ARTICLE

OBC
www.rsc.org/obc

New 2+2, 3+3 and 4+4 macrocycles derived from 1,2-diaminocyclohexane and 2,6-diformylpyridine†

Janusz Gregoliński, Jerzy Lisowski* and Tadeusz Lis

Department of Chemistry, University of Wrocław, 14 F. Joliot-Curie, 50-383, Wrocław, Poland. E-mail: jurek@chem.uni.wroc.pl; Fax: 48 71 3282348; Tel: 48 71 3757 252

Received 27th April 2005, Accepted 23rd June 2005
First published as an Advance Article on the web 15th July 2005

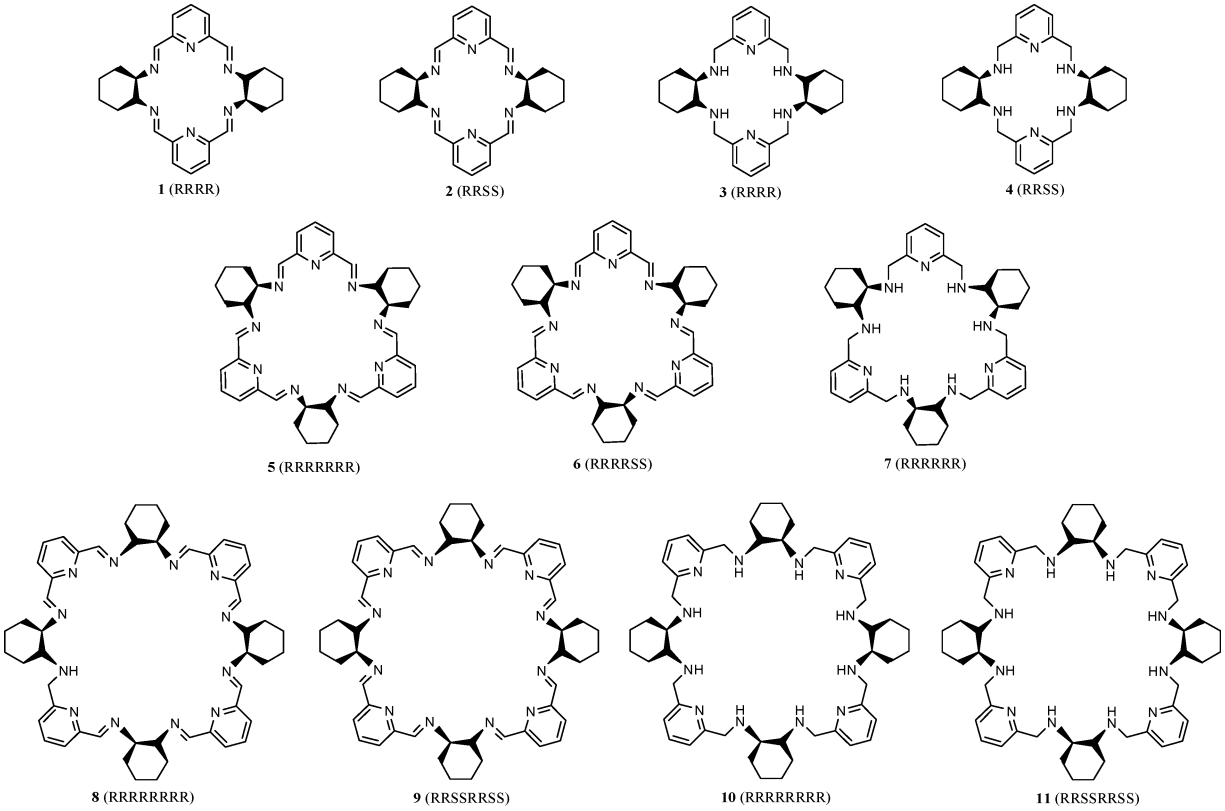
Two new Schiff base macrocycles – a 4+4 condensation product and a meso-type 2+2 condensation product – were obtained in a reaction of *trans*-1,2-diaminocyclohexane and 2,6-diformylpyridine. Reduction of these compounds led to the corresponding 4+4 and 2+2 macrocyclic amines. The macrocycles were characterised by NMR spectroscopy and electrospray mass spectrometry. The symmetry and stereochemistry of these macrocycles, as well as of new 3+3 and 4+4 diastereomers identified in solution, has been established. X-Ray structures of the 2+2 and 4+4 Schiff base macrocycles confirm the configurations determined on the basis of spectroscopic investigations. The crystal structures reveal that the centres of the square-shaped 4+4 macrocycles form channels as a result of columnar stacking.

Introduction

Condensation of dialdehydes with diamines leads to macrocyclic compounds that are interesting molecular hosts and ligands for metal ion complexation. In particular, templated condensation of both enantiopure and racemic *trans*-1,2-diaminocyclohexane results in interesting chiral lanthanide complexes of 2+2 macrocycle **1** (Scheme 1), that can be obtained both in enantiopure form[1–5] and as racemates,[4,6–8] respectively. The enantiopure Tb(III) and Eu(III) complexes of **1** have been shown to exhibit circularly polarised luminescence,[1] and the paramagnetic Eu(III) and Yb(III) complexes have been shown to form diastereoisomeric complexes with D- and L-aminoacids.[2] The dimeric lanthanide(III) complexes of **1** are rare examples of an artificial catalyst for the hydrolytic cleavage of DNA.[7]

