Thermally stable helical poly(4-carboxyphenyl isocyanide) with a helicity memory assisted by metal coordination

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INTRODUCTION

Helical polymers with a controlled handedness have the potential for developing novel helical polymer-based asymmetric catalysts as well as chiral materials for sensing and separating chiral molecules. Hence, a large number of helical polymers with an optical activity has been prepared to develop such chiral materials that have been in practical use during the past decades.[1,2] Among the helical polymers prepared so far, helical poly(phenylacetylene)s and poly(phenyl isocyanide)s bearing achiral functional pendant groups are unique,[1,2] because one of the helices can be induced in the as-prepared optically-inactive polymers through noncovalent interactions between the functional pendants and chiral molecules, and the induced helices can be further memorized after replacing the chiral molecules with achiral ones[3] and by simply removing the chiral molecules.[4] The former induced helices of the poly(phenylacetylene)s are dynamic, therefore, the use of achiral molecules are essential for the memory of the induced helical conformation except for a polyacetylene bearing 2,2′-biphenol-derived pendants.[5] In sharp contrast, achiral molecules are not required to memorize the induced helicity in the polyisocyanide. Typically, one of the helices is induced in the sodium salt of poly(4-carboxyphenyl isocyanide) (poly-**1**-**Na**) upon complexation with chiral amines, such as (*R*)-phenylglycinol ((*R*)-**2**), which is accompanied by the *syn-anti* configurational isomerization around the C=N backbones. Therefore, the induced helical structure of the polyisocyanide (***h***-poly-**1**-**Na**) is automatically memorized during the helicity induction process, thereby retaining its preferred-handed helicity even after the (*R*)-**2** is completely removed (Figure 1a).[4,6] The polyisocyanide (***h***-poly-**1**-**Na**) with the helicity memory is, however, thermally unstable and lost its helical memory at high temperature due to the *syn-anti* isomerization of the main-chain.[4,6,7] In order to overcome this problem, ***h***-poly-**1**-**Na** was cross-linked by diamines in water to produce a chemically cross-linked hydrogel, which maintained its optical activity derived from the helicity memory even at 90 °C.[8]

We envisioned that the thermal stability of ***h***-poly-**1**-**Na** would also be improved in the presence of divalent (M^{2+}) and trivalent (M^{3+}) metal ions that can coordinate to the pendant

carboxylate residues of **h**-poly-**1**-**Na**, thereby forming a noncovalently cross-linked network through an intra- and/or intermolecular coordination (Figure 1b,c). Noncovalent cross-linking with metal ions may be superior to the covalent cross-linking because the former metal-coordinated cross-linked helical polymers[9–11] can be recyclable and also applicable for the development of metal-catalyzed asymmetric catalysis.[12] To this end, **h**-poly-**1**-**Na** was noncovalently cross-linked with a series of divalent (M^{2+}) and trivalent (M^{3+}) metal ions in dilute and concentrated aqueous solutions, and the thermal stabilities of the resulting **h**-poly-**1**-**Na** complexed with metal ions in a solution and in a hydrogel were investigated by circular dichroism (CD) spectroscopy.

(Figure 1)

EXPERIMENTAL SECTION

An optically-inactive poly-**1**-**Na** was prepared by the polymerization of sodium 4-isocyanobenzoate with $NiCl_2 \cdot 6H_2O$ in water according to the reported method.[4,6] The number-average molecular weight (M_n) and its distribution (M_w/M_n) of poly-**1**-**Na** were estimated as its methyl esters by size-exclusion chromatography (SEC) with polystyrene standards (Tosoh). Poly-**1**-**Na** ($M_n = 2.7 \times 10^4$ and $M_w/M_n = 2.7$ or $M_n = 3.2 \times 10^4$ and $M_w/M_n = 2.5$) was then annealed with (R)-**2** in water at 50 °C for 45 days to induce a preferred-handed helicity. The resulting optically-active poly-**1**-**Na** was isolated in a similar manner as already reported,[4,6] producing **h**-poly-**1**-**Na** containing no (R)-**2**, but showed an optical activity due to its helicity memory (Figure 1a) (see Supplementary Information for more detailed experimental procedures).

