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HIGH YIELD SYNTHESIS, SEPARATION AND STRUCTURAL CHARACTERIZATION OF NEW [N+N]-POLYAZAMACROCYCLES

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Abstract – *t*-Bu- and isopropyl-substituted aromatic dialdehydes (**1a-c**) and diamines (**2a-f**) were used to synthesize a series of imine macrocycles (**3a-m**). The highly selective cyclization reaction resulted either in a [2+2] stoechiometry or in a mixture of different [n+n] cycles, depending on the diamine building block. For some defined macrocycles (**3b, 3d, 3e**) the structure was elucidated by single crystal X-Ray diffraction that revealed a column-like arrangement of the macrocycles in the solid state. Mixtures of macrocycles were investigated with a combination of MALDI-Tof and analytical GPC which brought significant improvements in the determination of the exact size distribution. Isolated higher homologues of polyimine cycles were made available by preparative GPC for the first time. The possibility to reduce the imine macrocycles quantitatively to their corresponding amine analogues was demonstrated exemplary by the reduction of two pyridine containing cycles (**4a-b**).

INTRODUCTION

The synthesis of macrocyclic compounds is a field of growing interest[1, 2, 3], because these structures provide extraordinary binding, complexation and self-assembling properties. Macrocycles, which are

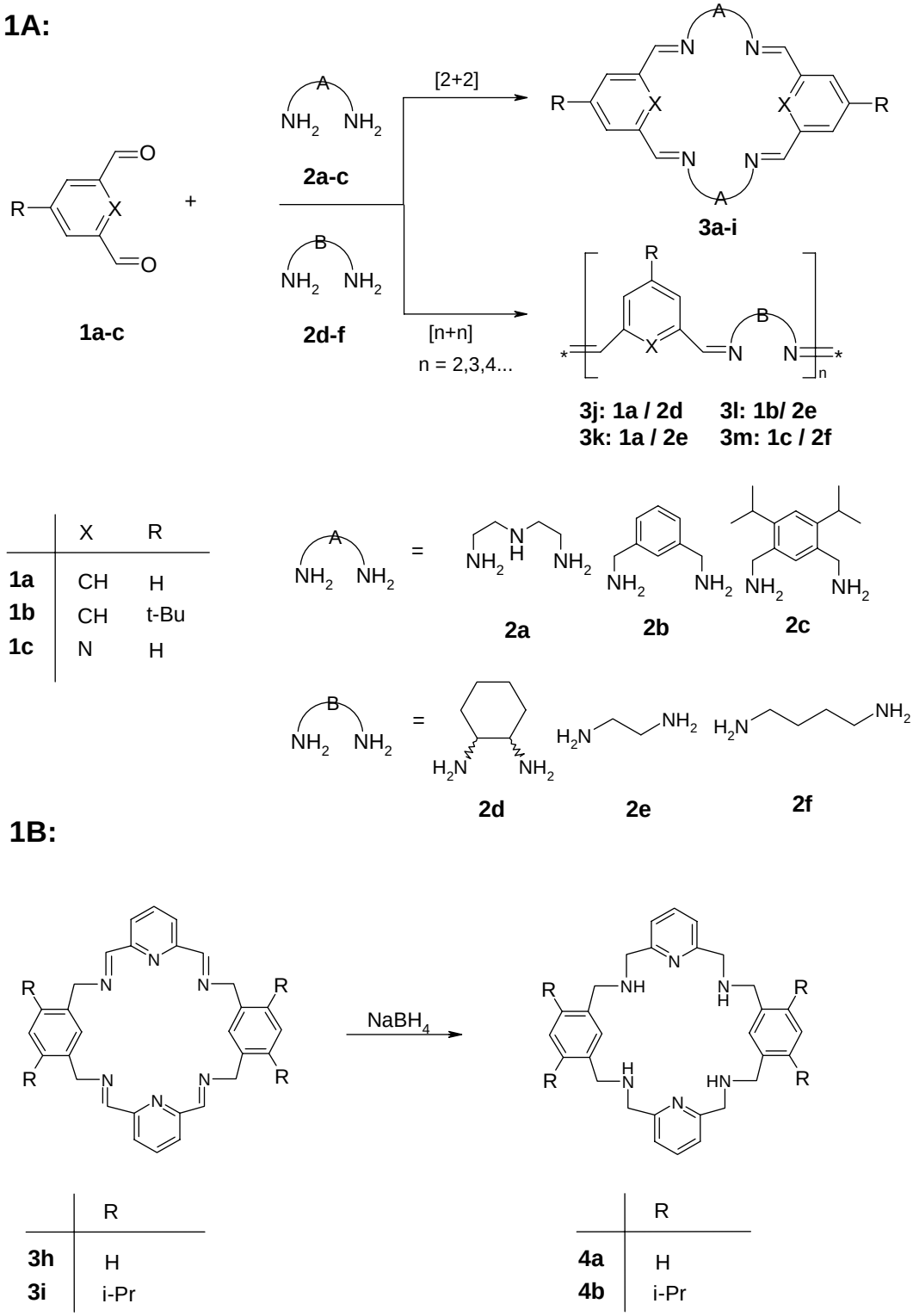
suitable for the complexation of two or more metal atoms for example, can preorient these centers relative to each other.[4, 5] In close relation, such compounds could give new impulses to the field of homogeneous and heterogeneous catalysis, in that they may provide enzyme-like activity and selectivity.[6, 5] Therefore, special emphasis has been put on the identification of efficient methods to synthesize macrocycles in a vide variety and with variable substitution. In the late 80's Lehn, Nelson and coworkers reported on a synthetic approach to obtain defined macrocyclic imines in good yield by a dipodal [2+2] condensation reaction of dialdehydes with diamines.[7] The cyclic products precipitate after reaction of the aldehyde with the amine in a suitable solvent under diluted conditions. Amongst others, Martell and coworkers demonstrated that the hydrogenation of such cyclic imines affords the corresponding saturated polyazamacrocyclic ligands in just one further step.[8] In this manner imine as well as amine aza-cycles are available quite easily in larger amounts.

However, reports were mostly limited to [2+2] cycles. The identification and separation of higher [n+n] species from mixtures is rare, whereas these larger macrocycles might be of special interest due to their higher number of chelate coordination sites. We present here our studies on the synthesis and characterization of a series of new polyimine (**3b-f, 3h, 3i**) and polyamine macrocycles (**4a,b**) with a variable substitution. Furthermore, the solid state structures of three selected compounds are characterized by single-crystal X-Ray analysis (**3b, 3d, 3e**). We use the combination of analytical GPC and MALDI-Tof experiments for determination of the size distribution and characterization of the different species in case of mixtures. Initial investigations on the use of preparative GPC allow to separate higher [n+n] cycles as pure substances from their mixtures.

