CONTROLLED RELEASE COMPOSITIONS

Background of the Invention

This invention relates generally to a composition for controlling the release of biologically active compounds. In particular, this invention relates to the use of certain calixarene compounds to control the release of biologically active compounds.

The ability to control release of biologically active compounds to a locus to be protected is important in the field of biologically active compounds. Typically, when a biologically active compound is added to a locus to be protected, the compound is rapidly released, whether or not it is needed. Controlled release compositions deliver the biologically active compound in a manner that more closely matches the need for the compound. In this way, only the amount of the biologically active compound needed is released into the locus to be protected. Controlled release offers the advantages of reduced cost, lowered toxicity and increased efficiency.

Various methods of controlled release are known. Such methods include encapsulation of the biologically active compound, adsorption of the biologically active compound on an inert carrier, such as silica gel, and clathration of the biologically active compound.

All of these methods have drawbacks to widespread commercial use, such as expensive starting materials, limited compatibility of the controlled release method to the compounds to be released or locus to be protected, and limited control of the release of the biologically active compounds. For example, whether a clathrate forms is solvent dependent, which limits available solvent choices. An additional problem with clathrates is that solvent, rather than the desired biologically active compound, is sometimes incorporated into the complex.

For example, EP 709 358 A (Suzuki et al.) discloses a clathrate of isothiazolones using a tetrakisphenol compound. Although these compositions provide some control of the release of the isothiazolone, the amount of control is

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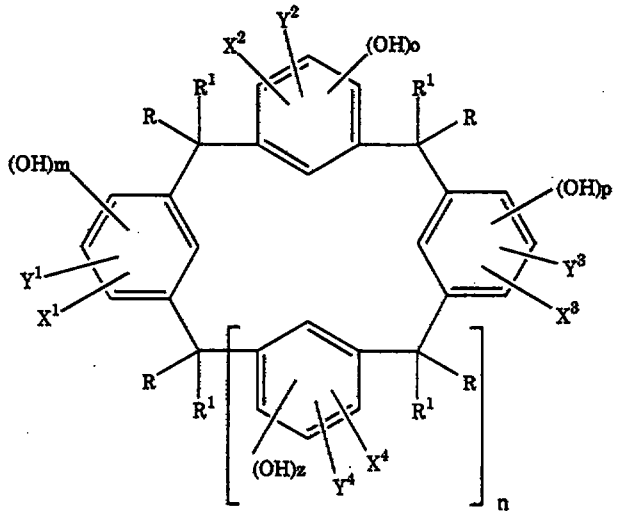
limited and the tetrakisphenol compound used to prepare the clathrate is very expensive. Suzuki et al. do not discuss calixarene compounds.

JP 07 003 191 A, assigned to Kurita, discloses a clathrate of isothiazolones with 5,5'-dichloro-2,2'-dihydroxydiphenylmethane for use in marine antifouling paints. These compositions have achieved limited success because 5,5'-dichloro-2,2'-dihydroxydiphenylmethane is banned in some countries.

There is therefore a continuing need for controlled release biologically active compositions that are inexpensive, compatible in a broad range of loci to be protected, and more effective at controlling the release of the biologically active compound than compositions currently available.

Summary of the Invention

The present invention is directed to a controlled release composition comprising a biologically active compound and a calixarene compound of the formula



(I)

wherein X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3 and Y^4 are independently selected from hydrogen, cyano, nitro, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, phenyl, substituted phenyl, (C_1-C_{10})aralkyl, substituted (C_7-C_{10})aralkyl, NR^2R^3, SR^4; X^1 and Y^1, X^2 and Y^2, X^3 and Y^3, and X^4 and Y^4 may be joined to form a 5- or 6-membered ring; R and R^1 are independently selected from hydrogen, (C_1-C_8)alkyl, cyclopropyl, phenyl, substituted phenyl, (C_7-C_{10})aralkyl,

and substituted (C_7-C_{10})aralkyl; R^2, R^3, and R^4 are independently selected from hydrogen, (C_1-C_4)alkyl, phenyl, and substituted phenyl; n = 1-7; and m, o, p and z are independently selected from 1-3.

The present invention is also directed to a method of controlling or inhibiting the growth of microorganisms in a locus comprising introducing into or onto the locus to be protected an effective amount of the composition described above.

The present invention is further directed to a method of eliminating or inhibiting the growth of marine organisms on a structure comprising introducing into or onto the structure to be protected an effective amount of the composition described above.

