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An ethylene cross-bridged pentaazamacrocycle and its Cu^{2+} complex: constrained ligand topology and excellent kinetic stability

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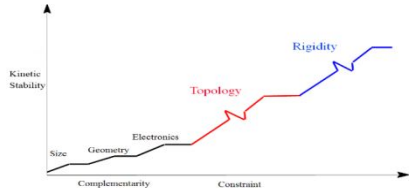
Rigid and topologically constrained ethylene cross-bridged tetraaazamacrocycles have been increasingly utilised for thirty years as they form remarkably stable transition metal complexes for catalysis, biomedical imaging, and inorganic drug molecule applications. Extending these benefits to pentaazamacrocycles has been achieved and a first transition metal complex prepared and structurally characterized.

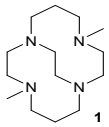
Coordination chemists can maximise binding affinity in their metal-ligand complexes by first optimising the first-order *complementarity* factors (**Fig. 1**) that match ligand and metal ion properties: size, geometric preference, and electronic properties.[1] Ni(cyclam)$^{2+}$ exemplifies these factors[2] as the ionic radius of Ni^{2+} fits nearly perfectly into the cyclam cavity; the square planar preference of d^8 Ni^{2+} coincides with the



arrangement of the cyclam's nitrogen donors; and the borderline hard/soft characteristics of the metal and ligand lead to favourable bonding. Yet the stability of this complex

Fig. 1. Graphical representation of the factors that can be optimized to produce increasing metal-ligand kinetic stability.

Fig. 2. Ethylene cross-bridged cyclam (**1**) and cyclen (**2**).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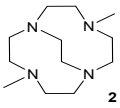
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can be overcome to release the metal ion, as exemplified by the cyanide removal of Ni^{2+} in the classical synthesis of the free cyclam.[2]

Additional complex stability must utilise factors beyond complementarity, such as ligand/complex rigidity and increasing ligand topological complexity. These factors can be grouped into a *constraint* category[1] that unlike complementarity factors do not, or at least as of yet have not, been ultimately exploited. Ethylene cross-bridged tetraazamacrocycles[3, 4] represent a successful effort at pushing those boundaries forward, as the short ethylene cross-bridge rigidifies the macrocycle, particularly upon metal ion binding, as well as giving the ligand the topological properties of the classical cryptands (**Fig. 2**). Numerous studies[5, 6] have demonstrated that the first-row transition metal complexes of these ethylene cross-bridged tetraazamacrocycles are among the most kinetically stable towards harsh acidic/basic conditions of known synthetic transition metal complexes. Yet, their tetradentate nature ensures labile coordination sites that allow reactivity and/or binding ability that has made these complexes favoured for catalytic,[7-21] biomedical imaging,[22-30] and inorganic drug compound[31-35] applications.

The ethylene cross-bridged tetraazamacrocycles introduced in the 1990's have become increasingly popular choices for applications requiring harsh aqueous conditions (365 references identified by SciFinder for an ethylene cross-bridged cyclam substructure (**1**); 684 references identified by SciFinder for an ethylene cross-bridged cyclen substructure (**2**)). We have added a new class of similarly topologically constrained azamacrocycle, the ethylene cross-bridged pentaazamacrocycle, to the toolbox for chemists in need of

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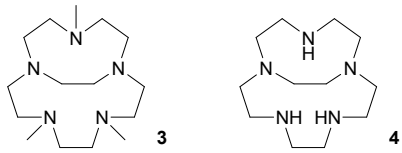
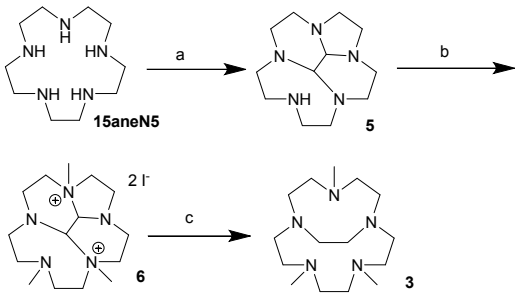


Fig. 3. Me_3-CB-15aneN5 (**3**) and H_3-CB-15aneN5 (**4**).

constructing stable transition metal complexes to survive under harsh conditions. It is our belief that the ethylene cross-bridged pentaazamacrocycles, as exemplified by the novel synthesis and initial structural characterization of (**3**), as well as structural and stability characterization of a first transition metal complex presented here ($Cu(\mathbf{3})^{2+}$), will have a similarly impactful future.

