

HIGHLIGHT

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Cite this: *Org. Chem. Front.*, 2023, **10**, 1570Shape-shifting *p*-cyclophanes as portals to switching, sensing, delivery and logic operations in water†Chao-Yi Yao,^a Hong-Yu Lin,^a Brian Daly,^a Ze-Qing Chen,^a Hannah S. N. Crory,^a H. Q. Nimal Gunaratne,^a Eric V. Anslyn^{a,b} and A. Prasanna de Silva^a

The hybridization state of carbon atoms between phenylene units in *p*-cyclophanes is shown to control the guest binding properties of these hosts. Dimeric cyclophanes can be shape-switched by redox so that small aromatics can be captured or released. Trimeric cyclophanes perform similar functions on polypyridineRu(II) complexes. Controlled capture and release are key to delivery of such cargos. The luminescence and electrochemical signals which are modulated during these processes serve as sensing functions. Some of these modulations are so strong that Boolean logic schemes can be applied. Small-scale serial integration of sequential and combinational logic is seen.

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Introduction

p-Cyclophanes have a 40-year history of binding molecular guests in water^{1–6} but there have only been a few instances of them being endowed with switchable properties.^{7–9} Some of these hosts have a pair of diphenylmethane ‘corner sections’ with a sp³-hybridized carbon ‘corner’ each which orient their phenylene units perpendicular to the mean macrocycle plane so that these ‘wall’ sections create a hydrophobic cavity.^{1–6} These diphenylmethane ‘corner sections’ are most commonly connected by two oligomethylene linkers to create the macrocycle. In other words, such hosts are alternating cyclodimers of a linker and a diphenylmethane ‘corner section’ which serve as co-monomers.

What if these corners were changed to sp²-hybridized carbon atoms? The phenylene units should then change their orientation so that their planes are in the mean macrocycle plane, as far as cross-conjugation allows. This should make the macrocycle cavity smaller, shallower and with less aromatic π -cloud lining, which should be less inviting for guests suited to the original cyclophane host (Fig. 1A). Guest binding should then be switched from ‘on’ to ‘off’. Such guest capture and release should enable delivery of guest from one place to another. Switching operations¹⁰ lie within the field of molecular logic, especially when several switching actions are articulated.^{11–26}

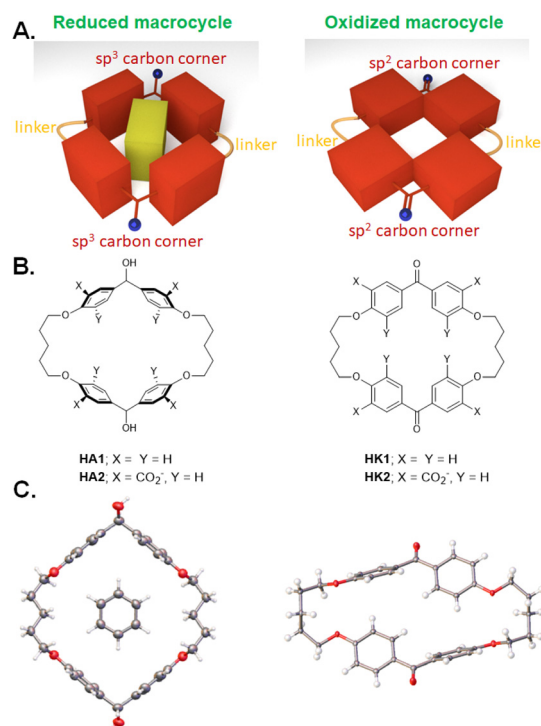


Fig. 1 A. Model of redox-switchable shape-shifting dimeric cyclophanes for the capture/release of aromatic guests. B. Molecular structures of such dimeric cyclophanes in their reduced (HA1 & HA2) and oxidized (HK1 & HK2) forms. C. X-ray crystallographic structures of HA1 (left) and HK1 (right). The structure of HA1 also includes a molecule of G1 as a guest. Adapted from ref. 27.

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So, the diphenylmethane 'corner section' can be altered to a benzophenone to produce the sp^2 -hybridized carbon 'corner'. A classical ketone reduction, *e.g.* with aqueous $NaBH_4$, would give a benzhydrol, a *sec*-alcohol with its sp^3 -hybridized carbon 'corner'. This has the advantage of permitting an equally classical alcohol oxidation back to the ketone, *e.g.* with aqueous $KMnO_4$. Redox interconversion of *sec*-alcohols and ketones becomes a practical implementation of this approach. When available, the diphenylmethane version serves as a reference for the benzhydrol carrying sp^3 -hybridized carbon 'corners'.

