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Substituent Effects on 3-Arylazaindole Photoswitches

Nadja A. Simeth,[†] Alfredo Bellisario,[‡] Stefano Crespi,^{*,†,§} Maurizio Fagnoni,[§] and Burkhard König^{*,†}[†]Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, 93040 Regensburg, Germany[‡]Department of Physics, Università di Pavia, Via Bassi 6, 27100 Pavia, Italy[§]PhotoGreen Lab, Università di Pavia, Via Taramelli 12, 27100 Pavia, Italy

Supporting Information

ABSTRACT: The development and investigation of hetero-azo switches has flourished in recent years. Because of their specific photophysical and photochemical properties, they find versatile applications from material science to medicine. However, a deep mechanistic understanding is needed to be able to predict the properties of such azoswitches. In particular, the effect of different substituents on the azo chromophore is of great interest as they are often crucial for embedding the molecular switch into a system of interest. Herein, we provide a detailed spectroscopic and computational study on the influence of substituents on 3-phenylazaindoles chosen as models. We will point out changes in absorption properties and analyze the photostationary state of the thermally labile Z isomers through computational means to provide a general structure–property relationship guideline for further use of these compounds.

INTRODUCTION

Photochromic compounds received a remarkably rising interest in the last two decades.^{1–3} They found various applications, for instance, as molecular memory and logic devices,^{4–6} in light-gated chemical reactions,^{7,8} material science,^{9–11} drug delivery,^{12,13} and control of cell death.^{14–16} Molecular photoswitching is based on bistable systems interconverting between two (or more) distinct isomeric forms by application of light as an external stimulus.¹⁶ In particular, azobenzenes are popular photochromes due to their large geometrical changes upon isomerization,^{17,18} their synthetically versatile availability,^{19,20} their high fatigue resistance,^{17,18} and the tunability of their photophysical properties.^{21–24} Upon irradiation, they interconvert from a thermodynamically stable *E*- to a metastable *Z*-isomer (Figure 1A). The reaction is reversible, and *Z*-to-*E* isomerization is triggered through irradiation with light of a longer wavelength or thermally. The incorporation of substituents on the molecular core has been frequently used to tune the properties of azobenzenes.^{2,21,25,26} In contrast, a scaffold-hopping approach^{27,28} to heterocyclic aromatic systems was only considered very recently. An increasing number of studies have focused on this aspect to broaden the selection of azo switches available. For instance, nitrogen-based heteroaryls like pyridine,^{29,30} imidazole,^{31,32} pyrazole,^{33,34} purine,³⁵ and very recently, the indole scaffold^{36,37} have been employed as arylazo switches.

Recently, we became interested in phenylazaindole-based photoswitches (PAIs), owing to their highly tunable properties depending on the position of the azo function and the solvent employed.³⁶ In particular, 5- (5-PAI, Figure 1B) and 6-phenylazaindoles (6-PAI, Figure 1B) behave similarly

compared to azobenzene in regard to both their spectroscopic properties and the lifetimes (τ) of the *Z*-isomer. In contrast, the spectrum of 2-phenylazaindole (2-PAI, Figure 1B) is bathochromically shifted, and the *Z*-isomer of the compound exhibits extremely short thermal lifetimes (<10 ns) due to the rotation transition state characterized by low barriers.³⁷ The 3-phenylazaindole derivative (1a,b, Figure 1B) is the most tunable scaffold of the series.³⁶ Indeed, the thermal lifetimes can be varied from the nanosecond range to the days, choosing the substituent on the indole nitrogen (–H or –Me) and the composition of the solvent mixture.³⁶ Such an effect is directly correlated to the molecule undergoing a thermal *Z*-to-*E* following different mechanisms, viz. inversion, rotation, or intermolecular hydrazone tautomerism.³⁶

Computational methods such as time-dependent density functional theory (TD-DFT) represent a viable tool to assess and predict the absorption characteristics of azo switches like phenylazaindoles. TD-DFT is reliable in providing predictions of both transition energies and oscillator strengths (f), allowing us to assign the nature of the transition type.^{38–40} Such an approach is necessary to design and to understand the photophysical characteristics of the molecule, even before its synthesis.

In this work, we simulated the UV/vis spectra of both photoisomers of a library of 14 heteroazo switches in toluene, dimethyl sulfoxide (DMSO), and methanol after performing a benchmark of a series of functionals and basis sets on compound 1a. We simulated the substituent effects on the

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Figure 1. (A) Schematic *E*-to-*Z* isomerization in azobenzene. (B) Phenylazaindoles (PAIs) investigated in our previous work. (C) PAIs studied in the present work.

Chart 1. Scope of the Computed and Synthesized Molecules^a

^aKey: (A) Variation of the substituents on the phenyl moiety in the synthesized compounds 1a,b and 2–7a. (B) X-ray structures of compounds 1b, 2a, 3a, and 4a. (C) Variations of the substituents of the phenyl moiety only considered in silico. (D) Perfluorination of the benzo moiety.

phenyl moiety of 3-phenylazaindoles and synthesized seven compounds to test the reliability of the method further and to study their thermal behavior upon photoisomerization. In addition, we varied the functionalization on the indole nitrogen and the benzo moiety of the indole unit and provided a structure–property relationship analysis of the whole library (Figure 1C). Finally, we developed a procedure from our computational methodology to analyze the photostationary distribution (PSD) at the photostationary state (PSS) of both photoisomers of the synthesized compounds. This method represents a valid alternative in case classical analytical methods such as NMR or HPLC cannot assign the PSD due to the fast *Z*-to-*E* isomerization kinetics.

