J. Am. Chem. Soc. 1994, 116, 11195−11196

Hydraamphiphiles: Novel Linear Dendritic Block Copolymer Surfactants

Toby M. Chapman,* Gregory L. Hillyer, Eric J. Mahan, and Katherine A. Shaffer

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Received June 6, 1994

We report the preparation of polymeric surfactants with hydrophobic terminal residues on a dendrimer attached to a hydrophilic tail of poly(ethylene oxide) (PEO). The latter also serves as the platform for facile dendrimer synthesis. PEO is a versatile polymer which has had wide use as the nonionic hydrophilic moiety of numerous important surfactants.[1] The insolubility of PEO in ether has led to its use in peptide,[2] oligonucleotide,[3] and polysaccharide syntheses.[4] Coupling and deprotection reactions are carried out in a homogeneous medium; reaction workup consists of precipitation in ether.

Our synthetic procedure is shown in Scheme 1. Methoxy-terminated PEO, M_n 4717 (VPO),[5] is esterified with Boc-glycine,[6] the protection is removed, and dendritic poly(α,ϵ-L-lysine)[7] is generated by repeated cycles of coupling with pentafluorophenyl *N*-α-*N*-ϵ-di-Boc-L-lysinate (**I**),[8] followed by deprotection with 1:1 trifluoroacetic acid (TFA):CH_2Cl_2.[9] Each cycle of deprotection/acylation doubles the number of terminal lysine residues and doubles the number of Boc-protected amines, verified by the ratio of polyether CH_2 to Boc CH_3 protons determined by ^{1}H-NMR. The characterization of the polymers is shown in Table 1. All nonpolymeric reagents and byproducts are ether soluble, including the activated lysine ester; precipitation of the products in ether as the trifluoroacetate or Boc form is without problem through generation 4. We name these chimerical molecules with multiple terminal hydrophobic *tert*-butyl groups hydraamphiphiles, the structures and synthesis paralleling the Hydra legend.[10] Fréchet[11,12] has attached preformed dendrimers to PEO, obtaining diblocks or triblocks. Some of these aggregate in aqueous media, but surfactant properties were not reported.[13] Fréchet et al. have also reported dendrimers with separate hydrophobic and hydrophilic termini.[14] Newkome[15] has studied the aggregation of hydrophilic arborols bonded at both ends of a long-chain hydrocarbon.

Scheme 1. PEO-Supported Synthesis of Dendritic Boc-Poly(α,ϵ-L-lysine)

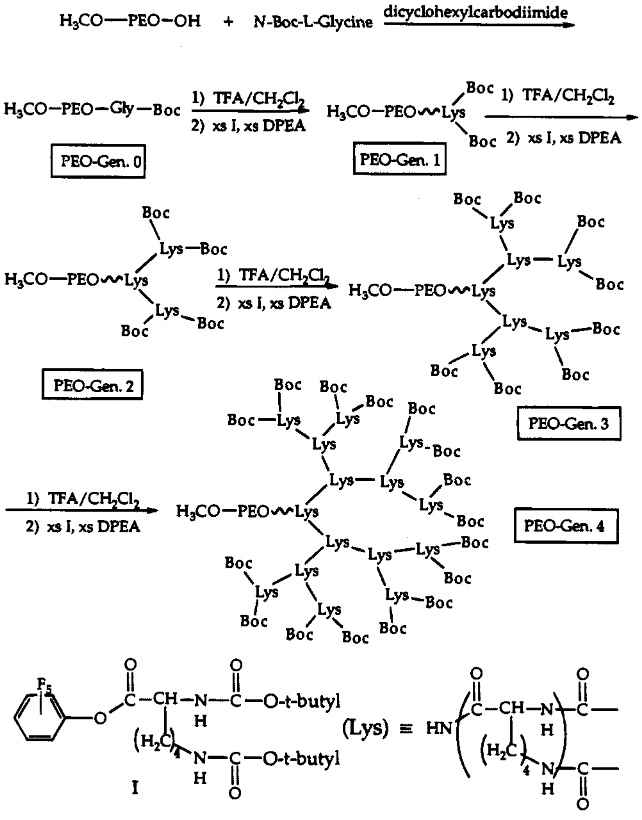

Table 1. Characterization of PEO−Boc-Lysine Dendrimers (Hydraamphiphiles)

