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FULL PAPER

π-Bridge Substitution in DASAs: the Subtle Equilibrium Between Photochemical Improvements and Thermal Control

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Abstract: Donor–Acceptor Stenhouse Adducts (DASAs) are playing an outstanding role as innovative and versatile photoswitches. Until now, all the efforts have been spent on modifying donor and acceptor moieties, to modulate the absorption energy and improve the cyclization and reversion kinetics. However, there is a strong dependence on specific structural modifications and a lack of predictive behavior, mostly due to the complex photoswitching mechanism. Here, by means of a combined experimental and theoretical study, we systematically explore the effect of chemical modification of the π-bridge linking the donor and acceptor moieties, finding significant impact on the absorption, photocyclization and relative stability of the open form. Especially, a position along the π-bridge is found to be the most suited to red-shift the absorption while preserving cyclization. However, thermal back-reaction to the initial isomer is blocked. These effects are explained in terms of an increased acceptor capability offered by the π-bridge substituent that can be modulated. This strategy opens the path toward derivatives with infra-red absorption and a potential anchoring point for further functionalization.

Introduction

Molecular photoswitches, that is, molecules that can be interconverted between two states by light, have attracted the attention of scientists in the last decades due to their versatility and outstanding applications.[1–3] Nevertheless, new families of photoswitches continue to arise aimed mainly at increasing the range of properties and applications. A fascinating example is the emerging Donor−Acceptor Stenhouse Adducts (DASAs), firstly reported by Read de Alaniz in 2014.[4] DASAs are promising T-type photoswitches characterized by an efficient reversible conversion between a linear triene-colored-hydrophobic and a cyclic-colorless-hydrophilic form (Figure 1).[5]

Different experimental and computational studies have focused on distinct DASAs applications,[6–12] properties,[13–15] switching mechanism[16–20] or reactivity[21].

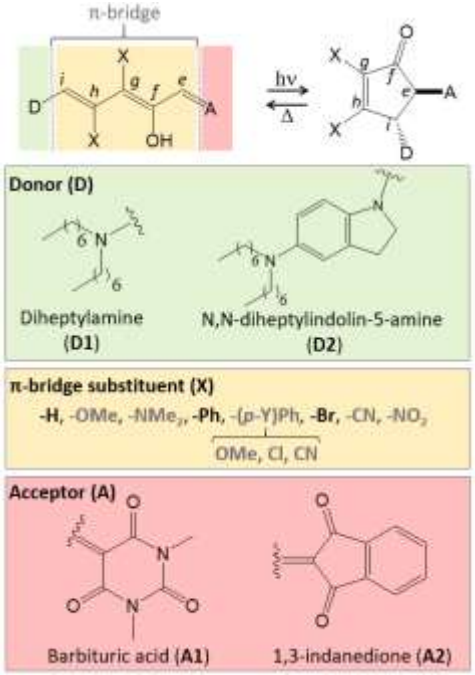

Figure 1. Upper panel: DASAs' overall reactivity. Photoisomerization coupled to cyclization generates the closed form while the extended form is thermally recovered. A general DASA structure is also given including the π-bridge (orange) connecting donor (green) and acceptor (red). Lower panels following the color code: donors, acceptors and π-bridge substituents (in grey if studied only theoretically) investigated in the present work. Theoretical models always include the diethylamino moiety in D, instead of the synthesized diheptylamino moiety.

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The photoswitch activation with visible and far-red/near-infrared light is a desired and crucial property for biological and materials applications, as it increases the tissue and surface penetration capability, respectively.[2,22,23] So far, several DASAs derivatives absorbing in the visible region have been reported.[5,24] Different generations of DASAs have been prepared in order to enhance the switchability of these molecules in polar and non-polar media and to red-shift the absorption spectra. It should be remarked that, up to now, this tunability has been achieved solely by changing two different DASA moieties: acceptor (A) and donor (D) (Figure 1). For instance, it was reported in 2014 that replacing 1,3-disubstituted barbituric acid-based acceptor group (A1 in Figure 1) by a 1,3-indanedione (A2 in Figure 1) results in a red-shift of *ca.* 30 nm in toluene.[25] Similarly, a second generation of DASAs with an even more red-shifted absorption was achieved by introducing novel aniline or indoline-based donors.[26,27] Recently, a third generation has emerged whose absorption tunability rises from novel structural changes of the carbon acid acceptor.[24] However, further shifting the absorption wavelength in the infrared region still constitutes a challenge.

Another key aspect of DASAs still poorly understood is the effect that the relative energy of each thermal isomer has on the overall photoswitching process. In contrast with other types of photoswitches, the complete mechanism for DASAs implies a photochemical step for the isomerization of a C=C double bond and several thermal steps that allow for the formation of the final structure, the closed form.[16,20,28] All these intermediates are in thermal equilibrium and could strongly affect the overall photoswitching process. In turn, the relative stability of these isomers can be modified by several factors. For instance, the effect of the solvent polarity has been deeply studied in these compounds.[5,15,17,18,24,27] Due to the marked difference in polarity of the open and closed forms, the change in the solvent polarity (for instance going from toluene to acetonitrile) greatly changes the switching process. The effect on both switching process and dark equilibrium could be changed not only by the type of solvent, but also by small structural modifications or concentration of the photoswitch.[13,16,20,27,29]

The basic design features of DASAs have been mainly maintained through the three generations reported. Changes in the D and A moieties have contributed to improve the performance in some cases, but also to the worsening of the photoswitching process or even the complete inactivation of the back reaction.[5,13,24,30] However, the π-bridge has been kept mainly intact, although it could be considered a potentially relevant modification point. Substitution on the bridge could not only directly alter the relative stability of the different thermally connected isomers, but it also could affect the optical properties and the overall switching process. Even more, substitution at the bridge could be also useful, in principle, as anchoring point for subsequent functionalization or to bind these compounds in different applications. Nevertheless, this could result in a substantial modification of the steric and/or electronic properties of the DASA, thus requiring investigations to clarify how and to which extent the photoswitching behavior would be affected. More in general, a study of the outcomes induced by chemical modifications of the DASA backbone on the overall switching mechanism, is of high interest as it could lead to better rationalize the complex interplay between the D-A push-pull effect, the photochemical reactivity, and the thermal intermediates until cyclization is accomplished.

Hence, in order to increase the knowledge on these systems and test the vability of π-bridge substitution, in this paper we present a comprehensive computational and experimental work mainly focused on the effect of substituting different positions of the π-bridge on the DASAs properties (Figure 1). It was found that DASAs with a modified π-bridge have different absorption properties, photochemical isomerization mechanism and thermal equilibria.