The present invention is further directed to a method of eliminating or inhibiting the growth of fungi, plants and insects comprising introducing into or onto the locus to be protected an effective amount of the composition described above.

Detailed Description of the Invention

As used throughout the specification, the following terms shall have the following meanings, unless the context clearly indicates otherwise.

The term "biologically active compounds" refers to microbicides, marine antifouling agents, and agricultural pesticides. "Microbicide" refers to a compound capable of inhibiting the growth of or controlling the growth of microorganisms at a locus. The term "microorganism" includes, but is not limited to, fungi, bacteria, and algae.

"Marine antifouling agent" includes algaecides and molluscicides. "Marine antifouling activity" is intended to include both the elimination of and inhibition of growth of marine organisms. Marine organisms controlled by marine antifouling agents suitable for use in this invention include both hard and soft fouling organisms. Generally speaking, the term "soft fouling organisms" refers to plants and invertebrates, such as slime, algae, kelp, soft corals, tunicates, hydroids, sponges, and anemones, while the term "hard fouling

organisms" refers to invertebrates having some type of hard outer shell, such as barnacles, tubeworms, and molluscs.

"Agricultural pesticides" include agricultural fungicides, herbicides and insecticides. "Agricultural fungicide" refers to a compound capable of inhibiting the growth of or controlling the growth of fungi in an agricultural application, such as treatment of plants and soil; "herbicide" refers to a compound capable of inhibiting the growth of or controlling the growth of certain plants; and "insecticide" refers to a compound capable of controlling insects.

"Alkyl" means straight chain, branched, cyclic, or any combination thereof; "halogen" and "halo" mean fluorine, chlorine, bromine, or iodine. "Substituted phenyl," and "substituted aralkyl" mean one or more of the hydrogens on the aromatic ring are replaced by another substituent, such as cyano, hydroxy, (C_1-C_4)alkyl, nitro, mercapto, (C_1-C_4)alkylthio, halo and (C_1-C_4)alkoxy. All amounts are percent by weight ("%wt"), unless otherwise noted and all %wt ranges are inclusive. As used throughout the specification, the following abbreviations are applied: mg = milligram; mL = milliliter; L = liter; HPLC = high performance liquid chromatography; rpm = revolutions per minute; DI = deionized; and ppm = parts per million.

The biologically active compounds useful in this invention are those which are hydrogen bond acceptors. That is, the compounds are those having one or more atoms selected from nitrogen, oxygen, fluorine or mixtures thereof. The nitrogen or oxygen may have single or multiple bonds, such as in a carbonyl, imine, nitrile, hydroxy, amide, alkoxy, ester, ether or amine group.

Suitable microbicides of the present invention include, but are not limited to: 5-chloro-2-methyl-3-isothiazolone; 2-methyl-3-isothiazolone; 2-n-octyl-3-isothiazolone; 4,5-dichloro-2-n-octyl-3-isothiazolone; 3-iodo-2-propynyl butyl carbamate; 1,2-dibromo-2,4-dicyanobutane; methylene-bis-thiocyanate; 2-thiocyanomethylthiobenzothiazole; tetrachloroisophthalonitrile; 5-bromo-5-nitro-1,3-dioxane; 2-bromo-2-nitopropanediol; 2,2-dibromo-3-nitrilopropionamide; N,N'-dimethylhydroxyl-5,5'-dimethylhydantoin; bromochlorodimethylhydantoin;

1,2-benzisothiazolin-3-one; 4,5-trimethylene-2-methyl-3-isothiazolone; 5-chloro-2-(2,4-dichlorophenoxy)phenol and 3,4,4'-trichlorocarbanilide.

