JACS

Waste Management of Chemically Activated Switches: Using a Photoacid To Eliminate Accumulation of Side Products

Luke A. Tatum, Justin T. Foy, and Ivan Aprahamian*

Department of Chemistry, Dartmouth College, 6128 Burke Laboratory, Hanover, New Hampshire 03755, United States

S *Supporting Information*

ABSTRACT: Molecular switches and machines that are powered by acid–base reactions are susceptible to low switching cycles because of the concomitant formation of waste products during their operation. Here, we demonstrate the fast, efficient, and reversible modulation of a hydrazone switch in methanol using a visible-light activated photoacid, with no generation of side products, high conversion rates (>95%), and no loss of activity over 100 cycles. TEG functionalization of the hydrazone switch allows for the process to be carried with high conversion (>90%) in water as well.

Chemically activated molecular switches have been used over the years in various applications ranging from drug delivery to molecular actuators.[1] Such switches typically require sacrificial reagents for their function, leading to the generation of waste and side products that eventually hinder continuous operation.[2] The use of such switches in real-life applications will require addressing this waste management problem. One way of making these proton driven processes cleaner is by the use of light energy, similar to how photosynthetic systems operate in nature. For example, bacteriorhodopsin proteins utilize reversible pK_a changes that occur when retinal bound protein undergoes *trans* to *cis* photoisomerization, to initiate a transmembrane proton pump.[3] Mimicking such processes that efficiently convert light energy into chemical output using molecular switches will pave the way to chemical systems[4] that exhibit complex behavior.

Liao and co-workers recently showed[5] that the merocyanine derivative **1-MEH** (Scheme 1a) can efficiently undergo a light induced ring-closing reaction to its spiropyran form (**1-SP**),[6] with the concomitant release of a proton to the environment. Not only is this process completely reversible, the photoacid[7] also functions in water, making it an excellent candidate for the activation of molecular switches in aqueous[8] and hence biologically relevant environments. Despite the huge potential of such systems in the control of proton driven switches, there have been only very few reports of such an application. For example, Credi et al. showed,[9] as a proof-of-principle, how a photoacid can be used in the reversible assembly of a pseudorotaxane.[10] As is the case in most such systems,[10] the switching efficiency is very low because of low conversion yields (40%) and very long (7 days) equilibration times. Hence, it remains to be shown that a photoacid can indeed be used in high yielding and efficient chemically activated switching processes, not to mention ones that occur in aqueous media.

Scheme 1. (a) Photochemical Ring Closing Reaction of 1-MEH to 1-SP, which Reverts under Dark; (b) Irradiation of a Mixture of 1-MEH and Hydrazone Switch 2 or 3 Leads to an Efficient Multistep Switching Process
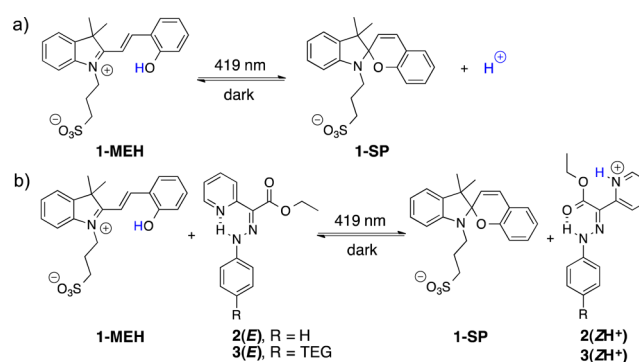
Our interest[11] in developing multistep and multicomponent switching cascades[12] led us to look into ways of addressing this waste management obstacle that has been plaguing the field for decades. Herein, we report how the coupling of the photoacid **1-MEH** with the pH-responsive hydrazone switch[13] **2** leads to a multicomponent system that can be repeatedly (100 times!) switched without waste production. We also report the synthesis of a new water-soluble hydrazone switch (**3**) and demonstrate how it too can be switched multiple times using **1-MEH** in water.

