CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200500621

Utilization of Self-Sorting Processes To Generate Dynamic Combinatorial Libraries with New Network Topologies

Isabelle Saur, Rosario Scopelliti, and Kay Severin*[a]

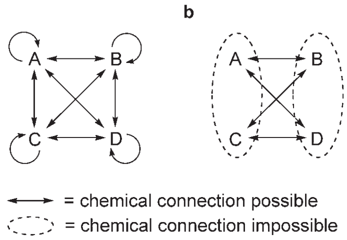
Abstract: The synthesis of water-soluble, organometallic macrocycles is described. They were obtained by self-assembly in reactions of the half-sandwich complexes [{Ru(C_6H_5Me)Cl_2}$_2$], [{Ru(*p*-cymene)Cl_2}$_2$], [{Rh(Cp)Cl_2}$_2$], and [{Ir(Cp*)Cl_2}$_2$] with the ligand 5-dimethylaminomethyl-3-hydroxy-2-methyl-4-(1*H*)-pyridone in buffered aqueous solution at pH 8. The structure of the Ru–(*p*-cymene) complex was determined by single-crystal X-ray crystallography. Upon mixing, these complexes undergo scrambling reactions to give dynamic combinatorial libraries. In combination with structurally related complexes based on amino-methylated 3-hydroxy-2-(1*H*)-pyridone ligands, an exchange of metal fragments but no mixing of ligands was observed. This self-sorting behavior was used to construct dynamic combinatorial libraries of macrocycles, in which two four-component sub-libraries are connected by two common building blocks. This type of network topology influences the adaptive behavior of the library as demonstrated in selection experiments with lithium ions as the target.

Keywords: combinatorial chemistry · iridium · macrocycles · receptors · ruthenium

Introduction

Starting with seminal publications by the groups of Sanders,[1] Lehn,[2] and others[3] in the mid 1990s, dynamic combinatorial chemistry has emerged as a powerful tool for the discovery of new receptors, drugs, catalysts, and materials.[4] The adaptive behavior of dynamic combinatorial libraries (DCLs) has received particular attention in this context. DCLs are formed by combinatorial assembly[5] of molecular building blocks under thermodynamic control. They represent chemical networks that are able to respond to changes in their environment.[6] Upon addition of a target molecule that selectively interacts with some members of the library, a re-equilibration occurs. This adaptation can be used to identify library members with a high affinity for the respective target.[4]

A key characteristic of a particular DCL is its network topology, which is controlled by the chemical reactivity of the constituent building blocks and other factors such as steric and geometric restraints. So far, experiments have mainly focused on two types of libraries. In the first type of DCL, a symmetrical coupling chemistry is employed. Consequently, each building block can assemble with each other building block and with itself (Scheme 1a). Systems of this kind have been realized with thiols, which were connected by oxidation to give exchange-labile disulfides,[7] or with the help of cross-metathesis reactions.[8] A second type of DCL is based on building blocks that display a directional chemical reactivity. This includes libraries that are formed by reactions between aldehydes and amines,[2c,9] or aldehydes and hydrazides,[10] among various others.[4] For such libraries,



Scheme 1. Schematic representation of chemical networks based on four different monofunctional molecules. a) In a fully connected network, each molecule can be connected to each other molecule and to itself. b) Directional chemical reactivity may lead to subgroups, for which intragroup connections are not possible.

---

[a] Dr. I. Saur, Dr. R. Scopelliti, Prof. K. Severin
Institut des Sciences et Ingénierie Chimiques
École Polytechnique Fédérale de Lausanne (EPFL)
1015 Lausanne (Switzerland)
Fax: (+41) 21-693-9305
E-mail: kay.severin@epfl.ch

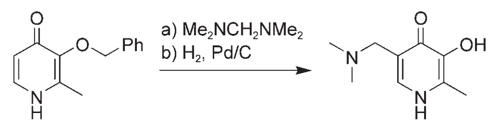
connections between one subgroup (e.g., aldehydes) and another subgroup (e.g., hydrazides) are possible, but connections *within* the subgroup (e.g., coupling of two aldehydes) do not occur (Scheme 1b). When multifunctional building blocks with two (or more) different connecting groups are employed (e.g., a molecule with an aldehyde and a hydrazide group), homoaggregations become possible, but still the complexity of the DCL is likely to be lower that which would be found for a symmetrical coupling chemistry.

In recent years, DCLs with more complex network architectures have been explored. One approach is to simultaneously utilize several types of coupling chemistry for the construction of the library. For example, noncovalent interactions (hydrogen bonds) have been used in combination with dynamic covalent bonds (acyl hydrazones),[11] metal–ligand interactions have been employed in parallel to imine exchange reactions,[12] and thioester exchange reactions were combined with disulfide exchange reactions.[13] In the following we describe an alternative approach, which is based on the utilization of a self-sorting process[14] in combination with a metal–ligand assembly reaction. The resulting DCL displays a network architecture, in which two sub-libraries are connected by two common building blocks. As a consequence, a unique behavior is observed in selection experiments with lithium ions as the target.

Results and Discussion

In previous publications we have shown that trinuclear metallamacrocycles can be obtained in water at neutral pH by reaction of organometallic half-sandwich complexes of the general formula $[\{M(L)_nCl_2\}_2]$ ($M(L)_n = Ru(\eta^6\text{-arene})$, $Rh(\eta^5\text{-}C_5H_xMe_{5-x})$, $Ir(\eta^5\text{-}C_5H_xMe_{5-x})$) with aminomethylated 3-hydroxy-2(1*H*)-pyridone ligands.[15,16] These complexes act as potent and selective receptors for lithium ions, and we used them to build a colorimetric sensor that allowed us to detect Li^+ in water in the pharmacologically relevant concentration range of 1 mM with the "naked eye".[16] Another interesting feature of these complexes is that they easily undergo exchange reactions. Upon mixing of aqueous solutions of a Ru macrocycle with an Ir macrocycle, for example, mixed-metal complexes are rapidly formed. This allowed us to build simple model DCLs in order to study some very basic phenomena, such as the influence of the target concentration on the adaptive behavior of the DCL.[17]

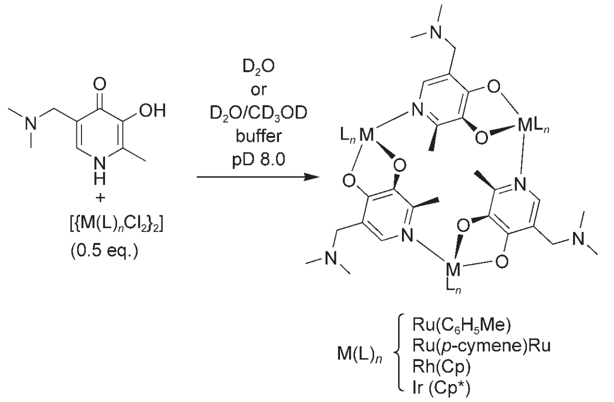
In continuation of this work, we were interested in obtaining organometallic macrocycles that are soluble in water, but which display a structure different from what was found for the 3-hydroxy-2(1*H*)-pyridone-based complexes. For these investigations, we synthesized the new heterocyclic ligand **1** by aminomethylation of 3-benzyloxy-2-methyl-4(1*H*)-pyridone[18] and subsequent cleavage of the benzyl group by hydrogenolysis (Scheme 2). The dimethylaminomethyl group of **1** was expected to enhance the solubility of the resulting complexes in aqueous solution (partial protonation at neutral pH) without interfering with the assembly reaction. The 3-hydroxy-2-methyl-4(1*H*)-pyridone core of ligand **1**, on the other hand, was known to support the formation of macrocyclic halfsandwich complexes.[19]



1

Scheme 2. Synthesis of ligand **1**.

Upon reaction of ligand **1** with half an equivalent of $[\{M(L)_nCl_2\}_2]$ ($M(L)_n = Ru(C_6H_5Me)$, Ru(*p*-cymene)Ru, Rh(Cp), Ir(Cp*)) in either D_2O or D_2O/CD_3OD (7:3)[20] containing phosphate buffer (pD = 8.0), a single new complex was formed in over 95% yield as evidenced by ^1H NMR spectroscopy (Scheme 3). The spectra displayed only one set of signals for ligand **1** and for the metal fragments $M(L)_n$, indicating highly symmetrical structures. For the NCH_2 protons, two doublets at 3.6–4.0 ppm were observed for all complexes. This observation showed that the pseudotetrahedral metals represent stereogenic centers that are configurationally stable on the NMR timescale.



Scheme 3. Self-assembly of organometallic macrocycles. The dimethylamino groups are partially protonated under those conditions (not shown).

