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Synthesis and Characterisation of PY2- and TPA-Appended Diphenylglycoluril Receptors and Their Bis-Cu(I) Complexes

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Abstract

A number of metallohosts mimicking dinuclear copper oxygenases have been designed and synthesized. These metallohosts combine a substrate binding site, i.e. the diphenylglycoluril basket receptor, with two types of metal binding ligands, viz. tri-coordinating (bis(2-ethylpyridine)amine (PY2) and tetra-coordinating tris(2-methylpyridine)amine (TPA). The preparation of the bis-Cu(I) complexes of the ligand-appended receptors and their characterization by NMR are reported. NMR data provide evidence for a dynamic inclusion behaviour of some of the pyridine moieties in the receptor of both the metal free ligands and the Cu(I) complexes.

Introduction

Copper proteins that transport or activate dioxygen are abundant in Nature.^{1,2,3,4} Hemocyanin transports O₂ in molluscs and arthropods,^{2,5,6} tyrosinase causes pigment formation in plants and animals,⁷ while dopamine- β -hydroxylase and peptidylglycine α -amidating mono-oxygenase assist in neurotransmitter biosynthesis/hormone regulation in vertebrate brains.^{8,9} These proteins have different functions, yet they all contain the same metal ion in their active site. A biological dinuclear copper site can bind dioxygen in a side-on μ - η^2 : η^2 mode, as was established by X-ray crystallography for oxy-hemocyanin (Figure 1A).⁵ A similar active site was recently observed by X-ray crystallography in

catechol oxidase^{10,11} (Figure 1B) and was suggested to be present in other enzymes by similarities in EXAFS and UV-Vis spectroscopic features.^{12,13} The dinuclear copper enzymes that bind and activate molecular oxygen for reaction with exogenous substrates use the same metal-containing active site for dioxygen binding as hemocyanin, but combine it with a binding site for organic substrates that is missing in hemocyanin.^{14,15}

--- FIGURE 1 ---

We have started a programme to develop synthetic mimics for the dinuclear copper proteins and enzymes, not only in order to better understand their mechanisms of action, but also to develop new selective clean catalysts for oxidation processes.¹⁶ In the design of these biomimetic catalysts, we covalently attach ligands for catalytically active metals to synthetic receptors such as diphenylglycoluril and cyclodextrins. An abundance of synthetic copper complexes that model biological oxygen binding and activation have been reported.^{1,3,4,17,18,19,20} A ligand that has been used to model biological tri-coordinated Cu(I) sites such as the ones shown in Figure 1 is bis(2-ethylpyridyl)-amine (PY2, **1**) (Figure 2, left), which is synthetically easily accessible and can be readily functionalised.²¹ Enzymes with tetracoordinate Cu ions are also found, e.g. Cu(II) in Cu,Zn superoxide dismutase, which is coordinated by four histidine residues.²² A synthetic tetradentate ligand is tris(2-methylpyridyl)amine (TPA, **2**) (Figure 2, right).²³ As shown in Figure 2, a $\mu\text{-}\eta^2\text{:}\eta^2$ dioxygen binding mode such as found in hemocyanin is observed for PY2, whereas a trans- $\mu\text{-}1,2$ peroxo dioxygen binding mode is observed for TPA.^{1,3,19}

--- FIGURE 2 ---

A receptor referred to as a ‘molecular clip’ which was previously designed by our group is based on diphenylglycoluril and selectively binds 1,3-dihydroxybenzenes (**3**, Figure 3, top).^{13,24,25} This clip has been enlarged to a so-called ‘molecular basket’ by attachment of two crown ether moieties (**4**, Figure 3, bottom).^{26,27} This molecular basket has two positions available (R) for attachment of two ligand sets for Cu(I) ions, creating the metal site in this synthetic model.

--- FIGURE 3 ---

We have previously reported on the dinuclear Cu(I) complex of a molecular basket in which two PY2 units are attached to the receptor via *m*-xylyl linkers (**5**, Figure 4).^{28,29} Dioxygen was bound by this complex in a $\mu\text{-}\eta^2\text{:}\eta^2$ species, which unfortunately was not stable and displayed oxidative N-dealkylation of the ligand, before it could attack exogenous substrates (Figure 4). One of the benzylic hydrogen atoms of the *m*-xylyl linker is in close proximity to the reactive Cu(II)₂O₂ complex. This benzylic position is oxidized, leading to the formation of the aldehyde of the ligand and free PY2 **1**.³⁰

--- FIGURE 4 ---

We now report on the synthesis and characterization of new biomimetic catalysts for dinuclear copper enzymes based on the diphenylglycoluril basket (Figure 5). In the design of the first type of mimic, the *m*-xylyl linker in **5** is replaced by an aliphatic butyl linker, affording receptor **6** (PY2-appended receptor), which no longer contains benzylic positions. For reasons of comparison the butyl linker in receptor **6** was selected to be approximately of the same length as the *m*-xylyl linker in receptor **5**, but it is of course much more flexible. In order to test the influence of the linker length on the oxygen binding capacity and oxidation reactivity of the dinuclear Cu(I) complexes of these receptors, receptor **7** was designed which only differs from receptor **6** with respect to the length of the linker (ethyl vs. butyl).

--- FIGURE 5 ---

In the second type of mimic a pyridyl linker is used instead of an *m*-xylyl linker, affording the TPA-appended receptors **8** and **9**, which contain two tetra-coordinating TPA ligands instead of the tri-coordinating ligands in receptors **6** and **7**. In **8** and **9**, no benzylic hydrogen atoms are in close proximity of the metal site. We expect a different reactivity of receptors **6** and **8** towards dioxygen and substrates. The reactivities of dinuclear Cu(I) complexes of **6** and **8** towards dioxygen and of the oxygenated complexes towards substrates will be described elsewhere.³¹ The synthesis and characterisation of the receptors are described here, along with detailed studies of the coordination of Cu(I) to the ligands in the receptors **6** and **8** by as determined by NMR spectroscopy.

Results and Discussion

Synthesis

PY2-appended diphenylglycoluril basket 6. The synthesis of receptor **6** is depicted in Scheme 1. Tetrapodand **10**³² and compound **11** (*tert*-butyl-*N*-(4-aminobutyl)carbamate)³³ were heated to reflux in acetonitrile for six days under Finkelstein conditions using sodium carbonate as a base. As a result compound **12** was obtained via a double ring closure reaction (60% yield).³⁴ Compound **13**, which contains two primary amino groups for further functionalisation, was obtained in a yield of 90 % by deprotection of compound **12** in a solvent mixture of trifluoroacetic acid (TFA) and dichloromethane (1:1 v/v). Receptor **6** was prepared by double addition of the primary amino groups of compound **13** to 2-vinylpyridine (4 molar equivalents) using one equiv. of acetic acid as a catalyst at high pressure (15 kbar) in a specialized setup. Receptor **6** was obtained in a yield of 94 % after basic work up and subsequent column chromatography on activated alumina (eluent: 2 % MeOH in CH₂Cl₂).

- - - SCHEME 1 - - -

The dinuclear Cu(I) complex of receptor **6** (named **6a** or [6·Cu(I)₂](ClO₄)₂) can be prepared by two methods. For preparation on a quantitative scale, one equiv. of **6** and two equiv. of [Cu(I)(CH₃CN)₄](ClO₄) were dissolved in dichloromethane and stirred for 10 minutes under standard Schlenk conditions. The resulting complex was precipitated by using diethyl ether as a non-solvent.³⁵ Complex **6a** was obtained as a yellow solid that is very air sensitive in the solid state, and even more air sensitive in solution. For the *in situ* preparation of a solution of **6a**, suitable for e.g. catalytic experiments or spectroscopy, one equiv. of receptor **6** and two equiv. of [Cu(I)(CH₃CN)₄](ClO₄) were dissolved in the desired solvent and then stirred for 10 minutes under standard Schlenk conditions.

Compound **7** was prepared in a similar fashion as **6** starting from tetrapodand **10** (Scheme 2). Compounds **10** and **14** (*tert*-butyl-*N*-(2-aminoethyl)carbamate) were heated at reflux temperatures under Finkelstein conditions to give **15** in 60 % yield. Deprotection of **16** with TFA in dichloromethane gave compound **16** in 70 % yield. Subsequent high-pressure addition of 2-vinylpyridine to **16** gave receptor **7**. Unfortunately, this compound could not be obtained in pure form due to decomposition during purification via column chromatography on activated alumina, evidenced by the large number of unidentified

aromatic signals in the NMR spectrum. This experiment was not repeated to investigate other means of purification.

- - - SCHEME 2 - - -

TPA-appended diphenylglycoluril baskets. The synthesis of receptor **8** is shown in Scheme 3. Tetrapodand **10** was reacted with benzyl amine under the conditions described above to yield compound **17**, which was deprotected by reduction under 20 bar of hydrogen pressure to give compound **18**.³⁶ Instead of palladium on carbon with 4 bars of hydrogen for 168 hours as in the literature procedure, palladium hydroxide on carbon was used with 20 bars of hydrogen for 72 hours. The yield in both cases was around 70 %, the reaction time was however shorter in the case of the modified procedure. The desired receptor **8** was prepared by the reaction of 6-TPA-Cl **19** with compound **18**. The synthesis of **19** has been described in the literature; it occurs via chlorination of 6-TPA-OH in a multi-step process.³⁷ To simplify this procedure a different route was used (Scheme 3), starting with the chlorination of [6-(hydroxymethyl)-2-pyridyl]methanol to give the protonated compound **20**, which was deprotonated with Na₂CO₃ to 2,6-di(chloromethyl)pyridine **21**. Compound **21** was subsequently coupled to *N,N*-di-(2-pyridylmethyl)amine (picolylamine) by stirring in THF with diisopropylethylamine (DIPEA) as a base for one week, affording **19** in a yield of 40 %.

The substitution of the chlorine group in **19** by the secondary amino nitrogen atoms of compound **18** was carried out under Finkelstein conditions with sodium carbonate as a base and an excess of **19** (3 equiv.). The resulting receptor **8** was obtained in pure form after column chromatography on activated alumina (2 % MeOH in CH₂Cl₂) in a yield of 60 %. The dinuclear Cu(I) complex of **8** (**8a** or [**8**·Cu(I)₂](ClO₄)₂) can be prepared using the two methods described above for **6a**, either on a quantitative scale or *in situ*, both under Schlenk conditions.³¹ Complex **8a** was obtained as a yellow solid that was very air sensitive in the solid state and in solution.

- - - SCHEME 3 - - -

The synthesis of receptor **9** (Scheme 4) is similar to that of receptor **8**, with the exception that a different chloro-TPA derivative is used, viz. 5-TPA-Cl (**22**). The synthesis of **22** (Scheme 4) started with the bromination of methyl 6-methylnicotinate using *N*-bromo succinimide to obtain compound **23**. Compound **24** was obtained by reaction of compound **23** with picolylamine, as was described above for the preparation

of **19**. The resulting methyl ester was reduced with lithium aluminium hydride to the alcohol derivative **25**, which was chlorinated to give chloro-TPA derivative **22**. The substitution of the chlorine group in **22** by the secondary amino nitrogen atoms of compound **18** was carried out under Finkelstein conditions with sodium carbonate as a base and an excess of **22** (3 equiv.). The resulting receptor **9** was obtained in crude form. Column chromatography as used for receptor **8** was carried out using activated alumina (eluent: 2 % MeOH in CH₂Cl₂); unfortunately this led to decomposition of receptor **9** as indicated by many unidentified peaks in the ¹H NMR spectrum. The lack of stability of a 5-substituted TPA was also observed in the case of compound **22**, compared to the equivalent compound **19**. Apparently, a chloro substituent on the 5-position of the pyridyl ring is much less stable than a chloro substituent on the 6-position of this ring. This difference is most probably also the reason why receptor **9** is less stable than receptor **8**.

