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Conjugating a Cyanine Dye to a Polymer Surface. In Search of a Monomeric Dye in Apolar Media

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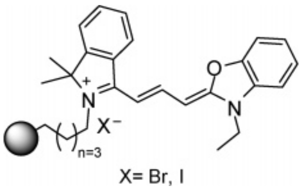

Solution and solid-phase syntheses of a cyanine dye conjugated to polystyrene beads (desired for potentially interesting electronic properties) are described.

Fascination with synthetic dyes can be traced back to 1856 when a precocious William Henry Perkin, only 18 years of age, converted a coal tar derivative, aniline, into a purple dye he called “mauve”. The discovery prompted Perkin to leave his Royal College of Chemistry and build a factory that manufactured his dye. Hundreds of synthetic dyes followed soon after Perkin’s discovery: magenta (Verguin, 1858); methyl violet (Lauth, 1861); Hofmann’s violet (Hofmann, 1862); alizarin (Graebe and Lightfoot, 1868), and malachite green (Dobner and Fisher, 1877) to name a few. A century-and-a-half after Perkin, we initiated our own particular approach to dye construction (although there are no immediate plans to abandon the comfort of a university!). In order to understand the motivation for our studies, certain important features of dye chemistry must be detailed, and this will be done via cyanine dyes of the type drawn in Figure 1a.

According to simple resonance theory, color arises from an electron delocalization in which the two identical nitrogens each bear exactly one-half of a positive charge. The longer the distance between the conjugated nitrogens, the longer the wavelength of light absorption. Now suppose nitrogen is replaced by carbon as in the analog in Figure 1b. This compound does not absorb in the visible range because there is far less electron delocalization compared with the cyanine dye. The comparison suggests that if one could somehow prevent delocalization effects in the cyanine dye (i.e., impose conditions that confine the compound to only one of the two delocalization contributors), then the color would vanish. Exposing the dye to “normal” conditions would cause the color to reappear. Thus, the elements of a “color/no-color” switch would be in hand.

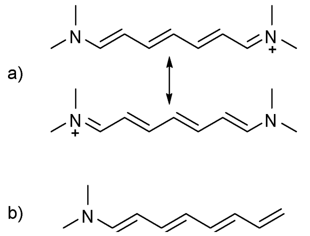

FIGURE 1. (a) Delocalization in a cyanine dye imparting +1/2 on each nitrogen. (b) A colorless carbon analogue of the dye.

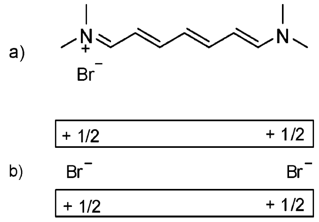

FIGURE 2. (a) A tight ion pair of the cyanine dye. (b) A dimer in which both ion-paring and delocalization stabilization are possible.

The challenge, of course, is to devise a transiently nonresonating cyanine system. One might presume that if the cyanine were forced into a tight ion pair with its counteranion (Figure 2a), then the positive charge would be localized only at the nitrogen proximate to the counteranion. Cyanine-type delocalization within the ion pair would be impeded because the cationic charge cannot readily shift to the other nitrogen. If this did happen, the cationic and anionic charges would be widely separated, imparting high energy to the contributor. Even if the counteranion located itself equidistant from the two nitrogens, charge separation would be substantial. In summary, the dye as a tight ion pair would likely have lost some or all of its color.

When cyanine dyes are dissolved in nonpolar solvents, conditions that favor tight ion pairing, their colors persist (in apparent conflict with our prediction). Yet in actual fact, this does not negate our speculations about possible color loss because cyanine dyes in nonpolar solvents form dimers (or higher J- and H-aggregates) in which both ion pairing and delocalization effects are both readily accommodated (Figure 2b).[1]

In order to preclude this complication, cyanine dyes must be constructed that remain monomeric even in nonionizing media.

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(1) (a) West, W.; Pearce, S. J. *Phys. Chem.* **1965**, 69, 1894. (b) Khairutdinov, R. F.; Serpone, N. *J. Phys. Chem. B* **1997**, 101, 2602. (c) Fidder, H.; Wursma, D. A. *Phys. Rev. Lett.* **1991**, *66*, 1501. (d) Perlatein, J.; Penner, T. L.; Witten, D. G. *Langmuir* **2000**, *16*, 9042. (e) Dähne, S.; Nolte, K. D. *Chem. Commun.* **1972**, 1076.

