Host–Guest Chemistry

Photorelease of an Organic Molecule in Solution: Light-Triggered Blockage of a Hydrogen-Bonding Receptor Site**

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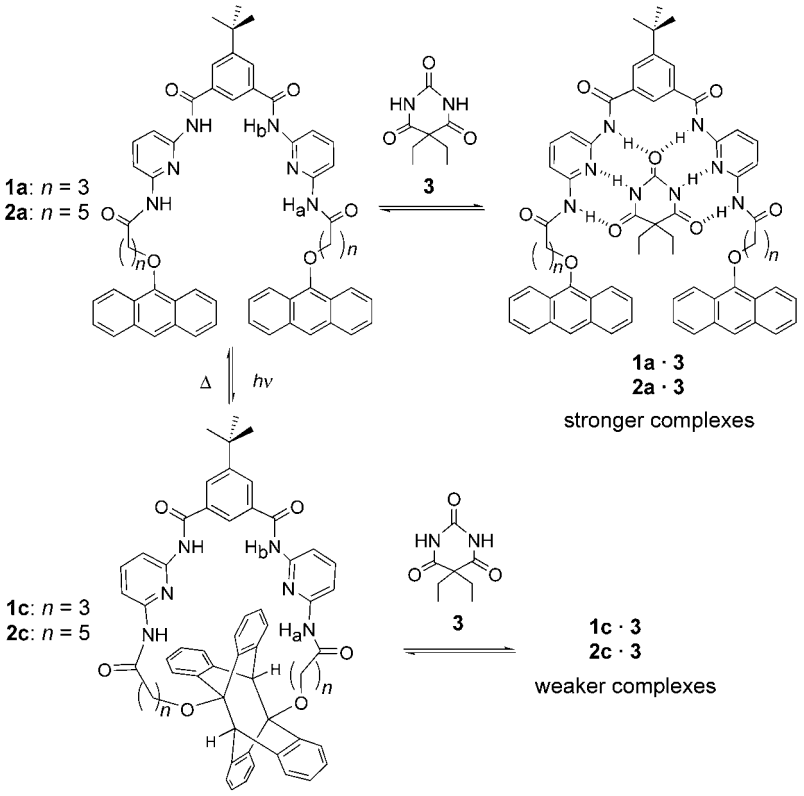
The selective recognition of a guest by a molecular host is a fundamental process whose understanding has led to the design of systems that are capable of controlled associative/dissociative behavior.[1] Such systems rely on an external physical or chemical stimulus to modulate reversible intermolecular forces that are responsible for the association of two or more species, and they are ubiquitous to all living organisms, wherein they play a vital role in complex signal-transmission, regulation, and amplification processes. There are now several examples of receptor molecules that contain photoresponsive units for which the strength of a binding interaction with a particular guest species in solution can be controlled by light.[2] The vast majority of these receptors rely on a photochromic auxiliary to impart a light-induced structural modification of a crown-ether-like cavity. Although the flexibility of the crown ether units facilitates the modulation of their binding properties, such systems have so far been focused on the binding of metal ions, whereas reports of photoresponsive receptors that bind organic species through multiple hydrogen-bonding interactions are rare.[2e,3]

Herein, we demonstrate how light controls the binding affinity of a hydrogen-bonding receptor towards a neutral organic molecule to such an extent that the bound guest (barbital) is effectively released upon photoirradiation.

Receptors **1a** and **2a** (Scheme 1; **a** denotes acyclic) were synthesized through a five-step reaction pathway starting from anthrone and were fully characterized (see Supporting Information).[4] Each receptor was designed to contain two



Scheme 1. Receptors **1a** and **2a** bind barbital (**3**) strongly in solution; photoirradiation of the receptors gives the macrocycles **1c** and **2c**, which are weaker binders of **3**.

pyridine-2,6-diamide units connected by a phenyl spacer group to generate a motif that has been shown to bind barbital (**3**) strongly in chlorinated solvents through six complementary hydrogen bonds.[5] The binding site was connected by an alkyl spacer group of variable length to two anthracene units, which were expected to undergo the well-characterized and thermally reversible $4\pi+4\pi$ photocycloaddition reaction through an intramolecular pathway[6] to result in a change in the structure of the receptor from acyclic to macrocyclic. Anthracene photodimerization is particularly versatile as it can proceed smoothly in a range of solvents.[6a]

As expected, both receptors **1a** and **2a** bound barbital strongly in chlorinated organic solvents to give complexes of 1:1 stoichiometry as determined by ^{1}H NMR spectroscopy. The addition of one equivalent of **3** to a solution of **1a** in $CDCl_3$ (8.5 mM) induced downfield shifts in the two signals that correspond to the four NH protons of the receptor (from $\delta = 8.04$ to 9.62 ppm for H_a; from $\delta = 8.40$ to 9.88 ppm for H_b). The addition of further amounts of **3** brought about no further significant changes to the spectrum which indicates the

