Organic & Biomolecular Chemistry

An Easily Accessible Isospiropyran Switch

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-08-2019-001822.R1
Article Type:	Communication
Date Submitted by the Author:	10-Sep-2019
Complete List of Authors:	Badjic, Jovica; Ohio State University, Department of Chemistry Neal, Taylor; Ohio State University, Department of Chemistry Neal, Jennifer; Ohio State University, Department of Chemistry Eippert, Allyson; Ohio State University, Department of Chemistry Moore, Curtis; Ohio State University, Department of Chemistry Allen, Heather; Ohio State University, Department of Chemistry

COMMUNICATION

An Easily Accessible Isospiropyran Switch

Taylor A. Neal, Jennifer F. Neal, Allyson B. Eippert, Curtis Moore, Heather C. Allen, Jovica D. Badjić*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

In the presence of $SiCl_4$, three molecules of 5′–bromo–2′–hydroxyacetophenone underwent an unexpected tandem aldol condensation to give novel isospiropyran switch (69%), with X-ray crystallography confirming its structure. Strong Brönsted acid CH_3SO_3H turned the colorless isospiropyran into its protonated and open form possessing red color. The process was reversed using Et_3N base, with the acid/base toggling repeatable for at least six times (UV-Vis). When printed on a silica plate, however, the isospiropyran formed blue-colored product due to, as posited, its stabilization by hydrogen bonding (HB) to silica. An exposure to HB-competing ethyl acetate temporarily "erased" the print only to be brought back by subjecting the plate to a higher temperature for evaporating the solvent. Here described isospiropyran is an easily accessible, chromic, modular and switchable compound that one can incorporate into dynamic materials or use for building chemosensors, molecular machines and organic electronic devices.

For more than a century,[1] chemists have studied spiropyrans (Figure 1A/B) undergoing large structural and electronic changes in the presence of physical or chemical stimuli. Thus, moiety and give highly conjugated and colored merocyanine (MC-**II**, Figure 1A). The toggling is facile, robust and reversible, thereby lending itself to the development of an impressive force (mechanochromism),[2] acids (acidochromism)[3] or other triggers[1a] could prompt SP-**I** (Figure 1A) to undergo 6π electrocyclic (or stepwise)[4] ring-opening of its chromene range light (photochromism),[5] heat (thermochromism),[6] mechanical of dynamic materials[1a] ranging from chemosensors,[7] channel regulators[8] to high-resolution imaging probes,[9] mechanical-stress indicators[10] and information-processing devices.[11] In this vein, the indoline-chromene spiropyran switches (Figure 1A) have dominated the field with the scavengers of toxic metals,[12] switchable biocatalysts[13] and ion- widespread interest resulting from their (a) rapid preparation, (b) facile functionalization and (c) controllable two-state transition.[14] On the other hand, spiro-compounds possessing 4*H*- or 2*H*-pyrane heterocycles (Figure 1B), instead of indoline, have attracted less attention due to more demanding synthesis[15] and substandard switching characteristics.[1b] For instance, dibenzospiropyran (Figure 1B) was found to be neither photochromic nor thermochromic[1b] while benzo-β-naphthospiropyran, benzo-β-naphthoisospiropyran or xanto-β-naphthospiropyran would undergo opening of their chromene ring at higher temperatures[1c] or after UV irradiation:[16] the process was found to necessitate a stabilization of the zwitterionic form of the molecule with proper substituents.[1b] Importantly, a rapid thermal reversion[17] of spiropyrans of type shown in Figure 2B, limited studies of their photochromism[16, 18] therefore rendering them less amenable to applications.[1b] In this vein, we hereby describe our serendipitous discovery about the preparation of isospiropyran **1** (Figure 1C) from abundant starting material and in a single step with this uniquely functionalized molecule being switchable and, perhaps, prone to further functionalization for optimizing its action.[1b]

