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Full Control of the Regiospecific *N*-Functionalization of *C*-Functionalized Cyclam Bisaminal Derivatives and Application to the Synthesis of their TETA, TE2A, and CB-TE2A Analogues

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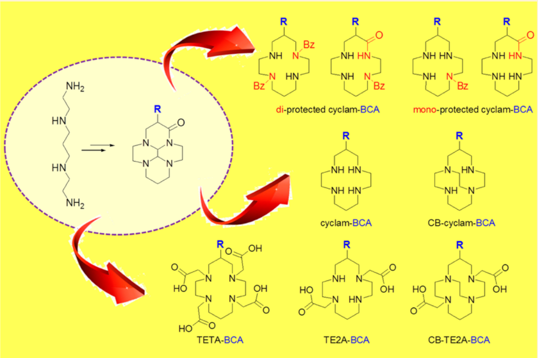
Supporting Information



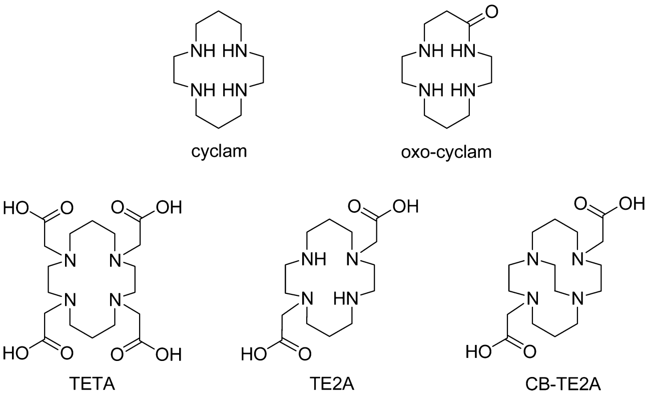
ABSTRACT: We describe an easy synthesis of original *C*-functionalized cyclam derivatives based on the efficient bisaminal template method. In the perspective of developing bifunctional chelating agents (BCAs), this new synthetic strategy offers the possibility of introducing various coupling functions on one carbon atom in the *β-N* position of the macrocycle, leaving the four nitrogen atoms available for the introduction of pendant coordinating arms. The methodology is based on a keystone *C*-functionalized oxo-cyclam bisaminal intermediate that is obtained by cyclization of a preorganized tetraamine using various methyl acrylate analogues. These compounds constitute valuable precursors for selective preparation of mono- and di-*N*-protected *C*-functionalized cyclams and *C*-functionalized cyclams, cross-bridged cyclams, and oxo-cyclam derivatives. This approach was successfully adapted to the synthesis of three BCAs with great interest especially for biomedical applications: TETA, TE2A, and CB-TE2A. The structures of different intermediates and Cu(II) complexes of *C*-functionalized cyclam derivatives were confirmed using single-crystal X-ray diffraction, while reactivity of the key intermediates was rationalized by the analysis of the electrostatic potentials calculated at the TPSSh/6-311G(d,p) level.

■ INTRODUCTION

In the past few decades, significant progress has been achieved in the field of nuclear medicine to find stable chelates for radioactive metal ions, particularly ^{68}Ga, ^{64}Cu, ^{99m}Tc, and ^{67}Cu.[1−5] The use of these radioisotopes for positron emission tomography (PET), single photon emission computed tomography (SPECT), and radio immunotherapy (RIT) requires the development of specific ligands able to form complexes of radioactive metal ions with high thermodynamic, kinetic, and electrochemical stability to avoid their trans-chelation in competitive biological media.[1]

Tetraazamacrocycles such as cyclam (Chart 1) are renowned as efficient chelating agents for numerous metal ions.[2] Owing to the presence of secondary amine functions, these macrocycles can be *N*-functionalized[3] with various coordinating groups, which allows the preparation of a wide range of ligands suitable for many applications such as molecular recognition, catalysis, purification of liquids, and the development of metal-based imaging and therapeutic agents in medicine.[4] In particular, *N*-functionalized cyclam derivatives such as TETA, TE2A, and CB-TE2A were chosen as Cu(II) chelators for radiolabeling applications (Chart 1).[5] These compounds were preferred to the well-known commercially available DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) because of their favorable coordinating properties: TETA or TE2A form Cu(II) complexes with very high thermodynamic stability[6] while CB-TE2A[7] provides complexes with exceptional inert-

Chart 1



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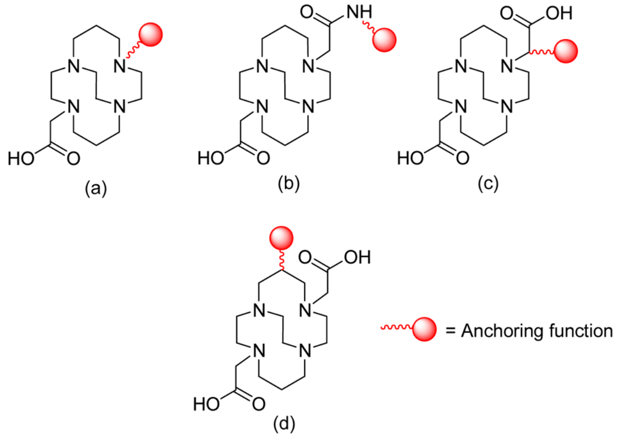
ness, which prevents their dissociation following either an acid-catalyzed pathway or a reduction of Cu(II) to Cu(I).[8] Among the other cyclam derivatives, oxo-cyclams containing one amide function in the cyclam backbone (Chart 1), first used as monoprotected macrocycles, have also been the subjects of numerous studies on ^{99m}Tc complexation for SPECT applications.[9]

However, many applications require a bifunctional chelating agent (BCA) bearing an additional specific group on the macrocyclic structure able to hold the ligand fixed on a solid support[10] (silica gel, resins, electrodes, nanoparticles...) or on specific biomolecular vectors[11] (antibodies, haptens, peptides, proteins...) for PET, SPECT, or RIT applications. Unlike cyclam or TE2A where the available secondary amines can be used to introduce a new coupling function, ligands such as TETA and CB-TE2A are incompatible for such applications. Different strategies were described in the literature to overcome this limitation: (a) the replacement of one of coordinating arms with coupling function;[12] (b) the modification of a coordinating group for instance by replacing a carboxylate function by an amide;[13] and (c) the introduction of a pendant arm bearing both the chelating group and the coupling function (Chart 2).[14]

Chart 2. Different Types of Cyclam-Based BCAs (Example of CB-TE2A)



The major drawbacks of approaches a and b are that both the removal of a coordinating arm and the introduction of an amide function, to replace a carboxylate group, are expected to decrease the binding affinity of the ligand toward a metallic ion. Strategy C, requires the previous preparation of the bifunctional arm in parallel with the synthesis of the macrocycle, which leads to overall poor yields. An alternative strategy is to introduce the coupling function on a carbon atom of the carbon skeleton such as in model compound d (Chart 2). An important advantage of this approach is that the additional anchoring group can be directly introduced during the cyclization step, thereby reducing the number of synthetic steps compared to traditional synthesis of these types of macrocycles.

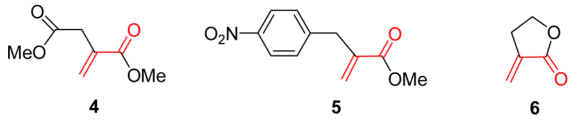
One of the best known methods for the synthesis of such tetraazamacrocycles (d) is the condensation of *N*-tosyl derivatives of linear tetraamines with a *C*-functionalized bis-electrophile such as a ditosylate.[15] Nevertheless, this method necessitates in the last deprotection step a strong acidic medium leading to low yields. Alternatively, *C*-functionalized cyclams can also be obtained by the condensation of a linear tetraamine with *C*-functionalized malonic esters. However, this type of condensation requires long reaction times and often gives low yields.[16] Another original way is the annelation reaction between an α,β-unsaturated ester and a linear tetraamine, with the pendant arm being provided either by the cyclizing reagent or by the polyamine.[17] The idea of a template effect induced by rigidifying a linear tetraamine by condensation with a dicarbonyl compound followed by the cyclization of the resulting bisaminal with a biselectrophilic reagent[18] emerged 20 years ago as a powerful synthetic tool for the synthesis of tetraazacycloalkanes and their selective *N*-functionalization.[19] Surprisingly, this approach has been scarcely employed for the preparation of *C*-functionalized macrocycles. To our knowledge, only two close examples have recently been simultaneously reported.[20,21] In these studies, the bisaminal bridge can be easily removed after the cyclization to give rise to cyclams bearing *C*-appended ester, acid, hydroxymethyl, or 4-nitrobenzyl groups with good yields. However, the limited availability of such cyclizing reagents is probably one of the reasons for the lack of applications of this strategy for the preparation of BCAs. Thus, the development of direct and efficient synthetic pathways for the preparation of bifunctional cyclam-based ligands constitutes a challenge of great importance in the field of azamacrocyclic chemistry.

In this paper, we report the synthesis of new bifunctional chelating agents, analogues of the cyclam-based macrocycles shown in Chart 1, as well as various regioselectively mono- and diprotected cyclams. Our method consists in the cyclization of the bisaminal of the linear tetraamine 1,4,8,11-tetraazaundecane with functionalized-α,β-unsaturated esters through the reaction of the secondary amines of the bisaminal via both an aza-Michael addition and a nucleophilic addition/elimination while generating an appended arm on the carbon skeleton.[22] This simple reaction leads to a new class of *C*-functionalized oxo-cyclam bisaminals, the keystone of our methodology. The bisaminal chemistry can subsequently be applied to these intermediates providing access to oxo-, "naked-", or mono-*N*-benzylated *C*-functionalized cyclam derivatives that constitute valuable precursors for the synthesis of macrocycles of major interest. X-ray diffraction studies were used to confirm the structure and the stereochemistry of each intermediate. In addition, DFT calculations were used to rationalize the reactivity of these intermediates. Finally, we also report X-ray structures of several Cu(II) complexes synthesized to investigate the influence of the coupling function on the complex structure. The overall methodology is presented in four parts: (i) synthesis of *C*-functionalized oxo-cyclam bisaminal derivatives; (ii) regiospecific mono- and di-*N*-protections of *C*-functionalized cyclam derivatives and extension to the synthesis of *C*-functionalized oxo-, "naked-", and cross bridged-cyclams; (iii) synthesis of *C*-functionalized TETA, TE2A, and CB-TE2A derivatives; and (iv) preliminary Cu(II) complexation studies.

■ RESULTS AND DISCUSSION

Synthesis of *C*-Functionalized Oxo-cyclam Bisaminal Derivatives. Our strategy consists in the cyclization of the preorganized tetraamine **1**, in its *cis*-bisaminal intermediate form **3**, with derivatives of methyl acrylate in order to achieve *C*-functionalization on the macrocycle skeleton. Cyclizing reagents **4**−**6** (Chart 3) are, respectively, the precursors of a methyl acetate, a 4-nitrobenzyl, or a hydroxyethyl group in α position of the carbonyl group of oxo-macrocycles **7**−**9** (Scheme 1). Compounds **4** and **6** are commercially available,

Chart 3. Cyclizing Reagents 4−6



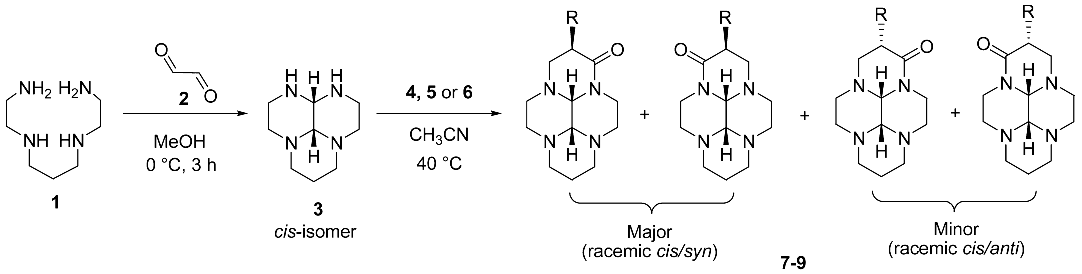
while **5** was synthesized according to previously described procedures.[23]

The synthesis of bisaminal **3** in its *cis*-configuration was performed using glyoxal **2** in methanol at 0 °C to minimize the formation of the undesirable *trans*-isomer because, to our knowledge, there is no known method for the deprotection for the *trans*-bisaminal bridge of azamacrocycles.[19d] The cyclization step involving reagents **4−6** was initially carried out in methanol as a conventional solvent for Michael-type reactions. ^{13}C NMR spectra of the crude reaction mixtures revealed the presence of two *cis*-diastereoisomers which differ by the relative position (*syn* or *anti*) of the chain R with respect to the hydrogen atom of the closer aminal carbon. However, small amounts of *trans*-isomers (about 20%) were also formed by isomerization of the bisaminal bridge during the cyclization step. All our attempts to isolate one of the *cis*-isomers were unsuccessful. Moreover, several byproducts resulting from the reaction between cyclizing reagents and methanol were observed. Further investigations showed that this undesired reaction occurs only under a basic catalysis such as that of the cyclization reaction medium. For all these reasons, the cyclization step of bisaminal **3** by reagents **4−6** was carried out in a less basic medium such as acetonitrile (Scheme 1).

