Thermal Racemization of Substituted Indolinobenzospiropyrans: Evidence of Competing Polar and Nonpolar Mechanisms

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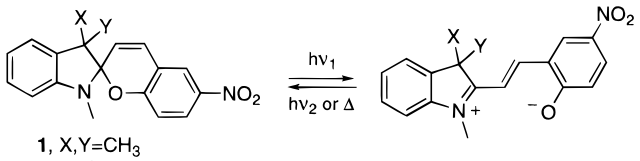
Abstract: A series of 6-substituted indolinobenzospiropyrans were resolved by chiral stationary phase HPLC and rate constants k_{rac} for their thermal racemization were measured by circular dichroism spectropolarimetry at 60 °C in three different solvents: cyclohexane, 90:10 hexanes/2-propanol, and acetonitrile. Results show that the spiropyrans undergo thermal racemization most rapidly in acetonitrile, with k_{rac} values ranging from 9.3×10^{-5} to $>5.0 \times 10^{-3}$ s^{-1}, and least rapidly in cyclohexane, with k_{rac} values ranging from 6.8×10^{-6} to 4.6×10^{-4} s^{-1}. V-shaped plots of log k_{rac} vs Hammett σ_p constants in 90:10 hexanes/2-propanol and acetonitrile suggest that thermal racemization of the 6-substituted spiropyrans proceed via two competing mechanisms: a polar mechanism involving heterolytic C(sp^3)−O bond cleavage with anchimeric assistance from the indoline nitrogen and a nonpolar electrocyclic ring opening mechanism with no anchimeric assistance from the indoline nitrogen. The outcome of this competition appears to be strongly influenced by solvent polarity: plots of log k_{rac} vs σ_p and σ^- in cyclohexane show a near-linear correlation with negative slope, which is consistent with the nonpolar mechanism. However, an increase in solvent polarity results in a shift toward a linear correlation with positive slope, which is consistent with the polar mechanism.

Introduction

Indolinobenzospiropyrans (spiropyrans) are one of the most studied families of organic dyes by virtue of their thermochromic, solvatochromic, and photochromic properties. These compounds are attractive as functional materials for a wide variety of applications, including high-density optical data storage, optical switching, and nonlinear optics.[1−3] In solution, a spiropyran can undergo ring opening to the corresponding *trans*-merocyanine, and the position of this equilibrium usually depends on solvent polarity and on the nature of substituents. One of the best known spiropyrans is 1′,3′,3′-trimethyl-6-nitrospiro[2*H*-1-benzopyran-2,2′-indoline] (**1**), which undergoes ring opening to a stable merocyanine form in polar solvents such as ethanol and/or upon irradiation in the near-UV (Scheme 1). However, much less attention has been paid to spiropyrans lacking a strong electron-withdrawing group because they tend to produce photostationary states with a negligible merocyanine concentration.[4] These so-called *nonactivated* spiropyrans have rather limited use in photochromic applications, but they have been under consideration as potential chiroptical switches for optically addressed liquid crystal spatial light modulators.[5]

Most chiroptical switches are photochromic compounds which can undergo interconversion between two chiral helical forms of opposite helicities, or between racemic and optically active forms by photoresolution.[6] The only spiropyran chiroptical switch reported thus far contains a chiral center at C-3′ in addition to the chiral spiro carbon (**2**). Switching is achieved by reversible photoisomerization between the spiropyran form, which exhibits circular dichroism as a 1.6:1 mixture of two diastereomers at equilibrium, and the planar merocyanine form, which exhibits no circular dichroism.[7] We are currently investigating an alternative approach toward a spiropyran chiroptical switch which consists of photoresolving a nonactivated liquid crystalline spiropyran using circularly polarized light to reversibly induce detectable chiral bulk properties such as a cholesteric helical pitch or a spontaneous polarization.[5,8] To undergo photoresolution, a chiral chromophore must undergo efficient photoracemization, yet maintain its configurational integrity in the absence of light.[9] Photoracemization can be achieved with nonactivated spiropyrans because the chiral spiro form undergoes ring opening to a short-lived prochiral merocyanine form which reverts back to the (*R*) or (*S*) enantiomers of the spiro form with equal probabilities. However, in this paper, we address the issue of configurational stability of

Scheme 1



1, X,Y=CH_3
2, X=C_2H_5,Y=*n*-C_3H_7

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(1) *Photochromism*; Brown, G. H., Ed.; Wiley: New York, 1971.

(2) *Photochromism-Molecules and Systems*; Dürr, H., Bouas-Laurent, H., Eds.; Elsevier: Amsterdam, 1990.

(3) Feringa, B. L.; Jager, W. F.; de Lange, B. *Tetrahedron* **1993**, *49*, 8267.

(4) Keum, S.-R.; Lee, K.-B.; Kazmaier, P. M.; Buncel, E. *Tetrahedron Lett.* **1994**, *37*, 1015.

(5) (a) Swansburg, S.; Choi, Y.-K.; Keum, S.-R.; Buncel, E.; Lemieux, R. P. *Liq. Cryst.* **1998**, *24*, 341. (b) Keum, S. R.; Lee, M.-J.; Swansburg, S.; Buncel, E.; Lemieux, R. P. *Dyes Pigments* **1998**, *39*, 383.

(6) (a) Burnham, K. S.; Schuster, G. B. *J. Am. Chem. Soc.* **1999**, *121*, 10245. (b) Huck, N. P. M.; Jager, W. F.; de Lange, B.; Feringa, B. L. *Science* **1996**, *273*, 1686. (c) Suarez, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1995**, *117*, 6732. (d) Feringa, B. L.; Huck, N. P. M.; van Doren, H. A. *J. Am. Chem. Soc.* **1995**, *117*, 9929.

(7) Eggers, L.; Buss, V. *Angew Chem. Int. Ed. Engl.* **1997**, *36*, 881.

(8) For examples of photoresolution in a nematic liquid crystal phase, see refs 6a,b.

(9) Rau, H. *Chem. Rev.* **1983**, *83*, 535.

