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Authors: Cristian Pezzato, Minh T Nguyen, Dong Jun Kim, Ommid Anamimoghadam, Lorenzo Mosca, and Fraser Stoddart

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Controlling Dual Molecular Pumps Electrochemically

Cristian Pezzato, Minh T. Nguyen, Dong Jun Kim, Ommid Anamimoghadam, Lorenzo Mosca, and J. Fraser Stoddart*

Abstract: Artificial molecular machines can be operated using either physical or chemical inputs. Light-powered motors display clean and autonomous operations, whereas chemically-driven machines generate waste products and are intermittent in their motions. Herein, we show that controlled changes in applied electrochemical potentials can drive the operation of artificial molecular pumps in a semi-autonomous manner – that is, without the need for consecutive additions of chemical fuel(s). The electroanalytical approach described in this communication promotes the assembly of cyclobis(paraquat-p-phenylene) rings along a positively charged oligomeric chain, providing easy access to the formation of multiple mechanical bonds by means of a controlled supply of electricity.

Control over the operation of artificial molecular machines (AMMs) has been achieved in the past by employing^[1] either physical or chemical inputs. In concert with the rise^[2] of overcrowded alkene-containing molecular motors, which operate autonomously by absorbing light, AMMs based on mechanical bonds^[3] have experienced a paradigm shift in design principles^[4] - i.e., from switches to ratchets^[5] - as well as in the way external stimuli^[6] - e.g., light irradiation, pH or redox changes - are transduced into motion or other functions.^[7] Early examples of bistable mechanically interlocked molecules (MIMs) in the form of simple [2]rotaxanes^[8] and [2]catenanes^[9], followed by molecular elevators^[10] and muscles^[11], have led to more sophisticated^[12] rotary and linear molecular motors^[13] and pumps^[14] capable of controlling the directional movements of their component parts on the molecular scale. Recent advances^[15] have drawn attention to establishing autonomous AMMs which work as a result of the consumption of chemical fuels, a typical property of biomolecular machines. In closed systems, however, the capability for AMMs to operate without generating waste products is seldom observed^[16] and remains an exclusive feature of light-driven^[12b] machines. Here, we describe how AMMs can be operated semiautonomously by controlling the supply of electrical current, thus avoiding the accumulation of waste products during repetitive cycles.

Previously, we have reported Mark I^[14a] and II^[14b] versions of artificial molecular pumps – i.e., AMMs capable of driving the confinement of multiple cyclobis(paraquat-p-phenylene) (**CBPQT**⁴⁺) rings onto a short oligomethylene chain. These pumps comprise (Figure 1a) a viologen unit (V²⁺) positioned between a

[*] Dr C. Pezzato, Dr. M. T. Nguyen, Dr. D. J. Kim, Dr. O. Anamimoghadam, Dr. L. Mosca, Professor J. F. Stoddart Department of Chemistry, Northwestern University 2145 Sheridan Road, Evanston, IL 60208 (USA) E-mail: <u>Stoddart@northwestern.edu</u>

> Professor J. F. Stoddart Institute of Molecular Design and Synthesis, Tianjin University, Nankai District, Tianjin 300072 (China)

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Coulombic barrier (PY⁺) and a steric speed-bump (IPP) which is attached, via a triazole linker (T), to a collecting-chain for the rings. We have shown^[14b] that the Mark II version operates much more rapidly thanks to the well-tuned noncovalent bonding interactions exerted between the PY⁺ and IPP units, allowing V²⁺ to attract and then quickly repel the **CBPQT⁴⁺** rings unidirectionally upon redox switching.



Figure 1. a) Graphical representations of structural formulas for the Mark II pump constitution and **CBPQT⁴⁺**. b) Schematic illustration of the pump's stroke. Upon reduction (either using Zn dust or electrochemically), V⁺⁺ and **CBPQT²⁽⁺⁾** radical cations associate to form a trisradical tricationic complex V⁺⁺ \subset **CBPQT²⁽⁺⁾**, whereas upon reoxidation (either using NOPF₆ or electrochemically), V²⁺ and **CBPQT⁴⁺** coexist as a metastable co-conformation with **CBPQT⁴⁺** located alongside the IPP unit, which subsequently rearranges into the corresponding rotaxane through energy dissipation. Grey labels = chemical fuels; black labels = electrochemical inputs. c) Energetic landscapes of the two redox states, illustrating the energy ratchet mechanism.