To establish the structure of the complexes, we tried to obtain single crystals suited for a crystallographic analysis. For the Ru(*p*-cymene) complex, this was possible by adding an excess of K_2HPO_4. The addition of the basic phosphate salt lead to a deprotonation of the dimethylamino groups and consequently to a reduced solubility in water. Alternatively, the complex can be precipitated by using CsOH as the base. The molecular structure of one enantiomer of the neutral macrocycle **2** is shown in Figure 1.

Complex **2** shows the expected[19] trigonal structure with a (crystallographic) C_3 symmetry. The metal centers are bridged by the two adjacent oxygen atoms and the nitrogen atom of the pyridonate ligand. The planes of the heterocyclic ligands are nearly perpendicular ($\Theta = 85.97°$) to the plane de-

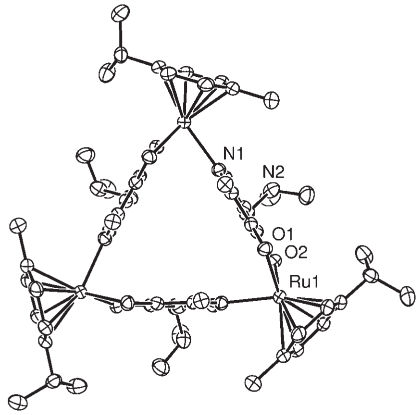
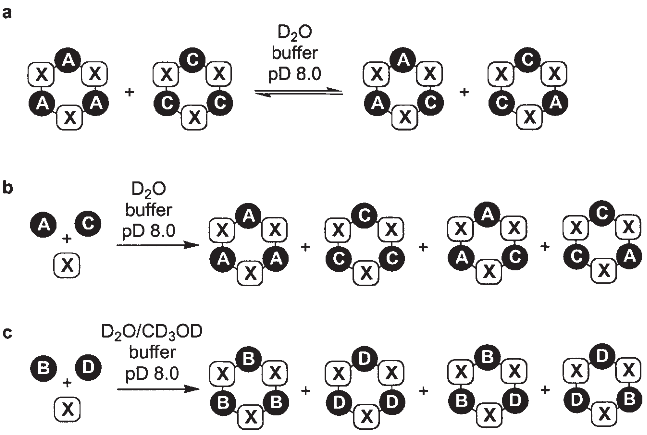


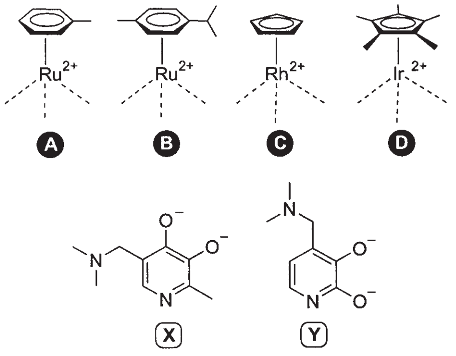
Figure 1. ORTEP[34] representation of the molecular structure of complex **2** in the crystal. The co-crystallized water solvent molecules and the hydrogen atoms are not shown for clarity. Selected bond lengths (Å) and angles (°): Ru1−O1 = 2.067(3), Ru1−O2 = 2.080(3), Ru1−N1′ = 2.174(3); O1-Ru1-O2 = 79.34(12), O1-Ru1-N1′ = 84.81(12), O2-Ru1-N1′ = 82.13(13).



Scheme 4. a) When solutions of the macrocycles $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ are combined, an equilibrium with the mixed macrocycles $\mathbf{AX}(\mathbf{CX})_2$ and $\mathbf{CX}(\mathbf{AX})_2$ is established b) A mixture of identical composition is obtained by self-assembly of the building blocks **A**, **C**, and **X**. c) A dynamic library of the macrocycles $(\mathbf{BX})_3$, $(\mathbf{DX})_3$, $\mathbf{BX}(\mathbf{DX})_2$ and $\mathbf{DX}(\mathbf{BX})_2$ is obtained by the self-assembly of the building blocks **B**, **D**, and **X**.

fined by the three ruthenium atoms. The Ru atoms are 7.277(1) Å apart from each other.

Having established that ligand **1** can be used for the assembly of trinuclear metallamacrocycles in water, scrambling reactions were investigated. It turned out that mixed-metal complexes are rapidly formed upon combination of two symmetrical macrocycles. For the discussion of these results, we will use the notation depicted below, in which the metal fragments are denoted by **A**–**D** and the bridging ligands by **X** and **Y**.



When aqueous solutions (5.0 mM, D_2O, phosphate buffer, pD 8.0) of the complexes $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ were mixed, the asymmetric complexes $\mathbf{AX}(\mathbf{CX})_2$ and $\mathbf{CX}(\mathbf{AX})_2$ could be observed by ^1H NMR spectroscopy within a few minutes. The final equilibrium was reached after 2 h (Scheme 4a). A mixture with an identical composition (^1H NMR spectroscopy) was obtained when the complexes were prepared in situ, by adding buffered D_2O to a mixture of ligand **1** and the two complexes $[\{Ru(C_6H_5Me)Cl_2\}_2]$ and $[\{Rh(Cp)Cl_2\}_2]$ (Scheme 4b). Similarly, addition of a buffered D_2O/CD_3OD (7:3) solution to a mixture of ligand **1** and the two complexes $[\{Ru(p\text{-cymene})Cl_2\}_2]$ and $[\{Ir(Cp^*)Cl_2\}_2]$ lead to the formation of the four complexes $(\mathbf{BX})_3$, $\mathbf{BX}(\mathbf{DX})_2$, $\mathbf{DX}(\mathbf{BX})_2$ and $(\mathbf{DX})_3$ (Scheme 4c). For the last reaction, a mixture of D_2O and CD_3OD (7:3) was employed due to the low solubility of Ir(Cp*)-containing complexes in plain D_2O.

The ^1H NMR spectrum of the equilibrated mixture generated from $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ showed eight signals for the aromatic CH group of the ligand **X** in the region from $\delta = 7.1$ to 7.4 ppm (Figure 2). One signal is expected for each of the symmetrical macrocycles $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ and three signals for each of the mixed complexes $\mathbf{AX}(\mathbf{CX})_2$ and $\mathbf{CX}(\mathbf{AX})_2$. In the aliphatic region of the spectrum, four signals corresponding to the methyl group of the C_6H_5Me π-ligand were observed. Again, this was in agreement with a scrambling reaction since one signal was expected for the symmetric macrocycle $(\mathbf{AX})_3$, one signal for the mixed complex $\mathbf{AX}(\mathbf{CX})_2$, and two signals for the macrocycle $\mathbf{CX}(\mathbf{AX})_2$. The relative intensities of the respective signals were approximately equal, which suggested a nearly statistical ratio of $(\mathbf{AX})_3$:$\mathbf{AX}(\mathbf{CX})_2$:$\mathbf{CX}(\mathbf{AX})_2$:$(\mathbf{CX})_3$ ~1:3:3:1.

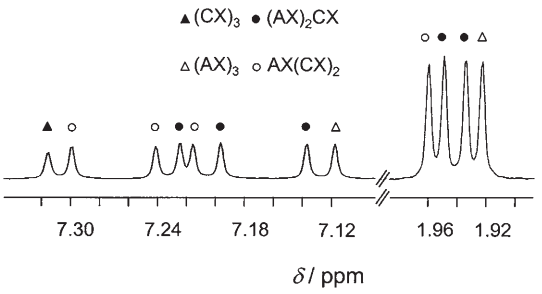


Figure 2. Part of the ^1H NMR spectrum of a mixture of $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ after equilibration (D_2O, phosphate buffer, pD 8.0). The signals correspond to the aromatic CH proton of the ligand **X** (7.1–7.4 ppm) and to the methyl group of the π ligand of **A** (1.9–2.0 ppm).

Very similar results were obtained for a mixture generated from $(\mathbf{BX})_3$ and $(\mathbf{DX})_3$: eight ^{1}H NMR signals were found for the aromatic CH group of the ligand **X** and the peak intensity was in agreement with a nearly statistical 1:3:3.1 ratio of the four different complexes.

The formation of four-component DCLs by scrambling was furthermore confirmed by ESI mass spectrometry. Isotope-resolved peaks were observed for the four different macrocycles, with the peaks of the mixed complexes being the dominant ones. Part of the spectrum obtained for a mixture of $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ is shown in Figure 3.