- - - SCHEME 4 - - -

Characterization

¹H NMR titrations of ligands **6** and **8** with Cu(I) were carried out in order to answer the following questions regarding the coordination of Cu(I): (i) Is Cu(I) coordinated selectively to the ligand sets or also non-selectively to the N and O in the crown ether moieties? (ii) Is a non-symmetric complex formed upon coordination of one equivalent of Cu(I), or does exchange occur between the two ligand sets? (iii) Can more than two equivalents of Cu(I) coordinate to the receptor and what is the structure of the resulting complex? All proton signals in the ¹H NMR spectrum of the metal-free receptors **6** and **8** were assigned with the help of COSY and 2D-NOESY experiments. The titrations of receptors **6** and **8** in CD₂Cl₂ with [Cu(I)(CH₃CN)₄]ClO₄ were carried out under exclusion of air, since air oxidation leads to formation of paramagnetic Cu(II) complexes.

Copper coordination to receptor 6. The positions of all peaks and the $\Delta\delta$ values (shifts in the signals) for **6** to **6a** are listed in Table 1. The first observation from the NMR spectrum (Figures 6 and 7) is that a broadening occurs upon addition of Cu(I), which obscures the coupling patterns in some cases; this may be due to a self-exchange electron transfer reaction caused by a small impurity of paramagnetic Cu(II) in the Cu(I) salt.³⁸

--- FIGURE 6, 7, TABLE 1 ---

The NMR spectrum of the complex of receptor **6** with one equivalent of Cu(I) shows only an average set of signals for the pyridyl protons of **6**, from which it can be concluded that copper binding is dynamic in the sense that the Cu(I) ion moves between the two PY2 ligand sets. The NMR spectrum of the complex of **6** with two equivalents of Cu(I), viz. **6a**, shows significant shifts in the pyridyl region compared to metal-free receptor **6** (Table 1). The observed downfield shifts in the pyridyl region are attributed to a decrease in electron density on the pyridyl ring as a result of electron donation to the Cu(I) ion. A more detailed description of the changes observed in the NMR spectrum of **6** is presented below.

Upon the addition of a third equivalent of Cu(I), resolved signals become visible for protons A and C in addition to a peak at 7.02 ppm, next to the signal for the phenyl protons of glycoluril (marked by filled squares, ■). In the aliphatic regions of the NMR spectrum several extra peaks are observed: a peak near D⁰ at 4.15 ppm, and two peaks at 3.48 and 3.53 ppm. It is not clear to which protons these peaks can be assigned. It is possible that the four pyridyl nitrogen donors and two amino nitrogen donors from the two PY2 units of **6** (a total of 6 N-donors) are shared among three Cu(I) ions, for example two N-donors per Cu(I). This type of coordination may result in the formation of intra- or intermolecular dimers or oligomers, bridged by Cu(I) ions. The additional peaks in the NMR spectrum point to a decrease in the symmetry of the complex; the structure of this complex is not yet clear.

The signals of the phenyl protons of glycoluril (■) do not shift upon titration with Cu(I), in line with the distant position with respect to the Cu(I) binding site. The signal of the side wall protons (marked by filled circles, ●, Figure 6), however, shifts upfield upon the addition of a first equivalent of Cu(I) and shifts back after the addition of the third equivalent. The observed upfield shift can be the result of the inclusion of a pyridyl group, possibly copper-coordinated, in the cavity of **6**. It is known that the association constant of an aromatic guest with clips and baskets increases with decreasing electron density on the guest.^{39,40} An increase was found in the acidity of the hydroxyl groups as well as strength of the π - π stacking interactions of dihydroxybenzene substrates in the presence of electron withdrawing groups. The observed downfield shift of the signal of the side wall protons of **6** can be a result of the expulsion of this pyridyl group from the cavity of the Cu(I)₃ complex, induced by the less dynamic overall structure described above.

To establish if Cu(I) can also bind to the O- and/or N-donors of the crown ether moiety, the shifts in this region of the NMR spectrum were studied (Figure 7). An upfield shift was observed for the O-methylene D-protons upon addition of one equivalent of Cu(I); the signal remains unchanged after the addition of an additional equivalent. Several alternative explanations were considered for this upfield shift. It could be due to the inclusion of a pyridyl group in the cavity; however, since no downfield shift of these protons was observed after the addition of the third equivalent of Cu(I) (expulsion of the pyridyl group) this cannot be the correct explanation. Another explanation of the observed upfield shift of the O-methylene D-protons is a conformation change, such as distortions in the torsion angles of the oxyethylene chains in the crown ether moiety, as has been described for a molecular basket appended with two chiral aza-R-groups.⁴¹ In the case of coordination of Cu(I) to the O- and/or N-donors, the signals of the other protons in this region would also be expected to shift; however no such shifts are observed (Table 1). From the above it can be concluded that no coordination of Cu(I) to O- and N-donors in the crown ether region occurs; it is, however, not exactly clear what causes the extra peaks in this region after addition of the third equivalent of Cu(I).

Distinct downfield shifts were observed for the overlapping signals of the protons of both methylene units (I) and (J) of the 2-ethylpyridyl moieties upon addition of one equivalent of Cu(I) and the signals became resolved upon the addition of the second equivalent. Together with the observed downfield shift of the spacer H-protons, this could point to the involvement of the amine N-donor of the PY2 ligand sets in copper coordination.

Upon the addition of $[\text{Cu(I)(CH}_3\text{CN)}_4]\text{ClO}_4$ to **6** an increasing amount of acetonitrile, being partly displaced from Cu(I) by the PY2 N-donors, is found in the NMR spectra. The integration of the acetonitrile signal, which would have given information about the exact number of acetonitrile molecules that were displaced, could however not be carried out due to line broadening. The fact that line broadening occurs may point to a slow exchange process between acetonitrile coordinated to copper and free acetonitrile in solution. It may furthermore be caused by the presence of some Cu(II) instead of Cu(I) as described above.

Based on the data presented above we can provide answers to the questions stated in the beginning of this section: (i) Cu(I) is coordinated selectively to the pyridyl and amine N-donor of the PY2 ligand sets, a conclusion that is in line with our EXAFS results,²⁷ (ii) in the complex of **6** with one equivalent of Cu(I), the binding of Cu(I) is dynamic, and (iii) a non-symmetric complex is formed upon the addition of three equivalents of Cu(I) to **6**. In addition, it has been observed that one of the pyridyl groups,

possibly coordinated to Cu(I), can bind in the cavity of **6** and that this pyridyl group is expelled upon the addition of a third equivalent of Cu(I).

Copper coordination to receptor 8. The positions of all peaks and the $\Delta\delta$ values found upon the titration of **8** with Cu(I) are listed in Table 2. The first observation in the NMR spectra (Figures 8 and 9) is that a broadening occurs upon addition of Cu(I), analogous to what has been described for receptor **6**. Two sets of signals are observed in the NMR spectrum (Table 2, Figure 8) for the pyridyl protons of a complex of **8** with one equivalent of Cu(I). The two distinct sets of signals are best resolved for the A protons. The signal of the metal-free receptor **8** at 8.46 ppm is broadened and shifts upon the addition of Cu(I), concomitant with the appearance of a signal of the A protons of Cu(I)-coordinated pyridyl at 8.55 ppm. The spectrum of the complex with two equivalents of Cu(I), viz. **8a**, shows only one signal for the A protons at 8.55 ppm. From the combined results it can be concluded that Cu(I) binding in **8** is not dynamic, in contrast to what is observed for **6**. Hence the observed broadening is due only to the presence of Cu(II) impurities.

- - - FIGURE 8, 9, TABLE 2 - - -

Upon the addition of a third equivalent of Cu(I), resolved signals are observed for protons A, C and C', pointing to a decrease in the symmetry of the complex, as also observed for **6**, possibly with the formation of intra- and intermolecular complexes (see below). The three Cu(I) ions in the complex with **8**, which contains two TPA units comprising 6 pyridyl N-donors and 2 amine N-donors, in contrast to only 4 pyridyl N-donors and 2 amine N-donors in **6**, each have almost three N-donors available instead of two in the case of the complex with **6**.

The Cu(I) NMR titration does not show a significant shift of the signals of the phenyl protons of glycoluril (**■**) like in the case of **6**. In the NMR spectrum of the complex of **8** with one equivalent of Cu(I) a small peak is observed at 6.4 ppm, which can be attributed to residual metal-free receptor **8**, indicating that less than one equivalent of Cu(I) per Cu binding site was actually present. For the complex of **8** with one equivalent of Cu(I), a large upfield shift of -0.59 ppm is observed for the signal of the side wall protons. Upon the addition of additional equivalents the signal remains unchanged. The observed upfield shift of the side wall protons could be the result of the inclusion of a pyridyl group, possibly copper-coordinated, in the cavity of **8**. A shift in the signals of the side wall protons as a result of inclusion has also been observed for

receptor **6**. The shift observed for the complex of **8** is of the same order of magnitude as the shifts that are usually observed for complexation of 1,3-dihydroxybenzene guests in the cavities of molecular clips and baskets, i.e. around -0.5 ppm.⁴²

In contrast to what is found for **6**, no downfield shift in the signal of the side wall protons is observed upon addition of a third equivalent of Cu(I), indicating no change in the inclusion behaviour in the cavity, hence no expulsion is observed. For receptor **6** it was observed that the binding of copper is dynamic in the complex with two equivalents of copper, and not dynamic in the complex with three equivalents of copper (see above). In the case of receptor **8**, however, the binding of copper is not dynamic in the complex with two equivalents of copper, and is dynamic in the complex with three equivalents of copper, wherein copper exchanges rapidly on the NMR timescale between the ligands. This would still enable one of the pyridyl groups, coordinated to copper or not, to be included in the cavity. A reason for this difference between the receptors **6** and **8** is that the latter contains more N-donor ligands, which would facilitate the coordination of a third Cu(I) ion in the complex. Furthermore, there is a difference in the chelation, i.e. 5- and 4-membered chelate rings for the Cu(I) complexes of **6** and **8**, respectively.

The signals of the pyridyl protons shift downfield upon coordination of Cu(I) and this downfield shift would compete with an upfield shift that can be expected upon the inclusion of a pyridyl group in the cavity. The “net” upfield shift for the signal of the pyridyl D-protons upon the addition of one equivalent of Cu(I) can be explained by the larger upfield shift as a result of inclusion compared to the downfield shift as a result of Cu(I) coordination. Upon the addition of a second and a third equivalent this initial “net” upfield shift of the pyridyl D-protons is completely cancelled by the downfield shift as a result of the coordination of additional Cu(I). The signals for the pyridyl B- and C-protons show the same effect, however, a smaller shift is observed, indicating that the pyridyl D-protons are bound more deeply in the cavity than the B- and C-protons. No NOE contacts have been observed between the pyridyl D-protons and the side wall protons, possibly indicating a fast exchange on the NMR timescale between different pyridyl groups in and out of the cavity.

The signal of the pyridyl C'-protons show, in contrast to the B-, C- and D-protons, only downfield shifts for each addition of Cu(I). This can be explained by the fact that these C' protons are protons of linker-pyridyl groups, which do not bind in the cavity and hence show no upfield shift. The position of the signal for protons D' could not easily be determined from the spectrum. A COSY experiment of **8a** showed the coupling of unidentified broad signals between 7.49 and 7.53 ppm with two signals

underneath the C/C' signal. These unidentified peaks might be attributed to the D' protons; the resulting downfield shift would be in line with the observations for C'.

