Molecular Machines

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Control of Planar Chirality: The Construction of a Copper-Ion-Controlled Chiral Molecular Hinge**

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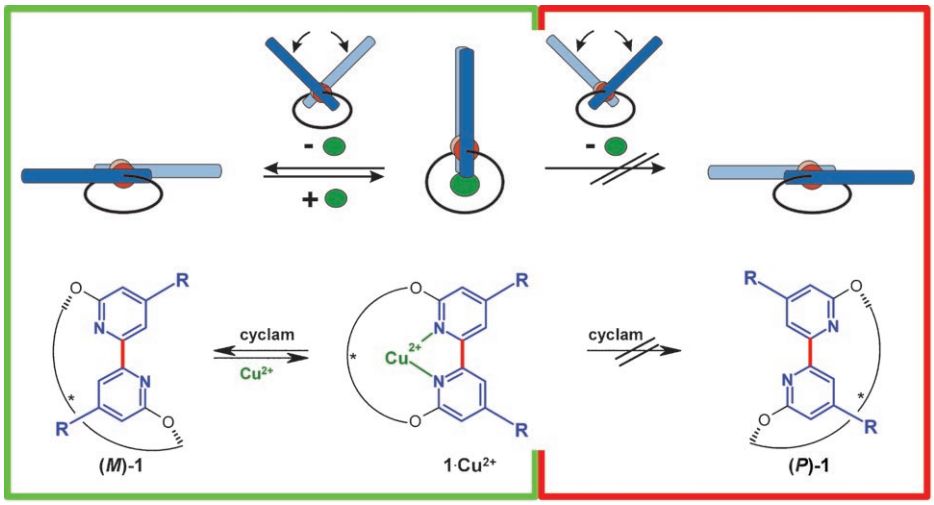
The control of the mechanical motion of single molecules by external stimuli is a rapidly growing scientific area of great contemporary interest.[1] Until now, a variety of molecular devices, such as motors, rotors, shuttles, ratchets, and tweezers, have been developed.[1,2] A crucial point is the construction of synthetic molecular machines that utilize—in analogy to their macroscopic pendants—the directional and synchronized movements of smaller parts. In these systems an external stimulus triggers the controlled, large-amplitude or directional mechanical motion of one component relative to another which results in a task being performed.[2a] Especially useful for this purpose are molecular devices in which unidirectional rotations are controlled by changes of configuration or conformation. Examples of such systems are unidirectional rotors rotating around single or double bonds,[3] catenanes showing unidirectional rotary motion,[4] and molecular scissors.[5] In the latter, irradiation triggers the opening and closing of the blades with an alteration of the angle between the blades from approximately 9° to 58°.

A unidirectional open–close mechanism with even higher relative amplitudes (around 180°) is possible with a hinge. The two flexible wings of the hinge (blue elements in Scheme 1) can be opened and closed by motion about the rotation axis (red element) in only one direction (area framed in green in Scheme 1); opening in the opposite direction is not possible (area framed in red). Closing at the hinge also occurs only in one direction; a flipping "inside out" (overrotation), a closing motion extending from a dihedral angle of 180° to an angle of 360°, is prevented by a fixing bracket (black element).

As a basis for the design of a molecular hinge with a unidirectional open–close motion we chose the 2,2′-biypridine unit (Scheme 1). Here the pivot is the C–C bond between the two pyridine units. In the uncomplexed state, 2,2′-bipyridine exhibits an N-C-C-N dihedral angle of 180°. This value changes to 0° when the bipyridine unit forms a complex with, for example, a copper(II) ion. The substituents *para* to the nitrogen atoms undergo a relative amplitude motion of 180°. The driving force for the closing process is the formation of the copper(II) bipyridine complex, whereas the driving force for the opening is the repulsive interaction between the hydrogens in positions 3 and 3′ of the bipyridine in the absence of copper(II) ions. The removal of the copper(II) ions can be achieved chemically by the addition of an even stronger Cu^{II}-complexing agent such as cyclam. To prevent an overrotation of the flexible pyridine unit, a medium-sized bridge is introduced, thus making the entire molecule planar chiral when it is not complexed. Consequently, the differentiation between the desired and the undesired open–close motion can be reduced to the selective formation of only one of two enantiomers ((*M*)-**1** and (*P*)-**1** in Scheme 1), in other words, the control of the planar chirality. The conformers (*M*)-**1** and (*P*)-**1** are diasteromers when a bridge with additional chiral units is used. Accordingly, the control of the direction of the open–close motion is essentially based on the choice of suitable diastereomers of type **1** in which the conformers (*M*)-**1** and (*P*)-**1** are so different in energy that only one of the two conformations is adopted.



