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Polycations. 4. Synthesis and Antihydrophobic Effect of Polycationic Strings

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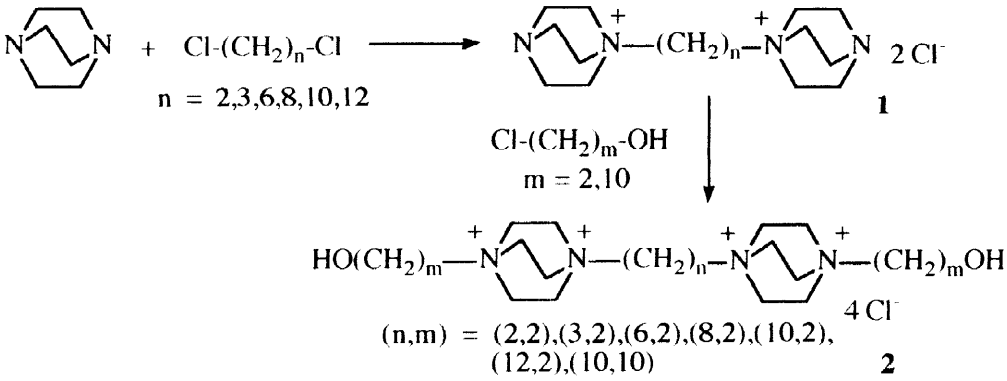
Abstract:
Two categories of polycationic "strings" have been synthesized and investigated for their effect on the aqueous solubility of hydrophobic organic compounds (benzene and 4-bromotoluene, the latter discussed here). Polycationic "strings" are compounds in which cationic sites (quaternary ammonium sites) are incorporated into the covalent structure along a linear chain with free-floating associated anions. The categories are: 1) defined length chains consisting of quaternized dabco units connected by intervening lengths of methylene groups, terminating with ω-alkanol units, and 2) α,ω-dimethylaminoalkane units quaternized with chain extending ω-alkanol units. The observed antihydrophobic effect depends on the total charge, the length of the charge-intervening linkages, and the terminating groups. © 1998 Elsevier Science Ltd. All rights reserved.

The preparation and investigation of ionene polymers has been a topic of interest for some time [1]. Prior efforts of this laboratory [2,3] have been directed toward the synthesis of branching (dendrimeric) and non-branching ("string") polycations. These reports have been concerned solely with the *syntheses* of polycationic strings and dendrimers, respectively. Polycationic strings, salts having cationic sites located at regular intervals along a linear chain of defined length, have potential for a variety of applications. One such potential application for these highly charged organic materials is to serve as antihydrophobic agents which would increase the aqueous solubilities of otherwise relatively insoluble organic solutes [4-8].

Polycationic strings based on dabco (1,4-diazabicyclo[2.2.2]octane) units wherein an even number of such units are incorporated along a chain have been synthesized as shown below. All new compounds exhibit ^{1}H and ^{13}C NMR spectra in accord with their proposed structures[‡] and elemental combustion analyses in accord with hydrated forms of the proposed structures.



Similarly, dicationic salts derived from α,ω-bis(dimethylamino)alkanes have been

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synthesized by quaternization with 6-chloro-1-hexanol and from α,ω-dichloroalkanes taken in reaction with 3-dimethylamino-1-propanol, as shown below. Again all new compounds exhibit ^1H and ^{13}C NMR spectra in accord with their proposed structures and elemental compositions in accord with hydrated forms of the proposed structures‡.

$$(CH_3)_2N(CH_2)_nN(CH_3)_2 \xrightarrow[CH_3CN]{Cl\text{-}(CH_2)_6\text{-}OH} HO(CH_2)_6\text{—}\overset{\overset{CH_3}{|}}{\overset{+}{N}}(CH_2)_n\overset{\overset{CH_3}{|}}{\overset{+}{N}}\text{—}(CH_2)_6OH \; 2Cl^-$$

n = 3,4,6 — **3**

$$HOCH_2CH_2CH_2N(CH_3)_2 \xrightarrow[CH_3CH_2OH]{Cl\text{-}(CH_2)_m\text{-}Cl} HO(CH_2)_3\text{—}\overset{\overset{CH_3}{|}}{\overset{+}{N}}(CH_2)_m\overset{\overset{CH_3}{|}}{\overset{+}{N}}\text{—}(CH_2)_3OH \; 2Cl^-$$

m = 3,6,8 — **4**

The effects of the polycationic strings on the solubility of weakly polar non-ionic organic substances in aqueous solution have been determined using ^{1}NMR spectrometry. Sodium pivaloate, used as an internal reference material, was dissolved in deuterium oxide to a defined concentration. A saturated thermally equilibrated sample of 4-bromotoluene in this reference medium was then investigated by comparative integration of the ^{1}H AA'BB' signal of the 4-bromotoluene relative to the upfield singlet of the pivaloate anion to determine the solubility of the 4-bromotoluene. Salts were then added to the solution in the presence of an excess of the 4-bromotoluene and the solution reequilibrated, noting the effect of these changes on the relative integrations of the AA'BB' signal and the pivaloate anion signal. For the baseline determination, weighed quantities of NaCl were added to the solution, while for investigations of the antihydrophobic effect of the polycationic strings the exact amount of salt added was determined by integration of the ^{1}H NMR signals of the salts.