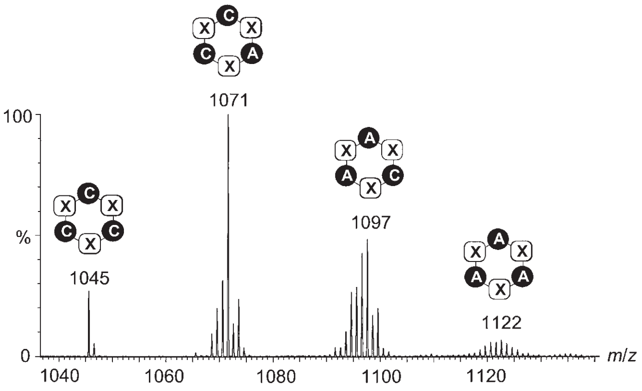
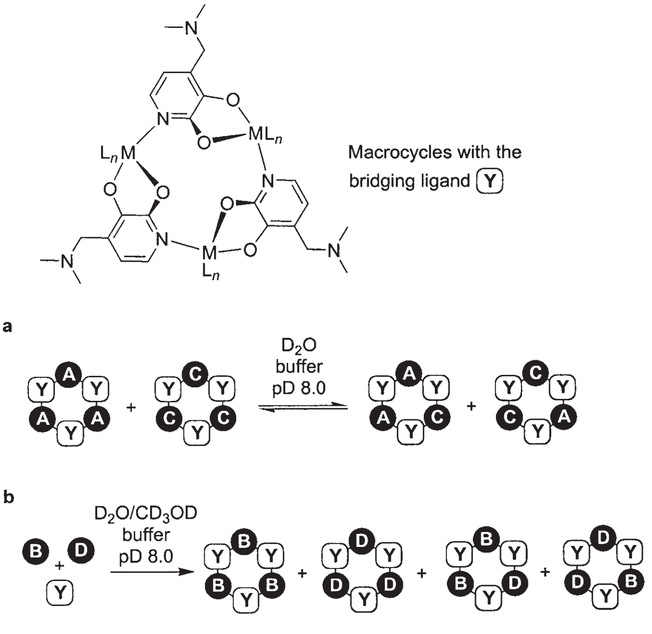


Figure 3. Part of the ESI mass spectrum of an equilibrated mixture of the complexes $(\mathbf{AX})_3$, $(\mathbf{CX})_3$, $\mathbf{AX}(\mathbf{CX})_2$, and $\mathbf{CX}(\mathbf{AX})_2$.

When macrocycles with the bridging ligand **Y** were employed, dynamic mixtures of homo- and heterometallic complexes were also formed in aqueous buffered solution at pD 8.0 as evidenced by NMR spectroscopy and ESI mass spectrometry. Thus, a combination of $(\mathbf{AY})_3$ and $(\mathbf{CY})_3$ gave rapidly the mixed complexes $\mathbf{AY}(\mathbf{CY})_2$ and $\mathbf{CY}(\mathbf{AY})_2$ (Scheme 5a). As it was observed for the corresponding mixtures with ligand **X**, four equally intense ^{1}H NMR signals for the methyl group of the π ligand of **A** were observed at $\delta = 1.8$–2.0 ppm in agreement with a nearly statistical distribution. For the self-assembly of the building blocks **B**, **D**, and **Y**, the ^{1}H NMR data supported a statistical distribution as well (Scheme 5b).



Scheme 5. a) When solutions of the macrocycles $(\mathbf{AY})_3$ and $(\mathbf{CY})_3$ are combined, an equilibrium with the mixed macrocycles $\mathbf{AY}(\mathbf{CY})_2$ and $\mathbf{CY}(\mathbf{AY})_2$ is established. b) Similar results are obtained for the self-assembly of the building blocks **B**, **D**, and **Y**.

Next, we investigated a more complex mixture containing the metal building blocks **A** and **C** as well as both bridging ligands **X** and **Y**. Analysis of the resulting dynamic combinatorial library of macrocycles by ^{1}H NMR spectroscopy revealed a surprisingly low complexity. In fact, the spectrum showed the species identified in mixtures of $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ and of $(\mathbf{AY})_3$ and $(\mathbf{CY})_3$, but no other complexes. This was confirmed by adding the equilibrated mixture depicted in Scheme 4a to the mixture shown in Scheme 5a. No further re-equilibration was observed by ^{1}H NMR spectroscopy (Figure 4). These data suggested that the assembly process of the building blocks **A**, **C**, **X**, and **Y** was strongly self-sorting: out of the 24 possible trinuclear macrocycles, only eight were formed (Scheme 6). These eight complexes contained either ligand **X** or ligand **Y**, but no combination of both.

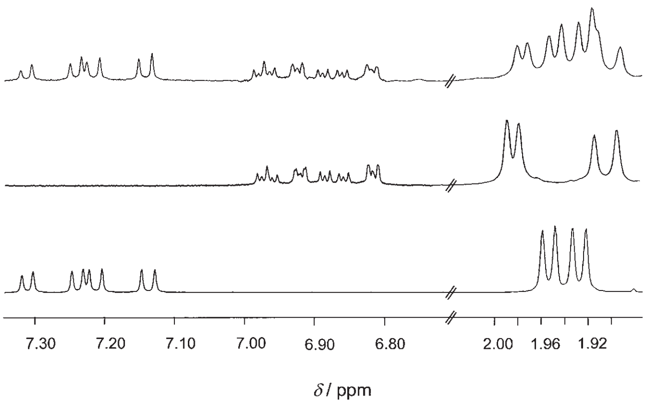
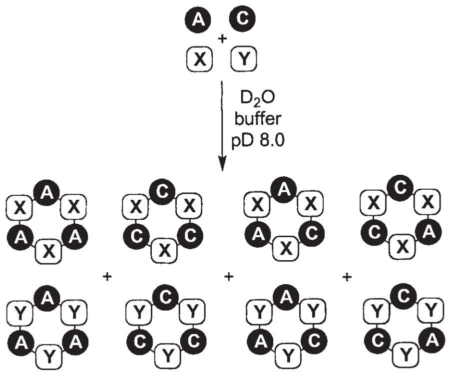


Figure 4. Part of the ^{1}H NMR spectra (D_2O, phosphate buffer, pD 8.0) of a mixture of $(\mathbf{AX})_3$ and $(\mathbf{CX})_3$ after equilibration (bottom), a mixture of $(\mathbf{AY})_3$ and $(\mathbf{CY})_3$ after equilibration (middle), and a mixture of $(\mathbf{AX})_3$, $(\mathbf{CX})_3$, $(\mathbf{AY})_3$, and $(\mathbf{CY})_3$ after equilibration (top). The signals correspond to the aromatic CH proton of the ligand **X** ($\delta = 7.1$–7.4 ppm), to one of the aromatic CH protons of the ligand **Y** ($\delta = 6.8$–7.0 ppm) and to the methyl group of the π-ligand of **A** ($\delta = 1.8$–2.0 ppm).

The self-sorting of **X**- and **Y**-containing macrocycles is likely the result of geometric restraints. Whereas complexes based on ligand **X** have a trigonal prismatic structure, complexes based on ligand **Y** have a concave, domelike structure (Figure 5). Apparently, there is no low-energy geometry for hypothetical complexes containing a mixture of the ligands **X** and **Y**.

To investigate the mechanism of the scrambling reactions, we have examined the reaction of the two symmetrical mac-



Scheme 6. Self-assembly of the building blocks **A**, **C**, **X**, and **Y** leads to the formation of eight different macrocycles. Complexes containing both the ligand **X** and the ligand **Y** are not observed.

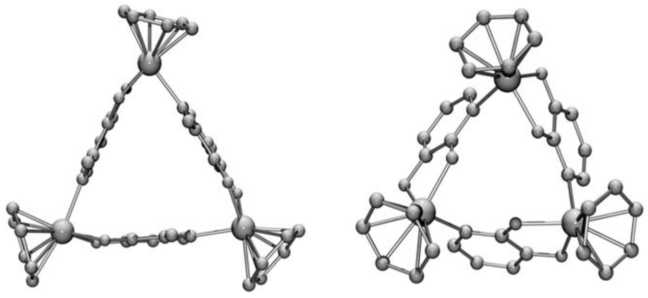
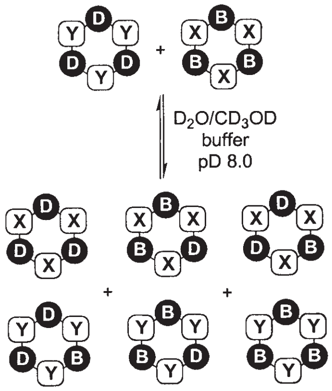


Figure 5. Ball and stick representation of the molecular structure of complex **2** containing the bridging ligand **X** (left) and of a macrocycle comprised of Ru(*p*-cymene) fragments and a bridging ligand of type **Y** (right).[35] To highlight the differences in geometry, the alkyl groups of the aromatic π ligand, the aminomethyl groups and the hydrogen atoms have been omitted.

rocycles $(\mathbf{DY})_3$ and $(\mathbf{BX})_3$. The weakest connection in these macrocycles is assumed to be the metal–nitrogen bond. For exchange reactions proceeding exclusively through a breakage of these bonds, no scrambling would be expected for the reaction of $(\mathbf{DY})_3$ with $(\mathbf{BX})_3$, given that mixed macrocycles containing both ligand **X** and **Y** are excluded due to self-sorting. However, if the metal–oxygen bonds are likewise labile, eight different macrocycles should form (Scheme 7).