Scheme 1. Schematic representation of the chiral molecular hinge **1** and its unidirectional open–close motion.

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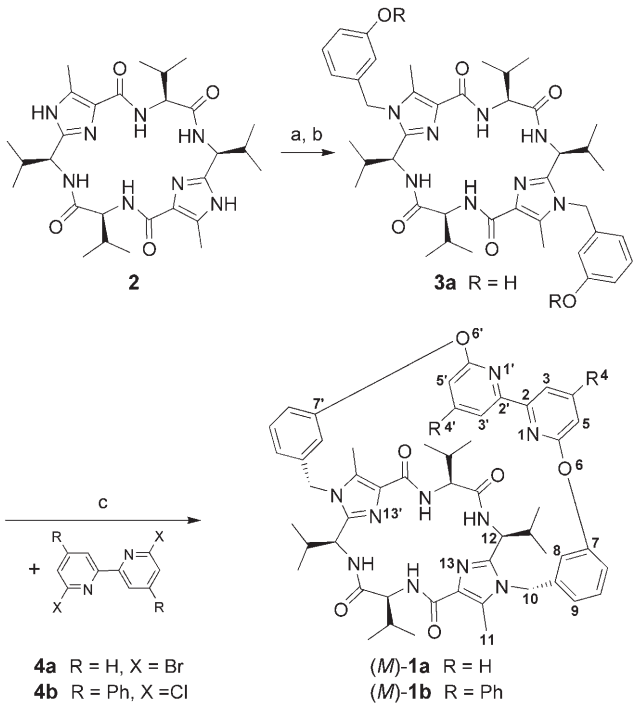
As we had already used cyclic peptides having imidazole and oxazole units in the backbone for the control of axial chirality[6] and for chirality transfer in C_3-symmetric compounds,[7] we decided to use this type of chiral clamp also for the design of a molecular hinge with unidirectional open–close motion. The synthesis of **1** is shown in Scheme 2. The chiral clamp **2**[6] can be alkylated with 3-methoxybenzyl bromide using Cs_2CO_3 as base. Removal of the methoxy groups with BBr_3 and subsequent nucleophilic aromatic substitution with the corresponding dihalogenobipyridines **4** led to the desired hinges (*M*)-**1**.



Scheme 2. Preparation of the chiral molecular hinges (*M*)-**1**. Reaction conditions: a) 3-methoxybenzyl bromide, Cs_2CO_3, CH_3CN, Δ, 66%; b) BBr_3, CH_2Cl_2, −78°C→RT, 95%; c) Cs_2CO_3, DMF, 110°C, 20% for (*M*)-**1a** and 25% for (*M*)-**1b**.

The essential feature of the hinge is the significant energetic discrimination of the *M* and *P* isomers so that the opening occurs selectively in only one direction. To determine the energy value by which the *M* isomer is stabilized relative to the *P* isomer as a result of the chiral clamp, DFT calculations were carried out.[8] The structures of (*M*)-**1** and (*P*)-**1** were determined by geometry optimizations using B3LYP and the 6-31G* basis set (see Figure 1). The calculated energy difference between the *M* and *P* isomers amounts to 42.2 kJ mol^{-1} for **1a** and 33.4 kJ mol^{-1} for **1b**. The calculated dihedral angle N1-C2-C2′-N1′ is 178° in (*M*)-**1a**, whereas in (*M*)-**1b** it is 163° and thus somewhat lower (for the numbering of the atoms in **1** see Scheme 2). The reason for the large energy gap between the isomers becomes clear when one looks at the position of the bipyridine units relative to the chiral peptidic scaffold: In the *P* isomers the axes C2–C2′ and N13–N13′ are almost parallel, whereas in the *M* isomers they

