ARTICLE TYPE

Synthesis and physico-chemical properties of the first water soluble Cu(II)@hemicryptophane complex

Aline Schmitt,[a] Solène Collin,[a] Christophe Bucher,[a] Vincent Maurel,[b] Jean-Pierre Dutasta*[a] and Alexandre Martinez*[a,c]

A hemicryptophane ligand soluble in water at neutral pH was obtained thanks to the derivatization of the cyclotribenzylene unit with three carboxylate groups. The corresponding Cu(II) complex was then synthesized and its spectroscopic and electrochemical properties in water were investigated, showing that
10 the water solubilisation retains the geometry of the complex around the metal center but strongly affects its redox properties, compared to previously reported Cu(II)@hemicryptophane complexes soluble in organic solvents.

Introduction

Hemicryptophanes[1] have revealed to be attractive molecular
15 receptors[2] and they have been used for the design of supramolecular catalysts[3] and molecular propellers or gyroscopic systems.[4] In particular, The introduction of a vanadium atom in the cavity of hemicryptophanes have for instance been found to yield oxidovanadium-hosts acting as haloperoxidase enzyme
20 mimics catalyzing sulfoxidation reactions.[3a]

As a general statement, the versatility and modularity of these host compounds have proved particularly suited to mimic enzymatic systems by combining lipophilic cavity and catalytic
25 site.[5-9] By this way, original nanoreactors can be synthesized and give rise to artificial metallo-enzymes. Such systems have been already studied in organic solvents.[10] Obviously, most biocatalytic processes in nature occur in aqueous media and to obtain a better understanding and control of such biological
30 processes, any synthetic systems should be able to work in water.[11] Water-solubilisation of biomimetic entities is highly challenging,[12] and very few water-soluble metalloenzymes models have been reported in the literature.[13]

Recently, we have reported several supramolecular systems,
35 based on hemicryptophane ligands, combining a biomimetic copper(II) coordination core and a lipophilic cavity.[14] The Cu(II) complexes have been found to be efficient catalysts in organic solution for the conversion of cyclohexane to cyclohexanol/cyclohexanone, using H_2O_2 as oxygen source. Both
40 the stability and the selectivity of the catalyst have been improved by encapsulating the active site.[3d] We have also described the first synthesis of a water-soluble hemicryptophane host and its recognition properties toward choline in a basic aqueous medium.[15]
45 By combining both water-solubility and Cu(II) complexation in a unique cage molecule we expected to get rise to a water-soluble metallo-enzyme model, presenting a copper site encaged in a closed-shell cavity. Herein, we thus report the synthesis of the first water-soluble copper@hemicryptophane complex together
50 with its spectroscopic characterization and redox properties.

Results and discussion

Synthesis of the water-soluble complex

Hemicryptophane **1** was synthesized in 6 steps, following a
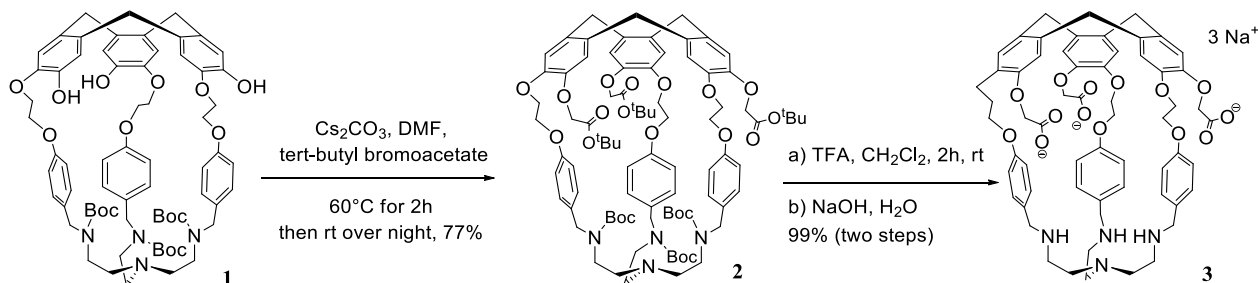
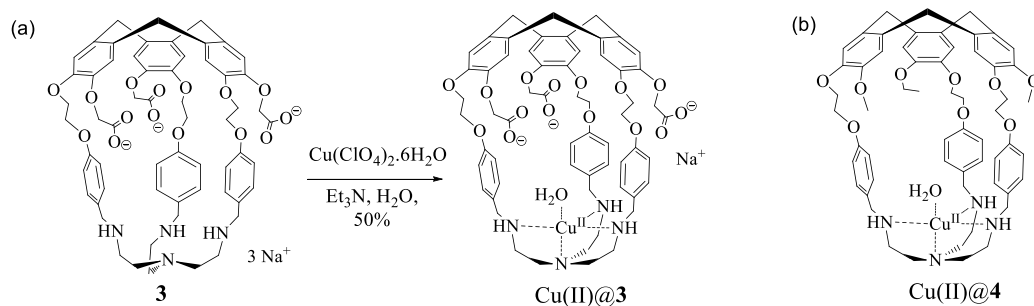**Scheme 1.** Synthesis of the water soluble ligand **3**.

