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New facile and convenient synthesis of bispolyazamacrocycles using Boc protection. Determination of geometric parameters of dinuclear copper(II) complexes using ESR spectroscopy and molecular mechanics calculations

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Summary – A new facile and convenient synthetic route has been designed for the preparation of bispolyazamacrocycles in high yields by direct condensation of the readily available intermediate *N,N'*-diboctriazamacrocycle or *N,N',N''*-triboctetraazamacrocycles with aromatic biselectrophiles, ie, *o*-, *m*-, *p*-xylyl and anthracenyl derivatives. The use of a versatile group, such as *tert*-butyloxycarbonyl (Boc), which is easily removed within 1 h by treatment with 6 M HCl or TFA, leads to polyazamacrocycles in which one nitrogen is discriminated from the others. The anthracenyl and *o*-xylyl dimers were synthesized by reacting diacyl chloride to give the corresponding diamides. Further reduction of the amide groups and elimination of the protecting Boc moieties were carried in a one-pot reaction with BH_3-THF followed by acid treatment. In parallel, exclusive mono-*N*-alkylation of the available secondary amine of the same protected macrocycle with the corresponding dibromoxylene gave the *meta* and *para* dimers; the protecting moieties were eliminated in a similar way. ESR measurements of spin-spin distances of the dicopper complexes were determined from the ratio of the intensity of the forbidden transition to the intensity of the allowed transitions. Molecular mechanics calculations were also undertaken in order to evaluate the Cu-Cu distance by using a new rule-based force field.

bispolyazamacrocycle / Boc protection / dicopper complex / ESR / molecular modeling

Résumé – Utilisation du groupement protecteur «Boc» pour la synthèse de bis-polyazamacrocycles. Détermination des paramètres géométriques de leurs complexes de cuivre(II) par spectroscopie RPE et calculs de mécanique moléculaire. *Une nouvelle voie d'accès à des bis-polyazamacrocycles est décrite. Elle est réalisée par condensation d'un intermédiaire* N,N'N''*-triboctétraazamacrocycle ou* N,N'*-diboctriazamacrocycle avec un dérivé bis-électrophile de l'*o-, m-, p-*xylène, ou de l'anthracène. L'utilisation du groupement protecteur* tert*-butyloxycarbonyle (Boc), aisément éliminé par action de HCl 6 M ou du TFA, permet d'obtenir les synthons protégés. Les dérivés bismacrocycliques pontés par un groupement anthracényle ou* o*-xylényle sont préparés au départ des précurseurs dichlorure d'acide: les diamides ainsi formés sont réduits par BH_3-THF puis la déprotection est effectuée par un traitement acide. La* N*-alkylation des macrocycles protégés par le 1,3- ou 1,4-bis(bromométhyl)benzène conduit aux bis-macrocycles correspondants, et les composés cibles sont obtenus après acidification du milieu. Des mesures par RPE de la distance spin-spin pour les complexes de cuivre ont été effectuées en évaluant le rapport entre l'intensité de la transition interdite et celle des transitions permises. Des calculs de mécanique moléculaire permettent également d'évaluer la distance Cu–Cu, en utilisant un champ de force basé sur de nouvelles règles générant ses paramètres.*

bis-polyazamacrocycle / Boc / complexe dinucléaire de cuivre(II) / RPE / modélisation moléculaire

Introduction

In the past few years, the chemistry of metal complexes in crown ethers [1, 2], porphyrin [3], cyclam or related tetraazamacrocycle series [4-7] has been extensively studied. Dinucleating ligands containing two macrocyclic rings have been prepared in order to study cooperative interaction of the two metallic sites because such dimetallic systems are of both fundamental and practical interest. Several dimetallic systems have been proposed as models of metalloproteins containing two or more proximate metal centers and bispolyazamacrocycles have been used as subunits of the dinucleating ligands [8-17]. More recently, it has been shown that such a ligand is of potential use as an anti-HIV agent since it has been proved that biscyclam derivatives interact at an early stage in the HIV replication cycle [18]. Generally, the two polyazamacrocycles of bismacrocyclic systems are tethered together, either through an aliphatic or an aromatic spacer linking two nitrogen atoms [8-10, 18], or by two covalently bonded carbon atoms [11-13, 16]. However, with the exception of the bisporphyrin ligands [19], in most cases the distance between the two macrocycles was not systematically var-

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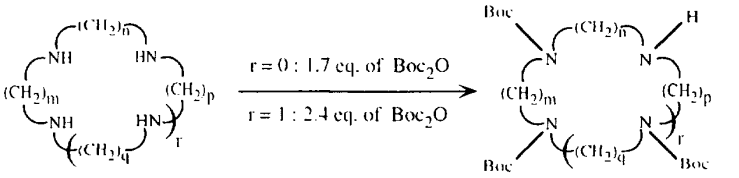

r = 1 : m, n, p, q = 2 : **1**
r = 1 : m, p = 2; n, q = 3 : **2**
r = 1 : m, n, p, q = 3 : **3**
r = 0 : m, n, p = 3 : **4**

r = 1 : m, n, p, q = 2 : **1a**
r = 1 : m, p = 2; n, q = 3 : **2a**
r = 1 : m, n, p, q = 3 : **3a**
r = 0 : m, n, p = 3 : **4a**

Fig 1. Synthesis of triprotected tetraazamacrocycles and diprotected triazamacrocycle.

ied and the properties of the metal complexes were not studied as a function of this distance. In a recent paper, the synthesis of a large range of bismacrocycles was described [18] but the ligands were obtained in a poor yield.

In the present paper, we report a new, facile synthesis of numerous bistetraazamacrocycles or bistriazamacrocycles possessing various inter-ring distances. Each compound has been characterized by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and microanalysis. Spin-spin distances of the corresponding dicopper complexes have been measured from the ratio of the intensity of the ESR-forbidden transition to the intensity of the allowed transitions. Moreover, quantum chemistry and molecular modeling have been used to calculate the intermacrocycle distance by studying a series of dicopper (*o*-, *m*-, *p*-xylyl and anthracenyl)-bridged bismacrocycles using a new rule-based force field.

Results and discussion

Synthesis

The best synthetic approach for bridging two macrocyclic units is to use a triprotected tetraazamacrocycle [8-10, 18] or a diprotected triazamacrocycle [20] to avoid the formation of polymers. In the past, tosyl groups have mainly been used to protect secondary amines. However, the detosylation reaction is often uncertain and depends upon the nature of the macrocycle [18]. Many side reactions are encountered, particularly for cyclen derivatives due to the harsh conditions of deprotection (H_2SO_4 or HBr/AcOH). Even if sodium amalgam is used to improve the deprotecting step, cleavage at the α carbon position of the aromatic spacer can occur. New protective groups, such as *tert*-butyloxycarbonyl (Boc), have been used to facilitate the synthesis of these bismacrocycles.