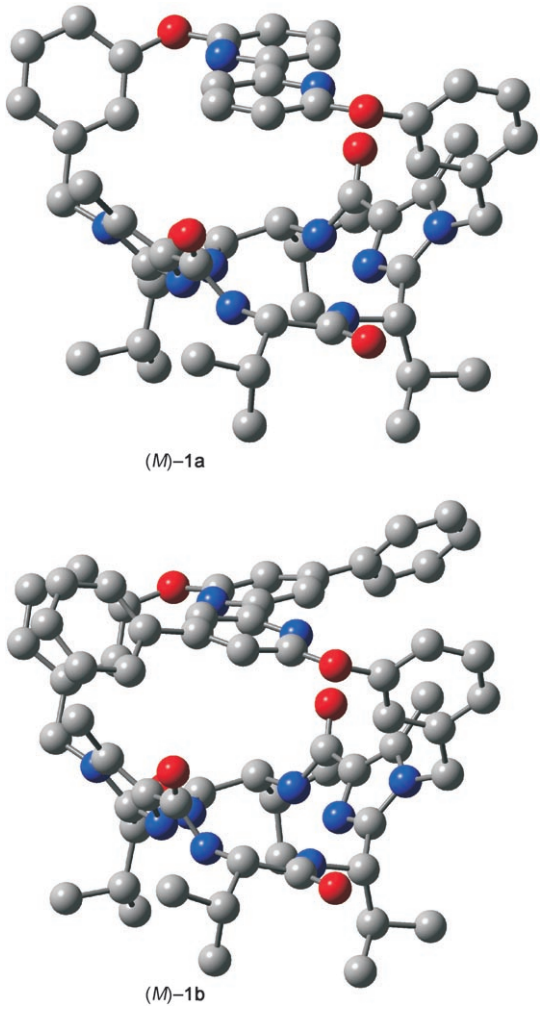


Figure 1. Molecular structures of (*M*)-**1a** and (*M*)-**1b** calculated using B3LYP/6-31G*. All hydrogen atoms have been omitted for clarity.

are virtually perpendicular to each other. As a result the C7–C7′ distance in the *P* isomers is greater than that in the *M* isomers: For (*P*)-**1a** the distance was calculated to be 9.80 Å, whereas in (*M*)-**1a** it amounts to only 8.98 Å (see Table 1). The greater C7–C7′ distance causes tension in the rigid peptidic scaffold, thus explaining the high energetic discrimination between the conformers.

The large energy difference between the isomers leads to the conclusion that in solution bipyridines **1** also adopt exclusively the *M* conformation at room temperature. To confirm this assumption we performed NMR experiments in $CDCl_3/CD_3OD$ as solvent. Since for **1a** all peaks in the aromatic area are separated, we were able to determine H–H distances from 2D NOESY experiments allowing conclusions about the three-dimensional structure. The most important values are compiled in Table 1. The deduced spatial structure corresponds unambiguously to the *M* conformation. The most important difference between the conformers is the distance between the protons H11 and H5 and the distance between the protons H11 and H3. For (*M*)-**1a** a very large H11–H5 distance is calculated (5.02 Å), whereas for (*P*)-**1a** it is distinctly smaller (2.97 Å). In the NMR experiment the H11–

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Table 1: Distances [Å] for **1a** obtained from NMR experiments and calculated distances [Å] for the conformers (*M*)-**1a** and (*P*)-**1a** using B3LYP/6-31G*.

