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SYNTHESIS OF DICARBOXYMETHYL TETRAAZACYCLODODECANE DERIVATIVES FOR POLYCONDENSATION

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Abstract-Three different routes to synthesize selectively protected tetraaza macrocycles bifunctionalized with carboxymethyl acid groups have been developed in order to obtain monomers for polycondensation. The first way has been carried out from cyclen, whose synthesis has been improved, requires 6 steps. The second way allowed to obtain the bifunctional protected macrocycle from ethylenediamine and diethyl iminodiacetate in 2 steps. The last way has consisted in synthesizing directly a monomer by cyclization from ethylenediaminetetraacetic acid bisanhydride and ethylenediamine.

Macrocyclic ligands chemistry has been extensively studied since the casual synthesis of a tetraaza macrocyclic coordinate in 1960[1]. Tetraazamacrocycles are able to form very stable complexes with transition metals cations[2]: Cu^{2+}, Co^{2+}, Fe^{3+}, and lanthanides[3] Gd^{3+}. Such molecules adapt remarkably to the coordination sphere of the metal ion and for that reason the complexes from macrocyclic ligands show a good thermodynamic stability, are kinetically inert with respect to dissociation and more selective than their acyclic analogues[4,5]. For example, the stability of the complex of DOTA[6] with gadolinium used as contrast agent[7] in Magnetic Resonance Imaging (M.R.I.) is better than with acyclic structures DTPA or EDTA.

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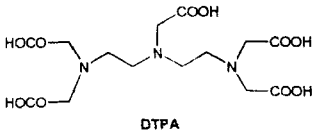
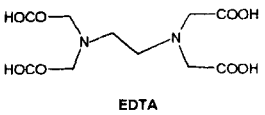


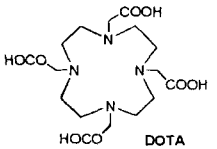
DTPA

diethylenetriaminepentaacetic acid



EDTA

ethylenediaminetetraacetic acid



DOTA

1,4,7,10-tetraazacyclododecane -1,4,7,10-tetraacetic acid

We have been particularly interested in the synthesis of a cyclic tetraaza structure analogous to DOTA. We were looking for macrocyclic monomers bifunctionalized in 1,4- or 1,7-positions. Lateral groups of this macrocycle should allow its immobilization in a polymer chain by polycondensation with bifunctional comonomers such as diols or diamines.

Three different general routes have been studied:

- a 6 steps way involving cyclen*, whose synthesis described in literature[8] has been improved. The selective protection of 4,10-positions by tosyl groups allows bifunctionalization by carboxymethyl acid groups in 1,7-positions.
- by cyclisation from ethylenediamine and diethyl iminodiacetate[9]. Amide groups protect the 4,10-positions of the obtained macrocycle and the bifunctionalization in 1,7-positions can be directly carried out. This way needs 2 steps.
- by cyclisation from ethylenediamine and EDTA bisanhydride[10]. This synthesis allows to get directly a bifunctionalized macrocycle but functionalized in 1,4-positions. It has been nevertheless studied since it allows to obtain a monomer in only one step.

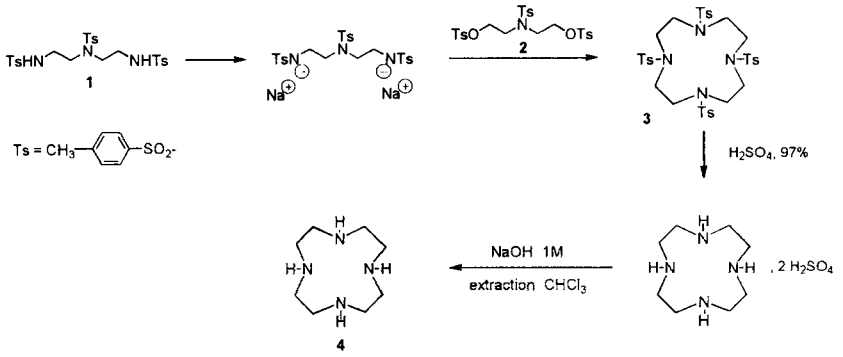
Synthesis of 1,7-dicarboxymethyl-4,10-ditosyl-1,4,7,10-tetraazacyclododecane from cyclen

Cyclen is a commercial but expensive product and its synthesis has been carried out according to the general procedure of Richman and Atkins[8].

First of all, we prepared the tetratosyl derivative from the disodium salt of [N, N', N''-tris(*p*-tolylsulfonyl)]diethylenetriamine **1** and from [N, O, O'-tris(*p*-tolylsulfonyl)]diethanolamine **2**, respectively obtained by amine and alcohol protection of diethylenetriamine and diethanolamine[4,11]. This type of reaction needs usually high dilution conditions to favour the

* trivial name of 1,4,7,10-tetraazacyclododecane

smallest cycle. However, in this case one can use a reasonable volume of solvent and obtain a yield of 86% in tetratosyl derivative **3**.