The protection reaction is shown in figure 1. The triprotection of tetraazamacrocycles was achieved in just one step starting from [12]aneN$_4$ (cyclen) **1**, [14]aneN$_4$ (cyclam) **2** or [16]aneN$_4$ (3333) **3** using 2.4 equiv of Boc_2O, and the diprotection of triazamacrocycle from [12]aneN$_3$ (333) **4** using 1.7 equiv of Boc_2O. With the exception of **3** (yield = 37%), the reaction yields varied from 67 to 72%. The experimental conditions were optimized by varying the amount of protective reagent and the dilution conditions. However, side products were always formed, mainly di- and tetrasubstituted tetraazamacrocycles, and mono- and trisubstituted triaazamacrocycle in the case of (333). Indeed, using 3 equiv of Boc_2O for triprotection and 2 equiv for diprotection, considerable amounts of tetraprotected tetraazamacrocycles and triprotected triaazamacrocycles were obtained, respectively.

The bismacrocycles were prepared by reaction of the tri- or di-*N*-protected azamacrocycles with the appropriate spacer group according to figure 2. By using dihalogenated xylyl derivatives agents, the bismacrocycles **(1-2)f** and **(1-2)g** were obtained in a high yield. The *o*-xylyl and anthracenyl dimers **(1-4)c** and **2i** were synthesized by reacting phthaloyl dichloride or anthracene-1,8-dicarbonyl dichloride with tri- or diprotected macrocycles. Reduction by BH_3-THF of the intermediate diamides followed by deprotection of the secondary amines by acid treatment led to the desired compounds. The yield of this one-pot reaction was close to 60%.

ESR study

Unfortunately, no X-ray crystallographic data for bismacrocyclic complexes were available, and so an alternative method using ESR spectroscopy was devised for probing the metal-metal distance and the structural characteristics in solution. The dicopper complexes were the best candidates for such a study.

The X-band ESR spectra (figs 3 and 4) of frozen solutions of these complexes exhibit a very strong absorption at $\approx$ 3 200 G and a weak one at $\approx$ 1 550 G (table I).

The strong absorption is attributable to the two allowed transitions $\Delta Ms = 1$ (fig 5), while the weaker one can be assigned to a forbidden $\Delta Ms = 2$ transition, which is characteristic of dicopper complexes [21, 22] and indicates the presence of an intramolecular electron exchange between the two copper elements. Seven lines are generally expected for each transition due to the hyperfine coupling between the two copper ions ($I_{Cu} = 3/2$). However, for the allowed transitions it is clear that the two sets of seven lines overlap due to the zero-field splitting parameter D values. Indeed,

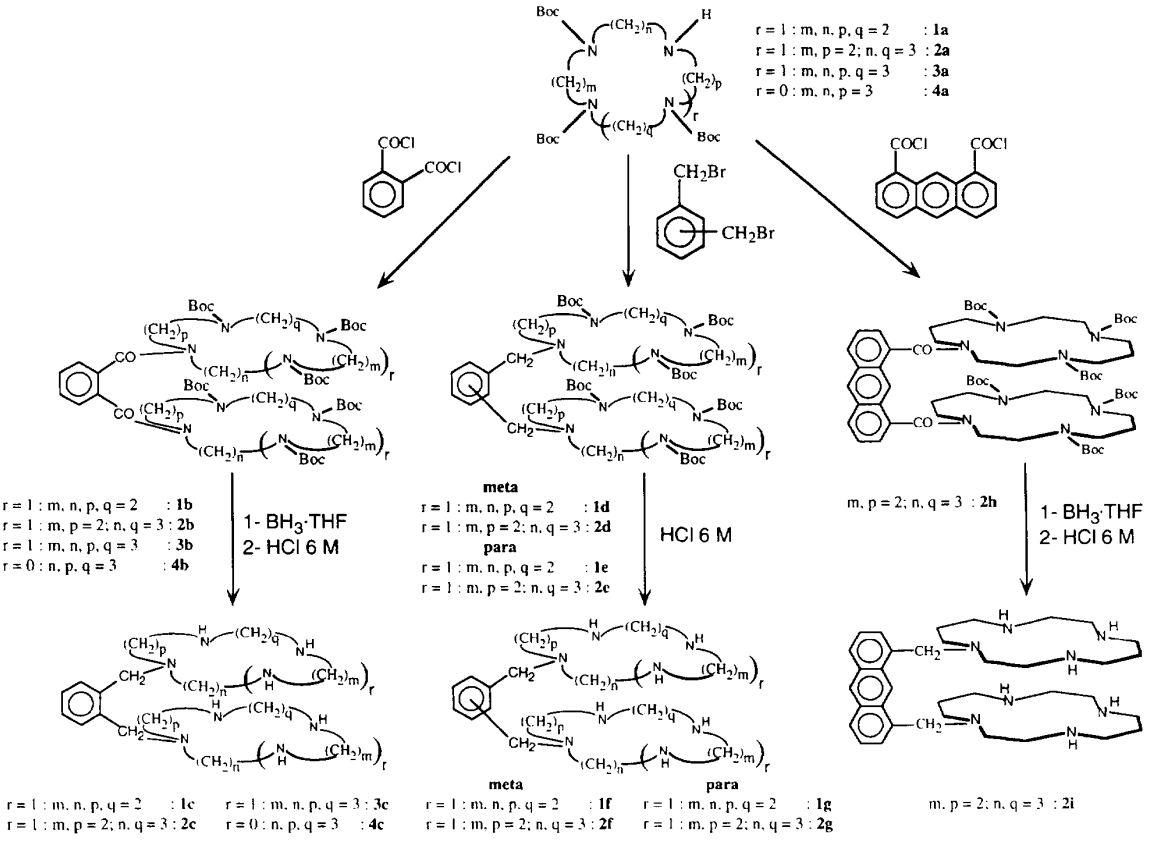

Fig 2. Synthetic scheme for the bismacrocycles.

Table I. ESR data for the dicopper complexes in frozen solution (MeOH/toluene) at 100 K.