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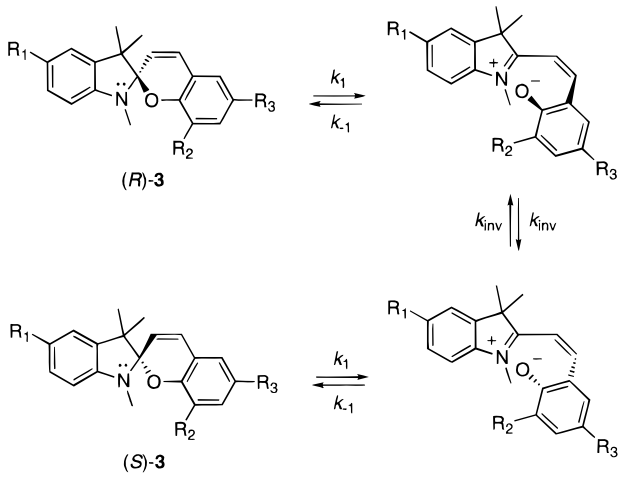
Scheme 2



spiropyrans as potential candidates for photoresolvable liquid crystalline chiroptical switches.

Few studies on the configurational stability of indolinobenzospiropyrans have been carried out so far. Zaichenko and co-workers measured free energies of activation for the inversion of configuration ($\Delta G^{\ddagger}_{inv}$) of a series of spiropyrans **3** at 25 °C by dynamic NMR spectroscopy in deuterated DMSO and correlated those values to Hammett σ_p constants for substituents R_1 and R_3, and to Taft σ^* constants for substituent R_2.[10] The results are consistent with a rate-determining heterolytic cleavage of the C(sp^3)−O bond to give a zwitterionic cisoid intermediate that can rapidly invert and close back to the spiropyran of opposite configuration, as shown in Scheme 2. Accordingly, the lowest $\Delta G^{\ddagger}_{inv}$ value (17 kcal/mol) was obtained for a spiropyran with substituents $R_2 = R_3 = NO_2$, which stabilize the negative charge buildup on the oxygen, and the highest $\Delta G^{\ddagger}_{inv}$ value (25.2 kcal/mol) was obtained for a spiropyran with a single substituent $R_1 = NO_2$, which destabilizes the positive charge buildup on nitrogen.

Mannschreck and co-workers resolved several spiropyrans and spirooxazines by chiral phase HPLC on microcrystalline triacetylcellulose and measured their $\Delta G^{\ddagger}_{inv}$ by on-line circular dichroism (CD) using methanol and ethanol as solvents.[11] Although this study did not focus on substituent effects, the $\Delta G^{\ddagger}_{inv}$ values reported for indolinobenzospiropyrans are consistent with those obtained by Zaichenko and co-workers. A more systematic investigation of substituent and solvent effects on $\Delta G^{\ddagger}_{inv}$ of chiral 2*H*-chromene systems, which model the benzopyran half of indolinobenzospiropyrans, was carried out by polarimetry using samples resolved preparatively by chiral phase HPLC on triacetylcellulose.[12,13] As with indolinobenzospiropyrans, substituent effects on $\Delta G^{\ddagger}_{inv}$ in polar solvents are consistent with a polar mechanism in which the C(sp^3)−O bond is cleaved heterolytically in the transition state of the rate-determining step. In the case of 7,8-benzo-2-benzyloxy-2*H*-chromene, $\Delta G^{\ddagger}_{inv}$ (60 °C) was shown to increase with solvents of decreasing polarity (e.g., $\Delta G^{\ddagger}_{inv}$(ethanol) = 102.8 kJ/mol and $\Delta G^{\ddagger}_{inv}$(*n*-hexane) = 105.9 kJ/mol).

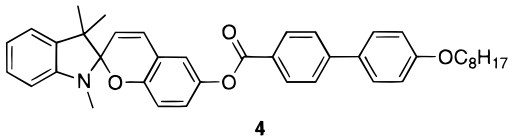
(10) Zaichenko, N. L.; Marevstev, V. S.; Arsenov, V. D.; Cherkashin, M. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1987**, *36*, 1518.

(11) Leiminer, A.; Stephan, B.; Mannschreck, A. *Mol. Cryst. Liq. Cryst.* **1994**, *246*, 215.

(12) Harié, G.; Samat, A.; Guglielmetti, R.; Van Parys, I.; Saeyens, W.; De Keukeleire, D.; Lorenz, K.; Mannschreck, A. *Helv. Chim. Acta* **1997**, *80*, 1122.

(13) Loncar-Tomaskovic, L.; Mintas, M.; Trotsch, T.; Mannschreck, A. *Enantiomer* **1997**, *2*, 459.

Recently, we reported the synthesis and characterization of a spiropyran derivative (**4**) which forms monotropic nematic, smectic A, and smectic C liquid crystal phases.[5a] Compound **4** was resolved by chiral phase HPLC but it could not be used as a liquid crystal chiroptical switch, or as a chiral dopant in liquid crystal hosts, due to its configurational instability. CD measurements have shown that the optical activity of **4** decays following



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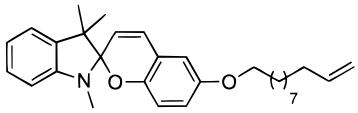

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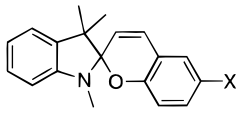


6a, X=NMe_2 **6g**, X=I
6b, X=OMe **6h**, X=Br
6c, X=Me **6i**, X=Cl
6d, X=*p*-$MeOC_6H_4$ **6j**, X=C(O)NHPh
6e, X=H **6k**, X=CO_2Ph
6f, X=C≡CC_4H_9 **6l**, X=CN

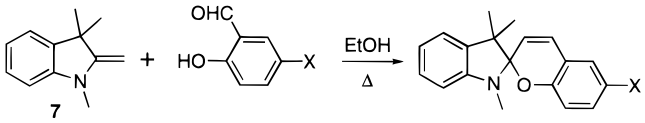
first-order kinetics with a half-life of 2.4 h at 60 °C in 90:10 hexanes/2-propanol, a solvent of relatively low polarity.[14] To increase the barrier to thermal racemization, we have introduced an alkenyloxy substituent at the 6-position of the indolinobenzospiropyran (**5**), which makes heterolytic ring opening less favorable by destabilizing a developing negative charge on the benzopyran oxygen. The terminal alkene also enables the addition of the spiropyran to a side-chain polysiloxane liquid crystal. Surprisingly, CD measurements have shown that **5** undergoes thermal racemization 10 times faster than **4** under the same conditions![14] To explain this unusual result, we have investigated the effect of substituents on the rate of thermal racemization of the indolinobenzospiropyrans **1** and **6a**−**l** using solvents that are less polar than those used in previous studies (vide supra).[10,11] In this paper, we report the measurements of rate constants for racemization (k_{rac}) of **1** and **6a**−**l** by CD spectropolarimetry in three different solvents and correlations of the k_{rac} values with Hammett σ_p and σ^- constants. These results strongly suggest that the thermal racemization of indolinobenzospiropyrans proceeds via competing polar and nonpolar mechanisms, and that the outcome of this competition is a function of solvent polarity.

