<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Discoveries from a phenanthroline-based dynamic combinatorial library: catenane from a copper(I) or copper(II) template?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author(s)</strong></td>
<td>Tong, KL; Yee, CC; Tse, YC; Au Yeung, HY</td>
</tr>
<tr>
<td><strong>Citation</strong></td>
<td>Inorganic Chemistry Frontiers, 2016, v. 3 n. 3, p. 348-353</td>
</tr>
<tr>
<td><strong>Issued Date</strong></td>
<td>2016</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10722/226306">http://hdl.handle.net/10722/226306</a></td>
</tr>
<tr>
<td><strong>Rights</strong></td>
<td>This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.</td>
</tr>
</tbody>
</table>
Discoveries from a Phenanthroline-based Dynamic Combinatorial Library: Catenane from Copper(I) or Copper(II) Template?

King-Lung Tong‡, Chi-Chung Yee‡, Yuen Cheong Tse and Ho Yu Au-Yeung∗∗

We report here a DCL study of a phenanthroline-based building block focusing on catenane formation with copper templates. Two [2]catenanes have been amplified by using Cu⁺ as template from the DCLs that contains no interlocked compound in the absence of copper. In addition, an unexpected Cu²⁺ template effect on the [2]catenane formation was discovered. The observed Cu²⁺ template effect was found to be originated from the in situ reduction of the divalent metal to Cu⁺.

Results and discussion

Building blocks designs and synthesis

The structure and synthesis of the phenanthroline-based building block 1 is depicted in Scheme 1. The bidentate phenanthroline-Cu¹ coordination is one of the most successful preorganization strategies for catenane assembly,⁶ we propose the use of building blocks derived from the phenanthroline ligand will efficiently generate DCLs of interlocked structures plus other complex topologies when templated by Cu⁺, allowing the study of complex molecular topologies under thermodynamically-controlled conditions. We report here our initial study on the use of a phenanthroline-based dialdehyde building block for the generation of dynamic combinatorial libraries of catenanes⁹ using hydrazone as the exchange reaction. The DCL behaviour, amplification of two [2]catenanes by Cu⁺ template and their characterisation are described. We also discovered an unexpected Cu²⁺ template effect on the assembly of the [2]catenanes. Further experiments on the coordination chemistry of model systems revealed that the observed template effect from Cu²⁺ is originated from the Cu⁺ generated by the in situ reduction of the divalent metal ion. This unexpected template effect of Cu²⁺ was also applied in the assembly of catenanes under non-DCL conditions. It is believed that the studies of the Cu⁺-phenanthroline coordination motif under DCL conditions could offer an unique opportunity for studying the assembly of catenane and other possible, but not necessarily predictable or imaginable, complex molecular topologies under thermodynamic control, and eventually unveil the rules governing the self-assembly process of these complicated molecular entities.

DCL studies and Cu¹-templated catenane formation

The first hydrazone DCL was prepared by dissolving 1 mM each of the building blocks 1 and 2 in CHCl₃/Methanol/CF₃COOH (10:10:1). The library solution was analysed by LCMS after 3 days. The HPLC chromatogram showed that the [1+1]macrocycle M₁ is the dominant species in the DCL, and it represents 96% of the library materials with the remaining 4% as the [2+2]macrocycles M₂ (Fig. 1).
Further analysis of the DCL at later time points (i.e. 5 and 7 days) revealed the same library composition, suggesting that the library has reached thermodynamic equilibrium. When the DCL was prepared in the presence of 0.5 mM Cu⁺, a library of a different composition was obtained. Addition of Cu⁺ to the DCL templated the formation of a new species (C1-Cu⁺), which was not detectable in the metal-free DCL, to 71% at the expense of other library members. Pure sample of C1-Cu⁺ can be obtained by preparative HPLC or flash column chromatography for further analysis (see ESI for details). Results from ESI-MS, HRMS and MS/MS studies on C1-Cu⁺ are consistent with an interlocked structure (Fig. 2). The mass spectrum of C1-Cu⁺ shows peaks at m/z = 571.4 [C1+Cu+3H]⁺, 761.5 [C1+Cu+2H]⁺ and 1141.3 [C1+Cu+H]⁺ that correspond to the tetra-, tri- and di-cation of C1-Cu⁺ respectively. Fragmentation of the ion at m/z = 1141.3 [C1+Cu+H]⁺ directly resulted in daughter ions at m/z = 1109.3 and 1171.3 that correspond to [M1+H]⁺ and [M1+Cu⁺].

Scheme 1. Synthesis of the dialdehyde building block 1, the dihydrazides 2 and 3, and the phenanthroline derivatives 4 and 5.

