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Alkali-Metal Cation Recognition Induced Isomerization of Spirobenzopyrans and Spironaphthoxazins Possessing a Crown Ring as a Recognition Site: Multifunctional Artificial Receptors

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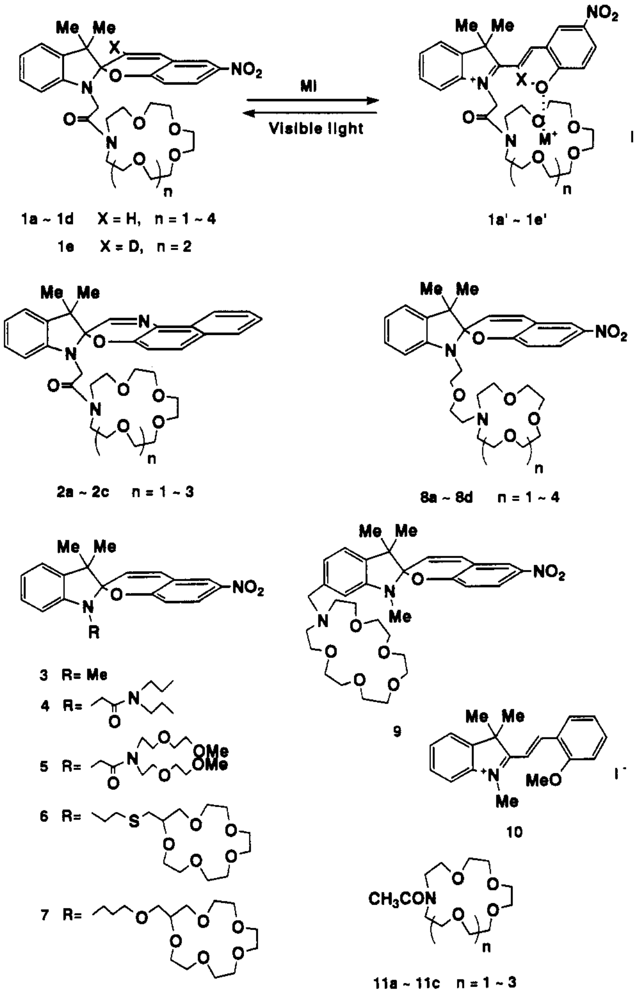
Spirobenzopyrans and spironaphthoxazins possessing a monoaza-crown ring were synthesized. Isomerization of these compounds to the open colored merocyanines was induced by recognition of alkali-metal cations and the selectivity of the coloration was found to be governed by several factors: (1) the size of the crown ring, (2) the position of recognition, (3) electric properties of both the complexed cations and the merocyanine dipoles, and (4) the length of the alkyl chains connecting the spirobenzopyran units and the crown units. The spirobenzopyrans represent rationally designed multifunctional artificial receptors for alkali-metal cations.

Introduction

A new class of host molecules whose optical properties are markedly perturbed by the presence of cations are of current interest and attracting much attention from the viewpoint of biomimmetic chemistry.[1] These "recognition and signaling" molecules may also stimulate the investigation of molecular sensors for biologically important alkali-metal ions. For this purpose, fluorescence spectroscopy is suitable because of its inherent sensitivity and selectivity. Thus, numerous fluoroionophores have been synthesized.[2] On the other hand, designing and synthesizing chromoionophores are also distinct and worthwhile subjects in their own right.[3] We recently introduced a new type of spirobenzopyran[4] possessing a monoaza-crown ring (1) as a recognition site, of which isomerization to the colored merocyanines (1′) was induced by recognition of alkali-metal cations.[5] This new type of chromoionophore is conceptually different from the crown ether dyes thus far synthesized, because in the latter cases, the absorption bands of chromophores are merely shifted by the complexation of cations. Here we describe the full details of a previous paper as well as other series of crown-linked spirobenzopyrans and spironaphthoxazins (Scheme I).

Scheme I



Synthesis

Spirobenzopyrans 1 and spironaphthoxazins 2 were prepared from crown-linked *exo*-methyleneindoline with 5-nitrosalicylaldehyde and 1-nitroso-2-naphthol, respectively. Spirobenzopyrans 6–8, in which the spirobenzopyran units were further separated from the crown units by alkyl chains than those in 1 and 2, were synthesized by standard synthetic methods. Spirobenzopyran 9, which is designed to be stabilized in the closed spiropyran rather than open merocyanine form by recognition of the alkali-metal cation, was made by using the Fischer-indole synthesis followed by condensation with 5-nitrosalicylaldehyde and monoaza-crown ether. Other compounds were commercially available or easily synthesized (Scheme II).

Results and Discussion

We previously reported that isomerization of spirobenzopyrans 1 was induced by recognition of alkali-metal cations (Li$^+$ for 1a and 1b; Na$^+$ for 1c) and that ^{1}H NMR investigations of the open colored merocyanines 1′ suggested a trans structure.[5] Some additional NMR studies were carried out in order to reinforce previous conclusions and to obtain further structural information for 1′.[6] The

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(1) For reviews: (a) Löhr, H.-G.; Vögtle, F. *Acc. Chem. Res.* **1985**, *18*, 65–72. (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112.

(2) (a) Fages, F.; Desverge, J.-P.; Bouas-Laurent, H.; Marsau, P.; Lehn, J.-M.; Kotzyba-Hibert, F.; Albrecht-Gray, A.-M.; Al-Joubbeh, M. *J. Am. Chem. Soc.* **1989**, *111*, 8672–8680, and references therein. (b) De Silva, A. P.; Niemal Gunaratne, H. Q. *J. Chem. Soc., Chem. Commun.* **1990**, 186–188. (c) Akkaya, E. U.; Huston, M. E.; Czarnik, A. W. *J. Am. Chem. Soc.* **1990**, *112*, 3590–3593. (d) Huston, M. E.; Engleman, C.; Czarnik, A. W. *J. Am. Chem. Soc.* **1990**, *112*, 7054–7056. (e) Hinschberger, J.; Desvergne, J.-P.; Bouas-Laurent, H.; Marsau, P. *J. Chem. Soc., Perkin Trans. 2* **1990**, 993–1000. (f) Fages, F.; Desvergne, J.-P.; Bouas-Laurent, H.; Lehn, J.-M.; Konopelski, J. P.; Marsau, P.; Barrans, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 655–658.

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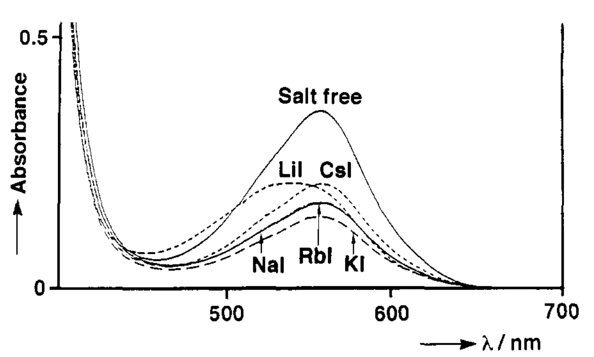
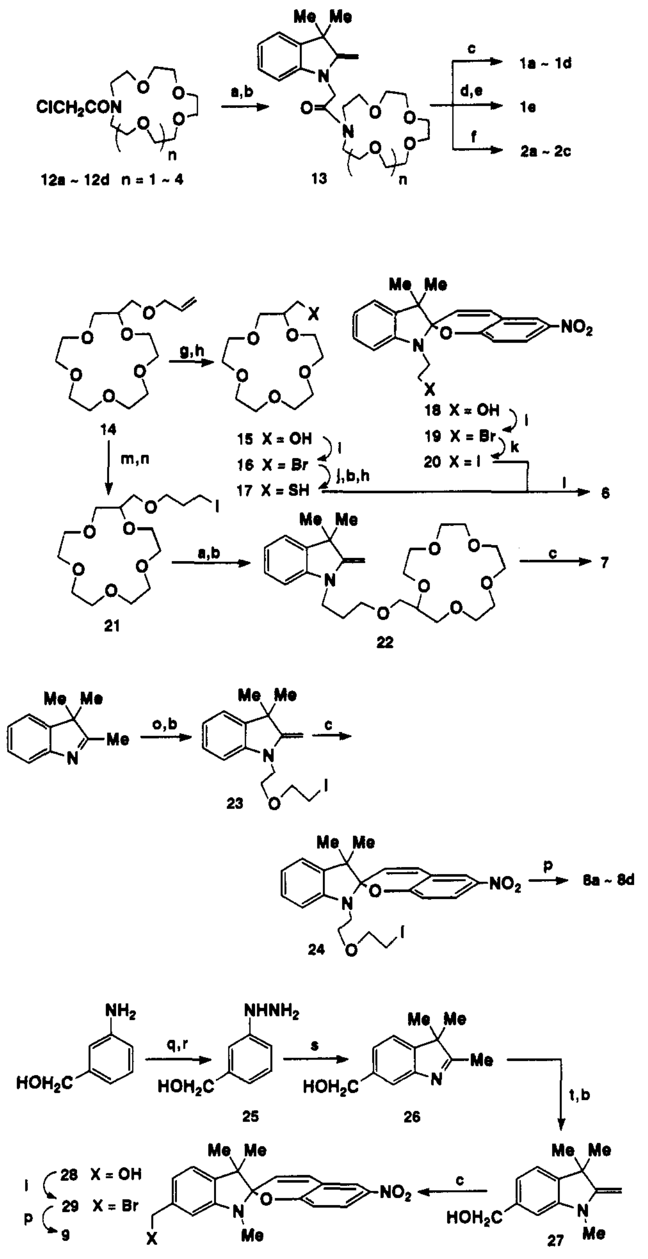


