Molecular Machines

DOI: 10.1002/anie.201004460

A Metal-Ion-Driven Supramolecular Chirality Pendulum**

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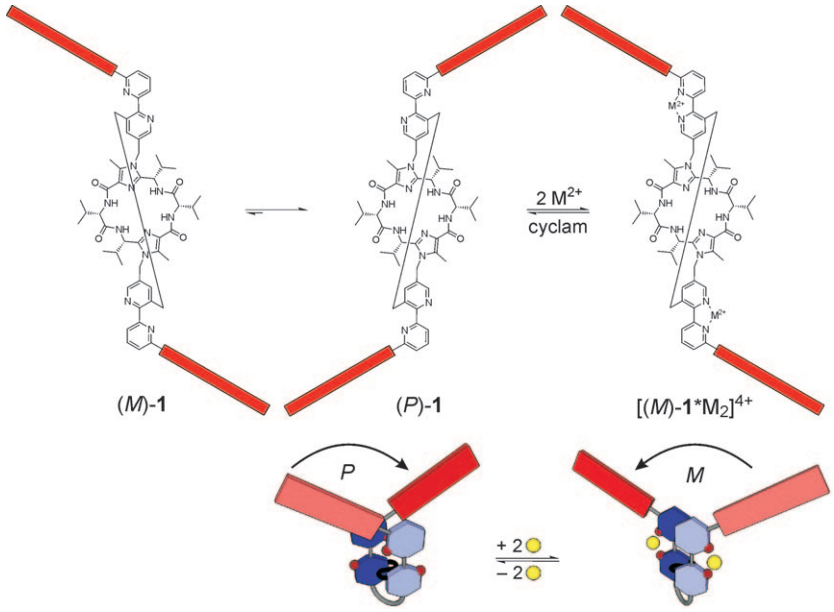
Dedicated to Professor Günter Helmchen on the occasion of his 70th birthday

The control of molecular states and the mechanical motion of single molecules by external stimuli is a rapidly expanding field that is the subject of extensive research.[1,2] A central aspect of this topic is the control of chirality in order to result in, for example, unidirectionally controllable rotary motions. Unidirectionality is one of the most important basic requirements for the construction of synthetic molecular machines whose functionality is based on the synchronized directed rotary motion of the machine parts, in analogy to their macroscopic models.[3–6]

A particular challenge is the construction of a chirality pendulum that, like a mechanically driven pendulum, can be completely and reversibly transferred from one configuration to the other with high-amplitude motion. The problem of constructing such a chirality pendulum lies in the nature of chirality, as enantiomers are energetically equal in an achiral environment. Thus it is not possible to shift the equilibrium toward one state by using achiral reagents. Therefore the creation of diastereomers is often applied as a trick for controlling a chiral state, as one or more additionally inserted chirality elements lead to the stabilization of the configuration of the desired chirality element. A higher stabilization results in a larger proportion of the system present in the desired configuration. However, the crux of the problem is that if a certain configuration is highly stabilized, it is difficult to find a condition that allows a reversible change of configuration, which requires the opposite configuration to also be stabilized. An inversion of configuration for the systems described to date, for example, biphenyls,[7] foldamers,[8] and atranes,[9] could therefore only be obtained by a nontrivial change, for example, solvent exchange. A complete and reversible inversion with high-amplitude motion has not been reported to date.[10]

We aimed to construct a supramolecular chirality pendulum that can be switched completely and reversibly with high-amplitude motion between two configurations. Such a system is presented in Scheme 1. The chiral peptidic clamp[11] in **1** results in the clamp-bound pyridine rings being fixed in a cycle, and thus these units adopt an unambiguous orientation with respect to each other. As 2,2′-biypridine units show an N-C-C-N dihedral angle of 180° in the noncomplexed state, in order to avoid the repulsion between the lone pairs of electrons on the nitrogen atoms and to allow a maximum conjugation over both heteroaromatic rings, the two arms (red rectangles) on the flexible pyridine rings of the bipyridine ligands have a definite relative spatial configuration (here the *P* configuration). A stronger discrimination by the chiral clamp results in a larger proportion of the *P* configuration in **1**. We did not wish to stabilize the *M* configuration of **1** during switching because this stabilization would lead to the above-mentioned difficulties; instead a rotation of the flexible pyridine rings of the bipyridine ligands should lead to the change of configuration. This design means that there should be no change of the overall orientation of the



Scheme 1. Principle of a metal-ion-driven supramolecular chirality pendulum: The diastereomer (*P*)-**1** is energetically stabilized with respect to (*M*)-**1** and can be reversibly converted into the pseudoenantiomer $[(M)\text{-}\mathbf{1}{*}M_2]^{4+}$ by addition of metal ions (M^{2+}).

