A supramolecular lanthanide separation approach based on multivalent cooperative enhancement of metal ion selectivity

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Multivalent cooperativity plays an important role in the supramolecular self-assembly process. Herein, we report a remarkable cooperative enhancement of both structural integrity and metal ion selectivity on metal-organic M4L4 tetrahedral cages self-assembled from a tris-tridentate ligand (L1) with a variety of metal ions spanning across the periodic table, including alkaline earth (CaII), transition (CdII), and all the lanthanide (LnIII) metal ions. All these M4L14 cages are stable to excess metal ions and ligands, which is in sharp contrast with the tridentate (L2) ligand and bis-tridentate (L3) ligand bearing the same coordination motif as L1. Moreover, high-precision metal ion self-sorting is observed during the mixed-metal self-assembly of tetrahedral M4L4 cages, but not on the M2L3 counterparts. Based on the strong cooperative metal ion self-recognition behavior of M4L4 cages, a supramolecular approach to lanthanide separation is demonstrated, offering a new design principle of next-generation extractants for highly efficient lanthanide separation.
Lanthanides, owing to their peculiar electronic structure, are used in a wealth of important applications, including batteries, display devices, contrast agents, magnetic or superconducting materials, and catalytic convertors. Because they tend to be distributed in relatively small concentrations and highly insoluble in their pure forms, solvent extraction has been the primary means to separate, purify and recycle lanthanides. Especially, separation from calcium, one of the primary associated elements in lanthanide minerals, such as cerite and loparite-Ce, with an ionic radius similar to those in the middle of the lanthanide series, is crucial in the refining of high-grade lanthanide concentrates. Moreover, nuclear reactors generate a wide variety of waste products including radioactive mixtures, lanthanides, and transition metals, which also require effective conversion and separation for long-term storage and recycling. Owing to the similar ionic radii and coordination numbers/geometries of the rare earth elements, as well as calcium and cadmium metal ions, traditional extraction processes must be conducted in a cascade for complete separation and purification of the desired element. New separation techniques that eliminate processing steps and waste are, therefore, of great importance with respect to economic and environmental concerns.

Selective binding of metal ions has been a classical research topic in supramolecular chemistry since the very beginning of the field. Covalent crown- or cryptand-based receptors possessing a complementary binding pocket are known to have specific ion-recognition properties. Meanwhile, designed metal ion hosts that utilize the preorganization effect of the supramolecular scaffold have also been widely studied. Moreover, a newly proposed solvent-free extraction/separation process is making use of resins derivatized with macrocyclic ligands. However, almost all of these traditional extractants rely on the selective formation of mononuclear complex from metal ion mixtures. Metal selectivity in multinuclear complexes, especially for lanthanides, has been overlooked for a long time, possibly as a result of the limited number of stable multinuclear lanthanide complexes that exist in solution. To the best of our knowledge, there are only a few examples of the control of lanthanide metal selectivity using self-assembly in the literature, and they are mainly based on the formation of dinuclear lanthanide helicate architectures.

Multivalency plays an essential role, both in the mediation of biological processes as well as in the construction of supramolecular structures. An important example of a multivalent interaction in nature is the interaction between a virus and its host cell, which leads to a stable initial adhesion. Remarkable enhancement in stability has also been proven for the self-assembly of three-dimensional architectures and capsules through the cooperative effect of a vast amount of noncovalent interactions. This strong multivalent cooperativity is believed to be the main driving force for the self-sorting phenomena observed in these multi-component assemblies, which bias the complicated system toward the selective formation of one well-defined structure. However, until now the term self-sorting has been predominantly used when referring to the organic components in a metal–organic assembly. In clear contrast, metal ion self-sorting has scarcely been studied, especially in the cases where ionic radii discrepancy is the only variable.

