Molecular Motion

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Controlled Folding, Motional, and Constitutional Dynamic Processes of Polyheterocyclic Molecular Strands

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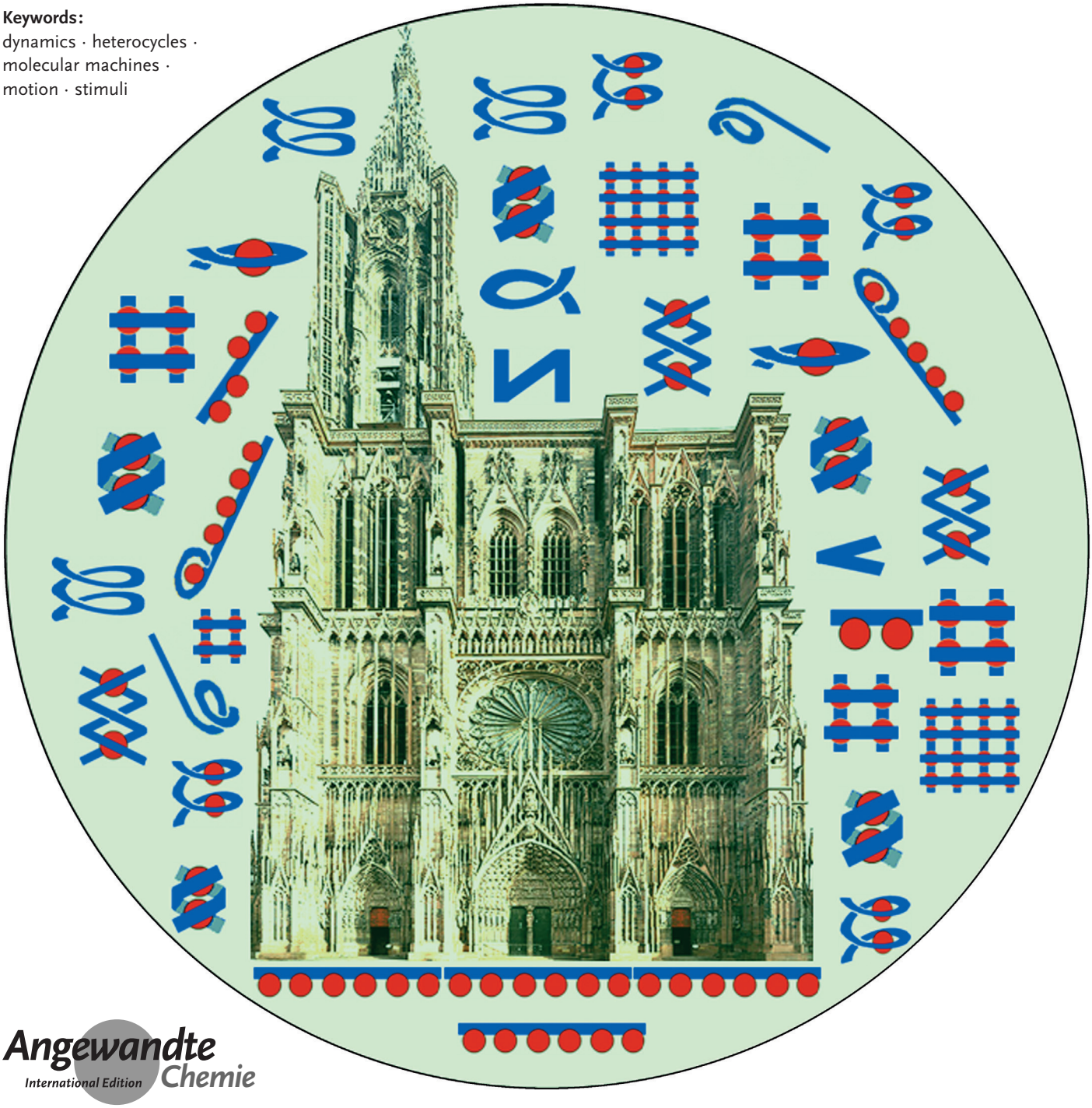
dynamics · heterocycles · molecular machines · motion · stimuli



General design principles have been developed for the control of the structural features of polyheterocyclic strands and their effector-modulated shape changes. Induced defined molecular motions permit designed enforcement of helical as well as linear molecular shapes. The ability of such molecular strands to bind metal cations allows the generation of coiling/uncoiling processes between helically folded and extended linear states. Large molecular motions are produced on coordination of metal ions, which may be made reversible by competition with an ancillary complexing agent and fueled by sequential acid/base neutralization energy. The introduction of hydrazone units into the strands confers upon them constitutional dynamics, whereby interconversion between different strand compositions is achieved through component exchange. These features have relevance for nanomechanical devices. We present a morphological and functional analysis of such systems developed in our laboratories.

From the Contents

1. Introduction

Precise control of the structure, shape, and conformation of molecules is a major goal of molecular chemistry and is of crucial importance for the designed generation of functional molecular properties. It is, in particular, the case for the biological activity of biomolecules, such as proteins, which depends on the correct folding of the polypeptide chains with different structural domains such as helices, turns, and sheets.[1] Extensive studies have been directed at understanding the factors and pathways that lead to the correct folding of protein molecules.

Controlled structural modification of the shapes and conformations of dedicated biomolecules[2] are the basic processes implemented for the generation of motion in living organisms. They are key to the functioning of motor proteins such as myosin in muscle action, of kinesins and dyneins,[3,4] of rotary motion in the multiprotein ATP synthase assembly,[5] and of contraction–extension motions of helical protein supercoils in the bacterial flagellar protofilament[2,6,7] etc. Such dynamic processes are mechanochemical in nature, involving ionic exchange, solvent binding, chemical reactions such as ATP/ADP interconversion, proton transfer, or ion binding. Extensive studies have been directed at mimicking the complex superstructures of natural machines by using biomolecular entities, based in particular on conformational changes of DNA-derived entities for the construction of DNA-based motors. Such devices have been shown to perform salt-dependent B-DNA to Z-DNA transformation to generate rotational motion[8] or intramolecular "pinching" via G-quartet formation fueled by ion-complexation processes.[9,10] Linear/circular conformational changes in DNA, reminiscent of biological DNA, are considered relevant for high-density information devices which can be controlled by temperature.[11] The folding/unfolding of the collagen triple helix is attributed to *cis–trans* conformational isomerization of proline residues through a zipper-like folding mechanism.[12]

The shape and folding of molecules as well as the generation of molecular motion and motor processes may

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also be subject to structure- and function-directed approaches not based on mimics of biomolecules but taking advantage of the great variety of molecular designs that may be imagined. Extensive studies have been directed in recent years at such fully synthetic systems, with the goal of generating and controlling molecular structure[13] and motion[14] in fully artificial systems.

Three main aspects may be considered within such a framework:

1) Structural and conformational features defining *folding (folded) states*; the set of all molecular and supramolecular folding states of a system may be considered to represent its *foldanome*.
2) Changes in structural and conformational molecular features (such as dihedral angles), that is, *changes in folding states* represent *molecular motions*.
3) Changes in the relative positioning of molecules, thus implying motion by the displacement of molecules with respect to one another (as in muscle action[3] or in pseudorotaxanes),[14f,g] within a noncovalent entity formally represent *supramolecular motions*.

The chemistry of molecular motions, motional chemistry, concerning so-called molecular nanomechanical processes, is a field clearly distinct from mechanochemistry.[15] One might thus wish to emphasize the purely motional features of these processes and term them *molecular kinematic processes* (kinesis = motion).

The motions may occur on the molecular and supramolecular levels, as a result of structural/conformational/configurational changes at either (or both) levels through nonbonded interactions of the intramolecular or intermolecular type, respectively. The latter are linked to recognition processes and to the corresponding types of interactions.

1.1. Context

Numerous systems demonstrating motional processes have been reported by a number of research groups. They belong to a variety of types and it is not possible to provide an exhaustive description herein. Furthermore, they have been the subject of a number of reviews elsewhere. We just very briefly mention here a number of them, referring the reader to the references given for more detailed information. Thus, dynamic motional systems and/or conformational changes studied by other research groups involve, in particular: 1) helical wrapping of quinquepyridine, bishydrazones, and pentaoxyethylene as well as other ligands around metal ions;[16a–g] 2) motional processes, switches, metallocomplexes, and sensors involving hydrazones;[16h,i] 3) folding/unfolding of a terpyridine complex;[16j] 4) extensions of helical molecules with formation of double-helical dimers;[16k] 5) solvent-induced[16l] or chaperone-assisted[16m] folding and unfolding or pH-modulated switches in helical strands (change of the helical pitch);[16n] 6) spring-like motion (partial unfolding and change of the helical pitch);[16o] 7) temperature-controlled pitch extension;[16p] 8) metal-ion-assisted processes;[16q–s] 9) an oligomeric *o*-phenylene helix that undergoes a redox-responsive dynamic motion;[16t] 10) reversible unwinding of an oligoresorcinol double helix;[16u] 11) the folding and unfolding of poly(ethylene glycol) and poly(ethylene imine) in solution;[16v] 12) anion-induced folding of aromatic amide-based oligomers;[16w] 13) linear-to-bent conformational switching of phenolic oligoamides;[16x] 14) photoswitchable foldamers;[17a,b] 15) acid-induced molecular folding and unfolding of a pyrimidine amide based oligomer;[17c] 16) complexation-induced unfolding of heterocyclic ureas;[17d] 17) folding/unfolding of electrochemically responsive molecules;[17e] 18) solvent-dependent folding/unfolding of oligomeric cholates[17f] or foldamers;[17g] 19) reversible unfolding of a helix with depolymerization;[17h] 20) stimuli-responsive folding and unfolding of a polymer;[17i] 21) pH-responsive wrapping[17j] or folding and unfolding of the DNA i-motif;[17k] 22) solvent-induced conformational changes of poly(*m*-ethynylpyridine)s;[17l] 23) accordion-like oscillations of helices[17m] or molecular springs;[17n] and 24) hydrazone-based di- and polynuclear complexes (often generated by unbending of bent ligands).[17o–u] Reviews on tunable helical structures[18a] and the functional role of foldamers[18b–f] have been published recently.

1.2. Specification

Considering all these results, we restrict the rest of this Review to our own contributions to the field. It involves a fully synthetic approach, based on the design of polyheter-

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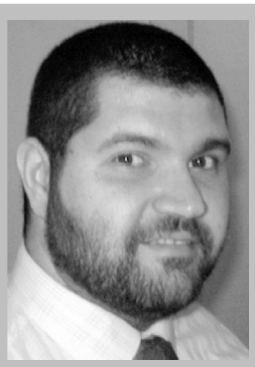
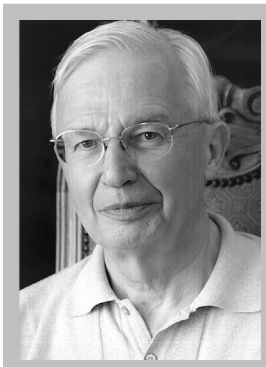


Adrian-Mihail Stadler is currently a CNRS researcher at ISIS at the University of Strasbourg, and principal investigator at the Institute of Nanotechnology of the KIT in Karlsruhe. He studied chemistry at the Universities of Bucharest, Paris XI, and Strasbourg as well as law at the Universities of Paris I Panthéon-Sorbonne and Strasbourg. He received his PhD in chemistry (2004) with Prof. Jean-Marie Lehn, in Strasbourg, for which he was awarded the Sigma–Aldrich Prize of the Société Française de Chimie and a Université Louis Pasteur of Strasbourg Prize. His research interests are coordination and supramolecular chemistry.

ocyclic molecular ligand strands and on the exploitation of their metal cation binding properties, involving: 1) determination of the molecular shape through conformation-enforcing codons, 2) shape switching by coordination of a metal ion, and 3) generation of reversible motion by interconversion between free and coordinated states. Furthermore, the morphological and functional features of the systems described here confer triple dynamic features upon them: motional dynamics through a change in shape between the free and complexed states, supramolecular metallodynamics through the reversible binding of metal cations, and covalent constitutional dynamics through the incorporation of groups into the strands that are capable of undergoing reversible covalent reactions and allow exchange of structural fragments/components.

2. Structural, Conformational, and Morphological Features of Polyheterocyclic Molecular Strands—Molecular Design and Shape Codons

The folding of biological macromolecules into the well-defined architectures that conditions their functional integrity is determined by the structural and conformational properties and the sequence of their residues, as well as by intramolecular noncovalent supramolecular interactions between them. Similarly, control over the shape of synthetic molecular strands is a particularly important goal of molecular design. It requires the introduction of suitable structural fragments that display specific conformational preferences. Such is the case for polyheterocyclic strands, whose shape will depend on the nature and the sequence of heterocyclic groups from which they are built. A particularly interesting type of strand is that consisting of a sequence of α,α′-linked aromatic aza-heterocyclic rings, in view of their widespread occurrence in coordination chemistry and the eclectic physical and chemical properties of their metal complexes. Thus, our investigations in this area were initiated by the realization that a strand consisting of a series of pyridine and pyrimidine groups did indeed wrap up in a helical fashion,[19a] while it extended into a linear shape on binding metal cations.[19b] The strands discussed here are oligomeric, well-defined ones, but polymeric, polydisperse species were also investigated.[19c] Moreover, an effective strategy for the construction of artificial molecular switches is to induce controlled changes in the molecular geometry through specific internal or external physical stimuli or chemical effectors. Intramolecular self-organization into folded architectures across a range of sizes, controlled by mastering molecular/supramolecular constitutional affinities, embodies the flow of structural information from the molecular level to nanoscale dimensions. It depends on factors such as the shape, orientation, and flexibility of the components.

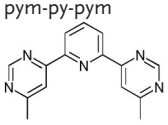
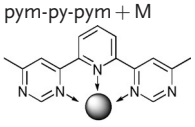
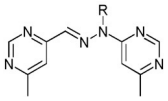
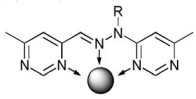
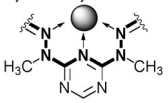
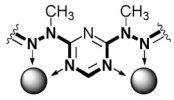
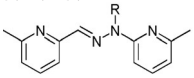
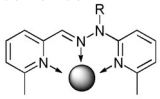
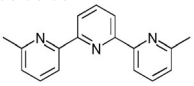
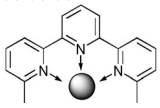


Jean-Marie Lehn became a Professor of Chemistry at the Université Louis Pasteur in Strasbourg in 1970 and from 1979 to 2010 he was a Professor at the Collège de France in Paris. He is currently a Professor at the University of Strasbourg Institute for Advanced Study (USIAS). He shared the Nobel Prize in Chemistry in 1987 for his studies on the chemical basis of "molecular recognition". His work led him to define "supramolecular chemistry", which concerns the chemical species held together by non-covalent intermolecular forces. It developed into "self-assembly" processes and "adaptive chemistry".

