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Macrocyclic *cis*- and *trans*-bis(α-amino acids) and their intraannular Cu(II) complexes. Conformational *in–out* dichotomy and crystal packing

Martin Bělohradský,[a] Miloš Buděšínský,[a] Ivana Císařová,[b] Václav Dekoj,[a] Petr Holý[a,*] and Jiří Závada[a,*]

[a]*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic*
[b]*Department of Inorganic Chemistry, Charles University, 128 40 Prague, Czech Republic*

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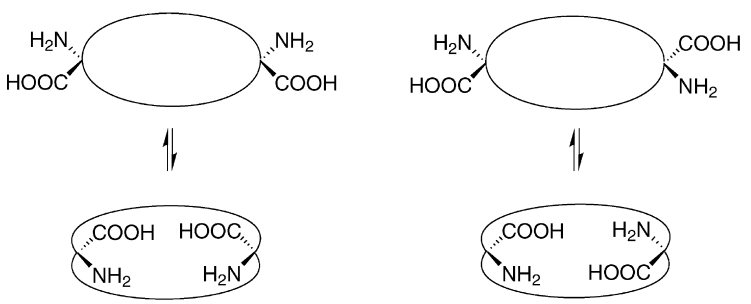
Abstract—Macrocyclic bis(α-amino acids) *cis*- and *trans*-**2a**-**b** were prepared from the selectively protected tris(hydroxymethyl)aminomethane **3**. The X-ray structures of the free bis(amino acids) and/or of the corresponding Cu(II) complexes have been determined allowing an unambiguous configurational assessment. At the same time, conformational *in–out* dichotomy of the functional groups has been demonstrated in the bis(amino acids) as well as in their Cu(II) complexes.

1. Introduction

Recently, we have designed[1] new α-amino acids **1** which combine the chelating capacity of the key functional groups with the coordinating potential of macrocyclic polyethers (crowns). The distinguishing feature of these novel compounds is 'crowning' of glycine, at the α-carbon, with a methylene-oligo(oxyethylene)-oxymethylene chain. Now we report the corresponding macrocyclic bis(α-amino acids) **2**, which arise in the form of *cis*- and *trans*-isomers. The unique feature of both the *cis*- and *trans*-bis(α-amino acids) is a conformational dichotomy allowing either *in*- or *out*-arrangement of the functional groups relative to the macroring cavity (Scheme 1).

One of the problems central to the design of host compounds is that of the placement of substituents in positions that converge on the functional or binding sites of guest molecules. Understanding *in–out* conformational equilibria in macrocyclic compounds represents thus a challenging task.

In the past decades, a systematic investigation of macro*bi*cyclic diamines[2–5] with bridgehead nitrogens has established occurrence of such equilibria involving *in*- vs *out*-arrangement of the lone electron pairs at the nitrogens. For more bulky functional groups, viability of the convergent *in*-arrangement has been amply demonstrated in conformationally biased macro*poly*cyclic systems, such as



Scheme 1. Schematic representation of the conformational *in–out* equilibria of bis(amino acids) *cis*- and *trans*-**2a**-**b**.

Keywords: crown ethers; amino acids and derivatives; X-ray crystal structures.
* Corresponding author. Fax: +420-2-3333-1733; e-mail: zavada@uochb.cas.cz

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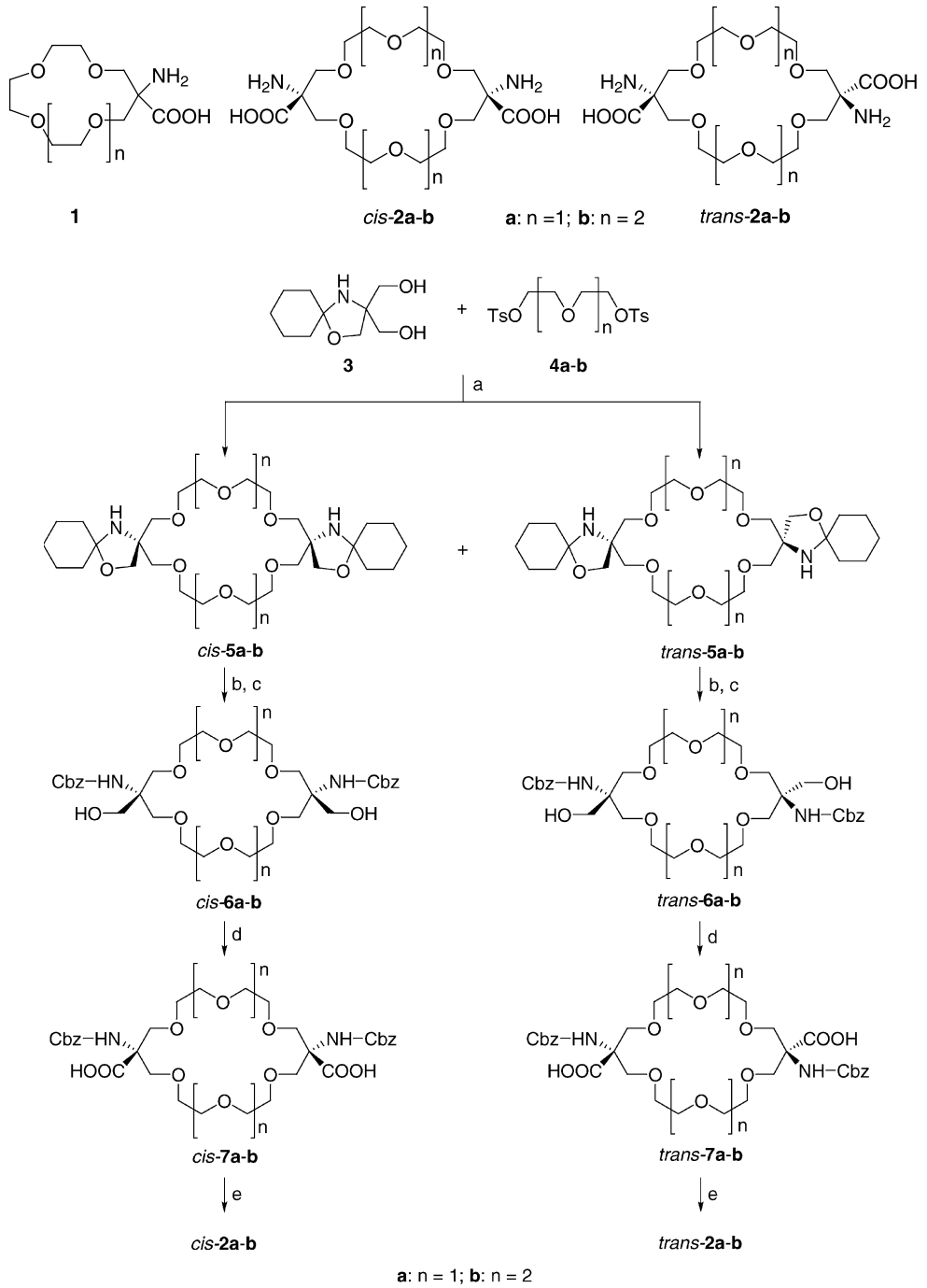

Scheme 2. *Reagents and conditions*: (a) KOH, dioxane, 80°C; (b) 3M HCl, 55°C; (c) CbzCl, $NaHCO_3$, H_2O/dioxane 1:1, 0°C; (d) TEMPO, NaClO, $NaHCO_3$, CH_3CN/H_2O 1:1; (e) 10% Pd/C, H_2, CH_3OH.

spherands[6,7] or calixarenes.[8] In a contrast, however, only sparse, and mostly indirect evidence is available in this respect concerning simple, conformationally unbiased, macro*mono*cyclic compounds.[9–12] For macrocyclic amino acids, no pertinent data have been reported as yet.

