Tuning the Thermal Stability and Photoisomerization of Azoheteroarenes through Macrocycle Strain

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Abstract

Azobenzene and its derivatives are one of the most-widespread molecular scaffolds in a range of modern applications, as well as in fundamental research. After photoexcitation, azo-based photoswitches revert back to the most stable isomer in a timescale ($t_{1/2}$) that determines the range of potential applications. Attempts to bring $t_{1/2}$ to extreme values prompted to the development of azobenzene and azoheteroarene derivatives that either rebalance the E- and Z- isomer stabilities, or exploit unconventional thermal isomerization mechanisms. In the former case, one successful strategy has been the creation of macrocycle strain, which tends to impact the E/Z stability asymmetrically, and thus significantly modify $t_{1/2}$. On the bright side, bridged derivatives have shown an improved optical switching owing to the higher quantum yields and absence of degradation. However, in most (if not all) cases, bridged derivatives display a reversed thermal stability (more stable Z-isomer), and smaller $t_{1/2}$ than the acyclic counterparts, which restricts their potential interest to applications requiring a fast forward and backwards switch. In this paper, we investigate the impact of alkyl bridges to the thermal stability of phenyl-azoheteroarenes using computational methods, and we reveal that is indeed possible to combine such improved photo-switching characteristics while preserving the regular thermal stability (more stable E-isomer), and increased $t_{1/2}$ values under the appropriate connectivity and bridge length.

1. Introduction

Molecular switches are able to modify their properties upon application of an external stimulus like heat, pressure, pH or light, the latter being particularly advantageous due to its selectivity and immediacy. As a result, photo-switches are being used in material sciences,1 medicine,2 biology,3 optical data storage,4 and molecular machines or actuators.5 One of the most studied families of photoswitches are azobenzene (AB) derivatives,6 which display a cis-trans isomerization upon excitation to the low-lying π* (S0→S1) or π* (S0→S2) bands. Once in its metastable state (generally the Z-isomer) the molecule can be switched back to its most stable state (generally the E-isomer) through either similar photochemical process, or through thermal relaxation in the ground state. The timescale associated with the latter process ($t_{1/2}$) is a key characteristic of a photoswitch, as it defines the range of potential applications for which it can be used. Those with $t_{1/2}$ in the order of nanoseconds are promising candidates to be used in real-time information transmission,7 while those with $t_{1/2}$ longer than a year can be used for optical data storage,4 as they ensure the integrity of the data for an extended period of time.

Such diversity of potential applications has motivated the development of new types of photoswitches. An example are azoheteroarenes, which replace one or the two Ph rings of AB by an heteroarene.8 The plethora of available heteroaryl rings offer a larger structural diversity and leads to a broader range of $t_{1/2}$ that spans from 281 ns for an azopyridine derivative,9 to 46 years for an ortho-substituted arylazopyrazole.10 A strategy to further modify $t_{1/2}$ is to incorporate the azo-bond into a macrocycle, as it generates ring strain that modifies the relative thermal stability of the E/Z isomers.11-17 Such strategy has been recently exploited to modify the half-life time ($t_{1/2}$) of a hydrazone-based photoswitch.18 The acyclic compound had an extraordinary half-life time of 5357 years, while that of bridged derivatives spanned 0.047 and 996 years.18 The impact of ring strain on cyclic AB-polymers has been discussed in the past by Rau,11,12 Nobuyuki13,14 and others.19,20 More recently, experimental21 and computational22-25 work described the photo-isomerization of a bridged-AB, in which the two phenyl rings are connected with an alkyl chain. The constrained AB presented several advantages compared to the acyclic AB: the band separation was larger, the quantum yield was enhanced, and the photo-isomerization was faster.21-25 As a side-effect, the bridge reversed the relative stability of the two isomers, converting the E-isomer into the metastable one, with a very fast thermal back-reaction to the Z-isomer of only 4.5 hours.19 The decrease of $t_{1/2}$ is, indeed, a general trend when bridges are employed together with azo-dyes. That is only useful for applications benefiting from a fast forward and backward switching, essentially limiting the range of applications of bridged azo-dyes. It is thus important to understand whether bridge azo derivatives...
unavoidably lead to reversed E/Z stabilities and short $t_{1/2}$, or alternatively, if it is possible to preserve the regular E/Z stability and increase $t_{1/2}$ through the adequate bridge length and design.

