How To Synthesize Macrocycles Efficiently by Using Virtual Combinatorial Libraries

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Abstract: The selection of different diimines **4a–c** by alkaline earth ions from a virtual combinatorial library (VCL) is described. The products were stabilized by reduction to the diamines **6a–c**; this allowed easy analysis. The library can be directed toward different target molecules **6a–c** upon addition of alkaline earth ions with different radii. Competition experiments show the possibility of synthesizing the macrocycles **6a**, **6b**, and **6c** simultaneously when using Mg^{2+}, Ca^{2+}, and Ba^{2+} as template ions. The scope of this thermodynamically controlled, reversible approach for macrocycle syntheses is illustrated.

Keywords: macrocycles · Schiff bases · template synthesis · virtual combinatorial library

Introduction

The efficiency of the formation of cyclic organic molecules depends very much on the size of the ring to be synthesized. While five- and six-membered rings form easily,[1] strain has to be overcome to synthesize small (three- and four-membered) and medium sized rings (eight- to approx. twelve-membered cycles). Larger *macro*cycles are often strain-free, but entropy complicates their synthesis, because the ends have to "find each other". Therefore tricks like the application of the high-dilution principle[2] or a consequent reduction of rotational freedom in the nonmacrocyclic precursor[3] have been used. Comparing different possibilities for the synthesis of macrocyclic compounds, the synthetic approaches can be divided into thermodynamically controlled and kinetically controlled macrocyclizations. In addition, each approach can be supported by template molecules or ions.

What are the advantages and disadvantages of these different approaches that use a reversible (thermodynamic control) or an irreversible (kinetic control) cyclization reaction? A kinetically controlled ring-closing reaction will yield macrocycles, and due to this control and the kinetic stability of each macrocycle, once it is formed, the macrocycle will remain a macrocycle. By using the high-dilution principle, the unfavorable statistics for an intramolecular cyclization relative to an intermolecular oligomerization can be overcome. But unfortunately undesired oligomers (cyclic or not) and polymers will remain unchanged, too, due to the kinetic control and stability.

By contrast, in a thermodynamically controlled macrocyclization, all products, the desired macrocycle and the undesired oligomers and polymers, are in a constant equilibrium, which is determined by the free enthalpies of formation ΔG for all starting materials and all products.

While the enthalpy of formation of a bond will be similar for unstrained macrocycles and polymers, the entropy will differ. In a macrocyclization, *many* macrocycles are formed while a polymerization gives *one* long macromolecule. Upon dilution, the entropic contribution to ΔG will therefore also favor the formation of macrocycles in the thermodynamically controlled approach.

In order to obtain the desired macrocycle in a high yield, the macrocycle must be the most stable molecule in the reaction mixtures, that is, its free enthalpy ΔG must be the smallest. The equilibrium then will eventually transform all molecules in the reaction mixture into the most stable one, the macrocycle. The equilibrium acts as a repair mechanism if, in a first reaction, oligomers or polymers were formed.

If the desired macrocycle is the most stable product of the equilibrium, thermodynamic control is the method of choice. Several macrocycles have been synthesized in such a fashion; for instance, bis-*N*,*O*-acetals,[4] disulfides,[5] calixarenes,[6–8] alkenes (through ring closing metathesis, RCM),[9, 10] cyclic, and three-dimensional supermolecules with metal centers serving as linkage between several molecules[11–14]. The formation of large macrocyclic assemblies is also controlled by thermodynamics.[15, 16]

If the desired macrocycle is *not* the most stable product, obviously the kinetically controlled approach could be utilized. In this particular case, no repair mechanism can turn

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oligomers and polymers into the desired macrocycle. It would therefore be advantageous to force the desired macrocycle to be the most stable product in order to exploit the repair mechanisms in an equilibrium of a thermodynamically controlled reaction.