Under these reaction conditions, only one of the *cis*-diastereoisomers (as a racemic mixture) was obtained exclusively with trace amounts of *trans*-isomers (<5%). However, ^{13}C NMR monitoring of the cyclization reaction revealed the formation of the other *cis*-isomer in the early stages of the reaction, which then disappeared. This can be explained by the reversible formation of this isomer through a retro-Michael reaction, which finally led to the formation of the most stable isomer. Compounds **8** and **9** progressively precipitated from the corresponding reaction mixtures and were isolated in 62% and 65% yield, respectively, while compound **7** was isolated in 30% yield after recrystallization from diethyl ether. Single crystals suitable for X-ray diffraction analysis were obtained for the three compounds. The X-ray structures of these compounds revealed the relative *syn*-position of the R groups with respect to the bisaminal bridge (Figure 1). In the case of compound **9**, the two *cis*/*syn* enantiomers with configurations *RRS* (C2, C11, and C12) and *SSR* (C22, C31, and C32) are present in the asymmetric unit. Compounds **7** and **8** also crystallize as racemic mixtures in which the two enantiomers are centrosymmetrically related. Density functional theory (DFT) calculations performed at the TPSSh/6-311G(d,p) level on **9** indicated that the *cis*/*syn*-isomer is more stable than the *cis*/*anti* one by 23.3 kJ·mol^{-1}. These results suggest that the cyclization step proceeds under thermodynamic control. One can note that reagents **4** and **5** necessitate longer reaction times than **6** (Table 1). This difference can be explained by the superior reactivity of **6** probably due to its cyclic nature blocked in synperiplanar conformation, which favors to the formation of the macrocycle. Moreover, the reaction yields are significantly higher with reagents **5** and **6** than with **4**. This result may be attributed to the progressive precipitation of **8** and **9** in the reaction medium, which displaces the equilibrium toward the formation of the macrocycle.

Regiospecific Mono- and Di-*N*-protections of *C*-Functionalized Cyclam Derivatives and Extension to the Synthesis of *C*-Functionalized Oxo-, "Naked-", and Cross-Bridged Cyclams. Regiospecific *N*-alkylation reactions of cyclam derivatives are a synthetic challenge, which prompted us to study the reactivity of *C*-functionalized oxo-macrocycle bisaminals toward electrophilic reagents. We focused our efforts on the derivative containing the hydroxyethyl group **9** due to its relatively fast synthesis and its inertness toward various solvents, electrophiles, or deprotecting reagents used for the *N*-functionalization of the macrocycle. In order to determine the influence of the amide group on the reactivity of **9**, the *C*-functionalized cyclam bisaminal analogue **10** was also synthesized using $NaBH_4$ according to a previously described procedure (Scheme 2).[24] Compounds **9** and **10** were reacted with benzyl bromide, a reagent of interest owing to its high reactivity and the easy removal of benzyl groups by Pd-catalyzed hydrogenolysis. The stoichiometric reaction of the electrophile on the oxo-macrocycle **9** in dry dichloromethane led quantitatively to the mono-*N*-benzylated derivative **11** as a white precipitate. Even when the reaction is performed in a solvent where **11** is completely soluble, such as acetonitrile, or in the presence of an excess of electrophile, no dialkylated compound was observed. These results make the new compound **9** a key intermediate for the regiospecific mono-*N*-functionalization of such *C*-functionalized cyclams. In contrast, the reaction of stoichiometric benzyl bromide with **10** gave, as expected, a mixture of two mono-*N*-benzylated regioisomers **12** and **12′** in an approximate 1:1 ratio (determined by NMR). Thus, compound **10** presents the

Scheme 1



$R = CH_2CO_2Me$ (**7**)
$CH_2C_6H_4NO_2$ (**8**)
CH_2CH_2OH (**9**)

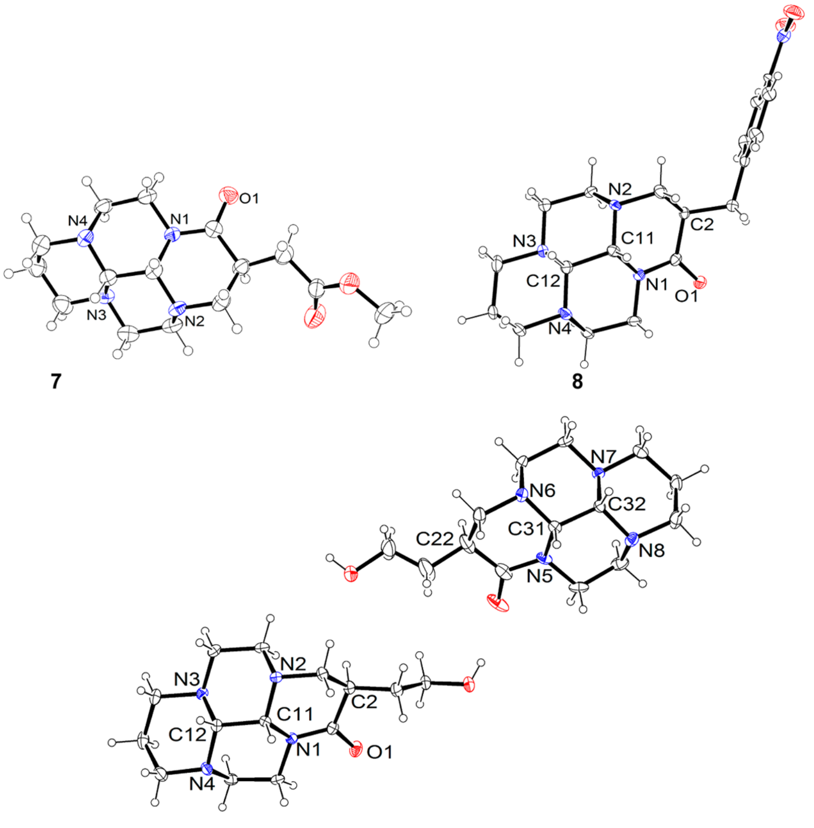
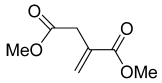
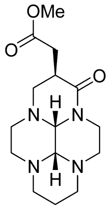
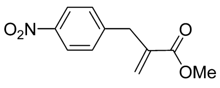
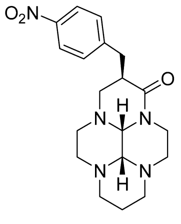
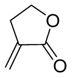
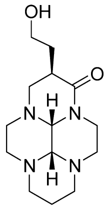
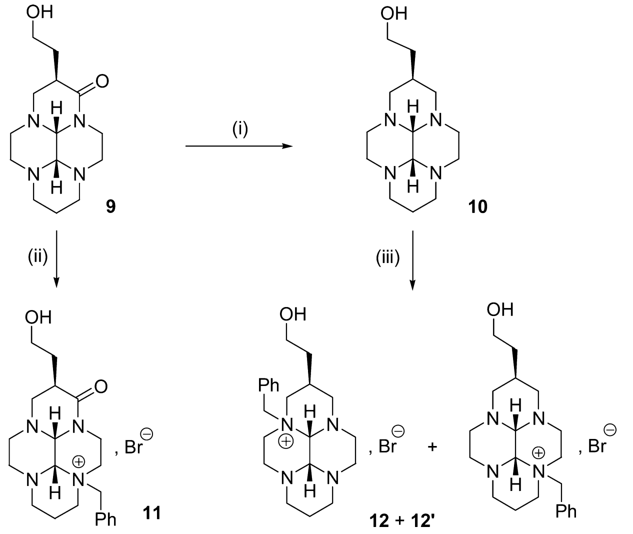


Figure 1. Views of the crystal structures of **7**−**9**. The ORTEP plots are at the 30% probability level.

Table 1. Isolated Compounds for the Cyclization of 3 with 4−6 in CH_3CN

Cyclizing reagent	Reaction time	Oxo-macrocycle	Yield
 **4**	8 days	 **7**	30%
 **5**	7 days	 **8**	62%
 **6**	4 days	 **9**	65%

Scheme 2[a]



[a]Reagents and conditions: (i) $NaBH_4$, H_2O, rt, 18 h, 90%; (ii) $PhCH_2Br$ (4 equiv), CH_2Cl_2, rt, 18 h, 98%; (iii) $PhCH_2Br$ (1 equiv), CH_2Cl_2, rt, 18 h, 90%.

same reactivity as the “naked” cyclam-glyoxal with two reactive nitrogen atom lone pairs situated in *trans*-positions. This result shows that the presence of the hydroxyethyl substituent in **10** does not affect its reactivity toward *N*-alkylation reactions (Scheme 2).

The structure of **11** was established by 2D NMR experiments (see HMBC $^1H-^{15}N$, HMQC/HMBC $^1H-^{13}C$, and COSY and TOCSY $^1H-^1H$ in the Supporting Information). These correlation experiments clearly confirmed the presence of the benzyl group on N4. The most significant structural information was gained from the HMBC $^1H-^{13}C$ spectrum, which exhibits a correlation between one of the diastereotopic hydrogen atoms on the carbon atom on *β* position with respect to the nitrogen of the amide group and the carbon atom on the benzylic position. In addition, slow evaporation of an aqueous solution of the ammonium salt gave single crystals of the bisaminal compound suitable for X-ray diffraction analysis (Figure 2). The crystal data confirm that *N*-benzylation occurred on N4. In addition, *N*-alkylation does not affect the configuration of the molecule, which retains its *cis*/*syn*-stereochemistry with the hydroxyethyl group in an equatorial position. Compound **11** crystallizes as a trihydrate, where two water molecules are involved in hydrogen-bonding interactions with the hydroxyl group and the third one with N2 and the bromide anion (Figure 2).

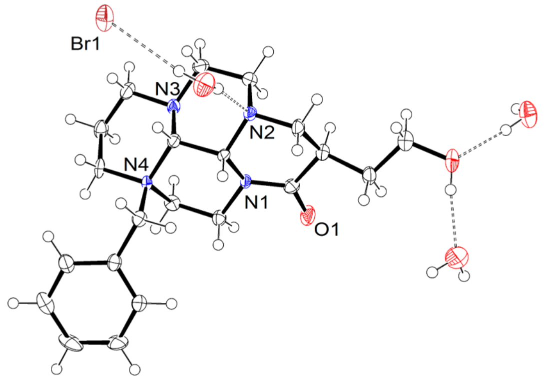


Figure 2. View of the crystal structure of **11**·$3H_2O$. The ORTEP plot is at the 30% probability level.

Theoretical studies were conducted in order to rationalize the reactivity of the oxo-macrocycle **9** with electrophilic reagents. Full geometry optimizations of **9** using DFT calculations (TPSSh functional) show a molecular geometry very similar to the corresponding X-ray structure described above. Subsequent molecular orbital calculations indicate that the HOMO of **9** presents very important contributions of the N2, N3, and N4 lone pairs, while the LUMO is mainly localized on the amide group. The lone pairs of N2 and N4 are pointing to the convex side of the molecule, while the lone pair of N3 points to the concave side. Consequently, N2 and N4 are expected to exhibit a more pronounced nucleophilic character (Figure 3). Molecular electrostatic potential (MEP)[25] calculations represent a well-established tool for investigating chemical reactivity, intermolecular interactions, and a range of other chemical phenomena.[26] Figure 3 shows the electrostatic potential on the molecular surfaces of compound **9** at the density functional TPSSh/6-311G(d,p) level, defined by the 0.001 electrons·bohr^{-3} contour of the electron density following the suggestion of Bader.[27] As expected, the most negative electrostatic potential on the molecular surface of this system is located at the oxygen atoms of the hydroxyl and the carbonyl groups. In addition, a region with substantial negative electrostatic potential is observed for N2, and particularly for N4, on the convex side of the molecule. Furthermore, the contribution of the N4 lone pair to the HOMO (41.6% according to Mulliken population analysis) is clearly higher than that of N2 (5.1%) and N3 (15.9%). These results point to a higher reactivity of N4 toward nucleophilic substitution compared to N2 and particularly N3 (Figure 3).

