

o-Fluoroazobenzenes as Readily Synthesized Photoswitches Offering Nearly Quantitative Two-Way Isomerization with Visible Light

David Bléger,^{*,†} Jutta Schwarz,[†] Albert M. Brouwer,^{*,‡} and Stefan Hecht^{*,†}

[†]Department of Chemistry, Humboldt-Universität zu Berlin, Brook-Taylor-Strasse 2, 12489 Berlin, Germany

[‡]Van't Hoff Institute for Molecular Sciences, University of Amsterdam, P.O. Box 94157, 1090 GD Amsterdam, The Netherlands

S Supporting Information

ABSTRACT: Azobenzene functionalized with *ortho*-fluorine atoms has a lower energy of the n-orbital of the *Z*-isomer, resulting in a separation of the *E* and *Z* isomers' n→ π^* absorption bands. Introducing *para*-substituents allows for further tuning of the absorption spectra of *o*-fluoroazobenzenes. In particular, electron-withdrawing ester groups give rise to a 50 nm separation of the n→ π^* transitions. Green and blue light can therefore be used to induce *E*→*Z* and *Z*→*E* isomerizations, respectively. The *o*-fluoroazobenzene scaffold is readily synthesized and can be inserted into larger structures via its aryl termini. These new azobenzene derivatives can be switched in both ways with high photoconversions, and their *Z*-isomers display a remarkably long thermal half-life.

Organic photochromism makes use of molecules that typically undergo pericyclic reactions or *E/Z* isomerizations of double bonds.¹ In the first case, the conjugation path in photochromes such as spiropyrans,² diarylethenes,³ or fulgides⁴ is dramatically affected, inducing marked changes in their color and frontier molecular orbitals. In the other case, molecules with the ability to photoisomerize (at least) one double bond undergo large geometrical changes that can be collected and further amplified, for example in the process of vision, resulting in mesoscopic/macroscopic phenomena.^{5,6} The simplest aromatic compounds presenting one isomerizable double bond are stilbenes and azobenzenes, the latter being readily synthesized and highly fatigue-resistant.⁷ These advantages have rendered azobenzenes one of the most attractive classes of molecular switches. For example, azo compounds have been used to modify biological systems^{8,9} such as peptides, oligonucleotides, and transmembrane proteins, allowing photocontrol over conformation, function, and even neuronal activities *in vivo*.¹⁰ In the context of materials science, azo compounds have found several applications based on their structural changes,¹¹ one of the most appealing being the direct conversion of light into mechanical energy.^{6,12,13}

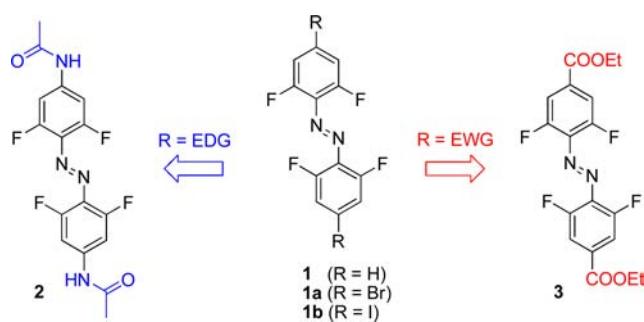
Despite the advantages mentioned above, azobenzenes generally suffer from two drawbacks that limit their practical use in biological and materials sciences. The first one is the utilization of UV light, necessary to induce the *E*→*Z* isomerization via π → π^* excitation, but potentially interfering with and destroying the surrounding environment. The second is the typically incomplete reverse *Z*→*E* photoisomerization,

