# Unexpected Regioselectivity in the Sulfonation of Leuco Xanthene Dyes

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In single- and multiphase aqueous chemical systems it is often necessary to impart water solubility to an organic substrate to optimize its performance. Sulfonation represents one of the most common means of enhancing water solubility, and one notable example of subsequent optimized performance is found in sulfonated polyaniline.[1] In addition, sulfonation can provide the opportunity to append other useful functionalities on an organic substrate, or it may impart other desirable properties to the substrate of interest.[2] In general, the regiochemistry of sulfonation is subject to kinetic or thermodynamic control, depending on reaction conditions.[3] However, in polycyclic aromatic substrates the regiochemistry of sulfonation is often unclear, and mixtures of regioisomers are sometimes obtained.[4] Thus, it is important to develop an understanding of the factors responsible for controlling regioselectivity in these reactions.

An interesting case in point is provided by sulfonation of xanthene-derived base-bleachable dyes such as **1a**, which are useful for color correction in color instant integral film products (Scheme 1).[5]

Dye **1a** acts as a red light filter during the neutral conditions of exposure and then deblocks under the basic processing conditions to give colorless **2a**. To maximize the performance of **1a** in Polaroid's photographic system it was found necessary to use the bis-sulfonated analog **1b** ($\lambda_{max}$ = 662 nm, $\epsilon$ = 88 000).[6] However, the exact position of the sulfonates on **1b** was never clearly defined,[7] and thus we set out to determine the regiochemistry.

The sulfonation reaction is carried out on a leuco precursor, as shown in Scheme 2. At the outset it would appear that there are four pairs of activated positions on **3a-c**: 2/7 and 4/5 on the xanthene and the 5′/5″ and 7′/7″ positions on the indolines.[8] Amine substituents are sometimes known to give *meta*-direction under acidic conditions, presumably due to the intermediacy of the ammonium salt. Thus, substitution at the 6′/6″ and 4′/4″ positions on the indolines remained a possibility.[9] In any event the chance of obtaining a mixture of products would seem high. However, it was found by NMR and HPLC that a single symmetric bis-sulfonate is formed in each case (**4a-c**).

COSY-$^1$H NMR analysis of **3b**, **3c**, **4b**, and **4c** allows complete assignment of the corresponding 1-D spectra. Upon sulfonation the three-spin xanthene spin system [H-1/8, H-2/7, H-4/5] remains intact, and the four-spin indoline aromatic spin system becomes a three-spin system, appearing to lose H-5′/5″. Thus, it is clear that sulfonation does not occur on the xanthene, but on the indolines. Observation of long-range coupling between H-2′/2″ and an aromatic "singlet" in the indoline spin system of **4c** (assigned as H-4′/4″) confirms the assignment of sulfonation at 5′/5″. However, to further verify the NMR assignment, independent unambiguous synthesis of the 5′/5″ and 6′/6″ isomers was undertaken.

Regioselective methods for the synthesis of 5-, 6-, and 7-sulfonylindolines have been developed and unequivocally established by X-ray crystallography.[10] Thus, dimethylsulfamoyl indolines **5** and **6** were synthesized (Scheme 3). *N*-Formylindoline undergoes sulfonation at the *para*-(5)-position; indoline itself is protonated under the reaction conditions and consequently gives the *meta*-(6)-isomer. Indolines **5** and **6** were then condensed with dichlorosulfofluorescein **7** and transformed further to yield **8** and **9** (Scheme 4). Leuco bis-sulfonate **4c** was then converted to bis-sulfonyl chloride **10** and treated with excess dimethylamine to yield a tris-sulfonamide completely identical to **8** by $^1$H/$^{13}$C NMR and IR, thus confirming the prior NMR assignment of sulfonation at 5′/5″.

It is important to note that the high yield obtained from the sulfonation reaction of **3a-c** (97% isolated yield for **4c**) indicates that the regioselectivity is quite high. With the exception of a small amount of deacylated material (3-8%), no other products are detectable by HPLC or $^1$H NMR in samples of the isolated bis-sulfonates. It is known that in general, sulfonation of aromatic substrates is reversible only under strong acid catalysis at elevated temperatures (>100 °C).[11] Since the present sulfonation reaction is carried out below 30 °C, kinetic factors are likely responsible for the observed selectivity.

The overwhelming preference for sulfonation on the indolines is unexpected, in that the xanthene would appear to be the most electron-rich ring system. Preliminary AM1

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(1) Yue, J.; Wang, Z. H.; Cromack, K. R.; Epstein, A. J.; MacDiarmid, A. G. *J. Am. Chem. Soc.* **1991**, *113*, 2665.

(2) (a) Sulfonated calixeranes: Shinkai, S.; Kawabata, H.; Arimura, T.; Matsuda, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1073. (b) O-Sulfonated cyclodextrins: Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030. (c) Sulfonated tetraphenylporphyrin: Panicucci, R.; Bruice, T. C. *J. Am. Chem. Soc.* **1990**, *112*, 6063. (d) Sulfonated phthalocyanines: Berezin, B. D.; Vopian, V. G. (translator) *Coordination Compounds of Porphyrins and Phthalocyanines*; John Wiley & Sons: New York, 1981; pp 20-21.

(3) (a) Chuchani, G. In *The Chemistry of the Amino Group*; Patai, S., Ed.; Interscience: New York, 1968; pp 250-265. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; J. Wiley & Sons: New York, 1985; pp 473-475.

