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Polycations. 6. Polycationic Heterocyclic Salts: Their Synthesis and Effect on Double-Stranded DNA

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ABSTRACT: *A new series of compounds, intermediate-sized ring systems in which cationic sites have been incorporated into the primary ring system at heteroatoms, were synthesized by the reaction of α,ω-dihalides with either α,ω-ditertiary amines or an α,ω-ditertiary phosphine. Judicious choice of the reaction conditions allowed these polycationic heterocycles to be generated in excellent yields, whereas prior reported efforts with similar reagents under other reaction conditions have led to only polymeric materials. These heterocyclic polycations exhibit an interaction with double-stranded DNA resulting in a change in the conformation of the DNA as evidenced through the circular dichroism (CD) spectrum.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 559–565, 1999

INTRODUCTION

In recent years, significant interest has been expressed in the characteristics of polycationic organic species of defined structure (nonpolymeric) as applied to a variety of systems. Such application areas include the investigation of metal complexation processes [1–3], the specific binding of anionic species [4], self-assembling processes [5], and catalytic agents for biological systems [6,7]. Prior efforts of this laboratory have also noted applicability for such (unbranched) polycationic species as antihydrophobic agents [8] and as modifiers of the conformation of DNA [9]. In most instances of prior investigations, the cationic sites have been ammonium ion sites produced by reversible protonation of amine sites in a parent molecule. Our efforts have been directed toward the preparation and investigation of polycationic species of defined structure (nonpolymeric) in which quaternary ammonium (or phosphonium) sites bear the positive charge.

The present work is directed toward the preparation and investigation of a particular category of such polyquaternary ammonium salts, those in which the cationic sites are incorporated within a medium-sized ring system. The applications noted previously for polycationic species prepared in our laboratory are of particular interest for investigation with such cyclic species. We desired to determine if such cyclic polycationic species might be able to serve as modifiers of DNA conformations [9] and if any selectivity could be identified, and to serve as structurally specific antihydrophobic agents [8], assisting in the mobilization of particularly sized normally hydrophobic species into aqueous medium. In addition to the syntheses performed, results for the first of these applications are noted here.

As previously noted, earlier efforts of this labo-

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Dedicated to Professor Alfred Schmidpeter on the 70th anniversary of his birth.
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ratory [8, 9, 10–21] have been directed toward the synthesis of structurally defined open-chain, nonbranching (string), and branching (dendrimeric) polycations. We herein turn our attention to the construction of heterocyclic polycationic salts by the reaction of α,ω-dihalides with α,ω-ditertiary amines. Prior investigations of this type of coupling reaction by other laboratories have resulted in the preparation of ionene polymers, relatively high molecular weight materials with components of variable chain length bearing numerous cationic sites [22].

These earlier efforts concerned with the reaction of α,ω-dihalides with α,ω-ditertiary amines have been performed in polar solvents, such as dimethyl formamide, which not only dissolve the reagents, but also maintain the ionic organic products of reaction in solution. Using this type of reaction system, polymerization occurs, yielding variable length chains bearing quaternary ammonium ion sites at regular intervals along those chains. If a poorer ion-solvating medium were used, it would be anticipated that precipitation of the cationic organic product would occur relatively early in the reaction process.

This approach to the construction of a new category of intermediate-sized heterocycles bearing positive charges at the heteroatoms has been realized in the current effort. A series of intermediate-sized polycationic heterocyclics (compounds **16–32**, structures shown in Table 1) has been prepared in good yield in a facile manner. The particular interactive characteristics of these various polycationic heterocycles toward anionic and hydrophobic species are currently under investigation; one of these interactive characteristics is reported here, specifically, the interaction with double-stranded DNA.

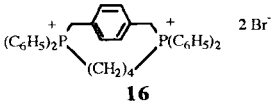
RESULTS AND DISCUSSION

Prior efforts of our laboratory concerned with the syntheses of several varieties of polycationic organic compounds have depended extensively on the use of acetonitrile as a solvent [10–21]. A polar solvent, which provides a moderate degree of solubilization of organic salts at elevated temperatures, acetonitrile at lower temperatures exhibits minimal solubility for ordinary quaternary ammonium salts, and precipitates them readily upon reaction of tertiary amines with haloalkanes. We herein report the synthesis of seventeen new polycationic heterocycles of intermediate ring size produced via cyclization reactions that depend on the use of acetonitrile in the manner stated.

