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(54) Title: NEW CALIX ARENE COMPOUNDS, THEIR PROCESS OF PREPARATION AND THEIR USE, PARTICULARLY AS ENZYMATIC MIMES

(57) Abstract: The present invention relates to new calix arene compounds of formula (I). It also relates to their process of prepa-
ration. The present invention also relates to complexes between a compound of formula (I) and an element chosen among a metal,
an actinide, a radioelement, a cationic guest or an anionic guest. The present invention also relates to a pharmaceutical composition
comprising a compound of formula (I) in association with a pharmaceutically acceptable carrier. The present invention also relates
to a process of preparation of water-soluble compounds, comprising a reaction of nitration or sulfonation or nitration, particularly of
compounds of formula (I), and also to the compounds such as obtained.



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NEW CALIX ARENE COMPOUNDS, THEIR PROCESS OF
PREPARATION AND THEIR USE, PARTICULARLY AS ENZYMATIC
MIMES

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The present invention relates to new calix arene compounds, their process of preparation and their use, particularly as enzymatic mimes.

Calix[4]arenes have been extensively studied for host-guest chemistry. However, because of their small size, they have mostly been used as a platform for the preorganization of a binding site. The larger calix[6]arenes appear more suitable to play the role of a molecular receptor, yet their higher conformational flexibility, due to facile ring inversion, represents an obstacle (C. D. Gutsche, *Calixarenes Revisited, Monographs in Supramolecular Chemistry*, 1998, J. F. Stoddart, Ed. The Royal Society of Chemistry, Cambridge, U.K.). It has been recently shown that rigidification of the calix[6]arene core could be achieved through the use of coordination chemistry (Blanchard, S. et al. *Angew. Chem. Int. Ed. Engl.* (1998) **37**, 2732-2735; S  n  que, O. et al. *J. Am. Chem. Soc.* (2000) **122**, 6183-6189; Le Clainche, L. et al. *C. R. Acad. Sci. Paris, S  rie IIc: Chem.* (2000) **3**, 811-819; Rondelez, Y. et al. *Chem. Eur. J.* (2000) **6**, 4218-4226; Le Clainche, L. et al. *Inorg. Chem.* (2000) **39**, 3436-3437; Rondelez, Y. et al. *J. Am. Chem. Soc.* (2002) **124**, 1334-1340).

Indeed, the binding of a metal ion to three amino groups that are covalently linked to the calix[6]arene small rim, can constrain the macrocycle into a cone conformation. The so-called *funnel complexes* present a biomimetic environment for Cu or Zn, which can coordinate a neutral guest inside the hydrophobic cavity (S  n  que, O. et al. *Chem. Commun.* (2001) 984-985; S  n  que, O. et al. *J. Am. Chem. Soc.* (2001) **123**, 8442-8443; Rondelez, Y. et al. *Angew. Chem. Int. Ed. Engl.* (2002), **41**, 1044-1046).

If the synthesis of calix[4](aza)crowns has already been explored (Bitter, I. et al. *Tetrahedron* (1997) **53**, 9799-9812; Tuntulani, T. et al. *Tetrahedron Lett.* (1997) **38**, 3985-3988; Oueslati, I. et al. *Tetrahedron Lett.* (2000) **41**, 8263-8267; Balazs, B. et al. *Eur. J. Org. Chem.* (2001) 61-71; Abidi, R. et al. *Tetrahedron Lett.* (2001) **42**, 1685-1689; Tuntulani, T. et al. *Tetrahedron Lett.* (2001) **42**, 5541-5544; He, Y. et al. *Tetrahedron Lett.* (2002) **43**, 6249-6253), only two recent examples of calix[6]arenes including diamide bridges have been reported (Chen, Y. et al. *Tetrahedron Lett.* (2000) **41**, 9079-9082; Chen, Y.-K. et al. *Org. Lett.* (2000) **2**, 743-745).

Furthermore, calix[6]arenes capped with a tripodal bridge are still rare (Grynszpan, F. et al. *J. Chem. Soc., Chem. Commun.* (1993) 13-16; Takeshita, M. et al. *J. Org. Chem.* (1994) **59**, 4032-4034; Araki, K. et al. *Chem. Lett.* (1994) 1251-1254; Janssen, R. G. et al., *Tetrahedron Lett.* (1994) **35**, 6555-6558; Otsuka, H. *J. Org. Chem.* (1995) **60**, 4862-4867; Nam, K. C. et al. *J. Org. Chem.* (1997) **62**, 6441-6443; Chen, Y.-Y. et al. *Tetrahedron* (1998) **54**, 15183-15188; Li, J.-S. et al. *Eur. J. Org. Chem.* (2000) 485-490; Zhang, Y. et al. *Tetrahedron* (2001) **57**, 4161-4165).

The aim of the present invention is to provide new compounds calix[6](aza)crown, and their process of preparation.

The aim of the present invention is to describe the synthesis of the first C_{3v} -symmetrical calix[6](aza)crown, where the small rim is capped with the tris(2-aminoethyl)amine tripodal unit.

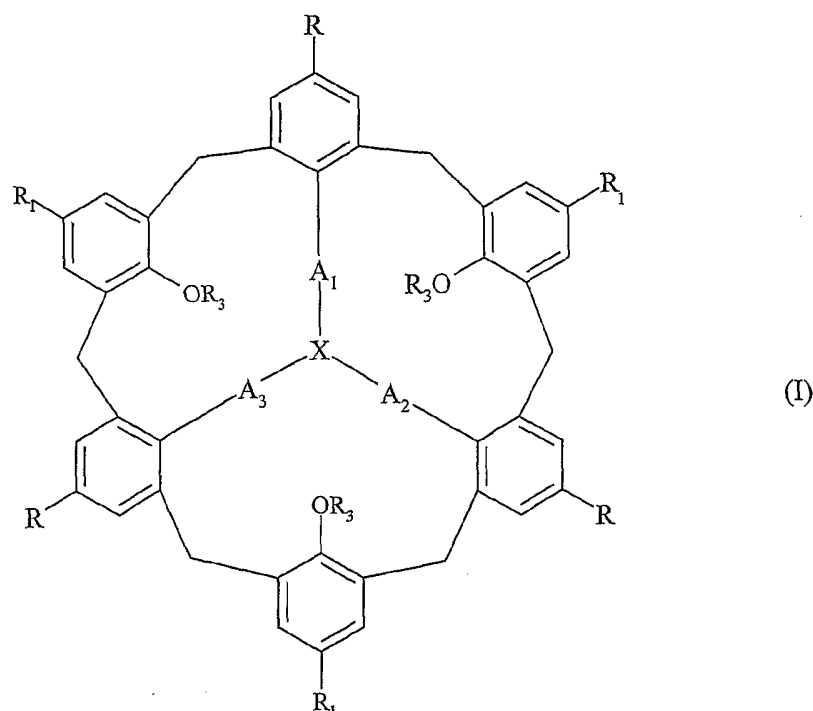
Such capped calix[6](aza)crown compounds present the following advantages:

A metal ion is not required anymore to constrain the calixarene in a cone conformation. The covalent aza-links at the small rim prevent the cone-cone inversion of the calixarene structure and maintain it in a conformation suitable for playing the role of a good and selective host for organic guests. The aza crown can bind a protic guest through hydrogen bonding for example but also a cationic species such as a metal ion. The coordinated metal is then strongly complexed by the aza crown and is highly resistant to decoordinating processes. Coordination of an organic molecule or inorganic ligand such as an anion will be highly controlled by the design of the calixarene host, thanks to its capping at the small rim. Finally, these compounds can be transformed into water-soluble hosts that will display selective coordinating abilities of small molecules or ions in biological media.

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The present invention relates to compounds of the following formula (I):



in which:

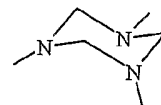
— R and R_1 , identical or different, represent: H , a halogen atom such as F , Cl , Br , I , an ester or a thioester group of 2 to 20 carbon atoms, a carboxylic group, an amide or a thioamide group, a sulfonamide group, SO_3^- , a phosphate, a carboxylate, NO_2 , or a primary, secondary or tertiary amine group and its derivatives such as a ketimine, an ammonium, a carbamate, a thiocarbamate, and an alkyl group of 1 to 20 carbon atoms, said alkyl group being possibly substituted with one of the functional groups as defined above;

— R_3 represents: H , an alkyl group or an alkyl chain of 1 to 20 carbon atoms possibly substituted by any other functional group, such as defined for R and R_1 , and is particularly a methyl group;

— X represents:

* a nitrogen atom, an ammonium N^+R_5 , or CR_5 group, with R_5 representing an H , NO_2 , OH or an alkyl group being possibly substituted with a halogen atom, an ester, a carboxylic group, an amide or a thioamide group, a sulfonamide group, SO_3^- , a phosphate, a carboxylate, NO_2 , a primary, secondary or tertiary amine group, a nitrilo, an alcohol, an ether, a thiol, a thioether derivative; and being preferably a methyl group;

* or X represents a group of formula (A):



or a corresponding ammonium salt of said formula (A), wherein at least one of the three nitrogen atoms bears a R_6 substituent, R_6 having the same definition as R_5 ;

– A_1 , A_2 and A_3 represent:

* an alkyloxy group of formula $-O-(CH_2)_p-$, possibly substituted on one of the methylene carbons by a group having the same definition than R_5 , wherein p represents an integer varying from 1 to 3, when X represents a group of formula (A), or a corresponding ammonium salt of said formula (A), wherein at least one of the three nitrogen atoms bears a R_6 substituent, R_6 having the same definition as R_5 ;

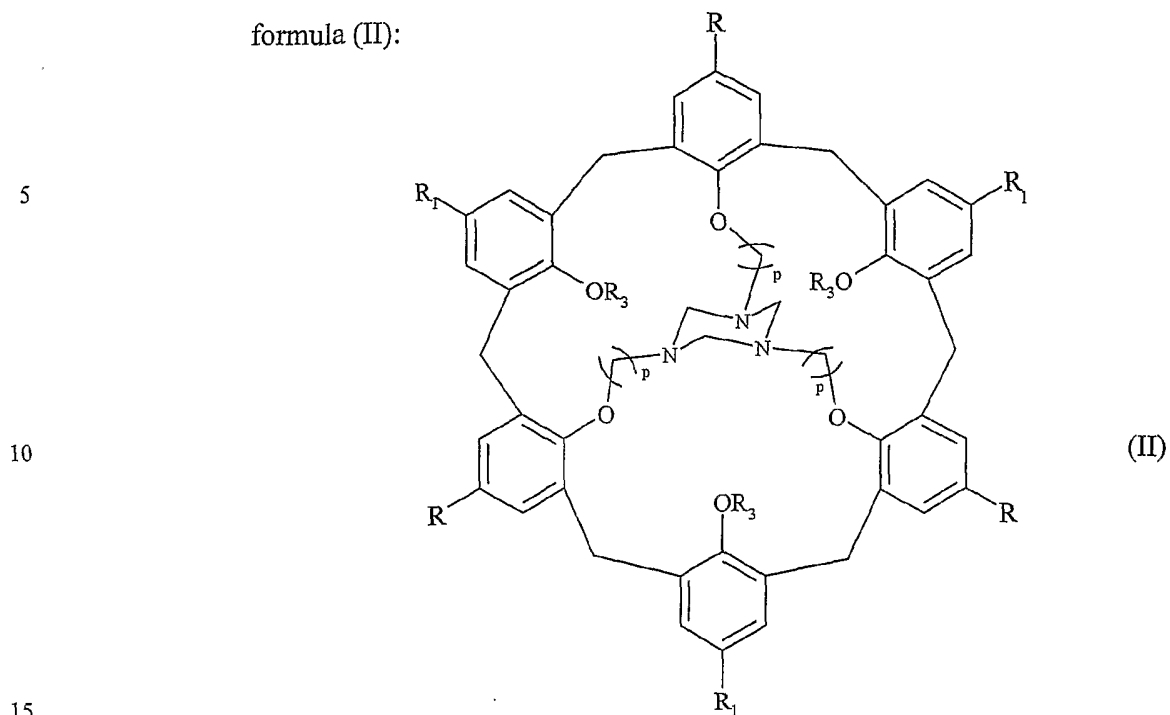
* or a group of formula : $-O-(CH_2)_n-NR_2-(CH_2)_m-$ or $-O-(CH_2)_n-N^+R_2R_4-(CH_2)_m-$ when X represents a nitrogen atom, an ammonium N^+R_5 or CR_5 group as mentioned above,

wherein m and n are integers varying from 1 to 3, and

R_2 and R_4 , identical or different, represent: H, an alkyl group of 1 to 20 carbon atoms, an ester or a thioester of 2 to 20 carbon atoms, a carboxylic acid of 1 to 20 carbon atoms, an amide or a thioamide of 1 to 20 carbon atoms, a sulfonamide of 1 to 20 carbon atoms, SO_3^- , a phosphate, a phosphine, a phosphonamide, a carboxylate, an hydroxy and its derivative such an ether-oxyde, or an amine of 1 to 20 carbon atoms and its derivatives such as a ketimine, an ammonium, a carbamate, a thiocarbamate.

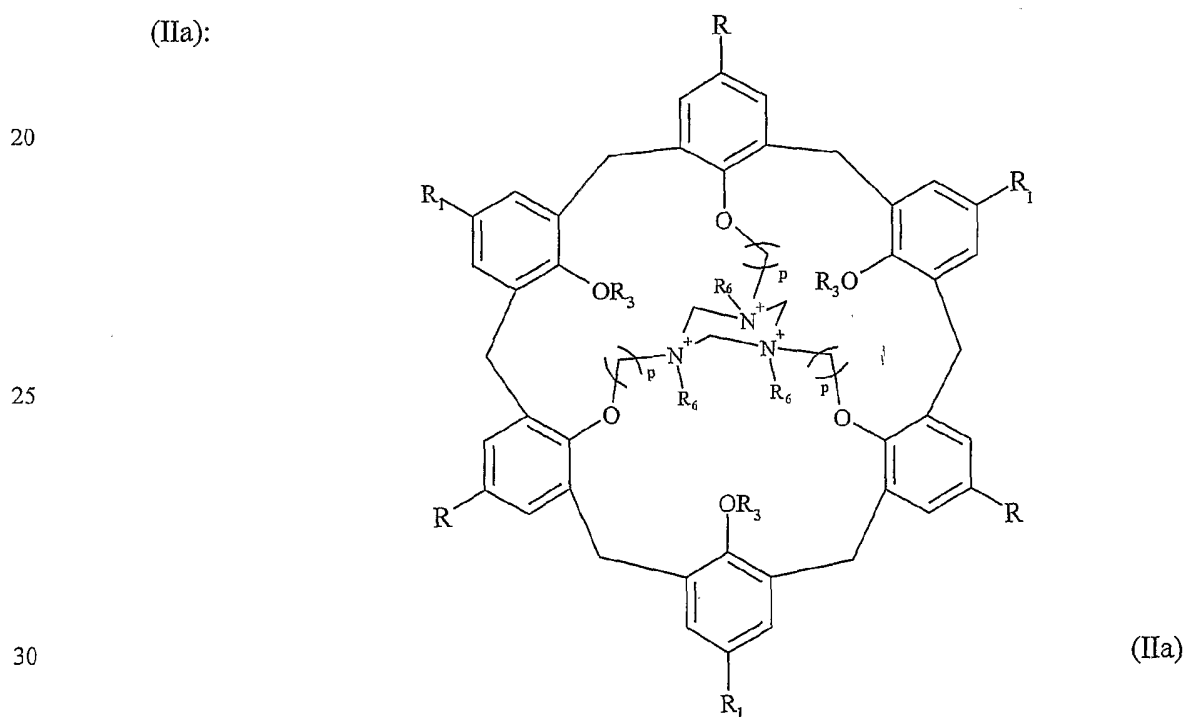
The present invention consists in a calix[6]arene capped with a C_{3v} -symmetrical azacrown bridge. Such a rigidified ligand should possess a reinforced complexation ability since the cap should prevent decomplexation processes by protecting the metal ion from the external medium, while maintaining a large degree of flexibility essential for the system in order to act as a biomimetic receptor.

The present invention also relates to compounds having the following formula (II):



wherein R, R₁, R₃ and p are such as defined above.

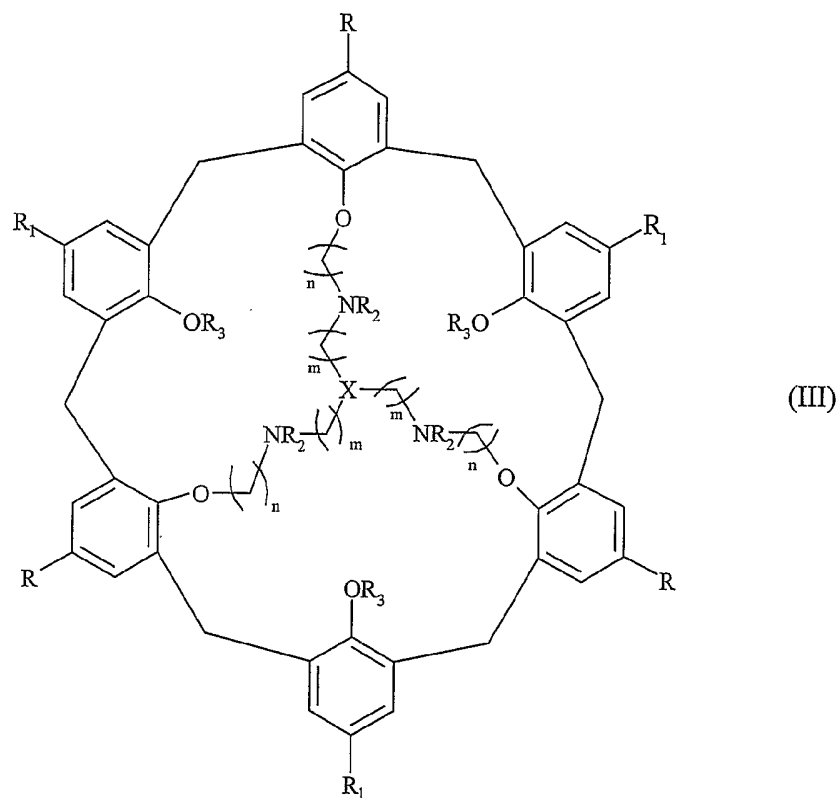
The present invention also relates to compounds having the following formula (IIa):



wherein R, R₁, R₃, R₆ and p are such as defined above.

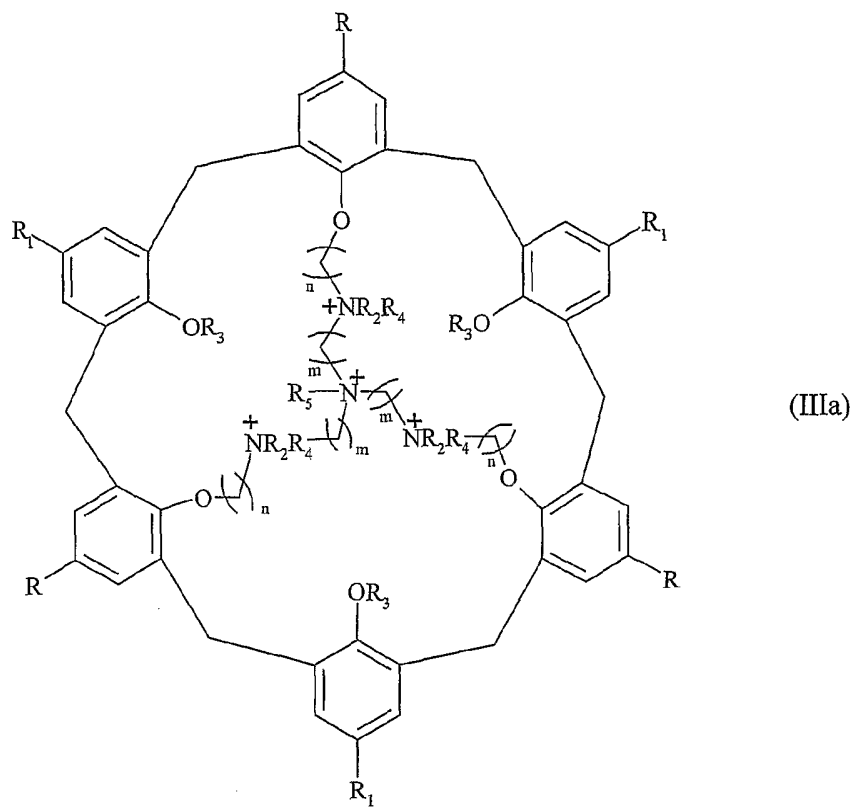
According to an advantageous embodiment, the compounds of the invention are characterised in that R and R₁ are tBu groups and R₃ represents a methyl group, and in that p is equal to 2.

The present invention also relates to compounds having the following formula (III):



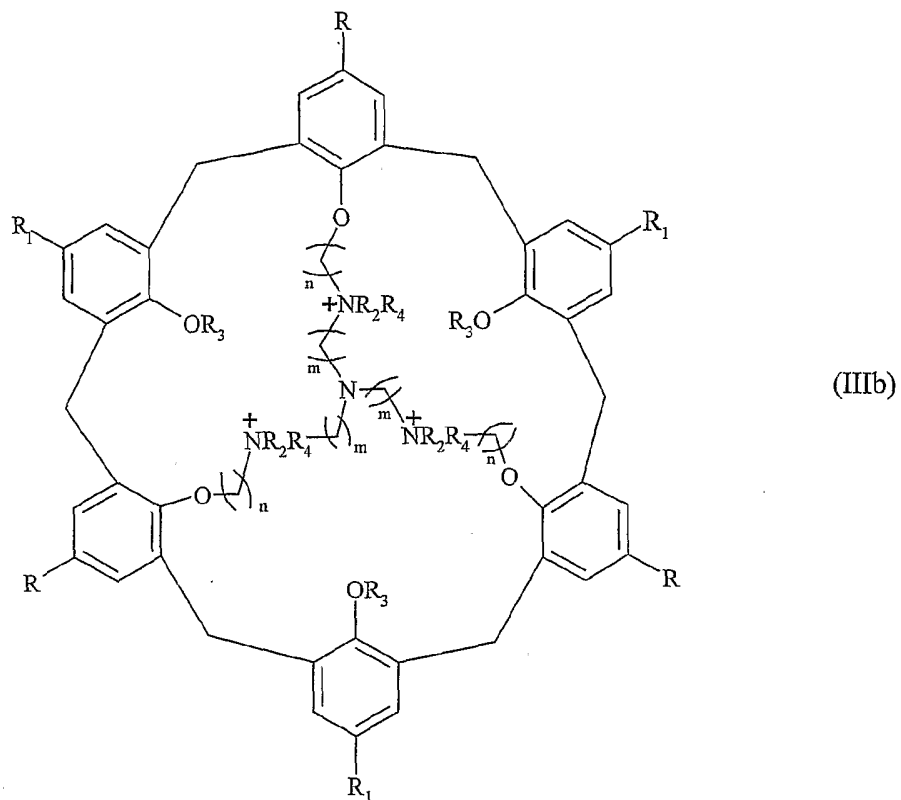
wherein m, n, R, R₁, R₂ and R₃ are such as defined above, and wherein X represents a nitrogen atom, an ammonium N⁺R₅, or CR₅ group, R₅ being such as defined above.

The present invention also relates to compounds having the following formula (IIIa):



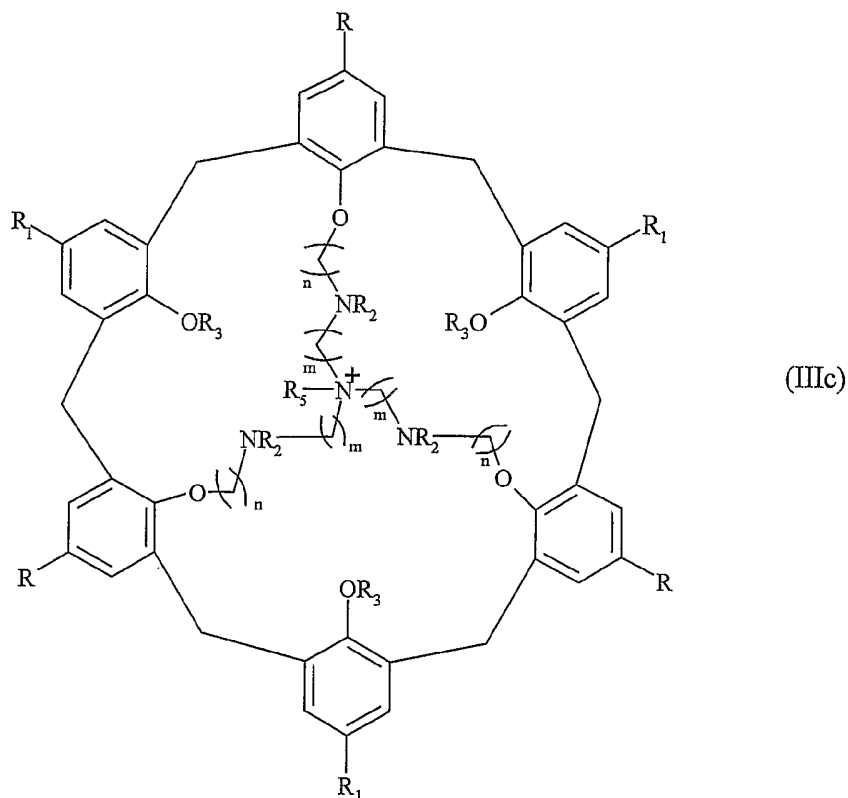
wherein m , n , R , R_1 , R_2 , R_3 , R_4 and R_5 are such as defined above.

The present invention also relates to compounds having the following formula (IIIb):



wherein m , n , R , R_1 , R_2 , R_3 and R_4 are such as defined above.

The present invention also relates to compounds having the following formula (IIIc):



wherein m , n , R , R_1 , R_2 , R_3 and R_5 are such as defined above.

According to an advantageous embodiment, the compounds of the invention are characterised in that R_3 represents a methyl group and R_2 , R_4 and R_5 represent a hydrogen atom.

According to an advantageous embodiment, the compounds of the invention are characterized in that R and R_1 represent *t*Bu groups.

According to an advantageous embodiment, the compounds of the invention are characterised in that R represents SO_3Na and R_1 represents NO_2 .

The present invention also relates to compounds such as defined above, characterised in that they are linked to:

- a function liable to bind, if necessary via a binding site, to molecules, such as antibodies, haptens or peptides, which are able to bind specifically with epitopes located at the surface of the cells of the organism, or to chemical or biological compounds located at the surface of a solid carrier, or

– a group carrying a function linked, if necessary via a binding site, to molecules as defined above.

The present invention also relates to complexes between a compound such as defined above, and an element chosen among:

- 5 – a metal, such as zinc, cadmium, mercury, copper, silver, gold, iron, cobalt, cesium;
- an actinide such as uranium, americium, plutonium or a lanthanide such as lanthanum, europium, gadolinium, ytterbium;
- a radioelement, more particularly chosen among α , β or γ emitter radiometals,
- 10 such as Tc, Re;
- a cationic guest such as an ammonium;
- an anionic guest such as a phosphate, a phosphonate, a sulfonate, a sulfate, a carboxylate, CN^- , F^- , Cl^- , Br^- , I^- ;

 said complexes resulting from the insertion of said element into the calix arene group and from interactions between said element and the coordination sites A_1 , A_2 , A_3 , and X, of the calix arene group of said compound.

The above-mentioned interactions between said element and the coordination sites A_1 , A_2 , A_3 , and X, of the calix arene group of said compound are preferably ionic interactions.

20 The present invention also relates to pharmaceutical compositions comprising a compound such as defined above, or a complex such as defined above, in association with a pharmaceutically acceptable carrier.

The present invention also relates to the use of compounds such as defined above:

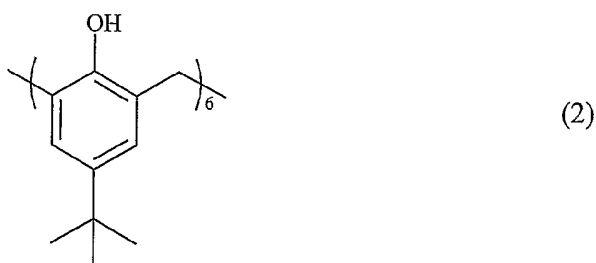
- 25 – for the preparation of selective metal extractants such as radioactive or precious metals;
- for the preparation of catalysts to be used in chemistry in aqueous or organic medium, and more particularly for the preparation of complexes between a compound such as defined above, and a metal active as a catalyst;
- for the *in vitro* detoxification after intoxication by heavy metals or drugs;
- 30 – for the preparation of pharmaceutical composition useful for the detoxification after intoxication by heavy metals or drugs;
- as depolluting agents in aquatic media, captors of molecules in gas phase, ligands in medical imaging, biological probes, carriers of therapeutic molecules,

stationary phases for gas chromatography, or stabilizers of compounds sensitive to the presence of metals.

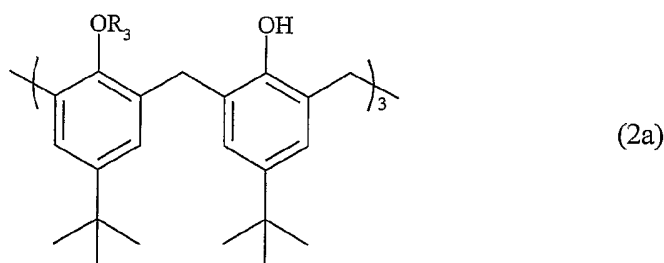
The present invention also relates to the use of a complex such as defined above, between a compound such as defined above and a radioelement for the manufacture of a medicament for radioimmunotherapy, in particular for the treatment of cancers, or for the treatment against metastase proliferation.

