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Copper(II) Complexes of the Tetraazamacrocyclic Tertiary Amide Ligand Alanyl-Cyclam

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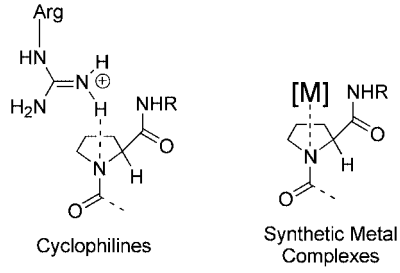
Hydrogen bonding to the electrically neutral tertiary carboxamide nitrogen atom of peptidyl-prolyl groups is known to facilitate the C–N bond rotation during peptide and protein folding. Since metal complexes with nitrogen-coordinated tertiary amide ligands are formally analogous, they may be used to model this so-called electrophilic activation. In this paper we report on the synthesis of a monoacylated cyclam complex, [(Boc-Ala-cyclam)Cu]$(CF_3SO_3)_2$ (**8**; Boc: *tert*-butyloxycarbonyl, Ala: alanine, cyclam: 1,4,8,11-tetraazacyclotetradecane). It contains a fully sp^3-hybridized metal-bound amide nitrogen atom. The resonance is completely cancelled and the observed C–N distance of 147 pm is consistent with a single bond. These features are exceptional among Werner-type complexes and define the maximal possible electrophilic distortion of an amide bond.

Introduction

The activation of tertiary carboxamides towards hydrolytic cleavage and C–N bond rotation is a topic of considerable interest. Two catchwords are the hydrolysis of β-lactam antibiotics[1] and the *cis*-*trans* isomerization about peptidyl–prolyl bonds in proteins.[2] The latter is often the slow step during protein folding and supposed to play an important role as a functional switch in different processes such as enzymatic substrate recognition[3] or neurodegenerative protein aggregation.[4] Isomerases, PPIases, are known to facilitate the amide rotation. How exactly they operate is not known, although different means to lower the rotational barrier have been discussed.[5] Particularly interesting for coordination chemists is a motif observed in the catalytic centre of cyclophilines,[6] and in histidyl peptides:[7] hydrogen bonding to the amide nitrogen atom is proposed to stabilize the pyramidal transition state structure at the nitrogen atom. This is formally analogous to the coordination of a metal ion as it has been proposed to explain the effect of siver(I) ions on the rotational barrier of dimethylacetamide.[8] An illustration of an arginine hydrogen bond in comparison with a coordinated metal center is shown in Scheme 1.



Scheme 1. Electrophilic activation of a tertiary amide group; hydrogen bonding in peptides and proteins (left), or metal coordination (right).

Based on this analogy, Lectka and colleagues have suggested that metal complexes could be developed into synthetic catalysts to trigger biological proline switches.[9] This perspective is highly interesting but suffers from the lack of information on coordination complexes containing nitrogen-bound tertiary carboxamide ligands. We have therefore started a systematic study of these unusual compounds.[10] Here we describe the synthesis and structural properties of copper(II) complexes with macrocyclic alanyl-cyclam ligands. Our aim was to place a metal ion in close proximity to an amide nitrogen atom in order to achieve full pyramidalization and complete cancellation of resonance. This limiting case is an important missing piece required for a quanitative understanding of the electrophilic amide activation.

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Results and Discussion

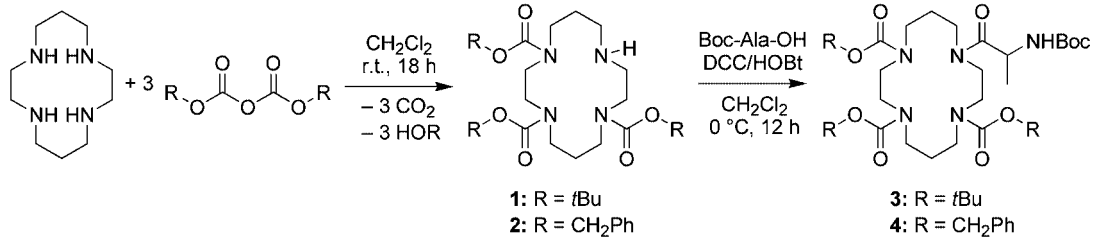
Synthesis

Our first aim was to prepare a cyclam ligand in which one of the amine functions is converted into a tertiary amide. Prior to monoacylation, three of the cyclam nitrogen atoms had to be protected. Scheme 2 shows the synthesis of triple-protected cyclam. We have synthesized the tris(*tert*-butoxycarbonyl) (Boc) and tris(benzoxycarbonyl) (Cbz) derivatives **1** and **2** according to a slightly modified route reported by Brandes et al.[11] The yields of 35–50% after flash column chromatography on silica gel were moderate in both cases. Coupling with *N*-*tert*-butoxycarbonyl-(*S*)-alanine [Boc-(*S*)-Ala-OH] was achieved by the well-established DCC/HOBt (DCC = dicyclohexylcarbodiimide, HOBt = *N*-hydroxybenzotriazole) method.[12] We have applied this method earlier to the synthesis of ruthenium-modified 1,4,7,10-tetraazacyclodecane (cyclen) ligands.[13] The isolated yields were moderate in the case of Boc-(*S*)-Ala-cyclam-Boc_3 (**3**, 70%) and low in the case of Boc-(*S*)-Ala-cyclam-Cbz_3 (**4**, 26%). The structures and the synthesis of both compounds are shown in Scheme 2.

