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Polycations. 17. Synthesis and properties of polycationic derivatives of carbohydrates

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ABSTRACT

In our continuing investigation of polycationic salts for purposes of antimicrobial action, ion-channel blocking, and construction of ionic liquids, we have prepared several series of polycationic salts derived from carbohydrate precursors. These salts are currently being investigated for optimal efficacy as antibacterials and antifungals, as well as for other applications. The syntheses of such series of salts are described here along with preliminary antibacterial testing results and a discussion of their properties indicating their potential utility for several purposes.

1. Introduction

Significant recent efforts of our laboratories have been directed toward the development of antimicrobial surfaces that would act against bacteria and fungi by a disruption of the cell wall.[1–6] Critical differences between the action of such surfaces and the antibacterial action commonly associated with antibiotics include the following: (a) The mode of action is via an electrostatic disruption of the existing cell wall subsequent to invasion by a lipophilic chain of specific length rather than interruption of some metabolic process; (b) the antimicrobial activity is continual with regard to the agent since it is not consumed in the process of invasion and disruption of the cell wall; and (c) it is unlikely that microorganisms could become resistant to this type of attack as it would involve a major modification of their cell-wall structure.

The mode of action of these antimicrobial surfaces depends on a microbial species impinging on a surface bearing numerous cationic lipid sites in relatively close proximity, such that the cell wall is pierced at several sites. This has been demonstrated to be particularly feasible for surfaces consisting of polymers of carbohydrate units wherein each unit bears a primary hydroxyl site that is readily functionalized. Thus, cellulosic species such as cotton fabric, paper, and wood are easily rendered antibacterial by the attachment of cationic lipid units through the numerous available 6-position hydroxyl groups that occur at regular and close intervals throughout the macrosurface.

The challenge for a non-surface activity of this type is to generate molecules that would bear several cationic lipid components in close proximity within the structure of the molecule, sufficient to cause such an effect on an impinging microbe. To this end, we have synthesized several series of polycationic derivatives of simple carbohydrates for investigation of their activity as antimicrobial agents. Preliminary results of our laboratories indicate this to be a successful strategy (see below). Our major current concern is with the syntheses of these agents, although preliminary biological results are presented herein.

With macrosurfaces, particular antibacterial and antifungal activities have been noted for the incorporation of lipid chains of 12 and 16 carbons directly attached to a nitrogen of a diazabicyclo[2.2.2]octane (DABCO) unit. While the 16-carbon chain species exhibits activity against the full range of Gram-positive bacteria and numerous fungi, certain Gram-negative species require a different chain length. Thus, while these chain lengths were most efficacious with macrosurface incorporation, a wider range of chain lengths and different quaternizing sites have been synthesized

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for investigation with the microsurface (molecular) species proposed as agents.

There exists a significant body of literature concerning the use of polycationic species in solution as antibacterial agents. This literature has been concerned primarily with polycationic species associated with amino acids and peptidic structures. For example, a series of structurally diverse cationic peptides have been noted to exhibit an antibacterial action on *Staphylococcus aureus* involving attack on the cytoplasmic membrane.[8] Further, introduction of a fatty acyl chain into the structure of a biologically inactive peptide provided the species with antibacterial (as well as with antifungal) activity.[9] Yet again, antibacterial activity toward a broad range of Gram-positive and Gram-negative bacteria has been noted for low-molecular-weight hydrogels generated using amino acid-based cationic amphiphiles.[10] For the present, we would also note that the effect of chain length and amino acid content of cationic peptides has been investigated with regard to their antibacterial activity.[11]

The design of polycationic carbohydrate species for these purposes appears to us to be a correspondingly suitable approach for the development of potential antibacterial pharmaceutical agents. Such species, derived from biological materials, provide important capabilities for selective binding at associated sites, thereby enhancing the capability of such species to serve their intended purposes. Further, they need to be subject to normal biological degradation processes that would lead to their removal from the organism once the antibacterial task is completed. This is a critical aspect for an antibacterial pharmaceutical agent; without such a characteristic allowing removal from the organism, continued activity would be present removing all microorganisms from it to its detriment. Further, proper design of the carbohydrate-derived scaffolding can allow a significantly greater charge density species to impinge upon the bacterial cell wall, a factor that has been noted not only in our earlier work,[1] but also in studies with other surfaces modified with polycationic species.[12]

In addition, efforts of collaborating laboratories[7] have indicated utility of related polycationic species as potential pharmaceutical agents acting as critical ion-channel regulators. Finally, in another area of potential application for these materials, the results of our efforts in the preparation of unique ionic liquids (liquid ionic phosphates, among others) suggest that carbohydrate-related cationic components of such materials can provide highly selective species that can fulfill the promise of ionic liquids to serve as 'designer solvents'. To these ends, we report the syntheses and properties of several series of polycationic carbohydrate derivatives.

2. Results and discussion

2.1. General

Several series of carbohydrates have been modified by the attachment of cationic lipid sites to the fundamental framework. Most notably these include methyl α-D-glucopyranoside, and the reduced carbohydrate species D-mannitol.