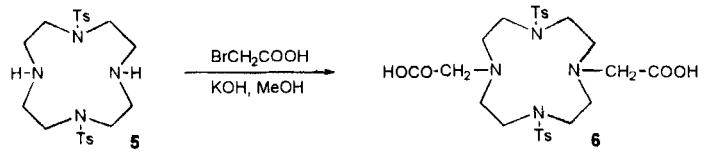


After hydrolysis of the tetratosyl derivative by sulfuric acid and neutralization by NaOH, extraction by chloroform gave cyclen with a yield of only 40%. So the aqueous layer was evaporated on a rotary evaporator and the solid residue was extracted by chloroform. This additional step allows to improve the yield (70%) compared to literature (59%)[12].

Bifunctionalization of the cyclen in 1,7-positions needs the protection of the two other nitrogen atoms in 4,10-positions, which was carried out by reaction of the cyclen with *p*-toluenesulfonylchloride in pyridine[13] leading exclusively to the 1,7-isomer. Obtaining of the pure 1,7-regioisomer was checked by ^{1}H NMR spectrum, which shows only two sets of peaks. Indeed, ^{1}H NMR spectrum of the 1,4-regioisomer should show four different sets of peaks. Moreover, mass spectrometry showed the absence of monotosylate or tritosylate derivatives.

The synthesis of the bifunctional macrocycle (1,7-dicarboxymethyl-4,10-ditosyl-1,4,7,10-tetraazacyclododecane) from 1,7-ditosyl-1,4,7,10- tetraazacyclododecane is the last step before polycondensation. This bifunctionalization has been carried out with carboxymethyl acid groups, whose acid functions can easily react with alcohol or amine functions. Syntheses as reported in literature[7,14-16]using chloroacetic or bromoacetic acid in a sodium hydroxide solution on ditosylate derivative **5** in water gave very poor yields, perhaps because of halogen hydrolysis.

So, another synthesis[17] using an anhydrous organic solvent (absolute methanol) was tested. The product **6** is then obtained in quantitative yield.

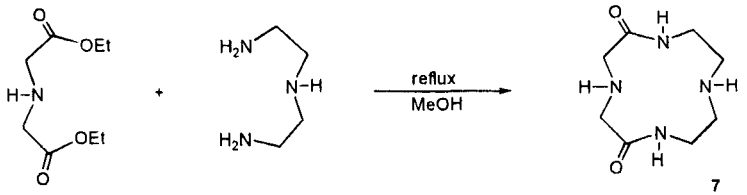


Characterization by ^{1}H NMR, ^{13}C NMR and IR showed the formation of the pure product 6 and potentiometric titration confirmed the presence of two acid functions per molecule.

The synthesis of a bifunctional macrocycle protected in 4,10-positions has been reached. However, too much steps is unfavourable for the global yield (20 %), so a shorter synthesis was needed.

Synthesis of 1,7-dicarboxymethyldioxocyclen

Dioxocyclen 7 has been obtained from diethyl iminodiacetate and diethylenetriamine[9]. The advantage of this synthesis is the direct protection of two nitrogen atoms as amide functions.



This condensation reaction needs quite high dilution conditions (C = 5.10^{-2} mol.L^{-1} in methanol) in order to favour obtaining of the smallest cycle.

A kinetic study of the macrocycle formation has been carried out by ^{1}H NMR spectroscopy to follow disappearance of the starting products. The results show the necessity of a reaction time of 5 days to obtain a complete conversion. Indeed, after 4 days, starting products are still present in the reaction medium.

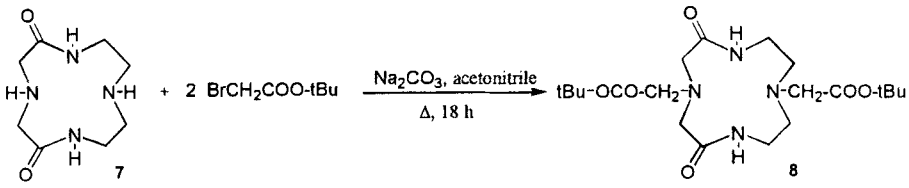
Use of ethanol as solvent instead of methanol, a higher reaction temperature and use of an inert atmosphere didn't allow to decrease the reaction time.

After 5 days, the solution was evaporated and after recristallization in methanol, dioxocyclen 7 was obtained (10%).

