# Preparation and Characterization of Novel Poly(alkylamine)-Based Hydrogels Designed for Use as Bile Acid Sequestrants

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*Received February 25, 1997; Revised Manuscript Received July 25, 1997*[⊗]

ABSTRACT: Preparation of novel poly(alkylamine)-derived hydrogels is described. Polymers are prepared via reaction of various diamines with dihalo compounds or diepoxides. N-substituted polymers are readily prepared by reaction of primary amines with dihalo compounds. The resulting covalently cross-linked polymers exhibit hydrogel behavior (high swell with water) when ionized to polyammonium species at low pH. At high pH, the polymers reside in the free base polyamine form and lose all hydrogel character (they no longer swell in water). Characterization of polymer structure with carbon-13 NMR, thermal analysis, and swell behavior reveals a structure which is highly branched and only loosely cross-linked. In the ionic polyammonium form thermal stability up to ∼300 °C is observed. The polymers exhibit activity as bile acid sequestrants significantly superior to cholestyramine, as evidenced by their ability to efficiently bind quantities of cholate when tested in vitro. This behavior indicates that these hydrogels should be very useful for the treatment of hypercholesterolemia.

## Introduction

The use of hydrogels in an ever increasing array of applications is becoming possible as refinement of their structure/property characteristics continues. Hydrogels are most commonly used as superabsorbents in diapers and other hygiene products. They are also finding uses in household articles, cosmetics, toys, agriculture, and medicine.[1,2] Medical applications include contact lenses, media for assays, ion separations, wound dressings, drug delivery systems, and artificial organs and limbs.[3,4] As pharmaceutical agents, hydrogels have most often found use in drug carrier applications, although their use as pharmaceutically active materials is gradually being recognized.[5]

Bile acid sequestrants represent a class of polymers with pharmaceutical utility as hypercholesterolemic agents. These polymers ionically interact with bile acids in the digestive tract causing a net decrease in available bile acid. Cholesterol is then used from the body to produce more bile acid. The net effect is a decrease in serum cholesterol.[6] Common polymers used as sequestrants are either quaternized polystyrene (cholestyramine) or quaternized poly(ethylenimine) (colestipol).[7] Both polymers are ionic in nature. Large quantities of these polymers are required daily (up to 24 g per day) to reduce serum cholesterol levels.[8] In addition to their limited potency, these sequestrants also suffer from poor patient compliance due to a gritty consistency which often leads to gastrointestinal distress.[9] The gritty, sandlike, consistency of current bile acid sequestrants suggested to us the use of hydrogels for this application. The soft gelatinous texture of a hydrogel should foster enhanced patient compliance. Increased activity should also be realized for a hydrogel-based sequestrant since more of the polymer should be available for molecular interaction due to increased availability of active sites throughout the hydrogel structure when swollen with water.[10] This paper describes the synthesis and methods of characterization of novel hydrogels designed specifically for use as bile acid sequestrants.

## Experimental Section

**General Data.** All ingredients were purchased from vendors and used as received with the notable exceptions of 1,10-dibromodecane and hexamethylenediamine, which were distilled, and 5,5′-methylenedifurfurylamine, which was prepared according to the literature.[11] Hexamethylenediamine was distilled at 190 °C and atmospheric pressure, and 1,10-dibromodecane was distilled at 138 °C and 3.2 mmHg vacuum. All reactions were conducted in an atmosphere of dry nitrogen.

**General Synthesis of Hydrogel Polymers.** Into a flask equipped with an overhead stirrer, reflux condenser, and nitrogen port were added a volume of solvent, the desired diamine (or amine), and the desired dihalide or diepoxide. The ratio of solvent (vol) to ingredients (mass) was held at ∼1.5. Addition of sodium carbonate was required at times to effect enhanced reaction times and yields. The resulting homogeneous solution was stirred rapidly at reflux. After a few minutes to a few hours the entire contents of the flask became a solid, colorless, soft gelled mass. Stirring was halted, and the flask was held at 25−40 °C for a minimum of 18 h. The resulting soft, translucent, gel was then cut apart with a spatula (if required—often it was broken up by the action of the agitator before stirring was stopped) and removed from the flask. In no case did the gel ever adhere to the reaction flask. The product gel was then chopped in a blender in the presence of aqueous ammonium hydroxide, washed with water and then methanol, acidified with aqueous hydrochloric acid, and washed with water and finally ethanol, until a neutral filtrate was detected. The gel was then dried in a vacuum oven with a nitrogen purge at 60 °C, and the resulting hard crumbs were then chopped in a coffee mill to yield a fine granular solid. All reported yields are isolated yields.

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⊗ Abstract published in *Advance ACS Abstracts,* September 15, 1997.

S0024-9297(97)00250-7 CCC: $14.00 

**Table 1. Hydrogels Prepared with Diamines and α,ω-Dibromoalkanes**

| polymer | ingredients | quantity (g; mol) | media mL/mL | $Na_2CO_3$ (g; mol) | reaction time (h) | yield (%) | swell factor (g of $H_2O$/g of polym) |
|---|---|---|---|---|---|---|---|
| 1 | 1,6-diaminohexane | 3.87; 0.033 | methanol/DMF | | 1 | 64 | 20 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| 2 | 1,3-diaminopropane | 2.47; 0.033 | methanol/DMF | | 5 | 48 | 35 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **3** | 1,4-diaminobutane | 2.93; 0.033 | methanol/DMF | | 3 | 51 | 12 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **4** | 1,5-diaminopentane | 3.40; 0.033 | methanol/DMF | | 3 | 64 | 9 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **5** | 1,7-diaminoheptane | 4.33; 0.033 | methanol/DMF | | 1 | 58 | 12 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **6** | 1,8-diaminooctane | 4.8; 0.033 | methanol/DMF | | 1 | 61 | 12 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **7** | 1,9-diaminononane | 5.26; 0.033 | methanol/DMF | | 1 | 22 | 8 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **8** | 1,10-diaminodecane | 5.73; 0.033 | methanol/DMF | | 1 | 56 | 4 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **9** | 1,12-diaminododecane | 6.66; 0.033 | methanol/DMF | | 1.5 | 63 | 0.1 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **10** | 1,3-diamino-2-hydroxypropane | 3.0; 0.033 | methanol/DMF | | 24 | 29 | 136 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **11** | 2-methyl-1,5-diaminopentane | 2.98; 0.0257 | methanol/DMF | | 4.5 | 63 | 45 |
| | 1,8-dibromooctane | 7.0; 0.026 | 12/12 | | | | |
| **12** | 1,4-dimethylaminocyclohexane | 71.1; 0.50 | methanol/DMAC | 63 ; 0.59 | 0.75 | 78 | 18 |
| | 1,8-dibromoocatane | 136; 0.50 | 150/150 | | | | |
| **13** | *N*-(3-aminopropyl)-1,3-propanediamine | 3.06; 0.023 | methanol/DMF | | 2 | 26 | 40 |
| | 1,10-dibromodecane | 7.0; 0.023 | 10/10 | | | | |
| **14** | JEFFAMINE EDR-148 ($H_2NCH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$) | 4.93; 0.033 | methanol/DMF 12/12 | | 2 | 47 | 72 |
| | 1,10-dibromodecane | 10; 0.033 | | | | | |
| **15** | 5,5′-methylenedifurfurylamine | 2.5; 0.012 | methanol/DMF | | 4 | 63 | 33 |
| | 1,10-dibromodecane | 3.65; 0.012 | 12/12 | | | | |

**General Procedure for the Determination of Swell.** Into a predried, tared, 150 mL coarse fritted funnel was added approximately 1 g of polymer. The stem of the funnel was sealed with a rubber stopper. The funnel was placed on a filter flask, and about 100 mL of distilled water at room temperature was added to the funnel. The contents were stirred, if necessary, to fully disperse the water and polymer. The contents were then left undisturbed for 15 min. The rubber stopper was then removed from the stem of the funnel, and suction was applied for 5 min. The stem and underside of the funnel were then rinsed with ethanol to remove any remaining water droplets, and suction was then continued for an additional 5 min. Any remaining water droplets were wiped off the funnel. The funnel and contents were then weighed to determine the weight of water retained by the polymer.

swell = (total mass of wet polymer + funnel) − (total mass of dry polymer + funnel)/mass of dry polymer

= wet mass of polymer − dry mass of polymer/dry mass of polymer

= mass water retained (g)/mass polymer (g)

Table 1 summarizes the synthesis of hydrogel via reaction of various diamines with dibromoalkanes.