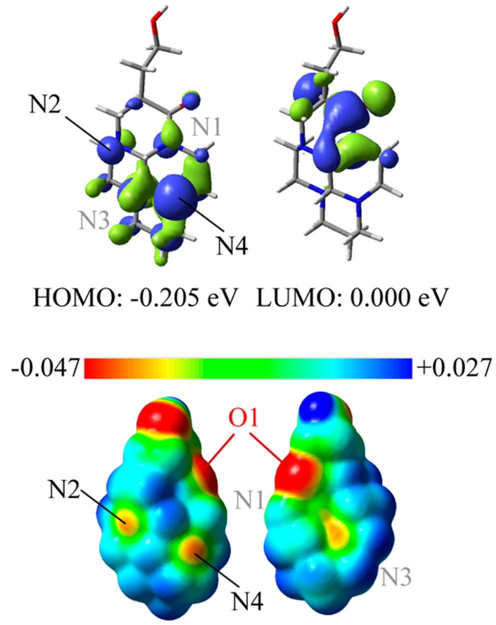
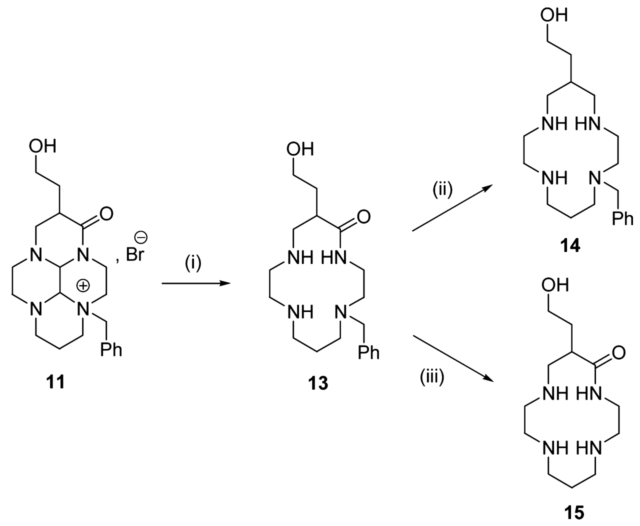


Figure 3. (Top) Calculated isosurface (0.03 au) of the HOMO and LUMO obtained from TPSSh/6-311G(d,p) calculations for **9**. (Bottom) Computed TPSSh/6-311G(d,p) electrostatic potential (hartree) of **9** on the molecular surface defined by the 0.001 electrons·bohr^{-3} contour of the electronic density.

The bisaminal bridge of monobenzylated compound **11** was easily removed using hydrazine monohydrate in ethanol to give monobenzyl oxo-cyclam derivative **13** with 70% yield (Scheme 3). Single crystals of **13** as a hydrobromide salt were obtained from the crude reaction mixture. The X-ray structure shows that the macrocycle is protonated on N3, which is involved in a hydrogen-bond interaction with the bromide anion (Figure 4).

Scheme 3[a]



[a]Reagents and conditions: (i) $NH_2NH_2\cdot H_2O$, EtOH, reflux, 4 h, 70%; (ii) $BH_3\cdot THF$ (4 equiv), THF, reflux 1.5 d; 72%; (iii) H_2, Pd/C, EtOH, rt, 4 d, 85%.

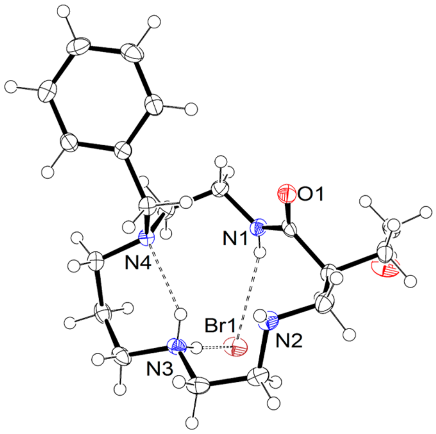


Figure 4. View of the crystal structure of **13**·HBr. The ORTEP plot is at the 30% probability level.

Compound **13** can be considered a *cis*-diprotected macrocycle because of the presence of both the amide function on N1 and the benzyl group on N4. Interestingly, these protections can be removed independently. Indeed, the reduction of the amide group of **13** was achieved using $BH_3\cdot THF$ to give the mono-*N*-benzylated cyclam derivative **14** with 72% yield, while Pd-catalyzed hydrogenolysis of **13** led to oxo-cyclam-EtOH **15** with 85% yield ("EtOH" is mentioned as suffix to characterize the nature of the additional chain). Because of their different protected positions and protecting groups, the new *C*-functionalized macrocycles **13**−**15** represent useful precursors for various regiospecific *N*-functionalizations. Additionally, as explained previously, oxo-cyclams can be attractive chelators for metal radioisotopes such as ^{99m}Tc[9] or transition-metal ions,[2] which also make them interesting BCAs for different applications.

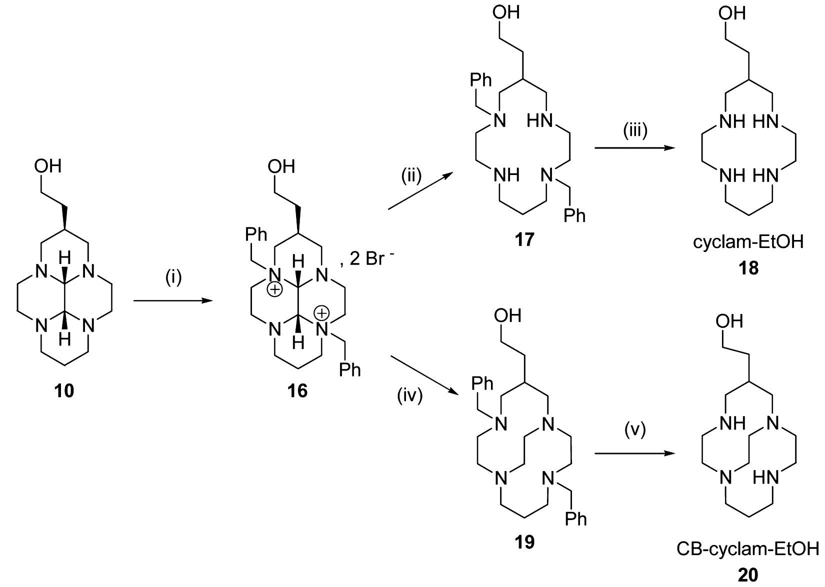
The results obtained with the stoichiometric reaction of benzyl bromide with bisaminal derivative **10** (Scheme 2) prompted us to explore the di-*N*-functionalization of this compound using an excess of electrophile. For this purpose, we used 10 equiv of electrophile and chose dry acetonitrile as a solvent. Under such conditions, the mono-*N*-benzylated intermediates **12** and **12′** are completely soluble and continue to react with the electrophile to form the expected *trans*-di-*N*-alkylated salt **16**, which is obtained as a white precipitate with 86% yield (Scheme 4). Single crystals of **16**·$2H_2O$ were obtained from a saturated aqueous solution of the compound. The X-ray diffraction data confirm the *trans*-dialkylation of the macrocycle (Figure 5).

The total deprotection of the bisaminal bridge of compound **16** was performed using hydrazine monohydrate to give the di-*N*-benzylcyclam derivative **17** with 85% yield. Compound **17** can be considered a precursor of *trans*-difunctionalized cyclam-based ligands (see below). The benzyl groups of **17** were then removed by Pd-catalyzed hydrogenolysis to give the *C*-functionalized cyclam (cyclam-EtOH) **18** with 75% yield. On the other hand, the partial cleavage of the bisaminal bridge of **16** was achieved with $NaBH_4$ in ethanol to give the cross-bridged cyclam analogue. The ^{13}C NMR spectrum of the crude reaction product showed two sets of signals with similar chemical shifts in an approximate 9:1 ratio. The major compound was recrystallized in acetonitrile with 85% yield. The elemental analysis showed that **19** was isolated in its nonprotonated form. Most likely the minor compound, soluble in acetonitrile, is a protonated species of **19** as often reported in the literature for cross-bridged tetraazamacrocycles, which are known to behave as proton sponges.[28] An elemental analysis performed on the crude reaction mixture of **19** revealed the presence of small amounts of bromide anion (about 4%), which is consistent with the hypothesis of the presence of a minor monoprotonated species of the cross-bridged cyclam analogue. Compound **19** was then debenzylated by hydrogenolysis to give the corresponding reinforced macrocycle CB-cyclam-EtOH **20** as a free base with 88% yield.

Synthesis of *C*-Functionalized TETA-EtOH, TE2A-EtOH, and CB-TE2A-EtOH. As described in the previous section, cyclam derivatives **17**, **18**, and **20** constitute key intermediates for the synthesis of a wide range of *C*-functionalized BCAs. Thus, we decided to *N*-functionalize these compounds with acetate functions in order to obtain *C*-functionalized TETA, TE2A, and CB-TE2A analogues as efficient Cu(II) chelators. The alkylation of the secondary amino functions of these macrocycles by *tert*-butyl bromoacetate led to TE2AtBu-EtOH **21b** (via the removal of *N*-benzyl protecting groups of **21a** by Pd-catalyzed hydrogenolysis), TETAtBu-EtOH **22**, and CB-TE2AtBu-EtOH **23** with very good yields (Scheme 5). Because of its remarkably basic character and its proton sponge behavior, the cross-bridged derivative **23** was exclusively isolated as its monohydrobromide salt. The ^1H NMR analysis of **23** confirms the presence of the hydrogen atom inserted into the cleft of the ligand with a characteristic downfield-shifted broad resonance at 10.2 ppm.[14b,28]

Finally, the deprotection of the *tert*-butyl ester groups by treatment with trifluoroacetic acid in dichloromethane at room temperature gave quantitatively the new ligands TE2A-EtOH

Scheme 4[a]



[a]Reagents and conditions: (i) $PhCH_2Br$ (10 equiv), CH_3CN, rt, 14 d, 86%; (ii) $NH_2NH_2{\cdot}H_2O$, reflux, 4 h, 85%; (iii) H_2, Pd/C, EtOH, rt, 4 d, 75%; (iv) $NaBH_4$ (40 equiv), EtOH, reflux, 18 h, 85%; (v) H_2, Pd/C, EtOH, rt, 4 d, 88%.

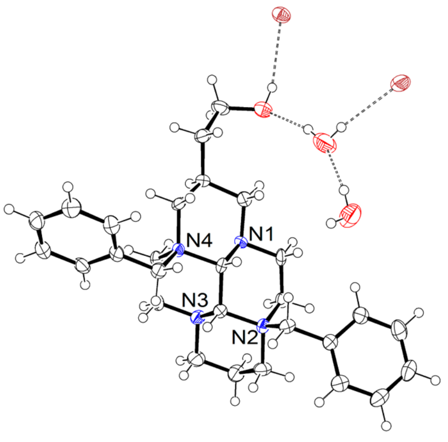


Figure 5. View of the crystal structure of **16**·$2H_2O$. The ORTEP plot is at the 30% probability level.

24, TETA-EtOH **25**, and CB-TE2A-EtOH **26** as trifluoroacetate salts. Attempts to perform the hydrolysis of the ester functions using hydrochloric acid solutions under reflux resulted in the formation of lactone derivatives due to the reaction of the hydroxyl group and one of the carboxylic groups. No trace of these lactones were observed in the relatively mild reaction conditions of the hydrolysis using trifluoroacetic acid.

