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(21) International Application Number: PCT/NL86/00033 (22) International Filing Date: 3 October 1986 (03.10.86) (31) Priority Application Number: 8502705 (32) Priority Date: 3 October 1985 (03.10.85) (33) Priority Country: NL (71) Applicant (for all designated States except US): NED-ERLANDSE CENTRALE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK [NL/NL]; 148, Juliana van Stolberg-laan, NL-2596 CL Den Haag (NL). (72) Inventors; and (75) Inventors/Applicants (for US only) : BAREND SZ, Anton, Willem [NL/NL]; 2, Karel Doormanlaan, NL-2225 TA Katwijk aan Zee (NL). NIEUWENHUIZEN, Maarten, Simon [NL/NL]; 73, Naaldwijkseweg, NL-2691 RC 's Gravenzande (NL).		(74) Agent: MOMMAERTS, J., H.; Octrooibureau Lux, 4, Willem Witsenplein, NL-2596 BK Den Haag (NL). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> <i>In English translation (filed in Dutch).</i>
(54) Title: A COMPOSITE SUBSTRATE, INTENDED FOR AN APPARATUS FOR QUANTITATIVE DETECTION OF A COMPONENT PRESENT IN A GAS OR LIQUID $(RO)_3Si(CH_2)_n-Y \quad (I)$ $Cl^- + N_2^+ - \text{C}_6\text{H}_4 - \text{C}_6\text{H}_4 - N_2^+ Cl^- \quad (II)$ (57) Abstract A substrate for an apparatus for quantitative detection of a component present in a gas or liquid, in which substrate elastic vibrations can be generated, said substrate being provided with a surface layer adapted to bond said component, so that the vibration behaviour of said layer is changed. At least the surface portion of said substrate consists of a substance with active sites (A) for covalent bonding situated at its free surface, to which sites (A) molecules of a substance (X) are covalently bonded which, on the other hand, possess active sites (B) for selectively and reversibly bonding by means of a coordinative bond of the molecules of the component (G) to be detected. In particular between each active site (A) of the substrate and a molecule of the component bonding substance (X) a molecule of a coupler (K) can be inserted, which is covalently bonded to an active site (A) of said substrate, and, on the other hand, is bonded by means of a second bond (C) with a molecule of the component bonding substance (X), said second bond being a substantially covalent bond or a substantially coordinative bond. The component bonding substance (X) can be a substance in the form of an inclusion compound (X₁), a complexing compound (X₂), a metal ion cluster (X₃), or an enzyme (X₄). The coupler (K) can be formed by a trialkoxysilane compound with general formula (RO)₃Si(CH₂)_n-Y, in which Y is adapted to provide the covalent or coordinative bond (C) with the component bonding substance (X), and comprises an active group, which coupler (K) can be a compound of the following kind (Formula I).		

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A composite substrate, intended for an apparatus for quantitative detection of a component present in a gas or liquid.

There is a large need for apparatuses for quantitative detection of a noxious gas or vapour in a mixture, e.g. in exhaust gases of internal combustion motors or chemical industries, poisonous vapours in containers, reaction chambers, hothouses or the like, as well as poisonous gases in the air, e.g. for military purposes.

Such apparatuses should be small, robust and relatively cheap, but should, nevertheless, operate dependably, and moreover requirements in respect of the sensitivity, response speed, stability etc. should be satisfied.

Moreover an apparatus intended for this purpose should be selective for a given component (or a restricted number of related components), and should also operate in such a reversible manner that concentration variations of the substance to be detected can be followed rapidly and dependably, and a continuous measurement can take place.

For a quantitative detection of components present in the liquid or gas apparatuses are known, comprising a substrate in which, by means of a piezo-electric transducer, elastic vibrations can be generated, said substrate being provided with a surface layer which is able to bond said component if it is being contacted with said layer, so that the vibration behaviour of said layer is changed, and said elastic vibration is transformed again into an electric vibration by means of a piezo-electric transducer so as to detect the change in the vibration behaviour of said layer. To that end reference can be made to US 4 312 228. In this known apparatus the component to be detected is absorbed in the surface region of the substrate, the absorbed mass changing the vibration behaviour of the surface layer of said substrate, and in particular the propagation velocity of the elastic surface wave generated in said layer, and said wave can be detected by means of a piezo-electric transducer which transforms said vibration into an electric signal. The frequencies used there-

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for can be very high, so that, in view of the propagation velocity of the elastic vibration in the substrate, a very small distance can contain a very large number of wave-lengths, so that the transit time variations can be determined very well.

