

Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 6 | Number 11 | 7 June 2008 | Pages 1857–2020



ISSN 1477-0520

RSC Publishing

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Chemical Biology

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1477-0520(2008)6:11;1-M

Chiral ferrocenes as novel rotary modules for molecular machines

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Received 10th December 2007, Accepted 25th February 2008

First published as an Advance Article on the web 11th April 2008

DOI: 10.1039/b718982f

Ferrocene, a double-decker organometallic compound that generates angular motion, can be used as a unique rotary module for molecular machines. By interlocking a ferrocene-based rotary module with a photochromic unit, we have developed novel molecular machines that operate *via* power-conversion mechanisms. This design strategy, which mimics real machines in our daily life, allows for remote control of molecular events.

Introduction

Automobiles are driven by the conversion of a piston action into a rotary motion, for which a variety of different moving components are integrated and interlocked with one another. Power transmission involving different interlocked movements *via* power conversion processes is one of the essential elements for the design of movable machines and robots. Molecules that undergo programmed motions in response to stimuli are called molecular machines. Examples of such synthetic molecular machines include molecular tweezers, catenanes, rotaxanes, and molecular rotors, which operate unique motions such as flipping, sliding and rotary motions in response to light or electric stimuli. However, while development of molecular machines¹⁻⁹ is a hot issue in nanotechnology, molecular mechanisms that allow for the realization of such interlocked movements have never been focused on.

Recently, we have developed novel molecular machines that consist of photochromic and ferrocene units. Since they are designed to interlock with one another, a motion occurring at the photochromic unit can be transmitted to the ferrocene unit.¹⁰⁻¹⁴ Hence, the cyclopentadienyl (Cp) rings of the ferrocene unit are

able to generate an angular motion in response to the photochemical isomerization of the attached photochromic unit. Here the ferrocene unit acts as a pivot that can convert configurational change (elongation/contraction) of the photochromic unit into angular motion. In the present account, we highlight the above-mentioned design strategy for molecular machines that operate *via* interlocking two or more movable units.

Synthesis and structures of molecular pliers

Ferrocene is a double-decker organometallic compound that has attracted attention as a component for redox-active modules, catalysts, and chiroptical probes, due to its unique structural and chemical properties.¹⁵ Besides these properties, the rotary motion of ferrocene is interesting. The two Cp rings, which sandwich an iron(II) center, have been reported to undergo a friction-free rotation at a rate 10^9 s⁻¹ even at 154 K.¹⁶ Several supramolecular systems have made use of ferrocene as a flexible hinge.¹⁷ However, ferrocene has never been used as a module for the design of molecular machines.

Ferrocene derivatives bearing more than two substituents on their Cp rings can be asymmetric due to a planar chirality. For our molecular design strategy, we chose 1,1'-3,3'-tetrasubstituted ferrocene derivatives and established a synthetic route to them.¹⁸ For example, the synthesis of molecular pliers **1** involves, as a key precursor, diido derivative **4**, which is obtained as a

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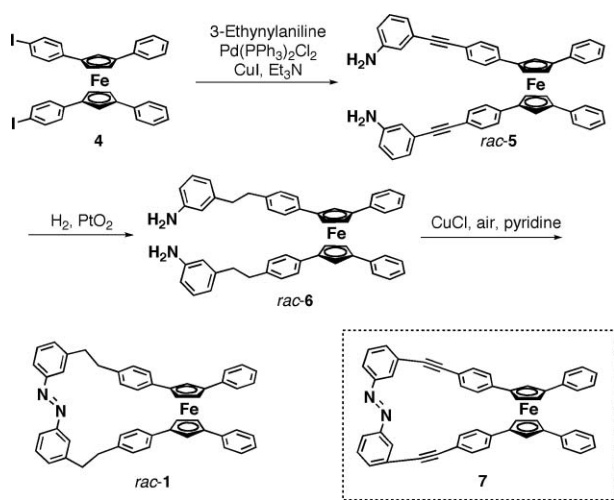
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racemate (*rac-4*) together with its meso form from 1-iodophenyl-3-phenylcyclopentadiene (Scheme 1).



