potassium ion and proton. This design is believed to be the first example of dual-responsive double-gated nanosystem, and paves a new way to investigate more intelligent bio-inspired nanofluidic system.**

## 1. Introduction

The gating of biological nanochannels is the basis of many cellular signal-transduction processes.[1] The gating process is controlled by gates that, once activated, move the channel between opened and closed states. Inspired by the genius designs, a variety of bio-inspired nanofluidic systems that mimic the gating functions have been developed by immobilizing responsive molecules onto the inner wall of synthetic nanochannels.[2] These intelligent nanochannels can be gated by changing conformations of the attached functional molecules in response to external stimuli, including ions,[3] pH,[4] voltage,[5] temperature,[6] light,[7] biomolecules,[8] and small molecules.[9] Ions diffuse in all of these nanochannels are simply governed by a single gate. However, most of biological nanochannels in nature, that conducting ions and molecules in and out of cell membrane, are more sophisticated.[10] A remarkable paradigm is the family of voltage-gated cation channels that possess double gates.[11] Even if one gate of the channel is in open state, the ion pathway can be closed by another gate. Two gates must be in their opening positions for the channel to conduct ions, and closure of either gate precludes ion flow. Also, some channels enable precisely control the direction of the ion transmission by alternate opening and closing of double gates in response to different external stimuli, which is beyond the reach of single-gated nanochannels.[10,12] Therefore, to develop a double-gated nanosystem with multiple intelligent response is a crucial challenge in the way toward biomimetic nanochannels, and has potential applications in intelligent nanofluids,[13] controlled drug release,[14] and biosensors.[15]

In this work, we report a bio-inspired double-gated nanochannel with dual response. Potassium ion ($K^+$) and pH driven gate was immobilized on the tip sides of a cigar-shaped nanochannel, respectively. The two separate gates could open and close alternately or simultaneously in response to appropriate stimuli. This novel bio-inspired double-gated nanosystem has the advantage that it is responsive to both $K^+$ and pH, which successfully mimics the dual-responsive double gates of ion channels in biology. Also, this nanosystem uses C-quadruplex (C4) and G-quadruplex (G4) DNA as the functional molecules. These DNA molecules enable switch reversibly between a structurally single-stranded state and a quadruple-helical state.[3a,16] Attached C4 and G4 DNA molecules alternately or simultaneously change their conformations can induce changes in chemical property and pore size of the nanochannel, resulting in gating of the two gates of this nanochannel.

The geometry and surface properties of nanochannel are two crucial factors to control the different ion transport behaviors.[17] Nowadays, nanochannel shape can be made cylindrical, conical, bullet-like, funnel-like, or cigar-like at will.[2d] In this work, cigar-shaped nanochannel is elected, because it has a large center and two separate small tips on each side that satisfy the need to build double-gated nanochannels. Once the shape of nanochannel is determined, the channel is gated by conformational changes of functional molecules on the inner wall. DNA molecules are widely used to perform gating functions inside the biomimetic nanochannels due to their physical and chemical properties. Martin and Siwy et al. reported the first DNA-nanotube artificial ion channel to help us to better

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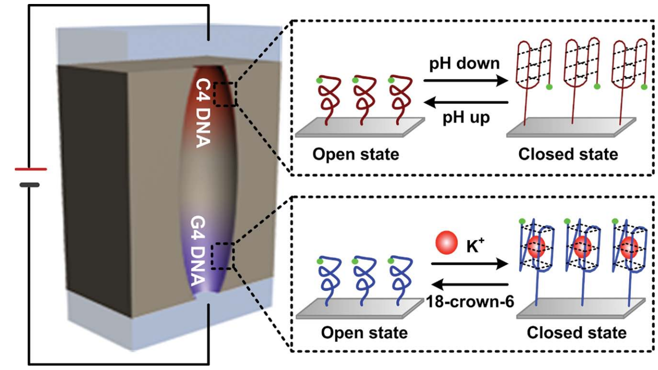

**Scheme 1.** Schematic illustration of the bio-inspired potassium and pH cooperative double-gated nanochannel. C4 and G4 DNA molecules were immobilized onto the inner wall of the top and bottom tip side of the cigar-shaped nanochannel, respectively. When the pH changed within a certain range, C4 DNA experienced pH-responsive conformational switches between four-stranded i-motif structures and random single-stranded structures (right and top). Meanwhile, when the $K^+$ concentration changed within a certain range, G4 DNA experienced potassium-responsive conformational switches between single-stranded structures and four-stranded tetraplex structures (right and bottom).

