Implantable medical devices, such as catheters, which comprise a calixarene-derived coating that resists adhesion and/or colonisation of bacteria and/or fungi are described. Also described are calixarene-derived coating materials, intermediates useful in their manufacture, processes for their preparation, and methods for coating of implantable medical devices with the calixarene compounds.
Medical Devices, Coatings and Compounds

Field of the Invention

The present invention relates to implantable medical devices, such as catheters, which comprise a calixarene-derived coating that resists adhesion and/or colonisation of bacteria, to calixarene-derived coating materials, intermediates useful in their manufacture, and to processes for their preparation and coating of said devices.

Background of the Invention

The use of implantable medical devices is prevalent in the healthcare sector, such devices being either totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which are intended to remain after the procedure. Associated with the use of implanted devices is the problem of biofilm build up resulting in irritation, inflammation and infection. Biofilms are thin layers of microorganisms, usually protozoa and bacteria, which aggregate on the surfaces of implanted devices causing the problems described.

Catheters are one of the most commonly utilised implantable medical devices and it is estimated that 25% of all hospital admissions use urinary catheterization to assist with bladder drainage. Catheter Acquired Urinary Tract Infections (CAUTI) develop quickly after insertion (~ 3% per day) and are currently the major cause of hospital acquired infections, accounting for 40% of all cases. Treatment of these infections involves a combination of medication and longer periods of hospitalisation, raising costs and not always providing a satisfactory outcome for the patients affected.

Current methods directed at reducing the incidence of catheter-associated infections include a range of catheters that utilise impregnated surfaces that elute toxic or therapeutic substances intended to kill organisms colonising the surfaces, in order to reduce biofilm formation and adherence of bacteria. Catheters are available that possess coatings such as chlorhexidine and silver sulfadiazine, heparin, benzalkonium chloride, or release anti-infective compounds, such as nitrofurazone.

United Kingdom Patent Application GB 2,448,153 is directed to coated implantable medical devices having a calixarene-derived surface coating that is both hydrophobic


There exists a need for alternative or improved products that address the problems associated with current implantable medical devices. In particular, there is a need for implantable medical devices having an increased resistance to the build-up of biofilm, preferably leading to a reduction in cases of irritation, inflammation or infection. Such devices would ideally possess an increased resistance to the adhesion and/or colonisation of bacteria. In the catheterisation field, it is desirable for new devices to be less susceptible to the adhesion and/or colonisation of bacteria that result in catheter-acquired urinary tract infections. In particular, catheters would have an improved resistance profile permitting their use for longer periods, reducing patient discomfort through reduced number of catheter changes, and reducing irritation, inflammation and infection rates. New medical devices, including catheters, that show even a modest reduction in infection rates would be welcomed and would have a great impact on efficacy and cost of healthcare systems.

Summary of the Invention

It is therefore an object of the present invention to provide medical devices, in particular, catheters, comprising a surface coating that helps to overcome these problems associated with current devices, ideally, such a catheter surface, or that of another device, would offer one or more of the following advantages:

- Provide superior resistance to biofilm development and encrustation.
- Biologically inert; will not cause inflammation or other side-effects.
- Durability; will remain attached to the device surface without leaching coating materials, effective for duration of the device's life-time.
- Form a smooth, thin surface minimizing patient discomfort.
- Non-pharmacologic, avoiding drug-drug / drug-patient interactions, eliminating the need for delivery systems, dosing, and drug testing, and does not stimulate the emergence of resistant organisms.
- Localised effect, limited to the exposed surfaces (interior and/or exterior) of the catheter.

The present invention accordingly provides an implantable medical device having a coating comprising a calixarene bonded to the surface of the device via one or more surface-linker groups on one rim of the calixarene, wherein the opposing rim of the calixarene is substituted by one or more polyethylene glycol, polypropylene glycol or polytrimethylene glycol groups, or a mixture thereof, said surface-linker groups may be bonded to the surface of the device via covalent bonds, ionic bonds, hydrogen bonds, or Van der Waals forces, said glycol groups are attached to the calixarene via (C₃ to C₄₅)alkylene spacer groups, said glycol groups, each independently, have from 2 to 250 repeating glycol units and may be optionally terminated by hydrogen or (C₃ to C₄)alkyl, said (C₃ to C₄₅)alkyl spacer groups may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds.

Preferably, the calixarene is bonded to the surface of the device via 2 to 8 surface-linker groups as described herein below. More preferably, the calixarene is bonded to the surface of the device via 2 to 8 surface-Linker groups. Most preferably, the calixarene is bonded to the surface of the device via 2 or 4 surface-linker groups. The bonding may be via covalent bonds, ionic hydrogen-bonds, or Van der Waals bonds. Preferably, said surface-linker groups are bonded to the surface of the device via covalent bonds.

The surface-linker groups on the calixarene compounds of the invention may be selected from any of the surface linker groups defined elsewhere herein. Suitably, the surface linker group is selected for covalent or ionic surface attachment: such linker groups may be selected from those that comprise acid chloride, chloroformate or silane functional groups; or ammonium, suifonium, phosphonium, or phosphate functional groups. In other embodiments, the surface linker group is selected for hydrogen-bonding
attachment to a surface; such as linker groups comprising a group selected from hydroxy!, (alkyl, alkenyl or alkynyl)hydroxy!, (alkyl, alkenyl or alkynyl)carboxyl! and (alkyl, alkenyl or alkynyl)amide. In other embodiments the surface linker group is selected for Van der Waals attachment to a surface: such linker groups may be selected from those that comprise long-chain alkyl, alkenyl, alkynyl, or ester, ether or amides thereof.

In a preferred aspect of the invention, the calixarene is covalently bonded to the surface of a device made from silicone or having a silicone coating thereon, via 2 to 8, preferably 2 to 6, most preferably, 2 or 4 surface linker groups.

In a preferred embodiment, the implantable medical device according to each aspect of the invention comprises a calixarene having a rim substituted by one or more polyethylene glycol groups.

The glycol groups of the invention (polyethylene glycol, polypropylene glycol or polytrimethylene glycol groups, or a mixture thereof) may be attached to the alkylene spacer group directly via the oxygen of the glycol or via another viable linker group. Other suitable Sinker groups include, for example, carbonate, glycol ether, glycolateether, carbamate, urea, α,β-amino ether, a-hydroxyacetamide ether, amide, imide, thioether, phosphate, phosphonate, sulphate, sulphonate and triazole.

When the medical device is implanted into a patient, the coating will preferably resist adhesion and/or colonisation of bacteria onto the surface of the device. Preferred embodiments of the device may provide a coating that, either as an alternative to, or in addition to resisting adhesion and/or colonisation of bacteria, has an antimicrobial effect. Said antimicrobial effect will ideally be exhibited at a surface concentration that also provides a safe pharmacological profile.

The present invention encompasses any implantable medical device and, in particular, covers a medical device, which is a stent, catheter, vascular graft, cardiac pacer lead, heart diaphragm, suture, needle, angioplasty device, artificial joint, heart valve, neurological stimulator, drug pump or surgical mesh implant as reinforcement or scaffolding. Medical devices having a surface, in whole or in part, which comprise silicone or a layer of silicone are preferred. Other preferred surfaces are metals (such as stainless steel and/or titanium). Catheters are the most preferred medical device to which the invention is directed.
Catheters may be made of any suitable material including, for example, silicone, latex, polyurethane, such as polycarbonate or polyether based materials, polyamides, such as nylon 11 and nylon 12, fluoropolymers, such as polytetrafluoroethylene, polyolefins, such as polyethylene, PVC, polyimides, or polyether etherketone. Most preferred are catheters made from silicone or having a silicone coating thereon.

In another aspect the invention also encompasses calixarene compounds for coating to a surface of a medical device; e.g. compounds of Formula (I) and/or Formula (II) as described herein below and preferred embodiments thereof. In yet another aspect the invention encompasses intermediates of the calixarene compounds of the invention; e.g. compounds of Formula (III) as described herein below and preferred embodiments thereof.

Methods of making the coated implantable medical devices of the invention, uses for / method of using the coated implantable medical devices of the invention; and methods for the synthesis of the calixarene compounds of the invention (e.g. compounds of Formulas (I), (II) and/or (III) are also encompassed within the scope of the invention.

It will be appreciated that, unless otherwise stated, preferred features of one aspect of the invention may be incorporated into any other aspect of the invention and that such combinations fall within the scope of the invention.

**Detailed Description of the Invention**

Calixarenes are macrocyclic molecules based on the condensation product of a phenol and an aldehyde and whose general structure is that of a molecular bowl on legs with the rim of the bowl lined by hydroxy! groups and the legs consisting of long-chain alky! groups. A detailed review of the different types of calixarenes and their methods of manufacture is given by Bohmer, Angew. Chem. Int. Ed. Engl. 1995, 34, 713-745. The surface properties of the calixarenes may be suitably modified to impart the desired properties by altering the substituents on either the rim or the legs.

There are three main types of calixarene that fall within the scope of the present invention, which are derived from phenols, resorcinols or pyrogallols, or mixtures thereof. Depending on the calixarene used in accordance with the invention, it may suitably be
prepared respectively from phenols, from resorcinoids (resorcinarene) and from pyrogaliols by condensation with aldehydes. The present invention is applicable to all these types of caixarenes, and encompasses devices having a coating derived from any one of them. Preferably, the invention covers a device wherein the caixarene is a resorcinarene.

In a preferred embodiment, the present invention provides an implantable medical device having a coating comprising a caixarene bonded to the surface of the device via one or more surface-linker groups on one rim of the caixarene wherein said caixarene is derived from a compound of formula (I)

wherein

\[ X \text{ is } H, (C_1-C_4)\text{alkyl, NH}_2, \text{NH(C}_1-C_4)\text{aikyl, N(d-d)alkyl}_2 \text{ or CH}_2\text{NH(d-d)alkyl, and } Y \text{ is OH, 0(d-d)alkyl or OCH}_2\text{CO}_2(d-d)\text{alkyl}; or } \]

\[ X \text{ is OH, 0(d-d)alkyl or OCH}_2\text{CO}_2(d-d)\text{alkyl, and } Y \text{ is H, (d-d)alkyl, NH}_2, \text{NH(d-d)alkyl, or N(d-d)alkyl}_2 \text{ or CH}_2\text{NH(d-d)alkyl}; or } \]

\[ X \text{ and } Y \text{ are each independently OH, 0(d-d)alkyl or OCH}_2\text{CO}_2(d-d)\text{alkyl; } \]

\[ Z \text{ is } H, \text{OH or methyl; } \]

\[ n \text{ is 1, 3 or 5; and } \]

\[ R \text{ is } -(C_3-ds)\text{alkylene-L}^2\text{-G-R}^1 \text{ where in said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds; } \]
L^3 is a bond or a Sinking group;
G is -0(CH_2CH_20)_m, -(CH_2CH(CH_3)0)_m, -0(CH(CH_3)CH_2Q)_m or -0(CH_2CH(CH_3)0)_m; 
m is 2 to 250;
R^1 is H or (C_1-C_4)alkyl;
and wherein each X, Y, Z, R and R^1 group may be the same or different.

