Wireless enantio-responsive valves

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Abstract: Microfluidic valves based on chemically responsive materials have gained considerable attention in recent years. Herein a wireless enantio-responsive valve triggered by bipolar electrochemistry combined with chiral recognition is reported. A conducting polymer actuator functionalized with the enantiomers of an inherently chiral oligomer was used as bipolar valve to cover a tube loaded with a dye, and immersed in a solution containing chiral analytes. When an electric field is applied, the designed actuator shows a reversible cantilever-type deflection, allowing the release of the dye from the reservoir. The tube can be opened and closed by simply switching the polarity of the system. Qualitative results show the successful release of the colorant, driven by chirality and redox reactions occurring at the bipolar valve. The device works well even in the presence of chemically different chiral analytes in the same solution. These systems open up new possibilities in the field of microfluidics, including also controlled drug delivery applications.

Keywords: Responsive materials, bipolar electrochemistry, conducting polymers, chiral recognition.

Introduction

Chemically responsive valves are essential devices in channel-based microfluidics.[1-3] Such systems selectively manipulate/control a small flow of liquid inside channels or compartments triggered by an external input. Commonly, microfluidic valves are design by using stimuli-responsive polymers as active material.[1,2] Different polymer-based valves, controlled by electric[4,5] or magnetic fields,[6] infrared light,[7,8] temperature,[9] and pH[10] have been developed. Nonetheless, the design of alternative chemically responsive devices, sensitive to different and far more complex physico-chemical parameters, such as chirality, is an interesting challenge. Chirality is a fundamental symmetry property of elemental particles, molecules or even macroscopic objects.[11] Commonly a system is defined as chiral if it exists as a pair of 'left-handed' and 'right-handed' mirror images that cannot be superimposed (enantiomers). Due to their numerous applications in medicine, chemistry or biochemistry, chiral molecules have gained considerable attention.[11] For example, for biological systems, a specific pharmaceutical compound can be designed for a defined biological receptor, where chirality is used to tune the nature of the interaction.[12] As such, enantiomeric interactions ultimately control and perturb biological functions, thus, enantiorecognition is of tremendous importance in biological systems. Although different spectroscopic methods have been developed for the efficient enantiorecognition of chiral probes,[13-15] the coupling to delivery systems is still a challenge. An interesting approach is to combine the outstanding enantiorecognition capability of inherently chiral conducting polymers with the highly efficient electromechanical actuation of polypyrrole,[16-19] triggered by bipolar electrochemistry (BE).

BE has gained considerable attention due to its broad range of applications from electroanalysis[20,21] and electrosynthesis[22,23] to motion generation.[24] The approach is based on the asymmetric polarization of a conducting object in the presence of an external electric field (ε).[25-28] This produces a polarization potential difference (ΔV) between the extremities of the object. When electroactive species are present in solution and ΔV exceeds the thermodynamic threshold potential (ΔV_{min}), redox reactions take place asymmetrically at both sides of the device, the so-called bipolar electrode (BPE). With such a concept, Bouffier et al. designed a wireless electrochemical valve based on a bubble accumulation/release mechanism.[29] Nonetheless, the closing process of the valve is irregular, due to the random detachment of bubbles. Thus, externally driven electromechanical actuation is presented as a promising alternative for the design of wireless enantioselective valves. Such electrochemically driven actuation is based on an asymmetric uptake/release of ions inside the polymer matrix, which causes a swelling/shrinking process.[30,31] Recently such wireless actuation has been successfully used as a powerful tool for the transduction of chiral information based on an electromechanical readout.[32-34] The approach is based on the coupling of the reduction of polypyrrole (Ppy) with the enantioselective oxidation of a chiral probe on the surface of an inherently chiral oligomer. Due to the energetically different interactions between the chiral oligomer surface and the probe

