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Synthesis and Structure of Macrocyclic Dioxa-, Dithia-, Diazatetralactams and Derivatives

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Abstract: The high yield stepwise synthesis of 18-membered dioxa-, dithia- and diazatetralactams is described. The two key steps are: i) the dissymetrization of the reactivity of a diacid via its cyclic anhydride and ii) the activation-cyclization of the intermediate diamide diacid avoiding the high-dilution technique. Two series of diazatetralactam derivatives are prepared: bibranched compounds bearing various substituents and macrobicyclic or macrotricyclic species with phenantroline units. The main conformer of the dioxatetralactam was found by ^{13}C nmr and molecular modelling to have a D_2 symmetry while the dithiatetralactam *in vacuo* and the Boc substituted diazatetralactam in the solid state have a C_2 symmetry.

INTRODUCTION

Macrocyclic tetralactams are of increasing interest in several fields such as i) synthetic intermediates of azacrowns,[1] azaparacyclophanes[2] or macropolycyclic polyethers (cages),[3] ii) artificial receptors of biological substrates,[4] enzyme models[5] or synthetic enzymes (synzymes),[6] iii) neutral ionophores for selective alkaline-earth ions extraction,[7] transport through a bulk membrane[8] or a ion-selective electrode incorporated membrane,[9] iv) luminescent lanthanide probes,[10] v) ligands for highly oxidizing transition metal complexes,[11] vi) linkers for distribution of donor chelating sites in binuclear complexes,[12] vii) interlocking moieties in neutral catenanes.[13]

In this paper the synthesis of two new series of 18-membered macrocyclic tetralactams (see figure 1), i.e. dithia- **2** and diazatetralactams **3**, is described and rationalized with that of the previously reported dioxatetralactams **1**.[14] Their structural analysis is also reported for compounds **1a**, **2** and **3a**. All the studied compounds were prepared by a stepwise synthesis starting from a commercially available diacid or anhydride via a diamide diacid intermediate. The macrocyclization step was particularly investigated in order to avoid the use of the high dilution techniques.

Bibracchial diazatetralactams **3c-f** were derived from their parent compound **3b** and studied for their complexing[15, 16] and ionophoric[16] properties. The excellent extracting properties for alkaline earth cations disclosed with dioxatetralactams **1**[7] were found again, but also for the zinc ion and with increased stabilities of the complexes due to the side-arm effect.[16] Macrobicyclic and macrotricyclic diazatetralactams **4a-b** were synthesized in the same way for their ability to chelate lanthanide ions.[10] Finally, dithiatetralactams were expected to involve specific and powerful interactions with soft heavy metal cations.

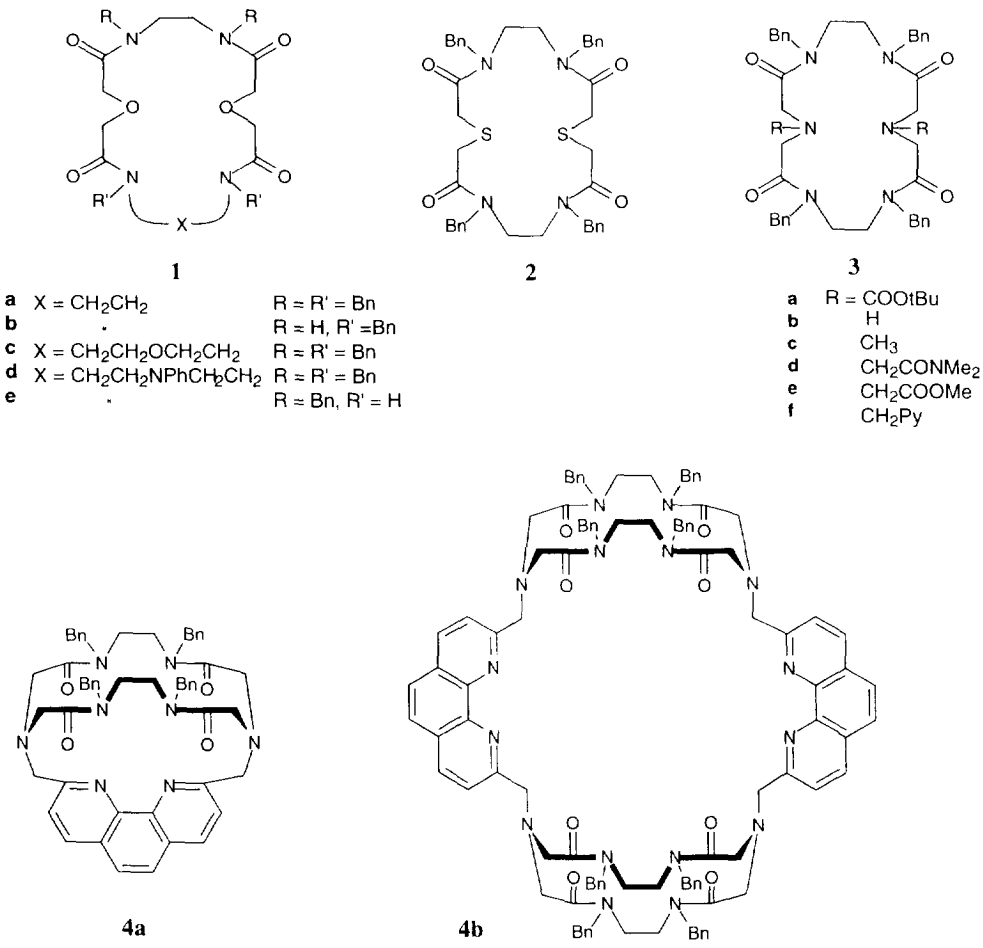
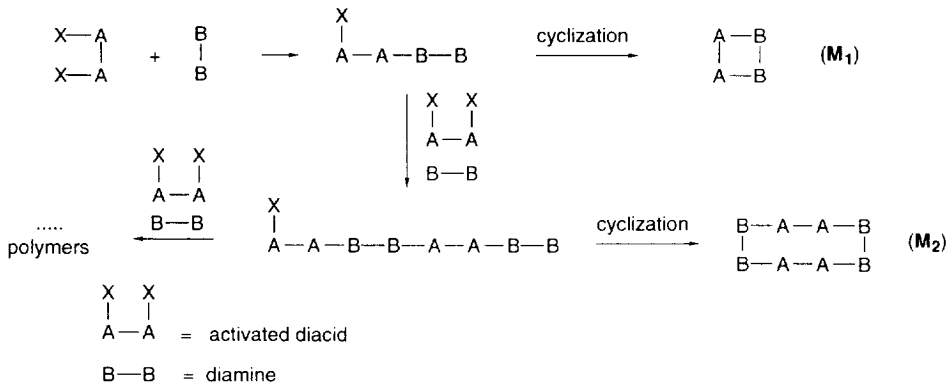


