NJC

PAPER

View Article Online
View Journal | View Issue

Cite this: *New J. Chem.*, 2016, **40**, 5829

Reinforced cyclam derivatives functionalized on the bridging unit†

Nicolas Sok,*[a] Isabelle Baglin,[b] Yoann Rousselin,[b] Frederic Boschetti,[c] Claire Bernhard,[b] Christine Goze[b] and Franck Denat*[b]

Received (in Montpellier, France) 8th December 2015,
Accepted 29th March 2016

DOI: 10.1039/c5nj03488d

www.rsc.org/njc

A new synthetic method has been developed for the preparation of reinforced cyclams (1,4,8,11-tetraazacyclotetradecane) C-functionalized on the bridging unit, by using a "one pot" reaction starting from the appropriate bis-aminal cyclam intermediate. The high reactivity of quaternized aminal moiety toward nucleophilic agent has been used to elaborate a new class of cross-bridged and side-bridged cyclam derivatives containing cyanide group on the ethylene bridge. Several chelators and corresponding copper(II) complexes have been prepared and characterized by X-ray diffraction. These new constrained polyazamacrocycles are valuable precursors of bifunctional chelating agents for the preparation of PET radiotracers.

Introduction

Cyclam based chelators are well known to form highly thermodynamically and kinetically stable complexes with various metal ions, especially with copper(II) ions.[1] Several strategies based on the functionalization of the cyclam framework have been investigated for the preparation of ^{64}Cu chelator-mediated radiopharmaceuticals (radioconjugates) for Positron Emission Tomography (PET) imaging applications. Indeed, the increasing use of copper radioisotopes (^{64}Cu, ^{67}Cu) in radiopharmaceutical science has led to extensive research in this field. A new class of topologically constrained cyclams ("side-bridged" and "cross-bridged" cyclams) has been developed, appearing to be promising candidates for the preparation of stable radioconjugates.[2] The remarkable *in vivo* kinetic inertness of these compounds is due to the presence of an ethylene bridge linking two non-adjacent ("cross-bridged") or adjacent ("side bridged") nitrogen atoms, which increases the rigidity of the macrocycle.[3] The corresponding radiolabeled compounds show remarkable *in vivo* stability in comparison to the "non bridged" H_4teta (1,4,8,11-tetrazacyclotetradecane-1,4,8,11-tetraacetic acid) derivatives.[4]

The preparation of ^{64}Cu radioconjugates containing a constrained cyclam scaffold requires the presence of an additional pendant arm for covalent attachment of the chelator to the biological vector. To this aim, several BiFunctional Chelating agents (BFCs) have been prepared by using well-established functionalization methods.[5] The functionalization of a carbon in beta position of the macrocycle is particularly relevant, since the nitrogen atoms remain available for further introduction of coordinating arms.[6] However, in major cases the synthetic routes suffer from shortcomings such as multi-step processes, the preparation of sophisticated precursors as well as low overall yields.

In this work we describe a new powerful route for the preparation of original C-functionalized constrained cyclams by taking advantage of the high reactivity of quaternized aminal intermediates toward nucleophilic agents. We have recently reported the synthesis of C-functionalized [13]aneN4 and triazacyclononanes derivatives by reacting sodium cyanide with an aminal intermediate.[7] Inspired by our previous work, we decided to combine our "cyanide strategy" with the procedure commonly used for the synthesis of side- or cross-bridged cyclams, for the preparation of the first generation of reinforced cyclams functionalized on the bridge. More precisely, we present in this paper a powerful and efficient route to obtain constrained cyclams in one step from bisaminal salts, carrying one or two nitrile groups on the bridge.

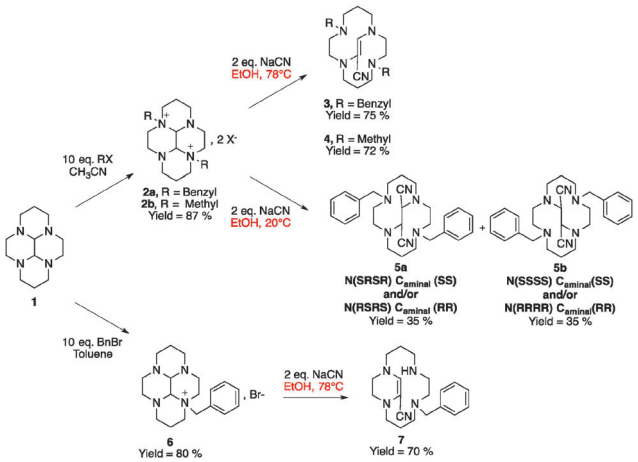
Results and discussion

Synthesis and characterization of reinforced cyclams

Constrained cyclams (1,4,8,11-tetraazacyclotetradecane) were prepared from bisaminal glyoxal cyclam **1**. Di- and mono-quaternized bisaminal salts with two or one benzyl groups were obtained by reacting **1** and alkyl halide in excess in acetonitrile or in toluene respectively, to give selectively compounds **2a**, **2b**

