DOI: 10.1002/ejoc.200800462

Remarkable Stability of Imino Macrocycles in Water[‡]

Vittorio Saggiomo[a] and Ulrich Lüning*[a]

Keywords: Combinatorial chemistry / Imines / Macrocycles / Pyridine / Templates

Imines **3**, **5** and **7** generated from 4-methoxypyridine-2,6-dicarbaldehyde (**1**) and several amines **2**, **4** and **6** show a remarkable stability in water. The 18-membered macrocyclic diimine **5** is stable and could be synthesized in good yield by using 2 equiv. of calcium ions as template in pure water, and even the non-macrocyclic diimine **3** survives in water/methanol (50:50) without any template effect. In a mixture of pyridinedicarbaldehyde **1** and two glycol-derived diamines **4** and **6**, a calcium template ion selects the 18-membered macrocycle **5** over the 20-membered one (**7**).

Introduction

Macrocyclic structures have gained enormous attention over the past decades.[1] However, macrocycles are not as easily prepared as five- or six-membered rings,[2] and thus special approaches have been developed for better syntheses. For kinetically controlled macrocyclizations, the use of the high-dilution technique[3] often increases yields considerably, whereas in thermodynamically controlled reactions, the template effect has proven to be the proper tool to shift the equilibrium to the desired product.[4–6] Many applications of macrocycles including the metal-ion-complexing abilities of crown ethers make use of *endo* functionalities. Therefore, it is self-evident that these functionalities can be exploited in the macrocyclic assembly process.[7] Unlike in a kinetically controlled reaction, the products of a thermodynamically controlled reaction are interconverted into one another constantly. The composition of the product mixture is depending on the relative thermodynamic stability of the products. The mixture is dynamic. If polyfunctional molecules or several starting materials are used, numerous different combinations are conceivable, and usually mixtures are formed. For these situations, the term dynamic combinatorial chemistry (DCC) has been coined.[8–11] Since decades,[4] the imine formation has been used to synthesize macrocycles, and templates have been found to shift the equilibria of the dynamic combinatorial libraries towards one product in good yield. Dynamic combinatorial libraries have been investigated by starting from a dialdehyde and one[12,13] or several[14] diamines. The coordinative bond between a transition-metal ion and an imine leads to an increased stability of the imines even in water.[15] But in general, imines are rather unstable and are hydrolyzed quickly if water is present.[16–18] However, converse results have also been reported.[19] In the DCC synthesis of macrocyclic imines, too, the sensitivity against water has to be investigated for several reasons: (i) every formation of an imine from an aldehyde and an amine forms a water molecule, (ii) the template salts often contain water,[14,20] (iii) the reactions are usually not carried out under strict exclusion of moisture and (iv) the hydrolysis plays an important rule in the reversibility of the imine bond formation.[21]

Results and Discussion

Due to the instability of imines under the conditions of many standard purification techniques, the analysis of an imine library is rarely[22] performed on the imine mixture itself but usually done by investigating the amine mixture obtained by reduction of the imines.[14] Besides HPLC-MS,[22] one other direct method to monitor the equilibrium is the observation of the imines by NMR spectroscopy. In this work, dynamic combinatorial libraries (DCL) derived from pyridine-2,6-dicarbaldehyde **1** and various diamines such as **2**, **4** or **6** have been investigated by ^{1}H NMR spectroscopy. One prerequisite for the analysis is the use of a 4-substituted pyridine-2,6-dicarbaldehyde such as 4-methoxypyridine-2,6-dicarbaldehyde (**1**) because the pyridine hydrogen atoms of 2,4,6-trisubstituted pyridines show a sharp singlet in the NMR spectra. If the dynamic combinatorial library gives a manageable number of products, their relative ratio can be determined by integration of these pyridine 3,5-H peaks. Quantitative measurements are possible if an internal standard (for instance dimethyl terephthalate, DMT) is added. Many components of a library can also be detected by ESI mass spectrometry, although no quantitative analysis is possible by this analytic technique. In the

