A Dynamic and Responsive Host in Action: Light-Controlled Molecular Encapsulation

Seán T. J. Ryan‡, Jesús del Barrio‡, Reynier Suardíaz, Daniel F. Ryan, Edina Rosta, Oren A. Scherman *

Abstract: The rational design of a flexible molecular box, oAzoBox‡‡, incorporating both photochromic and supramolecular recognition motifs is described. We exploit the E→Z photoisomerization properties of azobenzenes to alter the shape of the cavity of the macrocycle upon absorption of light. Imidizolium motifs are utilized as hydrogen bonding donor components, allowing for sequestration of small molecule guests in acetonitrile. Upon E→Z photoisomerization of oAzoBox‡‡, the guest is expelled from the macrocyclic cavity.

The encapsulation and active release of molecular species comprise an area of research that attracts constant attention and crosses both academic and industrial research interests, as encapsulation processes are ubiquitous in product synthesis and formulation.[1,2] One particular encapsulation strategy consists of the selective inclusion of guest compounds within the cavities of discrete, shape-persistent macrocycles and has been applied to the solubilization and/or stabilization of active ingredients and hazardous materials, sensing, separation and purification technologies.[3-9]

Owing to their dynamic nature, binding events in host-guest complexes can be controlled by a range of different stimuli. However, in spite of the many examples of non-covalent complexation, our ability to alter the interaction between a host and its guests is usually limited to invasive actions, such as the addition of strongly competing guest compounds or pH/redox switching.[10,11] Ideal triggering mechanisms should enable remote control over guest uptake-and-release in a well-defined spatiotemporal fashion by a practical and easily-operated stimulus, such as light. Indeed, the concept of photocontrolled uptake-and-release of guest species has been achieved by exploiting light-responsive guests and, less frequently, host species.[12-14]

Figure 1. Chemical structure of oAzoBox‡‡ (a), its synthesis (b) and small molecule guests used in this study (c).

A few groups have provided examples of both strategies by controlling the dynamic encapsulation properties of cyclodextrins, calixarenes, cucurbiturils, metal-organic cages and other systems with molecular switches, either appended to the host or as a guest molecule.[15-26] Systems which rely on the rearrangement or isomerization of a guest compound have a relatively limited scope of applicability. In our view, light-switchable molecular containers may impact a much wider spectrum of technological applications. However, they also suffer from undesirable drawbacks, such as cumbersome synthesis and hindered isomerisation properties by ring strain and molecular crowding.[37]
We report, here, the synthesis of oAzoBox$^{4+}$ (Figure 1), a photoresponsive molecular box produced by a facile 3-step synthetic procedure. We have made use of two o-xylene-bridged bis(imidazolium)-azobenzene motifs to impart both light-responsiveness and receptor-like$^{[28,29]}$ properties to our macrocycle. In contrast to the rigid structure of more conventional azobenzene-containing macrocycles,$^{[27,30]}$ oAzoBox$^{4+}$ exhibits a large and flexible architecture, which has two consequences: Firstly, the photochromic properties of oAzoBox$^{4+}$ are largely unaffected in comparison to model compound, AzoBi$^{2+}$ (Figure 1), by the embedment of the photoswitches in a cyclic architecture and secondly, its high flexibility is not detrimental to its recognition abilities. Therefore, oAzoBox$^{4+}$ is ideal for the realization of light-controlled catch-and-release in solution.

AzoBi$^{2+}$ was synthesized according to Figure 1b. Firstly, the reduction of commercially available 4-nitrobenzyl alcohol and subsequent reaction with CDI yielded intermediate 2. Cyclization of 2 with an equimolar amount of α,α′-dibromo-o-xylene, followed by salt metathesis, afforded oAzoBox 4BF$_3$ in approximately 25% yield after purification by recrystallization. The solid state structure (Figure 2) reveals that oAzoBox$^{4+}$ is substantially elongated, with a length of 21.05 Å, as measured by the distance between the centroids of the o-xylene bridges. The breadth of the box, measured as the average distance between the planes of the two sets of parallel azobenzene phenyl units, was found as 4.3 Å, affording an aspect ratio of approximately 5.

