Molecular Switch

DOI: 10.1002/ange.201108089

Reversible ON/OFF Nanoswitch for Organocatalysis: Mimicking the Locking and Unlocking Operation of CaMKII**

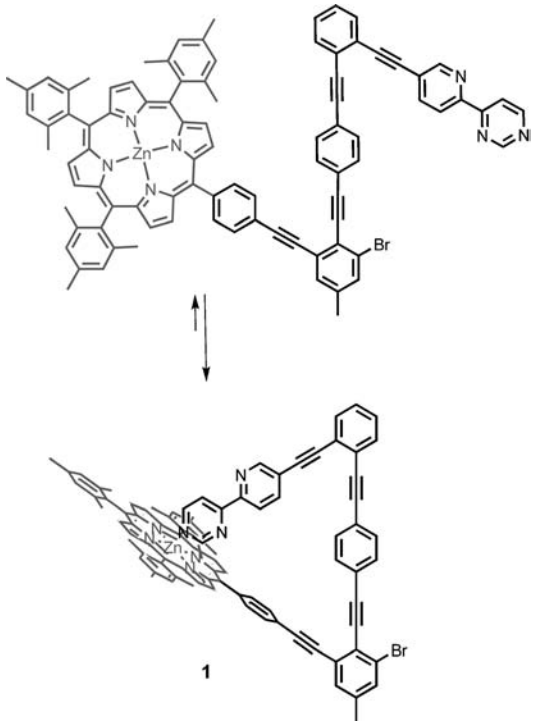
Michael Schmittel, Soumen De, and Susnata Pramanik*

In recent years, a variety of molecular machines that are capable of changing their state in response to external chemical, electrochemical, and photochemical stimuli have been prepared.[1,2] Among those, self-locking[3] systems constitute a highly topical category because of their structural attractiveness, their ability to operate as an ON/OFF toggle for hiding and exposing functional groups, and their potential as nanomechanical devices. Self-locking switches do require at least two distinct states with different properties: the locked and the unlocked state. In the locked state, two or more functional units are intramolecularly linked together by noncovalent interactions, and in the presence of an appropriate external stimulus the unlocked state is generated and new functions are exposed. So far, only a few self-locking systems have been reported,[3] and all of them, except one,[3j] are ouroborands given a recent definition by Durola and Rebek.[3l]

Self-locking systems, such as the calcium/calmodulin-dependent protein kinase II (CaMKII) that plays an important role during signal transduction,[4a] are well known in biology.[4] In CaMKII, there is an extended peptide residue known as the auto-inhibitory segment and it sterically inhibits a protein substrate and ATP from accessing the active site. To activate the system, a Ca^{2+}-loaded calmodulin wraps around the inhibitory segment and triggers its displacement from the active site. As a result, CaMKII starts to phosphorylate postsynaptic glutamate receptors, thus changing the electrical properties of the synapse. After signal transduction, the Ca^{2+}-loaded calmodulin leaves the inhibitory segment and CaMKII reverts to its inactive state.

In light of such fascinating biological examples, stimulus-responsive control of chemical catalysis in artificial molecular switches has received increasing interest lately.[3m,5] While a self-locking system has already been used for phototriggered catalysis,[3m] modulation or even clear cut ON/OFF regulation of catalytic activity by chemical stimuli has not been reported yet.

Herein, we report on the chemically triggered self-locking nanoswitch **1** and its reversible locking and unlocking (Scheme 1), which mimics in part the working principle of



Scheme 1. Open and locked state of the self-locking system **1**.