2.2. Methyl α-D-glucopyranoside

The glycoside is readily activated at the 6-position primary hydroxyl group for nucleophilic substitution by reaction with *p*-toluenesulfonyl chloride in pyridine or in aqueous sodium bicarbonate solution. This action functionalizes only the 6-position hydroxyl group leaving the remaining sites for other reactions. Isolation of the tosylate ester by evaporation of the pyridine or aqueous solution under reduced pressure at low temperature is easily accomplished. Use of the tosylate in acetonitrile solution with an equivalent of the appropriate tertiary amine provides a quaternary ammonium salt derivative of the parent carbohydrate.

In addition to a series of 1-alkyl-1-azonia-4-azabicyclo[2.2.2]octane salts prepared by previously reported methods in our laboratories,[6,13–16] several other tertiary amine species have been used for the construction of novel derived quaternary ammonium ion species. These mono-tertiary amines along with the resultant derived methyl α-D-glycopyranoside species are shown in Table 1.

2.3. Alditols

Alditols, bearing two primary hydroxyl groups per molecule, in addition to the several secondary alcohol sites, are readily tosylated selectively at the two primary hydroxyl sites. Thereby, introduction of two cationic units per scaffold molecule is readily accomplished. While mannitol has been the alditol of use in most of the new species synthesized, an important derivative of glycerol has also been constructed in which a single secondary hydroxyl site remains after introduction of the cationic units. The newly constructed molecules and their tertiary amine precursors are shown in Table 2.

2.4. Physical properties

The polycationic carbohydrate derivatives are generally hygroscopic, rendering the measurement of their melting points often difficult and causing them often to analyze as hydrates of the parent species. As anticipated, as the size of the cation increases, the melting point also increases. The mannitol derivatives **22**–**25** were found to be insoluble in acetone, dichloromethane, ether, ethyl acetate, hexanes, acetonitrile, and toluene. Further, the mannitol derivatives **23**–**25** gelate water. Compound **25** forms a clear gel in water with a w/v of 5.3%. This surfactant also forms a clear gel with ethanol (w/v 6.7%). Both gels were stable for up to two weeks. The surfactant **24** forms an opaque white gel with water at a w/v of 10%. This gel was found to be stable for at least 22 months. Surfactant **23** formed an unstable gel with water (w/v 30%), but a very stable gel with ethanol (w/v 3.3%). These gels are of particular interest in applications for antibacterial medical adjuncts. As anticipated, the surfactants **9**–**12** derived from methyl α-D-glucopyranoside exhibit lower melting points than do their mannitol counterparts. The melting points of the lower molecular weight salts exhibit some variability when compared to those of their mannitol counterparts. For example, **7** has a melting point range of 133–135 °C, which is quite similar to that of the mannitol derivative **21** (132–136 °C), and the methyl α-D-glucopyranoside derivative **6** has a large melting point range (60–69 °C) that is higher than that of its mannitol-derived counterpart **18** (56–66 °C). Similarly, the melting point range for **2** (127–131 °C) is higher than that for the related mannitol derivative **20** (108–112 °C). For the methyl α-D-glucopyranoside derivatives, **9**–**12** were insoluble in the common organic solvents diethyl ether, ethyl acetate, dichloromethane, hexane, acetonitrile, and toluene. Only **12** has been found to gelate water (with a w/v of 5%) and ethanol (with a w/v of 6.7%). Gelation results are summarized in Table 6.

2.5. Synthesis

The syntheses of new polycationic salts from the alditols are accomplished in a manner similar to that used for the derivatives of methyl-α-D-glucopyranoside. That is, the parent alditol was treated with 2 equivalents of *p*-toluenesulfonyl chloride and 2 equivalents of sodium bicarbonate in water. After partial evaporation of the water at reduced pressure without heating, 2 equiv of the appropriate tertiary amine were added, and the product was

Table 1
Derivatives of methyl α-D-glucopyranoside and the tertiary amines used in their construction

