RESEARCH ARTICLE

Photoresponsive Binding Dynamics in High-Affinity Cucurbit[8]uril-Dithienylethene Host-Guest Complexes

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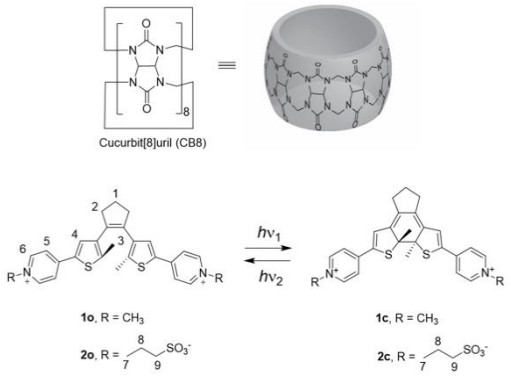
Abstract: The use of external stimuli to control the binding kinetics in supramolecular systems is of critical importance for the development of advanced molecular machines and devices. In this work we report a study focused on the kinetics of a water-soluble host-guest system based on cucurbit[8]uril and two dithienylethene (DTE) photoswitches. We show that for the DTE guest comprising two anionic sulfonate side arms appended to pyridinium moieties, the formation/dissociation of the pseudorotaxane structures is slowed down by more than 100000-fold with respect to its bipyridinium analogue. The decrease in ingression rate leads to the emergence of a competitive metastable product with the open DTE isomer that has an important influence in the overall binding kinetics. We also demonstrate that host-guest dissociation kinetics is approximately 100-fold slower for the closed DTE isomer ($t_{1/2}$ = 107 hours vs $t_{1/2}$ = 1.2 hours for the open isomer) allowing control over the dissociation rate with light.

Introduction

Supramolecular chemistry deals with the formation of self-assembled systems from molecular building blocks held together and organized by noncovalent bonds.[1] Owing to the kinetic lability and reversibility of these interactions, supramolecular assemblies are usually formed under thermodynamic control with their building blocks in dynamic equilibrium between bound and free states. This dynamicity constitutes the basis of some of the most appealing and widely explored features of supramolecular systems such as their ability to dissociate, reorganize, adapt and self-heal in response to external stimuli.[1–3] Despite of being a discipline traditionally dominated by chemical equilibria, non-equilibrium supramolecular systems that operate under kinetic control are critical to access complex properties and functions such as directional motion or transport of molecules and ions against concentration gradients. [4–9]

Macrocyclic host molecules are among the most popular building blocks to construct self-assembled systems owing to their ability to recognize a wide variety of complementary guest molecules and ions. Within the different classes of macrocycles, cucurbit[n]urils (CBn) constitute a particularly interesting family of barrel-shaped receptors that display ultrahigh affinity for suitable guests in aqueous solution.[10–15] Pioneering works on the kinetics of CBn-based host-guest complexes have already disclosed important mechanistic details about their binding dynamics and the structural, electronic and external factors that affect the complexation rates.[16–33] Of special interest for the design of stimuli-responsive systems are the studies demonstrating that the complexation kinetics can be controlled by protonation/deprotonation of the guest molecules.[23,28,34–37] Noteworthy, Kaifer and co-workers showed that the decoration of bipyridinium guests with anionic carboxylate groups introduces a significant activation barrier that slows down the formation/dissociation of the inclusion complexes due to repulsive interactions between the negatively charged carboxylate groups and the carbonyl portals of the CBn.[34–37] While carefully designed pH-responsive guests enable a high degree of control over the complexation dynamics, this stimulus may be unsuitable for some applications requiring remote application and spatiotemporal control. Light stimuli can, on the other hand, fulfill these conditions and a variety of light-responsive CBn host-guest complexes have been reported.[38–49] However, the use of light to control the binding dynamics of CBn inclusion complexes has seldomly been addressed and, to the best of our knowledge, examples showing substantial light-induced changes in the complexation rate constants are still lacking.[50]

Herein, we investigate the binding dynamics of the dithienylethene (DTE) photoswitches **1** and **2** with cucurbit[8]uril (CB8) (Scheme 1) and demonstrate that in addition to the thermodynamic stability, the mechanism and complexation kinetics of these guests with CB8 can also be modulated by light stimulus.



