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From 2 + 2 to 8 + 8 Condensation Products of Diamine and Dialdehyde: Giant Container-Shaped Macrocycles for Multiple Anion Binding

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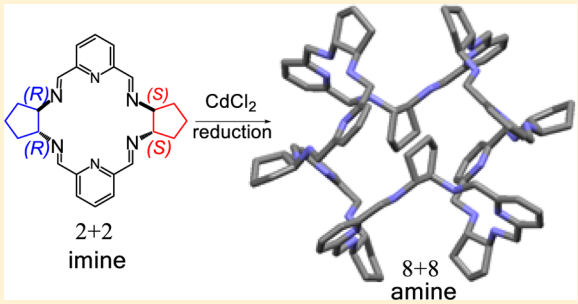
Supporting Information

ABSTRACT: The combination of 2,6-diformylpyridine and *trans*-1,2-diaminocyclopentane fragments results in 2 + 2, 3 + 3, 4 + 4, 6 + 6, and 8 + 8 macrocyclic imine condensation products. These imines can be reduced to the corresponding 2 + 2, 3 + 3, 4 + 4, 6 + 6, and 8 + 8 macrocyclic amines. The X-ray crystal structures of their protonated derivatives show a rich variety of macrocycle conformations ranging from a stepped 2 + 2 macrocycle to a multiply folded 8 + 8 macrocycle of globular shape. These compounds bind anions via hydrogen bonds: two chloride anions are bound above and below the macrocyclic ring of the 2 + 2 amine, one chloride anion is bound approximately in the center of the 3 + 3 macrocycle, and two chloride anions are deeply buried inside a folded container-shaped 4 + 4 macrocycle, while in the case of the previously reported 6 + 6 amine four chloride anions and two solvent molecules are buried inside a container-shaped macrocycle. Yet another situation was observed for a multiply folded protonated 8 + 8 macrocycle which binds six sulfate anions; two of them are deeply buried inside the container structure while four anions interact with the clefts at the surface of the container.



INTRODUCTION

Macrocyclic compounds constitute an important class of compounds both in organic and inorganic chemistry.[1−3] Because of their unique binding properties and the important role that these compounds play in living organisms, the synthesis of macrocycles is a thriving area of research. Apart from their often elegant structure and their importance in biological systems, these compounds continue to attract considerable attention due to their current and potential applications. For instance, metal complexes of macrocyclic ligands are used in catalysis and medical diagnostics. Macrocycles are also investigated in the context of chiral recognition and gas storage. Macrocyclic compounds can act as hosts both for metal cations and neutral organic guest molecules. In addition, many macrocycles such as polyamines or calixpyrroles turned out to be very effective hosts for anion binding.[4] In some cases very large macrocycles, e.g. polypyrrolic Schiff bases, are able to bind more than one anion within macrocycle core.[5]

For the reasons mentioned above there is continuing interest in the design and synthesis of ever more elaborate macrocyclic compounds,[2,3] for instance large shape-persistent macrocycles, guest responsive macrocycles, or chiral macrocycles. For the last class of compounds, *trans*-1,2-diaminocyclohexane (DACH) is often used as the chiral building block inferring chirality on the macrocyclic system. For instance, the condensation of enantiopure DACH with dicarbonyl compounds leads to 3 + 3 macrocyclic imines (trianglimines) that can be converted to the corresponding 3 + 3 amines (trianglamines).[6] In the case of 2,6-diformylpyridine (DFP) the condensation of enantiopure or racemic DACH in the presence of lanthanide(III) ions leads to chiral 2 + 2 macrocyles,[7] the condensation of racemic DACH in the presence of Cd(II) ions leads to 3 + 3 macrocycle,[8] and the application of DFP and racemic form of DACH without metal template leads to achiral meso-type 2 + 2 and 4 + 4 macrocyles.[9]

In a recent communication we have shown that the application of a similar racemic diamine, *trans*-1,2-diaminocyclopentane (DACP) in the condensation with DFP leads to 2 + 2, 4 + 4, and even larger macrocycles, depending on the reaction conditions.[10] In particular, the reaction of the preformed 2 + 2 imine templated by cadmium(II) ions resulted in the formation of a giant 6 + 6 imine complex of cadmium(II) that was converted to the corresponding 6 + 6 amine. This amine in its protonated form adopts an unusual container-like conformation and is able to bind four chloride anions and two solvent molecules in its interior. We have also mentioned the existence of even larger macrocycles as indicated by mass spectra of the crude reaction mixtures. In contrast, the reactions of enantiopure DACP with DFP results in a chiral 3 + 3 macrocycle as the preferred reaction product that can be converted into metal complexes of the corresponding 3 + 3 amine.[11]

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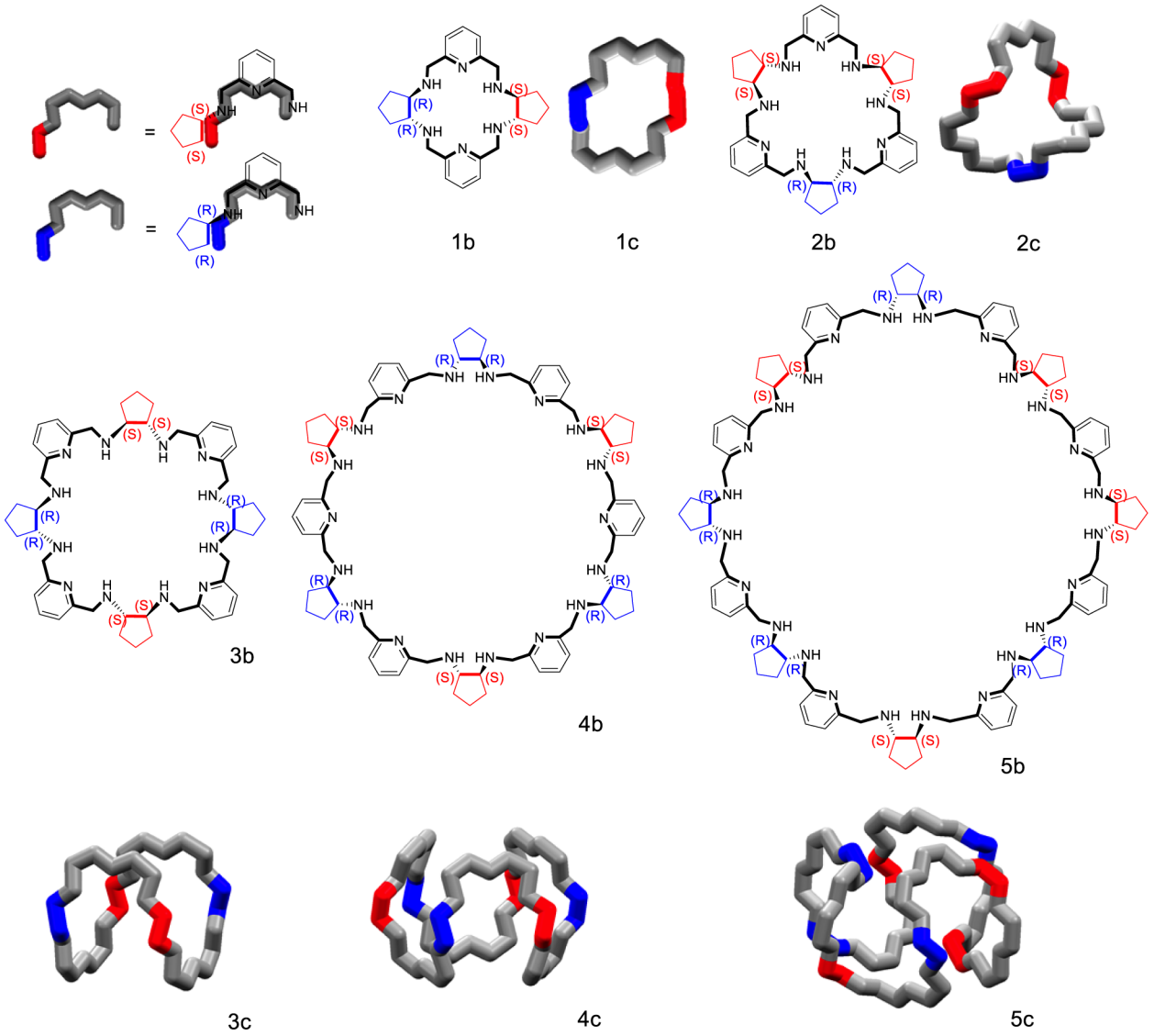

Figure 1. Amine macrocycles **1b**−**5b** (main cycles indicated in bold) and the conformations of main cycles of the protonated forms **1c**−**5c** of these macrocycles determined on the basis of XRD. Only one enantiomer of **2b** and **2c** is shown.