induced by irradiating in the visible region where the n→ π^* bands of *E* and *Z* isomers mostly overlap, hence preventing *E*-rich photostationary states (PSSs) after back-switching. These limitations can be circumvented by modifying azobenzene such that n→ π^* bands of *E* and *Z* isomers are separated.¹⁴ If the separation is large enough, the two n→ π^* bands, and thus visible light, can be used to isomerize both isomers selectively, with high to complete *E/Z* photoconversions. Siewertsen et al. recently identified such a system, i.e., an azobenzene covalently bridged in *ortho*-positions by an ethylene linker, in which a 100 nm splitting of the n→ π^* transitions of *E* and *Z* isomers allows for switching in both directions with visible light and almost complete photoconversions (100% *E*→*Z* and 92% *Z*→*E*).¹⁵ Woolley's group recently reported another interesting azobenzene derivative,¹⁶ in which four methoxy groups introduced in the *ortho*-positions led to a 36 nm splitting of *E* and *Z* isomers' n→ π^* bands and hence enabled photo-switching in the visible range as well, although the reported photoconversions (80% *E*→*Z* and 85% *Z*→*E*) were not as high as for the cyclic azobenzene. In these two examples the substituents *ortho* to the N=N bond cause a distortion of the typically planar *E*-isomers, which inevitably affects the energy of the π and π^* molecular orbitals. This distortion is most likely the origin of the splitting of the n→ π^* bands of both isomers in the case of the covalently bridged azobenzene,¹⁵ and it even renders the *Z*-form the most stable, whereas usually the *E*-isomer is thermodynamically favored. In the case of the *ortho*-methoxy compound,¹⁶ the separation results from repulsive interactions of the azobenzene n-orbitals with the relatively high-energy lone pair orbitals of the oxygen atoms, which increase the energy level of all orbitals.

As the separation of n→ π^* bands of both isomers is key to switching performance in the visible, we envisioned controlling the n→ π^* excitation energies by influencing the energy level of the n-orbitals, without inducing a dramatic distortion of the azo compounds. Indeed, for some applications it is desirable to maintain the planarity of the photochromes, especially when an effective conjugation along the π -system is targeted, or an assembly by π , π -stacking is required. Here we describe a new class of azobenzenes (Chart 1), in which the n→ π^* bands of *E* and *Z* isomers are well separated by the introduction of fluorine atoms *ortho* to the azo moiety, allowing for selective excitation of the two isomers in the visible range of the spectrum.¹⁷ In contrast to *ortho*-methoxy groups, which destabilize the n-

Received: October 24, 2012

Published: December 13, 2012

Chart 1. Synthesized and Investigated *o*-Fluoroazobenzene Derivatives 1–3

orbital of *Z*-azobenzene by repulsive interactions between O and N lone pair electrons, *ortho*-fluorine atoms reduce the electron density in the nearby N=N bond, hence lowering the *n*-orbital energy.¹⁸ Moreover, because the fluorine atom has a relatively small radius, they barely distort the planar geometry of *E*-azobenzene. Electron-donating and -withdrawing groups (EDGs and EWGs) have additionally been incorporated in *para*-positions to tune the spectral features, i.e., maxima of absorption and separation of the *n*→ π^* bands, and to introduce functional substituents, useful to attach the photochromes to other entities. Our design strategy, guided by molecular orbital (MO) theory calculations, has led to a series of readily synthesized azobenzene building blocks, which allow for nearly quantitative photoswitching in both directions via *n*→ π^* excitation in the visible range of the spectrum, and can readily be modified to incorporate them into functional macro- and supramolecular systems.

Within the framework of MO theory, the lowest excited states of azobenzenes can be quite well described using singly excited *n*→ π^* and π → π^* configurations. Although the separation of *n* and π orbitals by symmetry holds only for the planar *E*-isomers, the relevant orbitals, i.e., π , *n*, and π^* , are easily recognized in MO calculations even for the helically shaped *Z*-isomer. In azobenzene, the *n*→ π^* excitation energies of the two isomers are similar due to coincidentally similar shifts of π^* - as well as *n*-MOs (Figure 1a). In the *Z*-isomer, the π -electron delocalization is reduced due to the large dihedral angles about the N–C single bonds. As a result, the π^* orbital level is much higher than in the planar *E*-isomer. However, the *n*-orbital energy level in the *Z*-isomer is also much higher than

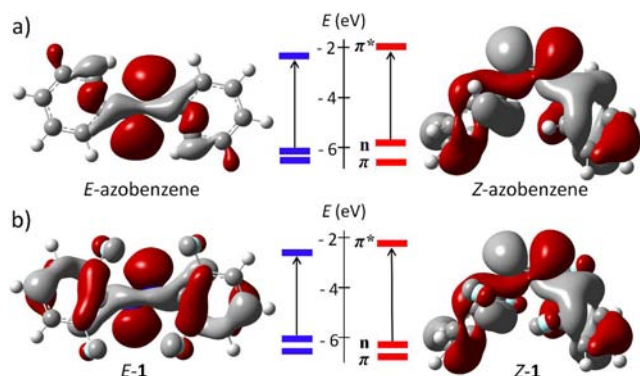


Figure 1. Energetic diagram of the π , *n*, and π^* orbitals of (a) azobenzene and (b) **1**, and representation of the *n*-orbitals (HOMOs) calculated at the B3LYP/6-31G(d) level of theory (arrows highlight *n*→ π^* transitions).