RESULTS AND DISCUSSION

Scope. In this study, we focused on varying the substituents on the phenyl moiety of the azoindoles and changing their electron demand (see Chart 1). Moreover, we considered more complex moieties such as acrylic acid (8), morpholine (5), or pyrrole (10) envisioning a potential photopharmaco-

logical application, as these structural motifs are commonly found in bioactive compounds and drugs.⁴¹ In doing so, we aimed to obtain a clearer picture of the influence substituents have on the UV/vis properties of the investigated molecules. Furthermore, we modified the substituent on the indole NH from –H (1a–11a) to –Me (1b–11b), –Ph (1c), and the sterically more demanding mesityl (Mes, 1d). We also investigated how perfluorination of the benzo moiety of the indole would alter the structural characteristics (12a–d). Having the experimental data of 1a and 1b in hand,³⁶ we synthesized compounds 2a–7a analogously to our previous work via diazonium salts of the corresponding anilines (for details, see the Supporting Information).³⁶ During the preparation, X-ray structures of 1b, 2a, 3a, and 4a (see Chart 1 and the Supporting Information; also see the Supporting Information for the side products 10a' and 10a'') could be obtained. Moreover, we investigated the compounds 2a–7a regarding their photochromic properties (vide infra, UV/vis Spectra section).

Structure Optimization and Simulation of the UV–vis Spectra. The computational investigation was carried out using Gaussian 09, Revision D.01, and Gaussian 16, Revision A.03, software packages. The energetically most stable conformers of the *E*- and *Z*-isomers were optimized using the B3LYP/6-311+G(2d,p) level of theory and confirmed to be minima via the absence of imaginary normal modes of vibrations. A benchmark study including 24 functionals and 14 basis sets using the previously investigated molecule **1a** as reference was carried out to identify PBE0/6-311+G(2d,p) as the best model describing the electronic properties of the compounds in TD-DFT simulations over the first 25 transitions. Figure 2 offers an overview of the performance of

Figure 2. Comparison of the wavelengths associated with the first electronically allowed transition between the experimental (in toluene) and the computed values of **1a** with different functionals and the HF method, in the TD framework, using the 6-311G+(2d,p) basis set in toluene (C-PCM). PBE0 performed better compared to the others in describing the $\pi\pi^*$ transition of **1a** accurately.

the different DFT functionals (with toluene as an implicit solvent, employing the C-PCM model⁴²) to predict the maximum of the $\pi\pi^*$ absorption maximum, compared to the experimental value (obtained in toluene³⁶) and the one calculated with the TD-Hartree–Fock method. A more detailed description of the stepwise structure optimization and the TD-DFT benchmark study is included in the Supporting Information.

Spectroscopic Analysis. UV–vis Spectra. The synthesized compounds **1a–7a** and **1b** were investigated using UV–vis spectroscopy (the data of compounds **1a** and **1b** were taken from our previous study³⁶) in order to compare the reproducibility of our computational method, optimized for **1a** (the results are summarized in Table 1; for a wider range of solvents, see Table S1 in the Supporting Information). In addition, the spectra of all the compounds included in this study were simulated using (C-PCM)⁴²-TD-PBE0/6-311+G(2d,p) as a single-point over the first 25 states (Table 1 for compounds **1a–7a** and **1b**; see Table S1 for additional data).

The λ_{max} of the main transition band of the synthesized compounds, which can be attributed to the $\pi\pi^*$ transition of the *E*-isomer (in accordance with previous reports), was compared with the main transition ($f > 0.8$) in TD-DFT, the second excited-state transition (as the first one, the $n\pi^*$, is formally forbidden, with an $f = 0$).¹⁸ The principal absorption band falls between 350 and 422 nm in the experiment. The

calculations tend to underestimate the transition energy of **1a–6a** by ca. 3–6 nm in toluene and by 4–8 nm in DMSO. The values in MeOH are more precise than the ones obtained in the other solvents, and the difference is found to be ca. 1–4 nm. Compound **7a** (*p*-nitro) is the only species affording poor correlation between the calculated and experimental values. The presence of the nitro chromophore causes the calculation to overestimate the $\pi\pi^*$ transition wavelength slightly. However, the chosen functional and basis set describe the trend of the electronic properties of **1a–7a** in solution robustly (see Figure 3) and are able to distinguish the nature of the transition (either $n\pi^*$ or $\pi\pi^*$). Hence, we are confident the TD-DFT simulations can be applied to analyze correctly the compounds which are only part of the in silico study.

Following these premises, we proceeded in the generalization of the effects of the substituents, as derived by the computations. To do so, we also evaluated the effect of the solvent on the simulated UV/vis spectra increasing the polarity of the bulk solvent, viz. toluene ($\epsilon = 2.3741$), MeOH ($\epsilon = 32.613$), and DMSO ($\epsilon = 46.826$). The results are summarized in Table 2 (for all of the spectra with the addition of the values obtained in vacuo, see the Supporting Information), where the first three transitions with the associated oscillator strength (f) are collected. The first transition is always associated with the symmetry nonallowed population of the $n\pi^*$ excited state. The solvent has a notable effect on the band position (as expected from the $n\pi^*$ nature). However, the band is not present in the majority of the cases subject to the study and, consequently, to the low oscillator strength values. In contrast, the *o*-morpholino substituent in *E*-**5a,b** results in a distortion of the planarity in the structure. The geometry change leads to an increase of the electronic transitions becoming allowed in the visible region of the spectrum (see Figure 4) and an increase of the f values of the associated $n\pi^*$ excitation. On the other hand, the solvent has a very limited effect on the main $\pi\pi^*$ electronic transition (the second one, with an almost unitary oscillator strength, in the majority of the cases). Only in *E*-**7a,b** (*p*-nitro) is the increased polarity accompanied by the red-shift of the transition, mirroring the increased polar character that the nitro group imparts to the molecule. In general, the substituents on the phenyl moiety of the switch have a bathochromic effect on the $\pi\pi^*$, compared to the unsubstituted *E*-**1a**. The pentafluorophenyl derivative *E*-**9a** is the only exception, given its spectrum shows hardly any difference compared to the parent *E*-**1a**. Thus, the main transition bands are red-shifted in *E*-**2a** (*o*-bromo), *E*-**3a** (*o*-hydroxy), *E*-**4a** (*o*-fluoro), *E*-**6a,b** (*p*-hydroxy), and *E*-**11a** (di-*m*-CF₃), up to ca. 25 nm. A more pronounced shift is present in the spectra of *E*-**5a** (*o*-morpholino), *E*-**7a** (*p*-nitro), *E*-**8a** (*p*-propenoic acid), and *o*-pyrrole derivative *E*-**10a** (cf. Figure 4, Table 2, and Table S1 and sections 3 and 7 in the Supporting Information). The effect can be explained by the presence of a push–pull azo system, as in the case of *p*-nitro in *E*-**7a** or the *p*-propenoic acid substituent in *E*-**8a**.⁵ On the other hand, an extended π -conjugation through the aromatic *o*-pyrrole substituent in *E*-**10a** can lower the transition energy of the molecule. Figure 4 shows the HOMO of *E*-**10a**, which expands throughout the molecule and exhibits extensive π -character. In contrast, in *E*-**5a** the sterically demanding *o*-morpholino substituent leads to torsion in the structure allowing more transition in the visible range (vide supra).

