



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US00/03052</p> <p>(22) International Filing Date: 4 February 2000 (04.02.00)</p> <p>(30) Priority Data: 09/244,795 5 February 1999 (05.02.99) US</p> <p>(71) Applicant (for all designated States except US): WATERS INVESTMENTS LIMITED [US/US]; 34 Maple Street, Milford, MA 01757 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): FISK, Raymond, P. [US/US]; 13 Creastwood Drive, Norton, MA 02766 (US). WALTER, Thomas, H. [US/US]; 54 Indian Brook Road, Ashland, MA 01721 (US). ZHIPING, Jiang [US/US]; 5 Sweetwood Circle, Westford, MA 01886 (US).</p> <p>(74) Agent: JANIUK, Anthony, J.; Waters Investments Limited, 34 Maple Street, Milford, MA 01757 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: POROUS INORGANIC/ORGANIC HYBRID PARTICLES FOR CHROMATOGRAPHIC SEPARATIONS AND PROCESS FOR ITS PREPARATION</p>		
<p>(57) Abstract</p> <p>Novel material for chromatographic separations, processes for its preparation, and separations devices containing the chromatographic material. In particular, the disclosure describes porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry, which desirably may be surface modified, and which offer more efficient chromatographic separations than that known in the art.</p>		

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POROUS INORGANIC/ORGANIC HYBRID PARTICLES FOR  
CHROMATOGRAPHIC SEPARATIONS AND  
PROCESS FOR ITS PREPARATION

5 BACKGROUND OF THE INVENTION

Packing materials for liquid chromatography (LC) are generally classified into two types: organic or polymeric carriers, e.g., polystyrene polymers; and inorganic carriers typified by silica gel. The polymeric  
10 materials are chemically stable against alkaline and acidic mobile phases; therefore, the pH range of the eluant used with polymeric chromatographic materials is wide, compared with the silica carriers. However, polymeric chromatographic materials generally result in polymeric columns with low efficiency, leading to inadequate separation performance, particularly with  
15 low molecular-weight analytes. Furthermore, polymeric chromatographic materials shrink and swell upon solvent changeover in the eluting solution.

On the other hand, silica gel-based chromatographic devices, e.g., HPLC columns, are most commonly used. The most common applications  
20 employ a silica which has been surface-derivatized with an organic functional group such as octadecyl (C<sub>18</sub>), octyl (C<sub>8</sub>), phenyl, amino, cyano group, etc. As a stationary phase for HPLC, these packing materials result in columns with high theoretical plate number/high efficiency, and do not evidence shrinking or swelling. Silica gel is characterized by the presence  
25 of silanol groups on its surface. During a typical derivatization process such as reaction with octadecyldimethylchlorosilane, at least 50% of the surface silanol groups remain unreacted. These residual, or free, silanol groups interact with basic and acidic analytes via ion exchange, hydrogen bonding and dipole/dipole mechanisms. The free silanol groups create  
30 problems including increased retention, excessive peak tailing and irreversible adsorption of the sample. The other drawback with silica-based columns is their limited hydrolytic stability. First, the incomplete derivatization of the silica gel leaves a bare silica surface which can be

readily dissolved under alkaline conditions, generally  $\text{pH} > 8.0$ , leading to the subsequent collapse of the chromatographic bed. Secondly, the bonded phase can be stripped off of the surface under acidic conditions, generally  $\text{pH} < 2.0$ , and eluted off the column by the mobile phase, causing  
5 loss of analyte retention, and an increase in the concentration of surface silanol groups.

To overcome the problems of free silanol group activity and hydrolytic instability of silica-based stationary phases, many methods have been tried including use of ultrapure silica, carbonized silica, coating  
10 of the silica surface with polymeric materials, endcapping free silanol groups with a short-chain reagent such as trimethylsilane, and the addition of suppressors such as amines to the eluant. These approaches have not proven to be completely satisfactory in practice.

One approach which has been taken is disclosed in U. S. Patent No.  
15 4,017,528. A process for preparing a "hybrid" silica is described wherein an alkyl functionality is coupled into both the skeleton structure and the surface of the silica. According to the '528 patent, the hybrid silica can be prepared by two methods. In the first method, a mixture of tetraethoxysilane (TEOS) and an alkyltriethoxysilane is cohydrolyzed in the  
20 presence of an acid catalyst to form a liquid material containing polyalkylethoxysiloxane (PAS) oligomers. Then, the PAS is suspended in an aqueous medium and gelled into porous particles in the presence of a base catalyst. In the second method, the material is prepared by a procedure similar to that described in the first method except that the  
25 suspension droplet is a mixture of alkyltriethoxysilane and polyethoxysiloxane (PES) oligomers; the latter is prepared by partial hydrolysis of TEOS.

Some problems have been associated with the '528 hybrid material. First, these hybrid materials contain a lot of micropores, i.e., pores having  
30 a diameter below  $30\text{\AA}$ . It is known that such micropores inhibit solute mass transfer, resulting in poor peak shape and band broadening.

Secondly, the pore structure of the '528 hybrid material is formed due to the presence of ethanol (a side product of the gelation process) within the suspension droplets during gelation, and serving as a porogen. The pore volume is controlled by the molecular weight of the PAS or PES, i.e., the degree of crosslinking. The lower the molecular weight or the lower the crosslinking degree of the PAS or PES, the more ethanol is generated by the gelation reaction and subsequently a larger pore volume is produced. However, part of the ethanol generated within the droplets of the suspension during the gelation is able to diffuse into the aqueous phase by partition. If the amount of the ethanol generated within the suspension droplets is too great, the partition of the ethanol will cause the structure of the droplets to collapse, forming irregularly-shaped particles. Therefore, the strategy to control the pore volume of the hybrid material described in the disclosure has certain limitations, particularly for preparing hybrid material where pore volume  $>0.8$  cc/g is required. Thirdly, the '528 hybrid material contains "shell-shaped" particles, which have undesirable chromatographic properties, including weak mechanical strength to poor mass transfer properties for solute molecules. This is a consequence of the gelation mechanism, where the base catalysts first react near the surface of the PAS droplet, forming a "skinned" layer of material having very small pores. Further gelation is then limited by the diffusion of catalyst through this layer towards the droplet center, leading to particles having "shell-shaped" pore morphology.

#### SUMMARY OF THE INVENTION

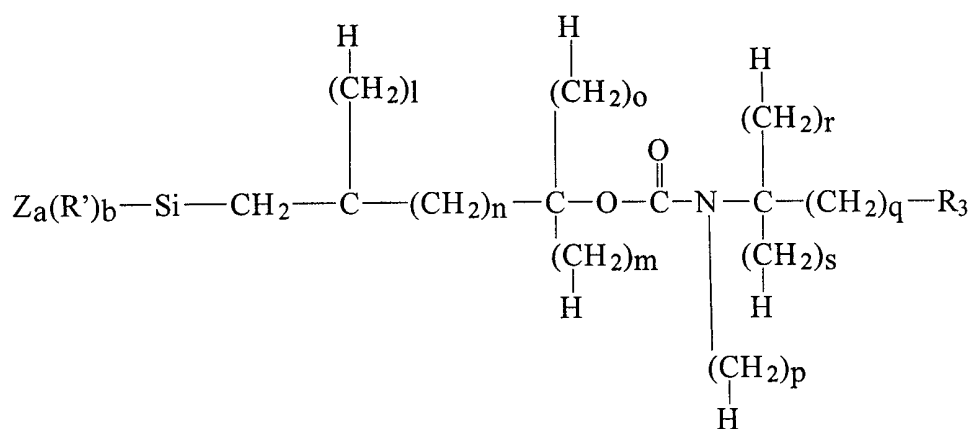
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The present disclosure relates to a novel material for chromatographic separations, processes for its preparation, and separations devices containing the chromatographic material. In particular, porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry are presented, which desirably may be surface modified, and which offer more efficient chromatographic separations than that known in the art. This new type of

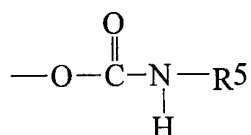
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packing material is chemically stable, does not have undesirable pore geometries, and shows excellent separation performance. The inorganic portion of the hybrid material may be, e.g., alumina, silica, titanium or zirconium oxides, or ceramic material; in a preferred embodiment, the  
 5 inorganic portion of the hybrid material is silica.

