Chemoselective Targeting of Fluorescence Probes in Polymer Networks. Detection of Heterogeneous Domains in Styrene–Divinylbenzene Copolymers

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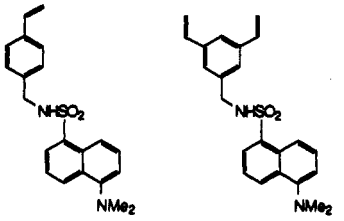
Despite widespread use of macroporous divinylbenzene (DVB) networks as supports for chemical reactions,[1] a detailed description of the gel phase of these materials remains elusive.[2] Most techniques for characterizing these complex networks yield information concerning *macroscopic* properties such as surface area, swelling, and porosity.[3] Recently, we reported the use of covalently incorporated fluorescent dansyl probes for providing detailed information regarding solvation and diffusion within the gel phase of DVB networks.[4,5] We now report that this fluorescence technique has been utilized for developing qualitative evidence for heterogeneity in the gel phase of these polymers.

Figure 1 illustrates two exteme representations of the gel phase of macroporous DVB networks. These are referred to as uniform (homogeneous) and nodular (heterogeneous). The latter type consists of highly cross-linked domains (nodules) that are interconnected by regions of lower cross-linking. The basis of the latter representation (nodular theory) arises[6] from reactivity ratio studies that show that, in the polymerization of technical-grade DVB (a mixture typically consisting of approximately equal parts of *m*- and *p*-divinylbenzene monomers and *m*- and *p*-ethylvinylbenzene isomers), the divinylbenzene isomers are incorporated more rapidly into the growing network than the monofunctional monomers of ethylvinylbenzene.[6] Initially, this gives rise to microdomains enriched in DVB, which upon further reaction of the pendent double bonds can form densely cross-linked nodules. The nodules can be interlinked, as the polymerization proceeds, by the remaining functionality in the microdomains and styrene monomers.

If the preceding description of the development of microdomains is correct, then the location of monofunctional and difunctional dansyl monomers, 1 and 2, should be



1 2

different when small amounts are copolymerized into otherwise identical materials. Probe 2 should locate (on average) within the less accessible, nodular region whereas probe 1 will reside in the more accessible, less cross-linked area. Such a difference in microenvironment of the two probes may manifest itself in the solvent-induced shift of the dansyl chromophore. That is, probes residing in more highly cross-linked microenvironments may exhibit smaller solvatochromic shifts (low polymer chain solvation) than probes residing in less highly cross-linked microenvironments (high polymer chain solvation).

The synthesis of 1 has been previously described.[4] Preparation of probe 2 required condensation of dansyl

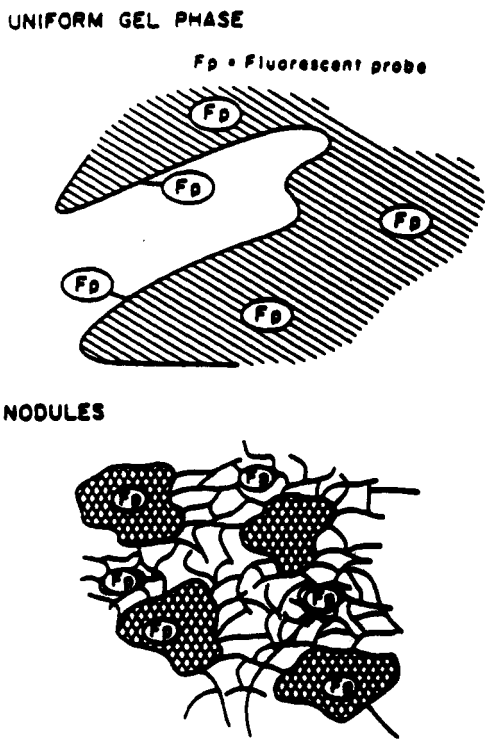


Figure 1. Two possible structures for the gel phase of divinylbenzene (DVB) networks.

chloride and 3,5-divinylbenzylamine, 8. The synthesis of 8 (Scheme I) began with bromination of ester 3 with NBS to yield bis(bromomethyl) ester 4. Reaction of 4 with triphenylphosphine followed by Wittig reaction of the bisphosphonium salt afforded divinyl ester 5. Reduction of the ester with LAH provided 6 in good yield. The resulting alcohol was converted via a two-step, one-pot reaction, to benzylazide 7. Reduction of 7 with LAH in ether provided the unstable primary amine 8, which, upon immediate dansylation, gave probe 2.