The present invention also relates to a process of preparation of compounds such as defined above, characterized in that it comprises the following steps:

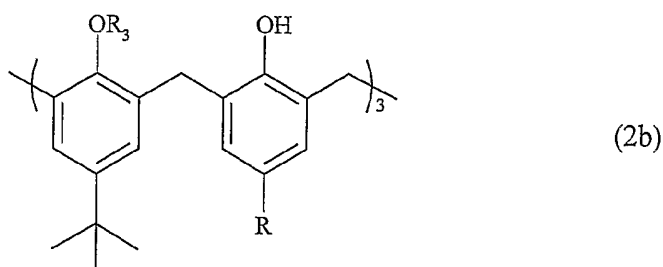
— a selective 1,3,5-trialkylation with alkyl halide R_3Y , R_3 being such as defined above and Y representing a leaving group, and particularly a halogen atom, such as Cl, Br and I, of compound 2 of following formula:



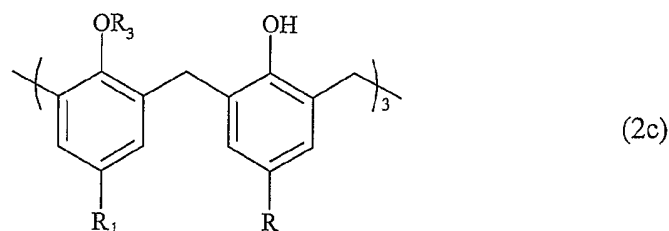
to obtain compound 2a having the following formula:



— the treatment of above-mentioned compound 2a with $AlCl_3$, and, if R is different from H in the compound of formula (I) to be obtained, the subsequent treatment with an electrophile chemically equivalent to R^+ , in order to obtain compound 2b having the following formula:



– the treatment of compound 2b such as obtained previously with AlCl_3 , followed by the treatment with R_1Z , Z being a halogen atom and R_1 being such as defined above, in order to obtain compound 2c having the following formula:

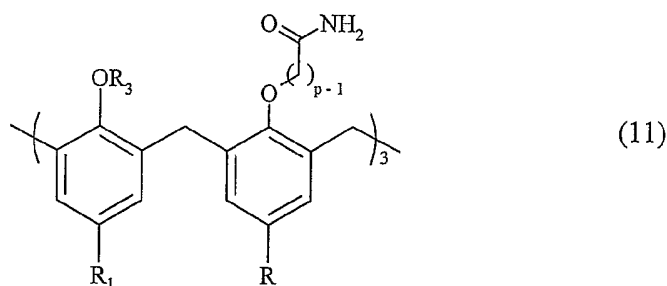


a) for the preparation of compounds of formula (II) or (IIa)

– the conversion by alkylation, particularly with compound of formula

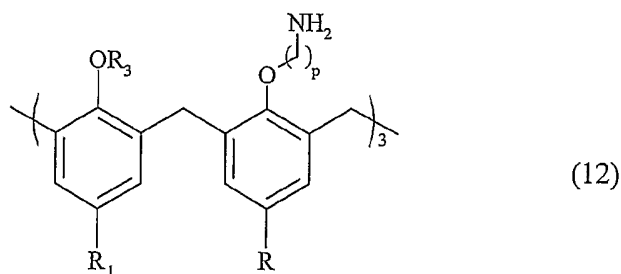
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following formula:



R , R_1 , R_3 and p being such as defined above,

– the reduction of the above-mentioned compound 11 with BH_3 , in order to obtain the following compound 12:

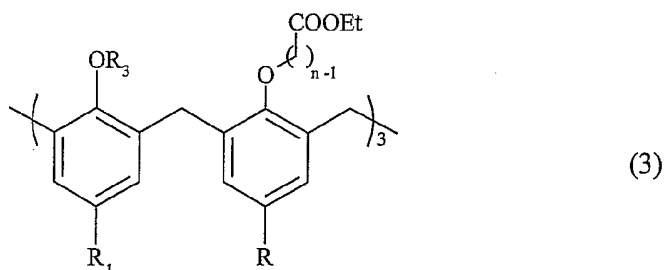


– the reaction with the triamine of formula (12) such as mentioned above with formaldehyde, in order to obtain the compound of formula (II) such as defined above, and

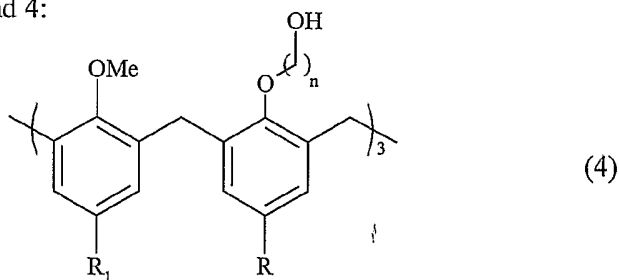
– possibly the alkylation of compound of formula (II) with R_6Y , Y being a leaving group, and particularly a halogen atom and R_6 being such as defined above, in order to obtain compound of formula (IIa) such as defined above.

b) for the preparation of compounds of formula (III), (IIIa), (IIIb) or (IIIc)

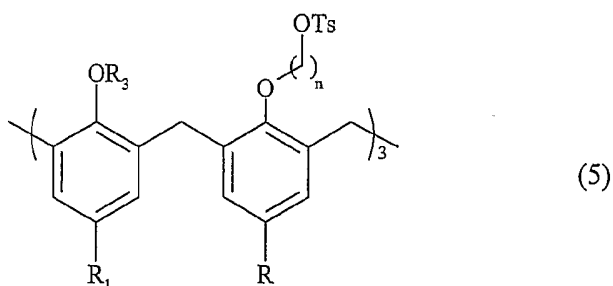
– the conversion by alkylation, particularly with compound of formula $Br-(CH_2)_{n-1}-COOEt$, of compound 2c into the triester derivative 3 having the following formula:



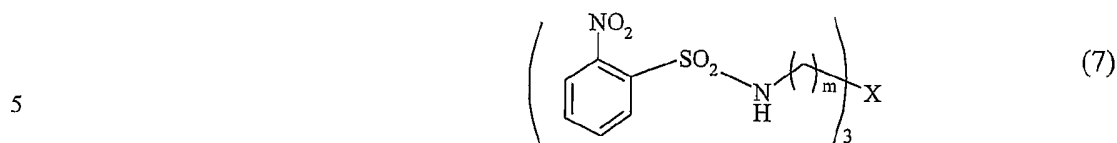
– the reduction by $LiAlH_4$ of the above-mentioned compound 3, in order to obtain the following compound 4:



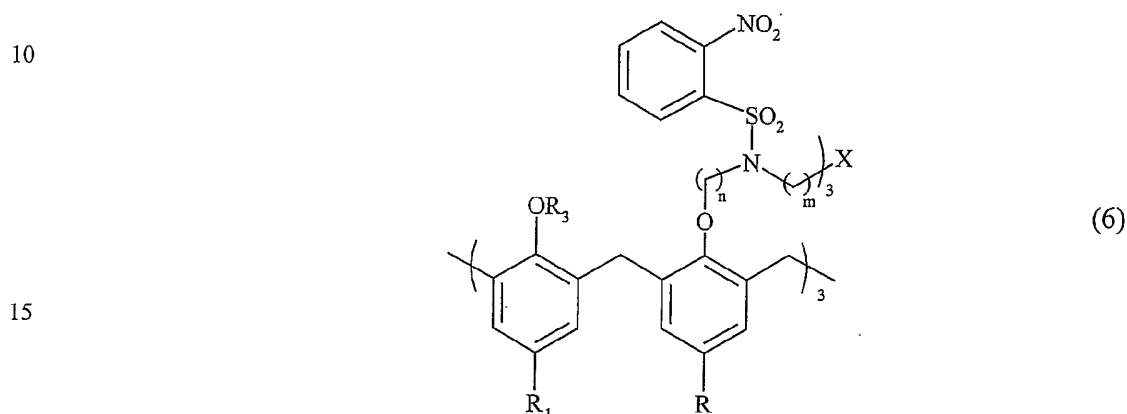
– the addition of $TsCl$ to compound 4 such as obtained previously, in order to obtain compound 5 having the following formula:



— a reaction of trialkylation of compound 5, such as obtained previously, with compound 7 having the following formula:



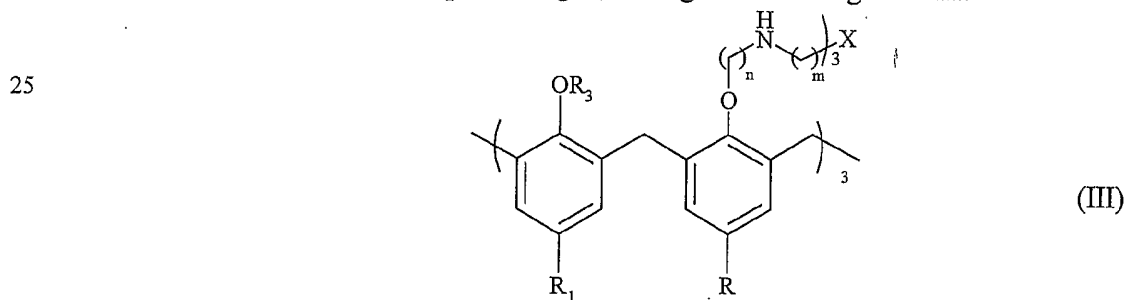
X being such as defined above, and m being such as defined above, in order to obtain compound 6 having the following formula:



compound 7 being obtained according to the reaction of compound having the following formula $\left(\text{H}_2\text{N}(\text{CH}_2)_m \right)_3 \text{X}$ with 2-nitrobenzenesulfonylchloride;

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— the deprotection of the amino groups of compound 6 such as obtained previously with thiophenol, in order to obtain compound of formula (III) such as defined above with R_2 representing H, having the following formula:



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— and possibly the alkylation of compound of formula (III) such as obtained previously with R_4Y , Y representing a leaving group, and particularly a halogen atom and R_4 being such as defined above, in order to obtain compound of formula (IIIb) such as defined above, or possibly the alkylation of compound of formula (III) such as obtained previously with R_5Y , Y representing a leaving group, and particularly a

halogen atom and R_5 being such as defined above, in order to obtain compound of formula (IIIc) such as defined above,

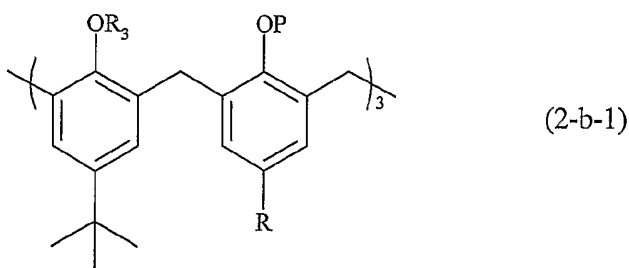
– and possibly the alkylation of compound (IIIb) such as obtained previously with R_5Y , Y representing a leaving group, and particularly a halogen atom and R_5 being such as defined above, or the alkylation of compound (IIIc) such as obtained previously with R_4Y , Y representing a leaving group, and particularly a halogen atom and R_4 being such as defined above, in order to obtain compound of formula (IIIa) such as defined above.

The process of preparation of compounds of formula (2b) from compounds of formula (2a) comprises eventually a step of treatment with an electrophile, which can be:

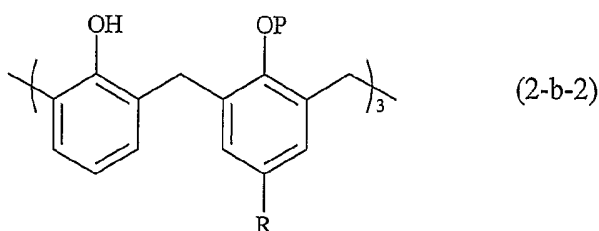
– a step of treatment with RZ, wherein R is such as defined above and is different from H and Z is a halogen atom, RZ being preferably HSO_3Cl or HNO_3 , or
 – a step of treatment with N-bromosuccinimide (wherein $R = \text{Br}$), or
 – a reaction of compound (2a) with an acyl- or an allylchloride (wherein R is an acyl or an allyl group), followed by a thermic rearrangement, or
 – a step of condensation of compound of formula (2a) with an aldehyde in the presence of an amine.

The process of preparation of compounds of formula (2c) from compounds of formula (2b) comprises the following steps:

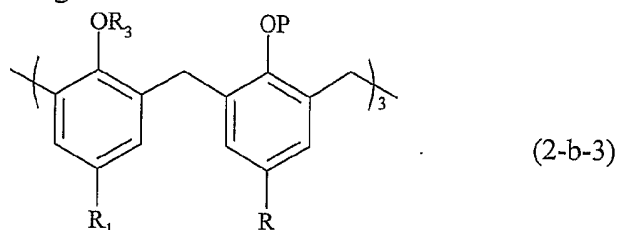
– a step of protection of the OH function by the reaction of compound of formula (2b) with a protecting group such as PCl, where P can be an acyl or a benzoyl group such as MeCO or PhCO, in order to obtain the following compound of formula (2-b-1):



– a step of treatment of the compound such as obtained previously of formula (2-b-1) with AlCl_3 in order to obtain the following compound of formula (2-b-2):

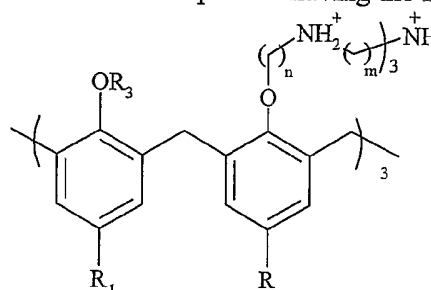


– a step of treatment of compound of formula (2-b-2) with R_1Z , Z being a halogen atom and R_1 being such as defined above, and a step of selective trialkylation with alkyl halide R_3Y , R_3 and Y being such as defined above, in order to obtain compound (2-b-3) of following formula:



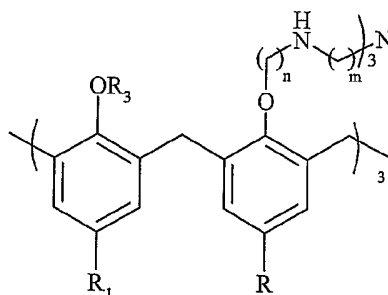
– a step of deprotection by basic hydrolysis of compound of formula (2-b-3) in order to obtain compound of formula (2-c) such as defined previously.

The present invention also relates to compounds having the following formula

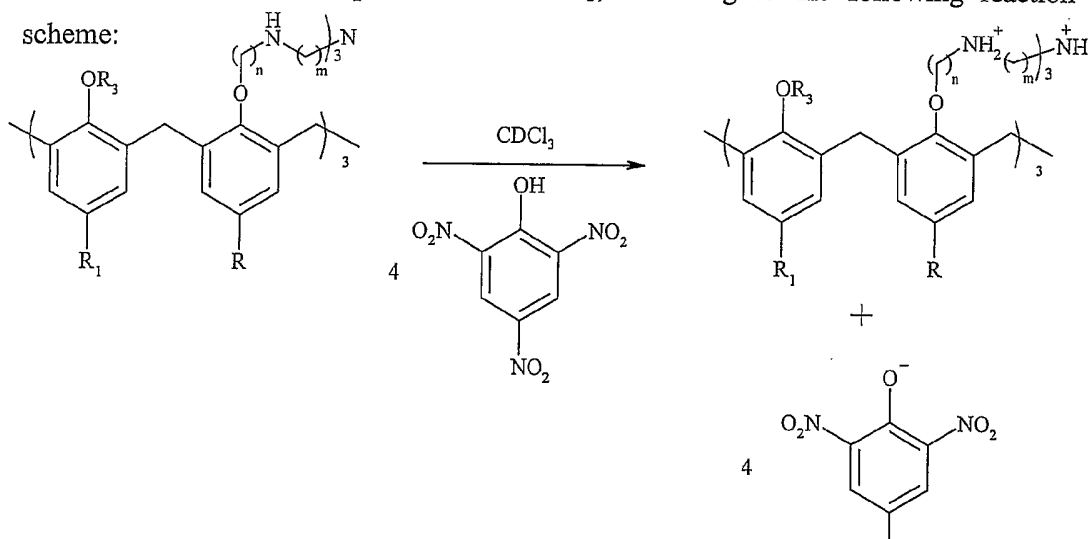


wherein R, R_1 , R_3 , m and n are as defined above for formula (I),

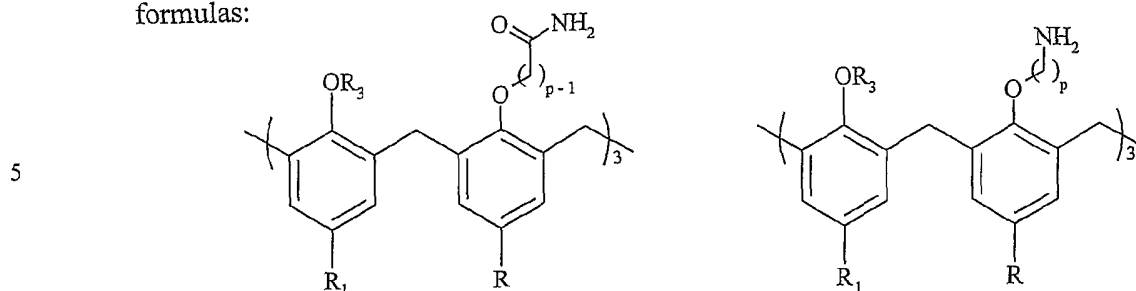
which can be obtained by the reaction of compound of the following formula



with picric acid in presence of $CDCl_3$, according to the following reaction



The present invention also relates to compounds having one of the following formulas:



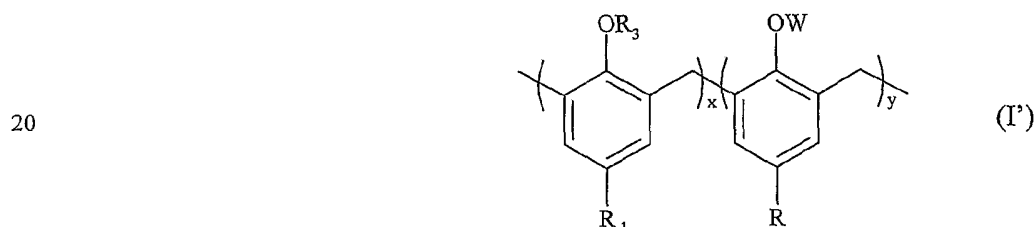
wherein R, R₁, R₃ and p are such as defined above,

10 said compounds being liable to be used as synthesis intermediaries for the preparation of compounds of formula (II) such as defined above,

provided that the compounds wherein R and R₁ represent tBu, R₃ represents a methyl group and p is 2, are excluded.

15 The present invention also relates to a process of preparation of water-soluble compounds, characterized in that it comprises the following steps:

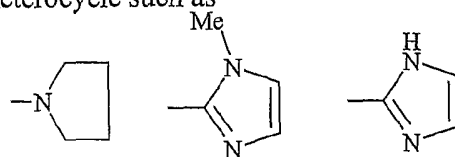
— a reaction of nitration or sulfonation of a compound of formula (I) such as defined above, or of a compound of the following formula:



wherein

- x and y are integers different from 0, x + y varying from 4 to 8,
- 25 — R, R₁ and R₃ are such as defined for formula (I), R and R₁ being different from SO₃⁻ and NO₂,
- W represents an alkyl group comprising 1 to 5 carbon atoms, said alkyl group being substituted with a protonable element chosen among:

30 * a heterocycle such as



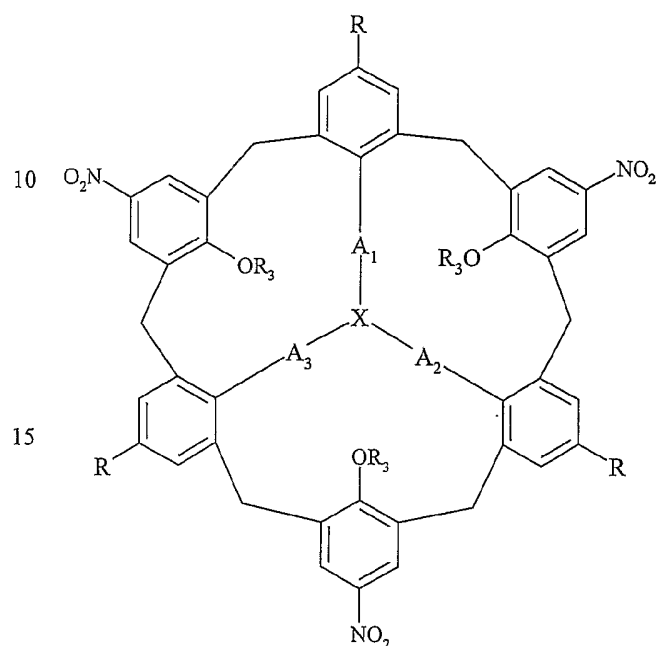
or pyridine, or benzimidazole,

* a primary, secondary or tertiary amine group, particularly NH₂ or NMe₂,

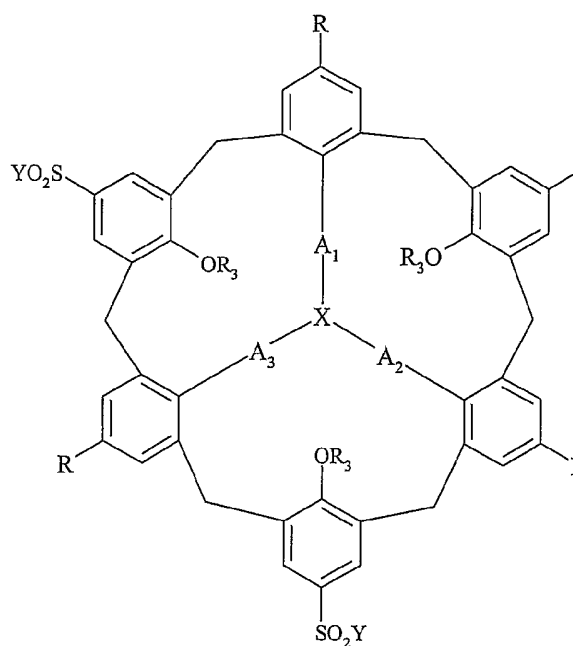
* a $-\text{CO}-\text{R}_7$ or $-\text{CS}-\text{R}_7$ group wherein R_7 represents a primary, secondary or tertiary amine group, particularly a NH_2 group, or heterocycles, particularly such as , or a $-\text{OR}_8$ group, wherein R_8 represents H or an alkyl group comprising from 1 to 10 carbon atoms, or

5 * a $-\text{OR}_8$ or $-\text{SR}_8$ group, wherein R_8 is such as defined above,

in order to obtain respectively a compound having one of the following formulas:

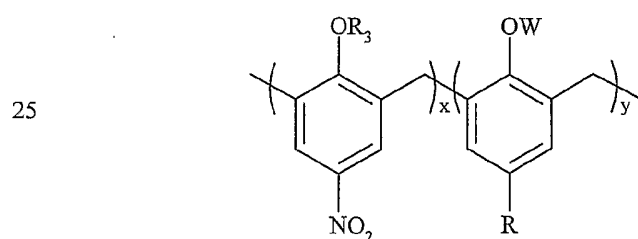


(I-a)

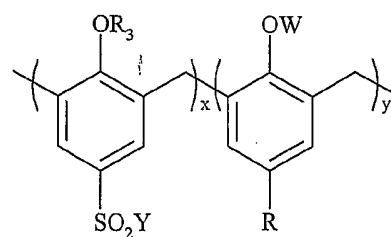


(I-b)

wherein A_1 , A_2 , A_3 , R , R_3 and X being such as defined above,



(I'-a)

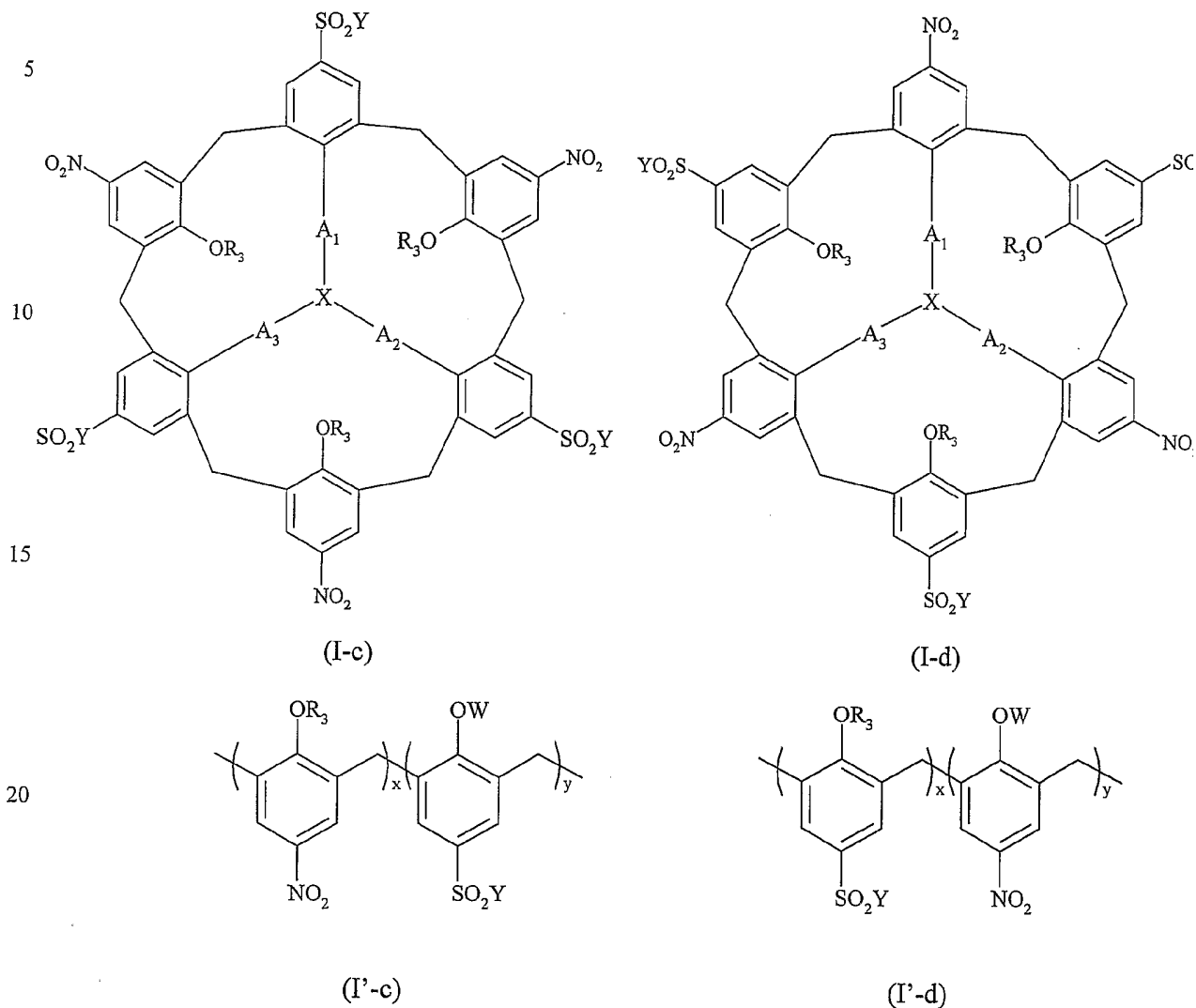


(I'-b)

30 Y representing OH, or an alkoxy group, or a primary or secondary amine group, or a halogen atom or a thioalkyl group,

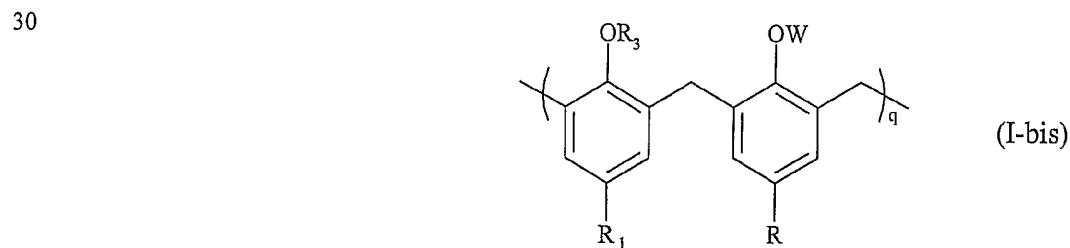
– and optionally a reaction of sulfonation or nitration of compound of one of the formulas (I-a), (I-b), (I'-a) or (I'-b), such as obtained previously,

in order to obtain respectively a compound having one of the following formulas:



The present invention also relates to a process of preparation of water-soluble compounds, characterized in that it comprises the following steps:

– a reaction of nitration or sulfonation of a compound of formula (I) such as defined above, or of a compound of the following formula:

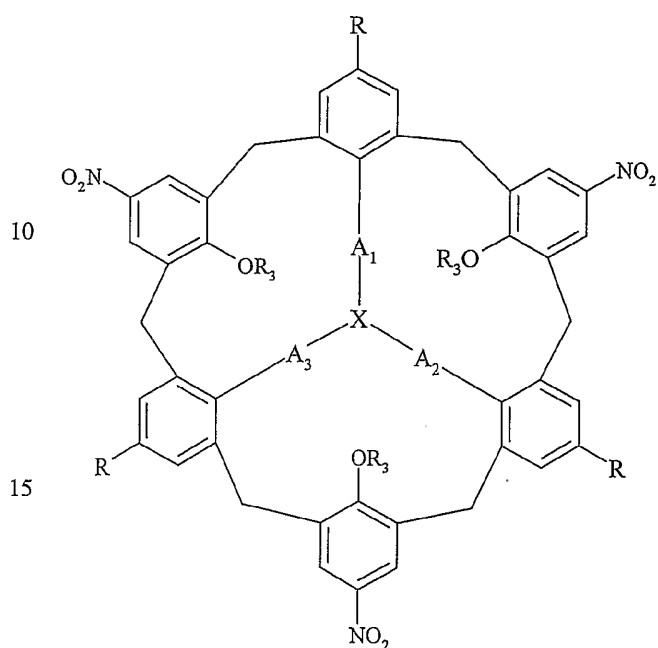


wherein

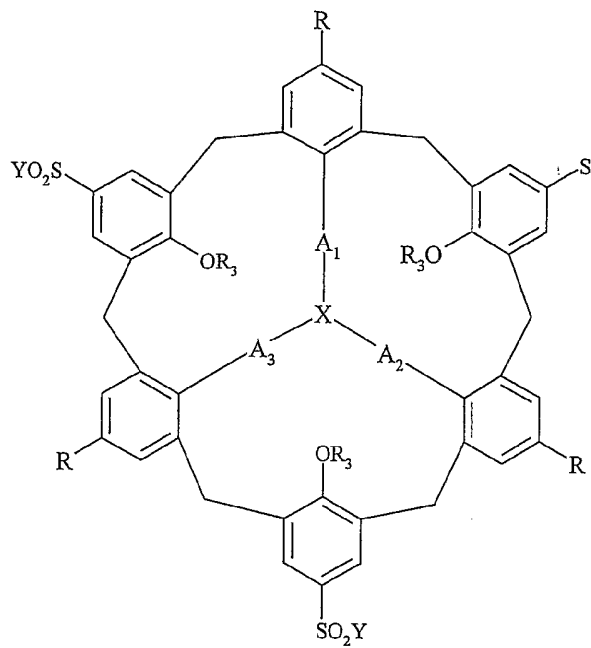
- q is an integer varying from 2 to 4, and
- R, R₁, R₃ and W are such as defined above,

in order to obtain respectively a compound having one of the following formulas:

5



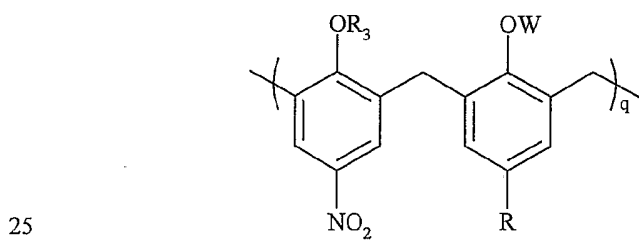
(I-a)



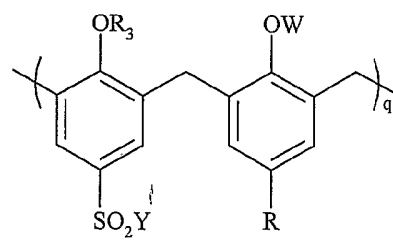
(I-b)

20

wherein A₁, A₂, A₃, R, R₃ and X being such as defined above,



(I-bis-a)



(I-bis-b)

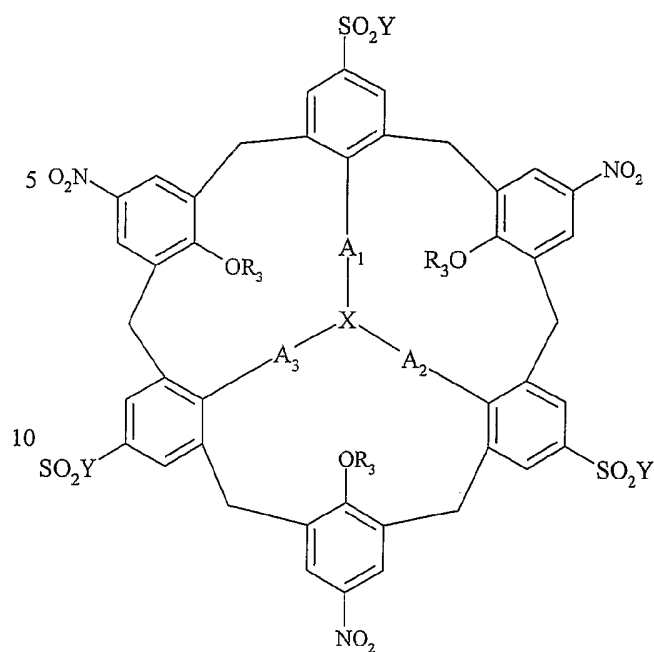
25

Y being such as defined previously,

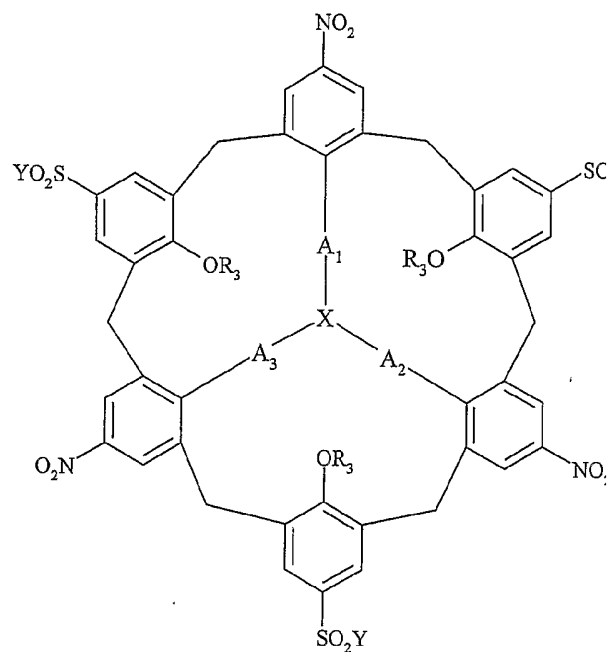
30

- and optionally a reaction of sulfonation or nitration of compound of one of the formulas (I-a), (I-b), (I-bis-a) or (I-bis-b), such as obtained previously,

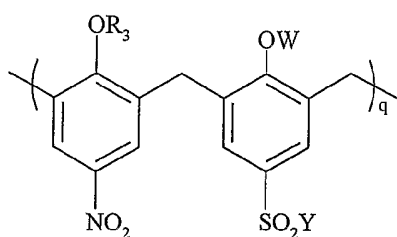
in order to obtain respectively a compound having one of the following formulas:



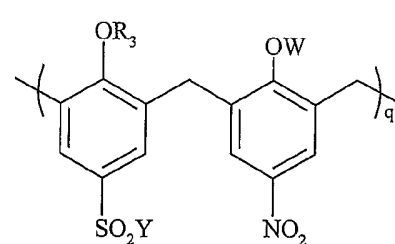
(I-c)



(I-d)



(I-bis-c)



(I-bis-d)

According to an advantageous embodiment, the process of the invention is a process wherein the reaction of sulfonation is carried out with the chlorosulfonic acid, and the reaction of nitration is carried out with the nitric acid.

