Near-Infrared Bis(indolium heptamethine cyanine) Dyes with a Spacer Derived from Oligo(ethylene glycol)

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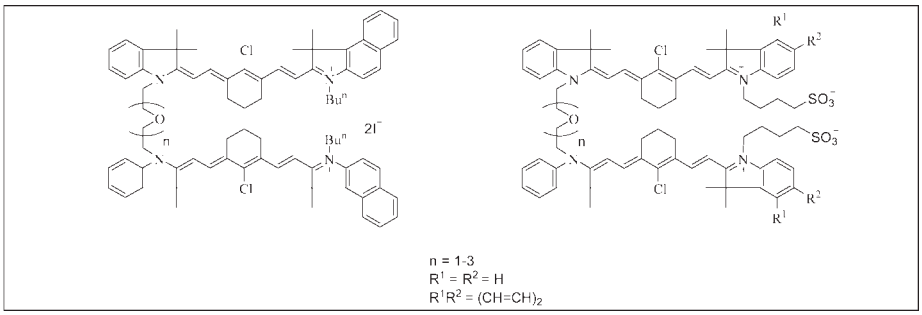
Received January 14, 2009
DOI 10.1002/jhet.171
Published online 2 September 2009 in Wiley InterScience (www.interscience.wiley.com).



Synthesis of a series of near-infrared dimeric dyes is presented. The intramolecular dimers contain two chromophores linked with a conformationally flexible ether or oligoether bridge. Optical properties of the dyes are discussed.

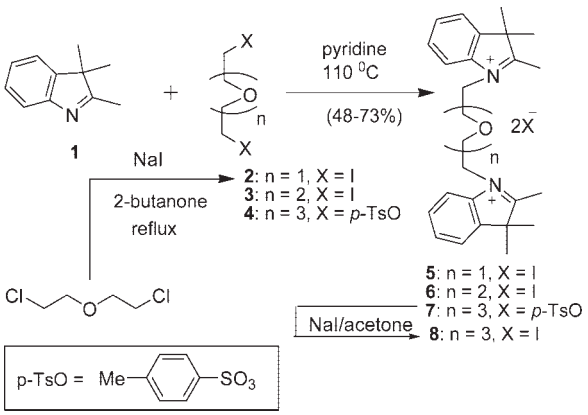
J. Heterocyclic Chem., **46**, 925 (2009).

INTRODUCTION

Currently, there is substantial interest in dimeric dyes in which two chromophoric subunits are linked by a conformationally flexible chain. Under low concentration conditions in aqueous solution, these bichromophoric molecules tend to exist in an intramolecular clam-shell conformation with the two chromophores in close proximity to each other. The intermolecular aggregation of such intramolecular foldamers becomes important with the increase in concentration. Normally, these are H-type stacking interactions characterized by hypsochromic absorption and low fluorescence quantum yield as compared to the characteristics of non-interacting dye molecules. In general, the stacking interactions are less important in solvents of low polarity. Several dimeric dyes have been designed as non-covalent labels for the detection of nucleic acids [2,3] and proteins [4–7]. More specifically, upon binding with a biopolymer, the intramolecular complex of a dimeric cyanine undergoes dissociation and the clam-shell of the inner complex opens 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. Several bichromophoric squaraines have been developed as cation-specific chemosensors [8–11]. These dimeric dyes bind metal cations and the resulting complexes show different spectral properties in comparison to non-complexed dyes. Finally, several bichromophoric cyanine dyes have been used as agents for latent fingerprint detection [5,12]. These dimeric dyes exhibit strongly enhanced fluorescence upon interaction with the hydrophobic fats of fingerprints that results in a clear fluorescence image of the fingerprint.

Synthesis of dimeric dyes **14–16** and **21–26** with an ether or oligoether linker in the molecule is described in this report. The molecules were designed as improved non-covalent labels for nucleic acids and proteins. The presence of oxygen atom(s) in the bridge linking the two dye moieties results in an increased solubility of the bifunctional molecules in water and aqueous buffers in comparison to the more hydrophobic analogs containing a polymethylene linker. The dimeric dyes **21–26** are additionally substituted with hydrophilic sulfonatobutyl groups. These dyes are bifunctional heptamethine cyanines that absorb and fluoresce in the near-infrared region (>700 nm). Few biomolecules absorb and fluoresce within the near-infrared region, and as a result Raman and Rayleigh light scattering are greatly reduced in this region. Consequently, improved signal-to-noise ratios are typically observed in the near-infrared region. In addition, typical impurities need not be considered because such species are not detected at wavelengths longer than 700 nm. All bis-dyes contain indolium moieties as end-heterocyclic subunits because such derivatives are relatively stable in solution [13].

