Communication

Isomer-Specific Hydrogen Bonding as a Design Principle for Bidirectionally Quantitative and Redshifted Hemithioindigo Photoswitches

Joshua E. Zweig, and Timothy R. Newhouse

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 27 Jul 2017

Isomer-Specific Hydrogen Bonding as a Design Principle for Bidirectionally Quantitative and Redshifted Hemithioindigo Photoswitches

Joshua E. Zweig and Timothy R. Newhouse*

Department of Chemistry, Yale University, 275 Prospect Street, New Haven, Connecticut 06520-8107, United States

Supporting Information Placeholder

ABSTRACT: A new class of bidirectionally quantitative photoswitches based on the hemithioindigo scaffold is reported. Incorporation of a pyrrole hydrogen-bond donor leads to a bathochromic shift allowing for quantitative bidirectional isomerization. Additionally, extending conjugation from the electron-rich pyrrole results in quantitative visible-light photoswitches, as well as photoswitches that isomerize with red and NIR light. The presence of the hydrogen bond leading to the observed redshift is supported by both computational and spectroscopic evidence.

Small molecule photoswitches have recently seen a surge of interest as a means for controlling biological systems at the molecular level. These compounds, which undergo geometric changes upon irradiation with light, have been used in the study of photopharmacology, peptide tertiary structure and function, and other macromolecular applications.[1] In order to optimally apply this technology to therapeutic development, a photoswitch should display quantitative photoconversion between its isomers using near-infrared light (650 – 900 nm) to allow for maximum tissue penetration.[2] Additionally, photoswitches that operate via double bond isomerization are needed for many biological applications in which large end-to-end distance changes are required to sufficiently modulate protein binding or other biochemical interactions.[1,3]

However, obtaining quantitative photoisomerization remains a challenge across many classes of *E/Z* photoswitches **(1-3)**.[4] As double bond isomerization does not intrinsically change the extent of π-conjugation, significant overlap in the absorption spectra of the two isomers often renders selective irradiation of either one unattainable. While their end-to-end distance changes and photostability make hemithioindigos (**3**) an attractive class of *E/Z* photoswitches for use in biological systems,[5] application has been limited in part as a result of the drawback of incomplete photoisomerization, generally 80-90%.[6] Derivatization of hemithioindigos has not overcome this limitation or led to therapeutically applicable near-infrared photoswitches. Herein, structural modifications to the hemithioindigo scaffold that enable selective bidirectional photoisomerization using red and near-infrared light are described.

It was hypothesized that the absorbance spectra of hemithioindigo isomers could be differentiated by replacement of the phenyl group of the hemithioindigo stilbene core with a hydrogen-bond donating heterocycle (Figure 1). In the *E*-isomer of such a modified hemithioindigo (*E*-**4**), the pyrrole N-H would donate an intramolecular hydrogen bond to the benzothiophenone ketone, resulting in a bathochromic shift of the *E*-isomer. With a sufficiently large bathochromic shift,

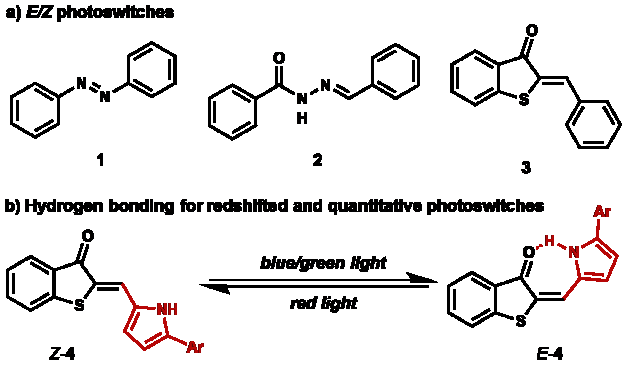


Figure 1. a) Small molecule *E/Z* photoswitches b) arylpyrrole hemithioindigo photoswitches show isomer-specific hydrogen bonding

irradiation with an appropriate wavelength of light should lead to selective and quantitative photoisomerization of either isomer. Furthermore, incorporation of an electron-rich pyrrole ring to the hemithioindigo core should lead to a redshift of both *E*- and *Z*- isomers.