Figure 1. Electronic absorption spectra of the acetonitrile solutions of 9 (1.7 mM) in the presence or absence of alkali-metal iodides (5-fold molar quantity).

conversion of **1b** to **1b′** in the stationary state was found to be about 50% under the conditions employed (**1b**, 50 μmol; LiI, 250 μmol; CD_3CN, 0.8 mL) on the basis of the integrations of the spectrum. Large downfield shifts were observed for *gem*-dimethyl protons (**1b**, 1.23 and 1.28 ppm; **1b′**, 1.86 ppm). These shifts might be attributed to the increased diamagnetic anisotropy of **1b′** compared with that of **1b**, in other words, **1b′** has a longer conjugation system. In the $^{13}C\{H\}$ NMR spectrum two lines at 182 and 186 ppm were assigned to the immonium and amide carbons of **1b′**. This result suggested that the open mercyanine structure existed in a really charge-separated zwitterionic form and not a neutral keto form, since the immonium carbon of **10**, which was a simple model compound of the former, appeared at 184 ppm. The resonances of **1b′** disappeared after irradiation with strong visible light. No NMR evidence was obtained for the open colored merocyanine under identical experimental conditions in the presence of other alkali-metal iodides in agreement with the UV spectra.

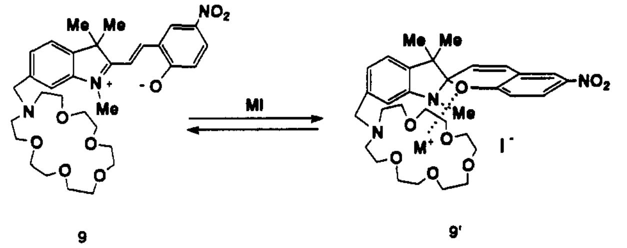
In order to determine the factors contributing to the coloration of the spirobenzopyrans (i.e., isomerization to the merocyanines), the following experiments were carried out. The absorption spectra of **3** and **4** were not at all affected by the alkali-metal iodides, and **5**, the corresponding acyclic analog of **1a**, showed much less Li^+ selectivity than **1a**. Furthermore, little change in the spectrum of **3** occurred even in the presence of 1 equiv of *N*-acetylmonoaza-18-crown-6 (**11b**) and the alkali-metal iodides. The position of the complexed cation in the molecule was also found to be important for the isomerization. Spirobenzopyran **9** was designed to recognize cations in which the complexed cations could interact with the ether oxygen of the closed spiropyran and not the phenolate oxygen of the opened merocyanine (Scheme III). Indeed, isomerization of **9** to the colored merocyanine was

Scheme II[a]



[a] (a) 2,3,3-Trimethyl-3*H*-indole, NaI, CH_3CN; (b) KOH or NaOH, H_2O; (c) 5-nitrosalicylaldehyde, EtOH; (d) D_2O; (e) 5-nitrosalicylaldehyde, EtOD; (f) 1-nitroso-2-naphthol, EtOH; (g) $(Ph_3P)_3RhCl$, DABCO, EtOH, H_2O; (h) HCl, H_2O; (i) Ph_3P, CBr_4, THF; (j) thiourea, EtOH; (k) NaI, acetone; (l) Cs_2CO_3, DMF; (m) B_2H_6, THF; (n) I_2, MeONa, MeOH; (o) bis(2-iodoethyl) ether, CH_3CN; (p) monoaza-crown ether, K_2CO_3 or Na_2CO_3, THF; (q) $NaNO_2$, HCl, H_2O; (r) $SnCl_2 \cdot 2H_2O$, HCl, H_2O; (s) 3-methyl-2-butanone, AcOH; (t) MeI, ether.

Scheme III



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(3) (a) Helgeson, R. C.; Czech, B. P.; Chapoteau, E.; Gebauer, C. R.; Kumar, A.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6339–6350, and references therein. (b) Reichardt, C.; Asharin-Fard, S.; *Angew. Chem., Int. Ed. Engl.* 1991, *30*, 558–559.

(4) (a) For general reviews of the chemistry of spiropyrans: Bertelson, R. C. In *Photochromism*; Brown, G. H., Ed.; Wiley-Interscience: New York, 1971. Irie, M. In *Molecular Models of Photoresponsiveness*; Montagnoli, G., Erlangered, B. F., Eds; Plenum Press: New York, 1983. *Chemistry of Functional dyes*; Yoshida, Z., Kitao, T., Eds; Mita Press: Tokyo, 1989. (b) Some spiropyrans have been utilized as photoresponsive functional molecules: Sunamoto, J.; Iwamoto, K.; Mohri, Y.; Kominato, T. *J. Am. Chem. Soc.* **1982**, *104*, 5502–5504. Winkler, J. D.; Deshayes, K.; Shao, B. *Ibid.* **1989**, *111*, 769–770. Ciardelli, F.; Fabbi, D.; Pieroni, O.; Fissi, A. *Ibid.* **1989**, *111*, 3470–3472. Sakai, H.; Ueno, A.; Anzai, J.; Osa, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1953–1956.

(5) Inouye, M.; Ueno, M.; Kitao, T.; Tsuchiya, K. *J. Am. Chem. Soc.* **1990**, *112*, 8977–8979. See, also: Kimura, K.; Yamashita, T.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1991**, 147–148.

(6) For discussions on the structures of spiropyrans and merocyanines: Flannery, J. B., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 5660–5671. Toppet, S.; Quintens, W.; Smets, G. *Tetrahedron* **1975**, *31*, 1957–1958. Aldoshin, S. M.; Atovmyan, L. O.; D'yachenko, O. A.; Gal'bershtam, M. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1981, 2720–2729. Aldoshin, S. M.; Atovmyan, L. O. *Mol. Cryst. Liq. Cryst.* **1987**, *149*, 251–290.

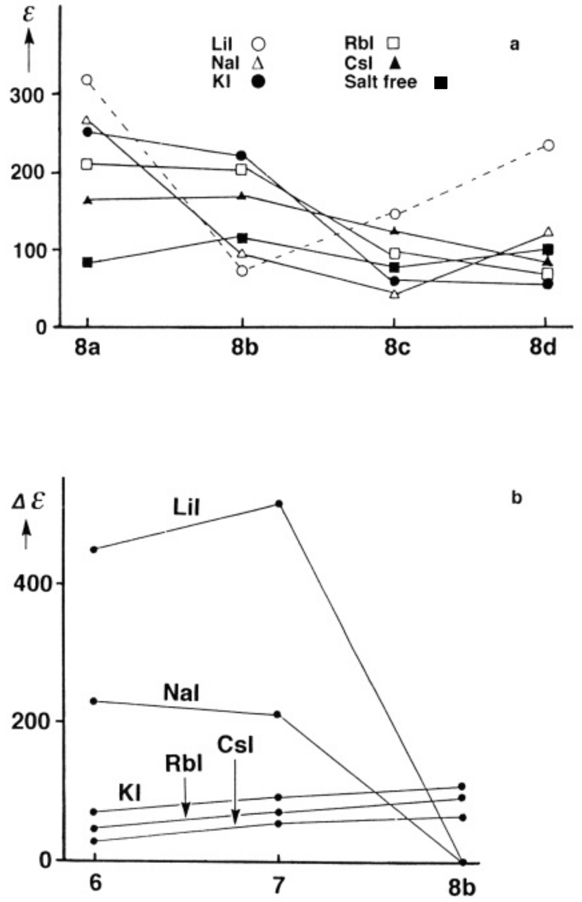

Figure 2. (a) Molar absorptivities (ϵ) of the acetonitrile solutions of **8a–d** in the presence or absence of alkali-metal iodides (5-fold molar quantity) and (b) $\Delta\epsilon$ values [$\Delta\epsilon = \epsilon$(alkali metal iodide) − ϵ(salt free)] of **6**, **7**, and **8b**.

most strongly *suppressed* by the presence of a potassium cation which was expected to be most strongly recognized by the crown ring (Figure 1). It was found, however, that the thermodynamic stabilities of *N*-acetylmonoaza-crown ethers **11**, which were thought to be "isolated" recognition sites of **1**, for alkali-metal cations were not compatible with "color selectivities" of **1** possessing a corresponding crown ether. For example, **1b** showed color selectivity for Li$^+$ but **11b** revealed the highest stability constant for Na$^+$.[7] Under identical experimental conditions, the degree of isomerization of the spironaphthoxazin counterparts **2** was too small to obtain any NMR evidence for the open merocyanine forms, although color selectivities of **2** were similar to those of **1** possessing the same crown ring. This finding is not surprising in view of the fact that the open colored forms of spironaphthoxazins are thought to be in their neutral keto forms,[4a] so that stabilization by an alkali-metal cation might not be essential. These previously mentioned results showed that isomerization of the spirobenzopyrans to the merocyanines was governed by not only recognition of alkali-metal cations with the crown rings at the suitable positions but also electric properties of both the complexed cations and the merocyanine dipoles.

