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A new, strongly absorbing red dipyrrole chromophore **1** suitable for exciton coupling studies has been synthesized and shown to exhibit an intense absorption ($\epsilon \sim 57,000$) at λ (max) ~ 520 nm and a strong fluorescence at λ (em) ~ 555 nm.

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Introduction.

Some twenty years ago, Lugtenburg *et al.* [1] described a synthetic dipyrromethene complex, 1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, which absorbs strongly in the red region of the visible spectrum (ϵ (max) 83,200, λ (max) 505 nm in ethanol) and is highly fluorescent (fluorescence quantum yield: 0.80, λ (em) 516 nm). As its sodium sulfonate derivative, this dye proved to be an excellent fluorescent probe in medical and biological assays [2]. It appeared to us that the chromophore might make an excellent red-shifted chromophore for exciton coupling studies [3] and also a chromophore suitable for fluorescence-detected circular dichroism spectroscopy [4]. For these purposes, we required a pigment with a non-sterically hindered carboxylic acid group oriented along the long axis of the chromophore, and hence aligned with the likely orientation of the chromophore's long wave length electric dipole transition moment. In the following we describe the synthesis and properties of such a compound **2** and its methyl ester **1**.

Synthesis.

As outlined in Scheme I, two component pyrroles are required for the synthesis of **1**, a new phenyl-substituted

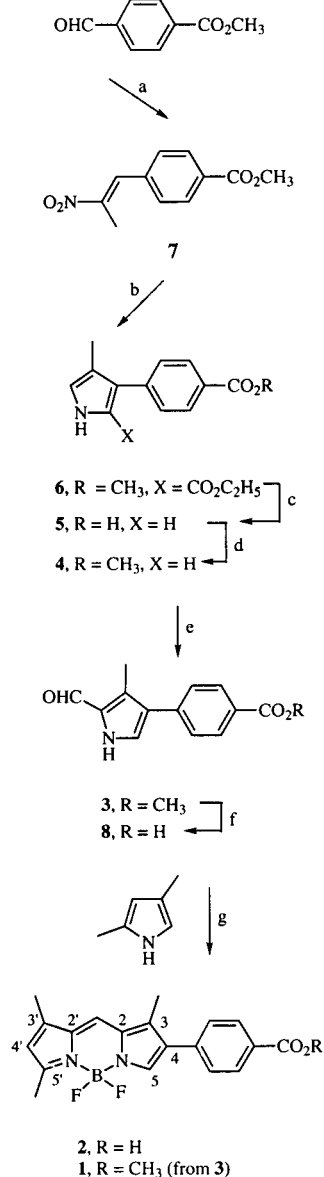
pyrrole **3**, and the well-known 2,4-dimethylpyrrole [5]. Pyrrole **3** was prepared in several steps *via* a Barton-Zard synthesis [6,7]. The nitrostyrene component **7** of the Barton-Zard synthesis was prepared by condensing methyl 4-formylbenzoate with nitroethane to afford a yellow crystalline solid in 85% yield. Base-catalyzed reaction of **7** with ethyl isocynoacetate gave a new pyrrole diester **6** as colorless crystals in 81% yield. The pyrrole carboethoxy group was removed, first by saponification, then heated in the basic solution to decarboxylate, thus affording acid **5**, which was esterified directly using diazomethane to give **4** in an excellent yield of 96% (from **6**). An aldehyde group was introduced onto the pyrrole ring of **4** using triethyl orthoformate in the presence of trifluoroacetic acid to give to a mixture of isomeric aldehydes, methyl 4-(2-formyl-3-methylpyrr-4-yl)benzoate (**3**) and methyl 4-(2-formyl-4-methylpyrr-3-yl)benzoate. The former is the major isomer and was obtained as light orange plates in 78% yield by crystallization of the mixture from ethanol. Condensation of **3** with 2,4-dimethylpyrrole [5] in dry benzene using boron trifluoride etherate as catalyst afforded the desired dipyrromethene **1** as red needles in 86% yield. The preparation of the free acid **2** was best achieved first by saponifying **3** to its acid

Table 1
Comparison of UV-visible Absorption and Fluorescence Data of **1** and **2** [a,b]

