

Conference paper

Shigehisa Akine*

Control of chirality inversion kinetics of triple-helical metallocryptands

<https://doi.org/10.1515/pac-2023-0207>

Abstract: Dynamic helical molecules, which can undergo a reversible chirality inversion between the *P* and *M* forms, are useful as a platform for switchable chiral functional molecules. The chirality inversion of these molecules has been extensively studied. However, it has mostly been discussed from the viewpoint of the equilibrated *P/M* ratios before and after the inversion; control of the response speeds or kinetic profiles has rarely been explored. In order to construct helical structures with controllable kinetic profiles, triple-helical metallocryptands, LM₃, have been designed and synthesized. These molecules can undergo a relatively slow dynamic *P/M* chirality inversion (helicity inversion) to produce an equilibrated mixture. The *P/M* equilibration was accelerated or decelerated based on the following two strategies. One is based on the guest binding in the cryptand cavity. The *P/M* racemization kinetics of LNi₃ was significantly decelerated by recognition of guanidinium ion in the cavity. The other strategy is based on the ligand exchange reactions at the octahedral cobalt(III) centers in LCo₃(amine)₆. The *P/M* chirality inversion speeds were controlled by changing the initial and entering amine ligands. In addition, a unique transient chirality inversion behavior was observed when chiral amine ligands were removed from the metallocryptand by the ligand exchange reaction with piperidine.

Keywords: Chirality transfer; cobalt; helical structures; helicity; ICPOC-25; molecular recognition; nickel.

Introduction

Helical structures have a useful chiral molecular scaffold with the right- and left-handed forms (*P* and *M* forms, respectively). In general, helical molecular scaffolds play an important role in providing a chiral environment for various kinds of chiral molecular functions, such as chiral discrimination [1], asymmetric catalysis in organic syntheses [2], chiroptical properties [3], etc. Typical helical molecules include biopolymers, such as DNA duplexes and α -helical peptides, as well as a variety of artificial helical molecules and polymers [4].

Some of the helical molecules can undergo a dynamic chirality inversion between the *P* and *M* forms; these are known as dynamic helical molecules [5]. The chirality inversion takes place if the structures have enough flexibility or are in equilibrium with a non-helical structure such as a random coil. These dynamic helical molecules have attracted increasing attention because they could be potentially useful as a molecular platform to enable stimuli-responsive switching of chiral functions [6]. If the stimulus converts a helical structure from *P*-rich to *M*-rich or vice versa, dynamic chirality inversion would take place (Fig. 1a). The stimuli-responsive *P/M* chirality inversion of a helical structure may lead to inversion of the chiral functions, such as chiroptical properties and enantioselectivities in asymmetric syntheses. In this regard, one can say that a helical molecule possesses the chirality information, i.e., the *P/M* isomeric ratio, which governs various kinds of chiral properties and functions.

Article note: A collection of invited papers based on presentations at the 25th International Conference on Physical Organic Chemistry which was held in Hiroshima, Japan on 10–15th July 2022.

***Corresponding author: Shigehisa Akine**, Nano Life Science Institute (WPI-NanoLSI), Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan; and Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan, e-mail: akine@se.kanazawa-u.ac.jp

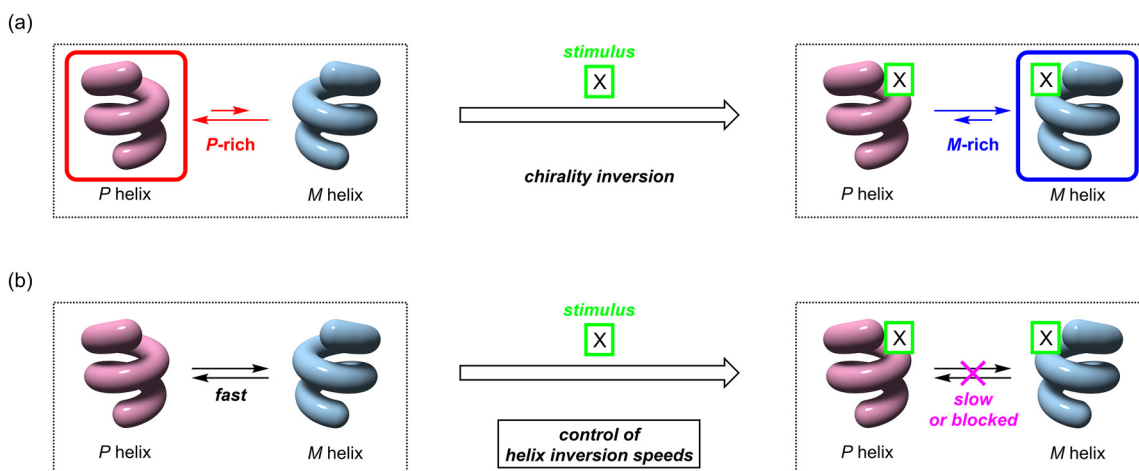


Fig. 1: Schematic drawings of the chirality inversion of dynamic helical molecules between the *P* and *M* forms. (a) A stimulus inverts the chirality from the *P*-rich to *M*-rich if the stimulus changes the *P*/*M* preference of the *P*/*M* equilibrium. (b) Control of the *P*/*M* equilibration speeds of a dynamic helical molecule by an external stimulus.

From the viewpoint of the processing of the chiral information, there are two important aspects. One is the difference between the equilibrated *P*/*M* ratios before and after the stimulation, because the *P*/*M* ratio directly determines the chiral properties, such as the sign and amplitudes of the chiroptical signals and enantioselectivities, in various types of chemical events. If the *P*/*M* preference is reversed upon the stimulation, this reversal will lead to the opposite chiral properties or functions (Fig. 1a). The other one is the response speeds for the changes in the *P*/*M* ratios (Fig. 1b). A fast *P*/*M* interconversion is desired when chiral information is recorded or erased, but the *P*/*M* interconversion should be slow when the recorded information has to be kept [7]. In this context, it is important to develop a rational strategy to accelerate or decelerate the dynamic *P*/*M* chirality inversion depending on the circumstances. However, the *P*/*M* chirality inversion has been mostly discussed from the viewpoint of the equilibrated *P*/*M* ratios before and after the inversion; tuning of the response speeds or controlling the kinetic profiles has rarely been investigated. This is mainly because the response speeds are principally governed by the intrinsic *P*/*M* chirality inversion rate of the helical framework, which is difficult to be altered by external stimuli.

In order to make a dynamic chiral structure with a controllable response speed, it is necessary to establish a strategy to efficiently stabilize or destabilize the transition state of the *P*/*M* interconversion. This can be achieved by the introduction of a binding site for a chemical species at a position where the transition state is directly influenced. From this structural viewpoint, the trinuclear metallocryptand, LM_3 , is advantageous (Fig. 2a) [8]. This molecule has a triple helical structure due to the rigid propeller-shaped triphenylbenzene scaffold, but it still has a dynamic feature that allows the interconversion between the *P* and *M* forms. The cryptand molecule has a three-dimensional cavity surrounded by three $[M(\text{saloph})]$ ($H_2\text{saloph} = N,N'$ -disalicylidene-*o*-phenylenediamine) arms connected with two pivotal benzene rings. Based on the structural features, there are two possible ways to alter the speed of the *P*/*M* chirality inversion (Fig. 2b). One is the guest binding in the cavity (strategy 1); the guest species accommodated in the cryptand cavity would significantly affect the transition state of the *P*/*M* chirality inversion. In fact, strong binding is expected because related oligo(metallosalen)-type structures are known to have an excellent binding affinity to cationic guest species [9]. The other one is the ligand exchange reactions at the constituent metal ions of the three $[M(\text{saloph})]$ arms (strategy 2); the reactivity of the ligand exchange can be altered by selecting a suitable combination of the initial and entering ligands [10]. In addition, if a chiral amine is introduced, removed, or exchanged with another one, the *P*/*M* ratio could be changed at the desired speed according to the reactivity.