Color selectivities of the spirobenzopyrans **8** were examined in which the spirobenzopyran units were much further separated from the crown ether units by alkyl chains than **1** and **2**. Although the behavior of the lithium cation is still unknown and remains to be clarified, **8a**, **8b**, and **8c** revealed the highest coloration for Na$^+$, K$^+$, and Cs$^+$, other than Li$^+$, respectively, which were slightly bigger ions than the size of the cavity of the crown ether of the respective spirobenzopyrans (Figure 2a). This finding suggests that in the opened merocyanines, alkali-metal ions are favorably located in the space made by the spirobenzopyran unit and the crown ether unit as depicted in Figure 3. Indeed, it was found that the length of the alkyl chains connecting the two units affected the color selectivity. Thus, **6**, **7**, and **8b** possessing the same size of crown ether but a different length of alkyl chain, which increased in that order (as judged by CPK molecular models), showed different color selectivities, and the coloring efficiencies for bigger ions increased in the same order (Figure 2b). In these spirobenzopyrans (**6–8**), the molar absorptivities in the presence of alkali-metal cations are considerably smaller when compared to those of **1**, and in particular, **8d** was scarcely affected upon addition of any alkali-metal iodides. The low coloring efficiency might result from the entropic disadvantage: reduced probability of the existence of the complexed cations in the neighborhood of the phenolate oxygen of the merocyanines.

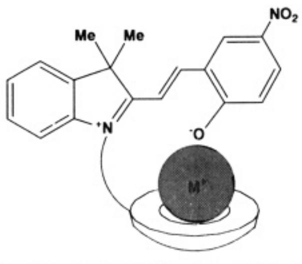

Figure 3. Schematic representation of the colored complex between the spirobenzopyran 8 and an alkali-metal cation.

Conclusion

We developed a new class of spirobenzopyrans and spironaphthoxazins possessing a monoaza-crown ring as a recognition site, which were conceptually new artificial receptors for alkali-metal cations, namely, "recognition–structural change–signaling" receptors. Isomerization of these compounds to the colored merocyanines was induced by the presence of alkali-metal cations. Several experiments showed that the isomerization was governed by not only recognition of alkali-metal cations with the crown rings at suitable positions but also the electric properties of both the complexed cations and the merocyanine dipoles. Furthermore, it was found that the length of the alkyl chains connecting the spirobenzopyran units and the crown rings affected the isomerization.

Experimental Section

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively. Melting points are uncorrected.

Materials. The starting materials were all commercially available and **3**,[8] **12**,[9] and **14**[10] were prepared according to literature procedures.

***exo*-Methyleneindolines 13a–d (Exemplified with 13b).** A solution of **12b**[9] (544 mg, 1.6 mmol), 2,3,3-trimethyl-3*H*-indole (303 mg, 1.9 mmol), and NaI (285 mg, 1.9 mmol) in CH_3CN (10 mL) was refluxed for 12 h. After evaporation of the solvent, the residue was dissolved in water. The aqueous solution was washed

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(7) K_a values of **11** for alkali-metal iodides were determined by Cram's method. **11a**, 22 (LiI), 22 (NaI), 15 (KI) × 10^4 M^{-1}; **11b**, 7.4 (LiI), 18 (NaI), 8.0 (KI) × 10^4 M^{-1}; **11c**, 2.0 (LiI), 3.8 (NaI), 60 (KI) × 10^4 M^{-1}. Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398–6405.

(8) Berman, E.; Fox, R. E.; Thomson, F. D. *J. Am. Chem. Soc.* **1959**, *81*, 5605–5608.

(9) McLain, S. J. *Inorg. Chem.* **1986**, *25*, 3124–3127.

(10) Ikeda, I.; Yamamura, S.; Nakatsuji, Y.; Okahara, M. *J. Org. Chem.* **1980**, *45*, 5355–5358.

with ether in order to remove the unreacted starting materials, then basified by the addition of NaOH (400 mg, 10 mmol), and stirred at rt for 10 min. Extractive workup with CH_2Cl_2 followed by column chromatography (silica gel; eluent, AcOEt:Et_3N = 20:1) afforded **13b**.

13a: yield 47% (315 mg); oil; IR (neat) 2850, 1650, 1610, 1490, 1450, 1350, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H), 3.49–3.92 (m, 22 H), 4.41 (s, 2 H), 6.50 (d, J = 7.3 Hz, 1 H), 6.76 (t, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.3 Hz, 1 H), 7.09 (d, J = 7.3 Hz, 1 H).

13b: yield 45% (333 mg); oil; IR (neat) 2850, 1640, 1610, 1490, 1450, 1350, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H), 3.62–3.89 (m, 26 H), 4.45 (s, 2 H), 6.49 (d, J = 7.3 Hz, 1 H), 6.75 (t, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.3 Hz, 1 H), 7.08 (d, J = 7.3 Hz, 1 H).

13c: yield 44% (357 mg); oil; IR (neat) 2850, 1650, 1610, 1490, 1450, 1350, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H), 3.53–3.86 (m, 30 H), 4.48 (s, 2 H), 6.49 (d, J = 7.3 Hz, 1 H), 6.75 (t, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.3 Hz, 1 H), 7.08 (d, J = 7.3 Hz, 1 H).

13d: yield 47%; oil (414 mg); IR (neat) 2850, 1650, 1610, 1490, 1450, 1340, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H), 3.47–3.92 (m, 34 H), 4.50 (s, 2 H), 6.51 (d, J = 7.3 Hz, 1 H), 6.75 (t, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.3 Hz, 1 H), 7.08 (d, J = 7.3 Hz, 1 H).

Spirobenzopyrans 1a–d (Exemplified with 1b). A solution of **13b** (333 mg, 0.72 mmol) and 5-nitrosalicylaldehyde (145 mg, 0.87 mmol) in EtOH (7.0 mL) was refluxed for 6 h. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel; eluent, AcOEt) to give **1b**.

1a: yield 80% (327 mg); mp 55–60 °C; IR (KBr) 2900, 1665, 1485, 1340, 1280, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.30 (s, 3 H), 3.43–3.90 (m, 20 H), 4.01 (d, J = 16.9 Hz, 1 H), 4.12 (d, J = 16.9 Hz, 1 H), 6.01 (d, J = 10.5 Hz, 1 H), 6.50 (d, J = 7.3 Hz, 1 H), 6.78 (d, J = 8.9 Hz, 1 H), 6.86 (t, J = 7.3 Hz, 1 H), 6.87 (d, J = 10.5 Hz, 1 H), 7.08 (d, J = 7.3 Hz, 1 H), 7.14 (t, J = 7.3 Hz, 1 H), 7.98 (d, J = 2.6 Hz, 1 H), 8.02 (dd, J = 2.6, 8.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.00, 26.25, 45.25, 49.99, 50.10, 52.95, 69.41–69.81, 106.44, 106.89, 115.70, 118.63, 119.72, 121.58, 122.17, 122.65, 127.83, 128.03, 133.51, 141.03, 146.67, 159.57, 169.23. Anal. Calcd for $C_{30}H_{37}N_3O_8$: C, 63.48; H, 6.57; N, 7.40. Found: C, 63.23; H, 6.90; N, 7.10.

1b: yield 79% (348 mg); mp 43–48 °C; IR (KBr) 2850, 1650, 1480, 1330, 1270, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.30 (s, 3 H), 3.50–3.75 (m, 24 H), 4.14 (s, 2 H), 6.03 (d, J = 10.4 Hz, 1 H), 6.48 (d, J = 7.3 Hz, 1 H), 6.76 (d, J = 9.2 Hz, 1 H), 6.85 (d, J = 10.4 Hz, 1 H), 6.85 (t, J = 7.3 Hz, 1 H), 7.07 (d, J = 7.3 Hz, 1 H), 7.14 (t, J = 7.3 Hz, 1 H), 7.97 (d, J = 2.4 Hz, 1 H), 8.01 (dd, J = 2.4, 9.2 Hz, 1 H); ^{13}C NMR (CD_3CN) δ 19.96, 26.57, 45.39, 47.49, 49.33, 53.54, 69.5–72.0, 107.27, 107.61, 116.42, 119.94, 120.06, 122.45, 122.59, 123.58, 126.43, 128.49, 129.02, 136.50, 141.97, 147.88, 160.33, 169.59. Anal. Calcd for $C_{32}H_{41}N_3O_9$: C, 62.83; H, 6.75; N, 6.86. Found: C, 62.53; H, 6.95; N, 6.48.