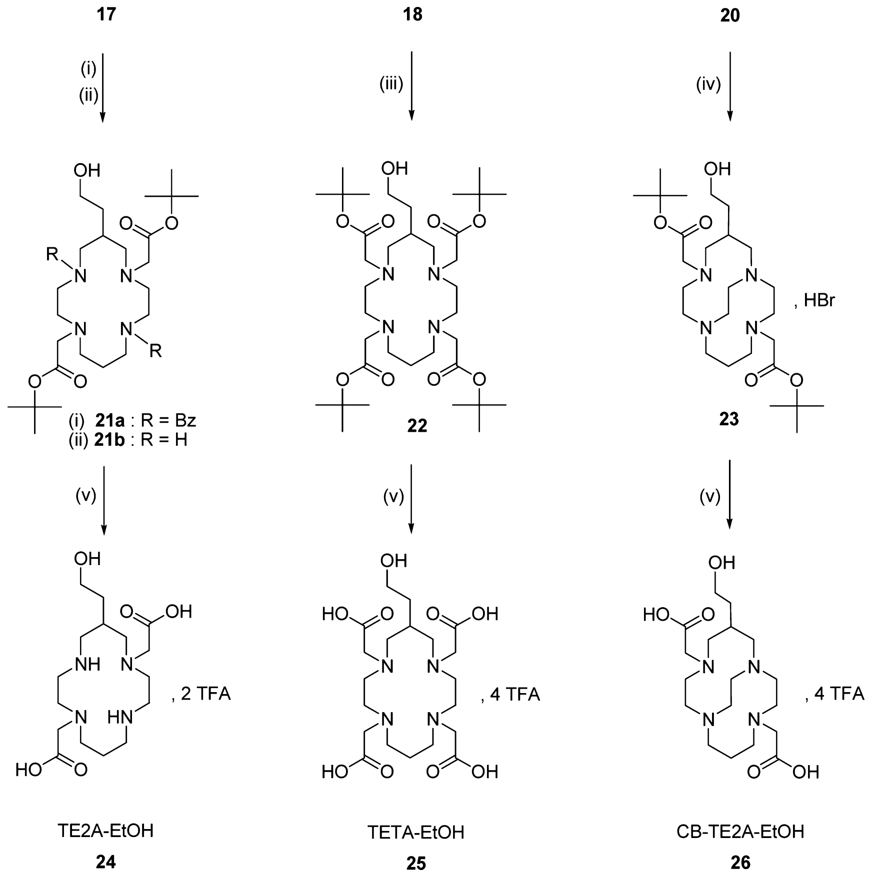
Cu(II) Complexes of *C*-Functionalized Cyclam Ligands. In order to evaluate the ability of the newly synthesized *C*-functionalized cyclam ligands to coordinate transition metal ions and to verify that the *C*-functionalization does not affect the overall complexation behavior of the ligands, we investigated the structure of the corresponding Cu(II) complexes. This metal ion was chosen because of the potential application of its radioisotopes (^{64}Cu or ^{67}Cu) in PET imaging or radio immunotherapy. These new ligands form stable Cu(II) complexes, but all our attempts to obtain single-crystals of the Cu(II) complexes of the "acetate" derivatives **24–26** were unsuccessful so far. However, the structures of the Cu(II) complexes with precursors **17–19** were obtained. Views of the structures of these complexes are shown in Figure 6, while bond distances of the metal coordination environments are given in Table 2. The crystal structures confirm that the hydroxyethyl group of the ligands does not participate in the coordination of the metal ion.

Two different structures of Cu(II) complexes of **17** have been determined: **17**·$CuBr(ClO_4)$ and **17**·$Cu(ClO_4)_2$. In **17**·$CuBr(ClO_4)$, the Cu(II) ion is directly bound to the four nitrogen atoms of the macrocycle and a bromide anion in a square pyramidal coordination. The basal plane of the pyramid is defined by the four nitrogen atoms of the ligand, with the bromide anion occupying the apical position. The overall structure of the complex resembles that of $[Cu(Me_4cyclam)Br]Br$.[29] In **17**·$Cu(ClO_4)_2$, the Cu(II) ion shows a Jahn–Teller distorted octahedral environment with tetragonal elongation, where the equatorial plane of the octahedron is defined by the four nitrogen atoms of the macrocycle and the axial positions are occupied by oxygen atoms of the perchlorate groups. The five-membered chelate rings also adopt the same conformation in both complexes $[(\lambda\lambda)]$,[30] with the six-membered chelate rings adopting chair conformations.

The metal coordination environment in **18**·$Cu(ClO_4)_2$ is very similar to that observed for **17**·$Cu(ClO_4)_2$. The six-membered chelate rings adopt also chair conformations, while the five-membered chelate rings present different helicities $[(\lambda\delta)]$. Tetragonally elongated octahedral coordination environments have been previously observed for Cu(II) complexes with cyclam-based ligands in the presence of weakly coordination anions such as perchlorate.[31]

Upon metal coordination, cyclam-based complexes may adopt five possible configurations depending on the spatial alignment of the NH protons, *RSRS*, *RSRR*, *SSRR*, *RSSR*, and *RRRR*, designed *trans*-I to *trans*-V, respectively.[32] The cyclam unit in **17**·$CuBr(ClO_4)$ and **17**·$Cu(ClO_4)_2$ adopts a *trans*-I configuration, which is usually favorable over the *trans*-III configuration in five-coordinated Cu(II) complexes of ligands

Scheme 5[a]



[a]Reagents and conditions: (i) *t*-$BuCO_2CH_2Br$ (2 equiv), CH_3CN, 80 °C, 2.5 d, 75%; (ii) H_2, Pd/C, EtOH, rt, 4 d, 86%; (iii) *t*-$BuCO_2CH_2Br$ (4 equiv), CH_3CN, 80 °C, 2 d, 84%; (iv) *t*-$BuCO_2CH_2Br$ (1.8 equiv), CH_3CN, rt, 18 h, 75%; (v) TFA, CH_2Cl_2, rt, quantitative yields.

containing cyclam units.[33] However, a *trans*-III conformation is observed in the case of **18**·$Cu(ClO_4)_2$.

Finally, in the complex of the dibenzyl cross-bridged ligand **19**·$CuBr(ClO_4)$ the Cu(II) ion is five-coordinated in a square-pyramidal coordination environment, with N3 occupying the apical position, due to an agostic interaction between the Cu(II) ion and a *ortho*-hydrogen of one of the benzyl pendant arms that is blocking the sixth potential coordination site (Cu(1)···H(26) = 2.56 Å, Figure 6).[34]

■ CONCLUSION

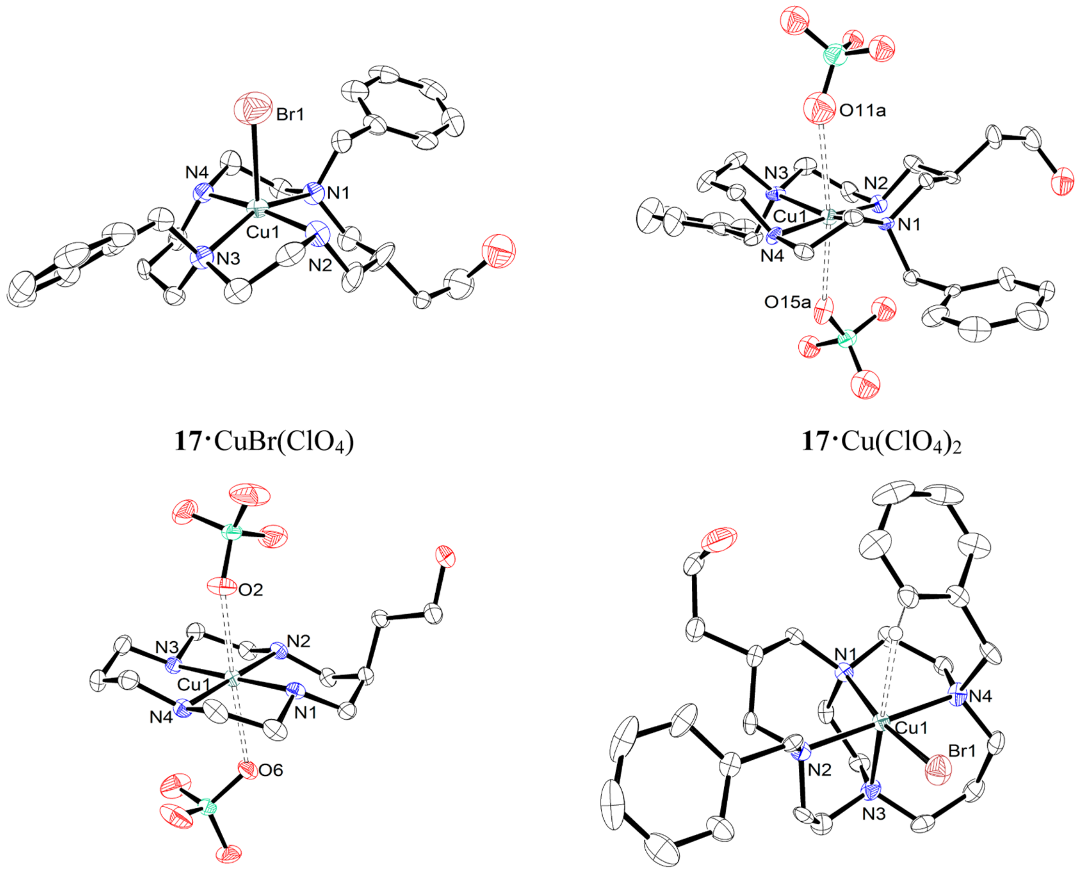
We have shown that the bisaminal approach can be an efficient tool for the development of a new synthetic route for the preparation of a wide variety of *C*-functionalized cyclam derivatives under mild reaction conditions and with limited protection/deprotection steps. This method offers the possibility of introducing various types of functions (hydroxyethyl, 4-nitrobenzyl, or methyl acetate substituents) on the carbon atom in *β-N* position of the carbon skeleton. The *C*-functionalized oxo-compounds obtained as direct products of the cyclization step are keystone intermediates for various regiospecific *N*-alkylations due to their different protected positions and their different protecting groups introduced in different stages of this new synthetic route. These key-intermediates are also precursors of cyclam and cross-bridged cyclam BCAs from which two examples bearing a hydroxyethyl function, cyclam-EtOH and CB-cyclam-EtOH, were isolated.

The *N*-functionalization with acetate groups of the *C*-functionalized macrocycle containing a hydroxyethyl unit led to very attractive bifunctional analogues of TETA, TE2A, and CB-TE2A. The same synthetic route could obviously be transposed to the two other versions of *C*-functionalized cyclams, thereby giving access to a large panel of compounds with a great importance in the field of nuclear medicine.

In addition to our ongoing coordination studies involving TE2A-EtOH, TETA-EtOH, and CB-TE2A-EtOH, we are also exploring different synthetic strategies in order to obtain more suitable anchoring functions for a future coupling to biomolecules such as antibodies or small peptides. These anchoring functions can be obtained for instance by activating the ester group or by transforming the hydroxyethyl or 4-nitrobenzyl groups into amine functions. Our current efforts are also focused on the generalization of our methodology to other starting polyamines to provide access to BCAs versions of other azamacrocycles.

■ EXPERIMENTAL SECTION

Materials and Methods. Bisaminal **3**[35] and cyclizing reagent **5**[23] were synthesized as previously described. 2D NMR $^1H-^1H$ homonuclear, $^1H-^{13}C$ and $^1H-^{15}N$ heteronuclear correlations, and homonuclear decoupling experiments were used for assignment of the ^1H and ^{13}C signals. The δ scales are relative to TMS (^1H, ^{13}C) and CH_3NO_2 (^{15}N). The signals are indicated as follows: chemical shift, intensity, multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; m, multiplet; q, quartet), coupling constants *J* in hertz (Hz), assignment: Hα, Cα and Hβ, Cβ correspond to CH or CH_2 located in



17·CuBr(ClO$_4$) **17**·Cu(ClO$_4$)$_2$

18·Cu(ClO$_4$)$_2$ **19**·CuBr(ClO$_4$)

Figure 6. Views of the crystal structures of Cu(II) complexes with ligands **17**−**19**. Uncoordinated anions and hydrogen atoms are omitted for simplicity. The ORTEP plots are at the 30% probability level.

the α or β position, respectively, of the considered nitrogen atom; Am, Ar, and Ph are the abbreviations used for aminal, aromatic, and phenyl, respectively). All analytical spectra and data are given in the Supporting Information.