Scheme 2. Generation of hydrazone DCL from dialdehyde 1 and dihydrazide 2. The [2]catenate C1-Cu⁺ was amplified by Cu⁺ template.
Indeed, the $^1$H NMR spectrum of $M_1$ does show at least six different sets of aromatic signals that are identified as the phenylene protons from the corresponding COSY spectrum (Fig. S19, S20), suggesting that both the syn and anti isomers of the hydrazone are present in $M_1$ (and also most likely in $C_1\cdot Cu^+$) that lead to the inequivalent aromatic chemical environments.

![Fig. 1](image)

**Fig. 1** HPLC analysis of a 1 mM DCLs of 1 and 2 (a) in the absence of template and in the presence of 0.5 mM of (b) Cu$^+$ and (c) Cu$^{2+}$. Absorbance was monitored at 285 nm.

The dynamic nature of the catenane assembly was studied by a series of equilibration experiments. First, instead of adding the Cu$^+$ template at the beginning of the DCL preparation, the metal ion was added to a DCL that has been equilibrated for 3 days. Concentration of $C_1\cdot Cu^+$ in the DCL gradually increased from undetectable to ca. 70% with the remaining 30% as $M_1$, which is almost the same as that of the DCL prepared when Cu$^+$ was introduced at the beginning of the DCL evolution (Fig. S28). The observation that the same equilibrium position could be reached from two different starting points suggests that the library is dynamic and is under thermodynamic control.11 Second, the effect of the building block concentration on the equilibrium position and yield of $C_1\cdot Cu^+$ was studied. DCLs with different concentrations of 1 and 2 were setup and their equilibrium compositions were compared. In accord with the Le Châtelier’s principle, an increase in the yield of $C_1\cdot Cu^+$ from 36% to 71% to 93% when the building block concentrations were increased from 0.1 mM to 1 mM to 5 mM at a building block/Cu$^+$ ratio of 2:1 (Fig. S26). Third, effect of the Cu$^+$ template to building block ratio was studied. DCLs with 0.1, 0.5, 1 and 2 eq. of Cu$^+$ relative to 1 were prepared. From 0.1 eq. to 0.5 eq. of Cu$^+$, an increase in the yield of $C_1\cdot Cu^+$ from 17% to 71% was observed. Further increasing the template concentration to 1 eq. and 2 eq. of Cu$^+$ relative to 1, on the other hand, lead to a decrease of the yield of $C_1\cdot Cu^+$ to 68% to 48% respectively (Fig. S27). Presumably, at Cu$^+$ concentration below 0.5 eq., increase in the concentration of Cu$^+$ templates the formation of the 2:1 phenanthroline-Cu$^+$ complex and lead to a higher yield of $C_1\cdot Cu^+$. However, further increase in Cu$^+$ concentration could shift the equilibrium towards the 1:1 phenanthroline-Cu$^+$ complex which favors the formation of the macrocycle instead of the [2]catenane.

![Fig. 2](image)

**Fig. 2** ESI-MS analysis of $C_1\cdot Cu^+$ and $C_1$. (a) The MS and (b) MS/MS spectra of $C_1\cdot Cu^+$. The MS/MS spectrum was obtained from fragmenting the peak at $m/z = 1141.3$. (c) The MS of spectrum $C_1$; and (d) the MS/MS spectrum from fragmentation of the peak at $m/z = 1132.3$.

A similar hydrazone DCL was also prepared from 1 and 3 under the same conditions (Scheme S4). The library mixture was analysed by LCMS which showed the [1+1]macrocycle $M_3$ as the only detectable library member. No [2+2]macrocycle similar to $M_2$ was found. Similar to the DCL of 1 and 2, the presence of 0.5 mM Cu$^+$ templates the formation of the [2]catenane $C_2\cdot Cu^+$ to 90% (Fig. S26). The interlocked structure of $C_2\cdot Cu^+$ and its metal-free form $C_2$ were also characterised by ESI-MS and MS/MS. Fragmentation behaviour...
similar to that of C1-Cu' and C1 was observed, confirming the catenane topology of C2-Cu2+ (Fig. S34, S35). Since building block 3 is designed with the π-rich dioxynaphthalene core for further molecular recognition with complementary π-designed with the π-rich dioxynaphthalene core for further consistent with the formation of [Cu(4)]2+ (Fig. S24).