Suitable marine antifouling agents of the present invention include, but are not limited to: manganese ethylenebisdithiocarbamate; zinc dimethyl dithiocarbamate; 2-methyl-4-t-butylamino-6-cyclopropylamino-s-triazine; 2,4,5,6-tetrachloroisophthalonitrile; N,N-dimethyl dichlorophenyl urea; zinc ethylenebisdithiocarbamate; copper thiocyanate; 4,5-dichloro-2-n-octyl-3-isothiazolone; N-(fluorodichloromethylthio)-phthalimide; N,N-dimethyl-N'-phenyl-N'-fluorodichloromethylthio-sulfamide; zinc 2-pyridinethiol-1-oxide; tetramethylthiuram disulfide; 2,4,6-trichlorophenylmaleimide; 2,3,5,6-tetrachloro-4-(methylsulfonyl)-pyridine; 3-iodo-2-propynyl butyl carbamate; diiodomethyl p-tolyl sulfone; bis dimethyl dithiocarbamoyl zinc ethylenebisdithiocarbamate; phenyl (bispyridil) bismuth dichloride; 2-(4-thiazolyl)-benzimidazole; pyridine triphenyl borane; phenylamides; halopropargyl compounds; or 2-haloalkoxyaryl-3-isothiazolones. Suitable 2-haloalkoxyaryl-3-isothiazolones include, but are not limited to, 2-(4-trifluoromethoxyphenyl)-3-isothiazolone, 2-(4-trifluoromethoxyphenyl)-5-chloro-3-isothiazolone, and 2-(4-trifluoromethoxyphenyl)-4,5-dichloro-3-isothiazolone.

Suitable agricultural fungicides of the present invention include, but are not limited to: dithiocarbamate and derivatives such as ferbam, ziram, maneb, mancozeb, zineb, propineb, metham, thiram, the complex of zineb and polyethylene thiuram disulfide, dazomet, and mixtures of these with copper salts; nitrophenol derivatives such as dinocap, binapacryl, and 2-sec-butyl-4,6-dinitrophenyl isopropyl carbonate; heterocyclic structures such as captan folpet, glyodine, dithianon, thioquinox, benomyl, thiabendazole, vinolozolin, iprodione, procymidone, triadimenol, triadimefon, bitertanol, fluoroimide, triarimol, cycloheximide, ethirimol, dodemorph, dimethomorph, thifluzamide, and, quinomethionate; miscellaneous halogenated fungicides such as: chloranil, dichlone, chloroneb, tricamba, dichloran, and polychloronitrobenzenes; fungicidal antibiotics such as: griseofulvin, kasugamycin and streptomycin; miscellaneous fungicides such as: diphenyl sulfone, dodine, methoxyl, 1-thiocyano-2,4-dinitrobenzene, 1-phenylthiosemicarbazide, thiophanate-methyl, and cymoxanil;

as well as acylalanines such as, furalaxyl, cyprofuram, ofurace, benalaxyl, and oxadixyl; fluazinam, flumetover, phenylbenzamide derivatives such as those disclosed in EP 578586 A1, amino acid derivatives such as valine derivatives disclosed in EP 550788 A1, methoxyacrylates such as methyl (E)-2-(2-(6-(2-cyanophenoxy)pyrimidin-4-yloxy)phenyl)-3-methoxyacrylate; benzo(1,2,3)thiadiazole-7-carbothioic acid S-methyl ester: propamocarb; imazalil; carbendazim; myclobutanil; fenbuconazole; tridemorph; pyrazophos; fenarimol; fenpiclonil; and pyrimethanil.

Suitable herbicides of the present invention include, but are not limited to: carboxylic acid derivatives, including benzoic acids and their salts; phenoxy and phenyl substituted carboxylic acids and their salts; and trichloroacetic acid and its salts; carbamic acid derivatives, including ethyl N,N-di(n-propyl)thiolcarbamate and pronamide; substituted ureas, substituted triazines, diphenyl ether derivatives such as oxyfluorfen and fluoroglycofen, anilides such as propanil, oxyphenoxy herbicides, uracils, nitriles, and other organic herbicides such as dithiopy and, thiazopyr.

Suitable insecticides of the present invention include, but are not limited to: acephate; aldicarb; alpha–cypermethrin; azinphos–methyl; bifenthrin; binapacryl; buprofezin; carbaryl; carbofuran; cartap; chlorpyrifos; chlorpyrifos methyl; clofentezine; cyfluthrin; cyhexatin; cypermethrin; cyphenothrin; deltamethrin; demeton; demeton–S–methyl; demeton–O–methyl; demeton–S; demeton–S–methyl sulfoxid; demephion–O; demephion–S; dialifor; diazinon; dicofol; dicrotophos; diflubenzuron; dimethoate; dinocap; endosulfan; endothion; esfenvalerate; ethiofencarb; ethion; ethoate–methyl; ethoprop; etrimfos; fenamiphos; fenazaflor; fenbutatin–oxide; fenitrothion; fenoxycarb; fensulfothion; fenthion; fenvalerate; flucycloxuron; flufenoxuron; fluvalinate; fonofos; fosmethilan; furathiocarb; hexythiazox; isazophos; isofenphos; isoxathion; methamidophos; methidathion; methiocarb; methomyl; methyl parathion; mevinphos; mexacarbate; monocrotophos; nicotine; omethoate; oxamyl; parathion; permethrin; phorate; phosalone; phosmet; phosphamidon; pirimicarb; pirimiphos–ethyl; profenofos; promecarb; propargite; pyridaben; resmethrin;