Scheme 7. Scrambling of the complexes $(\mathbf{DY})_3$ and $(\mathbf{BX})_3$ leads to the formation eight different macrocycles.

This corresponds to what was observed by ^{1}H NMR spectroscopy (Figure 6). Before equilibration, a single peak was observed in the region around $\delta = 7$ ppm, which can be attributed to the aromatic proton of the **X** ligand in $(\mathbf{BX})_3$. After equilibration, eight signals were found that correspond to $(\mathbf{BX})_3$ (one signal), $(\mathbf{DX})_3$ (one signal), $\mathbf{DX}(\mathbf{BX})_2$ (three signals), and $\mathbf{BX}(\mathbf{DX})_2$ (three signals). The remaining four complexes containing the **Y** ligand showed less separated signals in the ^{1}H NMR spectrum, but could still be identified. The formation of $(\mathbf{DX})_3$ from $(\mathbf{BX})_3$ was clear evidence that both the metal–nitrogen and the metal–oxygen bonds are readily exchanged.

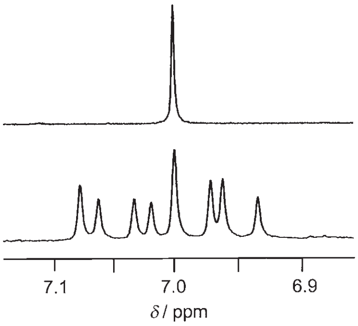
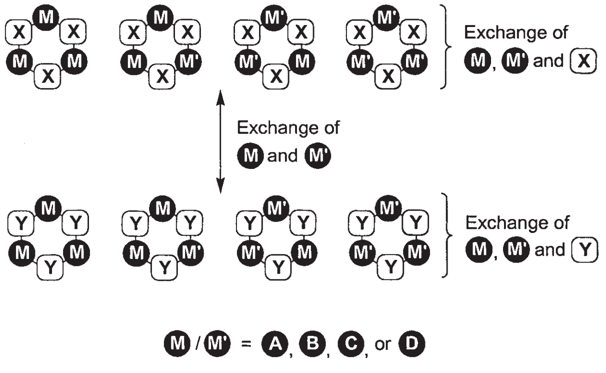


Figure 6. Part of the ^{1}H NMR spectra (D_2O/CD_3OD, 7:3, phosphate buffer, pD 8.0) of a mixture of $(\mathbf{DY})_3$ and $(\mathbf{BX})_3$ before (top) and after equilibration (bottom). The signals correspond to the aromatic CH protons of the ligand **X**.

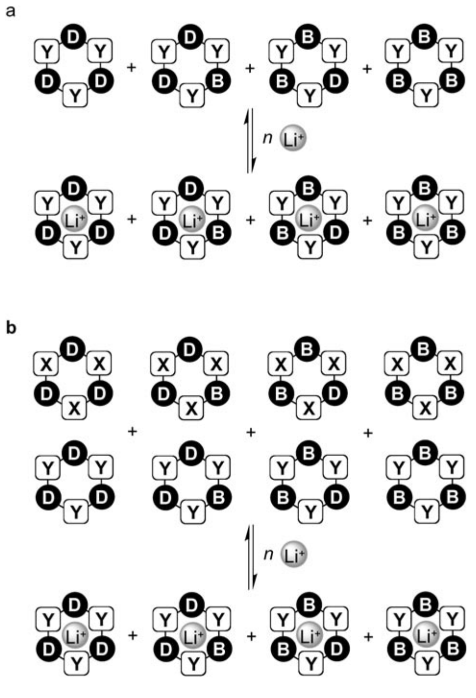
From the experiments described above, it can be concluded that upon mixing of two different metal fragments with the ligands **X** and **Y**, a DCL of eight macrocycles is formed. Each of these complexes contains exclusively one type of ligand; the 16 hypothetical macrocycles with mixed ligands are not formed, since the self-assembly process is strictly self-sorting. The eight members of the library can exchange metal fragments, but an exchange of ligands is only possible within the sub-library of complexes containing the same



Scheme 8. The assembly of two different metal fragments with the ligands **X** and **Y** leads to the formation of a dynamic library of eight macrocycles. The library can be dived into two sub-libraries, which are connected by exchange of metal fragments but not of ligands.

ligand (Scheme 8). This type of network topology leads to a distinct behavior in selection experiments as outlined below.

Recent theoretical[21] and experimental[17,22] studies have shown that the adaptation process of a DCL upon addition of a target is strongly dependent on the boundary conditions. Importantly, it is not necessarily the library member with the highest affinity to the target that is amplified the most. One of the parameters that was found to have a strong effect on the outcome of a selection experiment is the target concentration. This was demonstrated with a model DCL composed of the macrocyclic receptors $(\mathbf{DY})_3$, $(\mathbf{BY})_3$, $\mathbf{BY}(\mathbf{DY})_2$, and $\mathbf{DY}(\mathbf{BY})_2$ and lithium ions as the target.[17] All four complexes were able to act as a receptor for Li^+ and the binding affinity increases in the order $(\mathbf{DY})_3 < \mathbf{BY}(\mathbf{DY})_2 < \mathbf{DY}(\mathbf{BY})_2 < (\mathbf{BY})_3$.[23] Upon addition of small amounts of Li^+ to the four-component DCL, the dominant Li^+-containing complex was the best receptor $(\mathbf{BY})_3$. Upon increasing the Li^+ concentration, however, the lithium adduct of the second best receptor $\mathbf{DY}(\mathbf{BY})_2$ outcompeted the best one.



Scheme 9. Formation of host-guest complexes upon addition of lithium ions to a four (a) or eight-component DCL (b) comprised of the building blocks **B**, **D**, **Y** or **B**, **D**, **X**, **Y**, respectively.

It appeared interesting to compare the behavior of the more complex eight-component DCL obtained from the building blocks **B**, **D**, **X**, and **Y** (Scheme 9b) with the four-component DCL described above (Scheme 9a). For the former case, only the complexes containing the **Y** ligands were expected to bind to lithium ions, because the geometry of the **X** complexes does not permit a strong interaction with the alkali metal ion. Nevertheless, the four complexes with **X** ligands can affect the adaptation process, because they are coupled to the sub-library of **Y** complexes through metal-exchange reactions (Scheme 8).

Table 1. Ratio of the Li^+ complexes $[\mathbf{DY}(\mathbf{BY})_2{\cdot}Li^+]$ and $[(\mathbf{BY})_3{\cdot}Li^+]$ upon addition of increasing amounts of Li_2SO_4 to DCLs comprised of the building blocks **B**, **D**, **Y** or **B**, **D**, **X**, **Y**, respectively, as determined by ^{7}Li NMR spectroscopy.[a]

	$[Li^+]$ [mM]	4-component DCL $[\mathbf{DY}(\mathbf{BY})_2{\cdot}Li^+]$:$[(\mathbf{BY})_3{\cdot}Li^+]$	8-component DCL $[\mathbf{DY}(\mathbf{BY})_2{\cdot}Li^+]$:$[(\mathbf{BY})_3{\cdot}Li^+]$
1	1	0.23	0.19
2	5	0.41	0.28
3	25	1.30	0.60
4	50	3.91	1.50

[a] The solutions (D_2O/CD_3OD, 7:3, 100 mM phosphate buffer, pD 8.0) were equilibrated for 40 h at 40 °C. The total concentration of the four complexes containing **Y** ligands was in both cases 5 mM.