RESULTS AND DISCUSSION

The macrocycles of the present work were prepared by a Schiff base condensation reaction of three different aldehydes (**1a-c**) with a series of diamines (**2a-f**) under diluted conditions (Scheme 1A).[3, 9] The drop-wise addition of aldehydes in acetonitrile to a solution of the diamine in the same solvent, affords the formation of macrocycles, which precipitate as white crystalline solids. This one step procedure leads to cyclic imine products in good to quantitative yields. These structures consist either of only one defined size (**3a-i**; Table 1) or of a mixture of different sized macrocycles (**3j-m**, Scheme 1A). However, no linear condensation products could be detected.[12] Selected saturated polyazamacrocycles (**4a,b**; Scheme 1B) were readily achieved in nearly quantitative yield by $NaBH_4$ reduction of the corresponding imines (**3h,i**). A significant advantage of the amine cycles is their improved stability against hydrolytic scission. The compounds presented in Table 1 consist of defined [2+2] cycles in amounts larger than 95%, sometimes

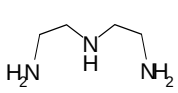
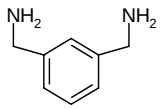
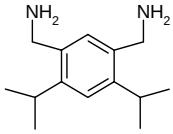
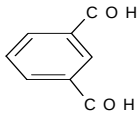
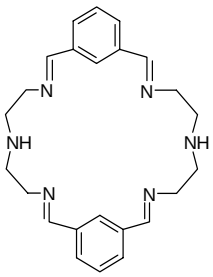
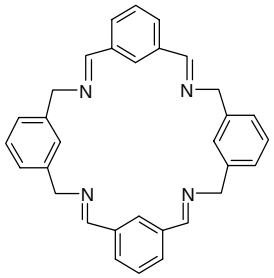
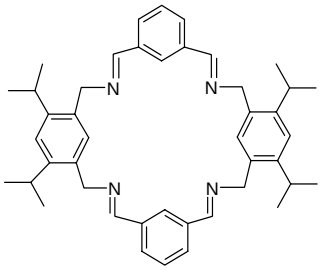
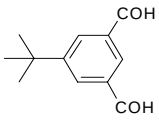
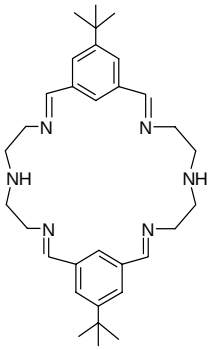
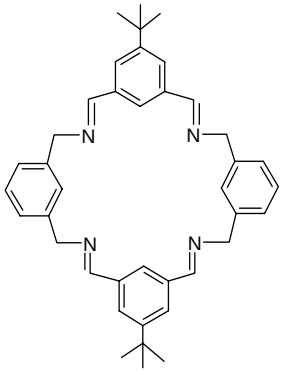
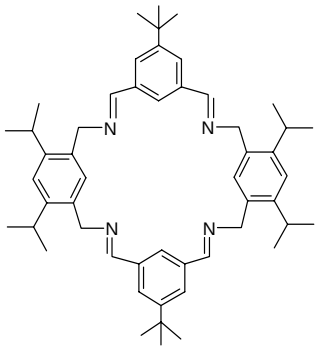
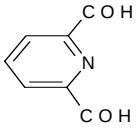
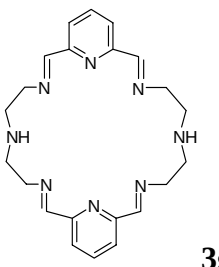
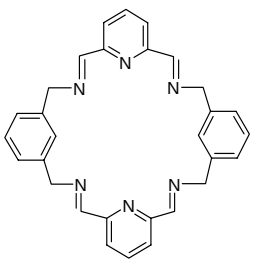
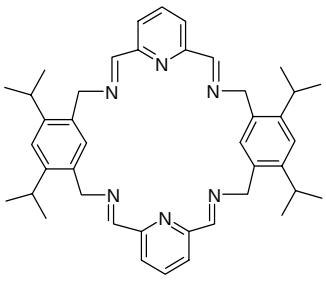
even completely. The remaining 5% contain higher [n+n] structures, so that one re-crystallization step gives pure [2+2] products.



Scheme 1. Reaction of dialdehydes with diamines to cyclic polyimines (1A); Saturated polyazamacrocycles from reduction of the imine cycles (1B).

The solubility which was rather poor for **3b,h** could be improved by the introducion of *t*-Bu and isopropyl substituents in **1b** (5-(*t*-Bu)-isophthalaldehyde) and **2c** (4,6-bisisopropyl-*m*-xylylendiamine), which afforded the species (**3b-f,i**). Interestingly, we found here no significant influence on the yield and the size distribution of the formed macrocycles by introduction of substituents. Again the substituted [2+2] macrocycles were formed in nearly quantitative yield.

Table 1. [2+2] macrocyclic imines (**3a-i**).

	 **2a**	 **2b**	 **2c**
 **1a**	 **3a**	 **3b**	 **3c**
 **1b**	 **3d**	 **3e**	 **3f**
 **1c**	 **3g**	 **3h**	 **3i**

However, preliminary results show that especially with less rigid amine precursors (**2d-f)** mixtures of different [n+n] macrocycles are accessible (**3j-m**; Scheme 1). A combination of MS techniques (CI, FAB, especially MALDI-Tof) was used to gain first insight into the size distribution.[11] However, it was difficult to determine the dispersity, especially for higher molecular weight products. Size exclusion chromatography (GPC) was used first on an analytical scale as a more powerful method for the characterisation and quantification of the amounts of different homologes. By using a column material for low molecular weight oligomers and chloroform as eluent we found sharp single GPC-traces for defined [2+2] cycles (e.g. **3d**) and nicely separated peaks for each [n+n] species in mixtures.

Variation of the diamine from the relatively rigid **2d** to the more flexible **2e** and **2f** analogues afforded increasing contents of larger cycles in the product mixtures (**3j - 3m),** as expected. The influence of substituents was tested by introducing a t-Bu group yielding the product (**3l**) instead of **3k**.

Compound (**3j**) consists of [2+2] and [3+3] species. In accordance with the MALDI-Tof spectrum the GPC chromatogram shows two single peaks (Figure 1), with a preference of the [2+2] cycle. The ratio of the two compounds was determined to 83 % [2+2] and 17 % [3+3] by analytical GPC.