Scheme 1

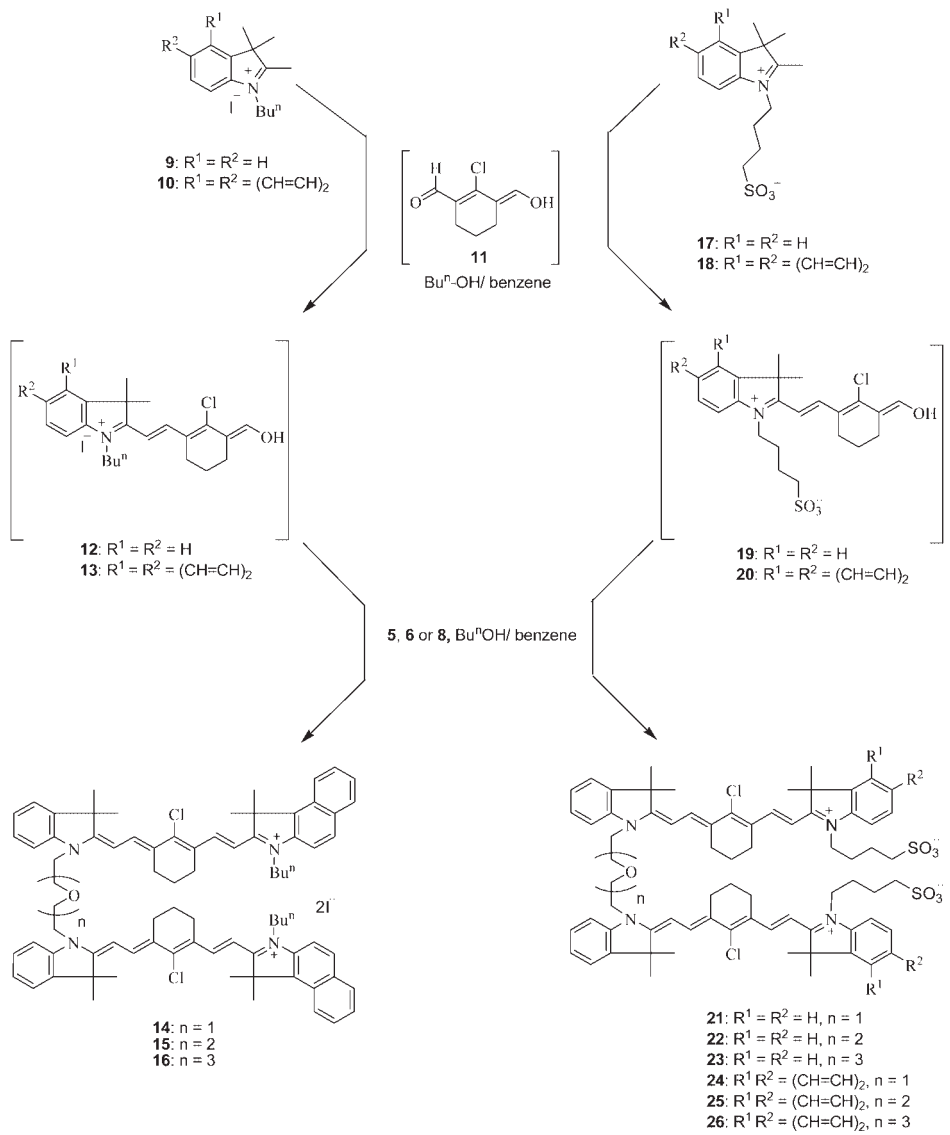


RESULTS AND DISCUSSION

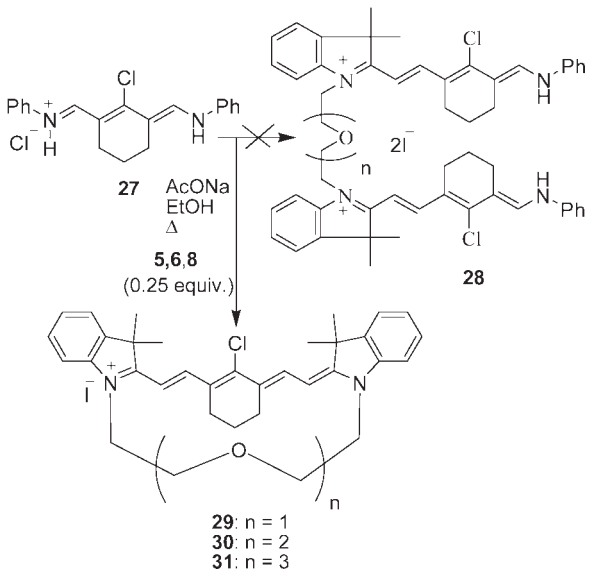
The key intermediate products are bis-indolium salts **5**–**7** (Scheme 1).

