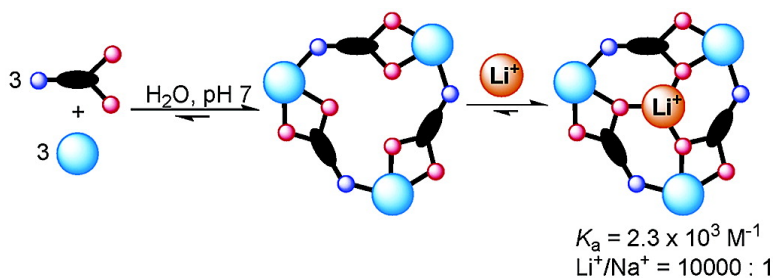## Communication

Selective Complexation of Li in Water at Neutral pH Using a Self-Assembled Ionophore

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$K_a = 2.3 \times 10^3 \text{ M}^{-1}$
$\text{Li}^+/\text{Na}^+ = 10000 : 1$

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Selective Complexation of Li$^+$ in Water at Neutral pH Using a Self-Assembled Ionophore

Zacharias Grote, Marie-Line Lehaire, Rosario Scopelliti, and Kay Severin*

*Institut de Chimie Moléculaire et Biologique, École Polytechnique Fédérale de Lausanne,
1015 Lausanne, Switzerland*

Received June 11, 2003; E-mail: kay.severin@epfl.ch

The design of ionophores, which are able to selectively bind lithium ions in water with high affinity, represents a challenging task. Because water itself is a good ligand for Li$^+$, ionophores face a difficult competition situation in this medium. The observed binding constants are thus generally low. Organic crown ethers of the formula $(CH_2CH_2O)_n$ ($n = 4-6$), for example, display association constants of $K \approx 1$ M^{-1} in water.[1] One of the highest values reported so far ($K = 3.2 \times 10^5$ M^{-1}) is found for the ionophore 2,1,1-cryptand, the size of which is ideally suited to encapsulate Li$^+$.[2] Yet the synthesis of this macrobicycle requires a multistep sequence, and the Li$^+$/Na$^+$ selectivity is only 200:1.[2] In the following, we describe an ionophore, which is able to bind lithium ions in water with high affinity and a Li$^+$/Na$^+$ selectivity of 10 000: 1. This receptor can be obtained simply by dissolving an organic ligand together with a commercially available ruthenium complex in buffered aqueous solution at neutral pH.

In continuation of our studies about macrocyclic organometallic complexes,[3,4] we have investigated the reaction of 3-hydroxy-4-piperidino-methyl-2-(1H)-pyridone (**1**) with complexes of the general formula $[L_nMCl_2]_2$ ($L_nM = (C_6Me_6)Ru$, $(C_6H_6)Ru$, (p-MeC$_6$H$_4^i$Pr)Ru, $(C_6H_5CO_2Et)Ru$, Cp*Rh, Cp*Ir) in water. The organic ligand **1** is easily available in a one-step procedure from commercially available starting materials.[5] It was chosen because it contains the 3-hydroxy-2-(1H)-pyridone structural motif which has successfully been used to construct trinuclear metallamacrocycles.[3] The piperidino group is basic but not a very good ligand for transition metals. It is thus expected to enhance the solubility of the resulting complexes (formation of ammonium groups) without interfering with the self-assembly process.

The reactions were carried out by adding 1.0 mL of a solution of **1** (15 mM) in degassed D$_2$O containing a phosphate buffer (100 mM, pH 7.0) to 7.5 μmol of the respective complex. After the mixture was stirred for several minutes, clear orange solutions were obtained which were analyzed by ^{1}H NMR spectroscopy. Contrary to what was found for reactions with simple 3-hydroxy- and 4-hydroxy-pyridone ligands performed in organic solvents,[3,4] pronounced differences are observed for the various metal complexes. Whereas a mixture of products was detected for $L_nM = (C_6Me_6)Ru$,[6] a single set of signals was observed for $L_nM = (C_6H_6)$-Ru, (p-MeC$_6$H$_4^i$Pr)Ru, (C$_6$H$_5$CO$_2$Et)Ru, Cp*Rh, and Cp*Ir. For the two latter complexes, however, the spectra were markedly different (Figure 1a and b).