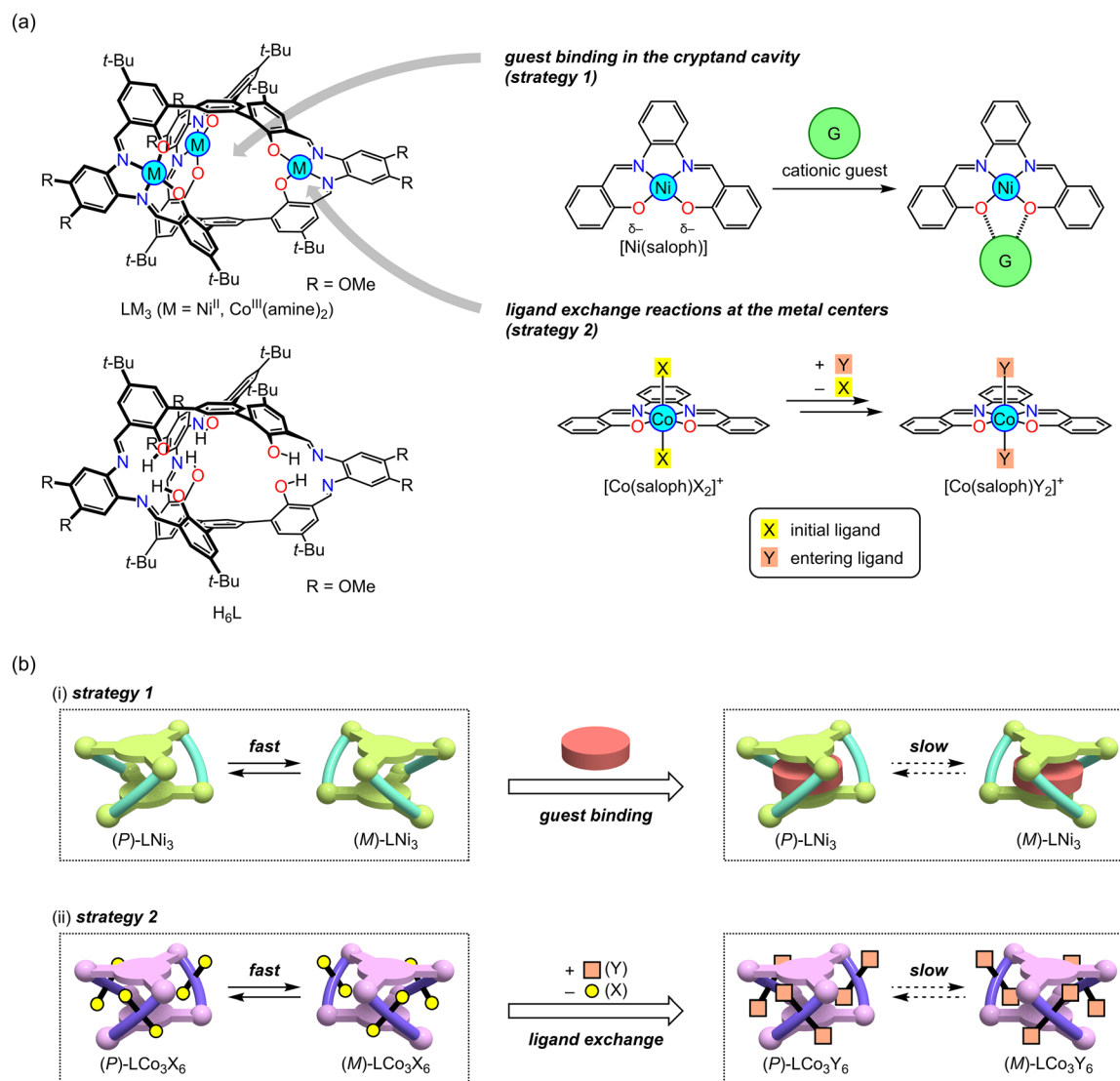


Fig. 2: Design of triple-helical metallocryptands LM₃ for controlling the *P/M* chirality inversion speeds. (a) Molecular structure of LM₃ and the possible interaction/reaction with a chemical species. The structure of the precursor H₆L is also shown. (b) Two strategies for controlling the helix inversion speeds: (i) guest binding in the cryptand cavity and (ii) ligand exchange reactions at the metal centers.

This article illustrates a series of the new *P/M* chirality inversion systems based on the helical LM₃ metallocryptand structures. The chirality inversion speeds are effectively controlled by taking advantage of the guest binding in the LNi₃ cryptand cavity or the ligand exchange reactions at the octahedral cobalt(III) centers in LCo₃X₆.

Control of *P/M* chirality inversion speeds by host–guest binding

In general, cryptand-like cage compounds show an excellent binding affinity to guest species in their three-dimensional cavity. The metallocryptand LM₃ molecule would have a strong cation binding affinity because it has three [M(saloph)] motifs that can strongly interact with cationic species [9]. Since this binding site is located within the cage cavity of LM₃, the guest binding would directly stabilize or destabilize the transition state of the

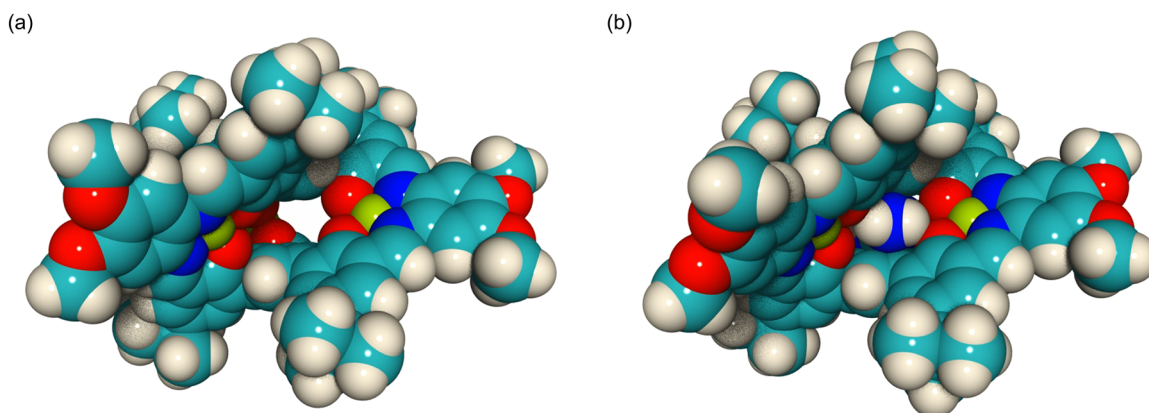


Fig. 3: Crystal structures of (a) LNi_3 and (b) LNi_3Gu .

P/M chirality inversion, which would effectively influence the *P/M* chirality inversion speed (Fig. 2b(i)). In this section, the design of a new helical cryptand molecule, LNi_3 , is described and the control of the *P/M* chirality inversion speed using the host–guest binding is discussed.