Preferably, at least one X is H and at least one Y is OH. In a convenient alternative at 
least one X is OH and at least one Y is H. In another alternative at least one X is H and
at least one X is OH, and at least one Y is H and at least one Y is OH. Conveniently, a
plurality of X moieties are H, and a plurality of Y moieties are OH (or vice versa). In
some preferred embodiments all Y moieties are OH, and H is selected from the options
given herein; and in some more preferred embodiments all X moieties are H and all Y
moieties are OH. In other preferred compounds both X and Y moieties may be OH.

In some embodiments the calixarene of Formula (1) is bonded to the surface directly via
a suitable interaction-bonding, e.g. hydrogen-bonding, Van der Waals, ionic and/or
cova lent attachment. In this case the calixarene is "derived from" the compound of
Formula (1) simply by way of selecting a suitable X and/or Y moiety / moieties; e.g. using
a hydroxyl group at an X or Y position. Conveniently for hydrogen-bonding to a suitable
surface a plurality of X and/or Y moieties are OH, which groups can hydrogen bond to a
wide range of substrates. In other embodiments the calixarene for adhering to the
surface of the implantable medical device is modified by substituting one or more of the
X and/or Y substituents with a 'surface linker group'.

In a preferred aspect of the present invention the calixarene, which is derived from a
compound of formula (l) or preferred embodiments thereof, is bonded to the surface of
the device via surface linker groups substituted for any one or more of the X or Y
substituents, or a combination thereof. Suitably, one or more (e.g. 2, 3, 4, 8, 8 or more,
such as all) OH groups on the calixarene (e.g. in X and/or Y positions) are modified to
incorporate a specific suitable surface linker group. Preferably, the calixarene is bonded
to the surface of the device via 2 to 8 surface-linker groups. Preferably, the surface inker
groups at X or Y, or a combination thereof, on the calixarene are derived from one or
more of the surface linker groups described herein.

Suitably, Z is H and/or suitably n is 1.
In some preferred compounds of Formula (I) R is \((-\text{C} \alpha \text{alkyiene}-\text{L})\) \(-\text{G-R}^{-}\); wherein more preferably, \(\text{L}^3\) is a linking group selected from those of Scheme A and Scheme B above. Still more preferably, \(\text{L}^3\) is a linking group selected from carbonate, carbamate, urea, phosphate and triazole, and most preferably, \(\text{L}^3\) is carbonate.

Preferably, G is \(-\text{G}(\text{CH}_2\text{CH}_2\text{O})_m\) and/or \(m\) is 3 150, and/or \(\text{R}^1\) is H or methyl. More preferably, \(m\) is 8 to 50, and most preferably, \(m\) is 15 to 25.

**Glycol Linker Groups:**

The calixarene compounds and derivatives useful as coatings for implantable medical devices in accordance with the invention are suitably able to resist biofilm formation thereon. Without being bound by any particular theory, it is believed that this biofilm resistive coating is achieved via modification of one rim of the calixarene compounds with one or more glycol-comprising substituent. Such compounds have been shown to successfully inhibit bacterial biofilm formation, as described in the Examples. The claimed compounds thus provide a structural scaffold that on one rim possessing the substitution pattern required to achieve the functional (e.g. anti-microbial) benefits of the coatings, i.e. to resist adhesion and/or colonisation of bacteria and/or fungus; and on the opposing rim possess suitable substituents for use as surface attachments / surface linker groups.

In a preferred embodiment, the implantable medical device according to each aspect of the invention comprises a calixarene having a rim substituted by one or more polyethylene glycol groups.

The glycol groups of the invention (polyethylene glycol, polypropylene glycol or polytrimethylene glycol groups, or a mixture thereof) may be attached to the alkylene spacer group directly via the oxygen of the glycol or via another viable linker group. Other suitable linker groups include, for example, carbonate, glycol ether, glycolateether, carbamate, urea, \(\alpha,\beta\)-amino ether, a-hydroxycetamide ether, amide, imide, thioether, phosphate, phosphonate, sulphate, sulphonate and triazole.

Suitable glycol linker groups include, for example, the following groups of Scheme A and Scheme B, which can be prepared using the methods shown.
Where X is an appropriate leaving group
Scheme B

**S-Lifiksrs**

\[
P \text{PEG-X} + \text{HS-C}_3\text{C}_{16}\text{Calixarene} \rightarrow \text{PEG-S-C}_3\text{C}_{16}\text{Calixarene}
\]

\[
P \text{PEG-N} + \text{HS-C}_3\text{C}_{16}\text{Calixarene} \rightarrow \text{PEG-N} + \text{C}_3\text{C}_{16}\text{Calixarene}
\]

\[
P \text{PEG-N} + \text{HS-C}_3\text{C}_{16}\text{Calixarene} \rightarrow \text{PEG-N} + \text{C}_3\text{C}_{16}\text{Calixarene}
\]

\[
P \text{PEG-S} + \text{HS-C}_3\text{C}_{16}\text{Calixarene} \rightarrow \text{PEG-S} + \text{C}_3\text{C}_{16}\text{Calixarene}
\]

**Cyclic Linkers**

\[
P \text{PEG-O-Alkyl} + N_3\text{C}_3\text{C}_{16}\text{Calixarene} \rightarrow \text{PEG-O-Alkyl}
\]

includes other cycloaddition chemistries eg. Dieis-Alder and photochemically initiated cycloadditions

**C-Linkers**

\[
P \text{PEG-O-Alkyl} + \text{C}_3\text{C}_{16}\text{Calixarene} \rightarrow \text{PEG-O-Alkyl}
\]

\[
P \text{PEG-O-Alkyl} + \text{AlkylP} + \text{C}_3\text{C}_{16}\text{Calixarene} \rightarrow \text{PEG-O-Alkyl}
\]

**Other Linkers**

\[
P \text{PEG-Nuc} + \text{C}_3\text{C}_{16}\text{Calixarene} \rightarrow P\text{EG-Nuc} + \text{C}_3\text{C}_{16}\text{Calixarene}
\]

\[
P \text{PEG-Nuc} + \text{N}_3\text{C}_3\text{C}_{16}\text{Calixarene} \rightarrow P\text{EG-Nuc} + \text{C}_3\text{C}_{16}\text{Calixarene}
\]

Where X is an appropriate leaving group

R is an appropriate aryi, aikey!, or PEG group

Nuc is \(O^-, NH_2, S\)
Preferably, the glycol groups are linked directly via the oxygen of the glycol, or may be attached via another linker group selected from carbonate, carbamate, urea, phosphate and triazole. Most preferably, when an intermediate linker group is used the glycol groups are attached to the alkylene spacer group via an intermediate carbonate linker.

**Surface Linker Groups:**

The 'surface linker groups', when used in accordance with the invention provide the function of attaching / bonding / linking / associating the calixarene compounds to a desired surface of a medical device. As such, the function can be achieved by a broad range of chemical groups, which may be selected according to the type and/or strength of interaction desired between the compound and the surface; and/or according to the surface material. Calixarene compounds and derivatives, such as those of the invention, can be attached to a desired surface of a medical device using any appropriate approach within the skill of a person in the art, and all such mechanisms for surface attachment and the respective surface linker groups are considered to be encompassed within the scope of the invention.

For instance, calixarene compounds can be attached to a surface through covalent or non-covalent interactions. Non-covalent interactions useful in accordance with the invention are ionic bonds, hydrogen bonds, or Van der Waals forces. Accordingly, there are four subsets of interaction that may be exploited for the attachment of the calixarene (preferably resorcinarene) coating to the target substrates, ionic, covalent, hydrogen-bonding and Van der Waals forces. Preferred are ionic, covalent and hydrogen-bonding interactions, more preferred are ionic and covalent interactions, and more preferred are covalent interactions.

Many surfaces to which it may be desirable to attach the calixarene derivatives of the invention may be hydrophobic. Calixarene compounds are known to readily attach to hydrophilic surfaces simply by bringing them into contact with the surface. For example, WO 97/39077 and [http://www.rsc.org/pdf/mcg/shefcotes.pdf](http://www.rsc.org/pdf/mcg/shefcotes.pdf) provide teaching on how to coat various different surfaces with the calixarene derivatives of the invention, and such teachings are incorporated herein by reference. As described in [http://www.rsc.org/pdf/mcg/shefcotes.pdf](http://www.rsc.org/pdf/mcg/shefcotes.pdf) calixarene compounds may be attached to hydrophobic surfaces simply by applying the compounds (e.g. in a solvent or other
solution) to the surface. Such non-covalent attachments may be effective in imparting the desired physical properties to the coated substrates, as demonstrated in this document. Accordingly, calixarene compounds can be applied to a surface using a 'dip-and-dry' technique relying on relatively weak electrostatic interactions, for example, as described in Charnley et al. (2009), which is also incorporated herein by reference. Although these interactions are relatively 'weak', they can be sufficiently strong to impart the required properties to the coated surfaces.

Alternative methods for coating a desired surface with calixarene compounds of the invention are described in WO 2005/1 12570, US 6702850, US 8602287, US 5053048, US 7070798 and US 2002/0102405; all of which are incorporated herein by reference. Furthermore, documents GB 2448153, WO 97/39077, WO 02/083176, and WO 2008/048649 amongst others, which are incorporated herein by reference, provide useful teachings of methods for coating medical devices and other surfaces. In this regard, documents GB 2448153 and WO 97739077 demonstrate the attachment of calixarene compounds to surfaces using weak hydrogen-bonding forces as an effective immobilisation strategy.