2. Results and discussion

2.1. Synthesis

The selectively protected tris(hydroxymethyl)aminomethane **3** has been employed as the cornerstone in the common synthesis of the macrocyclic mono(amino acids)[1] **1** and bis(amino acids) *cis*- and *trans*-**2a-b**. Treatment of **3** with an appropriate oligo(ethylene glycol) ditosylate **4a-b** under conditions of Williamson synthesis afforded mixture of macrocyclic mono- and bis(oxazolidines), from which the latter **5a-b** were chromatographically separated in the form of a *cis–trans* isomeric blend. Acidic hydrolysis of the bis(oxazolidines) followed by selective benzyloxycarbonyl-(*N*-Cbz) reprotection of the intermediary bis(amino alcohols) gave the bis(carbamates) *cis*- and *trans*-**6a-b**. Subsequent catalytic oxidation with the TEMPO-NaClO

tandem[1] led to the corresponding *N*-Cbz-protected bis (amino acids) *cis*- and *trans*-**7a**-**b**, and on hydrogenolytic deprotection of these yielded the target free bis(amino acids) *cis*- and *trans*-**2a**-**b** (Scheme 2).

The accompanying problem of *cis*–*trans* isomer separation was examined systematically along the outlined reaction scheme. Chromatographic separation of bis(oxazolidines) *cis*- and *trans*-**5a**-**b** and similarly also of the corresponding *N*-Cbz-protected bis(amino alcohols) *cis*- and *trans*-**6a**-**b** was successful only in the case of the lower homologues, **5a** and **6a**, respectively. In contrast, chromatography of the *N*-Cbz-protected bis(amino acids) **7a**-**b** allowed an efficient separation of both the homologous pairs *cis*- and *trans*-**7a** as well as *cis*- and *trans*-**7b**.

The corresponding Cu(II) complexes were prepared from the deprotected isomerically uniform bis(amino acids) *cis*-**2a**, *trans*-**2a**, *cis*-**2b** and *trans*-**2b** by treatment with basic Cu(II)carbonate. Recovery of the individual free bis(amino acids) from the metal complexes could be attained on treatment with hydrogen sulfide.

2.2. X-Ray diffraction analysis

Single-crystal diffraction analysis has been employed as the key instrument for a simultaneous determination of configuration, conformation and crystal packing of the investigated free bis(amino acids) as well as of their Cu(II) complexes.

2.2.1. Molecular structure of the free bis(amino acids) *cis*- and *trans*-2a. Both *cis*- and *trans*-isomers of the bis(amino acid) **2a** afforded crystals of X-ray quality. Their molecular structure is depicted in Figure 1a and b, respectively. The macroring geometry is unexceptional in both the geometric isomers, as it concerns bond angles and bond lengths. The electron pairs at the ethereal oxygen atoms converge partly into the macroring cavity. Both carboxyl groups are deprotonated and ammonium groups protonated giving rise to zwitterionic pairs in the *cis*- as well as *trans*-isomer. The arrangement of the functional groups in the two isomers is however entirely different.

In the *cis*-**2a** isomer, both the two ammonium as well as the two carboxylate groups protrude *outwards* the macroring, minimizing the coulombic repulsion between the identically charged *cis*-substituents across the ring (Fig. 1a).

In the *trans*-**2a** isomer, in a contrast, both the two ammonium as well as the two carboxylate groups are oriented *inwards* the macroring cavity. In this way, the oppositely charged functional groups approach each other closely across the macroring, being supported by the coulombic attraction and the transannular $NH_3^+\cdots{}^-OOC$ hydrogen bonds (Fig. 1b).

2.2.2. Molecular structures of the corresponding Cu(II) complexes. Molecular structures of the Cu(II) complexes arising from the bis(amino acids) *cis*- and *trans*-**2a** are depicted in Figure 2a and b, respectively. The macroring geometry of both the metal complexes is again unexceptional from the standpoint of bond lengths and angles, and allows the ethereal electron pairs to converge partly into the central cavity. Both carboxyl groups are deprotonated, but in contrast to the corresponding free amino acids, the complementary amino groups are not protonated in either of the two investigated metal complexes.

In the Cu(II) complex arising from the *cis*-**2a** isomer (Fig. 2a), both the two amino as well as the two carboxy-groups are inclined *inwards* the macroring cavity allowing intraannular *cis*-square chelation of the central Cu(II) ion. Additional contacts of two macroring oxygens (O7 and O17) augment the square tetra-coordination into square bipyramid hexa-coordination.

In the Cu(II) complex arising from the corresponding *trans*-**2a** isomer (Fig. 2b), on the other hand, both amino as well as both carboxylate groups are turned *outwards* the macroring, disallowing the intraannular chelation of the metal ion. Intermolecular chelation accordingly enters the stage. Amino and carboxylate groups from two neighboring molecules participate in an extraannular, *cis*-square tetra-coordination of the metal ion, which is further expanded into the bipyramidal hexacoordination by contacts with two proximate macroring oxygens. As an overall outcome, a

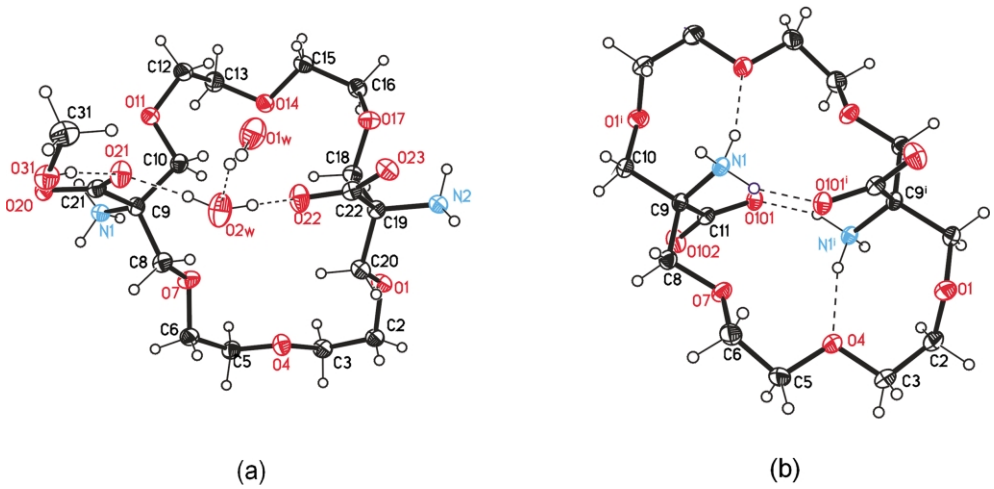

Figure 1. ORTEP drawings of the molecular structure of bis(amino acids) *cis*-**2a**·CH_3OH·$2H_2O$ (a) and *trans*-**2a** (b) with atom numbering (ellipsoids: 50% probability). For *trans*-**2a**, the second part of molecule is generated by center of symmetry. Hydrogen bonds are drawn as dashed lines.