1c: yield 92% (434 mg); oil; IR (neat) 2850, 1650, 1480, 1340, 1280, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.30 (s, 3 H), 3.47–3.73 (m, 28 H), 4.09 (d, J = 17.1 Hz, 1 H), 4.22 (d, J = 17.1 Hz, 1 H), 6.02 (d, J = 10.4 Hz, 1 H), 6.46 (d, J = 7.3 Hz, 1 H), 6.77 (d, J = 8.6 Hz, 1 H), 6.85 (d, J = 10.4 Hz, 1 H), 6.85 (t, J = 7.3 Hz, 1 H), 7.07 (d, J = 7.3 Hz, 1 H), 7.13 (t, J = 7.3 Hz, 1 H), 7.97 (d, J = 2.4 Hz, 1 H), 8.02 (dd, J = 2.4, 8.6 Hz, 1 H).

1d: yield 80% (403 mg); oil; IR (neat) 2880, 1650, 1480, 1340, 1280, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.30 (s, 3 H), 3.57–3.70 (m, 32 H), 4.06 (d, J = 16.9 Hz, 1 H), 4.21 (d, J = 16.9 Hz, 1 H), 6.02 (d, J = 10.3 Hz, 1 H), 6.48 (d, J = 7.3 Hz, 1 H), 6.77 (d, J = 8.9 Hz, 1 H), 6.85 (d, J = 10.3 Hz, 1 H), 6.85 (t, J = 7.3 Hz, 1 H), 7.07 (d, J = 7.3 Hz, 1 H), 7.13 (t, J = 7.3 Hz, 1 H), 7.98 (d, J = 2.8 Hz, 1 H), 8.02 (dd, J = 2.8, 8.9 Hz, 1 H).

Deuterated Spirobenzopyran 1e. A solution of deuterated *exo*-methyleneindoline (186 mg, 0.40 mmol), which was prepared by the treatment of **13b** with D_2O at rt for 1 h, and 5-nitrosalicylaldehyde (70 mg, 0.42 mmol) in EtOD (5.0 mL) was refluxed for 3 h. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel; eluent, AcOEt) to give **1e**: yield 67% (164 mg); mp 57–58 °C; IR (KBr) 2920, 1660, 1620, 1580, 1525, 1490, 1470, 1345, 1275, 1130, 1100, 1040, 940 cm^{-1}; ^1H NMR (CD_3CN) δ 1.22 (s, 3 H), 1.29 (s, 3 H), 3.38–3.69 (m, 24 H), 4.16 (s, 2 H), 6.46 (d, J = 7.3 Hz, 1 H), 6.76 (d, J = 9.2 Hz, 1 H), 6.83 (t, J = 7.3 Hz, 1 H), 7.02 (s, 1 H), 7.11 (t, J = 7.3 Hz, 1 H), 7.13 (d, J = 7.3 Hz, 1 H), 8.01 (dd, J = 2.4, 9.2 Hz, 1 H), 8.08 (d, J = 2.4 Hz, 1 H). Anal. Calcd for $C_{32}H_{40}N_3O_9D$: C, 62.73; H, 6.58; N, 6.86. Found: C, 62.05; H, 6.76; N; 6.38.

Spironaphthoxazins 2a–c (Exemplified with 2b). A solution of **13b** (1342 mg, 2.9 mmol) and 1-nitroso-2-naphthol (537 mg, 3.1 mmol) in EtOH (40 mL) was refluxed for 8 h. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel; eluent, AcOEt) to give **2b**.

2a: yield 40% (665 mg); mp 157–159 °C; IR (KBr) 2950, 1650, 1600, 1590, 1480, 1450, 1410, 1380, 1330, 1300, 1260, 1240, 1210, 1110, 1070, 1050, 990, 950, 810, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.43 (s, 3 H), 3.33–3.76 (m, 20 H), 4.08 (d, J = 17.1 Hz, 1 H), 4.16 (d, J = 17.1 Hz, 1 H), 6.51 (d, J = 7.9 Hz, 1 H), 6.86 (dt, J = 1.2, 7.3 Hz, 1 H), 7.02 (d, J = 9.2 Hz, 1 H), 7.06 (dd, J = 1.2, 7.3 Hz, 1 H), 7.14 (ddd, J = 1.2, 7.3, 7.9 Hz, 1 H), 7.38 (dt, J = 1.2, 7.9 Hz, 1 H), 7.55 (ddd, J = 1.2, 7.9, 9.2 Hz, 1 H), 7.66 (d, J = 9.2 Hz, 1 H), 7.74 (d, J = 7.9 Hz, 1 H), 7.87 (s, 1 H), 8.54 (d, J = 9.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.10, 25.81, 45.60, 50.02, 50.16, 52.53, 69.53, 69.77, 70.10, 70.62, 71.67, 98.50, 106.95, 117.05, 119.70, 121.48, 121.68, 122.94, 124.17, 127.04, 127.77, 127.99, 129.35, 130.07, 130.88, 135.15, 143.94, 146.79, 151.54, 169.03.

2b: yield 48% (860 mg); mp 96–98 °C; IR (KBr) 2950, 1660, 1620, 1600, 1490, 1470, 1420, 1390, 1360, 1310, 1280, 1260, 1230, 1170, 1120, 1090, 1060, 1010, 960, 830, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.44 (s, 3 H), 3.30–3.71 (m, 24 H), 4.21 (s, 2 H), 6.50 (d, J = 7.9 Hz, 1 H), 6.85 (dt, J = 1.2, 7.3 Hz, 1 H), 7.00 (d, J = 8.5 Hz, 1 H), 7.06 (dd, J = 1.2, 7.3 Hz, 1 H), 7.15 (ddd, J = 1.2, 7.3, 7.9 Hz, 1 H), 7.37 (ddd, J = 1.2, 7.3, 8.5 Hz, 1 H), 7.55 (ddd, J = 1.2, 7.3, 8.5 Hz, 1 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.73 (d, J = 8.5 Hz, 1 H), 7.89 (s, 1 H), 8.54 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.95, 25.76, 45.41, 46.38, 48.57, 52.47, 69.13, 70.01, 70.10, 70.34, 70.40, 70.44, 70.56, 70.64, 70.84, 71.09, 98.58, 106.68, 116.99, 119.42, 121.36, 121.62, 122.84, 124.07, 126.96, 127.67, 127.89, 128.29, 129.24, 129.91, 130.84, 135.03, 143.94, 146.85, 151.64, 169.11. Anal. Calcd for $C_{35}H_{43}N_3O_7$: C, 68.05; H, 7.02; N, 6.80. Found: C, 67.95; H, 7.10; N, 6.66.

2c: yield 45% (864 mg); oil; IR (neat) 2950, 1660, 1620, 1490, 1470, 1390, 1350, 1280, 1260, 1110, 1050, 1000, 950, 820, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.42 (s, 3 H), 3.27–3.69 (m, 28 H), 4.22 (s, 2 H), 6.49 (d, J = 7.9 Hz, 1 H), 6.84 (t, J = 7.3 Hz, 1 H), 7.01 (d, J = 9.2 Hz, 1 H), 7.06 (d, J = 7.3 Hz, 1 H), 7.14 (ddd, J = 1.2, 7.3, 7.9 Hz, 1 H), 7.37 (ddd, J = 1.2, 6.7, 8.5 Hz, 1 H), 7.52 (ddd, J = 1.2, 6.7, 8.5 Hz, 1 H), 7.64 (d, J = 9.2 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.87 (s, 1 H), 8.54 (d, J = 8.5 Hz, 1 H).

Spirobenzopyrans 4 and 5. These spirobenzopyrans were synthesized from the corresponding chloroacetamides in a manner similar to that described for **1**.

4: overall yield 38%; mp 182–183 °C; IR (KBr) 2995, 1650, 1510, 1470, 1330, 1260, 1160, 1090, 950, 810, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3 H), 0.88 (t, J = 7.3 Hz, 3 H), 1.27 (s, 3 H), 1.31 (s, 3 H), 1.52–1.63 (m, 4 H), 3.16–3.38 (m, 4 H), 3.89 (d, J = 16.5 Hz, 1 H), 4.00 (d, J = 16.5 Hz, 1 H), 6.01 (d, J = 10.4 Hz, 1 H), 6.42 (d, J = 7.3 Hz, 1 H), 6.78 (d, J = 9.2 Hz, 1 H), 6.86 (d, J = 10.4 Hz, 1 H), 6.87 (t, J = 7.3 Hz, 1 H), 7.08 (d, J = 7.3 Hz, 1 H), 7.15 (t, J = 7.3 Hz, 1 H), 7.99 (d, J = 3.1 Hz, 1 H), 8.03 (dd, J = 3.1, 9.2 Hz, 1 H). Anal. Calcd for $C_{26}H_{31}N_3O_4$: C, 69.47; H, 6.95; N, 9.35. Found: C, 69.01; H, 6.90; N, 9.29.