The same considerations hold with the methylated compounds *E*-**1–12b**. However, methylation of the indole

Table 1. Overview of Experimental and Calculated Maxima of the Different Synthesized Compounds in Toluene, DMSO, and MeOH and Their PSS Ratio Determined through Computational Analysis

Compound	Solvent ^a	$\lambda_{\max}$ [nm]	$\lambda_{\max}$	$\epsilon_{\lambda_{\max}}$	τ^g	PSD ^h [Z-E]
		PBE0	[nm]
Toluene ^a	366	362 ^f	15151 ^f	47.5 ms ^f	
	DMSO ^a	368	372 ^f	16447 ^f	6.5 s ^f	
	MeOH ^a	366	365 ^f	14716 ^f	6.8 ms ^f
Toluene ^a	373	366 ^f	14134 ^f	17.1 min ^f	
	DMSO ^a	376	380 ^f	15964 ^f	2.6 d ^f	85-15 ^f
	MeOH ^a	373	369 ^f	14338 ^f	2.4 h ^f
Toluene ^b	379	373	13956	51.4 s	94-6
	DMSO ^b	380	388	13248	1.41 s	19-81
	MeOH ^b	378	377	13582	13.1 ms	28-72
Toluene ^c	392	385	13890	12.1 ms	35-65
	DMSO ^c	392	389	15151	18.4 ms	46-54
	MeOH ^c	389	384	15556	7.76 ms	6-94
Toluene ^a	375	367	14148	136 s	90-10
	DMSO ^a	376	379	15592	1.02 s	19-81
	MeOH ^a	374	371	15552	9 ms	6-81
Toluene ^a	340 (412)	347 (388)	11018	1.49 ms	9-91
	DMSO ^a	341, 411	394	17192	<i>i</i>	57-43
	MeOH ^a	340, 410	384	16820	<i>i</i>	9-91
Toluene ^d	373	373	10710	10.2 s	87-13
	DMSO ^d	375	380	12450	5.74 s	86-14
	MeOH ^d	373	374	13752	<i>i</i>	7-93
Toluene ^e	427	399	11593	121 s	94-6
	DMSO ^e	442	422	14723	<i>j</i>	5-95
	MeOH ^e	438	407	15977	94.4 s	16-84

^a50 μ M concentration. ^b100 μ M concentration. ^c70 μ M concentration. ^d40 μ M concentration. ^e30 μ M concentration. ^fExperimental value taken from ref 36. ^gZ-to-E lifetimes were determined using laser-flash photolysis ($\tau < 1$ s) and UV/vis spectroscopy ($\tau > 1$ s). ^hDetermined with the computational method presented in the section "PSS Analysis" and in section 8 in the Supporting Information. ⁱLifetime not determined as the value was faster than the lower limit of detection of the instrument (<ns). ^jThe compound underwent a thermal reaction after one irradiation cycle, which was not further investigated.

nitrogen leads to a red-shift (ca. 10–20 nm) of the spectrum in the majority of the compounds compared to their NH analogue. The shift is strongly pronounced for *p*-propenoic acid *E*-8 and *o*-pyrrole azoindole *E*-10 (>30 nm). Moreover, in the compounds analyzed the introduction of a phenyl group on the indole nitrogen leads to a red-shift of the spectrum. The effect is more prominent comparing the parent 3-phenyl-azoindole *E*-1a and *E*-1c (40–48 nm) than the perfluorinated indole derivatives *E*-12a and *E*-12c (ca. 10 nm). In a similar

fashion, moving from NH to NMeS leads to less energetic transitions. In contrast to phenylation, the red-shift induced by the Mes substituent is more present in *E*-12d (2–11 nm) than in *E*-1d (24–39 nm).

Perfluorination of the homocyclic moiety of the indole in *E*-12a–d induces an overall blue-shift of the spectrum. Thereby, comparing NH and NMe derivatives, the attachment of fluoro substituents to the indole ring leads to a decrease of the wavelength maximum of 1–9 nm. The effect increases in

Figure 3. Comparison between the experimental and computed ((C-PCM)-TD-PBE0/6-311+G(2d,p)) wavelengths associated with the maximum of absorption of the $\pi\pi^*$ band of the azo compounds in toluene.

NMe derivatives (22–24 nm) and most significantly in NPh derivatives (37–40 nm).

The *Z*-isomers possess two main bands, at 220–240 nm and 320–370 nm (the latter one attributable to the $\pi\pi^*$ transition of the azo group). In some cases, namely in *Z*-2a,b (*o*-bromo), *Z*-3a,b (*o*-hydroxy), *Z*-4a,b (*o*-fluoro), *Z*-6a (*p*-hydroxy), *Z*-9a (3-perfluorophenylazindole), and *Z*-12a,c,d (perfluorinated benzo submoiety of the indole ring), the $n\pi^*$ (ca. 450–500 nm) becomes slightly allowed ($f < 0.1$). The $n\pi^*$ band is not always present; consequently, the T-shaped conformation the *Z*-forms is assumed when the azo is positioned in position 3 of an indole^{36,37} (and more generally when attached to five-membered heterocycles).⁴³ The $\pi\pi^*$ of the *Z*-isomers show significantly lower oscillator strength, ca. $f < 0.2$ in vacuum, $f < 0.3$ in DMSO, $f < 0.4$ in toluene, and in $f < 0.8$ MeOH compared to the *E*-isomers ($f = 0.6$ – 0.7 in vacuum and $f = 0.8$ – 1.4 in the different solvents; for the simulated spectra, see the [Supporting Information](#)) as expected for the azo chromophore.¹⁸ In contrast to the *E*-isomers, substituent effects can be observed, but no clear trends can be derived due to the superposition of the band at 220–240 nm with the $\pi\pi^*$.

