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An Azobenzene-Bipyridinium Derivative as Component in the Construction of Photoresponsive Pseudorotaxanes

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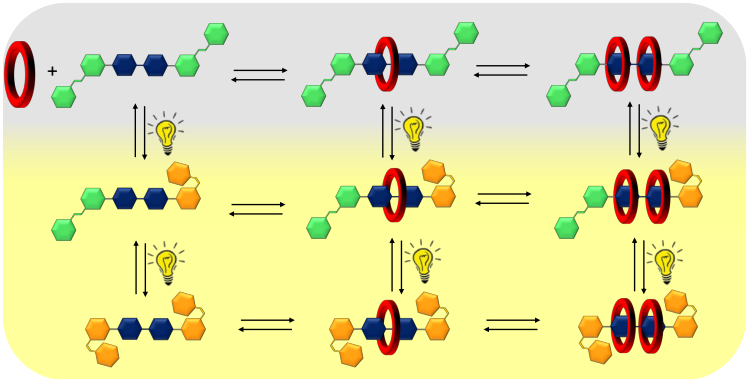

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Abstract We describe the synthesis and characterization of a bipyridinium derivative conjugated with two azobenzene groups (Azo_2Bpy^{2+}). The design allowed to retain the ability of the photoswitches to undergo *E* - *Z* isomerization upon irradiation to generate a mixture of *EE*, *EZ* and *ZZ* isomers. Moreover, Azo_2Bpy^{2+} proved to be able to self-assembly with dibenzo[24]crown-8 ether to generate [3]-pseudorotaxanes, driven by strong cooperative effect, in all its geometric isomers.

Key words Molecular device, crown ethers, photochemistry, supramolecular chemistry, photoisomerization

The bottom-up development of devices relies oftentimes on molecular switches as structural components to modulate their properties and define their function.[1] A quintessential example is represented by molecular machines and motors: the introduction into their molecular constituents of functional groups susceptible to reversible alteration of their features (e.g. geometry, charge distribution, redox state), in response to external stimuli, allowed to develop systems able to perform controlled and directional movements, leading to interesting functions that strive to mimic their natural counterparts.[2] Amongst the simplest prototypes of this kind, pseudorotaxanes are supramolecular complexes composed of a linear axle threaded through a macrocyclic component, held together by weak interactions, such as hydrogen bonding, charge transfer or π–π stacking, depending on the nature of the components. Despite the plethora of examples available in literature, the investigation and development of these systems is steadily ongoing, since they represent the foundation of mechanically interlocked molecules (MIMs).[3]

Bipyridinium (Bpy^{2+}) derivatives have found widespread application in several fields due to their ease of synthesis, stability and electrochromic properties.[4] They have been reported as guests for several macrocycle classes and are frequently found as redox active recognition sites in MIMs.[2a,5] However, the development of pseudorotaxane systems containing the couple dibenzo[24]crown-8 (DB24C8) and benzyl Bpy^{2+} derivatives is limited by their low association.[6] Only recently it was shown that the conjugation of Bpy^{2+} with aryl groups presenting electron-withdrawing moieties, enhances the stability of the Bpy^{2+}/ DB24C8 interactions, leading to the formation of [3]pseudorotaxanes.[7] Intrigued by such an observation, we speculated that if an akin result could be achieved conjugating Bpy^{2+} with photoswitches, it would open a way to a new class of photoactive supramolecular systems. Azobenzenes are ideal candidates to test this hypothesis: the diazenyl group should have such an electron-withdrawing effect to boost the interactions between the Bpy^{2+} recognition site and DB24C8. Moreover, azobenzenes undergo a clean, efficient and reversible $E \rightarrow Z$ isomerization *via* irradiation in the UV range, they can be easily synthetized and are amenable to functionalization to be introduced in complex architectures.[8] Hence, we designed the symmetric bis-azo-bipyridinium (Azo_2Bpy^{2+}) derivative *EE*-**3** (Figure 1): to prevent the loss in isomerization efficiency reported for linear *para*-conjugated azobenzene, the -N=N- group was introduced in *meta*- position relative to Bpy^{2+}.[9] The compound was characterized by NMR and UV-Vis spectroscopies, demonstrating that under UV irradiation it undergoes $E \rightarrow Z$ switching generating a mixture of *EE*, *EZ* and *ZZ* isomers. The self-assembly of **3** with DB24C8 (**4**) was then studied in acetonitrile, showing the cooperative formation of the [3]pseudorotaxane in all its isomeric configurations.

