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An Artificial Regulatory System with Coupled Molecular Switches**

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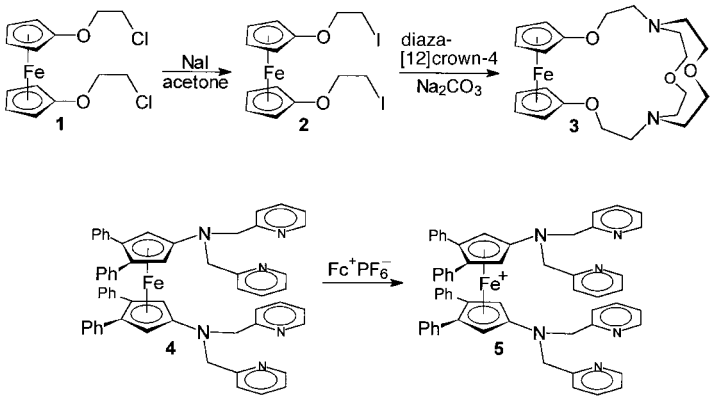
Living organisms rely on an efficient yet complex array of multiply interrelated molecular machines.[1] Recently synthetic chemists have been imitating some of the very basic functions realized in biological systems. This activity has resulted in a number of artificial systems, such as molecular switches,[2–9] sensors,[10] ratchets,[11] wires,[12] artificial enzymes,[13] and self-assembled species[14] to name but a few.[15] We set out to increase the complexity of such systems by designing an artificial regulatory unit in which several molecular components are coupled in a well-adjusted manner.[16, 17] Here, we demonstrate that the interaction of a redox-responsive chelating aminoferrocene, a redox-switchable oxaferrocene cryptand, a Zn^{2+} and a Na^+ salt, and a polyazamacrocycle leads to a system in which the availability of sodium ions can be controlled.

The basic components of the artificial regulatory system described here are two types of redox-active chelating ligands based on ferrocenes. Chelating aminoferrocenes form very stable complexes with soft transition metal ions and respond to the incorporation of metal ions by an anodic shift of the ferrocene redox potential.[18] Complexes of oxaferrocene cryptands with hard alkali and alkaline earth metal ions can become severely destabilized when the ferrocene is oxidized (redox-switching).[19, 20] The efficiency of redox-active ligands in general, crucially depends on the electronic communication between the metal centers involved,[21] and we have recently shown that it is very favorable when donor atoms of a chelating ligand are directly attached to the ferrocene unit.[22]

The construction of an artificial regulatory system based on such ferrocenes requires the careful assembly of several individual components: a redox-responsive ligand (chelating aminoferrocene), a cofactor (Zn^{2+} salt), a redox-switched ligand (oxaferrocene cryptand), a mediator (redox-equivalent), and a deactivator (cyclam = 1,4,8,11-tetraazacyclotetradecane). The individual tasks performed by these subunits are as follows: the redox-responsive ligand binds a cofactor (Zn^{2+}) to become an oxidizing agent, thus generating a redox-equivalent to act as a mediator. This mediator triggers the redox switch and strongly reduces the affinity of the redox-switched ligand for Na^+ ions. The removal of the cofactor by an added deactivator results in the reversal of the switching event and the reactivation of Na^+ binding. In the process as a whole, the availability of Na^+ ions is controlled indirectly by Zn^{2+} ions, by means of electron transfer.

The two types of ferrocenes needed for the artificial regulatory system were synthesized as described in Scheme 1. The dichloride **1** was treated with NaI in acetone to yield the diiodide **2** in 90% yield. The subsequent reaction of **2** with diaza[12]crown-4 generated the oxaferrocene cryptand **3** (Fccrypt) in 80% yield.[23] The simple addition of $NaCF_3SO_3$ to Fccrypt in acetonitrile, followed by evaporation of the



Scheme 1. Syntheses of the redox-active chelating ferrocenes. $Fc^+ = [Fe(C_5H_5)_2]^+$.

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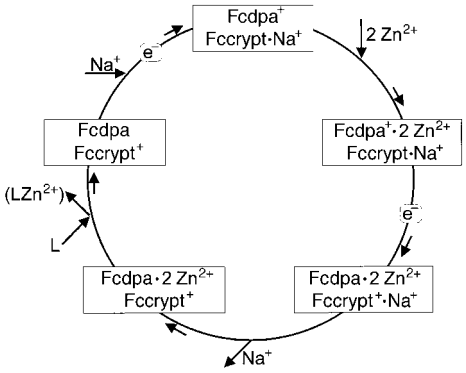
solvent, resulted in the quantitative formation of the corresponding sodium complex. Oxidation of the aminoferrocene **4** (Fcdpa; dpa = di(2-picolyl)amine)[18a] was performed with $Fc^+PF_6^-$ to generate the corresponding cation **5**. The identity of compounds **1**–**5** was established by ^1H, ^{13}C NMR spectroscopy, EI mass spectrometry, and elemental analysis.