Several recent examples have effectively utilized modification of photoswitch core structures to increase bathochromic shifts by perturbing the energies of the relevant molecular orbitals through electronic substituent effects or by enforcing geometric distortions.[7-11] For example, azobenzene (**1**) has been modified with *ortho*-fluoro, substituents[7c,h,j] which results in the stabilization of the non-bonding molecular orbitals of the *cis*-isomer and results in a larger bathchromic shift. Heteroazobenzenes with '*ortho*' subsitutents[8] and cyclic azobenzenes[9] have also been shown to undergo selective photoisomerizations due to their distorted geometries.

Electron-donating substituents have also been used to dramatically redshift the absorbance of azobenzenes.[7] Introduction of amino groups *para* and methoxy substituents *ortho* to the diazo functionality results in azobenzenes that can be isomerized with red light.[7a,b] Although susceptible to hydrolysis, a strong intramolecular Lewis-acid/Lewis-base interaction using a boron substituent has also been employed to redshift the absorbance of azobenzenes (up to 730 nm light).[10] On acylhydrazone scaffolds (**2**),[11] use of substituents, heterocycles, and π-extended systems was capable of producing photoswitches with absorption maxima between 400–425 nm.[11b] Peripheral substitution of the hemithioindigo core has similarly been effective:[6f,h] *Z*→*E* photoisomerization has been reported with 505 nm light (80% *E*) and *E*→*Z* isomerization with up to 625 nm (89% *Z*).

To validate our hypothesis that a heterocyclic N-H group could participate as a hydrogen bond donor, we conducted DFT studies on 2-pyrrolyl hemithioindigo **5** (Figure 2).[12] Two isomers were investigated: *E*-**5**, which could possess an intramolecular hydrogen bond, and *Z*-**5** where such an interaction is not possible. The calculated geometry of *E*-**5**, with an O···H distance of 1.75 Å and a C=O···H angle of 117°, is also characteristic of intramolecular hydrogen bonding.[13] These geometric features are in good agreement with crystal structures that have been obtained of β-(2-pyrrolo)-enones that adopt a seven-membered cyclic geometry.[14] Furthermore, NBO analyses of both **5** and **6** show an O···H Wiberg bond index of 0.08 and 0.07 respectively,[15] which indicates a hydrogen-bond strength comparable to six-membered O–H···O systems such as 1,3-dicarbonyls.[16]

In the *E*-isomer, where a hydrogen bond is geometrically feasible, a weaker C=O bond would be expected if the carbonyl serves as a hydrogen bond acceptor. Indeed, the calculated IR spectra indicate that the presence of a hydrogen bond decreases the stretching frequency by 52 cm^{-1}. This hydrogen bond is expected to stabilize the LUMO leading to a smaller HOMO-LUMO gap for the *E*-isomer, thereby increasing the bathochromic shift between *E*- and *Z*-isomers.

TD-DFT studies were then conducted to elucidate the effect of the intramolecular hydrogen bond on the absorption spectra of hemithioindigos. It was predicted that 2-pyrrolyl hemithioindigo (**5**) and 2-imidazolyl hemithioindigo (**6**) would have bathochromic shifts of 39 nm and 47 nm, respectively, surpassing a predicted shift of 29 nm for the parent carbocyclic system (**3**). Smaller bathochromic shifts were predicted for other heterocyclic hemithioindigos which lacked a hydrogen bond (**7**-**8**).

With theoretical support for the efficacy of the proposed hydrogen bond, several heterocyclic photoswitches were synthesized (see Supporting Information for details). We were pleased to discover that **5** displayed an improved bathochromic shift of 44 nm in CH_2Cl_2 solution, exceeding the 11 nm shift of parent hemithioindigo **3**. The imidazole analog, **6**, displayed a smaller bathochromic shift (35 nm) and was similarly less selective in its *E*→*Z* photoisomerization.[17] In agreement with calculations, thiophene and furan hemithioindigos **7** and **8** displayed bathochromic shifts comparable to that of the parent hemithioindigo, 19 and 15 nm, respectively. This suggests that the large bathochromic shift of **5** is not merely a general property of the electron-rich systems or a function of the sterics of introducing a five-membered heterocycle, but that the hydrogen bond is responsible for the increased bathochromic shift.

Further supporting our hypothesis, a 20 cm^{-1} reduction of the C=O stretching frequency of *E*-**5** relative to Z-**5** was observed experimentally. The proximity of the N-H and carbonyl in *E*-**5** is additionally supported by the observed properties of an *N*-methylated analog of **5**. This analog proved to be an exceptionally poor photoswitch – in fact, its *E*-isomers could not be generated in sufficient quantities to definitively ascertain its λ_{max}. Presumably, the same geometric constraints that place the heterocyclic N-H in position to hydrogen bond to the ketone result in a steric clash between the *N*-methyl group and ketone, disfavoring relaxation from the photoexcited state to the *E*-isomer.