In an embodiment, the particles are surface modified with a surface modifier having the formula  $Z_a(R')_bSi-R$ , where  $Z = Cl, Br, I, C_1 - C_5$  alkoxy, dialkylamino, e.g., dimethylamino or trifluoromethanesulfonate;  $a$  and  $b$  are each an integer from 0 to 3 provided that  $a + b = 3$ ;  $R'$  is a  $C_1 - C_6$   
 10 straight, cyclic or branched alkyl group, and  $R$  is a functionalizing group.  $R'$  may be, e.g., methyl, ethyl, propyl, isopropyl, butyl, t-butyl, sec-butyl, pentyl, isopentyl, hexyl or cyclohexyl; preferably,  $R'$  is methyl. The functionalizing group  $R$  may include alkyl, aryl, cyano, amino, diol, nitro, cation or anion exchange groups, or embedded polar functionalities.  
 15 Examples of suitable  $R$  functionalizing groups include  $C_1 - C_{20}$  alkyl such as octyl ( $C_8$ ) and octadecyl ( $C_{18}$ ); alkaryl, e.g.,  $C_1 - C_4$ -phenyl; cyanoalkyl groups, e.g., cyanopropyl; diol groups, e.g., propyldiol; amino groups, e.g., dialkylamino such as aminopropyl; and embedded polar functionalities, e.g., carbamate functionalities such as disclosed in U. S. Patent No.  
 20 5,374,755, the text of which is incorporated herein by reference. Such groups include those of the general formula



wherein l, m, o, r, and s are 0 or 1, n is 0, 1, 2 or 3, p is 0, 1, 2, 3 or 4, and q is an integer from 0 to 19; R<sub>3</sub> is selected from the group consisting of hydrogen, alkyl, cyano and phenyl; and Z, R', a and b are defined as above. Preferably, the carbamate functionality has the general structure indicated below:



wherein R<sup>5</sup> may be, e.g., cyanoalkyl, t-butyl, butyl, octyl, dodecyl, tetradecyl, octadecyl, or benzyl. Advantageously, R<sup>5</sup> is octyl or octadecyl. In a preferred embodiment, the surface modifier may be a halopolyorganosilane, such as octyldimethylchlorosilane or octadecyldimethylchlorosilane. In another embodiment, the particles are surface modified by polymer coating.

In another aspect, methods of preparing porous particles of hybrid silica having a chromatographically-enhancing pore geometry are disclosed, wherein porous hybrid silica particles are formed and the pore structure of the porous particles is modified to form hybrid silica particles having a chromatographically-enhancing pore geometry. In a preferred embodiment, the particles are ellipsoidal, e.g., ovoid or spherical, more preferably spherical. In an embodiment, an organoalkoxysilane and a tetraalkoxysilane are prepolymerized to produce a polyorganoalkoxysiloxane; an aqueous surfactant-containing suspension of the polyorganoalkoxysiloxane is prepared, and gelling in the presence of a base catalyst is conducted so as to produce porous particles, followed by modifying the pore structure of the porous particles by hydrothermal treatment to produce an intermediate product which advantageously has other uses, and surface modifying the porous particles. In an advantageous embodiment, the prepolymerization step comprises hydrolyzing and condensing a mixture of an organoalkoxysilane and a

tetraalkoxysilane in the presence of an acid catalyst to produce the polyorganoalkoxysiloxane.

In yet another aspect, the present disclosure relates to separation devices such as chromatographic columns, sample cleanup devices, e.g.,  
5 solid phase extraction columns, thin layer chromatographic (TLC) plates, filtration membranes, microtiter plates, and the like having a stationary phase which includes porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry. The stationary phase may be introduced by packing, coating, impregnation, etc., depending on the  
10 requirements of the particular device. In a particularly advantageous embodiment, the chromatographic device is a packed chromatographic column such as that used for HPLC.

In yet another aspect the disclosure relates to chromatographic columns having improved life which comprise a column having a  
15 cylindrical interior for accepting a packing material, and a packed chromatographic bed comprising porous particles of hybrid silica of the formula  $\text{SiO}_2/(\text{R}^p\text{R}^q\text{SiO}_t)_n$  or  $\text{SiO}_2/[\text{R}^6(\text{R}^r\text{SiO}_t)_m]_n$  wherein  $\text{R}^2$  and  $\text{R}^4$  are independently  $\text{C}_1 - \text{C}_{18}$  alkyl or aryl moiety (which may additionally be substituted with alkyl, aryl, cyano, amino, diol, nitro, and ion exchange or  
20 embedded polar functionalities),  $\text{R}^6$  is a substituted or unsubstituted  $\text{C}_1 - \text{C}_{18}$  alkylene, alkenylene, alkynylene or arylene moiety bridging two or more silicon atoms, p and q are 0, 1 or 2, provided that  $p+q = 1$  or 2, and that when  $p+q=1$ ,  $t=1.5$ , and when  $p+q=2$ ,  $t=1$ ; r is 0 or 1, provided that when  $r = 0$ ,  $t = 1.5$ , and when  $r = 1$ ,  $t = 1$ ; m is an integer greater than or  
25 equal to 2, and n is a number from 0.1 to 1, more preferably 0.2 to 0.5, wherein porous particles of hybrid silica are surface modified and have an average pore diameter of from about 100 to 300Å.

#### DETAILS OF THE INVENTION

30 The present invention will be more fully illustrated by reference to the definitions set forth below.



The language “chromatographically-enhancing pore geometry” includes the geometry of the pore configuration of the presently-disclosed porous inorganic/organic hybrid particles, which has been found to enhance the chromatographic separation ability of the material, e.g., as distinguished from other chromatographic media in the art. For example, a geometry can be formed, selected or constructed, and various properties and/or factors can be used to determine whether the chromatographic separations ability of the material has been “enhanced”, e.g., as compared to a geometry known or conventionally used in the art. Examples of these factors include high separation efficiency, longer column life, and high mass transfer properties (as evidenced by, e.g., reduced band spreading and good peak shape.) These properties can be measured or observed using art-recognized techniques. For example, the chromatographically-enhancing pore geometry of the present porous inorganic/organic hybrid particles is distinguished from the prior art particles by the absence of “ink bottle” or “shell shaped” pore geometry or morphology, both of which are undesirable because they, e.g., reduce mass transfer rates, leading to lower efficiencies.

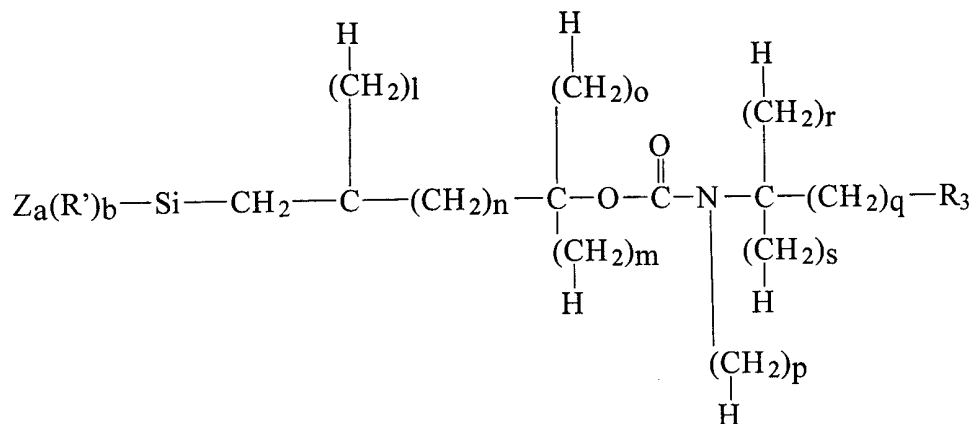
“Hybrid”, i.e., as in “porous inorganic/organic hybrid particles” includes inorganic-based structures wherein an organic functionality is integral to both the internal or “skeletal” inorganic structure as well as the hybrid material surface. The inorganic portion of the hybrid material may be, e.g., alumina, silica, titanium or zirconium oxides, or ceramic material; in a preferred embodiment, the inorganic portion of the hybrid material is silica. As noted before, exemplary hybrid materials are shown in U. S. Patent No. 4,017,528, the text of which is incorporated herein by reference. In a preferred embodiment where the inorganic portion is silica, “hybrid silica” refers to a material having the formula  $\text{SiO}_2/(\text{R}^2_p\text{R}^4_q\text{SiO}_t)_n$  or  $\text{SiO}_2/[\text{R}^6(\text{R}^2_r\text{SiO}_t)_m]_n$  wherein  $\text{R}^2$  and  $\text{R}^4$  are independently  $\text{C}_1 - \text{C}_{18}$  alkyl or aryl moiety (which may additionally be substituted with alkyl, aryl, cyano, amino, diol, nitro, and ion exchange or embedded polar functionalities),