Scheme 1 Synthetic route to **1** from diiodo derivative **4**.

Compound **4** is converted into amine **5** which is subjected to HPLC for the separation of *rac-5* from the meso form. Then, *rac-5* is hydrogenated at its triple bonds to form *rac-6*, which is subjected to a Cu(I)-mediated aerobic oxidation to furnish azo compound *rac-1*. Finally, *rac-1* is chromatographed on a silica gel column with a chiral stationary phase for optical resolution. Absolute configurations of the chiral precursors and compound **1** have been determined on the basis of an X-ray crystal structure of (*R*)-camphorsulfonamide **8**, derived from **6** and (*R*)-camphorsulfonyl chloride (Fig. 1).¹³ Hydrogenation of **5** is essential, since compound **7** hardly photoisomerizes.

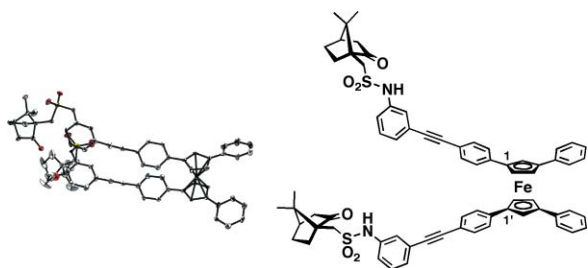


Fig. 1 Crystal structure of (*R*)-camphorsulfonamide **8**.

Light-powered motions of molecular pliers^{10,14}

Compound **1** consists of three essential components, *i.e.*, handles, blades, and a pivot (Fig. 2). The change in distance between the two handles, generated by photoisomerization of the azobenzene strap,¹⁹ is transformed through angular motion of the pivot into an open-close motion of the blade phenyl groups. X-Ray crystallographic analysis of *trans-1* indicates that the blade part is closed when the azobenzene strap adopts a *trans* configuration (Fig. 3),¹³ where the bite angle of the two phenyl groups is 8.8 degrees. On the other hand, as predicted by DFT calculation, the blade part of *cis-1* is open with a bite angle of the phenyl groups of 58.2 degrees.¹⁰

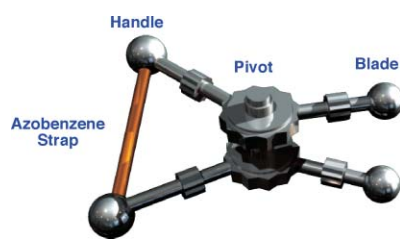


Fig. 2 Schematic illustration of molecular pliers **1**.

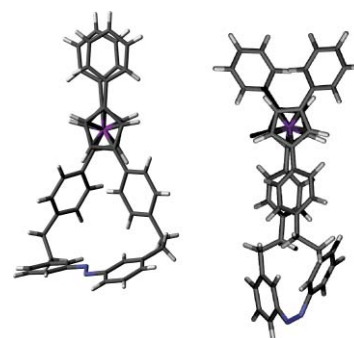
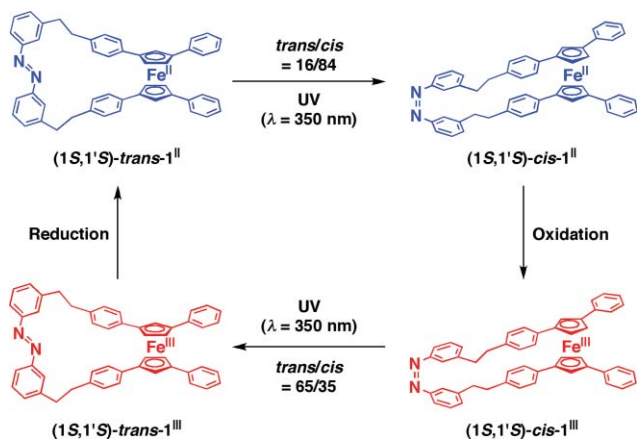


Fig. 3 Crystal structure of (*1S,1'S*)-*trans-1* (left) and optimized structure of (*1S,1'S*)-*cis-1* (right) by DFT calculation (B3LYP/3-21G*).

