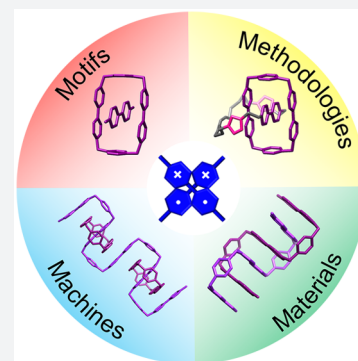# Introducing Stable Radicals into Molecular Machines

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ABSTRACT: Ever since their discovery, stable organic radicals have received considerable attention from chemists because of their unique optical, electronic, and magnetic properties. Currently, one of the most appealing challenges for the chemical community is to develop sophisticated artificial molecular machines that can do work by consuming external energy, after the manner of motor proteins. In this context, radical-pairing inter-actions are important in addressing the challenge: they not only provide supramolecular assistance in the synthesis of molecular machines but also open the door to developing multifunctional systems relying on the various properties of the radical species. In this Outlook, by taking the radical cationic state of 1,1′-dialkyl-4,4′-bipyridinium (BIPY$^{•+}$) as an example, we highlight our research on the art and science of introducing radical-pairing interactions into functional systems, from prototypical molecular switches to complex molecular machines, followed by a discussion of the (i) limitations of the current systems and (ii) future research directions for designing BIPY$^{•+}$-based molecular machines with useful functions.

INTRODUCTION

Living systems do a good job of stabilizing radical species—that otherwise would be kinetically and thermodynamically unstable in the environment—in naturally occurring macromolecules by employing a variety of mechanisms. Enzymes, for example, can control[1−3] the reactivity of radicals within their active sites by a combination of electrostatic interactions and steric effects. The recognition[4] of the importance of the steric factor in ensuring the stability of synthetic radicals—particularly the triphenyl-methyl radical (TPM$^{•+}$) (Figure 1a)—by Moses Gomberg at the turn of the 20th century has initiated the blossoming of the era of radical chemistry. Typically, because stable organic radical species contain at least one unpaired electron, they exhibit unique behavior associated with magnetic, conducting, and optical properties, which render radical species promising functional building blocks in materials.[5,6] Historically, among all the potential properties of organic radicals, owing to their highly ordered packing in the solid state, scientists first of all focused on[7−9] the conduction properties of these species in the crystalline form. As a result, the formation[10,11] of reversible weak noncovalent π-homodimers by radical species, particularly by tetrathiafulvalene (TTF$^{•+}$) and 1,1′-dialkyl-4,4′-bipyridinium (BIPY$^{•+}$), has received much attention in the past half-century because of the ease of their preparation and well-organized packing. For example, cationic radical TTF$^{•+}$ has been shown[12,13] to be able to form (Figure 1b) a stable continuous charge transfer π-stack in the solid state with the complementary anionic radical of tetracyanohydroquinone, TCNQ$^{•−}$, in a 1:1 ratio. Following this discovery, stacked structures[14−16] of the dimerized TTF$^{•+}$, driven by pimerization[17]—a recognition process, which is now well-known as the strong tendency of organic radicals to form dimerized spin-paired diamagnetic states—have also been reported. Those dimers are stable, however, only in the solid

state or at low temperatures in solution, and systematic studies[18−21] on their stabilities and properties in solution have been carried out by taking advantage of host−guest chemistry. On the other hand, it has been known since the 1960s, thanks to the pioneering work of Kosower,[22] that BIPY$^{•+}$ radicals can undergo dimerization in aqueous solution. After years spent investigating[23] the solution state, it took until 1990 to establish the nature of the stacking of BIPY$^{•+}$ radicals in the solid state: Kochi[24] demonstrated that these radicals form a continuous π-stack. Since 1990, the radical-recognition properties,[25] which were considered mainly in the context of conductivity,[26] have played a unique role in dictating the assembly of molecules, and in contributing to the rapid development of supramolecular chemistry.[27]