Scheme 1 - Structures of compounds investigated in this work.

Results and Discussion

The zwitterionic DTE **2** was readily obtained by treating its pyridine precursor with propanesultone (see Supporting Information). The open isomer **2o** can be quantitatively converted into the closed from, **2c**, upon irradiation at 365 nm ($\phi_{o\text{-}c}$ = 0.037 at 365 nm; see Supporting Information) and reverted to **2o** by performing the irradiation with visible/near-infrared light ($\phi_{c\text{-}o}$ = 0.00028 at 550 nm; see Supporting Information). As previously reported for **1**,[48] **2** also forms high-affinity host-guest complexes with CB8 (*vide infra*). The photochemical properties of the **2**:CB8 pseudorotaxane are in line with those previously observed for the **1**:CB8 inclusion complex: the photochemical cyclization of the **2o**:CB8 proceeds more efficiently ($\phi_{o\text{-}c}$ = 0.25 at 365 nm; see Supporting Information) than that of free **2o** to give **2c**:CB8 in quantitative yield (see Supporting Information). On the other hand, the photoinduced ring-opening remains practically unaffected in the complex ($\phi_{c\text{-}o}$ = 0.00033 at 550 nm; see Supporting Information).

Based on previous works, the installation of two anionic side arms in **2** was anticipated to slow down the kinetics of complexation.[36,37] However, mixing **2o** with 1 equiv. CB8 lead to the fast formation of a new species displaying an UV-Vis absorption spectrum with the maximum blue-shifted with respect to that of free **2o** (Figure 1a). Nevertheless, this species is not thermodynamically stable, evolving to a second, more stable, species in a timescale of minutes. As can be observed in Figure 1a, the kinetic trace can be satisfactorily fitted to a pseudo-first order rate law to give an observed rate constant of k_{obs} = 1.8×10^{-3} s^{-1}.

Further studies showed that k_{obs} is independent of the concentration of CB8 (all data can be globally fitted with k_{obs} = 1.8×10^{-3} s^{-1}, see Supporting Information) and that the spectra of equilibrated solutions of **2o** with different concentrations of host (Figure **2b**) suggests the formation of a 1:1 complex with a high binding constant of K_{2o} > 1×10^{7} M^{-1}.

To determine K_{2o} and the dissociation rate constant, a competitive guest (3-ammonium-1-adamantanol, K = 1.4×10^{7} M^{-1})[48] was added at different concentrations to previously equilibrated solutions of the **2o**:CB8 complex and the dissociation kinetics monitored by UV-Vis spectroscopy (see Supporting Information). The spectral variations were compatible with the dissociation of the complex and the first order rate constant (k_{out} = 1.6 ×10^{-4} s^{-1}) for this process was obtained.[30] From the spectra obtained for the equilibrated solutions of **2o**:CB8 in the presence of different concentrations of competitor, a value of K_{2o} = 2.5×10^{7} M^{-1} was obtained using a competitive binding model (see Supporting Information). This value is close to the one observed for **1o** (K_{1o} = 5.4×10^{7} M^{-1}) showing that the sulfonate side arms have a small effect on the thermodynamic stability of the complex.

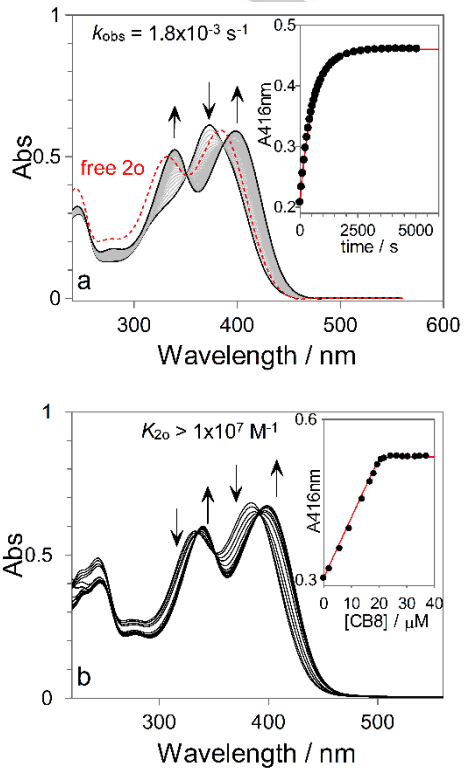


Figure 1 – (**a**) UV-Vis spectral variations observed upon mixing **2o** (19 µM) with 1 equiv. of CB8 in pure water. The red dotted spectrum corresponds to **2o** (19 µM) in the absence of CB8. (**b**) UV-Vis spectra of **2o** (24 µM) with different concentrations of CB8 at the equilibrium (around 2 hours between each addition of CB8).