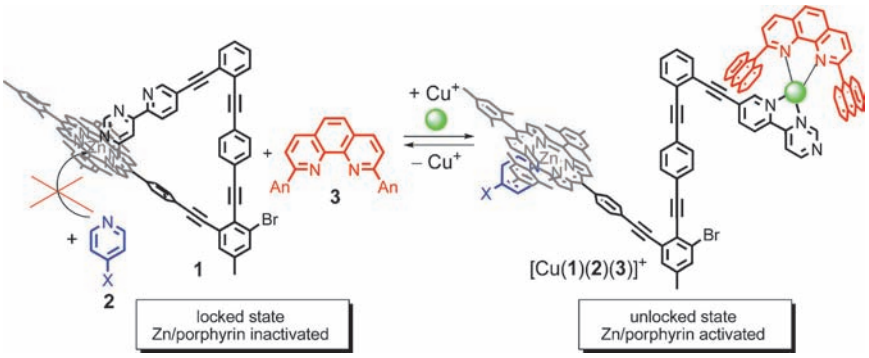
CaMKII. Specifically, the external input, copper(I)-loaded phenanthroline **3** (Scheme 2), wraps around the inhibitory segment, thus triggering its release from the zinc porphyrin unit.[6] As a result, the zinc porphyrin can now interact with an external guest, such as **2** or **7** (see Figure 3). When we use piperidine (**7**) as a guest, the self-locking system **1** serves as a reversible ON/OFF switch for an organocatalytic process, and maintains activity over several catalytic cycles.

The design of **1** combines the known zinc porphyrin·pyridine (or piperidine) coordination with the HETPHEN complexation motif,[7,8] the latter was developed by our group over the years. Both coordination patterns may be operated orthogonally to each other.[9] As the inhibitory segment we chose the 4-(2-pyridyl)pyrimidine (py-pym) unit as it allows coordination to either the zinc porphyrin unit or to Cu^{+}/**3** through HETPHEN complexation. Without additives, **1** is exclusively in the locked state, as the py-pym unit readily coordinates to the zinc porphyrin. In the presence of Cu^{+}/**3**

[*] Prof. Dr. M. Schmittel, S. De, S. Pramanik
Center of Micro and Nanochemistry and Engineering
Organische Chemie I, Universität Siegen
Adolf-Reichwein-Strasse 2, 57068 Siegen (Germany)
E-mail: schmittel@chemie.uni-siegen.de
Homepage: http://www.uni-siegen.de/fb8/oc/oc1/chef/index.-html?lang=de

[**] We are grateful to the Deutsche Forschungsgemeinschaft and the Universität Siegen for financial support. CaMKII = calcium/calmodulin-dependent protein kinase II.

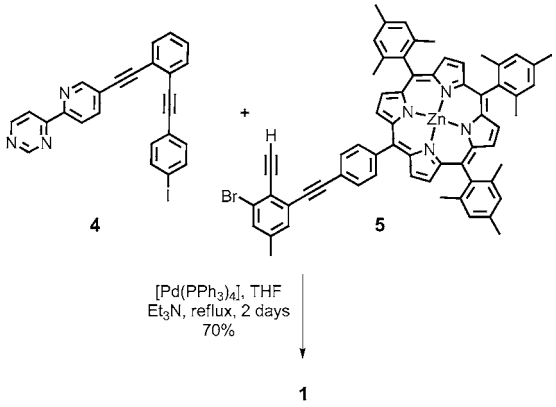
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201108089.



Scheme 2. Schematic representation of the reversible locking and unlocking of nanoswitch **1** (An = 9-anthracenyl).

the py-pym unit is expected to be released from the porphyrin to form the HETPHEN complex $[Cu(\mathbf{1})(\mathbf{3})]^+$, and in presence of **2** it is expected to form complex $[Cu(\mathbf{1})(\mathbf{2})(\mathbf{3})]^+$. The controlled switching between locked and unlocked states is displayed in Scheme 2. In some manner, the self-locking system **1** is related to ouroborands,[3h] with the cavity being replaced by an alternative binding site.

Compound **1**, synthesized by Sonogashira coupling (Scheme 3) of **4** and **5**, was unambiguously characterized by



Scheme 3. Synthesis of self-locking molecule **1**.