To further redshift the absorbance of the pyrrole hemithioindigos the π-extended series **4** was synthesized (Scheme 1) by coupling the fully elaborated aldehydes **11** and benzothiophenone **13**.[6d] The arylpyrroles **10** were synthesized via a Suzuki coupling with boronic acid **9** and the corresponding aryl bromides.[18] The resultant *N*-protected biaryls were then deprotected using NaOMe before regioselective formylation under Vilsmeier-Haack conditions. Simply treating thiophenoxyacetic acid (**12**) with excess TfOH[19] provided improved yields of **15** relative to the reported $AlCl_3$-mediated procedures. As an added benefit, material prepared by the TfOH protocol was less susceptible to oxidative decomposition. Synthesis of the arylpyrrole hemithioindigos was completed by treatment of the aldehydes **11** and benzothiophenone **13** with DBU in refluxing toluene. Apart from **4i**, which was purified by silica gel chromatography, all

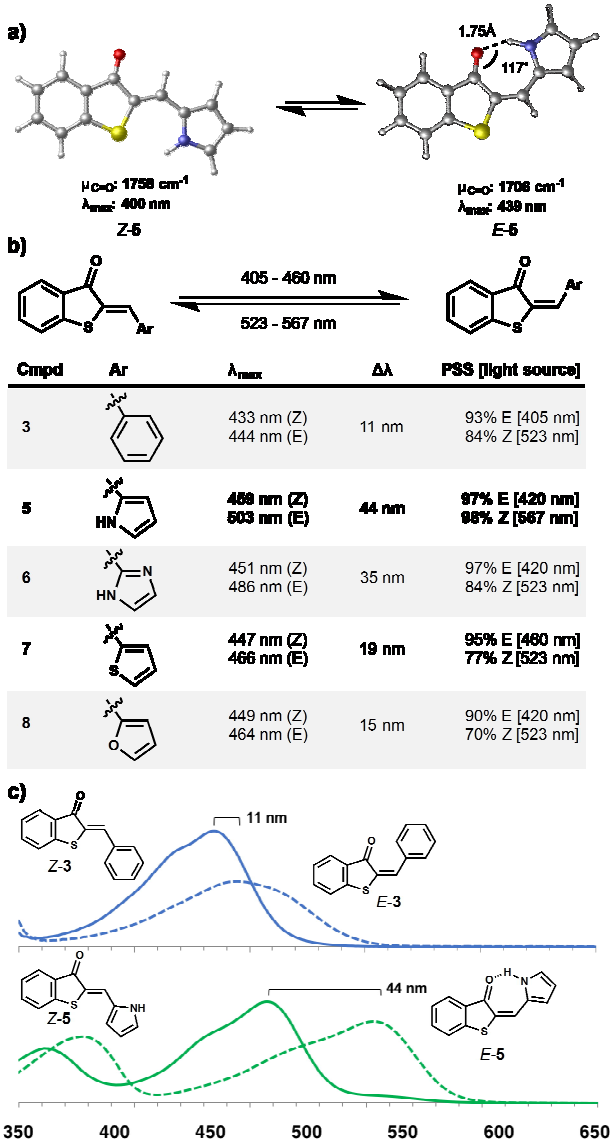
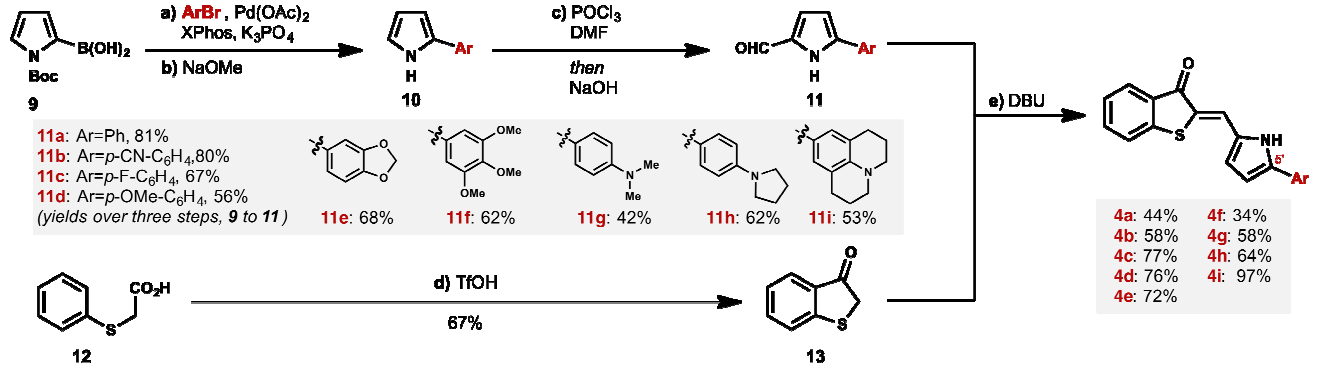