These compounds were obtained by quaternization of indolenine **1** with α,ω-diiodo-substituted ethers **2**, **3** or α,ω-bis-tosylate derivative **4**. In the latter case, the resultant bis-tosylate salt **7** was transformed into a more reactive diodide salt **8** by treatment with sodium iodide in acetone. The application of the intermediate dimeric salts **5**, **6,** and **8** in the synthesis of dimeric near-infrared cyanines **14**–**16** and **21**–**26** is shown in Scheme 2. The successful strategy for the synthesis of *N*-butyl derivatives **14**–**16** involved quaternization of 2,3,3-trimethylindole-nine and 2,3,3-trimethylbenzo[*e*]indolenine with *n*-butyl iodide followed by condensation of the

Scheme 2



Scheme 3



resultant indolium salts **9** and **10** with a dialdehyde **11**. The condensation reaction was conducted in a mixture of *n*-butanol and benzene with azeotropic removal of water.

Under these conditions, the formation of mono-condensation products **12** or **13** is strongly favored [14]. Crude products **12** and **13**, without purification, were then allowed to react with dimeric salts **5**, **6,** and **8** to furnish the corresponding final dyes **14–16**. In a similar way, quaternization of 2,3,3-indolenine or its benzo counterpart with 1,4-butanesultone yielded the respective 4-sulfonatobutyl inner salts **17** and **18** that were subsequently used for mono-condensation with dialdehyde **11**. The resultant products **19** and **20** were subjected to condensation with dimeric indolium salts **5**, **6,** and **8** to furnish the desired corresponding dimeric cyanines **21–26**.

A bis-anilinium derivative of the bis-aldehyde **11** [15] (**27**, structure in Scheme 3) is normally used in the synthesis of cyanine dyes by the reaction with methyl-substituted cationic heterocycles. The anilinium derivative **27** is more stable than the parent compound **11** and is easily purified by crystallization. The initial synthesis plan called for condensation of excess **27** with a dimeric salt **5**, **6,** or **8** followed by condensation of the expected product **28** with the indolium salt **9** or analogs. This approach failed because compound **28** (n = 1–3) was not formed. A detailed separation analysis showed the presence of the corresponding cyanine dye **29–31** in which the terminal indolium subunits are bridged by an ether moiety. By contrast, the half-dyes **12**, **13** and **19**, **20** were the major products of the reactions conducted with bis-aldehyde **11**. The procedure is simple in that crude bis-aldehyde **11** and crude half-dyes **12**, **13**, **19,** and **20** can be used for the condensation reaction. The final dimeric dyes, however, must be purified by chromatography. The final yields of these highly polar products are quite low, even for the optimized procedures described in the experimental section. Nevertheless, the described preparations are inexpensive and highly reproducible, and the final dyes are analytically pure, as judged by the results of the elemental, thin-layer-chromatographic, and spectral analyses.

The near-infrared spectra of dyes **14–16** and **21–26** are listed in Table 1. As can be seen, for the spectra of **14–16** taken in methanol, the maximum absorption wavelengths decrease in the order **14** > **15** > **16**, and these decreases parallel the increases in the length of the linker joining two terminal dye subunits in these dimeric compounds. A similar pattern is observed in the spectra of the individual series of NIR dyes **21–23**, and **24–26**. The differences between the shortest and the longest absorption wavelengths are remarkably similar (about 20 ± 1 nm) for each individual series of dyes. These large differences cannot be due to an electronic effect of the linker on the absorption because the corresponding monomeric dyes that are N-substituted with ethyl, butyl, or 2-hydroxyethyl groups all show similar absorption within 1 nm in methanol [7,16]. It can be suggested that the spectral differences reflect different foldamers in which two dye subunits are in close proximity to each other. More specifically, it appears that the length of the linker dictates the stereochemistry of the foldamer.

