Organic LETTERS

Letter

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# Synthesis and Structural Characterization of a Cyclen-Derived Molecular Cage

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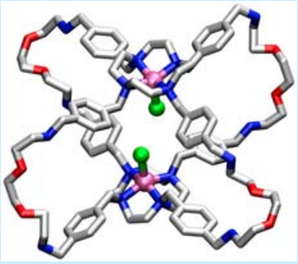
S *Supporting Information*

**ABSTRACT:** Reaction of a tetrafunctionalized cyclen derivative containing four aldehyde groups with an appropriate diamine followed by reduction and demetalation highly efficiently affords a bis(cyclen)-derived molecular cage. Potentiometric investigations show that this compound forms dimetallic complexes with copper(II), with the two metal ions selectively coordinated to the cyclen units. X-ray crystallography indicates that these complexes could give rise to new cascade complexes after incorporation of anions between the metal centers.



Cascade complexes are one of the oldest types of host−guest systems in supramolecular chemistry.[1,2] They typically comprise a macrocyclic or macrobicyclic ligand with two or more endocyclic coordination sites for transition metal ions and an anionic guest sandwiched between these metal centers. An example is the azacryptand-based complex shown in Figure 1, in which two tris(2-aminoethyl)amine (tren) units serve for metal coordination. The term *cascade* refers to the mechanism with which these complexes are formed, involving sequential binding of the individual guest ions.[2a] Binding selectivity can be controlled by varying the metals, $Cu^{2+}$, $Co^{2+}$, $Ni^{2+}$, and $Zn^{2+}$ being the ones most frequently used, and the structure of the linkers between the coordination sites. Accordingly, cascade complexes ranging from ones containing small inorganic anions to nucleotides have been described.[2] In addition, supramolecular probes for anions involving cascade complexes with indicators as reporter units are also known.[3]

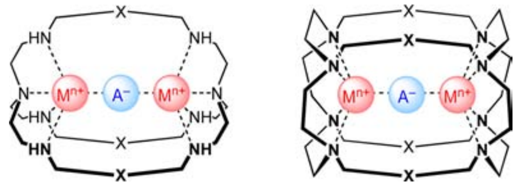


**Figure 1.** Schematic representation of cascade complexes derived from tren-based ligands (left) and from cyclen (right).

Despite the interest in cage-type cascade complexes, which often exhibit high binding selectivity,[2] the underlying design principle has been transferred to few other types of receptor systems. Notable ones are dimetallic bis(porphyrin) cages comprising two porphyrin−metal complexes connected intermolecularly via four bridging units.[4] Similarly to tren-based systems, these cages bind Lewis bases between the metal centers.

A ligand widely used in coordination chemistry that has not received much attention in the development of cage-type receptors is cyclen (1,4,7,10-tetraazacyclododecan).[5,6] Cyclen highly efficiently binds to transition metal ions forming complexes in which the four nitrogen atoms within the ring serve as donor atoms.[6] In the complexes with, for example, $Zn^{2+}$ and $Cu^{2+}$ a fifth coordination site remains vacant on the metal and is available for interaction with Lewis bases. Based on this motif, numerous cyclen-based receptors have been developed, many for the recognition of phosphates including nucleotides.[7]

Some of these receptors contain two or more cyclen units connected covalently by a single common bridging unit.[8] Bis(cyclens) have also been described having two linkers that bridge either opposite or adjacent cyclen nitrogen atoms,[9] but cyclen-based cages containing four linkers have, to the best of our knowledge, not been described so far. We wondered whether such cages, a schematic representation of which is shown in Figure 1, would give access to a new type of cascade complex with properties characteristically differing from the ones of tren-based systems because of the different coordination geometry at the metal centers, the different

**Received:** October 19, 2015
**Published:** November 17, 2015

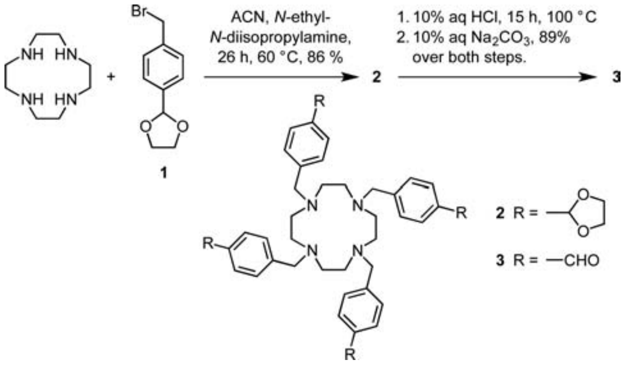
DOI: 10.1021/acs.orglett.5b03027
*Org. Lett.* 2015, 17, 5850−5853

overall symmetry, and the screening of the binding site by four linkers. Here, we report on the successful synthesis of the first cyclen-derived cage and its structural characterization.