Cyclization Step: Synthesis of *C*-functionalized Oxo-cyclam Bisaminal Derivatives. *Methyl 1-Oxo-10b,10c-cis-3a,5a,8a,10a-tetraazaperhydropyren-2-ylacetate (**7**).* A solution of dimethyl itaconate **4** (626 mg, 3.96 mmol) in CH$_3$CN (5 mL) was added dropwise to a solution of compound **3** (703 mg, 3.84 mmol) in CH$_3$CN (30 mL). The reaction mixture was heated at 40 °C for 8 d, and then the solvent was evaporated under reduced pressure. The crude reaction product was recrystallized in Et$_2$O to give **7** (355 mg, 30%) as white crystals. Mp: 150−152 °C. IR: $\tilde{\nu}$ = 1733 (C═O, strong, sharp), 1630 cm^{-1} (C═O, strong, sharp). ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C, TMS): δ = 4.32−4.26 (m, 1H), 4.25 (d, J = 3.0 Hz, 1H, N-C*H*-N), 3.57 (s, 3H, C*H*$_3$), 3.32 (td, J = 12.0, 3.0 Hz, 1H), 3.13 (td, J = 12.0, 2.5 Hz, 1H), 3.08 (d, J = 3.0 Hz, 1H, N-C*H*-N), 3.06−3.00 (m, 2H), 2.98−2.82 (m, 4H), 2.73−2.68 (m, 1H), 2.67 (d, J = 5.0 Hz, 1H), 2.62 (dt, J = 11.5, 2.0 Hz, 1H), 2.44 (dt, J = 10.5, 3.0 Hz, 1H), 2.37 (d, J = 6.5 Hz, 1H), 2.35−2.28 (m, 1H), 2.18 (td, J = 11.5, 3.0 Hz, 1H), 2.14−2.00 (m, 2H), 1.19−1.13 ppm (m, 1H). ^{13}C Jmod NMR (125 MHz, CDCl$_3$, 25 °C, TMS): δ = 172.3 (CO-amide), 170.6 (CO-ester), [75.9, 70.8] (N-CH-N), [55.7, 53.8, 53.1, 52.8, 44.3, 43.8, 40.4] (CH$_2$-α-N, CH$_2$-α-OH), 51.5 (COOCH$_3$), 33.0 (CH$_2$-β-OH), 32.3 (CH-β-N), 19.4 ppm (CH$_2$-β-N). MS (MALDI-TOF, matrix: dithranol): m/z 309.14 [M + H]$^+$. Anal. Calcd for $C_{15}H_{24}N_4O_3$·0.2H$_2$O: C, 57.75; H, 7.88; N, 17.96. Found: C, 57.76; H, 7.82; N, 18.19.

*2-(4-Nitrobenzyl)-10b,10c-cis-3a,5a,8a,10a-tetraazaperhydropyren-1-one (**8**).* A solution of methyl 2-(4-nitrobenzyl) acrylate **5** (2.89 g, 12.29 mmol) in CH$_3$CN (15 mL) was added dropwise to a solution of compound **3** (2.24 g, 12.29 mmol) in CH$_3$CN (100 mL). The reaction mixture was stirred at room temperature for 7 d, and then the white precipitate was isolated by filtration. The solid was washed with CH$_3$CN (2 × 15 mL) and then with Et$_2$O (2 × 15 mL) and finally dried under vacuum. Compound **8** was obtained as a white powder (2.86 g, 62%). Mp: 186−188 °C. IR: $\tilde{\nu}$ = 1631 cm^{-1} (C═O, strong, sharp). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 8.11 (d, J = 8.8 Hz, 2H, C*H*-Ar), 7.35 (d, J = 8.8 Hz, 2H, C*H*-Ar), 4.45 (d, J = 12.0 Hz, 1H), 4.26 (d, J = 3.2 Hz, 1H, N-C*H*-N), 3.51 (dd, J = 14.0, 4.0 Hz, 1H), 3.41 (td, J = 8.0, 3.2 Hz, 1H), 3.14−3.09 (m, 2H), 2.96−2.85 (m, 6H), 2.78 (td, J = 8.0, 3.2 Hz, 1H), 2.72−2.64 (m, 2H), 2.39−2.34 (m, 2H), 2.21−2.14 (m, 3H), 1.25−1.05 ppm (m, 1H). ^{13}C Jmod NMR (100 MHz, CDCl$_3$, 25 °C, TMS): δ = 173.3 (CO), [150.6, 149.5] (C*H*-Ar), [132.72, 126.59] (CH), [78.88, 73.76] (N-CH-N), 58.74 (CH$_2$-Ph), [56.80, 56.05, 55.89, 47.31, 46.83, 43.45] (CH$_2$-α-N), 39.63 (CH-β-N), 38.01 (CH$_2$-α-N), 22.47 ppm (CH$_2$-β-N). MS (MALDI-TOF, matrix: dithranol): m/z 372.17 [M + H]$^+$. Anal. Calcd for $C_{19}H_{25}N_5O_3$·0.5H$_2$O: C, 59.98; H, 6.89; N, 18.41. Found: C, 59.98; H, 6.72; N, 18.19.

*2-(2-Hydroxyethyl)-10b,10c-cis-3a,5a,8a,10a-tetraazaperhropyren-1-one (**9**).* A solution of α-methylene-γ-butyrolactone **6** (450 μL, 5.12 mmol) in CH$_3$CN (5 mL) was added dropwise to a solution of compound **3** (890 mg, 4.88 mmol) in CH$_3$CN (30 mL). The reaction mixture was heated at 40 °C for 4 d, and then the white precipitate was isolated by filtration. The solid was washed with CH$_3$CN (2 × 5 mL) and then with Et$_2$O (2 × 5 mL) and finally dried under vacuum. This process was repeated with the filtrate twice more to recover more material. The white powder of **9** was dried under vacuum (890 mg, 65%). Mp: 176−178 °C. IR: $\tilde{\nu}$ = 1613 cm^{-1} (C═O, strong, sharp). ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C, TMS) δ = 4.62 (br s, 1H, O*H*), 4.43 (d, J = 10.0 Hz, 1H), 4.30 (d, J = 3.0 Hz, 1H, N-C*H*-N), 3.76−3.72

Table 2. Selected Bond Distances (Å) and Bond angles (deg) for the Metal Coordination Environment in Cu(II) Complexes

	17·CuBr(ClO_4)	**17**·Cu(ClO_4)$_2$	**18**·Cu(ClO_4)$_2$	**19**·CuBr(ClO_4)
Cu(1)-N(1)	2.133(11)	2.098(10)	2.007(3)	2.132(6)
Cu(1)-N(2)	1.997(11)	1.973(9)	2.013(3)	2.088(6)
Cu(1)-N(3)	2.114(11)	2.055(9)	1.995(3)	2.189(7)
Cu(1)-N(4)	1.981(12)	1.996(9)	2.020(3)	2.056(6)
Cu(1)−Br	2.791(3)			2.4802(13)
N(1)−Cu(1)-N(2)	91.4(4)	90.4(6)	92.73(11)	94.6(2)
N(1)−Cu(1)-N(3)	155.6(4)	170.3(5)	178.02(11)	83.7(3)
N(1)−Cu(1)-N(4)	87.1(4)	86.6(4)	86.43(11)	85.5(2)
N(2)−Cu(1)-N(3)	86.9(5)	93.6(7)	86.14(11)	85.7(2)
N(2)−Cu(1)-N(4)	172.8(5)	171.1(7)	177.20(11)	179.6(3)
N(3)−Cu(1)-N(4)	91.6(5)	90.6(6)	94.78(11)	94.8(3)
N(1)−Cu(1)−Br(1)	101.2(3)			170.52(18)
N(2)−Cu(1)−Br(1)	91.4(3)			90.91(18)
N(3)−Cu(1)−Br(1)	103.2(3)			104.40(19)
N(4)−Cu(1)−Br(1)	95.8(3)			88.91(18)

(m, 1H), 3.62−3.58 (m, 1H), 3.40 (td, *J* = 12.0, 3.5 Hz, 1H), 3.18 (d, *J* = 3,0 Hz, 1H, N-C*H*-N), 3.16−3.04 (m, 2H), 3.01−2.88 (m, 4H), 2.82−2.76 (m, 2H), 2.69 (dt, *J* = 11.0, 2.5 Hz, 1H), 2.48 (dt, *J* = 11.0, 2.5 Hz, 1H), 2.44−2.37 (m, 1H), 2.25 (td, *J* = 11.0, 2.5 Hz, 1H), 2.21−2.10 (m, 2H), 1.95−1.88 (m, 1H), 1.45−1.38 (m, 1H), 1.28−1.20 ppm (m, 1H). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.5 (CO), [75.7, 70.6] (N-CH-N), [61.0, 55.6, 54.7, 52.9, 52.7, 44.1, 43.7, 40.2] (CH_2-α-N, CH_2-α-OH), 34.4 (CH-β-N), 31.8 (CH_2-β-OH), 19.3 ppm (CH_2-β-N). MS (MALDI-TOF, matrix: dithranol): *m*/*z* 281.10 [M + H]$^+$. Anal. Calcd for $C_{14}H_{24}N_4O_2 \cdot 0.4H_2O$: C, 58.47; H, 8.69; N, 19.48. Found: C, 58.64; H, 8.49; N, 19.39.

Synthesis of Mono-*N*-protected Cyclam Derivatives. *2-(10b,10c-cis-3a,5a,8a,10a-Tetraazaperhydropyren-2-yl)ethanol (**10**).* Sodium borohydride (4.05 g, 107.1 mmol) was added to a solution of compound **9** (3.00 g, 10.71 mmol) in H_2O (30 mL) at room temperature. The solution was stirred for 18 h and then saturated with NaOH pellets. The product was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtrated, and evaporated under reduced pressure to give **10** as a colorless oil (2.80 g, 90%). ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.60 (br s, 1H, O*H*), 3.45 (t, *J* = 7.0 Hz, 2H, C*H*$_2$OH), 3.40−3.25 (m, 2H), 2.94 (d, *J* = 2.5 Hz, 1H, N-C*H*-N), 2.84 (d, *J* = 2.5 Hz, 1H, N-C*H*-N), 2.80−2.70 (m, 5H), 2.60−2.50 (m, 2H), 2.45−2.35 (m, 1H), 2.30−2.15 (m, 3H), 2.15−2.00 (m, 3H), 2.00−1.90 (m, 1H), 1.65−1.50 (m, 1H), 1.17 (q, *J* = 6.5 Hz, 2H), 1.10−1.00 ppm (m, 1H). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = [76.6, 76.5] (N-CH-N), [61.9, 59.4, 58.4, 55.7, 54.0, 53.9, 52.2, 45.3, 44.4] (CH_2-α-N, CH_2-α-OH), 34.6 (CH_2-β-OH), 25.4 (CH-β-N), 19.3 ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{14}H_{27}N_4O^+$ [M + H]$^+$ 267.2179, found 267.2185.

*8a-Benzyl-2-(2-hydroxyethyl)-10b,10c-cis-3a,5a,8a,10a-tetraazaperhydropyren-1-one Bromide Salt (**11**).* Benzyl bromide (1.62 mL, 13.56 mmol) was added dropwise to a solution of compound **9** (950 mg, 3.39 mmol) in distilled CH_2Cl_2 (8.0 mL). The solution was stirred at room temperature for 4 d, and then the precipitate was isolated by filtration. The solid was washed with cold CH_2Cl_2 (2 × 5 mL) and then with Et_2O (2 × 5 mL) and finally dried under vacuum to give **11** as a white powder (1.50 g, 98%). IR: $\tilde{\nu}$ = 1639 cm^{-1} (C═O, strong, sharp). ^1H NMR (500 MHz, D_2O, 25 °C, TMS): δ = 7.65−7.55 (m, 5H, C*H*-Ar), 5.65 (d, *J* = 2.0 Hz, 1H, N-C*H*-N), 5.11 (d, *J* = 13.5 Hz, 1H, N-C*H*$_2$-Ph), 4.79 (d, *J* = 13.5 Hz, 1H, N-C*H*$_2$-Ph), 4.60−4.55 (m, 1H), 4.40−4.30 (m, 1H), 4.01 (d, *J* = 2.0 Hz, 1H, N-C*H*-N),3.85−3.60 (m, 4H), 3.45−3.30 (m, 3H), 3.30−3.20 (m, 2H), 3.15−3.05 (m, 3H), 2.80−2.70 (m, 1H), 2.70−2.60 (m, 1H), 2.55−2.45 (m, 1H), 2.25−2.15 (m, 2H), 1.85−1.80 (m, 1H), 1.75−1.65 ppm (m, 1H). ^{13}C Jmod NMR (125 MHz, D_2O, 25 °C, TMS): δ = 177.6 (CO), [135.9, 134.0, 132.2] (CH-Ar), 128.0 (C-Ar), [83.2, 67.8] (N-CH-N), [64.7, 62.7, 61.9, 55.8, 55.3, 54.6, 50.0, 44.7, 38.3] (CH_2-α-N, CH_2-α-OH), 35.5 (CH-β-N), 33.9 (CH_2-β-OH), 20.9 ppm (CH_2-β-N). MS (MALDI-TOF, matrix: HCCA): *m*/*z* 371.16 [M − Br$^-$]$^+$. Anal. Calcd for $C_{21}H_{31}BrN_4O_2 \cdot 1.5H_2O$: C, 52.72; H, 7.16; N, 11.71. Found: C, 53.01; H, 6.94; N, 11.60.

