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Mandelohydroxamic Acid as Ligand for Copper(II) 15-Metallacrown-5 Lanthanide(III) and Copper(II) 15-Metallacrown-5 Uranyl Complexes

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The formation of pentanuclear copper(II) complexes with the mandelohydroxamic ligand was studied in solution by electrospray ionization mass spectrometry (ESI-MS), absorption spectrophotometry, circular dichroism and ^{1}H NMR spectroscopy. The presence of lanthanide(III) or uranyl ions is essential for the self-assembly of the 15-metallacrown-5 compounds. The negative mode ESI-MS spectra of solutions containing copper(II), mandelohydroxamic acid and lanthanide(III) ions (Ln = La, Ce, Nd, Eu, Gd, Dy, Er, Tm, Lu, Y) or uranyl in the ratio 5:5:1 showed only the peaks that could be unambiguously assigned to the following intact molecular ions: $\{Ln(NO_3)_2[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^{2-}\}^-$ and $\{Ln(NO_3)[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^{3-}\}^-$, where MHA represents doubly deprotonated mandelohydroxamic acid. The NMR spectra of the pentanuclear species revealed only one set of peaks indicating a fivefold symmetry of the complex. The pentanuclear complexes synthesized with the enantiomerically pure *R*- or *S*-forms of mandelohydroxamic acid ligand, showed circular dichroism spectra which were mirror images of each other. The pentanuclear complex made from the racemic form of the ligand showed no signals in the CD spectrum. The UV/Vis titration experiments revealed that the order in which the metal salts are added to the solution of the mandelohydroxamic acid ligand is crucial for the formation of metallacrown complexes. The addition of copper(II) to the solutions containing mandelohydroxamic acid and neodymium(III) in a 5:1 ratio lead to the formation of a pentanuclear complex in solution. In contrary, titration of lanthanide(III) salt to the solution containing copper(II) and mandelohydroxamic acid did not show any evidence for the formation of pentanuclear species.
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Introduction

Hydroxamic acids, whether naturally occurring or synthetic, are an important family of organic bioligands.[1] One of the first biomedical applications of hydroxamic acids was associated with the uptake or removal of iron from the body.[2] In recent years it has become evident that these weak acids possess other types of biological activities.[3–7] Their role as potent and selective inhibitors of a range of metalloenzymes has been of special interest to inorganic chemists, because the biological activities of hydroxamic acids have been mainly attributed to their complexing properties toward transition-metal ions.[8] As a result, the transition-metal complexes of hydroxamic acids are frequently used as bioinorganic model compounds to investigate the enzymatic interactions and binding properties of these bioligands.

Hydroxamic acid ligands can exhibit different possible chelation modes, and this results in a rich variety of metal complex structures.[9,10] By far the most common mode of metal binding is the bidentate coordination mode through the deprotonated hydroxamate and carbonyl oxygen atoms, resulting in the formation of simple mononuclear complexes. The introduction of secondary coordinating groups can significantly modify the coordination behavior of hydroxamate ligands. For instance, aminohydroxamic acids can coordinate to metals through (*O*,*O*) as a singly deprotonated hydroxamate, through (*N*,*N*) of the amino and the deprotonated hydroxamic nitrogen, or as a (*N*,*N*)-(*O*,*O*) bridging bis-chelating ligand. Very often, the complexation to metal ions leads to formation of oligomeric or polymeric complexes.[9] However, under certain conditions, the formation of metallacrowns, types of compounds which are analogous to crown ethers in both structure and function, has been observed.[11–13] For example, a pentanuclear [12-metallacrown-4]copper(II) complex is self-assembled from solutions of copper(II) and β-alaninehydroxamic acid (Scheme 1, a). Besides the β-aminohydroxamic acids several other ligands like salicylhydroxamic acid (Scheme 1, b), 2-aminophenylhydroxamic acid, 2-pyridylacetohydroxamic acid and 3-naphthohydroxamic acid have also been used in the 12-metallacrown-4 synthesis.[14] In addition to the [12-metallacrown-4]copper(II) complexes, 12-metallacrown-4 complexes containing other ring metals such as manganese(II), manganese(III), iron(III), oxovanadium(IV) and gallium(III) have been synthesized.[15–21]