Today, one of the grand challenges for chemists is to mimic the complex chemical processes that have led to the emergence of life in order to develop[28] novel adaptive materials. In this context, by drawing inspiration from living systems—where numerous machines and motors work synergistically and cooperatively—chemists have designed and synthesized[29−31] artificial molecular machines. Indeed, constructing such molecular machines not only demonstrates the power of syn-thetic chemistry but also helps us unravel the secrets of the biological world and guides the construction of the next generation of artificial biomimetic materials. In living sys-tems, rotary and linear motors, such as ATP synthase[32] and the kinesins,[33] respectively, are well-known for their ability to display controlled motion by converting chemical energy into mechanical work. The efficiency of these biomolecular machines relies on a series of functions which include not only
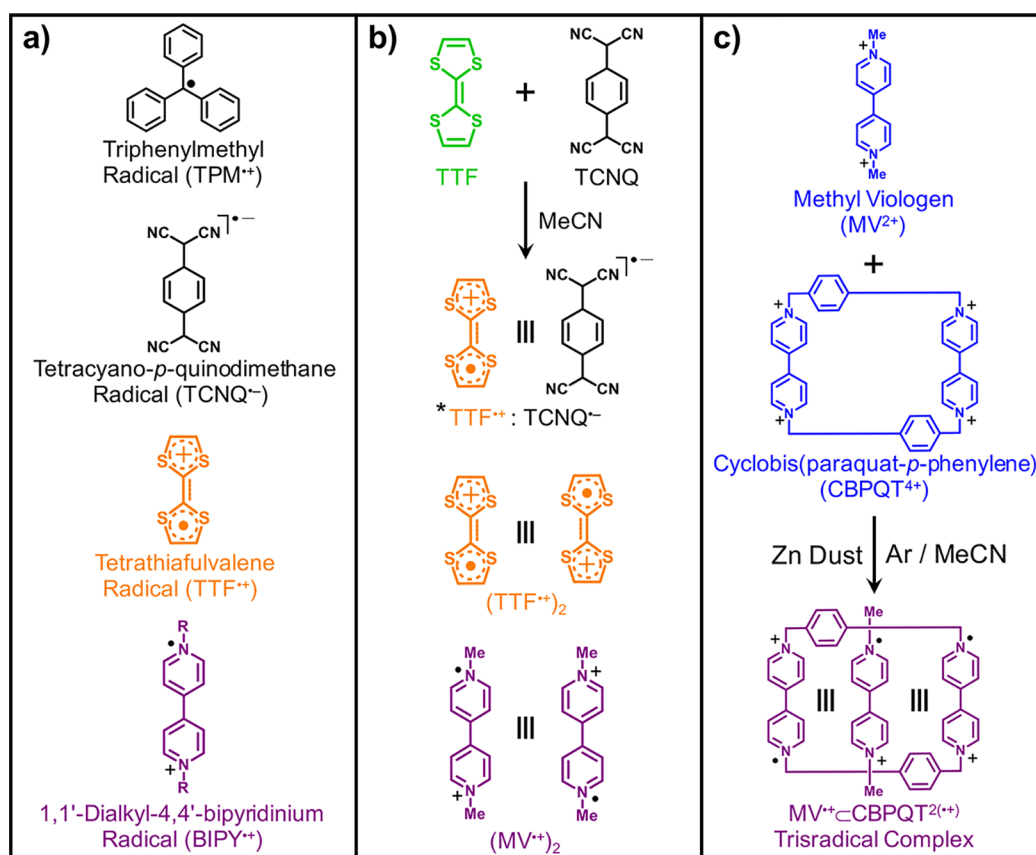
Figure 1. (a) Structural formulas of four selected organic radical species, including the triphenylmethyl radical (TPM$^{\bullet+}$), the tetracyano-*p*-quinodimethane radical (TCNQ$^{-\bullet}$), the tetrathiafulvalene radical (TTF$^{\bullet+}$), and the 1,1′-dialkyl-4,4′-bipyridinium radical (BIPY$^{\bullet+}$). (b) Formation of the radical pair TTF$^{\bullet+}$:TCNQ$^{\bullet-}$ and the structural formulas for the TTF$^{\bullet+}$ and methyl viologen (MV$^{\bullet+}$) radical dimers. (c) Formation of the tricationic trisradical inclusion complex MV$^{\bullet+}$⊂CBPQT$^{2(\bullet+)}$ upon reduction. *In the solid state, TTF$^{\bullet+}$ radical cations and TCNQ$^{\bullet-}$ radical anions stack separately to form homologous aggregations.[13]
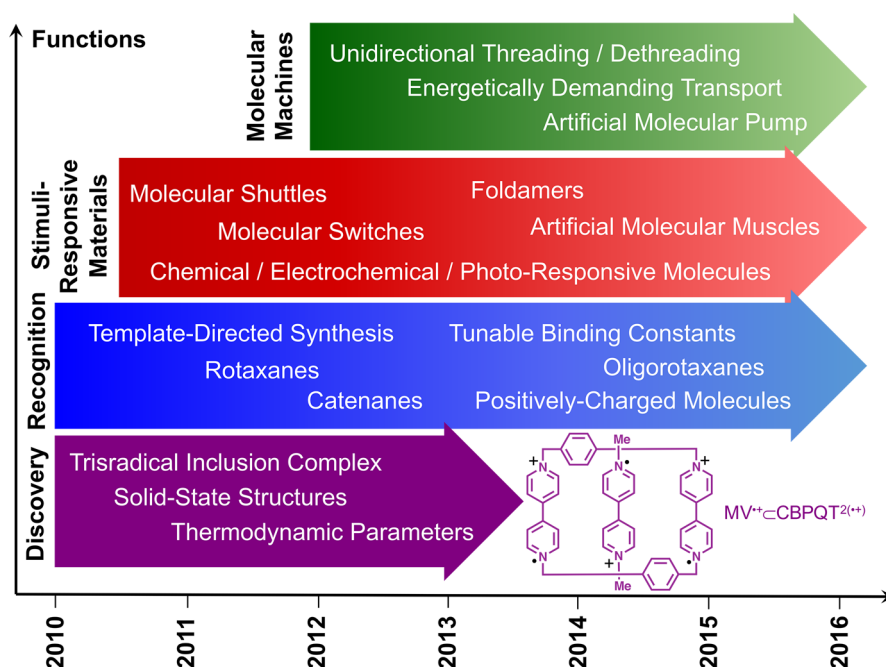