The azobenzene unit in **1** can reversibly isomerize in response to UV ($\lambda = 350 \pm 10$ nm) and visible ($\lambda > 400$ nm) light in THF, where the *trans* : *cis* isomer ratios at the photostationary states are 11 : 89 and 54 : 46, respectively. The *trans*-to-*cis* isomerization of (*1S,1'S*)-*trans-1*, upon UV-irradiation, is accompanied by a notable CD spectral change at the major absorption band of the tetraarylferrocene unit (240–300 nm). Upon irradiation with visible light ($\lambda > 400$ nm), the reverse CD spectral change occurs. On irradiation with UV and visible lights in an alternating manner, the sign of the Cotton effect, *e.g.*, at 280–290 nm is inverted from negative to positive and then from positive to negative. In particular, a reversible angular motion of the Cp rings occurs in response to the photoisomerization of the azobenzene unit.

Of interest, the oxidation state of the ferrocene pivot affects the photostationary states of **1**, thereby allowing a scissoring motion of **1** only by UV light.¹⁴ For this study, CH_2Cl_2 is used as the solvent. Analogous to the case in THF, (*1S,1'S*)-*trans-1* in CH_2Cl_2 photoisomerizes to its *cis* form upon exposure to UV light ($\lambda = 350 \pm 10$ nm), where the *trans* : *cis* isomer ratio of **1** at the photostationary state is 16 : 84. When this mixture is oxidized by 1 equiv. of 1,1'-dichloroferrocenium hexafluorophosphate and then irradiated with UV light, a backward isomerization of the oxidized form of **1** (**1^{III}**), in turn, takes place to furnish the *cis* content of 35%. Finally, reduction of this isomerized mixture by 1 equiv. of [bis(pentamethylcyclopentadienyl)iron(II)] affords neutral **1^{II}** with a *cis* content of 35%. Upon exposure to UV light again, the *cis* content increases further to reach 84%, which is identical to that finally attained in the UV-induced isomerization of neutral (*1S,1'S*)-*trans-1*. As shown in Scheme 2, the *trans* : *cis* isomer ratio of (*1S,1'S*)-**1** in this cycle switches reversibly between 16 : 84 and 65 : 35 only by UV light. Thus, pliers **1** responds to redox as well as light.



Scheme 2 Operation of molecular pliers **1** by light and redox.

Twisting of guests by molecular pliers with light

As an advanced version of the light-driven molecular pliers described above, we have developed light-powered molecular pliers (**2**) that can bind and deform guest molecules.¹¹ Compound **2** bears a zinc porphyrin unit at each cyclopentadienyl (Cp) ring of the ferrocene module (Fig. 4). Since zinc porphyrins are known to coordinate to nitrogenous bases, molecular pliers **2** can bind bidentate guests such as rotamer **9**, forming a stable host–guest complex **2**⊃**9**. For the synthesis of **2**, we have newly developed dibromodiiodo derivative **10**, which is converted into a dibromo version of molecular pliers **1**, followed by Suzuki–Miyaura coupling of the bromophenyl groups with a boronated zinc porphyrin derivative. For obtaining the enantiomers of **2**, an intermediate corresponding to **5** in Scheme 1 is optically resolved by chiral HPLC.