Further methods in the art that may be used for attaching calixarene compounds of the invention to a desired surface are described in Silver et al. (1999), Biomaterials, 20, 1533-1543 and Deiamarche et al. (2003), Langmuir, 19, 8749-8758 which particularly describe the silane attachment strategy useful for attaching chemical compounds to silicone surfaces; and Page et al. (1999), J. Am. Chem. Soc., 121, 6751-6752 which describes the Sviannich reaction method using for attaching amine groups to calixarene compounds of surface attachment.

The beneficial surface linker groups and attachment mechanisms are described in more detail below.

Covalent Surface Attachment

Covalent surface attachment is desirable for some aspects of the invention because the interaction is extremely strong and suitably lasts for the lifetime of the medical device.

Suitable linkers for covalent attachment to a surface include chloroformate groups, acid chloride groups and/or silane groups. The chloroformate and acid chloride chemistries
are closely related, and are particularly suitable for use in conjunction with medical devices having functionally-modified surfaces, e.g. plasma-modified polymers in which surface-exposed carbon chains have been oxidised to form alcohols. Exemplary chloroformate and acid chloride surface linkers attached to the phenyl group of a calixarene compound of the invention are shown below.

Acid chloride and chloroformate-containing linker groups are also applicable for polymer surfaces where the side-chains contain nucleophilic groups, e.g. polylsine. The synthesis of such linker groups attached to calixarene compounds can be achieved using any appropriate reaction scheme, such as those exemplified for attaching linker groups of ionic and hydrogen-bonding interactions below.

In particular, chloroformate-containing linkers may typically be prepared via the reaction of the calixarene phenols with phosgene solution; and acid chloride-containing linkers may typically be prepared via the reaction of the parent acid with thsnyl or oxalyl chloride.

Most preferably the surface linker group for covalent attachment to a surface of a medical device contains a silane functional group. Such silane function groups are especially suitable for bonding to a silicone surface of a medical device, with which they form one or more siloxane bonds. However, they may also be used for covalent attachment to other surfaces, such as metal oxides, stainless steel, and glass.

Suitable exemplary silane-containing surface linker groups include trialkoxy and trichloro silanes (as shown below), which are appropriate for attachment to glass, oxidised polymers, such as silicone, metal oxides and stainless steel. Such linker groups may be introduced to the calixarene compounds via the formation of cyclic Mannsch-type structures as depicted in Scheme C below; or by formation of resorcsnarene esters and amides as shown Scheme D below.
Exampiary silane-containing linker structures, where \( n \) may be 0 or 1; \( m \) may be 1 to 9; \( Z \) may be \( C_i \) or \( O \)-alkyl.

Yet more preferably, the silane-containing surface linker groups to be substituted at one or more of \( X \) and/or \( Y \) may, in accordance with the invention, be defined by the formula \( L^4 \text{-Si}(R^3)_3; \) or \( X \) and an adjacent \( Y \) group together form

\[
L^4 \text{ is a spacer group;} \\
R^3 \text{ is } (C_2-C_0)\text{-alkylene-Si}(R^2)_3, \text{ wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;} \\
\text{Si}(R^2)_3 \text{ is selected from } \text{Si}[(\text{O}(C_1-C_4)\text{-alkyl})_3, \text{ SiCl}_3, \text{ Si}[(\text{C}-C_4)\text{-alkyl}]_2\text{Cl} \text{ and } \text{Si}[(\text{C}_1-C_4)\text{-alkyl}]\text{Cl}_2; \text{ and wherein each alkyl and each surface linker group may be the same or different}

In such groups the silane functionality is for bonding to the surface of the medical device.

Preferably in these aspects of the invention, \( L^4 \) is selected from \( 0(C_2-C_0)\text{-alkylene, CH}_2\text{NH(C}_2-C_10)\text{-alkylene, OCH}_2\text{CO}_2(C_2-C_10)\text{-alkylene and OCH}_2\text{CONH(C}_2-C_10)\text{-alkylene; wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds.} \)
Ionic Surface Attachment

Ionic surfaces may be positively charged or negatively charged, and so for ionic attachment the linker group has the opposite charge. Primarily, a substrate, e.g. of medical devices, may naturally have a surface carrying an overall negative charge. Such substrates include glass, polymers – particularly functionally modified polymers (preferred being plasma-modified polymers), and metals, particularly those comprising native oxide (metal oxide) layers on the surface, such as stainless steel and/or titanium.

In these aspects and embodiments, therefore, the calixarene compounds are desirable modified to include one or more positively charged surface linkers. Suitable positively charged linker groups include ammonium and sulfoxonium groups, such as trialkylammonium and dialkylsulfonium salts as defined below.

Suitable linkers for ionic attachment to a surface have the general formula $L^1\cdot X$ or $L^2\cdot X$, where $X$ carries an opposite charge to that of the target surface. More suitably $X$ carries a positive charge, such as ammonium and sulfoxonium. Preferred linker groups are those wherein $X$ comprises alkylammonium and alkylsulfonium salts. $L^1$ and $L^2$ are any suitable spacer group, such as alkyl, alkenyl and alkynyl (e.g. selected from $C_1\cdot C_{20}$, $C_1\cdot C_{2}$, $C_1\cdot C_{3}$, $C_1\cdot C_{4}$, $C_{1}\cdot C_{20}$, $C_1\cdot C_{16}$, $C_{2}\cdot C_{12}$, or $C_4\cdot C_8$), and variations thereof, such as ether, ester, carbonyl, nitrate, nitro, amino, sulfonyl modified or substituted variants. $L^1$ and $L^2$ may be branched chain or linear, and are preferably linear; and may be saturated or unsaturated, and are preferably saturated. Exemplary $L^1$ and $L^2$ spacers include $CH_2CO_2$, $CH_2CONH$, $CO_2$ and $C(0)NH$. Preferred $X$ moieties are $N^+(Alkyl)_3$ or $S^+(Alkyl)_2$, wherein alkyl is defined as above, or is suitable $C_1\cdot Ce$ alkyl and preferably methyl; although $X$ moieties having one or more alkynyl and/or alkynyl group are also encompassed. In some linkers the alkyl, alkenyl or alkynyl may be optionally substituted by one or more (e.g. 1, 2 or 3) of fluoro, methyl or ethyl groups.

Surface linker groups for ionic attachment may be attached to the phenyl groups of calixarene compounds of the invention as illustrated below.
Modification of the caixarene compound to introduce these functional groups can be performed as shown in Scheme C in respect to a resorcinarene bowl.
Scheme C: Potential reaction schemes for the synthesis of trialkylammonium and dialkylsulfonium compounds. L¹, L² as defined above, e.g. suitably selected from CH₃CO₂, CH₃CONH, CO₂ and C(0)NH; X as defined above, e.g. selected from N⁺(alkyl)₃ or S⁺(alkyl)₂; Q = O, NH; Y is any appropriate leaving group, such as OSO₂Ar or halide.

The converse attachment chemistry, where a negatively charged calixarene compound of the invention is bound to a positively-charged surface is within the skill of the person in the art, and, where the surface concerned does not possess a natural positive charged, can be readily achieved by pre-modification of the substrate/surface to bear a net positive charge. The addition of primer layers to a substrate to achieve a general positive charge may be performed in accordance with methods known in the art.

An alternative methodology for ionic attachment to surfaces, particularly to metallic substrates, such as aluminium oxide, stainless steel and titanium is the use of phosphonic acid or phosphate surface tethers. The phosphonic acid and phosphate functional groups form a strong ionic interaction with the target substrates. Thus, the ionic surface linker group may have the formula L¹-X, where X comprises a phosphonic acid or phosphate group, and L¹ is as defined above. For example, X may suitably be -PO(OR)₂ or -OPO(OR)₂; wherein R⁰ is suitably hydrogen, or an alkyl, akenyl or alkynyl as defined above; more suitably is hydrogen or alkyl, e.g. C₁-C₆ alkyl; and preferably is hydrogen or methyl. Most preferably, X is -PQ(OH)₂ or -OPO(OH)₂.

Exemplary chemical mechanisms for attachment of phosphonic acid linkers to calixarene compounds of the invention are illustrated below, wherein n is 0 or 1; and m is 1 to 9.
Formation of phosphonic acid and phosphate-containing linkers may be achieved in a manner analogous to the trialkylammonium and dialkyilsulfonium salts in Scheme C above, and/or as illustrated in Scheme D below.

Scheme D: synthetic scheme for synthesis of calixarene compounds comprising phosphonic acid linker groups. In phosphate-comprising linkers it will be appreciated that the P-C bond / group of the phosphonic acid will be replaced with P-G-C group.

Hydrogen-Bonding Surface Attachment

Hydrogen-bonds may be used to attach / associate a calixarene compound to an appropriate surface. Suitable calixarene compounds may be of Formulas (I) and (1). Such a system is applicable to a wide number of substrates, including silicones, plastics, metals, glass and paper (Rebek et al., and others).
A most suitable example of hydrogen bond donors used for attachment of a caiixarene compound of the invention (e.g. a resorcinarene) to an appropriate surface is where at least one X and/or Y group of Formula (I) or (II) is hydroxy!. Thus, the parent phenolic OH group(s) are used.

Other approaches using superior hydrogen-bonding groups are also possible, such as where the surface linker groups comprise a carboxylate and/or amide moiety. Such linker groups may be made using any appropriate method – for example, by alkylation of a phenol group with an α-halo ester, and subsequent acidic hydrolysis of the resultant (resorcinarene) ester, in a manner well known to the person of skill in the art. In the case of an amide linker group, coupling with an alkyl amine is readily achieved using reaction Scheme E, below.

Scheme E: Exemplary reaction scheme for attachment of carboxyl and amido hydrogen-bond donors; where X is any appropriate leaving group, e.g. halide.

Van der Waals (hydrophobic) Surface Attachment

Hydrophobic interactions may be used to connect a caiixarene compound to a surface of a medical device in accordance with the invention. Hydrophobic / Van der Waals forces are generally the weakest of the four attachment systems described herein, but may be applicable for some applications – particularly if it is desired that the coating of the substrate be temporary or reversible.
Without being bound by any particular theory, in this attachment system it is thought that the 'tails' of the surface linker are required to penetrate the substrate to maximize the Van der Waals interactions. Such interactions may be applicable in cases where the surface comprises a hydrophobic polymer, such as polyethylene or polystyrene.