Table 2 summarizes the preparation of N-substituted hydrogel polymers and copolymers via reaction of primary amines and diamines with dibromoalkanes.

Table 3 describes the synthesis of various hydrogel polymers and copolymers from the reaction of selected diamines with dihaloalkenes.

Table 4 summarizes the synthesis of hydrogels prepared through reaction of various diamines with α,α′-dichloro-*p*-xylene.

Table 5 describes the synthesis of a number of hydrogels via reaction of various diamines with various diepoxides.

**$^{13}$C NMR Spectra of Polymer 1.** Carbon-13 NMR spectra were run in mixtures of dioxane-$d_8$/$D_2O$ using the dioxane-$d_8$ signal (66.5 ppm) as an internal standard. A sample of polymer **1** (150−300 mg) was placed in a 10 mm NMR tube, and dioxane-$d_8$ was added to the sample. The sample was stirred to make a slurry. To the slurry was added enough $D_2O$ to swell the sample. At this point additional dioxane-$d_8$ was added, and the slurry was mixed to a uniform gel. The final ratio of dioxane-$d_8$ to $D_2O$ was about 6 to 1. After the addition of both $D_2O$ and dioxane-$d_8$, the height of the gelled material in the NMR tube was 4−6 cm. To obtain solid swollen material for solid-state NMR, additional dioxane-$d_8$ was added to this sample to make it more mobile, and the material was then vacuum filtered. After filtration, the material appeared as a white fluffy solid.

The carbon-13 NMR solution spectra were run using an inverse gated decoupling sequence, to suppress the nuclear Overhauser effect, at 75 °C on a 300 MHz G. E. Omega widebore system where $^{13}$C appears at 75.576 MHz. All samples were run in a 10 mm probe, and the sweep width was set to 20000, the number of points to 32 K, the preacquisition delay to 20−30 s depending on the sample, and the line broadening to 5.

Solid state carbon-13 MAS NMR spectra were acquired at a carbon frequency of 90.5255 MHz on a Chemagnetics CMX-360 NMR spectrometer. The spectrum of the unswollen polymer presented in Figure 4 was obtained using an MAS spinning rate of 5 KHz and is the result of the accumulation of 12 000 time−domain transients. A carbon 90° pulse width of 4 μs and a pulse repetition delay of 15 s was used. Exponential multiplication with an 8-Hz line-broadening parameter was used on the time−domain data prior to Fourier transformation. For the swollen polymer (Figure 6), the corresponding MAS NMR parameters included a 3.5-KHz MAS rate, 36 072 transients, a 5 μs 90° pulse width, and a pulse repetition delay of 7 s. Apodization of the time−domain data from the swollen polymer was performed exactly as described for the nonswollen material. $^{13}$C NMR (swollen with dioxane-$d_8$/$D_2O$−magic-angle spinning/Bloch decay−single pulse with decoupling during acquisition, dioxane-$d_8$ lock): δ 24.11 (s,2, ϵ Cs of decane), 26.16 (m, 6, γ and δ Cs of decane and γ Cs of hexane), 29.5 (s, 4, β Cs of decane and hexane), 40.1 (s, 0.4, α Cs adjacent to primary ammonium), 48.2 (d, 1.9, α Cs adjacent to secondary ammonium), 53.4 (m, 1.6, α Cs adjacent to tertiary ammonium), 59.3 (m, 0.1, α Cs adjacent to quaternary ammonium).

**Table 2. Hydrogels Prepared with Amines and α,ω-Dibromoalkanes**

| polymer | ingredients | quantity (g; mol) | media mL/mL | $Na_2CO_3$ (g; mol) | reaction time (h) | yield (%) | swell factor (g of $H_2O$/g of polym) |
|---|---|---|---|---|---|---|---|
| **16** | 5-amino-1-pentanol | 3.43; 0.033 | methanol/DMF | 3.53; 0.033 | 72 | 23 | 24 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **17** | 4-(aminomethyl)piperidine | 3.80; 0.033 | methanol/DMF | 3.53; 0.033 | 0.75 | 59 | 19 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **18** | 1-(2-aminoethyl)piperazine | 4.30; 0.033 | methanol/DMF | 3.53; 0.033 | 1.5 | 63 | 35 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **19** | *N*-(2-aminoethyl)pyrolidine | 1.90; 0.0167 | methanol/DMF | 1.77; 0.017 | 2.5 | 47 | 81 |
| | 1,10-dibromodecane | 5.0; 0.0167 | 6/6 | | | | |
| **20** | *N*-(2-aminoethyl)piperidine | 2.14; 0.0167 | methanol/DMF | 1.77; 0.017 | 3.5 | 58 | 97 |
| | 1,10-dibromodecane | 5.0; 0.0167 | 6/6 | | | | |
| **21** | 4-(2-aminoethyl)morpholine | 4.33; 0.033 | methanol/DMF | 3.53; 0.033 | 96 | 36 | 191 |
| | 1,10-dibromodecane | 10.0; 0.033 | 12/12 | | | | |
| **22** | 4-(2-aminoethyl)morpholine | 3.96; 0.030 | methanol/DMF | 3.23; 0.030 | 36 | 44 | 73 |
| | 1,12-dibromododecane | 10.0; 0.030 | 12/12 | | | | |
| **23** | 1,6-diaminohexane | 1.93; 0.0167 | methanol/DMF | 3.53; 0.033 | 3.5 | 69 | 7 |
| | dodecylamine | 3.08; 0.0167 | 12/12 | | | | |
| | 1,10-dibromodecane | 10.0; 0.033 | | | | | |
| **24** | 1,6-diaminohexane | 4.0; 0.034 | methanol/DMF | 4; 0.04 | 3−6 | 56 | 14 |
| | dodecylamine | 2.0; 0.011 | 12.5/12.5 | | | | |
| | 1,10-dibromodecane | 13.6; 0.045 | | | | | |
| **25** | 1,6-diaminohexane | 4.0; 0.034 | methanol/DMF | 5; 0.05 | 1 | 69 | 13 |
| | butylamine | 1.0; 0.014 | 12/12 | | | | |
| | 1,10-dibromodecane | 14.4; 0.048 | | | | | |
| **26** | 1,6-diaminohexane | 1.93; 0.0167 | methanol/DMF | 3.53; 0.033 | 0.75 | 55 | 17 |
| | hexylamine | 1.68; 0.0167 | 12/12 | | | | |
| | 1,10-dibromodecane | 10.0; 0.033 | | | | | |
| **27** | 1,6-diaminohexane | 2.9; 0.025 | methanol/DMF | 3.53; 0.033 | 0.5 | 62 | 24 |
| | hexylamine | 0.84; 0.0083 | 12/12 | | | | |
| | 1,10-dibromodecane | 10.0; 0.033 | | | | | |
| **28** | 1,6-diaminohexane | 4.0; 0.034 | methanol/DMF | 2.0; 0.019 | 3−6 | 59 | 21 |
| | nonylamine | 2.0; 0.014 | 13/13 | | | | |
| | 1,10-dibromodecane | 14.5; 0.048 | | | | | |