It was of interest to compare spectral properties of the ether-linked NIR dyes with those of their oligomethylene-linked analogs, a limited number of which have been published by us previously [5–7]. A striking difference is the lack of correlation between the maximum absorption wavelength and the length of the polymethylene chain. Thus, the analogs of **21–23** containing 4, 6, 8, and 10 methylene (CH_2) units show absorption in methanol at 783 nm, 787 nm, 780 nm, and 787 nm, respectively. Yagi *et al*. [9] and Liang *et al*. [17] have synthesized a series of bichromophoric squarains containing intramolecular polymethylene chains of various length and reported their spectra. It escaped their attention, however, that, as in our analysis, there is no correlation between the length of a polymethylene linker and absorption wavelengths of the bichromophoric squaraines. The spectral differences between bichromophoric molecules containing polymethylene and ether chains can be explained in terms of their different conformational flexibility with the latter linkers showing more conformational freedom. This conclusion is strongly supported by conformational analysis of polyethylene $(CH_2CH_2)_n$, polyoxyethylene $(OCH_2CH_2)_n$, and related low molecular-weight molecules [18].

Table 1

Vis-NIR spectra of dyes **14–16**, and **21–26** taken in methanol.

Linker, No (C + O)	Dye	λ_{max}	Dye	λ_{max}	Dye	λ_{max}
5	**14**	817	**21**	794	**24**	818
8	**15**	799	**22**	776	**25**	802
11	**16**	797	**23**	775	**26**	797

We conducted conformational studies of dimeric dyes **14–16**. The conformations were computer-simulated in an aqueous environment and *in vacuo*, resembling conditions in solvents of high and low polarity, respectively. The technical aspects of the calculations are given in the experimental section. A general result is that there are a number of computed low-energy structures in an aqueous environment that contain the two cyanine subunits in close proximity to each other, strongly suggesting attractive hydrophobic interactions between these two subunits (not shown). By contrast, low-energy conformations of **14–16** in the absence of water contain an unfolded ether bridge and the two cyanine subunits away from each other. When the closed-shell conformations, as obtained from computing the structures in an aqueous environment, were taken as the starting structures for computation in the absence of water, all conformations opened-up, losing the presumed intramolecular interactions. The computed energy differences between the more stable solvated structures and the conformations in the absence of water are in the range of 70–100 kcal/mol. Compound **16** was selected for a detailed analysis. The molecular modeling work generated a number of water-induced conformations of **16** in which the two cyanine subunits are in close proximity to each other. Some of these structures are consistent with partial stacking of the planar portions of the dyes, suggesting a π–π interaction. Other computer-generated low-energy conformations of **16** in aqueous environment are consistent with hydrophobic interactions, but not stacking, between the cyanine chromophores. We have also conducted similar calculations for the analog of **16** in which the ether linkage is replaced by an eleven-methylene bridge. Despite the similar lengths of the two linkages, the number of low-energy conformations is larger for **16** than for its polymethylene analog. These computational results are consistent with the greater conformational flexibility of **16** in comparison to its analog containing an all-carbon bridge, as discussed earlier.

We have conducted preliminary binding studies of **14–16** and **21–26** with human serum albumin (HSA) and calf thymus DNA. All compounds bind with the protein, albeit the absorption and fluorescence differences between the compounds in the absence and presence of HSA are highly structure dependent. On the other hand, only the cationic molecules **14–16** bind with DNA as evidenced by the observed spectral changes. Molecules **21–26** that contain a zero net charge do not interact with anionic DNA. Complete biophysical studies will be reported in due course.

EXPERIMENTAL

General. Where applicable, products were purified on a chromatotron with silica gel-coated rotors. Melting points are greater than 300°C in all cases. All ^{1}H NMR spectra were taken at 400 MHz. Near-infrared (NIR) spectra were taken in methanol or dichloromethane for solutions with absorptivities <1.0. The intermolecular aggregation of cyanine dyes is negligible under such conditions.

Dimeric indolium salts 5, 6, 8. Bis(2-iodoethyl) ether (**2**) was prepared by refluxing bis(2-chloroethyl) ether with sodium iodide in 2-butanone for 24 h as reported previously [19]. A mixture of 2,3,3-trimethylindolenine (**1**, 0.48 g, 3 mmol), a diiodo derivative **2** or **3** (1.5 mmol), and pyridine (one drop) was heated to 110°C for 4 days to give the respective bis-salt **5** or **6**. In a similar way, product **7** was obtained by treatment of **1** with a bis-tosylate derivative **4**. Crude bis-tosylate salt **7** in acetone (10 mL) was treated with a saturated solution of sodium iodide (0.30 g, 2 mmol) in methanol, and the mixture was heated under reflux 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 silica gel chromatography eluting with methanol/ethyl acetate (1:3).