^{1}H and ^{13}C NMR, and ^{1}H-^{1}H COSY spectroscopy as well as ESI-MS, UV/Vis spectroscopy, and elemental analysis. The ESI-MS shows a single peak at *m*/*z* 1378.0 (see Figure S23 in the Supporting Information) corresponding to MH^+, and this assignment is supported by the correct isotopic splitting. In the ^{1}H NMR spectrum of **1**, the protons, labeled here a, b, and c, are shifted upfield to $\delta = 3.3$, 2.9, and 6.6 ppm, respectively, as a result of the immersion of the pyrimidine ring into the shielding zone of the porphyrin π system (Figure 1 b, and see Figure S1). In contrast, the reference compound **4** displays these ^{1}H NMR signals at $\delta = 9.3$, 8.4, and 8.9 ppm, respectively (Figure 1 a). The ^{1}H NMR signals of the pyrimidine protons in **1** are quite sharp. Moreover, these shifts prove to be independent of concentration (see Figure S4), thus indicating that the py-pym unit is intramolecularly coordinated to the zinc porphyrin. UV/Vis spectroscopic results further corroborated this assignment: the Soret absorption of **1** appears at $\lambda = 429$ nm, whereas that of porphyrin **5**, used as a reference, shows up at $\lambda = 422$ nm (see Figure S25). The 7 nm shift clearly indicates coordination of the py-pym unit to the zinc porphyrin of **1**. Intermolecular coordination was excluded by UV/Vis measurements as the wavelength remained constant when the concentrations of **1** were varied (10^{-6} to 10^{-4} M; see Figure S26). In summary, the experimental data show **1** to be self-locked at the py-pym···porphyrin interface.

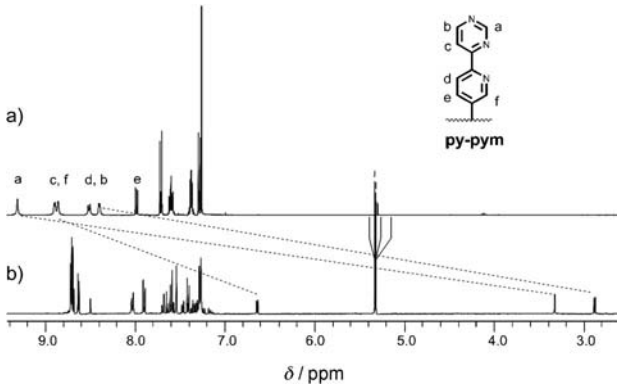


Figure 1. Comparison of the ^{1}H NMR spectra (298 K) of **4** (a) and **1** (b). Only the characteristic shifts of the pyrimidine protons are shown.

To drive the unlocking process by chemical input, we studied the reaction of **1** at its py-pym coordination site with the shielded phenanthroline **3** (Scheme 2) in presence of Cu^+ ions. Indeed, when **1** was reacted with one equivalent of $[Cu(\mathbf{3})]^+$, formation of the fully unlocked complex $[Cu(\mathbf{1})(\mathbf{3})]^+$ was ascertained from ^{1}H and ^{13}C NMR spectroscopy, ESI-MS, UV/Vis, and elemental analysis. In the ^{1}H NMR spectrum protons a and b of complex $[Cu(\mathbf{1})(\mathbf{3})]^+$ are shifted to $\delta = 7.4$ and 6.9 ppm, respectively, now appearing as sharp signals (see Figure S6 in the Supporting Information). The ESI-MS exhibits the expected peak for the heteroleptic complex at 1971.9 Da (see Figure S24) with the isotopic splitting perfectly matching that of the theoretical one. Quantitative formation of the unlocked complex is furthermore confirmed by its UV/Vis spectrum, which shows an absorption at $\lambda = 422$ nm that is typical for the non-coordinated porphyrin. Formation of complex $[Cu(\mathbf{1})(\mathbf{3})]^+$ was additionally studied by titrating a solution of **1** and **3** (10^{-6} M) against Cu^+ (10^{-4} M). The absorption at $\lambda = 429$ nm shifts to $\lambda = 422$ nm upon addition of one equivalent of Cu^+. In a related experiment, **1** was titrated with a solution of $[Cu(\mathbf{3})]^+$. As before, the absorption band at $\lambda = 429$ nm is fully shifted to $\lambda = 422$ nm upon addition of one equivalent of $[Cu(\mathbf{3})]^+$ (Figure 2).

