Relative contractile motion of the rings in a switchable palindromic [3]rotaxane in aqueous solution driven by radical-pairing interactions

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Artificial muscles are an essential component for the development of next-generation prosthetic devices, minimally invasive surgical tools, and robotics. This communication describes the design, synthesis, and characterization of a mechanically interlocked molecule (MIM), capable of switchable and reversible linear molecular motion in aqueous solution that mimics muscular contraction and extension. Compatibility with aqueous solutions was achieved in the doubly bistable palindromic [3]rotaxane design by using radical-based molecular recognition as the driving force to induce switching.

The concept of controlling molecular motion at will is an inspiring call to chemists. The design and synthesis of organic molecules that are capable of achieving movement is the first step towards translating that motion into a macroscopic effect through integration into larger systems. Some of the most impressive evidence that molecular motion can be translated into macroscopic motion comes from biology, wherein proteins and assemblies of proteins – themselves large molecules and supermolecules – routinely achieve incredible feats, from kinesin pulling organelles along microtubules, to the rotary motion of ATP synthase, to the propulsion that results from bacterial flagellum. When we turn to the synthetic world, there are still rather few comparable systems. One class of organic compounds is particularly well suited, however, to containing and exercising moving parts – namely, mechanically interlocked molecules (MIMs). Since MIMs consist of two or more components that cannot be separated without breaking a covalent bond, the bond(s) holding the molecule together is (are) called a mechanical bond. In the case of a rotaxane, a dumbbell-shaped component is encircled by a ring, and the inclusion of functional groups on the dumbbell, for which the ring has an affinity, provides recognition sites. When the affinity for one recognition site is increased or decreased relative to another one by a stimulus, this bistability serves as the driving force for the ring moving relative to the dumbbell. A unique interpretation of this design has been reported previously wherein the dumbbell contains two sets of identical recognition sites, in a constitutionally symmetric, or palindromic, design. Thus, in this prototypical design of a palindromic [3]rotaxane, the two rings achieve a linear contractile motion as they are switched between the inner and outer recognition sites. This motion (Fig. 1) mimics the molecular motion present in actin and myosin proteins within muscle tissue. In order to facilitate the next transition of the doubly bistable [3]rotaxane switches – from isolated molecules to integrated systems – and to enable biocompatible applications, these switches must operate in aqueous solution, the major medium of life itself.

Fig. 1  (a) Graphical representation of the relative motion of the ring components, which undergo a redox-stimulated contraction and expansion in a doubly bistable palindromic [3]rotaxane. (b) The contraction of the sarcomere in biological muscle is achieved through the ATP-driven molecular motion of actin and myosin proteins sliding relative to each other.
Recently, we have discovered the potential of radical–radical pairing interactions\(^8\) in the context of MIMs. It has been found that 4,4′-bipyridinium (BIPY\(^{2+}\)) units, upon reduction to their radical cationic state (BIPY\(^{+}\)), form strong inclusion complexes with the reduced diradical, dicationic (CBPQT\(^{2+}\)) form of cyclobis(paraquat-p-phenylene) (CBPQT\(^{4+}\)). The radical-based pairing interaction in the reduced state is strong and represents the driving force for switching to the radical state co-conformation\(^8\) (RSCC) in a MIM, a process that is eliminated in the oxidised state by electrostatic repulsions between the positive charges on both components. Thus, redox stimuli initiate rapid and readily reversible switching, but what’s more, this radical-based switching mechanism has been shown to occur in aqueous solution. Here, we incorporate this new switching mechanism into a palindromic [3]rotaxane.

The design of a doubly bistable palindromic [3]rotaxane requires two sets of identical recognition sites on the dumbbell. Our design utilises 1,5-dioxynaphthalene (DNP) units as the outer recognition sites, which enter into donor–acceptor interactions with the CBPQT\(^{4+}\) rings in the oxidised ground state co-conformation (GSCC). After reduction, the diradical, dicationic CBPQT\(^{2+}\) ring has a strong preference for the inner BIPY\(^{+}\) recognition sites and a decreased affinity for the DNP units, resulting in a shuttling motion whose reversal is facilitated by the electrostatic repulsion between the positive charges on both the BIPY\(^{2+}\) units and the tetracationic ring upon re-oxidation.

The synthesis of the bistable palindromic [3]rotaxane was performed following the protocol outlined in Scheme 1. In order to achieve higher yields of the desired [3]rotaxane than had previously been possible with clipping-based rotaxanation approaches,\(^6\) we sought to use a threading-followed-by-stoppering protocol for the rotaxane formation. Therefore, the first step was synthesising an axle component, A\(\cdot\)4PF\(_6\), with azide functionalities at each end to aid and abet the subsequent stoppering reaction. The synthesis of the axle begins with a DNP-tri(ethylene glycol) unit\(^9\) which was subjected to a monotosylation to induce desymmetrisation.\(^10\) The mono/tosylate\(^2\) was reacted with sodium azide in order to install an azide group\(^11\) in\(^3\). The remaining hydroxyl group on\(^3\) was then tosylated in order to form\(^4\) prior to its reaction with a bisviologen-based core\(^12\) 5·2PF\(_6\) to form the axle A·4PF\(_6\).