In this known apparatus, a polymer layer is provided on the substrate surface which serves as an absorbent for gases.

This known apparatus is not suitable for the above-mentioned purposes. In the first place absorption is not very selective, and moreover the reversibility of absorption is insufficiently fast for obtaining a quick adaptation to concentration variations. Moreover the polymer layer is relatively thick and does not form an essential part of the transfer path of the vibration which is mainly propagated along the substrate surface. This unfavourably influences the sensitivity. Moreover it is very difficult to produce such layers with a reproducible thickness and structure.

It is an object of the invention to provide a substrate for such an apparatus which is suitable for the above-mentioned purposes, said substrate being characterised in that at least the surface portion thereof consists of a substance with active sites for covalent bonding situated at its free surface, and in that, in said sites, molecules of a substance are covalently bond, said molecules possessing, on the other hand, active sites for selectively and reversibly bonding molecules of the component to be detected by means of a coordinative bond.

The coordinative bond with the component to be detected is relatively weak, so that the molecules of the component to be detected can be released relatively easily when the concentration of said component in the vicinity of the substrate is reduced, but said bond is strong enough for fixing said molecules, during the measurement, to the vibrating substrate. Such a layer is extremely thin, and comprises a large number of very regularly distributed bonding sites for said component, and said bond can be made very selective, and the mass variation in respect of the mass of the layer is substantial so that a sensitive and also reproducible measurement can be obtained. Said bonding molecules are, on the other

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hand, covalently bonded to the substrate, which bond is very strong, so that the bonding substance remains strongly connected to the substrate, and obtains, at the same time, a very good and uniformly distributed vibration coupling with said
5 substrate.

The molecules of said bonding substance are relatively large, which can unfavourably influence the bond with the substrate. It can, therefore, be advisable to insert, between the active sites of the substrate and said bonding
10 substance molecules, a coupler which, on the one hand, is covalently bonded to the active sites of the substrate, and, on the other hand, is bonded by means of a second bond to the bonding substance molecules. Said coupler forms therefore an adaptation between the available active sites of the sub-
15 strate and the extremity of the bonding substance molecules directed towards the substrate.

The second bond can be also a substantially covalent bond, in order to form a strong connection with the bonding molecule. However it can sometimes be favourable to use, for
20 the second bond, a bond of the coordinative kind, and then one of the active sites available for bonding the component to be detected can be used. The weaker bond enables to remove the bonding substance and to replace it by a different one, and sometimes such a bond can increase the selectivity of the
25 remaining active sites.

In order to increase the bonding power for the component to be detected, it can sometimes be favourable to connect a stack of molecules of the bonding substance with a common active site of the substrate, each of said molecules
30 having active sites for bonding said component.

As the active sites of the substrate, for instance OH groups at the surface of the substrate can be considered. In particular the substrate or a surface layer thereof consists of a metal oxide.

35 It is preferred to use as the substrate a silicon wafer covered with a silicon oxide layer, said silicon oxide comprising the OH groups. Manufacturing such wafers is known from the semiconductor technology, and obtaining oxide layers with the desired thickness and structure does not offer any

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difficulties anymore .Moreover electric (micro) circuits can be formed on such a wafer by means of the current semiconductor techniques, said circuits being required for signal generation and processing.

5 The surface part of the substrate can also consist of a piezo-electric metal oxide as, for instance, ZnO, which serves for generation and transforming the elastic vibration as well as for bonding the bonding substance. If, on the other hand, such piezo-electric oxide layers are only provided at
10 the transducer electrodes, it is advisable to treat the surface thereof so that it becomes insensitive for the component to be detected. This can be done in substantially the same manner as mentioned for bonding to the surface layer of a substance sensitive for this component, but then a similar
15 substance without active sites for bonding said component is to be used.

For these purposes various kinds of compounds are suitable which will be mentioned below in more detail.