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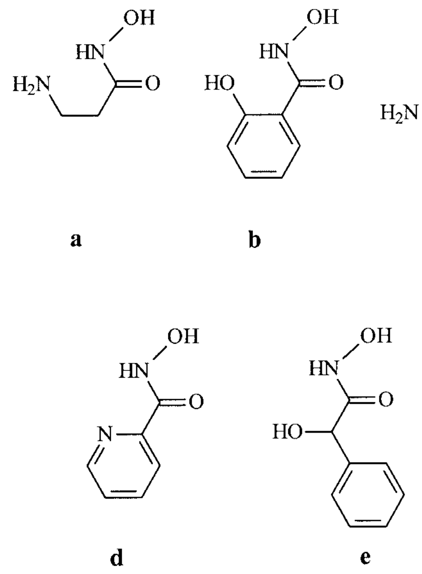


Scheme 1. Precursor ligands used for the synthesis of metallacrown complexes. (a) β-Alaninehydroxamic acid; (b) salicylhydroxamic acid; (c) α-aminohydroxamic acid; (d) picolinehydroxamic acid; (e) mandelohydroxamic acid.

In contrast to the numerous 12-metallacrown-4 structures reported so far, there are only very few examples of ligands capable of forming planar rings of the larger 15-metallacrown-5 structure type. Up to now, only α-aminohydroxamic acids and picolinehydroxamic acid (Scheme 1, c–d) have been found to form planar 15-metallacrown-5 complexes. The key property of these two ligand scaffolds is that they are able to form two fused five-membered chelate rings, which allows five metals and five ligands to form a planar 15-metallacrown-5 structure.[22,23] The planar 15-metallacrown-5 complexes formed in this way are capable to incorporate in their central cavity cations with a larger ionic radius and with a higher coordination number than 12-metallacrown-4 complexes. As a result, lanthanide(III)[24–28] and uranyl (UO_2^{2+})[23,28,29] ions have been incorporated in the center of a 15-metallacrown-5 ring.

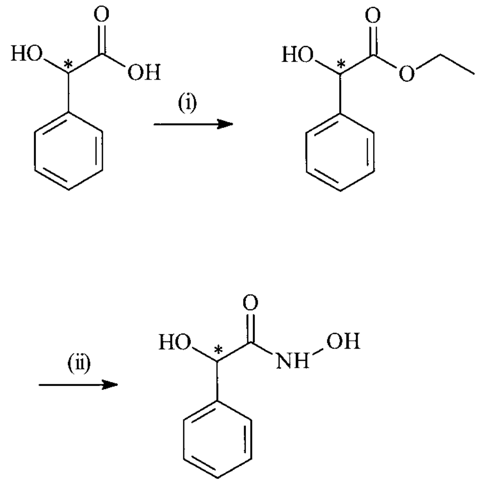
The limited number of ligands that are reported to form planar 15-metallacrown-5 complexes creates a challenge for the predesigned synthesis of these structural motifs. The geometry of a particular ligand and its known interaction with a metal ion should contain all the information required for the successful self-assembly of the metallacrown compounds. Therefore, when planning the synthesis of metallacrowns, the general choice of ligand type, ligand geometry, metal type and reaction conditions have to be considered. Although many metal complexes of hydroxamic acids and their derivatives have been studied in detail, the coordination chemistry of mandelohydroxamic acid (Scheme 1, e) is virtually unexplored. A few complexes of divalent cations have been prepared through precipitation in aqueous solution,[30,31] and the metal-ligand stability constants for some mononuclear complexes have been reported.[32] However, no structural data are available for this type of metal complexes.

In this paper, we show that in the presence of copper(II) and lanthanide(III) ions, mandelohydroxamic acid forms stable 15-metallacrown-5 complexes in solution by self-assembly. The copper(II) ion was chosen as the ring metal, as it can form complexes of square-planar geometry, and because its relatively labile metal–ligand bonds should allow the rearrangement of initially formed kinetic products into the thermodynamically stable product. The role of lanthanide(III) and uranyl ions as central templating ions for the self-assembly was examined, as well as conditions which are necessary for the formation of 15-metallacrown-5 complexes.