Here we present crystal structures and detailed characterization of various macrocyclic imine compounds **1a**−**5a** formed in the reaction of racemic DACP and DFP, amine macrocycles **1b**−**5b** obtained after reduction with $NaBH_4$, and their protonated forms with fully protonated amine groups **1c**−**5c** (Figure 1). In particular, we present the synthesis, X-ray crystal structure, and spectroscopic characterization of a giant protonated derivative of the 8 + 8 macrocyclic amine, **5c**, containing 24 amine nitrogen atoms in its main cycle. We also discuss experimental and theoretical indications of the role of the templating cadmium(II) ions in the formation of the discussed macrocycles.

RESULTS AND DISCUSSION

Synthesis and Theoretical Calculations. In a general case, the reactions of dicarbonyl compounds with diamines lead to various n + n macrocyclic imines as well as linear oligomeric condensation products, which are regarded as a dynamic combinatorial library.[6,8,12] This dynamic library can be "frozen" by subsequent reduction to the corresponding amines. In the case of the reaction of racemic DACP with DFP the composition of the mixture of condensation products strongly depends on the applied reaction conditions such as temperature and solvent. Thus, the reaction carried out in refluxing methanol leads selectively (ca. 97%) to **1a** and is driven by its poor solubility in this solvent. In refluxing acetonitrile the crude reaction mixture contains apart from **1a** macrocycle also **2a** and **3a** macrocyclic Schiff bases (in molar ratio **1a**/**2a**/**3a** 1/0.07/0.01) and traces of other unidentified condensation products. In refluxing chloroform the molar ratio **1a**/**2a**/**3a** changes in favor of bigger macrocycles and is 1/1.43/0.21. In the condensation run for 1 h in the mixture of benzene/methanol (25/1) at rt the amount of larger macrocycles increases and the molar ratio **1a**/**2a**/**3a** equals 1/4/1. It is worth mentioning that the 3 + 3 imine, **2a**, is also a dominant product (ca. 80%) when the reaction is carried out in methanol at rt for a short time (15−30 min). By a suitable optimization of reaction conditions and tedious fractional recrystallizations from benzene, pure **2a** and **3a** can be obtained from these mixtures. The isolated macrocycles **1a**, **2a**, and **3a** afford macrocyclic amines **1b**, **2b**, and **3b**, respectively, after reduction with $NaBH_4$. Alternatively, these amine macrocycles can be obtained omitting the recrystallization step by reduction

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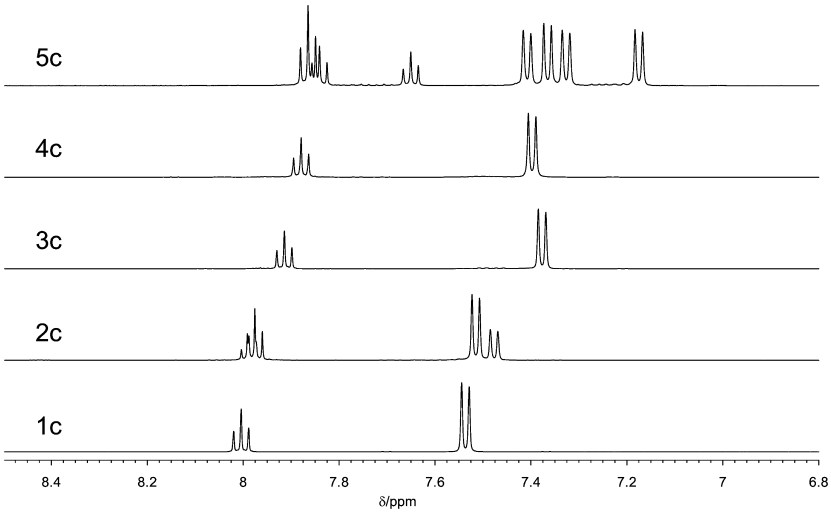

Figure 2. Fragments of ^{1}H NMR spectra (500 MHz, D_2O) of **1c**·4Cl·4CH_3OH·2CH_3CN, **2c**·6Cl·6H_2O, **3c**·8Cl·8H_2O, **4c**·12Cl·9H_2O,[10] and **5c**·8SO_4·32H_2O.

of a mixture of imines **1a**, **2a**, and **3a**, and subsequent separation of the corresponding amines by gel permeation chromatography (for the characterization of pure compounds, see Figure 2 and Supporting Figures S1−S27).

The composition of the dynamic library of imines derived from DACP and DFP is greatly affected by the application of a Cd(II) template (for theoretical insight see the end of this section). Due to the very poor solubility of the cadmium complexes of the resulting macrocyclic imines the dynamic library of imines is in this case not fully reversible. The poor solubility of cadmium containing macrocycles also makes their reduction with $NaBH_4$ sluggish and difficult. The reaction of DACP with DFP run for 24 h at room temperature in methanol/chloroform afforded selectively a cadmium(II) complex of the heterochiral 3 + 3 imine macrocycle **2a** (ca. 90% in the crude reaction mixture) as the main product (Supporting Figures S28 and S29). Similarly the Cd(II) template selectively directed the analogous reaction of DACH toward 3 + 3 imine macrocycles.[6i,8] Under these conditions the condensation of DACP at room temperature is not under thermodynamic control and the Cd(II) complex of **2a** is a kinetic product. This macrocyclic complex can be demetalated and selectively transformed into **2b**. In contrast, the same reaction carried out under reflux conditions for 6 days affords a mixture of compounds. The main components this time are larger condensation products such as 6 + 6 and 8 + 8 macrocycles **4a** and **5a**, respectively, as indicated by ESI MS spectra of the library "frozen" by reduction with sodium borohydride (Supporting Figure S30). Thus, the mixture of the larger macrocycles seems to be the main thermodynamic product of the template reaction. This is further confirmed by prolonged reflux of the Cd(II) complex of **2a** in a methanol/chloroform mixture, followed by reduction with $NaBH_4$. An ESI MS spectrum of the thus obtained crude product shows the presence of larger macrocycles (Supporting Figure S31).

The most convenient way to obtain the giant macrocycles 6 + 6 and 8 + 8 was the Cd(II)-templated conversion of 2 + 2 imine **1a**. The precipitated crude cadmium(II) complex of **4a** (Supporting Figures S28 and S29) can be isolated in this reaction,[10] and by its reduction pure **4b** amine (25−30% of total yield) is obtained. The filtrate contains cadmium complexes of **4a**, **5a**, and most likely other 6 + 6 and 8 + 8 isomers as well as even larger macrocyclic imines. The imine macrocycles present in this filtrate can be reduced to a mixture of **4b**, **5b**, and other amines (Supporting Figure S32). The pure 8 + 8 macrocycle can be selectively precipitated from this mixture in low total yield (5%) as protonated amine **5c** in the reaction with sulfuric acid.

Interestingly the **1a** substrate affords only the even-number condensation products such as 6 + 6, 8 + 8, 10 + 10, or 12 + 12 macrocycles (Supporting Figure S32). In contrast, additional odd-number condensation products, such as a 7 + 7 macrocycle, are observed among the products obtained from the Cd(II)-templated condensation of DACP and DFP after refluxing the mixture for 6 days (Supporting Figure S30). This difference suggests that the system is not fully reversible; as a consequence, the odd condensation products are not formed in noticeable amounts in the synthesis based on an even 2 + 2 substrate **1a**. The summary of the template and nontemplate reactions observed in the discussed system is presented in the Supporting Scheme 1.

The macrocyclic imine Cd(II) complexes were unfortunately either present in complicated mixtures or were too insoluble to be well characterized by NMR or XRD. For these reasons we have undertaken the theoretical study of the possible modes of coordination of Cd(II) ions in the discussed large macrocyclic Schiff bases. Density functional theory (DFT) calculations with the dispersion-corrected hybrid B3LYP-D3 functional and double-ζ polarized Gaussian basis set[13] support the templating role of the Cd(II) ions (see Supporting Information for details of computational methodology). The binding energy of the complex of **3a** 4 + 4 imine with four $[CdCl]^+$ units is 434.62 kcal/mol (108.65 kcal/mol per one Cd(II) unit), and the metal is coordinated in a trigonal bipyramid arrangement by three nitrogen atoms and two chloride ions (see Supporting Figure S42). The square-planar arrangement (coordination by three N and one Cl ligands) is found for the large **5a** 8 + 8 complex with eight metal units and a binding energy of 434.28 kcal/mol (54.29 kcal/mol per one metal unit, Supporting Figure S43). Removal of the $[CdCl]^+$ moieties from the complexes results in relaxation of the structures toward the general arrangement found in the solid state for the protonated amines **3c** and **5c** (see Supporting Figures S42 and S43). These results support the templating role of the cadmium ions which, due to the planar coordination of the metal center by three nitrogen atoms, help the growing macrocycle to attain proper conformation. These sets of three nitrogen atoms correspond to loop sections of large macrocycles

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(each consisting of one pyridine ring and two adjacent DACP fragments). The combination of several Cd(II)-organized loops of this type results in formation of large macrocycles such as **5a**. The binding energy is, within the DFT accuracy, the same for the 4 + 4 and 8 + 8 complex, which means that formation of a large 8 + 8 macrocycle does not involve an energetic penalty. However, a binding energy per one metal (and macrocycle) unit diminishes from the 4 + 4 to 8 + 8 system, and this might be among the limiting factors for the Cd(II)-templated macrocycle growth. It should be noted that the actual structures may be more complicated in comparison with the picture presented above due to factors such as solvent influence (including solvent coordination) and the role of protonation.