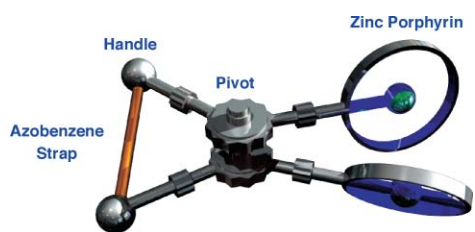
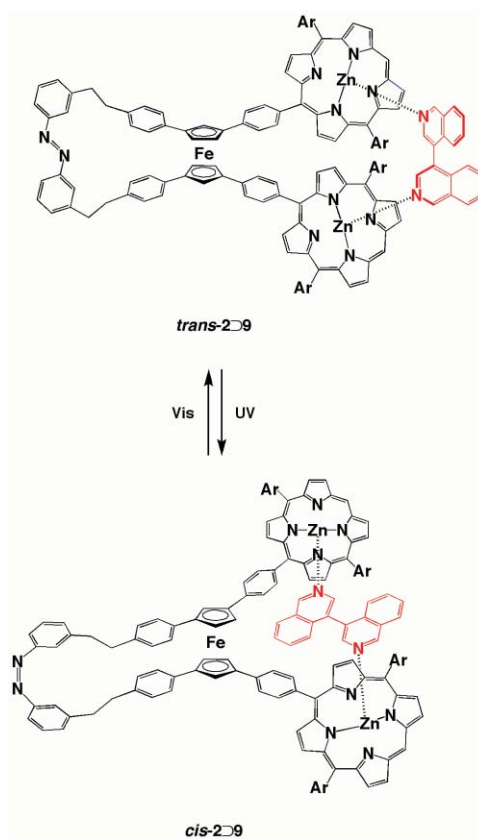


Fig. 4 Schematic illustration of molecular pliers **2**.

The association constant (K_{assoc}) between **9** and *trans*-**2** to form *trans*-**2**⊃**9** is $1.3 \times 10^6 \text{ M}^{-1}$, suggesting their two-point complexation (Scheme 3). Such a tight host–guest docking is essential for the pedal motion to transmit from **2** to **9**. Not only *trans*-**2** but also *cis*-**2** forms a stable 1 : 1 complex with **9** (*cis*-**2**⊃**9**), where K_{assoc} ($2.6 \times 10^6 \text{ M}^{-1}$) is as large as that of *trans*-**2** with **9**. When guest **9** is bound to *trans*-**2**, the CD intensity originating from the zinc porphyrin units in *trans*-**2** is enhanced, suggesting that the guest-binding site of the molecular pliers preferentially adopts a chirally twisted geometry. Interestingly, when *trans*-**2** upon complexation with **9** is allowed to isomerize into *cis*-**2** by UV irradiation, a large CD spectral change, even with an inversion of its sign at the final stage, takes place at the zinc porphyrin absorption band. Upon exposure of the resulting complex to visible light to allow backward isomerization, an inverse CD spectral



Scheme 3 Photoisomerization of guest-binding molecular pliers **2**⊃**9** upon exposure to UV and visible light.

change takes place. The large spectral changes, thus observed for the photoisomerization of **2**⊃**9**, indicate that photoinduced contraction and elongation of the azobenzene strap generate a pedal-like motion of the guest-bound zinc porphyrin units.

Compound **9** is achiral due to the free rotation around the C–C bond that connects the isoquinoline rings. However, when **9** is bound to the chirally twisted binding site of (*R*)- or (*S*)-**2**, it shows chiroptical activity at its absorption band (250–350 nm). Furthermore, the chiroptical activity changes in response to the opening–closing motion of the blade part. Fig. 5 shows differential CD spectra between **2**⊃**9** and a reference complex **2**⊃**11** at 270–350 nm, which clearly display Cotton effects at 259 and 307 nm. Since the differential CD spectra are analogous to those of the enantiomers of 4,4'-di-(3-methylisoquinoline) **12**, which are separable due to a restricted conformational change, guest **9** indeed adopts a chirally twisted geometry. Furthermore, the CD spectral change profile clearly indicates that guest **9** alters its dihedral angle in response to the photoisomerization of the azobenzene strap. Thus, when a CH_2Cl_2 solution of **2**⊃**9** is irradiated with UV light, isomerization of *trans*-**2** occurs to furnish a molar ratio *trans*-**2** : *cis*-**2** of 22 : 78. Synchronously, the Cotton effects at 270–350 nm due to **9** become smaller and finally almost disappear (Fig. 5). Subsequently, when the resulting complex is irradiated with visible light to allow its backward isomerization, these CD bands appear again and increase with time. It is clear that the CD spectral change of **9** upon photoisomerization is synchronous to that observed for the zinc porphyrin units of **2**.