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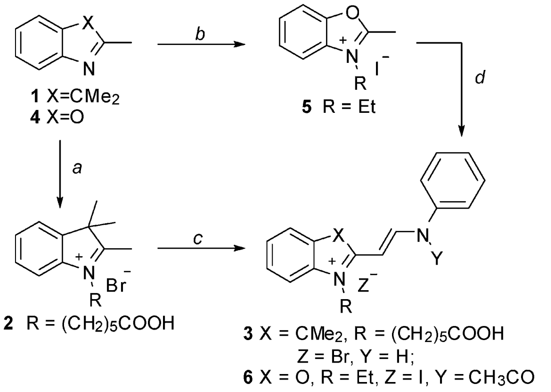
10.1021/jo7027294 CCC: $40.75

SCHEME 1 [a]



[a] Reagents and conditions: (a) $Br(CH_2)_5COOH$ (2 equiv), 120 °C, 24 h, 40%; (b) EtI, CH_3CN, reflux, 54%; (c) $HC(OEt)_3$, (1.05 equiv), aniline (1.2 equiv), 120 °C, 30 min, 78%; (d) $PhN{=}CNHPh$ (1.1 equiv), Ac_2O, 30 min reflux, 76%.

We reasoned that this is best accomplished by attaching isolated dye molecules to a solid apolar surface such as provided by polystyrene beads. Consequently, dye/polystyrene bead systems became a synthetic objective described herein.

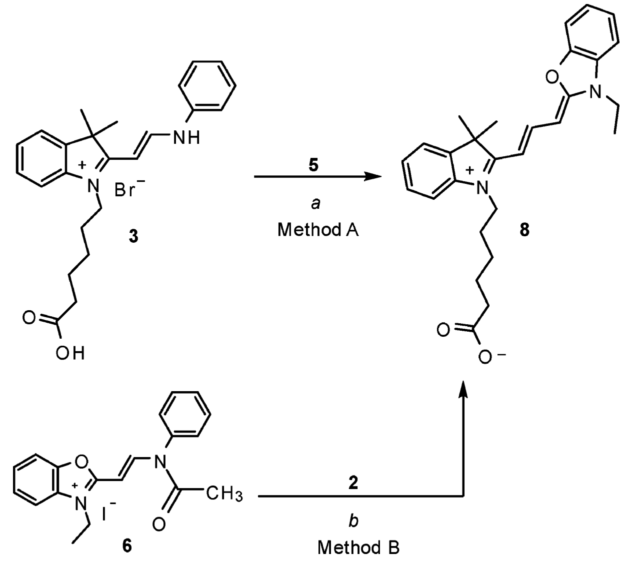
Although dye/polymer and other dye/solid systems have been widely examined, most of them involve noncovalent association.[2] For example, cyanine dyes, adsorbed from ethanol onto the surface of single-crystal rutile, exist predominantly as monomer.[3] However, since ethanol, which probably coadsorbed, is not a good ion-pairing medium, the results may not be relevant to our interests. In many solid-phase syntheses of various cyanines, polymer beads were merely a synthetic aid to be removed as quickly as possible.[4]

A cyanine dye bearing a carboxyalkyl chain on one of its nitrogens was initially selected for our studies because it is relatively easy to couple carboxylic acids to hydroxylmethyl and chloromethyl substituents on polystyrene supports.[5] The required *N*-carboxyalkyl salt was prepared from 2,3,3-trimethylindolenine **1** and 6-bromohexanoic acid (Scheme 1), following the method of Almeida,[6] by heating at 120 °C for 24 h in the absence of solvent.

Quaternary salt **2** was obtained in excellent purity, in 40% yield, by triturating the resulting solid mass with boiling acetone. *N*-Carboxyalkyl indoleninium bromide **2** was then converted into the vinyl aniline **3** in a good yield by heating a mixture of **2**, triethyl orthoformate, and aniline at 120 °C for 30 min (Scheme 1).

