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Coordination-Induced Switchable Nanoparticle Formation from Naphthyl-Bridged Bis(β-cyclodextrin)

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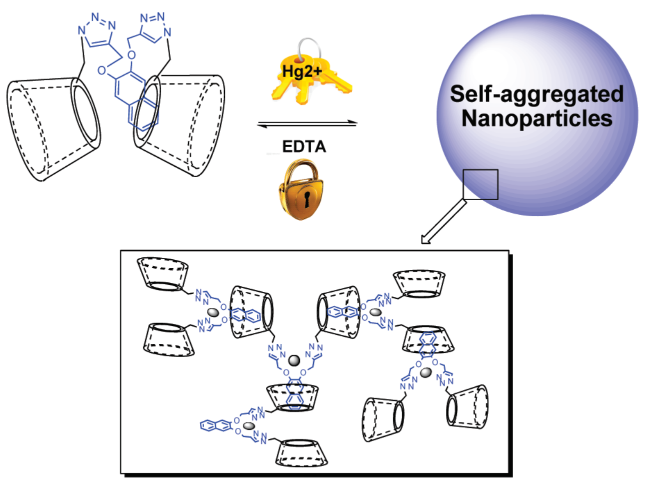

Naphthyl-bridge bis(β-cyclodextrin) (**1**) was synthesized via "click chemistry", and its self-assembly behavior was investigated by NMR, UV−vis, circular dichroism spectra, transmission electron microscopy, and atomic force microscopy. The results obtained indicate that the coordination of Hg^{2+} with triazole rings in **1** induces the naphthyl moiety to move from being a self-included complex to the formation of nanoparticles through intermolecular self-aggregation. Furthermore, the formation and disassembly of nanoparticle was reversibly controlled by adding or removing Hg^{2+}.

The reversibly switchable supramolecular architectures by employing stimuli like pH,[1] temperature,[2] photoirradiation,[3] redox,[4] etc. have attracted extensive attention because of their application among vesicles, supramolecular fibrils, and hydrogels in nanotechnology. On the basis of the principles of metal ions changing the conformation of ligand units,[5] metal-directed self-assembly has also been utilized to achieve well-designed multicomponent architectures in one, two, or three dimensions.[6] The most well-known reversibly converting example controlled by metal ions is Sauvage catenene system.[7] However, in comparison to those systems developed in organic solution, its counterpart in the aqueous phase is far more behind. In aqueous solutions, cyclodextrins (CDs) are extensively studied not only for molecular recognition but also as building blocks for functional supramolecular architectures.[8] Those supramolecular architectures of CDs are mainly built on the inclusion complexation of the cavities of CDs toward other neutral and ionic organic molecules or macromolecules.[9] As metal ions are not preferred by CDs, the most common way to introduce metals to CD systems is including metal ligands; for example, we had built up metal-coordinated CD pseudopolyrotaxanes[10] by including 4,4′-bipyridine in CD to coordinate with nickel(II) ions. In this work, we demonstrate a new method, in which a self-locked building block (**1**) could be activated to form self-aggregated nanoparticles by using metal ions chelating to the linker of **1**. This process can be reversibly switched by adding and taking off the metal ions.

Compound **1** was prepared by the reaction of 6-deoxy-6-azide-β-CD with 2,3-bis(prop-2-ynyloxy)naphthalene (Np), followed by a typical procedure as we reported before.[11] It is