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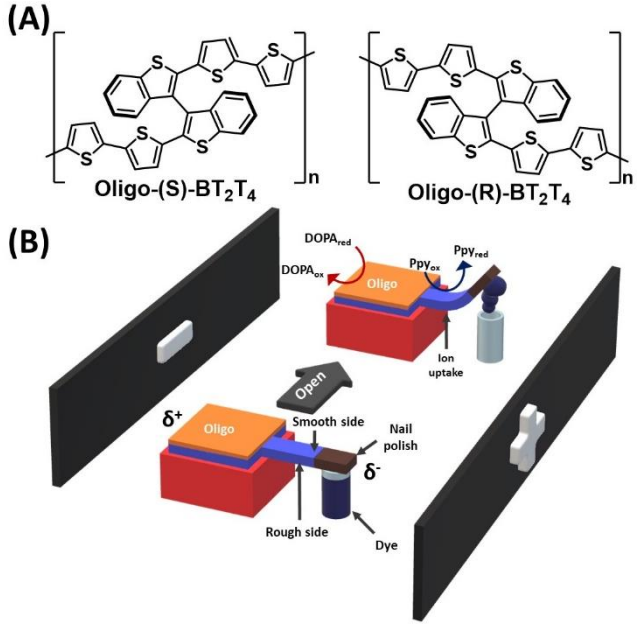
in solution, enantiodiscrimination in terms of difference in oxidation potentials can be achieved. Thus, when an external electric field is applied, the chiral BPE present in solution is polarized, leading to a preferential oxidation of one of the two antipodes. Consequently, only when the right enantiomer of the deposited inherently chiral oligomer reacts specifically with the corresponding molecular probe in solution, an electromechanical deformation of the Ppy can be observed. Herein, we present a wireless enantioselective valve, obtained by combining the attractive electromechanical properties of a Ppy strip with the enantioselectivity of an inherently chiral oligomer, oligo-2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene (BT_2T_4) (Scheme 1A). The enantioselective valve is then placed in a bipolar setup containing a solution with the antipodes of a chiral analyte (Scheme 1B). The setup is designed in analogy to what has been reported for enantioselective actuators.[33-34] The functionalized Ppy strip is properly tailored to cover a capillary tube loaded with a dye. In the presence of the enantiomers of a chiral analyte dissolved in solution, and by applying a specific voltage, the mechanical deformation of the Ppy occurs only in the case when the right analyte antipode is oxidized on the oligomer with the matching configuration. The induced upward bending allows opening of the tube and the release of the dye. The Ppy lid can be easily closed by switching the polarity of the applied electric field. The process is reversible meaning that the opening/closing loop can be repeated several times until no dye is left in the reservoir.



SCHEME 1 (A) Chemical structures of the oligo-(*S*) and oligo-(*R*)-2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene (oligo(*S*)- and oligo-(R)-BT_2T_4). (B) Schematic illustration of the bipolar set-up used for the wireless enantioselective valve with a representation of the chemical reactions, the electromechanical actuation and the release of the dye. The orange part stands for the BT_2T_4 oligomer, whereas light and dark blue symbolizes the Ppy film and the dye, respectively. The light orange colour represents the varnish used to cover the Ppy tip.

Materials and Methods

SYNTHESIS OF THE OLIGO-PPY FILM

The polymeric valve was designed in a two-step process. First, the electropolymerization of the Ppy film was carried out using a 0.25 M dodecylbenzene sulfonate (DBS, Sigma Aldrich) and 0.2 M pyrrole (Sigma-Aldrich) aqueous solution, by chronopotentiometry applying 4 mA for 1.5 h. A classic three-electrode set-up, coupling two gold-coated glass slides, used as working and counter electrode, respectively, and a Ag/AgCl as reference electrode, was used. After polymerization, the Ppy film was washed with water, dried, and peeled off from the gold substrate. In the second step, the oligomerization of the chiral monomer, 2,2'-bis[2-(5,2'-bithienyl)]-3,3'-bithianaphthene (BT_2T_4), was carried out in a 0.1 M $LiClO_4$/ACN solution containing 1 mM of monomer, applying by chronopotentiometry 2 mA for 40 min (Scheme S1A). The smooth side of the so-obtained Ppy substrate was used as working electrode, together with a Pt mesh and Ag/AgCl as counter and reference electrodes, respectively. After deposition, the oligo-(BT_2T_4)-polypyrrole films were cut into strips of 15 x 5 mm. The bipolar devices were fixed on a support with the smooth side upwards. All solutions were prepared with deionized water (MilliQ Direct-Q®).