*Compounds **12** and **12′**.* Benzyl bromide (170 μL, 1.31 mmol) was added dropwise to a solution of compound **10** (350 mg, 1.31 mmol) in distilled CH_2Cl_2 (3.0 mL). The solution was stirred at room temperature for 18 h and then evaporated under reduced pressure. The white solid resulting was dissolved in CH_3CN (3 mL). A small amount of precipitate was formed and eliminated by filtration. The filtrate was concentrated under vacuum to give the mixture of **12** and **12′** as a white powder (510 mg, 90%). ^1H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 7.70−7.40 (m, 10H, C*H*-Ar), 5.20−5.00 (m, 2H), 4.90−4.65 (m, 2H), 4.45−4.25 (m, 2H), 4.25−4.10 (m, 2H), 3.80−3.40 (m, 10H), 3.40−2.90 (m, 18H), 2.85−2.60 (m, 2H), 2.60−2.00 (m, 12H), 1.85−1.70 (m, 1H), 1.60−1.35 ppm (m, 5H). ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = [136.2 (× 2), 134.0 (× 2), 132.3 (× 2)] (CH-Ar), [128.54, 128.54] (C-Ar), [84.8, 84.5, 72.4, 72.2] (N-CH-N), [66.7, 65.5, 65.4, 62.7, 62.4, 61.7, 61.2, 60.5, 59.8, 56.8, 56.2, 56.1, 54.8, 54.2, 52.1, 51.3, 49.5, 49.4, 45.7, 44.8] (CH_2-α-N, CH_2-α-OH), [36.1, 35.1] (CH_2-β-OH), [28.8, 27.3] (CH-β-N), [21.3, 20.9] ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{21}H_{33}N_4O^+$ [M − Br$^-$]$^+$ 357.2649, found 357.2650.

*1-Benzyl-6-(2-hydroxyethyl)-1,4,8,11-tetraazacyclotetradecan-5-one (**13**).* Hydrazine monohydrate (4.0 mL, 64% in water, 82.38 mmol) was added dropwise to a solution of compound **11** (4.33 g, 9.59 mmol) in EtOH (50 mL). The reaction mixture was heated at reflux for 4 h, and then the solution was concentrated in vacuo. HCl (10 mL, 3 M) was added to the residue, a first extraction with $CHCl_3$ (5 × 25 mL) was performed to eliminate organic impurities, and then the pH of the aqueous layer was adjusted to 14 by the addition of NaOH pellets. The product was extracted with $CHCl_3$ (5 × 25 mL). The combined organic fractions were dried over $MgSO_4$, filtrated, and removed under reduced pressure to give **13** as a yellow oil (2.35 g, 70%). IR: $\tilde{\nu}$ = 1637 cm^{-1} (C═O, strong, sharp). ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.62 (br s, 1H, CO-N*H*), 7.40−7.20 (m, 5H, C*H*-Ar), 3.77 (d, *J* = 13.0 Hz, 1H, N-C*H*$_2$-Ph), 3.75−3.60 (m, 3H), 3.31 (d, *J* = 13.0 Hz, 1H, N-C*H*$_2$-Ph), 3.25−3.15 (m, 1H), 3.00−2.90 (m, 1H), 2.90−2.85 (m, 2H), 2.80−2.65 (m, 3H), 2.65−2.55 (m, 4H), 2.55−2.50 (m, 1H), 2.50−2.40 (m, 1H), 2.40−2.30 (m, 1H), 1.95−1.85 (m, 1H), 1.85−1.75 (m, 1H), 1.75−1.65 (m, 1H), 1.65−1.55 (m, 1H), 1.18 (br s, 2H, N*H*). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 175.7 (CO), 137.9 (C-Ar), [129.6, 128.1, 127.1] (CH-Ar), [59.8, 57.6, 54.2, 53.0, 50.6, 50.2, 49.1, 45.8] (CH_2-α-N, CH_2-α-OH), 42.8 (CH-β-N), [35.5, 32.9] (CH_2-α-N, CH_2-β-OH), 23.8 ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{19}H_{33}N_4O_2^+$ [M + H]$^+$ 349.2598, found 349.2599. Anal. Calcd for $C_{19}H_{32}N_4O_2 \cdot 0.09HCl \cdot 0.7H_2O$: C, 62.63; H, 9.26; N, 15.38, Cl 0.88. Found: C, 62.67; H, 8.90; N, 15.54, Cl 0.82.

*2-(1-Benzyl-1,4,8,11-tetraazacyclotetradecan-6-yl)ethanol (**14**).* A solution of BH_3·THF (17.0 mL, 1.0 M, 17.00 mmol) was added dropwise to a solution of compound **13** (1.49 g, 4.28 mmol) in distilled THF (30 mL) under a nitrogen atmosphere. The solution was stirred at room temperature for 1 h and then heated at reflux for 1.5 d. After cooling to room temperature, water (20 mL) was added to the reaction mixture, then the solvent was evaporated under reduced pressure. HCl (30 mL, 3 M) was added to the residue and the solution was refluxed for 1 h. After cooling down to room temperature a first extraction with $CHCl_3$ (5 × 50 mL) was performed to eliminate organic impurities, then the pH of the aqueous layer was adjusted to 14 by the addition of NaOH pellets. The product was extracted with $CHCl_3$ (5 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvent concentrated under reduced pressure to give **14** as a colorless oil (1.03 g, 72%). ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.30−7.10 (m, 5H, C*H*-Ar), 3.55−3.50 (m, 1H), 3.50−3.35 (m, 4H), 2.85−2.75 (m, 1H), 2.75−2.56 (m, 6H), 2.53 (d, *J* = 13.5 Hz, 1H), 2.53−2.35 (m, 6H), 2.35−2.25 (m, 2H), 1.85−1.75 (m, 2H), 1.75−1.65 (m, 1H), 1.50−1.35 ppm (m, 2H). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 138.3 (C-Ar), [129.0, 127.9, 126.8] (CH-Ar), [59.0, 57.5, 53.5, 52.9, 52.4, 52.3, 48.3, 48.2, 47.5, 46.5] (CH_2-α-N, CH_2-α- OH), 35.5 (CH-β-N), 35.1 (CH_2-β-OH), 26.0 ppm (CH_2-β-N). MS (MALDI-TOF, matrix: dithranol): *m*/*z* 335.20 $[M + H]^+$. Anal. Calcd for $C_{19}H_{34}N_4O{\cdot}0.4HCl{\cdot}0.5H_2O$: C, 63.73; H, 9.96; N, 15.65. Found: C, 64.06; H, 9.58; N, 15.28.

*Oxo-cyclam-EtOH: 6-(2-Hydroxyethyl)-1,4,8,11-tetraazacyclotetradecan-5-one (**15**).* Compound **13** (1.00 g, 2.87 mmol) was dissolved in EtOH absolute ethanol (30 mL). 10% Pd/C-activated (300 mg) was added, and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 4 d. The mixture was then filtered through Celite and the solvent was evaporated under reduced pressure. The resulting yellow oil was dissolved in water (5 mL) and the organic impurities were extracted with Et_2O (3 × 10 mL). The aqueous layer was evaporated under reduced pressure to give compound **15** as a yellow oil (630 mg, 85%). IR: $\tilde{\nu}$ = 1648 cm^{-1} (C═O, strong, sharp). ^1H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 3.85−3.70 (m, 1H), 3.70−3.40 (m, 2H), 3.10−2.90 (m, 1H), 2.90−2.30 (m, 14H), 1.90−1.35 ppm (m, 4H). ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = 180.4 (CO), [62.2, 53.0, 50.4, 49.4, 49.3, 48.7 (× 2), 40.9] (CH_2-α-N, CH_2-α-OH), 46.0 (CH-β-N), 35.2 (CH_2-β-OH), 29.5 ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{12}H_{27}N_4O_2^+$ $[M + H]^+$ 259.2129, found 259.2133.

Synthesis of Di-*N*-protected Cyclam Derivatives and Their Deprotected Analogues. *2-(3a,8a-Dibenzyl-10b,10c-cis-3a,5a,8a,10a-tetraazaperhydropyren-2-yl)ethanol Dibromide Salt (**16**).* A solution of benzyl bromide (6.20 mL, 51.80 mmol) in distilled CH_3CN (20 mL) was added dropwise to a solution of compound **10** (1.38 g, 5.18 mmol) in distilled CH_3CN (25 mL). The solution was stirred at room temperature for 14 d, and then the precipitate was isolated by filtration. The solid was washed with CH_3CN (2 × 10 mL) and then with Et_2O (2 × 10 mL) and finally dried under vacuum to give **16** as a white powder (2.70 g, 86%). ^1H NMR (500 MHz, D_2O, 25 °C, TMS): δ = 7.70−7.55 (m, 10H, C*H*-Ar), 5.34 (d, *J* = 13.0 Hz, 1H, N-CH_2-Ph), 5.30 (d, *J* = 13.0 Hz, 1H, NCH_2-Ph), 5.14 (d, *J* = 12.5 Hz, 2H, N-C*H*-N), 4.90−4.70 (m, 2H, N-CH_2-Ph), 4.55−4.40 (m, 2H), 3.85−3.75 (m, 2H), 3.75−3.55 (m, 4H), 3.55−3.40 (m, 5H), 3.40−3.20 (m, 4H), 2.95−2.80 (m, 1H), 2.65−2.45 (m, 2H), 2.40−2.25 (m, 1H), 2.00−1.90 (m, 1H), 1.65−1.45 ppm (m, 2H). ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = [136.1 (× 2), 134.3 (× 2), 132.4 (× 2)] (CH-Ar), [127.56, 127.51] (C-Ar), [79.8, 79.5] (N-CH-N), [67.3, 65.3, 65.2, 63.4, 61.2, 59.7, 54.1, 49.74, 49.68, 49.6, 48.9] (CH_2-α-N, $CH_2\alpha$-OH), 35.0 (CH_2-β-OH), 28.6 (CH-β-N), 20.9 ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{28}H_{40}N_4O^{2+}$ $[M - 2Br^-]^{2+}$ 224.1596, found 224.1603. Anal. Calcd for $C_{28}H_{40}Br_2N_4O{\cdot}H_2O$: C, 53.68; H, 6.76; N, 8.94. Found: C, 53.57; H, 6.81; N, 9.01.

*2-(1,8-Dibenzyl-1,4,8,11-tetraazacyclotetradecan-6-yl)ethanol (**17**).* Compound **16** (1.25 g, 2.06 mmol) was dissolved in hydrazine monohydrate (6.0 mL, 64% in water, 123.58 mmol), and the reaction mixture was heated at reflux for 4 h. The solution was cooled to 0 °C with an ice bath, which led to product precipitation, and then the excess of hydrazine was eliminated by filtration. The precipitate was dissolved in a solution of NaOH (3M, 15 mL), and the product was extracted with CH_2Cl_2 (3 × 30 mL). The organic fractions were dried over $MgSO_4$, filtrated, and evaporated under reduced pressure to give **17** (740 g, 85%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.30−7.10 (m, 10H, C*H*-Ar), 3.89 (d, *J* = 14.0 Hz, 1H, N-CH_2-Ph), 3.69 (d, *J* = 13.5 Hz, 1H, N-CH_2-Ph), 3.60−3.45 (m, 3H), 3.51 (d, *J* = 14.0 Hz, 1H, N-CH_2-Ph), 3.33 (d, *J* = 13.5 Hz, 1H, N-CH_2-Ph), 2.92−2.65 (m, 7H), 2.65−2.55 (m, 1H), 2.55−2.40 (m, 6H), 2.40−2.35 (m, 2H), 2.30−2.15 (m, 2H), 2.10−2.15 (m, 1H), 1.95−1.80 (m, 1H), 1.70−1.60 (m, 1H), 1.50−1.45 (m, 1H), 1.45−1.35 ppm (m, 1H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [137.3, 137.2] (C-Ar), [129.3 (× 2), 129.2 (× 2), 126.9 (× 2)] (CH-Ar), [58.9, 58.1, 57.5, 55.7, 53.9, 52.8, 52.2, 51.7, 49.6, 47.5, 46.7] (CH_2-α-N, CH_2-α-OH), 36.2 (CH_2-β-OH), 33.7 (CH-β-N), 26.0 ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{26}H_{41}N_4O^+$ $[M + H]^+$ 425.3275, found 425.3276.