The invention will be elucidated below in more detail .
20 by reference to a drawing, showing in:

Figs. 1A and B diagrammatic representations of a substrate with an active layer bonded thereto, for elucidating the principle on which the invention is based;

Fig. 2 a diagrammatic representation for elucidating
25 the concept of coordinative bonding;

Figs. 3A, B and C representations corresponding to Fig. 1 for elucidating the manner in which a part of the active surface of such a substrate can be made inactive;

Fig. 4 a number of structural formulae of compounds
30 suitable for the present purposes; and

Fig. 5 reaction equations for elucidating the attachment of such an active layer to the substrate.

In Fig. 1A a substrate in the form of a wafer D is diagrammatically shown. This wafer is provided with known
35 piezo-electric means not shown, by means of which acoustic surface waves can be generated near its free surface. A surface portion D' of this wafer consists of a metal oxide comprising active sites A provided by OH groups present in the oxide, by means of which covalent bonds can be formed.

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In particular the wafer D consists of Si, and the surface layer of SiO_2 . However, it is also possible to form a layer D' from, for instance, ZnO which is piezo-electric, and can be used also for forming vibration sources and sensors.

5 Molecules X are covalently bonded to these active sites A, said molecules having at least one active site B, the latter sites B being suitable for forming a so-called coordinative bond with a molecule G of a component of a gas or liquid to be contacted with said substrate D, the latter bond
10 being, in particular, more or less selective for said component.

For elucidating the concept of coordinative bonding, reference is made to Fig. 2. Therein L represents a so-called ligand which is neutral or charged, and which is, in particular, an organic compound. So-called donor atoms Z will, then,
15 interact with a metal ion M, and one or more free sites B of the latter will remain which are suitable for bonding the component G to be detected.

A coordinative bond is less strong than a chemical bond as, for instance, the covalent bond, but is stronger than
20 an adsorption bond (van der Waals forces). This is very favourable for the present purposes. For, if in the surface region of the substrate an acoustic wave is generated, the magnitude of the additional mass of attached molecules G should be unambiguously derivable from the change experienced
25 by such a wave as a consequence of said additional mass, so that the bond between the molecules G and the substrate D should be sufficiently strong. On the other hand said bond should not be so strong that the molecules G can only be released difficultly or not at all, so that, then, such a device
30 would not be usable again after a measurement. However the coordinative bond can be sufficiently easily broken so as to obtain always an equilibrium condition between the free molecules G near the substrate surface and the attached molecules, from which, of course after calibration of the apparatus, the
35 concentration of the free molecules G can be derived in a dependable manner.

Fig. 1B shows the case that the molecules X as such can not or not sufficiently attach to the active sites A. With these active sites A, molecules K of a coupler are now covalent-

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ly bonded, the latter, on the other hand, being able to bond the molecules X by means of bonds C. The bonds C can be covalent bonds as well, but can also be of an other kind, and in particular coordinative bonds, provided that said bond is
5 sufficiently strong for the purposes in view.

It is possible then to begin by bonding the molecules K to the molecules X, thus producing complex molecules which, as far as the effect aimed at is concerned, do not differ from the simple molecules X, and can be attached
10 as such to the active sites A of the substrate. However it can be favourable to provide first the substance K on the surface of the substrate D, and only thereafter the substance X. This can lead to a simplification of the process and an improvement of the effect.

15 Attaching the molecules G should only take place in those points where said molecules can effectively influence the produced acoustic waves. It is often desired not to expose the piezo-electric transducers used for generating and receiving the waves to said attachment. If said transducers, as
20 mentioned above, comprise a ZnO layer, bonding X or K resp. will take place there too.

It is, of course, possible not to provide X near said transducers, but then it cannot be avoided that, in the free sites A, other substances are bonded in an uncontrollable
25 manner.

Fig. 3 shows different solutions for avoiding the latter. At A is indicated that at a transducer T a substance X' is bonded to the sites A, which substance does not possess active sites B. Case B corresponds with case A, but now a
30 layer K has been provided first over the whole surface. This can simplify the separate bonding of the substances X and X' if the attachment of X and X' to K by means of the bonds C is simpler than the direct attachment by means of the bonds A. In case C the layer K is, again, provided everywhere, but
35 the substance X' is left out. This is possible if the bonds C give rise to a smaller extent to undesired attachment of other substances.

