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Modulation of the isomerization of iminothioindoxyl switches by supramolecular confinement†

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Here we present the formation of an iminothioindoxyl (ITI)-cage complex that retains the photochemical properties of the photo-switch within a confined environment in water. At the same time, besides ultrafast switching inside the cage, the ITI photoswitch displays an intriguing bifurcation of the excited state isomerization pathway when encapsulated.

The study of supramolecular coordination complexes is a captivating and fast-growing area of chemistry and materials science.^{1,2} A characteristic feature of these complexes is that they comprise self-assembled architectures formed by non-covalent interactions between metal ions and organic ligands (Fig. 1A). The resulting structures are applied in distinct fields, including catalysis,³ sensing,⁴ drug delivery⁵ and nanotechnology.⁶

Emerging targets within this context are embedded molecular photoswitches.^{11,12} These compounds can undergo discrete, reversible configurational changes upon stimulation by light at specific wavelengths, enabling external control over their chemical and physical properties.¹³ Displaying such switching behavior renders them suitable for a plethora of applications, ranging from smart

materials¹⁴ and optoelectronics¹⁵ to photopharmacology.^{16,17} Well-known representatives of photoswitchable molecules are azobenzenes,¹⁸ stiff-stilbenes,¹⁹ spiropyrans,²⁰ hydrazones,²¹ and diarylethenes,¹⁵ among others (Fig. 1B).

As there is an increasing demand for efficient and visible-light-responsive molecular photoswitches, a current focus is on combinations of key structural units. In this way hemithioindigo (HTI)-based molecular switches, consisting of a thioindigo and stilbene part,²² and iminothioindoxyl (ITI)-based systems, consisting of a thioindigo and azobenzene part,¹⁰ were recently developed. The latter molecules show activation with visible light and feature a large band separation of over 100 nm between the stable *Z*- and metastable *E*-isomer, along with short thermal half-lives of *E*-isomers (Fig. 1C).^{10,23}

Drawing from Nature, which has fine-tuned retinal in the process of vision by confining this prototypical optical switch inside the protein rhodopsin,^{12,24} chemists have confined and encapsulated switching entities into artificial pockets.^{25–27} This process significantly altered the chemical properties of switches,^{12,28} including modifications of the reaction kinetics and isomer stability.²⁹ Compared to studies in solution, the modification of the photochemical properties and excited state dynamics of photoswitches under confinement have been considerably less investigated.^{12,30,31} Ramamurthy and coworkers demonstrated the opening of new excited state dynamic pathways of azobenzenes by encapsulation.³² Recent efforts by the Klajn group^{7–9} (Fig. 1A and B) showed the switching in aqueous solution under confinement of otherwise water-insoluble azobenzenes.⁸ Furthermore, they demonstrated the ‘disequilibration’ of azobenzenes by triplet sensitization under confinement, distinctively favoring the formation of the *Z*-isomer over its *E* counterpart.¹¹ It is showcasing how an artificial environment akin to rhodopsin could effectively modulate the potential energy surface of electronically excited states of photoswitches.

In this study, we illustrate the influence exerted by a metal organic cage on the properties of ITI photoswitches (Fig. 1C), which are rendered water-soluble when embedded in a hydrophobic pocket (Fig. 1D). Furthermore, investigation of the

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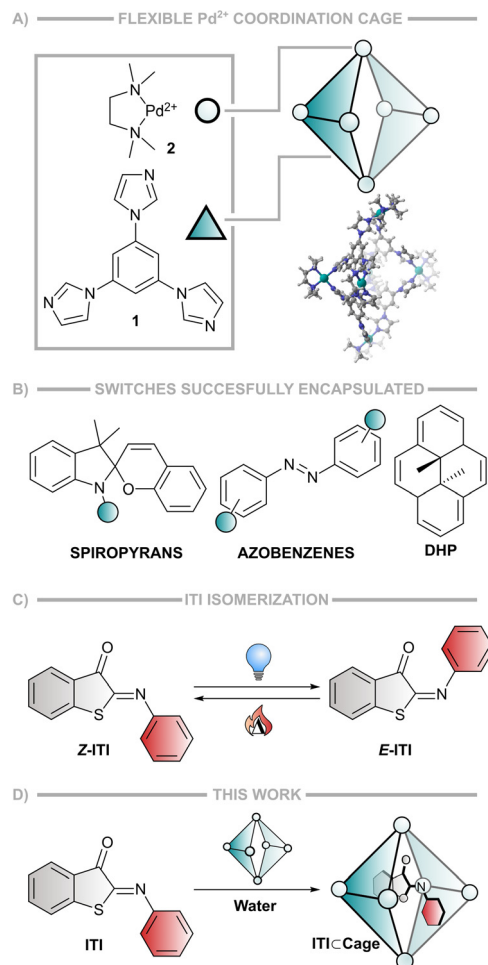


