Angewandte Chemie International Edition

DOI: 10.1002/anie.201006362

Molecular Machines

Dual Stimulus Switching of a [2]Catenane in Water**

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The most sophisticated and efficient nanoscale machines are those which reside in living cells in order to perform complex mechanical tasks, such as cell division and intracellular transport.[1] These motor molecules transduce[2] one form of energy (typically chemical, both covalent and noncovalent in nature) into another form (typically mechanical) for the most part in an aqueous environment. The rapid development of artificial molecular machinery[3] during the past two decades is rendering it possible to mimic and infiltrate biomolecular machines using wholly synthetic systems—even if the complexity and efficiency of the nonnatural counterparts are in no way comparable to their naturally occurring cousins. One of the most important, yet challenging, issues in the field is the development of artificial molecular machinery that is able to become part of an integrated system and still perform molecularly controlled work in aqueous environments, opening up opportunities for developing applications in nanoprosthetics to aid and abet in combating disease at the molecular level. Cyclodextrins[4] and cucurbiturils[5] are amongst some of the most highly investigated examples of building blocks suitable for the construction of water-friendly artificial molecular machinery, principally because both these receptors boast controllable molecular recognition towards many different substrates dissolved in water.

Tetracationic cyclophanes[6,7] (TCs^{4+}) are an important class of water-soluble synthetic receptors that demonstrate[8] excellent binding affinities towards π-electron-rich substrates in both organic solvents (when the counteranions are soft, e.g., PF_6^-, BF_4^-) and in aqueous solutions (when the counterions are hard, e.g., $CF_3CO_2^-$, Cl^-). The synthetic versatility[9,10] surrounding TCs^{4+} has enabled the elaboration of different, carefully designed molecular machines/switches[3] on the basis of these TCs^{4+} which have been studied extensively and applied to the development of nanoelectromechanical systems,[11] mechanized nanoparticles[12] for drug delivery, and nanoelectronic devices.[13] Surprisingly, despite their ability to exhibit molecular recognition in water, TCs^{4+} have seldom been used in building molecular switches/machines which work in aqueous media. Here, we report the design of a water-soluble, donor–acceptor [2]catenane in which the switching of both macrocyclic components can be addressed individually and orthogonally by external stimuli working in aqueous media.

In order to effect the circumrotation of both rings in a donor–acceptor [2]catenane independently, two nondegenerate mechanically interlocked rings, which can be addressed by

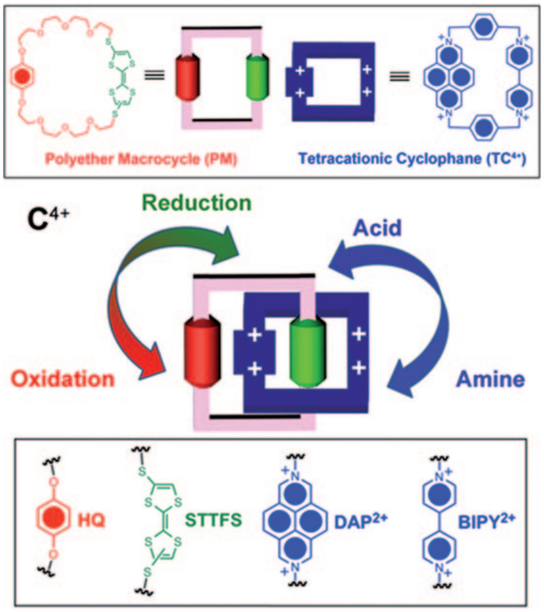

Figure 1. Formulas and schematic representations of the ground-state co-conformation of [2]catenane $\mathbf{C}^{4+}$ and the circumrotational movements of both the tetracationic cyclophane (TC^{4+}) as well as the polyether macrocycle (PM).