Spectroscopic Characterization. The successful formation of n + n macrocycles **1**−**5** were confirmed by their ESI MS spectra. Because for a given n + n macrocycle there is a possibility of various isomers differing in the chirality of diaminocyclopentane fragments, additional confirmation of the purity and identity of these compounds was based on NMR data. In all cases of the isolated derivatives discussed here, a single isomer was identified on the basis of NMR spectra (Figure 2, Supporting Figures S1−S27).

The ^{13}C and ^{1}H NMR spectra of 3 + 3 imine macrocycle **2a** are in accord with C_2 symmetry resulting from the heterochiral nature of this macrocycle existing as a mixture of enantiomers with the RRRRSS/SSSSRR chirality at the diaminocyclopentane carbon atoms. For instance, three different azomethine singlets of intensity 2H, a γ-pyridine triplet of intensity 2H coupled to two different β-pyridine doublets of intensity 2H each, and a AB_2 multiplet of intensity 3H originating from the protons of the pyridine ring positioned on the C_2 axis are observed. Similarly 18 signals are observed in the ^{13}C NMR spectrum in agreement with the proposed structure. The NMR spectra of the corresponding protonated amine **2c** are also consistent with the C_2 symmetry and the presence of heterochiral diaminocyclopentane fragments. For instance, six diastereotopic protons of three different methylene bridges are observed in the ^{1}H NMR spectrum of **2c** and a similar number of pyridine signals (Figure 2) as in the case for **2a**. On the other hand, the ^{1}H and ^{13}C NMR spectra of the neutral form of the 3 + 3 amine **2b** at first sight seem to correspond to a compound of higher symmetry due to severe signal overlap. For instance, without the expansion of the spectra two apparent signals of pyridine protons are observed in the ^{1}H NMR spectrum and seven apparent signals are observed in the ^{13}C NMR spectrum (Supporting Figures S3, S4). Closer inspection of these signals reveals, however, that many of them correspond to a set of overlapping peaks corresponding to analogous types of nuclei. The differences of chemical shifts of those analogous positions are much smaller in comparison with those observed for the protonated form of the amine **2c** or for the imine **2a**. For instance signals of the three inequivalent α-pyridine carbon atoms appear at 159.48, 159.41, and 159.35 ppm for **2b**; 153.17, 153.09, and 152.76 ppm for **2c**; and 162.06, 161.86, and 161.28 ppm for **2a**. These small chemical shift differences observed for all positions indicate the more fluxional nature of **2b** in comparison with **2a** or **2c**. For the latter two macrocyclic forms the structure is more rigid and in a given conformation clear differentiation of chemical shifts for analogous positions (arising e.g. from different ring current effect of aromatic pyridine fragments) is observed. For the neutral **2b** most likely multiple conformations are in fast chemical exchange. For this reason the variations of chemical shifts arising e.g. from the various orientations of analogous nuclei with respect to aromatic pyridine rings are averaged and to a large extent canceled. Effectively the NMR signals become much less sensitive to the chirality of the various cyclopentane rings. The overlapped signals of **2b** are somewhat more differentiated at lower temperatures (Supporting Figure S6) due to partial freezing of conformational changes. Partial resolution of ^{1}H NMR signals of **2b** is also observed for DMSO-d_6 solution (Supporting Figure S5).

For the **1b**, **1c**, **4b**, and **4c** macrocycles eight nonexchangeable ^{1}H NMR and seven ^{13}C NMR signals are observed. In the case of **1c** this situation corresponds to a higher effective symmetry than C_i observed in the solid (vide infra) due to conformational changes such as the flip-flop rearrangement of the diamniocyclopentane fragments, and in the case of **4c** it is in accord with the approximate D_{3d} symmetry observed for one of the crystalline forms. Similarly, for the free and protonated form of 4 + 4 amine **3b** and **3c** eight ^{1}H NMR (two pyridine, two diastereotopic methylene, and four cyclopentane) signals and seven ^{13}C NMR signals are observed indicating high effective symmetry. This effective symmetry is D_{2d} which results from fast, on the NMR time scale, averaging of the C_2 conformation observed in the solid state (vide infra) for **3c**, e.g. via the interchange of the pair of parallel pyridine A′ rings with the pair of pyridine rings A″, which are further apart (Supporting Figure 44). This process averages the shifts of four pyridine rings and leads to the averaged effective symmetry with the S_4 axis.

In the case of the **5c** derivative the ^{1}H NMR spectrum is much more complicated. Thus, three γ-pyridine triplets of the intensity 4H, 2H, and 2H, respectively, are observed. The triplet of 4H intensity is COSY correlated (Figure 3) to two different β-

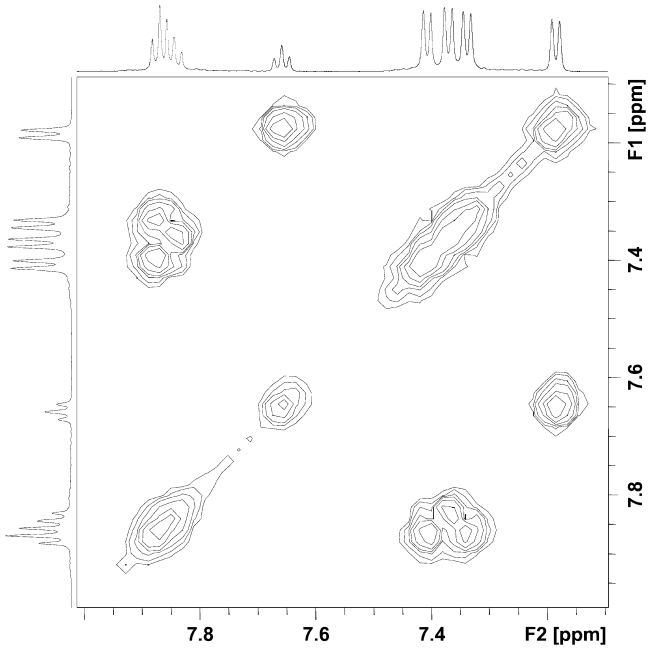

Figure 3. Fragment of the COSY spectrum of **5c**·8SO_4·32H_2O (D_2O) showing three types of pyridine rings.

pyridine doublets of intensity 4H each, while triplets of 2H intensity are each correlated to one β-pyridine doublet of intensity 4H. Similarly, the ^{13}C NMR and HMQC spectra show the presence of three different γ-pyridine carbons and four different β-pyridine carbons (Supporting Figures S20−S22). Thus, the COSY and HMQC spectra indicate the presence of

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two pairs of symmetrical pyridine rings (lying on the effective symmetry axes) and an additional four pyridine rings which are not symmetrical. The HMQC spectrum also reveals the presence of four types of methylene bridges and four types of methine cyclopentane positions (Supporting Figure S19). Out of many possible isomeric 8 + 8 macrocycles differing in the RR or SS chirality at the individual cyclopentane fragments, only the structure presented in Figure 1 corresponds to the above-mentioned situation. In particular, the isolated macrocycle is not of alternating RRSSRRSSRRSSRRSS chirality, analogous to the RRSSRRSSRRSS chirality of **4c**, since in that case analogous simple spectra consisting of eight nonexchangeable ^{1}H NMR and seven ^{13}C NMR signals would be observed. The effective symmetry of **5c** on the NMR time scale is C_{2h}, while the symmetry observed in the solid state (vide infra) is C_i due to folding and distortion of the macrocycle. The higher effective symmetry in solution reflects a dynamic averaging process of the conformation observed in the solid state, e.g. dynamic rearrangement of the positions of the loop sections.

