ORGANIC LETTERS

2012
Vol. 14, No. 3
788–791

Metal-Coordinated Water-Soluble Cavitands Act as C–H Oxidation Catalysts

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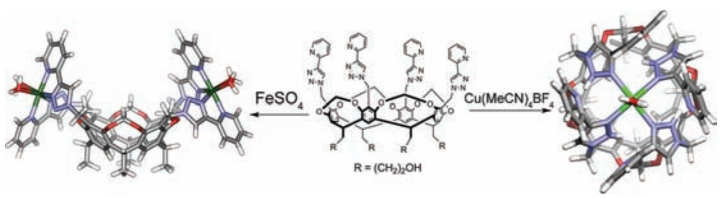
Received December 13, 2011

ABSTRACT



Cavitands can be smoothly derivatized by CuAAC chemistry to incorporate ligand species at the upper rim. These species can coordinate metal species in a number of different conformations, leading to self-assembly. The metal-coordination confers water solubility on the cavitands, and the iron-bound species are capable of catalytic C–H oxidations of fluorene under mild conditions.

A central feature of metalloenzymes is the presence of reactive metal species in the active site in close proximity with a defined cavity for substrate recognition.[1] Synthetic mimics of enzyme active sites often incorporate either a defined cavity[2] or an active metal species,[3] but seldom both. Combination of metal species with cavity-containing molecules is generally restricted to the formation of self-assembled cages where the metals play a purely structural role.[4] Reactive metal species have been coordinated to synthetic receptors,[5] but in the form of preformed porphyrins or salen complexes that are covalently attached. The scope of cavitands as catalysts can be increased by exploiting metal coordination to self-fold the host, leaving empty (or at least weakly coordinated) sites at the metal for reactions. Self-folding of cavitands is well-known via self-complementary hydrogen bonding, but this strategy is challenged when aqueous environments are desirable.[6] Metal coordination is commonly used in self-assembled systems to bring multiple ligand units together, but the use of metals as agents for organization (or self-folding) of cavitands is underutilized. Cavitands provide an alluring scaffold for the complexation of metal ions, in that they are capable of displaying four rigid coordinating motifs at defined distances.[7] The 4-fold symmetry of resorcinarene-based cavitands allows for binding of *two* octahedral metals by bidentate ligands, leaving empty sites for further reactivity at the metal sites.

Despite the advantages of using water as a solvent, most studies of metal-coordinated cavitands have been confined

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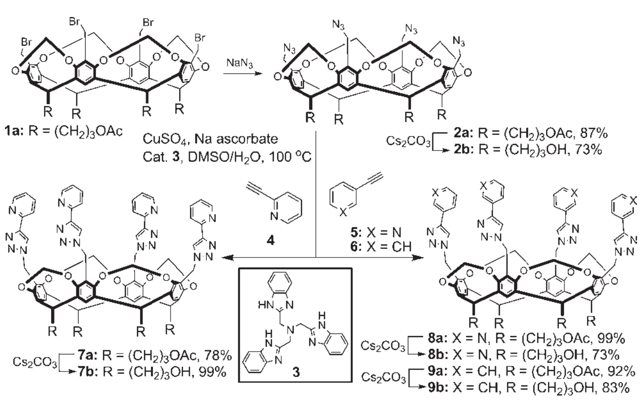
10.1021/ol203243j
Published on Web 01/24/2012

to organic solvents, and few water-soluble examples have been developed. This is in contrast with the extensive literature on self-assembled metal–ligand cages.[8] Water solubility can be conferred by a variety of methods including the incorporation of phosphate, sulfate, and/or carboxylate groups to the covalent structure.[9] In most cases, the polar groups are added solely for the purpose of solubility, and care must be taken so that the solubilizing groups do not interfere with the catalytically active groups.

Here we describe a novel approach to derivatizing cavitands whereby we confer water solubility upon the system via metal coordination and exploit this coordination for C–H oxidation catalysis.