***E*-to-*Z* Isomerization and Thermal Lifetimes.** To gain a deeper insight into the effects of substitution on the properties of the arylazindoles, we focused on studying the thermal *Z*-to-*E* isomerization of compounds 2a–7a. Indeed, upon irradiation with light of an appropriate wavelength (355 nm YAG laser or 400 nm LED), the azindole switches undergo a photochemical *E*-to-*Z* isomerization, which can be followed spectroscopically by the decrease of the $\pi\pi^*$ transition band of the *E*-isomer. The spectrum of 2a (-bromo) in toluene is exemplarily shown in [Figure 5](#) (more spectra can be found in the [Supporting Information](#)).

Removal of the light source leads to a quick recovery of the *E*-isomer characterized by the lifetime (τ) of the *Z*-isomer (see [Figure 5](#)). The lifetimes of the six newly synthesized compounds were determined through UV–vis spectroscopy or laser-flash photolysis and were in the range of milliseconds to seconds for NH phenylazindoles (only the parent compound 1a studied previously in more detail showed faster isomerization kinetics, while the methylated 1b can reach 2.6 d³⁶). In addition, the feasibility of an intermolecular hydrazone tautomer formation was qualitatively checked computationally.

All of the compounds possess a hydrazone tautomer that is almost isoenergetic with the *Z*-form.³⁷ We can conclude that the intermolecular hydrazone formation is a feasible path in the substituted 3-phenylazindoles as in 1a, given the presence of protic solvents to assist the proton transfer.³⁶

In particular, the investigated compounds isomerize mostly in the second range in toluene and DMSO, confirming a fast rotation mechanism³⁶ as the main actor of the thermal isomerization in the absence of protic solvent. MeOH activates the intermolecular hydrazone formation that competes with the rotation, as indicated by the drastic decrease of the thermal lifetimes in compounds *Z*-2a and *Z*-4–6a.³⁶ *Z*-3a (*o*-hydroxy) can be considered an exception of the previous mechanistic behavior. Indeed, even in toluene, the transient that we previously assigned to the hydrazone tautomer can be detected (see the [Supporting Information](#)). The presence of such tautomerism is reinforced by the hydrogen-bond interaction visible in the X-ray structure of the compound (cf. [Chart 1B](#)). An intramolecular formation of a hydrazone species from *Z*-3a could be claimed via the assistance of the *o*-hydroxy substituents, as often reported in the literature.³¹ However, the transition structures leading to the transfer of the proton from the OH to the N=N are too high in energy ($\Delta G^\ddagger = 33.4$ kcal/mol). We can then hypothesize that the *o*-hydroxy directs the intermolecular transfer of the NH of the indole to the N=N of a second molecule of *Z*-3a. In such a way, the hydroxy substituent will act as the protic solvent that mediates the intermolecular proton transfer in the unsubstituted 1a.³⁶ In contrast, the constitutional isomer *Z*-6a (*p*-hydroxy-3-phenylazindole) isomerizes in the second range in all of the investigated solvents. Hence, an intermolecular hydrazone pathway is less favored from a kinetic point of view in this derivative (while the intramolecular option is ruled out, due to the nonfavorable geometry of the *Z*-form). This finding reinforces our previous results,³⁶ evidencing the role of the NH proton compared to the OH. In contrast to the hydroxy-substituted azobenzenes, it is the indolic proton that is scrambled on the azo group and not the alcoholic one (as paralleled by the minor stability of the hydrazone obtained from the OH compared to the one obtained from the NH; all the energies are reported in the [Supporting Information](#)).

The difference between the *o*-morpholino (*Z*-5a) and the *p*-nitro substituent (*Z*-7a) is striking. The thermal lifetime of *Z*-5a diminishes so much in polar solvents that it is not detectable by the nanosecond laser flash photolysis apparatus. In contrast, the thermal lifetime of *p*-nitro derivative *Z*-7a remains unaltered when moving from toluene to MeOH (121 to 94.4 s; in DMSO, the compound was unstable after one isomerization cycle, and no further attempt to understand the nature of the reaction was made). The difference in the thermal isomerization pathway can be ascribed to both the steric and the electronic nature of the substituents. *o*-Morpholino-substituted *Z*-5a bears a sterically encumbered, electron-donating substituent that probably destabilizes the *Z*-form, as in 2-methyl-substituted 1a.³⁶ *Z*-7a (*p*-nitro), on the other hand, prefers to isomerize via a rotation mechanism, probably due to the push–pull effect exerted by the electron-rich indole and the electron-withdrawing nitro group.⁴³ The presence of the hydrazone pathway cannot be ruled out, however. The time scale of isomerization of 7a (in the second range) and its PSD in protic solvents (16% of *Z*-isomer in MeOH, see [Table 1](#)) limit the possibility of detecting the signal of the hydrazone intermediate using spectroscopic means. We

Table 2. First Three Predicted Transitions with the Associated Oscillator Strength (*f*) of the Compounds *E*-1–12 at the (C-PCM) TD-PBE0/6-311+G(2d,p) in Different Solvents