in the *E*-isomer, and the net result is that the *n*→ π^* excitation energies are very similar for both *E* and *Z* isomers.¹⁹ The *n*-orbital can be considered as a linear combination of the lone pair orbitals on the two neighboring N atoms. In the *E*-isomer, the lone pair orbitals interact through bonds, which renders the symmetric combination the highest in energy due to its mixing with the N–N σ -bond orbital.²⁰ The splitting of the bonding and antibonding combinations is large enough to place the *n*-MO (HOMO) well above the highest π -MO (HOMO-1). In the *Z*-isomer, the lone pair orbitals interact much more strongly through space, forming two combinations that resemble π and π^* MOs. The lower of these two cannot be identified in the MO calculations because it is of low energy and mixed with many other basis orbitals. The highest-energy combination is the HOMO of the molecule (Figure 1). In view of the relatively high *n*-MO levels in azobenzene caused by the repulsive interaction of the nitrogen lone pairs, we reasoned that reduction of the *n*-electron density by nearby σ -electron-withdrawing groups should lower the *n*-orbital energy. This can effectively be achieved by the introduction of fluorine substituents in the *ortho*-positions (see Figure 1b). Note that fluorine atoms have a superior inductive effect, while its mesomeric effect is rather negligible (Hammett constant $\sigma_{para} = 0.062$).²¹

o-Tetrafluoroazobenzene **1** was synthesized in one step starting from commercially available 2,6-difluoroaniline.²² The UV–vis spectrum of **1** in acetonitrile (see Figure 2) resembles that of the parent azobenzene, with a strong π → π^* absorption band at short wavelengths ($\lambda_{\pi\rightarrow\pi^*} \approx 305$ nm) and a weaker *n*→ π^* band centered around 458 nm. Recording the absorbance of **1** in different solvents resulted in essentially identical spectra; i.e., no solvatochromism was observed.²² The very slight blue shift in the π → π^* absorption when compared to the parent compound (for azobenzene $\lambda_{\pi\rightarrow\pi^*} \approx 316$ nm in acetonitrile) indicates that *E*-**1** is not significantly distorted from planarity.²³ Irradiation with UV light at 313 nm causes *E*→*Z* isomerization, resulting in the decrease of the π → π^* band typically observed in azobenzenes, producing a PSS containing 84% of the corresponding *Z*-isomer.²⁴ In the visible part of the spectrum, *E*→*Z* isomerization leads to the characteristic increase of the *n*→ π^* absorption, which—in contrast to the parent azobenzene—is accompanied by a significant blue-shift of 42 nm; i.e., the *n*→ π^* bands of the two isomers were effectively separated. Irradiation with visible light was therefore used to isomerize **1** in both directions, producing PSSs containing 91% of *Z*-**1** with green light ($\lambda > 450$ nm) and 86% of *E*-**1** with blue light (410 nm). Note that in addition to effectively inducing the *E*→*Z* isomerization, visible light produces higher *Z*/*E* ratios when compared to the π → π^* excitation by UV light (91% *Z* with green light vs 84% *Z* with UV light). Multiple *E*/*Z* isomerization cycles did not result in any noticeable degradation,²² highlighting the robustness of the *o*-tetrafluoroazobenzene scaffold. Remarkably, the *Z*-form of **1** is thermally exceptionally stable, with a half-life of ca. 700 days at 25 °C, corresponding to an activation barrier of 117 kJ/mol (i.e., 28 kcal/mol).²² To the best of our knowledge, such a high thermal stability has not been reported for an azobenzene derivative. In particular, the *Z*-form of the *o*-methoxyazobenzene derivative reported by Woolley et al. has a half-life of 14 days,¹⁶ whereas the half-life of the covalently bridged azobenzene described earlier¹⁵ is only 5 h.²⁵ The calculations predict that the σ -electron-withdrawing substitution leads to a stabilization of the *Z*-isomer. For the parent azobenzene, the energy difference

