Organic &
Biomolecular
Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-ART-03-2022-000472.R1
Article Type:	Paper
Date Submitted by the Author:	05-Apr-2022
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Back electron transfer rates determine the photoreactivity of donor-acceptor stilbene complexes in a macrocyclic host

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Abstract: Host-guest 2:1 complexation of photoreactive alkene guests improves the selectivity of [2+2] photodimerizations by templating alkene orientation prior to irradiation. Host-guest chemistry can also provide 1:1:1 complexes through the inclusion of electronically complementary donor and acceptor guests, but the photoreactivity of such complexes has not been investigated. We imagined that such complexes could enable selective cross-[2+2] photocycloadditions between donor and acceptor stilbenes. In pursuit of this strategy, we investigated a series of stilbenes and found 1:1:1 complexes with cucurbit[8]uril that exhibited charge-transfer (CT) absorption bands in the visible and near-IR regions. Irradiation of the CT band of an azastilbene, 4,4'-stilbenedicarboxylate, and cucurbit[8]uril ternary complex led to a selective cross-[2+2] photocycloaddition, while other substrate pairs exhibited no productive chemistry upon CT excitation. Using transient absorption (TA) spectroscopy, we were able to understand the variable photoreactivity of different stilbene donor-acceptor complexes. We found that the back electron transfer (BET) following CT excitation of the photoreactive complex is positioned deep in the Marcus inverted region due to electrostatic stabilization of the ground state, allowing [2+2] to effectively compete with this relaxation pathway. Control reactions revealed that the cucurbit[8]uril host not only serves to template the reaction from the ground state, but also protects the long-lived radical ions formed by CT from side reactions. This protective role of the host suggests that donor-acceptor host-guest ternary complexes could be used to improve existing CT-initiated photochemistry or access new reactivity.

INTRODUCTION

The [2+2] photodimerization of alkenes, especially stilbenes, coumarins, and cinnamates, has been extensively studied as a prototypical organic photoreaction.[1–11] In this reaction, light, typically with wavelengths of 350 nm or shorter, is used to promote an alkene to an excited stated from which it can engage in a thermally forbidden [2+2] cycloaddition with a second alkene to produce a cyclobutane. Pre-orienting the alkenes for the desired reaction using a macrocylic host molecule, such as γ-cyclodextrin or cucurbit[8]uril (**CB[8]**), can improve selectivity for the desired photocycloaddition.[1,12–22] The guests employed in these templating strategies are often donor-acceptor stilbenes, such as 4-styrylpyridine, which form a head-to-tail 2:1 complex due to favorable π-π interactions (**Figure 1a**). Host-guest templating of the [4+4] photocyloaddition of antracene guests by **CB[8]** is also well-established.[23,24] Besides improving regio- and diasteroselectivity in small-molecule photochemistry, host-guest complexation can provide photoresponsive supramolecular crosslinks in polymeric systems.[12–14,16,25–31]

Most examples of host-guest-templated photocycloadditions begin with the formation of a 2:1 complex followed by photodimerization.[1,12–20,23,24] Previous studies with cinnamates and coumarins have demonstrated size complementarity, in which steric hinderance prevents 2:1 complexation, as an effective means to achieve 1:1:1 complexation and thus selectivity for cross-products over dimers (**Figure 1b**).[32–36] Electronic donor-acceptor interactions between guests have also been shown to yield 1:1:1 donor-acceptor host-guest complexes, but such complexes have not been used to template subsequent photochemistry.[37,38] Moreover, donor-acceptor complexes can be excited by visible or even near-infrared light thanks to the emergence of charge transfer (CT) absorption bands.[38,39] We wondered if irradiation of these CT bands could be used to initiate [2+2] chemistry in appropriately designed donor-acceptor host-guest complexes. Directly accessing [2+2] chemistry from the CT state is generally considered improbable due to quick back electron transfer (BET) to the ground state following CT. [40–43] In fact, most studies of cross-[2+2] chemistry have viewed CT as a non-productive pathway.[3,44–46] However, there is no fundamental reason why [2+2] chemistry cannot be accessed by the radical ions produced by CT, though such reactivity might be accessible only to a small number of electronically "matched" substrates in which [2+2] can compete with BET.

We chose to investigate the [2+2] photoreactivity of a series of donor-acceptor stilbene complexes within a **CB[8]** host (**Figure 1c**). Pre-assembled 1:1:1 donor-acceptor host-guest complexes provide an ideal platform to investigate the influence of electronics on CT-initiated [2+2] chemistry because the identity of the substrates can be modified without changing the geometry or stoichiometry of the pre-assembled complex.[38] While anionic, cationic, and neutral donor stilbenes form 1:1:1 complexes with a dimethylazastilbene acceptor in **CB[8]**, only one combination led to productive CT-initiated cross-[2+2] photocycloaddition, indicating that this CT-intiated reaction is indeed very sensitive to the electronic "matching" of the substrates. We used ultrafast spectroscopy and computational modeling to show that slow back electron transfer (BET) following CT is necessary for productive [2+2] reactivity. We further found that the cucrbit[8]uril host not only serves to template the ternary complex, but also protects the radical ion intermediates formed by CT, suggesting that host-chemistry could be used to access or improve other CT-initiated reactions.[47]

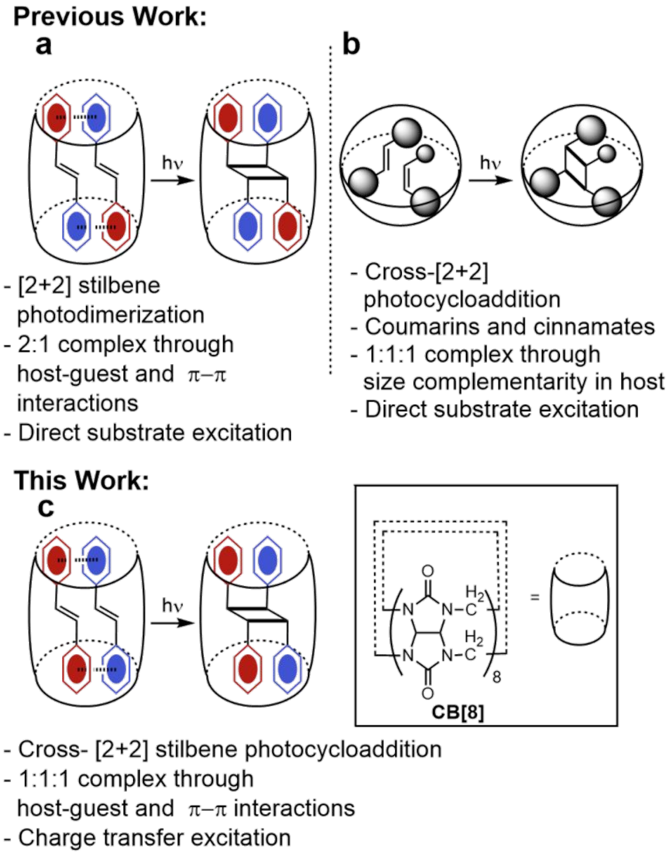
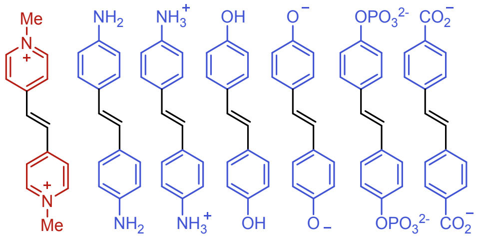


Figure 1. Previous work: **(a)** Head-to-tail [2+2] photodimerizations of donor-acceptor stilbenes templated by host-guest and π-π interactions. (red = electron acceptor, blue = electron donor). **(b)** Sterically controlled host-guest templated cross-[2+2] photocycloadditions of coumarins and cinnamates. **(c)** In this work, we explore whether electronic donor-acceptor and host-guest interactions can be used to template cross-[2+2] photocycloadditions. Structure of **CB[8]** is shown in the bottom right.