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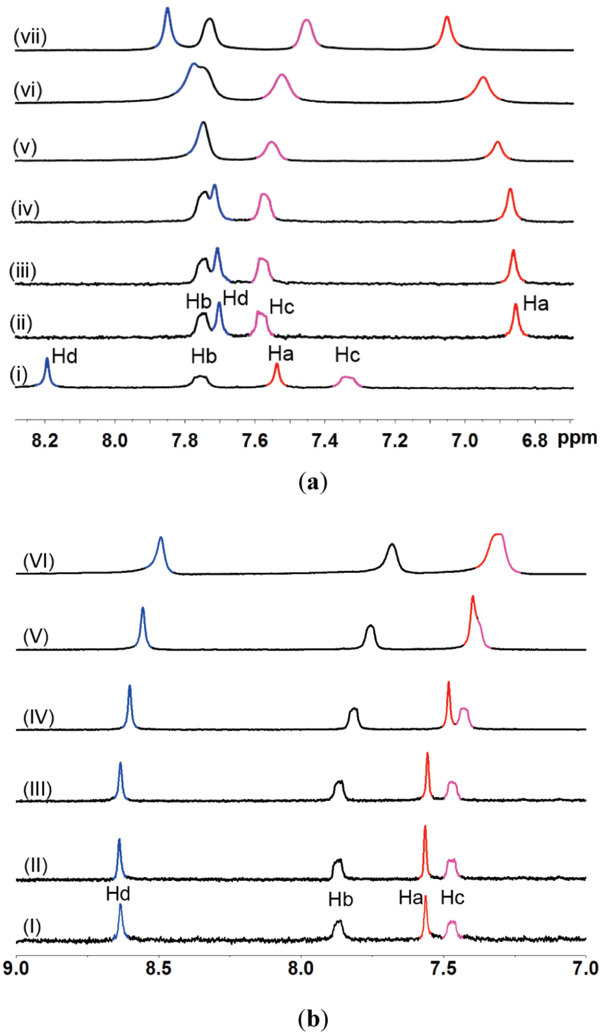

FIGURE 1. ^{1}H NMR (400 MHz) spectra of the aromatic region of **1**: (a) (i) 2.00, (ii) 0.63, (iii) 1.10, (iv) 1.90, (v) 3.80, (vi) 7.40, (vii) 20.0 mM (i in DMSO-d_6, ii−vii in D_2O); (b) (I) 0.60, (II) 1.20, (III) 2.60, (IV) 5.20, (V) 10.5, (VI) 21.0 mM in D_2O upon addition of Hg^{2+} (5 equiv to **1**), respectively.