Figure 2. a) Intramolecular hydrogen bonding predicts increased bathochromic shifts. (B3LYP/6-31G*) b) Pyrrole hemithioindigo (**6**) has an increased bathochromic shift and improved photostationary state (PSS) selectivity. c) Comparison of phenyl and pyrrole photoswitches (ca. 30 μM in CH_2Cl_2). Solid lines = *Z*-isomers. Dashed lines = *E*-isomers.

the arylpyrrole hemithioindigos could be obtained as single isomers by precipitation and trituration. In its entirety, this sequence comprises five steps from commercial materials and requires one chromatographic purification for most substrates.

Arylation at the 5' position (**4a**) redshifted the peak absorbance of the *Z*-isomer from 459 nm to 491 nm. Extension the π-system also intensified the photochromicity of the photoswitches, increasing the bathochromic shift from 44 nm (**5**) to a maximum of 67 nm (**4g**) (Figure 3). This property is readily observed in the color of the photoswitch solution before and after irradiation: in CH_2Cl_2 solution, *Z*-**4g** is pink, while *E*-**4g** is violet in color. This photochromicity is partially responsible for the nearly isomerically pure photostationary states. Regardless of substitution, all of these arylpyrrole hemithioindigos can be quantitatively isomerized to their *E*- isomers, and E→Z photoisomerization proceeds with >97% conversion for most members of the library.

Scheme 1. Convergent Assembly of Arylpyrrole-Hemithioindigo Photoswitches



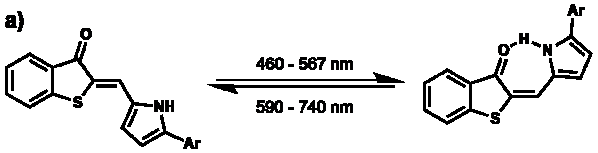
[a]Reagents and conditions: (a) ArBr (1.0 equiv), **11** (1.5 equiv), $Pd(OAc)_2$ (2 mol %), XPhos (4 mol %), K_3PO_4 (2.0 equiv), *n*-BuOH, 23 °C, 2 h; (b) NaOMe (1.1-1.5 equiv), THF, 23 °C, 30 min; (c) $POCl_3$ (1.05 equiv), DMF (1.2 equiv), then 3 M NaOH (aq.)/THF (1:1 v:v), 23 °C, 42 – 81% over three steps; (d) TfOH (5.0 equiv), CH_2Cl_2, 40 °C, 9 h, 66%; (e) DBU, PhMe, 110 °C, 2 h, 44 – 97%.

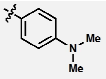
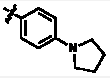
Following the same trend as carbocyclic hemithioindigos,[6,20] substituents such as –CN (**4b**) and –F (**4c**) resulted in observable (2-3 nm), but small blue shifts to the peak absorbance. The effects of electron donating substituents were much larger: *Z*-**4d** displayed a peak absorbance at 501 nm, and *E*-**4d** was sufficiently redshifted such that its *E*→*Z* isomerization could be induced with 623 nm light. Introduction of additional oxygen substituents *meta* to the pyrrole (**4e-f**) did not further redshift the absorbance of the photoswitches, but led to an increase in the selectivity of the *E*→*Z* photoisomerization. The redshifting effect was significantly larger for *N*-substituted compounds **4g-i** which displayed peak absorbance at as long as 559 nm for *Z*-**4i**. As a result, quantitative *Z*→*E* isomeration was possible with up to 567 nm light for switches **4h** and **4i**. For **4g-i**, *E*→*Z* isomerization was most effective with irradiation in the near-infrared window (660 nm). Furthermore, a photostationary state comprised of greater than 60% of *Z*-**4i** was obtained under irradiation with infrared 740 nm light. In toluene solution, the *E*-isomers of **4a-i** are more stable than their corresponding *Z*-isomers, and at 80 ˚C, compounds **4a-f** possess half-lives between 5-9 h and amino-substituted compounds **4g-i** possess half-lives between 0.3-2 h (see Table S1 in the Supporting Information for details).