RESULTS AND DISCUSSION



1 **2a** **2b** **2c** **2d** **2e** **2f**

Chart 1. Electron acceptor (**1**) and donor (**2a – 2f**) stilbenes studied in this work.

Ramamurthy and coworkers previously showed that protonated 4-styrylpyridines undergo selective UV-mediated photodimerization as 2:1 complexes in **CB[8]**.[1] To enable photochemical studies under both acidic and basic conditions, we chose to investigate an electron-poor dimethylazastilbene dication (**1, Chart 1**) as the electron acceptor. We also selected several *para*-substituted stilbenes with variable donating ability and charge as the electron donors (**2a-2f**, see ESI for synthetic details). We then formed 1:1:1 complexes of the donor, acceptor, and **CB[8]** in water (to provide the requisite hydrophobic host-guest interactions)[48] and characterized these complexes by ^{1}H NMR and UV-Vis spectrophotometry.

To study the formation of 1:1:1 complexes, we added one equivalent of each of the electron-rich stilbenes to a 1.5 mM solution of **CB[8]** and **1** in neutral, acidic (1 M D_2SO_4), or basic (0.1 M Na_2CO_3) D_2O (see ESI for full experimental details). Acidic or basic solutions were used to protonate or deprotonate the donor stilbenes, respectively; 0.1 M Na_2CO_3 was used because **1** degraded in more basic 1 M NaOD (likely *via* single electron reduction by hydroxide, as has been reported for methyl viologen).[49] The ^{1}H NMR peaks of acceptor **1** shifted upfield upon addition of **CB[8]** due to shielding, indicative of host-guest complexation.[48] The relative integrated areas of **CB[8]** and **1** and binding titrations (discussed below) indicate the formation of a 1:1 complex, **CB[8]•1**. Addition of the donor stilbenes leads to further upfield shifts of the signals of **1**. As an example, **Figure 2a** shows the ^{1}H NMR spectrum of **1** upon addition of **CB[8]** followed by **2c**. Relative integrated areas of the signals of **1**, **2c**, and **CB[8]** and binding tirations indicate the formation of a 1:1:1 complex, **CB[8]•1•2c**. ^{1}H NMR spectra for other complexes can be found in ESI (Figures S8-S14). We followed the shifts of **1** or appearance of new peaks (depending on the timescale of exchange) while titrating **CB[8]** and/or donor stilbenes to determine the binding constants for all of the relevant supramolecular interactions (see Figures S15-S22 for titration data). These data are presented in **Table 1**, where "**CB[8]•1•2x**" refers to the association constant between donor stilbene **2x** and the pre-formed complex **CB[8]•1**. During these experiments, we discovered that the phenoxide stilbene, **2d**, degraded in ambient conditions over the course of an hour. Some of the ternary complexes formed quantitatively even at the lowest concentrations detectable *via* ^{1}H NMR, indicating binding constants greater than 10^5 M^{-1}.[50] Phosphate stilbene **2e** exhibits unique behavior among the donor stilbenes. Addition of **CB[8]** to **1•2e** leads to downfield shifts of **2e** signals, suggesting that **2e** does not form a ternary complex with **CB[8]** and **1**, but instead competes with **CB[8]** for binding to **1.** Unfavorable interactions between the partially negatively charged oxygens of the **CB[8]** portal and the highly negatively charged phosphate group of **2e** likely prevent its inclusion in a ternary complex (see Figure S12).[48] The carboxylate-containing stilbene, **2f**, weakly binds **1** outside of **CB[8]**, but the host-guest and ternary interactions are at least 1,000 times stronger, such that >99.9% of the interactions between **1** and **2f** take place within **CB[8]**.

Interaction	Condition	Binding Constant (M^{-1})
CB[8]•1	D_2O	(1.3 ± 0.2) X 10^5
CB[8]•1•2a	D_2O	$> 10^5$
CB[8]•1•2b	1 M D_2SO_4	(3.8 ± 0.5) X 10^2
CB[8]•1•2c	D_2O	$>10^5$
CB[8]•1•2f	0.1 M Na_2CO_3 in D_2O	$>10^5$
1•2e	0.1 M Na_2CO_3 in D_2O	(4.1 ± 0.2) X 10^2
1•2f	0.1 M Na_2CO_3 in D_2O	(3.37 ± 0.07) X 10^2

Table 1. Binding constants of relevant supramolecular interactions. See ESI for additional details.

We measured UV-Vis spectra of all the 1:1:1 complexes, in addition to those of the water-soluble stilbenes (**2a**, **2b**, **2d**, **2e**, and **2f**) on their own. Each of the stilbenes exhibited structured absorption bands in the near-UV with onsets between 300 and 350 nm (Figure S6). The complexes additionally revealed broad, weak, charge transfer (CT) bands in the visible region (**Figure 2b**). The **CB[8]•1•2a** complex CT band extends well into the near-IR, with an absorption onset of about 900 nm.

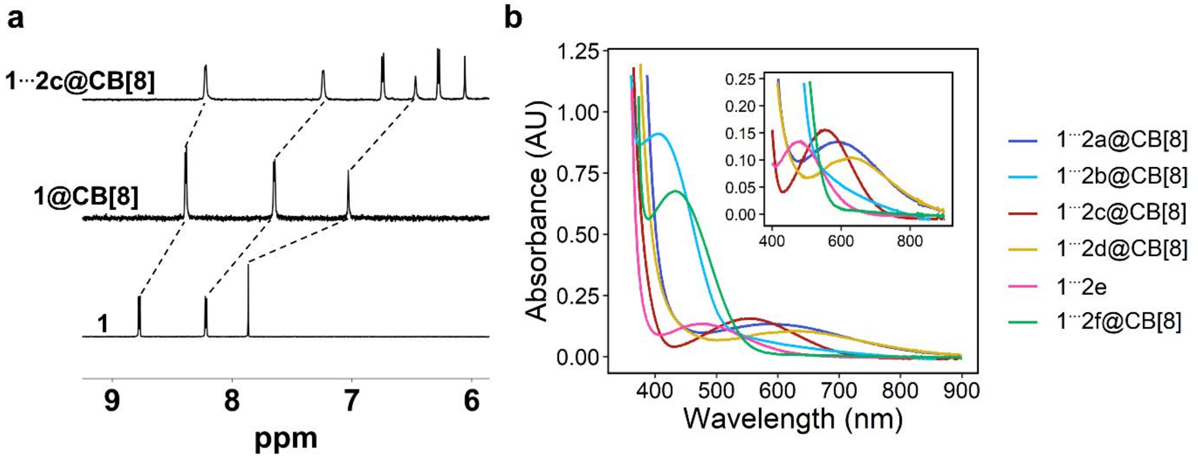
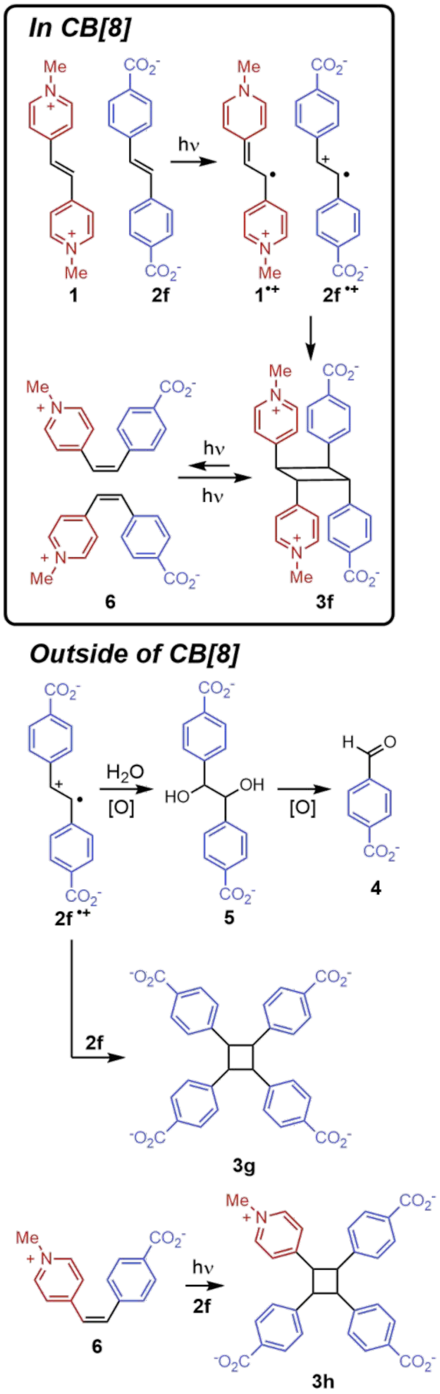