The triple-helical metallocryptand, LNi_3 [8], was obtained by the reaction of the corresponding free H_6L ligand with nickel(II) acetate. The X-ray crystal structural analysis unambiguously revealed the molecular structure of this trinickel(II) metallocryptand (Fig. 3a). The LNi_3 molecule has a well-defined three-dimensional cavity surrounded by three $[\text{Ni}(\text{saloph})]$ arms arranged in a triple-helical fashion. The cavity is surrounded by six phenoxo oxygen atoms and two pivotal benzene rings, and this electron-rich nature was found to be suitable for the recognition of cationic guest species (see below). In addition, the flat-shaped cavity sandwiched by the two pivotal benzene rings was suitable for shape-complementary binding with a planar guest species. The distance between the two pivotal benzene rings is 5.523 Å, which is slightly narrower than the size appropriate for the recognition of a π -conjugate molecule. Therefore, when the guest is bound, the cavity should be expanded, which would influence the transition state of the *P/M* chirality inversion.

The binding affinity of LNi_3 to alkali metal ions was investigated by spectroscopic methods (Table 1) [11]. The binding constants $\log K_a$ were in the range of 5.3 and 8.1, indicating the excellent binding affinity of LNi_3 to these guest ions. In particular, the selectivity for larger ions such as Rb^+ and Cs^+ was clearly demonstrated. Importantly, the LNi_3 metallocryptand binds alkali metal ions much stronger than the corresponding metal-free host, H_6L , by 1–2 orders of magnitude. This can be explained by the more negatively charged phenoxo groups in the $[\text{Ni}(\text{saloph})]$ motifs, while the uncomplexed phenol groups in H_6L are less negatively charged. This is the same trend observed for the already reported macrocyclic and acyclic oligo(metallosalen)-type compounds [9, 12, 13].

This LNi_3 complex also showed a particularly strong binding affinity to guanidinium ion (**Gu**); the binding constant was $\log K_a > 8$ [8]. This strong binding is probably due to the good shape complementarity of the guanidinium ion to the flat three-fold symmetrical cavity of LNi_3 . The ^1H NMR signal of the bound guanidinium ion was observed at 5.06 ppm, which was significantly upfield shifted from that of the uncomplexed guest (6.98 ppm).

Table 1: Binding constants $\log K_a$ of cryptand hosts (H_6L and LNi_3) for alkali metal ions^{a,b}.

	Na^+	K^+	Rb^+	Cs^+
Ionic radius (Å) ^c	1.32	1.65	1.75	1.88
H_6L	3.37 (3.29, 2.41) ^d	4.94	5.66	6.67
LNi_3	5.32	6.85	8.04	7.83

^aIn DMSO/chloroform (1:9) or DMSO-*d*₆/CDCl₃ (1:9). (ref. [11]). ^bThe binding constants for 1:1 host–guest complexation. ^cIonic radius for octacoordinate ions (ref. [14]). ^dThe binding constants for 1:1 and 1:2 host–guest complexation are given in parenthesis.

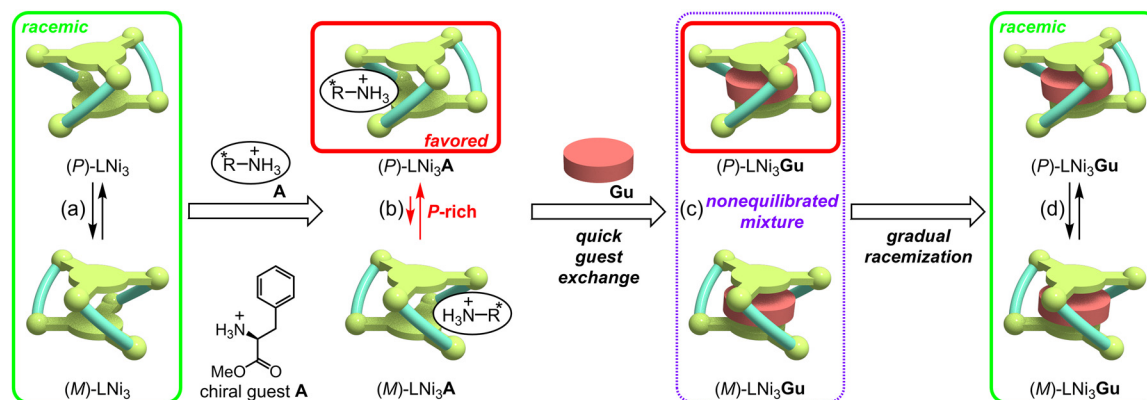


Fig. 4: Deceleration of the P/M chirality inversion speed of LNi_3 by binding with the guanidinium ion (**Gu**) in the cryptand cavity.

This clearly indicated that the guanidinium ion was completely encapsulated inside the cavity sandwiched by the two pivotal benzene rings. The crystal structure of the guanidinium complex, LNi_3 **Gu**, unambiguously demonstrated the complete encapsulation of the guanidinium ion in the LNi_3 cavity (Fig. 3b). This guest binding undoubtedly expanded the cryptand cavity; the pivot–pivot distance was elongated from 5.523 Å to 6.059 Å. The distance between the guanidinium ion and the pivotal benzene rings was around 3 Å, which suggests the cation– π interactions between them. In addition, six-fold $N-H\cdots O$ hydrogen-bonding interactions were found between the phenoxo oxygen atoms and guanidinium hydrogen atoms, which would be the major interactions explaining the strong host–guest binding.

Since the LNi_3 metallocryptand has a dynamic helical molecular framework with no chiral auxiliary, equimolar amounts of the P and M forms are present in the absence of any external chiral sources (Fig. 4a). However, if this helical metallocryptand LNi_3 interacts with a chiral guest, the P and M forms become a diastereomer pair, which makes the thermodynamic stabilities of the two forms different from each other (Fig. 4b). This would shift the P/M equilibrium to one side. This is the principle of the dynamic helicity control [5], which has been observed in various kinds of dynamic chiral systems such as helical polymers and helical metal complexes [4, 15]. As the chiral guest, chiral ammonium ions, such as L-phenylalanine methyl ester (protonated form) (**A**), were found to be effective to shift the P/M equilibrium of LNi_3 , which was evidenced by the appearance of the CD signals. The binding constant was determined to be $\log K_a = 3$ for guest **A**, which is lower than that for the guanidinium ion.

The P/M equilibrium shift caused by the binding with chiral guest **A** was found to be fast. The CD signal immediately appeared and became constant after the addition of the chiral guest **A** ($t_{1/2} < 12$ s). Interestingly, this P/M chirality inversion rate of LNi_3 was significantly decelerated by the very strong host–guest binding with the guanidinium ion. This was clearly demonstrated by the following guest exchange experiments. Since the chiral guest **A** efficiently shifted the P/M equilibrium (Fig. 4b) and guanidinium ion has a much higher binding affinity to LNi_3 , the biased P/M ratio might remain unchanged after the $\mathbf{A} \rightarrow \mathbf{Gu}$ guest exchange, even if the resultant host–guest complex LNi_3 **Gu** has no chiral auxiliary (Fig. 4c).

The complete and rapid $\mathbf{A} \rightarrow \mathbf{Gu}$ guest exchange was confirmed by a ^1H NMR experiment, which showed the characteristic upfield shifted signal of the bound guanidinium ion at 5.06 ppm 3 min after addition of the guanidinium ion. However, the induced CD signals remained almost unchanged even after the complete guest exchange with the achiral guanidinium ion. This indicated that the P/M equilibration of the guanidinium complex LNi_3 **Gu** was significantly slow. The resultant nonequilibrated P/M mixture (Fig. 4c) underwent a slow racemization to give an equimolar P/M mixture (Fig. 4d), which was confirmed by the gradual decay of the CD signal to zero. The half-life was determined to be $t_{1/2} = 37$ min, which was at least 180 times slower than that of the LNi_3 metallocryptand in the presence of the chiral guest **A**. As a result, this LNi_3 complex acted as a new chirality information storage system [7, 16], in which the P/M ratio remained unchanged after removal of the chiral source, based on the combination of the dynamic helical molecular scaffold with the strong host–guest binding.