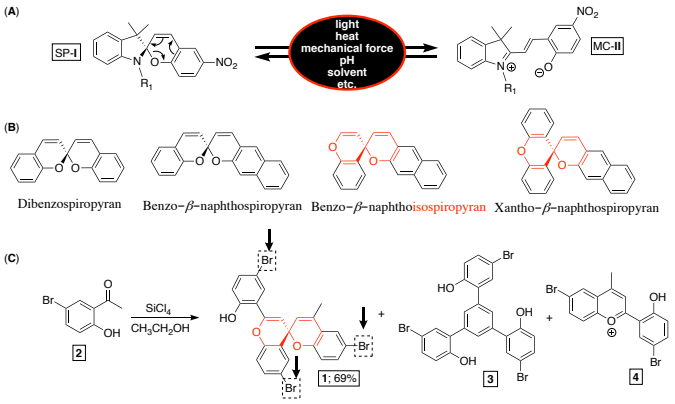

Figure 1. (A) Chemical structures of open (spiropyran, SP-I) and closed (merocyanine, MC-II) forms of indoline-chromene spiropyran switches. (B) Four originally examined spiropyrans. (C) Self-condensation of **2**, in anhydrous ethanol containing $SiCl_4$, gave isospiropyran **1** in 69% isolated yield.

Department of Chemistry & Biochemistry, The Ohio State University
100 West 18th Avenue, 43210 Columbus, Ohio USA. E-mail: badjic.1@osu.edu
† Electronic Supplementary Information (ESI) available: [Experimental details, additional spectra and computations]. See DOI: 10.1039/x0xx00000x

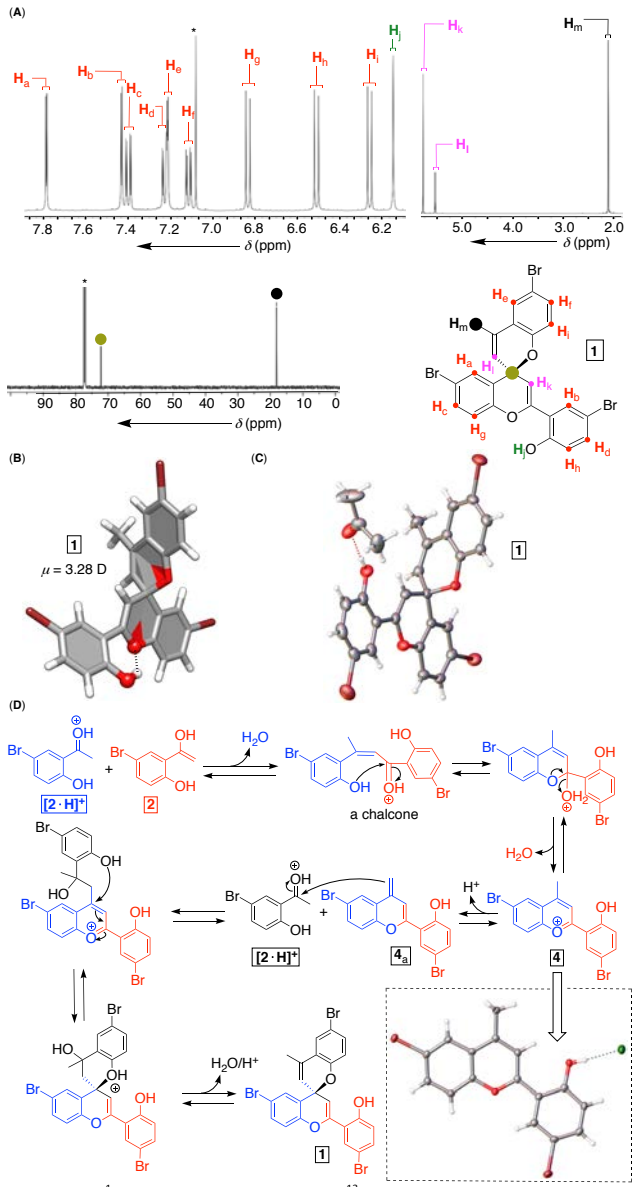

Figure 2. (A) ^{1}H NMR (600 MHz, 298 K) and ^{13}C NMR (600 MHz, 298 K) spectra of **1** in $CDCl_3$. (B) Computed (DFT; B3LYP: 6-311+G**) and (C) solid-state (ORTEP) structures of **1**. (D) A postulated mechanism for the formation of isospiropyran **1** from **2**; for clarity, some steps are intentionally omitted; solid-state structure of **4** (ORTEP).