To gain more insights on the complexation mechanism, the kinetics for the formation of the metastable species observed immediately after mixing **2o** with CB8 was investigated by stopped-flow experiments. Figure 2a shows, as an example, the typical UV-Vis spectral variations observed upon mixing **2o** with CB8 which clearly indicate the formation of a metastable complex from free **2o** in less than 0.1 seconds. Representation of the observed spectra approximately 70 ms after mixing against the concentration of CB8 (Figure 2b) shows spectral variations compatible with the formation of a 1:1 host-guest complex with a binding constant of K'_{2o} = 1.2×10^{6} M^{-1}. As expected for a metastable species, this binding constant is lower than that observed for the equilibrium species. The time-dependent UV-Vis spectroscopic data was globally fitted to a reversible bimolecular kinetic model (see Supporting Information) which allowed the determination of the two rate constants k'_{in} = 7.0×10^{6} M^{-1} s^{-1} and k'_{out} = 3.9 s^{-1}.

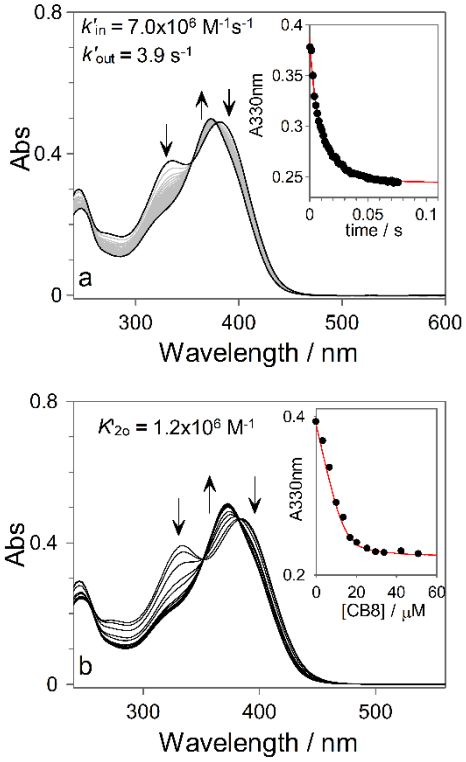
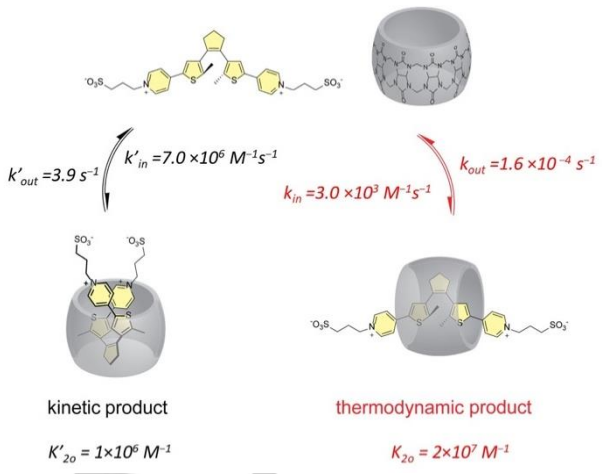


Figure 2 – (**a**) UV-Vis time-dependent spectral variations observed upon mixing **2o** (15 μM) with 17 μM of CB8 in pure water. (**b**) UV-Vis spectra of **2o** (15 μM) with different concentrations of CB8 at the pseudo-equilibrium (70 ms after mixing).

Based on the results described above, we propose a mechanism that considers the fast formation of a metastable 1:1 complex between CB8 and **2o** in either a *twisted* antiparallel or parallel conformation with the thiophene rings perpendicular to the cyclopentene (a kinetic product) and the competitive, slower formation of a thermodynamically stable pseudorotaxane-like complex between **2o** in the most common antiparallel conformation (Scheme 2).