(4) (a) See ref 1 above. (b) See ref 2c above. (c) See ref 2d above. (d) Gilbert, E. E. *Sulfonation and Related Reactions*; Robert E. Krieger Publishing Co.: Huntington, NY, 1977; p 91.

(5) (a) Foley, J. W.; Locatell, L. Jr.; Zepp, C. M. U. S. Patent 4 258 118, March 24, 1981. (b) Carlier, P. R.; Filosa, M. P.; Lockshin, M. P. U. S. Patent 5 187 282, Feb 16, 1993. (c) Carlier, P. R.; Filosa, M. P.; Lockshin, M. P. U. S. Patent 5 264 322, Nov 23, 1993.

(6) (a) Cournoyer, R. L.; Foley, J. W. U. S. Patent 4 258 119, March 24, 1981. (b) Cournoyer, R. L.; Foley, J. W. U. S. Patent 4 290 950, Sept 22, 1981.

(7) On the basis of $^{13}$C NMR the original investigators tentatively proposed sulfonation at the 2 and 7 positions (ref 6). Upon reexamination of this work, we decided the original structural assignment was inconclusive.

(8) Substitution between two *meta* situated *o,p*-directing groups (i.e., at 4/5) is sterically disfavored (ref 3b, p 459). Electrophilic substition of indolines normally occurs at the 5 or 6 position, depending on the nitrogen substituent (*vide infra*) However, at the outset we cannot absolutely rule out substitution at 4/5 on the xanthene or substitution at 7′/7″ on the indolines.

(9) Inspection of molecular models suggests that the aryl sulfonamide ring of **3a-c** should effectively block substitution at the 1/8 position.

(10) (a)Borror, A. L.; Chinoporos, E.; Filosa, M. P.; Herchen, S. R.; Petersen, C. P.; Stern, C. A.; Onan, K. D. *J. Org. Chem.* **1988**, *53*, 2047. (b) Locatell, L., Jr.; Zepp, C. M.; Cieciuch, R. F. U. S. Patent 4 405 788, Sept 20, 1983.

(11) Room-temperature desulfonation of aryl sulfonates occurs only in cases of extreme steric hindrance, such as when two groups are present ortho to the sulfonate (ref 4d, p 431).

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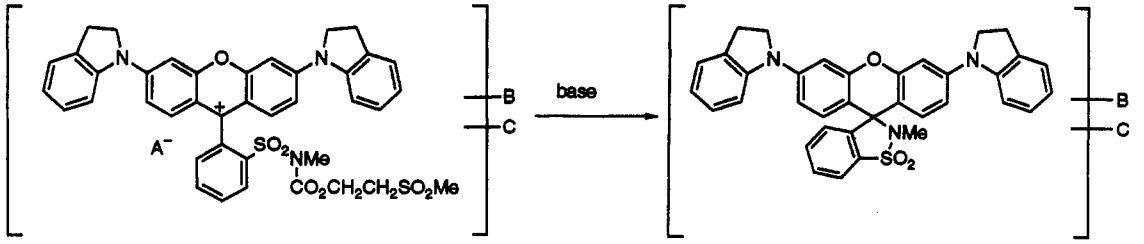
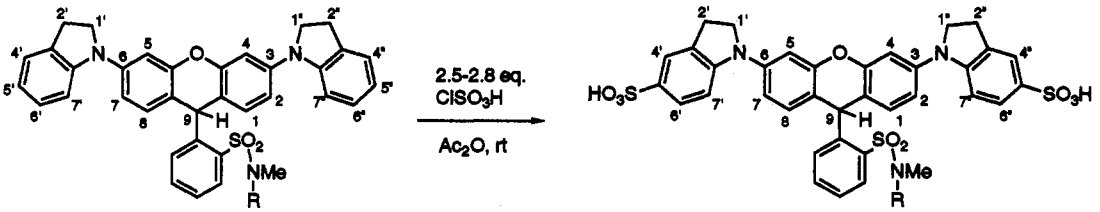
**Scheme 1**




| | A⁻ | B | C |
|---|---|---|---|
| 1a | $Br^-$ | H | H |
| 1b | — | $SO_3H$ | $SO_3^-$ |

| | B | C |
|---|---|---|
| 2a | H | H |
| 2b | $SO_3^-$ | $SO_3^-$ |

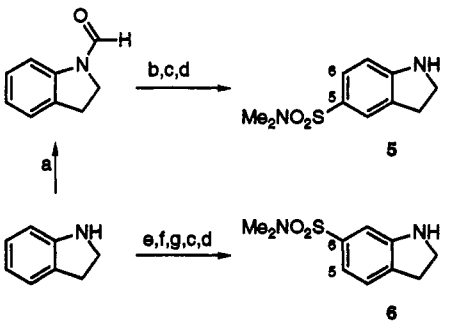
**Scheme 2**




**3a:** R = $-CO_2CH_2CH_2SO_2Me$
**3b:** R = $-CO(p\text{-}ClC_6H_4)$
**3c:** R = -Ac

**4a** (86%)
**4b** (91%)
**4c** (97%)

**Scheme 3**[a]




[a] Key: (a) $HCO_2H$; (b) $ClSO_3H$; (c) $Me_2NH(aq)/CH_2Cl_2$; (d) HCl(g); (e) $H_2SO_4$, 27–33% $SO_3$; (f) $Ac_2O$, AcOH; (g) $POCl_3$.

calculations[12] on **3c** confirm that on the basis of both atomic charges and HOMO atomic orbital coefficients, electrophilic attack at 2/7 should be very competitive with attack at 5′/5″.[13] Therefore, the observed preference for sulfonation at 5′/5″ must be the result of increased steric hindrance on approach to the 2/7 positions on the xanthene.