previously published procedure (Scheme S-1).[15] The strongly basic conditions (pH = 12) which are required to solubilize **1** in water are not compatible with its use in biological environments. The substitution of the phenol groups in **1** by carboxylate moieties was performed in order to obtain the hemicryptophane **3**, which was found to be soluble in water at physiological pH (pH ≈ 7). The strategy used to synthesize compound **3** is depicted in Scheme 1. The first step involves the reaction of compound **1** with tert-butyl-bromoacetate in DMF in the presence of Cs_2CO_3 to yield the protected tri-ester derivative **2**. Deprotection of both the amine and the ester functions in **2**, using trifluoroacetic acid, afforded the water-soluble hemicryptophane **3**. Following this synthetic pathway, host **3** has been obtained from commercially available products in 8 steps with an overall yield of 6 %.
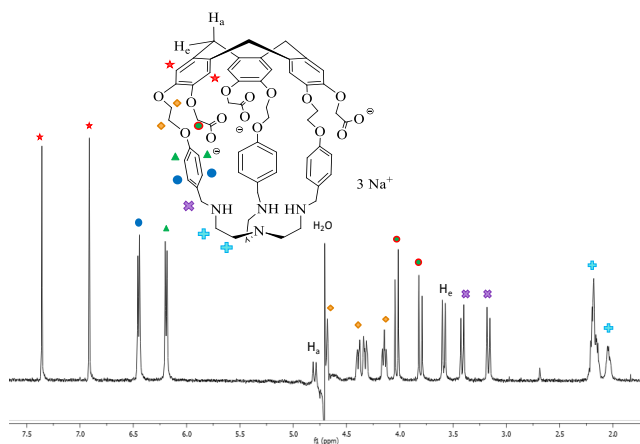
Figure 1. ^{1}H NMR spectrum (500.1 MHz, D_2O, 298 K, pD ≈ 7) of hemicryptophane **3**

The ^{1}H NMR spectrum of **3** in D_2O (pD ≈ 7) indicates that this molecule is on average of C_3 symmetry. It displays the expected signals for the cyclotribenzylene unit (Figure 1): two singlets for the aromatic protons, and the characteristic AB system for the $ArCH_2$ bridges. Two doublets for the aromatic protons of the linkers and the multiplets for the OCH_2 groups are also observed in the spectra. The NCH_2 protons of the tren unit appear as a complex pattern between 2.0 and 2.25 ppm.