In this computational study we aim at answering this point by investigating the impact of alkyl bridges to the thermal stability of phenyl-azoheteroarenes based on 3-pyrazole and 2-imidazole. Our selection is based on the fact that these heteroarene families showed E/Z thermal stabilities that were at the edge of the explored values in a recent computational screening. Herein, we present the evolution of the half-life times associated with both the inversion and rotation thermal relaxation mechanisms with bridge length. While bridges tend to shorten $t_{1/2}$, we could identify some cases in which the E-isomer remains as the most stable, and $t_{1/2}$ is enhanced with respect to the acyclic compound. Given the importance of steric constrains on the molecular motion, we also investigated the photo-isomerization mechanism and kinetics of selected bridged derivatives using surface hopping molecular dynamics. The impact of bridges on the photo-isomerization is significant, especially in shorter ones, leading to much faster relaxation kinetics, and to the photoswitch exclusively exploring the rotational mechanism, which is traditionally associated to higher quantum yields. Therefore, this study might contribute to the design of improved azoheteroarenes undergoing a fast and efficient (i.e. with high quantum yield) photo-isomerization, and extreme $t_{1/2}$ values.

2. Methodology and Computational Details

2.1 Compounds and Nomenclature

![Scheme 1](image)

Scheme 1. (top) Nomenclature scheme and (below) representation of the heteroarene families explored in this manuscript. The red numbers are used in the series nomenclature to indicate the bridge anchoring sites.

The compounds studied in this work are derived from 3-pyrazole and 2-imidazole, in which an alkyl bridge connects the phenyl and heteroarene rings. The length of the bridge varies, generating series of compounds based on the same heteroarene and connectivity. The nomenclature of those series follows a three-digit code. The first number indicate the heteroarene fragment (1 for 3-pyrazole, 2 for 2-imidazole). The second and third digit indicate the position (see Scheme 1) to which the bridge is attached on the phenyl and heteroarene rings (in this order). To mention a specific compound in a serie, a fourth digit indicates the number of carbon atoms in the akyl bridge. In the first serie, labelled 111n, the alkyl bridge connects the ortho position of the Ph group, and the ortho C-atom of the 3-Pz. This serie spans bridges having from 1 to 6 C atoms (i.e. from 1111 to 1116). The equivalent serie using 2-imidazole as heteroarene leads to serie 211n, which also spans from 2111 to 2116 (n=1-6). A difference with respect to the 111n serie is that in 211n the bridge is attached to the heteroarene through the N atom. Finally, the substitution in ortho (Ph) and the meta C atom (het) is studied in the serie labelled 112, which spans from 1122 to 1128 (n=2-8). Preliminary studies have been carried out exploring other possible connectivities (section S4). However, the impact of the bridge on $t_{1/2}$ was found to be either much smaller, or very similar to that of the main series discussed here. Therefore, we did not pursue a more complete study.

2.2 Rotation vs. Inversion Mechanism of Thermal Relaxation

The rotation and inversion mechanisms compete in the photo- and thermal- isomerization of AB and its derivatives. Under light irradiation, the preferred pathway depends on the region of the $S_1$ Potential Energy Surface (PES) that is explored after excitation (and subsequent decay) to either $S_0$ or $S_2$. In turn, the thermal relaxation occurs completely in the ground state ($S_0$) PES, without involvement of any excited state. In that case, inversion occurs through a transition state (TS) with one of the CNN angles at ca. 180° ($TS_{inv}$), whereas rotation goes through a TS with a CNNC dihedral angle of ca. 90° ($TS_{rot}$). Under the thermal pathway, the rotation mechanism along $S_0$ requires the hemolytic cleavage of the azo N=N bond at sufficiently-twisted geometries. Therefore, the TS needs to be described as either a triplet (T1) or as a singlet bi-radical (open-shell singlet, OSS), with one unpaired electron in each azo N atom (both states are very close in energy). Notice that the in latter case, the OSS description must be forced within DFT by using the Broken Symmetry (BS) approach.