2.1. Shape Codons—Shape Control

The shape of polyhetocyclic strands is enforced and may be controlled by means of shape codons (see Table 1), which are defined as structural subunits of a molecule that contain the necessary and sufficient information to define its shape. The sequence of the heterocyclic units in the strands constitutes the primary structure, while the secondary structure (helical, linear) is induced by the structural codons that enforce a particular shape upon the strand. Supplementary stabilizing interactions (π-π stacking) may appear in the secondary structure, thus reinforcing it.

Table 1: Structural codons based on sequences of aromatic aza-heterocyclic groups in the free state and on tridentate coordination to a metal cation. **H** (helical) and **L** (linear) indicate the shape induced by the codons.[a]

Shape codons	Metallocodons
pym-py-pym 	pym-py-pym + M 
pym-hyz-pym 	pym-hyz-pym + M 
hyz-trz-hyz + M 	hyz-trz-hyz + 2 M 
py-hyz-py 	py-hyz-py + M 
py-py-py 	py-py-py + M 

[a] py = 2,6-disubstituted pyridine, pym = 4,6-disubstituted pyrimidine, trz = 4,6-disubstituted triazine, hyz = hydrazone group, M = metal ion.

In the free ligand strands, the codons control the conformation of the molecule through stereoelectronic interactions (attractions and/or repulsions) or intra-/intermolecular hydrogen bonds. The information encoded at the codon scale is transmitted, through the sequence of the codons, to the whole molecule. For example, local structural information on the bending or twisting leads to a helical local or global shape of the molecular strand. Moreover, a conformational change operated at the codon level by the action of a given effector that is able to interact with it (H^+, metal ion, solvent) will induce a change in the shape of the molecule (Table 1).

The basic codon is binary, composed of two α,α′-linked aromatic aza-heterocyclic (ahet) groups from the series pyridine, pyrimidine, pyridazine, pyrazine, triazine, tetrazine. A binary unit (ahet-ahet′) represents a *folding codon* (*foldon*). The *transoid* conformation about the connecting NC–CN bond in α,α′-bipyridine,[20] is strongly favored over the *cisoid* one by about 25–30 kJ mol^{-1}, thus enforcing specific molecular shapes.

A similar enforcing of the *transoid* form holds for other azaheterocyclic groups, namely five-membered ones as well as heterocyles containing heteroatoms other than nitrogen (for example, thiophene[20l] or furan; Figure 1).

As a consequence, extended (py-py) sequences will result in a linear shape, as in the linear strand $(py)_6$ (Figure 2a).[20k] On the other hand, the introduction of a pyrimidine group (pym) to give the unit α,α′-(py,pym) will cause a bend, so that (py-pym)[17,21a–d] sequences strongly enforce winding of the strand, thereby resulting in a helical shape. The α,α′-(py-pym) sequence thus represents a general *helicity codon* that induces molecular self-organization of the strand into a helical form.

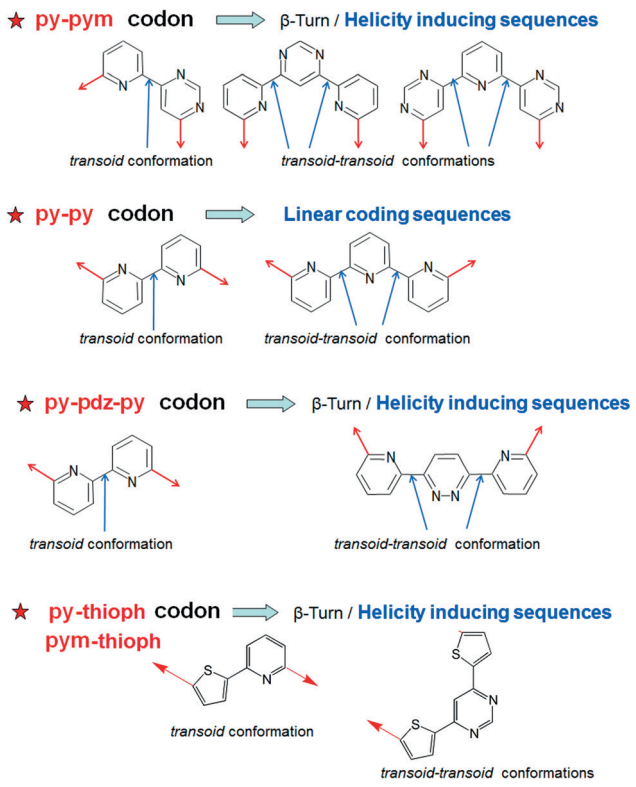


Figure 1. Basic codons used in the design of polyheterocyclic strands.

Strands of the py′-(py-pym)$_n$-py-py′ type (where terminal py′ are 2-substituted pyridines, internal py are 2,6-disubstituted pyridines, and pym are 4,6-disubstituted pyrimidines) with $n = 1,3,4$ have indeed been found to adopt helical structures[21a–c] in solution and in the solid state (for the two-turn helix $\mathbf{H_5}$ obtained for $n = 4$, see Figure 2b). This approach was further developed towards extended oligomers, up to one with 27 heterocycles that forms a four-turn helix.[21d] Theoretical investigations demonstrate the potential of such helical structures to exhibit specific second-order nonlinear optical properties.[21e]

The intrinsic features of such *chiral helical structures* as well as their occurrence in many biological systems have made the understanding of the factors governing chiral self-organization particularly significant.[22] It is clear that such shapes present either *P* or *M* helicity and are generated, in principle, as racemic *PM* mixtures. Helical chirality may be induced by the introduction of a chiral center/subunit, as is the case, for example, in double-stranded helicates (see Section 3) built from strands containing stereogenic carbon centers.[23]

Interestingly, the insertion of a pyridine moiety between two (py-pym) strands, as in the strand **2H** (Figure 2c), results in a morphology with two enantiomeric helical domains of opposite helicity. This represents the intriguing case of a fully helical molecule of *meso*-type in which the helical strand undergoes a helicity inversion at the central py group.[24]

The introduction of heterocyclic units of larger size or with different angular dispositions leads to helical strands of larger diameter. Such is the case for strands containing pyridine-pyridazine[21f,g] or pyridine-naphthyridine[25] subunits. α,α′-Disubstituted 1,8-naphthyridine (naphy) is an equivalent of the py unit, but of larger size, but presents the same angle of 120° between the two substituents. Consequently, (pym-napht) strands also adopt a helical shape, but with a larger diameter than the (py-pym) strands (Figure 2d). They present a very polar internal cavity with a diameter of about 3.5 Å that is able to bind cationic species, which subsequently promote helix aggregation and folding themselves.[25] Similarly, helical structures with larger cavities result on the introduction of 3,6-pyridazine spacers between two pym groups.[25]

The isomorphic correspondence between a 2,6-disubstituted pyridine ring and a hydrazone (hyz) group (Figure 2e) allows for the introduction of novel valuable features into the molecular sequence: 1) easier synthetic access by facilitation of the formation of inter- C–C connections between heterocycles through hydrazine-carbonyl condensation;[26] 2) covalent dynamics that make it possible to exchange groups through reversible formation of the imine linkage of the hydrazone group; 3) possibility to manipulate the -NR- site by either ionization (when R = H) or introduction of specific (functional) substituents.

Helical ligands having an even number of hydrazone functions (for a 10-hyz ligand $\mathbf{H_{10}}$, see Figure 2e) were obtained by a route involving desymmetrization steps fol-

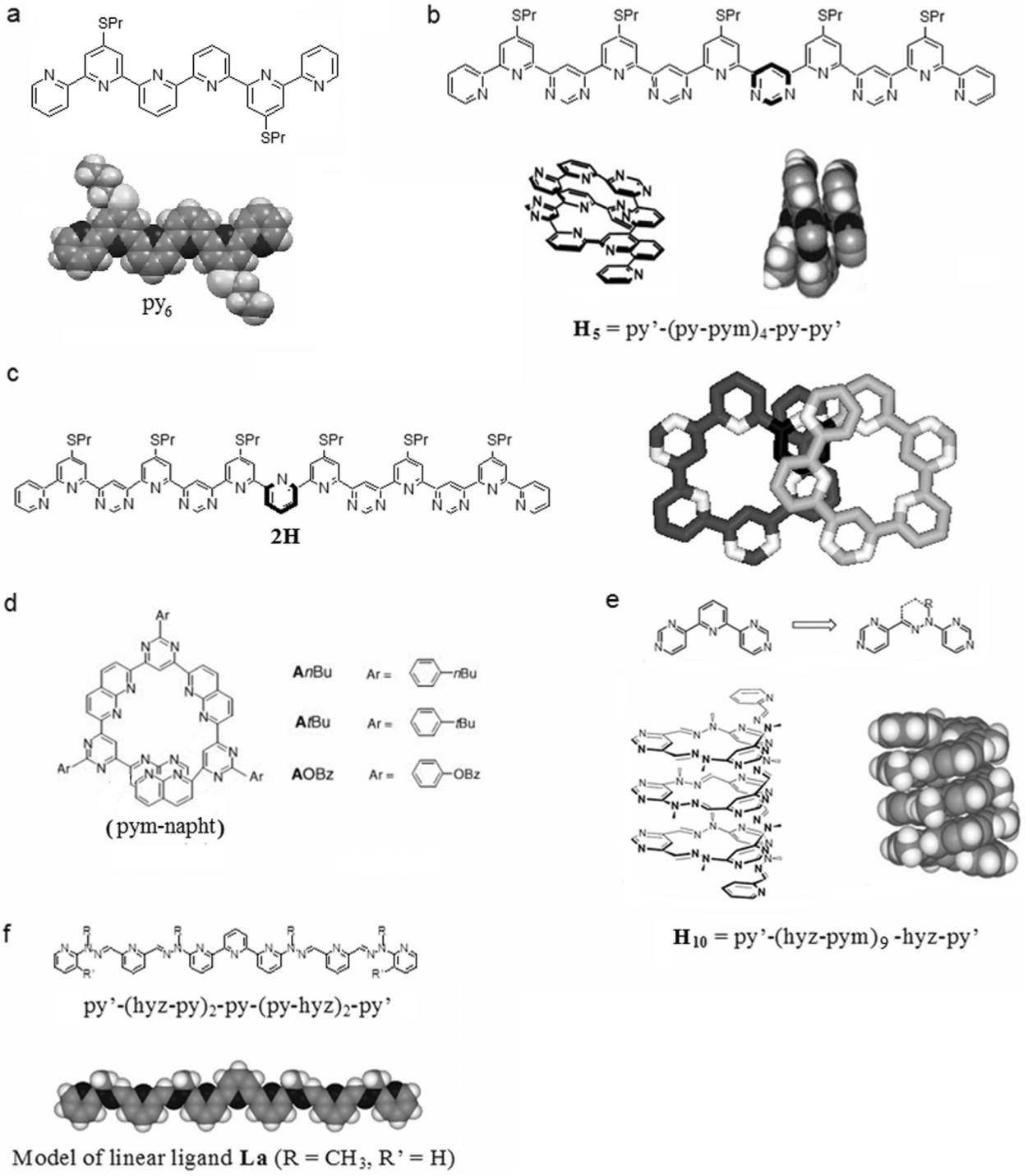


Figure 2. a) A linear (py-py) type strand[20k] and its X-ray structure; b) a helical (py-pym) strand and its X-ray structure; c) a combination of helicity- and linearity-enforcing codons: generation of a strand presenting two helical domains connected by a short py-py-py linear domain; d) a helical pyrimidine-naphthyridine (pym-naphth) type sequence; e) isomorphic correspondence between a py and a hyz unit; structural formula and X-ray structure of a helical (hyz-pym) strand; f) a linear hyz/py-py strand and its molecular model. hyz = hydrazone, py = 2,6-disubstituted pyridine, py′ = 2-substituted pyridine, pym = 4,6-disubstituted pyrimidine.

lowed by a final symmetrical double-chain extension.[26b] The same procedure has been applied to extended sequences for the synthesis of linear strands containing both (py-py) sequences and their analogues (py-hyz), such as in molecule **La** (Figure 2 f).[27]

It is of special interest that the presence of reversibly interconvertible C=N bonds confers to hyz-containing strands covalent dynamics that connect the design and properties of molecular strands to the attractive features of dynamic covalent chemistry.[28] Thus, it was, for example, shown that

constitutional rearrangement of two starting strands containing py, pym, and hyz units in the presence of metal ions led to component recombination driven by coordination of a metal cation, with generation of a novel strand capable of forming a [2×2] grid type tetranuclear metal complex.[29]

It may be noted that poly(*m*-ethynylpyridine)s adopt unfolded conformations in less-polar media such as many organic solvents and undergo a profound conformational change in polar media, thereby leading to helical chiral architectures.[12,30]

3. Structural Features of Metal Complexes of Polyheterocyclic Strands: Metallofoldamers—Metallocodons and Shape Switching by Coordination of Metal Cations

The polyheterocyclic molecular strands considered above contain subunits that may function as ligands and bind metal cations, thus yielding novel shapes according to the type of subunit and the coordination features of the metal ion.

On complexation, the metal cations enforce a conformational conversion about the α,α′-linkage between the heterocyclic groups from the *transoid* to the *cisoid* form, so as to generate a coordination site for cation binding (Figure 3). The complexed sites define *metallocodons*, which may be bidentate or tridentate. They lead to overall structural interconversion between helical and linear shapes by unfolding helical ligand strands or by inducing helical folding into linear ones, as indicated in Table 1 and Figures 1 and 3.

Diverse metallosupramolecular architectures are obtained by the reaction of polyheterocylic ligands with metal ions, including the broad class of metallofoldamers.[16r,31] A special class of ligands is represented by strands in which the coordination subunits (such as bipy and terpy) are separated by spacer groups. On binding metal ions, they yield helical metal complexes, which have been termed *helicates*.[32] The field has developed extensively since the initial double-helical trinuclear complex, self-assembled from a tris-bipy strand and three Cu^+ cations,[32] with generation of a wide variety of helicates having a wide range of structural, physicochemical, and reactional features.[16c,33] These helicates will not be considered further here.

