Supramolecular chemistry with organometallic half-sandwich complexes

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Organometallic half-sandwich complexes of the late transition metals are versatile building blocks for supramolecular chemistry. They can be used to build metallamacrocyclic receptors and coordination cages, to study the adaptive behavior of dynamic combinatorial libraries and to generate indicator displacement assays for the detection of biologically interesting analytes such as peptides and aminoglycosides.

Introduction

Organometallic half-sandwich complexes are ubiquitous in organometallic synthesis and catalysis. Over recent years, it has become clear that they are also very interesting building blocks for supramolecular chemistry. The following feature article summarizes some recent developments in this field with focus on contributions from our own group. Much of this work involves (arene)Ru^{II} and (cyclopentadienyl)M^{III} (M = Rh, Ir) complexes (Fig. 1). These compounds are frequently used because they show a number of interesting characteristics. First of all, easily accessible starting materials are available. (Arene)Ru chemistry commonly begins with the dimers $[(arene)RuCl_2]_2$, which can be obtained by reaction of $RuCl_3(H_2O)_n$ with cyclohexadienes[1] or by arene exchange at elevated temperatures.[2] The complexes $[(benzene)RuCl_2]_2$ and $[(p\text{-cymene})RuCl_2]_2$ are commercially available as well. Most of the rhodium and iridium chemistry is based on the dimers $[Cp^*RhCl_2]_2$ and $[Cp^*IrCl_2]_2$, which can be obtained by reaction of the metal chlorides with pentamethylcyclopentadiene[3] or from commercial sources. $[(Arene)RuCl_2]_2$ and $[Cp^*MCl_2]_2$ (M = Rh, Ir) complexes are remarkably robust: they can be stored without a protecting inert atmosphere and solutions are only moderately air sensitive. The dimers are generally well soluble in standard organic solvents such as chloroform and interestingly, they are also soluble in water (monomeric aqua complexes are formed).

The organic π-ligands of (arene)Ru and (cyclopentadienyl)M (M = Rh, Ir) complexes are relatively inert towards substitution reactions. Consequently, they mostly act as spectator ligands. Nevertheless, they can be used to fine-tune the solubility and the redox properties of the complexes. The three facial coordination sites opposite to the π-ligand can be used to coordinate various ligands with N-, O-, S- or P-donor groups. Generally, the resulting complexes are thermodynamically stable but still undergo exchange reactions. The lability of ligands bound opposite to the π-ligands is illustrated by the aqua complex $[Cp^*Rh(H_2O)_3]^{2+}$, for which a water exchange rate constant of $k = 1.6 \times 10^5\ s^{-1}$ has been determined.[4] This is in sharp contrast to the homoleptic complex $[Rh(H_2O)_6]^{3+}$ with highly inert aqua ligands ($k = 2.2 \times 10^{-9}\ s^{-1}$).[5] The fact that the three coordination sites opposite to the π-ligand are labile is of central importance for

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Kay Severin was born in 1967 in Germany. He obtained his PhD in 1995 for a thesis carried out in the group of Prof. W. Beck, University of Munich. Subsequently, he joined the group of Prof. M. R. Ghadiri, Scripps Research Institute, USA, as a postdoctoral fellow. In 1997, he started independent research projects at the Department of Chemistry, University of Munich. Since 2001 he has been professor at the Institute of Chemical Sciences and Engineering at the Swiss Federal Institute of Technology, Lausanne (EPFL). In his research group, new catalysts, receptors and sensors are developed. Towards this goal, a multidisciplinary approach combining classical organometallic chemistry with bioinorganic, polymer and supramolecular chemistry is followed.

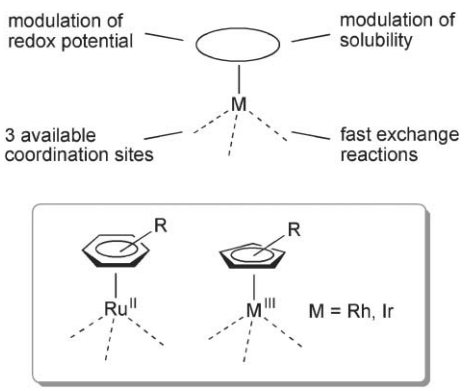


Fig. 1 Organometallic half-sandwich complexes of Ru^{II}, Rh^{III} and Ir^{III} as versatile building blocks in supramolecular chemistry.

the work described below, for which error correction processes and fast exchange reactions are essential.

Macrocycles and cages

The three available coordination sites of (arene)Ru or (cyclopentadienyl)M (M = Rh, Ir) complexes can be used to construct metallamacrocyclic complexes as well as coordination cages. One possibility to obtain rectangular macrocycles is to combine (π-ligand)M complexes with linear, difunctional ligands such as diisocyanides,[6–8] 4,4′-bipyridine,[8–11] cyanamide[12] or cyanide[13] (Fig. 2(a), (b)).

An alternative approach for the synthesis of macrocycles is the combination of half-sandwich complexes with trifunctional ligands. In this case, two of the donor atoms form a chelate complex with one metal fragment and the remaining donor atom coordinates to an adjacent metal fragment. Using this strategy, tri-, tetra- and hexanuclear metallamacrocycles have been obtained (Fig. 2(c)–(e)). Cationic, trinuclear complexes comprised of Cp*Rh complexes and adenine-derivatives as the bridging ligands were studied extensively by the group of Fish.[14–21] Structurally related compounds with (arene)Ru^{II}, Cp^*Ir^{III} and Cp^*Rh^{III} complexes were reported by the groups of Sheldrick[22–24] and Yamanari.[25,26] Relatively small changes in the bridging nucleobase ligand may result in large changes in the overall structure of the assembly: 9-alkyl-substituted adenine ligands gave trinuclear complexes[15] whereas the free adenine ligand gave a tetranuclear complex.[23,24] With 9-ethylhypoxanthine a trimeric structure was observed[20] but for the thio-derivative 6-purinethione a tetranuclear macrocycle[27] and for the thio-derivative 6-purinethione riboside a hexanuclear assembly was found.[28] Cationic trimers were also obtained using amino acidate ligands.[29–34] Here, the metal fragments are connected *via* the two carboxylate O-atoms and the amino-group.