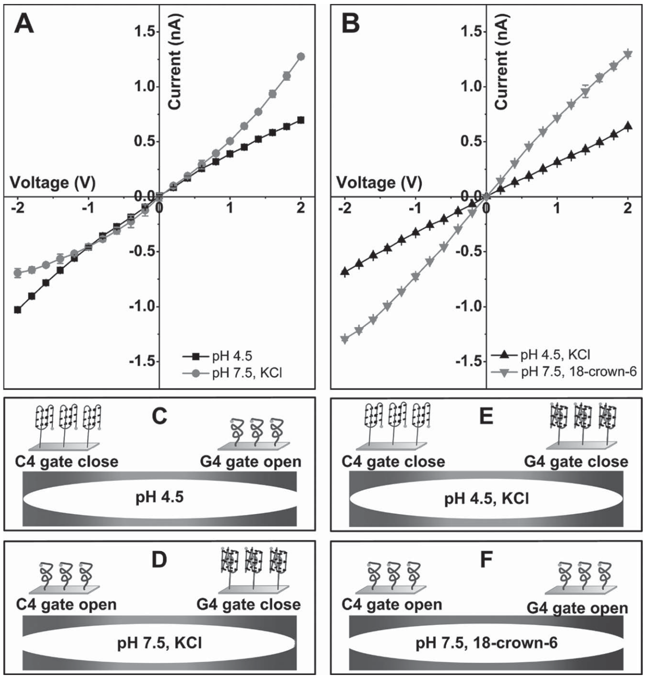

**Figure 1.** A,B) Current–voltage (*I–V*) properties of the double-gated nanochannel under symmetric pH 4.5 (squares), pH 7.5, KCl (circles), pH 4.5, KCl (up triangles), and pH 7.5, 18-crown-6 (down triangles) conditions. C–F) Schematic diagrams of the double-gated nanochannel under different conditions.

understand the role of an electromechanical gate that responds to the applied voltage.[5a] Recently, we described a pH-responsive single-gate nanosystem where conical nanopores could be reversibly gated by switching DNA motors immobilized inside the nanopores.[16]

As shown in **Scheme 1**, we prepared a single cigar-shaped nanochannel membrane with well-developed surfactant controlling and ion track-etching technique. The nanochannel was symmetric. And the diameter of small tip at both sides was 21 ± 1.9 nm, while that of the center was 152 ± 8.3 nm. During etching process, carboxyl groups were generated onto the surface and inner pore walls. Then, C4 and G4 DNA molecules were immobilized onto the top and bottom tip side of the nanochannel, respectively, by an asymmetric modification method,[4a,18] to build the double-gated system. In this nanosystem, the C4 DNAs experienced pH-responsive conformational switches between four-stranded i-motif structures (at pH 4.5) and random single-stranded structures (at pH 7.5).[16] While the G4 DNA molecules underwent potassium-responsive conformational switches between random-coil single-stranded structures (no $K^+$) and four-stranded tetraplex (G4) structures (presence of $K^+$).[3a] These potassium/pH-response conformational conversions could lead to four gating states of this double-gated nanochannel, including close/open, open/close, close/close, and open/open of the C4/G4 gate.

