J. Am. Chem. Soc. **2001,** *123,* 2699−2700

A Self-Assembled Metallomacrocyclic Ionophore with High Affinity and Selectivity for Li$^+$ and Na$^+$

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Received November 18, 2000

Since the pioneering work of Pedersen, Lehn, and Cram, most of the research about synthetic ionophores has focused on covalent receptors such as crown ethers, cryptands, and calixarenes.[1] More recently, self-assembled metallomacrocycles have emerged as a promising new class of ionophores offering a variety of advantages, compared to their classical counterparts.[2] The synthesis of these compounds often proceeds in excellent yields using simple starting materials. The resulting receptors are generally rather rigid, thereby presenting a high degree of preorganization, an important prerequisite for ionophores with high affinity and selectivity. Furthermore, the special structural and spectroscopic characteristics of the metal complexes employed in the self-assembly process may give rise to new functional properties. In the following we describe the synthesis and the structure of a redox-responsive organometallic analogue of 12-crown-3 which displays a very high affinity for Li$^+$ and Na$^+$ and a nearly perfect selectivity for Na$^+$ over K$^+$.

The macrocyclic receptor **1** was obtained by reaction of [(cymene)RuCl$_2$]$_2$ with 3-hydroxy-2-pyridone in the presence of base (Cs$_2$CO$_3$ or K$_2$CO$_3$) (Scheme 1). The self-assembly process is completely diastereoselective[3] and proceeds in almost quantitative yields.

The trinuclear structure of **1** was confirmed by mass spectroscopy and single-crystal X-ray analysis (Figure 1). The dianion of 3-hydroxy-2-pyridone acts as a bridging, tridentate ligand, and the ruthenium centers display the expected tetrahedral coordination geometry. Comparable trinuclear structures were found for some cationic, water soluble complexes with nucleobases as the bridging ligands.[4] It is interesting to note that we were also able to obtain a triangular macrocycle with (cymene)Ru corners using 3-oxy-2-methyl-4-pyridonate bridges although the coordination vector of this ligand is quite different.[5] However, contrary to the concave structure of **1** the heterocyclic ligands were found to be almost perpendicular to the plane defined by the three metal atoms, resulting in a larger metal−metal distance of 7.24 Å (for **1**: 5.36 Å).

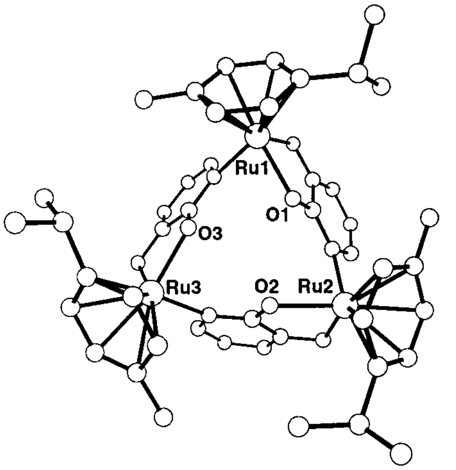
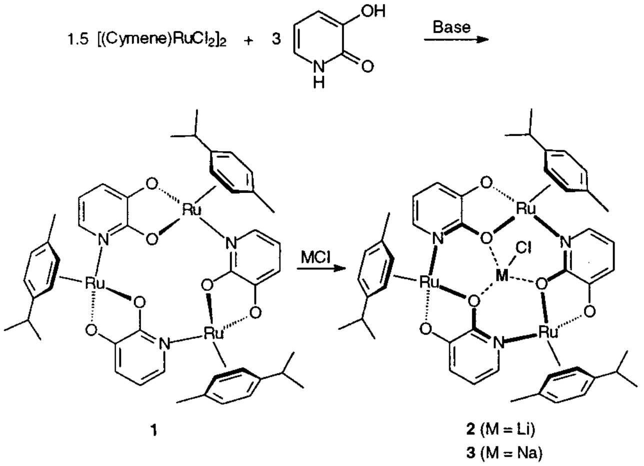


Figure 1. Molecular structure of **1** in the crystal. The hydrogen atoms are omitted for clarity.