In order to study if the proton released by **1-MEH** could be used to drive the acid initiated switching process of a hydrazone switch, a 2:1 mixture[14] of **1-MEH** and **2**[15] in CD$_3$OD was studied using ^{1}H NMR spectroscopy (Figure 1). The mixture was irradiated, and a photostationary state was reached in 5 min resulting in the complete conversion of **2** to **2(ZH$^+$)** (Figure 1e). The protonation of **2** results in a significant downfield shift of the pyridine ring protons H2, H3, and H4 from $\delta = 7.40$, 7.92, and 8.09 to $\delta = 7.90$, 8.57, and 8.55 ppm, respectively.[13b] Also, the ester methylene (CH$_2$) protons of **2** shift downfield from $\delta = 4.37$ to 4.54 ppm. The absence of extraneous peaks from $\delta = 4.6$ to 4.3 ppm makes the CH$_2$ protons useful as a diagnostic tool for quantifying the hydrazone switching process. All of the hydrazone signals within the irradiated mixture align well with the spectrum of **2(ZH$^+$)** obtained by protonation with TFA (Figure S3 in the Supporting Information). The thermal ring opening of **1-SP** reverts the process back to the
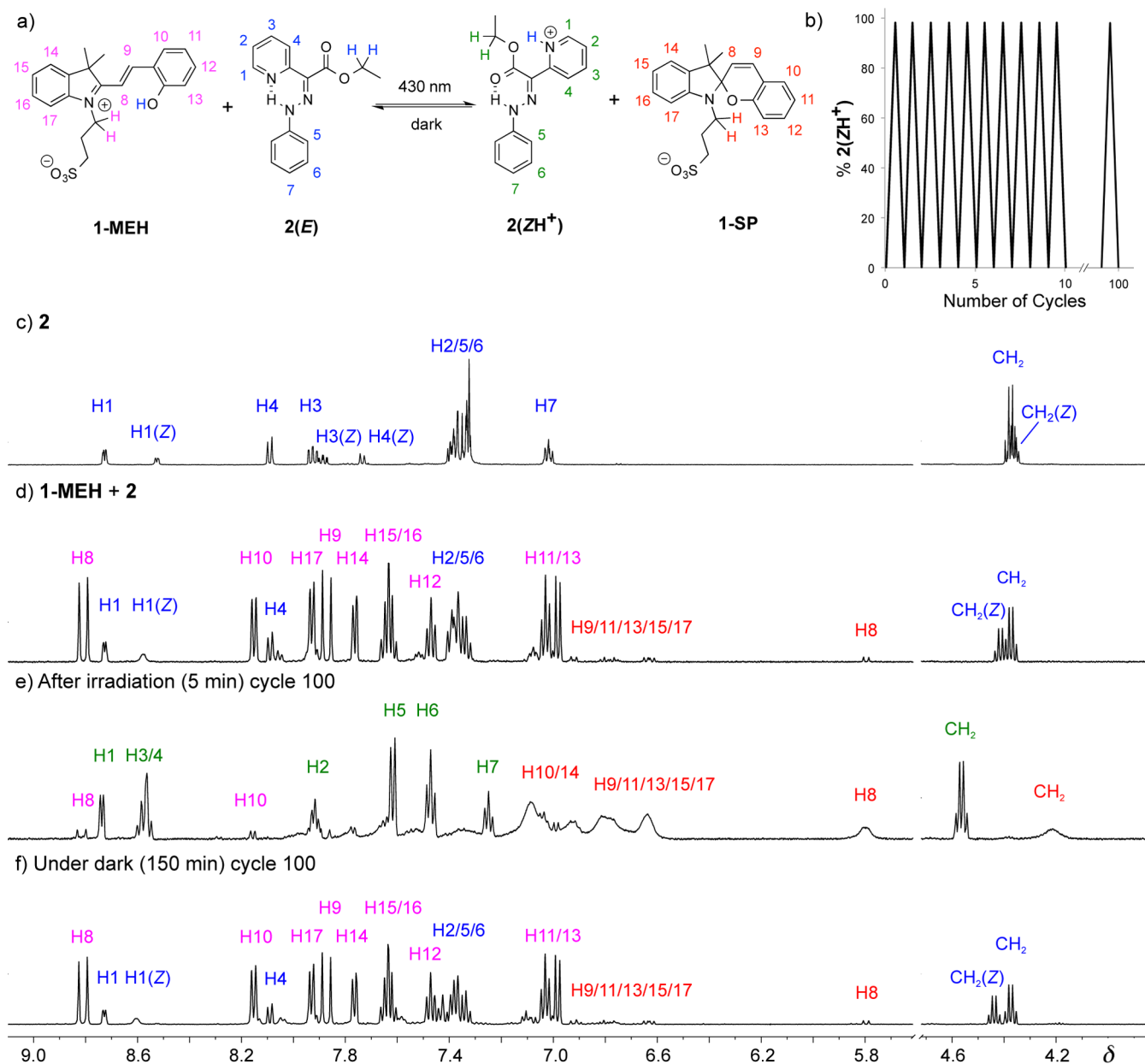
Figure 1. (a) Scheme of the photoinitiated proton transfer between **1-MEH** and **2**. (b) The plot showing the photoacid initiated cycling of **2** to **2(ZH⁺)**. The ^{1}H NMR spectra (500 MHz, CD$_3$OD) of (c) **2**, (d) **1-MEH** and **2** before irradiation, (e) the photostationary state reached after irradiation for 5 min with 430 nm light, cycle 100 is shown, and (f) after sitting under dark for 150 min, cycle 100 shown.