Figure 1. Tetralactams and derivatives described in this study

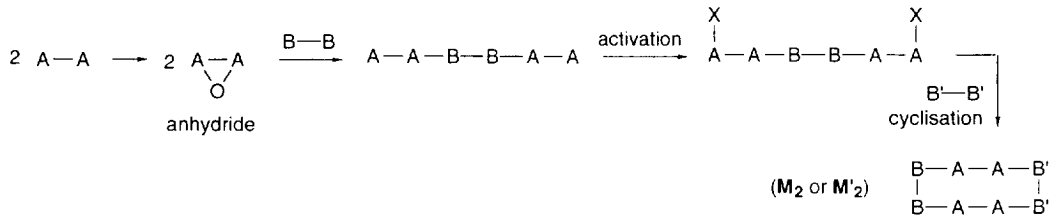
RESULTS AND DISCUSSION

Synthesis

Direct macrocyclization by reaction of diamines and activated dicarboxylic acids (scheme 1) affords generally low yields in dimeric macrocycles M_2, i.e. tetralactams, unless rigid aromatic rings are present in reactants.[17] On the other hand, when the access to 18-membered tetralactams is required, the one step "statistical" synthesis can afford, in addition to the 2:2 cyclization product tetralactam M_2, the 1:1 cyclization product dilactam M_1 despite its unfavourable 9-membered size, making tedious the purification of the reaction mixture. One example is highlighted by the reaction between N,N'-dibenzylethylenediamine and an activated derivative of diglycolic acid giving a mixture of 18-membered tetralactam (20-25%) and 9-membered dilactam (20%).[18]



Scheme 1: Direct macrocyclization



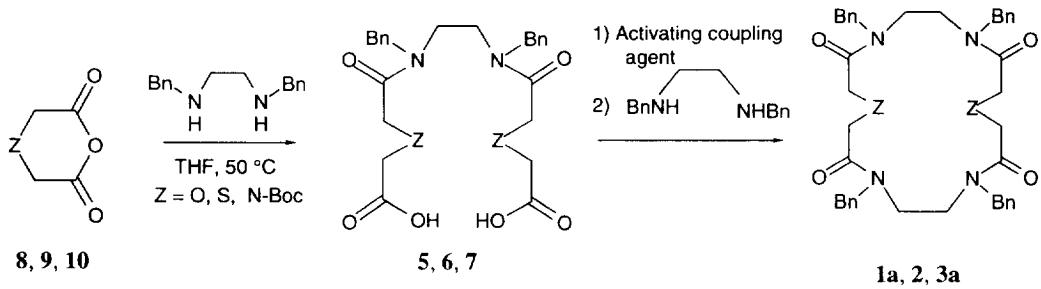
Scheme 2: Stepwise synthesis

A stepwise synthesis (scheme 2) is much more convenient, avoiding M_1/M_2 di/tetralactam competition and providing the tetralactams in good yields and with higher purity. In a previous paper,[14] we used a cyclic anhydride to dissymetrize the functionalization of a diacid by action of a diamine. The subsequent diamide diacid was then activated and reacted with the same diamine (giving symmetrical tetralactams M_2) or a different diamine (dissymmetrical tetralactams M'_2). The crucial step in the reaction sequence is the macrocyclization step where the choice of the activation type of the acid functions in the intermediate diamide diacid is essential. In these diacids the presence of amide functions does not allow the preparation of diacid chloride.[19] Thus, several coupling reagents used in peptide chemistry for the preparation of amides were investigated.[14] Activation achieved through thiazolidine-2-thione or diphenylphosphoryl azide (DPPA) appears to be the most effective ones. With these coupling agents the macrocyclization reaction is carried out at room temperature and does not require high dilution techniques.

Therein, from the results[14] obtained for dioxatetralactam **1**, we extent this diamide diacid strategy to the synthesis of dithia- and diazatetralactams (scheme 3).

Synthesis of the dioxatetralactam **1a**.[14] The diamide diacid **5** was obtained by reacting N,N'-dibenzylethylenediamine with the diglycolic anhydride in dry THF solution in a 70% yield. Using bis(thiazolidine-2-thione) activated derivatives, the macrocyclization step affords the 18-membered ring **1a** with a 70% yield and an overall yield of 49% (activation and cyclization). It is noteworthy that unlike the primary aliphatic diamines[20] the aminolysis rate of bis(thiazolidine-2-thione) derivatives by the secondary aliphatic diamines is slow;[14] so the ring closure reaction can be carried out in low-dilution conditions ($5x10^{-3}$

M). On the other hand, Mertes[21] reported a 58% yield (activation and cyclization steps) for tetralactam **1a** by using the same diamide diacid strategy and an excess of DPPA as *in situ* activating-coupling agent.