Results and Discussion

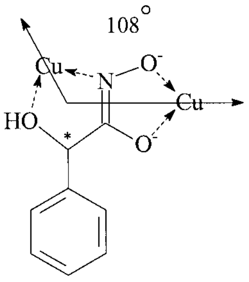
Complexation of Mandelohydroxamic Acid to Copper(II)

Mandelohydroxamic acid (MHA) was synthesized from mandelic acid according to Scheme 2. The racemic DL and the enantiomerically pure (*S*)-(+) and (*R*)-(–) forms of the MHA ligand were obtained depending on the stereochemistry of the starting material. Our intention to use mandelohydroxamic acid (MHA) as the ligand for the formation of 15-metallacrown-5 complexes was based on the fact that this ligand possesses a secondary coordinating hydroxy group, and that bidentate coordination through this hydroxy group and the hydroxamate nitrogen would form five-membered chelate rings. The additional coordination by two oxygen atoms can lead to the formation of two five-membered chelate rings (Scheme 3), with an angle of 108° between the two metal atoms. This is, according to the rational design, a geometrical prerequisite for the formation of the 15-metallacrown-5 structure.[21]



Scheme 2. Synthesis of mandelohydroxamic acid. Conditions: (i) ethanol, H_2SO_4, (ii) $NH_2OH·HCl$, KOH, methanol.

Previous studies of the mandelohydroxamic acid (MHA) ligand have shown that in the presence of divalent metal ions 1:1 and 2:1 complexes are formed, in which the coordination of the MHA occurs by the formation of five-membered chelates through the deprotonated hydroxamate and carbonyl oxygen atoms.[30–32] The coordination of the hy-



Scheme 3. Rationale for the formation of planar 15-metallacrown-5 complexes.

droximato nitrogen and hydroxy oxygen to the metal ions has not been observed.

Mixing of copper(II) and the enantiomerically pure *R*- or *S*-form of MHA in aqueous solutions resulted in the formation of a green solid after few hours of stirring. Similar reactions occurred when methanol or ethanol were used as solvents. The elemental analyses carried out for the precipitate isolated from methanolic or ethanolic solutions indicated the formation of a complex with the stoichiometry [CuL]. However, the insolubility of this solid in all conventional solvents suggests a polymeric nature of the complex. Polymeric complexes of hydroxamic acids which possess a secondary coordinating group have been previously reported.[33]

When racemic DL-mandelohydroxamic acid was used instead of the enantiomerically pure *S*- or *R*-form, the equimolar mixture of $Cu(OAc)_2$ and MHA in methanol or ethanol remained clear during the course of several weeks. The UV/Vis spectrum of the green solution exhibits an absorption maximum at 650 nm, which is equal to the values observed in $[Cu(acetohydroxamate)_2]$ (λ_{max} = 653 nm)[34] and other copper(II) complexes with deprotonated hydroxamate and carbonyl oxygen donors.[35] The ESI-MS spectra did not show any evidence for the presence of metallacrown species, so it is likely that the complex formed in solution is the mononuclear $Cu(MHA)_2$ complex in which the coordination to copper(II) occurs by the deprotonated hydroxamate and carbonyl oxygen donors. This finding is in sharp contrast to the analogous reaction between α-aminohydroxamic acids and copper(II), in which exclusively the $[Cu_5(\alpha\text{-aha})_4]^{2+}$ (aha = aminohydroxamic acid) 12-metallacrown-4 complex is formed in solution.[12] In that metallacrown complex the coordination of aminohydroxamic acid occurs also by the deprotonated hydroxamate and carbonyl oxygen atoms; however, the second five-membered ring is also formed through the coordination of hydroximato nitrogen and amino nitrogen to copper(II). This leads to the formation of a puckered structure with four copper(II) ions in the backbone of the metallacrown and a cavity which accommodates the fifth copper(II) ion.

Although the coordination geometries of α-aminohydroxamic acids and mandelohydroxamic acid are almost identical, the main difference between these two ligands is that mandelohydroxamic acid possesses a hydroxy group instead of the amino group of α-aminohydroxamic acids. The presence of the hydroxy group, which is a weaker ligating group for copper(II) ions, probably prevents the formation of the second chelating ring, and thus the formation of a 12-metallacrown-4 metallacrown structure.

