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# Controlling the Isomerization Rate of an Azo-$BF_2$ Switch Using Aggregation

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Supporting Information

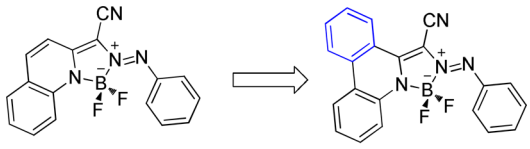
**ABSTRACT:** A novel visible-light activated azo-$BF_2$ switch possessing a phenanthridinyl $\pi$-system has been synthesized, and its switching properties have been characterized as a function of concentration. The switch self-aggregates through $\pi-\pi$ interactions, and the degree of aggregation modulates the $Z \rightarrow E$ thermal isomerization rate. This property allows for the active tuning of the thermal relaxation half-life of the same switch from seconds to days.

The modulation of the prolyl *cis-trans* isomerization rate by peptidyl prolyl *cis–trans* isomerases results in a molecular timer that regulates a variety of physiological events, such as cell cycle, cell signaling, and gene expression.[1−3] A similar *in situ* control over the isomerization rate of photochromic compounds can enable the development of photoactive molecules that can be used in the control of not only molecular motions and functions but also their timing.[4] While photoswitchable molecules have been extensively studied and applied in areas ranging from biological systems to material science,[5−8] the active modulation of the isomerization rates of such systems has not been explored in-depth.[9]

Azobenzene is one of most popular photochromic compounds in the literature, mainly because of its ease of synthesis, tunable wavelength, and high photostability.[10] Recently there has been a push in the field to developed azo compounds that can be activated using solely visible and/or near-infrared light sources.[11,12] This strategy will enable the use of azobenzene in photopharmacology,[13] because visible light is more biocompatible, and has a deeper penetration through tissue[14] than UV light. This approach is expected to open the way to the noninvasive control over biological activity through the use of azobenzene-coupled drugs. One important point to consider when developing such light-activated drugs is that visible light is ubiquitous, and hence, it might be challenging to fully control the "ON" and "OFF" function of the drug in the open! Thus, it seems necessary to have orthogonal spatial and temporal control over the function of the drug so it can be activated when and where it is needed, even in a well-lit room. A possible way to achieve this objective is by mimicking biology and actively controlling the thermal relaxation half-life of photochromic compounds. Using this strategy, the lifetime of the "ON" state of a photoactivatable drug will be dependent on two factors (i.e., presence of visible light and the stimulus that controls the half-life), similar to an AND logic gate. In general, azobenzene derivatives possess an invariable half-life at constant temperature. These half-life values can range from nanoseconds to days, where different half-lives may be associated with different functions (e.g., real-time information-transmission in organisms[15] to ultrahigh-density optical data storage[16]). In most cases though, changing the thermal stability of photoswitches relies on molecular structure modifications, which can be time-consuming, tedious, and low yielding.[17] Moreover, once the structural variations are made the half-life of the system *cannot* be changed. Herein, we demonstrate how aggregation can be used in the *in situ* tuning of the thermal isomerization rate of a photochromic compound.

We recently reported on a series of azo-$BF_2$ complexes that can be isomerized using visible[18] and NIR light sources.[19] These systems are highly efficient and show a range of $Z$ to $E$ isomerization rates (i.e., seconds to hours). During our structure property analyses we discovered that electron donating *para*-substituents red-shift the activation wavelength of these systems; however, this effect is accompanied by significant shortening of the isomerization half-lives, especially of the NIR activated systems. To investigate whether expansion of the $\pi$-system from a quinolinyl to a phenanthridinyl group (blue aromatic ring in Scheme 1) would lead to a red shift in the activation wavelength, without the deleterious effect on the isomerization rate, we synthesized the azo-$BF_2$ switch **1**. Compound **1** shows a small red shift in the activation wavelength relative to the parent switch. More importantly, the phenanthridine system forms supramolecular aggregates in solution, the degree of which drastically modulates the $Z \rightarrow E$ thermal isomerization rate. This aggregation behavior allowed us to control the isomerization rate of the *same* compound by at least a factor of 1800 (from seconds to days). This unprecedented finding (specifically with an azobenzene

**Scheme 1. Structural Evolution of Azo-$BF_2$ Switch 1**




Parent 1

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derivative)[20] opens a new way for controlling the thermal properties of photochromic compounds.