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[**] The research described here was sponsored in part by the National Center for Nano Technology Research at the King Abdulaziz City for Science and Technology (KACST). We thank Dr. Turki S. Al-Saud and Dr. Soliman H. Alkhowaiter at KACST for their generous support of this program of research at Northwestern University (NU). We also acknowledge support from the Air Force Office of Scientific Research (AFOSR) under the Multidisciplinary Research Program of the University Research Initiative (MURI), Award FA9550-07-1-0534 entitled "Bioinspired Supramolecular Enzymatic Systems". L.F. acknowledges the support of a Ryan Fellowship and a Non-Equilibrium Research Center (NERC) Fellowship from NU. A.C.F. thanks the National Science Foundation (NSF) for the award of a NSF Graduate Research Fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201006362.

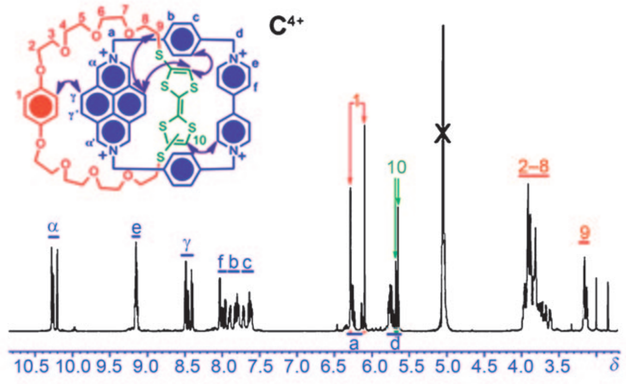

Figure 2. ^{1}H NMR spectrum of **C**$\cdot$4 CF_3CO_2 in D_2O at 277 K with all the resonance peaks assigned. The intercomponent nuclear Overhauser effects observed in ^{1}H-^{1}H ROESY experiment are shown as purple arrows.

two different external stimuli, are a requirement. In this context, a π-electron-rich polyether macrocycle (PM) and a π-electron-deficient TC^{4+} ring—both containing two different molecular recognition sites—need to be employed (Figure 1) as the two catenated components. On the one hand, we have arranged for the PM to contain two π-electron-rich recognition units—namely, a 4,4′(5′)-bisthiotetrathiafulvalene (STTFS) unit and a hydroquinone (HQ) unit, both of which interact to some degree with TC^{4+}. On the other hand, we have arranged for TC^{4+} to contain two π-electron-deficient recognition units—that is, a bipyridinium ($BIPY^{2+}$) unit and a diazapyrenium[7,14,15] (DAP^{2+}) unit—which will both interact, to some extent, with the PM. Once assembled into the [2]catenane $\mathbf{C}^{4+}$, these two ring components will [π⋯π] stack in unison with each other and form a “donor–acceptor–donor–acceptor” array, thus stabilizing[10] the [2]catenane on account of [π⋯π] charge transfer (CT) and hydrophobic interactions. Since TC^{4+} binds the STTFS unit more strongly than it does the HQ unit, while the PM has a higher affinity for the DAP^{2+} unit than it has for the $BIPY^{2+}$ unit, the ground-state co-conformation (GSCC) is expected to correspond to the catenane geometry illustrated in Figure 1. The controlled switching of each individual ring can be addressed using different stimuli. While the STTFS can be oxidized,[16] either chemically or electrochemically, and hence induce the circumrotation of the PM ring, the DAP^{2+} unit forms[14] an adduct with amines that should lead to the circumrotation of the TC^{4+} ring.[15]

On the basis of this blueprint, the designed [2]catenane **C**$\cdot$4 CF_3CO_2, containing two bistable and complementary rings, was synthesized (see the Experimental Section and the Supporting Information) by employing a template-directed protocol.[17] The pure product, a dark green solid, was isolated using preparative HPLC following the formation of the TC^{4+} ring under the templation of the PM ring. Analytical HPLC of **C**$\cdot$4 CF_3CO_2 revealed (Supporting Information) two peaks, which eluted close to each other, corresponding to the [2]catenanes containing a mixture of *cis*- and *trans*-STTFS units.