Given the very acidic reaction conditions, it is also somewhat suprising that the indoline nitrogen in **3a–c** does not act a *meta*-director, as in the case of indoline itself. The regiochemistry of sulfonation of N-alkyl/aryl-substituted indolines has not been extensively studied.[14] The *para*-direction observed in the present case is likely due to the extreme nonbasicity of diarylamines.[15] For example, diphenylamine itself has a $pK_B$ of only 0.79, vs 4.85 for *N*-methylaniline.[16] This extremely low basicity, coupled with the deactivativing effect of the protonation, presumably causes the predominant reaction pathway to be sulfonation on unprotonated **3a–c**, leading to the 5′/5″-regioisomer.[17] Thus, in the present case sulfonation regiochemistry is apparently controlled by a combination of electronic and steric factors.

## Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. The $^1H$ NMR and $^{13}C$ NMR spectra were recorded on 300- and 400-MHz spectrometers. $^1H$ NMR signal multiplicities are given as apparent multiplicities from 1-D experiments. Mass spectra were recorded on a double-focusing

(12) AM1 calculations performed on a Silicon Graphics Personal Iris 4D/35 using Spartan 2.0.

(13) In the minimum energy conformation of **3c** the indoline rings are skewed significantly out of plane with the xanthene; this skewing appears to be the cause of a small $2p_z$ atomic orbital coefficient in the HOMO at 4/5. Thus, we can rationalize the lack of sulfonation at 4/5 on frontier molecular orbital grounds.

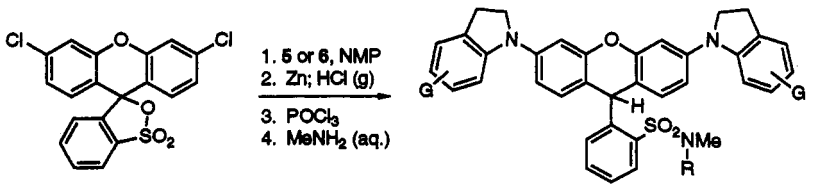
(14) To the best of our knowledge there are no reports in the literature of the sulfonation of an *N*-arylindoline. Diphenylamine is reported to be sulfonated in the *para* position (Merz, V. *Chem. Ber.* **1873**, *6*,1512; Gnehm, R. *Z. Ang.* **1899**, *12*, 1027, 1051). At high temperatures, the sulfonation of methyldiphenylamine is also reported to occur in the *para* position (Wieland, H. *Chem. Ber.* **1919**, *52*, 890; Gibson, C. *J. Chem. Soc.* **1923**, *123*, 835–838). However, in neither case is proof of the regiochemistry given. More recently, the sulfonation of β-carbolines has been reported to occur *para* to nitrogen (Guzman, M. C. C. et al. *Can. J. Chem.* **1989**, *67*, 720–726). However, it should be noted that in addition to the amino group, indolines also possess an alkyl directing group. Therefore, the relevance of these examples to the sulfonation of **3a–c** is not clear.

(15) "In acid (which is the most common medium for electrophilic substitutions) amino groups may direct *meta*. However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, *ortho, para* direction is often found even under acidic conditions." ref 3b, p 455). See also ref 4d, pp 62–80.

(16) See ref 3a, pp 188–189.

(17) $ClSO_3H$ is an extremely strong acid and could be estimated to have a $pK_A$ of between −3 and −5.6, based on values in water for $H_2SO_4$ and $FSO_3H$ (King, J. F. In *The Chemistry of Sulphonic Acids, Esters and their Derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1991; p 256). So, in actuality, the majority of **3a–c** would be at least monoprotonated under these conditions. However, sulfonation on monoprotonated **3a–c** would occur on the more reactive unprotonated indoline. So, whether the reaction proceeds via a very small amount of unprotonated material or through a relatively much larger amount of monoprotonated material the result is the same.

**Scheme 4**

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8: G = 5-$SO_2NMe_2$, R = H
9: G = 6-$SO_2NMe_2$, R = H
[10: G = 5-$SO_2Cl$, R = Ac]


mass spectrometer using both EI and FAB techniques. Microanalyses were performed by Galbraith Laboratories (USA) and Medac Ltd (Uxbridge, UK). 2-[3,6-Bis(indolino)xanthen-9-yl]-*N*-methylbenzenesulfonamide[18] and 3,6-dichlorosulfofluorescein[19] were prepared as described previously.

