Selective Host Amplification from a Dynamic Combinatorial Library of Oligoimines for the Syntheses of Different Optically Active Polyazamacrocycles

Almudena González-Álvarez,[a] Ignacio Alfonso,[a] Fernando López-Ortiz,*[b] Ángel Aguirre,[c] Santiago García-Granda,[c] and Vicente Gotor*[a]

Keywords: Dynamic combinatorial library / Macrocycles / Molecular diversity / NMR spectroscopy / Template synthesis

Two different macrocyclic hosts are amplified and expressed by metal guests from the same dynamic combinatorial library (DCL) of oligoimines. We studied the thermodynamic template effect and the structure of the final compounds by a combination of ESI-MS, UV and NMR spectroscopy, and X-ray crystallography techniques. The use of Ba^{II} or Cd^{II} metal salts allows the selective synthesis of dimeric [2+2] or trimeric [3+3] cyclic structures, respectively. We observed a cooperative molding effect for the Cd ion-templated process. A study of the DCL behavior in situ demonstrated a second level of molecular diversity, based on the imine/α-methoxyamine equilibrium. This process is probably promoted by metal ion coordination and shows an interesting diastereoselectivity in the formation of the new chiral centers. Semiempirical (PM3) theoretical calculations also support these experimental observations. Reduction of the imine bonds allows the selective preparation and isolation of each macrocyclic polyamine on a synthetic scale and in a one-pot procedure.

Introduction

Dynamic combinatorial chemistry (DCC) is becoming a useful tool for the discovery and isolation of new host and guest compounds.[1] A dynamic combinatorial library (DCL) of compounds is a mixture of building blocks connected through reversible bonds that are able of undergoing exchange under thermodynamic control.[2] Addition of the guest changes the equilibrium mixture towards its best host. Final quenching of the exchange process allows the identification of the selected host and it also can be used for its expression, amplification, and isolation.[3] This molecular evolution concept has been proposed as a new method for screening[4] and discovering[5] drugs, but there are few examples of synthetic applications.[3,6] Transimination[5a−5c,7] and metal coordination processes,[7a,8] among others,[3,6,9] have been used previously to generate DCLs.

On the other hand, very recently, a simple non-templated [3+3] cyclocondensation between enantiopure *trans*-cyclohexane-1,2-diamine and aromatic dialdehydes was reported.[10] These results were explained in terms of the conformational requirements of both the cyclohexane and aromatic moieties of the diimine.[10a] Actually, [3+3] products were isolated for the 1,4-disubstituted aromatic moiety, while some amounts of the [2+2] cyclic oligomers were readily observed for some of the 1,3-dialdehyde derivatives.[10b] The effect of the diimine conformation on the macrocyclization has been established recently for phenolic dialdehydes in which an intramolecular hydrogen bond stabilizes the *s-trans* conformation of the diimine moiety.[11] Intriguingly, when the aromatic ring is a pyridine unit, the [2+2] cyclic oligoimine was obtained in moderate to low yields.[12] This result can be explained by considering the different conformational requirements of pyridylimine compounds.[13] Here we report the molecular amplification of two receptors from this DCL of macrocyclic imines, by templating with different metal salts. The equilibrium mixture can be frozen by simple in situ reduction of the C=N bonds, which in this case leads to different optically active macrocyclic polyamine receptors in a one-pot methodology and from the same initial DCL.

[a] Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo,
Julián Clavería 8, 33071 Oviedo, Spain
Fax: (internat.) + 34-(0)985103448
E-mail: vgs@sauron.quimica.uniovi.es
[b] Area de Química Orgánica, Universidad de Almería,
Carretera de Sacramento s/n, 04120-Almería, Spain
Fax: (internat.) + 34-(0)950-015481
E-mail: flortiz@ual.es
[c] Departamento de Química Física y Analítica, Universidad de Oviedo,
Julián Clavería 8, 33071 Oviedo, Spain
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Results and Discussion

1. Generation of the Library

Based on pyridylimine's conformational preferences and preliminary theoretical calculations, we envisioned that the introduction of a pyridine ring in the dialdehyde would allow us to build a true DCL of oligoimines. This concept is, in fact, what the ESI-MS spectrum[14] (Figure 1) of an equimolecular mixture of (*R*,*R*)-cyclohexane-1,2-diamine (**1**) and pyridine-2,6-dicarboxaldehyde (**2**) in methanol indicates (Scheme 1). Imine formation takes place after a few minutes of mixing reactants, as evidenced in the ^{1}H NMR spectrum by the rapid disappearance of the aldehyde HC=O signal (δ = 10.04 ppm) and the appearance of an imine HC=N signal (δ = 8.33 ppm). Acquisition of ^{1}H NMR spectra after several hours, to ensure that equilibrium is reached, showed broad signals. This dynamic process can be due to a combination of conformational equilibria, imine *cis*−*trans* configurational mixtures, or an interconversion between differently sized oligomeric imines, ranging from the cyclic [2+2] to [6+6] products (Scheme 1, Figure 1).

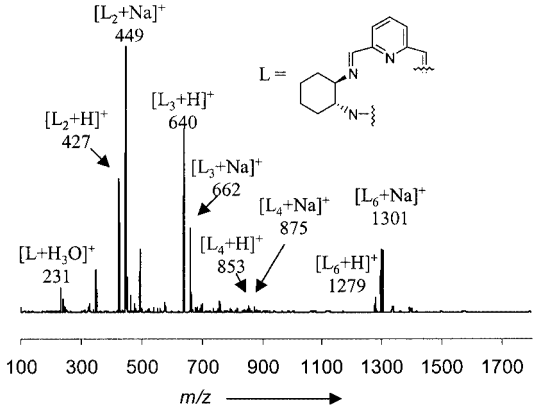
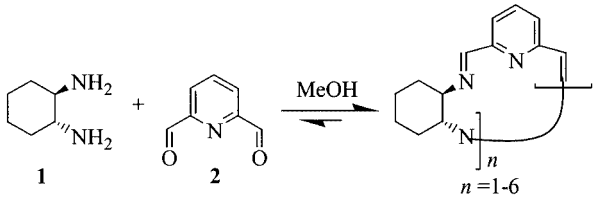


Figure 1. ESI-MS spectrum of the DCL of oligoimines



Scheme 1. Generation of the DCL of oligoimines

Surprisingly, during the preparation of this manuscript, a paper came out where the authors claimed that the same reaction in refluxing dichloromethane yielded exclusively the [3+3] cyclic imine in high yield.[15] In our hands, this procedure always led to a similar mixture to the one obtained in MeOH at room temperature, as shown by the ESI-MS spectrum of the crude product (Figure 1 and Figure S1 in the Supporting Information; for Supporting Information see the footnote on the first page of this article). Heating this DCL of oligoimines under reflux in different solvents (CH_2Cl_2, EtOAc, THF, toluene) for several hours did not shift the equilibrium to a unique cyclic product. An increase in the signal corresponding to the cyclic trimer was observed, however, in the ESI-MS spectrum after careful recrystallization from EtOAc (Figure S2). We must point out that heating and cooling processes in different solvents can change the product distribution because of the dynamic nature of the system. For this reason, we truly believe that the results reported are a consequence of a post-processing procedure. These manipulations would drive the equilibrium to a given compound in the solid state, with the DCL-mixture remaining in solution (see Supporting Information).

On the other hand, as previously stated, this dynamic library can be frozen by reduction of the imine bonds in situ. To stop the dynamic process, which would lead to misleading interpretation of the results, we decided to carry out borohydride reduction of the DCL. In both cases (condensation carried out in CH_2Cl_2 or in MeOH) this reduction yielded a mixture of at least dimeric and trimeric cyclic oligoamines as the major products (detected by ESI-MS spectrometry).[16]

2. Selection and Amplification of the Members of the DCL

Because of the potential recognition properties of both the pyridine and imine functional groups, we screened this DCL for its cation complexation ability (Table 1). The compound obtained clearly depends on the added cation. For instance, addition of Ba^{II} led to the [2+2] cyclic imine **3**, whereas addition of Cd^{II} resulted in almost-quantitative formation of the cyclic [3+3] derivative **4** (Figure 2). Other cations [Cs^+, Ni^{2+}, Zn^{2+}, Pb^{4+}, NBu_4^+] yielded mixtures having different product distributions. These results can be clearly checked by means of the ESI-MS spectra of the reduced compounds **5** and **6** (Table 1, Figure 2).