[a] *AgroSupDijon, UMR PAM, PCAV team, 1 Esplanade Erasme, 21000 Dijon, France. E-mail: nicolas.sok@agrosupdijon.fr*
[b] *ICMUB, UMR CNRS 6302, Université de Bourgogne Franche-Comté, 9 avenue Alain Savary, 21000 Dijon, France. E-mail: franck.denat@u-bourgogne.fr*
[c] *Chematech, 9 Avenue Alain Savary, 21000 Dijon, France*

† Electronic supplementary information (ESI) available. CCDC 1439077–1439082. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5nj03488d



Scheme 1 Synthesis of bisaminal salts **2a**, **2b**, **6**, and constrained cyclams **3**, **4**, **5a**, **5b** and **7**.

and **6** as shown in Scheme 1. This selectivity is due to the precipitation of the monoquaternized salt **6** in toluene, which prevents further alkylation.

The formation of the side bridged compound **7** could be explained by (i) the nucleophilic attack of cyanide ion on the aminal carbon atom of **6**, which is rendered highly electrophilic by the quaternization of the adjacent nitrogen atom, resulting in the cleavage of the C–N bond, (ii) the removal of the proton on the same carbon atom by CN^- or OH^-, the consequent formation of the double bond and cleavage of the bond between the second aminal carbon and an adjacent nitrogen atom, driven by the formation of a thermodynamically favored six-membered ring and the conjugated group –N–C=C–CN. The formation of the cross bridged cyclams **3** or **4** by reacting NaCN with the diquaternized bisaminal compound **2a** or **2b** can be explained by a similar mechanism: the nucleophilic substitution on one of the two equivalents aminal carbon atom as described above (step i) followed by an elimination step, in this case facilitated by the quaternization of a second nitrogen atom in trans position, which imposes the cleavage of the bond between the second aminal atom and the adjacent N^+ atom.

Compounds **3** and **4** were isolated and monocrystals have been obtained by recrystallization in diethyl ether. The chemical structure of compounds **3** and **4** were obtained by X-ray diffraction and are shown in Fig. 1.

Both structures crystallize in a centrosymetric space group ($P\bar{1}$), therefore having both enantiomers in the unit cell. In both compounds, the bridge connecting the two nitrogen atoms N2 and N4 imposes a strong constraint to the macrocycle besides to the presence of a double bond between C41–C42 and C11A–C12A atoms with a distance of 1.361(3) Å and 1.358(2) Å respectively. The orientation of the nitrogen atoms N1 and N3 are different in both structures. The benzyl groups are on the opposite side of the handle, whereas for the compound **4** the methyl group can be found sometimes on the same side and sometimes on the opposite side of the handle.

When the reaction of two equivalents of NaCN with the diquaternized bisaminal compound is performed at room

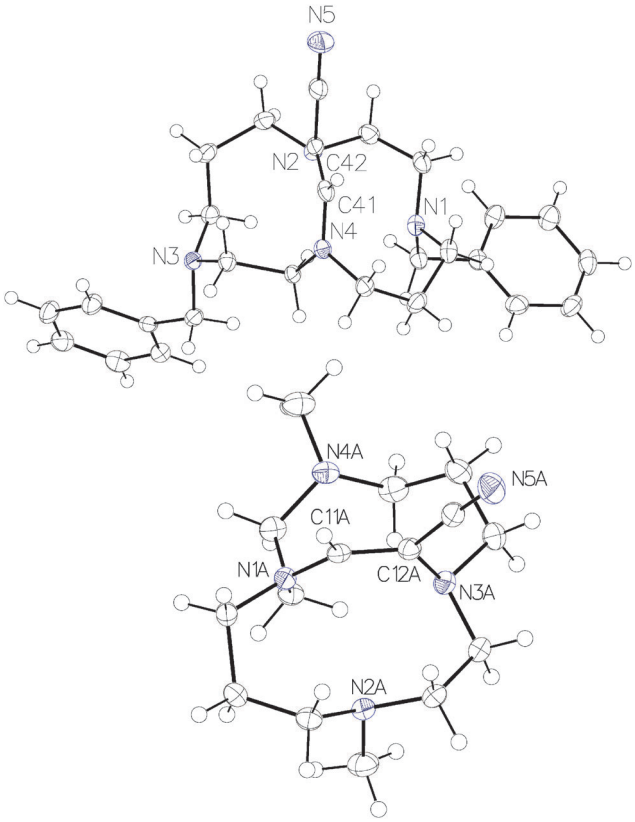


Fig. 1 ORTEP view of compound **3** (top) and **4** (down) showing thermal ellipsoids at the 50% probability level.

