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Molecular Gears from Solution to Surfaces

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Dedicated to Professor Ben Feringa on the occasion of his 70th birthday.

Abstract

This review highlights the major efforts devoted to the development of molecular gears over the past forty years, from the pioneering covalent bis-triptycyl systems undergoing intramolecular correlated rotation in solution, to the most recent examples of gearing systems anchored on a surface, allowing for intermolecular transmission of mechanical power. Emphasis is laid on the different strategies devised progressively to control the architectures of molecular bevel and spur gears, as intramolecular systems in solution or intermolecular systems on surfaces, while aiming at increased efficiency, complexity and functionality.

Preprint

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1. Introduction

Molecular machines are ubiquitous in biological processes, where they perform specific tasks as a consequence of a stimulus, with a high level of control and efficiency.^[1] Over the last decades, tremendous progress in synthetic and supramolecular chemistry has opened the way for the emergence of artificial molecular machines, carefully designed to master motions at the molecular level. This flourishing field was recently recognized by the Nobel committee with the 2016 prize awarded to J.-P. Sauvage,^[2] Sir J. F. Stoddart^[3] and B. L. Feringa^[4] for their pioneering investigations on mechanically-interlocked molecules and overcrowded alkenes, respectively. A broad variety of molecular architectures programmed to perform work have been reported to date and investigated in solution^[5] or on surface.^[6] Some of them have been designed in a technomimetic^[7] way, i.e. taking macroscopic machines as an inspiration, such as molecular scissors,^[8] pumps,^[9] wheels,^[10] wheelbarrows,^[11] vehicles,^[6b-e,12] winches,^[13] elevators^[14] and robotic arms.^[15]

Integration of several such machines into nanoscale machineries is highly desirable as it would allow the emergence of complex functional devices, but this remains a challenging task since it requires the interconnection of individual molecular units.

At the macroscopic scale, transmission of mechanical power between distinct machine elements is performed, among others, by gear systems, which in particular allow a modulation of speed and torque by an appropriate choice of the meshed cogwheels. Macroscopic gears are classified according to two criteria: i) the relative (external or internal) contact between cogwheels and ii) the relative orientations of rotation axes. External gears undergo synchronized disrotatory motion of the meshed cogwheels, and within this category, spur gears display parallel rotation axes while bevel gears are defined by the presence of intersecting rotation axes (Figure 1).

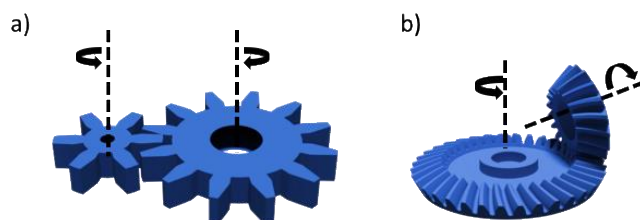


Figure 1. a) Structure of a macroscopic spur gear system with parallel rotation axes; b) Structure of a macroscopic bevel gear system with intersecting rotation axes.

Incidentally, micrometric gearing systems were recently found in nature, as part of the exoskeleton of the planthopper *Issus coleoptratus*, an insect recognized for its impressive jumps.^[16] Studies revealed that the function of such meshed cogwheels located on the insect's hind legs are to provide mechanical coupling leading to highly synchronized movements. In contrast, man-made decimeter-scale gears dedicated to the transfer of mechanical power were already available during the Hellenistic period, giving rise to highly sophisticated machineries as evidenced by the Antikythera Mechanism (150-100 BC) that was discovered in a shipwreck in 1901.^[17] Since ancient Greek times, numerous systems of increasing complexity have been engineered, exploiting gears as key elementary mechanical units. The size of cogwheels could be gradually reduced over the centuries as a consequence of technological progress and miniaturization could be pursued down to the nanometer scale using e-beam lithography to produce the smallest solid-state cogwheels reported to date, with a diameter of 70 nm.^[18] However,

this top-down strategy aiming at an ultimate miniaturization of cogwheels is now reaching its physical limits. As an alternative, technomimetic bottom-up approaches have been devised during the past 40 years to design and synthesize cogwheels at the molecular scale, and subsequently assemble them in a controlled manner into functional gearing systems.

This review aims at highlighting major progress in this field, from the pioneering work of Iwamura^[19] and Mislow^[20] on covalently linked triptycyl moieties undergoing intramolecular correlated rotation in solution, to the most recent examples of gearing systems anchored on a surface, allowing for the intermolecular transmission of mechanical power.

2. Intramolecular Gears in Solution

In the 70's, Oki investigated the rotation around single C(sp³)-C(sp³) bonds in overcrowded systems, such as bonds located at the bridgehead positions of triptycene moieties.^[21] In most cases, the energy barriers were high enough to isolate the different rotamers, thus revealing restricted rotary motion due to non-bonded interactions in these sterically-hindered structures. In contrast, unexpectedly low rotation barriers were also encountered in highly congested systems, where the correlated rotation of two sub-molecular units becomes the most energetically-favorable pathway, thus opening the way for the development of intramolecular gearing systems.

2.1. Bevel gears: from historical bis-triptycyl systems to switchable gears

The first systems involving meshed sub-molecular fragments and allowing for correlated motion were described by Iwamura in 1980.^[19] These pioneering examples of intramolecular gears consisted of two triptycene units, acting as cogwheels, arranged in an angular way around an oxygen atom or a methylene CH₂ group (Figure 2). In spite of the significant steric hindrance, as evidenced by the wide angles around the oxygen or carbon atoms, nearly unhindered rotation of both triptycene moieties down to -94°C was evidenced by Variable Temperature NMR spectroscopy. These results highlighted that the coupled rotation of two interlocked sub-molecular units in overcrowded systems may lead to conformational changes at very low energetic cost, by comparison with the independent rotation of a single subunit relative to the other.

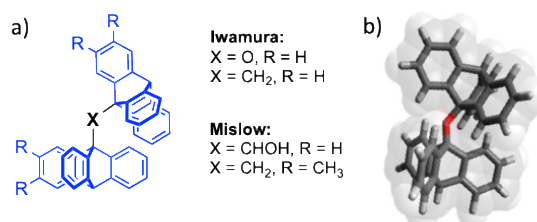


Figure 2. a) Molecular structure of the series of bis-triptycyl bevel gears initially reported by Iwamura and Mislow; b) X-ray crystal structure of bis(triptycyl)ether, with faded CPK model to highlight steric congestion and meshing of the triptycene cogwheels.