	Toluene		MeOH		DMSO			Toluene		MeOH		DMSO	
	λ [nm]	<i>f</i>	λ [nm]	<i>f</i>	λ [nm]	<i>f</i>		λ [nm]	<i>f</i>	λ [nm]	<i>f</i>	λ [nm]	<i>f</i>
440	0.00	434	0.00	434	0.00		476	0.00	477	0.00	477	0.00
	366	0.93	366	0.88	368	0.91		427	0.94	438	0.87	442	0.89
	308	0.01	313	0.01	313	0.01		352	0.01	366	0.01	366	0.01
438	0.00	432	0.00	432	0.00		475	0.00	476	0.00	476	0.00
	373	0.99	373	0.95	376	0.97		437	1.02	449	0.94	453	0.97
	308	0.01	313	0.01	313	0.01		352	0.01	366	0.01	366	0.01
461	0.00	455	0.00	455	0.00		464	0.00	459	0.00	459	0.00
	410	0.85	410	0.82	413	0.84		422	1.42	422	1.36	425	1.39
	329	0.03	334	0.03	334	0.03		336	0.01	342	0.01	342	0.01
440	0.00	435	0.00	435	0.00		478	0.00	472	0.00	472	0.00
	373	1.07	372	1.03	374	1.05		456	1.28	457	1.24	460	1.27
	311	0.01	314	0.01	315	0.01		349	0.07	355	0.06	356	0.06
454	0.00	448	0.00	448	0.00		440	0.04	432	0.04	433	0.05
	379	0.86	378	0.82	380	0.85		366	0.84	365	0.81	367	0.82
	320	0.02	323	0.01	324	0.02		322	0.02	326	0.02	326	0.02
453	0.00	446	0.00	446	0.00		438	0.06	431	0.06	431	0.07
	387	0.93	385	0.90	388	0.92		372	0.91	371	0.87	373	0.89
	319	0.01	323	0.01	324	0.02		321	0.02	325	0.02	325	0.02
423	0.00	420	0.00	420	0.00		450	0.01	443	0.01	443	0.01
	392	0.87	389	0.85	392	0.89		385	0.52	381	0.63	383	0.67
	323	0.10	323	0.07	323	0.07		371	0.23	363	0.11	363	0.09
447	0.00	439	0.00	439	0.00		467	0.02	460	0.02	460	0.02
	390	0.96	389	0.91	392	0.94		413	0.72	412	0.69	414	0.71
	313	0.04	316	0.02	316	0.02		384	0.01	377	0.00	377	0.00
444	0.00	437	0.00	438	0.00		443	0.00	438	0.00	438	0.00
	375	0.92	374	0.88	376	0.90		377	0.89	376	0.85	378	0.87
	316	0.01	320	0.01	320	0.01		326	0.01	330	0.01	330	0.01
443	0.00	436	0.00	436	0.00		442	0.00	437	0.00	437	0.00
	382	0.99	381	0.95	384	0.97		384	0.97	383	0.93	386	0.95
	316	0.01	320	0.01	320	0.01		325	0.01	329	0.01	330	0.01
445	0.09	439	0.09	440	0.11		441	0.00	435	0.00	435	0.00
	412	0.34	410	0.31	411	0.32		361	0.88	361	0.83	363	0.86
	340	0.42	340	0.39	341	0.40		292	0.02	296	0.03	296	0.03
445	0.12	439	0.13	439	0.15		441	0.00	434	0.00	434	0.00
	412	0.39	411	0.35	412	0.36		368	0.92	369	0.88	371	0.90
	343	0.41	344	0.38	345	0.38		293	0.01	296	0.02	297	0.02
427	0.00	422	0.00	422	0.00		444	0.00	438	0.00	438	0.00
	373	1.02	373	0.97	375	1.00		370	0.99	370	0.94	372	0.97
	302	0.01	306	0.01	306	0.01		296	0.02	299	0.02	299	0.02
426	0.00	420	0.00	421	0.00		460	0.00	454	0.00	454	0.00
	380	1.07	380	1.03	382	1.05		395	0.82	394	0.79	396	0.81
	304	0.00	307	0.00	308	0.00		309	0.02	312	0.02	312	0.02

computed the energy change associated with the protonation of the N atom in the benzylic position with respect to the nitrophenyl moiety. The protonation of this position is slightly less favored compared to **1a** (ΔG ca. 4 kcal/mol; see section

6.4 in the [Supporting Information](#)). This difference could influence the thermal isomerization pathway followed by the molecule, making the intramolecular rotation more feasible compared to the intermolecular hydrazone.

Figure 4. (A) Optimized structure (TD-PBE0/6-311+G(2d,p) in vacuum, left) and the relative UV-vis spectrum (right) of *E*-1a are depicted. (B) The HOMO (TD-PBE0/6-311+G(2d,p) in vacuum, left) and the relative UV-vis spectrum (right) of *E*-10a are depicted. (C) Optimized geometry of *E*-5a (TD-PBE0/6-311+G(2d,p) in vacuum, left) shows a pronounced distortion of the usually planar *E*-isomer, resulting in a red-shifted UV-vis absorption spectrum (right).¹⁶

PSS Analysis. Due to the fast, thermal *Z*-to-*E* isomerization of compounds 2a–7a, the PSD could not be assigned using classical means like NMR or HPLC analysis. Therefore, the use of more elaborate equipment such as in situ illumination–NMR(–UV/vis) spectroscopy has to be used to analyze the abundance of thermally unstable *Z*-isomers.⁴⁸ Recently, the group of Fuchter reported a method quantifying the PSD of thermally labile heteroaryl azo switches by calculating the spectrum of the pure *Z*-isomer from UV-vis studies.⁴³ However, having a benchmark-proven in silico method in hand, we decided to obtain the value of the PSS by comparing the experimental with one simulated by mixing the computed spectra of the pure *E*- and *Z*-isomers (see the Supporting Information). Comparing the computed PSS of the thermally stable photoswitch 1b in DMSO with the experimentally one through NMR,³⁶ we attributed the share of the *Z*-isomer to be 85% with both methods (Figure 6 and the Supporting

Information). Once the method was proven to be significantly accurate, we consequently used the same approach to analyze the PSS compositions of the thermally more labile compounds tested in this study. The results can be found in Table 1 and are depicted exemplarily in Figure 6 showing the comparison of the experimental and simulated spectra of compound 1b in toluene. Additionally, we were able to automatize this procedure by developing a Matlab-based code (see the Supporting Information). Hence, the method is viable enough to be easily extended to other azo switches and photo-switchable scaffolds in general.