The synthesis of **1** is straightforward, starting from the hydrazone-based switch,[21] followed by the coupling reaction with $BF_3{\cdot}OEt_2$ (Scheme S1 in the Supporting Information).[22] The product and its precursors were fully characterized using NMR spectroscopy and mass spectrometry (Figures S1–S15 in the Supporting Information). An equilibrated solution (under dark) of **1** shows an absorption maximum ($\lambda_{max}$) at 535 nm, with an absorption coefficient constant ($\varepsilon$) of 12 356 $M^{-1}{\cdot}cm^{-1}$ (Figure 1), which is assigned to the *E* isomer. Upon irradiation

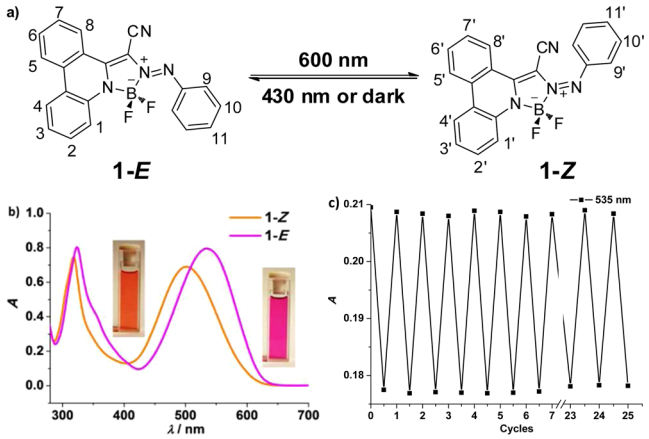


**Figure 1.** (a) Visible light induced *E*/*Z* isomerization of azo-$BF_2$ **1**; (b) UV–vis spectra ($6.5 \times 10^{-5}$ M) of **1**-*E* (purple) and **1**-*Z* (orange) isomers in $CH_2Cl_2$ (aerated); (c) Isomerization cycles of **1** ($2.1 \times 10^{-5}$ M) in $CH_2Cl_2$ upon alternating irradiation using 600 and 430 nm light sources. The change in the absorption intensity of the $\lambda_{max}$ of the *E* isomer was monitored.

with a 600 nm light source, *E* to *Z* isomerization takes place (isosbestic points at 318, 406, and 508 nm) leading to a new band with a $\lambda_{max}$ at 501 nm and $\varepsilon$ of 11 209 $M^{-1}{\cdot}cm^{-1}$. The isomerization is accompanied by a significant color change of the solution from purple to dark orange (Figure 1b). This type of negative photochromism, while rare,[23] is typical of azo-$BF_2$ switches.[18,19] As expected the *E* and *Z* isomers exhibit 5 and 21 nm bathochromic shifts, respectively, relative to the absorption maxima of the parent azo-$BF_2$ switch (Scheme 1).[18] These shifts are attributed to the increased $\pi$-conjugation of the phenanthridinyl ring system. The *Z* isomer switches back to *E* upon 430 nm light irradiation (Figure 1b). This reversible *E*/*Z* isomerization process can be repeated at least 25 times without fatigue upon alternating visible light irradiation cycles (Figure 1c).[24]

$^1$H NMR spectroscopy was employed to evaluate the photoswitching efficiency of **1** in $CD_2Cl_2$ ($5.3 \times 10^{-4}$ M). The equilibrated switch (under dark) exists as a mixture of *E* and *Z* isomers (>95% *E* isomer; Figure S16a in the Supporting Information). The *E*-dominant sample was irradiated using 600 nm light ($1.09 \times 10^{16}$ quanta·$s^{-1}$) for 60 s to reach a photostationary state ($PSS_{600}$) consisting of 91% *Z* isomer (Figure S16b in the Supporting Information). The quantum yield ($\Phi$) for this process was calculated to be 55 ± 4%. As for the $Z \rightarrow E$ isomerization process, 430 nm light ($1.50 \times 10^{16}$ quanta·$s^{-1}$) irradiation for 10 s yields a $PSS_{430}$ consisting of 65% *E* isomer with $\Phi_{Z\rightarrow E}$ of 77 ± 3% (Figure S16c in the Supporting Information).[25]

Single crystallographic analysis (Figure 2a) reveals that the azo-$BF_2$ complex adopts the *E* configuration in the solid state.

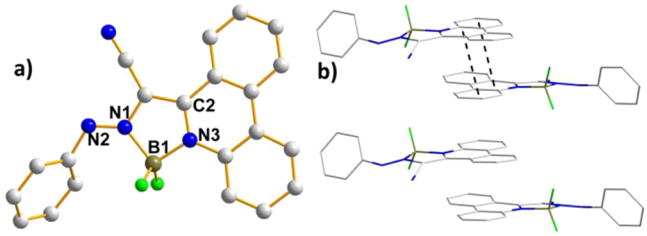


**Figure 2.** (a) Ball–stick drawing of the single crystal of **1**; (b) head-to-head crystal packing through $\pi$–$\pi$ interactions (black dashes); the hydrogen atoms have been omitted for clarity.

