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Croconines: new acidochromic dyes for the near infrared region

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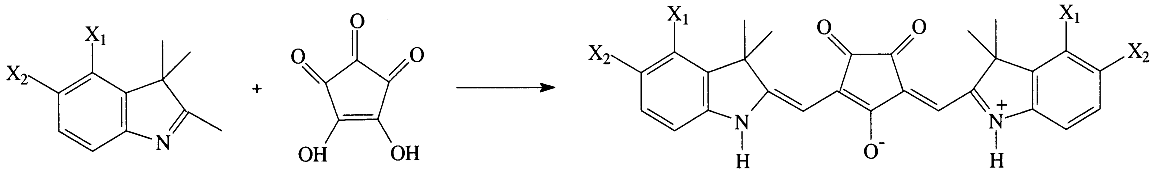
Abstract—The synthesis and characterization of new nor-indocrococyanine dyes are described. The acid form of the obtained dyes has an absorbance maxima in the 759–800 nm range. They present spectral changes at pH 6.5–9.7. © 2002 Published by Elsevier Science Ltd.

In recent years there has been intensive work in the synthesis of new acidochromic dyes that absorb in the near infrared region for application in optical sensors.[1] Research in this field attempts to take advantage of the availability of inexpensive optical devices (diode laser sources, photodetectors…) that work in this low interference spectral region. Croconic acid dyes are known since the last decade.[2] Nevertheless, they have been investigated and synthesized to a much lesser degree than similar squarines.[2b] The more convenient croconine dyes have advantages over squaric acid ones, due to their stronger absorption, greater photostability[3] and better yield. Moreover, croconines absorb at longer wavelengths than the homologous squarines.

These extreme properties have drawn our attention for the design of new croconines with absorption bands in the near infrared region to be used as pH-sensitive components in optical sensors. The preparation of dyes is rather simple and fast. They are synthesized by condensation of an aromatic base (regularly, heterocyclic derivatives) with croconic acid in a benzene/butanol mixture, usually without a catalyst. Azeotropic water extraction is recommended. We have found that free bases of substituted 2,3,3-trimethylindolenines **1a**–**f** react with croconic acid **2**[4] resulting in nor-indocrococyanine dyes **3a**–**f** (Scheme 1).[5]

They present the absorbance maximum in the near infrared region and lower pK_a values than those of the corresponding alkylated derivatives of the croconines which are obtained similarly from the quaternary salts of bases. All of the studied dyes exhibit sharp and intense absorption bands in ethanol with maximum absorbance wavelengths of the acid form in the 759–800 nm range (Table 1).

The introduction of substituents in the benzene ring of the terminal heterocycle produces important bathochromic shifts of the acid absorption band. The extent of those shifts depends on the nature of the substituent. All of them present an acid-base behavior, similar to that shown in Fig. 1, corresponding to com-



1a-f **2** **3a-f**

Scheme 1.

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Table 1. Yields, spectroscopic characteristics and pK_a values in ethanol of synthesized dyes

Dye	X_1	X_2	λ_{acid} (nm)	λ_{basic} (nm)	ε (M cm)$^{-1}$	pK_a	Yield (%)
3a	H	H	759.0	626.0	1.5×10^5	9.7	76
3b	H	C_4H_9	775.0	642.5	1.7×10^5	9.1	63
3c*	-(CH=CH)$_2$-		800.0	650.0	7.1×10^4	8.6	64
3d	H	OCH_3	793.5	638.5	5.8×10^4	9.6	36
3e*	H	NO_2	793.0	630.0	1.5×10^5	6.5	70
3f	H	$NHCOCH_3$	798.5	639.5	4.4×10^4	9.4	35

* 10% DMFA

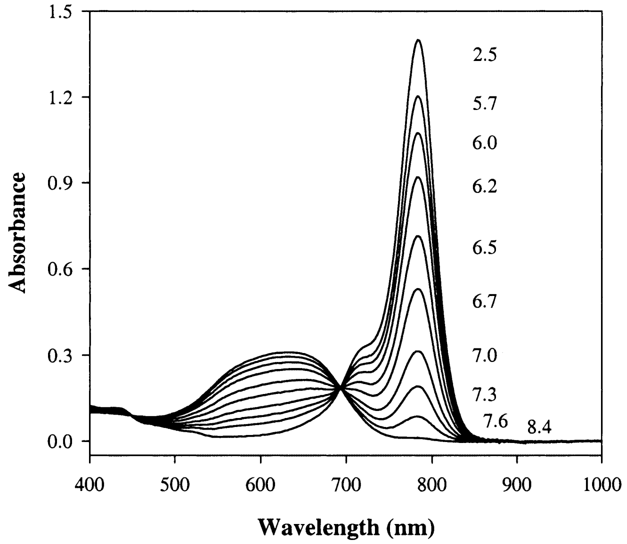

Figure 1. Absorbance spectra of dye **3e** in ethanol at indicated pH.

pound **3e** as a typical example of the absorption spectra changes with pH.