Figure 2. A timeline from 2010 to 2016 summarizing the growth of research on developing functional systems using the radical-pairing interactions between BIPY$^{\bullet+}$ radical cations since the discovery and characterization of the trisradical inclusion complex MV$^{\bullet+}$⊂CBPQT$^{2(\bullet+)}$ in 2010.

the harvesting of energy and its conversion into mechanically adaptive motion but also the ability to tune the binding affinities for specific substrates by cycles of coconformational changes. As a result, in order to augment the capabilities of living systems, the artificial counterparts must be capable of being integrated into one system, where organic radicals can assist in raising these expectations. In this Outlook, we will take the BIPY$^{\bullet+}$ radical cation as the tip of the iceberg in order to demonstrate the development of radical chemistry during the past several decades by introducing (i) the properties associated with the radical-pairing behavior of BIPY$^{\bullet+}$ as we understand it so far and (ii) how the artificial systems relying on these properties evolve (Figure 2) from simple molecular switches to functional molecular machines.

> Indeed, constructing such molecular machines not only demonstrates the power of synthetic chemistry but also helps us unravel the secrets of the biological world and guides the construction of the next gener-ation of artificial biomimetic materials.
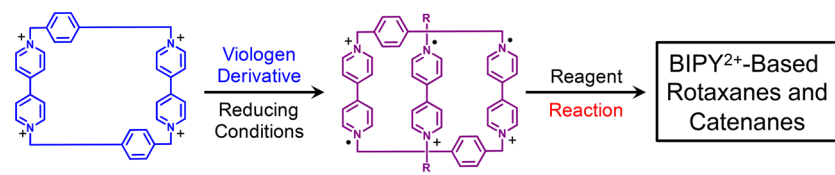
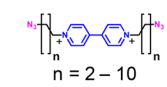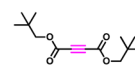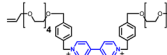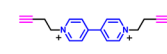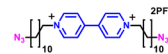### ■ RADICAL-PAIRING INTERACTIONS IN MOLECULAR RECOGNITION

Radical-pairing interactions have attracted much attention by scientists who are interested in incorporating them into organized structures. Historically, prior to the development of organized assemblies based on the BIPY$^{\bullet+}$ radical cation, the chemistry of the oxidized BIPY^{2+} form is much better known[20] to the supramolecular community for its ability to interact with electron-rich units by dint of donor−acceptor interactions. These interactions have been harnessed in the preparation of

host−guest complexes[34] and diverse structures, including synthetic foldamers[35] and mechanically interlocked molecules[36] (MIMs). By contrast, while the radical-pairing interactions can induce pimerization between BIPY$^{\bullet+}$ units and control[37−40] the manner of molecular assembly in solution, these interactions are too weak (*vide infra*) to be harnessed for efficient template-directed synthesis. In order to enhance the radical recognition between BIPY$^{\bullet+}$ units and to overcome this bottleneck, we have focused on our discovery[41] of the formation of the tricationic trisradical inclusion complexes (Figure 1c) between the radical state of methyl viologen (MV$^{\bullet+}$) and cyclobis(paraquat-*p*-phenylene) (CBPQT$^{2(\bullet+)}$), a process ($K_a = 5.04 \times 10^4$ M^{-1}, 298 K, MeCN) which is orders of magnitude stronger[42] than the dimerization[24] of MV$^{\bullet+}$ ($K_a < 6 \times 10^2$ M^{-1}) under the same conditions.

