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Polytryptophane Terminated Dendritic Macromolecules[1]

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Abstract: The synthesis and characterization of dendritic macromolecules coated with tryptophan moieties are described. A direct relationship between the molecular ellipicity ( ) and the number of surface tryptophans has been demonstrated.

Denkewalter et al.[2] were the first to synthesize a related series of globular poly(α,ε-*L*-Lysine) biopolymers, which were subsequently shown by Aharoni et al.[3] to be dense, monodisperse, nondraining spherical, globular macromolecules and were suggested as molecular size markers. Although related polypeptides have been described,[4] we recently reported a novel class of readily available four-directional poly(ether-amide) cascade macromolecules,[5] which are homogenous spherical polymers possessing a predetermined porosity, precise molecular size, and structurally similar to a new series of unimolecular micelles.[6] Variation of the hydrophilic surface and lipophilic internal functionality of these spherical polymers will provide insight to the inclusion of biomolecules within a micellar environment. We herein report our preliminary studies on the introduction of tryptophan moieties onto surface of these dendritic macromolecules.

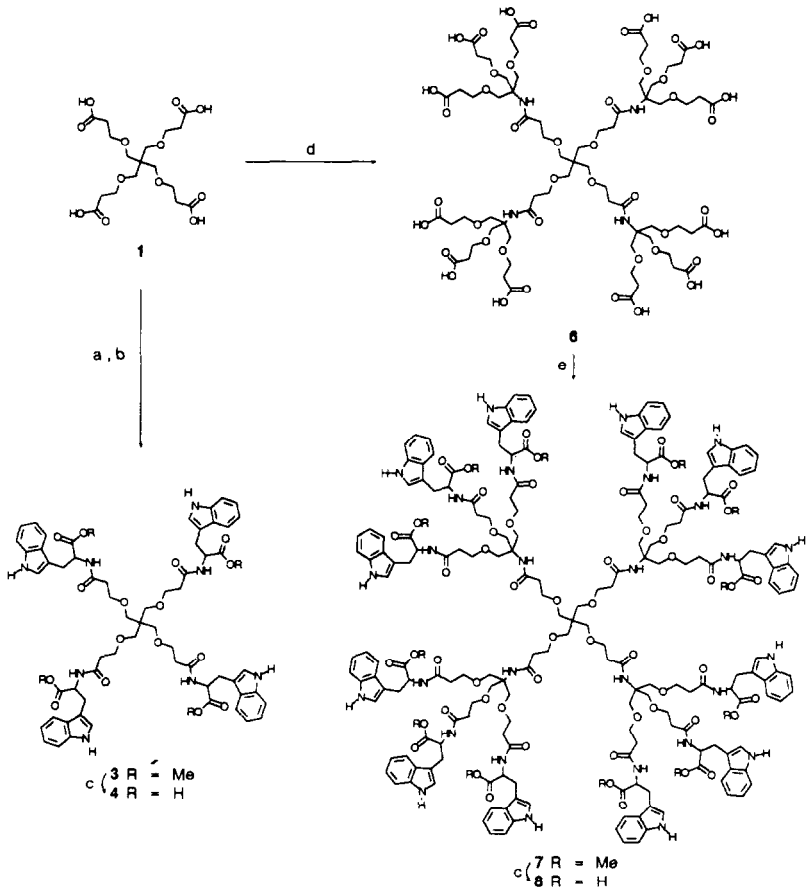
These cascade polymers are comprised of (i) a molecular core, which defines the directionality; (ii) monomer units [building block(s)], which instill the density and fractal characteristics; and (iii) surface functionality. A series of four-directional core molecules has been developed[5,7] to control the inner density and to incorporate sufficient space[8,9] to circumvent the chemical retardation caused by the juxtaposition of the branching quaternary carbon centers. The white crystalline tetraacid core **1**, prepared[5] in three simple steps from pentaerythritol, when treated with purified[10] $SOCl_2$ in CH_2Cl_2 afforded (>95%) the tetraacyl chloride **2**, which was used without further purification. Treatment of **2** with tryptophan methyl ester hydrochloride in dimethoxyethane and Et_3N gave (96%) the desired [4]-tryptophan methyl ester **3**.[11] Successful amidation was indicated (^{13}C NMR) by new peaks at 52.7 (CONH*C*) and 172.5 ppm (*C*ONH) assigned to the internal amide moieties. The IR spectrum of **3** exhibited the desired signals at 1653 (CONH) and 1738 (COO) cm^{-1}.

Under controlled reaction conditions to ensure retention of both the internal ether and amide bonds, hydrolysis of ester **3** with dilute (20%) aqueous NaOH in MeOH (1:4) at 25 °C afforded (70%) the crystalline [4]-tryptophan tetraacid **4**,[12] mp 122-126 °C. Successful hydrolysis was indicated (^{13}C NMR) by a downfield

shift of the C=O resonance from 171.8 ppm in ester **3** to 173.6 ppm in acid **4**, and disappearance of the CH_3 signals (δ 52.4).

Dodecaacid **6** was prepared (50% overall) by treatment of tetraacid **1** with *tris*[carboxyethoxymethyl]aminomethane (**5**)[5] using standard DCC peptide conditions,[13] followed by hydrolysis. Treatment of [12]-acid **6** with tryptophan methylester hydrochloride in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC) and Et_3N in THF/MeCN (1:1) gave (55%) the [12]-tryptophan methyl ester **7**.[14] Complete amidation was indicated by the spectral (NMR) symmetry and the ratio of peak intensities.