^{1}H NMR and ^{13}C NMR were consistent with obtaining of 7. Mass spectrometry confirmed the synthesis of dioxocyclen together with higher macrocycles. In order to determine the

composition of the medium reaction, HPLC and SEC analyses were envisaged. Use of these analyses needs a good solubility of the analysed products in usual solvents, which is not the case of 7. So, a diester derivative of dioxocyclen was prepared.

The ditertiobutyl diester was synthesized [18] from dioxocyclen and tertiobutyl bromoacetate.



SEC analysis (Fig.1) showed the presence of the diester derivative **8**, which confirmed the initial synthesis of the dioxocyclen 7. In addition to the tertiobutyl bromoacetate and the monofunctional macrocycle, which result from the esterification, the chromatogramm also showed the presence of higher macrocycles from the dioxocyclen synthesis.

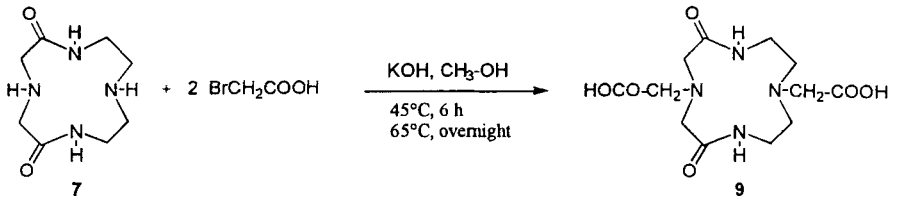
In order to specify the constituents percentage, a preparative HPLC at limit solubility conditions (acetonitrile/water 70/30) was carried out on the diester derivative.

Three peaks were obtained and the nature of each constituent has been identified after separation in three fractions and ^{1}H NMR analysis:

- at t = 12.1 min: 17 % of 7,
- at t = 16.7 min: 3 % of the monofunctional product,
- at t = 19.8 min: 72 % of the diester derivative **8**,
- at t = 27.5 min: 8 % of higher macrocycles.

This preparative HPLC has allowed to reach the pure product **8** which was used to synthesize the diacid macrocycle by hydrolysis[19].

A poor yield (15%) and the presence of residual tertiobutyl groups made this way unattractive and dioxocyclen was directly bifunctionalized by bromoacetic acid according to the same operating conditions as for the derivative **5**.



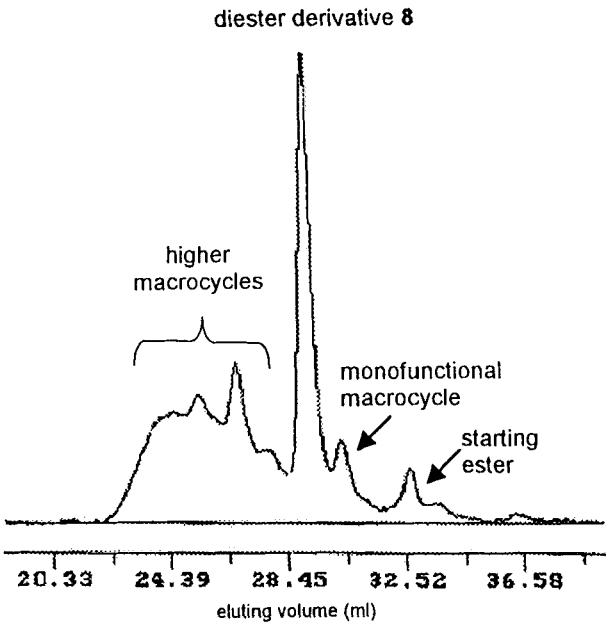


Fig. 1: SEC chromatogramm in THF of the products resulting of the synthesis of **9**

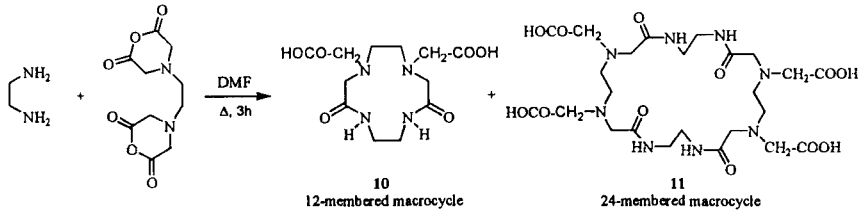
This synthesis[17] using absolute methanol led to the monomer **9** with a nearly quantitative yield (93%).

The bifunctionality of the macrocycle was confirmed by potentiometric titration.

This second synthesis leads to a 1,7-bifunctional macrocycle protected by amide groups in 4,10-positions in fewer steps than the first synthesis. Nevertheless, the overall yield of 9.3% is also very weak. Attemps to increase the yield of the first step are in progress.