Scheme 1. Synthesis of Metal-Coordinating Water-Soluble Cavitands



The core scaffold is shown in Scheme 1. Tetrabromocavitand **1a**[9e,10] can be accessed from 2-methyl resorcinol and 2,3-dihydrofuran in four steps, and reaction with sodium azide provides tetrazide cavitand **2a** in 87% yield. The cavitands were synthesized with their alcohol "feet" protected as acetate groups in order to increase their solubility in organic solvents. Simple saponification with Cs_2CO_3 cleaved the protecting groups, allowing access to the alcohol counterparts.

Slow evaporation of a chloroform/methanol solution of **2b** allowed access to single crystals that were suitable for X-ray diffraction analysis; ORTEP representations are shown in Figure 1 (CCDC #862080: for full details, see the Supporting Information). In the solid state, the cavitands were oriented in a "head-to-head" conformation so that the alcohol feet were intercalated. The cavities (and interstitial space between cavities) were occupied by disordered chloroform solvent. The azide groups at the rim showed significant disorder in the solid state due to free rotation. As can be seen by the structure in Figure 1, no hindrance is expected at the cavitand rim. The four azide groups in **2b** allow reaction with various substituted acetylenes by CuAAC chemistry to yield cavitands with multiple substituted triazoles at the rim. These triazoles can be tailored for variable metal coordination, and the initial tests are shown in Scheme 1. Two different arms were targeted to allow metal coordination. Reaction of **2a** with 2-ethynylpyridine **4** allows access to cavitand **7a**, which features a bidentate coordination motif between the triazole nitrogen and the 2-pyridyl, whereas the 3-pyridyl (**8a**) and phenyl (**9a**) counterparts should be unable to coordinate in this manner.

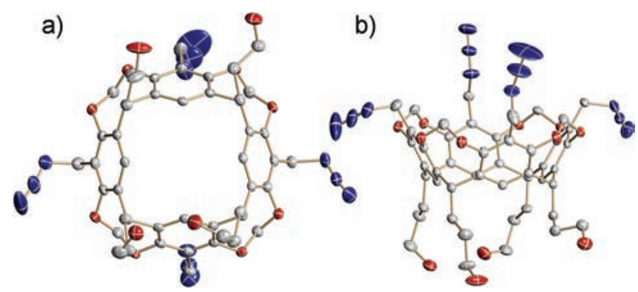


Figure 1. ORTEP representations of the structure of **2b**, as determined by X-ray diffraction analysis. The large ellipsoids for the azides are due to their disorder in the solid state structure.

Interestingly, CuAAC reaction of tetrazide cavitand **2a** proved challenging. Benzylic azides are well-known to react quickly at room temperature under standard CuAAC conditions.[11] In this case, however, forcing conditions were required for the coupling of acetylenes **4**, **5**, and **6** with **2a**. Reaction at ambient temperature gave very little conversion, and solvent mixtures such as CH_2Cl_2/MeOH or THF/water/*t*-BuOH (3:1:1) were ineffective. Performing the transformation at elevated temperatures (100 °C in a 4:1 DMSO/water mixture) and the use of $B(Im)_3$ catalyst **3**[12] allowed access to cavitands **7a** and **8a** in 78 and 99% yield, respectively. Simple saponification with Cs_2CO_3 gave the corresponding alcohol-footed cavitands **7b** and **8b**.

The sluggish CuAAC reaction could be ascribed to coordination of the catalyst by the products. While the azides in **2a**/**b** are not hindered in their reaction, the cycloaddition products are capable of binding the catalytic copper ions, reducing the effectiveness of reaction. The four triazole units that result from CuAAC reaction with suitable acetylenes are positioned so that their dipoles can be oriented directly toward the center of the cavitand and coordinate suitable metal ions. Residual copper that was coordinated during the CuAAC reaction could be removed by heating the product mixture in the presence of sodium EDTA.