Generally, to utilise Van der Waals forces, the surface linker group comprises a long alkyl, fluoroalkyl ester, ether or amide, and aikenyi or alkynyl variants, which may be straight chain or branched. Suitable long alkyl groups may contain at least 18 carbon atoms, e.g. C$_{18}$-C$_{100}$, C$_{16}$-C$_{60}$, C$_{16}$-C$_{40}$ or C$_{16}$-C$_{30}$. Preferably, the linker may contain 16 to 22 carbon atoms (C$_{16}$-C$_{22}$). By way of example, surface linker groups for Van der Waals interactions may be attached to calixarene compounds of the invention using the method exemplified in Scheme E above, wherein the aikyl is a long alkyl, aikenyi or alkynyl as described above.

In such aspects and embodiments of the invention, the deposition of the calixarene compound onto a viable surface would be primarily via Langmuir-Biodgett or Langmuir-Schaeffer deposition, although the use of inert matrices of long chain surfactants as a co-deposition is an alternative, as will be understood by the person of skill in the art.

_Calixarene Compounds and intermediates;

In a further aspect, the present invention provides a compound of formula (I)
wherein
X is H, (C₁-C₄)alkyi, NH₂, NH(C₁-C₄)alkyl, N(C₁-C₄)alkyl₂ or GH₂NH(C₁-C₄)alkyi, and Y is
OH, 0(Cl-C₄)alkyl or OCH₂CO₂(C₁-C₄)alkyl; or
X is OH, 0(C₁-C₄)alkyl or OCH₂CO₂(C₁-C₄)alkyl, and Y is H, (C₁-C₄)alkyl, NH₂, NH(C₁-C₄)alkyl, N(C₁-C₄)alkyl₂ or CH₃NH(C₁-C₄)alkyi; or
X and Y are each independently OH, 0(C₁-C₄)alkyl or OCH₂CO₂(C₁-C₄)alkyi; or
Z is H, OH or methyl;
n is 1, 3 or 5; and
R is -(C₅-C₁₈)alkylene-L₃-G~ R¹ wherein said aikyiene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;
L³ is a bond or a linking group:
G is -O(H₂CH₂O)m−, -O(CH₂CH(CH₃)O)m−, -O(CH(CH₃)CH₂O)m−, or -O(CH₂CH₂CH₂O)m−;
m is 2 to 250;
R¹ is H or (Cl-C₄)alkyl;
and wherein each X, Y, Z, R and R¹ group may be the same or different;
with the proviso that when X is H; Y is OH; Z is H; and n is 1; R is not -(C₃)alkylene-
G(CH₂CH₂O)₄CH₃.
In some preferred embodiments, X is H and Y is OH; Z is H; and/or n is 1.
In some preferred embodiments, R is -(C₂:0)alkylene-L₃-G-R¹. Preferably, L³ is a linking group selected from those of Scheme A and Scheme B above. More preferably, L³ is a linking group selected from carbonate, carbamate, urea, phosphate and triazoi. More preferably, L³ is carbonate.
Preferably, G is -O(CH₂CH₂O)m−. Preferably, m is 3 to 150. More preferably, m is 6 to 50. Most preferably, m is 15 to 25.
Preferably, R¹ is H or methyl.
It will be appreciated that preferred features of the compounds of the invention may be selected individually or in any combination.
In a further aspect, the present invention provides a compound of formula (I):
wherein

\[ X_i \text{ is } H, \text{ } \text{CC} \text{aikyl, } \text{NH}_{2}, \text{ NH}(\text{C}_1-\text{C}_4)\text{alkyl, } N(\text{C}_1-\text{C}_4)\text{alkyl}_2 \text{ or } \text{CH}_{2}\text{NH}(\text{C}_1-\text{C}_4)\text{alkyl, and } Y \text{ is } \text{OH, } 0(\text{C}_1-\text{C}_4)\text{alkyl or } 0\text{CH}_2\text{C}0_2(\text{C}_1-\text{C}_4)\text{alkyl; or } \]

\[ X \text{ is } \text{OH, } 0(\text{Cl-C}_4)\text{alkyl or } \text{OCH}_2\text{C}0_2(\text{C}_1-\text{C}_4)\text{alkyl, and } Y \text{ is } H, \text{ (C}_1-\text{C}_4)\text{alkyl, } \text{NH}_{2}, \text{ NH}(\text{C}_1-\text{C}_4)\text{alkyl, } N(\text{C}_1-\text{C}_4)\text{alkyl}_2 \text{ or } \text{CH}_2\text{NH}(\text{C}_1-\text{C}_4)\text{alkyl; or } \]

\[ X \text{ and } Y \text{ are each independently } \text{OH, } 0(\text{C}_1-\text{C}_4)\text{alkyl or } \text{OCH}_2\text{C}0_2(\text{C}_1-\text{C}_4)\text{alkyl; } \]

and any one or more \( X \) or \( Y \) groups, individually or in combination, may be substituted for a surface linker group;

\[ Z \text{ is } H, \text{ OH or methyl; } \]

\[ n \text{ is } 1, 3 \text{ or } 5; \text{ and } \]

\[ R \text{ is } -(\text{C}_3-\text{C}_{16})\text{alkylene-L}^3\text{-G- } R' \text{ wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds; } \]

\[ L^3\text{ is a bond or a linking group; } \]

\[ G \text{ is } -O(\text{CH}_2\text{CH}_20)_m, -O(\text{CH}_2\text{CH}(\text{CH}_3)0)_m, -Q(\text{CH}(\text{CH}_3)\text{CH}_20)_m, \text{ or } -Q(\text{CH}_2\text{CH}_2\text{CH}_20)_m; \]

\[ m \text{ is } 2 \text{ to } 250; \]

\[ R' \text{ is H or } (\text{C}_1-\text{C}_4)\text{alkyl; } \]

and wherein each \( X, Y, Z, R \) and \( R' \) group, and each surface-linker group, may be the same or different.
Preferably, the surface-linker groups substituted at X and/or Y, or a combination thereof, on the caiixarene are selected from any of the surface linker groups defined herein. Preferably, the surface linker group is selected for covalent or ionic surface attachment, e.g. the moiety at the X and/or Y positions comprises a group selected from acid chloride, chloroformate or silane functional groups; or ammonium, sulfonium, phosphonium, or phosphate. In other embodiments, the surface linker group is selected for hydrogen-bonding attachment, e.g. the moiety at the X and/or Y positions comprises a group selected from (alkyl, aikenyl or alkynyl)hydroxyl, (alkyi, alkenyl or alkynyl)carboxy! and {alkyl, alkenyl or alkynyl}amde; or long-chain alkyl, alkenyl, alkynyl, or ester, ether or amides thereof.

More preferably, the surface-linker groups X or Y, or a combination thereof, on the caiiixarene are silane functional groups, which may form one or more siloxane bonds with a device having a silicone surface.

Yet more preferably, the surface-linker groups X and/or Y are L^4-Si(R^3)_3, or X and an adjacent Y group together form

![Caiixarene](image)

L^4 is a spacer group;
R^3 is (C_2-C_10)alkylene-Si(R^2)_3, wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;
Si(R^2)_3 is selected from Si[0(d-d)alkyl]_3, SiCl_3, Si[(d-d)alkyl]_2Cl and Si[(d-d)alkyl]Cl_2; and each aikyi and each surface-linker group may be the same or different.

Preferably, L^4 is selected from O(C_2-C_10)alkylene, CH_2NH(C_2-C_10)alkylene, OCH_2C=0 d-d aikylene and OCH_2CONH(C_2 d-d)alkylene, wherein said alkySene may...
be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds.

Preferably, \( X \) is \( \text{H} \) and \( Y \) is \( \text{OH} \). Preferably, \( Z \) is \( \text{H} \). Preferably, \( n \) is \%.

Preferably, \( R \) is \(-\text{C}_{10}\text{alkylene}-L^3\text{-G-R}^1\). Preferably, \( L^3 \) is a linking group selected from those of Scheme A and Scheme B above. More preferably, \( L^3 \) is a linking group selected from carbonate, carbamate, urea, phosphate and triazole. More preferably, \( L^3 \) is carbonate.

Preferably, \( G \) is \(-0\text{(CH}_2\text{CH}_2\text{O})_m\text{-} \). Preferably, \( m \) is 3 to 150. More preferably, \( m \) is 6 to 50. Most preferably, \( m \) is 15 to 25.

Preferably, \( R^3 \) is \( \text{H} \) or methyl.

In a preferred aspect, the compound of formula (ii) is

\[
\begin{align*}
\text{R}^3
\end{align*}
\]

or

wherein

\( R \) is \(-\text{C}_{10}\text{alkylene-OC(O)O-(CH}2\text{CH}_2\text{O})_m\text{-OH; and} \)
R is \((\text{C}_3)\text{alkylene-Si(OEt)}\) or a combination thereof. Preferably, m is 3 to 150. More preferably, m is 8 to 50. Most preferably, m is 15 to 25.

In a further aspect, the present invention provides a compound of formula (M1)

\[
\begin{array}{c}
\text{R} \quad \text{X} \\
\text{Y} \\
\text{Z} \\
\text{n}
\end{array}
\]

wherein
X, Y, Z and n are as defined herein including all aspects and preferred embodiments thereof; and

R is -(C\(_3\)-C\(_{18}\))alkylene-OH or -(C\(_2\)-C\(_{15}\))alkylene-CH\(_2=\text{CH}_2\) wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;
and wherein each X, Y, Z and R group may be the same or different;
with the proviso that when X is H, OH, CH\(_3\) or OCH\(_3\); Y is OH; Z is H; and n is 1; R is not -(C\(_6\))alkylene-CH\(_2=\text{CH}_2\).

**Methods and Medical Devices:**

in a further aspect, the present invention provides a process / method for coating a surface of an implantable medical device, as defined herein. Any suitable implantable medical device may be coated (or partially coated) using calixarene compounds of the invention to prevent microorganism growth, as described elsewhere. Suitably, the medical device is a catheter, and more particularly, a urinary tract catheter.
The surface of the medical device may comprise a metal (e.g. metal oxide, stainless steel, titanium), polymer or glass. Preferred substrates for attachment of calixarene compounds of the invention are functionally-modified polymers, e.g. plasma-modified polymers, and more suitably, comprising silicone surfaces. Thus, the coated medical devices of the invention may suitably comprise a plasma-activated silicone surface; and the methods of the invention may suitably comprises plasma activation of a silicone surface of the device, followed by reaction with a compound of formula (II) as defined herein.