RESULTS AND DISCUSSION

h-Poly-**1**-**Na** ($M_n = 2.7 \times 10^4$, $M_w/M_n = 2.7$) with a macromolecular helicity memory prepared by the previously reported method[4,6] showed an induced circular dichroism (ICD) in the iminomethylene backbone (ca. 300−460 nm) as well as in the aromatic pendant regions (200−ca.

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300 nm) solely due to the preferred-handed helical structure (Figure 2a,b, red lines).[4,6] However, the helical structure of **h**-poly-**1**-**Na** is not thermally stable and readily unfolds into the corresponding optically-inactive, as-prepared poly-**1**-**Na** in water at high temperature through the configurational isomerization of the C=N double bonds.[6]

The thermal stability of **h**-poly-**1**-**Na** was then evaluated in the presence of a series of divalent and trivalent metal ions (Figure 2c,d) in a dilute aqueous solution of **h**-poly-**1**-**Na** by measuring the CD of the solution after heating at 90 °C for 20 min, through which the optical activity of **h**-poly-**1**-**Na** completely disappeared in water in the absence of metals as already mentioned. Figures 2a and b show the typical CD and absorption spectra of **h**-poly-**1**-**Na** in the presence of 0.4 equiv. of divalent Co^{2+} and 0.2 equiv. of trivalent Tb^{3+} ions before (blue lines) and after (dashed blue lines) heating at 90 °C for 20 min, respectively. Upon complexation with the Co^{2+} and Tb^{3+} ions, the CD spectral patterns of **h**-poly-**1**-**Na** significantly changed, in particular, those in the pendant aromatic regions (200− ca. 300 nm), accompanied by a remarkable enhancement of the CD intensities along with a change in their absorption spectra with a red-shift, indicating a change in the chiral arrangement of the aromatic groups along the helical polymer backbone through metal coordination.

Interestingly, the macromolecular helicity memory of the **h**-poly-**1**-**Na**, namely, its preferred-handed helical structure was almost retained upon heating at 90 °C for 20 min once complexed with the Co^{2+} and Tb^{3+} ions. The estimated relative CD intensities of the **h**-poly-**1**-**Na** complexed with the Co^{2+} and Tb^{3+} ions before and after heating based on the first Cotton effect (CD_{1st}) intensities of the **h**-poly-**1**-**Na**-metal complexes before heating as the base values were 91 and 88%, respectively (Figure 2c,d), indicating that the thermal stability of the helical structure of **h**-poly-**1**-**Na** was significantly improved mostly due to an intramolecular physical cross-linking by metal coordination (Figure 1b).

In a similar way, the effects of the metal species on the stability of the helical structure of **h**-poly-**1**-**Na** were then investigated by measuring the CD spectra of **h**-poly-**1**-**Na** in the presence of a

variety of divalent (M^{2+}) (0.2 and 0.4 equiv.) and trivalent (M^{3+}) (0.2 equiv.) metal ions before and after heating at 90 °C for 20 min, and the relative CD intensities (CD_{1st}) are summarized in Figures 2c and d, respectively. The CD intensities of **h-poly-1-Na** with 0.2 equiv. of divalent metal ions, except for the Cu^{2+} ion, drastically decreased at 90 °C showing the relative CD intensities of 6–21% (Figure 2c, black bars), while the Cu^{2+} ion, which is known to have a higher binding affinity toward carboxylate anions among the divalent metal ions used in the present study,[13,14] effectively stabilized the **h-poly-1-Na** helix with the relative CD intensity of 53% (Figure 2c). In the presence of 0.4 equiv. of divalent metal ions, however, the thermal stability of **h-poly-1-Na** was significantly improved in the following order based on the relative CD intensity: Cu^{2+} and Co^{2+} (91%) > Ni^{2+} (87%) > Zn^{2+} (85%) > Ca^{2+} (79%) > Mg^{2+} (64%). This order is consistent with the binding affinity of the divalent metal ions toward carboxylate anions.[13,14] It should be noted that the **h-poly-1-Na** helix with an excess handedness was almost completely retained upon complexation with 0.4 equiv. of Cu^{2+} and Co^{2+} ions. The CD titration experiments of Cu^{2+} (Supplementary Figure S1) and Co^{2+} (Supplementary Figure S2) ions with **h-poly-1-Na** and subsequent annealing at 90 °C for 20 min revealed that 0.3 equiv. of Cu^{2+} ions is sufficient to stabilize the helical structure of **h-poly-1-Na**.