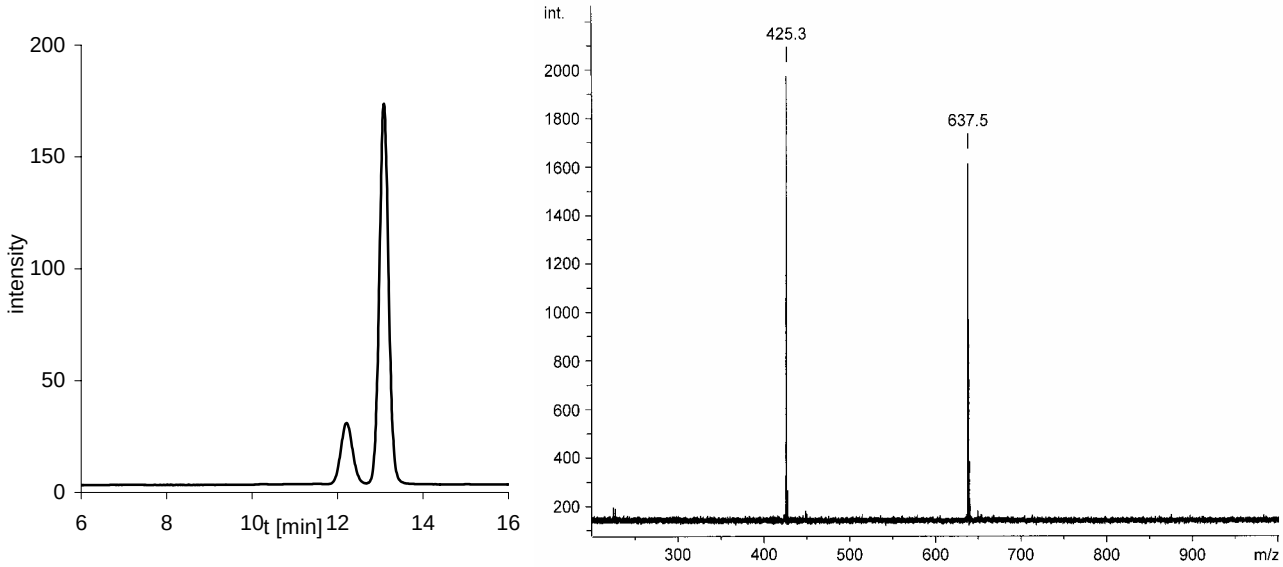


Figure 1. GPC and MALDI-Tof of the mixture (**3j**) (higher [n+n] cycles elute earlier).

Macrocycles up to a size of [12+12] could be detected by MALDI-Tof (Figure 2, **3k**) if the diamine (**2e**) is used for cyclization in combination with dialdehyde (**1a**). GPC analysis allows only the detection of species up to [5+5], due to the limited size exclusion volume of the column material. Comparable results are obtained if the *t*-Bu substituted dialdehyde (**1b**) is applied for cyclization reactions together with the diamine (**2e**). Also here, the macrocyclic product (**3l**) consists of a mixture of higher cycles with [3+3] as major component (Figure 3). The corresponding species of **3l** elute somewhat earlier than in case of **3k** due to the larger and more shielding *t*-Bu substituents.

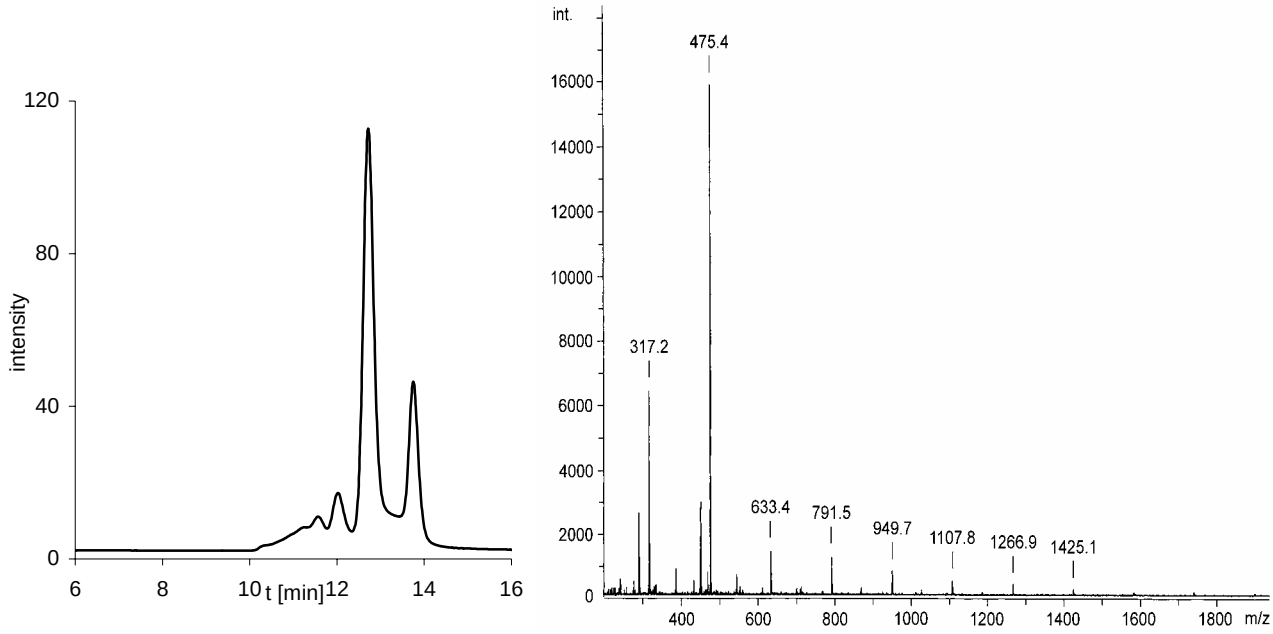


Figure 2. GPC and MALDI-Tof of the mixture (**3k**).

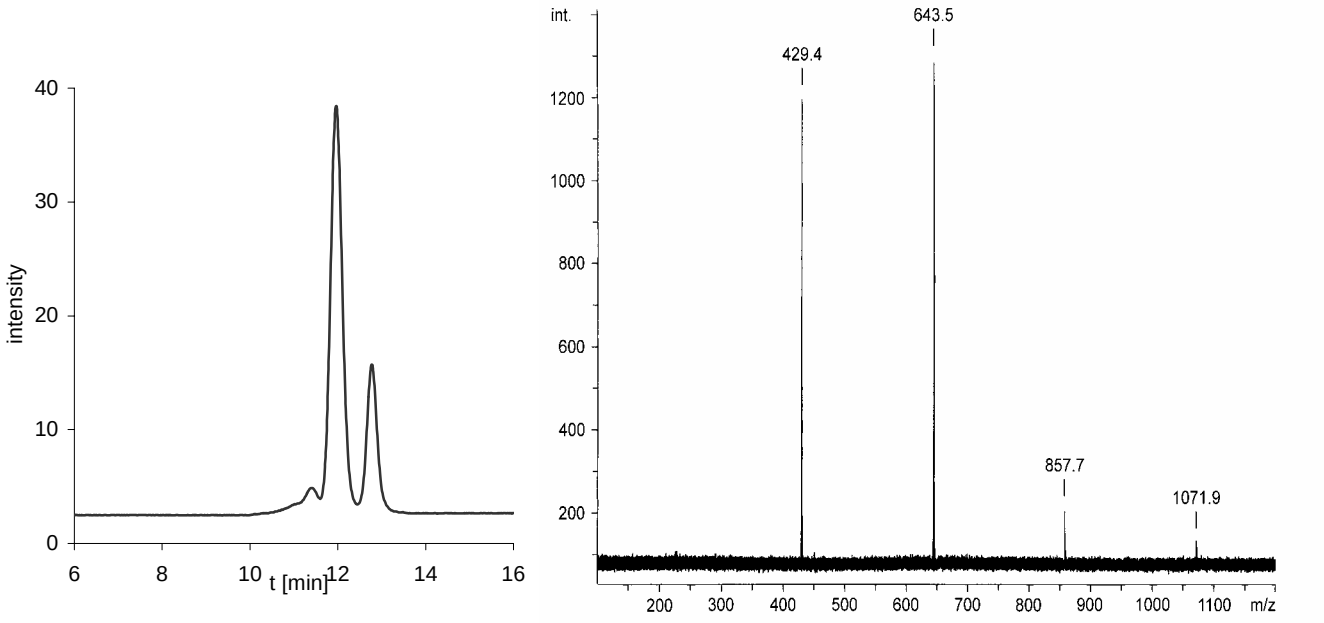


Figure 3. GPC and MALDI-Tof of the mixture (**3l**).