Probes 1 and 2 were independently incorporated into two macroporous 50% cross-linked divinylbenzene networks prepared in bulk by free-radical polymerization (Scheme II).[4] Several materials were prepared which differed only with respect to the diluent used in the polymerization. In one set of polymer networks, a good solvent (porogen), toluene, was used (DVB-50-B-T(1,2)) whereas the other group was prepared in the presence of a poor solvent, acetonitrile (DVB-50-B-A(1,2)).

The solvatochromic shift of these networks was then studied by soaking the polymers in six select solvents and recording their fluorescence emission spectra. Plots of the experimental vs calculated fluorescence emission maxima[4] for these materials are shown in Figures 2 and 3. Each figure contains two reference lines: the fluorescence emission wavelength of dry polymer (cross-hatching) and the fluorescence emission wavelengths of monomeric probe 1 in the indicated pure solvents (straight line).[7] These references provide extremes for the emission maxima of probes bound to solvent-imbibed polymers. Highly solvated polymer bound probes exhibit a fluorescence emission similar to that of the probe in pure solvent (correlation line) whereas probes in poorly solvated domains emit near the dry polymer region.

In materials prepared with toluene as porogen (Figure 2), the monofunctional probe 1 is clearly more accessible to all solvents (closer "fit" to the pure-solvent correlation line) than the difunctional probe 2 even though they reside in an identical polymer. *Such a disparity suggests that the two probes reside in different microdomains of*

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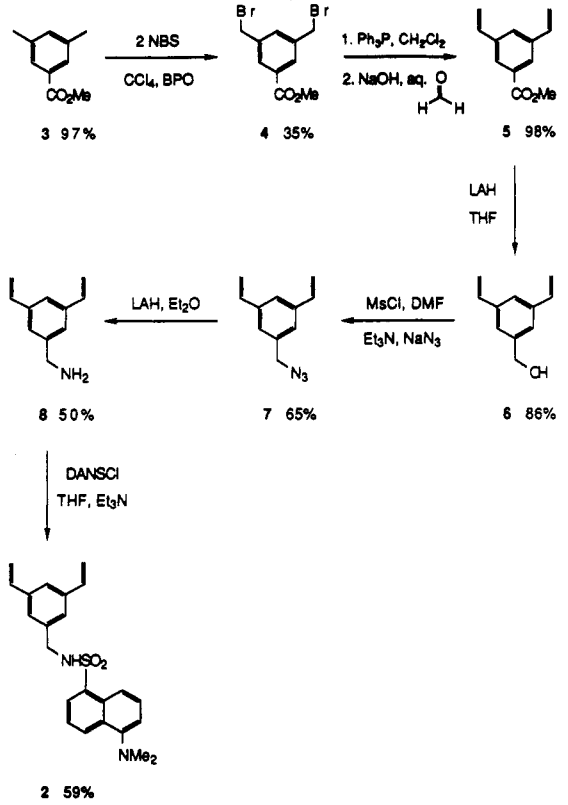
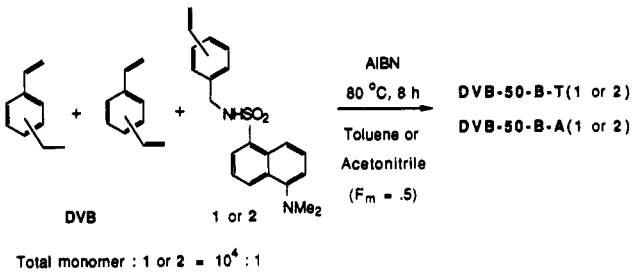
Scheme I
Synthesis of Difunctional Probe 2



Scheme II
Synthesis of DVB Networks Doped with 1 and 2



Total monomer : 1 or 2 = 10^4 : 1

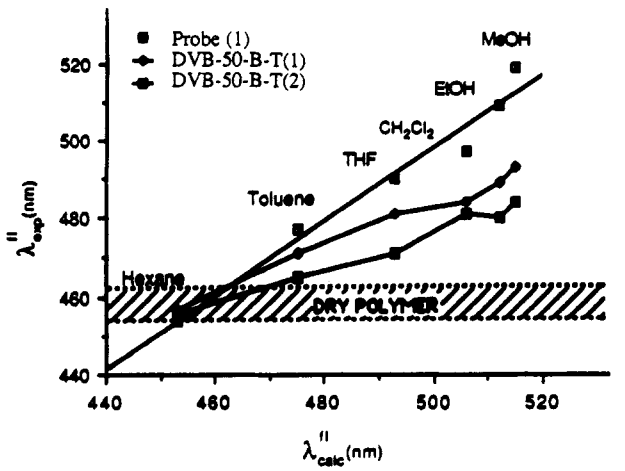


Figure 2. Fluorescence emission (λ_{ex}^{max} = 360 nm) of macroporous DVB networks prepared by bulk polymerization with toluene as diluent and doped with 1 or 2.