The photoisomerization properties of model azobenzene, AzoBi$^{2+}$, were first examined by electronic absorption spectroscopy. AzoBi$^{2+}$ (Figure S1) exhibits a characteristic strong π-π* absorption band at short wavelengths ($\lambda_{\text{max}} = 321$ nm) and a weaker n-π* absorption band at longer wavelengths ($\lambda_{\text{max}} = 445$ nm). Upon UV light irradiation (350 nm), the intensity of the band corresponding to the π-π* transition strongly decreased, whereas that of the n-π* transition slightly increased. These spectroscopic changes can be directly ascribed to the E→Z photoisomerization, which can be reverted using visible light (420 nm). The electronic absorption spectrum of oAzoBox$^{4+}$ matches that of AzoBi$^{2+}$. The spectral changes associated to the $E\rightarrow Z$ photoisomerization of oAzoBox$^{4+}$ are analogous to those of AzoBi$^{2+}$. Therefore, it was estimated that the $E\leftrightarrow Z$ photoisomerization behaviors of AzoBi$^{2+}$ and oAzoBox$^{4+}$ should closely resemble one another.

The $^1$H NMR spectrum of a freshly prepared solution of oAzoBox$^{4+}$ (Figure 3c) shows nine distinct resonances, which are consistent with the all-trans E,E-oAzoBox$^{4+}$ stereoisomer. When a solution of E,E-oAzoBox$^{4+}$ is irradiated with UV light, a new set of signals arises, which evidences the generation of an isomeric mixture of multiple components. The new aliphatic signals in the 5.00-5.50 ppm region are shifted upfield relative to the H$_{\text{α}}$ proton resonance of E,E-oAzoBox$^{4+}$, which is consistent with the changes associated to the E→Z AzoBi$^{2+}$ photoisomerization. Furthermore, the intensity of the H$_{\text{α}}$ proton resonance of E,E-oAzoBox$^{4+}$ decreases and three additional sharp and well-resolved resonances, which are associated to the same type of H$_{\text{α}}$ resonance, appear at 7.95, 6.88 and 6.75 ppm. In combination, these results suggest that the UV light promoted E→Z isomerization generates a mixture of three distinct stereoisomers which, at the photostationary state, can be identified as E,E-oAzoBox$^{4+}$ (18%), E.Z-oAzoBox$^{4+}$ (38%) and Z.Z-oAzoBox$^{4+}$ (44%). The complete assignment of all proton resonances of each individual stereoisomer was achieved using two-dimensional COSY and ROESY $^1$H NMR (Figures S3-S10). Irradiation with visible light largely restores the initial spectrum, which parallels our electronic absorption spectroscopy results (E,E-oAzoBox$^{4+}$: 64%, E.Z-oAzoBox$^{4+}$: 28% and Z.Z-oAzoBox$^{4+}$: 9%). Smooth cycling between the two E- and Z-predominant states was demonstrated without any noticeable degradation (Figure S11).

Thermal relaxation of the Z-predominant oAzoBox$^{4+}$, via the stepwise pathway outlined in Figure 15, was monitored by thermal array $^1$H NMR at 313, 318, 323 and 328 K, as their stabilities are important considerations with regard to the potential of oAzoBox$^{4+}$ to act as a photoswitchable
molecular container. Fitting the data to the appropriate kinetic models (equations S4-S7) and the Eyring equation (equations S8-S9) allowed extraction of the rate constants $k_1$ and $k_2$ and the thermodynamic parameters $\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ (Table 1, Figures S16-S34, Tables S1-S8).

<table>
<thead>
<tr>
<th>Switching Species</th>
<th>$\Delta G^\ddagger$ kcal mol$^{-1}$</th>
<th>$\Delta H^\ddagger$ kcal mol$^{-1}$</th>
<th>$\Delta S^\ddagger$ kcal mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z^--E,E$-oAzoBox$^{4+}$</td>
<td>19.23 ± 1.06</td>
<td>22.46 ± 0.31</td>
<td>11.01 ± 0.97</td>
</tr>
<tr>
<td>$E,E$-oAzoBox$^{4+}$</td>
<td>22.24 ± 4.53</td>
<td>23.85 ± 2.30</td>
<td>5.48 ± 7.85</td>
</tr>
<tr>
<td>$Z^--3$-AzoBI$^{4+}$</td>
<td>19.66 ± 4.2</td>
<td>22.66 ± 1.21</td>
<td>9.55 ± 3.77</td>
</tr>
</tbody>
</table>

The activation energy barrier ($\Delta G^\ddagger$) of $ZZ$-oAzoBox$^{4+}$→$E,Z$-oAzoBox$^{4+}$ is very similar to that of $Z$-AzoBI$^{4+}$→$E$-AzoBI$^{4+}$ at 293 K (Figures S24, S34). $\Delta G^\ddagger$ of $E,Z$-oAzoBox$^{4+}$→$E,E$-oAzoBox$^{4+}$ is slightly higher at 22.24 kcal mol$^{-1}$ (Figure S25), likely on account of the length disparity of $E$ and $Z$ azobenzene. The magnitudes of the $\Delta G^\ddagger$ values were corroborated by computational studies (Tables S9-S10).

