**Title:** POLYQUATERNIUM-I SYNTHESIS METHODS

**Abstract:** The present embodiments relate to a novel method of making quaternary ammonium polymers comprising the steps of: a) mixing 1,4-bis-dimethylamino-2-bulene, triethanolamine, water and an acid; and b) introducing a 1,4-diha!o-2-butene to the mixture so as to initiate a reaction resulting in the quaternary ammonium polymer.

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**Figure 3a**

![Graph showing absorption vs. retention time](image)
POLYQUATERNIUM-1 SYNTHESIS METHODS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present embodiments relate to novel synthesis methods for polyquaternium-1 and related molecules.

Description of the Related Art

[0002] Quaternary ammonium polymers in which the ammonium moieties are part of the linear polymeric chains have been used as antimicrobial agents in several industries. Polyquaternium-1 (PQl) is a polymeric quaternary ammonium anti-microbial agent that has been used, for example, in preserving ophthalmic compositions and disinfecting contact lenses. PQl is effective against bacteria, algae and fungi.

[0003] U.S. Patent No. 3,931,319, which is hereby incorporated in its entirety by reference, describes a two-step method for PQl synthesis which requires a high reaction temperature. This leads to significant degradation of the target molecule into impurities from which the desired PQl is difficult to separate.

[0004] U.S. Patent No. 4,027,020, which is hereby incorporated in its entirety by reference, describes a procedure for polyquaternium-1 synthesis which results in less degradation of the resulting PQl than the method described in U.S. 3,931,319 but still produces a rather low yield. The procedure disclosed in U.S. 4,027,020 entails mixing 1,4-bis-dimethylamino-2-butene with triethanolamine (TEA), the molar ratio of the 1,4-bis-dimethylamino-2-butene to the TEA amine being from 2:1 to 30:1 followed by the addition of 1,4-dichloro-butene to the mixture in a molar amount equal to the sum of the molar amount of the 1,4-bis-dimethylamino-2-butene plus one-half the molar amount of TEA. The reaction time is 1-10 hours.

[0005] A major weakness of the method taught in U.S. 4,027,020 is that the TEA end-capping efficiency is low. As such, the final product contains a significant amount of polymers with no end caps or polymers end-capped with groups other than TEA. These malformed polymers are difficult to separate from polyquaternium-1 because of the similarity
in the main chain of the polymeric molecules. Degraded or malformed polymers of PQI have reduced anti-bacterial efficacy and cannot substitute for PQI in clinical use.

SUMMARY OF THE INVENTION

Some embodiments relate to a method of making one or more quaternary ammonium polymers comprising the steps of:

a) mixing 1,4-bis-dimethylamino-2-butene, triethanolamine and an acid; and

b) introducing a 1,4-dihalo-2-butene to the mixture so as to initiate a reaction resulting in the quaternary ammonium polymer.

In some embodiments, the 1,4-dihalo-2-butene is 1,4-dichloro-2-butene.

In some embodiments the quaternary ammonium polymers comprise Polyquaternium-1.

In some embodiments the acid is selected from the group consisting of HCl, H₂SO₄ and H₃PO₄.

In some embodiments the acid is HCl.

Some embodiments further comprise the step of adding water to the mixture.

In some embodiments the 1,4-bis-dimethylamino-2-butene, triethanolamine and acid are mixed before the addition of the 1,4-dihalo-2-butene.

In some embodiments the 1,4-dihalo-2-butene is added drop-wise.

In some embodiments the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine is from about 10:1 to about 1:5.

In some embodiments the molar ratio of triethanolamine to acid is from about 10:1 to about 1:10.

In some embodiments the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine to acid is from about 10:9:5 to about 10:9:8.

In some embodiments the reaction temperature is from about 10 °C to about 90 °C.

In some embodiments the reaction time is from about 1 hour to about 40 hours.

Some embodiments relate to a method of making Polyquaternium-1 at a yield of at least about 50% comprising the steps of:
[0022] a) mixing 1,4-bis-dimethylamino-2-butene, triethanolamine and an acid; and

[0023] b) introducing a 1,4-dihalo-2-butene to the mixture so as to initiate a reaction.