The hemicryptophane copper(II) complex was then synthesized by reaction of **3** with a stoechiometric amount of copper(II) perchlorate in water to produce Cu(II)@**3** isolated in a 50 % yield as a pale green solid (Scheme 2).
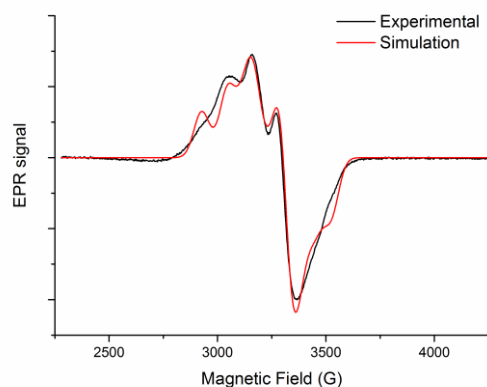
Electronic Spectroscopy
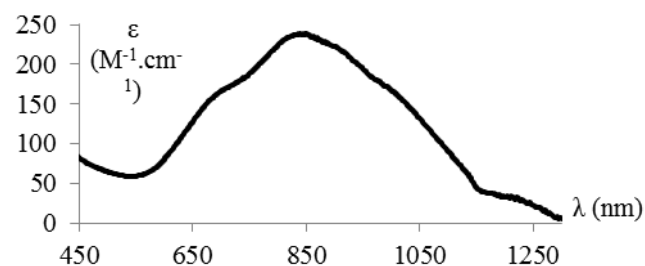
Figure 2. Near-IR/vis spectrum of Cu(II)@hemicryptophane-**3** (H_2O/NaOH, pH ≈ 8, 298 K)

The Near-IR/vis absorption spectrum of the hemicryptophane complex Cu(II)@**3** in CH_2Cl_2 displays a broad asymmetrical band centred at 850 nm which is a diagnostic signature supporting the trigonal-bipyramidal geometry of the complexed copper (II) ions (Figure 2). These observations are fully consistent with those previously observed with the parent Cu(II)@**4** complex soluble in organic solvents (Scheme 2(b)).[14,16]

EPR Measurements

The EPR spectrum of the Cu(II)@**3** complex was recorded in frozen water at 70 K (Figure 3). A pseudo-axial EPR signal (g_1 = 2.015, g_2 = 2.135 and g_3 = 2.220) with a resolved hyperfine structure (A_1 = 193 MHz, A_2 = 158 MHz and A_3 = 363 MHz) was obtained, giving a R value (g_2–g_1)/(g_3–g_2) equals to 1.41.[17] These values (g_1 < 2.04 and R > 1) are typical for a N_4X coordination sphere with a distorted geometry close to trigonal-bipyramidal geometry.[18] The g-values are very similar to that previously obtained with the Cu(II)@**4** complex (g$_1$ = 2.010, g$_2$ = 2.136, g$_3$ = 2.220; R = 1.50),[14] indicating that water solubilisation did not induce strong distortion of the initial geometry. Complexes Cu(II)@**3** and Cu(II)@**4** present a five-coordination sphere with the copper ion bound to the four nitrogen atoms of the tren unit and to one solvent molecule.


Scheme 2. (a) Synthesis of the water soluble Cu(II)@hemicryptophane-**3** complex. (b) structure of its no-water soluble parent Cu(II)@**4**.

Figure 3 : EPR spectra of Cu-(II)@**3** in frozen water solution (H$_2$O/NaOH, pH ≈ 8, T = 70 K) (black= line: experimental spectra ; red line: simulated spectra).). Experimental conditions: ν = 9.655 GHz, power = 2 mW and modulation amplitude = 2.0 G. Best fit parameters: g_1 = 2.015, g_2 = 2.135 and g_3 = 2.220 ,A_1 = 193 MHz, A_2 = 158 MHz and A_3 = 363 MHz for a lwpp=70G Gaussian lineshape.

Electrochemical Studies.