initial state within 150 min under the dark (Figure 1f). The rapid reversion of excess[14] **1-SP** to **1-MEH** broadened the signals of the former making it difficult to fully assign its peaks. The switching sequence was then cycled (i.e., the sample was irradiated for 5 min with 430 nm light, then placed in the dark for 150 min)[16] in order to monitor the process over multiple iterations. The system was found to be very robust, switching over and over again at least one hundred times (Figure 1d−f) without degradation and more importantly without the formation of waste products![17]

In order to assess the effectiveness of the switching process in water, the hydrazone switch was substituted with a triethylene glycol monomethyl ether (TEG) side chain, to increase its water solubility. The new switch was obtained in three steps (Scheme 2); first, *para*-nitrophenol was substituted with TEG to yield **5**. This was followed by reduction of the nitro group

with Pd/C and hydrogen to yield the amine (**6**). Finally, diazotization of **6** with sodium nitrite followed by coupling with ethyl 2-pyridylacetate (**7**) resulted in hydrazone **3** as a yellow oil. The compound was characterized using ^{1}H and ^{13}C NMR spectroscopies (Figures S1 and S2 in the Supporting Information) and high-resolution mass spectrometry.

TEG functionalization significantly improves the water solubility of **3** (~1 mg/mL) compared to **2**, which is insoluble in water. The acid−base switching of **3** was studied in D$_2$O using ^{1}H NMR spectroscopy. Initially, a mixture of *E* and *Z* isomers can be observed for **3**, with the *E* configuration being the major form (Figure 2b). The addition of 2 equiv of acid (TFA) fully converts the mixture to the protonated **3(ZH⁺)** form (Figure 2c). A general downfield trend could be observed in the aliphatic and aromatic signals. The latter is an indication for the formation of the pyridinium cation and switching of the