Fig. 1 (A) Structure of a flexible Pd^{2+} coordination cage. (B) Various photoswitches encapsulated in the Pd^{2+} cage: spiropyran,⁷ azobenzenes⁸ and dihydropyrenes (DHP).⁹ (C) Photochemical isomerization of ITI.¹⁰ (D) This work: encapsulation of ITI photoswitch.

excited state dynamics of ITI under confinement reveals a slowdown and a remarkable bifurcation of the excited state process within the constrained spatial domain compared to organic solutions or polymeric media.

The photoactive molecule (ITI), ligand (1), and Pd-precursor (2) for the Cage were synthesized through modification of reported procedures (see ESI†). Pure ligand 1, formed by reacting imidazole with 1,3,5-tribromobenzene, employing K_2CO_3 as a base and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ as catalyst, was obtained through recrystallization from MeOH. Pd-precursor 2 was synthesized by reacting PdCl_2 with tetramethylethylenediamine (TMEDA) in MeCN, yielding $\text{Pd}[\text{TMEDA}]\text{Cl}_2$.^{33,34} The Pd-complex was then converted with AgNO_3 in water as solvent and the aqueous solution of Pd-precursor 2 obtained pure after washing with chloroform. Next, 2 was dissolved in deionized H_2O , added dropwise to 1 and filtered over cotton wool yielding the Cage. It is important to note that all reactions involving the Pd species were conducted under the exclusion of light. Modifications to the ITI synthesis were made as well,¹⁰ reducing its environmental impact by using *p*-toluenesulfonic acid for the

ring closure of (phenylthio)acetic acid instead of AlCl_3 and by performing the condensation reaction in toluene instead of benzene (see ESI† for detailed reaction conditions).

To study the response of the ITI photoswitch towards confinement and different viscous environments, ITI was encapsulated within the Cage. To prepare the ITI@Cage complex, an excess of ITI was added to an aqueous solution of Cage (1.00–1.45 mM) followed by stirring the solution for approximately 24 h. The remaining free ITI was removed by filtration over cotton wool, where encapsulation of ITI was indicated by the change of color to intense yellow. For a direct comparison of its behavior in different constrained environments, ITI was also embedded in a poly(methyl methacrylate) (PMMA) matrix by spin-coating the ITI-containing mixture onto a glass surface.

The successful formation of the inclusion complex ITI@Cage was confirmed by NMR and UV-Vis spectroscopies (NMR and UV-Vis Spectroscopy section in ESI†, Fig. S1, S3 and S4). A distinct absorption band around 420 nm, attributed to the ITI, was observed in the measured spectrum of the ITI@Cage compared to the Cage itself (see Fig. 2A). Molecular dynamics simulations of different conformations of ITI inside the Cage at the GFN-FF level confirm that the ITI@Cage is more energetically feasible than the bare switch dissolved in water (Fig. 2B and Molecular dynamics simulations section in ESI†).

After the successful preparation of the PMMA film and the ITI@Cage complex, transient absorption spectroscopy was performed to study the effect of encapsulation on the photodynamics of the switch and compare it to its behavior in solution (MeOH). The femtosecond transient spectroscopy experiments showed that in both constrained environments, the excited state dynamics upon irradiation at 400 nm qualitatively resembled the ones in solution.¹⁰ Indeed, instantaneously upon excitation, an intense excited state absorption band was observed, decaying on the sub-ps timescale, in support of the retention of an ultra-fast isomerization process in more constrained media (see Femtosecond TAS section in ESI†).