In AB, evidences for both mechanisms associated with thermal relaxation can be found in the literature. A computational study at the CASPT2 level and earlier experimental work suggest that a non-adiabatic rotational pathway ($S_0$→T1→$S_0$) should be accessible and lower in energy. However, experimental studies showed that the rate of isomerization and the activation free volume are independent of the solvent polarity, which excludes the rotational pathway (since the associated TS is polar). In push-pull AB derivatives (ppAB), it has been reported that the mechanism depends on the solvent, with a preference...
we assume that higher-energy conformers can interconvert conformers at each stationary point (minima and TS). Thus, we have employed the metadynamics for specific systems. In Eyring equation, we describe the bridge, and a more thorough evaluation using the ring conformers, an energy scan along dihedral angles in section S1. It includes the explicit evaluation of the Eyring equation. To do so, we have used the protocol significant changes to among them, since errors in the evaluation of it is hardly possible to anticipate the preferred thermal relaxation pathway of the systems studied herein. Therefore, we considered both inversion and rotation as possible mechanisms. As we will see later, the results suggest that inversion is the active thermal pathway.

2.3 Half-life times and Conformers

The rate constant \( k \) of the thermal relaxation and its corresponding half-life time \( t_{1/2} \) are calculated from the relative free energy difference \( \Delta G \) between the lowest TS and the metastable state, using Eyring equation with \( T=300 \) K and assuming a first-order relaxation kinetics (for \( k \)). The transmission coefficient is taken as 1 for simplicity, although a study determined that it ranges between 0.2 and 0.4 for AB and a ppAB.\(^{59}\) Eyring equation is routinely used to assess the thermal relaxation in azo-dyes.\(^{46,50}\)

The minima and TS of the acyclic azoheteroarenes 1 and 2 have multiple conformers since the two aromatic rings attached to the azo group are different, and the heteroarenes are non-symmetric upon rotation about the NNCC/N angle. In alkyl bridged derivatives, the conformational space is further enlarged due to the rotational flexibility of the bridge. It is important to search for the most stable conformers among them, since errors in the evaluation of \( \Delta G \) lead to significant changes to \( t_{1/2} \) due to the exponential term in Eyring equation. To do so, we have used the protocol described in section S1. It includes the explicit evaluation of the ring conformers, an energy scan along dihedral angles in the bridge, and a more thorough evaluation using metadynamics for specific systems. In Eyring equation, we have employed the \( \Delta G \) computed from the lowest-energy conformers at each stationary point (minima and TS). Thus, we assume that higher-energy conformers can interconvert towards the most stable without a barrier. An alternative is to Boltzmann-weight the different conformer energies in the calculation of the rate constants and the resulting \( t_{1/2} \). This has been done for serie 1111, with negligible changes on the estimated \( t_{1/2} \) values.

2.4 Computational details

The optimization of the E- and Z-isomer minima, and the TS search has been done at the \( \omega B97X-D/6-31G(d) \) level as implemented in Gaussian09.\(^{45}\) Computations using the PBE0-D3BJ and M06-L functionals can be found in section S2. All zero-gradient points are further verified with a frequency computation, which also provides the thermal corrections to evaluate the free energy of each point.

The metadynamics mentioned in Section 2.3 ran at the xTB level (see Section S3).\(^{52}\) The output of such metadynamics is a trajectory consisting of a large collection of conformers. These are then clustered (see Fig. 5) using the T-distributed Stochastic Neighbor Embedding (t-SNE) projection, and the OPTICS algorithm as implemented in the Scikit-learn package.\(^{53}\) The two t-SNE main coordinates are obtained from dihedral angles inside the ring containing the azo group, and hence the clustering focuses on conformers created by the alkyl bridge.