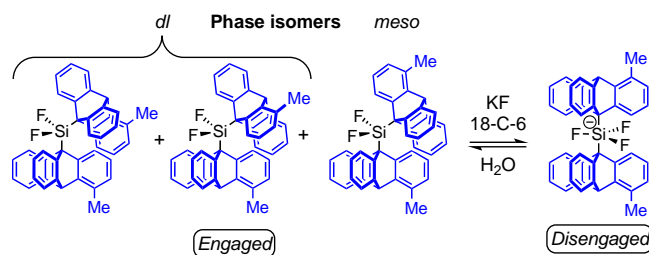
Correlated motion in such systems was further investigated by Mislow, who reported the same year an independent theoretical and experimental study on similar bis-triptycyl systems with CHOH or CH₂ as central fragments (Figure 2).^[20] Importantly, a single benzene ring in each triptycene moiety was substituted with methyl groups on the 2,3-positions, thus allowing for the discrimination of one tooth of each cogwheel. This labeling strategy was exploited to probe dynamic gearing in these early systems by use of stereochemical analysis, and such desymmetrization of cogwheels has been applied ever since to investigate correlated motion in a variety of intra- and intermolecular gear prototypes.

These pioneering works from Iwamura and Mislow unveiled the possibility of unhindered rotation in overcrowded molecular structures, thus opening the way for the development of numerous intermeshed systems undergoing intramolecular correlated motion in solution. In a technomimetic approach, various types of molecular gear-like architectures have been synthesized to mimic the different gearing arrangements used in macroscopic machinery, such as coaxial gearing systems^[22] and more frequently spur- and bevel-gears. In the latter cases, triptycene moieties have been extensively exploited as prototypical molecular cogwheels with intrinsic-*C*₃ symmetry.

In line with Iwamura and Mislow's preliminary reports, efforts have initially focused on molecular Trp₂X bevel gears, composed of two triptycyl (Trp) cogwheels connected via their bridgehead position to a variety of central linkers (X), such as single-atoms (NH,^[23] PH,^[24] SiH₂,^[25] GeH₂^[25]) or molecular fragments (ethylene^[26] or pyridine-2,6-dicarboxamide^[27]). The influence of the linker (affecting the angle between rotation axes and the Trp-Trp distance) and of the triptycene substitution pattern on the efficiency of the gearing process was investigated.^[28]

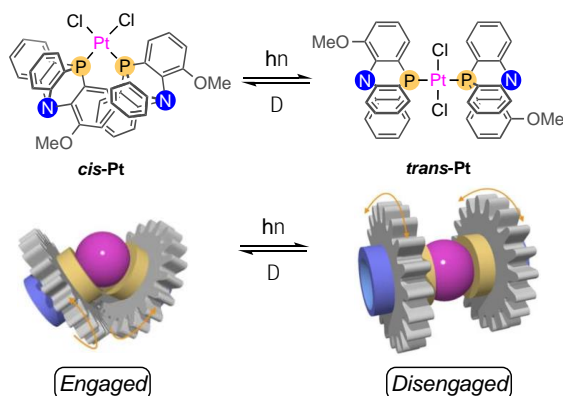
In the bevel gear systems involving a single atom as linker, a very low activation energy of 1-2 kcal.mol⁻¹ is required for coupled disrotatory motion of the triptycenes, whereas conrotatory motion leading to gear slippage occurs with a high energy barrier of 32-45 kcal.mol⁻¹.^[28] As a consequence, geared rotation in such bis-triptycenes is much more favorable than slippage, which can be quantified by *gearing fidelity*, defined as the average number of disrotatory geared rotations per conrotatory slipping rotations ($F_{\text{gear}} = k_{\text{gearing}} / k_{\text{slippage}}$).^[29] The large difference in activation energies between gearing vs slippage pathways leads to gearing fidelities at 298 K above 10²³ for these systems.^[30] These outstanding efficiencies can be explained by the difficulty required for the cogwheels to escape from their meshed configuration, which would require further enlargement of the wide angles between rotation axes.

Following these fundamental studies, major improvements in the functionality of such bis-triptycyl gearing systems were brought by possible stimuli-responsive variations of the angle between the rotation axes, *i.e.* by introducing clutch-declutch mechanisms in a technomimetic mindset. The first example of a switchable gearing system was reported in 2008 by Setaka, Kira *et al.*,^[31] with two meshed triptycene units connected to a central silicon difluoride linker (Scheme 1). The authors showed that addition of potassium fluoride in combination with 18-crown-6 efficiently induced fluorination of the silane linker to afford the corresponding penta-substituted silicate anion. This resulted in a change from a tetrahedral to a trigonal bipyramid geometry, with the triptycyl moieties located on both apical positions. Accordingly, the angle between Si-C rotation axes was increased to 178°, thus preventing correlated rotation of the triptycenes. This process could be reversed by addition of excess water, showing that this silicon-based bevel gear system can be selectively clutched or declutched under the action of an external chemical stimulus.



Scheme 1. Example of a chemical stimulus-responsive intramolecular bevel gear system, allowing for selective and reversible clutch-declutch mechanism via a geometry change at the central silicon atom. It must be noted both phase isomers (*dl* and *meso*) act as meshed molecular gears.

Other molecular systems featuring clutching mechanisms were developed later, taking advantage of different stimuli to achieve redox-, photo- or thermally-controlled gear coupling or uncoupling.^[32] In particular, a notable metallo-organic bevel gear based on a square planar platinum(II) complex was shown to undergo engagement or disengagement of the triptycene-derived cogwheels as a consequence of heating or photoirradiation, respectively (Scheme 2).^[33] In this very elegant example, Shionoya and collaborators present the design and synthesis of azaphosphatriptycene monodentate ligands with a methoxy group as a chemical tag on one benzene ring, allowing for coordination of transition metals through the phosphine moiety.



Scheme 2. Bis(azaphosphatriptycene)platinum(II) dichloride complex as an example of metallo-organic bevel gear system, undergoing reversible disengagement and engagement as a consequence of photo- and thermally-induced *cis-trans* isomerization. Adapted with permission from Ref. 33. Copyright 2017, Springer Nature.

This ligand was employed to synthesize the corresponding *cis*-bis(azaphosphatriptycene)platinum(II) dichloride complex, as a prototype of meshed bevel gear system displaying correlated rotation of both ligands. Irradiation of this square planar complex efficiently promoted *cis-trans* isomerization, resulting in a configuration where the two coordinated cogwheels stand opposite to each other and are thus disengaged. This light-induced declutch mechanism could be reversed through thermal equilibration back to the favored *cis*-complex.

Molecular bevel gears involving two triptycenes as cogwheels have been thoroughly investigated, with a striking evolution of their design to display very elegant switch function. In contrast, the development of intramolecular spur gears, with cogwheels meshed in a parallel arrangement, is still in its infancy.