The [2]catenane **C**$\cdot$4 CF_3CO_2 is readily soluble in water, forming an emerald green aqueous solution in the process. ^{1}H NMR spectra (Figure 2) of **C**$\cdot$4 CF_3CO_2 in D_2O were recorded at a range of temperatures from 277 up to 343 K. Based on ^{1}H-^{1}H-g-DQF-COSY and ^{1}H-^{1}H-ROESY spectra (see the Supporting Information), all the resonances can be assigned with some precision. Although the existence of *cis*- and *trans*-isomers of the STTFS unit lead to all the ^{1}H NMR signals separating into two sets of peaks, the otherwise simple spectrum suggests that only one of the four possible translational isomers is populated in aqueous solution. The major co-conformation of **C**$\cdot$4 CF_3CO_2 in water was deduced from the nuclear Overhauser effects observed (see the Supporting Information) in the ROESY spectrum. The through-space interactions between the STTFS, HQ, $BIPY^{2+}$, and DAP^{2+} units indicate that the TC^{4+} ring encircles the STTFS unit,

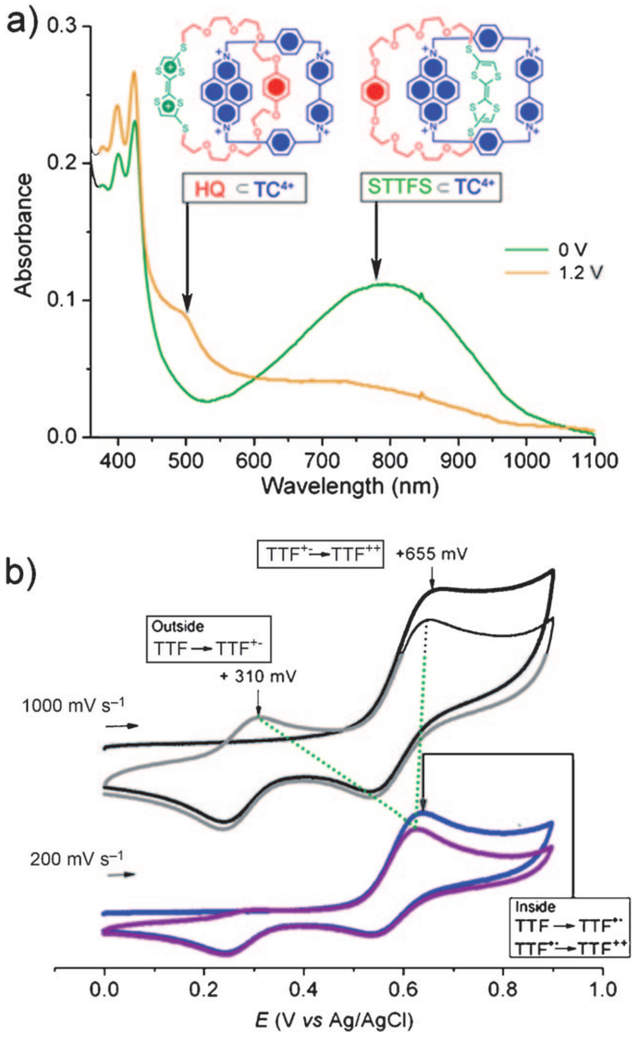

Figure 3. a) UV/Vis spectroelectrochemistry of $\mathbf{C}^{4+}$ recorded at 0 V (green line) and 1.2 V (orange line) in water. $[\mathbf{C}^{4+}] = 2.34 \times 10^{-4}$ mol L^{-1}; electrolyte = tetrabutylammonium chloride (TBACl) (0.1 mol L^{-1}); $T = 298$ K; $l = 1$ mm. b) Cyclic voltammetry measurements of $\mathbf{C}^{4+}$ at different scan rates (the current intensities are normalized). $[\mathbf{C}^{4+}] = 1 \times 10^{-3}$ mol L^{-1}; electrolyte = TBACl (0.1 mol L^{-1}). 1000 mV s^{-1}: the first scan is black, the second scan is gray; 200 mV s^{-1}: the first scan is blue, the second scan is purple.