The CV curve recorded for Cu-(II)@**3** in an electrolytic aqueous medium exhibits a fully irreversible reduction waves E_{pc} = − 0.59V attributed to the formation of Cu-(I)@**3** at the electrode interface. This irreversible feature, observed at all the investigated scan rates, *ie* from 0,02 to 10 V.s^{-1}, is due to the existence of an isomerisation process triggered by the electrochemical reduction of the Cu(II) center. The associated EC process[19] can indeed be modelled as a classic square scheme involving changes in the coordination sphere around the Cu(I) center in the pentacoordinated Cu-(I)@**3** species to produce a more stable tetrahedral Cu(I) complex noted Cu-(I)@**3'**.[20] These hypotheses are supported by the observation of an irreversible oxidation wave at E_{pa}= 0.14 V on the reverse scan, the large amplitude of the potential shift seen between E_{pc} and E_{pa} being in agreement with a net decrease of the number of coordinated atoms on the copper center, from 5 in Cu-(II)@**3** to 4 in Cu-(I)@**3'**. It should be mentioned that a similar EC process was postulated for Cu(II)@**4** in dichloromethane; the reduction wave and the associated re-oxidation being observed in theses conditions at E_{pc}= − 0.91V / ECS and E_{pa} = 0.45 V / ECS, respectively.[14]

These differences observed between organic and aqueous media highlight the key role of water which is most probably both involved in the solvation and coordination shells of the cupric and cuprous complexes.
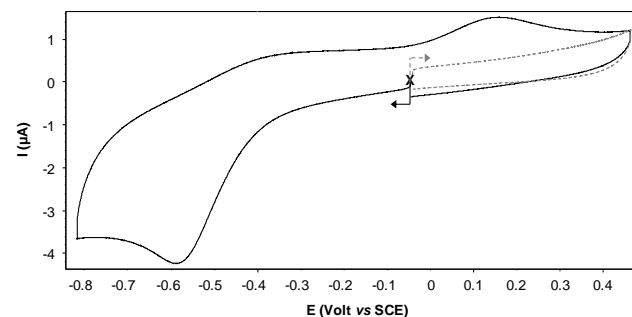
Figure 4 : Cyclic voltammogram of Cu(II)@**3** recorded under argon in water (NaNO$_3$ (0,1 M), NaOH (1,5 mM)) (carb., Ø = 3 mm; ν = 0.05 V s^{-1}).

Conclusion

In conclusion, the synthesis of the first water soluble copper@hemicryptophane complex has been described. This represents a rare example of water-soluble cage compound trapping a copper ion in the confined space of its cavity. The physico-chemical studies indicated that the solubilisation in water affects only weakly the geometry of the complex, but strongly modifies its redox behavior. This novel water-soluble metallo-enzyme model featuring a copper (II) site encaged in a closed-shell cavity open up the way to new bio-inspired catalytic systems.

Experimental Section

General methods

All reactions were carried out under argon by means of an inert gas/vacuum double manifold and standard Schlenk techniques. Dichloromethane was first dried over molecular sieves and then passed through an activated alumina column followed by an argon flush on a solvent station. ^{1}H and ^{13}C NMR spectra were recorded at 500.10 MHz and 125.76 MHz, respectively. Chemical shifts are reported relative to the residual protonated solvent signal (CDCl$_3$), or relative to residual ethanol for the spectra in D$_2$O. Mass spectra were recorded by the Centre de Spectrométrie de Masse, Institute of Chemistry, Lyon. Compound **1** was prepared according to the published procedure.[15] EPR spectra were obtained from a Bruker EMX spectrometer and fitted with Easyspin[21] software.

Cyclic voltammetry (CV) data were recorded using an ESP-300 Biologic potentiostat equipped with a 1 A/48 V booster and an analog linear scan generator. All the experiments were conducted under an argon atmosphere in a standard one-compartment, three-electrode electrochemical cell placed in a faraday cage. An automatic ohmic drop compensation procedure was systematically implemented prior to recording CV data. All the electrodes were purchased from ALS Co. Ltd. Vitreous carbon (Φ = 3 mm) working electrodes were polished with 1 mm diamond paste before each recording. A saturated ECS electrode was used as a reference. HPLC grade water + sodium nitrate (0.1M) was used as the electrolyte.

