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**HIDEKO KANAZAWA: "Temperature-responsive chromatography using poly-(N-isopropylacrylamide) Hydrogel- Modified silica" ANALYTICAL SCIENCES, vol. 18, January 2002 (2002-01), pages 45-48, XP002245104 TOKYO, JAPAN**  
**PATENT ABSTRACTS OF JAPAN vol. 010, no. 369 (P-525), 10 December 1986 (1986-12-10) & JP 61 162750 A (TORAY IND INC), 23 July 1986 (1986-07-23)**  
**B. GALLI: "HPLC Resolution of Atropoisomeric Compounds on a CSP Derived From (1R; 2R)- Diaminocyclohexane" CHIRALITY, vol. 4, no. 6, 1992, pages 384-388, XP008018676**



# DESCRIPTION

## Technical Field of the Invention

**[0001]** The invention is set in the field of enantioselective molecular recognition of middle-low molecular weight molecules. In particular, the invention relates to novel polymeric composite chiral stationary phases of brush type suitable for the separation and/or the purification of enantiomers of organic and organometallic compounds at an analytical and preparative level. The invention further relates to the preparation and to the applications of such phases.

## Prior state of the art

**[0002]** The Classic methods for enantiomer separation envisage the formation of diastereomeric derivatives by interaction with a chiral agent and subsequent separation of the diastereoisomer exhibiting different chemical and physical features, by crystallisation, distillation, extraction or chromatography. Recent technological developments enabled to tackle the problem in a more profitable manner, exploiting the high efficiency of the modern chromatography techniques and the employ of chiral stationary phases, in which an enantiomer of a chiral molecule (selector) is immobilized on an insoluble support. By this approach, it is possible to separate the enantiomers of various compounds, over short times and in a reproducible manner, both at an analytical level (micrograms) and at a semipreparative or preparative level (grams, kg, etc.).

**[0003]** The chiral stationary phases described in literature employ a wide range of chiral selectors. There are commonly employed low-molecular weight molecules, totally synthetic or derived from the natural chiral pool [Gasparrini F, Misiti D, Villani C, High-performance liquid chromatography chiral stationary phases based on low-molecular-mass selectors, J. Chromatogr. A 2001, 906, 35-50], or high-molecular weight polymer molecules, in this case as well synthesised *ex novo* or obtained by modifications of natural chiral polymers [Haginaka J, protein-based chiral stationary phases for high-performance liquid chromatography enantioseparations, J. Chromatogr. A 2001, 906, 253-73 ; Yashima E, Polysaccharide-based chiral stationary phases for high-performance liquid chromatographic enantioseparation J. Chromatogr. A 2001, 906, 105-25].

**[0004]** Low-molecular weight selectors, once immobilized on the insoluble silica based support, entail the advantage of ensuring quick processes of solute mass transfer between the mobile and the stationary phases, resulting in a high chromatographic efficiency, which however is often accompanied by a modest enantioselectivity and, above all, by a limited application field.

**[0005]** The chromatographic columns prepared with such chiral stationary phases likewise exhibit a high permeability, thereby allowing to operate with modest pressure drops also at high linear velocities of the in-column eluent.

**[0006]** The polymeric selectors immobilized according to the classic procedure often lead to chromatographic columns generally characterised by a poor chromatographic efficiency and by a reduced permeability, whereas their three-dimensional structure may favour the enantiomer discrimination process independently from the presence of specific functional groups (shape selectivity), resulting in a good enantioselectivity and in a wide application field.

**[0007]** A class of widely marketed polymeric chiral stationary phases consists of polysaccharide derivatives (cellulose, amilose) physically adsorbed on macroporous silica microparticles. Several such stationary phases, e.g. cellulose tris-(3,5-dimethylphenylcarbamate) and amilose tris-(3,5-dimethylphenylcarbamate), are capable of separating the enantiomers of a large number of chiral species, and find wide application in different fields of organic and pharmaceutical chemistry [Okamoto Y, Yashima E, Polysaccharide derivatives for chromatographic separation of enantiomers, Angew. Chem. Int. Ed. 1998, 37, 1020-43]. However, such phases entail drawbacks, essentially due to the fact that the polymeric chiral selector is not covalently bound to the silica-based support: this precludes the employ of eluents in which the same selector is soluble (chlorinated solvents, THF, etc.) and often poses serious limitations in preparative applications and anyhow in cases when the solute is insoluble in the mobile phase compatible with the stationary phase (hexane/alcohol mixtures).

**[0008]** A second drawback concerns the kinetic performances of the stationary phase, which are often deteriorated due to the thickness of the polymeric layer slowing down solute transfer between stationary and mobile phases.

**[0009]** EP 0 249 078 (MERCK PATENT GMBH) reports adsorbents based on optically active poly(meth)-acrylamides which is said to be used for separating racemic mixtures into their optical antipodes.

[0010] Kanazawa H. et al. [Analytical Sciences, vol. 18, pages 45-48 (2002)] reports an alleged new method of HPLC using packing materials modified with cross-linked poly(N-isopropylacrylamide) hydrogel and involves temperature-responsive chromatographic separation.

[0011] JP 61 162750 (TORAY IND INC) reports an alleged new packing material for optical resolution.

[0012] US 5 493 979 (MACK MARGOT et al.) reports separating materials for thin-layer chromatography, based on sorbent-coated supports.

[0013] EP 0 780 408 reports chiral polymers which are bonded to a support and have improved properties, a process for the preparation of these materials and their use as chiral stationary phases in the chromatographic separation of optical isomers, in particular of racemates into their enantiomers.

[0014] Galli B. et al. (Chirality, vol. 4, no. 6, 1992, pages 384-388) reports the preparation and a preliminary chromatographic evaluation of an alleged novel polymeric chiral stationary phase based on a radical copolymerization process between mercaptopropyl silica and N,N'-diacryloyl-(1R,2R)-diaminocyclohexane.

[0015] EP 0 379 917 (BAYER AG) reports an optically active N-(meth)acryloyl amino acid amide which is polymerized and optionally bound to a support such as silica, and can then be used for the chromatographic separation of racemic mixtures of pharmacologically active compounds.

[0016] The article "Temperature-responsive chromatography using poly-(N-isopropylacrylamide) Hydrogel-Modified silice" (Hideko Kanazawa - Analytical Sciences - vol.18 (2002-01), pages 45-48 - XP00224104) refers to a method of HPLC using packing materials modified with cross-linked poly(N-isopropylacrylamide) hydrogel and involves temperature-responsive chromatographic separation.

[0017] EP 0 780 408 (BAYER AG) reports chiral polymers which are bonded to a support and have improved properties, a process for the preparation of these materials and their use as chiral stationary phases in the chromatographic separation of optical isomers, in particular of racemates into their enantiomers.

[0018] Although different types of polymeric chiral stationary phases for chromatographic applications are known, there exists in the state of the art no stationary phase of practical use concomitantly having high enantioselectivity, high chromatographic efficiency and wide application field associated to high permeability and full compatibility with organic and aqueous solvents of various nature.

[0019] Scope of the present invention is to provide novel polymeric composite chiral stationary phases of brush type capable of combining the high chromatographic efficiency and the elevated permeability typical of the monomeric chiral stationary phases of brush type to the good enantioselectivity and the wide application field of the classical polymeric phases.

[0020] A further scope of the invention is to provide stable stationary phases having a fully compatibility with the common chromatographic eluents of organic or aqueous nature and an elevated chemical passivation.