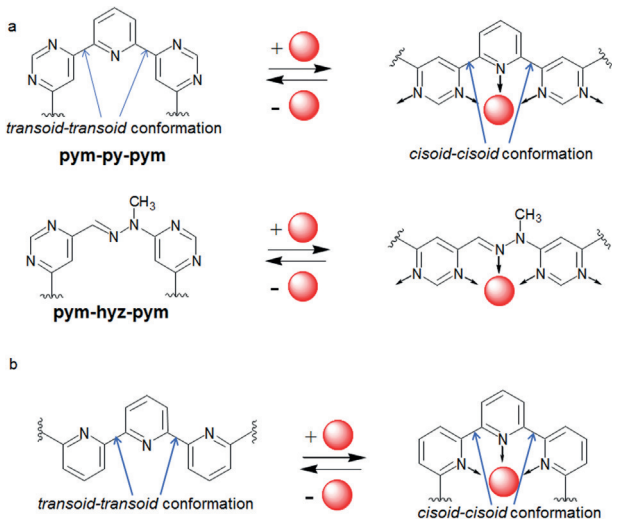


Figure 3. Folding/unfolding interconversions: a) Conversion of the β-turn/helicity-inducing form of the free pym-py/pym-hyz ligand fragments into an extended linear shape upon binding of a metal ion; b) conversion of a linear ligand fragment py-py into a β-turn/helicity-inducing form upon binding of a metal cation.

3.1. Complexes Formed by (py-py) and (py-hyz) Strands

The α,α′-linked oligopyridine (py-py) or the mixed (py-hyz) chains adopt a linear form. Upon binding a metal cation in a tridentate fashion, they undergo helical folding, with the ligand wrapping in a helical fashion around the metal ions. During this process, the length of the ligand is markedly shortened compared to the extended linear free ligand (Figure 4a).[34]

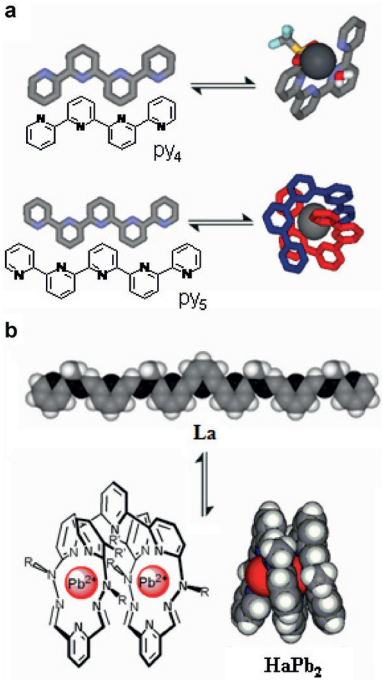


Figure 4. Folding of a ligand chain by coordination of a metal cation: a) Crystal structures of Pb^{2+} complexes of py_4 (top) and py_5 (bottom);[34a] b) structural formula and model (left) of the linear ligand **La** (Figure 2fxfigr2>) and structural formula and X-ray structure of its dinuclear Pb^{2+} complex $\mathbf{HaPb_2}$ (triflate anions and solvent molecules are omitted for clarity).[27]

The complexation of Pb^{2+} cations by the linear (py-hyz)-based ligand **La** yields a dinuclear complex $\mathbf{HaPb_2}$, which consists of a single molecular strand wrapped around two Pb^{2+} ions in about two helical turns (for the X-ray structure of $\mathbf{HaPb_2}$, see Figures 4b and 11).[27] The shorter ligand py-hyz-trz-hyz-py (trz = 4,6-disubstituted triazine), an analogue of the ligand py-hyz-pym-hyz-py, binds a Pb^{2+} ion to give a helical complex $\mathbf{HcPb_1}$. An excess of Pb^{2+} may convert

this mononuclear helical complex into a dinuclear linear one (see Figure 13).

3.2. Complexes Formed by (py/hyz-pym) Strands

The helical molecular strands based on folding codons (pym-py-pym or pym-hyz-pym) containing two to ten such terpy-type sites undergo uncoiling on binding metal ions, with formation of the corresponding complexes in which the strand adopts a linear shape. Thus, adding at least *n* equivalents of Pb^{2+} ions to a helical ligand strand with *n*-sites generated the corresponding rack-like, linear complexes, as has been confirmed by extensive NMR studies, as well as by determination of the solid-state X-ray structures of di- and tetranuclear rack-type (**$LaPb_2$**, **$LaPb_4$**, **$LbPb_2$**, **LPb_5**; Figure 5a,b) and multinuclear grid-type[35] (**$GaPb_4$**, Figure 5d) complexes.

Treatment of several ligands containing two binding sites with Pb^{2+} triflate in molar ratio of 1:1 resulted in tetranuclear Pb^{2+} [2×2] grid-like[36] structures (**$GaPb_4$**, Figure 5d). Treating ligands **Ha_4** and **Hb_4** containing four sites with Pb^{2+} triflate in a molar ratio of 1:2 gave the [4×4] grid arrays[37] (for the X-ray structure of **$GbPb_{16}$**, see Figure 5c). Interestingly, reaction of the (py-pym) ligands **Hb_4** and **Hc_4**, containing three pym rings (i.e. 4 terpy-like subunits), with silver triflate resulted in the generation of double-helical entities **DH_4**, which contain two strands and two silver ions.[38] NMR studies and determination of the solid-state molecular structure indicate that the duplex is stabilized by the coordination of each Ag^+ ion to two terminal bipyridine units, one from each strand, together with close π-π stacking between the internal heterocycles of the strands, thereby yielding a very robust double-helical structure (for the X-ray structure of **DHc_4**, see Figure 5e). This displays complementary positioning of the stacked heterocyclic units for molecular recognition. Accordingly, chiral double-helical channels are generated in the solid state, with an interior void of about 1.8 Å. The silver ions are arranged into an approximately linear array that fits tightly into the central cavity of the double-helical channel. Similarly, a double-helical dinuclear complex **DH_2** is formed on complexation of Ag^+ by the bent py′-hyz-pym-hyz-py′ ligand **Ha_2** (Figure 5f).[39] These complexes form polymeric, highly ordered solid-state structures, with wire-like linear, discontinuous, polycationic arrays of Ag^+ ions.

The strand py-naphy-pym-naphy-py **pnpnp** undergoes extension on formation of tetranuclear Ru^{II} and Rh^{II} complexes $\{[M_2(\mu\text{-}CH_3CO_2)_3]_2$ **pnpnp**$\}^{2+}$ (M = Rh, Ru; Figure 5g).[40]

3.3. Protonated Forms of Oligopyridine-Carboxamide Strands

Treatment of carboxamide strands (see Figures 20a,b and 21) containing *n* diaminopyridine units with *n* equivalents of acid resulted in the formation of the corresponding protonated species (see Figure 21). Spectrometric studies and determination of the solid-state structure indicated that the helical form underwent uncoiling, with the protons playing the role of the metal cations, as discussed in Section 3 for the polyheterocyclic strands (Figure 21). Protonation occurs regioselectively at the pyridine nitrogen atoms of the 2,6-diaminopyridine moieties, while the 2,6-pyridinedicarbonyl fragments remain unprotonated.[41]

4. Motional Extension/Contraction Dynamics Induced by Reversible Interconversion of Free and Complexed Heterocyclic Molecular Strands

4.1. Types of Dynamic Processes

In a broad sense, dynamic chemistry may be envisaged to occur through three types of processes:[42,43]

- *reactional dynamics*, that is, the kinetics and mechanisms of chemical reactions.
- *motional dynamics*, comprising external reorientations (such as overall molecular reorientations in liquids, for example in pyridine or benzene),[44] internal motions (such as rotations around bonds or site inversions), dynamics in soft matter (polymer chains, colloids etc.),[45] morphological dynamics involving changes in molecular shape, as well as "molecular machine or motor" type processes, in particular with the goal of generating oriented molecular motions.[46]
- *constitutional dynamics*, whereby a chemical entity, be it molecular or supramolecular, undergoes continuous change in its constitution through dissociation into various components and reconstitution into the same entity or into different ones.

For an application of these concepts to polyheterocyclic strands discussed herein, see Table 2.

A wide variety of shape changes and motional processes occur through reversible bending (unbending) or folding (unfolding) of polyheterocyclic ligand strands induced by the coordination of metal ions (Figure 6). A first type (Figure 6a) concerns the extension/unfolding of coiled strands. Bent or helical ligands can produce double helicates (partial extension and increase of helical pitch) or architectures where they adopt a linear conformation, for example in grid-type or rack-type complexes (extension).[19b,47] Metalated helices and double helicates can generate grids or racks. Z-Shaped strands can produce linear rack complexes. Conversely, within the second class (Figure 6b), linear ligand strands can undergo contraction/folding into helical mono- or dinuclear complexes. Subunits capable of performing extension and contraction motions can be incorporated in a same strand to generate a third class (Figure 6c) of motions: coupled motions combining extension and contraction within the same strand (see Figure 16). Examples of related artificial folding/unfolding (coiling/uncoiling) processes resulting in large changes in molecular size are found for synthetic chains of amino acids,[48] aromatic helical backbones,[49] responsive polymers,[50,51] and other species, including peptides and biologically inspired cholate backbones,[52] which undergo important shape changes, for example, folding/unfolding, rotation, or linear motions in response to external stimuli (light, temperature, pressure, or medium).

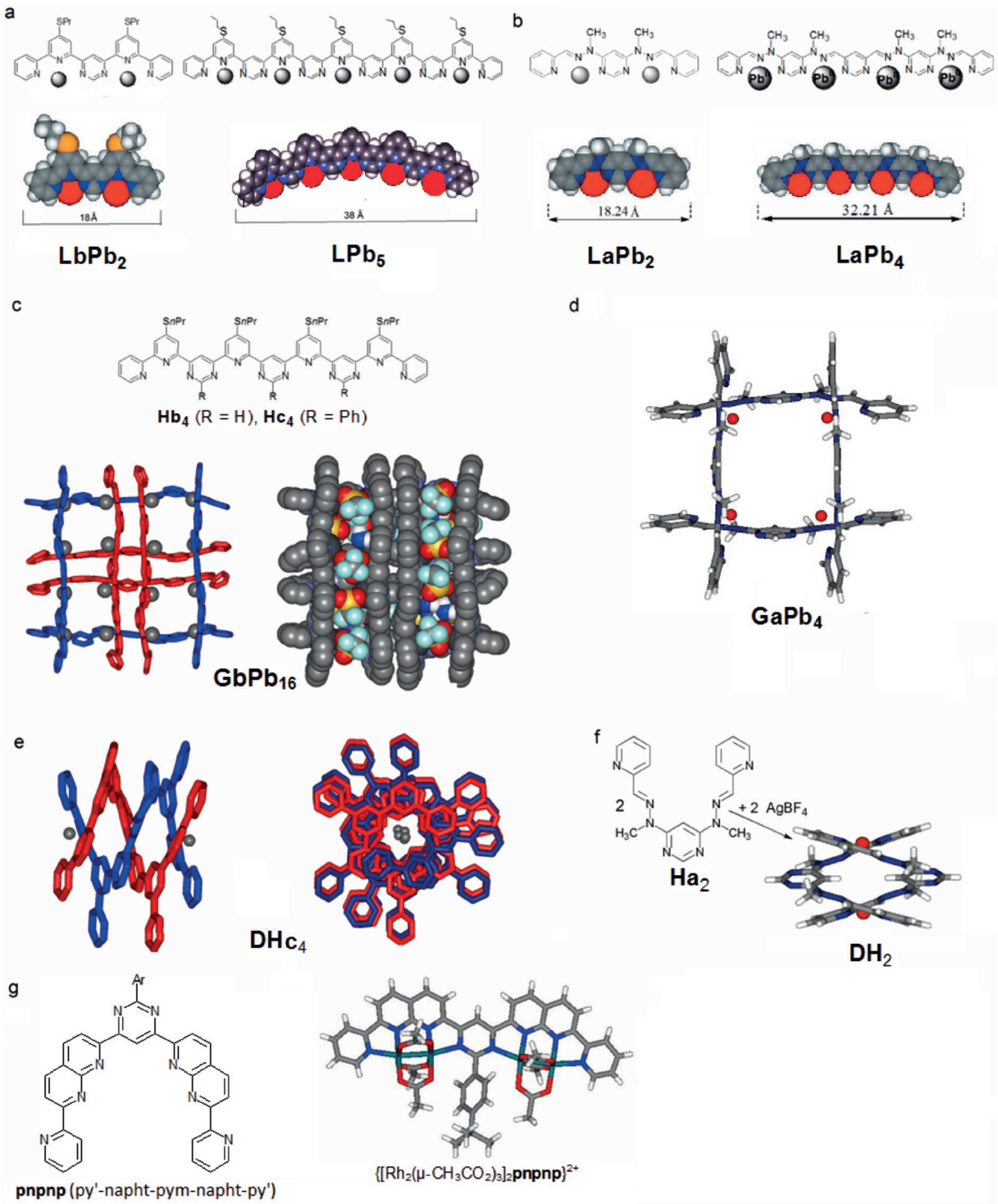


Figure 5. Representation of complexed polyheterocyclic strands: a) Structural formula (top) and X-ray structure (bottom) of the dinuclear and pentanuclear Pb^{2+} complexes of py-pym ligands;[42] b) structural formula (top) and X-ray structure (bottom) of the dinuclear and tetranuclear Pb^{2+} complexes of a py-hyz-pym ligand (reprinted from Ref. [35a] with permission); c) X-ray structure of a Pb^{2+} hexadecanuclear [4×4] grid-like complex of a py′-(py-pym)$_3$-py-py′ **Hb$_4$** ligand in stick (left) and in space-filling (right) representation, including the triflate anions bound in the cavities of the assembly (reprinted from Ref. [37] with permission, Copyright 2003 American Chemical Society); helical strands **Hb$_4$** and **Hc$_4$** are shown, for clarity, in their linear representation; d) X-ray structure of the Pb^{2+} tetranuclear [2×2] grid-like complex of the bidentate ligand **Ha$_2$**;[35a] e) double-helical Ag^+ complex[38] lateral view (left) and front view (right); f) double-helical Ag^+ complex[39] **DHc$_4$** of a pyrimidine-dihydrazone-based ligand. Anions and solvent molecules are omitted for clarity in (a), (b), (d), (e), and (f); g) helical naphthyridine-based strands **pnpnp** and crystal structure of the complex cation $\{[Rh_2(\mu\text{-}CH_3CO_2)_3]_2\mathbf{pnpnp}\}^{2+}$ (solvent molecules and PF_6^- ions omitted for clarity).[40]

Table 2: Architectures, dynamics, and interconversions in the explored systems.