***N*,*N*′-(3-Oxopentane-1,5-diyl)-bis(2,3,3-trimethyl-3*H*-indolium) diiodide 5.** This compound was obtained in a 63% yield; ^{1}H NMR (DMSO-d_6): δ = 1.26 (s, 12H), 3.18 (s, 6H), 4.35 (t, J = 5Hz, 4H), 5.02 (t, J = 5Hz, 4H), 7.41 (m, 8H). Anal. Calcd for $C_{26}H_{34}I_2N_2O_2$: C, 48.46; H, 5.32; N, 4.35. Found: C, 48.28; H, 4.98; N, 4.29.

***N*,*N*′-(3,6-Dioxaoctane-1,8-diyl)-bis(2,3,3-trimethyl-3*H*-indolium) diiodide 6.** This compound was obtained in a 58% yield; ^{1}H NMR (DMSO-d_6): δ = 1.49 (s, 12H), 2.76 (s, 6H), 3.66 (t, J = 5Hz, 4H), 3.79 (t, J = 5Hz, 4H), 4.67 (t, J = 5Hz, 4H), 7.61 (m, 4H), 7.85 (d, J = 8Hz, 2H), 7.92 (d, J = 8Hz, 2H). HR-MS (ESI). Calcd for $(C_{28}H_{38}N_2O_2)^{2+}$: m/z = 217.1464. Found: m/z = 217.1456. Anal Calcd for $C_{28}H_{38}I_2N_2O_2$: C, 48.84; H, 5.56; N, 4.07. Found: C, 48.95; H, 5.62; N, 4.03.

***N*,*N*′-(3,6,9-Trioxaundecane-1,11-diyl)-bis(2,3,3-trimethyl-3*H*-indolium) diiodide 8.** This compound was obtained in a 73% yield; ^{1}H NMR (DMSO-d_6): δ = 1.50 (s, 12H), 2.35 (s, 6H), 3.25 (t, J = 5Hz, 4H), 3.34 (t, J = 5Hz, 4H), 3.83 (t, J

= 5Hz, 4H), 4.71 (t, J = 5Hz, 4H), 7.59 (m, 4H), 7.84 (d, J = 8Hz, 2H), 7.98 (d, J = 8Hz, 2H); ^{13}C NMR (DMSO-d_6): δ = 14.8, 21.9, 47.9, 54.2, 66.6, 69.4, 69.6, 115.6, 123.5, 128.8, 129.3, 140.8, 141.6, 189.1. HR-MS (ESI). Calcd for $(C_{30}H_{42}N_2O_3)^{2+}$: m/z = 239.1592. Found: m/z = 239.1592.

Near-infrared dyes 14–16 and 21–26. A mixture of bis-aldehyde **11** [14] (173 mg, 1 mmol), a quaternary salt [5,19] **9**, **10**, **17,** or **18** (1 mmol), *n*-butanol (50 mL), and benzene (15 mL) was stirred at 23°C for 2 h. The resultant crude product **12**, **13**, **19,** or **20**, without isolation, was treated in the same flask with a dimeric salt **5**, **6,** or **8** (0.5 mmol) and the mixture was heated under reflux for an additional 12 h. The product was isolated by concentration of the mixture on a rotary evaporator followed by chromatography eluting with dichloromethane/methanol (10:1 for **14–16** and 9:1 for **21–26**).

3‴-Oxapentane-1‴,5‴-diyl[bis[2-[7′-(3″-butyl-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 14. This compound was obtained in a 17% yield;[1]H NMR ($CDCl_3$): δ = 1.02 (t, J = 6Hz, 6H), 1.54 (m, 4H), 1.68 (s, 12H), 1.90 (m, 4H), 1.94 (m, 4H), 2.02 (s, 12H), 2.74 (m, 8H), 4.05 (m, 4H), 4.36 (m, 8H), 6.20 (d, J = 11Hz, 2H), 6.32 (d, J = 11Hz, 2H), 7.09 (d, J = 6Hz, 2H), 7.18 (t, J = 6Hz, 2H), 7.26 (t, J = 6Hz, 2H), 7.34 (d, J = 6Hz, 2H), 7.44 (d, J = 6Hz, 2H), 7.48 (t, J = 6Hz, 2H), 7.63 (t, J = 6Hz, 2H), 7.96 (m, 4H), 8.13 (d, J = 6Hz, 2H), 8.28 (d, J = 11Hz, 2H), 8.48 (d, J = 11Hz, 2H); NIR: λ_{max} = 817 nm. Anal. Calcd for $C_{80}H_{90}Cl_2I_2N_4O{\cdot}2H_2O$: C, 64.73; H, 6.38; N, 3.77. Found: C, 64.85; H, 6.22; N, 3.85.

