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Design and synthesis of covalently tethered "isoG-star" as a recyclable host for selective cesium separation†

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The isoguanosine self-assembled pentamer (isoG-star) exhibits remarkable selectivity for Cs^+ binding over competing alkali and alkali earth metal cations, rendering it a promising extractor for radioactive waste ^{137}Cs separation. However, to make isoG-star a practical material for Cs^+ isolation, the development of a recyclable isoG-star material is required. In this study, a systematic screening of functional isoG derivatives was performed. By employing well-defined complex formation and post-assembly modification, a covalently tethered $isoG_5$-star was prepared through olefin metathesis, utilizing a designed isoG monomer. The application of this newly developed covalently linked isoG-star enabled selective Cs^+ extraction, followed by controlled solvent-induced H-bond dissociation. This resulted in the creation of a recyclable Cs^+ extractor, demonstrating excellent cation selectivity and good reusability (over seven cycles) for the first time. Consequently, this new supramolecular macrocycle offers a practical new platform for the treatment of radiocesium (^{134}Cs and ^{137}Cs) in an environmentally friendly and highly effective manner.

Introduction

Radiocesium ions represent significant constituents of radioactive wastewater in nuclear power plants, necessitating efficient treatment and isolation methods for cesium (Cs) ions.[1–3] In 2011, the Fukushima Daiichi Nuclear Power Plant (FDNPP) accident resulted in the release of substantial amounts of radiocesium (^{134}Cs and ^{137}Cs with half-lives of 2.07 and 30.1 years, respectively) into the environment, further highlighting the requirement for novel systems to effectively extract Cs cations from aqueous solutions with a focus on ecological security and sustainable development.[4–7] Considering the abundant existence of sodium (Na) and potassium (K) cations in aqueous solutions, along with their chemical similarities, achieving selective separation of Cs^+ from such solutions can pose significant challenges.[8–11] Crown ethers and calixarene derivatives are typical receptors for Cs^+ separation. Reinhoudt and Ungaro made a fundamental contribution to the hybrids of calix[4]arene and crown ethers as excellent Cs^+ selective ionophores.[12–15] Selective binding is the first part of recognition and subsequent controlled release is critical for practical application. Although certain crown ether and calixarene derivatives can selectively coordinate with Cs^+ through ion–dipole interaction or cation–π interaction, making them promising Cs^+ extractants, concerns arise regarding their limited operating pH range and poor recyclability for practical applications. Sessler and co-workers developed calix[4]pyrrole which could extract Cs^+ from an aqueous phase while allowing its subsequent release by the addition of K^+. Calix[4]pyrrole-containing diblock copolymers are demonstrated to be more effective as extractants than the corresponding free ion pair receptors.[16–21] The development of new systems exhibiting high Cs^+ binding selectivity and practical operational conditions is thus of paramount importance for environmental protection and energy sustainability.

Molecular self-assembly is a prevalent process in nature that gives rise to various receptors, providing a powerful approach for designing selective ionophores.[22–24] Guanosine (G) rich nucleic acids are recognized for their ability to coordinate alkali and alkaline earth cations through the formation of a hydrogen-bonded G_4-quartet motif.[25–33] This rigid macrocyclic structure exhibits a high binding affinity towards K^+, Sr^{2+}, and Ba^{2+}.[34–39] However, despite its structural reversibility, the H-bonding supramolecular architecture lacks flexibility and tends to maintain a fixed size to maximize H-bonding interactions. Consequently, the G_4-quartet demonstrates no binding affinity towards Cs^+ due to a size mismatch. Interestingly, the structural isomer of G, known as isoguanosine (isoG, also referred to as 2-hydroxy-adenosine) features a