Results and Discussion

The paper is organized as follows. First, the design of several DASAs substituted on the π-bridge is presented. Several positions and functional groups were considered. Next, the absorption of selected candidates was thoroughly analyzed. One of the main aims for these compounds is the activation using far red or even near infrared light. Then, the photoisomerization was explored. This is the first step in the mechanistic path, and it is related with the potential energy surface in the excited state. Finally, the thermal equilibrium was computed. This final part of the mechanism may be related with the dark equilibria found in these species and responsible for the cyclization process. For all these sections, complementary experimental results will be presented.

Design and synthesis of π-bridge-substituted DASAs

Up to five different positions are, in principle, susceptible for modification in DASAs' π-bridge. The selection of the substitution site among the different possibilities (*e* to *i,* Figure 1) was done based on several mechanistic, synthetic and computational criteria. First, the hydroxyl group in *f* has been shown to be crucial to secure DASA functioning,[30] hence it was preserved. Second, the typical synthetic route for DASAs, consisting of the opening of a furan ring by the donor moiety, points out the central positions, *g* and *h*, as preferred over the lateral ones, *e* and ***i*** (Scheme 1). Thus, we initially considered both *g*- and *h*-substituted DASAs from a computational point of view. However, experimentally we aimed for the substitution of furan with Br and Ph to yield *g*-substituted DASAs, as they can be prepared by accessible building blocks and their effect could be relevant enough to change the properties of DASAs. Moreover, both Br and Ph groups could be further functionalized, if required for specific applications.

Regarding the acceptor and donor moieties under study, they have been selected based on different motivations. First, we aimed to evaluate the effect of the bridge substitution on both first (D1 derivatives) and second (D2 derivatives) generation DASAs. D1 and D2 were chosen because DASAs derivatives including these moieties present quite blue and red-shifted absorption, respectively[5,26] and hence, evaluating the additive character of bridge substitution effect on their maximum absorption wavelength is worthwhile. Considering the acceptor moiety, A1 was selected as numerous data has been already reported for DASAs derivatives including this moiety and so, comparison with our results could be straightforward. In addition, A2 was chosen as it is one of DASAs acceptors giving a significant red-shifted absorption (together with other acceptor recently reported).[24] Hence, the evaluation of derivatives including D2 and A2 moieties could aid in testing the limit of DASAs' red-shift absorption.

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Preliminary calculations using time dependent-density functional theory (TD-DFT, see Computational Details) were performed to understand the main effects that π-bridge modification could cause on the electronic distribution of these molecules. It is remarkable the fact that, the nature of the X-substituent group is crucial, since the π-bridge, when unsubstituted, is almost neutral, *i.e.,* it acts as a mere linker between D and A moieties. Nonetheless, appropriate substitutions in this part of the molecule can result in important modifications of the electronic properties of the bridge and, due to this, of the whole DASA. Careful selection of substitution may lead the π-bridge to behave as a D- or A-moiety, hence strikingly increasing the charge transfer character of the $S_0 \rightarrow S_1$ vertical transition. Therefore, we may propose a set of substituents to unveil the chemical nature of the π-bridge, spanning from strong donors (-OMe, $-NMe_2$) to strong acceptors (-CN, $-NO_2$), also including substituents with mixed inductive and resonance effects (-Br, -Ph and its derivatives -(*p*-OMe)Ph, -(*p*-Cl)Ph, -(*p*-CN)Ph). In terms of absorption properties and electronic densities, our TD-DFT results surprisingly suggest that the substituted π-bridge acts as an acceptor in all cases. Indeed, when analyzing the $S_0 \rightarrow S_1$ absorption, mainly described by a HOMO → LUMO transition, it is evident that the LUMO orbital shows an increased electronic density on the π-bridge group X, even for $-NMe_2$ (Figure S2). Hence, the π-bridge naturally acts as an acceptor, increasing the overall DASA acceptor ability by coupling through conjugation with the ending A moiety (A1/A2 in Figure 1).

Such electron density displacement toward the newly established acceptor (π-bridge and A1/A2), typical of the S_1 charge transfer character, can be therefore improved by selecting X-substituents with large acceptor strength. Nevertheless, such strength cannot be increased indefinitely: in Figure 2 we compare the calculated charge transfer character of three D2-X-A2 compounds with increasing X-acceptor strength: -Br < -CN < $-NO_2$. The -Br derivative already shows how the π-bridge and A form a unified acceptor moiety; in the -CN derivative the acceptor character is partially displaced toward the π-bridge, maintaining an overall D-A electronic molecular structure; while the $-NO_2$ derivative results in a D-A-D molecule, since the conventional ending A moiety is converted into a donor. Hence, concerning the photoreactivity, the $-NO_2$ derivative is expected to behave differently compared to other π-bridge substituted DASAs (see Photoswitching Mechanism section).

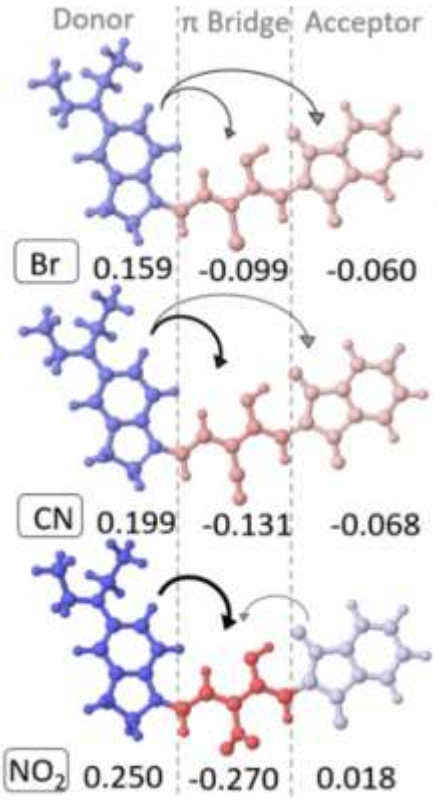

Figure 2. $S_0 \rightarrow S_1$ charge transfer character of D2-X-A2 (X = -Br, -CN, $-NO_2$), calculated by TD-DFT (B3LYP/6-31+G(d)) in toluene, applying natural bond order analysis. Electron displacement among the moieties (donor, π-bridge and acceptor) is shown by arrows from positive (blue) to negative (red) regions. The thickness of the arrows is related to the amount of charge transfer.