## 2. Results and Discussion

Ion transport properties of the nanochannel before and after DNA immobilization were examined by transmembrane current measurements. The current was recorded under symmetric electrolyte conditions, for 0.1 M LiCl solutions containing $K^+$ or not, and with pH values between 4.5 and 8.5. The original nanochannel exhibited symmetric quasi-linear and S-type current–voltage (*I–V*) curves under pH 4.5 and 7.5 conditions, respectively. And the currents showed no obvious change under different conditions used in this work (Figure S2, Supporting Information). After C4/G4 DNA modification, the current decreased. In addition, owing to the elements of phosphorus, fluorine, and nitrogen containing in Bodipy493/503 labeled DNA molecules, DNA modified PET membranes were also determined by the water contact angle measurements and the X-ray photoelectron spectroscopy analysis (see Supporting Information, Figure S3, S4, and Table S1).

**Figure 1** shows *I–V* properties of the double-gated nanochannel under different conditions. There were obvious differences compared with the original nanochannel. Two asymmetric *I–V* curves could be observed under the pH 4.5 and pH 7.5, KCl conditions (Figure 1A). And by changing the condition from pH 4.5, KCl to pH 7.5, 18-crown-6, a significant increase in the ion current was observed (Figure 1B). These phenomena could be attributed to the attached C4 and G4 DNA molecules alternately or simultaneously changed their conformations under specific condition. CD experiments in solution clearly showed that C4 DNA molecules experienced reversible conformational change between rigid quadruplex i-motif structure at pH 4.5 and random single-stranded structure at pH 7.5 (Figure S5a, Supporting Information). In addition, G4 DNA converted to G4 conformation after reacting with $K^+$ (Figure S5b, Supporting Information). And with the help of 18-crown-6, a potassium chelator, G4 DNA molecules could reversibly switch between random and G4 conformation (**Figure 2**).[19] It was known that DNA molecules were negatively charged in solutions. And the folded i-motif and G4 structure were assumed to be less charged. So the structural transition of DNA molecules

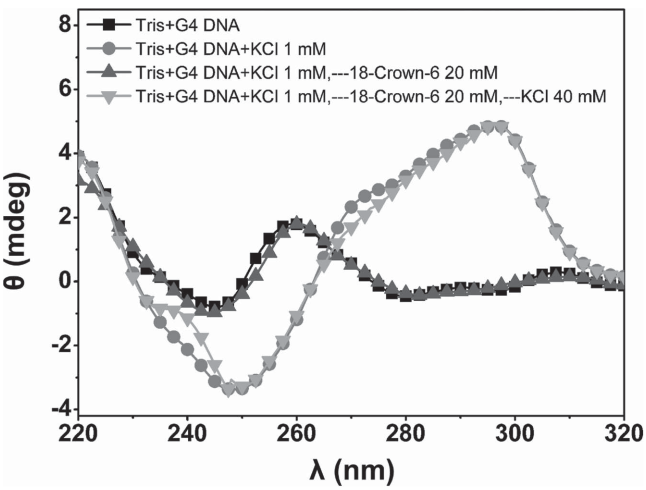

**Figure 2.** CD spectra of G4 DNA (5′-$(NH_2)$-$(CH_2)_6$-AAAAAAAAAAGGGT-TAGGGTTA GGGTTAGGG(Bodipy493/503)-3′) in response to successive treatment with $K^+$ and with 18-crown-6. G4 DNA in Tris, pH 7.5 (squares), G4 DNA in 1 mM KCl, Tris, pH 7.5 (circles), G4 DNA, already treated to 1 mM KCl, was now made up to 20 mM 18-crown-6 (up triangles), G4 DNA was treated sequentially to 1 mM KCl and 20 mM 18-crown-6, and was then made up to 40 mM KCl (down triangles), all in buffer Tris, pH 7.5.

might result in the change of charge density and effective pore size. Under the pH 4.5 condition, the C4 gate closed to i-motif state while the G4 gate remained open and single-stranded state (Figure 1C). Conversely, under the pH 7.5, KCl condition, the C4 gate opened to random state whereas the G4 gate closed to folded G4 state (Figure 1D). Therefore, the asymmetric ion transport properties of the nanochannel under the pH 4.5 and pH 7.5, KCl conditions were ascribed to the asymmetric surface charge redistribution induced by the alternative closing of two gates. When the nanochannel was treated with pH 4.5, KCl, the C4 gate and G4 gate were simultaneously closed, and precluded ion transport through the channel, resulting in low conductivity (Figure 1E). The result coincided with our previous studies.[3a,16] However, by changing the condition to pH 7.5, 18-crown-6, the two gates opened together, and the attached DNA molecules loosely packing on the channel wall could not efficiently reduce the effective pore size (Figure 1F). Thus, a high current was observed.