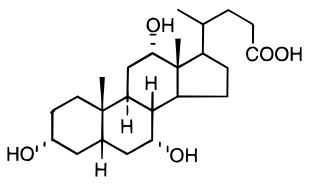
**Table 3. Hydrogels Prepared with Diamines and *trans*-1,4-Dihalo-2-butene**

| polymer | ingredients | quantity (g; mol) | media mL/mL | $Na_2CO_3$ (g; mol) | reaction time (h) | yield (%) | swell factor (g of $H_2O$/g of polym) |
|---|---|---|---|---|---|---|---|
| **29** | 4,4′-methylenebis(cyclohexylamine) | 8.4; 0.040 | methanol/DMF | 2.1; 0.02 | 0.33 | 64 | 9 |
| | *trans*-1,4-dichloro-2-butene | 5.0; 0.040 | 12/12 | | | | |
| **30** | 1,4-diaminocyclohexane | 4.56; 0.040 | methanol/DMF | 2.1; 0.02 | 0.5 | 41 | 30 |
| | *trans*-1,4-dichloro-2-butene | 5.0; 0.040 | 10/10 | | | | |
| **31** | 4,4′-trimethylenedipiperidine | 8.40; 0.040 | methanol/DMF | 2.1; 0.02 | 0.66 | 64 | 28 |
| | *trans*-1,4-dichloro-2-butene | 5.0; 0.040 | 12/12 | | | | |
| **32** | 1,4-bis(aminomethyl)cyclohexane | 7.12; 0.050 | methanol/DMAC | 5.3; 0.05 | 0.25 | 55 | 6 |
| | *trans*-1,4-dibromo-2-butene | 10.7; 0.050 | 29/29 | | | | |
| **33** | 1,10-diaminodecane | 8.62; 0.050 | methanol/DMAC | 6.5; 0.06 | 0.167 | 58 | 5 |
| | *trans*-1,4-dibromo-2-butene | 10.7; 0.050 | 20/20 | | | | |
| **34** | 1,4-diaminocylohexane | 2.28; 0.020 | methanol/DMF | 2.1; 0.02 | 0.5 | 49 | 32 |
| | 4,4′-methylenebis(cyclohexylamine) | 4.20; 0.020 | 12/12 | | | | |
| | *trans*-1,4-dichloro-2-butene | 5.0; 0.040 | | | | | |
| **35** | 4,4′-methylenebis(cyclohexylamine) | 4.2; 0.020 | methanol/DMF | 2.1; 0.02 | 0.25 | 72 | 7 |
| | 4,4′-trimethylenedipiperidine | 4.2; 0.020 | 12/12 | | | | |
| | *trans*-1,4-dichloro-2-butene | 5.0; 0.040 | | | | | |
| **36** | 1,4-diaminocyclohexane | 2.28; 0.020 | methanol/DMF | 2.1; 0.02 | 0.25 | 72 | 9 |
| | 4,4′-trimethylenedipiperidine | 4.20; 0.020 | 12/12 | | | | |
| | *trans*-1,4-dichloro-2-butene | 5.0; 0.040 | | | | | |

**Equilibrium Binding of Cholate to Hydrogels.** Equilibrium binding of cholic acid to the hydrogels presented in this paper was determined using isotonic ionic conditions at 37 °C, in order to roughly approximate physiological conditions. Carbon-14 ($^{14}C$) labeled bile acid dissolved in phosphate-buffered saline (PBS) at pH 7 was prepared at 10 reciprocal concentrations ranging from 0.454 to 30.0 mM (45 nCi of $^{14}C$/mL). The series of concentration levels was chosen to afford relatively even distribution of empirical data along the semilogarithmic saturation binding curves. Details of the determination of binding parameters are described elsewhere.[12]

## Results and Discussion

**Bile Acid Sequestration.** The human body produces many different bile acids and steroids which flow into the intestinal tract and participate in digestive processes. While all of these compounds differ in the placement of functionality upon the basic steroidal scaffold, they also tend to share common structural characteristics. The key structural feature exhibited by bile acids is the presence of a hydrophobic face, that side of the molecule on which the methyl groups reside, and a hydrophilic face, the side of the molecule occupied by hydroxyl groups. Cholic acid provides a structural




**Cholic Acid**

**Table 4. Hydrogels Prepared with Diamines and α,α′-Dichloro-*p*-xylene**

| polymer | ingredients | quantity (g; mol) | media mL/mL | $Na_2CO_3$ (g; mol) | reaction time (h) | yield (%) | swell factor (g of $H_2O$/g of polym) |
|---|---|---|---|---|---|---|---|
| **37** | 1,4-diaminocyclohexane | 6.51; 0.057 | methanol/DMF | 3.0; 0.028 | 0.5 | 73 | 7 |
| | α,α′-dichloro-*p*-xylene | 10.0; 0.057 | 12/12 | | | | |
| **38** | 4,4′-methylenebis(cyclohexylamine) | 12.0; 0.057 | methanol/DMF | 3.0; 0.028 | 0.25 | 77 | 4 |
| | α,α′-dichloro-*p*-xylene | 10.0; 0.057 | 12/12 | | | | |
| **39** | 1-(2-aminoethyl)piperazine | 5.16; 0.040 | methanol/DMF | 2.61; 0.025 | 0.33 | 66 | 10 |
| | α,α′-dichloro-*p*-xylene | 7.0; 0.040 | 12/12 | | | | |
| **40** | 1,10-diaminodecane | 7.88; 0.046 | THF/methanol | 4.8; 0.046 | 0.5 | 47 | 13 |
| | α,α′-dichloro-*p*-xylene | 8.0; 0.046 | 20/15 | | | | |
| **41** | 1,12-diaminododecane | 6.18; 0.031 | THF/methanol | 3.63; 0.034 | 2 | 35 | 3 |
| | α,α′-dichloro-*p*-xylene | 6.0; 0.034 | 20/15 | | | | |
| **42** | 1,4-diaminobutane | 3.02; 0.034 | THF/methanol | 3.63; 0.034 | 2 | 53 | 7 |
| | α,α′-dichloro-*p*-xylene | 6.0; 0.034 | 15/15 | | | | |
| **43** | 1,6-diaminohexane | 3.32; 0.028 | THF | | 16 | 20 | 22 |
| | α,α′-dichloro-*p*-xylene | 5.0; 0.028 | 50 | | | | |
| **44** | *N*,*N*′-bis(3-aminopropyl)ethylenediamine | 5.97; 0.034 | THF/methanol | 3.63; 0.034 | 1 | 70 | 26 |
| | α,α′-dichloro-*p*-xylene | 6.0; 0.034 | 15/15 | | | | |
| **45** | *N*-(3-aminopropyl)-1,3-propanediamine | 4.5; 0.034 | THF/methanol | | 1.5 | 75 | 12 |
| | α,α′-dichloro-*p*-xylene | 6.0; 0.034 | 20/10 | | | | |

