VISIBLE BIS(INDOLIUM TETRAMETHINE HEMICYANINE) DYES WITH A SPACER DERIVED FROM OLIGO(ETHYLENE GLYCOL)

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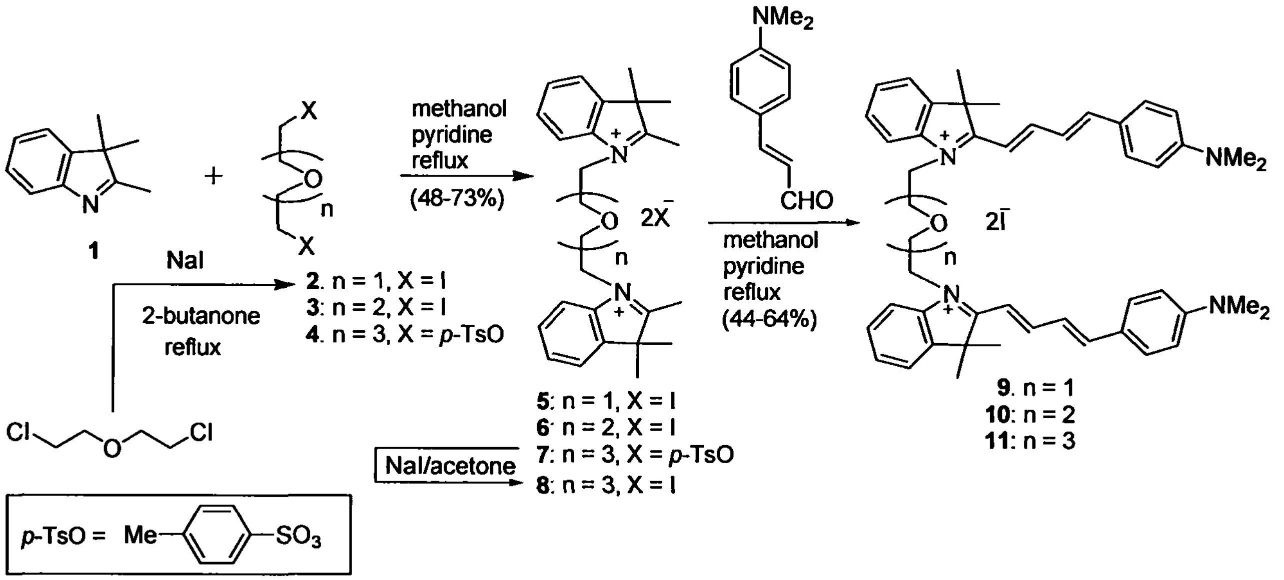
Abstract: Synthesis of three dimeric dyes is presented. The intramolecular dimers contain two chromophores linked with a conformationally flexible ether or oligoether bridge. Properties of the dyes are discussed.

Dimeric dyes in which two chromophoric subunits are linked by a conformationally flexible chain tend to form in aqueous solution an intramolecular foldamer with the two chromophores in close proximity to each other. In general, the stacking interactions are less important in a solvent of low polarity. These features have guided the design of dimeric dyes as non-covalent labels for the detection of nucleic acids[1,2] and proteins,[3-5] as cation-specific chemosensors[6-9] and as agents for latent fingerprint detection.[3,10] In particular, depending on the structure of the dimeric dye, upon binding with a biopolymer the intramolecular foldamer can undergo dissociation with the clam-shell of the inner complex opening up. Binding of the open form of the dimeric dye usually results in a batochromic shift in absorption and a greatly increased quantum yield of fluorescence. As the cation-specific chemosensors, several bichromophoric dyes bind metal cations and the resulting complexes show different spectral properties in comparison to non-complexed dyes. Finally, several bichromophoric cyanine dyes exhibit strongly enhanced fluorescence upon interaction with hydrophobic fats of fingerprints, which results in a clear fluorescence image of the fingerprint.

Synthesis of dimeric dyes **9 – 11** with an ether or oligoether linker in the molecule is described in this report. The presence of hydrophilic oxygen atom(s) in the bridge linking the two dye moieties results in a good solubility of the bifunctional molecules in water and aqueous buffers. More specifically, concentrations that are suitable for absorption and fluorescence studies are easily attained.