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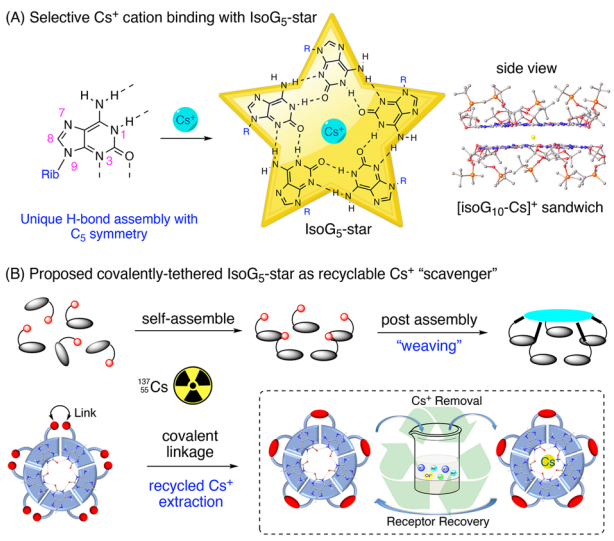
larger H-bond donor and acceptor angle (108° in isoG compared to 90° in the G-quartet), leading to the formation of a pentameric assembly, isoG$_5$, in contrast to the tetrameric G$_4$-quartet.[40–46] With a significantly larger central core, isoG$_5$ exhibits strong binding affinity towards Cs$^+$ (radii = 174 pm) and excellent selectivity over Na$^+$ and K$^+$ (Scheme 1A).[47–50] Although self-assembly is a powerful tool for creating supramolecular scaffolds, it faces challenges as a stable molecular host due to non-covalent bond dissociation, limiting its practical applications. To address these limitations and improve the binding affinity (minimizing the entropy penalty associated with self-assembly) and practical usability (recyclability), we have directed our efforts towards the development of the first covalently tethered isoG$_5$-star through post-assembly supramolecular modification (Scheme 1B).

In theory, covalently tethered supramolecular scaffolds can be achieved through two approaches: (A) covalent linkage of a monomer to a template or (B) post-assembly modification. The first approach offers greater synthetic accessibility, allowing for easy functional group modification.[51–54] However, it requires precise template design to ensure the establishment of self-assembly with optimal non-covalent binding, which can be challenging. On the other hand, the post-assembly modification approach ensures the formation of a supramolecular assembly with strong non-covalent interactions, similar to the self-assembly process. However, it requires compatible synthetic methods and appropriate linkage design to ensure the appropriate weaving of supramolecular scaffolds without disrupting the non-covalent binding. Nonetheless, in either approach, the availability of good synthetic handles and the establishment of effective self-assembly are critical factors.

To evaluate different building blocks in the formation of isoG$_5$-star, various isoG derivatives were synthesized and applied in the Cs$^+$ binding experiments (Fig. 1A). Typically, the



Scheme 1 (A) Cs$^+$ templated isoG$_5$-star pentaplex formation and (B) the proposed covalently tethered isoG$_5$-star as a recyclable Cs$^+$ extractor.

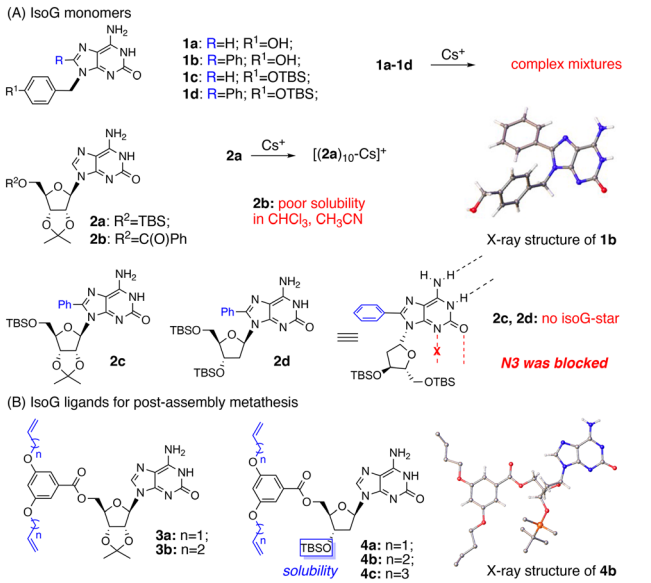


Fig. 1 (A) Non-sugar isoG derivatives **1** and 8-phenyl-isoG derivatives **2**; (B) isoG ligands **3** and **4** for post-assembly weaving.