Thus the desired macrocycle has to be stabilized relative to the oligomers and polymers. Template molecules or template ions fulfill this job, and such a template effect has already been exploited for the synthesis of many macrocycles and other target molecules from a complex reaction mixture (Figure 1).[17–23]

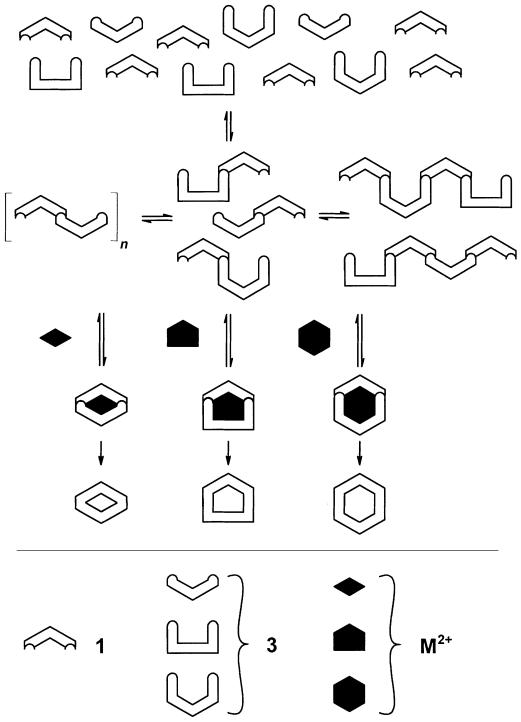
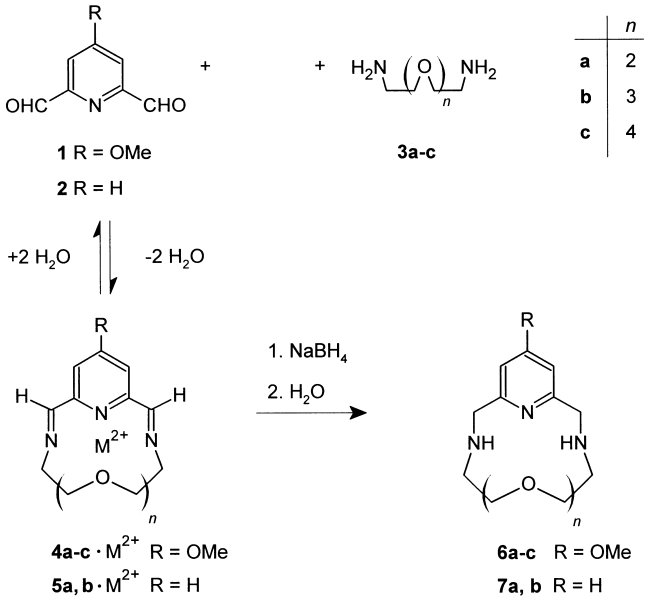


Figure 1. Representation of some possible members of the virtual combinatorial library examined.

The equilibria discussed above form virtual combinatorial libraries (VCL).[24–27] All members of such a library are constantly undergoing interconversion into each other. The use of a feasible template can select the proper macrocycle from such a library. The application of the metal-ion-template effect to the formation of macrocyclic pyridine diimines dates back to the work of Nelson.[28–30] Here, we would like to demonstrate the selection of a macrocycle from a VCL for the formation of macrocyclic diimines **4a–c** and macrocyclic diamines **6a–c**, which can easily be obtained from **4a–c** by reduction (Scheme 1). The resulting diamines **6** are less potent ligands for alkaline earth ions than diimines **4**, and thus metal free macrocycles **6** can be isolated. This template reaction has already been utilized for the synthesis of a single macrocycle from the dialdehyde **1** and a diamine **3**, for instance, in the reaction sequence for bimacrocyclic concave pyridines,[31–33] which possess appealing selectivities in the acylation of alcohols and monosaccharides with ketenes.[34–36] We have now investigated the possibility of controlling the selection of different macrocycles from the *same* reaction mixture by the use of different templates. Finally the parallel synthesis of more than one macrocycle by the simultaneous use of more than one template has been investigated.