Control of *P/M* chirality inversion rates by ligand exchange reactivity

As already described, the helical complex LNi_3 can undergo a *P/M* chirality inversion upon suitable stimulation. If such an inversion behavior of LM_3 is coupled with a slow chemical conversion, the *P/M* equilibrium ratio can be altered at the desired speed. For this purpose, the kinetic rate of the chemical conversion should be easily controllable as desired. If the conversion is slower than the intrinsic *P/M* chirality inversion, the *P/M* ratio would show a time-dependent change at the same speed as the chemical conversion that can be controllable [17]. The ligand exchange reaction at an inert low spin cobalt(III) center would be one of the suitable chemical conversions, because the reaction can be easily accelerated or decelerated depending on the initial and entering ligands [10, 18]. Thus, the triple helical complex LCo_3X_6 , which has three octahedral cobalt(III) ions, was employed [19]. This complex undergoes a dynamic *P/M* chirality inversion as seen in the nickel(II) analogue, LNi_3 . In addition, each of the cobalt(III) centers has two additional monodentate ligands X to complete an octahedral geometry. This allows the LCo_3X_6 molecule to undergo a six-step ligand exchange reaction if each of the $[\text{Co}(\text{saloph})\text{X}_2]^+$ sites undergoes the two-step $\text{X} \rightarrow \text{Y}$ ligand exchange reaction (Fig. 2b(ii)).

When the ligand X is achiral, the *P* and *M* forms of the helical metallocryptand LCo_3X_6 would be an enantiomer pair, giving rise to an equilibrated racemic mixture due to the dynamic *P/M* interconversion in solution (Fig. 5a). However, when this achiral amine ligand X is replaced with a chiral ligand Y, the *P* and *M* forms become a diastereomer pair. Therefore, this ligand exchange would cause a *P/M* equilibrium shift (Fig. 5b). In addition, the speed of the *P/M* equilibrium shift would be controllable because the reaction rate of the $\text{X} \rightarrow \text{Y}$ ligand exchange can be altered by changing the initially-coordinating amine X and added amine Y.

As the starting ligand X to be introduced into LCo_3X_6 , monodentate achiral amines, such as dimethylamine and piperidine, were selected. If the achiral amine X is replaced by a chiral amine, such as **A1** and **A2**, then the *P/M* equilibrium is shifted according to the progress of the ligand exchange (Fig. 5b).

The starting complexes LCo_3X_6 , which have six achiral amine ligands X ($\text{X} = \text{Me}_2\text{NH}$, pip), were obtained by the reaction of the free H_6L ligand with cobalt(II) acetate in the presence of the achiral amines X under aerobic conditions [20]. These tricobalt(III) complexes also had a triple-helical structure as observed for the nickel(II) complex, which was confirmed by X-ray crystallography. Each of the cobalt(III) ions had an octahedral geometry, which had two amine ligands at the axial positions. The corresponding metallocryptands LCo_3X_6 having chiral amine ligands ($\text{X} = \text{A1}$, **A2**) were prepared in a similar manner. It is noteworthy that the metallocryptand $\text{LCo}_3((R)-$

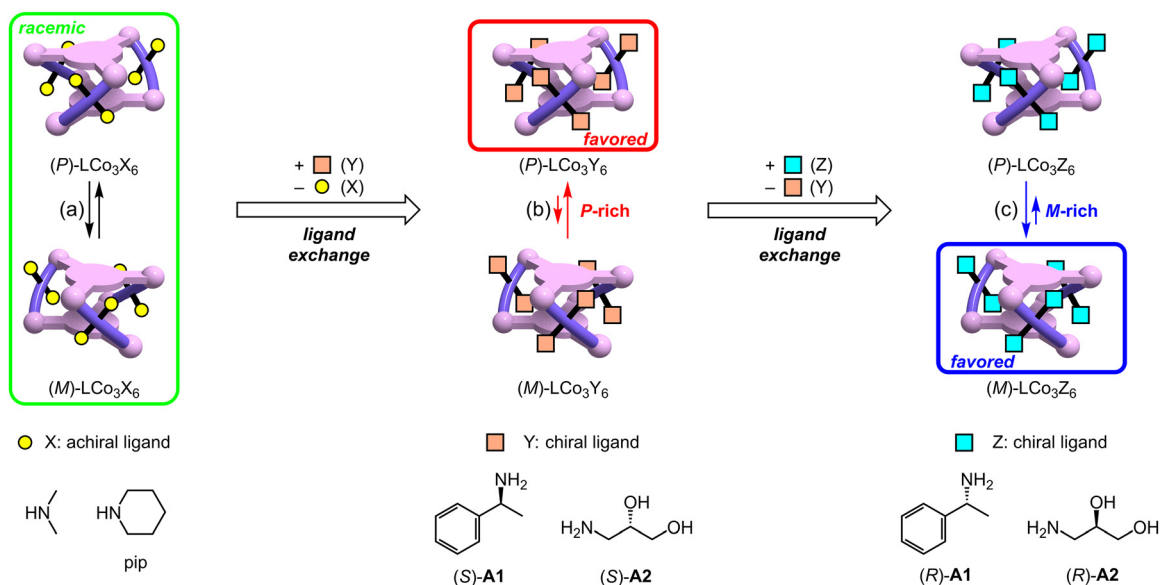


Fig. 5: *P/M* equilibrium shifts of LCo_3X_6 driven by the $\text{X} \rightarrow \text{Y} \rightarrow \text{Z}$ ligand exchange reactions at the cobalt(III) centers.

$A1_6$, which has optically-active ligands (*R*)-**A1**, formed crystals only containing the left-handed form (*M,R*) due to the energy difference between the (*M,R*) and (*P,R*) diastereomers. This isolated left-handed helical complex showed a positive CD signal at around 550 nm in a methanol solution. Therefore, the *P/M* equilibrium shift can be monitored from the increase/decrease of the CD signal at 550 nm.

As expected, the achiral amine *X* in the helical metallocryptands LCO_3X_6 (*X* = Me_2NH , pip) can be easily exchanged with the chiral amine, **A1** or **A2**, just by mixing (Fig. 5a $\rightarrow$ b) [20]. The ligand exchange at the cobalt(III) centers gradually proceeded, which can be monitored by the time course change in the CD spectra. For example, the dimethylamine-coordinating helical complex, $LCO_3(Me_2NH)_6$, was converted into $LCO_3((S)\text{-}A2)_6$ by the reaction with the chiral amine (*S*)-**A2** (12 equiv). During the reaction, the intensity of the negative CD signals at 550 nm gradually increased and became almost constant after 3 h (Fig. 6a, b). This indicated that the *P/M* chirality inversion equilibrium was gradually shifted to give a *P*-rich mixture, which was driven by the ligand exchange reaction from dimethylamine to the chiral amine (*S*)-**A2**.

The advantage of this system is that the speed of the *P/M* equilibrium shift can be altered by changing the combination of the initial achiral amine *X* and the added chiral amine *Y* (Fig. 6b). When a different chiral amine (*S*)-**A1** was added instead of (*S*)-**A2**, the starting complex $LCO_3(Me_2NH)_6$ underwent a slightly faster *P/M* equilibrium shift. On the other hand, when the initial amine was changed from Me_2NH to piperidine, the equilibrium shift became significantly slower. These response speeds were quantitatively evaluated in terms of the initial rates (Table 2). The dimethylamine-coordinating complex, $LCO_3(Me_2NH)_6$, underwent an up to 60 times faster *P/M* equilibrium shift than the piperidine-coordinating complex, $LCO_3(pip)_6$.