For X and K many different substances are already available. It will be clear that the choice of a substance X

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will be determined, in the first place, by the character of the component G to be detected, by the desired selectivity and the like, and in the case of a direct bond to the substrate D also by the character of the latter. The choice of the coupler K is, of course, determined by the character of the chosen substance X and the substrate D, and by the desired strength of the bond C.

For X the following substances are, for example, usable:

- 10 X_1 : substances in the form of an inclusion compound, activated or not with metal ions, e.g. a cyclodextrin or a crown ether;
 X_2 : complexing compounds;
 X_3 : metal ion clusters; or
 15 X_4 : enzymes.

Examples of X_2 are phthalocyanine compounds, comprising H, Si or a metal ion, ferrocene compounds or compounds of this kind with a metal other than iron, and β -diketones or aminopolycarboxylates such as, for example EDTH, comprising
 20 a metal ion and, in particular, a lanthanide ion.

As the coupler K, a trialkoxysilane compound with the general formula $(RO)_3Si(CH_2)_nY$ can be used in particular, in which Y can provide the covalent or coordinative bond C with the component bonding substance X, R being an alkyl group
 25 with 1..6 C-atoms, and $n = 1..6$. Y then comprises an active group such as a carboxylate, amino, pyridine derivative, imidazole, aldehyde, halogen, diazo, acid halide, azide, sulphonate, thioketone or hydroxyl group. An other coupler is a diazo compound such as $Cl^- N_2^+ - \text{C}_6\text{H}_4 - \text{C}_6\text{H}_4 - N_2^+ Cl^-$.

30 Fig. 4 shows the structural formulae of a number of compounds suitable for the bonding substance X, and Fig. 5 shows the reaction equations when using a coupler K for bonding a bonding substance X with OH groups of a SiO_2 substrate layer.

The following examples will provide a further
 35 elucidation of a practical realisation of the inventive idea.

Example 1: Preparation of aminopropyl glass.

3 wafers of Corning glass with a diameter of 40 mm and a thickness of 0,2 mm (about 2,7 g) were cleaned by a treatment in fuming nitric acid during 10 min. Subsequently

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said wafers were submerged in 150 ml water with 17 ml γ -amino-propyltriethoxysilane. The pH was adjusted at about 4 by means of 3 N HCl. After 2 h heating at 75 °C, the wafers were removed, washed with distilled water, and finally dried during 4 h at 120 °C, and during 2 h at 150 °C.

Example 2: Preparation of N-(3-triethoxysilylpropyl)-p-nitrobenzamide.

p-nitrobenzoic acid (10 g; 60 mmol) was added to 15 g thionylchloride. This mixture was heated during 2 h under reflux. Subsequently the thionylchloride was removed at reduced pressure. To the remainder γ -aminopropyltriethoxysilane (13,3 g; 60 mmol) was added, dissolved in 50 ml diethylether with 10 g triethylamine. After 2 h agitation at room temperature, the mixture was filtered. The filtrate was evaporated at reduced pressure. The remainder was washed in water, filtered, and dried at reduced pressure over KOH. Yield: 9,5 g (43 %). Melting point 99..105 °C.

Example 3: Coupling of p-nitrobenzoic acid to alkylamine glass.

A wafer of alkylamine glass of Example 1 was submerged in 150 ml 0,03 M phosphoric acid (temperature 4 °C). Subsequently DCMI, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide-metho-p-toluenesulphonate (400 mg; 95 mmol) and p-nitrobenzoic acid (250 mg; 1,53 mmol) were added. After 16 h agitation, during which the temperature rose to room temperature, the wafer was removed, washed and dried at 100 °C. The UV spectrum showed no perceptible absorption of the p-nitrobenzamide chromophore.

Example 4: Coupling of N-(3-triethoxysilylpropyl)-p-nitrobenzamide to glass.

By means of the method of Example 1, the benzamide of Example 2 was coupled to glass. The UV spectrum showed an absorption at 270 nm. The estimated load was 0,05 mmol/m².

Example 5: Preparation of the N-(3-triethoxysilylpropyl)-amide of meso-tetra-(4-carboxyphenyl)-porphyrine.