To reversibly lock and unlock **1**, cyclam, known for its very high affinity towards Cu^+, was used. Alternatively, we may

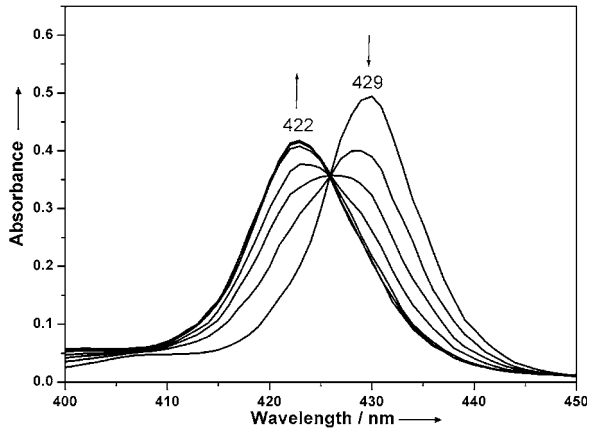


Figure 2. UV/Vis titration of compound **1** (10^{-6} M) versus $[Cu(\mathbf{3})]^+$ (10^{-4} M) at 298 K with each addition corresponding to 0.25 equiv of $[Cu(\mathbf{3})]^+$.

use ligand **8** (Figure 3), as it forms the very strong homoleptic complex $[Cu(\mathbf{8})_2]^+$ (see Figure S13 in the Supporting Information). As expected, addition of one equivalent of cyclam

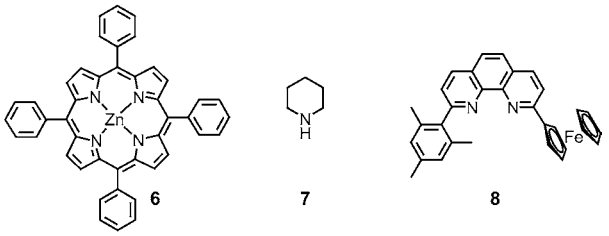
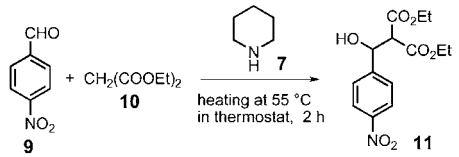


Figure 3. Compounds used for complexation.

extracted Cu^+ from $[Cu(\mathbf{1})(\mathbf{3})]^+$, thus generating **1** in its locked state. The unlocked state $[Cu(\mathbf{1})(\mathbf{3})]^+$ was regenerated by adding Cu^+ to the mixture. Altogether this protocol worked with reversibility for up to three cycles and was monitored by ^{1}H NMR spectroscopy (see Figure S9). In a titration of $[Cu(\mathbf{1})(\mathbf{3})]^+$ (10^{-4} M) against cyclam (10^{-2} M) the absorption at $\lambda = 422$ nm shifted to $\lambda = 429$ nm upon adding a total of one equivalent of cyclam (see Figure S27).