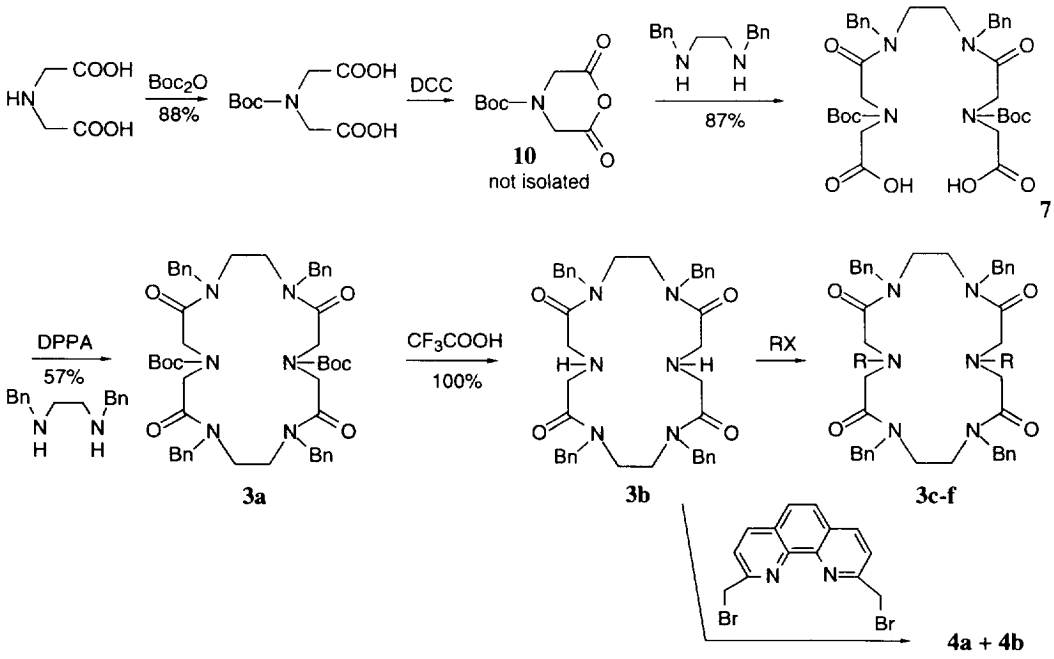


8, 9, 10 **5, 6, 7** **1a, 2, 3a**

Scheme 3

Synthesis of the dithiatetralactam **2**. The thiodiglycolic anhydride **9** commercially available or prepared from the thiodiglycolic acid by heating with acetic anhydride was reacted with the N,N'-dibenzylethylenediamine in THF to afford the diamide diacid **6** in a 72% yield. A subsequent activation-cyclization process with DPPA and the diamine in anhydrous DMF ($1.7\ 10^{-2}$ M) leads to the dithiatetralactam **2** in 42% yield.

Synthesis of the diazatetralactam **3a**. The commercially available iminodiacetic acid was used as starting material to provide a ready access to multigram quantities following scheme 4.



Scheme 4. Synthesis of Diazatetralactams **3a-f** and derivatives

The first step of the synthesis consisted in the protection of the amine function of the iminodiacetic acid by the Boc group of standard use in peptide synthesis to give the known[22] protected diacid. The synthetic methods described for the preparation of the diglycolic anhydride[14] or of the dianhydrides derived from EDTA or EGTA [23] proved to be unsuccessful to obtain **10**. The addition under reflux of acetic anhydride used in these preparations unprotects the amine function and gives polymeric compounds. On the contrary, the use of DCC in anhydrous tetrahydrofuran was an efficient method and it was possible to characterize, for the first time, the anhydride **10** by ^1H nmr and infrared techniques (see experimental section). However, this compound hydrolyzes quickly and it was necessary to use it for the subsequent step without isolation. The derived diamide-diacid **7** was obtained in high yield by adding the N,N'-dibenzylethylenediamine to the anhydride solution at 50 °C. The next macrocyclization step was realized after activation of the diacid function by DPPA[21] while the thiazolidine-2-thione activation successfully used for previous dioxatetralactam macrocyclizations[14] gave poor results. This latter activating-group yields no more than 5% of compound **3a**. Using DPPA the yield raises to 57% despite the low dilution conditions (10^{-2}M). The four-step synthesis of **3a** was thus achieved with an overall yield of 44%.

Synthesis of diazatetralactam derivatives **3b-f, 4a-b**. Removal of the Boc protecting group of **3a** by CF_3COOH-CH_2Cl_2, followed by an aqueous base treatment led quantitatively to the key diazatetralactam **3b** which is a versatile precursor for macrocyclic receptors with pendant chains or cryptands. Thus, bibracchial macrocycles **3c-3f** were prepared by simple alkylation of macrocycle **3b** with the appropriately functionalized halides under basic conditions (Na_2HPO_4, CH_3CN), yielding after purification by liquid chromatography pure **3c-f** products (73-97%). On the other hand dropwise addition of 2,9-bis(bromomethyl)-1,10-phenanthroline to a solution of compound **3b** in refluxing CH_3CN and in presence of Na_2CO_3 gave the macrobicyclic cryptand **4a** and the cylindrical macrotricyclic cryptand **4b** in 7% and 54% yield respectively. These two compounds were isolated as their NaBr complexes (**4a**.NaBr and **4b**.2NaBr) after liquid chromatography. The orientation of this macrocyclization reaction essentially towards the macrotricyclic compound of dimeric structure is clearly different from the exclusive macrobicycle formation observed by Lehn[24] for analogous cryptands derived from 4,13-diaza-18-crown-6 following the same procedure. For the formation of these later compounds, a marked sodium template effect has been found facilitating the cyclization process toward the monomer. In our case a different conformational behaviour and a least affinity for sodium cation of the starting diazatetralactam[16] with respect to the diaza-18-crown-6 used by Lehn might explain this different orientation. The high yield of macrotricycle formation obtained without using high dilution techniques (see experimental section) may result from a rigid group effect of the introduced bridging unit.

Structural Analysis

The analysis will be restricted to the 18-membered macrocyclic tetralactams **1a**, **2** and **3a** by ^{13}C NMR and molecular modelling methods.

The NMR spectra are very complex due to the occurrence of several conformers related to the phenomenon of hindered internal rotation around the carbon nitrogen bond of the amide group[25] as yet observed for tetralactams.[26] ^{13}C NMR spectra are simpler than ^1H spectra but none structural information can be extracted at room temperature otherwise the multiplicity of conformers. At the opposite, if we analyze at low temperature the ^{13}C NMR spectrum of a solid sample dissolved in $CDCl_3$ previously cooled to -45 °C

simplifications are observed which are not occurring on the ^{1}H spectra still displaying broadened signals. The barrier to *trans* → *cis* isomerization of the RR'N-C=O group being sufficiently high (~17 Kcal.mol^{-1}), the ^{13}C spectrum reflects the crystalline molecule before it has sufficient time to isomerize,[27] thus giving pertinent information on the symmetry of the solid state isomer.

With the two **1a** and **3a** tetralactams (**2** is not soluble in $CDCl_3$ at low temperature) simplifications are observed (fig. 2, table 1) particularly on the Ci (quaternary aromatic carbon) and C=O signals (fig. 3): for each of these carbons two signals at -40 °C vs. four at room temperature (**3a**) or even one vs. three (**1a**). If we suppose that only one conformation is evidenced in these low temperature spectra - that of the solid state - the two tetralactams have two kind of symmetries, particularly of superior order for **1a**.