As anticipated, 0.2 equiv. of the trivalent metal ions enhanced the thermal stability of the **h-poly-1-Na** helix when compared to 0.2 equiv. of the divalent metal ions (Figure 2c,d). Importantly, the macromolecular helicity memory of the **h-poly-1-Na** was almost retained upon complexation with 0.2 equiv. of lanthanide ions after heating at 90 °C for 20 min irrespective of the kinds of lanthanides used, showing the relative CD intensities of 83–91% (Figure 2d), and the **h-poly-1-Na** complexed with the Yb^{3+} ions retained its helicity memory with the relative CD intensity of 50% upon further heating at 90 °C for 16 h in water. The observed high stability of the **h-poly-1-Na** helix assisted by the trivalent lanthanide coordination is attributed to their large effective ionic radii[15] as well as the preference of high coordination numbers and high binding affinities toward carboxylate anions.[16–18]

(Figure 2)

Interestingly, when the ***h*-poly-1-Na** concentration was higher than 30 mg ml^{-1} in water, a solution of the ***h*-poly-1-Na** became viscous and gelled within 1.5 h after the addition of a small amount of Tb^{3+} ions (0.025–0.050 equiv.), thus producing an optically-active hydrogel (gel$_{Tb}$-***h*-poly-1-Na**) through noncovalent intermolecular cross-linking with the Tb^{3+} ions (Figure 1c). The hydrogel (gel$_{Tb}$-***h*-poly-1-Na**) composed of ***h*-poly-1-Na** (50 mg/ml) with 0.050 equiv. of Tb^{3+} ions exhibited an ICD (Figure 3a, blue line) whose CD spectral pattern was similar to that of the ***h*-poly-1-Na** complexed with 0.2 equiv. of Tb^{3+} ions in a dilute solution (Figure 2b, blue line). More interestingly, the helical structure of the ***h*-poly-1-Na** chains with the helicity memory in the hydrogel (gel$_{Tb}$-***h*-poly-1-Na**) cross-linked by metal coordination with 0.050 equiv. of Tb^{3+} ions was unexpectedly stable and preserved its excess handedness showing the relative CD intensity at 354 nm of ca. 90% even at 90 °C as revealed by temperature jump experiments monitored by CD (Figure 3b, filled circles), whereas the ***h*-poly-1-Na** completely lost its helicity memory at 80 °C in water (Figure 3b, black line) as previously reported.[4]

(Figure 3)

CONCLUSIONS

We have developed a highly versatile method for stabilizing an excess-handed helical polyisocyanide induced and memorized in the polymer backbone using divalent and trivalent metal ions as a noncovalent cross-linker through intra- and/or intermolecular metal coordination. Among the metal ions investigated, lanthanide ions were proved to be the most efficient and remarkably improved the thermal stability of the helical polyisocyanide in a solution as well as in a gel. The present lanthanide-coordinated helical polyisocyanides with heat resistance will be applicable for developing novel helical polymer-based asymmetric catalysts and chiral/chirality sensing reagents

since lanthanide ions complexed with chiral ligands have been reported to catalyze a wide range of enantioselective transformations with an excellent enantioselectivity[19] and to sense the chirality of a variety of chiral molecules with a high sensitivity by CD, NMR, and circularly polarized luminescence (CPL)[20].

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

References

(1)   Yashima, E., Maeda, K., Iida, H., Furusho, Y. & Nagai, K. Helical polymers: synthesis, structures, and functions. *Chem. Rev.* **109**, 6102–6211 (2009).

(2)   Yashima, E., Ousaka, N., Taura, D., Shimomura, K., Ikai, T. & Maeda, K. Supramolecular helical systems: helical assemblies of small molecules, foldamers, and polymers with chiral amplification and their functions. *Chem. Rev.* **116**, 13752–13990 (2016).

(3)   Yashima, E., Maeda, K. & Okamoto, Y. Memory of macromolecular helicity assisted by interaction with achiral small molecules. *Nature* **399**, 449–451 (1999).

(4)   Ishikawa, M., Maeda, K., Mitsutsuji, Y. & Yashima, E. An unprecedented memory of macromolecular helicity induced in an achiral polyisocyanide in water. *J. Am. Chem. Soc.* **126**, 732–733 (2004).