rotenone; tebufenozide; temephos; TEPP; terbufos; thiodicarb; tolclofos–methyl; triazamate; triazophos and vamidothion.

The biologically active compound is preferably a microbicide or a marine antifouling agent. Especially preferred are 2-methyl-3-isothiazolone, 5-chloro-2-methyl-3-isothiazolone, 2-n-octyl-3-isothiazolone, 4,5-dichloro-2-n-octyl-3-isothiazolone, benzisothiazolone, 4,5-trimethylene-3-isothiazolone, 3-iodo-2-propynyl butyl carbamate; 5-chloro-2-(2,4-dichlorophenoxy)phenol and 3,4,4'-trichlorocarbanilide.

The calixarene compounds useful in this invention include, but are not limited to: 2,8,14,20-tetrapropylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol; 2,8,14,20-tetramethylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol; 2,8,14,20-tetraphenylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol; and 2,8,14,20-tetra-tert-butylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol.

The calixarene compounds useful in this invention are generally commercially available or may be prepared by methods known in the literature. For example, Hogberg, J. Org. Chem., 45, 4498-4500 (1980); Hogberg, J. Am. Chem. Soc., 102, 6046-6050 (1980); and Tunstad et al., J. Org. Chem., 54, 1305-1312 (1989) disclose the preparation of various calixarenes and are herein incorporated by reference to the extent they teach how to make the calixarenes of the present invention.

The compositions of the present invention can be prepared by mixing a solution of the biologically active compound with a solution of the calixarene compound. In the alternative, either the biologically active compound or the calixarene compound may be added neat to a solution of the other component. For example, a calixarene compound may be added neat to a solution of the biologically active compound. The solvent can be removed by any means, such as

under reduced pressure, to yield a solid or liquid composition. The solvent used to dissolve the biologically active compound may be the same or different from that used to dissolve the calixarene compound. When different solvents are used to dissolve the biologically active compound and the calixarene compound, it is preferred that they be miscible with each other. Mixtures of solvents may also be used. Suitable solvents include alcohols, such as methanol, ethanol, and propanol; esters, such as ethyl acetate and butyl acetate; ketones, such as acetone and methyl iso-butyl ketone; nitriles, such as acetonitrile; and the like. In the alternative, either the biologically active compound or the calixarene compound or both may be blended as a melt. When a melt is used to prepare the compositions of the present invention, it is preferred that the biologically active compound is melted and the calixarene combined with the melt. When the compositions of the present invention are oils, it is preferred that they be taken up in a carrier.

The calixarene compounds of the present invention may be loaded with generally from 0.1 %wt to 95 %wt of the biologically active compound, based on the weight of the calixarene compound. Thus, the weight ratio of biologically active compound to calixarene compound in the compositions is generally from 0.1:99.9 to 95:5. Preferably, the weight ratio is from 1:10 to 9:1 and more preferably from 1:3 to 4:1.

More than one biologically active compound may be used in the compositions of the present invention as long as the compounds do not irreversibly react with, or otherwise destabilize, each other and are compatible with the calixarene compound. This has the advantage of controlling the release of multiple biologically active compounds which may provide a broader spectrum of control than one compound alone. Also, this may reduce the cost of treatment when multiple biologically active compounds must be used. When more than one biologically active compound is used, the ratio of the total amount of the biologically active compounds to the calixarene compound is generally from 0.1:99.9 to 95:5.

The compositions of the invention may further comprise a carrier, such as water, organic solvent or mixtures thereof. Suitable organic solvent carriers include, but are not limited to: acetonitrile, ethyl acetate, butyl acetate, toluene, xylene, methanol, ethanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol, and glycol ethers. When the compositions of the invention are to be used in an agricultural application, it is preferred that the carrier be an agronomically acceptable carrier.