[‡] Dynamic Combinatorial Chemistry, 2. Part 1: Ref.[14]

[a] Otto-Diels-Institut für Organische Chemie,
Christian-Albrechts-Universität zu Kiel,
Olshausenstr. 40, 24098 Kiel, Germany
Fax: +49-431-880-1558
E-mail: luening@oc.uni-kiel.de

present study, three different amines [*n*-butylamine (**2**), a triethylene glycol derived diamine **4** and a bis(homo) analogue **6**] have been used. From the resulting imines **3**, **5** and **7**, only the largest macrocycle **7** was well detected by ESI [M + H^+], whereas the smaller macrocycle **5** appeared as an [M + Ca^{2+}]/2 signal, and the butyl compounds could not be detected at all (Figure 1).

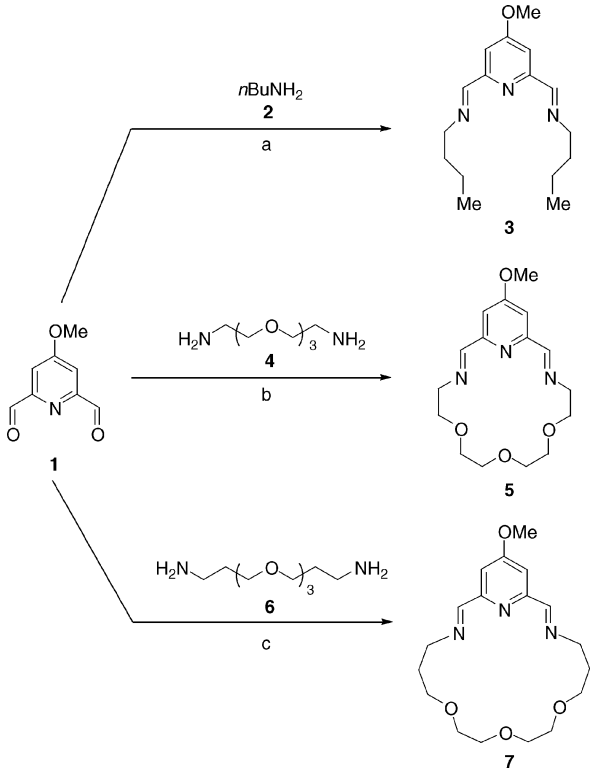

Figure 1. (a) CD_3OD/D_2O in various ratios, 12 h, room temp.; (b) CD_3OD/D_2O in various ratios with 1 equiv. of $CaCl_2$, 12 h, room temp., and pure D_2O with various equiv. of $CaCl_2$, 12 h, room temp.; (c) CD_3OD/D_2O in various ratios with 1 equiv. of $CaCl_2$ 12 h, room temp.

However, all three compounds gave nice and clear signals in the NMR spectra, well distinguishable from each other or from oligomer signals. The individual imine synthesis, as well the imine-based libraries, usually is carried out in methanol,[6,20,14] and consequently the reaction of 4-methoxypyridine-2,6-dicarbaldehyde (**1**) with *n*-butylamine (**2**) gave the respective diimine **3** in good yield. Increasing percentages of water reduced the yield of **3** as could be deduced from the integrations of the respective signals in the NMR spectrum (Figure 2, for instance NH_2CH_2 of the free butyl chains at δ = 2.7 ppm, and CH of the aldehyde in its hydrate or hemiacetal form at $\delta \approx$ 5.5 ppm). If more than 50% of water was added, the solvent became too polar to dissolve the starting materials completely. However, the diimine **3** proved to be rather stable, and 68% of it was still detected when the solvent contained 50% of water. Next, the formation of macrocyclic diimine **5** was investigated in the presence of 1 equiv. of calcium ions. In methanol with various percentages of water, no change in the composition could be detected. With 50% of water, still 90% of macrocycle **5** exists. This surprising stability led us to an experiment in pure water by using various amounts of templating calcium ions. In pure water, the quantitative analysis of the NMR signals against the standard DMT cannot be carried out anymore due to DMT's insolubility, but, to calculate the yield, the intensities of the imine peak and the aldehyde peak can be compared according to literature.[16] With 1 or less equiv. of calcium ions, the reaction mixture was not a solution, but a suspension, due to the fact that aldehyde **1** does not have sufficient solubility in water.