### **Summary of the Invention**

[0021] The present invention is based on the unexpected discovery that novel polymeric composite chiral stationary phases having the desired above-mentioned features are obtainable by chiral monomer polymerisation directly from the surface of solid supports. Such polymers covalently immobilized on a solid support form chiral stationary phases suitable for the resolution of racemic mixtures and for the purification of individual enantiomers, and in general of stereoisomers, of organic and organometallic compounds, as well as for their chemical purification.

[0022] Object of the invention are novel polymeric composite chiral stationary phases of "brush-type" containing a chiral polyamide polymer covalently bound to the inorganic matrix and obtained by polymerisation of chiral monomers N-(meta)acryloyl derivatives of diamines, amines, amino alcohols, amino acids, all in form of optically pure enantiomers.

[0023] Such polymers covalently immobilized on a solid support form chiral stationary phases suitable for the resolution of racemic mixtures and for the purification of individual enantiomers, and in general of stereoisomers, of organic and organometallic

compounds, as well as their chemical purification. In particular, the invention is based on a novel method for the preparation of polymeric chiral stationary phases in which the polymer is synthesized directly onto the surface of the solid support starting from chiral monomers, in an enantiomerically pure form. The method foresees that the solid support bearing -NH<sub>2</sub>, -OH, -SH groups onto its surface be reacted with an active form of an  $\alpha, \alpha'$ -azo-bis-(cyanocarboxylic) acid, which is thus immobilized on the support surface. Then, the reaction product obtained is reacted with monomers in form of pure enantiomers, selected among chiral N-(meta)acryloyl derivatives of amines, diamines, amino alcohols, amino acids, and such monomers are polymerised directly onto the support surface. In fact, the residue containing the azo group is capable, by thermal treatment, of generating radical species. These trigger the polymerisation reaction of the monomeric units by an attack to the activated double C-C bond. The originality of the approach leads to the obtainment of a chiral polymer of brush type, i.e. bearing side residues that are regularly oriented and perpendicular to the polymer structure and to the same structure of the solid support, to which the polymer is covalently bound.

**[0024]** The novel chiral stationary phases thus obtained combine the advantages of the monomeric chiral stationary phases of brush type (high efficiency, elevated permeability and wide compatibility with solvents) to those of the polymeric phases (wide application field and good enantioselectivity, etc.). Hence the new hybrid name of polymeric composite chiral stationary phases of brush type.

**[0025]** The stationary phases described in the present application are used in the separation of enantiomers of organic and organometallic compounds, in high-efficiency chromatographic processes as well as in low-efficiency chromatographic processes, both with organic and aqueous solvents. Other objects of the invention will be apparent in the light of the following detailed description.

### **Description of the figures**

**[0026]**

**Figure 1:** figure 1 illustrates the synthesis process of two stationary phases according to the present invention. The chiral stationary phase of general structure as per structure 1 provides as selector a chiral polymer obtained by polymerisation of a N,N'-diacryloyl derivative of a diamine. Structure 2 provides a polymer obtained by polymerisation of an N-acryloyl derivative of variously substituted monoamines.

**Figure 2:** figure 2 illustrates the synthesis process of a chiral stationary phase providing as selector a polymer obtained using N-(2-acryloylamino-(1R,2R)-cyclohexyl)-acrylamide as monomer.

**Figure 3:** figure 3 reports examples of chiral monomers used in the present invention.

**Figure 4:** figure 4 reports a few examples of compounds resolved in their enantiomer form by chromatography on stationary phase according to the invention.

### **Detailed description of the Invention**

**[0027]** The method for the preparation of the polymeric chiral stationary phases according to the invention provides the direct polymerisation of monomers starting from the surface of the solid support. The microparticles used may be silica, silicates, aluminates, or it may consist of polymeric resins like polyacrylamide, polymethacrylate, polystyrene or of polymeric materials like carbohydrates. Macroporous silica is used as preferred inert support, and it consists of particles having a size in the order of from 1 to 10  $\mu\text{m}$ , and a surface of about from 100 to 120  $\text{m}^2/\text{g}$ . The pores have an average diameter of about 300

$\text{\AA}$   
and a total volume equal to about 0.93 ml/g.

**[0028]** The surface of the solid support material is usually pretreated with reagents capable of inserting functional groups facilitating the subsequent immobilization of the chiral polymer. These functional groups may be -NH<sub>2</sub>, -OH, -SH groups, or any other equivalent group. In case meso/macroporous silica is used, the surface may be activated with 3-aminopropyl-trialkoxysilane, specifically 3-aminopropyl-triethoxysilane or equivalent reactants. The reaction is conducted in anhydrous organic solvent, e.g. toluene, at reflux temperature under inert atmosphere.

[0029] The material thus obtained is subsequently activated with a bifunctional reactant comprising a -N=N- (azo) group, under reaction conditions allowing reactant immobilization, yet preserving the azo group capability of generating radical species.

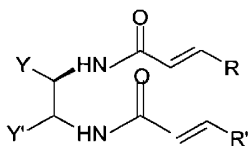
[0030] In particular, this activation step envisages the reaction between the support material functionalised as above disclosed and a chemically reactive and bifunctional form of an  $\alpha,\alpha'$ -azo-bis-(cyanocarboxyl) acid like the 4,4'-azo-bis-(4-cyanopentanoic) acid (also denominated 4,4'-azo-bis-(4-cyano valeric) acid) or the 4,4'-azo-bis-(4-cyanobutanoic) acid. Chemically reactive forms are the corresponding dichlorides or anhydrides.

[0031] The reaction is conducted in anhydrous organic solvent, e.g. toluene, and at low temperature, using a stoichiometric excess of the active form of the azo derivative. This, reacting with the functional groups (NH<sub>2</sub>, OH, etc.) onto the surface of the solid support, will be immobilized to the same surface by means of an amide, ester or thioester covalent bond, depending on the material used. The support treated as described is subsequently contacted to an anhydrous organic solution of the N-(meta)acryloyl chiral monomer in form of enantiomer having an elevated enantiomeric excess, or preferably in an optically pure form. The reaction is conducted under inert atmosphere and at a temperature sufficiently high to induce formation by the azo-derivative of free radicals capable of initiating the polymerisation process. Heating to a >50°C temperature or preferably to a  $\geq 60^\circ\text{C}$  temperature was demonstrated to suffice.

[0032] In a preferred embodiment of the invention, the polymerisation is conducted on pretreated macroporous silica gel, and it leads to the formation of a brush type polymer (which is ordered), allowing easy access of the analytes in the pore structure of the same support.

[0033] The preparation method is illustrated in its entirety in figure 1, in which stationary phases of structures 1 or 2 were obtained using chiral monomers of different general formula. The same method is illustrated in figure 2, summarising the synthesis of the chiral stationary phase 1 (CSP1) which represents the preferred embodiment of the invention.

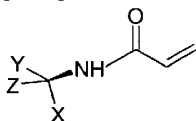
[0034] The monomers used in accordance with the present invention are chiral compounds in which one or more amine or hydroxyl groups are acylated in form of ester or of amide with a residue of acrylic, metacrylic, cinnamic acid or of other  $\alpha\text{-}\beta$  unsaturated carboxylic acid, containing C-C double bonds capable of polymerising. In general, the monomeric compound may be a derivative of a chiral diamine bearing a vinyl fragment or other C-C double bond, it also capable of polymerising. An example of suitable monomer is that represented by the general formula I



Formula I

where Y and Y' are identical or different, each representing a phenyl, diphenyl, benzyl group, also substituted, a C<sub>1</sub>-C<sub>10</sub> linear or branched alkyl group, also substituted, or an aryl-C<sub>1</sub>-C<sub>10</sub> alkyl group, also substituted, or where Y and Y' together represent a polycondensed aromatic group or a polymethylene ring comprising the chain -(CH<sub>2</sub>)<sub>n</sub>- where n is an integer equal to 2,3,4,5 or 6, and where R and R' are identical or different and represent H or a C<sub>1</sub>-C<sub>10</sub> linear or branched alkyl group, also substituted, or a phenyl or benzyl group, also substituted.