***N*-(p-Chlorobenzoyl)-2-[3,6-bis(indolino)xanthen-9-yl]-*N*-methylbenzenesulfonamide (3b).** To a solution of 2-[3,6-bis-(indolino)xanthen-9-yl]-*N*-methyl)benzenesulfonamide (20.0 g, 34.1 mmol) in dry THF (200 mL) under a nitrogen atmosphere was added potassium *tert*-butoxide (1M in THF, 41 mL, 41 mmol) dropwise over 10 min. After the mixture was stirred for 30 min, a solution of *p*-chlorobenzoyl chloride (9.0 g, 29.1 mmol) in THF (10 mL) was added. After the solution was stirred overnight, the product was collected by filtration, washed with THF, and air dried, affording 25.7 g (95%) of a pale cyan solid. The product crystallizes with 1 molar equiv of associated THF. An analytically pure sample was prepared by flash chromatography (70/30/1 $CH_2Cl_2$/hexanes/$CH_3OH$). Mp: >250 °C. $^1$H-NMR ($CDCl_3$): $\delta$ 8.00 (1H, d, $J$ = 8 Hz), 7.49 (1H, t, $J$ = 8 Hz), 7.41 (2H, d, $J$ = 9 Hz), 7.34 (2H, d, $J$ = 9 Hz), 7.32 (1H, t, $J$ = 8 Hz), 7.17 (4H, two overlapping doublets, $J$ = 8 Hz), 7.09 (2H, t, $J$ = 8.1 Hz), 6.97 (2H, d, $J$ = 2 Hz), 6.85 (2H, d, $J$ = 9 Hz), 6.80 (2H, dd, $J$ = 9, 2 Hz), 6.77 (2H, t, $J$ = 8 Hz), 6.02 (1H, s), 3.94 (4H, t, $J$ = 8 Hz), 3.49 (3H, s), 3.13 (4H, t, $J$ = 8 Hz). THF resonances omitted. $^{13}$C-NMR ($CDCl_3$): $\delta$ 170.32, 151.45, 147.27, 146.32, 144.07, 138.12, 137.06, 134.60, 133.68, 132.66, 131.40, 130.38, 129.83, 129.76, 128.65, 127.14, 126.65, 125.11, 119.30, 115.73, 112.81, 108.66, 104.33, 51.92, 37.67, 34.92, 28.07. THF resonances omitted. MS (FAB$^+$): 724 (M + 1). IR: 1695, 1340 cm$^{-1}$. Anal. Calcd for $C_{43}H_{34}ClN_3O_4S$: C, 71.31; H, 4.73; N, 5.80. Found: C, 71.29; H, 4.80; N, 5.69.

***N*-Acetyl-2-[3,6-bis(indolino)xanthen-9-yl]-*N*-methylbenzenesulfonamide (3c).** The reaction was performed as for **3b**. To a solution of 2-[3,6-bis(indolino)xanthen-9-yl]-*N*-methylbenzenesulfonamide (25.3 g, 43.2 mmol)in dry THF (250 mL) was added potassium *tert*-butoxide (1 M in THF, 52 mL, 52 mmol) followed by a solution of acetyl chloride (4.6 mL, 5.1 g, 64.8 mmol) in THF (20 mL). After the solution was stirred for 90 min, the product was collected by filtration, washed with THF, and air dried, affording 26.6 g (98%) of a pale cyan solid. An analytically pure sample was prepared by flash chromatography (70/30/1 $CH_2Cl_2$/hexanes/$CH_3OH$). Mp: >250 °C. $^1$H-NMR ($CDCl_3$): $\delta$ 7.83 (1H, d, $J$ = 8 Hz), 7.49 (1H, t, $J$ = 7 Hz), 7.344 (2H, t, $J$ = 7 Hz), 7.34 (1H, t, $J$ = 8Hz), 7.21 (2H, d, $J$ = 7 Hz), 7.17 (1H, d, $J$ = 7 Hz), 7.09 (2H, t, $J$ = 7 Hz), 6.97 (2H, d, $J$ = 2 Hz), 6.96 (2H, d, $J$ = 8 Hz), 6.86 (2H, dd, $J$ = 8, 2 Hz), 6.77 (2H, t, $J$ = 7 Hz), 6.03 (1H, s), 3.96 (4H, t, $J$ = 9Hz), 3.44 (3H, s), 3.12 (4H, t, $J$ = 9 Hz), 2.42 (3H, s). $^{13}$C-NMR ($CDCl_3$): $\delta$ 170.84, 151.32, 147.72, 146.33, 144.08, 137.06, 134.41, 134.02, 131.35, 130.18, 127.64, 127.09, 126.63, 125.06, 119.25, 115.70, 112.90, 108.68, 104.43, 51.91, 37.63, 33.20, 28.03, 25.32. MS (FAB$^+$): 627 (M). IR: 1710, 1340 cm$^{-1}$. A sample determined by $^1$H NMR to have 0.2 equiv incorporated $CH_2Cl_2$ was analyzed. Anal. Calcd for $C_{38}H_{33}N_3O_4S$·0.2 equiv of $CH_2Cl_2$: C, 71.16; H, 5.22; N, 6.52. Found: C, 71.02; H, 5.27; N, 6.31.

(18) See ref 5a.
(19) Cournoyer, R. L.; Foley, J. W. U. S. Patent 4 307 017, Dec 21, 1981.