Compounds	*Allowed transition*				*Half-field transition*		
	$g_{//}$	$g_{\perp}$	$A_{//}$ (10^{-4} cm^{-1})	D (10^{-4} cm^{-1})	g (10^{-4} cm^{-1})	A Å	r_{Cu-Cu}
1c	2.25	2.07	82	52	4.39	169	8.6
1f	2.20	2.07	102	40	4.34	140	9.2
1g	2.21	2.06	93	32	4.39	–	>9.9
2c	2.20	2.02	91	64	4.41	174	7.9
2f	2.19	2.06	107	32	4.35	211	9.9
2g	2.19	2.06	104	35	4.42	–	>9.6 (11.56)[a]
2i	2.19	2.05	101	66	4.39	–	7.8
3c	2.23	2.06	149	46	4.40	–	8.9
4c	2.27	2.07	183	–	–	–	–
Cyclam Cu^{2+}	2.19	2.05	204	–	–	–	–

[a] Values in parentheses are the corresponding dinickel structure [8].

the D values (table I) are close to half the $A_{//}$ coupling constant and the spacing between the two seven-peak parallel signals ($2D$) is close to $A_{//}$ (fig 3) [8]. It is important to note that, except for **3c** and **4c**, the $A_{//}$ coupling constant is about half the monomer value, which is to be expected for a copper dimer showing magnetic exchange. In the absence of calculated spectra, the parallel and perpendicular lines of the spectra for the allowed transitions are reasonably assigned by comparison with monomer copper complexes. The parallel lines are thus attributable to the low-field part of the spectra (≈ 3 050 G) while the high-field part (≈ 3 250 G) is assigned to the perpendicular component. Perpendicular coupling was never observed.

The spectra led us to determine the distance r between the two copper ions. Indeed, two ESR methods are usually used to determine the interspin distance between two unpaired electrons. Firstly, in the case of a pure dipolar interaction, the separation $2D$ (fig 5) between the two sets of seven lines in the high-field region can be used to obtain r following equation (1) [21, 23].

$$r^3 = 0.65 g_{//}^2 / D \text{ with } D \text{ in } cm^{-1} \text{ and } r \text{ in Å} \qquad (1)$$

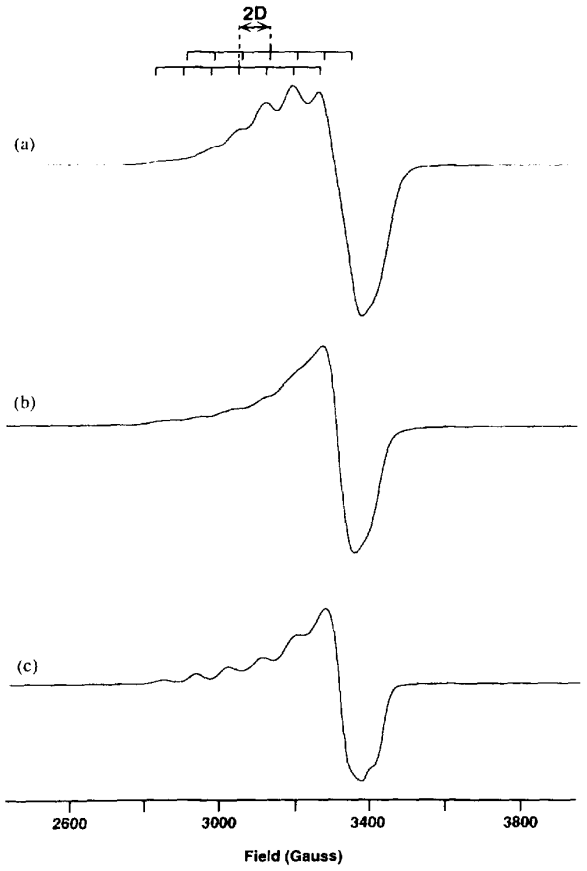

Fig 3. X-band ESR spectra of the allowed transitions for (a) **1c**, (b) **1f** and (c) **1g** at 100 K in 1:1 MeOH/toluene solution.

However, this method does not give accurate results when the dipolar coupling value is of the order of the nuclear hyperfine coupling value. This is due to a significant overlap of the two heptets precluding an estimation of the value of $2D$. Thus $2D$ values can only be obtained from these spectra by computer simulation.

Another approach is to use the half-field $\Delta Ms = 2$ transition when dipolar interactions are analyzed. It has been shown that the ratio of the intensity of the forbidden transition ($\Delta Ms = 2$) to the intensity of the allowed transitions ($\Delta Ms = 1$) is directly dependent on r according to equation (2) [21, 22].

$$\text{Relative intensity} = 20/r^6 \qquad (2)$$

Intermetallic distances calculated following this method can be correlated with the values obtained from X-ray data on the dicopper cofacial diporphyrin complex [24] and dinitroxyl radicals [21]. We used this approach to determine the copper-copper distance for each dimetallic complex. The knowledge of the r value allowed us to evaluate the zero-field splitting parameter D following equation (1).

The experimental data are reported in table I. The values range from 7.8 to 9.9 Å depending upon the relative position of the macrocycles. Slight differences were observed by changing the nature of the macrocycle but, as expected, more pronounced differences were observed by varying the length of the bridging unit. In the case of the *p*-xylyl derivatives, the poorly resolved signal of the forbidden transition meant that we could not determine accurate values for the copper-copper distance. The low intensity of the signal is due to the large intermacrocycle distance ($\approx$ 11.5 Å). In contrast, for the other bistetraazaamacrocycles, the experimental metal-metal distances agree well with the calculated distance determined by molecular modeling (see below). No half-field signal was observed for the bistriazamacrocycle because the metallation reaction leads to a monocopper complex [17].

Molecular modeling studies

Molecular mechanics (MM) calculations for organic molecules [25-27] have been applied to the study of organometallic complexes using a variety of force fields [28-30], but the study of transition or other heavy-metal-containing species remains a difficult task. The polarizability of the metal ion depends on its overall coordination environment which also has a strong effect on the force-field parameterization. A new rule-based force field has been used in this study. The *extensible systematic force field* (ESFF) [31] is based on atomic parameters coupled with rules for generating significant parameters. The main aim of the MM calculations in this work was to predict the molecular geometry of different bismacrocycles and to compare the calculated parameters with those obtained by spectroscopy.

An MM calculation was undertaken to check the new force field. We thus determined the structural parameters of the thia-1,5,8,12-tetraazabicyclo[10.5.2]nonadecane copper(II) cation, for which X-ray data have been reported [32]. All the bond lengths were reproduced to within ±0.02 Å and the mean angle deviation was found to be within ±5° of the observed X-ray values. The Cu^{2+}[12]aneN$_4$ and Cu^{2+}[14]aneN$_4$ tetraazamacrocycles have four and five conformational isomers, respectively (fig 6). Systematic MM calculations were made using the ESFF force field to determine the relative stabilities of all the possible conformations. In the Cu^{2+}[12]aneN$_4$ conformer series, the *trans*-I conformer was found to be much more stable than the others. This finding is in good agreement with a previous study [33]. Two of the five conformers of the Cu^{2+}[14]aneN$_4$ series were found to be approximately equal in energy (the difference between the relative strain energies is less than 0.3 kcal/mol). The *trans*-III conformer was found to be the most stable, which agrees with the geometric parameter observed for Ni^{2+}[14]aneN$_4$. The copper atom of the *trans*-I Cu^{2+}[12]aneN$_4$ conformer is predicted to lie nearly 0.5 Å outside the four mean nitrogen planes. In contrast, the metal atom of the *trans*-I Cu^{2+}[14]aneN$_4$ is predicted to lie in the plane of the four nitrogens.