Global analysis of the transient absorption data (see ESI† for details) revealed that in PMMA, the intense excited state absorption band peaking at about 520 nm observed soon after excitation, decreased its intensity on a very fast 140 fs timescale

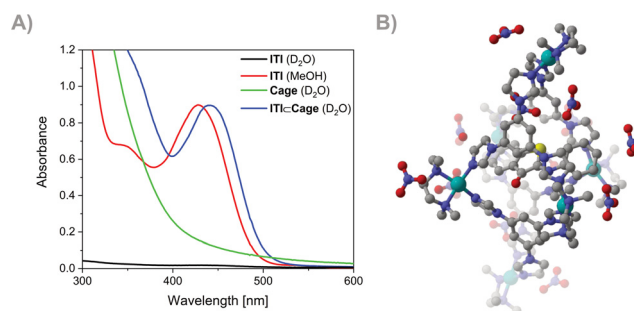


Fig. 2 (A) UV-Vis spectroscopy of ITI in D_2O (black), ITI in MeOH ($c = \sim 2.5 \times 10^{-4}$ M, red), Cage in D_2O ($c = \sim 1 \times 10^{-3}$ M, green) and ITI@Cage in D_2O ($c = \sim 9 \times 10^{-4}$ M, blue) at 10 °C. (B) Optimized ITI@Cage at the GFN-FF level, with 12 NO_3^- counterions.



(limit of time resolution of our setup). A second evolution associated decay spectrum (EADS) was distinguished, presenting a negative band around 425 nm, which was assigned to the ground state bleaching of the Z-isomeric form. In parallel with observations in solution (MeOH), the positive band around 475 nm also observed in the second spectral component, was assigned as a hot ground state absorption band of the photoproducts.¹⁰ Over time, the signal intensity diminished, and the positive band experienced a slight blue shift within roughly 11 ps, resulting from the vibrational cooling in the ground state (Fig. S7 in ESI†; the final spectral component, which represents the *E/Z* difference spectrum, persists longer than the timescale accessed with the setup). The spectra of the **ITI**≡**Cage** complex exhibit features consistent with those observed in other organic solvents.¹⁰ Comparing the obtained results of the **ITI**≡**Cage** complex with **ITI** in PMMA and methanol, a slower decay of the initial spectral component can be observed. Indeed, the kinetic analyses of **ITI** in MeOH and PMMA are almost superimposable, while the decay within the cage appears to be slower, however, all retrieved time constants from the performed global analysis are very similar. The main difference between the kinetics measured within **Cage** in comparison to the other media, resides in the relative weight of the first- and second-time component, being higher in comparison to MeOH and PMMA (Fig. S9 in ESI†). This finding suggests a specific interaction between the switch and metal-organic **Cage** in the excited state.

Studies on the effect of confinement on the photoswitching dynamics for some other systems,¹² for example azobenzenes, suggest slower excited state dynamics under confinement than in solution.³² Those results were interpreted using a kinetic model considering the involvement of a distorted excited state configuration from which the molecule would isomerize on a slower timescale.³² When performing global analysis with a sequential scheme (see Fig. S8, ESI†), the main difference observed for **ITI**≡**Cage** compared to **ITI** in PMMA and solvents is that only in the case of **ITI**≡**Cage** the second EADS has residual intensity above 550 nm, while for all other cases, it goes almost to zero in the red region of the spectrum. This may suggest that the excited state population does not completely decay within the lifetime of the initial EADS and that a specific kinetic scheme is needed to better describe the spectral dynamics of **ITI**≡**Cage**. We performed a target analysis on the transient absorption data to explore the feasibility of a bifurcation mechanism to the **ITI**≡**Cage** complex, employing the kinetic scheme shown in Fig. 3A. According to this scheme, after the light pulse, **Z-ITI**≡**Cage** populates an initial excited state (component 1, black), which branches, bringing the system both towards an intermediate excited state (component 2, red) or directly towards the conical intersection and the hot ground state (component 3, green) in 0.3 ps (k_1 and k_1'). The intermediate excited state then evolves towards the hot ground state but on a slower timescale (3.5 ps, k_2). The different behavior observed in **ITI**≡**Cage** underlines the effect of the supramolecular confinement of the Pd^{2+} cage in modifying the excited state dynamics of **ITI** (see Fig. 3B), compared to