On the basis of this knowledge, we have substituted the MV$^{\bullet+}$ radical cation with other viologen derivatives—that can undergo further reactions after the formation of the corresponding inclusion complex—in an attempt to develop radical template-directed strategies for synthesizing BIPY^{2+}-only based MIMs, a development which opens up the possibility of synthesizing artificial molecular machines that operate away from equilibrium. To the present, we have developed several synthetic protocols to address this challenge, where the radical recognition and mechanical bond formation—which it has been shown (Table 1) can be achieved by (i) S$_N$2 reactions,[43] (ii) strain-promoted copper-free azide−alkyne cycloadditions,[44,45] and (iii) olefin metathesis catalyzed by a Grubbs catalyst[46]—occur in tandem with each other. By employing these protocols, we have synthesized (i) a highly positively charged octacationic homo[2]catenane,[43] which exists as a persistent radical in an ambient environment and has six redox states that could be incorporated[47] into electro-memory devices; (ii) a series of homologuous [2]rotaxanes,[44−46] whose radical states exhibit a range of behaviors toward resisting oxidation by oxygen in the air; and (iii) a redox-switchable hetero[2]-catenane.[46] More recently, we have (iv) developed[48] a copper-based approach, where the Cu metal enables the generation of BIPY$^{\bullet+}$ radical cations in MIM precursors, while the metal

Table 1. A Summary of the Approaches Developed for Constructing MIMs Taking Advantage of Radical-Pairing Interactions between BIPY$^{\bullet+}$ Units[a]

Viologen Derivative	Reducing Conditions	Reagent	Reaction
	Zn Dust / Ar / MeCN		S$_N$2
n = 2 − 10	Ru(bpy)$_3^{2+}$ / Triethanolamine(TEOA) / MeCN		Copper-Free Azide-Alkyne Cycloaddition
	Zn Dust / Ar / Me$_2$CO	The 2nd-Generation Hoveyda−Grubbs Catalyst	Olefin Metathesis
	Cu Dust / Ar / MeCN		CuAAC

[a]More diversified examples can be found in ref 48.

itself, which is oxidized to Cu(I), catalyzes azide—alkyne cycloaddition (CuAAC) reactions, resulting in the convenient and efficient syntheses of $BIPY^{2+}$-only based MIMs. It is noteworthy that the constrained environment introduced by the mechanical bonds, as in the case of the homo[2]catenane[43] and the [2]rotaxanes,[45] stabilizes the radical species trapped within these MIMs. These observations, which are reminiscent of the steric and electronic radical stabilization induced by the enzymatic environment[2,49,50] in biological systems, set the stage for the introduction of electronic properties, such as electron delocalization and mixed-valence states, into artificial molecular machines. Overall, these new synthetic strategies demonstrate that radical-pairing interactions can template the formation of MIMs, making it possible to produce multifunctional systems based on their mechanically interlocked structures.

■ MULTISTIMULUS-RESPONSIVE MATERIALS

In addition to providing supramolecular assistance in the syntheses, radical-pairing interactions between $BIPY^{\bullet+}$ units identify themselves in a unique manner when compared with other recognition motifs (Figure 3a) by introducing switching behavior into the resulting MIMs along with optical, conducting, and magnetic properties. While the $BIPY^{\bullet+}$ radical

> As a result, in order to augment the capabilities of living systems, the artificial counterparts must be capable of being integrated into one system, where organic radicals can assist in raising these expectations.

cations in MIMs show a strong affinity to each other at the reduced state, once the system is oxidized, strong Coulombic repulsion repels $BIPY^{2+}$ units away from each other.[41,51] As a consequence, this redox-driven switching process induces the components—e.g., the $BIPY^{2+}$-containing dumbbell and a ring which is usually $CBPQT^{4+}$—of the resulting MIMs to undergo relative motion. More importantly, the conversion between the $BIPY^{\bullet+}$ and $BIPY^{2+}$ can be achieved reversibly by (i) chemical, (ii) electrochemical,[52] and (iii) photochemical approaches, rendering it possible to construct functional redox-active MIMs that response to various external stimuli.