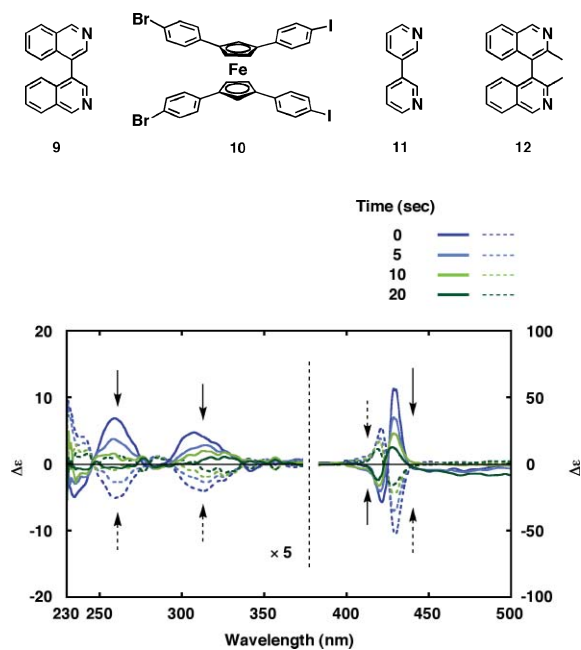


Fig. 5 Differential CD spectra by subtraction of the CD spectra of *trans*-2 \rightarrow 11 from those of *trans*-2 \rightarrow 9 ($[trans\text{-}2] = 7.2 \times 10^{-6}$ M, $[9]/[trans\text{-}2] = [11]/[trans\text{-}2] = 1.0$) in CH_2Cl_2 at 20°C upon UV irradiation ($\lambda = 350 \pm 10$ nm) for 5, 10 and 20 seconds (solid curves, (+)-*trans*-2; broken curves, (-)-*trans*-2).

Finally, it is important to discuss if the light-powered pedal motion of **2** is indeed transmitted as a twisting power to rotary guest **9**. Photoisomerization of azobenzene derivatives is known to occur on a timescale of subpicoseconds to picoseconds.¹⁹ Examples relevant to our system include azobenzene-containing cyclic oligopeptides,²⁰ where photoisomerization of the azobenzene unit under such a constrained environment takes place in picoseconds, which is followed by conformational change of the connecting peptide units on a timescale of picoseconds to nanoseconds. Meanwhile, the Cp rings in ferrocene derivatives are known to rotate on a timescale of nanoseconds.¹⁶ Thus, the ferrocene unit in **2** can respond rapidly through rotation to the photoisomerization of the azobenzene unit and subsequent conformational changes of the connecting units, and thereby induces the guest-binding zinc porphyrin units to undergo a pedal- or scissor-like motion. On the other hand, the dissociation events of **9** from *trans*- and *cis*-**2** occur in 0.6 and 0.2 milliseconds, respectively, as evaluated by ^1H NMR line shape analysis of *trans*-**2** \rightarrow **9** and *cis*-**2** \rightarrow **9**. These are at least six orders of magnitude slower than photoisomerization of azobenzene derivatives. Therefore, at the single molecular level, it is obvious that **9** remains associated with **2** in the process of its photoinduced pedal motion and therefore physically twisted.