**Table 5. Hydrogels Prepared with Diamines and Diepoxides**

| polymer | ingredients | quantity (g; mol) | medium mL | $Na_2CO_3$ (g; mol) | reaction time (h) | yield (%) | swell factor (g of $H_2O$/ g of polym) |
|---|---|---|---|---|---|---|---|
| **46** | 1,10-diaminodecane | 4.13; 0.024 | methanol | | 0.167 | 77 | 15 |
| | butanediol diglycidyl ether | 4.85; 0.024 | 10 | | | | |
| **47** | 1,10-diaminodecane | 6.88; 0.040 | methanol | | 0.167 | 74 | 11 |
| | 1,3-butadiene diepoxide | 3.44; 0.040 | 10.3 | | | | |
| **48** | 1,10-diaminodecane | 4.90; 0.0285 | methanol | | 1 | 68 | 28 |
| | 1,2,7,8-diepoxyoctane | 4.05; 0.0285 | 26.9 | | | | |
| **49** | JEFFAMINE EDR-192 | 6.03; 0.031 | methanol | | 0.5 | 58 | 64 |
| | ($H_2NCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$) | | 8.7 | | | | |
| | 1,3-butadiene diepoxide | 2.70; 0.031 | | | | | |
| **50** | JEFFAMINE EDR-192 | 5.20; 0.027 | methanol | | 0.75 | 74 | 22 |
| | ($H_2NCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$) | | 9.0 | | | | |
| | 1,2,7,8-diepoxyoctane | 3.85; 0.027 | | | | | |
| **51** | 1,12-diaminododecane | 7.01; 0.035 | methanol | | 0.25 | 68 | 17 |
| | 1,3-butadiene diepoxide | 3.01; 0.035 | 10 | | | | |
| **52** | 1,12-diaminododecane | 4.80; 0.024 | isopropanol | | 0.67 | 77 | 4 |
| | 1,2,7,8-diepoxyoctane | 3.41; 0.024 | 8.2 | | | | |
| **53** | 1,3-diaminopropane | 2.97; 0.040 | methanol | | 0.25 | 56 | 23 |
| | 1,3-butadiene diepoxide | 3.44; 0.040 | 10 | | | | |
| **54** | 1,3-diaminopropane | 2.59; 0.035 | methanol | | 0.5 | 80 | 9 |
| | 1,2,7,8-diepoxyoctane | 4.98; 0.035 | 7.6 | | | | |
| **55** | 1,4-diaminobutane dihydrochloride | 6.44; 0.040 | methanol | 3.2; 0.08 | 0.167 | 81 | 10 |
| | 1,2,7,8-diepoxyoctane | 5.69; 0.040 | 9.2 | | | | |
| **56** | 1,6-diaminohexane | 3.48; 0.030 | methanol | | 0.167 | 84 | 8 |
| | 1,3-butadiene diepoxide | 2.58; 0.030 | 6.0 | | | | |
| **57** | 1,6-diaminohexane | 3.48; 0.030 | methanol | | 0.5 | 83 | 7 |
| | 1,2,7,8-diepoxyoctane | 4.31; 0.030 | 10 | | | | |
| **58** | 1,8-diaminooctane | 6.68; 0.046 | methanol | | 0.25 | 74 | 11 |
| | 1,3-butadiene diepoxide | 3.98; 0.046 | 10.7 | | | | |
| **59** | 1,8-diaminooctane | 4.42; 0.031 | methanol | | 0.67 | 77 | 16 |
| | 1,2,7,8-diepoxyoctane | 4.37; 0.031 | 13.2 | | | | |
| **60** | JEFFAMINE EDR-148 | 5.32; 0.036 | methanol | | 0.167 | 53 | 39 |
| | ($H_2NCH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$) | | 8.5 | | | | |
| | 1,3-butadiene diepoxide | 3.09; 0.036 | | | | | |
| **61** | JEFFAMINE EDR-148 | 4.50; 0.030 | methanol | | 0.67 | 77 | 17 |
| | ($H_2NCH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$) | | 8.5 | | | | |
| | 1,2,7,8-diepoxyoctane | 4.31; 0.030 | | | | | |

example. Bile acids tend to form face-to-face micelles where the hydrophobic faces interact with one another and the hydrophilic faces interact with an aqueous environment. Often, bile acids will interact with hydrophobic fatty molecules (long chain alkanes) to aid in solubilizing the material for digestion.[13]

Current bile acid sequestrants (cholestyramine and colestipol) rely on acid−base interactions (between the acid functionality of the bile acid and a quaternary amine appended to a polymer) for complexation of bile acid molecules and ultimate removal from the body. Our strategy has been to create polymer structures which will provide molecular environments with which the entire bile acid molecule can interact. Toward this end, we have directed our synthetic efforts to the production of hydrogels which contain both ionic centers which will interact with the acid portion of the bile acid and hydrophobic regions with which the bile acid can form micellelike interactions.

**Polymer Synthesis.** The use of quaternary amines in combination with cross-linked polymeric structures for sequestration of bile acids is well-known. Typically, diamine and dihalo species are stirred together in any of a number of solvents at moderate temperatures to produce polymer. Usually great care is taken to avoid cross-linking, thus maintaining polymer solubility. Of-

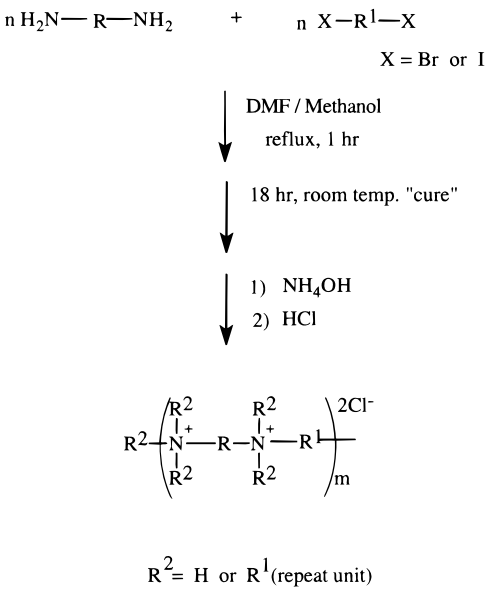
ten tertiary diamines are employed to ensure no unwanted cross-linking takes place. Other approaches involve the polymerization of secondary or primary diamines under very mild conditions followed by reaction to produce quaternized amines after polymerization. When desired, cross-linking is often accomplished after the initial polymer structure has been formed.[14]

We have found that high temperature polymerization of primary amines (or diamines) with dihaloaliphatics rapidly produces cross-linked polyammonium species. When the ingredients are judiciously chosen, the resulting ionic polymer is a highly swellable hydrogel. Typical synthetic conditions include the addition of equivalent amounts of a selected diamine and dihaloaliphatic to a 1:1 mix of methanol and dimethylformamide (DMF). A relatively low ratio of solvent to ingredients is maintained (2:1.3 (v/w)) to promote efficient polymerization and cross-linking. The ingredients are rapidly stirred and heated at reflux. Highly swollen cross-linked polymer is usually produced within a few hours (often less than an hour). The polymer often imbibes all of the solvent in the reaction flask to form a highly swollen, transparent, soft gel which easily crumbs. Additional "cure" time is required to allow desired cross-link density and high yields. Short reaction times and/or lower temperatures tend to produce less cross-linking (lower cross-link density) and thus a higher degree of swelling. When dihaloalkanes are employed, dibromo- or diiodoaliphatics have proven to be best suited for production of high yields of cross-linked polymers. Dichloroaliphatics tend to react sluggishly and produce low yields of low quality polymer. We have found that many diamines will produce desirable gelled polymer as long as the linear aliphatic dihalide co-reactant contains seven or more methylene groups. When the dihalide is shorter, generally poor polymerization is observed. The inability to produce high quality polymer with shorter chain dihalides may reflect a tendency for the free halide end to "bite back" on the immediately adjacent amine to form small ring "dead ends".

The resulting counterions associated with the polymer are easily exchanged by treatment of the polymer with aqueous base followed by subsequent treatment with an acid from which the desired counterion can be derived. Alternatively, routine ion exchange processes may be employed. Generally, chloride is the counterion of choice for pharmaceutical applications. Schemes 1 and 2 illustrate typical polymerizations. Isolated yields are typically around 60% due to incomplete gel formation (a soluble fraction) and losses during the ion exchange process. Low yields generally indicate poor gel formation (cross-linking) leading to a predominance of soluble linear and lightly branched polymer. Thus, isolated yield can be used as a crude measurement of the efficiency of cross-linking processes which ultimately produce an insoluble gel. Note that the methodology illustrated in Scheme 2 provides direct access to hydrogels carrying substituents along the polymeric backbone which emanate from nitrogen centers. In many cases polymerization to a gel can be accomplished without addition of base; however, addition of a base such as sodium carbonate (as is Scheme 2) tends to produce quicker reaction times, more consistent polymer quality, and higher yields.

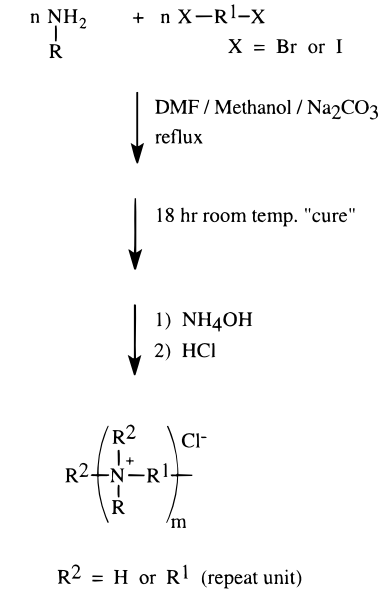
Our new polyammonium ionomers swell significantly when introduced to water. For our purposes we measure swell as the mass of water imbibed by a given mass of polymer (e.g. g of water/g of polymer). Treatment with

**Scheme 1**




base at pH ~10 will usually neutralize the ionic ammonium groups to free amines, and the polymer will then deswell. Highly pure polymer can be obtained by alternate swelling and deswelling with aqueous base and acid along with washing with polar organics (e.g. methanol or ethanol) when the polymer is in the swellable ionic form. Tables 1 and 2 summarize a number of polymers which have been synthesized as in Schemes 1 and 2 respectively. The cross-linked nature of the final polymeric product does not allow dissolution or melt processing; therefore, all characterization of the polymer must be carried out either in the dry solid state or the swollen gel state.