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[**] This work was generously supported by the Deutsche Forschungsgemeinschaft (DFG). The author thanks Dr. Andreea Schuster and Dipl.-Chem. Silvia Ernst for helpful support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004460.

bipyridine ligands, as during the transition from (*P*)-**1** to (*M*)-**1**; only the distal parts of the bipyridine ligands should be rotated by complexation of the 2,2′-bipyridine ligands with M^{2+} ions (e.g., Zn^{2+} or Cu^{2+}), such as during the transition from (*P*)-**1** to $[(M)\text{-}\mathbf{1}{*}M_2]^{4+}$.[12] Nevertheless, the result is the same: in both cases, the arms on the bipyridine ligands are *M*-configured. As the complexation of 2,2′-bipyridine ligands by M^{2+} ions is a process that goes to completion very rapidly,[13] a complete chirality inversion with high-amplitude motion can occur. Removal of the M^{2+} ions by addition of a very strong complexing agent, such as 1,4,8,11-tetraazacyclotetradecane (cyclam) makes the system reversible.[13]

The synthesis of the chirality pendulums **1** is shown in Scheme 2. The tetrabromide **5**, which contains two ethano-bridged pyridine units, can be obtained in a few steps from the commercially available pyridine **2**. The secondary nitrogen atoms of the imidazole units in the chiral clamp **6**[11] can be alkylated with the tetrabromide **5** by using Cs_2CO_3 as a base. A double Stille coupling with the tin compound **8** leads to the chirality pendulum **1a**, which has two bromine atoms as arms. These arms can be elongated by the substitution of the bromine atoms by methoxyphenylacetylene in a Sonogashira reaction (**1b**) or by a zinc tetraarylporphyrin in a Suzuki reaction (**1c**).

The first essential requirement for a chirality pendulum is a distinct energetic discrimination of the *P* isomer with respect to the *M* isomer, so that only the former exists in solution. To verify whether the effect of the peptidic clamp indeed provides the required discrimination, the energies of the *M* and *P* configurations of **7**, which is the basic scaffold of all chirality pendulums, and the energies of **1a**,**b** were calculated.[15,16] The H–H distances in **7** and **1a** were determined by 2D NOESY experiments, and CD measurements of **1a–c** were carried out and compared with the calculated spectra of **1a**,**b**.

The structures of (*M*)-**7**, (*P*)-**7**, (*M*)-**1a**,**b**, and (*P*)-**1a**,**b** were determined by geometry optimization using B3LYP and the 6-31G* basis set (Figure 1). The obtained energy difference between the *P* and *M* isomers amounts to 21.7 kJ mol^{-1} for **7**, 32.6 kJ mol^{-1} for **1a**, and 28.3 kJ mol^{-1} for **1b**. Thus, in all cases, there is an unambiguous preference of the *P* configuration. On the basis of the Boltzmann distribution, the chirality pendulums **1** should almost completely (> 99.99 %) adopt the *P* configuration.