To examine whether the zinc porphyrin docking station was able to operate as a platform for binding (in the unlocked state) and release (in the locked state) of an external guest, one equivalent of 4-iodopyridine (**2**: X = I) was added to $[Cu(\mathbf{1})(\mathbf{3})]^+$. In the ^{1}H NMR spectum, the α and β protons of **2** (X = I) are shifted upfield to $\delta = 4.2$ and 6.5 ppm (see Figure S10 in the Supporting information) respectively, thus indicative of binding. In addition, the UV/Vis titration of $[Cu(\mathbf{1})(\mathbf{3})]^+$ with **2** (X = I)shows an absorption change (see Figure S28) of the Soret band from $\lambda = 422$ nm to $\lambda = 429$ nm with four equivalents of **2** ((X = I); $\log K = 3.43 \pm 0.1$).[10] A Job plot shows a perfect 1:1 stoichiometry (see Figure S29). Thus, both UV/Vis and NMR data strongly support that **2** (X = I) is effectively coordinated to the free zinc porphyrin (host station) of $[Cu(\mathbf{1})(\mathbf{3})]^+$ in its unlocked state. In contrast, when one equivalent of **2** (X = I)is added to **1** (at varying concentrations $c = 1.0$–7.5×10^{-4} M; $\log K = -0.19 \pm 0.01$), its NMR spectrum remains unchanged (see Figure S11), thus indicating that **2** (X = I) is unable to displace the py-pym unit from the zinc porphyrin in the absence of other external stimuli. An analogous titration of **1** with **2** (X = I) using UV/Vis did not provide much information as both complexes absorb at the same wavelength.

After establishing a reversibly operated nanoswitch that allowed the controlled release and binding of a guest (see Figure S12 in the Supporting Information), we further explored whether a suitable guest would be able to catalyze a meaningful reaction. After screening various amines, piperidine (**7**) was found to be a promising candidate (Scheme 4). While **7** (10 mol%) catalyzes the Knoevenagel reaction of **9** and **10** in presence of the self-locked **1** (10 mol%), no product is formed once **1** is unlocked, that is, in presence of Cu^+ and **3** (see Figure S21).



Scheme 4. Reaction used for organocatalysis.

To understand the ongoing process, mechanistic studies were performed with zinc porphyrin **6** and piperidine (**7**). Notably, the catalytic reaction **9** + **10**→**11** did not occur with **7** when zinc porphyrin **6** was present. In the ^{1}H NMR analysis of a mixture of **6** and **7**, the piperidine protons are diagnostically shifted upfield, thereby suggesting coordination of the piperidine nitrogen atom to the zinc porphyrin. Hence in this complex, **7** is no more available for catalysis. In $[Cu(\mathbf{1})(\mathbf{3})]^+$, that is, the unlocked state, the zinc porphyrin site is equally available for coordination to **7** ($\log K = 5.15 \pm 0.04$). From a look at the ^{1}H NMR data (see Figure S14 in the Supporting Information) it becomes evident that in **7**···$[Cu(\mathbf{1})(\mathbf{3})]^+$ the piperidine nitrogen atom is coordinated