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formation of a strongly bound 1:1 complex. As shown in Figure 1, the addition of **3** to a solution of **2a** in CH_2Cl_2 (2.15×10^{-5} M) did not affect the anthracene ^1L_a absorption band (300–400 nm) in the UV/Vis spectrum of the receptor,[2b] but

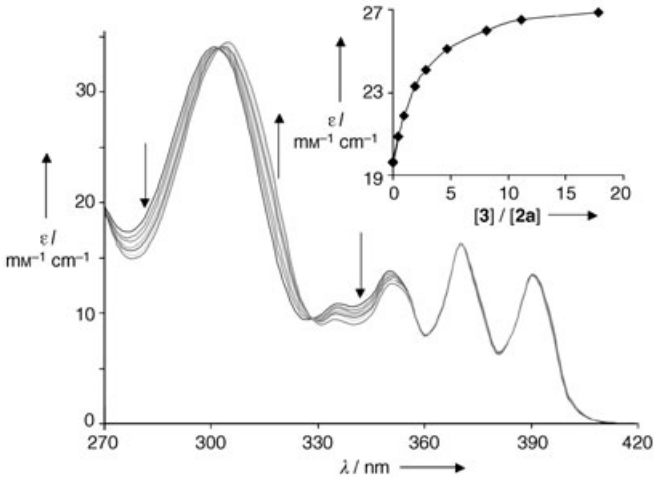

Figure 1. The binding of **3** by receptor **2a** as followed by UV/Vis spectroscopy; [**2a**] = 2.15×10^{-5} M with additions of 0, 0.5, 1, 2, 3, 5, and 8 equivalents of **3**. The inset shows the increase in the observed molar absorption coefficient (ε) at $\lambda = 315$ nm upon addition of **3**.

induced a bathochromic shift in the pyridine band (from $\lambda_{max} = 298$ to 304 nm) which reflects a bonding interaction between the guest and both pyridine units.[7] The binding constants $K = [\text{complex}]/[\text{host}]\times[\mathbf{3}]$ (host = **1a** or **2a**) were determined for each receptor by using the Letagrop program.[8] The values (Table 1) are in the same range as those for previously described acyclic barbiturate receptors in chlorinated solvents.[5a,c]

Table 1: Binding constants for the complexation of barbital (**3**) by the receptors in their acyclic (**1a** and **2a**) and macrocyclic forms (**1c** and **2c**).

	K [M^{-1}]	
Receptor	Acyclic form (**a**)	Cyclic form (**c**)
1	$38\,000\pm2500$[a]	38 ± 6[b]
2	$27\,000\pm3000$[a]	8320 ± 575[a]

[a] Determined by UV/Vis spectroscopy measurements in CH_2Cl_2, receptor concentration $\approx 2\times10^{-5}$ M. [b] Determined by ^{1}H NMR spectroscopy measurements in CD_2Cl_2, receptor concentration = 1.7×10^{-3} M.

Continued irradiation (Hg lamp, lead filter) of solutions of **1a** and **2a** (5×10^{-4} M) in degassed dichloromethane during five hours resulted in the disappearance of the ^1L_a anthracene band in the absorption spectra of the receptors. Upon removal of the solvent, the photodimers **1c** and **2c** (Scheme 1, **c** denotes cyclic) were isolated as air-stable solids in essentially quantitative yield according to the ^{1}H NMR spectra of **2a** in $CDCl_3$ before and after photoirradiation (Figure 2, see Supporting Information for ^{1}H NMR spectra of **1a** and **1c**). The new signal at $\delta = 4.43$ ppm (Figure 2b) corresponds to the two bridgehead protons on the photodimer subunit and

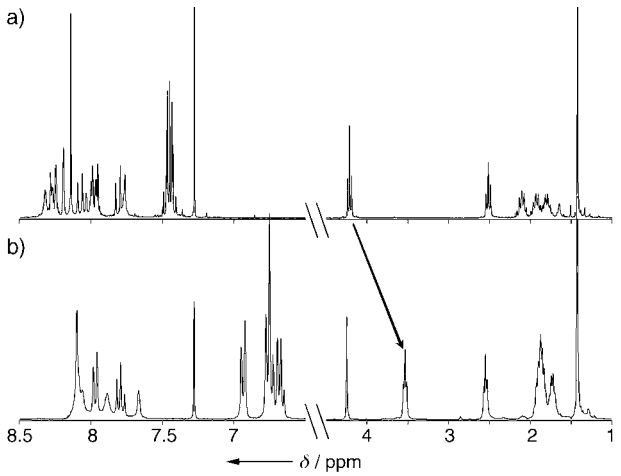

Figure 2. ^{1}H NMR spectra of **2a** in $CDCl_3$ before and after photoirradiation: a) initial spectrum of **2a** and b) spectrum after 5 h (compound **2c**).