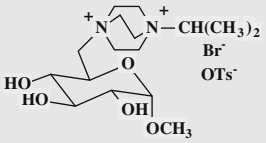
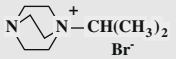
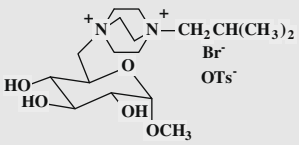
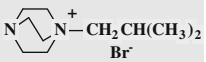
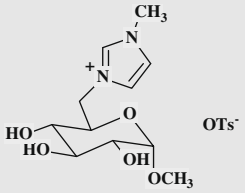
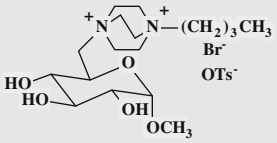
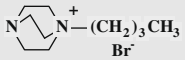
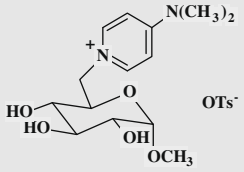
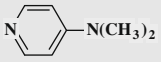
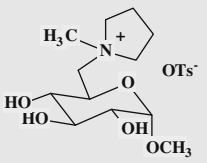
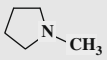
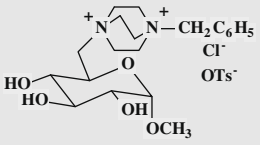
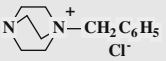
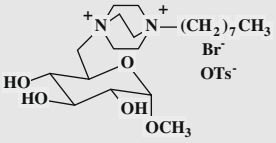
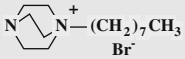
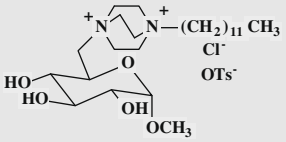
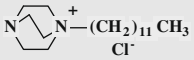
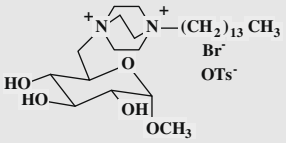
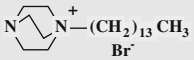
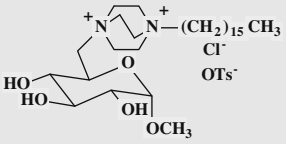
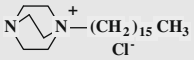
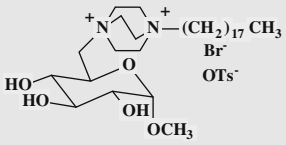
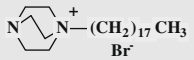
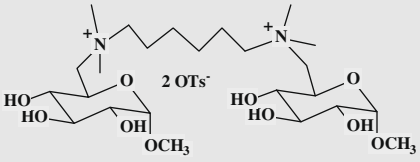
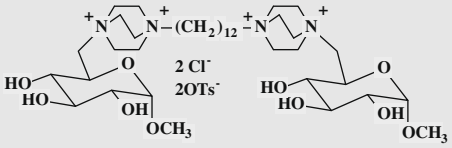
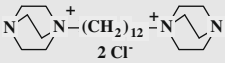
Product number	Product structure	Parent tertiary amine
1		
2		
3		
4		
5		
6		
7		
8		

Table 1 (*continued*)

Product number	Product structure	Parent tertiary amine
9		
10		
11		
12		
13		$(CH_3)_2N(CH_2)_6N(CH_3)_2$
14		

isolated by evaporation of the solvent under reduced pressure. For all new materials ^{1}H and ^{13}C NMR spectra were measured along with quantitative elemental analyses and they were found to be in accord with the proposed structures. These results are given in Table 3 for the methyl α-D-glucopyranoside derivatives. Corresponding data for the alditol derivatives synthesized herein are presented in Table 4. In addition, melting points and specific rotation data have been obtained for most of the materials, and these data are presented in Table 5 along with yields for their syntheses.

2.6. Gels

The gels prepared with these polycationic carbohydrate surfactants are anticipated to exhibit antimicrobial properties. Other carbohydrate-based cationic surfactants have been synthesized with the goal of developing new antimicrobial agents for topical disinfection.[17] Our new materials were found to exhibit such antimicrobial properties against a range of Gram-positive and Gram-negative bacteria and one fungal species. Results for the Gram-positive bacterium, *S. aureus* are summarized in Table 6. While antimicrobial activity was investigated against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Aspergillus niger*, more detailed studies were directed toward *S. aureus*. The gels were tested by adding 25 μL each of the gel and 5×10^4 *S. aureus* to Luria–Bertani broth. The samples were incubated overnight, and the change in turbidity of the medium was noted as a measure of the bacterial growth. Each incubation experiment was performed with an accompanying control run (no gel added) to determine the extent of growth inhibition. These results are presented in Table 7. In all instances, the growth of bacteria in the presence of the gel was less than 2% of the growth in the absence of gel. The system has not been optimized for activity, either with regard to amount of gel or time of incubation.

2.7. Antibacterial activity

The antibacterial activity of a selection of the polycationic carbohydrate-derived salts has been investigated with regard to *S.*

Table 2
Derivatives of alditols and the tertiary amines used in their construction