Originally, we aimed to examine anion-complexing characteristics of **3** at a surface (Figure 1C), and therefore probed its preparation via cyclotrimerization (aldol condensation)[18] of **2**. In this reaction, the formation of benzopyrilium **4** could, from this particular substrate, take place as well.[19] After 5′-bromo-2′-hydroxyacetophenone **2** was dissolved in anhydrous ethanol containing $SiCl_4$[20] and the reaction left to stir overnight, the starting compound gradually vanished while the principal product formed (TLC) only to be isolated by precipitation. ESI-MS analysis of the product showed an ion at m/z = 588.8643 a.u. (Figure S1) congruent with the anticipated $[\mathbf{3}+H]^+$ (Figure 1C). ^{1}H NMR spectrum (Figure 2A), however, revealed a set of nine distinct resonances in the aromatic region to imply the formation of a C_1 symmetric compound possessing three non-equivalent and 1,2,5-trisubstituted benzene rings. Clearly, the principle reaction's product was neither **3** nor **4**. ^{13}C NMR spectrum showed 24 resonances with two under 100 ppm (Figure 2A; Figure S3): the resonance at 18 ppm denoted a methyl group (^{1}H-^{13}C HSQC, Figure S6) while the signal at 72 ppm an sp^3-hybridized quaternary carbon (^{1}H-^{13}C HMBC, Figure S7). Using two-dimensional correlations from COSY (Figure S4), ^{1}H-^{13}C HSQC (Figure S6), ^{1}H-^{13}C HMBC (Figure S7) and ^{13}C-^{13}C INADEQUATE NMR (Figure S8), we assigned all proton and carbon resonances to isospiropyran **1** (Figure 2A)! For this molecule, the observed downfield shift of O**H**$_j$ at 6.18 ppm, in addition to NOE cross peaks (Figure S5), marked the formation of intramolecular O–H···O hydrogen bonding, which was also in line with the energy-minimized structure (DFT; B3LYP: 6-311+G** with no frequency calculation and using the Spartan software, Figure 2B) of a conformer of **1** whereby $D_{O\text{-}O}$ = 2.694 Å and Θ = 138.73º.[21] At last, single crystals of **1** were grown by a slow evaporation of its acetone solution. X-ray structural analysis validated the spirocyclic nature of **1** with 2H- and 4H-pyran rings being almost perpendicular to one another (Figure 2C) and the hydroxyl group hydrogen bonded to acetone ($D_{O\text{-}O}$ = 2.716 Å and Θ = 176.39º).[21]

How did three molecules of **2** combine to give isospiropyran **1**? First, we reasoned that either HCl or silicon-based species[20b, 22] ought to be acting as catalysts to facilitate the conversion. With this in mind, we arbitrarily chose to depict the transformation as a Brønsted acid catalysis (Figure 2D).[20b] The reaction begins with aldol condensation of **2** giving a chalcone intermediate, which in the presence of acid forms flavylium ion **4**.[19a] Under the experimental conditions, compound **4** could lose a proton to ethanol solvent and give a sufficient quantity of $\mathbf{4}_a$ capable of acting as a nucleophile and reacting with electrophilic $[\mathbf{2}\cdot H]^+$.[19b] Finally, intramolecular 6-exo-trig cyclization followed by elimination of H_2O furnishes isospiropyran **1**; upon the reaction's completion, a basic work-up was required to isolate **1** (*vide infra*). When 95% ethanol solution of **1,** containing concentrated $HCl_{(aq)}$, was left to stand at room temperature, a small quantity of solid crystalline precipitate formed with the X-ray analysis revealing the formation of flavylium **4**·Cl having its hydroxyl group hydrogen bonded to the chloride anion ($D_{O\text{-}Cl}$ = 2.086 Å and Θ = 173.32º, Figure 2D). According to the mechanism, a retro-aldol reaction of **1** should, in the presence of water, give flavylium salt **4** so that its isolation, under particular conditions, provides evidence to support the mechanistic postulate.