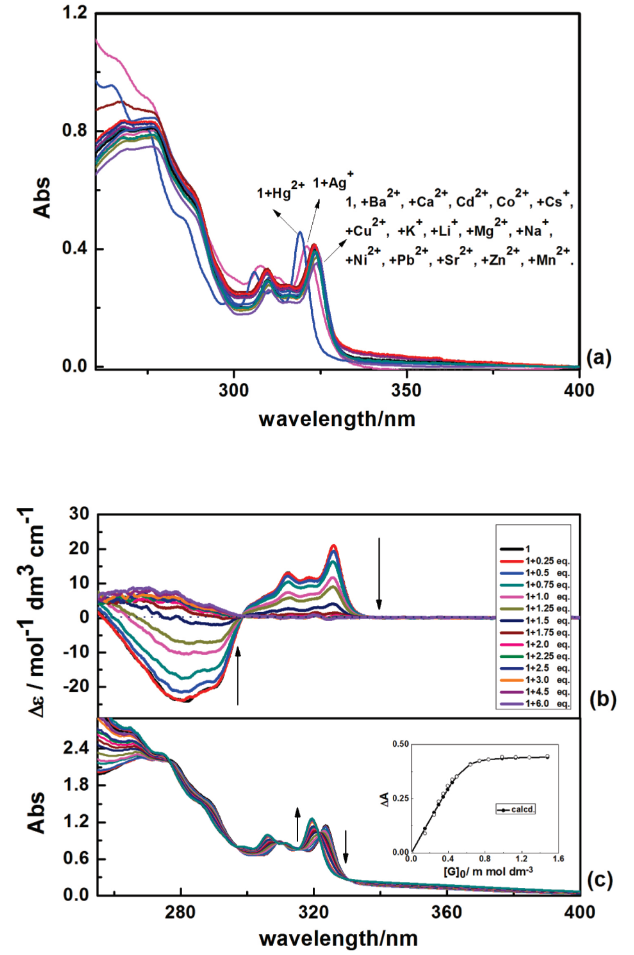

FIGURE 2. (a) UV−vis spectra of **1** (**1** = 2.0×10^{-4} M), with the addition of ClO_4^- salts of Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Ag^+, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, and Pb^{2+} (ions = 4.0×10^{-3} M) in aqueous solution. (b) Circular dichroism spectra of **1** (4.0×10^{-4} mol/L) with the addition of of $Hg(ClO_4)_2$ (0, 1.0×10^{-4}, 2.0×10^{-4}, 3.0×10^{-4}, 4.0×10^{-4}, 5.0×10^{-4}, 6.0×10^{-4}, 7.0×10^{-4}, 8.0×10^{-4}, 9.0×10^{-4}, 1.0×10^{-3}, 1.2×10^{-3}, 1.8×10^{-3}, and 2.4×10^{-3} mol/L) in aqueous solution. (c) UV titration of host **1** (5.0×10^{-4} mol/L) with the addition of Hg^{2+} ($0-1.5 \times 10^{-3}$ mol/L) at 25 °C in aqueous solution. Inset: nonlinear least-squares analysis.

well-known that Np can be included in the cavity of β-CD in aqueous solution.[12] In order to figure out whether the conformation of **1** is self-included or intermolecularly included, ^{1}H NMR spectra of **1** in DMSO-d_6 and D_2O solution were first compared. In DMSO-d_6 solution (Figure 1a (i)), there is no hydrophobic interaction between Np and CD. Four downfield proton signals (δ = 8.19, 7.76, 7.58, 7.32 ppm) are attributed to protons of triazole (Hd) and naphthyl (Hb, Ha, Hc) of a free conformation of **1**, respectively. In contrast, in D_2O solution (Figure 1a (ii)), Ha, Hd shift upfield 0.73, 0.60 ppm, while Hb, Hc shift downfield 0.07, 0.21 ppm, respectively. However, as the solvation effect in these two deuterated solvent could not be easily excluded, the 2D ROESY spectrum of **1** in D_2O (1.90 mM) was further carried out. It is shown that there are strong cross-peaks of Hb with H-5 of CD and weak cross-peaks of Ha with H-5. No other NOE correlation between Hc with H-3 or H-5 of CDs is found (see the Supporting Information, Figure S5a). In an aqueous solution of **1** (0.40 mM), there is a pair of strong induced circular dichroism (ICD) signals shown in the circular dichroism spectrum (Figure 2b).

On the basis of Kajita's rule,[13] the positive Cotton effect peak at 323 nm ($\Delta\varepsilon$ = +21.06 M^{-1} cm^{-1}) and the negative Cotton effect peak at 275 nm ($\Delta\varepsilon$ = −23.63 M^{-1} cm^{-1}) reveal that Np in **1** lies on the primary side of the CD moiety with partial self-inclusion. These results are consistent with each other and prove the formation of an intramolecular inclusion complex. Further varying the concentration of **1** in D_2O from 0.63 to 20 mM gives a stepwise chemical shift of Ha−Hd. As shown in Figure 1a (ii−vii), Ha and Hd shift downfield 0.20 and 0.15 ppm, but Hc shifts upfield 0.13 ppm. The broad peaks at high concentration indicate that the self-inclusion is fast exchange at NMR time scale. Meanwhile, in the high concentration solution (20 mM) of **1**, the stronger