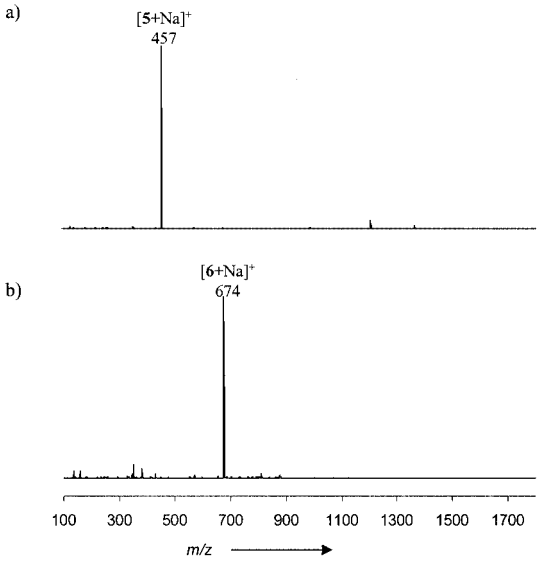


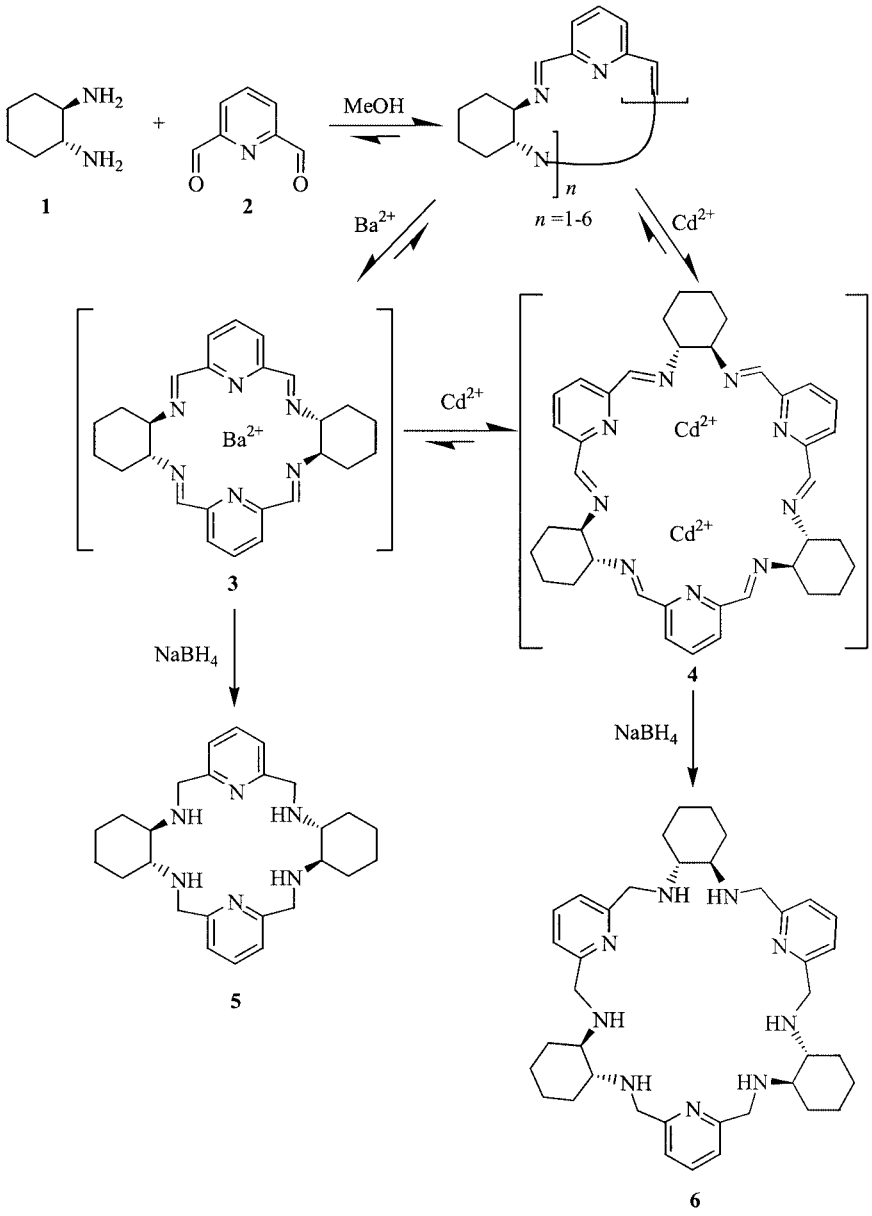
Figure 2. ESI-MS spectra of the macrocyclic polyamine obtained in the presence of (a) Ba and (b) Cd salts

Table 1. Proportions of macrocyclic polyamines obtained using different templates (estimated from peak intensities of the ESI-MS spectra)

	Ionic radii (pm)	Dimer **5** (%)	Trimer **6** (%)
No metal	–	36	64
Ni^{II}	78	53	47
Zn^{II}	83	27	73
Pb^{IV}	84	67	33
Cd^{II}	103	–	100
Ba^{II}	136	100	–
Cs^{I}	170	23	77
NBu_4^+	–	20	80

The formation of cyclic **3** in the presence of Ba^{II} salts has been described previously as a simple kinetic template effect. Our results, however, are identical when performing the condensation between **1** and **2** in the presence of the metal salt or by pre-forming the DCL of imines and subsequent addition of the metal template, which shifts the equilibrium towards the preferred host. Moreover, addition of an excess of Cd^{II} salt to the cyclodimer [**3**·Ba^{II}] complex and reduction led to the unique formation of the [3+3] product **6** (Scheme 2). Therefore, we conclude that this system is a real DCL under thermodynamic control.

By comparing the results obtained using different cations (Table 1), we observe that there is no clear correlation between the ionic radii of the cation and the size of the cyclic oligoimine. Noteworthy examples are the cases of Ba^{II} and Cd^{II}, where the smallest cation templates the largest receptor. An explanation for this behavior might be the formation of dinuclear complexes with the Cd^{II} ion



Scheme 2. Effect of metal templates on the DCL of oligoimines. Synthesis of macrocyclic polyamines **5** and **6**

(Scheme 2).[17] Different independent experiments were performed to test this hypothesis. First of all, an ESI-MS spectrum of **6** was obtained in the presence of an excess of $CdCl_2$ and showed a peak at $m/z = 982$ corresponding to the $[\mathbf{6}\cdot Cd_2Cl_3]^+$ species (by full analysis of the isotopic pattern, see Figure S4), which suggests that two metal ions can fit inside this macrocyclic cavity.

On the other hand, we performed UV titration experiments of the imines' DCL in the presence of increasing amounts of Cd^{II}. The UV spectra are shown in Figure 3. Absorbance at 227 nm decreased upon addition of Cd and a new band at 210 nm clearly appeared. The transition in the UV spectra was observed at a 1:2 molar ratio of cyclic **4** to Cd^{II}.[18] Again, this observation supports the formation of a dimetallic complex of **4** with Cd ions. Unfortunately, all our attempts to obtain crystals of the trimeric imine complexed with Cd for X-ray structural analysis were unsuccessful.