confirms the 4π+4π photocycloaddition reaction between the central rings on each anthracene unit.[2b] A close inspection of the ^{1}H NMR spectral pattern for the aromatic resonances of **1c** and **2c** suggests a head-to-tail (HT) structure rather than the anticipated head-to-head (HH) structure.[9] This was confirmed by X-ray diffraction studies of crystals of **1c** and **2c**, which were grown from $CDCl_3$ and THF/hexane, respectively (Figure 3).[10] A plausible explanation is the much lower

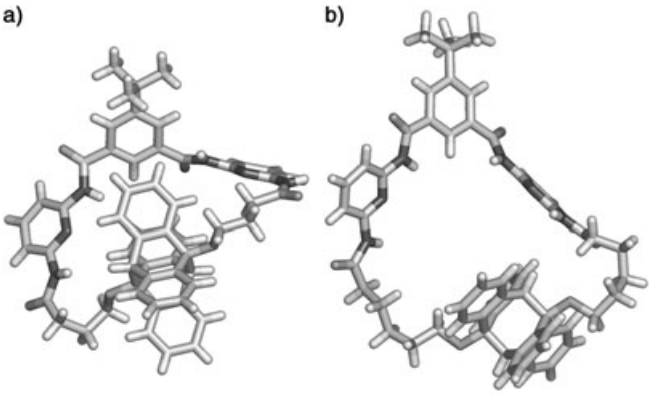

Figure 3. Representations of the head-to-tail structures of a) **1c** (triclinic, space group $P\bar{1}$) and b) **2c** (monoclinic, space group $C2/c$) obtained by X-ray crystallography. Solvent molecules ($CDCl_3$ for **1c** and THF for **2c**) have been omitted for clarity.

thermal stability of 9-alkoxy-substituted anthracene HH photodimers,[6b] which, if formed, would be expected to undergo a relatively rapid thermal retrocyclization reaction to yield the starting materials. In the case of **1c** (Figure 3a), the size and shape of the binding cavity are strongly affected by the four bulky *ortho*-xylene units of the photodimer. Furthermore, one of the four N–H bonds points away from the cavity. In **2c** (Figure 3b), although all six hydrogen-bonding groups point inwards, the binding site is distinctly

nonplanar with an angle of 77.5(2)° between the pyridine planes.

Preliminary studies revealed that **1c** and **2c** are fairly stable at room temperature (as usually observed for HT anthracene photodimers[6b]), but can be switched back to the starting materials (open form) upon gentle heating (e.g., after heating a solution of **1c** in toluene at $\approx 80\,^{\circ}C$ for two days, $\geq 90\,\%$ of the starting material **1a** was regenerated).

To assess the photoswitched binding behavior of these systems, the binding of barbital by the two photoproducts was evaluated by ^1H NMR spectroscopy (**1c**) and by UV/Vis spectroscopy (**2c**). It was immediately apparent that the binding between **3** and **1c** was much weaker than with its acyclic counterpart because in contrast to **1a**, a large excess of guest was required to bring about significant changes to the NMR spectra. Figure 4 depicts the aromatic and aliphatic

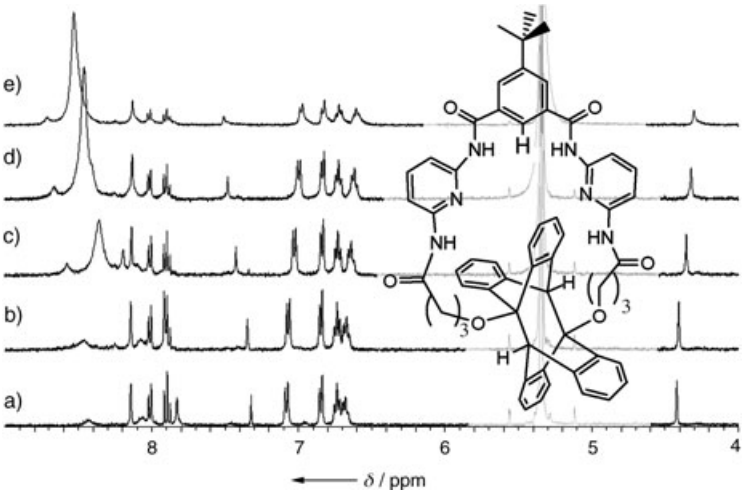

Figure 4. Evolution of the ^1H NMR spectrum of **1c** in CD_2Cl_2 upon addition of **3**. [**1c**] = 1.7×10^{-3} M and remains constant during the titration. a) **1c**, b) [**3**]/[**1c**] = 1, c) [**3**]/[**1c**] = 6, d) [**3**]/[**1c**] = 11, and e) [**3**]/[**1c**] = 15.