An efficient strategy to synthesize the azacryptands underlying tren-based cascade complexes, particularly the ones containing aromatic units in the linkers, involves treatment of tren with an appropriate dialdehyde.[2d] Product formation involves initial formation of a hexaimine, which is subsequently reduced to the corresponding hexaamine. This reaction benefits from the reversibility of imine formation[10] and often from the insolubility of the intermediate hexaimines, which selectively precipitate from the reaction mixtures. Other cage-type receptors have been prepared along similar routes, sometimes by making use of template effects to induce product formation. The bis(porphyrin) cage obtained by treating a zinc-porphyrin tetraaldehyde with 1,2-diaminoethane in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) is an example.[4c] Because of its versatility, allowing facile structural variation of the reaction partners, we used the same approach for the preparation of the targeted bis(cyclen) cages.

A cyclen derivative was therefore required containing either four amino or four aldehyde groups. Because of the availability of a wide range of diamines differing in the distance of the two amino groups and their overall rigidity, we decided to introduce the aldehyde groups into the cyclen building block. Moreover, we used aromatic aldehydes because of the higher stability of the respective imines. The corresponding tetraaldehyde **3** was synthesized by treating cyclen with 2-(4-(bromomethyl)-phenyl)-1,3-dioxolane **1** followed by cleavage of the acetal groups and neutralization (Scheme 1).

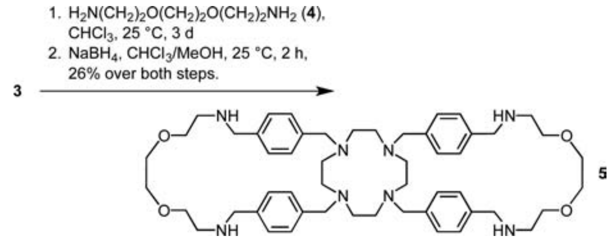
**Scheme 1**



Initial attempts to prepare bis(cyclen) cages involved treatment of **3** with 2 equiv of different diamines varying from aliphatic $\alpha,\omega$-diamines to aromatic diamines. All reactions were performed in $CDCl_3$ on an analytical scale, and their course was followed by $^1H$ NMR spectroscopy. The disappearance of the aldehyde signal and appearance of a signal at ca. 8 ppm in the spectra of the reaction mixtures indicated imine formation. The complexity of the resulting spectra provided information about whether the respective reaction yielded a single symmetrical product or not.

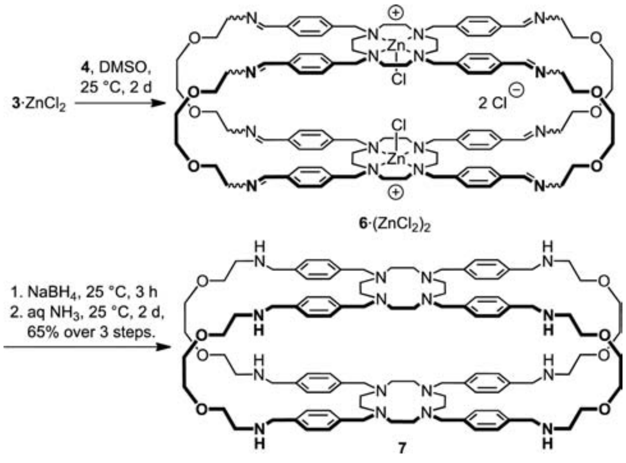
While most reactions ended up in complex product mixtures which were not investigated further, treatment of **3** with 2,2′-(ethane-1,2-diylbis(oxy))diethanamine **4** afforded a single product. Interestingly the same reaction with the analogous all-carbon diamine 1,8-diaminooctane proceeded significantly less cleanly, leading to the formation of a mixture of imines. Mass spectrometry showed that the reaction between **3** and **4** did not yield the desired cage, but instead a tetraimine containing one cyclen ring and two linking units. This result was confirmed by performing the reaction on a preparative scale and isolating the corresponding octaamine **5** after reduction of the imine groups (Scheme 2). Crystallographic characterization of the product clearly demonstrated the bridging of pairs of adjacent cyclen nitrogen atoms (see Figure S2).