Scheme 2. Synthesis of the Water-Soluble Hydrazone Switch 3
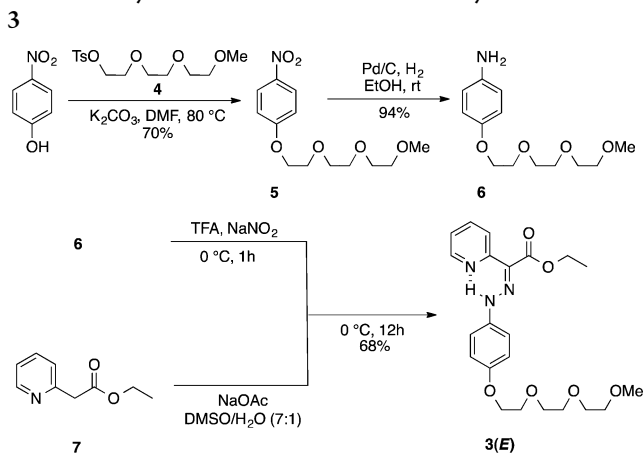
system.[13] The deprotonation of **3(ZH⁺)** was accomplished by the addition of 2 equiv of base (NEt₃) to yield the original E/Z mixture of **3** (Figure 2d). Notably, after three switching cycles the solubility of the switch decreases, likely because of the concomitant accumulation of triethylammonium and trifluoroacetate side products, making it difficult to continue the process.
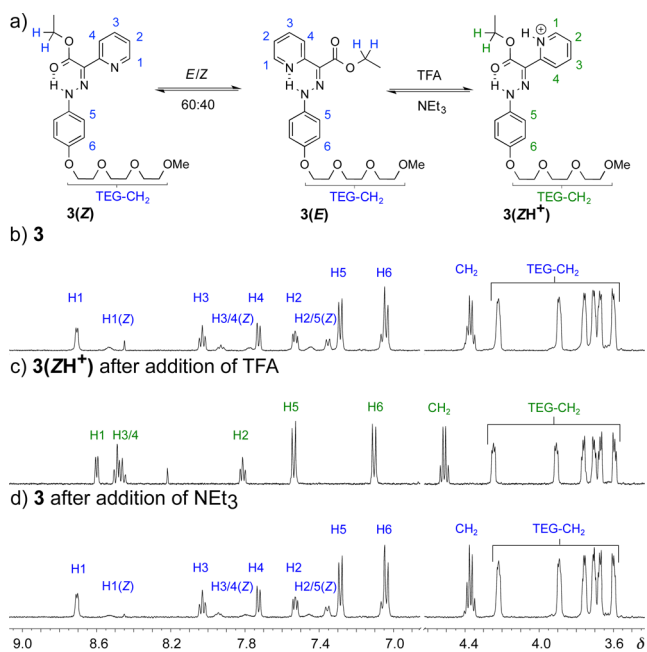

Figure 2. (a) Scheme of the acid−base switching of hydrazone switch **3**. The ^{1}H NMR spectra of (500 MHz, D₂O) of (b) **3** (E/Z mixture), (c) **3(ZH⁺)** after the addition of TFA, and (d) neutralized **3** after the addition of NEt₃.

The photoinitiated proton transfer between **1-MEH** and the water-soluble molecular switch **3** was studied in D₂O as well (Figure 3). A mixture of **1-MEH** and **3** was irradiated with violet light (430 nm), and a photostationary state was reached after 5 min (Figure 3c). Similar to the process in CD₃OD, the incomplete photoisomerization, and rapid reversion of **1-SP** to **1-MEH** in D₂O[18] (Figure S18 in the Supporting Information) made it necessary to use a 2:1 molar ratio of **1-MEH** to **3**, respectively to achieve >90% conversion of **3** to **3(ZH⁺)**. The short half-life of **1-SP** and low solubility of **1-MEH** in D₂O
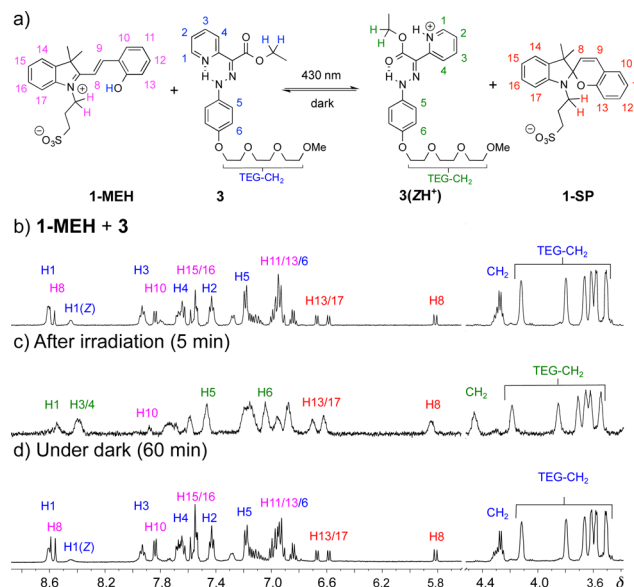

Figure 3. (a) Scheme of the photoinitiated proton transfer between **1-MEH** and **3**. The ^{1}H NMR spectra (500 MHz, D₂O) of (b) **1-MEH** and **3**, (c) the photostationary state reached after 5 min irradiation with 430 nm light, first cycle, and (d) the resulting spectrum after sitting in the dark (60 min).