Photoswitch **4d** was investigated in greater detail as a representative example. The quantum yield for the photoisomerization of *Z*-**4d** to *E*-**4d** with 405 nm light was measured to be 0.13. In 1:1 DMSO:phosphate buffer, 10 μm reduced glutathione and 5 μm TCEP, no detectable reduction of **4d** was observed over a six-hour period. This reduction pathway is a well-established obstacle for the introduction of azobenzene chromophores in certain biological applications.[7] Additionally, **4d** displayed no discernible signs of photobleaching in CH_2Cl_2 over 20 irradiation cycles using 460 nm and 590 nm light; more electron rich photoswitches such as **4g-i** displayed loss of absorbance between 1-5% per cycle. Quantitative photoisomerization of **4d** could also be observed in solvents with a wide range of dielectric constants (e.g. >97% in both directions for CCl_4 and MeCN). While switching was effective in isopropanol, photoswitching in aqueous media was less selective (see Table S2 in the Supporting Information for details).

In conclusion, the combined redshifting from an intramolecular hydrogen bond, electron-rich heterocycle, and extension of the π-system with an electron-rich arene allow for photoisomerization within the optimal window for therapeutic applications (660-740 nm). The use of isomer-selective hydrogen bonding to create large bathochromic shifts and thus quantitative isomerization may have utility in other contexts. The properties of these photoswitches: quantitative photoisomerization, red and near-infrared absorbance, and resistance to photo- and biodegradation suggest that these photoswitches may serve as tools for the construction of light-controlled systems in biological tissues, and numerous other applications.

a)



Cmpd	Ar	λmax	Δλ	PSS [light source]
4a	Ph	491 nm (Z) 550 nm (E)	59 nm	>99% E [460 nm] 97% Z [590 nm]
4b	***p*-CN-C$_6$H$_4$**	**488 nm (Z) 548 nm (E)**	**60 nm**	**98% E [460 nm] 92% Z [590 nm]**
4c	*p*-F-C$_6$H$_4$	489 nm (Z) 549 nm (E)	60 nm	99% E [460 nm] 97% Z [590 nm]
4d	***p*-OMe-C$_6$H$_4$**	**501 nm (Z) 564 nm (E)**	**63 nm**	**99% E [460 nm] 97% Z [623 nm]**
4e		495 nm (Z) 559 nm (E)	64 nm	99% E [460 nm] 99% Z [623 nm]
4f		**492 nm (Z) 555 nm (E)**	**63 nm**	**99% E [460 nm] 99% Z [623 nm]**
4g		531 nm (Z) 598 nm (E)	67 nm	>99% E [490 nm] 89% Z [660 nm]
4h		**539 nm (Z) 603 nm (E)**	**64 nm**	**>99% E [567 nm] 88% Z [680 nm]**
4i		559 nm (Z) 619 nm (E)	60 nm	>99% E [567 nm] 62% Z [740 nm]

b)

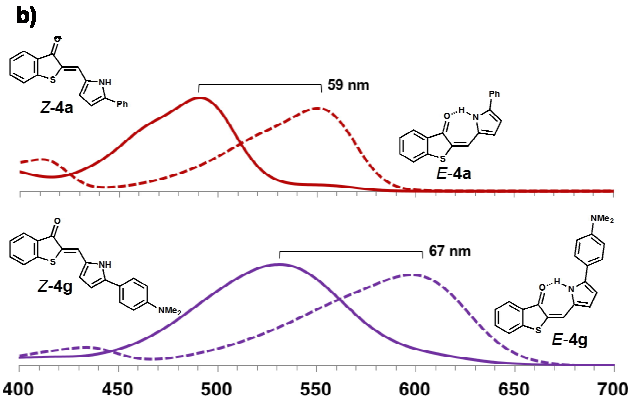


Figure 3. a) Properites of substituted arylpyrrole hemithioindigos. b) UV/Vis spectra. (ca. 30 μM in CH_2Cl_2) Solid lines = *Z*-isomers. Dashed lines = *E*-isomers.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data for all new compounds, including ^{1}H- and ^{13}C-NMR spectra, UV/Vis spectra, and details of HPLC and computational experiments. Half-lives, solvent effects, quantum yield. The Supporting Information is available free of charge on the ACS Publications website at DOI:

ORCID

Timothy R. Newhouse: 0000-0001-8741-7236

AUTHOR INFORMATION

timothy.newhouse@yale.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Yale University and the NSF (GRF to J.E.Z.) are acknowledged for financial support.