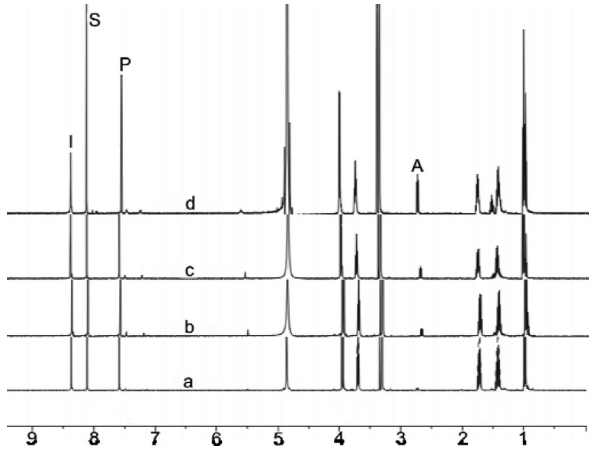

Figure 2. ^1H NMR spectrum (500 MHz, 298 K) of imine **3** in: (a) CD_3OD, (b) CD_3OD/D_2O, 98:2, (c) CD_3OD/D_2O, 90:10, (d) CD_3OD/D_2O, 50:50. All ratios are expressed in v/v. Capital letters indicate prominent resonances: I = imine, S = DMT, P = pyridine, A = free amine chain.

However, with 2 equiv. of calcium ions, the solution became clear, and only one product **5**, as the calcium complex, was detected (Figure 3). Thus, even in water, a calcium ion stabilizes the macrocyclic diimine **5** to such an extent that it becomes the only product! In contrast to the stabilization of a macrocycle by transition-metal ions, which bind donor atoms by coordinative bonds, here, the interactions between the calcium ion and the donor atoms of the macrocycle are predominantly dipol–ion interactions. But these interactions are strong enough to withstand the competing solvation by 55 M water, and macrocycle **5** is found exclusively.

The reaction with the longest diamine **6**, which contains two aminopropylene groups instead of aminoethylene ones, gave less clear results. Also in methanol, the macrocyclic diimine **7** was formed in good yield (Figure 4a) and could be analyzed by ESI mass spectrometry or NMR spectroscopy. However, in contrast to the macrocycle formation of **5**, the addition of water disturbs the formation of the macrocyclic diimine **7** (Figure 4). The NMR signals broaden, and increasing amounts of free diamine **6** appear. But also in this case, the addition of templating calcium ions favors the formation of the macrocycle, and for instance with 10 equiv. of $CaCl_2$ in CD_3OD/D_2O (50:50), only the signals of the macrocycle **7** were observed again.

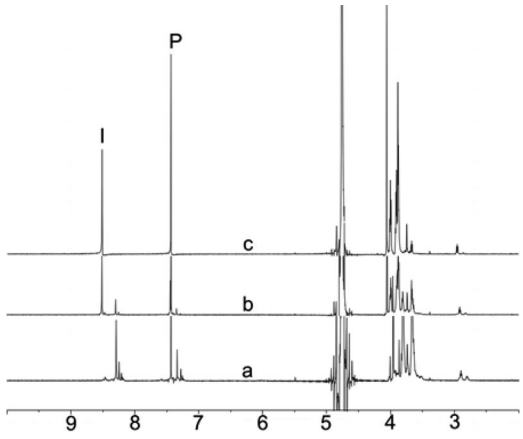

Figure 3. ^{1}H NMR spectrum (500 MHz, D_2O, 298 K). Synthesis of imine **5** in pure D_2O with: (a) no $CaCl_2$, (b) 1 equiv. of $CaCl_2$, (c) 2 equiv. of $CaCl_2$. Capital letters indicate prominent resonances: I = imine, P = pyridine.

