An efficient artificial molecular pump ☆

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A B S T R A C T

Despite the fact that artificial molecular machines are on the rise, there is a long way to go to eventually fill the yawning gap that exists between biological and man-made machines in terms of both their mechanisms of action and efficiencies of operation. Herein, we describe our recent efforts directed towards the development of a second-generation (more efficient) artificial molecular pump — a wholly synthetic compound, which operates to compartmentalise highly charged rings in a high-energy state on an oligomethylene chain. The optimized artificial molecular pump operates rapidly, thanks to well-tuned noncovalent bonding interactions, paving the way to address enthalpically and entropically demanding polymers that would be difficult to obtain with the available repertoire of synthetic methods.

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1. Introduction

The awesome efficiency of biochemical machinery[1] represents a compelling source of inspiration to chemists[2–7] who have taken up the challenge to create and improve the performance of their synthetic counterparts in incremental steps. The design of Artificial Molecular Machines[8] (AMMs) has evolved and diversified over time, spanning the period from the integration of the mechanical bond[9] into the first prototypes we called molecular shuttles[10–12] to the introduction of molecular switches[12–14] which, when subjected to some outside source of energy, displayed relative movements[15,16] of the component parts of these Mechanically Interlocked Molecules[17] (MIMs).[18]

Notwithstanding the fact that MIMs epitomize a means of understanding and mastering some of the key features required for realizing[19–22] AMMs — e.g., the design principles associated with energy ratchet[23,24] and information ratchet[25–27] mechanisms — the speed[28] at which a particular AMM operates is dictated by the kinetics[29,30] associated with the relative motion of their component parts, as well as by the overall efficiency of the energy

transduction[31] pathways with respect to the local environment. The elegant conceptual advance exemplified by the small molecular motor reported recently by Leigh,[32] which represents the first example of an AMM capable of operating autonomously using chemical energy, takes AMMs one step closer to their natural counterparts,[33–37] while (i) the ever-increasing speed and scope achieved by Feringa's light-driven molecular rotors,[38–46] as well as (ii) the ability of recent systems, reported by Credi[47] and Giuseppone[48,49] to operate under photostationary conditions, draw attention to the attributes of using external physical energy[50,51] sources.

For our part, we reported recently an example of an artificial molecular pump[20,52] — a wholly synthetic compound which operates by compartmentalizing rings in a high-energy state on the axle portion of its dumbbell component. The pump[52] — referred (Fig. 1a) to here as **DBRef³⁺** — consists of a dumbbell-shaped component bearing a redox-active Viologen unit (V^{2+}) situated between a Coulombic barrier (PY^+) which acts as a pseudo-stopper and a steric speed-bump (IPP) that is capable of pumping cyclobis(paraquat-*p*-phenylene) (**CBPQT⁴⁺**) rings onto a long oligomethylene chain terminated by a stopper (S) using redox energy and precisely located noncovalent bonding interactions (Fig. 1b).