REFERENCES

(1) For recent reviews, see: (a) Fehrentz, T.; Schönberger, M.; Trauner, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 12156–12182. (b) Brieke, C.; Rohrbach, F.; Gottschalk, A.; Mayer, G.; Heckel, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8446–8476. (c) Szymański, W.; Beierle, J. M.; Kistemaker, H. A. V.; Velema, W. A.; Feringa, B. L. *Chem. Rev.* **2013**, *113*, 6114–6178. (d) Zhang, J.; Zou, Q.; Tian, H. *Adv. Mater.* **2013**, *25*, 378–399. (e) Velema, W. A.; Szymanski, W.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 2178–2191. (f) Göstl, R.; Senf, A.; Hecht, S. *Chem. Soc. Rev.* **2014**, *43*, 1982–1996. (g) Bléger, D.; Hecht, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 11338–11349. (h) Broichhagen, J.; Frank, J. A.; Trauner, D. *Acc. Chem. Res.* **2015**, *48*, 1947–1960. (i) Yu, Z.; Hecht, S. *Chem. Commun.* **2016**, *52*, 6639–6653.

(2) (a) Kalka, K.; Merk, H.; Mukhtar, H. *J. Am. Acad. Dermatol.* **2000**, *42*, 389−413. (b) Weissleder, R. *Nat. Biotechnol.* **2001**, *19*, 316–317.

(3) For applications of other photoswitches to materials and energy sciences: (a) Feringa, B. L.; Jager, W. F.; de Lange, B. *Tetrahedron* **1993**, *49*, 8267–8310. (b) Berkovic, G.; Krongauz, V.; Weiss, V. *Chem. Rev.* **2000**, *100*, 1741–1754. (c) Tian, H.; Yang, S. *Chem. Soc. Rev.* **2004**, *33*, 85–97. (d) Lukyanov, B. S.; Lukyanova, M. B. *Chem. Heterocycl. Compd.* **2005**, *41*, 281–311. (e) Klajn, R. *Chem. Soc. Rev.* **2014**, *43*, 148–184. (f) Irie, M.; Fukaminato, T.; Matsuda, K.; Kobatake, S. *Chem. Rev.* **2014**, *114*, 12174–12277.

(4) For an *E*/*Z* photoswitch review, see: García-Iriepa, C.; Marazzi, M.; Frutos, L. M.; Sampedro, D. *RSC Adv.* **2013**, *3*, 6241–6266.

(5) For applications of hemithioindigo photoswitches to biological contexts, see: (a) Seki, T.; Tamaki, T.; Yamaguchi, T.; Ichimura, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 657–663. (b) Eggers, K.; Fyles, T. M.; Montoya-Pelaez, P. J. *J. Org. Chem.* **2001**, *66*, 2966–2977. (c) Lougheed, T.; Borisenko, V.; Hennig, T.; Rück-Braun, K.; Woolley, G. A. *Org. Biomol. Chem.* **2004**, *2*, 2798–2801. (d) For a review on the use of hemithioindigos in chromopeptides, see: Kitzig, S.; Thilemann, M.; Cordes, T.; Rück-Braun, K. *ChemPhysChem* **2016**, *17*, 1252–1263.