The above-mentioned macrocycles are mostly polycationic species. Consequently, they are often soluble in water. In terms of host–guest chemistry, this may be advantageous if hydrophobic interactions are the main driving force for guest inclusion.[17–19] For the binding of cationic guests, however, these macrocyclic complexes are generally not very suited. This is very different for neutral metallamacrocycles. Trinuclear complexes with a net charge of zero were formed with the following ligands: 2,3-dihydroxypyridine (Fig. 3(b)),[35,36] 3-acetamido-2-hydroxypyridine,[36] 2,3-dihydroxyquinoline,[37] 2,3-dihydroxyquinoxaline,[37] 6-methyl-2,3-phenazinediol

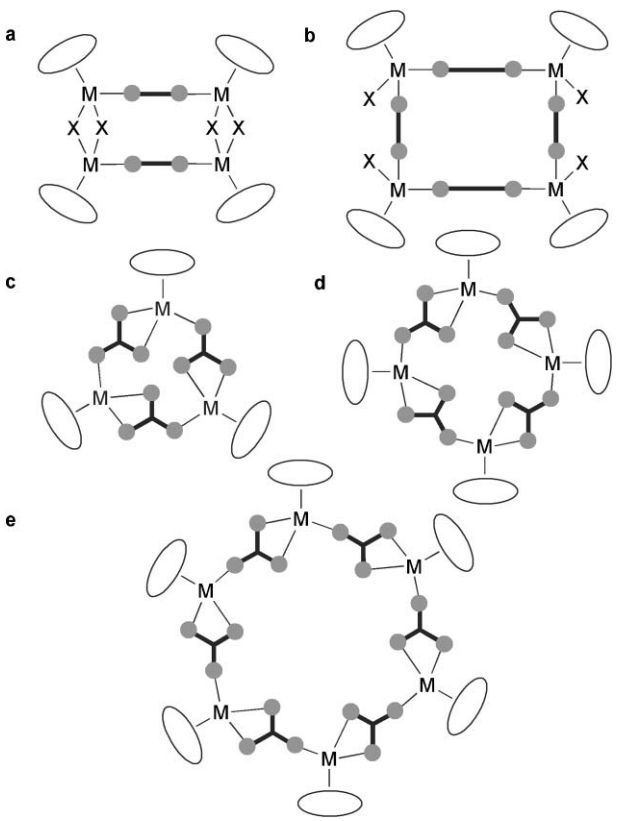


Fig. 2 Metallamacrocyclic complexes can be obtained by reaction of organometallic half-sandwich complexes of Ru, Rh or Ir with di- (a), (b) or trifunctional bridging ligands (c)–(e).

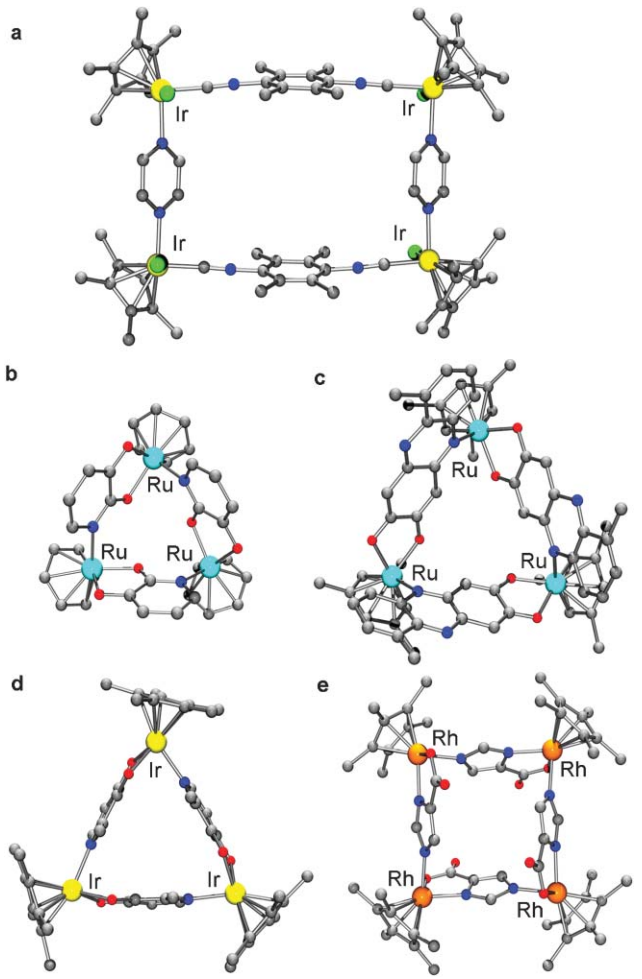


Fig. 3 The structure of selected organometallic macrocycles in the crystal (C = grey, N = blue, O = red, Cl = green). They were obtained by reaction of: (a) a Cp*Ir complex with 1,4-diisocyano-2,5-dimethylbezene and pyrazine; (b) a (benzene)Ru complex with 2,3-dihydroxypyridine; (c) a (1,3,5-trimethylbenzene)Ru complex with 6-methyl-2,3-phenazinediol; (d) a Cp*Ir complex with 3,4-dihydroxy-2-methylpyridine; (e) a Cp*Rh complex with 4-imidazolecarboxylic acid. The hydrogen atoms have been omitted for clarity.