***N*-(*p*-Chlorobenzoyl)-2-[3,6-bis(5-sulfoindolino)xanthen-9-yl]-*N*-methylbenzenesulfonamide (4b).** *p*-Chlorobenzoyl leuco dye **3b** (5.08 g, 6.38 mmol) was suspended in acetic anhydride (35 mL). A solution of chlorosulfonic acid (1.2 mL, 2.1 g, 17.9 mmol) in $CH_2Cl_2$ (2 mL) was added over 2 min, giving a dark blue slurry. After being stirred overnight, the reaction mixture had become a pale cyan pasty solid. The solid was suspended in $Et_2O$, collected by filtration, washed repeatedly with $Et_2O$, and air dried, affording 5.48 g (91%) of a light gray solid. The product crystallizes with 1 molar equiv of acetic acid. Mp: >250 °C. $^1$H-NMR (DMSO-$d_6$): $\delta$ 8.06 (1H, d, $J$ = 8 Hz), 7.65 (2H, d, $J$ = 9 Hz), 7.62 (1H, t, $J$ = 8), 7.57 (2H, d, $J$ = 9 Hz), 7.46 (1H, t, $J$ = 8 Hz), 7.39 (2H, s), 7.34 (2H, d, $J$ = 8 Hz), 7.19 (1H, d, $J$ = 8 Hz), 7.03 (2H, d, $J$ = 8 Hz), 6.96 (2H, broad s), 6.94 (2H, dd, $J$ = 9, 3 Hz), 6.87 (2H, d, $J$ = 9 Hz), 6.13 (1H, s), 3.98 (4H, t, $J$ = 9 Hz), 3.49 (3H, s), 3.10 (4H, t, $J$ = 9 Hz). Acetic acid resonance omitted. $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 169.81, 150.64, 146.54, 146.28, 143.18, 138.09, 137.16, 136.75, 134.66, 133.20, 132.69, 131.05, 130.22, 130.11, 128.60, 128.57, 127.25, 125.13, 122.72, 115.58, 112.92, 106.78, 104.03, 51.71, 37.00, 35.74, 27.03. Acetic acid resonances omitted. MS (FAB$^+$): 922 (M + K$^+$). IR: 3440, 1690, 1175 cm$^{-1}$.

***N*-Acetyl-2-[3,6-bis(5-sulfoindolino)xanthen-9-yl]-*N*-methylbenzenesulfonamide (4c).** Reaction was performed as above for **4b**, using acetyl leuco dye **3c** (21.7g, 34.5 mmol), acetic anhydride (210 mL), chlorosulfonic acid (6.6 mL, 11.6 g, 100.3 mmol), and 10 mL of $CH_2Cl_2$. Yield: 26.4 g (97%) of a pale cyan powder. Mp: >250 °C. $^1$H-NMR (DMSO-$d_6$): $\delta$ 7.94 (1H, d, $J$ = 8 Hz), 7.60 (1H, t, $J$ = 8 Hz), 7.45 (1H, t, $J$ = 8 Hz), 7.42 (2H, broad s), 7.36 (2H, d, $J$ = 9 Hz), 7.19 (1H, d, $J$ = 8 Hz), 7.09 (2H, d, $J$ = 9 Hz), 7.01 (2H, dd, $J$ = 8, 2 Hz), 7.00 (2H, broad s), 6.93 (2H, d, $J$ = 8 Hz), 6.06 (1H, s), 3.99 (4H, t, $J$ = 9 Hz), 3.47 (3H, s), 3.10 (4H, t, $J$ = 9 Hz), 2.36 (3H, s). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 171.23, 150.65, 146.65, 146.21, 143.28, 138.46, 137.30, 134.51, 133.10, 131.01, 130.12, 128.38, 127.12, 125.14, 122.75, 115.56, 113.04, 106.87, 104.06, 51.75, 36.48, 33.32, 27.08, 24.67. IR: 3400, 1705, 1160 cm$^{-1}$. HRMS (FAB$^-$): calcd for $C_{38}H_{32}N_3O_{10}S_3$: 786.1250, found 786.1243.

***N*-Formylindoline.** Indoline (145 g, 1.22 mol) and formic acid (90%, 92 g, 2.00 mol) were combined in toluene (500 mL) and heated at reflux with removal of water *via* a Dean-Stark apparatus. After 6 h the reaction was cooled, washed with water, and concentrated. Trituration with diethyl ether/hexanes afforded an off-white solid which was washed with hexanes and air dried. Yield: 158 g (88%). Mp: 62–63 °C (lit.[20] mp 62–63 °C). $^1$H-NMR ($CDCl_3$) due to hindered rotation of the formyl group the spectrum consists of a mixture of endo[21] (denoted by *) and exo isomers in a 4.3:1 ratio: $\delta$ 8.90* 8.58 (1H, s), 4.08 4.03* (2H, m), 3.19, 3.11* (2H, m). $^{13}$C-NMR ($CDCl_3$): $\delta$ 159.34, 157.53*, 141.21, 141.01*, 132.08, 131.89*, 127.51*, 127.46, 126.01*, 124.85, 124.50, 124.19*, 116.50, 109.38*, 46.90, 44.58*, 27.69, 27.11*. MS (EI$^+$): 148 (M + 1). IR: 3240, 1660, 1370, 1340, 1270 cm$^{-1}$.

(20) Shaw, J. T.; Tyson, F. T. *J. Am. Chem. Soc.* **1956**, *78*, 2538.
(21) The use of the terminology "endo" and "exo" for the rotational isomers of acylated indolines is explained in ref 10a. See also, Jones, R. A. Y.; Katritsky, A. R.; Shapiro, B. B. *Tetrahedron* **1970**, *26*, 721.