In our previous work, the first stereoselective self-assembly of chiral lanthanide tetrahedral cages was accomplished with intriguing ligand self-sorting behavior owing to the strong supramolecular cooperative mechanical-coupling effect. Herein, we report the unprecedented self-assembly capacity of with metal ions spanning across the periodic table, including alkaline earth (Ca), transition (Cd), and all the lanthanide (Ln) metal ions, ascribed to the appropriate rigidity of the symmetrical scaffolding, high assembly adaptability and adequate chelating affinity with lanthanide ions of the neutral coordination motif. More importantly, this versatile ligand displayed rare and rather high discrimination between metal ions with identical coordination geometries as well as extremely small ionic difference, arising from supramolecular multivalent cooperativity, resulting in absolute or highly efficient metal ion self-recognition during mixed-metal self-assembly process. During both one-pot mixed-metal self-assembly and post-synthetic metal-metathesis experiments, we have observed unprecedented discrimination in favor of including the smaller lanthanide ions in the tetranuclear complexes. For comparison purpose, monodentate (L) and bis-tridentate (L) ligands, bearing the same coordination motif as L, have been synthesized; they turned out to be either unable to self-assemble, or form very fragile mononuclear and dinuclear complexes and no analogous high-precision metal ion self-recognition as that in the mixed-metal self-assembly of tetrahedral cages. For comparison purpose, monodentate (L) and bis-tridentate (L) ligands, bearing the same coordination motif as L, have been synthesized; they turned out to be either unable to self-assemble, or form very fragile mononuclear and dinuclear complexes and no analogous high-precision metal ion self-recognition as that in the mixed-metal self-assembly of tetrahedral cages.
single species was first confirmed by \(^1\)H NMR (nuclear magnetic resonance) spectroscopy, where a single set of signals was observed, pointing to the equivalence of the ligand strands in the complex (Fig. 1a). The high symmetry of the product is further suggested by the \(^1\)H-\(^1\)H COSY spectrum, which shows the ligands experiencing identical magnetic environments (Supplementary Fig. 30). Furthermore, \(^1\)H diffusion ordered spectroscopy (DOSY) shows that all the protons of the tetrahedral cages have the same diffusion coefficient, with a dynamic radii calculated with Stokes-Einstein equation to be about 14.5 Å (Supplementary Fig. 63), consistent and isostructural with the reported Eu\(_4\)(L\(_1\))\(_4\) cage\(^{51}\). High-resolution electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) analyses further confirmed the chemical formula of the isolated tetrahedral cage to be [Ca\(_4\)(L\(_1\))\(_4\)](CF\(_3\)SO\(_3\))\(_8\), as shown in Fig. 1b. The spectrum features a series of peaks corresponding to multi-charged species with progressive loss of anions: for instance, peaks with m/z equal to 677.3736, 815.0914, and 1007.9010 could be assigned to the charged molecular [Ca\(_4\)(L\(_1\))\(_4\)](CF\(_3\)SO\(_3\))\(_n\) with n = 1 (7 + ), 2 (6 + ), and 3 (5 + ). The assignments were also verified by carefully comparing the simulated isotopic distributions of the peaks with high-resolution experimental data.

Similarly, 1D and 2D NMR, ESI-TOF-MS confirmed the formation of a transition metal Cd\(_4\)(L\(_1\))\(_4\) cage under the same reaction conditions by replacing the metal source with Cd (ClO\(_4\))\(_2\)6H\(_2\)O (Fig. 1c, d, Supplementary Figs. 32, 64, and 210). The structure of this tetrahedral complex was unambiguously confirmed by single-crystal X-ray diffraction studies. Crystals of Cd\(_4\)(L\(_1\))\(_4\)(ClO\(_4\))\(_8\) were obtained by slow vapor diffusion of dichloromethane into an acetonitrile solution of the complex. The X-ray structure of Cd\(_4\)(L\(_1\))\(_4\) shares most of the common features as that of the known Eu\(_4\)(L\(_1\))\(_4\) tetrahedral complex, except for crystallizing in a different P\(_6\)\(_2\)\(_2\) space group (Fig. 2, Supplementary Data 1, Supplementary Figs. 1–3 and Supplementary Table 7). It is worth pointing out that in this case all Cd\(_{II}\) centers adopt nine-coordinating trigonal prismatic geometry. This is clearly different from the known Cd\(_4\)(L\(_1\))\(_4\)-type cage assembled from another tris-tridentate ligand reported by Rizzuto et al.\(^{54}\) recently, where the Cd\(_{II}\) adopted a six-coordinating octahedral geometry. So the crystal structure of our Cd\(_4\)(L\(_1\))\(_4\) cage represents the first example of discrete supramolecular framework using nine-coordinated Cd\(_{II}\) as vertices.

In similar reaction conditions as above, isostructural Ln\(_4\)(L\(_1\))\(_4\) tetrahedral complexes were also obtained by reaction of L\(_1\) with different Ln\(_{III}\) metal salts, as confirmed by 1D and 2D NMR spectroscopy (for La\(_{III}\), Ce\(_{III}\), Pr\(_{III}\), Nd\(_{III}\), Sm\(_{III}\), Yb\(_{III}\), Lu\(_{III}\), and Y\(_{III}\)) and ESI-TOF-MS (Supplementary Figs. 35–72, 211–219). The self-assembled complexes of diamagnetic Y\(_{III}\), La\(_{III}\), Lu\(_{III}\) and weakly paramagnetic Sm\(_{III}\) show small chemical shifts compared to those of the ligands, while paramagnetic Ln\(_{III}\) ions (Ce\(_{III}\), Pr\(_{III}\), Nd\(_{III}\), Eu\(_{III}\), Yb\(_{III}\)) shift the complexes resonances downfield and upfield obviously (Supplementary Table 1 and Fig. 62).