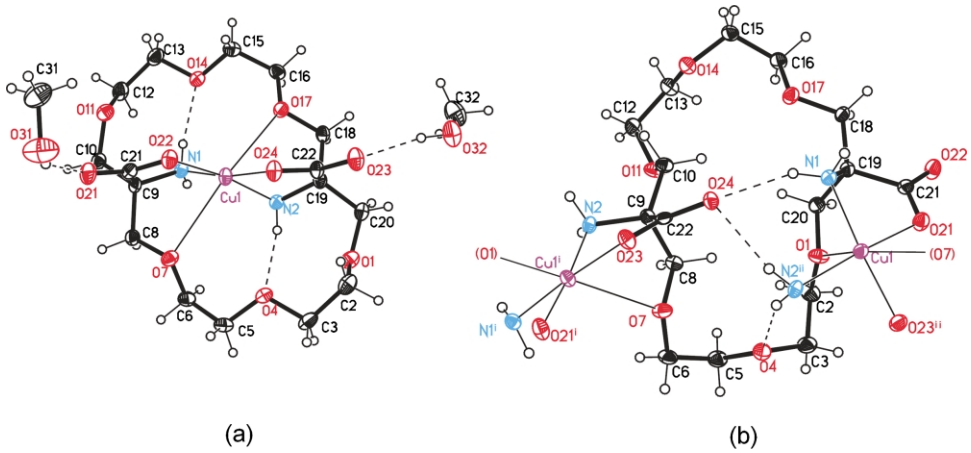

Figure 2. ORTEP drawings of the molecular structure of complexes Cu(II)/*cis*-**2a**·2CH_3OH (a) and Cu(II)/*trans*-**2a** (b) (a part of an infinite chain) with atom numbering (ellipsoids: 50% probability). Polymeric structure in (b) is formed by Cu(II)-coordination and follows symmetry of two-fold screw axis along *c*. Hydrogen bonds are drawn as dashed lines.

polymeric complex is produced from *trans*-**2a** isomer, in a contrast to the monomeric metal complex species arising from *cis*-**2a**.

2.2.3. Effect of configuration upon *in–out* dichotomy in the free amino acids and in the corresponding Cu(II) complexes. From the above inspection of the individual molecular structures presented in Figures 1a and b and 2a and b, it follows that configuration plays a key role in the *in–out* conformational equilibrium of the investigated macrocyclic bis(amino acids) as well as of their Cu(II) complexes. In the case of the free amino acids, the *cis*-isomer prefers the *out*-conformation whereas *trans*-isomer prefers the *in*-arrangement. In the case of the corresponding Cu(II) complexes, on the other hand, the Cu(II)/*cis*-**2a** complex rests on the *in*-conformation, whereas the Cu(II)/*trans*-**2a** complex exploits the *out*-arrangement. Thus, an exactly opposite relationship exists between *cis–trans* configuration and *in–out* conformation in the free amino acids and in the respective Cu(II) complexes.

As we have already suggested, electrostatic interactions between the charged functional groups across the macroring explain well the observed relationship in the free bis(amino acids). In the corresponding Cu(II) complexes, electrostatic interactions are however insignificant and the operation of some other effect must be accordingly considered.

Model examination suggests that steric strain accompanying the intraannular chelation of the metal ion may be the responsible factor. According to the models, the strain is smaller in the intraannular Cu(II) complex arising from the *cis*-**2a** isomer than in the intraannular (hypothetical) complex corresponding to the other isomer. Upon macroring enlargement, such discriminating steric effect is expected to disappear.

2.2.4. Effect of macroring size. In order to probe the role which macroring size may play in the *in–out* conformational equilibrium, we have extended our crystallographic study to the Cu(II) complexes arising from the homologous pair of the bis(amino acids) *cis*- and *trans*-**2b**. Inspection of the molecular structures (Fig. 3a and b, respectively) shows that both the isomeric bis(amino acids) give rise to intraannular complexes, in a contrast to the lower homologues. In this way, the proposed role of steric strain in the *in–out* conformational equilibrium has been supported.

2.2.5. Effect of solvent inclusion on crystal structure and color in the investigated Cu(II) complexes. Blue and violet crystals arise side by side on crystallization of both Cu(II)/*cis*-**2b** as well as Cu(II)/*trans*-**2b** complexes from protic solutions. According to the X-ray diffraction analysis, the two types of crystals differ each from the other by solvent inclusion.

The structure of the violet crystals arising from the Cu(II)/*cis*-**2b** as well as Cu(II)/*trans*-**2b** complexes, which are solvent-free, has been already disclosed (Fig. 3a and b, respectively). The corresponding structure of the accompanying blue, solvated, crystals are in Figure 4a and b, respectively. As a comparison of the corresponding violet and blue crystals shows, all the main structure features, including the coordination of the metal ion and the arrangement of the chelating groups are essentially unaffected by the solvent inclusion either in *cis*- or in *trans*-isomeric complexes.

No unambiguous explanation can be given concerning the observed effect of solvent inclusion upon the violet-blue crystal color transition. The observed engagement of the solvent molecules in the second coordination sphere of the central metal ion (Fig. 4a and b) might be the responsible factor, weakening the donating ability of the hydrogen-bonded chelating groups. However, another effect of the solvent inclusion must be also taken into account, concerning the geometry of the macroring. As a closer inspection of the interatomic distances in Table 1 may show, the macroring oxygens which serve as the apical ligands in the Cu(II) hexacoordination, are much closer to the central metal ion in the presence than in the absence of the solvent, as a consequence of subtle changes of the macroring conformation accompanying the solvent inclusion. In this way, the solvent diminishes deformation involved in the octahedral coordination, which may cause the observed color changes in accord with the operation of the Jahn–Teller effect.

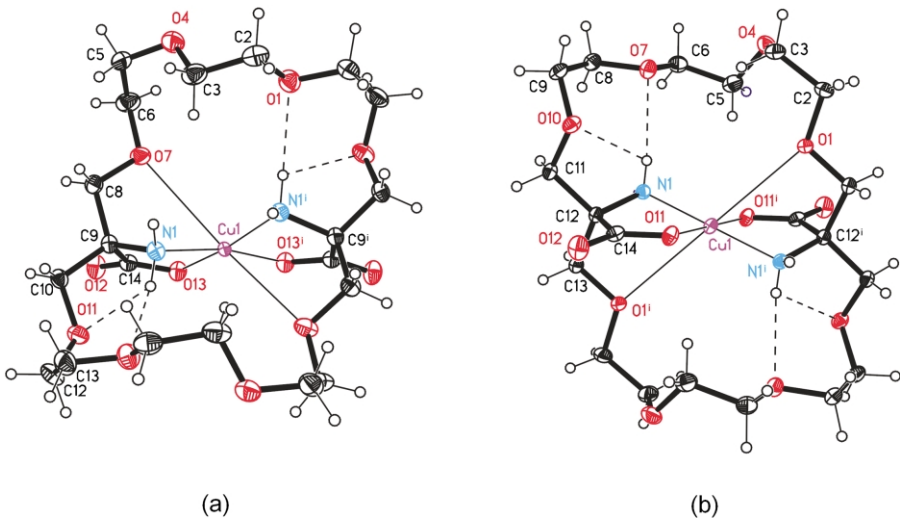

Figure 3. ORTEP drawings of the molecular structure of unsolvated (violet) complexes Cu(II)/*cis*-**2b** (a) and Cu(II)/*trans*-**2b** (b) with atom numbering (ellipsoids: 50% probability). The second part of molecule in (a) and (b) is generated by two-fold rotational axis and by center of symmetry, respectively. Hydrogen bonds are drawn as dashed lines.

