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## Coupled molecular motions driven by light or chemical inputs: *spiropyran* to *merocyanine* isomerisation followed by *pseudorotaxane* formation

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**We have designed and prepared a new dual stimuli-responsive guest molecule containing a *spiropyran* fragment and a *pyridinium* moiety. Acid addition or UV-light irradiation induces guest transformation to a *merocyanine* isomer, promoting the threading motion through a 24-crown-8 macrocycle and the formation of a [2]*pseudorotaxane* complex.**

Biological systems at the nanoscale level are characterized for complex molecular motions. The ATP synthase is among the most relevant systems; these protein complexes perform ATP synthesis through the coupled rotary motion of its diverse components powered by chemical reactions.<sup>1</sup> There are also biological processes driven by light, such as the vision; the fundamental photochemical reaction is the *cis/trans* isomerisation of the 11-*cis*-retinal present in the rhodopsin protein. This process causes a series of conformational changes and triggers the vision phenomenon.<sup>2</sup>

Significant efforts have been devoted to mimic some of the systems observed in *Nature*, resulting in the construction of artificial molecular machines.<sup>3</sup> In this regard, photo sensitive host-guest systems have been prepared and investigated over the years.<sup>4</sup> A common characteristic of these assemblies is the presence of photoactive groups like stilbenes,<sup>5</sup> fumaramides,<sup>6</sup> azobenzenes,<sup>7</sup> dithienylethenes<sup>8</sup> or *spiropyran*s.<sup>9</sup> All these species undertake reversible structural changes after interacting with light, inducing in some cases, the relative movement of the assembly components.

An interesting feature of the *spiropyran* moiety is its dual responsiveness to chemical and photo stimulation, leading to its transformation to a *merocyanine* isomer and causing significant structural and electronic changes.<sup>10</sup> These properties were previously used for driving the motion of a Leigh-type macrocycle, by irradiation with UV-light, from a peptide station to a zwitterionic *merocyanine* site in a rotaxane molecular shuttle.<sup>11</sup>

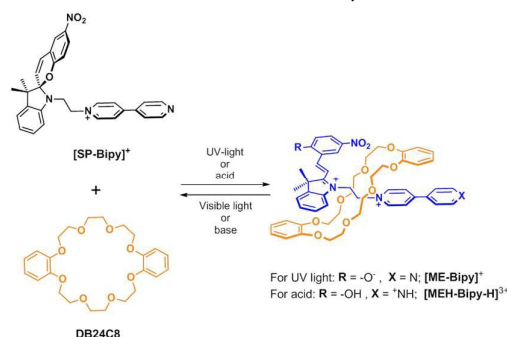
Based on these observations, we proposed that the incorporation of the *spiropyran* group into host-guest systems could

lead to the development of responsive systems capable of performing coupled molecular motions.

Herein, we present the design, synthesis and association behaviour of a dual stimuli-responsive guest molecule containing a *spiropyran* moiety. Upon acid addition or UV-light irradiation an isomerisation to a *merocyanine* form is expected and a recognition motif would be generated in the guest, promoting a threading motion through a macrocycle to yield a *pseudorotaxane* complex.

Our design is based on the bis(pyridinium)ethane recognition motif, studied by Loeb *et al.*,<sup>12</sup> which combined with 24-membered crown ether macrocycles gives rise to *pseudorotaxane* complexes in solution. In this work, we replace a *pyridinium* with a *spiropyran* moiety, so that we could be able to turn on/off the recognition site in the molecule by chemical or optical perturbations (Fig. 1).

The association process between the macrocycle and the guest would depend on the isomer. The guest in its *spiropyran* form (**SP**) would not show any association with dibenzo-24-crown-8 ether (**DB24C8**), because of poor geometrical and electronic complementarity. Nonetheless, transformation into the *merocyanine* isomer (**ME** or **MEH**) would induce the emergence of a positive charge on the indole ring and the planar arrangement of the *merocyanine* fragment, adequate for ion-dipole and  $\pi$ -stacking interactions, as well as an *anti* configuration in the ethylene unit, complementary with the macrocycle cavity. These combined effects would generate a recognition motif on the guest suitable for *pseudorotaxane* formation with the macrocycle.