The thermodynamics of our artificial regulatory system are governed by the redox potentials of the chelating ferrocenes Fcdpa, Fccrypt, and their respective metal complexes, and it is essential that all four redox potentials are separated by more than 200 mV.[24] The following redox potentials were measured by cyclic voltammetry (CH_3CN, nBu_4NPF_6, with reference to ferrocene ($E = +0.40$ V) or cobaltocene ($E = -0.94$ V)): E(Fccrypt) = +0.15 V, E(Fccrypt · $NaCF_3SO_3$) = +0.395 V, E(Fcdpa) = −0.13 V, E(Fcdpa · 2 $Zn(CF_3SO_3)_2$) = +0.665 V. It is apparent from these data that $Fcdpa^+$ is a very weak oxidant, while $Fcdpa^+ \cdot 2\,Zn^{2+}$ is a fairly strong oxidizing agent. Accordingly only $Fcdpa^+ \cdot 2\,Zn^{2+}$ is able to oxidize Fccrypt · $NaCF_3SO_3$, which results in a drastic decrease in the Na^+ ion affinity of the ferrocene cryptand.[25] For strong complexes it is possible to calculate (to a reasonable approximation) the decrease in the stability constant K for $Fccrypt^+ \cdot Na^+$ compared to K for Fccrypt · Na^+ from the difference of the redox potentials $\Delta E = E_{LM} - E_L$ (L = ligand, M = metal).[26] In the case of Fccrypt and Fccrypt · Na^+, the value of $\Delta E =$ 245 mV corresponds to a decrease in the stability of the sodium complex by at least 1.6×10^4 upon oxiation of Fccrypt.

Once the thermodynamic requirements have been satisfied by the selection of suitable redox partners, the actual experiment is very simple (Scheme 2). Starting from an equimolar



Scheme 2. Electron-transfer mediated regulation of the Na^+ concentration by Zn^{2+} ions. L = cyclam. The compounds in the boxes only indicate the elementary steps and do not imply isolated intermediates.

mixture of Fccrypt · $NaCF_3SO_3$ and $Fcdpa^+PF_6^-$ in acetonitrile, the addition of two equivalents of $Zn(CF_3SO_3)_2$ leads to the complexation of Zn^{2+} by Fcdpa. The aminoferrocenium salt is thus converted into a strong oxidant, which is capable of oxidizing Fccrypt · Na^+ quantitatively. The oxidized oxaferrocenium cryptand then displays a drastically decreased affinity for Na^+ ions. Finally the ability to bind Na^+ ions by the ferrocene cryptand can be re-established by adding a strong ligand to the reaction mixture that is capable of removing Zn^{2+} ions from the Fcdpa · Zn^{2+} complex. Consequently, upon addition of two equivalents of cyclam, the much more stable Zn^{2+}-cyclam complex is formed. At this point—that is without complexed Zn^{2+}—Fcdpa becomes a reducing agent that can be easily oxidized by $Fccrypt^+$ to form $Fcdpa^+$. The neutral Fccrypt species can now form a stable complex with a Na^+ ion and one finally returns to the situation given at the top of Scheme 2, in which $Fcdpa^+$ and Fccrypt · Na^+ coexist.

However, it should not be forgotten that the redox potentials listed above only prove the thermodynamic feasibility of our regulatory device; it is important to check by NMR competition experiments that Zn^{2+} ions alone cannot displace Na^+ ions from the oxaferrocene cryptand. Thus, one equivalent of $Zn(CF_3SO_3)_2$ was titrated to a solution of Fccrypt · $NaCF_3SO_3$ in CD_3CN. In the presence of two equivalents of Et_3N, the ^1H NMR spectrum remained unchanged when the zinc salt was added, indicating a the Na^+ selectivity of Fccrypt. However, in the absence of base, the addition of $Zn(CF_3SO_3)_2$ immediately leads to marked changes in the ^1H and ^{13}C NMR spectra characteristic of monoprotonated Fccrypt, since zinc ions can easily acidify adventitious water in the reaction mixture.