Initial architecture	Dynamics	Final architecture	Interconversion
helical or bent	motional	grid	unfolding/folding
		rack (stick)	unfolding/folding
		double helix	double folding/folding
	constitutional	grid (with a final ligand smaller than the initial one)	unfolding/folding with component exchange
linear	motional	helix	folding/unfolding
mixed (helical + linear)	motional	mixed (linear + helical)	unfolding/folding folding/unfolding

Constitutional dynamics are based on the exploitation of constitutional dynamic chemistry (CDC),[53,54] which provides an evolutional approach to the generation of chemical diversity on both the molecular (dynamic covalent chemistry, DCC)[28,53] and supramolecular (dynamic noncovalent chemistry, DNCC)[53] levels through the implementation of reversible covalent reactions and noncovalent inter- or intramolecular interactions, respectively. It bears a resemblance to the motional dynamics of molecular strands through the dynamic constitutional exchange of components linked by reversible covalent linkages so as to generate ligand strands capable of undergoing shape changes on the binding and release of metal ions. It is represented, for example, by the generation of a suitable helical ligand through component exchange of an initial folded strand and its unfolding driven by the binding of metal cations to yield a grid-type complex.[29]

4.2. Strategy for Performing Extension/Contraction Molecular Motions

The architectures of the free and bound states of the polyheterocyclic ligands described above represent the initial and final states of potential dynamic motional processes involving the reversible folding/unfolding of molecular strands through the coordination and release of metal ions (Table 2). Interconversion between the free and complexed states of the polyheterocyclic ligand strands may be achieved through reversible interaction with metal cations, so as to convert the shape codons present in the initial entity into those in the final one. Thus, upon binding a metal ion, a helical ligand strand may be converted into a complex in which it has a linear shape, or, conversely, a linear ligand acquires a helical shape in the complexed state, without any change in the constitution of the molecular entity.

Such interconversions may be realized by a process involving three stages:

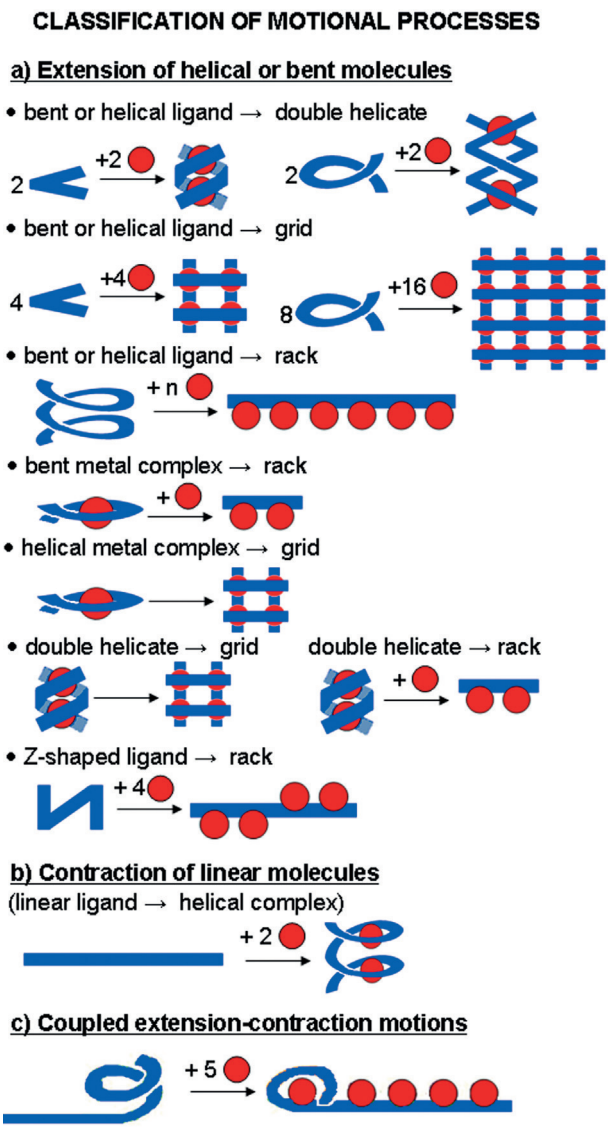


Figure 6. Types of metal ion induced motional processes depending on the shapes of the starting and resulting architectures (the starting species is that which is the less metalated): extension of helical species (a), contraction of linear species (b), and coupled motions (c).

1) Binding of metal cations to the heterocyclic subunits of the ligand strand or removal of the metal cations bound to the strand.
2) Addition of a competing ligand that sequesters the metal cations by binding them more strongly than the polyheterocyclic ligand strand itself.
3) Modulation of the metal cation affinity of the competing ligand by an external factor, such as protonation/deprotonation through sequential addition of acid/base.

A suitable competing ligand may, for example, be an acyclic (e.g. tris(aminoethylene)amine, tren) or a macrocyclic (e.g hexacyclen) polyamine or a macrobicyclic cryptand[55,56] (e.g. [2.2.2]). It should be able to reversibly bind a metal ion in the parent state and release it on protonation, so as to make it available again for binding to the ligand strand.

The ligands and their complexes may be characterized by various physical methods (X-ray crystallography, 1D, 2D, NOESY, and ROESY NMR spectroscopy, as well as mass spectrometry and UV/Vis absorption spectroscopy).

The rates of the coiling/uncoiling interconversion processes are determined by the rates of the complexation and release of the metal ion by either the ligand strand under investigation or the competing complexing agent employed. The rates are generally fast (a few seconds or minutes) and may be easily followed by ^{1}H NMR spectroscopy.

Such reversible motional processes were first achieved in the transformation of helical free ligand strands into the corresponding linear complexes by the sequential binding and release of several metal ions (see Figure 8, Section 4.3).[42] It offered the unique opportunity to set up a reversible motional process in which the molecular entities undergo sequential extension/contraction phases through metal-ion exchange, triggered and controlled by the alternating addition of acid/base effectors (Figure 8).[42] One may consider that such extension/contraction processes represent linear molecular motions fueled by acid/base neutralization. Several types of interconversions represented in Figures 6 and 7 illustrate some specific examples. On the other hand, the α,α′-linked (py-py) chains adopt a linear shape and undergo contraction by wrapping in a helical manner around metal ions (Figure 4a).[34a] Similar processes take place with ligand strands in which pyridine groups have been replaced by isosteric hydrazone units.[26,35] In addition to the processes modulated by interaction with metal cations, shape changes may also be induced simply by protonation/deprotonation of a strand (such as oligopyridine-carboxamides)[41] or also involve other factors (solvent change, temperature, concentration).[12b]

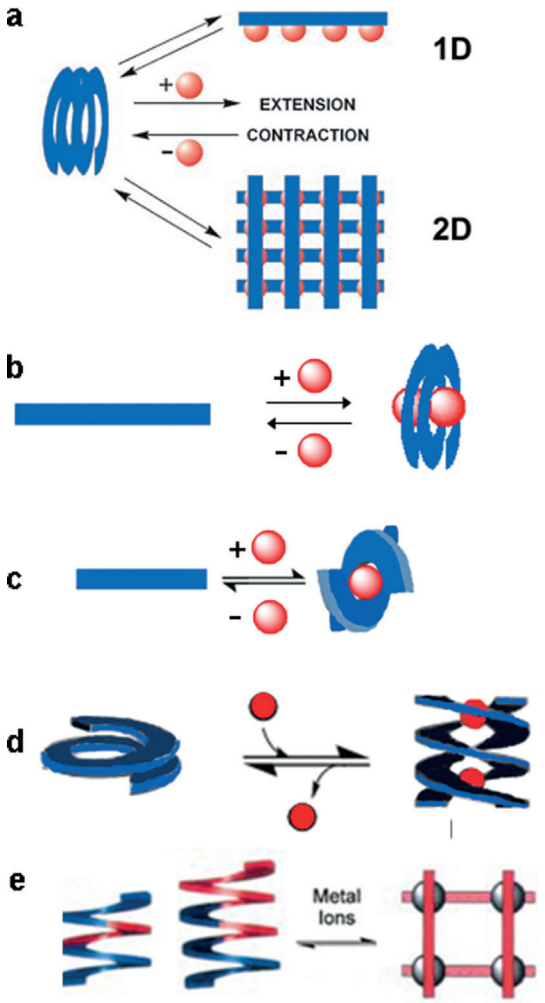


Figure 7. Representation of the motional and constitutional dynamic processes induced by interconversion between free ligand strands and their metal-ion complexes: a) Reversible unfolding of helical ligands -(hyz/py-pym)- in a one-dimensional (1D)[35a,42] or a two-dimensional (2D)[35a,37] process; b) reversible folding of linear ligands -(hyz/py-py)-,[27] c) metal-induced bending of two linear strands to produce a double helicate,[34a] d) reversible formation of double-helical complexes of -(py-pym)- ligands,[38,39] and e) metal ion driven evolution of a dynamic library of helical ligands towards unfolding with formation of a [2×2] grid-like complex.[29,54]

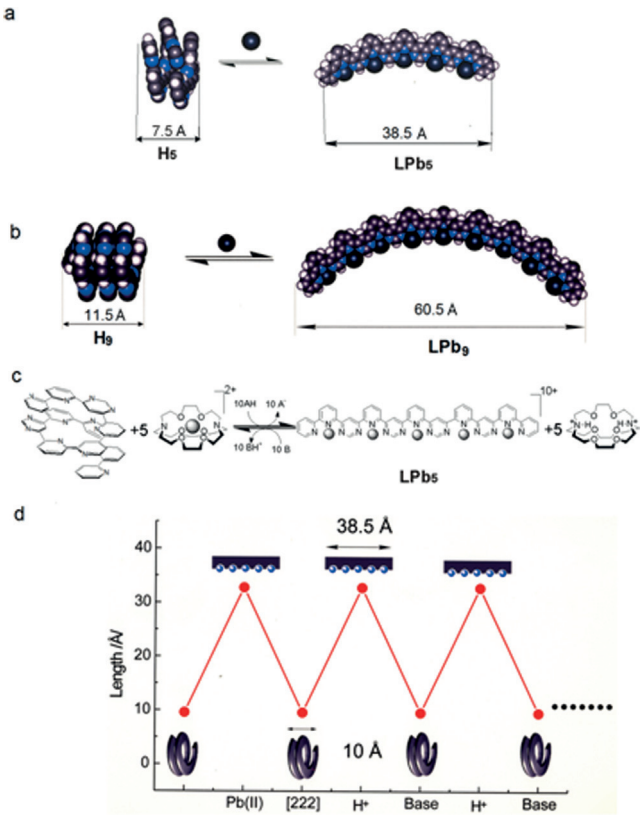


Figure 8. a) Reversible extension of the py-pym helical ligand a) **H_5** and b) **H_9** into the linear complexes **LPb_5** and **LPb_9**, respectively. c) Modulation of coiling/uncoiling motions by interconversion of **H_5** and **LPb_5** by alternate cation binding/removal through coupling to the reversible protonation-dependent interconversion of cryptand[2.2.2]/cryptate [$Pb^{2+}\subset$2.2.2]. The gray spheres represent Pb^{2+} ions; AH = CF_3SO_3H, B = Et_3N. d) Sequential modulation of the coiling/uncoiling, contraction/extension process **$H_5 \rightleftarrows LPb_5$** performed through structural switching induced by ion complexation/pH alternation through coupling to a protonation-sensitive competing ligand. Reprinted from Ref. [42].

4.3. Extension/Contraction Motions of Helical Ligands: Helical Ligand (H_n)⇄Linear Complex (LM_n)

The interconversion, helical ligand (**H_n**)⇄linear complex (**LM_n**), between coiled free-ligand strands and uncoiled ligands in the complexes generates molecular motions of large amplitude.[42] Treatment of the helical ligand **H_5** with Pb^{2+} ions in a molar ratio of 1:5, leads to the corresponding linear complex (Figures 6a, 7a, 8a,b). At the codon level, all the *transoid* N-C-C-N conformations are transformed by the binding of metal ions into the *cisoid* conformations. This process induces, at the molecular scale, the uncoiling of the helical free ligand, thereby causing a large change in the size. Reversible pulses of Pb^{2+} ions were produced by taking advantage of the properties of the macrobicyclic ligand, cryptand [2.2.2], which forms cryptate inclusion complexes [M^+⊂2.2.2] with numerous metal ions.[57a] In particular Pb^{2+} yields a very stable cryptate [Pb^{2+}⊂2.2.2][57b,c] Protonation of the bridgehead nitrogen sites leads to the diprotonated species [$2H^+$⊂2.2.2], with release of the included Pb^{2+} ion from the cryptate. Thus, one may imagine setting up a multicomponent/multitrigger system involving a helical ligand strand, Pb^{2+} ions, cryptand [2.2.2], acid, and base.

Considering a specific case for the sake of illustration, a system containing the ligand py′-(py-pym)$_4$-py-py′, **H_5**, undergoes the following sequence of reactions (Figure 8c):

- uncoiling of the ligand strand by complexation of a metal ion:

helical ligand **H_5** + $n\,Pb^{2+}$→linear complex **LPb_5**

- removal of the metal ions with a competing ligand, a cryptand, with formation of the corresponding cryptate and liberation of the free ligand in its helical form:

linear complex **LPb_5** + 5[2.2.2]→helical ligand **H_5** + 5[Pb^{2+}⊂2.2.2]

- release of the metal ions from the cryptate complexes by protonation followed by their binding to the unprotonated helical ligand strand:

helical ligand **H_5** + 5[Pb^{2+} ⊂2.2.2] + 10 H^+→linear complex **LPb_5** + 5[$2H^+$⊂2.2.2]

- addition of base to deprotonate the protonated cryptand and sequestering of the metal ions through cryptate formation:

linear complex **LPb_5** + 5[$2H^+$⊂2.2.2] + 10(base)→helical ligand **H_5** + 5[Pb^{2+} ⊂2.2.2] + 10(base, H^+)

Extension/contraction is realized as a controlled motion in an oscillatory periodic mode by sequential addition of acid and base. It amounts to a two-stroke, linear motor action with a very large stroke amplitude, with the linear dimension changing by a factor of 5, from 7.5 Å to 38 Å, for the ligand py′-(py-pym)$_4$-py-py′ **H_5** (py′ = 2-substituted pyridine; Figure 8a) and from 11.5 Å to 60.5 Å for the ligand py′-(py-pym)$_8$-py-py′ **H_9** (Figure 8b). This mechanochemical process is fueled by protonation/deprotonation, that is, by the acid/base neutralization energy.[42]

In a similar sequence of operations, dynamic interconversion between the helical and linear forms of a (hyz-pym) molecular strand was produced by coupling the ion-binding process by the heterocyclic ligand to that of a competing ligand, whose ion affinity could be modulated by the addition of acid/base. Sequestering Pb^{2+} ions from the rack-type complexes **LPb_n**, which contain the linear L_n forms of the ligands, was accomplished in this case by using $N(CH_2CH_2NH_2)_3$ (tren)[35a,58] as the competing complexing agent. It results in the spontaneous coiling of the free ligand thus liberated, to give the corresponding helical form H_n. On protonation of the Pb^{2+}-tren complex formed, the metal ion is released and binds again to the helical ligand H_n to regenerate **LPb_n**. Subsequent treatment with base, restores the free tren, which binds the metal ions and the cycle is reinitiated. The cases of **Ha_4** and **H_{10}** are illustrated in Figure 9a,b.