	(*M*)-**1a** (calcd)	**1a** (NMR)	(*P*)-**1a** (calcd)
O6–O6′	8.24		8.12
C7–C7′	8.98		9.80
H10a–H10b	1.75	1.75[a]	1.74
H10a–H9	2.35	2.18	2.98
H11–H10a	2.49	2.41	2.45
H11–H9	3.52	3.02	4.98
H11–H8	3.72	3.00	2.47
H11–H5	5.02	–[b]	2.97
H11–H4	2.96	2.49	3.57
H11–H3	2.72	2.36	4.93

[a] The distance between the diastereotopic protons H10a and H10b was used as a reference for calibration. [b] In the 2D NOESY spectrum no cross-peaks between H11 and H5 were observed.

H5 distance could not be determined because corresponding cross peaks are not observed in the 2D NOESY spectra. This indicates that this distance is greater than 4 Å. The situation is reversed for the H11–H3 distance: Here the B3LYP calculations attribute a value of 2.72 Å to (*M*)-**1a** and 4.93 Å to (*P*)-**1a**. The distance determined experimentally with the NOESY technique amounts to 2.36 Å; this is not a mean value for the two individual diastereomers. In solution, too, only the *M* conformer is present.

The closing at the hinge by complexation with Cu^{II} ions was examined by high-resolution mass spectrometry as well as by CD and UV spectroscopy. When $Cu(OTf)_2$ was added to a solution of **1a** (or **1b**) in dichloromethane, the formation of the corresponding Cu bipyridine complexes was observed. In the case of **1a** the newly formed copper–bipyridine band appears at 335 nm, whereas in **1b** owing to the two phenyl rings it shows a bathochromic shift to 340 nm. After addition of 2.5 equiv Cu^{II} ions bipyridines **1** were completely transformed into the corresponding **1**·Cu^{2+} complexes, and thus a further addition of Cu^{II} ions (for example, 3.0 equiv in total) led to no change in the spectra. High-resolution mass spectra of **1a** and **1b** show unambiguously that under these conditions, the mononuclear **1**·Cu compounds are formed. In contrast, with **3b** (R = Me), which is the chiral clamp without bipyridine units, no complexation of Cu^{II} ion was observed under equivalent conditions. This means that in **1** the complexation of copper(II) ions takes place at the bipyridine units.

The formation of the copper–bipyridine complex, which is complete after the addition of 2.5 equiv Cu^{II} ions, can also be observed in the CD spectra of **1a** and **1b** (Figure 2). Additionally, the CD spectra reveal the changes of conformation caused by the complexation with copper(II) ions. The CD spectrum of (*M*)-**1a** shows negative Cotton effects at 293 nm and 256 nm and positive Cotton effects at 272 nm and 242 nm (Figure 2a). The complex formation effected by the addition of Cu^{II} ions causes a drastic change in the CD spectrum. The broad negative band at 293 nm disappears completely and the spectrum shows even slightly positive values in this area. Furthermore, the positive band at 272 nm disappears and only two bands—the negative Cotton effect at 266 nm and the positive Cotton effect at 236 nm—remain. This result is consistent with the expected behavior of the hinge: In the open state **1a** exhibits planar chirality[9] and as a result of the chiral peptidic scaffold only the *M* conformation is adopted. The negative band at 293 nm and the positive band at 272 nm reflect the presence of planar chirality. Closing at the hinge leads to a loss of the planar-chiral elements and the **1a**·Cu^{2+} complex shows merely the chiral elements of the clamp. Indeed, the shape of the CD spectrum of the **1a**·Cu^{2+} complex strongly resembles the spectrum of **3b** (R = Me), which is the chiral clamp without bipyridine units, under analogues conditions (Figure 2c).