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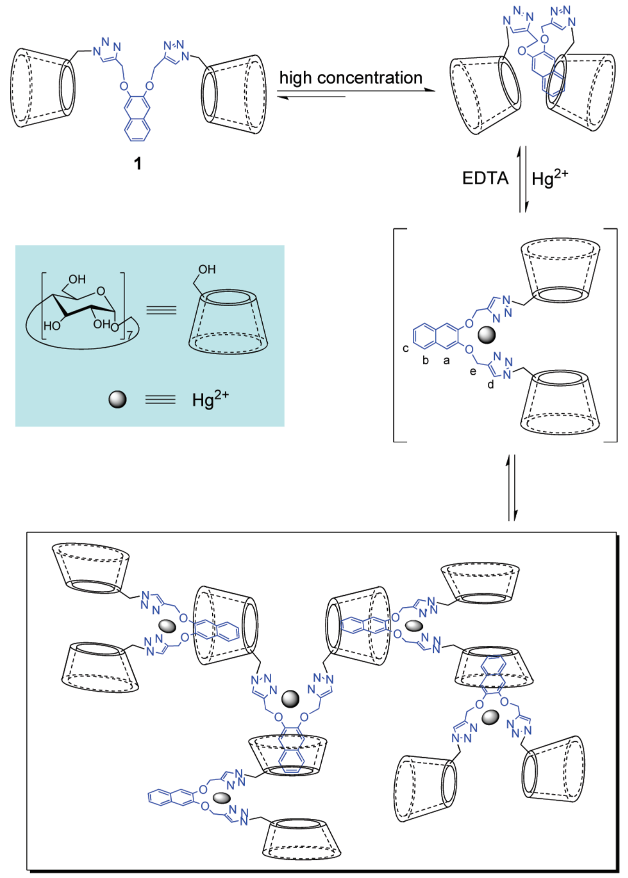
SCHEME 1. Suggested Pathways of Forming of Intra-/Intermolecular Complexes



NOE correlations between Ha, Hb, Hc of naphthyl group and H-5 of CD and the weaker cross-peaks between Hb, Hc and H-3 of CD can be newly found (see the Supporting Information, Figure S5b), which indicates that the self-included conformation is more stable in a condensed solution, as illustrated in Scheme 1.

Although the Np moiety is linked by a rigid spacer, the main purpose of our work was to construct a self-aggregated nanoparticle. The fact that Np is self-included is not the main concern. The Np self-inclusion is probably due to the highly efficient cooperativity between the two CDs on **1**, which provides a suitable binding site for Np rather than forming intermolecular complexes. In order to eliminate the unexpected cooperativity and return to the initial design, the Np moiety needs to be pulled from the CDs' cavities. The most common way is by using adamantane derivatives to compete with the Np moiety. The disadvantage is that this attempt will fill all the CD cavities to prevent the next intermolecular aggregation forming. A more accessible way is using metal chelation to pull Np part out, as there are potential binding sites available for metal ions, which are composed by two triazole rings and oxygen atoms of **1** nearby. By screening perchlorate salts of Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Ag^+, Cu^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Hg^{2+}, Cd^{2+}, and Pb^{2+} by monitoring the absorption spectra of **1**, it is found that a significant blue shift with 4 and 2 nm could be found in the presence of Hg^{2+} and Ag^+, respectively (Figure 2a). The IR spectra of **1** show the vibrations of C=C, C=N bands and the C−N band of the triazole ring at $\nu_{C=N}$ = 1651 cm^{-1} and ν_{C-N} = 1077 cm^{-1} have 47 and 9 cm^{-1} blue shifts, respectively, after coordination with Hg^{2+} and Ag^+. A typical Hg−O vibration band and a Ag−O band are separately observed at 627 and 619 cm^{-1} (see the Supporting Information, Figure S8). A Job's plot (see the Supporting Information, Figure S9) gives a 1:1 stoichiometry of Hg^{2+}/**1** complex. The association constant of **1** with $Hg(ClO_4)_2$, $AgClO_4$, and $Cu(ClO_4)_2$ determined by UV titration in aqueous solution are 9.0×10^4, 3.3×10^4, and 57 M^{-1}, respectively (Figure 2c and Table S1 in the Supporting Information). The largest binding affinity of **1** with Hg^{2+} among these metal ions suggests that Hg^{2+} ions should be the best candidate to demonstrate the whole process clearly.[14]