SUMMARY AND CONCLUSION

In summary, we simulated the UV/vis spectra of a series of substituted 3-phenylazindoles in various solvents using C-PCM-TD-DFT studies on the PBE0/6-311+G(2d,p) level of theory. For comparison, several derivatives were additionally

Figure 5. Compound **2a** in toluene at thermal equilibrium (Δ black line) and at the photostationary state (PSS, red line, generated registering the spectrum under irradiation with a LED at 400 nm).

synthesized and characterized through UV/vis spectroscopy regarding their photophysical and photochemical behavior. Gratifyingly, the theoretically and experimentally obtained values were in excellent agreement. Combining the spectroscopic and the computed results we found that all compounds except the *o*-morpholino derivative **E-5** exhibit the classical profile of arylazo compounds with a maximum between ca. 350 and 420 nm. Thus, the energy of the transition band depends on the solvent and the substituents. Indeed, functional groups, which extend the π -system or generate an azo-push-pull system, lead to more pronounced bathochromic shifts in the spectra. In addition, NMe, NPh or NMes substitutions result in a red-shift of the absorption spectrum. Thus, the steric demand of the *N*-substituents appears to be less important for the transitions energies. In contrast, perfluorination of the benzo moiety of the indole induces a hypsochromic shift. By analyzing the thermal stability of the *Z*-isomers of the synthesized compounds, we found that they, in general, relax in the millisecond to second range with some notable exceptions. Indeed, compounds **5a** (*o*-morpholino) and **6a** (*p*-hydroxy) isomerize with subnanosecond lifetimes.^{44–46} As the fast isomerization kinetics makes the determination the PSD unviable through established methods like NMR or HPLC analysis, we used the simulated spectra of *E*- and *Z*-

isomers to compare the experimentally obtained spectra at the PSS with the simulated ones. In this manner, we were able to assign the ratio of the thermally labile *Z*-isomers in the PSS. In conclusion, we deem that our study and method may lead to a rationalization of the design of novel scaffolds and to a clearer interpretation of the data obtained.

EXPERIMENTAL SECTION

General Information. All reactions were performed under magnetic stirring at room temperature unless otherwise specified. All reagents and solvents were obtained from commercial suppliers and used without further purification, if not otherwise stated. For TLC, silica-coated aluminum plates (Macherey-Nagel ALUGRAM Xtra SIL G UV 254, 0.2 mm) were utilized. Visualization was carried out with a UV lamp at 254 nm.

Isolation of the Compounds. For MPLC, a Biotage Isolera One Flash Purification System with manually packed columns using Macherey-Nagel GmbH & Co. KG 60 M (0.04–0.063 mm, 230–400 grain diameter) was used. For preparative HPLC, a 1260 Infinity LC System from Agilent with a reversed-phase Phenomenex Luna 10 μ C18(2) column (250 $\times$ 21.2 mm, 100 Å) was used. HPLC conditions were the following: solvent A = water (Millipore), solvent B = MeCN (Fisher scientific, gradient grade); flow rate = 22 mL/min.

Analysis. Nuclear magnetic resonance spectroscopy (NMR) was carried out using a Bruker Avance 400 MHz spectrometer (^1H : 400 MHz, ^{13}C : 101 MHz, $T = 300$ K). Chemical shifts are reported in δ (ppm) relative to an internal standard (solvent residual peak). The solvents used are indicated for each spectrum. Coupling constants are reported in hertz (Hz). Characterization of the signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = doublet of doublet, dt = doublet of triplet. Integration is directly proportional to the number of the protons. Characterization of the ^{13}C NMR signals: (+) for CH_3 or CH , (–) for CH_2 , and (q) for quaternary C atoms. The latter assignment resulted from DEPT135. High-resolution mass spectra (HR-MS) were recorded with an Agilent Tech 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer. IR spectroscopy was done using an Agilent Cary 630 FTIR. Melting points were determined using an SRS MPA100 OptiMelt melting point apparatus.

UV/vis Spectroscopy. For UV/vis measurements, an Agilent 8453 spectrometer was employed. For temperature control, a Varian Cary Single cell Peltier apparatus was used. Irradiation of the compounds (for online PSS measurements) was carried out at a 90° angle with respect to UV/vis recording so that irradiation could be performed online during the measurement. For irradiation, a 400 nm Edison Edixeon EDEV-SL-C1–03 (700 mA) was used.

Laser-Flash Photolysis. The laser pulse photolysis apparatus consisted of a Flashlamp pumped Q-switched SpitLight-100

Figure 6. (A) Experimental absorption spectrum of **E-1b** in toluene (black line) and its PSS under irradiation at 366 nm (red line). (B) Calculated spectrum at the (C-PCM)-TD-PBE0/6-311+G(2d,p) (solvent: toluene) of **E-1b** (black line) and **Z-1b** (blue line) and the PSS calculated using a Lorentzian fit with full width at half maximum of 67.98 nm (red line). The PSD was computed to be 85:15 *Z/E*, fitting the experimental value nicely.

Nd:YAG laser from InnoLas, used at the third harmonic of its fundamental wavelength. It delivered a maximum power of 10 mJ at 355 nm with 6 ns pulse duration. The LP920-K monitor system (supplied by Edinburgh Instruments), arranged in a cross-beam configuration, consisted of a high-intensity 450 W ozone free Xe arc lamp (operating both in pulsed and in the continuous wave), a Czerny-Turner with triple grating turret monochromator, and a five-stage dynode photomultiplier. The signals were captured by means of a Tektronix TDS 3012C digital phosphor oscilloscope, and the data were processed with the L900 software supplied by Edinburgh Instruments. The solutions to be analyzed were placed in a fluorescence cuvette ($d = 10$ mm).

Synthesis. General Procedure I for Diazonium Salt Formation. Aniline (1 equiv, typically 3 g) was dissolved in HBF_4 (15 mL, 32% aq) and cooled to -15°C (NaCl/crushed ice). Then NaNO_2 (1 equiv) in water (4 mL, sonicated) was added dropwise. The reaction mixture was stirred for 30 min, and then the white precipitate was sucked off and washed with ice-cold Et_2O (5 mL) and $\text{Et}_2\text{O}/\text{MeOH}$ (1:1, 5 mL). After washing, vacuum was applied for 15 more minutes in order to dry the diazonium salt before it was employed directly in the azo-coupling or stored in the freezer (-18°C , up to 10 days).