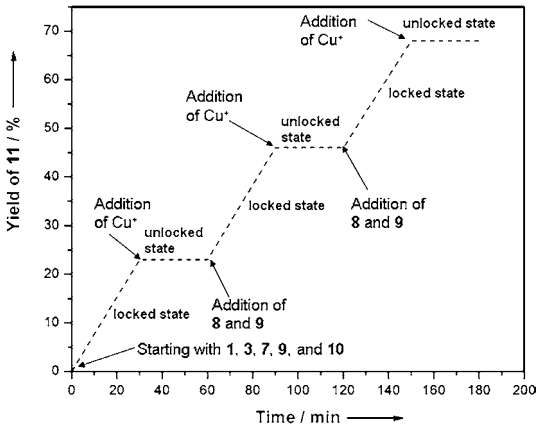
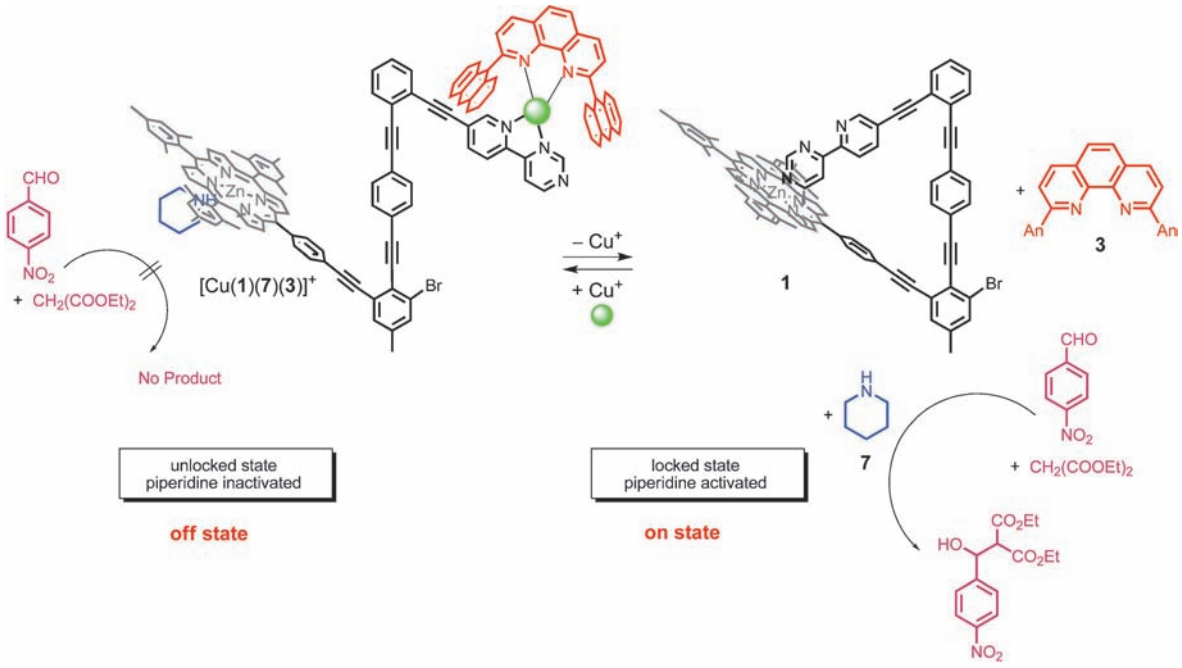


Figure 4. Reversible switching between the ON (locked) and OFF (unlocked) state of **1** (3.2 mM) in $CDCl_3$ and its effect on the catalytic formation of **11**.[13]



Scheme 5. Representation of the ON/OFF triggering of the catalytic cycle.

to the zinc porphyrin, thus explaining nicely why the organocatalytic process stops. In contrast, **7** binds only weakly to **1** that represents the locked state ($\log K = 2.39 \pm 0.14$) and thus is liberated into the solution giving rise to catalysis.

After establishing that the locked state leads to catalysis (ON) and the unlocked state is catalytically inactive (OFF; see Figure S21 in the Supporting Information), the reversible switching of the catalytic process between ON and OFF was tested (Figure 4). Reacting the locked system **1** (3.2 mM) with **3** + **7** + **9** + **10** (at 1:1:1:10:1000 to set up a pseudo-first-order reaction with respect to **9**) at 55 °C for 30 minutes generates **11** in 23 % yield.[11] Addition of Cu^+ terminated catalysis by generating the unlocked system $[Cu(\mathbf{1})(\mathbf{3})]^+$, which proves to be catalytically inactive at 55 °C (30 min). To regenerate the locked state, phenanthroline **8**[12] is added to trap the Cu^+ ions by forming the highly stable homoleptic complex $[Cu(\mathbf{8})_2]^+$ (see Figure S13), which restarts the catalytic reaction (Scheme 5) without loss of activity (measured over three subsequent cycles; each cycle yields **11** in $[23 \pm 1]$ % yield[13]).

In conclusion, we report on the synthesis of the self-locking system **1** and its reversible quantitative switching between locked and unlocked states using copper(I) ions, phenanthroline **3**, and cyclam. As such, the switching process is reminescent of that in kinase II activation and deactivation. In addition, we investigated the utility of **1** with respect to reversibly triggering catalysis in an ON/OFF manner. In the locked state, **7** is not coordinatively trapped at the porphyrin docking station of **1**. As a consequence, **7** is catalytically active in a Knoevenagel reaction (ON). In the presence of Cu^+/**3** as external stimuli, **1** is unlocked, thus allowing for strong coordination of **7** to the zinc porphyrin docking station. In this state, catalysis stops (OFF). Upon addition of **8** to **7**···$[Cu(\mathbf{1})(\mathbf{3})]^+$ the complex breaks down to release the catalytically active **7**. Thus, through repeatedly adding first Cu^+ and then ligand **8**, the catalytic Knoevenagel reaction **9** + **10**→**11** was turned OFF and ON in a highly reproducible manner with no observable loss of activity over three cycles.