**Fig. 1** Isomerisation of a *spiropyran*-based molecule (black) to a *merocyanine* guest (blue) by chemical or light stimulus and its association behaviour towards crown ether.

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Compound **[SP-Bipy][OTf]** was synthesized by reacting 4,4'-bipyridine with *N*-(2-bromoethyl)spirobenzopyran<sup>13</sup> followed by anion exchange with sodium triflate. Electronic absorption spectroscopy, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, single-crystal X-ray diffraction and high-resolution mass spectrometry were used to characterize this compound (see ESI).

The optical behaviour of compound **[SP-Bipy][OTf]** to acid/base and light inputs was analysed by electronic absorption spectroscopy (Fig. 2a). A solution of compound **[SP-Bipy][OTf]** ( $1 \times 10^{-4}$  M, CH<sub>3</sub>CN) is colourless and its absorption spectrum does not show any band above 400 nm. Upon addition of 3 mol equivalents of triflic acid, the solution turns yellow and the appearance of an absorption band at 422 nm is observed, reaching its maximum after 12 hours, indicating a complete transformation to the *merocyanine* species **[MEH-Bipy-H][OTf]<sub>3</sub>**. By <sup>1</sup>H NMR analysis could be established that, immediately after acid addition, the bipyridinium unit is protonated giving rise to **[SP-Bipy-H]<sup>2+</sup>**, which is slowly transformed to the *merocyanine* species **[MEH-Bipy-H]<sup>3+</sup>**, formed by the protonation of the phenolic group and the bipyridinium unit. An entire transformation to the *merocyanine* species was observed after 12 hours in the dark. Compound **[MEH-Bipy-H][OTf]<sub>3</sub>** was fully characterized by NMR spectroscopy and HR-MS (see ESI). After addition of base to a solution containing **[MEH-Bipy-H][OTf]<sub>3</sub>**, the bipyridinium unit and phenolic group are both deprotonated, resulting in the formation of **[ME-Bipy]<sup>+</sup>**, which contains a zwitterionic *merocyanine* moiety; responsible for the emergence of a new absorption band at 582 nm and the observed purple colour. The species **[ME-Bipy]<sup>+</sup>** can be also obtained by irradiating a **[SP-Bipy]<sup>+</sup>** solution with UV light at 254 nm; the photo conversion is ca. 16% (see fig. S34). Due to its short lifetime, **[ME-Bipy]<sup>+</sup>** was not characterised by NMR spectroscopy. Finally, compound **[SP-Bipy]<sup>+</sup>** can be recovered by visible light irradiation of a solution containing **ME** species or by deprotonation of **MEH** species. Absorption spectra of the switching cycle are shown in fig. 2b. The differences in the absorption properties of the isomers formed during the cycle can be distinguished with the naked eye as shown in fig. 2c.

In order to obtain information regarding complex formation between **DB24C8** and the aforementioned species; **[SP-Bipy]<sup>+</sup>**, **[MEH-Bipy-H]<sup>3+</sup>** and **[ME-Bipy]<sup>+</sup>**; the previous switching cycle was performed in the presence of **DB24C8**. Despite trying several different experimental conditions, no changes were observed in the electronic spectra. This result would indicate that, at the working concentration, very low amount of complex is formed, reflecting a relatively low association constant. In order to prove complex formation we turn our efforts to higher concentration solutions and NMR methods.

Recorded <sup>1</sup>H NMR spectra of an acetonitrile solution of **[SP-Bipy][OTf]** with increasing amounts of **DB24C8**, display minor changes on the chemical shifts and shape of some resonances (see fig. S26). This suggests a very weak interaction between **[SP-Bipy]<sup>+</sup>** and **DB24C8**, as expected. Nevertheless, a completely different behaviour is observed when the *merocyanine* isomer is used; upon addition of several amounts of **DB24C8** to a solution of **[MEH-Bipy-H][OTf]<sub>3</sub>**, the <sup>1</sup>H NMR spectra show important modifications on the chemical shifts (see fig. S28). This provides evidence of the formation of a host-guest complex between **DB24C8** and **[MEH-Bipy-H]<sup>3+</sup>**.