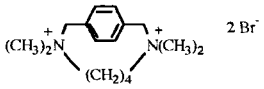
Specifically, α,ω-dinucleophiles, both ditertiary amines and diphosphines, in reaction with the α,ω-bishaloalkane α,α'-dibromo-*p*-xylene (**1**) in acetonitrile solution have been used to prepare a new series of intermediate-sized heterocyclic salts related to the intriguing paracyclophanes. In a similar manner, other polycationic heterocyclic salts have been synthesized starting with the α,ω-bishaloalkanes: 4,4′-bis(bromomethyl)biphenyl (**2**), *cis*-1,4-dichloro-2-butene (**3**), 1,6-dichlorohexane (**4**), 1,8-dibromoöctane (**5**) and 1,9-dibromononane (**6**). New polycationic heterocycles prepared here have been generated by reaction of these α,ω-bishaloalkanes with a series of α,ω-dinucleophiles, including the diphosphine species 1,4-bis(diphenylphosphino) butane (**7**), two commercially available α,ω-bis-(dimethylamino)alkanes, those being specifically 1,4-bis(dimethylamino)butane (**8**) and 1,6-bis(dimethylamino)hexane (**9**), and four diazobicyclo[2.2.2] octyl) octane derivatives previously reported from our laboratory, specifically the 1,6-bis(1-azonia-4-azobicyclo[2.2.2]octyl)hexane dichloride (**10**), the 1,8-bis-(1-azonia-4-azobicyclo[2.2.2]octyl)octane dichloride (**11**), the 1,9-bis-(1-azonia-4-azobicyclo[2.2.2]octyl)nonane dibromide (**12**), and finally, the 1,10-bis-(1-azonia-4-azobicyclo[2.2.2]octyl)decane dichloride (**13**). For all new salts prepared, appropriate ^{1}H, ^{13}C and (where relevant) ^{31}PNMR spectra have been obtained (all ammonium compound spectra were measured in D_2O; the phosphonium spectrum was measured in DMSO-d_6), as well as satisfactory quantitative elemental analyses.[23] In addition to the correspondence of these analytical data with that anticipated for the indicated structures, the signals that would result from unreacted starting materials, products of partial reaction, or polymeric products are specifically noted to be absent from the spectral observations. Data concerning the characterizations of these materials and other newly synthesized salts, along with yields of products, are summarized in Table 2. (The open-chain compound α,α'-bis(dimethyl-[3-hydroxypropyl]azonia)-*p*-xylene (**14**) has also been synthesized for evaluation of the diamagnetic anisotropic effect in compounds derived from **1**.)

For polycationic heterocyclic salts derived from **7**, **8**, and **9**, a nearly quantitative yield of the pure salt is obtained following the mixture of the reagents in acetonitrile solution. After stirring at room temperature for several hours, the resultant precipitate is recovered by filtration, washed with ethyl acetate followed by diethyl ether, and dried under high vacuum. These products exhibit ^{1}H and ^{13}C NMR spectra in perfect accord with the proposed structures. These salts are mildly hydroscopic and exhibit quantitative elemental analyses in accord with simple hydrated forms of the proposed structures. (All

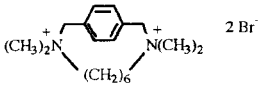
TABLE 1 Structures of Synthesized Polycationic Heterocyclics



16
(formed from **1** + **7**)



17
(formed from **1** + **8**)



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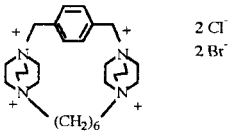
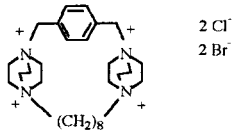
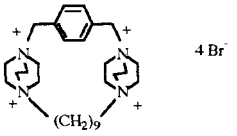


19
(formed from **1** + **10**)



20
(formed from **1** + **11**)



21
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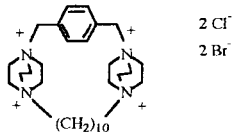
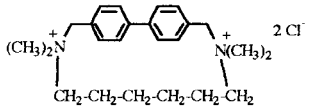
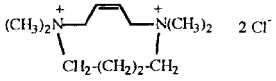


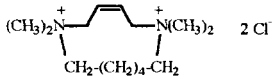
22
(formed from **1** + **13**)



23
(formed from **2** + **9**)



24
(formed from **3** + **8**)



