

ANTI-MICROBIAL COMPOSITIONS COMPRISING QUATERNARY ORGANOSILANE COMPOUNDS

The present invention relates to an anti-microbial composition, a method of making an anti-microbial composition and a method of reducing the number of microbes on a surface
5 using an anti-microbial composition.

Many different substances are known for use of disinfectants, both for use by animals, more particularly humans, and on inanimate surfaces. In particular quaternary ammonium compounds are known for this use.

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Although they are beneficial in reducing the number of micro-organisms on a surface, there is a need for improved anti-microbial compositions which will provide improved disinfection.

15 The present invention seeks to provide an improved anti-microbial composition.

According to the present invention there is provided an antimicrobial composition comprising at least two quaternary ammonium compounds selected from:

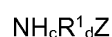
20 (i) a quaternary ammonium compound having the formula:



and

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(ii) a quaternary ammonium compound having the formula:



30 wherein in each of the at least two quaternary ammonium compounds A, R, R¹, a, Z and n are independently selected, and:

A is a member selected from the group consisting of alkoxy radicals, alkylether alkoxy radicals, and alkyl radicals;

R is a divalent hydrocarbon radical;

35 each R¹ is independently a member selected from the group consisting of benzyl, alkyl radicals, alkyl ether hydrocarbon radicals, hydroxyl-containing alkyl radicals, and nitrogen-containing hydrocarbon radicals;

Z is a member selected from the group consisting of chloride, bromide, iodide, tosylate, hydroxide, sulfate and phosphate;

a is 0, 1 or 2, b is 1, 2 or 3, and the sum of a and b is 3;

c is 0, 1, 2 or 3, d is 1, 2, 3 or 4, and the sum of c and d is 4; and

5 n is 1, 2 or 3; and

wherein the composition comprises at least two quaternary ammonium compounds of formula (i).

Preferably, A is a member selected from the group consisting of alkoxy radicals of 1 to 10 carbon atoms, alkylether alkoxy radicals of 2 to 10 carbon atoms, and alkyl radicals with 1 to 10 carbon atoms; and/or

R is a divalent hydrocarbon radical with 1 to 10 carbon atoms; and/or

each R¹ is independently a member selected from the group consisting of benzyl, alkyl radicals with 1 to 30 carbon atoms, alkyl ether hydrocarbon radicals of 2 to 30 carbon atoms, hydroxyl-containing alkyl radicals of 1 to 30 carbon atoms, and nitrogen-containing hydrocarbon radicals of 1 to 30 carbon atoms.

Conveniently, the composition comprises two quaternary ammonium compounds of formula (i) and no quaternary ammonium compounds of formula (ii).

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Advantageously, the composition comprises two quaternary ammonium compounds of formula (i) and one quaternary ammonium compound of formula (ii).

Preferably, an R¹ group of one of the quaternary ammonium compounds, is different from the R¹ group or groups of the other quaternary ammonium compound or compounds.

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Conveniently, at least one R¹ group has 18 carbon atoms.

Advantageously, one of the quaternary ammonium compounds is 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride.

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Preferably, one of the quaternary ammonium compounds is alkyl silyl dimethyl benzyl ammonium chloride.

Conveniently, one of the quaternary ammonium compounds is dioctyl silyl dimethyl ammonium bromide.

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Advantageously, the composition comprises water and/or ethanol.

Preferably, the composition comprises the quaternary ammonium compounds in a concentration of from about 0.1 to about 5% by volume, preferably about 0.5 to about 2% by volume.

According to an aspect of the invention, there is provided a method of making an anti-microbial composition as defined in any of the preceding paragraphs, the method comprising admixing the at least two quaternary ammonium compounds.