**Scheme 2**




Polymers of Table 1 illustrate the importance of backbone hydrophilicity in maintaining a polymer structure which will readily absorb water. When more hydrophobic character is incorporated into the polymer structure (e.g. hydrocarbon spacing between ionic centers is increased) swell values can be reduced substantially. Figure 1 illustrates this effect for polymers in which diamine chain length is systematically altered.

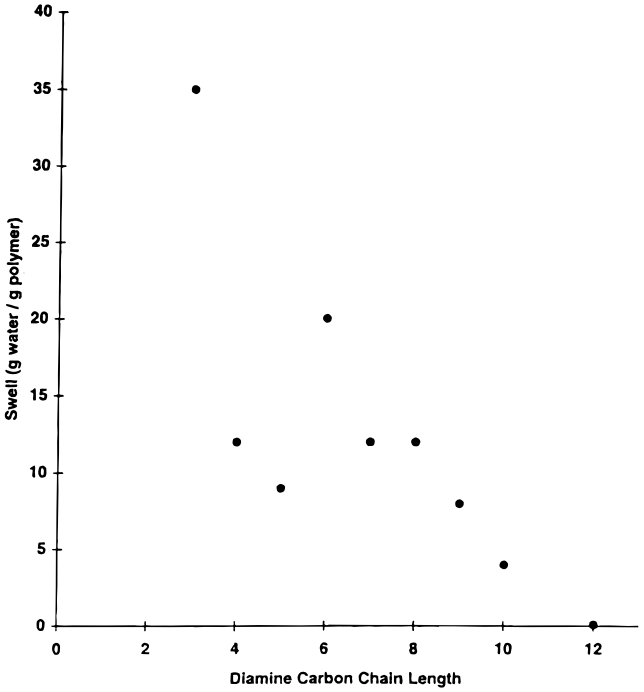



**Figure 1.** Swell as a function of diamine chain length for decane-based hydrogels.

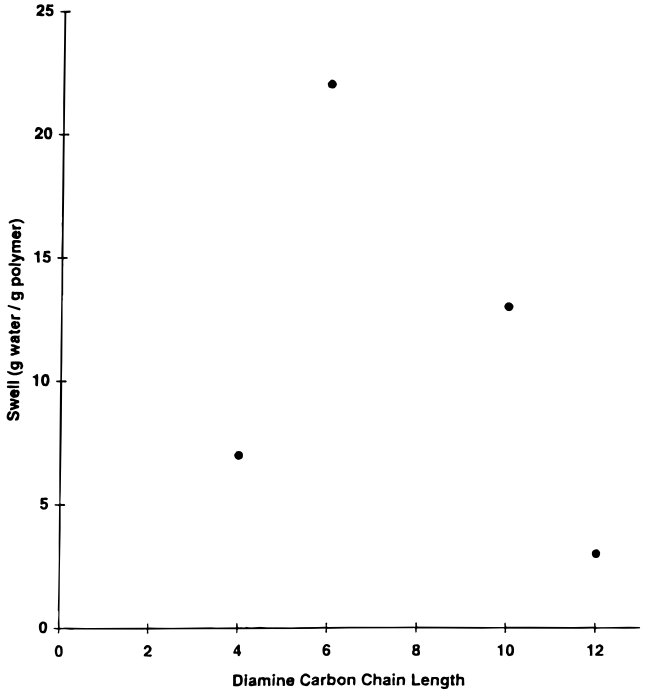



**Figure 2.** Swell as a function of diamine chain length for *p*-xylene based-hydrogels.

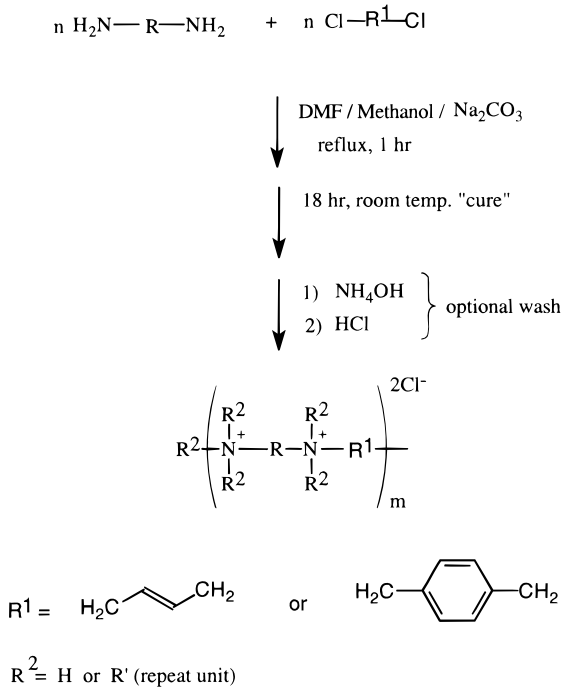
Polymer **2** exhibits significantly enhanced swell, probably due to a high concentration of ionic character (only three carbons separate ionic centers) which impart a high degree of hydrophilic character. The low swell values of polymers **3** and **4** (four and five carbon diamines) may be explained by excessive cross-link density or incomplete ionization of the nitrogen centers to ammonium ions. Polymer **11** may show enhanced swell due to decreased cross-link density caused by steric hindrance of the amine site closest to the methyl substituent. In contrast to the previous examples, added polar or hydrophilic character significantly enhances water absorption (see polymers **10**, **13**, **14**, and **15**).

Table 2 summarizes polymers and copolymers prepared to contain sidechains originating at the amine chain-link points. Generally, these polymers tend to swell more—presumably due to lowered cross-link density resulting from steric hindrance of the reactive amine site. When co-polymers are produced which contain linear aliphatics, swell values tend to be similar to those observed in Table 1.

As stated previously, the use of saturated dichloroaliphatics produces an inferior polymer with greatly reduced yield due to poor reactivity with amines under our polymerization conditions. Generally, chlorinated ingredients are desirable for use in the synthesis due to factors of mass, cost, and desirability of the chloride counterion in pharmaceutically active formulations. We have found that "activated dichlorides" which bear chlorine atoms conjugated to $\pi$ electron systems readily react to form polymer. Thus, *trans*-1,4-dichloro-2-butene and $\alpha,\alpha'$-dichloro-*p*-xylene readily produce hydrogel structures when polymerized with a wide variety of diamines. Scheme 3 illustrates these polymerizations. Tables 3 and 4 summarize examples of polymers which can be produced under these conditions.

Both *trans*-1,4-dichloro-2-butene and $\alpha,\alpha'$-dichloro-*p*-xylene are significantly more rigid than saturated long chain aliphatics. Therefore, the polymers produced from these ingredients tend to yield a more fixed structure

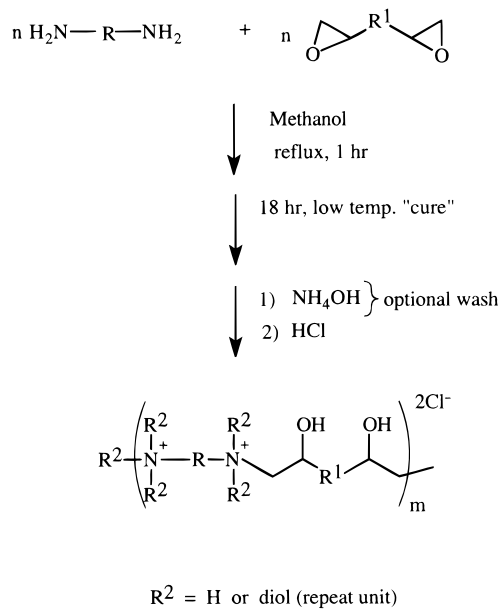
**Scheme 3**




which is less able to "stretch" to accommodate large quantities of imbibed water. Thus, the polymers described in Tables 3 and Table 4 tend to exhibit somewhat lower swell values. Note, however, that low yields (low cross-link density) and polar polymer ingredients still tend to increase the resulting polymer's ability to absorb water. The dichlorinated ingredients also provide dihalide derived links shorter than seven carbon atoms in length which will not undergo "back-biting" due to their rigid nature. Thus, polymeric structures with enhanced nitrogen density can potentially be produced with these ingredients.