Solvent	UV-Visible of 1 [a]	UV-Visible of 2 [b]	Fluorescence of 1 [d]		Fluorescence of 2 [d]	
	λ_{max} (ϵ_{max}) [c]	λ_{max} (ϵ_{max}) [c]	λ_{em}	ϕ_f	λ_{em}	ϕ_f
chloroform	520 (57100)	520 (48600)	556	0.43 1	554	0.48
benzene	524 (57800)	524 (45300)	559	0.43 1	557	0.46
acetone	511 (57000)	512 (48300)	554	0.39 1	553	0.48
acetonitrile	510 (53900)	510 (45500)	554	0.37 1	549	0.51
methanol	511 (57300)	512 (47700)	552	0.38	553	0.39
ethyl acetate	513 (56700)	514 (47700)	553	0.43	553	0.48
tetrahydrofuran	516 (55000)	516 (48400)	556	0.37	555	0.39
dimethylformamide	515 (50400)	515 (46700)	560	0.35	560	0.32
dimethylsulfoxide	515 (52400)	515 (46700)	557	0.35	559	0.36
acetic acid	514 (53800)	515 (54300)	556	0.38	550	0.49

[a] solutions were 9.23×10^{-6} M. [b] solutions were 8.72×10^{-6} M. [c] λ_{max} in nm/ ϵ_{max} in M⁻¹ cm⁻¹. [d] λ_{em} in nm at maximum emission/ ϕ_f = fluorescence quantum yield.

Scheme I



- a, CH₃CH₂NO₂, NH₄OAc, 12 hours reflux
 b, CNCH₂CO₂C₂H₅, tetrahydrofuran, 1,8-diazabicyclo[5.4.0]undec-7-ene, 12 hours
 c, (CH₂OH)₂, NaOH, 3 hours reflux
 d, CH₂N₂, ether
 e, HC(OC₂H₅)₃, trifluoroacetic acid, 0°, 10 minutes
 f, KOH/CH₃OH
 g, BF₃·Et₂O, benzene, 4 hours

then condensing the acid with 2,4-dimethylpyrrole to yield **2** in 90% yield as a red powder.

Spectroscopic Properties.

Methyl ester **1** exhibits good solubility properties in most organic solvents; the free acid **2** is much less soluble. As with many dipyrromethenes, **1** and **2** are red compounds, which give red solutions with an intense long wavelength

absorption lying near 510-520 nm (Table 1). Both **1** and **2** are highly fluorescent, giving fluorescent solutions with emission wavelength maxima near 555 nm. The fluorescence quantum yields ϕ_f were only about one-half the expected values based on those seen in analogs without a phenyl group ($\phi_f \sim 0.8$) [1,2]. Presumably, the attached phenyl group, which can rotate about the carbon-carbon bond point of attachment to the dipyrromethene chromophore, provides an alternative deexcitation route (internal motion) to that of luminescence.

Concluding Comments.

The red dipyrromethene chromophores of **1** and **2** can be expected to have use as a "red-shifted" chromophore in exciton coupling/chirality spectroscopic studies [3] and as a potential chromophore for use in fluorescence detected circular dichroism spectroscopy [4]. However, because **1** and **2** are very sensitive to bases, at present our attempts to couple **2** to diols have been unsuccessful.

EXPERIMENTAL

General.

The nmr spectra were recorded on a Varian Unity 500 MHz spectrometer or a General Electric QE-300 MHz spectrometer using chloroform-d as solvent, unless otherwise noted, and tetramethylsilane as an internal standard. Specific carbon and proton assignments were made by a combination of nuclear Overhauser effect and HMQC and HMBC determinations. Chemical shifts are reported in ppm downfield from tetramethylsilane ($\delta = 0$). All uv-visible spectra were recorded on a Perkin-Elmer Lambda 12 spectrometer, and fluorescence spectra were recorded on a Perkin-Elmer MPF-44A spectrophotometer. Corrected fluorescence quantum yields were determined using fluorescein as reference ($\phi_f = 0.84$, in 0.1 M sodium hydroxide). Combustion analyses were carried out by the Desert Analytics Laboratory in Tucson, Arizona. Melting points are uncorrected. Nitroethane and 4-carbomethoxybenzaldehyde were from Aldrich Chemical Co. Ethyl isocyanacetate, 1,8-diazabicyclo[5.4.0]undec-7-ene, boron trifluoride etherate, trifluoroacetic acid and triethyl orthoformate were from ACROS Organics. Chloroform-d (99.9% d), dimethyl sulfoxide-d₆ (99.9% d₆), dimethylformamide-d₇ (99.5% d₇) and acetone-d₆ (99.9% d₆) were from Cambridge Isotope Labs. (Other solvents and chemicals were from Fisher Chemicals. Tetrahydrofuran was distilled from sodium.)