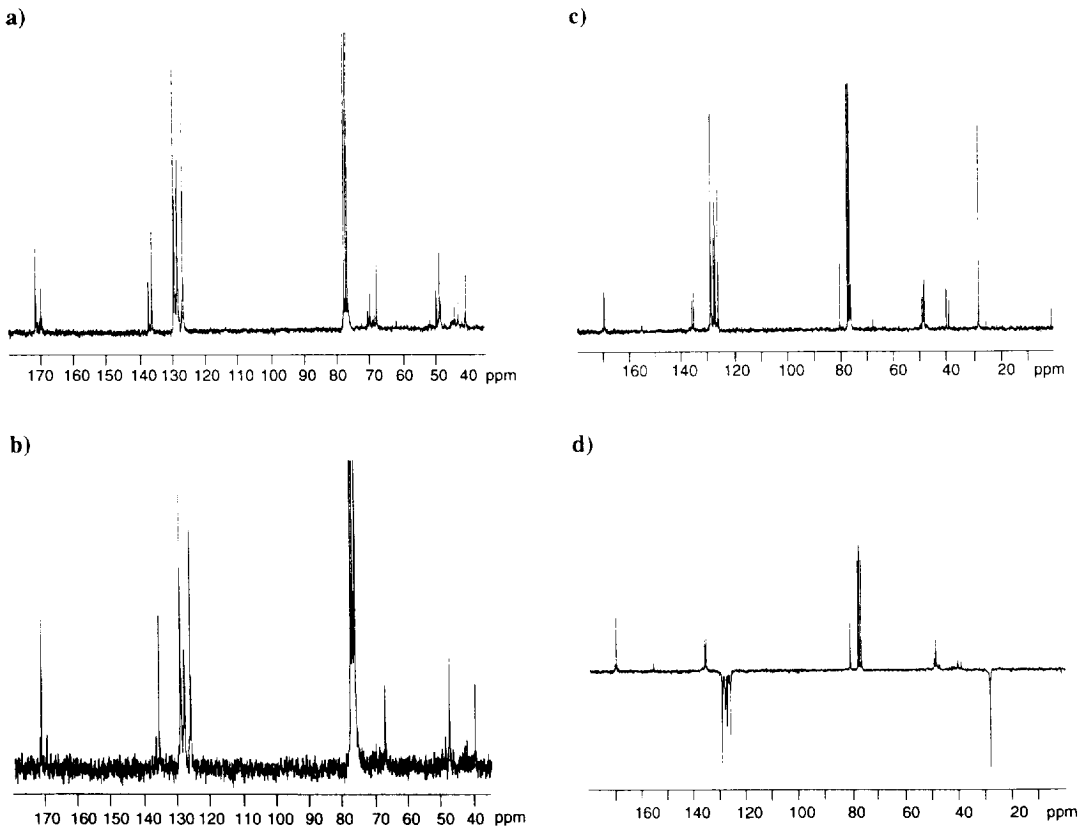


Figure 2. ^{1}H-Decoupled or J-modulated ^{13}C NMR spectra at 50.3 MHz in $CDCl_3$ of dioxatetralactam **1a** a) 25 °C, b) -27°C, and diazatetralactam **3a** c) 25 °C, d) -40 °C

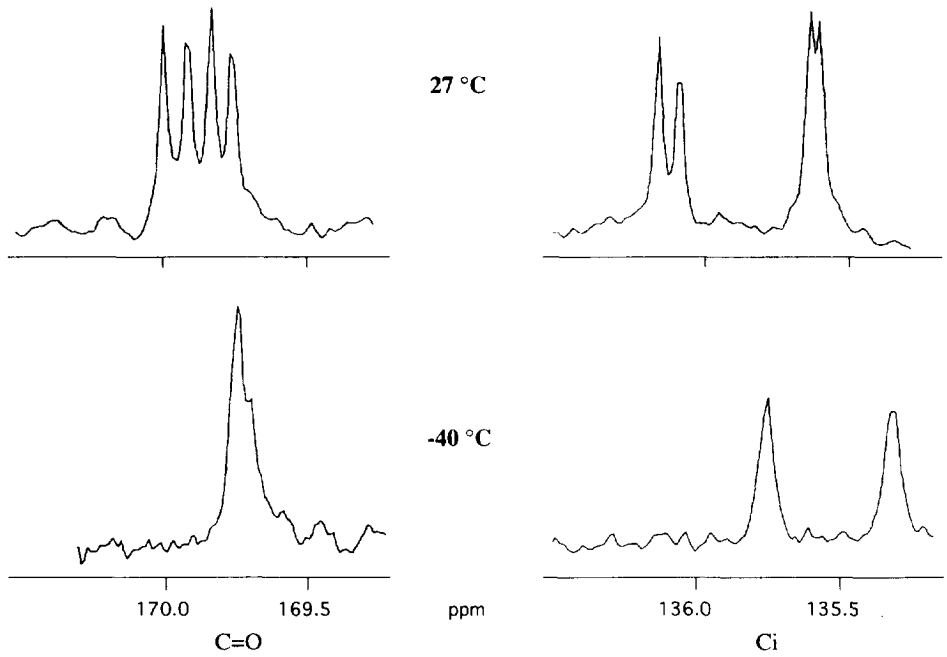


Figure 3. ^{1}H-decoupled ^{13}C NMR spectra at 50.3 MHz in $CDCl_3$. Multiplicity of the C=O and Ci (quaternary aromatic carbon) resonances at 25 °C and -40 °C for the diazatetralactam **3a**.

Table 1. ^{13}C NMR Data ($CHCl_3$, 50.3 MHz) for tetralactams **1a**, **2** and **3a**

Compound	**1a**				**2** [a]				**3a**			
Type	25 °C			-27 °C [b]	25 °C				25 °C		-40 °C	
N-CH_2	40.5	42.6	44.1	40.7	40.8	44.4	45.9		39.4	40.3	39.2	40.3
CH_2CO	67.6	69.8	70.6	67.6	32.3	32.8	35.4		48.7 [c]	49.3 [c]	49.2	
Ph-CH_2	48.5	48.6	49.6	48.2	50.1	50.3	52.9		48.8 [c]	48.9 [c]	48.6	
Ci	135.6	135.8	136.7	135.6	135.8	136.3	137.2		135.56 136.06	135.57 136.13	135.3	135.8
Cα	128.8	129.1		129.2	128.7	129.1	129.2		128.2	129.0	129.0	129.3
Cβ	127.8	128.0		127.9 128.0	127.7	128.0	128.2		127.7	127.8	127.9	128.1
Cγ	126.3-127.0			126.1 126.3	126.3	126.9			126.4	127.3	126.2	127.3
C=O	169.2	170.9	171.1	170.9	169.8	169.9	170.2		169.75 169.9	169.85 170.0	169.7	170.1
C=O Boc	-			-	-				155.3		155.3	
Ci Boc	-			-	-				82.7		81.1	
CH_3	-			-	-				28.4		28.4	

a) Insoluble at low temperature. Carbon assignments were made using the CSPEC programme.[28]
b) Limit temperature before crystallizing. The reported resonances are those of the pre-eminent conformer.
c) These signals may be interchanged.