Increasing amounts of Li_2SO_4 were added to solutions of the respective DCL (100 mM phosphate buffer, pD 8.0) in D_2O/CD_3OD (7:3) . The mixtures were tempered at 40 °C for 40 h and the concentration of the Li^+ adducts of the high-affinity receptors $(\mathbf{BY})_3$ and $\mathbf{DY}(\mathbf{BY})_2$ was approximated by integration of the corresponding ^{7}Li NMR signals.[24] The results are summarized in Table 1. For low Li^+ concentrations with respect to the total macrocycle concentration, the dominant host–guest complex was found to be in both cases $[(\mathbf{BY})_3{\cdot}Li^+]$ with a $[(\mathbf{BY})_3{\cdot}Li^+]$:$[(\mathbf{DY})(\mathbf{BY})_2{\cdot}Li^+]$ ratio of 4:1 or 5:1, respectively (entry 1). Interesting differences, however, were observed at higher lithium concentrations. At $[Li^+] = 25$ mM, the dominant lithium complex in the four-component DCL was the adduct $[\mathbf{DY}(\mathbf{BY})_2{\cdot}Li^+]$, whereas in the eight-component DCL it was still the complex of the receptor with the highest affinity for Li^+, $(\mathbf{BY})_3$ (Table 1, entry 3 and Figure 7). The preferential formation of $[(\mathbf{BY})_3{\cdot}Li^+]$ was also observed for other lithium concentrations.

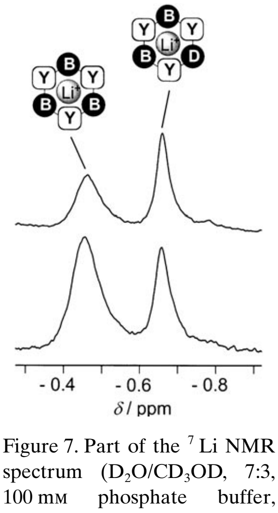


Figure 7. Part of the ^{7}Li NMR spectrum (D_2O/CD_3OD, 7:3, 100 mM phosphate buffer, pD 8.0) of DCLs comprised of the building blocks **B**, **D**, **Y** (top) or **B**, **D**, **X**, **Y** (bottom) highlighting the signals of the complexes $[\mathbf{DY}(\mathbf{BY})_2{\cdot}Li^+]$ and $[(\mathbf{BY})_3{\cdot}Li^+]$. Concentrations: $[\mathbf{Y}]_{total} = 15$ mM, $[Li^+] = 25$ mM.

The different result obtained for the eight-component DCL can be explained by the fact that the sub-library of **X** complexes can act as a reservoir for the metal fragment **B**, which is required for the formation of the high affinity receptors $(\mathbf{BY})_3$ and $\mathbf{DY}(\mathbf{BY})_2$. The competition between $(\mathbf{BY})_3$ and $\mathbf{DY}(\mathbf{BY})_2$ is therefore "buffered" by the four additional DCL members. A related situation is found for virtual combinatorial libraries, that is, DCLs in which the monomeric building blocks are the dominating species. Here, the competition between the aggregates is buffered by the excess of monomeric building blocks. As a result, an improved correlation between binding affinity and amplification factor is found in selection experiments.[21a]

Conclusion

Over the last years, selection experiments with DCLs have been used to discover new receptors for a given target as well as new guest molecules for a given host. The power of the approach is highlighted by a recent report of Sanders et al., in which an acetylcholine target was shown to amplify a high-affinity catenane receptor from a DCL of macrocycles with hydrazone linkages.[25] It would have been very difficult to discover this receptor with a more traditional "design approach".[26] So far, research in the field of dynamic combinatorial chemistry has focused on relatively simple DCLs, but libraries with more complex network topologies are increasingly being investigated.[11–13] In the present work, we have demonstrated that self-assembled metallamacrocycles with two types of pyridone ligands form dynamic libraries with a unique network topology. Since the assembly process is strictly self-sorting with respect to the bridging ligand, only eight out of 24 possible macrocycles are formed. The eight different complexes can be divided into two partially orthogonal sub-libraries. Within these sub-libraries, an exchange of metal fragments *and* ligands is possible, but communication between the sub-libraries is restricted to an exchange of metal fragments. This partial orthogonality is reflected in selection experiments as demonstrated in reactions with Li^+ ions as targets.

Experimental Section

General: The complexes $[\{Ru(C_6H_5Me)Cl_2\}_2]$,[27] $[\{Ru(p\text{-cymene})Cl_2\}_2]$,[28] $[\{Rh(Cp)Cl_2\}_2]$,[29] and $[\{Ir(Cp^*)Cl_2\}_2]$[30] and the ligand 4-dimethylaminomethyl-3-hydroxy-2-(1*H*)-pyridone[31] were prepared according to literature procedures. The synthesis of all complexes was performed under an atmosphere of dry dinitrogen, using standard Schlenk techniques. The ^1H and ^{13}C spectra were recorded on a Bruker Avance DPX 400 spectrometer by using the residual protonated solvents (^1H, ^{13}C) as internal standards or LiCl in water as an external standard. All spectra were recorded at room temperature. The ESI MS studies were performed with solutions of the respective macrocycles (total concentration of macrocycles: 2.5 mM) in water/acetonitrile (3:1) containing a 50 mM phosphate buffer (pH ~ 8).

5-Dimethylaminomethyl-3-hydroxy-2-methyl-4-(1*H*)-pyridone (1): Palladium on charcoal (43 mg) was added to a solution of 3-benzyloxy-5-dimethylaminomethyl-2-methyl-4-(1*H*)-pyridone (504 mg, 1.85 mmol) in ethanol (45 mL). The mixture was stirred for 20 h under an atmosphere of dihydrogen. The catalyst was then eliminated by filtration. Evaporation of the ethanol under vacuum gave ligand **1** as a white solid (yield: 223 mg, 63 %). ^1H NMR (400 MHz, D_2O): $\delta = 2.34$ (s, 3H; CH_3), 2.62 (s, 6H; $N(CH_3)_2$), 3.90 (s, 2H; NCH_2), 7.54 ppm (s, 1H; CH); ^{13}C NMR (400 MHz, D_2O): $\delta = 16.71$ (CH_3), 45.52 ($N(CH_3)_2$), 58.37 (NCH_2), 118.7, 134.7, 136.3, 152.1, 174.1 (pyridone); elemental analysis calcd (%) for $C_9H_{14}N_2O_2 \cdot 0.5\,H_2O$: C 56.53, H 7.91, N 14.65; found: C 56.28, H 7.84, N 15.18.

General procedure for the synthesis of the complexes $(AX)_3$, $(BX)_3$, $(CX)_3$, $(DX)_3$, $(AY)_3$, $(BY)_3$, $(CY)_3$, and $(DY)_3$: D_2O or D_2O/CD_3OD (7/3) (2.0 mL, 100 mM phosphate buffer, pD 8.0) was added to the respective pyridone ligand (30 µmol) and the $[M(L)_nCl_2]_2$ complex (15 µmol). The mixture was stirred for 2 h until a clear solution was obtained.

Complex $(AX)_3$: ^1H NMR (400 MHz, D_2O): $\delta = 1.94$ (s, 9H; $C_6H_5\mathit{Me}$), 2.41 (s, 9H; CH_3), 2.79 (s, 18H; $N(CH_3)_2$), 3.60 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.08 (d, $^2J = 13$ Hz, 3H; NCH_2), 5.29 (d, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 5.34 (d, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 5.47 (t, $^3J = 5$ Hz, 3H; $C_6\mathit{H}_5Me$), 5.78 (t, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 5.86 (t, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 7.14 ppm (s, 3H; CH, pyridone).

Complex $(BX)_3$: ^1H NMR (400 MHz, D_2O): $\delta = 1.09$ (d, $^3J = 7$ Hz, 9H; $CH(\mathit{CH_3})_2$), 1.14 (d, $^3J = 7$ Hz, 9H; $CH(\mathit{CH_3})_2$), 1.79 (s, 9H; CH_3), 2.41 (s, 9H; CH_3), 2.65 (sept, $^3J = 7$ Hz, 3H; $\mathit{CH}(CH_3)_2$), 2.73 (s, 18H; $N(CH_3)_2$), 3.58 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.01 (d, $^2J = 13$ Hz, 3H; NCH_2), 5.15 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 5.38 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 5.73 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 5.76 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 7.06 ppm (s, 3H; CH, pyridone).

Complex $(CX)_3$: ^1H NMR (400 MHz, D_2O): $\delta = 2.43$ (s, 9H; CH_3), 2.76 (s, 18H; $N(CH_3)_2$), 3.68 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.08 (d, $^2J = 13$ Hz, 3H; NCH_2), 5.72 (s, 15H; CH, Cp), 7.33 ppm (s, 3H; CH, pyridone).

Complex $(DX)_3$: ^1H NMR (400 MHz, D_2O/CD_3OD: 7/3): $\delta = 1.49$ (s, 45H; CH_3, Cp*), 2.38 (s, 9H; CH_3), 2.66 (s, 18H; $N(CH_3)_2$), 3.55 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.13 (d, $^2J = 13$ Hz, 3H; NCH_2), 6.98 ppm (s, 3H; CH, pyridone).