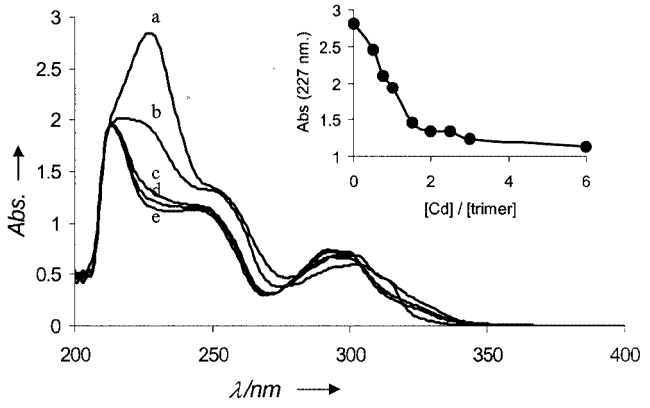


Figure 3. UV spectra of a mixture of **1** and **2** (1.2×10^{-4} M each) with (a) no metal and in the presence of increasing amounts of Cd^{II} with respect to the trimer (**4**:Cd molar ratios of (b) 1:1; (c) 1:2; (d) 1:3; (e) 1:6). Inset: UV titration of the **1** + **2** mixture with $Cd(ClO_4)_2$ for the determination of the stoichiometry (mole ratio method)

3. In Situ Analysis of the Behavior of the DCL

We used NMR spectroscopy to obtain greater structural information about the evolution of our DCL in the presence of the metal templates (Figure 4). Addition of a Ba^{II} salt to the imines' DCL showed a compound having an effective D_2 symmetry in the NMR spectroscopic time scale with a rigid structure, as suggested by the multiplicity and different chemical shifts observed for axial and equatorial protons of the cyclohexane moiety (Figure 4, b). The imine, cyclohexane, and pyridine methine signals moved downfield, supporting the assumption of pyridyldiimine−metal coordination. The changes observed for the pyridine protons are especially interesting. In the absence of the metal ion, all the signals of the pyridine protons appear as a multiplet at $\delta = 7.7$ ppm. Addition of the Ba^{II} salt split the signals corresponding to protons in position 3 (doublet at $\delta = 7.90$ ppm) from those in position 4 (triplet at $\delta = 8.25$ ppm) of the pyridine ring. All of this data supports a rigid D_2-symmetrical imine−Ba complex.

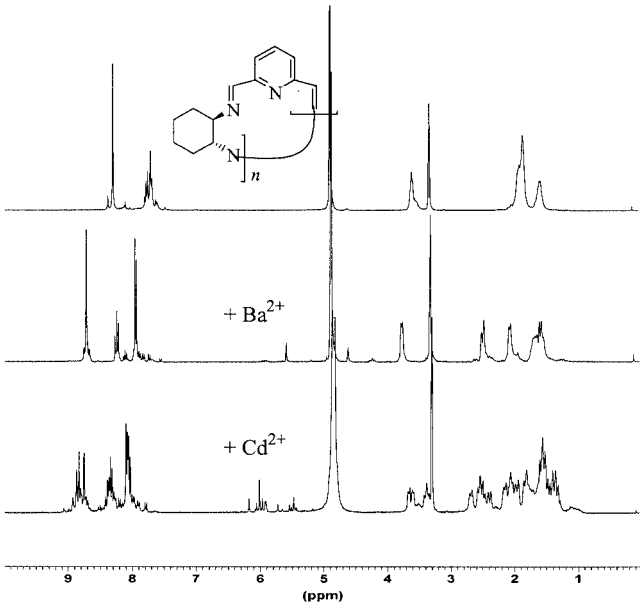


Figure 4. NMR spectra of the DCL of oligoimines (a) in the absence of template and in the presence of (b) Ba and (c) Cd salts. Small signals in (b) correspond to an α-methoxyamine derivative (see text)

Titration of the same DCL with Cd^{II} was also monitored by NMR spectroscopy. At low loading, the spectra provide evidence for the formation of a complex mixture (Figure 4, c), which became notably simplified when an excess of Cd^{II} was added. Significantly, the crude reaction mixture showed the presence of a series of signals of low intensity in the range $\delta = 5.3-5.8$ ppm, even in the absence of metal catalysts, corresponding to hemiaminal [O−C(sp^3)*H*−NH] type methine protons. The intensity of these signals grows proportionally with the concentration of Cd^{II} added. As a matter of fact, these kinds of signals was also present at a lower concentration in the Ba-templated ^1H NMR spectrum (i.e., the singlet at $\delta = 5.5$ ppm in Figure 4, b).

It is noteworthy that at a 1:2 ratio of the trimer **4** to Cd^{II} ions, the hemiaminal proton signal having the largest value of its integral arises from a broad singlet at $\delta = 5.89$ ppm (temperature 293 K), which becomes resolved into two singlets ($\delta = 5.89$ and 5.90 ppm) of equal intensity when the temperature is lowered to 253 K. Moreover, the two singlets exhibit cadmium satellites [$^3J(^{111/113}Cd^1H) \approx 5$ Hz; Figure S5 in the Supporting Information]. Interestingly, the water signal also splits into two singlets derived from its free and complexed environments at low temperature ($\delta = 5.13$ and 5.35 ppm, respectively; measured at 253 K).

Cadmium complexation also promotes a downfield shift of all the proton signals. For the imine protons the coupling to cadmium is clearly observed even at room temperature [$^3J(^{111/113}Cd^1H) \approx 35$ Hz]. Because of the relative simplification of the spectra achieved by the addition of an excess

of Cd salt, we attempted a structural characterization of the species formed at a 1:24 stoichiometry of the trimer **4** to Cd ions. The sample was prepared following the procedure used for the bulk reaction, but deuterated solvent was used in this case (CD_3OD/D_2O, 9:1). The following discussion refers to spectra measured in a field of 11.7 Tesla. When this excess of Cd salt is present, the dynamic process observed previously was slow on the NMR spectroscopic time scale, which allowed the observation of three intense, sharp singlets for the hemiaminal protons at δ = 5.88, 5.90, and 5.91 ppm, even at room temperature (Figure 5, a). The ^{13}C NMR spectrum showed a relatively reduced number of signals, suggesting that the mixture was composed by highly symmetrical species (Figure S8 in the Supporting Information). As expected, the existence of hemiaminal linkages was supported by two signals appearing at δ = 94.0 and 94.4 ppm. In addition, we observed two rather-intriguing broad signals barely above the noise in the range δ = 54−57 ppm (Figure 6, a). Considering the solvent mixture used, we suspected that the hemiaminal moiety could be formed by the addition of perdeuterated methanol to the imine functional groups, leading to the formation of α-d_3-methoxyamines. The splitting of the signals of the carbon atoms in the OCD_3 groups as a result of coupling with the deuterium atoms and the unfavorable relaxation characteristics render those signals practically unobservable under standard measuring conditions. Further evidence to support this hypothesis was demonstrated by acquiring the ^{13}C NMR spectrum with simultaneous proton and deuterium decoupling.[19] Under these conditions, two signals emerged at δ = 54.55 and 54.66 ppm and those around 56 ppm became slightly broadened (Figure 6, b).

To avoid the loss of structural information derived from deuterated substituents linked to the compounds under study, we decided to prepare a new sample in exactly the same way as before, but in non-deuterated solvents.[20] Although the dynamic range of the signals was very high, it was possible to obtain a workable ^1H NMR spectrum using

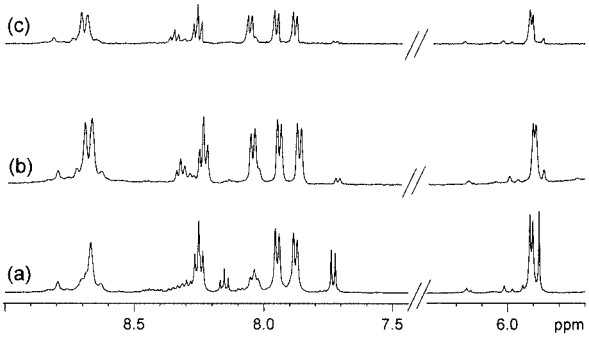


Figure 5. Expansions of the ^1H NMR spectra (500.13 MHz) of the complexes of trimer **4** and Cd (1:24). (a, b): One-pulse sequence of the samples prepared in CD_3OD/D_2O (9:1) and CH_3OH/H_2O (9:1), respectively. (c) LED spectrum of the sample prepared in CH_3OH/H_2O (9:1), with the magnetic pulse field gradient strength set to 95% and a diffusion delay of 55 ms. 32 Scans were accumulated in all cases. Vertical scales are multiplied by a factor of 12 in (a), 18 in (b), and 2 in (c). The complete data sets are given in the Supporting Information