Figure 2. (a) ^1H NMR demonstrating supramolecular interactions of **1**, **CB[8]**, and **2c**. Measured at 1 mM in D_2O. Dotted lines are added to indicate upfield shifts. **(b)** UV-Vis of charge transfer bands of stilbene donor-acceptor complexes (15 mM with respect to **1**). Inset shows the same data with a zoomed-in y axis. Samples containing **2d**, **2e**, or **2f** were in 0.1 M Na_2CO_3. Samples containing **2b** were in 1 M H_2SO_4. All other samples were in neutral H_2O.

To investigate whether CT could be used to initiate cross-[2+2] reactions, we prepared 1.5 mM solutions of each complex (the ternary complexes of each pair in **CB[8]**, and **1•2e** without **CB[8]**) in nitrogen-purged H_2O. We irradiated the charge-transfer bands of each complex using appropriate LEDs: red (626 nm) for **2a** and **2d**, amber (605 nm) for **2c**, green (525 nm) for **2e**, and violet (400 nm) for **2b** and **2f**. We analyzed the samples via LCMS following 24 hours of irradiation. The only samples that exhibited conversion were **CB[8]•1•2f** and **CB[8]•1•2d**, but the latter complex containing **2d** underwent degradation to a mixture of undetermined products, which had also occurred in the absence of the complex. For the reaction of **CB[8]•1•2f**, LCMS analysis revealed a species with *m/z* consistent with the desired cross-[2+2] product, **3f** (**Scheme 1**).

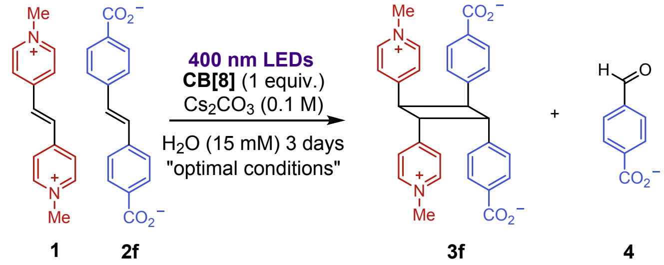
To verify the identity and investigate the stereochemistry of the adduct between **1** and **2f**, we subjected the crude reaction mixture after 2 days of irradiation to semi-prep HPLC purification to isolate adduct **3f**. We confirmed the *syn* stereochemistry of the product by 2D-NOESY NMR and by the large splitting of the cyclobutane protons, which is predicted by the Karplus relationship (see Figures S28-S31). The *syn* stereochemistry is consistent with the expected face-to-face π-π interaction of the stilbenes in the complexes. The primary side product was 4-carboxybenzaldehyde, **4**, which we isolated *via* HPLC and assigned *via* mass spectrometry, ^{1}H NMR, and ^{13}C NMR spectroscopies (see Figures S32-34). This compound is likely formed through oxidative cleavage of **7.** Based on previously reported oxidations of stilbenes in water, we believe that this product is formed *via* diffusion of **2f**$^{\bullet+}$ away from **1**$^{\bullet+}$ following the initial CT event.[4,51,52] **2f**$^{\bullet+}$ is attacked by water then further oxidized by **1** or its derivatives to form a diol, **5**, which is oxidatively cleaved to the benzaldehyde (**Scheme 1**). In support of this hypothesis, subjecting an authentic sample of diol **5** (1:1 dr) to the reaction conditions yielded exclusively **4**. Rigorous exclusion of oxygen via freeze-pump-thaw cycles and reaction under argon did not suppress formation of the benzaldehyde byproduct, supporting the role of **1** and its derivatives as terminal oxidants in these unwanted reactions (see SI). Irradiation of **2f** with 400 or 350 nm light in the absence of **1** and **CB[8]** led only to *cis-trans* isomerization.

A control reaction between **1** and **2f** conducted without **CB[8]** led to greater production of benzaldehyde byproduct **4** in addition to two new byproducts. Using LCMS and ^{1}H NMR, these new byproducts were determined to be **3g**, the cyclobutane produced by [2+2] dimerization of **2f**, and **3h**, an asymmetric cyclobutane containing three *p*-benzoate groups and one methylpyridinium (see Figures S35 – S38). Side products **4** and **3g** would both be produced via diffusion of **2f**$^{\bullet+}$ away from the initial CT complex. Benzaldehyde **4** arises through the oxidative pathway described above, while cyclobutane **3g** arises from attack by a second molecule of **2f**. The asymmetric cyclobutane product, **3h**, could arise *via* retro-[2+2] of **3f** to produce an asymmetric *cis*-stilbene, **6**, which then reacts with **2f** or **2f**$^{\bullet+}$. UV-Vis spectroscopy of **3f** reveals an absorption tail in the visible region, such that retro-[2+2] could plausibly be slowly initiated by the 400 nm LEDs (Figure S7). Identification of these products reveals that **CB[8]** acts not just to pre-assemble **1** and **2f** into a CT complex prior to irradiation, but also to prevent diffusion of reactive intermediates produced by irradiation, including **2f**$^{\bullet+}$ and the asymmetric stilbene produced by retro-[2+2]. A similar protective role for a macrocyclic host has previously been demonstrated for a pillar[6]aren-azastilbene system.[1,53]



Scheme 1. Proposed mechanism for the reaction of **1** and **2f**. The upper portion are steps facilitated by the donor-acceptor host-guest interaction inside of **CB[8]**. Steps outside of **CB[8]** are suppressed by removal of free **2f** by **CB[8]**. The relative stereochemistries of **3g** and **3h** were not determined.