The Non-Adiabatic Molecular Dynamics (NAMD) simulations were performed with Newton-X\(^{54,55}\) interfaced with G09.\(^{56}\) Based on previous benchmarks,\(^{26,57,58}\) we used linear-response TDDFT\(^{59,60}\) within the Tamm-Dancoff approximation (TDA), the \( \omega B97X-D \) functional\(^{51,62}\) and the 6-31G(d) basis set. 500 Initial conditions were generated from the Wigner distribution based on the harmonic oscillator, four states (\( S_0-S_4 \)), a Lorentzian broadening of 0.1 eV, an anharmonicity factor of 3, and a temperature of 300 K. From these initial conditions, we obtain the initial geometries and velocities for the trajectories. The trajectories are initiated at \( S_1 \) and \( S_2 \) using the respective FC energies and a width of +/- 0.1 eV.
25 trajectories are propagated for each state and compound. Time-derivative couplings were computed between all states except $S_0$, which is excluded due to the difficulties of TDA to describe the multi-reference character of the electronic wavefunction near a $S_1$-$S_0$ conical intersection. Accordingly, trajectories ran for a maximum of 1000 fs or until an $S_1$-$S_0$ energy gap below 0.1 eV is reached. In the latter case, it is assumed that the actual CoIn is be very similar to the final geometry, and that it should be reached immediately after in time. Trajectories are propagated in the microcanonical NVE ensemble, and the energy is conserved within 0.5 eV. Notice that the termination criterion does not presuppose the character of the $S_1$ (nπ* or ππ*). In practice, however, in all terminated trajectories, $S_1$ is the nπ* state. In general, we favour the nomenclature nπ*/ππ* to specifically refer to these states, and the $S_1$-$S_0$ nomenclature when the state character is not relevant, only the order.

3. Results and Discussion

E/Z Thermal Stability. In acyclic AB and azoheteroarene derivatives, the E-isomer is typically the most stable one, so the thermal relaxation refers to the conversion from the meta-stable Z-isomer to the most-stable E-isomer. That is the case of the bare 1 and 2, in which $\Delta G_{E-Z}$ is −12 and −10 kcal/mol, respectively. This scenario is reversed in the short bridge derivatives (n=1, 2) for the 111n and 211n series (positive $\Delta G_{E-Z}$, see Figure 1a). A major contribution to this trend is that shorter bridges enforce much more strain to the E- than to the Z-isomer (see Figure 1b), mainly on the aromatic system (see Figures S3.1 and S3.2). Such strain diminishes when using longer bridges, until recovering the regular E/Z thermal stability (negative $\Delta G_{E-Z}$ values in Figure 1a). This occurs from n=3 onwards in the ortho/ortho series (i.e. 111n and 211n), and from n=6 onwards in the ortho/meta serie (i.e. 112n). The latter case is particularly interesting since $\Delta G_{E-Z}$ never reaches similar values to the acyclic compounds (ca. −10 kcal/mol). That is because the E-isomer strain remains larger for long bridges under the ortho-meta substitution (112n case, see Figure 1c) than

under the ortho-ortho substitution (111n case, see Figure 1b). As a result, the E- and Z-isomers are almost-degenerate during a window of bridge lengths that extends from n=6 to a least n=8 (see Figure 1a). Within that window, none of the states is particularly destabilized, unlike the TS energies which are still largely affected by strain. That is the perfect scenario to obtain long half-life times.

Half-life Times ($t_{1/2}$). The half-life time of the metastable state is proportional to the energy difference between itself and the TS ($\Delta G^\ddagger$). As discussed above, shorter bridges penalize the stability of the E- more than the Z-isomer, which leads to a reversed thermal stability, and very short $t_{1/2}$ values (see Figure 2). Longer bridges reduce the strain on both the TS and the minima, but the strain penalty on the TS energies (both TS$_{inv}$ and TS$_{rot}$) remains larger (see Figure 1b-c). As a result, $\Delta G^\ddagger$ and the associated $t_{1/2}$ are systematically increased along with the bridge length (see Figure 2). Series 111n and 211n display the same trend, which suggests that the impact of the bridge is similar for 1 and 2. However, the 211n series is generally shifted towards shorter $t_{1/2}$ values with respect to the 111n one (compare blue and red lines in Figure 2). Such difference cannot be explained by the intrinsic differences in the heteroarene, since the acyclic compounds barely display any difference in $\Delta G_{E-Z}$ or $t_{1/2}$ (see stars in Figures 1 and 2). Instead, it might be due to the change in connectivity, since the bridge is attached to the heteroarene ring through either a C or a N atom in the 111n and 211n series, respectively. A similar observation is discussed in section S4.