Scheme 1. The reaction system examined, which consisted of dialdehydes **1** or **2**, diamines **3a–c** and alkaline earth metal ions M^{2+}.

Results and Discussion

The general procedure for the reaction of dialdehyde **1** with diamines **3a–c** was chosen to be comparable with established synthetic procedures.[31–33] These former experiments describe the use of a single template ion to obtain a single macrocycle (Mg^{2+} for **6a**, Ca^{2+} for **6b**, and Sr^{2+} for **6c**). The reaction times were now standardized for all experiments and therefore, in general, were longer than in the original procedure. The amount of solvent was also standardized at a high level; this resulted in lower overall concentrations. In all cases, the reduction of the diimines **4** was achieved by the same large excess of sodium borohydride (13.5 mmol). In contrast to former experiments, several alkaline earth salts were used at the same time. The yields were determined from the crude reaction mixtures by ^{1}H NMR spectroscopy after addition of a standard. All results are listed in Tables 1–4, below.

The reaction of dialdehyde **1** with all three diamines **3a–c** in the absence of any template salt and final reduction yielded only 9% of **6b** and literally no **6a** or **6c** (Table 1, entry 1). Presumably all reactants form some imine structures including oligo- and polymeric ones. However, none of these is especially favored, and this results in a large variety of different products after reduction. On addition of alkaline earth ions of increasing size to a mixture of dialdehyde **1** and diamine **3a**, the resulting yield of **6a** decreases as the ionic radii increase (entries 2–4). The small Mg^{2+} ion fits well into the macrocycle **4a**, the larger ions are less suitable for forming a [1+1] diimine complex **4a**·M^{2+}. Therefore the [2+2] dimer **8a** could be found in notable quantities when larger template ions were used (entries 3 and 4). The yield of

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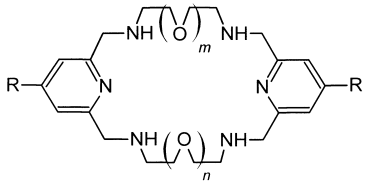
Table 1. Reaction of dialdehyde **1** with diamines **3a–c** in the presence of various alkaline earth template ions. The resulting cyclic diimines **4a–c** were analyzed as cyclic diamines **6a–c** after reduction. In some cases, crude yields of [2+2] tetraamines **8** are also listed.

	dialdehyde **1** [mmol]	**3a** [mmol]	**3b** [mmol]	**3c** [mmol]	$MgCl_2 \cdot 6H_2O$ [mmol]	$CaCl_2$ [mmol]	$SrCl_2 \cdot 6H_2O$ [mmol]	**6a**	**6b**	**6c**	**8**[b]	crude yield [mg]
								[% of max. possible yield][a]				
1	3.02	1.03	1.02	1.01				–	**9**[a]	–		1237
2	1.00	1.00			1.00			**86**				270
3	1.00	1.00				1.00		**60**			**22**[c]	272
4	1.01	0.99					1.00	**45**			**34**[c]	270
5	1.01		1.01		1.06				**34**			341
6	1.00		1.00			1.01			**79**			305
7	1.00		1.00				1.00		**6**			80
8	1.00			1.00	1.04					**61**		344
9	0.99			1.00		1.00				**70**		338
10	1.01			1.03			1.00			**24–74**		345
11	3.00	1.03	1.00	1.01	1.00	1.00	1.00	**60–84**[a]	**22**[a]	**27–62**[a]		711–825

[a] In most cases, the amount of dialdehyde **1** is yield-limiting. In the specified cases, the amount of diamine **3a–c** is yield-limiting. [b] The yield-limiting factor is the dialdehyde, but note that for each [2+2] molecule **8** two molecules of the dialdehyde **1** are required. [c] Yield of **8a**.