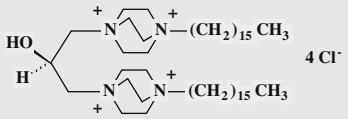
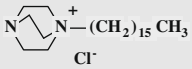
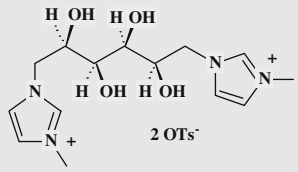
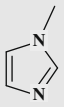
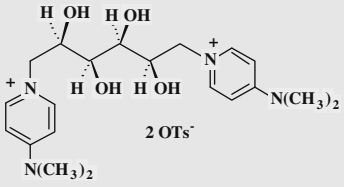
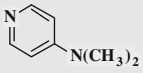
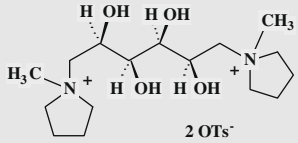
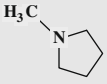
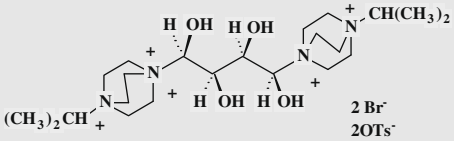
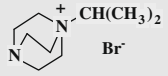
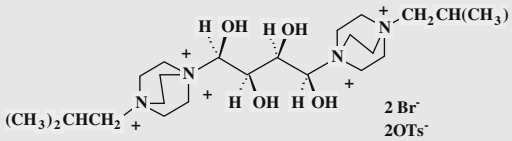
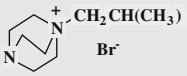
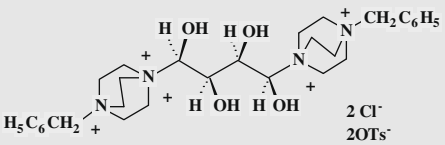
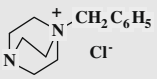
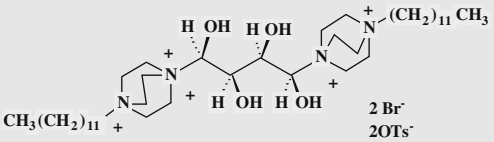
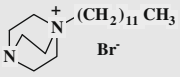
Product number	Product structure	Parent tertiary amine
15		
16		
17		
18		
19		
20		
21		
22		

Table 2 (*continued*)

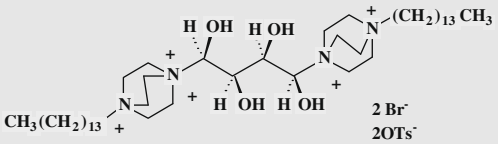
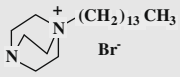
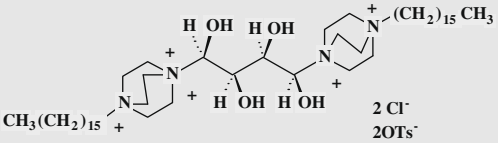
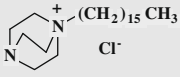
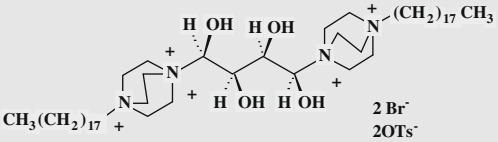
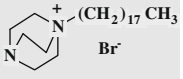
Product number	Product structure	Parent tertiary amine
23		
24		
25		