Moreover, single-crystal X-ray diffraction analysis of La\(_4\)(L\(_1\))\(_4\) confirmed the tetrahedral molecular structure arrangement, consistent and isostructural with the reported Eu\(_4\)(L\(_1\))\(_4\) cage (Supplementary Figs. 2, Supplementary Figs. 4–6 and Supplementary Table 8)\(^{53}\). Although the discrete M\(_4\)(L\(_1\))\(_4\)-type tetrahedral complexes are “isostructural” in nature, there are some distinct differences between the Cd\(_{II}\) complex and the La\(_{III}\) complex in their packing diagrams in the crystal states. Cd\(_4\)(L\(_1\))\(_4\) tetrahedral cages are very loosely packed in the ab plane and there are infinite channels with diameters of ca. 2.24 nm along the c axis. As a result, “void” occupancy as much as 32.5% “void” occupancy is found by PLATON (Supplementary Fig. 7)\(^{55}\). As a result, crystals of Cd\(_4\)(L\(_1\))\(_4\) diffract much more weakly than those of La\(_4\)(L\(_1\))\(_4\).

The formation of M\(_4\)L\(_4\) cages with various metal sources was inspiring, considering the facts that, until now, there was only one known discrete tetrahedral structure (Mg\(_4\)L\(_4\)) made from AE\(_{II}\) (alkaline earth metal ions), which was self-assembled from anionic 1,3-dicarbonyl ligand\(^{56}\); and transition metal Cd\(_{II}\) has been known to form only M\(_4\)L\(_4\)-type cages with tris-tridentate ligands\(^{54}\); and furthermore, in general, both AE\(_{II}\) and TM\(_{II}\) (transition metal ions) favor smaller coordination numbers instead of nine-coordinating trigonal prismatic geometry in their supramolecular coordination compounds\(^{57–59}\).

**High-precision metal ion selectivity in M\(_4\)L\(_4\)**: Given the high self-assembly versatility of the tris-tridentate ligand (L\(_1\)), metal ion selectivity was examined through mixed-metal self-assembly experiments (Ln\(_{III}\)/Ln\(_{III}\)/L\(_1\) = 1/1/1) and high-precision metal ion self-sorting behavior was observed due to the multivalent cooperative effect. When self-assembly of L\(_1\) (1.00 equiv) with an equimolar mixture of Ca(ClO\(_4\))\(_2\)•4H\(_2\)O (1.00 equiv) and La (ClO\(_4\))\(_3\)•6H\(_2\)O (1.00 equiv) was performed, absolute metal-selective self-organization, or in other words, narcissistic metal ion self-recognition, was observed, as the \(^1\)H NMR analysis showed only resonances corresponding to La\(_4\)(L\(_1\))\(_4\) tetrahedral complexes (Supplementary Fig. 140). The exclusive formation of the homometallic La\(_4\)(L\(_1\))\(_4\) complex was also confirmed by ESI-TOF-MS, in which only multiple charged species ascribed to [La\(_4\)(L\(_1\))\(_4\)](ClO\(_4\))\(_m\)•nH\(_2\)O (m=12–m+n) were found (Supplementary Fig. 240).

Analogous to the above self-assembly process, reaction of L\(_1\) (1.00 equiv) with metal ion mixtures of Cd\(_{II}\)/La\(_{III}\) (1.00 equiv of each) led to the formation of homometallic tetrahexahedra of La\(_4\)(L\(_1\))\(_4\), as ascertained by \(^1\)H NMR and ESI-TOF-MS (Supplementary Figs. 141 and 241). This absolute self-organization behavior in the mixture of metal ions of identical coordination geometry properties is likely due to the strong supramolecular cooperative mechanical-coupling effect on the tetrahedral cages, facilitating the distinction between metal ions with different electron configurations, ionic charges, and ionic radii.

As for rare earth elements themselves, such absolute self-recognition is much more challenging and intriguing, considering their inherent similar physical and chemical properties, and thus an intricate mixture of heterometallic complexes is predicted in...
the mixed-lanthanide complexation process. To our delight, reaction of L1 (1.00 equiv) with an equimolar mixture of LaIII/EuIII (1.00 equiv of each) turned out to be an absolute self-sorting process, with Eu4(L1)4 as the only product, as confirmed by 1H NMR and ESI-TOF-MS (Supplementary Figs. 148 and 247). This complete metal-selective binding phenomenon was totally beyond our expectation as the difference in the ionic radii of LaIII and EuIII is only 0.10 Å, and in general isostructural compounds will be formed from the same ligand25.