(Fig. 3(c))[37] and 3,4-dihydroxy-2-methylpyridine (Fig. 3(d)).[38] All these macrocycles were obtained by reaction of the chloro-bridged complexes $[(\pi\text{-ligand})MCl_2]_2$ (π-ligand = arene, Cp*; M = Ru, Rh, Ir) with the respective ligands in the presence of base. Similarly, a tetranuclear complex was formed by reaction of $[Cp^*RhCl_2]_2$ with 4-imidazolecarboxylic acid and Ag_2O (Fig. 3(e)).[37]

The combination of metal complexes having three available coordination sites with trifunctional ligands can also be used to build coordination cages, given that the three donor groups are not able to bind to the same metal fragment. The synthesis of cubic structure with half-sandwich complexes has been investigated extensively by the group of Rauchfuss.[13,39–42] They used cyanometallates such as $[CpCo(CN)_3]^-$ and $[Cp^*Rh(CN)_3]^-$ as 'ligands' in combination with other metal complexes such as $[(C_6H_3Me_3)Mo(CO)_3]$, $[Cp^*RhCl_2]_2$, $[Cp^*Rh(NCCH_3)_3](PF_6)_2$ and $[Cp^*Ru(NCCH_3)_3]PF_6$. A representative example of such a cubic complex is shown in Fig. 4(a). Depending on the stoichiometry and the building blocks employed, 'defect' cyanometalate boxes with seven instead of eight metal fragments were also obtained.[40,43–45] An interesting variation of the cubic structural motif was observed for the reaction of the tricyanoborate $[PhB(CN)_3]^-$ with the cationic complex $[Cp^*Rh(CH_3NO_2)_n]^{2+}$, which resulted in the formation of a hexagonal bipyramidal cage $[\{PhB(CN)_3\}_6\{Cp^*Rh\}_6]^{6+}$.[46]

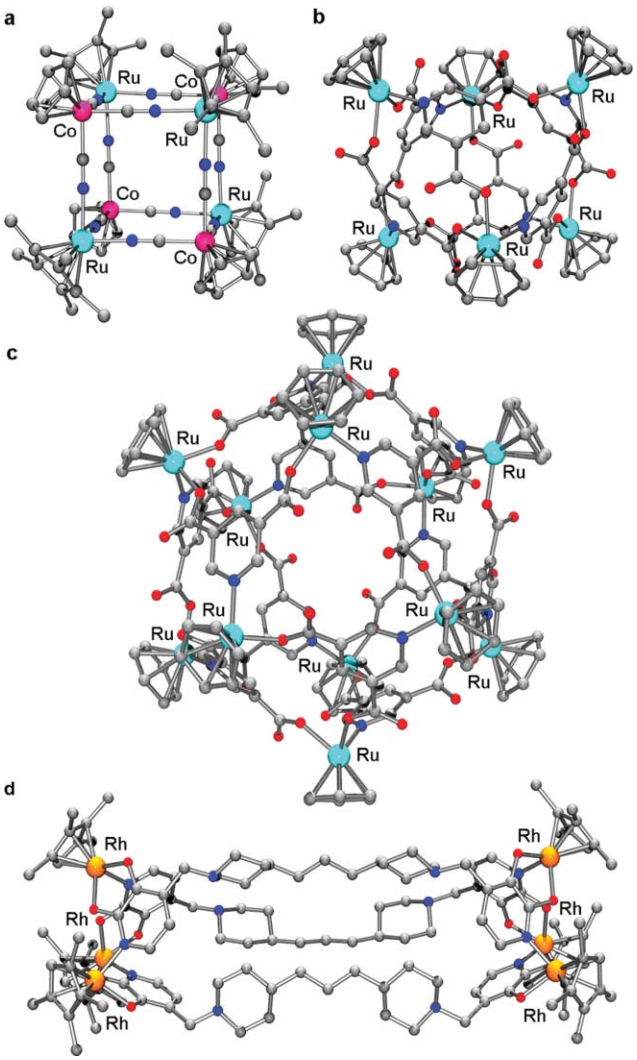


Fig. 4 A cubic cage, a trigonal antiprismatic cage, an icosahedral cage and a cylindrical structure based on organometallic half-sandwich complexes (C = grey, N = blue, O = red). They were obtained by reaction of: (a) PNN$[CpCo(CN)_3]$ with $[Cp^*Ru(NCCH_3)_3]PF_6$; (b) $[(p\text{-cymene})Ru(NO_3)_2]$ with 3,5-pyridinedicarboxylic acid; (c) $[(p\text{-cymene})Ru(NO_3)_2]$ with 3,5-pyridinedicarboxylic acid in the presence of KOAc; (d) $[(C_5Me_4H)RhCl_2]_2$ with a bridged dihydroxypyridine ligand in the presence of base. The hydrogen atoms and the side chains of the *p*-cymene ligands are not shown for clarity.

We have recently investigated the reaction of the Ru complex $[(p\text{-cymene})Ru(NO_2)_2]$ with the trifunctional ligand 3,5-pyridinecarboxylic acid. When the two compounds were mixed in water, an orange precipitate was formed. This complex turned out to be a hexanuclear cage, in which the (*p*-cymene)Ru fragments are connected by 3,5-pyridinedicarboxylate ligands (Fig. 4(b)).[47] The cage is neutral and acts as an *exo*-receptor for alkali metal ions such as K^+ and Cs^+. Upon addition of an excess of these ions, a rearrangement into a dodecanuclear complex was observed (Fig. 4(c)). Of special interest is the icosahedral geometry of this cage which resembles the geometry of many natural cage structures such as spherical viruses.