We further investigated in more detail the changes of ion transport properties of the nanochannel, where one gate was fixed to open or closed state and the other gate was gradually switched from closed to open. The degree of ionic rectification was defined as the ratio$_{+/-}$ of absolute values of ion currents recorded at a given positive voltage (+2 V, anode facing the C4 side of the nanochannel) and at the same absolute value of a negative voltage (–2 V, anode facing the G4 side of the nanochannel). **Figure 3**A shows, when the pH change from 4.5 to 8.5, the *I*–*V* curves change from asymmetric to almost symmetric, with the ratio$_{+/-}$varying from 0.72 ± 0.02 to 0.98 ± 0.03. This phenomenon could be explained by the mechanism shown in Figure 3E. As pH changing from 4.5 to 8.5, the C4 gate changed from close to open, while the G4 gate kept open (no $K^+$). When the double-gated nanochannel was treated by KCl solutions with pH from 4.5 to 8.5, the *I*–*V* curves changed from quasi symmetric to asymmetric, and the ratio$_{+/-}$ changed from 0.94 ± 0.04 to 2.27 ± 0.13 (Figure 3B). This behavior was attributed to that the G4 gate maintained close while C4 gate changed from close to open with pH from 4.5 to 8.5 (Figure 3F). It is worth mentioning that the transmembrane ionic current progressively increased with the increasing of pH from 4.5 to 8.5, regardless of the presence of $K^+$ or not. And there was remarkable ion current increase when the pH was changed from 6.0 to 7.5, compared with changing the pH from 4.5 to 6.0, and from 7.5 to 8.5. CD experiments showed that C4 DNA molecule maintained i-motif structure at and below pH 6.0, and exhibited a pH responsive transition into single-stranded conformation above pH 7.5, which was coincided with previous reports.[20] Changing the pH from 6.0 to 7.5 promoted drastic