[2+2] and [3+3] species are no longer clearly preferred if the even more flexible precursor 1,4-diaminobutane (**2f**) is used, leading to higher cycles in larger amounts (Figure 4, **3m**).

The successful baseline detection of homologeous macrocycles by analytical GPC prompted us to look also for a preparative separation. First experiments with **3k** show that the application of prepatative GPC coloums might be successful. Elugram **1** (Figure 5) depicts the size distribution of the original mixture (**3k**) as it is obtained from preparation. Elugram **2** represents the first preparative GPC fraction containing

mainly [3+3] species with a small amount of the corresponding [2+2] cycles. The second fraction (**3**) contains predominantly [2+2] cycles.[12]

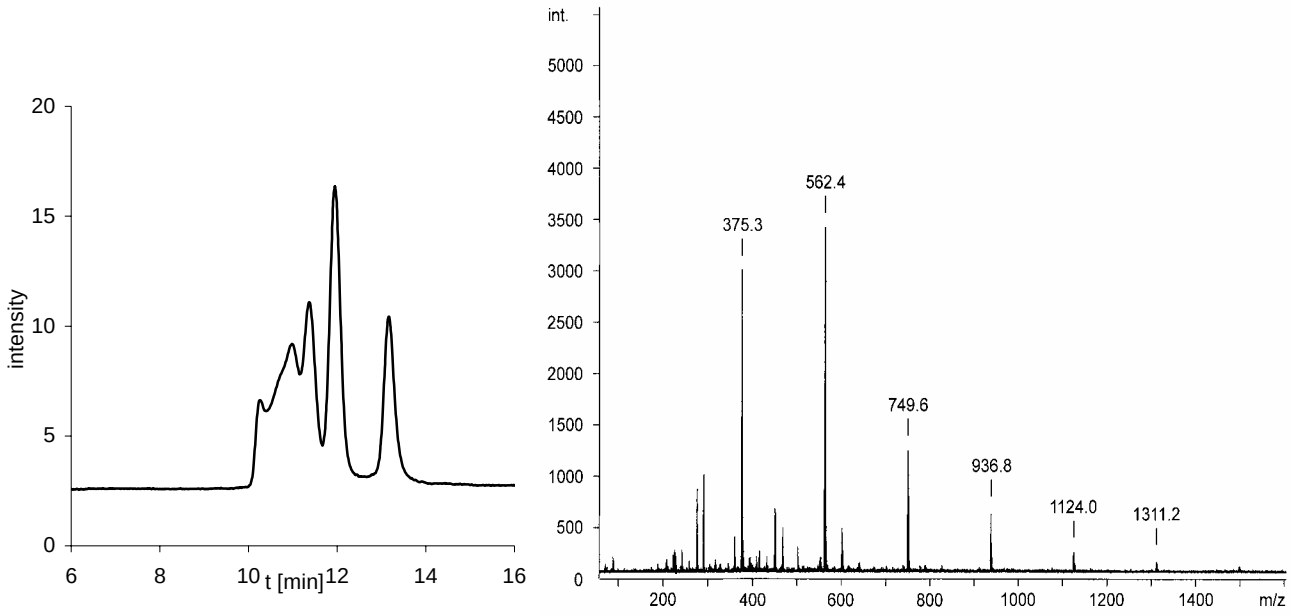


Figure 4. GPC and MALDI-Tof of the mixture (**3m**).

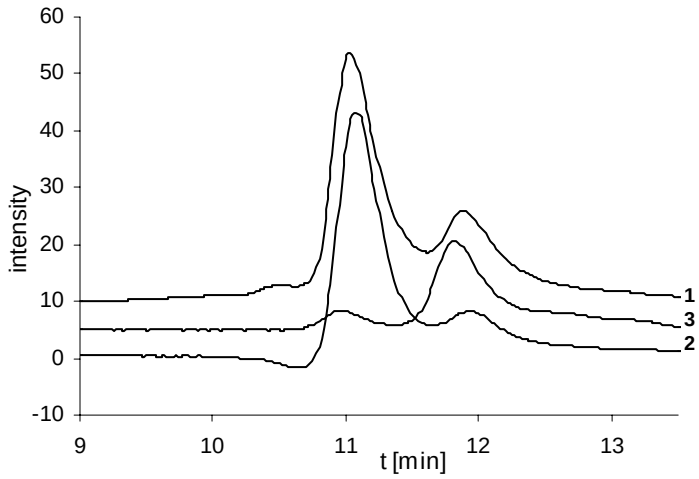


Figure 5. Preparative GPC of the mixture (**3k**) **(1:** size distribution of **3k** ; **2**: first fraction; **3**: second fraction).

STRUCTURAL INVESTIGATIONS

The relative orientation of the individual imine-cycles of **3b**, **3d** and **3e** in the solid state was investigated by single-crystal X-Ray diffraction. **3b** and **3e** were both crystallized from a concentrated acetonitrile solution at 0°C. Suitable crystals of **3d** were obtained by diffusion of diethyl ether into a chloroform solution of the cycle.

The relatively complicate ^{1}H-MNR spectrum of **3d** suggested the existence of isomers being present in solution. This can be explained by a facile intramolecular nucleophilic attack of a NH-group to one of the neighbored imine fragments (**3d**), leading to the reversible formation of 18-membered diimine imidazolidine macrocyles (**3d'**) (Figure 6).[13] This equilibrium is supported by an X-Ray structure investigation, performed on **3d'**, which crystallizes in the monoclinic space group P 2_1/c and possesses a center of inversion (Table 2).[14]

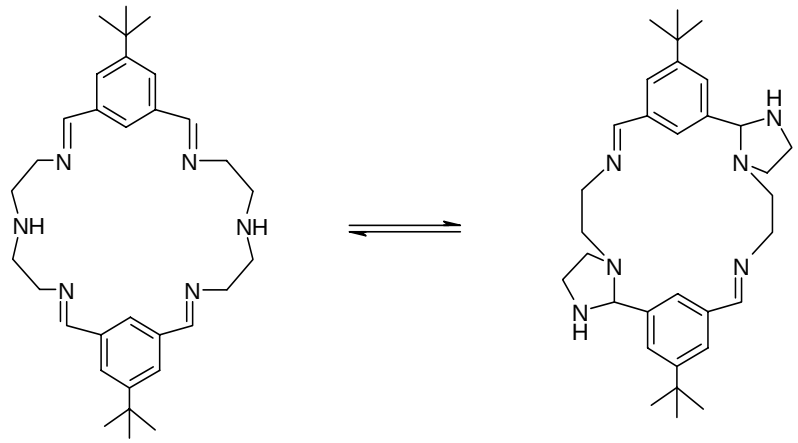


Figure 6. Isomers of **3d**.

