Fourfold Double-Bond Substituted Hemiindigo: Highly Functionalized Red-Light Responsive Photoswitches

Maximilian Sacherer[†], *Frank Hampel*[†], *Henry Dube*[†]*

[†] Friedrich-Alexander Universität Erlangen-Nürnberg, Department of Chemistry and Pharmacy, Nikolaus-Fiebiger-Str. 10, 91058 Erlangen, Germany

* E-mail: henry.dube@fau.de

Abstract

Molecular photoswitches are indispensable tools for responsive chemical nanosystems and are nowadays used in virtually all branches of the natural sciences. Hemiindigo (HI) derivatives were recently introduced as potent photoswitches but full applicability was hampered by the limited possibilities for their functionalization and structural alteration. Here we report on a short and easy to diversify synthesis yielding fourfold double-bond substituted HIs. The resulting chromophores are shown to offer an advantageous property profile combining red-light responsiveness, high thermal bistability, strong isomer accumulations in both switching directions, and strong photochromism. With this progress a new structural realm has been opened up for HI photoswitches, that can now be synthetically tailored to highly advanced applications in e.g. molecular machines and multi-switching research, photoisomerization mechanism studies, or smart and addressable materials generation.

Introduction

Molecular photoswitches have occupied a prominent place in all chemistry-related fields as they allow facile introduction of responsiveness at the nanoscale.[1, 2] The field of photoswitch research has developed rapidly especially over the past decade. In its wake the utility of photoswitches has expanded to vastly different areas of applications bringing increasingly complex phenomena under the control of light-signaling in a truly bottom-up fashion. With the aid of photoswitches it has become possible to remote-control bioactivity of drug-like molecules,[3-6] change properties of materials,[7-11] steer catalytic selectivity,[12, 13] influence supramolecular assemblies,[14-16] or move molecular machines.[17-20] The impressive progress showcases the tremendous potential of this diverse class of molecular enablers. Progress like this is inevitably tied to advances at the fundamental level and consequentially new molecular photoswitch classes,[21] new modes of geometry changes, new modes of electronic alterations, and new types of photoreactions have been discovered. Recent examples are modified azobenzene,[22-29] hydrazone-,[30] Stenhouse dye-, imidazolyl-radical-,[31] or indigoid photoswitches,[32-37] each of which offering unique advantages. Our group has investigated indigoid chromophores intensively and transformed many of long known dyes in this class into capable photoswitching motives. A distinct advantage is the responsiveness of indigoid core-chromophores to visible light, so that no damaging UV-irradiation is needed for their operation. Additionally, geometries are typically rigid with only limited degrees of freedom facilitating precise control over shapes and spatial relations of functional groups upon switching. Hemithioindigo (HTI) is a prominent representative,[38] consisting of a thioindigo fragment and a stilbene fragment fused together via a photoisomerizable double bond (Figure 1a). Distinct advances in applicability and photoswitching performance of HTI were made when facile synthetic access of fourfold-double bond substitution was achieved.[39, 40] With this particular substitution pattern it became possible to directly evidence a long proposed basic photoreaction, the hula twist,[41] discover a hitherto unknown photoreaction, the dual single bond rotation (DSBR),[42] devise fundamentally new types of molecular motors with unique modes of motion and working mechanisms,[43, 44] build highly advanced multi-state photoswitches,[34, 42] or establish the first energy-powered molecular gearing system.[45]

The related HI structure features an indigo-fragment instead of the thioindigo fragment (Figure 1b) and shows similar high potential. Threefould double bond substituted HIs bearing strong electron donors at the stilbene fragment represent nearly perfect photoswitches delivering almost quantitative isomer conversions in both switching directions, red-light responsiveness, high extinction, strong photochromism, sizable quantum yields, and solvent independent high thermal bistability.[36] Nitrogen substitution at the indoxyl fragment allows for facile functionalization resulting in unique applications e.g. as chiroptical switches with unusual electronic circular dichroism (ECD) responses[37] or ionic chromophores for gas phase photoswitching.[46] Likewise, HI applications in biological context to photomodulate HIV-1 RNA binding[47] or photoswitching in the presence of bovine serum albumin[48] have been demonstrated already. For these reasons it can be stated that HI structures are highly promising yet underexplored as molecular photoswitches. In light of the advances made with HTI, fourfold-double bond substitution would be a fundamentally important next step to significantly elevate the capacity of HI photoswitches. The resulting structures would harbor three (or even four if the indoxyl benzene ring is also functionalized) different substitution sites, the spatial relations of which will be fully controllable during switching.

