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A photoswitchable supramolecular complex with release-and-report capabilities†

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A self-assembled supramolecular platform has been designed for reversibly controlling the concentration of a compound in solution, *via* a photochemical reaction. The system utilizes metal–ligand interactions between a Zn-porphyrin dimer and a pyridine-appended dithienylethene (DTE) photoswitch. In addition to reversible compound release, the spectral properties of the release scaffold provide a fluorescence-based reporting function.

Controlling when and where a substance is released and/or captured has great potential in a wide range of applications, *e.g.* the release of therapeutic compounds, sensing agents, or extraction of hazardous chemicals and pollutants. The unique properties of light sets it aside as a triggering stimulus for applications requiring spatiotemporally well-resolved, waste-free operation.[1] A number of approaches have been investigated in pursuit of light-operated release systems and these efforts have consequently stimulated a rapidly progressing and inventive research field. A majority of the so far reported light-controlled release systems, however, are designed to exhibit irreversible release. This is typically achieved by light-induced cleavage of covalent bonds either directly using photolabile groups/linkers[2] or second-hand by first generating for instance heat.[3] Another well explored approach is the preparation of light-responsive drug loaded materials such as porous materials[4] and/or micro/nanoparticles.[5]

An additional level of control is attained if the photo-release can be made reversible, as it allows for dynamic bidirectional control of the concentration profile in combination with precise timing of the dosage. Realization of such systems typically demands a photoswitchable component capable of interacting non-covalently with a host compound to form a supramolecular complex. There are several examples where this concept has been successfully implemented to manipulate for instance the release of small ions,[6] as well as small molecules[7] in a reversible manner. A particularly elegant example of photoreversible compound release was reported in the recent work by Clever and co-workers in which a photoswitchable coordination cage composed of Pd-coordinating dithienylethenes (DTEs) was shown to reversibly encapsulate inorganic guest molecules in response to light.[7b]

In this work, we report a conceptually different coordination-based approach for compound (capture and) release. Here, the differences in binding mode and binding strength between the two isomeric forms of a pyridine-appended DTE photoswitch (**1**, see Fig. 1) and a porphyrin dimer ($\mathbf{P_2}$) are combined into a self-assembled platform with release-and-report capabilities for lone pair-carrying guest molecules.

Since its discovery, the DTE-backbone has found regular use in photoswitching applications due to its renowned high degree of photoconversion, thermal stability, and resistance to photofatigue.[8] The photoinduced ring-closing (**1o** → **1c**) is achieved with 302 nm UV-light ($\Phi_{o\rightarrow c} = 0.57$)[9] and converts the sample to virtually 100% **1c**. Subsequent visible light exposure ($\lambda > 550$ nm) completely opens the sample to **1o** ($\Phi_{c\rightarrow o} = 0.02$). This switching cycle can be repeated several times without notable photodegradation[10] (see Fig. S3 for absorption spectra of **1**, and ESI† for details on isomerization quantum yield).

Porphyrin macrocycles have been included in numerous molecular and supramolecular constructs as building blocks with fluorescent, sensitizing, and/or energy/electron transfer capabilities.[11] The two porphyrin units constituting the herein used $\mathbf{P_2}$ have a near-barrierless rotation around the central diethyne axis, thus allowing an even distribution of rotamers in the dimer.[12] The aliphatic side chains (Ar and R in Fig. 1) effectively prevent dimer stacking, as no aggregation was detected up to mM concentrations. As for coordination to $\mathbf{P_2}$, the two DTE-isomers **1o** and **1c** are notably different. The ring-closed isomer (**1c**) coordinates axially to one Zn-center in $\mathbf{P_2}$ by donating a pyridine electron lone pair. This complexation occurs in a consecutive 1 : 1 → 1 : 2 manner, with binding