To investigate possible coordination of Cu(I) to the O- and/or N-donors of the crown ether moieties the NMR spectrum of the crown ether region was studied. No downfield shift was visible for the spacer H-protons, as was observed in the case of **6**, which could be an indication that the amine N-donor of the TPA units is not coordinated to copper. However, a large downfield shift (0.42 ppm) was observed for the signal of the N-methylene G-protons (Table 2, Figure 9), in contrast to **6**, suggesting the participation of the aza crown ether N-donor in the coordination of Cu(I). It is proposed that copper is coordinated by two of the three pyridyl groups of a TPA ligand set and by the aza crown ether N-donor, to give a tri-coordinated copper complex. The third pyridyl group of the TPA ligand set is not coordinated and forms a “free dangling” pyridyl group. This is in line with the conclusions from our EXAFS study,²⁷ which show that at least one of the pyridyl groups of **8a** is detached from the Cu(I) ion.

Similar results have been reported in the literature. It has been shown by X-ray that in a complex of TPA with Cu(I) and an additional PPh₃ ligand, one of the pyridyl groups is detached from the copper ion.⁴³ Another report describes NMR data for a Cu(I) complex of TPA, showing that at room temperature broad signals are observed which sharpen upon cooling to -50 °C.⁴⁴ This was ascribed to exchange processes that occur between the pyridyl arms, with one of the pyridyl groups dangling free at every moment. In solution such free dangling pyridyl groups seem to be more general than in the solid state. To further investigate whether inclusion behaviour of a pyridyl group in the cavity of the host is structurally possible, CPK modelling was carried out, revealing that a pyridyl group, either coordinated to Cu(I) or not, can be included in the cavity. Our NMR study (see above) shows that inclusion of a pyridyl group in the cavity is dynamic and is favoured by Cu(I)-coordination to the pyridyl groups. A schematic representation of this type of behaviour is illustrated in Figure 10.

- - - *FIGURE 10* - - -

To obtain more evidence for the proposed inclusion behaviour, binding studies were carried out with receptor **8** as a host and olivetol (5-pentyl-1,3-dihydroxybenzene) as a guest in dichloromethane. NMR studies were carried out using either **8** or **8a**, with zero, one and ten equivalents of olivetol. The signal of the side wall protons of **8** or **8a** is a probe for complexation of a guest and is observed at 6.63 and 6.05 ppm, respectively. For **8** an upfield shift to 6.53 and 6.26 ppm was observed upon addition of one and ten

equivalents of olivetol, respectively, indicating olivetol binding in receptor **8**. For **8a** a downfield shift to 6.07 and 6.12 ppm was measured upon addition of one and ten equivalents of olivetol, respectively, indicating a change in the inclusion behaviour of the cavity of receptor **8a**, possibly as a result of the binding of olivetol and the expulsion of the pyridyl ligand.

Surprisingly, no NOE contacts between the protons of the side walls and the protons of the pyridyl groups were detected with either 2D NOESY or ROESY experiments (see Experimental for details).

Conclusions

Two new receptors, PY2-appended receptor **6** and TPA-appended receptor **8**, have been synthesized, as well as their Cu(I) complexes **6a** and **8a**. Furthermore, the design and preparation of two other receptors, **7** and **9**, have been described; they were synthesized but could not be purified.

NMR studies have provided information about structural and dynamic aspects of the coordination of Cu(I) to both **6** and **8**. The coordination of pyridyl groups to Cu(I) in the complex of receptor **6** with one equivalent of Cu(I) is dynamic and fast on the NMR timescale; exchange of pyridyl groups to the Cu(I) takes place at room temperature. The complex of receptor **8** with two equivalents of Cu(I) does not display this type of dynamic behaviour, since distinct sets of signals were observed for the protons of coordinated and non-coordinated pyridyl groups.

Furthermore, large changes in the signals of the side wall protons of receptor **8** occurred, while only very small changes were observed for receptor **6**. These large changes in the NMR spectrum of receptor **8** are ascribed to the inclusion of one of the pyridyl groups of the ligand in the receptor cavity. This inclusion is induced by coordination of Cu(I), which decreases the electron density of the pyridyl group, thereby increasing its affinity for the cavity. This inclusion of a pyridyl group can be partially disrupted by the addition of a guest, namely olivetol. However, binding of one of the pyridyl groups is stronger than binding of olivetol, perhaps due to the intramolecular (entropy) effect. In addition, the aza crown ether N-donors of receptor **8** were shown to assist in copper coordination, whereas the spacer N-donors do not assist in copper coordination. In line with our EXAFS results²⁷ it is concluded that only two out of the three pyridyl groups coordinate to the copper ion, while one of the pyridyl groups is dangling free.

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Experimental

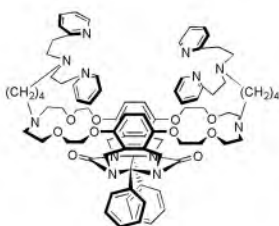
General procedures. $[\text{Cu}(\text{I})(\text{CH}_3\text{CN})_4](\text{ClO}_4)$ was synthesized from copper oxide according to a literature procedure by Kubas.⁴⁵ **Caution:** perchlorate salts are potentially explosive and should be handled with care. Diethyl ether, THF, toluene and *n*-hexane were distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane, chloroform, methanol and acetonitrile were distilled from CaH_2 . Triethylamine was dried on KOH. Diisopropylamine was distilled over ninhydrin and subsequently over KOH. 2-Vinylpyridine was vacuum distilled. Ethylacetate, hexane, chloroform and dichloromethane used for column chromatography were rotary evaporated prior to use. NaCO_3 and NaI were dried in an oven at 150 °C. All other solvents and chemicals were commercial materials and were used as received. Merck Silica Gel (60H) and Aldrich Neutral Alumina 90 were used for column chromatography. Alumina was activated to activity III according to the Brockmann scale.⁴⁶ To this end the alumina was dried overnight in a vacuum oven at 150 °C. Subsequently 6 % of water (w/w) was added and the mixture was equilibrated by rotation in a round-bottom flask on a rotary evaporator, at atmospheric pressure. Merck Silica Gel F254 plates and aluminum oxide 60 F254 neutral plates on plastic or tin foil were used for thin layer chromatography.

Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected. Infrared spectra were recorded on a BioRad FTS-25 spectrometer. NMR spectra were recorded on Bruker WM-200, Bruker AM-300, Varian Unity Inova 400 HR NMR or Bruker DRX-500 instruments. Chemical shifts are reported in ppm downfield from internal standard (tetramethylsilane) at 0.00 ppm in the case of ^1H -NMR spectra in CDCl_3 , otherwise the solvent peak was used as a reference (CD_3OH : 3.31 ppm). In the case of ^{13}C -spectra, the solvent peak was used as a reference (CDCl_3 : 77.0 ppm). Abbreviations used are: s = singlet, d = doublet, m = multiplet, b = broad. ESI-MS spectra were recorded on a Thermo Finnigan MAT900S double focusing mass spectrometer coupled to an ICIS data system using ElectroSpray Ionization. EI and FAB mass spectra were recorded on a VG-7070E instrument. The matrix used for FAB was 3-

nitrobenzylalcohol. Elemental analysis were determined with a Carbo Erba Ea 1108 instrument.

Syntheses. Compounds **10**,³² **11**,³³ **14**,³³ **20**,³⁰ and **23**⁴⁷ were prepared according to literature procedures.

8,25-Di(4-di[2-(2-pyridyl)ethyl]aminobutyl)-36,37-diphenyl-2,5,11,14,19,22,28,31-octa-8,25,35,38,43,45-hexaazaocyclo[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]-pentaconta-1(47),15,17,32,40,48-hexaene-44,50-dione (**6**)

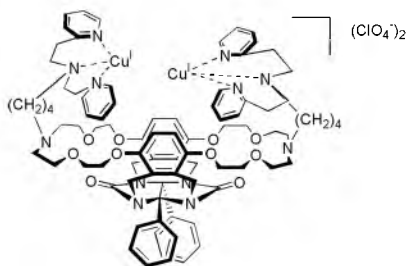


A solution was prepared of 275 mg (0.27 mMol) of **13** in a few mL of a 1:1 (v/v) mixture of MeOH and CH₂Cl₂. To this were added 231 mg of 2-vinylpyridine (2.2 mMol, 8 equiv.) and 71 mg of acetic acid (1.1 mMol, 4 equiv.). The yellow solution was transferred to a 7.5 mL Teflon high-pressure vessel and a few grains of the radical trap (5-(*tert*-butyl)-2-[4-(*tert*-butyl)-2-hydroxy-5-methyl-phenyl]-sulfanyl-4-methylphenol) were added. After filling with the solvent mixture and closing the cap tightly, the vessel was placed in a special high-pressure apparatus and kept at 15 kbar and 50 °C for 16 hrs.²⁹ After removal of the pressure the Teflon vessel appeared dented since the volume was decreased during the reaction. The bright red solution was concentrated *in vacuo* at room temperature to yield a red brown oil. This oil was redissolved in dichloromethane and extracted with aqueous base (NaOH). The organic layer was dried over MgSO₄ and evaporated. The compound was obtained as a yellow solid in 94 % yield after column chromatography over alumina (activity III) (eluent: 2% MeOH in CH₂Cl₂).

M.p. 156 °C; IR (KBr pellet): ν 1710 and 1590 (C=O), 1123 (C-O-C) cm⁻¹; ¹H-NMR (CDCl₃, 500 MHz): δ 8.50 (d, 4H; *ortho* J =4.0 Hz, PyC⁶H), 7.52-7.49 (m, 4H; PyC⁴H), 7.11 (m, 10H; ArH glycoluril), 7.09-7.05 (m, 8H; PyC³H + PyC⁵H), 6.62 (s, 4H; ArH side wall), 5.65 (d, 4H; J =16.0 Hz, NCHHAr *out*), 4.14-4.10 (m, 4H; ArOCHH *out*), 3.98-2.83 (m, 4H ArOCHH *in* + 16 H CH₂O + 4H NCHHAr *in*), 2.94 (m, 8H; PyCH₂CH₂N), 2.88-2.81 (m, 8H; NCH₂CH₂O), 2.60-2.56 (m, 8H; NCH₂(CH₂)₂CH₂N), 1.30-1.27 (m, 8H; NCH₂(CH₂)₂CH₂N). ¹³C-NMR +HETCOR (CDCl₃, 75.5MHz): δ 160.7 (N(C=O)N glycoluril), 157.4 (PyC²), 150.9 (ipso-C of Ar side walls), 149.1 (PyC⁶), 136.0 (PyC⁴), 134.2/128.8/128.4 (Ar glycoluril), 123.3 (PyC⁵), 121.0 (PyC³), 114 (Ar side walls), 85.0 (N₂CPh-CPh, glycoluril), 69.7/69.3/69.0 (CH₂O) 55.8/53.7/53.5 (CH₂N), 36.9 (NCH₂Ar glycoluril), 36.1 (PyCH₂), 25.2 (NCH₂(CH₂)₂CH₂N). MS-FAB

m/z 1438.78 (M+H)⁺. Anal. for C₈₄H₁₀₂N₁₂O₁₀: C 78.97, H 8.04, N 12.99 (calc. C 78.84, H 8.03, N 13.13).

*Cu(I)*₂ complex of receptor **6** (**6a**)

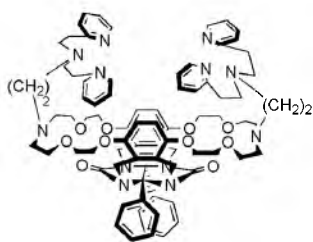


This complex was either prepared *in situ* or via precipitation; the product obtained was the same for both methods. A magnetic stirring bar, 10.8 mg (7.5 mMol) of **6** and 4.9 mg (2 equiv.) of [Cu(I)(CH₃CN)₄](ClO₄) were transferred to an Schlenk flask. Five cycles of evacuation and filling with pre-dried nitrogen were applied. In a separate

flask 15 mL of distilled dichloromethane (or acetone) was collected under nitrogen and transferred to the solids under nitrogen. The resulting yellow solution was stirred for 10 min. until the solids were dissolved. This *in situ* prepared solution was used directly for spectroscopy, while for other purposes the product was obtained as a solid via precipitation. The solution was concentrated under reduced pressure to ca. 1 mL and under argon diethyl ether (distilled and collected under nitrogen) was slowly layered on top of the dichloromethane. This solvent system was allowed to equilibrate over night in the freezer. The yellow precipitate was collected via decantation.