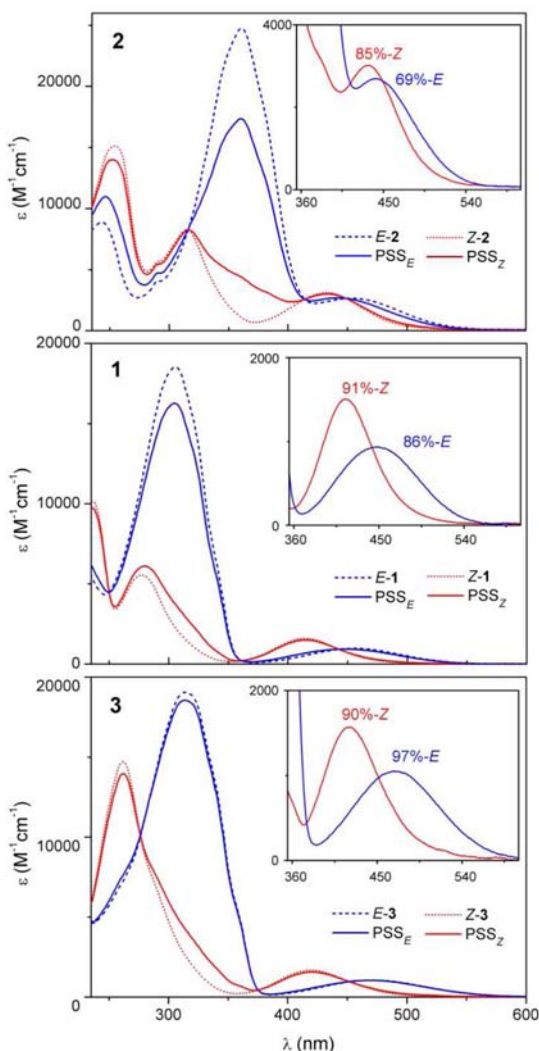


Figure 2. Absorption spectra of 1–3 as their *E* and *Z* isomers as well as their PSS mixtures in acetonitrile at 25 °C. Insets show the $n \rightarrow \pi^*$ bands and indicate the compositions (as determined by liquid chromatography) of the PSS mixtures upon irradiation with visible light ($\lambda > 450$ or 410 nm for 1, $\lambda > 500$ or 410 nm for 2, and $\lambda > 500$ or 410 nm for 3). Pure *Z*-isomer spectra were calculated from spectra of pure *E*-isomer and PSS mixtures with known PSS compositions.

between the two isomers is calculated to be 15.2 kcal/mol,²⁶ whereas for the fluorine-substituted **1** it is reduced to 8.1 kcal/mol. The reduced driving force is reflected in a higher activation barrier.

In order to prepare building blocks suitable for further chemical modification, for example by catalyzed cross-coupling reactions, halogen atoms have been attached at both ends of **1** (see **1a,b**, Chart 1). The halogenated derivatives were synthesized in two steps starting from 2,6-difluoroaniline. Building blocks **1a,b** present photochromic properties similar to those of the parent compound **1**, with a 40 nm splitting of the $n \rightarrow \pi^*$ bands and hence the possibility to photoswitch in both directions in the visible range.²²

With the intention to maximize the separation of the $n \rightarrow \pi^*$ bands, which would allow for exciting the two isomers more selectively and hence reaching higher photoconversions, we envisioned to introduce electroactive substituents *para* to the azo moiety. Calculations indicate that EDGs in *para*-positions raise the energy of the highest occupied orbitals and counteract

the effect of the σ -electron-withdrawing fluorine atoms; i.e., the $n \rightarrow \pi^*$ separation will be smaller than in the parent *ortho*-tetrafluoro compound (see Table S4). On the other hand, EDGs lower all relevant orbital energies in the order $\pi^*(E) > \pi^*(Z) > n(Z) > \pi(E) > \pi(Z) = n(E)$. The net result is a small shift to longer wavelength of the $n \rightarrow \pi^*$ absorption of the *E*-isomer relative to that of the *Z*-isomer. In combination with the fluorine effect, this should give rise to an increased splitting of the $n \rightarrow \pi^*$ bands of the *E* and *Z* isomers.