The synthesis of *EE*-**3** involved three steps (Scheme 1). First, nitro- functionalized azobenzene **1** was obtained in 80% yield via Mills' coupling between 3-nitro-aniline and nitrosotoluene in acetic acid, followed by the reduction of the nitro- group with sodium sulfide to afford the corresponding aniline **2** in 90% yield. Target compound *EE*-**3**[10] was isolated in 70% yield as the hexafluorophosphate (PF_6^-) salt, after Zincke reaction between **2** and 1,1'-bis(2,4-dinitrophenyl)-4,4'-bipyridinium dichloride. (See ESI for synthetic procedures and characterization)

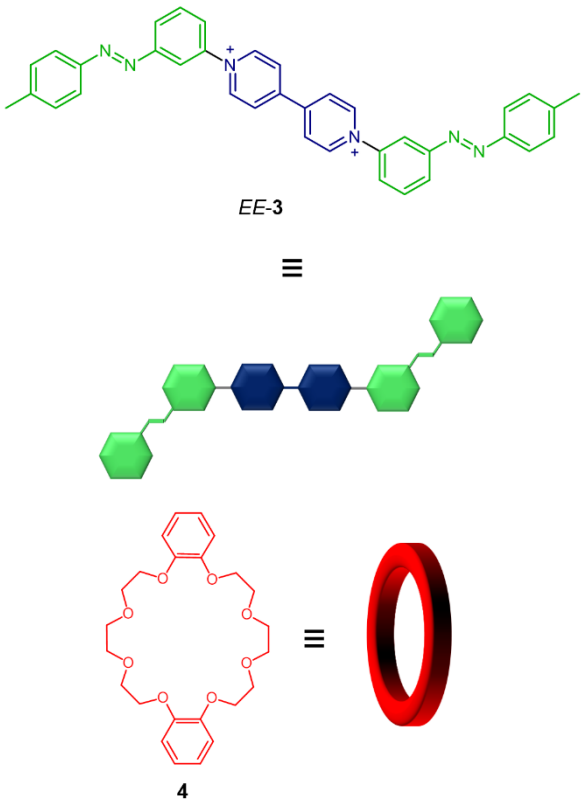
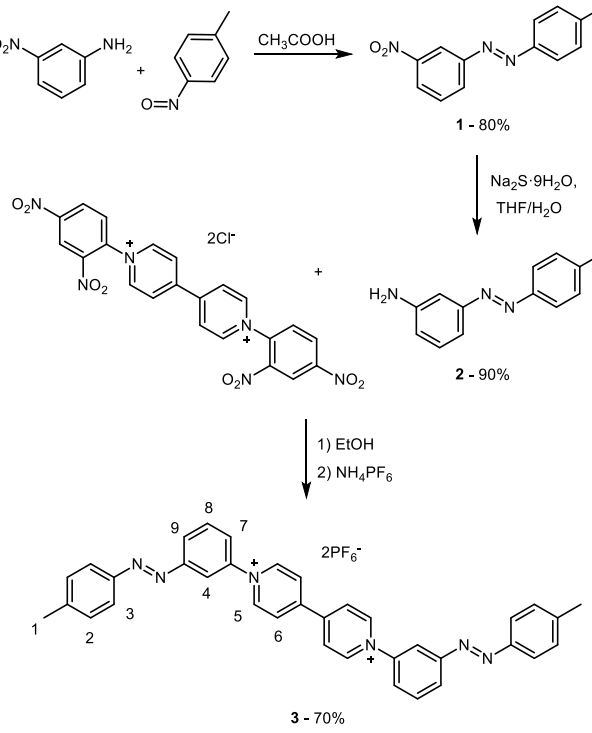