More surprisingly, highly efficient metallic self-organization was also discovered in the case of lanthanide pairs with much smaller ionic radii difference. For example, reaction of ligand L1 (4 μmol) with an equimolar mixture of LaIII/CeIII (4 μmol of each) resulted in Ln4(L1)4 tetrahedral coordination cages containing 10.7 % LaIII and 89.3% CeIII, as determined by 1H NMR spectroscopy (Fig. 3). Two sets of signals were observed in the 1H NMR spectrum of the mixed-metal self-assembled complexes, corresponding to the LaIII- and CeIII-coordination environments27, as the chemical shifts of proton resonances on the ligand are mainly affected by the coordination environment. The proton signals are identified through comparison with homometallic complexes and further confirmed through post-synthetic metathesis experiments (Supplementary Figs. 142, 197, and 242). Based on the highly symmetrical 1H NMR spectrum and the ESI-TOF-MS data, we speculated that Ce4(L1)4 and trace amounts of hetero-metallic tetrahedral complex La1Ce3(L1)4 were formed. Nonlinear curve fitting of simulated isotopic patterns in the mass spectrum revealed a composition of 90% CeIII and 10% LaIII, which is in accordance with the 1H NMR analysis (Fig. 3d, Supplementary Figs. 242 and 243). The formation of Ln4(L1)4 tetrahedral cages was also confirmed by DOSY spectra (Supplementary Fig. 144). The 1H NMR spectrum of the mixed-metal complexes appears to be insensitive to variations in reaction time and temperature (Supplementary Fig. 143), which indicates that the selectivity is thermodynamically favored.

Given the above observation of effective metal ion self-recognition properties, additional one-pot mixed-metal self-assembly experiments (28 combinations in total) were performed to further investigate the degree of metal ion self-recognition (Supplementary Figs. 145–173 and 244–272). In general, L1 demonstrates a clear and high preference for smaller sized metal ions in multi-component self-assembly process along the lanthanide series and the selectivity increases with the ionic radii difference, making it an ideal candidate for high-efficiency lanthanide separation and purification (Fig. 4, Supplementary Table 3). Moreover, one-pot tri-metallic self-assembly experiments were also conducted and selectivity results comparable to
those of bimetallic systems were obtained, thus expanding the high self-recognition ability of L\textsuperscript{1} to multi-metal self-assembled systems (Supplementary Figs. 195, 196 and 273, 274). Mixed-metal self-assembly experiments with total metal ions to ligand ratios equal to 1:1 (Ln\textsuperscript{3}/Ln\textsuperscript{3}/L\textsubscript{1} = 0.5/0.5/1) were also carried out, resulting in the biased formation of two homometallic cages instead of statistically-distributed mixtures of [Ln\textsuperscript{n}Ln\textsubscript{b}Ln\textsubscript{c}Ln\textsubscript{d}L\textsubscript{1}]	extsuperscript{2+} (n = 0–4) species, especially with lanthanide pair of La\textsuperscript{III}/La\textsuperscript{III}, implying the powerful metal ion selectivity of L\textsuperscript{1} (Supplementary Figs. 174–176 and 275–279).

We envisioned that the tiny difference in lanthanide ions was amplified by strong cooperative mechanical-coupling effects during the multi-component self-assembly process, resulting in the observed high fidelity metal ion self-recognition behavior. A series of experiments were conducted to verify the vital function of supramolecular cooperativity in this surprising lanthanide separation and purification.

**Discussion**

To verify the extent of the multivalent cooperative effect in the unprecedented selective formation of M\textsubscript{4}L\textsubscript{4} tetrahedral cages, ligands L\textsubscript{2} and L\textsubscript{3} (Fig. 5), which contain the same pyridine-2,6-dicarboxamide chelating moiety and are known to form mononuclear M(L\textsubscript{2})\textsubscript{3} and dinuclear M\textsubscript{2}(L\textsubscript{3})\textsubscript{3} complexes with lanthanides, were synthesized according to known procedures\textsuperscript{22,60}.

Titration experiments were performed in CD\textsubscript{3}CN/CDCl\textsubscript{3} for L\textsubscript{1}–3 and Ca\textsuperscript{II} with increasing [M]/[L] ratios (Supplementary Figs. 106–114 and 234–239). Titration experiments of Cd\textsuperscript{II} and Eu\textsuperscript{III} with L\textsubscript{1}–3 gave similar variation tendency of stability as that of Ca\textsuperscript{II} (Supplementary Figs. 106–114 and 234–239). The enhanced structural stability from monometallic, dimetalllic to tetrametalllic self-assembly complexes followed the trend of increasing number of components and coordination interactions, which in turn confirmed the multivalent cooperative effect on the structural integrity of self-assembly systems.