Whatever the ligand, linear molecular mechanical alternating extension/contraction motions similar to an artificial muscle[59] are generated and induced by a reversible ionic process and fueled by sequential acid/base neutralization. These motions again display especially large amplitudes (with extension factors of up to about 500–600 % for a strand with 10 subunits) compared to those displayed by either biological or other synthetic molecular entities.[60] Ignoring π-π stacking,[61] the work required to transform the helical ligand into its extended, linear form is the total energy necessary to convert all the N-C-C-N *transoid* conformations (in the helix) into *cisoid* ones (in the extended strand in the complex).

Values of 25–30 kJ mol^{-1} have been calculated for the conversion of 2,2′-bipyridine from its *transoid* into its *cisoid* state[20c] and an energy difference of about 33 kJ mol^{-1} has been obtained for the same conversion in the py-pym case.[63] Assuming that a hydrazone has features comparable to a pyridine group, there are two such *transoid*-to-*cisoid* torsions (each amounting to about 30 kJ mol^{-1}) per terpy-like pym-hyz-pym coordination subunit, that is, a conversion energy of about 60 kJ mol^{-1} per subunit and 300 kJ mol^{-1} in total for strand **H_{10}** with 10 subunits.

Selecting and combining appropriate heterocyclic units offers the possibility of enforcing the global shape of a molecular ligand strand, such as a helically folded one, **Ha_4**, versus an undulating zigzag tape, **Hz_4** (Figure 9c).[62] Furthermore, the grafting of het-hyz sequences on a central heterocyclic unit of the core allows control of both the amplitude and especially the relative direction of the motions generated on the binding of metal ions. In particular, the replacement of a central 4,6-disubstituted pyrimidine unit (pym) by a 2,5-disubstituted pyrazine (pz) produces a decrease in the amplitude of the subsequent molecular motions, but also, more importantly, a change in the nature of the relative motions of the branches connected to these rings, from "flapping"-type (*dis*-sense) motions (pym) to "twirling"-type (*con*-sense) motions (pz).[62] In general terms, the appropriate combination of different encoding units within ligand strands provides access to the designed generation of various types of strand folding as well as to specific combined molecular motions.

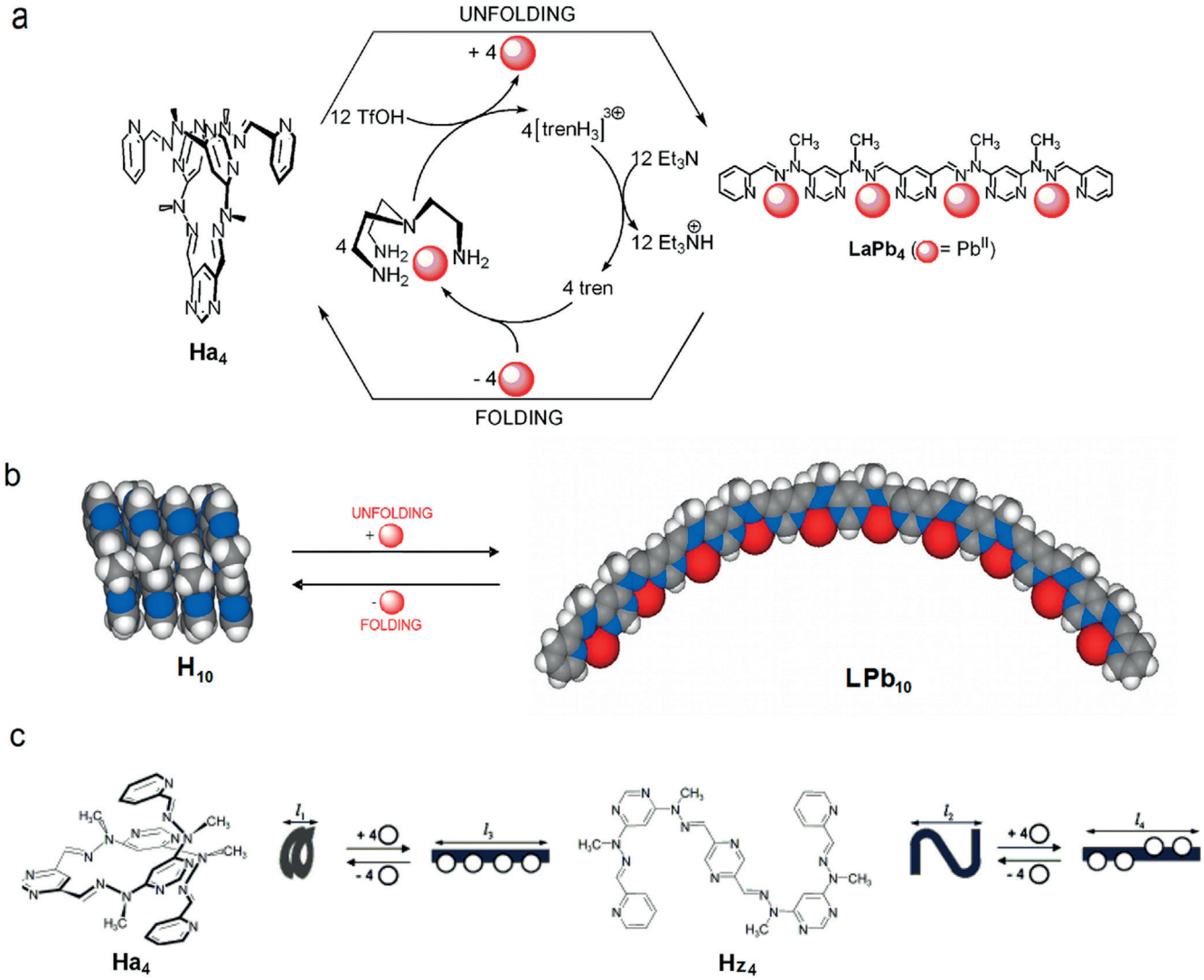


Figure 9. Reversible extension/contraction motions of hydrazone-based ligand strands. a) Acid-/base-fueled reversible extension/contraction motion generated by uncoiling/coiling of a helical molecular strand (**Ha_4**) on binding metal ions (Pb^{2+}). The process is triggered by the sequential sequestering and release of the metal ions by the competing ligand tren, induced by protonation/neutralization reactions; TfOH = CF_3SO_3H (reprinted from Ref. [35a] with permission). b) Reversible extension of the helical ligand **H_{10}** into the linear complex **HPb_{10}**[35a] (see Figure 2e). c) Control of the amplitude of the motion on cation coordination through the enforcement of the global shape of a molecular ligand strand (folded helix **Ha_4** versus undulating zigzag **Hz_4**) by selecting and combining appropriate heterocyclic units. Reprinted from Ref. [62] with permission.

4.4. Helical Ligand (H_n)⇔Grid-Like Complex (GM_m, $m = n^2$)

In addition to the one-dimensional (1D) type of motion discussed above, the uncoiling of helical ligands on binding metal ions can also undergo orthogonal motions when grid-type metallosupramolecular architectures, for example [2 × 2] or [4 × 4], are generated.[35–37] The formation of such grid-type architectures may be considered as producing two-dimensional (2D) molecular motion, as the molecular helices lead to linear strands stretched out in two perpendicular directions (Figure 10). One may surmise that it should be possible to induce sequential 2D contraction/extension motions through pH modulation of the reversible binding of the Pb^{2+} ions in a manner similar to that described above.

Both the py′-py-pym-py-py′[64] and py′-hyz-pym-hyz-py′ **Ha_2**[35] (Figure 5f) ligands containing two terpy-like sites form

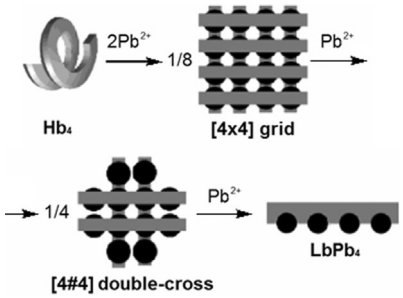


Figure 10. Conversion of the helical ligand **Hb_4** (for its extended representation, see Figure 5c) into the linear complex **$LbPb_4$** via the corresponding [4 × 4] grid-like complex **$GbPb_{16}$** and the [4#4] double-cross complex.[37] Adapted from Ref. [37].

tetranuclear [2×2] grid-like square complexes defined by four linear organic units held in an orthogonal orientation by octahedral coordination with four metal ions (molar ratio 1:1). The linear shape of the ligand with two sites in the grid is similar to that in the linear 1D complex.[35,64]

The four-site py′-(py-pym)-py-py′ helical ligand **Hb_4** leads, on binding of Pb^{2+} ions to the terpy-like subunits, to the self-assembly of three different polynuclear metallosupramolecular architectures of nanometric size containing the uncoiled coordinated form of the ligand.[37] The nature of the architecture depends on the Pb^{2+}/ligand molar ratio: 2:1→[4×4] grid, 3:1→[4#4] double-cross, 4:1→linear complex (Figure 10). The overall external dimensions of the [4×4] grid and of the [4#4] double-cross are 29 Å (ligand length) and 10.2 Å (height), while the total volumes are $V \approx 8.6\ nm^3$ and $6.9\ nm^3$, respectively. These geometrical features place these entities within the nanostructural domain.

Similarly, the helical ligand **Ha_4** with four sites slowly forms the hexadecanuclear [4×4] grid-type complex **$GaPb_{16}$** on addition of two equivalents of $Pb(OTf)_2$. This is indicated by the ^1H NMR spectrum, which displays signals for two different—internal and external—coordinated unfolded ligands.[35a]

The generation of molecular motions in two directions by ligand uncoiling on formation of grid-type and related structures confers to these systems the features of *two-dimensional nanomechanical dynamic devices.*

4.5. Contraction/Extension Motions of Linear Strands: Linear Ligand (L)⇄Helical Complex (HM_n).

The above principles of molecular extension/contraction motions based on the uncoiling of helical ligands by complexation of metal ions may be extended to the reverse process, that is, the coiling of linear strands around complexed metal cations. Indeed, considering the shape information encoded in six-membered aromatic N-heterocycles, a sequence of α-α′-connected (py-py) units enforces a linear shape into a polypyridine sequence. Similarly, (py-hyz) analogues also present a linear shape.[27] In particular, py′-hyz-py-hyz-py′[65] ligands give mononuclear pincer-like complexes.[66] Furthermore, the linear free ligand **L** yields a helical complex **HPb_2** by coiling around two Pb^{2+} ions. It allows for setting up a reversible motional process opposite to that described above, whereby a linear molecular strand undergoes reversible contraction/coiling and extension/uncoiling on binding and release of metal cations, respectively (Figure 11). The process may be made reversible by coupling to an external chemical effector, such as the ligand tren, and sequential acid/base treatment, following the principles presented before. It amounts to a two-stroke, linear-type motion with a very large amplitude (from 7 Å to 40 Å), fueled by the neutralization energy (Figure 11).[27]

4.6. Helical Ligand (H_n)⇄(DH_n) Double-Helical Complex

The coordination of a metal cation to each end of a helical ligand strand may bring two (or three) such strands together and thus generate a double- (or triple-) helical complex. In the process, the single helical ligand strands (ca. 3.6 Å) undergo partial uncoiling on formation of the double-helical complex (ca. 10.3 Å) with respect to the free ligands, nevertheless with a significant change in end-to-end distance, thus generating an extension/contraction motion[67] of pronounced amplitude (Figure 11a).

Such a double-helical dinuclear Ag^+ complex **DHb_4** (for the X-ray structure of complex **DHc_4**, see Figure 5e) is formed by reaction of ligand **Hb_4** with AgOTf (Figure 12a). Again, as discussed above, reversible interconversion of the single and double helix may be achieved by coupling with a competing cryptand that is capable of sequestering the Ag^+ ions and of releasing them on protonation (Figure 12b). Interconversions of the helical entity **Hb_4** and the double-helical complex **DHb_4** can be pursued in this way by

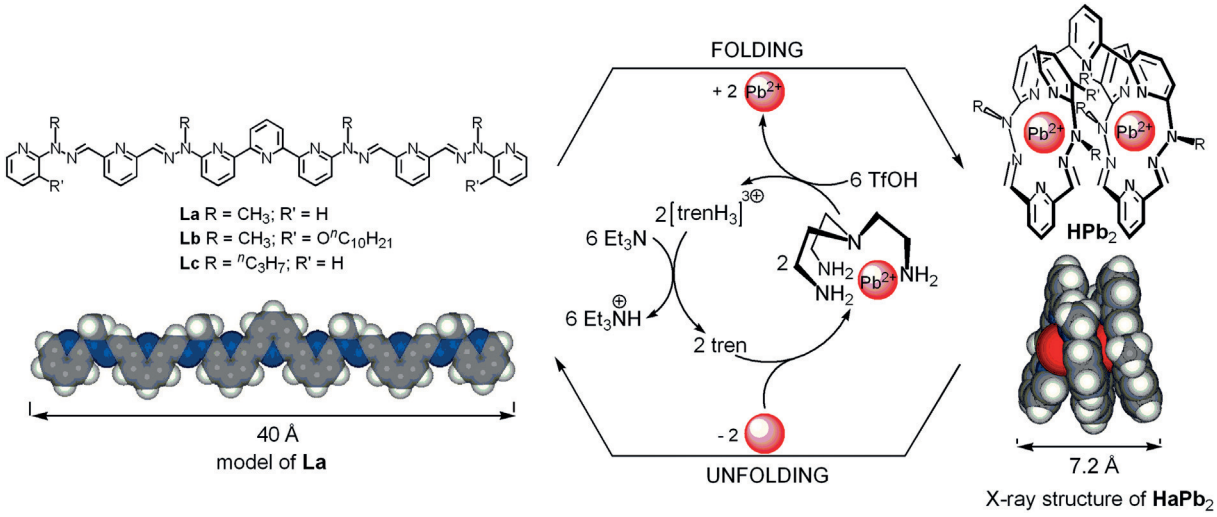


Figure 11. Acid-/base-fueled reversible coiling/uncoiling, contraction/extension motion of molecular strands triggered by sequential binding and release of Pb^{2+} ions induced by protonation/neutralization reactions; TfOH = CF_3SO_3H.[27] Reprinted from Ref. [27].