In contrast, in the absence of a metal ion template, condensation of enantiopure (1*R*,2*R*)-1,2-diaminocyclohexane with 2,6-diformylpyridine leads to enantiopure 3+3 macrocycle **5**[9] (Scheme 1). Compound **5** is a member of a family of chiral, enantiopure 3+3 macrocycles derived from aromatic dialdehydes and 1,2-diaminocyclohexane[10–12] that have been studied in the context of enantioselective catalysis.[13] Another example of this family of 3+3 macrocycles is the derivative of 2,6-diformylphenol,[14,15] which in its reduced amine form is able to bind simultaneously three transition metal ions. 2,6-Diformylphenols and diamines can also form very rare

† Electronic supplementary information (ESI) available: ESI MS of the macrocyclic amines **4** and **11**, and crystal structure data for **2** and **9**. See http://dx.doi.org/10.1039/b505909g



Scheme 1

DOI: 10.1039/b505909g

4+4 macrocycles, which can be obtained in a one-step metal templated condensation[16,17] or in a step-wise synthesis from acyclic precursors.[18] In some cases the 4+4 macrocycles are also observed as components of the mixtures of Schiff bases obtained from direct condensation of diamines and dialdehydes.[13a,19]

In general, the condensation of aromatic dialdehydes with diamines leads to a dynamic library of macrocyclic and acyclic products[19,20] and the composition of these libraries can be influenced by the selection of an appropriate template. In this report we illustrate the flexibility of the system based on *trans*-1,2-diaminocyclohexane and 2,6-diformylpyridine in the formation of Schiff base macrocycles, and discuss the effect of chirality of the diamine on the type of the preferred condensation product. We present the synthesis and characterisation of four new macrocycles: the Schiff base meso-type 2+2 macrocycle **2** and the 4+4 macrocycle **9**, and their reduced forms, amine macrocycles **4** and **11**, respectively (Scheme 1). We also document the formation in solution of a new 3+3 macrocycle **6** and the 4+4 macrocycles **8** and **10**.

Results and discussion

Synthesis and solution study of new macrocycles

Reaction of racemic *trans*-1,2-diaminocyclohexane with 2,6-diformylpyridine in methanol leads to formation of a product that has previously been reported to be ligand **1**.[6] Although the spectroscopic characterisation of the reaction product has not been reported previously due to poor solubility of the material obtained, our ^{1}H NMR study shows that a mixture of products is actually obtained. When the reaction is run for 24 h, the isolated precipitate consists of two components in the molar ratio 6 : 1, and this ratio remains practically constant for reaction times up to 72 h. Electrospray ionisation mass spectrometry of the product shows two signals at *m*/*z* 449.2 and 875.5, corresponding to the 2+2 macrocyclic condensation product [Na·**2**$^+$] and 4+4 macrocyclic condensation product [Na·**9**]$^+$, respectively. Careful separation of this mixture under mild conditions allows the isolation of both macrocycles in pure form, as confirmed by their ESI MS and NMR spectra. The pure macrocycle **2** was obtained by fractional recrystallisation of the mixture from chloroform. Isolation of **9** was based on the different affinity of the two macrocycles towards lanthanide(III) ions. Compound **2** easily coordinates these ions and can be removed as complex soluble in methanol, while **9** remains uncoordinated and can be separated by filtration.

The NMR signals were assigned on the basis of analysis of COSY and HMQC spectra. Both macrocycles **2** and **9** exhibit eight ^{1}H NMR signals and seven ^{13}C NMR signals, in accord with the presence of macrocycles of high symmetry containing a cyclohexyl ring, an azomethine group and a pyridine fragment. However, the chemical shifts of **2** and **9** are clearly different (Fig. 1), indicating substantial differences in macrocyle conformation leading to differences in ring current effects.

The stability of both macrocycles is limited. Thus solutions of **2** kept for several days exhibit molecular peaks of **9** and 3+3 macrocycles in their ESI MS spectra. Similarly the 4+4 macrocycle **9** on standing in solution for several days rearranges partially to macrocyle **2** and 3+3 macrocycles. This behaviour is in accord with the reversible cleavage of the imine bond and rearrangement of the respective fragments into other products, including **2** and **9**. As solids, the macrocycles **2** and **9** are thermodynamic condensation products, which can be separated from the reaction mixture due to their low solubility. In solution, however, they exist in equilibrium with other Schiff bases. At room temperature this equilibrium is practically frozen, hence separation of the two components by fractional recrystallisation is possible. However, long storage or heating of the **2** or **9** in solution results in restoration of the dynamic equilibrium, and rearrangement of the pyridine and cyclohexyl fragments takes place.