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8a *m,n* = 2 , R = OMe

4a (or **6a**) formed with a Mg^{2+} template is quite good and proves former results (entry 2).[31]

For the macrocyclic diamine **6b**, the maximum yield of 79% is obtained with Ca^{2+} (entry 6); this is slightly less than that observed in former experiments under slightly different reaction conditions (88%).[31] The yield of **6b** from the reaction of **1** and **3b** in the presence of Sr^{2+} is very low (entry 7), but so is the crude yield. The small amount of isolated substance (about 70% less than with the other ions) indicates some problems with the workup. This observation will be discussed below.

The formation of the largest macrocycle **4c** (detected as the reduced product **6c**) is accomplished in good yield with every ion used (entry 8-10), but there were some problems with the reproducibility when using Sr^{2+} (entry 10).

In experiments 2–10, the influence of template ions on the product yields has been examined for VCLs containing only one diamine **3a**, **3b**, *or* **3c**. However, if all three diamines **3** are present, an even larger library will result that consists of many cyclic [1+1] and [2+2] products, cyclic and acyclic oligomers and polymers. Surprisingly, the simultaneous use of all three ions and all three diamines **3a–c** also resulted in good yields of **6a** and **6c**, but gave a disappointing result of 22% for **6b** (entry 11). A comparison with entry 7 suggests that the simultaneous use of **3b** and Sr^{2+} seems to be responsible for a low yield of **6b** (**4b**).

To prove the reversibility of the diimine formation, a smaller virtual library consisting of dialdehyde **1**, two diamines **3a** and **3b**, and the corresponding template ions Mg^{2+} and Ca^{2+} was investigated. After the formation of the diimine metal-ion complexes $\mathbf{4} \cdot M^{2+}$ in a first reaction cycle of stirring and heating as above, a second equilibrating cycle of stirring and heating was carried out. In this second cycle, additional ions were added to the reaction mixture. Experiment 17 (Table 2) shows the product distribution when every component (both diamines **3** and both template ions) was present

Table 2. Reactions of dialdehyde **1** or **2** with diamines **3a–b**. Experiments to prove the reversibility of the diimine formation (**4a**, **4b**, **5a** and **5b**).

	first reaction cycle[a]						second reaction cycle[b]				
	dialdehyde **1** [mmol]	dialdehyde **2** [mmol]	**3a** [mmol]	**3b** [mmol]	$MgCl_2 \cdot 6H_2O$ [mmol]	$CaCl_2$ [mmol]	$MgCl_2 \cdot 6H_2O$ [mmol]	$CaCl_2$ [mmol]	**6a** or **7a**[c]	**6b** or **7b**[c]	sum[c]
									[% of max. possible product]		
12	1.01		0.99	1.03	2.01		–	–	**57**	**5**	62
13	1.00		1.01	1.05	2.01		–	2.00	**19**	**17**	36
14	1.01		0.99	0.99	1.99		–	2.01[d]	**13**	**25**	38
15	1.01		1.03	1.00		2.00	–	–	**6**	**71**	77
16	1.01		1.05	1.04		2.01	2.01	–	**1**	**35**	36
17	0.99		1.00	1.02	2.01	2.01	–	–	**2**	**29**	31
18	1.00		1.05	1.00			2.00	2.02	**traces**	**29**	29
19a	1.00		1.03		1.00		[e]				
19b		1.02		1.02		1.00	[e]				
19									**10/5**	**18/14**	28/19
20		1.01	1.02		1.00		–	–	**72**		
21		1.01		1.01		1.00	–	–		**95**	

[a] As given in the Experimental Section, immediate workup with no addition of further ions. [b] Instead of the reduction at the end of the first reaction cycle, additional ions were added, and a second cycle was carried out according to the general procedure. [c] With both aldehydes **1** and **2** present in the reaction, the results are listed as **6a**/**7a** and **6b**/**7b**. [d] The reaction time had been tripled. [e] These two samples were combined for the second cycle.