temperature, the elimination step is slowed and a double nucleophilic substitution mechanism is favored, resulting in the formation of two dinitrile compounds **5a** and **5b**. These two compounds could be easily separated, since **5a** crystallized in the reaction mixture. Monocrystals of **5a** and **5b** have been obtained and their X-ray structure are shown in Fig. 2. These two compounds appeared as two diastereoisomers, the chirality of the nitrogen atoms resulting from the rigidity of the macrobicyclic scaffold, which hampers the independent inversion of the two nitrogen atoms.

The compound **5a** has both benzyl groups on the same side of the bridge bearing nitrile groups, while in the compound **5b** benzyl groups were found in an opposite way to the bridge. The X-ray diffraction analysis clearly shows that the two different crystalline compounds correspond to the *meso* and *erythro* form of **5a** and **5b** respectively. They crystallize in a centrosymetric space group $C2/c$ and $P2_1/c$, which means that both enantiomers are present in each crystal.

^{1}H and ^{13}C NMR experiments were also performed to confirm the formation of the two diastereoisomers. Fig. 3 shows the superimposition of ^{1}H NMR spectra of compound **5a** and **5b**. Different signals corresponding to the diastereotopic geminal protons Ha and Hb of the CH_2 of benzyl groups can be observed. These protons appear as an AB system centered around δ = 3.50 ppm in the ^{1}H spectrum of **5a** (black line), while they give rise to two doublets at δ = 3.10 ppm and δ = 3.70 ppm in the spectrum of compound **5b** (red line). A significant difference

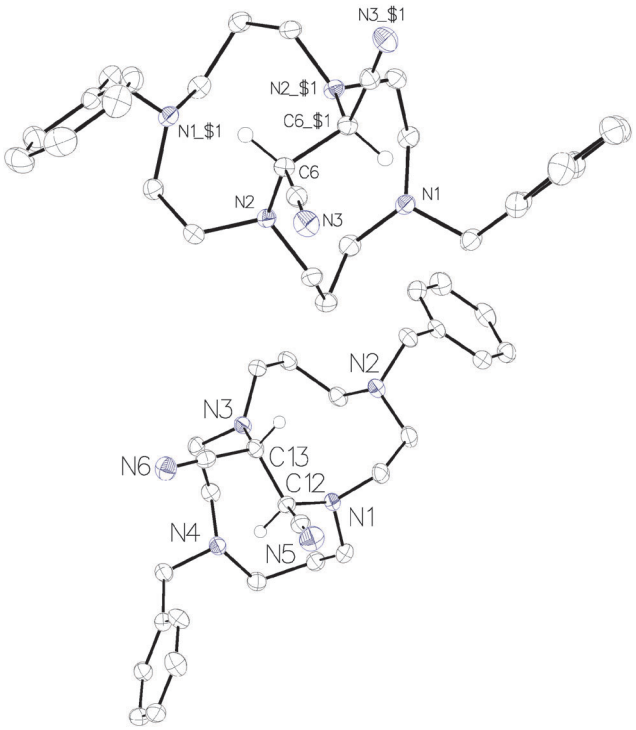


Fig. 2 ORTEP view of compound **5a** (top) and **5b** (down) showing thermal ellipsoids at the 50% probability level. Only H-atoms on the bridge were shown for clarity.

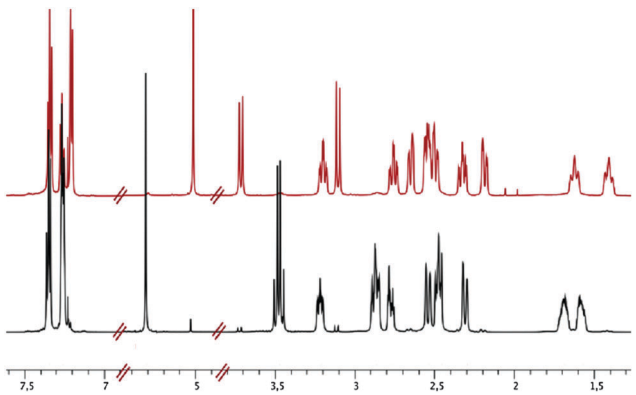


Fig. 3 Superimposition of partial ^{1}H NMR spectra (600 MHz) of compound **5a** (black) and **5b** (red) in $CDCl_3$ at 298 K.

could also be observed on the chemical shift of the signal of hydrogen on the carbon atom bearing the cyanide group. This singlet signal appears at δ = 5.60 ppm in compound **5a** and at δ = 5.00 ppm in compound **5b**.