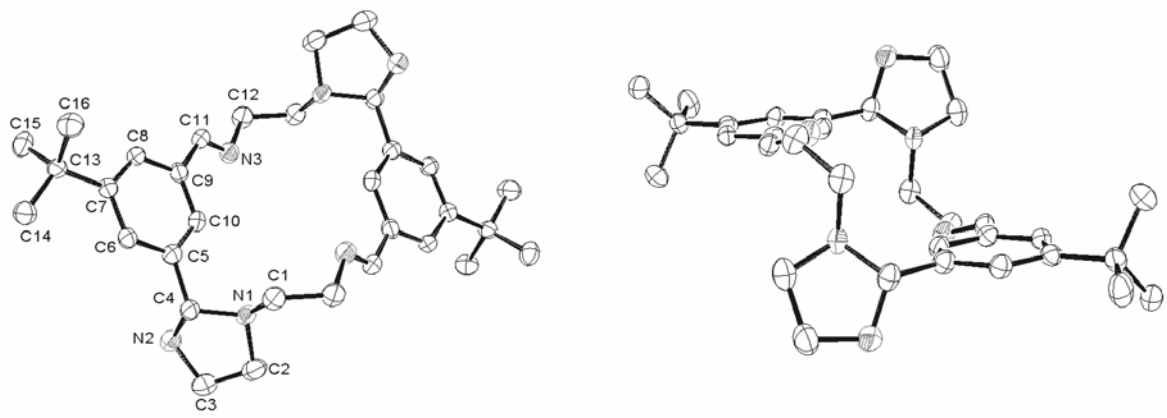


Figure 7. Top (view normal to (001)) and side view of **3d** (hydrogens are omitted for clarity).

The two aromatic units and the two imidazolidine rings were found to be coplanar relative to each other (Figure 7). The aromatic and the imidazolidine systems are in a nearly perpendicular arrangement, leading to a ring conformation that bears an inversion center.

3b and **3e** which do not contain diethylenetriamine units but result from aromatic dialdehydes and *m*-xylylenediamine building blocks, cannot enter into the above described equilibrium. Therefore, they exist exclusively in form of 24-membered cycles, each possessing again a center of inversion, with four

imine bonds and four aromatic units. In both cycles the aromatic rings of the adjacent dialdehyde building blocks and of the m-xylylene rings are coplanar (Figure 8). A major difference between **3b** and **3e** in the solid state results from the orientation of the diformylated aromatic units relative to each other, which causes in case of **3b** a "chair-like" conformation of the macrocycles. This characteristic structural feature is absent in macrocycle (**3e**), due to the collinear arrangement of the bulky *t*-Bu substituents (Figure 9).

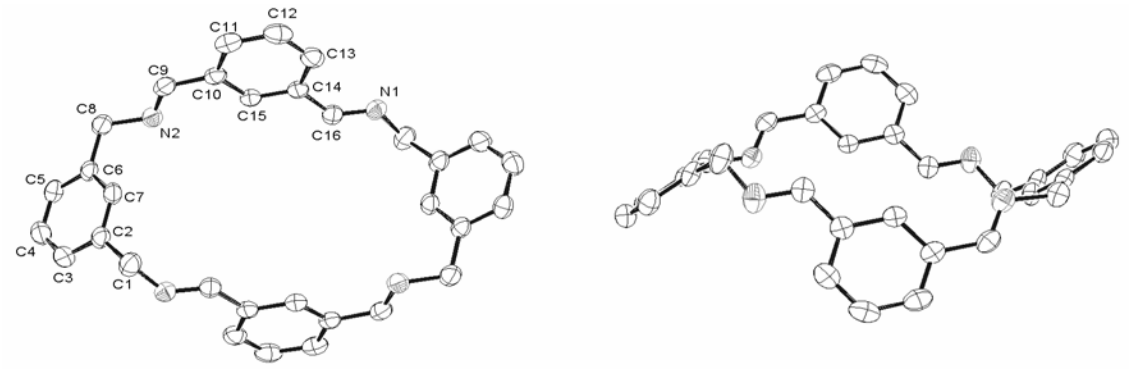


Figure 8. Top and side view of **3b** (hydrogens are omitted).

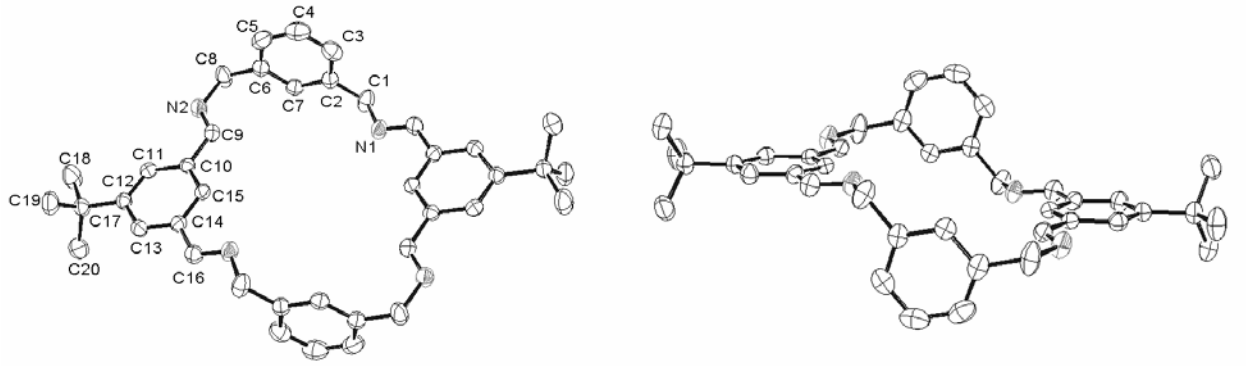


Figure 9. Top and side view of **3e** (solvent molecules and hydrogen atoms omitted).

The same *t*-Bu substituents play also a significant role in the three dimensional packing of **3b** and **3e**. **3b** forms a columnar structure with isolated stacks of superimposed, "chair-like" macrocycles (Figure 10A) of parallel column axes (10B). One explanation might be π-stacking of two adjacent aromatic rings of two consecutive chairs in one stack. This is supported by their distance (3.77 – 3.79 Å) which is similar to that in graphite (3.35 Å).

The structure of the *t*-Bu substituted cycle (**3e**) does not consist of isolated stacks but rather shows an overlap of two neighbored columns. Diamine aromatic units are grouped together in an ABA-arrangement of the individual layers, leading to an enlarged distance of the cycles within one column (Figure 11B). Figure 11A might induce the impression of channels. However, the distance of approximately 7-8 Å between separate molecules in **3e** is definitely too large for channel structures.