25
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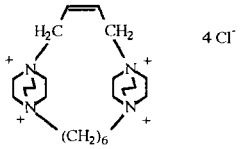
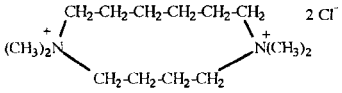


26
(formed from **3** + **10**)



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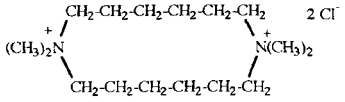
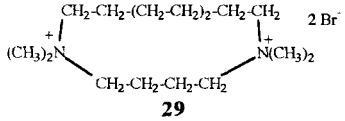
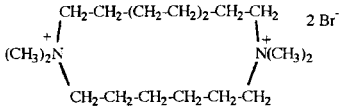
(formed from **4** + **8**)



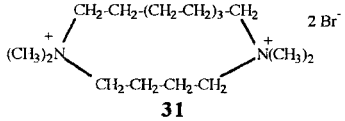
28
(formed from **4** + **9**)



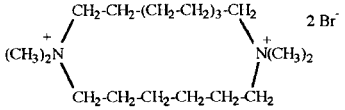
29
(formed from **5** + **8**)



30
(formed from **5** + **9**)



31
(formed from **6** + **8**)



32
(formed from **6** + **9**)