(5)   Shimomura, K., Ikai, T., Kanoh, S., Yashima, E. & Maeda, K. Switchable enantioseparation based on macromolecular memory of a helical polyacetylene in the solid state. *Nat. Chem.* **6**, 429–434 (2014).

(6)   Hase, Y., Nagai, K., Iida, H., Maeda, K., Ochi, N., Sawabe, K., Sakajiri, K., Okoshi, K. & Yashima, E. Mechanism of helix induction in poly(4-carboxyphenyl isocyanide) with chiral amines and memory of the macromolecular helicity and its helical structures. *J. Am. Chem. Soc.* **131**, 10719–10732 (2009).

(7)   Hase, Y., Ishikawa, M., Muraki, R., Maeda, K. & Yashima, E. Helicity induction in a poly(4-carboxyphenyl isocyanide) with chiral amines and memory of the macromolecular helicity in aqueous solution. *Macromolecules* **39**, 6003–6008 (2006).

(8)   Ishikawa, M., Taura, D., Maeda, K. & Yashima, E. An optically active hydrogel composed of cross-linked poly(4-carboxyphenyl isocyanide) with a macromolecular helicity memory. *Chem. Lett.* **33**, 550–551 (2004).

(9)   Takashima, S., Abe, H. & Inouye, M. Copper(II)-mediated chiral helicity amplification and inversion of *meta*-ethynylpyridine polymers with metal coordination sites. *Chem. Commun.* **47**, 7455–7457 (2011).

(10)   Makida, H., Abe, H. & Inouye, M. Highly efficient stabilisation of *meta*-ethynylpyridine polymers with amide side chains in water by coordination of rare-earth metals. *Org. Biomol. Chem.* **13**, 1700–1707 (2015).

(11)   Prince, R. B., Okada, T. & Moore, J. S. Controlling the secondary structure of nonbiological oligomers with solvophobic and coordination interactions. *Angew. Chem. Int. Ed.* **38**, 233–236 (1999).

(12)   Suginome, M., Yamamoto, T. & Nagata, Y. Poly(quinoxaline-2,3-diyl)s: A fascinating helical macromolecular scaffold for new chiral functions. *J. Synth. Org. Chem., Jpn.* **73**, 1141–1155 (2015).

(13) Roma-Luciow, R., Sarraf, L. & Morcellet, M. Complexes of poly(acrylic acid) with some divalent, trivalent and tetravalent metal ions. *Eur. Polym. J.* **37**, 1741–1745 (2001).

(14) Porasso, R. D., Benegas, J. C. & Van den Hoop, M. A. G. T. Chemical and electrostatic association of various metal ions by poly(acrylic acid) and poly(methacrylic acid) as studied by potentiometry. *J. Phys. Chem. B* **103**, 2361–2365 (1999).

(15) Shannon, R. D. Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides. *Acta Cryst.* **A32**, 751–767 (1976).

(16) Qi, X., Wang, Z., Ma, S., Wu, L., Yang, S. & Xu, J. Complexation behavior of poly(acrylic acid) and lanthanide ions. *Polymer* **55**, 1183–1189 (2014).

(17) Alexander, V. Design and synthesis of macrocyclic ligands and their complexes of lanthanides and actinides. *Chem. Rev.* **95**, 273–342 (1995).

(18) Kogej, K., Fonseca, S. M., Rovisco, J., Azenha, M. E., Ramos, M. L., Seixas de Melo, J. S. & Burrows, H. D. Understanding the interaction between trivalent lanthanide ions and stereoregular polymethacrylates through luminescence, binding isotherms, NMR, and interaction with cetylpyridinium chloride. *Langmuir* **29**, 14429–14437 (2013).

(19) Kobayashi, S., Sugiura, M., Kitagawa, H. & Lam, W. W.-L. Rare-earth metal triflates in organic synthesis. *Chem. Rev.* **102**, 2227–2302 (2002).