According to an advantageous embodiment, the process of the invention is characterized in that it comprises the possible step of transformation of the functions NO_2 and SO_2Y , in one of the following respective functions:

- amine, ammonium, amide, thioamide,
- sulfonate, sulfonamide, sulfonic ester, sulfothioester.

A catalytic hydrogenation is carried out with the NO_2 function in order to obtain a NH_2 function, which can then be alkylated in order to obtain a primary, secondary or tertiary amine group, or an ammonium group.

The function NO_2 is treated with an acyl chloride or a sulfonyl chloride, in order to obtain a sulfonamide function, or is treated with a thioacid chloride in order to obtain a thioamide function.

The transformation of the SO_2Y group into a sulfonamide function is carried out by the reaction with an amine; the transformation of the SO_2Y group into a sulfothioester function is carried out by the reaction with a thiol and the transformation of the SO_2Y group into a sulfonic ester function is carried out by the reaction with an alcohol.

According to an advantageous embodiment, the process of the invention is characterized in that it comprises the following steps:

— a reaction of nitration of a compound of formula (I) such as defined above, or of a compound of formula (I') or (I-bis) such as defined above,

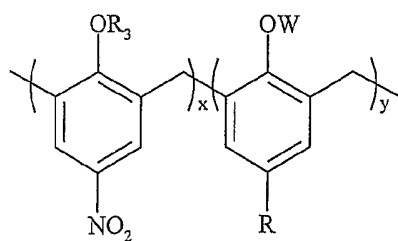
in order to obtain a compound having the respective formulas (I-a) or (I'-a) or (I-bis-a) such as defined above,

— and a reaction of sulfonation of the compound such as obtained previously of formula (I-a) or (I'-a) or (I-bis-a),

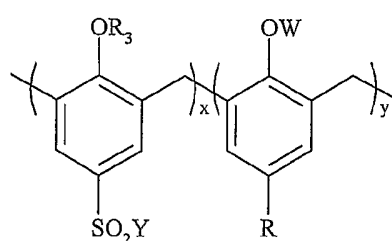
in order to obtain a compound having the respective formulas (I-c) or (I'-c) or (I-bis-c), such as defined above.

According to an advantageous embodiment, the process of the invention is characterized in that R and R_1 represent tBu groups.

The present invention also relates to compounds having one of the following formulas:



(I'-a)



(I'-b)

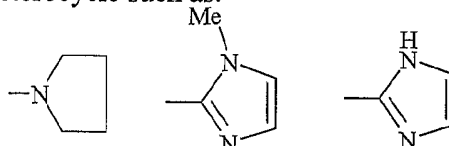
wherein:

– R and R₃ are such as defined above for formula (I), R being different from NO₂ and SO₃⁻,

– x and y are integers different from 0, x + y varying from 4 to 8,

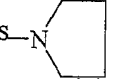
– W represents an alkyl group comprising 1 to 5 carbon atoms, said alkyl group being substituted with a protonable element chosen among:

* a heterocycle such as:



or pyridine, or benzimidazole,

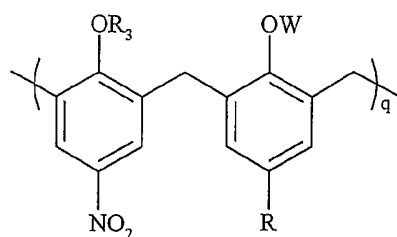
* a primary, secondary or tertiary amine group, particularly NH₂ or NMe₂,

* a -CO-R₇ or -CS-R₇ group wherein R₇ represents a primary, secondary or tertiary amine group, particularly a NH₂ group, or heterocycles, particularly such as , or a -OR₈ group, wherein R₈ represents H or an alkyl group comprising from 1 to 10 carbon atoms, or

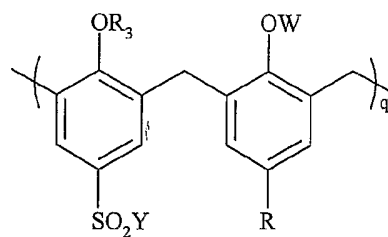
* a -OR₈ or -SR₈ group, wherein R₈ is such as defined above,

– Y represents OH, or an alkoxy group, or a primary or secondary amine group, or a halogen atom or a thioalkyl group.

The present invention also relates to compounds having one of the following formulas:



(I-bis-a)



(I-bis-b)

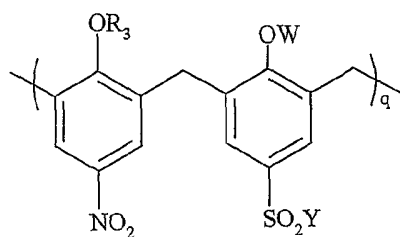
wherein:

– q is an integer varying from 2 to 4,

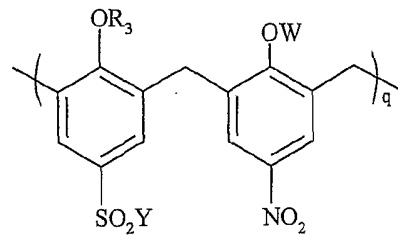
– R, R₃, W and Y are such as defined above,

These compounds are new water-soluble compounds.

Preferred compounds according to the invention have one of the following formulas:



(I-bis-c)



(I-bis-d)

wherein R_3 , q , W and Y are such as defined above.

According to an advantageous embodiment, the compounds of the invention are characterized in that R_3 represents a methyl group.

DESCRIPTION OF THE FIGURES

Figure 1. ^1H NMR spectrum of compound **5-a** in CDCl_3 at 298K.

Figure 2. ^1H NMR spectrum of compounds **6-a** in CDCl_3 at 298K.

Figure 3-a. ^1H NMR spectrum of compound **7-a** in CDCl_3 at 298K.

Figure 3-b. ^1H NMR spectrum of compound **8-a** in CDCl_3 at 298K.

+ : residual water or solvent peaks (CHCl_3 and CH_3CN ; this latter was present in elemental analysis characterization of compound **8-a**).

Figure 4-a. ^1H NMR spectrum of compound **10-a** in CDCl_3 at 298K.

Figure 4-b. ^1H NMR spectrum of complex **10-a**/ $\text{MeNH}_3^+\text{Cl}^-$ in CDCl_3 at 298K.

Solvent, water and reference are labelled S, W and R, respectively.

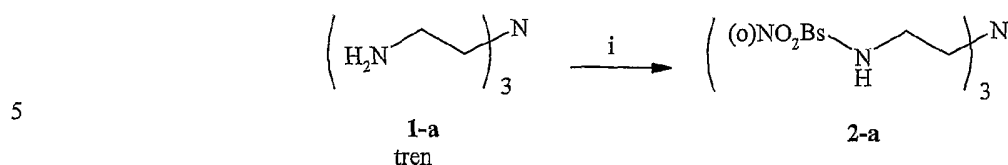
EXAMPLES

I – Synthesis of compound **8-a**

Compound **8-a** is a compound of formula (III) wherein $m = n = 2$, $R = R_1 = \text{tBu}$, $R_2 = \text{H}$, $X = \text{N}$ and $R_3 = \text{Me}$.

A classical route for the synthesis of azacrowns consists in the use of a poly-toluenesulfonamide salt for the alkylation reaction (*Macrocyclic Synthesis, a Practical Approach*, Ed. D. Parker, Oxford University Press, 1996). Thus, in order to obtain the desired triply bridged calix[6]arene, the present inventors chose to attempt the tris-alkylation reaction between the trianion of a tris-arylsulfonamide derivative of tris(2-aminoethyl)amine (tren) **1-a** and a tris-tosylcalix[6]arene derivative. For this purpose, we first prepared the tris-protected tren **2-a** by the reaction between tren **1-a** and 3.4 equivalents of 2-nitrobenzenesulfonyl chloride in the presence of triethylamine (76 % yield) (Scheme 1). The 2-nitrobenzenesulfonyl protected group [(o) NO_2Bs] was chosen instead of the more classical tosyl one since it can be removed under milder conditions. It is noteworthy that compound **2-a** is an amorphous and hygroscopic solid that could

not be recrystallized, consequently it was only purified by flash chromatography on silica gel.

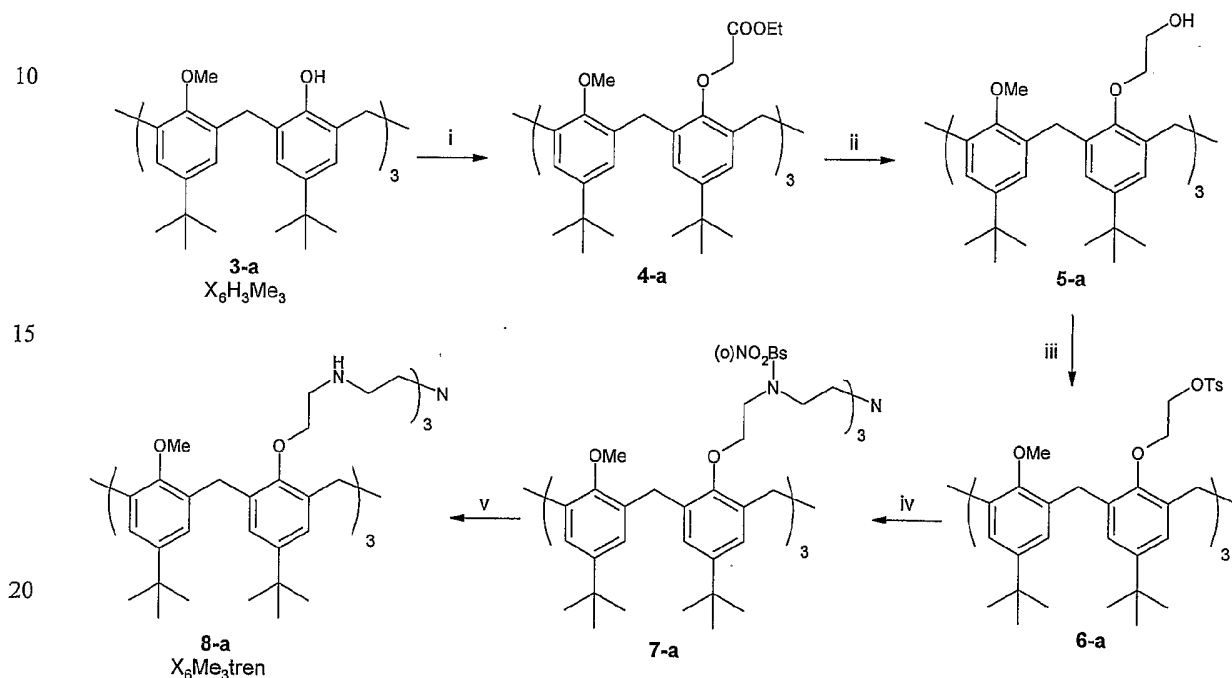


Scheme 1. i) (o)NO₂BsCl, TEA, THF, 0 °C then rt, 76 %.

The required tris-tosyl calix[6]arene was prepared from the known X₆H₃Me₃ **3-a** (Scheme 2)(Janssen, R. G. et al. *Synthesis* (1993) 380-385)[obtained by selective 1,3,5-trimethylation of *p*-*t*Bu-calix[6]arene (X₆H₆)(Gutsche, C. D. et al. *Org. Syn.* (1990) **68**, 238-242] in an efficient three step sequence (54 % overall yield). First, X₆H₃Me₃ **3-a** was converted into the triester derivative **4-a** by alkylation with an excess of ethylbromoacetate in the presence of NaH in 77 % yield (Takeshita, M. et al. *Chem. Lett.* (1994) 1349). A subsequent reduction by LAH afforded the tris-hydroxy derivative **5-a** in 82 % yield. The latter was reacted at low temperature with an excess of TsCl in a mixture of anhydrous pyridine and chloroform giving the tris-tosyl calix[6]arene **6-a** in 86 % yield (Scheme 2). This reaction necessitated a careful respect to the reaction conditions (essentially the low temperature and reaction time), otherwise unidentified calixarene-type by-products were formed, lowering the yield. The ¹H NMR spectra of compounds **4-a** (not shown), **5-a** (Figure 1) and **6-a** (Figure 2), recorded at 298 K in CDCl₃, are characteristic of a major flattened cone conformation of C_{3v} symmetry (The ¹H NMR spectrum of **6-a** revealed the presence of minor conformational isomers). The high-field shift of the methoxy protons of compounds **4-a** and **6-a** (δ_{OMe} = 2.27 and 2.07, respectively) indicates that these groups are included inside the cavity, projecting the bulky ethyl ester or tosyl groups outside. In the case of calix[6]arene **5-a**, the methoxy groups present a quasi-normal resonance (δ_{OMe} = 3.47) suggesting that they are involved in an intramolecular hydrogen bonding network with the hydroxylated arms. This was confirmed by the high-field shift observed for these groups (δ_{OMe} = 3.01) when a protic solvent (CD₃OD) was added. It is also noteworthy that, in contrast to compounds **4-a** and **5-a**, sharp signals are observed for the ArCH₂Ar methylene protons of tris-tosyl calix[6]arene **6-a** (two doublets at 3.29 and 4.40 ppm). It shows

that, with these bulky tosyl arms, the cone-cone interconversion of **6-a** is slower than the NMR time scale.

Key-step formation of the triply bridged calix[6]arene was conducted under standard conditions, reacting **6-a** and **2-a** in the presence of Cs_2CO_3 as a base in DMF. After flash chromatography on silica gel, the expected capped calix[6]arene **7-a** was isolated in 31 % yield. Finally, deprotection of the amino groups was performed by $\text{S}_\text{N}\text{Ar}$ substitution of the (o) NO_2Bs groups by thiophenate, giving rise to the desired calix[6]azacrown **8-a** ($\text{X}_6\text{Me}_3\text{tren}$) with a 75 % yield (Scheme 2).



Scheme 2. i) Ethylbromoacetate, NaH, THF, reflux, 77 %. ii) LAH, ether, reflux, 82 %. iii) TsCl, Pyridine, CHCl_3 , -20°C , 86 %, iv) **2**, Cs_2CO_3 , DMF, rt then 90°C , 31 %. v) PhSH, Na_2CO_3 , DMF, 50°C , 75 %.

The ^1H NMR spectra of capped calixarenes **7-a** and **8-a** are displayed Figures 3-a and 3-b. Their profiles are remarkably simple attesting to a major C_{3v} -symmetrical rigid cone conformation. Evidence for the rigidification of the cone conformation due to the capping is given by the sharp and well-defined signals corresponding to the ArCH_2Ar methylene protons. Some unusual features however are specifically observed for compound **8-a**. Its methoxy groups are less high-field shifted than for compound **7-a** ($\delta_{\text{OMe}} = 3.05$ instead of 2.40 ppm), suggesting that they are more distant from the C_3 axis. The very small difference of resonance between the two tBu signals of **8-a**

($\Delta\delta_{\text{tBu}} = 0.02$ ppm) also indicates that all tBu groups have similar orientations. This stands in contrast to the classical alternate *in* and *out* positions adopted by the tBu groups of calixarenes with the same symmetry (Sénèque, O. et al. *Eur. J. Inorg. Chem.* (2001) 2597-2604) (for example, $\Delta\delta_{\text{tBu}} = 0.51, 0.37, 0.63$ and 0.47 ppm for calixarenes **4-a**, **5-a**, **6-a** and **7-a**, respectively). This shows that the skeleton of calix[6]azacrown **8-a** has a more straight and regular cone conformation. As in the case of compound **5-a**, these features might well be due to the establishment of hydrogen bonds between the anisole units and their neighboring phenoxy protic substituents, namely the tren-NH groups in the case of **8-a**. Indeed, addition of CD₃OD induced a split of the tBu resonances attesting to a conformational change. Finally, a variable temperature ¹H NMR study showed some broadening of the spectra at low temperature. However, the axial and equatorial ArCH₂Ar methylene protons were differentiated over the whole temperature range (240-330 K), indicating that the cone-cone inversion did not occur on the NMR time scale.

In conclusion, the present invention describes the synthesis of the first C_{3v}-symmetrical calix[6](aza)crown **8-a**. A ¹H NMR study has shown that the alternate 1,3,5-azabridge at the small rim rigidifies the whole edifice preventing ring inversion and constraining the calixarene core in a straight cone conformation.

Experimental Section

General Procedures. THF and ether were distilled over sodium/benzophenone under argon. Pyridine was distilled over KOH under argon. Chloroform was distilled over P₂O₅ under argon. DMF was distilled over MgSO₄ and stored over 4 Å molecular sieves under argon. TsCl was recrystallized (dichloromethane/pentane) before use. ¹H and ¹³C NMR spectra were recorded respectively at 200 and 50 MHz. Thin-layer chromatographies (TLC) were performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230-400 mesh) was used for flash chromatography separations. All reactions were performed under an inert atmosphere. Elemental analyses were performed at the Laboratoire de Microanalyse Organique, IRCOF, France.

N,N',N''-tri-2-nitrobenzenesulfonyl-2,2',2''-nitrilotriethylamine 2-a. At 0 °C, triethylamine (TEA)(3.9 mL, 27.75 mmol) was added to a solution of tren 1-a (1.0 mL, 6.68 mmol) in 20 mL of anhydrous THF. (o)NO₂BsCl (5.03 g, 22.7 mmol) was added by small portions over the course of 20 min time and then the reaction mixture was stirred for 16 h at room temperature. After removal of the solvent under reduced pressure, addition of water and extraction with dichloromethane, the resulting crude residue was purified by flash chromatography yielding **2-a** (3.56 g, 76 %) as an amorphous yellow solid that could not be recrystallized. mp: 85-88 °C (decomp.). IR (CHCl₃): ν 3340, 1542, 1362 cm⁻¹. ¹H NMR (CDCl₃) δ 2.63 (t, J = 5.5 Hz, 6H), 3.10 (q, J = 5.5 Hz, 6H), 5.76 (t, J = 5.5 Hz, 3H), 7.69-7.87 (m, 9H), 8.04-8.13 (m, 3H). ¹³C NMR (CDCl₃) δ 41.77, 54.78, 125.7, 131.0, 133.1, 133.2, 133.9, 148.2. MS (FAB) m/z 702.4 (M-H⁺, calcd 702.1).

5,11,17,23,29,35-Hexa-tert-butyl-37,39,41-trimethoxy-38,40,42-tris(2-hydroxy-ethoxy)calix[6]arene 5-a. To a solution of **4-a** (4.15 g, 3.26 mmol) in 350 mL of anhydrous Et₂O was added LAH (1.43 g, 37.6 mmol) at -4 °C. After 16 h of refluxing, the reaction mixture was cooled to 0 °C and 50 mL of an aqueous solution of HCl (4 M) was added slowly. After dichloromethane (500 mL) extraction, the organic layer was washed twice with 50 mL of an aqueous solution of HCl (4 M). The solvent was removed under reduced pressure and the resulting residue was dissolved in 200 mL of chloroform. The insoluble material was removed by filtration and the chloroform was removed under reduced pressure giving a white solid which was purified by recrystallization in ethanol. Thus, pure compound **5-a** (3.06 g, 82%) was obtained as a white solid. mp: 227 °C (decomp.). IR (CHCl₃): ν 3660 to 3120, 1480 cm⁻¹. ¹H NMR (CDCl₃) δ 0.91 (s, 27H), 1.28 (s, 27H), 3.30 (s, 6H), 3.43 (s, 6H), 3.47 (s, 9H), 3.92 (s, 12H), 6.65 (s, 6H), 7.13 (s, 6H). ¹³C NMR (CDCl₃) 30.90, 31.36, 31.64, 34.12, 34.15, 34.31, 60.33, 61.73, 75.23, 124.4, 127.2, 133.1, 133.2, 145.8, 146.2, 153.2, 153.4. Anal. Calcd for C₇₅H₁₀₂O₉, 2 EtOH: C, 76.54; H, 9.27. Found: C, 76.74; H, 9.04.

5,11,17,23,29,35-Hexa-tert-butyl-37,39,41-trimethoxy-38,40,42-tris(2-tosylethoxy)calix[6]arene 6-a. TsCl (0.997 g, 5.23 mmol) was added to a solution of **5-a** (1.00 g, 0.87 mmol) in 1 mL of anhydrous CHCl₃ then, at -10 °C, anhydrous pyridine (3.0 mL, 36.79 mmol) was slowly added under vigorous stirring. The flask containing the reaction mixture was placed in a freezer at -20 °C for 16 h. The solvents were removed under high vacuum and 10 mL of ethanol were added to the crude

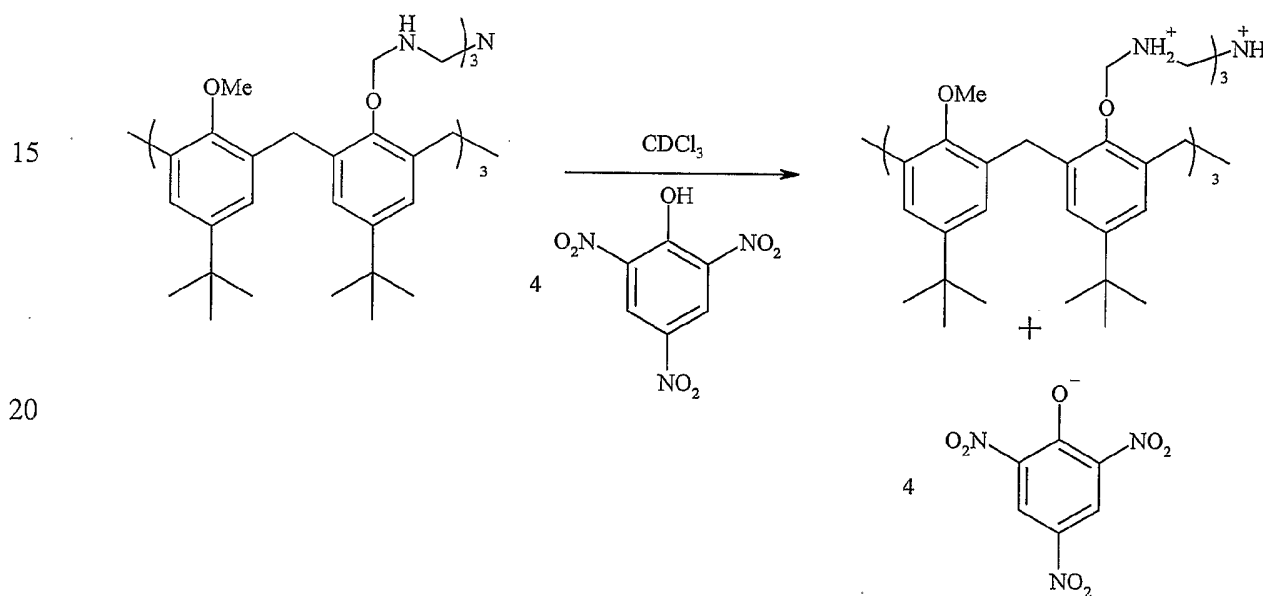
residue. The resulting solid was isolated by filtration and washed twice with cold ethanol yielding compound **6-a** (1.20 g, 86 %) as a white solid. mp: 153-154 °C. IR (CHCl₃): ν 1598, 1482, 1361, 1175 cm⁻¹. ¹H NMR (CDCl₃) δ 0.74 (s, 27H), 1.37 (s, 27H), 2.07 (s, 9H), 2.37 (s, 9H), 3.29 (d, J = 15.6 Hz, 6H), 4.11 (t, J = 4.7 Hz, 6H), 4.40 (d, J = 14.9 Hz, 6H), 4.42 (t, J = 4.7 Hz, 6H), 6.58 (s, 6H), 7.21 (s, 6H), 7.28 (d, J = 7.8 Hz, 6H), 7.82 (d, J = 7.8 Hz, 6H). ¹³C NMR (CDCl₃) 21.77, 29.67, 31.18, 31.76, 34.06, 34.36, 60.05, 68.97, 70.16, 123.7, 128.1, 130.1, 132.9, 133.5, 145.2, 146.0, 146.3, 151.1, 154.4. Anal. Calcd for C₉₆H₁₂₀O₁₅S₃, 2 H₂O: C, 70.04; H, 7.59. Found: C, 70.37; H, 7.22.

Capped calix[6]arene 7-a. Cs₂CO₃ (0.815 g, 2.50 mmol) was added to a solution of **6-a** (1.152 g, 0.715 mmol) in 25 mL of anhydrous DMF at room temperature. The reaction mixture was vigorously stirred and a solution of **2-a** (0.506 g, 0.721 mmol) in 25 mL of anhydrous DMF was slowly added (for 1h) at room temperature. After 2 h at room temperature the reaction mixture was heated at 90 °C for 16 h. The DMF was removed under reduced pressure and 50 mL of water were added. After dichloromethane extraction and concentration, a flash chromatography (dichloromethane/EtOAc, 99:1 then 98:2) afforded **7-a** (0.398 g, 31 %) as a yellow solid. An analytical sample was obtained by recrystallization in a mixture of EtOH/CHCl₃. mp: 264 °C (decomp.). IR (CHCl₃): ν 1546, 1481, 1372, 1167 cm⁻¹. ¹H NMR (CDCl₃) δ 0.87 (s, 27H), 1.34 (s, 27H), 2.40 (s, 9H), 2.88-3.05 (m, 6H), 3.06 (d, J = 14.1 Hz, 6H), 3.89-4.10 (m, 12H), 4.11-4.20 (m, 6H), 4.37 (d, J = 14.1 Hz, 6H), 6.88 (s, 6H), 7.20 (s, 6H), 7.22-7.50 (m, 9H), 8.27 (d, J = 7.8 Hz, 3H). ¹³C NMR (CDCl₃) 28.73, 31.08, 31.76, 34.22, 34.37, 48.67, 49.10, 54.69, 61.20, 73.48, 115.4, 123.8, 124.0, 127.7, 131.3, 132.4, 133.1, 133.3, 133.6, 133.9, 146.3, 146.5, 147.8, 150.0, 154.5. Anal. Calcd for C₉₉H₁₂₃N₇O₁₈S₃, H₂O: C, 65.58; H, 6.95; N, 5.41. Found: C, 65.82; H, 7.18; N, 5.88.

X₆Me₃tren 8-a. Na₂CO₃ (0.604 g, 5.70 mmol) was added to a solution of **7-a** (0.641 g, 0.357 mmol) in 30 mL of anhydrous DMF at room temperature. The reaction mixture was vigorously stirred and thiophenol (0.293 mL, 2.85 mmol) was added leading to a greenish coloration. After 24 h at 50 °C, the DMF was removed under reduced pressure and 50 mL of an aqueous solution of NaOH (1M) were added. After dichloromethane extraction and concentration, the resulting residue was dissolved in 3 mL of dichloromethane and 5 mL of acetonitrile were added. The resulting precipitate

was isolated by suction filtration and washed twice with acetonitrile giving **8-a** (0.330 g, 75 %) as a white solid. mp: 251-252 °C (decomp.). IR (CHCl₃): ν 3660 to 3110, 1480 cm⁻¹. ¹H NMR (CDCl₃) δ 1.06 (s, 27H), 1.08 (s, 27H), 2.58 (m, 6H), 2.82 (m, 6H), 2.92 (m, 6H), 3.05 (s, 9H), 3.41 (d, J = 14.9 Hz, 6H), 3.92 (m, 6H), 4.49 (d, J = 14.9 Hz, 6H), 6.93 (s, 6H), 7.04 (s, 6H). ¹³C NMR (CDCl₃) 30.08, 31.44, 31.49, 34.17, 34.24, 48.80, 49.79, 55.25, 61.00, 73.54, 125.6, 126.2, 133.2, 133.4, 145.7, 145.9, 152.4, 154.2. Anal. Calcd for C₈₁H₁₁₄N₄O₆, 2.5 H₂O, 0.5 CH₃CN: C, 75.45; H, 9.30; N, 4.83. Found: C, 75.34; H, 9.17; N, 4.78.