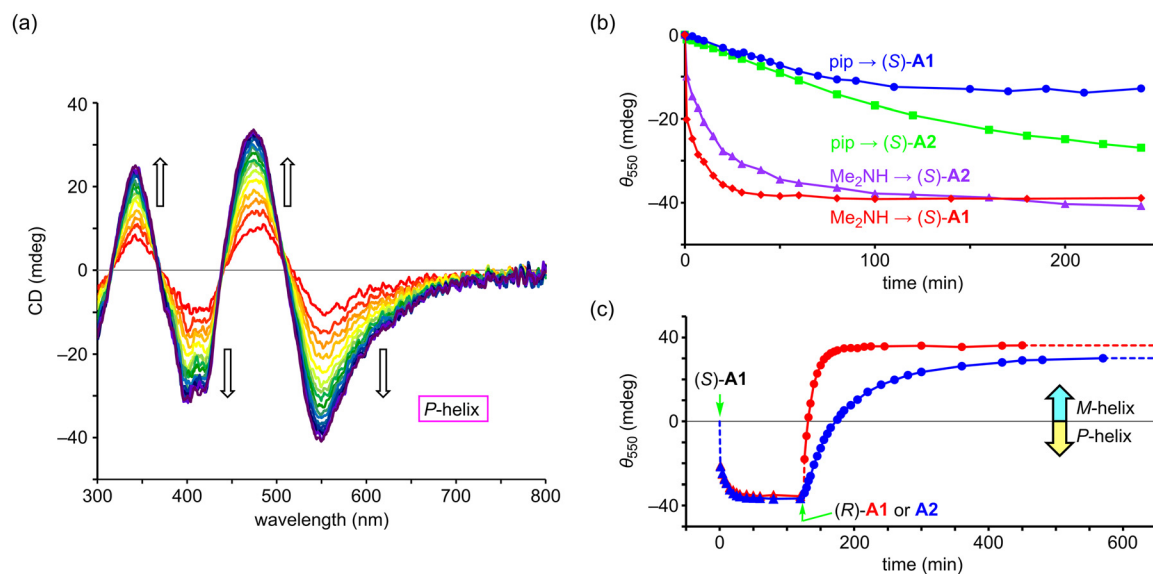


Fig. 6: Time-course CD spectral changes upon the ligand exchange of LCO_3X_6 . (a) Full spectra for the exchange of $Me_2NH \rightarrow (S)\text{-}A2$. (b) Time-course changes in the CD intensity at 550 nm for the exchange of achiral amines with the chiral amines (12 equiv). (c) The *P* $\rightarrow$ *M* chirality inversion of LCO_3X_6 by the second amine, (*R*)-**A1** or (*R*)-**A2** (120 equiv). Reproduced with modification from ref. [20] with permission, Copyright 2019, Wiley-VCH Verlag GmbH & Co. KGaA.

Table 2: Initial rates of *P/M* equilibrium shift of LCO_3X_6 driven by the ligand exchange with the chiral amines.

Starting complex	Added amine ^a	Initial rate (%de/min) ^b
$LCO_3(Me_2NH)_6$	(<i>S</i>)- A1	20
$LCO_3(Me_2NH)_6$	(<i>S</i>)- A2	10
$LCO_3(pip)_6$	(<i>S</i>)- A1	0.33
$LCO_3(pip)_6$	(<i>S</i>)- A2	0.42

^a12 equiv of amines were added. ^bReaction rates were determined in methanol by CD spectroscopy (ref. [20]).

If the initial and entering amines are both chiral but have opposite stereoconfigurations, the P/M equilibrium bias would be inverted from one side to the other side according to the reaction progress of the ligand exchange (Fig. 5b $\rightarrow$ c) [20]. Indeed, the P -rich mixture, which was produced by the addition of the first chiral amine (S)-**A1** (12 equiv), was inverted to an M -rich mixture by the addition of an excess amount of (R)-**A1** (120 equiv), i.e., the same chiral amine with the opposite stereoconfiguration. This inversion was clearly demonstrated by the time-dependent CD spectral changes (Fig. 6c); the negative CD signal at around 550 nm rapidly weakened and turned positive after 8 min, and became almost constant within 1 h. This $P \rightarrow M$ chirality inversion timescale can also be altered by changing the second chiral amine. When (R)-**A2** was added instead of (R)-**A1**, the $P \rightarrow M$ chirality inversion became significantly slower. The CD signal inversion required 49 min, which is six times longer than in the case of (R)-**A1**. Therefore, this series of complexes worked as a controllable system in which the speeds of the P/M equilibrium shift and the $P \rightarrow M$ chirality inversion can be finely tuned by selecting the combination of the initial and entering amines.

The reverse reaction, i.e., the exchange of chiral amine Y in the helical complex LCo_3Y_6 with achiral amine X, showed unexpected time-dependent changes in the CD spectra. This reaction would finally give a P/M equimolar racemic mixture because the P and M forms of LCo_3X_6 constitute an enantiomer pair. During this reaction, the six chiral auxiliary ligands Y in LCo_3Y_6 are completely removed by the $Y \rightarrow X$ ligand exchange (Fig. 5b $\rightarrow$ a).

As already described, the $\text{LCo}_3((S)\text{-A1})_6$ metallocryptand showed a negative CD signal at around 550 nm because the P/M chirality equilibrium is shifted to P -rich (Figs. 7a and 8a). If the (S)-**A1** ligands are replaced by achiral amine ligands, this CD signal would gradually weaken and finally become silent according to the reaction progress. However, the reaction of $\text{LCo}_3((S)\text{-A1})_6$ with piperidine (120 equiv) showed an unexpected non-trivial two-step feature during the time-dependent change [21]. The negative CD signal first turned positive within several minutes, then the resultant positive signal slowly decayed to zero for 2 d. This indicated that the chirality was inverted from P to M before the complete racemization. Usually, when a right-handed chiral compound undergoes racemization, the right-handed form is always dominant and the enantiomeric excess monotonically decreases to give a racemic mixture. The left-handed form will never be dominant. Consequently, the time-dependence observed in the racemization of $\text{LCo}_3((S)\text{-A1})_6$ upon the addition of piperidine was really unexpected, because the M form was transiently generated during the racemization of the P form.

In order to clarify the reason for the unique time dependent changes, the intermediate state after 1 h, at which time the CD signal was transiently inverted to positive, was analyzed by spectroscopic methods [21]. The mass spectrometric measurements clearly demonstrated that the initial chiral amine ligands (S)-**A1** were completely exchanged with the achiral piperidine ligands within 1 h, i.e., at an early stage of the overall CD