polymer	no. of lysine residues	no. of terminal Boc residues	M_n calcd	M_n GPC[b]	M_w/M_n (GPC)	OCH2: Boc proton ratio	intrinsic viscosity (DMF)
CH_3O-PEO	0	0	4717[a]	7150	1.02		0.13
PEO-generation 1	1	2	5103	7819	1.03	26.9	
PEO-generation 2	3	4	5560	8018	1.02	12.3	
PEO-generation 3	7	8	6473	8698	1.02	5.90	
PEo-generation 4	15	16	8299	9363[c]	1.04	2.98[d]	0.15

[a] Determined by VPO. [b] THF, Waters Ultrastyragel linear and 10^3 Å 7.8 × 300 mm columns in series, polystyrene standards. [c] M_n by VPO = 8040. [d] Calculated ratio based on M_n 4717 CH_3O-PEO = 2.96.

Shaking the hydraamphiphiles in water gives a foam with good temporal stability (1−2 weeks). The hydraamphiphiles can be solubilized by sonication in water; the more concentrated solutions exhibit a slight turbidity due to light scattering by the aggregates that form. The surfactant properties of the generation 4 polymer have been examined. Surface tension measurements

---

(1) Schönfeldt, N. *Surface Active Ethylene Oxide Adducts*; Pergamon: Oxford, 1969.

(2) Mutter, M.; Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 88−89.

(3) Bonora, G. M. *Gazz. Chim. Ital.* **1987**, *117*, 379−380.

(4) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5095−5097.

(5) Purchased from Polysciences as M_n 5000.

(6) Methoxy-PEO (25 g, 0.005 m), Boc-glycine (3.67g, 0.021 m), and dicyclohexylcarbodiimide (4.67g, 0.024 m) were stirred for 19 h in 60 mL of CH_2Cl_2 and then precipitated into 1600 mL of anhydrous ether. The product was washed profusely with ether. Yield: 22.4 g, 87%.

(7) The first polymeric dendrimer was a poly(α,ϵ-L-lysine): Denkewalter, R. G.; Kolc, J.; Lukasavage, W. J. U.S. Patent 4,289,872, Sept 15, **1981**; Aharoni, S. M.; Crosby, C. R.; Walsh, E. K. *Macromolecules* **1982**, *15*, 1093−1098. A recent solid-phase synthesis has been reported: Roy, R.; Zanini, D.; Meunier, S. J.; Romanowska, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1869−1872.

(8) Prepared from *N*-α-*N*-ϵ-di-(*tert*-butoxycarbonyl)-L-lysine, pentafluorophenol, and DCI in ethyl acetate. The product was recrystallized from hexanes followed by 3:2 ethanol:water, mp 106.5−109 °C (lit. mp 104−106 °C: Schön, I.; Szirtes, T.; Überhardt, T.; Scehi, A. *J. Org. Chem.* **1983**, *48*, 1916−1919). Data: IR ν 3368, 1782, 1684; MS (EI) *m/z* 513 (M + 1); HRMS calcd for $C_{14}H_{13}N_2O_6F_5$ (M − $2C_4H_8$) 400.0694, found 400.0659. ^{13}C-NMR and ^{1}H-NMR spectra were consistent with the structure. See supplementary material for details.

(9) Coupling reactions were carried out by stirring together in DMF ammonium trifluoroacetate-terminated polymer, 3 equiv of lysine active ester, and 1.5 equiv of ethyldiisopropylamine (DPEA) for each equivalent of ammonium salt for 24 h. Removal of the Boc-amine protection was carried out in 1:1 TFA:methylene chloride for 2 h. All products were recovered by precipitation into a minimum 10-fold excess of anhydrous ether and washing profusely with the ether. Yields from one generation to the next ranged from 73 to 84%. Completion of reaction was monitored by the ratio of the PEO CH_2 to *tert*-butyl CH_3 proton resonances centered at δ 3.62 and 1.43 ppm, respectively. The excess lysine active ester can by recovered by evaporation of the condensation reaction filtrates and recrystallization from hexanes. PEO-generation 4: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, *tert*-butyl), 1.65 (br m, $(CH_2)_3$), 3.08 (br m, CH_2-N), 3.65 (s, PEO); IR (KBr) ν 3330, 2886, 1690, 1647, 1528, 1466, 1342, 1148, 1109, 963, 843.