2.2. Spur gears

The first example of a molecular structure displaying two triptycene units with parallel rotation axes was reported in 1999 by Bryan *et al.*^[34] Both triptycenes were incorporated symmetrically in crown ethers via their bridgehead positions, to yield bis(9,10-triptycyl)-26-crown-6 and bis(9,10-triptycyl)-32-crown-8 derivatives (Figure 3). Crystal structure analysis of both molecules demonstrated that the crown cavity is forced open by the bulky triptycene subunits, but to the best of our knowledge, correlated rotation was not confirmed due to the flexibility of the crown ether framework.

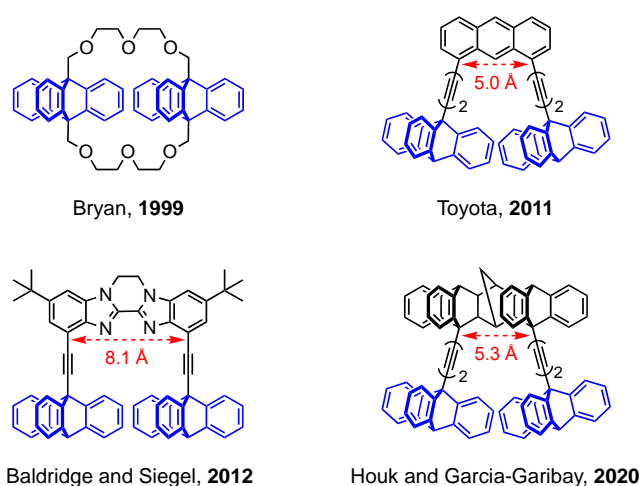


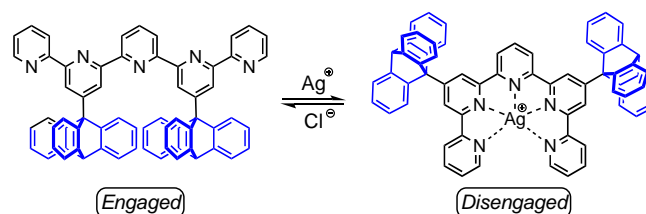
Figure 3. Structure of a macroscopic spur gear system and molecular structures of reported bis-triptycyl spur gears, incorporating a variety of stators.

Ten years later, in a perspective article, Siegel detailed the requirements for the development of bis-triptycyl spur gears in a technomimetic way, *i.e.* using a rigid stator capable of maintaining two triptycene cogwheels in a parallel alignment by means of tailored shafts.^[29] Importantly, in order for the cogwheels to be engaged, it is crucial that an entire benzene ring of one triptycene fits between two benzene rings of the neighboring triptycene, which is more challenging than in angular bis-triptycyl bevel gears. This highlights the utmost importance of the distance between parallel rotation axes in the design of intramolecular spur gears, as a compromise between attractive van der Waals interactions and excessive strain preventing rotation. While acetylene and bisacetylene fragments were constantly used as shafts, various designs of rigid stators were reported, with distances between the points of shaft attachment in the 5.0 - 8.1 Å range (Figure 3). Prototypes of spur gears with the shortest distance were reported by Toyota *et al.*, who exploited anthracene as stator,^[35] whereas a bis(benzimidazole) scaffold with a distance of 8.1 Å was selected by Siegel *et al.* based on computational models.^[30] In both cases, X-ray crystal structures reveal that the alkyne shafts are bent, respectively outward and inward, due to interactions between triptycenes.

Very recently, Houk and Garcia-Garibay focused on norbornane-fused dibenzobarrelene as stator since this structure mimics the fusion of two triptycenes and may thus provide suitable inter-cogwheel distance.^[36] However, none of these prototypes exhibited a strong preference for geared rotation over gear slippage, and in most cases, geared rotation could not be clearly evidenced by Variable Temperature NMR experiments.

2D metadynamics simulations were thus performed to establish the energy landscape for the rotational motion of both cogwheels, and energy barriers for gear slippage *vs* geared rotation were obtained by these potential mean force calculations. Interestingly, this theoretical study showed that gearing is favoured over slippage in the case of the bis(benzimidazole) spur gear reported by Siegel, since the activation barrier for slippage is higher (3.5 kcal.mol⁻¹) than for gearing (2.4 kcal.mol⁻¹). However, at room temperature, both gearing and slippage are expected to occur very rapidly, which strongly limits the functionality of such gear. Finally, for both prototypes with shorter inter-axes distances, barrier to slippage is lower than that to gearing, leading to a higher preference for slippage. To date, no example of a spur gear has been shown to exhibit high gearing fidelity, thus underlining the difficulties associated with the design of such systems, which appears much more challenging than for bevel gears.

A stimuli-responsive clutch-declutch mechanism was explored for spur gears with two triptycene cogwheels covalently linked to the second and fourth pyridine groups of a switchable quinquepyridine stator (Scheme 3).^[37] In the absence of a metal ion, the foldamer adopts a linear conformation, due to electronic repulsion between adjacent pyridyl moieties, which results in the engagement of both triptycenes. Upon addition of silver cations, the formation of a mononuclear silver complex leads to a large-amplitude conformational change which brings the triptycyl units to lateral positions, in a disengaged state. Addition of chloride anions induces decomplexation, and the quinquepyridine stator recovers its linear conformation associated with meshed cogwheels, thus demonstrating the reversibility of the switch function.



Scheme 3. Example of a chemical stimulus-responsive intramolecular spur gear system, allowing for a selective and reversible clutch-declutch mechanism via a conformational change resulting from silver complexation.

The intramolecular gear systems described in the first parts of this review all involve triptycene derivatives as cogwheels, owing to their bulkiness, rigidity, rather straightforward synthesis and highly symmetrical shape reminiscent of macroscopic paddlewheels. However, it is important to note that such prototypical scaffolds with three-fold symmetry are not ideal technomimetic candidates, since macroscopic three-toothed solid gears are not well-suited for correlated motion. Moving away from the seminal bis-triptycyl architectures, efforts have been devoted to the development of intramolecular gearing systems displaying increased complexity, with i) various cogwheel structures and higher teeth numbers, ii) higher numbers of meshed cogwheels, and iii) gearing ratios different from the 1:1 ratio obtained with two identical cogwheels.

2.3. Increasing the complexity of gearing systems

Apart from triptycene derivatives, a few examples of scaffolds used as cogwheels in intramolecular functional gears have been reported in the literature, such as the four-toothed pentiptycenes,^[38] tetraphenylcyclobutadienes,^[39] and porphyrins.^[40]

To achieve a propagation of rotation over longer distances, an organized and robust arrangement of more than two cogwheels has to be set up, allowing for tight control over the relative distances and orientations between cogwheels. Diverse strategies have thus been explored to increase the number of cogwheels, based either on covalent or coordination frameworks.