While a clear distinction of the chemical shifts of the analogous types of protons is observed for **5c**, the ^{1}H NMR spectrum of the corresponding neutral form **5b** of this protonated 8 + 8 amine is surprisingly simple; in particular, one apparent doublet and one apparent triplet of the pyridine protons are observed, although these signals are partly resolved at lower temperatures (Supporting Figure S15). Similarly as it was observed for **2b**, the structure of the neutral form has to be more flexible, looser, and less organized. The dynamic rearrangement of various conformations of the macrocycle averages the contributions to the chemical shifts (such as aromatic ring current effects of pyridine fragments) of various conformers in such a way that the chemical shifts for the different types of pyridine rings and various types of cyclopentane rings are becoming practically equal. It should be noted that the ^{1}H NMR spectrum of **5b** obtained by neutralization of **5c** is practically identical to the spectrum of the main component of the crude free 8 + 8 amine from which **5c** was isolated. This may or may not indicate that **5b** was a main component of this crude amine. Because the various inequivalent fragments, such as diaminocyclopentane rings of different chirality of **5b**, cannot be distinguished for the nonprotonated form, it is likely that various inequivalent fragments belonging to different isomeric 8 + 8 macrocyclic amines may also be undistinguishable; i.e., the crude amine may be a mixture of isomeric 8 + 8 macrocycles giving rise to exactly the same ESI MS signals and practically the same, overlapping NMR signals (a similar situation was observed for the 3 + 3 heterochiral amine based on DFP and DACH with an admixture of an analogous homochiral 3 + 3 macrocycle).[6f]

The ESI mass spectra of the discussed macrocycles not only confirm the identity of compounds but also indicate the tendency of the protonated macrocycles to bind anions via hydrogen bonds and/or formation of ion pairs. Anion-bound species are observed both for the protonated derivatives **2c**−**5c** and for the neutral amines **2b**−**5b**. In the studied cases (Supporting Figures S32−S41) the binding of multiple anions is observed, although without clear selectivity as to the number of bound anion guests. For instance, the ESI MS spectrum of giant macrocyclic 8 + 8 amine **5b** recorded in the presence of sodium sulfate indicates signals which correspond to adducts containing from one to five sulfate anions (Supporting Figure S39). In the case of the protonated form **5c** of this macrocycle, an even greater number of bound sulfates was observed. Similarly 6 + 6 macrocycle **4b** in the presence of NaCl forms adducts where the number of chloride anions ranges from one up to nine (Supporting Figure S37).

X-ray Crystal Structures. The molecular structure of the meso-2 + 2 imine **1a** crystallized from chloroform is similar to the structure reported previously by us for a different crystalline form obtained also from chloroform[10] as well as to its cyclohexane counterpart.[9] It corresponds to a rather compressed macrocycle with a characteristic parallel arrangement of the pyridine rings related to a stepped conformation and Z-arrangement of the molecule viewed from a side (Figure 4 and Supporting Figure S45). This type of conformation is typical also for other 2 + 2 Schiff base macrocycles derived from aromatic dicarbonyl compounds and diamines.[14]

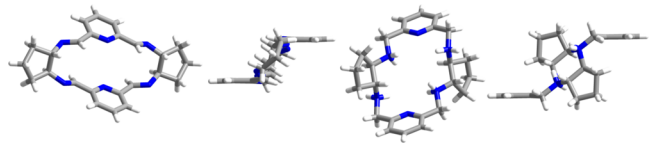

Figure 4. From left to right: top and side views of the 2 + 2 imine **1a** and top and side views of the protonated 2 + 2 amine **1c** (anions and solvent molecules present in **1c**·4Cl·2MeOH crystal omitted).

The molecular structure of the protonated 2 + 2 amine counterpart **1c** also shows a parallel arrangement of the pyridine rings (Figure 4, Supporting Figure S46); the cyclopentane rings, however, are positioned differently. The two cyclopentane fragments are pointing to the opposite sides of the pyridine planes, and the whole molecule is of C_i symmetry in contrast to its imine counterpart **1a** of approximate C_{2h} symmetry. The protonated amine nitrogen atoms are hydrogen bonded to two chloride anions. The chloride anions are too big to be positioned in the center of the macrocycle; instead, they are bound above and below the average plane determined by the four amine nitrogen atoms (Figure 5).

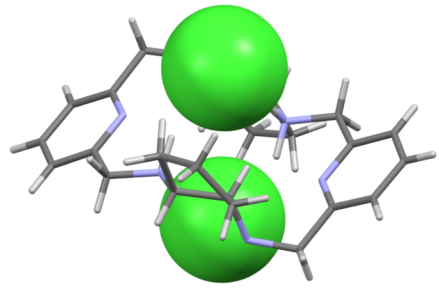

Figure 5. View of the protonated 2 + 2 macrocycle **1c** with two chloride anions bound at the two sides of the macrocycle.

The molecular structure of the heterochiral 3 + 3 protonated amine **2c** bears some resemblance to the more symmetrical 3 + 3 homochiral macrocycle derived from DACH[6i] (Figure 6); for instance, the three pyridine rings are in propeller arrangement. Both macrocycles in their protonated forms bind a chloride anion in the center. The structure of **2c** is, however, more folded, much less regular, and less flat (Figure 6, Supporting Figure S47). On the other hand, the conformation of the macrocycle observed for the neutral homochiral isomer of **2b** is even more folded and less regular.[11]

Crystallization of the isolated 4 + 4 amine hydrochloride (**3c**·8Cl·8H_2O) from a methanol/acetonitrile solution gave two polymorphic forms: monoclinic **3c**·8Cl·9H_2O (with protonated

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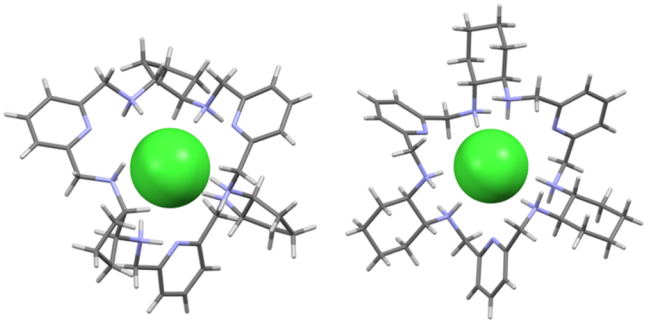

Figure 6. Comparison of the structure of the protonated heterochiral 3 + 3 amine **2c** based on diaminocyclopentane (left) with that of the potonaded 3 + 3 homochiral amine based on diamincyclohexane (right).[6i] The green speheres represent the chloride anions bound in the center of each macrocyle.

amine lying in a special position, on a 2-fold axis) and triclinic **3c**·8Cl·4H_2O (with highly disordered cation in general position). The overall geometry of the protonated amine present in both polymorphs is very similar (Figures 7 and 8). The crystal

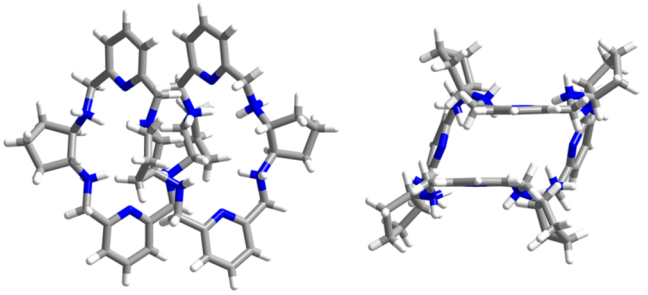

Figure 7. Side and top view of the protonated 4 + 4 amine **3c** (from the monoclinic form **3c**·8Cl·9H_2O, anions and solvent molecules omitted).

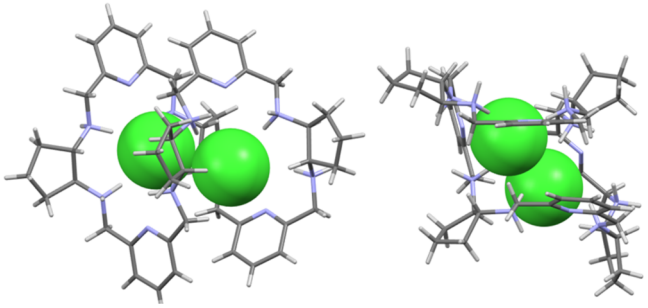

Figure 8. Side and top view of the protonated 4 + 4 amine **3c**, from the triclinic form **3c**·8Cl·4H_2O embracing two chloride anions. Disorder is not shown.

structure of **3c**·8Cl·9H_2O shows a highly compact conformation of **3c** with two chloride anions buried inside a container formed by the folding of a large macrocycle. The extent of the folding is much bigger in comparison with the parent neutral imine macrocycle, which is more flat.[10] The macrocycle **3c** in the monoclinic form is of C_2 symmetry (and of approximate C_2 symmetry in the triclinic form), in contrast to D_{2d} effective symmetry observed in solution. The C_2 symmetry can be viewed as a result of distortion of a more regular D_{2d} structure, which includes the S_4 axis. The top view of the molecule (Figure 7, Supporting Figure S48) corresponds to a parallelogram, while the top view of the ideal D_{2d}-symmetric structure would correspond to a square. The pyridine rings are arranged into two approximately parallel pairs; the distance between the centroids of pyridine rings from the pair is equal to 7.02 Å for one pair, being much larger than the corresponding distance 4.17 Å for the other pair. The nitrogen atoms of all four pyridine rings point to the inside of the container. This protonated macrocycle can be viewed as a cyclic combination of four U-shaped compartments or loops, which are arranged in an alternating up and down orientation. Each of these compartments is built from a pyridine fragment and two adjacent cyclopentane diamine fragments of opposite chirality. In this respect the protonated 4 + 4 meso-type macrocyclic amine is analogous to the recently reported protonated 6 + 6 meso-type macrocyclic amine **4c**, which can be viewed as a cyclic combination of six alternating U-shaped compartments.[10] From a different point of view the conformation of the amine **3c** can also be regarded as a figure-eight type of macrocycle.