Cu2+ templates catenane formation in DCL
In addition to Cu+, other metal ions including Li+, Na+, K+, Mg2+, Ca2+, Al3+, Mn2+, Fe2+, Fe3+, Co2+, Ni2+, Cd2+, Ce3+ and Er3+ were also tested as templates for the DCL of 1 and 2. While these metal ions did not perturb the equilibrium position and the same library compositions as the metal-free DCL were observed (Fig. S25), C1-Cu+ was amplified by addition of Cu2+. While the redox switching of Cu2+/Cu+ has been demonstrated to induce the circumrotation and conformation change of catenanes and other complex topologies with variable coordination geometry and coordination number, templating [2]catenane assembly from two bidentate phenanthroline precursors by Cu2+ is not known as far as we are concerned. Compared with the Cu+ template, Cu2+ only amplifies C1-Cu+ to 44% of the library materials. The lower efficiency of Cu2+ to template C1 in the DCL may suggest that 1) Cu2+-coordination to the [2]catenane is thermodynamically less stable than that of Cu+ or 2) the mechanism of Cu2+ template involves not only Cu2+-phenanthroline coordination.

In situ reduction of Cu2+ to Cu+
To elucidate the origin of Cu2+ template effect on the [2]catenane assembly, the coordination chemistry of the phenanthroline derivative 4 and 5 to Cu2+ was studied. Complexation of 4 to CuCl2 in 2:1 ratio in CH3CN/MeOH at room temperature initially resulted in a yellow solution that gradually turned red. UV-Vis analysis showed that the red species has an absorption maximum at 445 nm which is consistent with the reported MLCT band of CuI-phenanthroline (Fig. 3a). The absorption spectrum also resembles to that of the independently synthesized [Cu(4)2][PF6], indicating a reduction of Cu2+ to Cu+ upon coordination of 4 under the experimental conditions. Similar Cu+ to Cu2+ reduction has also been observed in cross-coupling reactions involving copper as the catalysts, but such effect in molecular self-assembly involving the metal is not known. By comparing the relative absorbance, a ca. 60% conversion of Cu+ to Cu2+ has been estimated, which correlates very well with the observed relative yields (71% vs. 44%) of C1-Cu+ in the corresponding DCLs. The observed in situ reduction is also supported by 1H NMR studies. The red solution obtained from a 2:1 mixture of 4 and CuCl2 in CD3CN showed no paramagnetically shifted resonances due to the d9 CuII, and that the 1H spectrum is consistent with the formation of [Cu(4)(μ)]2+ (Fig. S24).

Presumably, the tetrahedral coordination geometry enforced by the two phenanthrolines modulates the reduction potential of Cu2+ such that Cu2+ could be reduced to Cu+, possibly by protic reagents, upon coordination to the bidentate ligand under the experimental conditions. X-ray structure of [Cu(4)(μ)][PF6] revealed the expected tetrahedral coordination geometry around the metal (Fig. 4a). In addition, the observed π-stacking interaction between the phenanthroline and the aromatic substituents may also reinforce the stability of the tetrahedral coordination motif and facilitate the in situ reduction. Indeed, the complexation reaction of 5 to Cu2+ resulted in a much less efficient reduction to Cu+ as evident by both UV-Vis and 1H NMR studies (Fig. 3b and S24). X-ray diffraction study of the crystalline product obtained from a 2:1 mixture of 5 and CuCl2 showed only the coordinated [Cu(5)Cl2] with a distorted square pyramidal structure (Fig 4b). The formation of such 1:1 complex suggests that Cu2+-phenanthroline coordination alone is not sufficient to explain the observed amplification of the [2]catenane in the DCL because the required preorganized ML2 complex could not be formed. Together with the UV-Vis and NMR data, it is believed that the reduction of Cu2+ to Cu+, and the subsequent formation of the tetrahedral ML2 complex constitute the main part of the observed template effect.
1.955(2), Cu1–N2 2.135(2), Cu1–O1 2.256(2); N1–Cu1–N2 74.1(3), O1–Cu1–Cl1 105.8(1).

**Acknowledgements**

Financial supports from the URC, The University of Hong Kong under the Seed Funding programme for Basic Research (project code 201310159019) and the Croucher Foundation are gratefully acknowledged. We thank Dr. Lap Szeto and Mr. Kai Wang for technical assistance on X-ray crystallography and ESI-MS analysis, respectively. KLT and CCY also thank The University of Hong Kong for the provision of Postgraduate Scholarship. YCT is a recipient of the Summer Research Fellowship administered by the Faculty of Science, The University of Hong Kong.

**Notes and references**


11 Attempt to reverse the library composition from the catenane to the macrocycle by removal of the Cu⁺ template was not tested because of the incompatibility of common demetallating reagents such as CN⁻ with the acidic DCL condition.