(6) For reports on derivatization and/or measuring photostationary states of hemithioindigo photoswitches, see: (a) Friedländer, P. *Chem. Ber.* **1906**, *39*, 1060–1066. (b) Friedländer, P.; Woroshzow, N. *Justus. Liebigs Ann. Chem.* **1912**, *388*, 1-23. (c) Ichimura, K.; Seki, T. Tamaki, T.; Yamaguchi, T. *Chem. Lett.* **1990**, *19*, 1645-1646. (d) Yamaguchi T.; Seki, T.; Tamaki, T.; Ichimura, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 649-656. (e) Steinle, W.; Ruck-Braun, K. *Org. Lett.* **2003**, *5*, 141-144. (f) Maerz, B.; Wiedbrauk, S.; Oesterling, S.; Samoylova, E.; Nenov, A.; Mayer, P.; de Vivie-Riedle, R.; Zinth, W.; Dube, H. *Chem. – Eur. J.* **2014**, *20*, 13984–13992. (g) Guentner, M.; Schildhauer, M.; Thumser, S.; Mayer, P.; Stephenson, D.; Mayer, P. J.; Dube, H. *Nat. Commun.* **2015**, *6*, 8406. (h) Kink, F.; Collado, M. P.; Wiedbrauk, S.; Mayer, P.; Dube, H. *Chem. – Eur. J.* **2017**, *23*, 6237–6243. For reviews on hemithioindigos: (i) Konieczny, M. T.; Konieczny, W. *Heterocycles,* **2005**, *65*, 451–464. (j) Wiedbrauk, S.; Dube, H. *Tetrahedron Lett.* **2015**, *56*, 4266–4274.

(7) For substituted azobenzenes, see: (a) Sadovksi, O.; Beharry, A. A.; Zhang, F.; Woolley, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 1484–1486. (b) Beharry, A. A.; Sadovski, O.; Woolley, G. A. *J. Am. Chem. Soc.* **2011**, *133*, 19684–19687. (c) Bléger, D.; Schwarz, J.; Brouwer, A. M.; Hecht, S. *J. Am. Chem. Soc.* **2012**, *134*, 20597–20600. (d) Samanta, S.; Beharry, A. A.; Sadovski, O.; McCormick, T. M.; Babalhavaeji, A.; Tropepe, V.; Woolley, G. A. *J. Am. Chem. Soc.* **2013**, *135*, 9777–9784. (e) Samanta, S.; Babalhavaeji, A.; Dong, M. X.; Woolley, G. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 14127–14130. (f) Samanta, S.; McCormick, T. M.; Schmidt, S. K.; Seferos, D. S.; Woolley, G. A. *Chem. Commun.* **2013**, *49*, 10314–10316. (g) Knie, C.; Utecht, M.; Zhao, F.; Kulla, H.; Kovalenko, S.; Brouwer, A. M.; Saalfrank, P.; Hecht, S.; Bléger, D. *Chem. – Eur. J.* **2014**, *20*, 16492–16501. (h) Dong, M.; Babalhavaeji, A.; Hansen, M. J.; Kálmán, L.; Woolley, G. A. *Chem. Commun.* **2015**, *51*, 12981–12984. (i) Castellanos, S.; Goulet-Hanssens, A.; Zhao, F.; Dikhtiarenko, A.; Pustovarenko, A.; Hecht, S.; Gascon, J.; Kapteijn, F.; Bléger, D. *Chem. – Eur. J.* **2016**, *22*, 746–752. (j) Konrad, D. B.; Frank, J. A.; Trauner, D. *Chem. – Eur. J.* **2016**, *22*, 4364–4368. (k) Bandara, H. M. D.; Burdette, S. C. *Chem. Soc. Rev.* **2012**, *41*, 1809. (l) Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.* **2011**, *40*, 4422–4437.

(8) For heteroazobenzenes, see: (a) Wendler, T.; Schütt, C.; Näther, C.; Herges, R. *J. Org. Chem.* **2012**, 77, 3284−3287. (b) Weston, C. E.; Richardson, R. D.; Haycock, P. R.; White, A. J. P.; Fuchter, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 11878–11881. (c) Weston, C. E.; Richardson, R. D.; Fuchter, M. J. *Chem. Commun.* **2016**, *52*, 4521–4524. (d) Calbo, J.; Weston, C. E.; White, A. J. P.; Rzepa, H. S.; Contreras-García, J.; Fuchter, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 1261–1274. (e) Coelho, P. J.; Carvalho, L. M.; Fonseca, A. M. C.; Raposo, M. M. M. *Tetrahedron Lett.* **2006**, *47*, 3711–3714.

(9) For examples of bridged azobenzenes, see: (a) Siewertsen, R.; Neumann, H.; Buchheim-Stehn, B.; Herges, R.; Näther, C.; Renth, F.; Temps, F. *J. Am. Chem. Soc.* **2009**, *131*, 15594–15595. (b) Sell, H.; Näther, C.; Herges, R. *Beilstein J. Org. Chem.* **2013**, *9*, 1–7. (c) Hammerich, M.; Schütt, C.; Stähler, C.; Lentes, P.; Röhricht, F.; Höppner, R.; Herges, R. *J. Am. Chem. Soc.* **2016**, *138*, 13111–13114.