purine C-8 and N-9 positions provide potential synthetic sites without disrupting H-bond formation. Non-sugar isoG derivatives **1a–1d** were synthesized and subjected to Cs$^+$ binding.[55] While these compounds were able to be effectively extracted from an aqueous solution, analysis using NMR and MS revealed the presence of complex reaction mixtures with no clear detection of isoG-star formation (Fig. S1 and S2†). This outcome is attributed to the formation of various stacking isomers. Further investigation revealed that the structure of isopropylidene-modified isoG **2a** could form a stable decamer $[(\mathbf{2a})_{10}Cs]^+$. However, the introduction of a benzyl group at the 5′-position, serving as a potential synthetic handle, significantly reduced solubility in organic solvents. Modification of the C-8 position with a phenyl group gave compounds **2c** and **2d**, both of which exhibited good solubility in organic solvents. However, despite their favourable solubility properties, neither of these compounds was able to form isoG-star. The X-ray crystal structures of **2c** and **2d** revealed that their configurations are energetically favored by avoiding repulsion.[49] As a result, O5′ was placed close to N3, blocking the critical H-bonding in isoG$_5$ formation. With this mechanistic understanding, our research focused on exploring the isopropylidene-modified isoG derivatives **3a–b** and the 2′-deoxy isoG derivatives **4a–4c** with the intention of striking a balance between solubility and H-bonding formation (Fig. 1B).

With the incorporation of a longer ester chain, both compounds **3a** and **3b** exhibited improved solubility compared to **2b**. Treatment of isoG **3a** in $CDCl_3$ solution with CsCl and $NaBPh_4$ (in an aqueous solution) resulted in one set of signals in the ^{1}H NMR spectra. The proton integration ratio of the isoG ligand to the anion was 10 : 1. Both N1–H (at 13.60 ppm) and N6–H$_A$ (at 11.02 ppm) protons displayed clear downfield shifts, indicating the formation of $[(\mathbf{3a})_{10}Cs]^+(BPh_4^-)$ and the

successful extraction of Cs^+ into the organic layer. Interestingly, the $BARF^-$ anion led to the formation of a different Cs^+ complex, $[(\mathbf{3a})_5Cs]^+(BARF^-)$, with a 5 : 1 integration ratio, suggesting a specific role of the BARF anion in this assembly. Additionally, isoG **3b**, with one extra carbon on the side chain, could also form similar Cs^+ complexes, $[(\mathbf{3b})_{10}Cs]^+(BPh_4^-)$ and $[(\mathbf{3b})_5Cs]^+(BARF^-)$. The detailed NMR spectra are provided in Fig. S3 and S4.†

Following isoG-star formation, we proceeded with the supramolecular weaving process in an attempt to covalently link the isoG-star through olefin metathesis. Both the decamer and pentamer from **3a** and **3b** were treated with the Hoveyda–Grubbs-II (HG-II) catalyst, and the reaction process was monitored by MALDI-TOF. Subsequent analysis through NMR and MS confirmed the occurrence of metathesis when treating $[(\mathbf{3a})_{10}Cs]^+(BPh_4^-)$ and $[(\mathbf{3a})_5Cs]^+(BARF^-)$ with HG-II. However, a mixture of oligomers was observed, and the desired formation of pentameric $isoG_5$-star did not materialize. Our hypothesis is that the ester linker might not be sufficiently long to establish a connection with neighboring isoG units. As expected, treating $[(\mathbf{3b})_{10}Cs]^+$ with HG-II led to the detection of alkene-linked cyclic $isoG_5$ by MALDI-TOF with an MW of 2829.15. However, the resulting cyclic structure showed very poor solubility in $CHCl_3$, precipitating from the reaction mixture, which makes it unsuitable for the proposed Cs^+ extraction application.