TABLE 2 Data for New Compounds

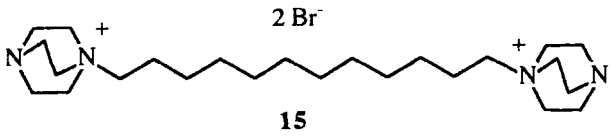
Cmpd.	*^{1}H NMR* (δ) $-$ *^{13}P NMR* (δ)	*^{13}C NMR* (δ)	Elemental Analyses	Yield
12	1.28, 10H, br; 1.69, 4H, br; 3.10–3.45, 28H, br	21.16, 25.54, 28.04, 28.17, 44.22, 52.08, 64.68	$C_{21}H_{42}Br_2 \cdot H_2O$ Calc. C, 50.41; H, 8.86 Found C, 50.29; H, 9.01	86.1%
14	2.02–2.19, 4H, br; 3.03, 12H, s; 3.32–3.41, 4H, m; 3.60–3.69, 4H, m; 4.49, 4H, s; 7.65, 4H, s	25.27, 50.06, 58.33, 62.16, 67.29, 128.93, 133.77	$C_{18}H_{34}N_2Br_2 \cdot 2H_2O$ Calc. C, 45.85; H, 7.69 Found C, 46.11; H, 8.02	95.7%
15	1.18–1.25, 16H, br; 1.65, 4H, br; 3.02–3.18, 16H, br; 3.24–3.32, 12H, br	21.46, 25.88, 28.47, 28.76, 28.88, 44.52, 52.37, 65.01	$C_{24}H_{48}N_4Br_2 \cdot H_2O$ Calc. C, 50.53; H, 8.83 Found C, 50.61; H, 8.58	91.3%
16	1.55, 4H, br; 3.04, 4H, br; 4.73, 4H, br; 6.80, 4H, br; 7.60–7.85, 20H, br $-$ ^{31}P 27.92δ	16.10, 20.38, 26.20, 115.87, 128.26, 129.04, 129.10, 131.59, 133.20	$C_{36}H_{36}P_2Br_2 \cdot 3.5\ H_2O$ Calc. C, 57.31; H, 5.74 Found C, 57.38; H, 5.89	86.2%
17	1.87–2.15, 4H, br; 3.02, 12H, s; 3.47–3.52, 4H, br; 4.53, 4H, s; 7.65, 4H, s	18.17, 48.38, 62.45, 66.14, 128.27, 133.43	$C_{16}H_{28}N_2Br_2 \cdot 3\ H_2O$ Calc. C, 41.57; H, 7.41 Found C, 41.65; H, 7.25	84.2%
18	1.40, 4H, br; 1.86, 4H, br; 2.96, 12H, s; 3.29, 4H, s; 4.26, 4H, s; 7.61, 4H, s	21.52, 24.72, 48.99, 64.26, 66.41, 129.11, 133.03	$C_{18}H_{32}N_2Br_2 \cdot 2\ H_2O$ Calc. C, 45.77; H, 7.68 Found C, 45.43; H, 7.95	92.1%
19	1.36, 4H, br; 1.76, 4H, br; 3.50, 4H, br; 3.75–4.15, 24H, br; 4.83, 4H, s; 7.69, 4H, s	22.71, 26.09, 52.27, 52.54, 66.34, 69.12, 129.59, 135.52	$C_{26}H_{44}N_4Br_2Cl_2 \cdot 7\ H_2O$ Calc. C, 40.58; H, 7.60 Found C, 40.25; H, 7.75	86.9%
20	1.28, 8H, br; 1.59–1.79, 4H, br; 3.40–3.53, 4H, m; 3.76–4.09, 24H, br; 4.82, 4H, s; 7.69, 4H, s	23.61, 27.22, 30.07, 53.09, 53.30, 67.50, 69.91, 130.41, 136.33	$C_{28}H_{48}N_4Br_2Cl_2 \cdot 3\ H_2O$ Calc. C, 46.36; H, 7.50 Found C, 46.07; H, 7.82	77.5%
21	1.27, 10H, br; 1.72, 4H, br; 3.35–3.52, 4H, br; 3.75–4.15, 24H, br, 4.82, 4H, s; 7.69, 4H, s	22.48, 26.04, 28.83, 29.08, 51.83, 52.01, 66.29, 68.61, 129.10, 135.05	$C_{29}H_{50}N_2Br_4 \cdot 3\ H_2O$ Calc. C, 42.05; H, 6.81 Found C, 41.87; H, 7.02	71.4%
22	1.11–1.36, 12H, br; 1.72, 4H, br; 3.47, 4H, br; 3.75–4.12, 24H, br; 4.82, 4H, s; 7.69, 4H, s	22.64, 26.39, 29.31, 29.52, 52.12, 52.29, 66.60, 68.94, 129.42, 135.34	$C_{30}H_{52}N_4Br_2Cl_2 \cdot 3\ H_2O$ Calc. C, 47.82; H, 7.76 Found C, 47.65; H, 7.83	85.0%
23	1.40, 4H, br; 1.86, 4H, br; 2.97, 12H, s; 4.46, 4H, s; 7.76, 4H, AA′BB′	22.24, 25.48, 49.72, 64.64, 67.56, 127.15, 127.86, 133.73, 141.85	$C_{24}H_{36}N_2Cl_2 \cdot H_2O$ Calc. C, 65.29; H, 8.68 Found C, 65.10; H, 8.53	87.6%
24	1.85, 4H, br; 3.03, 12H, s; 3.42, 4H, br; 4.12, 4H, d; 6.21–6.34, 2H, m	21.51, 52.89, 62.80, 65.75, 129.12	$C_{12}H_{26}N_2Cl_2 \cdot H_2O$ Calc. C, 50.17; H, 9.82 Found C, 50.22; H, 9.74	96.0%
25	1.36, 4H, br; 1.76, 4H, br; 3.02, 12H, s; 3.12–3.35, 4H, m; 4.07, 4H, d; 6.20–6.31, 2H, m	21.51, 24.70, 49.67, 59.77, 63.84, 126.33	$C_{14}H_{30}N_2Cl_2 \cdot 2\ H_2O$ Calc. C, 50.44; H, 10.28 Found C, 50.13; H, 10.46	97.2%
26	1.40, 4H, br; 1.80, 4H, br; 3.47, 4H, br; 3.84–4.10, 24H, br; 3.50, 4H, br; 6.39, 2H, br	22.57, 25.94, 52.22, 52.46, 61.64, 66.14, 127.75	$C_{22}H_{42}N_4Cl_4 \cdot 2\ H_2O$ Calc. C, 48.89; H, 8.58 Found C, 48.61; H, 8.72	96.1%
27	1.36, 4H, br; 1.72–1.80, 8H, br; 3.06, 12H, s; 3.23–3.31, 8H, br	19.64, 22.34, 25.65, 50.95, 63.66, 64.80	$C_{14}H_{32}N_2Cl_2 \cdot 2\ H_2O$ Calc. C, 50.14; H, 10.82 Found C, 49.89; H, 11.03	98.2%
28	1.34, 8H, br; 1.82, 8H, br; 2.96, 12H, s; 3.23, 8H, br	23.19, 26.53, 51.54, 65.37	$C_{16}H_{36}N_2Cl_2 \cdot 2\ H_2O$ Calc. C, 52.88; H, 11.09 Found C, 52.61; H, 11.23	94.2%
29	1.55, 8H, br; 1.62–1.85, 8H, br; 3.00, 12H, s; 3.16–3.38, 8H, br	19.13, 21.80, 25.25, 27.89, 50.38, 62.91, 64.35	$C_{16}H_{36}N_2Br_2 \cdot 3\ H_2O$ Calc. C, 40.86; H, 9.00 Found C, 40.51; H, 9.02	91.3%
30	1.24–1.44, 12H, br; 1.68, 8H, br; 2.96, 12H, s; 3.20, 8H, br	20.16, 20.19, 23.50, 23.71, 26.38, 48.58, 62.26, 62.57	$C_{18}H_{40}N_2Br_2 \cdot 3\ H_2O$ Calc. C, 43.38; H, 9.30 Found C, 43.24; H, 9.41	89.2%
31	1.30, 10H, br; 1.62–1.88, 8H, br; 3.01, 12H, s; 3.18–3.39, 8H, br	18.73, 21.42, 24.92, 27.55, 27.71, 49.99, 62.48, 63.96	$C_{17}H_{38}N_2Br_2 \cdot 2\ H_2O$ Calc. C, 43.78; H, 9.08 Found C, 43.62; H, 9.35	92.1%
32	1.21–1.40, 14H, br; 1.68, 8H, br; 2.96, 12H, s; 3.17–3.29, 8H, br	22.39, 22.43, 25.72, 26.03, 28.67, 28.84, 50.87, 64.44, 64.81	$C_{18}H_{34}N_2Br_2 \cdot 2\ H_2O$ Calc. C, 45.85; H, 7.69 Found C, 46.11; H, 8.02	88.6%