2.3.1. Correlated motion in intermeshed covalent frameworks

An early example of linearly arranged triptycyl trimers, with oxygen atoms as linkers, was reported in 1986 by Iwamura.^[41] This extended bevel gear system indeed underwent disrotatory correlated motion, but further increments of cogwheel number in such linear architecture were not attempted. Another strategy towards increased numbers of simultaneously meshed gears was the design of macrocyclic frameworks incorporating three to six triptycene units connected by both bridgehead positions.^[42] Such macrocyclic structures were mostly synthesized through successive cross-coupling reactions with bis(ethynyl)triptycene as precursors, leading to a variety of shapes as a function of coupling partners. An example of triangular macrocycle with six cogwheels operating as three independent pairs of bevel gears is depicted in Figure 4. Despite being very elegant, these systems display weak meshing because of their inherent flexibility.

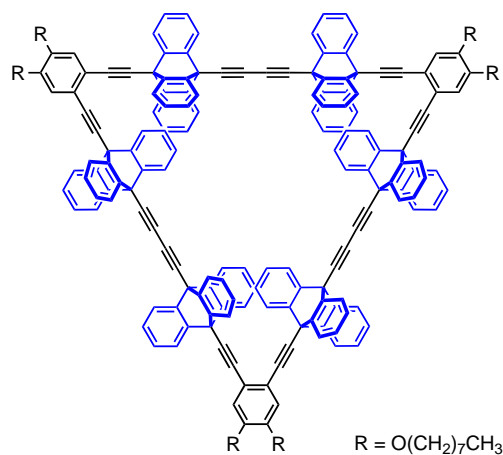


Figure 4. Covalent macrocyclic framework incorporating three pairs of engaged triptycene units in a constraint triangular configuration.

As an alternative, six mutually intermeshed triptycene moieties were circularly arranged around a central benzene core via ethynyl linkers (Figure 5).^[43] This very hindered hexasubstituted benzene derivative was synthesized through a cobalt-catalyzed cyclotrimerization of triyne precursors, carrying two triptycenes at their extremities. X-ray diffraction analysis of the product revealed a strong structural engagement of the six triptycenes, involving pi-pi stacking between lateral benzene rings of neighboring cogwheels, and coupled rotation was evidenced by Variable Temperature ¹H NMR spectroscopy.

Interestingly, in this study an unusual way to hinder the correlated motion of the six triptycene fragments was achieved by addition of a $[\text{RuCp}^*(\text{NCMe})_3]\text{PF}_6$ complex, leading to the coordination of RuCp^* to one of the triptycenes' aromatic rings. As a result, the whole motion within the molecule was significantly restricted, and the RuCp^* fragment can thus be considered as a chemical shim. The corresponding ruthenium complex appeared to be very stable and robust and could be isolated by chromatography before characterization. This shimming process is thus irreversible, not allowing for a stimuli-responsive reversible control of correlated motion.

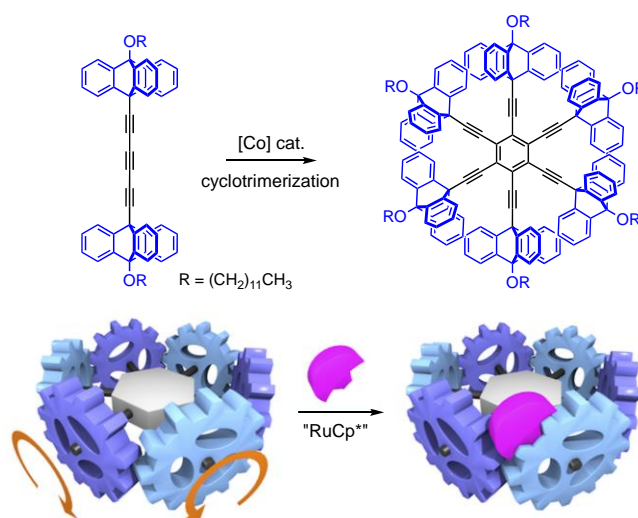


Figure 5. Synthesis of a circularly arranged sextuple triptycene gear molecule (top) and its rotation control by coordination of an organometallic shim (RuCp^*) (bottom). Adapted with permission from Ref. 43. Copyright 2017, American Chemical Society.

Beside covalent frameworks, another strategy towards intramolecular gears with increased complexity relies on coordination frameworks, with weaker bonds acting as shafts for the cogwheels composing the mechanical system. The combination of a wide variety of metallic centers and ligands allows for more synthetic modularity and leads to a broader range of accessible architectures, thanks to the variety of coordination modes.

2.3.2. Correlated motion in intermeshed coordination frameworks

A second notable example of circularly arranged multiple gear system was reported by Shionoya *et al.*, consisting of a lantern-type dirhodium complex surrounded by four hexamethyltriptycene carboxylate ligands acting as meshed gears (Figure 6a).^[44] In this complex, two additional ligands such as diethyl ether or pyridine derivatives, located on axial positions, were successfully exploited as control units to modulate the rate of correlated rotation, based on their steric hindrance.^[45]

The versatility of coordination chemistry was also exploited to access new cogwheel structures, thus opening the way for the implementation of gearing ratios, which is a key function in macroscopic gears. In 1997, Stevens and Richards reported the design and synthesis of a cobalt-based metallocene complex, involving a tetraphenylcyclobutadienyl ligand meshed with a lateral triptycene unit (Figure 6b).^[39] In

this organometallic gearing system, correlated motion thus occurs between four- and three-toothed wheels, as one of the rare examples of gearing ratio at the molecular scale.

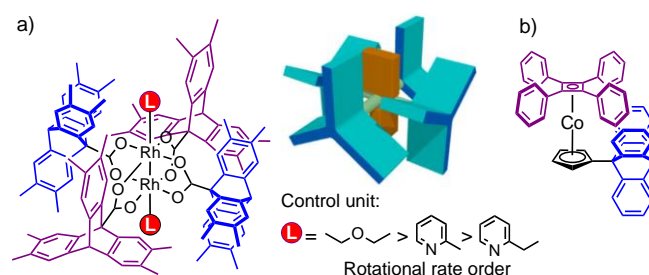


Figure 6. Examples of bevel gears incorporated in coordination frameworks. Adapted with permission from Ref. 44. Copyright 2016, American Chemical Society.

Finally, Shinkai, Takeuchi *et al.* synthesized an impressive multi-porphyrinic architecture with different porphyrin sub-units used as suitable central cores for cogwheels, owing i) to their coordination ability to a wide variety of metal centers and ii) to multiple possibilities of functionalization on their outer rim. The central metal thus acts as a connector to the gear shaft, which is an apical ligand, while peripheral substituents, in particular located on *meso* positions, act as the teeth. This modular platform was exploited in different prototypes of structurally complex molecular bevel gears displaying correlated motion of four-toothed cogwheels.^[40] One of these systems, which displays three intermeshed porphyrinic cogwheels, is depicted in Figure 7.^[40a] The central bis(porphyrinate)lanthanum heteroleptic double decker incorporates one of the cogwheels, with the lanthanum atom acting as rotation axis, and the lower deck is further *trans*-functionalized with two lateral rhodium porphyrins via pyridyl units as shafts.