the gel phase. We are not aware of such direct experimental evidence for multiple domains in DVB networks. The fact that the divinyl probe 2 exists in a *less accessible* domain compared to 1 also corroborates the nodular gel-phase hypothesis.[8]

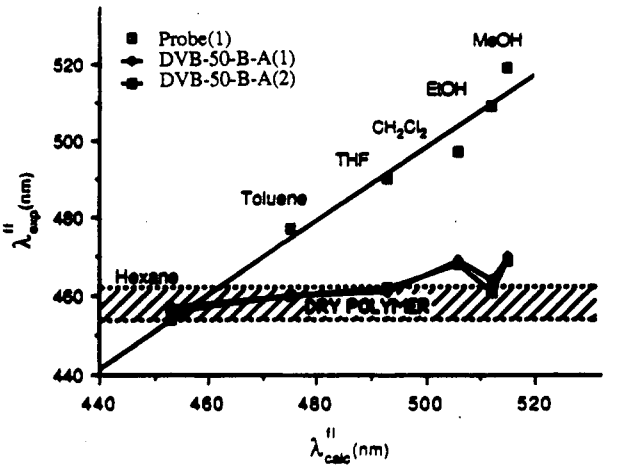


Figure 3. Fluorescence emission (λ_{ex}^{max} = 360 nm) of macroporous DBV networks prepared by bulk polymerization with acetonitrile as diluent and doped with 1 or 2.

An interesting question concerns the effect of diluent on the heterogeneity of the resulting network. When acetonitrile is used as porogen, these networks are typically impervious to solvent.[4] Unfortunately, this reduction in solvent accessibility precludes the detection of different microenvironments for probes 1 and 2. That is, their solvatochromic shifts are identical and near the dry polymer region.

The chemoselective targeting of fluorescence probes to different polymer microdomains combined with their diagnostic value will allow for a more detailed evaluation of polymer microstructure. Efforts to exploit this capability, for example, in measuring the difference in diffusion rates in the microdomains, are currently being studied.

Experimental Section

The preparation of macroporous DVB polymers has been described previously.[4,5] The polymer code refers to, respectively, the cross-linking monomer (DVB = technical-grade divinylbenzene), percent cross-linking in the monomer mixture (a typical analysis of distilled technical-grade DVB consists of 50 ■ 3% *m*- and *p*-divinylbenzene and 50 ± 3% *m*- and *p*-ethylvinylbenzene), type of polymerization (B = bulk), and porogen (T = toluene, A = acetonitrile). A complete description of the morphology of these materials can be found in the above references. The molar ratio of probe–monomer = 10^{-4}.

Methyl 3,5-Bis(bromomethyl)benzoate (4). A suspension of methyl-3,5-dimethylbenzoic acid (8.69 g, 53.0 mmol), *N*-bromosuccinimide (18.8 g, 106 mmol), and benzoyl peroxide (0.183 g, 0.755 mmol) in CCl_4 (50 mL) was refluxed for 2 h, after which time no starting material remained (TLC). The mixture was cooled to room temperature and filtered, and the solid was washed with CCl_4. The combined organics were evaporated to yield a clear viscous oil. Two successive crystallizations from hexane provided clear needles (5.96 g, 35%, mp 99–100 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.99 (d, 2 H, *J* = 1.6 Hz, Ar*H*), 7.61 (m, 1 H, Ar*H*), 4.49 (s, 4 H, ArCH_2Br), 3.92 (s, 3 H, CO_2CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 166.3, 139.4, 134.3, 131.8, 130.5, 52.9, 32.5. IR (KBr): 2952, 1728, 1605, 1450, 1436, 1321, 1233, 1218, 1132, 1108, 995, 908, 898, 772, 699 cm^{-1}.