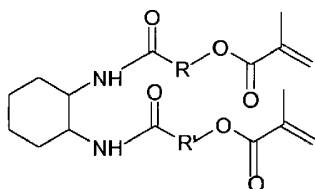
[0035] A second example of monomer is represented by the general formula II,



Formula II

where Y, Z, X, represent independently the one from the other an H, a C<sub>1</sub>-C<sub>10</sub> linear or branched alkyl group, also substituted, a phenyl, biphenyl, benzyl or aryl-C<sub>1</sub>-C<sub>10</sub> alkyl group, also substituted, or a molecular radical comprising functional groups or other stereogenic elements.

[0036] An additional example of suitable monomer has the general formula III,



Formula III

where R and R' are identical or different and represent linear or branched chains of -CH<sub>2</sub>-groups alternate to -NH-, -O-, -OCO-groups.

**[0037]** Practical examples of monomeric compounds used for the preparation of matrixes of the invention are: propranolol N-acryloyl (PROPRAN-ACR); 1,2-*trans*-diphenylethylenediamine-di-acryloyl (DPEDA-ACR); 1,2-*trans*-diaminocyclohexane-di-acryloyl (DACH-ACR); norephedrine N-acryloyl (NOREPH-ACR); 1,2-*trans*-diaminocyclohexane-di-2-(metacryloyloxy) ethyl succinate (DACH-METACR-2); cinnamoyl 1,2-*trans*-diaminocyclohexane (DACH-CINN); 1,2-*trans*-diaminocyclohexane-di-(3-isopropenylphenyl)-1-methylethyl ureide (DACH-IPDB); 1,2-*trans*-diaminocyclohexane-di-(2-methylacryloyloxy)-ethyl-ureide (DACH-METACR-1); all reported in Figure 3.

**[0038]** Given the ease of synthesis of the chiral selector, it is possible to prepare relevant amounts (50-100 g) of chiral stationary phase, above all when macroporous silica is used as inert support. The availability of relevant amounts of chiral support enables the use of these stationary phases not merely in analytical HPLC, but also in semi-preparative and preparative processes of racemate resolution and/or of enantiomer purification. To this end, the stationary phase comprising the polymeric selector may be packed in chromatographic columns suitable for analytical or preparative liquid chromatography. In particular, high-efficiency techniques are, e.g., HPLC, SMB, SFC or supercritical fluid chromatography, whereas low-efficiency techniques are open column chromatography or flash chromatography.

**[0039]** The abovedescribed stationary phases provide the following advantageous features:

- ease of preparation of the chiral monomer and of the derivatised support;
- chemical, stereochemical and thermal stability, making them suitable for the employ with organic and aqueous solvents and with supercritical fluids, comprising acid and basic modifiers (CH<sub>3</sub>COOH, CF<sub>3</sub>COOH, Et<sub>3</sub>N) and under extreme temperature conditions (of from - 80 °C to +100 °C);
- elevated chromatographic efficiency and elevated permeability, due to the effective passivation of the silica surface and to the formation of a polymeric film having a controlled and regular thickness, making the chromatographic material suitable for the enantiomeric analysis of trace materials;
- wide field of application;
- elevated enantioselectivity ( $\alpha > 4$ ) toward specific compound classes.

**[0040]** Hereinafter, the invention will be detailed by means of examples reported merely by way of illustration, and not meant to limit its protective scope.

**[0041]** Example 1:

**preparation of 3-aminopropyl silica gel:**

**[0042]** 10.0 g Daisogel<sup>®</sup> SP-300-5P silica (particle size: 5  $\mu$ m; surface area: 115 m<sup>2</sup>/g; pore diameter: 300 Å; pore volume: 0.93 ml/g), previously dried under reduced pressure (0.1 mbar) at 150°C for 2h (drying loss: 2.5 %), is dispersed in 240 ml toluene. The obtained dispersion is reflux heated to 110°C under mechanical stirring and inert atmosphere (argon), and in 1h 25 ml distilled product are collected. The reaction mixture is let back to room temperature and 5.0 ml (21.5 mmoles) 3-aminopropyl-triethoxysilane are added. The reaction mixture is refluxed for 4h, under mechanical stirring and inert atmosphere (argon). After cooling, the modified silica is isolated by filtration, washed with 200 ml toluene, methanol, dichloromethane fractions and dried under reduced pressure (0.1 mbar) at 60°C to constant weight.

[0043] Elementary analysis % C 1.35; % H 0.54; % N 0.48

[0044] FT-IR (DRIFT) 3432, 2978, 2935, 1874, 1630, 1095, 954, 802  $\text{cm}^{-1}$ .

**Example 2:**

**Preparation of N-(2-acryloylamine-(1R,2R)-cyclohexyl)-acrylamide:**

[0045] 12.0 ml diisopropylethylamine (70.06 mmoles) are added to a (1R,2R)-diaminecyclohexane (4.0 g; 35.03 mmoles) solution in 50 ml of a 2.5/1 (v/v) anhydrous chloroform/toluene mixture. To the resulting solution, cooled to 0°C, an acryloyl chloride solution (5.7 ml; 70.06 mmoles) in 100 ml of a 2.5/1 (v/v) anhydrous chloroform/toluene mixture is added, dropwise, in 1h 30 min, under magnetic agitation and inert atmosphere (argon). The reaction mixture is kept at 0°C, under magnetic agitation and inert atmosphere (argon), for 35 min. The white precipitate formed is isolated by filtration, washed with toluene and hexane and dried under reduced pressure (0.1 mbar) at room temperature to constant weight (6.34 g; weight yield: 82 %). Separately, the mother liquors are vacuum evaporated (rotary evaporator at about 250 mbar) and dried to constant weight (11.857 g). The obtained solid is dispersed in 60 ml of the  $\text{CHCl}_3$ /toluene mixture in order to recover additional product; the obtained dispersion is filtered through buchner; the isolated solid is washed with toluene and hexane and is dried under reduced pressure (0.1 mbar) to constant weight (205.2 mg). The reaction course is monitored by TLC (eluent: dichloromethane/methanol 90/10;  $R_f = 0.41$ ).

[0046] Elementary analysis: %C 63.31, %H 7.99, %N 12.06. Theoretical for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2$  % C 64.83, % H 8.16, % N 12.61.

[0047] Specific rotatory power  $[\alpha]_{\text{D}}^{20} = +85.4^\circ$  ( $c = 1.0$ ; DMSO)

[0048]  $^1\text{H-NMR}$  ( $^2\text{H}_6\text{DMSO}$ )  $\delta$ : 1.20-1.30 (m, 4H), 1.60-1.70 (m, 2H), 1.85-1.95 (m, 2H), 3.60-3.70 (m, 2H), 5.52 (dd,  $J = 9.90$  Hz, 2.44 Hz, 2H), 6.02 (dd,  $J = 17.09$  Hz, 2.44 Hz, 2H), 6.15 (dd,  $J = 17.09$  Hz, 9.90 Hz, 2H), 7.85 (d, 2H).

[0049] FT-IR (KBr) 3284, 3075, 3033, 1656, 1625, 1550, 1410  $\text{cm}^{-1}$ .