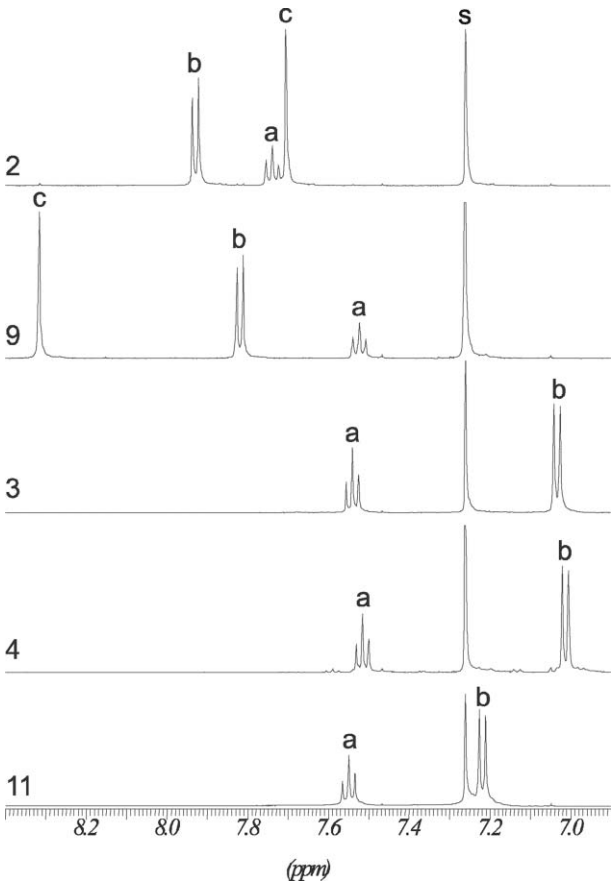


Fig. 1 Sections of ^{1}H NMR spectra (298 K, $CDCl_3$) of macrocycles **2**, **9**, **3**, **4** and **11**. a, b and c denote the signals of the γ-pyridine, β-pyridine and azomethine protons, respectively; s denotes the residual solvent signal.

Both macrocycles can be reduced by sodium borohydride to the corresponding amines. The formation of 2+2 macrocycle **4** and 4+4 macrocycle **11** is confirmed by ESI MS spectra (see ESI†) that show peaks of ionised forms H**4**$^+$, and [Na·**4**]$^+$ at *m*/*z* 435.3, and 457.3, respectively, as well as H**11**$^+$, at *m*/*z* 869.4. ^{1}H NMR spectra of both compounds indicate the formation of diastereotopic methylene bridges in place of azomethine bridges, and confirm successful amine formation. As for the pair of macrocycles **2** and **9**, the NMR spectra of **4** and **11** are distinctly different (Fig. 1). However, the ^{1}H NMR spectrum of **4** is very similar to the spectrum of the authentic sample of **3** obtained from enantiopure (1*R*,2*R*)-1,2-diaminocyclohexane.[21] In fact, the chemical shifts of these two compounds are so close (Fig. 1), that it was necessary to record the spectrum of their mixture to unequivocally confirm that **3** and **4** are not identical, and that **4** is not the racemic mixture of **3**. At this point the question of the structure of **4** arises. Compounds **4** and **3** have the same molecular weight, as indicated by their ESI MS, so they have to be isomers. The only isomer of **3** that would exhibit one set of pyridine, one set of diastereotopic methylene, and one set of diastereotopic cyclohexyl ring signals is the meso-type macrocycle **4**, with one cyclohexyl fragment in the *RR* configuration and the other in the *SS* configuration (Scheme 1). This macrocycle should have real or effective C_{2h} symmetry that results in simple ^{1}H and ^{13}C NMR spectra. Since the structures of **3** and **4** are very similar, their NMR spectra are almost identical.

The above assignment of the structure of **4** implies that the Schiff base macrocycle **2** from which it is obtained is also a meso-type macrocycle of *RRSS* configuration at the respective carbon atoms. Since we do not have an authentic sample of **1** (*vide infra*) we could not directly compare the two compounds. Fortunately it was possible to compare the enantiopure lanthanide(III) complexes of **1**[2] to the complexed forms of **2** obtained in solution from free ligand and lanthanide(III) nitrate. In the case

of diamagnetic lanthanum(III) complexes, the two derivatives give rise to almost identical NMR spectra, *e.g.* the signals of the azomethine protons appear at 8.63 ppm and 8.58 ppm for $[La\cdot\mathbf{2}]^{3+}$ and $[La\cdot\mathbf{1}]^{3+}$ complexes, respectively. This observation indicates that the two complexes have a very similar structure, as in the case of the pair of free macrocycles **3** and **4**. Some of the lanthanide(III) ions give rise to favourable spreading of NMR signals without severe broadening of lines.[22] It has been shown that the NMR spectra of macrocyclic lanthanide(III) complexes are very sensitive to any modification of the complex.[2,5,23] We took advantage of this property in comparing europium(III) complexes of **1** and **2**. In this case a clear difference is observed between the ^{1}H NMR spectra of complexes of the two macrocycles, *e.g.* the azomethine signal of the europium(III) complex of **1** appears[2] at −19.99 ppm, while that of europium(III) complex of **2** appears at −18.38 ppm. In this way it can be unequivocally confirmed that the macrocyclic Schiff base **2** is not the racemic form of **1**.

The exact stereochemistry of the previously obtained[6] macrocylic product of the condensation of racemic *trans*-1,2-diaminocyclohexane with 2,6-diformylpyridine has not been discussed in detail. However, the X-ray crystal structures of the racemic complexes,[24] obtained after reduction of this Schiff base macrocycle to amine form, show the presence of chiral macrocycle **3**, which implies that the condensation product contained the racemic form of **1**. On the other hand, the analogous 2+2 condensation product derived from 2,6-diacetylpyridine has been shown to be a meso-type macrocyle with an *RRSS* configuration.[6] It should be noted, however, that the above-described synthesis of **1** used a shorter reaction time (3 h) than the synthesis of **2** described in this work. Although we were unable to obtain pure macrocycle **1** neither in racemic nor in enantiopure form, this macrocycle is apparently formed in racemic form as a component of a mixture, that, after reduction, was separated by column chromatography.[24] To further clarify the issue of formation of **1** in non-templated condensation, we have undertaken more detailed studies of condensation of both racemic and enantiopure *trans*-1,2-diaminocyclohexane with 2,6-diformylpyridine using varying reaction times, solvents and temperatures. While under specific reaction conditions pure macrocycles, such as **5**, can be precipitated as solids and separated, the ESI MS and NMR spectra of crude reaction mixtures show that in every case mixtures of products were formed. In particular, the ESI MS analysis of products of the condensation of enantiopure (1*R*,2*R*)-diaminocyclohexane shows that not only **5** but also **1** and a small amount of the 4+4 macrocycle **8**, which all have to be in the *R* configuration, are formed. Similarly, the ESI MS spectra of crude mixtures of condensation products of racemic *trans*-1,2-diaminocyclohexane indicate formation of a 3+3 macrocycle, in addition to **2** and **9**. The ^{1}H NMR spectra do not confirm that this 3+3 macrocycle is **5**. Thus, the diastereomer of **5**, *i.e.* the racemic *RRRRSS* and *SSSSRR* 3+3 macrocycle **6**, must be formed. A similar *RRRRSS* diastereomer was observed for the 3+3 Schiff base macrocycle derived from *trans*-1,2-diaminocyclohexane and terephthalaldehyde.[11] An additional difficulty in the characterisation of the above-discussed mixtures of products by NMR spectroscopy arises from the basic character of the obtained macrocycles and the tendency to form protonated forms, which further complicate the spectra.