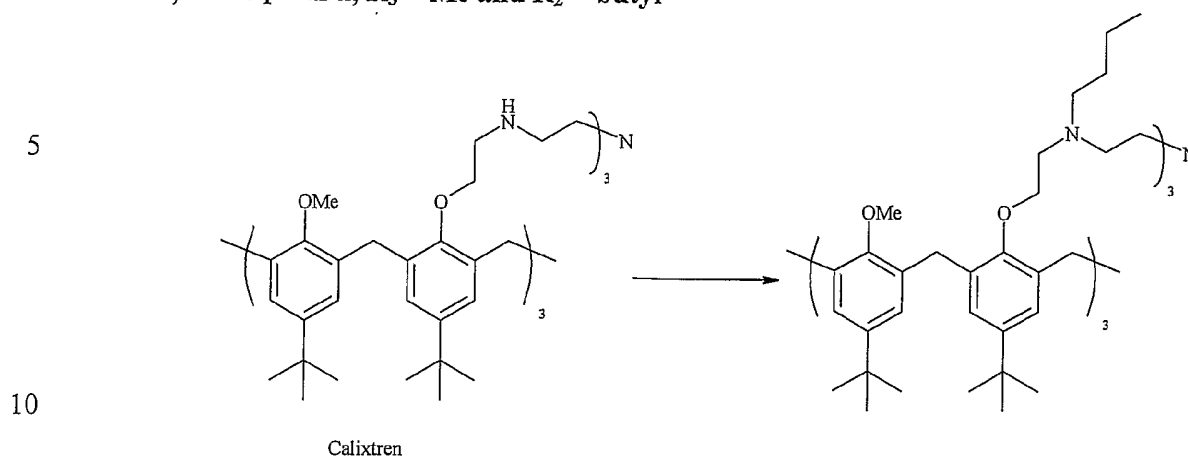
The compounds of formula **8-a** can then react with picric acid in presence of CDCl₃, according to the following reaction scheme:



The procedure is as follows: to tetramine (2.5 mg, 0.002 mmol) in 0.7 mL of CDCl₃ was added 0.24 mL (0.008 mmol) of a CDCl₃ solution (0.0338 mol.l⁻¹) of picric acid. The ¹H NMR spectra of the resulting solution was compatible with the formation of a tetrammonium salt.

¹H NMR (CDCl₃) δ 0.81 (s, 27H), 1.17 (s, 27H), 2.93 (s, 9H), 3.35 (s, 6H), 3.48 (d, J = 14.9 Hz, 6H), 3.58 (s, 6H), 3.89 (s, 6H), 4.20 (d, J = 14.1 Hz, 6H), 4.34 (s, 6H), 6.66 (s, 6H), 7.12 (s, 6H), 8.97 (s, 8H).

Process of preparation of compound of formula (III) wherein $X = N$, $m = n = 2$, $R = R_1 = tBu$, $R_3 = Me$ and $R_2 = butyl$



This compound is prepared from compound **8-a** (Calixtren).

Experimental section

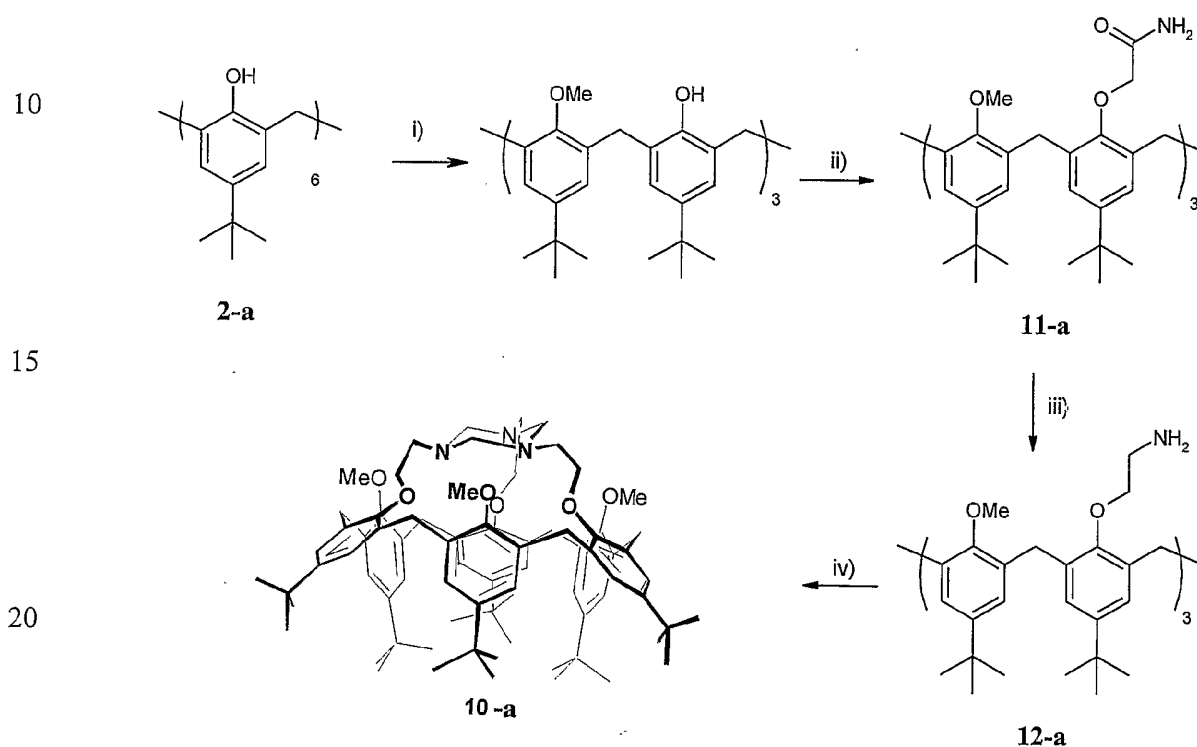
Under an inert atmosphere, butyraldehyde (0.020 mL, 0.099 mmol) was added to a solution of calixtren (**8-a**) (20.5 mg, 0.017 mmol) in 1 mL of anhydrous dichloromethane. After 1 h at room temperature, the reaction mixture was cooled at 0°C and $NaBH(OAc)_3$ (54 mg, 0.255 mmol) was added. After 15 h at room temperature, 5 mL of dichloromethane and then 5 mL of a saturated aqueous solution of $NaHCO_3$ were added. The reaction mixture was stirred 15 min and the aqueous layer was extracted twice with 10 mL of dichloromethane. The dichloromethane was removed under reduced pressure and 1 mL of ethanol was added to the crude residue. The resulting white solid was isolated by centrifugation and the washing process was repeated one more time. Thus 21.5 mg (90 % yield) of the final product as a white solid were obtained.

1H NMR (200 MHz, $CDCl_3$) δ 0.79 (s, 27H), 0.91 (t, $J = 7.0$ Hz, 9H), 1.21-1.58 (m, 12H), 1.40 (s, 27H), 2.30 (s, 9H), 2.55-2.72 (m, 6H), 2.62 (t, $J = 8.1$ Hz, 6H), 2.80-2.92 (m, 6H), 3.15 (t, $J = 6.3$ Hz, 6H), 3.37 (d, $J = 15.6$ Hz, 6H), 4.21 (t, $J = 5.5$ Hz, 6H), 4.64 (d, $J = 14.9$ Hz, 6H), 6.73 (s, 6H), 7.29 (s, 6H).

II - Synthesis of compound 10-a ($R = R_1 = tBu$, $R_3 = Me$)

Compound **10-a** is a compound of formula (II) wherein $p = 2$, $R_3 = Me$ and $R = R_1 = tBu$.

Compound **10-a** was synthesized in 2 steps with a yield of 85 % from calix[6]arene **11-a**, which is itself obtained in two steps according to a process described in literature (Janssen, R. G. et al. *Synthesis* (1993) 380-385) from *p*-*t*Bu-calix[6]arene **2-a**:



i) *Lit.* (Janssen, R. G. et al. *Synthesis* (1993) 380-385)

ii) Bromoacetamide, NaH, THF, reflux, 91%.

iii) BH_3 /THF, reflux then EtOH, reflux, 95%.

iv) HCHO aq., $CDCl_3$, $0^\circ C$ then rt, 89%.

Experimental section

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris(carbamoylmethoxy)calix[6]arene 11-a. A solution of **2** (2.435 g, 2.40 mmol) in 20 mL of anhydrous THF was added to a solution of NaH (60% in oil, 0.335 g, 8.37 mmol) in 80 mL of anhydrous THF. The reaction mixture was stirred for 20 min at room temperature and a solution of bromoacetamide (2.005 g, 14.5 mmol) in 10 mL of

anhydrous THF was introduced. After 24 h of refluxing, the solvent was removed under reduced pressure and the resulting residue was dissolved in dichloromethane and washed with 25 mL of an aqueous HCl solution (1M). After dichloromethane extraction and solvent evaporation, the resulting crude compound was purified by flash chromatography (acetone/dichloromethane; 3:7) giving pure $X_6Me_3Amide_3$ **11-a** (2.59 g, 91%) as a white solid. mp: 201 °C (decomp.). IR (CHCl₃): ν 1673 cm⁻¹. ¹H NMR (CDCl₃) δ 0.94 (s, 27 H, *t*Bu), 1.30 (s, 27H, *t*Bu), 3.60 (s, 9H, OCH₃), 3.86 (s, 18H, ArCH₂Ar, OCH₂), 5.09 (s, 6H, NH₂), 6.55 (s, 6H, ArH), 7.17 (s, 6H, ArH). ¹³C NMR (CDCl₃) δ 31.2, 31.5, 34.0, 34.3, 59.7, 71.5, 124.4, 127.6, 132.9, 146.0, 147.2, 152.1, 153.2, 171.0. Anal. Calcd for C₇₅H₉₉N₃O₉, 2 H₂O: C, 73.68; H, 8.49; N, 3.44. Found: C, 73.71; H, 8.17; N, 3.52.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris(2-aminoethoxy)calix[6]arene 12-a. A solution of BH₃/THF (78.0 mL, 1M) is slowly added to triamide **11-a** (3.18 g, 2.70 mmol) and the medium is heated under reflux for 24h. Ethanol is added slowly at 0°C until the release of gas ends. After evaporation of the solvent under reduced pressure, 108 mL of ethanol are added to the residue and the reaction medium is heated under reflux for 48h. After evaporation of the ethanol under reduced pressure, the solid residue is vacuum-dried at 50°C for 48h to give triamine **12-a** pure (2.92 g, 95 %) as a white solid. FP: 180 °C (decomp.). RMN ¹H (CDCl₃) δ 1.00 (s, 27 H, *t*Bu), 1.22 (s, 27H, *t*Bu), 2.66 (s, 9H, OCH₃), 2.90 (s, 6H, CH₂N), 3.66 (s, 6H, CH₂O), 3.94 (s, 12H, ArCH₂Ar), 6.84 (s, 6H, ArH), 7.09 (s, 6H, ArH). RMN ¹³C (CDCl₃) δ 29.9, 31.1, 31.5, 34.0, 34.2, 60.3, 61.4, 133.0, 133.2, 145.8, 146.0. IR (CHCl₃): ν 2960, 1480, 1203 cm⁻¹.

Compound 10-a. An aqueous solution (30%) of formaldehyde (0.050 mL, 0.54 mmol) is added at 0°C to a solution of triamine **12-a** (66 mg, 0.057 mmol) in 1 mL of CDCl₃. The temperature of the reaction is allowed to increase slowly until room temperature and the evolution of the reaction is followed by ¹H RMN. After 50 min, 1 mL water is added, the organic phase is separated and the aqueous phase is extracted with chloroform. The organic phases are sampled, the solvent is evaporated under reduced pressure and the obtained residue is recrystallised in a mixture CHCl₃/acetonitrile to give the compound **10-a** pure (60 mg, 89%) as a white solid. RMN ¹H (CDCl₃) δ 0.73 (s, 27 H, *t*Bu), 1.37 (s, 27H, *t*Bu), 2.66 (s, CH₂N), 3.22 (s,

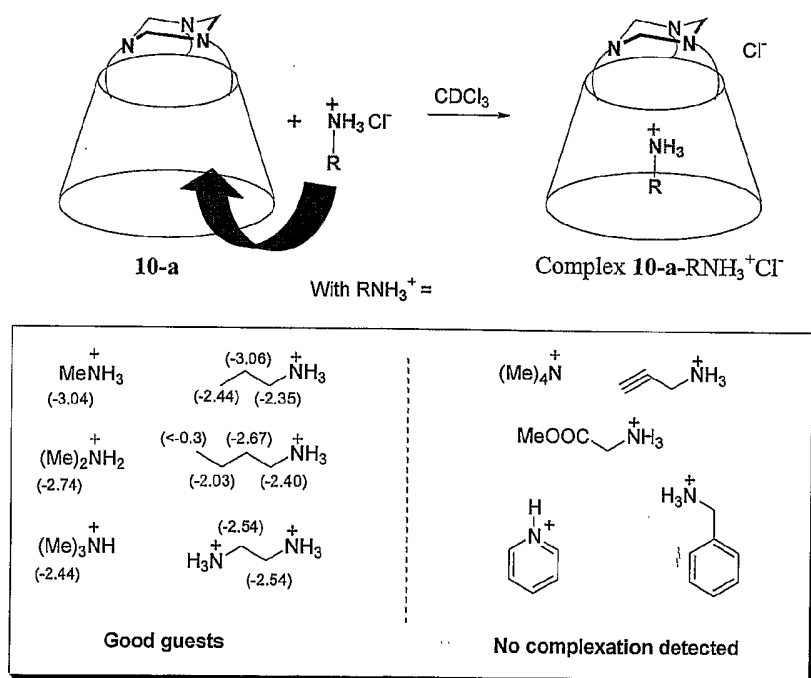
6H, CH₂O), 3.38 (d, $J = 16$ Hz, 6H, Ar- α -CHeq), 3.75 (s, 9H, OCH₃), 3.78 (d, $J \sim 10$ Hz, 3H, NCH₂N), 4.04 (d, $J = 12$ Hz, 3H, NCH₂N), 4.59 (d, $J = 16$ Hz, 6H, Ar- α -CHax), 6.53 (s, 6H, ArH), 7.26 (s, 6H, ArH). ¹³C NMR (CDCl₃) δ 29.70, 31.17, 31.64, 33.88, 34.16, 52.95, 60.18, 69.56, 70.34, 122.9, 127.9, 132.7, 132.8, 145.0, 145.2, 152.5, 155.1. IR (CHCl₃): ν 3018 cm⁻¹.

III – Properties of the compounds of the invention

These new compounds can be used as ligands to coordinate a metal ion. They also have host-guest properties (neutral or charged molecules recognition).

With the aim of building biomimetic artificial receptors, the host-guest chemistry of calixarenes toward ammonium cations has been extensively studied the past decade (C. D. Gutsche, *Calixarenes Revisited*, *Monographs in Supramolecular Chemistry*, 1998, J. F. Stoddart, Ed. The Royal Society of Chemistry, Cambridge, U.K.). However, on one hand, the hydrophobic cavity of calix[4]arenes is too small for the inclusion of guest ammoniums and these macrocycles have only been used as a platform for the preorganization of a binding site (Tuntulani, T. et al. *Tetrahedron*, 2002, **58**, 10277-10285). On the other hand, larger calixarenes have been scarcely studied since, in order to act as efficient receptors, their flexibility have to be restricted. Indeed, the importance of the rigidification of the calixarene core in the recognition process of ammoniums has already been pointed out (Takeshita, M. et al. *J. Org. Chem.* 1994, **59**, 4032-4034; Casnati, A. et al. *Tetrahedron* (1995) **51**, 591-598; Chen, Y. et al. *Tetrahedron* (1998) **54**, 15183-15188; Sansone, F. et al. *Tet. Lett.* (1999) **40**, 4741-4744; Arduini, A. et al. *Eur. J. Org. Chem.* (2000) 2325-2334; Chen, Y. et al. *Chem. Lett.* (2000) 484-485; Li, J.-S. et al. *Eur. J. Org. Chem.* (2000) 485-490). Thus, the goal of the invention is to design new receptors based on a calix[6]arene core larger enough for the inclusion of small molecules and possessing a cage structure through rigidification by an aza-crown cap. It was observed that the tripodal aza-crown cap prevents ring inversion, constraining the calixarene core in a straight cone conformation ideal for host-guest chemistry. The new compounds of the invention C_{3v}-symmetrical calix[6](aza)crown are useful for the complexation of ammoniums through cation- π interactions.

Host behavior of receptor 10-a toward ammoniums. ^1H NMR complexation studies were carried out at room temperature by introducing excess of solid ammoniums chloride ($\text{RNH}_3^+\text{Cl}^-$) in a solution of **10-a** in CDCl_3 . Thus, addition of $\text{MeNH}_3^+\text{Cl}^-$ to receptor **10-a** led to a new C_{3v} -symmetrical compound including one equivalent of the cationic ammonium species in the hydrophobic cavity. Indeed, besides free $\text{MeNH}_3^+\text{Cl}^-$, a sharp quadruplet corresponding to the methyl group of the ammonium included in the heart of the cavity was detected at -0.25 ppm while the NH_3^+ resonance was observed at *ca.* 4.9 ppm (Figure 4-b). This first result shows the remarkable affinity of the receptor **10-a** towards cationic ammonium species since at room temperature the complexation-decomplexation process is slower than the NMR time scale. Similar complexation experiments were conducted with other ammoniums and the results are summarized in Scheme 4. When separated signals were observed at 298 K in CDCl_3 for the included and free ammoniums, the ammoniums was considered as a good guest.



Scheme 4. ^1H NMR complexation study between **10-a** and various ammoniums $\text{RNH}_3^+\text{Cl}^-$. The observed $\Delta\delta$ shifts are indicated in brackets next to the corresponding atoms [$\Delta\delta = \delta(\text{complexed ammonium}) - \delta(\text{free ammonium})$; peaks overlapping caused sometimes an absence of a precise determination].

In all cases, complexation of a given ammonium species led to NMR spectra with similar profiles for the calixarene core suggesting that its conformation should not

deeply change upon the nature of the guest. Indeed, a downfield shift of the CH_2N and CH_2O resonances belonging to the arms and an important upfield shift of one of the two signals corresponding to the NCH_2N protons was observed in all cases (see Figures 4-a and 4-b for an example).

5 The upfield shifts measured for the proton resonances of the included ammoniums can indicate its spatial position in the aromatic cavity. Thus, the protons at the α - and β -position of the nitrogen atom display the higher shift values suggesting that they sit in the centre of the cavity. These data are compatible with the establishment of π -cationic interactions between the aromatic ring and the positively charged nitrogen atom.

10 **Complexation studies between 10-a and ammonium chlorides.** Excess of the ammonium chlorides were added in an NMR tube containing **10-a** in CDCl_3 . Sonification was used when the ammonium chloride revealed extremely insoluble in CDCl_3 . ^1H NMR spectra were recorded at room temperature.

15 **Complexation of neutral molecules by (8-a). Zn^{2+}**

The formation of a mononuclear complex of Zn-hydroxo **13** type was demonstrated by ^1H RMN when the ligand **8-a** is in presence of Zn^{2+} ions. Contrary to what is usually obtained with the already known similar complexes, no formation of polynuclear complexes was observed when ZnCl_2 was used for the complexation. This shows that the presence of an aza-crown cap protects the metal ion from the external medium and constrains it in a mononuclear environment.

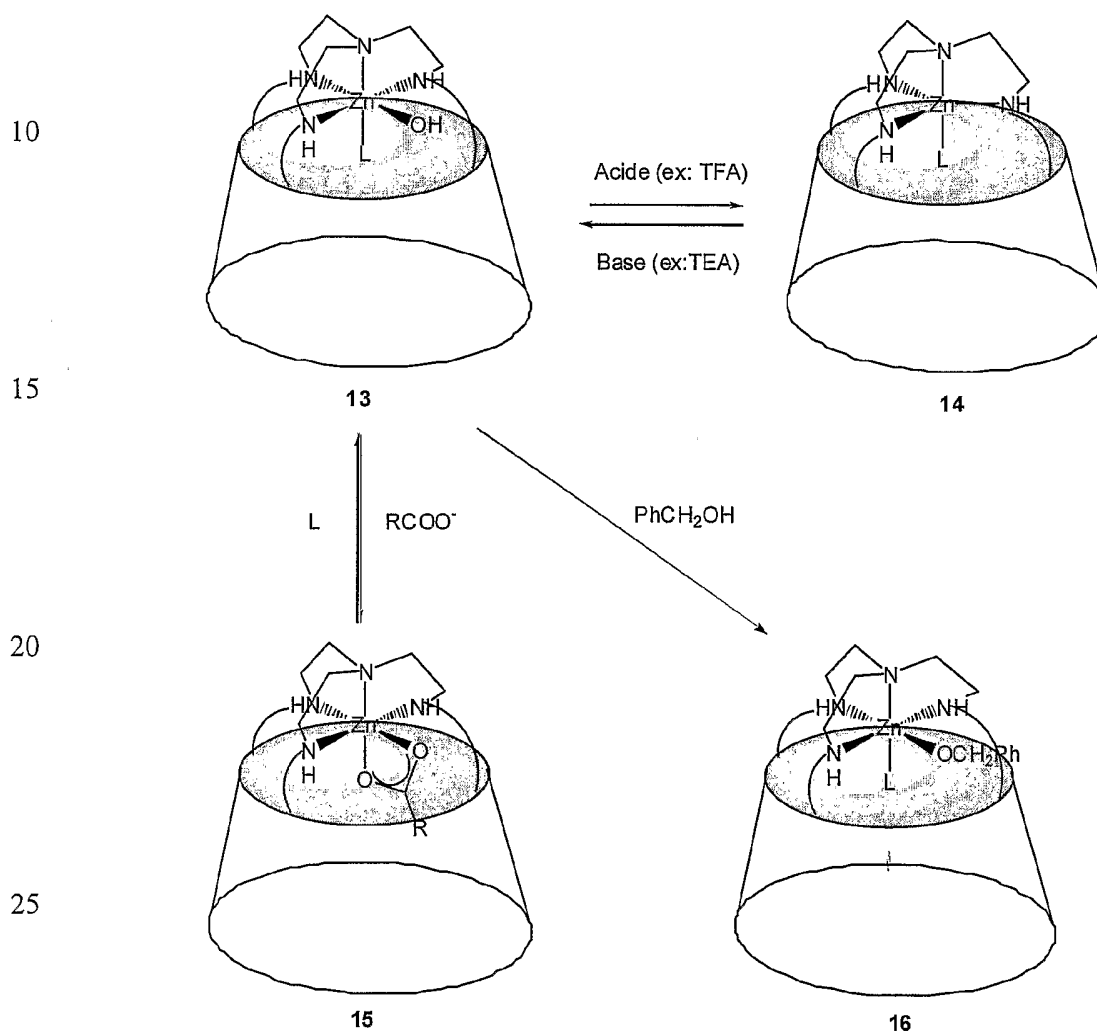
20 The complex **13** is in equilibrium with its acid form **14** and the equilibrium can be moved according to the pH. Thus, the addition of an acid such as trifluoroacetic acid (TFA) moves the equilibrium towards species **14** and the subsequent addition of a base such as triethylamine (TEA) moves again the equilibrium towards the initial form **13**.

25 The presence of neutral molecules (L) into the hydrophobic cavity was studied by ^1H RMN. In fact, the addition of small neutral molecules (examples: alcohols, amines I, aldehydes, imidazoles, nitriles, etc...) to the complexes **13** or **14** leads to their coordination with the metal ion in the centre of the cavity.

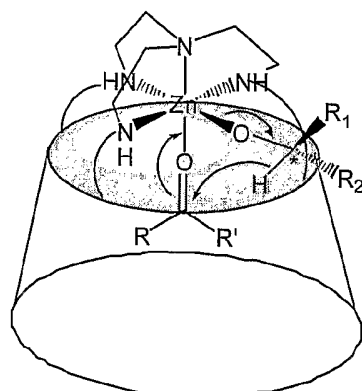
30 Furthermore, it was demonstrated that the addition of a strong base ($n\text{Bu}_4\text{OH}$) or of a strong acid (TFA) on complex **13** does not imply the decomplexation of the metal contrary to what was observed with the similar complexes that are known until now.

The addition of a carboxylate $\text{RCOO}^{(-)}$ to the complex **13** leads to the formation of a new complex **15** in equilibrium. The carboxylate anion inside the cavity coordinates on a divalent way the metal ion. This new complex **15** does not act any more as a receptor for neutral guest molecules (L). However, the addition of guest molecules L to the complex **15** can move the equilibrium towards the formation of the complex **13**.

It has also been shown that the addition of benzylic alcohol (PhCH_2OH) on complex **13** led to its coordination inside the cavity (complex **16**).



The complexes **13** and **16** are particularly interesting as they can be used in catalysis. Thus, these complexes are very good biomimetic models for enzymes such as peptidases or esterases. These complexes can be used for the catalysis of hydrolysis reactions or of enantioselective transfer of hydrides.



Complexation of cations

The interaction of ligands **8-a** and **10-a** with ammonium cations was shown by ^1H RMN.

It was shown that the ligand **10-a** can complex ammoniums derived from amine I such as MeNH_3^+ , PrNH_3^+ , BuNH_3^+ , but also derived from amine II such as Me_2NH_2^+ , but also derived from amine III such as Me_3NH^+ or bis-ammoniums such as $\text{H}_3^+\text{NCH}_2\text{CH}_2\text{NH}_3^+$. In each case, the ligand affinity for the ammoniums is very high as the ^1H RMN analysis shows two distinct signals for the free form of the ammonium and for its form as a complex.

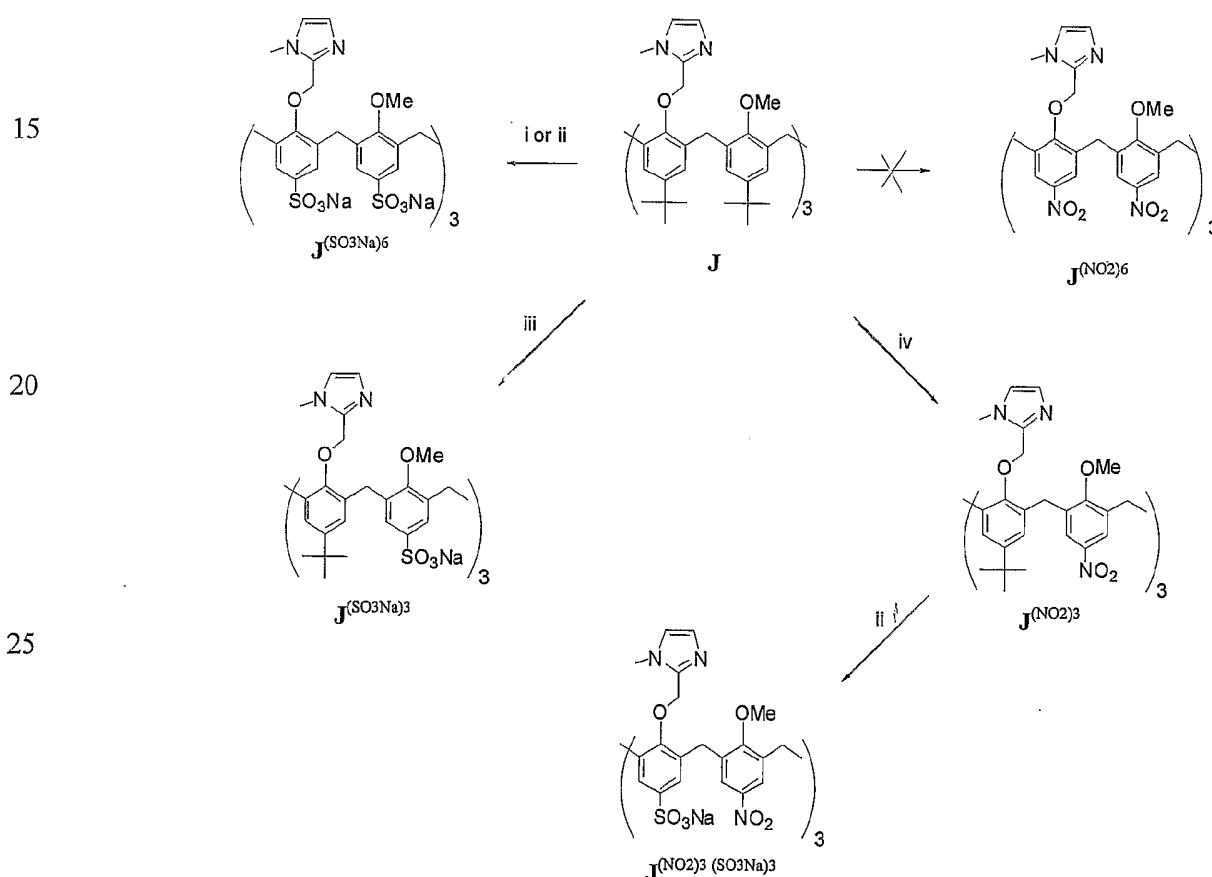
Complexation of anions

The nitrogen atoms of the cap of the ligands of the invention can readily be protonated or alkylated (by MeI) to obtain the corresponding ammoniums. These polyammoniums are very good candidates for the anion complexation.

IV – Process of preparation of water-soluble compounds

In the past few years, some novel supramolecular coordination chemistry based on the assembly of a transition metal ion has been developed with a calix[6]arene-based tris-imidazolyl ligand that acts as a funnel for a neutral guest molecule interacting with the metal centre. Recently, it was shown that these biomimetic organo-soluble systems could be transposed in water thanks to the selective introduction of three sulfonate groups on the large rim of the calixarene structure. The disymetrisation of the large rim

was achieved at the level of a calixarene presenting mixed phenol/anisol units in alternate position. After the selective removal of three *t*Bu groups with AlCl_3 , the free positions needed to be protected by bromine substituents since the sulfonation step with H_2SO_4 is known to be a non selective process. Indeed, the only selective *ipso* reaction reported so far is nitration of partially *O*-alkylated calixarenes that preferentially react in *para* position of the phenol units. The present inventors have described the first examples of selective *ipso* reactions that allow the disymetrisation of the large rim of a fully *O*-alkylated calixarene. The methodology is of wide utility as it allows the direct replacement of *t*Bu groups by either sulfonato or nitro substituents in specific positions of the calixarene structure. This opens the route for a new range of water soluble derivatives bearing ammonium, sulfonate or sulfonamide groups.



Scheme 5. Selective Functionalization of Calix[6]arenes at the Large Rim. Conditions: i) H_2SO_4 , then aq. NaOH; ii) HSO_3Cl , CH_2Cl_2 , reflux; then aq. NaOH; iii) HSO_3Cl , CH_2Cl_2 , RT; then aq. NaOH; (iv) HNO_3/HOAc , CH_2Cl_2 , RT.

Since sulfuric and nitric acids are the only two reagents that are known to be efficient for the *ipso* reaction on *t*Bu-calixarenes, they were tested on the tris-imidazole based ligand **J**. Indeed, when **J** was heated in conc. H₂SO₄ at 60 °C, *ipso* sulfonation took place on all phenolic units. The corresponding hexa-sulfonated product **J**^{(SO₃Na)₆} was isolated after a basic treatment with aq. NaOH (Scheme 5). Shortening the reaction time or lowering the temperature did not allow to isolate any intermediate that would be only partially sulfonated. The new hexa-anionic ligand **J**^{(SO₃Na)₆} was highly soluble in water and its ¹H-NMR spectrum in D₂O attested to a major cone conformation as its organo-soluble parent **J**.

In strong contrast, reacting **J** with nitric acid in excess leads to its partial *ipso* nitration. When the reaction was initiated at 0°C in a 1:1 (v/v) mixture of fuming HNO₃ and glacial AcOH in dry CH₂Cl₂, then continued at room temperature for 1 hour, a tris-nitrated compound (**J**^{(NO₂)₃}) was isolated in 80% yield (Scheme 5). On the other hand, increasing either the reaction time, the temperature or the concentration of the reagents did not allow to isolate the corresponding hexa-nitrated product. Such harsher experimental conditions actually lead to the decomposition of the compounds.