Dimeric cyclophanes

Synthesis and X-ray crystallography

We began with analogues of Koga's original structures,⁴ but found it convenient to start with a macrocyclization of 4,4'-dihydroxybenzophenone and 1,5-diiodopentane *via* ether formation under basic conditions.²⁷ Although insoluble in water, diketone **HK1** (Fig. 1B) and its reduction product dialcohol **HA1** provided an early test of parts of the hypothesis given above. X-ray crystallography showed the macrocycle cavity of diketone **HK1** had only two phenylenes presenting their π -faces towards the cavity interior (Fig. 1C). The other two phenylenes thrust their C–H units into the cavity so that free space is constricted. In contrast, dialcohol **HA1** had the planes of its four phenylene rings orthogonal to the mean macrocycle plane so that a cavity of considerable depth was created, *cf.* that seen in diketone **HK1**. As a bonus, the X-ray structure of dialcohol **HA1** contained a molecule of the crystallizing solvent **G1** (Fig. 2A)

nestled in the cavity by means of a set of C–H– π interactions²⁸ where the π functionalities originate in the macrocycle and the C–H units belong to the guest.

Water-solubility of the diketone macrocycle was arranged by outfitting it with a carboxylate group at each 2-position of the phenylene units. This relied on a remarkable $Ag(I)$ -promoted iodination at these 2-positions,²⁹ followed by a $Pd(0)$ -catalyzed carbonylation.³⁰ This gave diketonetetracarboxylate **HK2** (Fig. 1B). Aqueous $NaBH_4$ reduced **HK2** into dialcoholtetracarboxylate **HA2**. Aqueous $KMnO_4$ smoothly oxidized dialcoholtetracarboxylate **HA2** back to diketonetetracarboxylate **HK2**. Thus, redox interconversion of the two macrocycles **HA2** and **HK2** was secured.

¹H NMR and fluorescence spectroscopy

The stage was set for testing the capture/release of prospective guest **G2** (Fig. 2A) in water. ¹H NMR spectroscopy showed significant complexation-induced chemical shift changes ($\Delta\delta$ values) for most protons of host and guest. The relative magnitudes of these $\Delta\delta$ values allowed the conclusion that **G2** orients axially within the cavity of dialcohol **HA2**. Concentration-dependence of $\Delta\delta$ values fitted a binding constant (β) of around $10^4\ M^{-1}$. In contrast, near-zero $\Delta\delta$ values were found for all protons in the potential diketone host (**HK2**)-guest (**G2**) system showing no evidence of binding, in keeping with our hypothesis. The idea of a wall collapse or erection causing mobility or restriction of individuals seen in molecules *e.g.* **HA2/HK2** and **G2**,²⁷ can also be found in human behaviour in personal and social situations.

Guest binding/unbinding behaviour when the macrocycle is reduced (**HA1** & **HA2**) or oxidized (**HK1** & **HK2**) corresponds to a computer memory at the molecular scale.^{15,27,31} A computer memory holds its state for an indefinite period until a specific command is given to change to the other state. Alcohol/ketone systems, *e.g.* **HA1/HK1** or **HA2/HK2**, maintain the alcohol state when a reducing agent is introduced. The alcohol state is preserved even if more reductant is added or if the reductant is later removed. This alcohol state shifts to the ketone state only when an oxidizing agent is introduced. The ketone state is preserved even if more oxidant is added or if the oxidant is removed subsequently. A simple computer memory of this type, known as a RS flip-flop,^{15,27,31} is symbolically pictured in Fig. 3A in terms of an array of OR and NOT gates.

Such identification of computing phenomena within (bio) chemical reactions and interactions is one of the goals of molecular logic-based computation.^{11–26} This is the Boolean approach to molecular information processing where supramolecular chemistry has much to offer. The title of a review written by Lehn soon after his Nobel prize, 'Perspectives in supramolecular chemistry – from molecular recognition towards molecular information-processing and self-organization',³² recognized this general path.