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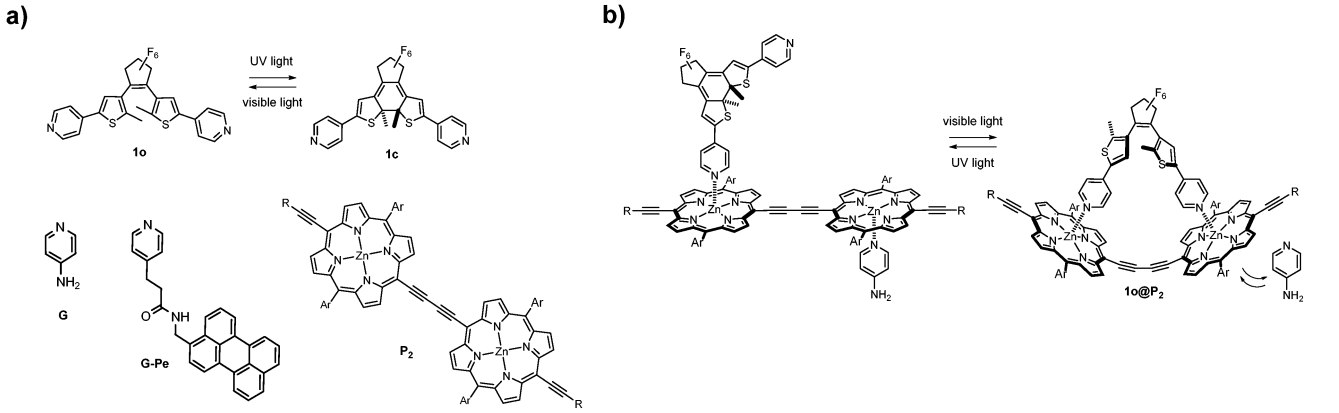

Fig. 1 (a) Isomerization scheme of **1** and molecular structures of 4-aminopyridine (**G**), the perylene functionalized analog (**G-Pe**), and the porphyrin dimer ($\mathbf{P_2}$). (b) Photo-release principle. Ar = $Si(C_6H_{13})_3$, R = 3,5-di(*tert*-butyl)phenyl.

constants of $K_{a1} = 6.1 \times 10^5\ M^{-1}$ and $K_{a2} = 6.0 \times 10^4\ M^{-1}$, respectively as determined by UV/Vis titrations (see ESI† for titration details). For non-cooperative binding to a two-site host; $K_{a1} = 4 \times K_{a2}$, indicating that binding of the second **1c** to $\mathbf{P_2}$ exhibits slightly negative cooperativity, possibly due to minor steric interactions. In sharp contrast, the structural flexibility of the ring-opened isomer (**1o**) allows it to stretch and instead form a 1 : 1 staple-like complex (**1o@P$_2$**, Fig. 1). As a result of the double axial Zn-coordination, the latter binding is significantly stronger ($K_a = 5.5 \times 10^6\ M^{-1}$), in effect causing initially bound compounds to be released into solution as a result of competitive binding. The **1o@P$_2$** 1 : 1 binding stoichiometry is strongly supported by the existence of no less than 8 isosbestic points throughout the **1o** to $\mathbf{P_2}$ titration (Fig. S4, ESI†). There is also a clear resemblance to the spectral changes seen upon $\mathbf{P_2}$ planarization using static (non-photochromic) ligands.[12] Furthermore, the **1o@P$_2$** binding mode has been assessed by computational means.[10] Binding of **1** to $\mathbf{P_2}$ has no significant effect on the rate of the photoinduced ring-opening reaction, while the corresponding closing rate is reduced by a factor of 6. This is likely due to coordination-induced restrictions in the conformational flexibility required for the isomerization process to occur. The usefulness of combining photoswitchable units and metalloporphyrins/porphyrinoids in supramolecular strategies is evidenced by the wide variety of processes brought under reversible photonic control using these building blocks. These include emission intensity,[13] energy transfer,[14] electron transfer,[15] magnetic properties,[16] and singlet oxygen generation.[17]

Here, the drug chosen to illustrate the release event is the well known small molecule neurotransmitter 4-aminopyridine (**G**, see Fig. 1).[18] In principle, any monodentate Lewis base can be used, the main prerequisite being adequate coordination capabilities (*i.e.* suitable binding strength) to Zn in $\mathbf{P_2}$. However, any change in the UV/Vis absorption of **G** upon coordination to $\mathbf{P_2}$ is obscured by the corresponding changes of the latter. Hence, a more straightforward means of monitoring binding/release of **G** is needed. Therefore, **G-Pe** was synthesized as a fluorescent model compound. **G** and **G-Pe** have identical binding modes to $\mathbf{P_2}$. The binding constants are: $K_{a1} = 3.2 \times 10^5\ M^{-1}$, $K_{a2} = 1.2 \times 10^5\ M^{-1}$ and $K_{a1} = 1.3 \times 10^5\ M^{-1}$, $K_{a2} = 3.6 \times 10^4\ M^{-1}$ for **G** and **G-Pe** respectively. The choice of the perylene fluorophore is motivated by the excellent spectral overlap between the emission spectra of **G-Pe**, and the $\mathbf{P_2}$ Soret band. Hence, binding to $\mathbf{P_2}$ efficiently quenches the **G-Pe** emission by excitation energy transfer (EET, R_0 = 66 Å, see Fig. S12 for details, ESI†), possibly in combination with electron transfer (ET). Accordingly, the observed **G-Pe** emission originates exclusively from compound free in solution. It should be noted that **G-Pe** has nothing to do with the function of the release scaffold *per se*; it is used merely as a tool for monitoring the release.