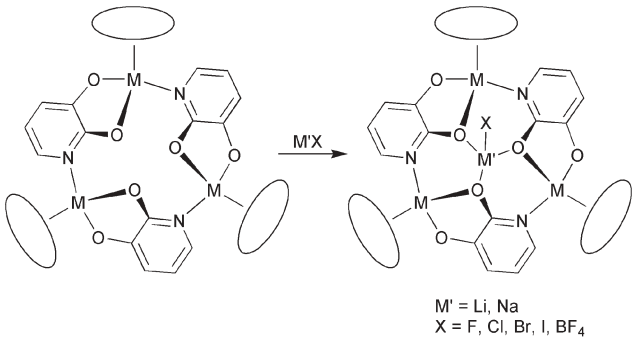
Cylindrical structures with a lengths of up to 2.8 nm have been obtained by reaction of $[(C_6H_5Me)RuCl_2]_2$ or $[(C_5Me_4H)RhCl_2]_2$ with bis(dihydroxypyridine) ligands.[48] A representative example is shown in Fig. 4(d). These hexanuclear complexes are composed of two 12-metallacrown-3 fragments, which are connected by three flexible spacers. Since the metallacrowns are chiral, the complexes can be regarded as expanded, triple-stranded helicates.

The group of Amouri has reported the synthesis of organometallic cryptates.[49] They were obtained by reaction of $[Cp^*M(solv)_3](BF_4)_2$ (M = Rh, Ir) with *m*-xylylenediamine or derivatives as the bridging ligands. Some of these complexes are able to tightly encapsulate a BF_4^- anion.

Specific receptors for small cations and anions

Metallacrown complexes are analogues of crown ethers, in which metal atoms constitute an integral part of the macrocyclic framework. Compounds of this kind were first reported in 1989 by the group of Pecoraro.[50,51] So far, metallacrown complexes with ring sizes between 9 and 30 atoms are known.[52] Similar to their organic counterparts, metallacrowns can selectively bind metal ions with high affinity. Trinuclear complexes derived from organometallic half-sandwich complexes and 2,3-dihydroxypyridine ligands represent analogues of 12-crown-3. It was found that these complexes display a very high affinity for lithium and sodium salts (Scheme 1).[35,36,53] In all cases, the alkali metal ion M′ is coordinated to the three adjacent oxygen atoms of the receptor. In the solid state and in apolar organic solvents, the salt M′X is bound as an ion pair.

The selectivity of these metallacrown complexes strongly depends on the nature of the π-ligand. Whereas the $(C_6H_6)Ru$, (*p*-cymene)Ru and $(C_6H_5CO_2Et)Ru$ complexes bind both Li^+



Scheme 1 Trinuclear metallamacrocycles comprised of (arene)Ru, Cp*Rh or Cp*Ir half-sandwich complexes and 2,3-dihydroxypyridine ligands can be regarded as analogues of 12-crown-3. They are able to bind lithium and sodium salts with very high affinity and selectivity.

and Na^+ salts, the $(C_6H_3Et_3)Ru$, $(C_6Me_6)Ru$, Cp*Rh and Cp*Ir complexes are specific for Li^+ salts.[36] None of the receptors are able to bind K^+ salts. This pronounced selectivity for small cations is a result of the steric requirements of the π-ligands.

The stabilities of the Li^+ and Na^+ adducts are remarkably high. Competition experiments with various organic ionophores have revealed that in chloroform, the binding affinity of the 12-metallacrown-3 complexes for LiCl and NaCl is significantly higher than that of classical crown ethers and comparable to that of cryptands.[36] This can be attributed to several facts: (a) the receptors are very rigid and ideally preorganized to bind lithium or sodium ions; (b) the salts are bound as an ion pair; (c) the energetic costs for the desolvation of the receptors are very low because a maximum of one solvent molecule can fit inside the binding cavity; (d) the oxygen donor atoms have a high partial negative charge.[54]

The outstanding affinity of the 12-metallacrown-3 complexes for lithium and sodium salts was utilized to capture molecular LiF[55] and Na_2SiF_6[56] (Fig. 5). The stabilization of these compounds in molecular form represents a challenging task due to the high lattice energy of the salts, which makes the crystalline form a thermodynamic trap.

Based on the observation that 12-metallacrown-3 complexes can capture LiF, a specific chemosensor for the pharmacologically as well as toxicologically interesting fluoride ion was developed.[57] The basic concept is shown in Scheme 2. A lithium ion is coordinated inside a 12-metallacrown-3 complex

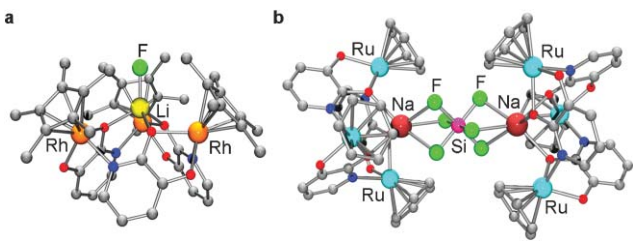
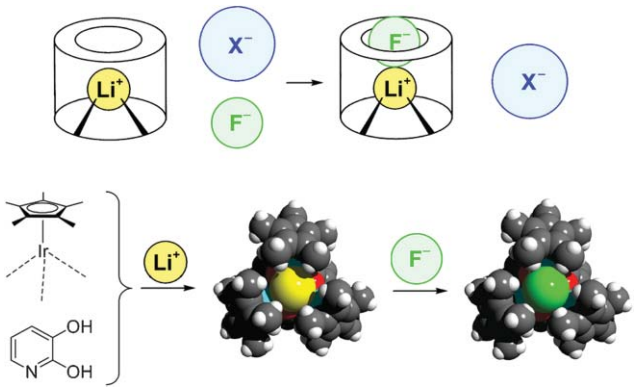


Fig. 5 Stabilization of molecular LiF and Na_2SiF_6 by 12-metallacrown-3 complexes (C = grey, N = blue, O = red): (a) LiF bound to a $[Cp^*Rh(C_5H_3NO_2)]_3$ receptor; (b) Na_2SiF_6 encapsulated by two $[(p\text{-cymene})Ru(C_5H_3NO_2)]_3$ receptors. The hydrogen atoms and the side chains of the *p*-cymene ligands are not shown for clarity.