Methyl 4-(2-Nitropropen-1-yl)benzoate (**7**).

Into 200 ml of nitroethane were dissolved methyl 4-formylbenzoate (16.4 g, 0.1 mole) and ammonium acetate (7.7 g, 0.1 mole). The solution was heated at reflux for 15 hours, then, the solvent was removed by distillation. The residue was taken up into 200 ml of methylene chloride. The methylene chloride solution was washed by water (3 x 200 ml), dried over anhydrous sodium sulfate and evaporated. The compound was crystallized from methylene chloride-hexane (1:1) to afford yellow needles (18.9 g, 85%). It had mp 125-126°, ¹H-nmr: δ 2.46 (s, 3H, CH₃), 3.95 (s, 3H, CO₂CH₃), 7.50 (d, 2H, J = 8.5 Hz, Ar-H), 8.09 (s, 1H, CH), 8.12

(d, 2H, *J* = 8.5 Hz, Ar-H) ppm; ¹³C-nmr: δ 14.0, 52.3, 129.7, 130.0, 131.1, 132.1, 136.8, 149.2, 166.2 ppm.

Anal. Calcd. for C₁₁H₁₁NO₄ (221.2): C, 59.73; H, 5.01; N, 6.33. Found: C, 59.47; H, 5.08, N, 6.37.

Methyl 4-(2-Carbomethoxy-4-methylpyrr-3-yl)benzoate (6).

Into 100 ml of dry tetrahydrofuran were dissolved 8.10 g (36.7 mmol) of methyl 4-(2-nitropropen-1-yl)benzoate (7) and 4.20 g (37.2 mmol) of ethyl isocyanoacetate. The solution was stirred and cooled in an ice-water bath. Into the stirred solution was added 12 g (79.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene by pipette. After addition, the mixture was stirred at room temperature overnight (12 hours). The reaction mixture was then diluted with 50 ml of chloroform, washed with water (3 x 100 ml), dried over anhydrous sodium sulfate and evaporated. The residue, an oil, was crystallized from 95% ethanol as white plates (8.52 g, 81%). It had mp 113–114°; ¹H-nmr: δ 1.13 (t, 3H, *J* = 7.5 Hz, CH₃), 1.99 (s, 3H, CH₃), 3.94 (s, 3H, CH₃), 4.18 (q, 2H, *J* = 7.5 Hz, CH₂), 6.83 (d, 1H, *J* = 2.0 Hz, pyrrole-H), 7.46 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.13 (d, 2H, *J* = 8.5 Hz, Ar-H), 9.15 (br, 1H, N-H) ppm; ¹³C-nmr: δ 10.5, 14.1, 52.0, 60.1, 119.1, 120.4, 120.6, 128.3, 128.7, 129.8, 130.4, 140.0, 161.0, 167.2 ppm.

Anal. Calcd. for C₁₆H₁₇NO₄ (287.3): C, 66.89; H, 5.97; N, 4.88. Found: C, 66.95; H, 5.85, N, 4.82.

Methyl 4-(4-Methylpyrr-3-yl)benzoate (4).

A mixture of 2.8 g (0.01 mol) of methyl 4-(2-carbomethoxy-4-methylpyrr-3-yl)benzoate (6), 10 g of sodium hydroxide, and 50 ml of ethylene glycol was heated to reflux for one hour. The mixture was cooled in an ice-water bath and neutralized with 36% hydrochloric acid. When hydrochloric acid was added, carbon dioxide was evolved. After carbon dioxide stopped evolving, the mixture was transferred to a separatory funnel. Into the separatory funnel were added 200 ml of water and 200 ml of chloroform. The chloroform layer was separated, and the aqueous solution was extracted with another 100 ml of chloroform. The chloroform extracts were combined, washed once with 200 ml of water, dried over anhydrous sodium sulfate and evaporated. The residue was 4-(4-methylpyrr-3-yl)benzoic acid (5). It was used directly in the next step and had ¹H-nmr: δ 2.29 (s, 3H, CH₃), 6.68 (d, 1H, *J* = 1.0 Hz, pyrrole-H), 7.01 (m, 1H, pyrrole-H), 7.56 (d, 2H, *J* = 8.8 Hz, Ar-H), 8.20 (d, 2H, *J* = 8.8 Hz, Ar-H), 8.15 (br, 2H, COOH and N-H) ppm.