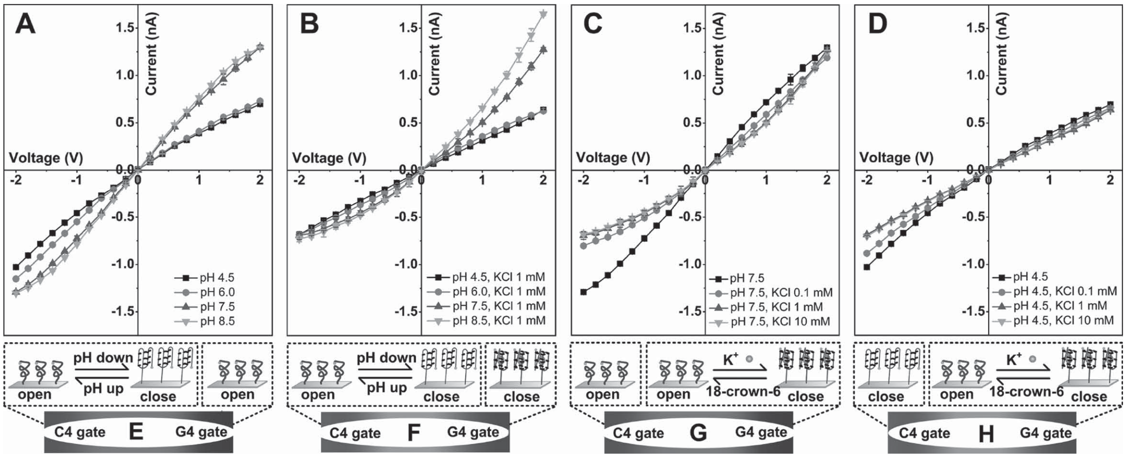

**Figure 3.** *I*–*V* properties of the double-gated nanochannel, where one gate kept open or closed and the other gate changed from closed to open. A) *I*–*V* characteristics were recorded under pH 4.5 (squares), pH 6.0 (circles), pH 7.5 (up triangles), and pH 8.5 (down triangles). B) *I*–*V* characteristics were recorded under pH 4.5, KCl 1 mM (squares), pH 6.0, KCl 1 mM (circles), pH 7.5, KCl 1 mM (up triangles), and pH 8.5, KCl 1 mM (down triangles). C) *I*–*V* characteristics were recorded under pH 7.5 (squares), pH 7.5, KCl 0.1 mM (circles), pH 7.5, KCl 1 mM (up triangles), and pH 7.5, KCl 10 mM (down triangles). D) *I*–*V* characteristics were recorded under pH 4.5 (squares), pH 4.5, KCl 0.1 mM (circles), pH 4.5, KCl 1 mM (up triangles), and pH 4.5, KCl 10 mM (down triangles). E–H) Explanations of ionic transport properties of this double-gated nanosystem under different pH values and $K^+$ concentrations.

changes in the conformational state of C4 DNA, which would result in C4 gate changing from closed to open, and therefore the ion current was correspondingly increased. By changing the pH from 4.5 to 6.0, and from 7.5 to 8.5, the conformational state of the C4 DNA stayed nearly unchanged. In this case, there was no change of the state of C4 gate, and the ionic current change coming from the conductivity changes due to pH variations, the same as ionic transport properties of the original nanochannel.

Figure 3C shows *I–V* properties of the double-gated nanochannel under different concentrations of K$^+$ at pH 7.5. The currents decreased with K$^+$ concentration increasing from 0 to 1 mM, and then changed a little when the concentration range from 1 to 10 mM. Upon addition of K$^+$, the *I–V* curves became asymmetric, and the ratio$_{+/-}$ changed from 1.49 ± 0.04 to 1.87 ± 0.10. We attributed these results to the K$^+$ induced conformational changes of G4 DNA in the nanochannel. As the K$^+$ concentration increasing from 0 to 10 mM, the G4 gate changed from open to close while the C4 gate kept open at pH 7.5 (Figure 3G), which led to asymmetric surface charge distribution and thus asymmetric *I–V* curves. Figure 3D shows *I–V* characteristics under different concentration of K$^+$ at pH 4.5. Compared to the high-pH state, the ionic current showed a similar decreasing trend with K$^+$ concentration from 0 to 10 mM. However, the current significantly decreased by changing pH from 7.5 to 4.5. The key reason was that C4 gate maintained close, and blocked the ion transport on its side at pH 4.5. Additionally, DNA molecules were negatively charged in solution, similarly to the carboxyl groups, which might also be responsible for the current difference. The C4 gate kept close state and the G4 gate transformed from open to close with K$^+$ concentration changing from 0 to 10 mM (Figure 3H), which resulted in asymmetric surface charge distribution changed to quasi symmetric, and thus asymmetric *I–V* curves switched to quasi symmetric. The ratio$_{+/-}$ changed from 0.72 ± 0.02 to 0.94 ± 0.03.