**Example 3:**

**Preparation of the dichloride of 4,4'-azo-bis-4-cyanovaleric acid:**

[0050] 8.0 g phosphor pentachloride (38.4 mmoles) are dispersed in 40 ml anhydrous dichloromethane, degassed with Helium (dispersion A). 2.0 g 4,4'-azo-bis-4-cyanovaleric acid (9.6 mmoles) are dispersed in 55 ml anhydrous dichloromethane degassed with Helium (dispersion B).

[0051] To the dispersion A, put in a three-neck flask under inert atmosphere and magnetic agitation and cooled to 0°C in ice bath, there is added in 55 min the dispersion B, by loading funnel. It is left under magnetic agitation and inert atmosphere (argon), letting the temperature raise to 20°C, for 6h. The solid possibly formed during the reaction is removed by filtration, the reaction mixture is vacuum concentrated (rotary evaporator at about 250 mbar) and the precipitate formed is removed by filtration. The residual liquid is auditioned with hexane (about 20 ml) and stored at low temperature (4°C) for 12h. The hexane is removed from the obtained precipitate by suction; the solid is dried under reduced pressure (0.1 mbar), at room temperature, to constant weight (1.80 g; weight yield: 76.7 %) and stored under inert atmosphere (argon) at low temperature (-20°C).

[0052] FT-IR (Nujol) 2240, 1789, 1462  $\text{cm}^{-1}$ .

**Example 4:**

**Functionalization of the aminopropyl silica gel with the dichloride of 4,4'-azo-bis-(4-cyanovaleric) acid:**

[0053] 3.0 g aminopropyl silica gel are dispersed in 25 ml anhydrous toluene under inert atmosphere (argon) and mechanical stirring. To such dispersion, cooled to 0°C, a 1-methoxy-2-methyl-1-(trimethylsiloxy)-1-propene solution (500 µl; 2.45 mmoles) is added dropwise in 5 ml anhydrous toluene.

[0054] A 4,4'-azo-bis-(4-cyanovaleric) acid dichloride solution (336 mg; 1.22 mmoles) is added dropwise to 10 ml anhydrous toluene, under inert atmosphere (argon) and mechanical stirring, at 0°C. The reaction mixture is let back to room temperature and then left 2h 45min under mechanical stirring and inert atmosphere at room temperature.

[0055] The modified silica is isolated by filtration, washed with acetone, methanol, acetone, dichloromethane, dried under reduced pressure (0.1 mbar) at room temperature to constant weight and stored under inert atmosphere (argon) at low temperature (4°C).

[0056] Elementary analysis % C 3.70, % H 0.78, % N 1.21 DSC  $T_{dec} = 120^{\circ}\text{C}$ ;  $I_{dec} = 96 \text{ Jg}^{-1}$

[0057] FT-IR (DRIFT) 2978, 2941, 2898, 2244, 1649, 1548, 1446  $\text{cm}^{-1}$ .

#### Example 5:

#### Preparation of the polymeric chiral stationary phase (FSC 1):

[0058] 450 mg N-(2-acryloylamine-(1*R*,2*R*)-cyclohexyl)-acrylamide (2.03 mmoles) are dissolved in 50 ml anhydrous chloroform degassed with Helium, at 60°C and under mechanical stirring. 3.0 g silica, derivatized with the 4,4'-azo-bis-(4-cyanovaleric) acid dichloride, are added to the obtained solution. The reaction mixture is kept at 60°C for 5h 10min under mechanical stirring and inert atmosphere (argon) and then refluxed for 1h.

[0059] The obtained silica is isolated by filtration, washed with methanol, acetone, dichloromethane and dried under reduced pressure (0.1 mbar) at 60°C to constant weight.

[0060] Elementary analysis % C 10.36, % H 1.68, % N 2.19

[0061] FT-IR (KBr) 3078, 2941, 2860, 2237, 1646, 1542, 1451  $\text{cm}^{-1}$ .

[0062] The data reported in Table 1 illustrate the recovery rate of the stationary phase CSP1.

[0063] The computations were carried out in the light of the result of elementary analysis for Nitrogen.

Table 1

	Stage I	Stage II	Stage III
% Carbon	1.35	3.70	10.36
% Hydrogen	0.54	0.78	1.68
% Nitrogen	0.48	1.21	2.19
mmoles substrate / g silica	353.03	141.76	450.87
moles substrate/ g matrix	342.61	133.07	386.86
mmoles substrate / $\text{m}^2$	3.07	1.23	3.92
Weight increase (%)	3.04	6.53	16.55
Average distance among groups (Å)	7.37	11.63	6.52

#### Applicative examples:

[0064] In a series of practical applications, the modified silica CSP1, produced according to examples 1 to 5 (scheme reported in figure 2), was packed by slurry technique in steel columns (4.0x250 mm size) and employed in the direct resolution of racemates of a wide range of molecules having central, axial and planar chirality and characterised by the presence of various functional groups (alcohols, acids, amides, heterocyclic compounds).

[0065] Some chiral substances whose racemates have been resolved are reported in figure 4.

[0066] As it is illustrated in Table 2, in all cases individual enantiomers having elevated chemical and stereochemical purity values were obtained.

[0067] Chromatographic data:

the values  $K'_1$  and  $K'_2$  relate to the two enantiomers of a same substance.

[0068] The value  $K'$  (retention factor) is given by the following formula:

$(t_1 - t_0) / t_0$ , where  $t_1$  and  $t_0$  are dilution times of the enantiomer and  $t_0$  is the elution time of an unretained standard compound (1,3,5-tri-*t*-butylbenzene).  $\alpha$  (enantioselectivity factor) indicates the  $k'_2/k'_1$  ratio.

TABLE 2

Compound (see scheme 2)	$k'_1$	$k'_2$	$\alpha$	Eluent
1	0.13	0.20	1.58	CH <sub>2</sub> Cl <sub>2</sub> /MeOH 97/3
2	0.38	0.62	1.60	" "
3	1.25	1.47	1.18	" "
4	1.44	6.18	4.29	" "
5	1.51	5.89	3.89	" "
6	5.64	11.63	2.06	" "
7	1.74	3.30	1.90	" "
8	4.54	5.02	1.10	Hexane/CH <sub>2</sub> Cl <sub>2</sub> 80/20 + 0.5% MeOH
9	2.81	3.06	1.09	Hexane/CH <sub>2</sub> Cl <sub>2</sub> 80/20 + 0.5% MeOH
10	4.67	5.12	1.10	Hexane/CH <sub>2</sub> Cl <sub>2</sub> 90/10 + 0.5% MeOH

## REFERENCES CITED IN THE DESCRIPTION

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- JP61162750A [0011]
- US5493979A [0012]
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- EP0379917A [0015]

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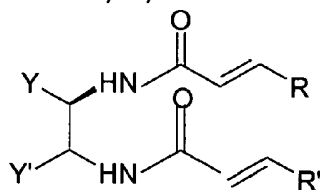
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- **HAGINAKA J**protein-based chiral stationary phases for high-performance liquid chromatography enantioseparationsJ. Chromatogr. A, 2001, vol. 906, 253-73 [\[0003\]](#)
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- **OKAMOTO YYASHIMA E**Polysaccharide derivatives for chromatographic separation of enantiomersAngew. Chem. Int. Ed., 1998, vol. 37, 1020-43 [\[0007\]](#)
- **KANAZAWA H. et al.**Analytical Sciences, 2002, vol. 18, 45-48 [\[0010\]](#)
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- **HIDEKO KANAZAWA**Temperature-responsive chromatography using poly-(N-isopropylacrylamide) Hydrogel-Modified siliceAnalytical Sciences, 2002, vol. 18, 45-48 [\[0016\]](#)