Scheme 2 A lithium ion, coordinated to a receptor comprised of three Cp*Ir complexes with bridging 2,3-dihydroxypyridine ligands, acts as a highly specific binding site for the fluoride anion.

based on a Cp^*Ir^{III} complex. The accessibility of the Li^+ centre is controlled by the steric requirements of the Cp* ligands. The π-ligands efficiently block large anions X^- whereas the small F^- is able to enter the cavity and coordinate to the Li^+ ion. The selective formation of LiF ion-pairs is further enhanced by the intrinsic affinity of the hard Lewis acid Li^+ to the hard Lewis base F^-. The presence of F^- can be detected electrochemically: upon addition of F^-, the Cp*Ir receptor was significantly easier to oxidize ($\Delta E = -203$ mV) whereas only small changes were observed for Cl^-, Br^-, NO_3^-, HSO_4^- or ClO_4^- salts ($\Delta E < 24$ mV).[57]

Lithium salts are among the most frequently used drugs for patients suffering from bipolar disorder.[58] Recent studies suggest that lithium could also be used for the treatment of schizophrenia and of Alzheimer's disease.[59] Given the pharmacological relevance, it is not surprising that considerable efforts have been devoted towards the development of Li^+-specific receptors and sensors.[60] In this context, the host–guest chemistry of the 12-metallacrown-3 complex $[(C_6H_5CO_2Et)Ru(C_5H_3NO_2)]_3$ proved to be of special interest. Although this receptor is principally able to bind Na^+ ions, it shows an outstanding affinity and selectivity for Li^+ salts. This was demonstrated by the following experiment: if an aqueous solution containing LiCl (50 mM) and a large excess of NaCl, KCl, CsCl, $MgCl_2$ and $CaCl_2$ (1 M each) was shaken with a chloroform solution of this receptor, the exclusive and quantitative extraction of LiCl was observed.[61] This is remarkable because the extraction of LiCl from water is in principle a very difficult thing to accomplish due to the high solvation energy of Li^+ and Cl^-. Furthermore, the solvation energy of the other alkali metal ions is much smaller. The exclusive extraction of LiCl is therefore indicative of an extremely high selectivity.

A lithium-selective receptor which could be used directly in water would be advantageous for analytical applications. We therefore investigated the possibility to solubilize 12-metallacrown-3 complexes using polar functional groups. The attachment of dialkylaminomethyl groups to the bridging 2,3-dihydroxypyridine ligand *via* a simple Mannich reaction proved to be the key to success. With the resulting ligands it is possible to generate macrocycles in water at neutral pH: all that is required is to dissolve the aminomethyl-substituted

ligand with the corresponding $[(\pi\text{-ligand})MCl_2]_2$ complex in phosphate buffer. The macrocycles are then formed by self-assembly in quantitative yield (Fig. 6).[62,63]

The binding constant for the complexation of Li^+ in water was found to depend on the nature of the (π-ligand)M fragment and on the pH. Using the commercially available complex $[(p\text{-cymene})RuCl_2]_2$, it was possible obtain to a receptor which binds Li^+ with an association constant of $K = 6 \times 10^4\ M^{-1}$.[63] This value is sufficient to achieve a nearly quantitative complexation of Li^+ at the pharmacologically relevant concentration of $\sim$1 mM. Sodium salts do not interfere with the complexation because the binding constants are four orders of magnitude lower. To obtain a chemosensor, a unique way to transduce the binding of lithium ions into a signal was devised.[63] When $FeCl_3$ was added to an aqueous solution of the receptor, a color change from orange to dark brown was immediately observed. In the presence of lithium ions, this reaction was kinetically inhibited and addition of $FeCl_3$ lead to no color change. This difference in reactivity can be used for the 'naked eye' detection of low millimolar concentrations of lithium ions in water.

The host–guest chemistry of cubic cage complexes comprised of organometallic cyanometallates has been studied by the group of Rauchfuss. It was found that the cage $[\{CpCo(CN)_3\}_4\{Cp^*Rh\}_4]$ (Fig. 4(a)) acts as a potent receptor for small cations (Scheme 3).[41,42] Competition experiments showed that there is a kinetic preference for K^+ over Cs^+ but a thermodynamic preference for Cs^+ over K^+.

Dynamic combinatorial chemistry

Dynamic combinatorial chemistry has emerged as a potent tool for the discovery of new drugs,[64–66] receptors,[67] catalysts,[68] sensors,[69] and materials.[70,71] The adaptive behavior of dynamic combinatorial libraries (DCLs) has received particular attention in this context. DCLs are formed by combinatorial assembly of molecular building blocks *via* reversible covalent or non-covalent bonds. Upon addition of a target compound that selectively interacts with some aggregates of the DCL, a re-equilibration occurs. This adaptation can be used to identify library members with a high affinity for the respective target.