(20) Tsukube, H. & Shinoda, S. Lanthanide complexes in molecular recognition and chirality sensing of biological substrates. *Chem. Rev.* **102**, 2389–2403 (2002).
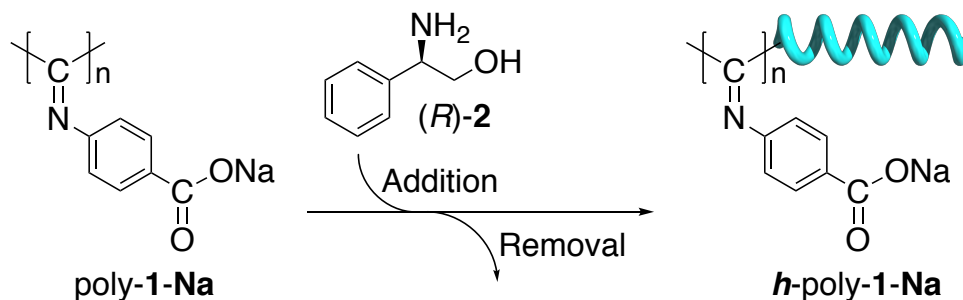
Figure Legends

Figure 1 Schematic illustrations of (a) a preferred-handed helicity induction with (*R*)-**2** in poly-**1**-**Na** in water and memory of the helicity (*h*-poly-**1**-**Na**) after complete removal of (*R*)-**2**, and (b) intramolecular and (c) intermolecular physical cross-linking of *h*-poly-**1**-**Na** with divalent (M^{2+}) and trivalent (M^{3+}) metal ions in water.
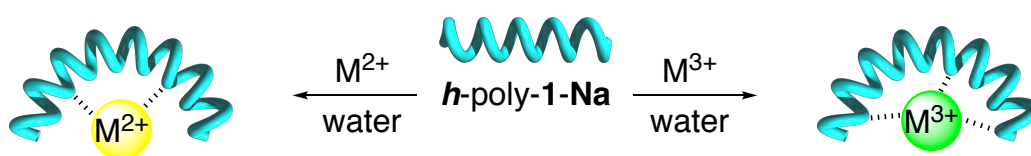

Figure 2 (a and b) CD and absorption spectra of *h*-poly-**1**-**Na** (0.050 mg ml^{-1}) in water in the absence (red lines) and presence of (a) Co^{2+} (0.4 equiv.) and (b) Tb^{3+} (0.2 equiv.) ions before (blue lines) and after (dashed blue lines) heating at 90 °C for 20 min. (c and d) Relative CD intensities (%) of *h*-poly-**1**-**Na** in the presence of a series of (c) divalent (0.2 (black bars) and 0.4 equiv. (white bars)) and (d) trivalent (0.2 equiv.) (black bars) ions before and after heating at 90 °C for 20 min. The relative CD intensities (%) were estimated based on the first Cotton effect (CD_{1st}) intensities of *h*-poly-**1**-**Na** with metal ions before heating as the base values.

Figure 3 (a) CD and absorption spectra of *h*-poly-**1**-**Na** (1.0 mg ml^{-1}) in water (red lines) and gel$_{Tb}$-*h*-poly-**1**-**Na** ([*h*-poly-**1**-**Na**] = 50 mg ml^{-1}, [Tb^{3+}]/[monomer units of *h*-poly-**1**-**Na**] = 0.050) (blue lines) at room temperature. The CD intensity of gel$_{Tb}$-*h*-poly-**1**-**Na** was normalized using the molar absorptivity at 354 nm (ε_{354} = 1509). The contribution of the linear dichroism (LD) caused by the macroscopic anisotropy derived from gels was negligible. The inset shows a photograph of gel$_{Tb}$-*h*-poly-**1**-**Na**. (b) Temperature-dependent CD intensity changes at 354 nm of *h*-poly-**1**-**Na** in water (black line) and gel$_{Tb}$-*h*-poly-**1**-**Na** (filled circles) investigated by a temperature jump method. The gel was allowed to stand at fixed temperature and its CD was then measured at room temperature. *h*-Poly-**1**-**Na** (M_n = 3.2 × 10^4 and $\Delta\varepsilon_{360}$ = −10.2) was used.