The molecular modelling of the dioxatetralactams was performed with the PCMODEL program version 5.13 and the MMX force field.[29] The GMMX program[29] was used to search conformational space and to reach the lowest energy unique conformation following the methods described by the Still group.[30] In order to simplify the calculations, compounds with a benzylic substituent were replaced by the same molecules but with a methyl substituent (marked with a prime label); this approximation was already used by Lifson.[31] The GMMX statistical search was achieved by the cartesian procedure with the dioxa- and dithiatetralactams **1'a** and **2'** and the mixed method (alternating cartesian and internal coordinates) with the diazatetralactam **3'a** bearing Boc side chains. The search was optimized by a molecular dynamic simulation at 300 °K.

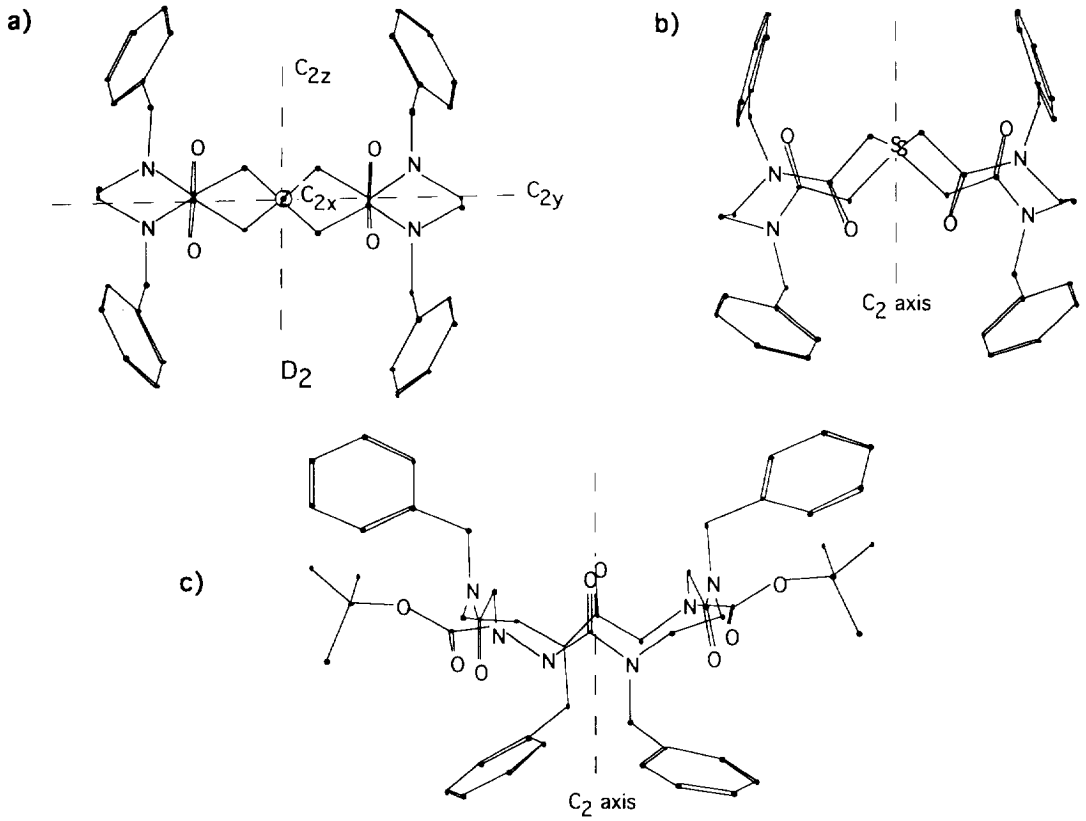


Figure 4. Most stable conformation of tetralactams **1a** (a), **2a** (b) and **3a** (c) as determined with PCMODEL

The most stable conformation (6.6 Kcal.mol^{-1}) was disclosed for dioxatetralactam **1'a** with a D_2 symmetry while the next one in the stability order is unsymmetrical and 5 Kcal.mol^{-1} higher. For **2'** these conformations are respectively of C_2 (fig. 4b) and D_2 (fig. 4a) symmetries, a difference with compound **1'a** which is correlated to bulky sulfur atoms and longer C-S than C-O bonds. The gap between these two conformations is reduced for **2'** (1.1 Kcal.mol^{-1}) and even more for **3'a** (< 0.1 Kcal.mol^{-1}). But, for this latter, the problem is more complex related to the presence of a double urethane side-chain so that the number of conformers is twice (C=O urethanes *syn* or *anti* vs. the plane of the ring), the barrier to the rotation around the C-N bond of the urethane function being around 16 Kcal.mol^{-1}. These two positions are possible and

effectively encountered for molecules differing only by 0.5 Kcal.mol^{-1} with a preference for the *syn* arrangement.

Now, if we consider compounds **1'a** and **2'**, their methyl → benzyl conversion on the most stable conformations reduces the previously defined gap i.e. 1.2 Kcal.mol^{-1} for **1a** and 1.0 Kcal.mol^{-1} for **2** without inversion in the order of stability relative to the conformation of the macrocycle. The multiplicity observed in the ^{13}C spectrum of **1a** at 25 °C may be related to the presence of the two forms suggested by molecular modelling one symmetrical and the other unsymmetrical. Their ratio about 1/1 deduced from the height of the peaks indicates an energy difference less marked than that indicated by molecular modelling and might result from a solvent effect.

In the case of compound **3a**, the ^{13}C nmr spectrum at low temperature shows two signals for the C=O and Ci carbon atoms and twice at room temperature with equal intensity (fig. 3). A conformation like that of figure 4c with a C_2 symmetry and *syn* Boc groups may explain the low temperature spectrum while an additional symmetrical conformation of around the same energy but with an *anti* Boc arrangement may compete at 25 °C.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 883 spectrophotometer in potassium bromide discs. ^1H magnetic resonance spectra (80 MHz unless otherwise indicated) and ^{13}C magnetic resonance spectra (50.3 or 62.9 MHz) were recorded on Bruker AC-80, AC-200, AC-250 and AC-400 spectrometers. Data are reported in the following order: chemical shift, spin multiplicity (s = singulet, d = doublet, t = triplet, m = multiplet), integration and assignment (n = number of signals). Mass spectra (MS) were performed with a NERMAG R10-10C spectrometer using the Fast Atom Bombardment (FAB, Gly or Gly-thiogly matrix) or desorption chemical ionization (DCI/NH_3) techniques. Elemental analyses were carried out by the "Service Commun de Microanalyse élémentaire UPS-INP" in Toulouse. Precoated sheets (Merck silicagel 60F-254) were used for TLC analyses. Compounds were detected with UV light (254 nm) and/or iodine chamber. rf values refer to relative mobilities on TLC plates. Preparative chromatography columns were packed with Amicon silicagel 60 (70-200 mesh).
The following compounds were prepared as described in the literature; N,N-dimethylbromoacetamide,[32] 2,9-bis(bromomethyl)-1,10-phenanthroline.[33]

Syntheses of Ligands

Thiodiglycolic anhydride **9**: 30 g (0.2 mol) of thiodiglycolic acid and 47 g (0.6 mol) of acetyl chloride were refluxed 2 hrs until the chlorhydric acid was completely evolved. Refluxing was continued for 2 additional hours. After cooling, white crystals appeared and were filtered and washed with dry ether. 65% yield. m.p.: 97-100 °C (99-100 °C)[34]; IR (KBr) ν: 1800 (CO sym), 1753 (CO asym) cm^{-1}; ^1H NMR (DMSO, 80 MHz) δ: 3.88 (s, 4H, CH_2).