BIPOLAR ENANTIOSELECTIVE VALVE

For the bipolar chiral valve, the enantiopure (*R*)- or (*S*)-oligo-BT_2T_4-Ppy device was fixed in the center of a bipolar cell, comprising a capillary glass tube loaded with a blue dye solution (Crystal violet, Sigma-Aldrich). Two graphite feeder electrodes were positioned at the extremities of the cell at a distance of 5 cm. Enantiomeric recognition was carried out in 8 mL of an aqueous 0.2 M $LiClO_4$ solution, in the presence of 5 mM L- or D-3,4-dihydroxyphenylalanine (L- or D-DOPA) at a constant applied electric field (1.6 V cm^{-1} or 1.7 V cm^{-1}, respectively). For the double bipolar valve, the enantiopure (*R*)- and (*S*)-oligo-Ppy bipolar devices were fixed face-to-face at the center of a bipolar cell, containing two glass tubes filled with the blue and a pink dye (Rose Bengal, Sigma-Aldrich), respectively. Double bipolar recognition was carried out in an aqueous 0.2 M $LiClO_4$ solution, in the presence of an equimolar solution (5 mM) of L-DOPA and L-Tryptophan (L-Tryp), at a constant applied electric field (1.6 V cm^{-1}). Experiments were monitored by using a charge-coupled device (CCD) camera (CANON EOS 70D, Objective Canon Macro Lens 100 mm 1:2.8). Images were processed with ImageJ software.

Results and Discussion

In order to evaluate the opening/closing mechanism of the valve, triggered by bipolar electrochemistry, a non-enantioselective Ppy valve was tested. The bipolar electrode was designed as follows. From a 15 mm Ppy strip, a 5 x 2 mm (length and width) section, corresponding to the dimensions of cathodic part of the actuator, and a broader part (10 x 5 mm) corresponding to the anodic extremity were cut out. This asymmetric geometry was used in order to maximize the electron flow from the anode to the cathode during the BE measurement. The device was then immobilized at its larger extremity on a support with the smooth face upwards. The obtained non-modified valve was placed in a bipolar cell containing an aqueous 0.2 M $LiClO_4$, 5 mM L-DOPA solution. Only the extremity of the actuator was used to cover a tube loaded with dye. The tip of the cantilever was painted with a non-conductive commercial nail-varnish in order to improve its adhesion to the opening of the tube and to facilitate the bending of the actuator, due to a localized swelling/shrinking process (Scheme S1B). When an electric field of 2 V cm^{-1} is applied, the asymmetric polarization of the Ppy device takes place. This leads to the oxidation of L-DOPA and the reduction of Ppy at the anodic and

cathodic extremity of the polymeric film, respectively. Since the reduction of Ppy preferentially takes place on the rough side of the film, facing downwards in the present set-up, the asymmetric swelling, due to an uptake of cations, causes an upward bending of the cantilever. Such motion leads to the opening of the tube and consequently to the release of the dye (Figure S1a, b, c). Due to the efficient and reversible uptake and release of ions by Ppy, it is possible to induce a downward bending by inverting the polarity of the feeder electrodes, which allows closing the dye reservoir (Figure S1d). It is important to highlight that under these conditions the oxidation of Ppy at the δ^+ extremity is accompanied either by the reduction of the Ppy substrate at its δ^- end, or of the quinoidal species formed during the oxidation of DOPA on the other side. Nonetheless, this *umpolung* can be repeated for several cycles without damaging the Ppy strip, making the process reversible (Movie S1).