¹H-NMR (CDCl₃, 500 MHz): δ 8.57 (m, 4H; PyC⁶H), 7.77 (m, 4H; PyC⁴H), 7.26 (m, 8H; PyC³H + PyC⁵H), 7.04 (m, 10H; ArH glycoluril), 6.56 (s, 4H; ArH side wall), 5.52 (4H; J=15.6 Hz; NCHHAr out), 3.98 (m, 4H; ArOCHH out), 3.8-3.74 (m, 4H ArOCHH in + 16 H CH₂O) 3.64 (d, 4H; J=16.5 Hz, NCHHAr in), 2.97 (s, 8H; PY2CH₂CH₂N), 2.89 (s, 8H; PY2CH₂CH₂N), 2.72 (s, 8H; NCH₂CH₂O), 2.59 (4H; PY2NCH₂CH₂CH₂) 2.50 (4H; ONCH₂CH₂CH₂), 1.49 (8H; NCH₂(CH₂)₂CH₂N). Anal. for C₈₄H₁₀₂N₁₂O₁₈Cl₂Cu₂ ·(0.5CH₂Cl₂): C 56.14, H 5.70, N 9.28 (calc. C 56.13, H 5.74, N 9.29).

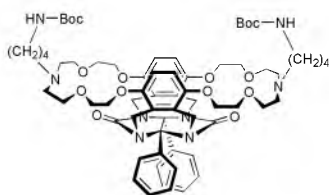
8,25-Di(2-di[2-(2-pyridyl)ethyl]aminoethyl)-36,37-diphenyl-2,5,11,14,19,22,28,31-octaaza-8,25,35,38,43,45-hexaazaocyclo[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]-pentaconta-1(47),15,17,32,40,48-hexaene-44,50-dione (**7**)



A solution of 135 mg (0.14 mMol) of **16** in a few mL of a 1:1 solvent mixture of MeOH and CH₂Cl₂ was prepared. To this were added 115 mg of 2-vinylpyridine (1.1 mMol, 8 equiv.) and 35 mg of acetic acid (0.55 mMol, 4 equiv.). The yellow solution was transferred to a 7.5 mL Teflon high pressure vessel and a few grains of radical trap (5 (*tert*-butyl)-2-[4-(*tert*-

butyl)-2-hydroxy-5-methylphenyl]sulfanyl-4-methylphenol) were added. The vessel was completely filled with the solvent mixture and the cap was tightly screwed. This vessel was placed in a special high-pressure apparatus and kept at 15 kbar and 50 °C for 16 hrs. The orange solution was evaporated at room temperature to yield a yellow-brown oil. The compound decomposed during column chromatography on activated alumina (III) (eluent: 2% MeOH in CH₂Cl₂).

8,25-Di(tert-butyl-N-(4-aminobutyl)carbamate)-36,37-diphenyl-2,5,11,14,19,22,28,31-octa-oxa-8,25,35,38,43,45-hexa-azaocatacyclo[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]-pentaconta-1(47),15,17,32,40,48-hexaene-44,50-dione (12)



A solution of 380 mg (0.38 mMol) of **10** in 100 mL of freshly distilled and degassed acetonitrile was prepared. To this solution were added 4.1 g of NaI (28.2 mMol) and 1.6 g of Na₂CO₃ (15.1 mMol). One equiv. (71.5 mg) of **11** was added to this white suspension and the reaction mixture was refluxed for 16 hrs. A solution of 2 equiv. of **11** (143 mg) in 6 mL acetonitrile was slowly added to the solution over the next 36 hrs. The resulting suspension was refluxed for 96 hrs. The acetonitrile was removed under reduced pressure and the residue was redissolved in 500 mL of chloroform. The organic solution was washed twice with water (500 mL), once with NaHCO₃ (sat. 500 mL), and once again with water (500 mL). The organic layer was evaporated under reduced pressure and the product redissolved in 2 mL of distilled chloroform. The resulting solution was added dropwise to 50 mL of distilled *n*-hexane while stirring. The white precipitate was collected via filtration and purified via column chromatography on silica with MeOH/Et₃N/CHCl₃ (10:1:89 v/v) as the eluent. The product (R_f 0.2) was obtained as a white solid in a yield of 60%.

M.p. 184°C; IR (KBr pellet): ν 3373 (b, NH), 2927 (b, CH), 1713 (C=O), 1170-1135 (C-O), 1068 (C-N) cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz): δ 7.09 (m, 10H, ArH glycoluril), 6.71 (s, 4H, ArH side walls), 5.65 (d, 4H, J= 16.1 Hz, NCHHAr *out*), 4.90 (b, 2H, NHC=O Boc-group), 4.20-4.13 (m, 8H, ArOCH₂), 3.99-3.78 (m, 16H, CH₂O), 3.71 (d, 4H, J= 16.1 Hz, NCHHAr *in*), 3.14 (m, 4H, Boc-HNCH₂), 2.88 (m, 8H, O-CH₂CH₂N), 2.62 (m, 4H, Boc-HN(CH₂)₃CH₂N), 1.68 (m, 8H, NCH₂(CH₂)₂CH₂N), 1.45 (s, 18H, C(CH₃)₃). ¹³C-NMR (CDCl₃, 75.5 MHz): δ 157.3 (NH(C=O)), 156.0 (N(C=O)N glycoluril), 150.0 (Ar glycoluril), 134.2/128.9/128.4/113.9 (Ar side walls + Ar glycoluril), 85.0 (N₂CPh-CPh), 78.9 (NCH₂Ar), 70.2 (CH₂NHC=O), 69.6/69.4 (CH₂O) 55.4/53.7/40.4 (CH₂N), 37.0 (C(CH₃)₃), 28.5 (NCH₂(CH₂)₂CH₂N), 27.9 (CH₃). MS *m/z* 1219 (M+H)⁺. Anal. for C₆₄H₉₀N₈O₁₄: C 79.98, H 8.98, N 11.03 (calc. C 79.62, H 9.11, N 11.26).

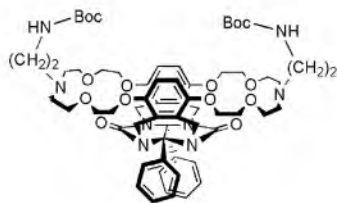
8,25-Di(4-aminobutyl)-36,37-diphenyl-2,5,11,14,19,22,28,31-octaoxa-8,25,35,38,43,45-hexa-azaocyclo-[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]pentaconta-1(47),15,17,32,40,48-hexaene-44,50-dione (**13**)



A solution of 860 mg (0.71 mMol) of **12** in 5 mL of dichloromethane was slowly added to a mixture of 10 mL of TFA and 5 mL of dichloromethane at 0°C. The solution was stirred for 1 h at 0°C after which 250 mL of dichloromethane was added. The organic solution was washed twice with NaOH (250 mL) and concentrated *in vacuo*. The residue was redissolved in 2 mL of distilled chloroform and added dropwise to distilled *n*-hexane while stirring. The white precipitate was collected via filtration and obtained in a yield of 90%.

M.p. dec. >210°C; IR (KBr pellet): ν 3434(NH), 2931(CH), 1700/1692(C=O) cm^{-1} ; $^1\text{H-NMR}$ (MeOH/ CDCl_3 , 400 MHz): δ 7.15 (s, 10H, ArH glycoluril), 6.84 (s, 4H, ArH side walls), 5.48 (d, 4H, $J = 15.7$ Hz, NCHHAr *out*), 4.32-4.30 (m, 8H, ArOCH₂), 4.03-3.74 (m, 16H, CH₂O + 4H, NCHHAr *in*), 2.83-2.82 (m, 4H, NH₂CH₂ + 8H OCH₂CH₂N), 2.62 (m, 4H, NH₂(CH₂)₃CH₂N), 1.68 (m, 8H, NCH₂(CH₂)₂CH₂N); $^{13}\text{C-NMR}$ (MeOH/ CDCl_3 , 75.5 MHz): δ 157.3 (N(C=O) glycoluril), 150.5 (Ar glycoluril), 133.2/128.7/128.0/114.7 (Ar side walls + Ar glycoluril), 85.5 (N₂CPh-CPh), 78.9 (NCH₂Ar), 70.0/69.8/68.6 (CH₂N), 54.9/54.1 (CH₂O), 40.0/37.0 (NCH₂(CH₂)₂CH₂N); MS m/z 1019 (M+H)⁺.

8,25-Di(*tert*-butyl-*N*-(2-aminoethyl)carbamate)-36,37-diphenyl-2,5,11,14,19,22,28,31-octaoxa-8,25,35,38,43,45-hexa-azaocyclo[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]-pentaconta-(47),15,17,32,40,48-hexaene-44,50-dione (**15**)



To a solution of 2 g (2.02 mMol) of tetrapodand **10** in 500 mL of freshly distilled and degassed acetonitrile was added 20 g of NaI (134 mMol) and 6.5 g of Na₂CO₃ (61 mMol). One equiv. (323 mg) of **14** was added to this white suspension and the reaction mixture was refluxed for 16 hrs. A solution of 2 equiv. of **14** (646 mg) in 6 mL acetonitrile was slowly added to the solution over the next 36 hrs. The resulting suspension was refluxed for another four days. The acetonitrile was removed under reduced pressure and the residue was redissolved in 500 mL of chloroform. This was extracted twice with water (500 mL), washed with saturated aqueous NaHCO₃ (500 mL) and water (500 mL). The organic layer was evaporated under reduced pressure and the product was redissolved in 2 mL of distilled chloroform. This solution was added dropwise to 50 mL of distilled hexane

while stirring. The white precipitate that was formed was filtrated of and dried. The product was obtained as a white solid in 52% yield after column chromatography on silica (eluent: 10 % MeOH and 1 % Et₃N in CHCl₃).

M.p. 207°C; IR (KBr pellet): ν 3365 (b, NH), 2929/2871 (b, CH), 1712 (C=O); ¹H-NMR (CDCl₃, 200MHz): δ 7.08 (m, 10H, ArH glycoluril), 6.70 (s, 4H, ArH side wall), 5.76 (b, 2H, NHC=O Boc group), 5.64 (d, 4H, J= 16.0 Hz, NCHHAr out), 4.16-4.07 (m, 8H, ArOCH₂), 4.00-3.66 (m, 16H CH₂O +4H NCHHAr in), 3.21-3.19 (m, 4H, Boc-HNCH₂), 2.89-2.83 (m, 8H, O-CH₂CH₂N), 2.72-2.67 (m, 4H, Boc-HNCH₂CH₂N), 1.39 (s, 18H, C(CH₃)₃); ¹³C-NMR (CDCl₃, 50.3 MHz): δ 157.5 (NH(C=O)), 156.6 (N(C=O)N glycoluril), 150.7 (Ar glycoluril), 134.0/128.5/113.8 (Ar side walls + Ar glycoluril), 85.0 (CPh-CPh), 78.6 (NCH₂Ar), 70.0 (CH₂NHC=O), 69.6/69.3 (CH₂O) 54.3/53.9 (CH₂N), 36.9 (C(CH₃)₃), 28.4 (CH₃). MS *m/z* 1186 (M +Na)⁺. Anal. for C₆₂H₈₂N₈O₁₄: calc. C 79.28, H 8.79, N 11.93; found C 79.34, H 8.71, N 11.95.