Syntheses

Hemicryptophane 2

Hemicryptophane **1**, (257 mg, 0.212 mmol) was dissolved in anhydrous DMF (20 mL) and Cs_2CO_3 (276 mg, 0.848 mmol) was added to the solution which was stirred at 60°C for 15 minutes.
Then *tert*-butylbromoacetate (0.141 mL, 0.945 mmol) was added and the mixture was stirred at 60°C for 2 hours, then at room temperature overnight. The solvent was removed and $CHCl_3$ (20 mL) and H_2O (20 mL) were added to the residue. The two layers were separated and the aqueous phase was extracted with $CHCl_3$ (20 mL). The combined organic solutions were washed with H_2O (2 x 20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography on silica gel, using CH_2Cl_2 and a gradient of EtOAc (10% to 50%) as eluent. Compound **2** was obtained as a foamy white solid (252 mg, 77 %). ESI-MS *m/z* observed 1551.7991 ([M + H]$^+$, calculated 1551.7991 for $C_{87}H_{115}N_4O_{21}$). ^{1}H NMR (CDCl$_3$, 298 K, 500.10 MHz): δ 7.13-6.91 (br, 6H, ArH), 6.91-6.82 (br, 6H, ArH) , 6.82-6.66 (br, 6H, ArH), 4.65 (d, 3H, J=13.7 Hz, ArCH$_2$Ar), 4.56 (d, 3H, J=16.0 Hz, CH$_2$COO) 4.48-4.05 (m, 21H, CH$_2$COO; O(CH$_2$)$_2$O; ArCH$_2$N), 3.47 (d, 3H, J=13.7 Hz, ArCH$_2$Ar), 3.07-2.60 (br, 6H, N(CH$_2$)$_2$N), 2.50-2.15 (br, 6H, N(CH$_2$)$_2$N), 1.51-1.32 (br, 54H, C(CH$_3$)$_3$ BOC et ^{t}Bu-ester). ^{13}C NMR (CDCl$_3$, 298 K, 125.76 MHz): δ 168.59 (CH$_2$$\underline{C}$(O)O) 157.97, 155.92 and 155.36 (N$\underline{C}$(O)O), 147.49 (C$_{Ar}$), 147.30 (C$_{Ar}$), 134.00 (C$_{Ar}$), 133.08 (C$_{Ar}$), 130.99 (C$_{Ar}$), 129.42 (C$_{Ar}$), 128.74 (C$_{Ar}$), 118.77 (C$_{Ar}$), 117.53 (C$_{Ar}$), 115.19 (C$_{Ar}$), 82.06 (O$\underline{C}$ (CH$_3$)$_3$), 79.70 (O$\underline{C}$(CH$_3$)$_3$), 68.49 and 68.25 (OCH$_2$), 66.77 (OCH$_2$), 52.92 (N(CH$_2$)$_2$N), 50.45 and 49.78 (NCH$_2$Ar), 45.12 (N(CH$_2$)$_2$N), 36.52 (ArCH$_2$Ar), 28.67 (CH$_3$), 28.26 (CH$_3$). Mp: 229.185 °C. IR v = 2974, 2918, 1749, 1686, 1612, 1509, 1456, 1408, 1365, 1246, 1143cm^{-1}.