In a further aspect, the present invention provides an implantable medical device preparable by a coating process as defined herein.

Included within the scope of the present invention are all stereoisomers, geometric isomers, tautomeric forms, and all medically acceptable isotopically-labeled compounds of formula (I), (II) and (III), and all implantable medical devices derived therefrom.

Microorganisms:

The coatings of the invention desirably prevent the undesirable colonisation of surfaces of implantable medical devices with microorganisms, such as bacteria and fungi. Suitably the microorganism is a gram-negative or gram-positive bacteria, and most suitably, is a gram-negative bacteria.

There are a number of microorganisms associated with infections arising from implantable medical devices. For example, microorganisms that may be involved in both standard urinary tract infections (UTI) and in catheter-associated urinary tract infections (CAUTI) include:

*Escherichia coli*, or uropathogenic *E. coli* (UPEC), a gram negative bacterium, which is a part of the faecal flora and is the most common cause of both UTI (90%) and CAUTI (50%). It is also the standard gram negative bacterium used in ISO 22198 tests.

*Enterococcus faecalis*, a gram positive bacterium, which is also a part of the gut flora and often associated with CAUTI. It is resistant to many commonly used antibiotics.
Pseudomonas aeruginosa, a gram negative bacterium, that usually comes from the environment or the skin. It is increasingly common in hospital environments, especially in intensive care units. It is often found in catheter biofilms and is well known for its ability to form biofilms on medical devices and for its high resistance to a range of different antibiotics.

Klebsiella pneumonia, a gram negative bacterium found on the skin and in the intestines and is often associated with CAUTI.

Typically, therefore, the bacteria is a gram negative bacteria. However, it is desirable to prevent biofilms of gram positive bacteria also. Other relevant gram positive species include Streptococci and Staphylococci, which may also sometimes be found in CAUTI. Indeed, materials for medical devices are often tested against Staphylococcus aureus (of which MRSA is a variant), and it is a 'standard' gram positive bacterium recommended for ISO 22198 tests.

In some cases Candida albicans may also be involved in infections associated with implantable medical devices, and the coatings of the invention also suitably prevent colonisation of such yeast or fungus.

The coatings of the invention may be suitable for targeting of both gram negative and gram positive bacteria, and also fungi if some relevant applications.

Processes for preparing caisxarens compounds:

The compounds and devices of the present invention as described herein may be prepared according to the following methods.
Formation of Protected Resorcinarene 'PEG acceptors'

Scheme 1-Compound 1 synthesised according to Reinhoudt reference (Synthesis, 1995, 989) provided from suitable phenol and aldehyde or acetal in an alcoholic solvent such as ethanolic under acid catalysis. Z=H, OH, Me.

Compound 2; PG=Suitable protecting group, such as tButoxycarbonyl.

Compound 4; X= Appropriate leaving group-halide, mesyl, tosyf or sulfonyl derivative such as 4-nitrophenylsulfonyl.

Conditions: i) Appropriate protection sequence- representative is di-tertbutyl dicarbonate with a nucleophilic catalyst (e.g. pyridine or 4-dimethylaminopyridine) in a suitable solvent, such as dichloromethane. Another common one is appropriate acetyl chloride, e.g. trimethylacetyl chloride with suitable base, e.g. triethylamine, diisopropylethylamine in suitable solvent, e.g. dichloromethane.

ii) Borane or suitable alkylborane, such as dicyclohexylborane at G-3°C in a solvent such as tetrahydrofuran, followed by hydrogen peroxide and aqueous solution of suitable hydroxide base such as sodium hydroxide.

iii) Suitable phosphine, e.g. triphenylphosphine, halide donor such as carbon tetrabromide in dichloromethane or similar, or a sulfonyl chloride, e.g. p-toluenesulfonyl chloride, base such as triethylamine, pyridine, 4-dimethylaminopyridine in suitable solvent, e.g. dichloromethane.

iv) Azide donor, such as sodium azide, trimethylsilyl azide in suitable solvent, e.g. tetrahydrofuran.
v) Suitable phosphine, e.g. triphenylphosphine in appropriate solvent, e.g. dichloromethane, or hydrogen and palladium on carbon in appropriate solvent, e.g. ethanol.

\[ \text{Scheme 2} \]

Conditions: vi) thiolacetic acid, suitable radical initiator such as azo(bisisobutyryl)nitriie, heated to 80°C or irradiated with a UV lamp in toluene or similar solvent vii) Suitable thioacetate salt, such as potassium thioacetate in appropriate solvent, e.g. tetrahydrofuran. viii) Suitable base, such as piperidine, pyrrolidine, ammonium hydroxide. Alternative is reductant such as lithium aluminium hydride in suitable solvent, e.g. tetrahydrofuran. ix) N-chlorosuccinimide, hydrochloric acid, appropriate solvent such as acetonitrile.
Conditions: x) Suitable phosphine, e.g. triphenylphosphine, suitable azodicarboxylic ester e.g. diethylazodicarboxylate, triphenylmethanethiol in suitable solvent such as dichloromethane or tetrahydrofuran. xi) triphenylmethanethiol, suitable base, e.g. sodium hydride or potassium tertbutoxide in suitable solvent, e.g. tetrahydrofuran. xii) trifluoroacetic acid, suitable silane, e.g. triisopropyliosilane in appropriate solvent, e.g. dichloromethane.

Scheme 4: Compound 11: $X = $ Appropriate halide, such as Cl, Br
Compound 12: $Y = $ Appropriate substituent, e.g. alkoxy, trimethylsioxy
Compound 14: $Y_2 = $ Appropriate halide, e.g. Cl, Br.

Conditions: xiii) phosphorus oxychloride (3 equivalents) or similar P(V) compound in suitable solvent, e.g. dichloromethane, or phosphorus trichloride (3 equivalents) or similar then suitable oxidant, e.g. $\cdot H_2$, and base such as pyridine in appropriate solvent, e.g. acetonitrile. xiv) suitable phosphate eg. triethylphosphite heated at 130-160°C. xv) An alkylsilyle halide, such as trimethylsilylbromide in suitable solvent, e.g. dichloromethane, followed by methanol. xvi) Appropriate halide donor, such as thionyl chloride.
Conditions: xvii) appropriate oxidant such as meta-chloroperbenzoic acid in suitable solvent, e.g. dichloromethane.

**Formation of PEG-resorcsnarene conjugates**

Scheme 5

Conditions: xvii) appropriate oxidant such as meta-chloroperbenzoic acid in suitable solvent, e.g. dichloromethane.
Scheme 6: Compounds 17, 21; A = appropriate spacer group
R₂= Hailde, aikoxy

Compound 18, 20, 21; D = O, NH, CH₃
PEG= poly(ethylene glycol) repeat unit >3, terminus OH, OaiKoxy

Conditions: xviii) Suitable deprotection strategy, e.g. heating under vacuum to 130°C for PG=C₀₂Bu. xix) 37% aq. formaldehyde (25 equivalents), suitable α,ω-aminosilane eg. 3-[(aminopropy)triethoxysilane. Refluxed in an alcoholic solvent, e.g. ethanol. xx) suitable PEG-electrolyte, e.g. PEG-chloroformate, PEG-isocyanate, appropriate amine base, e.g. triethylamine in a suitable solvent, e.g. dichloromethane, tetrahydrofuran.
Scheme 7: Compounds 22-24; E = O, NH, S

Conditions: xxi) Suitable nucleophilic-terminated PEG, such as alcohol, amine or thiol-terminated PEG, appropriate base, e.g. sodium hydride or triethylamine in a suitable solvent, e.g. tetrahydrofuran.
Scheme 8: Compound 27; suitable spacer group; e.g. alkyl

Compound 28; \( Y_3 = \text{PEG, alkyl, aryl} \)

Conditions: xxii) Appropriate alkyne-terminated PEG species, catalytic Cu(I) salt.

Suitable solvent, xxiii), suitable solvent, e.g. 2:1 tetrahydrofuran: water
Scheme 9
Conditions: xxiv) suitable maleimide-terminated PEG, appropriate solvent, e.g. dichloromethane. xxv) suitable α-haloamide-terminated PEG, e.g. a-bromoacetarnidyli PEG, suitable solvent, e.g. tetrahydrofuran. xxvi) appropriate olefin-terminated PEG, e.g. O-allyl PEG, suitable solvent, e.g. tetrahydrofuran. xxvii) appropriate PEG species, e.g. methoxyPEG-350, suitable base, e.g. triethylamine, pyridine, 4-dimethylaminopyridine, suitable solvent, e.g. dichloromethane.
Scheme 10: Compounds 37-42; \( Y_4 = 0 \), OPEG.

Conditions: xxvisi) suitable PEG, e.g. methoxyPEG-350, suitable base, e.g. triethylamine, appropriate solvent, e.g. dichloromethane.
Scheme 11
Conditions: xxix) appropriate aldehyde-terminated PEG, e.g. PEGOCH₂CHO, suitable strong base, e.g. potassium tert-butoxide, suitable solvent, e.g. N,N-dimethylformamide. xxx) Suitable olefin metathesis catalyst, e.g. Grubb's 2nd generation catalyst, suitable solvent, e.g. toluene. xxxi) appropriate reduction, e.g. Lindlar's catalyst, hydrogen, suitable alcoholic solvent, e.g. ethanol.
Scheme 12: Compounds 49-51; E = O, NH, S

Conditions: As previously described

Methods for the preparation of the resorcinarene of formula (I) and processes for coating materials are disclosed in WO 97/39077 and at http://www.rsc.org/pdf/mcg/shefcotes.pdf. Other suitable methods for coating medical devices are known to those skilled in the art and include, e.g. methods described in WO 2005/112570, US 6702850, US 6602287, US 5053048, US 7070798 and US 2002/0102405. The surface of the medical devices may also be subject to treatment to modify the surface properties prior to coating such as disclosed in US 4445998 and Kim, Surface and Coatings Technology, 171, 2003, 312-316.