Spiropyrans undergo protonation and opening of their chromene moiety to turn into conjugated and colored products.[1b] Upon an incremental addition of CH_3SO_3H (pK_a = –2.0)[18] to a solution of isospiropyran **1** in chloroform, we noted a set of ^{1}H NMR signals growing at the expense of **1** along with red color developing (Figure 3A). As with one equivalent of the acid the resonances from **1** disappeared, we wondered if conjugated $\mathbf{1}_a$ dominated the equilibrium (Figure

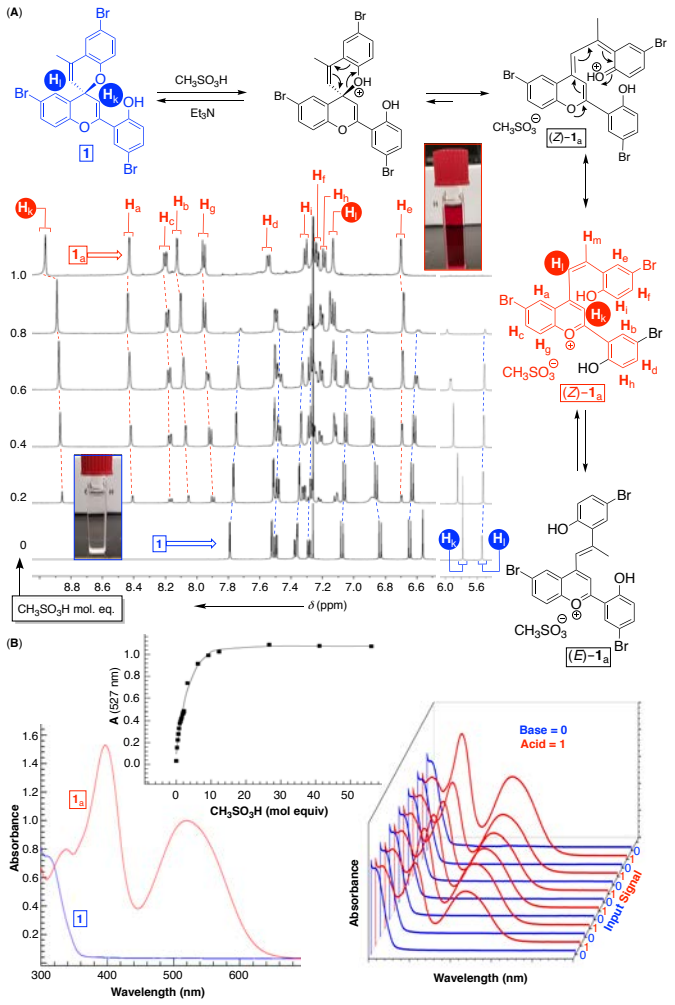

Figure 3. (A) Isospiropyran **1** can be converted into $\mathbf{1}_a$ using CH_3SO_3H in chloroform; (*Z*) and (*E*) stereoisomers of $\mathbf{1}_a$ are shown on the right. ^{1}H NMR spectra (600 MHz, 298 K) of 60 mM **1** in $CDCl_3$ upon an incremental addition of CH_3SO_3H. (B) UV-Vis spectra of **1** (blue) and $\mathbf{1}_a$ (red), with (top) a change in the absorbance (527 nm) of 0.1 mM solution of **1** obtained after a titration of CH_3SO_3H (Figure S19). (Right) Consecutive additions of circa one molar equivalent of CH_3SO_3H (acid, red) and Et_3N (base, blue) to 0.1 mM solution of **1** in $CHCl_3$ were monitored with UV-Vis spectroscopy.