To validate that the [2+2] reaction between **1** and **2f** occurs *via* CT, we tested the reaction under various conditions (**Table 2**). We found that irradiation of a 15 mM solution of the CT complex with 400 nm LEDs in 0.1 M Cs_2CO_3 provides the highest yield of **3f** (67%, Table 2, Entry 1, see ESI for details). Irradiation with higher-energy 350-nm light led to a decreased yield of **3f** relative to **4**, likely due to increased excitation of free **2f** instead of the CT complex (Entry 2). The reaction could proceed under 470 nm irradiation, albeit with slightly lower yield compared to 400 nm, while lower-energy light provided very little product (Entries 3 and 4). Longer irradiation times did not change the product distribution or yields. Light was required for both desired and side reactions to occur (Entry 5). These irradiation experiments suggest that the [2+2] reaction between **1** and **2f** is initiated by CT. Consistent with the contributions of supramolecular and diffusion processes in this reaction, concentration had a significant effect on reaction efficiency, with 15 mM conditions leading to a higher yield of **3f** relative to 1.5 mM conditions (Entry 6). As discussed above, **CB[8]** improves the selectivity for and yield of **3f** (Entry 8).



Entry	Deviation from optimal conditions	Yield of **3f** (%)	Yield of **4** (%)
1	**none**	**67 (25 % isolated yield)**	**20**
2	350 nm lamps	31	30
3	Blue (470 nm) LEDs	55	28
4	Green (525 nm) LEDs	9	5
5	No light	0	0
6	1.5 mM	23	37
7	Na_2CO_3 instead of Cs_2CO_3	13	5
8	No **CB[8]**	20	16

Table 2. Yield of desired cyclobutane product **3f** and undesired aldehyde side product **4** under various reaction conditions. The optimal conditions are indicated in the chemical equation above the table. Yields determined by LCMS with an internal standard of butylhydroxytoluene (see ESI). All values represent the average of two experiments, with a range of less than 5% for all cases except for entry 5, which has a range of 15%. Isolated yield for Entry 1 was determined following purification by HPLC (see ESI).

Having confirmed that **1** and **2f** engage in a CT-initiated cross-[2+2] reaction, we sought to understand why this was the only pair of substrates that exhibited the desired photoreactivity despite the similar complexation behavior exhibited by other stilbenes. We modelled the ternary complexes of **2a**, **2b**, **2c**, and **2f** with **1** and **CB[8]** using DFT using B3LYP functional, 6-31G(d) basis set, and a CPCM H_2O solvent model, which have been used to model donor-acceptor host-guest ternary complexes with **CB[8]** before (see ESI for computational details).[38] The energy-minimized structures all exhibited similar geometries, with the alkenes nearly parallel (<15°) and well within the

4.2 Å distance defined by the Schmidt criterion for [2+2] reactions,[12] indicating that the differences in reactivity were not due to the geometry of the CT complexes (**Figure 3a**).

We hypothesized that the primary pathway that competes with the desired [2+2] reaction following CT excitation is back electron transfer (BET). To investigate this hypothesis, we measured the rates of BET following CT using transient absorption (TA) spectroscopy (**Figure 3b**). We found that the successful **CB[8]•1•2f** complex exhibited much slower BET (τ = 40 ps), than the other pairs (τ between <0.3 and 10 ps). The relatively longer lifetime of **1**$^{\bullet+}$ and **2f**$^{+}$ indicates that the [2+2] reaction is quite slow, and is consistent with the role of **CB[8]** in protecting these intermediates. The relative inefficiency of the [2+2] reaction is further evidenced by the long reaction times required (3 days).

What is the origin of the dramatic differences in BET, and thus reactivity? We turned to the classical Marcus relationship, which relates the rate of electron transfer, k_{BET}, to the associated free energy change according to Eq. 1:

$$k_{\text{BET}} = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}} \qquad (1)$$

where k_B is Bolzmann's constant, T is temperature, h is Planck's constant, R is the gas constant and $\Delta G^{\ddagger}$ is the free energy of activation given by Eq. 2.

$$\Delta G^{\ddagger} = \frac{\lambda}{4}\left(1 + \frac{\Delta G_{\text{BET}}}{\lambda}\right)^2 \qquad (2)$$

In Eq. 2, λ is the reorganization energy and ΔG_{BET} is the free energy change of the back electron transfer. ΔG_{BET} represents a combination of the energy difference between the LUMO of one molecule and the HOMO of the other, ΔE_{CT}, and the Coulombic work associated with charge separation and recombination (see ESI for a full derivation). The parameters that change between our various substrate pairs are ΔE_{CT} and the charge of the electron-rich stilbene. The effect of different ΔE_{CT} produces the well-known Marcus curve, wherein electron transfer is accelerated by greater CT energy changes up until the reorganization energy, after which greater free energy changes lead to deceleration in the "Marcus inverted region". The effect of charge can be understood qualitatively. If the CT state has weaker electrostatic stabilization than the ground state, then BET will be more favorable than would be predicted based solely on CT energy as calculated using the energy levels of isolated substrates or measured by UV-Vis.