Rotaxanation was achieved by a threading-followed-by-stoppering approach wherein an excess of CBPQT·4PF\(_6\) was incubated with the axle in MeCN at room temperature for a week. An electron-deficient alkyne\(^13\) 6 was added to form the stoppers as a result of copper-free Huigsen cycloadditions.\(^14\) The desired [3]rotaxane 3R·12PF\(_6\) was obtained in 46% yield, along with a small amount (8%) of a [2]rotaxane byproduct (2R·8PF\(_6\)). See synthetic procedures in the ESI.†

Scheme 1  Synthetic route to the palindromic [3]rotaxane 3R·12PF\(_6\) using a threading-followed-by-stoppering approach.
$^1$H NMR spectroscopy of 3R·12PF$_6$ confirmed the hypothesis that, in the non-reduced GSCC, the CBPQT$_{4+}$ rings reside on the DNP recognition units. Fig. 2 shows partial $^1$H NMR spectra comparing the dumbbell D·4PF$_6$, the [3]rotaxane 3R·12PF$_6$ and the [2]rotaxane 2R·8PF$_6$. An upfield shift was observed for the peaks corresponding to the DNP protons (labelled H$_{4R}$, H$_{2R}$, and H$_{3R}$) in the [2] and [3]rotaxanes, indicating that the DNP units are encircled by CBPQT$_{4+}$ rings. This co-conformation was confirmed by through-space interactions observed in the $^1$H--$^1$H ROESY NMR spectrum, shown in Fig. S9 in the ESI.† Variable temperature $^1$H NMR spectra, which were recorded on the [2]rotaxane 2R·8PF$_6$ demonstrate that, in the GSCC, the inner BIPY$_{2+}$ recognition sites serve as electrostatic barriers preventing the shuttling of the ring from one DNP recognition site to the other. See Fig. S11 in the ESI.†

Following the characterisation of the [3]rotaxane 3R·12PF$_6$, we were interested in investigating its switching properties, particularly in aqueous solution. The solubility of the [3]rotaxane can be modulated by counterion exchange, given the fact that the PF$_6$– salt is highly soluble in organic solvents such as MeCN and Me$_2$CO, and the Cl$^-$ salt is soluble in aqueous solution. Counterion exchanges were achieved using NH$_4$PF$_6$ and nBu$_4$NCl. The shuttling of the CBPQT$_{4+}$ rings between the recognition sites, following reduction to the hexarcadic, hexacationic RSCC, was monitored electrochemically and also by UV-Vis-NIR spectroscopy since NMR characterisation of the paramagnetic species was not possible.

The reduction potential for 3R·12Cl in aqueous solution was determined (Fig. 3) by differential pulse voltammetry using Ag/AgCl as a reference. Compared to the free BIPY$_{2+}$ units in the dumbbell structure (−615 mV) and in the ring (−410 mV), the reduction potential of the [3]rotaxane was significantly shifted (−368 mV). The shift of the BIPY$_{2+}$ signal in the [3]rotaxane toward more positive potential indicates the formation of the trisradical complex between the BIPY$_{2+}$ and CBPQT$_{4+}$. Spectroelectrochemistry (SEC) performed (Fig. 4) at an applied potential of −750 mV showed evidence for the shuttling of the reduced diradical, dicationic CBPQT$_{4+}$ rings from the DNP recognition sites to the inner BIPY$_{2+}$ sites. This was revealed by a change in the charge-transfer band corresponding to the interaction between the CBPQT$_{4+}$ rings and the DNP units in the GSCC. A comparison of the spectra of the reduced [3]rotaxane species with those of the dumbbell D$_{4+}$ and ring CBPQT$_{2+}$ in their reduced states showed an absorption band centred at 1125 nm characteristic of the trisradical interaction in the hexaradical, hexacationic [3]rotaxane 3R$_{4+}$. SEC also showed significantly different absorption profiles for the reduced versus oxidised states of the [3]rotaxane. See Fig. S2 in the ESI.† In addition to electrochemical stimuli, switching was also achieved by chemical means – Na$_2$S$_2$O$_4$ and

![Image](14x290 to 26x354)

![Image](43x93 to 46x122)

![Image](315x273 to 544x447)

![Image](495x790)
Zn dust for reduction in H$_2$O and MeCN respectively, and O$_2$ (air) for oxidation. See Fig. S3 and S4 in the ESL.†

In summary, by combining new advances in radical-based MIM motifs with a design that results in relative contractile motion of the rings, we have produced a ‘next generation’ palindromic [3]rotaxane capable of redox switching in aqueous solution. The radical-pairing recognition motif is incredibly versatile, since it is amenable to switching by electrochemical or chemical stimuli in different media, including aqueous solution. This system brings the dream of artificial muscles that function employing the same mechanism natural muscle uses – namely molecular motion – one step closer. Operating in aqueous solution enables the integration of this molecular muscle mimic with biological interfaces. Future work will focus on the preparation of derivatives that include conjugation handles for incorporating this molecular switch into micro- and macroscopic materials and biological systems.

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Notes and references