5: overall yield 6%; oil; IR (neat) 2850, 1650, 1480, 1330, 1270, 1110, 950, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.30 (s, 3 H), 3.30 (s, 3 H), 3.36 (s, 3 H), 3.38–3.74 (m, 16 H), 4.01 (d, J = 17.1 Hz, 1 H), 4.20 (d, J = 17.1 Hz, 1 H), 6.00 (d, J = 10.4 Hz, 1 H), 6.48 (d, J = 7.3 Hz, 1 H), 6.77 (d, J = 8.6 Hz, 1 H), 6.85 (d, J = 10.4 Hz, 1 H), 6.85 (t, J = 7.3 Hz, 1 H), 7.07 (d, J = 7.3 Hz, 1 H), 7.13 (t, J = 7.3 Hz, 1 H), 7.98 (d, J = 3.1 Hz, 1 H), 8.02 (dd, J = 3.1, 8.6 Hz, 1 H).

(Hydroxymethyl)-15-crown-5 (15). A solution of **14**[10] (2904 mg, 10.0 mmol), Wilkinson's catalyst (463 mg, 0.5 mmol), and 1,4-diazabicyclo[2.2.2]octane (56 mg, 0.5 mmol) in EtOH–water (2–8 mL) was heated at 60–70 °C for 12 h. The reaction mixture was acidified with 0.1 N HCl, refluxed for 12 h, and filtered. The filtrate was continuously extracted with CH_2Cl_2 (20 h). The extract was evaporated to give **15**: yield 95% (2378 mg); oil; IR (neat) 3300, 2850, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.55–3.85 (m, 22 H). This product was identical to that synthesized by Okahara et al.[10]

(Bromomethyl)-15-crown-5 (16). To a THF solution (12 mL) of **15** (751 mg, 3.0 mmol) and CBr_4 (1990 mg, 6.0 mmol) was added a THF solution (9.0 mL) of PPh_3 (1731 mg, 6.6 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm slowly to rt, stirred for an additional 12 h, filtered, and evaporated. A small amount of ether was added to the residue, and the resulting precipitate of Ph_3PO was filtered. The filtrate was evaporated and chromatographed (alumina; eluent, hexane:AcOEt = 3:1) to give **16**: yield 87% (817 mg); oil; IR (neat) 2810, 2780, 1090, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.40–3.93 (m, 21 H); ^{13}C NMR ($CDCl_3$) δ 33.51, 70.38, 70.46, 70.54, 70.72, 70.90, 71.31, 71.65, 78.91.

(Mercaptomethyl)-15-crown-5 (17). An EtOH solution (10 mL) of **16** (3132 mg, 10 mmol) and thiourea (913 mg, 12 mmol) was refluxed for 12 h. Sodium hydroxide (600 mg, 15 mmol) was added to the reaction mixture, and the reaction mixture was refluxed for an additional 12 h and acidified with diluted sulfuric acid. After removal of the solvent, the residue was dissolved in water. The aqueous solution was continuously extracted with CH_2Cl_2 (12 h). The extract was evaporated to give **17**: yield 89% (2371 mg); oil; IR (neat) 2910, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (t, *J* = 7.9 Hz, 1 H), 2.55–2.70 (m, 2 H), 3.57–3.86 (m, 19 H); ^{13}C NMR ($CDCl_3$) δ 26.31, 70.16, 70.22, 70.26, 70.36, 70.62, 70.94, 71.89, 78.18, 80.39.

***N*-(2-Hydroxyethyl)spirobenzopyran 18.** A CH_3CN solution (20 mL) of 2,3,3-trimethyl-3*H*-indole (1592 mg, 10 mmol) and 2-bromoethanol (1500 mg, 12 mmol) was refluxed for 24 h. After evaporation of the solvent, the resulting solid mass was recrystallized from $CHCl_3$ to give *N*-(2-hydroxyethyl)-2,3,3-trimethyl-3*H*-indolium bromide. An aqueous solution of the indolium bromide was basified with NaOH and extracted with ether. The ether extract was then evaporated to afford the corresponding *exo*-methyleneindoline. An EtOH solution (10 mL) of the *exo*-methyleneindoline and 5-nitrosalicylaldehyde (1053 mg, 6.3 mmol) was refluxed for 3 h. After evaporation of the solvent, the residue was recrystallized from ethanol to give **18**: overall yield 33% (733 mg); mp 172–173 °C; IR (KBr) 3400, 1600, 1500, 1470, 1330, 1280, 1090, 950, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.29 (s, 3 H), 3.29–3.82 (m, 4 H), 5.88 (d, *J* = 10.5 Hz, 1 H), 6.67 (d, *J* = 7.3 Hz, 1 H), 6.76 (d, *J* = 8.6 Hz, 1 H), 6.90 (t, *J* = 7.3 Hz, 1 H), 6.91 (d, *J* = 10.4 Hz, 1 H), 7.10 (d, *J* = 7.3 Hz, 1 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.99 (d, *J* = 2.8 Hz, 1 H), 8.02 (dd, *J* = 2.8, 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.06, 25.93, 46.14, 52.87, 60.90, 106.75, 106.93, 115.56, 118.59, 120.03, 121.91, 121.99, 122.78, 125.99, 127.87, 128.29, 135.87, 141.23, 147.01, 159.34.

***N*-(2-Bromoethyl)spirobenzopyran 19.** To a THF solution (80 mL) of **18** (7050 mg, 20 mmol) and CBr_4 (13 270 mg, 40 mmol) was added a THF solution (50 mL) of Ph_3P (10 750 mg, 41 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm slowly to rt and stirred at that temperature for an additional 12 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, hexane:AcOEt = 10:1) to give **19**: yield 95% (7890 mg); mp 147–149 °C; IR (KBr) 1515, 1480, 1330, 1260, 1080, 950, 810, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3 H), 1.28 (s, 3 H), 3.37–3.71 (m, 4 H), 5.91 (d, *J* = 10.4 Hz, 1 H), 6.60 (d, *J* = 7.3 Hz, 1 H), 6.75 (d, *J* = 8.5 Hz, 1 H), 6.89–6.95 (m, 2 H), 7.09 (dd, *J* = 1.2, 7.3 Hz, 1 H), 7.21 (dt, *J* = 1.2, 7.3 Hz, 1 H), 8.01 (s, 1 H), 8.05 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.86, 25.91, 29.75, 45.64, 53.01, 106.56, 115.62, 118.51, 120.27, 121.78, 122.11, 122.86, 126.05, 127.91, 128.58, 135.89, 141.31, 145.98, 159.16. Anal. Calcd for $C_{20}H_{19}N_2O_3Br$: C, 57.84; H, 4.61; N, 6.75. Found: C, 57.76; H, 4.47; N, 6.55.

***N*-(2-Iodoethyl)spirobenzopyran 20.** An acetone solution (40 mL) of **19** (6230 mg, 15 mmol) and NaI (6750 mg, 45 mmol) was stirred at rt for 12 h. After removal of the solvent, CH_2Cl_2 was added to the residue, and the resulting precipitate was filtered. The filtrate was evaporated and chromatographed (silica gel; eluent, hexane:AcOEt = 10:1) to give **20**: yield 81% (5620 mg); mp 149–152 °C; IR (KBr) 1515, 1480, 1330, 1260, 1085, 950, 810, 745; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3 H), 1.28 (s, 3 H), 3.16–3.73 (m, 4 H), 5.96 (d, *J* = 10.4 Hz, 1 H), 6.57 (d, *J* = 7.3 Hz, 1 H), 6.70 (d, *J* = 10.4 Hz, 1 H), 6.86–6.96 (m, 2 H), 7.10 (d, *J* = 7.3 Hz, 1 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 7.96–8.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 3.31, 19.82, 25.91, 46.53, 53.01, 106.58, 115.60, 118.49, 120.25, 121.76, 122.11, 122.86, 126.03, 127.89, 128.58, 135.87, 141.29, 145.82, 159.12. Anal. Calcd for $C_{20}H_{19}N_2O_3I$: C, 51.96; H, 4.14; N, 6.06. Found: C, 52.27; H, 3.89; N, 5.98.

Spirobenzopyran 6. A suspension of **17** (2660 mg, 10 mmol) and Cs_2CO_3 (3580 mg, 11 mmol) in DMF (10 mL) was stirred at 0 °C for 2 h. After the addition of **20** (4160 mg, 9.0 mmol) at that temperature, the reaction mixture was allowed to warm slowly to rt and stirred for an additional 48 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, AcOEt) to give **6**: yield 37% (2000 mg); oil; IR (neat) 2950, 1490, 1340, 1120, 1100, 815, 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.28 (s, 3 H), 2.55–2.98 (m, 6 H), 3.44–3.80 (m, 19 H), 5.96 (d, *J* = 10.4 Hz, 1 H), 6.60 (d, *J* = 7.4 Hz, 1 H), 6.74 (d, *J* = 10.4 Hz, 1 H), 6.83–6.95 (m, 2 H), 7.09 (d, *J* = 7.4 Hz, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 7.99 (s, 1 H), 8.01 (d, *J* = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.76, 25.87, 31.51, 34.30, 43.82, 52.71, 70.26, 70.32, 70.38, 70.46, 70.50, 70.78, 71.05, 72.34, 79.46, 79.58, 106.48, 115.44, 118.47, 119.62, 121.76, 121.95, 122.65, 125.77, 127.71, 128.17, 135.79, 140.97, 146.28, 159.32.

