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High-yield synthesis of potentially ditopic coordinating cryptands and their metal complexes

Laura Chaloner^a, Xavier Ottenwaelder^{a,*}

^a Department of Chemistry and Biochemistry, Concordia University, 7141 Sherbrooke Street West, Montreal, Canada H4B 1R6

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ABSTRACT

Cryptands containing a tetradentate tris(aminoethyl)amine moiety have been prepared in high-yield via copper-catalyzed alkyne–azide cycloaddition followed by a templated 3+3 condensation. Silver and zinc complexes of the cryptands are reported. Weak interactions between a chloride anion and the cryptand suggest possible ditopic coordination.

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Propelled by the importance of anions in environmental and biomedical processes,^{1,2} anion recognition is now an important branch of supramolecular chemistry.^{3,4} In order to efficiently and selectively bind anions, ligands incorporate functionalities such as hydrogen bond donors,^{5,6} metal coordination sites,⁷ π -systems,^{8–10} or combinations thereof.^{11–13} Furthermore, anion encapsulation is particularly selective with cryptands due to the geometric constraints imparted by their rigidity. Presented here are the high-yielding syntheses of novel cryptands with two different binding sites, one hard polyamine site and one soft tris(triazole) site. As described recently,^{14–17} the polarized C–H bonds of the triazoles are conducive to bind anions and thus impart the cryptands with attributes to serve as a heteroditopic ligand for anion recognition.

The macrobicyclic scaffold was prepared in two steps from 3-(2-propyn-1-yloxy)benzaldehyde, **1**, and tris(2-azidoethyl)amine, **2** (**CAUTION**),¹⁸ which syntheses were reported previously (Scheme 1).^{19,20} The end caps of the cryptands were constructed successively, first by copper-catalyzed azide-alkyne cycloaddition (CuAAC) to yield 93% of **3**, then by a [3+3] reversible condensation with tris(2-aminoethyl)amine (tren) to yield triimine cryptand **4**. Though **4** can be isolated, a same-pot borohydride reduction was preferred as it yielded larger quantities of cryptand **5**. The amine groups of **5** can be easily functionalized, as demonstrated by a methylation to yield cryptand **6**. The ¹H NMR of cryptands **4**, **5**, and **6** in CDCl₃ indicate C_3 symmetry in solution. Complete assignment of ¹H chemical shifts, was realized via COSY and NOESY experiments (see Supplementary information).

The [3+3] condensation was implemented under both template and semi-dilute conditions. Templating with lanthanum(III) nitrate proved to be an efficient procedure, with a 72% yield for the onepot, two-step $3 \rightarrow 5$ sequence, compared with 30% under nontemplated conditions. Different metal ions were tested as templating agents. Cobalt(II) chloride, zinc(II) chloride, and silver(I) nitrate were chosen as they form complexes with 5 (see below), but lanthanum(III) nitrate was by far the best templating agent. With zinc and silver, yields of 30% were obtained, likely due to the difficulty in purifying 5. Cobalt(II) chloride had a negative effect on the reaction by inhibiting the formation of the cryptand completely. No complexes were observed between lanthanum nitrate and 3, 4, or 5 by ESI-MS in 1:1 methanol/dichloromethane, consistent with a kinetic templating effect. The lanthanum ion likely coordinates to tren, as previously reported,^{21,22} and this complex is poised to react with trialdehyde 3. Once the cryptand is formed, the oxophilic lanthanum(III) ion is easily removed during work-up with the oxygen-rich EDTA ligand. In contrast, removal of cobalt, zinc, and silver ions from the formed cryptand proved difficult as these ions form stable complexes in the nitrogen-rich environment of 5.

X-ray diffraction analysis of single crystals of $\mathbf{6}$ -Et₂O indicate that methylated cryptand $\mathbf{6}$ adopts an endo-endo conformation (Fig. 1), as is customary with cryptands bearing tren moieties.²³ The molecular structure of $\mathbf{6}$ has a C₁ symmetry due to the *anti*

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^{*} Corresponding author. Tel.: +1 514 848 2424x8934; fax: +1 514 848 2424x2868.

E-mail address: dr.x@concordia.ca (X. Ottenwaelder).



Scheme 1. Synthesis of cryptands **4–6**. Conditions: (i) CuSO₄, NaAsc, *t*-BuOH:H₂O 1:1, 24 h, 93%; (ii) tren, La(NO₃)₃, MeOH:THF 10:1, 48 h, 48%; (iii) NaBH₄, MeOH:THF 10:1, 3 h, 72% over 2 steps; (iv) CH₂O, HCO₂H, 24 h reflux, 80%.