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While the triazole arms in **7** and **8** (and presumably the azide arms in **2**) are freely rotating in the absence of metal, addition of copper(I) salts rigidifies the system through coordination with the donor atoms. Because of their well-known abilities in hydrocarbon oxidation reactions,[13] we focused on the coordination of copper and iron salts by pyridyl cavitands **7** and **8.** The metal-containing complexes could be isolated by reaction of either acetate or hydroxyl-footed cavitand **7a**/**b** with a weakly coordinated metal salt (e.g., $Cu(CH_3CN)_4BF_4$, $FeSO_4$) in methanol. The metal complexes precipitated from solution and could be isolated by simple filtration. ^{1}H NMR and MALDI mass spectrometric analysis were used to analyze the metal binding properties of the system.

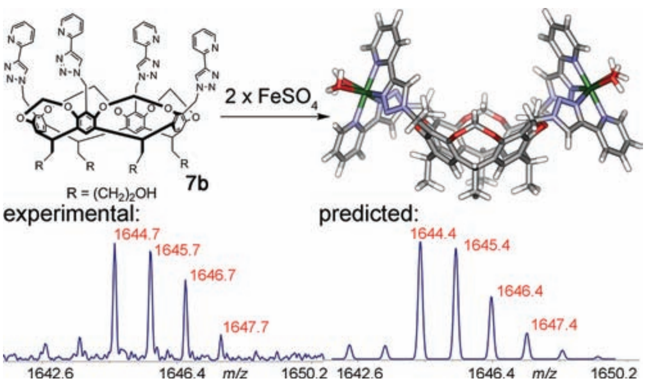

Figure 2. Coordination of iron(II) ions by the pyridyl−triazole unit (SPARTAN, Hartree−Fock forcefield).

Molecular modeling suggested that cavitand **7** would coordinate two octahedral metals, where each metal is coordinated between two bidentate ligands formed by the triazole nitrogen and the 2-pyridyl groups (Figure 2). Sonicating cavitand **7b** with excess $FeSO_4$ for 5 min at room temperature allowed the formation of our predicted structure (**7b·Fe₂**), where four binding sites are occupied by the triazole and pyridyl groups and the remaining two sites coordinate water. Formation of product was analyzed by MALDI mass spectrometry *m*/*z* 1645, which corresponds to the monocation of cavitand **7b** + 2Fe, incorporating sulfate ion, water, and hydroxide. The isotope pattern matches well with that predicted for cavitand **7b** binding two iron atoms. In order to further test the accuracy of our model, cavitands **8b** and **9b** were synthesized and tested for their ability to bind iron(II) salts. We rationalized that neither the 3-pyridyl group in **8b** nor the phenyl group in **9b** would be able to form a bidentate ligand with the triazole and should consequently not coordinate iron. Both cavitands **8b** and **9b** were sonicated with $FeSO_4$, and as expected no coordination of iron was observed. Only free cavitand was observed by MALDI-MS, and no change was observed in the ^{1}H NMR spectra.

In contrast, upon reaction of **7b** with $Cu(CH_3CN)_4BF_4$, only one copper ion is bound by the cavitand ($[M + Cu]^+$ observed at $m/z = 1465$, see the Supporting Information). Molecular modeling illustrates the most favorable conformation of the complex, as shown in Figure 3. The Cu(I) can adopt a square pyramidal geometry and coordinate all four triazole units through their N3 atoms (the final empty valence is occupied by solvent in Figure 3, although no solvent was observed in the molecular ion in the MS). This conformation is possible for all cavitands **7**−**9**, and copper coordination is observed in each case upon sonication at ambient temperature with $Cu(CH_3CN)_4BF_4$. While iron(II) salts are poorly coordinated at the triazoles, copper(I) salts are strongly bound, no matter the rim functionality; this indicates that coordination of the copper catalyst in the CuAAC reaction occurs at the triazole motif, limiting conversion under mild conditions. It is notable that the hydroxyl-footed metal-coordinated cavitands are soluble in pure water. Iron coordination confers greater water solubility than copper(I), and while **7b·Fe₂** is soluble to 4 mM, **7b·Cu** is only sparingly soluble. All metal-coordinated cavitands are soluble in water upon addition of a small amount of acetonitrile.