Benzoxazolium iodide **5** was synthesized by heating under reflux in an inert atmosphere a solution of **4** with an excess of ethyl iodide in acetonitrile.[6] The resulting salt was readily separated in excellent purity from the crude reaction mixture by precipitation via addition of diethyl ether. Further purification, although not strictly necessary, was carried out by crystallization from methanol/ether mixture. Compound **5** was then transformed into the corresponding *N*-acetanilide **6** by treatment with diphenylformamidine in refluxing acetic anhydride for 30 min according to the procedure developed by Almeida[6] and Glazer.[7] Pure **6** was obtained in 76% yield after crystallization from methanol/ether mixture.

SCHEME 2 [a]



[a] Reagents and conditions: (a) method A: **5** (1 equiv), pyridine, reflux, 3 h, 58%; (b) method B: **2** (1 equiv), NEt_3 (2 equiv) ethanol, reflux, 30 min, 90%.

The synthesis of the key trimethine dye **8** was accomplished via two different methods (Scheme 2). Method A involved the reaction between compound **3** and benzoxazolium iodide **5** in refluxing pyridine for 3 h. The crude dye was then precipitated from the reaction mixture, previously cooled to room temperature, with diethyl ether, and the resulting amorphous mass was washed copiously with ether and crystallized from acetonitrile/diethyl ether mixture. The workup difficulties and modest yields forced us to attempt method B. Thus, the cyanine **8** was also prepared through the base-catalyzed condensation of acetanilide **6** with bromide **2** that gave us, with only 30 min of reflux, a cleaner product in higher yields (90%) after precipitation with diethyl ether and further crystallization from acetonitrile/ether.

Dye **8**, red powder, was finally coupled with Merrifield polystyrene (loading 1.1 mmol/g) using a procedure developed by Frenette and co-workers (Scheme 3).[5b] This was obtained by shaking a suspension of Merrifield resin in DMF with carboxylate 8 together with cesium carbonate (3 equiv relative to the acid) and catalytic amount of potassium iodide (0.5 equiv) for 48 h at 80 °C. The reaction was judged complete when a colorimetric test for chloromethyl groups on the polymer using 4-(4-nitrobenzyl)pyridine proved negative.[8] Presence of a band at 1733 cm^{-1} in the IR spectra of polymer confirmed the presence of the carbonyl group. The solid dye/polystyrene conjugate **9** was dark-orange in color.

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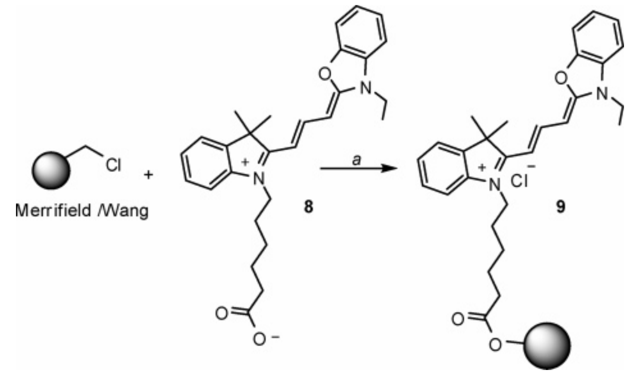
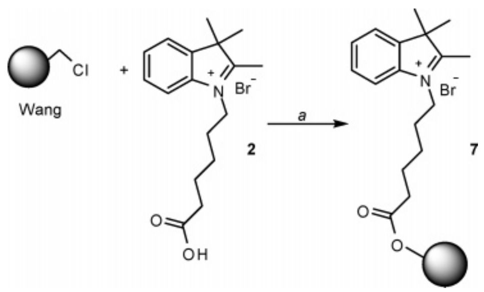
SCHEME 3 [a]



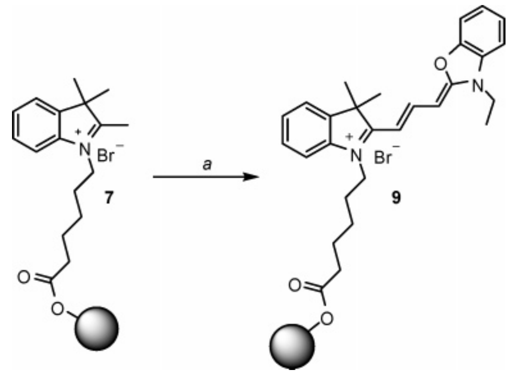
[a] Reagents and conditions: (a) Cs_2CO_3 (3 equiv), KI (0.5 equiv), DMF, 80 °C, 2 days.