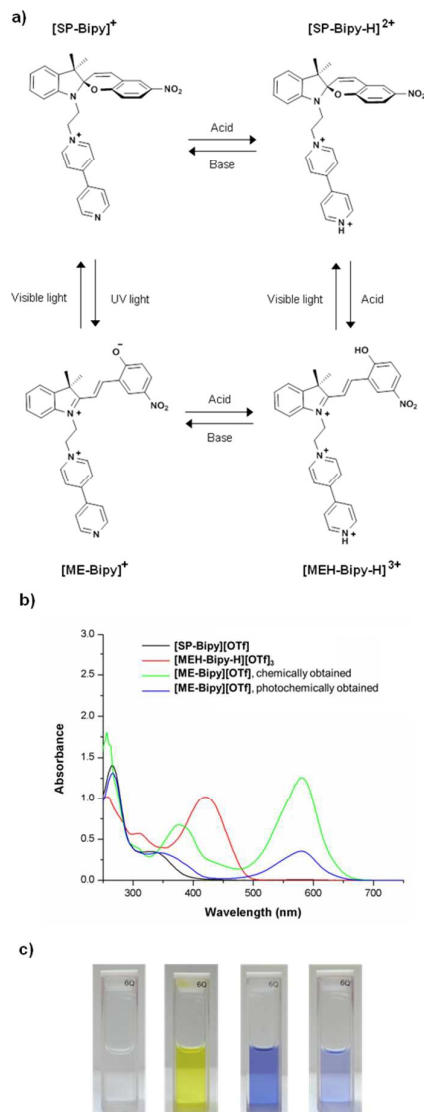


Fig. 2 a) Switching cycle of **[SP-Bipy][OTf]** molecule; b) Absorption spectra of **[SP-Bipy][OTf]**; **[MEH-Bipy-H][OTf]<sub>3</sub>** and **[ME-Bipy][OTf]** ( $4 \times 10^{-5}$  M, CH<sub>3</sub>CN, 293 K); c) Pictures corresponding to, from left to right: **[SP-Bipy]<sup>+</sup>**; **[MEH-Bipy-H]<sup>3+</sup>** and **[ME-Bipy]<sup>+</sup>**, obtained by base addition or by irradiation with 254 nm light, respectively ( $1 \times 10^{-4}$  M, CH<sub>3</sub>CN, 293 K).

The <sup>1</sup>H NMR spectra of an equimolar mixture containing **DB24C8** and **[MEH-Bipy-H]<sup>3+</sup>** show a single set of peaks because of fast exchange on the NMR time scale between free and complexed species, probably because of the terminal nitrogen protonation on the guest. The resonances showing the most remarkable changes are those corresponding to protons located on: a) the *ethylene* unit, b) the *bipyridinium* fragment and c) the *merocyanine* double bond. Upon saturation with **DB24C8**, protons on the *ethylene*, are clearly shifted to higher frequencies; whilst resonances related to protons on the *bipyridium* unit are shifted to lower frequencies.

These observations indicate hydrogen-bonding and  $\pi$ -stacking interactions, respectively. Protons on the *merocyanine* moiety are shifted considerably regarding its initial position suggesting an intermolecular interaction with the macrocycle. All observed changes in chemical shifts are consistent with a host-guest complex in a rotaxane-like geometry with the cavity of the macrocycle encircling the *ethylene* unit of the guest and the aromatic rings of **DB24C8** in close proximity to the *bipyridinium* fragment. The association constant for this complex,  $K_a$ , was estimated by an NMR titration experiment and a non-linear least-squares fit<sup>14</sup> of the data. The  $K_a$  value obtained by this procedure is  $13.9 (\pm 0.5) \text{ M}^{-1}$  (fig. S29).

In order to corroborate the previous structural information for the complex, a slow exchange process on the NMR time scale was studied. This was attained by incorporation of a bulky benzyl group on the guest at the *N* terminus. Compound **[SP-Bipy-Bn][OTf]<sub>2</sub>** was prepared by reacting **[SP-Bipy][Br]** with benzyl bromide in  $\text{CH}_3\text{CN}$  to obtain the corresponding bromide salt, followed by anion exchange with sodium triflate. The corresponding *merocyanine* isomer, **[MEH-Bipy-Bn][OTf]<sub>3</sub>**, was obtained *in situ* by addition of HOTf. Both benzyl-derivatives were characterized by NMR techniques and HR-MS (see ESI).