Proposed acid–base equilibrium of synthesized croconium dyes consists in a protonation–deprotonation of the acidic nitrogen. As pH is increased, deprotonation of the nitrogen occurs, avoiding the charge delocalization and therefore, producing a hypsochromic shift of the maximum wavelength. The pK_a values obtained from titration curves lie between 6.5 and 9.7 units. Due to the high electron-withdrawing properties of nitro substituent, dye **3e** presents the lowest pK_a value. Back-and-forth experiments demonstrate a total reversibility of the spectral changes. Croconines are scarcely soluble in water presenting good solubility in the polymeric plasticizer commonly used in optical sensors.

These results confirm that the synthesized croconium dyes present promising characteristics, worthy of being integrated as NIR active components in optical pH-sensitive membranes with laser diode sources emitting at 780 nm.

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4. Compound **2** was obtained by the procedure reported in: Yamada, K.; Hirada, Y. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 550. It was immediately used in the synthesis of croconines.
5. Representative procedure for **3a**: 636 mg (4 mmol) of 2,3,3-trimethylindolenine **1a** and 290 mg (2 mmol) of croconic acid **2** were heated at reflux in a mixture of 10 ml butanol and 10 ml benzene; the water was removed azeotropically using a Dean–Stark trap. The reaction was monitored by UV–vis/NIR spectroscopy until complete disappearance of precursor bands. The reaction mixture was kept overnight at −20°C. The crystals were filtered out and washed with ether. A second crop is obtained by evaporation of the resulting solution and treatment of the oily material with hexane. Further recrystallization with methanol gave a high purity compound. Yield: 643 mg (76%). ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm, 1.50 (s, 12H), 5.97 (s, 2H), 7.21–7.41 (m, 8H). Anal. calcd for $C_{27}H_{24}O_3N_2$; C, 76.40; H, 5.70; N, 6.60. Found; C, 75.60; H, 5.73; N, 6.47. MALDI *m*/*z* 424.1 (M^+, 100%), 447.2 (M^++Na, 98%). **3b**: Yield: 681 mg (63%). ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm, *J* Hz; 0.83–0.94 (m, 6H), 1.29–1.38 (m, 4H), 1.47 (s, 12H), 1.55–1.61 (m, 4H), 2.62 (t, *J*=7.8 Hz, 4H), 5.92 (s, 2H), 7.18 (d, *J*=8.4 Hz, 2H), 7.36–7.40 (m, 4H). Anal. calcd for $C_{33}H_{40}O_3N_2$; C, 78.33; H, 7.51; N, 5.23. Found; C, 77.97; H, 7.58; N, 5.05. MALDI *m*/*z* 536.2 (M^+, 100%), 537.2 (M^++H, 62%). **3c**: Yield: 209 mg (64%). ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm, 1.50 (s, 12H), 5.96 (s, 2H), 7.21–7.56 (m, 12H). Anal. calcd for $C_{35}H_{28}O_3N_2$; C, 80.13; H, 5.38; N, 5.34. Found; C, 79.85; H, 5.28; N, 5.24. MALDI *m*/*z* 637.1 (M^++C_4H_9–H, 100%), 638.1 (M^++2C_4H_9, 44%). **3d**: Yield: 174 mg

(36%). ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm, J Hz; 1.48 (s, 12H), 3.80 (s, 6H), 5.89 (s, 2H), 6.93 (dd, J=8.6 Hz, J=2.0 Hz, 2H), 7.24 (d, J=2.0 Hz, 2H), 7.44 (d, J=8.6 Hz, 2H). Anal. calcd for $C_{29}H_{28}O_5N_2$; C, 71.88; H, 5.82; N, 5.78. Found; C, 71.52; H, 5.77; N, 5.49. MALDI m/z 541.4 (M^++C_4H_9, 100%), 542.4 (M^++C_4H_9+H, 35%). **3e**: Yield: 304 mg (70%). ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm, J Hz; 1.58 (s, 12H), 6.15 (s, 2H), 7.74 (d, J=8.7 Hz, 2H), 8.31.(dd, J=8.7 Hz, J=2.5 Hz, 2H), 8.55 (d, J=2.5 Hz, 2H). Anal. calcd for $C_{27}H_{22}O_7N_4$; C, 63.03; H, 4.31; N, 10.89. Found; C, 62.80; H, 4.48; N, 10.39. MALDI m/z 627.4 (M^++2C_4H_9–H, 100%), 628.2 (M^++2C_4H_9, 34%). **3f**: Yield: 565 mg (35%). ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm; 1.47 (s, 12H), 2.05 (s, 6H), 5.95 (s, 2H), 7.42–7.51 (m, 4H), 7.79 (s, 2H), 10.10 (s, 2H). Anal. calcd for $C_{31}H_{30}O_5N_4$; C, 69.13; H, 5.61; N, 10.40. Found; C, 63.40; H, 5.45; N, 10.20. MALDI m/z 651.6 (M^++2C_4H_9–H, 100%), 652.6 (M^++2C_4H_9, 36%).