Table 3
Newly synthesized cationic derivatives of methyl α-D-glucopyranoside

Product number	^{1}H NMR (solvent) (δ)	^{13}C NMR (δ)	Analysis
1	(D_2O) 1.36 (6H) d, 2.31 (3H) s, 3.33 (3H) s, 3.28–3.80 (20H) br, 7.28–7.62 (4H) *AA′BB′*	15.5, 20.5, 44.0, 47.8, 55.1, 60.6, 68.3, 69.6, 71.2, 71.6, 73.1, 99.3, 125.4, 129.5, 139.5, 142.5	Calcd for $C_{23}H_{39}BrN_2O_8S{\cdot}8.5H_2O$: C, 37.50; H, 7.66. Found: C, 37.53; H, 7.37
2	(D_2O) 1.01 (6H) d, 2.21 (1H) br, 2.30 (3H) s, 3.35 (3H) s, 3.33–3.87 (21H) m, 7.27–7.60 (4H) *AA′BB′*	20.6, 21.9, 22.9, 44.0, 51.2, 55.1, 60.6, 69.6, 71.3, 71.6, 73.1, 74.2, 99.3, 125.4, 129.6, 139.6, 142.5	Calcd for $C_{24}H_{41}BrN_2O_8S{\cdot}9H_2O$: C, 37.94; H, 7.83. Found: C, 38.12; H, 7.79.
3	(D_2O) 2.27 (3H) s, 3.32 (3H) s, 3.78 (3H) s, 3.27–3.78 (7H) m, 7.22–7.55 (4H) *AA′BB′*, 7.55 (2H) br, 8.44 (1H) s	20.5, 35.2, 55.0, 60.6, 69.6, 71.2, 71.6, 73.1, 99.3, 119.9, 122.8, 125.3, 129.4, 135.1, 139.5, 142.4	Calcd for $C_{18}H_{26}N_2O_8S{\cdot}3.5H_2O$: C, 43.80; H, 6.74. Found: C, 43.59; H, 6.51
4	(D_2O) 0.83 (3H) t, 1.28 (2H) m, 1.64 (2H) m, 2.29 (3H) s, 3.29–3.50 (5H) br, 3.69–3.80 (16H) br, 3.81 (3H) br, 7.26–7.58 (4H) *AA′BB′*	12.7, 18.9, 20.5, 43.9, 46.2, 50.7, 55.0, 60.5, 65.1, 69.5, 71.2, 71.5, 73.0, 99.2, 125.3, 129.5, 139.4, 142.5	Calcd for $C_{24}H_{41}BrN_2O_8S{\cdot}5H_2O$: C, 41.92; H, 7.48. Found: C, 41.65; H, 7.76
5	(D_2O) 2.26 (3H) s, 3.03 (6H) s, 3.30 (3H) s, 3.26–3.77 (7H) m, 6.67 (2H) d, 7.21 (2H) d, 7.54–7.85 (4H) *AA′BB′*	20.4, 39.1, 54.9, 60.5, 69.5, 71.2, 71.5, 73.0, 99.2, 106.7, 125.3, 129.4, 139.2, 142.4, 157.1	Calcd for $C_{21}H_{30}N_2O_8S{\cdot}2.5H_2O$: C, 48.92; H, 6.84. Found: C, 48.83; H, 6.48.
6	(D_2O) 1.09–2.08 (4H) br, 2.34 (3H) s, 2.84 (3H) s, 2.97 (2H) m, 3.30–3.37 (5H) br, 3.45–3.92 (7H) br, 7.32–7.64 (4H) *AA′BB′*	20.5, 22.8, 40.6, 55.0, 55.8, 60.6, 69.6, 71.2, 71.6, 73.1, 99.3, 125.4, 129.5, 139.5, 142.5	Calcd for $C_{19}H_{31}NO_8S{\cdot}7H_2O$: C, 39.78; H, 7.90. Found: C, 40.01; H, 8.27
7	(D_2O) 2.34 (3H) s, 3.36 (3H) s, 3.32–3.84 (19H) br, 4.66 (2H) br, 7.32–7.64 (9H) br	20.5, 44.1, 50.6, 55.0, 60.6, 69.0, 69.6, 71.3, 71.6, 73.1, 99.3, 125.4, 126.3. 129.5, 129.6, 131.4, 133.0, 139.5, 145.5	Calcd for $C_{27}H_{39}ClN_2O_8S{\cdot}4H_2O$: C, 50.54; H, 6.99. Found: C, 50.51; H, 7.00