Methyl 3,5-Divinylbenzoate (5). A solution of 4 (0.816 g, 2.53 mmol) and triphenylphosphine (1.33 g, 5.07 mmol) in CH_2Cl_2 (25 mL) was refluxed for 24 h. The solvent was evaporated to leave a sticky white solid. This was dissolved in 37% aqueous formaldehyde (8.41 mL, 112 mmol) and stirred at room temperature. To this was added dropwise 12.5 M NaOH (2.74 mL, 34.3 mmol) via addition funnel. After addition was complete, the reaction was stirred for 2 h. The mixture was extracted with ether (3 × 50 mL) and the combined organics were dried ($MgSO_4$). Evaporation of the solvent provided an oil, which was columned on silica with ether–hexane (1/1) as eluent. The product was a clear oil (0.468 g, 98%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.96 (d, 2 H, *J* = 1.6 Hz, Ar*H*), 7.58 (m, 1 H, Ar*H*), 6.73 (dd, 2 H, *J* = 10.9

and 17.6 Hz, vinyl), 5.83 (d, 2 H, J = 17.6 Hz, vinyl), 5.32 (d, 2 H, J = 10.9 Hz, vinyl), 3.92 (s, 3 H, CO_2CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 167.5, 138.7, 136.4, 131.3, 128.9, 127.7, 115.9, 52.8. IR (neat): 2952, 1725, 1594, 1447, 1437, 1308, 1293, 1261, 1217, 1119, 990, 912, 897, 773 cm^{-1}. MS (CI, isobutane, relative percent): m/z 189 (MH^+, 100), 177 (4), 175 (3), 157 (4), 131 (1), 128 (1). High-resolution MS. Calcd for $C_{12}H_{12}O_2$: 188.0837. Found: 188.0838.

3,5-Divinylbenzenemethanol (6). To a suspension of LAH (0.101 g, 2.66 mmol) in THF (15 mL) at room temperature was added **5** (0.334 g, 1.77 mmol). This was monitored by TLC (ether–hexane, 1/1) and was complete after 15 min. The reaction was then quenched with water (5 mL) followed by 10% NaOH (5 mL) and stirred for 30 min. The mixture was extracted with ether (3 × 20 mL), and the combined organics were dried ($MgSO_4$). Evaporation of the solvent provided a white solid (0.245 g, 86%, mp 59–61 °C). ^1H NMR (250 MHz, $CDCl_3$): δ 7.36 (s, 1 H, ArH), 7.32 (s, 2 H, ArH), 6.72 (dd, 2 H, J = 10.9 and 17.6 Hz, vinyl), 5.77 (d, 2 H, J = 17.6 Hz, vinyl), 5.27 (d, 2 H, J = 10.9 Hz, vinyl), 4.69 (s, 2 H, ArCH_2OH), 1.71 (s, 1 H, ArCH$_2$OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 142.0, 138.8, 137.2, 124.8, 124.3, 115.1, 65.9. IR (KBr): 3250 (br), 2926, 1594, 1456, 1348, 1261, 1158, 1029, 991, 914, 868, 722 cm^{-1}. MS (EI, 70 eV, relative percent): m/z 160 (M^+, 100), 141 (10), 131 (50), 128 (31), 117 (54), 105 (28), 91 (69), 77 (33), 51 (29). High-resolution MS. Calcd for $C_{11}H_{12}O$: 160.0888. Found: 160.0875.

3,5-Divinyl(azidomethyl)benzene (7). To a solution containing **6** (0.318 g, 1.98 mmol), DMF (10 mL), sodium azide (0.258 g, 3.96 mmol), and triethylamine (0.550 mL, 3.95 mmol) at 0 °C was added dropwise methanesulfonyl chloride (0.307 mL, 3.97 mmol). The reaction was stirred for 2 h at 0 °C and then allowed to warm to room temperature. Monitoring by TLC (ether–hexane, 1/9) revealed that the reaction was complete after 15 h. Water (15 mL) was added, and the mixture was extracted with ether (3 × 30 mL). The organics were combined, dried ($MgSO_4$), and evaporated to yield a clear light yellow oil (0.239 g, 65%). ^1H NMR (250 MHz, $CDCl_3$): δ 7.39 (s, 1 H, ArH), 7.24 (s, 2 H, ArH), 6.71 (dd, 2 H, J = 10.9 and 17.6 Hz, vinyl), 5.78 (dd, 2 H, J = 0.8 and 17.6 Hz, vinyl), 5.29 (dd, 2 H, J = 0.6 and 10.7 Hz, vinyl), 4.33 (s, 2 H, ArCH_2N_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 139.1, 136.9, 136.8, 136.6, 125.9, 124.8, 115.5, 55.3. IR (neat): 3089, 3009, 2983, 2929, 2100 (s), 1593, 1444, 1342, 1273, 1244, 990, 913, 859, 719 cm^{-1}. MS (CI, isobutane, relative percent): m/z 186 (MH^+, 5), 185 (9), 172 (3), 158 (46), 143 (100), 131 (5), 117 (5), 91 (4), 79 (5). High-resolution MS. Calcd for $C_{11}H_{11}N_3$: 185.0983. Found: 185.0969.