To address the solubility issue, we investigated the metathesis reaction with 2′-deoxy isoG derivatives **4a–4c**. Fig. 2A illustrates the treatment of deoxy isoG derivatives **4a** and **4b** in $CDCl_3$ solution with CsCl and NaBARF aqueous solution, leading to the formation of simple complexes exhibiting a single set of signals in the ^1H NMR spectra. Diffusion NMR experiments with deoxy isoG derivatives confirmed the presence of *C*5-symmetric decamers with the formulas $[(\mathbf{4a})_{10}Cs_2]^{2+}(BARF^-)_2$ and $[(\mathbf{4b})_{10}Cs_2]^{2+}(BARF^-)_2$. This finding establishes that the enhanced $CDCl_3$ solubility of these deoxy-isoG derivatives enables effective Cs^+ extraction into the organic layer through straightforward procedures. Moreover, it is noteworthy that these deoxy-isoG derivatives can also form isoG-star structures with both Na^+ and K^+. To assess the binding selectivity of these alkene-modified isoG compounds, extractions of Cs^+ in the presence of competing Na^+ and K^+ were performed. The summarized results are presented in Fig. 2B and C.

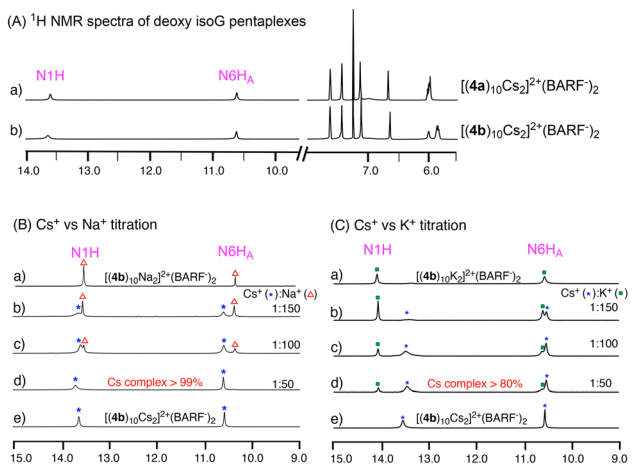


Fig. 2 (A) Self-assembly experiments of **4a** and **4b**: (a) ^1H NMR spectrum of $[(\mathbf{4a})_{10}Cs_2]^{2+}(BARF^-)_2$ in $CDCl_3$ and (b) ^1H NMR spectrum of $[(\mathbf{4b})_{10}Cs_2]^{2+}(BARF^-)_2$ in $CDCl_3$. (B) ^1H NMR experiments of **4b** with a Cs^+ and Na^+ mixture at 25 °C in $CDCl_3$, (a) $[(\mathbf{4b})_{10}Na_2]^{2+}(BARF^-)_2$, with a $Cs^+ : Na^+$ molar ratio of: (b) 1 : 150, (c) 1 : 100, (d) 1 : 50, and (e) $[(\mathbf{4b})_{10}Cs_2]^{2+}(BARF^-)_2$. The concentrations of Cs^+ in aqueous solution are the same in all cases. (C) ^1H NMR experiments of **4b** with a Cs^+ and K^+ mixture at 25 °C in $CDCl_3$, (a) $[(\mathbf{4b})_{10}K_2]^{2+}(BARF^-)_2$, with a $Cs^+ : K^+$ molar ratio of (b) 1 : 150, (c) 1 : 100, (d) 1 : 50, and (e) $[(\mathbf{4b})_{10}Cs_2]^{2+}(BARF^-)_2$. The concentrations of Cs^+ in aqueous solutions are the same in all cases. Partial ^1H NMR spectra for the region correspond to N1H and N6H$_A$ peaks.

As anticipated, the ^1H NMR spectra demonstrated excellent Cs^+ cation binding selectivity over Na^+ and K^+ cations. At a Cs^+/Na^+ ratio of 1 : 50, the deoxy isoG derivative **4b** formed over 99% Cs^+ complex, with minimal Na^+ complex formation being observed. Slightly reduced Cs^+ selectivity was observed when treating **4b** with a large excess of K^+, resulting in 80% Cs^+ complex formation with a 1 : 50 Cs^+/K^+ mixture. Other alkaline earth metal cations (Mg^{2+}, Ca^{2+}, and Ba^{2+}) were applied to investigate their influence on the selectivity of Cs^+. Nearly zero amount of Mg^{2+}, Ca^{2+}, and Ba^{2+} was extracted in the competition experiments with a 1 : 100 Cs^+/alkaline earth metal ion mixture separately. Remarkably, at a Cs^+/Mg^{2+} ratio of 1 : 150, the Cs^+ complex was still dominant in solution. Slightly reduced Cs^+ selectivity was observed when treating **4b** with a large excess of Ca^{2+}, resulting in 90% Cs^+ complex formation with a 1 : 150 Cs^+/Ca^{2+} mixture (Fig. S9–S11†).