***N*-Formyl-5-(chlorosulfonyl)indoline.**[22] *N*-formylindoline (88.2 g, 0.6 mol) was added in portions over 30 min to mechanically-stirred chlorosulfonic acid (348 g, 3.0 mol) at 0 °C. Upon completion of the addition the solution was heated on a steam bath for 15 min, until gas evolution ceased. The reaction solution was poured slowly into ice (3 L). [Caution: a violent and exothermic reaction ensues.] After the solution was stirred for 1 h the white slurry was filtered, washed with water (3 × 500 mL), and dried in vacuo at 60 °C. Yield: 123.5 g (83%). Mp: 132 °C. $^1$H-NMR ($CDCl_3$) due to hindered rotation of the formyl group the spectrum consists of a mixture of endo (denoted by *) and exo isomers in a 2.4:1 ratio: δ 9.04* 8.58 (1H, s), 4.27 4.17* (2H, m), 3.32 3.25* (2H, m). $^{13}$C-NMR ($CDCl_3$): δ 160.20, 157.84*, 147.31*, 139.28*, 133.85*, 128.39*, 128.35, 125.19*, 123.90, 116.46, 109.38*, 47.39, 45.52*, 27.30, 26.65*. MS (EI$^+$): 245 (m). IR: 1680, 1360, 1340, 1310, 1280, 1180 cm$^{-1}$.

***N*-Formyl-5-(dimethylsulfamoyl)indoline.** *N*-Formylindoline-5-sulfonyl chloride (17.22 g, 0.07 mol) was dissolved in $CH_2Cl_2$ (100 mL), and a solution of 40% aqueous dimethylamine (9.0 g solution, 0.077 mol) was slowly added. The reaction was complete after 15 min. The organic solution was washed with water (3 × 100 mL), dried ($Na_2SO_4$), filtered, and evaporated. Yield: 14.5 g (81%). Mp: 165–166 °C. $^1$H-NMR ($CDCl_3$) due to hindered rotation of the formyl group the spectrum consists of a mixture of endo (denoted by *) and exo isomers in a 1.6:1 ratio: δ 8.99* 8.55 (1H, s), 4.22 4.13* (2H, m), 3.27 3.23* (2H, m), 2.69* 2.68 (6H, s). $^{13}$C-NMR ($CDCl_3$): δ 159.90, 157.73*, 145.09*, 133.10*, 130.91*, 128.43*, 128.36, 125.69*, 124.49, 116.31, 109.20*, 47.26, 45.24*, 37.96*, 27.46, 26.84*. MS (EI$^+$): 255 (M + 1). IR: 1680, 1370, 1330, 1280, 1190, 1150 cm$^{-1}$.

**5-(Dimethylsulfamoyl)indoline (5).** *N*-Formyl-5-(dimethylsulfamoyl)indoline (10.16 g, 0.04 mol) was stirred in $CH_3OH$ (100 mL) and purged with HCl gas for 3 min. After the solution was stirred at room temperature for 16 h, the solvents were evaporated. The resulting solid was dissolved in water (150 mL) and ethyl acetate (150 mL). Potassium bicarbonate was added to neutralize the reaction, and the organic phase was separated, washed with water (100 mL), dried ($Na_2SO_4$), filtered, and then evaporated. Yield: 7.55 g (83%) of white solid. Mp: 113.5–114 °C. $^1$H-NMR ($CDCl_3$): δ 7.38 (1H, s), 7.34 (1H, d, $J$ = 10 Hz), 6.52 (1H, d, $J$ = 10 Hz), 4.1 (1H, br m), 3.59 (2H, t, $J$ = 10 Hz), 2.99 (2H, t, $J$ = 10 Hz), 2.58 (6H, s). $^{13}$C-NMR (DMSO-$d_6$): δ 156.52, 129.10, 128.87, 123.78, 120.13, 106.20, 46.27, 37.70, 28.16. MS (EI$^+$): found 226 (M). IR: 3380, 1610, 1320, 1270, 1170 cm$^{-1}$. Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38; S, 14.17. Found: C, 53.24; H, 6.32; N, 12.27; S, 14.78.

***N*-Acetylindoline-6-sulfonic Acid–Pyridine Adduct.** Indoline-6-sulfonic acid[23] (19.92 g, 0.10 mol) was slurried in acetic acid (100 mL). Acetic anhydride (10 mL) and pyridine (50 mL) were added. The solution was stirred at room temperature for 24 h and concentrated. The resulting oily brown solid was triturated with toluene and dried in vacuo. Yield: 27.0 g (84%). Mp: 185–186° C. $^1$H-NMR: (DMSO-$d_6$): δ 8.95 (2H, d, $J$ = 6 Hz), 8.63 (1H, t, $J$ = 8 Hz), 8.34 (1H, s), 8.10 (2H, t, $J$ = 6 Hz), 7.28 (1H, d, $J$ = 8 Hz), 7.13 (1H, d, $J$ = 8 Hz), 4.06 (2H, t, $J$ = 9 Hz), 3.09 (2H, t, $J$ = 8 Hz), 2.14 (3H, s). $^{13}$C-NMR: (DMSO-$d_6$): δ 168.47, 147.03, 146.41, 142.33, 142.11, 132.31, 127.27, 123.64, 120.54, 113.44, 48.36, 27.06, 23.99. MS (EI$^+$): 321 (M + 1). IR: 3440, 1660, 1490, 1420, 1250, 1220, 1180, 1090 cm$^{-1}$.