The reactions shown in Scheme 2 can be monitored easily by UV/Vis spectroscopy, since the spectra of Fcdpa, $Fcdpa^+$, Fcdpa · 2 Zn^{2+} and $Fcdpa^+ \cdot 2\,Zn^{2+}$ display very characteristic absorptions. Fccrypt and associated species could not be observed spectroscopically in the reaction mixture since their extinction coefficients are almost two orders of magnitude weaker. To verify the process described in Scheme 2 experimentally, two equivalents of $Zn(CF_3SO_3)_2$ were titrated to an equimolar solution of $Fcdpa^+PF_6^-$ and Fccrypt · $NaCF_3SO_3$, with two equivalents of Et_3N, all dissolved in CH_3CN. It is apparent from the UV/Vis spectra (Figure 1) recorded after

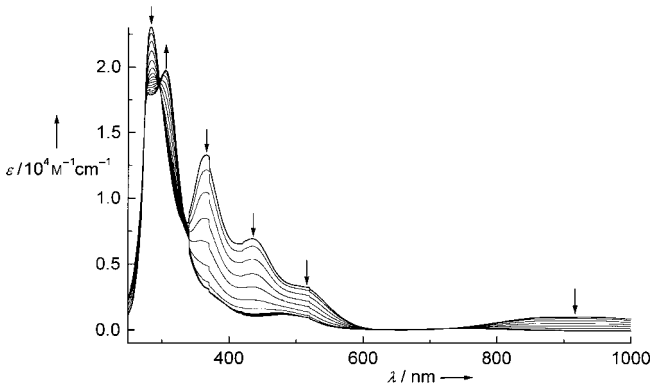


Figure 1. UV/Vis spectra of the titration of $Fcdpa^+PF_6^-$, Fccrypt · $NaCF_3SO_3$, and Et_3N with $Zn(CF_3SO_3)_2$ in CH_3CN ($c = 10^{-4}$ M). Arrows indicate increasing or decreasing extinction during the course of the experiment. The initial UV/Vis spectrum is identical to that of $Fcdpa^+$, while after addition of $Zn(CF_3SO_3)_2$ the resulting spectrum is identical to that of Fcdpa · 2 $Zn(CF_3SO_3)_2$.

each titration step, that the prominent absorptions associated with $Fcdpa^+$ disappear during the course of the experiment giving way to the simple spectrum of Fcdpa · 2 $Zn(CF_3SO_3)_2$. Finally two equivalents of cyclam were added to the reaction mixture, leading to the reappearance of the characteristic UV/Vis spectrum of $Fcdpa^+$.

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Since the UV/Vis experiments only provide information on different Fcdpa species, the titration was monitored in a further experiment by ^{1}H NMR spectroscopy to obtain information on the ferrocene cryptand and its sodium complex (Figure 2). Addition of $Zn(CF_3SO_3)_2$ in CD_3CN to

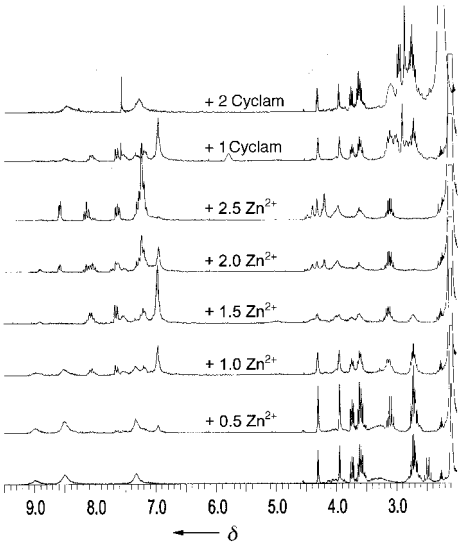

Figure 2. ^{1}H NMR titration experiment of $Fcdpa^+PF_6^-$, $Fccrypt \cdot NaCF_3SO_3$, and Et_3N (in CD_3CN, $c = 10^{-3}$ M) with the addition of four times 0.5 equivalents of $Zn(CF_3SO_3)_2$ followed by two times one equivalent of cyclam. Characteristic resonances associated with Fcdpa species are found between $\delta = 6.8 - 9.1$ (hatched in gray); characteristic resonance signals associated with Fccrypt species are found between $\delta = 3.4 - 4.6$ (hatched in gray).

an equimolar solution of $Fcdpa^+PF_6^-$ and $Fccrypt \cdot NaCF_3SO_3$ with two equivalents of Et_3N, leads to the disappearance of the ^{1}H NMR resonances associated with $Fccrypt \cdot Na^+$ (instead several broad humps are observed because of paramagnetic line broadening) and the appearance of signals assigned to $Fcdpa \cdot 2Zn^{2+}$. The reversal of the electron transfer after addition of two equivalents of cyclam is indicated by the reappearance of $Fccrypt \cdot Na^+$ resonances. We have not yet investigated the rates of the respective metal ion and electron transfer processes, however, no induction periods were observed in the above-mentioned titration experiments.

The experiments described here show that the combination of two redox-active ligands enables a regulatory event to be modeled. However, the artificial regulatory system described here is only operative when *all* individual components cooperate and are well adjusted in their binding and redox behavior. It should be noted that the simple addition of a Zn^{2+} salt as a redox-inactive cofactor is sufficient to initiate the electron transfer process and to switch the Na^+ complexation. The removal of the cofactor by addition of cyclam initiates the reverse electron transfer, and restores the binding ability of the oxaferrocene cryptand.

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