The compositions of the invention are useful wherever the biologically active compound would be useful. When the biologically active compound is a microbicide, the compositions of the invention are useful in controlling or inhibiting the growth of microorganisms, such as bacteria and fungi, in a locus. The compositions of the invention are suitable for use in any locus requiring protection from microorganisms. Suitable loci include, but are not limited to: cooling towers; air washers; mineral slurries; pulp and paper processing fluids; paper coatings; swimming pools; spas; adhesives; caulks; mastics; sealants; agriculture adjuvant preservation; construction products; cosmetics and toiletries; shampoos; disinfectants and antiseptics; formulated industrial and consumer products; soaps; laundry rinse waters; leather and leather products; wood, including lumber, timber, fiberboard, plywood, and wood composites; plastics; lubricants; hydraulic fluids; medical devices; metalworking fluids; emulsions and dispersions; paints, including marine paints; varnishes, including marine varnishes; latexes; odor control fluids; coatings, including marine coatings; petroleum processing fluids; fuel; oil field fluids; photographic chemicals; printing fluids; sanitizers; detergents; textiles, such as fibers; and textile products, such as clothes and carpets.

When compositions of the invention comprise a microbicide, they can either be added directly to the locus to be protected or added as a composition further comprising a suitable carrier. Suitable carriers useful for microbicidal applications include, but are not limited to, water; organic solvent, such as ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol, xylene, toluene, acetone, methyl iso-butyl ketone, or esters; or mixtures thereof. The

compositions may also be formulated as microemulsions, microemulsifiable concentrates, emulsions, emulsifiable concentrates, pastes, or may be encapsulated. The particular formulation will depend upon the locus to be protected and the particular microbicide used. The preparation of these formulations is by well known, standard methods.

When the compositions comprise a microbicide, the amount of the compositions of the invention necessary to control or inhibit the growth of microorganisms depends upon the locus to be protected, but is typically sufficient if it provides from 0.5 to 2500 ppm of microbicide, at the locus to be protected. Microbicides are often used in loci that require further dilution. For example, the compositions of the invention may be added to a metal working fluid concentrate, which is then further diluted. The amounts of the compositions of the invention necessary to control microorganism growth in the final metal working fluid dilution are sufficient if they provide generally from 5 to 50 ppm of the microbicide in the final dilution. In loci such as a paint, which is not further diluted, the amount of the compositions of the invention necessary to control microorganism growth are sufficient if they provide generally from 500 to 2500 ppm of the microbicide.

When the biologically active compound of the present invention is a marine antifouling agent, the compositions of the present invention can be used to inhibit the growth of marine organisms by application of the compositions onto or into a marine structure. Depending upon the particular marine structure to be protected, the compositions of the present invention can be directly incorporated into the marine structure, applied directly to the marine structure, or incorporated into a coating which is then applied to the marine structure.

Suitable marine structures include, but are not limited to: boats, oil platforms, piers, pilings, docks, elastomeric rubbers, and fish nets. The compositions of the present invention are typically directly incorporated into structures such as elastomeric rubber or fish net fibers during manufacture. Direct application of the compositions of the invention is typically made to structures such as fish nets or wood pilings. The compositions of the invention

can also be incorporated into a marine coating, such as a marine paint or varnish.

When the compositions of the invention comprise a marine antifouling agent, the amount of the compositions of the invention necessary to inhibit or prevent the growth of marine organisms is typically sufficient if it provides from 0.1 to 30 %wt of marine antifouling agent alone, based on the weight of the structure to be protected or based on the weight of the coating to be applied. When the compositions of the invention are directly incorporated into or directly applied onto a structure, the amount of the compositions necessary to inhibit the growth of marine organisms is generally sufficient if it provides 0.1 to 30 %wt of marine antifouling agent alone, based on the weight of the structure. It is preferred that the amount of the compositions of the invention be sufficient to provide 0.5 to 20 %wt of marine antifouling agent alone; more preferably, 1 to 15 %wt. When incorporated into a coating, the amount of the compositions of the invention suitable to inhibit the growth of marine organisms is generally sufficient if it provides 0.1 to 30 %wt of marine antifouling agent alone, based on the weight of said coating. The amount of the compositions of the invention preferably provides 0.5 to 15 %wt of marine antifouling agent alone; more preferably, 1 to 10 %wt.

In general, the compositions of the invention comprising a marine antifouling agent are incorporated in a carrier such as water; organic solvent, such as xylene, methyl isobutyl ketone, and methyl isoamyl ketone; or mixtures thereof.