3‴,6‴-Dioxaoctane-1‴,8‴-diyl[bis[2-[7′-(3″-butyl-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 15. This compound was obtained in a 26% yield; [1]H NMR ($CDCl_3$): δ = 1.02 (t, J = 7Hz, 6H), 1.54 (m, 4H), 1.73 (s, 12H), 1.90 (m, 4H), 1.97 (m, 4H), 2.01 (s, 12H), 2.76 (m, 8H), 3.56 (s, 4H), 3.92 (m, 4H), 4.32 (m, 4H), 4.41 (m, 4H), 6.29 (d, J = 14Hz, 2H), 6.34 (d, J = 14Hz, 2H), 7.24 (m, 4H), 7.40 (m, 6H), 7.49 (t, J = 6Hz, 2H), 7.62 (t, J = 6Hz, 2H), 7.94 (m, 4H), 8.13 (d, J = 8Hz, 2H), 8.32 (d, J = 14Hz, 2H), 8.45 (d, J = 14Hz, 2H); NIR: λ_{max} = 799 nm. Anal. Calcd for $C_{82}H_{94}Cl_2I_2N_4O_2{\cdot}2H_2O$: C, 64.43; H, 6.46; N, 3.66. Found: C, 64.44; H, 6.48; N, 3.64.

3‴,6‴,9‴-Trioxaundecane-1‴,11‴-diyl[bis[2-[7′-(3″-butyl-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 16. This compound was obtained in a 12% yield; [1]H NMR ($CDCl_3$): δ = 1.02 (t, J = 6Hz, 6H), 1.53 (m, 4H), 1.72 (s, 12H), 1.94 (m, 8H), 2.02 (s, 12H), 2.77 (m, 4H), 3.56 (m, 12H), 3.96 (m, 4H), 4.38 (m, 8H), 6.28 (d, J = 14Hz, 2H), 6.33 (d, J = 14Hz, 2H), 7.22 (m, 4H), 7.35 (m, 4H), 7.48 (m, 4H), 7.63 (m, 2H), 7.95 (m, 4H), 8.13 (m, 2H), 8.31 (d, J = 14Hz, 2H), 8.47 (d, J = 14Hz, 2H); NIR: λ_{max} = 797 nm. Anal. Calcd for $C_{84}H_{98}Cl_2I_2N_4O_3{\cdot}4H_2O$: C, 62.73; H, 6.64; N, 3.48. Found: C, 62.88; H, 6.42; N, 3.38.

3⁗-Oxapentane-1⁗,5⁗-diyl[bis[2-[7′-[1″-(4‴-sulfonatobutyl)-3″,3″-dimethylindolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 21. This compound was obtained in a 16% yield; [1]H NMR (DMSO-d_6): δ = 1.58 (s, 12H), 1.66 (s, 12H), 1.76 (m, 16H), 2.50 (m, 4H), 2.69 (m, 4H), 3.84 (m, 4H), 4.28 (m, 8H), 6.19 (d, J = 13Hz, 2H), 6.46 (d, J = 14Hz, 2H), 7.25 (m, 8H), 7.44 (m, 2H), 7.55 (m, 4H), 7.65 (d, J = 7Hz, 2H), 8.13 (d, J = 14Hz, 2H), 8.28 (d, J = 13Hz, 2H); NIR: λ_{max} = 794 nm. Anal. Calcd for $C_{72}H_{84}Cl_2N_4O_7S_2{\cdot}5H_2O$: C, 64.41; H, 7.06; N, 4.17. Found: C, 64.29; H, 6.82; N, 4.02.

3⁗,6⁗-Dioxaoctane-1,8-diyl[bis[2-[7′-[1″-(4‴-sulfonatobuty-l)-3″,3″-dimethylindolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 22. This compound was obtained in a 14% yield; [1]H NMR (DMSO-d_6): δ = 1.62 (s, 12H), 1.68 (s, 12H), 1.78 (m, 16H), 2.71 (m, 8H), 3.38 (m, 4H), 3.45 (s, 4H), 4.20 (m, 4H), 4.30 (m, 4H), 6.35 (d, J = 13Hz, 2H), 6.44 (d, J = 14Hz, 2H), 7.27 (m, 6H), 7.44 (m, 6H), 7.62 (m, 4H), 8.24 (d, J = 13Hz, 2H), 8.27 (d, J = 14Hz, 2H); NIR: λ_{max} = 776 nm. Anal. Calcd for $C_{74}H_{88}Cl_2N_4O_8S_2{\cdot}5H_2O$: C, 64.08; H, 7.12; N, 4.04. Found: C, 63.97; H, 6.94; N, 3.81.