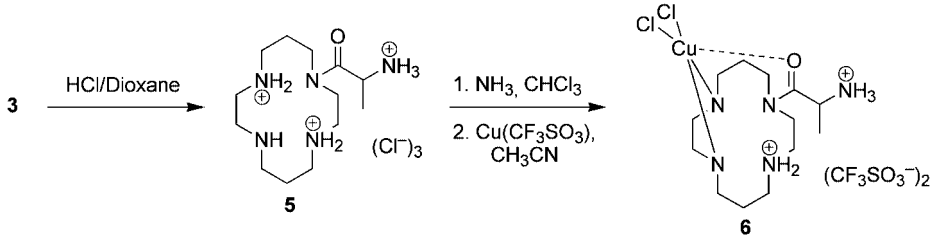
Acid deprotection of Boc-(*S*)-Ala-cyclam-Boc_3 was achieved with aqueous HCl in dioxane.[13] Scheme 3 shows the structure of the tris(hydrochloride) salt **5** which was characterized by an X-ray structure analysis (Figure 1). In order to facilitate binding of a copper(II) ion inside the macrocyclic ring and to enhance the solubility of the ligand in organic aprotic solvents, we attempted to remove most of the HCl. An interesting and revealing result was obtained with a ligand sample obtained by passing an NH_3 stream through a suspension of **5** in chloroform. The soluble product was isolated and reacted with copper(II) triflate in acetonitrile. Unfortunately, we were not able to obtain single crystals of the complex formed. However, its IR spectrum shows a shift of the carbonyl band from 1625 cm^{-1} to 1592 cm^{-1}. This clearly indicates that the metal ion does not bind to the amide nitrogen atom which would cause a high energy shift due to the reduced amide resonance.[14] We propose the structure **6** shown in Scheme 3 with a bidentate ethylenediammine part of the cyclam ligand and two chloride ions coordinated to the copper(II) ion. This is based on the analogy to observations in related acylated triazacyclononane complexes by Houser et al.[15] and supported by C,H,N,S elemental analysis data. The shift of the carbonyl IR band indicates that the amide oxygen atom may also coordinate.

We concluded from the results summarized in Scheme 3 that complete removal of HCl from the ligand **5** is a prerequisite for the coordination of the tertiary amide nitrogen atom in copper complexes. Since this required a strong base, NaOH in dichloromethane was applied to prepare the acid-free ligand. Subsequent reaction with $Cu(CF_3SO_3)_2$ in acetonitrile and layering with diethyl ether yielded a violet material with elemental analysis data indicating the constitution $[(Ala\text{-}cyclam)(H_2O)Cu](CF_3SO_3)_2 \cdot 0.25Et_2O$. There is no evidence for the presence of chloride in the sample and an IR band at 1756 cm^{-1} is consistent with a nitrogen-bound amide ligand. However, a second IR band at 1592 cm^{-1} with a shoulder at 1649 cm^{-1} indicates that a mixture of N- and O-coordinated tertiary amide complexes is present and we were not able to separate these species. It is not yet clear whether trace impurities of chloride or an unknown coordination mode involving the free amine function of the amino acid moiety is responsible for this behaviour.

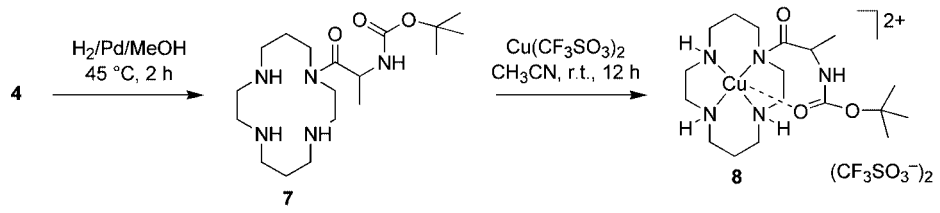
Our failure to obtain well-defined N-coordinated amide complexes from the protonated ligand **5** reflects the difficulties involved in the synthesis of such compounds. Even though the cyclam framework should strongly favour coordination of a copper(II) ion within the ring, the system avo-



Scheme 2. Synthesis of the Boc- and Cbz-protected Boc-(*S*)-alanylcyclam derivatives Boc-(*S*)-Ala-cyclam-Boc_3 (**3**) and Boc-(*S*)-Ala-cyclam-Cbz_3 (**4**).



Scheme 3. Acid deprotection of Boc-(*S*)-Ala-cyclam-Boc_3 (**3**) and the reaction of Ala-cyclam·3HCl (**5**) with copper(II) triflate.



