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Polycations. 19. The synthesis of symmetrical dicationic lipids with internal dimethylazonia functionalities separated by a spacer unit and pendant chains

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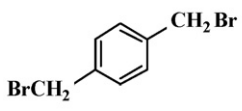
ABSTRACT

Herein is reported the preparation of several series of symmetrical polyammonium salts that serve as cationic lipids or precursors thereof, and are structurally based on several series of parent diamines where dimethylazonia functionalities are present, separated by a central structural unit, and pendant terminal chains. The resultant materials are of significant interest for a variety of purposes, such as serving as antihydrophobic species and as transfectins, the details of which are provided in separate reports. Attempts to effect selective alkylation to provide the corresponding unsymmetrical cationic lipids were without success, always leading to relatively useless mixtures of products.

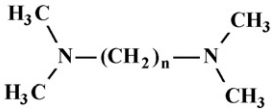
1. Introduction

In the course of our investigations of polyammonium salts for their application to a variety of purposes, we had cause to prepare several series of cationic lipids wherein the bulk of the molecule was arranged structurally in a flexible linear manner. Such polycationic species have been referred to as polycationic "strings." In a recent report (Engel et al., in press) we have discussed the syntheses of several series of such polycationic strings in which the cationic sites were located at the nitrogens of 1,4-diazabicyclo[2.2.2]octane (dabco) components incorporated along the string. In the current work we are reporting the syntheses of several series of similar polycationic lipids that are structurally based on: (a) several α,ω-bis(dimethylamino)alkanes (as shown below) with the nitrogen atoms again providing the cationic sites, and (b) α,ω-dihalo species which can be used in alkylation of *two* substituted dimethylaminoalkane units.

Although most of the new compounds synthesized and reported herein are prepared by alkylation of simple di-tertiary amines of the type α,ω-bis(dimethylamino) alkanes, this is not the situation in all instances. In certain instances other approaches toward the construction of such species have been used, for example, those syntheses wherein "end-components" bearing a tertiary amine have been used in displacement reaction upon a "central-component" bearing two reactive halogen sites. An example of this type of system is provided by using a dihalo reagent such as α,α′-dibromo-*p*-xylene (shown below as **A**) in reaction with two equivalent amounts of a terminal dimethylaminoalkane (shown below as **B**).



A



B

Dicationic lipids of this type (regardless of their route of synthesis) can provide salts bearing structural features of varying types rendering them useful for numerous applications. Included among these types are gemini lipids for which application has been found in the construction of artificial membranes (Iwamoto et al., 2000, 2004; Bhattacharya and Bajaj, 2007; Bajaj et al., 2008) and as transfectins (Camilleri et al., 2000; Martin et al., 2005). The polycationic lipids reported herein are based on relatively simpler structures (polycationic strings) and can be anticipated to exhibit properties varying as a function of terminal chain length, charge separation, and appended functional groups (hydroxyl groups) as noted.

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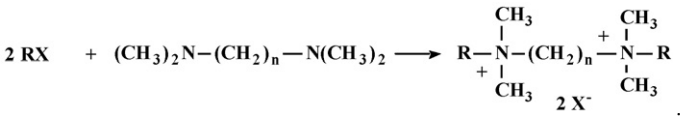
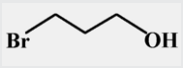
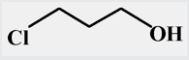
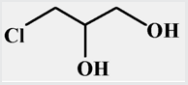
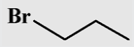
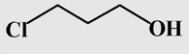
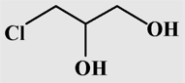
Table 1
Analytical and yield data for newly synthesized dicationic strings.