Scheme 2 – Proposed mechanism for the complexation of **2o** with CB8.

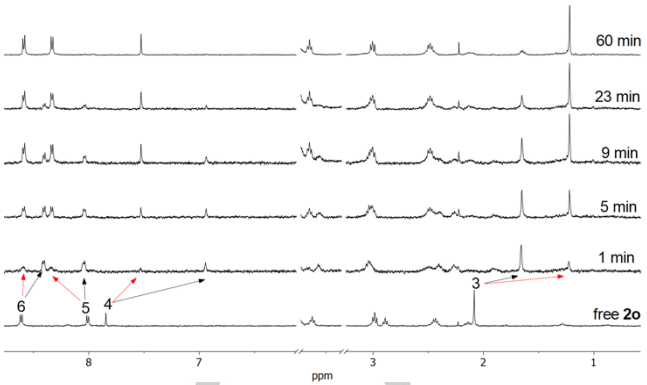


Figure 3 – ^{1}H NMR spectra of **2o** before (810 μM) and after (740 μM) mixing with excess CB8 in D_2O at different time intervals. The arrows highlight the observed complexation-induced chemical shifts for the kinetic (black) and thermodynamic (red) **2o**:CB8 host-guest complexes.

^{1}H NMR experiments (Figure 3) acquired ca. 1 min after mixing **2o** with an excess of CB8, allowed the detection of the transiently formed kinetic product showing complexation-induced upfield shifts compatible with the deep inclusion of the DTE unit into the CB8 cavity. At the equilibrium (reached after 60 min), the observed ^{1}H NMR spectrum of the thermodynamically stable complex suggests a pseudorotaxane structure in the regular antiparallel conformation in which the DTE unit is also enclosed into the host cavity, similarly to what was previously reported for **1o**.[48] Noteworthy, while for the kinetic product the signal assigned to thiophene protons *4* is the one showing the largest upfield shift, for the more stable pseudorotaxane product, the largest upfield shift is observed for methyl protons *3*. This agrees with the proposed structure for **2**o in the kinetic product wherein each thiophene proton *4* faces the other thiophene ring deep inside the CB8 cavity and the methyl groups face the walls closer to the portals. The opposite situation holds for the thermodynamic product as the complexation-induced shifts are now larger for the methyl protons. It must also be mentioned that a small amount of metastable complex (< 10%) can be detected at the final equilibrium on account of the fact that the binding constant for the stable species is only ≈ 20-fold higher than the one of the metastable species.

Based on the mechanism proposed in Scheme 2, the steady-state approximation can be applied for both free **2o** and CB8 allowing the derivation of equation 1 (see Supporting Information). This expression accounts for the formation of the thermodynamically stable complex (TP) from the kinetic product (KP) through first order kinetics with a k_{obs} that is independent of the CB8 concentration, as experimentally observed. Considering that, according to equation 1, the k_{obs} for the formation of the thermodynamically stable complex is $k_{obs} = (k_{out}k'_{in}+k_{in}k'_{out})/(k_{in}+k'_{in}) = 1.8\times10^{-3}$ s^{-1} and that k'_{in}, k_{out} and k'_{out} were previously determined, a value of $k_{in} = 3.0\times10^3$ M^{-1}s^{-1} was calculated. This value can be combined with k_{out} to afford $K_{2o} = k_{in}/k_{out} = 1.9\times10^7$ M^{-1}, in reasonable agreement with the value obtained from the competitive titration (see above) and thus supporting the proposed mechanism.

$$[TP] = \frac{k_{in}k'_{out}[KP]_0}{(k_{out}k'_{in} + k_{in}k'_{out})}\left(1 - e^{-\frac{(k_{out}k'_{in}+k_{in}k'_{out})}{k'_{in}+k_{in}}t}\right) \quad (1)$$