Results

Synthesis and Resolution. Most of the spiropyrans used in the kinetics experiments were obtained by condensation of 2-methylene-1,3,3-trimethylindoline (**7**) with the corresponding 5-substituted salicylaldehyde, as shown in Scheme 3. The spiropyrans **6j** and **6k** were obtained from the corresponding carboxylic acid. The spiropyrans **1** and **6a**−**l** were resolved by

(14) A detailed investigation of the kinetics of racemization, including measurements of Arrhenius parameters in polar and nonpolar solvents, will be published elsewhere.

Scheme 3



semi-prep chiral phase HPLC. Baseline resolution was achieved using a Daicel Chiralcel OJ column with either 90:10 hexanes/ethanol or 90:10 hexanes/2-propanol as eluant. Each resolved enantiomer was characterized by CD spectropolarimetry. Resolved enantiomeric pairs gave CD spectra with the expected mirror image relationship and maximum ellipticities at wavelengths in the range of 241−255 nm.

Thermal Racemization. The thermal racemization of spiropyrans according to Scheme 2 is treated as a reversible first-order reaction starting from one enantiomer in optically active form. By applying a steady-state approximation, it can be shown that:

$$k_1 = k_{rac} \tag{1}$$

where k_1 is the rate constant for cleavage of the C(sp^3)−O bond and k_{rac} is the rate constant for racemization of the spiropyran.[12] Rate constants for racemization k_{rac} at 60 ± 0.1 °C were measured by CD spectropolarimetry in 90:10 hexanes/2-propanol, acetonitrile, and cyclohexane. For each spiropyran, the ellipticity (θ) of an enantiomerically enriched solution was measured at the wavelength of maximum ellipticity (λ_{CD}) every 5−20 s over a minimum of 3 half-lives and the k_{rac} value was derived from a plot of ln θ_t vs time according to eq 2, where θ_0 and θ_t are ellipticities at times $t = 0$ and $t \neq 0$. Three reproducible runs were performed in each solvent. The k_{rac} data are shown in Table 1 and the errors represent two standard deviations.

$$\ln \theta_t = -k_{rac}t + \ln \theta_0 \tag{2}$$

Throughout the course of each experiment, the spiropyran solution was kept in the cavity of the spectropolarimeter under constant exposure to the excitation beam. To rule out the contribution of a photochemical mechanism to spiropyran racemization in the cavity of the spectropolarimeter, the thermal racemization of **6a** in 90:10 hexanes/2-propanol was followed by measuring the ellipticity of the sample every 3 min and removing the sample from the path of the excitation beam between measurements. A plot of ln θ_t vs t gave a k_{rac} value of 1.0×10^{-3} s^{-1}, which is the same, within experimental error, as that obtained in the standard experiment, i.e., 0.93×10^{-3} s^{-1}. None of the spiropyrans used in this study appear to form any significant amount of colored *trans*-merocyanine that is detectable to the eye in the three solvents used (over the course of a kinetic run).

Free Energy Relationships. Rate constants for racemization of the spiropyrans **1** and **6a**−**l** were correlated initially to Hammett σ_p constants for substituents X.[15] In 90:10 hexanes/2-propanol, a plot of log k_{rac} vs σ_p does not give a linear correlation, as shown in Figure 1. Instead, it confirms our preliminary observations that both electron-donating and electron-withdrawing substituents increase the rate of racemization. The relatively symmetric V-shaped plot suggests that thermal racemization in 90:10 hexanes/2-propanol proceeds via two competing mechanisms, with one mechanism predominating when X is electron withdrawing and the other predominating when X is electron donating. In acetonitrile, a plot of log k_{rac} vs σ_p for eight spiropyrans gives a V-shaped correlation which is slanted toward electron-withdrawing substituents, as shown in Figure 2. In this solvent, the nitro-substituted spiropyran **1** racemized so rapidly that we were unable to obtain an accurate value of k_{rac}; the corresponding data point in Figure 2 represents an estimated lower limit. In contrast, a plot of log k_{rac} vs σ_p in cyclohexane (Figure 3) shows the opposite trend: electron-donating groups increase the rate of racemization to a much greater extent than electron-withdrawing groups. Some of the electron-withdrawing groups actually slow the rate of racemization relative to X = H. As a result, the V-shape correlation gives way to a moderately linear correlation with a negative slope. A comparative analysis of these data reveals that the increase in solvent polarity results in a increase in k_{rac} for all spiropyrans, and that the increase in k_{rac} is more substantial when X is electron withdrawing, as shown in Figure 4 for five representative examples.

Rate constants for racemization of spiropyrans with electron-withdrawing substituents were also correlated to σ^- constants. As shown in Figure 5, the plots of log k_{rac} vs σ^- in 90:10 hexanes/2-propanol and acetonitrile give very good linear correlations with positive slopes ($R^2 = 0.980$ and 0.977, respectively). However, in cyclohexane, the plot of log k_{rac} vs σ^- appears to be scattered, although a reasonably good linear correlation with negative slope can be found ($R^2 = 0.932$) if one ignores the data point for X = NO_2, as shown in Figure 6. These results are consistent with one mechanism predominating in 90:10 hexanes/2-propanol and acetonitrile and another mechanism predominating in cyclohexane except for spiropyran **1** which contains the strongest electron-withdrawing substituent.

Dependence of k_{rac} on Solvent Polarity. We evaluated the effect of solvent polarity on k_{rac} for three representative spiropyrans, **1**, **6a**, and **6e**, using a form of the Grunwald−Winstein equation (eq 3) where Y is the solvent ionizing power

$$\log k_{rac} = mY + c \tag{3}$$

and m is a measure of the dependence of k_{rac} on solvent polarity.[16] Rate constants k_{rac} were measured by CD spectropolarimetry at 30 ± 0.1 °C in acetonitrile/water mixtures and plotted versus the corresponding Y values.[17] The solvent mixtures ranged in proportion from 90:10 to 60:40 acetonitrile/water.