from the very beginning: 2% of **6a** and 29% of **6b** giving a total of 31% of the cyclic diamines **6**. Just the first cycle with $MgCl_2 \cdot 6H_2O$ (entry 12) leads to 57% of **6a** and 5% of **6b**. The subsequent addition of $CaCl_2$ (entry 13) changes these results to 19% and 17%, respectively, whilst expansion of the second cycle to a reaction time three times as long (entry 14) gives 13% for **6a** and 25% for **6b**, this shifts the yield ratio **4a/4b** toward the expected one (entry 17). The interconversion of **4a**·Mg^{2+} to **4b**·Ca^{2+} requires a ring opening of the template-stabilized macrocycle **4a** and a transamination. The kinetics for this reaction seem to be slower than the rates of interconversion of the diimines (mostly acyclic) formed in the standard reactions. The slower kinetics may also explain the lower yields[37] of **6** when more than one reaction cycle was carried out. However this slow interconversion proves the reversibility.

When dialdehyde **1** condenses with diamine **3b** or **3a** in the presence of Ca^{2+}, **6b** is formed in 71% and **6a** in 6% yield (entry 15). Even when the diamines **3a** and **3b** and dialdehyde **1** are reacting with one another in a 1:1:1 ratio in the absence of any template salt (presumably resulting in various [1+2] diimines), the subsequent equilibration in the presence of Mg^{2+} and Ca^{2+} (entry 18) results in the same product distribution as if Mg^{2+} and Ca^{2+} were present from the very beginning (entry 17).

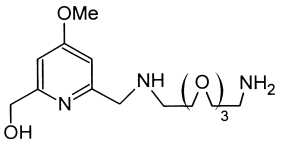
An interconversion should also occur when different aldehydes **1** and **2** are used. In the first cycle, the diimine-template ion complexes **4a**·Mg^{2+} and **5b**·Ca^{2+} were formed (entries 19a and b). The reduction step would only lead to two different diamines **6a** and **7b**. But these mixtures were combined for a second cycle and, after reduction, were analyzed as diamines **6a** (10%), **6b** (18%), **7a** (5%) and **7b** (14%). The fact that all four diamines could be found showed the interconversion and reversibility of the imine formation. For comparison, experiments 20 and 21 were carried out to obtain **7a** and **7b**.

In reactions 1–11, the ratio between dialdehyde **1** and diamines **3a–c** was always chosen to be 1:1. Table 3 explores the efficacy of the template stabilization of **4a–c**, even in the presence of excess competing diamines, to give [1+1] macrocycles **4** rather than [1+2] acyclic diimines (resulting from one dialdehyde **1** and two diamines **3**), which would be favored stoichiometrically.

Of the three diimines **4**, Ca^{2+} stabilizes diimine **4b** best; this results in a good yield of **6b** (73%, entry 23). Entry 22 shows that Mg^{2+} is capable of selecting **4a**, but that **4b** is formed in minor yield, too. Again, Sr^{2+} gives unexpected results (entry 24).

Higher concentrations of all participating reactants cause decreases in all observed yields (entry 25–27), probably by favoring *inter*molecular reactions: i) the *uni*molecular ring closure of the remaining aldehyde and amine functions of a monoimine gives a [1+1] macrocyclic diimine, ii) the *inter*molecular reaction between the monoimine–monoaldehyde intermediate and further diamine **3** gives a [1+2] nonmacrocyclic diimine. The competition between these two reactions is concentration dependent.

When the template ions are used in excess, the formation of **4a**, **4b**, and **4c** seems to be quite resistant to a higher concentration of the best "fitting" template salt (entries 28–30). When all three diamines **3** were present but the template ion concentration was chosen to match the total diamine **3** concentration, Mg^{2+} and Ca^{2+} gave even better yields of **4a** (73%, entry 31) and **4b** (81%, entry 32). Again the Sr^{2+} results (entry 33) cannot be rationalized easily.