Both for the Schiff base and amine macrocycles there are four possible diasteromers corresponding to 4+4 macrocycles. Only two of them, the D_4-symmetric diastereomer of *RRRRRRRR* configuration and the D_{2d}-symmetric diastereomer of *RRSS-RRSS* configuration (presented as **10** and **11** in Scheme 1, respectively) are symmetric enough to give rise to simple ^{1}H NMR spectra consisting of nine signals of the amine form. The above symmetries refer to the "flat" conformations depicted in Scheme 1. Since considerable bending can be expected for 4+4 macrocycles, these symmetries would be more like those achieved in solution by averaging of the macrocycle conformation. It was not possible to identify NMR signals of the above-mentioned Schiff base 4+4 macrocycle **8** of *RRRRRRRR* configuration, as it was present as a minor component of the complicated mixture. Fortunately the ^{1}H NMR signals of reduced macrocycles are better separated, and differentiation between two high-symmetry diastereomers of 4+4 macrocycles was possible. When the crude reaction mixture obtained by condensation of enantiopure (1*R*,2*R*)-1,2-diaminocyclohexane and 2,6-diformylpyridine is reduced by $NaBH_4$, the ^{1}H NMR spectrum (Fig. 2) of the reduction products shows no trace of **11** (this was also checked by adding an authentic sample of **11** to the mixture). However, the mixture contained **10**, as shown by ESI MS. In the NMR spectra (Fig. 2), the triplet at 7.59 ppm and doublet at 7.20 ppm can be tentatively assigned to the pyridine signals of **10**. It follows that the obtained 4+4 amine is not **10**, and both synthesised macrocycles **9** and **11** correspond to the *RRSSRRSS* configuration.

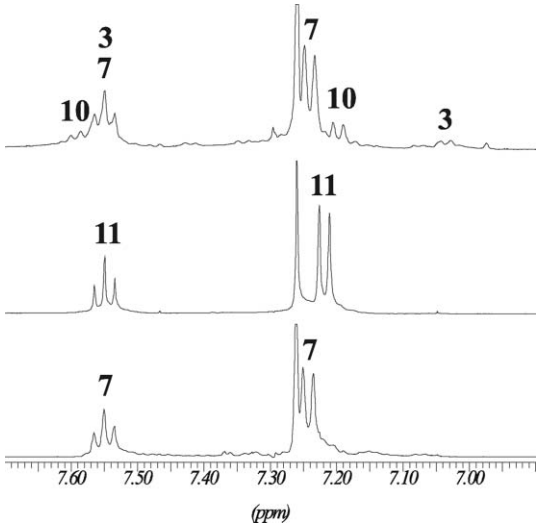


Fig. 2 ^{1}H NMR spectra (pyridine region, 298 K, $CDCl_3$) of macrocycle **7** (bottom), **11** (middle) and the mixture of macrocycles (top) obtained from enantiopure (1*R*,2*R*)-1,2-diaminocyclohexane (see text for details).

X-Ray crystal structures of macrocycles 2 and 9

The single crystals of **2** and **9** were obtained by slow evaporation of toluene solutions. In both cases the crystallisation process was long enough to observe the above-discussed partial rearrangement of diamine and dialdehyde building blocks. This process resulted in growth of a mixture of crystals of **2** and **9** from both solutions of pure parent compounds. Nevertheless, the identity and purity of both compounds was established on the basis of spectroscopic methods, as described in the previous section. In this situation the obtained X-ray crystal structures constitute firm, additional confirmation of the stereochemistry of **2** and **9**.

The macrocycle **2** adopts a stepped conformation (Fig. 3), similar to that of the analogous macrocycle derived from 2,6-diacetylpyridine[6] or 2+2 tetraiminodiphenol Robson-type macrocycles.[25] As expected, the two cyclohexyl rings are of opposite chirality and the structure is of C_{2h} symmetry, in accord with the symmetry observed in solution. The two pyridine rings are parallel and the distance between the planes of these pyridine rings is 5.369(2) Å. The main difference between the structure of **2** and the structure of the 2,6-diacetylpyridine derivative is the smaller distance between pyridine planes for **2**.