As pioneering practitioners of cross-bridged tetraazamacrocyclic chemistry, we have seen their increased use and sophistication, which has led us to consider additional opportunities to influence the field. It occurred to us that analogous ethylene cross-bridged pentaazamacrocycles - with an additional nitrogen donor, one open coordination site, and potentially similar stability properties - may provide a foundation for the development of a new generation of cross-bridged azamacrocycle coordination chemistry (**Fig. 3**). Whereas cross-bridge cyclen (**2**) may be thought of as two fused TACN's, Me_3-CB-15aneN5 (**3**) is a TACN fused with a cyclen. Simple methylation of the unbridged nitrogen atoms was our target, as the all-tertiary nitrogen ligands **1** and **2** are more stable than cross-bridged tetraazamacrocycles with secondary amines[18, 21] that are vulnerable to oxidation which provides a pathway for complex decomposition.[36] We also did not want additional donor-containing pendant arms as we targeted an open coordination site for potential binding of substrate or oxidants for catalysis.

Initial literature searching found no match for target **3**. However, the tris secondary amine analogue, H_3-CB-15aneN5 (**4**) and various tris oxygen-donor pendant armed derivatives designed for biological imaging, have appeared in the patent literature.[37-42] Due to the complexity and lack of details in the patent multistep synthetic routes and familiarity with the short and efficient glyoxal condensation route to ethylene cross-bridged tetraazamacrocycles,[3, 21, 43] we hypothesized that a



similar glyoxal condensation route to ethylene cross-bridged

Fig. 4. Synthetic route to Me_3-CB-15aneN5 (3): a) 1 eq 40% aq glyoxal, MeOH, 16h, RT, 85% yield; b) i. 10 eq MeI, MeCN, 5d, RT; ii. Evaporate to solid, wash with DCM, not isolated—contains isomers; c) i. 20 eq $NaBH_4$, 95% EtOH, 5d, RT, N_2; ii. 6M HCl, evaporate, 30% aq KOH, $CHCl_3$ extraction, 32% yield. Full experimental details and characterization data in ESI.

Fig. 5. Structural isomers possible for glyoxal condensation with 15aneN5.

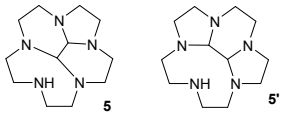
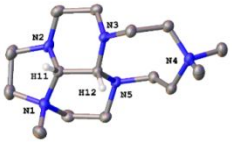


Fig. 6. X-ray crystal structure of a byproduct **6'**, a methylation isomer of **6** demonstrating the connectivity of glyoxal condensate **5**. Selected protons **H11** and **H12** shown.

pentaazamacrocycles, similar to **1** and **2**, might be possible. Although less efficient than for tetraazamacrocycles due to complications from the fifth amine, this route was indeed successful (**Fig. 4**). Further, benzylation of **5** has allowed the independent synthesis, upon debenzylation of the benzylated



analogue of **3**, to yield **4** by our new glyoxal route. Production of this tris secondary amine will allow the addition of a variety of pendant arms to allow the same kind of spread of this ligand into other areas of chemistry. This work will be published later.

The synthesis of **3** may be best thought of as a "one-pot" approach. Multiple isomers of **5**, **6**, and **3** are likely present after each step. Yet, it appears either the multiple isomers converge to **3**, or those that don't can be removed upon extraction of **3** into a nonpolar organic solvent, while any quaternized amine products remain in the aqueous layer. Although the full set of isomers at each step have not been fully characterized, the un-optimized "one-pot" approach yields **3** in high purity.