Coupling guest binding/unbinding behaviour with other follow-up actions can offer more complex logic arrays, beside creating opportunities for sensing. For instance, complexation of guest **G2** by cyclophane dialcoholtetracarboxylate **HA2** is signalled

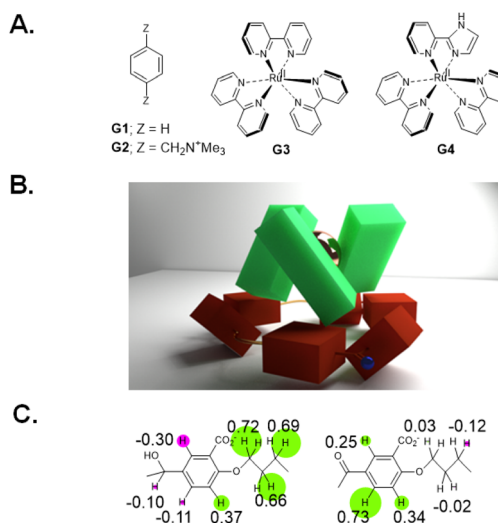


Fig. 2 A. Molecular structures of prospective guests **G1**, **G2**, **G3** & **G4**. B. Model of guest **G3** perching on oxidized form of trimeric cyclophane **HK4**. C. $\Delta\delta$ maps of hosts **HA4** (left) and **HK4** (right) when bound to guest **G3**. $\Delta\delta$ values are given on partial molecular structures and their relative magnitudes are illustrated by the radii of circles centred on each proton. Negative or positive $\Delta\delta$ values are shown by green or red circles respectively.



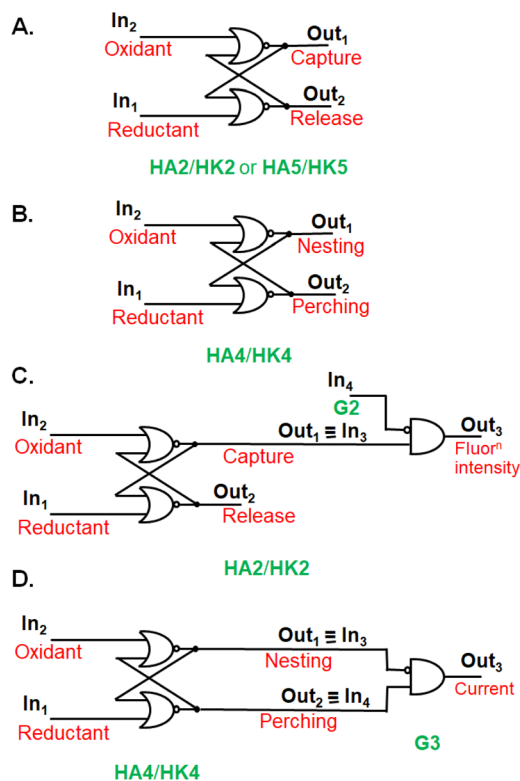


Fig. 3 A. Electronic representation of a RS flip-flop (**HA2/HK2** or **HA5/HK5**) where capture or release of a guest occurs. B. A RS flip-flop (**HA4/HK4**) where the guest binding mode switches between perching and nesting. C. The fluorescence output₃ of **HA2/HK2** host system behaving as a RS flip-flop integrated with an INHIBIT logic gate, where the disabling input₄ is the guest **G2**. D. The current output₃ of guest **G3** corresponding to a RS flip-flop (**HA4/HK4**) physically integrated with an INHIBIT logic gate (**G3**). The role of diversity in logic inputs and outputs¹⁵ is on view in these cases.

by quenching of the fluorescence of **HA2**. Photoinduced electron transfer (PET)^{33,34} is thermodynamically feasible here. This means that output₁ of the RS flip-flop serves as input₃ of an INHIBIT gate receiving **G2** as the disabling input₄. When input₃ = 1 and input₄ = 0, the fluorescence output₃ is 1. When input₃ = 1 and input₄ = 1, the fluorescence output₃ becomes 0 (Fig. 3C).

It is interesting that our neurons release stored neurotransmitters so that downstream neural processing events can occur.³⁵ Fluorescence 'on-off' signalling of the occupation of a receptor, as discussed above, shows this concatenation of information storage and information processing (Fig. 3C). In digital electronics, information storage concerns sequential logic whereas the history-independent information processing represents combinational logic.