while the PM ring encircles the DAP^{2+} unit, leaving the HQ and $BIPY^{2+}$ units to occupy alongside orientations. This observation matches our expectation as to the preferred co-conformation (Figure 1) based on the relative binding affinities of the four different units, i.e., STTFS > HQ in binding to TC^{4+} and $DAP^{2+} > BIPY^{2+}$ in binding to PM. No significant changes in the ^{1}H NMR spectrum in D_2O were observed on heating the sample up to 343 K or cooling it down to 277 K in keeping with the belief[18] that $\mathbf{C}^{4+}$ exists, to all intents and purposes, as a single co-conformation. This property of the [2]catenane in aqueous solution renders switching much more precise.[19]

The UV/Vis absorption spectrum of $\mathbf{C}{\cdot}4\,CF_3CO_2$ in water reveals (Figure 3a) a strong broad absorption band centered on 800 nm. This peak is characteristic[16c] of a CT interaction formed between STTFS and $BIPY^{2+}/DAP^{2+}$ units when the STTFS unit is encircled by the TC^{4+} ring ($STTFS \subset TC^{4+}$). Since the STTFS unit can be oxidized electrochemically to its $STTFS^{2+}$ dication, cyclic voltammetry (CV) of the [2]catenane in water (with 0.1 mol L^{-1} TBACl as the electrolyte) was recorded. The first scan showed (Figure 3b) only one major oxidation peak at +655 mV, an observation which provides yet another piece of strong evidence that the STTFS unit is all but located inside the TC^{4+} ring. This conclusion is reflected in the fact that both the first and second oxidation processes appear in combination[20]—an indication that the STTFS is firmly ensconced inside the TC^{4+} ring. It is well known that, upon oxidation, Coulombic repulsion between the dicationic $STTFS^{2+}$ unit and the TC^{4+} ring will force the PM ring to circumrotate into a co-conformation in which the HQ unit resides inside the TC^{4+} ring. On reduction,[21] the $STTFS^{2+}$ unit undergoes two one-electron reduction processes to its neutral state while the $STTFS^{2+}$ unit is located alongside the TC^{4+} ring with the HQ unit inside.

Such a metastable co-conformation (MSCC) eventually relaxes back to the GSCC as a result of the PM ring circumrotating around the TC^{4+} ring such that the STTFS unit moves back inside the TC^{4+} ring. This process can be confirmed (Figure 3b) by monitoring the oxidation process associated with the STTFS unit in the second cycle of the CV experiment while varying the scan rates. If the oxidation-reduction cycle is fast enough, then the characteristic oxidation peak of the MSCC will be observed at around +300 mV during the second cycle. Indeed, when the scan rate was increased to 1000 mV s^{-1}, the second CV scan revealed an oxidation process occurring at +310 mV where the integrated peak area equaled that of the peak observed at +650 mV. By varying the scan rate, the kinetics of the relaxation process (MSCC→GSCC) could be obtained (see the Supporting Information). The half-life of the MSCC was found to be 1.21 ± 0.12 s at 298 K, corresponding to a free energy of activation of 17.5 ± 0.2 kcal mol^{-1} for the process in water.

The electrochemically driven circumrotation of the PM ring can also be monitored (Figure 3a) by UV/Vis spectroelectrochemistry. On setting the voltage of the mesh-shaped working electrode to +1.2 V, the CT band at 800 nm disappeared and a new absorption band—which can be assigned to the CT band formed between the HQ unit and the TC^{4+} ring—emerged at ca. 500 nm.[6c] This blue shift provides evidence for the circumrotation of the TC^{4+} ring from the STTFS unit to the HQ unit on the PM ring.