Synthesis of 6,11-dioxo-1,4,7,10- tetraazacyclododecan-1,4-diacetic acid

A third synthetic route has been studied although the obtained macrocycle is slightly different since it is functionalized in 1,4-positions with 7,10-positions protected as amide functions, but it needs only one step.



10
12-membered macrocycle

11
24-membered macrocycle

Reaction of ethylenediamine and EDTA bisanhydride under high dilution conditions in order to favour the smallest cycle[10] led to a mixture of 6,11-dioxo-1,4,7,10-tetraazacyclododecan-1,4-diacetic acid and higher macrocycles mainly 6,11,18,23-tetraoxo-1,4,7,10,13,16,19,22-octaazacyclotetracosan-1,4,13,16-tetraacetic acid **11** which proportions are depending on reaction conditions (Table). These products were isolated by differences of solubility[10]. **10** precipitates on addition of water to the concentrated product and then **11** with THF.

The influence of the medium concentration has been studied in order to reach a better yield in 12-membered macrocycle compared to literature. The 24-membered macrocycle isolated yield is independent of the concentration contrary to that of the 12-membered macrocycle. It seems that the optimum conditions to obtain the smallest cycle with the best yield are reached with a medium concentration $C = 2 \cdot 10^{-2}$ mole.l^{-1}. The reaction with a less concentrated medium didn't allow to increase the yield in cyclic structures probably because of partial hydrolysis of anhydride functions before the reaction occurs. Use of a higher concentration doesn't favour the cycles formation because of the competition of chain extension.

The presence of higher macrocycles (36, 48 and 60-membered macrocycles) has been proved by MALDI-TOF MS (Fig.2), their yields being too low to be detected by NMR spectroscopy. **10** and **11** characterized only by elemental analyses in literature[10] have been characterized by ^{1}H NMR and ^{13}C NMR, IR and mass spectrometry.

Synthesis of macrocycles bifunctionalized with carboxymethyl acid groups has been carried out as precursors of polycondensates in which macrocycles are inserted in the main chain. Three different routes were studied.

The first route from cyclen, synthesized in 4 steps, whose synthesis has been improved, allowed to reach the 1,7-dicarboxymethyl-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane (in 2 steps), whose amine functions are protected by tosyl groups but with a global yield of 20.2%.

Table: Influence of the reaction conditions on the isolated yields during the synthesis of the macrocycle **10** in DMF

[C] (mol.l^{-1})	Temp. (°C)	**10** (%)	**11** (%)
$4 \cdot 10^{-2}$	60	27.1	2
$2 \cdot 10^{-2}$	60	38	3
$1 \cdot 10^{-2}$	60	10.4	3

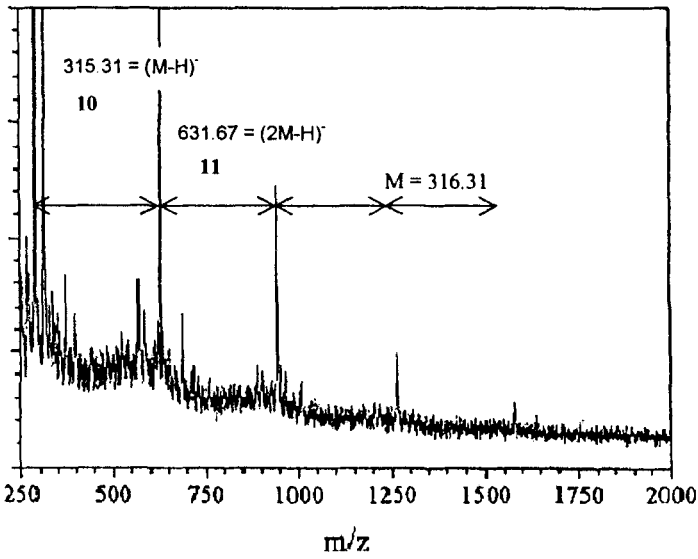


Fig. 2: MALDI-TOF MS spectrum of the products resulting of the synthesis of **10**

The second route has been carried out from dioxocyclen, synthesized in one step, and has allowed to obtain the 1,7-dicarboxymethyldioxocyclen, whose 4,10-positions are protected as amide groups with a total yield of only 9.3% in spite of only 2 steps.

The third route allowed to reach directly in one step a bifunctional carboxymethyl acid macrocycle but in 1,4-positions, whose 7,10-positions are protected by amide groups, which can also be used in polycondensation. Its synthesis has also been improved with regards to literature and has allowed to obtain this macrocycle with a yield of 38%.

The polycondensation of these three bifunctional macrocycles with diols or diamines in order to obtain polymeric complexing structures will be the subject of a further publication[20].