Metallamacrocyclic complexes formed in reactions of $[L_nMCl_2]_2$ with **1** are chiral because the metal atoms represent stereogenic centers. Monomeric halfsandwich complexes with pyridonate chelate ligands are likewise chiral, but they are known to undergo fast epimerization in polar solvents such as water.[4,7] The observation of diastereotopic groups by ^{1}H NMR spectroscopy is therefore a good indication for the presence of macrocyclic products. According to this criterion, polynuclear complexes (**2**–**5**) were formed in
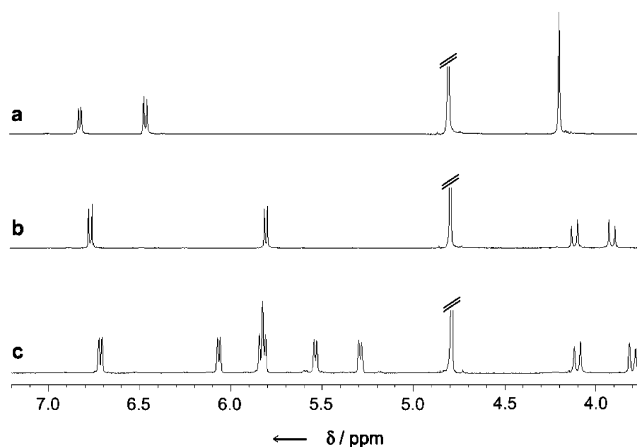

Figure 1. Part of the ^{1}H NMR spectra (D$_2$O) of the products obtained in reactions of ligand **1** with (a) [Cp*RhCl$_2$], (b) [Cp*IrCl$_2$]$_2$, and (c) [(p-MeC$_6$H$_4^i$Pr)RuCl$_2$]$_2$ (for reaction conditions, see text). Two doublets for diastereotopic NCH$_2$ protons at $\delta \sim 4$ ppm are only observed for (b) and (c).

>95% yield in reactions with [(C$_6$H$_6$)RuCl$_2$]$_2$, [(p-MeC$_6$H$_4^i$Pr)-RuCl$_2$]$_2$, [(C$_6$H$_5$CO$_2$Et)RuCl$_2$]$_2$, and [Cp*IrCl$_2$]$_2$ because diastereotopic NCH$_2$ protons at $\delta = 3.7-4.2$ ppm could be observed (Figure 1b and c). On the basis of the coordinate vectors of the bridging ligand,[3] complexes **2**–**5** were likely to display a trinuclear geometry (Scheme 1). The ^{1}H NMR data for reactions with [Cp*RhCl$_2$]$_2$, on the other hand, suggested the formation of a mononuclear complex (Figure 1a). For $L_nM = (C_6Me_6)Ru$, the data point to the presence of a mixture of two mononuclear complexes. Apparently, the success of the self-assembly process depends decisively on both electronic (Cp*Rh vs Cp*Ir) and steric effects (large (C$_6$Me$_6$)Ru vs smaller (C$_6$H$_6$)Ru).

The pH of the solution is likewise of importance for the assembly process. If buffer is omitted, mononuclear complexes are detected
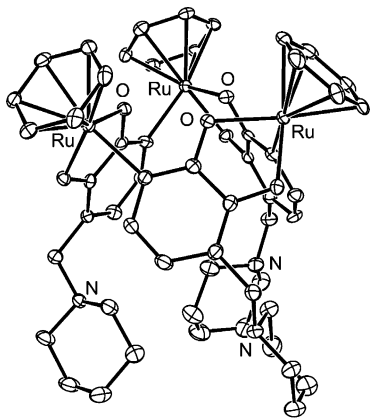
Scheme 1

	L$_n$M
2	(C$_6$H$_6$)Ru
3	(p-MeC$_6$H$_4^i$Pr)Ru
4	(C$_6$H$_5$CO$_2$Et)Ru
5	Cp*Ir
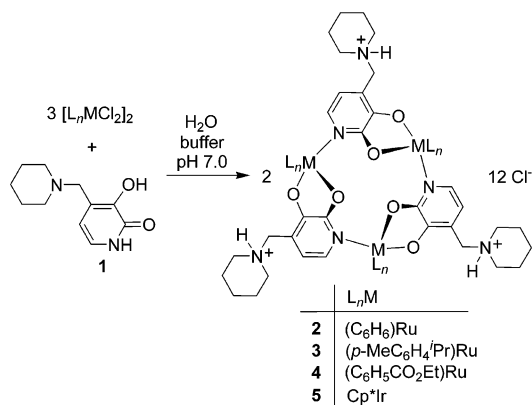
Figure 2. ORTEP plot of the molecular structure of **6** in the crystal. The hydrogen atoms and the side chains of the aromatic π-ligands are not shown for clarity.