The bond lengths of N(1)=N(2) (1.280(2) Å), B(1)–N(1) (1.638(3) Å), and B(1)–N(3) (1.563(3) Å) are almost identical to those of the parent azo-$BF_2$ compound.[18] More importantly, the analysis shows that, unlike in the parent quinolinyl-based system, the switch crystallizes into a cylindrical structure through head-to-head $\pi$–$\pi$ stacking (3.4956(0) and 3.4658(0) Å) (Figure 2b).[26] It has been previously shown[27] that phenanthridine can self-associate in solution into aggregates via $\pi$–$\pi$ stacking, which inspired us to study whether the interactions found in **1** persist in solution. The self-aggregation behavior of **1** was studied using $^1$H NMR spectroscopy.[28] At $2.9 \times 10^{-2}$ M (Figure S17 in the Supporting Information), the proton signals in the $^1$H NMR spectrum are broad, owing to a dynamic exchange process between different species in solution, and indicating the existence of self-aggregated species.[29] The resonance signals gradually become sharp upon dilution (down to $7.9 \times 10^{-4}$ M), as a result of the disassembly of the aggregates.[30] Consequently, the phenanthridinyl protons H1–8 are slightly downfield shifted, while the chemical shifts of the phenyl protons H9–11 remain almost unchanged (Figure S17 and Table S1 in the Supporting Information). This result indicates that the azo-$BF_2$ molecules form aggregates in solution through head-to-head interactions similar to those observed in the solid state (Figure 2b).[26]

To have a better understanding of this phenomenon and how it is affected by isomerization, we used dynamic light scattering (DLS) spectroscopy to study the formation of the aggregates in the concentration range $2.2 \times 10^{-5}$ to $8.3 \times 10^{-3}$ M (Table 1 and Figures S30–S34 in the Supporting Information). The radius of the particles in solution grows from 5 ± 2 to 92 ± 3 nm when changing the concentration from $1.0 \times 10^{-4}$ to $8.3 \times 10^{-3}$ M. Irradiation of the sample with 600 nm yields the *Z* isomer of **1**, and the particle radius slightly decreases (from 92 to 84 nm) during the photoisomerization. The DLS data clearly show that the aggregates increase in size

**Table 1. Concentration Dependent Half-Life and Hydrodynamic Radius of Switch 1**

| concn/M | half-life | size (*E* isomer)[a] | size (*Z* isomer)[a] |
|---|---|---|---|
| $2.2 \times 10^{-5}$ | 390 ± 11 s | – | – |
| $6.1 \times 10^{-5}$ | 2.4 ± 0.6 h | – | – |
| $1.0 \times 10^{-4}$ | 27 ± 2 h | 5 ± 2 nm | 4 ± 1 nm |
| $1.3 \times 10^{-4}$ | 45 ± 2 h | 15 ± 2 nm | 13 ± 1 nm |
| $1.5 \times 10^{-3}$ | 79 ± 3 h | 22 ± 3 nm | 17 ± 2 nm |
| $8.3 \times 10^{-3}$ | 195 ± 4 h | 92 ± 3 nm | 84 ± 4 nm |

[a]Measured with a DLS instrument having a 658 ± 2 nm laser.



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as concertation increases and that they are not disrupted as a result of switching. No DLS signals were observed at $6.1 \times 10^{-5}$ M and below, indicating that either the particle size is below the DLS detection limit or monomers are present at these concentrations.

To discern the effect of aggregation on the isomerization process we monitored the $Z \rightarrow E$ thermal isomerization rate of **1** at different concentrations using UV−vis and NMR spectroscopies. The half-life of a sample at $2.3 \times 10^{-5}$ M in $CH_2Cl_2$ was determined to be 390 ± 11 s (Figure S35 in the Supporting Information), which is around 4 times smaller than the half-life of the parent azo-$BF_2$ compound.[18] Based on this fact, in addition to the DLS data that show no signals at this concentration, we hypothesize that **1** is mainly in the monomeric form at this concentration. When the concentration is raised to $6.1 \times 10^{-5}$ M the half-life increases to 2.4 ± 0.6 h, indicating that aggregation is already taking place. This trend continues on, and at $8.3 \times 10^{-3}$ M the half-life is enhanced 1800 times to about 8.1 days (Figures 3 and S36−S43 in the Supporting Information)! Such an unusual concentration-dependent thermal relaxation has not been observed, to the best of our knowledge, in azobenzene derivatives.[20] A possible explanation for this aggregation induced half-life enhancement is the prevalence of the rotation rather than inversion isomerization mechanism in nonsubstituted azo-$BF_2$ compounds.[31] Upon aggregation, rotation will be hindered by neighboring molecules, leading to the observed slowing down of the isomerization rate.[32] The bigger the aggregate the slower the process, which is exactly what we observe experimentally.