[0024] In some embodiments the acid is selected from the group consisting of HCl, H₂SO₄ and H₃PO₄.

[0025] In some embodiments the 1,4-dihalo-2-butene is 1,4-dichloro-2-butene.

[0026] In some embodiments the acid is HCL.

[0027] Some embodiments further comprise the step of introducing water into the mixture.

[0028] In some embodiments the 1,4-bis-dimethylamino-2-butene, triethanolamine and acid are mixed before the addition of the 1,4-dichloro-2-butene.

[0029] In some embodiments the 1,4-dichloro-2-butene is added drop-wise.

[0030] In some embodiments the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine is from about 10:1 to about 1:5.

[0031] In some embodiments the molar ratio of triethanolamine to acid is from about 10:1 to about 1:10.

[0032] In some embodiments the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine to acid is from about 10:9:5 to about 10:9:8.

[0033] In some embodiments the reaction temperature is from about 10 °C to about 90 °C.

[0034] In some embodiments the reaction time is from about 1 hour to about 40 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] FIG. 1 shows GPC chromatograms for the products of the reaction as described below in comparative example 1 with no acid added to the reaction mixture.

[0036] FIG. 2 shows the spectrum of the large PQI molecules at retention time of 6.3 minutes and at 9.5 minutes of the products of the reaction as described below in comparative example 1 without acid added.

[0037] FIG. 3 shows the GPC chromatograms for the products of the reaction as described in example 1 with acid added.
FIG. 4 shows the spectra of the synthesized crude product at 6 hours reaction time at 6.3 and 9.5 minutes retention time, respectively of the products of the reaction described in example 1 with acid added.

FIG. 5 shows the GPC chromatograms for the products of the reaction as described in comparative example 2.

DETAILED DESCRIPTION

The present embodiments relate to methods for the synthesis of quaternary ammonium polymers. Some embodiments relate to methods for the synthesis of PQI. Some methods involve the addition of acids to the reaction admixture to prevent impurity generation and the degradation of the synthetic quaternary ammonium polymers, including PQI during the synthesis of the compounds. Recent experiments have shown that past methods of synthesis of quaternary ammonium polymers as described above are not as efficient as originally thought. This is due in party to the fact that too little TEA is used in the reaction admixture.

Without intending to be bound by the structures shown, in some embodiments, PQI can be synthesized by the following reaction:

\[
\begin{align*}
\text{Cl}^- & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{Cl}^-
\end{align*}
\]

\[
\begin{align*}
\text{Cl}^- & \quad \text{N} & \quad \text{N} & \quad \text{Cl}^-
\end{align*}
\]

\[
\begin{align*}
\text{Cl}^- & \quad \text{N} & \quad \text{N} & \quad \text{Cl}^-
\end{align*}
\]

\[
\begin{align*}
\text{Cl}^- & \quad \text{N} & \quad \text{N} & \quad \text{Cl}^-
\end{align*}
\]
Some embodiments relate to a method of synthesizing PQI which includes the addition of acid to the admixture. Regardless of the molar ratio of TEA used, PQI synthesized with the methods described in patents 4,027,020 and 3,931,319 invariably results in significant PQI degradation during the reaction process. The molecular structure of PQI can be expressed as:

\[
(HOCH_2CH_2)_nN\underset{+}{|}\underset{Cl^-}{|} \underset{+}{|}\underset{Cl^-}{|} \underset{+}{|}\underset{Cl^-}{|} N(CH_2CH_2OH)_3
\]

The majority of the degraded molecules are:

A) \((HOCH_2H_4)3NCH2CH=CHCH2(N(CH3)2CH2CH=CHCH_2)_n\cdot N(CH3)2\)

and

B) \(H_2C=CHCH=CH(N(CHS)_2CH_2CH=CHCH_2)_n\cdot N(HOC\_H_2OH)_3\).

These degraded molecules are very difficult to separate from PQI since both are polymeric quaternary amine-based like PQI. Degraded or malformed polymers of PQI have reduced anti-bacterial efficacy and cannot be substituted for PQI in clinical use.