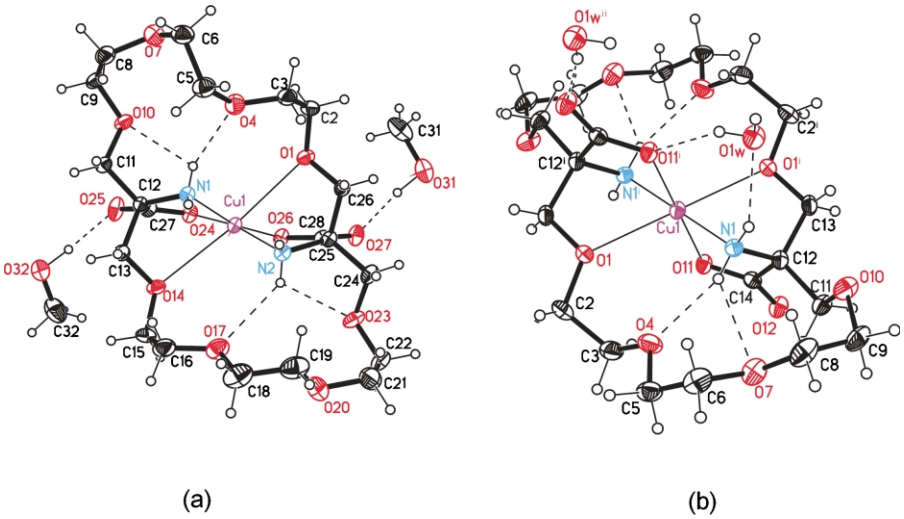

Figure 4. ORTEP drawings of the molecular structure of solvated (blue) complexes Cu(II)/*cis*-**2b**·CH_3OH (a) and Cu(II)/*trans*-**2b**·$2H_2O$ (b) with atom numbering (ellipsoids: 50% probability). For *cis*-complex (a), two solvent molecules (each of 50% occupancy) are shown. For *trans*-complex (b), the second part of molecule is generated by center of symmetry. Hydrogen bonds are drawn as dashed lines.

Table 1. Distances between the transannular quaternary carbon atoms (C_{q1}–C_{q2}) and between the adjacent *cis*-substituents (positions specified by the corresponding N and/or carboxylic C atoms in the complementary *cis*-pairs)

Compound	C_{q1}–C_{q2} (Å)	First pair (Å)	Second pair (Å)
cis-**2a**·$CH_3OH.2·H_2O$	C9–C19 5.821(2)	N1–N2 8.394(2)	C21–C22 5.970(2)
Cu(II)/*cis*-**2a**·$2CH_3OH$	C9–C19 5.314(3)	N1–N2 2.947(2)	C21–C22 5.158(4)
trans-**2a**	C9–C9′ 4.973(2)	N1–C11′ 3.623(1)	N1′–C11 3.623(1)
Cu(II)/*trans*-**2a**	C9–C19 5.257(3)	N1–C22 4.215(3)	N2–C21 8.093(3)
Cu(II)/*cis*-**2b**	C9–C9′ 5.527(3)	N1–N1′ 3.092(2)	C14–C14′ 5.180(3)
Cu(II)/*cis*-**2b**·CH_3OH	C12–C25 5.386(2)	N1–N2 3.078(2)	C27–C28 5.144(2)
Cu(II)/*trans*-**2b**	C12–C12′ 5.631(3)	N1–C14′ 4.084(2)	N1′–C14 4.084(2)
Cu(II)/*trans*-**2b**·$2H_2O$	C12–C12′ 5.478(3)	N1–C14′ 4.108(2)	N1′–C14 4.108(2)

Primed atoms were generated by following symmetry operations: *trans*-**2a**: $2-x$, $1-y$, $1-z$; Cu(II)/*cis*-**2b**: $-x$, y, $1/2-z$; Cu(II)/*trans*-**2b**: $1-x$, $1-y$, $-z$; Cu(II)/*trans*-**2b**·$2H_2O$: $-x$, $1-y$, $1-z$.

2.2.6. Relationship between the *in–out* dichotomy and crystal packing. The majority of the crystal structures investigated in this study exhibit a highly ordered stacking of the individual macrorings into infinite columns. The stacking does not appear to be a privilege either of the free bis(amino acids) or of the corresponding Cu(II) complexes, and also it cannot be attributed to any particular configuration, either *cis*- or *trans*.

On the other hand, a close relationship can be found

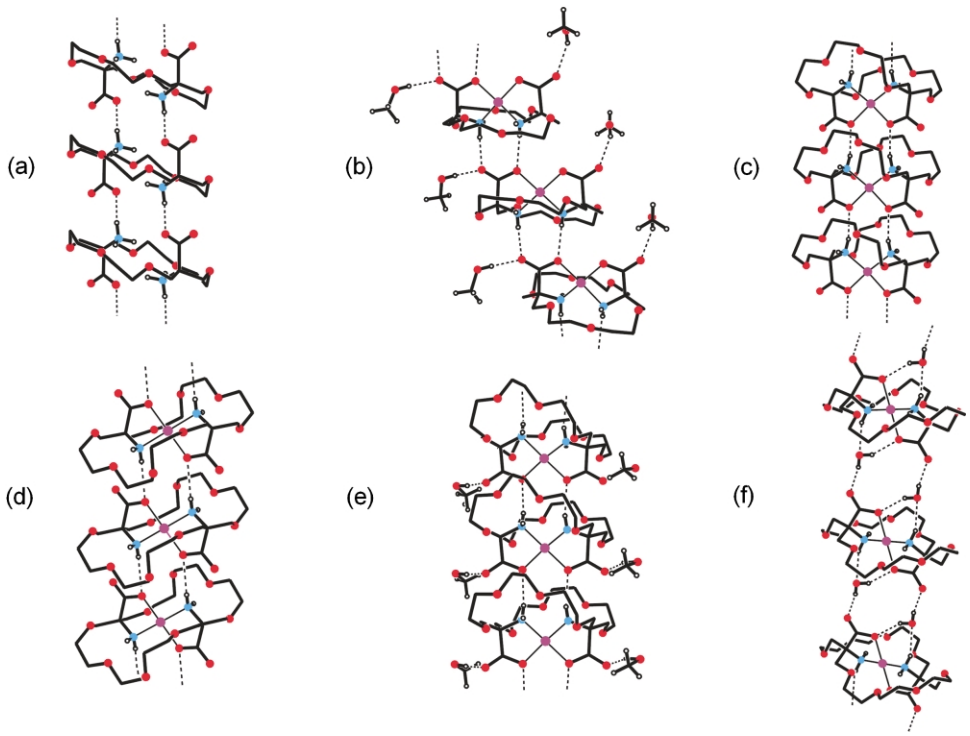

Figure 5. Crystal stacking of macrorings in compounds distinguished by *in*-conformation: *trans*-**2a** (a), Cu(II)/*cis*-**2a**·2CH_3OH (b), Cu(II)/*cis*-**2b** (c), Cu(II)/*trans*-**2b** (d), Cu(II)/*cis*-**2b**·CH_3OH (e), Cu(II)/*trans*-**2b**·2H_2O (f). Carbon atoms are omitted and only intermolecular hydrogen bonds are indicated (dashed lines). Atoms of oxygen, nitrogen and copper are represented with red, blue and violet circles, respectively.