of the polycationic salts are somewhat hydroscopic. Exposure to air results in the immediate adsorption of various amounts of water.) In order to eliminate the possibility of the isolated salts resulting from the addition of more than one unit each of starting α,ω-bishaloalkane and α,ω-dinucleophiles (to generate a polycationic heterocycle some multiple of the size as noted here), the crossover reaction of a mixture of α,α'-dibromo-*p*-xylene (**1**) with an equimolar mixture of 1,4-bis(dimethylamino)butane (**8**) and 1,6-bis(dimethylamino)hexane (**9**) was performed in acetonitrile. By ^{13}C and ^{1}H NMR it was determined that the only products generated were those previously isolated from the reaction of **1** with **8** and of **1** with **9.**

For polycationic heterocyclic salts derived from **10, 11, 12,** and **13,** recovery of the pure product is complicated by the fact that the dinucleophile starting material is in itself dicationic and requires heating to be dissolved in the acetonitrile; a portion of it is recovered in the initial filtration of the product precipitate, as is readily noted from the ^{1}H and ^{13}C NMR spectra. Repeated washing of the recovered solid with hot acetonitrile, ethyl acetate, or ethanol is required for the isolation of the pure polycationic heterocyclic product. Final washing is performed using diethyl ether. Isolation of the purified cyclic product is determined by the absence of starting material (or polymer) signals in the ^{1}H and ^{13}C NMR spectra, and by elemental analyses.

The ^{1}H and ^{13}C NMR spectra of the polycationic heterocyclic products are rendered relatively simple and distinct from that of starting materials, partially reacted species, or polymeric species by the inherent symmetry of their structures. For example, the ^{13}C NMR spectrum of the polycationic heterocyclic product **18** exhibits a total of seven signals, assignable as shown in Figure 1a. This is a particularly interesting system with regard to NMR analysis; the ^{1}H chemical shifts for **18** are shown in Figure 1b. Molecular modeling (Chem 3D+) of **18** indicates that the hydrogen atoms attached to the central two carbon atoms between the ammonium sites are located between 470 and 570 pm directly above the aromatic ring, a position in which a diamagnetic anisotropic shift of their NMR signals should be observable. (For other species, e.g., **17,** the bridging hydrogens are closer to the aromatic ring, but lie more toward the side of the aromatic ring rather than directly above the aromatic ring, in a zero-effect region with regard to a diamagnetic anisotropic effect; with yet other salts the bridging hydrogens are significantly more distant from the aromatic ring, albeit above it.) In fact, an upfield shift of 0.21 δ is observed (Figure 1c) for the bridging β hydrogens of the cyclic system **18** as compared with the β hydrogens of an open-chain analog **14.**

Both upper and lower limits are observed with regard to ring size for the facile formation of the polycationic heterocyclic salts. Attempts to generate polycationic heterocyclic salts by the general approach of addition of the α,ω-dihalide to a solution of the α,ω-ditertiary amine in acetonitrile fail when α,α'-dibromo-*p*-xylene (**1**) is treated with 1,3-(dimethylamino)propane or with 1,12-bis(1-azonia-4-azobicyclo[2.2.2]octyl)dodecane dibromide (**15**). In these instances, the macrocycle, eleven-membered from 1,3-(dimephylamino) propane and twenty-six membered from **15**), forms only to a limited extent (less than 40%) with most of the starting reagents yielding ionene polymer, relative amounts being estimable from ^{1}H NMR spectra.