Figure 1 Structures of the components of the pseudorotaxane system bis-azo-bipyridinium *EE*-**3**, crown ether **4** and their cartoon representation



Scheme 1 Synthetic route to bis-azobenzene-bipyridinium derivative **3**

The photoisomerization of *EE*-**3** was investigated by UV-Vis spectroscopy. The absorption spectrum of *EE*-**3** displays the typical features of azobenzene units, with an intense π-π* band around 330 nm (overlapping with the absorption of the bipyridinium unit)[11] and a weak n-π* band around 430 nm (Figure 2). Upon irradiation at λ = 365 nm, a decrease of the π-π* band together with an increase of the n-π* band was observed, until a photostationary state (PSS) was achieved (75% *Z* isomer). These changes are consistent with the *E*-*Z* photoisomerization of the two azobenzene units and the photokinetics was fitted to determine the quantum yields of the process (Φ_{EZ}= 6.6%, Φ_{ZE}= 11.9%, see ESI for further details).

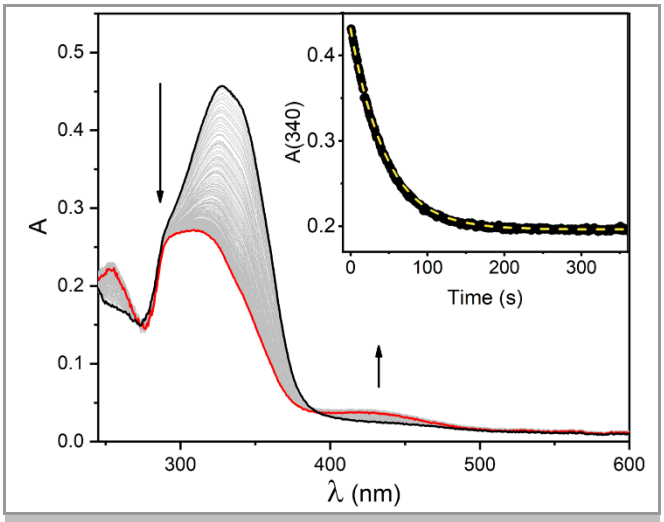


Figure 2 Time-dependent absorption spectra of a CH_3CN solution of *EE*-**3** (7.6×10^{-6} M, black to red lines) upon irradiation at 365 nm. Inset: Absorption changes at 340 nm (black dots) together with the fitting of the data (yellow dashed line).

The photoinduced isomerization of *EE*-**3** was also monitored by ^{1}H NMR spectroscopy. Following the irradiation at λ = 369±5 nm of a 5 mM solution of *EE*-**3** in CD_3CN showed the appearance of a new set of signals that could be associated with the *E*→*Z* isomerization (Figure S12). The splitting of the NMR peaks shows that at the photostationary state (PSS), in solution three species are present – namely, the *EE*, *EZ* and *ZZ* isomers – which can clearly be identified in the evolution of the signal associated with proton H_6 at δ = 8.71 ppm for *EE*-**3** (Figure 3a,b). In these conditions, at PPS the composition of the mixture is *EE* = 22 %, *EZ* = 48%, *ZZ* = 30% (Figure 3c).