Complex $(AY)_3$: ^1H NMR (400 MHz, D_2O): $\delta = 2.00$ (s, 9H; $C_6H_5\mathit{Me}$), 2.66 (s, 18H; $N(CH_3)_2$), 3.97 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.03 (d, $^2J = 13$ Hz, 3H; NCH_2), 5.24 (d, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 5.52 (t, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 5.56 (d, $^3J = 5$ Hz, 3H; $C_6\mathit{H}_5Me$), 5.84 (d, $^3J = 7$ Hz, 3H; CH, pyridone), 5.88 (t, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 6.10 (t, $^3J = 6$ Hz, 3H; $C_6\mathit{H}_5Me$), 6.80 ppm (d, $^3J = 7$ Hz, 3H; CH, pyridone).

Complex $(BY)_3$: ^1H NMR (400 MHz, D_2O): $\delta = 1.25$ (d, $^3J = 7$ Hz, 9H; $CH(\mathit{CH_3})_2$), 1.28 (d, $^3J = 7$ Hz, 9H; $CH(\mathit{CH_3})_2$), 1.82 (s, 9H; CH_3), 2.66 (s, 18H; $N(CH_3)_2$), 2.82 (sept, $^3J = 7$ Hz, 3H; $\mathit{CH}(CH_3)_2$), 3.86 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.07 (d, $^2J = 13$ Hz, 3H; NCH_2), 5.25 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 5.50 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 5.81 (d, $^3J = 6$ Hz, 3H; CH, pyridone), 5.81 (d, $^3J = 6$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 6.04 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 6.71 ppm (d, $^3J = 7$ Hz, 3H; CH, pyridone).

Complex $(CY)_3$: ^1H NMR (400 MHz, D_2O): $\delta = 2.69$ (s, 18H; $N(CH_3)_2$), 4.02 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.08 (d, $^2J = 13$ Hz, 3H; NCH_2), 5.78 (s, 15H; CH, Cp), 5.99 (d, $^3J = 7$ Hz, 3H; CH, pyridone), 6.98 ppm (d, $^3J = 7$ Hz, 3H; CH, pyridone).

Complex $(DY)_3$: ^1H NMR (400 MHz, D_2O): $\delta = 1.65$ (s, 45H; CH_3, Cp*), 2.71 (s, 18H; $N(CH_3)_2$), 4.02 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.11 (d, $^2J = 13$ Hz, 3H; NCH_2), 5.80 (d, $^3J = 7$ Hz, 3H; CH, pyridone), 6.79 ppm (d, $^3J = 7$ Hz, 3H; CH, pyridone).

Synthesis of complex 2: A suspension of the $[\{Ru(p\text{-cymene})Cl_2\}_2]$ (17.8 mg, 29.1 µmol) and ligand **1** (10.6 mg, 58.2 µmol) in water (3.5 mL) was stirred for 2 h until a red solution was obtained. CsOH (116 µmol) was added and complex **2** precipitated as an orange powder which was isolated by centrifugation and dried under vacuum (yield: 21.3 mg, 87 %). Single crystals of complex **2** were obtained from a concentrated aqueous solution of $(\mathbf{BX})_3$ after addition of an excess of K_2HPO_4. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$ (d, $^3J = 7$ Hz, 9H; $CH(\mathit{CH_3})_2$), 1.32 (d, $^3J = 7$ Hz, 9H; $CH(\mathit{CH_3})_2$), 2.09 (s, 9H; CH_3), 2.13 (s, 18H; $N(CH_3)_2$), 2.38 (s, 9H; CH_3), 2.64 (d, $^2J = 13$ Hz, 3H; NCH_2), 2.73 (sept, $^3J = 7$ Hz, 3H; $\mathit{CH}(CH_3)_2$), 3.41 (d, $^2J = 13$ Hz, 3H; NCH_2), 4.96 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 4.97 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 5.09 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 5.30 (d, $^3J = 5$ Hz, 3H; $Me\mathit{C_6H_4}i\mathrm{Pr}$), 6.79 ppm (s, 3H; CH, pyridone); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 17.60$, 18.02, 22.60, 23.15 (CH_3), 31.42 ($\mathit{CH}(CH_3)_2$), 44.98 ($N(CH_3)_2$), 55.08 (NCH_2), 79.42, 79.57, 80.14, 80.63 (CH, $Me\mathit{C_6H_4}i\mathrm{Pr}$), 94.10, 99.17 (C, $Me\mathit{C_6H_4}i\mathrm{Pr}$), 115.77, 140.81, 141.81, 157.13, 167.62 ppm (pyridone); elemental analysis calcd (%) for $C_{57}H_{78}Ru_3N_6O_6 \cdot H_2O$: C 54.14, H 6.38, N 6.65; found: C 53.86, H 6.38, N 6.78.

Preparation of a four-component DCL

Method A: A D_2O solution (2.0 mL, 100 mM phosphate buffer, pD 8.0) was added to a mixture of ligand **L** (**L** = **X**, **Y**, 30 µmol), [{Ru-

$(C_6H_5Me)Cl_2\}_2]$ (3.9 mg, 7.5 μmol), and $[\{Rh(Cp)Cl_2\}_2]$ (3.6 mg, 7.5 μmol). The mixture was equilibrated for 2 h at RT.

Method B: A solution of the macrocycle $(\mathbf{AL})_3$ (5.0 mM, 100 mM phosphate buffer, pD 8.0) in D_2O (1.0 mL) was mixed with a solution of the macrocycle $(\mathbf{CL})_3$ (5.0 mM, 100 mM phosphate buffer, pD 8.0) in D_2O (1.0 mL) and equilibrated for 2 h at RT (**L** = **X**, **Y**).

DCLs containing the metal fragment **B** and **D** were prepared following the method A with D_2O/CD_3OD (7:3) instead of D_2O as the solvent. The composition of the library was analyzed using ^1H NMR spectroscopy. In order to verify that the final equilibrium was reached, NMR spectra were recorded at later times.

Preparation of an eight-component DCL containing A and C: *Method A*: A D_2O solution (2.0 mL, 100 mM phosphate buffer, pD 8.0) was added to a mixture of ligand **X** (5.5 mg, 30 μmol), ligand **Y** (5.1 mg, 30 μmol), $[\{Ru(C_6H_5Me)Cl_2\}_2]$ (7.9 mg, 15 μmol) and $[\{Rh(Cp)Cl_2\}_2]$ (7.2 mg, 15 μmol). The mixture was equilibrated for 2 h at RT.

Method B: A solution of an equilibrated mixture of the macrocycles $(\mathbf{AX})_3$, $\mathbf{AX}(\mathbf{CX})_2$, $\mathbf{CX}(\mathbf{AX})_2$, and $(\mathbf{CX})_3$ ($[\mathbf{X}]_{total} = 30$ mM, 100 mM phosphate buffer, pD 8.0) in D_2O (1.0 mL) was mixed with a solution of an equilibrated mixture of the macrocycles $(\mathbf{AY})_3$, $\mathbf{AY}(\mathbf{CY})_2$, $\mathbf{CY}(\mathbf{AY})_2$, and $(\mathbf{CY})_3$ ($[\mathbf{Y}]_{total} = 30$ mM, 100 mM phosphate buffer, pD 8.0) in D_2O (1.0 mL) and stirred for 2 h at RT.

Preparation of an eight-component DCL containing B and D: A solution of the macrocycle $(\mathbf{BX})_3$ (10 mM, 100 mM phosphate buffer, pD 8.0) in D_2O/CD_3OD (7:3; 1.0 mL) was mixed with a solution of the macrocycle $(\mathbf{DY})_3$ (10 mM, 100 mM phosphate buffer, pD 8.0) in D_2O/CD_3OD (7:3; 1.0 mL) and equilibrated for 2 h at RT. The composition of the library was analyzed using ^1H NMR spectroscopy. In order to verify that the final equilibrium was reached, NMR spectra were recorded at later times.

Reaction of a four-component DCL with Li^+: After addition of various amounts of a Li_2SO_4 stock solution (D_2O, 50 mM, 0.5 M or 2.0 M) to the equilibrated mixture of the macrocycles $(\mathbf{BY})_3$, $\mathbf{DY}(\mathbf{BY})_2$, $\mathbf{BY}(\mathbf{DY})_2$, and $(\mathbf{DY})_3$ ($[\mathbf{Y}]_{total} = 15$ mM, D_2O/CD_3OD (7:3), 100 mM phosphate buffer, pD 8.0), the reaction mixture was tempered at 40 °C for 40 h.

Table 2. Crystallographic data for complex **2**.