15aneN5 was synthesized by a modified literature method.[44] Two potential structural isomers were envisioned for the initial condensation of glyoxal with 15aneN5 (**Fig. 5.**). Based on the analogous tetraazamacrocyclic chemistry where 6-membered rings are favoured, it was hypothesised that **5** (internal rings: 6,5,6,8), would be thermodynamically favoured over **5'** (internal rings: 5,6,5,9). Although only one major MS^+ peak at m/z = 238 (LH^+) was observed, the ^1H and ^{13}C NMR spectra (see ESI) gave evidence of more than a single isomer being present. For example, sixteen ^{13}C signals were reproducibly observed even though the compound has only twelve carbon atoms. It is hypothesised that both **5** and **5'** are present (this would help explain four different ^{13}C resonances between 78-86 ppm) and that additional *cis*/*trans* isomers (with respect to the two methyne protons of the two-carbon bridge) may also exist in the mixture. However, the synthetic route in **Fig. 4** might reasonably be expected to succeed even with such a mixture of isomers, so no purification was attempted prior to continued reaction.

Many attempts were made to structurally characterize **5** without success. However, a byproduct of the methylation step (discussed below) to prepare **6** fortuitously crystallized and demonstrated the predicted glyoxal condensate

connectivity (**Fig. 6**). This structure has two quaternary nitrogens: **N4** is dimethylated and **N1** is monomethylated. **Fig. 6** also shows **H11** and **H12** in a cis relationship, a key to the cross-bridging synthesis of **1** and **2** (Fig. 1).[3, 21, 43]

As expected if a mixture of isomers of **5** is used as the starting material, and as demonstrated in **Fig. 6**, the methylation of **5** shown in **Fig. 4** does not proceed to only one product. Again based on experience with tetraazamacrocyclic systems, methylation was expected to proceed first with the secondary amine of **5** or **5'**, then at two non-adjacent tertiary nitrogens. The mixture of solid quaternary nitrogen salts (at least **6** and **6'**) was not purified as it was deemed simpler to purify the reduced neutral compound **3**. The crystallized

Fig. 7. X-ray crystal structure of a $\mathbf{H_3 3^{3+}}$.

byproduct **6'** notwithstanding, it appears that the predicted methylation product **6** is the major product, as **3** is realized as the major product of the reductive ring cleavage final step. Separation of the neutral **3** from the reduced product of **6'**, which would maintain at least one quaternary nitrogen (**N5**) and a positive charge, occurred during the extraction into chloroform from a highly basic aqueous phase.

An X-ray crystal structure of **3** was obtained and is shown in **Fig. 7**. In this figure, the fused nature of the TACN moiety on the left with the cyclen moiety on the right is evident. This structure contains a triprotonated trication of **3**, $\mathbf{H_3 3^{3+}}$, with one bridgehead nitrogen, **N5**, and two methylated nitrogens, **N2** and **N4** protonated. The protons all lie within the 3-dimensional

cavity of the ligand, which is a familiar arrangement for protonated cross-bridged tetraazamacrocycles as well. This cavity is thus primed for transition metal complexation.

Complexation of **3** with Cu^{2+} utilized rigorously dry MeOH, under an inert atmosphere to prevent ligand protonation. To demonstrate the coordination properties of the ligand, the synthetic details of the Cu^{2+} complex are included in the ESI, and an X-ray crystal structure of this complex, $Cu(\mathbf{3})^{2+}$ is pictured in **Fig. 8**. The Cu^{2+} ion is engulfed in the cavity that was occupied by three protons in $\mathbf{H_3 3^{3+}}$. It is bound to all five nitrogens of **3** in a distorted square pyramidal structure with