It is known in the literature that \((HOCH_2H_4)3NH+\) is not a nucleophilic agent and does not normally react with \(ClCH2CH=CH2(K(CH3)2CH2CH=CHCH2)n\cdot 1N(CH3)2CH2CH=CHCH2Cl\) in the end-capping step of the reaction to form PQI. Therefore, the current literature view is that acids should be avoided in the nucleophilic reaction of the present embodiments for fear that acid could convert the nucleophilic agent \((HOCH_2H_4)3N\) into inactive \((HOCH_2H_4)3NH+\) ions. However, contrary to the current literature view, the present embodiments relate to a synthesis wherein the addition of acid to the reaction mixture does not prevent the TEA end-capping reaction.

In the methods of the prior art that do not include the addition of acid to the reaction mixture, when 1,4-bis-dimethylamino-2-butene, triethanolamine and water are mixed, the hydroxide concentration is very high, usually greater than about \(10^{-3}\) M. Since the nucleophilicity of hydroxide is much stronger than that of TEA and 1,4-bis-dimethylamino-2-butene, large amounts of 1,4-dihalo-2-butene are attacked by hydroxide in the prior art methods, resulting in \(HOCH_2CH=CHCH_2Cl\) or \(HOCH_2CH-CHCH_2OH\). As discussed below, hydroxide also competes with TEA in the end-capping reaction of PQI resulting low yield.
and high impurities for PQl. Therefore, in the present embodiments the presence of acid is advantageous in the reaction admixture to prevent PQl degradation, improve the reaction yield and reduce product impurity, regardless of the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine.

[0049] In some embodiments, significant PQl degradation during the synthesis process can be prevented by adding acid to the reaction admixture. As shown in the Examples and figures below, addition of acid greatly reduces the formation of degraded impurities and increases the yield of PQl in the reaction.

[0050] Some embodiments relate to a synthesis method of PQl involving 1,4-dihalo-2-butene. The 1,4-dihalo-2-butene can be, for example, 1,4-dichloro-2-butene, 1,4-difluoro-2-butene, 1,4-dibromo-2-butene, 1,4-diiodo-2-butene. In a preferred embodiment, the 1,4-dihalo-2-butene is 1,4-dichloro-2-butene.

[0051] The following examples are provided for illustrative purposes only, and are in no way intended to limit the scope of the present invention.

**COMPARATIVE EXAMPLE 1**

[0052] PQl was synthesized as described in U.S. Patent No. 4,027,020 using a reactant admixture of 1,4-bis-dimethylamino-2-butene with TEA in which the molar ratio of 1,4-bis-dimethylamino-2-butene to TEA was about 5:1 and the molar ratio of 1,4-dichloro-butene to 1,4-bis-dimethylamino-2-butene was about 1.1:1. The reaction was carried out at 65 °C. The proton NMR spectra were obtained for the final product after it was purified with ultrafiltration. The results are summarized in Table 1, where the peaks at the chemical shift of 6.5 ppm and 3.7 ppm are for vinyl protons in repeating units and alylic protons adjacent to the nitrogen in the ending group of the PQl molecules, respectively.

[0053] Table 1 one shows that the TEA end-capping efficiency is low in 6 hours reaction at which the reaction was believed by the authors of the 4,027,020 patent to be complete. The reaction time was then extended from 6 to 10 hours and the results show that the amount of proton in the end cap group of the polymers is still increasing. Therefore, the
end-capping reaction for PQl synthesis is not completed at 6 hours and is approximately only 71% complete.

Table 1

<table>
<thead>
<tr>
<th>Reaction Time</th>
<th>Peak area at 6.5 ppm Chemical shift</th>
<th>Peak area at 3.7 ppm Chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hours</td>
<td>1.000</td>
<td>0.0343</td>
</tr>
<tr>
<td>10 hours</td>
<td>1.000</td>
<td>0.0481</td>
</tr>
</tbody>
</table>

[0054] The low end-capping efficiency is due to the low amount of TEA in the reactant admixture. The low TEA concentration in the reaction mixture slow down its kinetic reaction rate with \( \text{C}_1\text{CH}_2\text{CH}-\text{CHCH}_2(\text{N(CH}_3)_2\text{CH}_2\text{CH}=\text{CHCH}_2)_n\text{CH}_2\text{CH}=\text{CHCH}_2\text{Cl} \). Meanwhile, water molecules and hydroxide ions (OH-) in the solution may compete with TEA to form \( \text{OHCH}_2\text{CH}=\text{CHCH}_2(\text{N(CH}_3)_2\text{CH}_2\text{CH}=\text{CHCH}_2)_n\text{CH}_2\text{CH}=\text{CHCH}_2\text{OH} \).