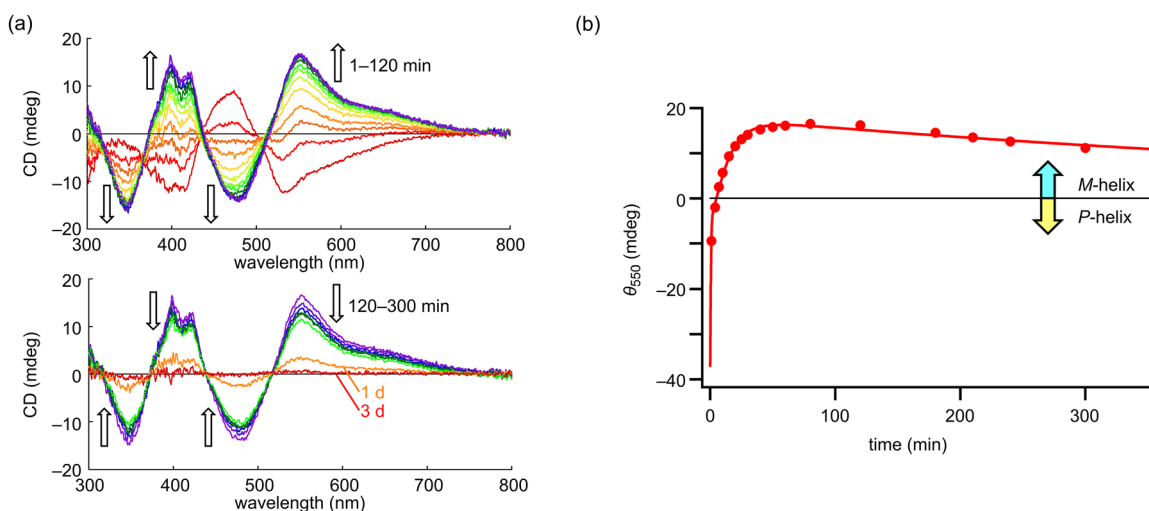


Fig. 7: Time course CD spectral changes of metallocryptand $\text{LCo}_3((S)\text{-A1})_6$ upon the ligand exchange with piperidine (120 equiv). (a) Full CD spectra. (b) The CD intensity at 550 nm. Reproduced from ref. [21].

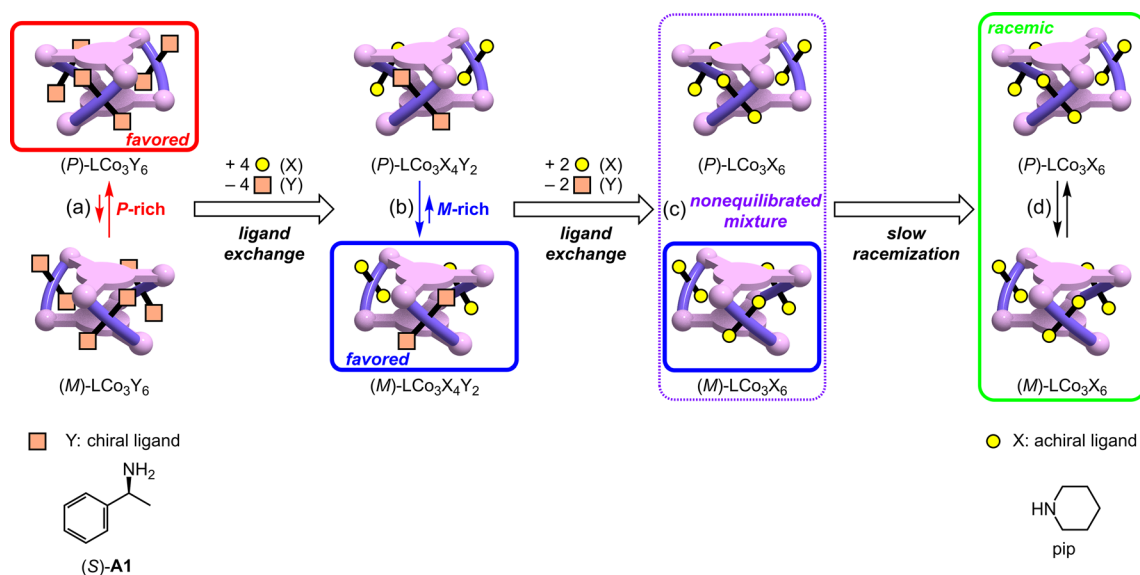


Fig. 8: Transient *P/M* chirality inversion observed during the racemization of $\text{LCo}_3((S)\text{-A1})_6$ by the ligand exchange with piperidine.

spectral changes. Since the *P* and *M* forms of the $\text{LCo}_3(\text{pip})_6$ are an enantiomer pair, i.e., the exact mirror images of each other, there is no thermodynamic preference to one of the two forms. Therefore, some of the intermediates containing one or more chiral ligands (S)-A1 should have a preference for the *M* form. A detailed analysis of the time-dependent mass spectra indicated that the tetra-exchanged intermediate $\text{LCo}_3((S)\text{-A1})_2(\text{pip})_4$, which has only two chiral amine ligands (S)-A1, prefers the *M* form to give an *M*-rich mixture (Fig. 8b), which should be the origin of the unique transient chirality inversion. The *P/M* ratio of the *M*-rich mixture remained almost unchanged after 1 h, although the resultant species $\text{LCo}_3(\text{pip})_6$ had no chiral auxiliary ligand, (S)-A1 (Fig. 8c). The complete racemization required 2 d; the very slow racemization can be explained by the six bulky piperidine ligands in the final product $[\text{LCo}_3(\text{pip})_6]$. Due to this steric hindrance, the transition state of the *P/M* chirality inversion should be destabilized enough to practically maintain the *P/M* ratio of the nonequilibrated mixture (Fig. 8c $\rightarrow$ d).

It is noteworthy that this *P* $\rightarrow$ *M* transient chirality inversion was observed only during the racemization by the ligand exchange of (S)-A1 with piperidine (Fig. 5b $\rightarrow$ a) [21], whereas the *P* chirality was always dominant without showing the unique transient chirality inversion during the reverse reaction, i.e., the ligand exchange of piperidine with (S)-A1 (120 equiv) (Fig. 5a $\rightarrow$ b). Since the *M* chirality transiently appeared only in one of the forward and reverse steps, this can be regarded as a hysteretic cycle. This unique feature could originate from the reasonably slow *P/M* chirality inversion of the LCo_3X_6 metallocryptand scaffold, which occurs on a timescale comparable to the six-step ligand exchange reactions at the cobalt(III) center.

Conclusions

The metallocryptand structures, LM_3 , were found to act as a useful platform to cause a stimuli-responsive *P/M* chirality inversion because of the reasonably slow *P/M* chirality inversion kinetics. The response speed of the stimuli-responsive structural change can be controlled by two strategies; one is based on the guest binding in the LNi_3 cryptand cavity that is surrounded by the three $[\text{Ni}(\text{saloph})]$ arms. The *P/M* chirality inversion equilibrium of LNi_3 was decelerated by at least 180 times due to the very strong binding to the guanidinium ion with the binding constant of $\log K_a > 8$. The other strategy is based on the ligand exchange reactions at the cobalt(III) centers of LCo_3X_6 , which occur on a timescale of minutes to hours. The unique time dependence of the *P/M* ratios can be explained by the relatively slow six-step ligand exchange reactions which simultaneously occur with the *P/M* chirality inversion.

The LM₃ metallocryptand structures described in this article have metal complex moieties in their chiral framework, which can exhibit a variety of metal-derived properties and functions. In particular, the *P/M* ratio of this LM₃ framework determines the sign and amplitudes of the chiroptical signals and enantioselectivities of various kinds of chemical events. Therefore, in combination with the time-dependent *P/M* chirality change of the LM₃ metallocryptands, these chiral properties and functions can be changed over time as desired. Thus, advanced materials with unique time-dependent functions would be created by using a series of LM₃ metallocryptand molecules as a basic backbone.

Acknowledgments: The author thanks Prof. Tatsuya Nabeshima (University of Tsukuba) and Dr. Yoko Sakata (Kanazawa University) for their valuable discussions during the research described in this article. Also, the author thanks Mr. Masato Miyashita, Ms. Shunjin Piao, and Mr. Shunsuke Chiba for performing the experiments described in this article.