The release of **G-Pe** is demonstrated in Fig. 2, where an initial cocktail of $\mathbf{P_2}$, **1o**, and **G-Pe** gives rise to high emission, as the strongly coordinating **1o** occupies both Zn binding-sites in $\mathbf{P_2}$. Subjecting the solution to UV-light causes a **1o** → **1c** isomerization, whereafter each DTE-unit cannot coordinate more than one Zn-center. In response, **G-Pe** binds to the liberated coordination site,

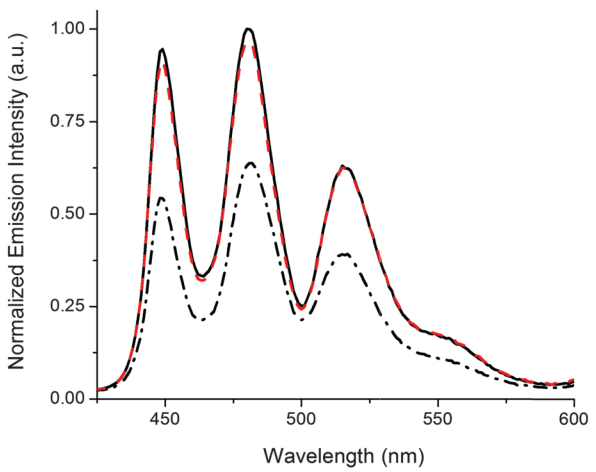

Fig. 2 Reversible release of **G-Pe** in response to light monitored by the emission intensity of the uncomplexed **G-Pe** population. Applied concentrations; [$\mathbf{P_2}$] = 280 μM, [**1**] = 300 μM, [**G-Pe**] = 1 μM. Initially, **1** is in the open form **1o** (solid black line). 2 min 302 nm UV-exposure triggers isomerization to **1c** (dash-dotted black line). Subsequent visible light isomerizes the sample back to **1o** (λ > 550 nm, 3 min, dashed red line). Please note that the experimental conditions/setup allows emission intensities unaffected by isomerization-induced inner filter effects.‡

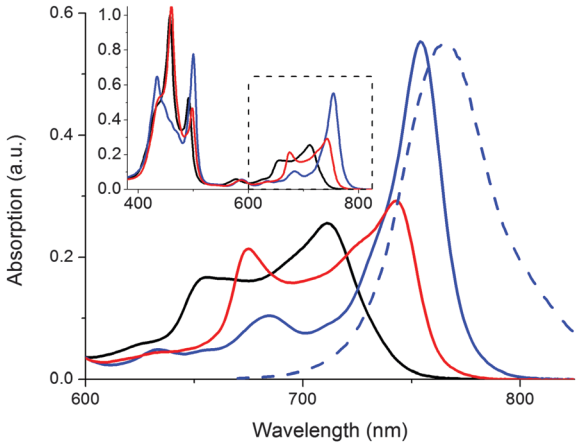

Fig. 3 Absorption spectra of supramolecular $\mathbf{P_2}$-complexes in toluene: $\mathbf{P_2}$ (black line), $\mathbf{2G@P_2}$ (red line), and the planarized $\mathbf{1o@P_2}$ (blue line). The blue dashed line shows the $\mathbf{1o@P_2}$ emission spectra (λ_{exc} = 510 nm). Inset: Absorption from 380–825 nm.