General Procedure II for Diazonium Salt formation. The appropriate aniline (1 equiv, typically 3 g) was dissolved in HBF_4 (15 mL, aq, 32%) and cooled to -15°C using a bath of NaCl/crushed ice. Then, NaNO_2 (1 equiv) in water (4 mL, sonicated) was added dropwise. The salt was filtered off (using precold equipment as some of the salts turned out to be extremely sensitive to temperature) and directly employed for azo-coupling.

General Procedure for Azo-Coupling. The appropriate indole (1 equiv, typically 2.00 mmol) was dissolved in DMF (5 mL). Diazonium salt (1 equiv) was added in small portions. The color immediately changed to red. The reaction mixture was stirred at ambient temperature for 16 h and then poured into water (200 mL). The organic compounds usually formed red droplets which were collected through extraction of the aqueous solution with DCM (3×100 mL). The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude material was purified through MPLC (ethyl acetate in petroleum ether $35 \rightarrow 100\%$ for **2a**, **3a**, **4a**, **6a**; MeOH in DCM $0 \rightarrow 20\%$ for **7a**). For spectroscopic purity, the product was further purified in preparative HPLC (MeCN in H_2O : $40 \rightarrow 100\%$).

(E)-3-((2-Bromophenyl)diazenyl)-1H-indole (2a). The compound was prepared following the general procedure I for the synthesis of diazonium salts (using 2.00 mmol of indole) and the general procedure for azo-coupling.

Compound **2a** was obtained as a brown solid (251 mg, 0.84 mmol, 42%). ^1H NMR (400 MHz, chloroform- d): $\delta = 8.76\text{--}8.72$ (m, 1H), 8.67 (b s, 1H), 8.07 (s, 1H), 7.76 (dt, $J = 7.9, 1.3$ Hz, 2H), 7.46–7.30 (m, 4H), 7.23 (ddd, $J = 8.0, 7.2, 1.6$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform- d): $\delta = 137.8$ (s, q), 136.3 (s, q), 133.5 (s, +), 132.0 (s, +), 130.1 (s, +), 127.9 (s, +), 124.8 (s, +), 123.8 (s, q), 123.6 (s, q), 118.5 (s, q), 117.1 (s, +), 111.3 (s, q), 110.0 (s, +), 104.35 (s, q). IR (neat) (cm^{-1}): $\tilde{\nu}$ 3392 (m), 2922 (s), 2855 (s), 1513 (m), 1379 (m), 1200 (m), 1099 (m), 738 (s). HR-MS (ESI^+) m/z : $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{14}\text{H}_{11}\text{BrN}_3^+$ 300.0131, found 300.0132 (^{79}Br), 302.0114 (^{81}Br). Mp: $185\text{--}188^\circ\text{C}$. R_f : 0.45 (DCM). The structure was confirmed through X-ray analysis. The compound was previously reported and characterized through elemental analysis.⁴⁷

(E)-2-((1H-Indol-3-yl)diazenyl)phenol (3a). The compound was prepared following the general procedure II for the synthesis of diazonium salts (using 2.00 mmol of indole) and the general procedure for azo-coupling.

Compound **3a** was obtained as a brown solid (43 mg, 0.18 mmol, 9%). ^1H NMR (300 MHz, methanol- d_4): $\delta = 8.48\text{--}8.38$ (m, 1H), 8.07 (s, 1H), 7.81 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.53–7.41 (m, 1H), 7.32–7.15 (m, 3H), 7.08–6.98 (m, 1H), 6.92 (dd, $J = 8.2, 1.3$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, methanol- d_4): $\delta = 164.9$ (s, q), 153.3 (s, q), 139.3 (s, q), 138.6 (s, q), 135.2 (s, q), 131.8 (s, +), 131.3 (s, +), 125.3 (s, +), 123.7 (s, +), 123.6 (s, +), 120.8 (s, +), 120.0 (s, q), 118.6 (s, +), 113.0 (s, q). IR (neat) (cm^{-1}): $\tilde{\nu}$ 3064 (m), 2743 (m),

2106 (w), 1610 (m), 1539 (m), 1487 (m), 1051 (s), 973 (s), 749 (s), 678 (s). HR-MS (ESI^+) m/z : $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{14}\text{H}_{12}\text{N}_3\text{O}^+$ 238.0975, found 238.0975. Mp: dec $>195^\circ\text{C}$. R_f : 0.40 (DCM). The structure was confirmed through X-ray analysis.

(E)-3-((2-Fluorophenyl)diazenyl)-1H-indole (4a). The compound was prepared following the general procedure II for the synthesis of diazonium salts (using 9.03 mmol of indole) and the general procedure for azo-coupling.

Compound **4a** was obtained as highly viscous red-brown oil (796 mg, 3.34 mmol, 37%). ^1H NMR (400 MHz, acetone- d_6): $\delta = 8.54\text{--}8.45$ (m, 1H), 8.30 (s, 1H), 7.79 (td, $J = 8.0, 1.8$ Hz, 1H), 7.59–7.49 (m, 1H), 7.47–7.38 (m, 1H), 7.36–7.23 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, acetone- d_6): $\delta = 159.2$ (q, d, $J = 252.9$ Hz), 141.6 (q, d, $J = 7.2$ Hz), 137.2 (s, q), 136.9 (s, q), 133.5 (s, +), 130.2 (s, +, d, $J = 8.0$ Hz), 124.4 (s, +, d, $J = 3.8$ Hz), 124.2 (+), 122.8 (s, +, d, $J = 8.3$ Hz), 118.5 (s, q), 116.9 (s, +), 116.7 (s, +), 116.5 (s, +), 112.0 (s, +). ^{19}F NMR (377 MHz, acetone- d_6): $\delta = -126.38$ (ddd, $J = 11.2, 7.8, 5.1$ Hz). IR (neat) (cm^{-1}): $\tilde{\nu}$ 3381 (w), 3214 (w), 2963 (w), 2922 (w), 1521 (m), 1484 (m), 1387 (m), 1260 (w), 1092 (s), 1014 (s), 742 (s). HR-MS (ESI^+) m/z : $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{14}\text{H}_{11}\text{FN}_3^+$ 240.0932, found 240.0938. R_f : 0.7 (20% EA in petroleum ether). The structure was confirmed through X-ray analysis.