Figure 2 illustrates swell level as a function of diamine chain length (hydrophobic character) in our

**Scheme 4**




*p*-xylene-based polymers. As in Figure 1, swell tends to decrease as diamine length increases except for diamines spaced with fewer than six methylene groups, where swell is quite low. This swell behavior again implies increased reactivity for the short chain diamine leading to higher cross-link density and/or an inability to attain fully ionized nitrogen centers to produce ammonium species. Both sets of data suggest preferred spacing for ionic centers to achieve desired swell values.

An alternate methodology for the production of novel hydrogel structures makes use of the reactivity of diepoxides with diamines. As illustrated in Scheme 4, we have found that an appropriately chosen diepoxide will react with a number of diamines to produce highly swellable hydrogel structures. As with the previous reactions, the polymerization is usually quite rapid when conducted in methanol. A possible advantage to this methodology is the absence of a halogen-derived counterion until it is introduced as desired through acidification. Additionally, the added hydroxyl functionality carried along the backbone of the polymer affects the hydrophilic nature of the hydrogel. Table 5 summarizes examples of hydrogels prepared with various diepoxides.

Generally, these reactions proceed very rapidly to the gel point and produce high yields of polymer. Although hydroxyl groups are available along the backbone of these polymers, swell values tend to be moderate to low. It should be noted, however, that the use of the more hydrophilic JEFFAMINEs tends to produce higher swell hydrogels. The generally lower swell values are probably due to a relatively high cross-link density. Rapid polymerization producing high yields of gelled polymer would tend to favor enhanced cross-link density and thus produce lower swelling hydrogels.

**Characterization.** The polymers reported in this paper are all cross-linked polymeric structures. These structures are infinite networks whose molecular weight is only bounded by the size of the polymer granules themselves.[15] The samples are completely insoluble and nonmeltable; thus, modes of characterization were used which explore the polymer's molecular structure and thermal characteristics. Many of the polymers reported have been partially characterized; however, polymer **1** has been fully characterized using all of the methods

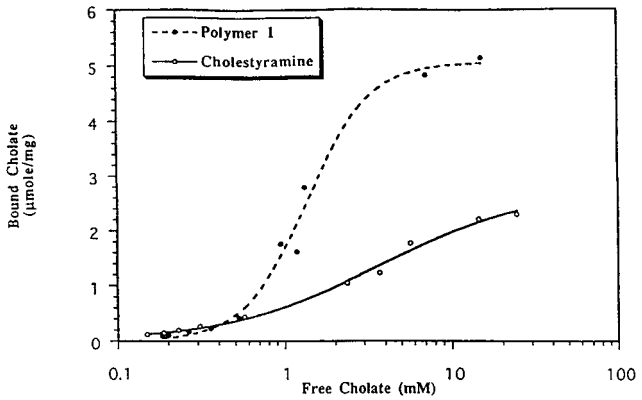



**Figure 3.** Cholate equilibrium binding of polymer **1** and cholestyramine.

herein described and is generally considered representative of the hydrogels reported in this paper. Our purpose is not to report full characterization of all of the polymers herein synthesized; instead, we wish to exemplify appropriate methodologies for use in characterization of this family of hydrogels.

**Bile Acid Binding Studies.** The bile acid binding ability of our new hydrogels prepared in Table 1 was determined by allowing $^{14}C$ labeled bile acids to equilibrate with the polymers at varying concentrations to generate a plot as illustrated in Figure 3. The data was analyzed using a ligand−ligand interaction model isotherm represented by the following equation:[12]

$$B = (B_{max}/2)\{1 + ((F/K_d) - 1)/[((F/K_d) - 1)^2 + (4F/\omega K_d)]^{1/2}\}$$

The maximum binding concentration ($B_{max}$), expressed as $\mu$mol (bound bile salt)/mg (polymer), is determined by the value of the upper plateau region (Figure 3). The equilibrium dissociation constant ($K_d$), expressed in units of mM, is the concentration of free bile salt at which there is half maximal binding. $F$ is the free bile acid concentration, and $\omega$ is the ligand−ligand interaction parameter or cooperativity parameter and reflects cooperativity in bile acid binding. A steeper inflection yields a large $\omega$ value and indicates more positive cooperativity associated with binding. In general, a polymer will bind a large quantity of bile acid very tightly when $B_{max}$ and $\omega$ are high and $K_d$ is low. It is often convenient to use $B_{max}/K_d$ as a measure of binding efficiency. $B_{max}/K_d$ reflects both the total number of binding sites or binding capacity and the binding affinity of the bile acid sequestrant for bile acid. The higher this ratio is, the more effective a bile acid sequestrant is predicted to be. Table 6 summarizes the binding properties of some of the polymers. For these hydrogels, $B_{max}$ values range from ~2.6 to ~5.9 $\mu$mol/mg and $K_d$ values span a range from ~0.6 to ~1.35 mM, depending on polymer composition. Values of $B_{max}/K_d$ encompass a somewhat narrower range (~3.2 to 5.9 $\mu$mol/(mg/mM)). All of the polymers exhibit $\omega$ values greater than 1; some are very high. This implies that the binding of one bile acid facilitates the binding of other bile acids. Table 6 also contains values for cholestyramine.

In general, our new hydrogel polymers **1**−**15** exhibit enhanced $B_{max}$ and lower $K_d$ values than cholestyramine. The superior $B_{max}/K_d$ exhibited by these new hydrogels indicate that they should provide significantly enhanced bile acid sequestration. Preclinical studies demon-

**Table 6. Binding of Methylcholate with Polyammonium Hydrogels**

| polymer | $B_{max}$ | $K_d$ | $\omega$ | $B_{max}/K_d$ |
|---|---|---|---|---|
| cholestyrami ne | 3.53 | 9.06 | <1 | 0.39 |
| **1** | 5.12 | 1.34 | 7.55 | 3.82 |
| **2** | 4.51 | 1.11 | 4.65 | 4.06 |
| **3** | 5.88 | 1.25 | 7.89 | 4.70 |
| **4** | 3.03 | 0.79 | 9.0 | 3.84 |
| **5** | 4.05 | 0.96 | 2.93 | 4.22 |
| **6** | 5.34 | 1.02 | 2.40 | 5.24 |
| **7** | 3.53 | 0.60 | 1.09 | 5.88 |
| **8** | 3.34 | 0.58 | 1.27 | 5.76 |
| **9** | 2.68 | 0.61 | 1.02 | 4.39 |
| **10** | 5.26 | 0.90 | 3.28 | 5.84 |
| **11** | 4.70 | 1.02 | not calcd | 4.05 |
| **15** | 3.35 | 1.16 | 1.07 | 3.28 |

strated that polymer **1** does indeed provide enhanced in vivo bile acid binding, leading to improved reduction in cholesterol levels over incumbent cholestyramine.[16] Additionally, clinical studies attest to polymer **1**'s safety, tolerability, and cholesterol-lowering activity in hypercholesterolemic subjects.[17]