As M(L\textsubscript{2})\textsubscript{3} is not applicable to the mixed-metal complexation process due to the rather low structural stability, metal ion selectivity during the formation of M\textsubscript{2}L\textsubscript{3} and M\textsubscript{4}L\textsubscript{4} was then compared using ligands L\textsubscript{3} and L\textsubscript{1} under similar experimental procedure and it was found that the ditopic ligand L\textsubscript{3} has much poorer ion selectivity compared with L\textsubscript{1} (Fig. 6, Supplementary Figs. 177–188 and 280–288).

The highly efficient recognition observed during the mixed-metal self-assembly process indicates a substantial difference in
the binding affinity of L1 toward different lanthanide ions. Post-synthetic metal-metathesis experiments were conducted to shed light on the mechanism of this highly controlled metal-selective self-assembly process. It is worth mentioning that the substitution rate and idealized relative formation constants for each metal combination depend on the difference in the ionic radii, and a larger difference results in faster substitution process and larger relative formation constants (Supplementary Figs. 197−203 and 295). Eu3(L1)4 for instance, has a formation constant of at least nine orders of magnitude higher than that of La3(L1)4 (Supplementary Table 4). Such a huge difference in formation constants serves as the primary driving force for the highly efficient metal ion recognition, and explains the complete EuIII selectivity observed in the LaIII/EuIII mixed-metal self-assembly discussed above.

Post-synthetic metal-metathesis experiments were also performed using L2 for comparing relative formation constants with L1 (Supplementary Figs. 204−208). Compared with the Ln4(L1)4 complexes, Ln3(L2)3 has much smaller relative formation constants for the same metal combinations (Supplementary Table 5). The increased thermodynamic stability and metal ion selectivity on going from dimetallic to tetrametallic complexes confirm that the cooperativity is dramatically enhanced with increased numbers of multitopic ligand chelation.

In addition to supramolecular multivalent cooperativity, structural stability of the supramolecular polyhedra and the rational choice of the multidentate coordination sites also contribute to the high-efficient metal ion selectivity. As a precondition for efficient metal ion selective self-assembly, the structural stability relies on both framework rigidity of the ligand and chelating affinity of the coordinating moieties for metal ions. Hamacek’s group has reported a pyridine-2,6-dicarboxamide (pcam) based tripodal ligand with flexible bridging units 1,1,1-tris(aminomethyl)ethane. Tetrahedral complexes [Ln4L4]12+ (Ln = Eu, Tb, Lu) were formed in the self-assembly process. 1H NMR and ESI-MS titration show the appearance of other species when either ligands (LnL3, LnL2, Ln2L3, Ln3L4) or metal ions (Ln3L2, Ln3L3) are in excess. Moreover, the 1H NMR spectrum excluded the formation of a tetrahedral complex with LaIII. The rather low stability is speculated to derive from the flexibility of the ligand. Moreover, the Ln4L4 complexes assembled from the flexible ligand have rather small relative formation constants, with \( \log K_{La/Eu} = 0.5 \) and \( \log K_{Tb/Lu} = 1.4 \) (ref. 61). Reaction of lanthanide ions with a rigid triadonal ligand, three pcam coordination units connected with rigid triptycene moiety, generates low symmetry complexes in presence of excess ligand and a trinuclear sandwich complex [Eu3L2]6+ when the metal/ligand ratio [Eu]/[L] reaches 3:2 (ref. 62). For tris(tridentate) ligands with similar coordination moieties, both scaffold rigidity and geometry exert great influence on the structural stability. We hypothesize ligands with moderate rigidity operate as levers between the four metal centers on the tetrahedral vertices, in a way that a small distortion in coordination geometry on one metal center is transferred to the other three vertices, leading to an enlarged energy barrier in comparison with the perfectly symmetrical tetrahedral framework. However, changing one of the metal ions on a flexible tetrahedron does not have such an effect. Thus, we conclude that ligand rigidity enhances mechanical-coupling effects within the framework, and in turn contributes to cooperative enhancement of both stability and metal ion selectivity.