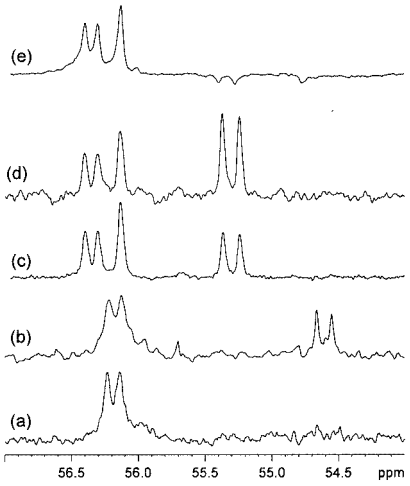


Figure 6. Expansions of the ^{13}C NMR spectra (125.7 MHz) of the complexes of the trimer **4** and Cd (1:24): (a, b) measured in CD_3OD/D_2O (9:1), (c−e) measured in CH_3OH/H_2O (9:1). (a, c) $^{13}C\{^1H\}$ spectra. (b) $^{13}C\{^1H, ^2H\}$ spectrum. (d) DEPT-135 spectrum. (e) DEPT-90 spectrum. The temperature was set at 303 K for all spectra. The complete data sets are given in the Supporting Information

the conventional pulse sequence without resorting to solvent suppression techniques (Figure 5, b and S6b). In this way, two methoxy signals are now clearly visible at δ = 3.56 and 3.57 ppm (Figure S6b). The multiplet at δ = 3.37 ppm, however, observed in the spectrum of the deuterated sample (Figure S6a), lies buried under the intense methanol signal. Several solvent suppression schemes were checked with the aim of improving the quality of the spectrum without affecting the signals of interest. The best results were obtained by resorting to diffusion experiments based on the application of magnetic pulse field gradients. Small molecules diffuse faster than do large ones. Thus, at the moment of the detection, its transverse magnetization continues spreading out while that one arising from slowly diffusing molecules is partially refocused by the action of the pulse field gradients. As a consequence, the solvent signals are efficiently cancelled.[21] Figure 5 (c) and S6c show the result of applying the LED pulse scheme[22] to our sample. The solvent signals are almost completely eliminated, revealing those signals that they had hidden (compare Figures S6b and S6c). Notwithstanding this finding, in this particular case the decrease of the signal-to-noise ratio of the solute signals was too high to use this solvent suppression technique as part of the preparation period of homo- or hetero-nuclear correlation pulse sequences (vide infra).

One additional important consequence of the use of non-deuterated solvents is the different balance achieved among the equilibrating species. Compared with the sample measured in CD_3OD/D_2O, the relative concentration of the compound characterized by the signals at δ = 5.87, 7.72 (d, J = 7.3 Hz), and 8.14 (t, J = 7.3 Hz) ppm decreased, while the one identified by the signals at δ = 8.05 (d, J = 7.8 Hz), 8.33 (t, J = 7.8 Hz), and 8.7 ppm [satellites, $^3J(^{111/113}Cd^1H) \approx 35$ Hz)], increased. Considering that the only difference between both samples is the presence or ab-

sence of deuterium in the methanol being added to the imine linkage, we assign the differences observed in these signals' intensities to isotope effects. This isotope effect could be explained in terms of lower acidity (due to lower mobility) of deuterons relative to protons.[23] Deuterated sample shows a larger shift to α-methoxyamine moieties, while non-deuterated sample shows a higher concentration of imine linkages. The imine/α-methoxyamine equilibrium can be seen as a β-elimination of methanol from the α-methoxyamine functional group, which is more efficient when the acidity of the proton (or deuteron) attached to the nitrogen atom is higher. Consequently, this elimination is thermodynamically favored when deuterons are substituted by protons.

The presence of α-methoxyamines is also evidenced in the ^{13}C NMR spectrum by two methoxy signals at δ = 55.28 and 55.40 ppm (Figure 6, c), which are missing in the DEPT-90 spectrum (Figure 6, e). Furthermore, a methine carbon atom at δ = 56.1 ppm is now clearly visible.

Our next task was to identify the different complexes present in the MeOH/H_2O sample. For that purpose, we made use of the standard battery of 2D NMR spectroscopy experiments. The proton spin systems were identified through the correlations observed in the gCOSYDQF spectrum.[24] With this information in hand, the gHMQC spectrum afforded the assignment of the carbon atoms bearing at least one proton atom (Figure S9). The connection between the pyridine and cyclohexyl fragments was established based on the analysis of the gHMBC and gNOESY spectra (Figures S10 and S11, respectively). In addition, coordination to cadmium was revealed by acquiring a ^1H,^{113}Cd gHMQC spectrum (Figure 7). As far as we know, this is the first example of a gradient-enhanced ^1H,^{113}Cd correlation experiment.[25]

For the following discussion, it must be kept in mind that the isolated final product is a cyclic trimer arising from the reduction of the reaction mixture under analysis. Therefore, we will assume that the precursors of amine **6** are also trimers,[26] although the symmetry of the structures will only allow us to identify the repeating unit of the molecule by NMR spectroscopy. Thus, at a trimer **4**/Cd stoichiometry of 1:24, the mixture consists of four compounds, **7**, **8**, **9**, and **10**, in a ratio 30:61:6:3.[27] The proposed structures for these species are depicted in Scheme 3.

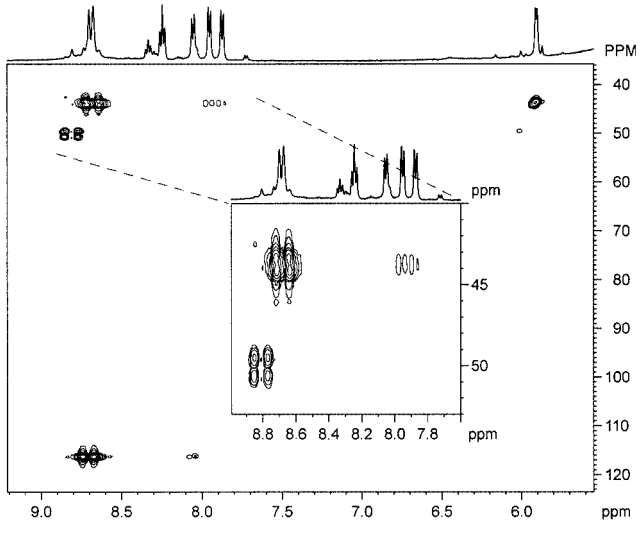


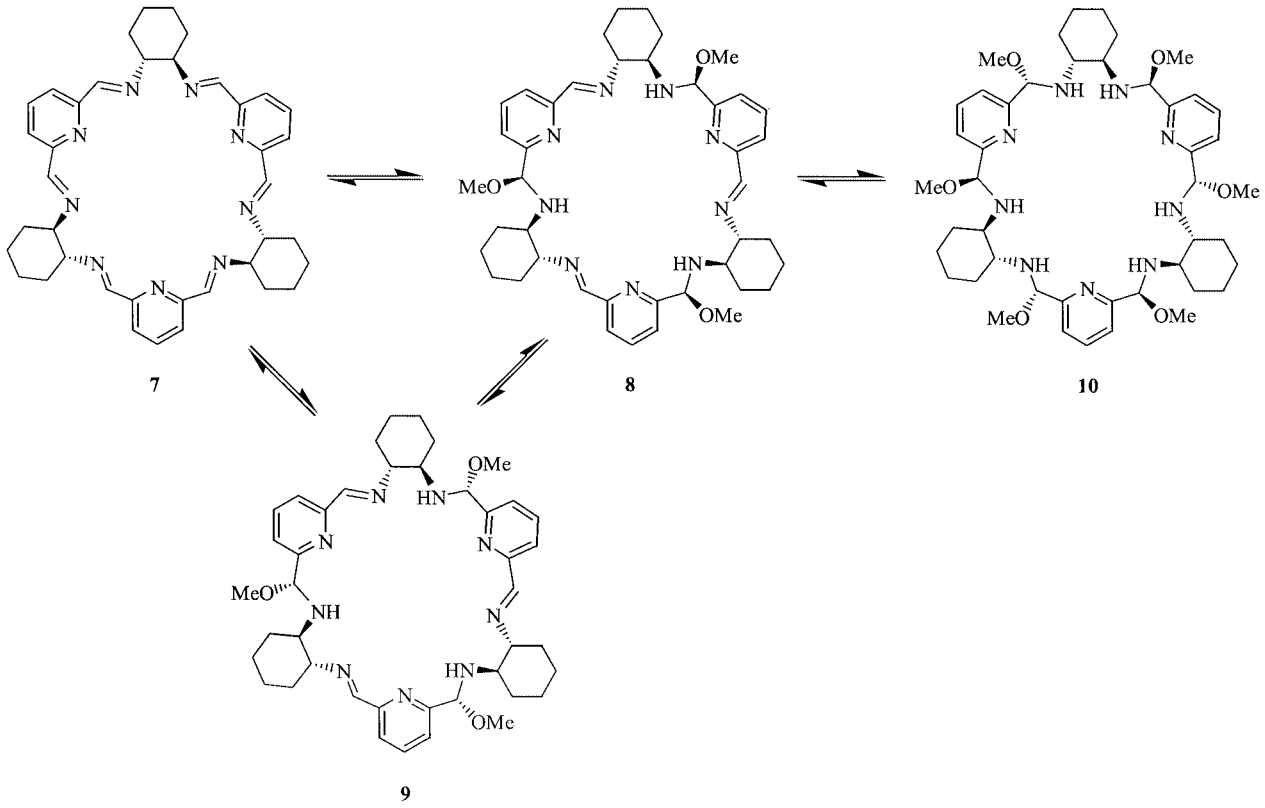
Figure 7. ^1H,^{113}Cd gHMQC spectrum (500.13 MHz) of the complexes formed from trimer **4** and Cd ions (1:24) measured in CH_3OH/H_2O (9:1) at a temperature of 303 K