Inspired by these prospective computational data and within the limits imposed by the acceptor strength of the π-bridge X-substituent, a set of novel DASAs has been synthetized through a modification of the standard procedures[25,26,31] in order to include π-bridge substituents, as shown in Scheme 1. This implies the preparation of substituted furans that are subsequently opened by the donor moiety to afford the final compounds. A series of DASAs with the general notation D-X-A were prepared in which the donor moiety (D), the acceptor moiety (A) and the π-bridge substituent (X) were modified. Figure 1 includes the structure of the compounds prepared (D: diheptylamine or *N*,*N*-diheptylisoindoilin-5-amine; A: barbituric acid or 1,3-indanedione; X: H, Br or Ph). With this set of compounds in hand, we could determine the effect of every part of the DASA molecule on the different properties.

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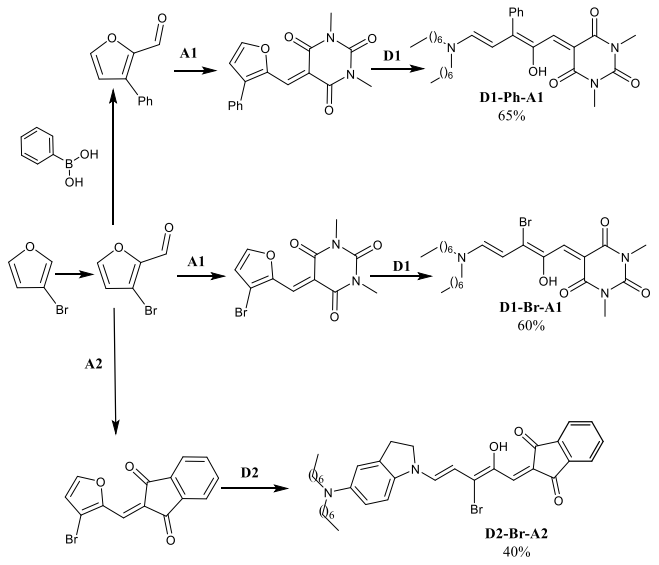

Scheme 1. Synthetic path for π-bridge substituted DASAs.

Preparation of the unsubstituted DASAs (D-H-A) implies the condensation of furfural with the corresponding acceptor followed by opening of the furan by the donor moiety (see Supporting Information). In contrast, π-bridge substituted compounds require the preparation of the corresponding furan derivative prior to the condensation and ring opening (Scheme 1). To do this, 3-bromofuran was reacted with $POCl_3$ to prepare the bromofuran carbaldehyde. This compound could be used to prepare the Br-substituted compounds or further reacted under Suzuki conditions to yield 3-phenylfuran-2-carbaldehyde. It is important to note that this synthetic route allows only for the preparation of *g*-substituted compounds. This is due to the regiochemistry in the carbonylation step, in which the aldehyde group is placed in position 2 of the furan while the Br is located in 3 (Scheme 1). The synthesis of such type of *g*-substituted compounds was already proposed, although with different donor and acceptor moieties, and not attempting a photochromic neither mechanistic study.[32]

Absorption spectra

A critical feature of photoswitches is the absorption wavelength needed to be activated. This is especially relevant for DASAs as these compounds absorb in the visible region. Careful structural modifications have been used to shift the absorption energy until reaching the red window of the spectrum.[24,26] This is important for many applications requiring low energy light like, for instance, biological media. A general screening of relevant DASAs including the prepared compounds and additional potential candidates was done through prospective absorption energy calculations. We used the TD-DFT framework, recognized as qualitatively correct in previous DASA studies[14,15,17,18,20,30] (see Computational Details). Then, the effect of π-bridge substitution was considered. First, we evaluate the effect of X-substitution in both positions *g* and *h*. Our data show that the *g* position leads to more consistent red-shifts compared to the *h* position, especially when increasing the acceptor ability of the X-substituent (Table 1).

Table 1. Absorption energy computed at the B3LYP/6-31+G(d) level of theory for compounds D1-X-A1, considering both the *g* or *h* substitution sites (see Figure 1). The solvent effect (toluene) is applied by polarizable continuum model. Please note that these are qualitative values. Quantitative values are given in Table 2, by applying the ADC2 level of theory.

Substituent (X)	Substitution site	Absorption energy eV (nm)
H	-	2.516 (493)
Br	*g*	2.351 (527)
	h	2.436 (509)
Ph	*g*	2.398 (517)
	h	2.475 (501)
CN	*g*	2.299 (539)
	h	2.530 (490)
NO_2	*g*	1.931 (642)
	h	2.440 (508)

With the computational absorption spectra and the prepared compounds in hand, we could focus on the effect of the π-bridge X-substituent on DASA absorption properties. In Figure 3 and Table 1 we show both theoretical and experimental results. It should be noted that, to reduce the computational cost, the diheptylamino group in D1/D2 of synthesized DASAs has been replaced by the diethylamino group since, comparing their simulated absorption spectra (Figure S1), only a 5 nm bathochromic shift has been found, due to almost negligible electron density differences.

Regarding the results, a quantitative agreement between the experimental and predicted wavelength at maximum absorbance, λ_{max}, was achieved by performing calculations with the second-order algebraic diagrammatic construction (ADC(2)) single-configuration reference method. Indeed, on one hand TD-DFT can achieve only a qualitative agreement, with considerable shifts from the experimental value, as shown by our results (Table S2) and previous works on DASAs.[14] On the other hand, the use of more sophisticated multi-configurational methods is not needed to predict DASA absorption, since it can be described by a single HOMO → LUMO transition. Apart from λ_{max} values, the spectral shape is the other important aspect to reproduce accurately absorption spectra, and this can be properly simulated at TD-DFT level when including the vibrational resolution (Figures S4-S6).[14,33–36] Hence, we have applied an energy shift to the vibrationally-resolved TD-DFT spectra in order to match the ADC(2) λ_{max} values (Figure 3b). By applying this computational strategy, a quite good agreement with experiment of both spectral energetics and shape has been found, with a wide $S_0 \rightarrow S_1$ absorption band characterized by a tail extending to shorter wavelengths.

Focusing on D1-X-A1 compounds, we observed that by introducing a π-bridge substituent, the absorption spectrum is red-shifted (Table 2 and Figure 3a). In particular, increasing the X-acceptor strength (-Br < -CN < -NO_2) results in an amplified absorption red-shift.

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The smallest red-shift (~0.1 eV) is induced by –Ph. Due to steric constraints, it is placed almost orthogonal to the π-bridge (Figure S6B), hence considerably reducing its resonant effect and mainly acting through its limited inductive effect.