Upon mixing an acetonitrile solution of **[MEH-Bipy-Bn][OTf]<sub>3</sub>** with **DB24C8**, the resulting <sup>1</sup>H NMR spectrum clearly shows the formation of an inclusion complex (Fig. 3). A new set of signals is observed (highlighted in blue in fig. 3b), corresponding to a host-guest complex in slow exchange with free guest and macrocycle. This chemical exchange was verified by 2D T-ROESY NMR experiment (Fig. 3d). This technique was useful for the assignment of the proton resonances corresponding to the new species formed.

Comparing the position and the integrals of the signals from the complex with those of the free species, we were able to confirm a [2]*pseudorotaxane* complex. The chemical shifts observed for this species are similar to those noted for the fast exchange equilibrium, pointing out that the interpenetrated structure in both cases is closely related.

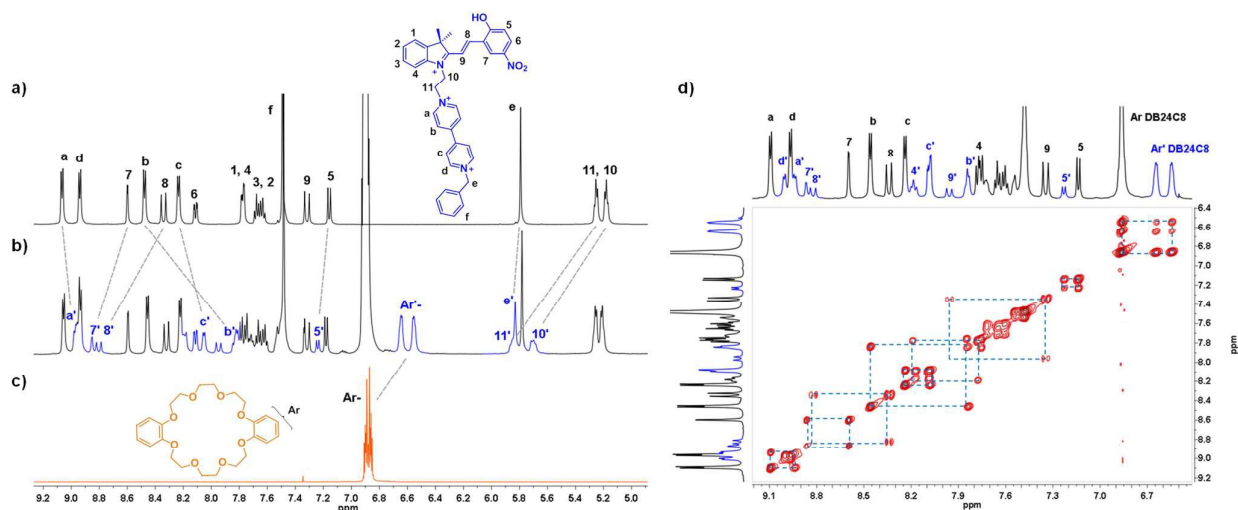
Resonances of the protons present on the *ethylene* unit of the complexed guest,  $\text{H}_{10'}$  and  $\text{H}_{11'}$ , are shifted to higher frequencies ( $\Delta\delta = +0.53 \text{ ppm}$ ), while the aromatic proton signals of  $\text{H}_a$ ,  $\text{H}_b$ , and  $\text{H}_c$  undergo a shielding effect ( $\Delta\delta = -0.16, -0.60, -0.17$ , respectively). The signals corresponding to the aromatic protons of the complexed macrocycle ( $\text{H}_{Ar'}$ ) are shifted to lower frequencies ( $\Delta\delta = -0.30 \text{ ppm}$ ), probing the existence of the  $\pi$ -stacking interaction between these rings and the *bipyridinium* unit of the guest. Protons  $\text{H}_g$  and  $\text{H}_g'$  on the *merocyanine* moiety, undergo a deshielding effect ( $\Delta\delta = +0.5$  and  $+0.6 \text{ ppm}$ ) probably due to the proximity of the oxygen atoms present in **DB24C8** cavity. The association constant of the *pseudorotaxane* was estimated by the single point method, giving a  $K_a$  value of  $11 (\pm 2) \text{ M}^{-1}$ . This constant is of the same order of magnitude than the one observed for **[MEH-Bipy-H]<sup>3+</sup>**. The observed low association constants are probably related to weaker  $\pi$ -stacking and ion-dipole interactions regarding the Loeb's motif.