Characterization of copper(II) complexes

Complexation of copper(II) by different constrained cyclams was performed and crystals of Cu(II) complex from compounds **4** and **5a** have been obtained. This Cu(II) cross-bridged cyclams were prepared from $Cu(NO_3)_2$ and the ligand in reflux of methanol. Both complexes adopt a folded *cis*-V configuration with the copper(II) positioning within the macrocyclic cavity.[8]

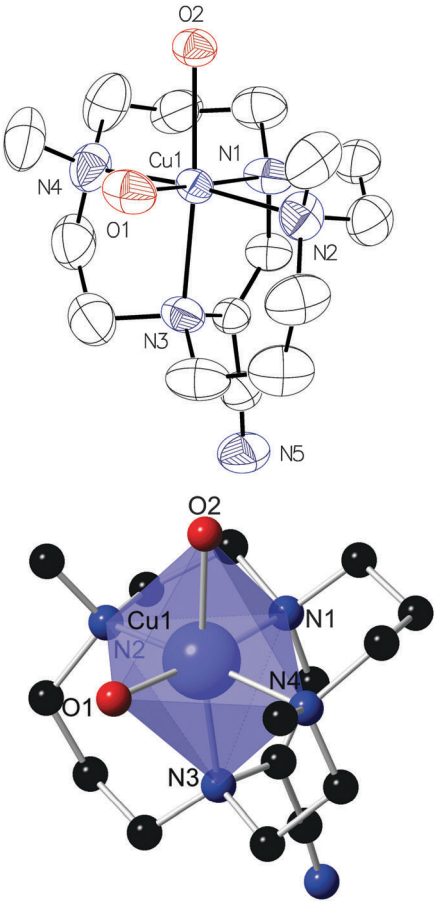


Fig. 4 ORTEP view of compound $[Cu(\mathbf{4})(H_2O)_2]^{2+}$ (top) showing thermal ellipsoids at the 50% probability level. H-atoms and nitrate counterion are omitted for clarity. View of coordination polyhedron (down). Selected bond lengths (Å): Cu1–O2 = 2.339(5), Cu1–O1 = 1.989(5), Cu1–N3 = 2.255(6), Cu1–N1 = 2.056(6), Cu1–N2 = 2.107(7), Cu1–N4 = 2.133(7).

Copper complex $[Cu(\mathbf{4})(H_2O)_2](NO_3)_2$ (Fig. 4) adopts an O_h symmetry, for which the four nitrogen atoms of the ligand and two water molecules complete the coordination sphere of the metal. The equatorial plane is determined by the three nitrogen donor atoms N1, N2, N4 and one oxygen donor atom O1. In the literature, analog complexes are available without the ethylenic bridge and form a square-based pyramid geometry where the copper coordination sphere was completed by one halogen.[9] One notices octahedron elongation in the N3–Cu1–O2 axis. This deformation is related to the d^9 copper(II) electronic configuration and reflects an energy stabilization of the complex by lowering of symmetry, according to the Jahn–Teller effect. Intermolecular hydrogen bonds between coordinated water molecules and nitrate counterion provide crystalline stability.

In the $[Cu(\mathbf{5})(NO_3)](NO_3)(CH_3OH)$ complex (Fig. 5) the coordination sphere is completed by a nitrate counterion disordered over two positions (52%/48%), instead of water molecules, and the pendant arms are directed away from the macrocycle. As a consequence, the coordination polyhedron undergone most distorded than previously. The continuous shape measure (CShM) criterion $S_Q(P)$, introduced by Avnir and co-workers,[10] reflects the minimal normalized square