Scheme 1



To investigate the ability of the metallomacrocyclic crown ether **1** to complex alkali metal salts we have performed a variety of experiments. After stirring **1** with an excess of LiCl or NaCl in methanol, evaporation of the solvent, and extraction with chloroform, the adducts **2** and **3** were obtained in quantitative yields. For KCl, on the other hand, no complexation could be detected. The formation of **2** and **3** was evidenced by NMR and mass spectroscopy as well as X-ray crystallographic analyses. The ^{1}H NMR spectra (CDCl$_3$) of **2** and **3** differ significantly from that of **1**: the protons of the pyridonate ligand as well as the aromatic cymene CH protons are shifted toward lower fields. Pronounced differences are found, especially for the cymene CH protons with $\Delta\delta$ of up to 0.7 ppm, indicating that complexation occurs close to the arene ligands (see Supporting Information). The exchange of the alkali guest is slow on the NMR time scale. This was confirmed by recording the ^{1}H NMR spectrum (CDCl$_3$) of an equimolar mixture of **1** and **2** (or **3**) which shows two separate sets of signals. First evidence for the high stability of the alkali complexes was the fact that **2** and **3** can be dissolved in unpolar

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(3) Complex **1** was obtained as a racemic mixture of R_{Ru},R_{Ru},R_{Ru} and S_{Ru},S_{Ru},S_{Ru}.

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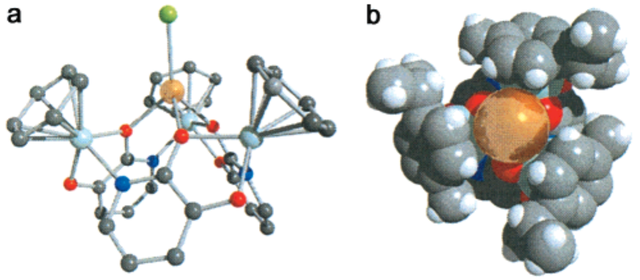

Figure 2. Molecular structure of **3** in the crystal. (a) View from the side; the cymene side chains as well as the hydrogen atoms are omitted for clarity. (b) View along the pseudo-C_3 axis without the chloride ion (CPK model). The sodium ion perfectly fits the cavity generated by the arene ligands.

organic solvents such as benzene and that they can be chromatographed on silica gel without decomplexation.

The X-ray structural analyses of **2** and **3** confirmed the expected coordination of the cation to the three adjacent O-atoms of the bridging pyridonate ligands (Figure 2). Overall, the structures of **2** and **3** are very similar: the alkali metal halide is bound as an ion pair with a tetrahedral coordination geometry for M^+ (Li−O = 1.95 Å, Li−Cl = 2.42 Å; Na−O = 2.23 Å, Na−Cl = 2.53 Å). The short Na−Cl bond is most likely the result of the unusual geometry with Na^+ having the low coordination number four and Cl^- being a terminal ligand. A structural comparison of **1**−**3** reveals that the geometry of the macrocycle (e.g., the distances of the coordinating O-atoms, 3.0 ± 0.1 Å) does not change upon complexation of MCl in agreement with a very high degree of preorganization.

To quantify the stability of the complexes **2** and **3** we have performed competition experiments with various crown ethers and cryptands. First, **1** was added to a solution of NaCl and 18-crown-6 in methanol (molar ratio: 1:1:10). After evaporation of the solvent the mixture was examined by ^{1}H NMR ($CDCl_3$). Despite the large excess of crown ether the quantitative formation of **3** was observed, indicating that the stability of **3** is at least 3 orders of magnitude higher than that of 18-crown-6 × NaCl. Similar results were obtained for **1**, LiCl, and 18-crown-6 or 12-crown-4, respectively (molar ratio: 1:1:10). Detectable amounts of the free receptor **1** were only observed in competition experiments with cryptands which are specific for the respective alkali metal ion (molar ratio: 1:1:1).[6] These investigations have shown that in $CDCl_3$ the binding constant K_{NaCl}(**1**) is at least[7] 1 order of magnitude higher than that of 2,2,1-cryptand and that the stability of **2** is higher than that of 2,1,1-cryptand × LiCl. The relative affinity is solvent dependent: in a more polar solvent mixture such as $CDCl_3$/MeOH (9:1) the respective cryptates were shown to be slightly more stable than **2** or **3**.