Upon addition of Hg^{2+} (10 mM) in a D_2O solution of **1** (1.90 mM), the ^{1}H NMR spectrum shows that Ha, Hb, and Hd in **1** shift downfield 0.71, 0.12, and 0.92 ppm, as well as Hc upfield 0.11 ppm (see the Supporting Information, Figure S4). The chemical shifts of H(a−d) in the presence of Hg^{2+} are similar to those protons of **1** without Hg^{2+} in DMSO-d_6 solution (Figure 1a−i and 1b−I), which indicates Np probably had been pulled out from its original located CD cavity. Furthermore, both the intensity of the positive ICD peak at 323 nm and the negative ICD at 275 nm decrease upon addition of Hg^{2+}. Upon continuous addition of Hg^{2+} salts until all the binding sites are saturated, ICD signals at 323 nm reverse from a positive to a weak negative peak, while the signals at 275 nm increasing from a negative to a positive peak. All this information from circular dichorism spectra indicates that the intramolecular self-inclusion mode of **1** is reversed to a free expanded mode. The 2D ROESY spectrum of **1** with Hg^{2+} (2.0 mM **1** and 10 mM Hg^{2+}) shows that there is no NOE correlation between Ha, Hb, Hc of naphthyl groups and inner protons of β-CD (see the Supporting Information, Figure S6). This clearly suggests that the Np moiety is pulled out of its original located CD cavity (Scheme 1). Upon increasing the concentration of **1**·Hg (Hg^{2+} 5 equiv to **1**) from 0.60 and 1.20 mM to 20 mM, the signals of Ha, Hb, Hc, Hd are upfield shifted about 0.14, 0.19, 0.25, and 0.18 ppm, respectively (Figure 1b). The ROESY spectra of **1**·Hg at higher concentration (20 mM **1** and 100 mM Hg^{2+}, see the Supporting Information, Figure S7) show that NOE correlations between Hb, Hc with H-3, H-5 of the CD and correlations between Ha with H-3 of CD can be newly found. This indicates that the Np moiety is stepwise included into another CD's cavity to form the intermolecular aggregations with increased concentration (Scheme 1).

According to the above results, increasing the concentration of **1**·Hg might result in intermolecular dendrimeric self-aggregates, which is well validated by the experiments of both transmission electron microscopy (TEM) and atomic force microscopy (AFM). There are numerous sphere particles of **1**·Hg with an average diameter of 30−50 nm in the TEM image (Figure 3a), while only amorphous aggregates of **1** can be found (see the Supporting Information, Figure S11). The AFM image shows that the diameter of sphere particles is about 40−50 nm (Figure 3b), which is consistent with the results of the TEM experiments. The height of these particles

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(14) The association constants of Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+}, and Pb^{2+} with **1** are all smaller than 30 M^{-1} with a small change in the UV−vis titration.

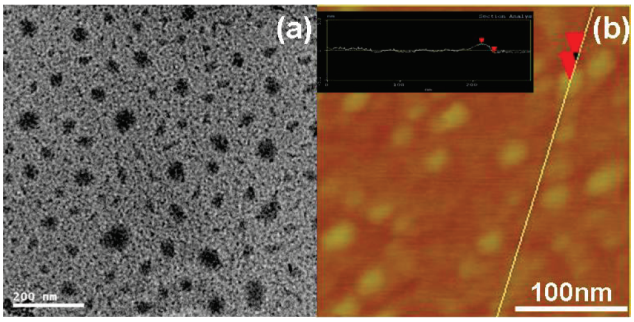

FIGURE 3. (a)TEM image of **1**·Hg (5 mM) and (b) AFM image of **1** after addition of 5.0 equiv of $Hg(ClO_4)_2$ in aqueous solution.

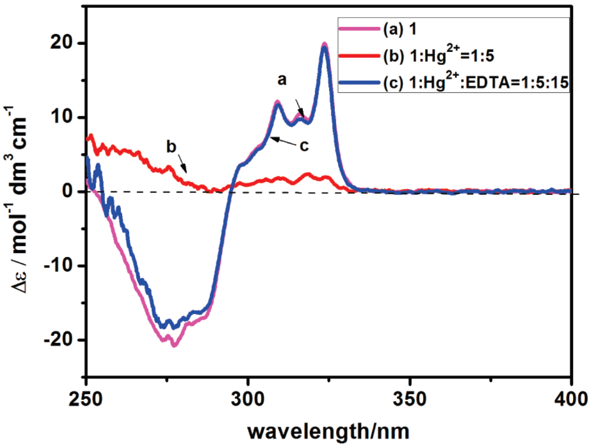

FIGURE 4. Circular dichroism spectra of (a) **1** (4.0×10^{-4} mol/L), (b) **1** (4.0×10^{-4} mol/L) + Hg^{2+} (2.0×10^{-3} mol/L), and (c) **1** (4.0×10^{-4} mol/L) + Hg^{2+} (2.0×10^{-3} mol/L) + EDTA (6.0×10^{-3} mol/L) in aqueous solution.