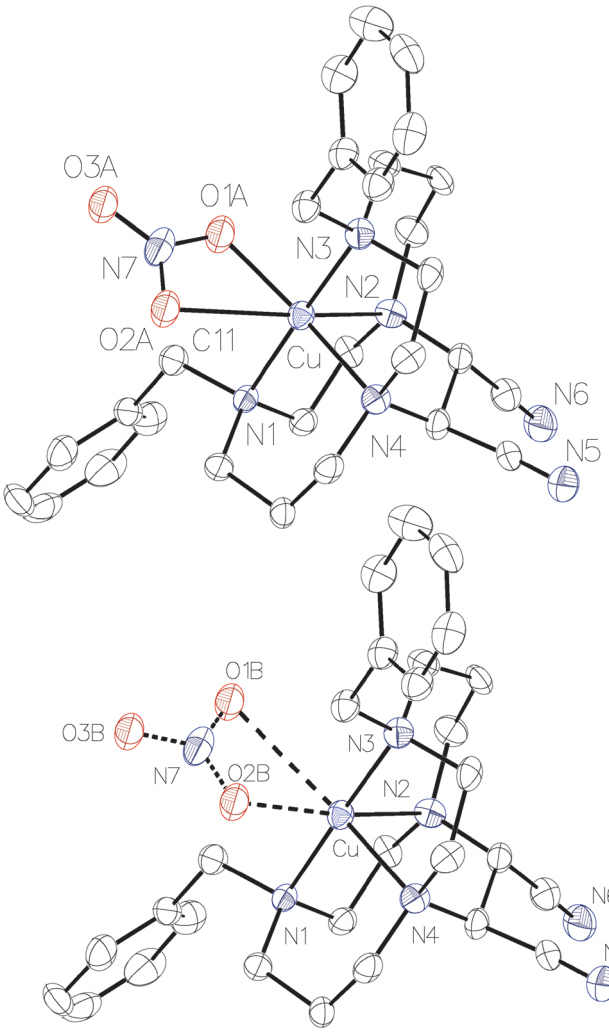


Fig. 5 ORTEP view of compound $[Cu(\mathbf{5})(NO_3)]^+$ with major disordered part (top) and minor disordered part (down) showing thermal ellipsoids at the 50% probability level. H atoms, solvent and counterion are omitted for clarity. Selected bond lengths (Å): Cu–N1 = 2.102(7), Cu1–N2 = 2.184(7), Cu–N3 = 2.079 (7), Cu–N4 = 2.120(6), Cu–O1A = 1.968(11), Cu–O2A = 2.641(12), Cu–O1B = 2.715(16), Cu–O2B = 2.042(16).

deviation between the Cartesian coordinates of each vertex that belongs to the actual coordination polyhedron Q and a perfect reference geometry P. Accordingly, $S_Q(P)$ ranges between 0 and 100, a closer structural match that gives a lower $S_Q(P)$ value. Casanova and co-workers reported shape maps and reference polyhedra for six-vertex structures. The lowest values of $S_Q(P)$ was determined, for different shape with 5 or 6 vertices, by continuous shape measure calculations using the SHAPE 2.1 Program.[11] The $S_Q(P)$ parameter for $[Cu(\mathbf{4})(H_2O)_2](NO_3)_2$ has a minimal value of 0.824 for OC-6 (Octahedron) geometry. In compound $[Cu(\mathbf{5})(NO_3)](NO_3)(CH_3OH)$, the minimal $S_Q(P)$ value was found for vOC-5 (Johnson square Pyramid (J1)) geometry. Furthermore, the distance Cu–O2A and Cu–O1B in $[Cu(\mathbf{5})(NO_3)](NO_3)(CH_3OH)$ are unusually long that confirm geometry shown in Fig. 6.

Such a coordination environment was already described in the literature by Archibald *et al.* for bis-benzyl cross-bridged cyclam derivatives coordinated to copper(II).[12] The X-ray

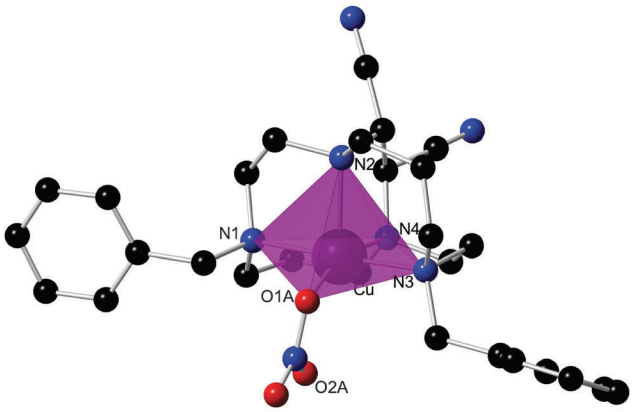


Fig. 6 View of coordination geometry of compound $[Cu(\mathbf{5})(NO_3)]^+$ with major disordered part.

structure of these complexes showed an interesting variation in the coordination environment and the potential for distortion in the Cu–N bonds of the macrocyclic chelator.

Conclusions

The work described herein reports the synthesis of a new family of constrained cyclams bearing one or two nitrile groups on the bridging unit. The reaction of two equivalents of sodium cyanide on quaternized bisaminal derivatives in ethanol at 80 °C resulted in the unexpected formation of an acrylonitrile bridge, either linking two adjacent nitrogen atoms starting from the mono-quaternized bisaminal salt, or two opposite nitrogens starting from the diquaternized bisaminal derivative. The expected dinitrile cross-bridged compound was obtained as two diastereoisomers when the reaction was performed at room temperature. The results were fully supported by X-ray structures and NMR analyses. Two copper complexes were prepared and X-ray diffraction shows that both of them adopt a folded *cis*-V conformation with the copper atom lying within the cavity of the macrobicycle, as described in the literature for crossbridged cyclams. Further work is ongoing for the preparation of bifunctional chelating agents (BFC) starting from these valuable constrained macrocyclic precursors. This will imply one or several of the following steps: (i) the removal of benzyl groups through catalytic hydrogenolysis, (ii) the introduction of coordinating acetate arm(s) on the resulting secondary amine(s), (iii) the reduction of nitrile group(s) and introduction of a suitable function to allow further bioconjugation of the BFC. Physicochemical studies will also be performed in order to evaluate the stability of the complexes and the kinetic of formation. The compounds thus obtained could represent a promising alternative to the BFC previously used for the synthesis of ^{64}Cu radioconjugates.