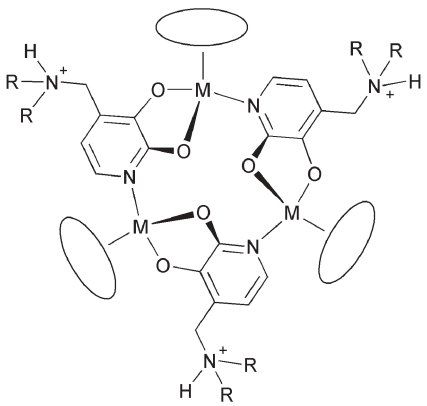
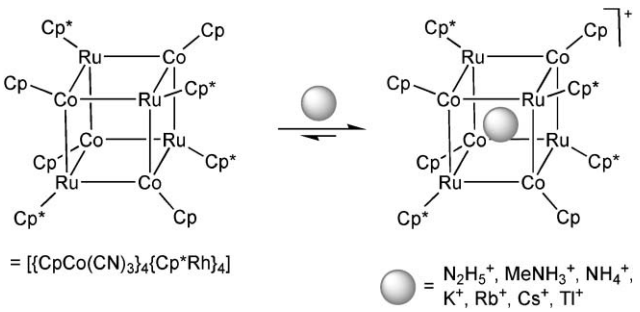


Fig. 6 Water-soluble 12-metallacrown-3 complexes are obtained by functionalization with dialkylaminomethyl groups. The complexes act as Li^+-specific receptors with binding constants of up to $K = 6 \times 10^4\ M^{-1}$.

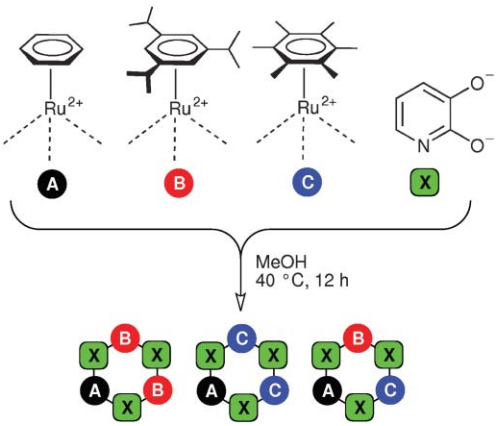


Scheme 3 The cubic complex $[\{CpCo(CN)_3\}_4\{Cp^*Rh\}_4]$ acts as a receptor for small cations.

Metallamacrocycles based on organometallic half-sandwich complexes turned out to be well suited to study the behavior of DCLs. A first question that was addressed was the correlation between the thermodynamic stability and the relative concentration of the respective library member. This issue is of central importance because for selection experiments it is generally assumed that an increased thermodynamic stability due to interaction with a target will lead to an increased relative concentration.

For the experiments, trinuclear metallamacrocycles based on 2,3-dihydroxypyridine ligands and three different (arene)Ru complexes were employed.[72] The Ru complexes were chosen to have sterically very different π-ligands: a small benzene ligand, a large 1,3,5-triisopropybenzene ligand and a likewise very large hexamethylbenzene ligand. As a result of steric congestion, macrocycles with the two latter π-ligands were expected to be less stable than those containing the benzene ligand. A combinatorial assembly of the three Ru complexes could potentially give a dynamic library of up to 10 complexes with a different composition. The most stable members of this library should be the compound having three (benzene)Ru fragments followed by the macrocycles having two (benzene)Ru fragments. The equilibrated mixture, however, showed only three species in significant amounts, all of which possess only one (benzene)Ru fragment (Scheme 4).[72]

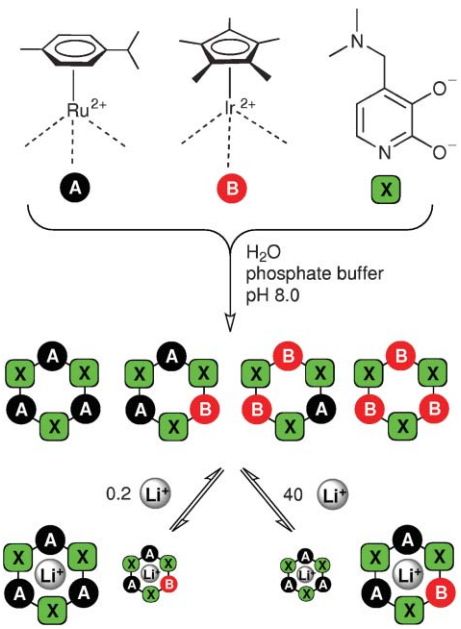
The experiments described above represented a first demonstration that a higher thermodynamic stability of a DCL member does not necessarily correlate to an elevated concentration. Soon after, this subject was examined by comprehensive computational studies[73,74] as well as by further experimental investigations.[75–77] A key conclusions from all these studies is that under certain conditions, it is not the assembly with the highest affinity to a given target that is amplified the most. Quite contrary, it is possible that the addition of a target molecule will lead to a decreased steady state concentration of the best binder. The probability of such a situation strongly depends on the boundary conditions of the experiment. One parameter that was identified to be of central importance is the target concentration. The addition of a large excess of target with respect to the DCL members tends to favor the amplification of weaker binders on behalf of the best one. This was demonstrated experimentally using a mini-library of four water-soluble metallacrown complexes



Scheme 4 The combinatorial assembly of three different (arene)Ru complexes leads to the formation of three aggregates, all of which contain only one sterically favorable building block 'A'. The most stable aggregate $(AX)_3$ is not observed.

comprised of Cp*Ir and (*p*-cymene)Ru complexes (Scheme 5).[76] The complexes are able to bind Li^+ with the best receptor being the homotrimer $(AX)_3$ followed by the heterotrimer $(AX)_2(BX)$. The adduct formation was investigated by ^7Li NMR. For low concentration of the target Li^+, the dominant host–guest complex was the adduct of the best receptor $(AX)_3$. A high Li^+ concentration, however, was shown to favor the receptor $(AX)_2(BX)$ of intermediate affinity for Li^+.