In the case of the unsubstituted spiropyran **6e**, a plot of log k_{rac} vs Y gave an excellent linear fit ($R^2 = 0.998$) with a slope m of 0.76, which indicates a relatively strong dependence of k_{rac} on the solvent polarity. A similar plot was obtained for the 6-dimethylaminospiropyran **6a** ($R^2 = 0.988$), although the slope m of 0.53 indicates a lesser dependence of k_{rac} on solvent polarity, as shown in Figure 7. The 6-nitrospiropyran **1**, as well as other electron-deficient spiropyrans such as **6k** and **6l**, racemized too rapidly in acetonitrile/water for any meaningful data to be acquired. The k_{rac} data for **6a** and **6e** in acetonitrile/water were also correlated to Reichardt's solvent parameter E_T, which gave linear fits of lesser quality ($R^2 = 0.958$ and 0.941) with slopes of 0.61 and 0.46, respectively, as shown in Figure 8. The E_T parameters were measured for each solvent mixture using Reichardt's dye (2,6-diphenyl-4-(2,4,6-triphenylpyridinio)-phenolate).[18]

(15) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(16) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700.

(17) Bentley, T. W.; Dau-Schmidt, J.-P.; Llewellyn, G.; Mayr, H. *J. Org. Chem.* **1992**, *57*, 2387.

(18) Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 98.

Table 1. Rate Constants k_{rac} for Thermal Racemization of Indolinobenzospiropyrans **1** and **6a-l** Measured in 90:10 Hexanes/Isopropanol, Acetonitrile and Cyclohexane at 60 °C

					$10^4\ k_{rac}\ (s^{-1})^a$		
compd	λ_{CD} (nm)[b]	X	σ_p[c]	σ^-[c]	90:10 hexanes/IPA	acetonitrile	cyclohexane
1	254	NO_2	0.78	1.27	7.9 ± 2.0	>50	0.62 ± 0.39
6a	251	NMe_2	−0.83		9.3 ± 2.0	19 ± 2	4.6 ± 0.9
6b	254	OMe	−0.27		7.2 ± 1.0	12 ± 3	3.5 ± 0.5
6c	242	Me	−0.17		1.4 ± 0.5	3.4 ± 0.7	0.77 ± 0.11
6d	253	*p*-$MeOC_6H_4$	−0.08		0.95 ± 0.07		
6e	241	H	0		0.63 ± 0.30	1.3 ± 0.04	0.23 ± 0.03
6f	249	$C{\equiv}CC_4H_9$	0.03	0.53[d]	1.0 ± 0.4	2.0 ± 0.1	0.54 ± 0.01
6g	255	I	0.18	0.27	0.7 ± 0.2		
6h	243	Br	0.23	0.25	0.52 ± 0.07	0.93 ± 0.03	1.2 ± 0.3
6i	242	Cl	0.23	0.19	0.56 ± 0.10		
6j	250	C(O)NHPh	0.41	0.70[e]	2.2 ± 0.7		
6k	250	CO_2Ph	0.44	0.75[f]	1.8 ± 0.4	9.0 ± 1.0	0.098 ± 0.029
6l	242	CN	0.66	1.00	3.3 ± 0.5	22 ± 2	0.068 ± 0.020

[a] Error is ±2 standard deviations. [b] Wavelength for CD measurements. [c] From ref 15. [d] Value for X = C≡CH used. [e] Value for X = $C(O)NMe_2$ used. [f] Value for X = CO_2Me used.

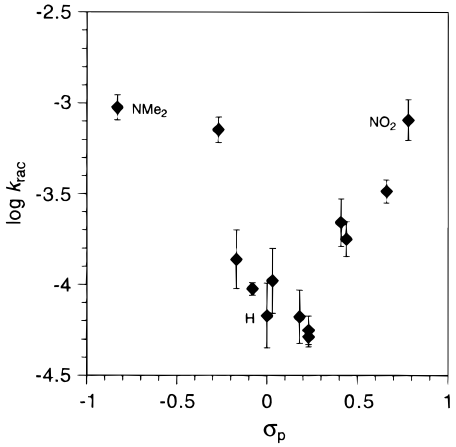


Figure 1. Plot of log k_{rac} vs σ_p for the thermal racemization of spiropyrans **1** and **6a**−**l** in 90:10 hexanes/2-propanol at 60 °C. Error bars represent ±2 standard deviations.

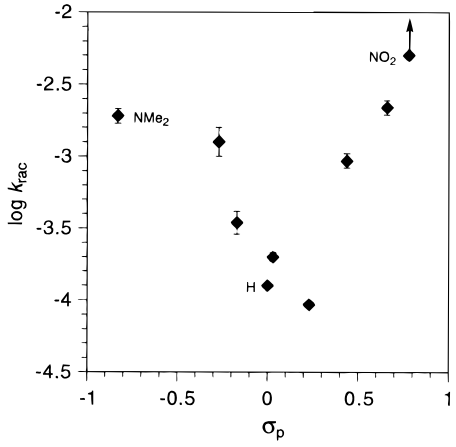


Figure 2. Plot of log k_{rac} vs σ_p for the thermal racemization of spiropyrans **1** and **6a**−**c**,**e**,**f**,**h**,**k**,**l** in acetonitrile at 60 °C. The data point for **1** (X = NO_2) is a lower limit estimate. Error bars represent ±2 standard deviations.

Discussion

Our study has revealed a remarkable contrast in the effect of solvent polarity on the rate of racemization as a function of substituents. Thus, the rate of racemization of spiropyrans with electron-donating substituents is much less sensitive to solvent polarity than that of spiropyrans with electron-withdrawing groups. In going from acetonitrile to cyclohexane, k_{rac} for **6a** (X = NMe_2) decreases only by a factor of 4 whereas k_{rac} for **6l** (X=CN) decreases by more than two orders or magnitude. These observations are consistent with the correlations of log k_{rac} with Grunwald−Winstein and Reichardt solvent parameters (Figures 7 and 8) and suggest that two mechanisms are operative in the thermal racemization of the spiropyrans. An examination of the

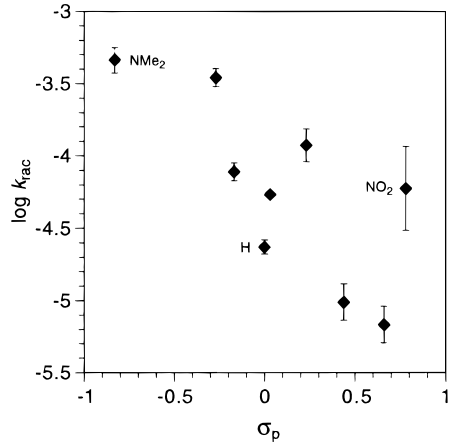


Figure 3. Plot of log k_{rac} vs σ_p for the thermal racemization of spiropyrans **1** and **6a**−**c**,**e**,**f**,**h**,**k**,**l** in cyclohexane at 60 °C. Error bars represent ±2 standard deviations.