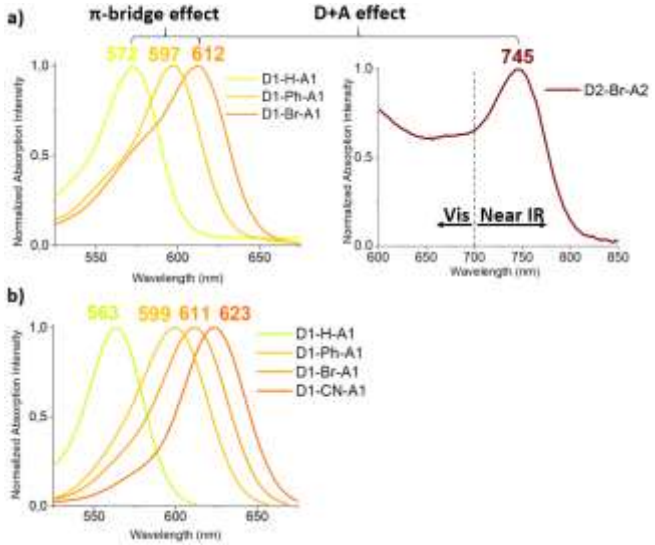

Figure 3. a) Absorption spectra experimentally recorded in toluene, with color code corresponding to λ_{max}, indicated at the top of each spectrum. Two series are shown, including (left) the effect of the π-bridge substitution in D1-X-A1 (X: -H, -Ph, -Br), and (right) the effect of changing both donor and acceptor (D2 and A2), when X: -Br. b) ADC(2)//DFT spectrum simulation of D1-X-A1 (X: -H, -Ph, -Br, -CN).

This trend is confirmed for D2-X-A2, D1-X-A2 and D2-X-A1 compounds (Table 2). Hence, we demonstrate that by changing the π-bridge X-substituent, irrespective of D and A moieties, a significant red-shift of the absorption can be achieved, reaching 0.21-0.23 eV when considering the most effective -CN (Table S6). As aforementioned, $-NO_2$ has a quite different electronic distribution that could affect the switching mechanism (*vide infra*). In addition, the red-shift caused by each X-substituent is a constant value, *i.e.* the same shift has been computed for D1-X-A1 and D2-X-A2 families (0.13-0.14 eV for -Ph, 0.14-0.18 for -Br and 0.21-0.23 for -CN). A similar additive effect has been computed for the D and A moieties, reaching a 0.25-0.28 eV red-shift when modifying D1-X-A1 into D2-X-A2, irrespective of the X-substituent (Table S7).

Photoswitching mechanism

Once checked the effect of the π-bridge substituent on the optical properties, the next step in the reaction mechanism is the light-induced photoisomerization of the adequate C=C double bond. To investigate this issue we have calculated, at the TD-DFT level, the excited-state minimum-energy path of **D2-Br-A2**, **D2-CN-A2** and **D2-NO_2-A2** in toluene, through the polarizable continuum model (Figure 4).[37] As explained in the previous section, the nitro group seriously affects the electronic structure of the molecule. The computed results confirm the expectations: on one hand, **D2-Br-A2** and **D2-CN-A2** reach a planar S_1 minimum, typical of DASA photochemistry.[28] Indeed, a S_1 energy barrier along the torsion coordinate is expected to connect this minimum with a S_1/S_0 conical intersection corresponding to a 90 degrees twisted structure around the C_g=C_f photoisomerizable bond, constituting the first step toward cyclization. On the other hand, **D2-NO_2-A2** reaches directly an unproductive S_1/S_0 intersection region, corresponding to pyramidalization of the -NO_2 group, hence conferring only photostability (*i.e.* internal conversion) properties to the compound and hampering the photoisomerization (Figures 4 and S3).

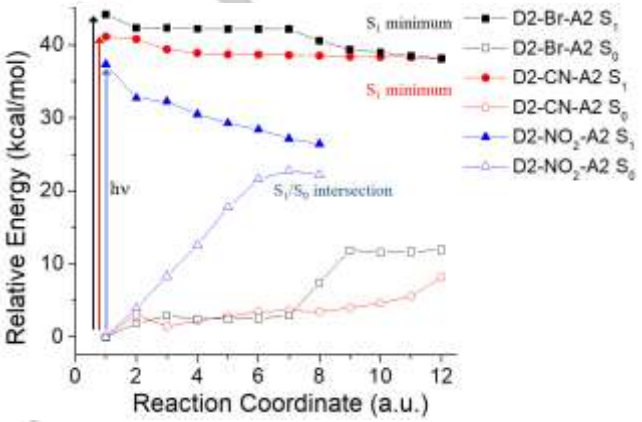

Figure 4. S_1 minimum energy path computed in toluene starting from the Franck–Condon structure (reaction coordinate = 1) at the B3LYP/6-31+G(d) level of theory for the **D2-Br-A2**, **D2-CN-A2** and **D2-NO_2-A2** derivatives. -Br (black) and -CN (red) derivatives reach a planar minimum in the excited state (S_1, full symbols), whereas the -NO_2 derivative reaches an intersection region with the ground state trough pyramidalization of the N atom of the -NO_2 group.

Table 2. Calculated (ADC(2) level, black) and experimentally determined (solvent: toluene, blue) λ_{max}, given in eV (nm). The coupled effects of different donor D and acceptor A groups, as well as various π-bridge X-substituents, are shown.

	Donor D1					Donor D2				
π-bridge X:	-H	-Ph	-Br	-CN	-NO_2	-H	-Ph	-Br	-CN	-NO_2
Acceptor A1	2.20 (564) 2.17 (572)	2.07 (599) 2.08 (597)	2.03 (611) 2.02 (612)	1.99 (623)	1.86 (667)	1.97 (629)		1.79 (693)		
Acceptor A2	2.16 (574)		2.02 (614)			1.94 (639)	1.80 (689)	1.78 (697) 1.66 (745)	1.71 (725)	1.71 (725)

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To further explore the photochemical part of the mechanism, we computed the key structures along the path for the available experimental compounds (Figure 5). As can be seen, this part of the mechanism is only slightly affected as the main features are maintained for the substituted DASAs. Relevant changes are the red-shift in the absorption spectra and the lowering or even the vanishing of the energy barrier in the excited state which should imply an even faster photoreaction for the π-bridge substituted compounds.

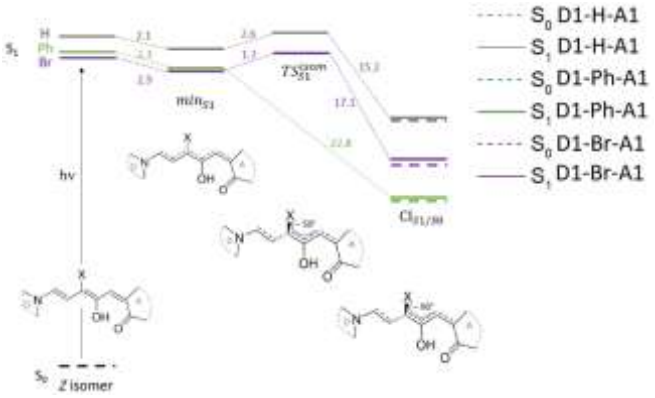

Figure 5. TD-DFT excited state stationary points along the photochemical reaction path in toluene for the π-bridge (Ph, Br) substituted DASAs at the *g* position, compared to unsubstituted DASA (H). Franck-Condon structure (*Z* isomer), S_1 minimum and S_1 transition state leading to the S_1/S_0 conical intersection (CI) are shown for D1-X-A1.