The *trans*-I Cu^{2+}[12]aneN$_4$ conformer was used to build the three bistetraazamacrocycles (**1c**, **1f** and **1g**) possessing *o*-, *m*- and *p*-xylyl space linkers. A full minimization was carried out for the three complexes and the minimized structures of the most stable conformers are shown in figure 7. The calculated Cu-Cu distances

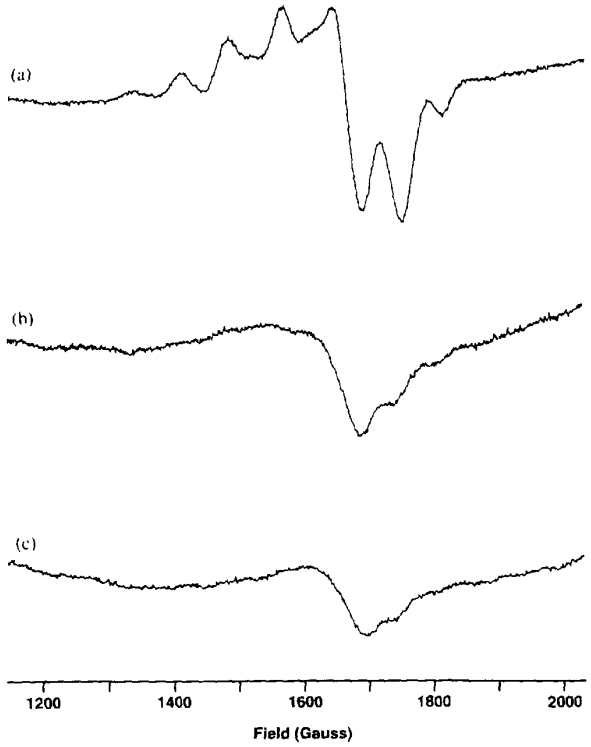

Fig 4. X-band ESR spectra of the half-field transition for (a) **1c**, (b) **1f** and (c) **1g** at 100 K in 1:1 MeOH/toluene solution.

are reported in table I and compared with the experimental distances obtained by ESR. MM calculations were also used to study the structures and geometries of other two biscyclams (**2c** and **2i**) and data relative to the *trans*-III Cu^{2+}[14]aneN$_4$ were used to model these two complexes. The Cu-Cu separation of the most stable minimized structures (table I) shows a good overall agreement between spectroscopic and calculated values. Considering the relative errors reported in table II, it is clear that the *p*-xylyl dicopper biscyclen complex has the highest relative error due to the difficult determination of the half-field ESR signal integration.

Table II. Comparison of the Cu-Cu distance obtained from ESR spectra or by calculation for the dicopper bismacrocycles.

Compounds	r_{Cu-Cu} *(Å) from ESR*	r_{Cu-Cu} *(Å) from MM*	*Relative error (%)*
1c	8.6	8.35	3
1f	9.2	9.88	7
1g	>9.9	11.32	14
2c	7.9	8.30	5
2i	7.8	7.65	2

It is interesting to note that the X-ray crystal data of the *p*-xylyl dinickel biscyclam species [8] give a Ni-Ni distance equal to 11.56 Å, which is close to our value determined by MM calculation.

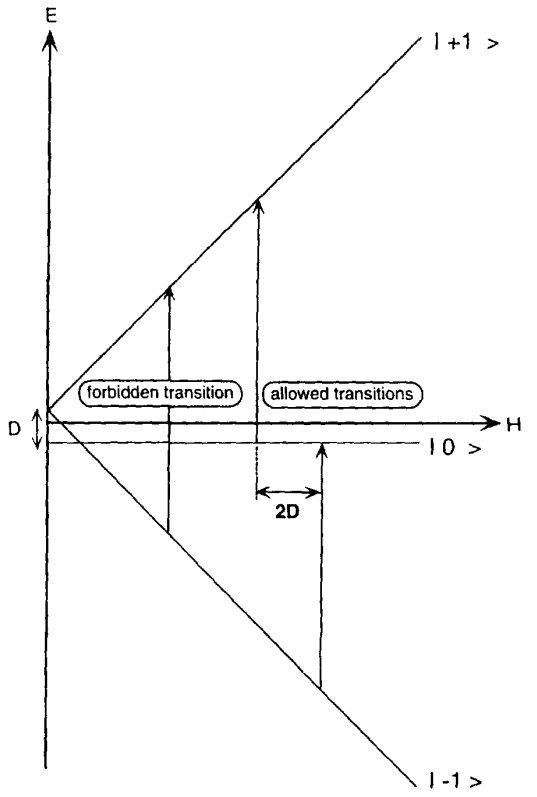

Fig 5. Energy level diagram for a triplet state when the magnetic field is along the *z* axis of the dipole tensor.

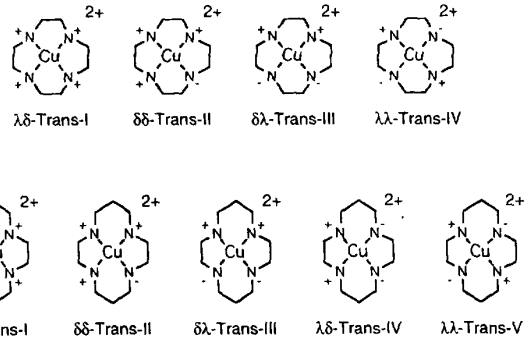

Fig 6. Configurational isomers of Cu^{2+}[12]aneN$_4$ and Cu^{2+}[14]aneN$_4$ tetraazamacrocycles. The + indicates that the hydrogen of the NH group is above the plane defined by the four N atoms and – indicates that it is below.

In conclusion, this paper describes a facile synthetic route to series of bismacrocycles in high yields starting from easily available reagents. An intramolecular electron exchange between the two central metals for the corresponding dicopper complexes has been deduced from ESR data. Moreover, it is possible to predict the geometry of these dicopper complexes by molecular modeling. The calculated data are in good agreement with the Cu-Cu distances deduced from ESR measurements.