After having demonstrated that in such a set-up the Ppy strip can act as an electrochemically responsive valve, an analogue, but enantioselective, system has been built. Theoretically, by functionalizing the Ppy strip with inherently chiral oligomers, the opening and the closure of the valve should be controlled essentially by the diastereomeric interactions between the inherently chiral oligomers and the chiral analytes dissolved in solution. The outstanding enantiorecognition capability of these oligomer substrates in terms of redox potentials has been demonstrated previously.[35] This is a crucial point in the development of the enantioselective valve, since it is possible to oxidize exclusively one enantiomer on the surface of the functionalized Ppy, if the proper electric field is applied. The overall experimental set-up is illustrated in Scheme 1B. The hybrid enantioselective valve, composed of enantiopure (*R*)- or (*S*)-oligomer BT_2T_4 (orange) electrodeposited onto Ppy (blue), was used as a bipolar electrode. The experimental procedure is the same described above for the non-modified Ppy valve. Two enantioselective devices, together with a small capillary-type reservoir loaded with blue dye, were fixed separately in a bipolar cell containing an aqueous 0.2 M $LiClO_4$ solution of 5 mM L- or D-DOPA.

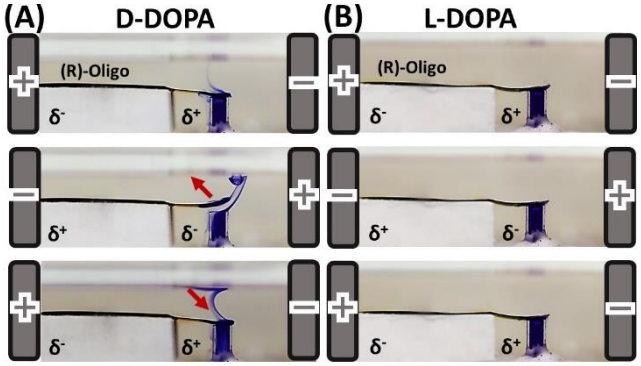


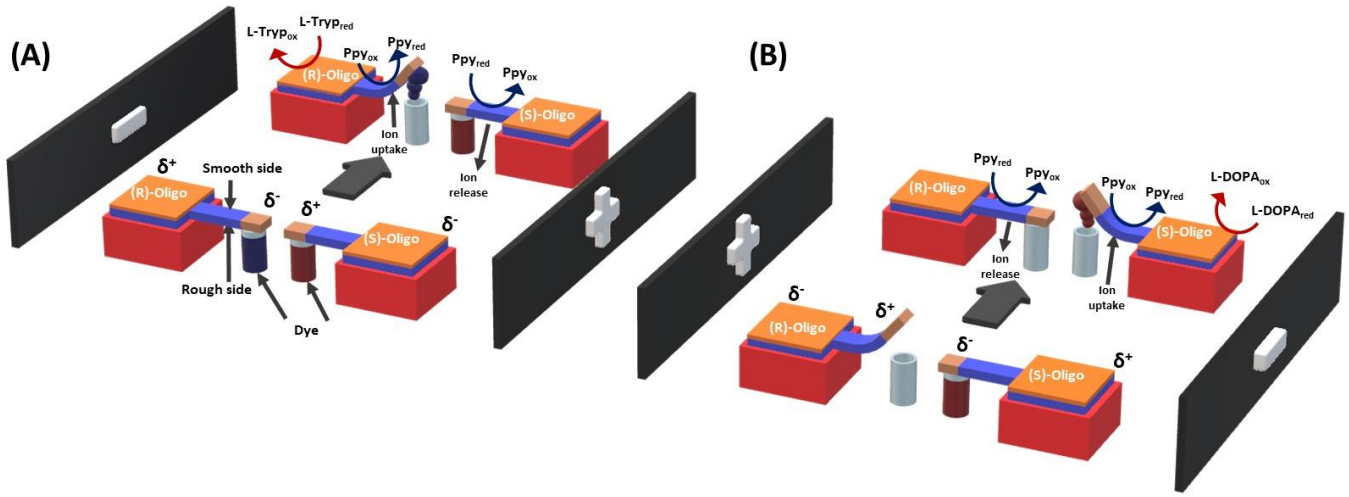
FIGURE 1 Bipolar enantioselective valve (1.5 cm long) operating with a Ppy actuator functionalized with (*R*)-oligo-BT_2T_4 dipping in an aqueous 0.2 M $LiClO_4$ solution of (A) 5mM D-DOPA and (B) 5mM L-DOPA. The pictures in sequence (top to bottom) represent the opening and closing process of the valve by switching the polarity between feeder electrodes at a constant applied electric field of 1.7 V cm^{-1}. The red arrows show the upwards and downwards movement of the cantilever.