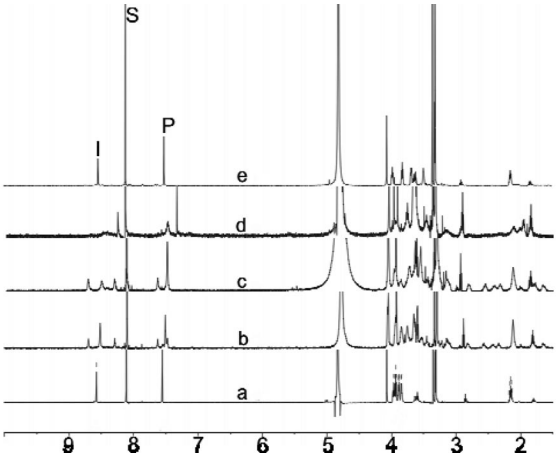

Figure 4. ^{1}H NMR (500 MHz, 298 K) of imine **7** in: (a) CD_3OD, (b) CD_3OD/D_2O, 98:2, (c) CD_3OD/D_2O, 90:10, (d) CD_3OD/D_2O, 50:50, (e) CD_3OD/D_2O, 50:50, and 10 equiv. of $CaCl_2$. All ratios are expressed in v/v. Capital letters indicate prominent resonances: I = imine, S = DMT, P = pyridine.

Finally, we investigated a dynamic combinatorial library derived from the dialdehyde **1** and both diamines **4** and **6**. In the first experiment, a mixture of $CaCl_2$, dialdehyde **1** and the propylenediamine **6** was prepared, and the respective imines were allowed to form. Then, 5% of water and 1 equiv. of ethylenediamine **4** were added one after the other, and each mixture was analyzed by NMR spectroscopy (Figure 5). First, the typical broadening of the signals of the propylenemacrocycle **7** appeared (see Figures 4 and 5b), and after addition of **4**, the most stable macrocyclic diimine **5** was formed exclusively (shift of imine peak from δ = 8.60 to 8.64 ppm), and free propylenediamine **6** was detected (see for instance $CH_2CH_2CH_2$ of the free amine chain: δ = 1.75 ppm), proving the formation of the more stable 18-membered macrocycle in this dynamic combinatorial library.

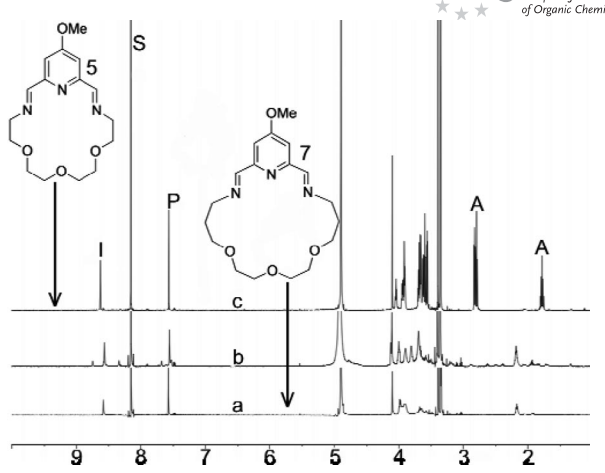

Figure 5. Exchange experiment. (a) 1 equiv. of dialdehyde **1**, 1 equiv. of diamine **6**, and 1 equiv. of $CaCl_2$ in CD_3OD give the macrocyclic diimine **7**; (b) addition of 5% of D_2O interfers with the exclusive formation of **7**; (c) after addition of diamine **4** and equilibration for 12 h, the most stable diimine complex **5** is exclusively formed on the cost of the larger macrocycle **7** with liberation of diamine **6**. Capital letters indicate prominent resonances: I = imine, S = DMT, P = pyridine, A = free amine chain.