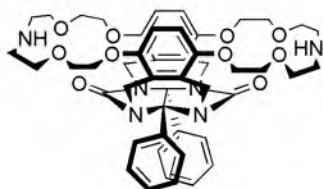
8,25-Di(2-aminoethyl)-36,37-diphenyl-2,5,11,14,19,22,28,31-octa-oxa-8,25,35,38,43,45-hexaazaoctacyclo-[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]pentaconta-1(47),15,17,32,40,48-hexaene-44,50-dione (**16**)



A solution of 120 mg (0.10 mMol) of **15** was dissolved in 5 mL of dichloromethane. A mixture of 10 mL of TFA and 5 mL of dichloromethane was cooled in ice to 0 °C. The solution of **15** was slowly added to the solvent mixture and the resulting solution was stirred for 1 h at 0 °C. After the reaction 250 mL of dichloromethane was added and the solution was extracted twice with NaOH (250 mL). The organic layer was evaporated under reduced pressure; the residue was redissolved in 2 mL of distilled chloroform and added drop wise to stirring distilled hexane. The white precipitated was filtered of and the product was obtained in a yield of 80 %.

M.p. dec. >220°C; IR (KBr pellet): ν 3426(NH), 2923(CH), 1697(C=O); ¹H-NMR (MeOH/CDCl₃, 200MHz): δ 7.16 (m, 10H, ArH glycoluril), 6.77 (s, 4H, ArH side wall), 5.46 (b, 1H, NH₂), 5.48 (d, 4H, J= 15.9 Hz, NCH₂Ar out), 4.23-4.20 (m, 8H, ArOCH₂), 3.97-3.73 (m, 16H CH₂O + 4H NCH₂Ar in), 2.96-2.76 (m, 16H, NH₂CH₂); MS *m/z* 985 (M+Na)⁺.

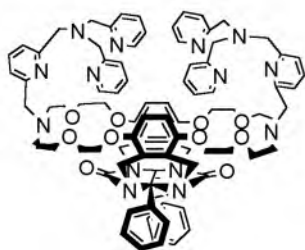
36,37-Diphenyl-2,5,11,14,19,22,28,31-octaoxa-8,25,35,38,43,45-hexaazaocyclaclo-
[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]pentaconta-1(47),15,17,32,40,48-hexaene-
44,50-dione (**18**)



This compound was prepared according to a modified literature procedure.³⁶

Compound **17** (1.5 g, 1.4 mMol) was dissolved in 25 mL of acetic acid. To this solution was added a large excess of palladium hydroxide on carbon (~1 g). The resulting black suspension was transferred to an autoclave and stirred for 72 hrs at 55 °C under 20 bars of hydrogen. The reaction mixture was filtered over Celite and the resulting yellow solution was concentrated. The solvent was evaporated twice with toluene (100 mL) to remove acetic acid. The residue was dissolved in 2 mL of distilled chloroform and added dropwise to distilled *n*-hexane while stirring. The white precipitate was obtained in a yield of 70 %. Characterization was consistent with the literature.³⁶

8,25-Di[6-{methyl-*N,N*-di(2-pyridylmethyl)amine}-2-pyridyl)methyl]-36,37-diphenyl-
2,5,11,14,19,22,28,31-octaoxa-8,25,35,38,43,45-hexaazaocyclaclo-
[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]pentaconta-1(47),15,17,32,40,48-hexaene-
44,50-dione (**8**)

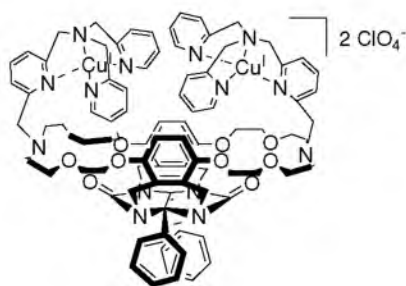


To a solution of 50 mg (0.07 mMol) of **18** in 10 mL of acetonitrile was added 45 mg (2.2 equiv.) of 6-TPA-Cl (**23**), 285 mg (40 equiv.) of Na₂CO₃ and 400 mg (40 equiv.) of NaI. The resulting suspension was refluxed for 120 hrs. After cooling to room temperature the reaction mixture was concentrated *in vacuo* and redissolved in dichloromethane (200mL). The organic layer was washed twice with water and once with saturated aqueous Na₂HCO₃. The organic layer was dried over Na₂SO₄ instead of MgSO₄, since magnesium ions will irreversibly coordinate to TPA. After concentration the residue was redissolved in 2 mL of chloroform and added dropwise to distilled *n*-hexane while stirring. The product precipitated as a light yellow solid and was obtained in pure form after column chromatography on activated alumina (activity III) (eluent: 2 % MeOH in CH₂Cl₂) with a yield of 60 %.

M.p. 86 °C; IR (KBr pellet): ν 1709 and 1572 (C=O) cm⁻¹; ¹H-NMR (CDCl₃, 500 MHz): δ 8.53 (d, 4H; ^{ortho}J=4.7 Hz, PyC⁶H), 7.66-7.58 (m, 10H; PyC^{4/4'/3}H), 7.50-7.42 (m, 2H; PyC³H), 7.13-7.10 (m, 10H; PyC^{5/5'}H + ArH glycoluril), 6.65 (s, 4H; ArH side walls), 5.67 (d, 4H; J=16.0 Hz, NCHHAr *out*), 3.96-3.93 (m, 4H; ArOCHH *out*), 3.90-3.75 (m,

4H ArOCHH *in* + 16 H CH₂O + 12 H PyCH₂N), 3.72 (d, 4H; ^{ortho}J= 16.4 Hz, NCHHAr *in*), 2.95 (m, 8H; NCH₂CH₂). ¹³C-NMR (CDCl₃, 75.5MHz); δ 159.5 (N(C=O)N glycoluril), 150.8 (Ar glycoluril), 149.0 (PyC⁶), 136.8-136.4 (PyC^{3/3'}), 128.5-127.1 (Ar glycoluril), 122.9 (PyC⁴), 122.0 (PyC^{5/5'}), 121.2 (PyC^{4'}), 120.8/113.9 (Ar side walls), 70.1-69.4 (CH₂O), 61.5-60.2 (CH₂Py), 54.1 (CH₂CH₂N), 37.0 (NCH₂ Ar glycoluril). MS-FAB m/z 1480.0 (M+2H)⁺. No satisfactory elemental analysis could be obtained. However, a satisfactory high-resolution mass spectrum was obtained. HR-MS (MH⁺): Calcd. For C₈₆H₉₃N₁₄O₁₀: 1481.71991; Found: 1481.72082 (-0.61 ppm).

***Cu(I)*₂-complex of receptor **8** (**8a**)**



This complex was either prepared *in situ* or via precipitation; the product obtained was the same for both methods. A magnetic stirring bar, 11.1 mg (7.5 mMol) of **8** and 4.9 mg (2 equiv.) of [Cu(I)(CH₃CN)₄](ClO₄) were transferred to a Schlenk flask. Five cycles of evacuating and filling with pre-dried nitrogen were applied. In a

separate flask 15 mL of distilled dichloromethane (or acetone) was collected under nitrogen and transferred to the solids under nitrogen. The resulting yellow solution was stirred for 10 min. until the solids were dissolved. This *in situ* prepared solution was used directly for spectroscopy, while for other purposes the product was obtained as a solid via precipitation. The solution was concentrated under reduced pressure to ca. 1 mL and under argon diethyl ether (distilled and collected under nitrogen) was slowly layered on top of the dichloromethane. This solvent system was allowed to equilibrate over night in the freezer. The yellow precipitate was collected via decantation.

¹H-NMR (CD₂Cl₂, 500 MHz): δ 8.62 (m, 4H; PyC⁶H), 7.70 (m, 4H; PyC⁴H), 7.61 (m, 42H; PyC⁴H), 7.24 (m, 8H; PyC³H + PyC^{3'}H), 7.13 (m, 10H; ArH glycoluril), 6.99 (m, 4H; PyC⁵H), 6.12 (s, 4H; ArH side wall), 5.67 (4H; J=16 Hz; NCHHAr *out*), 4.21 (m, 4H; ArOCHH *out*), 4.10-3.70 (m, 4H ArOCHH *in* + 16 H CH₂O + 12H PyCH₂) 3.75 (d, 4H; J=16 Hz, NCHHAr *in*), 3.41-3.30 (br, 8H; CH₂N).

***2,6-Di(chloromethyl)pyridine.HCl* (**20**)**

A flask containing 0.99 g (7.1 mMol) of [6-(hydroxymethyl)-2-pyridyl]methanol was cooled in ice to 0°C. By means of an addition funnel 15 mL of thionyl chloride was added over a period of 1 h. After warming up to room temperature the reaction mixture was heated to reflux for 4 hrs. After cooling to room temperature 10 mL of toluene was

slowly added in order to precipitate the product. After vacuum filtration the product was washed at least 4 times with toluene to remove excess of thionyl chloride. Finally, the product was obtained as a white solid. The product was not characterized but used directly in the next reaction to obtain **21**.

2,6-Di(chloromethyl)pyridine (21)

The hydrochloric acid salt **20** was dissolved in 200 mL of water and solid NaHCO₃ was added slowly until a pH of 7 was reached. The product precipitated out and was filtrated and washed repeatedly with water. The product was recrystallized from petroleum ether (40-64°C) and the pure product was obtained as colourless needles in a yield of 53% for the last two steps.

M.p. 71°C; IR (KBr pellet): ν 3020, 2980, 1600, 1570, 1470 (Pyr) cm⁻¹; ¹H-NMR (CDCl₃, 200MHz): δ 7.81-7.73 (t, 1H; Py-CH⁴, ^{ortho}J=7.9Hz), 7.46-7.26 (d, 2H; Py-CH^{3,5}, ^{ortho}J=7.5Hz), 4.67 (s, 4H; Py-CH₂Cl). ¹³C-NMR (CDCl₃, 50.3 MHz): δ 156 (PyC^{2,6}H), 138 (PyC⁴H), 122 (PyC^{3,5}H) 46 (PyCH₂Cl); MS *m/z* 175 (M+H)⁺. Anal. Calcd for C₇H₇NCl₂: C: 47.73; H: 3.73; N: 7.81; (Calc. C: 47.76; H: 4.01; N: 7.96).

N-[[6-(Chloromethyl)-2-pyridyl]methyl]-N,N-di(2-pyridylmethyl)amine (19)

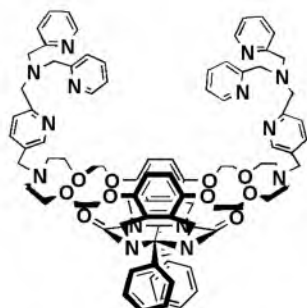
A solution of 0.41 g (2.1 mMol) of *N,N*-di(2-pyridylmethyl)amine (picolyl amine), 0.36 g (1 equiv.) of **21** and 1 g of diisopropylethylamine (DIPEA)(3.7 equiv.) in 10 mL of distilled THF was transferred to a pressure vessel. After stirring under exclusion of air for one week a precipitate of DIPEA-HCl was formed. After decanting and evaporation the crude product was obtained as a brown oil. Column chromatography (neutral alumina 90, Activation III) with a gradient eluent of EtOAc:hexane (55:45 to 45:55 v/v) provided the product as white solid in a yield of 40%.