8	(D_2O) 0.76 (3H) t, 1.17–1.24 (10H) br, 1.69 (2H) br, 2.29 (3H) s, 3.36 (3H) s, 3.30–3.78 (21H) br, 7.26–7.58 (4H) *AA′BB′*	13.3, 20.4, 21.3, 21.9, 25.2, 28.0, 28.1, 30.9, 43.9, 50.7, 55.0, 60.5, 65.3, 71.2, 71.5, 73.0, 99.2, 125.3, 129.4, 139.4, 142.5	Calcd for $C_{28}H_{49}BrN_2O_8S{\cdot}2H_2O$: C, 48.76; H, 7.74. Found: C, 48.77; H, 7.80
9	(D_2O) 0.84 (3H) t, 0.86–1.01 (18H) br, 1.24 (2H) br, 2.19 (3H) s, 3.32 (3H) br, 3.43–3.76 (21H) br, 7.08–7.57 (4H) *AA′BB′*	13.7, 20.8, 21.2, 22.5, 23.8, 28.2, 29.3, 29.4, 29.6, 29.7, 30.2, 31.8, 43.9, 46.9, 50.9, 55.0, 60.5, 69.5, 71.2, 71.5, 73.0, 99.2, 125.6, 129.1, 139.8, 141.2	Calcd for $C_{32}H_{57}BrN_2O_8S{\cdot}2H_2O$: C, 51.53; H, 8.24. Found: C, 51.46; H, 8.31
10	(D_2O) 0.84 (3H) t, 0.86–1.01 (22H) br, 1.24 (2H) br, 2.19 (3H) s, 3.32 (3H) s, 3.43–3.76 (21H) br, 7.04–7.58 (4H) *AA′BB′*	13.9, 21.0, 21.7, 21.9, 22.8, 26.0, 26.3, 29.1, 29.7, 29.8, 30.0, 30.1, 32.2, 44.1, 46.4, 50.8, 55.1, 60.6, 64.7, 69.6, 71.3, 71.6, 73.2, 99.3, 125.8, 129.1, 139.8, 142.1	Calcd for $C_{34}H_{61}BrN_2O_8S{\cdot}2H_2O$: C, 52.77; H, 8.47. Found: C, 52.83; H, 8.52
11	(D_2O) 0.81 (3H) t, 1.19 (26H) br, 1.69 (2H) br, 2.15 (3H) s, 3.32 (3H) s, 3.44–3.87 (21H) br, 6.94–7.55 (4H) *AA′BB′*	14.1, 21.2, 22.7, 26.1, 26.9, 28.9, 29.4, 29.5, 29.66, 29.68, 29.73, 29.8, 29.9, 32.7, 44.2, 45.2, 50.6, 55.3, 60.8, 69.7, 71.6, 71.7, 73.4, 99.3, 125.8, 129.1, 140.1, 141.9	Calcd for $C_{36}H_{65}ClN_2O_8S{\cdot}5H_2O$: C, 46/56; H, 9.55. Found: C, 46.53; H, 9.18
12	(D_2O) 0.86 (3H) t, 1.24 (30H) br, 1.69 (2H) br, 2.29 (3H) s, 3.04 (2H) br, 3.31 (3H) s, 3.19–3.85 (19H) br, 7.11–7.47 (4H) *AA′BB′*	13.9, 21.2, 22.0, 22.8, 24.3, 26.2, 26.9, 28.9, 29.44, 29.47, 29.50, 29.6, 29.67, 29.70, 29.75, 29.8 29.9, 32.7, 44.6, 45.7, 50.9, 55.4, 61.0, 69.9, 71.6, 71.8, 73.7, 99.6, 125.4, 128.0, 141.0, 142.1	Calcd for $C_{38}H_{69}BrN_2O_8S{\cdot}5H_2O$: C, 51.63; H, 9.01. Found: C, 5155; H, 9.23
13	(D_2O) 1.22 (4H) br, 1.55 (4H) br, 2.88 (12H) s, 2.93 (8H) br, 3.25 (6H) s, 3.42–3.76 (16H) br, 7.20–7.60 (8H) *AA′BB′*	20.5, 23.7, 25.0, 42.5, 55.0, 57.5, 60.5, 69.5, 71.2, 71.5, 73.0, 99.2, 125.3, 129.4, 139.4, 142.4	Calcd for $C_{38}H_{64}O_{16}N_2S_2{\cdot}2H_2O$: C, 50.43; H, 7.57. Found: C, 50.21; H, 7.83
14	(D_2O) 1.12–1.43 (16H) br, 1.64 (4H) br, 2.26 (6H) s, 3.25 (6H) s, 3.29–3.76 (42H) br, 7.23–7.58 (8H) *AA′BB′*	20.5, 21.4, 25.3, 28.1, 28.5, 30.2, 43.9, 50.6, 55.0, 60.5, 65.3, 69.5, 71.2, 73.0, 99.2, 125.3, 129.5, 139.5, 142.4	Calcd for $C_{52}H_{88}Cl_2N_4O_{16}S_2{\cdot}2H_2O$: C. 52.21; H, 7.75. Found: C, 52.08; H, 7.91