Conclusions

Even in water, the macrocyclic diimine **5** can be formed in excellent yields, provided that enough calcium ions are present. These have two functions: they stabilize this product by their template effect and they solubilize the complex by the introduction of charge. But not only the templating of the macrocycle contributes to the remarkable stability of diimine **5** in water. Even the non-macrocyclic diimine **3** is still formed in good yield in a solvent mixture containing 50% of water and 50% of methanol. This stability is probably caused by the pyridine unit and its conjugation with the imine groups.[23]

Experimental Section

General Remarks: *n*-Butylamine (**2**), 4,7,10-trioxa-1,13-tridecanediamine (**6**), and sodium cyanoborohydride were obtained commercially from Fluka and used without further purification. 4-Methoxypyridine-2,6-dicarbaldehyde (**1**)[20] and 3,6,9-trioxa-1,11-undecanediamine (**4**)[20] were synthesized according to literature procedures. NMR spectra were recorded with Bruker DRX 500 or AV 600 instruments. Assignments are supported by COSY, HSQC and HMBC. All chemical shifts were referenced to the residual proton (^{1}H) or carbon (^{13}C) signal of the solvent [CD_3OD, δ = 3.35 (^{1}H), 49.0 (^{13}C) ppm]. Mass spectra were recorded with a Finnigan MAT 8200 or MAT 8230. ESI mass spectra were recorded with an Applied Biosystems Mariner Spectrometry Workstation.

General Procedure for the Preparation of Stock Solutions: To solutions of 4-methoxypyridine-2,6-dicarbaldehyde (**1**, 9.6 mg, 0.058 mmol), dimethyl terephthalate (DMT, 5.6 mg, 0.029 mmol) and $CaCl_2$ (6.4 mg, 0.058 mmol) in CD_3OD (5 mL), various diamines **2**, **4** or **6** (1.05 to 1.5 equiv.) were added. The solutions were stirred at room temp. for 12 h and were then transferred into NMR tubes with various percentages of D_2O. These solutions were al-

lowed to stand for at least 4 h in order to equilibrate. In another set of experiments, water was added before the amines to start the reaction in aqueous media. The final volume for all NMR experiments was 600 μL, the tube's atmosphere was replaced with nitrogen, and the tubes were capped with Teflon caps.

2,6-Bis(*n*-butyliminomethyl)4-methoxypyridine (3): A stock solution was prepared as follows: 4-methoxypyridine-2,6-dicarbaldehyde (**1**, 5 mg, 0.03 mmol) and DMT (2.15 mg, 0.011 mmol) were dissolved in CD_3OD (2.5 mL). *n*-Butylamine (**2**, 6.2 μL, 0.063 mmol) was added, and the solution was stirred at room temp. for 12 h. Then, various percentages of water (2%, 10%, 50% v/v) were added, and ^1H NMR spectra were recorded after 4 h. Yields calcd. from the ratio between signals of aromatic protons of DMT [δ = 8.15 (s, 4 H), 3.97 (s, 6 H) ppm] and imine protons: pure CD_3OD: 91%, 2% D_2O: 88%, 10% D_2O: 71%, 50% D_2O: 68%. ^1H NMR (600 MHz, 298 K, CD_3OD) of **3** in the mixture: δ = 8.40 (t, J = 1.2 Hz, 2 H, CH=N), 7.62 (s, 2 H, Py), 4.00 (s, 3 H, OMe), 3.77 (m, 4 H, CH=NCH_2), 1.76 (quint, J = 6 Hz, 4 H, N=$CH_2C\mathit{H}_2CH_2CH_3$), 1.45 (m, 4 H, N=$CH_2CH_2C\mathit{H}_2CH_3$), 0.98 (t, J = 7.8 Hz, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, 298 K, CD_3OD): δ = 168.79 [C-2,6 (Py)], 163.09 (CH=N), 157.04 [C-4 (Py)], 109.43 [C-3,5 (Py)], 61.88 (N=CH_2), 56.38 (OMe), 33.77 ($CH_2\mathit{C}H_2CH_2$), 21.38 ($\mathit{C}H_2CH_3$), 14.12 ($CH_2\mathit{C}H_3$) ppm. HRMS: calcd. for $C_{16}H_{25}N_3O$ 275.19977, found 275.19992; calcd. for $C_{15}{}^{13}CH_{25}N_3O$ 276.20313, found 176.20323.