The cyclization was experimentally confirmed for all prepared compounds. For instance, upon irradiation on the band maximum of the open **D1-Br-A1**, this compound isomerizes to the closed form (see Figure 6, a). However, it was found that a combined effect of light and heat was operating in these compounds. That is, although the cyclization process is considerably faster upon irradiation, these compounds were found to isomerize also in the dark. This isomerization process can be easily followed by UV as the band corresponding to the open form (λ_{max} = 610 nm) disappears while the band for the closed transparent form (below 250 nm) grows. This agrees well with the previously studied DASAs and with our theoretical results: absorption for the cyclized form of **D1-(*g*)Br-A2**, at B3LYP/6-31G+(d) level in toluene, falls in the window 254-263 nm. In order to isolate the effect of light and heat in the cyclization, we followed the disappearance of the band at 610 nm in a sample kept in the dark at 20ºC. After that, the sample was irradiated at the same temperature (Figure 6, b). As it can be seen, the cyclization takes place even in the dark, although it is considerably slower (estimated half-life of *ca*. 18h). However, once light is activated, the closing process takes place more rapidly with a measured half-life for the open form of 1422 ± 1 s (i.e. approximately 0.4 hours). Thus, it is evident from Figure 6 b, that the isomerization and closing process for these compounds takes place either by effect of light or temperature, although it is clearly faster under irradiation in the band maximum. From the practical point of view, the thermal cyclability of these compounds may hamper their use in some applications. This will be further studied in the next section.

During the photoisomerization, it was also noted the formation of non-specific bands between 300 - 400 nm. While these bands could be assigned to one or several intermediates along the photoisomerization pathways, it may also be due to partial decomposition. Indeed, an absorption peak lying in the spectroscopic window between reactants and products was already found for some first-generation DASAs, although no explanation was attempted.[27] To find a possible explanation, we have hypothesized the presence of a complex ground-state equilibrium between different *E*/*Z* isomers, as recently suggested.[16,20] Especially, three different conformations were considered (*EEZ*, *EZZ* and *EEE*, fixing the stereochemistry on D-H-A compounds), as they were experimentally observed.[20] While confirming that the *EEZ* conformation is always the most stable, this stability decreases for Ph- and even more for Br-derivatives, therefore suggesting a more prominent role of *EZZ* and *EEE* conformations when Br-substitution takes place (see Figure S10 and Table S8). Although their absorption does not lead to clear differences in the spectrum, as expected for structures conserving essentially the same conjugation length, we do expect that the irradiation of *EEZ*, *EZZ* and *EEE* Br-derivatives could lead to additional intermediates absorbing at 400nm, which should not be observed when irradiating the only stable conformer, *EEZ*, of H- and Ph-derivatives. The absorption of several intermediates in this region does not rule out the possible decomposition of some of the species in equilibrium. In fact, the increase of these bands at longer times may suggest this alternative. However, even if these bands are due to decomposition, this should be partial and involve mainly the open form and /or the intermediates as the closed forms were found to be stable.

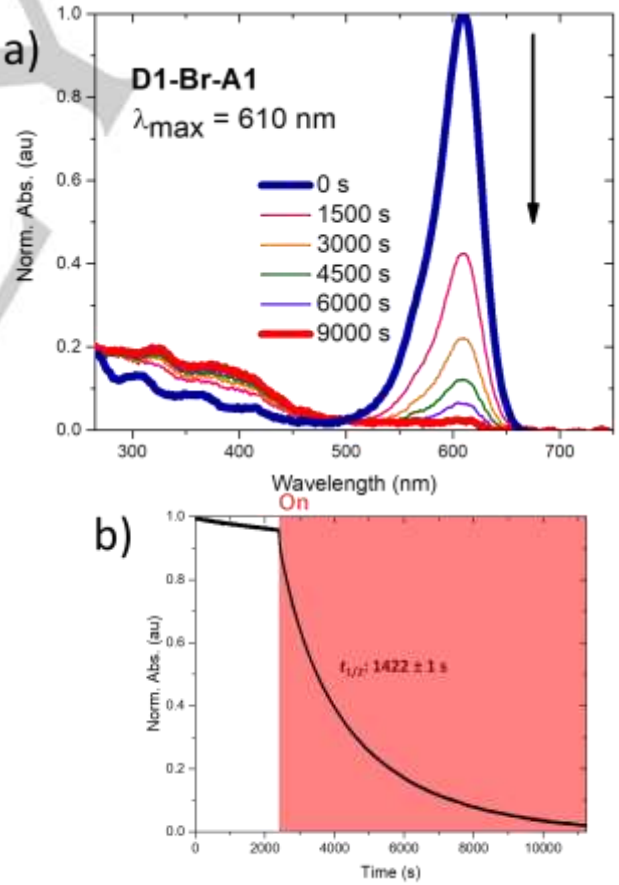

Figure 6. a) Isomerization of **D1-Br-A1** upon irradiation with 610 nm light in CH_2Cl_2.b) Monitoring of the disappearence of the open form in the dark at 20ºC (white background) and in the presence of 610 nm light (orange background).

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Thermal equilibria

These newly prepared DASAs feature excellent optical properties. Nevertheless, the complete switching mechanism implies not only the formation of the closed form upon irradiation, but also the reversible recovery of the open form under different stimulus, usually thermal activation. This type of switches has been reported to have a marked sensitivity to external factors such as the solvent, but also to slight modifications in their structure.[5,24] Thus, we then aimed to check the reversibility of these compounds under different stimuli. For all π-bridge substituted compounds D-X-A, the photoreaction from the open to the closed form is performed swiftly under red light. However, these compounds showed no appreciable reversibility back to the open form even when different reaction conditions were tried. After cyclization, the open form could not be recovered by the use of apolar solvents (toluene, dichloromethane), heating (closed forms were found to be thermally stable at reflux temperature of different solvents) or light (using the wavelength of maximum absorbance, *ca*. 350 nm). These results have two clear implications. First, as these compounds could not be reverted to the initial state, their use as switches is seriously hampered. Second, the thermal part of the switching mechanism is modified somehow by the π-bridge substitution to strongly stabilize the closed form.

In order to further explore these effects, we computed all the ground state stationary points along the complete path for the π-bridge substituted Br and Ph DASAs in both the *g*- and *h*-positions (Figure 7).

