Organic Letters
Letter
pubs.acs.org/OrgLett

# One-Pot Synthesis of Strained Macrocyclic Pyridone Hexamers and Their High Selectivity toward $Cu^{2+}$ Recognition

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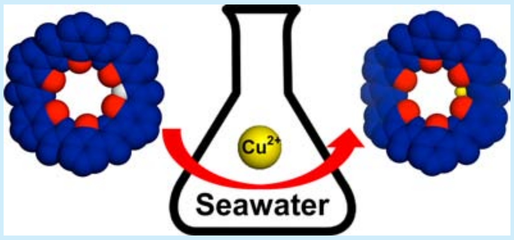
*Supporting Information*

**ABSTRACT:** The removal of $Cu^{2+}$ ions is relevant to environmental pollution control and neurodegenerative disease treatment. A novel family of strained macrocyclic pyridone hexamers, which exhibit highly selective recognition of $Cu^{2+}$ ions and reduce copper content in artificial seawater by 97% at a very low [host]:[$CuCl_2$] molar ratio of 2:1, is documented.



Although copper is the third most abundant trace element after iron and zinc in the body with a typical blood concentration of up to 0.15 ppm[1a] and plays an important role in many biological processes, excess intake of $Cu^{2+}$ ions might lead to liver damage[1b] and serious neurodegenerative diseases including Wilson's disease,[1c] Alzheimer's disease and Parkinson's disease. As a result of intensive industrial mining and agricultural activities, hazardous $Cu^{2+}$ ions exceeding the USEPA's recommended maximum contaminant concentration of 1.3 ppm are often found in industrial wastewater, drinking water or groundwater. Thus, highly selective removal of toxic metal ions including $Cu^{2+}$ ions continuously presents a considerable challenge to the field.[2]

On the other hand, substantial progress has been made over the years to develop H-bonded macrocyclic foldamers with aromatic backbones rigidified by intramolecular H-bonds.[3] Aside from their great structural diversity,[3] many interesting functions have also been demonstrated, including G-quadruplex stabilization,[4a] ion transportation[4b] and recognition,[4c−f] solvent gelation,[4g,h] reaction catalysis[4i] and liquid-crystallize materials.[4j] In particular, a powerful H-bonding-assisted one-pot macrocyclization strategy recently advanced by Gong[3a] and others[3b,c] makes many such H-bonded macrocycles readily available, greatly facilitating their further functional study and applications.

Along the same line, our efforts toward developing "greener" one-pot macrocyclization protocols led to discovery of $POCl_3$ and BOP as the efficient macrocyclization reagents for rapid production of H-bonded macrocyclic pentamers derived from alkoxybenzene[5a−d] and pyridone[5e] units. In these protocols, energetically more stable pentamers always are produced as the dominant products with the corresponding energetically less stable macrocyclic hexamers remaining either undetectable or as a minor product. Our recent investigation, however, identified trimethylaluminum [$Al(Me)_3$] as a surprising macrocyclization reagent that selectively produces strained macrocyclic alkoxybenzene-based hexamers, rather than the more stable pentamers, as the major product.[5f] This unusual finding suggests the likely production of pyridone- or fluorobenzene[5g]-based strained macrocyclic hexamers. This may lead to a new class of ion-binding macrocyclic hexamers distinctively different from the corresponding pentamers (Figure 1c) with an ability to recognize larger cations such as $Cs^+$, $Ba^{2+}$ and $Tl^+$ preferentially over many other smaller metal ions.[4e] In this communication, we show that BOP and only BOP can be used to produce the strained macrocyclic pyridone hexamers via one-pot macrocyclization and that the produced hexamers specifically bind and efficiently remove $Cu^{2+}$ ions from artificial seawater. This constitutes the first report on the highly selective recognition and removal of $Cu^{2+}$ ions by either aliphatic[6a] or aromatic[3,6b] foldamers of great diversity and varying functions.