**Solubility.** All of the previously described hydrogels have been found to be insoluble in water, ethanol, methanol, acetone, dimethylformamide, ethylene diamine, butyl alcohol, hexane, DMSO, dimethylacetamide, chloroform, methylene chloride, carbon tetrachloride, toluene, acetic acid, and sulfuric acid (10%) at solids levels of 0.5−2% and room temperature. Elevated temperatures do not induce solubility. Attempts to induce solubilization by neutralizing the polymer to a free polyamine and then exposing it to the listed solvents failed. The complete insolubility of these polymers is taken as evidence of the presence of a cross-linked network structure.[15]

**Swell.** In general, swell in water is controlled by polymer cross-link density and hydrophilicity as brought about by ionization of the nitrogen centers to ammonium species. When ionized to a polyammonium structure via exposure to acid, the subject polymers exhibit swell behavior when exposed to various solvents. Relatively nonpolar hydrocarbons tend to produce very little swell, while more polar solvents (e.g., water, methanol, DMSO, formic acid, sulfuric acid, *N*-methylacetamide, and *N*-methylformamide) can produce significant swell. In order to quantify the swell characteristics of each polymer a known weight of polymer is exposed to a large excess of deionized water at room temperature for 15 min. Upon drying the sample either at room temperature (for days) or in an oven, the hydrogels completely deswell and revert to near their original volume. Further exposure to water again swells the polymer fully. When the hydrogels exist as polyalkylammonium species, they readily undergo completely reversible swelling when exposed to water and deswelling when dried. The details of swell measurement are discussed in the experimental section of this paper. The polymers can also be reversibly deswollen by exposure to aqueous media of pH 10 or greater. Nitrogen centers found in polymer treated in this manner exist as free amine centers and do not exhibit enough hydrophilicity to produce significant swell. Again, upon further exposure to acid media (to create ammonium centers), all swell characteristics of the polymers are regained.

The use of these polymers for internal consumption as bile acid sequestrants precludes their preparation for maximum swell characteristics. In fact, maximum bile acid binding activity at minimal swell is highly important, since a high degree of swelling in the digestive tract could be quite uncomfortable and physiologically dangerous. We have found that a minimum swell value of ∼10 g of water/g of polymer is required to achieve maximum bile acid binding interactions in vivo. Swell can be controlled by judicious choice of such reaction conditions as solvent, monomer concentration, temperature, reaction time, the addition of base (e.g. sodium carbonate), and agitation. Solvent effects can be quite large in the synthesis of these polymers. Some reaction solvents used alone, such as water or ethanol, produce polymers which swell very little in water. However, a number of mixed solvent combinations, and occasionally neat methanol, produce highly water swellable polymers. We have yet to find any clear correlation between any type of solvation parameter and final swell properties achieved in the resulting polymer.

**Moisture Regain.** Polymer samples were exposed to various levels of relative humidity for 3−5 week periods, after which time a Karl-Fischer determination of water content was performed. Even at 0% relative humidity approximately 1% water was present in the polymer—indicating the inherent difficulty of completely drying these hydrogels. At humidity ranges from 15% to 85%, a moisture content of 4−14% was observed. At 100% relative humidity, the polymers are found to contain >60% water. It is important to note that although these polymers can absorb many times their mass in water, under normal atmospheric humidity an equilibrium value of 5−10% moisture is maintained within the polymer structure.

**Thermal Analyses.** Differential scanning calorimetry (DSC) was performed on polymer **1** after it was thoroughly dried. DSC analysis on undried polymer produces variable glass transition ($T_g$) values dependent on moisture content. Initial heating produces a very broad endotherm centered at ∼120 °C; however, cooling analysis does not reveal any recrystallization. This behavior may be a combination of glass transition, stress-relaxation, and water evaporation. A second heat cycle produces a shallow $T_g$ at ∼70 °C and no endotherm. These observations are entirely consistent with initial residual moisture retention within the polymer structure and its subsequent release upon heating. Once the water is driven off, the endotherm is no longer present and a relatively dry $T_g$ can be observed. The DSC analysis of polymer **1** indicates a highly amorphous structure.

Thermal gravimetric analysis (TGA) of polymer **1** indicates that the polymer is quite stable up to ∼300 °C (5−10% weight loss). The initial weight loss at a relatively low temperature is 2%. The polymer then remains quite stable close to 300 °C. The 2% low temperature weight loss is again consistent with the loss of residual water contained in the polymer. Additional TGA-IR analyses have confirmed that water is indeed lost very rapidly from the polymer.

**NMR.** Although the hydrogels described in this paper are all covalently cross-linked, and therefore insoluble, all of the polymers are highly swellable in aqueous media. Swollen polymer behaves as a very concentrated solution and allows acquisition of excellent NMR spectra. The polymers can be first slurried in deuterated dioxane, which induces a slight swelling. They are then further swollen to the desired degree by addition of appropriate amounts of deuterated water. The use of this media and an inverse decoupling sequence (to suppress the nuclear Overhauser effect) using a 20−30 s preacquisition delay and heating to 75 °C produces

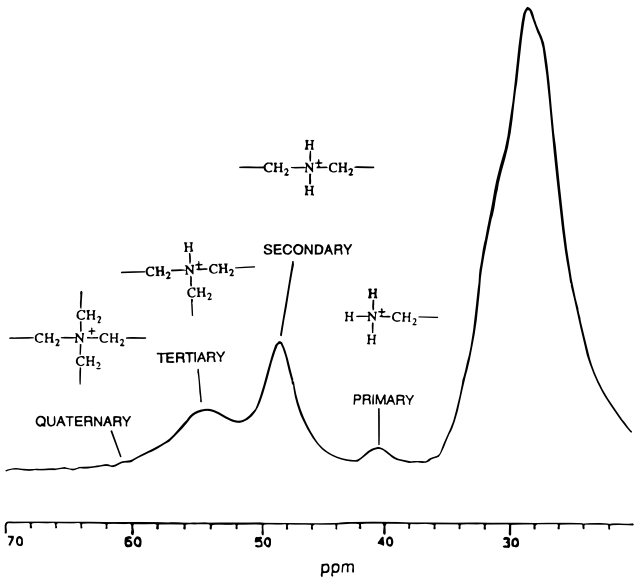



**Figure 4.** Magic-angle spinning/Bloch decay/solid-state carbon-13 NMR spectrum (90 MHz) of unswollen polymer **1**.

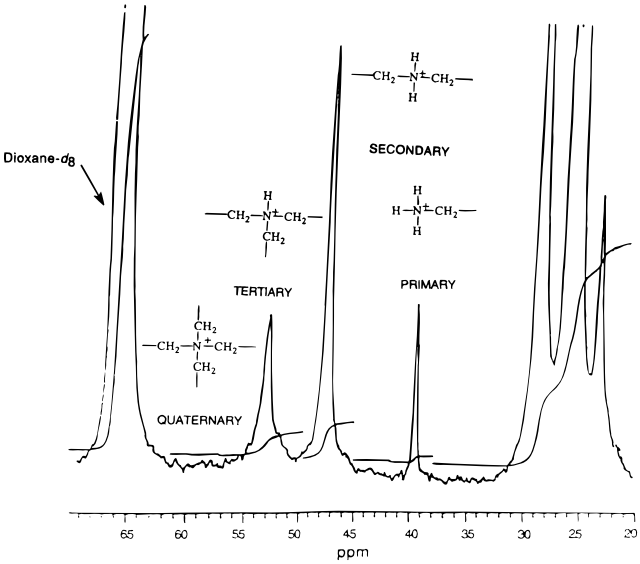



**Figure 5.** Solution-state carbon-13 NMR spectrum at 75 MHz of swollen polymer 1 in deuterated dioxane/water at 75 °C.

excellent $^{13}$C NMR spectra. However, this methodology is difficult to reproduce and carries a high level of uncertainty as to whether the entire polymer sample is represented in the spectra obtained. (If portions of the polymer swell less than others, relaxation times could vary and final spectra would not be representative of the entire sample.) $^{13}$C NMR spectra of excellent resolution and reproducibility can be obtained via solid state (magic-angle spinning with MAS−Bloch decay) techniques performed on the swollen polymer gel after all excess solvent is removed. This methodology takes advantage of the greater mobility of the polymer in a "solvated" state along with the solid state techniques which allow analysis of all the carbon atoms in the sample. The method is also highly reproducible. Figures 4−6 compare $^{13}$C NMR spectra of polymer **1** run in the unswollen state as a solid (Figure 4); run in the swollen state as a "solution" (Figure 5), and run in the swollen state as a "solid" (Figure 6). It is clearly evident that the spectra of Figure 6 provides the highest resolution (note that the carbons adjacent to quaternary