The key intermediate products **5**, **6** were obtained by quaternization of indolenine **1** (0.48 g, 3 mmol) with α,ω-diiodo-substituted ethers **2**,[11] **3** by heating the mixture containing a catalytic amount of pyridine to 110 °C for 4 days. In a similar way, product **7** was obtained by treatment of **1** with α,ω-bis-tosylate derivative **4**. The resultant bis-tosylate salt **7** was transformed into a diodide salt **8** by treatment with sodium iodide (0.30 g, 2.0 mmol) in acetone under reflux Conditions for 2 h. Cooling of the mixture to 0 °C for several hours caused precipitation of sodium *p*-tosylate, leaving bis-indolium diiodide **8** in solution. The diiodides **5**, **6**, and **8** were purified by chromatography on silica gel eluting with methanol/ethyl acetate (1:3). In the preparation of the desired dimeric dyes **9** –**11**, a solution of 4-(dimethylamino)cinnamaldehyde (0.39 g, 2.2 mmol), bis-indolium salt **5**, **6** or **8** (1mmol), and a catalytic amount (1 drop) of pyridine in methanol (20 ml) was heated under reflux for 15 h. After concentration on a rotary evaporator the crude products **9** – **11** were purified by chromatography on silica gel eluting with dichloromethane/methanol (10:1) and then crystallized from ethanol.

The visible spectral data of dyes **9** – **11** taken in methanol are listed below.[12] As can be seen, the maximum absorption wavelengths decrease in the order **9** > **10** > **11**, and these decreases parallel the increases in the length of the linker joining two terminal dye subunits in these dimeric compounds. It appears that the length of the linker dictates stereochemistry of the foldamer which, in turn, affects absorption properties of the molecule. Our preliminary studies have shown that these dyes bind with duplex DNA and proteins and the complex formation strongly affects spectral properties of the dyes. Complete biophysical studies will be published in due course.

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12. ***N,N′*-(3-Oxapentane-1,5-diyl)-bis[2-[4-[4-(dimethylamino)phenyl]buta-1,3-dien-1-yl]-3,3-dimethyl-3*H*-indolium] diiodide (9).** This compound was obtained in a 64% yield; ^{1}H NMR (DMSO-d_6): δ 1.61 (s, 12H), 3.09 (s, 12H), 3.92 (m,4H), 4.51 (m, 4H), 6.81 (d, J = 8Hz, 4H), 6.88 (m, 2H), 7.19 (dd, J = 10Hz, J = 5Hz, 2H), 7.39 (m, 4H), 7.51 (d, J = 8Hz, 2H), 7.55 (d, J = 8Hz, 4H), 7.71 (m, 4H), 8.23 (dd, J = 10Hz, J = 5Hz, 2H); VIS: λ_{max} 617 nm. Anal. Calcd for $C_{48}H_{56}I_2N_4O$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.93; H, 5.91; N, 5.75.
    ***N,N′*-(3,6-Dioxaoctane-1,8-diyl)-bis[2-[4-[4-(dimethylamino)phenyl]buta-1,3-dien-1-yl]-3,3 dimethyl-3*H*-indolium] diiodide (10).** This compound was obtained in a 58% yield; ^{1}H NMR (DMSO-d_6): δ 1.65 (s, 12H),3.07 (s, 12H), 3.40 (s, 4H), 3.72 (m, 4H), 4.48 (m, 4H), 6.81 (d, J = 9 Hz, 4H), 6.94 (m, 2H), 7.23 (dd, J = 10 Hz, J = 5Hz, 2H) 7.46 (m, 4H), 7.56 (d, J = 9Hz, 2H), 7.59 (m, 4H), 7.74 (m, 4H), 8.28 (dd, J = 10Hz, J = 5Hz, 2H); VIS: λ_{max} 604 nm. Anal. Calcd for $C_{50}H_{60}I_2N_4O_2{\bullet}0.5H_2O$: C, 59.35; H, 6.08; N, 5.54. Found: C, 59.25; H, 6.09; N, 5.44.
    ***N,N′*-(3,6,9-Trioxaundecane-1,11-diyl)-bis[2-[4-[4-(dimethylamino)phenyl]buta-1,3-dien-1- yl]-3,3-dimethyl-3*H*- indolium] diiodide (11).** This compound was obtained in a 54% yield; ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 12H), 3.07 (s,12H), 3.33 (t, J = 4Hz, 4H), 3.45 (t, J = 4Hz, 4H), 4.03 (t, J = 4Hz, 4H), 4.72 (t, J = 4Hz, 4H), 6.65 (d, J = 9Hz, 4H), 7.51 (m, 18H), 8.15 (dd, J = 10 Hz, J = 5 Hz, 2H); VIS: λ_{max} 596 nm. Anal. Calcd for $C_{52}H_{64}I_2N_4O_3{\bullet}2H_2O$: C, 57.67; H, 6.23; N, 5.17. Found: C, 57.91; H, 6.26; N, 5.02.

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