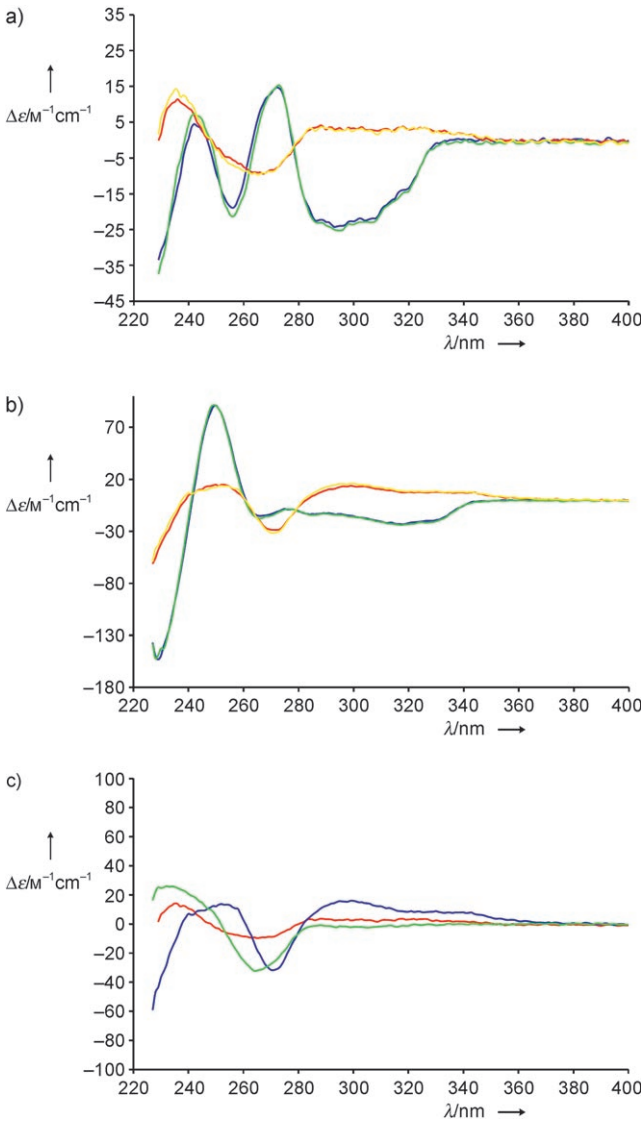

Figure 2. a) CD spectra of **1a** (blue) with 2.5 (red) and 3.0 (yellow) equiv $Cu(OTf)_2$ and with 3.0 equiv $Cu(OTf)_2$ plus 6.0 equiv cyclam (green) ([**1a**] = 1.0×10^{-5} M in dichloromethane). b) CD spectra of **1b** (blue) with 2.5 (red) and 3.0 (yellow) equiv $Cu(OTf)_2$ and with 3.0 equiv $Cu(OTf)_2$ plus 6.0 equiv cyclam (green) ([**1b**] = 1.0×10^{-5} M in dichloromethane). c) CD spectra of **1a** (red), **1b** (blue), and **3b** (R = Me; green) each with 3.0 equiv $Cu(OTf)_2$ ($c = 1.0\times10^{-5}$ M in dichloromethane).

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Also in case of (*M*)-**1b** closing at the molecular hinge by copper complexation can be observed as a drastic change in the CD spectrum. As a result of the better chromophore in (*M*)-**1a**, all CD bands effected by the planar-chiral element are more pronounced than in (*M*)-**1a** (Figure 2b). In this case, too, the closing motion at the molecular hinge **1b** by copper complexation leads to a spectrum resembling the spectrum of **3b** (R = Me) under analogues conditions (Figure 2c).

The opening at the hinge can be achieved chemically by addition of an excess of cyclam, which binds copper(II) ions much better than the bipyridine units of **1**. After addition of cyclam, the CD spectra of **1a** and **1b** return to their original shape (green curves in Figure 2a,b). Consequently, the molecular hinge can be opened and closed reversibly and unidirectionally. The stimulus for closing by copper(II) ions and subsequent opening can be repeated over a number of cycles.[10]

In conclusion, we have succeeded in the design of a molecular hinge showing a unidirectional open–close motion by using a chiral peptidic clamp. The high change of amplitude caused by the unidirectional rotation and the relatively simple preparation of the hinge open up the possibility for using this concept for even more-complex molecular machines.

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