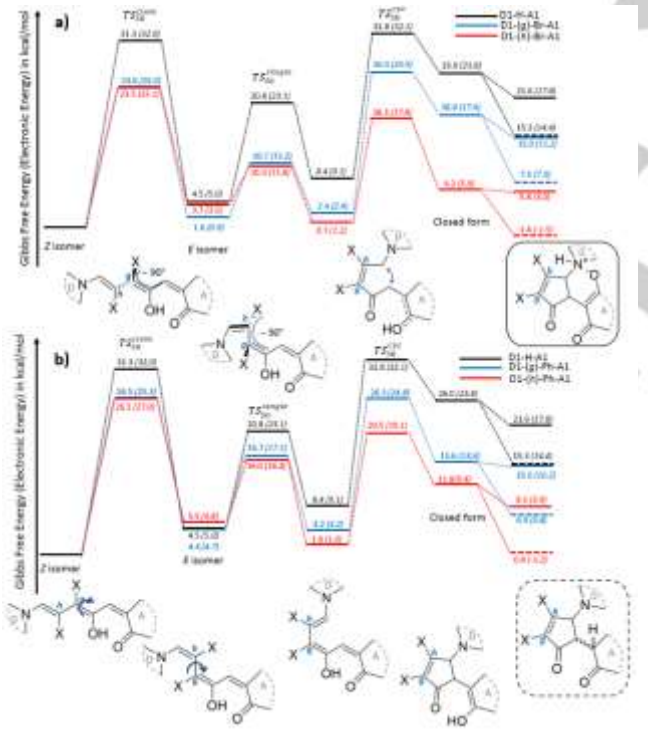

Figure 7. DFT ground state stationary points (minima and connecting transition states) along the mechanistic path for **D1-X-A1**, computed in toluene. a) Br atom in positions *g* and *h*. b) Ph group in positions *g* and *h*. For comparison purposes, the path computed for the unsubstituted DASA is also shown (black line).

As can be seen, several key aspects are preserved when including substituents in the π-bridge. For instance, the high energy barrier for *Z* / *E* isomerization (thus, requiring light activation) is maintained, although it is reduced by 8 and 5 kcal/mol for the Br and Ph derivatives, respectively. Similarly, the energy barrier for the cyclization is lowered, especially for *h*-substituted compounds. This should imply a faster thermal equilibrium in which the abundance of the different isomers will be controlled by their relative energies, as it was experimentally confirmed by this work. Most of the intermediates are stabilized, especially the final closed forms. For both Br and Ph substituted compounds, there is a clear stabilizing effect, higher for the *h*-substituted compounds. This implies that once formed the closed form, the reverse reaction to the open form will be much slower or even not taking place for the π-substituted compounds, as experimentally found here for the *g*-substituted Br and Ph DASAs. As shown by our computational data, this result could be extended to the *h*-substituted compounds, although their synthesis was not performed.

Finally, we should note that the substituents proposed here do not imply relevant steric effects on the calculated backbone geometry along the whole cyclization path, when compared to unsubstituted DASAs. Nevertheless, the incorporation of different, more bulky, substituents, could in principle add significant steric effects to the noticed electronic ones, and should be therefore carefully evaluated.

In the application point of view, especially considering their capacity to be covalently anchored and their solvent dependence, π-bridge substituted DASAs could be proposed as fine-tuned molecular probes or as novel substrate for DASA's reactivity.[21] Also, depending on the type of closed form that is generated (zwitterionic or non-zwitterionic, see Figure 7), new applications could be envisioned taking advantage of the infrared DASA chemical transformation as a first step of a sequence. An inspirational example could be retinal in visual rhodopsin, where retinal undergoes *cis-trans* photoisomerization within the opsin cavity as a first step, followed by charge migration from retinal to opsin, and requiring replacement of a new retinal molecule within opsin to start a new cycle.[38] In any case, the detailed mechanistic information gathered here, should be useful in the design of new species and their application in different systems.

Steric effects

Until now, we have mainly considered electronic effects, due to the donor-acceptor intrinsic nature of this type of compounds. Nevertheless, it should be noted that, especially when substituting at ***g*** position, some steric constraints could arise, mainly due to potential 1,3 allylic strain generated when converting (photochemically, Figure 5, or thermally, Figure 7) the *Z* isomer into the *E* isomer. Therefore, we have analyzed both optimized structures (*i.e.* the respective calculated energy minima) by comparing **D1-(*g*)H-A1**, **D1-*(g)*Br-A1** and **D1-*(g)*Ph-A1**. Driven by previous studies on *Z*/*E* isomerization,[3,38] we have focused on two key geometrical parameters: the C(*f*)=C(*g*) bond length and the C(*e*)-C(*f*)=C(*g*)-C(*h*) dihedral angle (see Figure 1 for atom labeling). We have found that an increase of the steric constraint corresponds to a notable increase of the C(*f*)=C(*g*) bond length for both *Z* (-H: 1.402 Å, -Br: 1.412 Å, -Ph: 1.419 Å) and *E* (-H: 1.406 Å, -Br: 1.416 Å, -Ph: 1.424 Å) isomers. At the same time, the out-of-plane distortion also increases with the steric constraint, being the C(*e*)-C(*f*)=C(*g*)-C(*h*) dihedral angle 179.5º (-H), 179.1º (-Br) and 173.1º (-Ph) for the *Z* isomer, while 0.05º (-H), 0.64º (-Br) and 12.1º (-Ph) for the *E* isomer.

The much higher influence of Ph can be associated with the fact that the aromatic ring is not perpendicular to C(*f*)=C(*g*), but it

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forms an angle of 66 degrees (*Z* isomer) and 63 degrees (*E* isomer). This affects more the *E* isomer due to the 1,3 allylic strain. In terms of reactivity, on one hand these data support the photochemical mechanism proposed in Figure 5, since a lower C(*f*)=C(*g*) double bond character and a more pronounced C(*e*)-C(*f*)=C(*g*)-C(*h*) pre-twist can suggest an explanation of the lower excited state barrier found when substituting -H with -Br, and even more the absence of such a barrier when X= -Ph (*i.e.* D1-*(g)*Ph-A1 is expected to undergo the fastest photoisomerization).

On the other hand, we do not find a clear relationship relying steric effects with thermal reactivity, since the *E* isomer, with respect to the *Z* isomer, is more destabilized for the unsubstituted compound (4.5 kcal/mol), followed by -Ph (4.4 kcal/mol) and -Br (1.6 kcal/mol) substitutions.

In this case, we should therefore conclude that the driving force is mainly of electronic nature, as analyzed in the previous sections.