Diamide diacid **6**: 3g (2.27 10^{-2} mol) of thiodiglycolic anhydride **9** were dissolved under argon in 50 mL anhydrous THF and heated to 50 °C. 2.73 g (1.136 10^{-2} mol) of N,N'-dibenzylethylene diamine dissolved in 20 mL THF were added dropwise and the reaction mixture was stirred 3 days at 50 °C. The solvent was then removed and the solid material dissolved in 70 mL $CHCl_3$. The organic layer was neutralized by 1N HCl and extracted with ethyl acetate. The organic layers were finally dried and the solvent removed to obtain the pure product (72% yield). m.p.: 166 °C; IR (KBr) ν: 1728 (CO acid), 1599 (CO amide) cm^{-1}; ^1H NMR (DMSO, 80 MHz) δ: 3.35-3.37 (m, 8H, NCH_2, SCH_2COOH), 3.47-3.57 (m, 4H, SCH_2CON), 4.4-4.6 (m, 4H, CH_2Ph), 7.1-7.3 (m, 10H, Ar); ^{13}C NMR (DMSO, 50.32 MHz) δ: 32.4-32.8, 33.2 (CH_2CON), 43.0, 44.2, 44.6, 45.6 (CH_2N, CH_2COOH), 47.6, 48.1, 51.2, 51.7 (CH_2Ph), 126.7, 127.0 (Cp Ar), 127.3, 127.4 (Cm Ar), 128.3, 128.6 (Co Ar), 137.0, 137.6, 137.7 (Ci Ar), 166.4, 166.7, 169.0 (CO amide), 170.9, 171.0 (CO acid); Anal. calcd for $C_{24}H_{28}N_2O_6N_2$, H_2O: C, 55.16; H, 5.79; N, 5.36; Found C, 55.12; H, 5.66; N, 5.26.

Dithiatetralactam **2**: To 4.41 g (8.75 10^{-3} mol) diamide diacid **6** dissolved under argon in 500 mL anhydrous DMF were added 2.1 g (8.75 10^{-3} mol) N,N'-dibenzylethylene diamine in 26 mL DMF and 4.42 g (4.375 10^{-2}

mol) anhydrous triethylamine. After 10 min. stirring was added 12.04 g (4.375 10^{-2} mol) diphenylphosphoryl azide. The solution was kept under stirring at room temperature 3 days. Then, the solvent was removed *in vacuo* and the remaining solution was diluted with CH_2Cl_2, washed with 10% aqueous NaOH solution, water, 1N HCl and saturated NaCl solution. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The residue, after evaporation of the solvent, was chromatographed on a silicagel column eluting with 97:3 CH_2Cl_2/MeOH to give the pure product as a white solid powder (42% yield). m.p.: 200 °C; IR (KBr) ν: 1627, 1657 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 3.2-3.5 (m, 8H, CH_2N), 3.5-3.8 (m, 8H, CH_2Ph), 4.45-4.53, 4.69-4.76 (m, 8H, CH_2S), 7.1-7.4 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ: 32.3, 32.8, 35.4 (CH_2S), 40.8, 44.4, 45.9 (CH_2N), 50.1, 50.3, 52.9 (CH_2Ph), 126.3, 126.9 (Cp Ar), 127.7, 128.0, 128.2 (Cm Ar), 128.7, 129.1, 129.2 (Co Ar), 135.8, 136.3, 137.2 (Ci Ar), 169.8, 169.9, 170.2 (C=O); Anal. calcd for $C_{40}H_{44}O_4N_4S_2$, 0.5 CH_3OH: C, 67.10; H, 6.40; N, 7.73; Found C, 66.77; H, 6.26; N, 7.90.

N-tert-butoxycarbonyl iminodiacetic acid: 8.31 g (6.25 10^{-2} mol) of iminodiacetic acid were dissolved in a mixture of 120 ml of dioxane, 40 ml of water and 40 ml of sodium hydroxide (2N). The solution was cooled with an ice bath, then a solution of ditertbutyl dicarbonate (15.01 g; 6.88 10^{-2} mol) in dioxane was added dropwise. The reaction was stirred for 18 hrs at room temperature. The dioxane was removed under vacuum and the residual mixture was acidified with 20% aqueous citric solution to pH 3. The solution was extracted three times with ethyl acetate and the solvent removed. The pure product was obtained as a white solid (88% yield). m.p.: 131 °C; IR (KBr) ν: 3178 (OH acid), 1728 (CO acid), 1660 (CO Boc) cm^{-1}; ^1H NMR (DMSO-d6, 200.13 MHz) δ: 1.36 (s, 9H), 3.88 and 3.92 (d, 4H); ^{13}C NMR (DMSO-d6, 50.32 MHz) δ: 27.7 (3C, CH_3), 48.97 and 49.50 (2C, CH_2), 79.46 (1C, Cq Boc), 154.66 (1C, C=O Boc), 171.08 (2C, C=O acid).