M.p. 98°C; IR (KBr pellet): ν 3500/3400 (N-H), 1591/1436 (Pyr); ¹H-NMR (CDCl₃, 200MHz): δ 8.54 (d, 2H; ^{ortho}J=4.9 Hz, ^{meta}J=1.0 Hz, PyC⁶H), 7.69 (d, 1H; J=7.8 Hz, PyC⁴H), 7.66 (dd, 2H; ^{ortho}J=7.5 Hz, ^{meta}J=1.2 Hz, PyC⁴H), 7.58 (d, 2H; J=7.6 Hz, PyC³H), 7.54 (d, 1H; J=7.6 Hz, PyC³H), 7.33 (d, 1H; 7.6 Hz, PyC⁵H), 7.15 (dd, 2H; J=6.0 Hz, PyC⁵H), 4.65 (s, 2H, PyCH₂-Cl) 3.90 (s, 6H; PyCH₂-N). Anal. Calcd for C₁₉H₁₉N₄Cl: C: 67.40; H: 5.50; N: 16.12; (Calc. C: 67.35; H: 5.65; N: 16.54).

8,25-Di[(5-{methyl-*N,N*-di(2-pyridylmethyl)amine}-2-pyridyl)methyl]-36,37-diphenyl-2,5,11,14,19,22,28,31-octa-8,25,35,38,43,45-hexaazaocyclo-

[30.15.2.1^{35,38}.0^{15,41}.0^{18,40}.0^{33,47}.0^{36,45}.0^{37,43}]-pentaconta-

1(47),15,17,32,40,48-hexaene-44,50-dione (**9**)



To a solution of approx. 145 mg (0.43 mMol) of **22**, 750 mg (20 equiv.) of NaCO₃ and 1 g (20 equiv.) of NaI in 20 mL of acetonitrile was added 125 mg (1/3 equiv.) of **18**. The resulting suspension was heated to reflux for 120 hrs. After cooling of the reaction mixture the solvent was evaporated and the residue was dissolved in dichloromethane (200 mL).

The organic layer was washed twice with water and once with saturated aqueous NaHCO₃, dried over Na₂SO₄ (magnesium will irreversibly coordinate to TPA) and evaporated *in vacuo*. The residue was dissolved in 2 mL of chloroform and added dropwise to about 25 mL of distilled hexane while stirring. The product precipitated as a beige solid. It decomposed during an attempt to purify it by column chromatography on activated alumina (Act. III, eluent: 2% MeOH in CH₂Cl₂).

Methyl 6-[[di(2-pyridylmethyl)amino]methyl]nicotinate (24)

A solution of 156 mg (0.8 mMol) of *N,N*-di(2-pyridylmethyl)amine, 185 mg (1 equiv.) of **23** and 130 mg of diisopropylethylamine (DIPEA)(3.7 equiv.) in 10 mL of dry THF was transferred to a pressure vessel. After stirring under exclusion of air for one week a precipitate of DIPEA-HCl was formed. After decanting and evaporation the crude products was obtained as a brown oil. After two crystallizations from petroleum ether 40/65 (v/v) the product was isolated as a white solid in a yield of 18 % (this low yield is probably due to the second crystallization, which was necessary to remove impurities).

¹H-NMR (CDCl₃, 200MHz): δ 9.16 (d, 1H; ^{para}J=0.5Hz, PyC^{6'}H), 8.64 (br d, 2H; ^{ortho}J=4.8Hz, PyC⁶H), 8.19-8.14 (dd, 1H; ^{ortho}J=7.9Hz, ^{meta}J=2.2Hz, PyC^{4'}H), 7.79-7.70 (dt, 2H; ^{ortho}J=7.5Hz, PyC⁵H), 7.63 (d, 1H; ^{ortho}J=9.4Hz, PyC^{3'}H), 7.54 (d, 2H; ^{ortho}J=8.0Hz, PyC³H), 7.28-7.2 (dt, 2H; ^{ortho}J=8.0Hz, ^{meta}J=1.3Hz, PyC⁴H), 4.04 (s, 4H; NCH₂Py), 3.96 (s, 2H; NCH₂Py').

(6-[Di(2-pyridylmethyl)amino]methyl-3-pyridyl)methanol (25)

Argon was led through a solution of 150 mg (0.43 mMol) of **24** in 10 mL of dry, freshly distilled diethyl ether for 20 min. A solution of 29 mg of LiAlH₄ (1.8 equiv.) in 3 mL of dry, freshly distilled diethyl ether was prepared and added drop wise under an argon atmosphere at 0 °C to the solution of **24**. The resulting mixture was stirred over night at

room temperature after which it was cooled again to 0 °C. Subsequently, 1 mL of water, 1 mL of 10 % NaOH and 1 mL of water were added drop wise. The resulting mixture was stirred at room temperature for 1 hour after which it was extracted with ether. The mixture was filtrated over a plug of Celite and washed with 25 mL of diethyl ether. The resulting ether layer was dried over NaSO₄ and evaporated *in vacuo* to yield a yellow oil. Due to the instability of the product it was used directly without further purification in the following step.

¹H-NMR (CDCl₃, 300MHz): δ 8.53 (d, 1H; *ortho*J=6.6 Hz, PyC⁶H), 7.69-7.56 (m, 4H, Py-H), 7.17-7.14 (m, 2H; Py-H), 4.70 (s, 2H; CH₂OH), 3.88 (s, 2H; NCH₂PyCH₂OH), 3.74 (s, 4H; NCH₂Py).

N,N-Di(2-pyridylmethyl)-[5-(chloromethyl)-2-pyridyl]methanamine (**22**)

A solution of **25**, prepared as described above, approx. 0.43 mMol, in 5 mL of chloroform was added drop wise at 0° C to a solution of 256 mg of SOCl₂ (5 equiv.) in 10 mL of chloroform. The resulting mixture was stirred over night at room temperature and evaporated *in vacuo* to give a greenish foam. The product was dissolved in 5 mL of THF and 600 mg of DIPEA was added under argon at 0 °C. The resulting mixture was stirred for 3 hrs at room temperature, filtrated over a plug of Celite and washed with 25 mL of THF. The resulting solution was evaporated *in vacuo* to yield the above compound as a brown oil that slowly crystallizes upon standing. The product was used directly in the following reaction (to prepare **11**) without further purification because of the good NMR spectrum.

¹H-NMR (CDCl₃, 200MHz): δ 8.53 (d, 1H; *ortho*J=6.6 Hz, PyC⁶H), 7.69-7.57 (m, 4H, Py-H), 7.16-7.13 (m, 2H; Py-H), 4.57 (s, 2H; CH₂Cl), 3.88-3.85 (s, 4H; NCH₂Py).

NMR titration experiments. NMR titrations were carried out on a Bruker DRX 500 instrument at 298 K. The Cu(I) containing solutions were prepared in a glove box under nitrogen atmosphere, because of the air sensitivity of these complexes. For the titration of Cu(I) to receptor **6** two solutions were prepared: A) 2.95 mg of **6** in 2 mL of CD₂Cl₂ (1.03 mM), and B) 2.95 mg of **6** and 2.05 mg of [Cu(I)(CH₃CN)₄](ClO₄) in 2 mL of CD₂Cl₂ (1.03 and 3.13 mM resp.). Four NMR tubes were prepared with 0.6/0.4/0.2/0.0 mL of A and 0.0/0.2/0.4/0.6 mL of B, affording samples with 0/1.01/2.03/3.04 equiv. of Cu(I), respectively.

For the titration of Cu(I) to receptor **8**, two solutions were prepared in oxygen free and dry CH₂Cl₂, A) 1.0 mM of **8**; B) 2 mM [Cu(I)(CH₃CN)₄](ClO₄). These two solutions were mixed under argon in the desired ratios by use of syringes and the resulting

solutions of Cu(I) complexes of **8** were stirred for 5 min and concentrated *in vacuo* outside the glove-box. The dry residues were transported back into the glove-box and redissolved in CD₂Cl₂ after which the NMR-tubes were filled. The NMR tube for the NOESY and ROESY experiment was sealed under vacuum by melting to prevent oxidation by air during the experiments. The NOESY mixing times used in the experiments were 50 ms and 200 ms, the ROESY mixing time used was 300 ms. The relaxation delay in all experiments was 1.5 s.

Figure captions

Figure 1. Crystal structures of active sites: (top) Hemocyanin subunit II from the horseshoe crab (*Limulus polyphemus*).⁵ (bottom) Catechol oxidase from sweet potatoes (*Ipomoea batatas*),¹⁰ a OH⁻ ion coordinates between the Cu(I) ions.

Figure 2. Structure and dioxygen reactivity of the tri-coordinating ligand **1** (top)²¹ and the tetra-coordinating ligand **2** (bottom).²³

Figure 3. Molecular clip **3** and molecular basket **4**.

Figure 4. Oxidative *N*-dealkylation of **5**.Cu(I)₂.O₂

Figure 5. Structures of target receptors.

Figure 6. ¹H-NMR spectra of metal-free receptor **6** (bottom trace) with one, two (**6a**), and three equivalents of Cu(I) in the region of 8.5 to 6.4 ppm.

Figure 1. ¹H-NMR spectra of metal-free receptor **6** (bottom trace) with one, two (**6a**), and three equivalents of Cu(I) in the region of 4.2 to 2.4 ppm.

Figure 8. ¹H-NMR spectra of metal-free receptor **8** (bottom trace) with one, two (**8a**), and three equivalents of Cu(I) in the region of 8.8 to 5.5 ppm.

Figure 9. ¹H-NMR spectra of metal-free receptor **8** (bottom trace) with one, two (**8a**), and three equivalents of Cu(I) in the region of 4.3 to 2.8 ppm.

Figure 10. Schematic representation of inclusion of a pyridyl group in the cavity of **8a**.

Tables.

Table 1. Chemical shift values for metal-free receptor **6**, and its complexes with one, two (**6a**), and three equivalents of [Cu(I)(CH₃CN)₄]ClO₄.

Proton (symbol, Figure)	0 equiv.(6)	1 equiv.	2 equiv.(6a)	3 equiv.	$\Delta\delta$ 6 to 6a ^{a)}
PyH ⁶ (A, 3-6)	8.40	8.43	8.57	8.57+8.66	+0.17
PyH ⁶ (C, 3-6)	7.47	7.62	7.77	7.78	+0.30
ArH glycoluril (■, 3-6)	7.06	7.06	7.06	7.04	0
PyH ^{3/5} (B,D, 3-6)	7.00	7.13	7.26	7.30	+0.26
ArH side walls (●, 3-6)	6.61	6.54	6.56	6.64	-0.05
NCH ₂ Ar out	5.53	5.52	5.52	5.53	-0.01
ArOCH ₂ out (D ⁰ , 3-7)	4.04	3.98	3.99	3.96	-0.05
ArOCH ₂ in (D ¹ , 3-7)	3.86	3.81	3.80	3.76	-0.06
CH ₂ O (E, 3-7)	3.76	3.75	3.74	3.74	-0.02
NCH ₂ Ar in (●, 3-7)	3.62	3.64	3.64	3.65	+0.02
PyCH ₂ CH ₂ N (J, 3-7)	2.82	2.86	2.95	2.97	+0.13
PyCH ₂ CH ₂ N (I, 3-7)	2.82	2.86	2.89	2.91	+0.07
NCH ₂ CH ₂ O (F, 3-7)	2.71	2.70	2.72	2.70	+0.01
Py2-NCH ₂ (CH ₂) ₂ CH ₂ (H, 3-7)	2.49	2.55	2.59	2.61	+0.10
Py2-NCH ₂ (CH ₂) ₂ CH ₂ (G, 3-7)	2.43	2.44	2.46	2.47	+0.03
Py2-NCH ₂ (CH ₂) ₂ CH ₂	1.53	1.53	1.49	1.48	-0.04

a) + sign, downfield shift; – sign; upfield shift

Table 2. Chemical shifts for metal-free receptor **8**, and its complexes with one, two (**8a**), and three equivalents of [Cu(I)(CH₃CN)₄]ClO₄.