The molecular structure of the protonated 4 + 4 amine **3c** present in the triclinic crystalline form **3c**·8Cl·4H_2O is a slightly more distorted version of the structure discussed above. In both forms the protonated macrocycle can be viewed as a kind of container embracing two chloride anions (Figure 8, Supporting Figure S49). Additional chloride anions are bound at the surface of the folded macrocycle, occupying the U-shaped compartments.

The molecular structure of the protonated 8 + 8 macrocyclic amine **5c** shows a very large macrocycle with the main cycle consisting of 72 atoms, including 24 core nitrogen atoms (Figures 9 and 10). The structure of this heterochiral meso-type

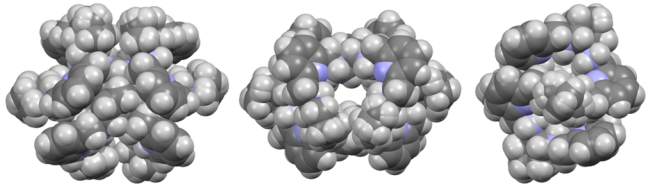

Figure 9. Three perpendicular views of the 8 + 8 macrocyclic amine **5c**·(the disorder, anions, and solvent molecules are omitted for simplicity).

macrocycle contains four diaminocyclopentane fragments of *RR* chirality and four diaminocyclopentane fragments of *SS* chirality. Unlike in the case of **3c** and **4c**,[10] these fragments in **5c** are not arranged in an alternate fashion, and the chirality of the corresponding free macrocycle **5b** presented in Figure 1 can be labeled as *RRRRSSRRSSSSRRSS*. This giant protonated macrocycle is multiply folded and adopts a complicated compact globular shape (Figure 9, Supporting Figure S50) of C_i symmetry (two crystallographically independent cations lie on an inversion center).

To some extent the shape of **5c** can be compared to that of **4c** (Figure 10, Supporting Figure S51). The latter molecule can be viewed as a cyclic combination of six U-shaped compartments or loops, which are arranged in an alternating up and down orientations.[10] **5c** can be also viewed as a combination of six up and down U-shaped compartments. This time the compartments are less symmetrical, four of them ("small" compartments) are built from a pyridine fragment and two adjacent cyclopentane diamine fragments each. There are also two "large" U-compartments constructed of two pyridine and three diaminocyclopentane fragments each (Figure 11).

The protonated 8 + 8 macrocyclic amine **5c** interacts with eight sulfate anions (Figure 12, Supporting Figures S50, S51).

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J. Org. Chem. 2016, 81, 5285−5294

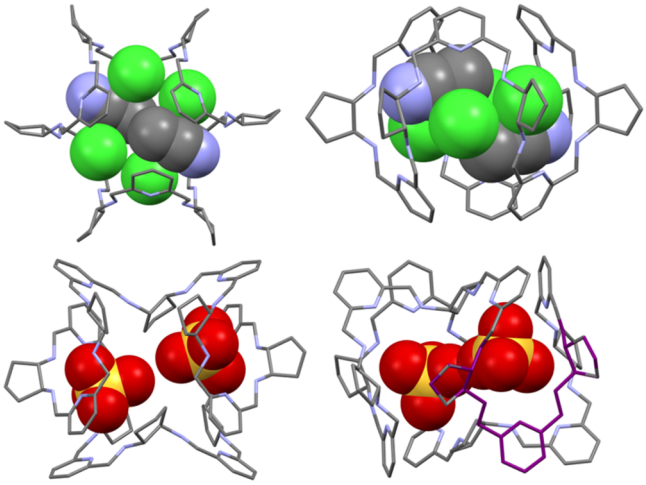

Figure 10. Comparison of the folded structue of **4c** from **4c**·12Cl·2CH_3CN·12H_2O[10] (top) and one of the two crystallographically independent cations **5c** present in the **5c**·8SO_4·31H_2O crystal (bottom). Left views corespond to a bottom-up direction of the alternating U-loops, and right views correspond to a side view of the alternating U-loops. The spacefill representaion indicates the guests inside the containers (four chloride anions and two acetonitrile moclecules in the case of **4c**, and two sulfate anions in the case of **5c**). Hydrogen atoms, disorder, and part of the anions and solvent molecules are omitted for simplicity.

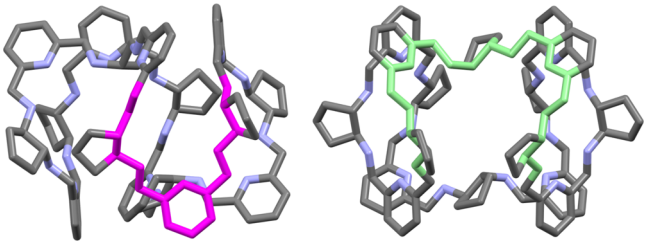

Figure 11. Two "side" views presenting the "small" U-compartment/loop (purple) and "big" U-compartment/loop (green) of one of the two crystallographicaly independent cations **5c**. Hydrogen atoms, disorder, anions, and solvent molecules omitted for simpicity.

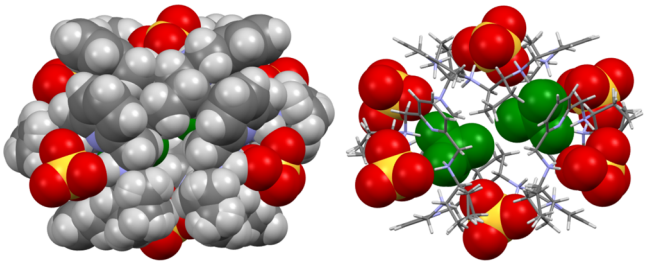

Figure 12. (Left) The spacefill representation of the eight sulfate anions bound by the protonated 8 + 8 macrocyle **5c** in crystal structure of **5c**·8SO_4·31H_2O. (Right) The same view with the macrocyle represented as capped sticks. The two sulfate anions burried inside a container-like molecule are represented in green. Only one of the two symmetry-independent **5c** cations is presented, and dissorder is omitted.

The folded globular conformation of the macrocycle results in formation of a large central empty void, which is occupied by two sulfate anions. Thus, **5c** can be considered as a container-like molecule. The remaining six sulfate anions are bound at the clefts at the surface of the globular molecule. Four of them interact via three hydrogen bonds each with "small" U-loops, while two of them interact via five H-bonds each with "big" U-loops (Figure 12). The outer H-bonded sulfate anions bound in "small" loops are shared by clefts of neighboring symmetry-independent macrocycles.

CONCLUSIONS

By suitable variations of the reaction conditions, various macrocyclic condensation products derived from DACP and DFP, ranging from the 2 + 2 to the 8 + 8 macrocycles, can be obtained in a pure form. The investigated system of imine products seems not to be under full thermodynamic equilibrium. We think that the binding motif corresponding to a Cd(II) ion positioned in a "loop" is key to the formation of large macrocycles based on DACP, and the combination of such loops leads to 6 + 6, 8 + 8, and 10 + 10 macrocyclic Cd(II) complexes. These imine products can be converted to the corresponding giant macrocyclic amines, which exhibit interesting multifolded globular conformations. The protonated forms of these large macrocycles may be regarded as molecular containers embracing multiple anion molecules.

EXPERIMENTAL SECTION

Methods. MS and HRMS data were obtained on a Q-ToF mass spectrometer using positive or negative polarity electrospray ionization mode, (+)ESI or (−)ESI, respectively. The NMR spectra were taken on 500 MHz (^{1}H NMR measurements) and 125 MHz (^{13}C NMR measurements) spectrometers. ^{1}H NMR data are reported as follows: chemical shift in parts per million (δ, ppm) from either residual $CHCl_3$ (7.26 ppm) and DMSO-d_6 (2.49 ppm) or DSS (0 ppm) signals. For ^{13}C NMR data the chemical shifts are reported in ppm from either $CHCl_3$ (77.0 ppm) or DSS (0 ppm). Coupling constants (J) are reported in Hz. Standard abbreviations s, d, t, ABq, and m refer to singlet, doublet, triplet, AB quartet, and multiplet.

Recyclic gel permeation chromatography (GPC) was carried out by application of an HPLC GPC chromatograph equipped with RID and DAD detectors and a preparative GPC column (size 20.0 mm ID × 300 mm L) using chloroform as eluent with a flow rate of 2 mL/min at ambient temperature.