(0.05 mg/mL) led to broadening of the signals in general and limited their full assignment. However, the signals of **3(ZH⁺)** were discernible and could be matched to those obtained from the acid/base switching with TFA/NEt₃ (Figure 2c). Most importantly, the spectrum displays the characteristic CH₂ shift from δ = 4.28 to 4.41 ppm, which was used as a quantitative measure of hydrazone switching. Allowing the mixture to sit under the dark for 1 h yields the original mixture of **1-MEH** and **3** (Figure 3d). As expected, the use of a recyclable acid source, unlike the use of TFA/NEt₃, resulted in no change in solubility of the mixture, which allowed us to switch the system 20 times in D₂O with no appreciable decrease in efficacy (Figure S9 in the Supporting Information). However, prolonged exposure of the photoacid to water led to the hydrolysis of the merocyanine to its constituting starting materials.[19] This is evident in the ^{1}H NMR spectrum (Figure S8 in the Supporting Information) by the appearance of two singlets at δ = 9.86 and 1.49 ppm, which were assigned to the aldehyde proton of salicylaldehyde and the methyl groups at the 3 position of indolenine, respectively. This process is the limiting factor of the number of cycles that can be performed in D₂O.

In summary, it was shown that the photoacid **1-MEH** can effectively be used in switching a pH-responsive hydrazone switch. This process is very fast, efficient, and robust in methanol, with full conversion over 100 cycles and no formation of deleterious waste products. A TEG-functionalized hydrazone switch **3** was synthesized as well, and its E/Z isomerization was studied in water using acid and base inputs. This switch was also modulated efficiently (>90% conversion; 20 cycles) through the photoinitiated proton transfer from **1-MEH**. The hydrolysis of the photoacid, however, eventually hampered the number of cycles that can be performed. Future stabilization of the photoacid toward hydrolysis will lead to highly robust proton transfer systems[11] that can be effectively and repeatedly used in controlling biological processes.[20]

ASSOCIATED CONTENT

S Supporting Information

Experimental details, synthetic procedures, irradiation methods, and NMR data are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ivan.aprahamian@dartmouth.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) (a) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72−191. (b) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines—Concepts and Perspectives for the Nanoworld*; Wiley-VCH: Weinheim, 2008. (c) Stoddart, J. F. *Chem. Soc. Rev.* **2009**, *38*, 1802−1820. (d) Feringa, B. L.; Browne, W. R., Eds. *Molecular Switches*; Wiley-VCH: Weinheim, 2011. (e) Coskun, A.; Banaszak, M.; Astumian, R. D.; Stoddart, J. F.; Grzybowski, B. A. *Chem. Soc. Rev.* **2012**, *41*, 19−30.

(2) Balzani, V.; Credi, A.; Venturi, M. *Chem. Soc. Rev.* **2009**, *38*, 1542−1550.

(3) (a) Oesterhelt, D.; Stoeckenius, W. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 2853−2857. (b) Lanyi, J. K.; Schobert, B. *J. Mol. Biol.* **2003**, *328*, 439−450.

(4) (a) Ludlow, F. R.; Otto, S. *Chem. Soc. Rev.* **2008**, *37*, 101−108. (b) Nitschke, J. R. *Nature* **2009**, *462*, 736−738.

(5) Shi, Z.; Peng, P.; Strohecker, D.; Liao, Y. *J. Am. Chem. Soc.* **2011**, *133*, 14699−14703.

(6) Klajn, R. *Chem. Soc. Rev.* **2014**, *43*, 148−184.

(7) Arnaut, L. G.; Formosinho, S. J. *J. Photochem. Photobiol., A* **1993**, *75*, 1−20.