Received: November 17, 2011
Revised: January 13, 2012
Published online: March 8, 2012

Keywords: copper · heteroleptic complexes · nanoswitch · organocatalysis · porphyrinoids

[1] For some recent reviews, see: a) B. Champin, P. Mobian, J.-P. Sauvage, *Chem. Soc. Rev.* **2007**, *36*, 358; b) S. Saha, J. F. Stoddart, *Chem. Soc. Rev.* **2007**, *36*, 77; c) K. Kinbara, T. Muraoka, T. Aida, *Org. Biomol. Chem.* **2008**, *6*, 1871; d) V. Balzani, A. Credi, M. Venturi, *Chem. Soc. Rev.* **2009**, *38*, 1542; e) S. Silvi, M. Venturi, A. Credi, *Chem. Commun.* **2011**, *47*, 2483; f) J. E. Beves, B. A. Blight, C. J. Campbell, D. A. Leigh, R. T. McBurney, *Angew. Chem.* **2011**, *123*, 9428; *Angew. Chem. Int. Ed.* **2011**, *50*, 9260.

[2] For some recent papers, see: a) T. Kudernac, N. Ruangsupapichat, M. Parschau, B. Maciá, N. Katsonis, S. R. Harutyunyan, K.-H. Ernst, B. L. Feringa, *Nature* **2011**, *479*, 208; b) M. J. Barrell, A. G. Campaña, M. von Delius, E. M. Geertsema, D. A. Leigh, *Angew. Chem.* **2011**, *123*, 299; *Angew. Chem. Int. Ed.* **2011**, *50*, 285; c) G. T. Carroll, G. London, T. F. Landaluce, P. Rudolf, B. L. Feringa, *ACS Nano* **2011**, *5*, 622; d) G. Haberhauer, *Angew. Chem.* **2011**, *123*, 6539; *Angew. Chem. Int. Ed.* **2011**, *50*, 6415; e) H. Li, A. C. Fahrenbach, A. Coskun, Z. Zhu, G. Barin, Y.-L. Zhao, Y. Y. Botros, J.-P. Sauvage, J. F. Stoddart, *Angew. Chem.* **2011**, *123*, 6914; *Angew. Chem. Int. Ed.* **2011**, *50*, 6782.

[3] a) S. Shinkai, M. Ishihara, K. Ueda, O. Manabe, *J. Chem. Soc. Perkin Trans. 2* **1985**, 511; b) A. Ueno, I. Suzuki, T. Osa, *J. Am. Chem. Soc.* **1989**, *111*, 6391; c) R. Corradini, A. Dossena, R. Marchelli, A. Panagia, G. Sartor, M. Saviano, A. Lombardi, V. Pavone, *Chem. Eur. J.* **1996**, *2*, 373; d) P. R. Ashton, R. Ballardini, V. Balzani, S. E. Boyd, A. Credi, M. T. Gandolfi, M.