Hemicryptophane 3

Trifluoroacetic acid (TFA, 780 µL, 10 mmol) was added to a solution of hemicryptophane **2** (120 mg, 77 µmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 2h at room temperature and the solvent and TFA were removed under vacuum. Several additions and evaporations of $CHCl_3$ were carried out to facilitate the evaporation of TFA. Distilled water (1.5 mL) and NaOH (19.6 mg, 490 µmol) were added to the residue and the mixture was stirred for 30 minutes. Water was then evaporated to give **3** as a yellow solid (quantitative). ESI-MS *m/z* observed 1081.4500 ([M + 2H]$^-$, 1081.4452 calculated for $C_{60}H_{65}N_4O_{15}$). ^{1}H NMR (D$_2$O, 298 K, 500.10 MHz): δ 7.36 (s, 3H, ArH), 6.91 (s, 3H, ArH), 6.45 (d, 6H, J=8.4 Hz, ArH), 6.19 (d, 6H, J=8.4 Hz, ArH), 4.80 (d, 3H, J=13.8 Hz, ArCH$_2$Ar), 4.69-4.65 (m, 3H, O(CH$_2$)$_2$O), 4.42-4.36 (m, 3H, O(CH$_2$)$_2$O), 4.36-4.28 (m, 3H, O(CH$_2$)$_2$O), 4.19-4.10 (m, 3H, O(CH$_2$)$_2$O), 4.03 (d, 3H, J=15.4 Hz, O$\underline{C}$H$_2$COO), 3.80 (d, 3H, J=15.4 Hz, O$\underline{C}$H$_2$COO), 3.59 (d, 3H, J=13.8 Hz, ArCH$_2$Ar), 3.41 (d, 3H, J=13.6 Hz, ArCH$_2$N), 3.17 (d, 3H, J=13.6 Hz, ArCH$_2$N), 2.25-2.00 (m, 12H, N(CH$_2$)$_2$N). ^{13}C NMR (D$_2$O, 298 K, 125.76 MHz): δ 176.07 ((C=O)O), 157.68 (C$_{Ar}$O), 145.85 (C$_{Ar}$O), 145.47 (C$_{Ar}$O), 133.41 (C$_{Ar}$), 132.79 (C$_{Ar}$), 130.00 (C$_{Ar}$H), 129.27 (C$_{Ar}$), 116.38 (C$_{Ar}$H), 115.82 (C$_{Ar}$H), 114.19 (C$_{Ar}$H), 69.12 (O(CH$_2$)$_2$O), 66.71 (O$\underline{C}$H$_2$C(O)O), 66.32 (O(CH$_2$)$_2$O), 52.92 (N(CH$_2$)$_2$N), 50.51 (ArCH$_2$N), 44.79 (N(CH$_2$)$_2$N), 35.26 (ArCH$_2$N). Mp: 219.3 °C. IR v = 3400, 2923., 2856., 1681, 1605, 1509, 1425, 1335, 1259, 1204, 1176, 1127 cm^{-1}.

Complex Cu(II)@hemicryptophane-3.

To a solution of hemicryptophane **3** (15.6 mg, 14 µmol) in milli-Q water (3 mL) was added $Cu(ClO_4)_2.6H_2O$ (5.1 mg, 14 µmol) and Et$_3$N (9 µL, 67 µmol). The solution was stirred for 5 minutes and water and Et$_3$N were removed under vacuum. Milli-Q water (1.5 mL) was added and the blue solid was triturated in this solvent. The solution was centrifuged and the supernatant was removed. This last step was repeated with 1 mL of milli-Q water and the residue was dried under vacuum. A blue solid was obtained (7.9 mg, 50 %). ESI-MS *m/z* observed 1142.3646 ([M]$^-$, calculated 1142.3591 for $C_{60}H_{63}^{63}CuN_4O_{15}$). EPR (H$_2$O/NaOH; pH = 8; 70 K) g$_1$ = 2.015 (A$_1$ = 193 MHz); g$_2$ = 2.135 (A$_2$ = 158 MHz); g$_3$ = 2.220 (A$_3$ = 363 MHz).Vis-Near IR spectroscopy (H$_2$O, 298 K) λ_{max} = 850 nm, ε = 237 M^{-1}.cm^{-1}, shoulder band around 700 nm, ε = 165 M^{-1}.cm^{-1}. Cyclic Voltammetry: E$_{pc}$ = -0.34 V and E$_{pa}$ = 0.30 V vs E$_{1/2}$ [FcMeOH$^{0/+}$] (H$_2$O, NaOH (1.5 mM), 12-Cu^{II} (5.10^{-4} M), NaNO$_3$ (0.1 M), working electrode: carbone, 50 mV.s^{-1})