EXPERIMENTAL

Products

Chloroform, methylene chloride, ethanol, diethyl ether, methanol and water were purified according to standard procedures. Acetonitrile, n-pentane, pyridine, *N,N*-dimethylformamide (DMF), tetrahydrofurane (THF) and deuterated solvents used in NMR were commercial products (ACROS, purity>99%) used without further purification. Ethylenediaminetetraacetic acid bisanhydride, ethylenediamine, bromoacetic acid, triethylamine, diethanolamine, diethylenetriamine, tosyl chloride, acetic acid, diethyl iminodiacetate, tertiobutyl bromoacetate, LiOH, H_2O, NaOH, KOH, Na_2CO_3, $NaHCO_3$, Na_2SO_4, $MgSO_4$ and sulfuric acid 97% were commercial products (ACROS) used without further purification.

Hydrochloric acid solution 6 $mol.L^{-1}$ was prepared from a commercial 37% hydrochloric acid solution (ACROS).

Methods

Nuclear Magnetic Resonance spectra were carried out on a Bruker AC 200 spectrometer for ^1H NMR (200 MHz) and for ^{13}C NMR (50 MHz). Chemical shifts expressed in ppm were referenced to tetramethylsilane (TMS) when deuterated solvent was chloroform ($CDCl_3$) or DMSO D_6 and to sodium 2,2-dimethyl-2-sila-5-pentyl sulfonate (DSS) in D_2O or D_2O + NaOD.

The infrared spectra were measured in the 4000-500 cm^{-1} range from a Fourier transform Bruker IFS 66 spectrometer. The samples were KBr pellets for solids. The reported absorptions are expressed in wavenumber (cm^{-1}).

Size-Exclusion Chromatography (SEC) in water was carried out with PW 5000 and PW 6000 columns. The eluent was H_2O/(ammonium acetate 0.1$mol.L^{-1}$, NaN_3 100 mg/L). The selectivity domain was 1000 to 2.10^6 and results were calculated by reference to Pullulan standards. Differential refractometer was used as detector.

High Performance Liquid Chromatography (HPLC) analyses were performed on a WATERS modular chromatograph equipped with two detectors (UV-vis spectrometer and differential refractometer), two Model 510 pumps and a Model U6 K injector. Various columns were used in relation with the applications: a Waters RCM Radialpak, Nova-pak C18 column (100•5

mm i.d., particle size of 4 μm) in analytical mode with methanol as eluent (flow 1 mL/min) ; a μ Bonda-pak C18 column (150•19 mm i.d., particle size of 10 μm) in semi-preparative mode with methanol (flow 2 mL/min).

Mass spectrometry analyses were carried out on a VG PLATFORM FISONS spectrometer in PCI mode.

MALDI-TOF MS spectra have been carried out as a favour by M^{r} Brunelle of Université d'Orsay.

Elemental analyses were performed by the Service Central d'Analyse du Centre National de la Recherche Scientifique, Vernaison (France).

[N, N', N''-tris(*p*-tolylsulfonyl)]diethylenetriamine (1)

To a solution of diethylenetriamine (21.7 g: 0.19 mol) and sodium hydroxide (160 ml) in water (100 ml) was added dropwise a solution of toluene-*p*-sulfonyl chloride (114 g: 0.6 mol) in diethyl ether (300 ml). The reaction mixture was stirred for 1-2 h at room temperature, during which time the product slowly cristallised. The colourless tosyl derivative was filtered off, washed with water then diethyl ether, and recristallised from methanol to give the white product **1** (Yield: 62.3 g ; 58 %). Mp 172°C.

^{1}H NMR DMSO-D_6 δppm: 2.4 (9H, s, aryl CH_3), 2.51 (1H, s, NH), 2.85 (4H, t, *J* 6.3Hz, CH_2N), 3.04 (4H, t, *J* 6.3Hz, CH_2N), 3.38 (1H, s, NH), 7.4-7.7 (12H, m, Ts)

^{13}C NMR DMSO-D_6 δppm: 21.83 (CH_3), 42.45 (CH_2NHTs), 49.25 (CH_2NTs), 127.40, 127.69, 130.53, 130.73, 136.23, 137.81, 143.61, 144.31 (aryl C)

[N, O ,O'-tris(*p*-tolylsulfonyl)]diethanolamine (2)

Tosyl chloride (233 g: 1.223 mol) was dissolved in CH_2Cl_2 (400 ml) in a 2L flask at 0°C with stirring. To this solution was added dropwise a solution of diethanolamine (42 g: 0.4 mol) and triethylamine (180 ml) in CH_2Cl_2 (200 ml) at 0°C. Stirring was continued overnight at room temperature after the addition was completed. The precipitate generated from the reaction was filtered off, and the solution was washed with water, dilute HCl and saturated $NaHCO_3$ and dried (Na_2SO_4). After evaporation to dryness, 100 ml of ethanol were added. Crystals appeared, after the solution stood at room temperature for several hours, which were collected and washed with cold 95% ethanol to give the product **2** (Yield: 182 g ; 81 %). Mp 88°C.