When comparison between experimental and computational $t_{1/2}$ values is possible, differences of one order of magnitude are common in the literature. For instance, the ortho-methyl-substituted analogues of 1 and 2 (1′ and 2′) showed experimental (computed) $t_{1/2}$’s of 74 (33) days and 9 (19) hours, respectively. In that case, the computational results were obtained with PBE0-D3 (similar ones were obtained with M06-2x) and concerned the inversion pathway, since it was found that rotation was unfavorable.
Interestingly, the rotational pathway is systematically much faster than inversion. The greatest difference between pathways is found for the acyclic azoheteroarenes, with $t_{1/2}$ in the order of 30 and 3 seconds for 1 and 2, respectively (compared to 321 and 89 days for inversion). These are much smaller than the experimental $t_{1/2}$ reported in similar N-containing heteroarenes, even considering the computational error. It is therefore unlikely than the rotation pathway is actually accessible under experimental conditions, at least not in all compounds, in line with the interpretation in recent literature. A possible explanation could be drawn from the thiazole-based heteroarenes reported by Velasco and coworkers. These systems are able to undergo a rapid thermal isomerization under the ns timescale, and with a dependence on the solvent polarity, as expected for systems following the rotation mechanism. It is possible that these sulfur-containing heteroarenes increase the rate of (S$_0$→T$_1$→S$_0$) intersystem crossing (associated with the rotational pathway) by virtue of the larger spin-orbit coupling of the heavy atom, making the non-adiabatic rotation pathway competitive to the inversion one. However, such possibility seems discarded when considering the heavy-atom-free arylazoindazoles of Otten and coworkers, which according to DFT computations of the energy barrier and activation entropy, show a preference for the rotation mechanism. Another possibility is that either the functional, or the environment (i.e. gas-phase), might be misrepresenting the rotational pathway. To test this possibility, we have recomputed the inversion and rotation pathways of the main series using the hybrid PBE0-D3BJ functional and the meta-GGA M06L functional, and obtained the same picture than with ωB97X-D (see Section S2). The incorporation of water or dichloromethane solvent using the PCM implicit model also does not change the picture provided by any of the investigated functionals. Therefore, it remains as an open question why most heteroarenes explore the inversion mechanism for thermal isomerization while having a rotational transition state lower in energy, as described by our and previous computations.

Our computations for the unsubstituted 1 and 2, carried out with the ωB97X-D functional, lead to $t_{1/2}$ values of 321 and 89 days, respectively, for the same inversion pathway. While these cannot be directly compared to the aforementioned results on 1′ and 2′ (74 days and 9 hours), such significant difference suggests that ωB97X-D overestimates $t_{1/2}$. Using PBE0+D3BJ, the resulting $t_{1/2}$ for 1 and 2 are 43 and 3 days, much closer to the values reported for 1′ and 2′. The significant difference in $t_{1/2}$ among functionals results from a change of only $\sim$ 2 kcal/mol in the evaluation of $\Delta G^\ddagger$, which highlights the difficulty of predicting $t_{1/2}$ values accurately. However, both functionals retrieve the same relative $t_{1/2}$ between 1 and 2, which suggests that the trends are correct. This point is further confirmed by the results contained in section S2. Therefore, for the main discussion we prioritized the results with ωB97X-D for the sake of its better description of the photochemistry of azo-dyes.

Photochemistry of short- and long-bridged derivatives. To evaluate the impact of the bridge on the photochemistry of the azoheteroarene derivatives, we have studied compounds 2113 and 1127. These are examples of a short- and long-bridge derivatives, respectively. We have selected these specific compounds because both feature the E-isomer as the most stable one. That is an advantage for practical reasons; the E-isomer has brighter transitions at Franck-Condon (FC) than the Z- (see Tables S5.1 and S5.2 for nπ* and ππ* state energies and osc. strength), and also for the sake of comparison, because recent literature has dealt with the E-to-Z photo-isomerization of 1 and 2, providing an excellent opportunity to compare the photochemistry of bridged vs. non-bridged azoheteroarenes. Moreover, using a compound with a shorter bridge than 2113 would have implied the study of the Z-to-E isomerization, which is expected to be less affected by a bridge. To study the photo-isomerization of 2113 and 1127, we have used the same computational protocol as in ref. 48. That is, we performed non-adiabatic molecular dynamics simulations (NAMD) based on the fewest-switches surface hopping method. Swarms of 25