1^4-Methoxy-6,9,12-trioxa-3,15-diaza-1(2,6)-pyridinahexadecacyclophan-2,15-diene (5). (a): A stock solution was prepared as follows: 4-methoxypyridine-2,6-dicarbaldehyde (**1**, 8.7 mg, 0.052 mmol), DMT (6.2 mg, 0.032 mmol), and $CaCl_2$ (5.7 mg, 0.052 mmol) were dissolved in CD_3OD (5 mL). 3,6,9-Trioxa-1,11-undecanediamine (**4**, 10.9 mg, 0.057 mmol) was added, and the solution was stirred for 12 h. Various percentages of water (2%, 10%, 50%) were added to different tubes, and ^1H NMR spectra were recorded after 5 h. Yields calcd. from the ratio between signals of aromatic protons of DMT [δ = 8.15 (s, 4 H), 3.97 (s, 6 H) ppm] and imine protons: CD_3OD: 92%, 2% D_2O: 90%, 10% D_2O: 90%, 50% D_2O: 90%. ^1H NMR (600 MHz, 298 K, CD_3OD) of **5** in the mixture: δ = 8.64 (t, J = 1.2 Hz, 2 H, CH=N), 7.58 (s, 2 H, Py), 4.11 (s, 3 H, OMe), 4.05 (t, J = 4 Hz, 4 H, CH=NCH_2), 3.96–3.91 [overlapping signals, 12 H, $(CH_2OCH_2)_3$] ppm. ^{13}C NMR (150 MHz, 298 K, CD_3OD): δ = 169.87 [C-2,6 (Py)], 163.45 (CH=N), 153.05 [C-4 (Py)], 113.82 [C-3,5 (Py)], 70.92, 70.04, 69.74, 69.36, 69.05, 68.72 [$(CH_2OCH_2)_3$], 56.90 (N=CH_2), 55.92 (OMe) ppm. HRMS: calcd. for $C_{16}H_{23}N_3O_4$ 321.16885, found 321.16899; calcd. for $C_{15}{}^{13}CH_{23}N_3O_4$ 322.17221, found 322.17218. **(b):** A stock solution was prepared as follows: 3,6,9-trioxa-1,11-undecanediamine (**4**, 10.9 mg, 0.057 mmol) was added to a solution of 4-methoxypyridine-2,6-dicarbaldehyde (**1**, 8.7 mg, 0.052 mmol) in D_2O (5 mL). Then various equivalents of $CaCl_2$ were added to the solution in different NMR tubes, and the solutions were left to equilibrate for 12 h. Then the ^1H NMR spectra were recorded. ESI-MS (positive ions) of the water solution with 2 equiv. of $CaCl_2$: calcd. for $C_{16}H_{23}CaN_3O_4$ 361.13, found 180.554 [M + Ca^{2+}]/2.