$R^6$  is a substituted or unsubstituted  $C_1 - C_{18}$  alkylene, alkenylene, alkynylene or arylene moiety bridging two or more silicon atoms, p and q are 0, 1 or 2, provided that  $p+q = 1$  or 2, and that when  $p+q=1$ ,  $t=1.5$ , and when  $p+q=2$ ,  $t=1$ ; r is 0 or 1, provided that when  $r = 0$ ,  $t = 1.5$ , and when  $r = 1$ ,  $t = 1$ ; m is an integer greater than or equal to 2, and n is a number from 0.1 to 1, more preferably 0.2 to 0.5.  $R^2$  may be additionally substituted with a functionalizing group R.

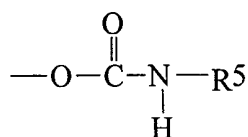
“Functionalizing group” includes (typically) organic functional groups which impart a certain chromatographic functionality to a chromatographic stationary phase, including, e.g., octadecyl ( $C_{18}$ ), phenyl, ion exchange, etc. Such functionalizing groups are present in, e.g., surface modifiers such as disclosed herein which are attached to the base material, e.g., via derivatization or coating and later crosslinking, imparting the chemical character of the surface modifier to the base material. In an embodiment, such surface modifiers have the formula  $Z_a(R')_bSi-R$ , where  $Z = Cl, Br, I, C_1 - C_5$  alkoxy, dialkylamino, e.g., dimethylamino or trifluoromethanesulfonate; a and b are each an integer from 0 to 3 provided that  $a + b = 3$ ;  $R'$  is a  $C_1 - C_6$  straight, cyclic or branched alkyl group, and R is a functionalizing group.  $R'$  may be, e.g., methyl, ethyl, propyl, isopropyl, butyl, t-butyl, sec-butyl, pentyl, isopentyl, hexyl or cyclohexyl; preferably,  $R'$  is methyl.

The functionalizing group R may include alkyl, aryl, cyano, amino, diol, nitro, cation or anion exchange groups, or embedded polar functionalities. Examples of suitable R functionalizing groups include  $C_1 - C_{20}$  alkyl such as octyl ( $C_8$ ) and octadecyl ( $C_{18}$ ); alkaryl, e.g.,  $C_1 - C_4$ -phenyl; cyanoalkyl groups, e.g., cyanopropyl; diol groups, e.g., propyldiol; amino groups, e.g., aminopropyl; and embedded polar functionalities, e.g., carbamate functionalities such as disclosed in U. S. Patent No. 5,374,755, the text of which is incorporated herein by reference. In a preferred embodiment, the surface modifier may be a halopolyorganosilane, such as octyldimethylchlorosilane or octadecyldimethylchlorosilane. Embedded

polar functionalities include carbamate functionalities such as disclosed in U. S. Patent No. 5,374,755, the text of which is incorporated herein by reference. Such groups include those of the general formula



- 5 wherein l, m, o, r, and s are 0 or 1, n is 0, 1, 2 or 3 p is 0, 1, 2, 3 or 4 and q is an integer from 0 to 19; R<sub>3</sub> is selected from the group consisting of hydrogen, alkyl, cyano and phenyl; and Z, R', a and b are defined as above. Preferably, the carbamate functionality has the general structure indicated below:



10

- wherein R<sup>5</sup> may be, e.g., cyanoalkyl, t-butyl, butyl, octyl, dodecyl, tetradecyl, octadecyl, or benzyl. Advantageously, R<sup>5</sup> is octyl or octadecyl. In a preferred embodiment, the surface modifier may be a halopolyorganosilane, such as octyldimethylchlorosilane or
- 15 octadecyldimethylchlorosilane. In another embodiment, the particles are surface modified by polymer coating.

The term "aliphatic group" includes organic compounds characterized by straight or branched chains, typically having between 1 and 22 carbon atoms. Aliphatic groups include alkyl groups, alkenyl

20 groups and alkynyl groups. In complex structures, the chains can be branched or cross-linked. Alkyl groups include saturated hydrocarbons

having one or more carbon atoms, including straight-chain alkyl groups and branched-chain alkyl groups. Such hydrocarbon moieties may be substituted on one or more carbons with, for example, a halogen, a hydroxyl, a thiol, an amino, an alkoxy, an alkylcarboxy, an alkylthio, or a nitro group. Unless the number of carbons is otherwise specified, "lower aliphatic" as used herein means an aliphatic group, as defined above (e.g., lower alkyl, lower alkenyl, lower alkynyl), but having from one to six carbon atoms. Representative of such lower aliphatic groups, e.g., lower alkyl groups, are methyl, ethyl, n-propyl, isopropyl, 2-chloropropyl, n-butyl, sec-butyl, 2-aminobutyl, isobutyl, tert-butyl, 3-thiopentyl, and the like. As used herein, the term "nitro" means -NO<sub>2</sub>; the term "halogen" designates -F, -Cl, -Br or -I; the term "thiol" means SH; and the term "hydroxyl" means -OH. Thus, the term "alkylamino" as used herein means an alkyl group, as defined above, having an amino group attached thereto. Suitable alkylamino groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms. The term "alkylthio" refers to an alkyl group, as defined above, having a sulfhydryl group attached thereto. Suitable alkylthio groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms. The term "alkylcarboxyl" as used herein means an alkyl group, as defined above, having a carboxyl group attached thereto. The term "alkoxy" as used herein means an alkyl group, as defined above, having an oxygen atom attached thereto. Representative alkoxy groups include groups having 1 to about 12 carbon atoms, preferably 1 to about 6 carbon atoms, e.g., methoxy, ethoxy, propoxy, tert-butoxy and the like. The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous to alkyls, but which contain at least one double or triple bond respectively. Suitable alkenyl and alkynyl groups include groups having 2 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms.

The term "alicyclic group" includes closed ring structures of three or more carbon atoms. Alicyclic groups include cycloparaffins or naphthenes

which are saturated cyclic hydrocarbons, cycloolefins which are unsaturated with two or more double bonds, and cycloacetylenes which have a triple bond. They do not include aromatic groups. Examples of cycloparaffins include cyclopropane, cyclohexane, and cyclopentane.

- 5 Examples of cycloolefins include cyclopentadiene and cyclooctatetraene. Alicyclic groups also include fused ring structures and substituted alicyclic groups such as alkyl substituted alicyclic groups. In the instance of the alicyclics such substituents can further comprise a lower alkyl, a lower alkenyl, a lower alkoxy, a lower alkylthio, a lower alkylamino, a
- 10 lower alkylcarboxyl, a nitro, a hydroxyl, -CF<sub>3</sub>, -CN, or the like.

The term "heterocyclic group" includes closed ring structures in which one or more of the atoms in the ring is an element other than carbon, for example, nitrogen, sulfur, or oxygen. Heterocyclic groups can be saturated or unsaturated and heterocyclic groups such as pyrrole and

15 furan can have aromatic character. They include fused ring structures such as quinoline and isoquinoline. Other examples of heterocyclic groups include pyridine and purine. Heterocyclic groups can also be substituted at one or more constituent atoms with, for example, a halogen, a lower alkyl, a lower alkenyl, a lower alkoxy, a lower alkylthio, a lower

20 alkylamino, a lower alkylcarboxyl, a nitro, a hydroxyl, -CF<sub>3</sub>, -CN, or the like. Suitable heteroaromatic and heteroalicyclic groups generally will have 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl,

25 indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl.