Trimeric cyclophanes

Synthesis and X-ray crystallography

During the synthesis of diketone **HK1**, traces of triketone **HK3** (Fig. 4B) were identified in the reaction mixture. Since linear copolymers are commonly found during macrocyclizations under

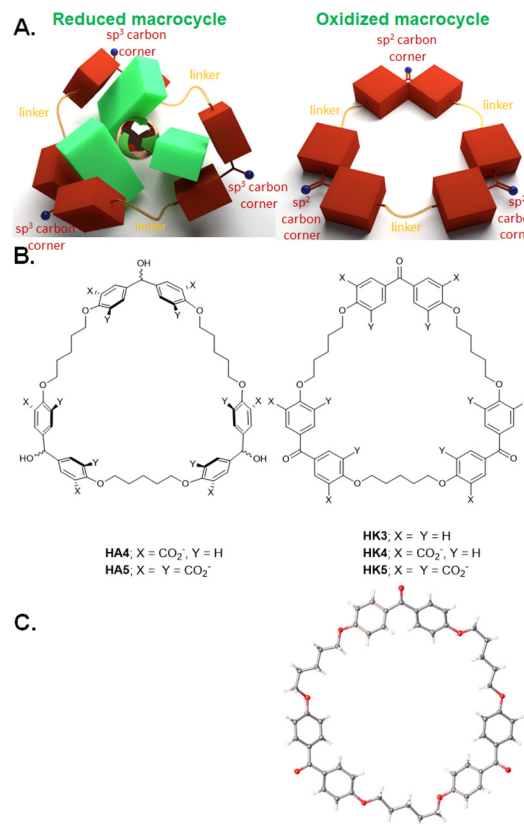


Fig. 4 A. Model of redox-switchable shape-shifting trimeric cyclophanes for the capture/release of polypyridine metal complexes. B. Molecular structures of such trimeric cyclophanes in their reduced (**HA4** & **HA5**) and oxidized (**HK3**, **HK4** & **HK5**) forms. C. X-ray crystallographic structure of **HK3**. Adapted from ref. 37.

practical high-dilution conditions, the formation of **HK3** can be understood as step-growth of a linear alternating co-trimer, followed by cyclization at that stage.³⁶ **HK1** would have been formed by a similar cyclization of the corresponding co-dimer. By careful adjustment of the conditions of dropping the reactants into the solvent and base, the triketone **HK3** became the major non-polymeric product.³⁷ X-ray crystallography of triketone **HK3** showed all the phenylene units aligned in the mean macrocycle plane. None of the phenylenes presented their π -faces towards the cavity interior (Fig. 4C). The X-ray crystallographic packing diagram showed the macrocycles were stacked to create channels. Such packing could have influenced the high-degree of π -conjugation between the carbonyl groups and their flanking phenylenes which was observed.

Functionalization of triketone **HK3**, as done for the dimeric cyclophanes, proceeded smoothly to give triketonehexacarboxylate **HK4** (Fig. 4B). Aqueous NaBH_4 reduced **HK4** into trialcoholhexacarboxylate **HA4**. Aqueous KMnO_4 oxidized trialcoholhexacarboxylate **HA4** back to triketonehexacarboxylate **HK4**.

¹H NMR and luminescence spectroscopy

Since these trimeric cyclophanes were unprecedented, we needed to explore potential guests. Fortunately, tris(bipyridine)



Ru(II) (**G3**) proved to be a suitable guest according to ^1H NMR $\Delta\delta$ values. We could conclude from the relative magnitudes of these $\Delta\delta$ values that each bipyridine blade of **G3** was cradled within the wedge of each benzhydrol unit of **HA4**. A binding constant (β) of over 10^6 M^{-1} was estimated from concentration-dependent studies. An accurate assessment ($10^{7.3} \text{ M}^{-1}$) was done by analyzing the enhancement of luminescence intensity of **G3** as a function of increasing host **HA4** concentration. By forming a nesting complex of guest **G3** inside host **HA4**, the hydration-induced deexcitation of the metal-to-ligand charge transfer (MLCT) triplet excited state of **G3** was suppressed.