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According to an aspect of the invention, there is provided a method of reducing the number of micro-organisms on a surface, comprising contacting said surface with an antimicrobial composition comprising at least two quaternary ammonium compounds selected from:

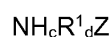
(i) a quaternary ammonium compound having the formula:



and

20

(ii) a quaternary ammonium compound having the formula:



wherein in each of the at least two quaternary ammonium compounds A, R, R¹, a, Z and n are independently selected, and:

A is a member selected from the group consisting of alkoxy radicals of 1 to 10 carbon atoms, alkylether alkoxy radicals of 2 to 10 carbon atoms, and alkyl radicals with 1 to 10 carbon atoms;

R is a divalent hydrocarbon radical with 1 to 10 carbon atoms;

each R¹ is independently a member selected from the group consisting of benzyl, alkyl radicals with 1 to 30 carbon atoms, alkyl ether hydrocarbon radicals of 2 to 30 carbon atoms, hydroxyl-containing alkyl radicals of 1 to 30 carbon atoms, and nitrogen-containing hydrocarbon radicals of 1 to 30 carbon atoms;

Z is a member selected from the group consisting of chloride, bromide, iodide, tosylate, hydroxide, sulfate and phosphate;

a is 0, 1 or 2, b is 1, 2 or 3, and the sum of a and b is 3;

c is 0, 1, 2 or 3, d is 1, 2, 3 or 4, and the sum of c and d is 4; and
n is 1, 2 or 3; and

wherein the composition comprises at least two quaternary ammonium compounds of formula (i).

5

Advantageously, A is a member selected from the group consisting of alkoxy radicals of 1 to 10 carbon atoms, alkylether alkoxy radicals of 2 to 10 carbon atoms, and alkyl radicals with 1 to 10 carbon atoms;

R is a divalent hydrocarbon radical with 1 to 10 carbon atoms; and

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each R¹ is independently a member selected from the group consisting of benzyl, alkyl radicals with 1 to 30 carbon atoms, alkyl ether hydrocarbon radicals of 2 to 30 carbon atoms, hydroxyl-containing alkyl radicals of 1 to 30 carbon atoms, and nitrogen-containing hydrocarbon radicals of 1 to 30 carbon atoms;

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Preferably, the composition is as defined in any of the above paragraphs.

Conveniently, the surface is skin.

Advantageously, the surface is an inanimate surface.

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Preferably, the anti-microbial composition is used as a spray, foam, mist, fog or wipes.

The present invention will now be described, by way of example, with reference to the following embodiments.

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Quaternary ammonium compounds are widely used as disinfectants. These compounds can remain on surfaces to give a persistent effect, allowing them to remain active on surfaces after cleaning.

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Chemically, the quaternary compounds are organically substituted ammonium compounds having four substituents (e.g. alkyl or heterocyclic radicals of a given size or chain length), and an associated anion, such as a halide, sulfate, or similar moiety. These compounds exhibit antimicrobial characteristics. Some known quaternary ammonium compounds used in healthcare are alkyl dimethyl benzyl ammonium chloride, didecyl dimethyl ammonium chloride, dialkyl dimethyl ammonium chloride, didecyl dimethyl ammonium bromide and dioctyl dimethyl ammonium bromide.

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The bactericidal action of the quaternary compounds has been attributed to the inactivation of energy-producing enzymes, denaturation of essential cell proteins, and disruption of the cell membrane.

5 The quaternary compounds used as hospital disinfectants are generally fungicidal, bactericidal, and virucidal against lipophilic (enveloped) viruses. More recent quaternary compounds have been found to have improved efficacy, for example with activity against spores, *Mycobacterium tuberculosis*, and virucidal against hydrophilic (nonenveloped) viruses.

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Compositions comprising these antimicrobial compounds are used in ordinary environmental sanitation of surfaces, especially hard surfaces, such as floors, furniture, and walls. Some specific quaternary ammonium compounds are also appropriate to use for disinfecting medical equipment that contacts intact skin (e.g., blood pressure cuffs),
15 and food preparation surfaces.

Examples

Tests were performed to verify the efficacy of anti-microbial compositions in accordance with the invention. The tests were performed on sample patches of worktop material
20 (2 cm² surface) which were contaminated with a measured amount of a microbe (10,000 CFU *Staph. aureus*). The samples were then subjected to treatment with compositions (compositions 1, 2 and 3 detailed below) followed by testing for the level of microbes with daily cleaning.

25 Tests were performed with compositions comprising a single silicon-containing quaternary ammonium compound, two silicon-containing quaternary ammonium compounds and three silicon-containing quaternary ammonium compounds. The compounds were used as solutions in a water/ethanol mixture. The concentration of each composition was 1% by volume of the quaternary ammonium compound(s) in 17% ethanol/82% sterile water.