*Cyclam-EtOH: 2-(1,4,8,11-Tetraazacyclotetradecan-6-yl)ethanol (**18**).* Compound **17** (1.00 g, 2.36 mmol) was dissolved in EtOH absolute ethanol (30 mL). 10% Pd/C-activated (300 mg) was added, the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 4 d, the reaction mixture was filtered through Celite, and the solvent was evaporated under reduced pressure. The residue was dissolved in distilled H_2O (15 mL), and the organic impurities were extracted with Et_2O (3 × 20 mL). The aqueous layer was concentrated under vacuum. The addition of CH_3CN (10 mL) to the resulting yellow oil led to the formation of a precipitate which was filtered and dried under vacuum to give compound **18** as a white powder (433 mg, 75%). Mp: 129−131 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.50−3.30 (m, 2H), 2.70−2.40 (m, 14H), 2.40−2.20 (m, 2H), 1.80−1.55 (m, 1H), 1.55−1.40 (m, 2H), 1.40−1.30 ppm (m, 2H). ^{13}C Jmod NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = [59.0, 53.6, 50.0, 48.64, 48.61] (CH_2-α-N, CH_2-α-OH), 36.0 (CH-β-N), 35.2 (CH_2-β-OH), 29.0 ppm (CH_2-β-N). MS (MALDI-TOF, matrix: dithranol): *m*/*z* 245.17 $[M + H]^+$. Anal. Calcd for $C_{12}H_{28}N_4O$: C, 58.98; H, 11.55; N, 22.93. Found: C, 58.68; H, 11.64; N, 23.10.

*2-(4,11-Dibenzyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-6-yl)-ethanol (**19**).* Sodium borohydride (998 mg, 66.0 mmol) was slowly added to a solution of compound **18** (1.00 g, 1.65 mmol) in 95% EtOH (50 mL). The mixture was refluxed for 18 h, then the solvent was evaporated under reduced pressure. A precipitate was formed after addition of CH_2Cl_2 (50 mL) and was eliminated by filtration. The filtrate was concentrated under vacuum. This process was repeated twice to recover more material. The major product was recrystallized in CH_3CN. Compound **19** was obtained as a white powder (744 mg, 85%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.50−7.00 (m, 10H, C*H*-Ar), 4.80−4.70 (m, 1H), 4.05−3.85 (m, 1H), 3.85−3.50 (m, 5H), 3.45−3.30 (m, 1H), 3.30−2.80 (m, 5H), 2.70−2.35 (m, 8H), 2.35−2.00 (m, 4H), 1.75−1.40 (m, 3H), 1.40−1.15 ppm (m, 1H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [140.6, 137.9] (C-Ar), [129.4, 128.9, 128.4, 128.1, 127.2, 126.6] (CH-Ar), [64.4, 62.5, 61.4, 59.9, 59.2, 57.7, 56.6, 54.5, 53.5, 52.8, 51.9, 50.1, 43.6] (CH_2-α-N, CH_2-α-OH), 39.0 (CH_2-β-OH), 35.9 (CH-β-N), 25.2 ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{28}H_{44}N_4O^{2+}$ $[M + 2H]^{2+}$ 226.1752, found 226.1757, error = −2.2 ppm. Anal. Calcd for $C_{28}H_{42}N_4O.1{\cdot}1H_2O$: C, 71.48; H, 9.47; N, 11.91. Found: C, 71.70; H, 9.16; N, 11.84.

*CB-cyclam-EtOH: 2-(1,4,8,11-Tetraazabicyclo[6.6.2]hexadec-6-yl)ethanol (**20**).* Compound **19** (2.70 g, 5.99 mmol) was dissolved in EtOH absolute ethanol (100 mL). 10 % Pd/C-activated (810 mg) was added, the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 4 d, the mixture was then filtered through Celite, and the solvent was evaporated under reduced pressure. The resulting oil was dissolved in distilled H_2O (20 mL), and the organic impurities were extracted with Et_2O (3 × 30 mL). The aqueous layer was concentrated under vacuum to give compound **20** as a yellow oil (1.45 g, 88%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.20−3.50 (br s, 1H), 3.28 (t, *J* = 6,0 Hz, 2H), 2.85−2.70 (m, 1H), 2.70−2.25 (m, 15H), 2.25−2.00 (m, 6H), 1.90−1.70 (m, 1H), 1.15−0.90 ppm (m, 3H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [66.3, 59.2, 58.6, 58.5, 57.5, 54.8, 51.1, 50.4, 49.2, 44.00, 44.04] (CH_2-α-N, CH_2-α-OH), 34.8 (CH_2-β-OH), 26.9 (CH-β-N), 22.0 ppm (CH_2-β-N). HRMS (ESI): *m*/*z* calcd for $C_{14}H_{32}N_4O^{2+}$ $[M + 2H]^{2+}$ 136.1283, found 136.1284.

Synthesis of *C*-Functionalized TETA-EtOH, TE2A-EtOH, and CB-TE2A-EtOH. *2-(1,8-Dibenzyl-4,11-(2-tert-butoxy-2-oxoethyl)-1,4,8,11-tetraazacyclotetradecan-6-yl)ethanol (**21a**).* A solution of *tert*-butyl bromoacetate (390 μL, 2.68 mmol) in distilled CH_3CN (5 mL) was added dropwise to a suspension of compound **17** (570 mg, 1.34 mmol) and K_2CO_3 (1.48 g, 10.72 mmol) in distilled CH_3CN (20 mL). The reaction mixture was stirred at 80 °C for 2.5 d. After being cooled to room temperature, the solution was filtrated and the filtrate was evaporated under reduced pressure. The resulting yellow oil was dissolved in $CHCl_3$ (10 mL). The organic fraction was washed with a solution of NaOH (3M, 3 × 25 mL), dried over $MgSO_4$, filtrated, and evaporated to give compound **21a** as a yellow oil (660 mg, 75%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40−7.10 (m, 10H, *C*H-Ar), 3.70−3.30 (m, 6H), 3.15−3.00 (m, 4H), 2.90−2.75 (m, 1H), 2.75−2.45 (m, 10H), 2.45−2.30 (m, 2H), 2.30−2.10 (m, 2H), 1.90−1.75 (m, 1H), 1.70−1.45 (m, 3H), 1.45−1.10 (m, 3H), 1.35 ppm (s, 18H, CH_3). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [170.4, 170.2] (CO), [139.0, 138.0] (*C*-Ar), [129.2, 128.6, 128.0, 127.8, 127.0, 126.5] (CH-Ar), [80.4, 80.3] ($C(CH_3)_3$), [61.1, 60.6, 60.5, 59.7, 59.0, 57.2, 56.5, 51.5, 51.0, 50.9, 50.6, 48.8] (CH_2-α-N, CH_2-α-OH), 37.6 (CH_2-β-OH), 35.4 (CH-β-N), [27.90, 27.86] (CH_3), 24.7 ppm (CH_2-β-N). HRMS (ESI): *m/z* calcd for $C_{38}H_{61}N_4O_5^+$ [M + H]$^+$ 653.4636, found 653.4639.

*TE2AtBu-EtOH: 2-(1,8-Di(2-tert-butoxy-2-oxoethyl)-1,4,8,11-tetraazacyclotetradecan-6-yl)ethanol (**21b**).* Compound **21a** (660 mg, 1.00 mmol) was dissolved in EtOH absolute ethanol (30 mL). 10% Pd/C-activated (200 mg) was added, the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 4 d, the mixture was filtrated through Celite, and the solvent was evaporated under reduced pressure. The resulting yellow oil was dissolved in distilled H_2O (8 mL), and then the organic impurities were extracted with Et_2O (3 × 15 mL). The aqueous layer was evaporated to give **21b** as a pale solid (410 mg, 86%). ^1H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 3.80−3.50 (m, 4H), 3.50−2.50 (m, 17H), 2.50−2.15 (m, 1H), 2.15−1.70 (m, 2H), 1.70−1.30 (m, 3H), 1.55 ppm (s, 18H, CH_3). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [170.3, 170.2] (CO), [80.51, 80.48] ($C(CH_3)_3$), [59.2, 55.7, 54.6, 54.2, 53.4, 52.55, 52.52, 49.2, 47.5, 46.6] (CH_2-α-N, CH_2-α-OH), 36.0 (CH_2-β-OH), 34.0 (CH-β-N), 28.0 (CH_3 × 2), 26.2 ppm (CH_2-β-N). HRMS (ESI): *m/z* calcd for $C_{24}H_{49}N_4O_5^+$ [M + H]$^+$ 473.3696, found 473.3697.

*TETAtBu-EtOH: 2-(1,4,8,11-Tetra(2-tert-butoxy-2-oxoethyl)-1,4,8,11-tetraazacyclotetradecan-6-yl)ethanol (**22**).* A solution of *tert*-butyl bromoacetate (3.48 mL, 23.88 mmol) in distilled CH_3CN (10 mL) was added dropwise to a suspension of compound **18** (1.46 g, 5.97 mmol) and K_2CO_3 (6.60 g, 47.76 mmol) in distilled CH_3CN (50 mL) heated to 80 °C. The suspension was stirred for 2 d, at the same temperature, cooled to room temperature, and filtered. After the removal of the solvent under vacuum, the residue was dissolved in $CHCl_3$ (20 mL). The organic fraction was washed with a solution of NaOH (3M, 5 × 35 mL), dried over $MgSO_4$, filtrated, and evaporated under reduced pressure to give **22** as a yellow oil (3.50 g, 84%). If necessary, the compound can be purified by aluminum oxide chromatography ($CHCl_3$/MeOH, 100:0−94:6). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.70−3.60 (m, 2H), 3.40−3.10 (m, 8H), 2.90−2.50 (m, 13H), 2.40−2.10 (m, 3H), 1.90−1.70 (m, 1H), 1.70−1.35 (m, 5H), 1.45 (s, 18H, CH_3), 1.44 ppm (s, 18H, CH_3). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = [170.7, 170.3] (CO), [81.0, 80.6] ($C(CH_3)_3$), [61.1, 60.3, 57.6, 56.7, 51.7, 51.0, 50.9] (CH_2-α-N, CH_2-α-OH), 37.6 (CH_2-β-OH), 36.0 (CH-β-N), 28.1 (× 12) ($C(CH_3)_3$), 25.4 ppm (CH_2-β-N). HRMS (ESI): *m/z* calcd for $C_{36}H_{69}N_4O_9^+$ [M + H]$^+$ 701.5059, found 701.5059.

*CB-TE2AtBu-EtOH, HBr: 2-(1,8-Bis(2-tert-butoxy-2-oxoethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadec-6-yl)ethanol Hydrobromide (**23**).* A solution of *tert*-butyl bromoacetate (375 μL, 2.32 mmol) in distilled CH_3CN (2 mL) was added dropwise to a suspension of compound **20** (350 mg, 1.29 mmol) and K_2CO_3 (712 mg, 5.16 mmol) in distilled CH_3CN (13 mL). The reaction mixture was stirred at room temperature for 18 h, the reaction mixture was filtrated, and the filtrate was concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography on aluminum oxide ($CHCl_3$/MeOH, 98:2−85:15) to give **23** as a monohydrobromide salt (750 mg, 75%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.40−10.20 ppm (br s, 1H), 4.70−4.20 (br s, 1H), 3.90−3.45 (m, 5H), 3.40−2.90 (m, 10H), 2.90−2.20 (m, 12H), 1.80−1.20 (m, 4H), 1.34 (s, 9H, CH_3), 1.33 ppm (s, 9H, CH_3). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [170.4, 169.9] (CO), [81.9, 81.2] ($C(CH_3)_3$), [65.5, 62.0, 57.8, 57.5, 56.4, 56.0, 55.8, 54.9, 54.7, 50.7, 49.9, 49.2, 48.3] (CH_2-α-N, CH_2-α-OH), 33.2 (CH_2-β-OH), 28.0 (CH-β-N), 27.9 (CH_3, × 2), 25.7 ppm (CH_2-β-N). HRMS (ESI): *m/z* calcd for $C_{26}H_{51}N_4O_5^+$ [M + H]$^+$ 499.3854, found 499.3857.

*TE2A-EtOH: 6-Hydroxyethyl-1,4,8,11-tetraazacyclotetradecane-1,8-diacetic Acid, Ditrifluoroacetic Acid (**24**).* Compound **21** (350 mg, 0.74 mmol) was dissolved in a mixture of anhydrous CH_2Cl_2/TFA 1:1 (10 mL). The solution was stirred at room temperature for 18 h then the solvent was evaporated under reduced pressure at room temperature to give a yellow oil which was lyophilized. Compound **24** was obtained as an off-white powder (430 mg, quantitative yield). ^1H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 3.8−3.45 (m, 4H), 3.45−3.20 (m, 3H), 3.20−2.85 (m, 8H), 2.85−2.30 (m, 8H), 2.20−2.00 (m, 1H), 2.00−1.60 (m, 2H), 1.45−1.20 ppm (m, 2H). ^{13}C Jmod NMR (75 MHz, D_2O, 70 °C, TMS): δ = [179.1, 178.9] (CO), 165.3 (q, $^2J_{CF}$ = 35.3 Hz, CF_3CO_2H), 119.7 (q, $^1J_{CF}$ = 262.5 Hz, CF_3CO_2H), [65.8, 62.1, 59.8, 58.0, 57.7, 57.0 (× 2), 52.6 (× 2), 48.5, 48.3] (CH_2-α-N, CH_2-α-OH), 35.8 (CH_2-β-OH), 33.6 (CH-β-N), 25.8 ppm (CH_2-β-N). ^{19}F NMR (282 MHz, 25 °C, CD_3OD, 1-fluoro-2-nitrobenzene secondary reference set at −121.56 ppm): δ = −77.78 ppm (the integration of this peak with respect to the reference $FC_6H_4NO_2$ used in this experiment is consistent with the formulation $C_{16}H_{32}N_4$.2TFA). HRMS (ESI): *m/z* calcd for $C_{16}H_{33}N_4O_5^+$ [M + H]$^+$ 361.2445, found 361.2445.