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In the simultaneous experiment with all three diamines **3a–c** and all three template ions, the latter in a threefold excess (entry 34), **4a** and **4c** display the same results as found for the experiment with a single diamine **3a** or **3c** (entries 28 and 30, respectively). No **6b** could be found, a result even worse than in the parallel template experiment 11. Runs 11 and 34 call for a closer investigation of the reaction of

Table 3. Reaction of dialdehyde **1** with diamines **3a–c** in the presence of various alkaline earth metal ions; variations in concentration of all reaction partners and ion concentrations. The resulting cyclic diimines **4a–c** were analyzed as cyclic diamines **6a–c** after reduction.

	dialdehyde **1** [mmol]	**3a** [mmol]	**3b** [mmol]	**3c** [mmol]	$MgCl_2 \cdot 6H_2O$ [mmol]	$CaCl_2$ [mmol]	$SrCl_2 \cdot 6H_2O$ [mmol]	**6a** [% of max. possible yield][a]	**6b**	**6c**	crude yield [mg]
22	1.00	1.05	1.01	1.01	1.00			**44**	**7**	–	454
23	1.01	1.01	1.06	1.03		1.00		–	**73**	–	471
24	1.00	1.00	1.03	1.02			1.00	–	**19**	**2**	368
25	3.01	2.95	3.00	3.06	3.01			**13**	**6**	–	1041
26	3.01	3.00	3.02	3.04		3.05		–	**53**	–	1608
27	3.01	3.01	2.99	3.00			3.02	–	**2**	–	909
28	1.01	1.04			3.00			**75**			271
29	1.01		1.00			3.01			**72**		277
30	0.99			1.03			3.00			**76**	334
31	1.01	1.01	1.00	0.99	3.00			**73**	**9**	–	513
32	1.00	1.14	1.00	1.01		3.00		–	**81**	–	499
33	1.00	0.99	1.03	0.97			3.00	**traces**	**2**	**6**	337
34	3.01	1.05	1.01	1.01	2.98	3.01	3.00	**53–75**[a]	**0**[a]	**76**[a]	635
35	1.00		1.00		2.98	3.02	3.00		**0**[b]		98
36	1.00		1.00			8.99			**23**		184

[a] In most cases the amount of dialdehyde **1** is yield-limiting. In the specified cases the amount of diamine **3a–c** is yield-limiting. [b] Instead of **6b**, **9** could be isolated in 29% of the maximum possible yield.

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dialdehyde **1** with diamine **3b** in the presence of an excess of *all* three template ions (entry 35).

When Mg^{2+}, Ca^{2+}, and Sr^{2+} were each present in a threefold excess, no **6b**, but a nonmacrocyclic hydroxyaminoamine **9** could be isolated in 29% yield (entry 35). The use of a ninefold excess of Ca^{2+} only resulted in 23% of **6b** (entry 36); this showed i) the incompatibility of **6b** (**4b**) and Sr^{2+} (entry 35) and ii) that the template-ion concentration chosen should not be too high (entry 36).

The use of strontium as a template for **4b** and all other experiments with Sr^{2+} and **4b** present at the same time led to unpredicted results and remarkably low crude yields (see above). Maybe, in the presence of Sr^{2+}, the reactants form products that are more soluble in water than in dichloromethane and therefore disappear during the workup process. Alternatively, **4b** is formed and is reduced to **6b**, but in the workup process Sr^{2+} forms some water-soluble complex with **6b** and therefore escapes detection. And indeed, in an extraction experiment with isolated **6b** in $CDCl_3/D_2O$ the ^1H NMR signals of **6b** in the $CDCl_3$ layer were diminished to a third upon addition of $SrCl_2 \cdot 6H_2O$ to the sample. According to these results, concentrated alkaline sodium citrate solution was added to the aqueous phase to decomplex Sr^{2+} from **6b**$\cdot Sr^{2+}$. But analysis of 130 mg of extracted material showed no additional **6b**. Instead IR and MS spectra of the extracted material point to some diimine structure, which may be diimine **4b**. This would imply that the complex **4b**$\cdot Sr^{2+}$ is stable enough to withstand the reduction by sodium borohydride. The complexes of **5a**$\cdot M^{2+}$ with Ca^{2+} and Sr^{2+} have been isolated before.[38]