As shown in **Figure 4**, the ratio$_{+/-}$ of the double-gated nanosystem increased with the K$^+$ concentration increasing from 0 to 1 mM. On continuing to raise K$^+$ concentration from 1 to 10 mM, the ratio$_{+/-}$ unchanged. For example, at pH 8.5, the ratio$_{+/-}$ changed from 0.98 ± 0.03 to 2.27 ± 0.13 when the K$^+$ concentration increased from 0 to 1 mM. This result could be attributed to the K$^+$ responsive G4 DNA transition from the random structure to G4 conformation. C4 DNA at C4 gate kept random single-stranded structure at pH 8.5. So the conformation of G4 DNA at G4 gate could induce the change of surface charge distribution of the nanochannel. Also, it could be observed that, at different K$^+$ concentrations, the ratio$_{+/-}$ decreased with the decrease of pH from 8.5 to 6.0, and then increased a little. At acid environment, the ratios$_{+/-}$ were less than 1. For pH 6.0, with the K$^+$ concentration increasing, the ratio$_{+/-}$ increased from 0.66 ± 0.01 to 0.92 ± 0.03. It could be concluded that C4 gate closed to rigid i-motif structure at acid conditions, therefore the preferential direction of ion flow was from the G4 gate towards the C4 gate at the voltage in this work. As the pH changing from 8.5 to 7.5, or from 6.0 to 4.5, the state of C4 gate unchanged, and the changes in ratio$_{+/-}$ were due to the changes in surface charge of the nanosystem caused by pH variations.

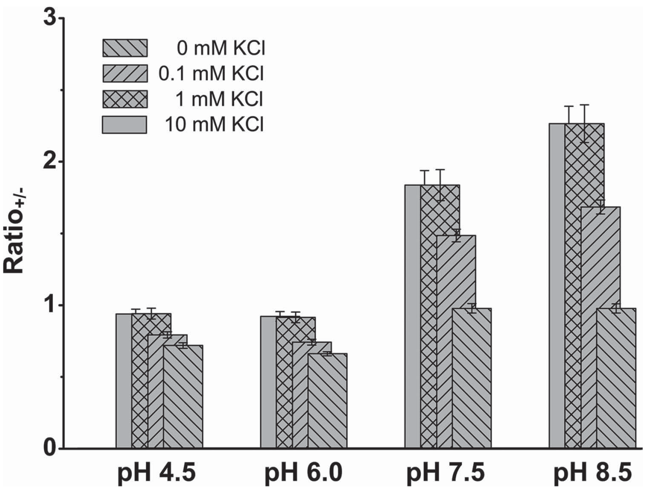

**Figure 4.** Ion current rectifications of the double-gated nanochannel at 2 V.

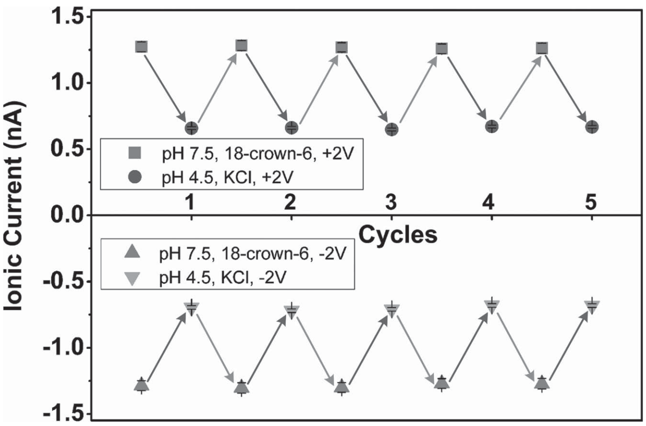

**Figure 5.** Reversibility and stability of the double-gated nanochannel. Reversible transform of the ion current of the double-gated nanochannel at +2 V (pH 7.5, 18-crown-6, squares; pH 4.5, KCl, circles) and −2 V (pH 7.5, 18-crown-6, up triangles; pH 4.5, KCl, down triangles).

To inspect the reversibility and stability of the double-gated nanochannel, we examined the ion transport properties of the nanochannel after repeat alternately treated with pH 7.5, 18-crown-6 and pH 4.5 KCl. As shown in **Figure 5**, repeated addition and removal of the effectors (both K$^+$ and H$^+$ ions) led to a reversible and highly robust off-on switching of the current, with the low conductance defining the "off " state while the high conductance defining the "on" state. This observation reflected that our double-gated nanochannel had excellent stability and reversibility. Furthermore, additional samples proved that the bio-inspired double-gated system has good reproducibility (see Figure S6 in Supporting Information).