Proton (symbol, Figure)	0 equiv.(8)	1 equiv.	2 equiv.(8a)	3 equiv.	$\Delta\delta$ 8 to 8a ^{a)}
PyH ⁶ (A, 3-8)	8.46 (d)	8.54+8.46	8.55(d)	8.55 ^{b)}	+0.09
PyH ⁵ (B, 3-8)	7.03	6.94	6.98	7.04	-0.05
PyH ⁴ (C, 3-8)	7.58	7.53	7.56 ^{b)}	7.56	-0.03
PyH ^{4'} (C', 3-8) ^{d)}	7.58	7.62	7.66 ^{b)}	7.71 ^{b)}	+0.08
PyH ³ (D, 3-8)	7.55	7.18-7.15	7.18-7.15	7.25-7.15	~-0.40
PyH ^{3'} (D', 3-8)	7.37 (dd)	~7.49	~7.49-7.53	~7.65	~+0.14
ArH glycoluril (■, 3-8)	7.08	7.06	7.05	7.05	-0.03
ArH side walls (●, 3-8)	6.64	6.05	6.05	6.05	-0.59
NCHHAr out (□, 3-8)	5.55 (d)	5.59 (d)	5.60 (d)	5.60(d)	+0.05
ArOCHH out (E ^o , 3-8)	4.14	4.12	4.17	4.20-4.09	+0.03
ArOCHH in (E ⁱ , 3-8)	3.96-3.70	4.00-3.50	4.00-3.66	4.05-3.60	-
CH ₂ O (F, 3-8)	3.96-3.70	4.00-3.50	4.00-3.66	4.05-3.60	-
PyCH ₂ (H, 3-8)	3.82-3.80	3.80-3.74	3.78-3.72	3.78-3.72	-
NCHHAr in	3.71 (d)	3.67 (d)	3.68 (d)	^{c)}	-0.03
CH ₂ N (G, 3-8)	2.89	3.38-3.20	3.31-3.26	3.35-3.20	+0.42

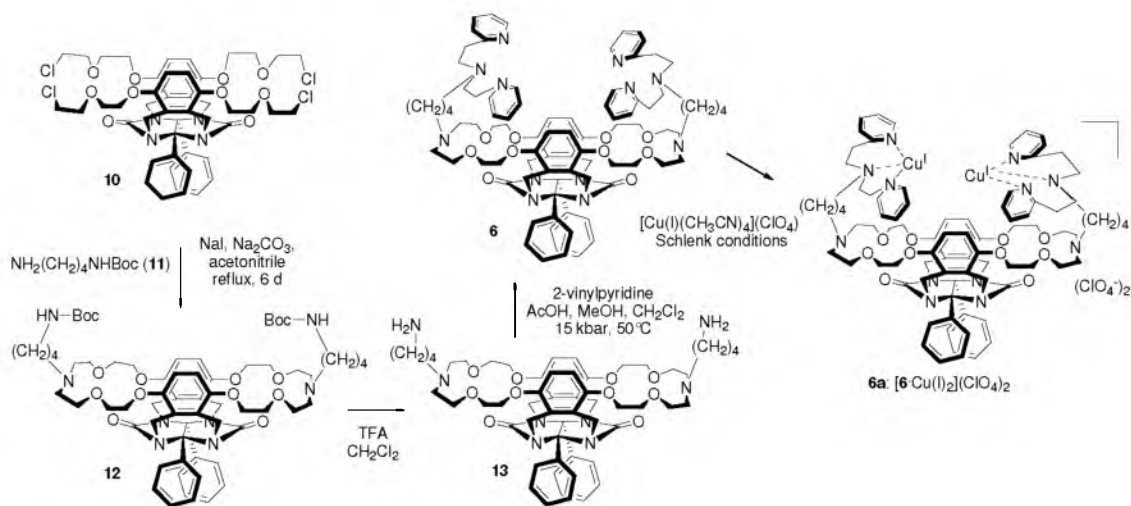
a) + sign, downfield shift; – sign; upfield shift

b) an extra peak is observed

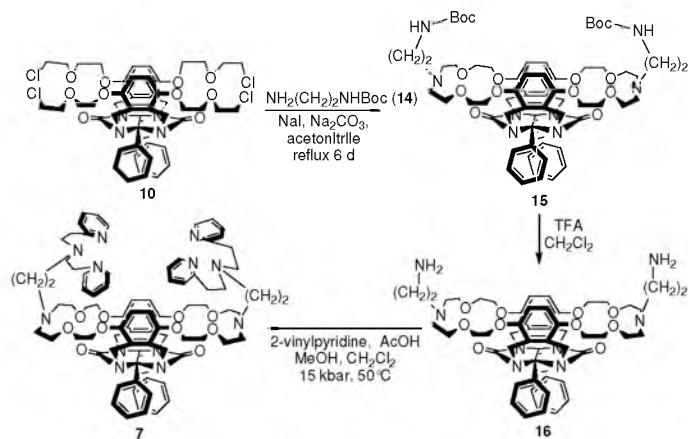
c) could not be clearly determined

d) signals for linker-pyridyl groups are denoted with ' to distinguish them from the 'free' pyridyl groups

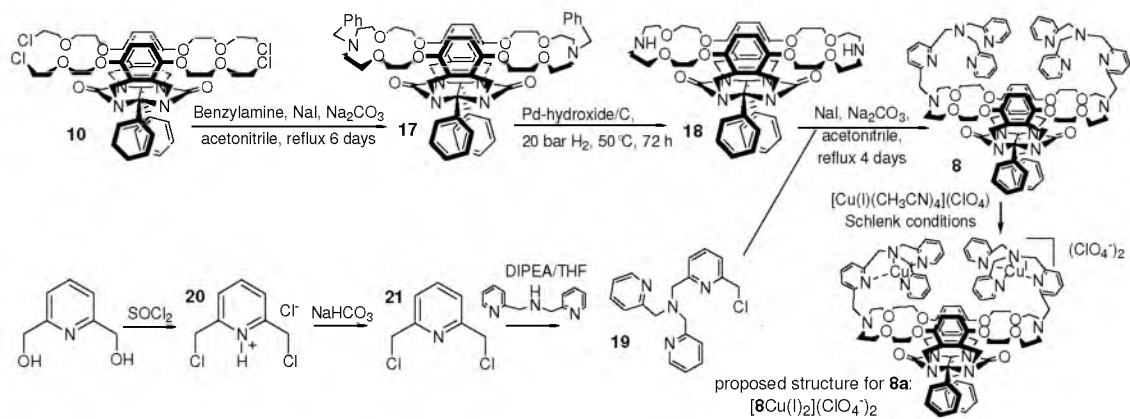
Scheme 1. Synthesis of receptor **6** and its bis-Cu(I) complex **6a**.



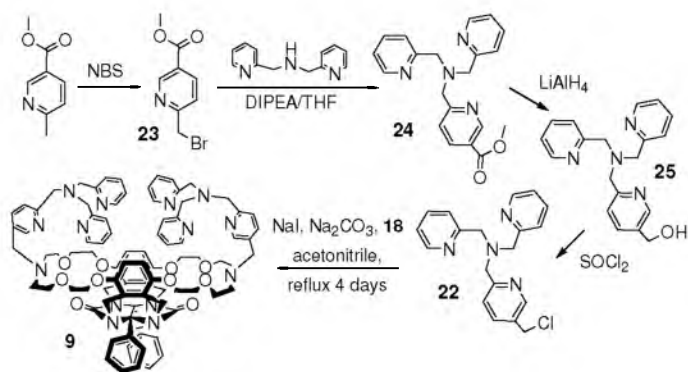
Scheme 2. Synthesis of receptor **7**.



Scheme 3. Synthesis of receptor **8** and complex **8a**.



Scheme 4. Synthesis of receptor **9**.



Figures

Figure 1.

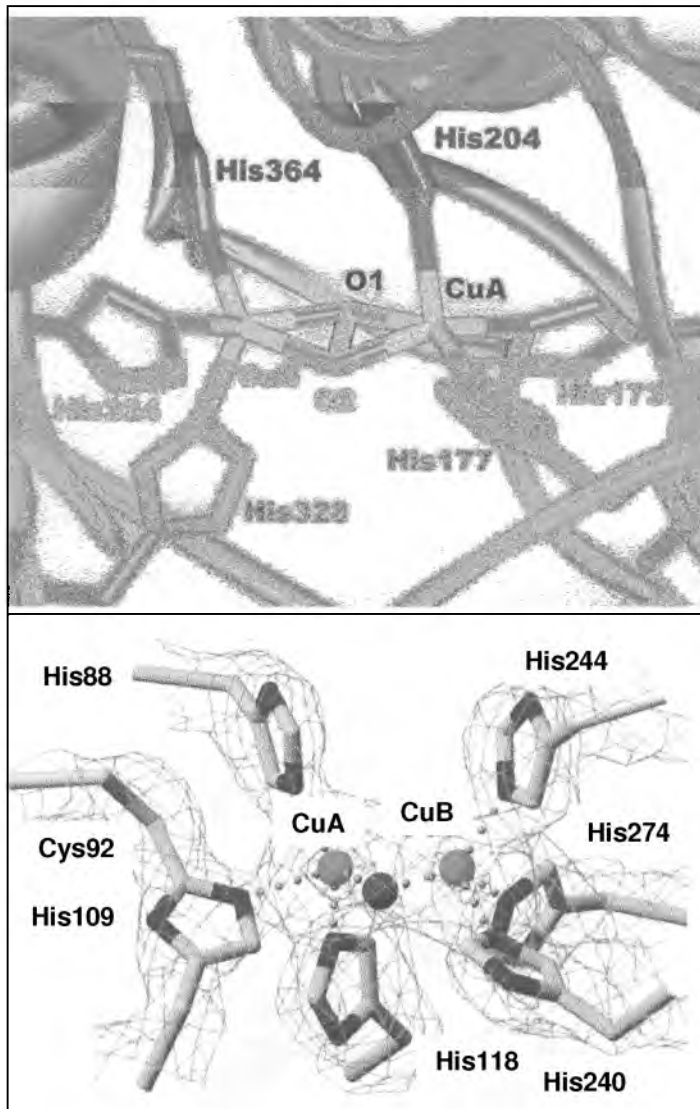


Figure 2.

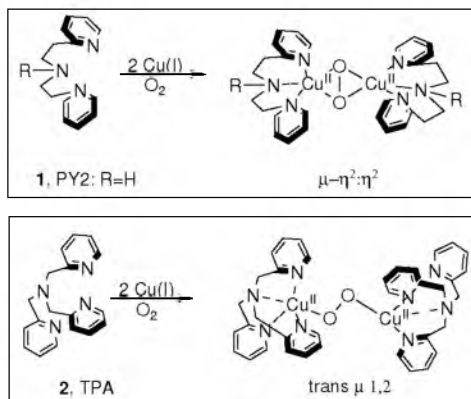


Figure 3.

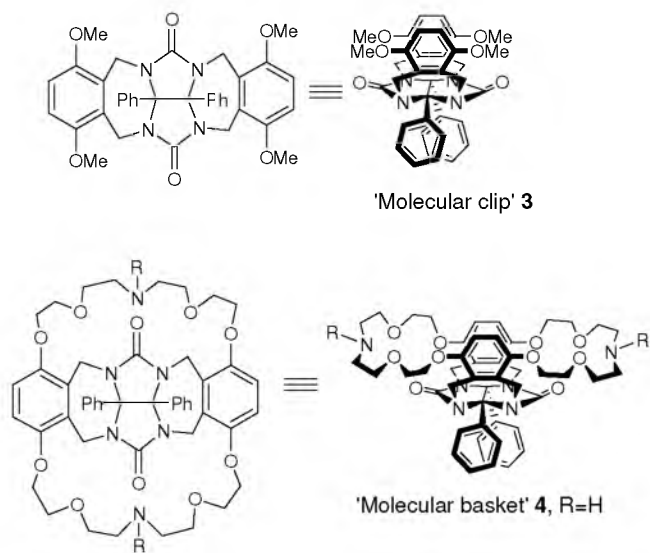


Figure 4.