*TETA-EtOH: 6-Hydroxyethyl-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic Acid, Tetratrifluoroacetic Acid (**25**).* Compound **22** (300 mg, 0.43 mmol) was dissolved in a mixture of anhydrous CH_2Cl_2/TFA 1:1 (12 mL). The solution was stirred at room temperature for 36 h, and then the solvent was evaporated under reduced pressure at room temperature to give a brown oil which was lyophilized. Compound **25** was obtained as an off-white solid (400 mg, quantitative yield). ^1H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 4.20−3.75 (m, 2H), 3.75−3.50 (m, 6H), 3.50−2.50 (m, 18H), 2.25−2.10 (m, 1H), 2,10−1,85 (m, 1H), 1,85−1,60 (m, 1H), 1,50−1,30 ppm (m, 2H). ^{13}C Jmod NMR (125 MHz, D_2O, 50 °C, TMS): δ = [172.2, 171.5] (CO), 162.5 (q, $^2J_{CF}$ = 36.3 Hz, CF_3CO_2H), 116.5 (q, $^1J_{CF}$ = 288.6 Hz, CF_3CO_2H), [62.1, 59.1, 55.6 (× 2), 55.5, 51.4, 50.8] (CH_2-α-N, CH_2-α-OH), 33.1 (CH_2-β-OH), 29.5 (CH-β-N), 20.8 ppm (CH_2-β-N). ^{19}F NMR (282 MHz, 25 °C, CD_3OD, 1-fluoro-2-nitrobenzene secondary reference set at −121.44 ppm): δ = −77.71 ppm (the integration of this peak with respect to the reference $FC_6H_4NO_2$ used in this experiment is consistent with the formulation $C_{20}H_{36}N_4O_9$·4TFA). HRMS (ESI): *m/z* calcd for $C_{20}H_{37}N_4O_9^+$ [M + H]$^+$ 477.2555, found 477.2560.

*CB-TE2A-EtOH: 6-Hydroxyethyl-1,4,8,11-tetraazabicyclo[6.6.2]-hexadecane-1,8-diacetic Acid, Tetratrifluoroacetic Acid (**26**).* Compound **23** (430 mg, 0.74 mmol) was dissolved in a mixture of anhydrous CH_2Cl_2/TFA 1:1 (12 mL). The solution was stirred at room temperature for 2 d, and then the solvent was evaporated under reduced pressure at room temperature to give a brown oil which was lyophilized. Compound **26** was obtained as an off-white solid (610 mg, quantitative yield). ^1H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 4.10−3.70 (m, 2H), 3.70−2.70 (m, 25H), 2.60−2.40 (m, 1H), 2.40−2.15 (m, 1H), 1.80−1.60 (m, 1H), 1.50−1.30 ppm (m, 2H). ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = [175.1, 174.9] (CO), [67.0, 65.3, 62.1, 61.3, 60.8, 58.0 (× 2), 56.0, 55.9, 51.4, 50.8, 50.5, 50.1] (CH_2-α-N, CH_2-α-OH), 34.8 (CH_2-β-OH), 29.3 (CH-β-N), 22.3 ppm (CH_2-β-N). ^{19}F NMR (282 MHz, 25 °C, CD_3OD, 1-fluoro-2-nitrobenzene secondary reference set at −121.52 ppm): δ = −77.55 ppm (the integration of this peak with respect to the reference $FC_6H_4NO_2$ used in this experiment is consistent with the formulation $C_{18}H_{34}N_4O_5$·4TFA). HRMS (ESI): *m/z* calcd for $C_{18}H_{35}N_4O_5^+$ [M + H]$^+$ 387.2602, found 387.2603.

Synthesis of Cu(II) Complexes of C-Functionalized Cyclam Based Ligands. In each case, a slight excess of $Cu(ClO_4)_2$·$6H_2O$ (0.18 mmol) was added to a solution of the ligand (0.15 mmol) in 10 mL of water, and if necessary, the pH of the solution was adjusted to ∼7 with an aqueous solution of KOH . The mixture was steered at 90 °C for 24

Table 3. X-ray Crystal Data Collection and Refinement Details of Organic Compounds

	7	**8**	**9**	**11**	**13**	**16**
formula	$C_{15}H_{24}N_4O_3$	$C_{19}H_{25}N_4O_3$	$C_{28}H_{48}N_8O_4$	$C_{19}H_{33}BrN_4O_2$	$C_{21}H_{37}BrN_4O_5$	$C_{28}H_{44}Br_2N_4O_3$
MW	308.38	371.44	560.74	429.40	505.46	644.49
crystal system	orthorhombic	monoclinic	orthorhombic	monoclinic	monoclinic	monoclinic
space group	*Pbcn*	$P2_1/c$	$Pna2_1$	$P2_1/c$	*Cc*	$P2_1$
T (K)	170(2)	170(2)	170(2)	170(2)	170(2)	170(2)
a (Å)	13.0852(13)	13.4633(18)	8.0687(5)	7.0723(2)	19.9358(19)	8.5713(6)
b (Å)	11.4562(12)	13.1738(15)	16.6793(10)	9.7167(3)	8.2953(6)	16.2981(9)
c (Å)	20.7283(19)	10.3885(14)	20.4007(11)	30.2173(12)	14.5790(14)	10.6625(8)
α (deg)	90	90	90	90	90	90
β (deg)	90	94.933(11)	90	97.090(4)	106.925(11)	104.408(8)
γ (deg)	90	90	90	90	90	90
v (Å^3)	3107.3(5)	1835.7(4)	2745.5(3)	2060.64(12)	2306.6(4)	1442.70(17)
F(000)	1328	792	1216	904	1064	668
Z	8	4	4	4	4	2
λ (Å) (Mo Kα)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
D_{calc} (g cm^{-3})	1.318	1.344	1.357	1.384	1.456	1.484
μ (mm^{-1})	0.094	0.094	0.093	2.015	1.822	2.845
θ range (deg)	3.07−26.36	3.41−26.37	2.80−26.36	2.90−30.50	3.73−26.36	3.50−26.36
R_{int}	0.1175	0.1411	0.0350	0.0422	0.0542	0.0381
reflns collect	22375	13921	20000	20240	8530	11129
unique reflns	3173	3744	5583	6226	3295	4781
GOF on F^2	0.841	0.923	1.072	0.858	0.909	0.905
R1^a	0.049	0.0650	0.0556	0.0330	0.0394	0.0355
wR2 (all data)^b	0.0849	0.1086	0.1441	0.0630	0.0711	0.0616
largest diff peak and hole (e Å^{-3})	0.156 and −0.144	0.163 and −0.191	0.466 and −0.343	0.690 and −0.536	0.522 and −0.292	0.689 and −0.317

^{a}R1 = $\sum||F_0| - |F_c||/\sum|F_0|$. ^{b}wR2 = $\{\sum[w(||F_0|^2 - |F_c|^2)^2]/\sum[w(F_0^4)]\}^{1/2}$.

Table 4. X-ray Crystal Data Collection and Refinement Details of the Cu(II) Complexes

	17·CuBr(ClO$_4$)	**17**·Cu(ClO$_4$)$_2$	**18**·Cu(ClO$_4$)$_2$	**19**·CuBr(ClO$_4$)
formula	$C_{52}H_{78}Br_2Cl_2Cu2N_8O_{11}$	$C_{26}H_{38}Cl_2CuN_4O_9$	$C_{12}H_{28}Cl_2CuN_4O_9$	$C_{28}H_{42}BrClCuN_4O_5$
MW	1349.02	685.04	506.82	693.56
crystal system	triclinic	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/c$
T (K)	170(2)	170(2)	170(2)	170(2)
a (Å)	13.3503(14)	8.9495(16)	8.6196(8)	13.0582(9)
b (Å)	14.8457(14)	13.606(2)	30.658(2)	10.9400(7)
c (Å)	15.8604(14)	25.842(5)	8.3348(9)	20.2904(13)
α (deg)	92.710(7)	77.317(15)	90	90
β (deg)	94.643(8)	82.748(14)	118.123(13)	91.285(6)
γ (deg)	110.551(9)	89.651(14)	90	90
v (Å^3)	2924.1(5)	3044.6(9)	1942.5(3)	2897.9(3)
F(000)	1392	1428	1052	1436
Z	2	4	4	4
λ, Å (Mo Kα)	0.71073	0.71073	0.71073	0.71073
D_{calc} (g cm^{-3})	1.532	1.494	1.733	1.590
μ (mm^{-1})	2.249	0.950	1.454	2.270
θ range (deg)	2.91−20.92	3.16−25.35	3.44−28.28	3.54−26.37
R_{int}	0.0909	0.1624	0.0490	0.1425
reflns collect	13515	21667	17132	21830
unique reflns	6109	11071	4822	5925
GOF on F^2	0.882	0.853	1.053	1.008
R1^a	0.0853	0.0886	0.0468	0.0802
wR2 (all data)^b	0.2480	0.2101	0.1068	0.1445
largest diff peak and hole (e Å^{-3})	0.982 and −0.992	0.671 and −0.512	0.570 and −0.399	0.550 and −0.583

^{a}R1 = $\sum||F_0| - |F_c||/\sum|F_0|$. ^{b}wR2 = $\{\sum[w(||F_0|^2 - |F_c|^2)^2]/\sum[w(F_0^4)]\}^{1/2}$.

h, solid impurities were filtered off, and the solution was concentrated. The crystals of the Cu(II) complexes used for X-ray study were obtained by slow evaporation of the solvent (water) at room temperature.

Computational Methods. All calculations were performed employing DFT within the hybrid meta-generalized gradient approximation (hybrid meta-GGA), with the TPSSh exchange-correlation functional,[36] and the Gaussian 09 package (Revision A.02).[37] Full geometry optimizations of **9** were performed in vacuo by using the standard 6-311G(d,p) basis set. No symmetry constraints have been imposed during the optimizations. The default values for the integration grid ("fine") and the SCF energy convergence criteria (10^{-8}) were used. The stationary points found on the potential energy surfaces as a result of the geometry optimizations have been tested to represent energy minima rather than saddle points via frequency analysis. Relative free energies of the *cis*/*syn* and *cis*/*anti* isomers of **9** include nonpotential energy contributions (zero point energies and thermal terms) obtained from frequency analysis. The electrostatic potential $V(r)$ that the electrons and nuclei create at any point r in the surrounding space was calculated at the MPWLYP/6-311G** level according to eq 1

$$V(r) = \sum_{A} \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')\, dr'}{|r' - r|} \qquad (1)$$

where Z is the charge on nucleus A, located at R_A, and $\rho(r)$ is the electron density of the molecule.

X-ray Diffraction Measurements. Single-crystal X-ray diffraction data were collected with graphite-monochromatized Mo Kα radiation ($\lambda = 0.71073$). Crystal data and structure refinement details are given in Tables 3 and 4. Unit cell determination and data reduction, including interframe scaling, Lorentz, polarization, empirical absorption, and detector sensitivity corrections, were carried out using attached programs of Crysalis software (Oxford Diffraction).[38] Structures were solved by direct methods and refined by full matrix least-squares method on F^2 with the SHELXL[39] suite of programs. The hydrogen atoms were identified at the last step and refined under geometrical restraints and isotropic U-constraints.[40] CCDC 977486−977496 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C NMR, MS, HRMS, and IR spectra and microanalysis. X-ray data for **7**−**9**, **11**, **13**, **16**, $\mathbf{17}\cdot CuBr(ClO_4)$, $\mathbf{17}\cdot Cu(ClO_4)_2$, $\mathbf{18}\cdot Cu(ClO_4)_2$, and $\mathbf{19}\cdot CuBr(ClO_4)$ (CIF) and optimized Cartesian coordinates of **9** obtained with DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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