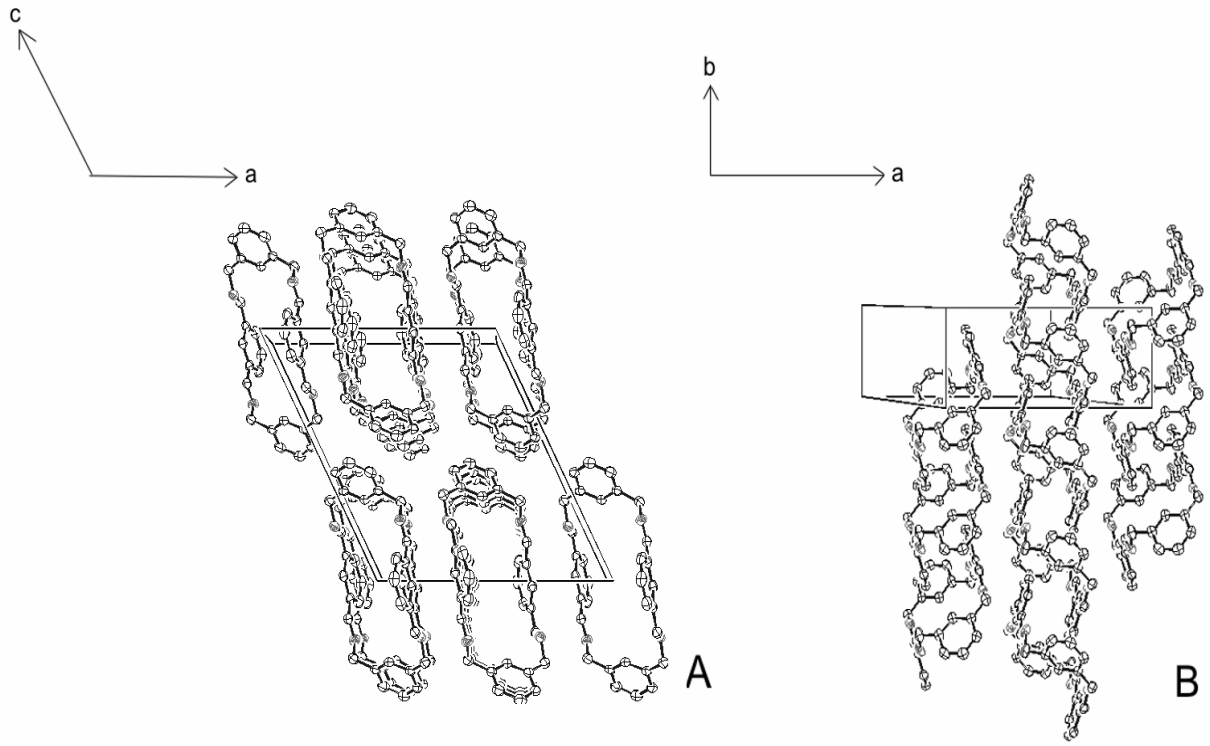


Figure 10. Arrangement of macrocycles (**3b**) in the solid state; **A**: Part of the structure along y axis; **B**: view perpendicular to bc-plane.

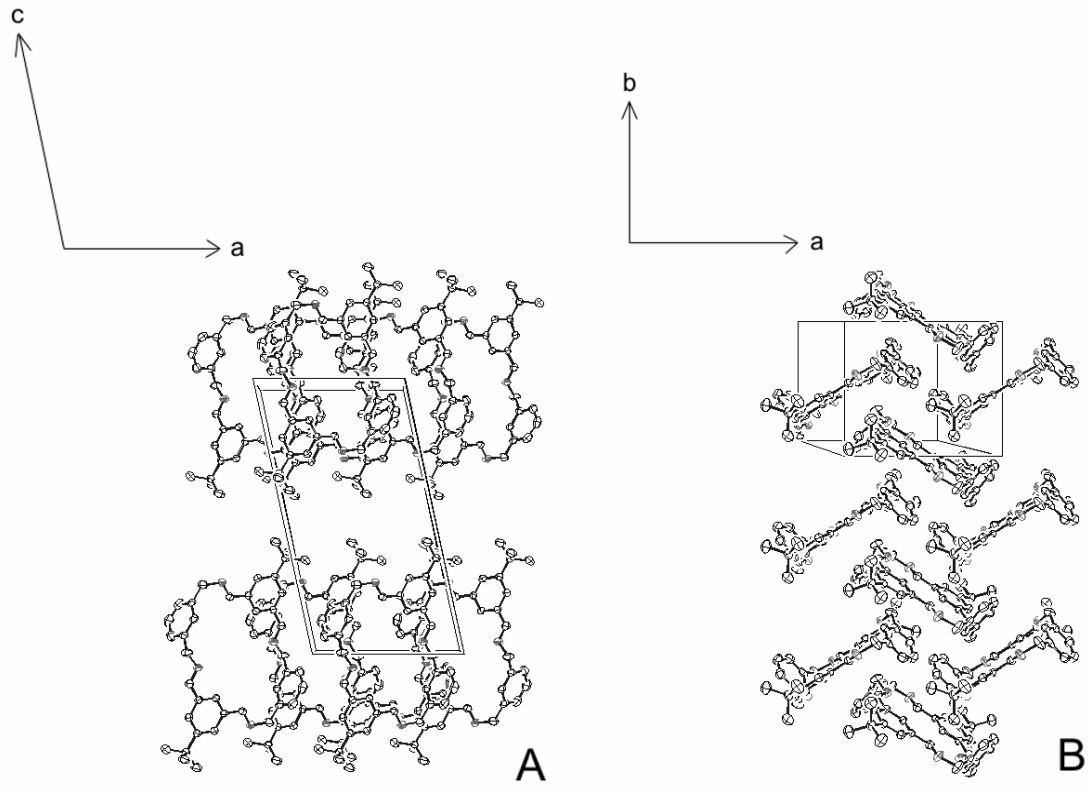


Figure 11. Arrangement of macrocycles (**3e**) in the solid state; **A**: Part of the structure along y axis; **B**: view perpendicular to bc-plane.

Table 2. Crystallographic data overview.

Compound	**3b**	**3d**	**3e**
Chemical formula	$C_{32}H_{28}N_4$	$C_{32}H_{46}N_6$	$C_{40}H_{44}N_4 \bullet (MeCN)_2$
Molecular mass [g/mol]	468.58	514.75	662.93
Crystal size [mm]	0.73 × 0.23 × 0.23	0.35 × 0.26 × 0.25	0.29 × 0.15 × 0.08
Crystal color	Colorless	colorless	colorless
Crystal system	Monoclinic	monoclinic	monoclinic
Space group	P 21/a	P 21/c	P 21/a
a [Å]	14.518(2)	12.298(3)	10.6578(16)
b [Å]	6.2592(6)	11.576(2)	9.2214(11)
c [Å]	15.560(2)	10.241(3)	20.051(3)
α [°]	90.00	90.00	90.00
β [°]	117.748(15)	94.85(2)	102.007(18)
γ [°]	90.00	90.00	90.00
V [Å ^{3}]	1251.3(3)	1452.7(6)	1927.5(5)
Z	2	2	2
D_{calcd}[g/cm^3]	1.244	1.177	1.142
T [K]	220(2)	193(2)	200(2)
Refl. Collected	9357	2768	14519
Refl. unique	2323	2609	3708
Refl. observed [I>2σ(I)]	1551	1753	2003
Variables	163	172	231
R [I>2σ(I)]	0.0314	0.0642	0.0439
R_w [I>2σ(I)]	0.0623	0.1617	0.0801
S (Gof)	1.002	1.036	0.991

CONCLUSION

The highly selective organization of diamines and dialdehydes into [2+2] macrocycles provides an easy synthetic approach to this family of molecules bearing two defined chelate binding sites for metal ions. This basic approach was extended to the formation of mixtures containing different sized [n+n] macrocycles with accordingly more binding functions. The analytical identification of the macrocycles and most importantly their preparative separation *via* GPC was successfully demonstrated. The introduction of alkyl substituents does not affect yield and ring size of the cyclic products, but widens the scope of accessible structures. Surprisingly, no linear side products could be detected. The reason for the high selectivity of the cyclization reaction, however, remains unclear. Further work will therefore be addressed to elucidate the kinetics of the cycle formation.