The term "aromatic group" includes unsaturated cyclic hydrocarbons containing one or more rings. Aromatic groups include 5- and 6-membered single-ring groups which may include from zero to four

30 heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and

pyrimidine, and the like. The aromatic ring may be substituted at one or more ring positions with, for example, a halogen, a lower alkyl, a lower alkenyl, a lower alkoxy, a lower alkylthio, a lower alkylamino, a lower alkylcarboxyl, a nitro, a hydroxyl,  $-CF_3$ ,  $-CN$ , or the like.

5 The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 20 or fewer carbon atoms in its backbone (e.g.,  
10  $C_1$ - $C_{20}$  for straight chain,  $C_3$ - $C_{20}$  for branched chain), and more preferably 12 or fewer. Likewise, preferred cycloalkyls have from 4-10 carbon atoms in their ring structure, and more preferably have 4-7 carbon atoms in the ring structure. The term "lower alkyl" refers to alkyl groups having from 1 to 6 carbons in the chain, and to cycloalkyls having from 3 to 6 carbons in  
15 the ring structure.

Moreover, the term "alkyl" (including "lower alkyl") as used throughout the specification and claims includes both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the  
20 hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino,  
25 arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by  
30 those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be

further substituted, e.g., with the substituents described above. An "aralkyl" moiety is an alkyl substituted with an aryl, e.g., having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, (e.g., phenylmethyl (benzyl)).

5           The term "aryl" includes 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, unsubstituted or substituted benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl groups also include  
10 polycyclic fused aromatic groups such as naphthyl, quinolyl, indolyl, and the like. The aromatic ring can be substituted at one or more ring positions with such substituents, e.g., as described above for alkyl groups. Suitable aryl groups include unsubstituted and substituted phenyl groups. The term "aryloxy" as used herein means an aryl group, as  
15 defined above, having an oxygen atom attached thereto. The term "aralkoxy" as used herein means an aralkyl group, as defined above, having an oxygen atom attached thereto. Suitable aralkoxy groups have 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, e.g., O-benzyl.

20           The term "amino," as used herein, refers to an unsubstituted or substituted moiety of the formula  $-NR_aR_b$ , in which  $R_a$  and  $R_b$  are each independently hydrogen, alkyl, aryl, or heterocyclyl, or  $R_a$  and  $R_b$ , taken together with the nitrogen atom to which they are attached, form a cyclic moiety having from 3 to 8 atoms in the ring. Thus, the term "amino"  
25 includes cyclic amino moieties such as piperidinyl or pyrrolidinyl groups, unless otherwise stated. An "amino-substituted amino group" refers to an amino group in which at least one of  $R_a$  and  $R_b$ , is further substituted with an amino group.

30           The present porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry generally have a mean particle size of 0.5 to 100 $\mu$ m, preferably about 1 to 50 $\mu$ m, and most

preferably about 1 to 20 $\mu\text{m}$ . The specific surface area, as measured by  $\text{N}_2$  sorption analysis, is generally about 50 to 800 $\text{m}^2/\text{g}$ , preferably about 75 to 600 $\text{m}^2/\text{g}$ , most preferably about 100 to 200 $\text{m}^2/\text{g}$ . The specific pore volume of the particles is generally about 0.25 to 1.5  $\text{cm}^3/\text{g}$ , preferably about 0.4 to 1.2  $\text{cm}^3/\text{g}$ , more preferably about 0.5 to 1.0  $\text{cm}^3/\text{g}$ . The porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry have an average pore diameter of generally about 50 to 500 $\text{\AA}$ , preferably about 60 to 500 $\text{\AA}$ , more preferably about 100 to 300 $\text{\AA}$ .

10 Porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry may be made as described below and in the specific instances illustrated in the Examples. Porous spherical particles of hybrid silica may, in a preferred embodiment, be prepared by a four-step process. In the first step, an organoalkoxysilane  
15 such as methyltriethoxysilane, and a tetraalkoxysilane such as tetraethoxysilane (TEOS) are prepolymerized to form a polyorganoalkoxysiloxane (PAS) by co-hydrolyzing a mixture of the two components in the presence of an acid catalyst. In the second step, the PAS is suspended in an aqueous medium in the presence of a surfactant  
20 and gelled into porous spherical particles of hybrid silica using a base catalyst. In the third step, the pore structure of the hybrid silica particles is modified by hydrothermal treatment, producing an intermediate hybrid silica product which may be used for particular purposes itself, or desirably may be further processed below. The above three steps of the  
25 process allow much better control of the particle morphology, pore volume and pore sizes than those described in the prior art, and thus provide the chromatographically-enhancing pore geometry.

In the fourth step, the remaining surface silanol groups of the hybrid silica are derivatized into organic functional groups, such as by  
30 reacting with a halopolyorganosilane such as octadecyldimethylchlorosilane. The surface of the thus-prepared material



is then covered by the alkyl groups embedded during the gelation and the organic groups added during the derivatization process. The surface coverage by the overall organic groups is higher than in conventional silica-based packing materials, and subsequently the surface concentration of the remaining silanol group in the hybrid silica is smaller. The resulting material, used as a stationary phase for LC, shows excellent peak shape for base analytes, and better hydrolytic stability than other silica-based packing materials.

Where the prepolymerization step involves co-hydrolyzing a mixture of the two components in the presence of an acid catalyst, the content of the organoalkoxysilane can be varied, e.g., from 0.2 to 0.5 mole per mole of the tetraalkoxysilane. The amount of the water used for the hydrolysis can be varied, e.g., from 1.10 to 1.35 mole per mole of the silane. The silane, water and the ethanol mixture, in the form of a homogeneous solution, is stirred and heated to reflux under a flow of argon. After it is refluxed for a time sufficient to prepolymerize to form polyorganoalkoxysiloxane (PAS), the solvent and the side product, mainly ethanol, is distilled off from the reaction mixture. Thereafter, the residue is heated at an elevated temperature, e.g., in the range of 120 to 140°C under an atmosphere of argon for a period of time, e.g., 1.5 to 16 h. The residue is further heated at this temperature, e.g., for 1 to 3 h under reduced pressure, e.g.,  $10^{-2}$ - $10^{-3}$  torr, to remove any volatile species.

In the second step, the PAS is suspended into fine beads in a solution containing water and ethanol at 55°C by agitation. The volume percent of ethanol in the solution is varied from 10 to 20%. A non-ionic surfactant such as TRITON X-100 or TRITON X-45 is added into the suspension as the suspending agent. The surfactant, having a structure of alkylphenoxy polyethoxyethanol, is believed to be able to orient at the hydrophobic/hydrophilic interface between the PAS beads and the aqueous phase to stabilize the PAS beads. The surfactant is also believed to enhance the concentration of water and the base catalyst on the surface

of the PAS beads during the gelation step, through its hydrophilic groups, which induces the gelling of the PAS beads from the surface towards the center. Use of the surfactant to modulate the surface structure of the PAS beads stabilizes the shape of the PAS beads throughout the gelling  
5 process, and minimizes or suppresses formation of particles having "shell-shaped" morphology.

It is also possible to suspend a solution containing PAS and toluene in the aqueous phase, instead of PAS alone. The toluene, which is insoluble in the aqueous phase, remains in the PAS beads during the  
10 gelation step and functions as a porogen. By controlling the relative amount of toluene in the PAS/toluene solution, the pore volume of the final hybrid silica can be more precisely controlled. This allows the preparation of hybrid silica particles having large pore volume, e.g., 0.8-1.2 cc/g.

15 The gelation step is initiated by adding the basic catalyst, e.g., ammonium hydroxide into the PAS suspension agitated at 55°C. Thereafter, the reaction mixture is agitated at the same temperature to drive the reaction to completion. Ammonium hydroxide is preferred because bases such as sodium hydroxide are a source of unwanted  
20 cations, and ammonium hydroxide is easier to remove in the washing step. The thus-prepared hybrid silica is filtered and washed with water and methanol free of ammonium ions, then dried.

