Terminal Alkylation of Linear Polyamines

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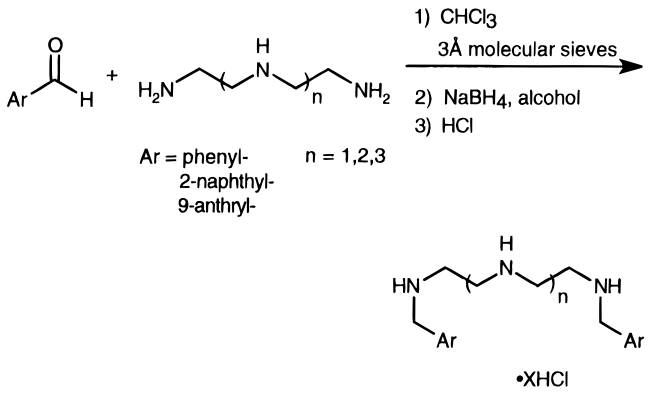
Introduction

Polyamines, both linear and macrocyclic, have been a pervasive feature in the literature over the past several years. They have been studied extensively for their binding properties with several varieties of non-covalently associated guests.[1] Spermine and its precursors (present in all cells[2]) have been widely examined for their roles in biology. They can influence DNA morphology[3] and are likely to be involved in various steps of protein synthesis.[2] They have been shown to participate in allosteric modulation of the *N*-methyl-D-aspartate receptor in brain chemistry.[4] Many of these functions have suggested medical applications for compounds based on these and other linear polyamines and their synthetic conjugates with other moieties (for NMDA receptor,[5] systemic lupus erythematosus,[6] and heart disease[7]). In addition, recent antineoplastic strategies have been targeted toward polyamine biosynthetic pathways.[8]

Accordingly, several strategies have been devised to selectively modify linear polyamines by protection/deprotection schemes.[8a,9] Reductive amination has been shown to be a useful method for alkylating the terminal nitrogens of polyamines with protected internal amines.[10] Martell[11] elaborated on the work of Lehn and Pascard indicating that the protection step may not be necessary. We are interested in the potential use of bis-terminally substituted linear polyamines as fluorescence probes for metal ions. Proper complexation of a metal ion by such a species may induce a conformation in which intramolecular excimer formation provides a fluorescent signal. We report here the general use of a simple reductive amination sequence for the alkylation of terminal amines in linear polyamines. No products from reaction at internal (secondary) amine sites are observed. Our efforts to synthesize these compounds using a simple substitution reaction on chloromethylarenes,[12] or by substitution on tosylate protected polyamines, were unsuccessful.

Scheme 1



Synthesis

Two equivalents of the aryl aldehyde are treated with the polyamine in chloroform solution. For benzaldehyde, bis-imine formation is complete in less than 2 h. For anthraldehyde, the addition of molecular sieves is necessary and the mixture must be heated to a gentle reflux for 2 h or stirred at room temperature overnight. The imine is not purified[13] but is dissolved in alcoholic solution and treated with an excess of $NaBH_4$. After a few hours at reflux, the solvent is removed and the HCl salt of the polyamine can be isolated after a series of simple extractions (Scheme 1). Further purification by recrystallization from ethanol or water is necessary for some adducts. A similar synthesis of the monosubstituted polyamines (as described by Czarnik[12b]) can be effected in high yield by using 1 equiv of the aldehyde and an excess (5-fold) of the polyamine. All new products have been fully characterized by ^1H and ^{13}C NMR, mass spectrometry, and elemental analysis or high resolution mass spectrometry.

Experimental Section

General. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Mass spectral analyses were performed at the North Carolina State University Mass Spectrometry Laboratory for Biotechnology. All starting materials were obtained from Aldrich Chemical Co.