SCHEME 4 [a]



[a] Reagents and conditions: (a) 2 (1.5 equiv), Cs_2CO_3 (3 equiv), KI (0.5 equiv), DMF, 80 °C, 2 days.

SCHEME 5 [a]



[a] Reagents and conditions: (a) **6** (5 equiv), NEt_3 (2 equiv), pyridine, 80 °C, 24 h.

It also seemed desirable to construct the dye on the polymer itself. Solid-phase synthesis of cyanine dyes has not been extensively explored in the literature, and to the best of our knowledge only a few examples are known.[4] In all of these cases, the dye was cleaved from the polymeric support since dye/polymer conjugates per se were not the objective. In our pursuit of a polymer-bound dye, we initially used the chlorinated Wang resin. Thus, compound **2** was successfully anchored to benzyloxybenzyl chloride, polymer bound (100−200 mesh, 1% cross-linked with DVB, 1.1 mmol/g) by using cesium carbonate and potassium iodide protocol as depicted in Scheme 4.

The reaction was judged complete when the colorimetric test specific for benzyl chlorides was negative.[6] Polymer **7** was then subjected to IR analysis (revealing the presence of a carbonyl signals at 1718 cm^{-1}) and elemental analysis which gave a nitrogen percentage of 1.22 corresponding to a loading of 0.87 mmol/g. The final step of the synthesis was accomplished by shaking a suspension of polymer **7**, acetanilide **6** (5 equiv), and triethylamine (2 equiv) in pyridine for 24 h as outlined in Scheme 5. Formation of an orange polymeric bead occurred immediately after the addition of compound **6**. Control experiments showed that neither polymer **7** nor compound **6** turns colored under the reaction conditions. Following cleavage of the dye from the polymer[9] with 80% TFA in DCM, a reddish solid was obtained. Mass spectrometry and ^1H NMR analysis were consistent with **8**, as prepared in Scheme 2.

In summary, we utilized a quick and reliable method to bind a cyanine dye to a hydrophobic polystyrene matrix. Since very reactive species have been successfully isolated on highly cross-linked polymer supports[10] we are optimistic, but without direct proof, that monomeric dye has been achieved with Merrifield polymers at 0.5 mmol/g Cl. At this low loading, the normally red dye becomes pale yellow-orange. It is unclear whether this color change is due to ion pairing, low surface concentration, or both. At any rate, with the synthesis problem now solved, we are in a position to examine the spectroscopic properties of conjugated dye exposed to apolar media where ion pairing, and thus reduced delocalization (if our postulate is correct), is possible. Technical problems remain. Careful drying of the dye/polymer, reducing further the loading, extending the conjugation, or shortening of the linker may be necessary for further success. High-level calculations on free and ion-paired dye are also anticipated.

Experimental Section

Preparation of 2-[3-[1-[(5-Carboxypentyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-ylidene]-1-propenyl]-1-ethylbenzoxazol-3-ium Inner Salt 8. Method A. A mixture of the salt **3** (0.80 g, 1.75 mmol) and benzoxazolium bromide **5** (0.51 g, 1.75 mmol) was refluxed in 15 mL of dry pyridine for 3 h under a nitrogen atmosphere. After the mixture was cooled to room temperature, diethyl ether was added and the resulting mixture refrigerated to allow complete precipitation. The solvent was decanted, and the resulting gummy mass was triturated with cold diethyl ether until a deep red powder was formed. Crystallization from acetonitrile/diethyl ether mixture gave the final product **8** as deep red powder (0.45 g, 58%). Method B. A mixture of the salt **2** (0.80 g, 2.26 mmol), enamide **6** (0.98 g, 2.26 mmol), and dry triethylamine (4.5 mmol, 0.45 g, 0.63 mL) in absolute ethanol (20 mL) was refluxed for 30 min under nitrogen. The mixture was allowed to cool to room temperature and diethyl ether was slowly added until complete precipitation occurred. The red residue was filtered, washed with cold ether and further crystallized from acetonitrile/diethyl ether mixture to give the dye **8** as a deep red powder (0.9 g, 90%). IR (neat): 2974, 2936, 2736, 2674, 2599, 2489, 1563, 1468, 1432, 1396, 1383, 1169, 1067, 1033, 848, 803 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 8.39 (1H, t, $J = 13.2$ Hz), 7.93 (1H, d, $J = 7.6$ Hz), 7.88 (1H, d, $J = 7.6$ Hz), 7.53−7.63 (3H, m), 7.43 (1H, t, $J = 7.8$ Hz), 7.38 (1H, d, $J = 8.4$ Hz), 7.25 (1H, t, $J = 7.6$ Hz), 6.50 (1H, d, $J = 13.6$ Hz), 6.34 (1H, d, $J = 13.2$ Hz), 4.41 (2H, t, $J = 7.2$ Hz), 4.06 (2H, t, $J = 7.2$ Hz), 2.27 (2H, t, $J = 7.6$ Hz), 1.75 (2H, m), 1.70 (6H, s), 1.62 (2H, m), 1.45 (5H, t, $J = 7.2$ Hz). ^{13}C NMR (150 MHz DMSO-d_6): δ 174.2, 171.4, 161.5, 147.7, 146.7, 140.1,