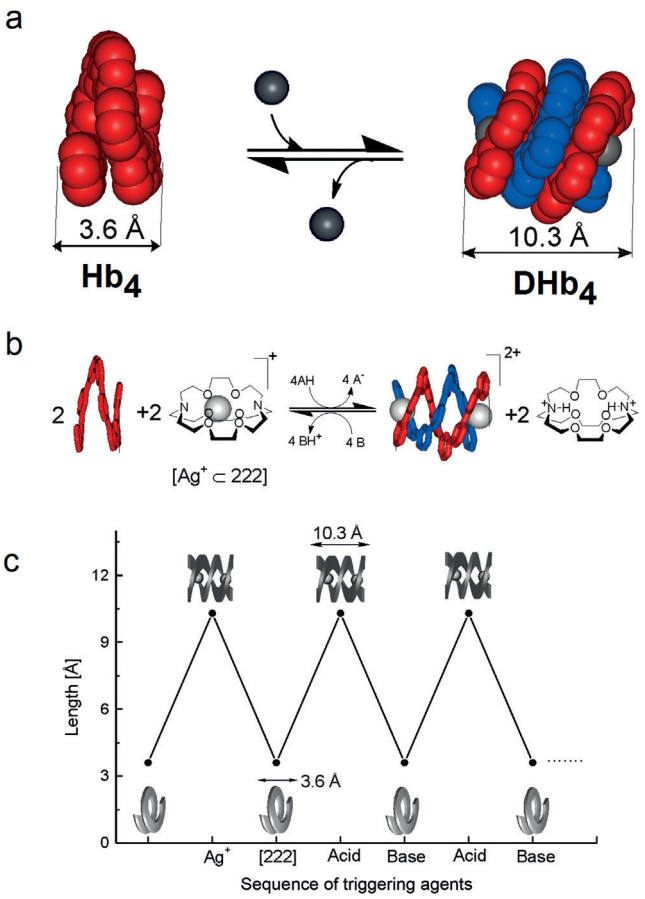


Figure 12. a) Reversible extension/contraction motion by interconversion of the py-pym helical ligand **Hb_4** and the double-helical complex **DHb_4**; b) modulation of coiling/uncoiling motions through sequential acid/base processes; c) ionomechanical cycles involving coupled ion-/pH-induced structural switching between the single/double helix **Hb_4**⇄**DHb_4** and generation of compression/extension nanomechanical motion. The gray spheress represent Ag^+ ions; AH = CF_3SO_3H, B = Et_3N. Reprinted from Ref. [38] with permission.

successive additions of acid and base, through the repetitive exchange of Ag^+ between the ligand **Hb_4** and the [2.2.2]cryptand (Figure 12 b,c).[38]

With ligand **Ha_2** (Figure 5 f), Ag^+ was found to bind preferentially to the terminal hyz-py units in a distorted tetrahedral fashion, thus conserving the general helical shape of the ligand and forming a double helix **DH_2** (for its X-ray structure, see Figure 5 f), as has been observed in the case of py-pym strands. Reversible interconversion between the free bent ligand **Ha_2** and the double-helical complex **DH_2** ($[Ag_2(\mathbf{Ha_2})_2](BF_4)_2$) may again be induced by addition of a competing tren ligand through an acid/base neutralization process.[39]

5. Shape Changes Induced by Interconversion of Different Metallosupramolecular Architectures

5.1. Metal Ion Modulated Interconversion between Two Metal Complexes: Bent "Pincer" Complex ($HcPb_1$)⇄Linear Complex ($LcPb_2$).[68]

The conversion[68] of a mononuclear pincer-like bent Pb^{2+} complex into the corresponding dinuclear stick-like Pb^{2+} complex represents a metal ion induced modulation of extension/contraction type motion between two metal complexes of different shapes. Such a process has been made possible by the introduction of a 4,6-disubstituted triazine (trz) binding group into the ligand py′-hyz-trz-hyz-py′ **Hc**, which, depending on the Pb^{2+}/ligand molar ratio, may act in a py mode (1:1→pincer-like helical complex **$HcPb_1$**) or in a pym mode (2:1→stick-like linear complex **$LcPb_2$**).

Reversible motion (Figure 13) may be generated by successive complexation/decomplexation steps with a competing ligand (tren in this case) and external stimuli (acid/base), in the manner presented above.

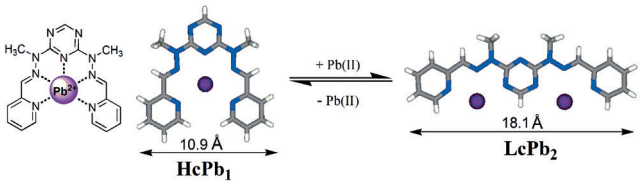


Figure 13. Distances in the molecular extension/contraction motions of pincer- and stick-like Pb^{2+} complexes of the ligand py′-hyz-trz-hyz-py′. In terms of amplitude, this conversion represents a variation of 7.2 Å (Figure 13). Adapted from Ref. [68].

5.2. Solvent-Modulated Interconversion between Two Complexes: [2×2] Grid⇄Pincer-Like Complex[69]

On coordination of Co^{2+} ions, the ligand **Hd** leads to two different complexes containing the coordinated ligand either in a linear (the grid complex) or in a bent, helical-type shape (Figure 14). Dissolution of crystals of the [2×2] grid **$GdCo_4$** in acetonitrile results in a slow partial conversion (ca. 25% after 11 days at 55°C) into the pincer **$HdCo_1$**, as observed by ^1H NMR spectroscopy. A reverse pincer-to-grid conversion (ca. 70% after 4 days at 70°C) was observed by dissolving crystals of the pincer in nitromethane. This type of solvent-dependent structural interconversion can be understood by

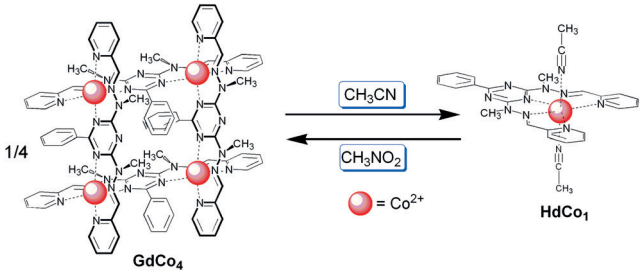


Figure 14. Solvent-modulated reversible conversion of the grid complex **$GdCo_4$** into the pincer-like complex **$HdCo_1$**. Adapted from Ref. [69].

taking into account the dual coordinative behavior of the ligand, modulated by the stronger coordinative aptitude of acetonitrile with respect to nitromethane. The formation of the grid takes place in a poorly coordinating solvent, thereby enforcing the coordination of Co^{2+} solely by the ligand and thus the assembly of the tetranuclear complex grid-type complex. On the other hand, the stronger coordination ability of acetonitrile molecules stabilizes a complex of the pincer form that allows for the binding of solvent molecules to the Co^{2+} center. An agent that coordinates more strongly to the Co^{2+} center than CH_3CN, such as propylamine, accelerates the grid to pincer conversion by facilitating the dissociation of the former and stabilizing the latter (Figure 14).

5.3. Double-Helicate/Grid Interconversion[70a]

The interconversion between different shapes of the same strand in a complex can also be performed by modification of the coordination features of the metal cations, for example by changes in the oxidation state (Figure 15). Thus, a bent

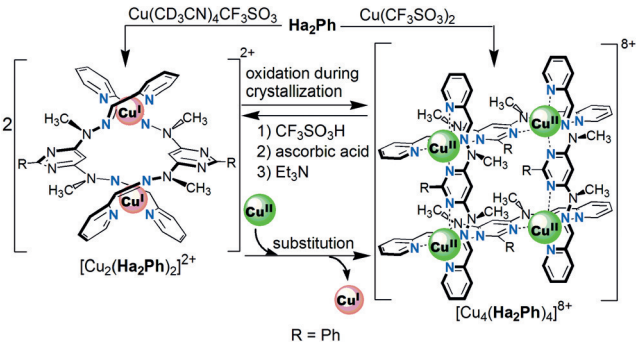


Figure 15. Interconversion between a Cu^{+} double helicate and a Cu^{2+} grid. Both complexes are generated by the same hydrazone-based ligand **Ha_2Ph**. Adapted from Ref. [70a].

bishydrazone ligand generates a double helicate[70a] with tetracoordinated Cu^{+}[70b] ions and a $[2\times2]$ grid-type structure on oxidation to Cu^{2+}. Correlatively, the centroid-to-centroid distance between the terminal pyridine rings of a ligand changes from about 8 Å to about 13.5 Å. The grid can be converted back into the double helicate by protonation of the ligand, reduction of Cu^{2+} with ascorbic, and neutralization.

As has been shown in the above examples, there are a number of ways to generate nanomechanical motions of various amplitudes following the approach typified by the unfolding/folding reversible processes. However, such processes may also be induced by constitutional variations that may result in unfolding/folding changes by incorporation/removal of subunits presenting other conformation-enforcing features, thus giving access to the formation of new ligands and to their complexes.

6. Coupled Molecular Motions in Hybrid Polyheterocyclic Ligand Strands[71]

A particularly intriguing type of molecular motion may be expected to result from the combination[72a,c–e] of alternating extension/contraction motions in different domains of the same molecule. Such processes have indeed been achieved in shape-hybrid polyheterocyclic strands generated by connection of a linear motif to a helical one, thereby resulting in a mixed ligand that possesses, in its free unmetalated form, an unfolded part (y in Figure 16) and a folded one ($x+z$ in

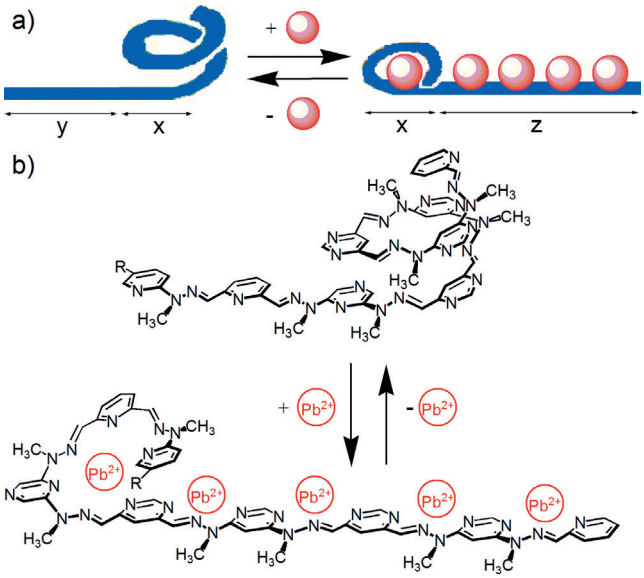


Figure 16. Coupled molecular motions generated by a hybrid ligand containing both a linear and a helical domain that undergo opposite motional processes on cation binding and removal: a) schematic representation; b) structural formulas. Adapted from Ref. [71].

Figure 16).[71] On reaction with metal cations, one expects the linear part to fold and the folded part to unfold. Such is the case on addition of $Pb(CF_3SO_3)_2$ to a hybrid ligand (Figure 16) followed by treatment with tren, which restores the initial shape of the helical and linear domains of the unmetalated heterocyclic ligand. Protonation[72b] of tren to $trenH_3^{3+}$ causes the release of the Pb^{2+} ions that bind again to the ligand and induce a new coupled motion. Finally, deprotonation of $trenH_3^{3+}$ by a competing base (Et_3N) yields tren that can again bind Pb^{2+} ions, thus regenerating the free ligand. The full process produces coupled molecular motion, where folding/unfolding and contraction/extension thus oscillate between the two domains of the full strand.

7. Network Representation of Effector-Induced Motional Processes

The connections between the members of a constitutional dynamic library can be represented in terms of a network that defines agonistic and antagonistic relationships between the constituents.[44b,54b] The effector-induced shape changes dis-

cussed here may also be arranged in the form of a square *motional dynamic network* that links the entities undergoing effector-induced shape interconversions. The motional dynamics described above operate under the action of metal ions (or possibly other effectors) and are modulated by protonation/deprotonation processes. The addition of metal ions to the ligand strand leads to complexation and produces the complex, thereby resulting in the first motional step. Subsequent addition of a competing ligand sequesters the cations and removes them from the complexed heterocyclic strand, thus restoring the initial ligand shape. Thereafter, the addition of acid leads to protonation of the competing ligand, thereby releasing the cations from their complex with the competitor so that they can again bind to the ligand, thus completing the cycle/network. The addition of each of the stimuli (acid and base[72b,f]) induces the adaptation of the system through a reorganization of the coordination and protonation/deprotonation states with a suitably chosen ligand and competitor. These interconversions can be represented by a square network in which the four vertices correspond to the free ligand, its complex, the complexed competing agent, and its protonated form, as represented in Figure 17 for the case of Pb^{2+} cations and tren as competing ligand. The vertices link antagonistic species and the diagonals connect the agonists[54b].

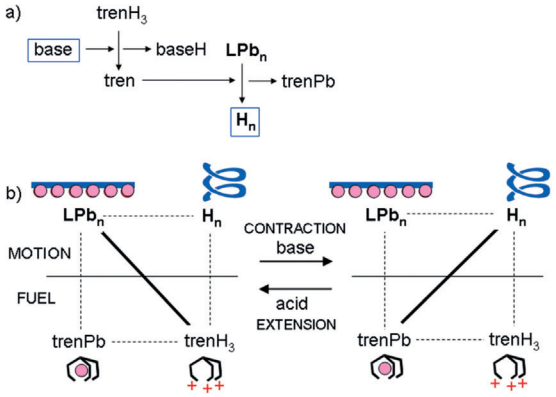


Figure 17. a) Representation of the motion-generating interconversions: Addition of base to a mixture containing the protonated form $trenH_3^{3+}$ of tren (stylized representation) produces tren ligand that sequesters Pb^{2+} ions from the **LPb$_n$** complex and generates the free ligand **H$_n$** (see also Figures 9 and 11). b) Representation of metal-induced stimuli-modulated motional dynamics in terms of a square motional dynamic network. Charges and stoichiometric coefficients are omitted for simplicity.

