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(54) Titre : PROCEDE DE FABRICATION DE COMPLEXES METALLIQUES DE DERIVES D N-β-HYDROXY ALKYL-TRI-N-CARBOXYALKYL-1,4,7,10-TETRAAZACYCLODODECANE ET DE N- β HYDROXYALKYL-TRI-N-CARBOXYALKYL-1,4,8,11-TETRAAZACYCLOTETRADECANE

(54) Title: PROCESS FOR THE PRODUCTION OF METAL COMPLEXES OF N-β-HYDROXYALKYL-TRI-N-CARBOXYALKYL-1,4,7,10- TETRAAZACYCLODODECANE AND N-β-HYDROXYALKYL-TRI-N- CARBOXYALKYL-1,4,8,11 TETRAAZACYCLOTETRADECANE DERIVATIVES

(57) Abrégé/Abstract:
A new process for the production of metal complexes of N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives is described.

Abstract

A new process for the production of metal complexes of N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives is described.

Process for the production of metal complexes of N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives

The invention relates to the process for the production of metal complexes, characterized in the claims, of N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives.

Because of their importance as imaging diagnostic agents (DE OS 36 25 417), especially NMR diagnostic agents, the production of metal complexes of N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives has been tried in varied ways without a satisfactory method of synthesis, especially for their production on an industrial scale, previously having been able to be found.

In German laid-open specification DE 36 25 417 A1 a process for the production of metal complexes of N substituted tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane derivatives is described, in which tri-N-ethoxycarbonylmethyl-1,4,7,10-tetraazacyclododecane derivatives, that have a substitutent on the fourth nitrogen atom, are converted after cleavage of the still present carboxy protective groups into the metal complexes. The cyclic initial material needed for this process is obtained by specific ring synthesis. Thus a start is made from two

reactants, which are cyclized according to methods known from the literature [e.g., Richman, Org. Synthesis 58, 86 (1978); Atkins, J. Amer. Chem. Soc. 96, 2268 (1974)]; one of the two reactants contains a protected nitrogen atom and carries on the chain end two leaving groups (e.g., bromine, mesyloxy, tosyloxy, triflate or alkoxycarbonyl groups) that is nucleophilically displaced from the terminal nitrogen atoms of the second reactant of a -- different from the first reactant -- protected triaza compound.

The protective group chemistry used in the process of DE 36 25 417 A1 always leads to additional reaction steps in which the protective group must be removed again. Further large amounts of salts accumulate in the cleavage that then must be disposed of. Therefore an avoidance of protective groups, especially for a process that is to be used on an industrial scale, is desirable.

Tweedle et al. describe in European patent application 292 689 A7 and in publication Inorg. Chem. 1991, 30, 1265-1269 that starting from the unsubstituted macrocyclic compound 1,4,7,10-tetraazacyclododecane, the N-formyl compound can be obtained by a tricyclic intermediate stage. This compound still carrying three unprotected nitrogen atoms can now be trialkylated, deformylated and converted to the tetrasubstituted tetraazamacrocycle with haloacetic ester derivatives. After cleavage of the carboxy protective groups the tetrasubstituted complexing agent is obtained that can be reacted to the complex.

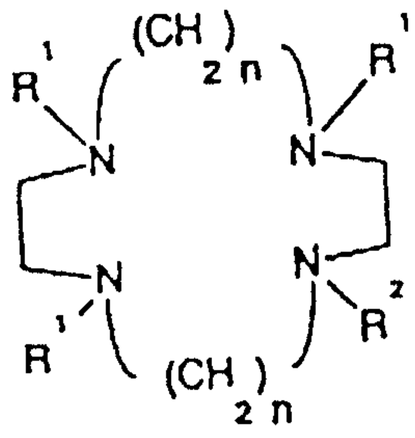
The synthesis method for the metal complexes described by Tweedle et al. for N substituted tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane derivatives has not only the disadvantage

of an unsatisfactorily high number of steps but it is not very suitable because of the high expenses for purification of the intermediate steps and high costs for large amounts of ion exchangers necessary for the production on an industrial scale. Further although a reaction of tri-N-carboxymethyl-1,4,7,10-tetraazacyclododecane (DO3A, compound (2) in Inorg. Chem. Vol. 30, No. 6, 1991, 1267) with primary epoxides is possible, however, the yields for the reaction with secondary epoxides are clearly inferior and poorly suitable for use on an industrial scale.

Therefore it continues to be the object to make available a process for the production of metal complexes of N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives, that as much as possible does not restrict the selection of the electrophiles needed in the process for the reaction and that above all is suitable for the reaction of sizable amounts of substance.

This object is achieved by this process.

It was found that the production of metal complexes of N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives of general formula I



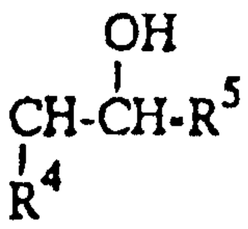
(I)

in which

R^1 means $-CH_2-COOY$

Y means hydrogen, a metal ion equivalent of an element of atomic numbers 21-32, 37-39, 42-51 or 57-83 provided that at least two substituents Y stand for metal equivalents

n means the numbers 2 or 3

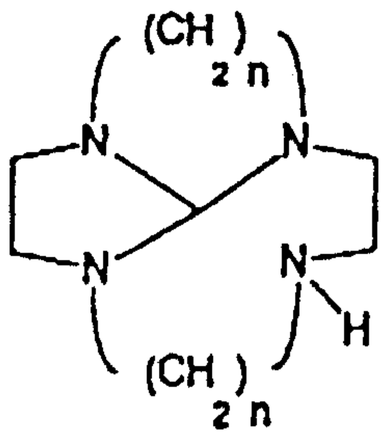
R^2 means a  group

R^4 and R^5, independent of one another, each stand for a hydrogen atom, a C_1-C_{20} alkyl radical optionally interrupted by 1 to 10 oxygen atom or atoms, a phenylene, phenylenoxy or phenylenedioxy group, which is optionally substituted by 1 to 3 C_1-C_6 alkyl, 1 to 3 trifluoromethyl, 1 to 7 hydroxy, 1 to 3 C_1-C_7 alkoxy or aralkoxy, 1 to 2 CO_2R^6 radicals,

in which R^6 stands for a hydrogen atom, a C_1-C_6 alkyl group, a C_6-C_{10} aryl or a C_6-C_{10}-Ar(C_1-C_4)alkyl group, and/or 1 to 2 phenoxy or phenyl groups optionally substituted by 1 to 2 chloro, bromo, nitro or C_1-C_6 alkoxy radicals,

and the optionally present hydroxy radicals optionally are present in protected form,

characterized in that the compound obtained from 1,4,7,10-tetraazacyclododecane or 1,4,8,11-tetraazacyclotetradecane of general formula II