Compound **7** is a trimer exclusively containing imine linkages. Its most characteristic signals are the imine CH units [$\delta(^1H)$= 8.7 ppm, $^3J(^{111/113}Cd^1H) \approx 35$ Hz] and those corresponding to the symmetrically substituted pyridine ring [$\delta(^1H)$ = 8.33 ppm, t, J = 8.3 Hz; $\delta(^1H)$ = 8.05, br. d, J = 8.3 Hz]. The imine proton correlates with a cadmium at $\delta(^{113}Cd)$= 116.2 ppm in the ^1H,^{113}Cd gHMQC spectrum (Figure 7).

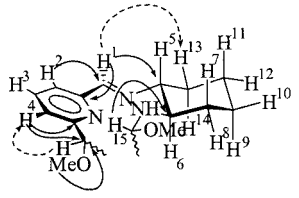
For the major product **8**, the pyridine substituents are different. One of them is an imine linkage [$\delta(^1H)$= 8.67 ppm, br. s] showing Cd satellites [$^3J(^{111/113}Cd^1H) \approx$ 36 Hz], whereas the other one is a hemiaminal fragment [$\delta_{\mathbf{CH}(OMe)NH}$ = 5.90 and 5.91 ppm] derived from the addition of a molecule of methanol to the C=N bond. Some key correlations for its assignment that are observed in the HMBC spectrum (Figure S10) are depicted in Figure 8. Compound **8** shows near-C_3 symmetry, which implies that three molecules of MeOH have added to the same face of the alternating imine linkages of **7**.

The fact that the proton spectrum of **8** exhibits two hemiaminal signals of equal intensity and, apparently, only one pyridine and imine moiety, was surprising. This paradox was solved by weighting the spectrum with a strong Gaussian term prior to Fourier transformation. In this manner, the imine proton appeared duplicated. Moreover, the higher resolution achieved revealed the existence of a long-range coupling between the imine protons and the methine unit of the cyclohexyl fragment (^4J = 2.7 Hz).[28] Not unexpectedly, the relatively broad signals of the cyclohexyl protons prevented any separation of multiplets corresponding to different moieties. The duplication of signals observed could be explained by invoking the existence of a conformational equilibrium, and the dynamic process involving the hemiaminal protons at low loading of cadmium would support this hypothesis. This dynamic behavior was apparently frozen, however, when an excess of cadmium ions was added. This situation is inconsistent with a possible restricted rotation and points to the metal ion coordination as the source of signal duplicity. Under this assumption, compound **8** would be best described by a structure containing two very similar semi-structures, each one being complexed to a cadmium ion. Furthermore, to preserve a high degree of symmetry, each cadmium ion would coordinate to opposite faces of the trimer. Such a structure would be in agreement with the results of the UV spectroscopy and MS studies, which have clearly established a stoichiometry of 1:2 for the trimer:Cd in the reaction product.

The ^1H,^{113}Cd gHMQC spectrum provides definitive support for the structure proposed for **8**. For each semi-structure, the imine proton, the *meta* protons of the pyridine



Scheme 3. Proposed structures for the interconverting species **7**−**10**. Both the presence and relative configuration of the α-methoxyamines were elucidated by a combination of NMR spectroscopy experiments and semi-empirical (PM3) theoretical calculations (see text)



8

Figure 8. Selected correlations observed in the gHMBC (plain arrows) and gNOESY (dashed arrows) spectra for **8**. The sample was prepared in CH_3OH/H_2O (9:1) at a temperature of 303 K

ring, and the protons of the hemiaminal units, all correlate with a cadmium ion [$\delta(^{113}Cd)$ = 43.3 and 44.1 ppm; Figure 7]. Considering the sensitivity of transition metals to very subtle structural changes,[29] the small chemical shift difference shown by the two metal ions bound to the trimer is remarkable. The possibility of explaining the similarities observed in the ^1H and ^{113}Cd NMR spectra through a rapid exchange process could be ruled out by taking into account that an exchange fast enough to render a near-C_3-symmetrical complex would preclude the observation of any $^{113}Cd,^1H$ coupling at room temperature, or at least would reduce its magnitude significantly. It must be remembered that the correlation between the hemiaminal protons and the corresponding Cd nuclei proceeds from $^3J(^{111/113}Cd^1H) \approx 5$ Hz.

Consequently, it appears that any exchange, if existing, would be slow and this behavior suggests that the trimethoxylated trimer is able to coordinate to two cadmium ions, which gives rise to a very stable complex, **8**.

Chemical shift differences were larger in the ^{13}C NMR spectrum, although not all signals of the two semi-structures were duplicated. Those most affected were the imine carbon atoms and the CH unit of the cyclohexane ring. In fact, in one semi-structure the chemical shift difference of these latter carbon atoms exceeds 8 ppm. Curiously, only one signal was observed for the CH unit of the hemiaminal. The gNOESY spectrum shed light on the possible conformation of **8** (Figure S11). The most significant correlations were those observed between the imine protons and an equatorial proton of a CH_2 group of the adjacent cyclohexane ring, and between the hemiaminal protons and the water and pyridine protons. This information affords two interesting conformational constraints: (i) the cyclohexane ring must be rotated with respect to the imine moiety in such a way as the protons of the CH groups linked to nitrogen atoms lie well separated, and (ii) the hemiaminal protons are also relatively far away from the cyclohexane fragment, but close to the pyridine moiety. Additionally, the combination of the NOEs observed and the correlations shown in the gCOSYDQF spectrum allowed us to assign all the protons of the cyclohexane ring.

To propose a structure of **8**, we turned out attention to semi-empirical (PM3) theoretical calculations. We found a minimum energy trimeric structure that complexes two Cd ions and has three molecules of MeOH added to alternated

imine bonds. The C_3 symmetry is broken by the Cd ion complexation, which divides the macrocyclic structure into two semistructures, each one connected to a Cd atom. This structure is shown in Figure 9 and the distances between the hydrogen atoms can explain the observed NOEs.

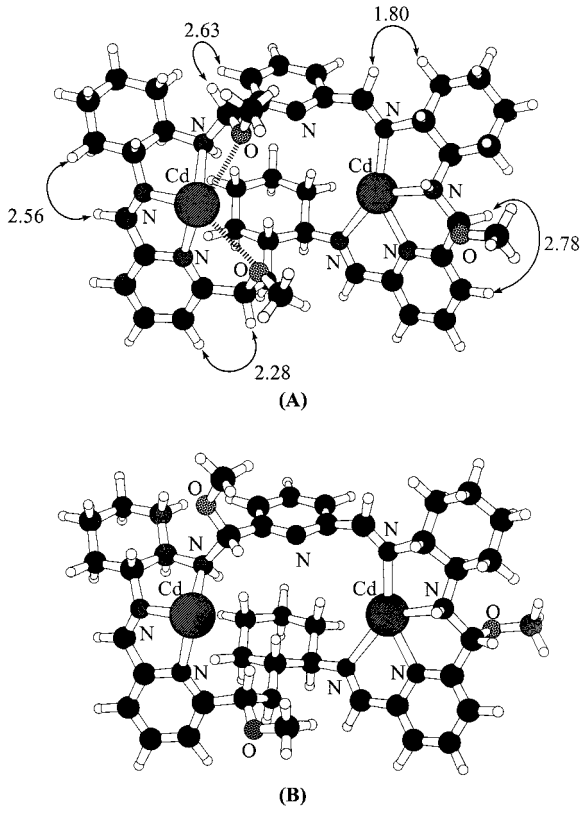


Figure 9. PM3-optimized structures of diastereoisomeric compounds (**A**) **8** and (**B**) **9**. Selected distances in (**A**) are given in Å