3A)? In fact, two-dimensional correlations from ^{1}H-^{1}H COSY (Figure S11), ^{1}H-^{13}C HSQC (Figure S12) and ^{1}H-^{13}C HMBC (Figure S13) corroborated the formation of $\mathbf{1}_a$. The transition of **1** into $\mathbf{1}_a$ was thus accompanied with large magnetic perturbations of (a) $\mathbf{H}_k$ becoming deshielded ($\Delta\delta$ = 3.2 ppm, Figure 3A) in response to the conversion of an olefinic into an aromatic carbon framework and (b) spiro-carbon moving 90 ppm downfield due to, in part, changing its hybridization from sp^3 to sp^2 (Figure S10). And finally, there was a large downfield shift of the olefinic $\mathbf{H}_l$ proton. The acidochromic behaviour of isospiropyran **1** was also verified with UV-Vis spectroscopy (Figure 3B) whereby the formation of $\mathbf{1}_a$ was characterized with the growth of two absorption bands at circa 400 and 527 nm.[1a, 19b] By adding Et_3N to $\mathbf{1}_a$, we fully restored isospiropyran **1** (Figure 3B).[3] When $\mathbf{1}_a$ was dissolved in 1,2-dichloroethane and the solution exposed to pentane vapors there followed crystallization. A diffraction analysis revealed the unit cell including both closed **1** and open (*Z*)–$\mathbf{1}_a$ forms of the

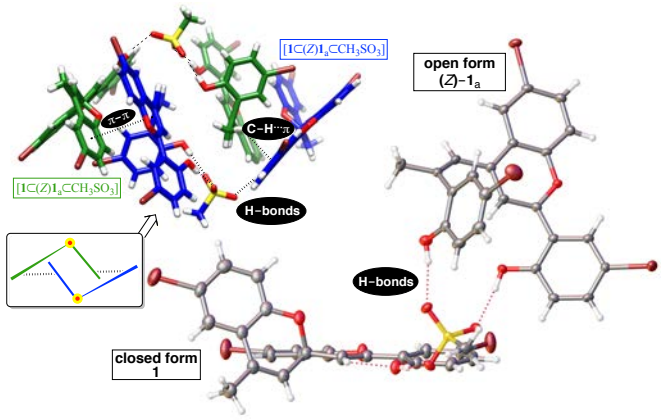

Figure 4. X-ray structures (ORTEP) of **1** and (*Z*)–$\mathbf{1}_a$ hydrogen bonded to a mesylate anion. (Top left) A stick representation (Chimera) of the assembly of two entangled [**1**⊂(*Z*)–$\mathbf{1}_a$⊂CH_3SO_3] complexes (green and blue) in the solid state.

isospiropyran (Figure 4). Particularly interesting is that the open $\mathbf{1}_a$ adopted a folded shape[23] with two hydroxyl groups forming O–H···O hydrogen bonds ($D_{O\text{-}O}$ = 2.627–2.714 Å, Θ = 169.72–174.12º)[21] with the mesylate. On the other hand, the conformation of isospiropyran **1** was akin to the one described in Figure 2C although its OH group was hydrogen bonded to the mesylate. In the solid state, U-shaped [**1**⊂(*Z*)–$\mathbf{1}_a$⊂CH_3SO_3] was actually interwoven with another complex of the same type with two ternary complexes held together by π–π stacking (3.373 Å) and C–H···π interactions (D = 3.693 Å and α = 124.79º).[24]