(5-Iodo-2-oxapentyl)-15-crown-5 (21). To a THF solution (20 mL) of **14**[10] (5810 mg, 20 mmol) was added a THF solution of borane–THF complex (221 mg, 8.0 mmol) dropwise at 0 °C, and the reaction mixture was then allowed to warm slowly to rt and stirred at that temperature for 12 h. Methanol (400 μL) followed by iodine (5080 mg, 20 mmol) and a methanol solution of NaOMe (5.12 M, 20 mmol) were added at 0 °C, and the reaction mixture was allowed to warm slowly to rt and stirred at that temperature for 12 h. A saturated $Na_2S_2O_3$ aqueous solution was added to the reaction mixture until it became colorless. After removal of the solvent, extractive workup with CH_2Cl_2 was followed by column chromatography (alumina; eluent, hexane:AcOEt = 2:1) to give **21**: yield 35% (2930 mg); oil; IR (neat) 2910, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00–2.11 (m, 2 H), 3.27 (t, *J* = 6.7 Hz, 1 H), 3.48–3.89 (m, 23 H); ^{13}C NMR ($CDCl_3$) δ 3.31, 33.39, 70.28, 70.40, 70.56, 70.60, 70.66, 70.82, 70.92, 71.03, 71.11, 71.33, 71.39, 78.69.

***exo*-Methyleneindoline 22.** A solution of **21** (837 mg, 2.0 mmol) and 2,3,3-trimethyl-3*H*-indole (350 mg, 2.2 mmol) in CH_3CN (10 mL) was refluxed for 48 h. After evaporation of the solvent, the reaction mixture was dissolved in water. The aqueous solution was washed with ether in order to remove the unreacted starting materials, basified by the addition of KOH (10 mmol), and stirred at rt for 10 min. Extractive workup with CH_2Cl_2 followed by column chromatography (silica gel; eluent, AcOEt:hexane:Et_3N = 10:10:1) afforded **22**: yield 67% (602 mg); oil; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 1.89 (quint, *J* = 6.1 Hz, 2 H), 3.43–3.92 (m, 27 H), 6.59 (d, *J* = 7.3 Hz, 1 H), 6.74 (dt, *J* = 1.2, 7.3 Hz, 1 H), 7.05–7.14 (m, 2 H).

Spirobenzopyran 7. A solution of **22** (899 mg, 2.0 mmol) and 5-nitrosalicylaldehyde (535 mg, 3.2 mmol) in EtOH (10 mL) was refluxed for 1 h. After evaporation of the solvent, the reaction mixture was subjected to column chromatography (silica gel; eluent, AcOEt) to give **7**: yield 95% (1138 mg); oil; IR (neat) 2900, 1490, 1340, 1285, 1130, 1100, 960, 810, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3 H), 1.27 (s, 3 H), 1.83–1.96 (m, 2 H), 3.13–3.88 (m, 25 H), 5.85 (dd, *J* = 3.1, 10.4 Hz, 1 H), 6.63 (d, *J* = 7.9 Hz, 1 H), 6.73 (d, *J* = 10.4 Hz, 1 H), 6.84–6.93 (m, 2 H), 7.07 (d, *J* = 6.7 Hz, 1 H), 7.17 (t, *J* = 6.7 Hz, 1 H), 7.96–8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.82, 25.99, 29.14, 40.50, 52.69, 68.68, 68.78, 70.34, 70.38, 70.52, 70.60, 70.82, 70.94, 71.13, 71.31, 71.45, 78.85, 106.77, 115.50, 118.57, 119.38, 121.64, 121.97, 122.01, 122.67, 125.83, 127.77, 127.13, 135.91, 140.91, 147.17, 159.65.

***N*-(5-Iodo-3-oxapentyl)-*exo*-methyleneindoline 23.** To an acetonitrile solution (80 mL) of bis(2-iodoethyl) ether (19 600 mg, 60 mmol), which was prepared by the treatment of bis(2-chloroethyl) ether with NaI in acetone, was added an acetonitrile solution (40 mL) of 2,3,3-trimethyl-3*H*-indole (1600 mg, 10 mmol) dropwise at reflux temperature. After the completion of the addition, the reaction mixture was refluxed for a further 30 h, evaporated, and dissolved in water. The aqueous solution was washed with ether in order to remove the unreacted starting materials, basified to pH 9–10 by the addition of NaOH, and stirred at rt for 10 min. Extractive workup with ether was followed by column chromatography (silica gel; eluent, hexane:AcOEt = 20:1) to give **23**: yield 64% (2290 mg); oil; IR (neat) 3000, 2950, 2900, 1660, 1610, 1490, 1470, 1460, 1380, 1350, 1130, 1030, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6 H), 3.19 (t, *J* = 6.7 Hz, 2 H), 3.64–3.77 (m, 6 H), 3.85 (d, *J* = 1.0 Hz, 1 H), 3.92 (d, *J* = 1.0 Hz, 1 H), 6.65 (d, *J* = 7.3 Hz, 1 H), 6.78 (t, *J* = 7.3 Hz, 1 H), 7.08–7.16 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 2.83, 30.13, 42.68, 44.26, 66.90, 71.98, 73.49, 105.63, 118.69, 121.85, 127.55, 137.37, 145.98, 161.63.

N-(5-Iodo-3-oxapentyl)spirobenzopyran 24. A solution of **23** (786 mg, 2.2 mmol) and 5-nitrosalicylaldehyde (401 mg, 2.4 mmol) in EtOH (20 mL) was refluxed for 3 h. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel; eluent, hexane:ether = 3:1) to give **24**: yield 70% (780 mg); mp 111–112 °C; IR (KBr) 2900, 2800, 1610, 1510, 1480, 1330, 1280, 1090, 1010, 950, 800, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.18 (s, 3 H), 1.28 (s, 3 H), 3.19 (t, J = 6.7 Hz, 2 H), 3.29–3.72 (m, 6 H), 5.96 (d, J = 10.4 Hz, 1 H), 6.64 (d, J = 7.3 Hz, 1 H), 6.73 (d, J = 7.9 Hz, 1 H), 6.88 (t, J = 7.3 Hz, 1 H), 6.90 (d, J = 10.4 Hz, 1 H), 7.09 (dd, J = 1.2, 7.3 Hz, 1 H), 7.18 (dt, J = 1.2, 7.3 Hz, 1 H), 7.99 (d, J = 2.4 Hz, 1 H), 8.01 (dd, J = 2.4, 7.9 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 2.88, 19.86, 25.95, 43.57, 52.81, 69.02, 71.67, 106.62, 106.72, 115.44, 118.61, 119.64, 121.76, 122.39, 122.69, 125.79, 127.73, 127.97, 135.81, 141.01, 146.77, 159.51. Anal. Calcd for $C_{22}H_{23}N_2O_4I$: C, 52.19; H, 4.58; N, 5.53. Found: C, 52.50; H, 4.63; N, 5.51.

Spirobenzopyrans 8a–d (Exemplified with 8a). To a THF suspension (5 mL) of monoaza-12-crown-4[11] (263 mg, 1.5 mmol) and finely ground K_2CO_3 (429 mg, 3.1 mmol) was added a THF solution (5 mL) of **24** (157 mg, 0.31 mmol) dropwise at reflux temperature. The reaction mixture was refluxed for a further 12 h, evaporated, and subjected to column chromatography (silica gel; eluent, AcOEt:Et$_3$N = 20:1) to give **8a**.

8a: yield 59% (101 mg); oil; IR (neat) 2800, 1600, 1470, 1330, 1270, 1110, 1080, 950, 900, 800, 710 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.16 (s, 3 H), 1.27 (s, 3 H), 2.66–2.74 (m, 6 H), 3.28–3.68 (m, 18 H), 5.89 (d, J = 10.4 Hz, 1 H), 6.69 (d, J = 7.3 Hz, 1 H), 6.74 (d, J = 8.6 Hz, 1 H), 6.87 (t, J = 7.3 Hz, 1 H), 6.89 (d, J = 10.4 Hz, 1 H), 7.08 (dd, J = 1.2, 7.3 Hz, 1 H), 7.18 (dt, J = 1.2, 7.3 Hz, 1 H), 7.99 (d, J = 2.4 Hz, 1 H), 8.00 (dd, J = 2.4, 8.6 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 19.88, 25.93, 43.55, 52.81, 55.56, 56.13, 69.37, 69.97, 70.36, 71.19, 106.68, 106.72, 115.50, 118.59, 119.56, 121.70, 122.21, 122.69, 125.83, 127.75, 128.03, 135.77, 141.01, 146.91, 159.57.