regions of the ^1H NMR spectra of **1c** in CD_2Cl_2 (1.7 mM) in the presence of increasing amounts of **3**. Upon the addition of 15 equivalents of barbital, changes were observed in the signals for the protons of the photoadduct: the bridgehead protons moved upfield from $\delta = 4.42$ to 4.29 ppm, the proton at C-2 of the isophthaloyl group shifted from $\delta = 7.32$ to 7.52 ppm, and the amide protons H_a and H_b (see Scheme 1) underwent relatively small downfield shifts (H_a: from $\delta = 7.82$ to 8.56 ppm), which is consistent with a weak hydrogen-bonding interaction. The binding constant for a 1:1 complex was calculated from the chemical shift values for proton H_a by using the EQNMR program.[11] The value obtained ($K = 38\,M^{-1}$, Table 1) confirms that photodimerization of **1a** dramatically affects the ability of **1c** to form a strong complex with barbital, with an approximately 1000-fold decrease observed in the binding constant. An explanation for this change can be obtained from the X-ray crystal structure of **1c** (Figure 3a), which clearly shows that it is impossible for the receptor to accommodate barbital within its cavity. Instead, it is likely that, at any one time, only one side of the guest is weakly bound by one pyridinediamide unit, whereas the other unit is blocked by the photoadduct. The value of the binding constant is, in fact, lower than those obtained for unhindered three-point hydrogen-bonding interactions with the pyridine-2,6-diamide motif in chlorinated solvents.[12]

As found for the **1a**/**1c** system, photodimerization of **2a** into **2c** lowers the binding constant with barbital (Table 1), but the decrease is less significant at approximately threefold, with $K_{(2a)}/K_{(2c)} = 3.3 \pm 0.6$. From the crystal structure of **2c** (Figure 3b), it is clear that the longer spacer unit prevents the photoadduct from blocking the cavity and enables the guest to be stabilized by six hydrogen bonds. This was borne out by the ^1H NMR spectra in $CDCl_3$ which indicated relatively large shifts of the signals for the protons H_a and H_b upon addition of approximately one equivalent of barbital (from $\delta = 7.88$ and 8.05 ppm to 9.23 and 9.61 ppm, respectively). The presence of **3** also has a strong influence on the excited-state behavior of **1a** and **2a**. In particular, the observed decrease in the quantum yield for photodimerization (0.07 and 0.07 versus 0.01 and 0.05 for the formation of **1c** and **2c** in the absence and presence of **3**, respectively) probably reflects a lowered photoreactivity of the complexes **1a**·**3** and **2a**·**3**.

Finally, a photoirradiation experiment was performed on the **1a**/**1c** system in the presence of barbital to examine whether photoswitched binding could be observed in situ. A solution of **1a** in CD_2Cl_2 (5×10^{-4} M) which contained 0.95 equivalents of **3** (to ensure that the guest was fully complexed) was continuously irradiated and monitored by ^1H NMR spectroscopy over time (see Supporting Information). The study revealed that the signal for the proton of the imide group of barbital shifted upfield from $\delta = 12.16$ ppm (before irradiation) to $\delta = 9.79$ ppm (after 3 h irradiation). At the same time, the signals for the receptor changed from those of almost fully complexed **1a** (H_a and H_b signals at $\delta = 9.20$ and 9.47 ppm respectively) to those of essentially uncomplexed **1c** (H_a and H_b signals at $\delta = 7.82$ and 8.41 ppm, respectively; signal for the proton at C-2 of the isophthaloyl group at $\delta = 7.31$ ppm). These observations are consistent with the ejection of the guest from the receptor upon photodimerization [Eq. (1)].

$$\mathbf{1a}\cdot\mathbf{3} \xrightarrow{h\nu} \mathbf{1c} + \mathbf{3} \qquad (1)$$

In conclusion, these studies have shown how light can be used to control both the binding and the in situ release of a neutral guest molecule through structural changes to a hydrogen-bonding receptor. The latter, designed to bind barbital and other biologically relevant molecules such as urea derivatives, offers the possibility to photoregulate the release of such species in a reversible manner.

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