DFT calculations (B3LYP-D3(BJ)/TZVP, Figure S41) revealed that the lowest energy molecular configuration of $ZZ$-oAzoBox$^{4+}$ is 10.97 kcal mol$^{-1}$ greater than that of $E,Z$-oAzoBox$^{4+}$, which is in turn 14.43 kcal mol$^{-1}$ greater than that of $E,E$-oAzoBox$^{4+}$. Such a result, combined with the similarity of the $\Delta G^\ddagger$ values (Tables 1), indicates that ring strain$^{[3]}$ does not play a significant role in affecting the thermal isomerization mechanism for oAzoBox$^{4+}$.

Figure 4. High resolution mass spectrometry of $E,E$-oAzoBox$^{4+}$→4DPDO (average values: $x = 0.2507$, $y = 0.3338$) (a). Global fit by non-linear regression of the $^1$H NMR shifts of the $H\alpha$, $H\beta$, $H\gamma$ and $H\eta$ resonances to a 1:1 binding model$^{[32]}$ (b).

The large size of $E,E$-oAzoBox$^{4+}$ led us to consider whether small organic guest compounds could be accommodated within the cavity of the macrocycle. The representative compounds, 2,2'-dipropyl N,N'-dioxide (2DPDO), 4,4'-dipropyl N,N'-dioxide (4DPDO), 4-phenylpyridine N-oxide (PPO) and biphenyl-4,4'-dicarboxylate (BPDC) were chosen to test the interaction of $E,E$-oAzoBox$^{4+}$ with hydrogen bond acceptor aromatic structures (Figure 1c). $^1$H NMR revealed a binding interaction between $E,E$-oAzoBox$^{4+}$ with 4DPDO, PPO and BPDC (Figures 3b, S36-S37). However, no interaction was detected between $E,E$-oAzoBox$^{4+}$ with 2DPDO, presumably on account of steric effects. All cases of binding exhibited upfield shift perturbations of the aromatic resonances, $H\alpha$ and $H\beta$, whereas proton resonances $H\gamma$-shifted downfield. The encapsulated guest proton resonances shifted upfield on account of the shielding by the azobenzene moieties at the long sides of $E,E$-oAzoBox$^{4+}$.

$4$DPDO was selected as a representative example to illustrate the encapsulation potential of $E,E$-oAzoBox$^{4+}$ in acetonitrile. A $^1$H NMR titration of $4$DPDO into $E,E$-oAzoBox$^{4+}$ provided an association constant on the order of $10^3$ M$^{-1}$ (Figure 4) corresponding to an association free energy of $\sim -4$ kcal mol$^{-1}$, which is consistent with the computationally obtained value of $-4.06$ kcal mol$^{-1}$ (see SI). The formation of $E,E$-oAzoBox$^{4+}$→4DPDO was also confirmed by mass spectrometry (Figures 4a, S38). A control $^1$H NMR experiment, whereby 4DPDO was mixed with an equimolar amount of $E,Azo$Box$^{4+}$, showed no evidence of interaction, suggesting that macrocyclic preorganization is a requirement for strong binding in our system (Figure S13). Similar conclusions were obtained from an analogous experiment with 4DPDO and $\alpha,\alpha'$-bis[3-(1-methylimidazolium)]-o-xylene, a model subcomponent analogue of the o-xylene bridging unit of oAzoBox$^{4+}$ (Figure S14).

The inclusion geometry assigned to the bimolecular complex was corroborated by quantum mechanical calculations (Figure 2). The energy minimized structure of $E,E$-oAzoBox$^{4+}$→4DPDO shows that the container adopts a cage-like conformation with the phenyl rings of the azobenzene moieties lying in parallel planes and the 4DPDO guest included in the cavity of the macrocycle. Each of the oxygen atoms of the guest are hydrogen bonded to two of the four of acidic $H\delta$ protons in an approximately symmetric fashion (Figure S42). This interpretation of the binding is supported by the significant downfield shift of the $H\delta$ proton resonance and a series of $^1$H NMR titration experiments (see SI). Calculations also reveal that the macrocycle adopts a significantly expanded conformation in comparison to that of the solid state structure upon guest sequestration with an appreciably reduced aspect ratio of $\sim 3$. Similar conclusions were also established by quantum mechanical calculations for $E,E$-oAzoBox$^{4+}$→BPDC (Figure S46).