Our initial attempt to use $Al(Me)_3$ failed to produce macrocyclic pyridone hexamers from their corresponding monomers (Figure 1a). Starting from the dimers, however, strained macrocyclic hexamers **1** and **2** both could be produced with satisfactory yields of 31−56% by using BOP, but not $Al(Me)_3$ or $POCl_3$, in a mixed solvent containing anhydrous dichloromethane ($CH_2Cl_2$) and DMF (2:1, v/v). After many unsuccessful attempts, the X-ray-quality single crystals were eventually obtained by slowly diffusing 1 mL of acetonitrile into 1 mL of **2**-containing DMSO solution for a few weeks at room temperature. The determined structure reveals an expected folding of **2** into a circular arrangement stabilized by a continuous intramolecular H-bonding network (Figure 1b). The folding convergently orients the six electron-rich carbonyl O atoms inward to enclose a noncollapsible ion-binding cavity of ~4.6 Å in diameter exclusive of the atomic volumes of O atoms. An intrinsic propensity for the monomeric pyridone units to produce a planar macrocyclic pentagonal structure[5f] (Figure 1c) possibly explains why the macrocyclic hexameric backbone is slightly distorted (Figure 1b) and energetically less stable by 0.50 kcal/mol per building block than the pentamer.

**Received:** September 24, 2015
**Published:** December 7, 2015

DOI: 10.1021/acs.orglett.5b02780
*Org. Lett.* 2015, 17, 5946−5949

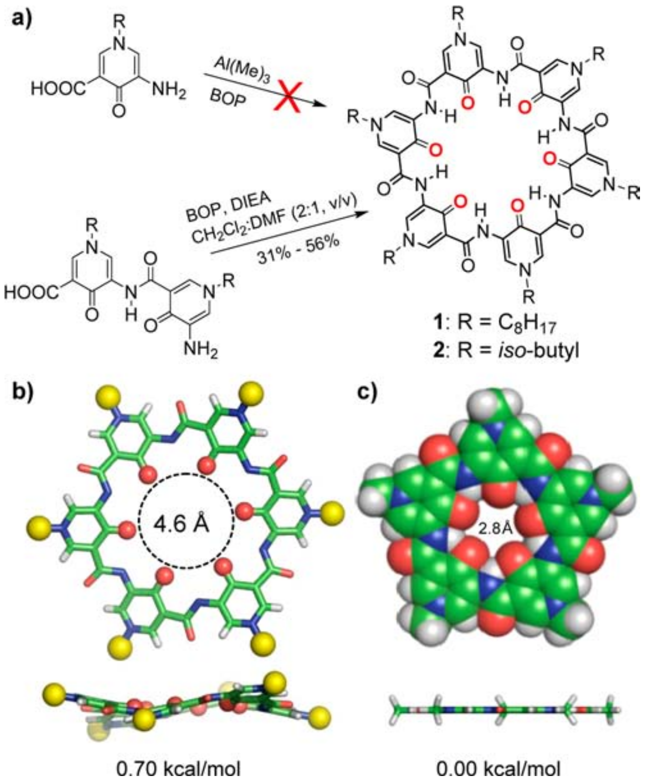


**Figure 1.** (a) BOP-mediated H-bonding-assisted one-pot synthesis of strained macrocyclic hexamers **1** and **2** under mild conditions and top and side views of (b) the crystal structure of **2** deviating from planarity and (c) the computationally determined planar structure of a pyridone pentamer. In (b), the five *tert*-butyl groups were replaced by yellow atoms for clarity of view, and the red balls refer to the carbonyl O atoms. Computationally, hexamer is less stable than pentamer by 0.70 kcal/mol per building block at the B3LYP/6-31G(d,p) level in the gas phase. For an ORTEP view of **2** at the 70% probability level, see Figure S2.