Figure 1. ORTEP representation at 50% thermal ellipsoid probability of **6**-Et₂O. The co-crystallized diethyl ether and hydrogen atoms (except H28A) were omitted for clarity.

conformation of the N1–C31–C32–N10 linkage while the other two tren nitrogens (N2 and N6) adopt a *syn* conformation in relation to N1 through their respective ethylene links. The only significant intramolecular contact within the cryptand is a C–H··· π interaction between two triazole units (H28A···C12 = 2.684 and H28A···C13 = 2,792 Å, van der Waals radii: C, 1.70; H, 1.20 Å).

The coordination ability of cryptands **5** and **6** resides principally in the multi-chelating tren moiety, as illustrated here with monomeric silver(I) and zinc(II) complexes of **5**. Attempts to isolate dinuclear complexes involving coordination to the triazole moieties^{24,25} have yet to be successful. Addition of silver(I) nitrate to a hot solution of **5** in methanol led to a crystalline precipitate after cooling. The structure of this complex, [**5**Ag](NO₃)·CH₃OH, was solved by X-ray diffraction (Fig. 2). The inner-sphere complex, [**5**Ag]⁺, has a pseudo-C₃ symmetry. The Ag atom is coordinated to the tren moiety, despite the potential to coordinate with the triazole groups, as shown in the literature.^{26–28} Two of the triazoles are facing each other, and a weak C-H··· π interaction exists



Figure 2. ORTEP representations at 50% thermal ellipsoid probability of: (a) the cationic part of [**5**Ag](NO₃)·CH₃OH, and (b) [**5**ZnCl](Cl). The hydrogen atoms were omitted for clarity. Selected bond lengths (Å) and angles (°) for [**5**Ag](NO₃)·CH₃OH: Ag1-N1 = 2.506(5), Ag1-N2 = 2.398(5), Ag1-N3 = 2.385(4), Ag1-N4 = 2.370(5), N1-Ag1-N2 = 74.85(15), N1-Ag1-N3 = 74.99(15), N1-Ag1-N2 = 75.29(15); for [**5**ZnCl](Cl): Zn1-N1 = 2.245(5), Zn1-N2 = 2.104(4), Zn1-N7 = 2.160(5), Zn1-N1 1 = 2.110(4), Zn1-Cl = 2.2861(14).

between two triazole units, thus competing with coordination at this site. The Ag atom sits in a distorted trigonal–pyramidal environment composed of the nitrogen atoms of three tren moiety, with the Ag sitting below the equatorial plane. The out-of-plane effect is commonly found in silver complexes with tren.^{29–36}

The ditopic nature of cryptand **5** is revealed upon solid-state characterization of its zinc(II) chloride complex. A mononuclear complex of formula [**5**ZnCl](Cl)·H₂O was obtained by mixing **5** with zinc(II) chloride in hot methanol and letting the solution cool down. Formation of the complex was confirmed in solution with ESI-MS, the major peaks corresponding to the isotopic pattern of [**5**ZnCl]⁺. Single crystals amenable to X-ray diffraction analysis were grown by slow diffusion of diethyl ether into a methanol solution of the compound. The complex crystallizes as [**5**ZnCl](Cl) in the chiral P2₁ space group (Fig. 2).³⁷ The cryptand adopts an endo–endo conformation and has an overall C₁ symmetry. Akin to free ligand **6** and silver complex [**5**Ag]⁺, this structure reveals a weak C–H··· π interaction between two triazole units (H40A on Fig. 3). The Zn atom adopts a trigonal–bipyramidal coordination geometry within the tren moiety with the chloride (Cl1)



Figure 3. Zoom of the ORTEP representation (50% thermal ellipsoid probability) of [**5**ZnCl](Cl). The hydrogen atoms were omitted for clarity except those involved in weak contacts. Selected distances (Å): Cl2…H12A = 2.601, Cl2…H26A = 2.657, Cl2…H13A = 2.728, Cl2…H28A = 2.893, H40A…N3 = 2.614, H40A…N4 = 2.774.