The ¹H NMR spectrum of **J**^{(NO₂)₃} in CDCl₃ displayed a very simple profile with a unique resonance for the *t*-Bu substituents that integrated for 27 protons. The formation of this C_{3v} symmetrical compound must thus result from the selective *ipso* nitration on alternate position at the lower rim of the calixarene. Due to the relative broadness of the peaks, probably related to some conformational fluxionality, the exact position of the remaining *t*-Bu groups could not be determined by NMR C_T-H correlaton experiments directly run on **J**^{(NO₂)₃}. In order to rigidify the calixarene structure, the corresponding zinc complex [**J**^{(NO₂)₃}.Zn](ClO₄)₂ was prepared by reacting 1 equivalent of Zn(ClO₄)₂.6H₂O with **J**^{(NO₂)₃} in THF. The ¹H NMR spectrum of the Zn complex, recorded in CD₃CN, displayed very well defined and narrow resonances, in agreement with the formation of a tetrahedral dicationic species with an average C_{3v} symmetry (Scheme 6). We have previously shown with this family of complexes that the phenolic units necessarily adopt an alternate *in* and *out* position, projecting their *O*-substituent in opposite direction. The normal chemical shifts for the *t*-Bu and methoxy groups (δ = 1.43 and 3.78 ppm, respectively) observed for complex [**J**^{(NO₂)₃}.Zn](ClO₄)₂ indicates that they all are situated in out-position relatively to the calixarene cavity. This suggests

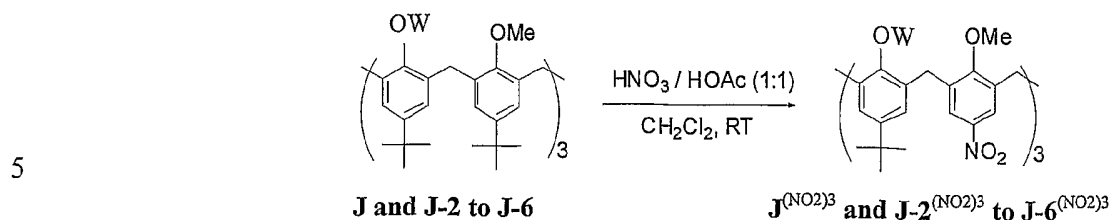
that the methoxy and *t*-Bu groups are not linked to the same phenol units. This was indeed confirmed by HMQC and HMBC NMR experiments, which allowed the assignment of each proton and carbon of the complex. Hence, it was possible to deduce that nitration selectively proceeded in *para* position of the three anisole units.

5

Willing to test other acidic reagents for a possible selective functionalization at the lower rim of the calixarene, the reaction was tried with HSO₃Cl, in spite of the fact that there is no example of *ipso* reaction on calixarenes with this reagent reported so-far. Indeed this reagent is smoother than H₂SO₄, and selective chlorosulfonation with partially *O*-alkylated calixarenes has been reported. When **J** was treated with HSO₃Cl in dry CH₂Cl₂ at room temperature, selective *ipso* chlorosulfonation took place at the *t*-Bu groups situated in *para* position to the methoxy substituents (Scheme 5). Because the resulting chlorosulfonyl derivative **J**^{(SO₂Cl)₃} underwent irreversible (and unidentified) decomposition processes within a few hours, it was directly hydrolyzed by aq. NaOH to the corresponding tri-sulfonate **J**^{(SO₃Na)₃}. The characterization of the compound was carried out in the exact same way as for the tris-nitrated product. The ¹H NMR profile indicated that the *ipso* reaction took place in alternate phenolic positions. The ¹H NMR analysis of the corresponding Zn complex confirmed that, as in the case of the nitration, the anisole units were those who underwent the substitution process. In contrast with the *ipso* nitration process however, *per*-chlorosulfonation could be carried out on the same starting material **J**, provided that slightly harsher conditions were employed. When **J** was reacted with HSO₃Cl under reflux of CH₂Cl₂ instead of room temperature, the hexa-sulfonate product **J**^{(SO₃Na)₆} was obtained after NaOH hydrolysis.

As far as we know, such a selectivity for an *ipso* substitution at the large rim of the calixarene has been reported. In order to gain some insights on the reasons that drive the electrophilic reagent to preferentially attack the anisole groups than the imidazolyl-substituted phenoxy units, the reaction of nitration was tested on calix[6]arenes other than **J**, bearing various substituents instead of the imidazole groups (Scheme 6). Therefore, we synthesized calix[6]arenes functionalized in alternate position by methoxy groups (as in **J**) and primary amines (**J-2**), tertiary amines (**J-3**), amides (**J-4** and **J-5**), acids (**J-6**), esters (**J-7**), alcohols (**J-8**) or alkyl groups of similar bulkiness (**J-9**). All these compounds were submitted to the exact same experimental procedure as that described for the selective nitration of **J** (Scheme 6, Table 1). The results are collected in Table 1.

30



Scheme 6. Selective nitration of calix[6]arenes bearing various W substituents

10

Table 1. Nitration of calix[6]arenes **J** and **J-2** to **J-9** in CH₂Cl₂

Starting Material	W	Product	yield	pKa [§]
J	CH ₂ (Me-Im)	J^{(NO₂)₃}	80	ImH ⁺ /Im : 7
J-2	CH ₂ CH ₂ NH ₂	J-2^{(NO₂)₃}	55	-NH ₃ ⁺ / -NH ₂ : 10-11
J-3	CH ₂ CH ₂ NMe ₂	J-3^{(NO₂)₃}	96	-NMe ₂ H ⁺ / -NMe ₂ : 10-11
J-4	CH ₂ C(O)N(CH ₂) ₄	J-4^{(NO₂)₃}	56	-C(OH ⁺)NR ₂ / -C(O)NR ₂ : -1
J-5	CH ₂ CONH ₂	J-5^{(NO₂)₃}	62	-C(OH ⁺)NR ₂ / -C(O)NR ₂ : -1
J-6	CH ₂ CO ₂ H	J-6^{(NO₂)₃}	82	-C(OH ⁺)OH / -CO ₂ H : -6
J-7	CH ₂ CO ₂ Et	J-7^{(NO₂)_n}	*	-C(OH ⁺)OR / -CO ₂ R : -6.5
J-8	CH ₂ CH ₂ OH	J-8^{(NO₂)_n}	*	-CH ₂ OH ₂ ⁺ / -CH ₂ OH : -2
J-9	CH ₂ CH(CH ₃) ₂	J-9^{(NO₂)₆}	60	-

* A complicated mixture of polynitrated products was observed by NMR spectroscopy.

15

[§] For HNO₃ / NO₃⁻, pKa = - 1.4.

20

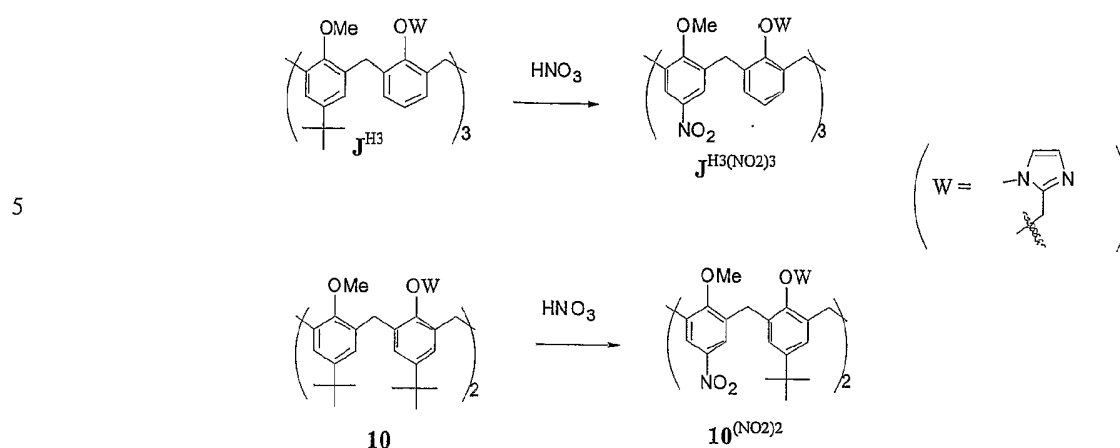
For compounds **J-2** to **J-6**, selective tris-nitration proceeded as above described for **J** and calixarenes **J-2^{(NO₂)₃}** to **J-6^{(NO₂)₃}** were isolated in 55-96% yield. The almost quantitative yield obtained with **J-3** attests to the high regioselectivity of the *ipso* substitution. The relatively moderate yields for **J-2**, **J-4** and **J-5** may be attributable to competitive degradation processes of the nitrogenous arms since no other product could be isolated. In strong contrast with these results, compound **J-9** yielded the hexa-nitrated calixarene **J-9^{(NO₂)₆}** as the sole isolable reaction product in 60% yield (Table 1). This last result is in accordance with those previously reported in the literature related to

calixarenes (Mogck, O. et al., *J. Am. Chem. Soc.* (1997) 119, 5706-5712; Jakobi, R. A. et al. *New J. Chem.* (1996) 20, 493-501; Verboom, W. et al., *J. Org. Chem.* (1992) 57, 1313-1316). Compounds **J-7** and **J-8** represent intermediate cases: a mixture of poly-nitrated products was obtained. Although for **J-7**, the tris-nitrated could clearly be identified by NMR and mass spectrometry out of the crude reaction mixture, it could not be isolated properly.

Obviously, the nature of R₁ groups plays a key role in directing the nitration positions. A possible explanation might well be related to the presence of a protonable site in γ-position of the phenolic oxygen atom. Indeed, for compounds **J** and **J-1** to **J-3**, due to their basic character, all nitrogeneous arms must be protonated under the strongly acidic reaction conditions. This protonated nitrogen group is in an ideal position for hydrogen-bonding to the phenolic oxygen atom, thereby deactivating the whole aromatic cycle towards electrophilic attack by removing electron density. Likewise, for compounds **J-4** to **J-8**, a protonable oxygen atom is situated in γ-position. According to their pK_a relative to nitric acid (see Table 1), compounds **J-6** to **J-8** are not efficiently protonated by nitric acid, whereas the amides **J-4** and **J-5** are. Therefore, these two latter are cleanly and selectively tris-nitrated, which is not the case for the ester **J-7**. The much higher acidity of the carboxylic proton in **J-6**, compared to that of the hydroxyl of alcohol **J-8**, can explain as well the selectivity of the substitution for **J-6** and not for **J-8**. In the case of **J-9**, such a deactivation process does not exist and the nitration proceeds on all phenol groups without discrimination.

Interestingly, the reaction was tested on a compound **J^{H3}** where the three tBu groups in para position of the amino arms have been removed (Scheme 7). The nitration remained selective and the tris-nitrated compound **J^{H3(NO2)3}** resulting from three ipso reactions was isolated with a relatively good yield (60%). This means that the deactivation process due to the protonation of the imidazole groups overpasses the fact that the free para position should be more reactive than the others.

Finally, the same experimental procedure applied to the calix[4]arene **J-10** analogue to **J** yielded the corresponding **J-10^{(NO2)2}** with an excellent yield (80%).



Scheme 7. Selective ipso-substitution of calixarene J^{H3} and J-10.

15 This explanation is consistent with the selectivity observed for the *ipso* chlorosulfonation with HSO_3Cl at room temperature, which also involves strong acidic conditions leading to the protonation of the imidazole groups. For this process however, the reagent (HSO_3Cl) does not present the oxidizing character of HNO_3 and increasing the temperature did not yield to the decomposition of the calixarene but rather allow the process to occur on the three other positions to provide $J^{(\text{SO}_3\text{Na})_6}$. This opened the possibility of a sequential combination of both reactions: selective nitration of J

20 followed by chlorosulfonation yielded a mixed compound $J^{(\text{NO}_2)_3(\text{SO}_3\text{Na})_3}$ where all t-Bu groups have been removed and selectively replaced by nitro and sulfonato functionalities in alternate position.

25 In conclusion, new synthetic routes leading to the selective functionalization of the large rim of calix[6]arenes are described. These allowed the direct introduction of three nitro and/or three sulfonato groups in alternate position. Such a selectivity is unprecedented and is related to the nature of the substituents R borne by the phenolic units of the calixarene. Indeed, the presence of a protonable hetero-atom in R deactivates the corresponding phenolic unit toward electrophilic substitution. It is also

30 noteworthy to mention that this is the first time that *ipso* chlorosulfonation is reported. These new routes are also remarkable because they open synthetic perspectives for selectively functionalized calix[6]arenes. Indeed the nitro groups can be easily reduced leading to amino and amido derivatives. The procedure described for the chlorosulfonation can also be used for the synthesis of sulfonamide derivatives.

Experimental

General methods: The following solvents were distilled and stored under argon: THF, from sodium benzophenone ketyl; CH₂Cl₂, from CaH₂; DMF, from CaH₂. Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were obtained with a Perkin Elmer Spectrum One apparatus. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AM-250 spectrometer at 300K (except when specified in the text). HMBC, HMQC experiments were performed on a Bruker AM-500 spectrometer. Electrospray mass spectra (ESMS) were recorded with a Thermo Finnigan LCGTM Duo system by direct sample introductions. Elemental analyses were carried out by the Service de Microanalyse, I.C.S.N., Gif-sur-Yvette.

J (Seneque, O. et al., *Journal of the American Chemical Society* (2000) **122**, 6183-6189), **J-2** (compound **12-a** such as defined previously), **J-3** (Seneque, O. et al., *European Journal of Inorganic Chemistry* (2001) **10**, 2597-2604), **J-5** (compound **11-a** such as defined previously) and **J-6** (Casnati, A. et al., *J. Chem. Soc. Chem. Commun.* (1991) 1413-1414; van Duynhoven, J. P. M. et al., *J. Am. Chem. Soc.* (1994) **116**, 5814-5822; Araki, K. et al., *Chem. Lett.* (1994) 1251-1254) were prepared.

5,17,29,11,23,35-Hexa-tert-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-pyrrolidinedecarbonyl)-methoxy]calix[6]arene (J-4): (COCl)₂ (1 mL, 11.45 mmols, 27.2 eq.) was added to a solution of **J-6** (500 mg, 0.42 mmol) in anhydrous CH₂Cl₂ (40 mL) under argon. After 4 h at reflux, the mixture was evaporated under vacuum to dryness. The resulting crude product was dissolved in anhydrous benzene (40 mL), cooled to 0°C and a solution of pyrrolidine (117 µL, 1.39 mmol, 3.3 eq.) and Et₃N (538 µL, 3.78 mmols, 9 eq.) in benzene (40 mL) was added dropwise. After 24 h at room temperature, the organic layer was washed with water (2 × 50 mL), dried (MgSO₄) and evaporated to dryness. The crude product was purified by crystallization (CHCl₃/MeOH) to yield **J-4** as a colourless solid (567.8 mg, 100%). Mp: 257-259 °C. ¹H NMR (250 MHz, CDCl₃): δ 7.21 (s, 6H, Ar), 6.61 (s, 6H, Ar), 4.55 (s, 6H, OCH₂CO), 4.46 (d, 6H, *J* = 8.9 Hz, ArCH₂Ar), 3.74 (m, 6H, NCH₂), 3.68 (m, 6H, NCH₂), 3.43 (d, 6H, *J* = 8.9 Hz, ArCH₂Ar), 2.19 (s, 9H, OCH₃), 1.91 (m, 6H, CH₂), 1.87 (m, 6H, CH₂), 1.37 (s, 27H, *t*-Bu), 0.76 (s, 27H, *t*-Bu). Anal. calcd for **J-4**·2H₂O (C₈₇H₁₂₁N₃O₁₁, 1383.90): C 75.45, H 8.81, N 3.03; Found: C 75.54, H 8.31, N 2.78.

5,11,17,23,29,35-Hexa-tert-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-methylpropyloxy)-calix[6]arene (J-5): A solution of 1,3,5-trimethoxy-*p*-tert-butyl calix[6]arene (Janssen, R. G. et al., *Synthesis* (1993) 380-386)(155 mg, 0.15 mmol) in

anhydrous THF (3 mL) was added under argon to a mixture of NaH (60%, 177 mg, 4.5 mmols, 30 eq., washed with pentane prior to use), in THF (3 mL) and DMF (1.5 mL). After 15 min. at rt., (CH₃)₂CHCH₂I (170 µL, 1.48 mmol, 10 eq.) was added. After 7 days at reflux, the usual workup with CH₂Cl₂/H₂O gave the crude product that was filtered over silica gel using EtOAc/cyclohexane (3:7) to give **J-5** as a colourless solid (152 mg, 92%). Mp: 191-193 °C. ¹H NMR (250 MHz, CDCl₃): δ 7.26 (s, 6H, Ar), 6.67 (s, 6H, Ar), 4.49 (bs, 6H, ArCH₂Ar), 3.62 (d, 6H, *J* = 6.4 Hz, OCH₂), 3.50 (bs, 6H, ArCH₂Ar), 2.27 (s, 9H, OCH₃), 2.18 [m, 3H, CH(CH₃)₂], 1.37 (s, 27H, *t*-Bu), 1.09 [d, 18H, *J* = 6.7 Hz, CH(CH₃)₂], 0.82 (s, 27H, *t*-Bu). Anal. calcd for **J-5**·2H₂O (C₈₁H₁₁₈O₈, 1219.80): C 79.82, H 9.75; Found: C 79.79, H 9.75.

5,17,29-Tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene (J^{H3}): A solution of 5,17,29-tri-*tert*-butyl-37,39,41-tri-hydroxy-38,40,42-trimethoxycalix[6]arene [van Duynhoven, 1994 #37] (300 mg, 0.35 mmol) was added under argon to a mixture of NaH (60% in oil, 420 mg, 10 mmol, 30 eq., washed with pentane prior to use), in THF (12 mL) and DMF (3 mL). After 15 min. at rt., 2-chloromethyl-1-methyl-1*H*-imidazole hydrochloride (360 mg, 2.1 mol, 6 eq) was added. After 16 h at reflux, the usual work-up with CH₂Cl₂/H₂O gave the crude product that was filtered over silica gel using CH₂Cl₂/MeOH (9:1) to give **J^{H3}** as a colourless solid (347 mg, 88%). For elemental analysis purpose, further purification was achieved by recrystallisation from acetonitrile. ¹H NMR (200 MHz, CDCl₃): δ 7.11 (s, 6H, Ar), 7.00 (s, 3H, Im), 6.87 (s, 3H, Im), 6.68 (bs, 9H, Ar), 4.90 (bs, 6H, OCH₂Im), 3.84 (bs, 12H, ArCH₂Ar), 3.61 (bs, 9H, NCH₃), 2.69 (s, 9H, OCH₃), 1.27 (s, 27H, *t*Bu). Anal. calcd for **J^{H3}**·H₂O (C₇₂H₈₆N₆O₇, 1146.66): C 75.36, H 7.55, N 7.32; Found: C 75.26, H, 7.46, N, 7.37.

Typical procedure for selective nitration: A mixture of fuming nitric acid (4.7 mL, 117 mmol) and glacial acetic acid (4.7 mL) was added dropwise under argon to a solution of hexa-*tert*-butylcalix[6]arene derivative (0.77 mmol) in anhydrous CH₂Cl₂ (78 mL) cooled to 0°C. The temperature was then allowed to rise to 25°C and the colour of the solution quickly changed from violet to orange-yellow. After 1 h at rt., the mixture was carefully poured to aq. 2.5 % ammonia (200 ml) and the organic layer was washed with water (2 × 80 mL), dried (Na₂SO₄) and evaporated to dryness. Compounds **J^{(NO2)3}** and **J-2^{(NO2)3}** to **J-7^{(NO2)3}** and **J-9^{(NO2)6}** were prepared according to this procedure.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene [J^{(NO2)3}]: from **J** (1 g, 0.77 mmol); the

crude product was filtered over silica gel using MeOH/CH₂Cl₂/conc. aq. NH₃ (5:95:0.25) as eluant to give J^{(NO₂)₃} as a pale-yellow solid (779 mg, 80%). IR: ν(NO₂) = 1518 cm⁻¹; Mp (EtOAc/C₅H₁₂): 273-274 °C. ¹H NMR (250 MHz, CDCl₃, 330K): δ 7.72 (s, 6H, Ar), 6.95 (s, 6H, Ar), 6.87 (s, 3H, Im), 6.70 (s, 3H, Im), 4.71 (s, 6H, CH₂Im), 3.79 (s, 12H, ArCH₂Ar), 3.23 (s, 9H, OCH₃), 3.16 (s, 9H, NCH₃), 1.13 (s, 27H, *t*-Bu).
 5 Anal. calcd (C₇₂H₈₃N₉O₁₃, 1281.61): C 67.43, H 6.52, N 9.83; Found: C 67.46, H 6.39, N 9.32.

[J^{(NO₂)₃}.Zn](ClO₄)₂: Zn(ClO₄)₂.6H₂O (28 mg, 0.075 mmol) was added to a solution of J^{(NO₂)₃} (100 mg, 0.078 mmol) in THF (2 mL) under Ar. After 10 min.,
 10 pentane was added, and the precipitate was filtered off and dried under vacuum (104 mg, 90 %). ¹H NMR (250 MHz, CD₃CN): δ 7.50 (s, 6H, Ar), 7.46 (s, 3H, Im), 7.09 (s, 6H, Ar), 6.96 (s, 3H, Im), 5.04 (s, 6H, CH₂Im), 4.05 (d, 6H, J_{AB} = 16.1 Hz, ArCH₂Ar), 3.78 (s, 9H, OCH₃), 3.67 (d, 6H, ArCH₂Ar), 3.62 (s, 9H, NCH₃), 1.43 (s, 27H, *t*-Bu).
 Anal. calcd for [J^{(NO₂)₃}.Zn](ClO₄)₂.4H₂O (C₇₂H₈₉Cl₂N₉O₂₄Zn, 1597.47): C 54.02, H
 15 5.60, N 7.87; Found: C 53.63, H 5.33, N 7.61.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(2-amino)ethoxy]calix[6]arene [J-2^{(NO₂)₃]}: from J-2 (100 mg, 0.087 mmol). All direct attempts to purify directly this compound failed. However, its purification could be achieved at the level of its (NH-Boc)₃-protected derivative.

Derivatization of crude J-2^{(NO₂)₃} by (Boc)₂O: (Boc)₂O (86 mg) and Et₃N (0.2 mL) were added to a solution of the crude nitrated product in CH₂Cl₂ (0.6 mL) and MeOH (1 mL). After 18 h at room temperature, H₂O (20 ml) was added and the mixture was extracted with CH₂Cl₂ (2 × 20 mL). The organic layer was dried (Na₂SO₄), evaporated to dryness, and purified by chromatography on silica gel (1:3
 25 EtOAc/cyclohexane) to give Boc-protected J-2^{(NO₂)₃} as a colourless solid (67 mg, 55% from 2). ESMS: m/z 1434 [M + Na]⁺. Anal. calcd for Boc-J-2^{(NO₂)₃}.3H₂O (C₇₈H₁₀₈N₆O₂₁, 1464.76): C 63.92, H 7.43, N 5.74; Found: C 63.74, H 7.15, N 5.48.

Boc deprotection: TFA (0.1 mL) was added to a solution of Boc-J-2^{(NO₂)₃} (30 mg) in CHCl₃ (0.9 mL). After 1 h at room temperature, NaOH (1 M, 1 mL) was added
 30 and the mixture was extracted with CH₂Cl₂ (2 × 5 mL). The organic layer was dried (Na₂SO₄) and evaporated to dryness to yield pure J-2^{(NO₂)₃}.CF₃COOH as a yellow solid. The yield was quantitative. Mp: 246-248 °C. IR: ν(NO₂) = 1522 cm⁻¹; ¹H NMR (250 MHz, CDCl₃ + NaOD): δ 7.68 (s, 6H, Ar), 7.08 (s, 6H, Ar), 3.97 (s, 12H, ArCH₂Ar),

3.53 (s, 9H, OMe), 3.40 (t, 6H, $J = 4.8$ Hz, OCH₂), 2.52 (t, 6H, NCH₂), 2.13 (bs, 6H, NH₂), 1.28 (s, 27H, *t*-Bu). Anal. calcd for **J-2**^{(NO₂)₃}.CF₃COOH (C₆₅H₇₉F₃N₆O₁₄, 1225.35): C 63.71, H 6.50, N 6.86; Found: 63.87, H 6.69, N 6.56.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris
 5 **[(N,N-dimethylamino)ethoxy]calix[6]arene [J-3**^{(NO₂)₃}**]:** from **J-3** (102 mg, 0.083 mmol); the crude product was filtered over silica gel (10:90 MeOH/CH₂Cl₂) to give **J-3**^{(NO₂)₃} as a pure, pale-yellow solid (95 mg, 96%). Mp: 149-151 °C. IR: $\nu(\text{NO}_2) = 1520 \text{ cm}^{-1}$; ¹H NMR (250 MHz, CDCl₃): δ 8.04 (s, 6H, Ar), 6.77 (s, 6H, Ar), 4.00 (s, 12H, ArCH₂Ar), 3.87 (t, 6H, $J = 6.3$ Hz, OCH₂), 2.80 (s, 9H, OMe), 2.70 (t, 6H, NCH₂),
 10 2.27 (s, 18H, NMe₂), 1.00 (s, 27H, *t*-Bu). Anal. calcd for **J-3**^{(NO₂)₃}.H₂O (C₆₉H₉₂N₆O₁₃, 1212.67): C 68.29, H 7.64, N 6.93; Found: C 68.06, H 7.61, N 6.81.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris
pyrrolidinecarbonyl)methoxy]calix[6]arene [J-4^{(NO₂)₃}**]:** from **J-4** (55 mg, 0.041 mmol); the crude product was purified by chromatography on silica gel using
 15 MeOH/CH₂Cl₂/conc. aq. NH₃ (5:95:0.25) as eluant to yield **J-4**^{(NO₂)₃} as a pale-yellow solid (30 mg, 56%). Mp (CH₃CN): 191-194 °C. IR: $\nu(\text{NO}_2) = 1521 \text{ cm}^{-1}$; ¹H NMR (250 MHz, CDCl₃, 330K): δ 8.04 (s, 6H, Ar), 6.76 (s, 6H, Ar), 4.49 (s, 6H, OCH₂CO), 4.07 (brs, 12H, ArCH₂Ar), 3.51 (s, 12H, NCH₂), 2.99 (s, 9H, OMe), 1.86 (m, 12H, CH₂), 0.95 (s, 27H, *t*-Bu). Anal. calcd for **J-4**^{(NO₂)₃}.H₂O (C₇₅H₉₂N₆O₁₆, 1332.66): C 67.55, H
 20 6.95, N 6.30; Found: C 67.26, H 6.81, N 6.26.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-
tris(carbamoylmethoxy)calix[6]arene [J-5^{(NO₂)₃}**]:** from **J-5** (52 mg, 0.044 mmol); the
 crude product was purified by chromatography on silica gel using MeOH/CH₂Cl₂/conc.
 aq. NH₃ (5:95:0.25) as eluant to yield **J-5**^{(NO₂)₃} as a yellow solid (32 mg, 62%). Mp:
 25 219-221 °C. ¹H NMR (250 MHz, CDCl₃): δ 7.51 (s, 6H, Ar), 7.21 (s, 6H, Ar), 4.10 (bs, 18H, OCH₂CO + ArCH₂Ar), 3.61 (s, 9H, OMe), 1.32 (s, 27H, *t*-Bu). Anal. calcd for **J-5**^{(NO₂)₃}.CH₃OH (C₆₄H₇₆N₆O₁₆, 1185.32): C 64.85, H 6.46, N 7.09; Found: C 64.93, H 6.74, N 6.59.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris
 30 **(carbomethoxy)calix[6]arene [J-6**^{(NO₂)₃}**]:** from **J-6** (48 mg, 0.040 mmol), with slightly modification of the workup: after 1 h at room temperature, CH₂Cl₂ (10 mL) was added to the reaction mixture and the organic layer was washed with water (2 × 5 mL), dried (Na₂SO₄) and evaporated to dryness. The crude product is precipitated with a mixture of

Et₂O/pentane (50:50) to yield **J-6^{(NO₂)³}** as a pale-yellow solid (45 mg, 82%). Mp (Et₂O/pentane): 215-217 °C. ¹H NMR (250 MHz, CDCl₃): δ 7.28 (s, 6H, Ar), 7.22 (s, 6H, Ar), 4.09 (bs, 12H, ArCH₂Ar), 3.82 (s, 9H, OMe), 3.78 (s, 6H, OCH₂CO), 1.39 (s, 27H, *t*-Bu). Anal. calcd for **J-6^{(NO₂)³}**·4H₂O (C₆₃H₇₇N₃O₂₂, 1228.29): C 61.60, H 6.32, N 3.42; Found: C 61.56, H 5.94, N 3.68.

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris(ethoxycarbonylmethoxy)calix[6]arene [J-7^{(NO₂)³]}: from **J-7** (54 mg, 0.042 mmol); the crude product was purified by chromatography on silica gel using EtOAc/CH₂Cl₂ (5:95) as eluant to yield **J-7^{(NO₂)³}** (42 mg). Its purity determined by ¹H NMR spectroscopy was 80% (yield: 62%). ESMS: m/z 1240 [M+H]⁺. ¹H NMR (250 MHz, CDCl₃): δ 8.01 (s, 6H, Ar), 6.74 (s, 6H, Ar), 4.71 (s, 6H, OCH₂CO), 4.20 (q, 6H, *J* = 7.1 Hz, OCH₂CH₃), 4.06 (bs, 12H, ArCH₂Ar), 3.05 (s, 9H, OMe), 1.25 (t, 9H, *J* = 7.1 Hz, OCH₂CH₃), 0.96 (s, 27H, *t*-Bu).

5,11,17,23,29,35-Hexanitro-38,40,42-trimethoxy-37,39,41-tris[(2-methyl)propyloxy]calix[6]arene [J-9^{(NO₂)⁶]}: from **J-9** (54 mg, 0.04 mmol); the crude product was purified by chromatography on silica gel (2:98 EtOAc/CH₂Cl₂) to give **J-9^{(NO₂)⁶}** as a colourless powder (31 mg, 60%). Mp: >300 °C. IR: ν(NO₂) = 1522 cm⁻¹; ¹H NMR (250 MHz, CDCl₃): δ 7.82 (s, 6H, Ar), 7.59 (s, 6H, Ar), 4.08 (s, 12H, ArCH₂Ar), 3.74 (s, 9H, OMe), 3.63 (d, 6H, *J* = 6.5 Hz, OCH₂), 2.06 (m, 3H, CHMe₂), 0.89 (d, 18H, *J* = 6.5 Hz, CHMe₂). Anal. calcd for **J-9^{(NO₂)⁶}** (C₅₇H₆₂N₆O₁₉, 1134.41): C 60.31, H 5.51, N 7.40; Found: C 59.98, H 5.25, N 7.41.