To circumvent the problem that occurs when using Sr^{2+}, the next larger alkaline earth ion was considered as a template ion. The ion radius of Ba^{2+} is 1.34 Å, and therefore there is a larger difference between it and the Ca^{2+} (0.99 Å) and Mg^{2+} ions (0.66 Å) than there is for Sr^{2+} (1.12 Å).[39] The larger Ba^{2+} ion is supposed to have altered interactions with the intermediates and products on the road to **4b**. Nevertheless the barium ion is able to template the formation of diimine **4c** in a satisfactory manner (Table 4, entry 39). When using diamine **3a**, it favors the formation of the [2+2] macrocycle **8a** (48%) over **6a** (8%); this is in good agreement with the increased ion radius compared with Sr^{2+} (entry 37). In contrast to the use of Sr^{2+} (entry 7), the templating of the reaction of **1** with **3b** by Ba^{2+} results in 24% of **6b** (entry 38). The crude yield is reasonable; this indicates that there is no workup problem when Ba^{2+} is used. The most important fact is that the barium ion is sufficiently capable of serving as a template in the competition of the formation of **4a**, **4b**, and **4c** at the same time and that it favors **4b** and **4c** (entry 40). At higher concentrations of Ba^{2+} the preference is shifted to **4c** over **4b** (entry 41).

Finally in a reaction mixture that is able to form all diimines **4** (entry 42), all three are formed in a good manner; this leads to the resulting diamines **6a–c** in yields between 71 and 84%.

Conclusion

A system consisting of many different diimines (cyclic, acyclic) of different sizes (monomers, oligomers, polymers) and from different building blocks (one or more of each kind) can be directed to a mixture containing only a few well-defined species. And with a proper fixation (in this case an irreversible reduction to diamines) the resulting library can be read. It is possible to obtain *different* target molecules starting from the *same* system or to obtain even *several* target molecules *at the same time*.

Experimental Section

General Remarks: The following chemicals were obtained commercially and used without further purification:[40] barium chloride dihydrate (Merck), calcium chloride (Merck), 1,8-diamino-3,6-dioxaoctane (**3a**) (Aldrich), magnesium chloride hexahydrate (Merck), sodium borohydride (Fluka), strontium chloride hexahydrate (Merck), and dimethyl terephthalate (Fluka). The dialdehydes **1** and **2** were prepared according to literature procedures.[32] The diamines **3b** and **c** were also synthesized by known procedures.[32, 33] Dry methanol was obtained by distillation from magnesium. Dichloromethane was distilled from CaH_2. The NMR spectra were recorded on a Bruker AM300 (300 MHz) spectrometer in $CDCl_3$, with TMS as internal standard. IR spectra were recorded on a Perkin Elmer 1600 Series. MS spectra were recorded on a Finnigan MAT 8230.

General procedure for the synthesis of diamines 6a–c, 7a, and **7b**: Dialdehyde **1** or **2** and template salts (amounts as given in the Tables) were dissolved in dry methanol (80 mL). Under argon, the diamines **3a–c**, dissolved in dry methanol (30 mL), were added dropwise over 30 min. The reaction mixture was stirred for 1 h and then heated for 2 h. After cooling the mixture to 0 °C, sodium borohydride (13.5 mmol) was added in several portions. The mixture was stirred at room temperature for another 15 h. Water (25 mL) was added, and stirring was continued for 4 h. Methanol was removed in vacuo, and the remaining aqueous phase was extracted four times with dichloromethane (25 mL). The organic layer was dried with magnesium sulfate, and the solvents were removed in vacuo. The oily residue was analyzed without further purification.