(10) For introduction of Lewis-acid substituents to azobenzenes, see: (a) Yang, Y.; Hughes, R. P.; Aprahamian, I. *J. Am. Chem. Soc.* **2014**, *136*, 13190–13193. (b) Qian, H.; Wang, Y.-Y.; Guo, D.-S.; Aprahamian, I. *J. Am. Chem. Soc.* **2017**, 139, 1037–1040.

(11) For acylhydrazone photoswitches, see: (a) Vantomme, G.; Hafezi, N.; Lehn, J. M. *Chem. Sci.* **2014**, *5*, 1475–1483. (b) van Dijken, D. J.; Kovaříček, P.; Ihrig, S. P.; Hecht, S. *J. Am. Chem. Soc.* **2015**, *137*, 14982–14991.

(12) For computational studies on hemithioindigos, see: (a) Bhattacharya, S.; Pradhan, T. K.; De, A.; Chaudhry, S. R.; De, A. K.; Gangluy, T. *J. Phys. Chem. A.* **2006**, *110*, 5665–5673. (b) Cordes, T.; Schadendorf, T.; Priewisch, B.; Rück-Braun, K.; Zinth, W. *J. Phys. Chem. A* **2008**, *112*, 581–588. (c) Cordes, T.; Schadendorf, T.; Rück-Braun, K.; Zinth, W. *Chem. Phys. Lett.* **2008**, *455*, 197–201. (d) Plotner, J.; Dreuw, A. *J. Phys. Chem. A* **2009**, *113*, 11882–11887. (e) Nenov, A.; Cordes, T.; Herzog, T. T.; Zinth, W.; de Vivie-Riedle, R. *J. Phys. Chem. A* **2010**, *114*, 13016–13030. (f) Wiedbrauk, S.; Maerz, B.; Samoylova, E.; Reiner, A.; Trommer, F.; Mayer, P.; Zinth, W.; Dube, H. *J. Am. Chem. Soc.* **2016**, *138*, 12219–12227.

(13) For a relevant review on hydrogen-bond interactions, see: Etter, M. C. *Acc. Chem. Res.* **2002**, *23*, 120–126.

(14) (a) Sigalov, M.; Shainyan, B.; Chipanina, N.; Oznobikhina, L.; Strashnikova, N.; Sterkhova, I. *J. Org. Chem.* **2015**, *80*, 10521–10535. (b) Sigalov, M. V.; Shainyan, B. A.; Chipanina, N.; Oznobikhina, L. P. *Eur. J. Org. Chem.* **2017**, 1353–1364.

(15) Wiberg, K. B. *Tetrahedron*, **1968**, *24*, 1083–1096.

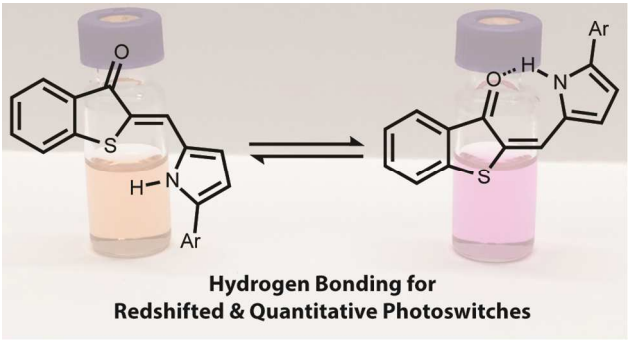
(16) For a recent review on strong intramolecular hydrogen-bonding, see: Hansen, E. H.; Larsen-Spanget, J. *Molecules* **2017**, 22, 552–555 and references therein.

(17) Del Bene, J. E.; Cohen, I. *J. Am. Chem. Soc.* **1978**, 100, 5285–5290.

(18) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, 41, 1461–1473.

(19) For examples of metal-free Friedel-Crafts acylation: Oliverio, M.; Nardi, M.; Costanzo, P.; Cariati, L.; Cravotto, G.; Giofrè, S. V.; Procopio, A. *Molecules* **2014**, 19, 5599–5610.

(20) H. Kauffmann, W. Franck, *Chem. Ber.* **1906**, *39*, 2722–2726.


O
S
H
N
Ar
O
H
N
Ar
S
Hydrogen Bonding for
Redshifted & Quantitative Photoswitches