In an embodiment, the pore structure of the as-prepared hybrid material is modified by hydrothermal treatment, which enlarges the  
25 openings of the pores as well as the pore diameters, as confirmed by nitrogen (N<sub>2</sub>) sorption analysis. The hydrothermal treatment is performed by preparing a slurry containing the as-prepared hybrid material and a solution of organic base in water, heating the slurry in an autoclave at an elevated temperature, e.g., 143 to 168°C, for a period of 6 to 28 h. The pH  
30 of the slurry is adjusted to be in the range of 8.0 to 9.0 using concentrated acetic acid. The concentration of the slurry is in the range of 1g hybrid

material per 4 to 10 ml of the base solution. The thus-treated hybrid material is filtered, and washed with water and acetone until the pH of the filtrate reaches 7, then dried at 100°C under reduced pressure for 16 h. The resultant hybrid materials show average pore diameters in the range  
5 of 100-300Å.

The surface of hybrid silica prepared so far still contains silanol groups, which can be derivatized by reacting with a reactive organosilane. The surface derivatization of the hybrid silica is conducted according to standard methods, for example by reaction with  
10 octadecyldimethylchlorosilane in an organic solvent under reflux conditions. An organic solvent such as toluene is typically used for this reaction. An organic base such as pyridine or imidazole is added to the reaction mixture to catalyze the reaction. The thus-obtained product is then washed with water, toluene and acetone and dried at 100°C under  
15 reduced pressure for 16 h. The resultant hybrid silica can be further reacted with a short-chain silane such as trimethylchlorosilane to endcap the remaining silanol groups, by using a similar procedure described above.

The surface of the hybrid silica particles may also be surface  
20 modified with a surface modifier, e.g.,  $Z_a(R')_b\text{Si-R}$ , where  $Z = \text{Cl, Br, I, C}_1 - \text{C}_5$  alkoxy, dialkylamino, e.g., dimethylamino or trifluoromethanesulfonate;  $a$  and  $b$  are each an integer from 0 to 3 provided that  $a + b = 3$ ;  $R'$  is a  $\text{C}_1 - \text{C}_6$  straight, cyclic or branched alkyl group, and  $R$  is a functionalizing group, and by polymer coating.  $R'$  may be, e.g., methyl, ethyl, propyl,  
25 isopropyl, butyl, t-butyl, sec-butyl, pentyl, isopentyl, hexyl or cyclohexyl; preferably,  $R'$  is methyl.

The functionalizing group  $R$  may include alkyl, aryl, cyano, amino, diol, nitro, cation or anion exchange groups, or embedded polar functionalities. Examples of suitable  $R$  functionalizing groups include  $\text{C}_1 - \text{C}_{20}$  alkyl such as octyl ( $\text{C}_8$ ) and octadecyl ( $\text{C}_{18}$ ); alkaryl, e.g.,  $\text{C}_1 - \text{C}_4$ -phenyl;  
30 cyanoalkyl groups, e.g., cyanopropyl; diol groups, e.g., propyldiol; amino

groups, e.g., aminopropyl; and embedded polar functionalities, e.g., carbamate functionalities such as disclosed in U. S. Patent No. 5,374,755, the text of which is incorporated herein by reference and as detailed hereinabove. In a preferred embodiment, the surface modifier may be a  
5 halopolyorganosilane, such as octyldimethylchlorosilane or octadecyldimethylchlorosilane. Advantageously, R is octyl or octadecyl.

Polymer coatings are known in the literature and may be provided generally by polymerization or polycondensation of physisorbed monomers onto the surface without chemical bonding of the polymer layer to the  
10 support (type I), polymerization or polycondensation of physisorbed monomers onto the surface with chemical bonding of the polymer layer to the support (type II), immobilization of physisorbed prepolymers to the support (type III), and chemisorption of presynthesized polymers onto the surface of the support (type IV). *see, e.g., Hanson et al., J. Chromat. A656*  
15 *(1993) 369-380*, the text of which is incorporated herein by reference.

The porous inorganic/organic hybrid particles has a wide variety of end uses in the separation sciences, such as packing materials for chromatographic columns (wherein such columns will have extended lives), thin layer chromatographic (TLC) plates, filtration membranes,  
20 microtiter plates, and the like having a stationary phase which includes porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry. The stationary phase may be introduced by packing, coating, impregnation, etc., depending on the requirements of the particular device. In a particularly advantageous embodiment, the  
25 chromatographic device is a packed chromatographic column, e.g., HPLC.

The present invention may be further illustrated by the following non-limiting examples describing the preparation of porous inorganic/organic hybrid particles, and their use.

## EXAMPLE 1

802g of tetraethoxysilane (3.87 mol) is mixed with 137.2g of methyltriethoxysilane (0.774 mol), 400 mol of ethanol and 108.6 of 0.1 N hydrochloric acid (~6.03 mol of water) in a flask. The resulting solution is agitated and refluxed for 16 h in an atmosphere of argon. After the ethanol in the solution is distilled off the distillation residue is heated at 140° C for 1.5 h in the atmosphere of argon and further heated at the same temperature under reduced pressure for another 1.5 h to remove any volatile species. The thus-prepared polymethylethoxysiloxane is a colorless viscous liquid. By using a similar procedure, other polyorganoalkoxy-siloxanes are prepared. Product g was prepared from 1000 g of tetraethoxysilane (4.80 mol) and 851 g of 1,2-bis(triethoxysilyl)ethane (2.40 mol). The contents of the starting materials used to prepare these products are summarized in Table 1.

15

TABLE 1

Product	R <sup>2</sup>	Molar ratio of organoalkoxysilane to tetraalkoxysilane in starting mixture	Molar ratio of H <sub>2</sub> O to the sum of organoalkoxysilane and tetraalkoxysilane in starting mixture
a	methyl	0.20	1.30
b	methyl	0.20	1.25
c	methyl	0.35	1.25
d	methyl	0.50	1.25
e	ethyl	0.25	1.20
f	phenyl	0.25	1.25
g	ethylene bridged	0.50	1.25

A mixture of 20g of TRITON X-100 surfactant, 240 ml of ethanol and 960 mL of deionized water is heated at 55°C for 0.5h, leading to a solution. Under rapid agitation, 240g of polymethylethoxysiloxane (product a in Table 1) is added into the above solution and emulsified in it. Thereafter, 150 ml of 30% NH<sub>4</sub>OH is added into the emulsion to gel the emulsion beads. Suspended in the solution, the gelled product is stirred at 55°C for

20

16 h, then filtered and washed with water and methanol repeatedly, and finally dried at 100°C under reduced pressure for 16 h.  $\text{SiO}_2/[\text{R}^2\text{SiO}_{1.5}]_n$  materials derived from other polyorganoalkoxysiloxanes are prepared using a similar procedure described above. The specific surface areas, specific pore volumes and the average pore diameters of these materials are measured using the multi-point  $\text{N}_2$  sorption method and the data are listed in Table 2.

TABLE 2

Product	$\text{R}^2$	Molar ratio of organosiloxane to $\text{SiO}_2$ in products	Specific surface area ( $\text{m}^2/\text{g}$ )	Pore Volume (cc/g)	Avg Pore Diameter ("APD") (Å)
a	methyl	0.2	325	0.45	49
b	methyl	0.5	502	0.43	36
c	ethyl	0.25	743	0.98	56
d	methyl	0.25	616	0.52	43

10

## EXAMPLE 2

A mixture of 24g of TRITON X-45 surfactant, 285ml of ethanol and 1200ml of deionized water is heated at 55°C for 0.5h, leading to a white liquid. Under rapid agitation, a solution containing 60ml of toluene in 249g of polymethylethoxysiloxane (product d in Table 1) is added into the ethanol/water/TRITON X-45 mixture, and emulsified in the aqueous phase. Thereafter, 190ml of 30%  $\text{NH}_4\text{OH}$  is added into the emulsion to gel the emulsion beads. Suspended in the solution, the gelled product is stirred at 55°C for 16h.  $\text{SiO}_2/[\text{R}^2\text{SiO}_{1.5}]_n$  materials derived from other polyorganoalkoxysiloxanes are also prepared using a similar procedure described above. The specific surface areas, specific pore volumes and the average pore diameters of these materials are measured using the multi-point  $\text{N}_2$  sorption method and the data are presented in Table 3.