is about 1.5 nm in the AFM image, which is also consistent with the diameter of β-CD's secondary face.[15]

Then, ethylenediamine tetraacetate (EDTA) was introduced to test whether the process described above is reversible, as EDTA is a well-known strong ligand for Hg^{2+}. Both the chemical shifts and the ICD signals of **1** are completely recovered upon addition of EDTA to the solution of **1**·Hg^{2+} (Figure 4 and Figure S12, Supporting Information). These observations clearly indicate that once the metal ions are removed from **1**, the strong cooperativity of CDs will spontaneously destroy the intermolecular inclusion and lock the Np moiety again as a self-inclusion conformation (Scheme 1). That is to say, the formation and the disassembly of nanoparticles based on **1** can be reversibly controlled by addition and removal of Hg^{2+}.

In conclusion, we have validated, in the absence of Hg^{2+}, that the cooperativity of two CDs in **1** could lock the potential building block, Np moiety, and prevent formation of aggregations in aqueous solution. In the presence of Hg^{2+}, the coordination process induces the Np moiety in **1**, leaving the cavity of CD into that of another **1**, leading to the formation of nanoparticles with the increase of the concentration. Significantly, the two distinctly different inclusion modes can be reversibly modulated by controlling the coordination and release of Hg^{2+}. This new protocol suppressing intramolecular interaction and inducing the intermolecular binding by coordinated with metal ions is quite promising in catalysis and nanomaterials.

Experimental Section

Preparation of 2,3-Naphthalenediol-Bridged Bis(β-cyclodextrin) (1). To a solution of 2,3-propargyloxynaphthalene (100 mg, 0.424 mmol) in THF (20 mL) was added 6-deoxyl-6-azido-β-CD (1.1 g, 0.949 mmol) in H_2O (10 mL) with stirring. To the resulting solution were added $CuSO_4 \cdot 5H_2O$ (430 mg) and then sodium ascorbate (900 mg) dissolved in water (10 mL). The mixture was heated at about 60 °C for 48 h. The mixture was then dried under reduced pressure, and the residue was dissolved in DMF. Insoluble precipitates were removed by filtration, the crude product obtained was further purified by MPLC (reversed phase) with a water−alcohol eluent, and the collected fraction was freeze-dried to obtain a colorless powder in 60% yield: ^1H NMR (DMSO-d_6, 300 MHz, ppm) δ 8.19 (s, 2H), 8.14 (m, 2H), 7.54 (s, 2H), 7.34 (m, 2H), 5.80−5.74 (m, 28H), 5.22 (s, 4H), 5.05−4.83 (m, 14H), 4.36 (m, 12H), 3.63 (m, 30H), 3.36 (m, 46H, overlapped with the DOH peak), 2.89 (m, 8H); ^{13}C NMR (D_2O, 400 MHz, ppm) δ 147.3, 142.3, 129.1, 127.0, 126.0, 125.6, 102.0, 101.9, 101.8, 101.5, 101.4, 82.7, 81.4, 80.9, 80.7, 80.6, 80.4, 73.0, 72.0, 71.9, 71.8, 62.5, 62.4, 60.5, 60.1, 60.0, 59.6, 59.2, 51.1, 44.5; MALDI-MS *m/z* 2577.8336 ($[M + Na]^+$). Anal. Calcd for $C_{100}H_{150}N_6O_{70} \cdot 18H_2O$: C, 41.70; H, 6.51; N, 2.92. Found: C, 41.50; H, 6.46; N, 3.23.

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Supporting Information Available: ^{13}C NMR spectra, 2D NMR spectra, MALDI-MS spectra, FT-IR spectra, and Job's plot of **1** and **1**·Hg. This material is available free of charge via the Internet at http://pubs.acs.org.

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