[0055] FIGs Ia, Ib and Ic represent the GPC chromatograms for PQl synthesized with admixtures of 1 mole of 1,4-bis-dimethylamino-2-butene, 0.9 moles of TEA, and 1.15 moles of 1,4-dichlo-butene at 65 °C at 2, 6 and 10 hours respectively. A GPC-HPLC chromatograph was used to trace the PQl molecular size. The experimental conditions were: an aqueous solution of 0.045 M \( \text{KH}_2\text{PO}_4 \), 0.45% NaCl and 9.1% \( \text{CH}_3\text{CN} \) as a mobile phase in a Phenomenex BioSep-SEC-S 2000 column and an Agilent 1100 Series HPLC system equipped with PDA detector. PQl molecules have an absorbance peak at 205nm but do not have an absorbance peak at 228 nm. However, the degraded molecules have an absorbance maximum at 228 nm. Therefore the detection wavelengths of 205 nm and 228 nm are used to trace PQl and its degradated segments, respectively, during the reaction process.

[0056] The broad peak shown in FIGs Ia, Ib and Ic which ranges from 6 to 10 minutes retention time represents polymeric molecules of PQl and its degraded products. The larger the polymeric molecules, the shorter the retention time will be. The water solvent peak locates at about 10 minutes. The peaks beyond 10 minutes represent non-polymeric small molecules of either the reactants or bi-products.

[10057] As can be seen in FIG. 2, the crude PQl product synthesized as described in the 4,027,020 patent without adding acid shows absorbance at 228 nm. The absorbance
peak shifts Io a longer retention time with increase of reaction time from 8.4 min at 2 hours (see Fig Ia) to 9 minutes at 10 hours (see Fig. Ic). Figure 2 further shows that the spectrum of the large PQI molecules at retention time of 6.3 minutes has no absorbance at 228 run and that the spectrum at 9.5 minutes possess a strong absorbance at 228 nm. Clearly, there are two or more types of different polymeric quaternary amines generated in the product mixture. The large polymers are close to PQI and the small polymers correspond to the degraded PQI.

[0058] In the present embodiments, any acid can be used in the synthetic method. In preferred embodiments, the acid used does not contain a strong nucleophilic group. Preferred acids include HCl, H₂SO₄, and H₃PO₄ but the present embodiments are not limited to these acids. Additional suitable acids include acetic acid, succinic acid, and citric acid, among others.

**COMPARATIVE EXAMPLE 2**

[0059] FIG. 5 shows the GPC chromatograms for the products of the reaction as described above in Comparative Example 1 except with a specific reaction admixture of 1 mole of 1,4-bis-dimethylamino-2-butene, 1.2 moles of TEA, and 1.2 moles of 1,4-dichlorobutene at 60 °C for 18 hours. No acid was added to the reaction admixture.

[0060] The severe degradation during synthesis process is shown with strong absorption at 228 nm. The long retention time also indicates that PQI was degraded into smaller molecular size. Another indication of PQI degradation in the absence of acid is the increase of peak area at the retention time of 10.5 minutes over reaction time from FIGs 1 and 5. This peak corresponds to non-polymeric small molecules with similar absorbance spectrum maximum at 225 nm as that of 228 nm for one of the degraded PQI molecules. It is likely that all PQI will eventually be degraded in to the small molecules during reaction or storage if the time is long enough.

**COMPARATIVE EXAMPLE 3**

[0061] In order to prevent the side end-capping reaction and increase the main end-capping reaction rate, the amount of TEA in the admixture of the reactants was increased.
Table 2 shows the proton NMR spectrum data for PQI synthesized at 65°C with admixture of 1 mole of 1,4-bis-dimethylamino-2-butene, 0.9 moles of TEA, and 1.15 moles of 1,4-dichloro-butene (the molar ratio of 1,4-bis-dimethylamino-2-butene with TEA is 1.1 1:1 instead of 5:1 as in Example 1 above). The far right column of Table 2 lists the end-capping percentage over the reaction time. It can be seen that even at the presence of large excess amount of TEA, the reaction is still not complete until a time of 4 hours. See FIGs 1 and 2.