(10) Bulfinch, T. *The Age of Fables*; Heritage Press: New York, 1942; p 146.

(11) Gitsov, I.; Wooley, K. L.; Fréchet, J. M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1200−1202.

(12) Gitson, I.; Wooley, K. L.; Hawker, C. J.; Ivanova, P. T.; Fréchet, J. M. J. *Macromolecules* **1993**, *26*, 5621−5627.

(13) Gitsov, I.; Fréchet, J. M. J. *Macromolecules* **1993**, *26*, 6536−6546.

(14) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1287−1297.

(15) Newkome, G. R.; Lin X.; Yaxiong, C.; Escamilla, G. H. *J. Org. Chem.* **1993**, *58*, 3123−3129.

0002-7863/94/1516-11195$04.50/0

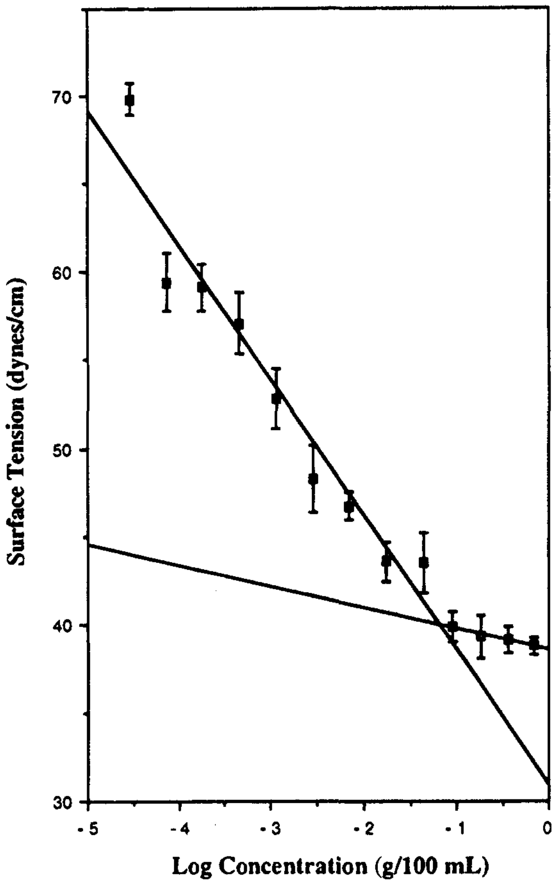

Figure 1. Surface tension vs log concentration measurements for the generation 4 hydraamphiphile. The error bars signify the standard deviation.

(Wilhelmy)[16] are shown in Figure 1. Each point represents the average of a single measurement taken on four consecutive days at 23 ± 1 °C. Readings repeated after 10 min were not reproducible, and re-equilibration of the surface may be slow. 2,4-Di-*tert*-butylphenol decaglycol ether may take as long as 1000 min to reorganize its surface.[17] Menger had similar problems with the "Gemini" surfactants.[18] Extrapolation of the least-squares lines through the four points of highest concentration and the 11 points of lowest concentration gives an intercept at 0.066 g/100 mL (8×10^{-5} M), which should approximate the critical micelle concentration (cmc). The slope of the latter plot, −7.65 dyn/cm, gives a surface area per molecule of 123 Å^2, a circle 12.5 Å in diameter, from the Gibbs equation.[19] Aharoni[7] determined a radius of 11.4 Å for generation 4 poly(α,ε-L-lysine) from intrinsic viscosity measurements. A hydrodynamic sphere diameter for the PEO moiety of 36.3 Å is calculated by the method of Mettille and Hester.[20] Thus, both the polyether coil and the dendrimer must be tightly compressed at the surface.

Aqueous solutions of the generation 4 hydraamphiphile solubilize the dye Orange-OT.[21] The results shown in Figure 2[22] demonstrate that the amount of solubilized dye generally increases with the concentration of surfactant and that below a transition concentration there is essentially no dye absorbed. A plot of grams of dye absorbed per gram of surfactant vs log concentration shows the ratio to be low at high surfactant concentration and to increase dramatically as the lower transition concentration is approached, whereupon the ratio abruptly plummets. A similar experiment reported with Triton X-100 shows a constant ratio at high concentration, which then falls as the cmc is reached.[23] The transition concentration is lower than the cmc determined by the surface tension results, perhaps the result of the dye affecting the aggregation. The increase at very low concentration is an artifact.