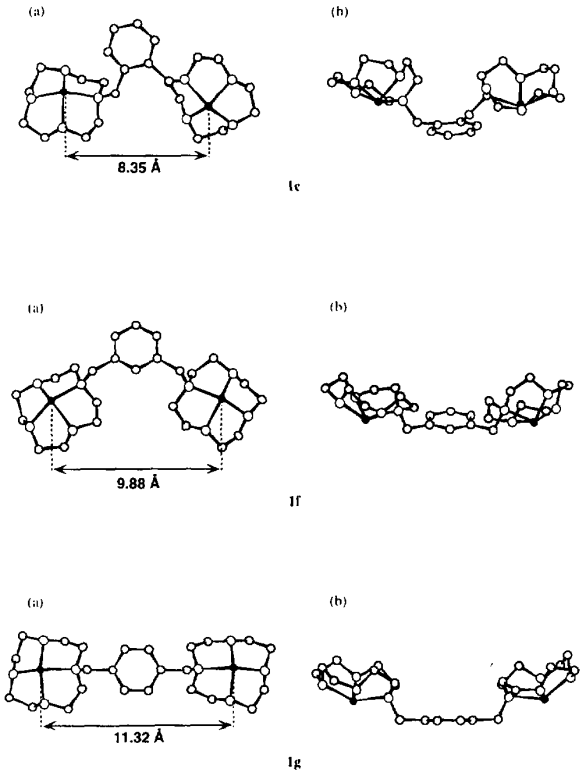

Fig 7. MM views for the xylyl-bridged derivatives **1c**, **1f** and **1g** (a) from the front and (b) on one side, showing the relative orientation of each macrocycle.

Experimental section

ESR spectra were obtained on a Bruker ESP 300 coupled to a Microware computer at microwave powers that did not cause saturation of the signal. To improve the signal-to-noise ratio of the spectra of the half-field transition, all spectra were recorded using modulation amplitudes up to about 10 G. The intensity of the transitions were measured by double-integration. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz on a Bruker WM 400 or at 200 MHz on a Bruker AC200 spectrometer of the Centre de spectroscopie moléculaire de l'université de Bourgogne. All chemical shifts were referenced to tetramethylsilane as an internal standard. Mass spectra were obtained on a Kratos Concept 321 S Spectrometer using DCI ionization mode. Microanalyses were performed by the Service Central d'Analyse du Centre National de la Recherche Scientifique, Vernaison, France. The MM calculations reported in this study were carried out with the Discover module of Biosym molecular modeling package on a Silicon Graphics Indigo 2 workstation [31]. All the parent tetraazamacrocycles were synthesized in our laboratory [34-37]. The anthracene-1,8-dicarbonyl dichloride linker was prepared following a literature procedure [38, 39]. THF was distilled under argon over the sodium benzophenone complex. All other chemicals were commercial derivatives (Janssen Chimica) and were used without further purification.

General procedure **A**: *synthesis of* **1a–4a**

The required polyazamacrocycle **1–4** was dissolved in dichloromethane (50 mL/mmol) and a solution of di-*tert*-butyl dicarbonate in dichloromethane (5 mL/mmol) was slowly added under stirring. After 2 h, the solvent was evaporated and the residue was purified over a silica-gel column.

• *1,4,7-Tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane* **1a**

The general procedure **A** applied to 4.00 g of 1 (23.2 mmol) and 12.2 g of di-*tert*-butyl dicarbonate (55.9 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 96:4), the title compound (m = 7.68 g; yield = 70%).

^{1}H NMR ($CDCl_3$): 1.42 (s, 18H), 1.44 (s, 9H), 2.81 (m, 4H), 3.26–3.35 (m, 8H), 3.60 (m, 4H).

^{13}C NMR ($CDCl_3$): 28.9, 29.0, 46.1, 49.9, 51.2, 79.4, 79.6, 155.8, 156.0.

DCIMS (m/z): 474 ($[M + H]^+$).

Anal calc for $C_{23}H_{44}N_4O_6$: C, 58.45; H, 9.38; N, 11.85; O, 20.31%. Found: C, 58.2; H, 9.3; N, 11.8; O, 19.8.

• *1,4,8-Tris(*tert*-butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane* **2a**

The general procedure **A** applied to 5.00 g of **2** (25.0 mmol) and 13.6 g of di-*tert*-butyl dicarbonate (62.5 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 95:5), the title compound (m = 8.34 g; yield = 67%).

^{1}H NMR ($CDCl_3$): 1.45 (s, 27H), 1.70 (m, 2H), 1.92 (m, 2H), 2.60 (t, 2H), 2.77 (t, 2H), 3.27–3.39 (m, 18H).

^{13}C NMR ($CDCl_3$): 29.1, 44.7, 46.5, 47.3, 48.3, 50.6, 51.1, 79.8, 156.0, 156.8.

DCIMS (m/z): 501 ($[M + H]^+$).

Anal calc for $C_{25}H_{48}N_4O_6.0.5H_2O$: C, 58.93; H, 9.62; N, 11.00; O, 20.43%. Found: C, 58.9; H, 9.5; N, 10.9; O, 20.4.

• *1,5,9-Tris(*tert*-butyloxycarbonyl)-1,5,9,13-tetraazacyclohexadecane* **3a**

The general procedure **A** applied to 3.00 g of **3** (13.2 mmol) and 7.18 g of di-*tert*-butyl dicarbonate (33.0 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 85:15), the title compound (m = 1.28 g; yield = 37%).

^{1}H NMR ($CDCl_3$): 1.41 (s, 27H), 1.78 (m, 8H), 2.75 (t, 4H), 3.16–3.27 (m, 12H).

^{13}C NMR ($CDCl_3$): 28.5, 29.3, 30.2, 46.3, 46.7, 47.0, 47.4, 80.2, 156.2, 156.3.

DCIMS (m/z): 530 ($[M + H]^+$).

Anal calc for $C_{27}H_{52}N_4O_6$: C, 61.33; H, 9.91; N, 10.60; O, 18.10%. Found: C, 61.0; H, 10.0; N, 10.4; O, 18.5.

• *1,5-Bis(*tert*-butyloxycarbonyl)-1,5,9-triazacyclododecane* **4a**

The general procedure **A** applied to 0.80 g of **4** (4.68 mmol) and 1.53 g of di-*tert*-butyl dicarbonate (7.00 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 90:10), the title compound (m = 0.93 g; yield = 72%).

^{1}H NMR ($CDCl_3$): 1.41 (s, 18H), 1.72 (q, 4H), 1.88 (q, 2H), 2.60 (t, 4H), 3.20 (t, 4H), 3.25 (t, 4H).

^{13}C NMR ($CDCl_3$): 27.6, 28.3, 28.6, 29.1, 46.2, 46.7, 47.2, 63.8, 79.4, 156.5.

DCIMS (m/z): 373 ($[M + H]^+$).

Anal calc for $C_{19}H_{37}N_3O_4$: C, 61.43; H, 10.04; N, 11.31; O, 17.23%. Found: C, 61.1; H, 10.2; N, 11.3; O, 17.3.