Extension to design of self-locking molecule

Use of photo-switchable inter- and intramolecular interactions allows for the design of self-locking molecule **3** (Fig. 6), which operates by the combined use of 1,2-bispyridylethylene (**13**) as a photoresponsive key. Host **3** is composed of a ferrocene unit as a rotary module, which bears zinc porphyrin and aniline units at each cyclopentadienyl (Cp) ring. The rotary motion of **3** allows for the aniline groups to come closer to the zinc porphyrin units,

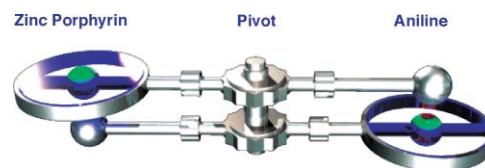
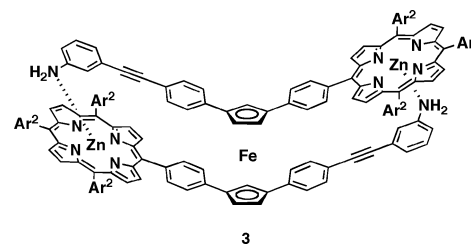
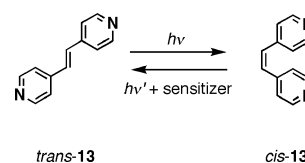


Fig. 6 Schematic illustration of self-locking molecule **3**.

forming two Zn–N coordination bonds simultaneously. Although interaction between zinc porphyrins and aniline is rather weak, such double intramolecular Zn–N coordination is strong enough to lock the rotary motion of **3** (internal double lock) (Fig. 7). Thus, compound **3** adopts an internally locked conformation in apolar solvents such as benzene.



Photoresponsive key **13** carries two pyridine units, capable of coordinating to the zinc porphyrin units in **3**, in competition with the internal aniline groups. This compound is photochromic, where UV irradiation allows for its *trans*-to-*cis* isomerization, while visible light irradiation of the resulting *cis* form in the presence of triplet sensitizers such as zinc porphyrins gives rise to its backward isomerization (Scheme 4). According to CPK model studies, *trans*-**13** adopts an extended geometry, while *cis*-**13** an angular geometry. These two isomeric forms show quite different affinities toward rotary host **3**, where *cis*-**13** is much favored over *trans*-**13**. Host **3** is kept self-locked conformationally when mixed with, e.g., 5 equivalents of *trans*-**13**, since **3** hardly interacts with *trans*-**13** under the conditions employed. However, when *trans*-**13** is photochemically isomerized into its *cis* form (Fig. 7, I), **3** turns to accommodate resultant *cis*-**13** at its binding site, to form stable cyclodimeric **3** \rightarrow *cis*-**13** having two zinc–pyridyl coordination bonds (II). Namely, the internal double lock is released, and **3** spontaneously transforms into an externally locked state. The conformational change of **3** along with photoisomerization of *trans*-**13** is supported by a clear CD spectral change of an enantiomer of **3** ((+)-**3**), where the CD band due to (+)-**3** in the Soret absorption region (415–455 nm) is significantly enhanced and turns to show a split Cotton effect. These spectral changes indicate that the two zinc porphyrin units in (+)-**3** are forced, by ligation with *cis*-**13**, to come closer to one another and exhibit exciton coupling. Even more important, the CD band centered at 350 nm due to the ferrocene module of (+)-**3** displays an inversion



Scheme 4 Isomerization of photoresponsive key **13**.