Experimental section

General

NMR spectra were recorded with a Bruker 300, 500, or 600 spectrometer (300, 500, or 600 MHz for ^1H; 75, 125, or 150 MHz for ^{13}C).

Chemical shifts are reported in δ ppm referenced to the residual peak of [D]chloroform (δ = 7.25 or 77.00 ppm for ^{1}H or ^{13}C). The following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br.: broad. Elemental analyses were performed at the PACSMUB at the University of Burgundy. Mass spectra were obtained by ESI (electrospray ionization) with a Bruker MicroTOF-Q spectrometer. Infrared spectra were recorded with a Bruker Vector 22 spectrometer in ATR mode.

Bisaminal cyclam **1** was purchased from Chematech SA. Compound **2a**, **2b** and **6** were prepared using the procedure detailed by Wong and Weisman.[13] All other chemicals and solvents were of analytical reagent grade and were used as received. **Caution**: NaCN is highly toxic and should be handled with care.

X-ray crystallography

CCDC deposition numbers 1439077–1439082 for compound **3**, **4**, [Cu(**4**)(H_2O)$_2$](NO_3)$_2$, **5a**, **5b** and [Cu(**5**)(NO_3)](NO_3)(CH_3OH). For each experimental structure details please refer to the ESI.† Some B alerts (short intra H···H contact) are generated for [Cu(**4**)(H_2O)$_2$](NO_3)$_2$ and [Cu(**5**)(NO_3)](NO_3)(CH_3OH) because there is poor data quality or large amount of disorder in the structure.

4,11-Dibenzyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-15-ene-15-carbonitrile (3). 0.30 g of sodium cyanide (7.80 mmol) was added to a suspension of **2a** (1.0 g, 3.9 mmol) in ethanol (20 mL) at reflux. The mixture was stirred during 2 hours. Then, the mixture was filtrated and the solvent was removed by evaporation. The compound **3** was obtained as a white powder (m = 0.54 g, 1.25 mmol, yield = 75%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ (ppm): 1.44–1.88 (m, 5H), 2.37–2.94 (m, 16H), 3.51 (m, 2H), 3.71 (m, 3H), 6.48 (s, 1H), 7.32 (m, 10H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6, 373 K) δ (ppm): 26.3, 27.3 (CH_2-β), 51.4, 51.5, 51.6, 52.7, 54.4, 55.6, 55.9, 59.0, 61.1 (CH_2-α), 118.7 (CN), 127.1, 127.2, 128.4, 129.1, 129.8, 140.1 (C alkene and C-Ar), 148.4 (CH alkene).

4,11-Dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-15-ene-15-carbonitrile (4). This compound was synthesized according to the procedure used for **3** starting from **2b** (m = 0.5 g, 0.9 mmol) and NaCN (0.1 g, 1.9 mmol). Compound **4** was obtained as colorless crystals (m = 0.2 g, 0. 72 mmol, yield = 72%). ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ (ppm): 1.35–1.59 (m, 2H), 1.67–1.82 (m, 2H), 2.20 (s, 3H), 2.29 (s, 3H), 2.34–2.91 (m, 15H), 3.07 (m, 1H), 6.38 (s, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$, 300 K) δ (ppm): 23.7, 25.7 (CH_3), 26.6 (*2) (CH_2-β), 44.8, 47.8, 51.9, 52.2, 54.6, 55.0, 55.9, 58.1, 59.9 (CH_2-α), 119.2 (CN), 140.3 (C alkene), 147.2 (CH-alkene). ESI-TOF: m/z = 300.2 [M + H]$^+$.