Conclusion

We have studied a new generation of DASAs by modifying the π-bridge through chemical substitution at the *g* and *h* positions. Especially, *h* substituted DASAs were investigated only computationally, while the most suitable *g* substituted DASAs were studied both computationally and experimentally. This new π-bridge substituted DASAs can be easily synthetized with high yields and the synthetic path could be straightforwardly modified to get novel analogues or to link these compounds to different substrates. Regarding the optical properties, both the D-A and π-bridge substitution effects were found to be additive to the spectral energy shift, allowing to reach infra-red absorption. More in general, methodology shown here allows to predict from scratch the optical properties of these compounds and their photochemical behavior. The acceptor electronic nature of these π-substituted DASAs was established, including their limit to preserve the photoswitching function.

Clearly, substitution in the π-bridge has profound implications for the properties of DASAs and their switching mechanism. On one hand, a significant and consistent red-shift in the absorption maxima could be achieved. As this effect was found to be additive, substitution in the bridge could be combined with other structural modifications to allow for the use of long wavelengths with these compounds. Nevertheless, experiments on *g*-substituted DASAs reveal, that cyclization in the dark is relevant and may constitute a significant reaction pathway.

On the other hand, this specific type of substitution has several limitations that affect the switching process. As shown by the computational results on the $–NO_2$ derivative, the photoisomerization could be affected if the substituent is not adequately chosen. Even if photoisomerization takes place with a different set of substituents, thermal reversion is not possible in these derivatives. Results shown herein allow for a detailed description of the behavior of a new set of DASAs. However, further efforts would be necessary to design and prepare different π-bridge compounds that could maintain the excellent optical properties while keeping reasonable switching ability.

Experimental Section

Materials and methods.

All solvents were distilled prior to use. Some solvents such as dichloromethane, diethyl ether, acetonitrile and tetrahydrofuran were distilled with the solvent purification system Pure solvtm 4-MD. Thin Layer chromatography (TLC) was performed using Polygram Sil G/UV254 F254 plates (0,2mm silica gel layer with fluorescence indicator on pre-coated plastic sheets). Column chromatography was carried out with silica gel (230-240 mesh) as stationary phase. Mixtures of hexane/ethyl acetate were used as mobile phase. ^{1}H and ^{13}C spectra were recorded on a Bruker ARX-300 and/or a Bruker Avance 400 spectrometers. $CDCl_3$ and CD_3OD have been used as the usual deuterated solvent with TMS as internal standard. Chemical shifts are given in ppm and coupling constants in hertz. Absorption molecular spectra were recorded on two distinct equipment: HP-8453A UV-VIS-NIR diode array spectrophotometer (190-1100 nm) or HP 8451A diode array spectrophotometer (190-820 nm). All the experiments were carried out in quartz cuvettes (1 cm path length). Electrospray mass spectra were recorded on a HP 5989B mass spectrometer with an HP59987A interface in positive-ion mode. High resolution mass spectrometry was performed in a HP Bruker Microtof-Q with an Apollo II electrospray source in positive-ion mode.

Synthesis and Characterization of D1-Br-A1

Barbituric acid (3 mmol, 470 mg, 1 equiv.) and 3-bromofuran-2-carbaldehyde (3.3 mmol, 580 mg, 1.1 equiv.) were dissolved in water and reacted at 70º C for 2 hours. After that, the reaction was cooled to rt and the solid was isolated by filtration. The product did not need further purification and could be used immediately in the next step. The adduct (0.1 mmol, 31.3 mg, 1 equiv.) was dissolved in THF at 0ºC, then diheptylamine (0.11 mmol, 23.43 mg, 1.1 equiv.) was added dropwise. Promptly, the solution changed its color from yellow to blue-purple. The reaction was stirred for additional 15 minutes. The final compound was purified by HPLC as a bluish solid (60%), using a linear gradient 95-0% water (containing 0.1% TFA) / acetonitrile over a period of 30 minutes. The open form was found to be unstable in solution at rt and clear NMR data could not be obtained. The following NMR data correspond to the closed form. **^{1}H NMR** (300 MHz, Methanol-d_4) δ 7.91 (d, J = 2.3 Hz, 1H), 4.81 (dd, J = 3.6 Hz, J = 2.3 Hz, 1H), 3.94 (d, J = 3.6 Hz, 1H), 3.23 (m, 10H), 1.66 (m, 4H), 1.29 (m, 16H), 0.90 (m, 6H). **^{13}C NMR** (75 MHz, MeOD) δ (ppm) 198.6, 164.9, 154.6, 151.3, 132.8, 85.3, 67.8, 45.3, 32.7, 32.7, 29.9, 29.8, 28.1, 27.5, 27.4, 27.3, 23.6, 14.4. **UV-VIS** (CH_2Cl_2, open form): λ (nm) 610 (ε = 15768 $M^{-1}cm^{-1}$). **EM-ES** (+)**:** calcd for $C_{25}H_{41}N_3O_4Br$ $[M+H]^+$ 526.2280, found 526.2275.

Synthesis and Characterization of D1-Ph-A1

3-Bromofuran-2-carbaldehyde (1.91 mmol, 335 mg, 1 equiv.) was dissolved in 1,2-dimethoxyethane (DME) and, to this solution was added phenylboronic acid (7.64 mmol, 931 mg, 4 equiv.), tetrakistriphenylphosphine palladium (0) (0,382 mmol, 446 mg, 0.2 equiv.) and potassium carbonate (6.68 mmol, 474 mg, 3.5 equiv.). This mixture was under reflux for 48 hours. The reaction was monitored by TLC and when it was completed, the solvent was removed under reduced pressure. Then, the crude was extracted three times with (CH_2Cl_2:H_2O) and the organic fractions were collected. The solvent was removed and the pure compound was purified by column chromatography on silica gel using as eluent a mixture of hexane and ethyl acetate (4:1). In the next step, the condensation of 3-phenylfuran-2-carbaldehyde (0.87 mmol, 150 mg, 1.1 equiv.) and barbituric acid (0.79 mmol, 101 mg, 1 equiv.) was performed. Both compounds were dissolved in water, and the reaction was heated at 70ºC for 2 hours. Then, the reaction was cooled to RT, and the resulting solid was filtrated. This compound did not need further purification. Finally, this adduct (0.1 mmol, 0,31 mg, 1 equiv.) was dissolved in THF at 0ºC, then diheptylamine (0.11 mmol, 23.43 mg, 1.1 equiv.) was added dropwise. Promptly, the solution changed its color from yellow to blue-purple. The reaction was stirred for additional 15 minutes. The final compound was purified by HPLC as a bluish solid (65%), using a linear gradient 95-0%