^{1}H NMR $CDCl_3$ δppm: 2.46 (9H, s, aryl CH_3), 3.37 (4H, t, *J* 5.9Hz, CH_2N), 4.12 (4H, t, *J* 5.9Hz, CH_2N), 7.3-7 8 (12H, m, Ts)

^{13}C NMR $CDCl_3$ δppm: 21.53, 21.67 (CH_3), 48.44 (CH_2NTs), 68.29 (CH_2OTs), 127.23, 127.95, 129.98, 130.04, 132.39, 135.24, 144.17, 145.23 (aryl C)

1,4,7,10-tetrakis(*p*-tolylsulfonyl)-1,4,7,10-tetraazacyclododecane (3)

The entire synthesis was conducted under a dry N_2 atmosphere. [N, N', N''-tris(*p*-tolylsulfonyl)]diethylenetriamine (28 g: 0.05 mol) was dissolved in DMF (400 ml) and NaH (55-65% in paraffin oil, 10g: 0.23-0.27 mol) was added in small portions with stirring to produce the disodium salt of the amine. The solution was stirred during 2 h and the excess of NaH filtered off. To the filtrate heated to 110-120°C, a solution of [N, O ,O'-tris(*p*-tolylsulfonyl)]diethanolamine (28 g: 0.05 mol) in DMF (200 ml) was added dropwise, the resulting mixture stirred 2 h, then allowed to cool at room temperature and transferred to a flask (3 L) equipped with a mechanical stirrer. The addition of water (1 L) with vigorous stirring produced a white solid, which was filtered off, washed with water (500 ml) and dried in vacuum overnight (Yield: 34.1 g ; 86 %). Mp 96°C.

^{1}H NMR $CDCl_3$ δppm: 2.44 (12H, s, aryl CH_3), 3.43 (16H, s, CH_2N), 7.3-7.7 (12H, m, Ts)

^{13}C NMR $CDCl_3$ δppm: 21.52 (CH_3), 52.28 (CH_2NTs), 127.69, 129.86, 133.90, 143.94 (aryl C)

1,4,7,10-tetraazacyclododecane (4)

1,4,7,10-Tetrakis(p-tolylsulfonyl)-1,4,7,10-tetraazacyclododecane (34.1 g: 0.043 mol) was treated in 97% H_2SO_4 (100 ml) during 48 h at 100°C. The resulting brown mixture was cooled to room temperature and 400 ml of ethanol, followed by 350 ml of diethyl ether, were slowly added. The brown precipitate was filtered off, washed with ethanol and diethyl ether, and dried under vacuum for 6 h. The solid was then divided into three equal portions, each of which was dissolved in 100 ml NaOH (1 $mol.L^{-1}$) and extracted one time with $CHCl_3$ (200 ml). The three chloroform extracts were dried ($MgSO_4$) and evaporated. The resulting solid **4** was then dried in vacuum overnight. A second fraction was obtained by evaporation of the aqueous extracts, followed by dissolution of the residue in 350 ml of chloroform overnight under stirring. The filtrate was then dried ($MgSO_4$) and evaporated. The resulting solid **4** was dried in vacuum overnight. These two fractions gave the white solid **4** (Yield: 5.2 g ; 70%). Mp 110°C.

^{1}H NMR $CDCl_3$ δppm: 2.15 (4H, s, NH), 2.69 (16H, s, CH_2N)

^{13}C NMR $CDCl_3$ δppm: 46.11 (CH_2N)

1,7-ditosyl-1,4,7,10-tetraazacyclododecane (5)

To a solution of tosyl chloride (4.98 g: 26.2 mmol) in pyridine (50 ml) chilled to 0°C, a solution of **4** (2.25 g, 13.1 mmol) in pyridine (25 ml) was added dropwise at 0°C. The reaction mixture was stirred during 4 h at room temperature after completing the addition. Pyridine was

evaporated in a rotavapor, the residue was taken up by 20 ml of water and the mixture was stirred during 3 h. The insoluble material was the product **5**. It was thoroughly washed with water, with a saturated aqueous solution of Na_2CO_3 and finally with water. The product **5** was obtained as a yellow solid (Yield: 5.9 g ; 94%). Mp 235°C.