When applying the optimized electric field, the involved redox reactions that take place at respective extremity of the BPE are the oxidation of DOPA and the reduction of Ppy. For example, the (*R*)-oligo-Ppy valve shows actuation when applying an electric field of 1.7 V cm^{-1} in the presence of D-DOPA (Figure 1A, Movie S2 upper video), whereas, in the presence of L-DOPA no mechanical deformation was observed under exactly the same conditions (Figure 1B, Movie S2 bottom video). As stated above, the selective oxidation of D-DOPA, coupled with the reduction of Ppy, triggers the upward bending, allowing the opening of the valve accompanied by a massive release of blue dye. In addition, by periodically inverting the polarity of the electric field, it is possible to observe a reversible opening/closing of the reservoir.

In order to confirm the enantioselectivity of the valve as function of the configuration of the inherently chiral oligomer, a mirror experiment was carried out by depositing the opposite oligomer configuration ((*S*)-oligo-BT_2T_4) on the Ppy strip, and testing the device in an aqueous 0.2 M $LiClO_4$ solution of 5 mM L- or D- DOPA (Figure S2). Under these conditions the (*S*)-oligo-Ppy device exhibits actuation only when it is immersed in a solution of L-DOPA, whereas absolutely no mechanical deformation is observed in a solution of D-DOPA (Figure S2). From these results one can conclude that such electromechanical systems can act as enantioselective valves since the opening/closing mechanism is governed by the diastereomeric interactions between the chiral probe in solution and the inherently chiral oligomer. This opens up the possibility to design systems that selectively open or close in the presence of more than one relevant probe dissolved in the same solution.

In order to extend this concept to more sophisticated systems, a double enantioselective valve was designed. In this device, the opening/closing mechanism is controlled by the orientation of the applied electric field and the respective diastereomeric interactions. First we evaluated the electric field induced control by placing two non-enantioselective Ppy actuators face-to-face, at the centre of a bipolar cell comprising two glass tubes loaded with a blue and a red colorant, in an aqueous 0.2 M $LiClO_4$ solution of 5 mM L-DOPA (Scheme S2). When a high enough electric field is applied, the Ppy valve that is facing the positive feeder electrode opens, due to the uptake of ions, whereas the opposite valve closes, due to the release of ions from the polymer. The inverse behaviour is observed when changing the orientation of the electric field. As it can be seen in Figure S3, by applying an electric field of 2 V cm^{-1}, it is possible to trigger a continuous opening/closing process of the two non-enantioselective Ppy valves. For the same electric field value, but opposite polarities, the process is switching from a state where the red valve is open and the blue valve is closed, to the inverse configuration. In addition, the *umpolung* is reversible and can last for several cycles.