3⁗,6⁗,9⁗-Trioxaundecane-1⁗,11⁗-diyl[bis[2-[7′-[1″-(4‴-sulfonatobutyl)-3″,3″-dimethylindolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 23. This compound was obtained in a 12% yield; [1]H NMR (DMSO-d_6): δ = 1.62 (s, 12H), 1.65 (s, 12H), 1.73 (m, 16H), 2.59 (m, 8H), 3.27 (m, 4H), 3.37 (m, 4H), 3.71 (m, 4H), 4.24 (m, 4H), 4.36 (m, 4H), 6.35 (d, J = 14Hz, 2H), 6.39 (d, J = 15Hz, 2H), 7.41 (m, 16H), 8.20 (d, J = 14Hz, 2H), 8.25 (d, J = 15Hz, 2H); NIR: λ_{max} = 775 nm. Anal. Calcd for $C_{76}H_{92}Cl_2N_4O_9S_2{\cdot}5H_2O$: C, 63.80; H, 7.18; N, 3.91. Found: C, 64.01; H, 6.92; N, 3.81.

3⁗-Oxapentane-1⁗,5⁗-diyl[bis[2-[7′-[3″-(4‴-sulfonatobutyl)-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 24. This compound was obtained in a 26% yield; [1]H NMR (DMSO-d_6): δ = 1.56 (m, 4H), 1.59 (s, 12H), 1.79 (m, 4H), 1.93 (s, 12H), 1.95 (m, 4H), 2.52 (m, 8H), 2.74 (m, 4H), 3.84 (m, 4H), 4.28 (m, 4H), 4.42 (m, 4H), 6.16 (d, J = 14Hz, 2H), 6.55 (d, J = 15Hz, 2H), 7.16 (m, 2H), 7.25 (m, 2H), 7.55 (m, 4H), 7.67 (m, 2H), 7.88 (m, 2H), 8.10 (m, 6H), 8.31 (m, 2H), 8.41 (d, J = 15Hz, 2H); NIR: λ_{max} = 818 nm. Anal. Calcd for $C_{80}H_{88}Cl_2N_4O_7S_2{\cdot}5H_2O$: C, 66.60; H, 6.84; N, 3.88. Found: C, 66.58; H, 6.70; N, 3.66.

3⁗,6⁗-Dioxaoctane-1⁗,8⁗-diyl[bis[2-[7′-[3″-(4‴-sulfonatobutyl)-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-in-dol-1-ium]] diiodide 25. This compound was obtained in a 25% yield; [1]H NMR (DMSO-d_6): δ = 1.64 (s, 12H), 1.81 (m, 4H), 1.93 (s, 12H), 1.98 (m, 4H), 2.51 (m, 8H), 2.66 (m, 4H), 2.74 (m, 4H), 3.47 (s, 4H), 3.72 (m, 4H), 4.24 (m, 4H), 4.41 (m, 4H), 6.24 (d, J = 14Hz, 2H), 6.53 (d, J = 14Hz, 2H), 7.18 (m, 2H), 7.25 (m, 2H), 7.33 (m, 2H), 7.54 (m, 4H), 7.65 (m, 2H), 7.85 (m, 2H), 8.08 (m, 4H), 8.18 (d, J = 14Hz, 2H), 8.27 (m, 2H), 8.40 (d, J = 14Hz, 2H); NIR: λ_{max} = 802 nm. Anal. Calcd for $C_{82}H_{92}Cl_2N_4O_8S_2{\cdot}2H_2O$: C, 68.74; H, 6.75; N, 3.91. Found: C, 68.43; H, 6.79; N, 3.82.