20

TABLE 3

Product	R <sup>2</sup>	Molar ratio of methylsiloxane to SiO <sub>2</sub> in products	Ratio of toluene to Polymethylethoxy-siloxane (ml/g)	Specific surface area (m <sup>2</sup> /g)	Pore Volume (cc/g)	Avg. Pore Diameter (Å)
a	methyl	0.5	0.24	689	0.93	43
b	methyl	0.5	0.12	644	0.73	39
c	methyl	0.35	0.12	466	0.81	60
d	methyl	0.2	0.12	358	0.72	72

5

## EXAMPLE 3

A mixture of 11.8g of Triton X-45 surfactant, 7.8g of Triton X-100  
 10 surfactant, 232 mL ethanol and 980 mL deionized water is heated at 50C,  
 leading to a white liquid. Under rapid agitation, a solution containing 24  
 mL toluene in 203g poly(ethylene-bridged)ethoxysiloxane (product g in  
 Table 1) is added to the ethanol/water/triton mixture and emulsified in  
 the aqueous phase. Thereafter, 154 mL of 30% NH<sub>4</sub>OH is added into the  
 15 emulsion to gel to gel the beads. Suspended in the solution, the gelled  
 product is stirred at 55C for 16 h, then filtered and washed with water and  
 methanol repeatedly, and finally dried at 100C under reduced pressure for  
 16 h. The resulting product had a specific surface area of 869 m<sup>2</sup>/g, pore  
 volume of 0.80 cc/g, and average pore diameter of 34Å.

20

## EXAMPLE 4

13 g of product a from Table 2 is mixed with 130mL of 0.1M  
 tris(hydroxymethyl)aminomethane in water, yielding a slurry. The pH of  
 the slurry is adjusted to 8 by adding concentrated acetic acid. The  
 25 resultant slurry is then enclosed in a stainless autoclave and heated at  
 143°C for 20 h. After the autoclave cools down to room temperature the  
 product is filtered and washed repeatedly using water and acetone, and  
 then dried at 100°C under reduced pressure for 16 h. Hydrothermal

treatment of other hybrid silica materials is also carried out using a similar procedure described above. The specific surface areas, specific pore volumes and the average pore diameters of these materials are measured using the multi-point N<sub>2</sub> sorption method and the data are listed in Table 4.

TABLE 4

Product	Composition of the Hybrid Materials	N <sub>2</sub> sorption Data (as-prepared)			N <sub>2</sub> sorption Data (after hydrothermal treatment)			Conditions of Hydrothermal Treatment		
		SSA (m <sup>2</sup> /g)	SPV (cc/g)	APD (Å)	SSA (m <sup>2</sup> /g)	SPV (cc/g)	APD (Å)	pH	T (°C)	t (h)
a	SiO <sub>2</sub> /(CH <sub>3</sub> SiO <sub>1.5</sub> ) <sub>0.2</sub>	325	0.45	49						
a1		130	0.41	103	8.0	143	20			
b	SiO <sub>2</sub> /(CH <sub>3</sub> SiO <sub>1.5</sub> ) <sub>0.2</sub>	358	0.72	72						
b1		151	0.71	159	8.1	143	20			
b2		135	0.67	173	8.4	155	20			
c	SiO <sub>2</sub> /(CH <sub>3</sub> SiO <sub>1.5</sub> ) <sub>0.35</sub>	466	0.81	60						
c1		160	0.72	139	8.0	143	20			
d	SiO <sub>2</sub> /(CH <sub>3</sub> SiO <sub>1.5</sub> ) <sub>0.5</sub>	689	0.93	43						
d1		225	0.90	123	8.30	143	20			
d	SiO <sub>2</sub> /(CH <sub>3</sub> SiO <sub>1.5</sub> ) <sub>0.5</sub>	729	0.76	38						
d1		188	0.70	125	8.30	143	20			
d2		155	0.69	148	8.75	148	20			
d3		125	0.62	168	9.0	163	20			
e	SiO <sub>2</sub> /(C <sub>2</sub> H <sub>5</sub> SiO <sub>1.5</sub> ) <sub>0.25</sub>	743	0.98	56						
e1		267	0.94	139	8.28	143	20			
f	SiO <sub>2</sub> /(C <sub>6</sub> H <sub>5</sub> SiO <sub>1.5</sub> ) <sub>0.25</sub>	616	0.52	43						
f1		327	0.52	80	8.43	143	20			
g	SiO <sub>2</sub> /[C <sub>2</sub> H <sub>4</sub> (SiO <sub>1.5</sub> ) <sub>2</sub> ] <sub>0.5</sub>	869	0.80	34	287	0.79	111	9.0	165	20

## EXAMPLE 5

The particles of hybrid silica prepared according to Example 3 are sized to ~5 μm. The surfaces of the particles are modified with octadecyldimethylchlorosilane (ODS) and trimethylchlorosilane as follows, 4.5g ODS and 1.32g imidazole are added to a mixture of 8g of hybrid silica (product a1 in Table 4) in 90 ml of toluene and the resultant mixture is refluxed for 2h. The modified hybrid silica particles are filtered and washed successively with water, toluene, 1:1 acetone/water and acetone,



and then dried at 100°C under reduced pressure for 16 h. The surface coverage of octadecyl groups is determined to be 2.74  $\mu\text{mol}/\text{m}^2$  based on elemental analyses.

Trimethylchlorosilane (1.65g) and imidazole (1.32g) are added to a mixture of the above ODS-modified hybrid silica in 65 ml of toluene and the resultant mixture is refluxed for 4h. The thus-modified hybrid silica particles are filtered and washed successively with water, toluene, 1:1 acetone/water and acetone, and then dried at 100°C under pressure for 16 h. Surface modification of other hybrid silica is also carried out using a similar procedure described above. The specific surface area, specific pore volume, ODS surface coverage and average pore diameter data for these materials are listed in Table 5.

TABLE 5

Product	Composition of the base hybrid silica	Specific surface area ( $\text{m}^2/\text{g}$ )	Pore Volume (cc/g)	Avg. Pore Diameter (Å)	Surface coverage of ODS ( $\mu\text{mol}/\text{m}^2$ )
a	$\text{SiO}_2/(\text{CH}_3\text{SiO}_{1.5})_{0.2}$	130	0.41	103	2.73
b	$\text{SiO}_2/(\text{CH}_3\text{SiO}_{1.5})_{0.35}$	173	0.73	140	2.50
c	$\text{SiO}_2/(\text{CH}_3\text{SiO}_{1.5})_{0.5}$	177	0.61	113	2.18
d	$\text{SiO}_2/(\text{CH}_3\text{SiO}_{1.5})_{0.5}$	225	0.90	123	2.15

15

The above derivatized hybrid silica is used for separation of a mixture of neutral, polar and basic compounds listed in Table 6. The chromatographic columns are packed using a slurry packing technique, and the analysis conditions are shown in Table 7.

20

TABLE 6

	Product b in Table 5	Product c in Table 5	Product d in Table 5
k' of Acenaphthene	10.02	11.35	13.40
Relative Retention (r)			
Propranolol/Acenaphthene	0.157	0.149	0.139
Butyl paraben/Acenaphthene	0.226	0.216	0.223
Dipropyl Phthalate/Acenaphthene	0.411	0.405	0.403
Naphthalene/Acenaphthene	0.437	0.436	0.437
Amitriptyline /Acenaphthene	1.483	1.525	1.395
USP Tailing Factor			
Amitriptyline	1.06	1.41	1.41
Propranolol	0.98	0.98	0.98

5

TABLE 7

Temperature	23 °C
Mobile phase	35% v/v 20.0 mM K <sub>2</sub> HPO <sub>4</sub> pH 7.00/65% methanol
Flow rate	1.4 ml/min

The hydrolytic stability of the columns packed by the hybrid silica shown in Table 5, as well as some commercial columns based on silica gel bonded with octadecyl groups are evaluated using the following procedure. The columns are placed in a 50°C water bath and flushed with a solution of 50 mM triethylamine buffer (pH 10) in water. Acenaphthene is injected at a flow rate of 1 ml/min at predetermined intervals and the theoretical plate numbers are recorded.