Experimental Details

Instrumentation:

All NMR spectra were recorded on a Bruker AV400 spectrometer operating at 400MHz for $^1$H and 101MHz for $^{13}$C, a Bruker AV250 operating at 250MHz for $^1$H and 63MHz for $^{13}$C, or a Bruker DPX operating at 400MHz for $^1$H and 101MHz for $^{13}$C, with chemical shifts reported in parts per million (ppm). $^1$H spectra were referenced against the appropriate residual solvent signal; CDCl$_3$ = 7.26ppm, Acetone = 2.05ppm. $^{13}$C spectra
were also referenced against the appropriate solvent signal; CDC$_3$ = 77.16ppm, Acetone = 206.26ppm.

Mass spectra were obtained on a Waters LCT spectrometer for electrospray (ES) experiments, and a Bruker Reflex IN for matrix-assisted laser desorption ionisation (MALDI) experiments.

Infrared (IR) spectra were obtained on either a Perkin Elmer Paragon 1000 spectrometer equipped with a SensIR Technologies DuroSampler ATR accessory, or a Perkin Elmer Spectrum 100 spectrometer fitted with an ATR attachment.

Plasma treatment of samples was performed in a home-built plasma generator, operating at a pressure of 1x10$^{-1}$mbar, and at a forward power of approx. 100W at 13.5MHz.

**Chemicals and Materials:**

All reagents were purchased from Sigma-Aldrich, Aifa-Aesar or Fisher Scientific. Air-sensitive reactions were performed in flame-dried glassware, and under a N$_2$ atmosphere. Anhydrous solvents were obtained from a Grubbs solvent purification system except for acetone, which was purchased from Fisher Scientific. Flash column chromatography was performed using Davisil silica gel, and visualised on precoated Merck F$_{254}$ silica plates using UV light or KMnO$_4$ dip.

Silastic catheters were obtained from Bard, USA, and sheet Silastic silicone was obtained from Dow Chemicals.

Decenyi resorcinarene

![Decenyi resorcinarene](image)

To an ice-cold solution of resorcinol (10.0g, 90.82mmol.) in 3:1 EtOHx.HCl, undecylenic aldehyde (18.87mL, 90.82mmol) was added dropwise under N$_2$. Once addition was
complete, to reaction was warmed to 25°C, then to 75°C, and stirred for 48 h. The reaction was cooled, and any precipitate filtered off. The filtrate was poured into ice-water, and any further precipitate filtered off. The combined solid was recrystallised twice from MeCN to yield the title compound (10.98 g, 46%) as light orange/beige powder.

\[ \text{(100 MHz, Acetone)} \delta (ppm) = 7.58 (s, 4H, Ar H), 6.25 (s, 4H, Ar H), 5.82 (ddt, J = 17.0, 10.2, 6.7 Hz, 4H, CH\text{CHalkyl}), 5.07 - 4.86 (m, 8H, CH\text{CHAalkyl}), 4.30 (t, J = 7.9 Hz, 4H, ArCHAr), 2.30 (dd, J = 14.3, 7.6 Hz, 8H, CH\text{CHGCHCH}_2CH_2), 1.45 - 1.17 (m, 64H, alkyl H).

\[ \text{(101 MHz, Acetone)} \delta (ppm) = 152.89, 139.92, 125.52, 125.24, 114.78, 103.67, 34.62, 34.43, 34.37, 30.64, 30.53, 30.41, 29.98, 29.87, 29.11.

MS (ES\textsuperscript{+}) m/z = 1042 ([M+H\textsubscript{f}]\textsuperscript{+}, 9%), 1059 ([M+H\textsubscript{f}]\textsuperscript{+}, 100%).

HRMS (ES\textsuperscript{+}) m/z = 1041.7233, C\textsubscript{56}H\textsubscript{67}O\textsubscript{8} requires 1041.7183.

IR (powder) \nu (cm\textsuperscript{-1}) = 3192.0 (br s, str., OH stretch), 2923.8, 2853.0 (str., CH stretch), 1640.8 (C=C stretch), 1616.8, 1497.1 (Ar ring), 1443.6 (CH deformation).

Octa-Boc decenyS resorcinarene 2

A stirred solution of 21 (2.00 g, 1.92 mmol.), Boc\textsubscript{2}O (3.69 g, 16.90 mmol.), and pyridine (0.1 mL) in acetone (25 mL) was heated under N\textsubscript{2} for 15 h at reflux. The reaction was concentrated \textit{in vacuo} to give the title compound (3.20 g, 90%) as viscous clear brown oil, which was used without further purification.

\[ \text{(400 MHz, CDCl\textsubscript{3}) \delta (ppm) = 6.91 (br s, 3H, Ar H), 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 4H, CH\text{CHalkyl}), 5.05 - 4.83 (m, 8H, CH\text{CHGCHCH}_2CH_2), 4.31 (t, J = 7.4 Hz, 4H, ArCHAr), 2.07 - 1.94 (m, 15H), 1.85 - 1.80 (m, 8H), 1.48 (s, 72H, Me\textsubscript{3}CO), 1.40 - 1.14 (m, 58H, alkyl H).

\[ \text{(63 MHz, CDCl\textsubscript{3}) \delta (ppm) = 184.33, 151.48, 147.37, 139.31, 132.66, 126.21, 116.78, 114.19, 82.76, 36.59, 35.17, 33.93, 29.94, 29.78, 29.29, 29.09, 28.10, 27.80, 1.95.}

MS (MALDI\textsuperscript{+}) m/z (arb. intensity units) = 1864 ([M+Na\textsuperscript{+}]\textsuperscript{+}, 140), 1880 ([M+K\textsuperscript{+}]\textsuperscript{+}, 270).
IR (oil) ν (cm⁻¹) = 2983.0, 2926.7, 2852.5 (str., CH stretches), 1754 (str., C=0 stretch), 1601.0, 1498.4 (Ar ring), 1461.2 (CH deformations), 1396.0, 1369.3, 1241.7, 1139.6 (str., C-O stretch).

ω-hydroxydecyl octa-Boc resorcinarene 3

To an ice-cold stirred solution of 2 (3.20g, 1.73mmol.) in THF (40mL), BH₃·THF complex (9.69mL, 1M solution in THF) was added dropwise. The reaction was stirred at 0°C for 30min under N₂, then warmed to 25°C and stirred for 5 days. To the reaction H₂O (2mL) was added slowly at 0°C, followed by H₂O₂ (5mL, 100vol.) and 1M NaOH (5mL). This was stirred at 25°C for 1h, then at 50°C for 4h. The crude reaction mixture was poured into H₂O, and extracted with DCM. The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo to yield the title compound (2.846g, 86%) as extremely viscous clear colourless oil.

¹H NMR (250 MHz, CDCl₃) δ = 6.82 (br.s, 4H, Ar H), 4.26 (t, J = 7.1 Hz, 4H, ArCHAr), 3.49 (t, J = 5.9 Hz, 8H, CH₂OH), 1.44 (s, 72H, Me₃CO), 1.18 (d, J = 8.2 Hz, 76H, alkyl chain).

¹³C (101 MHz, CDCl₃ 5 (ppm) = 151.41, 107.96, 82.74, 63.00, 36.45, 32.78, 29.73, 29.66, 29.45, 29.14, 27.67, 25.77, 23.93, 1.03.

MS (MALDI) m/z (arb. intensity units) = 1936 ([M+Na]⁺·SO).
A flask containing 3 (2.89g, 1.51mmol) was heated at 130°C under vacuum until the molten resorcinarene re-solidified. This gave the title compound (1.29g, 77%) as a yellow/white powder once scratched from the flask.

$^1$H NMR (400 MHz, Acetone) δ (ppm) = 8.48 (br. s, 8H, ArOH), 7.56 (s, 4H, ArH), 6.24 (s, 4H, ArH), 4.31 (t, J = 7.9 Hz, 4H, ArCHAr). 3.54 (t, J = 6.5 Hz, 8H, CH$_2$GH), 2.95 (br. s, 4H, OH), 2.37 - 2.22 (m, 8H, CH$_2$CH$_2$OH), 1.58 - 1.44 (m, 8H, (Ar)$_2$CHCH$_2$), 1.43 - 1.22 (m, 72H, alkyl chain).

$^{13}$C NMR (101 MHz, Acetone) δ (ppm) = 152.84, 125.60, 125.37, 103.88, 62.69, 34.47, 34.38, 33.91, 30.70, 30.56, 30.53, 29.12, 26.90.

MS (MALDI) m/z (arb. intensity units) = 1120 ([M+Lip, 310], 1136 ([M+Nap, 270]).

IR (solid) ν (cm$^{-1}$) = 3222.6 (br. str., OH stretch), 2923.1, 2852.4 (sh. str., CH stretches), 1619.4, 1495.0, 1444.0, 1293.8, 1155.5, 1085.9, 1049.9, 845.5.

Siiane S
A stirred solution of 4 (250mg, 0.22mmol.), formaldehyde (0.50mL, 5.50mmol, 37% aq. solution) and (3-aminopropyl)triethoxysilane (0.41 mL, 1.76mmol.) in EtOH (5mL) was heated at reflux for 16h. The voiiatSes were removed in vacuo, and the residue triturated in hexane twice, giving the title compound (419mg, 91%) as red/orange solid.

Partial $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) = Characteristic signals at 4.70, 4.40 (s, ArCH$_2$N), 3.80 (q, OCH$_2$CH$_3$), 3.70 (s, OCH$_2$N), 1.25 (t, OCH$_2$CH$_3$).

IR (solid) $\nu$ (cm$^{-1}$) = 3346.6 (br. OH stretch), 2970.4, 2925.5, 2853.4 (sir. CH stretches), 1598.9, 1468.7 (Ar ring), 1100.3, 1073.0 (sh.,str. C-0 and Si-O stretches), 952.0, 882.8, 775.0 (br., str. C-Si stretch).

MonoMethyl PEG-350 chloroformate 8

To a flask containing ice-cold phosgene solution (4.26mL, 20% in PhMe), PEG-350 (2.10g, 8.00mmol.) was added slowly. The mixture was stirred at 25°C under N$_2$ for 4h, and then purged with a flow of N$_2$ for 20min to remove excess phosgene. The solvent was removed in vacuo to yield the title compound (2.35g, 95%) as clear colourless oil.