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**Figure 3.** Space of CNN and CNNC angles featured by the relevant geometries in all trajectories of (left) 1, from ref. 48, (middle) 2113 and (right) 1127. The CNNC angle is evaluated as the deviation from planarity, with 0° corresponding to the E-isomer, and 90° corresponding to CNNC either +90 or −90 degrees. In color, the geometries that reached an S$_0$/S$_2$ CoIn before the time limit (1 ps). The color code indicates trajectories initiated at S$_1$ (red) and S$_3$ (green). In dark grey, all geometries at which a hopping between S$_1$ and S$_3$ occurred. These results are extracted from NAMD trajectories at the ωB97X-D/6-31G(d) level.
trajectories were initiated at both the $S_1$ ($\pi\pi^*$) and $S_2$ ($\pi\pi^*$) states for 1127 and 2113, which are located at 433/268 nm and 449/300 nm, respectively, at the Franck-Condon geometry (the evolution of the $\pi\pi^*$ and $\pi\pi^*$ bands with the bridge length can be found in section S5, revealing a significant increase of band separation for short-bridged derivatives). The trajectories are then propagated until an $S_1$–$S_0$ energy gap below 0.1 eV is reached (see Comp. Details). At this point, it is assumed that population transfer to the ground state will occur, leading to either of the two minima (E or Z).

The mechanism of photo-isomerization in both AB and azoheteroarenes is determined by the character of the $S_i$/$S_j$ conical intersection (CoIn) that is reached during the trajectory. The main CoIn are associated with the rotation (CoInR) and inversion (CoInI) motions. CoInR and CoInI are indeed the extremes of a crossing seam, with the former (latter) at the low- (high-) energy end, as in AB. Unsubstituted compounds 1 and 2 feature a similar distribution of CoInR- and CoInI-like structures within the crossing seam, which indicates that both rotation and inversion pathways are accessible. Such scenario is completely different in bridged azoheteroarenes; we observe in Figure 3 a pronounced preference of both 1127 and 2113 towards the rotation pathway. One reason is that the E-isomer minima of both compounds already show a non-planar CNNC angle, so the initial structures are indeed closer to the CoInR-like region of the crossing seam than in acyclic heteroarenes. This has been previously identified as a driving force towards a fast photoisomerization in bridged-AB. Another reason is that the opening of the CNN angles associated with the inversion pathway is energetically too unfavorable, presumably due to the steric constrains: the trajectories of 2113 barely explore CNN angles above 140° (see Figure S5.2), which is where the inversion-like CoIn appear in 1 and 2. The longer bridge in 1127 alleviates the steric hindrance, so this region is increasingly explored along the trajectories (see Figure S5.2), and thus the distribution of CoIn extends more towards inversion (see Figure 3).

The photoisomerization kinetics is significantly faster for the bridged azoheteroarenes 2113 and 1127 than for the acyclic parent compounds 1 and 2. That is mainly assessed from the time required to reach a CoIn in our trajectories ($t_{CoIn}$), and also with $t_{\Delta t}$ and $t_{\Delta E}$, described as the time spent in $S_1$ and $S_2$ states, respectively. In unsubstituted azoheteroarenes, the $S_2$/$S_1$ decay is ultrafast (100-200 fs), while the overall time to reach an $S_1$/S0 CoIn after irradiation is ca. 500 fs, with small differences depending on the compound and on the excitation energy. In the bridged heteroarenes 2113 and 1127, the photoisomerization is significantly faster. In the case of 2113, all 25 trajectories initiated at $S_1$ and $S_2$ reach an $S_1$/S0 CoIn at an average $t_{CoIn}$ of 27 and 165 fs, respectively. In both cases, the $S_1$ PES leads very efficiently towards a CoIn, with very short residence times in $S_1$ ($t_{S1}$) of 27 and 37 fs. Thus, the longer $t_{CoIn}$ associated with the $S_2$ excitation is exclusively due to the extra $S_2$→$S_1$ relaxation step, whose timescale ($t_{\Delta E}$ = 128 fs) is indeed very similar to the non-bridge compound ($t_{\Delta E}$ = 113 fs). That is because the $S_2$→$S_1$ relaxation occurs at geometries close to the E-isomer minima, and thus it does not require significant molecular motion that could be affected by the steric hindrance caused by the bridge. The kinetics of 1127, with a longer bridge than 2113 (n=7 vs. 3), lies between those of 1 and 2113, in terms of both the $S_1$→$S_1$ and $S_2$→$S_2$ relaxation times (compare $t_{S1}$ and $t_{\Delta E}$, respectively). In contrast to 2113, excitation to the $\pi\pi^*$ state ($S_2$) leads to a shorter $t_{S1}$ than under direct excitation to $S_1$. That is also the case of the acyclic 1 and 2, and is due to warmer molecules having access to a broader region of the crossing seam (see Figure S5.2), thus reaching a CoIn faster. It is, thus, only in the case of the short-bridged 2113 that both $S_1$ and $S_2$ excitations lead to photo-isomerization in the same time-scale.