a Helicity induction and memory

poly-**1**-**Na**   (*R*)-**2**   *h*-poly-**1**-**Na**

b Intramolecular cross-linking by metal coordination

M^{2+} / water   *h*-poly-**1**-**Na** M^{3+} / water

c Intermolecular cross-linking by metal coordination

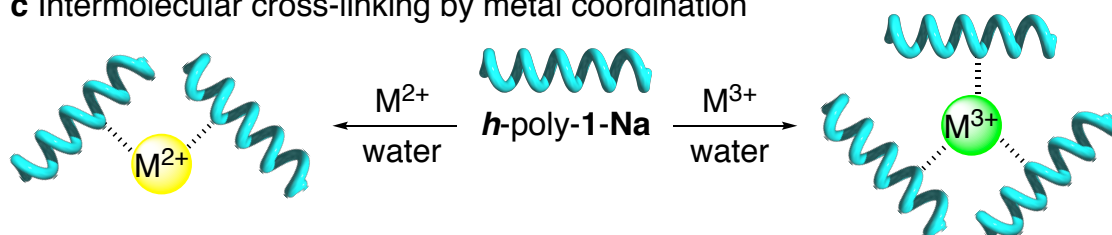M^{2+} / water   *h*-poly-**1**-**Na** M^{3+} / water