$^1$H (400MHz, CDCl$_3$) $\delta$ (ppm) = 4.46 - 4.38 (m, 2H, CW$_2$OCOCI), 3.78 - 3.70 (m, 2H, OCH$_2$CH$_2$OCOCI), 3.67 - 3.57 (m, 2H, OC$H_2$), 3.51 (dd, 5.8, 3.6Hz, 2H, CH$_2$OMe), 3.34 (s, 3H, OMe).

$^{13}$C (101MHz, CDCl$_3$) $\delta$ (ppm) = 150.81, 71.98, 70.83, 70.71, 70.83, 70.56, 68.31, 59.07.


IR (oil) $\nu$ (cm$^{-1}$) = 2869.6 (br., str. CH stretch), 1775.1 (sh., str., C=O stretch), 1098.5 (br.,str. C-0 stretch), 842.6 (str., C-Cl stretch).

PEG-350 carbonate 7
To a stirred ice-cold solution of 5 (419mg, 0.20mmol.) and triethylamine (0.15mL, 0.84mmol.) in DCM (20mL), 6 (41.3mg, 1.00mmol.) in DCM (5mL) was added dropwise. The reaction was stirred at 25°C for 16h, and then diluted with DCM. The organic phase was washed with H₂O, and then dried over MgSO₄, filtered, and concentrated in vacuo to give the title compound (702mg, 98%) as viscous clear orange oil, which solidified to a gel on standing.

Partial ¹H NMR (400 MHz, CDCl₃) δ (ppm) = Characteristic signals appear at 3.85 (m, GCH₂CH₂O), 3.4 (s, OCH₃).

IR (solid) ν (cm⁻¹) = 2970.9, 2923.7, 2888.0 (CH stretches), 1746.9 (sh, carbonate C=O stretch), 1682.5, 1467.6, 1389.9, 1348.5, 1251.6, 1073.7 (str., C-O stretch), 950.6, 780.5 (sh. Si-O stretch).

Surface Protocols:

Air plasma modification of silicone samples

Sheet silicone was cut into 10x10mm squares, peeled away from the PTFE backing, rinsed briefly with ethanoi and dried under N₂ to remove dust, and stored in 30 well plates until used.

Sections of silicone were pumped down in the plasma chamber to a base pressure of 1x10⁻⁵mbar. The air inlet was then adjusted until a constant pressure of 1x10⁻¹mbar was
achieved, and the signal generator gain increased until the plasma ignited. The signal was then optimised to a forward power of ca. 1W, and then maintained for 120 s. The plasma chamber was evacuated to a pressure of 1x10⁻²mbar prior to removal of the samples.

Surface Attachment of 7 to Oxidised Silicone

A 5% (w/v) stock solution of 7 was prepared in ethanol, with the solution heated under N₂ at 60°C if dissolution was difficult. 0.5% (w/v) deposition solutions (5mL total volume) were prepared by diluting fresh 5% stock solution (0.50mL) with dd.H₂O (0.25mL), ethanol (4.25mL) and glacial acetic acid (5μL).

Plasma-modified samples were immediately immersed in the freshly prepared deposition solutions, agitated briefly, and incubated for 120 min. The samples were then rinsed thrice with ethanol, sonicated for 10 min in clean ethanol, rinsed with ethanol, water, then ethanol and dried under a stream of nitrogen.

Biological Tests:

Assessment of the antifouling properties of coated surfaces

The coated catheter material was tested under laboratory conditions to assess effectiveness against relevant urinary tract microorganisms.

Experimental procedures

Coated and uncoated silicone coupons were sterilised prior to testing by exposing to 250 nm UV light for 30 min on each side and placed into sterile 6-well micropiates. The inoculum of *Proteus mirabilis* strain NCTC 11938 was prepared from an overnight culture in Tryptic Soy Broth (TSB; Oxoid, UK), which was washed three times in Phosphate Buffered Saline (PBS) prior to use.

Sterile coupons were submerged in 3 m TSB and seeded with 10⁵ cfu/mL of *Proteus mirabilis* strain NCTC 11938. Cells were allowed to attach for 1 hour at room temperature, and non-attached cells were removed by shaking in sterile PBS at 120 rpm for 20 min. Coupons were then transferred to fresh wells containing 3 m TSB, the
Microplasias were sealed with parafilm and incubated at 37°C. The growth medium was replaced daily by aseptically transferring discs to fresh wells containing 3 ml TSB.

At regular intervals, biofilm formation was monitored by colony counts. Non-attached cells were removed by incubation in PBS with shaking at 120 rpm for 20 min. Coupons were then transferred to tubes containing 10 ml PBS and 10 sterile glass beads, and biofilms were removed by vortexing for 30 seconds.

Bacterial cells were enumerated by serial dilution and spreading onto TSB agar plates, which were incubated at 37°C for 18-24 hours.

Results

The coating was demonstrated to modulate the adhesion and reproduction of the key organism responsible for urinary tract infections, *Pr. Mirabilis*: it does not appear to cause a reduction in the adherent cell number, but rather cellular attachment leads to the death of most cells in contact with the surface leading to a 90% reduction in colonization after four days.

By following similar protocols coatings of the invention were found to modulate the adhesion and reproduction of *E. coli*. 
Claims

1. An implantable medical device having a coating comprising a calixarene bonded to the surface of the device \textit{via} one or more surface-linker groups on one rim of the calixarene,
   wherein the opposing rim of the calixarene is substituted by one or more polyethylene glycol, polypropylene glycol or polytrimethylene glycol groups, or a mixture thereof,
   said surface-linker groups may be bonded to the surface of the device \textit{via} covalent bonds, ionic bonds, hydrogen bonds, or Van der Waals forces,
   said glycol groups are attached to the calixarene \textit{via} (C$_3$ to C$_{16}$)alkylene spacer groups,
   said glycol groups, each independently, have from 2 to 250 repeating glycol units and may be optionally terminated by hydrogen or (C$_1$ to C$_4$)alkyl,
   said (C$_3$ to C$_{16}$)alkyl spacer groups may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds-

2. An implantable medical device according to claim 1, which is a stent, catheter, vascular graft, cardiac pacer lead, heart diaphragm, suture, needle, angioplasty device, artificial joint, heart valve, neurological stimulator or drug pump.

3. An implantable medical device according to claim 2, which comprises a silicone surface.

4. An implantable medical device according to claim 3, which is a catheter,

5. An implantable medical device according to any one of claims 1 to 4, wherein the calixarene is bonded to the surface of the device \textit{via} 2 to 8 surface-linker groups; or \textit{via} 2 or 4 surface-linker groups.

6. An implantable medical device according to any one of claims 1 to 5, wherein said surface-linker groups are bonded to the surface of the device \textit{via} covalent bonds, ionic bonds, hydrogen-bonds or Van der Waals bonds.

7. An implantable medical device according to claim 6, wherein said surface-linker groups are selected from one or more of:
(i) a group comprising acid chloride, chloroformate or silane functional groups;
(ii) a group comprising ammonium, sulfonium, phosphonium, or phosphate functional groups;
(iii) a group comprising hydroxy, alkyl hydroxy, aikeny hydroxy, aikeny carboxyl, aikeny carboxyl, alkyl amide, aikeny amide or aikeny amide;
(iv) a group comprising long-chain (e.g. C_{16-30}) alkyl, aikeny, aikeny, or ester, ether or amides thereof.

8. An implantable medical device according to any one of claims 1 to 7, wherein the rim of the calixarene is substituted by one or more polyethylene glycol groups.

9. An implantable medical device according to any one of claims 1 to 8, wherein said glycol groups are attached to the \{C_3 to C_{16}\} alkylene spacer groups directly or via another linker group.

10. An implantable medical device according to any one of claims 1 to 8, wherein said glycol groups are attached to the alkylene spacer group directly via the oxygen of the glycol or via another linker group.

11. An implantable medical device according to claim 9 or claim 10, wherein the glycol linker group is selected from carbonate, carbamate, urea, phosphate and triazoie.

12. An implantable medical device according to any one of claims 1 to 11, wherein said calixarene is derived from phenols, resorcinols or pyrogallols, or mixtures thereof.

13. An implantable medical device according to any one of claims 1 to 12, wherein said calixarene is a condensation product of phenols and aldehydes, resorcinols and aldehydes, or pyrogallols and aldehydes, or mixtures thereof.

14. An implantable medical device according to any one of claims 1 to 12, wherein said calixarene is derived from a compound of formula (I)
wherein

\[ X \text{ is H, } (C_{1-4})_{\text{alkyl}}, \text{NH}_2, \text{NH}(C_{1-4})_{\text{alkyl}}, \text{N}(C_{1-4})_{\text{alkyl}}_2 \text{ or } \text{CH}_2\text{NH}(C_{1-4})_{\text{alkyl}}, \text{and } Y \text{ is OH, } 0(C_{1-4})_{\text{alkyl}} \text{ or } \text{OCH}_2\text{CG}_2(C_{1-4})_{\text{alkyl}}; \text{ or} \]

\[ X \text{ is OH, } 0(C_{1-4})_{\text{alkyl}} \text{ or } \text{OCH}_2\text{CO}_2(C_{1-4})_{\text{alkyl}}, \text{ and } Y \text{ is H, } (C_{1-4})_{\text{alkyl}}, \text{NH}_2, \text{NH}(C_{1-4})_{\text{alkyl}}_2 \text{ or } \text{CH}_2\text{NH}(C_{1-4})_{\text{alkyl}}; \text{ or} \]

\[ X \text{ and } Y \text{ are each independently OH, } 0(C_{1-4})_{\text{alkyl}} \text{ or } \text{OCH}_2\text{CO}_2(C_{1-4})_{\text{alkyl}}; \]

\[ Z \text{ is H, OH or methyl; } \]

\[ n \text{ is 1, 3 or 5; and} \]

\[ R \text{ is } -(C_{3-15})_{\text{alkylene-L}}^3-G-R^1 \text{ wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds; } \]

\[ L^3 \text{ is a bond or a linking group; } \]

\[ G \text{ is } -\text{O}(\text{CH}_2\text{CH}_2\text{O})_m-, -0(\text{CH}_2\text{CH}(\text{CH}_3)0)_m-, -0(\text{CH}(\text{CH}_3)\text{CH}_20)_m-, \text{ or } -0(\text{CH}_2\text{CH}_2\text{CH}_20)_m; \]

\[ m \text{ is 2 to 250; } \]

\[ R^1 \text{ is H or } (C_{1-4})_{\text{alkyl}}; \]

and wherein each X, Y, Z, R and R' group may be the same or different.