To date, we have described in the literature a few systems where the actuation of viologen-based MIMs can be easily

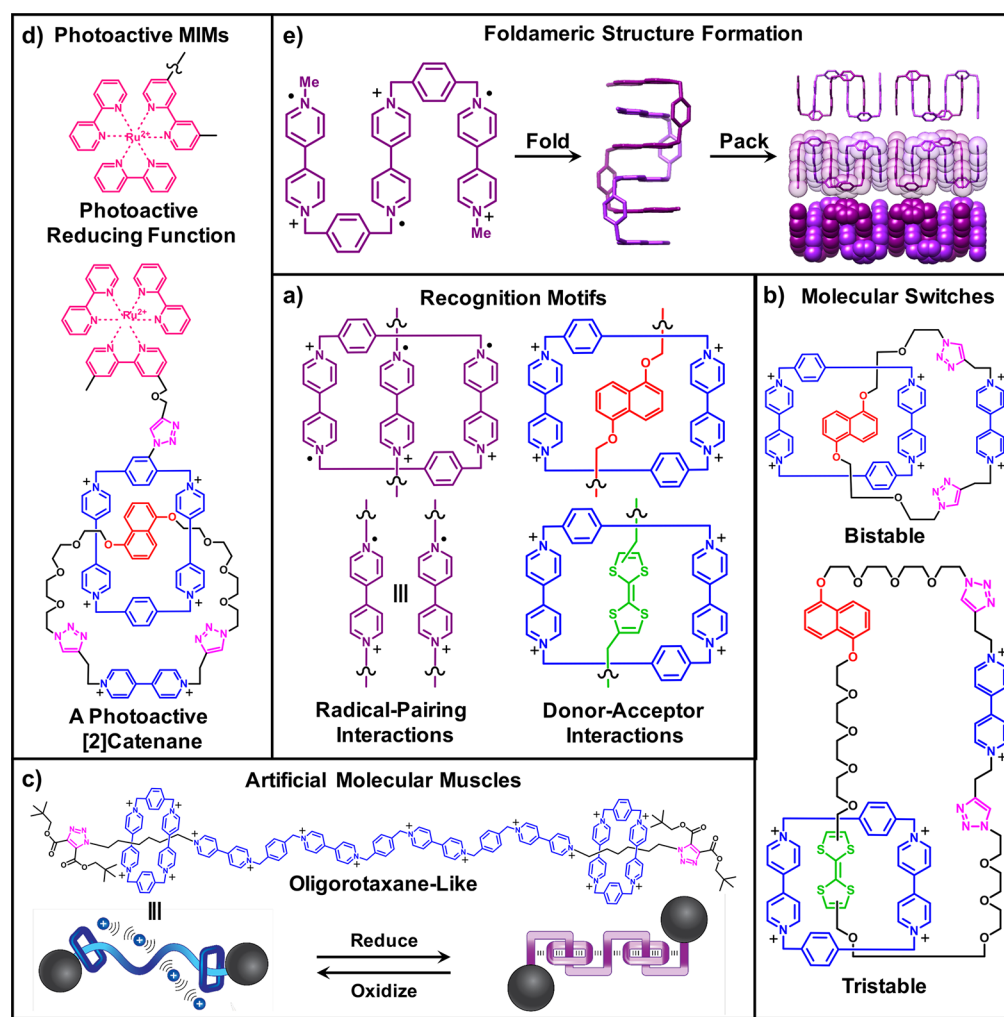**Figure 3.** Examples of multistimulus-responsive materials, constructed by taking advantage of (a) radical-pairing and donor—acceptor interactions, including (b) bi- and tristable catenanes as molecular switches, (c) oligorotaxanes as prototypes of artificial molecular muscles, (d) a $Ru(bpy)_3^{2+}$-incorporated photoactive [2]catenane, and (e) oligoviologens that can fold under reducing conditions.
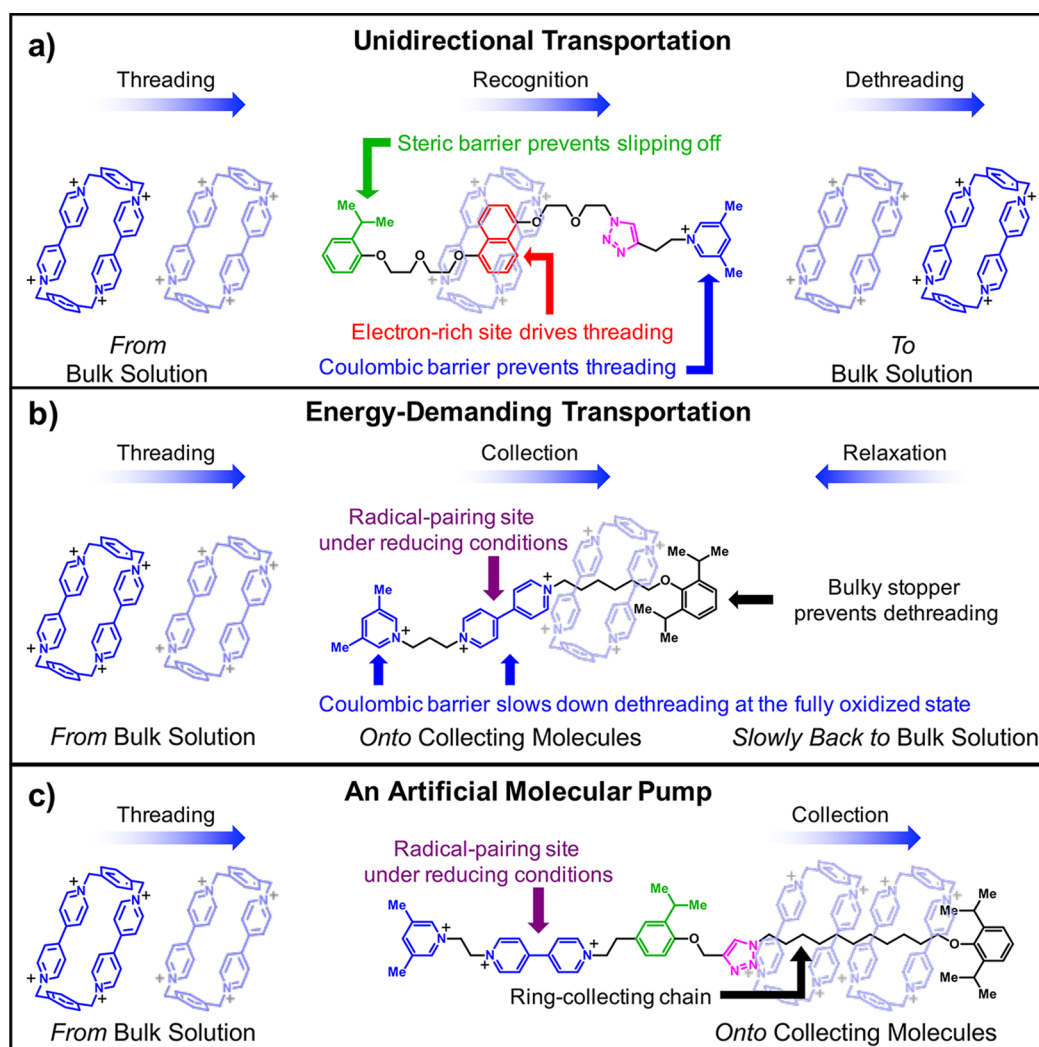
Figure 4. Schematic illustrations of the working mechanisms involved in BIPY[•+]-based molecular machines. (a) A system designed for unidirectional cargo transport, where the ring component (cargo) threads onto the dumbbell component from the neutral steric barrier (green), driven by donor–acceptor interactions, followed by its dethreading over the Coulombic barrier (blue) upon reduction. Since the ring components go back into the solution after dethreading, the net work is zero for the whole process. (b) The supramolecular pump, whereupon applying redox stimuli, the CBPQT[2(•+)] ring components are trapped temporarily on the collecting chain before slowly relaxing back into the solution. (c) The artificial molecular pump, where the CBPQT[2(•+)] ring components are pumped and trapped permanently on the collecting chain under redox stimuli, driven by radical-pairing interactions and Coulombic repulsion. The blue arrows in panels a–c indicate the relative direction of motion of the ring components.