The PY^+ and IPP units are of crucial importance as they allow V^{2+} to attract and repel **CBPQT⁴⁺** rings upon redox switching, thereby enabling an energy ratchet mechanism[23,24] (Fig. 1c) to operate with a minimalistic[52] design. The first generation (Mark I) artificial molecular pump, however, suffers from operating too slowly — i.e., the **CBPQT⁴⁺** rings reach the collecting
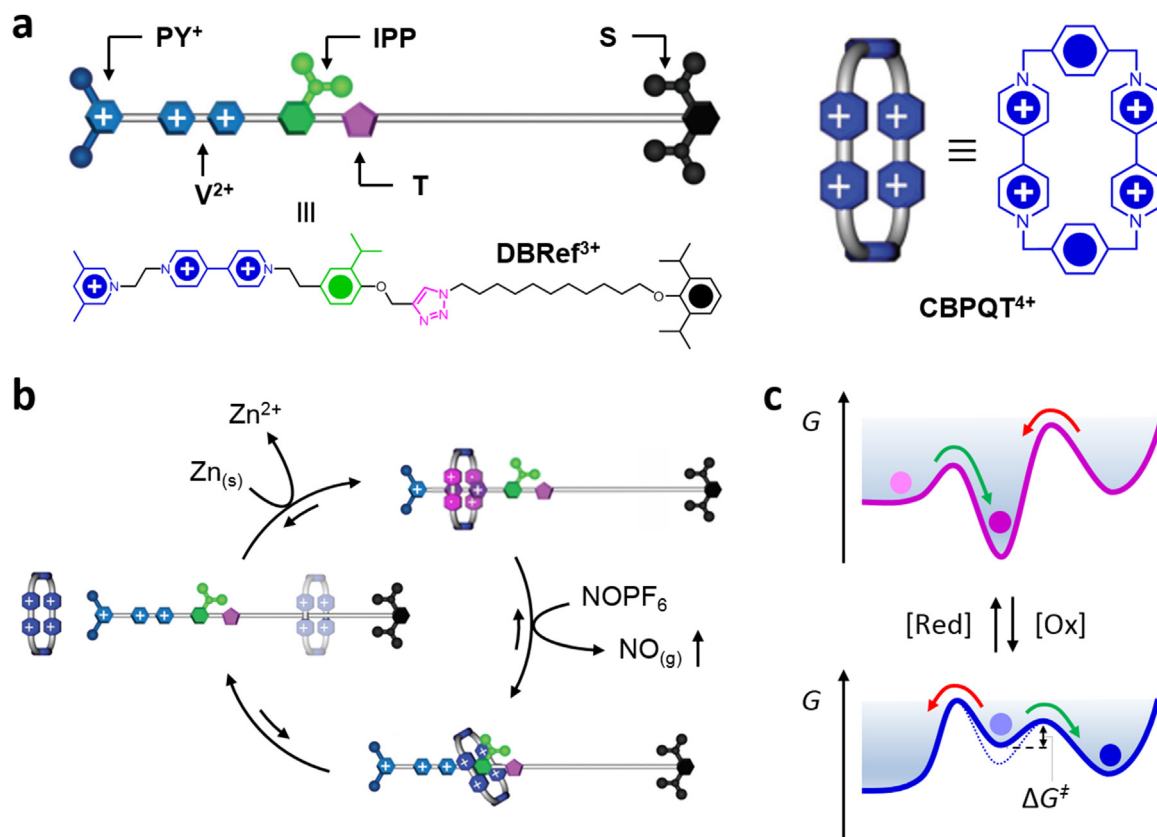
Fig. 1. a) Graphical representations of structural formulae for **DBRef³⁺** and **CBPQT⁴⁺**. **DBRef³⁺** comprises a redox-active viologen unit (V^{2+}) between a Coulombic barrier (PY^+) and a steric speed bump (IPP) connected to a ring-collecting chain through a triazole (T) linker. The ring-collecting chain terminates with a bulky 2,6-diisopropylphenyl unit as the stopper (S). PF_6^- counterions are omitted for the sake of clarity. b) Schematic illustration of the operation of the pump: in the oxidized state the two components repel each other by means of Coulombic repulsions. In the first stage, the addition of activated zinc dust reduces both V^{2+} and **CBPQT⁴⁺** to the corresponding radical cations, $V^{·+}$ and **CBPQT²⁽·⁺⁾**, which associate spontaneously to form a thermodynamically stable trisradical tricationic complex $V^{·+} \subset$ **CBPQT²⁽·⁺⁾**. In the second stage, the addition of $NOPF_6$ oxidizes $V^{·+} \subset$ **CBPQT²⁽·⁺⁾** back to V^{2+} and **CBPQT⁴⁺**, generating a metastable co-conformation with **CBPQT⁴⁺** located alongside the IPP unit. In the third stage, the stroke of the pump is completed with a co-conformational rearrangement resulting in the formation of the [2]rotaxane, **DB³⁺** < **CBPQT⁴⁺**. We have used[52] the minus symbol < in the label **DB³⁺** < **CBPQT⁴⁺** to denote that the ring component encircles the dumbbell in the absence of stabilizing interactions. Repetition of the same cycle starting with **DB³⁺** < **CBPQT⁴⁺** leads to the kinetic trapping of another ring — i.e., the formation of **DB³⁺** < (**CBPQT⁴⁺**)₂. c) Graphical representation of the energy ratchet mechanism highlighting the decreasing of the energy barrier, $\Delta G^{\ddagger}$, associated to the completion of the pump's stroke.

oligomethylene chain only after ca. 2 h at 42 °C — on account of a rather stable high-energy co-conformation where the **CBPQT⁴⁺** ring resides alongside the IPP speed-bump, prior to its moving under thermal energy onto the oligomethylene chain to complete the stroke of the pump. Herein, we demonstrate how the performance can be enhanced significantly by tuning carefully the non-covalent bonding interactions that assist in the workings of the pump.

2. Results and discussion

Considering the crucial role played by Coulombic interactions during the operation of the pump (see below), we reasoned that the energy barrier, $\Delta G^{\ddagger}$, associated with the completion of the pump stroke could be decreased (bottom energy profile in Fig. 1c) through enhancing the electrostatic repulsion between V^{2+} and **CBPQT⁴⁺** — i.e., by decreasing the length of the spacer between the V^{2+} and IPP units. As a result of these considerations, we have designed and synthesized a new dumbbell-shaped compound (Fig. 2) which bears a different PY^+ unit and only one methylene bridge, located between V^{2+} and IPP, instead of two. Making the change from 3,5- to 2,6-disubstitution by Me groups on the PY^+ unit assures the unidirectionality of the pumping mechanism on account of geometrically favorable steric hindrance — i.e., the Me groups point

towards the V^{2+} unit. The ring-collecting chain, comprising 12 methylene groups in length, is connected through a triazole (T) to the IPP unit and is terminated by a bulky 2,6-diisopropyl stopper (S).

2.1. Synthetic strategy

The Mark II artificial molecular pump **DB**·3PF₆ has been prepared (Scheme 1) in good overall yield in 10 steps from inexpensive starting materials. The first step relies on a variation of the Reimer-Tiemann reaction[53] in which CCl_4 replaces $CHCl_3$ in order to yield a carboxylic acid, rather than an aldehyde: 2-isopropylphenol was reacted with CCl_4 in an aqueous solution of KOH using Cu metal as a catalyst.[54] The acid **1** was obtained in 32% yield, following gravimetric chromatography, and its carboxyl group was reduced selectively with BH_3·THF[55] to afford (83%) the benzylic alcohol **2**. The third step in the reaction sequence is a selective S_N2 reaction where, in the presence of a mild base, the phenolate derived from **2** was reacted[56] with propargyl bromide to yield the corresponding propargylated derivative **3**, which was then converted into **4** using PBr_3 as the brominating agent in an overall yield of 91%. Compound **6**·2PF₆, which can be obtained in moderate yield (21% over two steps) according to literature procedures,[57] was reacted with the benzylic bromide **4** to give **7**·3PF₆, after counterion exchange.