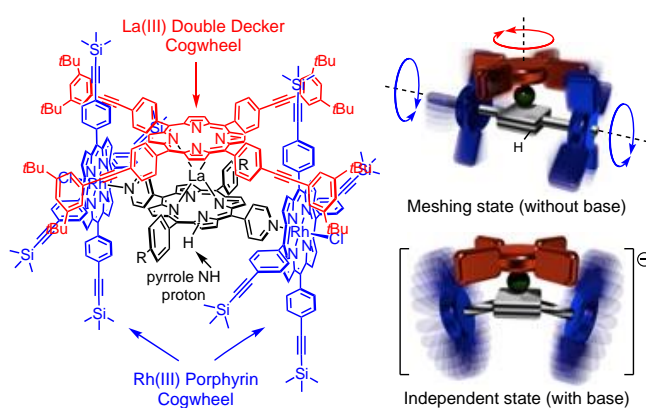


Figure 7. Molecular structure (left) of a porphyrin-based bevel gear. Two porphyrinorhodium(III)-based cogwheels (blue) are connected to pyridyl groups at the *meso* position of the porphyrin in the La(III) double decker unit. The rotational motion of the La(III) double decker cogwheel (red) was decreased by adding a base, while the rotation rate of both rhodium(III) cogwheels was dramatically increased, thanks to the conformational change from the uncoordinated pyrrole NH group to a deprotonated N^- group. Consequently, the bevel-gear-shaped rotor was converted from a meshing state to an independent state. Adapted with permission from Ref. 40b. Copyright 2011, Wiley-VCH.

Intrinsically, both rhodium porphyrins (in blue) have a higher rotation rate than the lanthanum double decker, but it has been shown that the rotation rate of the lateral rhodium cogwheels within this complex was decreased due to meshing interactions with the central porphyrin. In addition, the authors nicely showed that it is possible to disengage the cogwheels by basic treatment. Indeed, addition of triethylamine resulted in a dramatic increase in the rotation rate of lateral porphyrins, following a conformational change of the lanthanum double-decker triggered by the deprotonation of the uncoordinated pyrrole core. This disengagement is reversed through addition of trifluoroacetic acid, thus leading to a chemically controlled clutch-declutch system.

Multiple strategies to enhance complexity in molecular gearing systems, and in particular to increase the number of intermeshed cogwheels, have been envisioned but remain limited to intramolecular rigid structures, dictating the relative distance and orientation of cogwheels. Due to the continuous random motion of molecules in solution, it is indeed not conceivable to design intermolecular gears in such medium, which is a strong limitation for the development of multi-component nanomachineries. Moreover, the macroscopic picture of one cogwheel actuating the next one, *i.e.* of the transmission of mechanical power, is not relevant in solution as both cogwheels undergo thermally-induced random oscillations, which are harnessed in disrotatory coupled rotations due to mechanical engagement.

To propagate rotation over longer distances, new strategies were envisioned to control the orientation of molecules and their relative distances, including the preparation of 3D-frameworks such as amphidynamic crystals (Figure 8). Such very promising structures, which allow for a compromise between molecular order and molecular motion with liquid-like dynamics, have been reviewed recently.^[46] As a complementary strategy towards long distance propagation of motion, the confinement of gearing systems in two dimensions has been envisioned, with the possibility to probe mechanical behaviors down to the single-molecule scale thanks to Scanning Probe Microscopy techniques.

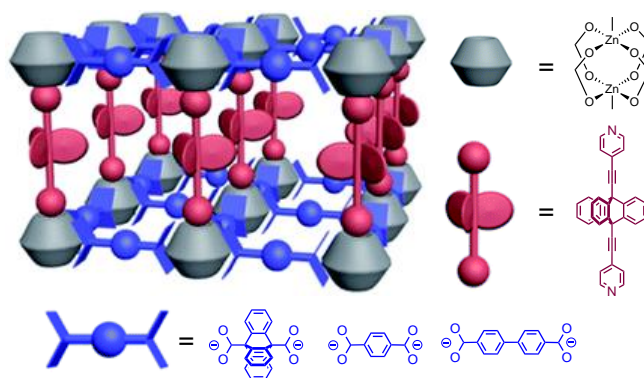


Figure 8. Structure of amphidynamic crystals composed of spacer (in blue: dicarboxylates such as terephthalate, biphenyl-4,4'-dicarboxylate, and triptycene-9,10-dicarboxylate), metal cluster (in grey) and rotor units featuring meshed triptycene cogwheels. Reproduced/Adapted with permission from Ref. 46. Copyright 2020, Royal Society of Chemistry.

3. Intermolecular Gears on Surfaces

Adsorption of molecular cogwheels on a surface offers a key asset to promote intermolecular gearing since the relative orientation of independent molecules can be controlled, which has prompted the development of spur gears. As in intramolecular systems, a crucial prerequisite for correlated motion is an appropriate and constant distance between the cogwheels, thus implying that molecular diffusion must be prevented. Preliminary studies on intermolecular gearing have been performed at low temperature (77 K or 5 K), taking advantage of Scanning Tunneling Microscopy (STM) under Ultra-High Vacuum (UHV) to monitor motion with sub-molecular resolution. Since STM is not time-resolved, rotation of single-molecule cogwheels is evidenced by comparison of successive images, which usually requires the presence of a steric or chemical tag in the molecular structure. In addition to imaging capabilities, the tip of a STM can also be used for the mechanical actuation of single molecules, leading to their translation or rotation. Therefore, starting from motionless cogwheels organized in a train of gears at low temperature (5 K), it can be envisioned to induce the rotation of the first cogwheel by mechanical actuation with the STM tip and observe the transmission of mechanical power from one molecule to the next through disrotatory correlated motion. However, before focusing on single molecules, the first studies of gearing systems on surfaces were achieved in self-assemblies of cogwheels.

3.1. Self-assembled gearing devices on surface

Already back in 1998, Gimzewski *et al.* investigated by STM the behavior of propeller-shaped hexa-*tert*-butyldecacyclene molecules on a Cu(111) surface under UHV.^[47] At monolayer coverage, a self-assembled 2D network of immobile molecules was observed, whereas a coverage slightly below one complete monolayer allowed for the thermally-driven rotation of some single-molecule propellers within the bearing formed by the surrounding molecules. This pioneering work about (non-directional) molecular rotors on surfaces raised key questions about the mechanics of surface adsorbed molecular systems.