between the macroring stacking and *in*–*out* dichotomy in the investigated compounds, all the stacked structures possessing the *in*-conformation. Out of the eight crystal structures presented in this study, six exhibit the *in*-conformation (Figs. 1b, 2a, 3a, 3b, 4a, 4b) and these all are stacked (Fig. 5a–f). The remaining two structures (Figs. 1a, 2b) show the *out*-conformation and both are unstacked.

Inspection of the individual stacked structures invariantly shows that the stacking is organized by intermolecular hydrogen bonding between the proximate ammonium (or amino) and carboxylate groupings. Pre-organization of the participating groups inside the macroring cavity, which distinguishes the *in*-conformation, appears to be an indispensable prerequisite for such a supramolecular organization.

In the Cu(II)/*cis*-**2b**·MeOH complex, the solvent molecules are stacked parallely along the stacked macrorings via hydrogen bonding with oxygen donors at the proximate carboxylate groups (Fig. 5e). In the Cu(II)/*trans*-**2b**·2H_2O complex, the molecules of water are sandwiched between the stacked macrorings, participating in the hydrogen bridges which link the proximate amino and carboxy-groups at the neighboring macrorings (Fig. 5f).

3. Conclusions

Macrocyclic bis(α-amino acids) *cis*- and *trans*-**2a**-**b** have been prepared from the selectively protected tris(hydroxymethyl)aminomethane **3** and appropriate oligo(ethylene glycol) ditosylates **4a**-**b** under conditions of Williamson synthesis. The X-ray structure of the free bis(amino acids) and/or of the corresponding Cu(II) complexes has been determined allowing an unambiguous configurational assessment. At the same time, conformational *in*–*out* dichotomy of the functional groups in respect to the macroring cavity has been demonstrated, both in the bis(amino acids) as well as in their Cu(II) complexes. It has been found that the dichotomy depends on configuration, Cu(II) chelation and also on the macroring size. *In*-conformation has been found to be a prerequisite for the macroring stacking in the crystal.

4. Experimental

4.1. General remarks

^1H and ^{13}C NMR spectra were measured on FT NMR spectrometer Varian UNITY 500 (^1H at 500 MHz and ^{13}C at 125.7 MHz) in $CDCl_3$, DMSO and/or D_2O. Proton chemical shifts are referenced to TMS (in $CDCl_3$), DMSO ($\delta_{(DMSO)}$ 2.50) or HDO ($\delta_{(HDO)}$ 4.80). Carbon chemical shifts are referenced to $CDCl_3$ ($\delta_{(CDCl3)}$ 77.0), DMSO ($\delta_{(DMSO)}$ 39.7) and DSS (as secondary reference in D_2O). FAB MS spectra were recorded with ZAB-EQ VG analytical instrument using a mixture of glycerol-thioglycerol matrix. ES MS spectra were recorded with Finnigan instrument formed by P 1000 pump, SCM 1000 degasser and MS detector LCQ (ESI ionization with recording of positive ions, capillary temperature 275°C) in methanol/water 90/10 as mobile phase (flow rate 0.2 mL/min) with sample volume 5 μL (spray voltage 4.5 kV, capillary voltage 38 V, tube lens offset voltage 5 V). Analytical samples were dried at 60°C/5 kPa for 24 h. TLC chromatography was performed on Kieselgel GF_{254} using Dragendorff spraying reagent.

2,2-Bis(hydroxymethyl)-1-aza-4-oxaspirodecane[13] (**3**) and oligo(ethylene glycol) ditosylates[14] **4a**-**b** were prepared according to known procedures.

4.2. Synthetic procedures

Two alternative procedures, A and B, have been employed for the *cis*–*trans* isomer separation in the course of the synthesis. According to procedure A, which is applicable only for the lower homologue, the isomer separation follows immediately the macrocyclization step. In procedure B, on the other hand, the crude reaction mixture which results from the macrocyclization is subjected to hydrolysis, N-Cbz-reprotection and oxidation prior to the isomer separation.

4.3. Procedure A

4.3.1. Isomerically uniform bis(oxazolidines) *cis*- and *trans*-5a. Solutions of diol **3** (12 g, 60 mmol) in dry dioxane (350 mL) and ditosylate **4a** (27 g, 65 mmol) in dry dioxane (350 mL) were added slowly (30 mL/h) by dual syringe pump to a vigorously stirred suspension of freshly powdered KOH (85%; 14 g, 200 mmol) in dry dioxane (300 mL) at 80°C. After heating and stirring for another 10 h and subsequent cooling the deposited salts were filtered off, washed with dioxane (200 mL) and the solvent was evaporated. The residue was subjected to column chromatography (silica gel; 900 g; chloroform–methanol–triethylamine 95:4:1) yielding a mixture of *cis*-**5a** and *trans*-**5a** (7.1 g, 43%). The mixture was re-chromatographed (silica gel; 900 g, chloroform–methanol 98:2) yielding the individual isomers.

cis-**5a**. Yield 2.4 g (15%); colorless crystals; mp 76–78°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.69 (m, 20H, C_6H_{10}), 2.39 (bs, 2H, NH), 3.51 (d, 4H, J=9.0 Hz, CH_2O), 3.52 (d, 4H, J=9.0 Hz, CH_2–O), 3.58–3.67 (m, 16H, CH_2CH_2O), 3.73 (s, 4H, CH_2O). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 23.72 (CH_2), 25.12 (CH_2), 37.55 (CH_2), 64.81 (>C<), 69.73 (CH_2O), 70.60 (CH_2O), 71.09 (CH_2O), 73.78 (CH_2O), 95.65 (>C<). FAB$^{(+)}$ MS m/z (%): 543 ([M+H]$^+$, 100%). Anal. calcd for $C_{28}H_{50}N_2O_8$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.71; H, 9.50; N, 4.93.

trans-**5a**. Yield 2.5 g (15%); colorless crystals; mp 89–91°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.70 (m, 20H, C_6H_{10}), 2.12 (bs, 2H, NH), 3.50 (d, 4H, J=9.0 Hz, CH_2–O), 3.52 (d, 4H, J=9.0 Hz, CH_2–O), 3.60–3.66 (m, 16H, CH_2CH_2–O), 3.72 (s, 4H, CH_2–O). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 23.71 (CH_2), 25.20 (CH_2), 37.56 (CH_2), 64.79 (>C<), 69.69 (CH_2O), 70.57 (CH_2O), 71.08 (CH_2O), 73.74 (CH_2O), 95.63 (>C<). FAB$^{(+)}$ MS m/z (%): 543 ([M+H]$^+$, 100%). Anal. calcd for $C_{28}H_{50}N_2O_8$. 0.5H_2O: C, 60.92; H, 9.31; N, 5.08. Found: C, 60.77; H, 9.19; N, 5.05.