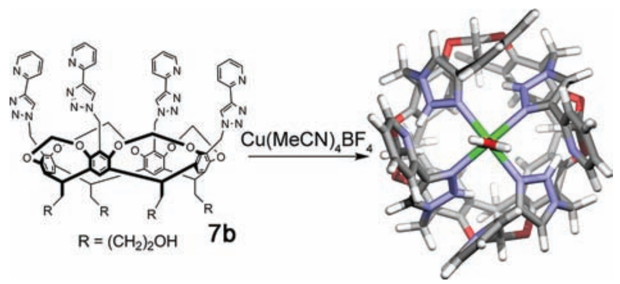

Figure 3. Coordination of copper(I) ions by the pyridyl−triazole unit (SPARTAN, Hartree−Fock forcefield).

We were unable to grow X-ray quality crystals of the **7b·Cu** complex, so to corroborate the modeling experiment, alternate coordinating motifs were added to the cavitand rim. To verify that the triazole ligands were the primary coordinators of the metal ions, the pyridyl group was moved away from the cavitand core by the introduction of amide spacers. Ligands **10** and **11** were synthesized from propargylamine and the corresponding 2- and 4-pyridylcarboxylic acids in good yields. CuAAC coupling with **2a** proceeded smoothly as before to yield amide cavitands **12a** and **13a**. Saponification gave alcoholic cavitands **12b** and **13b**, and the metal-coordinating properties were tested as before. 4-Pyridylamide cavitand **13b** behaved as expected; a single copper ion was coordinated by the complex (**13b·Cu** showed an ESI peak at 1693.5797 $(M + H)^+$), and no affinity was observed for iron because the 4-pyridyl groups are unable to contribute toward metal coordination.

The 2-pyridylamide cavitand **12b** showed anomalous behavior. Upon treatment of **12b** with $Cu(CH_3CN)_4BF_4$,

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two species were observed by MALDI analysis, corresponding to the presence of one and two copper ions ($M^+ = 1692$ and 1755, respectively). While the singly bound copper species is most likely the conformation shown in Figure 4, the structure of the doubly bound species is unclear. The ^1H NMR spectrum is broad, so determination of the products was not possible, and crystal growth from the product mixture was unsuccessful.

Interestingly, 2-pyridylamide cavitand **12b** was also able to coordinate a single iron(II) cation, despite the poor affinity of the smaller cavitands **8** and **9** for iron(II). Treatment of **12b** with $FeSO_4$ allowed the isolation of cavitand **12b·Fe**, *m*/*z* 1684.

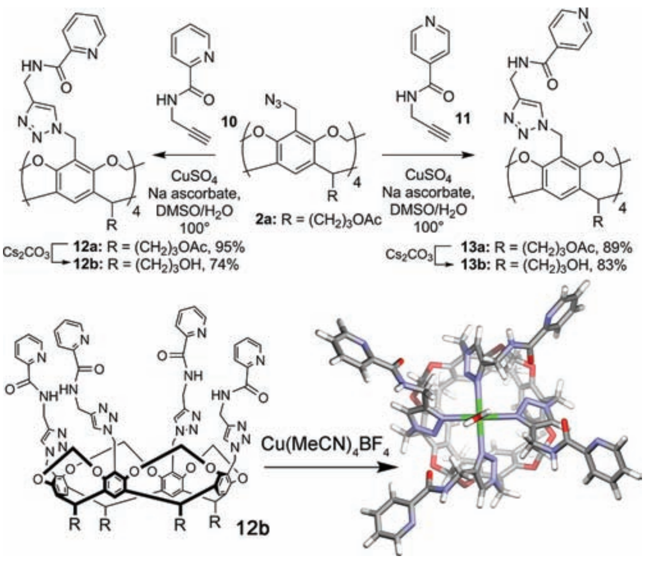
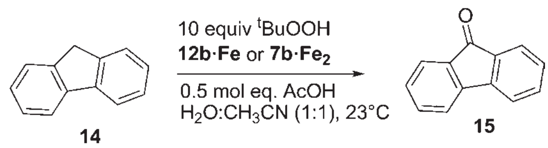