Remarkably, the resulting Cs^+ complexes derived from isoG **4b** remain stable even at a very low concentration (0.0001 M) with no significant dissociation. Variable-temperature NMR (VT-NMR) experiments confirmed that these Cs^+ complexes maintained stability even at an elevated temperature (55 °C, see dilution and VT NMR in Fig. S8†). These results strongly support the potential of using deoxy isoG **4** as a new host for Cs^+ extraction even in the presence of excess alkali metal and alkaline earth metal cations.

Following the confirmation of Cs^+ binding selectivity, excellent solubility, and good complex stability, we investigated the possibility of forming covalently-linked isoG-star using the deoxy-isoG derivatives **4a–4c**. Complexes derived from these compounds were treated with the HG-II catalyst, and the metathesis reactions were monitored using NMR and MALDI-TOF. As depicted in Fig. 3A, both the isoG ligand and the Cs^+ complex $[(\mathbf{4})_{10}Cs_2]^{2+}(BARF^-)_2$ were treated with the HG-II catalyst (5 mol%). Interestingly, no olefin metathesis products were observed while reacting with monomer **4**, likely due to the catalyst being quenched by the purine moiety. In the presence of the complex $[(\mathbf{4})_{10}Cs_2]^{2+}(BARF^-)_2$, the metathesis reaction was observed with complete consumption of the terminal olefin within 8 h in $CHCl_3$ at 55 °C. Monitoring the process with MALDI-TOF suggested the formation of an isoG trimer and tetramer with allyl ether **4a**, indicating that the chain

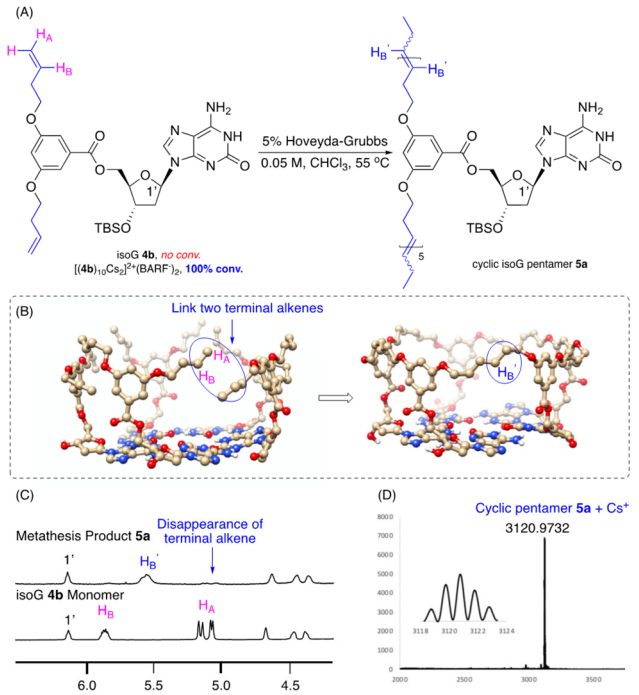


Fig. 3 Chemical structure, model and characterization of cyclic deoxy isoG pentamer **5a**. (A) Macrocyclization process through olefin metathesis; (B) computational model of the cyclic pentamer; (C) ^{1}H NMR spectra of the deoxy isoG **4b** monomer and the metathesis product, cyclic deoxy isoG pentamer **5a** in DMSO; (D) MALDI-TOF spectrum showing the effective extraction of Cs^{+} from the aqueous phase.

length was not sufficient enough to accommodate $isoG_5$-pentamer cyclization, leading to complex dissociation after pentamer formation. With a longer linker, the desired cyclic pentamer was successfully observed with m/z = 3120.9732, consistent with the covalently linked cyclic $isoG_5$ containing one Cs cation ($C_{145}H_{195}N_{25}O_{35}Si_5Cs^{+}$, Fig. 3D). The overall yield was over 90%, forming the cyclic deoxy isoG pentamer **5a** as the dominant product. Compound **5a** could be readily purified through column chromatography, with no terminal olefin signals observed in the ^{1}H NMR spectra. Similar cyclic isoG-pentamer structures were observed with **4c**, with the ligand containing an even longer chain. However, complex NMR was obtained, likely due to the overly flexible side arms.