4. Conclusions

We have evaluated the thermal stability and the thermal relaxation half-life times ($t_{1/2}$) of phenyl-azoheteroarene photoswitches based on 3-pz (1) and 2-im (2), in which the two rings are connected through an alkyl bridge. We have explored bridges of varying length, and anchored at different positions on the aromatic rings. We obtained wide range of half-life times that spans 15 orders of magnitude (in the inversion pathway only), from the microsecond to the year timescale. That supports the use of bridges to tune the thermal stability of azoheteroarenes, as proposed in the literature for other families of photoswitches. Our results support the general trend observed in experiments that bridges tend to reduce $t_{1/2}$. However, we show that it is possible to recover, or even increase, the half-life times of acyclic compounds, using long bridges. Moreover, while short bridges reverse the E/Z thermal stability, a window of bridge lengths exists for which the regular stability can be preserved. This behavior is the result of the variable impact

| Table 1. Comparison of the photo-isomerization kinetics of compounds 2113 and 1127, with a short- and a long alkyl bridge, respectively, and the unsubstituted compounds 2 and 1, studied in reference 48. It is shown the (top) Ratio of trajectories reaching a CoIn before the time limit (1 ps), and (bottom) the characteristic times described in the main text. See table S5.3 for an assessment of the error associated with these values. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Initial State                  | Compound                        | $t_{CoIn}$                      | $t_{S1}$                        | $t_{E2}$                        |
| $S_1$                          | 2113                            | 165                             | 37                              | 386                             |
| $S_2$                          | 1127                            | 27                              | 27                              | 330                             |
| $S_1$                          | 1                               | 37                              | 27                              | 260                             |
| $S_2$                          |                                 |                                 |                                 | 160                             |
| $t_{CoIn}$                     | $S_1$                           | 1                               | 1                               | 0.84                            |
| $t_{CoIn}$                     | $S_2$                           | 1.0                             | 0.96                            | 0.56                            |
| $t_{S1}$                       | $S_1$                           | 27                              | 330                             | 282                             |
| $t_{S1}$                       | $S_2$                           | 165                             | 373                             | 366                             |
| $t_{E2}$                       | $S_1$                           | 27                              | 330                             | 282                             |
| $t_{E2}$                       | $S_2$                           | 37                              | 260                             | 160                             |
| $t_{E2}$                       |                                 |                                 |                                 | 250                             |
The impact of the bridge on the photo-isomerization kinetics has been studied using surface-hopping molecular dynamics on two systems representing extreme cases. A 2-imidazole heteroarene with a 3C-bridge attached in ortho positions (2113) features a regular E/Z stability, one of the shortest $t_{1/2}$ (ca. 10 ms), and it undergoes the E-to-Z photo-isomerization 10 times faster than the acyclic parent compound, under both $S_1$ and $S_2$ excitation. In turn, a 3-pyrazole derivative with a long 7C bridge attached in ortho (Ph) and meta (het) positions (1127) features a regular E/Z stability, the longest computed $t_{1/2}$ (ca. 47 years), and a comparatively fast E-to-Z photo-isomerization. In both cases, the photo-isomerization proceeds through the rotational pathway, which is associated with a higher efficiency (better quantum yields), as reported in other constrained azo-dyes.21

Overall, we unravel how alkyl bridges modify the relative E/Z thermal stability of two azoheteroarene families, the associated half-life times (through the TS energies), and the photo-isomerization pathway and kinetics.

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Dataset

The dataset will be available at Zenodo upon publication.

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Conflicts of interest

There are no conflicts to declare

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64. Notice that strain is not the only effect that dictates the \( T_{S_{\text{inv}}} \) and \( T_{S_{\text{rot}}} \) energies. The usual electronic effects and non-covalent interactions also contribute, albeit such terms are not explicitly evaluated.

65. There seems to be an inconsistency between the values given in Table S4 and Figure S29 of that reference. For Figure S29 to be correct, the values in Table S4 should be in hours and not in seconds as specified in the caption.

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