Figure 4. Synthesis of amide cavitands and their coordination of copper(I) ions by the pyridyl–triazole unit (SPARTAN, Hartree–Fock forcefield).

The iron-coordinated cavitands **12b·Fe** and **7b·Fe$_2$** are underligated; i.e., the ligands only occupy four of the six coordination sites at the metal. Ligands of this type are well-precedented to perform C–H oxidation reactions under mild conditions, inspired by the mode of action of the Rieske nonheme iron oxygenases.[1,14] The ability of **12b·Fe** and **7b·Fe$_2$** to perform oxidation reactions was tested. Activation of hydrocarbons such as cyclohexane or methylcyclohexane was unsuccessful, but the more activated fluorene **14** could be smoothly converted to fluorenone **15**. Reactions were performed at room temperature in water/acetonitrile with catalytic acetic acid (0.5 equiv) and 10–20 mol % loading of the cavitand catalyst. Hydrogen peroxide and benzoyl peroxide were tested as oxidants; however, no reaction was observed using hydrogen peroxide, and oxidation with benzoyl peroxide lead to the formation of multiple unidentified side-products. *tert*-Butyl hydroperoxide (TBHP) was a successful oxidant, and GC analysis showed clean oxidation of **14** to **15**.



catalyst	% cat.	% **15**, 24h	% **15**, 48h
12b•Fe	20	74	91
7b•Fe$_2$	10	100	--
$FeSO_4$	20	4	16

Figure 5. Fluorene oxidation by metalated cavitands.

Both cavitands **12b·Fe** and **7b·Fe$_2$** were capable oxidants. The bis-iron catalyst **7b·Fe$_2$** showed the fastest oxidation, with 100% conversion (GC) after 24 h. Mono-iron amide cavitand **12b·Fe** was a less effective catalyst (Figure 5) but showed significant conversion of **14** to **15** after 48 h. Some oxidation of **14** to **15** was observed when $FeSO_4$ was used as control catalyst, but $FeSO_4$ was far less effective than **12b·Fe** and **7b·Fe$_2$** and essentially only displayed *substoichiometric* reactivity. It is important to note that the cavitands are stable to the conditions of the oxidation, even over a period of 7 days: the coordination of cavitand to the oxidizing metal stabilizes the active species, allowing turnover and catalysis.

In conclusion, we have shown that cavitands can be smoothly derivatized by CuAAC chemistry to incorporate ligand species at the cavitand rim. Depending on the rim functionality, these species can coordinate metal ions in one of two conformations, with the metal positioned either directly over the central cavity through triazole coordination, or with two metal species bound at the sides, via coordination with both triazole and appended 2-pyridyl groups. Metal coordination confers water solubility on complexes *without* the need for covalent introduction of solubilizing groups such as sulfates or phosphates, and the molecules are capable of C–H oxidation reactions of fluorene under mild conditions due to the empty coordination sites on the bound metal. Further study of the properties of metal-bound cavitands in molecular recognition and directed oxidation reactions are underway.

Acknowledgment. R.J.H. acknowledges the donors of the American Chemical Society Petroleum Research Fund for support of this research. D.D.R. is a MARC-U-STAR Scholar.

Supporting Information Available. Experimental details and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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The authors declare no competing financial interest.