Meso-tetra-(4-carboxyphenyl)-porphyrine (0,59 g; 0,65 mmol) was added to 10 ml thionylchloride. This mixture was heated during 7 h at 80..90 °C. Subsequently the thionylchloride was removed at reduced pressure. To the remainder

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γ -aminopropyltriethoxysilane (0,289 g; 1,26 mmol) was added, dissolved in 20 ml N,N-dimethylphormamide (DMF) with 1,5 ml triethylamine. After 6 h agitation at room temperature the mixture was filtered, and thereafter the filtrate was poured
5 in 500 ml water at pH = 2. After standing over night the obtained deep-green solid was filtered off and dried over H_2SO_4 at reduced pressure.

The yield was 0,15 g product, containing 1,5..2,0 amide groups per porphyrine molecule.

10 Example 6: Coupling of meso-tetra-(4-carboxyl)-porphyrine to alkylamine glass.

By means of the method of Example 3 the meso-tetra-(4-carboxyphenyl)-porphyrine was coupled to alkylamine glass. The derivatised glass showed a clearly dark hue in the visible
15 range. The UV spectrum showed absorptions at 415 nm and 210 nm. The estimated loading was 0,06 mmol/m².

Example 7: Coupling of the N-(3-triethoxysilylpropyl)-amide of meso-tetra(4-carboxyphenyl)-porphyrine to glass.

By means of the method of Example 1 the N-(3-tri-
20 ethoxysilylpropyl)-amide of meso-tetra(4-carboxyphenyl)-porphyrine of Example 5 was coupled to glass. The UV spectrum showed absorptions at 420 nm and 210 nm. The estimated loading was 0,08 mmol/m².

25 Example 8: Preparation of the N-(3-triethoxysilylpropyl)-amide of Cu(II)-tetracarboxyphthalocyanine.

The acid chloride of Cu(II)-tetracarboxyphthalocyanine (200 mg; 0,2 mmol) was dissolved in 20 ml DMF which also contained 0,28 ml γ -aminopropylsilane and 1,5 ml triethylamine. The solution was agitated during 6 h, and was
30 poured subsequently in 500 ml water at pH = 1. The obtained blue solid was filtered off and dried. The yield was 200 mg product.

Example 9: Coupling of Cu(II)-tetra(chloorcarboxyl)phthalocyanine to alkylamine glass.

35 By means of the method of Example 3, the acid chloride of Cu(II)-tetracarboxyphthalocyanine was coupled to alkylamine glass. The UV spectrum showed absorptions at 600, 320 and 230 nm. The estimated loading was 0,57 mmol/m².

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Example 10: Coupling of the N-(3-triethoxysilylpropyl)-amide
Cu(II)-tetracarboxyphthalocyanine to glass.

By means of the method of Example 1 the N-(3-triethoxysilylpropyl)-amide of Cu(II)-tetracarboxyphthalocyanine of Example 8 was coupled to glass. The UV spectrum showed absorptions at 320 and 230 nm. The estimated loading was 0,43 mmol/m².

The laboratory experiments described in the preceding examples have shown that the attachment according to the invention to substrates can be realised in the desired manner. In practice often preference will be given to substrates with surface layers of a pure oxide such as SiO₂ or ZnO instead of glass, but such layers will behave in the same manner as the examined glass wafers.

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C l a i m s

1. Composite substrate, intended for being included in an apparatus for quantitative detection of a component present in a gas or liquid, in which substrate elastic vibrations can be generated by means of a piezo-electric transducer, said substrate being provided with a surface layer adapted to bond said component if being contacted with said layer, whereby the vibration behaviour of said layer is changed, said elastic vibration being transformed again into an electric vibration by means of a piezo-electric transducer in order to detect the change in the vibration behaviour of said layer, characterised in that at least the surface portion of said substrate consists of a substance with active sites (A) for covalent bonding at its free surface, and in that in said sites (A) molecules of a substance (X) are covalently bonded, which molecules, on the other hand, comprise active sites (B) for selectively and reversibly bonding by means of a coordinative bond the molecules of the component (G) to be detected.

2. The substrate of claim 1, characterised in that between each active site (A) of the substrate and a molecule of the component bonding substance (X) a molecule of a coupler (K) is inserted, which is covalently bonded to an active site (A) of the substrate, and which, on the other hand, is bonded by means of a second bond (C) with a molecule of the component bonding substance (X).

3. The substrate of claim 2, characterised in that the second bond is a substantially covalent bond.

4. The substrate of claim 2, characterised in that the second bond is a substantially coordinative bond.

5. The substrate of any one of claims 1..4, characterised in that the component bonding substance (X) consists of one or more molecules with a number of active sites (B).