These results altogether prove the coupling between the isomerisation motion on the guest and the threading process through the macrocycle triggered by a chemical stimulus.

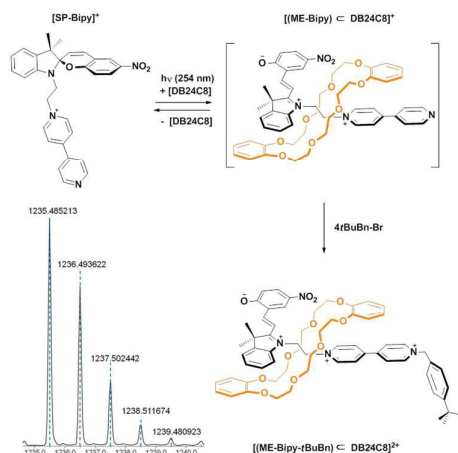
It is worth to notice that dissociation of the inclusion complexes formed between *merocyanine* isomers and **DB24C8** could be attained if the corresponding *spiropyran* compound is restored by addition of base (pyridine) to the solution. Unfortunately, only two cycles could be performed since guest decomposition is observed.

Once acid-induced complex formation was demonstrated, we turned our efforts to photo activation. As previously mentioned, **[ME-Bipy]<sup>+</sup>** species has a very short lifetime and its NMR characterization is hampered, including any complexes related. So, we decide to kinetically trap the *pseudorotaxane* complex by *in situ* transformation to a [2]rotaxane, under suitable experimental conditions.

An acetonitrile solution containing **[SP-Bipy][OTf]**, excess **DB24C8** and 4-*tert*butylbenzyl bromide, as end-capping agent, was irradiated with UV light at 254 nm during 18 hours in a quartz tube. After this period, a precipitate was recovered and analysed by <sup>1</sup>H NMR and HR-MS.



**Fig. 3** Partial <sup>1</sup>H NMR spectra (500 MHz,  $\text{CD}_3\text{CN}$ , 298 K) of **a**) **[MEH-Bipy-Bn][OTf]<sub>3</sub>**; **b**) 1 : 3 mixture of **[MEH-Bipy-Bn][OTf]<sub>3</sub>** ( $2.2 \times 10^{-2} \text{ M}$ ) and **DB24C8**, and **c**) free macrocycle; **d**) 2D T-ROESY NMR experiment showing cross peaks for free and complexed species (EXSY-related peaks). Blue peaks correspond to the [2]*pseudorotaxane*.



**Fig. 4** Synthesis of [2]rotaxane complex from zwitterionic species. HR-MS for rotaxane complex is shown.

Spectroscopic studies revealed the presence of the expected [2]rotaxane complex, among other products, mainly end-capped thread and unreacted free thread, reflecting the relatively low stability of the pseudorotaxane complex, in addition to the low SP-ME photo conversion. In the HR-MS spectrum (Fig. 4), a peak due to the rotaxane species  $[(\text{ME-Bipy-tBuBn})\cdot(\text{DB24C8})\cdot(\text{OTf})]^+$  was observed at  $m/z = 1235.4852$  uma, in good agreement with the predicted value of  $m/z = 1235.4869$  uma (relative error of 1 ppm). Despite several trials under different experimental conditions, the [2]rotaxane complex could only be detected in low concentration; even though the transformation is not quantitative, we garnered evidence relating the coupling between the isomerisation and threading motions induced by light in a two-component molecular system.

In conclusion, we have obtained a chemical- and optical-responsive guest molecule containing a *spiropyran* fragment that can be isomerised into a *merocyanine* species. This process involves important electronic changes and spatial arrangements, which are coupled with the threading motion of the guest through the cavity of a crown ether macrocycle, generating a [2]pseudorotaxane. These outcomes suggest that SP/ME isomerisation could be used to obtain optical molecular switches; investigation on this area is in progress in our group.

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