<table>
<thead>
<tr>
<th>Reaction Time</th>
<th>Peak area at 6.5 ppm Chemical shift</th>
<th>Peak area at 3.7 ppm Chemical shift</th>
<th>End-capping efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>1.000</td>
<td>0.108</td>
<td>94.7%</td>
</tr>
<tr>
<td>4 hours</td>
<td>1.000</td>
<td>0.114</td>
<td>100%</td>
</tr>
<tr>
<td>6 hours</td>
<td>1.000</td>
<td>0.114</td>
<td>100%</td>
</tr>
</tbody>
</table>

**EXAMPLE 1**

(0062) 10.14 grams (71.3 mmoles) of 1,4-bis-dimethylamino-2-butene, 6.4 grams (42.8 mmoles) of TEA, 4.92 ml of 6N HCl (29.5 mmoles), 18.8 grams of water and a stir bar were combined in a 100 ml three-mouth flask. The flask was submerged into an ice water bath. 9.8 grams of (78.4 mmoles) of 1,4-dichloro-2-butene were slowly added drop-wise into the flask under constant stirring. The ice-bath was removed after the 1,4-dichloro-2-butene was completely added and the flask was submerged in a warm-water bath (25 - 40 °C) for 20 minutes. The water bath was heated until the temperature inside the flask reached 70 °C. The reaction was stopped after 21 hours by removing the flask from the water bath. Variations can be made to the procedure by those skilled in the art for larger scale production to release the heat generated at the initial stage of the reaction before raising the temperature to above 60 °C.

(0063) FIGs 3a, 3b and 3c are the GPC chromatograms for the above admixtures with HCl added. The peak at 205 nm in each chromatogram shows the presence of PQI, while the lack of peak at 228 nm indicates the absence of degradation products. FIG. 4 is the spectra of the synthesized crude product at 6 hours reaction time at 6.3 and 9.5 minutes retention time, respectively. It can be seen that there is no absorbance at 228 nm in the whole 10 hours reaction period when the acid is added to the reaction mixture, indicating that no
degraded PQl has been formed. Fig.4 further confirms that there is no absorbance peak at 228 nm at the whole retention time range of 6 - 10 minutes. This result indicates that the addition of the acid effectively prevented the formation of degraded PQl.

Table 3
Summary of Peak Retention Time for the Products Synthesized with and without Acid

<table>
<thead>
<tr>
<th>Reaction Time</th>
<th>Peak retention time without acid</th>
<th>Peak retention time with acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>205 nm</td>
<td>228 nm</td>
</tr>
<tr>
<td>2 hours</td>
<td>6.7</td>
<td>8.4</td>
</tr>
<tr>
<td>6 hours</td>
<td>7.3</td>
<td>8.9</td>
</tr>
<tr>
<td>10 hours</td>
<td>7.6</td>
<td>9.0</td>
</tr>
</tbody>
</table>

[0064] The absorbance at 205 nm is mainly from the molecule back-bone structure. Table 3 further shows that the polymer molecular size distribution measured at 205 nm is stable in the system where the acid is added.

[0065] As one of ordinary skill in the art will appreciate, the above crude PQl products can be purified by removing the excess amount of TEA, the acid, 1,4-dichloro-2-butene and other small molecule byproduct/impurities which are shown up at the retention time of > 10 minutes in Figure 1 and 3 using methanol and/or acetone as solvents.

EXAMPLE 2
Polvquaternium-1 Synthesis Procedure for Sample #2 in Table 4

[0066] 10.14 grams (71.3 mmoles) of 1,4-bis-dimethylamino-2-butene, 6.4 grams (42.8 mmoles) of TEA, 4.92 ml of 6N HCl (29.5 mmoles), 18.8 grams of water and a stir bar were combined in a 100 ml three-mouth flask. The flask was then submerged into an ice water bath. 9.8 grams (78.4 mmoles) of 1,4-dichloro-2-butene were added (drop-wise) into the flask under constant stirring. The ice-bath was removed after all of the 1,4-dichloro-2-butene was completely added and the flask was submerged into a warm-water bath (25 - 40 °C) for 20 minutes. The water bath was heated until the temperature in the flask reached 70 °C. The reaction was stopped after 21 hours by removing the flask from the water bath.