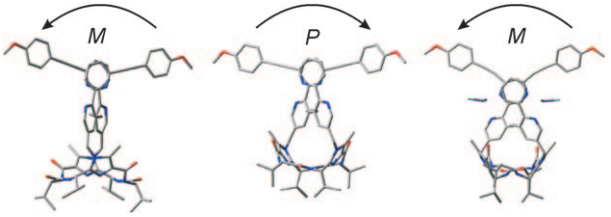
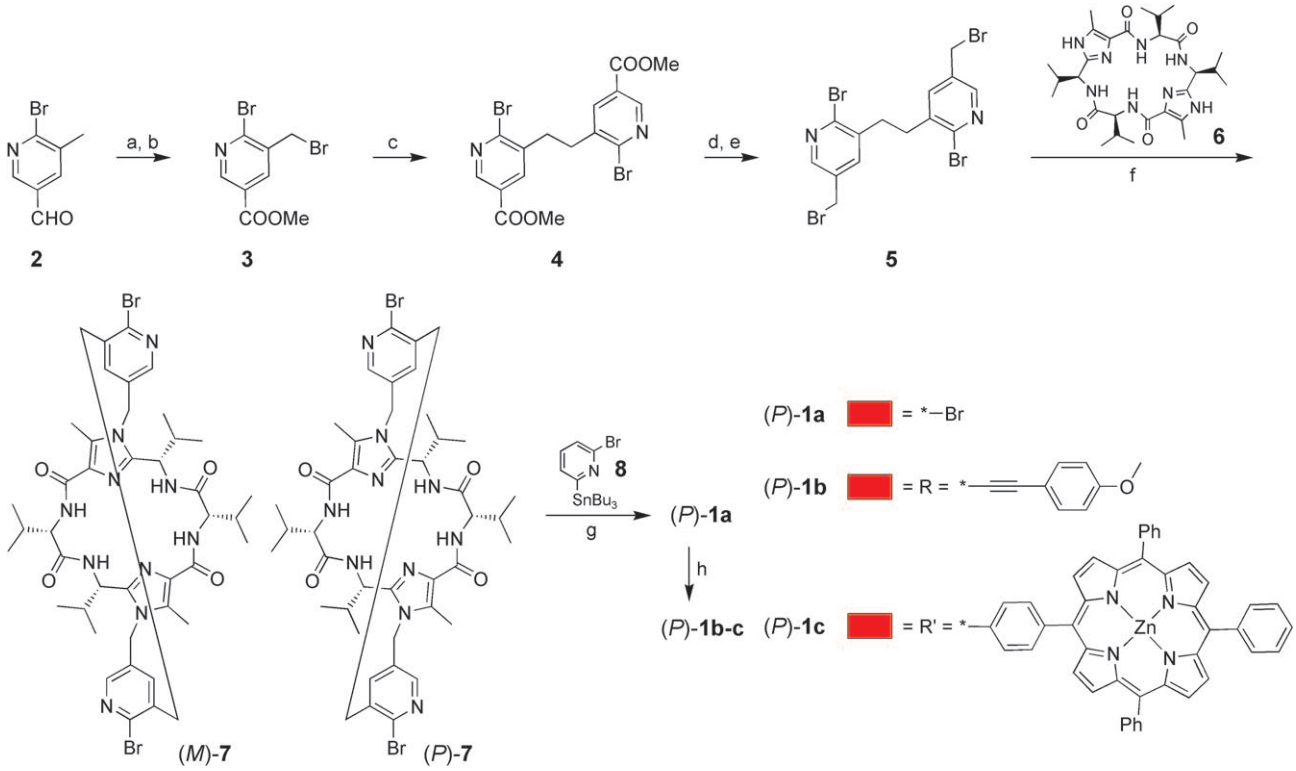


Figure 1. Molecular structures of (*M*)-**1b**, (*P*)-**1b**, and $[(M)\text{-}\mathbf{1b}{*}(ZnF_2)_2]$ calculated by B3LYP/6-31G*. All hydrogen atoms were omitted for clarity.



Scheme 2. Synthesis of the chirality pendulums (*P*)-**1**. Reaction conditions: a) *N*-iodosuccinimide, MeOH; b) *N*-bromosuccinimide, CCl_4, 56 % (2 steps); c) $[CoCl(PPh_3)_3]$, toluene, 56 %; d) $LiAlH_4$, CH_2Cl_2; e) HBr/AcOH 90 % (2 steps); f) Cs_2CO_3, CH_3CN, reflux, 40 %; g) $[Pd(PPh_3)_4]$, toluene, 35 %, h) RH, $[PdCl_2(PPh_3)_2]$, CuI, Et_3N, DMF, 55 % (for (*P*)-**1b**); $[Pd(PPh_3)_4]$, $R'B(C_6H_{12}O_2)$,[14] K_2CO_3, H_2O, toluene, 45 % (for (*P*)-**1c**).

A further proof for the exclusive existence of **7** and **1** in the *P* configuration can be found in the ^{1}H NMR spectra, which contain only one single set of signals and the protons of the ethano bridge between the bipyridine ligands show a typical AA′BB′ set of signals, which indicates a fixed conformation of this bridge. Moreover, from the H–H distances in **7** and **1a** (determined by 2D NOESY experiments) the three-dimensional structure of **7** and **1** can be concluded. The spatial structure, which was obtained on the basis of the distances between the hydrogen atoms, contains spatially fixed pyridine units that are unambiguously *P*-configured.