Would switching the host trialcoholhexacarboxylate **HA4** to triketonehexacarboxylate **HK4** result in the binding of **G3** being switched from 'on' to 'off'? This dream schematized in Fig. 4A was not observed, but a remarkable switching of the binding mode was found. ^1H NMR $\Delta\delta$ values showed that guest **G3** perched on the host **HK4**. The ends of each bipyridyl blade of **G3** engaged in C–H– π interactions with a phenylene of each benzophenone corner of host **HK4** (Fig. 2B). This was supplemented by the presence of a hydrophobic patch in each phenylene to overlap with a hydrophobic region on the outer edge of each bipyridine ligand of **G3**. Indeed, the $\Delta\delta$ map across all protons of the triketonehexacarboxylate host **HK4** showed the opposite pattern to that seen with trialcoholhexacarboxylate host **HA4** (Fig. 2C). Large $\Delta\delta$ values were noticed for the aliphatic protons in the linkers of host **HA4**, along with tiny $\Delta\delta$ values found for the host aromatic protons. The reverse situation showed up in host **HK4**. The binding constant (β) of the perching complex was measured from concentration-dependent ^1H NMR spectroscopy to be 10^5 M^{-1} . As might be anticipated, perching binding is of a lower affinity than nesting binding between related host–guest pairs. Fig. 3B is the overall logic representation.

Switching the binding of **G3** from 'on' to 'off' should become possible if perching binding to the host could be prevented, e.g. in a host like triketonedodecarboxylate **HK5** (Fig. 4B) which has minimized the hydrophobic regions for C–H– π interactions. **HK5**'s redox partner, trialcoholdodecarboxylate **HA5**, has an equatorial belt of hydrophobicity to allow the nesting binding of guest **G3** with significant affinity.

Trialcoholdodecarboxylate **HA5** was prepared by starting with analogues of Koga's original materials,⁴ and by macrocyclizing a linear alternating co-trimer *via* ether formation under basic conditions.³⁷ Triketonedodecarboxylate **HK5** was the synthetic precursor of **HA5**. As seen before with analogues, these two compounds could be interconverted with classical redox reagents like KMnO_4 and NaBH_4 .

^1H NMR spectroscopy showed nesting binding of guest **G3** by trialcoholdodecarboxylate host **HA5**, with an association constant of $10^{4.4} \text{ M}^{-1}$. In contrast, no complexation-induced chemical shift differences were found for a mixture of triketonedodecarboxylate **HK5** and **G3**. The switching of binding of **G3** from 'on' to 'off' was therefore demonstrated and the dream of Fig. 4A was realized. Luminescence spectroscopy also confirmed this remarkable result by showing a significant

enhancement of intensity of **G3** only in the presence of host **HA5**.

Cyclic voltammetry of **G3**

Electrochemical measurements of guest **G3** also produced evidence of complexation by the cyclophane hosts. Cyclic voltammetry of **G3** gave a 20 mV cathodic shift of the Ru(II)/Ru(III) couple upon perching binding by triketonehexacarboxylate host **HK4** without a significant decrease in current. On the other hand, the nesting binding of **G3** by trialcoholhexacarboxylate **HA4** suppressed the current by a factor of *ca.* 5, because of the relative inaccessibility of **G3** to the electrode. The 20 mV cathodic shift was still seen, because of the rather hydrophobic environment of **G3** upon complexation. Such large host-induced effects are very suitable for Boolean representation, as shown in Fig. 3D.

In situ redox switching

Experiments on switchable binding of guests with hosts are best conducted *in situ*, i.e. when both components are present in the same solution. This was especially important because guest **G3** was known to be more redox active than hosts **HA4** and **HK4**. Indeed, many applications of **G3** depended on its redox activity. Therefore, we had to choose redox switching protocols with some care. In practice, the oxidation of trialcohol **HA4** with KMnO_4 gave triketone **HK4** while converting **G3** to its Ru(III) form. However, treatment of the mixture with the mild reductant methanol recovered **G3** in its original Ru(II) form, while leaving triketone **HK4** untouched. Also, reduction of triketone **HK4** to trialcohol **HA4** with NaBH_4 did not disturb **G3**. Once these conditions were established, smooth cycling between the two redox forms of the hosts **HA4**/**HK4**, and also **HA5**/**HK5**, could be demonstrated in the presence of guest **G3**.

Phenolate quenching of luminescence of **G3**

Although the 'on'/'off' binding of guest **G3** with switchable hosts influenced its luminescence and electrochemical properties, influencing of photochemical reactions was yet to be demonstrated. **G3** was known to be a photosensitizer for phenolate oxidation.³⁸ The shielding of **G3** by hosts should therefore hinder such reactions. The quenching of luminescence of **G3** by phenolates was found to be suppressed by nearly two orders of magnitude upon nesting binding by trialcoholhexacarboxylate **HA4** or by trialcoholdodecarboxylate **HA5**. As might be imagined, perching binding by triketonehexacarboxylate **HK4** had a smaller, but still significant, suppression of reactivity, whereas triketonedodecarboxylate **HK5** had almost no effect at all.