[0067] Table 4 lists PQl synthesized with addition of acid to the reaction mixture. Each sample was prepared as described above for Sample #2 except with different molar
ratios of reactants. No absorbance was observed at 228 nm, i.e., no degradation of PQI occurred for any of the samples. The molecular weight was measured by the proton NMR method.

Table 4

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Molar ratio</th>
<th>Reaction Time</th>
<th>Reaction Temperature</th>
<th>PQI Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DA*/TEA</td>
<td>DA/DCB*/HCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.83</td>
<td>1/1.2/0.83</td>
<td>5 hours</td>
<td>70 °C</td>
</tr>
<tr>
<td>2</td>
<td>1.67</td>
<td>1/1.1/0.41</td>
<td>21 hours</td>
<td>70 °C</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>1/1.1/0.55</td>
<td>8 hours</td>
<td>75 °C</td>
</tr>
<tr>
<td>4</td>
<td>0.83</td>
<td>1/1.2/0.83</td>
<td>8 hours</td>
<td>60 °C</td>
</tr>
<tr>
<td>5</td>
<td>1.11</td>
<td>1/1.15/0.62</td>
<td>6 hours</td>
<td>60 °C</td>
</tr>
<tr>
<td>6</td>
<td>5.0</td>
<td>1/1.1/1</td>
<td>18 hours</td>
<td>75 °C</td>
</tr>
</tbody>
</table>

* DA = 1,4-bis-dimethylamino-2-butene, DCB = 1,4-dichloro-butene

[0068] As described in U. S. Patent No. 4,027,020, PQI synthesis without the addition of acid to the reaction mixture is not effective outside the range of DA/TEA molar ratio of 2:1 - 30:1. Table 4 above shows that the methods of the present embodiments are effective with a much larger range of DA/TEA molar ratios. In some embodiments, PQI can be effectively formed at DA/TEA molar ratio < 2:1. In fact, the molecular size of PQI is related to the ratio of DA/TEA: the higher the ratio, the higher the PQI molecular weight.

[0069] The preferred molar ratio of the total amines (DA+TEA) to acid is from about 10:1 to about 1:2 and most preferably from about 5:1 to about 1:1. The preferred DA/TEA ratio is from about 0.3; 1 to about 30:1 and most preferably from 0.8; 1 to about 5:1.

[0070] The molecular weights are deduced from the proton NMR spectrum of the product according to the equation: raw =133.5 (u/v - 1) + 290, where u is the peak area at the chemical shift of 6.5 ppm which is from the vinyl protons in the repeating units, and v is peak area at the chemical shift of 3.7 ppm which is from the allylic protons adjacent to nitrogen in the ending groups of the PQI molecules.
An experiment was done to test the anti-bacterial effect of PQI synthesized in the presence of acid in comparison to PQI molecules synthesized without the presence of acid. Several contact lens multi-purpose solutions were formulated by dissolving the ingredients in Table 5 in deionized water. Antimicrobial activity was tested by methods known in the art against the FDA contact lens disinfection panel. Log reductions at 6 hours solution contact are reported at the bottom of Table 5.

Table 5

<table>
<thead>
<tr>
<th></th>
<th>%w/w</th>
<th>%w/w</th>
<th>%w/w</th>
<th>%w/w</th>
<th>%w/w</th>
<th>%w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>PQ-I</td>
<td>0.000075</td>
<td>0.0001</td>
<td>0.00015</td>
<td>0.000075</td>
<td>0.0001</td>
<td>0.00015</td>
</tr>
<tr>
<td>PQ-I synthesized with acid added (sample# 5 in Table 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose (HPMC)</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>Tris HCl</td>
<td>0.055</td>
<td>0.055</td>
<td>0.055</td>
<td>0.055</td>
<td>0.055</td>
<td>0.055</td>
</tr>
<tr>
<td>Tris (base)</td>
<td>0.021</td>
<td>0.021</td>
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<td>0.021</td>
<td>0.021</td>
<td>0.021</td>
</tr>
<tr>
<td>Taurine</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
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<td>0.05</td>
</tr>
<tr>
<td>Edetate Disodium</td>
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<td>0.01</td>
<td>0.01</td>
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* Synthesized according to the conditions described in Comparative Example 2 except the reaction time is 40 hours.