4.3.2. Isomerically uniform *N*-Cbz protected bis(amino alcohols) *cis*- and *trans*-6a. 3 M HCl (50 mL) was added to an appropriate isomer of **5a** (2 g, 3.7 mmol) and the mixture was stirred and heated at 55°C for 5 h. Hydrochloric acid was evaporated, the resulting bis(amino alcohol hydrochloride) was dissolved in 1:1 mixture of dioxane and water (70 mL) and treated with sodium hydrogen carbonate (4.2 g, 50 mmol). Benzyl chloroformate (1.2 mL, 8 mmol, in 15 mL of dioxane) was added during 2 h under a vigorous stirring at 0°C and the reaction mixture was stirred another 2 h at ambient temperature. Dioxane was evaporated, the residue was dissolved in water and extracted with ethyl acetate (5×70 mL). The organic layer was dried over $MgSO_4$, evaporated and the crude product was purified by column chromatography (150 g of silica gel, 0.5–2% of methanol in chloroform).

cis-**6a**. Yield 1.8 g (75%); colorless crystals; mp 65°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56–3.63 (m, 16H, CH_2CH_2O), 3.73 (d, 4H, J=9.6 Hz, CH_2O), 3.82 (d, 4H, J=9.6 Hz, CH_2O), 3.82 (bs, 4H, CH_2OH), 4.03 (bs, 2H, OH), 5.05 (s, 4H, CH_2Ph), 5.72 (bs, 2H, NH), 7.30–7.38 (m, 10H, C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 59.74 (>C<), 64.68 (CH_2OH), 66.76 (CH_2Ph), 70.65 (CH_2O), 70.94 (CH_2O), 71.17 (CH_2O), 128.20(C_6H_5), 128.21(C_6H_5), 128.51(C_6H_5), 136.25(C_6H_5), 156.31 (OCONH). FAB$^{(+)}$ MS m/z (%): 651 ([M+H]$^+$, 45%). Anal. calcd for $C_{32}H_{46}N_2O_{12}$: C, 59.06; H, 7.13; N, 4.31. Found: C, 59.34; H, 7.26; N, 4.11.

trans-**6a**. Yield 1.9 g (79%); oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56–3.66 (m, 16H, CH_2CH_2O), 3.63 (d, 4H, J=9.6 Hz, CH_2O), 3.75 (d, 4H, J=9.6 Hz, CH_2O), 3.82 (bs, 4H, CH_2OH), 4.02 (bs, 2H, OH), 5.06 (s, 4H, CH_2Ph), 5.84 (bs, 2H, NH), 7.28–7.37 (m, 10H, C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 59.55 (>C<), 64.89 (CH_2OH), 66.66 (CH_2Ph), 70.68 (CH_2O), 71.00 (CH_2O), 71.05 (CH_2O), 128.11 (C_6H_5), 128.14 (C_6H_5), 128.51 (C_6H_5), 136.36 (C_6H_5), 156.33 (OCONH). FAB$^{(+)}$ MS m/z (%): 651 ([M+H]$^+$, 75%). Anal. calcd for $C_{32}H_{46}N_2O_{12}$: C, 59.06; H, 7.13; N, 4.31. Found: C, 59.08; H, 7.27; N, 4.09.

4.3.3. Isomerically uniform *N*-Cbz-protected bis(amino acids) *cis*- and *trans*-7a. *N*-Cbz-protected bis(amino alcohol) *cis*- or *trans*-**6a** (1.7 g, 2.6 mmol) was dissolved in 1:1 mixture of H_2O and CH_3CN (130 mL) and treated with $NaHCO_3$ (0.5 g, 7.7 mmol) and TEMPO (0.4 g, 2.6 mmol). NaClO (15 mL of 0.7 M aqueous solution) was added in several portions under stirring at room temperature and the reaction was monitored by TLC. After 1–2 h, the reaction mixture was evaporated to dryness and the solid residue was treated with chloroform. Deposited salts were filtered off and the crude product was purified by column chromatography (200 g of silica gel, chloroform–methanol–aq. ammonia: 100:20:3) followed by ion exchange (Dowex 50, H^+ form).

cis-**7a**. 1.19 g (68%); glassy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53 (m, 8H, CH_2CH_2O), 3.66 (m, 4H, CH_2CH_2O), 3.78 (m, 4H, CH_2CH_2O), 3.90 (d, 4H, J=9.4 Hz, CH_2O), 4.10 (d, 4H, J=9.4 Hz, CH_2O), 5.03 (s, 4H, CH_2Ph), 6.58 (bs, 2H, NH), 7.26–7.37 (m, 10H, C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 63.26 (>C<), 65.92 (CH_2 Ph), 68.69 (CH_2O), 69.27 (CH_2O), 70.63 (CH_2O), 127.70 (C_6H_5), 127.79 (C_6H_5), 128.35 (C_6H_5), 136.87 (C_6H_5), 154.98 (OCONH), 174.97 (COOH). FAB$^{(-)}$ MS m/z (%): 677 ([M−H]$^-$, 100%), 699 ([M+Na−H]$^-$, 80%). FAB$^{(+)}$ MS m/z (%): 739 ([M+K+Na]$^+$, 100%), 723 ([M+2Na]$^+$, 75%). Anal. calcd for $C_{32}H_{40}N_2O_{14}$·2H_2O: C, 53.78; H, 6.48; N, 3.92. Found: C, 53.96; H, 6.17; N, 3.93.

trans-**7a**. 1.17 g (66%); colorless crystals; mp 173°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50–3.70 (m, 16H, CH_2CH_2O), 3.96 (bd, 4H, J=9.5 Hz, CH_2O), 4.07 (bd, 4H, J=9.5 Hz, CH_2O), 5.10 (s, 4H, CH_2Ph), 6.17 (bs, 2H, NH), 7.27–7.37 (m, 10H, C_6H_5). ^{13}C NMR (125.7 MHz, CD_3SOCD_3) δ 61.95 (>C<), 65.35 (CH_2Ph), 68.94 (CH_2O), 69.74 (CH_2O), 70.71 (CH_2O), 127.80 (C_6H_5), 127.95 (C_6H_5), 128.50 (C_6H_5), 137.17 (C_6H_5), 154.76 (OCONH), 172.08 (COOH). FAB$^{(-)}$ MS m/z (%): 677 ([M−H]$^-$, 100%). Anal. calcd for $C_{32}H_{42}N_2O_{14}$: C, 56.64; H, 6.24; N, 4.13. Found: C, 56.55; H, 6.24; N, 3.80.