The lifetime of the column is defined as the time when the plate number drops to 50% of the initial value. The results are shown in Table 8.

TABLE 8

Column	Lifetime (h)
Commercial Column A (C18 type)	8
Commercial Column B (C18 type)	11
Commercial Column C (C18 type)	16
Commercial Column D (C18 type)	19
Commercial Column E (C18 type)	30
Commercial Column F (C18 type)	34
Packing Material of Product c in Table 5	48
Packing Material of Product d in Table 5	50
Packing Material of Product a in Table 5	51

5

It can be seen that the durability of the packing materials based on the hybrid silica is greatly improved over the commercial silica gels.

#### EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using  
10 no more than routine experimentation, numerous equivalents to the  
specific procedures described herein. Such equivalents are considered to  
be within the scope of this invention and are covered by the following  
claims. The contents of all references, issued patents, and published  
patent applications cited throughout this application are hereby  
15 incorporated by reference.

*What is claimed is:*

1. A porous inorganic/organic hybrid material, comprising porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry.
- 5 2. The hybrid material of claim 1 wherein said inorganic portion of said hybrid material is selected from the group consisting of alumina, silica, titanium or zirconium oxides, and ceramic materials.
3. The hybrid material of claim 1 wherein said inorganic portion of said hybrid material is silica.
- 10 4. The hybrid material of claim 1 having the formula  $\text{SiO}_2/(\text{R}^2_p\text{R}^4_q\text{SiO}_t)_n$  or  $\text{SiO}_2/[\text{R}^6(\text{R}^2_r\text{SiO}_t)_m]_n$  wherein  $\text{R}^2$  and  $\text{R}^4$  are independently  $\text{C}_1 - \text{C}_{18}$  alkyl or aryl moiety (which may additionally be substituted with alkyl, aryl, cyano, amino, diol, nitro, and ion exchange or embedded polar functionalities),  $\text{R}^6$  is a substituted or unsubstituted  $\text{C}_1 - \text{C}_{18}$  alkylene, alkenylene, alkynylene or arylene moiety bridging two or more silicon  
15 atoms,  $p$  and  $q$  are 0, 1 or 2, provided that  $p+q = 1$  or 2, and that when  $p+q=1$ ,  $t=1.5$ , and when  $p+q=2$ ,  $t=1$ ;  $r$  is 0 or 1, provided that when  $r = 0$ ,  $t = 1.5$ , and when  $r = 1$ ,  $t = 1$ ;  $m$  is an integer greater than or equal to 2, and  $n$  is a number from 0.1 to 1.
- 20 5. The hybrid material of claim 4 wherein  $n$  is a number from 0.20 to 0.50.
6. The hybrid material of claim 1, wherein said particles have been surface modified by polymer coating.
7. The hybrid material of claim 1 wherein said particles have a mean  
25 particle size of about 0.5 to  $100\mu\text{m}$ , said particles have a specific surface area of about 50 to  $800\text{m}^2/\text{g}$ , said particles have specific pore volumes of about 0.25 to  $1.5\text{cm}^3/\text{g}$ , and said particles have an average pore diameter of about 50 to  $500\text{\AA}$ .

8. The hybrid material of claim 1, wherein said particles have been surface modified with a surface modifier having the formula  $Z_a(R')_bSi-R$ , where  $Z = Cl, Br, I, C_1 - C_5$  alkoxy, dialkylamino or trifluoromethanesulfonate; a and b are each an integer from 0 to 3 provided that  $a + b = 3$ ;  $R'$  is a  $C_1 - C_6$  straight, cyclic or branched alkyl group, and R is a functionalizing group.
9. The hybrid material of claim 8 wherein  $R'$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, t-butyl, sec-butyl, pentyl, isopentyl, hexyl and cyclohexyl.
10. The hybrid material of claim 8, wherein the functionalizing group R is selected from the group consisting of alkyl; aryl; cyano, amino, diol, nitro, a cation or anion exchange group, or an embedded polar functionality.
11. The hybrid material of claim 8, wherein said functionalizing group R is a  $C_1 - C_{20}$  alkyl group.
12. The hybrid material of claim 8, wherein said surface modifier is selected from the group consisting of octyldimethylchlorosilane and octadecyldimethylchlorosilane.
13. A method of preparation of porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry, comprising the steps of
- a) forming porous inorganic/organic hybrid particles; and
  - b) modifying the pore structure of said porous particles, forming inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry
14. The method of claim 13 wherein said method further comprises surface modifying said porous particles.
15. The method of claim 14 wherein said surface modification step includes surface modifying said porous particles with a surface modifier having the formula  $Z_a(R')_bSi-R$ , where  $Z = Cl, Br, I, C_1 - C_5$  alkoxy,

dialkylamino or trifluoromethanesulfonate; a and b are each an integer from 0 to 3 provided that  $a + b = 3$ ; R' is a C<sub>1</sub> - C<sub>6</sub> straight, cyclic or branched alkyl group, and R is a functionalizing group.

16. The method of claim 15 wherein R' is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, t-butyl, sec-butyl, pentyl, isopentyl, hexyl and cyclohexyl.
17. The method of claim 15, wherein said functionalizing group R is selected from the group consisting of alkyl; aryl; cyano, amino, diol, nitro, a cation or anion exchange group, or an embedded polar functionality.
18. The method of claim 15 wherein said functionalizing group R is a C<sub>1</sub> - C<sub>20</sub> alkyl group.
19. The method of claim 15 wherein said surface modifier is selected from the group consisting of octyldimethylchlorosilane and octadecyldimethylchlorosilane.
20. The method of claim 15 wherein any free silanol groups remaining from said surface modification procedure are endcapped.
21. The method of claim 14 wherein said particles have been surface modified by polymer coating.
22. The method of claim 13 wherein said porous particles are prepared by prepolymerizing an organoalkoxysilane and a tetraalkoxysilane to produce a polyorganoalkoxysiloxane, and preparing an aqueous suspension of said polyorganoalkoxysiloxane, and gelling in the presence of a base catalyst so as to produce said porous particles.
23. The method of claim 22 wherein said pore structure of said porous particles is modified by further including a surfactant in said suspension, and by subjecting said porous particles to hydrothermal treatment.

24. The method of claim 22 wherein said prepolymerization step comprises hydrolyzing and condensing a mixture of an organotrialkoxysilane and a tetraalkoxysilane in the presence of an acid catalyst to produce said polyorganoalkoxysiloxane.
- 5 25. The method of claim 22 wherein the molar ratio of said organoalkoxysilane and tetraalkoxysilane is from about 0.5:1 to 0.2:1.
26. The method of claim 22 wherein said suspension further comprises a porogen.
27. The method of claim 26 wherein said porogen is toluene.
- 10 28. The method of claim 22 wherein said base catalyst is free of alkali or alkaline earth metal cations.
29. The method of claim 22 wherein said base catalyst is ammonium hydroxide.
30. The method of claim 22 wherein said tetraalkoxysilane has the  
15 formula  $\text{Si}(\text{OR}^1)_4$ , where  $\text{R}^1$  is a  $\text{C}_1 - \text{C}_3$  alkyl moiety.
31. The method of claim 22 wherein said tetraalkoxysilane is selected from the group consisting of tetramethoxysilane and tetraethoxysilane.
32. The method of claim 22 wherein said organoalkoxysilane has the  
20 formula  $\text{R}^2\text{Si}(\text{OR}^1)_3$  or  $\text{R}^6[\text{Si}(\text{OR}^1)_3]_m$  where  $\text{R}^2$  is a  $\text{C}_1 - \text{C}_{18}$  aliphatic or aromatic moiety,  $\text{R}^1$  is a  $\text{C}_1 - \text{C}_4$  alkyl moiety,  $\text{R}^6$  is a  $\text{C}_1 - \text{C}_{18}$  alkylene, alkenylene, alkynylene or arylene moiety bridging two or more silicon atoms, and  $m$  is an integer greater than or equal to two.
33. The method of claim 32 wherein  $\text{R}^2$  is methyl, ethyl or phenyl, and  $\text{R}^1$  is ethyl; or  $\text{R}^6$  is a bridging ethylene group,  $m = 2$ , and  $\text{R}^1$  is ethyl.
- 25 34. The method of claim 13 wherein said porous inorganic/organic hybrid particles have the formula  $\text{SiO}_2/(\text{R}^2_p\text{R}^4_q\text{SiO}_t)_n$  or  $\text{SiO}_2/[\text{R}^6(\text{R}^2_r\text{SiO}_t)_m]_n$  wherein  $\text{R}^2$  and  $\text{R}^4$  are independently  $\text{C}_1 - \text{C}_{18}$  alkyl or aryl moiety (which may additionally be substituted with alkyl, aryl, cyano, amino, diol, nitro, and ion exchange or embedded polar