General procedure **B**: *syntheses of* **1b–4b** *and* **2h**

Acid dichloride was dissolved in THF (5 mL/mmol) and was added under argon to a solution of the corresponding *N,N'*-bis(*tert*-butyloxycarbonyl)-*N,N',N''*-triazacycloalkane

4a or *N,N',N''*-tris(*tert*-butyloxycarbonyl)-*N,N',N'',N'''*-tetraazacycloalkanes **1a–3a** in THF (10 mL/mmol) in presence of 2 equiv of triethylamine. The resulting mixture was stirred for 1 h at room temperature before neutralization by a potassium hydroxide solution (2 mol/L). The aqueous solution was then extracted with chloroform, the organic layer dried over magnesium sulfate, filtered and evaporated. The crude product thus obtained was purified by chromatography on silica.

• *1,1'-Phthaloylbis[4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane]* **1b**

The general procedure **B** applied to 5.30 g of **1a** (11.2 mmol) and 1.14 g of phthaloyl dichloride (5.6 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 98:2), the title compound (m = 6.00 g; yield = 99%).

^{1}H NMR ($CDCl_3$): 1.38 (s), 1.41 (s), 3.15–3.60 (m), 7.20 (m), 7.40 (m).

^{13}C NMR ($CDCl_3$): 28.3, 28.4, 47.7, 49.1–51.5, 80.0, 80.3, 80.6, 126.3, 128.6, 135.0, 155.7, 156.8, 157.1, 170.9.

DCIMS (m/z): 1 076 ($[M + H]^+$).

Anal calc for $C_{54}H_{90}N_8O_{14}$: C, 60.31; H, 8.44; N, 10.42; O, 20.83%. Found: C, 60.9; H, 8.5; N, 10.6; O, 20.3.

• *1,1'-Phthaloylbis[4,8,11-tris(*tert*-butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane]* **2b**

The general procedure **B** applied to 8.00 g of **2a** (16.0 mmol) and 1.62 g of phthaloyl dichloride (8.0 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 95:5), the title compound (m = 8.47 g; yield = 94%).

^{1}H NMR ($CDCl_3$): 1.41 (s), 1.45 (s), 1.47 (s), 1.72–1.79 (m), 3.30–3.35 (m), 7.27 (m), 7.37 (m).

^{13}C NMR ($CDCl_3$): 26.2, 27.6, 29.1, 44.5–50.4, 126.5, 129.2, 135.8, 156.1, 156.3, 156.6, 170.8.

DCIMS (m/z): 1 132 ($[M + H]^+$).

Anal calc for $C_{58}H_{98}N_8O_{14}$, $2H_2O$: C, 59.70; H, 8.75; N, 9.60; O, 21.90%. Found: C, 60.1; H, 9.3; N, 9.5; O, 20.9.

• *1,1'-(Anthracene-1,8-dicarbonyl)bis[4,8,11-tris(*tert*-butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane]* **2h**

The general procedure **B** applied to 4.95 g of **2a** (9.9 mmol) and 1.5 g of anthracene-1,8-dicarbonyl dichloride (4.95 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 97:3), the title compound (m = 5.8 g; yield = 95%).

^{1}H NMR ($CDCl_3$): 1.45 (s), 1.49 (s), 1.61 (s), 1.72–1.83 (m), 2.79–3.62 (m), 7.50 (dd + d), 8.01 (d), 8.22 (m), 8.46 (s).

^{13}C NMR ($CDCl_3$): 28.3, 28.7, 28.9, 29.1, 44.6–50.5, 121.6, 121.8, 124.2, 124.5, 125.6, 128.1, 128.7, 128.8, 129.7, 129.9, 132.1, 135.4, 155.8, 156.1, 156.3, 156.7, 171.2.

DCIMS (m/z): 1 132 ($[M - Boc]^+$).

Anal calc for $C_{66}H_{102}N_8O_{14}.2H_2O$: C, 62.55; H, 8.37; N, 8.84; O, 20.20%. Found: C, 62.7; H, 8.4; N, 8.9; O, 20.0.

• *1,1'-Phthaloylbis[5,9,13-tris(*tert*-butyloxycarbonyl)-1,5,9,13-tetraazacyclohexadecane]* **3b**

The general procedure **B** applied to 0.82 g of **3a** (1.55 mmol) and 0.16 g of phthaloyl dichloride (0.77 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 95:5), the title compound (m = 0.80 g; yield = 87%).

^{1}H NMR ($CDCl_3$): 1.36 (s), 1.44 (s), 1.72–1.81 (m), 3.00–3.20 (m), 3.46 (m), 7.24 (m), 7.35 (m).

^{13}C NMR ($CDCl_3$): 28.9, 44.8, 47.4, 48.9, 80.0, 126.4, 129.0, 135.8, 155.9, 160.0, 175.0.

DCIMS (m/z): 1 188 ($[M + H]^+$).

Anal calc for $C_{62}H_{106}N_8O_{14}$: C, 62.71; H, 9.00; N, 9.44; O, 18.86%. Found: C, 61.9; H, 9.2; N, 8.7; O, 18.4.

• *1,1'-Phthaloylbis[5,9-bis(*tert*-butyloxycarbonyl)-1,5,9-triazacyclododecane]* **4b**

The general procedure **B** applied to 0.85 g of **4a** (2.31 mmol) and 0.13 g of phthaloyl dichloride (1.16 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 98:2), the title compound (m = 1.00 g; yield = 98%).

^{1}H NMR ($CDCl_3$): 1.36 (s), 1.44 (s), 1.79 (m), 1.97 (m), 3.28–3.50 (m), 7.21 (m), 7.32 (m).

^{13}C NMR ($CDCl_3$): 27.8, 28.3, 29.1, 32.0, 42.2, 45.9, 46.6, 47.7, 48.1, 80.4, 126.6, 129.2, 136.1, 156.8, 157.0, 171.3.

DCIMS (m/z): 874 ($[M + H]^+$).

Anal calc for $C_{46}H_{76}N_6O_{10}$: C, 63.28; H, 8.77; N, 9.62; O, 18.32%. Found: C, 63.0; H, 8.9; N, 9.6; O, 18.3.

General procedure **C***: synthesis of* **1c–4c** *and* **2i**

The bridged bismacrocycles **1b–4b** and **2h** were smoothly reduced under argon with a large excess of a refluxing THF solution of diborane (1 mol/L) for 48 h. After cooling to 0 °C and treatment with MeOH/H_2O, the mixture was evaporated and refluxed in 6 M HCl for 1 h. After cooling, the neutralized water solution (NaOH) was extracted with chloroform. The organic layer was dried over magnesium sulfate, filtered and evaporated to yield the pure product as a white solid.