EXPERIMENTAL

General Remarks:

Acetonitrile for the cyclization reactions was purchased from Roth HPLC-grade (water <0.005%). Other chemicals and solvents used in the reactions were reagent grade from Aldrich and Merck and were used without further purification. Pyridinisophthalaldehyde,[15] 5-*t*-Bu-isophthalaldehyde[16] and 4,6-bisisopropyl-*m*-xylylenediamine[17] were prepared as previously described. ^{1}H-NMR and ^{13}C-NMR spectra were measured with a Bruker AMX400. IR-spectra were recorded (KBr) on a Bruker IFS 113V and IFS 66V. MS spectra (CI and FAB) were both recorded on a Finnigan SSQ 7000. MALDI-Tof spectra were performed on a Bruker Daltonics Reflex 3. Elemental analyses were determined in the Microanalytical Laboratory of the University of Ulm. Melting points were determined with a Büchi B540.

GPC investigations: The analytical separations were performed on a Waters GPC system (pump: 600, controller 600, differential refractometer: 410, 717 plus autosampler) over styragel (Waters Ultrastyragel®, HR3, HR4; eluent: chloroform, 1 ml/min; p = 400 – 420 psi). Preparative GPC: Waters GPC system (pump: 600, controller 600, refractive index Detector 2410); Waters Styragel (eluent: chloroform; 5 ml / min; p = 800 – 1000 psi). 2 – 4 mg of the macrocycle mixtures were used per run.

General synthesis of macrocyclic polyimine ligands (**3b** – **3f** and **3h**-**3m**):

In a typical reaction the aldehyde (1 mmol) in 20 mL of acetonitrile was added dropwise to a stirred solution of the amine (1 mmol) in about 30 mL of acetonitrile. The addition was done over 1-2 h at rt. After stirring the reaction mixture for 24 h the crystalline precipitates were filtered off and washed with acetonitrile in small portions. If necessary the products were recrystallized from chloroform/acetonitrile. The compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, MS spectra and elemental analysis.[18] All imine compounds were found to decompose above 240-260°C.

3b.

Yield 55%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1644 (s) – Anal. Calcd for $C_{32}H_{28}N_4$: C, 82.02; H, 6.02; N, 11.96. Found : C, 81.57; H, 6.05; N 11.90. – ^{1}H-NMR ($CDCl_3$): δ = 8.3 (m, 4H), 8.0 (m, 2H), 7.75 (m, 4H), 7.4-7.1 (m, 10H), 4.7 (m, 8H) – ^{13}C-NMR ($CDCl_3$): δ = 161.3, 139.3-126.8, 64.9. – CI-MS, FAB-MS, MH^+: 469 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 469.41.

3c.

Yield 81%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1644 (s) – Anal. Calcd for $C_{44}H_{52}N_4$: C, 82.97; H, 8.23; N, 8.80. Found : C, 82.51; H, 8.21; N, 8.76. – ^{1}H-NMR ($CDCl_3$): δ = 8.2 (m, 4H), 7.9 (m, 2H), 7.75-7.65 (m,

4H), 7.2 – 7.35 (m, 4H), 6.85-7.0 (m, 2H), 4.75 (m, 8H), 2.9-3.3 (m, 4H), 1.15-1.2 (m, 24H) – ^{13}C-NMR ($CDCl_3$): δ = 161.3, 146.0, 136.6, 133.0, 130.1, 129.8, 128.8, 128.4, 122.4, 61.3, 28.9, 23.9. – CI-MS, FAB-MS, MH^+: 637 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 637.56.

3d.

Yield 78%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1650 (s) – Anal. Calcd for $C_{32}H_{46}N_6$: C, 74.67; H, 9.01; N, 16.33. Found : C, 74.51; H, 8.98; N, 16.25. – ^{1}H-NMR ($CDCl_3$): δ = 8.1 (m, 2H), 7.85 (m, 2H), 7.45 (m, 2H), 7.35 (m, 2H), 3.15-4.0 (m, 14H), 2.25-2.4 (m, 4H), 1.85 (s, 2H), 1.2 (m, 18H) – ^{13}C-NMR ($CDCl_3$): δ = 160.8, 150.3, 140.1, 135.9, 128.2, 126.0, 120.6, 83.4, 58.4, 51.4, 51.1, 43.9, 33.6, 30.3. – CI-MS, FAB-MS, MH^+: 515 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 515.38.

3e.

Yield 75%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1645 (s) – Anal. Calcd for $C_{40}H_{44}N_4$: C, 82.72; H, 7.64; N, 9.65. Found : C, 81.35; H, 7.45; N, 9.48. – ^{1}H-NMR ($CDCl_3$): δ = 8.2-8.3 (m, 4H), 7.7-7.85 (m, 6H), 7.1-7.25 (m, 8H), 4.75 (m, 8H), 1.25 (m, 18H) – ^{13}C-NMR ($CDCl_3$): δ = 161.9, 152.1, 139.3, 136.3, 128.7-125.8, 65.1, 34.9, 31.3. – CI-MS, FAB-MS, MH^+: 581 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 581.94

3f.

Yield 88%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1645 (s) – Anal. Calcd for $C_{52}H_{68}N_4$: C, 83.37; H, 9.15; N, 7.48. Found : C, 83,61 ; H, 8.96; N, 7.64. – ^{1}H-NMR ($CDCl_3$): δ = 8.2 (m, 4H), 7.8-7.7 (m, 6H), 7.2 (m, 2H), 7.0-6.9 (m, 2H), 4.75 (m, 8H), 3.25-3.1 (m, 4H), 1.3-1.15 (m, 42H) – ^{13}C-NMR ($CDCl_3$): δ = 161.4, 151.9, 146.5, 136.5, 133.1, 131.2, 126.8, 126.2, 122.6, 62.0, 34.8, 31.3, 29.0, 24.0 – CI-MS, FAB-MS, MH^+: 749 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 750.05.

3h.

Yield 95%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1645 (s) – Anal. Calcd for $C_{30}H_{26}N_6$: C, 76.57; H, 5.57; N, 17.86. Found : C, 76.27; H, 5.79; N, 17.93. – ^{1}H-NMR ($CDCl_3$): δ = 8.5-8.45 (m, 4H), 8.05-7.95 (m, 4H), 7.75-7.7 (m, 2H), 7.35–7.25 (m, 8H), 4.9-4.85 (m, 8H) – ^{13}C-NMR ($CDCl_3$): δ = 161.5, 154.3, 138.9, 137.0, 128.8, 128.0, 127.1, 122.5, 64.8 – CI-MS, FAB-MS, MH^+: 470 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 471.64.

3i.

Yield 89%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1647 (s) – Anal. Calcd for $C_{42}H_{50}N_6$: C, 78.96; H, 7.89; N, 13.15. Found : C, 78.98; H, 7.76; N, 13.14. – ^{1}H-NMR ($CDCl_3$): δ = 8.35 (m, 2H), 8.2 (m, 2H), 7.9 (m, 4H), 7.65 – 7.5 (m, 2H), 7.2 (m, 2H), 7.0 (m, 1H), 6.7 (s, 1H), 4.8 (m, 8H), 3.4-3.1 (m, 4H), 1.2 (m, 24H) – ^{13}C-NMR ($CDCl_3$): δ = 162.5-161.8, 154.2, 146.2, 136.9, 132.9, 129.6, 122.4, 121.9, 61.9-61.2, 29.1, 23.9 – CI-MS, FAB-MS, MH^+: 639 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 639.97.