Research funding: The research described in this article was supported by the Japan Society for the Promotion of Science (KAKENHI Grants JP16H06510 [Coordination Asymmetry], JP26288022, JP18H03913, JP20K21206, and JP21H05477 [Condensed Conjugation]) and the World Premier International Research Initiative, Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

- [1] (a) Y. Okamoto, T. Nakano, S. Habaue, K. Shiohara, K. Maeda. *J. Macromol. Sci., Pure Appl. Chem.* **A34**, 1771 (1997), <https://doi.org/10.1080/10601329708010307>.
 (b) E. Yashima. *Anal. Sci.* **18**, 3 (2002), <https://doi.org/10.2116/analsci.18.3>.
 (c) R. Amemiya, M. Yamaguchi. *Org. Biomol. Chem.* **6**, 26 (2008), <https://doi.org/10.1039/b713700a>.
- [2] (a) Z. Peng, N. Takenaka. *Chem. Rec.* **13**, 28 (2013), <https://doi.org/10.1002/tcr.201200010>.
 (b) S. Shirakawa, S. Liu, S. Kaneko. *Chem.-Asian J.* **11**, 330 (2016), <https://doi.org/10.1002/asia.201500951>.
- [3] (a) J. M. Fox, T. J. Katz, S. van Elshocht, T. Verbiest, M. Kauranen, A. Persoons, T. Thongpanchang, T. Krauss, L. Brus. *J. Am. Chem. Soc.* **121**, 3453 (1999), <https://doi.org/10.1021/ja983633a>.
 (b) S. K. Jha, K.-S. Cheon, M. M. Green, J. V. Selinger. *J. Am. Chem. Soc.* **121**, 1665 (1999), <https://doi.org/10.1021/ja983202s>.
 (c) H. Fenniri, B.-L. Deng, A. E. Ribbe. *J. Am. Chem. Soc.* **124**, 11064 (2002), <https://doi.org/10.1021/ja026164s>.
 (d) F. Sanda, K. Terada, T. Masuda. *Macromolecules* **38**, 8149 (2005), <https://doi.org/10.1021/ma051529p>.
 (e) T. Biet, A. Fihey, T. Cauchy, N. Vanthuyne, C. Roussel, J. Crassous, N. Avarvari. *Chem. Eur. J.* **19**, 13160 (2013), <https://doi.org/10.1002/chem.201301095>.
- [4] (a) E. Yashima, K. Maeda, H. Iida, Y. Furusho, K. Nagai. *Chem. Rev.* **109**, 6102 (2009), <https://doi.org/10.1021/cr900162q>.
 (b) E. Yashima, N. Ousaka, D. Taura, K. Shimomura, T. Ikai, K. Maeda. *Chem. Rev.* **116**, 13752 (2016), <https://doi.org/10.1021/acs.chemrev.6b00354>.
- [5] (a) B. L. Feringa, A. M. Schoevaars, W. F. Jager, B. de Lange, N. P. M. Huck. *Enantiomer* **273**, 325 (1996).
 (b) I. L. Karie. *Biopolymers (Peptide Science)* **60**, 351 (2001), [https://doi.org/10.1002/1097-0282\(2001\)60:5<351::AID-BIP10174>3.0.CO;2-U](https://doi.org/10.1002/1097-0282(2001)60:5<351::AID-BIP10174>3.0.CO;2-U).
 (c) K. Maeda, K. Morino, E. Yashima. *Macromol. Symp.* **201**, 135 (2003), <https://doi.org/10.1002/masy.200351116>.
 (d) H. Miyake, H. Tsukube. *Chem. Soc. Rev.* **41**, 6977 (2012), <https://doi.org/10.1039/c2cs35192g>.
 (e) H. K. Bisoyi, Q. Li. *Angew. Chem., Int. Ed.* **55**, 2994 (2016), <https://doi.org/10.1002/anie.201505520>.
 (f) Z. Lv, Z. Chen, K. Shao, G. Qing, T. Sun. *Polymers* **8**, 310 (2016), <https://doi.org/10.3390/polym8080310>.
 (g) S. Akine. *Inorganics* **6**, 80 (2018), <https://doi.org/10.3390/inorganics6030080>.
 (h) S. Akine, H. Miyake. *Coord. Chem. Rev.* **468**, 214582 (2022), <https://doi.org/10.1016/j.ccr.2022.214582>.
 (i) D. Sahoo, R. Benny, N. Kumar KS, S. De. *ChemPlusChem* **87**, e202100322 (2022), <https://doi.org/10.1002/cplu.202100322>.
- [6] (a) M. Sugimoto, T. Yamamoto, Y. Nagata, T. Yamada, Y. Akai. *Pure Appl. Chem.* **84**, 1759 (2012), <https://doi.org/10.1351/pac-con-11-08-23>.
 (b) K. Shimomura, T. Ikai, S. Kanoh, E. Yashima, K. Maeda. *Nat. Chem.* **6**, 429 (2014), <https://doi.org/10.1038/nchem.1916>.
- [7] (a) K. Maeda, K. Morino, Y. Okamoto, T. Sato, E. Yashima. *J. Am. Chem. Soc.* **126**, 4329 (2004), <https://doi.org/10.1021/ja0318378>.
 (b) L. Rosaria, A. d'Urso, A. Mammanna, R. Purrello. *Chirality* **20**, 411 (2008), <https://doi.org/10.1002/chir.20464>.
- [8] S. Akine, M. Miyashita, S. Piao, T. Nabeshima. *Inorg. Chem. Front.* **1**, 53 (2014), <https://doi.org/10.1039/c3qi00067b>.
- [9] For reviews, see:
 (a) S. Akine, T. Nabeshima. *Dalton Trans.*, 10395 (2009), <https://doi.org/10.1039/b910989g>.
 (b) S. Akine. *J. Inclusion Phenom. Macrocycl. Chem.* **72**, 25 (2012), <https://doi.org/10.1007/s10847-011-0026-3>.
 (c) S. Akine. The Chemistry of metal phenolates. in *Patai's Chemistry of Functional Groups*, J. Zabicky (Ed.), Vol. 2, pp. 153–194, John Wiley