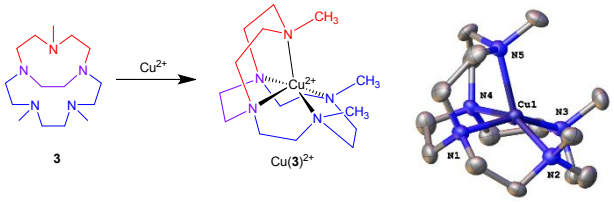


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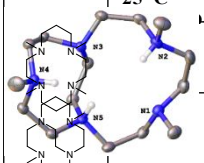
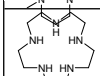
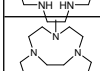
Fig. 8. Complexation scheme (TACN atoms are red, cyclen atoms are blue and atoms belonging to both rings are purple.) and X-ray crystal structure of $Cu(\mathbf{3})^{2+}$ illustrating the fused TACN (N1-N4-N5) and cyclen (N1-N2-N3-N4) moieties. §

four nitrogens of the cyclen moiety serving as the base of the pyramid and the remaining non-bridgehead nitrogen belonging to the TACN moiety serving as the apex of the pyramid. The τ_5 parameter quantifying the geometry of 5-coordinate transition metal complexes[45] is τ_5 = 0.03, in agreement with the assignment of a square pyramidal coordination geometry. Typical Jahn-Teller distortion for d^9 Cu^{2+} is observed with the square base Cu1-N bond distances averaging 2.031 Å and the Cu1-N5 apical bond length of 2.168(6) Å.

Table 1. Half-lives of selected copper(II)

	25 °C	50 °C 5M HCl	ref
		------	46
		7.3 days	18
	------	< 2 minutes	This work
	------	5.3 days	This work

Finally, a key property of ethylene cross-bridged tetraazamacrocycles resulting from their rigidity and topological constraint (*vide supra*) is the kinetic stability of their transition metal complexes under harsh conditions that would normally destroy complexes very quickly. This property has lately been systematically quantified using the half-life of the complex in 5 M HCl at various temperatures.[18, 21, 27] For example, $Cu(\mathbf{1})^{2+}$ in 5 M HCl at 50 °C has a half-life of 7.3 d, while the unbridged $Cu(tmc)^{2+}$ (tmc = tetramethylcyclam) in 1 M HNO_3 at 25°C has a half-life of only 2.0 s (see **Table 1**). We have determined the half-life of $Cu(\mathbf{15aneN5})^{2+}$ in 5 M HCl at 50°C as less than 2 minutes. Adding the ethylene cross-bridge dramatically increases the half-life of $Cu(\mathbf{3})^{2+}$ under the same conditions to 5.3 d, a value very similar to that of $Cu(\mathbf{1})^{2+}$. These results indicate that complexes of **3** should survive harsh conditions present in many catalytic and biomedical applications.

Preliminary complexation studies of **3** with a range of other transition metal ions (Cr^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}) has been successful, utilizing dry aprotic solvents, such as MeCN and DMF, under inert atmosphere to prevent ligand protonation. Understanding the syntheses and properties of these complexes is ongoing.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

§ Selected Bond Lengths (Å) and Angles (°):

Cu(1)-N(1) 2.013(6); Cu(1)-N(2) 2.035(6); Cu(1)-N(3) 2.034(6); Cu(1)-N(4) 2.042(6); Cu(1)-N(5) 2.162(6); N(1)-Cu(1)-N(3) 152.3(2); N(1)-Cu(1)-N(2) 86.3(2); N(2)-Cu(1)-N(4) 154.1(2); N(2)-Cu(1)-N(5) 119.2(2); N(3)-Cu(1)-N(2) 87.9(2); N(1)-Cu(1)-N(4) 86.2(3); N(3)-Cu(1)-N(4) 87.3(3); N(1)-Cu(1)-N(5) 84.7(2); N(3)-Cu(1)-N(5) 121.5(2); N(4)-Cu(1)-N(5) 84.7(2)

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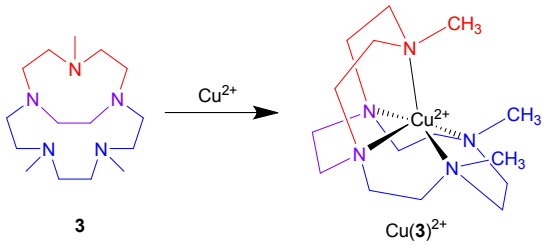
Table of Contents Entry



3 $Cu(\mathbf{3})^{2+}$

Extending the benefits of ethylene cross-bridging to pentaazamacrocycles has been achieved and a transition metal complex prepared and structurally characterized.