8. Shape Change of Polyheterocyclic Strands Induced by Constitutional Modification

Dynamic constitutional variations also lead to reversible motional-type processes through interconversion of constituents with different molecular shapes. Among the molecular ligand strands mentioned above, suitable candidates are ligands containing the hyz unit, as its C=N bond allows for reversible component exchange and rearrangement (Figure 18).[29,73]

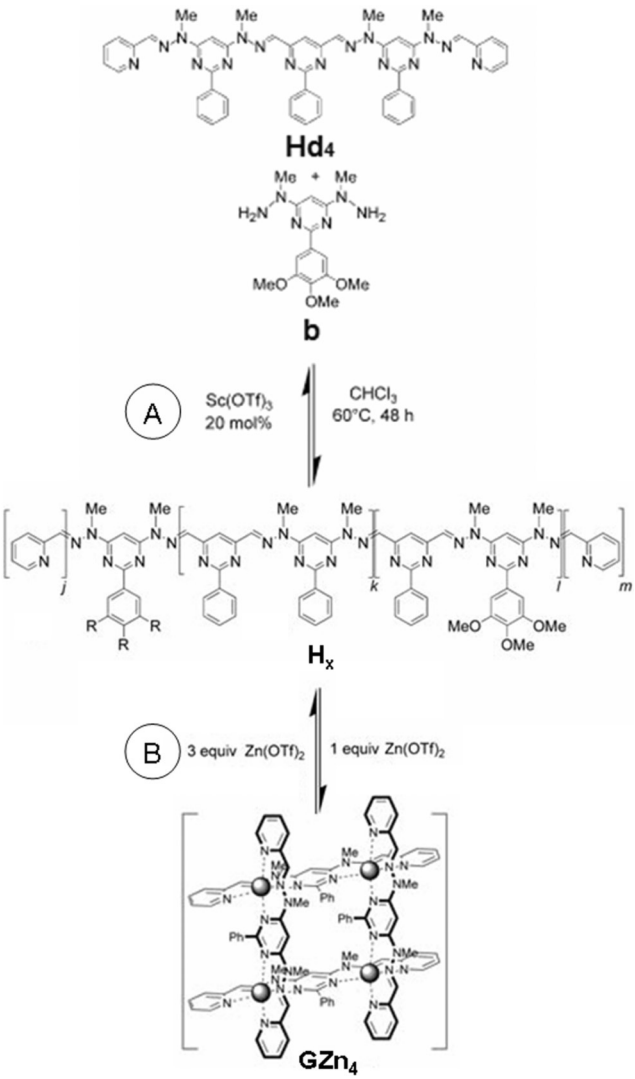


Figure 18. A) Generation of a highly diverse dynamic covalent library of helicity-encoded molecular strands by recombination between the helical compound **Hd$_4$** with four hyz groups and the dihydrazine **b** in $CDCl_3$. B) Evolution of the dynamic library of **H$_x$** constituents driven by coordination of metal cations: the addition of $Zn(OTf)_2$ leads to the amplification the ligand strand that allows for the generation of the [2×2] grid complex **GZn$_4$**. In the process, the helical entities uncoil to the linear form present in the complex.[29,73] Helical strands **Hd$_4$** and **H$_x$** are shown, for clarity, in their linear representation. Adapted from Ref. [29].

Thus, a one-turn helical strand containing four hydrazone groups **Hd$_4$** underwent exchange of its two bishydrazine components with the bishydrazine **b** under catalysis by $Sc(OTf)_3$ (Figure 18). This resulted in full recombination between **Hd$_4$** and **b**, with generation of a dynamic constitutional library of 28 compounds comprising expanded helices **H$_x$** of up to ten hydrazone sites (more than three helical turns). Treatment of this dynamic library with $Zn(OTf)_2$ under equilibrating conditions led to the amplification, enforced by coordination of metal ions, of that two-site ligand strand capable of forming the [2×2] grid-type complex **GZn$_4$** (as the major tetranuclear grid; Figure 18). The result

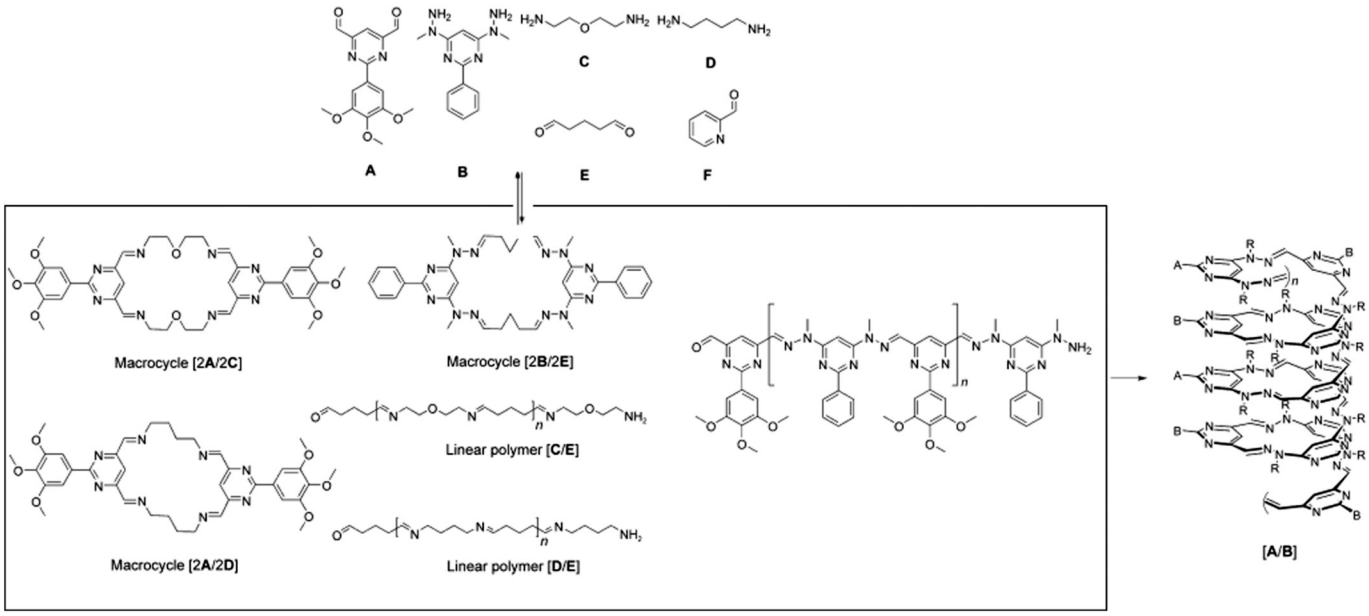


Figure 19. Dynamic imine and hydrazone library resulting from condensation of carbonyl- (A,E) and amino-containing (B,C,D) components with final amplification of the helical polymer [A/B] generated by polycondensation of pyrimidine dialdehyde A with pyrimidine bishydrazine B.[74] Lateral groups (R = Me, A = Ph, B = 3,4,5-$(MeO)_3C_6H_2$) are omitted for clarity (right). Reprinted from Ref. [74] with permission.

corresponds to an unfolding of the initial free helical strand into a linear ligand in the grid complex.

Conversely, the constitutional evolution of a dynamic covalent library of macrocyclic components into polyaromatic helical strands was achieved through three- and four-component exchange reactions. The generation of the extended helical strand in high yield may be attributed to the preferential formation of a compact structure through helical wrapping (Figure 19). In terms of the change in size, the process converts macrocyclic constituents into extended helical structures.[74]

9. Shape Generation and Proton-Induced Molecular Motions in Hydrogen Bonding Induced Helical Polyheterocyclic Strands

9.1. Hydrogen Bonding Induced Helical Polyheterocyclic Strands

Polyheterocyclic strands with folding codons based on hydrogen-bonding interactions have been designed for generating helically folded molecular strands. Among them, sequences of oligopyridine-carboxamides R-(CO-NH-py-NH-CO-py)$_x$-CO-NH-py-NH-CO-R, consisting of alternating dicarboxypyridine and diaminopyridine groups, have been synthesized and studied.[75] They present a helical shape, as confirmed by NMR spectroscopy and X-ray crystallography. Helically preorganized oligopyridine-dicarboxamide strands with five or seven (Figure 20) pyridine rings are furthermore found to undergo dimerization into double-helical supramolecular architectures. The various types of hydrogen-bonding-based foldamers developed in the past years have been extensively reviewed and will not be considered further here.[13] On the other hand, the combination of the heterocycle-based codons with hydrogen bonding allows for changes of the linear and helical shape of hybrid molecular strands by exchange between pyridine and pyrimidine groups.[75d]

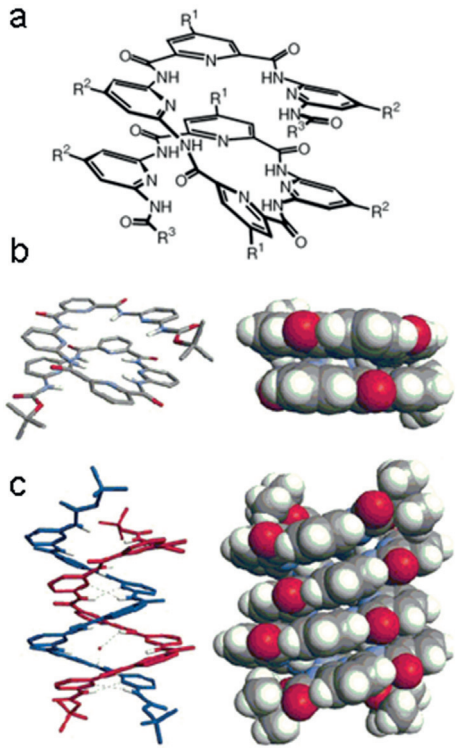


Figure 20. a) Folded helical structure of 7-py oligopyridine-carboxamides, R^1 = -$OC_{10}H_{21}$, R^2 = H, R^3 = -C_9H_{19}; b) crystal structure of the single helix **Hg_4** (reprinted from Ref. [75b] with permission); c) crystal structure of the double-helix dimer **$(Hg_4)_2$** (reprinted from Ref. [75c] with permission).

9.2. Interconversion between Two States of Hydrogen-Bonded Molecular Strands: Double Helix⇄Helix

Helically preorganized oligopyridine-dicarboxamide strands have been found to undergo dimerization with formation of supramolecular double-stranded helical entities.[75a–c] The process is illustrated for the dimerization of the helical strand **Hg_4** to give the double helix **$(Hg_4)_2$**, which consists of two intertwined monomeric strands (Figure 20). In terms of the amplitude of the motion induced by the interconversion of **Hg_4** and **$(Hg_4)_2$**, the end-to-end distance of the dimer is twice that of the monomer.

9.3. Proton-Modulated Molecular Motions: Helical Strand (H_n)⇄Protonated Linear Strand (LH_n)

The ionomechanical cycles described above rely on the complexation and release of metal cations to generate the motions resulting from the coiling/uncoiling of a molecular ligand strand through coupled ion/pH-induced structural switching. Considering a potential implementation of such types of motional processes in biosystems, it would be desirable to design systems that could be modulated directly by protonation/deprotonation steps, without intervention of metal cation complexes. Indeed, reversible folding/unfolding may be induced by protonation/deprotonation of pyridine-oligoamide molecular strands,[41a] which had previously shown to adopt a helical conformation both in solution and in the solid state.[75a–c]

The mechanochemical consequence of this pH-dependent switching on the molecular scale is the change in the length of the molecule, from 6 Å (coiled form **He_4**) to 29 Å (uncoiled **LHe_4^+**) for the heptamer **He_4** and from 12.5 Å to 57 Å (uncoiled **LHe_8^+**) for the pentadecamer **He_8** (Figure 21).[76]

10. Dynamic Switching Devices: Allosteric Changes, Functional Tweezers, and Zipper Systems

The design of functional chemical devices potentially enabling information storage is an important facet of supramolecular chemistry.[77] Photonic systems undergoing dynamic structural changes may be considered to encompass two types of behavior: a) *light-induced nanomechanical processes* of molecular or supramolecular systems that undergo reversible changes in shape triggered by light, thereby allowing the reversible modulation of a given property such as electronic conjugation and b) conversely, *effector-triggered structural* (constitutional or conformational) *switching of optical properties* of systems that transform chemical processes such as electron transfer or ion binding into specific molecular motions and result in modulation of optical output properties.

Of special interest are photo-ionic devices that undergo reversible ionic modulation of their optical properties, that is, modulation of their photochemical properties through shape changes induced by ion binding.[78] Such is the case for the ionic modulation of photoluminescence properties in a motional process involving the reversible switching between a highly luminescent ligand **L_{Pyr}** in a W-shaped state and its poorly luminescent metallosupramolecular U-shaped complex **L_{Pyr}TZn** (Figure 22 a).[78a]

The transformation of the W-shaped free ligand **L_{Pyr}** into the corresponding U-shaped form of the ligand in the complex **L_{Pyr}TZn**, triggered by ion complexation/decomplex-

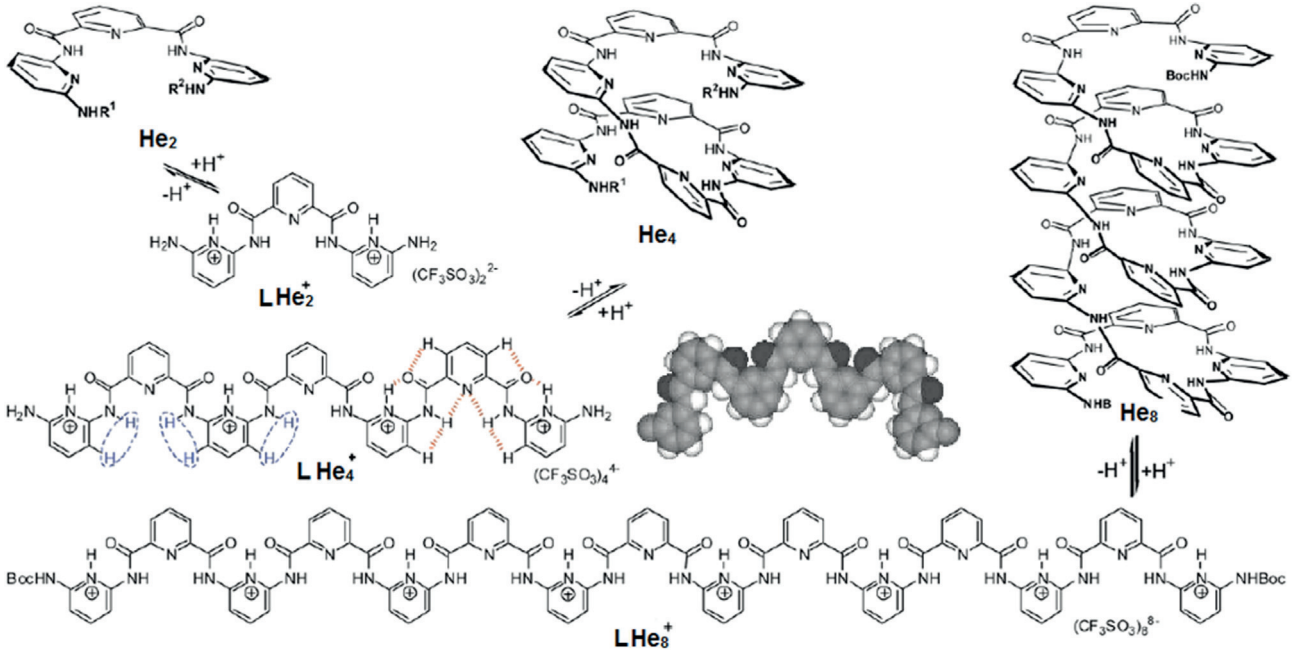


Figure 21. Reversible unfolding of oligoamides **He_2**, **He_4**, **He_8** to the corresponding extended forms **LHe_2^+**, **LHe_4^+**, **LHe_8^+** by protonation with triflic acid.[41a] The X-ray structure of the tetraprotonated ligand **LHe_4^+** is shown (triflate anions and solvent molecules are omitted for clarity). Adapted from Ref. [41a].

