Qualifying Exam Question from Dr. Weber

Anionic ionomers based on polymers with pendant ionized sulfonic acid groups have been shown to have potential both as spermicidal and anti-AIDS virus activity. Give an overview of the polymers that have activity in this area. Discuss the methods used to prepare such polymers. Are there any solubility problems? Do cationic ionomers also have biomedical applications?

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There are several types of anionic ionomers that behave as microbicides, with activity as spermicides and/or anti-viral agents. One group contains the sulfated polysaccharides: cellulose sulfate, and kappa- and lambda-carrageenan. The other group features aryl sulfates: polystyrene sulfate and PRO2000, a naphthalene sulfate polymer. These polymers can be seen in Figure 1.[1]

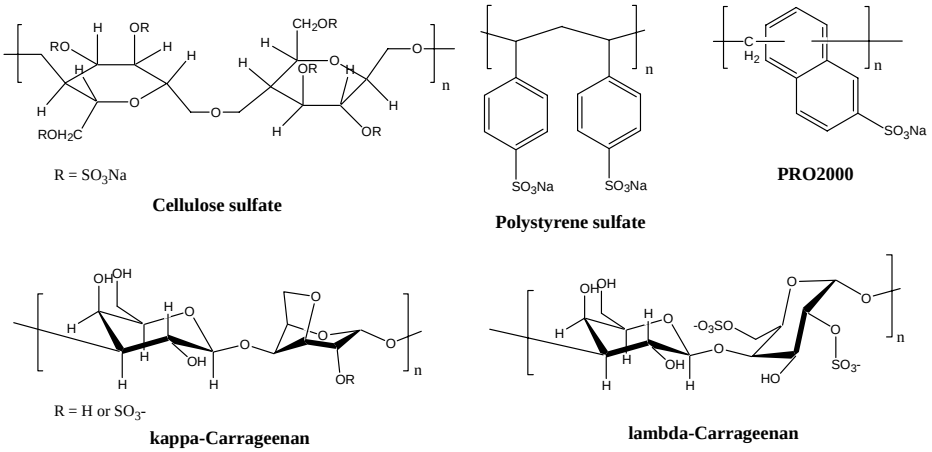

Figure 1. Microbicidal anionic ionomers.

Sodium cellulose sulfate can be prepared by going through the cellulose nitrite ester.[2] This method allows for the D.S. of the polysaccharide to be controlled. The D.S. is the average number of substituted hydroxyl groups per glucose unit.[3] Another feature about this method is that only a stoichiometric to slight excess of the sulfating agent is necessary. The procedure begins with suspending cotton linter pulp in DMF and stirring mechanically while the flask is under a drying tube filled with calcium chloride. Via a dropping funnel, a solution of N_2O_4 in DMF is added slowly over half an hour, and then continued to stir until a clear highly viscous solution is obtained. A saturated solution of DMF-SO_3 complex[4] is then slowly added to the nitrite ester solution over about half an hour with continuous stirring and cooling in an ice bath to maintain a temperature around ten to fifteen degrees C. The amount of SO_3 is calculated stoichiometrically to result in

the desired degree of sulfation. The reaction mixture is then mixed with a small amount of methanol, which removes any residual nitrite groups. After transferring to a large beaker, the cellulose sulfate is neutralized with an aqueous sodium bicarbonate solution. During neutralization, strong agitation and cooling are required. The sodium cellulose sulfate is precipitated by the addition of methanol, washed with 70% aqueous methanol, and dried. The yield from this method is quantitative.

The carrageenans are alternating copolymers of 1,3-linked beta-D-galactose and 1,4-linked 3,6-anhydro-alpha-D-galactose. The designations of kappa and lambda refer to the number and position of the sulfate ester substituents on the sugars and the extent to which the 1,4-linked residues exist as the 3,6-anhydro derivative.[5]

The sulfated polysaccharides known as carrageenans are from the marine plants: *Chondus crispus, Gigartina stellata*, and other red algae.[6] The two most distinct types of sulfated galactan are kappa-carrageenan, which is precipitated in the presence of potassium ions, and lambda-carrageenan, which may be recovered from the residual solution.[7] The fraction that was insoluble in 0.25 M potassium chloride can vary from 41 to 75%, depending on habitat and season of harvesting.[8] The reason for kappa-carrageenan's insolubility in potassium chloride solutions is that intermolecular cross-linkages of the "salt bridge" type that are specific for the arrangement of the sulfate groups along the polysaccharide's chain.[9] To get the carrageenans, the seaweed is washed to remove soluble salts and debris. The seaweed is extracted with hot water at a slightly alkaline pH. The aqueous extract, that contains about 1% carrageenan, is filtered and concentrated to about 3% carrageenan. The polysaccharide is recovered by alcohol precipitation, dried, and milled.[10]

Polystyrene sulfate can be prepared through an emulsion copolymerization of styrene and sodium styrene sulfonate, with reaction conditions as follows.[11] Styrene is freshly distilled and distilled water is deaerated before use by boiling and then cooled in a nitrogen atmosphere. Styrene, sodium styrene sulfate, water, n-dodecylthiol (chain transfer agent), sodium dodecyl sulfonate (emulsifier), and potassium persulfate ($K_2S_2O_8$ – initiator) are all placed in a small glass pressure bottle along with a magnetic stir bar to enhance agitation. The bottle is purged with nitrogen and capped. The bottle is placed behind a safety screen in a mechanical shaker equipped with a water bath with a thermostat set to 50 degrees C, and is shaken for 6 hours. The bottle is removed and a small amount of a hydroquinone solution is added via syringe. The bottle is then shaken for an additional 10 minutes, cooled, and opened. The polymer is coagulated by adding methanol with some sodium chloride added. The polymer comes out as a very fine precipitate that is difficult to filter, so it is made into a slurry and brought down by centrifugation at 2000 rpm for 45 minutes. The solid polymer is then washed two to three times with distilled water and brought down by centrifugation each time. After drying, the resultant polymer is a white powder.