8b: yield 68% (109 mg); oil; IR (neat) 2800, 1600, 1500, 1480, 1320, 1260, 1100, 940, 800, 740 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.16 (s, 3 H), 1.27 (s, 3 H), 2.71 (t, J = 6.1 Hz, 2 H), 2.79 (t, J = 6.1 Hz, 4 H), 3.33–3.68 (m, 22 H), 5.89 (d, J = 10.4 Hz, 1 H), 6.63 (d, J = 7.3 Hz, 1 H), 6.74 (d, J = 8.6 Hz, 1 H), 6.87 (t, J = 7.3 Hz, 1 H), 6.89 (d, J = 10.4 Hz, 1 H), 7.08 (dd, J = 1.2, 7.3 Hz, 1 H), 7.18 (dt, J = 1.2, 7.3 Hz, 1 H), 7.99 (d, J = 2.4 Hz, 1 H), 8.00 (dd, J = 2.4, 8.6 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 19.90, 25.97, 43.55, 52.83, 55.10, 55.93, 69.37, 69.95, 70.18, 70.44, 71.03, 106.72, 115.52, 118.61, 119.58, 121.74, 122.25, 122.73, 125.87, 127.77, 128.07, 135.79, 140.28, 146.95, 159.59.

8c: yield 31% (62 mg); oil; IR (neat) 2850, 1620, 1480, 1330, 1265, 1100, 950, 800, 740 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.16 (s, 3 H), 1.27 (s, 3 H), 2.77 (t, J = 6.1 Hz, 2 H), 2.86 (t, J = 5.5 Hz, 4 H), 3.26–3.69 (m, 26 H), 5.89 (d, J = 10.4 Hz, 1 H), 6.63 (d, J = 7.3 Hz, 1 H), 6.74 (d, J = 8.5 Hz, 1 H), 6.87 (t, J = 7.3 Hz, 1 H), 6.90 (d, J = 10.4 Hz, 1 H), 7.08 (dd, J = 1.2, 7.3 Hz, 1 H), 7.18 (dt, J = 1.2, 7.3 Hz, 1 H), 7.99 (d, J = 3.1 Hz, 1 H), 8.01 (dd; J = 3.1, 8.5 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 19.92, 25.99, 43.57, 52.85, 54.59, 54.81, 69.37–70.88, 106.74, 106.77, 115.54, 118.63, 119.62, 121.76, 122.27, 122.75, 125.89, 127.77, 128.11, 135.81, 141.05, 146.99, 159.61.

8d: yield 64% (136 mg); oil; IR (neat) 2900, 1610, 1490, 1340, 1280, 1100, 960, 920, 810, 740 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.16 (s, 3 H), 1.27 (s, 3 H), 2.72 (t, J = 6.1 Hz, 2 H), 2.80 (t, J = 5.5 Hz, 4 H), 3.31–3.74 (m, 30 H), 5.89 (d, J = 10.4 Hz, 1 H), 6.63 (d, J = 7.3 Hz, 1 H), 6.74 (d, J = 8.5 Hz, 1 H), 6.87 (t, J = 7.3 Hz, 1 H), 6.89 (d, J = 10.4 Hz, 1 H), 7.08 (dd, J = 1.2, 7.3 Hz, 1 H), 7.18 (dt, J = 1.2, 7.3 Hz, 1 H), 7.99 (d, J = 3.0 Hz, 1 H), 8.01 (dd, J = 3.0, 8.5 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 19.90, 25.97, 43.57, 52.83, 54.59, 54.75, 69.35–71.05, 106.72, 115.52, 118.61, 119.58, 121.74, 122.25, 122.73, 125.85, 127.77, 128.07, 135.79, 141.03, 146.95, 159.59.

6-(Hydroxymethyl)-2,3,3-trimethyl-3*H*-indole (26). To a concentrated HCl aqueous solution (16 mL) of *m*-aminobenzyl alcohol (12200 mg, 40 mmol) was added an aqueous solution (14 mL) of NaNO$_2$ (2760 mg, 40 mmol) at 0 °C. After 30 min of stirring, a concentrated HCl aqueous solution (28 mL) of $SnCl_2 \cdot 2H_2O$ (27100 mg, 120 mmol) was added to the reaction mixture at that temperature. The reaction mixture was stirred for an additional 30 min, washed with ether, neutralized with NaOH, and extracted with ether. The ether extract was evaporated to afford **25**, which was used for the next reaction without further purification. A solution of **25** and 3-methyl-2-butanone (3445 mg, 40 mmol) in AcOH (20 mL) was stirred at 100 °C for 2 h. The reaction mixture was evaporated and subjected to column chromatography (silica gel; eluent, AcOEt) to give **26**: yield 5% (379 mg) based on *m*-aminobenzyl alcohol; oil; IR (neat) 3300, 2800, 1570, 1410, 1010, 810 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.28 (s, 6 H), 2.26 (s, 3 H), 4.72 (s, 2 H), 7.22–7.27 (m, 2 H), 7.53 (s, 1 H); ^{13}C NMR (CDCl$_3$) δ 15.35, 23.10, 53.46, 65.30, 118.73, 121.26, 124.05, 141.05, 145.01, 153.93.

6-(Hydroxymethyl)-*exo*-methyleneindoline 27. A solution of **26** (1079 mg, 5.7 mmol) and CH$_3$I (4045 mg, 28.5 mmol) in ether (10 mL) was refluxed for 12 h. The reaction mixture was evaporated and the residue was dissolved in water. The aqueous solution was washed with ether in order to remove the unreacted starting materials, basified to pH 8–9 with NaOH, and extracted with ether. The ether extract was evaporated and subjected to column chromatography (silica gel; eluent, hexane:AcOEt = 1:1) to give **27**: yield 80% (927 mg); oil; IR (neat) 3300, 2800, 1640, 1600, 1440, 1390, 1120, 950, 800 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.33 (s, 6 H), 3.05 (s, 3 H), 3.85 (s, 2 H), 4.64 (s, 2 H), 6.59 (s, 1 H), 6.73 (d, J = 7.3 Hz, 1 H), 7.05 (d, J = 7.3 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 28.80, 29.91, 65.89, 73.41, 103.83, 117.11, 121.74, 137.41, 140.75, 146.91.

6′-(Hydroxymethyl)spirobenzopyran 28. A solution of **27** (915 mg, 4.5 mmol) and 5-nitrosalicylaldehyde (819 mg, 4.9 mmol) in EtOH (10 mL) was refluxed for 2 h. The reaction mixture was evaporated and subjected to column chromatography (silica gel; eluent, hexane:AcOEt = 4:3) to give **28**: yield 86% (1520 mg); mp 167–168 °C; IR (KBr) 3400, 2900, 2800, 1610, 1510, 1460, 1340, 1280, 1090, 1010, 950, 800, 740 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.19 (s, 3 H), 1.29 (s, 3 H), 2.76 (s, 3 H), 4.69 (s, 2 H), 5.86 (d, J = 10.4 Hz, 1 H), 6.61 (s, 1 H), 6.77 (d, J = 8.5 Hz, 1 H), 6.87 (d, J = 7.3 Hz, 1 H), 6.93 (d, J = 10.4 Hz, 1 H), 7.06 (d, J = 7.3 Hz, 1 H), 8.00 (d, J = 2.4 Hz, 1 H), 8.02 (dd, J = 2.4, 8.5 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 20.00, 25.89, 28.90, 52.17, 65.85, 105.96, 106.56, 115.48, 118.53, 118.69, 121.26, 121.56, 121.60, 122.73, 125.91, 128.35, 141.05, 148.21, 158.78, 159.75.

6′-(Bromomethyl)spirobenzopyran 29. To a THF solution (3 mL) of **28** (187 mg, 0.53 mmol) and CBr$_4$ (352 mg, 1.06 mmol) was added a THF solution (1 mL) of Ph$_3$P (278 mg, 1.06 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm slowly to rt and stirred at that temperature for an additional 12 h. After removal of the solvent, the residue was chromatographed (silica gel, eluent, hexane:AcOEt = 5:1) to give **29**: yield 21% (46 mg); mp 201–204 °C; IR (neat) 2900, 1610, 1510, 1330, 1260, 1090, 1010, 950, 800, 740, 650 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.18 (s, 3 H), 1.28 (s, 3 H), 2.75 (s, 3 H), 4.53 (s, 2 H), 5.84 (d, J = 10.4 Hz, 1 H), 6.57 (d, J = 1.8 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 6.91 (dd, J = 1.8, 7.3 Hz, 1 H), 6.93 (d, J = 10.4 Hz, 1 H), 7.02 (d, J = 7.3 Hz, 1 H), 8.00 (d, J = 3.1 Hz, 1 H), 8.03 (dd, J = 3.1, 8.5 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 19.96, 25.85, 28.88, 34.58, 52.23, 106.42, 107.65, 115.52, 118.65, 120.63, 121.42, 121.76, 122.75, 125.67, 125.95, 128.42, 136.89, 137.57, 148.27, 159.67. Anal. Calcd for $C_{20}H_{19}N_2O_3Br$: C, 57.85; H, 4.61; N, 6.75. Found: C, 57.64; H, 4.54; N, 6.61.