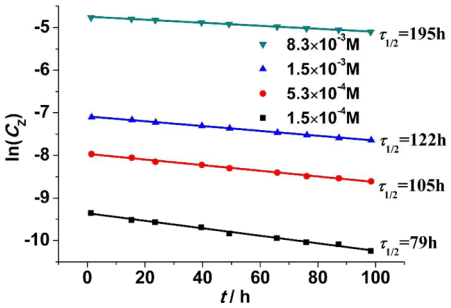


**Figure 3.** Concentration dependent $Z \rightarrow E$ isomerization half-lives of the azo-$BF_2$ switch **1** in $CD_2Cl_2$ at rt.

The analysis of the rate data ($k$) as a function of concentration shows that the aggregation induced decline in isomerization rate goes through two steps (Figures S49−S51 in the Supporting Information). Between $2.3 \times 10^{-5}$ to $1.5 \times 10^{-4}$ M, there is an acute decrease in rate (ca. 730 times), which then tapers off until $8.3 \times 10^{-3}$ M is reached, at which point the rate decreases by ca. 2.5 times. Using these data we were able to determine the critical aggregation concentration (CAC) of the process to be $1.4 \times 10^{-4}$ M.[33] The two aggregation regimes define two linear relationships between the double logarithmic plot of $k$ as a function of concentration (Figure S49 in the Supporting Information). Based on these correlations we should be able to dial into a large range of function-dependent isomerization rates, just by changing the concentration of the *same* molecular switch! This finding opens the door to a completely new strategy for the control of the isomerization rates of photochromic compounds.

The dependence of the isomerization half-life on the size of the aggregate enabled us to introduce concentration as a second orthogonal stimulus by which to control the switching of **1**. The *in situ* temporal control was achieved by consecutively diluting and concentrating a solution of **1** between $1.7 \times 10^{-3}$ and $1.2 \times 10^{-3}$ M and monitoring the rate of the $Z \rightarrow E$ isomerization process using NMR spectroscopy. At $1.7 \times 10^{-3}$ M, the half-life was determined to be 132 ± 2 h; after dilution it decreased to 117 ± 3 h (Figure 4). This reversible switching of half-life was repeated for two cycles, by which time the volume of the NMR tube precluded us from continuing on (Figures S44−S48 in the Supporting Information).

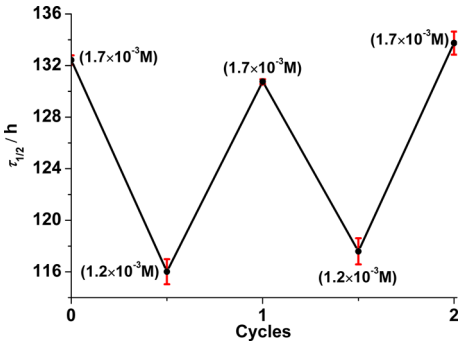


**Figure 4.** *In situ* switching of the isomerization half-life of switch **1**, achieved by consecutively diluting and concentrating the NMR sample solution between $1.7 \times 10^{-3}$ and $1.2 \times 10^{-3}$ M. The red error bars were calculated from the standard deviation of the average of three experiments.

In conclusion, we have synthesized a novel visible light induced azo-$BF_2$ switch having an extended $\pi$-system. This switch can self-aggregate into large assemblies in concentrated solutions as well as in the solid state through head-to-head $\pi-\pi$ interactions between its phenanthridinyl groups. Uniquely, the thermal $Z \rightarrow E$ isomerization rate displays a linear dependency on the degree of aggregation in solution; the higher the concentration, the bigger the size of aggregates, and the slower the isomerization rate. This correlation can lead to photoactivatable drugs having different response rates depending on concentration. This property could enable the design of visible and NIR light activated switchable drugs that will have long-lived "ON" states exclusively at target sites (e.g., through accumulation in cancer cells), while being "OFF" elsewhere via fast thermal isomerization even in well-lit rooms.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10982.

General methods, experimental procedures, NMR spectra of key compounds, concentration-dependent studies, kinetic studies (PDF)

Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.



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