Direct applications of the compositions of the invention may be by any conventional means, such as dipping, spraying, or coating. Fish nets, for example, may be also protected by dipping the fish nets into a composition comprising the compositions of the invention and a carrier or by spraying the fish nets with said composition.

Structures such as wood pilings and fish nets may be protected by directly incorporating the compositions of the invention into the structure. For example,

a composition of the invention further comprising a carrier may be applied to wood used for pilings by means of pressure treatment or vacuum impregnation. These compositions may also be incorporated into a fish net fiber during manufacture.

Marine coatings comprise a binder and solvent and optionally other ingredients. The solvent may be either organic solvent or water. The compositions of the invention are suitable for use in both solvent- and water-based marine coatings. Solvent-based marine coatings are preferred.

Any conventional binder may be utilized in the marine antifouling coating incorporating the compositions of the invention. Suitable binders include, but are not limited to: polyvinyl chloride in a solvent-based system; chlorinated rubber in a solvent based system; acrylic resins in solvent-based or aqueous systems; vinyl chloride-vinyl acetate copolymer systems as aqueous dispersions or solvent-based systems; butadiene-styrene rubbers; butadiene-acrylonitrile rubbers; butadiene-styrene-acrylonitrile rubbers; drying oils such as linseed oil; asphalt; epoxies; siloxanes; and the like.

The marine coatings of the present invention may optionally contain one or more of the following: inorganic pigments, organic pigments, or dyes, and controlled release materials, such as rosin. Water-based coatings may also optionally contain: coalescents, dispersants, surface active agents, rheology modifiers, or adhesion promoters. Solvent-based coatings may also optionally contain extenders, plasticizers, or rheology modifiers.

A typical marine coating comprises 2 to 20 %wt binders, up to 15 %wt rosins/modified rosins, 0.5 to 5 %wt plasticizers, 0.1 to 2 %wt antisettling agent, 5 to 60 %wt solvent/diluent, up to 70 %wt cuprous oxide, up to 30 %wt pigments (other than cuprous oxide), and up to 15 %wt marine antifouling agent.

Marine coatings containing the compositions of the invention may be applied to a structure to be protected by any of a number of conventional means.

Suitable means of application include, but are not limited to, spraying; rolling; brushing; or dipping.

When the biologically active compound is an agricultural pesticide, the compositions of the invention may be applied to plants or soil or may be used as seed treatments. The compositions may be used directly or formulated as dusts, granules, flowables, emulsifiable concentrates, microemulsifiable concentrates, emulsions, microemulsions, or may be encapsulated.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any aspect.

Example 1

The following are examples of compositions of the present invention prepared according to the following general method.

A solution or slurry of the calixarene compound in methanol or acetone was placed in a flask. To this solution or slurry was added a solution of 4,5-dichloro-2-n-octyl-3-isothiazolone in the same solvent as the calixarene compound. The amount of the 4,5-dichloro-2-n-octyl-3-isothiazolone added was such that the final product contained from 29-60 %wt of the 4,5-dichloro-2-n-octyl-3-isothiazolone, based on the weight of the composition. After thorough mixing, the solvent was then removed in vacuo at 50° C to yield either a solid or an oil. The yields of the final products were 95-100%. The compositions are reported in Table 1.

Calixarene Compound

A = 2,8,14,20-tetrapropylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol

B = 2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol

C = 2,8,14,20-tetraphenylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol

D = 2,8,14,20-tetra-tert-butylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol

Table 1: Compositions of the Invention

Sample	Calixarene Compound	4,5-Dichloro-2-n-octyl-3-isothiazolone (%wt)	Physical State
1	A	60	Oil
2	B	50	Solid
3	C	29	Solid
4	D	59	Solid

Example 2

The compositions of Example 1 were evaluated for their rate of release of biologically active compound according to the following procedures.