Scheme 4. Hydrogenation of the Cbz-protected compound **4** to the free ligand **7** and synthesis of the copper complex [{Boc-(*S*)-Ala-cyclam}Cu]$(CF_3SO_3^-)_2$ (**8**).

ids coordination of the weak amide donor. It is therefore not surprising that amide nitrogen coordination was unknown before the 1990s and has been categorically ruled out in several important older articles on amide complexes.[16] We reasoned that in our case a protecting group would be preferable which can be removed without protonation of the ligand. The Cbz function turned out to be a good choice.[17] It is cleaved off by hydrogenation in the presence of a palladium catalyst in methanol. This and the following reaction of Boc-(*S*)-Ala-cyclam (**7**) with $Cu(CF_3SO_3)_2$ is shown in Scheme 4. The copper complex [{Boc-(*S*)-Ala-cyclam}Cu]$(CF_3SO_3)_2$ (**8**) was obtained with a yield of 74%. Its composition was confirmed by C,H,N,S elemental analysis and FAB mass spectrometry. The IR spectrum shows two bands at 1742 cm^{-1} for the amide function and 1658 cm^{-1} for the Boc protecting group. The blue shift of the amide band is in excellent agreement with our data on a $Cu(CF_3SO_3)_2$ of dipicolyl-*N*-boc-glycylamide[10a] and confirms amide nitrogen coordination in the bulk sample. An X-ray structure analysis of the complex is discussed below.

X-ray Structure Analyses

Single crystals were obtained from the ligand tris(hydrochloride) salt **5** and the copper complex **8**. An ORTEP plot representing the structure of the cation in **5** is shown in Figure 1. All hydrogen atoms were localized in the electron density map. The alanyl nitrogen atom N5 and the two cyclam atoms N2 and N4 are positively charged. Hydrogen bonds between those ammonium functions and the chloride ions loosely connect individual molecules in a three-dimensional network. Most important for our study is the geometry of the tertiary amide function. Deviations from planarity are most conveniently described by two quantitative parameters defined by Winkler and Dunitz.[18] One is the twist angle τ between the C1–C10 and the C12–O1 axes which ranges from 0° to 90°. The second is the pyramidalization χ_N at the nitrogen atom. It varies between 0° for a planar environment and ca. 60° for a fully pyramidal geometry. We will later discuss how the binding of metal ions deplanarize an amide group and how this activation affects the C–N bond length. In this context, ligand structures are useful for comparison. The C11–N1 bond length in **5** of 135.7 pm and the small twist angle τ = 9.3° are typical for an undistorted amide function. Interestingly, a significant pyramidalization at the nitrogen atom of χ_N = 17.7° is observed. This is larger than in related dipicolylamide derivatives[10b] although not unusual for carboxamides. Large deviations from planarity are possible because the energy barrier for out-of-plane wagging is rather low.[19] An examination of amide structures by Gilli et al. reveals that χ_N can reach values of over 20° without a significant elongation of the C–N bond.[20] Much effort of organic chemists focused on the effects of distortion on non-planar amides which model different stages during the C–N-bond rotation.[21] It was shown that geometric strain can enforce significant twisting and pyramidalization. However, the effects on the C–N bond lengths are generally rather small and the variety of different compounds having the amide group as a part of an acyclic, cyclic, or polycyclic structure make quantitative correlations difficult. An examination of different structures leads to the conclusion that the amide C–N bond is only affected when χ_N reaches values of ca. 30°. This has not been specifically addressed by other authors but it is interesting in the context of our observations on metal complexes. We will show below that the latter provide a better basis for quantitative structure correlations since their amide groups are not forced into a rigid structure which may obscure changes in the C–N bond length. A key compound in our studies is the copper complex **8** which contains a fully pyramidalized amide nitrogen atom.

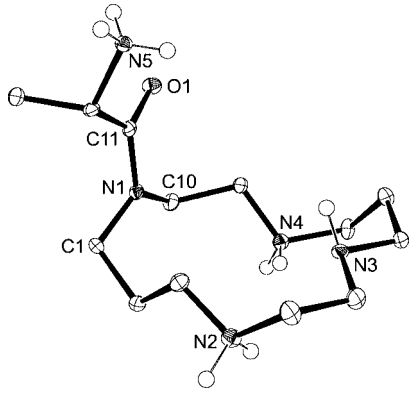


Figure 1. ORTEP plot at 50% probability of the cation Ala-cyclam·$3H^+$ (**5**) (hydrogen atoms except for NH are omitted for clarity); selected bond lengths [pm], angles [°], τ [°], and χ_N [°]: C11–N1 135.7(2), C11–O1 123.3(2); C1–N1–C10 118.1(2), C1–N1–C11 124.3(2), C10–N1–C11 115.3(2); τ = 9.3; χ_N = 17.7.