The very first example of intermolecular gearing was reported in 2007 in a molecular rack-and-pinion device exploiting penta(*p-tert*-butylphenyl)-(*p-tert*-butylpyrimido)benzene as six-pointed star-shaped molecule.^[48] The self-assembled monolayer obtained on Cu(111) at low temperature acts here as the rack, displaying indentations on its border. The STM lateral manipulation of a single molecule along the edge of this molecular island, with the STM tip precisely located above the central benzene ring, results in a rotation of the molecule in addition to the STM-induced translation. This rotary motion was evidenced by comparison of successive STM images following the relative positions of the heteroaromatic pyrimidine tooth behaving as a chemical tag. The concept is illustrated in Figure 9.

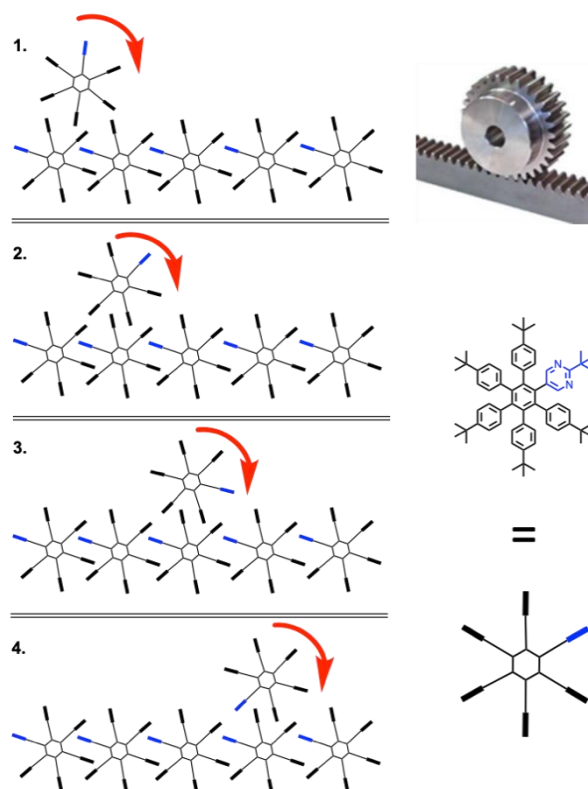


Figure 9. Different steps 1 to 4 of the geared rotation of a single molecular pinion along the edge of the rack of a self-assembled monolayer of the same molecules. A macroscopic rack-and-pinion (top right) and the chemical structure of the cogwheels (middle right). The pyrimidine chemical tag of the moved cogwheel is indicated in blue.

The rotation results from the interlocking between the *tert*-butyl groups of the self-assembled rack and those of the single molecule, thus acting as a pinion. It is important to note that in this experiment, diffusion of molecular species is prevented since i) the rack stands as a self-assembled monolayer and ii) the pinion is trapped under the STM tip, which provides a rotation axis.

Following this first example of an external gearing system built on a surface, further studies were performed at the single-molecule scale to achieve the transfer of mechanical power from one molecule to the next one via synchronized disrotatory motion. As shown in this rack-and-pinion system, adsorption of custom-made molecules on a surface allows for a homogeneous orientation of rotation axes over the population of molecular gear prototypes. The critical point to build trains of molecular gears stands now in the anchoring of individual cogwheels. Indeed, all attempts using pairs of the above-mentioned molecules in close contact failed to transfer rotation from one molecule to the next, due to the favored diffusion of the second molecule over its desired rotation.

3.2. Anchoring of single-molecule cogwheels on surface to build trains of gears

3.2.1. Single metal atoms as rotation axes

Following the seminal work on the rack-and-pinion device, the same hexa(aryl)benzene cogwheel prototype, incorporating a pyrimidyl chemical tag, was studied at the single-molecule scale on a Au(111)

surface.^[49] Even at low-temperature (5 K), such molecules displayed high mobility on Au(111), but it was demonstrated that an atomic scale impurity located at the elbow of the herringbone reconstruction can efficiently act as a stable pinning center. Indeed, once mounted and centered on top of this defect via STM lateral manipulation, the molecule underwent stepwise concentric rotations upon mechanical actuation by the STM tip. While the random distribution of atomic scale impurities hampers their use to build trains of anchored molecular cogwheels, this pioneering concept was recently extended to the use of single metal atoms as pinning centers. On a Pb(111) surface at 5 K, single Cu atoms were successfully exploited as fixed rotation axes for the same hexa(aryl)benzene cogwheel prototype.^[50] First, the six-pointed molecule is translated towards a single Cu atom by STM lateral manipulation and centered on top of it, owing to privileged interactions between copper and the central benzene ring (Figure 10). Then, a second molecule is approached and entangled with the first one. Importantly, this second molecule is not mounted on a Cu single atom, as it acts as a handle to stabilize the cogwheel and drive its controlled and concentric rotation. Finally, another cogwheel centered on top a Cu single atom is approached by STM lateral manipulation to build a molecular gear system, involving two cogwheels with Cu shafts and one additional handle for the driver molecule. The distance between Cu rotation axes was carefully optimized as it should be i) small enough to allow meshing of the cogwheels, leading to transmission of rotation by repulsive interactions between the teeth, but ii) large enough to avoid attraction between cogwheels, which would generate a stable supramolecular dimer unable to undergo correlated motion. With an optimal Cu-Cu distance of 1.9 nm, a functional gear system was built and the rotation of the driver molecule (induced by STM mechanical manipulation of the handle) was successfully transmitted to the second molecular cogwheel.

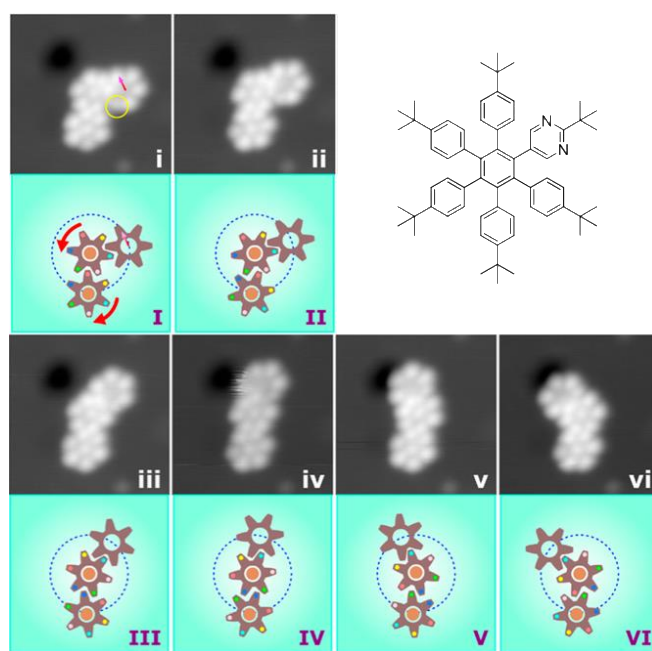


Figure 10. Structure of the molecular cogwheel (top right) and STM images showing the disrotatory correlated motion of two cogwheels anchored on single Cu atoms, when actuated via a molecular handle. Adapted from Ref. 50 with permission from the ACS, Copyright 2019.