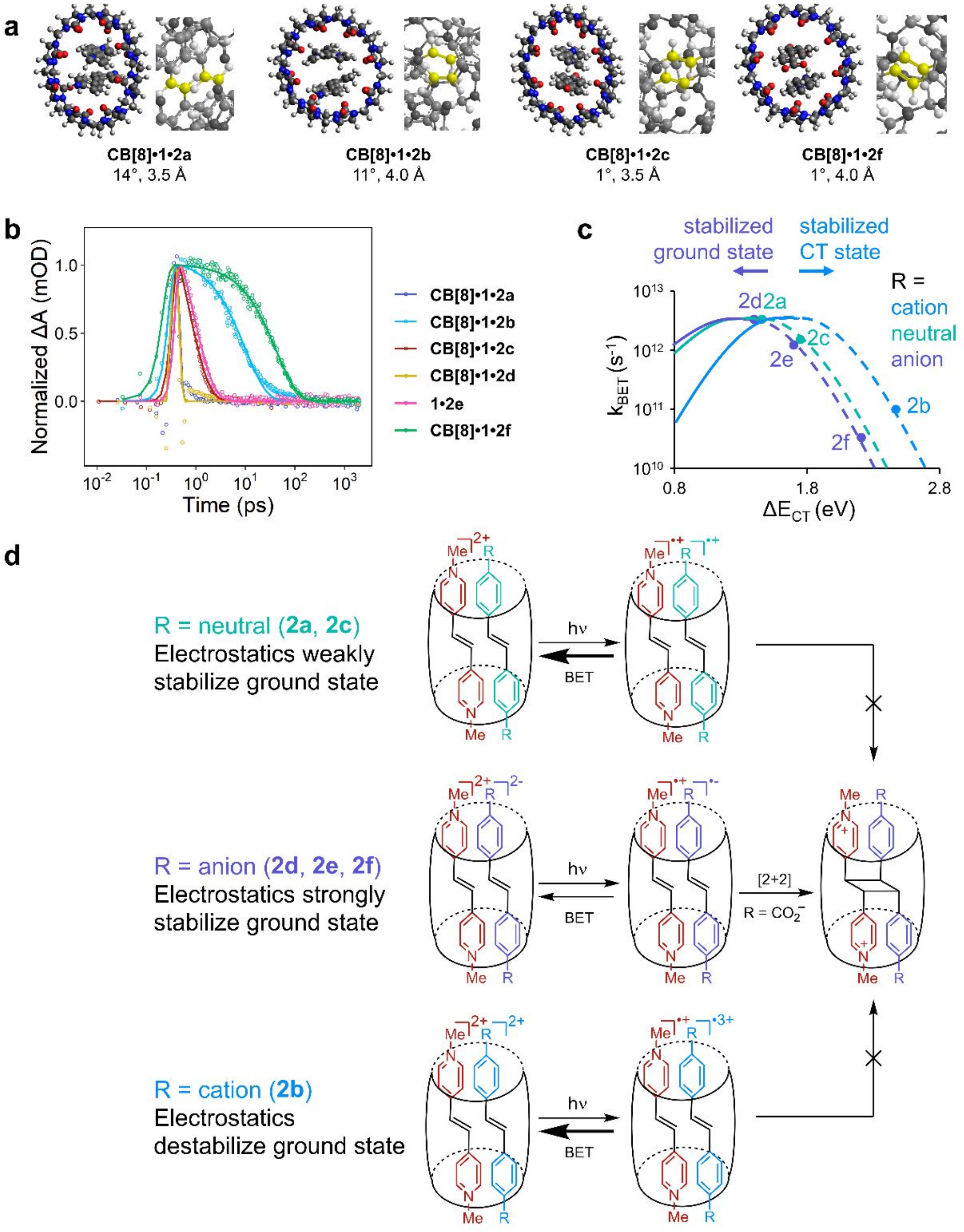

a
CB[8]•1•2a
14°, 3.5 Å
CB[8]•1•2b
11°, 4.0 Å
CB[8]•1•2c
1°, 3.5 Å
CB[8]•1•2f
1°, 4.0 Å
b
Normalized ΔA (mOD)
1.0
0.5
0.0
10-2
10-1
100
101
102
103
Time (ps)
CB[8]•1•2a
CB[8]•1•2b
CB[8]•1•2c
CB[8]•1•2d
1•2e
CB[8]•1•2f
c
stabilized ground state
stabilized CT state
R =
cation
neutral
anion
kBET (s-1)
1013
1012
1011
1010
0.8
1.8
2.8
ΔECT (eV)
2d
2a
2c
2e
2b
2f
d
R = neutral (2a, 2c)
Electrostatics weakly stabilize ground state
R = anion (2d, 2e, 2f)
Electrostatics strongly stabilize ground state
R = cation (2b)
Electrostatics destabilize ground state
Me
N
R
2+
•+
•+
2-
•-
•3+
hν
BET
[2+2]
R = CO2−
+

Figure 3. (a) DFT-computed energy-minimized structures of several complexes. The images on the right highlight the potentially reactive double bonds in yellow, and the angle and distances below each structure indicate the angle and distance between them. **(b)** BET monitored by transient absorption spectroscopy following excitation of the charge transfer (CT) complexes in water (7.5 mM). The CT band of the complexes were excited with a pump pulse (540 nm for **2a** and **2d**, 490 nm for **2c**, and 440 nm for all others) and time-resolved optical spectra were measured with a delayed pump pulse. The plot shows the decay of the signal of the singly oxidized stilbenes (600 nm for **2a**, 550 nm for **2c**, 540 nm for **2d**, 490 nm for **2e**, and 480 nm for **2f**). The solid curves show mono-exponential fits. **(c)** Electron transfer rate vs. charge transfer energy determined by UV-vis absorption onset. Labels next to each data point indicate the electron donor. The lines qualitatively represent the Marcus relationship predicted by Eq. 1-4. The position of the Marcus curve along the x-axis depends on the charge of the donor stilbene, while the position of each data point on the curve is determined by the CT energy of the corresponding donor-acceptor pair. Dotted lines indicate the Marcus inverted region. **(d)** CT excitation produces radical pairs that can either react in a formal [2+2] cycloaddition or relax through back electron transfer (BET) to the ground state. The relative electrostatic stabilities of the CT and ground states are determined by the charge (anionic, neutral, or cationic) of the electron donor.

The fact that the substrate pair with the slowest BET also has the greatest CT energy as measured by UV-vis suggests that the BET process falls within the Marcus inverted region, where greater energy differences between the charge separated and ground state serve to slow down BET. A plot of BET rate determined from TA vs. CT energy determined from the onsets of UV-vis absorption indeed reveals decreased BET rate with greater CT energy (**Figure 3c**). This Marcus inversion effect is enhanced by the differences in electrostatic interactions between the various substrate pairs (**Figure 3d**). Weaker electrostatic interactions in the CT state relative to the ground state push the BET process of the **CB[8]•1•2f** deeper into the Marcus inverted region. This effect also explains why the **CB[8]•1•2b**, which has a very similar CT energy to the successful pair, has slower BET: electrostatic interactions in this pair make the free energy change of BET less negative, accelerating it by pulling it out of the Marcus inverted region. These trends are depicted qualitatively by the lines in **Figure 3c**.

Although we chose to study the [2+2] photocycloaddition of stilbenes, BET and its dependence on electrostatics should play a critical role in any CT-initiated cross-photocyloadditions, including [2+2] reactions of other alkene substrates or [4+4] reactions of anthracenes. Among the para-substituted symmetric stilbenes we studied, **1** and **2f** were a uniquely productive pair for the cross-[2+2] photoreaction. On the one hand, small CT gaps are favored since irradiating CT bands selectively requires them to be in the visible, with red-shifted CT excitations being desirable. However, smaller CT gaps pull BET out of the Marcus inverted region, leading to faster BET that outcompetes the desired reaction. A possible solution to this conundrum is to introduce charge to the substrates, which pushes BET back into the Marcus inverted region *via* the electrostatic terms in Eq. 3. However, introducing too much negative charge to a substrate shuts down host-guest interactions due to repulsion by the partially negatively charged **CB[8]** portal, as is the case with **2e**. Thus, **2f** appears to possess a delicate balance of energy levels and charge such that it can engage in ternary complexation with **1** and **CB[8]**, form a CT complex in the visible range, and undergo cycloaddition competitive with BET.

Intrigued by the potentially unique reactivity of **1** and **2f**, we used DFT to calculate the electronic structure of 36 different *para*-substituted symmetric stilbenes, then used Eqs. 1-4 to predict the relative BET rates between **1** and each stilbene following charge transfer (see ESI for DFT results). We estimated the reorganization energy and dielectric constant within **CB[8]** based on previous studies of electron transfer in **CB[8]**.[48,54] We emphasize that these calculations were not meant to quantitatively predict BET rates, but rather to compare BET rates in possible stilbene pairs. No neutral stilbenes exhibited both visible CT (i.e. <2.8 eV CT gap) and relatively slow BET. The only anionic stilbenes that met these criteria were **2f**, other more highly charged anionic substrates such as **2e**, and a sulfonate-substituted stilbene **2g**. We synthesized **2g** (see ESI), but it produced an insoluble complex with **1** and **CB[8]**, preventing further study. Our predictions, along with the experimental results of **2e** as representative highly charged anion, suggest that **2f** is the only para-substituted symmetric stilbene among the 36 we modeled able to undergo host-guest templated, CT-initiated cross-[2+2] with **1**.