5,17-Dinitro-11,23-di-*tert*-butyl-26,28-dimethoxy-25,27-di[(1-methyl-2-imidazolyl)methoxy]calix[6]arene [J-10^{(NO₂)²]}: from **J-10** (50 mg, 0.058 mmol); the crude product was filtered over silica gel using MeOH/CH₂Cl₂/conc. aq. NH₃ (5:95:0.25) as eluant to yield **J-10^{(NO₂)²}** as a yellow solid (40 mg, 80%). The analysis sample was obtained by precipitation in EtOAc/cyclohexane. Mp (EtOAc/cyclohexane): 238-241 °C. ¹H NMR (250 MHz, CDCl₃, 340K): δ 7.72 (s, 4H, Ar), 7.08 (s, 2H, Im), 6.95 (s, 2H, Im), 6.76 (s, 4H, Ar), 4.87 (s, 4H, CH₂Im), 3.84 (d, 4H, *J* = 13.6 Hz, ArCH₂Ar), 3.45 (bs, 13H, OMe + NMe + ArCH₂Ar), 1.10 (s, 27H, *t*-Bu). Anal. calcd for **J-10^{(NO₂)²}**·0.5EtOAc (912.46): C 67.83, H 6.92, N 9.31; Found: C 67.35, H 6.59, N 9.19.

5,17,29-Trinitro-38,40,42-trimethoxy-37,39,41-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene [J^{H3}(NO₂)³]: from **J^{H3}** (68 mg, 0.06 mmol); the crude product

was filtered over silica gel using MeOH/CH₂Cl₂/conc. aq. NH₃ (3:97:0.25) to give J^{H₃(NO₂)₃} as a yellow solid (7 mg, 60%). The analysis sample was obtained by precipitation in CH₃CN. Mp (CH₃CN): 226-228 °C. ESMS: m/z 1096 [M+H]⁺. ¹H NMR (250 MHz, CDCl₃, 340K): δ 7.73 (s, 6H, Ar), 6.93 (d, 3H, *J* = 1 Hz, Im), 6.87 (d, 6H, *J* = 7.4 Hz, Ar), 6.75 (m, 6H, Ar + Im), 4.76 (s, 6H, CH₂Im), 3.82 (s, 12H, ArCH₂Ar), 3.45 (s, 9H, OMe), 3.17 (s, 9H, NMe). Anal. calcd for J^{H₃(NO₂)₃}·H₂O (1113.42): C 64.68, H 5.34, N 11.31; Found: C 64.51, H 5.31, N 11.35.

5,17,29-Tris-sulfonato-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris[(1-methyl-2-imidazolyl)methoxy]calix[6], tris-sodium salt [J^{(SO₃Na)₃}]:

To a solution of J (54 mg, 42 μmol) in anhydrous CH₂Cl₂ (1 mL) cooled to -10°C (NaCl/Ice bath) was added slowly HSO₃Cl (0.2 mL, 1.5 mmol). The temperature was allowed to rise to 20°C and the course of the reaction monitored through the evolution of gas. After 2 h, the bubbling rate had largely decreased, and the reaction was carefully quenched with ice. The inhomogeneous organic layer was separated, washed with water and evaporated to dryness. The brownish solid so obtained was dissolved in 1.5 mL of a 1:1 acetone/water mixture, and a NaOH solution (30%, 25 μL) was added, inducing solubilization. After 4 days, the white precipitate was separated, washed with acetone and dried (40 mg, 70%). ¹H NMR (250 MHz, DMSO) : δ (s, 6H, Ar), (s, 6H, Ar), (s, 3H, Im), (s, 3H, Im), (s, 6H, CH₂Im), (d, *J* = 18 Hz, 6H, ArCH₂Ar), (s, 9H, NCH₃), (d, *J* = 18 Hz, 6H, ArCH₂Ar), (s, 9H, OCH₃), s, 27H, *t*Bu)

5,11,17,23,29,35-Hexa-sulfonato-38,40,42-trimethoxy-37,39,41-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene, hexa-sodium salt [J^{(SO₃Na)₆}]:

– Procedure A: H₂SO₄

– Procedure B:

To a solution of J (50mg, 40 μmol) in anhydrous CH₂Cl₂ (1 mL) was added slowly HSO₃Cl (0.2 mL, 1.5 mmol). The mixture was heated to reflux for 3 hours, then cooled and carefully quenched with ice. The grayish precipitate was recovered by filtration, dried and dissolved in DMSO (1 mL). NaOH, (30 %, 50 μL) was added, and the resulting solution heated to 80 °C for 3 days. Precipitation with CH₂Cl₂ yielded an oil that was washed with EtOH, then dissolved in water and passed through an ion exchange resin (sephadex-H⁺). The resulting solution was evaporated, then once again dissolved in water and the pH adjusted to 9 with a NaOH solution. Concentration under vacuum, followed by precipitation with EtOH, finally yields a slightly brown product (30 mg, 50%) with the spectroscopic properties described previously.

^1H NMR (250 MHz, DMSO) : δ 7.53 (s, 6H, Ar), 7.24 (s, 6H, Ar), 7.22 (s, 3H, Im), 6.90 (s, 3H, Im), 5.00 (s, 6H, CH_2Im), 4.39 (d, $J = 14.4$ Hz, 6H, ArCH_2Ar), 3.72 (s, 9H, NCH_3), 3.11 (d, $J = 14.4$ Hz, 6H, ArCH_2Ar), 2.65 (s, 9H, OCH_3).

5,17,29-tris-nitro-11,23,35-tris-sulfonato-37,39,41-trimethoxy-38,40,42-tris
[(1-methyl-2-imidazolyl)methoxy]calix[6]arene, tris-sodium salt: $[\text{J}^{(\text{NO}_3)_3(\text{SO}_3\text{Na})_3}]$

– Procedure A: H_2SO_4

– Procedure B:

$\text{J}^{(\text{NO}_3)_3}$ (900 mg, 0.70 mmol) was dissolved in CH_2Cl_2 (11 mL), and HSO_3Cl (2 mL) was added dropwise at 0°C . The mixture is brought to reflux for 2 hours, cooled, and poured carefully on 50 g of ice. A beige precipitate is recovered by filtration. This precipitate is dissolved into DMSO (15 mL), and tris-(hydroxymethyl)methylamine (1 g) is added, and the mixture thus obtained is heated at 80°C for 12 h. At the end of the reaction, the product is precipitated with CH_2Cl_2 , then purified by dissolution in a basic medium and precipitated again at pH 4. This sequence, done twice, provides 600 mg of a yellow product. Yield: 61 %. P. F. > 260 (decomp.). ^1H RMN (250 MHz, D_2O , 350K): $\delta = 3.42$ (s, 9H, OCH_3), 4.13 (s, 9H, NCH_3), 4.50 (s, 12H, ArCH_2Ar), 5.36 (s, 6H, $\text{Im}-\alpha\text{CH}_2$), 6.70 (s, 6H, Im), 7.72 (s, 6H, $\text{H}_{\text{Im}}+\text{H}_{\text{Im}}$), 8.30 (s, 12H, $\text{ArH}+\text{ArH}$). FTIR (ATR): $\nu = 3440$ (H_2O), 2970, 1738, 1522, 1346, 1216 (SO_3^-), 1104, 1041 (SO_3^-) cm^{-1} .

5,11,17,23,29,35-Hexa[bis(2-(tert-butyl dimethylsilyloxy)ethyl)aminosulfonyl]-
37,39,41-trimethoxy-38,40,42-tris[(1-méthyl-2-imidazolyl)methoxy]-calix[6]arene
($\text{J}^{\text{SO}_2\text{DEATBDMS}_6}$) :

J (370 mg, 0.27 mmol) was dissolved in anhydrous CH_2Cl_2 (5mL) and the solution cooled in a NaCl/Ice bath. HSO_3Cl (1 mL) was then added at a slow rate and the mixture heated to reflux. After one hour, the reaction was cooled and carefully quenched with ice. The inhomogeneous organic layer was separated, washed with water and dried without heating. The brownish solid so obtained was dissolved in SO_2Cl_2 , and the mixture heated to reflux for 4 hours. SO_2Cl_2 was then removed under vacuum, using a garde filed with 1M NaOH and the resulting material was suspended in toluene and once again dried under vacuum. The material was suspended in CH_2Cl_2 cooled in ice and a mixture of triethylamine (580 μL , 3.6 mmol, 16 eq.) and $\text{HN}(\text{ETOTBDMS})_2$ (490 mg, 1.47 mmol, 6.6 eq.) was added, dropwise, causing dissolution. After 12 hours of stirring, CH_2Cl_2 is added and the solution was washed twice with water, then evaporated to dryness. The crude product was purified by flash chromatography on SiO_2 , using

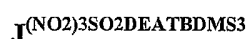
CH₂Cl₂/MeOH 97/3 as an eluant. 135 mg of a white product were obtained. Yield 18 %.

¹H NMR (250 MHz, CD₃CN, 300K): δ = 0.05 (s, 72H, CH₃), 0.90 (s, 108H, C(CH₃)₃), 2.95 (br, 6H; Ar-CH₂), 3.16 (br t, 12H, NCH₂), 3.30 (br t, 12H, NCH₂), 3.41 (br t, 12H, OCH₂), 3.72 (m, 30H, OCH₃ and NCH₃ and OCH₂), 4.0 (br, 6H; Ar-CH₂), 4.87 (s, 6H; Im-αCH₂), 6.83 (s, 3H; H_{Im}), 6.93 (s, 3H; H_{Im}), 7.31 (br s, 6H; H_{Ar}), 7.47 (br s, 6H; H_{Ar}); A better defined spectrum can be obtained by adding zinc perchlorate in the CD₃CN solution: ¹H NMR ([(Y-SO₂DEATBDMS)₆Me₃Imme₃Zn.CD₃CN](ClO₄)₂, 250 MHz, CD₃CN, 340K): δ = 0.03 (s, 36H, Si(CH₃)₂), 0.13 (s, 36H, Si(CH₃)₂), 0.89 (s, 54H, C(CH₃)₃), 0.96 (s, 54H, C(CH₃)₃), 3.15 (t, J = 5.8 Hz, 12H, NCH₂), 3.31 (d, J = 15.7 Hz, 6H; Ar-CH₂), 3.42 (t, J = 6.2 Hz, 12H, NCH₂), 3.63 (t, J = 5.8 Hz, 12H, OCH₂), 3.84 and 3.87 (two s, 18H, OCH₃ and NCH₃), 3.87 (t, J = 6.2 Hz, 12H, OCH₂), 4.12 (d, J = 15.7 Hz, 6H; Ar-CH₂), 5.12 (s, 6H; Im-αCH₂), 6.80 (s, 6H; H_{Ar}), 7.03 (d, J = 1.5 Hz, 3H; H_{Im}), 7.54 (d, J = 1.5 Hz, 3H; H_{Im}), 7.91 (s, 6H; H_{Ar}). CCM: CH₂Cl₂/MeOH 95/3 R_f = 0,2.

5,17,29-tris[bis(2-(tert-butyldimethylsilyloxy)ethyl)aminosulfonyl]-11,23,35-tris-tert-butyl-37,39,41-trimethoxy-38,40,42-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene (J^{SO₂DEATBDMS₃}) :

J (620 mg, 0.48 mmol) was dissolved in anhydrous CH₂Cl₂ (6mL) and the solution cooled in a NaCl/Ice bath. HSO₃Cl (1 mL) was then added at a slow rate, the mixture heated to room temperature and the course of the reaction monitored through the evolution of gas. After two hours, the bubbling rate had largely decreased, and the reaction was carefully quenched with ice. The inhomogeneous organic layer was separated, washed with water and dried without heating. The brownish solid so obtained was dissolved in SO₂Cl₂, and the mixture heated under reflux for 4 hours. SO₂Cl₂ was then removed under vacuum, using a garde filed with 1M NaOH and the resulting material was suspended in toluene and once again dried under vacuum. The material was suspended in CH₂Cl₂, cooled in ice and a mixture of triethylamine (740 μL, 7.4 mmol, 15 eq.) and HN(ETOTBDMS)₂ (820 mg, 2.46 mmol, 5 eq.) was added, dropwise, causing dissolution. After 48 hours of stirring, CH₂Cl₂ was added and the solution washed twice with water, then evaporated to dryness. The crude product was purified by flash chromatography on SiO₂, using CH₂Cl₂/MeOH 95/5 as an eluant. 400 mg of a white product were obtained. Yield 42 %. ¹H NMR (250 MHz, CD₃CN, 300K): δ = 0.08 (s, 72H, CH₃), 0.90 (br s, 135H, SiC(CH₃)₃ and ArC(CH₃)₃), , 3.27 (br t, 12H,

NCH₂), 3.45 (br d, 6H; Ar-CH₂), 3.76 (m, 30H, OCH₃ and NCH₃ and OCH₂), 4.35 (br d, 6H; Ar-CH₂), 4.96 (s, 6H; Im-αCH₂), 6.66 (br s, 6H; H_{Ar}), 6.90 (s, 3H; H_{Im}), 7.02 (s, 3H; H_{Im}), 7.75 (br s, 6H; H_{Ar}); A better defined spectrum can be obtained by adding zinc perchlorate in the CD₃CN solution : ¹H NMR ([(Y-SO₂DEATBDMS)₃Me₃X₃Imme₃Zn.CD₃CN](ClO₄)₂, 250 MHz, CD₃CN, 300K): δ = 0.01 (s, 36H, Si(CH₃)₂), 0.86 (s, 54H, C(CH₃)₃), 3.00 (t, J = 5.8 Hz, 12H, NCH₂), 3.3 (br, 6H; Ar-CH₂), 3.57 (t, J = 6.2 Hz, 12H, OCH₂), 3.66 and 3.69 (two s, 18H, OCH₃ and NCH₃), 4.1 (d, J = 15.5 Hz, 6H; Ar-CH₂), 5.19 (s, 6H; Im-αCH₂), 6.78 (s, 6H; H_{Ar}), 6.98 (d, J = 1.5 Hz, 3H; H_{Im}), 7.43 (s, 6H; H_{Ar}), 7.48 (d, J = 1.5 Hz, 3H; H_{Im}). ¹³C NMR ([(Y-SO₂DEATBDMS)₃Me₃X₃Imme₃Zn.CH₃CN](ClO₄)₂, 72.5 MHz, CD₃CN, 300 K): δ = -5.0 (SiCH₃), 18.8 (SiC), 26.4 (SiC(CH₃)₃), 30.3 (Ar-CH₂), 31.9 (Ar-C(CH₃)₃), 33.6 (NCH₃), 34.8 (Ar-C(CH₃)₃), 53.4 (NCH₂), 61.1 (OCH₃), 63.4 (OCH₂), 67.4 (Im-CH₂), 123.5, (C_{im}H) 124.7 (C_{Ar}H), 128.4 (C_{im}H), 130.8 (C_{Ar}H), 134.6 (C_{Ar}CH₂), 136.5 (C_{Ar}CH₂), 144.7 (C_{im}) 147.3 (C_{Ar}), 152.3 (C_{Ar}), 155.1 (C_{Ar}), 161.2 (C_{Ar}). CCM: CH₂Cl₂/MeOH 95:5 R_f = 0,3.



TBDMS deprotection

The silylated products were suspended in a 9/1 TFA/water mixture and stirred a room temperature overnight. The solvents were then evaporated and toluene was added and evaporated twice, giving a brownish oil. The products were then neutralized and purified.

5,11,17,23,29,35-Hexa[bis(2-hydroxyethyl)aminosulfonyl]-37,39,41-trimethoxy-38,40,42-tris[(1-methyl-2-imidazolyl)methoxy]-calix[6]arene (J^{SO₂DEA6}) :

The crude material was neutralized to the free base by precipitation from an EtOH/Et₃N mixture, and dried, yielding 80mg. Yield: 65%. ¹H NMR (250 MHz, CD₃OD, 300K): δ = 2.90 (br, 6H; Ar-CH₂), 3.08 (t, J = 5.4 Hz, 12H, NCH₂), 3.15 (t, J = 5.1 Hz, 12H, NCH₂), 3.26 (s, 9H, OCH₃), 3.67 (s, 9H, NCH₃), 3.74 (t, J = 5.4 Hz, 12H, OCH₂), 3.82 (t, J = 5.1 Hz, 12H, OCH₂), 4.10 (br, 6H; Ar-CH₂), 5.03 (s, 6H; Im-αCH₂), 6.93 (s, 3H; H_{Im}), 7.14 (s, 3H; H_{Im}), 7.30 (br s, 6H; H_{Ar}), 7.55 (br s, 6H; H_{Ar}). ESI-MS (H₂O/CH₃CN): m/z (%): 815.88 (100), calculated for [M+2H]²⁺ : 815.86 ; 1630.75 (71), calculated for [M+H]⁺ : 1630.72.

5,17,29-Tris[bis(2-hydroxyethyl)aminosulfonyl]-11,23,35-tris-tert-butyl-37,39,41-trimethoxy-38,40,42-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene (J^{SO_2DEA3}):

The crude material was dissolved in H₂O/acetone 10/1 (30 mL) and precipitated by addition of Et₃N, then purified by trituration in THF, yielding 100 mg of a white powder. Yield: 47%. ¹H NMR (250 MHz, CD₃CN, 300K): δ = 0.91 (br s, 27H, tBu), 2.6 (br, 9H, OCH₃), 3.0-4.4 (br, 12H; Ar-CH₂), 3.22 (m, 12H, NCH₂), 3.57 (m, 21H, NCH₂+NCH₃), 4.88 (br s, 6H; Im- α CH₂), 6.74 (br s, 6H; H_{Ar}), 6.94 (br s, 3H; H_{Im}), 7.04 (s, 3H; H_{Im}), 7.68 (br s, 6H; H_{Ar}). IRTF (ATR): ν = 2952, 1738, 1335 (sulfonamide), 1146 (sulfonamide), 990 cm⁻¹. ESI-MS (H₂O/CH₃CN): m/z (%): 982.32 (100), calculated for [M+2H]²⁺: 982.31 ; 1963.67 (22), calculated for [M+H]⁺: 1963.62.

(J^{SO_2DEA6}).Zn(ClO₄)₂ :

¹H NMR (250 MHz, CD₃CN, 300K): δ = (br, 6H; Ar-CH₂), 2.93 (t, J = 5.2 Hz, 12H, NCH₂), 3.38 (t, J = 5.5 Hz, 12H, NCH₂), 3.51 (m, 12H, OCH₂), 3.67 and 3.69 (two s, 9H and 9H, NCH₃ and OCH₃) 3.72 (m, 12H, OCH₂), 4.15 (br, 6H; Ar-CH₂), 5.29 (s, 6H; Im- α CH₂), 6.87 (s, 6H; H_{Ar}), 7.00 (d, J = 1.5 Hz, 3H; H_{Im}), 7.51 (s, J = 1.5 Hz, 3H; H_{Im}), 7.98 (s, 6H; H_{Ar}); FTIR (ATR) ν = 1585, 1448, 1328 (sulfonamide), 1142 (sulfonamide), 1102 (ClO₄⁻) 991, cm⁻¹.

(J^{SO_2DEA3}).Zn(ClO₄)₂ :

¹H NMR (250 MHz, CD₃CN, 300K): δ = 1.40 (s, 27H, C(CH₃)₃), 2.88 (t, J = 5.0 Hz, 12H, NCH₂), 3.25 (br, 6H; Ar-CH₂), 3.51 (m, 12H, OCH₂), 3.68 and 3.70 (two s, 9H and 9H, NCH₃ and OCH₃), 4.08 (br d, J = 13.5 Hz, 6H, Ar-CH₂), 5.22 (s, 6H; Im- α CH₂), 6.84 (s, 6H; H_{Ar}), 6.99 (d, J = 1.5 Hz, 3H; H_{Im}), 7.48 (s, 6H; H_{Ar}), 7.49 (s, J = 1.6 Hz, 3H; H_{Im}).

The present inventors have also synthesized a compound **J-11** having the formula of compound J wherein W is a -CH₂CH₂CH₂NMe₂ group.

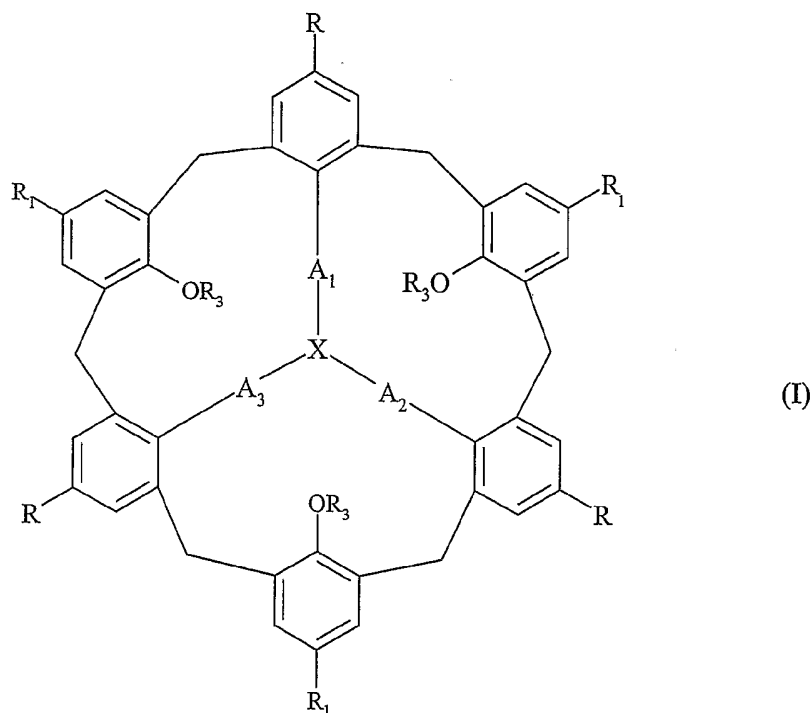
5,11,17,23,29,35-Hexa-tert-butyl-38,40,42-trimethoxy-37,39,41-tris[(N,N-dimethylamino)propyloxy]calix[6]arene (J-11): NaH (60% in oil, 118 mg, 2.95 mmol, 30 eq., washed with pentane prior to use) was added under argon to a solution of 1,3,5-trimethoxy-*p*-tert-butylcalix[6]arene (Janssen, R.G. et al., *Synthesis* (1993) 380-386) (100 mg, 0.1 mmol) in THF (4 mL) and DMF (1 mL). After 30 min. at room temperature, 3-(*N,N*-dimethylamino)propyl chloride hydrochloride (155 mg, 1 mol, 10

eq) was added. After 16 h at reflux, the usual work-up with CH₂Cl₂/H₂O gave the crude product that was recrystallized (CH₂Cl₂/CH₃CN) to give **J-11** as colorless crystals (95 mg, 76%). Mp(CH₂Cl₂/CH₃CN): ¹H NMR (250 MHz, CDCl₃): δ 7.26 (s, 6H, Ar), 6.64 (s, 6H, Ar), 4.55 (d, 6H, *J*_{AB} = 14.8 Hz, ArCH₂Ar), 3.92 (m, 6H, OCH₂), 3.40 (d, 6H, *J*_{AB} = 14.8 Hz, ArCH₂Ar), 2.53 (m, 6H, NCH₂), 2.26 (s, 18H, N(CH₃)₂), 2.21 (s, 9H, OCH₃), 2.03 (m, 6H, CH₂), 1.38 (s, 27H, *t*Bu), 0.78 (s, 27H, *t*Bu).

5,17,29-Trinitro-11,23,35-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tris [(*N,N*-dimethylamino)propyloxy]calix[6]arene [J-11^{(NO₂)₃]}: from **J-11** (37 mg, 0.03 mmol); the crude product was precipitated from CH₃CN/Et₂O to yield **J-11^{(NO₂)₃}** as a yellow solid (30 mg, 83%). ¹H NMR (250 MHz, CDCl₃): δ 8.06 (s, 6H, Ar), 6.74 (s, 6H, Ar), 4.08 (brs, 12H, ArCH₂Ar), 3.93 (m, 6H, OCH₂), 2.73 (s, 9H, OMe), 2.59 (m, 6H, NCH₂), 2.30 (s, 18H, N(CH₃)₂), 2.06 (m, 6H, CH₂), 0.96 (s, 27H, *t*Bu).

CLAIMS

1. Compounds of the following formula (I):



in which:

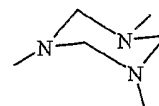
20 — R and R₁, identical or different, represent: H, a halogen atom such as F, Cl, Br, I, an ester or a thioester group of 2 to 20 carbon atoms, a carboxylic group, an amide or a thioamide group, a sulfonamide group, SO₃⁻, a phosphate, a carboxylate, NO₂, or a primary, secondary or tertiary amine group and its derivatives such as a ketimine, an ammonium, a carbamate, a thiocarbamate, and an alkyl group of 1 to 20 carbon atoms, said alkyl group being possibly substituted with one of the functional groups as defined above;

— R₃ represents: H, an alkyl group or an alkyl chain of 1 to 20 carbon atoms possibly substituted by any other functional group, such as defined for R and R₁, and is particularly a methyl group;

30 — X represents:

* a nitrogen atom, an ammonium N⁺R₅, or CR₅ group, with R₅ representing an H, alkyl, or an acid, nitrilo, NO₂, amino, alcohol, ether, thiol, thioether derivative, and being preferably a methyl group;

* or X represents a group of formula (A):



or a corresponding ammonium salt of said formula (A), wherein at least one of the three nitrogen atoms is substituted by a R_6 group, R_6 having the same definition as R and R_1 ;

5

— A_1 , A_2 and A_3 represent:

* an alkyloxy group of formula $-O-(CH_2)_p-$, wherein p represents an integer varying from 1 to 3, when X represents a group of formula (A), or a corresponding ammonium salt of said formula (A), wherein at least one of the three nitrogen atoms is substituted by a R_6 group, R_6 having the same definition as R and R_1

10

* or a group of formula : $-O-(CH_2)_n-NR_2-(CH_2)_m-$ or $-O-(CH_2)_n-N^+R_2R_4-(CH_2)_m-$ when X represents a nitrogen atom, an ammonium N^+R_5 or CR_5 group as mentioned above,

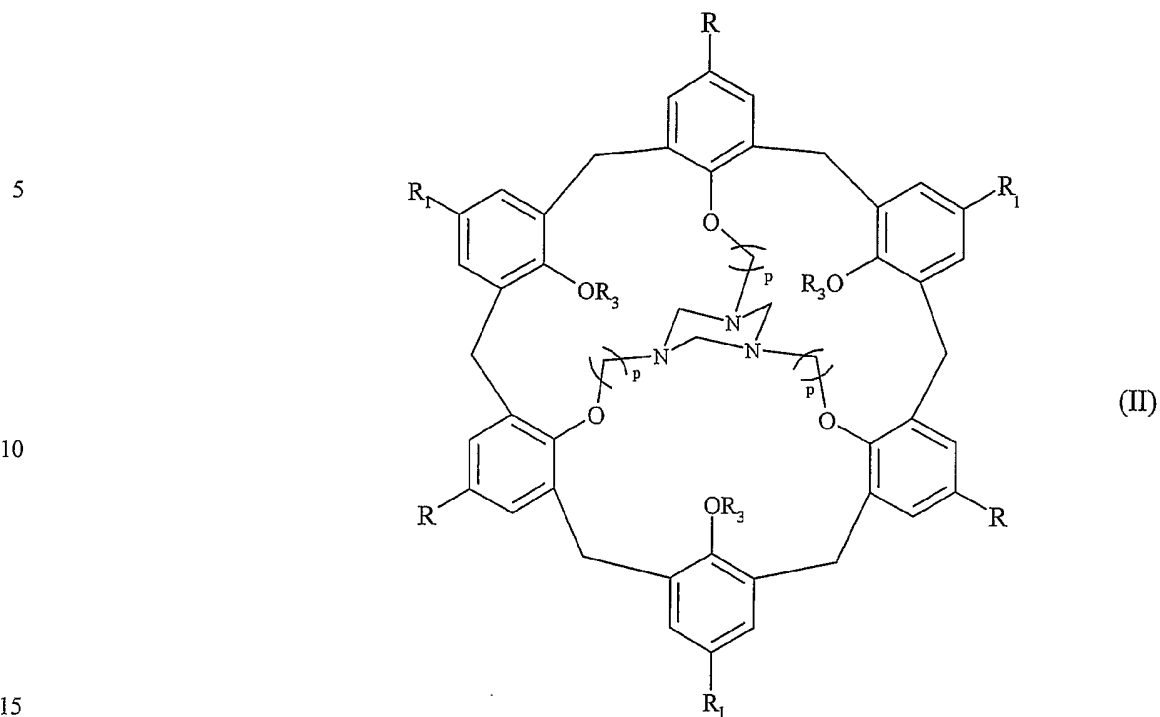
15

wherein m and n are integers varying from 1 to 3, and

R_2 and R_4 , identical or different, represent: H, an alkyl group of 1 to 20 carbon atoms, an ester or a thioester of 2 to 20 carbon atoms, a carboxylic acid of 1 to 20 carbon atoms, an amide or a thioamide of 1 to 20 carbon atoms, a sulfonamide of 1 to 20 carbon atoms, SO_3^- , a phosphate, a carboxylate, an hydroxy and its derivative such an ether-oxyde, or an amine of 1 to 20 carbon atoms and its derivatives such as a ketimine, an ammonium, a carbamate, a thiocarbamate.

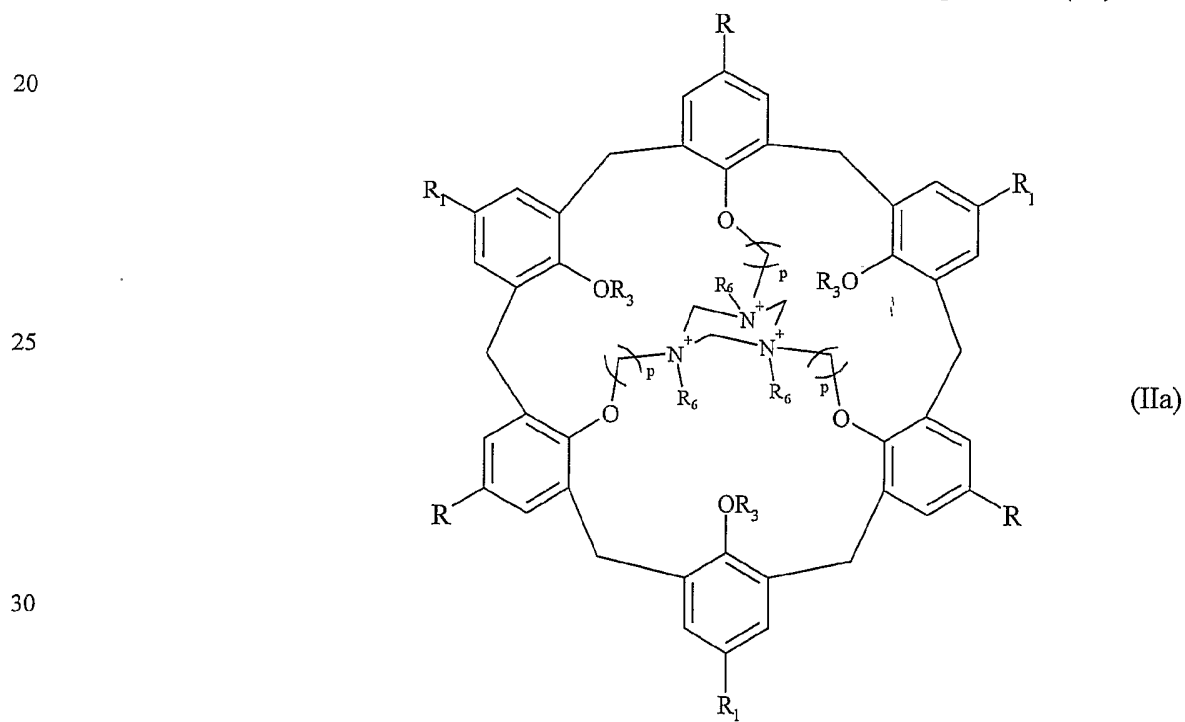
20

2. Compounds according to claim 1, having the following formula (II):



wherein R, R₁, R₃ and p are as defined in claim 1.