Higher chelating affinity between the coordinating moieties and metal ions would improve the structural stability but it has a complicated impact on metal ion selectivity. Ligands with ideal coordination sites for lanthanide separation in a supramolecular system are expected to coordinate with the entire lanthanide series while possessing distinct binding affinity toward different lanthanide ions. However, in addition to the efficient chelating ability of the ligand with all the lanthanide ions into specific structures, moderate binding affinity is necessary for practical usage. Overlarge binding affinity could result in kinetically trapped assembles and hinder further transformation into the thermodynamically favored product (needing high temperature or prolonged reaction time). Hooley’s group has reported an acylhydrazone-phenolate based bis(tridentate) ligand with

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![Simulated structure of Ln4L6](image)

**Fig. 7** Demonstration of a lanthanide separation strategy using the multivalent cooperative effect of the tetranuclear cage complexes. a Modified structures of ligands L4−6 for solvent extraction experiments; Phase separation properties for LaIII/LuIII mixed-metal self-assembly using b L4, c L5, and d L6; e Simulated structure of Ln4L6; f Separation factors (with ± 5% exp. error) obtained from lanthanide solvent extraction experiment.

| Metal combination | \( S_{Ln(a)/Ln(b)} \) |
|--------------------|---------------------|
| LaIII/PrIII        | 2.1                 |
| LaIII/EuIII        | 8.4                 |
| PrIII/EuIII        | 3.6                 |
| LaIII/LuIII        | 87.7                |
| EuIII/LuIII        | 9.4                 |

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The table above shows the separation factors obtained from lanthanide solvent extraction experiments.
anionic coordination sites, which assembles with lanthanide ions into Ln4L1 complexes in DMSO and shows kinetic discrimination among lanthanide ions with a preference for smaller metals and a thermodynamic preference for larger metals. However, in this system, the thermodynamic equilibrium is not reached even after 20 h. In comparison, the pcam-based Ln(L1)4 complexes dissolve in DMSO, implying much weaker binding affinity between ligands and metal ions and the thermodynamic equilibrium is reached on a minute timescale. Supramolecular systems that can rapidly achieve thermodynamic equilibrium are required for efficient lanthanide separation for economic and practical consideration. Moreover, the pcam-based ditopic and tritopic ligands possess much higher lanthanide ion selectivity in the thermodynamically favored complexes owing to their moderate chelating affinity (Supplementary Figs. 186–188 and Table 2).

Cooperative enhancement of lanthanide selectivity in the formation of the tetrahedral cages indicated that tris(tridentate) coordination of next-generation lanthanide extractants. Further application of metal ion self-sorting of tetrahedral cage complexes. Unprecedented properties and ionic radii between actinides and lanthanides. Treatment of radioactive waste and the recycling of minor actinide in the aqueous and organic phase (Supplementary Figs. 186–188 and Table 2).

Methods

Materials. Deuterated solvents were purchased from Admas and J&K scientific. 1D and 2D NMR spectra were measured on a Bruker-Biospin AVANCE III HD (400 MHz) spectrometer. 1H NMR chemical shifts were determined with respect to residual solvent signals of the deuterated solvents used. 1H NMR integrations were performed using TOPSPIN 2.1 software. ESI-TOF-MS were recorded on an Impact II UHR-TOF mass spectrometer from Bruker, with ESI-L low concentration tuning (Supplementary Figs. 186–188 and Element Technologies internal standard).

Data analyses and simulations of ESI-TOF-MS were processed with the Bruker Data Analysis software (Version 4.3). ICP-MS analysis was performed on a Thermo Finnigan high-resolution magnetic sector Element 2 ICP-MS instrument. Unless otherwise stated, all chemicals and solvents were purchased from commercial companies and used without further purification. Caution! Perchlorate salts are potentially explosive and should be handled carefully in small quantities.

Synthesis and physical properties of [M4L4]+ and [Ln4L1]2+. A solution of M(CF3SO3)3 (or M(ClO4)3, M = Ca, Cd) or Ln(CF3SO3)3·H2O (10.0 µmol, 1 equiv) ([Lu = La, Pr, Nd, Sm, Eu, Yb, Y]) in 0.5 mL CH3CN was added to a white suspension of L (either the R or S enantiomer form; 11.08 mg, 10.0 µmol, 1 equiv) in 1.0 mL CH3CN. After stirring at 40 °C for 1 h, the turbid suspension of ligands became clear within 5 min with gentle shaking, and 1H NMR and ESI-TOF-MS confirmed the exclusive formation of [Ln4(L1)4]12+ due to the poor solubility of their self-assembled complexes in CH3CN. However, in the existence of extra LnIII in mixed-metal one-pot self-assembly experiments, [Ce4(L1)4]2+ and [Lu4(L1)4]2+ have rather good thermodynamic preference for larger metals. However, in this study, no signals were observed in the negative range (~20–40 ppm) in the 1H NMR spectra.