• *1,1'-*o*-Xylylbis(1,4,7,10-tetraazacyclododecane)* **1c**

The general procedure **C** applied to 5.00 g of **1b** (4.65 mmol) with 60 mL of BH_3-THF solution afforded the title compound (m = 1.70 g; yield = 82%).

^{1}H NMR ($CDCl_3$): 2.51–2.73 (m), 3.64 (s), 7.12 (dd), 7.30 (dd).

^{13}C NMR ($CDCl_3$): 42.4, 43.6, 44.3, 48.9, 54.5, 124.2, 127.1, 134.5.

DCIMS (m/z): 448 ($[M + H]^+$).

Anal calc for $C_{24}H_{46}N_8$: C, 64.53; H, 10.38; N, 25.09%. Found: C, 64.7; H, 10.8; N, 24.5.

• *1,1'-*o*-Xylylbis(1,4,8,11-tetraazacyclotetradecane)* **2c**

The general procedure **C** applied to 2.50 g of **2b** (2.21 mmol) with 20 mL of BH_3-THF solution afforded the title compound (m = 0.80 g; yield = 72%).

^{1}H NMR ($CDCl_3$): 1.71 (q), 1.81 (q), 2.47–2.83 (m), 3.56 (s), 7.17 (dd), 7.49 (dd).

^{13}C NMR ($CDCl_3$): 27.1, 28.8, 48.1, 48.2, 48.3, 49.1, 50.6, 53.5, 55.2, 56.1, 127.1, 130.0, 138.1.

DCIMS (m/z): 504 ($[M + H]^+$).

Anal calc for $C_{28}H_{54}N_8.H_2O$: C, 64.61; H, 10.77; N, 21.53%. Found: C, 64.7; H, 10.9; N, 21.3.

• *1,1'-(Anthracene-1,8-dimethylene)bis(1,4,8,11-tetraazacyclotetradecane)* **2i**

The general procedure **C** applied to 5.2 g of **2h** (4.22 mmol) with 35 mL of BH_3-THF solution afforded the title compound (m = 0.81 g; yield = 32%).

^{1}H NMR ($CDCl_3$): 1.67 (q), 1.90 (q), 2.59–2.78 (m), 4.17 (s), 7.45 (dd), 7.76 (d), 7.90 (m), 8.44 (s), 8.79 (s).

^{13}C NMR ($CDCl_3$): 27.7, 29.1, 48.5, 48.6, 48.9, 49.2, 49.9, 50.7, 54.1, 56.3, 117.7, 125.5, 126.0, 127.8, 128.3, 131.1, 132.1, 135.7.

DCIMS (m/z): 604 ($[M + H]^+$).

Anal calc for $C_{36}H_{58}N_8$, $2H_2O$: C, 69.67; H, 9.67; N, 18.06; O, 5.03%. Found: C, 68.9; H, 9.5; N, 16.3; O, 5.3.

• *1,1′*-o-*Xylylbis(1,5,9,13-tetraazacyclohexadecane)* **3c**

The general procedure **C** applied to 0.75 g of **3b** (0.63 mmol) with 10 mL of BH_3-THF solution afforded the title compound (m = 0.19 g; yield = 55%).

^{1}H NMR ($CDCl_3$): 1.62 (m), 2.14 (m), 2.36 (m), 2.68 (m), 3.53 (s), 7.17 (m), 7.26 (m).

^{13}C NMR ($CDCl_3$): 26.4, 27.6, 43.6, 48.8, 52.3, 55.5, 56.2, 127.1, 130.2, 139.1.

DCIMS (m/z): 560 ($[M + H]^+$).

Anal calc for $C_{32}H_{62}N_8$, H_2O: C, 66.60; H, 11.20; N, 19.4; O, 2.80%. Found: C, 65.4; H, 12.1; N, 19.1; O, 3.3.

• *1,1′*-o-*Xylylbis(1,5,9-triazacyclododecane)* **4c**

The general procedure **C** applied to 0.85 g of **4b** (0.97 mmol) with 12 mL of BH_3-THF solution afforded the title compound (m = 0.80 g; yield = 85%).

^{1}H NMR ($CDCl_3$): 1.68–1.77 (2q), 2.52 (t), 2.71 (t), 2.85 (t), 3.50 (s), 7.20 (dd), 7.45 (dd).

^{13}C NMR ($CDCl_3$): 25.9, 26.2, 46.9, 49.4, 53.1, 55.4, 126.8, 129.4, 138.5.

DCIMS (m/z): 446 ($[M + H]^+$).

Anal calc for $C_{26}H_{48}N_6$: C, 70.22; H, 10.88; N, 18.90%. Found: C, 69.5; H, 11.7; N, 18.8.

General procedure **D***: synthesis of* **1d**, **2d**, **1e** *and* **2e**

The α,α'-dibromo-*p*-xylene or α,α'-dibromo-*m*-xylene was dissolved in dry acetonitrile (50 mL) and added to a solution of the triprotected macrocycle **1a** or **2a** in the same solvent (100 mL) in presence of anhydrous sodium carbonate (4.0 g). The resulting mixture was refluxed for 48 h. The solid was then filtered off and the solvent evaporated. The obtained crude product was purified by chromatography on silica.

• *1,1′*-m-*Xylylbis[4,7,10-tris(*tert-*butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane]* **1d**

The general procedure **D** applied to 3.00 g of **1a** (6.35 mmol) and 0.84 g of α,α'-dibromo-*m*-xylene (3.18 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 99:1), the title compound (m = 2.45 g; yield = 74%).

^{1}H NMR ($CDCl_3$): 1.38 (s), 1.41 (s), 1.46 (s), 2.59 (m), 3.20–3.52 (m), 3.68 (s), 6.98–7.17 (m).

^{13}C NMR ($CDCl_3$): 29.1, 29.3, 48.4, 50.4, 55.3–56.3, 57.7, 80.0, 80.1, 128.8, 129.8, 132.5, 137.4, 156.0, 156.5.

DCIMS (m/z): 1 048 ($[M + H]^+$).

Anal calc for $C_{54}H_{94}N_8O_{12}$: C, 61.93; H, 9.05; N, 10.70; O, 18.33%. Found: C, 61.7; H, 9.1; N, 10.8; O, 18.3.

• *1,1′*-p-*Xylylbis[4,7,10-tris(*tert-*butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane]* **1e**

The general procedure **D** applied to 3.00 g of **1a** (6.35 mmol) and 0.84 g of α,α'-dibromo-*p*-xylene (3.18 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 99:1), the title compound (m = 2.30 g; yield = 69%).

^{1}H NMR ($CDCl_3$): 1.38 (s), 1.42 (s), 2.60 (m), 3.19–3.34 (m), 3.54 (m), 3.67 (s), 7.14 (s).