6. The substrate of any one of claims 1..5, characterised in that the surface portion of the sub-

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strate consists of a metal oxide.

7. The substrate of claim 6, characterised in that the substrate consists of Si with a surface layer oxidised to SiO_2 .

5 8. The substrate of claim 6, characterised in that the surface portion of the substrate consists of a piezo-electric oxide such as ZnO .

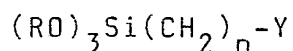
9. The substrate of any one of claims 1..8, characterised in that the active site (A) of the sub-
10 strate are formed by OH-groups.

10. The substrate of any one of claims 1..9, characterised in that the component bonding substance (X) is a substance in the form of an inclusion compound (X_1), activated or not by metal ions, such as a cyclodextrine or
15 a crown ether, or in the form of a complexing compound (X_2), a metal ion cluster (X_3) or an enzyme (X_4).

11. The substrate of claim 10, characterised in that the complexing compounds forming substance (X) is chosen on:

- 20 a) phthalocyanine compounds comprising H, Si or a metal ion;
b) porphyrine compounds, comprising or not H, Si or a metal ion;
c) ferrocene compounds or this kind with an other metal; and
d) -diketones or aminopolycarboxylates, comprising a metal
25 ion and in particular a lanthanide ion.

12. The substrate of any one of claims 2..11, characterised in that the coupler (K) is formed by a trialkoxysilane compound with the general formula:

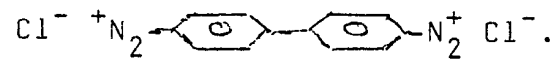


30 in which Y is adapted to provide the covalent or coordinative bond (C) with the component bonding substance (X), and R is an alkyl group with 1..6 C-atoms and n is a number of 1..6, Y comprising an active group such as a carboxylate, an amino compound, a pyridine derivative, an imidazole, an aldehyde,
35 a halogen, a diazo compound, an acid halogenide, an azide, a sulphonate, a thioketone or a hydroxyl compound.

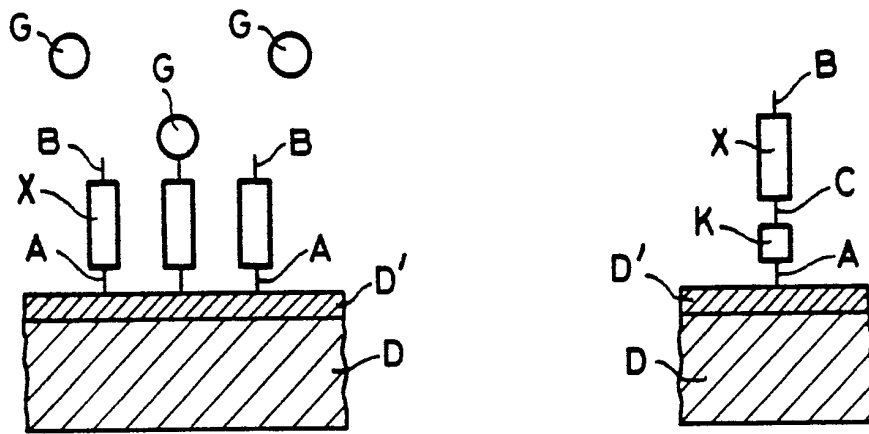
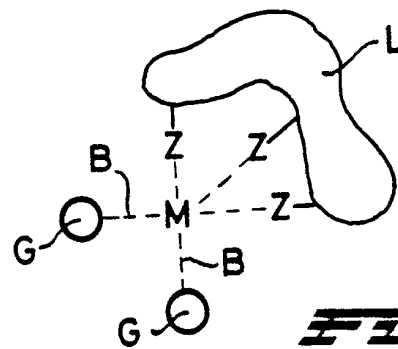
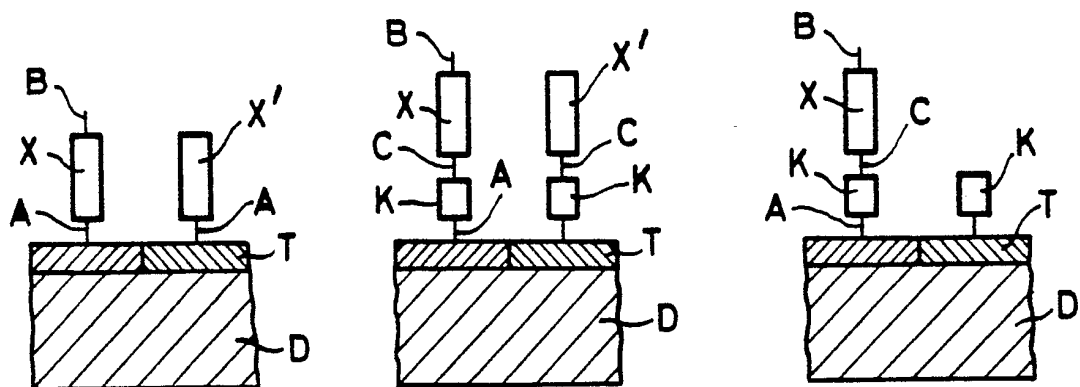
13. The substrate of any one of claims 2..12, characterised