**Scheme 2**



Assuming that metal complexes of **3** would be more rigid and better preorganized for cage formation because of an arrangement of the substituents on the same face of the cyclen ring, we next used the zinc complex **3**·$ZnCl_2$, obtained in quantitative yields by treatment of **3** with $ZnCl_2$, for the imine formation. Initial experiments were again performed on an analytical scale by NMR spectroscopy, albeit in DMSO-$d_6$ because of the low solubility of **3**·$ZnCl_2$ in chloroform. Among the various diamines used, two stood out, namely 1,2-diaminoethane and again diamine **4**, both causing clean formation of a single symmetrical product. In the case of **4**, the mass spectrometric analysis of the reaction mixture showed that the product had a composition consistent with the desired cage **6** (Scheme 3). Again, using 1,8-diaminooctane instead of **4** led to the formation of a product mixture. We attribute the different behaviors of **4** and 1,8-diaminooctane to the preferred *gauche*-conformations in the oxygen-containing diamine, which allow this compound to adopt the turn-conformation likely required for product formation. In the case of $\alpha,\omega$-diaminoalkanes, which prefer *anti*-conformations at the C−C bonds, accessing the same conformation would be thermodynamically unfavorable. A similar observation was made by Leigh in the synthesis of a pentafoil knot using a related synthetic approach.[11]

**Scheme 3**



Interestingly, reaction between $3\cdot ZnCl_2$ and 1,2-diaminoethane led to the formation of a tris(cyclen) according to mass spectrometry, in which each cyclen unit is presumably connected to the next one via two linkers. Unfortunately, the extreme low solubility of this compound, either in its metalated or its demetalated form after reduction, has so far prevented us from characterizing it and its properties in more detail. We thus concentrated on the bis(cyclen) $6\cdot(ZnCl_2)_2$ formed from $3\cdot ZnCl_2$ and **4**.

Synthesis of $6\cdot(ZnCl_2)_2$ was repeated on a preparative scale, and the obtained octaimine was immediately reduced in a one-pot reaction by using $NaBH_4$. The obtained material exhibited a complex NMR spectrum, which also showed typical signals of residual borane species (see p S24). Subsequent demetalation furnished the expected product **7**, as also corroborated by X-ray crystallography (see below), whose $^1H$ NMR spectrum is consistent with an averaged $D_{4h}$ symmetrical structure.

Considering that eight bonds are formed and subsequently reduced in the preparation of **7**, the overall isolated yield of 65% is very good. This yield is likely due to not only a good preorganization of $3\cdot ZnCl_2$ for cage formation but also presumably contributions from template effects of the metal ions, which stabilize the intermediate octaimine. Unfortunately, attempts to isolate $6\cdot(ZnCl_2)_2$ were unsuccessful so that no information is currently available about the potential intramolecular interactions that cause stabilization of this product. NMR spectroscopy just provided clear evidence that the tetraimine is also $D_{4h}$ symmetric and that all C=N bonds must therefore have either the *Z* or, more likely, the *E* configuration.

Initial experiments to characterize the properties of **7** involved potentiometric estimation of the basicity constants of the amino groups (Table 1). Out of a total of 16 possible protonation constants, 12 could be determined. The first eight constants are organized in groups of two and can presumably be ascribed to protonation of amino groups in the linkers, while the last four constants likely involve the amino groups in the cyclen units. This interpretation is consistent with the fact that cyclen is typically protonated in two steps (for 1,4,7,10-tetramethylcyclen the protonation constants log $K_1$ and log $K_2$ are 11.07 and 8.95, respectively).[12]

**Table 1. Logarithms of the Stepwise Basicity Constants of 7 Determined in 0.15 M NaCl at 298.1 K**

| reaction[a] | log *K* |
|---|---|
| $7 + 2H \rightleftharpoons H_27$ | 18.98(5)[b] |
| $H_27 + 2H \rightleftharpoons H_47$ | 16.98(2) |
| $H_47 + 2H \rightleftharpoons H_67$ | 15.73(2) |
| $H_67 + 2H \rightleftharpoons H_87$ | 14.65(2) |
| $H_87 + H \rightleftharpoons H_97$ | 6.73(7) |
| $H_97 + H \rightleftharpoons H_{10}7$ | 6.69(7) |
| $H_{10}7 + H \rightleftharpoons H_{11}7$ | 5.72(5) |
| $H_{11}7 + H \rightleftharpoons H_{12}7$ | 5.13(5) |

[a] Charges omitted. [b] Values in parentheses are standard deviations in the last significant figure.

The log *K* values attributed to cyclen protonation of **7** are organized in two groups, the first two with values around 6.7 and the last two with values of ca. 5.5 log units indicating that both cyclen rings are alternately protonated and the amino groups involved are significantly less basic than the ones of cyclen, presumably because of their tertiary nature[13] and the presence of the positive charges in the linkers. The corresponding speciation diagram (Figure S3) shows that at around pH 7 bis(cyclen) **7** is extensively protonated containing 8.2 protons on average.