These computational predictions were verified experimentally by introducing either N-acyl (compound **2**) or ester (compound **3**) groups *para* to the azo linkage. Compound **2** was synthesized starting from **1a** via a Buchwald-type N-arylation procedure, whereas compound **3** was prepared from 2,6-difluoroaniline via a bromination/cyanation/hydrolysis/esterification sequence followed by a final oxidative coupling. As typically observed in azobenzene with EDGs in *para*-positions,⁷ the $\pi \rightarrow \pi^*$ band of *E*-**2** is significantly red-shifted relative to that of the parent compound **1**, whereas the $n \rightarrow \pi^*$ band remains essentially unaffected (see Figure 2). Excitation of the $n \rightarrow \pi^*$ transition with light of $\lambda > 500$ nm effectively induces the *E*→*Z* isomerization (85% of *Z*-**2**); however, the separation of the $n \rightarrow \pi^*$ bands of the isomers is reduced to 22 nm (compared to 42 nm in **1**). Indeed, and as anticipated on the basis of the calculations, EDGs in *para*-positions counterbalance the effects of the *ortho*-fluorine atoms by pushing electron density into the N=N bond. Eventually the two isomers cannot be selectively excited in the visible range, leading to only 69% *Z*→*E* photoconversion (when irradiated at 440 nm).

The situation is reversed in compound **3**, in which the esters (EWGs) work in concert with the *ortho*-fluorine atoms, decreasing further the repulsive interactions between the N lone pair electrons in the *Z*-isomer. Indeed, azobenzene **3** presents the best photochromic characteristics of the series, with a 50 nm separation of the $n \rightarrow \pi^*$ bands, allowing for a selective excitation of either isomer with visible light, resulting in high (90% *E*→*Z* with $\lambda > 500$ nm) to almost complete (97% *Z*→*E* at 410 nm) photoconversions. Azobenzene **3** is moreover very robust, undergoing repeated isomerization cycles without apparent photobleaching,²² and is synthesized in 8% overall yield, allowing for a rapid, large-scale preparation. This last point is of importance, since in the two previous examples, in which azobenzenes addressable with visible light are functionalized for further attachment,^{16,27} overall yields of less than 1% preclude access to multigram quantities necessary in the context of potential materials science applications.

Guided by simple MO theory considerations, we have rationally synthesized a series of *o*-tetrafluoroazobenzenes in which *E* and *Z* isomers display distinct $n \rightarrow \pi^*$ transitions. This separation allows one to selectively address both isomers in the visible region of the spectrum, causing *E*/*Z* isomerizations with nearly quantitative photoconversions. Substituents *para* to the N=N bond were introduced to further optimize the spectral properties and provide functional groups suitable for subsequent chemical modification. Importantly, all building blocks are readily synthesized starting from commercially available 2,6-difluoroaniline. Photoswitching via the $n \rightarrow \pi^*$ transitions offers new opportunities in bulk applications such as photoswitchable MOFs²⁸ and optomechanical systems,⁶ in which the very strong absorption of azobenzenes in the UV range²⁹ drastically limits the light penetration into the materials

and hence the amplitude of the photoinduced motion/actuation.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental details including synthesis, photochemistry, and computational methods. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

david.bleger@chemie.hu-berlin.de; a.m.brouwer@uva.nl; sh@chemie.hu-berlin.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous support by the German Research Foundation (DFG via SFB 658, project B8) is gratefully acknowledged. BASF AG, Bayer Industry Services, and Sasol Germany are thanked for generous donations of chemicals.