15

We have previously demonstrated, through measurement of changes in the circular dichroism (CD) spectra, that polycationic strings can interact with double-stranded DNA to produce changes in the conformation and aggregation of the DNA [24]. Whereas polycationic strings might be capable of interacting with double-stranded DNA by associating helically with the phosphate-anion rich major groove of the DNA over an extensive distance along the helix, an individual unit of the currently synthesized polycationic heterocycles is anticipated to be capable of interaction only at a single, relatively short region of the helix.

In spite of this, a very significant change is observed in the CD spectra of double-stranded DNA when challenged with the polycationic heterocycles. As shown in Figure 2, the addition of **19** (7.6×10^{-5} M) to a solution of poly(dGdC)-poly(dGdC) (8.2×10^{-5} M in nucleotide phosphate) produces a very notable change in the nature of the DNA CD spectrum. The less conservative CD spectrum, curve *A* in Figure 2, which is typical of poly(dGdC)-poly(dGdC) solutions, is changed to a more conservative CD spectrum, curve *B* in Figure 2, upon addition of **19.** That is, for curve *B* the maximum and minimum at longer and shorter wavelength about 260 nm are of approximately the same magnitude. The half-saturation point for this change occurs with an addition of **19** to an extent of 3.3×10^{-5} M, at which concentration cationic sites of the polycationic heterocycle and

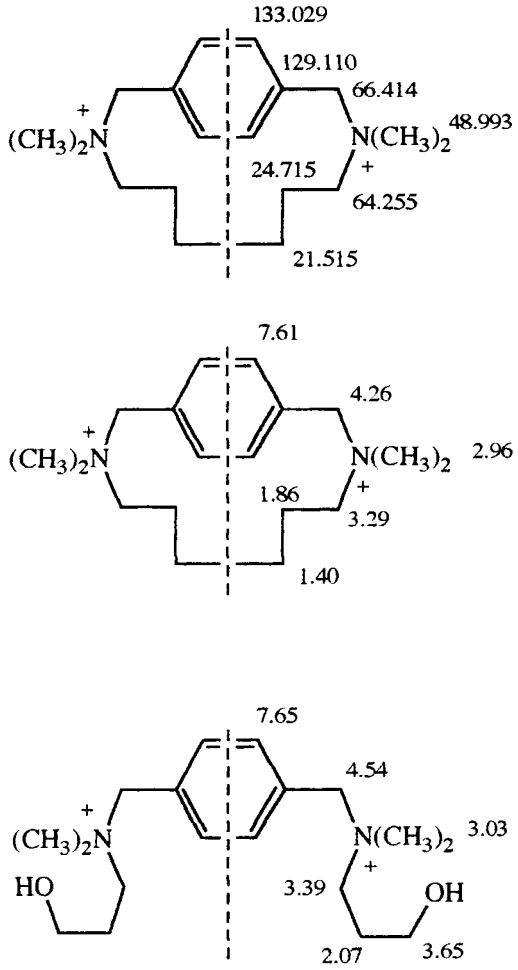


FIGURE 1 (a) ^{13}C chemical shifts of **18.** (b) ^{1}H chemical shifts of **18.** (c) ^{1}H chemical shifts of **14.**

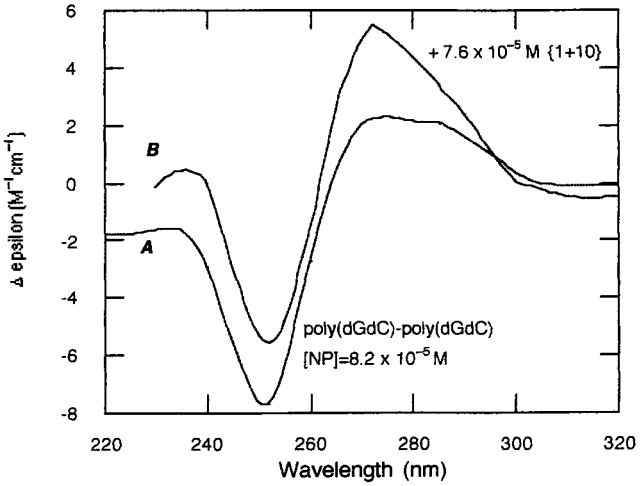


FIGURE 2 Effect of **19** on the CD of poly(dGdC)-poly(dGdC).

base pairs of the DNA are in a ratio slightly less than 1.