	$\mathbf{2} \times 19\,H_2O$
formula	$C_{57}H_{116}N_6O_{25}Ru_3$
M_r [$g\,mol^{-1}$]	1588.77
crystal size	0.33 × 0.20 × 0.20
crystal system	rhombohedral
space group	$R\bar{3}$
a [Å]	19.673(4)
b [Å]	19.673(4)
c [Å]	33.224(8)
α [°]	90
β [°]	90
γ [°]	120
V [Å^3]	11 135(4)
Z	6
ρ_{calcd} [$g\,cm^{-3}$]	1.422
T [K]	140(2)
μ [mm^{-1}]	0.678
θ range [°]	3.22 to 25.03
index ranges	$-22 \le h \le 23$
	$-23 \le k \le 23$
	$-39 \le l \le 39$
reflections collected	23 827
independent reflections	4381 ($R_{int} = 0.0691$)
absorption correction	semi-empirical
max/min transmission	0.9209 and 0.8879
data/restraints/parameters	4381/0/293
goodness-of-fit on F^2	1.024
final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0479$, $wR_2 = 0.1267$
R indices (all data)	$R_1 = 0.0671$, $wR_2 = 0.1395$
largest diff. peak/hole [$e\,Å^{-3}$]	1.221/−1.270

Reaction of an eight-component DCL with Li^+: After addition of various amounts of a Li_2SO_4 stock solution (D_2O, 50 mM, 0.5 M or 2.0 M) to the equilibrated mixture of the macrocycles $(\mathbf{BY})_3$, $\mathbf{DY}(\mathbf{BY})_2$, $\mathbf{BY}(\mathbf{DY})_2$, $(\mathbf{DY})_3$, $(\mathbf{BX})_3$, $\mathbf{DX}(\mathbf{BX})_2$, $\mathbf{BX}(\mathbf{DX})_2$, and $(\mathbf{DX})_3$ ($[\mathbf{X}]_{total} = 15$ mM, $[\mathbf{Y}]_{total} = 15$ mM, D_2O/CD_3OD (7:3), 100 mM phosphate buffer, pD 8.0), the reaction mixture was tempered at 40 °C for 40 h.

X-ray crystallography: Details about the crystal and the structure refinement of **2** are listed in Table 2, whereas some relevant geometrical parameters are included into the picture captions. Data collection was performed at 140(2) K on a marresearch mar345 IPDS diffractometer. Data reduction was carried out with CrysAlis RED, release 1.7.0.[32] Absorption correction was applied. Structure solution and refinement were performed with the SHELXTL software package, release 5.1.[33] The structure was refined by using the full-matrix least-squares on F^2 with all non-H atoms anisotropically defined. H atoms were placed in calculated positions using the "riding model" (except those belonging to the water molecules that were not included into the final model). The asymmetric unit contains 19/3 water molecules of which four (O3, O4, O7, O8) do not show any sign of disorder, two look disordered (O5 and O6) and have been treated with the split model and then their occupancy factor fixed, the remaining $1/3\,H_2O$ (O9) lies on a threefold symmetry axis. CCDC 271907 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

Acknowledgements

The work was supported by the Swiss National Science Foundation and by the EPFL.

---

[1] a) P. A. Brady, R. P. Bonar-Law, S. J. Rowan, C. J. Suckling, J. K. M. Sanders, *Chem. Commun.* **1996**, 319–320; b) S. J. Rowan, P. A. Brady, J. K. M. Sanders, *Angew. Chem.* **1996**, *108*, 2283–2285; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2143–2145; c) S. J. Rowan, D. G. Hamilton, P. A. Brady, J. K. M. Sanders, *J. Am. Chem. Soc.* **1997**, *119*, 2578–2579; d) S. J. Rowan, J. K. M. Sanders, *Chem. Commun.* **1997**, 1407–1408.

[2] a) B. Hasenknopf, J.-M. Lehn, B. O. Kneisel, G. Baum, D. Fenske, *Angew. Chem.* **1996**, *108*, 1987–1990; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1838–1840; b) B. Hasenknopf, J.-M. Lehn, N. Boumediene, A. Dupont-Gervais, A. Van Dorsselaer, B. Kneisel, D. Fenske, *J. Am. Chem. Soc.* **1997**, *119*, 10 956–10 962; c) I. Huc, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2106–2110.

[3] a) T. Hayashi, T. Asai, H. Hokazono, H. Ogoshi, *J. Am. Chem. Soc.* **1993**, *115*, 12 210–12 211; b) B. A. Katz, J. Finer-Moore, R. Mortezaei, D. H. Rich, R. M. Stroud, *Biochemistry* **1995**, *34*, 8264–8280; c) P. G. Swann, R. A. Casanova, A. Desai, M. M. Frauenhoff, M. Urbancic, U. Slomczenska, A. J. Hopfinger, G. C. LeBreton, D. L. Venton, *Biopolymers* **1996**, *40*, 617–625; d) S. Sakai, Y. Shigemase, T. Sasaki, *Tetrahedron Lett.* **1997**, *38*, 8145–8148; e) A. V. Eliseev, M. I. Nelen, *J. Am. Chem. Soc.* **1997**, *119*, 1147–1148; f) B. Klekota, M. H. Hammond, B. L. Miller, *Tetrahedron Lett.* **1997**, *38*, 8639–8642; g) A. V. Eliseev, M. I. Nelen, *J. Am. Chem. Soc.* **1997**, *119*, 1147–1148.

[4] For reviews see: a) J. D. Cheeseman, A. D. Corbett, J. L. Gleason, R. J. Kazlauskas, *Chem. Eur. J.* **2005**, *11*, 1709–1716; b) J.-L. Reymond, *Angew. Chem.* **2004**, *116*, 5695–5697; *Angew. Chem. Int. Ed.* **2004**, *43*, 5577–5579; c) O. Ramström, T. Bunyapaiboonsri, S. Lohmann, J.-M. Lehn, *Biochim. Biophys. Acta* **2002**, *1572*, 178–186; d) S. J. Rowan, 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; e) S. Otto, R. L. E. Furlan, J. K. M. Sanders, *Curr. Opin. Chem. Biol.* **2002**, *6*, 321–327; f) S. Otto, R. L. E.

Furlan, J. K. M. Sanders, *Drug Discovery Today* **2002**, *7*, 117–125; g) C. Karan, B. L. Miller, *Drug Discovery Today* **2000**, *5*, 67–75; h) J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455–2463; i) A. Ganesan, *Angew. Chem.* **1998**, *110*, 2989–2992; *Angew. Chem. Int. Ed.* **1998**, *37*, 2828–2831.

[5] The notion "assembly" includes reversible covalent bond formation under thermodynamic control.

[6] For reviews about complex dynamic networks see: a) S. H. Strogatz, *Nature* **2001**, *410*, 268–276; b) R. Albert, A.-L. Barbarási, *Rev. Mod. Phys.* **2002**, *74*, 47–97.

[7] a) A. L. Kieran, S. I. Pascu, T. Jarrosson, J. K. M. Sanders, *Chem. Commun.* **2005**, 1276–1278; b) S. Sando, A. Narita, Y. Aoyama, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2835–2838; c) A. M. Whitney, S. Ladame, S. Balasubramanian, *Angew. Chem.* **2004**, *116*, 1163–1166; *Angew. Chem. Int. Ed.* **2004**, *43*, 1143–1146; d) A. L. Kieran, A. D. Bond, A. M. Belenguer, J. K. M. Sanders, *Chem. Commun.* **2003**, 2674–2675; e) S. Otto, S. Kubik, *J. Am. Chem. Soc.* **2003**, *125*, 7804–7805; f) B. Brisig, J. K. M. Sanders, S. Otto, *Angew. Chem.* **2003**, *115*, 1308–1311; *Angew. Chem. Int. Ed.* **2003**, *42*, 1270–1273; g) Y. Krishnan-Ghosh, S. Balasubramanian, *Angew. Chem.* **2003**, *115*, 2221–2227; *Angew. Chem. Int. Ed.* **2003**, *42*, 2171–2173; h) S. Otto, R. L. E. Furlan, J. K. M. Sanders, *Science* **2002**, *297*, 590–593; i) S. Otto, R. L. E. Furlan, J. K. M. Sanders, *J. Am. Chem. Soc.* **2000**, *122*, 12063–12064; j) O. Ramström, J.-M. Lehn, *ChemBioChem* **2000**, *1*, 41–48.

[8] K. C. Nicolaou, R. Hughes, S. Y. Cho, N. Winssinger, C. Smethurst, H. Labischinski, R. Endermann, *Angew. Chem.* **2000**, *112*, 3981–3986; *Angew. Chem. Int. Ed.* **2000**, *39*, 3823–3828.