With added NaCl the anticipated "normal" decrease in solubility of a hydrophobic substance (4-bromotoluene) is observed upon increasing the ionic strength of the medium. This decrease in solubility is indicated in Figure 1 with the curve shown as curve (a). Such a phenomenon is the result of water-ion interactions which increase the ΔG° for cavity formation to accommodate a non-water-binding solute [9].

For added polycationic string salts the solubility of the hydrophobic material was determined in the same manner. In general, for the range of polycationic salts investigated, an increase in aqueous solubility for the hydrophobic test substance was noted at low concentrations of added polycationic string. The increase of 4-bromotoluene aqueous solubility upon addition of a selection of polycationic string species to particular concentrations is indicated in the Table. The antihydrophobic effect herein noted (salting-in effect) is understood to be a result of a direct "bridging" interaction between the water and the hydrophobic solute. The polycationic strings, bearing both those regions which do not have a favorable ΔG° for interaction with the water (hydrophobic) and those which, being ionic, *do* have a favorable ΔG° for interaction with the water, serve to associate favorably with both solute and solvent. It would *not* appear that the antihydrophobic effect observed here is the result of aggregate formation and encapsulation of solute, as would be found with a typical detergent effect. The antihydrophobic agent involved herein is: 1) completely soluble in the aqueous medium rather than forming a bilayer or micelle, and 2) is structurally quite different from typical detergents with localized hydrophobic and hydrophilic regions. The antihydrophobic effect of the polycationic strings is understood to be much closer to that of a small alcohol or polyol, serving as a "bridge" between the polar water and the non-polar hydrophobic solute.

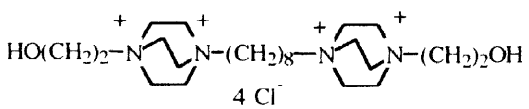
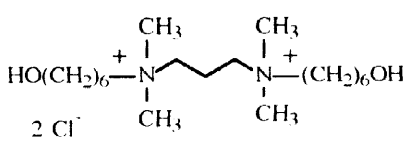
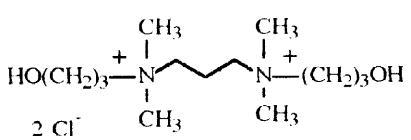
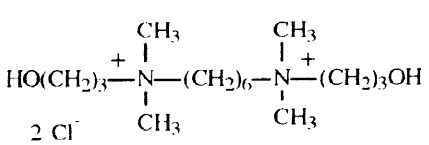
It was observed that upon continued addition of polycationic string salt species to the

aqueous medium, the solubility of the 4-bromotoluene began to decrease. (A similar decrease was noted in studies using benzene.) This variation in solubility with changing polycationic salt concentration is illustrated in the Figure; for added 1-(2-{1'-azonia-4'-(2-hydroxyethyl)azoniabicyclo[2.2.2]octyl}ethyl)azonia-4-(2-hydroxyethyl)azoniabicyclo[2.2.2]octane tetrachloride, **2** (n,m) = (2,2), the variation is shown in the curve indicated as curve (b), and as curve (c) for added salt **2** (n,m) = (6,2), 1-(6-{1'-azonia-4'-(2-hydroxyethyl)azoniabicyclo[2.2.2]octylhexyl)azonia-4-(2-hydroxyethyl)azoniabicyclo[2.2.2]octane tetrachloride.

A large increase in ionic strength, and thereby the water-ion interactions which increase the ΔG° for cavity formation to accommodate a non-water-binding solute [9], is attendant with increasing concentration of the polycationic species. At higher concentrations of the polycationic salts the bridging antihydrophobic effect of the "organic-like" cationic species is overcome by the rapidly increasing effect of the "salting-out" process, primarily due to the (more rapidly increasing) number of associated anions.

The polycationic string species clearly exhibit a significant antihydrophobic effect, increasing the aqueous solubility of hydrophobic organic materials. Continuing efforts are being made to expand the range of easily synthesized polycations exhibiting this effect and to apply it to biologically significant hydrophobic substances. Of particular current interest are polycationic derivatives of the cyclodextrins.