The movement of the TC^{4+} ring was achieved using an amine as the actuator. On adding 1,4-diazabicyclo[2.2.2]-octane (DABCO) to an aqueous solution of $\mathbf{C}{\cdot}4CF_3CO_2$, a new absorption band centered on 562 nm (an [n⋯π] CT band originating in the DABCO–DAP complex)[22] appeared and the CT band at 800 nm decreased ever so slightly (Figure 4a). The retention of the 800 nm CT band indicates that the STTFS unit was still encircled by the TC^{4+} ring after the formation of DABCO–DAP complex.

This complex formation between DABCO and the DAP^{2+} unit is a dynamic process which can be reversed on the addition of acid. On the basis of a UV/Vis absorption titration experiment (Supporting Information), the binding constant

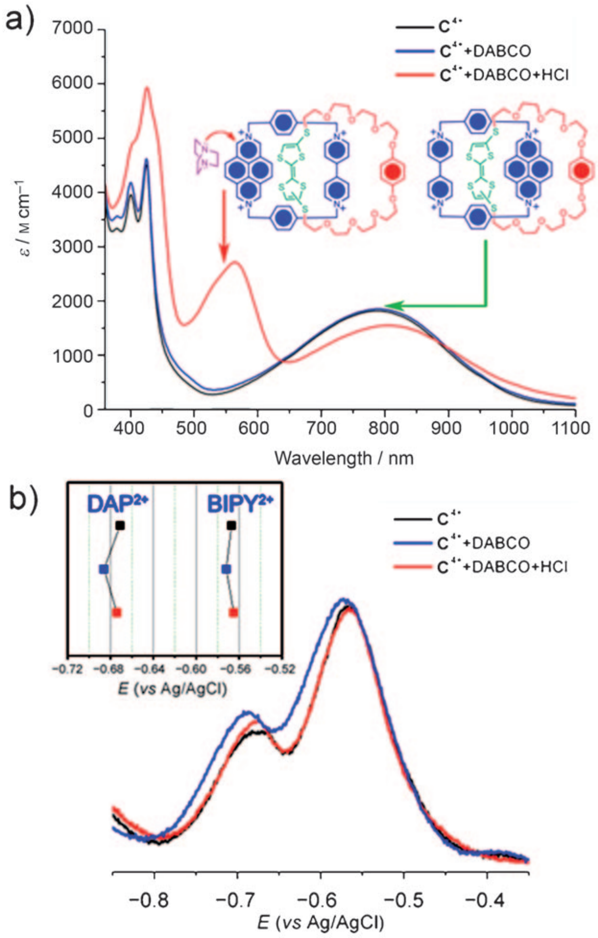

Figure 4. a) Normalized UV/Vis absorption spectrum of $\mathbf{C}{\cdot}4\,CF_3CO_2$ recorded in water (black line), as well as the spectrum upon the addition of excess of DABCO (blue line), and further addition of excess of trifluoroacetic acid (TFA) (red line). $[\mathbf{C}{\cdot}4\,CF_3CO_2] = 2.34 \times 10^{-4}$ mol L^{-1}, [DABCO] = 0.03 mol L^{-1}; [TFA] = 0.03 mol L^{-1}. (b) Differential pulse voltammetry measurements of $\mathbf{C}^{4+}$ (black line), upon the addition of excess of DABCO (blue line) and after further addition of excess of HCl (red line). $[\mathbf{C}^{4+}] = 2 \times 10^{-4}$ mol L^{-1}; electrolyte = TBACl (0.1 mol L^{-1}); [DABCO] = 0.02 mol L^{-1}; [HCl] = 0.02 mol L^{-1}. The inset is a diagram of potential values of the first reduction processes of $BIPY^{2+}$ and DAP^{2+} units before (black dots) and after (blue dots) the addition of DABCO, as well as that after further addition of HCl (red dots).