## 3. Conclusion

In summary, we have developed a bio-inspired double-gated nanochannel which is dual-responsive to potassium ion and pH. The two gates of the nanosystem can be turned on and off alternately or simultaneously by switching DNA conformations, which can realize four kinds of ionic transport properties. This novel system demonstrates the development of dual-responsive double-gated nanosystem by incorporating biological molecules with artificial devices, has potential applications in smart nanofluids, controlled drug release, and sensing devices. Moreover, one might expect the design of diverse functional double-gated nanochannel based on the proof-of-concept approach described in this work to meet the real-world application.

## 4. Experimental Section

*Nanochannel Preparation*: The cigar-like nanochannel was produced, by symmetric chemical etching of polyethylene terephthalate (PET) membranes (Hostaphan RN12 Hoechst, 12 μm thick, with single or multi-ion tracks in the center), using the surfactant-controlled track-etching method.[4h,21] Briefly, the PET membrane was fixed between the two halves of a conductivity cell at 60 °C. Then, both halves of the cell were filled with etching solution (6 M NaOH + 0.025% sodium dodecyl diphenyloxide disulfonate). A voltage of 1 V was applied across the membrane to monitor the etching process. After etching about 5 min, a 1 M KCl + 1 M HCOOH solution was added to both halves to slow down and finally stop the etching process. The etched membrane was soaked in Milli-Q water (18.2 MΩ) overnight for further use. The diameters and profiles of the nanochannels were characterized from multi-track membranes fabricated in the parallel etching experiments by scanning electron microscopy (SEM).

*DNA Immobilization*: C4 DNA (5′-$(NH_2)$-$(CH_2)_6$-AAAAAAAAAACCCTTACCCTTACCCTTACCC(Bodipy493/503)-3’) and G4 DNA (5′-$(NH_2)$-$(CH_2)_6$-AAAAAAAAAAGGGTTAGGGTTAGGGTTAGGG(Bodipy493/503)-3′) molecules were immobilized onto the tip sides of the nanochannel by asymmetric modification of molecules in solution.[4a,18] In brief, the etched membrane was mounted between the two halves of a cell. The modification was performed in two steps. Firstly, a solution of EDC (15 g $L^{-1}$) and NHS (3 g $L^{-1}$) was introduced only at the left tip side of the nanochannel, while the right tip side of the membrane was in contact with stopping medium 10 mM PBS, pH 9.0. After activating 10 min, the membrane was washed thoroughly with 25 mM MES buffer from both sides. And a solution of 1 μM C4 DNA was added to the left tip side of the membrane, whereas the other tip side of the membrane was in contact with 25 mM MES buffer. The reaction time was kept constant at 4 h, which was followed by a thorough wash of the membrane with 25 mM MES buffer. Subsequently, G4 DNA was immobilized onto the right tip side of the nanochannel using the same method. The solutions used for DNA attachment were prepared in 25 mM MES, pH 6.0. After the second modification step, the membrane was washed and stored in 10 mM Tris-HCl buffer, pH 7.4 for next experiment.

*Current–Voltage Measurements*: The ion transport properties of the double-gated nanochannel were studied by measuring ion current through the single nanochannels before and after DNA modification. A single cigar-shaped PET membrane was mounted between two halves of the cell filled with a 0.1 M LiCl solution prepared in 10 mM Tris-HCl buffer. The Ag/AgCl electrode was inserted into each half-cell solution, and a Keithley 6487 picoammeter (Keithley Instruments, Cleveland, OH) was used to measure the ion current. The anode was placed at left side (C4 gate) of the membrane. The main transmembrane potential used here was a scanning voltage varied from –2 to +2 V with a 40 s period. The pH of the electrolyte was adjusted by 1 M HCl. Current measurement was conducted on the sample treated with different stimuli for 1 h before data collection. And each test was repeated five times to obtain the average current value. It should be noted that all the pH values and ionic currents in this work are measured at 23 °C.

## Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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