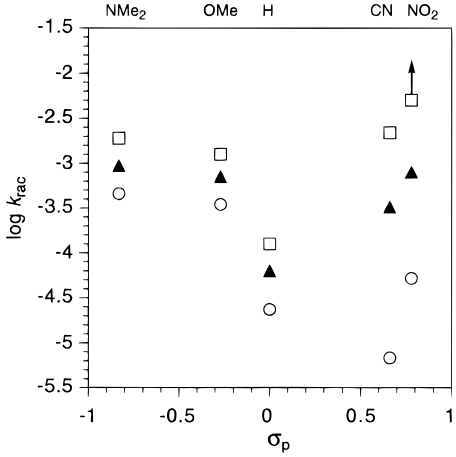


Figure 4. Plot of log k_{rac} vs σ_p for the thermal racemization of spiropyrans **1** and **6a**,**b**,**e**,**l** in 90:10 hexanes/2-propanol (triangles), acetonitrile (squares), and cyclohexane (circles) at 60 °C. The data point for **1** (X = NO_2) in acetonitrile is a lower limit estimate. The error bars are omitted for clarity.

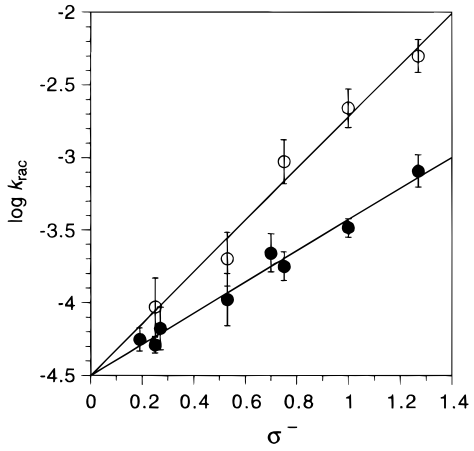


Figure 5. Plot of log k_{rac} vs σ^- for the thermal racemization of spiropyrans **1** and **6f**−**l** in 90:10 hexanes/2-propanol at 60 °C (filled circles) and spiropyrans **1** and **6f**,**h**,**k**,**l** in acetonitrile at 60 °C (open circles). Error bars represent ±2 standard deviations.

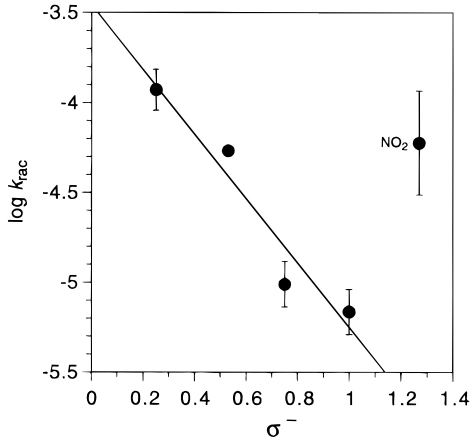


Figure 6. Plot of log k_{rac} vs σ^- for the thermal racemization of spiropyrans **1** and **6f**,**h**,**k**,**l** in cyclohexane at 60 °C. The data point for X = NO_2 is omitted in the least-squares fit. Error bars represent ±2 standard deviations.

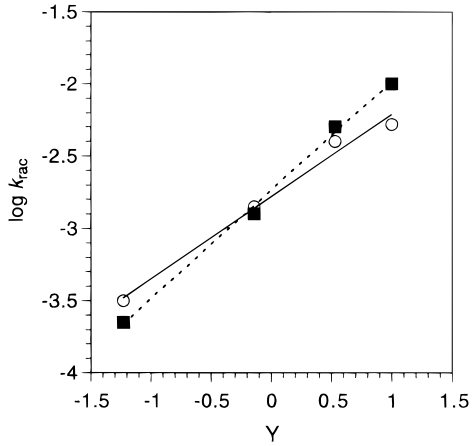


Figure 7. Plot of k_{rac} vs Grunwald−Winstein solvent ionizing power Y for the thermal racemization of spiropyrans **6a** (circles) and **6e** (squares) in acetonitrile/water mixtures at 30 °C. The error bars are omitted for clarity.

three log k_{rac} vs σ_p plots (Figures 1−3) in order of increasing solvent polarity, from cyclohexane to acetonitrile, also suggests that the latter has a strong influence on the outcome of a competition between the two mechanisms.

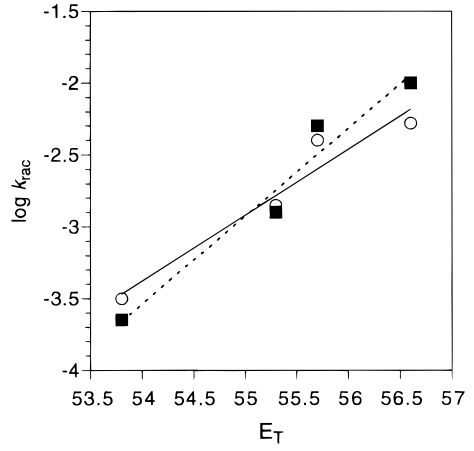


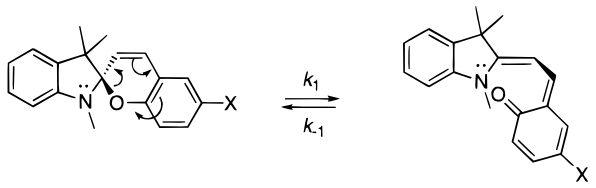
Figure 8. Plot of k_{rac} vs Reichardt's solvent parameter E_T for the thermal racemization of spiropyrans **6a** (circles) and **6e** (squares) in acetonitrile/water mixtures at 30 °C. The error bars are omitted for clarity.