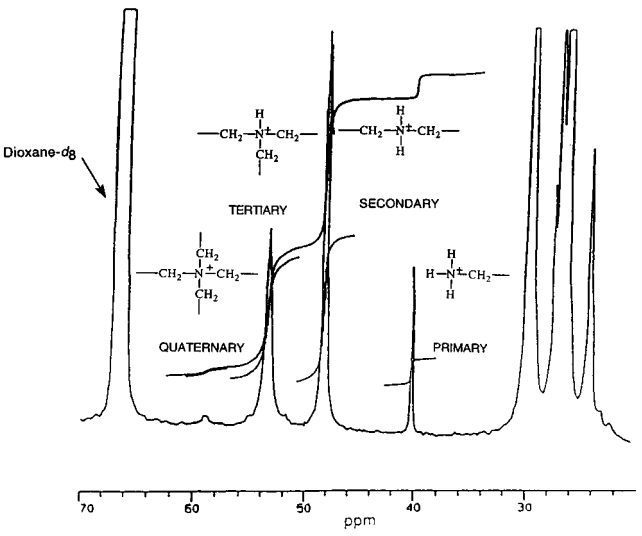



**Figure 6.** Magic-angle spinning/Bloch decay/solid-state carbon-13 NMR spectrum (90 MHz) of swollen polymer **1** in deuterated dioxane/water after vacuum filtering.

amines are readily observed, whereas they are virtually undetectable via the other methods).

The downfield signals of Figure 6 at 40, 49, 53, and 59 ppm correspond to carbon atoms immediately adjacent to primary, secondary, tertiary, and quaternary ammonium ions respectively (as confirmed by model compounds). For polymer **1** all additional carbon signals occur upfield as defined in the Experimental Section. Integration of the downfield peaks can be normalized to represent the relative abundance of nitrogen atom types by dividing each integral by the number of carbons surrounding that nitrogen type. For example, the peak at 49 ppm would be divided by 2 (two carbon atoms are associated with a secondary ammonium nitrogen). Upon normalizing the peak areas, it can be calculated that polymer **1** contains approximately 21% primary nitrogens, 50% secondary nitrogens, 28% tertiary nitrogens, and 1% quaternary nitrogens. The primary nitrogens are, by necessity, end groups. Approximately half of the nitrogens are secondary and must make up linear portions of the polymer between branches and cross-links. Finally, 29% of the nitrogens are tertiary or quaternary and must be considered junction points within the network which lead to either branching or cross-linking. The high swell values associated with these polymers would indicate a rather low level of cross-linking and, therefore, high branch levels.[15]

**Crosslink Density.** The cross-link density of polymer **1** is calculated to be $5.2 \times 10^{-5}$ mol/cm$^3$ (~1% of available nitrogens) via solvent swelling. This value is calculated from equilibrium swelling data by means of the Flory−Rehner equation,[18] which relates $v_e$ to parameter $v_2$. The measurable $v_2$ is the volume fraction of polymer in a sample which has reached its equilibrium swollen state. $X_1$, the interaction parameter, is assumed to be 0.35, judging from similar interactions between polymer and solvent; the cross-link functionality $f$ is assumed to be 3. No quaternary cross-links are assumed in this calculation.

$$v_e = -[\ln(1 - v_2) + v_2 + \chi_1 v_2^2][V_1(v_2^{1/3} - 2v_2/f]^{-1}$$

and

$$v_2 = (1/\rho_p)\,[(SR/\rho_s) + (1/\rho_p)]^{-1}$$

where $v_e$ is the cross-link density in mol/cm$^3$, $V_1$ is the molar volume of solvent = 18.062 cm$^3$/mol for water, $\chi_1$ is the solvent-polymer interaction parameter ~0.35, f is the cross-link functionality ~3, $\rho_p$ is the polymer density = 1.1589 g/cm$^3$, $\rho_s$ is the density of the water at 25 °C = 0.9971 g/cm$^3$, and SR is the swell ratio, grams of solvent sorbed per gram of polymer = 19.036 g/g.

**Elemental Analysis.** The analysis of polymer **1** shows 58.03% C, 10.50% H, 7.60% N, and 18.84% chlorine. Calculated values based on a linear, nonbranched structure of very high molecular weight are 58.72% C, 11.01% H, 8.56% N, and 21.71% Cl. A worst case estimate indicates that we have achieved at least 85% hydrochlorination for polymer **1**. The discrepancy of actual and calculated elemental content may be caused by a number of factors including incomplete hydrochlorination, branching and cross-linking, and the presence of a small amount of water and ethanol (a final wash solvent) entrapped within the polymer's structure.

**Infrared Analysis.** FT-IR analysis of polymer **1** exhibits strong bands at 3400−2400 cm$^{-1}$ which correspond to C−H and N−H stretching modes. Weaker bands are observed at 2010, 1860, and 1580 cm$^{-1}$, characteristic of bending and stretching modes associated with ammonium ions. A prominent strong band at 1465 cm$^{-1}$ and a weaker one at 1385 cm$^{-1}$ are bending modes for the $-(CH_2)_x-$ chains. A broad band at 1040 cm$^{-1}$ represents C−N stretching modes. A small band at ~790 cm$^{-1}$ is attributed to N−H bending within the ammonium species, and a final band at 725 cm$^{-1}$ is characteristic of bending associated with hydrocarbon chains greater than 4 methylene groups in length. When the polymer is prepared in a media containing DMF, a spurious peak is observed at 1680 cm$^{-1}$. Further analysis via model compounds and $^{13}$C NMR indicate that this signal may be derived from a formamide carbonyl group bearing a methylene functionality.

**Counterions.** Polymer **1** was prepared with a number of different counterions, including chloride, bromide, iodide, phosphate, nitrate, sulfonate, acetate, propionate, formate, and citrate. In all cases the polymer retains its hydrogel character; however, swell factors and polymer characteristics vary dependent on the choice of counterion. Generally, small inorganic counterions provide polymer which is quite glassy and brittle when dry and exhibits maximum swell when hydrated. Larger organic-based counterions (e.g. acetate, propionate, formate, citrate) tend to yield polymer which is "soft" or "rubbery" when dry and swells to a lesser degree when exposed to water. Larger inorganic counterions (e.g. phosphate, nitrate, sulfonate) tend to increase hygroscopicity and decrease overall swell in water.

## Summary and Conclusions

A number of novel polyammonium-derived hydrogels have been prepared via synthetic methodology which takes advantage of the reactivity of various organic dihalides or diepoxides with amines. The polymers readily swell in water when the nitrogens contained in the structure have been converted to their ionic ammonium form. Swell values depend on the polar nature of the polymer, the relative stiffness of the polymer chains, and the level of cross-linking attained in the system. Generally, polymers which are less stiff (more amorphous or less crystalline) will exhibit a greater degree of swell than polymers derived from stiff ingredients. Polymers which are relatively more polar (or hydrophilic) in nature tend to swell more, as do polymers which exhibit a lower cross-link density. Lower cross-link densities tend to correlate with lower isolated yields of insoluble polymer since cross-linking is responsible for insolubility. Thus, often polymers which are produced in low yield exhibit very high swell. Neutralization of the ionic nitrogens to free amine causes immediate deswelling. Complete characterization of polymer **1** indicates that the polymer is a highly branched, lightly cross-linked network which is quite thermally stable in the ionic form. We have observed similar characteristics for all polymers reported in this paper. The ionic and aqueous swell characteristics of these polymers makes them well-suited candidates for sequestration of bile acids. Initial studies indicate that these novel polymers do indeed exhibit superior bile acid sequestration ability over that of commercial cholestyramine.

## References and Notes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MA9702509