The ratchet mechanism of these pumps was operated by the consecutive addition of redox reagents – Zn dust for the reduction of V²⁺ and **CBPQT⁴⁺** to their corresponding radical cations V⁺⁺ and **CBPQT²⁽⁺⁺⁾**, and NOPF₆ for the reverse oxidation reactions (Figure 1b and c, grey labels). It turned out to be difficult, however, to perform multiple redox cycles on a solution of starting materials, most likely because of interferences originating from the waste products, namely Zn(PF₆)₂ and NO_(g). Additionally, Zn dust has been shown to over-reduce^[17] viologen-based compounds to their neutral forms, a flaw which could decrease the pumping efficiency. Herein, we show that cycles of controlled-potential electrolysis (CPE) can drive (Figure 1b and c, black labels) repetitively the operation of the Mark II pump in solution. Moreover, we demonstrate the double addition^[7] of **CBPQT⁴⁺** rings to a chain by locating two Mark II pumps at both ends of a dicationic oligomer.

First of all, we focused our attention on designing an oligomeric dual pump – referred hereafter to as **DP**⁸⁺ – which comprises (Scheme 1) two Mark II pumps attached, by means of a triazole linker, to a 36-carbon atom chain incorporating two dimethylammonium centers. This chain is expected to act as the axle for the collection of multiple **CBPQT**⁴⁺ rings. We chose this

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quaternary ammonium-based chain for three main reasons: they are (i) facile synthesis, (ii) high solubility in MeCN of the corresponding PF₆⁻ salt and (iii) the possibility of investigating^[18] the enthalpically and entropically unfavorable assembly of polycationic species. The axle was prepared (Scheme 1) in good overall yield (67%) in three steps, starting from 1,12-dibromododecane by reacting it with **1** to give **2**•2Br, which was converted into **3**•2PF₆ after reaction with NaN₃ and counterion exchange (NH₄PF₆ / H₂O). **DP**•8PF₆ was isolated in satisfactory yield (120 mg, 78%), following a click reaction between **3**•2PF₆ and the pump precursor^[14b] **4**•2PF₆. See the Supporting Information for more details.



Scheme 1. Synthetic route for the preparation of the dual molecular pump DP^{s_+} , which is isolated as its PF_6^- salt. A graphical representation of DP^{s_+} is provided below the structural formula.

Next, we performed CPE experiments (Figure 2a) on a solution of DP-8PF₆ (50 µM) and CBPQT-4PF₆ (1.0 mM) in dry and degassed MeCN (30 mL) maintained at 40 °C. Our approach entailed the alternation of two constant potentials, namely (i) -0.7 V for the reduction^[19] of bipyridinium dications to radical cations, and (ii) +1.4 V for the reverse oxidation^[20] process. In a first experiment, we carried out a 20-min cycle where reduction (10 min) at -0.7 V was followed immediately by re-oxidation (10 min) at +1.4 V. ¹H NMR Spectroscopic analysis of the reaction mixture revealed the presence of a third species, along with CBPQT⁴⁺ and DP⁸⁺. It was shown to be a [3]rotaxane, hereafter referred to as [3] \mathbb{R}^{16+} , that is $DP^{8+} < (CBPQT^{4+})_2$. The product distribution, however, was only $(75:25) \pm 6$ for **DP**⁸⁺: [3]R¹⁶⁺, as calculated from ¹H NMR integrations. See Supporting Information. Bearing in mind that, after re-oxidation, the stroke of the Mark II pump is very rapid^[14b] at 40 °C, we ascribed this result to kinetically slow complex formation between the CBPQT²⁽⁺⁺⁾ rings and DP⁽²⁺⁾⁽⁶⁺⁾. Thus, we modified (Figure 2b) the CPE protocol introducing "resting" periods of 20 and 10 min after reduction and re-oxidation, respectively, which allow for the completion of (i) complex formation before re-oxidation and (ii) co-conformational isomerization before starting a second cycle. In a repetition of the experiment, we subjected the same solution firstly to a potential of -0.7 V for 10 min, followed by 20 min of off-current, and then to a potential of +1.4 V for 10 min, followed by 10 min of off-current. The redox processes were followed (Figure 2c) by monitoring the