[Cd4(L1)4(CF3SO3)4]·2H2O (10.0 µmol, 1 equiv) was synthesized to be used as the model compound for the self-assembly of Ln(CF3SO3)3 or Ln(ClO4)3 complexes.

[Cd4(L1)4(CF3SO3)4]·2H2O (10.0 µmol, 1 equiv) was synthesized to be used as the model compound for the self-assembly of Ln(CF3SO3)3 or Ln(ClO4)3 complexes. In view of the poor water stability of the core assembly, followed by the addition of the same distribution coefficient of Ln(aq)/Ln(org), was calculated to be ca. 87.7 without further optimization of the metal-selective self-assembly process. No change in the NMR spectra was observed in the 1H NMR spectra.

In summary, this supramolecular lanthanide extraction and separation approach has been established based on an exclusive metal ion self-sorting of tetrahedral cage complexes. Unprecedented separation abilities have been achieved by taking advantage of the multivalent supramolecular cooperativity of these complexes. As such, this study provides new insights into the design of next-generation lanthanide extractants. Further application of this strategy to lanthanide/actinide separation, or purification of other metals in general, is expected.
Synthesis and physical properties of \([\text{Ln}_4\text{L}_4^{-6}]\). A solution of \([\text{Ln}_4\text{L}_4^{-6}]\) (10.0 μmol, 1 equiv) in 1.0 mL CD$_3$CN/CDCl$_3$ (1/1 v/v) was treated with an equimolar mixture of \(\text{Ln}^{III}(\text{ClO}_4)_3\) with \(\text{Ln} = \text{La}, \text{Pr}, \text{Eu}, \text{Lu}\) in 5.0 mL CD$_3$CN was added to a suspension of \(\text{L}_4^{-6}\) (10.0 μmol, 1 equiv) in 1.0 mL CD$_3$CN/CDCl$_3$ (1/1 v/v).

Homogeneous yellow solution was obtained after stirring at room temperature for 1 h. NMR and TOF-MS spectra showed the quantitative formation of \([\text{Ln}_4\text{L}_4^{-6}]\).

\[\text{[Eu}_1\text{L}_2\text{3}]^3\text{(ClO}_4\text{)}_3, \text{[La}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6, \text{[Nd}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6, \text{[Sm}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6, \text{[Yb}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\text{]}_2\text{[CF}_3\text{SO}_3\text{]}_2\text{]}_2\text{ and [La}_4\text{L}_4\text{3}]^3\text{(ClO}_4\text{)}_6\text{]}_2\text{ can be seen in Supplementary Methods.}

NMR and TOF-MS characterization of \([\text{Eu}_1\text{L}_2\text{3}]^3\text{(ClO}_4\text{)}_3\), \([\text{La}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\), \([\text{Nd}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\), \([\text{Sm}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\), \([\text{Yb}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\text{]}_2\text{[CF}_3\text{SO}_3\text{]}_2\text{ and [La}_4\text{L}_4\text{3}]^3\text{(ClO}_4\text{)}_6\text{]}_2\text{ can be seen in Supplementary Methods.}

NMR and ESI-TOF-MS characterization of \([\text{Eu}_1\text{L}_2\text{3}]^3\text{(ClO}_4\text{)}_3\) \([\text{La}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\), \([\text{Nd}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\), \([\text{Sm}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\), \([\text{Yb}_2\text{L}_3\text{3}]^3\text{(ClO}_4\text{)}_6\text{]}_2\text{[CF}_3\text{SO}_3\text{]}_2\text{ and [La}_4\text{L}_4\text{3}]^3\text{(ClO}_4\text{)}_6\text{]}_2\text{ can be seen in Supplementary Methods and Supplementary Figs. 73–89, 109–114, 220–226.}

General procedure for mixed-metal one-pot self-assembly of \(\text{L}^{3+}\) (6.0 μmol) was treated with an equimolar mixture of \(\text{Ln}^{III}(\text{ClO}_4)_3\) and \(\text{Ln}^{III}(\text{ClO}_4)_3\) (6.0 μmol of each) in CD$_3$CN (0.6 mL) at 40 °C for 1 h and the turbid suspension of ligands gradually turned clear. The resulting yellow solution was characterized by 1H NMR and ESI-TOF-MS. The resulting yellow solution was characterized by 1H NMR and ESI-TOF-MS. This solution can be seen in Supplementary Methods and Supplementary Figs. 73–89, 109–114, 220–226.