As previously mentioned, **2o** can be quantitatively converted into **2c** upon light irradiation allowing the investigation of its complexation kinetics and thermodynamics with CB8. As can be observed in Figure 4a, the UV-Vis host-guest titration of **2c** with CB8 is compatible with the formation of 1:1 complex with a high affinity constant (K_{2c} > 1×10^7 M^{-1}). The accurate determination of K_{2c} by competition experiments was precluded by the slow thermal ring opening of free **2c** into **2o** ($t_{1/2}$ = 1356 hours at 23 ºC, see Supporting Information) which results in partial disappearance of **2c** before complete dissociation of the complex. Nevertheless, as the thermal cycloreversion is inhibited in the **2c**:CB8 complex (see Supporting Information), the dissociation rate constant could be obtained by the initial rate method (see Supporting Information), leading to a value of k_{out} = 1.8×10^{-6} s^{-1} ($t_{1/2}$ = 107 hours) that is approximately two orders of magnitude slower than the one observed for the open form **2o** ($t_{1/2}$ = 1.2 hours). The apparent kinetics for the formation of the **2c**:CB8 pseudorotaxane complex showed that for this species the equilibrium is reached faster and thus its monitorization was performed by stopped-flow (Figure 4b). The kinetic data reported in Figure 4b was globally fitted to a second order rate equation to give a complexation rate constant for **2c** with CB8 of k_{in} = 4.9×10^3 M^{-1} s^{-1} (due to the very slow dissociation rate constant, the complexation was assumed to be irreversible). From the ratio of the complexation and dissociation rate constants, a nanomolar binding constant of K_{2c} = k_{in}/k_{out} = 2.7×10^9 M^{-1} was determined which is, as also observed for **2o**, only slightly lower than that observed for the dicationic analogue **1c**.[48]

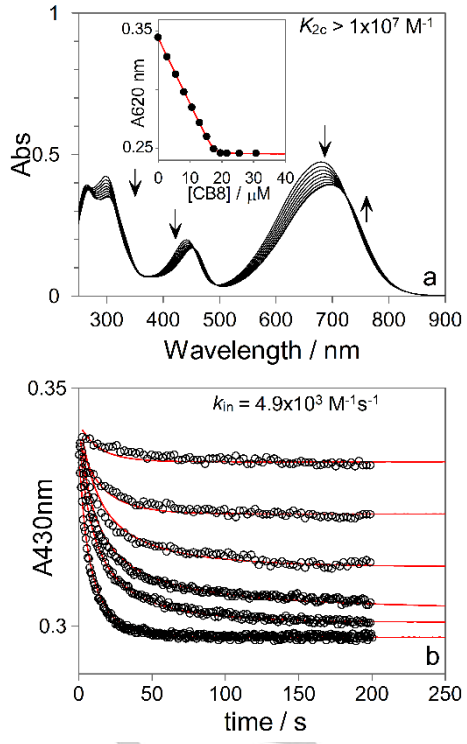


Figure 4 – (**a**) UV-Vis spectra of **2c** (18 μM) with different concentrations of CB8. All spectra were acquired 5 minutes after mixing to allow equilibration. (**b**) Observed stopped-flow kinetic traces (UV-Vis at 430 nm) after mixing **2c** (20 μM) with 3.4, 6.8, 13, 16, 19 and 30 μM of CB8 in pure water. Due to photochemical interconversions induced by the analyzing Xe lamp of this equipment, the kinetics where monitored at 430nm using a band-pass filter which significantly reduced the light absorption and consequently the photoinduced ring-opening of 2c during the complexation timescale.

In order to compare the binding kinetics of **1** towards CB8 with those observed for **2**, the complexation of both **1o** and **1c** with CB8 were firstly investigated but their kinetics were found to be faster than our stopped-flow mixing time (≈ 2 to 3 ms). Therefore, we attempted the measurement of the dissociation rate constants (k_{out}) using 1-adamantylammonium as competitor guest. These kinetics were found to be slow enough to be measured by stopped-flow and fitting the data to a first-order rate equation leads to values of k_{out} = 35 s^{-1} and 0.39 s^{-1} for the dissociation of the **1o**:CB8 and **1c**:CB8 complexes respectively (see Supporting Information). Then, using these values together with the previously reported binding constants,[48] k_{in} values can be calculated. The calculated k_{in} values are ≈ 2×10^9 M^{-1} s^{-1} for both **1o** and **1c**, approaching the diffusion-controlled limit (k_{diff} = 7.4×10^9 M^{-1} s^{-1} at 25 ºC)[51] and showing that the activation energy is similar for both isomers. The kinetic and thermodynamic data obtained for the complexation of **1** and **2** in their closed and open forms with CB8 are summarized in Table 1 and in Scheme 3.