The symmetrical V-shaped correlation obtained in 90:10 hexanes/2-propanol (Figure 1) suggests that the two mechanisms are evenly matched in this solvent and that the competition is controlled primarily by substituent effects. An increase in solvent polarity, from 90:10 hexanes/2-propanol to acetonitrile, causes a general increase in k_{rac}, which is most pronounced for spiropyrans with electron-withdrawing substituents (Figure 2), thus resulting in a distortion of the V-shape correlation toward a possible linear correlation with positive slope (i.e., domination of one mechanism regardless of substituent effects). Unfortunately, we were unable to further test this hypothesis due to the lack of transparency of more polar solvents in the 241−255 nm range, although we know from the work of Zaichenko et al. that a positive linear correlation was found in DMSO.[10] However, a further decrease in solvent polarity, from 90:10 hexanes/2-propanol to cyclohexane, produced the opposite effect: a general decrease in k_{rac}, which is most pronounced for spiropyrans with electron-withdrawing substituents (Figure 3), thus resulting in a distortion of the V-shape correlation toward a linear correlation with negative slope (i.e., domination of the other mechanism regardless of substituent effects). These results are consistent with a competition between the well-established polar mechanism shown in Scheme 2 and a "nonpolar" mechanism in which there is relatively little charge separation in the transition state.

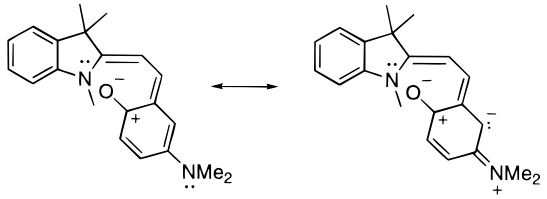
In the polar mechanism, ring opening proceeds via a transition state in which there is a significant amount of charge separation by virtue of anchimeric assistance from the indoline nitrogen. The polar transition state is stabilized by polar solvents and the developing negative charge on the benzopyran oxygen is stabilized by electron-withdrawing substituents at the 6-position. This stabilizing effect is described more explicitely by σ^- constants, as shown by the very good correlation found between log k_{rac} and σ^- in acetonitrile and 90:10 hexanes/2-propanol (Figure 5).

Under most circumstances reported thus far in the literature, i.e., polar solvents and electron-withdrawing substituents at the 6- and 8-positions, the polar mechanism appears to be the predominant, if not the exclusive pathway for thermal racemization of spiropyrans. However, under circumstances which disfavor charge separation in the transition state, i.e., nonpolar solvents and electron-donating substituents which destabilize a developing negative charge on the benzopyran oxygen, a nonpolar mechanism appears to be predominant. For this mechanism, we propose an electrocyclic ring opening to a

Scheme 4



Scheme 5



quinoid intermediate which does not involve formal participation of the indoline nitrogen, as shown in Scheme 4. The ring-opened quinoid intermediate can then undergo rapid conformational inversion, followed by ring closure to the other enantiomer. This electrocyclic ring-opening mechanism should proceed via a different transition state structure, with different conformational degrees of freedom, than in the polar mechanism even though the quinoid intermediate may be viewed as an extreme canonical form of the zwitterionic intermediate.

Interestingly, the rate of racemization of the electron-rich spiropyran **6a** ($X = NMe_2$) does show a moderate dependence on solvent polarity, which suggests that racemization by the "nonpolar" mechanism proceeds via a transition state with some degree of charge separation. The charge distribution in the transition state for electrocyclic ring opening of a spiropyran with an electron-donating substituent (i.e., $X = NMe_2$) may be modeled by the canonical forms shown in Scheme 5, in which the developing partial positive charge *para* to C-6 would be stabilized by an electron-donating substituent via a π-polarization effect; the latter is otherwise insulated from conjugative interaction with the *para* carbon.[19] This would be consistent with the negative slope of the log k_{rac} vs σ_p and σ^- plots obtained in cyclohexane. In these two plots, the rate constant for compound **1** ($X = NO_2$) does not fit the observed trend, which suggests that the polar mechanism still contributes to some extent to thermal racemization in cyclohexane when a very strong electron-withdrawing group is present. The V-shaped correlations obtained in the more polar solvents suggest that the nonpolar mechanism predominates when X is electron donating, but gives way to the polar mechanism when X is electron withdrawing. In highly polar solvents such as DMSO, the nonpolar mechanism appears to be completely suppressed in favor of the polar mechanism.

Summary

Indolinobenzospiropyrans are under investigation as potential liquid crystalline chiroptical switches based on the principle of photoresolution. One of the basic requirements of such materials is that they must be configurationally stable in the absence of light. Hence, rates of thermal racemization for a series of 6-substituted indolinobenzospiropyrans were measured by CD spectropolarimetry at 60 °C in three solvents of varying polarity. Results show that the 6-substituted spiropyrans **1** and **6a**−**l** undergo thermal racemization most rapidly in acetonitrile, with k_{rac} values ranging from 9.3×10^{-5} to $>5.0 \times 10^{-3}$ s^{-1}, and least rapidly in cyclohexane, with k_{rac} values ranging from 6.8×10^{-6} to 4.6×10^{-4} s^{-1}. Plots of log k_{rac} vs Hammett σ_p and σ^- constants suggest that thermal racemization of the spiropyrans proceed via two competing mechanisms: a polar mechanism involving heterolytic $C(sp^3)-O$ bond cleavage with anchimeric assistance by the indoline nitrogen, and a nonpolar electrocyclic ring-opening mechanism with no anchimeric assistance by the indoline nitrogen. The outcome of this competition appears to be strongly influenced by solvent polarity: plots of log k_{rac} vs σ_p and σ^- in cyclohexane give a near-linear correlation with negative slope, which is consistent with the nonpolar mechanism, and an increase in solvent polarity results in a shift toward a linear correlation with positive slope, which is consistent with the polar mechanism. Overall, these results suggest that 6-substituted indolinobenzospiropyrans are configurationally too labile, regardless of the nature of the substituent, to be useful as photoresolvable chiroptical switches.