Figure 4. ¹H NMR titration of [5ZnCl](Cl) with AgTfO in acetonitrile-d₃ at 60 °C. Aliquots of a 125 mM solution of AgTfO were added to a 41.6 mM solution of [5ZnCl](Cl).

and central nitrogen (N1) atoms in the axial positions and the remaining nitrogens in the equatorial positions. The second chloride ion, Cl2, interacts with the hydrogens of two NH groups from the tren moiety of a neighboring molecule $(Cl_2 + H_2C^i - N_2^i) = 2.324$, $Cl_{2} \cdots H7B^{i} - N7^{i} = 2.356 \text{ Å}; i = 1 - x, 0.5 + y, 1 - z; vdW radii: H,$ 1.20: Cl. 1.75 Å) and is involved in four contacts with the cryptand itself (Fig. 3). Two of these contacts are with H–C(triazole) groups $(Cl_2 \cdots H12A = 2.601, Cl_2 \cdots H26A = 2.658 \text{ Å})$, likely the result of the triazole rings being electron-deficient.¹⁵ The two other H. Cl2 contacts are with CH₂ groups, one adjacent to a triazole (Cl2···H13A = 2.728 Å) and the other adjacent to the tertiary nitrogen N6 (Cl2···H28A = 2.893 Å). This set of weak yet multiple interactions is responsible for the cryptand to splay open to accommodate Cl2. This demonstrates a possible role of the triazole part of the cryptand to act as a secondary binding site and suggests that, with a proper substrate, cryptand **5** will act as a ditopic ligand.

To test this hypothesis, we carried out solution studies of chloride binding followed by ¹H NMR. To a solution of [5ZnCl](Cl) H₂O in acetonitrile-d₃ was added increasing amounts of silver triflate (AgTfO) dissolved in acetonitrile-d₃ (0-2.5 equiv per Zn). After addition of each aliquot, AgCl precipitated and the NMR spectral evolution was recorded (Fig. 4 and Supplementary Fig. S15).³⁸ This experiment highlighted two types of protons that are the most susceptible to the abstraction of chloride ions: C (triazole C-H bond) and H (on the benzene ring). Addition of the first equivalent of AgTfO affects the triazole protons C more than any other, while benzene protons H are more sensitive to the second equivalent of AgTfO. Notwithstanding conformational reorganization, this behavior is consistent with a weak $Cl \cdots H_{triazole}$ interaction that is disrupted first, while the second abstraction requires chloride decoordination from Zn^{2+} . In addition, the fact that protons H are sensitive to the chloride abstraction and not the other protons on the benzene ring suggests that protons H are oriented toward the inside of the cryptand where the chloride abstractions occur.

In conclusion, we have synthesized novel cryptands in high yields by choosing reactions such as CuAAC and taking advantage of the templating capability of the lanthanum(III) ion. Cryptand **5** has demonstrated its ability to coordinate transition metals such as silver, zinc and cobalt. Weak interactions in the zinc complex suggest that the cryptand can be used for ditopic binding through the coordinating tren moiety (for a metal ion) and the triazole functions (for an anion or substrate). Current investigations into the binucleating and docking properties of the cryptands are underway.

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Supplementary data

Supplementary data (¹H and ¹³C NMR spectral assignments, elemental analyses and X-ray crystallography data) associated with this article can be found, in the online version, at http:// dx.doi.org/10.1016/j.tetlet.2013.04.074. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