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water (containing 0.1% TFA) / acetonitrile over a period of 30 minutes. The open form was found to be unstable in solution at rt and clear NMR data could not be obtained. The following NMR data correspond to the closed form. **^{1}H NMR** (300 MHz, Methanol-d_4) δ 7.84 (d, *J* = 7.7 Hz, 2H), 7.77 (s, 1H), 7.42 (d, *J* = 6.9 Hz, 3H), 4.93 (s, 1H), 3.99 (d, *J* = 3.9 Hz, 1H), 3.27 (s, 10H), 1.70 (s, 4H), 1.28 (s, 16H), 0.89 (s, 6H). **^{13}C NMR** (75 MHz, Methanol-d_4) δ 204.2, 165.2, 154.7, 148.5, 146.8, 131.9, 130.6, 129.5, 128.9, 86.0, 66.7, 52.7, 49.9, 47.9, 32.7, 29.8, 28.4, 27.5, 25.8, 23.6, 14.38. **UV-VIS** (CH_2Cl_2, open form): λ (nm) 590 (ε = 18040 $M^{-1}cm^{-1}$). **EM-ES** (+)**:** calcd for $C_{31}H_{46}N_3O_4$ $[M+H]^+$ 524.3488, found 524.3482.

Synthesis and Characterization of D2-Br-A2

1,3-indandione (1 mmol, 132 mg, 1 equiv.) was dissolved in water. To this solution, 3-bromofuran-2-carbaldehyde (1.1 mmol, 175 mg, 1.1 equiv.) was added dropwise and then, the mixture was heated at 70ºC for 2 hours. After that, the reaction was cooled to rt, and the resulting precipitate was filtered and used without further purification. This adduct (0.1 mmol, 30 mg, 1 equiv.) was dissolved in THF at 0ºC, then *N*,*N*-diheptylindolin-5-amine (0.11 mmol, 36 mg, 1.1 equiv.) was added dropwise. Promptly, the solution changed its colour from yellow to blue-purple. The reaction was stirred for additional 15 minutes. The final compound was purified by HPLC as a bluish solid (40%), using a linear gradient 95-0% water (containing 0.1% TFA) / acetonitrile over a period of 30 minutes. The open form was found to be unstable in solution at rt and clear NMR data could not be obtained. The following NMR data correspond to the closed form. **^{1}H NMR** (300 MHz, Methanol-d_4) δ 8.07 (d, *J* = 7.9 Hz, 1H), 8.01 (dd, *J* = 6.7, 1.8 Hz, 1H), 7.97 (s, 1H), 7.92 (s, 2H), 7.25 (s, 1H), 6.96 (s, 1H), 6.47 (d, *J* = 8.6 Hz, 1H), 5.30 (s, 1H), 3.75 (s, 1H), 3.70 (s, 1H), 3.51 (s, 6H), 3.14 (s, 2H), 1.51 (s, 4H), 1.29 (s, 16H), 0.90 (s, 6H). **^{13}C NMR** (75 MHz, Methanol-d_4) δ 200.5, 199.2, 198.0, 162.1, 152.9, 144.0, 143.1, 137.3, 137.0, 134.5, 128.8, 126.9, 124.3, 123.9, 122.8, 119.1, 107.5, 60.3, 60.1, 47.3, 32.6, 29.8, 28.8, 27.2, 26.2, 23.5, 14.3. **UV-VIS** (CH_2Cl_2, open form): λ (nm) 750 (ε = 15033 $M^{-1}cm^{-1}$). **EM-ES** (+)**:** calcd for $C_{36}H_{46}BrN_2O_3$ $[M+H]^+$ 633.2692, found 633.2686.

Computational Methods

Ground state stationary points of all compounds were optimized on the ground state at the B3LYP[39,40]/6-31+G(d) level of theory, followed by a frequency calculation to ensure that the optimized structure corresponds to a minimum or a transition state on the S_0 potential energy surface. As mentioned in the text, both TD-DFT and ADC(2)[41] calculations were performed to describe excited state properties, being the former only qualitatively correct, while the latter can be also quantitatively compared with the experiment. Concerning the TD-DFT calculations, a benchmark was performed on **D1-Br-A1**, finding out that the B3LYP functional can be used also for excited state calculations (Table S1). The effect of the basis set on the absorption energy was also benchmarked, finally selecting the 6-31+G(d) basis set (Table S2). The intramolecular charge transfer in D2-(*g*)X-A2 compounds, during irradiation, was analyzed by Natural Bond Order (NBO) analysis[42] at the B3LYP/6-31+G(d) level of theory, including toluene as solvent (Figure 2 and Table S3). In order to perform more affordable calculations, the diheptylamino moiety of synthesized compounds was substituted with the diethylamino one, showing for **D2-(*g*)Br-A2** how this modifications affects only negligibly the overall absorption spectrum (Figure S1). The shape of the absorption spectra was modeled at B3LYP/6-31+G(d) level including the vibrationally-resolved resolution,[33–36] in order to match the experimental shape, as suggested elsewhere[14] (Figures S4-S6). The ground state and excited state stationary points shown in Figures 5 and 7 have been also computed with the M062X functional (Figures S8 and S9), validating the general trend found with the B3LYP functional.

Concerning ADC(2) calculations of the absorption spectrum, a basis set benchmark was performed, showing that convergence can be reached only when employing the aug-cc-pVTZ (Table S4). Also, the contribution of single and double excitations was checked by ADC(2) molecular orbital analysis (Figure S7 and Table S5), showing a small but non-negligible participation of double excitations, that could suggest the discrepancy in λ_{max} values between TD-DFT and ADC(2) methods, although maintaining a correct description of the electronic nature.

Solvent effects were taken into account by the Polarizable Continuum Model using the Integral Equation Formalism variant (IEF-PCM).[43,44]

All DFT and TD-DFT calculations were performed with the Gaussian16[45] suite of programs, while ADC(2) calculations were carried out with the Turbomole 7.3[46] program.

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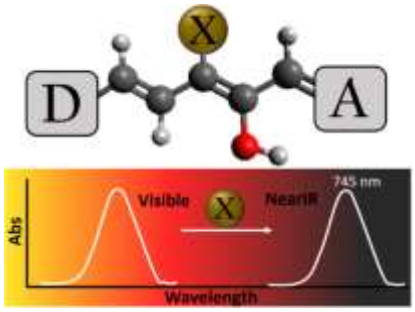
Entry for the Table of Contents



A new set of Donor-Acceptor Stenhouse adducts was computationally studied and prepared through the substitution on the π-bridge. This allows for the modification of absorption, photocyclization and relative stability of the isomers. This change provides a consistent red-shift in the absorption maximum and a structural entry point for subsequent derivatization, although the reversibility is blocked.

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