4,11-Dibenzyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-15,16-dicarbonitrile (5a). A suspended solution of compound **2** (3.60 g, 6.40 mmol) and NaCN (0.62 g, 12.80 mmol) in ethanol (20 mL) was stirred for 3 days at room temperature. The compound **5a** was obtained after filtration. The residual white solid was taken in chloroform (20 mL). The impurities salts were eliminated by filtration. After evaporation of solvent, the colorless oil was taken in diethyl ether, the compound **5a** was obtained as colorless crystals (m = 1.06 g, 2.30 mmol, yield = 35%). ^{1}H NMR (600 MHz, $CDCl_3$, 300 K) δ (ppm): 1.42 (m, 2H), 1.62 (m, 2H), 2.20 (m, 2H), 2.37 (m, 2H), 2.49–2.55 (m, 8H), 2.66 (m, 2H), 2.77 (m, 2H), 3.13 (bs, 2H), 3.20 (m, 2H), 3.72 (m, 2H), 7.30 (m, 10H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 300 K) δ (ppm): 25.9 (CH_2-β), 47.9, 52.6, 55.0, 57.6, 58.9, 59.0, 59.1 (CH and CH_2-α), 116.5 (CN), 127.5, 128.7, 129.2, 138.8 (CH and C-Ar). ESI-TOF: m/z = 457.31 [M + H]$^+$. IR (cm^{-1}): 2221 (CN). Elemental analysis: $C_{28}H_{36}N_6$, calculated: C (73.65%), H (7.95%), N (18.40%), found: C (73.61%), H (8.80%), N (18.27%). M_p = 193.8 ± 0.5 °C.

4,11-Dibenzyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-15,16-dicarbonitrile (5b). After isolation of compound **5a**, filtrate was concentrated. The residual oil was taken in methanol. The compound **5b** was obtained as colorless crystals after slow evaporation of solvent (m = 1.06 g, 2.30 mmol, yield = 35%). ^{1}H NMR (600 MHz, $CDCl_3$, 300 K) δ (ppm): 1.58 (m, 2H), 1.69 (m, 2H), 2.31 (m, 2H), 2.47 (m, 4H), 2.54 (m, 2H), 2.77 (m, 2H), 2.87 (m, 4H), 3.22 (m, 2H), 3.48 (m, 4H), 5.31 (s, 2H), 7.26 (m, 6H), 7.35 (m, 4H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 300 K) δ (ppm): 29.2 (CH_2-β), 53.2, 53.6, 54.9, 56.7, 60.2, 60.7 (CH and CH_2-α), 116.9 (CN), 127.7, 128.7, 129.3, 138.8 (C-Ar). ESI-TOF: m/z = 457.31 [M + H]$^+$.

5-Benzyl-1,5,8,12-tetraazabicyclo[10.2.2]hexadec-15-ene-15-carbonitrile (7). This compound was synthesized according to the procedure used for the synthesis of **3** starting from compound **6** (1.94 g, 4.94 mmol) and NaCN (0.48 g, 10.0 mmol). The compound **7** was obtained as a colorless oil (m = 1.32 g, 3.90 mmol, yield = 70%). ^{1}H NMR (600 MHz, $CDCl_3$, 300 K) δ (ppm): 1.72 (m, 3H), 1.91 (m, 1H), 2.22 (m, 1H), 2.37 (m, 1H), 2.45 (m, 2H), 2.55 (m, 2H), 2.70 (m, 1H), 2.84–3.17 (m, 8H), 3.38 (m, 2H), 3.60 (m, 2H), 6.48 (s, 1H), 7.23 (m, 5H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 300 K) δ (ppm): 25.8, 28.2 (CH_2-β), 43.9, 46.6, 47.7, 48.2, 50.2, 51.7, 53.3, 56.5, 58.3 (CH_2-α), 120.9 (CN), 126.8, 128.1, 128.9, 135.7 (C alkene and C-Ar), 139.1 (CH-alkene). ESI-TOF: m/z = 340.24 [M + H]$^+$.

Preparation of complexes [Cu(4)(H_2O)$_2$](NO_3)$_2$ and [Cu(5)(NO_3)](NO_3)(CH_3OH). Compounds [Cu(**4**)(H_2O)$_2$](NO_3)$_2$ and [Cu(**5**)(NO_3)](NO_3)(CH_3OH) were obtained as blue crystals after cooling of a solution of Cu(NO_3)$_2$ (0.08 mmol) in 2 mL MeOH and of compound **4** or **5a** (0.08 mmol) in 15 mL of MeOH heated at reflux during 30 min.

Acknowledgements

Support was provided by the CNRS, the University of Burgundy and the Conseil Régional de Bourgogne through the 3MIM Project. N. S. and C. B. thank the French Ministry of Research for PhD Grant.

References

1 T. J. Wadas, E. H. Wong, G. R. Weisman and C. J. Anderson, *Chem. Rev.*, 2010, **111**, 2858–2902; E. K. Barefield, *Coord. Chem. Rev.*, 2010, **254**, 1607–1627; X. Liag and P. J. Sadler, *Chem. Soc. Rev.*, 2004, **33**(4), 246–266.