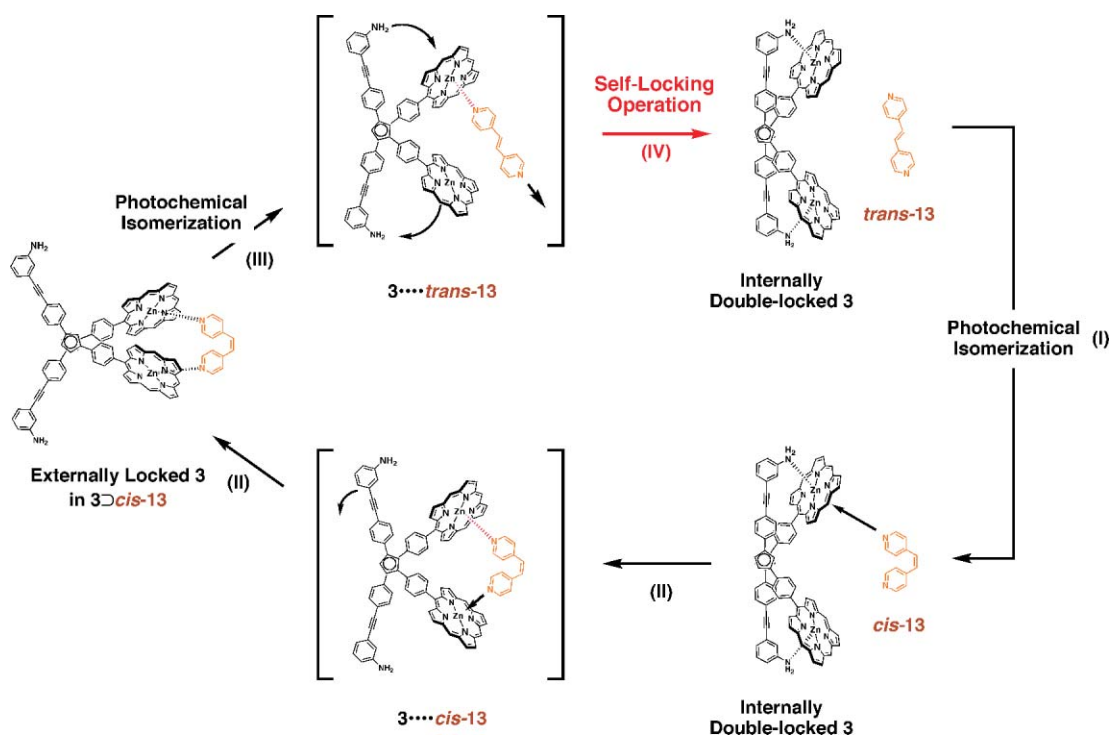


Fig. 7 Molecular structures of internally double-locked **3** and externally locked $3 \supset \text{cis-13}$, and schematic representation of the self-locking operation in response to photochemical isomerization of **13**. Ar groups are omitted for clarity.

of its sign from positive to negative, indicating a rotary motion of the ferrocene module.

When *cis-13* in $3 \supset \text{cis-13}$ is isomerized into its *trans* form, the resultant *trans-13* detaches from rotary host **3**, thereby disabling the external locking (Fig. 7, III). Consequently, **3** spontaneously retrieves, *via* a rotary motion, the internally double-locked state (IV). Thus, compound **13** is regarded as a photoresponsive key for executing the self-locking operation of **3**.

Conclusions

Among a variety of molecular machines so far reported,¹ those highlighted in this article are unique in that they operate *via* power conversion like commodity machines in our daily life. The design strategy features a chiral ferrocene, which enables a friction-free but restricted rotary motion. By interlocking the ferrocene module with a photochromic unit, a piston-like motion, powered by light, can be transformed into a rotary motion, and further converted for manipulating guest motions. In spectral visualization of these interlocked motions, chiral ferrocene derivatives also play an essential role. As modules that are able to generate angular motions, metal-sandwiched double and triple decker porphyrins^{21,22} are potential alternatives of chiral ferrocene derivatives. Along the line of these studies, one of the big challenges would be to construct molecular and supramolecular systems that are able to transmit a force precisely to a distant point with minimum energy loss. Also interesting is to integrate these molecular systems with logic-gate mechanisms responsive to multiple input stimuli. If this dream comes true, one may design molecular robots that act differently in response to different applied forces.

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