Experimental Section

General. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained in deuterated chloroform, deuterated DMSO, or deuterated acetone on Bruker ACF-200 and Avance 300 spectrometers. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane. Low-resolution EI mass spectra were obtained using a Fisons VG Quattro triple quadrupole mass spectrometer; peaks are reported as *m*/*z* (percent intensity relative to base peak). High-resolution EI mass spectra were obtained by the University of Ottawa Regional Mass Spectrometry Centre. Melting points were measured using a Uni-Melt Thomas-Hoover melting point apparatus and are uncorrected. Semi-prep chiral HPLC resolutions were performed on a system consisting of a Waters 501 HPLC pump, a Supelguard C18 LC-Si guard column (2 cm × 4.0 mm i.d.), a semi-prep Daicel Chiracel OJ chiral stationary phase column (25 cm × 10 mm i.d.), and a D-Star DWW-10 variable-wavelength UV detector. Hexanes/ethanol (90:10) and hexanes/2-propanol (90:10) mixtures were used as eluant (3 mL/min). Circular dichroism (CD) spectra were recorded on a Jasco J-715 spectropolarimeter in hexanes/2-propanol (90:10), cyclohexane, acetonitrile, and acetonitrile/water mixtures. Temperature control for the kinetics measurements was achieved using a water-jacketed quartz cell (0.1 cm path length) and a NESLAB RTE-111 Bath/Circulator with microprocessor control.

Materials. All reagents and chemicals were obtained from commercial sources and used without further purification unless otherwise noted. Toluene was distilled over Na/benzophenone under nitrogen, and CH_2Cl_2 was distilled over P_2O_5 immediately prior to use. Hexanes for chiral HPLC resolutions was distilled over molecular sieves. 2-Methylene-1,3,3-trimethylindoline (**7**) was obtained from Aldrich. 5-(*N*,*N*-Dimethylamino)salicylaldehyde (**8**), 5-iodosalicylaldehyde (**9**), and 5-cyanosalicylaldehyde (**10**) were prepared according to literature procedures.[20−22] The spiropyrans **1**, **6b**,[23] **6c**,[24] **6e**, **6g**,[25] **6h**, **6i**, and 1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2-indoline]-6-carboxylic acid (**11**) were prepared according to the method of Keum et al. and shown to have the expected physical and spectral properties.[26] 6-(4-Methoxyphenyl)-1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2-indoline] (**6d**) was provided by Prof. S.-R. Keum. All spiropyrans were purified by recrystallization from either spectral grade hexane or acetonitrile after filtration through 0.45 μm PTFE syringe filters prior to resolution by chiral phase HPLC.

(19) Reynolds, W. F. *Prog. Phys. Org. Chem.* **1983**, *14*, 165.

(20) Ando, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2433.

(21) Pavia, M. R.; Cohen, M. P.; Dilley, G. J.; Dubuc, G. R.; Durgin, T. L.; Forman, F. W.; Hediger, M. E.; Milot, G.; Powers, T. S.; Sucholeiki, I.; Zhou, S.; Hangauer, D. *Bioorg. Med. Chem.* **1996**, *4*, 659.

(22) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 1751.

(23) Hosangadi, B. D.; Thakur, S. K. *Synthesis* **1997**, 1137.

(24) Hinnen, A.; Audic, C.; Gautron, R. *Bull. Chem. Soc. Fr.* **1968**, 2066.

(25) Cho, Y. J.; Rho, K. Y.; Keum, S. R.; Kim, S. H.; Yoon, C. M. *Synth. Commun.* **1999**, *29*, 2061.

(26) (a) Keum, S.-R.; Lee, K.-B.; Kazmaier, P. M.; Manderville, R.; Buncel, E. *Magn. Reson. Chem.* **1992**, *30*, 1128. (b) Keum, S.-R.; Hur, M.-S.; Kazmaier, P. M.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 1940.

Purification of Copper(I) Iodide. A mixture of copper(I) iodide (5.3 g), saturated KI (25 mL), and activated charcoal was stirred for 3 h, then filtered through Celite. Water was added to the filtrate to precipitate the CuI, which was collected by filtration and washed with water, ethanol, and ether (3 × 20 mL each). The purified CuI was dried under vacuum and stored in a desiccator in the dark.

6-(*N*,*N*-Dimethylamino)-1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2-indoline] (6a). A solution of **8** (35 mg, 0.21 mmol) and 2-methylene-1,3,3-trimethylindoline (**7**, 60 mg, 0.35 mmol) in EtOH (3 mL) was refluxed for 3 h. After cooling, the solution was concentrated and the solid residue purified by chromatography on silica gel (90:10 hexanes/EtOAc) to give 42 mg (63%) of **6a** as a pink solid: mp 105−108 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22−7.02 (m, 2H), 7.03 (d, 1H, J = 7.2 Hz), 6.48 (d, 1H, J = 6.8 Hz), 5.70 (d, 1H, J = 10.6 Hz), 2.92 (s, 6H), 2.69 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.4, 147.0, 145.2, 137.0, 129.8, 127.5, 121.5, 120.0, 118.9, 115.7, 115.3, 112.0, 106.7, 103.7, 51.6, 41.9, 30.0, 29.0, 25.9, 20.3; MS *m*/*z* 320 (M+, 29), 305 (9), 161 (67), 159 (100), 144 (49); HRMS calcd for $C_{21}H_{24}N_2O$ 320.1889, found 320.1907.

5-(1-Hexynyl)salicylaldehyde (12). This reaction wa carried out on a Schlenck line. A round-bottom flask containing **9** (1.01 g, 4.1 mmol), CuI (41 mg, 0.22 mmol), and $(Ph_3P)_2PdCl_2$ (0.168 g, 0.24 mmol) was evacuated and flushed with Ar (3×). Degassed toluene (5 mL) and diisopropylamine (5 mL) were added by syringe and stirred at room temperature. After 10 min, 1-hexyne (0.58 g, 7.1 mmol) was added dropwise by syringe and the mixture was stirred under Ar overnight. The mixture was diluted with toluene and washed with 2 M aqueous HCl (3×) and brine, dried ($MgSO_4$), and concentrated. The solid residue was purified by chromatography on silica gel (hexanes) to give 0.50 g (60%) of **12** as a pale yellow solid: mp 27−28 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.00 (s, 1H), 9.82 (s, 1H), 7.58 (d, 1H, J = 2.4 Hz), 7.51 (dd, 1H, J = 8.6, 2.0 Hz), 6.89 (d, 1H, J = 8.6 Hz), 2.38 (t, 2H, J = 6.8 Hz), 1.61−1.52 (m, 4H), 0.93 (t, 3H, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.1, 160.8, 139.9, 136.6, 120.4, 117.8, 116.1, 89.9, 78.7, 30.8, 22.0, 19.0, 13.6; MS *m*/*z* 202 (M^+, 34), 187 (26), 173 (19), 159 (100), 145 (53); HRMS (EI) calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0999.