(8) (a) Fang, L.; Basu, S.; Sue, C.-H.; Fahrenbach, A. C.; Stoddart, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 396−399. (b) Fang, L.; Wang, C.; Fahrenbach, A. C.; Trabolsi, A.; Botros, Y. Y.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1805−1809. (c) Forgan, R. S.; Gassensmith, J. J.; Cordes, D. B.; Boyle, M.; Hartlieb, K. J.; Friedman, D. C.; Slawin, A. M. Z.; Stoddart, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 17007−17010. (d) Grunder, S.; McGrier, P. L.; Whalley, A. C.; Boyle, M. M.; Stern, C.; Stoddart, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 17691−17694. (e) Panman, M. R.; Bakker, B. H.; Uyl, D. d.; Kay, E. R.; Leigh, D. A.; Buma, W. J.; Brouwer, A. M.; Geenevasen, J. A. J.; Woutersen, S. *Nat. Chem.* **2013**, *5*, 929−934.

(9) Silvi, S.; Arduini, A.; Pochini, A.; Secchi, A.; Tomasulo, M.; Raymo, F. M.; Baroncini, M.; Credi, A. *J. Am. Chem. Soc.* **2007**, *129*, 13378−13379.

(10) (a) Zhou, W.; Chen, D.; Li, J.; Xu, J.; Lv, J.; Liu, H.; Li, Y. *Org. Lett.* **2007**, *9*, 3929−3932. (b) Silvi, S.; Constable, E. C.; Housecroft, C. E.; Beves, J. E.; Dunphy, E. L.; Tomasulo, M.; Raymo, F. M.; Credi, A. *Chem. Commun.* **2009**, *12*, 1484−1486. (c) Silvi, S.; Constable, E. C.; Housecroft, C. E.; Beves, J. E.; Dunphy, E. L.; Tomasulo, M.; Raymo, F. M.; Credi, A. *Chem.—Eur. J.* **2009**, *15*, 178−185. (d) Zhou, W.; Zhang, H.; Li, H.; Zhang, Y.; Wang, Q.-C.; Qu, D.-H. *Tetrahedron* **2013**, *69*, 5319−5325.

(11) Ray, D.; Foy, J. T.; Hughes, R. P.; Aprahamian, I. *Nat. Chem.* **2012**, *4*, 757−762.

(12) (a) Campbell, V. E.; de Hatten, X.; Delsuc, N.; Kauffmann, B.; Huc, I.; Nitschke, J. R. *Nat. Chem.* **2010**, *2*, 684−687. (b) Pramanik, S.; De, S.; Schmittel, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4709−4713.

(13) (a) Landge, S. M.; Aprahamian, I. *J. Am. Chem. Soc.* **2009**, *131*, 18269−18271. (b) Landge, S. M.; Tkatchouk, K.; Benitez, D.; Lanfranchi, D. A.; Elhabiri, M.; Goddard, W. A., III; Aprahamian, I. *J. Am. Chem. Soc.* **2011**, *133*, 9812−9823. (c) Su, X.; Aprahamian, I. *Org. Lett.* **2011**, *13*, 30−33. (d) Su, X.; Robbins, T. F.; Aprahamian, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 1841−1844. (e) Su, X.; Aprahamian, I. *Org. Lett.* **2013**, *15*, 5952−5955.

(14) The incomplete photoisomerization of **1-MEH** to **1-SP**, evident by the former's signals in Figure 1e, and the rapid reversion process made it necessary to use a 2:1 molar ratio of **1-MEH** to **2** to achieve full conversion of the hydrazone switch.

(15) Switch **2** exists as a mixture of *E* and *Z* isomers (60:40) in MeOD.

(16) We attempted to reverse the process photochemically by irradiating the sample with 290 nm light; however, this method was found to be less efficient than the thermal reversion process, as we quickly obtained a photostationary state that favors the **1-SP** form.

(17) We speculate that the relative longevity of the **1-SP** form and the effectiveness of both the photocyclization reaction and switching of the hydrazone are responsible for the efficient switching process.

(18) Johns, V.; Wang, Z.; Li, X.; Liao, Y. *J. Phys. Chem. A* **2013**, *117*, 13101−13104.

(19) Hilvert, D.; Stafforst, T. *Chem. Commun.* **2009**, 287−288.

(20) (a) Velema, W. A.; Szymanski, W.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 2178−2191. (b) Fehrentz, T.; Schönberger, M.; Trauner, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12156−12182.