The conservative aspect of the CD spectra of polynucleotide duplexes has been shown to be related to the relative displacement of the twist axis joining the paired bases from the dyad (or twofold) axis of the helix [24]. The polycationic heterocycles such as **19** clearly have a strong influence on the duplex structure of DNA as evidenced by these results.

EXPERIMENTAL

General

All chemicals used in syntheses, purification, and comparison analyses were of commercial reagent quality and were used without purification. Three of the α,ω-ditertiaryamine compounds, specifically, 1,6-bis(1-azonia-4-azobicyclo[2.2.2]octyl)hexane dichloride (**10**), 1,8-bis(1-azonia-4-azobicyclo[2.2.2]-octyl)octane dichloride (**11**), and 1,10-bis(1-azonia-4-azobicyclo[2.2.2]octyl)decane dichloride (**13**) were prepared as previously reported [14]. All NMR spectra were measured using a Brüker 400 MHz DPX400 instrument. Elemental analyses (Table 1) were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Preparation of 1,9-Bis(1-azonia-4-azobicyclo[2.2.2]octyl)nonane Dibromide (**12**).

To a solution of 1,4-diazabicyclo[2.2.2]octane (15.7 g, 0.14 mol) in acetonitrile (50 mL) in a 250 mL round-bottom flask fitted with a magnetic stirrer and dropping funnel was added dropwise a solution of 1,9-dibromononane (5.0 g, 0.017 mol) in acetonitrile (50 mL). The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was evaporated under reduced pressure, and the solid residue was washed with portions of ethyl acetate followed by portions of diethyl ether and dried under high vacuum to give the pure **12.**

Preparation of 1,12-Bis(1-azonia-4-azobicyclo [2.2.2]octyl)dodecane Dibromide (**15**).

To a solution of 1,4-diazabicyclo[2.2.2]octane (10.94 g, 0.098 mol) in a mixture of acetonitrile (50 mL) and methanol (75 mL) in a 250 mL round-bottom flask fitted with a magnetic stirrer and dropping funnel was added dropwise a solution of 1,12-dibromododecane (4.0 g, 0.012 mol) in acetonitrile (50 mL). The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was evaporated under reduced pressure, and the solid residue was washed with portions of ethyl acetate followed by

portions of diethyl ether and dried under high vacuum to give the pure **15.**

*Preparation of α,α′-Bis(dimethyl-3-hydroxypropylazonia)-p-xylene Dibromide (***14***).*

To a solution of **1** (3.0 g, 0.014 mol) in acetonitrile (75 mL) in a 250 mL round-bottom flask fitted with a magnetic stirrer, heating bath, and reflux condenser was added 3-dimethylamino-1-propanol (2.35 g, 0.023 mol). The reaction mixture was heated at reflux with stirring for 2 days. After this time, the solution was cooled, and the white solid precipitate was collected by suction filtration, washed with portions of acetonitrile and diethyl ether, and dried under high vacuum to give the pure **14.**

General Procedure for Preparation of Polycationic Heterocyclic Salts.

To a solution of the α,ω-dihalide (~0.004 mol) in acetonitrile (75 mL) in a 250 mL round-bottom flask fitted with a magnetic stirrer, heating bath, reflux condenser, and dropping funnel was added dropwise the α,ω-ditertiary amine (~0.004 mol) with stirring. The reaction mixture was then heated to reflux for seven days. After cooling, the resultant precipitate was collected by suction filtration, washed with portions of diethyl ether, and dried under high vacuum. For reactions wherein the α,ω-ditertiary amine was an organic salt (compounds **10, 11, 12** and **13**), repeated washings with hot acetonitrile were performed until complete removal of unreacted α,ω-ditertiary amine was obtained (as observed by NMR spectrometry), giving the pure target salts.

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