CONCLUSION

We hypothesized that donor-acceptor host-guest ternary complexes could template [2+2] photocycloadditions to achieve selective cross-reactivity. We investigated a series of model stilbene substrates and found that although many pairs formed the desired ternary complexes, only one exhibited the desired photoreactivity following CT excitation. We attribute this divergent reactivity to highly variable BET rates measured by transient absorption spectroscopy. The optimal pair of donor and acceptor stilbenes exhibit relatively slow back electron transfer following CT, allowing the desired reaction to occur before charge recombination. This slow BET, in turn, is a product of the energy levels and complementary charges of the substrates, which stabilize the ground state relative to the CT state and thus slow down BET *via* Marcus inversion. We were able to translate our mechanistic understanding of photoreactivity into a computational screen of stilbene substrates that recapitulated our experimental results. By illustrating the critical role of BET in determining photoreactivity, our work can enable analogous computational screens for the discovery of additional host-guest reactions initiated by CT. We further found that the host-guest interaction provided by **CB[8]** not only templates the reaction, but also serves to protect the initially generated radical ions following CT from side reactions. This work illustrates the beneficial role that host-guest chemistry can play in discovering and optimizing CT-initiated photochemistry.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

ACKNOLWEDGEMENTS

This research was primarily supported by an Army Research Office Young Investigator Program grant (#72846-CH-YIP to J.A.K.). C.T.E. acknowledges support from a National Science Foundation Graduate Research Fellowship (grant no. DGE-1842165). C.O. acknowledges support from an Academic Year Undergraduate Research Grant from Northwestern University. S.P., M.C.H., and E.A.W. acknowledge support from the Northwestern University Materials Research Science and Engineering Center (MRSEC) (NSF DMR-1720139). This work made use of the IMSERC at Northwestern University, which has received support from the Soft and Hybrid Nanotechnology Experimental (SHyNE) Resource (NSF ECCS-1542205), the State of Illinois, and the International Institute for Nanotechnology (IIN). This research was supported in part through the computational resources and staff contributions provided for the Quest high performance computing facility at Northwestern University, which is jointly supported by the Office of the Provost, the Office for Research, and Northwestern University Information Technology.

REFERENCES

(1) Maddipatla, M. V. S. N.; Kaanumalle, L. S.; Natarajan, A.; Pattabiraman, M.; Ramamurthy, V. Preorientation of Olefins toward a Single Photodimer: Cucurbituril-Mediated Photodimerization of Protonated Azastilbenes in Water. *Langmuir* **2007**, *23* (14), 7545–7554. https://doi.org/10.1021/la700803k.

(2) Rao, K. S. S. P.; Hubig, S. M.; Moorthy, J. N.; Kochi, J. K. Stereoselective Photodimerization of (E)-Stilbenes in Crystalline γ-Cyclodextrin Inclusion Complexes. *J. Org. Chem.* **1999**, *64* (22), 8098–8104. https://doi.org/10.1021/jo9903149.

(3) Doi, T.; Kashida, H.; Asanuma, H. Efficiency of [2 + 2] Photodimerization of Various Stilbene Derivatives within the DNA Duplex Scaffold. *Org. Biomol. Chem.* **2015**, *13* (15), 4430–4437. https://doi.org/10.1039/C4OB02520B.

(4) Lewis, F. D.; Bedell, A. M.; Dykstra, R. E.; Elbert, J. E.; Gould, I. R.; Farid, S. Photochemical Generation, Isomerization, and Oxygenation of Stilbene Cation Radicals. *J. Am. Chem. Soc.* **1990**, *112* (22), 8055–8064. https://doi.org/10.1021/ja00178a031.

(5) D'Auria, M.; Racioppi, R. The Photodimerisation of Coumarin. *J. Photochem. Photobiol. Chem.* **2004**, *163* (3), 557–559. https://doi.org/10.1016/j.jphotochem.2004.02.012.

(6) Jiang, Y.; Wang, C.; Rogers, C. R.; Kodaimati, M. S.; Weiss, E. A. Regio- and Diastereoselective Intermolecular [2+2] Cycloadditions Photocatalysed by Quantum Dots. *Nat. Chem.* **2019**, *11* (11), 1034–1040. https://doi.org/10.1038/s41557-019-0344-4.

(7) Alonso, R.; Bach, T. A Chiral Thioxanthone as an Organocatalyst for Enantioselective [2+2] Photocycloaddition Reactions Induced by Visible Light. *Angew. Chem. Int. Ed.* **2014**, *53* (17), 4368–4371. https://doi.org/10.1002/anie.201310997.

(8) Yoon, T. P. Visible Light Photocatalysis: The Development of Photocatalytic Radical Ion Cycloadditions. *ACS Catal.* **2013**, *3* (5), 895–902. https://doi.org/10.1021/cs400088e.

(9) Pattabiraman, M.; Natarajan, A.; Kaliappan, R.; Mague, J. T.; Ramamurthy, V. Template Directed Photodimerization of Trans-1,2-Bis(n-Pyridyl)Ethylenes and Stilbazoles in Water. *Chem. Commun.* **2005**, *36*, 4542–4544. https://doi.org/10.1039/B508458J.

(10) Ischay, M. A.; Ament, M. S.; Yoon, T. P. Crossed Intermolecular [2 + 2] Cycloaddition of Styrenes by Visible Light Photocatalysis. *Chem. Sci.* **2012**, *3* (9), 2807–2811. https://doi.org/10.1039/C2SC20658G.

(11) Tong, F.; Xu, W.; Guo, T.; Lui, B. F.; Hayward, R. C.; Palffy-Muhoray, P.; Al-Kaysi, R. O.; Bardeen, C. J. Photomechanical Molecular Crystals and Nanowire Assemblies Based on the [2+2] Photodimerization of a Phenylbutadiene Derivative. *J. Mater. Chem. C* **2020**, *8* (15), 5036–5044. https://doi.org/10.1039/C9TC06946A.

(12) Ramamurthy, V.; Sivaguru, J. Supramolecular Photochemistry as a Potential Synthetic Tool: Photocycloaddition. *Chem. Rev.* **2016**, *116* (17), 9914–9993. https://doi.org/10.1021/acs.chemrev.6b00040.

(13) Maddipatla, M. V. S. N.; Pattabiraman, M.; Natarajan, A.; Srivastav, K.; Mague, J. T.; Ramamurthy, V. Regioselective Photodimerization of Pyridyl-Butadienes within Cucurbit[8]Uril Cavities. *Org. Biomol. Chem.* **2012**, *10* (46), 9219–9222. https://doi.org/10.1039/C2OB26743H.

(14) Jon, S. Y.; Ko, Y. H.; Park, S. H.; Kim, H.-J.; Kim, K. A Facile, Stereoselective [2 + 2] Photoreaction Mediated by Cucurbit[8]Uril. *Chem. Commun.* **2001**, *19*, 1938–1939. https://doi.org/10.1039/B105153A.

(15) Nakamura, A.; Irie, H.; Hara, S.; Sugawara, M.; Yamada, S. Regiospecific [2 + 2] Photocyclodimerization of Trans-4-Styrylpyridines Templated by Cucurbit[8]Uril. *Photochem. Photobiol. Sci.* **2011**, *10* (9), 1496–1500. https://doi.org/10.1039/C1PP05079F.

(16) Gromov, S. P.; Vedernikov, A. I.; Kuz'mina, L. G.; Kondratuk, D. V.; Sazonov, S. K.; Strelenko, Y. A.; Alfimov, M. V.; Howard, J. A. K. Photocontrolled Molecular Assembler Based on Cucurbit[8]Uril: [2+2]-Autophotocycloaddition of Styryl Dyes in the Solid State and in Water. *Eur. J. Org. Chem.* **2010**, *2010* (13), 2587–2599. https://doi.org/10.1002/ejoc.200901324.