Table 1. Equilibrium constants (K / M^{-1}), Gibbs free energy (ΔG / kJ.mol^{-1})[a], rate constants (k_{in} / M^{-1} s^{-1} and k_{out} / s^{-1}) and Gibbs energy of activation ($\Delta G^{\ddagger}$ / kJ.mol^{-1})[b] for the complexation of the open (**o**) and closed (**c**) isomers of the water-soluble dithienylethenes **1** and **2** with CB8. T = 23 ºC.

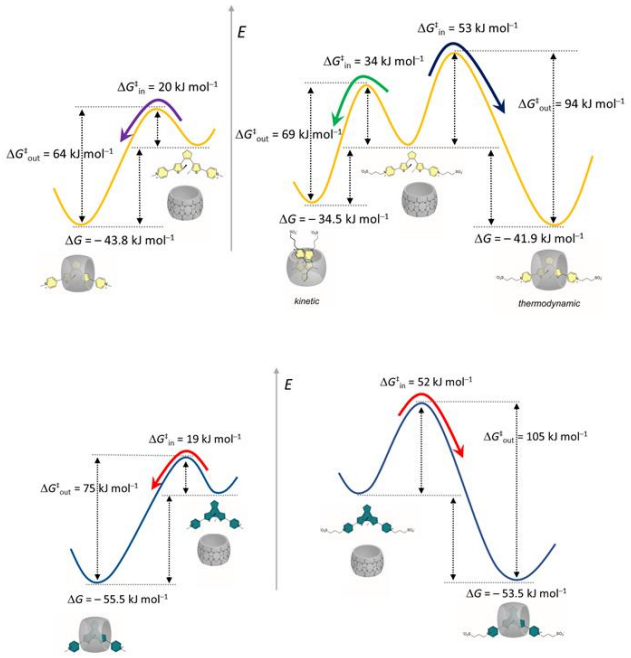
	K	ΔG	k_{in}	$\Delta G^{\ddagger}_{in}$	k_{out}	$\Delta G^{\ddagger}_{out}$
1o	5.4×10^7[c]	−43.8	1.9×10^9	19.9	35	63.8
1c	6.2×10^9[c]	−55.5	2.4×10^9	19.3	0.39	74.8
2o(KP)[d]	1.2×10^6	−34.5	7.0×10^6	33.7	3.9	69.2
2o(TP)[d]	2.5×10^7	−41.9	3.0×10^3	52.8	1.6×10^{-4}	94.1
2c	2.7×10^9	−53.5	4.9×10^3	51.6	1.8×10^{-6}	105.1

[a] Calculated from $\Delta G = -RT\ln K$, where R is the gas constant and T the absolute temperature. [b] Calculated using the Eyring–Polanyi equation assuming the transmission coefficient equal to 1. [c] K values from reference [48]. [d] KP = kinetic product and TP = thermodynamic product.

From the analysis of the kinetic data reported in Table 1 some conclusions emerge: for both **1** and **2**, the k_{in} values for the formation of CB8-inclusion complexes with the open and closed forms are very similar, showing that in these cases the preorganization of the guest presents a roughly negligible effect on the complexation rate constants. On the other hand, the electrostatic barrier imposed by the sulfonate groups in **2** results in a very significant decrease of the association rate constants of approximately 6 orders of magnitude (from ≈ 10^9 M^{-1} s^{-1} to ≈ 10^3 M^{-1} s^{-1}). From the differences between the Gibbs energy of activation for **1** ($\Delta G^{\ddagger}$ ≈ 20 kJ.mol^{-1}) and **2** ($\Delta G^{\ddagger}$ ≈ 50 kJ.mol^{-1}) one can estimate a $\Delta\Delta G^{\ddagger}$ ≈ 30 kJ.mol^{-1} barrier to thread the sulfonate groups throughout the CB8 cavity that is independent of the guest structure (i.e. open vs closed).