functionalities),  $R^6$  is a substituted or unsubstituted  $C_1 - C_{18}$  alkylene, alkenylene, alkynylene or arylene moiety bridging two or more silicon atoms, p and q are 0, 1 or 2, provided that  $p+q = 1$  or 2, and that when  $p+q=1$ ,  $t=1.5$ , and when  $p+q=2$ ,  $t=1$ ; r is 0 or 1, provided that when  $r = 0$ ,  $t = 1.5$ , and when  $r = 1$ ,  $t = 1$ ; m is an integer greater than or equal to 2, and n is a number from 0.1 to 1.

35. The method of claim 13, wherein said particles have a mean particle size of about 0.5 to 100 $\mu$ m, said particles have a specific surface area of about 50 to 800 $m^2/g$ , said particles have specific pore volumes of about 0.25 to 1.5  $cm^3/g$ , and said particles have an average pore diameter of about 50 to 500 $\text{\AA}$ .

36. A separations device having a stationary phase comprising porous inorganic/organic hybrid particles having a chromatographically-enhancing pore geometry of claims 1-12.

37. The separations device of claim 36, wherein said device is selected from the group consisting of chromatographic columns, cartridges, filtration membranes, sample cleanup devices, and microtiter plates.

38. A chromatographic column having improved lifetime, comprising

a) a column having a cylindrical interior for accepting a packing material, and

b) a packed chromatographic bed comprising porous particles of hybrid silica of the formula  $SiO_2/(R^2_p R^4_q SiO_t)_n$  or  $SiO_2/[R^6(R^2_r SiO_t)_m]_n$  wherein  $R^2$  and  $R^4$  are independently  $C_1 - C_{18}$  alkyl or aryl moiety (which may additionally be substituted with alkyl, aryl, cyano, amino, diol, nitro, and ion exchange or embedded polar functionalities),  $R^6$  is a substituted or unsubstituted  $C_1 - C_{18}$  alkylene, alkenylene, alkynylene or arylene moiety bridging two or more silicon atoms, p and q are 0, 1 or 2, provided that  $p+q = 1$  or 2, and that when  $p+q=1$ ,  $t=1.5$ , and when  $p+q=2$ ,  $t=1$ ; r is 0 or 1, provided that when  $r = 0$ ,  $t =$



1.5, and when  $r = 1$ ,  $t = 1$ ;  $m$  is an integer greater than or equal to 2, and  $n$  is a number from 0.1 to 1, said porous hybrid silica chromatographic matrix having a chromatographically-enhancing pore geometry and average pore diameters of from about 100 to 300Å, and said porous particles of hybrid silica have been surface modified.

39. A method of preparation of porous particles of hybrid silica having a chromatographically-enhancing pore geometry, comprising the steps of
- prepolymerizing a mixture of an organoalkoxysilane and a tetraalkoxysilane in the presence of an acid catalyst to produce a polyorganoalkoxysiloxane;
  - preparing an aqueous suspension of said polyorganoalkoxysiloxane, said suspension further comprising a surfactant, and gelling in the presence of a base catalyst so as to produce porous particles; and
  - modifying the pore structure of said porous particles by hydrothermal treatment.
40. The method of claim 39 wherein said surfactant is an alkylphenoxy polyethoxyethanol.
41. The method of claim 39 wherein said suspension further comprises a porogen.
42. The method of claim 39 wherein said tetraalkoxysilane is selected from the group consisting of tetramethoxysilane and tetraethoxysilane.
43. The method of claim 39, wherein said hybrid silica particles have the formula  $\text{SiO}_2/(\text{R}^2_p\text{R}^4_q\text{SiO}_t)_n$  or  $\text{SiO}_2/[\text{R}^6(\text{R}^2_r\text{SiO}_t)_m]_n$  wherein  $\text{R}^2$  and  $\text{R}^4$  are independently  $\text{C}_1 - \text{C}_{18}$  alkyl or aryl moiety (which may additionally be substituted with alkyl, aryl, cyano, amino, diol, nitro, and ion exchange or embedded polar functionalities),  $\text{R}^6$  is a substituted or unsubstituted  $\text{C}_1 - \text{C}_{18}$  alkylene, alkenylene, alkynylene or arylene moiety bridging two or more silicon atoms,  $p$  and  $q$  are 0, 1 or 2,

provided that  $p+q = 1$  or  $2$ , and that when  $p+q=1$ ,  $t=1.5$ , and when  $p+q=2$ ,  $t=1$ ;  $r$  is  $0$  or  $1$ , provided that when  $r = 0$ ,  $t = 1.5$ , and when  $r = 1$ ,  $t = 1$ ;  $m$  is an integer greater than or equal to  $2$ , and  $n$  is a number from  $0.1$  to  $1$ .

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/03052

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC(7) : Please See Extra Sheet.  
 US CL : Please See Extra Sheet.  
 According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 U.S. : 427/212, 215, 220, 221, 487, 489, 495; 428/403, 404, 407; 502/150, 158, 240; 556/170, 173, 400, 450, 451, 457, 465, 466.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 WEST 1.2, STN


**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 4,017,528 A (UNGER et al) 12 April 1977, entire document.	1-43
X	US 5,565,142 A (DESHPANDE et al) 15 October 1996, col. 2, line 60 to col. 3, line 30; col. 4, lines 35-44; col. 6, Example 1 (average pore radius and surface area pore volume).	1-43
A	US 4,724,207 A (HOU et al) 09 February 1988, entire document.	1-43
A	US 5,378,790 A (MICHALCZYK et al) 03 January 1995, entire document.	1-43
A	US 5,637,135 A (OTTENSTEIN et al) 10 June 1997, entire document.	1-43

Further documents are listed in the continuation of Box C.  See patent family annex.

<p>* Special categories of cited documents:</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>*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</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*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</p> <p>*G* document member of the same patent family</p>
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Date of the actual completion of the international search 18 MAY 2000	Date of mailing of the international search report <b>13 JUN 2000</b>
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer H. THI LE Telephone No. (703) 308-0661 <div style="text-align: right; margin-top: 10px;">                       DEBORAH THOMAS                      PARALEGAL SPECIALIST                 </div>
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/03052

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,856,379 A (SHIRATSUCHI et al) 05 January 1999, entire document.	1-43
A,P	US 5,965,202 A (TAYLOR-SMITH et al) 12 October 1999, entire document.	1-43

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/03052

**A. CLASSIFICATION OF SUBJECT MATTER:**

IPC (7):

B01J 21/06, 21/08, 21/12, 31/02, 31/06; B05D 7/00; B32B 5/16; C07F 5/06, 7/02; C08F 4/00

**A. CLASSIFICATION OF SUBJECT MATTER:**

US CL :

427/212, 215, 220, 221, 487, 489, 495; 428/403, 404, 407; 502/150, 158, 240; 556/170, 173, 400, 450, 451, 457, 465, 466.