Synthesis. ***3a***·C_6H_6·H_2O, $C_{48}H_{52}N_{12}$·C_6H_6·H_2O. Obtained as described previously.[10] Anal. calcd (found) for $C_{54}H_{60}N_{12}O$: C, 72.62 (72.52); H, 6.77 (6.54); N, 18.82 (18.68).

Racemic trans-1,2-Diaminocyclopentane Dihydrochloride. Prepared according to the literature procedure.[15,16] The free racemic amine *trans*-1,2-diaminocyclopentane has been obtained from this precursor by neutralization with KOH. In a typical procedure 1298 mg (7.499 mmol) of solid *trans*-1,2-diaminocyclopentane dihydrochloride were reacted with an excess of KOH (10 g) in 15 mL of water, and the product was extracted five times with 12 mL of diethyl ether. The organic phase was dried over solid KOH, filtered, and dried to yield 652.1 mg (86.8%) of free amine as an oil, which solidifies in the freezer and whose NMR data are in accord with the literature data.[17]

*Mixture of Imine Macrocycles **1a**, **2a**, **3a** (Nontemplated Synthesis).* The solution of 865.4 mg (5.000 mmol) of racemic *trans*-1,2-diaminocyclopentane dihydrochloride and 1012 mg (10.00 mmol) of trietylamine was combined with the solution of 675.6 mg (5.000 mmol) of 2,6-diformylpyridine in 250 mL of benzene and stirred for 1 h. The mixture was filtered in order to remove triethylamine hydrochloride, concentrated on a rotary evaporator to ca. 100 mL, and filtered again. The filtrate was further concentrated to ca. 60 mL and left to stand in the freezer. The obtained precipitate of **1a** (65.0 mg) was filtered off, washed with 2 mL of cold benzene, and dried under vacuum. The above-mentioned steps of reducing the volume of filtrate, cooling down in the freezer, and filtration were repeated four times (the volume was reduced to ca. 15 mL, 5 mL, 2.5 mL, and finally evaporated to dryness) to yield four fractions of a mixture of **1a**, **2a**, **3a** in a 0.028/1/0.11, 0.027/1/0.252, 0.229/1/0.352, and 3.25/1/2.32 ratio, respectively, as judged by the integration of ^{1}H NMR signals of aforementioned mixtures.

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***2a*·0.667C_6H_6, $C_{36}H_{39}N_9$·0.667C_6H_6.** 226.0 mg of the mixture of **1a**, **2a**, **3a** in a 0.028/1/0.11 molar ratio were suspended in 57 mL of benzene and stirred for 30 min at room temperature; the solid was filtered off, washed with 2 mL of cold benzene, and dried in vacuum. Total yield 102.6 mg (10.3% based on the starting 2,6-diformylpirydyne, recrystallization yield 52.6%). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{36}H_{40}N_9^+$ 598.3401; Found 598.3395. ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 2H, Cγ-pyrC*H*N); 8.12 (s, 2H, Cγ-pyrC*H*N); 8.09 (s, 2H, Cγ-pyrC*H*N); 8.04 (dd, J_1 = 7.7 Hz, J_2 = 1.1 Hz, 2H, β-pyr); 8.02 (dd, J_1 = 7.7 Hz, J_2 = 1.1 Hz, 2H, β-pyr); 7.73 (t, J = 7.7 Hz, 2H, α-pyr); 7.70 (m, 3H, α-pyr and β-pyr);3.88 (m, 4H, NC*H*CH_2 (CP)); 3.75 (m, 4H, NC*H*CH_2 (CP)); 2.20−1.93 (m, 18H, (CP)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1 (Cγ-pyrCHN); 161.9 (Cγ-pyrCHN); 161.3 (Cγ-pyrCHN); 154.0 (γ-pyr); 154.0 (γ-pyr); 153.9 (γ-pyr); 136.8 (α-pyr); 136.7 (α-pyr); 124.9 (β-pyr); 122.0 (β-pyr); 121.8 (β-pyr); 78.0 (NCHCH_2 (CP)); 77.1 (NCHCH_2 (CP)); 76.7 (NCHCH_2 (CP)); 32.7; (CHCH_2CH_2 (CP)); 32.7; (CHCH_2CH_2 (CP)); 22.4 (CH_2CH_2CH_2 (CP)); 22.1 (CH_2CH_2CH_2 (CP)). Anal. calcd (found) for $C_{40}H_{43}N_9$: C, 73.93 (73.70); H, 6.67 (6.95); N, 19.40 (19.13).

2b*·1.25H_2O, $C_{36}H_{51}N_9$·1.25H_2O. *Method A. 96.0 mg (0.148 mmol) of **2a**·0.667·C_6H_6 were added gradually to the solution of 400 mg of $NaBH_4$ in 20 mL of methanol, and the mixture was stirred overnight and evaporated to dryness. The residue was combined with 5 mL of 2 M water solution of NaOH and extracted three times with 3 mL of chloroform. The combined organic fractions were dried over sodium sulfate and filtered, and the solvent was evaporated to give 89.0 mg (95%) of amine **2b**. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{36}H_{52}N_9^+$ 610.4340; Found 610.4331. ^{1}H NMR ($CDCl_3$) δ 7.55 (t, J = 7.6 Hz, 1H, α-pyr); 7.54 (t, J = 7.6 Hz, 2H, α-pyr); 7.11 (d, J = 7.6 Hz, 6H, β-pyr); 3.93−3.74 (m, 12H, Cγ-pyrCH_2NH); 2.79 (m, NHC*H*CH_2, 4H (CP)); 2.74 (m, NHC*H*CH_2, 2H (CP)); 2.41 (s (broad), 6H, N*H*); 1.91 (m, 6H, (CP)); 1.63 (m, 6H, (CP)), 1.36 (m, 6H, (CP)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (γ-pyr); 159.4 (γ-pyr); 159.4 (γ-pyr); 136.7 (α-pyr); 120.6 (β-pyr); 120.5 (β-pyr); 120.5 (β-pyr); 64.8 (NHC*H*CH_2 (CP)); 53.5 (Cγ-pyrCH_2NH); 53.4 (Cγ-pyrCH_2NH); 53.4 (Cγ-pyrCH_2NH); 31.4 CHCH_2CH_2 (CP)); 31.3 CHCH_2CH_2 (CP)); 31.3 CHCH_2CH_2 (CP)); 21.8 (CH_2CH_2CH_2 (CP)); 21.6 (CH_2CH_2CH_2 (CP)). Anal. calcd (found) for $C_{36}H_{53.5}N_9O_{1.25}$: C, 68.38 (68.40); H, 8.53 (8.82); N, 19.93 (19.70).

Method B. The solution containing 1.752 g (10.12 mmol) of racemic *trans*-1,2-diaminocyclopentane dihydrochloride and 2.048 g (20.24 mmol) of triethylamine in 10 mL of methanol was combined with the solution of 1.367 g (10.12 mmol) of 2,6-diformylpyridine in 500 mL of benzene. After 1 h of stirring the mixture at room temperature, the precipitated triethylamine hydrochloride was filtered off (0.968 g) and the solution was concentrated to the volume of ca. 200 mL and filtered again to remove the remaining hydrochloride salt (1.949 g) contaminated with the **1a** macrocycle (molar ratio of NEt_3·HCl/**1a** = 1/0.025). The volume of the filtrate was reduced on a rotary evaporator to 100 mL, and the flask was allowed to stand in a freezer overnight. The precipitate (86 mg) of a mixture of **1a**/**2a**/**3a** macrocycles (with molar ratio of 1/0.071/0.059) was filtered off and discarded. The above-mentioned steps of reducing the volume of filtrate, cooling down in the freezer, and filtration were repeated twice (the volume was reduced to ca. 50 and 10 mL) to yield two fractions of mixtures of **1a**/**2a**/**3a** macrocycles in a 0.082/1/0.391 (1.168 g), 0.389/1/0.501 (0.394 g) molar ratio, respectively.

The suspension of a 641 mg fraction of macrocycles **1a**/**2a**/**3a** (molar ratio of 0.082/1/0.391) in 300 mL of benzene was added dropwise to the solution of 1200 mg of sodium borohydride in 300 mL of methanol. After 6 h of stirring at rt, the mixture was evaporated to dryness and 20 mL of 2 M aqueous NaOH solution were added. The residue was extracted three times with 20 mL of chloroform. The organic fractions were dried over anhydrous sodium sulfate and evaporated to dryness to give 653 mg of crude mixture of amine products. This mixture was separated by GPC chromatography using chloroform as eluent to give 238.8 mg (20.3%) of **2b** and 122.6 mg (10.7%) of **3b** macrocyclic amines.