**Table 1. Extraction Efficiencies of $Cu^{2+}$ (0.72 Å) and $Cs^+$ (1.67 Å) Ions in Their Nitrate Salts by Host 1 at 25 °C at pH 6.4 under Various Conditions As Determined by Inductively Coupled Plasma Mass Spectrometry (ICP-MS)**

| | | | [**1**]/[$Cu^{2+}$] | | | | | |
|---|---|---|---|---|---|---|---|---|
| entry | metal ions | concn (mM) | 2 | 5 | 10 | 20 | 50 | 100 |
| 1[a] | $Cu^{2+}$ | 0.01 | 13 | 23 | 33 | 50 | 90 | 93 |
| 2[a] | $Cs^+$ | | | | | | 7 | 14 |
| 3[b] | $Cu^{2+}$ | 0.1 | 65 | 82 | 89 | 96 | *d* | *d* |
| 4[b] | $Cs^+$ | | 4.6 | 11 | 20 | 40 | *d* | *d* |
| 5[c] | $Cu^{2+}$ | | 70 | 90 | 92 | 94 | *d* | *d* |
| 6[c] | $Cs^+$ | | 3.3 | 8.9 | 19 | 31 | *d* | *d* |
| nonextractable ions[a] | | | | | | | | |
| $Rb^+$ (1.52 Å), $Tl^+$ (1.50 Å), $Ba^{2+}$ (1.35 Å), $K^+$ (1.38 Å), $Ag^+$ (1.15 Å), $Na^+$ (1.02 Å), $Ca^{2+}$ (1.00 Å), $Cd^{2+}$ (0.95 Å), $Pb^{2+}$ (0.86 Å), $Mn^{2+}$ (0.83 Å), $Li^+$ (0.76 Å), $Co^{2+}$ (0.75 Å), $Zn^{2+}$ (0.74 Å), $Mg^{2+}$ (0.72 Å), $Ni^{2+}$ (0.69 Å), $Fe^{3+}$ (0.645 Å), $Cr^{3+}$ (0.62 Å), $Al^{3+}$ (0.535 Å) | | | | | | | | |

[a] Extractions carried out in a biphasic system using equal volumes of $H_2O$ containing 0.01 mM of individual metal ions and $CHCl_3$ containing 0.02−1.00 mM of**1**. [b] Extractions carried out using $H_2O$ containing 0.1 mM of $Cu^{2+}$ or $Cs^+$ ions and $CHCl_3$ containing 0.2−2.0 mM of **1**. [c] Extractions carried out using $H_2O$ containing 20 metal ions, each at 0.1 mM, and $CHCl_3$ containing 0.2−2.0 mM of **1**. [d] Not determined. Ions are 6-coordinate unless indicated.[9]

Incorporation of one more building block, however, does enlarge the cavity diameter from 2.8 Å as found in the pentamer (Figure 1c) to 4.6 Å as in the hexamer (Figure 1b), thereby suggesting differential ion-binding profiles between them.

The ion-binding profile of more soluble hexamer **1** toward 20 different metal ions (0.54−1.67 Å in radius) was evaluated by a biphasic water−chloroform extraction system.[4e] In a typical experimental setup, the concentration of each individual metal ion in $H_2O$ is set constant at 0.01 mM or 0.1 mM, while that of **1** in $CHCl_3$ is varied from 0.02 to 1.0 mM or from 0.2 to 2.0 mM. After the biphasic water−$CHCl_3$ solution was shaken for 24 h at 25 °C, ion extractions from aqueous phase to chloroform layer were measured by using inductively coupled plasma mass spectrometry (ICP-MS). Averaging the data over six runs gave the final extraction data with relative errors of ≤1.5%. Among all the 20 tested metal ions, **1** selectively extracts only $Cu^{2+}$ ions with extraction efficiencies reaching 93% when the molar ratio of [**1**]/[$Cu^{2+}$] is varied from 2 to 100 (entry 1, Table 1). Under these conditions, extractions of 7% and 14% $Cs^+$ ions were also observed (entry 2, Table 1), while the other 18 metal ions remain nonextractable at a high [**1**]/[metal ion] molar ratio of 100 within the instrument's sensitivity range. When the concentration of metal ions is increased from 0.01 to 0.1 mM (entry 3, Table 1), the extraction ability of **1** toward $Cu^{2+}$ ions dramatically increases with extraction efficiencies of 65%, 82%, 89%, and 95% at **1**/$Cu^{2+}$ molar ratios of 2, 5, 10, and 20, respectively.