An amount of Sample 2 sufficient to provide 20mg/L of 4,5-dichloro-2-n-octyl-3-isothiazolone if all the 4,5-dichloro-2-n-octyl-3-isothiazolone were released was weighed into a 100 mL glass jar. To this solution was added 100 mL of DI water containing 0.3 %wt of sodium dioctyl sulfosuccinate as surfactant. The solution was then gently stirred. Aliquots (0.5 mL) were taken at various time points and placed in a micro centrifuge tube and centrifuged at 14,000 rpm for 3 minutes. The resultant clear aqueous layer was then analyzed for 4,5-dichloro-2-n-octyl-3-isothiazolone. The centrifuge tube was then washed with 0.5 mL of fresh water/surfactant solution and the wash solution was then returned to the glass jar. This ensured that none of the particles removed during sampling were lost and that the volume stayed constant. The aliquots were

analyzed by HPLC for the amount of 4,5-dichloro-2-n-octyl-3-isothiazolone released. The cumulative percentages of 4,5-dichloro-2-n-octyl-3-isothiazolone released are reported in Table 2.

Table 2: % of 4,5-Dichloro-2-n-octyl-3-isothiazolone Released

Sample	4 Days	7 Days	10 Days
2	9	18	23

From these data, it can be clearly seen that the compositions of the present invention slowly release the 4,5-dichloro-2-n-octyl-3-isothiazolone over a period of days.

Example 3

The compositions of Example 1 were evaluated for the control of the release of biologically active molecules in a marine paint.

A blank paint, that is, one that contained no biologically active molecules, was dosed with Sample 1. The amount of the sample added was such that the total amount of 4,5-dichloro-2-octyl-3-isothiazolone in the paint was 5.6 %wt, based on the total dry weight of the paint. A control paint was prepared by adding 4,5-dichloro-2-octyl-3-isothiazolone alone. Glass slides were painted with the treated paint as well as the control paint and allowed to dry in a hood for 6 days. The slides were then submerged in a tank of synthetic sea water. The slides were removed after 14 days and the paint film extracted. The extracts were analyzed by HPLC to determine the amount of 4,5-dichloro-2-octyl-3-isothiazolone remaining. The amount of 4,5-dichloro-2-octyl-3-isothiazolone released from the paints is reported in Table 3.

Table 3: % of 4,5-Dichloro-2-n-octyl-3-isothiazolone Released

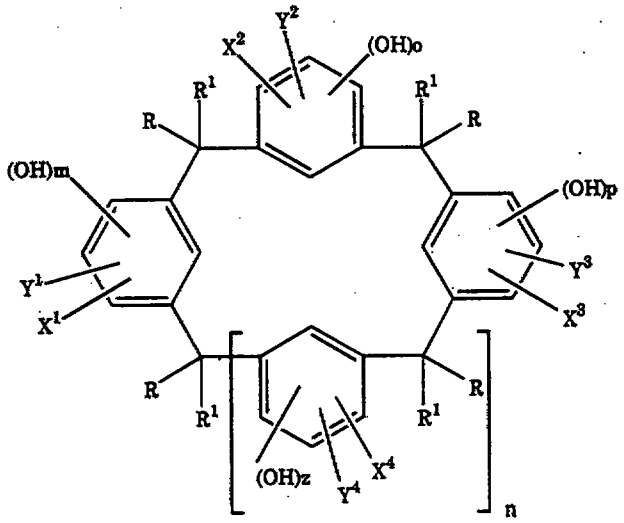
Sample	14 Days
1	14.6

These data clearly show that the compositions of the present invention slowly release biologically active molecules from a paint film.

* C L M S *

What is Claimed:

1. A controlled release composition comprising a biologically active compound and a calixarene compound of the formula



(I)

wherein:

X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3 and Y^4 are independently selected from hydrogen, cyano, nitro, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, phenyl, substituted phenyl, $(C_1\text{-}C_{10})$aralkyl, substituted $(C_7\text{-}C_{10})$aralkyl, NR^2R^3, SR^4; X^1 and Y^1, X^2 and Y^2, X^3 and Y^3, and X^4 and Y^4 may be joined to form a 5- or 6-membered ring;

R and R^1 are independently selected from hydrogen, $(C_1\text{-}C_8)$alkyl, cyclopropyl, phenyl, substituted phenyl, $(C_7\text{-}C_{10})$aralkyl, and substituted $(C_7\text{-}C_{10})$aralkyl;

R^2, R^3, and R^4 are independently selected from hydrogen, $(C_1\text{-}C_4)$alkyl, phenyl, and substituted phenyl;

n = 1-7; and

m, o, p and z are independently selected from 1-3.