Table 4
Newly synthesized cationic derivatives of alditols

Product number	^{1}H NMR (solvent) (δ)	^{13}C NMR (δ)	Analysis
15	(D_2O) 0.77 (6H) t, 1.04–1.27 (56H) br, 3.11–3.37 (28H) br, 3.37–4.01 (5H) br	13.8, 21.6, 22.6, 23.7, 28.5, 29.19, 29.23, 29.55, 29.61, 29.70, 29.76, 29.82, 29.89, 30.05, 30.20, 44.23, 45.59, 51.0, 52.1, 64.2, 70.3	Calcd for $C_{47}H_{96}Cl_4N_4O$: C, 61.96; H, 11.06. Found: C, 61.82; H, 11.11
16	(D_2O) 2.26 (6H) s, 3.55–3.78 (8H) m, 3.78 (6H) s, 7.23–7.58 (8H) *AA′BB′*, 7.57 (4H) m, 8.44 (2H) s	20.4, 35.2, 63.2, 69.2, 70.8, 119.9, 122.8, 125.3, 129.4, 135.0, 139.3, 142.4	Calcd for $C_{30}H_{38}N_2O_{10}S_2{\cdot}H_2O$: C, 51.71; H, 5.79. Found: C, 51.80; H, 6.01
17	(D_2O) 2.28 (6H) s, 3.03 (12H) s, 3.51–3.75 (8H) br, 6.69–7.88 (8H) *AA′BB′*, 7.23–7.56 (8H) *AA′BB′*	20.4, 39.1, 63.2, 69.2, 70.8, 106.8, 125.3, 129.4, 139.4, 140.1, 142.4, 157.0	Calcd for $C_{34}H_{46}N_4O_{10}S_2$: C, 55.57; H, 6.31. Found: C, 55.21; H, 6.63
18	(D_2O) 2.00 (8H) br, 2.34 (6H) s, 2.85 (6H) s, 2.98 (4H) br 3.60–3.83 (12H) br, 7.32–7.64 (8H) *AA′BB′*	20.5, 22.8, 40.6, 55.8, 63.2, 69.3, 70.9, 125.4, 129.5, 139.5, 142.5	Calcd for $C_{30}H_{48}N_2O_{10}S_2{\cdot}H_2O$: C, 53.03; H, 7.42. Found: C, 53.22; H, 7.69
19	(D_2O) 1.36 (12H) d, 2.31 (6H) s, 3.55–3.78 (34H) br, 7.30–7.60 (8H) *AA′BB′*	15.5, 20.6, 44.0, 47.8, 63.3, 68.4, 69.3, 125.4, 129.6, 139.6, 142.6	Calcd for $C_{38}H_{64}Br_2N_4O_{10}S_2{\cdot}14.5H_2O$: C, 37.35; H, 7.67. Found: C, 37.26; H, 7.69
20	(D_2O) 1.01 (12H) d, 2.24 (2H) br, 2.31 (6H) s, 3.32 (4H) d, 3.58–3.86 (32H) br, 7.27–7.62 (8H) *AA′BB′*	20.5, 21.8, 22.8, 44.0, 51.3, 63.2, 69.3, 70.9, 72.8, 125.4, 129.4, 139.5, 142.5	Calcd for $C_{40}H_{68}Br_2N_4O_{10}S_2$: C, 41.10; H, 7.59. Found: C, 40.85; H, 7.30
21	(D_2O) 2.28 (6H) s, 3.67–3.84 (32H) br, 4.62 (4H) s, 7.25–7.58 (8H) *AA′BB′*, 7.45–7.49 (10H) br	20.5, 44.0, 50.5, 63.2, 69.0, 69.3, 70.9, 125.0, 125.4, 129.5, 129.6, 131.5, 133.0, 139.5, 142.5	Calcd for $C_{46}H_{64}Cl_2N_4O_{10}S_2{\cdot}12.5H_2O$: C, 46.30; H, 7.52. Found: C, 46.30; H, 7.58
22	(D_2O) 0.51 (6H) t, 1.10–1.20 (36H) br, 1.58 (4H) br, 2.25 (6H) s, 3.20 (4H) br, 3.48–3.69 (32H) br, 7.18–7.57 (8H) *AA′BB′*	13.7, 20.7, 21.3, 22.6, 23.8, 28.4, 29.4, 29.5, 29.6, 29.8, 30.2, 31.9, 46.9, 55.1, 60.5, 71.2, 73.1, 99.2, 125.7, 129.2, 139.9, 141.2	Calcd for $C_{56}H_{100}Br_2N_4O_{10}S_2{\cdot}3H_2O$: C, 53.07; H, 8.43. Found: C, 52.96; H, 8.48
23	(D_2O) 0.51 (6H) t, 1.10–1.20 (44H) br, 1.58 (4H) br, 2.25 (6H) s, 3.20 (4H) br, 3.48–3.69 (32H) br, 7.18–7.57 (8H) *AA′BB′*	13.8, 21.0, 21.8, 21.9, 22.7, 26.1, 26.3, 29.2, 29.8, 30.0, 30.2, 32.2, 44.0, 46.4, 55.1, 60.7, 64.7, 71.2, 73.2, 99.3, 125.9, 129.2, 139.8, 142.2	Calcd for $C_{60}H_{108}Br_2N_4O_{10}S_2{\cdot}3H_2O$: C, 54.45; H, 8.68. Found: C, 54.37; H, 8.72
24	(D_2O) 0.86 (6H) t, 1.24 (56H) br, 2.29 (6H) s, 3.36–3.68 (36H) br, 7.11–7.48 (8H) *AA′BB′*	14.2, 21.2, 22.7, 26.1, 26.9, 28.9, 29.4, 29.5, 29.6, 29.7, 29.81, 29.84, 21.89, 32.7, 44.3, 45.2, 55.3, 60.8, 69.7, 71.8, 73.4, 99.3, 125.9, 129.2, 140.1, 141.9	Calcd for $C_{64}H_{116}Cl_2N_4O_{10}S_2{\cdot}2H_2O$: C, 65.55; H, 10.31. Found: C, 65.42; H, 10.37
25	(D_2O) 0.86 (6H) t, 1.24 (60H) br, 1.68 (4H) br, 2.29 (6H) s, 3.28–3.66 (36H) br, 7.14–7.48 (8H) *AA′BB′*	13.4, 21.2, 22.1, 22.8, 24.4, 26.2, 28.8, 29.41, 29.48, 29.51, 29.58, 29.68, 29.70, 29.76, 29.80, 32.7, 45.7, 50.2, 55.5, 69.9, 71.7, 71.8, 73.7, 99.6, 125.5, 128.1, 141.0, 142.1	Calcd for $C_{68}H_{124}Br_2N_4O_{10}S_2{\cdot}9H_2O$: C, 52.90; H, 9.27. Found: C, 53.10; H, 9.14

aureus. Minimum inhibitory concentrations have been measured for these salts, and the results are presented in Table 8. From these results, it becomes evident that, while antibacterial effects can be noted for simple salts containing a single lipophilic chain attached through a cationic site, greater antibacterial activity can be anticipated for species where more than one such linkage is present

Table 5
Melting points and specific rotation data for newly synthesized compounds

Product number	Melting point (°C)	Specific rotation $[\alpha]_D^{25}$	Synthetic yield (%)
1	135–138	+46.6	94
2	127–131	+44.0	95
3	Very hygroscopic	+63.5	89
4	102–107	+22.5	98
5	108–110	+63.0	92
6	60–69	+69.8	90.7
7	133–135	+39.2	99
8	164–166	+42.8	99
9	130–132	+29.3	99
10	128–130	+33.9	99
11	124–128	+42.9	91
12	174–176	+25.3	99
13	105–107	+61.7	79
14	177–179	+40.6	83
15	132–133	Inactive	91
16	Very hygroscopic	−3.08	97
17	106–116	−4.8	59.2
18	55–66	−97.4	99
19	100–108	+1.5	99
20	109–112	−20.3	82
21	132–136	−4.6	87
22	154–157	−1.2	96
23	135–142	−7.9	99
24	158–168	+1.4	80
25	224–230	−2.2	97

Table 6
Gelation of solvents by newly synthesized polycationic carbohydrate derivatives[a]

Product number	Water	Ethanol	1-Butanol
12	G	G	S
19	S	I	I
21	S	I	I
22	S	I	X
23	G	G	X
24	G	G	G
25	G	G	I

[a] G: forms gel, S: forms solution, I: insoluble, and X: not tested.