3⁗,6⁗,9⁗-Trioxaundecane-1⁗,11⁗-diyl[bis[2-[7′-[3″-(4‴-sulfonatobutyl)-1″,1″-dimethylbenzo[*e*]indolin-2″-ylidene]-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium]] diiodide 26. This compound was obtained in a 12% yield; [1]H NMR (DMSO-d_6): δ = 1.66 (s, 12H), 1.83 (m, 12H), 1.95 (s, 12H), 2.69 (m, 4H), 2.77 (m, 4H), 3.40 (m, 8H), 3.76 (m, 4H), 4.35 (m, 4H), 4.42 (m, 4H), 6.33 (d, J = 14Hz, 2H), 6.53 (d, J = 15Hz, 2H), 7.22 (m, 2H), 7.36 (m, 4H), 7.56 (m, 4H), 7.69 (m, 2H), 7.89 (m, 2H), 8.12 (m, 4H), 8.18 (d, J = 14Hz, 2H), 8.32 (m, 2H), 8.33 (d,

J = 15Hz, 2H); NIR: λ_{max} = 797 nm in methanol. Anal. Calcd for $C_{84}H_{96}Cl_2N_4O_9S_2 \cdot 4H_2O$: C, 66.91; H, 6.92; N, 3.70. Found: C, 66.61; H, 6.65; N, 3.63.

Macrocyclic dyes 29–31. A mixture of Vilsmeier-Haack reagent **27** [15] (360 mg, 1 mmol), sodium acetate (82 mg, 1 mmol), and a dimeric salt, **5**, **6,** or **8** (732 mg, 1 mmol) in ethanol (30 mL) was stirred at 35°C for 1 h. The crude dye **29–31** was purified by chromatography eluting with dichloromethane/methanol (10:1) and then crystallized from ethanol/hexanes.

***N,N″*-(3‴-Oxapentane-1‴,5‴-diyl)-[2-[7′-(3″,3″-dimethylindolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium] iodide 29.** This compound was obtained in a 10% yield; ^{1}H NMR (DMSO-d_6): δ = 1.57 (s, 12H), 1.62 (m, 2H), 2.66 (m, 4H), 3.91 (m, 4H), 4.46 (m, 4H), 6.31 (d, J = 14Hz, 2H), 7.24 (m, 2H), 7.36 (m, 4H), 7.57 (m, 2H), 8.18 (d, J = 14Hz, 2H). HR-MS (ESI). Calcd for $(C_{34}H_{38}ClN_2O)^+$: m/z = 525.2667. Found: m/z = 525.2687.

***N,N″*-(3‴,6‴-Dioxaoctane-1‴,8‴-diyl)-[2-[7′-(3″,3″-dimethylindolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium] iodide 30.** This compound was obtained in a 20% yield; ^{1}H NMR (DMSO-d_6): δ = 1.57 (s, 12H), 1.84 (m, 2H), 2.63 (m, 4H), 3.52 (s, 4H), 3.72 (m, 4H), 4.29 (m, 4H), 6.32 (d, J = 14Hz, 2H), 7.24 (m, 2H), 7.38 (m, 4H), 7.58 (m, 2H), 8.14 (d, J = 14Hz, 2H); Anal. Calcd. for $C_{36}H_{42}ClIN_2O_2 \cdot H_2O$: C, 60.46; H, 6.20; N, 3.91. Found: C, 60.61; H, 6.11; N, 3.85.

***N,N″*-(3‴,6‴,9‴-Trioxaundecane-1‴,11‴-diyl)- [2-[7′-(3″,3″-dimethylindolin-2″-ylidene)-4′-chloro-3′,5′-trimethylene-1′,3′,5′-heptatrien-1′-yl]-3,3-dimethyl-3*H*-indol-1-ium] iodide 31.** This compound was obtained in a 32% yield; ^{1}H NMR ($CDCl_3$): δ = 1.54 (s, 12H), 2.00 (m, 2H), 2.72 (m, 4H), 3.72 (m, 4H), 3.81 (m, 4H), 3.99 (m, 4H), 4.53 (m, 4H), 5.96 (d, J = 15Hz, 2H), 7.24–7.46 (m, 8H), 8.52 (d, J = 15Hz, 2H); NIR: λ_{max} = 777 nm. Anal Calcd. for $C_{38}H_{46}ClIN_2O_3 \cdot 2H_2O$: C, 58.72; H, 6.48; N, 3.60. Found: C, 58.92; H, 6.19; N, 3.48.

Molecular modeling. Energy minimizations were performed using SYBYL (running on SGI O_2 station) using MMFF94 force field and the minimum energy change of 0.01 kcal/mol per Å as a convergence criterion. Charges were calculated using the MMFF94 method as implemented in SYBYL. The molecules in aqueous environment were minimized using the Molecular Silverware option in SYBYL, which resulted in change of energy (E_{min}) and in the conformation of dyes. The values of E_{min} decreased of about 70–100 kcal/mol when the environment was changed from vacuum to aqueous solution. In vacuum, the structures are opened, and in water, the individual cyanine moieties of the dimeric molecules are close to each other in all cases studied.

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