4.4. Procedure B

4.4.1. One-pot synthesis of *cis*–*trans*-mixture of *N*-Cbz-protected bis(amino alcohols) 6a-b. A mixture of diol **3** (14 g, 60 mmol), ditosylate **4a** or **4b** (65 mmol) and freshly powdered KOH (85%; 15 g, 200 mmol) in dry dioxane (800 mL) was vigorously stirred and heated at 80°C for 12 h. After cooling, the deposited salts were filtered off (Cellite), washed with dioxane (200 mL) and the solvent was evaporated. To the crude residue was added 3 M aqueous HCl (250 mL) and the reaction mixture was stirred and heated at 55°C for 5 h. Hydrochloric acid was evaporated, the resulting crude mixture of amino alcohol hydrochlorides was dissolved in 1:1 mixture of dioxane and water (150 mL) and treated with sodium hydrogen carbonate (30 g). Benzyl chloroformate (10 mL, 8 mmol) in 50 mL of dioxane was added slowly during 2 h under vigorous stirring at 0°C and the reaction mixture was stirred another 2 h at ambient temperature. Dioxane was evaporated and the residue was extracted with ethyl acetate (4×100 mL). The organic layer was dried over $MgSO_4$, evaporated and the crude product was purified by column chromatography (1000 g of silica gel, 1–4% of methanol in chloroform) yielding the corresponding mixture of *cis*- and *trans*-**6a** or **6b** in about 1:1 isomeric ratio.

Mixture of *cis*- and *trans*-**6a**: yield 5.87 g (25.8%); oil, identical with the corresponding products of the procedure A.

Mixture of *cis*- and *trans*-**6b**. Yield 2.50 g (9.7%); oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55–3.65 (m, 28H, CH_2CH_2O), 3.76/3.77 (d, 4H, J=9.5 Hz, CH_2O), 3.83 (m, 4H, CH_2OH), 4.00 (bs, 2H, OH), 5.04/5.05 (s, 4H, CH_2Ph), 5.77/6.00 (bs, 2H, NH), 7.28–7.37 (m, 10H, C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 59.48 (>C<), 64.53/64.83 (CH_2OH), 66.48/66.52 (CH_2Ph), 70.25/70.31 (CH_2O), 70.60 (CH_2O), 70.90/70.95 (CH_2O), 128.03/128.06(C_6H_5), 128.08/128.09(C_6H_5), 128.48/128.54(C_6H_5), 136.45/136.51 (C_6H_5), 156.14/156.19 (OCONH). FAB$^{(+)}$ MS m/z (%): 739 ([M+H]$^+$, 78%). Anal. calcd for $C_{36}H_{54}N_2O_{14}$: C, 58.52; H, 7.37; N, 3.79. Found: C, 58.18; H, 7.47; N, 3.88.

4.4.2. *cis*–*trans* Mixture of *N*-Cbz-protected bis(amino acids) 7a-b and isomer separation. A mixture of *cis*- and *trans*-**6a** or **6b** (2 mmol) was dissolved in 1:1 mixture of H_2O and CH_3CN (100 mL) and treated with $NaHCO_3$ (0.5 g, 5.9 mmol) and TEMPO (0.3 g, 2 mmol). NaClO (12 mL of 0.7 M aqueous solution) was subsequently added in several portions under stirring at room temperature and the reaction was monitored by TLC. After 1–2 h, the reaction mixture was evaporated to dryness and the solid residue was treated with chloroform. Deposited salts were filtered off and the crude product was separated by column chromatography (200 g of silica gel, chloroform–methanol–aq. ammonia: 100:20:3) and desalted by subsequent ion exchange chromatography (Dowex 50, H^+ form).

cis-**7a**. Yield 0.48 g (35.4%); glassy solid, identical with the corresponding product of the procedure A.

trans-**7a**. Yield 0.47 g (34.7%); colorless crystals; mp 173°C, identical with the corresponding product of the procedure A.

cis-**7b**. Yield 0.55 (35.8%); colorless crystals; mp 144–146°C. ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD, 95:5) δ 3.40–3.63 (m, 24H, CH_2CH_2O), 3.69 (bs, 4H, CH_2O), 4.06 (bs, 4H, CH_2O), 5.08 (s, 4H, CH_2Ph), 6.68 (bs, 2H, NH), 7.26–7.38 (m, 10H, C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$+CD_3OD, 95:5) δ 64.91 (>C<), 65.97 (CH_2Ph), 69.86 (CH_2O), 70.33 (CH_2O), 71.10 (CH_2O), 127.85 (C_6H_5), 128.04 (C_6H_5), 128.24 (C_6H_5), 136.66 (C_6H_5), 154.70 (OCONH), 173.61 (COOH). FAB$^{(-)}$ MS m/z (%): 765([M−H]$^-$, 100%). FAB$^{(+)}$ MS m/z (%): 789 ([M+Na]$^+$, 100%), 811 ([M+2Na]$^+$, 20%). Anal. calcd for $C_{36}H_{50}N_2O_{16}.1.5H_2O$: C, 54.46; H, 6.73; N, 3.53. Found: C, 54.86; H, 6.67; N, 4.16.

Trans-**7b**. Yield 0.56 (36.5%); colorless crystals; mp 48–50°C. ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD, 95:5) δ 3.46–3.66 (m, 24H, CH_2CH_2O), 3.89 (d, 4H, J=9.6 Hz, CH_2O), 4.11 (d, 4H, J=9.6 Hz, CH_2O), 5.05 (s, 4H, CH_2Ph), 6.72 (bs, 2H, NH), 7.27–7.36 (m, 10H, C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$+CD_3OD, 95:5) δ 63.50 (>C<), 65.83 (CH_2Ph), 68.79 (CH_2O), 69.20 (CH_2O), 69.48 (CH_2O), 70.05 (CH_2O), 127.68 (C_6H_5), 127.77 (C_6H_5), 128.25 (C_6H_5), 136.68 (C_6H_5), 154.76 (OCONH), 175.28 (COOH). FAB$^{(-)}$ MS m/z (%): 765([M−H]$^-$, 100%), 787 ([M+Na−H]$^-$, 30%). FAB$^{(+)}$ MS m/z (%): 789 ([M+Na]$^+$, 100%), 811 ([M+2Na]$^+$, 80%), 833 ([M+3Na]$^+$, 45%). Anal. calcd for $C_{36}H_{48}N_2O_{16}.2H_2O$: C, 53.86; H, 6.78; N, 3.49. Found: C, 53.89; H, 6.56; N, 3.40.

4.4.3. Hydrogenolysis of *N*-Cbz-protected bis(amino acids) *cis*- and *trans*-7a-b and conversion of the resulting free acids into Cu(II)/*cis*-2a-b and Cu(II)/*trans*-2a-b complexes. Individual isomers *cis*- and *trans*-**7a** or **7b** (0.5 mmol) were dissolved in methanol (30 mL), 10% Pd/C catalyst (50 mg) was added and hydrogen was bubbled through the reaction mixture for 3 h. The catalyst was filtered off and the solvent was evaporated. The residual white solid was dissolved in water (30 mL) and treated with basic copper(II)carbonate (0.44 g, 2 mmol). The reaction mixture was refluxed for 5 min, filtered and evaporated to dryness. The residue was dissolved in methanol (8 mL) and crystallized by diffusion of diisopropyl ether vapors overnight.

Complex Cu(II)/*cis*-**2a**. Yield 0.21 g (90%); blue crystals; mp>360°C. ES MS m/z (%): 495 ([M+Na], 27%), 965 ([2M+Na], 100%), 1436 ([3M+Na], 38%). Anal. calcd for $C_{16}H_{28}CuN_2O_{10}.H_2O$: C, 39.22; H, 6.17; N, 5.72. Found: C, 39.31; H, 6.02; N, 5.56.