Having successfully prepared cyclic-isoG **5a**, aqueous extraction experiments to evaluate its Cs^{+} extraction capabilities were performed. As expected, this covalently-linked isoG-star effectively extracts Cs^{+} from the aqueous solution, forming Cs^{+} complexes in $CHCl_3$. The formation of new complexes was confirmed by ^{133}Cs NMR, where 25 ppm and 53 ppm signals clearly proved the coordination between Cs^{+} and the cyclic pentamer product. In recyclability experiments, protic solvent MeOH can disrupt the H-bond in the deoxy isoG pentamer and cause the decomposition of the isoG complex. Upon treating the complex MeOH, complex dissociation occurred, resulting in the release of Cs^{+}. The fact that cyclic pentamer **5a** is not soluble in MeOH leads to its precipitation from solution.

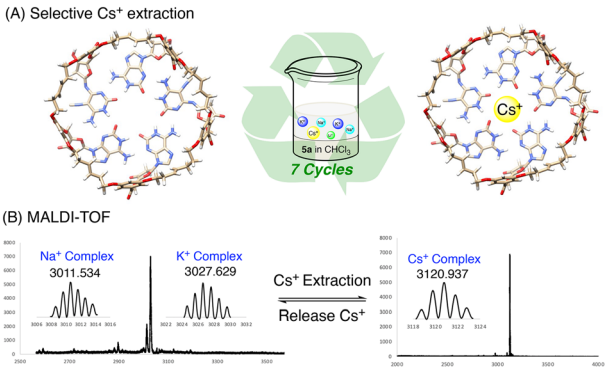


Fig. 4 Selective Cs^{+} extraction by cyclic pentamer **5**. (A) 7 cycles of extraction without a significant efficiency decrease; (B) MALDI-TOF spectra of Cs^{+} extraction and release.

The receptor itself can be regenerated after filtration. In this way, Cs^{+} can be released or stored in another container by adding MeOH solvent, giving $C_{145}H_{195}N_{25}O_{35}Si_5Na^{+}$ and $C_{145}H_{195}N_{25}O_{35}Si_5K^{+}$ on MALDI-TOF. The resulting recycled cyclic isoG **5a** could be reapplied for Cs^{+} extraction by dissolving it in $CHCl_3$ and reacting it with Cs^{+} containing aqueous solution. Remarkably, this process was performed for multiple cycles (7 times) without losing Cs^{+} selectivity and binding affinity (Fig. 4). The detailed results for each cycle are provided in Fig. S14.† Furthermore, the influence of pH on Cs^{+} selective extraction was investigated, showing effective extraction of Cs^{+} between pH = 1 and pH = 14. The effective pH range covers a broad region, making the cyclic deoxy isoG pentamers widely applicable ionophores. To the best of our knowledge, this is the first covalently-linked isoG-star that has been synthesized, and its ease of operation for effective Cs^{+} extraction demonstrates its potential as a promising strategy for the treatment of radioactive Cs^{+} waste.

Conclusion

In summary, we have successfully developed the first covalently-linked isoG-star through olefin metathesis with selected deoxy-isoG derivatives. The resulting cyclic isoG-star has demonstrated exceptional performance in Cs^{+} extraction and separation with ease of operation and excellent recyclability. This breakthrough not only offers a novel material for potential Cs^{+}-containing radioactive nuclear waste treatment, but also introduces a new strategy for the preparation of extra-large macrocycles through post-assembly modification. We anticipate that this strategy will be applicable in the development of new supramolecular hosts, and our ongoing investigations in the laboratory are currently exploring its potential applications.

Author contributions

M. L. conducted the experiments, performed the characterization, and analyzed the results and data; Y. H. analyzed the

results and data; L. W. solved and refined the crystal structures; X. S. conceived the original idea, set research directions, and designed the experiments.

Conflicts of interest

There are no conflicts to declare.

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