3,5-Divinylbenzenemethanamine (8). To a suspension of LAH (0.0666 g, 1.75 mmol) in ether (20 mL) at room temperature was added **7** (0.217 g, 1.17 mmol). The mixture was stirred at room temperature and monitored by TLC (ether–hexane, 1/9). After 8 h the reaction was complete and water (10 mL) was added followed by 10% NaOH (5 mL). This was stirred at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated to provide a yellow oil (0.0923 g, 50%). Due to instability, this compound was carried immediately into the next step without characterization.

5-(Dimethylamino)-*N*-[(3,5-divinylphenyl)methyl]-1-naphthalenesulfonamide (2). To a solution containing **8** (0.0923 g, 0.580 mmol), THF (20 mL), and triethylamine (0.163 mL, 1.17 mmol) at room temperature was added dansyl chloride (0.316 g, 1.17 mmol). This was stirred overnight, after which time the salts were filtered and washed with THF. The combined filtrates were dried ($MgSO_4$) and evaporated to leave a yellow-green oil. This was chromatographed on silica with ether–hexane (1/2) as eluent to give a light green oil. Light green needles were grown from benzene–hexane (0.135 g, 59%, mp 107–108 °C). ^1H NMR (250 MHz, $CDCl_3$): δ 8.52 (d, 1 H, J = 8.0 Hz, ArH), 8.27 (m, 2 H, ArH), 7.56 (dd, 1 H, J = 7.7 and 8.6 Hz, ArH), 7.49 (dd, 1 H, J = 7.4 and 8.5 Hz, ArH), 7.18 (m, 2 H, ArH), 6.91 (s, 2 H, ArH), 6.49 (dd, 2 H, J = 10.9 and 17.7 Hz, vinyl), 5.54 (dd, 2 H, J = 0.6 and 17.6 Hz, vinyl), 5.17 (dd, 2 H, J = 0.6 and 10.9 Hz, vinyl), 4.94 (t, 1 H, J = 6.4 Hz, SO_2NH), 4.09 (d, 2 H, J = 6.2 Hz, ArCH_2NH), 2.89 (s, 6 H, N(CH_3)$_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 138.6, 137.2, 136.9, 136.7, 135.1, 131.3, 130.7, 130.6, 130.2, 129.2, 125.5, 124.3, 123.8, 119.3, 115.9, 115.2, 47.8, 46.1. IR (KBr): 3283, 2940, 2830, 2775, 1588, 1576, 1459, 1445, 1312, 1232, 1148, 1139, 1073, 1062, 988, 948, 903, 881, 788, 693 cm^{-1}. MS (EI, 70 eV, relative percent): m/z 392 (M^+, 8), 171 (100), 154 (5), 143 (3), 128 (9), 115 (5), 91 (2), 77 (3), 51 (1). High-resolution MS. Calcd for $C_{23}H_{24}N_2O_2S$: 392.1558. Found: 392.1553.

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(7) It should be noted that monomeric probes **1** and **2** exhibited identical solvent-induced shifts in all six solvents.

(8) A reviewer has made the interesting suggestion that the solvatochromic data may be interpreted in terms of the distribution of dansyl groups between bulk polymer and the surface. If dansyl groups are concentrated at the surface during phase separation in an effort to minimize interfacial free energy, the difference between probes **1** and **2** would then be explained by the lesser mobility of the cross-link **2** that prevents it from coming to the interface as the pores are formed. The importance of this suggestion is difficult to access but several lines of reasoning argue that it may not be a major factor in the fluorescence studies. First, the porogen of interest is toluene. The similar solvent characteristics of toluene and polystyrene would provide little driving force for the segregation of the more polar dansyl molecules from the bulk polymer. Second, the results of chemical quenching studies of dansyl probes embedded in these materials[5] reveal that quencher molecules must diffuse through bulk polymer rather than merely react on the surface. Finally, materials prepared with acetonitrile and toluene *both* have high internal surface areas (200–400 m^2/g). Soaking these materials in organic solvents produces marked differences in solvatochromic behavior (probe **1**).[4] If probe molecules were concentrated on the surface, their behavior would be expected to be similar. Our efforts are continuing to utilize the fluorescent probe diagnostic to evaluate microdomains, including differentiation between surface bound and bulk.

Registry No. (1)(DVB)(ethylvinylbenzene) (copolymer), 131236-16-3; (**2**), 117317-02-9; (**2**)(DVB)(ethylvinylbenzene) (copolymer), 131236-17-4; **4**, 51329-15-8; **5**, 131236-11-8; **6**, 131236-12-9; **7**, 131236-13-0; methyl-3,5-dimethylbenzoic acid, 25081-39-4.