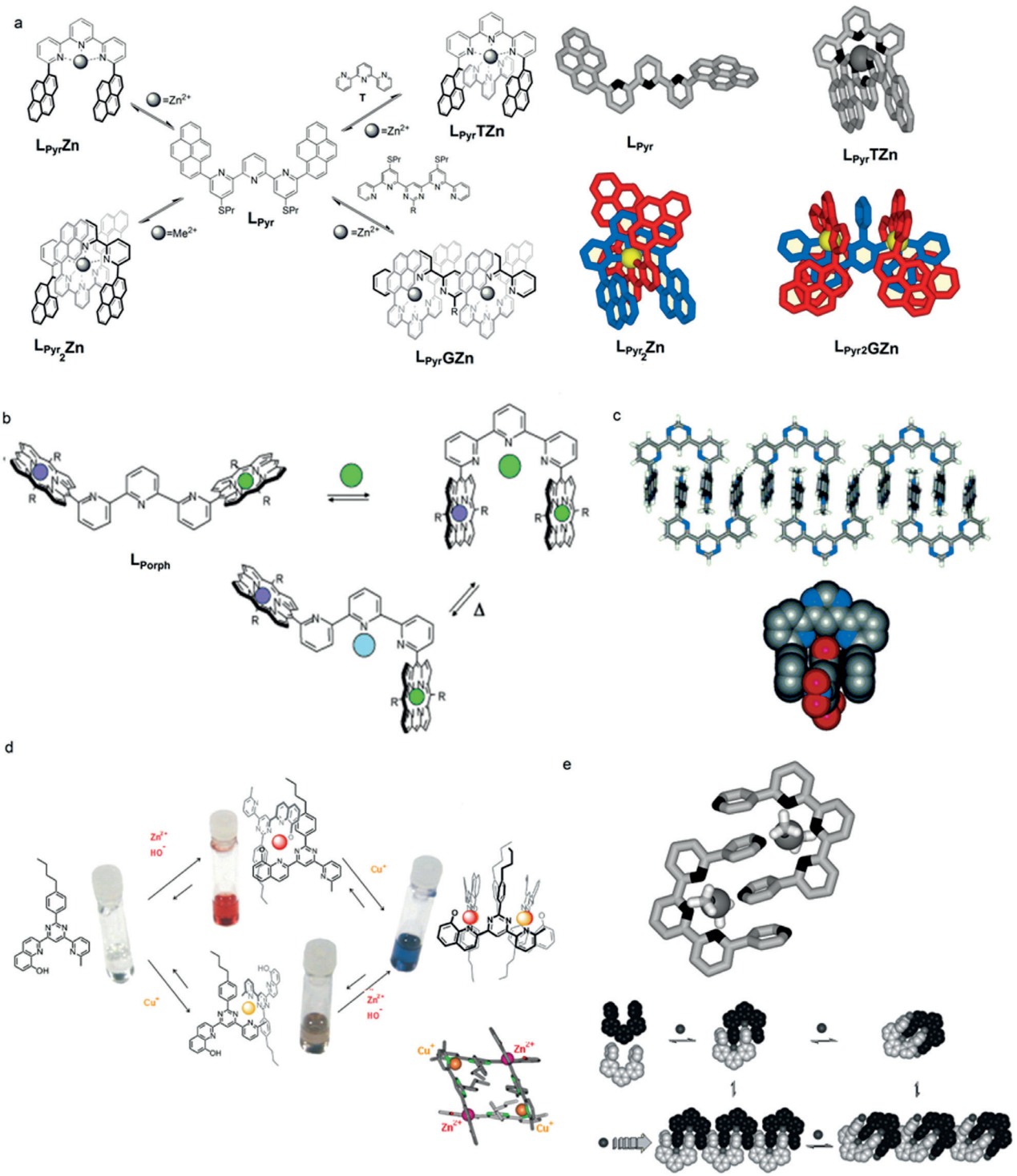


Figure 22. Dynamic chemical devices. a) Synthetic scheme for preparation of multicomponent dynamic devices. Crystal structure of the extended W form of the free ligand L_{Pyr}; crystal structure of the U-type complexes $L_{Pyr}TZn$ and $L_{Pyr2}Zn$ as well as the rack-type complex $L_{Pyr2}GZn$[78a,b] (reprinted from Ref. [78a,b] with permission). b) Representation of the three-stage molecular-shape-switching processes induced by binding of metal ions to the terpy(bisporphyrin) ligand, L_{Porph}, or by heating. The different colors mean that the porphyrin moieties exist either as free bases or are coordinated to different metal atoms, which can additionally be used as triggers to switch from the W to the U conformation. Ditopic ligands such as amines can also function as triggers, while heat can induce a reversible transformation to another species[78c] (reprinted from Ref. [78c] with permission). c) Molecular tweezers: self- and molecular recognition through shape switching of the receptor-induced metal coordination (reprinted from Ref. [79a] with permission; Copyright 2003 American Chemical Society). d) Regioselective coordination/ion binding in molecular tweezers (reprinted from Ref. [81] with permission). e) Side view in stick representation and one-dimensional self-organization of π-π-stacked metallosupramolecular zippers and their shape-switching induced by the coordination of metal ions[80] (reprinted from Ref. [80] with permission).

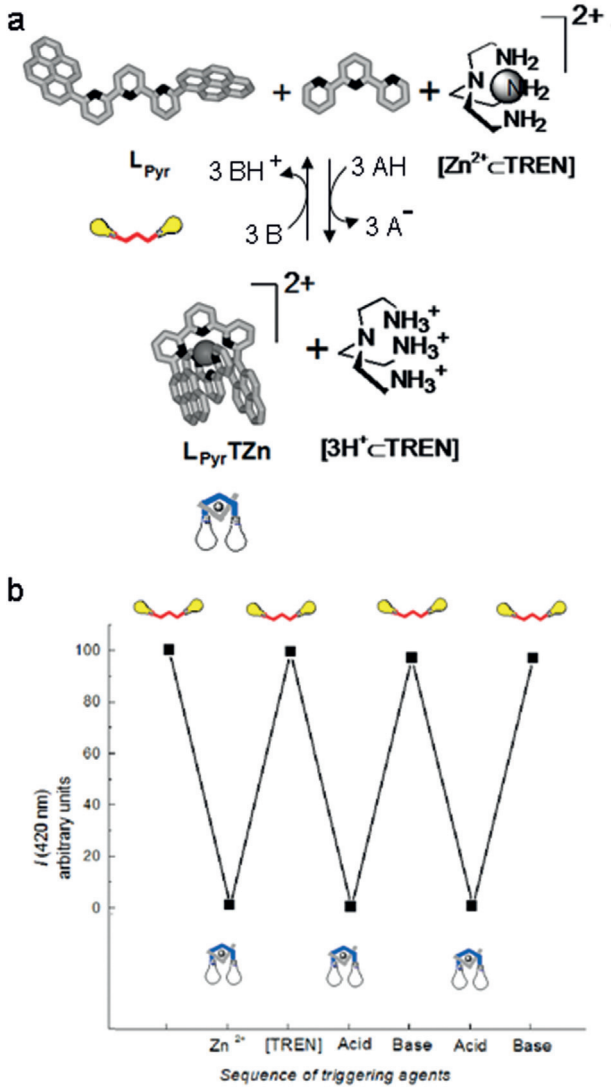


Figure 23. a) Ionic modulation of the coupled fluorescence and extension/contraction switching process of the system $\mathbf{L_{Pyr}}/\mathbf{L_{Pyr}TZn}$ on successive addition of different triggering agents; b) photoswitching cycles generated by ion-/pH-induced ionomechanical structural interconversion of the coupled fluorescence-extension/contraction processes. Reprinted from Ref. [78a] with permission.

ation reactions following the strategy described above, is depicted schematically in Figure 23. Since the overall centroid–centroid distance between the two pyrene moieties is about 16.5 Å in the W-shaped ligand $\mathbf{L_{Pyr}}$ and 6.90 Å in the U-shaped Zn^{2+} complex $\mathbf{L_{Pyr}TZn}$, the $\mathbf{L_{Pyr}}/\mathbf{L_{Pyr}TZn}$ interconversion generates a marked sequential extension/contraction motion between two states with different luminescence outputs in terms of both their energy and intensity. The modulation of the fluorescence and the extension/contraction structural switching processes (Figure 23) is again induced by coupling ion binding and protonation events and is fueled by acid/base neutralization reactions.[78a]

Moreover, the incorporation of multiple ligands that can adapt their geometrical features along a multivalent bridge in a donor–bridge–acceptor ligand scaffold presents attractive features. Indeed, the host–guest interactions between the vicinal multiple chromophoric sites may be mediated by the bridge, which can control the electronic coupling of the donor (D) and the acceptor (A) groups. These principles can be applied to the construction of multichromophoric rack-type complexes (Figure 22a).[78b] Furthermore, the W⇄U switching process can be doubly controlled through the binding of metal ions and of ditopic (diamine) substrates to the Zn^{2+}-porphyrin sites of the terpy(bisporphyrin) ligand, which strongly depends on the conformational state of the device (Figure 22b).[78c]

Metallomolecular tweezers[40b,79] or zipper systems[80] represent an attractive step toward adaptive devices in which the binding of a substrate is allosterically controlled through shape switching of the receptor induced by coordination of metal ions (Figure 22c[79a] and e[80]). Moreover, different conformational states and assembly levels can be controlled by regioselective coordination/ion binding (Figure 22d).[81] Other different molecular platforms have been used for the preparation of very selective sensing or catalyst systems.[82] Other more complex switchable resorcinarenes were synthesized which interconvert between vase (close) and kite (open) conformations with large amplitude expansion/contraction motions.[83]

Constitutional, morphological, and motional dynamics may be combined in a single system when the implementation of a morphological change triggered by a metal ion triggers in turn a reversible conversion between two different constitutional states through dynamic covalent processes.[84] Such processes will only be mentioned briefly here. They may, for example, be based on the ability to switch a tridentate terpyridine-type ligand molecule reversibly between an "extended" W-shaped state and a "compact" U-shaped state through the binding and removal of a metal ion (Figure 24). One such switch of a morphologically controlled system, which incorporates reversible covalent connections, has been shown to perform the interconversion between macrocycles and polymers.[84] In more general terms, this example shows

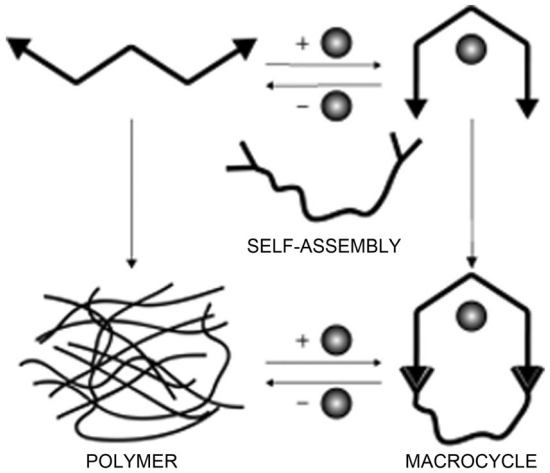


Figure 24. Principle of the switching process between a polymer and a metallomacrocycle on interconversion of a ligand component between W and U shapes through binding and removal of a metal ion in a dynamic covalent process.[84] Reprinted from Ref. [84] with permission.

that a constitutional dynamic system can be switched between two different constitutional states by a controlled modulation of morphological information.

11. Conclusions

The systems described here form a class of molecular entities, polyheterocyclic molecular strands, which may be designed, through the correct choice of structural subunits, so as to present a specific folded shape. They function as programed molecular actuators and display controlled motions, of the contraction/extension type, on undergoing interconversion between different folding states, induced principally by interaction with metal cations. As such, they are amenable to perform mechanical work in a periodic manner, undergoing ionomechanical cycles, fueled by acid/based neutralization, through coupling to a suitable ancillary ligand. Using rationally designed molecular components and straightforward chemical mechanisms, it is possible to control, through ion binding, ligand coiling/uncoiling processes, such as helix/chain and single-/double-helix transformations, as well as the reversible ionic modulation of the physical properties (photo-ionic devices). The coupling of ionically triggered changes of shape with the modification of physicochemical properties gives, in principal, access to molecular signalization processes involving interconversion between ionic and conformational signals reminiscent of biological signal transduction. These systems offer a range of motional devices that regulate well-defined changes in shape and size, which could be particularly attractive for inclusion into more complex functional devices that require exact control of the shape and amplitude changes. Moreover, the combined features—controlled generation and interconversion of molecular shapes, dynamic constitutional diversity, and potential addressability—make species and processes such as those presented here of interest for the development of a constitutional dynamic[28b,54] "self-fabrication" approach to nanoscience and nanotechnology, toward systems of increasing behavioral complexity. A further step toward processes of increasing complexity could involve ligands of different dimensionality or library diversification with ligands that undergo reversible structural interconversion through component exchange. It provides, in particular, an opening towards the implementation of adaptive features that respond to physical stimuli and/or chemical effectors on the way towards adaptive chemistry.[44b,53,54]

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