(E)-4-((1H-Indol-3-yl)diazenyl)phenylmorpholine (5a). Compound **4a** (104 mg, 0.43 mmol) and morpholine (1515 mg, 1.5 mL, 17.40 mmol) were dissolved in DMSO (3 mL). K_2CO_3 (60 mg, 0.43 mmol) was added. The suspension was stirred at ambient temperature for 72 h. The reaction process was followed by TLC, and the reaction mixture was poured onto water (30 mL) after no further conversion was observed. The aqueous phase was extracted with EtOAc (3×30 mL), and the combined organic phases were dried over Na_2SO_4 . The volatiles was removed in vacuo. The compound was directly purified via preparative HPLC.

Compound **5a** was obtained as a yellow-brown viscous oil (112 mg, 0.37 mmol, 84%). ^1H NMR (400 MHz, acetone- d_6): $\delta = 8.63\text{--}8.47$ (m, 1H), 8.29 (s, 1H), 7.70 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.37 (ddd, $J = 8.6, 7.1, 1.6$ Hz, 1H), 7.30 (ddd, $J = 6.9, 3.9, 2.3$ Hz, 3H), 7.15 (ddd, $J = 8.3, 7.1, 1.4$ Hz, 1H), 3.99–3.91 (m, 5H), 3.47–3.32 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, acetone- d_6): $\delta = 147.1$ (s, q), 145.9 (s, q), 137.1 (s, q), 136.9 (s, q), 133.1 (s, +), 129.7 (s, +), 124.1 (s, +), 123.5 (s, +), 122.6 (s, +), 122.5 (s, +), 118.9 (s, +), 118.4 (s, q), 116.8 (s, +), 112.1 (s, +), 66.6 (s, –), 53.2 (s, –). IR (neat) (cm^{-1}): $\tilde{\nu}$ 3191 (w), 2960 (w), 2851 (w), 1730 (m), 1614 (m), 1461 (m), 1331 (w), 1200 (m), 1115 (s), 932 (m), 749 (s). HR-MS (ESI^+) m/z : $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{18}\text{H}_{19}\text{N}_4\text{O}^+$ 307.1553, found 307.1554. R_f : 0.1 (DCM).

(E)-4-((1H-Indol-3-yl)diazenyl)phenol (6a). The compound was prepared following the general procedure II for the synthesis of diazonium salts (using 2.00 mmol of indole) and the general procedure for azo-coupling.

Compound **6a** was obtained as brown solid (4 mg, 0.017 mmol, 1%). ^1H NMR (300 MHz, methanol- d_4): $\delta = 8.48\text{--}8.34$ (m, 1H), 7.99 (s, 1H), 7.72 (d, $J = 8.9$ Hz, 1H), 7.48–7.39 (m, 1H), 7.29–7.13 (m, 2H), 6.93–6.81 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, methanol- d_4): $\delta = 159.9$ (s, q), 158.2 (s, q), 148.4 (s, q), 143.7 (s, q), 138.2 (s, q), 137.1 (s, q), 131.5 (s, +), 124.7 (s, +), 124.2 (s, +), 123.6 (s, +), 123.0 (s, +), 120.2 (s, q), 116.5 (s, +), 112.6 (s, +). HR-MS (ESI^+) m/z : $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{14}\text{H}_{12}\text{N}_3\text{O}^+$ 238.0975, found 238.0977. R_f : 0.50 (10% MeOH in DCM). Further analytical data could not be obtained due to limited material.

(E)-3-((4-Nitrophenyl)diazenyl)-1H-indole (7a). The compound was prepared following the general procedure II for the synthesis of diazonium salts (7.24 mmol of indole) and the general procedure for azo-coupling.

Compound **7a** was obtained as a dark red highly viscous oil (327 mg, 1.23 mmol, 17%). ^1H NMR (600 MHz, acetone- d_6): $\delta = 8.55\text{--}8.48$ (m, 1H), 8.42 (s, 1H), 8.41–8.35 (m, 2H), 8.09–7.95 (m, 2H), 7.61–7.49 (m, 1H), 7.37–7.19 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, acetone- d_6): $\delta = 158.6$ (s, q), 148.2 (+, only visible in HMBC), 138.1 (s, q), 138.0 (s, q), 136.6 (s, +), 125.6 (s, q), 125.4 (s, +), 124.2 (s, +), 123.7 (s, +), 122.9 (s, +), 119.2 (s, q), 113.1 (s, +). IR (neat) (cm^{-1}): $\tilde{\nu}$ 3690 (w), 2960 (m), 2922 (m), 2855 (m), 1446 (m) 1375

(m), 1092 (s), 1033 (s), 682 (s). HR-MS (ESI⁺) *m/z*: [M + H]⁺ calcd for C₁₄H₁₁N₄O₂⁺ 267.0877, found 267.0881. *R*_f: 0.3 (DCM).

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02973.

Detailed information regarding NMR spectra, UV–vis spectra, Lifetime experiments, X-ray data, computational analysis, simulated UV–vis spectra and, computational PSS analysis (PDF)

X-ray data for compound 2a (CIF)

X-ray data for compound 1b (CIF)

X-ray data for compound 3a (CIF)

X-ray data for compound 4a (CIF)

X-ray data for compound 10a' (CIF)

X-ray data for compound 10a'' (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: stefano.crespi@ur.de.

*E-mail: burkhard.koenig@ur.de.

ORCID

Stefano Crespi: 0000-0002-0279-4903

Burkhard König: 0000-0002-6131-4850

Notes

The authors declare no competing financial interest.

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