An unambiguous assignment of the preferred configuration of the arms on the bipyridine ligands should also be possible on the basis of the CD spectra of **1**. The CD spectra of **1a–c** were measured in highly dilute CH_2Cl_2 solution (Figures 2 and 3). For a better assignment and interpretation,

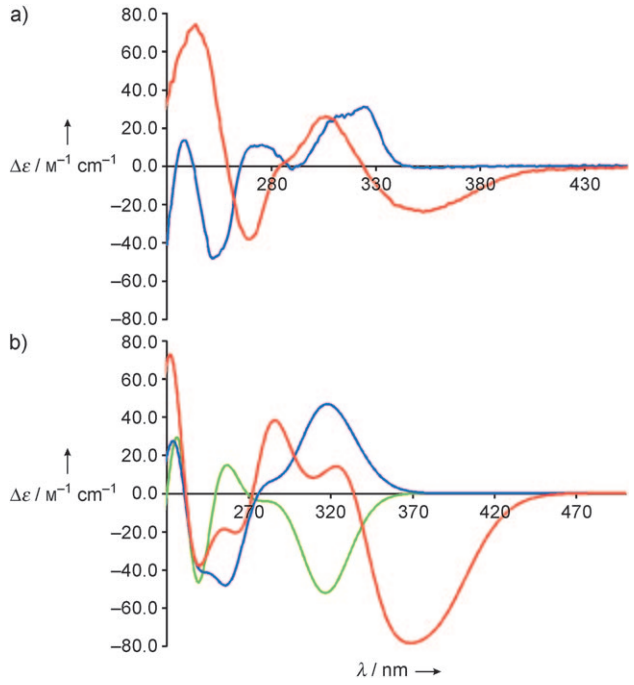


Figure 2. a) CD spectra of (*P*)-**1b** (blue) and with 6.0 equiv $Zn(OTf)_2$ (→[(*M*)-**1b***Zn_2]$^{4+}$, red; $c = 1.0\times10^{-5}$ M in CH_2Cl_2). b) CD spectra of (*P*)-**1b** (blue), (*M*)-**1b** (green), and [(*M*)-**1b***$(ZnF_2)_2$] (red) calculated using TD-DFT-PBE1PBE/6-31G* in CH_2Cl_2.

the CD spectra of (*M*)-**1a**,**b** and (*P*)-**1a**,**b** in CH_2Cl_2 were simulated with time-dependent density functional theory (TD-DFT) with the PBE1PBE functional, and by employing the 6-31G* basis set.[15] As the intensities of the calculated curves are always higher, they were normalized to the experimentally determined intensities.

Comparison of the measured with the calculated CD spectra shows that both **1a** and **1b** adopt the *P* configuration in solution, as can be most clearly observed in the absorption band of the bipyridine ligands. In the case of **1a**, this band occurs at 297 nm with a positive Cotton effect (+42). Calculations show that this band only exhibits a positive

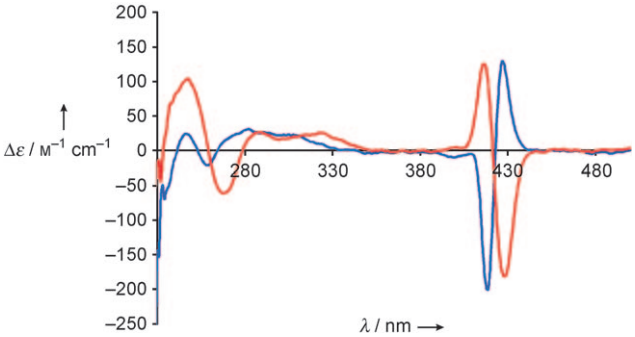


Figure 3. CD spectra of (*P*)-**1c** (blue) and with 6.0 equiv $Zn(OTf)_2$ (→ [(*M*)-**1c***Zn_2]$^{4+}$, red; $c = 1.0\times10^{-6}$ M in CH_2Cl_2).