15. An implantable medical device according to claim 14, wherein the calixarene is derived from a compound of formula (I) by substituting one or more of the X or Y substituents with a surface linker group.

16. An implantable medical device according to claim 14 or claim 15, wherein:
(i) $X$ is H and $Y$ is OH;
(ii) $Z$ is H;
(iii) $n$ is 1;
(iv) $R$ is $-(C_{10})$alkylene-$L^3$-$G$-$R^1$;
(v) $L^3$ is a linking group selected from carbonate, carbamate, urea, phosphate and triazole;
(vi) $G$ is $-0(CH_2CH_20)_m$;
(via) $R^1$ is H or methyl; and/or
(viii) $m$ is 3 to 150.

17. An implantable medical device according to any one of claims 14 to 16, wherein $L^3$ is carbonate.

18. An implantable medical device according to any one of claims 14 to 17, wherein $m$ is 8 to 50, or wherein $m$ is 15 to 25.

19. An implantable medical device according to any one of claims 14 to 18, wherein said caiixarene is bonded to the surface of the device via surface-linker groups substituted for any one or more of the X or Y substituents, or a combination thereof.

20. An implantable medical device according to claim 19, wherein the surface-linker groups X or Y, or a combination thereof, on the caiixarene are derived from acid chloride, chloroformate or silane functional groups.

21. An implantable medical device according to claim 19 or claim 20, wherein the surface-linker groups are derived from silane functional groups, which form one or more siloxane bonds with a device having a silicone surface.

22. An implantable medical device according to any one of claims 18 to 20, wherein the surface-linker groups X and/or Y are $L^4$-$Si(R^1)_3$, or $X$ and an adjacent $Y$ group together form
L⁴ is a spacer group;
R³ is (C₂-C₁₀)alkylen-Si(R³)₃, wherein said alkylen may be optionally substituted by
one or more fluoro, methyl or ethyl groups and may optionally contain one or more
unsaturated bonds;
Si(R³)₃ is selected from SiO(C₁₋C₄)alkyl]₃, SiCl₃, Si[(CrC₄)alkyl]Cl and
Si[(CrC₄)alkyl]Cl₂;
each alkylen and each surface-linker group may be the same or different; and
said silane providing functionality for bonding to the surface of the device.

23. An implantable medical device according to claim 22, wherein L⁴ is selected from
O(C₂₋C₁₀)alkylen, CH₂NH(G₂₋C₁₀)alkylen, OCH₂CO₂(C₂₋C₁₀)alkylen and
OCH₂CONH(C₂₋C₁₀)alkylen, wherein said alkylen may be optionally substituted by one
or more fluoro, methyl or ethyl groups and may optionally contain one or more
unsaturated bonds.

24. An implantable medical device according to claim 19, wherein the surface-linker
groups X or Y, or a combination thereof, on the calixarene are derived from ammonium,
sulfonium, phosphonium or phosphate functional groups.

25. An implantable medical device according to claim 19 or claim 24, wherein the
surface-linker groups X or Y, or a combination thereof, on the calixarene comprise one or
more of trialkylammonium, dialkylsulfonium, alkylphosphonic acid and alkylphosphate.

26. A compound of formula (I)
wherein

X is H, \((d-d)\)alkyl, NH\(_2\), NH\((d-d)\)alkyl, N\((C\text{C}_4)\)alkyl or CH\(_2\)NH\((C\text{C}_4)\)alkyl, and Y is

- OH, 0\((C\text{C}_4)\)alkyl or OCH\(_2\)CO\(_2\)(Cl-C\(_4)\)alkyl; or
- X is OH, 0\((Cl-C\text{C}_4)\)alkyl or OCH\(_2\)CO\(_2\)(Cl-C\(_4)\)alkyl, and Y is H, \((d-d)\)alkyl, NH\(_2\), NH\((d-C\text{C}_4)\)alkyl, N\((Cl-C\text{C}_4)\)alkyl or CH\(_2\)NH\((Cl-C\text{C}_4)\)alkyl; or
- X and Y are each independently OH, G\((d-C\text{C}_4)\)alkyl or OCH\(_2\)CO\(_2\)(C\(_1-C\text{C}_4)\)alkyl;
- Z is H, OH or methyl;

- n is 1, 3 or 5; and
- R is -CC\(_3\)-(C\(_1\))alkylene-L\(^3\)-G- R\(^1\) wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;
- L\(^3\) is a bond or a linking group;
- G is -0(CH\(_2\)CH\(_2\)O\(_m\)), -0(CH\(_2\)CH\(_2\)CH\(_3\)O\(_m\)), -0(CH\(_3\)CH\(_2\)CH\(_2\)O\(_m\)), or -0(CH\(_2\)CH\(_2\)CH\(_2\)O\(_m\));
- m is 2 to 250;
- R\(^1\) is H or \((C\text{C}_4)\)alkyl;

and wherein each X, Y, Z, R and R\(^1\) group may be the same or different;

with the proviso that when X is H, Y is OH, Z is H, and n is 1; R is not -(C\(_3)\)alkylene-

27. A compound according to claim 26 as defined in any one of claims 16 to 18.

28. A compound of formula (II)
wherein

X is H, (Cl-C₄)alkyl, NH₂, NH(C₁-C₄)alkyl, N(C₁-C₄)alkyl₂ or CH₂NH(C₇-C₄)alkyl, and Y is

OH, 0(C₁-C₄)alkyl or OCH₂CO₂(C₁-C₄)alkyl; or

X is OH, 0(C₁-C₄)alkyl or OCH₂CO₂(C₁-C₄)alkyl, and Y is H, (d-C^alkyl, NH₂, NH(C₁-C₄)alkyl, N(C₁-C₄)alkyl₂ or CH₂NH(C₇-C₄)alkyl; or

X and Y are each independently OH, 0(C₁-C₄)alkyl or OCH₂CO₂(C₁-C₄)alkyl;

and any one or more X or Y groups, individually or in combination, is substituted for a surface-linker group;

Z is H, OH or methyl;

n is 1, 3 or 5; and

R is -(C₃-C₆)alkylene-L³-G- R¹ wherein said aikylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;

L³ is a bond or a linking group;

G is -0(CH₂CH₂O)ₘ-, -0(CH₂CH(CH₃)O)ₘ-, -0(CH(CH₃)CH₂O)ₘ-, or -0(CH₂CH₂CH₂O)ₘ-;

m is 2 to 250;

R¹ is H or (Cl-C₄)alkyl;

and wherein each X, Y, Z, R and R¹ group, and each surface-linker group, may be the same or different.
29. A compound according to claim 28, wherein the surface-linker groups X or Y, or a combination thereof, on the calixarene are acid chloride, chloroformate or silane functional groups.

30. A compound according to claim 28 or 29, wherein the surface-linker groups X or Y, or a combination thereof, on the calixarene are silane functional groups, which may form one or more siloxane bonds with a device having a silicone surface.

31. A compound according to any one of claims 28 to 30, wherein the surface-linker groups X and/or Y are \( L^4\)-Si(R^2)_3, or X and an adjacent Y group together form \( \text{Ca}^{\text{hexarene}} \)

\[ \text{Ca}^{\text{hexarene}} \]

\[ \text{N} \]

\[ \text{R}^3 \]

15 \( L^4 \) is a spacer group;
\( R^3 \) is \((C_2\text{-}C_{10})\text{alkylene-Si(R}^2\text{)}_3 \), wherein said alkyiene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;
\( \text{Si(R}^2\text{)}_3 \) is selected from \( \text{Si}[(0\text{-}C_4\text{-}C_4)\text{alkyl}]_3 \), \( \text{SiCl}_3 \), \( \text{Si}[(\text{C}_1\text{-}C_4)\text{alkyl}]_2\text{SiCl}_2 \) and \( \text{Si}[(\text{Cl-C}_4)\text{alkyl}]_2\text{SiCl}_2 \); and each alkyl and each surface-linker group may be the same or different.

32. A compound according to claim 31, wherein \( L^4 \) is selected from \( G(C_2\text{-}C_{10})\text{alkyiene}, \) \( \text{CH}_2\text{NH(C2-C}_{10})\text{alkyiene, GCH}_2\text{CO}_2(C_2\text{-}C_{10})\text{alkyiene and OCH}_2\text{CONH(C2-C}_{10})\text{alkyiene} \), wherein said alkyiene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds.

33. A compound according to claim 28, wherein the surface-linker groups X or Y, or a combination thereof, on the calixarene are derived from ammonium, sulfonium, phosphonium or phosphate functional groups.
34. A compound according to claim 28 or claim 33, wherein the surface-linker groups X or Y, or a combination thereof, on the calixarene comprise one or more of trialkylammonium, dialkylsulfonium, dialkylphosphonic acid and dialkylphosphate.

35. A compound according to any one of claims 28 to 34 wherein the substituents X, Y, Z, n, R, L, G and R¹ are as defined in any one of claims 16 to 18.

36. A compound according to claim 28, which is

wherein
R is -(C₁₀)alkylene-OC(O)O-(CH₂CH₂O)ₘ-OH; and/or
R³ is (C₂)alkylene-Si(OEt)₃ or a combination thereof.

37. A compound according to either claim 35 or claim 36 wherein m is as defined in claim 16 or claim 18.

38. A compound of formula (III)
wherein
X, Y, Z and n are as defined in either claim 28 or claim 27; and
R is -(C₃₋C₈)alkylene-OH or -(C₂₋C₁₅)alkylene-CH₂=CH₂ wherein said alkylene may be optionally substituted by one or more fluoro, methyl or ethyl groups and may optionally contain one or more unsaturated bonds;
and wherein each X, Y, Z and R group may be the same or different;
with the proviso that when X is H, OH, CH₃ or OCH₃; Y is OH; Z is H; and n is 1; R is not -(C₃)alkylene-CH₂=CH₂.

39. A process for coating a silicone surface of an implantable medical device, as defined in any one of claims 3 to 25, which comprises plasma activation of the silicone surface of the device followed by reaction with a compound of formula (II) as defined in any one of claims 28 to 37.

40. An implantable medical device preparable by a coating process as defined in claim 39.