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[9] Cleavage of the dye from Merrifield resin gave poor yields even under forcing conditions.

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140.1, 130.5, 128.3, 126.2, 125.8, 123.9, 122.2, 111.9, 111.4, 110.4, 98.4, 90.8, 48.2, 42.9, 33.4, 28.0, 26.3, 25.6, 24.1, 13.0; MS (ESI) *m/z*: 445.24 (M + H, 100), 430.22 (15). HRMS [$C_{28}H_{33}N_2O_3^+$]: expected 445.2413, observed 445.2428. UV (methanol) λ_{max}: nm (ϵ): 521 (145250). Mp: 120−122 °C.

General Procedures To Anchor Dye 8 onto Polymeric Support. Merrifield resin (0.5 g, 1.1 mmol/g) was suspended in dry DMF (10 mL) for 30 min. To the suspension were then added dye **8** (0.37 g, 0.82 mmol, 1.5 equiv), Cs_2CO_3 (0.54 g, 1.65 mmol, 3 equiv), and potassium iodide (0.044 g, 0.27 mmol, 0.5 equiv) and the resulting mixture heated at 80 °C for 48 h. The resin was filtered, washed with DMF (4 × 5 mL), DMF/water 1:1 (4×), methanol (4×), and DCM (4×), and finally dried under vacuum overnight for 24 h at room temperature affording a bright red bead. IR: 1733 (C=O), 1372 cm^{-1}. The same procedure was applied when Wang resin was employed.

Synthesis of Polymer 7. Wang resin (1.34 g, 1.1 mmol/g) was suspended in dry DMF (20 mL) for 30 min. To the suspension was then added acid **2** (0.78 g, 2.21 mmol, 1.5 equiv), Cs_2CO_3 (1.44 g, 4.42 mmol, 3 equiv), and KI (0.12 g, 0.74 mmol, 0.5 equiv), and the resulting mixture was stirred at 80 °C for 48 h. After the mixture was allowed to cool at room temperature, the polymer was filtered and sequentially washed with MeOH/THF/MeOH/$CHCl_3$/MeOH/ DCM and finally dried in vacuo for 24 h at room temperature. Polymer **7** was obtained as bright orange beads. IR: 1718 (C=O), 1152 (CO) cm^{-1}. Anal. Calcd: N, 1.50; Cl, 0. Found: N, 1.22; Cl, 0.46 (loading 0.87 mmol/g). The residual chloride represent unreacted $-CH_2Cl$ groups in wang polymer.

Synthesis of Polymer 9. Polymer **7** (1.50 g, loading 0.87 mmol/g) was suspended in pyridine (10 mL) and allowed to swell for 30 min. After that time, to the suspension was added a solution of 2-methyl-3-ethylbenzoxazol-3-ium iodide **5** (1.88 g, 6.52 mmol, 5 equiv) in pyridine (2 mL) and 0.36 mL of triethylamine (0.26 g, 2.61 mmol, 2 equiv). After a few minutes, the resin bed turned from orange to red and the mixture was shaken at 80 °C for further 24 h. After the mixture was allowed to cool at room temperature, the polymer was filtered and sequentially washed with MeOH/THF/MeOH/$CHCl_3$/MeOH/DCM and finally dried in vacuo for 24 h at room temperature affording a bright red bead. IR: 1733 (C=O), 1372 cm^{-1}.

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Supporting Information Available: General experimental procedure, cleavage procedure, and copies of ^1H and ^{13}C NMR spectra for dye **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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