**6-(Dimethylsulfamoyl)indoline (6).** *N*-Acetylindoline-6-sulfonic acid–pyridine complex (10.00 g, 32.2 mmol) was slurried in acetonitrile (100 mL) containing phosphorus oxychloride (9.4 mL, 100 mmol) and two drops of DMF. The solution was heated at reflux temperature for 1 h and then concentrated to give a pale yellow oil which was poured into ice (100 g) to give a white precipitate. This solid was collected by suction filtration and immediately redissolved in $CH_2Cl_2$ (150 mL). A solution of 40% aqueous dimethylamine (30 mL, 0.30 mol) was added at a rate sufficient to maintain the temperature between 22 and 26 °C. The reaction was complete after 2 h. The solution was washed with water (100 mL), 1 N HCl (100 mL), and brine (100 mL), dried ($Na_2SO_4$), and filtered, and the solvents were evaporated. The *N*-acetyl-6-(dimethylsulfamoyl)indoline was then slurried in $CH_3OH$ (100 mL) and purged with HCl gas for 3 min. The solution was stirred at room temperature for 2 h and then evaporated. The resulting solid was dissolved in a saturated aqueous solution of potassium bicarbonate (150 mL) and ethyl acetate (150 mL). The organic phase was separated, washed with water (100 mL), dried ($Na_2SO_4$), and filtered, and the solvents were evaporated. Yield: 4.73 g (65%) of white solid. Mp: 109–110 °C. $^1$H-NMR ($CDCl_3$): δ 7.13 (1H, d, $J$ = 7 Hz), 7.01 (1H, dd, $J$ = 7, 1 Hz), 6.87 (1H, d, $J$ = 1 Hz), 3.58 (2H, t, $J$ = 9 Hz), 3.02 (2H, t, $J$ = 9 Hz), 2.62 (6H, s). $^{13}$C-NMR (CDCl3): δ 152.21, 134.69, 134.10, 124.62, 118.31, 107.39, 47.40, 38.07, 29.50. MS (EI$^+$): 226 (M). IR: 3400, 1610, 1500, 1460, 1320, 1260, 1150 cm$^{-1}$. Anal. Calculated for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38; S, 14.17. Found: C, 53.03; H, 6.35; N, 12.14; S, 14.27.

***N*-Acetyl-2-[3,6-bis[5-(dimethylsulfamoyl)indolino]xanthen-9-yl]-*N*-methylbenzenesulfonamide (8).** In a nitrogen atmosphere 5-(dimethylsulfamoyl)indoline (5) (2.942 g, 13 mmol) was added to a slurry of 3,6-dichlorosulfofluorescein (7) (2.026 g, 5 mmol), magnesium oxide (0.529 g, 13 mmol), and *N*-methylpyrrolidinone (30 mL) and heated to 100 °C. After 3 h the reaction was cooled to ambient temperature, zinc dust (1.10 g, 17 mmol) was added, and the reaction was heated to 100 °C for 1 h. At this point the reaction was purged with HCl gas for 2 min. After being cooled to room temperature, the solution was decanted away from the remaining zinc salts into a pressure-equalizing funnel. This solution was added dropwise to phosphorus oxychloride (65 mL, 42.8 g, 0.28 mol) in dry acetonitrile (50 mL), maintaining the temperature between 22 and 26 °C by means of an ice bath. When the addition was complete the reaction was stirred for an additional 3.5 h and then poured carefully with vigorous stirring into a slurry of $CH_2Cl_2$ (200 mL), 40% aqueous methylamine (160 mL, 64 g, 2.04 mol), and ice (200 g). The organic phase was separated, washed with 1 N HCl (3 × 100 mL), and dried over $MgSO_4$ (ca. 20 g). The solution was then treated with silica gel (ca. 15 g) to remove low $R_f$ impurities, filtered, concentrated, and triturated with $CH_3OH$ to give 8 as a white solid. Yield: 2.983 g (74%). This solid was purified further by chromatography (silica gel eluted with 2.5% $CH_3OH$ in $CH_2Cl_2$). See alternate preparation for analytical data.

***N*-Acetyl-2-[3,6-bis[6-(dimethylsulfamoyl)indolino]xanthen-9-yl]-*N*-methylbenzenesulfonamide (9).** According to the procedure described above for 8: 3,6-dichlorosulfofluorescein (7) (2.026 g, 5 mmol) and 6-(dimethylsulfamoyl)indoline (6) (2.942 g, 13 mmol) provided 1.14 g (29%) of 6′,6″-bis(dimethylsulfamoyl) leuco dye 9 as a white solid. Mp: >250° C. $^1$H-NMR (DMSO-$d_6$): δ 8.16 (1H, m), 7.86 (1H, d, $J$ = 8 Hz), 7.51(1H, t, $J$ = 7 Hz), 7.35–7.43 (3H, overlapping peaks), 7.25 (2H, s), 6.86–7.14 (9H, overlapping peaks), 6.32 (s, 1 H), 4.07 (4H, t, $J$ = 8 Hz), 3.20 (4H, t, $J$ = 8 Hz), 2.73 (3H, s), 2.61 (2H, s). $^{13}$C-NMR (DMSO-$d_6$): δ 150.65, 150.28, 146.73, 146.61, 142.53, 137.31, 133.42, 133.32, 132.99, 130.81, 127.42, 125.53, 118.62, 117.30, 116.38, 113.25, 105.42, 104.59, 51.94, 37.65, 36.43, 28.70, 27.21. IR: 1600, 1500, 1410, 1320, 1260, 1150 cm$^{-1}$. HRMS (FAB$^+$): calcd for $C_{40}H_{42}N_5O_7S_3$ (M + H): 800.2246, found: 800.2229.