Cpd. no.	RX	*n*	Yield	^{1}H NMR (solvent) (δ)	^{13}C NMR (δ)	Analyses
1		2	82.5%	(D_2O) 1.88–1.91 (4H) *br*, 3.12 (12H) *s*, 3.30–3.50 (8H) *br*, 3.65 (4H) *t*	26.1, 53.3, 60.4, 62.6, 64.8	Calcd: $C_{12}H_{30}N_2O_2Br_2(H_2O)$; C: 34.96%; H: 7.82%; found: C: 34.71%; H: 7.87%
2		3	61.5%	(D_2O) 0.88 (6H) *t*, 1.70 (4H) *br*, 2.20 (2H) *br*, 3.03 (12H) *s*, 3.21–3.32 (8H) *br*	9.7, 15.7, 16.7, 50.6, 60.1, 66.2	Calcd: $C_{13}H_{32}N_2Br_2$; C: 41.50%; H: 8.57%; found: C: 41.31%; H: 8.66%
3		3	64.0%	(D_2O) 1.90–2.01 (4H) *br*, 2.22–3.20 (2H) *br*, 3.10 (12H) *s*, 3.33–3.55 (8H) *br*, 3.69 (4H) *t*	19.1, 27.4, 53.2, 60.4, 62.6, 64.8	Calcd: $C_{13}H_{32}N_2O_2Cl_2$; C: 48.90%; H: 10.10%; found: C: 48.99%; H: 10.39%
4		3	88.0%	(D_2O) 2.33 (2H) *br*, 3.17 (6H) *s*, 3.19 (6H) *s*, 3.44–3.54 (12H) *br*, 4.23 (2H) *m*	16.9, 51.9, 52.1, 61.2, 61.4, 63.6, 66.0, 66.2	Calcd: $C_{13}H_{32}N_2O_2Cl_2(H_2O)$; C: 48.59%; H: 10.66%; found: C: 48.31%; H: 10.84%
5	$Cl(CH_2)_6OH$	3	74.2%	(D_2O) 1.30–1.37 (8H) *br*, 1.45–1.62 (4H) *br*, 1.68–1.78 (4H) *br*, 2.20–2.28 (2H) *br*, 3.07 (12H) *s*, 3.25–3.34 (8H) *m*, 3.51 (4H) *t*	14.8, 20.0, 22.8, 23.3, 29.1, 48.8, 58.1, 59.7, 62.9,	Calcd: $C_{19}H_{44}N_2O_2Cl_2$; C: 56.56%; H: 10.99%; found: C: 56.81%; H: 10.70%
6	$CH_3(CH_2)_{11}Br$	3	74.3%	($CDCl_3$) 0.82 (6H) *t*, 1.12–1.35 (34H) *br*, 1.66 (4H) *br*, 1.87 (4H) *br*, 3.30 (12H) *s*, 3.46–3.52 (8H) *br*	14.1, 20.9, 22.6, 22.8, 26.2, 29.2, 29.26, 29.34, 29.4, 29.5, 31.8, 45.2, 51.4, 55.6, 64.1	Calcd: $C_{31}H_{68}N_2Br_2$; C: 59.22%; H: 10.90%; found: C: 59.13%; H: 10.98%
7		4	54.3%	(D_2O) 1.23–1.38 (4H) *m*, 1.40–1.55 (4H) *br*, 2.98 (12H) *s*, 3.17–3.32 (8H) *br*, 3.50 (4H) *t*	20.0, 22.6, 51.3, 62.3, 63.7, 65.0	Calcd: $C_{14}H_{34}N_2O_2Cl_2$; C: 50.44%; H: 10.28%; found: C: 50.80%; H: 10.21%
8	$Cl(CH_2)_6OH$	4	73.0%	(D_2O) 1.33–1.47 (8H) *br*, 1.48–1.49 (4H) *br*, 1.61–1.64 (8H) *br*, 3.16 (12H) *s*, 3.33 (8H) *m*, 3.69 (4H) *t*	18.8, 21.5, 24.2, 24.9, 30.6, 50.2, 61.2, 62.5, 63.9	Calcd: $C_{20}H_{46}N_2O_2Cl_2$; C: 57.54%; H: 11.11%; found: C: 57.27%; H: 11.40%