After demonstrating the efficient electric field control of the opening/closing mechanism of the double valve system, its diastereomeric selectivity has been evaluated. In this case a (*S*)- and (*R*)-oligo-Ppy device were placed face-to-face, at the center of a bipolar cell comprising two glass tubes loaded with a blue and a pink dye, in an aqueous 0.2 M $LiClO_4$ solution. Although it is relatively straightforward to assume that in the presence of L- and D-DOPA, at a given applied electric field, the *umpolung* process will operate, we were interested in testing more complex systems, including mixtures of molecules with the same chiral configuration. In previous electrochemical experiments it has been demonstrated that L-DOPA reacts preferentially with (*S*)-oligo-BT_2T_4, whereas L-Tryp has a higher affinity for (*R*)-oligo-BT_2T_4.[36,37] Thus, by applying an optimized electric field, each enantioselective valve will open only in the presence of the analyte with the right stereochemical configuration.



SCHEME 2 Schematic illustration of the bipolar set-up used for the double recognition with wireless enantioselective valves with a representation of the related chemical reactions, the resulting electromechanical actuation and the final release of the dyes. The orange part stands for the BT_2T_4 oligomers, whereas light blue color symbolizes the Ppy film. The light orange color stands for the varnish used to cover the Ppy tip. The tubes are loaded with two dyes represented here as dark blue and red. (A-B) represents a full opening/closing cycle; (A) oxidation of L-Tryp on the (*R*)-oligomer with blue dye release; (B) oxidation of L-DOPA on the (*S*)-oligomer with red dye release.

In Scheme 2 one opening and closure cycle of the double bipolar valve is illustrated in the simultaneous presence of L-DOPA and L-Tryp. Under the influence of the proper electric field, the (*R*)-oligo-Ppy actuator, that is facing the positive feeder electrode, favors the selective oxidation of L-Tryp, with a concomitant deformation of its cantilever and a subsequent release of blue dye. At the same time the (*S*)-oligo-Ppy actuator is not deformed, keeping the tube closed due to the ion release (Scheme 2A). When switching the polarity, reactions are inverted, thus on the (*S*)-oligo-Ppy the oxidation of L-DOPA occurs, coupled to the opening of the tube loaded with red colorant, whereas the other strip is reoxidized and shrinks, thus preventing the release of blue dye (Scheme 2B).

In order to test this mechanism, we first studied the opening/closing of the double enantioselective system in the presence of a 5 mM L-Tryp solution (Movie S3). At a constant electric field (1.6 V cm^{-1}) only the Ppy strip functionalized with the (*R*)-oligomer undergoes mechanical deformation, causing the release of dye. Even more importantly, when the orientation of the electric field is changed, the opposite strip, does not react with L-Tryp either, since it is modified with the oligomer with the wrong stereochemistry ((*S*)-oligomer) (Figure S4). Finally, the double enantioselective opening/closing mechanism was tested in an aqueous 0.2 M $LiClO_4$ solution in the presence of an equimolar mixture (5 mM) of L-DOPA and L-Tryp. Figure 2 presents three cycles of closing/opening of the enantioselective valves by switching the polarity. Under an electric field of 1.6 V cm^{-1}, the (*R*)-oligo-Ppy valve, that is facing the negative feeder electrode, remains closed, whereas the (*S*)-oligo-Ppy valve, that is facing the positive electrode, opens. By switching the polarity, the reactions are inverted causing the opening of the (*R*)-oligo-Ppy valve and the closing of the (*S*)-oligo-Ppy device (Movie S4). Once again, due to the outstanding electromechanical properties of Ppy, the double *umpolung* mechanism is reversible and lasts several cycles.