**Patentkrav**

1. Brushtype chiral stationær fase til væskechromatografi opnået ved:

- (a) at behandle et fast bærestof af makroporøs silica med en reagens der er i stand til at forbinde en funktionel gruppe til bærestoffet,
- 5 (b) at danne et aktiveret bærestof ved at immobilisere en aktiveret bifunktionel reaktant indeholdende en azogruppe på bærestoffet fra (a) mens azogruppens evne til at danne radikale specier bevarer,
- (c) at omsætte det aktiverede bærestof fra (b) med chirale monomerer valgt blandt N-(meta)acryloylderivater af aminer, diaminer, aminoalkoholer, og aminosyrer under en inert atmosfære ved en
- 10 temperatur der er tilstrækkelig høj til at sætte azogruppen i stand til at inducere dannelse af frie radikaler for at polymerisere de chirale monomere direkte på det aktiverede bærestof for at danne en chiral polymer; hvor de chirale monomerer er i form af enantiomerer med et forhøjet enantiomert overskud.
- 15

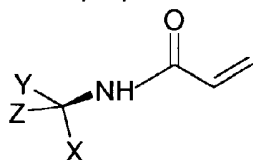
2. Brushtype chiral stationær fase ifølge krav 1, hvor den chirale monomer er et N-diacryloylderivat med formel I:



Formel I

- 20 hvor Y og Y', de samme eller forskellige, er valgt blandt phenyl, diphenyl, eventuelt substitueret benzyl og en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe; eller Y og Y' tilsammen danner en polymethylenring med formel -(CH<sub>2</sub>)<sub>n</sub>- hvor n er et heltal svarende til 2, 3, 4, 5 eller 6; og hvor R og R',
- 25 de samme eller forskellig, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl og eventuelt substitueret benzyl.

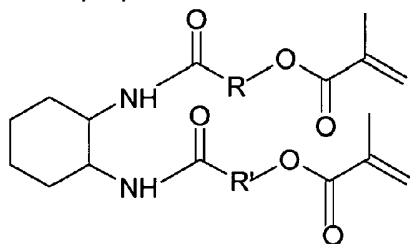
3. Brushtype chiral stationær fase ifølge krav 1, hvor den chirale monomer er et N-acryloylderivat med formel II:



Formel II

- 30 hvor Y, Z og X, de samme eller forskellige, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl, biphenyl, benzyl, og eventuelt substitueret aryl-C<sub>1</sub>-C<sub>10</sub> alkyl; eller en molekylær radikal omfattende
- 35 funktionelle grupper eller andre stereogene elementer.

4. Brushtype chiral stationær fase ifølge krav 1, hvor den chirale monomer er et N-acryloylderivat med formlen III:



Formel III

- 5 hvor R og R<sup>1</sup>, de samme eller forskellige, er en lineær kæde af -CH<sub>2</sub>-grupper vekslende fra -NH-, -O-, -OCO-grupper.
5. Brushtype chiral stationær fase ifølge krav 1, hvor den chirale monomer er valgt blandt propranolol N-acryloyl, 1,2-trans-diphenyl-ethylendiamin-di-acryloyl, 10 1,2-trans-diamino-cyclohexan-di-acryloyl, norephedrin N-acryloyl, 1,2-trans-diaminocyclohexan-di-2-(metacryloyloxy)-ethylsuccinat, cinnamoyl 1,2-trans-diaminocyclohexan, 1,2-trans-diaminocyclohexan-di-(3-isopropenylphenyl)-1-methylethyl-ureid og 1,2-trans-diaminocyclohexan-di-(2-methylacryloyloxy)-ethyl-ureid.
- 15 6. Brushtype chiral stationær fase ifølge krav 1, hvor den aktiverede bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af en α,α'-azo-bis-(cyanocarboxyl)syre.
- 20 7. Brushtype chiral stationær fase ifølge krav 6, hvor den aktiverede bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af 4,4'-azo-bis-(4-cyanovaleriane)syre eller 4,4'-azo-bis-(4-cyanobutan)syre.
- 25 8. Brushtype chiral stationær fase ifølge krav 7, hvor den aktiverede form er anhydridet eller dichloridet af 4,4'-azo-bis-(4-cyanovaleriane)syren eller 4,4'-azo-bis-(4-cyanobutan)syren.
- 30 9. Brushtype chiral stationær fase ifølge krav 1, hvor den funktionelle gruppe forbundet med bærestoffet er valgt blandt -NH<sub>2</sub>, -OH og -SH.
- 35 10. Brushtype chiral stationær fase ifølge krav 9, hvor reagensen der er i stand til at forbinde en funktionel gruppe med bærestoffet er en 3-aminopropyl-trialkoxysilan.
- 40 11. Brushtype chiral stationær fase ifølge krav 10, hvor 3-aminopropyl-trialkoxysilanen er 3-aminopropyl-triethoxysilan.
12. Brushtype chiral stationær fase ifølge krav 1, hvor det makroporøse silica behandles med 3-aminopropyl-triethoxysilan.
13. Brushtype chiral stationær fase ifølge krav 1, hvor den dannede chirale polymer bærer siderester som er regelmæssigt orienterede og perpendikulære til

polymerstrukturen og til det faste bærestof hvortil den chirale polymer er kovalent bundet.

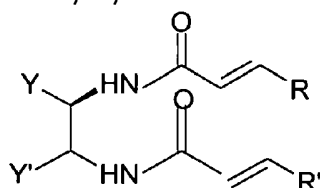
5 **14.** Fremgangsmåde til fremstilling af en brushtype chiral stationær fase til væskechromatografi, hvilken fremgangsmåde omfatter:

(a) at behandle et fast bærestof af makroporøs silica med en reagens der er i stand til at forbinde en funktionel gruppe til bærestoffet,

10 (b) at danne et aktiveret bærestof ved at immobilisere en aktiveret bifunktionel reaktant indeholdende en azogruppe på bærestoffet fra (a) mens azogruppens evne til at danne radikale specier bevares,

15 (c) at omsætte det aktiverede bærestof fra (b) med chirale monomerer valgt blandt N-(meta)acryloylderivater af aminer, diaminer, aminoalkoholer, og aminosyrer under en inert atmosfære ved en temperatur der er tilstrækkelig høj til at sætte azogruppen i stand til at inducere dannelse af frie radikaler for at polymerisere de chirale monomerer direkte på det aktiverede bærestof for at danne en chiral polymer; hvor de chirale monomerer er i form af enantiomerer med et forhøjet enantiomert overskud.

20 **15.** Fremgangsmåde ifølge krav 14, hvor den chirale monomer er et N-diacryloylderivat med formlen I:

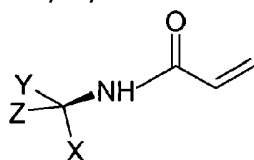


Formel I

25 hvor Y og Y', de samme eller forskellige, er valgt blandt phenyl, diphenyl, eventuelt substitueret benzyl og en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe; eller Y og Y' tilsammen danner en polymethylenring med formelen -(CH<sub>2</sub>)<sub>n</sub>- hvor n er et heltal svarende til 2, 3, 4, 5 eller 6; og hvor R og R', de samme eller forskellig, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl og eventuelt substitueret benzyl.

30

**16.** Fremgangsmåde ifølge krav 14, hvor den chirale monomer er et N-acryloylderivat med formlen II:

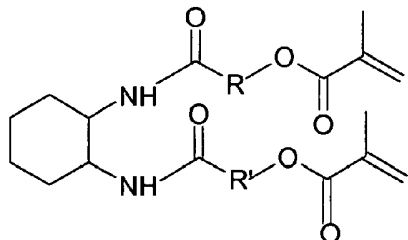


Formel II

hvor Y, Z og X, de samme eller forskellige, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl, biphenyl, benzyl, og eventuelt substitueret aryl-C<sub>1</sub>-C<sub>10</sub> alkyl; eller en molekylær radikal omfattende funktionelle grupper eller andre stereogene elementer.