The X-Ray crystal structure of **9** is to the best of our knowledge the first structure of a 4+4 Schiff base macrocycle. It confirms the presence of two cyclohexane rings of *RR* chirality on opposite sides of the macrocycle and a similar pair of rings of *SS* chirality. The conformation of this square-shaped macrocycle

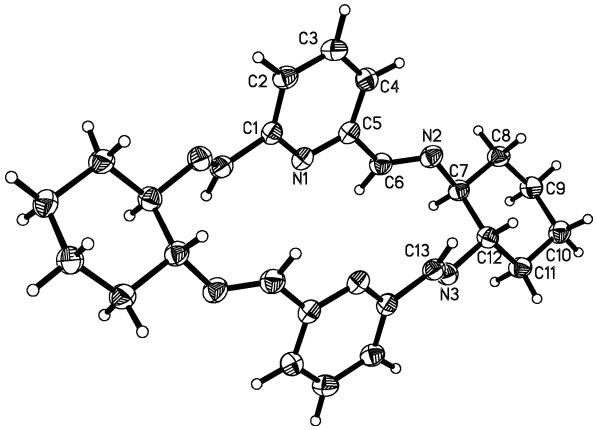


Fig. 3 View of the macrocycle **2**.

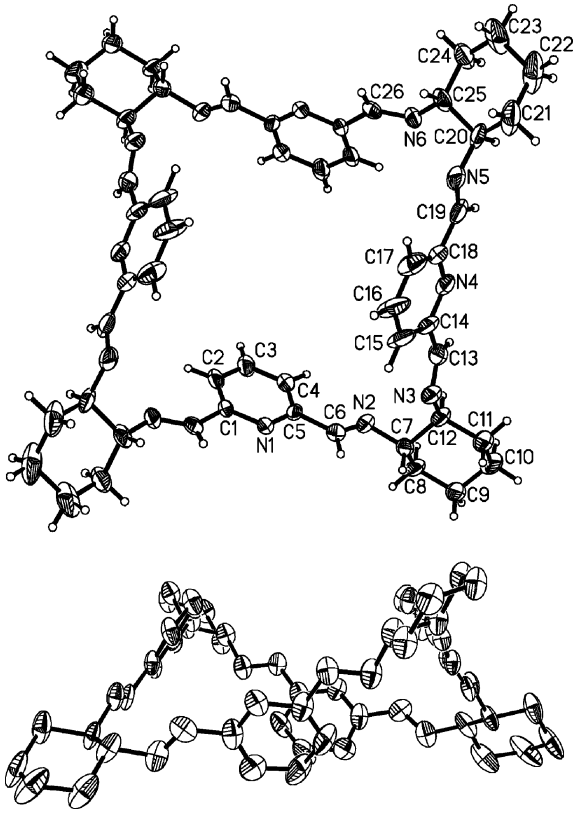


Fig. 4 Top and side view of macrocycle **9**.

can be described as 'twisted saddle' (Fig. 4). The macrocycle is significantly folded along the opposite cyclohexane fragments. The nitrogen atoms of the two opposite pyridine rings point to one side of the mean macrocycle plane, and the nitrogen atoms of the other two rings point to opposite side of the plane. The spatial arrangement of the nitrogen atoms does not predispose them for the simultaneous coordination of the metal ions. This can explain the very different affinity of **2** and **9** towards lanthanide(III) ions. Because of the folding and twisting of the macrocycle, the C_2 rotational axes and symmetry planes expected for the "flat" structure presented in Scheme 1 are missing. The molecule is of approximate S_4 symmetry, which should give rise to fifteen ^{1}H NMR signals. The observation of eight signals indicates conformational averaging of **9** in solution resulting in effective D_{2d} symmetry.

The macrocyclic units of **9** form pillars, which leads to formation of a channel-like structure (Fig. 5). For this reason this compound may be regarded as an organic zeolite. A similar type of structure is formed by 3+3 Schiff base macrocycles derived from *trans*-1,2-diaminocyclohexane and aromatic dialdehydes.[11]

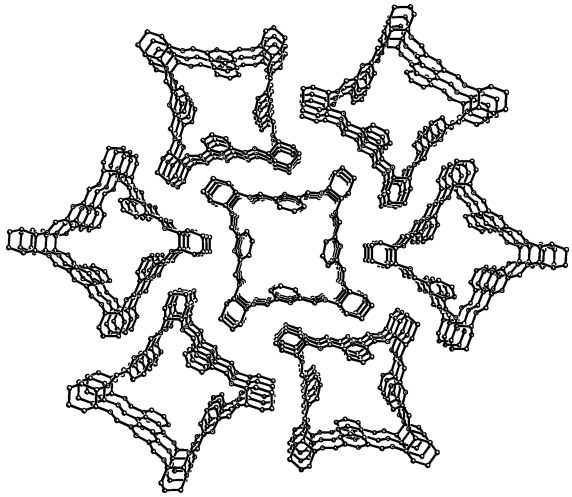


Fig. 5 Packing diagram of the macrocycle **9**, viewed along the *c* axis.

The larger size of the 4+4 macrocycle **9** corresponds to a larger channel diameter than for the 3+3 macrocycles.

Conclusions

The spectroscopic and X-ray results show that two new types of products – meso 2+2 and 4+4 macrocycles – are formed by condensation of *trans*-1,2-diaminocyclohexane with 2,6-diformylarenes. The preferred product of condensation of 2,6-diformylpyridine in this reaction depends on the chirality of the diamine and the presence of a metal substrate. Thus, the meso-type 2+2 macrocycle **2** and the 4+4 macrocycle **9** are preferred products of condensation of racemic *trans*-1,2-diaminocyclohexane, and the chiral 3+3 macrocycle **5** is the preferred product of condensation of enantiopure *trans*-1,2-diaminocyclohexane. The main driving force for the formation of **2** and **9** is probably their lower solubility than other possible condensation products. In the presence of lanthanide ions, the condensation reaction is directed towards the chiral 2+2 macrocycle **1** for both racemic and enantiopure *trans*-1,2-diaminocyclohexane. This macrocycle is apparently best suited for binding of metal ions, and can adjust itself to the geometric requirements of the lanthanide ion more effectively than macrocycle **2**. The all-*R* configuration predisposes ligand **1** to a 'helical twist' conformation; in this conformation the dimensions of the macrocyclic core are reduced to match the size of lanthanide ion.