- and Sons, Ltd, Chichester, UK (2018), <https://doi.org/10.1002/9780470682531.pat0909>.
- (d) M. T. Chaudhry, S. Akine, M. J. MacLachlan. *Chem. Soc. Rev.* **50**, 10713 (2021), <https://doi.org/10.1039/d1cs00225b>.
- [10] For a review, see: S. Akine. *Dalton Trans.* **50**, 4429 (2021), <https://doi.org/10.1039/d1dt00048a>.
- [11] S. Akine, M. Miyashita, T. Nabeshima. *Inorg. Chem.* **60**, 12961 (2021), <https://doi.org/10.1021/acs.inorgchem.1c01376>.
- [12] For ion recognition by macrocyclic oligo(metallosalen)-type compounds, see:
- (a) S. Akine, S. Sunaga, T. Taniguchi, H. Miyazaki, T. Nabeshima. *Inorg. Chem.* **46**, 2959 (2007), <https://doi.org/10.1021/ic062327s>.
- (b) T. Nabeshima, H. Miyazaki, A. Iwasaki, S. Akine, T. Saiki, C. Ikeda, S. Sato. *Chem. Lett.* **35**, 1070 (2006), <https://doi.org/10.1246/cl.2006.1070>.
- (c) S. Akine, F. Utsuno, T. Nabeshima. *Chem. Commun.* **46**, 1029 (2010), <https://doi.org/10.1039/b915722k>.
- (d) S. Akine, S. Sunaga, T. Nabeshima. *Chem. Eur. J.* **17**, 6853 (2011), <https://doi.org/10.1002/chem.201100122>.
- (e) S. Akine, Z. Varadi, T. Nabeshima. *Eur. J. Inorg. Chem.* **2013**, 5987 (2013), <https://doi.org/10.1002/ejic.201300917>.
- (f) S. Akine, F. Utsuno, S. Piao, H. Orita, S. Tsuzuki, T. Nabeshima. *Inorg. Chem.* **55**, 810 (2016), <https://doi.org/10.1021/acs.inorgchem.5b02288>.
- (g) Y. Sakata, S. Kobayashi, S. Akine. *Chem. Commun.* **53**, 6363 (2017), <https://doi.org/10.1039/c7cc02641b>.
- (h) M. Cametti, Y. Sakata, J. Martí-Rujas, S. Akine. *Inorg. Chem.* **58**, 14871 (2019), <https://doi.org/10.1021/acs.inorgchem.9b02587>.
- (i) M. T. Chaudhry, B. O. Patrick, S. Akine, M. J. MacLachlan. *Org. Biomol. Chem.* **20**, 8259 (2022), <https://doi.org/10.1039/d2ob01511k>.
- [13] For ion recognition by acyclic oligo(metallosalen)-type compounds, see:
- (a) S. Akine, T. Taniguchi, T. Nabeshima. *Angew. Chem., Int. Ed.* **41**, 4670 (2002), <https://doi.org/10.1002/anie.200290011>.
- (b) S. Akine, T. Taniguchi, T. Saiki, T. Nabeshima. *J. Am. Chem. Soc.* **127**, 540 (2005), <https://doi.org/10.1021/ja046790k>.
- (c) S. Akine, T. Taniguchi, T. Nabeshima. *J. Am. Chem. Soc.* **128**, 15765 (2006), <https://doi.org/10.1021/ja0646702>.
- (d) S. Akine, S. Kagiya, T. Nabeshima. *Inorg. Chem.* **46**, 9525 (2007), <https://doi.org/10.1021/ic701585x>.
- (e) S. Akine, T. Taniguchi, T. Nabeshima. *Inorg. Chem.* **47**, 3255 (2008), <https://doi.org/10.1021/ic702255s>.
- (f) S. Akine, Y. Morita, F. Utsuno, T. Nabeshima. *Inorg. Chem.* **48**, 10670 (2009), <https://doi.org/10.1021/ic901372k>.
- (g) S. Akine, S. Kagiya, T. Nabeshima. *Inorg. Chem.* **49**, 2141 (2010), <https://doi.org/10.1021/ic9019926>.
- (h) S. Akine, T. Matsumoto, S. Sairenji, T. Nabeshima. *Supramol. Chem.* **23**, 106 (2011), <https://doi.org/10.1080/10610278.2010.514906>.
- (i) S. Akine, T. Tadokoro, T. Nabeshima. *Inorg. Chem.* **51**, 11478 (2012), <https://doi.org/10.1021/ic3012525>.
- (j) S. Akine, T. Matsumoto, T. Nabeshima. *Angew. Chem., Int. Ed.* **55**, 960 (2016), <https://doi.org/10.1002/anie.201508065>.
- [14] R. D. Shannon. *Acta Crystallogr.* **A32**, 751 (1976), <https://doi.org/10.1107/s0567739476001551>.
- [15] For helicity control of helical oligo(metallosalen)-type compounds, see:
- (a) S. Akine, T. Taniguchi, T. Nabeshima. *Tetrahedron Lett.* **47**, 8419 (2006), <https://doi.org/10.1016/j.tetlet.2006.09.125>.
- (b) S. Akine, T. Matsumoto, T. Nabeshima. *Chem. Commun.*, 4604 (2008), <https://doi.org/10.1039/b810426c>.
- (c) S. Akine, S. Hotate, T. Matsumoto, T. Nabeshima. *Chem. Commun.* **47**, 2925 (2011), <https://doi.org/10.1039/c0cc04998k>.
- (d) S. Akine, S. Hotate, T. Nabeshima. *J. Am. Chem. Soc.* **133**, 13868 (2011), <https://doi.org/10.1021/ja205570z>.
- (e) S. Akine, S. Sairenji, T. Taniguchi, T. Nabeshima. *J. Am. Chem. Soc.* **135**, 12948 (2013), <https://doi.org/10.1021/ja405979v>.
- (f) S. Sairenji, S. Akine, T. Nabeshima. *Tetrahedron Lett.* **55**, 1987 (2014), <https://doi.org/10.1016/j.tetlet.2014.02.009>.
- (g) S. Sairenji, S. Akine, T. Nabeshima. *Chem. Lett.* **43**, 1107 (2014), <https://doi.org/10.1246/cl.140263>.
- (h) S. Sairenji, S. Akine, T. Nabeshima. *Dalton Trans.* **45**, 14902 (2016), <https://doi.org/10.1039/c6dt02635d>.
- [16] Helicity inversion speeds of some helical metal complexes were controlled by changing its core metal ion, see:
- (a) S. Akine, T. Taniguchi, T. Matsumoto, T. Nabeshima. *Chem. Commun.*, 4961 (2006), <https://doi.org/10.1039/b610641b>.
- (b) H. Miyake, H. Kamon, I. Miyahara, H. Sugimoto, H. Tsukube. *J. Am. Chem. Soc.* **130**, 792 (2008), <https://doi.org/10.1021/ja0768385>.
- [17] Helicity changes driven by a chemical reaction, see: S. Sairenji, S. Akine, T. Nabeshima. *Sci. Rep.* **8**, 137 (2018), <https://doi.org/10.1038/s41598-017-16503-1>.
- [18] Ligand exchange reactions at cobalt(III) centers in dinuclear macrocyclic complexes, see:
- (a) Y. Sakata, C. Murata, S. Akine. *Nat. Commun.* **8**, 16005 (2017), <https://doi.org/10.1038/ncomms16005>.
- (b) Y. Sakata, M. Tamiya, M. Okada, S. Akine. *J. Am. Chem. Soc.* **141**, 15597 (2019), <https://doi.org/10.1021/jacs.9b06926>.
- (c) Y. Sakata, M. Okada, M. Tamiya, S. Akine. *Chem. Eur. J.* **26**, 7595 (2020), <https://doi.org/10.1002/chem.202001072>.
- (d) Y. Sakata, M. Okada, S. Akine. *Chem. Eur. J.* **27**, 2284 (2021), <https://doi.org/10.1002/chem.202004487>.
- [19] The cobalt(III) metallocryptand framework was originally investigated from the viewpoint of its slow guest uptake/release behavior:
- (a) S. Akine, M. Miyashita, T. Nabeshima. *J. Am. Chem. Soc.* **139**, 4631 (2017), <https://doi.org/10.1021/jacs.7b00840>.
- (b) S. Akine, M. Miyashita, T. Nabeshima. *Chem. Eur. J.* **25**, 1432 (2019), <https://doi.org/10.1002/chem.201805359>.
- (c) S. Akine, Y. Sakata. *Chem. Lett.* **49**, 428 (2020), <https://doi.org/10.1246/cl.200017>.
- [20] Y. Sakata, S. Chiba, M. Miyashita, T. Nabeshima, S. Akine. *Chem. Eur. J.* **25**, 2962 (2019), <https://doi.org/10.1002/chem.201805799>.
- [21] Y. Sakata, S. Chiba, S. Akine. *Proc. Natl. Acad. Sci. U. S. A.* **119**, e2113237119 (2022), <https://doi.org/10.1073/pnas.2113237119>.