for all mixtures. When the solution is buffered at pH 8, the partial formation of a macrocyclic complex can also be observed for reactions with [Cp*RhCl$_2$]$_2$.[8] The basic piperidine side chains are essential for the solubility of complexes **2**−**5** at neutral pH. When the piperidine groups are deprotonated by raising the pH above 11, orange precipitates are immediately formed. For L$_n$M = (p-MeC$_6$H$_4^i$Pr)Ru, we have investigated this in more detail. Under basic conditions, the complex **6** is formed in excellent yield (for experimental and spectroscopic data, see Supporting Information). This compound is well soluble in nonpolar organic solvents. Recrystallization from diethyl ether gave single crystals, which were examined by X-ray analysis. The structure in the crystal confirmed the expected trinuclear geometry (Figure 2). The ruthenium atoms are bridged by the two-fold deprotonated pyridonate ligand **1** with the metal atoms being 5.33 Å apart form each other. The N-atoms of the methyl-piperidine side chains are not involved in binding.

Complexes **2**−**5** represent analogues of 12-crown-3.[9] Yet, contrary to their organic counterparts, they are very rigid with three oxygen donor atoms being preorganized for the complexation of metal cations. Furthermore, theoretical investigations were recently presented which show that the metal−oxygen bonds in metalla-crown complexes are very polar.[10] The coordination of cationic guests is therefore favored due to electrostatic reasons.

Metallamacrocycles **2**−**5** were investigated for their ability to bind alkali metal ions in water using ^{1}H NMR spectroscopy.[11] For the iridium complex **5**, the complexation of alkali metal ions could not be observed, even upon addition of a large excess of the respective salt.[12] The ruthenium complexes **2**−**4**, on the other hand, were found to act as specific receptors for Li$^+$ ions. For complex **3**, a weak complexation of Na$^+$ ions was also observed, but none of the receptors was able to bind the larger cations K$^+$ and Cs$^+$ to a measurable extent. The Li$^+$ binding constants of **2**−**4** depend to a large extend on the nature of the arene π-ligand (Table 1). The highest value ($K = 2.3 \times 10^3$ M^{-1}) was observed for the (p-MeC$_6$H$_4^i$Pr)Ru complex **3**. This points to the fact that the two electron-donating alkyl side chains are beneficial for binding (rather than the electron-withdrawing ester side chains of **4**), but further investigations are needed to clarify this point.[13] Overall, the affinity and selectivity of the 12-metallacrown-3 complex **3** for Li$^+$ is remarkable: its binding constant is 3 orders of magnitude higher than that of classical crown ethers. This affinity is sufficient for nearly quantitative complexation reactions in the millimolar range, an important prerequisite if applications in sensing are envisioned.[14,15] With a Li$^+$/Na$^+$ selectivity of 10 000:1, complex **3** represents one of the most selective ionophores for lithium ions described so far.[15]

Table 1. Association Constants [M^{-1}] of Macrocycles **2**−**5** for the Complexation of Lithium and Sodium Ions[a]

	L$_n$M	Li$^+$	Na$^+$
2	(C$_6$H$_6$)Ru	$8.4\ (\pm 0.6) \times 10^2$	$<5 \times 10^{-2}$
3	(p-MeC$_6$H$_4^i$Pr)Ru	$2.3\ (\pm 0.4) \times 10^3$	$2.1\ (\pm 0.2) \times 10^{-1}$
4	(C$_6$H$_5$CO$_2$Et)Ru	$2.7\ (\pm 0.4) \times 10^1$	$<5 \times 10^{-2}$
5	Cp*Ir	$<1 \times 10^{-1}$	$<5 \times 10^{-2}$

[a] The experiments were performed using a solution of the respective macrocycle (5 mM) in D$_2$O containing 100 mM phosphate buffer (KH$_2$PO$_4$/K$_2$HPO$_4$; 4:6). After addition of LiOAc (10, 50, or 200 mM) or Na$_2$HPO$_4$ (200 mM), respectively, the amount of free and complexed ionophores was determined by integration of the corresponding signals using ^{1}H NMR spectroscopy.

In summary, we have reported a new ionophore, which is able to selectively bind Li$^+$ ions in water at neutral pH. A major advantage of our approach is the fact that this potent receptor can be generated in situ, simply by mixing the commercially available complex [(p-MeC$_6$H$_4^i$Pr)RuCl$_2$]$_2$ with the appropriate amounts of ligand **1**.[16] For potential applications, this feature may be a central advantage.

Supporting Information Available: Experimental preparation and crystallographic data in CIF format for complex **6** and NMR data for macrocycles **2**−**5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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