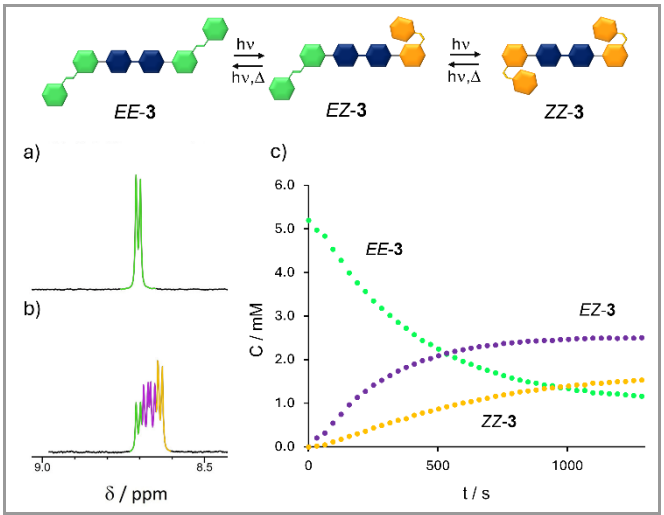


Figure 3 Partial ^{1}H NMR spectra (500 MHz, CD_3CN, 298 K) highlighting the

chemical shift changes of the signal associated with protons H_6 in the thread upon irradiation a) *EE*-**3** (5 mM); b) solution (a) after irradiation at λ = 369±5 nm; c) Traces showing the variation of concentration of the three geometric isomers during irradiation time. *EE*-**3**: green, *EZ*-**3**: purple, *ZZ*-**3**: orange.

Upon mixing *EE*-**3** with crown ether **4** in 1:1 ratio in CD_3CN, two new sets of signals appeared in the ^1H NMR spectrum (Figure 4a,b): one was assigned to the [2]pseudorotaxane *EE*-**3⊂4** (pink), present in lower concentration, while the other was assigned to the [3]pseudorotaxane *EE*-**3⊂(4)**$_2$ (cyan) (Figure 4c, Figures S13-S16). The significant shift of the signals associated with the Bpy^{2+} unit. suggests that in both species the macrocycle(s) encircle(s) it. The threading/dethreading reaction rates are slow in the ^1H NMR timescale. On the other hand, the threading kinetic of the macrocycle through *E* azobenzene is fast, i.e. in the time required for component mixing and starting NMR acquisition the system had reached equilibrium. The titration of *EE*-**3** with **4** shows that the formation of *EE*-**3⊂(4)**$_2$ is favoured over *EE*-**3⊂4** (Figure 4d). The association constants in CD_3CN, determined by single point measurement, in CD_3CN were found to be $K_{1,\,EE}$ = 55±5 M^{-1} and $K_{2,\,EE}$ = 760±30 M^{-1}. The calculation of the cooperativity factor $\alpha = 4(K_{2,EE}/K_{1,EE})$ = 55, in line with similar systems,[7] demonstrated a positive cooperative effect, possibly induced by the increased electron-deficient character of the conjugated bipyridinium, which is more efficiently counterbalanced by the electron-rich cavities of two macrocycles rather than one. Nonetheless, further investigation will be needed to clarify this aspect.

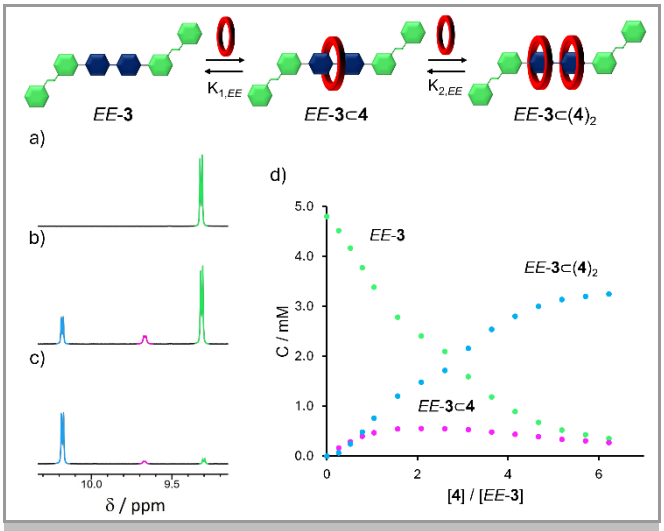


Figure 4 Partial ^1H NMR spectra (500 MHz, CD_3CN, 298 K) highlighting the chemical shift changes of the signal associated with protons H_5 in the thread upon addition of **4**: a) compound *EE*-**3** (5 mM); b) solution (a) after the addition of 1.5 equivalents of **4**; c) after the addition of 6 equivalents of **4**; d) Traces showing the variation of concentration free and complexed species upon titration of *EE*-**3** (5 mM) with **4.** Signals are color coded to indicate: free *EE*-**3**: green, *EE*-**3⊂4**: pink, *EE*-**3⊂(4)**$_2$: cyan.