Analysis: The experiments were carried out one to three times. The yields listed in the Tables are averages. If values differed by more than 10% a range is given. The quantitative yield determination of the macrocyclic diamines **6a–c**, **7a**,and **7b** was carried out by ^1H NMR. The integrals of the aromatic hydrogen atoms were compared with the integral of a known amount of dimethyl terephthalate at $\delta = 8.11$ (s). The ratios of this integral

Table 4. Reaction of dialdehyde **1** with diamines **3a–c** as reported in Tables 1 and 3 but with Ba^{2+} instead of Sr^{2+}.

	dialdehyde **1** [mmol]	**3a** [mmol]	**3b** [mmol]	**3c** [mmol]	$MgCl_2 \cdot 6H_2O$ [mmol]	$CaCl_2$ [mmol]	$BaCl_2 \cdot 2H_2O$ [mmol]	**6a**	**6b**	**6c**	**8**[a]	crude yield [mg]
								[% of max. possible yield]				
37	1.01	0.99					1.00	**8**			**48**[b]	265
38	1.01		1.00				1.01		**24**			230
39	1.00			1.00			1.00			**56**		284
40	0.99	1.01	1.00	1.01			1.00	–	**34**	**18**		462
41	1.00	1.00	1.07	1.00			3.00	–	**7**	**25**		412
42	3.00	1.04	1.02	1.00	1.01	1.01	1.00	**81**	**74**	**71**		892

[a] The yield-limiting factor is the dialdehyde, but note that, for each [2+2] molecule **8**, two molecules of the dialdehyde **1** are required. [b] Yield of **8a**.

have been determined to be between 0.3 and 1.5 of the most intensive single integral. The chemical shifts of the aromatic protons are: **6a** at $\delta = 6.56$ (s), **6b** at $\delta = 6.60$ (s), **6c** at $\delta = 6.67$ (s), **7a** at $\delta = 7.01$ (d, $J = 7.5$ Hz, 2H) and 7.54 (t, $J = 7.5$ Hz, 1H), **7b** at $\delta = 7.03$ (d, $J = 7.5$ Hz, 2H) and 7.53 (t, $J = 7.5$ Hz, 1H). For complete spectroscopic data of **6a–c**, **7a**, and **7b** see refs. [32], [33].

The signals for the [2+2] tetraamines **8** could only be assigned without doubt for the noncompetition experiments (entries 2–4 and 37) and for the [2+2] tetraamine **8a**. The pyridine signal is located at $\delta = 6.70$ for **8a**; this is in good agreement with earlier results.[41, 42]

2-[*N*-(11-Amino-3,6,9-trioxaundecyl)aminomethyl]-6-hydroxymethyl-4-methoxypyridine (9): The general procedure with **1** (1 mmol), **3b** (1 mmol), $MgCl_2$ (2.98 mmol), $CaCl_2$ (3.02 mmol), and $SrCl_2$ (3 mmol) gives **8**. Yield: 98 mg (29%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.7$ (br, 4H; D_2O, NH_2, NH, OH), 2.84 (m, 4H), 3.55 (m, 2H), 3.6–3.7 (m, 6H), 3.8–3.9 (m, 11H), 4.68 (t, 0.63 Hz, 2H), 6.68 (d, 2.3 Hz, 1H), 6.75 (d, 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 40.15 (t), 47.63 (t), 53.64 (t), 54.24 (q), 63.29 (t), 69.18 (t), 69.35 (t), 69.45 (t), 71.16 (t), 76.35 (t), 103.49 (d), 106.09 (d), 158.93 (s), 160.91 (s), 165.90 (s); EI-MS (70 eV): *m*/*z* (%): 343 (15), 181 (100); CI-MS (*iso*-butane): *m*/*z* (%): 344 (100); HRMS ($C_{16}H_{29}N_3O_5$): calcd. 343.21072; found 343.21070; ($C_{15}{}^{13}CH_{29}N_3O_5$) calcd. 344.21408; found 344.21390.

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