3. Compounds according to claim 1, having the following formula (IIa):



wherein R, R₁, R₃, R₆ and p are as defined in claim 1.

4. Compounds according to claim 2 or 3, characterised in that R and R₁ are tBu groups and R₃ represents a methyl group, and in that p is equal to 2.

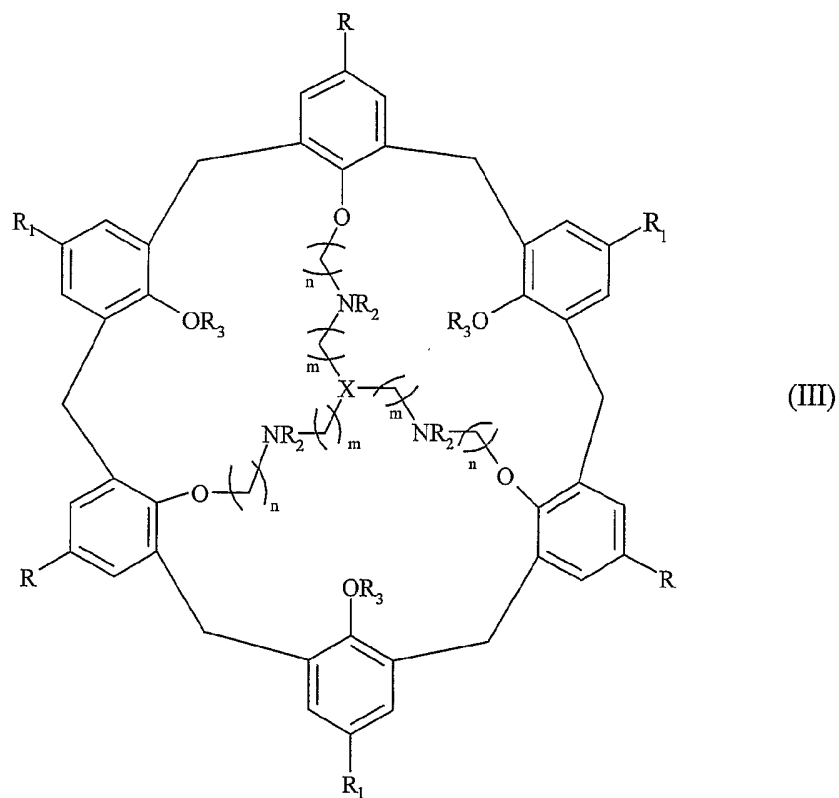
5. Compounds according to claim 1, having the following formula (III):

5

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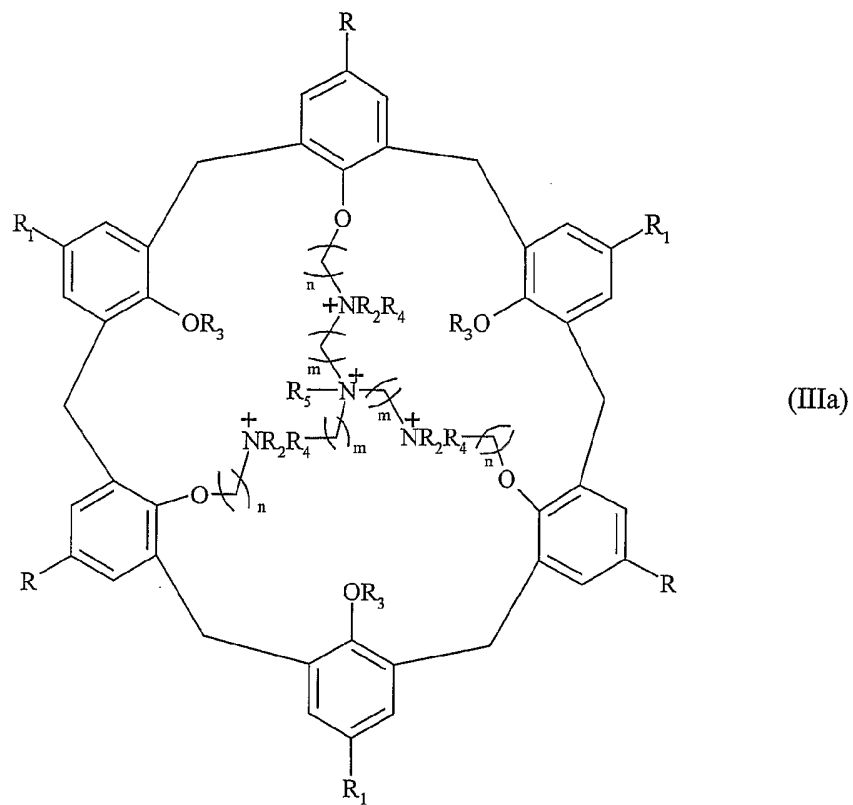
20



wherein m, n, R, R₁, R₂ and R₃ are as defined in claim 1, and wherein X represents a nitrogen atom, an ammonium N⁺R₅, or CR₅ group, R₅ being such as defined in claim 1.

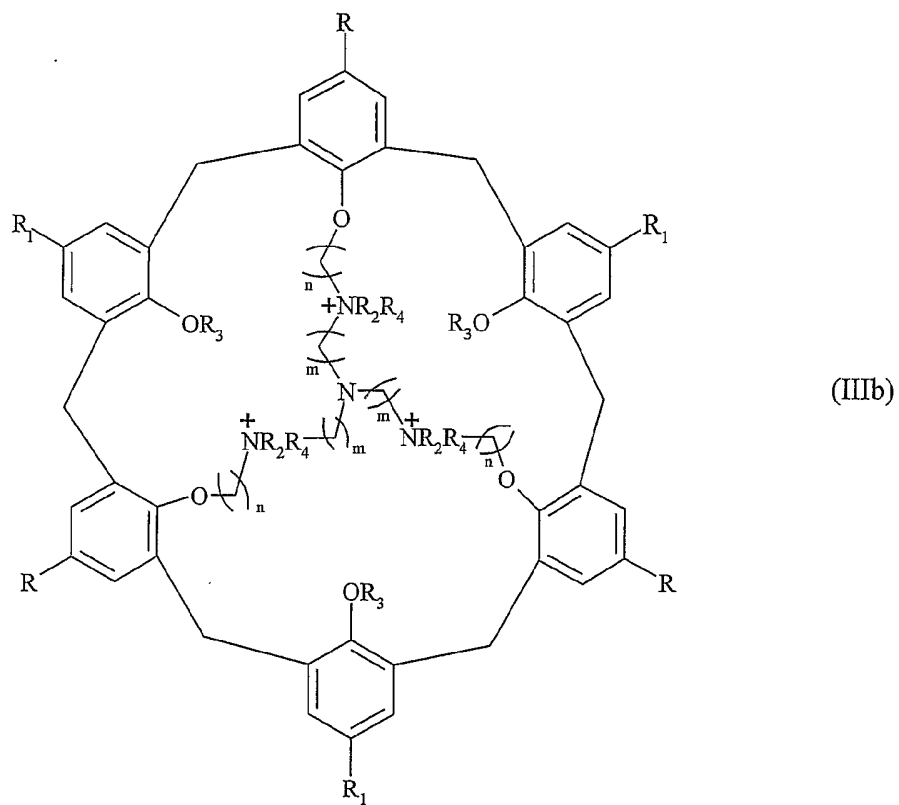
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6. Compounds according to claim 1, having the following formula (IIIa):



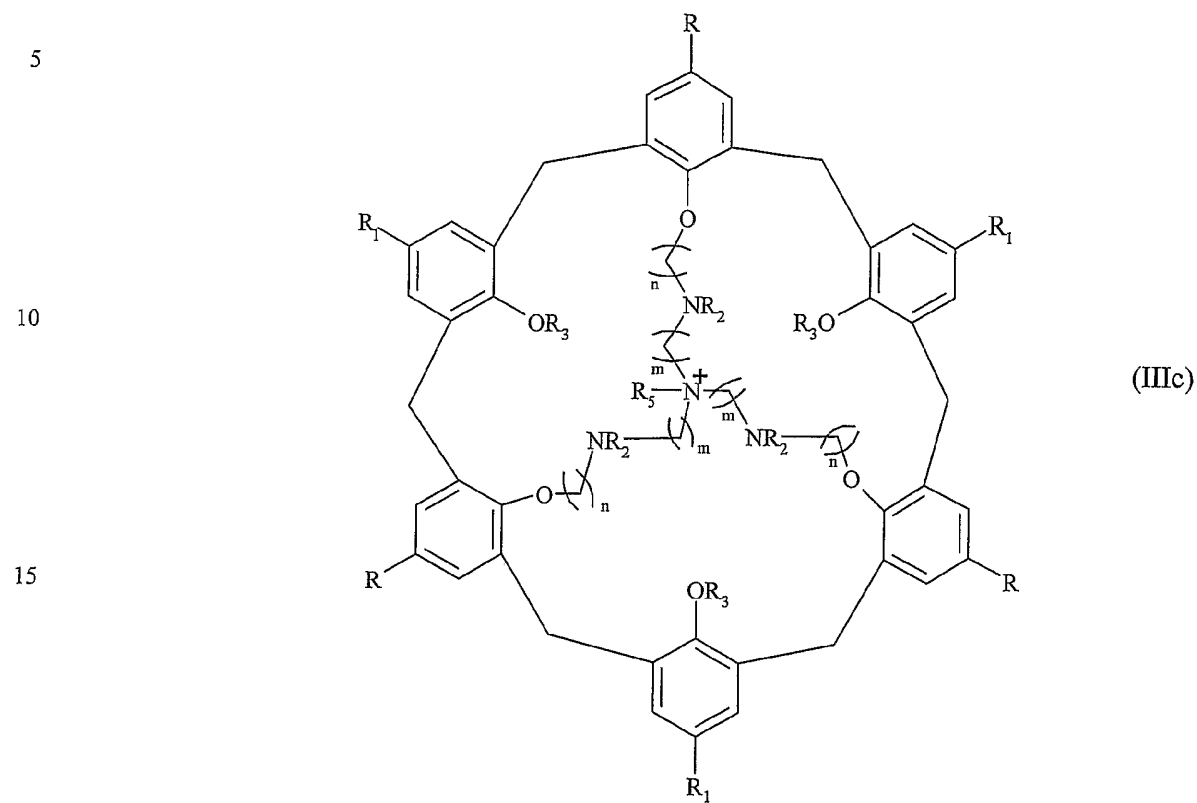
wherein m , n , R , R_1 , R_2 , R_3 , R_4 and R_5 are as defined in claim 1.

7. Compounds according to claim 1, having the following formula (IIIb):



wherein m, n, R, R₁, R₂, R₃ and R₄ are as defined in claim 1.

8. Compounds according to claim 1, having the following formula (IIIc):



wherein m, n, R, R₁, R₂, R₃ and R₅ are as defined in claim 1.

9. Compounds according to any of claims 5 to 8, characterised in that R_3 represents a methyl group and R_2 , R_4 and R_5 represent a hydrogen atom.

5 10. Compounds according to claim 9, characterized in that R and R_1 represent tBu groups.

11. Compounds according to claim 9, characterised in that R represents SO_3Na and R_1 represents NO_2 .

10

12. Compounds according to any of claims 1 to 11, characterised in that they are linked to:

- a function liable to bind, if necessary via a binding site, to molecules, such as antibodies, haptens or peptides, which are able to bind specifically with epitopes located at the surface of the cells of the organism, or to chemical or biological compounds located at the surface of a solid carrier, or
- a group carrying a function linked, if necessary via a binding site, to molecules as defined above.

20 13. Complexes between a compound according to any of claims 1 to 12, and an element chosen among:

- a metal, such as zinc, cadmium, mercury, copper, silver, gold, iron, cobalt, cesium;
- an actinide such as uranium, americium, plutonium or a lanthanide such as lanthanum, europium, gadolinium, ytterbium;
- a radioelement, more particularly chosen among α , β or γ emitter radiometals, such as Tc, Re;
- a cationic guest such as an ammonium;
- an anionic guest such as a phosphate, a phosphonate, a sulfonate, a sulfate, a carboxylate, CN^- , F^- , Cl^- , Br^- , I^- ;

30

said complexes resulting from the insertion of said element into the calix arene group and from interactions between said element and the coordinations sites A_1 , A_2 , A_3 , and X, of the calix arene group of said compound.

14. Pharmaceutical compositions comprising a compound according to any of claims 1 to 12, or a complex according to claim 13, in association with a pharmaceutically acceptable carrier.

5 15. Use of compounds according to any of claims 1 to 12:

– for the preparation of selective metal extractants such as radioactive or precious metals;

– for the preparation of catalysts to be used in chemistry in aqueous or organic medium, and more particularly for the preparation of complexes between a compound according to any of claims 1 to 12, and a metal active as a catalyst;

– for the *in vitro* detoxification after intoxication by heavy metals or drugs;

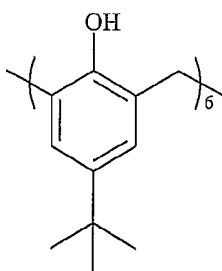
– for the preparation of pharmaceutical composition useful for the detoxification after intoxication by heavy metals or drugs;

– as depolluting agents in aquatic media, captors of molecules in gas phase, ligands in medical imaging, biological probes, carriers of therapeutic molecules, stationary phases for gas chromatography, or stabilizers of compounds sensitive to the presence of metals.

16. Use of a complex according to claim 13, between a compound according to claim 12 and a radioelement for the manufacture of a medicament for radioimmunotherapy, in particular for the treatment of cancers, or for the treatment against metastase proliferation.

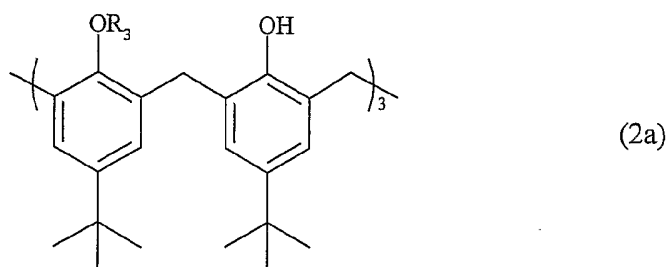
17. Process of preparation of compounds according to any of claims 1 to 11, characterized in that it comprises the following steps:

– a selective 1,3,5-trialkylation with alkyl halide R_3Y , R_3 being such as defined in claim 1 and Y representing a leaving group, and particularly a halogen atom, such as Cl, Br and I, of compound 2 of following formula:

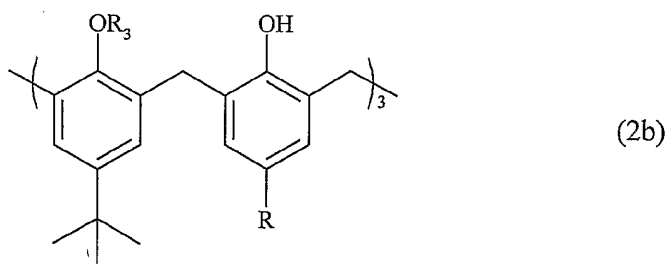


(2)

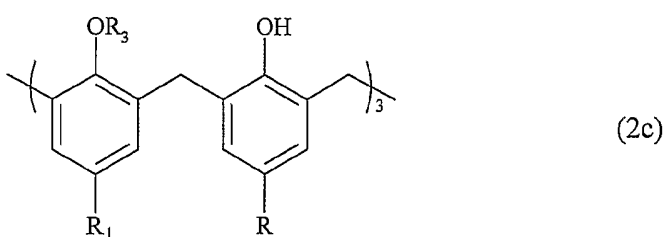
to obtain compound 2a having the following formula:



- 10
- the treatment of above-mentioned compound 2a with AlCl_3 , and, if R is different from H in the compound of formula (I) to be obtained, the subsequent treatment with an electrophile chemically equivalent to R^+ , in order to obtain compound 2b having the following formula:



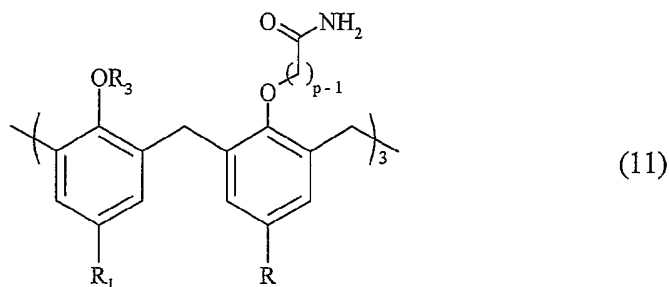
- 20
- the treatment of compound 2b such as obtained previously with AlCl_3 , followed by the treatment with R_1Z , Z being a halogen atom and R_1 being such as defined in claim 1, in order to obtain compound 2c having the following formula:



a) for the preparation of compounds of formula (II) or (IIa) according to any of claims 2 to 4

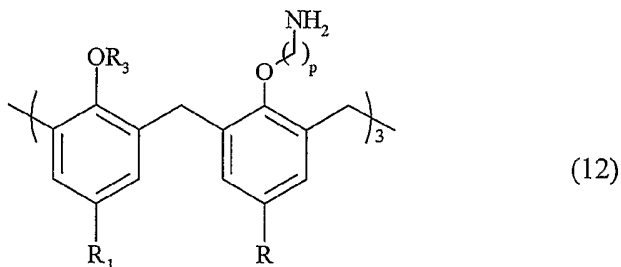
– the conversion by alkylation, particularly with compound of formula

5 $\text{Br}-\left(\text{CH}_2\right)_{p-1}-\text{C}(=\text{O})\text{NH}_2$ of compound 2c into the triamide derivative 11 having the following formula:



R, R₁, R₃ and p being such as defined in claim 1,

– the reduction of the above-mentioned compound 11 with BH₃, in order to obtain the following compound 12:

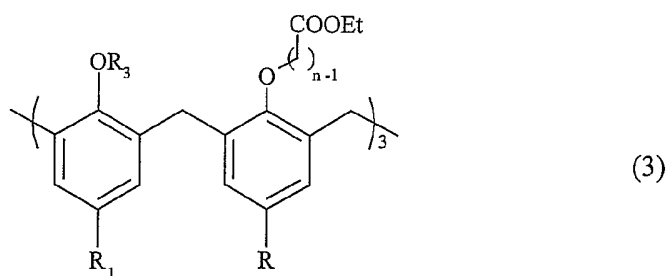


– the reaction with the triamine of formula (12) such as mentioned above with formaldehyde, in order to obtain the compound of formula (II) according to claim 2, and

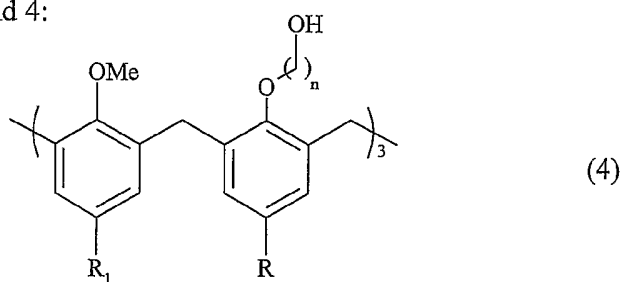
– possibly the alkylation of compound of formula (II) with R₆Y, Y being a leaving group, and particularly a halogen atom and R₆ being such as defined in claim 1, in order to obtain compound of formula (IIa) according to claim 3.

b) for the preparation of compounds of formula (III), (IIIa), (IIIb) or (IIIc) according to any of claims 5 to 11

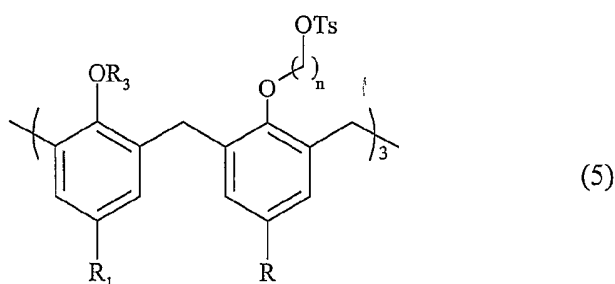
– the conversion by alkylation, particularly with compound of formula $\text{Br}-(\text{CH}_2)_{n-1}-\text{COOEt}$, of compound 2c into the triester derivative 3 having the following formula:



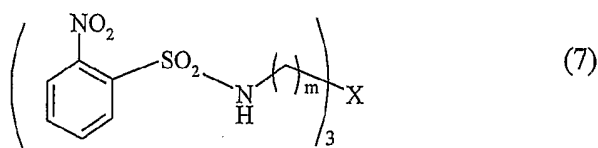
– the reduction by LiAlH_4 of the above-mentioned compound 3, in order to obtain the following compound 4:



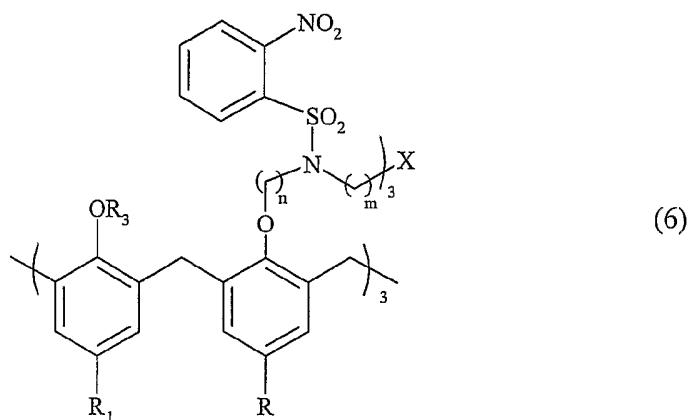
– the addition of TsCl to compound 4 such as obtained previously, in order to obtain compound 5 having the following formula:



– a reaction of trialkylation of compound 5, such as obtained previously, with compound 7 having the following formula:



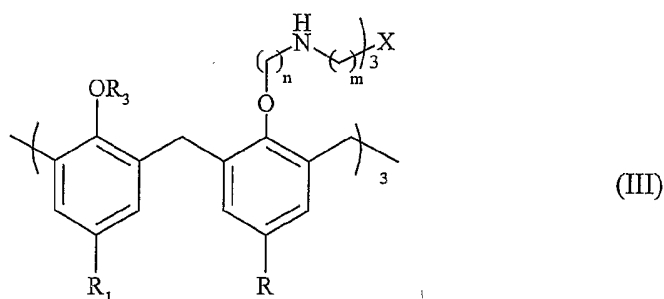
X being such as defined in claim 5, and m being such as defined in claim 1,
in order to obtain compound 6 having the following formula:



compound 7 being obtained according to the reaction of compound having the
following formula $\left(\text{H}_2\text{N} - \left(\text{CH}_2 \right)_m \right)_3 \text{X}$ with 2-nitrobenzenesulfonylchloride;

15

– the deprotection of the amino groups of compound 6 such as obtained previously with thiophenol, in order to obtain compound of formula (III) according to claim 5 with R₂ representing H, having the following formula:



25

– and possibly the alkylation of compound of formula (III) such as obtained previously with R₄Y, Y representing a leaving group, and particularly a halogen atom and R₄ being such as defined in claim 1, in order to obtain compound of formula (IIIb) according to claim 6, or possibly the alkylation of compound of formula (III) such as obtained previously with R₅Y, Y representing a leaving group, and particularly a halogen atom and R₅ being such as defined in claim 1, in order to obtain compound of formula (IIIc) according to claim 8,

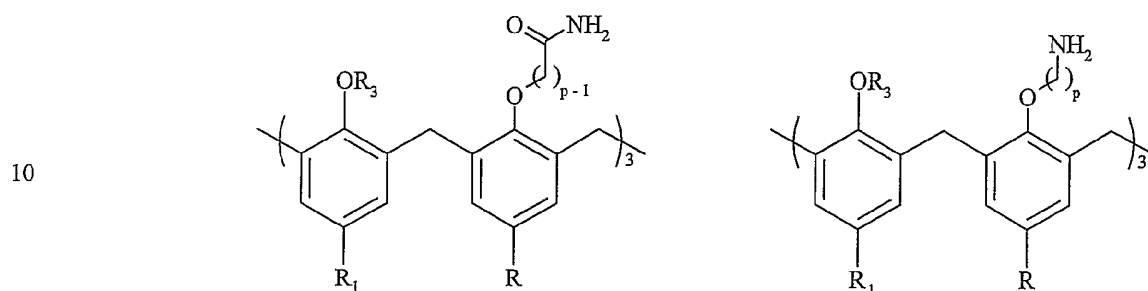
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– and possibly the alkylation of compound (IIIb) such as obtained previously with R₅Y, Y representing a leaving group, and particularly a halogen atom and R₅ being

such as defined in claim 1, or the alkylation of compound (IIIc) such as obtained previously with R_4Y , Y representing a leaving group, and particularly a halogen atom and R_4 being such as defined in claim 1, in order to obtain compound of formula (IIIa) according to claim 6.

5

19. Compounds having one of the following formulas:



wherein R, R_1 , R_3 and p are as defined in claim 1,

15

said compounds being liable to be used as synthesis intermediaries for the preparation of compounds of formula (II) according to claim 2,

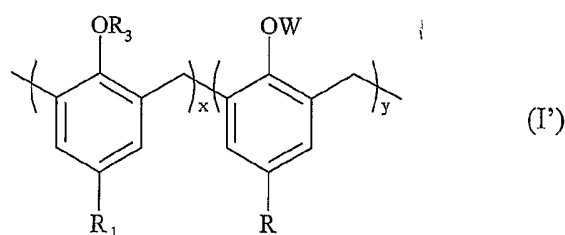
provided that the compounds wherein R and R_1 represent tBu, R_3 represents a methyl group and p is 2, are excluded.

20

20. Process of preparation of water-soluble compounds, characterized in that it comprises the following steps:

— a reaction of nitration or sulfonation of a compound of formula (I) such as defined in claim 1, or of a compound of the following formula:

25

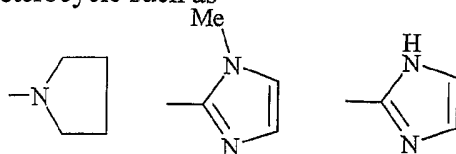


wherein

30

- x and y are integers different from 0, $x + y$ varying from 4 to 8,
- R, R_1 and R_3 are such as defined for formula (I), R and R_1 being different from SO_3^- and NO_2 ,
- W represents an alkyl group comprising 1 to 5 carbon atoms, said alkyl group being substituted with a protonable element chosen among:

* a heterocycle such as



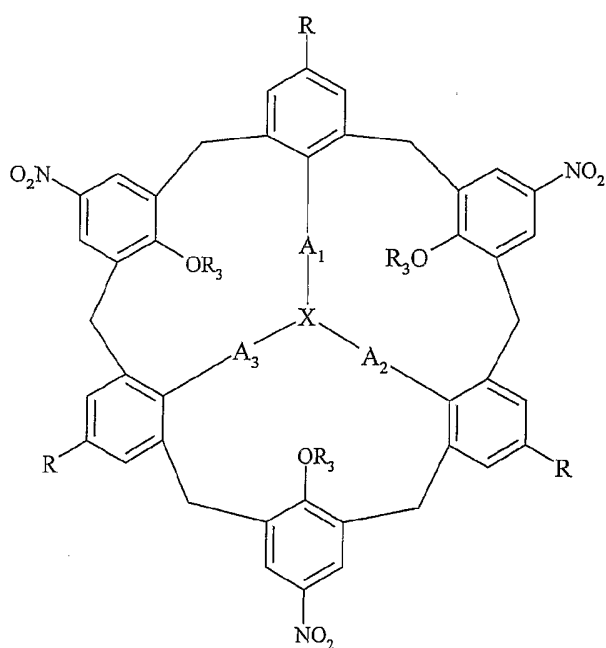
or pyridine, or benzimidazole,

* a primary, secondary or tertiary amine group, particularly NH_2 or NMe_2 ,

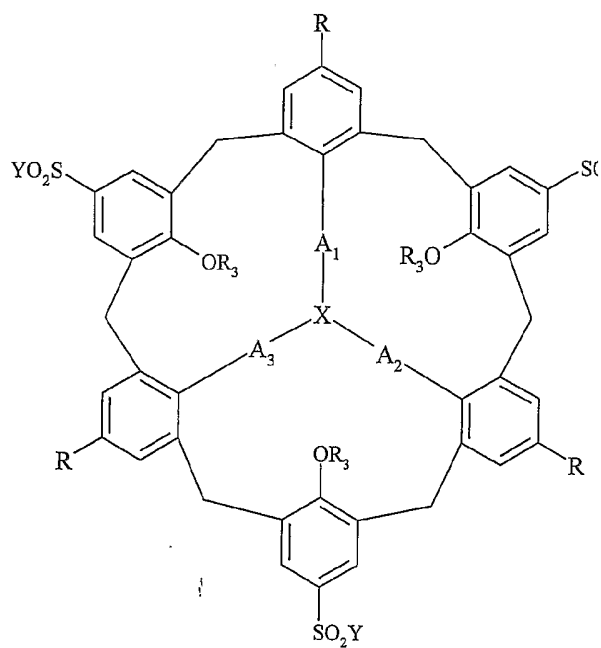
* a $-\text{CO}-\text{R}_7$ or $-\text{CS}-\text{R}_7$ group wherein R_7 represents a primary, secondary or tertiary amine group, particularly a NH_2 group, or heterocycles, particularly such as , or a $-\text{OR}_8$ group, wherein R_8 represents H or an alkyl group comprising from 1 to 10 carbon atoms, or

* a $-\text{OR}_8$ or $-\text{SR}_8$ group, wherein R_8 is such as defined above,

in order to obtain respectively a compound having one of the following formulas:

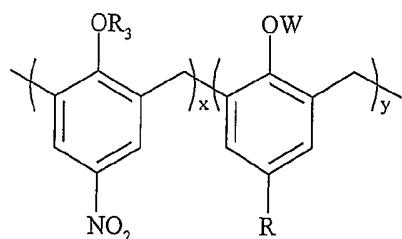


(I-a)

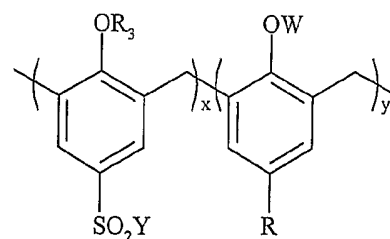


(I-b)

wherein A_1 , A_2 , A_3 , R , R_3 and X being such as defined in claim 1,



(I'-a)

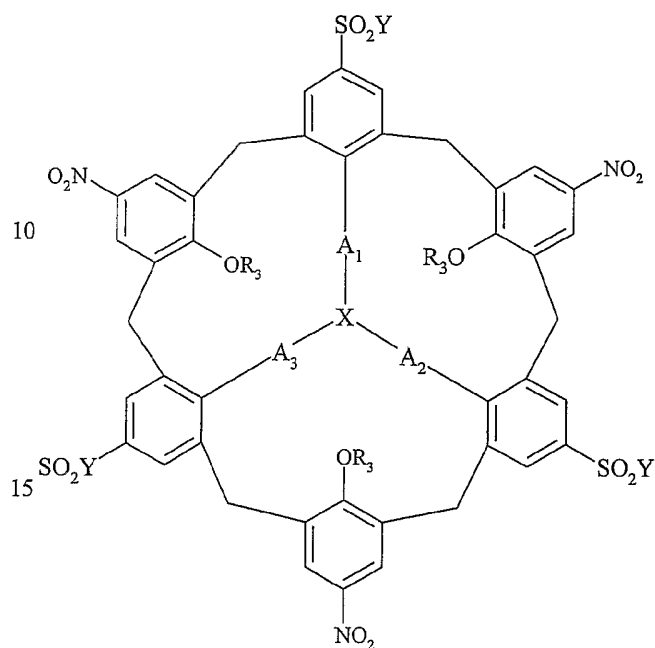


(I'-b)