The selective recognition of $Cu^{2+}$ and $Cs^+$ ions in the presence of other metal ions by **1** was then evaluated using an aqueous solution containing a total of 20 metal ions including $Cu^{2+}$ and $Cs^+$. In this experiment, the concentration of each metal ion is set to be 0.1 mM, and that of **1** is varied from 0.2 to 2.0 mM. As summarized in entries 5 and 6 of Table 1, host **1**, at a low **1**/$Cu^{2+}$ molar ratio of 5, is able to extract $Cu^{2+}$ by 90% with $Cs^+$ poorly extracted to 8.9%, and extractions of all the other 18 metal ions remain undetectable. Comparison of the extraction data of entry 3 with those of entry 5 confirms that $Cu^{2+}$ removal by **1** is not adversely impacted by the 18 metal ions including $Ag^+$, $Cd^{2+}$, $Mn^{2+}$, $Co^{2+}$, $Zn^{2+}$, $Ni^{2+}$, $Fe^{3+}$, and $Cr^{3+}$ ions. For comparison, at [**1d**] = 0.54 mM and [individual metal ion] = 0.1 mM, the analogous dimer **1d** (Scheme S1) displays a moderate extraction of $Hg^{2+}$ ions (52%), very low extractions toward $K^+$ (10%) and $Ag^+$ (18%), and no extraction of all the other 17 metal ions including $Cu^{2+}$ ions.

The above-demonstrated high selectivity of **1** in recognizing and removing $Cu^{2+}$ ions in the presence of many other interfering ions led us to further explore its possible application in the selective removal of $Cu^{2+}$ ions in the presence of $Na^+$, $K^+$, $Ca^{2+}$, and $Mg^{2+}$ ions commonly found in groundwater (Figure 2). In this regard, artificial groundwater containing 10 ppm (0.16 mM) $Cu^{2+}$, 100 ppm of $Na^+$ (4.3 mM), 5 ppm $K^+$ (0.13 mM), 60 ppm of $Ca^{2+}$ (1.5 mM), 25 ppm $Mg^{2+}$ (1.0 mM), and 349 ppm of $Cl^-$ ions at pH 7.4 was prepared. It was found that efficient removal of 89% $Cu^{2+}$ ions can be achieved using a low [**1**]:[$CuCl_2$] molar ratio of 5:1, reducing copper content from 10 ppm down to 1 ppm that meets the drinking water standard of 1.3 ppm for $Cu^{2+}$ ions set by USEPA (Figure 2). By replacing chloride with nitrate salts, a much smaller [**1**]/[$Cu(NO_3)_2$] molar ratio of 2:1 is sufficient to effect a 91% reduction of $Cu^{2+}$ ions (Figure S3).

Surprisingly, at the same [**1**]/[$CuCl_2$] molar ratio of 5:1 but in the absence of the other metal ions in solution, host **1** was

DOI: 10.1021/acs.orglett.5b02780
Org. Lett. 2015, 17, 5946−5949

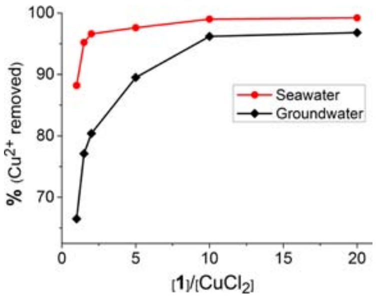


**Figure 2.** $Cu^{2+}$ removal by **1** at varying [**1**]/[$CuCl_2$] molar ratios from artificial groundwater or seawater containing 10 ppm of $Cu^{2+}$ ions.

