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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/linkers² 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 materials⁴ 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 molecules⁷ 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 (**P₂**) 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 photodegradation¹⁰ (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 **P₂** 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 **P₂**, the two DTE-isomers **1o** and **1c** are notably different. The ring-closed isomer (**1c**) coordinates axially to one Zn-center in **P₂** by donating a pyridine electron lone pair. This complexation occurs in a consecutive 1:1 → 1:2 manner, with binding

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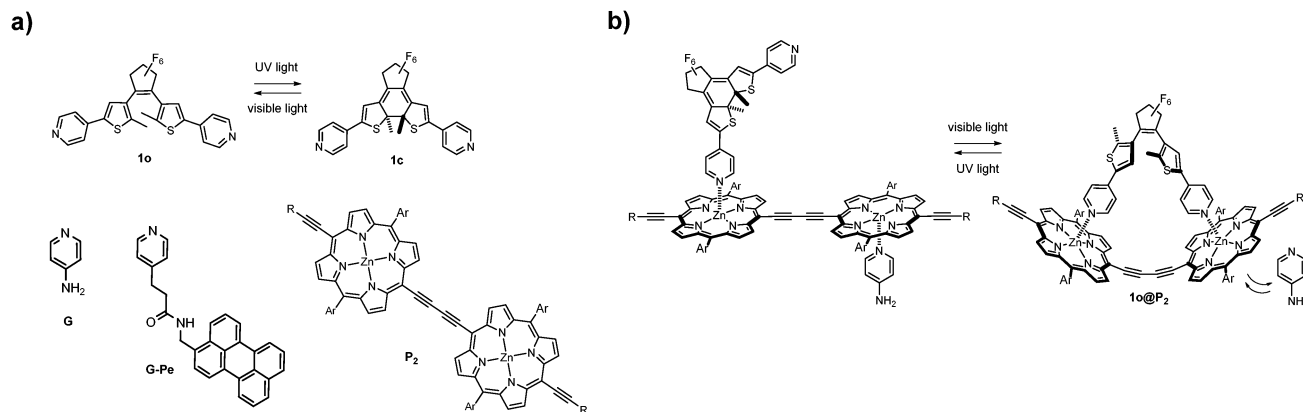


Fig. 1 (a) Isomerization scheme of **1** and molecular structures of 4-aminopyridine (**G**), the perylene functionalized analog (**G-Pe**), and the porphyrin dimer (**P₂**). (b) Photo-release principle. Ar = Si(C₆H₁₃)₃, R = 3,5-di(*tert*-butyl)phenyl.

constants of $K_{a1} = 6.1 \times 10^5 \text{ M}^{-1}$ and $K_{a2} = 6.0 \times 10^4 \text{ M}^{-1}$, 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 **P₂** 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@P₂**, Fig. 1). As a result of the double axial Zn-coordination, the latter binding is significantly stronger ($K_a = 5.5 \times 10^6 \text{ M}^{-1}$), in effect causing initially bound compounds to be released into solution as a result of competitive binding. The **1o@P₂** 1:1 binding stoichiometry is strongly supported by the existence of no less than 8 isosbestic points throughout the **1o** to **P₂** titration (Fig. S4, ESI†). There is also a clear resemblance to the spectral changes seen upon **P₂** planarization using static (non-photochromic) ligands.¹² Furthermore, the **1o@P₂** binding mode has been assessed by computational means.¹⁰ Binding of **1** to **P₂** 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 **P₂**. However, any change in the UV/Vis absorption of **G** upon coordination to **P₂** 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 **P₂**. The binding constants are: $K_{a1} = 3.2 \times 10^5 \text{ M}^{-1}$, $K_{a2} = 1.2 \times 10^5 \text{ M}^{-1}$ and $K_{a1} = 1.3 \times 10^5 \text{ M}^{-1}$, $K_{a2} = 3.6 \times 10^4 \text{ M}^{-1}$ for **G** and **G-Pe** respectively. The choice of the

peryene fluorophore is motivated by the excellent spectral overlap between the emission spectra of **G-Pe**, and the **P₂** Soret band. Hence, binding to **P₂** efficiently quenches the **G-Pe** emission by excitation energy transfer (EET, $R_0 = 66 \text{ Å}$, 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 **P₂**, **1o**, and **G-Pe** gives rise to high emission, as the strongly coordinating **1o** occupies both Zn binding-sites in **P₂**. 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,