1^4-Methoxy-7,10,13-trioxa-3,17-diaza-1(2,6)-pyridinaoctadecacyclophan-2,17-diene (7): A stock solution was prepared as follows: 4-methoxypyridine-2,6-dicarbaldehyde (**1**, 8.7 mg, 0.052 mmol), DMT (6.6 mg, 0.034 mmol), and $CaCl_2$ (5.7 mg, 0.052 mmol) were dissolved in CD_3OD (5 mL). 4,7,10-Trioxa-1,13-tridecanediamine (**6**, 17.1 μL, 0.078 mmol) was added, and the solution was stirred for 12 h. In different tubes, various percentages of water (2%, 10%, 50%) were added, and ^1H NMR spectra were recorded after 5 h. Yield calcd. from the ratio between signals of aromatic protons of DMT [δ = 8.15 (s, 4 H), 3.97 (s, 6 H) ppm] and imine protons: pure CD_3OD: 88%. ^1H NMR (600 MHz, 298 K, CD_3OD) of **7** in the mixture: δ = 8.60 (t, J = 1.2 Hz, 2 H, CH=N), 7.58 (s, 2 H, Py), 4.11 (s, 3 H, OMe), 4.01–3.92 [overlapping signals, 16 H, $CH_2(CH_2OCH_2)_3CH_2$, CH=NCH_2], 2.19 (quint, J = 6.6 Hz, 4 H, $CH_2C\mathit{H}_2CH_2$) ppm. ^{13}C NMR (150 MHz, 298 K, CD_3OD): δ = 171.58 [C-2,6 (Py)], 165.41 (CH=N), 154.59 [C-4 (Py)], 115.49 [C-3,6 (Py)], 71.54, 71.21, 70.92, 70.45, 69.64, 68.94, 58.14 [$CH_2(CH_2OCH_2)_3CH_2$, N=CH_2], 57.39 (OMe), 29.04 ($CH_2\mathit{C}H_2CH_2$) ppm. ESI-MS (positive ions) of the solution with 10% of water: calcd. for $C_{18}H_{27}N_3O_4$ 349.42, found 350.29 [M + H^+]. HRMS: calcd. for $C_{18}H_{27}N_3O_4$ 349.20016, found 349.20015; calcd. for $C_{17}{}^{13}CH_{27}N_3O_4$ 350.20352, found 350.20405.

Exchange Reaction between the Macrocyclic Diimines 7 and 5: A stock solution was prepared as follows: 4-methoxypyridine-2,6-dicarbaldehyde (**1**, 8.7 mg, 0.052 mmol), DMT (6.6 mg, 0.034 mmol), and $CaCl_2$ (5.7 mg, 0.052 mmol) were dissolved in CD_3OD (5 mL). 4,7,10-Trioxa-1,13-tridecanediamine (**6**, 17.1 μL, 0.078 mmol) was added, and the solution was stirred for 12 h. Then, the solution was transferred into an NMR tube with 5% of water and left at room temperature for 4 h. Next, 3,6,9-trioxa-1,11-undecanediamine (**4**, 1 equiv.) was added into the tube, and the reaction was left to equilibrate for 12 h. ^1H NMR spectra were recorded in each step.

Acknowledgments

We are grateful for the support by the Marie Curie Research Training Network (MRTN-CT-2006-035614), Dynamic Combinatorial Chemistry (DCC).