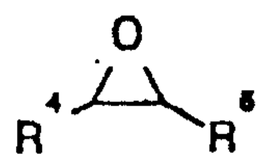


(II)

in which

n stands for the numbers 2 or 3

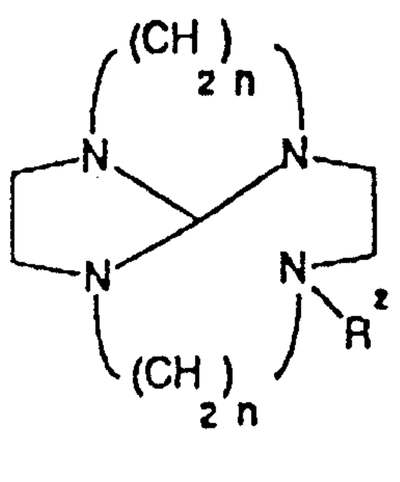
is reacted with an epoxide of general formula III



(III),

in which

R^4 and R^5 have the above-indicated meanings, and optionally present hydroxy or carboxy groups are optionally protected, to a intermediate of general formula IV



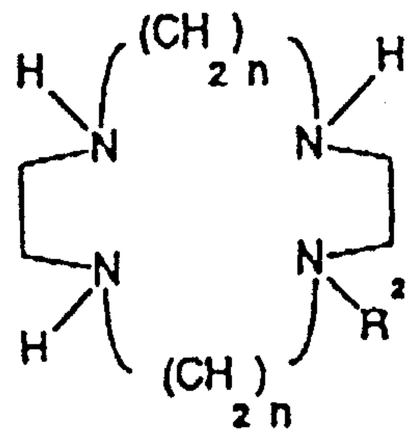
(IV),

in which

R^2 has the above-indicated meaning,

and optionally present hydroxy groups and/or carboxy groups are optionally protected,

the latter is saponified to an intermediate V



(V),

and the latter is reacted in the presence of a base with a compound of formula VI

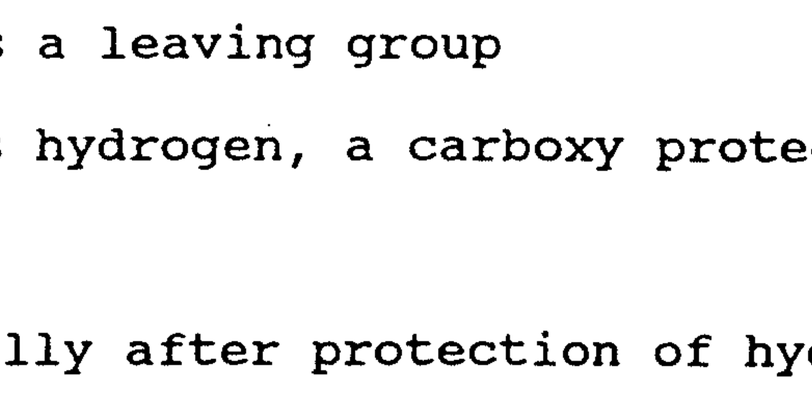
$$X\text{-}CH_2\text{-}COOZ \qquad (VI),$$

in which

X means a leaving group

Z means hydrogen, a carboxy protective group or a metal cation

optionally after protection of hydroxy or carboxy groups in a polar solvent at -10°C to 170°C within 1-100 hours, the protecting groups are optionally cleaved off and the thus obtained complexing agent of formula VII



(VII)

is reacted with a metal oxide or metal salt of an element of atomic numbers 21-32, 37-39, 42-51 or 57-83 and optionally still present hydrogen atoms are also substituted by cations of inorganic and/or organic bases, amino acids or amino acid amides or the still present acid groups are converted completely or partially into esters or amides.

The process according to the invention shows the following surprising effects:

1) The desired metal complexes of general formula (I) are obtained in a "one-pot reaction" under favorable operating conditions in higher yield than in the process of the prior art.

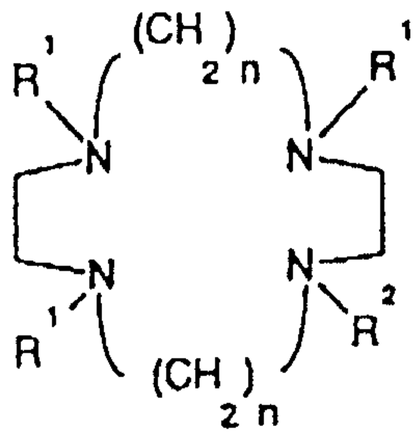
2) The intermediates are obtained in a so surprising high purity that their isolation and purification can be dispensed with.

3) In contrast with the process according to Tweedle et al. the reaction takes place with good yields even with secondary epoxides.

4) In comparison with the prior art, the process according to the invention comprises fewer steps.

5) The use of protective groups is indeed possible but not necessary for the process according to the invention.

A process is preferred that is characterized in that a compound of formula (I)



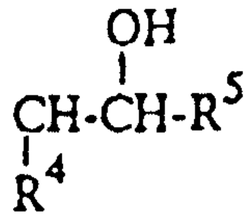
(I)

in which

R^1 means $-CH_2-COOY$

Y means a metal ion equivalent of an element of atomic numbers 21-32, 37-39, 42-51 or 57-83 provided that at least two substituents Y stand for metal equivalents

n means the number 2

R^2 means a  group

R^4 and R^5, independent of one another, each stand for a hydrogen atom, a C_1-C_{10} alkyl radical optionally interrupted by 1 to 5 oxygen atom or atoms, a phenylene, phenylenoxy or phenylenedioxy group, which optionally is substituted by 1 to 3 C_1-C_6 alkyl, 1 to 3 trifluoromethyl, 1 to 5 hydroxy, 1 to 3 C_1-C_7 alkoxy or 1 to 2 CO_2R^6 radicals,

and/or 1 to 2 phenoxy or phenyl groups optionally substituted by a nitro group or a C_1-C_6 alkoxy radical and

R^6 stands for a hydrogen atom, a C_1-C_6 alkyl group or a benzyl group, is reacted.