Conclusion

In the present contribution, the first enantioselective valve driven by bipolar electrochemistry is reported. This approach is based on the diastereomeric interactions between inherently chiral oligomers, used to functionalize a polypyrrole strip, and the chiral analytes dissolved in solution. The system is triggered by bipolar electrochemistry and can be considered as a wireless chiral valve. The design of the device allows the selective release of dye by applying a constant electric field and by switching the polarity between the feeder electrodes. These systems can detect different chiral analytes in a single experiment by reacting just with one of the two enantiomers of a chiral probe. The described set-up has characteristic dimensions in the millimeter scale, but can be in principle scaled down to smaller dimensions. The major advantage of these devices is their wireless nature, combined with a direct transduction of molecular chirality into a release of specific compounds. Thus, these valves might be interesting, among others, for the field of microfluidics in the frame of wireless drug release.

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Supporting information

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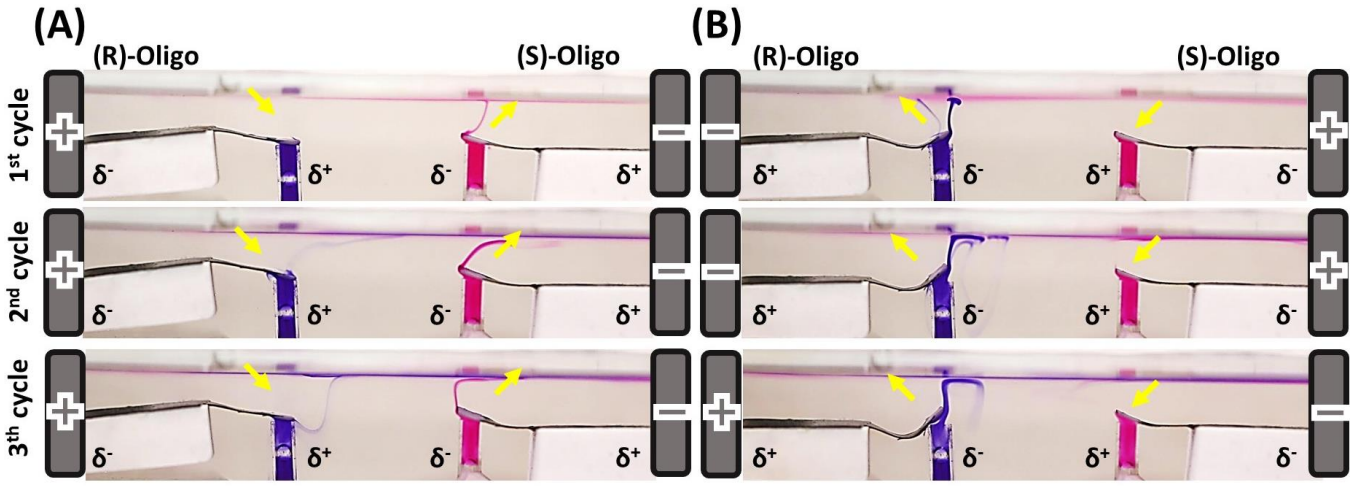

FIGURE 2 Subsequent closing and opening cycles of two bipolar chiral valves (1.5 cm long) obtained by switching the polarity between feeder electrodes and by functionalizing the Ppy actuators with (*R*)-oligo-BT_2T_4 and (*S*)-oligo-BT_2T_4, dipping in an aqueous 0.2 M $LiClO_4$ solution of 5mM L-DOPA and 5mM L-Tryp. Feeder electrodes are placed at a distance of 5 cm. A constant electric field of 1.6 V/cm is applied. The two tubes are loaded with two dyes, a blue and a pink one, respectively.

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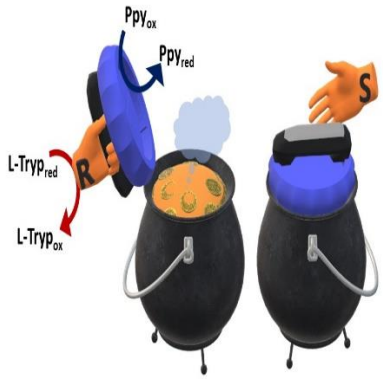
Graphical Abstract



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