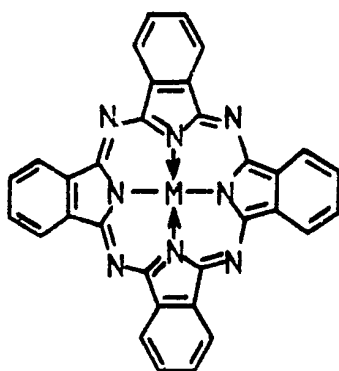
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r a c t e r i s e d in that the coupler (K) is a compound of the following kind:

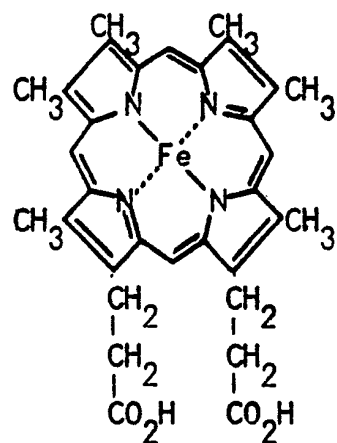


14. An apparatus for quantitative detection of a component of a gas or liquid, provided with a substrate of any one of claims 1..13.

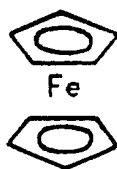
**FIG. 1.****FIG. 2.****FIG. 3.**



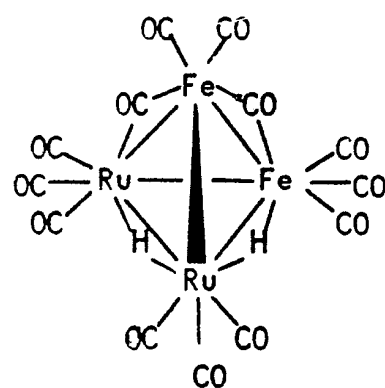
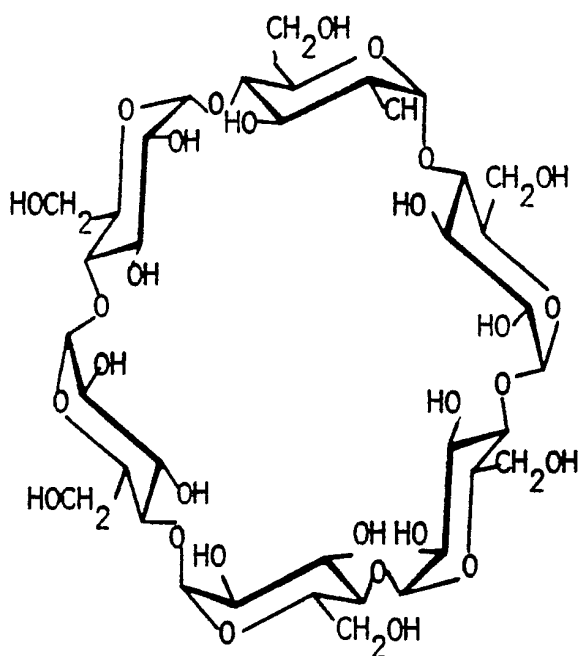
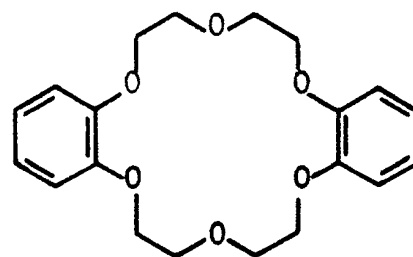
M(II)ftalocyanine



Fe(III)deuteroporphyrine



ferrocene

 $\text{Ru}_2\text{Fe}_2\text{H}_2(\text{CO})_{13}$ -verzameling α - cyclodextrine

dibenzo-18-kroonether-6

FIG: 4.