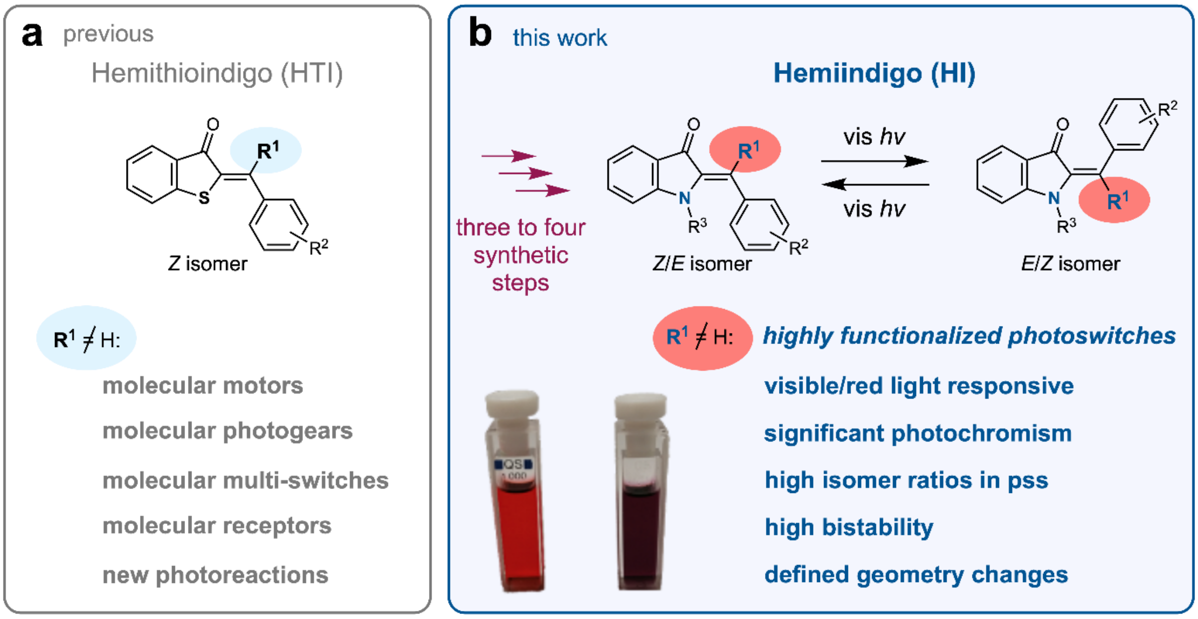
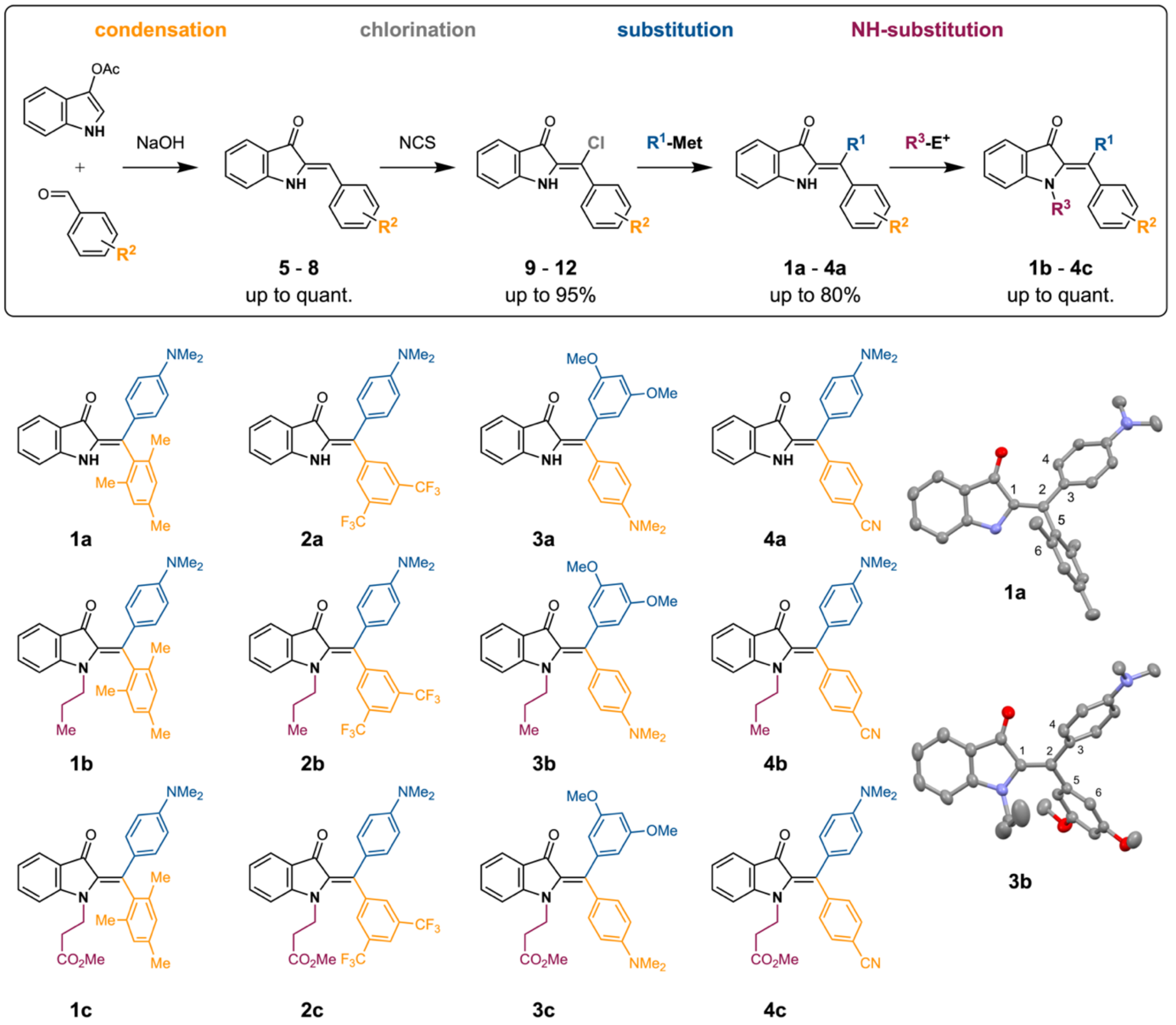