Method C. The solution of 652.1 mg (6.511 mmol) of racemic *trans*-1,2-diaminocyclopentane in 32 mL of methanol was combined with a solution of 879.7 mg (6.511 mmol) of 2,6-diformylpyridine in 32 mL of chloroform, and the mixture was stirred for 1 h. The mixture was diluted with 878 mL of chloroform and 814 mL of methanol, and 3.580 g (19.53 mmol) of solid $CdCl_2$ was added. Stirring was continued for 24 h, and the obtained crude cadmium complex of **2a** was filtered and dried (3.440 g). This product was suspended in 350 mL of methanol, and an excess (4.89 g) of solid sodium borohydride was added in portions with stirring at room temperature. After 12 h of stirring the formed metallic cadmium was filtered off. The filtrate evaporated to dryness, and 130 mL of 4 M NaOH solution added; after 18 h of stirring the formed cadmium hydroxide was filtered off, and the filtrate was extracted three times with 50 mL of chloroform The organic fractions were dried over sodium sulfate and filtered, and the solvent was evaporated to give 1171 mg (85.3%) of crude amine **2b**.

***2c*·6Cl·6H_2O, $C_{36}H_{51}N_9$·6HCl·6H_2O.** 90 μL (1.1 mmol) of 12 M HCl solution were added to the solution of 97.0 mg (0.159 mmol) of amine **2b** in 2 mL of methanol. The protonated amine was precipitated by the addition of 10 mL of acetonitrile, filtered, and dried under vacuum. Yield 140.0 mg (94%). ^{1}H NMR (D_2O) δ 7.99 (t, J = 7.8 Hz, 1H, α-pyr); 7.98 (t, J = 7.8 Hz, 2H, α-pyr); 7.51 (d, J = 7.8 Hz, 4H, β-pyr); 7.48 (d, J = 7.8 Hz, 2H, β-pyr); 4.67−4.38 (m, 12H, Cγ-pyrCH_2NH); 4.39 (m, 4H NHC*H*CH_2 (CP)); 4.10 (m, 2H, NHC*H*CH_2 (CP)); 2.46 (m, 6H, (CP)); 2.13−1.72 (m, 11H, (CP)), 1.72 (m, 1H, (CP)); ^{13}C NMR (125 MHz, D_2O): δ 153.2 (γ-pyr); 153.1 (γ-pyr); 152.8 (γ-pyr); 142.6 (α-pyr); 142.3 (α-pyr); 126.1 (β-pyr); 125.5 (β-pyr); 64.3 (NHCHCH_2 (CP)); 63.9 (NHCHCH_2 (CP)); 63.7 (NHC*H*CH_2 (CP)); 52.8 (Cγ-pyrCH_2NH); 52.4 (Cγ-pyrCH_2NH); 51.2 (Cγ-pyrCH_2NH); 30.8 (CHCH_2CH_2 (CP)); 30.7 (CHCH_2CH_2 (CP)); 30.6 (CHCH_2CH_2 (CP)); 24.7 (CH_2CH_2CH_2 (CP)); 24.4 (CH_2CH_2CH_2 (CP)). Anal. calcd (found) for $C_{36}H_{69}N_9Cl_6O_6$: C, 46.16 (46.08); H, 7.42 (7.38); N, 13.46 (13.68).

***3b*·0.75H_2O, $C_{48}H_{68}N_{12}$·0.75H_2O.** Obtained in the same synthesis as **2b** in method B using GPC chromatography. The mixture of 641 mg of **1a**/**2a**/**3a** obtained from a benzene solution (0.082/1/0.391 molar ratio) was used as a substrate for sodium borohydride reduction. Total yield 122.6 mg (10.7%).

An additional 238.8 mg (20.8%) of **3b** was acquired in the same way from 0.394 mg of the second fraction of the mixture **1a**/**2a**/**3a** (0.398/1/0.501 molar ratio).

HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{48}H_{69}N_{12}^+$ 813.5763; Found 813.5733; $[M + Na]^+$ Calcd for $C_{48}H_{68}N_{12}Na^+$ 835.5582; Found 835.5572. ^{1}H NMR ($CDCl_3$) δ 7.53 (t, J = 7.7 Hz, 4H, α-pyr); 7.13 (d, J = 7.7 Hz, 8H, β-pyr); 3.89, 3.80 (ABq, J_{AB} = 14.1 Hz, 16H, Cγ-pyrCH_2NH); 2.82 (m, 8H, NHC*H*CH_2 (CP)); 2.19 (s (broad), 8H, N*H*); 1.93 (m, 8H, (CP)); 1.63 (m, 8H, (CP)), 1.36 (m, 8H, (CP)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (γ-pyr); 136.7 (α-pyr); 120.4 (β-pyr); 64.9 (NHC*H*CH_2 (CP)); 53.7 (Cγ-pyrCH_2NH); 31.4 CHCH_2CH_2 (CP)); 21.7 (CH_2CH_2CH_2 (CP)). Anal. calcd (found) for $C_{48}H_{69.5}N_{12}O_{0.75}$: C, 69.74 (69.94); H, 8.47 (8.84); N, 20.33 (20.03).

***3c*·8Cl·8H_2O, $C_{48}H_{69}N_{12}$·8HCl·8H_2O.** 1190 μL (2.38 mmol) of 2 M HCl solution were added to the solution of 120 mg (0.148 mmol) of amine **3b** in 2 mL of methanol. The mixture was evaporated to dryness and redissolved in 2 mL of methanol, and the white protonated amine was precipitated by the addition of 8 mL of acetonitrile, filtered, and dried under vacuum. Yield 104 mg (56.3%). ^{1}H NMR (D_2O) δ 7.91 (t, J = 7.8 Hz, 4H, α-pyr); 7.38 (d, J = 7.8 Hz, 8H, β-pyr); 4.57, 4.32 (ABq, J_{AB} = 15.2 Hz, 16H, Cγ-pyrCH_2NH); 4.32−4.31 (m, 8H, NHC*H*CH_2 (CP)); 2.41 (m, 8H, (CP)); 2.01 (m, 8H, (CP)), 1.94 (m, 8H, (CP)); ^{13}C NMR (125 MHz, D_2O): δ 152.9 (γ-pyr); 142.0 (α-pyr); 124.8 (β-pyr); 64.8 (NHCHCH_2 (CP)); 52.7 (Cγ-pyrCH_2NH); 30.6 (CHCH_2CH_2 (CP)); 24.8 (CH_2CH_2CH_2 (CP)). Anal. calcd (found) for $C_{48}H_{92}N_{12}Cl_8O_8$: C, 46.16 (46.30); H, 7.42 (7.48); N, 13.46 (13.75).

*Crude Mixture of Amine Macrocycles **4b**, **5b** (Cd(II)-Templated Synthesis).* 1925 mg (10.50 mmol) of anhydrous $CdCl_2$ were added to the suspension of 728.9 mg (1.75 mmol) of 2 + 2 imine **1a**·H_2O in 940 mL of a methanol/chloroform mixture 1:1 v/v, and the mixture was stirred at room temperature for 24 h. The crude precipitate of the cadmium(II) complex of 6 + 6 imine **4a** was filtered off, and an excess of $NaBH_4$ (1.58 g) was added in portions with stirring to the filtrate. After 20 h of stirring at room temperature the mixture was evaporated to

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J. Org. Chem. 2016, 81, 5285−5294

dryness to give a reddish solid. This residue was dissolved in 25 mL of 10% sulfuric acid, and the obtained solution was stirred for 3 h; then, 4 g of solid NaOH were added carefully in small portions to the mixture cooled in a water bath to avoid overheating. The mixture was stirred for 3 h and extracted three times with 25 mL of chloroform. The organic fractions were dried over sodium sulfate and filtered, and the solvent was evaporated to give 513 mg of a crude mixture containing the macrocyclic 6 + 6, 8 + 8, and 10 + 10 amines **4b**, **5b**, and **6b**.