triggered by the addition of a reducing agent such as Zn dust[45] or cobaltocene,[53] or by applying an external potential[54] electrochemically. Examples include (i) [2]catenane-based molecular switches (Figure 3b), which can be switched reversibly between two states[55] or multistates[56] driven by both donor–acceptor and radical-pairing interactions; (ii) an electrochemically addressable [2]rotaxane[54] incorporated into a porous crystalline framework, which serves as a prototype of solid-state molecular switch; and (iii) a [c2]daisy chain[57] and an oligorotaxane-based[58] artificial molecular muscles (Figure 3c), an where the redox-induced movement of the ring component is accompanied by significant changes in the molecular dimensions. Finally, (iv) photoresponsive BIPY[2+]-based MIMs (Figure 3d), including a light-fueled [2]rotaxane[59] and a [2]catenane,[60] have also been reported by us. By shining visible light on these two MIMs, the photoresponsive complex ruthenium(II) tris(2,2′-bipyridine) ([Ru(bpy)$_3$][2+]) incorporated in the MIMs, which is well-known[61] for its photocatalytic electron-transfer behavior,

can reduce the BIPY[2+] units to their radical cationic states in the presence of a sacrificial reducing agent, for example, triethanolamine (TEOA), and consequently induces the switching in both aqueous and organic solution.