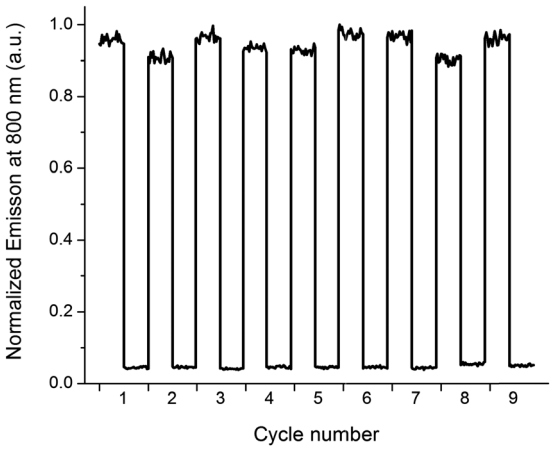

Fig. 4 Photoswitching performance of the release-and-report system, as monitored *via* the report function, *i.e.* emission intensity at 800 nm (λ_{exc} = 790 nm). Applied concentrations; [$\mathbf{P_2}$] = 280 μM, [**1**] = 300 μM, [**G**] = 1 μM. Each cycle starts with **1** in the open form **1o** (high intensity). 2 min 302 nm UV-exposure triggers isomerization to **1c** (low intensity). Subsequent visible light (λ > 550 nm, 3 min) isomerizes the sample back to **1o**.

and the emission is quenched. Subsequent visible light restores the high emission by reforming **1o** and displacement of **G-Pe** from $\mathbf{P_2}$.

In addition to triggering the compound release, formation of the doubly coordinated $\mathbf{1o@P_2}$ complex forces the two porphyrin macrocycles to adopt a coplanar conformation. With this restriction in $\mathbf{P_2}$ rotameric distribution comes characteristic changes in the absorption spectrum (Fig. 3).

In Fig. 3, the absorption spectral signatures of $\mathbf{P_2}$ and the two types of $\mathbf{P_2}$ complexes are shown. Monodentate species typically induce a red-shift in the $\mathbf{P_2}$ Q-band (711 nm → ~745 nm). The planar complex ($\mathbf{1o@P_2}$) exhibits a further red shifted, and significantly hyperchromic absorption band centered at 754 nm. The spectral features inherent to the rotational distribution of diethyne-linked porphyrin dimers and oligomers have been used to control the rate of electron transfer[19] as well as singlet oxygen generation,[20] by allowing selective excitation of planar or randomly oriented rotamers. In our laboratory, we have devised a molecular memory capable of non-destructive readout based on photochromic planarization of a porphyrin dimer.[10] Here, as the compound release proceeds concurrently with a marked increase in absorption of $\mathbf{P_2}$ around 750 nm, it is possible to read the state of the release scaffold to confirm the release event by probing the emission at 800 nm, following excitation at 790 nm. Hence, the inherent fluorescent properties of the scaffold are in line with the so-called release-and-report function.

The typical "release" (*e.g.* caged compounds[2b]) requires UV-light. For most light-controlled applications, this is not optimal, due to limited penetration depth and potential damage to surrounding tissue, materials, and/or the released compound itself. Here, a notable advantage is that both the release- and the report functions are triggered by low energy photons (λ up to *ca.* 700 nm and almost 800 nm, respectively). To illustrate the performance and stability of the release scaffold, we prepared a sample containing $\mathbf{P_2}$, **1o**, and **G**, and subjected the solution to alternating irradiation of 302 nm and visible light (λ > 550 nm), probing the report output after each irradiation step (Fig. 4).

It is clear that **1c** ⇌ **1o** isomerization causes dramatic differences in emission intensity from $\mathbf{P_2}$, and that switching between the two types of complexes is fully reversible, and proceeds with no apparent photodegradation.

The authors appreciate the limited biological compatibility of the solvents used throughout this proof-of-principle study. Thus, for use in biological environments, solubilization of the release scaffold needs to be addressed. In this context it deserves mentioning that metal–ligand coordination approaches to photo-release (albeit irreversible) in living organisms have been reported,[21] along with examples of porphyrin dimers[22] and DTEs[23] adapted for, and used in, biological applications.

A self-assembled system for reversible photo-control of compound release has been demonstrated. The unique spectral properties inherent to this system conveniently allows for fluorescence-based assessment of the state of the release scaffold, *i.e.* whether the compound is bound or not. This reporter ability has to our knowledge not been demonstrated in a reversible release system to date; thus this work represents a conceptually valuable addition to existing photo-operated release systems. The affinity of Zn-porphyrins for amine-based ligands implies that this reversible release system could be applied to a wide range of ligands, eliminating the need for guest-specific synthetic efforts.

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Notes and references

‡ Under the selected conditions, [**1**] and [$\mathbf{P_2}$] give rise to a significant optical density in the solution. It should therefore be noted that the emission measurements were performed in a 1 mm cuvette with front-face detection and excitation at an isosbestic point, λ_{exc} = 410 nm.

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