Especially preferred is a process for the production of metal complexes of 10-(1-hydroxymethyl-2,3-dihydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane and of metal complexes of 10-(2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

Quite especially preferred is a process for the production of gadolinium or dysprosium complexes of 10-(1-hydroxymethyl-2,3-dihydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-

tetraazacyclododecane and gadolinium or dysprosium complexes of 10-(2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

Preferred radicals R^4 and R^5 are the hydrogen atom, the methyl, ethyl, 2-hydroxyethyl, 2-hydroxy-1-(hydroxymethyl)ethyl, 1-(hydroxymethyl)ethyl, propyl, isopropyl, isopropenyl, 2-hydroxypropyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, butyl, isobutyl, isobutenyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-2-methylbutyl, 3-hydroxy-2-methylbutyl, 4-hydroxy-2-methylbutyl, 2-hydroxyisobutyl, 3-hydroxyisobutyl, 2,3,4-trihydroxybutyl, 1,2,4-trihydroxybutyl, pentyl, cyclopentyl, 2-methoxyethyl, hexyl, decyl, tetradecyl, triethylene glycol methyl ether, tetraethylene glycol methyl ether and methoxybenzyl group as well as the

$-CH_2-O-C_{11}H_{22}-OH-$,

$-CH_2-O-C_6H_4-O-(CH_2CH_2O)_2-CH_3-$,

$-CH_2-O-C_6H_4-O-(CH_2CH_2O)_3-C_5H_{11}-$,

$-CH_2-O-C_6H_4-O-C_4H_8-OH-$,

$-(CH_2CH_2O)_5-CH_3-$,

$-C_9H_{18}-COOH-$,

$-C_9H_{18}-OH-$,

$-CH_2-O-C_6H_4-O-C_6H_{12}-COOH-$,

$-CH_2-O-C_6H_4-O-C_4H_8-O-CH_2-CHOH-CH_2OH-$,

$-(CH_2CH_2-O)_3-C_5H_{11}-$,

$-CH_2-O-C_{10}H_{20}-COOH-$,

$-CH_2-O-C_6H_4-Cl-$,

$-CH_2-O-C_6H_4-NO_2-$,

$-CH_2-O-C_6H_3Cl_2-$,

$-CH_2-O-C_6H_4-O-CH_2-COOH-$,

$-CH_2-O-C_6H_4-O-CH_2-COOH-$ and

$-CH_2-O-C_6H_4-C_5H_{11}$ group.

As alkoxy substituents in R^4 and R^5 are meant straight chain or branched radicals with 1 to 6 or 1 to 7 C atoms such as, for example, methoxy, ethoxy, propoxy, isopropoxy.

As alkyl groups R^6 with 1-6 carbon atoms, straight chain or branched alkyl groups are suitable such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl. Especially preferred are methyl, ethyl, tert.-butyl.

Preferred aryl groups and aralkyl groups R^6 are phenyl, naphthyl and benzyl groups.

Especially preferred radicals R^6 are hydrogen, the methyl radical or benzyl radical.

The tetraazatricyclotridecanes or pentadecanes of general formula II used as feedstocks are available according to methods known from the literature, in that 1,4,7,10-tetraazacyclododecane or 1,4,8,11-tetraazacyclotetradecane is reacted with dimethylformamide dimethylacetal (US patents 4,085,106 and 4,130,715).

Advantageously this reaction step is included in the process according to the invention.

<u>Reaction conditions for the process steps</u>

1) (II) + (III) → (IV) → (V)

The reaction of the tricyclic intermediate step (II) with an epoxide of formula (III) takes place with or without solvent

between 0°C and 220°C, preferably between room temperature and 120°C, within 1 to 48 hours, preferably from 5 to 12 hours, optionally at a pressure of up to 100 atm.

The reaction mixture containing compound (IV), after cooling to -20°C to 80°C, preferably 0°C to 30°C, is mixed with a mixture of water/organic solvent, and stirred 0.5 to 12 hours, preferably 0.5 to 3 hours at -20°C to room temperature, preferably 0°C to room temperature.

By addition of an inorganic base or an acid at 0°C to 150°C, preferably room temperature to 120°C, within 1 to 72, preferably 6 to 24 hours, with stirring -- optionally followed by subsequent protective group removal in a manner usual in the art -- is reacted to the intermediate of formula V. The latter can also be isolated, if desired, as salt, preferably as hydrochloride.

As solvents for the reaction of the compounds of formula II with compounds of formula III, above all aprotic solvents such as, for example, benzene, tolene, dichloromethane, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, dimethylacetamide, dimethylsulfoxide, hexane or diethylether are suitable.

The solvents used in the mixture with water can be, e.g., methanol, ethanol, isopropanol, tetrahydrofuran, dioxane.

As base or acid, for example, alkali and alkaline-earth hydroxides, alkali and alkaline-earth carbonates or mineral acids such as, e.g., hydrochloric acid or sulfuric acid or methane sulfonic acid are suitable.

2) (V) + (VI) → (VII)

The bases added as acid traps in the further reaction of the intermediate of formula V with a compound of formula VI can be tertiary amines (e.g., triethylamine, trimethylamine, N,N-dimethylaminopyridine, 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN), 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU), alkali or alkaline-earth carbonates, alkali or alkaline-earth bicarbonates, or alkali or alkaline-earth hydroxides (e.g., lithium-, sodium-, magnesium-, calcium-, barium-, potassium-, -carbonate, -hydroxide and -bicarbonate).

The reaction takes place in polar solvents such as, for example, water, acetonitrile, dimethylformamide, dimethylsulfoxide, hexamethylphosphoric acid triamide or tetrahydrofuran as well as in alcohols with a chain length with up to 8 C atoms such as, e.g., methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol, tert.-butanol.

The reaction is performed at temperatures of -10°C-170°C, preferably at 0°-120°C, especially preferred at 40°-100°C, within 0.5-48 hours, preferably 3-24 hours.

The optionally performed introduction or cleavage of protective groups of carboxyl- or hydroxy functions takes place according to methods known in the literature.

As acid protective groups lower alkyl-, aryl- and aralkyl groups, for example, methyl-, ethyl-, propyl-, n-butyl-, tert.-butyl-, phenyl-, benzyl-, diphenylmethyl-, triphenylmethyl-, bis(p-nitrophenyl)-methyl groups, as well as trialkylsilyl groups are suitable.

The cleavage of the protective groups takes place according to processes known to one skilled in the art, for example, by hydrolysis, hydrogenolysis, alkaline saponification of the esters with alkali in aqueous alcoholic solution at temperatures of 0 to 50°C, acid saponification with mineral acids or in the case of e.g., tert.-butyl esters with the help of trifluoroacetic acid. As metal cations Z, metal cations of the elements of alkali or alkaline-earth metals are possible.

As hydroxy protective groups, e.g., benzyl-, 4-methoxybenzyl-, 4-nitrobenzyl-, trityl-, diphenylmethyl-, trimethylsilyl-, dimethyl-t-butylsilyl-, diphenyl-t-butylsilyl groups are suitable.

The hydroxy groups can also be present e.g., as THP-ether, α-alkoxyethylether, MEM-ether or as the esters with aromatic or aliphatic carboxylic acids, such as, e.g., acetic acid or benzoic acid. In the case of polyols, the hydroxy groups can also be protected in the form of ketals with, e.g., acetone, acetaldehyde, cyclohexanone or benzaldehyde.