[9] a) S. Zameo, B. Vauzeilles, J.-M. Beau, *Angew. Chem.* **2005**, *117*, 987–991; *Angew. Chem. Int. Ed.* **2005**, *44*, 965–969; b) A. Bugaut, J.-J. Toulmé, B. Rayner, *Angew. Chem.* **2004**, *116*, 3206–3209; *Angew. Chem. Int. Ed.* **2004**, *43*, 3144–3147; c) N. Guiseppone, J.-M. Lehn, *J. Am. Chem. Soc.* **2004**, *126*, 11448–11449; d) A. González-Álvarez, I. Alfonso, F. López-Ortiz, Á. Aguirre, S. García-Granda, V. Gotor, *Eur. J. Org. Chem.* **2004**, 1117–1127; e) H. Li, P. Williams, J. Micklefield, J. M. Gardiner, G. Stephens, *Tetrahedron* **2004**, *60*, 753–758; f) K. Oh, K.-S. Jeong, J. S. Moore, *J. Org. Chem.* **2003**, *68*, 8397–8403; g) M. Hochgürtel, H. Kroth, D. Piecha, M. W. Hofmann, K. C. Nicolau, S. Krause, O. Schaaf, G. Sonnenmoser, A. V. Eliseev, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 3382–3387; h) S. Gerber-Lemaire, F. Popowycz, E. Rodríguez-García, A. T. Carmona Asenjo, I. Robina, P. Vogel, *ChemBioChem* **2002**, *3*, 466–470; i) O. Storm, U. Lünig, *Chem. Eur. J.* **2002**, *8*, 793–798.

[10] a) T. Ono, T. Nobori, J.-M. Lehn, *Chem. Commun.* **2005**, 1522–1524; b) W. G. Skene, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 8270–8275; c) O. Ramström, S. Lohmann, T. Bunyapaiboonsri, J.-M. Lehn, *Chem. Eur. J.* **2004**, *10*, 1711–1715; d) S. L. Roberts, R. L. E. Furlan, S. Otto, J. K. M. Sanders, *Org. Biomol. Chem.* **2003**, *1*, 1625–1633; e) S. L. Roberts, R. L. E. Furlan, G. R. L. Cousins, J. K. M. Sanders, *Chem. Commun.* **2002**, 938–939; f) R. L. E. Furlan, Y.-F. Ng, G. R. L. Cousins, J. E. Redman, J. K. M. Sanders, *Tetrahedron* **2002**, *58*, 771–778; g) R. L. E. Furlan, Y.-F. Ng, S. Otto, J. K. M. Sanders, *J. Am. Chem. Soc.* **2001**, *123*, 8876–8877; h) T. Bunyapaiboonsri, O. Ramström, S. Lohmann, J.-M. Lehn, L. Peng, M. Goeldner, *ChemBioChem* **2001**, *2*, 438–444; i) G. R. L. Cousins, R. L. E. Furlan, Y.-F. Ng, J. E. Redman, J. K. M. Sanders, *Angew. Chem.* **2001**, *113*, 437–443; *Angew. Chem. Int. Ed.* **2001**, *40*, 423–428; j) M. G. Simpson, S. P. Watson, N. Feeder, J. E. Davis, J. K. M. Sanders, *Org. Lett.* **2000**, *2*, 1435–1438; k) R. L. E. Furlan, G. R. L. Cousins, J. K. M. Sanders, *Chem. Commun.* **2000**, 1761–1762; l) G. R. L. Cousins, S.-A. Poulsen, J. K. M. Sanders, *Chem. Commun.* **1999**, 1575–1576.

[11] a) N. Sreenivasachary, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 5938–5943; b) E. Kolomiets, J.-M. Lehn, *Chem. Commun.* **2005**, 1519–1521.

[12] a) N. Giuseppone, J.-L. Schmitt, J.-M. Lehn, *Angew. Chem.* **2004**, *116*, 5010–5014; *Angew. Chem. Int. Ed.* **2004**, *43*, 4902–4906; b) J. R. Nitschke, *Angew. Chem.* **2004**, *116*, 3135–3137; *Angew. Chem. Int. Ed.* **2004**, *43*, 3073–3075; c) J. R. Nitschke, D. Schultz, G. Bernardinelli, D. Gérard, *J. Am. Chem. Soc.* **2004**, *126*, 16538–16543; d) J. R. Nitschke, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 11970–11974; e) V. Goral, M. I. Nelen, A. V. Eliseev, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 1347–1352; f) D. M. Epstein, S. Choudhary, M. R. Churchill, K. M. Keil, A. V. Eliseev, J. R. Morrow, *Inorg. Chem.* **2001**, *40*, 1591–1596; g) B. Klekota, B. L. Miller, *Tetrahedron* **1999**, *55*, 11687–11697.

[13] J. Leclaire, L. Vial, S. Otto, J. K. M. Sanders, *Chem. Commun.* **2005**, 1959–1961.

[14] a) P. Mukhopadhyay, A. Wu, L. Isaacs, *J. Org. Chem.* **2004**, *69*, 6157–6164; b) A. Wu, L. Isaacs, *J. Am. Chem. Soc.* **2003**, *125*, 4831–4835, and references therein.

[15] Z. Grote, M.-L. Lehaire, R. Scopelliti, K. Severin, *J. Am. Chem. Soc.* **2003**, *125*, 13638–13639.

[16] Z. Grote, R. Scopelliti, K. Severin, *J. Am. Chem. Soc.* **2004**, *126*, 16959–16972.

[17] I. Saur, K. Severin, *Chem. Commun.* **2005**, 1471–1473.

[18] M. K. Patel, R. Fox, P. D. Taylor, *Tetrahedron* **1996**, *52*, 1835–1840.

[19] T. Habereder, M. Warchhold, H. Nöth, K. Severin, *Angew. Chem.* **1999**, *111* 3422–3425; *Angew. Chem. Int. Ed.* **1999**, *38*, 3225–3228.

[20] The Ir(Cp*) macrocycle showed a limited solubility in pure water. Addition of 30% CD_3OD lead to an improved solubility and experiments with this complex were thus performed in this solvent mixture.

[21] a) K. Severin, *Chem. Eur. J.* **2004**, *10*, 2565–2580; b) P. T. Corbett, S. Otto, J. K. M. Sanders, *Chem. Eur. J.* **2004**, *10*, 3139–3143.

[22] a) Z. Grote, R. Scopelliti, K. Severin, *Angew. Chem.* **2003**, *115*, 3951–3955; *Angew. Chem. Int. Ed.* **2003**, *42*, 3821–3825; b) P. T. Corbett, J. K. M. Sanders, S. Otto, *J. Am. Chem. Soc.* **2005**, *127*, 9390–9392.

[23] For an explanation of this trend see reference [16].

[24] The concentrations of the Li^+ adducts of the low affinity receptors $(\mathbf{DY})_3$ and $\mathbf{BY}(\mathbf{DY})_2$ can be neglected under those conditions.

[25] R. T. S. Lam, A. Belenguer, S. L. Roberts, C. Naumann, T. Jarrosson, S. Otto, J. K. M. Sanders, *Science* **2005**, *308*, 667–669.

[26] For a critical discussion of the limitations to design high-affinity receptors for a given target see: J. K. M. Sanders, *Chem. Eur. J.* **1998**, *4*, 1378–1383.

[27] M. A. Bennett, A. K. Smith, *J. Chem. Soc. Dalton Trans.* **1974**, *2*, 234–241.

[28] M. A. Bennett, T. -N. Huang, T. W. Matheson, A. K. Smith, *Inorg. Synth.* **1982**, *21*, 74–78.

[29] J. W. Kang, K. Moseley, P. M. Maitlis, *J. Am. Chem. Soc.* **1969**, *91*, 5970–5977.

[30] C. White, A. Yates, P. M. Maitlis, *Inorg. Synth.* **1992**, *29*, 228–234.

[31] a) A. Nakamura, K. Shozo, *Chem. Pharm. Bull.* **1968**, *16*, 1466–1471; b) A. G. Osborne, L. Jackson, *Spectrochim. Acta Part A* **1993**, *49*, 1703–1708.

[32] Oxford Diffraction Ltd., Abingdon, Oxfordshire, UK, **2003**.

[33] G. M. Sheldrick, University of Göttingen, Germany, **1997**; Bruker AXS, Inc., Madison, Wisconsin, 53719, USA, **1997**.

[34] ORTEP 3 for Windows version 1.076: L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.

[35] The graphic has been prepared using the crystallographic data of complex $[\{Ru(cymene)(C_8H_{12}N_2O_3)\}_3]$. For a more detailed description of this structure see reference [16].

Received: June 1, 2005