Experimental

General

Deuterated chloroform (Isotec) was purified by passing through short column filled with basic alumina (Merck). The NMR spectra were taken on Bruker Avance 500 and AMX 300 spectrometers. Chemical shifts are referenced to the residual solvent signal or TMS. The COSY and HMQC spectra were acquired using 256 × 1K data points and zero-filled to a 1K × 1K matrix. Low resolution electrospray mass spectra were obtained using a Finnigan TSQ-700 instrument equipped with an EST ion source, and high resolution ESI MS using an LCT (ESI-ToF) Micromass instrument. The elemental analyses were carried out on a Perkin–Elmer 2400 CHN elemental analyzer.

Synthesis

Macrocycles 3, 5, and 7. These have been obtained by a modified procedure described previously.[9,21]

Macrocyles 2 and 9. A solution of (±)-*trans*-1,2-diaminocyclohexane (1.941 g, 17 mmol) in 5 cm^3 of methanol

was combined with a solution of 2,6-diformylpyridine (2.297 g, 17 mmol) in 165 cm^3 of methanol, and the mixture refluxed for 48 h. The white precipitate of the mixture of macrocycles was filtered, washed with methanol and dried under vacuum, to give a combined yield of 3.523 g (97.2%). This product was purified by fractional recrystallisation from 300 cm^3 of chloroform to give pure **2** as a white powder (2.02 g, total yield 55.71%) as the less soluble product, and fractions obtained from the filtrate enriched in macrocycle **9**. 1.413 g of the enriched fraction containing 1.474 mmol of **2** and 0.919 mmol of **9** (based on NMR analysis) was refluxed for 1 h with $Sm(NO_3)_3 \cdot 6H_2O$ (0.655 g, 1.474 mmol) in 250 cm^3 of methanol. The suspension was filtered, washed with methanol and dried under vacuum to give pure **9** as a white powder (623 mg, total yield 17.17%).

2: Mp >370 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 7.71 (4H, s, N=C*H*), 7.93 (4H, d, β-pyridine), 7.74 (2H, t, γ-pyridine), 3.22 (4H, m, NC*H*), 1.96 (4H, m, NCHCH_{axial}), 2.13 (4H, d, NCHC$H_{equatorial}$), 1.50 (4H, m, NCHCH$_2$CH_{axial}), 1.91 (4H, d, NCHCH$_2$C$H_{equatorial}$); ^{13}C NMR ($CDCl_3$) δ 163.36 (α-pyridine), 154.38 (azomethine), 136.58 (β-pyridine), 121.60 (γ-pyridine), 70.88 (cyclohexyl), 30.05 (cyclohexyl), 24.11 (cyclohexyl); (Found: C, 73.43; H, 7.03; N, 19.48. $C_{26}H_{30}N_6$ requires C, 73.12; H, 7.09; N, 19.70%); *m*/*z* (ESI) 449.2430 ($C_{26}H_{30}N_6Na^+$ requires 449.2447).

9: Mp >340 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 8.32 (8H, s, N=C*H*), 7.82 (8H, d, β-pyridine), 7.52 (4H, t, γ-pyridine), 3.51 (8H, m, NC*H*), 1.73 (8H, br, NCHCH_{axial}), 1.73 (8H, br, NCHC$H_{equatorial}$), 1.49 (8H, m, NCHCH$_2$CH_{axial}), 1.85 (8H, d, NCHCH$_2$C$H_{equatorial}$); ^{13}C NMR δ 160.94 (α-pyridine), 154.15 (azomethine), 121.60 (β-pyridine), 136.80 (γ-pyridine), 70.92 (cyclohexyl), 32.86 (cyclohexyl), 24.35 (cyclohexyl); (Found: C, 70.32; H, 7.17; N, 18.84. $C_{52}H_{60}N_{12} \cdot 2H_2O$ requires C, 70.24; H, 7.26; N, 18.90%); *m*/*z* (ESI) 875.4962 ($C_{52}H_{60}N_{12}Na^+$ requires 875.4926).

Macrocycle 4. Solid $NaBH_4$ (1.440 g, 38.1 mmol) was added gradually over 4 h to a vigorously stirred suspension of **2** (1.349 g, 3.16 mmol) in 360 cm^3 of methanol–toluene (1 : 1 v/v). The obtained clear mixture was evaporated to dryness, the residue dissolved in 80 cm^3 of water, NaOH added until pH = 13 and the mixture extracted 3 times with 20 cm^3 of dichloromethane. The organic fractions were dried over Na_2SO_4, filtered and evaporated to dryness, to give the crude product (1.332 g, 96.91%). The amine was purified by dissolving in 28 cm^3 of methanol, adding 48% HBr until pH = 2 and filtering the resulting precipitate. The obtained bromide salt was dissolved in 150 cm^3 of 5% aq. NaOH solution. Repeated extraction with dichloromethane gave pure **4** as a white powder (1.068 g, 77.7%). Mp 218 °C; ^{1}H NMR ($CDCl_3$) δ 7.01 (4H, d, β-pyridine), 7.52 (2H, t, γ-pyridine), 3.99 (4H, d, pyridine–CH_2), 3.76 (4H, d, pyridine–CH_2), 2.22 (4H, s, NC*H*), 1.04 (4H, m, NCHCCH_{axial}), 2.15 (4H, d, NCHCC$H_{equatorial}$), 1.19 (4H, m, NCHCH$_2$CH_{axial}), 1.71 (4H, d, NCHCH$_2$C$H_{equatorial}$),^{13}C NMR δ 159.55 (α-pyridine), 136.13 (β-pyridine), 120.63 (γ-pyridine), 59.55 (cyclohexyl), 51.03 (*C*H$_2$N), 30.60 (cyclohexyl), 25.00 (cyclohexyl); (Found: C, 71.57; H, 8.58; N, 19.10. $C_{26}H_{38}N_6$ requires C, 71.85; H, 8.81; N, 19.34%); *m*/*z* (ESI) 435.3236 ($C_{26}H_{39}N_6^+$ requires 435.3216).