^{13}C NMR ($CDCl_3$): 29.3, 29.4, 48.2–50.5, 55.4–56.5, 57.3, 79.9, 80.0, 130.8, 136.3, 155.9, 156.3.

DCIMS (m/z): 1 048 ($[M + H]^+$).

Anal calc for $C_{54}H_{94}N_8O_{12}$: C, 61.93; H, 9.05; N, 10.70; O, 18.33%. Found: C, 61.9; H, 9.2; N, 10.9; O, 18.1.

• *1,1′*-m-*Xylylbis[4,8,11-tris(*tert-*butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane]* **2d**

The general procedure **D** applied to 4.10 g of **2a** (8.2 mmol) and 1.08 g of α,α'-dibromo-*m*-xylene (4.1 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 96:4), the title compound (m = 3.20 g; yield = 71%).

^{1}H NMR ($CDCl_3$): 1.35 (s), 1.38 (s), 1.41 (s), 1.42 (s), 1.63–1.86 (m), 2.32–2.56 (m), 3.20–3.35 (m), 3.47 (s), 7.02–7.25 (m).

^{13}C NMR ($CDCl_3$): 27.3, 29.1, 46.5–47.9, 52.0, 53.5, 60.3, 80.1, 80.3, 128.5, 128.8, 130.6, 139.0, 156.2.

DCIMS (m/z): 1 103 ($[M + H]^+$).

Anal calc for $C_{58}H_{102}N_8O_{12}$: C, 63.13; H, 9.32; N, 10.15; O, 17.40%. Found: C, 62.7; H, 9.4; N, 10.1; O, 17.7.

• *1,1′*-p-*Xylylbis[4,8,11-tris(*tert-*butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane]* **2e**

The general procedure **D** applied to 2.76 g of **2a** (5.52 mmol) and 0.73 g of α,α'-dibromo-*p*-xylene (2.76 mmol) gave, after purification by chromatography (CH_2Cl_2/MeOH 96:4), the title compound (m = 1.60 g; yield = 53%).

^{1}H NMR ($CDCl_3$): 1.34 (s), 1.38 (s), 1.39 (s), 1.41 (s), 1.61 (m), 1.85 (m), 2.31 (m), 2.55 (s), 3.29(m), 3.45 (s), 7.10 (s).

^{13}C NMR ($CDCl_3$): 27.1, 29.0, 46.5, 47.9, 52.0, 53.6, 59.9, 79.9, 80.1, 129.5, 137.8, 156.1.

DCIMS (m/z): 1 103 ($[M + H]^+$).

Anal calc for $C_{58}H_{102}N_8O_{12}$: C, 63.13; H, 9.32; N, 10.15; O, 17.40%. Found: C, 63.2; H, 9.3; N, 10.1; O, 17.4.

General procedure **E***: synthesis of* **1f**, **2f**, **1g** *and* **2g**

The bridged bismacrocycles **1d**, **2d**, **1e** and **2e** were dissolved in 80 mL of 6 mol/L hydrochloric acid. The mixture was heated at 80 °C for 1 h and after the gas evolution ceased, the solution was neutralized at 0 °C by addition of sodium hydroxide pellets until the pH reached 11–12. This aqueous solution was then extracted with chloroform, the organic layer dried over magnesium sulfate, filtered and evaporated to yield the pure product as a white solid.

• *1,1′*-m-*Xylylbis(1,4,7,10-tetraazacyclododecane)* **1f**

The general procedure **E** applied to 2.20 g of **1d** (2.10 mmol) gave the title compound (m = 0.80 g; yield = 85%).

^{1}H NMR ($CDCl_3$): 2.46 (m), 2.54 (t), 2.72 (t), 3.48 (s), 7.02–7.17 (m).

^{13}C NMR ($CDCl_3$): 45.7, 47.0, 47.8, 51.6, 59.7, 128.6, 130.3, 139.4.

DCIMS (m/z): 448 ($[M + H]^+$).

Anal calc for $C_{24}H_{46}N_8$: C, 64.53; H, 10.38; N, 25.09%. Found: C, 64.4; H, 10.8; N, 24.9.

• *1,1′*-p-*Xylylbis(1,4,7,10-tetraazacyclododecane)* **1g**

The general procedure **E** applied to 2.20 g of **1e** (2.10 mmol) gave the title compound (m = 0.90 g; yield = 96%).

^{1}H NMR ($CDCl_3$): 2.46–2.51 (m), 2.59 (t), 2.73 (t), 3.50 (s), 7.15 (s).

^{13}C NMR ($CDCl_3$): 45.7, 46.9, 47.8, 51.8, 59.6, 129.5, 138.2.

DCIMS (m/z): 448 ($[M + H]^+$).

Anal calc for $C_{24}H_{46}N_8$: C, 64.53; H, 10.38; N, 25.09%. Found: C, 64.5; H, 10.8; N, 24.7.

• *1,1′*-m-*Xylylbis(1,4,8,11-tetraazacyclotetradecane)* **2f**

The general procedure **E** applied to 3.20 g of **2d** (2.90 mmol) gave the title compound (m = 1.30 g; yield = 89%).

^{1}H NMR ($CDCl_3$): 1.63 (q), 1.81 (q), 2.43–2.86 (m), 3.50 (s), 7.11 (s), 7.21 (s), 7.24 (s).

^{13}C NMR ($CDCl_3$): 26.8, 29.0, 47.9, 48.5, 49.5, 49.8, 51.2, 53.7, 55.0, 58.5, 128.5, 130.9, 139.0.

DCIMS (m/z): 504 ($[M + H]^+$).

Anal calc for $C_{28}H_{54}N_8$: C, 66.89; H, 10.83; N, 22.29%. Found: C, 66.7; H, 11.0; N, 22.0.

• *1,1'*-p-*Xylylbis(1,4,8,11-tetraazacyclotetradecane)* **2g**

The general procedure **E** applied to 2.76 g of **2e** (2.50 mmol) gave the title compound (m = 1.60 g; yield = 90%).

^{1}H NMR ($CDCl_3$): 1.67 (q), 1.83 (q), 2.48–2.81 (m), 3.51 (s), 7.25 (s).

^{13}C NMR ($CDCl_3$): 26.7, 28.7, 48.1, 48.3, 49.4, 49.7, 51.1, 53.8, 54.7, 58.4, 129.7, 138.1.

DCIMS (m/z): 504 ($[M + H]^+$).

Anal calc for $C_{28}H_{54}N_8$: C, 66.89; H, 10.83; N, 22.29%. Found: C, 67.1; H, 11.1; N, 21.5.

Dicopper(II) complexes

Dimetallic complexes were obtained by mixing methanolic solutions of the ligand and copper(II) acetate (1:2 molar ratio) for 15 min. Evaporation of the solvent gave the dicopper derivative which was studied by ESR without further purification.

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