An exciting new development in the field of dynamic combinatorial chemistry is the investigation of DCLs with more complex architectures. A DCL can be regarded as a chemical network. The topology of this network is controlled

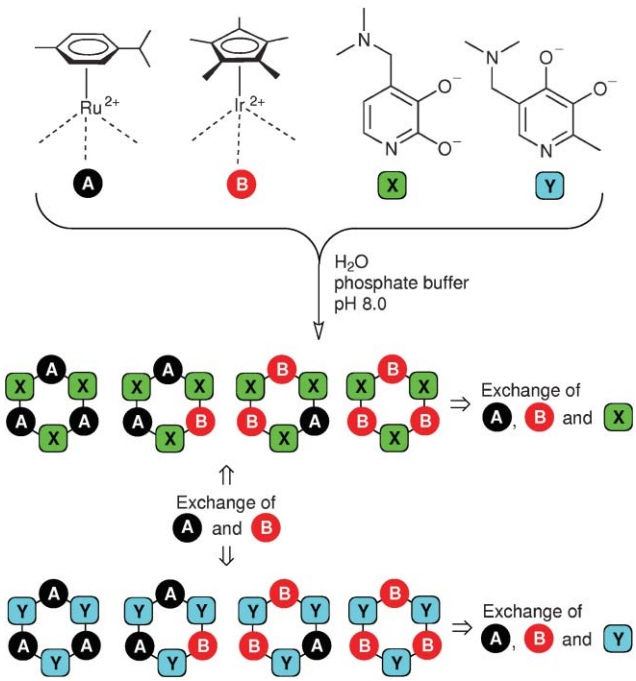


Scheme 5 The combinatorial assembly of a (*p*-cymene)Ru and a Cp*Ir complex leads to the formation of four metallamacrocyclic receptors for Li^+. Upon addition of a small amount of Li^+, the dominant host–guest complex is formed by the best receptor $(AX)_3$ whereas an access of Li^+ leads to the amplification of the second best receptor $(AX)_2(BX)$.

by the chemical reactivity of the constituent building blocks and of other factors such as steric and geometric restraints. One approach to build more complex DCLs is to utilize simultaneously several types of coupling chemistry. An alternative approach is based on the utilization of self-sorting processes. This was recently demonstrated by our group.[77] Metallamacrocycles comprised of Cp*Ir and (*p*-cymene)Ru complexes and two different dihydroxypyridine ligands form a DCL with a unique network topology. Since the assembly process is strictly self-sorting with respect to the bridging ligand, only 8 out of the 24 possible macrocycles are generated (Scheme 6). The 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 effects selection experiments as demonstrated in reactions with Li^+ as the target. The sub-library of macrocycles based on the ligand Y can act as a reservoir for the sub-library of Li^+ receptors with the ligand X. The relative concentration of the best lithium receptor $(AX)_3$ is therefore increased.[77]

Sensors for amino acids, peptides and aminoglycosides

A synthetic receptor, which is bound *via* non-covalent interactions to an indicator, is able to function as a chemosensor. The prerequisite is that the displacement of the indicator by an analyte results in a change of its optical properties. An indicator-displacement assay (IDA) of this kind



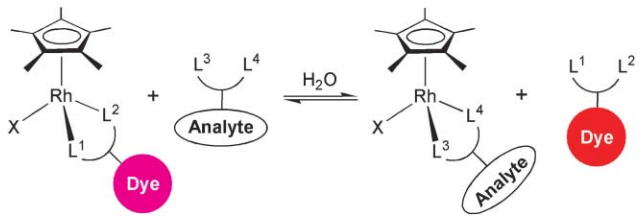
Scheme 6 The assembly of two different metal fragments A and B with the ligands X and Y leads to the formation of a dynamic library with a unique network topology. Due to a self-sorting process, only 8 metallamacrocycles are formed. The library can be dived into two sub-libraries, which are connected by exchange of metal fragments but not of ligands.

has been used to detect and quantify citrate, tartrate, phosphates and carbonate, among others.[78–80] The non-covalent attachment of the signaling unit makes IDAs very flexible because the nature of the indicator (color, affinity for the host, solubility) as well as the indicator : receptor ratio can be varied according to the sensing problem.

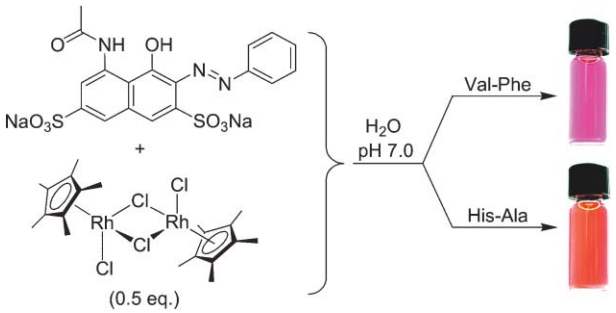
We have recently demonstrated that organometallic Cp^*Rh^{III} complexes are well suited to construct IDAs.[81–83] As the starting material it is possible to use the commercially available dimer $[Cp^*RhCl_2]_2$, which can be dissolved in buffered aqueous solution without the need of a protecting inert atmosphere. Upon addition of metal-binding dyes such as azophloxine, a sensing ensemble is obtained. The addition of an analyte, which is able to bind to the Cp*Rh fragment, leads to the replacement of the dye and to a change of color (Scheme 7). An important advantage of using a Cp*Rh receptor, as compared to receptors based on 3d transition metal complexes, is that the Cp*Rh complex displays very high binding constants, in particular for analytes with N- or S-donor ligands. This allows to perform IDAs at very low analyte concentrations.