Diamide diacid **7**: 1.77 g (8.62 mol) of dicyclohexylcarbodiimide were added under argon atmosphere to a solution of N-tert-butoxycarbonyl iminodiacetic acid (2.00 g, 8.62 mmol) in 50 mL of THF freshly distilled on sodium. The solution was stirred 24 hrs. The anhydride **10** [IR (KBr) ν: 1790 (CO sym), 1705 (CO asym) cm^{-1}; ^1H NMR (DMSO-d_6 80.13 MHz) δ: 1.35 (s, 3H, CH_3), 4.38 (s, 4H, CH_2)] was generally not isolated due to its instability. Then, 1.03 g (4.31 mmol) of N,N'-dibenzylethylenediamine was added and the reaction kept at 50 °C for 24 hrs. After filtration of the dicyclohexylurea, the solvent was removed under vacuum and the crude product was dissolved in 5% aqueous $NaHCO_3$. The aqueous solution was treated twice with $CHCl_3$, acidified with 20% citric acid, extracted with $CHCl_3$, and the organic layer dried over $MgSO_4$. After removal of the solvent, the pure product **7a** was obtained as a white solid (87% yield). m.p.: 123 °C; IR (KBr) ν: 1740 (CO acid), 1706 (C=O Boc), 1616 (C=O amide) cm^{-1}; ^1H NMR (DMSO-d6, 200.13 MHz) δ: 1.36 (s, 18H, CH_3), 3.40-3.41 (m, 4H, NCH_2CH_2N), 3.89-3.94 (4H, m, CH_2CO_2H), 4.16-4.20 (m, 4H, NCH_2CON), 4.50-4.56 (m, 4H, CH_2Ph), 7.37-7.26 (m, 10H, Ar); ^{13}C NMR (DMSO-d6, 50.32 MHz) δ: 43.46 (NCH_2CH_2N), 50.40-49.12 (CH_2Ph, $CH_2NCH_2CO_2H$), 79.65-79.35 (Cq Boc), 128.64-126.58 (Co,m,p Ar), 137.53-135.75 (Ci Ar), 154.83-154.72 (C=O Boc), 169.57-169.31 (C=O amide), 171.06 (C=O acid).

Diazatetralactam **3a**: 7.77 g (1.16 10^{-2} mol) of diacid diamide **7**, 2.78 g (1.16 10^{-2} mol) of N,N'-dibenzyl ethylene diamine and 8.07 mL (5.8 10^{-2} mol) of triethylamine were dissolved under argon atmosphere on 1.1 L of THF freshly distilled on sodium. After stirring for 10 mn, 10.05 mL (4.64 10^{-2} mol, 4 eq.) of diphenylphosphoryl azide were added. The solution was strongly stirred during 3 days at room temperature. After removal of the solvent the residue was dissolved in 50 mL CH_2Cl_2. Then, the organic layer was washed with 1N aqueous HCl solution and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed. The crude product was purified on silicagel column (eluent, CH_2Cl_2/MeOH, 88/2) to give the pure product **3a** as a white solid (57% yield). Rf = 0.35 ($(CH_3)_2CO$/petroleum ether; 30/70). m.p.: 136 °C. IR (KBr) ν: 1701 (C=O Boc), 1660 (C=O amide) cm^{-1}; ^1H NMR($CDCl_3$, 200.13 MHz) δ: 1.36 (s, 18H, CH_3), 2.34-2.62 (m, 8H, NCH_2CH_2N), 4.50-4.66 (m, 8H, CH_2CO), 3.48-3.61/3.72-3.86/4.72-4.79/5.03-5.13 (d, 8H, CH_2Ph), 7.21-7.32 (m, 20H, Bn). ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ: 28.4 (CH_3), 40.32-40.65 (n = 2, NCH_2), 48.87-48.65 (n = 2, CH_2Ph), 49.31 (NCH_2CO), 82.66 (CO Boc), 129.03-126.43 (n ≥ 9, CH Ar), 135.56-136.13 (Ci Ar), 155.27 (CO Boc), 169.77-170.01 (CO amide); MS (FAB/thiogly) m/z = 875 $[M+H]^+$ (100%), 775 $[M-Boc+2H]^+$, 675 $[M-2Boc+3H]^+$; Anal. calc. for $C_{50}H_{62}N_6O_8$, $1H_2O$: C, 67.24; H, 7.22; N, 9.41; found: C, 67.30; H, 7.20; N, 9.08.

Diazatetralactam **3b**: 0.644 g (7.36 10^{-4} mol) of **3a** were dissolved in 10 mL of CH_2Cl_2/CF_3CO_2H (1/1). The solution was stirred for 24 hrs at room temperature. Then the solvent and the excess of acid were removed *under vacuo*. The brown residue was dissolved in 20 mL ethyl acetate and the solution was washed with a 2N NaOH aqueous solution and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed to

afford the pure product **3b** as a white solid (100% yield). Rf = 0.20 (CH_2Cl_2/MeOH, 95/5). m.p.: 88 °C; IR (KBr) ν: 3328 (NH), 1656 (CO amide) cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz) δ: 3.14-3.96 (m, 16H, CH_2), 4.22-4.7 (m, 8H, CH_2Ph), 6.88-7.59 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ: 41.09-52.83 (n > 16, CH_2), 126.38-129.30 (n > 11, Co,m,p Ar), 135.63-136.82 (n > 8, Ci Ar), 169.11-172.25 (n > 8, CO amide). MS (DCI/NH_3) m/z = 675 [MH^+] (100%).

Diazatetralactam **3c**: 0.2 g (2.96 10^{-4} mol) of diazatetralactam **3b** was dissolved in 10 mL of anhydrous CH_3CN then 0.126 g (8.88 10^{-4} mol) of Na_2HPO_4 was added. Methyl iodide (5.92 10^{-4} mol) was dissolved in 5 mL of anhydrous CH_3CN, then this solution was added dropwise at 0 °C to the solution of N,N'-dibenzyléthylène diamine under argon atmosphere. The reaction was stirred for 18 additional hours. The solid materials were filtered and the solvent was removed. The residue was dissolved in 10 mL of $CHCl_3$ and extracted with 10 mL of water containing 2 g of ethylene diamine tetraacetic acid disodium salt. The mixture was strongly stirred for 2 hrs and the organic layer was dried over $MgSO_4$. After removing the solvent the residue was purified on silicagel column (CH_2Cl_2/MeOH; 96/4) and the pure product was obtained as a white solid (72% yield). Rf = 0.26 (CH_2Cl_2/MeOH, 95/5). m.p. = 94 °C (decomposition); IR (KBr) ν: 1647 (CO), 1605 (C=C) cm^{-1}; ^1H NMR($CDCl_3$, 200.13 MHz) δ: 1.98-2.66 (6H, NCH_3), 2.85-4.11 (16H, NCH_2CH_2N, NCH_2CON), 4.18-4.74 (8H, NCH_2Ph), 6.72-7.44 (20H, Ar); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ: 40.6-62.3 (n > 10, CH_2), 42.2-43.6 (n = 4, NCH_3), 125.99-129.14 (n > 12, Co,m,p Ar), 136.6-137.6 (n > 8, Ci Ar), 169.9-172.2 (n > 11, CO); MS (DCI/NH_3) m/z = 703 [MH^+](100%), 689 [$M-CH_3+2H]^+$. Anal. Calcd for $C_{42}H_{50}N_6O_4$, H_2O: C, 69.98; H, 7.27; N, 11.66; Found: C, 70,14; H, 7.04; N, 11.66.