As can be seen in Table 5, above, the antimicrobial activity is reduced considerably when PQI is generated without the presence of acid; that is, when PQI is degraded.
The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description details certain preferred embodiments of the invention and describes the best mode contemplated by the inventor. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.
WHAT IS CLAIMED IS:

A method of making one or more quaternary ammonium polymers comprising the steps of:

a) mixing 1,4-bis-dimethylamino-2-butene and triethanolamine and an acid; and

b) introducing a 1,4-dihalo-2-butene to the mixture so as to initiate a reaction resulting in the quaternary ammonium polymer.

The method of Claim 1, wherein the 1,4-dihalo-2-butene is 1,4-dichloro-2-butene.

The method of Claim 1, wherein the quaternary ammonium polymers comprise polyquaternium-1.

The method of Claim 1, wherein the acid is selected from the group consisting of HCl, H₂SO₄ and H₃PO₄.

The method of Claim 1, wherein the acid is HCl.

The method of Claim 1, further comprising the step of adding water to the mixture.

The method of Claim 1, wherein the 1,4-bis-dimethylamino-2-butene, triethanolamine and acid are mixed before the addition of the 1,4-dihalo-2-butene.

The method of Claim 1, wherein the 1,4-dihalo-2-butene is added drop-wise.

The method of Claim 1, wherein the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine is from about 10:1 to about 1:5.

The method of Claim 1, wherein the molar ratio of triethanolamine to acid is from about 10:1 to about 1:10.

The method of Claim 1, wherein the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine to acid is from about 10:9:5 to about 10:9:8.

The method of Claim 1, wherein the reaction temperature is from about 10 °C to about 90 °C.

The method of Claim 1, wherein the reaction time is from about 1 hour to about 40 hours.

A method of making Polyquaternum-1 at a yield of at least about 50% comprising the steps of:

a) mixing 1,4-bis-dimethylamino-2-butene, triethanolamine and an acid; and

b) introducing a 1,4-dihalo-2-butene to the mixture so as to initiate a reaction

The method of Claim 14, wherein the acid is selected from the group consisting of HCl, H₂SO₄ and H₃PO₄.

The method of Claim 14, wherein the 1,4-dihalo-2-butene is 1,4-dichloro-2-butene.

The method of Claim 14, wherein the acid is HCl.
The method of Claim 14, further comprising the step of introducing water into the mixture.

The method of Claim 14, wherein the 1,4-bis-dimethylamino-2-butene, triethanolamine and acid are mixed before the addition of the 1,4-dichloro-2-butene.

The method of Claim 14, wherein the 1,4-dichloro-2-butene is added drop-wise.

The method of Claim 14, wherein the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine is from about 10:1 to about 1:5.

The method of Claim 14, wherein the molar ratio of triethanolamine to acid is from about 10:1 to about 1:10.

The method of Claim 14, wherein the molar ratio of 1,4-bis-dimethylamino-2-butene to triethanolamine to acid is from about 10:9:5 to about 10:9:8.

The method of Claim 14, wherein the reaction temperature is from about 100°C to about 90°C.

The method of Claim 14, wherein the reaction time is from about 1 hour to about 40 hours.
Figure 3c

Wave length 205 nm

Wave length 228 nm

Retention Time (min)
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/US2008/060496

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**A. CLASSIFICATION OF SUBJECT MATTER**

According to International Patent Classification (IPC) or to both national classification and IPC

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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched,

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>US 3 874 870 A (GREEN HAROLD A ET AL) 1 April 1975 (1975-04-01) examples</td>
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**D**

Further documents are listed in the continuation of Box C. See patent family annex.

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<td>FR 2289544 A1</td>
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