In addition to MIMs, radical-pairing interactions have also found application in designing artificial foldamers. By using p-xylylene groups as linkers, we have reported[62] (Figure 3e) the syntheses of a series of oligoviologens. Notably, the recognition between the BIPY[•+] units is enhanced[23] when they are covalently linked. Solution and solid-state investigations suggest that these oligoviologens can fold into well-ordered secondary structures under reducing conditions, induced by either intra- or intermolecular radical-pairing interactions, depending on the number of viologen units present in the oligomer. This redox-controlled actuating behavior, which has also been observed in polypyrrole[63,64] and polyaniline-based[65] systems—where radical chemistry also plays an important role in governing their properties—makes it possible for these viologen-based

foldamers to be incorporated into polymeric materials to serve as fast-response actuators. Moreover, Li et al.[66] have reported polymers whose structures are composed of alternating TTF and BIPY^{2+} units. By switching on and off the radical-pairing interactions between BIPY$^{•+}$ units through redox chemistry, these polymers can change their folding conformations reversibly between two states.

MOLECULAR MACHINES

Accomplishing tasks at a molecular level powered by wholly synthetic molecular machines[67,68] has become an appealing and challenging field of research for chemists of late. Until now, several examples[69−79] of artificial molecular machines relying on different types of chemistry have been reported in the literature. Knowing how to modulate the behavior of individual BIPY^{2+}-based switchable molecules, we have become engaged in integrating these molecules into ordered assemblies to perform useful work, where the redox properties associated with the radical chemistry of BIPY$^{•+}$, again, show their power. The reduction−attraction and oxidation−repulsion behavior of the BIPY$^{•+}$/BIPY^{2+} redox couple can induce relative motions of the components in MIMs. As a result, BIPY^{2+}-only-based wholly synthetic MIMs, whose ground-state coconformations are denoted by Coulombic repulsion, provide us an easy access to systems operating away from equilibrium. This feature, which avoids the situation in the case of MIMs that operate under thermodynamic control—where work is undone when the switches are reset—is crucial when it comes to designing molecular machines. Simply imagine a system that starts at its ground state under thermodynamic control, where, after operating, it reaches a final state that is kinetically trapped in *local* minima on energy landscapes, hence resulting in a net difference in energy—i.e., delivered work—during the operation.

Recently, we have harnessed the redox-switchable properties of BIPY$^{•+}$ into supramolecular systems in order to achieve the unidirectional transportation of small molecules: this process bears some similarities to the cargo transportation across cell membranes in living systems.[80−82] As a proof of concept, we developed[83] a system (Figure 4a) where the cargo, namely, CBPQT^{4+} rings, thread unidirectionally from one side of a dumbbell-shaped molecule to the other, when fueled by light. At the outset, the enthalpically favored threading of the CBPQT^{4+} rings onto the dumbbells, driven by the donor−acceptor interactions between the π-electron deficient rings and the π-electron rich 1,5-dioxynaphthalene (DNP) recognition sites on the dumbbells, takes place selectively at the neutral 2-isopropylphenyl termini, rather than at the positively charged 3,5-dimethylpyridinium ones. Upon reduction, however, the resulting CBPQT$^{2(•+)}$ rings become less electron deficient so that they experience weakened donor−acceptor interactions as well as considerably diminished Coulombic repulsion with the dumbbells. As a result, the steric factor associated with the neutral 2-isopropylphenyl groups becomes more dominant[84] such that the entropically favored dethreading process occurs at the charged termini.

It should be noted that, when utilizing this prototypical system to design molecular pumps, the challenge is to avoid the rings coming from the bulk solution going back to the bulk solution following the unidirectional threading/dethreading process: no work is done. In order to address this challenge, the ring components must remain on collecting chains in the case of a molecular pump, where the entropic effect no longer

provides assistance for the unidirectional motion. As a result, we replaced the electron rich recognition site in the prototypical system with a recognition site based on radical-pairing interactions, where Coulombic repulsion can subsequently serve as a driving force for the unidirectional motion from an enthalpic perspective. Indeed, the thermodynamic parameters, governing the formation of the trisradical tricationic complex, bring with them many attributes into the construction of artificial molecular them pumps, including the possibility to tailor specific chemical interactions, reflecting the enzymatic nature of the protein motors at work in the biological counterparts.