6′-(Crown-linked)spirobenzopyran 9. To a THF suspension (1.0 mL) of monoaza-18-crown-6 (126 mg, 0.48 mmol)[11] and finely ground K$_2$CO$_3$ (66 mg, 0.48 mmol) was added a THF solution (1.0 mL) of **29** (40 mg, 0.096 mmol) dropwise at 60 °C. The reaction mixture was stirred at that temperature for an additional 5 h. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel; eluent, AcOEt:Et$_3$N = 20:1) to give **9**: yield 53% (30 mg); oil; IR (neat) 2800, 1730, 1600, 1500, 1460, 1330, 1260, 1100, 950, 800, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.17 (s, 3 H), 1.28 (s, 3 H), 2.73 (s, 3 H), 2.84 (t, J = 6.1 Hz, 4 H), 3.62–3.71 (m, 22 H), 5.85 (d, J = 10.4 Hz, 1 H), 6.58 (s, 1 H), 6.78 (d, J = 8.6 Hz, 1 H), 6.81 (d, J = 7.3 Hz, 1 H), 6.91 (d, J = 10.4 Hz, 1 H), 6.98 (d, J = 7.3 Hz, 1 H), 7.99 (d, J = 2.4 Hz, 1 H), 8.02 (dd, J = 2.4, 8.6 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 20.10, 26.01, 28.94, 52.17, 53.72, 60.21, 106.62, 107.86, 115.52, 118.75, 120.57, 121.18, 121.80, 122.71, 125.87, 128.19, 128.29, 141.01, 148.00.

3*H*-Indolium Iodide 10. A pyridine solution (2.0 mL) of 1,2,3,3-tetramethyl-3*H*-indolium iodide (301 mg, 1.0 mmol) and *o*-anisaldehyde diethyl acetal (210 mg, 1.0 mmol), which was

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[11] Krakowiak, K.; Bradshaw, J. S.; Zamecka-Krakowiak, D. *Chem. Rev.* **1989**, *89*, 929–972.

J. Org. Chem. **1992**, *57*, 5383–5394

prepared by the treatment of *o*-anisaldehyde with triethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid, was stirred at 80 °C for 3.5 h. The resulting precipitate was filtered, washed with ether, and recrystallized from CH_3CN to give **10**: yield 67% (280 mg); IR (KBr) 3020, 1605, 1545, 1485, 1465, 1315, 1260, 1170, 1035, 970, 770 cm^{-1}; ^1H NMR (CD_3CN) δ 1.74 (s, 6 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.14 (d, J = 7.9 Hz, 1 H), 7.53 (d, J = 16.5 Hz, 1 H), 7.56–7.62 (m, 3 H), 7.64–7.71 (m, 2 H), 7.96 (dd, J = 1.2, 7.3 Hz, 1 H), 8.50 (d, J = 16.5 Hz, 1 H); ^{13}C NMR (CD_3CN) δ 26.57, 35.50, 53.51, 57.07, 113.31, 113.79, 115.88, 118.65, 122.28, 123.80, 130.31, 130.71, 131.48, 136.72, 142.92, 144.38, 150.28, 161.22, 183.94.

***N*-Acetylmonoaza-crown Ethers 11a–c (Exemplified with 11a).** To a CH_2Cl_2 solution (2.0 mL) of monoaza-15-crown-5 (55 mg, 0.25 mmol)[11] and finely ground K_2CO_3 (69 mg, 0.5 mmol) was added acetyl chloride (39 mg, 0.5 mmol) dropwise at 0 °C. After 2 h of stirring at rt, evaporation of the solvent was followed by extractive workup with CH_2Cl_2 gave **11a**.

11a: yield 90% (59 mg); oil; IR (neat) 2800, 1600, 1440, 1350, 1250, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H), 3.49–3.85 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 21.60, 47.66, 49.03, 69.15–71.53, 171.03.

11b: yield 88% (67 mg); oil; IR (neat) 2800, 1620, 1420, 1350, 1230, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.59–3.72 (m, 24 H); ^{13}C NMR ($CDCl_3$) δ 21.68, 46.71, 49.92, 69.47–70.92, 171.01.

11c: yield 90% (79 mg); oil; IR (neat) 2800, 1620, 1440, 1350, 1240, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.58–3.73 (m, 28 H); ^{13}C NMR ($CDCl_3$) δ 21.70, 46.36, 49.88, 69.43–70.99, 171.03.

Supplementary Material Available: Proton NMR spectra of all new compounds for which elemental analyses are not given (29 pages). This material is contained in many 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.

New Symmetrical Chiral Dibenzyl- and Diphenyl-Substituted Diamido-, Dithionoamido-, Diaza-, and Azapyridino-18-crown-6 Ligands

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Eleven new chiral macrocycles (1–11, see Figure 1) of the pyridino-18-crown-6 type have been prepared. Nine diazapyridino-crown ligands contain two amide (**1**, R = benzyl; **4**, R = phenyl), two *N*-methylamide (**7**, R = phenyl), two thionoamide (**2**, R = benzyl; **5**, R = phenyl), two *N*-methylthionoamide (**8**, R = phenyl), two amine (**3**, R = benzyl; **6**, R = phenyl), or two *N*-methylamine (**9**, R = phenyl) groups incorporated into the macroring. The appropriate chiral diamine was treated with dimethyl 2,6-pyridinedicarboxylate (or 2,6-pyridinedicarbonyl dichloride), *O*,*O*′-dimethyl 2,6-pyridinedicarbothioate, or 2,6-pyridinedimethyl ditosylate to prepare these materials. The macrocyclic diamides were also converted to the macrocyclic dithionoamides using Lawesson's reagent and the latter macrocycles were reduced to the diamines. A new symmetrically substituted dimethylazapyridino-18-crown-6 ligand (**10**) and its *N*-acetyl derivative **11** were also prepared. The interactions of some of the new chiral ligands with (*R*)- and (*S*)-[α-(1-naphthyl)ethyl]ammonium perchlorate were studied by ^1H NMR spectral techniques. The degree of enantiomeric recognition was determined by the difference of the free energy of activation values ($\Delta\Delta G^*$) and the difference in log K values for these interactions. The X-ray analyses of the dithionoamido ligands (**2**, **5**, and **8**) showed severe deviations of the S and N atoms from the plane of the pyridine ring, especially in the case of **8**. The optical rotation of **8** changed with time due to conformational changes. The relevant conformations of **8** are discussed in light of the X-ray crystallography, molecular mechanics, and ^1H NMR spectra.

Introduction

Enantiomeric recognition phenomena play an important role in a variety of physical, chemical, and biological processes. Examples include sensing, determination of concentrations, and separations of enantiomers; catalysis reactions; and incorporation of single enantiomeric forms of amino acids and sugars in biochemical pathways.

Our interest in enantiomeric recognition has focused on the interaction of chiral macrocycles with chiral organic ammonium salts.[1–5] Since Cram and his co-workers published their pioneering studies on the use of chiral macrocyclic ligands in enantiomeric recognition,[6] a great number of chiral macrocycles have been synthesized and studied. Most of this work has been reviewed.[4,5,7,8]

In the past decade, we have particularly been interested in the interactions of chiral macrocycles containing pyridine units with organic ammonium salts.[1–5] These crown ethers were chosen for study because they form strong complexes with organic ammonium salts[1] and they also show appreciable enantiomeric recognition in certain cases.[1–5] Thus, diester[1,2,5] (X = O, Y = O, R = alkyl, phenyl), dithiono ester[1] (X = O, Y = S, R = methyl), and

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(1) Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1984**, *49*, 353.

(2) Bradshaw, J. S.; Thompson, P. K.; Izatt, R. M.; Morin, F. G.; Grant, D. M. *J. Heterocycl. Chem.* **1984**, *21*, 897.

(3) Bradshaw, J. S.; Colter, M. L.; Nakatsuji, Y.; Spencer, N. O.; Brown, M. F.; Izatt, R. M.; Arena, G.; Tse, P.-K.; Wilson, B. E.; Lamb, J. D.; Dalley, N. K.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1985**, *50*, 4865.

(4) Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1990**, *55*, 3129.

(5) Huszthy, P.; Bradshaw, J. S.; Zhu, C. Y.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1991**, *56*, 3330.

(6) Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692.

(7) Li, Y.; Echegoyen, L.; Martinez-Diaz, M. V.; Mendoza, J.; Torres, T. *J. Org. Chem.* **1991**, *56*, 4193.

(8) Izatt, R. M.; Zhu, C.-Y.; Huszthy, P.; Bradshaw, J. S. Enantiomeric Recognition in Macrocycle-Primary Ammonium Cation Systems in *Crown Ethers: Toward Future Applications*; Cooper, S. R., Ed.; VCH Press: New York, in press.

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