## Notes and references

[a] Dr. A. Schmitt, Dr. C. Bucher, Dr. J.-P. Dutasta, Pr. A. Martinez Laboratoire de Chimie, École Normale Supérieure de Lyon, CNRS, UCBL, 46, Allée d'Italie, F-69364 Lyon, France
[b] Dr Vincent Maurel, Laboratoire de Résonances Magnétiques, CEA-Grenoble/INAC/SCIB/LRM, UMR-E 3 CEA-UJF, 17, rue des Martyrs 38054 Grenoble CEDEX 09
[c] Pr. A. Martinez, Aix Marseille Universite, Centrale Marseille, CNRS, iSm2 UMR 7313, 13397, Marseille, France

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1   J. Canceill, A. Collet, J. Gabard, F. Kotzyba-Hibert and J.-M. Lehn, *Helv. Chim. Acta*, 1982, **65**, 1894;

2   (a) S. Le Gac and I. Jabin, *Chem. Eur. J.*, 2008, **14**, 548-557. (b) O. Perraud, V. Robert, A. Martinez and J.-P. Dutasta, *Chem. Eur. J.*, 2011, **17**, 4177-4182. (c) L. Wang, G.-T. Wang, X. Zhao, X.-K. Jiang and Z.-T. Li, *J. Org. Chem.*, 2011, **76**, 3531-3535. (d) O. Perraud, A. Martinez and J.-P. Dutasta, *Chem. Comm.*, 2011, **47**, 5861-5863. (e) O. Perraud, V. Robert, A. Martinez and J.-P. Dutasta, *Chem. Eur. J.*, 2011, **17**, 13405-13408. (f) O. Perraud, V. Robert, H. Gornitzka, A. Martinez and J.-P. Dutasta, *Angew. Chem. Int. Ed. Engl.*, **2012**, **51**, 504-508.

3   (a) A. Martinez and J-P Dutasta, *J. Catal.,* 2009, **267**, 188-192. (b) Y. Makita, K. Sugimoto, K. Furuyosho, K. Ikeda, S. I. Jujiwara, T. Shin-ike and A. Ogawa, *Inorg Chem*, 2010, **49**, 7220-7222; (c) Y. Makita, K. Ikeda, K. Sugimoto, T. Fujita, T. Danno, K. Bobuatong, M. Ehara, S. I. Jujiwara and A. Ogawa, *J. Organometall. Chem.*, 2012, **26**, 706, -707. (d) O. Perraud, A. B. Sorokin, J.-P. Dutasta and A. Martinez, *Chem. Commun.* 2013, **49**, 1288-1290.

4   (a) A. Martinez, V. Robert, H. Gornitzka and J.-P. Dutasta, *Chem. Eur. J.*, 2010, **16**, 520-527. (b) A. Martinez, L. Guy and J.-P. Dutasta, *J. Am. Chem. Soc.*, 2010, **132**, 16733-16734. (c) N. S. Khan, J. M. Perez-Aguilar, T. Kaufmann, P. A. Hill, O. Taratula, O.-S. Lee, P. J. Carroll, J. G. Saven and I. J. Dmochowski, *J. Org. Chem.,* 2011, **76** , 1418–1424.