Steady-state luminescence spectroscopy of **G4**

Following the successful binding and unbinding of guest **G3** with hosts **HA4**/**HK4** and **HA5**/**HK5**, we turned to analogues of **G3** with extra functionality. Ru(II) complex **G4** was interesting in this regard because of its ionizable proton.^{39–42} In order to proceed at significant rates, such ionizations require sufficient hydration, which might not be available in rather hydrophobic



cyclophane cavities and environments. In particular, proton ionization in the excited state would have to compete with luminescence. The effect of hosts on luminescence intensity-pH profiles proved to be dramatic,^{37,43} in that the luminescence of **G4** was switched 'on' at pH 7 due to nesting binding by trialcoholdecadecarboxylate host **HA5**, and to a slightly lesser extent by nesting host trialcoholhexacarboxylate **HA4**. Naturally, perching binding due to host **HK4** produced a smaller effect. The non-binding cyclophane **HK5** caused no effect at all. Binding of DNA to certain Ru(II) complexes is known to produce similar switching 'on' of luminescence.⁴⁴

Time-resolved luminescence spectroscopy of **G4**

Luminescence lifetimes of guest **G4** with cyclophane hosts also showed significant lengthening.⁴³ The combination of such lifetime data with quantum yield results obtained from steady state luminescence measurements allowed the extraction of radiative and nonradiative rate constants. The latter confirmed the conclusions of the previous paragraph, *i.e.* that the paucity of water in the cyclophane environment retarded proton ionization. The radiative rate constant was also significantly increased because the π -electron rich cyclophane environment was more polarizable than water. Corresponding experiments on guest **G3** showed a similar host effect on the radiative rate constants.

Conclusions and outlook

Outfitting the classical Koga cyclophanes with alcohol moieties did not alter their host properties towards small aromatics in water. However, facile oxidation of these alcohol units into ketones suppressed the host properties essentially completely. These host properties were recovered upon reduction of the ketones into alcohol moieties. The redox-induced alteration of the macrocycle cavity in terms of size, shape and nature was held responsible for the switching of host behaviour. Sensing applications were indicated by the fluorescence of the reduced form of the host being switched 'off' upon guest binding.

The serendipitous discovery of trimeric relatives of the classical Koga cyclophanes was developed into a useful synthesis so that their redox-switched host properties could be investigated. Serendipity intervened again when polypyridineRu(II) species were found to be suitable guests, opening up the control of many celebrated properties of these iconic metal complexes. Three states of nesting binding, perching binding and release were elucidated with two sets of trimeric cyclophanes carrying differing hydrophobic regions. Varying degrees of exposure of the polypyridineRu(II) complexes to water were achieved in this way so that their electrochemical and photochemical properties were modulated accordingly.

Such control of properties is an aspect of input-output systems which can receive Boolean descriptions.^{11–26} In the present instances, molecular memories, with or without downstream processors are found. Molecular logic-based compu-

tation¹⁵ is rarely seen in macrocyclic capture/release systems, although important examples of polymeric material versions do exist.^{45,46} So, the current line of research should develop into a broad avenue within molecular logic besides the more common avenue of fluorescent/luminescent sensing.

We value this opportunity to offer a general observation on molecular logic. Molecular logic-based computation originated from fluorescence sensing.^{11,15} Since it is an extremely wide field, its most vibrant growth is occurring in two populations essentially insulated from each other – supramolecular/analytical scientists^{12,15,22} and molecular/synthetic biologists.^{15,22,47} The challenge will be for these two communities which speak different languages and have different philosophical positions to find ways to appreciate their common origin and to share best practice for progressing towards common goals. One of the latter will be to recognize molecular logic within living systems and another will be to apply molecular logic devices to probe/perturb those systems.

This article has summarized the first steps in the command and control of elementary properties of some organic and coordination compounds by exposing or hiding them in shape-switchable cyclophanes.^{27,37,43} Since electron/proton-transfer in ground/excited states of iconic molecules like **G3** and derivatives like **G4** have already been controlled in this way for the first time, following studies should allow the control of applications of these compounds and relatives in photocatalysis, electrocatalysis and luminescence sensing.

Conflicts of interest

There are no conflicts to declare.

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