2. The composition of claim 1 wherein the biologically active compound is selected from the group consisting of: 5-chloro-2-methyl-3-isothiazolone; 2-methyl-3-isothiazolone; 2-n-octyl-3-isothiazolone; 4,5-dichloro-2-n-octyl-3-isothiazolone; 1,2-dibromo-2,4-dicyanobutane; methylene-bis-thiocyanate; 2-thiocyanomethylthiobenzothiazole; tetrachloroisophthalonitrile; 5-bromo-5-nitro-1,3-dioxane; 2-bromo-2-nitopropanediol; 2,2-dibromo-3-nitrilopropionamide;

N,N'-dimethylhydroxyl-5,5'-dimethylhydantoin; bromochlorodimethylhydantoin; 1,2-benzisothiazolin-3-one; 4,5-trimethylene-2-methyl-3-iosthiazolone; 5-chloro-2-(2,4-dichlorophenoxy)phenol; 3,4,4'-trichlorocarbanilide; manganese ethylenebisdithiocarbamate; zinc dimethyl dithiocarbamate; 2-methyl-4-t-butylamino-6-cyclopropylamino-s-triazine; 2,4,5,6-tetrachloroisophthalonitrile; N,N-dimethyl dichlorophenyl urea; zinc ethylenebisdithiocarbamate; copper thiocyanate; N-(fluorodichloromethylthio)-phthalimide; N,N-dimethyl-N'-phenyl-N'-fluorodichloromethylthio-sulfamide; zinc 2-pyridinethiol-1-oxide; tetramethylthiuram disulfide; 2,4,6-trichlorophenylmaleimide; 2,3,5,6-tetrachloro-4-(methylsulfonyl)-pyridine; 3-iodo-2-propynyl butyl carbamate; diiodomethyl p-tolyl sulfone; bis dimethyl dithiocarbamoyl zinc ethylenebisdithiocarbamate; phenyl (bispyridil) bismuth dichloride; 2-(4-thiazolyl)-benzimidazole; pyridine triphenyl borane; phenylamides; halopropargyl compounds; and 2-haloalkoxyaryl-3-isothiazolones.

3. The composition of claim 2 wherein the biologically active compound is selected from the group consisting of 2-methyl-3-isothiazolone, 5-chloro-2-methyl-3-isothiazolone, 2-n-octyl-3-isothiazolone, 4,5-dichloro-2-n-octyl-3-isothiazolone, benzisothiazolone, 4,5-trimethylene-3-isothiazolone, 3-iodo-2-propynyl butyl carbamate; 5-chloro-2-(2,4-dichlorophenoxy)phenol and 3,4,4'-trichlorocarbanilide.

4. The composition of claim 1 wherein the calixarene compound is selected from the group consisting of 2,8,14,20-tetrapropylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol; 2,8,14,20-tetramethylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol; 2,8,14,20-tetraphenylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol; and 2,8,14,20-tetra-tert-butylpentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol.



5. The composition of claim 1 wherein the weight ratio of biologically active compound to calixarene compound is from 0.1:99.9 to 95:5.

6. The composition of claim 5 wherein the weight ratio is from 1:10 to 9:1.

7. The composition of claim 1 further comprising a carrier selected from the group consisting of water, acetonitrile, ethyl acetate, butyl acetate, toluene, xylene, methanol, ethanol, acetone, methyl ethyl ketone, methyl iso-butyl ketone, ethylene glycol, diethylene glycol, propylene glycol, and dipropylene glycol.

8. A method for controlling or inhibiting the growth of fungi, bacteria, algae, marine fouling organisms, plants, and insects comprising introducing a composition of claim 1 to a locus to be protected.

9. The method of claim 8 wherein the locus to be protected is selected from: cooling towers; air washers; mineral slurries; pulp and paper processing fluids; paper coatings; adhesives; caulks; mastics; sealants; agriculture adjuvant preservation; construction products; cosmetics and toiletries; shampoos; disinfectants and antiseptics; formulated industrial and consumer products; soaps; laundry rinse waters; leather and leather products; wood; plastics; lubricants; hydraulic fluids; medical devices; metalworking fluids; emulsions and dispersions; paints; varnishes; latexes; odor control fluids; coatings; petroleum processing fluids; fuel; oil field fluids; photographic chemicals; printing fluids; sanitizers; detergents; textiles; textile products; marine structures; plants; soil; and seeds.

10. The method of claim 9 wherein the marine structure is selected from the group consisting of boats, oil platforms, piers, pilings, docks, elastomeric rubbers, and fish nets.