Upon irradiation of the [3]pseudorotaxane *EE*-**3⊂(4)**$_2$ at λ = 365 nm, its absorption spectrum displays changes consistent with the *E*→*Z* photoisomerization (Figure S24). The quantum yields determined from the photokinetics (Φ_{EZ}= 6.7%, Φ_{ZE}= 13.8%, see SI for details) were found to be the same, within experimental error, as the ones of *EE*-**3**. This observation suggests that the photoisomerization is not hampered by the presence of the macrocycles, and both azobenzene units can be switched to the *Z* isomer. The 1:1 mixture of the components was then irradiated at λ = 369±5 nm and the changes followed by ^1H NMR spectroscopy: the azobenzene groups in both [2]- and [3]-pseudorotaxane retained the ability to undergo *E*→*Z* isomerization, to generate a complex mixture (Figure 5d). The determination of the binding constants of *EZ*-**3** and *ZZ*-**3** with **4** in CD_3CN was achieved by ^1H NMR single point measurement, by adding 1 equivalent of **4** to a solution of **3** irradiated at λ = 369±5 nm to reach PSS. The calculated values for the complexes formed by *EZ*-**3** were $K_{1,\,EZ}$ = 30±5 M^{-1} and $K_{2,\,EZ}$ = 600±40 M^{-1} corresponding to $\alpha = 4(K_{2,EE}/K_{1,EE})$ = 80, while the values for the assemblies formed by *ZZ*-**3** were $K_{1,\,ZZ}$ = 15±5 M^{-1} and $K_{2,\,ZZ}$ = 70±10 M^{-1} corresponding to $\alpha = 4(K_{2,EE}/K_{1,EE})$ = 20. Overall, the data show that azobenzene isomerization destabilizes the interactions between Azo_2Bpy^{2+} and DB24C8, particularly switching from the *EE* thread to the *ZZ* one.[12] Finally, the evolution in time of the signal of H_5 (δ = 10.1 ppm) in the [3]pseudorotaxane presenting at least one *Z* azobenzene (blue peak, figure 5b,c), when DB24C8 is added to the irradiated thread, suggests a slow threading kinetic that reaches equilibrium in 5 hours. As previously demonstrated,[12] Z azobenzene can hinder the threading of DB24C8, acting as a kinetic stopper and an analogous behavior can be hypothesized here. Studies are ongoing to accurately characterize the system from a kinetic point of view.