^{1}H NMR $CDCl_3$ δppm: 2.45 (6H, s, aryl CH_3), 3.05 (8H, t, *J* 4.7Hz, CH_2N), 3.36 (8H, t, *J* 4.7Hz, CH_2NTs), 7.36 (4H, d, *J* 8Hz,Ts), 7.72 (4H, d, *J* 8Hz, Ts)

^{13}C NMR $CDCl_3$ δppm: 20.88 (CH_3), 48.62 (CH_2N), 48.92 (CH_2N), 127.04, 129.48, 133.38, 143.32 (aryl C)

MS (APCI): 482.08 (MH^+)

1,7-dicarboxymethyl-4,10-di(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane (6)

A solution of KOH (0.51 g; 9 mmol) in absolute methanol (6 ml) was cooled to 0°C and carefully added to a solution of bromoacetic acid (1.26 g; 9 mmol) in absolute methanol (10 ml) in such a way that the temperature never exceeds 5°C. This solution was then added to a mixture of **5** (1.92 g; 4 mmol) and of anhydrous Na_2CO_3 (0.96 g; 9 mmol) in absolute methanol (40 ml). The suspension was heated first at 45°C during 6 h and then at 65°C overnight. The methanol was evaporated under reduced pressure and the residue was dissolved in water (40 ml). The solution was filtered off and the filtrate acidified to pH 1 with 6 M HCl. The precipitated **6** was filtered off, washed with chilled water and dried (Yield: 1.8 g ; 76%). Mp 182°C.

^{1}H NMR (D_2O+NaOH) δppm: 2.39 (6H, s, aryl CH_3), 2.86 (8H, t, *J* 4.7Hz, CH_2N), 3.14 (4H, s, CH_2COOH), 3.20 (8H, t, *J* 4.7Hz, CH_2N), 7.41 (4H, d, *J* 8Hz, Ts), 7.71 (4H, d, *J* 8Hz, Ts)

^{13}C NMR (D_2O+NaOH) δppm: 18.9 (CH_3), 45.7 (CH_2N), 50.65 (CH_2N), 55.4 (CH_2COOH), 125.4, 127.5, 131.02, 143.2 (aryl C), 179.26 (CO acid)

IR (cm^{-1}): 3423, 2956, 1723, 1629, 1455, 1338, 1160

MS (APCI): 597 (MH^+)

dioxocyclen (7)

A three-neck flask was assembled with a condenser and two dropping funnel containing two solutions (5.10^{-2} mol.L^{-1}) of diethylenetriamine (2,58 g; $2,5.10^{-2}$ mol.L^{-1} in 500 ml of methanol) and of the diethyl ester of iminodiacetic acid (4,73 g; $2,5.10^{-2}$ mol.L^{-1} in 500 ml of methanol) first prepared. These solutions were simultaneously added dropwise in the three-neck flask heated to reflux. After addition (time: 5 h), the resulting solution was refluxed for 5 days. The solution was then evaporated and the obtained mixture was recristallised from methanol leading to a yellow product **7** (Yield: 1 g ; 10%).

^{1}H NMR (D_2O + NaOD) δppm: 2.65 (4H, m, CH_2NH), 3.24 (4H, s, NH-CH_2-CO), 3.26 (4H, m, CH_2-NH -CO)

^{13}C NMR (D_2O + NaOD) δppm: 35.1 (CH_2N), 42.6 (CH_2N), 169.6 (CON)

MS (APCI): 201.32 (MH^+)

1,7-di(tertiobutylmethylcarboxylate)dioxocyclen (8)

Na_2CO_3 (1,06 g: 10 mmol) and tertiobutyl bromoacetate (1,98 g: 10 mmol) were added to a solution of dioxocyclen **7** (1 g: 5 mmol) in acetonitrile (50 ml). The mixture was refluxed during 18 h. The white precipitate was filtered off and the orange liquid filtrate was evaporated leading to a brown past **8** (Yield: 1.72 g ; 80%).

^{1}H NMR $CDCl_3$ δppm: 1.5 (18H, s, tBut), 2.7 (4H, s, CH_2NH), 3.2 (8H + 4H, m, CH_2N + NH-CH_2-CO)

^{13}C NMR $CDCl_3$ δppm: 28.5 (CH_3), 37.6 (CH_2N), 54.3 (CH_2NH), 60.3 (NH-CH_2-CO), 62.1 (N-CH_2-CO), 82.7 (C*), 168.7 (CO ester), 172.5 (CO amide)

IR (cm^{-1}): 3374, 2978, 2933, 1732, 1662, 1154

1,7-dicarboxymethyldioxocyclen (9) from (8)

LiOH, H_2O (78 mg: 1.9 mmol) was added to a solution of **8** (400 mg: 0.9 mmol) in THF/H_2O (30 ml/24 ml). The mixture was refluxed during 24 h under stirring. THF was evaporated and aqueous solution was acidified. This aqueous solution was extracted by n-pentane/CH_2Cl_2 (98/2) and the organic layer was dried (Na_2SO_4) then evaporated to obtain the product **9** (Yield: 44 mg ; 15%).