In an attempt to increase the size of this gear system, the diameter of the cogwheels was extended by inserting an additional phenyl moiety in each tooth.^[51] The same set-up involving two cogwheels

mounted each on a Cu atom and an additional handle molecule was successfully implemented, but optimization of the inter-axis distance did not reveal any appropriate relative position of the cogwheels allowing for correlated motion. As mentioned above, attraction prevails at short distances and when the cogwheels are located further apart, the flexibility of the *p-tert*-butylbiphenyl teeth leads to gear slippage.

These pieces of work highlight the challenges encountered in the development of intermolecular single-molecule gear systems on surfaces, requiring the identification of appropriate surfaces and atomic scale rotation axes, in direct relationship with the structure of the molecular cogwheels. For the latter, the design of the central core is intimately related to the nature of rotation axes, while the teeth structure has to prevent flexibility. Since this field is still in its infancy, such empirical approaches by trial and error allow progressive identification of appropriate strategies towards intermolecular functional systems.

3.2.2. Direct chemical anchoring

An alternative approach to restrict diffusion of molecular cogwheels on a metallic surface consists of using direct chemical bonding. In 2008, Gao *et al.* reported the anchoring of single zinc phthalocyanines on Au(111) via a strong chemical bond arising between a gold adatom and one of the outer nitrogen atoms of the phthalocyanine structure.^[52] Such anchoring totally prevents molecular diffusion at 77 K while rotation of the molecular species is observed. However, the off-center position of this chemical rotation axis generated *in situ* leads to non concentric motion, which is a pre-requisite for geared rotation. Inspired by coordination chemistry and the known ability of cyclopentadienyl ligands to bind to a wide variety of metal centers with η^5 hapticity, Moresco *et al* focused on pentaarylcyclopentadienyl scaffolds as prototypes of star-shaped cogwheels.^[53] Sublimation of bromocyclopentadiene precursors led to the homolytic cleavage of the C-Br bond and, as a result, pentaarylcyclopentadienyl radicals were thus deposited on the Au(111) surface. Structural characterization by STM along with DFT simulations confirmed the adsorption geometry of the cogwheel, with the central cyclopentadiene core lying parallel to the surface. In this system, the five carbon atoms contribute to the bonding with three gold atoms underneath, which leads to concentric rotations around this chemical axis. Efficiency of such an anchoring strategy in molecular gearing was demonstrated with a sterically tagged cogwheel, incorporating a single *p-tert*-butylphenyl tooth among four shorter phenyl teeth. A train of three coupled cogwheels was built and upon mechanical actuation of the driver molecule by STM manipulation of the *tert*-butyl group, disrotatory motion of the two followers was observed (Figure 11). This chemically-anchored system, involving three meshed cogwheels, is the longest functional intermolecular train of gears reported to date.

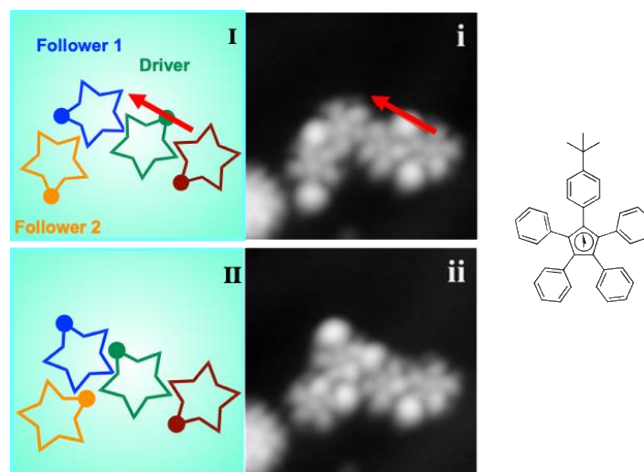


Figure 11. Structure of the star-shaped molecular cogwheel in its radical state (right) and STM images showing the disrotatory correlated motion of three cogwheels directly anchored on a Au(111) surface upon mechanical actuation by the STM tip (the red arrow highlights the trajectory of the tip) (left). The cogwheel on the right is not meshed with the driver, hence no rotation is observed. Adapted from Ref. 53 with permission from the ACS, Copyright 2020.

In the two previous strategies aimed at anchoring single molecule cogwheels on the surface, tailored cogwheels were synthesized as purely organic frameworks and assembly with the rotation axis was achieved *in situ* upon deposition on the surface. As an alternative, it was envisioned to take advantage of the concepts of coordination chemistry to pre-assemble prior to on-surface deposition the cogwheel and possible anchoring groups around a central metal atom which can act as rotation axis. In this way, the structure of the resulting functional metallo-organic species can be controlled and improved by modular synthetic routes, with the aim of reaching optimal mechanical properties.

3.3. Single-molecule cogwheels mounted on metallo-organic anchors

Molecular azimuthal rotors based on ruthenium complexes have been developed for two decades in our group with a variety of functions being targeted, such as motors,^[6f,6h,54] turnstiles,^[55] and winches.^[13] Importantly, these technomimetic molecular machines have been studied by STM at the single-molecule scale on metallic surfaces at low temperature. As a result, beside the ligand acting as an azimuthal rotor, the design of such ruthenium complexes includes a second ligand meant to act as anchoring unit on the surface, to preclude any diffusion process during on-surface investigations. Hydrotris(indazolyl)borates exhibiting a facial κ^3 coordination mode have in particular been widely exploited as tripodal stator subunit,^[54b,56] with specific functional groups appended to the 6-position of indazole cores. Ethylthioethers have been selected to provide tight adsorption on noble metals, and it has been shown that diffusion is indeed totally frozen at 5 K while translation of the ruthenium complexes by STM lateral manipulation is possible at 77 K. This property is particularly interesting to set up trains of molecular gears, since individual cogwheels pre-assembled with both their rotation axis and their anchoring unit could be moved at 77 K from their initial random location to build up linear arrangements of ruthenium complexes with controlled intermolecular distances. Lowering the temperature to 5 K would then lock this multi-molecular set-up, while mechanically-induced azimuthal rotation of the upper ligand would still be possible. In line with earlier reports about piano-stool ruthenium complexes acting as molecular machines, pentaarylcyclopentadienyl ligands were selected as prototypical star-shaped cogwheels to be

pre-assembled using ruthenium as a rotation axis, lifted up from the surface by a scorpionate ligand as anchoring unit.