Typical Experimental. N^1,N^5-Bis(9-anthrylmethyl)-tetraethylenepentaamin·5HCl (9). 9-Anthraldehyde (1.00g; 4.85 mmol) was dissolved in 100 mL of $CHCl_3$. To this solution were added tetraethylenepentamine (0.45g; 2.4 mmol) and 20 g of 3 Å molecular sieves. This mixture was heated at reflux for 2 h with stirring. Sieves were then removed by vacuum

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filtration, ground a with mortar and pestle, and washed with $CHCl_3$. The $CHCl_3$ solutions were pooled, and the solvent was removed by rotary evaporation to give an orange residue (presumably the bis imine). This residue was dissolved in 100 mL of hot methanol. $NaBH_4$ (0.31g; 8.0 mmol) was dissolved in 15 mL of methanol and added to the methanolic imine solution. This solution was stirred at reflux for 1.5 h and then at room temperature overnight. The solvent was removed by rotary evaporation to give an oily orange residue which was partitioned between 75 mL of $CHCl_3$ and 25 mL of 1 M NaOH. The aqueous phase was discarded. The organic layer was further extracted with 100 mL of 1M NaOH. Again, the aqueous phase was discarded. The organic layer was treated with 3 mL of concentrated HCl, and a sticky orange solid formed in the separatory funnel. H_2O (20 mL) was added, and after a few minutes the solid turned yellow. The organic layer remained yellow (probably 9-anthrylmethanol). The $CHCl_3$ layer was discarded, and the solid suspended in the aqueous layer was collected by vacuum filtration. This solid was dried over P_2O_5 *in vacuo* at 50 °C to give a yellow solid (1.16 g; 64%). This solid was easily purified by recrystallization from DMSO to give a pale yellow solid with clean NMR spectra or by recrystallization from H_2O (80% recovery): mp 195−210 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.0 (bs, 10NH), 8.76 (s, 2H), 8.59 (d, 4H), 8.16 (d, 4H), 7.62 (m, 8H), 5.31 (s, 4H), 3.76 (t, 4H), 3.55 (t, 4H), 3.46 (s, 8H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 130.63, 130.44, 129.60, 128.68, 126.80, 125.13, 124.11, 122.30, 43.63, 42.70, 42.35, 42.24; MS (FAB, NBA/DMSO) *m*/*z* (relative intensity) 571 (100.00, [M + H]$^+$ free base, $C_{38}H_{43}N_5$), 528 (17.84); high resolution FAB MS, *m*/*z* calcd for $C_{38}H_{43}N_5$ [M + H]$^+$ for free amine 570.3597, measured, 570.3602 ± 3σ.

***N*^{1},*N*^{3}-Dibenzyldiethylenetriamine3HCl (1):** yield 66%, no recrystallization necessary; mp dec 280+ °C; ^{1}H NMR (300 MHz, D_2O) δ 7.40 (s, 10H), 4.22 (s, 4H), 3.42 (s, 8H); ^{13}C NMR (300 MHz, D_2O) δ 130.05, 130.00, 129.88, 129.41, 51.69, 43.58, 42.57; MS (CI, methane) *m*/*z* (relative intensity) 284 (100.00, [M + H]$^+$ free base, $C_{18}H_{25}N_3$), 206 (10.92), 177 (49.87), 163 (30.78), 151 (37.64), 134 (31.67), 120 (17.28), 91 (46.88). Anal. Calcd for $C_{18}H_{25}N_3$·3HCl: C, 55.04; H, 7.19; N, 10.70; Cl, 27.08. Found: C, 54.83; H, 7.25; N, 10.54; Cl, 27.17.

***N*^{1},*N*^{4}-Dibenzyltriethylenetetramine·4HCl (2):** yield 43%, no recrystallization necessary; mp 221−258 °C dec; ^{1}H NMR (300 MHz, D_2O) δ 7.71 (s, 10H), 4.46 (s, 4H), 3.52−3.58 (m, 12H); ^{13}C NMR (300 MHz, D_2O) δ 131.69, 131.20, 131.13, 130.65, 52.42, 45.09, 44.58, 44.30; MS (CI, methane) *m*/*z* (relative intensity) 327 (100.00, [M + H]$^+$ free base, $C_{20}H_{30}N_4$), 249 (6.32), 237 (7.05), 206 (22.07), 177 (26.09), 151 (21.34). Anal. Calcd for $C_{20}H_{30}N_4$·4HCl: C, 50.86; H, 7.26; N, 11.86; Cl, 30.02. Found: C, 50.87; H, 7.34; N, 11.72; Cl, 29.74.