Gómez-López, S. Iqbal, D. Philp, J. A. Preece, L. Prodi, H. G. Ricketts, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 152; e) P. R. Ashton, M. Gómez-López, S. Iqbal, J. A. Preece, J. F. Stoddart, *Tetrahedron Lett.* **1997**, *38*, 3635; f) M. B. Nielsen, J. G. Hansen, J. Becher, *Eur. J. Org. Chem.* **1999**, 2807; g) V. Balzani, P. Ceroni, A. Credi, M. Gómez-López, C. Hamers, J. F. Stoddart, R. Wolf, *New J. Chem.* **2001**, *25*, 25; h) Y. Liu, A. H. Flood, J. F. Stoddart, *J. Am. Chem. Soc.* **2004**, *126*, 9150; i) G. Cooke, P. Woisel, M. Bria, F. Delattre, J. F. Garety, S. G. Hewage, G. Rabani, G. M. Rosair, *Org. Lett.* **2006**, *8*, 1423; j) T. Muraoka, K. Kinbara, T. Aida, *J. Am. Chem. Soc.* **2006**, *128*, 11600; k) D.-H. Qu, B. L. Feringa, *Angew. Chem.* **2010**, *122*, 1125; *Angew. Chem. Int. Ed.* **2010**, *49*, 1107; l) F. Durola, J. Rebek, Jr., *Angew. Chem.* **2010**, *122*, 3257; *Angew. Chem. Int. Ed.* **2010**, *49*, 3189; m) O. B. Berryman, A. C. Sather, A. Lledó, J. Rebek, Jr., *Angew. Chem.* **2011**, *123*, 9572; *Angew. Chem. Int. Ed.* **2011**, *50*, 9400.

[4] a) H. Schulman, *Curr. Opin. Cell Biol.* **1993**, *5*, 247; b) M. Lammers, R. Rose, A. Scrima, A. Wittinghofer, *EMBO J.* **2005**, *24*, 4176; c) K. Khafizov, G. Lattanzi, P. Carloni, *Proteins Struct. Funct. Genet.* **2009**, *75*, 919.

[5] a) F. Würthner, J. Rebek, Jr., *Angew. Chem.* **1995**, *107*, 503; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 446; b) H. Sugimoto, T. Kimura, S. Inoue, *J. Am. Chem. Soc.* **1999**, *121*, 2325; c) R. Cacciapaglia, S. Di Stefano, L. Mandolini, *J. Am. Chem. Soc.* **2003**, *125*, 2224; d) R. S. Stoll, S. Hecht, *Angew. Chem.* **2010**, *122*, 5176; *Angew. Chem. Int. Ed.* **2010**, *49*, 5054; e) J. Wang, B. L. Feringa, *Science* **2011**, *331*, 1429.

[6] Clearly, the size of phenanthroline **3** in $[Cu(\mathbf{3})]^+$ is important in the unlocking of **1**, as smaller sized ligands, for example, 2,9-dimesitylphenanthroline, do not work. As such, indeed the chemical input needs to wrap about the bipyridine binding site.

[7] M. Schmittel, A. Ganz, *Chem. Commun.* **1997**, 999.

[8] a) M. Schmittel, A. Ganz, D. Fenske, *Org. Lett.* **2002**, *4*, 2289; b) M. Schmittel, V. Kalsani, J. W. Bats, *Inorg. Chem.* **2005**, *44*, 4115; c) S. De, K. Mahata, M. Schmittel, *Chem. Soc. Rev.* **2010**, *39*, 1555.

[9] K. Mahata, M. L. Saha, M. Schmittel, *J. Am. Chem. Soc.* **2010**, *132*, 15933.

[10] Compare to literature values for **2** + **6** ($\log K = 3.78$) and for **7** + **6** ($\log K = 5.05$): C. H. Kirksey, P. Hambright, C. B. Storm, *Inorg. Chem.* **1969**, *8*, 2141.

[11] The catalytic reaction under identical reaction conditions, but in absence of the locked system **1**, furnishes **11** in 31% yield, as compared to 23% in the nanoswitch-activated catalysis. This finding is in full agreement with the binding constant of piperidine (**7**) to **1** at 55°C ($\log K = 1.85 \pm 0.15$), which suggests that in the ON state the nanoswitch releases 84% of piperidine (**7**) into solution (at 55°C, $c = 3.2$ mM for both **1** and **7**).

[12] Cyclam was not used to trap the Cu^+ as cyclam itself proved to catalyze the Knoevenagel reaction.

[13] To keep the kinetic situation comparable, the amount of **9** used up in the preceding cycle was replaced in each following cycle, that is, the second and third catalytic cycle.