The hydroxy protective groups can be released according to methods known from the literature to one skilled in the art, e.g., by hydrogenolysis, reductive cleavage with lithium/ammonia, acid treatment of the ethers and ketals or alkali treatment of the esters (see, e.g., "Protective Groups in Organic Synthetics", T.W. Greene, John Wiley and Sons 1981).

The intermediately obtained complexing agents of formula VII can be purified in an advantageous way by ion exchangers. For this purpose especially cation exchangers (in the H^+ form) which

are first washed with water and then, eluted with aqueous ammonia solution, yield the desired product. IR 120 (H^+) and AMB 252c (H^+) as well as Reillex® have proven to be especially advantageous exchangers. If Reillex® is used the complexing agent is eluted with water or aqueous alcohols.

3) (VII) → (I)

The production of the metal complexes according to formula I takes place in a way known in the art by the complexing agents of general formula VII being reacted with a metal oxide or metal salt of an element of atomic numbers 21-32, 37-39, 42-51 or 57-83 preferably in water and/or in aqueous solutions of lower alcohols (such as, e.g., methanol, ethanol or isopropanol) at temperatures of 20°C-110°C, preferably 80°C-100°C. The addition of 0.1-4 equivalents, preferably 0.5-2 equivalents, of an inorganic or organic acid, preferably acetic acid, has proved to be especially advantageous.

The thus obtained metal complex solutions can advantageously be purified by treatment on an ion exchange cascade or in a batch, consisting of an acid cation exchanger (H^+ form) and basic anion exchanger (OH^- form), preferably IR 120 H^+, AMB 252c/IRA 67.

The final cleaning is performed by crystallization from a lower alcohol, or an alcohol-water mixture. As alcohols there can be mentioned methanol, isopropanol, however ethanol is preferred.

The metal salts used can be, for example, nitrates, acetates, carbonates, chlorides or sulfates. The metals contained in the metal oxide or metal salt used can be an element of atomic numbers 21-32, 37-39, 42-51 or 57-83.

The following examples are used for detailed explanation of the object of the invention, however they are not to limit it.

Example 1

Gadolinium complex of 10-(1-hydroxymethyl-2,3-dihydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

a) 20 l (150.55 mol) of dimethylformamide dimethyl acetal is added (under nitrogen) to 20 kg (116.10 mol) of cyclene (=1,4,7,10-tetraazacyclododecane) in 140 l of toluene. It is slowly heated up and the azeotrope is distilled off from methanol/dimethylamine/toluene. Then, the solvent is completely distilled off by applying a vacuum. The remaining oil is allowed to cool to 50°C and then 18.7 kg (about 95%) (123.22 mol) of 4,4-dimethyl-3,5,8-trioxabicyclo-(5.1.0)-octane is instilled (under nitrogen). Then, it is stirred for 24 hours at 120°C. It is cooled to room temperature and a mixture of 100 l of water/150 l of methanol is instilled. Then, it is stirred for 1 hour at 50°C and 13.93 kg (348.3 mol) of sodium hydroxide is added. Then, it is refluxed for 8 hours. The solution is substantially evaporated to dryness, 200 l of water is added and again about 100 l of water is distilled off. Again, 100 l of water is added and this solution is extracted once with 200 l of n-butanol and then with 50 l of n-butanol. The combined butanol phases are evaporated to dryness in a vacuum and the residue is taken up in

300 l of water. Then, it is extracted twice with 50 l of ethyl acetate each. The water phase is separated and concentrated by evaporation to a volume of about 200 l.

b) 43.84 kg (464.4 mol) of chloroacetic acid is dissolved in 150 l of water and adjusted to pH 7 with 50% aqueous sodium hydroxide solution. The water phase concentrated by evaporation to a volume of about 200 l is added to this solution and heated to 80°C. The pH is kept between pH 9.5 - 10 by adding 50% aqueous sodium hydroxide solution. After 10 hours, another 10.96 kg (116.1 mol) of chloroacetic acid (previously neutralized as described above in 35 l of water with 50% aqueous sodium hydroxide solution) is added. It is stirred for 12 hours at 80°C and the pH is kept between 9.5 and 10. It is allowed to cool to room temperature and adjusted with concentrated hydrochloric acid to pH 0.8. Then, it is stirred for 2 hours at 60°C. The solution is substantially evaporated to dryness in a vacuum. The residue is mixed twice with a mixture of 200 l of methanol/200 l of ethanol and evaporated to dryness. Then, the residue is absorptively precipitated for 1 hour at 50°C with 400 l of methanol. It is filtered off from the precipitated sodium chloride, rewashed twice with 100 l of methanol and the combined filtrates are evaporated to dryness in a vacuum. The residue is dissolved in 200 l of water and added to an ion exchange column, filled with AMB 252c. It is washed with ample water and the product is eluted with a 10% aqueous ammonia solution. The product-containing fractions are substantially evaporated to dryness in a vacuum.

c) The residue is dissolved in 200 l of water and 16.31 kg (45 mol) of gadolinium oxide is added. It is refluxed for 3 hours. Then, 2 l of glacial acetic acid is added and refluxed for another 2 hours. 5 kg of activated carbon is added and stirred for 1 hour at 90°C. The solution is filtered and the filtrate is added several times on an ion exchange column cascade (consisting of IRA 67 (OH^- form)) AMB 252c (H^+ form) (under HPLC control). The eluate is concentrated by evaporation to a volume of 300 l and stirred for 3 hours with 2 l of acid ion exchanger IR 120 (H^+) as well as basic exchanger IRA 67 (OH^-) each. It is filtered off from the exchanger and rewashed twice with 10 l of water. 5 kg of activated carbon is added to the filtrate and stirred for 2 hours at 80°C. The solution is filtered and the filtrate is concentrated by evaporation in a vacuum. The residue is recrystallized from 95% aqueous ethanol (about 400 l). The precipitate is suctioned off, rewashed twice with 80 l of pure ethanol and dried for 48 hours at 70°C in a drying oven.

Yield: 47.6 kg (65.0% of theory) (corrected for water/ relative to cyclene) of colorless crystalline powder

Water content: 4.1%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	35.75	H	5.17	N	9.27	Gd 26.00
Fnd:	C	35.92	H	5.24	N	9.20	Gd 25.83

Example 2

Dysprosium complex of 10-[1-hydroxymethyl-2,3-dihydroxypropyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously, the corresponding dysprosium complex can be produced if, instead of gadolinium oxide, correspondingly 16.78 kg (45 mol) of dysprosium oxide is reacted.