At higher temperatures, spiropyrans undergo a scission of their C_{spiro}–O chromene bond (Figure 5A) to form zwitterionic, conjugated and colored and molecules of interest in the field of thermochromic materials.[25] Importantly, electron-withdrawing groups on the chromene moiety[1c] in addition to polar and hydrogen bonding solvents[17, 26] stabilize the negative charge in the zwitterionic state to facilitate color development.[1b, 1c] Accordingly, we decided to use polar CD_3SOCD_3 and probe the conversion of **1** into $\mathbf{1}_b$ at higher temperatures (Figure 5A; Figure S14). At 65 ºC, a set of ^{1}H NMR spectroscopic signals corresponding to isospiropyran **1** began to reduce intensity while another set of signals started to emerge. After roughly 5 hours, two sets of resonances reached almost a steady integration ratio although without any color development. The product(s) emerging from **1** missed methyl $\mathbf{H}_m$ protons (δ = 2.1 ppm, Figure 5A) while encompassing two hydroxyl groups $\mathbf{OH}_{p/p\text{-}1}$ (δ = 8.8–10.3 ppm, Figure 5A) and two nonequivalent alkene $\mathbf{H}_{n/o}$ protons (δ = 5.2–5.6 ppm, Figure 5A). ^{13}C NMR spectrum of this product (Figures S16/S18) showed the absence of resonances at less than 100 ppm (i.e. no sp^3-hybridized carbons). The spectroscopic results were in line with an opening of the spiro-system and rehybridization of the methyl group. While unable to chromatographically separate **1** from the product, we used 2D NMR spectroscopic methods (Figure S17-S18) to tentatively assign its structure to **5** (Figure 5A). Allegedly, 6π electrocyclic (or stepwise)[4, 27] opening of **1** gave a negligible quantity of $\mathbf{1}_b$ with the solution remaining colorless. Furthermore, a conformer of $\mathbf{1}_b$ with its methyl group juxtaposed to the

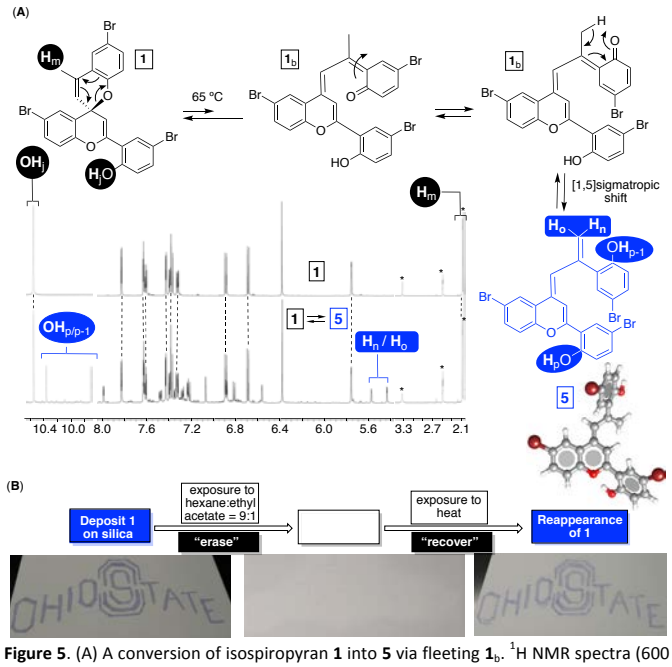

Figure 5. (A) A conversion of isospiropyran **1** into **5** via fleeting $\mathbf{1}_b$. ^{1}H NMR spectra (600 MHz) of **1** in CD_3SOCD_3 held at 65 ºC for 2 (top) and 300 minutes (bottom). (B) Colorless isospiropyran **1** was in dichloromethane (0.02 mM) deposited on a silica plate to develop blue color (left). The blue print was "erased" by treating it with hexane:ethyl acetate = 9:1 (middle). A removal of the solvent by exposing the plate to heat restored the image (right).

quinodal's carbonyl underwent [1,5]sigmatropic shift to give twisted and colorless **5** (Figure 5A/B; AM1, Spartan). At this point, it is important to note that our preliminary studies showed a reversible thermochromism with **1** having chlorine (more electronegative) instead of bromine substituents;[1b] the reaction's scope along with a screening of catalysts is to published soon. With $\mathbf{1}_b$ forming at higher temperatures, we wondered if polar hydrogen-bonding (HB) media could stabilize this open form of the switch under ambient conditions.[26] After a solution of **1** was deposited on a silica plate, a blue color developed (Figure 5B) with polar and HB-donating environment of silica[28] stabilizing $\mathbf{1}_b$ and giving the blue print.[29] An addition of competing hydrogen bonding solvent (hexane/ethyl acetate = 9:1), however, "erased" the print by simply abolishing the HB effect of silica.[28a] Finally, using a heat gun to evaporate the solvent brought the blue print back (Figure 5B); note that neat hexane had no effect on the deposited color.