Compound **9** is present in a very low concentration and the only significant structural information available was obtained from the $^{1}H,^{113}Cd$ gHMQC spectrum, which suggests that **9** also contains both hemiaminal (δ = 6.0 ppm) and imine (δ = 8.8 ppm, satellites $^{3}J(^{111/13}Cd^{1}H) \approx 38$ Hz) linkages. By contrast to **8**, although the imine proton correlates with two cadmium ions at δ = 49.5 and 50.6 ppm, the hemiaminal shows a correlation with only the most-shielded one. Even though this situation occurs, the existence of only one hemiaminal signal indicates that **9** has C_3 symmetry, a finding that supports its assignment as a diastereoisomer of **8** (Scheme 3). As a consequence, in the formation of **9**, the addition of methanol to the C=N bond occurred to the opposite face as to that which led to **8**. This conclusion also implies that the Cd ion-driven addition of methanol to **7** occurs with high diastereoselectivity (10:1). Semiempirical PM3 calculations of **9** (obtained by inversion of the configuration of all the α-methoxyamine centers of **8**) showed a less-stable structure, probably because of the impossibility of having electrostatic interactions between the methoxy groups and Cd ions (Figure 9).

Finally, compound **10** was identified as a D_3-symmetrical permethoxyaminal [$\delta_{CH(OMe)NH}$ = 5.87 ppm] that lacks any correlation with cadmium ions. Although its concentration in the MeOH/H_2O sample was also very low, it could be characterized from the sample prepared in deuterated solvents, where its concentration was raised to 12%. Again, PM3 theoretical calculations suggest that the most-favorable configuration at the α-methoxyamine centers is the same as that in **8**.

It is also interesting to point out that mixture **7**−**10** is stable in solution for several months, as confirmed by acquisition of ^{1}H NMR spectra. In addition, changes in temperature varied the proportion of the components, suggesting that the change is completely reversible. Again, the interconversion between these species is under thermodynamic control (Scheme 3).

All of these results reveal there are two levels of molecular diversity in our imines' DCL. In a first stage, the aldehyde−amine condensation yields linear and cyclic oligoimines of different sizes. The presence of the metal template shifts the equilibrium to a particular macrocyclic compound. For a given macrocyclic size, there is a second level of diversity resulting from the presence of the α-methoxyamines in equilibrium with the imine bonds. These α-methoxyamines are probably stabilized by coordination to the metal atoms. The tetrahedral O−C(sp^3)−N centers are intermediates for the transimination reaction that is necessary for the exchange between the members of the library. If we consider both processes as being interconnected, the number of the virtual members of the library is much larger than just those depicted in Scheme 2. It is noteworthy that the selectivity for the cadmium-promoted methanol addition to C=N bonds shows high diastereoselectivity. Additionally, an interesting thermodynamic isotopic effect is observed for the imine/α-methoxyamine equilibrium. Both sources of molecular diversity are eliminated after the efficient quenching of the dynamic processes by C=N reduction.

4. Crystal Structure of the Macrocyclic Amine 6

Large crystals of the hydrochloride salt of **6** were obtained by slow evaporation from a methanolic HCl solution. Figure 10 shows the structure obtained by X-ray diffraction analysis, which further confirmed the formation of the D_3-symmetrical trimer **6**. The compound crystallizes with three molecules of MeOH and one of water. All the cyclohexane-1,2-diammonium moieties are located in diequatorial positions of a chair conformation. The salt contains seven molecules of HCl; six of them protonate cyclohexanediamino nitrogen atoms, and pyridine ones remain as free bases. The chloride counterions alternate below and above the macrocyclic plane to conserve the ternary symmetry. The seventh HCl molecule protonates a water molecule on the symmetry axis. There is one chloride ion located in the middle of the molecule, filling the macrocyclic cavity and forming hydrogen bonds with all of the ammonium groups of the receptor. All the pyridine heterocycles are twisted to the same side, transferring chirality

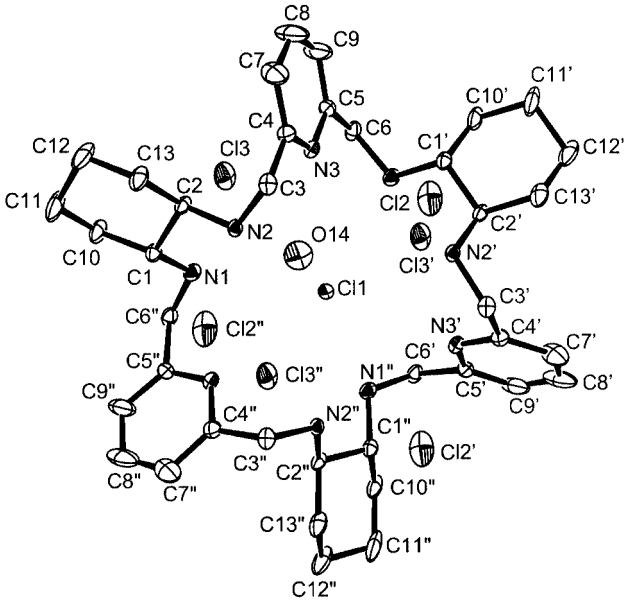


Figure 10. ORTEP drawing of the hydrochloride salt of **6**. Solvent molecules (MeOH) are omitted for clarity

throughout the whole ring and forming a right-handed helical structure.

Conclusion

We have used the DCC concept successfully for the selective syntheses of two optically active macrocyclic receptors in a simple one-pot procedure. Different cyclic structures are expressed and amplified by different metal ions from the same DCL. A combination of ESI-MS and UV and NMR spectroscopy techniques allowed us to study templating effects on the imines' DCL and proved that metal ion binding is the driving force. For one of the expressed members, we propose a cooperative molding effect by coordination of two metal ions. A study of the DCL behavior in situ was undertaken using different techniques. Transimination reactions in the presence of the metal salt produced two sources of molecular diversity. The first one arises from the different sizes of the macrocyclic structures. The second one comes from the presence of α-methoxyamine units in equilibrium with the imine bonds. This equilibrium is promoted by metal ion coordination and it probably helps with the inter-conversion between the members of the DCL. The mixture of compounds finally converged to the preparation of the desired receptor after imine reduction. The applications of these optically active receptors in chiral molecular recognition[30] are currently under study in our laboratory.

Experimental Section

General: All reagents were purchased from commercial suppliers and were used without further purification. Solvents were freshly distilled onto suitable desiccants and stored under nitrogen atmospheres. Melting points were recorded using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin−Elmer 241 polarimeter. IR spectra were recorded with a UNICAM Mattson 3000 FT infrared spectrometer. NMR spectra were obtained with Bruker spectrometers working in the ^1H frequency range from 200.13 to 500.13 MHz. All spectra were acquired at room temperature unless otherwise stated. Chemical shifts are quoted on the ppm scale using tetramethylsilane as internal standard for ^1H and ^{13}C NMR spectra, and 0.1 M $Cd(ClO_4)_2{\cdot}7H_2O$ in D_2O for ^{113}Cd. Coupling constants are given in hertz. Standard manufacturer software was used. For the 2D ^1H,^{113}Cd gHMQC pulse sequence, the gradient ratio used was 47.2:30:0. The spectrum was acquired in the magnitude mode. ESI mass spectra were acquired on a tandem mass spectrometer (Hewlett−Packard HP 1100 Series LC/MSD system) equipped with an electrospray interface working in the positive mode (for detection of positive ions). The samples were diluted to a concentration of ca. 10^{-5} M in MeOH/H_2O (9:1) and the composition of the effluent used in the LC system was also MeOH/H_2O (9:1). For amino compounds, the samples were basified by addition of 1 N NaOH. Mass spectra were obtained by introducing the samples using FIA technique (flow injection) while effluent was introduced into the ESI-MS apparatus at a pump flow rate kept at 0.3 mL min^{-1}. The temperature of the nitrogen drying gas was set at 350 °C for all the samples, except for the mixtures of imines, for which it was set at 100 °C to minimize thermal decomposition. All the injections were repeated at least three times at different fragmentor voltages (0−180 V).