Cotton effect for (*P*)-**1a**; for (*M*)-**1a** the Cotton effect is negative. The calculated spectra of **1a** show negative Cotton effects at approximately 240 nm for (*P*)-**1a** as well as for (*M*)-**1a**. These different effects are caused by the peptidic clamp, which has the same absolute configuration in both systems. The chirality pendulum **1b** also shows similar behavior (Figure 2). In this case, the absorption band of the bipyridine ligands is bathochromically shifted to 324 nm because of the conjugation with the methoxyphenyl moieties across the triple bond, and shows a positive Cotton effect (+31). This result is consistent with a *P* configuration of the phenylacetylene units, as, according to the calculations, the spectrum of the *P* isomer exhibits a positive Cotton effect, whereas the spectrum of the *M* isomer shows a negative band.

The interpretation of the CD spectrum of **1c** is even easier than the interpretation of the CD spectra of **1a**,**b**, for which calculations were needed to assign the CD bands. In this case, the arms on the bipyridine ligands are zinc porphyrin systems, which exhibit an intense absorption at approximately 420 nm (the Soret band), for which the rules of exciton chirality can be applied:[17] strongly absorbing chromophores result in a very intensive CD pair, and the relative orientation of the chromophores can be determined by the algebraic sign of the pair (defined as the algebraic sign of the component with the higher wavelength). A positive band at a higher wavelength corresponds to a *P* configuration. This feature is exactly what can be observed in the CD spectrum of **1c**. Accordingly, we could show that all chirality pendulums exist exclusively in the *P* configuration.

The second essential requirement for use as a chirality pendulum is the complexation of the bipyridine ligands with M^{2+} ions, which should lead to a 180° rotation of the flexible pyridine units (high-amplitude motion) and thus to an inversion of the configuration of their arms. Zn^{2+} and Cu^{2+} ions, both of which bind strongly to bipyridine ligands, were used in the complexation experiments. In order to prevent the formation of metal complexes with more than one bipyridine ligand per metal, the complexation experiments were carried out at high dilutions and with an excess of metal ions. The complexation was studied by analyzing the changes in the UV and CD spectra, which showed similar behavior for both metal salts. Additionally, the structure of the complex formed by coordination of (*P*)-**1b** with two fragments of ZnF_2 was determined by using B3LYP/6-31G*, and the CD spectrum of

this complex in CH_2Cl_2 was calculated with TD-DFT-PBE1PBE/6-31G*.

As expected, the calculation shows that the complexation of the bipyridine ligands of (*P*)-**1b** by the ZnF_2 fragments leads to an inversion of the configuration of the arms on the bipyridine ligands and that the complex [(*M*)-**1b***$(ZnF_2)_2$] adopts the *M* configuration (Figure 1). The complexation and the concomitant inversion of configuration can also be observed by comparing the CD spectra of **1b** before and after complexation, as the band for the absorption of the bipyridine ligands is bathochromically shifted to 353 nm upon complexation (Figure 2). There is also a simultaneous transition from a positive Cotton effect (+31 at 324 nm) to a negative Cotton effect (−24 at 353 nm), which is caused by the change of the configuration of the bipyridine arms. Both effects, that is, the bathochromic shift and the sign change of the Cotton effect, are also found in the DFT-calculated spectrum of [(*M*)-**1b***$(ZnF_2)_2$] (Figure 2). The inversion of chirality in the pendulum **1c**, which can be observed by monitoring the porphyrin Soret band, is particularly impressive; the inversion of configuration leads to a algebraic sign change of both bands, as predicted by the rules of exciton chirality.

Swinging of the pendulum in one direction (*P*→*M*) can thus be unambiguously proved. Swinging of the pendulum in the other direction (*M*→*P*), that is, the backward motion, occurs chemically by addition of cyclam, which forms stronger complexes with the Zn^{2+} and Cu^{2+} ions than the bipyridine ligands of **1**. After the addition of cyclam, the CD spectra of **1** again show the original curve shape. This forward and backward motion can be repeated several times.

In conclusion, we have shown that it is possible to construct a supramolecular chirality pendulum. Like the pendulum of a clock, the arms of the chirality pendulum are able to swing from one configuration to the other. This process is reversible, can be repeated several times, is complete compared to other reported chirality pendulums, and proceeds with a high change of amplitude. The two concomitant 180° rotary motions are therefore suitable for the construction of more complex molecular machines.

Received: July 21, 2010
Revised: August 16, 2010
Published online: October 21, 2010

Keywords: chirality · circular dichroism · molecular machines · molecular switches · stereocontrol

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