In conclusion, isospiropyran **1** is an accessible molecular switch[1a] that, so far, can be toggled with acid, temperature or silica for developing its colored form. An attractive feature of this molecule is in its unique framework: with three Ar–Br sites located at three distant corners, a conjugation of various molecules for tuning its physicochemical characteristics and integrating it into dynamic materials comes to mind.[1a] At present, we are investigating photochromic characteristics of isospiropyrans of type **1** with a goal of complementing the classical indoline-chromene switches.

Acknowledgements

This work was financially supported with funds obtained from the NSF under CHE–1606404 and ARO under W911NF-17-1-0140.

Notes and references

1. (a) R. Klajn, *Chem. Soc. Rev.*, 2014, **43**, 148; (b) L. Kortekaas and W. R. Browne, *Chem. Soc. Rev.*, 2019, **48**, 3406; (c) J. H. Day, *Chem. Rev.*, 1963, **63**, 65.
2. Y. Lin, M. H. Barbee, C.-C. Chang and S. L. Craig, *J. Am. Chem. Soc.*, 2018, **140**, 15969.
3. F. M. Raymo and S. Giordani, *J. Am. Chem. Soc.*, 2001, **123**, 4651.
4. S. Swansburg, E. Buncel and R. P. Lemieux, *J. Am. Chem. Soc.*, 2000, **122**, 6594.
5. D. Samanta, D. Galaktionova, J. Gemen, L. J. W. Shimon, Y. Diskin-Posner, L. Avram, P. Kral and R. Klajn, *Nat. Commun.*, 2018, **9**, 1.
6. P. Howlader, B. Mondal, P. C. Purba, E. Zangrando and P. S. Mukherjee, *J. Am. Chem. Soc.*, 2018, **140**, 7952.
7. P.-J. Wu, J.-L. Chen, C.-P. Chen and Y.-H. Chan, *Chem. Commun.*, 2013, **49**, 898.
8. (a) A. Kocer, M. Walko, W. Meijberg and B. L. Feringa, *Science*, 2005, **309**, 755; (b) X. Wang, J. Hu, G. Liu, J. Tian, H. Wang, M. Gong and S. Liu, *J. Am. Chem. Soc.*, 2015, **137**, 15262.
9. (a) D. Hu, Z. Tian, W. Wu, W. Wan and D. Q. Li Alexander, *J Am Chem Soc*, 2008, **130**, 15279; (b) H. Li and J. C. Vaughan, *Chem. Rev.*, 2018, **118**, 9412.
10. D. A. Davis, A. Hamilton, J. Yang, L. D. Cremar, D. Van Gough, S. L. Potisek, M. T. Ong, P. V. Braun, T. J. Martinez, S. R. White, J. S. Moore and N. R. Sottos, *Nature*, 2009, **459**, 68.
11. R. Klajn, P. J. Wesson, K. J. M. Bishop and B. A. Grzybowski, *Angew. Chem., Int. Ed.*, 2009, **48**, 7035.
12. T. Suzuki, T. Kato and H. Shinozaki, *Chem. Commun.*, 2004, 2036.
13. T. Sakata, Y. Yan and G. Marriott, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 4759.
14. (a) M. Kathan and S. Hecht, *Chem. Soc. Rev.*, 2017, **46**, 5536; (b) V. I. Minkin, *Chem. Rev.*, 2004, **104**, 2751; cG. Berkovic, V. Krongauz and V. Weiss, *Chem. Rev.*, 2000, **100**, 1741.
15. B. S. Lukyanov and M. B. Lukyanova, *Chem. Heterocycl. Compd.*, 2005, **41**, 281.
16. R. Heiligman-Rim, Y. Hirshberg and E. Fischer, *J. Chem. Soc.*, 1961, 156.
17. J. Piard, *J. Chem. Educ.*, 2014, **91**, 2105.
18. A. W. Amick and L. T. Scott, *J. Org. Chem.*, 2007, **72**, 3412.
19. (a) G. N. Dorofeenko and V. V. Tkachenko, *Khim. Geterotsikl. Soedin.*, 1974, 176; (b) J.-R. Chen and D.-Y. Yang, *Org. Lett.*, 2009, **11**, 1769.
20. (a) X.-Y. Cao, W.-B. Zhang, J.-L. Wang, X.-H. Zhou, H. Lu and J. Pei, *J Am Chem Soc*, 2003, **125**, 12430; (b) H. K. Gupta, N. Reginato, F. O. Ogini, S. Brydges and M. J. McGlinchey, *Can. J. Chem.*, 2002, **80**, 1546; (c) B. P. Dash, R. Satapathy, J. A. Maguire and N. S. Hosmane, *Organometallics*, 2010, **29**, 5230.
21. T. Steiner, *Angew. Chem., Int. Ed.*, 2002, **41**, 48.
22. (a) N. Goldberg, M. J. Almond, J. S. Ogden, J. P. Cannady, R. Walsh and R. Becerra, *Phys. Chem. Chem. Phys.*, 2004, **6**, 3264; (b) D. F. Peppard, W. G. Brown and W. C. Johnson, *J. Am. Chem. Soc.*, 1946, **68**, 70.
23. (a) J. T. C. Wojtyk, A. Wasey, N.-N. Xiao, P. M. Kazmaier, S. Hoz, C. Yu, R. P. Lemieux and E. Buncel, *J. Phys. Chem. A*, 2007, **111**, 2511; (b) R. A. Rogers, A. R. Rodier, J. A. Stanley, N. A. Douglas, X. Li and W. J. Brittain, *Chem. Commun.*, 2014, **50**, 3424; (c) P. K. Kundu, A. Lerner, K. Kucanda, G. Leitus and R. Klajn, *J. Am. Chem. Soc.*, 2014, **136**, 11276.