***5c*·8SO_4·32H_2O, $C_{96}H_{136}N_{24}$·8H_2SO_4·32H_2O.** 3.0 mL (5.4 mmol) of 10% sulfuric acid were added dropwise to the solution of 513 mg of a crude mixture of **4b**, **5b**, and **6b** in 10 mL of methanol. The mixture was allowed to stand for 2 days, and the formed crystalline precipitate was collected, washed with 1 mL of methanol, and dried under vacuum. Yield 70.3 mg (5.4%). ^{1}H NMR (D_2O) δ 7.87 (t, J = 7.8 Hz, 4H, α-pyr); 7.84 (t, J = 7.8 Hz, 2H, α-pyr); 7.65 (t, J = 8.0 Hz, 2H, α-pyr); 7.41 (d, J = 7.8 Hz, 4H, β-pyr); 7.37 (d, J = 7.8 Hz, 4H, β-pyr) 7.34 (d, J = 8.0 Hz, 4H, β-pyr) 7.18 (d, J = 7.8 Hz, 4H, β-pyr); 4.53−4.30 (m, 32H, Cγ-pyrCH_2NH); 4.18 (m, 12H NHCHCH$_2$ (CP)); 4.12 (m, 4H NHCHCH$_2$ (CP)); 2.37 (m, 8H, (CP));)); 2.26 (m, 8H, (CP)); 2.03−1.73 (m, 32H, (CP)); ^{13}C NMR (125 MHz, D_2O): δ 153.4 (γ-pyr); 153.2 (γ-pyr); 153.1 (γ-pyr); 153.0 (γ-pyr); 141.7 (α-pyr); 141.6 (α-pyr); 141.4 (α-pyr); 124.7 (β-pyr); 124.7 (β-pyr); 124.7 (β-pyr); 124.2 (β-pyr); 64.2 (NHCHCH$_2$ (CP)); 64.0 (NHCHCH$_2$ (CP)); 63.8 (NHCHCH$_2$ (CP)); 63.7 (NHCHCH$_2$ (CP)); 52.3 (Cγ-pyrCH$_2$NH); 52.2 (Cγ-pyrCH$_2$NH); 52.1 (Cγ-pyrCH$_2$NH); 51.6 (Cγ-pyrCH$_2$NH); 30.9 (CHCH$_2$CH$_2$ (CP)); 30.8 (CHCH$_2$CH$_2$ (CP)); 30.7 (CHCH$_2$CH$_2$ (CP)); 30.7 (CHCH$_2$CH$_2$ (CP)); 24.8 (CH$_2$CH$_2$CH$_2$ (CP)); 24.7 (CH$_2$CH$_2$CH$_2$ (CP)). Anal. calcd (found) for $C_{96}H_{216}N_{24}S_8O_{64}$: C, 38.60 (38.33); H, 7.29 (6.98); N, 11.25 (11.00).

***5b*·0.75H_2O, $C_{96}H_{136}N_{24}$·0.75H_2O.** 20.0 mg (6.69×10^{-3} mmol) of the protonated form **5c**·8SO_4·32H_2O were treated with 1 mL (2 mmol) of 2 M NaOH solution and extracted three times with 1 mL of chloroform. The combined organic phase was passed through a short column filled with anhydrous sodium sulfate and evaporated to dryness to give 13 mg (95.6%) of free 8 + 8 amine. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{96}H_{136}N_{24}Na^+$ 1648.1272; Found 1648.1265; [M + 2H]$^{2+}$ Calcd for $C_{96}H_{138}N_{24}^{2+}$ 813.5763; Found 813.5745; [M + NaH]$^{2+}$ Calcd for $C_{96}H_{137}N_{24}Na^{2+}$ 824.5672; Found 824.5654; [M + 2H]$^{2+}$ Calcd for $C_{96}H_{136}N_{24}Na_2^{2+}$ 835.5582; Found 835.5577. ^{1}H NMR ($CDCl_3$) δ 7.54 (t, J = 7.7 Hz, 8H, α-pyr); 7.16 (d, J = 7.7 Hz, 16H, β-pyr); 3.92−3.82 (m, 32H, Cγ-pyrCH_2NH); 2.84 (m, 16H, NHCHCH$_2$ (CP)); 2.16 (s (broad), 16H, NH); 1.94 (m, 16H, (CP)); 1.63 (m, 16H, (CP)), 1.35 (m, 16H, (CP)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (γ-pyr); 136.8 (α-pyr); 120.4 (β-pyr); 65.1 (NHCHCH$_2$ (CP)); 65.0 (NHCHCH$_2$ (CP)); 53.8 (Cγ-pyrCH$_2$NH); 31.4 CHCH$_2$CH$_2$ (CP)); 21.6 (CH$_2$CH$_2$CH$_2$ (CP). Anal. calcd (found) for $C_{96}H_{137.5}N_{24}O_{0.75}$: C, 70.32 (70.70); H, 8.45 (8.27); N, 20.50 (20.11).

Crystallographic Studies. Crystals of **1a** were grown from $CHCl_3$, **1c**·4Cl·2MeOH, **2c**·6Cl·9.2H_2O, **3c**·8Cl·9H_2O, and **3c′**·8Cl·4H_2O from the mixture MeOH/CH_3CN and **5c**·8SO_4·31H_2O from MeOH, respectively.

The crystallographic measurements were performed at 80(2)−100(2) K on a κ-geometry four-circle diffractometer with graphite-monochromatized Mo Kα radiation (see details in Supporting Table S1). Data were corrected for Lorentz and polarization effects. Data collection, cell refinement, data reduction, and analysis were carried out with *CrysAlis PRO* or *CrysAlis CCD* and *CrysAlis RED*, respectively.[18] Analytical or empirical (multiscan) absorption correction was applied to the data with the use of *CrysAlis RED*.

Structures were solved by direct methods using the SHELXL-97[19] program and refined on F^2 by a full-matrix least-squares technique using SHELXL-2014[20] with anisotropic thermal parameters for the ordered and fully occupied non-H atoms.

All H atoms in **1a**, **1c**·4Cl·2MeOH, **2c**·6Cl·9.2H_2O, and **3c′**·8Cl·4H_2O were found in difference Fourier maps and initially were refined freely. Those in **3c**·8Cl·9H_2O and **5c**·8SO_4·31H_2O were included from geometry. In the final refinement cycles, all C- and N-bound H atoms were refined using a riding model, with C−H = 0.95−1.00 Å, N−H = 0.91 Å, and with U_{iso}(H) = 1.2U_{eq}(C,N) for CH, CH$_2$, NH$_2$ or U_{iso}(H) = 1.5U_{eq}(C) for CH$_3$. Water H atoms in **2c**·6Cl·9.2H_2O and **3c**·8Cl·9H_2O were refined with O−H and H···H distances restrained to 0.840(2) and 1.380(2) Å, respectively, and with U_{iso}(H) = 1.5U_{eq}(O), and then they were constrained to ride on their parent atoms (AFIX 3 instruction in SHELXL-2014[20]). However, most of the positions of water molecules are partially occupied, their O atoms were refined with (an)isotropic thermal parameters, and their H atoms were not found in the Fourier maps (see details in CIFs and Figures S47−S50). The finally accepted formulas are as given in Table S1, but the amount of solvent molecules should be treated as a rough approximation. Some of the chloride anions in **2c**·6Cl·9.2H_2O, **3c**·8Cl·9H_2O, and **3c′**·8Cl·4H_2O, and sulfate anions in **5c**·8SO_4·31H_2O are disordered and were refined with iso- or anisotropic thermal parameters in two (or more) positions each, with details given in CIF files.

Macrocyclic cations in **1c**·4Cl·2MeOH and **3c**·8Cl·9H_2O lie in special positions: on an inversion center (**1c**) or a 2-fold axis (**3c**). In the crystal of **5c**·8SO_4·31H_2O, there are two crystallographically independent macrocyclic cations (**A** and **B**), both lying on an inversion center.

About a half of the cation in **3c′**·8Cl·4H_2O was found to be disordered and was refined isotropically (except for N atoms with higher s.o.f., which were refined anisotropically) in two positions with s.o.f. = 0.642(7) and 0.358(7). In **5c**·8SO_4·31H_2O, both of the macrocyclic cations are disordered. Cation *A* was refined with three from four of the cyclopentane rings partially disordered into two sites with s.o.fs. = 0.504(16)/0.496(16), 0.81(2)/0.19(2) and 0.699(18)/0.301(18), respectively (see Supporting Figure S50b). Cation *B* was modeled as fully disordered about the inversion center and thus was refined in two sites with s.o.f. = 0.5 each (see Supporting Figure S50c). Four from eight sulfates in **5c**·8SO_4·31H_2O are disordered and were refined in two (anions containing S2, S5, S7) or three (S8) positions, with s.o.fs. = 0.721(4)/0.279(4), 0.839(6)/0.161(6), 0.638(13)/0.362(13) and 0.385(5)/0.334(5)/0.280(4), respectively.

Some geometrical restraints (SAME instruction in SHELXL-2014[20]), restraints on anisotropic displacement parameters (SIMU), and constraints on the fractional coordinates and anisotropic displacement parameters (EXYZ and EADP instructions) were applied in the refinement procedures if appropriate. Some of the chloride anions and water molecules were refined with the linear restraint applied to some of the free variables (the sum of site occupation factors restrained with the SUMP instruction). Some of the water molecules in **5c**·8SO_4·31H_2O were refined with s.o.f. = 0.5 or 0.25.

Figures presenting the molecular structures were made using the DIAMOND and Mercury programs.[21] Details of structure refinements are given in Table S1, and the crystallographic information files (CIFs) are deposited at the Cambridge Crystallographic Data Centre (CCDC Nos. 1452081−1452086) and provided as ESI.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00531.

Figures S1−S51 (NMR and ESI MS spectra, views of molecular structures), Scheme S1, Table S1, details of computational study, Cartesian coordinates of optimized structures (PDF)

X-ray crystallographic information (CIF)

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Notes

The authors declare no competing financial interest.

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J. Org. Chem. 2016, 81, 5285−5294

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