5   M. Raynal, P. Ballester, A. Visal-Ferran, P. W. N. M. Van Leeuwen Chem. Rev. 2014, **43**, 1660-1733.

6   M. Raynal, P. Ballester, A. Visal-Ferran, P. W. N. M. Van Leeuwen Chem. Rev. 2014, **43**, 1734-1787.

7   A. J. Kirby, *Angew. Chem. Int. Ed.*, 1996, **35**, 707-724.

8   J. K. M. Sanders, *Chem. Eur. J.*, *1998*, **4**, 1378-1383.

9   J.-M. Lehn, *Rep. Prog. Phy.*, *2004*, **67**, 245-249.

10   Steed, J. W.; Atwood J. L., in *Supramolecular Chemistry,* 2nd ed., Wiley-VCH, Weinheim, **2009**.

11   G. V.Oshovky, D. N. Reinhoudt and W. Verboom, *Angew. Chem. Int. Ed.*, 2007, **46**, 2366-2393.

12   E. Klein, Y. Ferrand, N. P. Barwell and A. P. Davis, *Angew. Chem. Int. Ed*., 2008, **47**, 2693-2696.

13   (a) R. Breslow, *Acc. Chem. Res*., 1995**, 28**, 146; (b) E. Engeldinger, D. Armspach and D. Matt, *Chem. Rev.,* 2003, **103**, 4147; (c) D. M. Homden and C. Redshaw, *Chem. Rev.,* 2008, **108**, 5086. (d) G. Thiabaud, A. Brugnara, M. Carboni, N. Le Poul, B. Colasson, Y. Le Mest, and O. Reinaud *Org. Lett.*, 2012, **14**, 2500–2503

14   O. Perraud, J.-B. Tommassino, V. Robert, L. Khrouz, B. Albela, L. Bonneviot, J.-P. Dutasta and A. Martinez, *Dalton Trans*., 2013, **42**, 1530-1535.

15   A. Schmitt, V. Robert, J.-P. Dutasta and A. Martinez, *Org. Lett*., 2014, **16**, 2374–2377.

16   a) M. Duggan, N. Ray, B. Hathaway, G. Tomlinson, P. Brint and K. J. Pelin, *Chem. Soc. Dalton Trans.*, 1980, **8** , 1342-1348. (b) F. Thaler, C. D. Hubbard, F. W. Heinemann, R. Van Eldik, S. Schindler, I. Fabian, A. M. Dittler-Klingemann, F. Ekkehardt Hahn and C. Orvig, *Inorg. Chem.*, 1998, **37**, 4022-4029.

17   D. E. Billing, R. J. Dudley, B. J. Hathaway, and A. Tomlinso, *J. Chem. Soc. A*, 1971, 691-696

18   R. J. Dudley, B. J. Hathaway, P. G. Hodgson, P. C. Power and Loose, *J. Chem. Soc.-Dalton Trans.*, 1974, 1005-1009.

19   a) C. Bucher, E. Duval, J.-M. Barbe, J.-N. Verpeaux, C. Amatore and R. Guilard, *C. R. Acad. Sci. II C.* 2000, **3**, 211-222 ; b) C. Amatore, J.-M. Barbe, C. Bucher, E. Duval, R. Guilard and J.-N. Verpeaux, *Inorg. Chim. Acta* 2003, **356**, 267-278. c) C. Bucher, J.-C. Moutet, J. Pecaut, G. Royal, E. Saint-Aman, F. Thomas, S. Torelli and M. Ungureanu, *Inorg. Chem.* 2003, **42**, 2242-2252. d) C. Bucher, J.-C. Moutet, J. Pecaut, G. Royal, E. Saint-Aman and F. Thomas, *Inorg. Chem.* 2004, **43**, 3777-3779. e) U. Darbost, V. Penin, E. Jeanneau, C. Félix, F. Vocanson, C. Bucher, G. Royal and I. Bonnamour, *Chem. Commun.* 2009, **44**, 6774-6776.

20   The driving force of most reorganization reactions reported so far in the literature for electrogenerated Cu(I) complexes is the stabilization of the Cu(I) ion in a tetrahedral environment : See for instance ref 18 or J.-P. Sauvage, J.-P. Collin, S. Durot, J. Frey, V. Heitz, A. Sour and C. Tock, *Compte Rendus Chimie* 2010, **13**, 315-328.

21   S. Stoll, A. Schweiger, *J. Magn. Reson.* 2006, **178**, 42-55.

25

Table of contents entry
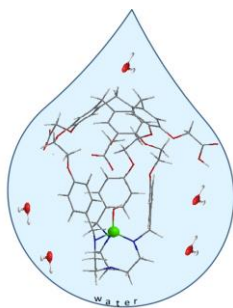
A water-soluble metallo-enzyme model featuring a copper (II) site encaged in a closed-shell cavity of a hemicryptophane has been synthesized and 30 studied.

35