(17) Pemberton, B. C.; Barooah, N.; Srivatsava, D. K.; Sivaguru, J. Supramolecular Photocatalysis by Confinement—Photodimerization of Coumarins within Cucurbit[8]Urils. *Chem. Commun.* **2009**, *46* (2), 225–227. https://doi.org/10.1039/B920605A.

(18) Ramamurthy, V.; Parthasarathy, A. Chemistry in Restricted Spaces: Select Photodimerizations in Cages, Cavities, and Capsules. *Isr. J. Chem.* **2011**, *51* (7), 817–829. https://doi.org/10.1002/ijch.201100065.

(19) Pattabiraman, M.; Sivaguru, J.; Ramamurthy, V. Cucurbiturils as Reaction Containers for Photocycloaddition of Olefins. *Isr. J. Chem.* **2018**, *58* (3–4), 264–275. https://doi.org/10.1002/ijch.201700100.

(20) Vallavoju, N.; Sivaguru, J. Supramolecular Photocatalysis: Combining Confinement and Non-Covalent Interactions to Control Light Initiated Reactions. *Chem. Soc. Rev.* **2014**, *43* (12), 4084–4101. https://doi.org/10.1039/C3CS60471C.

(21) Kang, Y.; Tang, X.; Yu, H.; Cai, Z.; Huang, Z.; Wang, D.; Xu, J.-F.; Zhang, X. Supramolecular Catalyst Functions in Catalytic Amount: Cucurbit[8]Uril Accelerates the Photodimerization of Brooker's Merocyanine. *Chem. Sci.* **2017**, *8* (12), 8357–8361. https://doi.org/10.1039/C7SC04125J.

(22) Tang, B.; Zhao, J.; Xu, J.-F.; Zhang, X. Cucurbit[n]Urils for Supramolecular Catalysis. *Chem. – Eur. J.* **2020**, *26* (67), 15446–15460. https://doi.org/10.1002/chem.202003897.

(23) Biedermann, F.; Ross, I.; Scherman, O. A. Host–Guest Accelerated Photodimerisation of Anthracene-Labeled Macromolecules in Water. *Polym. Chem.* **2014**, *5* (18), 5375–5382. https://doi.org/10.1039/C4PY00627E.

(24) Hu, X.; Liu, F.; Zhang, X.; Zhao, Z.; Liu, S. Expected and Unexpected Photoreactions of 9-(10-)Substituted Anthracene Derivatives in Cucurbit[n]Uril Hosts. *Chem. Sci.* **2020**, *11* (18), 4779–4785. https://doi.org/10.1039/D0SC00409J.

(25) Moorthy, J. N.; Venkatesan, K.; Weiss, R. G. Photodimerization of Coumarins in Solid Cyclodextrin Inclusion Complexes. *J. Org. Chem.* **1992**, *57* (12), 3292–3297. https://doi.org/10.1021/jo00038a012.

(26) Ji, J.; Wu, W.; Liang, W.; Cheng, G.; Matsushita, R.; Yan, Z.; Wei, X.; Rao, M.; Yuan, D.-Q.; Fukuhara, G.; Mori, T.; Inoue, Y.; Yang, C. An Ultimate Stereocontrol in Supramolecular Photochirogenesis: Photocyclodimerization of 2-Anthracenecarboxylate Mediated by Sulfur-Linked β-Cyclodextrin Dimers. *J. Am. Chem. Soc.* **2019**, *141* (23), 9225–9238. https://doi.org/10.1021/jacs.9b01993.

(27) Zhang, C.-C.; Zhang, Y.-M.; Zhang, Z.-Y.; Wu, X.; Yu, Q.; Liu, Y. Photoreaction-Driven Two-Dimensional Periodic Polyrotaxane-Type Supramolecular Nanoarchitecture. *Chem. Commun.* **2019**, *55*, 8138–8141. https://doi.org/10.1039/C9CC03705E.

(28) Guo, Q.-H.; Jia, M.; Liu, Z.; Qiu, Y.; Chen, H.; Shen, D.; Zhang, X.; Tu, Q.; Ryder, M. R.; Chen, H.; Li, P.; Xu, Y.; Li, P.; Chen, Z.; Shekhawat, G. S.; Dravid, V. P.; Snurr, R. Q.; Philp, D.; Sue, A. C.-H.; Farha, O. K.; Rolandi, M.; Stoddart, J. F. Single-Crystal Polycationic Polymers Obtained by Single-Crystal-to-Single-Crystal Photopolymerization. *J. Am. Chem. Soc.* **2020**, *142* (13), 6180–6187. https://doi.org/10.1021/jacs.9b13790.

(29) Schmidt Bernhard V. K. J.; Barner‐Kowollik Christopher. Dynamic Macromolecular Material Design—The Versatility of Cyclodextrin‐Based Host–Guest Chemistry. *Angew. Chem. Int. Ed.* **2017**, *56* (29), 8350–8369. https://doi.org/10.1002/anie.201612150.

(30) Kalayci, K.; Frisch, H.; Barner-Kowollik, C.; Truong, V. X. Wavelength-Dependent Stiffening of Hydrogel Matrices via Redshifted [2+2] Photocycloadditions. *Adv. Funct. Mater.* **2020**, *30* (15), 1908171. https://doi.org/10.1002/adfm.201908171.

(31) Blasco, E.; Wegener, M.; Barner‐Kowollik, C. Photochemically Driven Polymeric Network Formation: Synthesis and Applications. *Adv. Mater.* **2017**, *29* (15), 1604005. https://doi.org/10.1002/adma.201604005.

(32) Horiuchi, S.; Nishioka, Y.; Murase, T.; Fujita, M. Both [2+2] and [2+4] Additions of Inert Aromatics via Identical Ternary Host–Guest Complexes. *Chem. Commun.* **2010**, *46* (20), 3460–3462. https://doi.org/10.1039/C003191G.

(33) Nishioka, Y.; Yamaguchi, T.; Yoshizawa, M.; Fujita, M. Unusual [2+4] and [2+2] Cycloadditions of Arenes in the Confined Cavity of Self-Assembled Cages. *J. Am. Chem. Soc.* **2007**, *129* (22), 7000–7001. https://doi.org/10.1021/ja071591x.

(34) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. Functional Molecular Flasks: New Properties and Reactions within Discrete, Self-Assembled Hosts. *Angew. Chem. Int. Ed.* **2009**, *48* (19), 3418–3438. https://doi.org/10.1002/anie.200805340.

(35) Yoshizawa, M.; Takeyama, Y.; Okano, T.; Fujita, M. Cavity-Directed Synthesis within a Self-Assembled Coordination Cage: Highly Selective [2 + 2] Cross-Photodimerization of Olefins. *J. Am. Chem. Soc.* **2003**, *125* (11), 3243–3247. https://doi.org/10.1021/ja020718+.

(36) Clements, A. R.; Pattabiraman, M. γ-Cyclodextrin Mediated Photo-Heterodimerization between Cinnamic Acids and Coumarins. *J. Photochem. Photobiol. Chem.* **2015**, *297*, 1–7. https://doi.org/10.1016/j.jphotochem.2014.10.001.