(K_a) between DABCO and **C**·4 CF_3CO_2 was found to be 174 ± 8 $L\,mol^{-1}$ in water. This K_a value is comparable with that for DABCO with dibenzyl-diazapyrenium (264 ± 28 $L\,mol^{-1}$) in water (Supporting Information). In this equilibrium involving the [2]catenane $\mathbf{C}^{4+}$, the formation of the DABCO→DAP^{2+} adduct forces the TC^{4+} ring to undergo circumrotation with respect to the PM ring, such that the DAP^{2+} unit resides alongside, while the $BIPY^{2+}$ unit occupies the inside of the PM ring. The process is a result of 1) the steric hindrance of the DABCO→DAP^{2+} adduct and also 2) its decreased electron deficiency. The UV/Vis absorption spectrum is fully regenerated on neutralizing the DABCO by addition of an equivalent of an acid, e.g., CF_3CO_2H.

The circumrotation of the TC^{4+} ring with respect to the PM ring has been confirmed by carrying out electrochemical measurements on **C**·4 CF_3CO_2 in water before and after addition of DABCO. Differential pulse voltammetry (DPV) of the [2]catenane ($2\times10^{-4}\,mol\,L^{-1}$) from 0 to −800 mV in water reveals (Figure 4) two reduction peaks which could be assigned[15] to the first reduction processes of the alongside $BIPY^{2+}$ unit (−567 mV) and the inside DAP^{2+} unit (−671 mV), respectively. The shift of the DAP^{2+} reduction peak is caused by the formation of the DABCO→DAP^{2+} adduct. The 5 mV shift of the peak at −567 mV indicates[15] that the $BIPY^{2+}$ unit has located itself inside the PM ring after the addition of the DABCO—i.e., circumrotation of the TC^{4+} ring through the PM ring has occurred. On addition of 100 equiv of HCl,[23] the DPV trace was restored completely as a consequence of the complete recovery to the GSCC following the neutralization of DABCO.

We have demonstrated that the controllable mechanical movement of either the polyether macrocycle or the tetracationic cyclophane in a doubly bistable water-soluble [2]catenane can be effected using orthogonal external stimuli (redox and amine/acid). These reversible molecular motions can be controlled in aqueous media—it would appear, with even more precision than in organic solvents[19]—bringing us just a little closer to what nature can do and affording us a better chance to modify nature's catalysts (enzymes) and motor molecules with artificial molecular switches/machines. The organization of such molecular actuators onto polymer scaffolds,[24] the surfaces of nanostructures,[25] and into the struts of metal–organic frameworks[26] could provide the stepping stone for the creation of integrated complex systems. Water-compatible artificial molecular switches/machines could also act as molecular prosthetics[27] in living systems, providing us with an opportunity to regulate biological processes using correlated molecular motions at the nanoscale level.