Scheme I

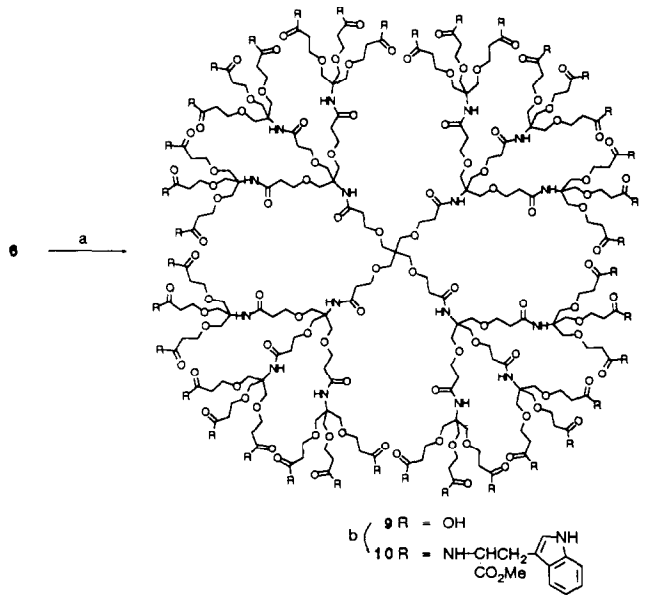


Reagents: (a) $SOCl_2$, CH_2Cl_2; (b) Trp Me ester•HCl, Et_3N, DME; (c) NaOH, MeOH; (d) $H_2NC(CH_2OCH_2CH_2CO_2Et)_3$ (**5**), DCC; NaOH, MeOH, 25 °C; (e) Trp Me ester•HCl, DEC, Et_3N, THF, MeCN.

Similarly, reaction of [36]-acid **9**, prepared (37%) from [12]-acid **6** with amine **5** via standard DCC amidation conditions, with tryptophan methyl ester hydrochloride with DEC and Et_3N in THF/MeCN gave

(35%) the related [36]-tryptophan methyl ester **10**.[15] Both polytryptophan esters possessed spectral patterns similar to the ones for the previously obtained analogues . By using DEC, as the coupling reagent, the urea by-product was water soluble and easily removed from the crude reaction mixture by washing with water.[16] The optical rotation [molecular ellipicity units (θ)] of these polytryptophans was obtained by measurement of their circular dichroism.[17] Experiments have shown that the θ increased proportionate to the number of surface tryptophan moieties. Preliminary attempts to incorporate the aminoacid moieties inside these macromolecules resulted in complete loss of chirality, a documented phenomenon[18] when using these coupling procedures.[19]

Scheme II



Reagents: (a) $H_2NC(CH_2OCH_2CH_2CO_2Et)_3$ (**5**), DCC; NaOH, MeOH, 25 °C; (b) Trp Me ester•HCl, DEC, Et_3N, THF, MeCN.

Research is continuing on the preparation of dendritic macromolecules terminated with peptide moieties in order to quantitively define the relationships between the optical rotation strength and the number of optical centers in these biopolymers.

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11. ^{13}C NMR ($CDCl_3$) δ 27.25 (CH_2Ar), 36.3 (CH_2CONH), 44.0 ($C_{4°}$), 52.4 (CH_3), 52.7 ($CHCO_2$), 66.4 (OCH_2CH_2), 69.8 ($C_{4°}CH_2$), 108.8 (7-Ar), 111.5 (3-Ar), 118.0 (4-Ar), 119.1 (5-Ar), 121.7 (6-Ar), 123.3 (2-Ar), 127.3 (9-Ar), 136.1 (8-Ar), 171.8 (CCO_2), 172.5 (CONH); CD (MeCN) $\theta \cdot 10^4 = 2.9$ (231 nm).
12. ^{13}C NMR (DMSO-d_6) δ 27.47 (CH_2Ar), 35.9 (CH_2CO), 45.0 ($C_{4°}$), 53.2 ($CHCO_2$), 67.2 (OCH_2CH_2), 69.0 ($C_{4°}CH_2$), 170.7 (CONH), 173.6 (CO_2H); CD (EtOH) $\theta \cdot 10^4 = 2.3$ (233 nm).
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14. ^{13}C NMR δ 27.5 (CH_2Ar), 36.5 (CH_2CONH), 45.2 [$C_{4°}$(core)], 52.5 (CH_3), 52.8 ($CHCO_2CH_3$), 59.4 ($CONHC_{4°}$), 66.9 (OCH_2CH_2), 68.8 ($C_{4°}CH_2O$), 109.2 (7-Ar), 111.7 (3-Ar), 118.3 (4-Ar), 119.4 (5-Ar), 121.9 (6-Ar), 123.3 (2-Ar), 127.5 (9-Ar), 136.3 (8-Ar), 171.7 (CONH), 172.7 (CO_2); CD (MeCN) $\theta \cdot 10^4 = 8.2$ (231 nm).
15. ^{13}C NMR δ 27.5 (CH_2Ar), 36.5 (CH_2CONH), 45.2 [$C_{4°}$(core)], 52.6 (CH_3), 52.8 $CHCO_2$), 59.4 ($CONHC_{4°}$), 67.0 (OCH_2CH_2), 69.0 ($C_{4°}CH_2$), 171.7 (CONH), 172.7 (CO_2); CD (MeCN) $\theta \cdot 10^4 = 28.7$ (232 nm).
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19. Circumvention of this problem will be discussed elsewhere.