Figure 1 Fourfold double bond substituted indigoid photoswitches. a) Synthetic access to fourfold double bond substitution in HTI allows for a plethora of unique and advanced applications. b) A short and high yielding synthetic access to fourfold double bond substituted HI chromophores delivers highly functionalized and capable photoswitches with distinct and advantageous properties.

In this work we disseminate the synthetic methodology for generating fourfold double-bond substituted HI chromophores (**1a**-**4c**) together with a comprehensive photophysical and photochemical analysis of their photoswitching properties. We demonstrate how these structures can be generated in a straight forward, easy to diversify, low-step count, and versatile synthesis and also evidence them as highly capable photoswitches with a large number of advantageous properties.

Results and Discussion

To develop a synthesis for fourfold double bond substituted HIs, important prerequisites need to be taken into consideration, as the synthesis of fourfold double bond substituted HTIs could not be adapted to access fourfold double bond substituted HIs (*Dieckmann*-type condensations of different anthranilic acids/acid chlorids/esters followed by chlorination with oxalylchloride were not successful and also condensations of indoxyl derivatives with ketones did not deliver the desired products). First, the parent HIs with one residual H-atom at the central photoisomerizable double bond are easily accessible in high yields by condensation of commercially available aldehydes (introducing R^2) and indoxyl acetate (Scheme 1). Therefore, the parent HIs would be ideal starting materials for introducing a fourth substituent at the double bond (R^1) as well as nitrogen substituents replacing the NH proton (R^3) later on. Second, introduction of a fourth substituent should be versatile and thus a common precursor allowing easy diversification by well-established broad-scope methodology was deemed preferable. Third, facile alkylation at the indoxyl nitrogen would allow to introduce functionalities for late-stage covalent connection of the HI photoswitches. For these reasons, chlorination of the double bond was chosen to enable subsequent chlorine-substitution reactions with a nucleophile (attempts for Heck reactions were equally unsuccessful as attempts of directly generating metal organic species by C-H activation at position R^1). The envisioned chlorination was inspired by the described substitution at the Michael system double bond (R^1) with a nucleophilic reactant such as KCN and subsequent oxidation[49] (note: attempts at subsequent cross coupling reactions of HIs with nitriles at position R^1 were not successful). However, employing related reactants such as KCl or KBr instead of KCN did not lead to halogenated product formation. Changing the electronic character of the reactant from a nucleophilic halide to an electrophilic halonium ion was then attempted for substituting at the desired position R^1. However, this electrophilic reaction faces selectivity problems as either the *para* or *ortho* position to the nitrogen at the indoxyl benzene are nucleophilic. It was thus found not surprisingly that halogenation with *N*-bromosuccinimide leads to dominant substitution of the electrophilic *para* position at the indoxyl benzene ring, similar to the literature known bromination of isatin.[50] Attempts at chemoselective bromination reactions at the β-position of the *Michael* system,[51] as well as bromination with elemental bromine also did not lead to successful functionalization at position R^1. With *N*-chlorosuccinimide the R^1 position was, to the best of our knowledge for the very first time, chemoselectively accessible without side reactions at the indoxyl benzene. Because of the inherent *Michael* system within the HI structure, exchange of the chloride could then be accomplished by a direct nucleophilic substitution, using cross coupling chemistry, or even radical chemistry if needed. A final introduction of an ester function at the indoxyl nitrogen atom (R^3) was deemed suitable as a versatile handle for facile implementation of HI photoswitches in e.g. peptides, natural products, or polymers. These considerations led to the synthesis shown in Scheme 1.



Scheme 1 Three to four step synthesis of highly functionalized and fourfold double bond substituted HI photoswitches **1a-4c**. Structure of *Z*-**1a** in the crystalline state with a torsion angle of –31.58° between atoms 1,2,3, and 4 and -71.36° between atoms 1,2,5, and 6. Structure of *Z*-**3b** in the crystalline state with a torsion angle of +38.00° between atoms 1,2,3, and 4 and +54.04° between atoms 1,2,5, and 6.

As described previously the condensation reaction between indoxyl acetate and different aldehydes leads to very high yields of the resulting threefold double bond substituted parent HIs **5** to **8**. Chlorination of parent HIs also proceeded in good to very good yields when using NCS typically at 22 °C in THF, with the notable exception of the electron rich HI **7** (R^2 = *p*-N(Me)$_2$). In this case substantial chlorination of the aniline is observed as side reaction. In general, aprotic solvents reduce side reactions at the indoxyl benzene, and high concentrations of the HI further improves the yield. The subsequent *Suzuki* cross coupling reactions with aromatic boronic acids delivered the corresponding fourfold double bond substituted HIs in moderate to high yields. A final *N*-alkylation of the indoxyl nitrogen (R^3) using either 1-

iodopropane or methyl acrylate delivered the highly functionalized HI photoswitches **1b-4c**. Crystals suitable for X-ray analysis were obtained for HIs **1a** and **3b** evidencing the twisted nature of the two aryl moieties as well as the constitution of the photoswitches (Scheme 1, right).

To establish the switching properties of fourfold double bond substituted HIs **1a-4c**, their thermal behavior in the dark was scrutinized first. In most cases slow isomerization takes place at elevated temperatures to establish an equilibrium with both *Z* and *E* isomers being present in significant amounts. This behavior also allows to directly measure the relative free enthalpy differences Δ*G* between isomers as summarized in Table 1. When analyzing the kinetics of thermal *E*/*Z* or *Z*/*E* isomerizations in the dark, the corresponding *Gibbs* free energies of activation $\Delta G^{\ddagger}$ could be obtained. All HIs exhibit high thermal bistability as manifested in sizable $\Delta G^{\ddagger}$ values, which are >25 kcal/mol giving rise to corresponding half-lives of isomers ranging from hours to >100 years at 25 °C (linearly extrapolated from elevated temperature measurements). The only exceptions are HIs **2b** and **3c**, which are thermally more labile with corresponding half-lives in the minute to hour range, respectively.