2 C. Cutler, H. Hennkens, N. Sisay, S. Huclier-Markai and S. Jurisson, *Chem. Rev.*, 2013, **113**, 858–883; S. P. Donnelly,

Dalton Trans., 2011, **40**, 999–1010; H. Cai, J. Fissekis and P. S. Conti, *Dalton Trans.*, 2009, 5395–5400; E. W. Price and C. Orvig, *Chem. Soc. Rev.*, 2014, **43**, 260–290; C. F. Ramogida and C. Orvig, *Chem. Commun.*, 2013, **49**, 4720–4739; M. Shokeen and C. J. Anderson, *Acc. Chem. Res.*, 2009, **42**, 832–841; D. N. Pandya, J. Y. Kim, J. C. Park, H. Lee, P. B. Phapale, W. Kwak, T. H. Choi, G. J. Cheon, Y. R. Yoon and J. Yoo, *Chem. Commun.*, 2010, **46**, 3517–3519.

3 T. J. Hubin, *Chem. Rev.*, 2003, **242**, 27–46; D. Zeng, Q. Ouyang, Z. Cai, X. Xie and C. J. Anderson, *Chem. Commun.*, 2014, **50**, 43–45; C. A. Boswell, C. A. S. Regino, K. E. Baidoo, K. J. Wong, A. Bumb, H. Xu, D. E. Milenic, J. A. Kelley, C. C. Lai and M. W. Brechbiel, *Bioconjugate Chem.*, 2008, **19**, 1476–1484; R. Ferdani, D. J. Stigers, A. L. Fiamengo, L. Wei, B. T. Y. Li, J. A. Golen, A. L. Rheingold, G. R. Weisman, E. H. Wong and C. J. Anderson, *Dalton Trans.*, 2012, **41**, 1938–1950; L. M. P. Lima, Z. Halime, R. Marion, N. Camus, R. Delgado, C. Platas-Iglesias and R. Tripier, *Inorg. Chem.*, 2014, **53**, 5269–5279.

4 C. A. Boswell, X. Sun, W. Niu, G. R. Weisman, E. H. Wong, A. L. Rheingold and C. J. Anderson, *J. Med. Chem.*, 2004, **47**, 1465–1474.

5 E. A. Lewis, R. W. Boyle and S. J. Archibald, *Chem. Commun.*, 2004, 2212–2213.

6 S. J. Archibald, *Annu. Rep. Prog. Chem., Sect. A: Inorg. Chem.*, 2011, **107**, 274–296; E. A. Lewis, R. K. Boyle and S. J. Archibald, *Chem. Commun.*, 2004, 2212–2213; Z. Halime, M. Frindel, N. Camus, P.-Y. Orain, M. Lacombe, M. Chérel, J.-F. Gestin, A. Faivre-Chauvet and R. Tripier, *Org. Biomol. Chem.*, 2015, **13**, 11302–11314; N. Camus, Z. Halime, N. Le Bris, H. Bernard, C. Platas-Iglesias and R. Tripier, *J. Org. Chem.*, 2014, **79**(5), 1885–1899.

7 Y. Rousselin, N. Sok, F. Boschetti, R. Guilard and F. Denat, *Eur. J. Org. Chem.*, 2010, 1688–1693; P. Désogère, Y. Rousselin, S. Poty, C. Bernhard, C. Goze, F. Boschetti and F. Denat, *Eur. J. Org. Chem.*, 2014, 7831–7838.

8 B. Bosnich, C. K. Poon and M. L. Tobe, *Inorg. Chem.*, 1965, **4**, 1102–1108.

9 T. J. Hubin, J. McCormick, N. W. Alcock, H. J. Clase and D. H. Busch, *Inorg. Chem.*, 1999, **38**, 4435–4446.

10 D. Casanova, M. Llunell, P. Alemany and S. Alvarez, *Chem. – Eur. J.*, 2005, **11**, 1479–1484; H. Zabrodsky, S. Peleg and D. Avnir, *J. Am. Chem. Soc.*, 1992, **114**, 7843–7851; M. Pinsky and D. Avnir, *Inorg. Chem.*, 1998, **37**, 5575–5582.

11 M. Llunell, D. Casanova, J. Cirera, P. Alemany and S. Alvarez, *SHAPE Program v. 2.1*, University of Barcelona, Spain, 2013.

12 J. D. Silversides, B. P. Burke and S. J. Archibald, *C. R. Chim.*, 2013, **16**, 524–530.

13 E. H. Wong, G. R. Weisman, D. C. Hill, D. P. Reed, M. E. Rogers, J. S. Condon, M. A. Fagan, J. C. Calabrese, K.-C. Lam, A. Guzei and A. L. Rheingold, *J. Am. Chem. Soc.*, 2000, **122**, 10561–10572.