Synthesis of Compound 5: A mixture of (*R*,*R*)-*trans*-cyclohexane-1,2-diamine (**1**, 114 mg, 1 mmol) and pyridine-2,6-dicarboxaldehyde (**2**, 135 mg, 1 mmol) in dry MeOH (20 mL, 0.05 M final concentration each) was stirred under nitrogen for 6 h. After this time, $BaCl_2{\cdot}2H_2O$ (146 mg, 0.7 mmol) was added and the reaction mixture was stirred overnight to permit the system to equilibrate. A large excess of $NaBH_4$ (162 mg, 4.25 mmol) was then added carefully and the mixture was reacted for 7 h before being hydrolyzed (conc. HCl, to acidity) at 0 °C and evaporated to dryness. The residue obtained was extracted thoroughly with NaOH (1 N) and CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated in vacuo. The oily polyamine **5** was dissolved in MeOH and an excess of conc. HCl was added to acidity. Evaporation of the methanolic solution gave rise to the final compound **5** as its tetrahydrochloride salt (223 mg, 86%). M.p. (decomposes without melting). $[\alpha]_D^{20} = -73.0$ ($c = 0.54$, H_2O). FTIR (KBr): $\tilde{\nu} = 3401, 1598\ cm^{-1}$. ^1H NMR ([D$_4$]MeOH, 200 MHz): δ = 1.43−1.66 (br. m, 8 H), 1.96−1.99 (br. m, 4 H), 2.56−2.63 (br. m, 4 H), 3.80−3.84 (br. m,4 H), AB system ($\delta_A = 4.52$, $\delta_B = 4.79$, $J_{AB} = 14.2$ Hz, 8 H), 7.54 (d, $^3J_{H,H} = 7.6$ Hz, 4 H), 7.95 (t, $^3J_{H,H} = 7.8$ Hz, 2 H) ppm. HRMS: calcd. for $C_{26}H_{38}N_6$ 434.31579, found 434.31581.

Synthesis of Compound 6: A mixture of (*R*,*R*)-*trans*-cyclohexane-1,2-diamine (**1**, 114 mg, 1 mmol) and pyridine-2,6-dicarboxaldehyde (**2**, 135 mg, 1 mmol) in dry MeOH (33.5 mL, 0.03 M final concentration of each) was stirred under nitrogen for 9 h. After this time, $CdCl_2$ (550 mg, 3 mmol) was added and a precipitate was formed, which was redissolved after stirring for 16 h. A large excess of $NaBH_4$ (115 mg, 3 mmol) was then added carefully and the mixture was reacted for 7 h before being hydrolyzed (conc. HCl to acidity) at 0 °C and evaporated to dryness. The residue obtained was continuously extracted with NaOH (1 N) and CH_2Cl_2 overnight. The combined organic layers were dried ($MgSO_4$) and the solvents evaporated in vacuo. The oily polyamine **6** was dissolved in MeOH and excess conc. HCl was added until acidic pH. Evaporation of

the methanolic solution yielded compound **6** as its hydrochloride salt (290 mg, quantitative). M.p. (decomposes without melting). $[\alpha]_D^{20} = -44.0$ ($c = 0.53$, H_2O). FTIR (KBr): $\tilde{\nu} = 3421$, 1596 cm^{-1}. ^1H NMR ([D_4]MeOH, 200 MHz): $\delta = 1.39-1.86$ (br. m, 20 H), 2.15−2.21 (br. m, 2 H), 2.33−2.40 (br. m, 4 H), 3.82−3.86 (br. m, 4 H), AB system ($\delta_A = 4.48$, $\delta_A = 4.56$, $J_{AB} = 15.5$ Hz, 12 H), 7.52 (d, $^3J_{H,H} = 7.91$ Hz, 6 H), 7.99 (t, 3 H, $^3J_{H,H} = 7.92$) ppm. HRMS: calcd. for $C_{39}H_{67}N_9$ 651.47369, found 651.47300.

Molecular Modeling:

All the structures were fully optimized at the cited level of theory using the Gaussian98 package.[31] Frequency analysis showed that all the stationary points were energy minima. For the optimized structures bearing Cd atoms,[32] the structures were pre-optimized in the absence of the metal ion (AM1 and PM3 semiempirical level of theory) and then Cd^{II} ions were added successively and the geometries obtained were again fully optimized.

X-ray Crystallography:

CCDC-229544 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

We especially thank Dr. Javier González for helpful discussions and assistance with the molecular modeling. Financial support of this work from the Spanish Ministerio de Ciencia y Tecnología (PPQ-2001−2683), Principado de Asturias (GE-EXP01−03), CICYT (BQU2000−0219), and FICYT (PR-01-GE-4) is gratefully acknowledged. A. G.-A. thanks III PRI (Principado de Asturias) for a predoctoral fellowship.

[1] For some recent reviews, see: [1a] S. J. Rowan, S. J. Cantrill, G. R. L. Cousin, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem. Int. Ed.* **2002**, *41*, 898−952. [1b] J.-M. Lehn, A. V. Eliseev, *Science* **2001**, *291*, 2331−2332. [1c] C. Karan, B. L. Miler, *Drug Discovery Today* **2000**, *5*, 67−75. [1d] G. R. L. Cousin, S.-A. Poulsen, J. K. M. Sanders, *Curr. Opin. Chem. Biol.* **2000**, *4*, 270−279. [1e] B. Klekota, B. L. Miller, *Trends Biotechnol.* **1999**, *17*, 205−209.

[2] J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455−2463.

[3] S. Otto, R. L. E. Furlan, J. K. M. Sanders, *Science* **2002**, *297*, 590−593.

[4] A. Ganesan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2828−2831.

[5] [5a] M. Hochgürtel, R. Biesinger, H. Kroth, D. Piecha, M. W. Hofmann, S. Krause, O. Schaaf, C. Nicolau, A. V. Eliseev, *J. Med. Chem.* **2003**, *46*, 356−358. [5b] C. Karan, B. L. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 7455−7456. [5c] I. Huc, J.-M. Lehn, *Proc. Nat. Acad. Sci. USA* **1997**, *94*, 2106−2110.

[6] [6a] B. Brisig, J. K. M. Sanders, S. Otto, *Angew. Chem. Int. Ed.* **2003**, *42*, 1270−1273. [6b] R. L. Furlan, Y.-F. Ng, S. Otto, J. K. M. Sanders, *J. Am. Chem. Soc.* **2001**, *123*, 8876−8877. [6c] G. R. L. Cousin, R. L. E. Furlan, Y.-F. Ng, J. E. Redman, J. K. M. Sanders, *Angew. Chem. Int. Ed.* **2001**, *40*, 423−428.

[7] [7a] D. M. Epstein, S. Choudhary, M. R. Churchil, K. M. Keil, A. V. Eliseev, J. R. Morrow, *Inorg. Chem.* **2001**, *40*, 1591−1596. [7b] V. Goral, M. I. Nelen, A. V. Eliseev, J.-M. Lehn, *Proc. Nat. Acad. Sci. USA* **2001**, *98*, 1347−1352. [7c] A. Star, I. Goldberg, B. Fuchs, *Angew. Chem. Int. Ed.* **2000**, *39*, 2685−2689.

[8] [8a] E. Stulz, Y.-F. Ng, S. M. Scott, J. K. M. Sanders, *Chem. Commun.* **2002**, 524−525. [8b] S. Choudhary, J. R. Morrow, *Angew. Chem. Int. Ed.* **2002**, *41*, 4096−4098. [8c] I. Huc, M. J. Krische, D. P. Funeriu, J. M. Lehn, *Eur. J. Inorg. Chem.* **1999**, 1415−1420. [8d] B. Hasenknopf, J. M. Lehn, N. Boumediene, A. Dupont-Gervais, A. van Dorsselaer, B. Kneisel, D. Fenske, *J. Am. Chem. Soc.* **1997**, *119*, 10956−10962. [8e] M. Albrecht, *J. Incl. Phenom. Macrocycl. Chem.* **2000**, *36*, 127−151.