- 1. Mateus, P.; Lima, L. M. P.; Delgado, R. Polyhedron 2013, 52, 25-42.
- Bianchi, A.; Bowman-James, K.; García-España, E. In Anion Coordination Chemistry; Wiley-VCH, 2011; pp 1–73.
- 3. Gale, P. A.; Gunnlaugsson, T. Chem. Soc. Rev. 2010, 39, 3595–3596.
- 4. Wenzel, M.; Hiscock, J. R.; Gale, P. A. Chem. Soc. Rev. 2012, 41, 480–520.
- Pramanik, A.; Powell, D. R.; Wong, B. M.; Hossain, M. A. Inorg. Chem. 2012, 51, 4274–4284.
- Lopez, N.; Graham, D. J.; McGuire, R.; Alliger, G. E.; Shao-Horn, Y.; Cummins, C. C.; Nocera, D. G. Science 2012, 335, 450–453.
- 7. Fabbrizzi, L.; Poggi, A. Chem. Soc. Rev. 2013, 42, 1681-1699.
- Brooker, S.; White, N. G.; Bauza, A.; Deya, P. M.; Frontera, A. Inorg. Chem. 2012, 51, 10334–10340.
- 9. Bauza, A.; Quinonero, D.; Deya, P. M.; Frontera, A. *Theor. Chem. Acc.* **2012**, *131*, 1–11.
- 10. Berryman, O. B.; Johnson, D. W. Chem. Commun. 2009, 3143-3153.
- 11. Mercer, D. J.; Loeb, S. J. Chem. Soc. Rev. 2010, 39, 3612–3620.
- 12. Perez, J.; Riera, L. Chem. Soc. Rev. 2008, 37, 2658-2667.
- 13. Mateus, P.; Delgado, R.; Brandão, P.; Félix, V. Chem. Eur. J. 2011, 17, 7020–7031.
- McDonald, K. P.; Hua, Y.; Lee, S.; Flood, A. H. Chem. Commun. 2012, 48, 5065– 5075.
- 15. Hua, Y.; Flood, A. H. Chem. Soc. Rev. 2010, 39, 1262-1271.
- Juwarker, H.; Lenhardt, J. M.; Pham, D. M.; Craig, S. L. Angew. Chem., Int. Ed. 2008, 47, 3740–3743.
- 17. Juwarker, H.; Lenhardt, J. M.; Castillo, J. C.; Zhao, E.; Krishnamurthy, S.;
- Jamiolkowski, R. M.; Kim, K.-H.; Craig, S. L. J. Org. Chem. **2009**, 74, 8924–8934. 18. Tris(2-azidoethyl)amine is explosive and should be treated with caution.
- Banert, K.; Wutke, J.; Rüffer, T.; Lang, H. Synthesis **2008**, 2008, 2603–2609.
- 20. Hans, R. H.; Guantai, E. M.; Lategan, C.; Smith, P. J.; Wan, B.; Franzblau, S. G.;
- Gut, J.; Rosenthal, P. J.; Chibale, K. Bioorg. Med. Chem. Lett. 2010, 20, 942–944.
 Forsberg, J. H.; Kubik, T. M.; Moeller, T.; Gucwa, K. Inorg. Chem. 1971, 10, 2656–
- 2660.
- 22. Johnson, M. F.; Forsberg, J. H. Inorg. Chem. **1976**, 15, 734–737.
- Chand, D. K.; Bharadwaj, P. K. Inorg. Chem. 1996, 35, 3380–3387.
 Struthers, H.; Mindt, T. L.; Schibli, R. Dalton Trans. 2010, 39, 675–696.
- Struthers, H.; Mindt, T. L.; Schibli, R. Dalton Trans. 2010, 39, 675–696.
 Crowley, J.; McMorran, D. In *Click Triazoles*; Košmrlj, J., Ed.; ; Springer: Berlin Heidelberg, 2012; Vol. 28, pp 31–83.
- 26. Crowley, J. D.; Bandeen, P. H. Dalton Trans. 2010, 39, 612-623.
- 27. Gower, M. L.; Crowley, J. D. Dalton Trans. 2010, 39, 2371-2378.
- 28. Fleischel, O.; Wu, N.; Petitjean, A. Chem. Commun. 2010, 46, 8454-8456.
- de Mendoza, J.; Mesa, E.; Rodríguez-Ubis, J.-C.; Vázquez, P.; Vögtle, F.; Windscheif, P.-M.; Rissanen, K.; Lehn, J.-M.; Lilienbaum, D.; Ziessel, R. Angew. Chem., Int. Ed. 1991, 30, 1331–1333.
- Wenzel, M.; Wichmann, K.; Gloe, K.; Gloe, K.; Buschmann, H.-J.; Otho, K.; Schroder, M.; Blake, A. J.; Wilson, C.; Mills, A. M.; Lindoy, L. F.; Plieger, P. G. *Cryst. Eng. Commun.* **2010**, *12*, 4176–4183.
- 31. Ray, D.; Bharadwaj, P. K. Eur. J. Inorg. Chem. 2006, 1771-1776.
- Adams, H.; Elsegood, M. R. J.; Fenton, D. E.; Heath, S. L.; Ryan, S. J. Inorg. Chem. 1999, 2, 139–142.
- Drew, M. G. B.; Harding, C. J.; Howarth, O. W.; Lu, Q.; Marrs, D. J.; Morgan, G. G.; McKee, V.; Nelson, J. *Dalton Trans.* **1996**, 3021–3030.
- Howarth, W. O.; Morgan, G.; McKee, V.; Nelson, J. Dalton Trans. 1999, 2097– 2102.
- Abidi, R.; Arnaud-Neu, F.; Drew, M. G. B.; Lahely, S.; Marrs, D.; Nelson, J.; Schwing-Weill, M.-J. *J.Chem. Soc., Perkin Trans.* 2 1996, 2747–2755.
- 36. Ma, Z.; Cao, R. J. Mol. Struct. 2005, 738, 137-142.
- The cobalt(II) chloride complex of 5 is isostructural to the zinc(II) chloride complex.
- ESI-MS measurements carried out after titration indicated zinc complexes exclusively: there was no evidence of Ag(I) coordinating to the triazole moeities nor substituting for the Zn(II) ion.