Exposure of $E,E$-oAzoBox$^{4+}$→4DPDO to UV light induces the $E$→$Z$ isomerization of the host and the release of 4DPDO, evidenced by the downfield shift of the $H\eta$ and $H\phi$ resonances (Figures 5, S51). This result can be rationalized by assuming the 4DPDO affinity of $E,Z$-oAzoBox$^{4+}$ and $ZZ$-oAzoBox$^{4+}$ is negligible in comparison to that of $E,E$-oAzoBox$^{4+}$. Indeed, when excess 4DPDO was added into a $Z$-predominant oAzoBox$^{4+}$ isomeric mixture, no evidence of interaction was detected between $ZZ$-oAzoBox$^{4+}$ and the guest molecule (unperturbed $ZZ$-$H\alpha$ resonances) and only extremely limited interaction was observed for $E,Z$-oAzoBox$^{4+}$ (Figures 3d and 3e). An attempt to quantify the 4DPDO affinity of the $E,Z$ stereoisomers was unsuccessful on account of the limited interaction between the guest and the host after UV light irradiation. In any event, irradiating the mixture with visible light reverses the system back to the $E,E$-oAzoBox$^{4+}$→4DPDO enriched state.
The thermal stability of Z-predominant oAzoBox\(^{4+}\) was unaffected by the presence of 4DPDO (Figure S35). The low 4DPDO affinity of E,Z-oAzoBox\(^{4+}\) and Z,Z-oAzoBox\(^{4+}\) can be attributed to a significant decrease in the size of the cavity of the macrocycle. Additionally, favorable orientation of the acidic H\(\delta\) protons towards the interior of the cavity is lost upon UV light irradiation, and consequently the possibility of establishing concerted hydrogen bonding interactions between the host and guest. This was supported by calculated structures of E,Z-oAzoBox\(^{4+}\) and Z,Z-oAzoBox\(^{4+}\) (Figures S39-S40) and the high energy levels associated with the putative E,Z-oAzoBox\(^{4+}\)⊂4DPDO and Z,Z-oAzoBox\(^{4+}\)⊂4DPDO complexes (Figures S43-S45). The concept of photocontrolled catch-and-release was also demonstrated for BPDC (Figure S37).

In conclusion, we have demonstrated how the photochromic macrocycle, oAzoBox\(^{4+}\), may be synthesized in three simple steps and allows for the realization of the remote controlled catch-and-release concept mediated by a photo-switchable molecular container. Our work illustrates how the incorporation of photochromic switching elements into a flexible macrocyclic framework, which does not compromise light-induced isomerization, can also exhibit relevant recognition properties. These have been achieved by exploiting the hereto unreported complementary hydrogen bonding H-donor imidizolium and H-acceptor N-oxide pairs, as well as the H-acceptor carboxylate. The incorporation of molecular switches into optimized organic container structures may be regarded as a general approach to regulate encapsulation, in a non-invasive fashion, of selected molecular species.

Such a strategy may also be used as a supramolecular host-guest logic system, as distinct switching between stereoisomeric mixtures may be achieved, where the predominant components posses association constants separated by orders of magnitude.

References


Entry for the Table of Contents (Please choose one layout only)

Layout 1:

**Catch Phrase:**

Author(s), Corresponding Author(s)*

**Title Text**

((The TOC Graphic should not exceed the size of this area))

Text for Table of Contents, max. 450 characters.

Layout 2:

**Photoinduced release**

Seán T. J. Ryan‡, Jesús del Barrio‡, Reynier Suárez, Daniel F. Ryan, Edina Rosta, Oren A. Scherman

A Dynamic and Responsive Host in Action: Light-Controlled Molecular Encapsulation

One ring to rule them all... and in the darkness bind them. A photoresponsive tetracationic macrocycle features a facile 3-step synthesis and allows for the non-covalent binding of a set of guest molecules, including N-oxide and carboxylate derivatives. These can be actively released by UV light irradiation in a remote fashion.