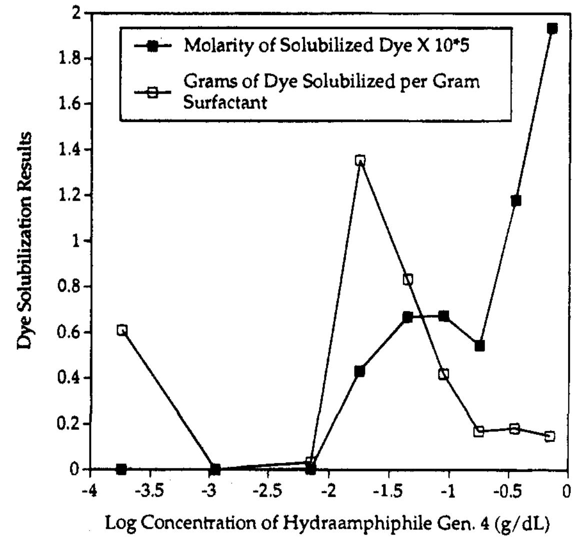

Figure 2. Solubilization of Orange-OT as a function of log concentration of the generation 4 hydraamphiphile.

The hydraamphiphiles described here contain three sections: one hydrophilic, one hydrophobic, and a central polar segment. These polymers could prove valuable in the solubilization of polar, water-insoluble molecules. They should also be biocompatible and degrade into benign fragments. Langer and coworkers[24] have recently described biodegradable diblock polymers of PEO and poly(lactic-*co*-glycolic acid) which may prove useful in drug delivery. The hydraamphiphiles may have similar properties. We are currently studying the structures of the water aggregates and are preparing analogs with fluorinated hydrophobes. We are also extending the use of PEO in dendrimer synthesis.

Acknowledgment. This research was supported by the Office of Naval Research, Grant No. N00014-92-J-1316. We thank Susana Steppan and Marilyn Kwiatkowski at Miles, Inc. for their technical assistance with surface tension methods and helpful discussions with Dr. Peter Wipf of the University of Pittsburgh Chemistry Department.

Supplementary Material Available: Details of dendrimer synthesis and spectral data for pentafluorophenyl *N*-α-*N*-ε-di-Boc-L-lysinate (**I**) (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(16) Cahn dynamic contact angle analyzer DCA-312.

(17) Heusch, R. Physical Methods as Aids in the Production and Development of Surfactants I. Surface Tension and Film Balance Measurements; Brinkmann Technical Bulletin.

(18) Menger, F. M.; Littau, C. *J. Am. Chem. Soc.* **1993**, *115*, 10083–10090.

(19) Hiemenz, P. C. *Principles of Colloid and Surface Chemistry*; Dekker: New York, 1977; pp 279–281.

(20) Mettille, M. J.; Hester, R. D. In *Water Soluble Polymers—Synthesis, Solution Properties, and Applications*; Shalaby, S. W., McCormick, C. L., Butler, G. B., Eds.; ACS Symposium Series 467; American Chemical Society: Washington, DC, 1991; pp 276–290.

(21) Purchased from TCI America, Orange Oil SS, 99% pure.

(22) Excess dye, 70 mg, was suspended in 5 mL of surfactant solution and stirred for 24 h at ambient temperature. After the solution was left to settle for 24 h, a portion was removed and filtered through glass wool. An aliquot of the filtrate was dissolved in DMF to make a 5% aqueous solution; the absorptivity was compared to that of a standard to determine the concentration of solubilized dye in the initial solution. The same features and transition concentration were observed with 12.5 mg of dye and settling times of 2 and 26 h.

(23) McBain, M. E. L.; Hutchinson, E. *Solubilization and Related Phenomena*; Academic Press: New York, 1955; pp 50, 82.

(24) Gref, R.; Minamitake, Y.; Peracchia, M. T.; Trubetskoy, V.; Torchilin, V.; Langer, R. *Science* **1994**, *263*, 1600–1603.