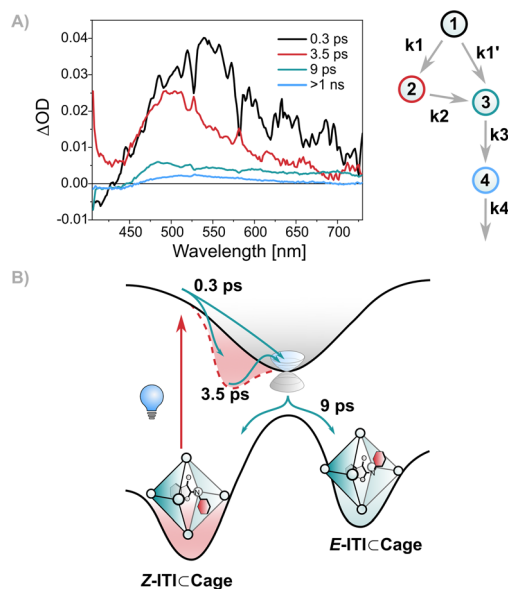


Fig. 3 (A) SADS (Species associated difference spectra) obtained from a global analysis of the transient absorption data performed by applying the kinetic scheme shown on the right part of the figure. (B) Pictorial representation of the excited state isomerization of the **ITI**≡**Cage** complex.

the dynamics in MeOH and PMMA. The dynamics in the ground state remain mostly unaltered: the hot ground state undergoes vibrational cooling throughout approximately 9 ps (k_3), and the final component (component 4, blue), representing the *E/Z* difference spectrum and the population of **E-ITI**≡**Cage**, decays on the timescale associated with thermal back-isomerization from *E*-to-*Z* (> 1 ns, k_4).

We further investigated the *E*-to-*Z* back-isomerization process, performing nanosecond transient absorption spectroscopy, showing that the **ITI** retained its thermal switching properties at room temperature under confinement. In particular, the **E-ITI**≡**Cage** complex relaxes to the stable *Z*-form in 3 ms, slightly faster than the reported 18.5 ms in MeOH,¹⁰ showing an effect of the supramolecular confinement also on the ground state motion. Confining **ITI** in PMMA, on the other hand, has a more peculiar outcome. Similarly to azobenzene in polymeric matrices,³⁵ **ITI** showed biexponential kinetics (0.16 and 7.7 ms, see Fig. S6 in ESI†), reflecting the different nature of the surroundings in the glassy polymer. This observation directly contrasts with the result obtained when confining the switch in the metal-organic **Cage**. In particular, our studies suggest that **ITI** when confined within the **Cage** forms a single species, i.e., **E-ITI**≡**Cage** (see Fig. 3B), via two different excited state pathways, due to the excited state stabilization by the cage. **E-ITI**≡**Cage** will then revert back to its *Z*-form, within the supramolecular **Cage**. Interestingly, under these conditions the excited state dynamics seem to be affected by the surroundings more than the thermal isomerization. The non-covalent π interactions between the cage and the switch appear to be responsible for stabilizing the excited state, while the flexible nature of the supramolecular cavity exerts only a limited hindrance to its ground state motion. In contrast, the switch in PMMA



experiences different degrees of spatial constraints, possibly due to the different porosities of the material, which have limited effect on the excited state, but considerably modify the ground state isomerization.

In summary, we have shown the formation of an **ITI**⊂**Cage** complex, wherein the hydrophobic cavity of the **Cage** is able to accommodate one equivalent of commonly water insoluble **ITI** switch. Our investigation using transient absorption spectroscopy showed that the **ITI** molecule retains its ultra-fast photochemical properties under confinement. Remarkably, the analysis of our results reveals that the decay from the electronically excited state of **ITI** confined within the **Cage** bifurcates, showcasing the interaction between the supramolecular cavity and the excited molecule. These results pave the way to further studies aimed to control the excited state dynamics and pathways of molecular switches by tailoring the supramolecular environment.

S. C. and B. L. F. conceived the project. D. D. synthesized, purified and characterized all molecules, carried out NMR and UV-Vis experiments. S. C., M. H., W. J. B., S. D. and M. D. D. carried out transient absorption spectroscopy measurements and related data processing. A.-K. R. performed computations, N. A. S. incorporated **ITI** in PMMA. D. D. and S. C. wrote the manuscript. M. D. D., B. L. F., W. S. and S. C. supervised the work. All authors discussed and commented on the manuscript. S. C. and B. L. F. acquired funding.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare no conflict of interest.

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