Compound **8** crystallizes in the acentric space group $P2_1$ with two independent complexes **A** and **B** in the asymmetric unit. They are depicted in Figure 2. In complex **8A** the copper ion is bound in the center of the cyclam ligand which

coordinates in the typical *trans*-III mode[22] with one five-membered chelate ring in the δ, one in the λ, and both six-membered rings in the chair configuration. The Boc protecting group is weakly bound at a distance Cu1–O2 of 248.8 pm and a triflate ion is positioned in the apical position of a distorted octahedron with a long contact of Cu1–O63 of 278.9 pm. The second complex **8B** also has a *trans*-III type cyclam ligand but one of the six-membered chelate rings is in the rare boat form.[23] As a consequence, the proton H20b of the central methylene group is only 270.5 pm away from the copper centre and there is no room for an apical triflate ion. The coordinated Boc group compensates for the lack of σ-donation and binds at a distance of Cu2–O5 of 230.5 pm, which is 13.3 pm shorter than the corresponding contact in **8A**. However, the coordinated tertiary amide function is not much affected by these differences.

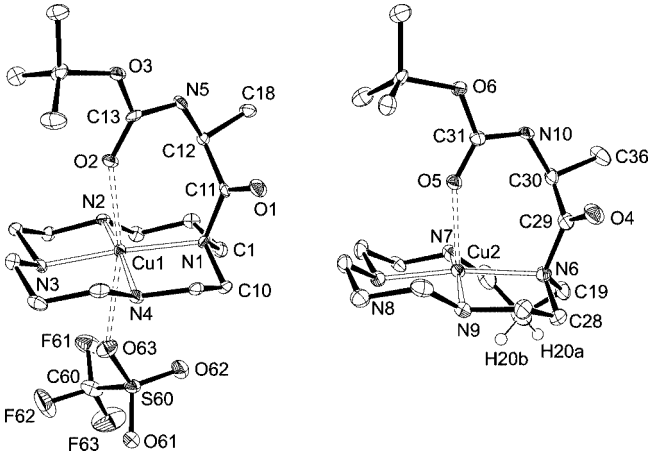


Figure 2. ORTEP plots at 50% probability of the two complexes **A** and **B** observed in the structure of [{Boc-(*S*)-Ala-cyclam}Cu]$(CF_3SO_3)_2$ (**8**) (hydrogen atoms except for those located at C20 in complex **B**, and the three non-coordinating triflate ions are omitted for clarity); selected distances [pm], angles [°], τ [°], and χ_N [°] of **A**: Cu1–N1 212.7(3), Cu1–N2 201.2(3), Cu1–N3 202.1(3), Cu1–N4 200.5(3), Cu1–O2 248.8(2), Cu1–O63 278.9, C11–N1 146.9(4), C11–O1 120.2(4); N1–Cu1–N2 95.3(2), N1–Cu1–N3 175.7(2), N1–Cu1–N4 86.7(2), N1–Cu1–O2 92.4(2), N2–Cu1–N3 86.7(2), N2–Cu1–N4 170.3(2), N2–Cu1–O2 92.7(2), N3–Cu1–N4 90.7(2), N3–Cu1–O2 91.4(2), N4–Cu1–O2 96.7(2), Cu1–N1–C1 112.4(2), Cu1–N1–C10 100.6(2), Cu1–N1–C11 112.8(2), C1–N1–C10 109.8(3), C1–N1–C11 112.8(2), C10–N1–C11 109.3(2); τ = 35.8; χ_N = 58.5; selected distances [pm], angles [°], τ [°], and χ_N [°] of **B**: Cu2–N6 214.7(3), Cu2–N7 203.1(3), Cu2–N8 200.9(3), Cu2–N9 202.1(3), Cu2–O5 230.5(2), Cu2–H20b 270.5, C29–N6 146.2(5), C29–O4 119.9(5); N6–Cu2–N7 96.3(2), N6–Cu2–N8 172.02(2), N6–Cu2–N9 85.3(2), N6–Cu2–O5 92.2(2), N7–Cu2–N8 85.5(2), N7–Cu2–N9 165.7(2), N7–Cu2–O5 97.3(2), N8–Cu2–N9 91.1(2), N8–Cu2–O5 93.3.4(2), N9–Cu–O5 96.8(2), Cu2–N6–C19 112.5(2), Cu2–N6–C28 102.6(2), Cu2–N6–C29 109.2(2), C19–N6–C28 110.4(3), C19–N6–C29 110.9(3), C28–N6–C29 111.1(2); τ = 30.6; χ_N = 56.9.

The stereochemistry of the amino acid part is in both cases (*S*) at the stereogenic α-carbon atom and (*Rp*) with respect to the chiral plane defined by the amide function. This implies that the methyl group is *exo* with respect to the seven-membered chelate ring formed by the coordinating Boc group and is analogous to the situation in a cadmium(II) complex of dipicolyl-Boc-alanylamide.[10a] The Cu–N(amide) distances (**8A**: 212.7 pm; **8B**: 214.7) are not much longer than the contacts between the copper ion and the secondary amine group which have typical values of 200–203 pm. A comparison with the few known copper(II) complexes with N-coordinated tertiary amide ligands shows that the Cu–N(amide) bond in **8** is unusually short. A recently published diisopropyl-triazacyclononane acetamide copper(II) chloride complex by Watkinson et al. has a Cu–N distance of 251.1 pm[24] and a paper by Schröder et al. reports on a related triazacyclononane derivative with a distance of 261.1 pm.[25] The closest contact observed in a dipicolylamide derivative is 216.4 pm in a copper(II) triflate complex from our group.[10c] The short Cu–N(amide) distance in **8** corresponds to a fully pyramidalized nitrogen atom as is evident from the pyramidalization parameter χ_N of almost 60° (**8A**: 58.5°; **8B**: 56.9°). Again, these values are exceptional in that they are the highest observed in Werner-type complexes to date.