Yield: 46.36 kg (62.7% of theory) (corrected for water/relative to cyclene)

Water content: 3.9%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	35.44	H	5.12	N	9.19	Dy 26.64
Fnd:	C	35.35	H	5.21	N	9.11	Dy 26.57

Example 3

Gadolinium complex of 10-(2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

a) 20 l (150.55 mol) of dimethylformamide dimethyl acetal is added (under nitrogen) to 20 kg (116.10 mol) of cyclene (=1,4,7,10-tetraazacyclododecane) in 140 l of toluene. It is slowly heated up and the azeotrope is distilled off from methanol/dimethylamine/toluene. Then, the solvent is completely distilled off by applying a vacuum. The remaining oil is allowed to cool to 50°C and then 10.11 kg (174.15 mol) of propylene oxide is instilled (under nitrogen). Then, it is refluxed for 24 hours and then excess propylene oxide is distilled off in a vacuum. It is cooled to room temperature and a mixture of 100 l of water/150 l of methanol is instilled. Then, it is stirred for 1 hour at

50°C and 13.93 kg (348.3 mol) of sodium hydroxide is added. Then, it is refluxed for 8 hours. The solution is substantially evaporated to dryness, 200 l of water is added and again about 100 l of water is distilled off. 100 l of water is again added, and this solution is extracted once with 200 l of n-butanol and then with 100 l of n-butanol. The combined butanol phases are evaporated to dryness in a vacuum and the residue is taken up in 300 l of water. Then, it is extracted twice with 50 l of ethyl acetate each. The water phase is separated and concentrated by evaporation to a volume of about 200 l.

b) 43.84 kg (464.4 mol) of chloroacetic acid is dissolved in 150 l of water and adjusted to pH 7 with 50% aqueous sodium hydroxide solution. The water phase concentrated by evaporation to a volume of about 200 l is added to this solution and heated to 80°C. The pH is kept between pH 9.5 - 10 by adding 50% aqueous sodium hydroxide solution. After 10 hours, another 10.96 kg (116.1 mol) of chloroacetic acid (previously neutralized as described above in 35 l of water with 50% aqueous sodium hydroxide solution) is added. It is stirred for 12 hours at 80°C and the pH is kept between 9.5 and 10. It is allowed to cool to room temperature and adjusted with concentrated hydrochloric acid to pH 0.8. The solution is substantially evaporated to dryness in a vacuum. The residue is mixed twice with a mixture of 200 l of methanol/200 l of ethanol and evaporated to dryness. Then, the residue is absorptively precipitated for 1 hour at 50°C with 400 l of methanol. It is filtered off from the precipitated sodium chloride, rewashed twice with 100 l of methanol and the

combined filtrates are evaporated to dryness in a vacuum. The residue is dissolved in 200 l of water and added to an ion exchange column, filled with AMB 252c. It is washed with ample water and the product is eluted with a 10% aqueous ammonia solution. The product-containing fractions are substantially evaporated to dryness in a vacuum.

c) The residue is dissolved in 200 l of water and 17.62 kg (48.6 mol) of gadolinium oxide is added. It is refluxed for 3 hours. Then, 2 l of glacial acetic acid is added and refluxed for another 2 hours. 5 kg of activated carbon is added and stirred for 1 hour at 90°C. The solution is filtered and the filtrate is added several times by an ion exchange column cascade (consisting of IRA 67 (OH^- form)) of AMB 252c (H^+ form) (under HPLC control). The eluate is concentrated by evaporation to a volume of 300 l and stirred for 3 hours with 2 l of acid ion exchanger IR 120 (H^+) as well as basic exchanger IRA 67 (OH^-) each. It is filtered off from the exchanger and rewashed twice with 10 l of water. 5 kg of activated carbon is added to the filtrate and stirred for 2 hours at 80°C. The solution is filtered and the filtrate is concentrated by evaporation in a vacuum. The residue is recrystallized from ethanol (about 300 l). The precipitate is suctioned off, rewashed once with 50 l of pure ethanol and dried for 48 hours at 70°C in a drying oven.

Yield: 45.22 kg (67.2% of theory) (corrected for water/relative to cyclene) of colorless crystalline powder

Water content: 3.5%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	36.55	H	5.23	N	10.03	Gd 28.15
Fnd:	C	36.68	H	5.31	N	9.91	Gd 28.03

Example 4

Dysprosium complex of 10-(2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogous to example 3c), the corresponding dysprosium complex can be produced, if, instead of gadolinium oxide, correspondingly 18.13 kg (48.6 mol) of dysprosium oxide is reacted.

Yield: 47.14 kg (65.3% of theory) (corrected for water/relative to cyclene)

Water content: 4.1%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	36.20	H	5.18	N	9.94	Dy 28.82
Fnd:	C	36.32	H	5.27	N	9.87	Dy 28.69

Example 5

Gadolinium complex of 10-(2-hydroxy-3-methoxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with 2,3-epoxypropylmethylether instead of propylene oxide as described in example 3. Thus, for example, 216.7 g (61% of theory) of the title compound is obtained from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane as colorless powder (crystallization from aqueous acetone).

Water content: 3.8%

Elementary analysis (relative to the anhydrous substance):

Cld: C 36.72 H 5.72 N 9.52 Gd 26.71

Fnd: C 36.51 H 5.83 N 9.39 Gd 26.57

Example 6

Gadolinium complex of 10-(2-hydroxy-3-benzyloxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with 2,3-epoxypropyl-benzylether instead of propylene oxide as described in example 3. 1.1 equivalents of epoxide is used relative to 1,4,7,10-tetraazacyclododecane. It is heated for 16 hours at 110°C (instead of 24 hours as described in example 3). Thus 249.2 g (62% of theory) of the title compound is obtained from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane (crystallization from isopropanol).

Water content: 4.2%

Elementary analysis (relative to the anhydrous substance):

Cld: C 43.36 H 5.31 N 8.43 Gd 23.65

Fnd: C 43.21 H 5.40 N 8.32 Gd 23.48

Example 7

Gadolinium complex of 10-(2,3,4-trihydroxybutyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with 2-(2,2-dimethyl-1,3-dioxolan-4-yl)-ethylene oxide instead of 4,4-dimethyl-3,5,8-trioxabicyclo-(5.1.0)-octane as described in example 1. 1.1 equivalents of epoxide is used relative to 1,4,7,10-

tetraazacyclododecane. It is heated for 16 hours at 110°C (instead of 24 hours as described in example 1). Thus 232.8 g (64% of theory) of the title compound is obtained as colorless, crystalline powder from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane (crystallization from 90% aqueous ethanol).