5

**17.** Fremgangsmåde ifølge krav 14, hvor den chirale monomer er et N-acryloylderivat med formel III:



Formel III

10 hvor R og R<sup>1</sup>, de samme eller forskellige, er en lineær kæde af -CH<sub>2</sub>-grupper vekslende fra -NH-, -O-, -OCO-grupper.

**18.** Fremgangsmåde ifølge krav 14, hvor den chirale monomer er valgt blandt propranolol N-acryloyl, 1,2-*trans*-diphenylethylendiamin-di-acryloyl, 1,2-*trans*-diaminocyclohexan-di-acryloyl, norephedrin N-acryloyl, 1,2-*trans*-diaminocyclohexan-di-2-(metacryloyloxy)ethylsuccinat, cinnamoyl 1,2-*trans*-diaminocyclohexan, 1,2-*trans*-diaminocyclohexan-di-(3-isopropenylphenyl)-1-methyl-ethyl-ureid og 1,2-*trans*-diaminocyclohexan-di-(2-methylacryloyloxy)-ethyl-ureid.

20

**19.** Fremgangsmåde ifølge krav 14, hvor den aktiverede bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af en α,α'-azo-bis-(cyanocarboxyl)syre.

25 **20.** Fremgangsmåde ifølge krav 19, hvor den aktiverede bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af 4,4'-azo-bis-(4-cyanovaleriane) syre eller 4,4'-azo-bis-(4-cyanobutan)syre.

30 **21.** Fremgangsmåde ifølge krav 20, hvor den aktiverede form er anhydridet eller dichloridet af 4,4'-azo-bis-(4-cyanovaleriane)syren eller 4,4'-azo-bis-(4-cyanobutan)syren.

35 **22.** Fremgangsmåde ifølge krav 14, hvor den funktionelle gruppe forbundet til bærestoffet er valgt blandt -NH<sub>2</sub>, -OH og -SH.

**23.** Fremgangsmåde ifølge krav 22, hvor reagensen der er i stand til at forbinde en funktionel gruppe med bærestoffet er en 3-aminopropyl-trialkoxysilan.

40 **24.** Fremgangsmåde ifølge krav 23, hvor 3-aminopropyl-trialkoxysilanen er 3-aminopropyl-triethoxysilan.

**25.** Fremgangsmåde ifølge krav 14, hvor det makroporøse silica behandles med 3-aminopropyl-triethoxysilan.

**26.** Fremgangsmåde ifølge krav 14, hvor den dannede chirale polymer bærer siderester som er regelmæssigt orienterede og perpendikulære til polymerstrukturen og til det faste bærestof hvortil den chirale polymer er kovalent bundet.

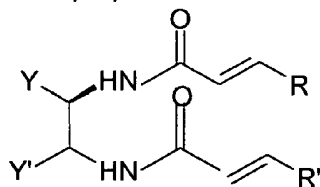
**27.** Kromatografisk søjle til opløsning af racemiske blandinger eller oprensning af individuelle enantiomerer omfattende en brusstype chiral stationær fase opnået ved:

(a) at behandle et fast bærestof af makroporøs silica med en reagens der er i stand til at forbinde en funktionel gruppe til bærestoffet,

(b) at danne et aktiveret bærestof ved at immobilisere en aktiveret bifunktionel reaktant indeholdende en azogruppe på bærestoffet fra (a) mens azogrupperens evne til at danne radikale specier bevares,

(c) at omsætte det aktiverede bærestof fra (b) med chirale monomerer valgt blandt N-(meta)acryloylderivater af aminer, diaminer, aminoalkoholer, og aminosyrer under en inert atmosfære ved en temperatur der er tilstrækkelig høj til at sætte azogruppen i stand til at inducere dannelse af frie radikaler for at polymerisere de chirale monomerer direkte på det aktiverede bærestof for at danne en chiral polymer; hvor de chirale monomerer er i form af enantiomerer med et forhøjet enantiomert overskud.

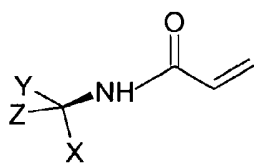
**28.** Kromatografisk søjle ifølge krav 27, hvor den chirale monomer er et N-diacryloylderivat med formlen I:



Formel I

hvor Y og Y', de samme eller forskellige, er valgt blandt phenyl, diphenyl, eventuelt substitueret benzyl og en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe; eller Y og Y' tilsammen danner en polymethylenring med formelen -(CH<sub>2</sub>)<sub>n</sub>- hvor n er et heltal svarende til 2, 3, 4, 5 eller 6; og hvor R og R', de samme eller forskellige, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl og eventuelt substitueret benzyl.

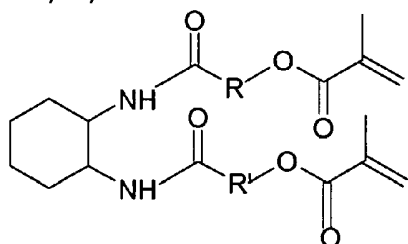
**29.** Kromatografisk søjle ifølge krav 27, hvor den chirale monomer er et N-acryloylderivat med formlen II:



Formel II

- hvor Y, Z og X, de samme eller forskellige, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl, biphenyl, benzyl, og eventuelt substitueret aryl-C<sub>1</sub>-C<sub>10</sub> alkyl; eller en molekylær radikal omfattende funktionelle grupper eller andre stereogene elementer.

**30.** Kromatografisk søjle ifølge krav 27, hvor den chirale monomer er et N-acryloylderivat med formelen III:



10 Formel III

hvor R og R<sup>1</sup>, de samme eller forskellige, er en lineær kæde af -CH<sub>2</sub>-grupper vekslende fra -NH-, -O-, -OCO-grupper.

- 15 **31.** Kromatografisk søjle ifølge krav 27, hvor den chirale monomer er valgt blandt propranolol N-acryloyl, 1,2-*trans*-diphenyl-ethylendiamin-di-acryloyl, 1,2-*trans*-diamino-cyclohexan-di-acryloyl, norephedrin N-acryloyl, 1,2-*trans*-diaminocyclohexan-di-2-(metacryloyloxy)-ethylsuccinat, cinnamoyl 1,2-*trans*-diamino-cyclohexan, 1,2-*trans*-diaminocyclohexan-di-(3-isopropenylphenyl)-1-methylethyl-ureid og 1,2-*trans*-diaminocyclohexan-di-(2-methylacryloyloxy)-ethyl-ureid.

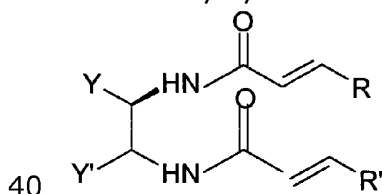
25 **32.** Kromatografisk søjle ifølge krav 27, hvor den aktiverede bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af en α,α'-azo-bis-(cyanocarboxyl)syre.

30 **33.** Kromatografisk søjle ifølge krav 32, hvor den aktiverede bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af 4,4'-azo-bis-(4-cyanovaleriane) syre eller 4,4'-azo-bis-(4-cyanobutan)syre.

**34.** Kromatografisk søjle ifølge krav 33, hvor den aktiverede form er anhydridet eller dichloridet af 4,4'-azo-bis-(4-cyanovaleriane)syren eller 4,4'-azo-bis-(4-cyanobutan)syren.