In accord with this finding the C–N distance of 146 pm is typical for a single bond (147 pm[26]) and indicates that the amide resonance[27] is completely cancelled. It is interesting to compare this result with the situation in Schröder's complex with its long Cu–N(amide) distance of 261.1 pm which is significantly larger than the sum of the ionic radii of a six-coordinate Cu^{2+} ion (87 pm) and the van der Waals radius of a nitrogen atom (160 pm).[26] This weak electrostatic interaction suffices to induce a significant pyramidalization at the nitrogen atom (χ_N = 30°), whereas the C–N distance of 135.7 pm is typical for an undistorted organic carboxamide. Further support for this interpretation is provided by Schindler et al.[28] who described the pyramidalization of a secondary amide group located 282.7 pm above the copper(II) ion the apical position of a square-pyramidal complex. These data are very important and confirm that with our new complex **8** Werner-type nitrogen-coordinated tertiary carboxamide complexes now span the whole range of electrophilic amide activation.

Conclusions

With the crystallographic characterization of **8**, we have shown that forcing a metal center into a macrocyclic cyclam ring with a neutral amide N-donor produces a completely non-resonant tertiary carboxamide. The complex defines an upper limit for nitrogen pyramidalization and C–N bond elongation achievable by purely electrophilic activation without geometric strain. In this respect, it complements the generation of a purely organic amino ketone in Kirby's most twisted amide, 3,5,7-trimethyl-1-azaadamantan-2-one.[29]

Experimental Section

General Methods: Spectra were recorded with the following instruments: IR: Mattson Polaris FT IR. UV/Vis: Varian Cary 1G spectrophotomer. ^1H and ^{13}C NMR: Bruker Avance DPX 300. All chemical shifts are referenced to TMS ($CDCl_3$) or TSP (D_2O) as

internal standards, with high frequency shifts recorded as positive. MS: Varian MAT 212 (FD, FAB) and Micromass ZabSpec (FAB) mass spectrometer. Elemental analysis: Carlo Erba Elemental Analyser 1106 (C,H,N), and Carlo Erba Elemental Analyser 1108 (C,H,N,S). All reactions except for the syntheses of cyclam-Boc_3 (**1**) and cyclam-Cbz_3 (**2**) were carried out in absolute solvents under dry nitrogen. The subsequent workup was performed under ambient laboratory conditions unless stated otherwise. The synthesis of cylam-Boc_3 is a slight modification of a literature procedure.[11] Absolute solvents (CH_2Cl_2, Et_2O, CH_3CN) were purchased from Fluka, stored under nitrogen and used without further purification. All other chemicals and deuterated solvents were obtained from Aldrich.

Syntheses

Cyclam-Boc_3 (1): A solution of di-*tert*-butyl pyrocarbonate (Boc_2O, 2.72 g, 12.5 mmol) in 150 mL of CH_2Cl_2 was added dropwise at room temperature over a period of 6 h to a stirred solution of cyclam (1.00 g, 5.00 mmol) in 300 mL of CH_2Cl_2. Stirring was continued for 12 h and the solvent stripped by rotary evaporation. The oily residue was dissolved in a minimum amount of diethyl ether. Rapid stripping of all solvent and drying under vacuum yielded a pale-yellow foam which was re-dissolved in CH_2Cl_2/CH_3OH (95:5) and purified by flash column chromatography on silica; using the solvent as the eluent yielded 1.08 g (2.13 mmol, 51.1%) of cyclam-Boc_3 as a colourless, hygroscopic solid. FD-MS [$CHCl_3$; $C_{25}H_{48}N_4O_6$ (500.68)]: *m*/*z* = 501 [M^+]. ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 27 H, Boc), 1.70 (m, 2 H, cyclam), 1.92 (m, 2 H, cyclam), 2.61 (t, 2 H, cyclam), 2.78 (t, 2 H, cyclam), 3.27–3.39 (m, 12 H, cyclam) ppm.