Macrocyle 11. Solid $NaBH_4$ (221 mg, 5.84 mmol) was added gradually over 3 h to a vigorously stirred suspension of **9** (208 mg, 0.24 mmol) in 120 cm^3 of methanol–toluene (1 : 1 v/v). The obtained mixture was evaporated to dryness and the residue dissolved in 100 cm^3 of 5% aq. NaOH solution. The mixture was extracted 3 times with 20 cm^3 of dichloromethane. The organic fractions were dried over Na_2SO_4, filtered and evaporated to dryness to give crude **11** as a yellow–green oil. This oil was dissolved in 3 cm^3 of methanol and combined with a solution of $(COOH)_2 \cdot 2H_2O$ (121 mg, 0.96 mmol) in 0.5 cm^3 of methanol. The resulting precipitate (294.3 mg) was filtered, dried and redissolved in 10 cm^3 of water. NaOH was added until pH = 13 and the solution was extracted three times with 5 cm^3 of dichloromethane. The organic fractions were dried over Na_2SO_4, filtered and evaporated to dryness to yield **11** as a glassy solid (182 mg, 87.25%). Mp 82 °C; ^{1}H NMR ($CDCl_3$) δ 7.22 (8H, d, β-pyridine), 7.55 (4H, t, γ-pyridine), 3.99 (8H, d, pyridine–CH_2), 3.78 (8H, d, pyridine–CH_2), 2.28 (8H, s, NC*H*), 1.04 (8H, m, NCHCH_{axial}), 2.07 (8H, d, NCHC$H_{equatorial}$), 1.17 (8H, m, NCHCH$_2$CH_{axial}), 1.68 (8H, d, NCHCH$_2$C$H_{equatorial}$); ^{13}C NMR δ 159.80 (α-pyridine), 136.76 (β-pyridine), 120.24 (γ-pyridine), 61.25 (cyclohexyl), 52.25 (*C*H$_2$N), 31.52 (cyclohexyl), 24.94 (cyclohexyl); (Found: C, 64.55; H, 8.02; N, 16.80. $C_{52}H_{76}N_{12} \cdot 1.5CH_2Cl_2$ requires C, 64.47; H, 7.99; N, 16.87%); *m*/*z* (ESI) 869.6394 ($C_{52}H_{77}N_{12}^+$ requires 869.6400).

The progress of the condensation reaction in solution was followed in various solvents. In a typical experiment, 5 mmol of (1*R*,2*R*)-1,2-diaminocyclohexane was refluxed with 5 mmol of 2,6-diformylpyridine in 250 cm^3 methanol. Small aliquots of homogenous solution were removed from reaction mixture and analysed by ^{1}H NMR and ESI MS. For the analogous reaction of racemic 1,2-diaminocyclohexane (13 mmol of each substrate in 130 cm^3 of methanol), small amounts of the resulting suspension were removed, filtered and the solid analyzed.

X-Ray crystal structure determination of macrocycles 2 and 9

X-Ray data were collected at 100(2) K on a Xcalibur PX, (Oxford Diffraction) using Cu–Kα radiation (λ = 1.5418 Å) for **9** and Mo–Kα radiation (λ = 0.71073 Å) for **2**. Data collection was made with a CCD, and computation of cell refinements with a CrysAlis RED program, version 1.171.

Structures were solved by direct methods using the SHELXS[26] program, and refined by a full-matrix least-squares technique using SHELXL-97.[27] All H atoms were included by geometry and not refined. The non-hydrogen atoms were refined with anisotropic thermal parameters. Only the relative and non-absolute configurations of chiral carbon atoms were determined. The Fourier difference map of **9** shows additional electron density corresponding to partial occupation of channels formed by the macrocycle units by an unknown chemical individual. Despite the efforts to refine the positions of this entity, it was not possible to unequivocally establish its identity. Its contribution was thus subtracted from the diffraction pattern by the "Squeeze" method.[28] This unknown guest molecule, most proably the toluene molecule partially occupying the macrocycle cavity, was not included in the molecular formula. All figures (packing diagrams, molecular structures) were made using XP.[29]

Crystal data for 2. $C_{26}H_{30}N_6$, M = 426.56, monoclinic, a = 6.936(2), b = 16.389(3), c = 9.833(3) Å, β = 92.78(3)°, V = 1116.4(5) Å^3, T = 100(2) K, space group $P2_1/c$, Z = 2, μ(Mo–K$_\alpha$) = 0.078 mm^{-1}, 26717 reflections measured, 6048 unique data points (R_{int} = 0.0426), 205 parameters, R_1 = 0.1100. The final $wR(F^2)$ was 0.1656 (all data). CCDC reference number 270351. See ESI for crystallographic data in CIF or other electronic format.†

Crystal data for 9. $C_{52}H_{60}N_{12}$, M = 853.13, orthorhombic, a = 15.577(4), b = 30.563(9), c = 5.460(3) Å, V = 2599.4(18) Å^3, T = 100(2) K, space group $P2_12_12$, Z = 2, μ(Cu–Kα) = 0.53 mm^{-1}, 6668 reflections measured, 4441 unique data points (R_{int} = 0.0833), 290 parameters, R_1 = 0.1073. The final $wR(F^2)$ was 0.1753 (all data). CCDC reference number 270352. See ESI for crystallographic data in CIF or other electronic format.†

Acknowledgements

This work was supported by KBN grant 3 T09A 11519.