The remarkably high stability of **2** and **3** in $CDCl_3$ is further manifested by the fact that NaCl and even LiCl can be extracted from water, a characteristic which is shared only by highly preorganized ionophores such as the spherands described by Cram.[8] When a solution of **1** ($CDCl_3$, 10 mM) was stirred with an aqueous solution of MCl (2.0 M, M = Li, Na, K) for 24 h, the quantitative (>98%) formation of **2** and **3** was observed by ^{1}H NMR. With KCl not even small amounts of an adduct could be detected. The Li^+/Na^+ selectivity was determined in a competition experiment using equimolar amounts of LiCl and NaCl (together 2 M). Integration of suitable ^{1}H NMR signals[9] of the respective adducts revealed that in $CDCl_3$ the affinity of **1** for LiCl is approximately twice as high as for NaCl.

The molecular structure of **3** provides an explanation for the perfect discrimination between Na^+ and K^+. The three cymene ligands form the walls of a rigid cavity in the middle of which Na^+ is tightly bound. The larger cation K^+, on the other hand, is blocked by the arene ligands (Figure 2b). These findings are of special interest since there is a demand for synthetic ionophores with high Na^+/K^+ selectivity due to possible applications such as sensing Na^+ in the intracellular fluid (Na^+−K^+ ratio of ~1:12).[10]

An additional feature of the metallacrown ether **1** is that the binding of M^+ can be detected electrochemically.[11] Compared to **1** the peak potential of **2** and **3** in CH_2Cl_2 is shifted by 450 ± 50 mV toward anodic potential.[12] This characteristic of **1** may be important for potential applications as an ion-selective sensor.

To summarize, we have described a redox-responsive metallomacrocyclic ionophore which is easily obtained by self-assembly using commercially available starting materials. The binding constant of the LiCl and the NaCl complex is comparable to that of high-affinity ionophores such as cryptands, and a nearly perfect selectivity for Na^+ over K^+ is observed. Preliminary results indicate that structurally related metallacrown ethers having different arene ligands (e.g., C_6Me_6, $C_3H_3Et_3$) instead of cymene can be assembled using the strategy described here. Since the selectivity of the ionophore is determined by these ligands, redox-responsive receptors with designed specificities and solublities can be envisioned. Research along these lines is currently being pursued in our laboratory.

Acknowledgment. K.S. thanks Professor Dr. W. Beck (LMU München) for his generous support and E. Karaghiosoff, B. Lotsch, and L. Hötzer for technical assistance. Financial funding from the Bayerischer Habilitations-Förderpreis (K.S.) is gratefully acknowledged.

Supporting Information Available: Synthetic schemes for **1**−**3** together with analytical data (^{1}H, ^{7}Li, and ^{13}C NMR, MS, elemental analysis) and descriptions of the CV and competition experiments (PDF). X-ray structural information for **1**−**3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[6] For reviews on cryptands, see ref 1 and: Lehn, J. M. *Acc. Chem. Res.* **1978**, *11*, 49−57.

[7] The determination of K_{MCl}(**1**):K_{MCl}(cyptand) is hampered by the fact that the kinetics for the ion transfer from the cyptate to **1** are very slow in pure $CDCl_3$: after several days at rt the relative amount of **2** (or **3**) compared to that of **1** was still increasing.

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[9] The adducts **2** and **3** can easily be distinguished by ^{1}H NMR.

[10] (a) Suzuki, K.; Sato, K.; Hisamoto, H.; Siswanta, D.; Hayashi, K.; Kasahara, N.; Watanabe, K.; Yamato, N.; Sasakura, H. *Anal. Chem.* **1996**, *68*, 208−215. (b) Yamamoto, H.; Shinkai, S. *Chem. Lett.* **1994**, 1115−1118.

[11] For a review on redox-responsive ionophores see: Beer, P. D. *Chem. Soc. Rev.* **1989**, *18*, 409−450.

[12] The accurate determination of ΔE_P is difficult because the peak corresponding to the first oxidation of **2** and **3** appears as a shoulder in the cyclic voltammogram.