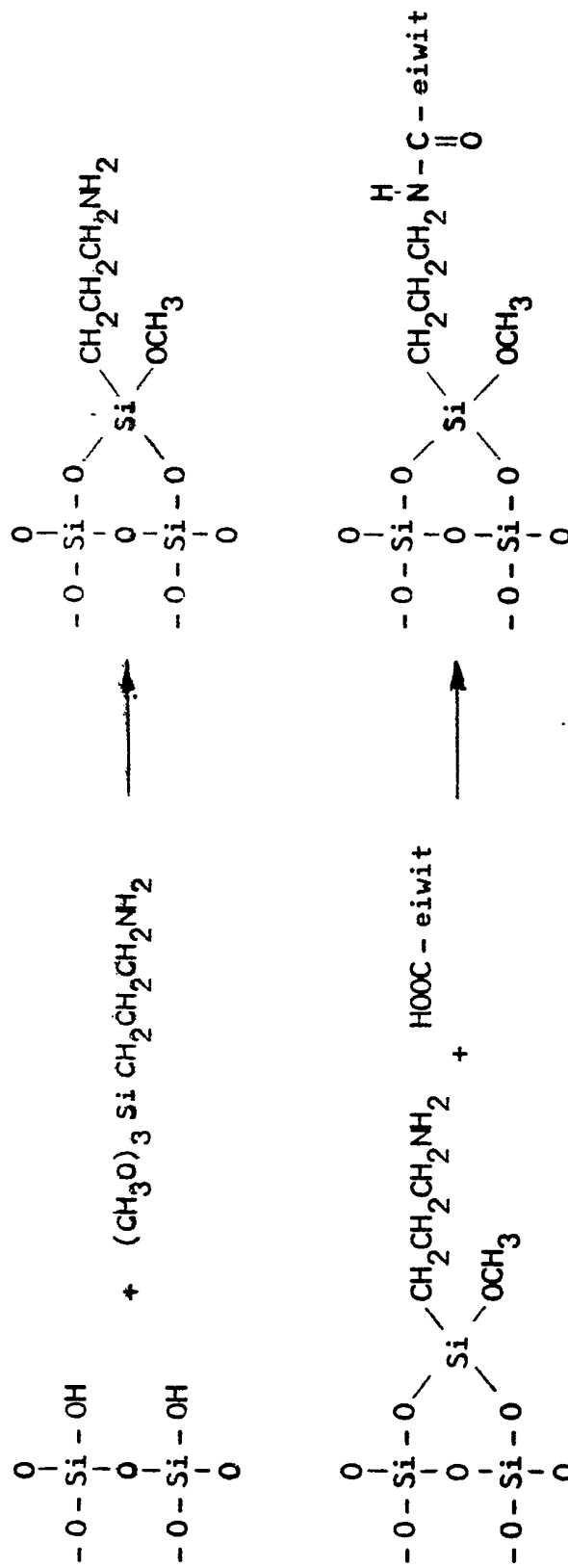


Fig. 5.

INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 86/00033

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁴ : G 01 N 29/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	G 01 N	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO, A, 83/01511 (D. LEE) 28 April 1983, see front-page; claims 1,11 --	1
A	Analytical Chemistry, volume 52, no. 12, October 1980, P.C. Konash et al.: "Piezoelectric crystals as detectors in liquid chromatography", pages 1929-1931, see page 1930, paragraph "surface modification" --	1
A	EP, A, 0100661 (SHIMADZU CORP.) 15 February 1984, see front-page --	1
A	US, A, 4314821 (T.K. RICE) 9 February 1982, see abstract --	1
A	FR, A, 2383440 (Y. FREY) 6 October 1978, see claim 1 -----	1
[*] Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
16th January 1987	10 Feb 1987	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	M. VAN MOL	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/NL 86/00033 (SA 14664)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/01/87

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