3j.

Yield 62%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1635 (s) – [2+2]: Anal. Calcd for $C_{28}H_{32}N_4$: C, 79.18; H, 7.54; N, 13.20. Found : C, 78.79; H, 6.53; N, 13.25. – ^{1}H-NMR ($CDCl_3$): δ = 8.25 (m, 4H), 8.0-7.15 (m, 8H), 3.35 (m, 4H), 2.0-1.4 (m, 16H) – ^{13}C-NMR ($CDCl_3$): δ = 161.9, 159.5, 136.3, 129.7, 128.8, 127.9, 75.4, 32.1, 24.4 – CI-MS, MH^+: 425, 637 (2+2 and 3+3 macrocycle), MALDI-Tof (dithranol): m/z = 425.3 [2+2], 637.5 [3+3].

3k.

Yield 82%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1644 (s) – [2+2]: Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.88; H, 6.32; N, 17.70. Found : C, 75.58; H, 6.48; N, 17.92.– ^{1}H-NMR ($CDCl_3$): δ = 8.4-7.3 (m, 12H), 3.95 (m, 8H) – ^{13}C-NMR ($CDCl_3$): δ = 161.9, 136.4, 129.7, 128.6, 127.9, 61.3– CI-MS, MH^+: 317, 475 (2+2 and 3+3 macrocycle), MALDI-Tof (dithranol): m/z = 317.2 [2+2], 475.4 [3+3], 633.4 [4+4], 791.5 [5+5], 949.7 [6+6], 1107.8 [7+7], 1266.9 [8+8], 1425.1 [9+9].

3l.

Yield 75%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1648 (s) – [2+2]: Anal. Calcd for $C_{28}H_{36}N_4$: C, 78.44; H, 8.40; N, 13.07. Found : C, 77.76; H, 8.42; N, 13.02.– ^{1}H-NMR ($CDCl_3$): δ = 8.4-8.0 (m, 4H), 8.0-7.4 (m, 6H), 3.95 (m, 8H), 1.3 (m, 18H) – ^{13}C-NMR ($CDCl_3$): δ = 162.5, 151.8, 136.2, 126.7, 125.8, 61.2, 34.7, 31.1 – CI-MS, MH^+: 429, 643 (2+2 and 3+3 macrocycle), MALDI-Tof (dithranol): m/z = 429.4 [2+2], 643.5 [3+3], 857.7 [4+4], 1071.9 [5+5].

3m.

Yield 58%. – FT IR (KBr, cm^{-1}): ν(C=N) = 1647 (s) – [2+2]: Anal. Calcd for $C_{22}H_{26}N_6$: C, 70.50; H, 6.94; N, 22.43. Found : C, 69.21; H, 7.16; N 21.92.– ^{1}H-NMR ($CDCl_3$): δ = 8.35 (s, 4H), 7.85 (m, 4H), 7.7 (m, 2H), 3.7 (m, 8H), 1.75 (m, 8H) – ^{13}C-NMR ($CDCl_3$): δ = 161.6, 154.1, 136.9, 122.1, 61.1, 28.3 –

MALDI-Tof (dithranol): m/z = 375.3 [2+2], 562.4 [3+3], 749.6 [4+4], 936.8 [5+5], 1124.0 [6+6], 1311.2 [7+7].

General synthesis for the reduction of the imine- to amine-macrocycles (**4a-b**):
Typically the imine-macrocycles (1 mmol) were suspended in 50 mL of methanol and $NaBH_4$ (10-15 mmol) was added in portions. After stirring for several hours at rt, a clear solution was obtained, which was evaporated to dryness. The white solid was dissolved in a mixture of dichloromethan/water (2:1) and the organic layer was separated and dried with Na_2SO_4. After removing the solvent, the product was recrystallized from ether.
The compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, MS spectra and elemental analysis. **4a** and **4b** were found to decompose above 240°C.

4a.
Yield 89%. – Anal. Calcd for $C_{30}H_{34}N_6$: C, 75.28; H, 7.16; N, 17.56. Found : C, 75.57; H, 7.05; N, 17.36. – ^{1}H-NMR ($CDCl_3$): δ = 7.45 (t, *J* = 7.6 Hz, 2H), 7.2 (m, 2H), 7.15 (m, 6H), 7.05 (s, 2H), 7.0 (s, 2H), 3.8 (s, 8H), 3.7 (s, 8H), 2.2 (s, 4H) – ^{13}C-NMR ($CDCl_3$): δ = 158.9, 140.2, 136.5, 128.2, 127.9, 126.9, 120.5, 54.4, 53.6 – CI-MS, FAB-MS, MH^+: 479 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 479.87.

4b.
Yield 92%. – Anal. Calcd for $C_{42}H_{58}N_6$: C, 77.97; H, 9.04; N, 12.99. Found : C, 78.23; H, 9.01; N, 12.76. – ^{1}H-NMR ($CDCl_3$): δ = 7.5 (t, *J* = 7.6 Hz, 2H), 7.1 (m, 8H), 3.85 (s, 8H), 3.75 (s, 8H), 3.2 (sept, *J* = 6.8 Hz, 4H), 2.0 (s, 4H), 1.15 (d, *J* = 6.8 Hz, 24H) – ^{13}C-NMR ($CDCl_3$): δ = 159.4, 146.0, 136.5, 133.9, 129.8, 122.0, 120.5, 55.1, 50.7, 28.5, 24.1 – CI-MS, FAB-MS, MH^+: 647 (2+2 macrocycle), MALDI-Tof (dithranol): m/z = 647.65.

X-Ray Crystallographic Study
Crystals of **3b** and **3e** were mounted on glass fibers. X-Ray data were collected on a STOE IPDS instrument using graphite monochromatized Mo Kα radiation, λ = 0.71073 Å. Crystal data are listed in Table 2 together with refinement details. Absorption corrections were not applied. The structures were solved by direct methods.[19] The atomic coordinates and anisotropic thermal parameters of the non-hydrogen atoms were refined using F^2 data.[20] Hydrogen atoms were included in the final refinement cycles in a riding mode.

The crystal data of macrocycles (**3d**) were collected on a Rigaku AFC7S four-circle diffractometer using graphite monochromatized Mo-Kα radiation, λ=0.71073Å. Intensities were corrected for Lorentz and polarization effect.[21] Direct methods were used in solving the structures. A full-matrix least squares refinement on F^2 was performed for all reflections using the *SHELX-97* program system.[20] All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were refined on calculated positions (riding model). Figures with the labelling scheme: *ORTEP3*.[22]

Crystal data of **3b, 3d** and **3e**, details about data collection, analysis and refinement were listed in Table 2.

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-199398, CCDC-197707 , CCDC-199399 for **3b, 3d** and **3e** respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223) 336-033; E-mail: deposit@ccdc.cam.ac.uk].

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