only capable of removing 64% instead of 89% of $Cu^{2+}$ ions when artificial groundwater was used. This suggests that **1**-mediated extraction of $Cu^{2+}$ ions be substantially promoted by the noncopper ions possibly via a "salting out" effect. This likelihood prompted us to study the performance of **1** in copper removal from artificial seawater, which was prepared to contain 10 ppm of $Cu^{2+}$ ions (0.16 mM $CuCl_2$), 600 mM NaCl, 20 mM KCl, 20 mM $CaCl_2$, and 60 mM $MgCl_2$ at pH 7.5. Remarkably, use of stoichiometric amount of **1** results in a dramatic reduction of $CuCl_2$ from the artificial seawater by 88%, a value that compares very favorably with a mere 67% removal of $CuCl_2$ from the artificial groundwater at the same molar ratio (Figure 2). At a [**1**]/[$CuCl_2$] molar ratio of ≥10, removal of $CuCl_2$ from the artificial seawater plateaus at 99%. As of now, only a few ligands highly effective in removing $Cu^{2+}$ ions from a solution as salty as seawater have been documented in the literature.[2] By switching the liquid−liquid extraction process to a liquid−solid extraction method and using poorly soluble **2** in its powder form, a [**2**]/[$CuCl_2$] molar ratio of 10:1 results in a very significant reduction of $Cu^{2+}$ ions by 98% from 10 ppm down to 0.2 ppm in artificial seawater.

To elucidate possible structural origins accounting for this unusual selectivity, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry was employed to analyze the metal complexes formed in the chloroform layer. A major peak at 1550.56 Da was identified and its identity is unambiguously confirmed to be a monocationic complex $[\mathbf{1}\cdot Cu]^+$ with one H atom lost from host **1** and with a molecular formula of $C_{84}H_{119}O_{12}N_{12}Cu$ via an excellent matching between the experimental isotope distribution pattern and that of the computer-simulated one (Figure S4). The existence of a monovalent cationic complex $[\mathbf{1}\cdot Cu{-}H]^+$ points to a plausible event where, upon binding of a $Cu^{2+}$ ion by **1**, one of the six amide protons in **1** was deprotonated to produce the negatively charged **1**, which subsequently interacts with the positively charged $Cu^{2+}$ ion. This scenario seems to be consistent with our recent finding,[7a] demonstrating that $Cu^{2+}$ ions promote metal ion-mediated deprotonation of phenolic hydroxyl groups to the largest extent in aqueous solution among 21 metal ions studied.

The above hypothesis, which emphasizes the use of a $Cu^{2+}$-promoted deprotonation mechanism to account for a highly specific and high-affinity recognition of $Cu^{2+}$ ions by the host, suggests extraction of $Cu^{2+}$ ions by **1** to be pH dependent. The data obtained from extractions carried out at different pH indeed fit very nicely into the theory-derived pH-dependent behavior. In more details, at a [**1**]/[$CuCl_2$] molar ratio of 5:1, the extraction efficiency of $Cu^{2+}$ ions from a plain water solution increases from 7.5% to 33%, 59%, 74% and 81% when the solution pH increases from 0 to 2, 4, 6/ and 8, respectively.

The existence of a monovalent complex $[\mathbf{1}\cdot Cu{-}H]^+$ and a pH-dependent extraction of $Cu^{2+}$ ions suggest the amide groups in **1** to be significantly more acidic than they should be. This increased acidity may result from a twisted hexameric backbone enforced by a macrocyclic ring constraint. To verify this hypothesis and to sensitively quantify the acidity of amide H atoms,[7b] we performed amide hydrogen−deuterium (H−D) exchange experiments that were initiated by adding 20 $\mu$L of $D_2O$ into 600 $\mu$L of 5 mM sample in deuterated solvents ($CDCl_3$/DMSO-$d_6$, 2:1, v:v).

In addition to **1**, pentamer **3** with a planar structure (Figure 1c) and dimer **4** containing no H bonds at all (Scheme S1) were also subjected to comparative H−D exchange analyses. Compared to the amide proton of **4** that resonates at 9.98 ppm, a substantial downfield shift in chemical shift to 12.21 and 13.54 ppm for the amide protons in **1** and **3**, respectively, provides a clear indication of the involvement of the amide protons from **1** and **3** in forming intramolecular H bonds, which generally makes the H-bonded protons more difficult for replacement by deuterium atoms from $D_2O$ molecules.[7b] Consistent with this expectation, the five equivalent amide protons in **3** show an exceptionally high stability with a half-life of 102.4 h, which is far much larger than the half-life value of 0.87 h for **4** that contains no H bonds (Figures S5 and S6). In sharp contrast, strained hexamer **1** undergoes an even faster H−D exchange than **4** by 0.21 h (Figure S5). This abnormal finding, however, is in good accord with our above hypothesis, speculating that a twisted conformation in **1** substantially increases the acidity of the amide protons and its exchange rate with deuterium atoms. This increased acidity works with the surrounding six cation-stabilizing carbonyl O atoms to possibly allow deprotonation of **1** to take place upon binding of a $Cu^{2+}$ ion.