total charge (Q) transferred as a function of time: ca. 7 C were consumed by the solution upon reduction, which is in good agreement with the expected value (ca. 6 C), assuming the concomitant monoreduction of CBPQT⁴⁺ and DP^{8+,[21]} In this case, we observed a product distribution of (22 : 78) \pm 9 in favor of the [3]R¹⁶⁺, an observation which confirms that the kinetics of association between the two CBPQT²⁽⁺⁺⁾ rings and DP⁽²⁺⁾⁽⁶⁺⁾ is indeed the rate-determining step.



Figure 2. a) Representative photograph of the CPE setup used in this work. b) Schematic illustration of the electrochemically controlled pump operation. c) Total charge (Q) consumed and released by the working solution during reduction (-0.7 V) and reoxidation (+1.4 V), respectively. d) Product distribution obtained after one or two cycles as determined by ¹H NMR integrations. Experimental conditions (CPE steps), 1^a : -0.7 V for 10 min followed by +1.4 V for 10 min; 1^b and 2^b : -0.7 V for 10 min followed 20 min of off-current, and +1.4 V for 10 min followed by 10 min of off-current

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Figure 3. Full ¹H NMR spectra (500 MHz, CD₃CN, 298 K) of (a) **DP**•8PF₆, (b) [3]**R**•16PF₆ and (c) [5]**R**•24PF₆ with all the proton resonances assigned. Each proton in the structural formulas of the dumbbell and ring components is labelled to aid rapid interpretation of the ¹H NMR spectra.

When we subjected the same solution to two consecutive redox cycles, ¹H NMR spectroscopic analysis revealed a decrease in the intensities of the resonances associated with **[3]R¹⁶⁺** in favor to a new species which was found to be a [5]rotaxane, hereafter referred to as **[5]R²⁴⁺**, that is DP⁸⁺ < (CBPQT⁴⁺)₄. Repetition of this experiment gave an average product distribution of (53 : 47) ± 13 for **[3]R¹⁶⁺** : **[5]R²⁴⁺**, indicating a small decrease (from 78 to 60%) in the efficiency of the second pumping cycle. This observation can be ascribed to the relatively short length of the 36-carbon atom chain which, along with two **CBPQT⁴⁺** rings, can facilitate (i) the folding of radical cationic form of **[3]R¹⁶⁺** sustained by radical-radical interactions^[22] developing amongst the two rings and the two pumps, thus limiting the association of subsequent rings even under reducing conditions and/or (ii) the dissociation of the additional **CBPQT⁴⁺** rings upon re-oxidation, because of

Coulombic repulsions between them and the central portion of **[3]R**²⁴⁺. Notwithstanding the low concentration employed to compensate for the adsorption phenomena^[23] at the working electrode, an average pumping efficiency of close to 70% was attained. In addition, no formation of [2]- or [4]rotaxanes was observed, indicating that the two pumps work independently.

After each experiment, **[3]R**¹⁶⁺ and **[5]R**²⁴⁺ were isolated as their PF₆⁻ salts after reverse-phase chromatography and counterion exchange (NH₄PF₆ / EtOH). The constitutions of **[3]R**•16PF₆ and **[5]R**•24PF₆ can be appreciated at a glance from Figure 3, which compares the respective ¹H NMR spectra with that of **DP**•8PF₆ (Figure 3a). In the case of **[3]R**•16PF₆, inspection of the ¹H NMR spectrum (Figure 3b) reveals one new set of four proton resonances – labelled α' , β' , Xyl' and CH₂' – suggesting a symmetrical situation where the two **CBPQT**⁴⁺ rings added to the