Table 1: Quantitative comparison of the physical and photophysical properties of HIs 1-4

HI	$\Delta G^{\ddagger}_{E\rightarrow Z}$/ $\Delta G^{\ddagger}_{Z\rightarrow E}$ [kcal · mol^{-1}]	ΔG [kcal · mol^{-1}]	$t_{1/2}^{eq\ 25\ ^{\circ}C}$[d]	isomer % in pss (at LED nm)	λ_{max} [nm] and ε_{max} [L · mol^{-1} · cm^{-1}] of *E*/*Z* isomers lowest energy absorption band	$\Delta\lambda_{max}$ [nm] and $\Delta\varepsilon_{max}$ [L · mol^{-1} · cm^{-1}] of *E* and *Z* isomers
1a	25.0[a]/25.3[a]	0.3[a]	1.5 d[a]	47% *E* (590 nm)[a] 94% *Z* (450 nm)[a]	477; 15300[c] / 518; 12200[c]	41; 3100[c]
1b	31.2[b]/31.4[b]	0.3[b]	118 a[b]	62% *E* (625 nm)[a] 100% *Z* (470 nm)[a]	499; 7700[c] / 539; 7700[c]	40; 0[c]
1c	31.4[b]/31.9[b]	0.5[b]	199 a[b]	63% *E* (625 nm)[a] 100% *Z* (470 nm)[a]	493; 9600[c] / 534; 7600[c]	41; 2000[c]
2a[e]	-	-	-	-	-	-
2b	22.9[a]/22.5[a]	0.4[a]	36 min[a]	79% *E* (625 nm)[a] 92% *Z* (490 nm)[a]	518; 9600[c] / 563; 8300[c]	45; 1300[c]
2c	29.2[a] /27.9[a]	1.3[a]	291 d[a]	85% *E* (625 nm)[a] 92% *Z* (470 nm)[a]	507; 6000[c] / 562; 5100[c]	55; 900[c]

3a	-^{b,f}	0.1^{b,f}	-^{b,f}	50% *E* (530 nm)^{a} 53% *Z* (450 nm)^{a}	477; 5900^{c} / 523; 4700^{c}	46; 1200^{c}
3b	27.4^{a}/27.5^{a}	0.1^{a}	74 d^{a}	62% *E* (590 nm)^{a} 92% *Z* (470 nm)^{a}	512; 9700^{c} / 542; 9000^{c}	30; 700^{c}
3c	24.5^{a}/24.6^{a}	0.1^{a}	14 h^{a}	46% *E* (550 nm)^{a} 72% *Z* (470 nm)^{a}	503; 8800^{c} / 541;7300^{c}	38; 1500^{c}
4a	-^{a,e}	-^{a,e}	-^{a,e}	-^{a,e}	-^{a,e}	-^{c,e}
4b	26.5^{a}/27.4^{a}	0.8^{a}	27 d^{a}	89% *E* (505 nm)^{a} 81% *Z* (625 nm)^{a}	561; 6500^{c} / 517; 7100^{c}	44; 600^{c}
4c	26.8^{a}/27.5^{a}	0.7^{a}	40 d^{a}	90% *E* (490 nm)^{a} 88% *Z* (625 nm)^{a}	560; 3600^{c} / 507; 4100^{c}	53; 500^{c}

^{a}in toluene-d_8. ^{b}in *o*-xylene-d_{10}. ^{c}in toluene/toluene-d_8. ^{d}linearly extrapolated to 25 °C. ^{e}values not determined due to photodegradation. ^{f}no change during heating. min = minute, d = day, h = hour, a = year.