A first implementation of the concept outlined in Scheme 7 was a sensor for histidine (His) and methionine (Met) containing peptides.[81] The coordination chemistry of organometallic half-sandwich complexes with amino acids and peptides is well established.[84] Peptides are known to preferentially bind to Cp^*Rh^{III}-, Cp^*Ir^{III}- and (arene)Ru^{II}-fragments *via* the terminal amino group and deprotonated amide bond(s). For histidine and methionine, an additional interaction between the N- or S-donor group of the side-chain and the metal is generally observed. These findings suggested that peptides containing histidine- or methionine residues close to the N-terminus should have a special affinity for the Cp*Rh receptor. This was conformed in displacement assays with the dye azophloxine. When a mixture of $[Cp^*RhCl_2]_2$ and azophloxine ([Rh] = [dye] = 50 μM) in buffered aqueous solution was mixed with one equivalent of His-Ala, the original red color of the free dye re-appeared. When the same experiments was performed with Val-Phe instead of His-Ala, however, one could observe the purple color of the Cp*Rh–azophloxine adduct (Scheme 8).[81] A more detailed analysis of competition experiments with various peptides using UV-Vis spectroscopy revealed that the assay is selective for peptides containing either His or Met in position one or two from the N-terminus. The detection limit of this assay was found to be 300 nM.

In direct extension of this work, we have shown that the selectivity of such assays can be increased significantly when



Scheme 7 The reaction of an analyte with a Cp*Rh–dye complex leads to a partial displacement of the dye. The associated change in color can be used to detect and quantify the analyte.



Scheme 8 Pronounced color changes are observed after equilibration of solutions containing of the receptor $[Cp^*RhCl_2]_2$, the dye azophloxine and the dipeptides His-Ala or Val-Phe, respectively.

the IDAs are performed in an array format.[82,83] In a sensor array, the response of several non-selective sensors, which show a differential response to a given analyte, is used to identify the analyte by a multivariate analysis.[85] Due to the intrinsic flexibility of IDAs, they are ideally suited to construct sensor arrays.[86] Cp*Rh-based sensors with a differential response were generated by changing the pH of the assay solution. A mini array of five sensors was created by mixing $[Cp^*RhCl_2]_2$ with the dye gallocyanine in buffered aqueous solution at pH 5.7, 6.3, 7.0, 7.6 and 9.0. As analytes, 15 amino acids without coordinating side chains were employed. The resulting UV-Vis 'fingerprint' of the five sensors was sufficient to identify the respective amino acid with an accuracy of >96% using a linear discriminant analysis.[82]

The clustering of the data can be visualized by a score plot of a principal component analysis (Fig. 7). The data appear in well separated groups with the only overlap found for valine and isoleucine. It is interesting to note that chemical and structural similarities of the amino acids are reflected to some extend by the relative position of the group. The data for the aromatic amino acids phenylalanine, tyrosine and tryptophan, for example, are positioned in proximity to each other as well as the data for the hydroxy amino acids serine and threonine.

More recently, we have used a similar technique to sense aminoglycosides.[83] Aminoglycosides are an important class of antibiotics, which contain two or more amino sugars linked by

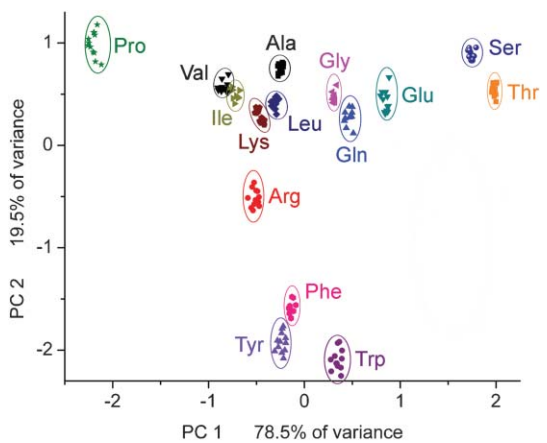


Fig. 7 Score plot of a principal component analysis for the identification of 15 different amino acids.

glycosidic bonds to an aminocyclitol unit. UV-Vis measurements at only three different pH values were found to be sufficient to identify the aminoglycosides kanamycin A, kanamycin B, amikacin, apramycin, paromomycin and streptomycin with high fidelity. Furthermore, the assays were used to characterize mixtures of aminoglycosides and to obtain quantitative information.

Conclusions

In the first part of this feature article, we have summarized efforts to use organometallic half-sandwich complexes of ruthenium, rhodium and iridium for the construction of metallamacrocycles and coordination cages. Some of these complexes show a highly interesting host–guest chemistry. Trinuclear macrocycles based on 2,3-dihydroxypyridine ligands, for example, were found to act as specific receptors for the pharmacologically important Li^+ ion. This was used to construct a colorimetric sensor, which allows to detect Li^+ in water by the 'naked eye'.

Trinuclear organometallic macrocycles have also been employed to study the adaptation of dynamic combinatorial libraries. These investigations have revealed that DCLs sometimes show an unexpected behavior: the addition of a target molecule may lead to the amplification of a mediocre receptor and not of the best one. This finding has to be considered for future selection experiments with DCLs.

As described in the final section, it is possible to use Cp*Rh-based displacement assays for the colorimetric detection of biologically interesting analytes such as amino acids, peptides and aminoglycosides. These assays are appealing from a practical point of view because the sensing ensemble is obtained by simply mixing $[Cp^*RhCl_2]_2$ with a commercially available dye in phosphate buffer. An intrinsic advantage of using an organometallic Cp*Rh complex as the receptor unit is that the assays can be performed at very low analyte concentration. The detection limit for the sensing of His-containing peptides, for example, was found to be 300 nM. The analytical power of such assays can be increased dramatically when they are performed in an array format. The implementation is again very easy because sensors with a differential response can be generated by changing the pH. It is conceivable that sensor arrays based on organometallic receptors can be constructed for other analytes or with different indicators (*e.g.* fluorescence dyes) and interesting developments can be expected for the near future.

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