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Composition 1 contained 3-(trimethoxysilyl) propyl dimethyl octadecyl ammonium chloride. Composition 2 additionally contained alkyl silyl dimethyl benzyl ammonium chloride. Composition 3 additionally contained dioctyl silyl dimethyl ammonium bromide.

35 So, Composition 1 contained a single quaternary ammonium compound. Composition 2 contained two quaternary ammonium compounds. Composition 3 contained three

quaternary ammonium compounds. All of the quaternary ammonium compounds used in the tests contained silicon.

Comparison of 3 Si Quat compounds

Results in CFU per cm ²	Day of treatment					
		7 days	14 days	21 days	28 days	3 months
3 x 2cm ² patches of work top contaminated with 10,000 CFU staph aureus and isolated tests performed prior to vigorous daily cleaning						
Before treatment	9889					
Compound 1 (single Si Quat)	3	3	4	9	167	2889
Before treatment	9878					
Compound 2 (2 x Si Quats)	0	0	3	3	87	683
Before treatment	9920					
Compound 3 (3 x Si Quats)	0	0	0	0	0	4

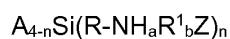
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The test demonstrates the efficacy of compositions of the invention having improved anti-microbial activity. In particular, the anti-microbial activity is long lived as the composition persists on the surface for a relatively long period of time.

- 10 One aspect of the invention is that the composition comprises at least two quaternary ammonium compounds as defined in the claims. At least two of the quaternary ammonium compounds are silicon-containing quaternary ammonium compounds. The quaternary ammonium compounds are defined below, forming an antimicrobial composition comprising at least two quaternary ammonium compounds selected from:

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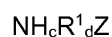
- (i) a quaternary ammonium compound having the formula:



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and

- (ii) a quaternary ammonium compound having the formula:



wherein in each of the at least three quaternary ammonium compounds A, R, R¹, a, Z and n are independently selected, and:

A is a member selected from the group consisting of alkoxy radicals of 1 to 10 carbon atoms, alkylether alkoxy radicals of 2 to 10 carbon atoms, and alkyl radicals with 1 to 10 carbon atoms;

R is a divalent hydrocarbon radical with 1 to 10 carbon atoms;

each R¹ is independently a member selected from the group consisting of benzyl, alkyl radicals with 1 to 30 carbon atoms, alkyl ether hydrocarbon radicals of 2 to 30 carbon atoms, hydroxyl-containing alkyl radicals of 1 to 30 carbon atoms, and nitrogen-containing hydrocarbon radicals of 1 to 30 carbon atoms;

Z is a member selected from the group consisting of chloride, bromide, iodide, tosylate, hydroxide, sulfate and phosphate;

a is 0, 1 or 2, b is 1, 2 or 3, and the sum of a and b is 3;

c is 0, 1, 2 or 3, d is 1, 2, 3 or 4, and the sum of c and d is 4; and

n is 1, 2 or 3; and

wherein the composition comprises at least two quaternary ammonium compounds of formula (i).

The compounds of formula (i) are silicon-containing ammonium quaternary compounds. The compounds of formula (ii) are quaternary ammonium compounds that do not contain silicon. The focus of the invention is based on compositions that contain more than one silicon-containing quaternary ammonium compound. The applicants have found that there are several advantages to such compositions over prior art compositions. A combination of silicon-containing quaternary ammonium compounds provides more effective anti-microbial action, both in terms of immediate effect and also long lasting (persistent) effect. The use of more than one silicon-containing quaternary ammonium compound allows for more effective cleaning. In addition to the combination of silicon-containing ammonium quaternary compounds, the compositions of the invention can also contain further components. These further components can include quaternary ammonium compounds that do not contain silicon, and/or other components, such as surfactants,.

Preferred compositions contain quaternary compounds in which, independently, A is a member selected from the group consisting of alkoxy radicals of 1 to 10 carbon atoms, alkylether alkoxy radicals of 2 to 10 carbon atoms, and alkyl radicals with 1 to 10 carbon atoms; and/or R is a divalent hydrocarbon radical with 1 to 10 carbon atoms; and/or each R¹ is independently a member selected from the group consisting of benzyl, alkyl radicals

with 1 to 30 carbon atoms, alkyl ether hydrocarbon radicals of 2 to 30 carbon atoms, hydroxyl-containing alkyl radicals of 1 to 30 carbon atoms, and nitrogen-containing hydrocarbon radicals of 1 to 30 carbon atoms.