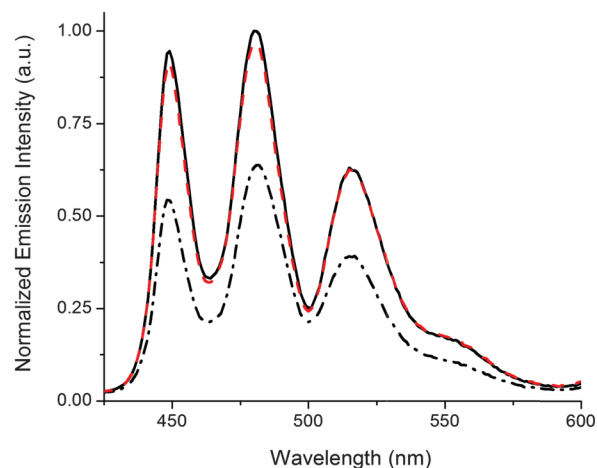


Fig. 2 Reversible release of **G-Pe** in response to light monitored by the emission intensity of the uncomplexed **G-Pe** population. Applied concentrations; [**P₂**] = 280 μM , [**1**] = 300 μM , [**G-Pe**] = 1 μM . Initially, **1** is in the open form **1o** (solid black line). 2 min 302 nm UV-exposure triggers isomerization to **1c** (dash-dotted black line). Subsequent visible light isomerizes the sample back to **1o** ($\lambda > 550 \text{ nm}$, 3 min, dashed red line). Please note that the experimental conditions/setup allows emission intensities unaffected by isomerization-induced inner filter effects.‡



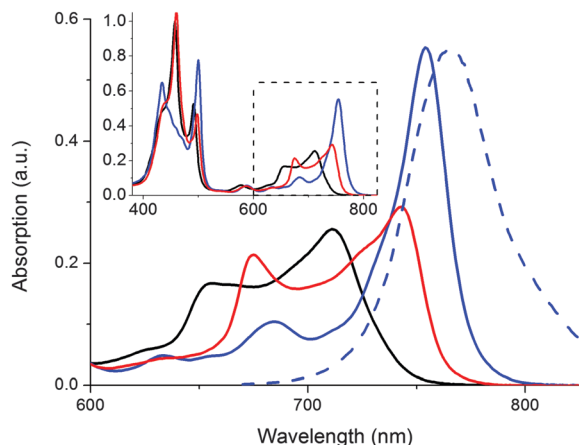


Fig. 3 Absorption spectra of supramolecular P_2 -complexes in toluene: P_2 (black line), $2G@P_2$ (red line), and the planarized $1o@P_2$ (blue line). The blue dashed line shows the $1o@P_2$ emission spectra ($\lambda_{exc} = 510$ nm). Inset: Absorption from 380–825 nm.

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

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

In Fig. 3, the absorption spectral signatures of P_2 and the two types of P_2 complexes are shown. Monodentate species typically induce a red-shift in the P_2 Q-band ($711\text{ nm} \rightarrow \sim 745\text{ nm}$). The planar complex ($1o@P_2$) 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 transfer¹⁹ 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 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 P_2 , $1o$, and G , and subjected the solution to alternating irradiation of 302 nm and visible light ($\lambda > 550\text{ nm}$), probing the report output after each irradiation step (Fig. 4).

It is clear that $1c \rightleftharpoons 1o$ isomerization causes dramatic differences in emission intensity from P_2 , and that switching

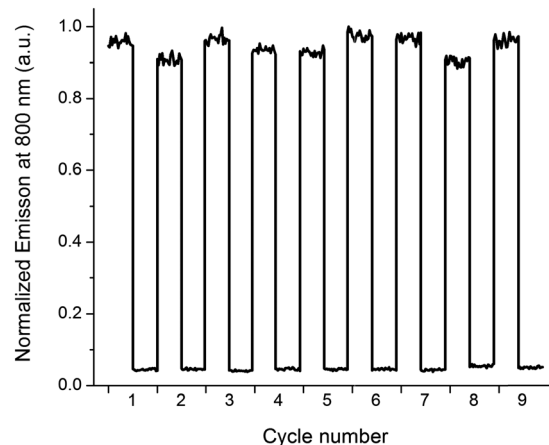


Fig. 4 Photoswitching performance of the release-and-report system, as monitored via the report function, i.e. emission intensity at 800 nm ($\lambda_{exc} = 790\text{ nm}$). Applied concentrations; $[P_2] = 280\text{ }\mu\text{M}$, $[1] = 300\text{ }\mu\text{M}$, $[G] = 1\text{ }\mu\text{M}$. Each cycle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

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 dimers²² and DTEs²³ 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 $[P_2]$ 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, $\lambda_{exc} = 410\text{ nm}$.

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