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Reversible folding/unfolding of linear molecular strands into helical channel-like complexes upon proton-modulated binding and release of metal ions

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The binding of appropriate metal ions to linear ligand strands obtained by hydrazone polycondensations generates channel-like complexes by reversible coiling of the ligand, thus allowing the generation of ion-induced, acid–base neutralisation fuelled, molecular nanomechanical contraction/extension motions of large amplitude.

The control of the self-organization of molecular strands into well-defined shapes has been actively investigated in recent years both in view of its relation to the folding of biopolymers and of the goal to direct the formation of specific molecular (as well as supramolecular) architectures.[1] To this end, structure enforcing subunits may be devised that induce folding of synthetic molecular strands. In our laboratory, sequences of azaheterocyclic groups[2] and of pyridine-dicarboxamides[3] have been developed as helicity codons enforcing the helical wrapping of molecular chains.

On the other hand, chemical effectors may be put to use to interconvert molecular shapes as has been achieved in the realization of acid–base fuelled, large amplitude extension/contraction (folding/unfolding) molecular motions by interconversion between a free helical state and a bound linear form through metal ion complexation[4] or protonation.[5] One may note that this amounts to the conversion of a free helicity codon into a bound linearity codon.

The reverse process would involve the effector induced interconversion between a free linear species and a bound helical one upon ion complexation and release (Fig. 1). Here we describe such a system, which furthermore provides an approach to a self-induced functional element of a molecular ion channel.

Whereas pyridine–pyrimidine sequences undergo helical wrapping,[2a–c] α,α′-linked oligopyridine chains[6] adopt a linear shape. It has been shown that a pyridine group may be replaced by the isosteric hydrazone functionality, retaining the same structure inducing features while making the synthesis of extended oligomeric strands much more accessible *via* simple amine (hydrazine)-carbonyl condensation.[7]

The 5-tridentate site (counting the hydrazone groups and the central pyridine) ligand strands **1a–c** (Fig. 2) were synthesized by a pathway based on hydrazone formation. The precursor **4** was obtained by a reaction between the alkylhydrazinopyridine **3** and the 2,6-pyridinedicarboxaldehyde, in a 1 : 1 molar ratio. The final double chain-extension was performed by a condensation between a bis(alkylhydrazino)terpyridine **5** and **4**, in a molar ratio of 1 : 2.[8] Their linear shape is based on proton NMR investigations (possible for **1b** and **1c**; **1a** is not soluble in usual NMR solvents) and on the X-ray crystallographic molecular structure determined for shorter 2-site ligand analogs (not shown). Based on the latter, its length may be estimated to lie around 40 Å.

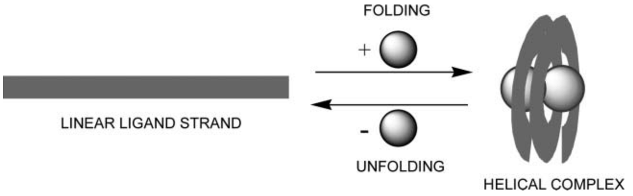

Fig. 1 Coiling/uncoiling, contraction/extension molecular motion induced by ion binding and release.

Treatment of a suspension of **1a–c** in acetonitrile with 2 equiv. lead(II) trifluoromethanesulfonate produced species **2a–c** presenting NMR (^{1}H, NOESY) spectral features in agreement with the formation of a complex containing a helically folded ligand strand. Determination of its X-ray crystallographic molecular structure on crystals grown from a solution of **1a** and 2 equiv. of Pb(OTf)$_2$ in acetonitrile (see Fig. 2)† showed that **2a** was a dinuclear complex (as confirmed also by ES-MS investigations for species **2a–c**) consisting of a ligand **1a** wrapped[9] around two Pb(II) ions in about two helical turns. The helix has a height of 7.2 Å, comparable to that of a 2-turn helically folded molecular strand, based on (pyrimidine–hydrazone) units.[7b] The nuclei of lead ions are 3.9 Å apart and one of them is separated by a bound water molecule from the triflate counterions located outside the helix.

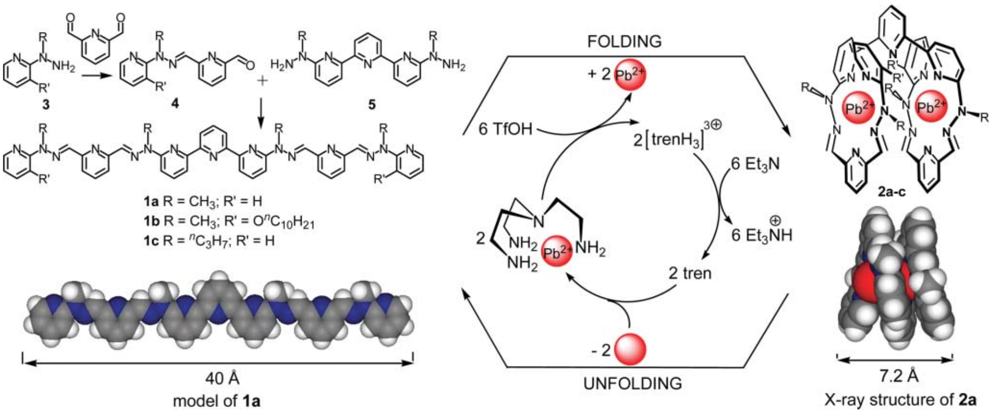

Fig. 2 Acid–base fuelled reversible coiling/uncoiling, contraction/extension motion of molecular strands triggered by sequential binding and release of lead(II) ions induced by protonation/neutralization reactions; TfOH = CF$_3$SO$_3$H. The indicated distances are internuclear distances.