[9] [9a] R. J. Lins, S. L. Flitsch, N. J. Turner, E. Irving, S. A. Brown, *Angew. Chem. Int. Ed.* **2002**, *41*, 3405−3407. [9b] S. Otto, R. L. E. Furlan, J. K. M. Sanders, *J. Am. Chem. Soc.* **2000**, *122*, 12063−12064. [9c] G. R. L. Cousins, S.-A. Poulsen, J. K. M. Sanders, *Chem. Commun.* **1999**, 1575−1576. [9d] S. J. Rowan, P. A. Brady, J. K. M. Sanders, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2143−2145. [9e] P. A. Brady, R. P. Bonar-Law, S. J. Rowan, C. J. Suckling, J. K. M. Sanders, *Chem. Commun.* **1996**, 319−320.

[10] [10a] J. Gawronski, H. Kolbon, M. Kwit, A. Katrusiak, *J. Org. Chem.* **2000**, *65*, 5768−5773. [10b] N. Kuhnert, A. M. Lopez-Periago, *Tetrahedron Lett.* **2002**, *43*, 3329−3332. [10c] M. Chadim, M. Budesinsky, J. Hadacova, J. Zavada, P. C. Junk, *Tetrahedron: Asymmetry* **2001**, *12*, 127−133. [10d] S. R. Koropoju, P. S. Zacharias, *Chem. Commun.* **1998**, 1267−1268.

[11] M. Kwit, J. Gawrosky, *Tetrahedron: Asymmetry* **2003**, *14*, 1303−1308.

[12] Both metal-templated and non-templated [2+2] cyclocondensations have been reported previously for this diamine and dialdehyde, but under our reaction conditions, the metal-free condensation always yielded a mixture of cyclic oligoimines. See: [12a] S. W. A. Bligh, N. Choi, W. J. Cummins, E. G. Evagorou, J. D. Kelly, M. McParlin, *J. Chem. Soc., Dalton Trans.* **1994**, 3369−3375. [12b] S. W. A. Bligh, N. Choi, E. G. Evagorou, W.-S. Li, M. McParlin, *J. Chem. Soc., Chem. Commun.* **1994**, 2399−2400. [12c] P. M. Fitzsimmons, S. C. Jackels, *Inorg. Chim. Acta* **1996**, *246*, 301−310.

[13] F. Tuna, J. Hamblin, G. Clarkson, W. Errington, N. W. Alcock, M. J. Hannon, *Chem. Eur. J.* **2002**, *8*, 4957−4963.

[14] ESI-MS is a very commonly used technique for the semi-quantitative analysis of DCLs. See, for instance: F. Hof, C. Nuckolls, J. Rebek Jr, *J. Am. Chem. Soc.* **2000**, *122*, 4251−4252.

[15] N. Kunhert, G. M. Rossignolo, A. López-Periago, *Org. Biomol. Chem.* **2003**, *1*, 1157−1170.

[16] We performed a semi-quantitative determination of the abundances of both dimer **5** and trimer **6** by ESI-MS. This technique can be used for quantification of mixtures when differences between the ionization properties of the components of the mixture are not very high. A calibration curve of the relative intensities of peaks of trimer/dimer versus the relative concentration of trimer/dimer (prepared by mixing known amounts of true samples of pure compounds) showed a linear relationship ($r = 0.99$) with a slope of 0.9556 (see Supporting Information).

[17] Dimetallic Cd^{II} complexes of a 24-membered ring polyazamacrocycle have been described. See: J. Faus, E. García-España, V. Marcelino, A. Bencini, A. Bianchi, *Inorg. Chim. Acta* **1990**, *172*, 203−209.

[18] K. A. Connors, *Binding Constants*, John Wiley & Sons, New York, **1987**.

[19] Deuterium decoupling was effected through the lock channel. The 90° pulse-width at maximum power (20 W) was 145 μs. Although the spectrum suffered from severe artifacts that could not be avoided because of the unavailability of specific frequency filters, the region of interest was not affected by them and could be observed cleanly.

[20] External lock was achieved through a coaxial capillary filled with D_2O. The spectra were measured at a temperature of 303 K.

[21] [21a] A. R. Waldek, P. W. Kuchel, A. J. Lennon, B. E. Chapman, *Prog. NMR Spectrosc.* **1997**, *30*, 39−68. [21b] C. S. Johnson Jr, *Prog. NMR Spectrosc.* **1999**, *34*, 203−256.

[22] S. J. Gibbs, C. S. Johnson Jr, *J. Magn. Reson.* **1991**, *93*, 395−402.

[23] [23a] P. K. Glasoe, F. A. Long, *J. Phys. Chem.* **1960**, *64*, 188−190. [23b] C. Geraldes, A. D. Sherry, M. P. Marques, M. C. Alpoin, S. Cortes, *J. Chem. Soc., Perkin Trans. 2* **1991**, 137−146.

[24] Considering that the presence of OCH_3 or OCD_3 groups is irrelevant for the map of correlations observed, because they do not show any coupling to nearby protons, we complemented this study by analyzing the gCOSYDQF spectrum of the CD_3OD/D_2O sample to take advantage of the much lower intensity of the solvent signals.

[25] [25a] T. Parella, *Magn. Reson. Chem.* **1998**, *36*, 467−495. [25b] D. J. Darensbourg, P. Rainey, D. L. Larkins, J. H. Reibenspies, *Inorg. Chem.* **2000**, *39*, 473−479.

[26] The possibility of the existence of different species (open linear oligomers and other cyclic products) in equilibrium that could be reduced to only one final product is obviated by the fact that borohydride reduction is very fast. It is also noteworthy that there is lack of open linear oligomers in solution that are observable by NMR spectroscopy.

[27] The proton spectrum contains three additional signals at δ = 5.97, 6.05, and 6.16 ppm that have very low intensity, which we have not included in the structural analysis. Most probably, they are diastereoisomers of compounds **8−10**. See the main text.

[28] A very small split of the pyridine signals was also observed in the proton spectrum of the sample prepared in deuterated solvents and measured at 263 K. In this case, water suppression through WATERGATE was applied and the FID was multiplied by a Gaussian function (LB = −2, GB = 0.2) prior to Fourier transformation. This processing also revealed the cadmium satellites of the hemiaminal signals: $^3J(^{111/113}Cd^1H)$ = 7.5 and 6.3 Hz for the signals at δ = 5.90 and 5.91 ppm, respectively. See Figure S3 in the Supporting Information.

[29] [29a] R. J. Goodfellow, in *Multinuclear NMR* (Ed.: J. Mason), Plenum Press, New York, **1987**, Chapter 21, p. 563. [29b] D. Rehder, *Coord. Chem. Rev.* **1991**, *110*, 161−210. [29c] H. Xia, G. D. Rayson, *Adv. Environ. Res.* **2002**, *7*, 157−167. [29d] E. Virtanen, J. Tamminen, J. Linnato, P. Mänttäri, P. Vainiotalo, E. Kolehmainen, *J. Incl. Phenom. Macrocycl. Chem.* **2002**, *43*, 319−327.

[30] For a general overview, see: [30a] A. Bianchi, K. Bowman-James, E. García-España, *The Supramolecular Chemistry of Anions*, Wiley-VCH, Weinheim, **1997**. [30b] J.-M. Lehn, *Supramolecular Chemistry*, Wiley-VCH, Weinheim, **1995**. For specific applications of cyclohexane-based azamacrocycles in chiral anion recognition: [30c] I. Alfonso, F. Rebolledo, V. Gotor, *Chem. Eur. J.* **2000**, *6*, 3331−3338. [30d] I. Alfonso, B. Dietrich, F. Rebolledo, V. Gotor, J.-M. Lehn, *Helv. Chim. Acta* **2001**, *84*, 280−295.

[31] Gaussian 98, Revision A.9, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.

[32] [32a] J. J. P. Stewart, *J. Comp. Chem.* **1991**, *12*, 320−341. [32b] R. W. Matthews, M. McPartlin, I. J. Scowen, *Chem. Commun.* **1996**, 309−310. [32c] R. R. Fenton, R. Gauci, P. C. Junk, L. F. Lindoy, R. C. Luckay, G. V. Meehan, J. R. Price, P. Turner, G. Wei, *J. Chem. Soc., Dalton Trans.* **2002**, 2185−2193.

Received October 6, 2003