***N*-Acetyl-2-[3,6-bis[5-(chlorosulfonyl)indolino]xanthen-9-yl]-*N*-methylbenzenesulfonamide (10).** Acetyl leuco dye bis-sulfonate 4c (13.1 g, 16.6 mmol), acetonitrile (200 mL), and dimethylformamide (12 mL, 166 mmol) were combined and cooled to ~5 °C. Phosphorus oxychloride (22 mL, 36.2 g, 236 mmol) was added dropwise, keeping the temperature below 12 °C (addition took approximately 15 min). After an additional 15 min at 5 °C, the reaction was allowed to warm to room temperature, eventually giving an evergreen-colored solution. Although complete by TLC analysis ($CHCl_3$) after 2 h, the reaction was stored overnight at 3 °C. The precipitated product was collected by filtration, washed with ether, and air dried to afford 10.2 g (74%) of a pale green powder. An analytically pure sample was prepared by flash chromatography ($CH_2Cl_2$). Mp: >250 °C. $^1$H-NMR ($CDCl_3$): δ 7.75 (2H, d, $J$ = 9 Hz), 7.75 (1H, d, $J$ = 8 Hz), 7.73 (2H, broad s), 7.52 (1H, t, $J$ = 9 Hz), 7.37 (1H, t, $J$ = 8 Hz), 7.32 (1H, d, $J$ = 8 Hz), 7.13 (2H, d, $J$ = 9 Hz), 7.08 (2H, d, $J$ = 9 Hz), 7.04 (2H, d, $J$ = 2 Hz), 6.93 (2H, dd, $J$ = 9, 2 Hz), 6.22 (1H, s), 4.14 (4H, t, $J$ = 9 Hz), 3.47 (3H, s), 3.25 (4H, t, $J$ = 9 Hz), 2.45 (3H, s). $^{13}$C-NMR ($CDCl_3$): δ 170.85, 152.76, 151.19, 146.66, 141.74, 137.39, 134.48, 133.94, 132.99, 132.31, 130.93,

(22) Procedure based on synthesis of *N*-acetylindoline-5-sulfonyl chloride given in ref 10a.

(23) Based on procedure given in ref 10b.

129.28, 127.24, 127.240, 124.00, 118.94, 115.13, 107.20, 106.94, 52.95, 37.72, 33.48, 27.13, 25.41. MS (FAB$^+$): 824 (M + 1). IR: 1705, 1165 cm$^{-1}$. Anal. Calcd for $C_{38}H_{31}Cl_2N_3O_8S_3$: C, 55.34; H, 3.79; N, 5.09. Found: C, 55.29; H, 3.87; N, 4.97.

**Synthesis of *N*-Acetyl-2-[3,6-bis[5-(dimethylsulfamoyl)-indolino]xanthen-9-yl]-*N*-methylbenzenesulfonamide (8) from 10.** Acetyl leuco dye bis-sulfony lchloride **10** (2.22 g, 2.69 mmol), acetonitrile (35 mL), and dimethylamine (40 wt % aqueous, 7 mL, 27.9 mmol) were combined and warmed on a steam bath. Within minutes a white solid began to precipitate. The reaction was heated for a total of 15 min and then allowed to stir at room temperature for an additional 20 min. The precipitated solids were collected by filtration, washed with 1 N HCl, and air dried, affording 2 g of an off-white solid (90%). The solid was purified by digestion in hot $CHCl_3$ (3 × 200 mL), filtration, and concentration in vacuo, affording 1.1 g (50%) of a pale gray solid. An analytically pure sample was prepared by flash chromatography (70/30/2.5 $CH_2Cl_2$/hexanes/methanol). Mp: >250° C. $^1$H-NMR (DMSO-$d_6$): $\delta$ 8.2 (1H, br), 7.85 (1H, d, $J$ = 7 Hz), 7.51 (1H, t, $J$ = 7 Hz), 7.47 (2H, s), 7.43 (2H, dd, $J$ = 9, 2 Hz), 7.38 (1H, t, $J$ = 7 Hz), 7.21 (2H, d, $J$ = 9 Hz), 7.16 (2H, d, $J$ = 8 Hz), 7.15 (1H, d, $J$ = 7 Hz), 7.07 (2H, s), 7.06 (2H, dd, $J$ = 8, 2 Hz), 6.32 (1H, s), 4.08 (4H, t, $J$ = 9 Hz), 3.19 (4H, t, $J$ = 9 Hz), 2.72 (3H, s), 2.57 (12H, s). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 150.60, 149.91, 146.74, 142.10, 137.29, 133.40, 133.00, 132.44, 130.70, 128.67, 127.50, 126.70, 124.34, 123.50, 117.83, 114.06, 107.06, 105.34, 52.05, 37.71, 36.52, 28.70, 26.79. MS (FAB$^+$): 800 (M + 1). IR: 3295, 1330, 1150 cm$^{-1}$. Anal. Cald for $C_{40}H_{41}N_5O_7S_3$: C, 60.06; H, 5.17; N, 8.75. Found: C, 60.03; H, 5.10; N, 8.63.

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**Supplementary Material Available:** 1-D and 2-D NMR spectra of the compounds listed in the Experimental Section and a summary of the AM1 calculation data (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.