9	$Cl(CH_2)_{10}OH$	4	68.5%	(D_2O) 1.35–1.49 (20H) *br*, 1.51–1.52 (8H) *br*, 1.63–1.66 (8H) *br*, 3.19 (12H) *s*, 3.35 (8H) *m*, 3.71 (4H) *t*	18.2, 18.5, 18.8, 19.2, 19.7, 21.5, 24.3, 24.9, 30.7, 50.2, 61.2, 62.6, 63.9	Calcd: $C_{28}H_{62}N_2O_2Cl_2$; C: 63.49%; H: 11.80%; found: C: 63.41%; H: 11.91%
10	$CH_3(CH_2)_{16}Br$	4	88.5%	($CDCl_3$) 0.81 (6H) *t*, 1.11–1.31 (52H) *br*, 1.68 (4H) *br*, 2.09 (4H) *br*, 3.21 (12H) *s*, 3.35 (4H) *br*, 3.86 (4H) *br*	14.2, 19.9, 22.7, 22.9, 26.3, 27.3, 29.2, 29.3, 29.4, 29.49, 29.51, 29.63, 29.66, 29.68, 29.72, 31.9, 42.7, 50.9, 63.7	Calcd: $C_{40}H_{86}N_2Br_2$; C: 63.64%; H: 11.48%; found: C: 63.62%; H: 11.57%
11	CH_3I	6	91.5%	(D_2O) 1.34 (4H) *br*, 1.71 (4H) *br*, 3.01 (18H) *s*, 3.23 (4H) *br*	22.2, 25.0, 52.8, 66.4	Calcd: $C_{12}H_{30}N_2I_2$; C: 31.59%; H: 6.63%; found: C: 31.48%; H: 6.72%
12		6	87.0%	(D_2O) 0.86 (6H) *t*, 1.29 (4H) *br*, 1.78 (8H) *br*, 2.94 (12H) *s*, 3.16 (8H) *br*	14.7, 18.2, 20.9, 24.2, 49.6, 62.9, 64.5	Calcd: $C_{16}H_{38}N_2I_2$; C: 37.51%; H: 7.48%; found: C: 37.44%; H: 7.62%
13		6	77.6%	(D_2O) 1.23–1.38 (8H) *m*, 1.38–1.51 (4H) *m*, 2.90 (12H) *s*, 3.12–3.25 (8H) *m*, 3.45–3.58 (4H) *t*	24.1, 26.8, 27.5, 52.8, 63.4, 66.0, 66.2	Calcd: $C_{16}H_{38}N_2O_2Cl_2(H_2O)$; C: 50.65%; H: 10.63%; found: C: 50.88%; H: 10.59%
14		6	47.0%	(D_2O) 1.32 (4H) *br*, 1.69 (4H) *br*, 3.05 (6H) *s*, 3.06 (6H) *s*, 3.28–3.34 (8H) *m*, 3.46–3.48 (4H) *m*, 4.15 (2H) *m*	21.8, 25.0, 51.5, 51.7, 63.6, 65.3, 65.6, 66.1	Calcd: $C_{16}H_{38}N_2O_4Cl_2$; C: 48.85%; H: 9.74%; found: C: 48.48%; H: 9.54%
15	$CH_3(CH_2)_3Br$	6	72.0%	(D_2O) 0.83 (6H) *t*, 1.29 (8H) *br*, 1.61 (8H) *br*, 2.92 (12H) *s*, 3.17 (8H) *br*	12.8, 19.0, 21.8, 23.8, 25.1, 42.5, 50.4, 63.6	Calcd: $C_{18}H_{42}N_2Br_2$; C: 48.44%; H: 9.48%; found: C: 48.21%; H: 9.59%
16	$Cl(CH_2)_6OH$	6	60.1%	(D_2O) 1.28–1.32 (12H) *br*, 1.43–1.49 (4H) *br*, 1.66–1.67 (8H) *br*, 2.94 (12H) *s*, 3.16–3.20 (8H) *m*, 3.49 (4H) *t*	22.2, 24.7, 24.9, 25.5, 25.6, 31.3, 46.1, 62.1, 64.1, 64.3	Calcd: $C_{22}H_{50}N_2O_2Cl_2$; C: 59.31%; H: 11.31%; found: C: 59.38%; H: 11.41%
17	$C_6H_5CH_2Cl$	6	37.0%	(D_2O) 1.33 (4H) *br*, 1.80 (4H) *br*, 2.91 (12H) *s*, 3.19 (4H) *br*, 4.28 (4H) *br*, 7.57 (10H) *br*	22.0, 25.2, 42.9, 49.6, 67.8, 127.2, 129.1, 130.8, 132.8	Calcd: $C_{24}H_{38}N_2Cl_2$; C: 71.47%; H: 7.89%; found: C: 71.48%; H: 8.13%