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chain are homotopic and reside on the oligomethylene chain adjacent to the triazole linkers. This conclusion is supported by the progressive upfield shifts exhibited by resonances for protons on C-19 up to C-27, an observation which contrasts with the almost unchanged chemical shifts for protons on C-33 up to C-36. In particular, the significant shielding of the protons on C-22 defines the relative location (co-conformation) of the rings on [3]R¹⁶⁺. This predominant co-conformation for [3]R¹⁶⁺ is supported by the upfield shifts for protons on C-16, C-17, C-18 and the concomitant downfield shifts for those on C-28 up to C-32, all of which suggest shuttling by the CBPQT⁴⁺ rings in the regions between the IPP units and the quaternary ammonium centers. The ¹H NMR spectrum (Figure 3c) of [5]R•24PF₆ displays only a new set of four proton resonances – labelled α ", β ", Xyl" and CH₂" – indicating the presence of two distinct pairs of CBPQT⁴⁺ rings symmetrically distributed along the chain. The dramatic upfield shift for the singlet arising from the proton on C-17. in keeping with the substantial upfield shifts observed for the resonances associated with protons on C-11, C-14, C-16 and C-18, suggests that each of the two additional rings encircles the triazole linkers adjacent to the IPP units. Homonuclear Correlation spectroscopy (COSY) indicates that the progressive shielding. experienced by the methylene protons across the IPP units and the quaternary ammonium centers, follows the same pattern as that observed in the case of [3]R¹⁶⁺. This observation, together with (i) the small downfield shifts and (ii) the signal broadening for protons in the vicinity of C-30, suggests that the CBPQT⁴⁺ rings are not prevented from shuttling across the two quaternary ammonium centers. Compelling evidence for the localization of the two homotopic pairs of heterotopic (inner as opposed to outer) rings emerge from Nuclear Overhauser Effect spectroscopy (NOESY), which shows through-space interactions between the protons of the oligomethylene chains and β' , and between the protons at C-15 and both α " and Xyl". See Supporting Information. In order to obtain more insights about the shuttling mechanism we carried out variable temperature (VT) ¹H NMR spectroscopy. In a temperature range from -40 °C to +40 °C, the symmetry of [5]R²⁴⁺ remains intact. Although the resonances associated to α' , β' , Xyl' and CH₂', together with those for the protons in the vicinity of the quaternary ammonium centers, broaden, they do not give rise to separate signals even at -40 °C. The resonances do, however, sharpen at higher temperature, presumably as a result of the fast exchange of their protons on the ¹H NMR timescale. All these observations support a shuttling (Figure 3c) of the rings along the chain in a manner that preserves molecular symmetry.

In conclusion, we have applied controlled-potential electrolysis to drive the simultaneous operation of two Mark II artificial molecular pumps in solution, without the generation and accumulation of waste products. This electrochemical approach harnesses AMMs to power the synthesis of discrete enthalpically and entropically demanding [n]rotaxanes^[17], which can be made progressively and repetitively through the controlled supply of electricity. We have isolated and characterized both [3]- and [5]rotaxanes, and investigated their mechanostereochemical properties by NMR spectroscopy. The high energy and dynamic nature of these MIMs emerge clearly in the case of the [5]rotaxane, whose constitutive rings undergo shuttling along the chain of the dumbbell component on account of the Coulombic repulsions that exist between the rings themselves and between the rings and

the chain of the dumbbell. We envision that applying this approach in polymer science could lead to the emergence of materials with unprecedented physicochemical properties. Currently, we are targeting the synthesis and investigation of polycationic poly[n]rotaxanes.

Experimental Section

General Procedure. DP-8PF₆ (4.2 mg, 1.5 µmol) and CBPQT-4PF₆ (33 mg, 30 µmol) were dissolved in MeCN (30 mL) containing tetrabutylammonium hexafluorophosphate TBAPF₆ (0.1 M) as the supporting electrolyte, and transferred into a BASi® bulk electrolysis cell under N₂ atmosphere. The solution was maintained at 40 °C and vigorous stirring (1000 rpm) while recording Coulometric responses during the CPE cycle(s) (Figure 2b). The resulting mixture was concentrated by rotary evaporation and washed with CH₂Cl₂ (3 × 40 mL) and EtOH (3 × 40 mL) to remove excess TBAPF₆. The obtained crude product was purified by reverse-phase chromatography (C₁₈-capped SiO₂, H₂O/MeCN 0.1% CF₃CO₂H 0-100%). Fractions containing the product were kept to dryness by N₂ flux and a saturated solution of NH₄PF₆ in EtOH was added till precipitation was complete (ca. 20 mL). The product was collected, washed with EtOH (3 × 20 mL) and dried overnight under vacuum. See Supporting Information for the full characterization.

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