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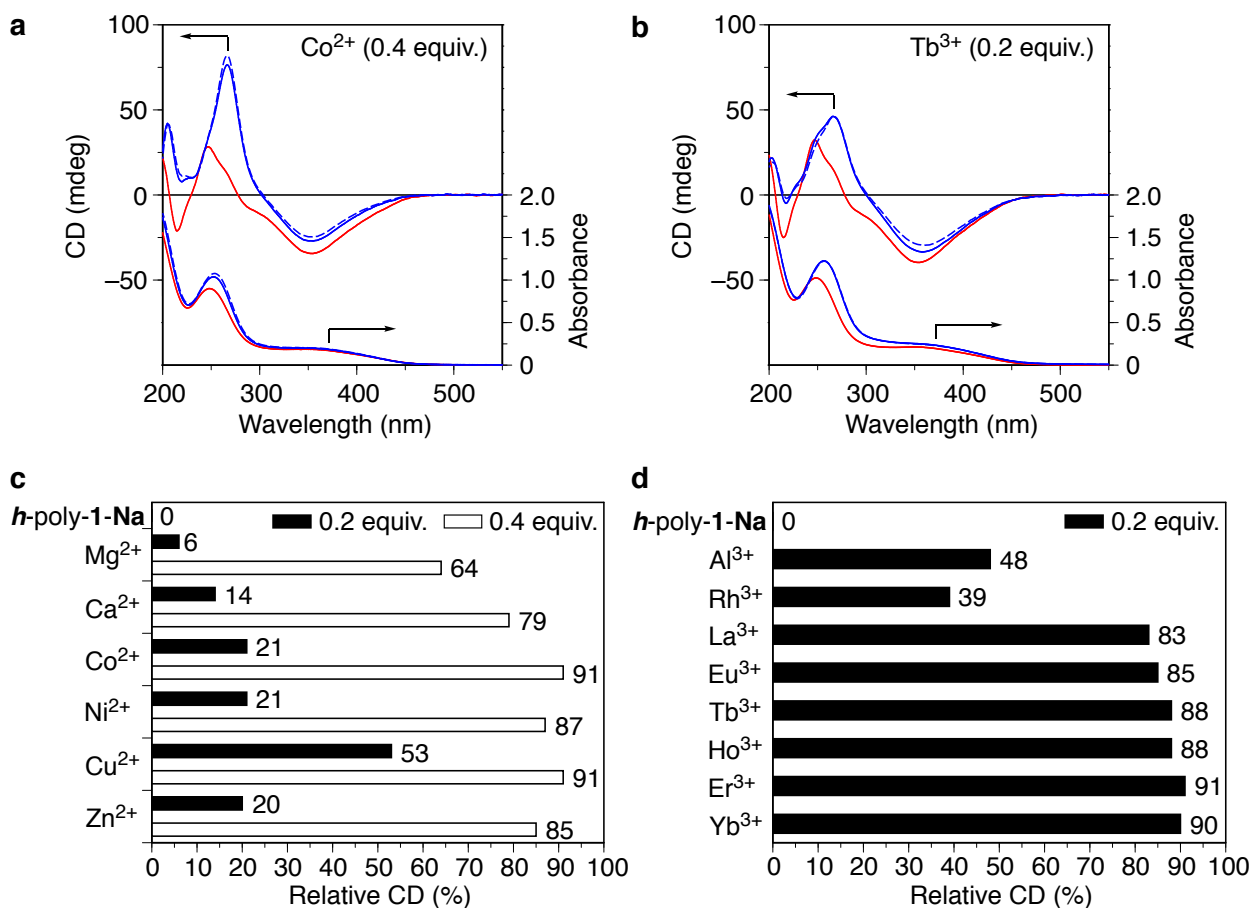
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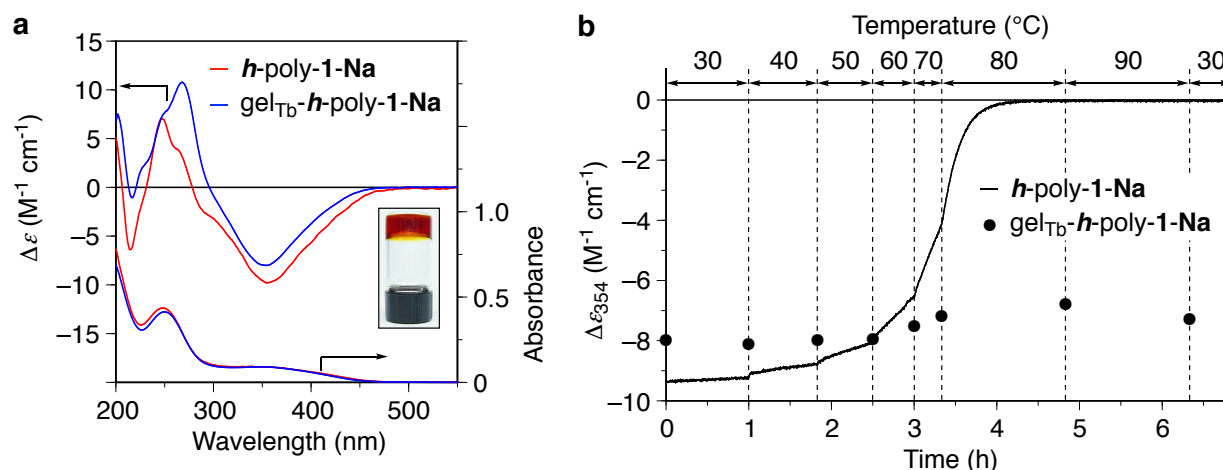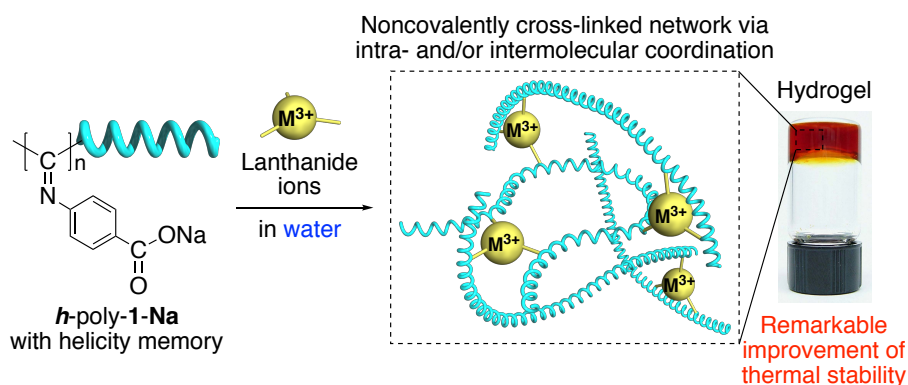
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For graphical abstract:

Thermally stable helical poly(4-carboxyphenyl isocyanide) with a helicity memory assisted by metal coordination

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Noncovalently cross-linked network via intra- and/or intermolecular coordination

Lanthanide ions

in water

h-poly-**1**-**Na** with helicity memory

Hydrogel

Remarkable improvement of thermal stability

A versatile method for stabilizing an excess-handed helical polyisocyanide induced and memorized in the polymer backbone has been developed using divalent and trivalent metal ions that can coordinate to the pendant carboxylate residues of the polyisocyanide, thereby forming a noncovalently cross-linked network through an intra- and/or intermolecular coordination. Among the metal ions investigated, lanthanide ions were proved to be the most efficient and remarkably improved the thermal stability of the helical polyisocyanide in a solution as well as in a gel.