Boc-(*S*)-Ala-cyclam-Boc_3 (3): Boc-Ala-OH (1.02 g, 5.40 mmol), **1** (2.45 g, 4.90 mmol), *N*-hydroxybenzotriazole (0.71 g, 5.22 mmol), and NEt_3 (1.41 mL, 9.98 mmol) were dissolved in 300 mL of CH_2Cl_2 and the mixture was stirred with cooling at 0 °C. Dicyclohexylcarbodiimide (1.76 g, 8.47 mmol) in 20 mL of CH_2Cl_2 was added in one portion. The solution was warmed slowly to room temperature after which stirring was continued for 12 h. The resulting mixture was filtered and the volume of the filtrate was reduced to 1/2 by rotary evaporation. Filtration was repeated after storage at –18 °C overnight. The filtrate was washed 3 times with aqueous 5% $NaHCO_3$ and 3 times with saturated aqueous NaCl, dried with solid $MgSO_4$ and filtered. All solvent was removed by rotary evaporation and the residue purified by flash column chromatography on silica gel using CH_2Cl_2/CH_3OH (95:5) as the eluent. All solvent was removed by rotary evaporation and the solid residue dissolved in a minimum amount of diethyl ether. Rapid stripping of the solvent and drying under vacuum yielded 2.42 g (3.60 mmol, 73.5%) of **3** as a colourless hygroscopic solid. $C_{33}H_{61}N_5O_9$·0.33H_2O (671.87+6.00): calcd. C 58.47, H 9.17, N 10.33; found C 58.65, H 10.59, N 10.33. FD-MS ($CHCl_3$): *m*/*z* = 672 [M^+]. ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 3 H, $^{\beta}CH_3$), 1.45 (m, 36 H, Boc), 1.74 (m, 4 H, cyclam), 3.14–3.69 (m, 16 H, cyclam), 4.56 (m, 1 H, $^{\alpha}$CH), 5.19–5.50 (m, 1 H, NH) ppm.

(*S*)-Ala-cyclam·3HCl (5): Compound **3** (2.42 g, 3.60 mmol) was treated with 15 mL of a cold 4 N HCl/dioxane solution with stirring at 0 °C. Stirring was continued without further cooling for 12 h. The product Boc-Ala-cyclam·3HCl·4H_2O formed 1.36 g (3.00 mmol, 83.4%) of a colourless precipitate which was collected on a glass filter funnel, washed with hot ethanol (3 × 50 mL) and diethyl ether (3 × 20 mL), and dried under vacuum. $C_{13}H_{29}N_5O$·3HCl·4H_2O (452.79): calcd. C 34.45, H 8.83, N 15.46; found C 34.39, H 9.15, N 15.29. ^{1}H NMR (D_2O): δ = 1.46 (d, 3 H, $^{\beta}CH_3$), 2.22 (m, 4 H, cyclam), 2.92–4.00 (m, 16 H, cyclam), 4.40 (q, 1 H, $^{\alpha}$CH) ppm. IR (KBr): $\tilde{\nu}$ = 3178 (NH_3^+), 1646 (amide) cm^{-1}.

[(Boc-Ala-cyclamH_2)$CuCl_2$](CF_3SO_3)$_2$ (6): Tris(hydrochloride) salt **5** (2.51 g, 6.02 mmol) was suspended in 100 mL of $CHCl_3$ and the solution cooled to 0 °C. A slow stream of NH_3 gas was passed through the reaction mixture. After 1.5 h, the mixture was warmed to room temperature. Precipitated ammonium chloride was filtered off, the filtrate concentrated to dryness and the residue treated with 50 mL of CH_2Cl_2. Insoluble material was removed by filtration and all solvent by rotary evaporation. Drying under vacuum afforded a colourless resin (1.62 g). This compound (1.31 g) was dissolved in 200 mL of CH_3CN. A solution of Cu(CF_3SO_3)$_2$ in 150 mL of CH_3CN was added dropwise with stirring over a period of 1 h. The reaction mixture turned deep blue. Stirring was continued at room temperature for 12 h. The solution was concentrated to dryness and the residue re-dissolved in a minimum amount of CH_3CN. Layering with diethyl ether and storage at –18 °C overnight afforded the product **6** as a blue precipitate which was isolated by filtration and dried under vacuum [2.46 g, 3.49 mmol, 72.2% based on Cu(CF_3SO_3)$_2$]. $C_{15}H_{31}Cl_2CuF_6N_5O_7S_2$ (706.01): calcd. C 25.52, H 4.43, N 9.92, S 9.08; found C 25.42, H 4.34, N 9.63, S 8.92. IR (KBr): $\tilde{\nu}$ = 3244 (R–NH_3^+), 1592 (amide) cm^{-1}. UV/Vis (CH_3CN): λ_{max} (lgε) = 619 (2.17 $M^{-1}cm^{-1}$) nm. FAB-MS (nitrobenzyl alcohol): *m*/*z* = 483 [M – 2 HCl – CF_3SO_3]$^+$.

[(Ala-cyclam)(H_2O)Cu](CF_3SO_3)$_2$·0.25Et_2O: A mixture of **5** (450 mg, 1.08 mmol) and excess $NaOH^{(s)}$ was suspended in ca. 50 mL of CH_2Cl_2 at room temperature. The suspension was stirred for 24 h. Insoluble material was removed by filtration and the clear filtrate concentrated to dryness. Drying under vacuum afforded the free base as a colourless oily residue. It was dissolved in 50 mL of CH_3CN and Cu(CF_3SO_3)$_2$ (340 mg, 0.94 mmol) was added in small portions to the stirred solution. Stirring was continued for 12 h. The mixture was filtered and the clear blue filtrate layered with Et_2O. Upon storage at –18 °C the product precipitated as a violet oily residue. Separation and drying under vacuum afforded the product (446 mg, 0.73 mmol, 77.7%) as a violet solid. FD-MS (CH_3CN): *m*/*z* = 484 [MH – CF_3SO_3]$^+$. $C_{15}H_{29}CuF_6N_5O_7S_2$·1$H_2O$·0.25$Et_2O$ (651.10+18.53): calcd. C 28.70, H 5.04, N 10.46; found C 28.60, H 4.78, N 10.17. IR (KBr): $\tilde{\nu}$ = 3342, 3226 (NH_3^+), 1756, 1649 (shoulder), 1592 cm^{-1}.