***N*^{1},*N*^{5}-Dibenzyltetraethylenepentamine·5HCl (3):** yield 31%, recrystallized from H_2O (84% recovery); mp 248−281 °C (dec); ^{1}H NMR (300 MHz, D_2O/DMSO-d_6, T = 80 °C) δ 7.37 (s, 10H), 4.14 (s, 4H), 3.31 (d, 16H); ^{13}C NMR (300 MHz, D_2O/DMSO-d_6, T = 80 °C) δ 131.31, 130.80, 130.74, 130.27, 52.25, 44.74, 44.48, 44.34, 43.72; MS (FAB, DEA/DMSO) *m*/*z* (relative intensity 371 (100.00, [M + H]$^+$ free base, $C_{22}H_{35}N_5$), 280 (3.38), 261 (3.34), 249 (4.19), 247 (7.38). Anal. Calcd for $C_{22}H_{35}N_5$·5HCl: C, 47.88; H, 7.31; N, 12.69; Cl, 32.12. Found: C, 47.95; H, 7.30; N, 12.58; Cl, 31.97.

***N*^{1},*N*^{3}-Bis(2-naphthylmethyl)diethylenetriamine·3HCl (4):** yield 56% no recrystallization necessary. Solid is not adequately soluble in standard NMR solvents. To obtain the free base, 60 mg of solid was partitioned between 10 mL of $CHCl_3$ and 10 mL of 3 M NaOH. The organic was dried over Na_2SO_4 and evaporated to a white solid residue: mp (salt) 230−280+ °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7−7.82 (m, 8H), 7.38−7.48 (m, 6H), 3.94 (s, 4H), 2.75 (octet, 8H), 1.72 (s, 3NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.14, 132.65, 131.86, 127.26, 126.90, 126.85, 125.80, 125.65, 125.19, 124.73, 53.25, 48.48, 48.04; MS (FAB, DEA/DMSO) *m*/*z* (relative intensity) 385 (100.00, [M + H]$^+$ free base, $C_{26}H_{29}N_3$), 249 (21.73), 247 (63.27), 207 (19.10); high resolution FAB MS, *m*/*z* calcd for $C_{26}H_{29}N_3$ [M + H]$^+$ for free amine 384.2440, measured 384.2443 ± 3σ.

***N*^{1},*N*^{4}-Bis(2-naphthylmethyl)triethylenetetramine·4HCl (5):** yield 52% no recrystallization necessary. Solid is not adequately soluble in standard NMR solvents. To obtain the free base, 600 mg of solid was partitioned between 50 mL pf $CHCl_3$ and 15 mL of 3 M NaOH. The organic was dried over Na_2SO_4 and evaporated to a pale yellow oily residue: mp (salt) 280+ °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.72 (m, 8H), 7.26−7.38 (m, 6H), 3.75 (s, 4H), 2.50−2.65 (m, 12H), 1.45 (s, 4NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.43, 132.71, 131.90, 127.21, 126.95, 126.91, 125.87, 125.58, 125.20, 124.72, 53.22, 48.65, 48.61, 48.18; MS (FAB, DEA/DMSO) *m*/*z* (relative intensity) 428 (100.00, [M + H]$^+$ free base, $C_{28}H_{34}N_4$), 396 (12.7), 404 (9.15), 390 (7.57), 388 (12.70), 360 (9.61), 312 (9.81). Anal. Calcd for $C_{28}H_{34}N_4$·3.9HCl·1H_2O: C, 57.31; H, 6.85; N, 9.55; Cl, 23.56. Found: C, 57.62; H, 6.59; N, 9.55; Cl, 23.53.