Table 7
Results of antibacterial studies of gels with *S. aureus*[a]

Product number	Solvent	% Survival of *S. aureus*
12	Water	1
12	Ethanol	1
24	Water	2
24	Ethanol	2
24	1-Butanol	2
25	Water	1
25	Ethanol	1

[a] These results represent the growth of bacterium in comparison to a blank.

Table 8
Measured antibacterial activity (MIC) for newly synthesized compounds against *S. aureus*

Product number	MIC (μM)	Comments
6	460	Glucopyranoside substituted at 6-position
7	5300	Glucopyranoside substituted at 6-position
8	>10,000	Glucopyranoside substituted at 6-position
10	270	Glucopyranoside substituted at 6-position
11	>10,000	Glucopyranoside substituted at 6-position
15	340	Disubstituted glycerol
18	>10,000	Mannitol derivative with small ring ammonium at 1- and 6-positions
22	>10,000	Glucopyranoside substituted at 6-position
24	9.1	Mannitol derivative with long chain ammonium at 1- and 6-positions
25	2.2	Mannitol derivative with long chain ammonium at 1- and 6-positions

within the salt. This would allow for multiple interactions with the bacterial cell wall.

3. Experimental

3.1. General

All chemicals and solvents used in these syntheses and purifications were of commercial reagent quality and were used without further purification. All ^{1}H and ^{13}C NMR spectra were measured with the samples in commercial deuterated solvents using a Brüker 400-MHz DPX400 instrument. Elemental analyses were performed by Schwarzkopf Microanalytical Services of Woodside, NY.

3.2. Syntheses of 6-position derivatives of methyl α-D-glucopyranoside (1–14)

General procedure. In 100 mL of water 5.0 g (0.026 mol) of methyl α-D-glucopyranoside was dissolved to which a small excess (2.35 g, 0.028 mol) of $NaHCO_3$ was added, followed by (4.96 g, 0.026 mol, 1 equiv) of *p*-TsCl. The mixture was stirred for 1 h at ambient temperature to allow formation of the 6-*O*-tosyl derivative. After this time 0.026 mol, 1 equiv, of the appropriate amine (0.013 mol in the instances of the diamines used for **13** and **14**) was added, and the reaction mixture was stirred under reflux for 14 h. After cooling, the solvent was evaporated under reduced pressure leaving a viscous liquid that became solid when residual solvent was removed under high vacuum. The impure solid was treated with 95% EtOH and any insoluble materials were removed by suction filtration. The remaining solvent was then evaporated under reduced pressure, and the remainder was dried under high vacuum to provide the target material. Yields, analytical data, and characteristics for these products are presented in Tables 3 and 5.

3.3. Syntheses of α,ω-position derivatives of alditols (15–25)

General procedure. In 100 mL of water the appropriate alditol (0.027 mol) was dissolved. $NaHCO_3$ (4.54 g, 0.054 mol, 2 equiv) was then added, followed by *p*-TsCl (10.3 g, 0.054 mol, 2 equiv). The mixture was stirred for 1 h at ambient temperature to allow formation of the α,ω-*O,O′*-ditosyl derivative. After this time the appropriate amine (0.054 mol, 2 equiv) was added, and the reaction mixture was stirred under reflux for 14 h. The solvent was then evaporated under reduced pressure, and the residual viscous liquid was placed under high vacuum to provide the solid target material. Yields, analytical data, and characteristics for these products are presented in Tables 4 and 5.

3.4. Formation of gels

General procedure. The gels were prepared by adding approximately 100 mg of the carbohydrate derivative to a clean vial. Then using an Eppendorf pipette, 1.0 mL of distilled water was added. The vials were sealed, and the mixture was heated to about 70 °C to allow the solid to dissolve. The solution was then cooled to room temperature, and the vial was then inverted to see if gelation had occurred. If there was no flow, it was the indication that a gel had formed. If gelation occurred, more solvent was added, and the steps described above were repeated to see if gelation continued. If gelation did not occur, more of the solid was added. Gel formation with water and other solvents is presented in Table 6.

3.5. Evaluation of antibacterial activity of gels and salts

General procedure. The gel (25 μL) and a stock solution of bacteria (5 μL, $\sim 5 \times 10^4$, *S. aureus*) were added to Luria–Bertani (LB) broth (2 mL). The growth medium was incubated overnight at 37 °C in a shaking water bath. The absorbance (abs, indicating turbidity of the medium) at 600 nm was recorded. The results were reported as percent growth = (abs of sample/abs of blank) × 100. The results are provided in Table 7. Minimum inhibitory concentrations were determined by preparing serial dilutions of each salt and adding the same amount of bacteria to each dilution. Dilutions were incubated overnight at 37 °C in a shaking water bath. Growth was observed visually.

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