With high bistability being established the photophysical and photochromic properties of HIs **1**-**4** were scrutinized next. All compounds show well separated UV/Vis absorption spectra for their *E* and *Z* isomers. In general, isomers in which the carbonyl group of the indoxyl fragment and the dimethylaniline substituent residing at the same side of the double bond possess bathochromically shifted absorption. They are referred to as bathochromic species in the following, and the corresponding other isomer as hypsochromic species. This behavior gives rise to pronounced photochromism with maxima differences reaching 40 nm. Associated with this good absorption separation is a significant color contrast between the two isomers in solution as shown in Figure 2 (see the Supporting Information for the corresponding photographs of all derivatives). Compared to structurally related threefold substituted HIs[36] or fourfold substituted HTIs,[40] the here presented fourfold substituted HIs show around 40 nm more redshifted UV-Vis absorption bands. Also in comparison to electron rich pyrrole heterocycles fused to HTIs,[52] the here presented systems exhibit more redshifted UV-Vis absorption bands and similar band separation of the corresponding isomers, although measured in less polar solvents. The molar extinction coefficients are in the range of 4,000 to 15,300 L · mol^{-1} · cm^{-1} and thus are perfectly suited for photoswitch applications. The noticeable decrease in molar extinction in comparison to threefold double bond substituted HIs[36] is owed to significantly twisted aromatic substituents as a result of their mutual steric hindrance (see also for the corresponding crystal structures the Supporting Information). A similar influence of molecular twisting on the molar extinction coefficients has been described i.a. for HTI photoswitches before.[53, 54] Photoisomerization reactions of the highly substituted HIs were quantified by UV/Vis and ^{1}H NMR spectroscopy to cover a range of concentrations and test the robustness of photoswitching. Photoisomerization reactions that led to enrichment of the bathochromic species resulted in nearly quantitative isomer enrichment in all cases except for HIs **3a** and **3c** for which 53% and 72% of the bathochromic species are obtained, respectively. Irradiation with light of longer wavelengths resulted in enrichment of the hypsochromic species with more variation in individual isomer yields (46% - 88%) in this case. Quantum yields were found to be below 1% for photoisomerization of bathochromic species to hypsochromic species of fourfold double bond substituted HIs. The quantum yields for photoisomerization of hypsochromic species to bathochromic species were determined to be between 4% to 6% (**2b**, **2c**, **4b**, and **4c**).