The 4-(4-methylpyrr-3-yl)benzoic acid (5) obtained above was treated by diazomethane (from 10 g of *N*-nitroso-*N*-methylurea) in ether. The ethereal solution was stirred at room temperature for one hour and then evaporated using aspirator suction. The residue was crystallized from methanol as prisms (1.34 g, 96%). It had mp 101–102°; ¹H-nmr: δ 2.27 (s, 3H, CH₃), 3.92 (s, 3H, CO₂CH₃), 6.66 (br, 1H, pyrrole-H), 6.97 (m, 1H, pyrrole-H), 7.52 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.03 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.08 (br, 1H, N-H) ppm; ¹³C-nmr: δ 11.7, 51.9, 116.9, 117.1, 117.7, 123.7, 126.9, 127.0, 129.8, 141.5, 167.3 ppm.

Anal. Calcd. For C₁₃H₁₃NO₂ (215.3): C, 72.54; H, 6.09; N, 6.51. Found: C, 73.44; H, 6.18; N, 6.38.

Methyl 4-(2-Formyl-3-methylpyrr-4-yl)benzoate (3).

Into stirring trifluoroacetic acid (20 ml) cooled in an ice-water bath, was dissolved 1.05 g (4.9 mmol) of methyl 4-(4-methylpyrr-3-yl)benzoate (3). After the pyrrole compound was completely dissolved, 5 ml of triethyl orthoformate was added.

The solution was stirred in an ice-water bath for 10 minutes and then was poured into 450 ml of ice-water. The resulting solid pyrrole aldehyde was collected by suction filtration and washed well with water. ¹H-nmr of the crude product indicated that it contained two isomers. The main isomer was separated and purified by crystallization from 95% ethanol (~35 ml) to give pure product as light orange plates, 0.93 g, 78%. It had mp 189–190°; ¹H-nmr: δ 2.50 (s, 3H, CH₃), 3.94 (s, 3H, CO₂CH₃), 7.25 (d, 1H, *J* = 3 Hz, pyrrole-H), 7.27 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.08 (d, 2H, *J* = 8.5 Hz, Ar-H), 9.71 (br, 1H, N-H), 9.74 (s, 1H, CHO) ppm; ¹³C-nmr: δ 9.8, 52.1, 124.6, 126.4, 127.7, 128.1, 129.1, 129.9, 130.6, 139.1, 167.0, 178.1 ppm.

Anal. Calcd. for C₁₄H₁₃NO₃ (243.3): C, 69.13; H, 5.39; N, 5.76. Found: C, 69.17; H, 5.45; N, 5.78.

4-(4-Carbomethoxyphenyl)-3,3',5'-trimethyl-2,2'-pyrromethen-1,1'-BF₂ Complex (1).

Into 5 ml of dry benzene were dissolved 96.6 mg (0.40 mmol) of methyl 4-(2-formyl-3-methylpyrr-4-yl)benzoate (3) and 95 mg (1.00 mmol) of 2,4-dimethylpyrrole [5]. Then 3 ml of boron trifluoride diethyl etherate was added with stirring, and stirring was continued at room temperature for 4 hours. The reaction was monitored by tlc. The reaction was considered to be finished when the spot (violet under uv lamp) due to formylpyrrole disappeared. The reaction mixture was diluted by 30 ml of chloroform, washed by water (2 x 20 ml), dried over anhydrous sodium sulfate and evaporated. The crude product was filtered through silica gel, eluted by chloroform, and crystallized from chloroform-hexane (1:1) to give 1 as red needles (126.2 mg, 86%). It had mp 221–222°; ¹H-nmr: δ 2.32 (s, 3H, 3'-CH₃), 2.43 (s, 3H, 3-CH₃), 2.59 (s, 3H, 5'-CH₃), 3.94 (s, 3H, CO₂CH₃), 6.17 (s, 1H, 4'-CH), 7.25 (s, 1H, central CH), 7.51 (d, 2H, *J* = 8.5 Hz, Ar-2,6), 7.80 (s, 1H, 4-CH), 8.07 (d, 2H, *J* = 8.5 Hz, Ar-3,5) ppm; ¹³C-nmr: δ 10.90 (3-CH₃), 11.49 (3'-CH₃), 15.15 (5'-CH₃), 52.09 (OCH₃), 121.0 (4'), 122.0 (central = CH), 127.3 (Ar-2,6), 128.1 (Ar-4), 129.7 (4), 130.0 (Ar-3,5), 133.1 (3'), 134.4 (3), 136.0 (5'), 138.8 (5), 138.9 (Ar-1), 145.0 (2), 162.2 (2'), 166.9 (CO₂CH₃) ppm.