[1] a) *Encyclopedia of Supramolecular Chemistry* (Eds.: J. L. Atwood, J. W. Steed), Marcel Dekker, New York, **2004**, p. 311–318; b) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, Wiley, Chichester, New York, Weinheim, Brisbane, Singapore, Toronto, **2005**, reprinted; c) *Core Concepts in Supramolecular Chemistry and Nanochemistry* (Eds.: J. W. Steed, D. R. Turner, K. J. Wallace), Wiley, Chichester, New York, Weinheim, Brisbane, Singapore, Toronto, **2007**.
[2] Third Schiemenz "law" of organic chemistry: "whenever five- or six-membered rings may be formed, they will". For an illustration of the three "laws" see: U. Lüning, *Organische Reaktionen – Eine Einführung in Reaktionswege und Mechanismen*, Elsevier – Spektrum, Spektrum Akademischer Verlag, Heidelberg, **2007**.
[3] See, e.g.: F. Vögtle, *Chem.-Ztg.* **1972**, *96*, 396–403.
[4] Probably the first example of a metal-ion template for the formation of imino macrocycles: N. F. Curtis, D. A. House, *Chem. Ind.* **1961**, *42*, 1708.
[5] D. H. Cook, D. E. Fenton, M. G. B. Drew, S. G. McFall, S. M. Nelson, *J. Chem. Soc., Dalton Trans.* **1977**, *5*, 446–449.
[6] U. Lüning, *Liebigs Ann. Chem.* **1987**, *11*, 949–955.
[7] A recent example for the use of organic molecules as templates for the formation of a family of *endo*-functionalized molecules: S. Lüthje, C. Bornholt, U. Lüning, *Eur. J. Org. Chem.* **2006**, 909–915.
[8] Imine formation in the presence of a carbonic anhydrase as template: I. Huc, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2106–2110.
[9] Steroid oligomers by transesterification: P. A. Brady, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1997**, *21*, 3237–3253.
[10] S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 938–993; *Angew. Chem. Int. Ed.* **2002**, *41*, 898–952.
[11] P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652–3711.

[12] A. González-Álvarez, I. Alfonso, F. López-Ortiz, A. Aguirre, S. Garcia-Granda, V. Gotor, *Eur. J. Org. Chem.* **2004**, 1117–1127.

[13] For a diastereoselective amplification of imine macrocyles, see: A. González-Álvarez, I. Alfonso, V. Gotor, *Chem. Commun.* **2006**, *21*, 2224–2226.

[14] O. Storm, U. Lüning, *Chem. Eur. J.* **2002**, *8*, 793–798.

[15] A recent example for the stability of an imine in water when forming a coordinative bond to a transition-metal ion: M. Hutin, C. A. Schalley, G. Bernardinelli, J. R. Nitschke, *Chem. Eur. J.* **2006**, *12*, 4069–4076, and cited references.

[16] C. Godoy-Alcantar, A. K. Yatsimirsky, J.-M. Lehn, *J. Phys. Org. Chem.* **2005**, *18*, 979–985.

[17] W. Lu, T. H. Chang, *J. Org. Chem.* **2001**, *66*, 3467–3473: the (sulfonimino)pyridine compound **27** (more stable than an imine) was hydrolyzed in THF/H_2O (1:1).

[18] For an example, see: T. Hirashita, Y. Hayashi, K. Mitsui, S. Araki, *J. Org. Chem.* **2003**, *68*, 1309–1313. Product **2a** was hydrolyzed with a small amount of water in the solvent; in MeOH/H_2O (1:1), the product was fully hydrolyzed.

[19] A. Simion, C. Simion, T. Kanda, S. Nagashima, Y. Mitoma, T. Yamada, K. Mimura, M. Tashiro, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2071–2078.

[20] U. Lüning, R. Baumstark, K. Peters, H. G. v. Schnering, *Liebigs Ann. Chem.* **1990**, *2*, 129–143.

[21] C. D. Meyer, S. Joiner, F. Stoddart, *Chem. Soc. Rev.* **2007**, *36*, 1705–1723.

[22] S. Zameo, B. Vauzeilles, J. M. Beau, *Eur. J. Org. Chem.* **2006**, *24*, 5441–5444.

[23] In preliminary experiments, the imine formation of isophthalic dialdehyde with amines **2** and **4** has been investigated in methanol/water mixtures, too. Due to the *endo*-hydrogen atom in 2-position of the isophthalic dialdehyde, macrocycles do not form as good as with pyridine-2,6-dicarbaldehyde **1**. But in the reaction of isophthalic dialdehyde with *n*-butylamine (**2**), imine signals can also be detected, and the amount of imine formed is comparable with that of diimine **3** obtained from pyridinedialdehyde **1**. This result shows the importance of conjugation in the imines **3**, **5** and **7**.

Received: May 9, 2008
Published Online: July 15, 2008