In the first series of prototypes, synthetic efforts were focused on the preparation of metallo-organic architectures incorporating C_5 -symmetric cogwheels with a variety of teeth and displaying increasing diameters.^[56b] The modular synthetic approach relied on a single-step post-functionalization of a penta(*p*-bromophenyl)cyclopentadienyl ruthenium(II) complex as key precursor,^[5758] via five-fold cross-coupling reactions. Teeth of increasing lengths and contact areas were thus incorporated, such as small methyl- and *tert*-butyl-substituted phenyl moieties, carbazoles, BODIPYs and finally flat bidimensional porphyrins, leading to cogwheel diameters over 5 nm.

In anticipation of on-surface investigations by STM, a second series of pentaporphyrinic prototypes were designed with a lower symmetry of the upper rotating subunit.^[58] Steric labelling was successfully achieved by varying the length of the spacer between the cyclopentadienyl core and the porphyrinic macrocycle, using a longer phenylethynylphenyl fragment instead of 4,4'-biphenylenes (Figure 12, top). Starting from penta(*p*-halogenophenyl)cyclopentadienyl ruthenium(II) as a key building block bearing a single pre-activated *p*-iodophenyl group, controlled insertion of the labelled tooth was achieved by a chemoselective Sonogashira cross-coupling followed by four-fold Suzuki–Miyaura reactions to append the shorter teeth.^[13] The same approach involving sequential chemoselective couplings was next applied to the synthesis of chemically-tagged cogwheels, expected to exhibit improved intermolecular mechanical interactions due to the homogeneity of the teeth shapes.

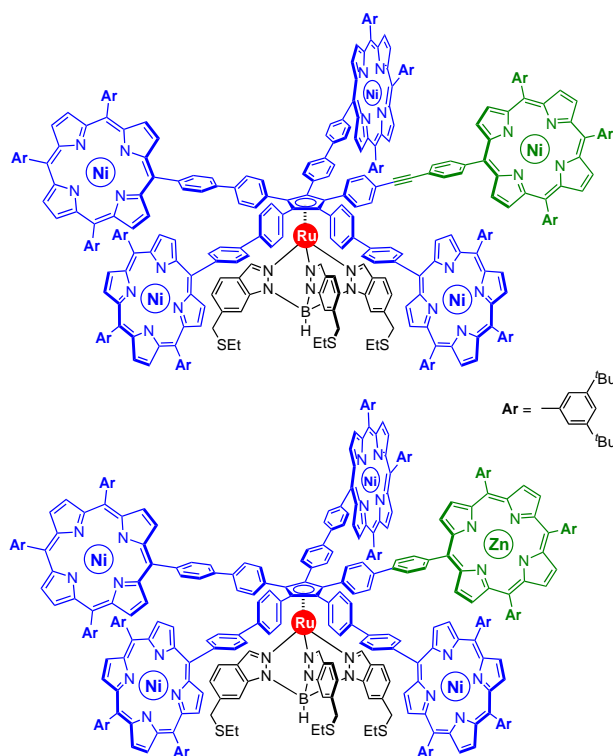


Figure 12. Structure of two desymmetrized pentaporphyrinic cogwheels mounted on metallo-organic anchors. The upper one has a longer tooth (in green) with an additional ethynyl spacer while the bottom one only differs by the metal coordinated in the porphyrins, one zinc (in green) and four nickel (in blue).

To induce sub-molecular contrast on STM images, the electronic properties of one single porphyrinic paddle were modulated as compared to the four others, either by changing the nature of the central metal atom or by appending electron-withdrawing substituents. In the example shown below (Figure 12, bottom), the organic skeletons of the cogwheels are perfectly symmetric but different metal ions (one zinc and four nickel) are coordinated in the porphyrins. The resulting desymmetrized prototypes of pentaporphyrinic cogwheels, pre-assembled to their ruthenium rotation axis and their scorpionate anchoring unit, are currently studied as single molecules on surface.

4. Summary and Outlook

Over the past forty years, tremendous efforts have been devoted to the development of functional gearing systems at the molecular scale. As pioneers in the field, Iwamura and Mislow unveiled correlated disrotatory motion as an energetically favorable pathway in highly constrained systems, and reported the first examples of intramolecular bevel gears based on covalently linked bis-triptycyl scaffolds. Ever since, progress in the field led to a variety of intramolecular bevel and spur gears, displaying increased levels of complexity and functionality, such as stimuli-responsive behaviors. We would like also to mention a very innovative approach to the transmission of molecular motion developed recently by the group of Harry Anderson.^[59] They successfully achieved correlated rotary motion of two oligopyridyl wheels, not by a direct gearing mechanism in a disrotatory pathway but through the intermediate of a polyporphyrinic belt leading to a conrotatory process. Contrary to the molecular gears reviewed in this article, the two wheels thus rotate in the same direction and these supramolecular systems including both wheels and the surrounding belt can be considered as caterpillar tracks according to technomimetic principles.

In these systems designed for in-solution studies, gearing mechanisms are however inherently limited to intramolecular correlated motion of sub-molecular fragments, which strongly limits their use in the quest for multi-molecular nanomachineries. Strategies for intermolecular gearing have thus been explored, including the preparation of 3D-frameworks and the confinement of molecular cogwheels in two dimensions. In the latter case, Scanning Tunneling Microscopy offers the opportunity to probe mechanical behaviors down to the single-molecule scale. The key parameter for successful correlated disrotatory motion between independent molecular cogwheels is the absence of diffusion. Several strategies have been devised for the anchoring of individual molecules on a surface. Specifically-designed cogwheels have been centered on top of a single metal atom acting as rotation axis, preassembled in solution to a metallo-organic anchor or directly chemically-bound to the metallic surface. This latter option has given rise to the longest functional intermolecular train of gears, involving three meshed cogwheels undergoing correlated disrotatory motion.

Following these milestones in the field, several challenges to increase the complexity and functionality of intermolecular gear systems remain to be tackled. First, rigid cogwheels with larger diameters and increasing numbers of teeth should be designed, possibly allowing for the implementation of gearing ratios on surfaces. In addition, the self-assembly of individual cogwheels into highly-ordered mono-dimensional networks with appropriate intermolecular distances would be highly desirable in order to generate trains of gears over long distances, without requiring STM manipulation to position each molecule. Finally, connection of gear trains to compatible molecular motors as sources of mechanical power should be investigated in anticipation of the development of multi-molecular machineries at the nanoscale.

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Keywords

cyclopentadienyl ligand • ruthenium • scanning tunneling microscopy • single molecule • triptycene

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