Based on this design, we have synthesized an artificial supramolecular pump,[85] which achieves (Figure 4b) the energetically demanding transference of one CBPQT^{4+} ring from bulk solution onto a collecting chain of a dumbbell-shaped molecule as a result of a reduction−oxidation cycle, after which the ring relaxes back slowly into the bulk solution. Specifically, the operating dumbbell portion of this pump, which is composed of a 3,5-dimethylpyridinium terminus and a 4,4′-bipyridinium site, plays a key role by serving as a one-way gate that (i) allows rings to pass over it under reducing conditions and (ii) forces rings onto an oligomethylene collecting chain with the aid of Coulombic repulsions upon oxidation. Following upon this advance, we have taken[86] this supramolecular system to the next stage by introducing an isopropylphenyl group into the dumbbell as a one-way kinetic barrier which prevents the CBPQT^{4+} rings from interacting with the 4,4′-bipyridinium sites upon reduction once they have been trapped on the oligomethylene chain. The outcome is that (Figure 4c) this artificial molecular pump has executed the permanent trapping of two rings onto the collecting chain after two sequential reduction−oxidation cycles, and provides the possibility to pump multiple rings. The radical recognition properties of BIPY$^{•+}$, which can change dramatically during redox cycles, demonstrate their potential in the functioning of this redox-controlled artificial molecular pump. The use of electrochemical input for the autonomous operation of molecular machines based on radical chemistry will pave the way for the translation of this fundamental science into a technological setting.

FUTURE DIRECTIONS

Since the first report of stable and persistent free radicals, organic radical chemistry has delivered on its promise to address challenges in chemical science in many ways over more than a century. This radical chemistry has led to not only the development of conducting materials back in the old days but also aiding and abetting the construction of wholly synthetic molecular machines, which can challenge the operation and performance achieved by their biological counterparts in the fullness of time. After years of endeavor into investigating and exploiting the properties associated with bipyridinium radical cations and their supramolecular assemblies, we have now characterized a wide range of viologen-based molecules, which can act as molecular switches, artificial molecular muscles, molecular machines and so on, both in solution and in the solid state.

It is worthy of note, however, that despite the development of BIPY^{2+}-based MIMs for accomplishing tasks at the molecular level, the properties associated with the BIPY$^{•+}$ radical cations are still underdeveloped.[87] On the one hand, the existing systems still need to undergo improvements in order to get closer to practical applications—for example, (i) integrating

This radical chemistry has led to not only the development of conducting materials back in the old days but also aiding and abetting the construction of wholly synthetic molecular machines, which can challenge the operation and performance achieved by their biological counterparts in the fullness of time.

artificial molecular muscles into larger systems so that the nanoscopic motion of each individual molecule can be coupled to perform a useful task at the macroscopic level and (ii) seeking applications for the artificial molecular pump—which operates progressively away from equilibrium after the collection of the rings—to dissipate its energy. While we have discussed in this Outlook artificial molecular machines inspired by those that perform work in the biological world, a fundamental question relates to the environment in which the artificial molecular machines need to operate. In the case of the artificial molecular pump, for example, one way to achieve complex functions could be that of integrating the system into a confined environment. By mimicking biology, the placing of artificial molecular pumps inside lipid membranes, such as vesicles, could enable transmembrane transport to be achieved in a directional manner as a result of generating a transmembrane chemical potential between the inside and the outside of the vesicle. The successful passage, which relies upon a ratchet mechanism, of the rings from the external to internal compartments prevents the work that has been done in one step from being undone in the next step as the machine is reset. Clearly, however, progress in our ability to integrate synthetic machines with materials, and particularly nanomaterials, is needed in anticipation of future engineering applications.

On the other hand, compared with biological systems, where biological machines achieve a cascade of complicated functions in an ordered manner, the tasks that can be done by their artificial counterparts are much easier to perform. For example, while their electronic properties enable the BIPY^{2+} units to accept electrons and trigger the actuating processes—reminiscent of enzymes and motors in living systems—the optical, conducting[9,88] as well as magnetic properties[37,89] of BIPY$^{\bullet+}$ have not been considered when designing MIMs. As a result, we are facing the challenge of developing systems that can take advantage of all these properties: there is a long way to go to exploit the full potential of artificial molecular machines in functioning devices. As a final remark, let us emphasize that our approach provides one possibility for realizing systems with multiple properties and functions, and hopefully other researchers can take this Outlook as an inspiration to design and synthesize more sophisticated systems.

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