Experimental Section

Synthesis of **C**·4 CF_3CO_2: The polyether macrocyle PM (76 mg, 0.107 mmol), diazapyrene (44 mg, 0.214 mmol), and bis(*p*-bromomethylbenzyl)-4,4′-bipyridinium bishexafluorophosphate (174 mg, 0.214 mmol) was dissolved in DMF and the mixture was stirred at room temperature for 4 days. After removing the solvent under reduced pressure, the resulting dark green residue was subjected to column chromatography (SiO_2: NH_4PF_6/CH_3COCH_3:5 $g\,L^{-1}$). The green band was collected and further purified by RP-HPLC (C18; H_2O–MeCN/0–100% in 30 min, with 0.1% TFA), to afford pure **C**·4 CF_3CO_2 as a dark green solid (66 mg, 38%). ^1H NMR (D_2O, 600 MHz, 25°C): $\delta = 3.12$–3.17 (m, 4H), 3.63–3.98 (m, 32H), 5.65–5.77 (m, 6H), 6.10–6.29 (m, 8H), 7.61–7.90 (m, 8H), 7.95–8.04 (m, 4H), 9.13–9.17 (m, 4H), 10.21–10.28 ppm (m, 4H). ^{13}C NMR (D_2O, 125 MHz, 25°C): $\delta = 34.1$, 34.3, 63.2, 64.7(m), 66.4(m), 67.4, 67.9, 68.5, 69.2, 69.3, 69.6, 69.7, 69.9, 106.1, 106.2, 114.5, 114.8, 116.2 (q, $J = 290$ Hz), 116.4, 116.7, 125.0, 125.2, 125.4, 126.2, 126.5, 127.0, 128.3, 129.2, 129.3, 129.5, 129.6, 130.5 (m), 135.9 (m), 139.4, 139.6, 139.9, 144.0, 144.2, 144.4, 145.1, 145.2, 145.3, 151.6, 151.9, 163.9 ppm (q, $J = 35$ Hz). ESI-MS: $m/z = 1601.33$ $[M-CF_3CO_2]^+$; 1487.33 $[M-CF_3CO_2-CF_3CO_2H]^+$; 744.15 $[M-2\,CF_3CO_2]^{2+}$; 687.16 $[M-2\,CF_3CO_2-CF_3CO_2H]^{2+}$. Analytical HPLC chromatogram of **C**·4 CF_3CO_2 shows (Supporting Information, Figure S1) two closely eluting peaks (12.3 min and 12.8 min) as a result of the existence of both *cis*- and *trans*-STTFS units in the catenane **C**·4 CF_3CO_2. The ratio of the peak integrals is 1.08:1 (12.3 min : 12.8 min).

Received: October 11, 2010

Keywords: artificial molecular machines · electrochemistry · translational isomerism · water-soluble catenane

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[19] The [2]catenane $\mathbf{C}^{4+}$ does not exhibit the same kind of precision in organic solvents. In CD_3CN, for example, the ^{1}H NMR spectrum (see the Supporting Information) of $\mathbf{C}\cdot 4\,CF_3CO_2$ reveals that the PM ring distributes itself between the STTFS unit being located inside the TC^{4+} ring in contradistinction to the HQ ring being located inside the TC^{4+} ring with a ratio of 1:1.8.

[20] It is well known that the first oxidation process of STTFS unit shifts drastically to more positive potential as a result of the TC^{4+} encirclement.

[21] It should be noted that the oxidation of STTFS unit becomes irreversible when it is exposed to oxidant for a relatively long time (>1 h). Meanwhile, a slow scan rate CV (50 mV s^{-1}) revealed that the integrals of the cathodic peaks are slightly smaller than those for the anodic peaks. We believe that this phenomenon originates from the slow decomposition of oxidized STTFS units in aqueous media. At the timescale of minutes, however, this system shows full redox reversibility. For previous examples describing the irreversible oxidation of TTF in aqueous media, see: a) M. J. Eddowes, M. Grätzel, *J. Electroanal. Chem.* **1983**, *152*, 143–155; b) J. Georges, S. Desmettre, *Electrochim. Acta* **1986**, *31*, 1519–1524.

[22] In order to investigate the nature of this [n⋯π] interaction, the ^{1}H NMR spectrum of a CD_3CN solution of dibenzyldiazapyrenium ditrifluoroacetate was recorded after the addition of DABCO. On the one hand, more than one distinct species can be identified, probably on account of the low binding constant between DAP^{2+} and DABCO. On the other hand, the resonance signals corresponding to α-protons in the DAP^{2+} unit were shifted upfield and became broad. These phenomena lead us to the conclusion that the electron lone pair on DABCO interacts primarily with the aforementioned α-protons while the equilibrium of the formation and dissociation of the [n⋯π] complex occurs at a rate slower than the ^{1}H NMR timescale. See the Supporting Information for the ^{1}H NMR spectrum.

[23] HCl was used in the DPV measurement, instead of TFA, in order to prevent counterion exchange in the TBACl electrolyte solution, so that the dominant counteranion in the solution remains the Cl^- one.

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