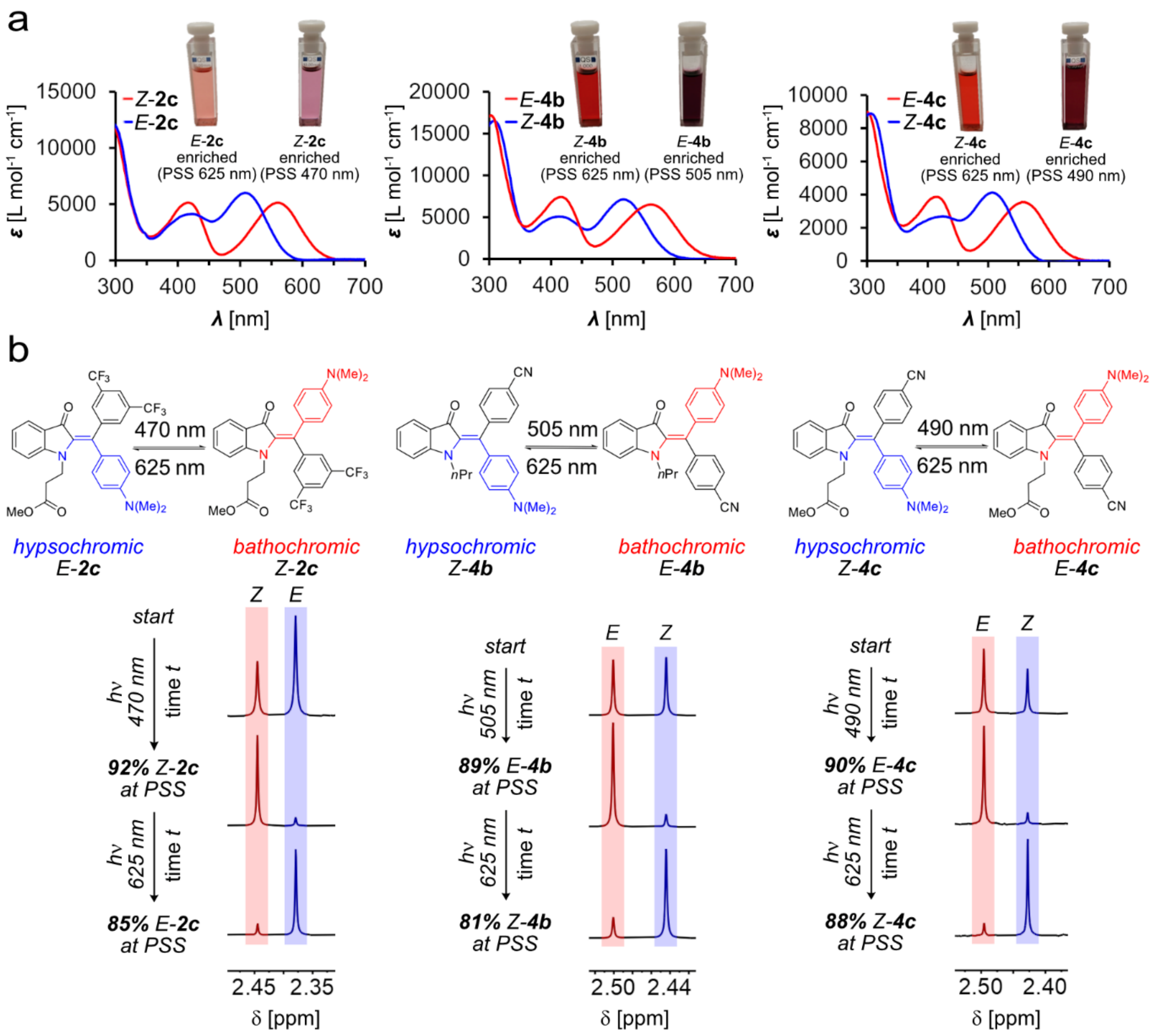


Figure 2 Switching properties of fourfold double bond substituted HIs. a) Molar extinctions of **2c**, **4b**, and **4c** in toluene and corresponding photographs of solutions after irradiation

to the respective pss. b) Indicative sections of ^{1}H NMR spectra (400 MHz, 23 °C, toluene-d_8) of **2c**, **4b**, and **4c** recorded after irradiation to the respective pss.

Taken together derivatives **2c**, **4b**, and **4c** possess the ideal combination of high thermal bistability, red-shifted absorptions, strong photochromism, strong enrichment of each isomer in the respective pss, red and blue light responsiveness, highest quantum yields in the series, and high level of functionalization. However, also derivatives **1b**, **1c**, and **3b** deliver quantitative isomer conversion at blue light irradiation and beyond 60% conversion with yellow and red light irradiation. Derivatives **1b** and **1c** are particularly interesting as they are extremely bistable with half-lives in the dark beyond 100 years at 25 °C (linearly extrapolated from high temperature measurements). Looking at the photophysical and photochemical properties of HI **1**-**4**, the following tendencies can be observed. The stronger the donor/acceptor system at the stilbene moiety, the more redshifted the UV/Vis absorption bands, the better the photochromism and the better the isomer enrichment in both switching directions. The substitution of the proton at position R^3 improves the photochemical behavior in terms of isomer content in both switching directions at pss and photochemical stability during irradiation. There is also a tendency, that thermal bistability increases if position R^3 is functionalized with alkyl substituents. Substituents at position R^3 comprising a stronger $-I$ effect exhibit slightly better thermal bistabilities than those comprising mostly a $+I$ effect. This is interesting as the thermal bistability $\Delta G^{\ddagger}_{Z \rightarrow E}$ of HI **1** can be improved from 25.3 kcal/mol (R^3 = H) to 31.9 kcal/mol ($R^3 = (CH_2)_2C(O)OCH_3$) by making use of inductive effects. Substitution of the indoxyl nitrogen proton to an alkyl group also improves the energy difference ΔG between the *E* and *Z* isomers of the photoswitches. Taken the results together, it is evident that a push-pull system cross-conjugated at the central double bond in combination with the substitution of the proton at the indoxyl nitrogen are most effective for high isomer enrichment in both photoswitching directions. However, also a combination of strong and weak electron donated aromatic substituents results in proper photoswitching behavior.

In summary, we report a new class of HI chromophores, which are fourfold substituted at the central double bond. Synthetic access to these compounds is straight forward and modular, such that a large variety of substitution pattern can be introduced not least for late-stage functionalization and covalent attachment of the photoswitches. The switching properties were quantified evidencing a suite of advantageous properties such as visible light responsiveness in both switching directions, significant photochromism, high thermal bistability, strong enrichment of each isomer in the pss, and large yet defined geometry changes upon switching. Building on the results of this study it will now be possible to investigate a large and unexplored structural space for this potent class of photoswitches. We are certain that numerous advanced applications of HI will result from the progress reported here.

Associated Content

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx

> Details of synthesis, photochemical, photophysical and thermal behavior, and crystal structural data.

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