Water content: 3.5%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	35.75	H	5.17	N	9.26	Gd 26.00
Fnd:	C	35.55	H	5.23	N	9.14	Gd 25.87

Example 8

Gadolinium complex of 10-(2-hydroxy-3-tert.-butoxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with 2,3-epoxypropyl-tert.-butyl ester instead of propylene oxide as described in example 3. 1.1 equivalents of epoxide is used relative to 1,4,7,10-tetraazacyclododecane. It is heated for 16 hours at 110°C (instead of 24 hours as described in example 3). Thus 225 g (59% of theory) of the title compound is obtained as colorless, crystalline powder from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane (crystallization from acetone/ethanol).

Water content: 4.0%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	39.99	H	5.91	N	8.88	Gd 24.93
Fnd:	C	39.81	H	6.05	N	8.73	Gd 24.82

Example 9

Gadolinium complex of 10-(2,6,7-trihydroxy-4-oxaheptyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with 2,2-dimethyl-4-(2',3'-epoxy)-propoxy-methyl-1,3-dioxolane instead of 4,4-dimethyl-3,5,8-trioxabicyclo-(5.1.0)-octane as described in example 1. 1.1 equivalents of epoxide is used relative to 1,4,7,10-tetraazacyclododecane. It is heated for 16 hours at 110°C (instead of 24 hours as described in example 1). Thus 242.2 g (62% of theory) of the title compound is obtained as colorless, crystalline powder from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane (crystallization from ethanol).

Water content: 3.6%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	37.03	H	5.44	N	8.64	Gd 24.24
Fnd:	C	36.91	H	5.58	N	8.49	Gd 24.13

Example 10

Gadolinium complex of 10-(2-hydroxy-3-isopropoxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with 2,3-epoxypropylisopropyl ether instead of propylene oxide as described in example 3. 1.1 equivalents of epoxide is used relative to 1,4,7,10-tetraazacyclododecane. It is heated for 16 hours at 110°C (instead of 24 hours as described in example 3). Thus 232.5 g (63% of theory) of the title compound is obtained as colorless,

crystalline powder from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane (crystallization from isopropanol).

Water content: 3.1%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	38.95	H	5.72	N	9.08	Gd 25.50
Fnd:	C	38.85	H	5.81	N	8.93	Gd 25.35

Example 11

Gadolinium complex of 10-(2-hydroxy-2-methyl-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with iso-butylene oxide instead of propylene oxide as described in example 3. Thus for example 209.4 g (60% of theory) of the title compound is obtained as colorless powder from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane (crystallization from aqueous acetone).

Water content: 4.0%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	37.75	H	5.46	N	9.78	Gd 27.46
Fnd:	C	37.61	H	5.53	N	9.70	Gd 27.38

Example 12

Gadolinium complex of 10-(2-hydroxy-3-phenoxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

Analogously it can be reacted with 2,3-epoxypropyl-phenyl ether instead of propylene oxide as described in example 3. 1.1 equivalents of epoxide is used relative to 1,4,7,10-tetraazacyclododecane. It is heated for 16 hours at 110°C

(instead of 24 hours as described in example 3). Thus 252.4 g (64% of theory) of the title compound is obtained as colorless, crystalline powder from 100 g (0.58 mol) of 1,4,7,10-tetraazacyclododecane (crystallization from aqueous acetone).

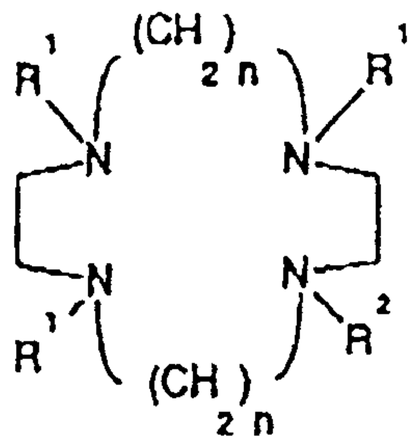
Water content: 3.7%

Elementary analysis (relative to the anhydrous substance):

Cld:	C	43.49	H	5.02	N	8.45	Gd 23.73
Fnd:	C	43.31	H	5.11	N	8.38	Gd 23.65

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for the production of a metal complex of an N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane and N-β-hydroxyalkyl-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivative of general formula I:



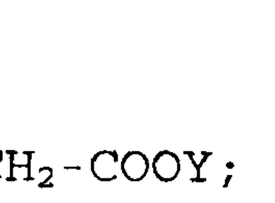
(I)

wherein

R^1 is $-CH_2-COOY$;

Y is a hydrogen atom, or a metal ion equivalent of an element of atomic numbers 21-32, 37-39, 42-51 or 57-83, provided that at least two substituents Y stand for metal equivalents;

n is 2 or 3; and

R^2 is a  group;

wherein R^4 and R^5, independent of one another, are selected from the group consisting of a hydrogen atom; a C_1-C_{20} alkyl group optionally interrupted by 1 to 10 oxygen atoms; a phenylene group; a phenylenoxy group; and a phenylenedioxy

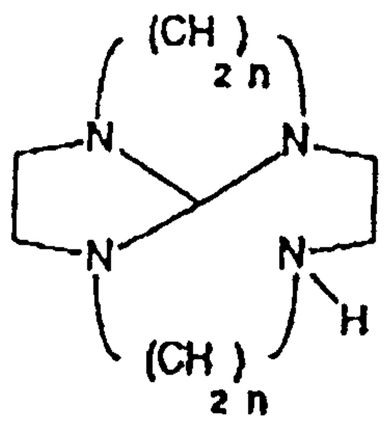
group; wherein R^4 or R^5 or both are optionally substituted by at least one substituent selected from the group consisting of 1 to 3 C_1-C_6 alkyl groups, 1 to 3 trifluoromethyl groups, 1 to 7 hydroxy groups, 1 to 3 C_1-C_7 alkoxy groups, 1 to 3 (C_6-C_{10})-aryl-(C_1-C_4) alkoxy groups, and 1 to 2 CO_2R^6 groups, wherein R^6 is a hydrogen atom, a C_1-C_6 alkyl group, a C_6-C_{10} aryl or a C_6-C_{10}-aryl(C_1-C_4)alkyl group;

and wherein hydroxy groups or carboxy groups, if present, are optionally protected;

or a salt thereof with at least one substance selected from an inorganic base, an organic base, an amino acid and, an amino acid amide;

the process comprising:

reacting a 1,4,7,10-tetraazacyclododecane or a 1,4,8,11-tetraazacyclotetradecane of general formula II:

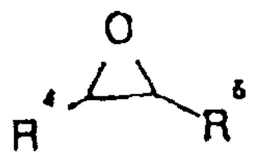


(II)

wherein

n is 2 or 3;

with an epoxide of general formula III:



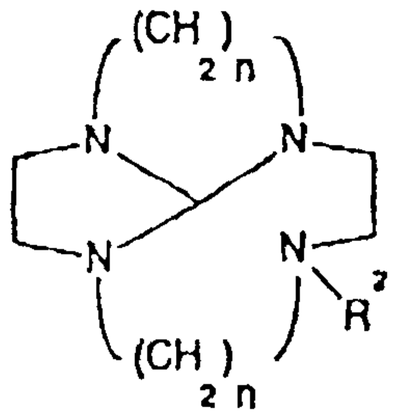
(III)

wherein

R^4 and R^5 are defined above; and

hydroxy groups or carboxy groups, if present, are optionally protected;

to produce a compound of general formula IV:



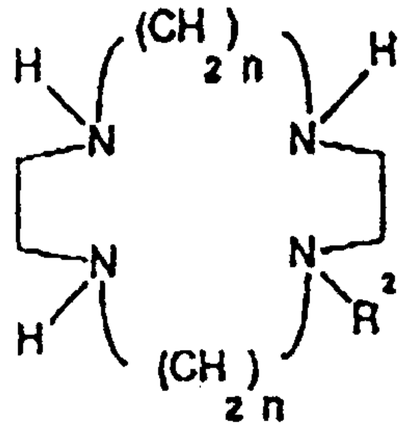
(IV)

in which

R^2 is defined above; and

hydroxy groups or carboxy groups, if present, are optionally protected;

saponifying the compound of general formula IV to produce a compound of general formula V:



(V)

reacting the compound of general formula V, in the present of an acid trap, with a compound of formula VI:

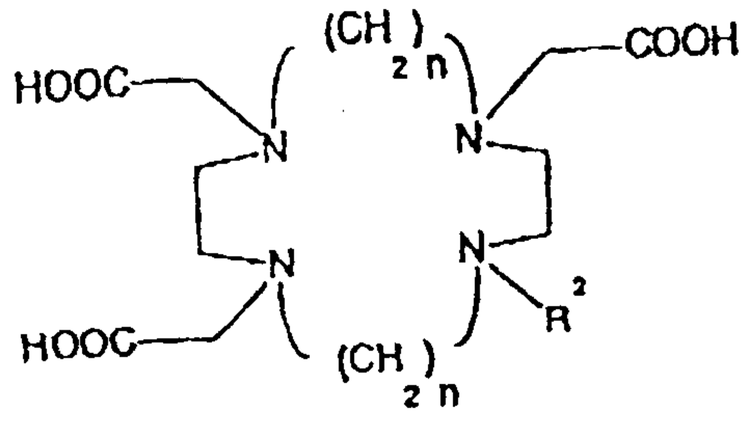
$$X\text{-}CH_2\text{-}COOZ \qquad (VI)$$

wherein

X is a leaving group; and

Z is a hydrogen atom, a carboxy protective group or a metal cation;

cleaving protecting groups, if present, in a polar solvent at -10°C to 170°C within 1-100 hours, to produce a compound of general formula VII:



(VII)

reacting the compound of general formula VII with a metal oxide or metal salt of an element of atomic numbers 21-32, 37-39, 42-51 or 57-83;

wherein, if necessary, still present hydrogen atoms are substituted by cations of at least one substance selected from the group consisting of an inorganic base, an organic base, an amino acid and an amino acid amide, or wherein, if necessary, still present acid groups are converted completely or partially into esters.

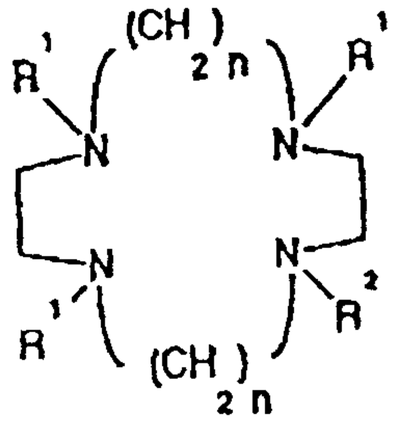
2. The process according to claim 1, wherein the reaction to produce the compound of general formula (IV) takes place at a temperature between 20°C and 120°C without solvent or in an aprotic solvent.

3. The process according to claim 1 or 2, wherein the reaction to produce the compound of general formula (V) takes place at temperatures between 0°C and 150°C in aqueous alcohol with addition of sodium hydroxide or potassium hydroxide or hydrochloric acid.

4. The process according to claim 1, 2 or 3, wherein the compound of formula (VI) is chloroacetic acid.

5. The process according to any one of claims 1 to 4, wherein the reaction of a compound of general formula (VII) takes place without protection of hydroxy or carboxy groups at temperatures between 40°C and 100°C in water within 3-24 hours.

6. The process according to claim 1, wherein a compound of formula (I)



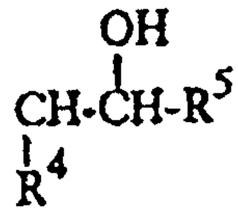
(I)

wherein

R^1 is $-CH_2-COOY$;

Y is a metal ion equivalent of an element of atomic numbers 21-32, 37-39, 42-51 or 57-83;

n is 2;

R^2 is a  group;

wherein R^4 and R^5, independent of one another, are selected from the group consisting of a hydrogen atom; a C_1-C_{10} alkyl group optionally interrupted by 1 to 5 oxygen atoms; a phenylene group; a phenylenoxy group; and phenylenedioxy group; wherein R^4 or R^5 or both are optionally substituted by at least one substituent selected from the group consisting of 1 to 3 C_1-C_6 alkyl groups, 1 to 3 trifluoromethyl groups, 1 to 5 hydroxy groups, 1 to 3 C_1-C_7 alkoxy groups and 1 to 2 CO_2R^6 groups, wherein R^6 is a hydrogen atom, a C_1-C_6 alkyl group or a benzyl group;

is obtained.