24. M. Nishio, Y. Umezawa, J. Fantini, M. S. Weiss and P. Chakrabarti, *Phys. Chem. Chem. Phys.*, 2014, **16**, 12648.
25. (a) S. Wang, W. Gao, X.-Y. Hu, Y.-Z. Shen and L. Wang, *Chem. Commun.*, 2019, **55**, 4137; (b) B. Mondal, A. K. Ghosh and P. S. Mukherjee, *J. Org. Chem.*, 2017, **82**, 7783.
26. Y. Shiraishi, M. Itoh and T. Hirai, *Phys. Chem. Chem. Phys.*, 2010, **12**, 13737.
27. J. T. C. Wojtyk, A. Wasey, P. M. Kazmaier, S. Hoz and E. Buncel, *J. Phys. Chem. A*, 2000, **104**, 9046.
28. J. D. Badjic and N. M. Kostic, *J. Mater. Chem.*, 2001, **11**, 408.
29. (a) J. Allouche, A. Le Beulze, J.-C. Dupin, J.-B. Ledeuil, S. Blanc and D. Gonbeau, *J. Mater. Chem.*, 2010, **20**, 9370; (b) T. Yamaguchi, A. Maity, V. Polshettiwar and M. Ogawa, *Inorg. Chem.*, 2018, **57**, 3671; (c) Y. Okabe and M. Ogawa, *RSC Adv.*, 2015, **5**, 101789; (d) P. Calero, E. Aznar, J. M. Lloris, M. D. Marcos, R. Martinez-Manez, J. V. Ros-Lis, J. Soto and F. Sancenon, *Chem. Commun.*, 2008, 1668.

1

A distinct, modular and switchable isospiropyran can now be prepared in a single step from abundant starting materials. The discovery opens a way for developing novel dynamic materials with unique responsive and switchable characteristics.