The other aryl sulfate polymer is PRO2000, a condensation copolymer of 2-naphthalenesulfonic acid and formaldehyde. According the latest patent,[12] the synthesis of PRO2000 is to combine 2-naphthalenesulfonic acid, sodium salt, 37% formaldehyde, concentrated sulfuric acid, and water and then heated in a sealed tube for about 24 hours at 120 to 130 degrees C. The reaction mixture is then diluted with water and neutralized to pH of 7 with sodium hydroxide. The neutralized reaction can be concentrated to dryness to obtain the polymer and salts. The polymer is then purified and characterized

by using a gel permeation chromatograph equipped with a light-scattering detector (GPC/LS).

The solubility of all ionomers, be they anionic or cationic, is related to the number of charges on the polymer. Their strong ionic associations make it difficult to dissolve them low polarity solvents. Depending on the concentration of the ionic groups, and to some extent the polymer concentration, attempts to dissolve a sulfonate-ionomer in an organic solvent, such as toluene, will result in three possibilities: insolubility; an extremely viscous solution; or a highly swollen gel.[13] Solubility improves upon addition of a small amount of a polar protic solvent, such as methanol. Solubility is further improved by using a solvent with a high dielectric constant, such as DMF. The result of attempts at dissolution in water is usually a gel. At high ion concentrations (at or near 30%), it is difficult to get the ionomers to go into any solvent.

Cationic ionomers also have biomedical applications. The net charge of most biological cell surfaces or proteins is negative because of the presence of sialic acid groups (Figure 2).[14] Most cationic polymers will therefore be attracted to these biological elements through electrostatic attraction. Usually an interaction such as this will cause many biological responses: polymer-protein complexation; cell agglutination; platelet adhesion; activation of the coagulation and immune systems; inhibition of tumor cell growth.[15]

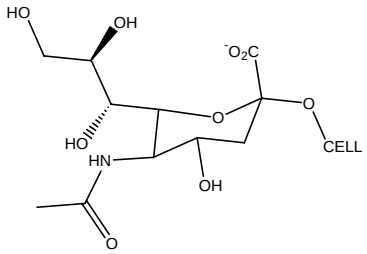

Figure 2. Structure of sialic acid.

Some cationic ionomers have been studied as immune stimulants or adjuvants: such as: the homopolymers of protonated or quaternized poly(ethylenimine); poly(propylenimine); poly(N-vinylimidazoline); poly(4-vinylpyridine N-oxide); and poly(N-vinylimidazolium),[16] all of which can be seen in Figure 3. Cationic ionomers such as: poly(4-vinylpyridine) and its quaternary salt; poly(2-methyl-5-vinylpyridine); and the quaternary slat of polyconidine, also shown in Figure 3, have also been studied as conjugates with immunogens or vaccines.[17] The antibacterial activity of poly(trialkylvinylbenzylammonium chlorides) (Figure 3) with various alkyl groups at the

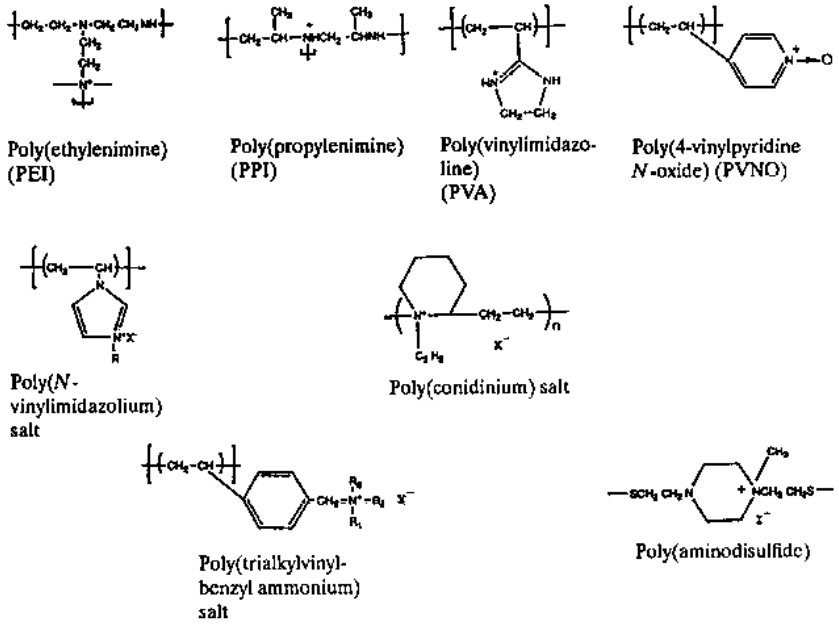

Figure 3. Examples of some biologically active cationic ionomers.

quaternary sites has also been reported.[18] Poly(aminodisulfide) (Figure 3) was evaluated as an antimicrobial agent as well.[19]

This survey of a few anionic ionomers included the preparation of the aforementioned polymers. In terms of solubility, gels are the usual form that the ionomers impart. The vast importance of electrostatic interactions in the biomedical field has a great number of opportunities for both anionic and cationic ionomers.

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