1H NMR spectra of the mixed-metal self-assembled complexes with non-aromatic self-recognition behavior were measured with d1 value set as 20 s to ensure the accuracy of the metal ion selectivity, which was calculated based on 1H NMR integration. The selectivity for smaller sized \(\text{Ln}^{III}\) in incomplete self-sorting mixed-metal self-assembly process is determined by 1H NMR. The highly symmetrical 1H NMR patterns described the formation of a dynamic mixture of complexes with low symmetry as a result of poor metal-ion selectivity, making it difficult for the identification of selectivity through 1H NMR integration. The selectivity for smaller sized \(\text{Ln}^{III}\) in incomplete self-sorting mixed-metal self-assembly process is determined by 1H NMR. The highly symmetrical 1H NMR patterns described the formation of a dynamic mixture of complexes with low symmetry as a result of poor metal-ion selectivity, making it difficult for the identification of selectivity through 1H NMR integration.
complete metal ion self-recognition was observed as ascertained by \(^1\)H NMR and ESI-TOF-MS (Supplementary Figs. 195 and 273).

**General procedure for post-synthetic metal-ion metathesis experiments.** Self-assembled complexes \([Ln_4L_{14}](\text{ClO}_4)_2\) (1.5 μmol) in CD\(_2\)CN were prepared in advance, followed by the addition of \(\text{Ln}(\text{ClO}_4)_2\cdot6\text{H}_2\text{O}\) (6.0 μmol), resulting in a total volume of CD\(_2\)CN of 0.6 mL. \(^1\)H NMR spectra were measured immediately after the addition of the second \(\text{Ln}(\text{ClO}_4)_2\cdot6\text{H}_2\text{O}\) at room temperature until the mixture reached the final thermodynamically stable state. The highly split \(^1\)H NMR signals and ESI-TOF-MS spectroscopy indicate the dynamic formation of multiple scrambled-metal cages \([Ln_4L_4]^{12+}\) (\(n=9–4\)) during the post-synthetic metal-ion metathesis experiments, which further indicates the metal-metathesis on four metal vertices of tetrahedral cages \([Ln_4L_4]^{12+}\) proceed stepwise. It is worth pointing out that the substitution rate depends on the difference of their ionic radius in each combination. With larger ionic radii difference, the substitution proceeds much faster and vice versa. As for La(III)/Ce(III) metal combination, the one-step substitution leading to \([\text{La}_2\text{Ce}_2L_4]^2+\) species proceed so fast that no metal-intermediates were observed (Supplementary Figs. 197–203 and 295). Post-synthetic metal-ion metathesis experiments of \(L_2\) were performed in the same method as that for \(L_1^2\) (Supplementary Figs. 204–208).

**Single-crystal X-ray diffraction studies.** The X-ray diffraction studies for complex \(\text{Cd}_2L_2^2(\text{ClO}_4)_2\) and \(\text{La}_4L_1^3(\text{ClO}_4)_2\) were carried out at the BL17B macromolecular crystallography beamline in Shanghai Synchrotron Radiation Facility. The collected diffraction data were processed with the HKL 3000 software program\(^{55}\). The structures were solved by direct methods and refined by full-matrix least-squares on \(F^2\) with anisotropic displacement using the SHELEX software package\(^{57}\). The crystals diffract only very weakly due to large amounts of solvent molecules and anions. For the structure of \(\text{Cd}_2L_2^2(\text{ClO}_4)_2\), where counter ions and solvent molecules were so highly disordered that they could not be reasonably located, the residual intensities were removed by PLATON/SQUEEZE routine\(^{55}\). Still one A-alert and some B-alerts are found by the (IUCr) check CIF routine, all of which are due to the poor diffraction nature of the crystals. Details on crystal data collection and refinement are summarized in Supplementary Tables 7 and 8.

**Investigation of thermodynamic stability of different lanthanide complexes.** Post-synthetic metal-ion metathesis experiments of \(\text{La}_4L_4^2(\text{ClO}_4)_2\) toward \([Ln_4L_4]^{12+}\) complexes in CH\(_3\)CN were identified by \(^1\)H NMR and ESI-TOF-MS and its Supplementary Information and its Supplementary Information files and from the corresponding authors on request.

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**Author contributions**

Q.-F.S. proposed the ideas and supervised the project. X.-Z.L and L.-L.Y synthesized all the compounds and conducted the experiments. L.-P. Z. contributed the mass measurements, Y.-M.D., Z.-L.B., X.-Q.S., J.D., S.W. performed the ICP-MS experiments and the compounds and conducted the experiments, L.-P. Z. contributed the mass measurements, Y.-M.D., Z.-L.B., X.-Q.S., J.D., S.W. performed the ICP-MS experiments and aided in the data analyses, X.-Z.L., J.-C.B., and Q.-F.S. wrote the manuscript with input from all the authors.

**Additional information**

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**Competing interests:** The authors declare no competing financial interests.

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