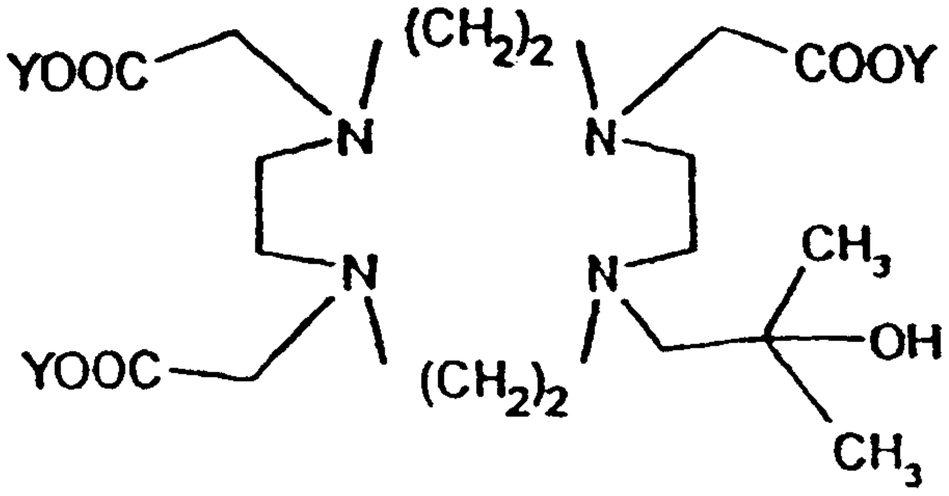
7. The process according to any one of claims 1 to 5, for the production of metal complexes of 10-(1-hydroxymethyl-2,3-dihydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

8. The process according to any one of claims 1 to 5, for the production of metal complexes of 10-(2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

9. The process according to any one of claims 1 to 5, for the production of gadolinium or dysprosium complexes of 10-(1-hydroxymethyl-2,3-dihydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

10. The process according to any one of claims 1 to 5, for the production of gadolinium or dysprosium complexes of 10-(2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

11. The process for the manufacture of metal complexes of N-(2-hydroxy-2-methyl-propyl)-tri-N-carboxyalkyl-1,4,7,10-tetraazacyclododecane derivatives or N-(2-hydroxy-2-methyl-propyl)-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclomethyl-propyl)-tri-N-carboxyalkyl-1,4,8,11-tetraazacyclotetradecane derivatives of the general formula Ia

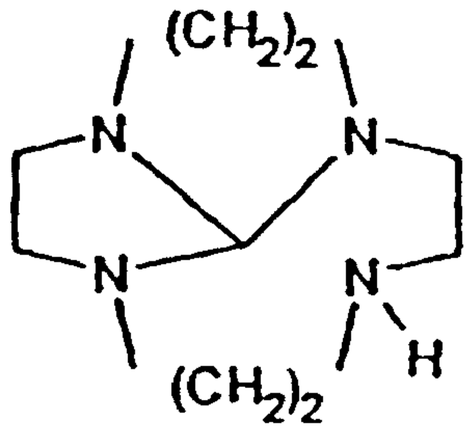


(Ia),

wherein

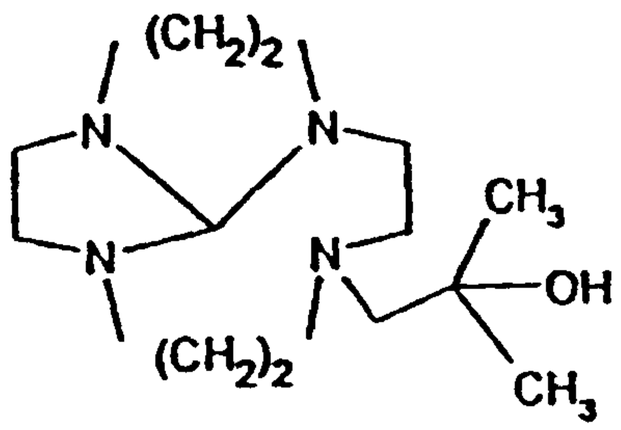
Y represents a hydrogen atom, or a metal ion equivalent of gadolinium, with the proviso that at least two substituents Y represent metal equivalents of gadolinium;

or a salt thereof with an inorganic base, an organic base, an amino acid or an amino acid amide, wherein the compound of the general formula IIa



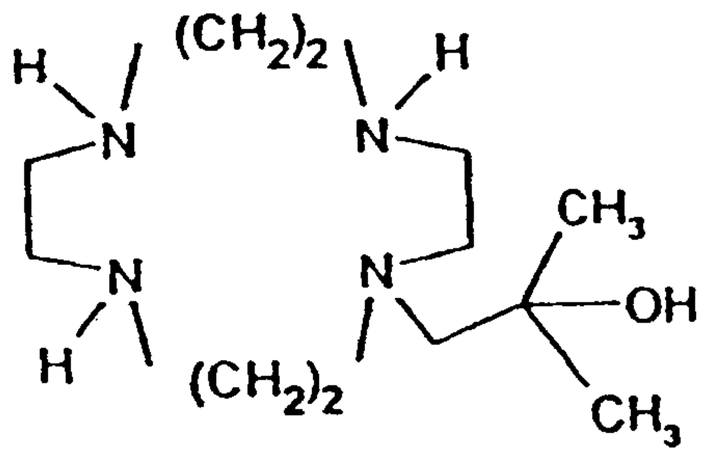
(IIa),

which is obtained from 1,4,7,10-tetraazacyclododecane or 1,4,8,11-tetraazacyclotetradecane, is reacted with isobutylene oxide to form an intermediate of the general formula IVa



(IVa),

that intermediate is hydrolysed to form an intermediate Va



(Va),

and that intermediate is reacted, in the presence of an acid acceptor, with a compound of the formula VI

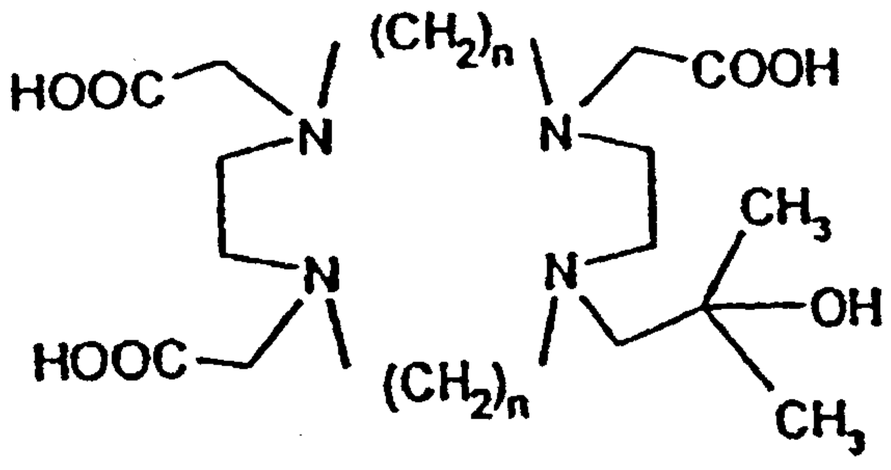
X-CH_2COOZ **(VI),**

wherein

X represents a leaving group, and

Z represents hydrogen, a carboxy-protecting group or a metal cation,

in a polar solvent at from -10°C to 170°C within a period of from 1 to 100 hours, and the complexing agent of the formula VIIa so obtained,



(VIIa),

is reacted with gadolinium oxide or a gadolinium salt, and if necessary hydrogen atoms still present are replaced by cations of an inorganic base, an organic base, an amino acid or an amino acid amide.