The comparison between the obtained k_{in} for the formation of the complex with **1o** ($\Delta G^{\ddagger}$ ≈ 20 kJ.mol^{-1}) in the regular antiparallel conformation and the metastable **2o** in the *twisted* antiparallel/parallel conformation ($\Delta G^{\ddagger}$ ≈ 34 kJ.mol^{-1}) is also worth of note. Although in the latter case the sulfonate groups are not threaded through the CB8 cavity, its k_{in} is considerably lower than that observed for **1o**. This can be tentatively ascribed to an activation penalty assigned to the conformational rearrangement required to set the molecule in this more constrained high energy

conformation and to the higher bulkiness imposed by the simultaneous inclusion of two thiophene rings.



Scheme 3 – Energy landscapes for the complexation of open (top) and closed (bottom) isomers of **1** and **2** with CB8.

The obtained values of k_{out} for **1** and **2** reveal again differences of more than 5 orders of magnitude that are ascribed to the presence the sulfonate groups which impose an electrostatic repulsion effect that increases the activation barrier for the dissociation of the complexes providing them with kinetic stability. It must be also noted that the activation energy difference between **1** and **2**, for the respective isomers, is again $\Delta\Delta G^{\ddagger} \approx 30$ kJ.mol^{-1}, as would be expected based on the principle of microscopic reversibility. Finally, the difference between the activation energies for the complexation and dissociation processes equals the Gibbs free energy of binding ($\Delta G^{\ddagger}_{in} - \Delta G^{\ddagger}_{out} = \Delta G$) showing that the increased barrier for dissociation of the closed isomer arises from the increased thermodynamic stability of the complexes formed between CB8 and these isomers (i.e. the absolute energy of the transition state is similar for both isomers).

Conclusion

In this work we demonstrate that the rate constants for the association/dissociation of the host-guest complex formed between the zwitterionic DTE **2** and CB8 are 100000-fold slower than the ones observed for the dicationic analog **1** due to the electrostatic barrier imposed by the repulsive interactions between the carbonyl portals of the host and the sulfonate groups of **2**. As a result of the slow ingression rate constants for the formation of the pseudorotaxane host-guest complex, which requires the threading of a sulfonate group through the cavity of the macrocycle, a competitive kinetic product was observed as a result of the complexation of **2o** in a *twisted* antiparallel/parallel conformation. This species, that forms in the subsecond timescale, evolves to the thermodynamically stable pseudorotaxane host-guest complex formed between CB8 and **2o** in the more common antiparallel conformation. Contrary to **2o**, the closed and more conformationally constrained **2c** guest seems to follow a simple threading mechanism to give the respective pseudorotaxane. As previously observed for **1**, the host-guest complex formed between **2c** and CB8 is approximately two orders of magnitude more stable than that formed with **2o**. In addition, this thermodynamic stability extends into the kinetics leading to significantly slower host-guest dissociation rate constants for **1c** ($t_{1/2}$ = 1.8 s) / **2c** ($t_{1/2}$ = 107 hours) than those observed for the **1o** ($t_{1/2}$ = 0.02 s) / **2o** ($t_{1/2}$ = 1.2 hours), opening the possibility to control the kinetic and thermodynamic stabilities of the resulting host-guest complexes using light stimuli. This may be of high interest for the new generation of water-soluble/water compatible molecular machines that operate in out-of-the equilibrium conditions and for the development of new supramolecular drug-delivery constructs that resist to dilution and competitive conditions that may be found in biological media.[52,53]

Acknowledgements

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Keywords: Kinetics • Supramolecular Chemistry • Photochemistry • Diarylethenes • Inclusion Complexes

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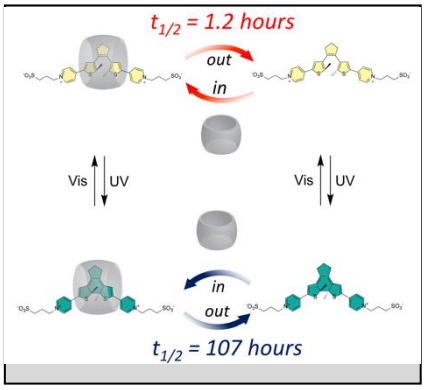

Kinetic studies on host-guest systems based on cucurbit[8]uril and dithienylethene (DTE) photoswitches shows that the more tightly bound closed DTE isomers are kinetically more stable that their open counterparts. This allows for the modulation of their binding dynamics with light stimulus constituting an attractive tool for the development of out of the equilibrium supramolecular systems.