- 5 Preferred compositions contain at least three quaternary ammonium compounds, of which at least two are silicon-containing quaternary compounds as defined in formula (i) above.

Compositions of the invention include compositions comprising two silicon-containing quaternary ammonium compounds of formula (i) and no quaternary ammonium
10 compounds of formula (ii); two quaternary ammonium compounds of formula (i) and one quaternary ammonium compound of formula (ii); two silicon-containing quaternary ammonium compounds of formula (i) and two silicon-containing quaternary ammonium compounds of formula (ii); two silicon-containing quaternary ammonium compounds of formula (i) and three quaternary ammonium compounds of formula (ii); three silicon-
15 containing quaternary ammonium compounds of formula (i) and no quaternary ammonium compounds of formula (ii); three silicon-containing quaternary ammonium compounds of formula (i) and one quaternary ammonium compound of formula (ii); three silicon-containing quaternary ammonium compounds of formula (i) and two quaternary ammonium compounds of formula (ii); three silicon-containing quaternary ammonium
20 compounds of formula (i) and three quaternary ammonium compounds of formula (ii); and so on.

The applicants have found that a composition comprising a mixture of quaternary ammonium compounds of the invention (containing at least two silicon-containing
25 ammonium quaternary compounds) is particularly effective at reducing and eliminating the number of micro-organisms on a surface. Preferably the ammonium compounds have a mixture of long chain groups. At least two of the quaternary ammonium compounds in the composition are silicon containing quaternary ammonium compound (i.e. a compound of formula (i) as set out above).

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As used herein the term micro-organism refers to a pathogen such as a virus or bacteria. Preferably, the micro-organism is a bacteria. A non-exhaustive list of pathogens is given below:

35 Bacteria:

Gram Positive Bacteria:

Citrobacter freundii

- Citrobacter diversus*
Corynebacterium diphtheriae
Diplococcus pneumoniae
Micrococcus sp. (I)
5 *Micrococcus* sp. (II)
Micrococcus sp. (III)
Mycobacterium spp.
Staphylococcus albus
Staphylococcus aureus
10 *Staphylococcus citreus*
Staphylococcus epidermidis
Streptococcus faecalis
Streptococcus pyogenes
- 15 Gram Negative Bacteria:
Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter agglomerans (I)
Enterobacter agglomerans (II)
20 *Escherichia coli*
Klebsiella pneumoniae
Nisseria gonorrhoeae
Proteus mirabilis
Proteus morganii
25 *Proteus vulgaris*
Providencia spp.
Pseudomonas
Pseudomonas aeruginosa
Pseudomonas fragi
30 *Salmonella choleraesuis*
Salmonella enteritidis
Salmonella gallinarum
Salmonella paratyphi A
Salmonella schottmuelleri
35 *Salmonella typhimurium*
Salmonella typhosa
Serratia marcescens

Shigella flexnerie Type II

Shigella sonnei

Virbrio cholerae

5 Viruses:

Adenovirus Type IV

Feline Pneumonitis

Herpes Simplex Type I & II

HIV-1 (AIDS)

10 *Influenza A (Japan)*

Influenza A2 (Aichi)

Influenza A2 (Hong Kong)

Norovirus

Parinfluenza (Sendai)

15 *Poliovirus*

Reovirus

Respiratory Syncytia

Fungi and Mould:

20 *Alternaria alternata*

Asperigillus niger

Aureobasidium pullulans

Candida albicans

Cladosporium cladosporioides

25 *Drechslera australiensis*

Gliomastix cerealis

Microsporum audouinii

Monilia grisea

Phoma fimetii

30 *Pithomyces chartarum*

Scolecobasidium humicola

Trychophyton interdigitale

Trychophyton mentagrophytes

35 The compositions of the invention generally contain the quaternary ammonium compounds in a solvent. The solvent is preferably aqueous, and more preferably a mixture

of water and alcohol, preferably ethanol. The composition may contain methanol, for example as a stabiliser.

5 The terminology used herein is for describing particular embodiments and is not intended to be limiting.

The term "pathogen" as used herein also includes gram positive and gram negative bacteria, viruses and fungi, including yeasts and moulds.