cyclam-Cbz_3 (2): A solution of dibenzyl pyrocarbonate (Cbz_2O, 7.20 g, 25.00 mmol) in 500 mL of CH_2Cl_2 was added dropwise at room temperature over a period of 6 h to a stirred solution of cyclam (2.00 g, 10.00 mmol) in 200 mL of CH_2Cl_2. Stirring was continued for 12 h and the solvent stripped by rotary evaporation. The oily residue was dissolved in a minimum amount of dichloromethane and the pale yellow solution was filtered through silica gel. The filtrate which contained benzyl alcohol was discarded and the compound was eluted with methanol. All solvent was removed by rotary evaporation and drying under vacuum. The residue was re-dissolved in a minimum amount of CH_2Cl_2/CH_3OH (98:2) and purified by flash column chromatography on silica using the solvent as the eluent. The colourless, oily compound was repeatedly treated with small quantities of diethyl ether which was stripped under vacuum until formation of a foam; 1.80 g (2.99 mmol, 35.9%) of the product **2** was obtained as a highly hygroscopic, colourless resin. FD-MS [$CHCl_3$; $C_{34}H_{42}N_4O_6$ (602.72)]: *m*/*z* = 603 [M^+]. ^{1}H NMR ($CDCl_3$): δ = 1.64 (m, 2 H, cyclam), 1.93 (m, 2 H, cyclam), 2.55 (m, 2 H, cyclam), 2.76 (m, 2 H, cyclam), 3.10–3.52 (m, 12 H, cyclam), 5.03 (s, 2 H, Ph-CH_2), 5.12 (s, 4 H, Ph-CH_2), 7.33 (m, 15 H, C_6H_5) ppm.

Boc-Ala-cyclam-Z_3 (4): Boc-Ala-OH (0.62 g, 3.28 mmol), **2** (1.79 g, 2.97 mmol), *N*-hydroxybenzotriazole (0.43 mg, 3.17 mmol), and

NEt_3 (0.85 mL, 6.06 mmol) were dissolved in 150 mL of CH_2Cl_2 and the mixture stirred with cooling at 0 °C. Dicyclohexylcarbodiimide (1.07 g, 5.14 mmol) in 10 mL of CH_2Cl_2 was added in one portion. The solution was warmed slowly to room temperature after which stirring was continued for 12 h. The resulting mixture was filtered and the volume of the filtrate was reduced to 1/2 by rotary evaporation. Filtration was repeated after storage at –18 °C overnight. The filtrate was washed 3 times with aqueous 5% $NaHCO_3$ and 3 times with saturated aqueous NaCl, dried with solid $MgSO_4$ and filtered. All solvent was removed by rotary evaporation and the residue purified by flash column chromatography on silica gel using CH_2Cl_2/CH_3OH (95:5) as eluent. All solvent was removed by rotary evaporation and the solid residue dissolved in a minimum diethyl ether. Drying under vacuum yielded 595 mg (0.77 mmol, 25.9%) of **4** as a colourless hygroscopic solid. $C_{42}H_{55}N_5O_9 \cdot 0.5Et_2O$ (773.91+37.06): calcd. C 65.16, H 7.46, N 8.64; found C 65.46, H 8.27, N 8.90. FD-MS ($CHCl_3$): *m*/*z* = 774 [M^+]. ^1H NMR ($CDCl_3$): δ = 1.26 (m, 3 H, $^{\beta}CH_3$), 1.43 (2 s, 9 H, Boc), 1.71 (m, 4 H, cyclam), 3.05–3.75 (m, 16 H, cyclam), 4.45 (m, 1 H, $^{\alpha}CH$), 4.86–5.19 (m, 7 H, Ph-CH_2 + NH), 7.13–7.45 (m, 15 H, C_6H_5) ppm.

Boc-Ala-cyclam (7): A solution of **2** (315 mg, 0.41 mmol) in absolute methanol was transferred to a flask containing catalytic amounts of Pd/C and equipped with a hydrogen inlet, a reflux condenser, a magnetic stir bar, and a mineral oil bubbler. Nitrogen was passed over the suspension for 15 min. The mixture was heated to 45 °C in an oil bath and a slow stream of H_2 was applied for 2 h. The flask was then flushed with N_2 and the suspension filtered through Celite at room temperature. Rotary evaporation of the solvent and drying under vacuum yielded 116 mg (0.31 mmol, 76.0%) of **4** as a hygroscopic resin. It was characterized by ^1H NMR spectroscopy and used without further purification. ^1H NMR ($CDCl_3$): δ = 1.29 (m, 3 H, $^{\beta}CH_3$), 1.42 (s, 9 H, Boc), 1.59–2.00 (m, 6 H, cyclam), 2.45–3.12 (m, 10 H, cyclam), 3.19–3.80 (m, 4 H, cyclam), 4.59 (m, 1 H, $^{\alpha}CH$), 5.41 (m, 1 H, NH) ppm.