Typical procedure for the synthesis of the products **3d-f:** 0.3 g (4.45 10^{-4} mol) of diazatetralactam **3b** were dissolved in 10 mL of anhydrous CH_3CN, then 0.189 g (1.33 10^{-3} mol) of Na_2HPO_4 and 9.35 10^{-4} mol of the appropriate bromide were added. The mixture was refluxed for 18 hrs. The solid materials were filtered and the solvent was removed. The residue was purified on silicagel column (CH_2Cl_2/MeOH, 95/5).

Diazatetralactam **3d**: White solid (93% yield). Rf = 0.39 (CH_2Cl_2/MeOH, 95/5); m.p. = 98 °C (decomposition); IR (KBr) ν: 1647 (CO) cm^{-1}; ^1H NMR (CD_3CN, 200.13 MHz) δ: 2.62-3.17 (m, 12H, N-CH_3), 3.21-4.92 (m, 28H, CH_2), 6.88-7.63 (20H, Ar); ^{13}C NMR (CD_3CN, 50.32 MHz) δ: 35.43, 37.37 (n = 2) (n = 4, CON($\underline{C}H_3)_2$), 43-57.9 (n > 20, CH_2), 127.65-129.63 (n > 8, Co,m,p Ar), 138-139.25 (n > 3, Ci Ar), 169-171.8 (n > 4, $\underline{C}ON$). MS (DCI/NH_3) m/z = 845 [$MH]^+$; Anal. calcd for $C_{48}H_{60}N_8O_6$, H_2O: C, 66.80; H, 7.24; N, 12.98; Found C, 66.63; H, 7.21; N, 12.71.

Diazatetralactam **3e**: White solid (97% yield); Rf = 0.40 (CH_2Cl_2/MeOH, 95/5); m.p. = 88 °C (decomposition); IR (KBr) ν: 1743 (CO ester), 1642 (CO amide) cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz) δ: 3.19-4.22 (m, 26H, CH_2, CH_3), 4.70 (m, 8H, NCH_2Ph), 6.95-7.41 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ: 40.74-57.46 (n > 18, CH_2), 51.50 (OCH_3), 126.25-129.21 (n > 11, Co,m,p Ar), 136.34-138.05 (n > 5, Ci Ar), 170.16-171.66 (n > 5, CO amide, ester); MS (FAB/gly, thiogly) m/z = 819 [MH^+] (100%); Anal. calcd. for $C_{46}H_{54}N_6O_8$, H_2O: C, 66.01; H, 6.74; N, 10.04; found: C, 65.88; H, 6.46; N, 9.90.

Diazatetralactam **3f**: purification CH_2Cl_2/MeOH/NH_3 95/5/0.5. White solid (73% yield); Rf = 0.18 (CH_2Cl_2/MeOH 95/5); m.p.: 96 °C (decomposition); IR (KBr) ν: 1643 (CO), 1589 (C=C, C=N) cm^{-1}; ^1H NMR (CD_3CN, 80 MHz) δ: 3.05-4.70 (m, 28H, CH_2), 6.70-7.59 (m, 26H, Ar, $H_{3,4,5}$ Py), 8.18-8.55 (m, 2H, H_6 Py); ^{13}C NMR (CD_3CN, 62.8 MHz) δ: 44.3-47.2 (n = 6, CH_2N), 48.5-52.4 (n = 6, CH_2Ph), 54.4-56.7 (n = 5, N-CH_2CO), 58.4-60.4 (n = 5, CH_2Py), 122.9-124.5 (n = 5, $C_{3,5}$ Py), 138.9-139.3 (n = 2, C_4 Py), 127.4-129.8 (n > 15, CH_2Ph), 137.4-137.9 (n = 4, CiPh), 123.9-124.5 (n = 3, $C_{3'}$), 149.9-150.0 (n = 2, $C_{2'}$) 171.2-172.2 (n = 2, CO); MS (FAB/gly) m/z = 857 [MH^+] (100%); Anal. calcd. for $C_{52}H_{56}N_8O_4$, H_2O: C, 71.37; H, 6.68; N, 12.80; found: C, 71.72; H, 6.52; N, 12.73.

Cryptands **4a, 4b**: A mixture of **3b** (0.341 g, 0.505 mmol) and Na_2CO_3 (0.535 g, 5.05 mmol) in acetonitrile (300 mL) was heated to reflux during 2 hrs, and a solution of 2,9-bis(bromomethyl)-1,10-phenanthroline in CH_3CN (100 mL) was added dropwise within 2 hrs under efficient magnetic stirring. The resulting mixture was refluxed for further 18 h. After cooling to room temperature, the insoluble solid was filtered off and the filtrate evaporated to dryness. The crude solid product was purified on a silicagel column with CH_2Cl_2/MeOH 90:10 to give the NaBr complex of monomer **4a** (7%) and dimer **4b** (54%).
4a: white solid, m.p. = 180°C; IR (KBr) ν: 1640 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.4-2.7 (m, 8H, CH_2N), 3.3-4.5 (m, 20H, CH_2CO, CH_2Ph, CH_2Phe), 6.7-7.4 (m, 20H, Ar), 7.49 (d, J = 8.1 Hz, 2H, H-4,7 Phe), 7.86 (s, 2H, H-5,6 Phe), 8.24 (d, J = 8.1 Hz, 2H, H-3,8 Phe); MS: FAB$^+$ (glycerol-thioglycerol matrix) m/z 879.1

(MH^+) (100%); Anal. calc. for $C_{54}H_{54}N_8O_4$, NaBr, $3H_2O$ (1036.03): C, 62.60; H, 5.84; N, 10.82; found C, 62.91; H, 5.45; N 10.98.

4b: white solid, m.p. > 230°C; IR (KBr) ν: 1640 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.4-2.7 (m, 16H, CH_2N), 3.3-5 (m, 40H, CH_2CO, CH_2Ph, CH_2Phe), 6.7-7.4 (m, 44H Ar, H-4,7 Phe), 7.81 (s, 4H, H-5,6 Phe), 8.06 (d, J = 8.1 Hz, 4H, H-3,8 Phe); MS: FAB$^+$ (glycerol-thioglycerol-trichloracetic acid matrix) m/z 1759.8 (MH^+) (100%); Anal. calc. for $C_{108}H_{108}N_{16}O_8$, 2 NaBr, 10 H_2O (2144.12): C 60.50, H 6.02, N 10.45; found C 60.14, H 5.58, N 10.87.

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