Complex Cu(II)/*trans*-**2a**. Yield 0.22 g (93%); blue crystals;

mp>360°C. ES MS *m/z* (%): 472 ([M+H], 28%), 495 ([M+Na], 64%), 965 ([2M+Na], 100%), 1436 ([3M+Na], 38%). Anal. calcd for $C_{16}H_{28}CuN_2O_{10}.H_2O$: C, 39.22; H, 6.17; N, 5.72. Found: C, 39.60; H, 6.17; N, 5.62.

Complex Cu(II)/*cis*-**2b**. Yield 0.25 g (89%); blue crystals; mp>360°C. ES MS *m/z* (%): 582 ([M+Na], 27%), 1142 ([2M+Na],100%). Anal. calcd for $C_{20}H_{36}CuN_2O_{12}$: C, 42.89; H, 6.48; N, 5.00. Found: C, 42.59; H, 6.69; N, 4.75.

Complex Cu(II)/*trans*-**2b**. Yield 0.26 g (93%); blue crystals; m.p.>360°C. ES MS *m/z* (%): 582 ([M+Na], 100%), 1142 ([2M+Na], 31%). Anal. calcd for $C_{20}H_{36}CuN_2O_{12}$: C, 42.89; H, 6.48; N, 5.00. Found: C, 42.67; H, 6.54; N, 4.83.

4.4.4. Decomposition of complexes Cu(II)/*cis*-2a-b and Cu(II)/*trans*-2a-b by hydrogen sulfide. Recovery of the free bis(amino acids) *cis*- and *trans*-2a-b. Hydrogen sulfide was bubbled through the aqueous solution of the appropriate copper complex Cu(II)/*trans*-**2a**-**b** for 3 min, the reaction mixture was stirred for another 30 min and ethanol was added (150 mL). After 1 h stirring, the precipitate was filtered off and the solvents were evaporated. The residue was crystallized from a mixture of methanol and diethyl or diisopropyl ether.

cis-**2a**. Yield 0.16 g (98%); colorless crystals; mp 210–215°C (decomp.). ^{1}H NMR (500 MHz, D_2O) δ 3.67–3.76 (m, 16H, CH_2CH_2O), 3.87 (s, 8H, CH_2O). ^{13}C NMR (125.7 MHz, D_2O) δ 67.94 (>C<), 72.40 (CH_2O), 73.04 (CH_2O), 73.17 (CH_2O), 175.15 (COOH). FAB$^{(+)}$ MS *m/z* (%): 411 ([M+H]$^+$, 100%). Anal. calcd for $C_{16}H_{30}N_2O_{10}.0.5H_2O$: C, 45.82; H, 7.45; N, 6.68. Found: C, 45.64; H, 7.43; N, 6.53.

trans-**2a**. Yield 0.15 g (91%); colorless crystals; mp 225–230°C (decomp.). ^{1}H NMR (500 MHz, D_2O) δ 3.67–3.75 (m, 16H, CH_2CH_2O), 3.87 (s, 8H, CH_2O). ^{13}C NMR (125.7 MHz, D_2O) δ 67.96 (2×>C<), 72.97 (CH_2O), 73.31 (CH_2O), 175.14 (COOH). FAB$^{(+)}$ MS *m/z* (%): 411 ([M+H]$^+$, 100%). Anal. calcd for $C_{16}H_{30}N_2O_{10}.H_2O$: C, 44.85; H, 7.53; N, 6.54. Found: C, 44.99; H, 7.56; N, 6.38.

cis-**2b**. Yield 0.19 g (95%); colorless crystals; mp 211°C. ^{1}H NMR (500 MHz, D_2O) δ 3.63–3.72 (m, 24H, CH_2CH_2O), 3.77 (d, 4H, J=10.6 Hz, CH_2O), 3.83 (d, 4H, J=10.6 Hz, CH_2O). ^{13}C NMR (125.7 MHz, D_2O) δ 68.04 (>C<), 72.49 (CH_2O), 72.53 (CH_2O), 73.03 (CH_2O), 73.06 (CH_2O), 175.21 (COOH). FAB$^{(+)}$ MS *m/z* (%): 499 ([M+H]$^+$, 100%). Anal. calcd for $C_{20}H_{38}N_2O_{12}\cdot 2H_2O$: C, 44.94; H, 7.92; N, 5.24. Found: C, 45.07; H, 7.78; N, 5.10.

trans-**2b**. Yield 0.18 g (90%); colorless crystals; mp 214°C. ^{1}H NMR (500 MHz, D_2O) δ 3.62–3.70 (m, 24H, CH_2CH_2O), 3.70 (d, 4H, J=10.4 Hz, CH_2O), 3.84 (d, 4H, J=10.4 Hz, CH_2O). ^{13}C NMR (125.7 MHz, D_2O) δ 68.22 (>C<), 72.59 (CH_2O), 72.65 (CH_2O), 72.91 (CH_2O), 72.98 (CH_2O), 175.33 (COOH). FAB$^{(+)}$ MS *m/z* (%): 499 ([M+H]$^+$, 100%). Anal. calcd for $C_{20}H_{38}N_2O_{12}\cdot 2H_2O$: C, 44.94; H, 7.92; N, 5.24. Found: C, 44.91; H, 7.85; N, 5.18.

4.5. X-Ray studies

Single crystals of free amino acids *cis*- and *trans*-**2a** and of the copper complexes Cu(II)/*cis*-**2b** were prepared by slow diffusion of diisopropyl ether (2–3 days) to an appropriate methanolic solution. Crystals of Cu(II)/*trans*-**2a** were prepared by dissolving the complex in a mixture of methanol, pyridine and saturated aqueous ammonia (2:2:1) followed by slow diffusion of diisopropyl ether (20 days).

The X-ray data for all structures were obtained at 150 K using Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with Mo K_α radiation (λ=0.71073 Å), a graphite monochromator, and the ϕ and ω scan mode. Data reductions were performed with DENZO-SMN method.[15] The absorption was neglected. Structures were solved by direct methods[16] and refined by full matrix least-square technique based on F^2 (SHELXL97[17]). Hydrogen atoms were treated in all structures similarly; those on carbon were calculated into ideal positions, riding during refinement on the respective pivot atom. The isotropic displacement parameters of hydrogen atoms were set to 1.2×U_{eq} of the attached atom (1.5×U_{eq} for methyl hydrogen atoms). Hydrogen atoms on N and O were found on difference Fourier map and refined isotropically. Crystal data, transannular distances and parameters of hydrogen bonds in the solved structures are in Supplementary materials.

Full crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 209552-209559 (*cis*-**2a**·$CH_3OH\cdot 2H_2O$: 209552, Cu(II)/*cis*-**2a**·$2CH_3OH$: 209553, *trans*-**2a**: 209554, Cu(II)/*trans*-**2a**: 209555, Cu(II)/*cis*-**2b**: 209556, Cu(II)/*cis*-**2b**·CH_3OH: 209557, Cu(II)/*trans*-**2b**: 209558, Cu(II)/*trans*-**2b**·$2H_2O$: 209559). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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