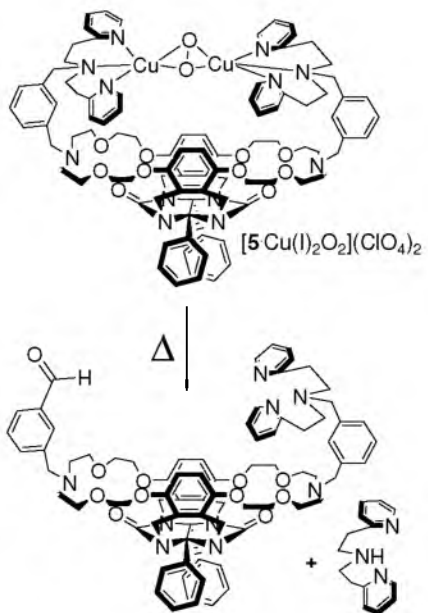


Figure 5.

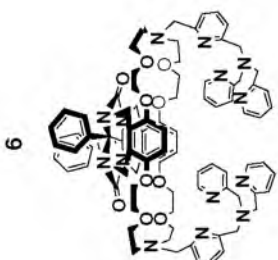
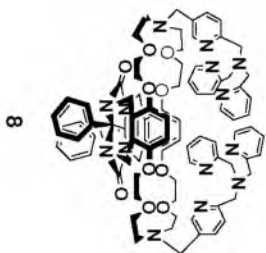
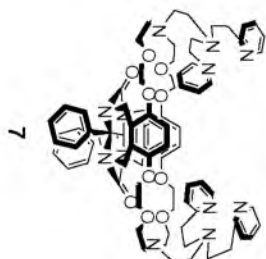
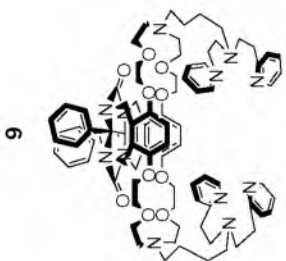


Figure 6.

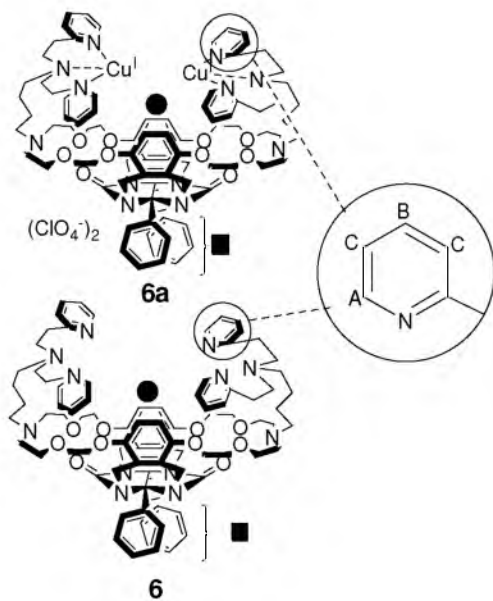
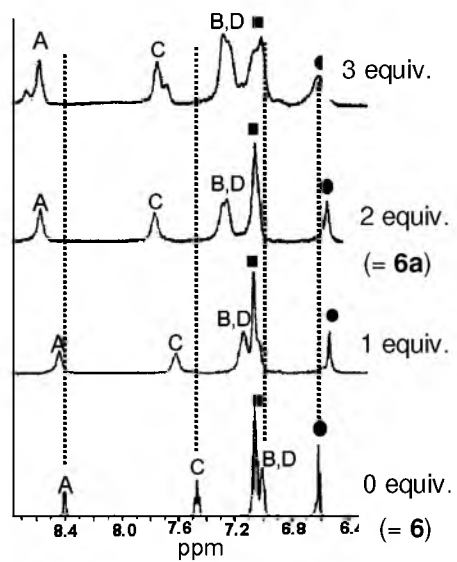


Figure 7.

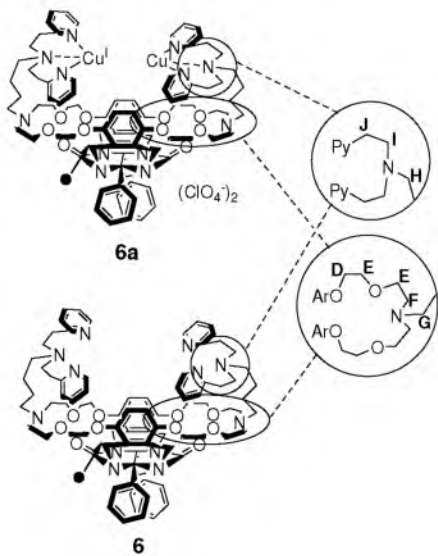
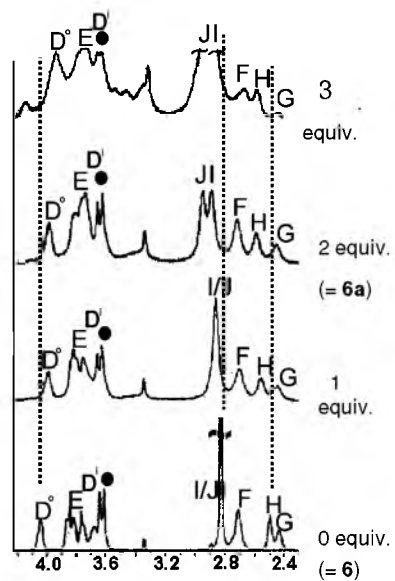


Figure 8.

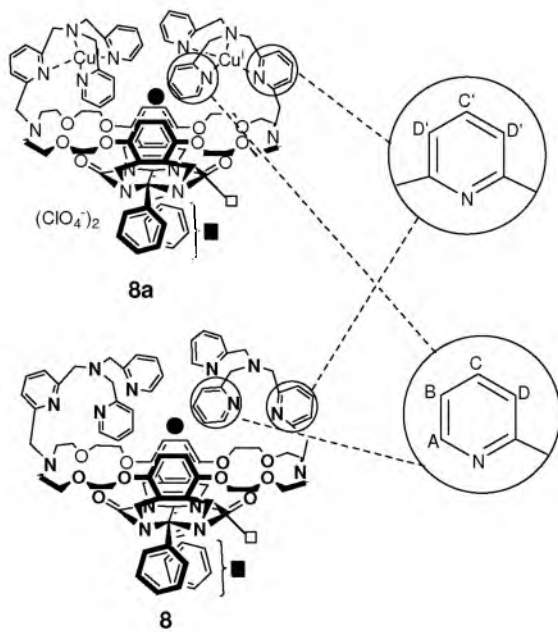
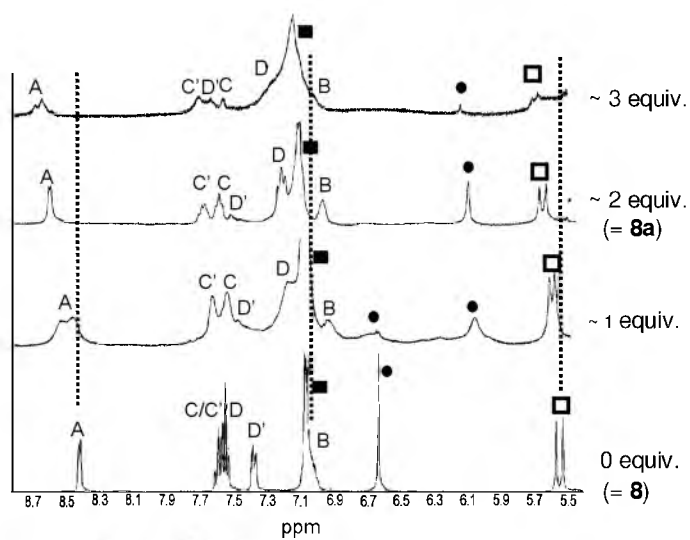


Figure 9.

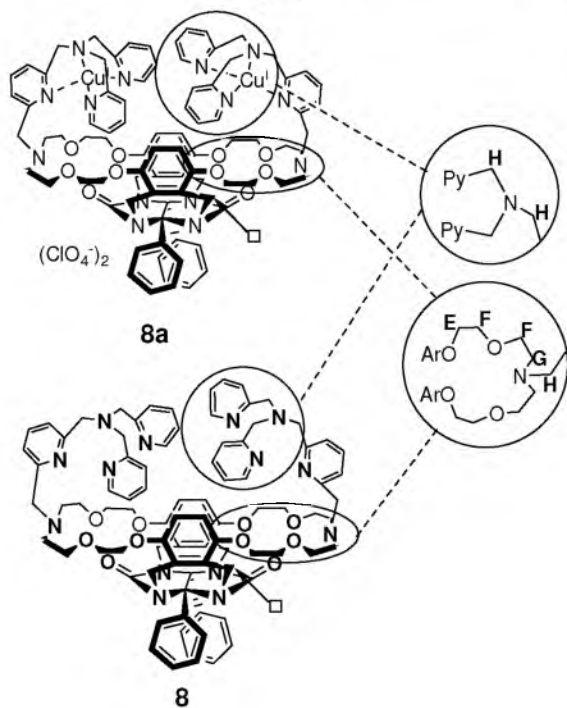
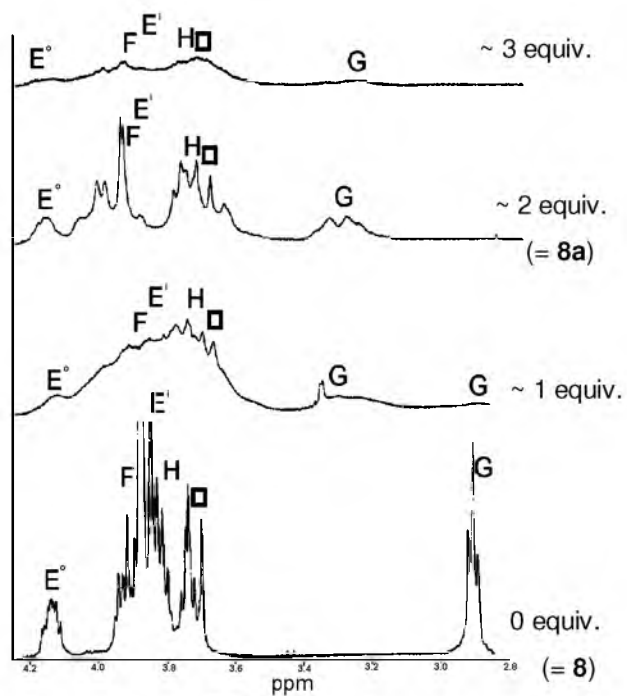
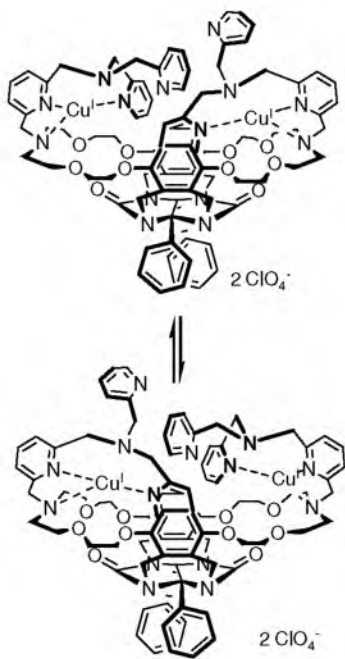


Figure 10.



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