Anal. Calcd. for C₂₀H₁₉BF₂N₂O₂ (368.2): C, 65.24; H, 5.20; N, 7.61. Calcd. for C₂₀H₁₉BF₂N₂O₂·1/4 H₂O (372.7): C, 64.46; H, 5.27; N, 7.52. Found: C, 64.67; H, 5.37; N, 7.44.

4-(4-Carboxyphenyl)-3,3',5'-trimethyl-2,2'-pyrromethen-1,1'-BF₂ Complex (2).

Methyl 4-(2-formyl-3-methylpyrr-2-yl)benzoate (3, 0.6 g, 2.5 mmol) and potassium hydroxide (1.8 g) were dissolved in 70 ml of 95% ethanol and 20 ml of water. The solution was stirred at room temperature for 2 hours, diluted with 50 ml of water, and extracted with 50 ml of chloroform. The aqueous solution was then acidified with 36% hydrochloric acid and extracted with a mixture of 50 ml of chloroform and 25 ml of 95% ethanol. The chloroform layer was washed with a mixture of 25 ml of 95% ethanol and 50 ml of water. Evaporation of the chloroform solution gave 0.4 g (71%) of 4-(2-formyl-3-methylpyrr-2-yl)benzoic acid (8). It was used directly in the next step and had ¹H-nmr (dimethyl sulfoxide-*d*₆): δ 2.47 (s, 3H, CH₃), 7.51 (d, 1H, *J* = 3.4 Hz, pyrrole-H), 7.59 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.95 (d, 2H, *J* = 8.5 Hz, Ar-H), 9.72 (s, 1H, CHO), 12.14 (s, 1H, N-H), 12.85 (s, 1H, COOH) ppm.

4-(2-Formyl-3-methylpyrr-2-yl)benzoic acid (0.4 g, 1.7 mmol) and 2,4-dimethylpyrrole (0.5 g, 5.2 mmol) were

dissolved in 60 ml of dry benzene. Into the stirred solution was added 20 ml of boron trifluoride etherate. The mixture was heated to 60° for 2 hours and to reflux for 30 minutes. The cooled reaction mixture was diluted with 100 ml of ethyl acetate, washed with water (2 x 200 ml), dried over anhydrous sodium sulfate, and evaporated. The residue was treated with tetrahydrofuran-hexane to give 0.56 g (90%) of **2** as a red powder. It had mp >300° dec; ¹H nmr (dimethylformamide-d₇): δ 2.42 (s, 3H, 3'-CH₃), 2.56 (s, 3H, 3-CH₃), 2.58 (s, 3H, 5'-CH₃), 6.43 (s, 1H, 4'-CH), 7.40 (s, 1H, central CH), 7.77 (s, 1H, J = 8 Hz Ar-2,6), 8.087 and 8.104 (two overlapping doublets and one singlet) ppm; (acetone-d₆): δ 2.39 (s, 3H, 3'-CH₃), 2.51 (s, 3H, 3CH₃), 2.56 (s, 3H, 5'-CH₃), 6.35 (s, 1H, 4'-CH), 7.70 (d, 2H, J = 8.5 Hz, Ar-2,6), 7.84 (s, 1H, central CH), 8.00 (s, 1H, 4-CH), 8.10 (d, 2H, J = 8.5 Hz, Ar-3,5) ppm; ¹³C-nmr (dimethylformamide-d₇): δ 10.67 (3-CH₃), 10.99 (3'-CH₃), 14.61 (5'-CH₃), 121.4 (4'), 124.6 (central = CH), 127.6 (Ar-2,6), 129.5 (Ar-4), 129.6 (4), 130.2 (Ar-3,5), 133.8 (3'), 135.5 (3), 136.4 (5'), 138.8 (5), 139.0 (Ar-1), 146.7 (2), 162.6 (2'), 167.6 (CO₂H) ppm.

Anal. Calcd. for C₁₉H₁₇BF₂N₂O₂ (354.2): C, 64.44; H, 4.84; N, 7.91. Found: C, 64.11; H, 4.79; N, 7.83.

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