(37) Lee, J. W.; Kim, K.; Choi, S.; Ko, Y. H.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Unprecedented Host-Induced Intramolecular Charge-Transfer Complex Formation. *Chem. Commun.* **2002**, *22*, 2692–2693. https://doi.org/10.1039/B208280B.

(38) Biedermann, F.; Scherman, O. A. Cucurbit[8]Uril Mediated Donor–Acceptor Ternary Complexes: A Model System for Studying Charge-Transfer Interactions. *J. Phys. Chem. B* **2012**, *116* (9), 2842–2849.

(39) Lewis, T. N.; Tonnelé, C.; Shuler, W. G.; Kasun, Z. A.; Sato, H.; Berges, A. J.; Rodriguez, J. R.; Krische, M. J.; Casanova, D.; Bardeen, C. J. Chemical Tuning of Exciton versus Charge-Transfer Excited States in Conformationally Restricted Arylene Cages. *J. Am. Chem. Soc.* **2021**. https://doi.org/10.1021/jacs.1c08176.

(40) Haga, N.; Nakajima, H.; Takayanagi, H.; Tokumaru, K. Exclusive Production of a Cycloadduct from Selective Excitation of the Charge-Transfer Complex between Acenaphthylene and Tetracyanoethylene in the Crystalline State in Contrast to Failure of Reaction in Solution. *Chem. Commun.* **1997**, *13*, 1171–1172. https://doi.org/10.1039/A702564E.

(41) Haga, N.; Nakajima, H.; Takayanagi, H.; Tokumaru, K. Photoinduced Electron Transfer between Acenaphthylene and Tetracyanoethylene: Effect of Irradiation Mode on Reactivity of the Charge-Transfer Complex and the Resulted Radical Ion Pair in Solution and Crystalline State. *J. Org. Chem.* **1998**, *63* (16), 5372–5384. https://doi.org/10.1021/jo9801824.

(42) Haga, N.; Takayanagi, H.; Tokumaru, K. The Factor Which Determines Whether Excitation of Charge-Transfer Complexes Leads to Final Net Products in Comparison with the Reactivity on Excitation of One of the Components. *Photochem. Photobiol. Sci.* **2003**, *2* (11), 1215–1219. https://doi.org/10.1039/B305196J.

(43) Haga, N.; Takayanagi, H.; Tokumaru, K. Photoinduced Electron Transfer between Acenaphthylene and 1,4-Benzoquinones. Formation of Dimers of Acenaphthylene and 1 : 1-Adducts and Effect of Excitation Mode on Reactivity of the Charge-Transfer Complexes. *J. Chem. Soc. Perkin Trans. 2* **2002**, *4*, 734–745. https://doi.org/10.1039/B200098A.

(44) Ushakov, E. N.; Nadtochenko, V. A.; Gromov, S. P.; Vedernikov, A. I.; Lobova, N. A.; Alfimov, M. V.; Gostev, F. E.; Petrukhin, A. N.; Sarkisov, O. M. Ultrafast Excited State Dynamics of the Bi- and Termolecular Stilbene-Viologen Charge-Transfer Complexes Assembled via Host–Guest Interactions. *Chem. Phys.* **2004**, *298* (1), 251–261. https://doi.org/10.1016/j.chemphys.2003.12.002.

(45) Ushakov, E. N.; Martyanov, T. P.; Vedernikov, A. I.; Sazonov, S. K.; Strelnikov, I. G.; Klimenko, L. S.; Alfimov, M. V.; Gromov, S. P. Stereospecific [2 + 2]-Cross-Photocycloaddition in a Supramolecular Donor–Acceptor Complex. *Tetrahedron Lett.* **2019**, *60* (2), 150–153. https://doi.org/10.1016/j.tetlet.2018.11.077.

(46) Martyanov, T. P.; Ushakov, E. N.; Nuriev, V. N.; Aleksandrova, N. A.; Sazonov, S. K.; Vedernikov, A. I.; Kuz'mina, L. G.; Klimenko, L. S.; Martyanova, E. G.; Gromov, S. P. Pseudodimeric Complexes of an (18-Crown-6)Stilbene with Styryl Dyes Containing an Ammonioalkyl Group: Synthesis, Structure, and Stereospecific [2 + 2] Cross-Photocycloaddition. *J. Org. Chem.* **2021**, *86* (4), 3164–3175. https://doi.org/10.1021/acs.joc.0c02514.

(47) Eckdahl, C.; Ou, C.; Padgaonkar, S.; Hersam, M.; Weiss, E.; Kalow, J. Photoreactivity of Donor-Acceptor Stilbene Complexes in a Macrocyclic Host. **2022**. https://doi.org/10.26434/chemrxiv-2022-hwsl7.

(48) Masson, E.; Ling, X.; Joseph, R.; Kyeremeh-Mensah, L.; Lu, X. Cucurbituril Chemistry: A Tale of Supramolecular Success. *RSC Adv.* **2012**, *2* (4), 1213–1247. https://doi.org/10.1039/C1RA00768H.

(49) Rieger, A. L.; Edwards, J. O. Methyl Viologen Reactions. 5. Rates and Mechanism of Cation-Radical Formation in Aqueous Base. *J. Org. Chem.* **1988**, *53* (7), 1481–1485. https://doi.org/10.1021/jo00242a025.

(50) Hibbert, D. B.; Thordarson, P. The Death of the Job Plot, Transparency, Open Science and Online Tools, Uncertainty Estimation Methods and Other Developments in Supramolecular Chemistry Data Analysis. *Chem. Commun.* **2016**, *52* (87), 12792–12805. https://doi.org/10.1039/C6CC03888C.

(51) Wu, X.; Davis, A. P.; Fry, A. J. Electrocatalytic Oxidative Cleavage of Electron-Deficient Substituted Stilbenes in Acetonitrile−Water Employing a New High Oxidation Potential Electrocatalyst. An Electrochemical Equivalent of Ozonolysis. *Org. Lett.* **2007**, *9* (26), 5633–5636. https://doi.org/10.1021/ol7026416.

(52) Halas, S. M.; Okyne, K.; Fry, A. J. Anodic Oxidation of Stilbenes Bearing Electron-Withdrawing Ring Substituents. *Electrochimica Acta* **2003**, *48* (13), 1837–1844. https://doi.org/10.1016/S0013-4686(03)00250-0.

(53) Xia, D.; Wang, P.; Shi, B. Controlling the Photochemical Reaction of an Azastilbene Derivative in Water Using a Water-Soluble Pillar[6]Arene. *Org. Biomol. Chem.* **2017**, *15* (36), 7618–7622. https://doi.org/10.1039/C7OB01441D.

(54) Zhang, W.; Gan, S.; Vezzoli, A.; Davidson, R. J.; Milan, D. C.; Luzyanin, K. V.; Higgins, S. J.; Nichols, R. J.; Beeby, A.; Low, P. J.; Li, B.; Niu, L. Single-Molecule Conductance of Viologen–Cucurbit[8]Uril Host–Guest Complexes. *ACS Nano* **2016**, *10* (5), 5212–5220. https://doi.org/10.1021/acsnano.6b00786.

FOOTNOTES

† Electronic Supporting Information (ESI) available: Full experimental procedures, ^{1}H and ^{13}C NMR spectra of newly synthesized compounds, UV-vis spectra of compounds and complexes, titration experiments, LED emission profiles, control reactions, full Marcus theory treatment, and coordinates of DFT-optimized geometries.