The structures of anionic complex $[\mathbf{1}\cdot(CuCl_2)(H_2O)]^-$ containing deprotonated anionic **1** (Figures S7a and S8) and neutral complex $[\mathbf{1}\cdot(CuCl_2)(H_2O)]$ containing neutral **1** (Figures S7c and S9) were computationally optimized at the B3LYP/6-31G(d,p) level in chloroform.[7c] Due to possible disturbances the crystal packing might have on the conformation of neutral **1**, its computationally optimized structure, rather than its crystal structure (Figure 1b), was used for comparison (Figure S7a). The optimized structures show that the cyclic hexameric backbone in anionic complex $[\mathbf{1}\cdot(CuCl_2)(H_2O)]^-$ (Figure S7b) is not more distorted than that in neutral **1** (Figure S7a). Both of them, however, are significantly less distorted than that of **1** in neutral complex $[\mathbf{1}\cdot(CuCl_2)(H_2O)]$ (Figure S7c). These differential distortions between anionic and neutral complexes suggest that the cyclic backbone of **1** be predisposed for forming an anionic complex, rather than a neutral complex that comes with a considerable entropic penalty. Enthalpywise, there might be more energy gains in forming an anionic complex than a neutral complex given that the $Cu^{2+}$ ion appears to sit comfortably in the binding pocket formed by two O atoms and one negatively charged N atom in an anionic complex, and is stabilized by three strong coordination bonds of ~2.0 Å (Figure S7b).

EPR study of the solid sample prepared by mixing **1** and $CuCl_2\cdot 2H_2O$ in a 10:1 ratio reveals a four line EPR spectrum for $Cu^{2+}$ ($I = 3/2$) with $g_{//} = 2.27$ being larger than $g_{\perp} = 2.05$ (Figure S10), suggesting that the unpaired electron in the copper center resides in the $d_{x^2-y^2}$ orbital and that the copper

DOI: 10.1021/acs.orglett.5b02780
Org. Lett. 2015, 17, 5946−5949

center adopts a square-pyramidal geometry with elongation along the $z$ axis as similarly seen in the computationally determined anionic complex $[\mathbf{1}\cdot(CuCl_2)(H_2O)]^-$ but not the neutral complex $[\mathbf{1}\cdot(CuCl_2)(H_2O)]$ that takes a trigonal-bipyramid geometry.

In summary, we have developed a novel class of circularly folded macrocyclic pyridone hexamers with a noncollapsible ion-binding cavity and demonstrated their excellent ability to selectively recognize and efficiently remove copper ions in the presence of many interfering transition metal ions and from artificial seawater. This high selectivity may arise from a distortion-enhanced acidity of the amide protons of the host. Moreover, the copper removal capacity of these hexameric hosts could be dramatically enhanced by other noncopper metal ions, resulting in a highly efficient removal of $Cu^{2+}$ ions by 97% from artificial seawater at a [host]/[$CuCl_2$] molar ratio of 2:1. This outstanding selectivity in high-capacity recognition of $Cu^{2+}$ ions may offer good opportunities in the making of specialty high-performance nanofiltration membranes or solid supports for water treatment and might also find uses as innovative copper-chelating medicines, applicable in particular to the treatment of Wilson's disease.[1a,c]

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02780.

Synthetic procedures and characterization data including $^1$H NMR, $^{13}$C NMR, MS, ICP-MS, MALDI-TOF, H/D exchange experiment, crystal data, molecular modeling, EPR, and UV−vis (PDF)

X-ray data for compound **2** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support for H.Z. by the Institute of Bioengineering and Nanotechnology (Biomedical Research Council, Agency for Science, Technology and Research, Singapore) is acknowledged.

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