10 The term "alkyl" as used herein refers to a straight chain or branched saturated hydrocarbon.

The term "alkylether alkoxy" as used herein refers to an alkyl ether moiety containing carbon-oxygen-carbon bonds and having a terminal oxygen atom bonded to the silicon
15 atom.

The term "alkyl ether" group as used herein refers to an alkyl group as defined above containing within the carbon chain a carbon-oxygen-carbon linkage. Polyethers are also included in this definition as being alkyl groups containing more than one carbon-oxygen-
20 carbon linkage.

The term "alkoxy" as used herein refers to alkyl groups defined as above which have a terminal carbon-oxygen linkage. "Lower" used herein in reference to alkyl, alkoxy and alcohols, indicates species and compounds having 1 to 4 carbons.
25

The term "antimicrobial" as used herein is used in reference to the ability of the compound composition or article to eliminate, remove, inactivate, kill or reduce microorganisms such as bacteria, viruses, fungi, moulds, yeasts and spores. The term antimicrobial as used herein to imply reduction and elimination of the growth and formation of microorganisms
30 such as described above.

The compositions of the invention can be used in many different applications in order to reduce and/or eliminate the number of pathogens. In particular they can be used on inanimate surfaces. They can be used in healthcare environments, in the home and other
35 situations in order to disinfect surfaces. Such applications include the food industry, water treatment and hospitals. The Applicants have found that the application of the composition to a surface reduces substantially the number of pathogens within a very short period of

time. In addition, the composition produces a long-lasting pathogenic effect from the application of the composition to a surface. The quaternary ammonium compounds of the compositions of the invention persist on the surface even if they are subjected to normal use, for a period of time. The compositions have been found to be effective against
5 viruses, and against norovirus in particular.

The anti-microbial compositions of the invention may be used in many different ways. Preferably, the composition of the invention is a liquid. For example, the composition could be used as a spray, to be sprayed onto surfaces. The surfaces are then either be left for
10 the composition to dry, or the composition may be wiped with a clean cloth or other implement and then left to dry. The composition of the invention can also be provided as a foam, to be applied to a surface. The composition could be released from a container which forms the foam, for example by entraining air. The composition may optionally contain components to aid in the formation of the foam. The composition of the invention
15 may also be used in the form of a wetted wipe. So, a wipe impregnated with the composition may be used to wipe a surface. Another way of applying the composition is through the generation of a fog. In other words, small liquid particles of the composition of the invention may be formed to generate a mist or fog, which can then contact surfaces to be disinfected.

20 It is believed that the compositions of the invention become more effective some time after being applied to a surface and left to dry. Without being bound by theory, the Applicants believe that at least some of the components of the composition may become bonded to the surface, giving a long lasting persistent anti-microbial effect. This could be, in the case
25 of a silicon-containing quaternary ammonium compound, hydrolysis in the formation of a bond with the material of the surface being disinfected.

It is believed that the mix of at least two different quaternary ammonium compounds is a factor in the efficacy of the compositions of the invention. In particular, it is believed that
30 having different organic groups, especially of different chain lengths, enhances efficacy. The compounds of the invention contain at least two different quaternary ammonium compounds, of which at least two are silicon-containing quaternary ammonium compounds as defined in formula (i) in the claims. Preferably, the composition contains at least two quaternary ammonium compounds, each having at least one pendant group
35 having at least eight carbon atoms. More preferably, each of the at least two quaternary ammonium compounds has such an organic moiety which has a different chain length from the other groups in the other quaternary ammonium compounds in the composition.

It is preferred for the quaternary ammonium compounds used in the invention to be provided in an aqueous solvent. Although the solvent could be essentially water, it is preferred that the solvent comprises water and an alcohol, such as ethanol. This reduces the drying time of the composition when applied to a surface. If desired, the composition can contain other optional components.

Compositions of the invention can be made, for example, by admixing the at least two quaternary ammonium compounds with a solvent. The compositions may be provided in a concentration which is ready to use, or may be provided in the concentrated form, ready for dilution to a more appropriate concentration when needed.

In addition to disinfecting inanimate surfaces, the compositions of the invention could be used to disinfect a surface of the living body, for example the skin.