Aqueous Solubility of 4-Bromotoluene as a Function of Selected Added Salts

Salt	Concentration	C_7H_7Br Solubility
None	-	4.6×10^{-4} *M*
NaCl	0.342 *M*	1.8×10^{-4} *M*
	0.0036 *M*	1.3×10^{-3} *M*
	0.0275 *M*	2.0×10^{-3} *M*
	0.0071 *M*	1.0×10^{-3} *M*
	0.0096 *M*	1.1×10^{-3} *M*

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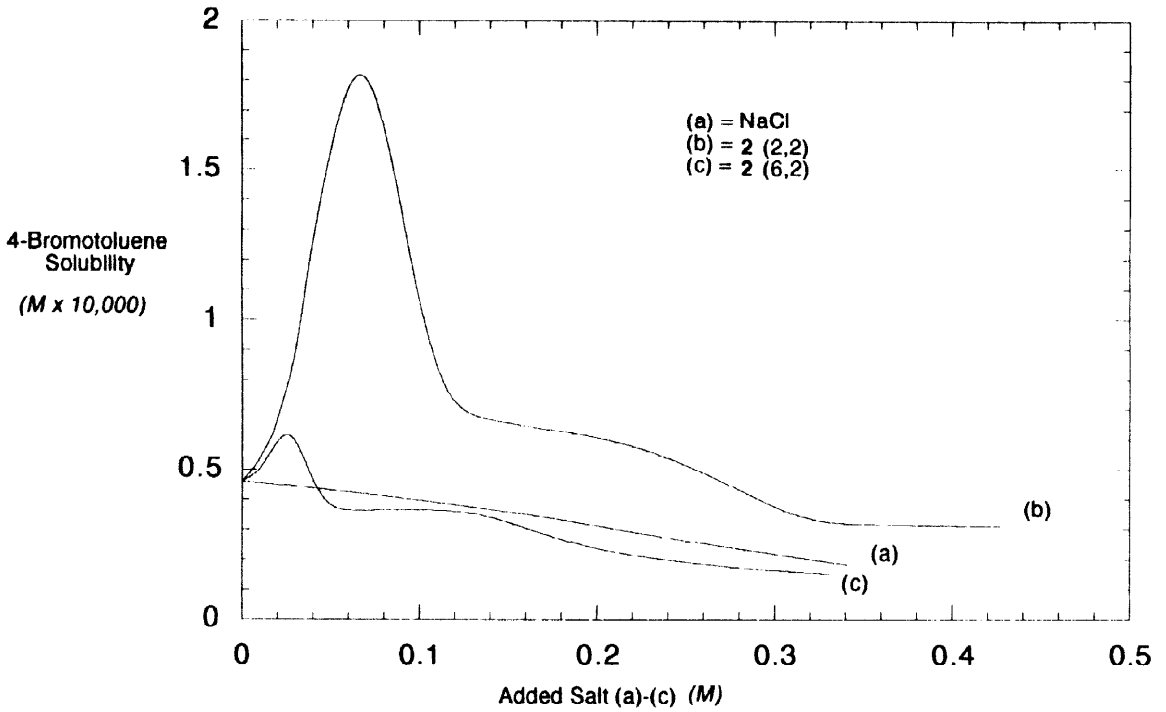
Variation in 4-Bromotoluene Aqueous Solubility with Changing Salt Concentration



‡ All ^{13}C NMR spectra for new compounds exhibit signals of the appropriate number and chemical shift for the proposed structures (δ, deuterium oxide) **1**(2)-45.37, 45.46, 54.30; **1**(3)-17.43, 46.35, 54.65, 62.67; **1**(6)-27.77, 31.89, 50.84, 58.74, 70.99; **1**(8)-23.59, 27.91, 30.44, 46.65, 54.49, 67.04; **1**(10)-22.67, 27.11, 29.68, 29.87, 45.73, 53.60, 66.22; **1**(12)-18.98, 23.43, 26.02, 26.32, 26.43, 42.06, 49.91, 62.56; **2**(2,2)-43.38, 43.90, 51.90, 52.62, 54.83; **2**(3,2)-15.26, 50.68, 51.01, 51.45, 53.99, 65.50; **2**(6,2)-21.77, 25.17, 51.44, 52.35, 55.25, 65.26, 66.71; **2**(8,2)-21.83, 25.42, 28.17, 51.55, 52.41, 55.30, 65.65, 66.72; **2**(10,2)-21.82, 25.54, 28.40, 28.59, 51.37, 52.36, 55.25, 65.68, 66.68; **2**(12,2)-20.49, 24.21, 27.09, 27.39, 27.50, 50.04, 51.04, 53.94, 60.01, 64.36; **2**(10,10)-17.13, 20.65, 20.74, 24.23, 24.41, 24.52, 27.28, 27.53, 27.63, 27.68, 27.71, 30.46, 43.39, 50.30, 61.09, 64.52, 64.54; **3**(3)-14.84, 20.04, 22.75, 23.36, 29.12, 48.81, 58.14, 59.67, 62.93; **3**(4)-19.97, 22.63, 25.38, 26.03, 31.73, 51.30, 62.31, 63.37, 65.04; **3**(6)-24.08, 26.83, 27.43, 27.52, 33.20, 34.08, 52.75, 63.95, 65.95, 66.22; **4**(3)-19.07, 27.37, 53.23, 60.45, 62.60, 64.79; **4**(6)-21.01, 24.19, 24.41, 49.91, 57.46, 60.80, 63.23; **4**(8)-20.97, 24.49, 25.02, 27.11, 49.77, 58.14, 60.58, 63.35.

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