References

1 T. Tsubomura, K. Yasaku, T. Sato and M. Morita, *Inorg. Chem.*, 1992, **31**, 447.
2 J. Lisowski, *Magn. Reson. Chem.*, 1999, **37**, 287.
3 J. Lisowski and P. Starynowicz, *Polyhedron*, 2000, **19**, 465.
4 J. Lisowski and J. Mazurek, *Polyhedron*, 2002, **21**, 811.
5 J. Lisowski, S. Ripoli and L. Di Bari, *Inorg. Chem.*, 2004, **43**, 1388.
6 S. W. A. Bligh, N. Choi, W. J. Cummins, E. G. Evagorou, J. D. Kelly and M. McPartlin, *J. Chem. Soc., Dalton Trans.*, 1994, 3369.
7 S. W. A. Bligh, N. Choi, E. G. Evagorou, M. McPartlin and K. N. White, *J. Chem. Soc., Dalton Trans.*, 2001, 3169.
8 J. Lisowski and P. Starynowicz, *Inorg. Chem. Commun.*, 2003, **6**, 593.
9 N. Kuhnert, G. M. Rossignolo and A. Lopez-Periago, *Org. Biomol. Chem.*, 2003, **1**, 1157.
10 J. Gawroński, H. Kołbun, M. Kwit and A. Kartusiak, *J. Org. Chem.*, 2000, **65**, 5768.
11 M. Chadim, M. Budesinsky, J. Hodacova, J. Zawada and P. C. Junk, *Tetrahedron: Asymmetry*, 2001, **12**, 127.
12 (*a*) N. Kuhnert, A. Lopez-Periago and G. M. Rossignolo, *Org. Biomol. Chem.*, 2005, **3**, 524; (*b*) N. Kuhnert, N. Burzlaff, C. Patel and A. Lopez-Periago, *Org. Biomol. Chem.*, 2005, **3**, 1911.
13 (*a*) J. Gao and A. E. Martell, *Org. Biomol. Chem.*, 2003, **1**, 2795; (*b*) J. Gao and A. E. Martell, *Org. Biomol. Chem.*, 2003, **1**, 2801.
14 (*a*) S. R. Korupoju and P. S. Zacharias, *Chem. Commun.*, 1998, 1267; (*b*) S. R. Korupoju, N. Mangayarkarasi, P. S. Zacharias, J. Mizuthani and H. Nishihara, *Inorg. Chem.*, 2002, **41**, 4099.
15 M. Kwit and J. Gawroński, *Tetrahedron: Asymmetry*, 2003, **14**, 127.
16 (*a*) I. J. Hewitt, J.-K. Tang, N. T. Madhu, B. Pilawa, C. E. Anson, S. Brooker and A. K. Powell, *Dalton Trans.*, 2005, 429; (*b*) S. Mohanta, K. K. Nanda, R. Werner, W. Haase, A. Mukherjee, S. K. Dutta and K. Nag, *Inorg. Chem.*, 1997, **36**, 4656; (*c*) K. K. Nanda, K. Venkatsubramanian, D. Majumdar and K. Nag, *Inorg. Chem.*, 1994, **33**, 1581.
17 Y. Sun, Q. Zeng, S. Gou, W. Huang, C. Duan and J. Yao, *J. Inclusion Phenom. Macrocyclic Chem.*, 2002, **42**, 131.
18 (*a*) M. Yonemura, H. Okawa, M. Ohba, D. E. Fenton and L. K. Thompson, *Chem. Commun.*, 2000, 817; (*b*) Y. Nakamura, M. Yonemura, K. Arimura, N. Usuki, M. Ohba and H. Okawa, *Inorg. Chem.*, 2001, **40**, 3739.
19 H. Shimakoshi, T. Kai, I. Aritome and Y. Hisaeda, *Tetrahedron Lett.*, 2002, **43**, 8261.
20 O. Storm and U. Lüning, *Chem. Eur. J.*, 2002, **8**, 793.
21 P. M. Fitzsimmons and S. C. Jackels, *Inorg. Chim. Acta*, 1996, **246**, 301.
22 I. Bertini and C. Luchinat, *Coord. Chem. Rev.*, 1996, **150**, 1.
23 J. Lisowski, J. L. Sessler, V. Lynch and T. D. Mody, *J. Am. Chem. Soc.*, 1995, **117**, 2273.
24 S. W. A. Bligh, N. Choi, E. G. Evagorou, W.-S. Li and M. McPartlin, *J. Chem. Soc., Chem. Commun.*, 1994, 2399.
25 B. Dutta, P. Bag, B. Adhikary, U. Florke and K. Nag, *J. Org. Chem.*, 2004, **69**, 5419.
26 G. M. Sheldrick, *SHELXS-97, Program for solution of crystal structures*, University of Göttingen, Germany, 1997.
27 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.
28 (*a*) P. Van der Sluis and A. L. Spek, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 1990, **46**, 194; (*b*) A. L. Spek, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 1990, **46**, C34.
29 *XP – Interactive Molecular Graphics, Version 4.3 for MSDOS*, Siemens Analytical X-ray Inst. Inc., 1992.