6-(1-Hexynyl)-1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2-indoline] (6f). The procedure used for the preparation of **6a** was repeated using 112 mg (0.65 mmol) of **7** and 97 mg (0.48 mmol) of **12** to give **6f** as an oil that was resolved by chiral phase HPLC without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.03 (m, 4H), 6.84−6.76 (m, 2H), 6.59 (d,1H, 8.1 Hz), 6.50 (d, 1H, J = 7.8 Hz), 5.67 (d, 1H, J = 10.2 Hz), 2.69 (s, 3H), 2.36 (t, 2H, J = 6.9 Hz), 1.60−1.41 (m, 4H), 1.26 (s, 3H), 1.14 (s, 3H), 0.92 (t, 3H, J = 7.2 Hz); ^{13}C NMR-(75 MHz, $CDCl_3$) δ 154.0, 148.1, 136.6, 133.0, 129.8, 129.0, 127.6, 121.6, 119.9, 118.7, 115.5, 115.0, 106.8, 104.5, 88.5, 80.8, 51.8, 31.0, 28.9, 25.9, 22.0, 20.1, 19.1, 13.6; MS *m*/*z* 357 (M^+, 11), 159 (100), 144 (26); HRMS (EI) calcd for $C_{25}H_{27}NO$ 357.2093, found 357.2095.

1′,3′,3′-Trimethyl-6-(*N*-phenylcarboxamide)spiro[2*H*-1-benzopyran-2,2-indoline] (6j). A solution of **11** (0.102 g, 0.32 mmol), aniline (0.092 g, 1.0 mmol), DCC (0.078 g, 0.37 mmol), and DMAP (0.016 g, 0.13 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for several days. The reaction mixture was concentrated and eluted through a short silica gel column (90:10 hexanes/ethyl acetate). The product was redissolved in EtOAc, washed with 10% aqueous NaOH (2×) and water (2×), dried ($MgSO_4$), and concentrated to give 114 mg (90%) of **6j** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65−7.58 (m, 3H), 7.57−7.30 (m, 2H), 7.21−7.04 (m, 4H), 6.92−6.54 (m, 4H), 6.50 (d, 1H, J = 2.2 Hz), 5.76 (d, 1H, J = 10.4 Hz), 2.72 (s, 3H), 1.29 (s, 3H), 1.16 (s, 3H); MS *m*/*z* 396 (M^+, 19), 304 (73), 261 (16), 159 (100), 144 (59); HRMS calcd for $C_{26}H_{24}N_2O_2$ 396.1838, found 396.1833.

Phenyl 1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2-indoline]-6-carboxylate (6k). The procedure used for the preparation of **6j** was repeated with 112 mg of **11** (0.35 mmol) and 94 mg of phenol (1 mmol) to give 54 mg (39%) of **6k**: mp 141−142 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98−7.93 (m, 2H), 7.45−7.37 (m, 2H), 7.28−7.15 (m, 4H), 7.08 (d, 1H, J = 7.2 Hz), 6.96−6.86 (m, 2H), 6.78 (d, 1H, J = 8.2 Hz), 6.54 (d, 1H, J = 7.4 Hz), 5.77 (d, 1H, 10.4 Hz), 2.74 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.7, 159.1, 151.1, 147.9, 136.4, 132.3, 129.4, 129.3, 128.9, 127.7, 125.7, 121.8, 121.5, 121.3, 120.3, 119.5, 118.7, 115.2, 106.9, 105.6, 52.0, 28.9, 25.9, 20.0; MS *m*/*z* 397 (M^+, 8), 304 (100), 261 (22), 158 (38), 144 (75); HRMS calcd for $C_{26}H_{23}NO_3$ 397.1768, found 397.1678.

6-Cyano-1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2-indoline] (6l). The procedure used for the preparation of **6a** was repeated with 60 mg of **7** (0.35 mmol) and 36 mg of **10** (0.25 mmol) to give 55 mg (74%) of **6l** as a pink solid: mp 153−156 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.33 (m, 2H), 7.24−7.05 (m, 2H), 6.89−6.81 (m, 2H), 6.74 (d, 1H, J = 8.8 Hz), 6.53 (d, 1H, J = 7.8 Hz), 5.79 (d, 1H, J = 10 Hz), 2.71 (s, 3H), 1.30 (s, 3H), 1.12 (s, 3H); MS *m*/*z* 302 (M^+, 28), 287 (21), 272 (13), 159 (100), 143 (96); HRMS calcd for $C_{20}H_{18}N_2O$ 302.1419, found 302.1431.

Kinetics Measurements. All spiropyrans were resolved by semi-prep chiral phase HPLC with 90:10 hexanes/2-propanol as eluant, except for **1**, **6a**, **6c**, and **6e** which were resolved with 90:10 hexanes/ethanol as eluant. For kinetics measurements in 90:10 hexanes/2-propanol, solutions of resolved spiropyrans were collected directly from the HPLC and transferred to the thermostated CD cell. Sample concentrations were adjusted when necessary to give CD spectra of acceptable quality (HT voltage in the 250−400 range). For kinetics measurements in cyclohexane, acetonitrile, and acetonitrile/water, as well as in hexanes/2-propanol for **1**, **6a**, **6c**, and **6e**, solutions of resolved spiropyrans were collected from the HPLC and the solvent was removed in the dark by rotary evaporation at room temperature. The resolved samples were kept under high vacuum for 24 h and redissolved in the appropriate solvent(s). Rate constants of thermal racemization (k_{rac}) were measured in 90:10 hexanes/2-propanol, cyclohexane, and acetonitrile at 60 ± 0.1 °C, and in acetonitrile/water mixtures at 30 ± 0.1 °C by CD spectropolarimetry. Solutions of optically active spiropyrans were allowed to thermally equilibrate for ca. 5 min in the thermostated cell before the start of data collection. The spectropolarimeter was programmed to record the ellipticity (θ) of each solution at the wavelength of maximum ellipticity (see Table 1) every 5 to 20 s, depending on the rate of racemization, over at least 3 half-lives. Three separate runs were carried out for each spiropyran. Rate constants k_{rac} were obtained from the slope of ln θ vs time plots.

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