^{1}H NMR (D_2O + NaOD) δppm: 2.7 (4H, s, CH_2 cycle), 3.2 (8H, s, CH_2 cycle), 3.5 (4H, s, N-CH_2)

^{13}C NMR (D_2O + NaOD) δppm: 35.1-42.6 (CH_2 cycle), 64.1 (N-CH_2) 169.5 (CO amide), 175 (CO acid)

1,7-dicarboxymethyldioxocyclen (9) from dioxocyclen

A solution of KOH (0.265 g: 4.6 mmol) in absolute methanol (3 ml) was cooled to 0°C and carefully added to a solution of bromoacetic acid (0.639 g: 4.6 mmol) in absolute methanol (5 ml) in such a way that the temperature never exceeds 5°C. This solution was then added to a mixture of **7** (0.4 g: 2 mmol) and of anhydrous Na_2CO_3 (0.49 g: 4.6 mmol) in absolute methanol (20 ml). The suspension was heated first at 45°C during 6 h and then at 65°C overnight. The methanol was evaporated under reduced pressure and the residue was dissolved in water (20 ml). The solution was filtered off and the filtrate acidified to pH 1 with 6 $mol.L^{-1}$

HCl. The precipitated **9** was filtered off, washed with chilled water and dried (Yield: 1.47 g ; 93%). Mp 182°C.

^{1}H NMR (D_2O + NaOD) δppm: 2.7 (4H, s, CH_2 cycle), 3.2 (8H, s, CH_2 cycle), 3.5 (4H, s, N-CH_2)

^{13}C NMR (D_2O + NaOD) δppm: 35.1-42.6 (CH_2 cycle), 64.1 (N-CH_2) 169.5 (CO amide), 175 (CO acid)

IR (cm^{-1}): 3420, 3070, 2953, 1737, 1652, 1555, 1251, 1059

MS (APCI): 317,43 (MH^+)

6,11-dioxo-1,4,7,10- tetraazacyclododecan-1,4-diacetic acid (10)

In a three-neck flask assembled with a condenser, a dropping funnel, and a nitrogen-inlet tube, ethylenediaminetetraacetic dianhydride (2.5 g: 8.0 mmol) was suspended in dry DMF (350 ml) with stirring under a nitrogen atmosphere. To the suspension was added dropwise a DMF solution (50 ml) containing ethylenediamine (0.48 g: 8.0 mmol) through the dropping funnel in a period of 2 h. The resulting reaction mixture was heated at 60°C for 3 h and left to stand at room temperature overnight. The precipitate formed was removed by filtration. The filtrate was concentrated by the use of rotary evaporator at a temperature below 60°C, and water (10 ml) was added to the resulting viscous liquid. The finely divided solid that was formed was separated from the mixture by filtration, washed with THF, and dried in vacuum, this product is the 12-membered macrocycle **10** (Yield: 0.96 g ; 38%). Anal. Calcd for $C_{12}H_{20}N_4O_6$: C, 45,56, H, 6,37; N, 17,71. Found: C, 45,69; H, 6,45; N, 17,27. Mp 254°C.

^{1}H NMR D_2O δppm: 2.32 (4H, s, $(CH_2)_2$-N), 2.85 (4H, s, $(CH_2)_2$-NH-), 2.93 (4H, s, CH_2-CO-NH), 3.17 (4H, s, CH_2-COOH)

^{13}C NMR D_2O δppm: 39.56 ($(CH_2)_2$-N), 56.47 ($(CH_2)_2$-NH-), 61.51 (N-CH_2-CO), 62.70 (CH_2-COOH), 177.63 (CO amide), 182.1 (CO acid)

IR (cm^{-1}): 3305, 3095.5, 1720, 1645, 1549

MS (APCI): 317 (MH^+)

The filtrate was concentrated in a rotary evaporator, and the resulting viscous solution was mixed with a large amount of THF. The colourless solid that precipitated was found to be the 24-membered macrocycle **11**. The product was collected on a glass filter, washed with THF, and dried in vacuum overnight (Yield: 0.15 g ; 3%). Mp 212°C.

^{1}H NMR D_2O δppm: 2.30 (4H, s, $(CH_2)_2$-N), 2.84 (4H, s, $(CH_2)_2$-NH-), 2.91 (4H, s, CH_2-CO-NH), 3.15 (4H, s, CH_2-COOH)

^{13}C NMR D_2O δppm: 38.55 (CH_2-N cycle), 54.84 (CH_2-NH- cycle), 61.44 (-CH_2-CO-NH-), 61.65 (CH_2-COOH), 176.08 (CO amide), 180.42 (CO acid)

IR (cm^{-1}): 3305, 3088.5, 1700, 1649, 1555

MS (APCI): 633 (MH^+)

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