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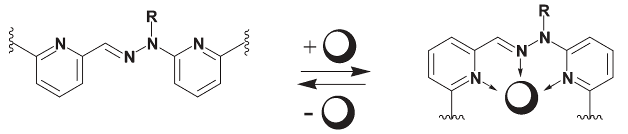

Fig. 3 Conversion of a free linearity unit (left) into a bound helicity inducing unit, a terpy-like site (right), by coordination of a cation.

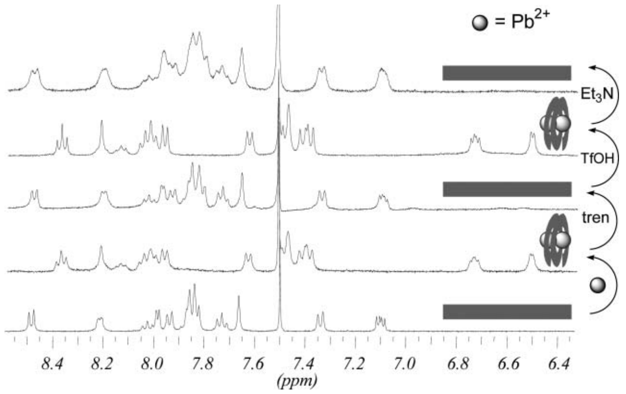

Fig. 4 Proton NMR (400 MHz) observation of the reversible coiling/uncoiling structural switching of ligand **1b** following the reaction cycle in Fig. 2; only the aromatic proton signals are shown; solvent $CDCl_3$–CD_3CN 3 : 2. Slow motions on the NMR time scale could be responsible for the poor resolution of some signals.

Binding of the Pb(II) ions imposes a terpyridine-type coordination geometry to the subunits of ligand molecule **1**, thus converting all transoid inter-heterocyclic connections into cisoid ones and resulting in coiling of the strand (Fig. 3).[9] Similar results were obtained with $Cd(OTf)_2$ and $Hg(OTf)_2$. The conversion of **1** into **2** represents also the formation of an element of a molecular ion channel induced by the specific ion itself; such a process of self-induced channel formation may present high ion selectivity, as only the ion capable of inducing the folding will be subject of facilitated transfer.

The transformation of the linear free ligand **1** into the corresponding helical complex **2** by the binding of two Pb(II) ions offers the opportunity to set up a reversible motional process in which a molecular entity undergoes sequential contraction and extension phases triggered by external chemical effectors. Such stretching/contracting actions occur in the folding/unfolding of proteins.[10]

A system producing reversible pulses of Pb(II) ions was achieved by means of the ligand $N(CH_2CH_2NH_2)_3$ (tren), which forms stable metal ion complexes that may be dissociated by protonation, thus releasing the bound ion.[11] It was assumed that this would also be the case for Pb(II) in an organic medium. Thus, a system involving ligands **1**, lead ions and tren should undergo the following reaction cycle (Fig. 2):

(1) complexation: linear ligand + 2 Pb(II) → helical complex;

(2) tren-complex formation: helical complex + 2 tren → linear ligand + 2 [Pb(II),tren];

(3) acidification and release of Pb(II): linear ligand + 2 [Pb(II),tren] + 6 H^+ → helical complex + 2 $[trenH_3]^{3+}$;

(4) basification and sequestering of Pb(II): helical complex + 2 $[trenH_3]^{3+}$ + 6 Et_3N → linear ligand + 2 [Pb(II),tren] + 6 Et_3NH^+.

Reversible contraction/extension molecular motions were indeed sequentially effected using the ligand **1b** and followed by proton NMR spectroscopy (Fig. 4). They amount to a two-stroke, linear motion-type action of very large amplitude (7 Å to 40 Å), fuelled by the neutralization energy.

The present results demonstrate the realization of periodic molecular motions, in phase opposition with respect to ion binding, compared to the systems described earlier.[4] They offer the possibility of combining both types of motions so as to produce locally resolved on/off type mechanical changes. Such studies are in progress.

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Notes and references

† Crystallographic data: $C_{43}H_{39}N_{15}Pb_2{\cdot}H_2O{\cdot}4\ SO_3CF_3{\cdot}CH_3CN$; 1835.61 g mol^{-1}; monoclinic; space group: $P12_1/c1$; a = 15.2500 (2), b = 17.5684 (2), c = 24.0749 (3) Å; β (deg) = 95.117 (5); V = 6424.4 $Å^3$ (1); T = 173 K; Z = 4; d_{calc} = 1.90 g·cm^{-3}; F(000): 3560; number of data measured: 19130; number of data with $I > 3\sigma(I)$: 11550; number of variables: 838; R = 0.071; R_w = 0.086; goodness-of-fit = 1.146; the hydrogen atoms on the coordinated water molecule could not be located. CCDC 237616. See http://www.rsc.org/suppdata/cc/b4/b407168a/ for crystallographic data in .cif format.

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