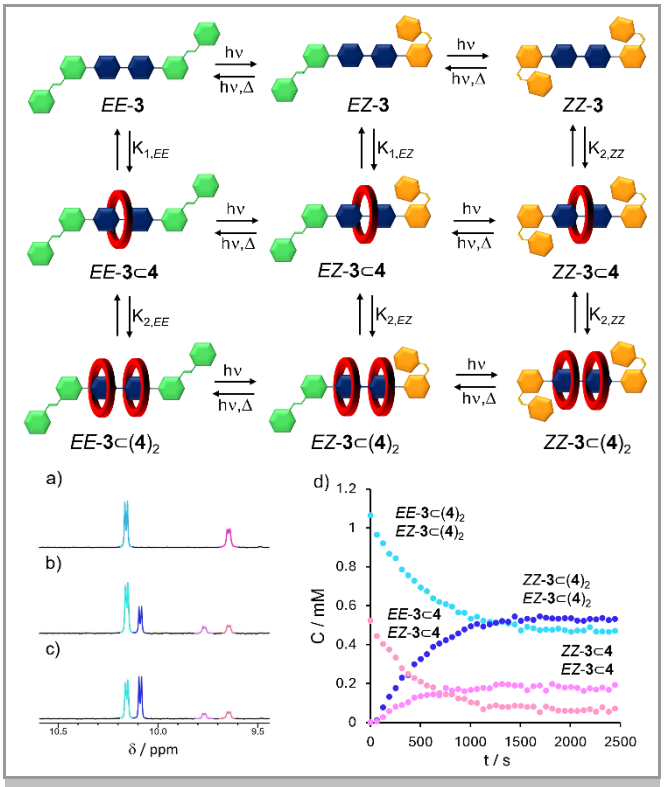


Figure 5 Partial ^1H NMR spectra (500 MHz, CD_3CN, 298 K) highlighting the chemical shift changes of the signal associated with protons H_5 in complexes *EE*-**3⊂4** and *EE*-**3⊂(4)**$_2$: a) a 1:1 mixture of *EE*-**3** and **4** (5 mM); b) a solution of *EE*-**3** (5 mM) irradiated to reach PSS at λ = 369±5 nm, 300 seconds after the addition of 4 (1 eq.); c) a solution of *EE*-**3** (5 mM) irradiated to reach PSS at λ = 369±5 nm, 5 hours after the addition of 4 (1 eq.); d) Traces showing the variation of concentration of the geometric isomers of the [2]- and [3]pseudorotaxanes . Signals are color coded to indicate: *EE*-**3⊂4** + *EZ*-**3⊂4**: light pink, *ZZ*-**3⊂4** + *EZ*-**3⊂4**: dark pink, *EE*-**3⊂(4)**$_2$ + *EZ*-**3⊂(4)**$_2$: cyan, *ZZ*-**3⊂(4)**$_2$ + *EZ*-**3⊂(4)**$_2$: blue.

In conclusion, we investigated the properties of a novel photoswitchable axle, consisting of two terminal azobenzene units conjugated to a central bipyridinium recognition site. Its association with a crown ether macrocycle was evaluated by ^{1}H-NMR, revealing the cooperative formation of a [3]pseudorotaxane complex (α>>1). The *E*→*Z* photoisomerization of the axle allows to control its affinity for the macrocycle, as a decrease of the association constants is observed going from the *EE* to the *ZZ* [2]- and [3]pseudorotaxane. The described system is a promising starting point to a new class of photoactive supramolecular devices, which present a potential for application in the development of molecular carriers and supramolecular switchable catalysts.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(10) **1,1'-bis(3-((E)-p-tolyldiazenyl)phenyl)-[4,4'-bipyridine]-1,1'-diium di-hexafluorophosphate (*EE*-3)**: 1,1'-bis(2,4-dinitrophenyl)-4,4'-bipyridinium dichloride (0.5 g, 0.8 mmol) and compound **2** (0.4 g, 1.8 mmol) were dissolved in ethanol (EtOH, 40 ml) and the solution was stirred at reflux temperature for 48 hours. The solvent was removed, and the solid residue was dissolved with water 50 ml and EtOAc (50 ml). The aqueous phase was extracted with EtOAc three times (3x50 ml). A saturated solution of ammonium hexafluorophosphate (NH_4PF_6 aq) was added to the aqueous phase, which contained the chloride salt of the product, to precipitate the product as the hexafluorophosphate salt. The solid was filtered and washed with water and EtOH, then dried under vacuum. The product was an orange solid obtained in 71% yield (0.5 g). ^{1}H NMR (5oo MHz, CD_3CN, 298 K) δ = 9.30 (d, J=6.5, 2H, H_5), 8.71 (d, J=6.5, 2H, H_6), 8.31 (d, J=8.0, 2H, H_7), 8.29 (s, 1H, H_4), 7.98 (t, J=8.0, 1H, H_8), 7.93-7.90 (m, 3H, H_3+H_9), 7.45 (d, J=8.2, 2H, H_2), 2.47 (s, 3H, H_1). ^{13}C NMR (125 MHz, CD_3CN, 298 K) δ = 154.6, 151.6, 151.3, 146.9, 144.7, 144.1, 132.8, 131.2, 128.5, 127.7, 127.3, 124.1, 118.8, 21.6.
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