[(Boc-Ala-cyclam)Cu](CF_3SO_3)$_2$ (8): Boc-Ala-cyclam (116 mg, 0.31 mmol) was dissolved in 25 mL of absolute acetonitrile and a solution of anhydrous $Cu(CF_3SO_3)_2$ (112 mg, 0.31 mmol) in 25 mL of absolute acetonitrile was added dropwise with stirring over a period of 30 min. The blue solution gradually turned deep purple. Stirring was continued at room temperature overnight and all solvent removed by evaporation under vacuum. The crude product was re-dissolved in CH_2Cl_2 and insoluble materials were removed by filtration. Drying of the filtrate under vacuum yielded the product as a deep purple solid; yield 209 mg (0.29 mmol, 92.0%). $C_{20}H_{37}CuF_6N_5O_9S_2 \cdot 2CH_2Cl_2$ (903.11): calcd. C 29.26, H 4.58, N 7.76; found C 29.34, H 4.60, N 8.05. IR (KBr): $\tilde{\nu}$ = 1742 (amide); 1658 (Boc) cm^{-1}. UV/Vis (CH_3CN): λ_{max} (lgε) = 540.4 (1.89 $M^{-1}cm^{-1}$) nm. FAB-MS (nitrobenzyl alcohol): *m*/*z* = 583 [M – CF_3SO_3]$^+$.

X-ray Structure Analyses: Colorless blocks of Ala-Cyclam·3HCl (**5**) were obtained by precipitation from diethyl ether/ethanol and recrystallization of the solid from D_2O upon slow evaporation of the solvent at room temperature. The copper complex salt **8**·1/8H_2O crystallized upon slow concentration of a dichloromethane/acetonitrile solution. Details of the X-ray structure analyses are summarized in Table 1. Suitable single crystals were embedded in protective perfluoropolyether oil and data were collected at 100 K with a Bruker-Nonius KappaCCD diffractometer using Mo-K_α radiation (λ = 0.71073 Å, graphite monochromator). Images were taken using φ- and ω-rotations with a rotation angle of 2.0° for **5** and 1.8° for **8**·1/8H_2O. An irradiation time of 80 s per frame was applied for **5** and 432 s per frame for **8**·1/8H_2O. Lorentz and polarization corrections were applied. Semi-empirical absorption corrections based on equivalent reflections were made using the program SADABS.[30] All structures were solved by direct methods and refined using full-matrix least-squares procedures on F^2 using the program package SHELXTL NT 6.12.[31] All non-hydrogen atoms were refined anisotropically. One of the triflate ions in **8**·1/8H_2O was disordered. Two positions with occupation factors of 0.75 and 0.25 were refined. All hydrogen atoms in **5** were located in the difference Fourier map and refined with isotropic displacement parameters being 1.2 or 1.5 times *U*(eq) of the corresponding C or N atom. All hydrogen atoms in **8**·1/8H_2O (except for those of the water which were located in the difference Fourier map and not refined) were geometrically positioned with isotropic displacement parameters being 1.2 or 1.5 times *U*(eq) of the corresponding C, N or O atom. CCDC-262792 (**5**) and -262793 (**8**·1/8H_2O) 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.

Table 1. Details of the crystal structure analyses.

Compound	**5**	**8**·1/8H_2O
Empirical formula	$C_{13}H_{32}Cl_3N_5O$	$C_{20}H_{37.25}CuF_6N_5O_{9.125}S_2$
Formula mass	380.79	735.46
Temperature [K]	100(2)	100(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
a [Å]	11.491(2)	11.762(2)
b [Å]	12.262(2)	13.274(1)
c [Å]	13.605(1)	19.890(2)
α [°]	90	90
β [°]	90	103.380(6)
γ [°]	90	90
Volume [Å^3]	1901.3(5)	3021.1(6)
Z	4	4
Calculated density [Mg/m^3]	1.330	1.617
Absorption coefficient [mm^{-1}]	0.491	0.953
F(000)	816	1521
Crystal size[mm]	0.24×0.23×0.14	0.23×0.15×0.05
θ range [°]	3.43–28.28	3.42–27.10
Index ranges	$-15 \le h \le 15$	$-14 \le h \le 14$
	$-16 \le k \le 15$	$-17 \le k \le 16$
	$-18 \le l \le 18$	$-25 \le l \le 25$
Reflections collected/unique	28742/4702	56796/12866
Refinement method	based on F^2	based on F^2
Data/restraints/parameters	4702/0/295	12866/1/830
Goodness-of-fit on F^2	1.069	0.925
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0318	*R*1 = 0.0430
	*wR*2 = 0.0635	*wR*2 = 0.0773
R indices (all data)	*R*1 = 0.0428	*R*1 = 0.0799
	*wR*2 = 0.0668	*wR*2 = 0.0874
Largest diff. peak/hole [e·Å^{-3}]	0.251/–0.289	0.601/–0.514

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