***N*^{1},*N*^{5}-Bis(2-naphthylmethyl)tetraethylenepentamine·5HCl (6):** yield 55%, recrystallized from H_2O (74% recovery). Solid is not adequately soluble in standard NMR solvents. To obtain the free base, 80 mg of solid was partitioned between 50 mL of $CHCl_3$ and 10 mL pf 3 M NaOH. The organic was dried over Na_2SO_4 and evaporated to a white solid residue: mp (salt) 242−253 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.82 (m, 8H), 7.38−7.48 (m, 6H), 3.90 (s, 4H), 2.72 (s, 8H), 2.68 (s, 8H), 1.92 (s, 5NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.85, 133.36, 132.53, 127.92, 127.57, 127.53, 126.50, 126.33, 125.88, 125.41, 53.92, 49.24, 49.20, 48.76, 48.72; MS (FAB, NBA/CH_2Cl_2) *m*/*z* (relative intensity) 470 (7.66), [M + H]$^+$ free base, $C_{30}H_{39}N_5$), 427 (28.14), 424 (19.14), 261 (100.00); high resolution FAB MS, *m*/*z* calcd for $C_{30}H_{40}N_5$ [M + H]$^+$ for free amine 470.3284, measured 470.3265 ± 3σ.

***N*^{1},*N*^{3}-Bis(9-anthrylmethyl)diethylenetriamine·3HCl (7):** yield 73% recrystallized from H_2O (71% recovery); mp 220+ °C (dec) ^{1}H NMR (300 MHz, DMSO-d_6, T = 80 °C) δ 8.78 (s, 2H), 8.58 (d, 4H), 8.16 (d, 4H), 7.62 (m, 8H), 5.30 (s, 4H), 3.74 (s, 4H), 3.48 (s, 4H); ^{13}C NMR (300 MHz, DMSO-d_6, T = 80 °C) δ 130.88, 130.69, 129.94, 129.04, 127.09, 125.54, 124.57, 122.85, 43.77, 42.95, 42.83; MS (FAB, NBA/DMSO) *m*/*z* (relative intensity) 485 (100.00, [M + H]$^+$ free base, $C_{34}H_{33}N_3$), 381 (2.62), 307 (4.84). Anal. Calcd for $C_{34}H_{33}N_3$·3HCl·1.5H_2O: C, 65.86; H, 6.34; N, 6.78. Found: C, 65.95; H, 6.32; N, 6.78.

***N*^{1},*N*^{4}-Bis(9-anthrylmethyl)triethylenetetramine·4HCl (8):** yield 69% recrystallized from H_2O/EtOH (80% recovery): mp 232−244 °C (dec) ^{1}H NMR (300 MHz, DMSO-d_6, T = 80 °C) δ 8.75 (s, 2H), 8.59 (d, 4H), 8.14 (d, 4H), 7.61 (m, 8H), 5.31 (s, 4H), 3.78 (t, 4H), 3.58 (t, 4H), 3.48 (s, 4H); ^{13}C NMR (300 MHz, DMSO-d_6, T = 80 °C) δ 130.61, 130.45, 129.58, 128.65, 126.77, 125.11, 124.17, 122.31, 43.61, 42.70, 42.62, 42.17; MS (FAB, NBA/DMSO) *m*/*z* (relative intensity) 528 (100.00, [M + H]$^+$ free base, $C_{36}H_{38}N_4$). Anal. Calcd for $C_{34}H_{33}N_3$·3.9HCl·2H_2O·2CH_3CH_2OH: C, 61.05; H, 6.77; N, 7.70; Cl, 18.99. Found: C, 60.76; H, 6.54; N, 7.77; Cl, 18.75.

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Supporting Information Available: Copies of ^{13}C NMR spectra for compounds **4**, **6**, and **9** for proof of purity where adequate elemental analyses were not available (3 pages). This material is contained in 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.

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