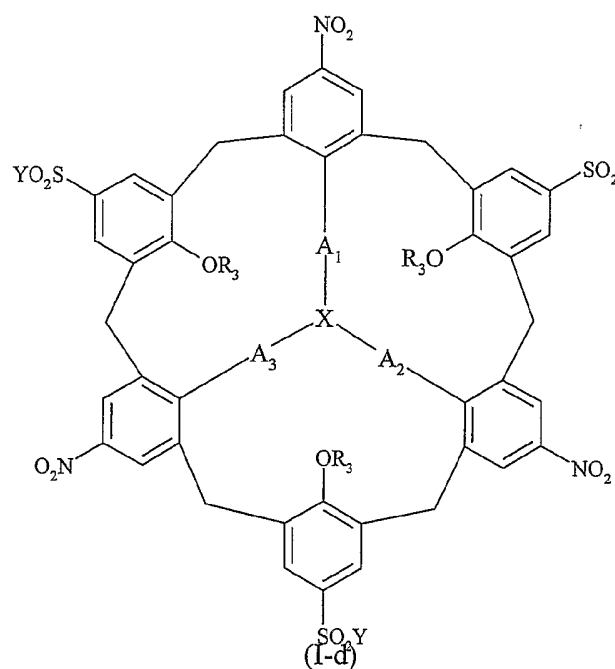
Y representing OH, or an alkoxy group, or a primary or secondary amine group, or a halogen atom or a thioalkyl group,

— and optionally a reaction of sulfonation or nitration of compound of one of the formulas (I-a), (I-b), (I'-a) or (I'-b), such as obtained previously,

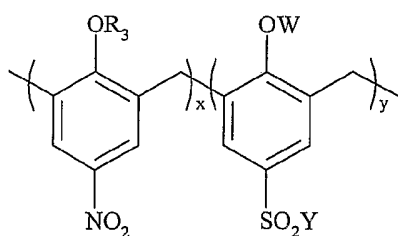
5 in order to obtain respectively a compound having one of the following formulas:



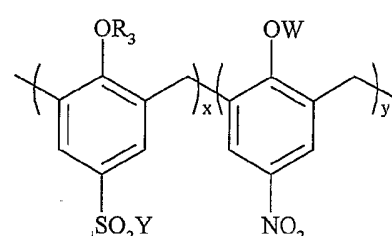
(I-c)



(I-d)



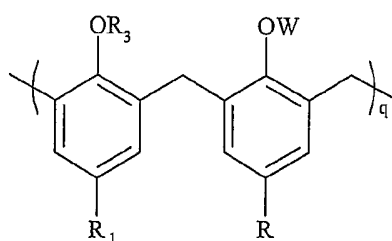
(I'-c)



(I'-d)

21. Process of preparation of water-soluble compounds, according to claim 20, characterized in that it comprises the following steps:

— a reaction of nitration or sulfonation of a compound of formula (I) such as defined in claim 1, or of a compound of the following formula:

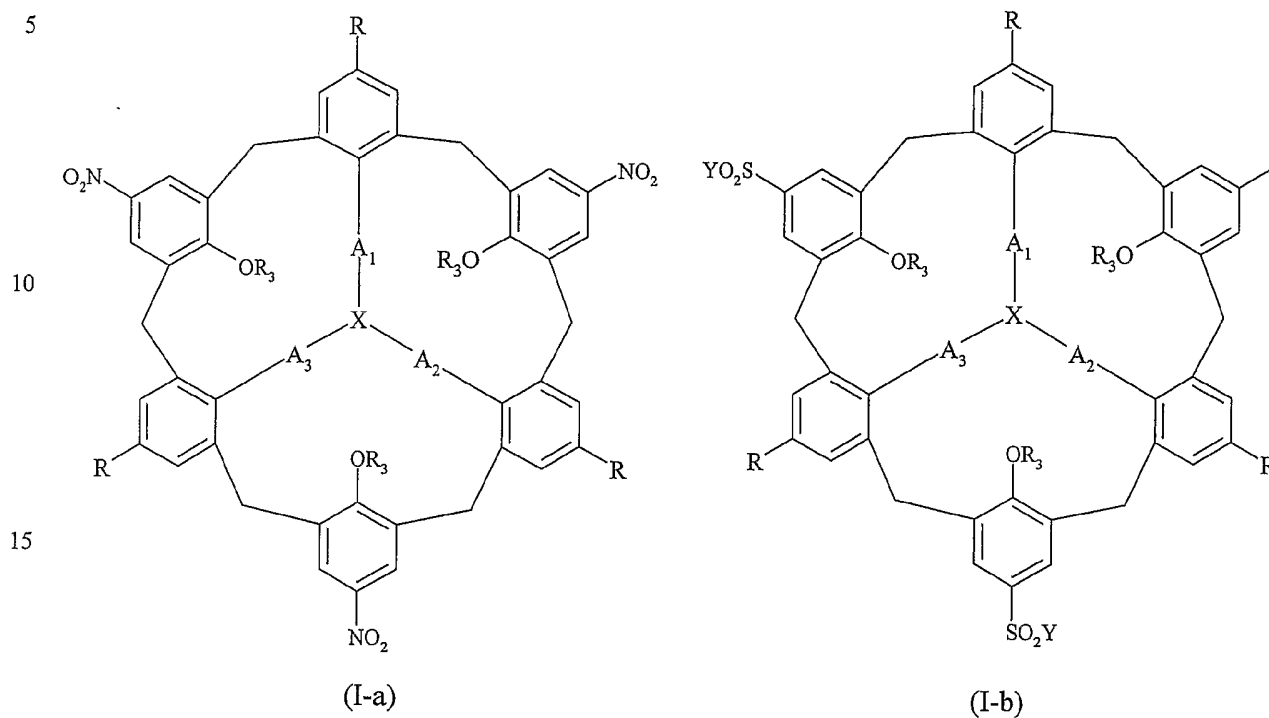


(I-bis)

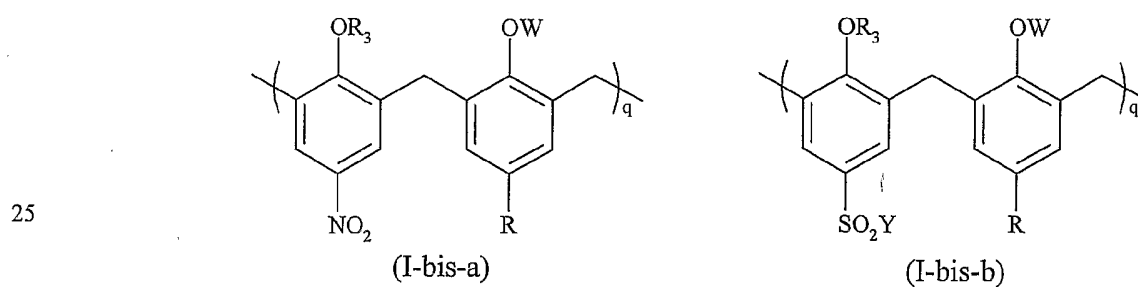
wherein

- q is an integer varying from 2 to 4, and
- R, R₁, R₃ and W are such as defined in claim 20,

in order to obtain respectively a compound having one of the following formulas:



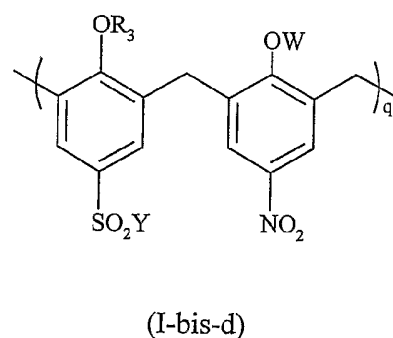
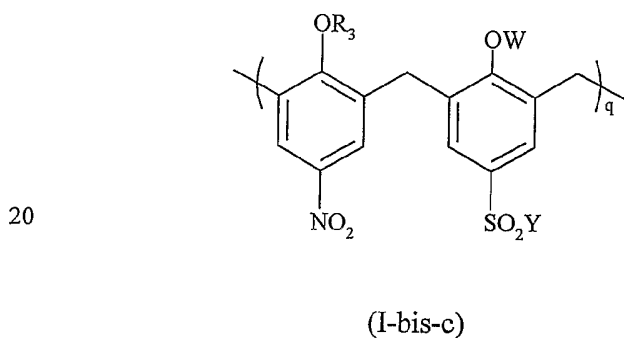
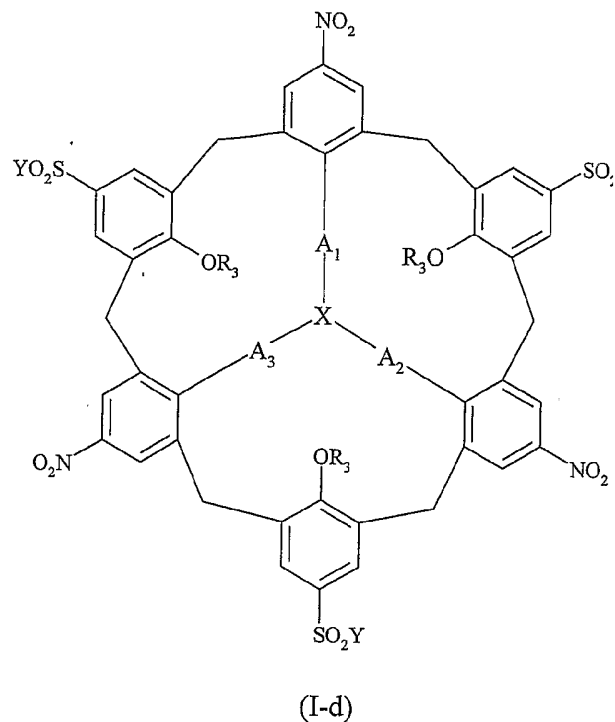
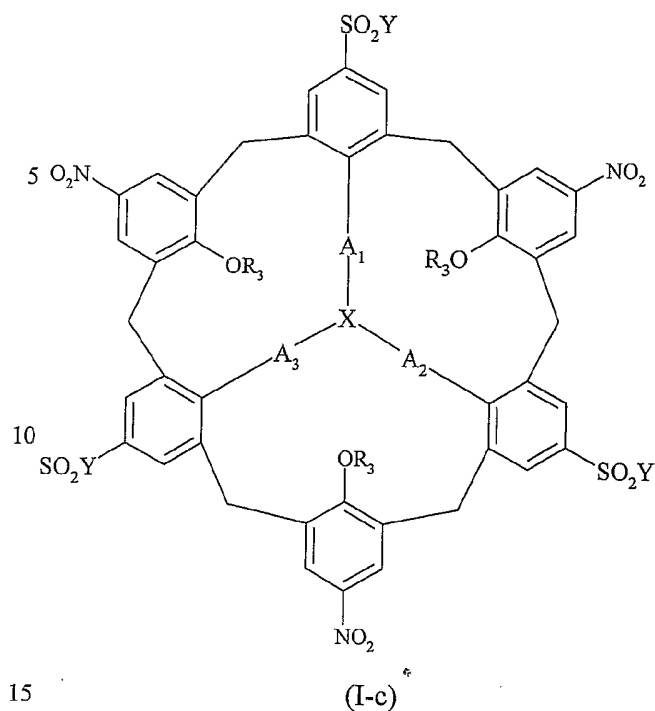
20 wherein A₁, A₂, A₃, R, R₃ and X being such as defined in claim 1,



Y being such as defined in claim 20,

30 - and optionally a reaction of sulfonation or nitration of compound of one of the formulas (I-a), (I-b), (I-bis-a) or (I-bis-b), such as obtained previously,

in order to obtain respectively a compound having one of the following formulas:



22. Process according to claim 20 or 21, wherein the reaction of sulfonation is carried out with the chlorosulfonic acid, and the reaction of nitration is carried out with the nitric acid.

23. Process according to any of claims 20 to 22, characterized in that it comprises the possible step of transformation of the functions NO₂ and SO₂Y, in one of the following respective functions:

- amine, ammonium, amide, thioamide
- sulfonate, sulfonamide, sulfonic ester, sulfothioester.

24. Process according to any of claims 20 to 23, characterized in that it comprises the following steps:

– a reaction of nitration of a compound of formula (I) such as defined in claim 1, or of a compound of formula (I') such as defined in claim 20 or (I-bis) such as defined in claim 21,

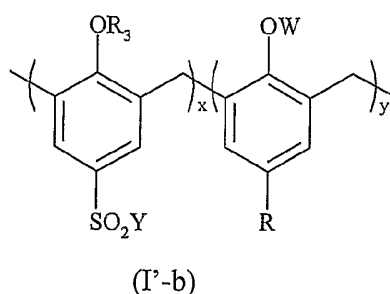
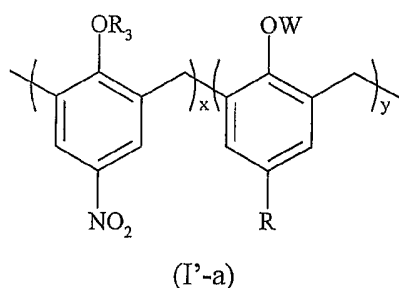
in order to obtain a compound having the respective formulas (I-a) or (I'-a) or (I-bis-a) such as defined in claim 20 or 21,

– and a reaction of sulfonation of the compound such as obtained previously of formula (I-a) or (I'-a) or (I-bis-a),

in order to obtain a compound having the respective formulas (I-c) or (I'-c) or (I-bis-c), such as defined in claim 20 or 21.

25. Process according to any of claims 20 to 24, characterized in that R and R₁ represent tBu groups.

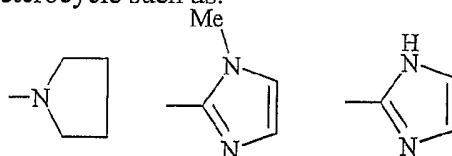
26. Compounds having one of the following formulas:



wherein:

- R and R₃ are such as defined for formula (I) in claim 1, R being different from NO₂ and SO₃⁻,
- x and y are integers different from 0, x + y varying from 4 to 8,
- W represents an alkyl group comprising 1 to 5 carbon atoms, said alkyl group being substituted with a protonable element chosen among:

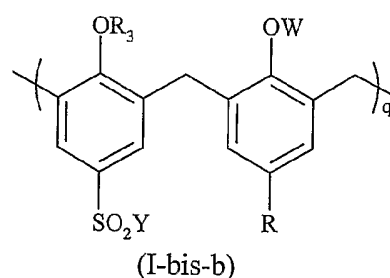
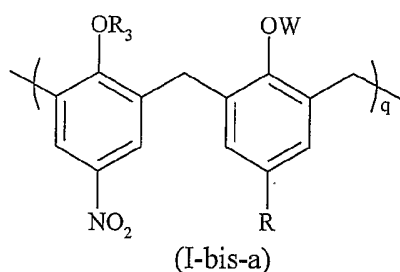
* a heterocycle such as:



or pyridine, or benzimidazole,

- * a primary, secondary or tertiary amine group, particularly NH_2 or NMe_2 ,
- * a $-\text{CO}-\text{R}_7$ or $-\text{CS}-\text{R}_7$ group wherein R_7 represents a primary, secondary or tertiary amine group, particularly a NH_2 group, or heterocycles, particularly such as , or a $-\text{OR}_8$ group, wherein R_8 represents H or an alkyl group comprising from 1 to 10 carbon atoms, or
- * a $-\text{OR}_8$ or $-\text{SR}_8$ group, wherein R_8 is such as defined above,
- Y represents OH, or an alkoxy group, or a primary or secondary amine group, or a halogen atom or a thioalkyl group.

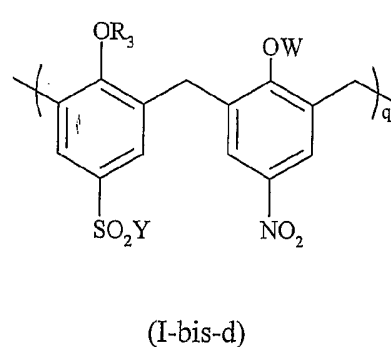
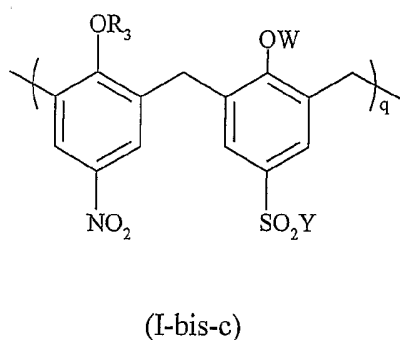
27. Compounds according to claim 26, having one of the following formulas:



wherein:

- q is an integer varying from 2 to 4,
- R, R_3 , W and Y are such as defined in claim 26,

28. Compounds according to claim 27, having one of the following formulas:



wherein R_3 , q, W and Y are such as defined in claim 27.

29. Compounds according to any of claim 27 or 28, characterized in that R_3 represents a methyl group.

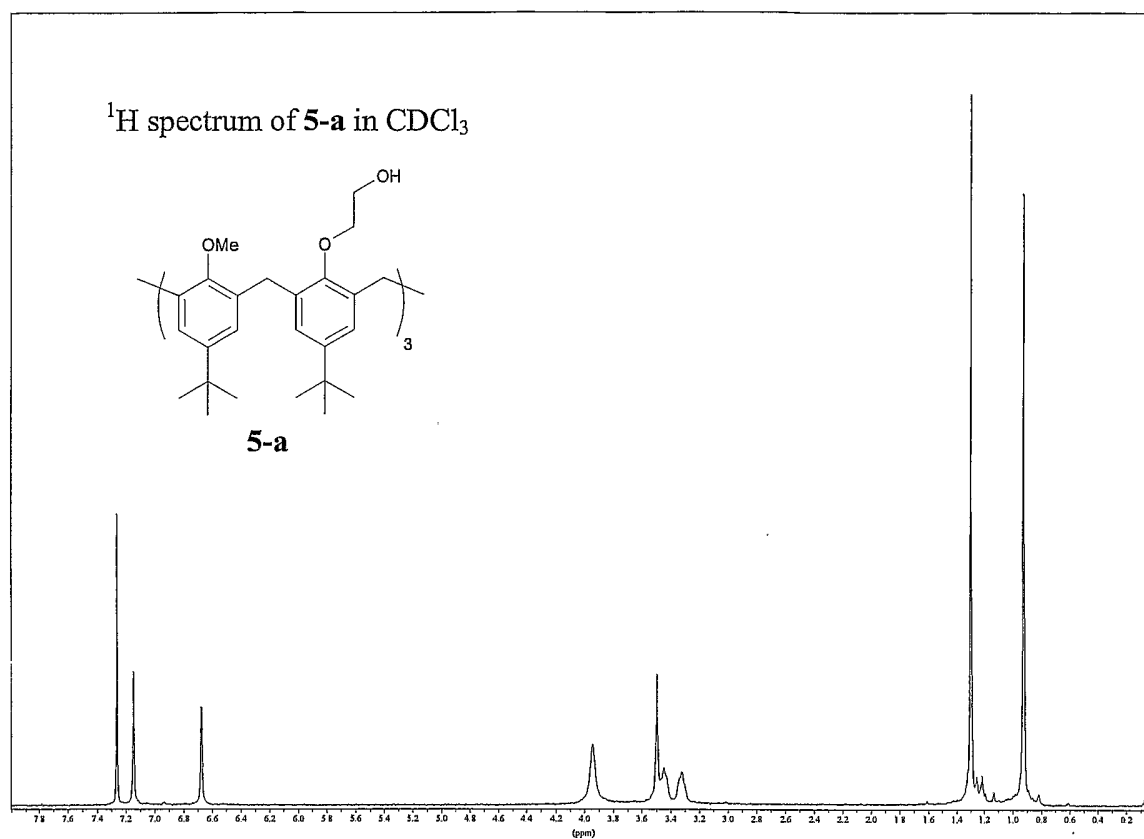


FIG 1

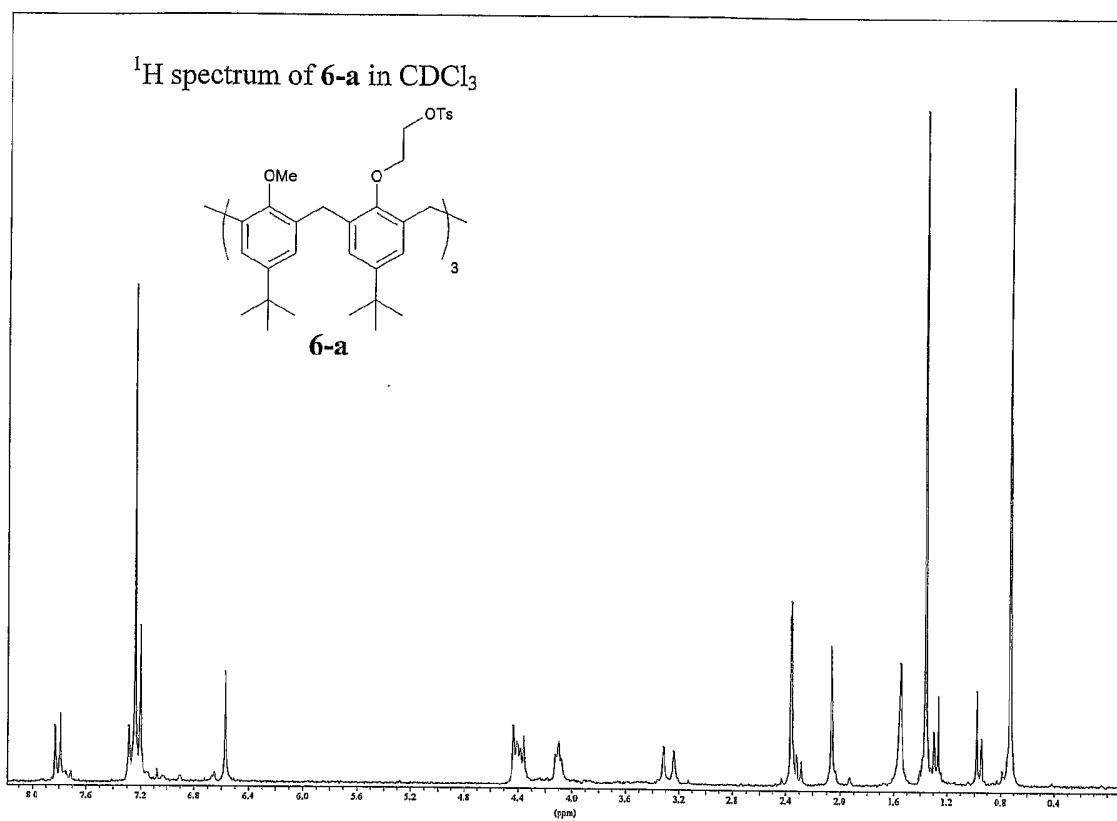


FIG 2

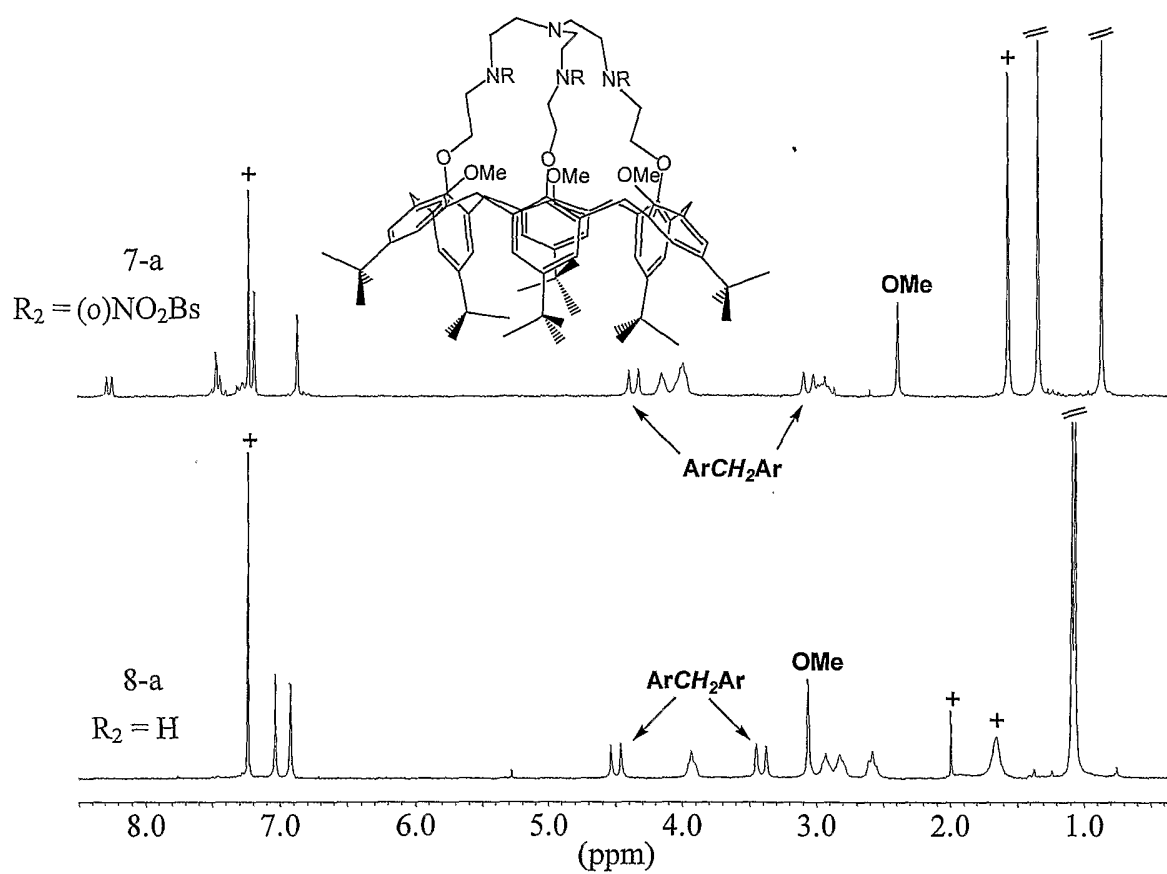


FIG 3

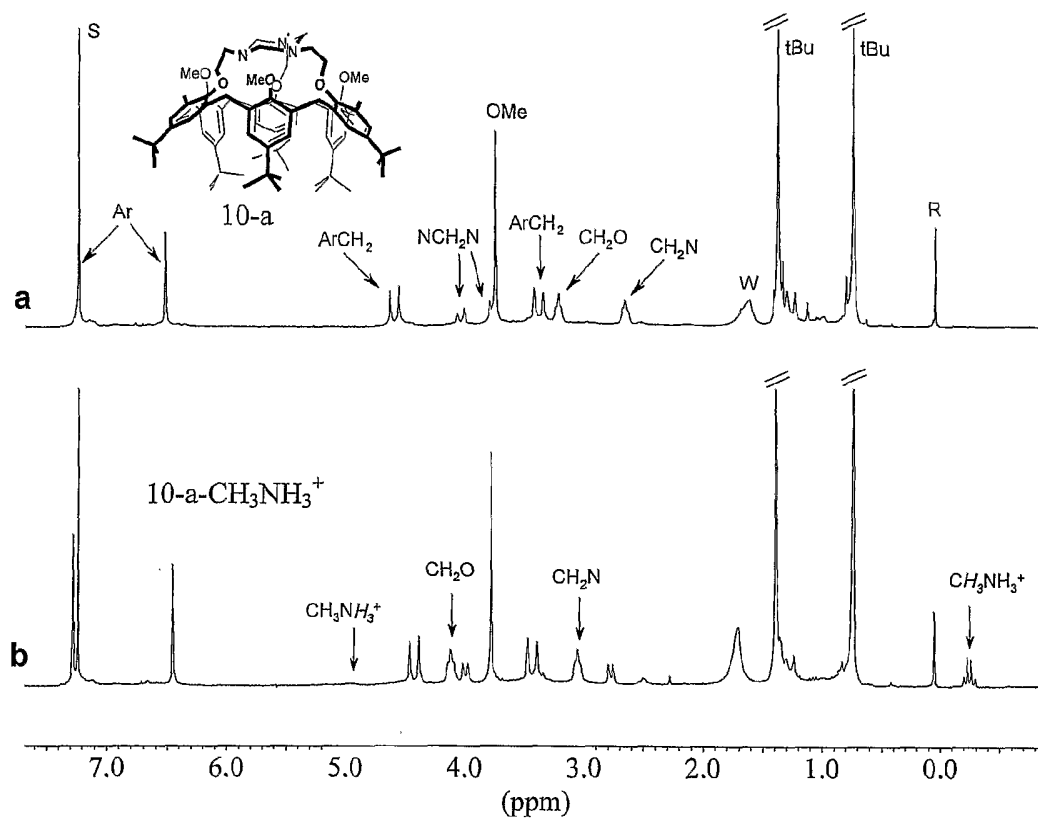


FIG 4

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/03045

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/22 C07D498/16 A61K31/555 A61P35/00

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)

IPC 7 C07D A61K

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 practical, search terms used)

CHEM ABS Data, BEILSTEIN Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YAN ZHANG: "A p-tert-butylcalix[6]arene capped with a triethanolamine-derived triple bridge" TETRAHEDRON, no. 57, 2001, pages 4161-4165, XP002265414 see the whole document	1-19
A	KOJI ARAKI: "Immobilization of the Ring Inversion Motion in Calix[6]arene by a cap with C3-Symetry" CHEMISTRY LETTERS, 1994, pages 1251-1254, XP009023264 see the whole document	1-19



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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.

"Z" document member of the same patent family

Date of the actual completion of the international search

17 December 2003

Date of mailing of the international search report

15.03.04

Name and mailing address of the ISA

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Authorized officer

Bedel, C

INTERNATIONAL SEARCH REPORT

International Application No

P EP 03/03045

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JINWEI ZHOU: "Polytopic Coreceptor from Conformationally Stabilized Calix[6]arene for Alkali Metal Ions" CHEMISTRY LETTERS, 1999, pages 345-346, XP009023245 see the whole document ---	1-19
A	JUN XING: "Two Stabilized Calix[6]cryptands Stereo Isomers used as Stationary Phases for Capillary Gas Chromatography" ANALYTICAL LETTERS, vol. 32, no. 15, 1999, pages 3071-3081, XP009023246 page 3071 -page 3074 ---	1-19
A	OLIVIA REYNAUD: "Calix[6]arene-Based N3-Donor- A Versatile Supramolecular System with Tunable Electronic and Steric Properties" EUR. J. INORG. CHEM., 2001, pages 2597-2604, XP002265415 see the whole document ---	1-19
A	WO 95 19974 A (HARRIS STEPHEN) 27 July 1995 (1995-07-27) claims -----	1,14-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/03045

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-19, 20-29 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-19, 20-29 (partially).

calix[6]arenes of formula (I), the metal complexes made therefrom, their use and their preparation as well as the intermediates. It also concerns the preparation of water soluble calix[6]arenes Ia-Id.

1.1. Claims: 2,3
compounds II and IIa

1.2. Claims: 5-11
compounds III and IIIa-IIIc

2. Claims: 20-29 (partially)

Process for making water-soluble calix[4-8]arenes other than Ia-Id as well as the said water soluble calix arenes

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

Information on patent family members

P/EP 03/03045

Form PCT/ISA/210 (patent family annex) (July 1992)