35 **35.** Kromatografisk søjle ifølge krav 27, hvor den funktionelle gruppe forbundet til bærestoffet er valgt blandt -NH<sub>2</sub>, -OH og -SH.

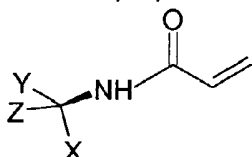
- 36.** Kromatografisk søjle ifølge krav 35, hvor reagensen der er i stand til at forbinde en funktionel gruppe med bærestoffet er en 3-aminopropyl-trialkoxysilan.
- 37.** Kromatografisk søjle ifølge krav 36, hvor 3-aminopropyl-trialkoxysilanen er 3-aminopropyl-triethoxysilan.
- 38.** Kromatografisk søjle ifølge krav 27, hvor det makroporøse silica behandles med 3-aminopropyl-triethoxysilan.
- 10 **39.** Kromatografisk søjle ifølge krav 27, hvor den dannede chirale polymer bærer siderester som er regelmæssigt orienterede og perpendikulære til polymerstrukturen og til det faste bærestof hvortil den chirale polymer er kovalent bundet.
- 15 **40.** Anvendelse af en kromatografisk søjle ifølge krav 27 til analytiske eller præparative separationsprocesser med høj- eller lav-effektivitet.
- 41.** Anvendelse ifølge krav 40 til HPLC, SMB, SFC eller superkritisk væskekromatografi.
- 20 **42.** Kromatografisk fremgangsmåde til opløsning af en racemisk blanding eller oprensning af individuelle enantiomerer omfattende anvendelse af en brushtype chiral stationær fase opnået ved:
- (a) at behandle et fast bærestof af makroporøs silica med en reagens der er i stand til at forbinde en funktionel gruppe til bærestoffet,
- (b) at danne et aktiveret bærestof ved at immobilisere en aktiveret bifunktionel reaktant indeholdende en azogruppe på bærestoffet fra (a) mens azogruppens evne til at danne radikale specier bevarer,
- (c) at omsætte det aktiverede bærestof fra (b) med chirale monomerer valgt blandt N-(meta)acryloylderivat af aminer, diaminer, aminoalkoholer, og aminosyrer under en inert atmosfære ved en temperatur der er tilstrækkelig høj til at sætte azogruppen i stand til at inducere dannelse af frie radikaler for at polymerisere de chirale monomerer direkte på det aktiverede bærestof for at danne en chiral polymer; hvor de chirale monomerer er i form af enantiomerer med et forhøjet enantiomert overskud.
- 43.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den chirale monomer er et N-diacryloylderivat med formel I:



Formel I

hvor Y og Y', de samme eller forskellige, er valgt blandt phenyl, diphenyl, eventuelt substitueret benzyl og en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe; eller Y og Y' tilsammen danner en polymethylenring med formelen -(CH<sub>2</sub>)<sub>n</sub>- hvor n er et heltal svarende til 2, 3, 4, 5 eller 6; og hvor R og R',  
 5 de samme eller forskellige, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl og eventuelt substitueret benzyl.

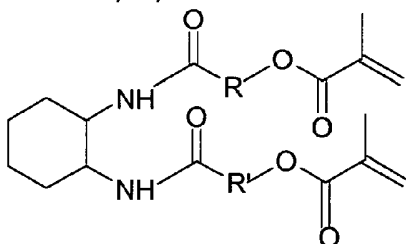
**44.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den chirale monomer er et N-acryloylderivat med formel II:



10 Formel II

hvor Y, Z og X, de samme eller forskellige, er valgt blandt H, en eventuelt substitueret C<sub>1</sub>-C<sub>10</sub> lineær eller forgrenet alkylgruppe, phenyl, biphenyl, benzyl, og eventuelt substitueret aryl-C<sub>1</sub>-C<sub>10</sub> alkyl; eller en molekylær radikal omfattende  
 15 funktionelle grupper eller andre stereogene elementer.

**45.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den chirale monomer er et N-acryloylderivat med formel III:



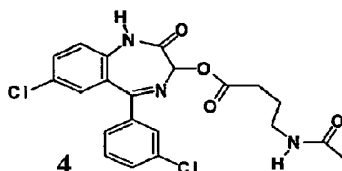
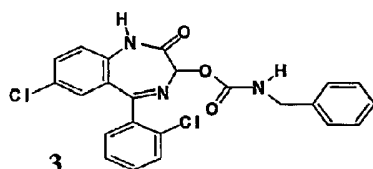
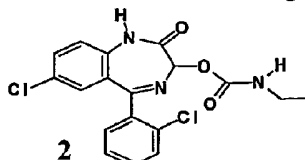
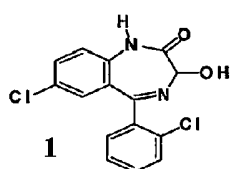
20 Formel III

hvor R og R<sup>1</sup>, de samme eller forskellige, er en lineær kæde af -CH<sub>2</sub>-grupper vekslede fra -NH-, -O-, -OCO-grupper.  
 25

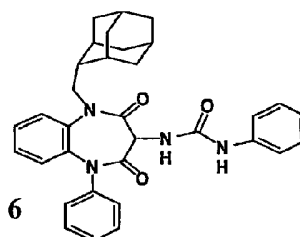
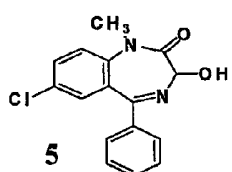
**46.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den chirale monomer er valgt blandt propranolol N-acryloyl, 1,2-*trans*-diphenyl-ethylendiamin-di-acryloyl, 1,2-*trans*-diamino-cyclohexan-di-acryloyl, norephedrin N-acryloyl, 1,2-*trans*-diaminocyclohexan-di-2-(metacryloyloxy)-ethylsuccinat, cinnamoyl 1,2-*trans*-diamino-cyclohexan, 1,2-*trans*-diaminocyclohexan-di-(3-isopropenylphenyl)-1-  
 30 methylethyl-ureid og 1,2-*trans*-diaminocyclohexan-di-(2-methylacryloyloxy)-ethyl-ureid.

**47.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den aktiverede  
 35 bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af en α,α'-azo-bis-(cyanocarboxyl)syre.

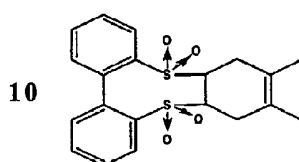
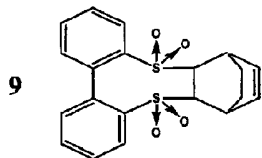
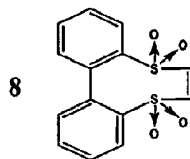
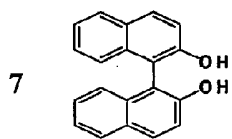
- 48.** Kromatografisk fremgangsmåde ifølge krav 57, hvor den aktiverede bifunktionelle reaktant indeholdende en azogruppe er en aktiveret form af 4,4'-azo-bis-(4-cyanovaleriane)syre eller 4,4'-azo-bis-(4-cyanobutan)syre.
- 5 **49.** Kromatografisk fremgangsmåde ifølge krav 48, hvor den aktiverede form er anhydridet eller dichloridet af 4,4'-azo-bis-(4-cyanovaleriane)syren eller 4,4'-azo-bis-(4-cyanobutan)syren.
- 50.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den funktionelle gruppe forbundet til bærestoffet er valgt blandt -NH<sub>2</sub>, -OH og -SH.
- 10 **51.** Kromatografisk fremgangsmåde ifølge krav 50, hvor reagensen der er i stand til at forbinde en funktionel gruppe med bærestoffet er en 3-aminopropyl-trialkoxysilan.
- 15 **52.** Kromatografisk fremgangsmåde ifølge krav 51, hvor 3-aminopropyl-trialkoxysilanen er 3-aminopropyl-triethoxysilan.
- 53.** Kromatografisk fremgangsmåde ifølge krav 42, hvor det makroporøse silica
- 20 behandles med 3-aminopropyl-triethoxysilan.
- 54.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den dannede chirale polymer bærer siderester som er regelmæssigt orienterede og perpendikulære til polymerstrukturen og til det faste bærestof hvortil den chirale polymer er kovalent
- 25 bundet.
- 55.** Kromatografisk fremgangsmåde ifølge krav 42, hvor den racemiske blanding eller enantiomerer omfatter en forbindelse med central, aksial eller planar chiralitet.
- 30 **56.** Kromatografisk fremgangsmåde ifølge krav 55, hvor forbindelsen er en hvilken som helst af forbindelserne 1 til 10 med følgende formler:



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## DRAWINGS

Scheme 1

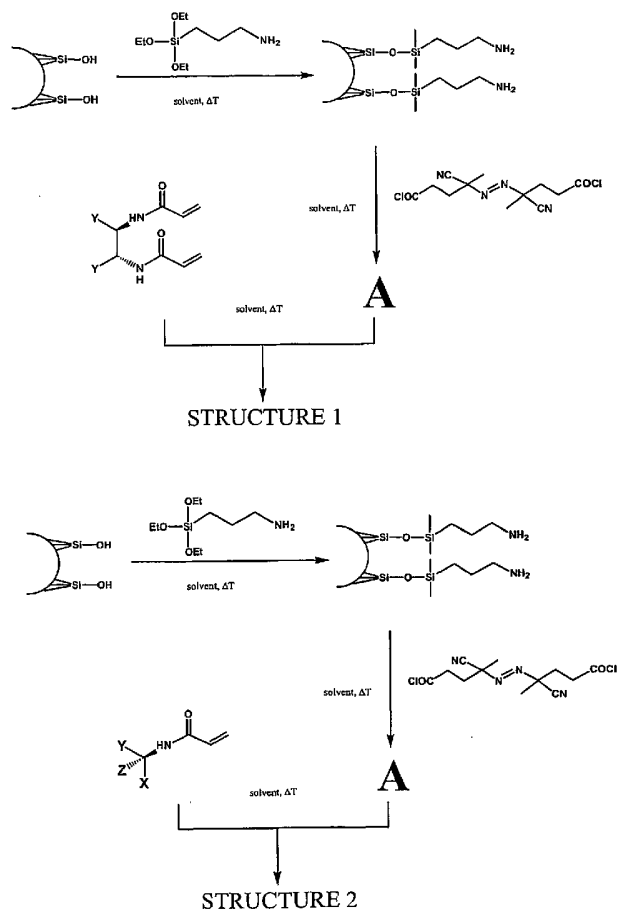


FIG. 1

Scheme 1a

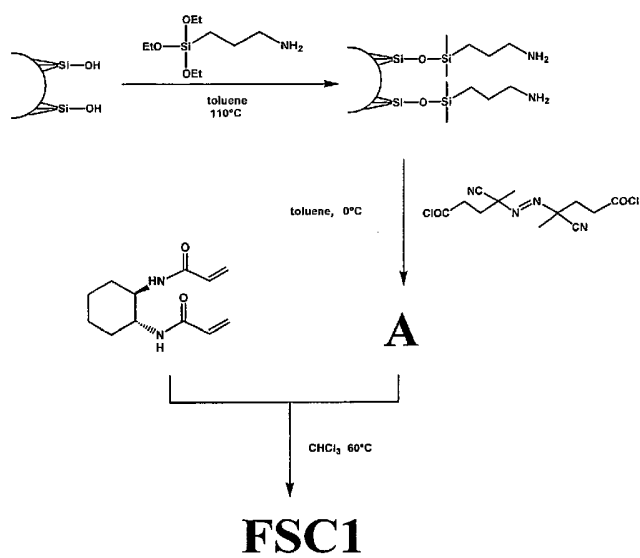


FIG. 2

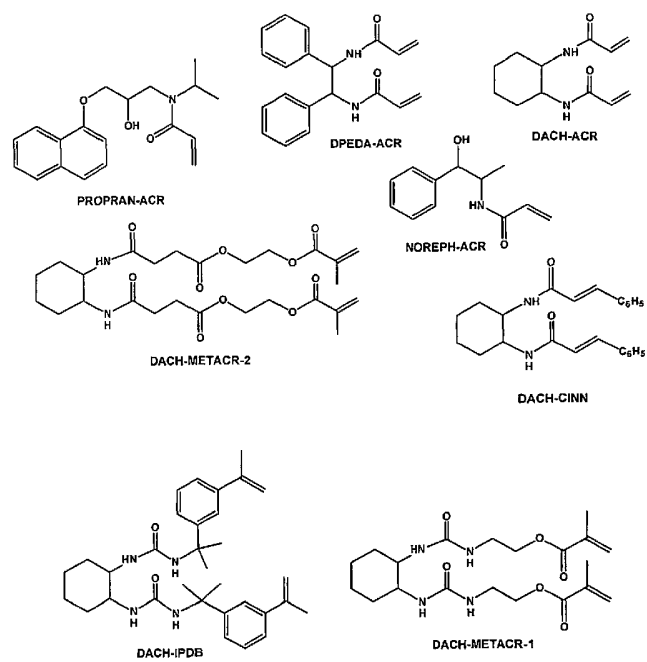


FIG. 3

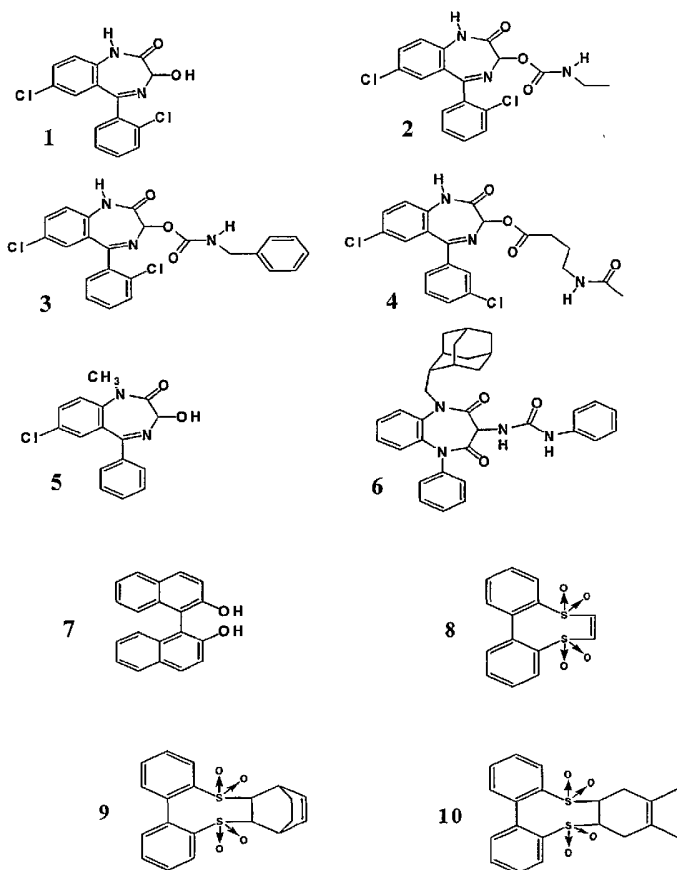


FIG. 4