■ REFERENCES

- (1) *Photochromism: Molecules and Systems*; Dürr, H., Bouas-Laurent, H., Eds.; Elsevier: Amsterdam, 2003.
- (2) Minkin, V. I. *Chem. Rev.* **2004**, *104*, 2751.
- (3) Irie, M. *Chem. Rev.* **2000**, *100*, 1685.
- (4) Whittall, J. In *Photochromism: Molecules and Systems*; Dürr, H., Bouas-Laurent, H., Eds.; Elsevier: Amsterdam, 2003; Chapter 9, pp 467–492.
- (5) *Cis-trans Isomerization in Biochemistry*; Dugave, C., Ed.; Wiley-VCH: Weinheim, 2006.
- (6) Bléger, D.; Yu, Z. L.; Hecht, S. *Chem. Commun.* **2011**, *47*, 12260.
- (7) For a general overview on the photoisomerization of azobenzene, see: Bandara, H. M. D.; Burdette, S. C. *Chem. Soc. Rev.* **2012**, *41*, 1809.
- (8) For reviews on azobenzene photoswitches for biomolecules, see: (a) Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.* **2011**, *40*, 4422. (b) Briek, C.; Rohrbach, F.; Gottschalk, A.; Mayer, G.; Heckel, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8446.
- (9) For a review on optochemical genetics, see: Fehrentz, T.; Schönberger, M.; Trauner, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12156.
- (10) For the restoration of light sensitivity to blind retina, see: Polosukhina, A.; Litt, J.; Tochitsky, I.; Nemargut, J.; Sychev, Y.; De Kouchkovsky, I.; Huang, T.; Borges, K.; Trauner, D.; Van Gelder, R. N.; Kramer, R. H. *Neuron* **2012**, *75*, 271.
- (11) *Smart Light-Responsive Materials*; Zhao, Y., Ikeda, T., Eds.; John Wiley & Sons: Hoboken, NJ, 2009.
- (12) Finkelmann, H.; Nishikawa, E.; Pereira, G. G.; Warner, M. *Phys. Rev. Lett.* **2001**, *87*, 015501.
- (13) Hugel, T.; Holland, N. B.; Cattani, A.; Moroder, L.; Seitz, M.; Gaub, H. E. *Science* **2002**, *296*, 1103.
- (14) Wegner, H. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4787.
- (15) Siewertsen, R.; Neumann, H.; Buchheim-Stehn, B.; Herges, R.; Nather, C.; Renth, F.; Temps, F. *J. Am. Chem. Soc.* **2009**, *131*, 15594.
- (16) Beharry, A. A.; Sadowski, O.; Woolley, G. A. *J. Am. Chem. Soc.* **2011**, *133*, 19684.
- (17) Note that the spectral properties of azobenzene derivatives *ortho*-functionalized with fluorine atoms were already described, but no separation of the $n \rightarrow \pi^*$ bands was reported: (a) Ishikawa, N.; Namkung, M. J.; Fletcher, T. L. *J. Org. Chem.* **1965**, *30*, 3878. (b) Namkung, M. J.; Naimy, N. K.; Cole, C. A.; Ishikawa, N.; Fletcher, T. L. *J. Org. Chem.* **1970**, *35*, 728. (c) Tang, Q.; Gong, C. B.; Lam, M. H. W.; Fu, X. K. *Sens. Actuators B-Chem.* **2011**, *156*, 100.
- (18) See Supporting Information (p S14) for a more detailed comparison of the effects of *ortho*-fluorine atoms and *ortho*-methoxy groups on the energetic levels of azobenzene.

(19) Note that in the parent azobenzene photoswitching upon $n \rightarrow \pi^*$ excitation is possible due to the fact that the *Z*-isomer exhibits a higher molar absorption coefficient than the *E*-isomer.

(20) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1.

(21) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.

(22) See Supporting Information.

(23) The calculations indicate that the energy surface for twisting about the C=C–N=N bonds is shallow up to $\sim 30^\circ$; see Figure S7.

(24) All PSS compositions were determined by ultraperformance liquid chromatography (UPLC) analyses using integration of the UV signal at the wavelengths of the isosbestic points.

(25) Note that in the covalently bridged azobenzene the *Z* form is thermodynamically favored over the *E*-isomer as a result of the ring strain.

(26) Note that calculations performed at the G3MP2 level of theory give an energy difference between the *E* and *Z* isomers in better agreement with the experimental value of 11.4 kcal/mol previously determined: Cammenga, H. K.; Emel'yanenko, V. N.; Verevkin, S. P. *Ind. Eng. Chem. Res.* **2009**, *48*, 10120.

(27) Samanta, S.; Qin, C.; Lough, A. J.; Woolley, A.; G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6452.

(28) (a) Park, J.; Yuan, D. Q.; Pham, K. T.; Li, J. R.; Yakovenko, A.; Zhou, H. C. *J. Am. Chem. Soc.* **2012**, *134*, 99. (b) Yanai, N.; Uemura, T.; Inoue, M.; Matsuda, R.; Fukushima, T.; Tsujimoto, M.; Isoda, S.; Kitagawa, S. *J. Am. Chem. Soc.* **2012**, *134*, 4501.

(29) The molar absorption coefficient of azobenzenes **1** and **3** is $\sim 20\,000\text{ M}^{-1}\text{ cm}^{-1}$ for the $\pi \rightarrow \pi^*$ transition vs $\sim 1000\text{ M}^{-1}\text{ cm}^{-1}$ for the $n \rightarrow \pi^*$ transition.