Potentiometric titrations were also performed in the presence of 1, 2, and 3 equiv of copper(II) perchlorate. Stability constants for the mononuclear and dinuclear $Cu^{2+}$ species could thus be determined (see Table S1). Importantly, none of these potentiometric titrations provided evidence for the presence of species containing more than two copper ions, indicating that copper complexation occurs only in the cyclen units.

To corroborate these results, HR-ESI-MS spectra of aqueous solutions of **7** (pH 9) containing 1, 2, or 3 equiv of copper(II) perchlorate were recorded. The spectrum of the solution containing 1 equiv of $Cu^{2+}$, recorded in the positive mode, showed the existence of the mononuclear species $[Cu(H_27)]^{4+}$ ($m/z$ = 454.5339) and $[Cu(H7)]^{3+}$ ($m/z$ = 605.7092). There was no evidence for the formation of complexes of higher nuclearity. The formation of binuclear complexes was observed in the spectrum of the solution containing 2 equiv of $Cu^{2+}$. Peaks at $m/z$ ratios of 469.7638, 638.0053, 649.9988, and 974.4937 were assigned to the species $[Cu_27]^{4+}$, $[Cu_27Cl]^{3+}$, $[Cu_2(H7)Cl_2]^{3+}$, and $[Cu_27Cl_2]^{2+}$, respectively. Again, no peaks for species of higher nuclearity could be detected. The spectrum of the solution containing 3 equiv of $Cu^{2+}$ does not differ significantly from the previous one.

Crystals of sufficiently high quality for X-ray crystallography were obtained by slow evaporation of an aqueous solution containing **7**, 6 equiv of $Cu(ClO_4)_2\cdot 6H_2O$, and an excess of NaCl at pH ca. 7. The molecular structure of the observed complex with the composition $[Cu_2(H_47)Cl_2]Cl_6\cdot 9H_2O$ is depicted in Figure 2 (see also the structure in the abstract).

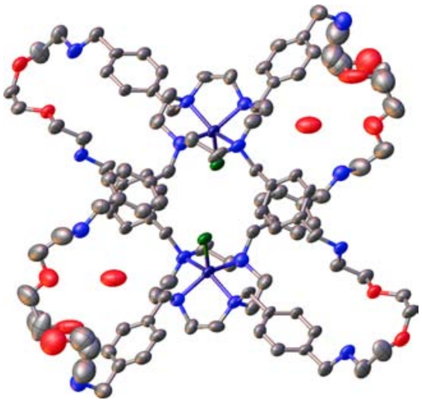


**Figure 2.** Molecular structure of $[Cu_2(H_47)Cl_2]Cl_6\cdot 9H_2O$. Hydrogen atoms, water molecules not included into the cage, and chloride ions not coordinating to copper ions are omitted for clarity.

Figure 2 shows that the complex thus obtained expectedly contains the two copper ions coordinated to the two cyclen units, both of which adopt the (3,3,3,3)-B square conformation.[14] The metal ions are coordinated in a square pyramidal fashion ($\tau$ = 0.04)[15] with the cyclen nitrogen donors at the equatorial position and a chlorido ligand placed at the axial position pointing toward the interior of the cage. The copper ions are located 0.55 Å above the mean plane defined by the amino groups of cyclen, as it is frequently observed for this ligand. The structure has an inversion center in the middle of each cage. The $Cu^{2+}$ ions are separated by 6.860(1) Å, and they are displaced from one another by 4.23 Å. Bond distances and angles are summarized in Table S2. There are eight chloride anions in the structure, two of them bound to the metal ions and the remaining six located outside the cavity where they form hydrogen bonds with amino groups in the linkers. The negative charge of the chloride ions is counterbalanced by the two $Cu^{2+}$ ions and by four protonated amino groups, one in each linker. Two water molecules are inside the cavity, interacting with amino groups in the linkers.

Thus, the crystal structure of this complex clearly demonstrates the potential of dimetallic complexes of **7** to form cascade complexes with anions bridging the two copper centers. The four linking units should be flexible enough to allow the complexation of anions of different sizes. Advantages of **7** are the high stability of the metal−cyclen complexes that renders demetalation under normal conditions unlikely. We therefore expect a rich coordination chemistry for **7**. Investigations in this direction are currently underway.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03027.

> Synthetic details of the preparation of compounds **2**−**7** including their NMR and MS spectra, experimental details and results of the potentiometric titrations (PDF)
>
> Crystallographic characterization of **3** (CIF)
>
> Crystallographic characterization of **5** (CIF)
>
> Crystallographic characterization of $[Cu_2(H_47)Cl_2]Cl_6\cdot 9H_2O$ (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Support by COST action CM1005 is kindly acknowledged. We are also grateful for funding from the Spanish MINECO and FEDER (Consolider-Ingenio and CTQ2013-48917-C3-1-P) and Generalitat Valenciana (PROMETEO II 2015/002).

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