Formation of 15-Metallacrown-5 Complex Monitored by ESI-MS

Our previous studies have shown that lanthanide(III) and uranyl ions have a large influence on the structure of the metallacrown complexes based on α-aminohydroxamic acid and copper(II) ion.[29,36,37] The addition of lanthanide(III) and uranyl ions to $[Cu_5(\alpha\text{-aha})_4]^{2+}$ induces a complete reassembly of the 12-metallacrown-4 structure to the 15-metallacrown-5 structure, in which lanthanide(III) or uranyl ions occupy the central cavity of the planar ring. Although lanthanide(III) ions seem to be essential for the synthesis of 15-metallacrown-5 complexes, their exact role has never been examined.[24] Previously, it has been suggested that lanthanide(III) ions are being merely recognized end-encapsulated by the 15-metallacrown-5 ring, and that this inclusion may contribute to the stability of the whole metallacrown structure. These findings prompted us to exploit lanthanide(III) and uranyl ion as possible templates for the formation of metallacrown complexes based on mandelohydroxamic acid and copper(II). When 0.25 equiv. of neodymium(III) were present in an equimolar solution of copper(II) and (*S*)-mandelohydroxamic acid, the color of the solution gradually changed from blue to green. The addition of sodium formate or sodium acetate salts resulted in the formation of a microcrystalline solid (see Exp. Section). Unfortunately, all attempts to isolate crystals of quality good enough for X-ray single crystal analysis were unsuccessful, but the elemental analysis results were consistent with the stoichiometry $Nd[Cu_5(MHA)_5]\cdot 3(HCOO)\cdot 3(H_2O)$ and $Nd[Cu_5(MHA)_5]\cdot 3(CH_3COO)\cdot (H_2O)$, where MHA represents the doubly deprotonated mandelohydroxamic acid. Crystallization techniques, such as evaporation of the solvent, diffusion techniques (vapor and liquid), and various co-crystallants were used on all three types of metallacrown complexes containing racemic DL and the enantimerically pure *S*-(+)and *R*-(–) forms of the mandelohydroxamate ligand. The only few crystals that were obtained were of insufficient quality for X-ray diffraction studies. The only reflections that could be observed were weak reflections in the small-angle region and were not suitable for the determination of the crystallographic unit cell. The solutions containing equimolar amounts of (*S*)-mandelohydroxamic acid and copper(II) acetate, in which 0.2 mol equivalents of different trivalent rare-earth ions (Ln = La, Ce, Nd, Eu, Gd, Dy, Er, Tm, Lu, Y) or uranyl ions (UO_2^{2+}) were present, have been further analyzed by electrospray ionization mass spectrometry (ESI-MS). In recent years, ESI-MS has been proven very useful for the analysis of self-assembled clusters. The results obtained by ESI-MS have been often regarded as indicative for the solution behavior of a species rather than for its gas-phase behavior.[38] The method has also been proven as very useful for confirming the integrity of metallacrown complexes in solution.[14] Several studies indicate that the results obtained by ESI-MS correlate very well with those obtained by other techniques, such as NMR and X-ray diffractometry.[38,39] Nonetheless, ESI-MS studies of large self-assembled metal complexes remain nontrivial and often require thorough optimization of the experimental parameters. All peaks detected in the mass spectra of Cu^{II}/MHA/Ln^{III} and Cu^{II}/MHA/UO_2^{2+} solutions appear as cluster peaks, because of the different copper(II) and lanthanide(III) isotopes in the detected complexes. Species with different degrees of protonation were detected in the ESI-MS spectra. This may be due to the deprotonation or protonation during the ionization process, or may be due to the different degree of protonation of mandeloxydroxamate ligand. It is possible that the deprotonation of the mandelohydroxamate ligand occurs not only on the hydroxamate nitrogen and oxygen atoms, like it was reported for other hydroxamate ligands that form 15-metalacrown-5,[24–29] but that the hydroxyl group may also be deprotonated. Both protonated and deprotonated forms of the hydroxyl group can bind to copper(II), and moreover, the Lewis acidity of the copper(II) may cause the deprotonation of the hydroxyl group upon binding. The peaks that were observed in the ESI-MS spectra are summarized in Table 1 and Table 2. The reported *m*/*z* values are the maxima of the cluster peaks. All the peaks detected in the negative mode (Table 1) could be unambiguously assigned to the following two intact molecular ions: $\{Ln(NO_3)_2[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^{2-}\}^-$ and $\{Ln(NO_3)[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^{3-}\}^-$, where MHA represents doubly deprotonated mandelohydroxamic acid (mandelohydroximate) (Figure 1). If the neodymium(III) perchlorate was used instead of neodynium(III) nitrate, peaks corresponding to $\{Nd(ClO_4)_2[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^{2-}\}^-$ and $\{Nd(ClO_4)_3[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^{2-}\}^{2-}$ species with two and three perchlorate counterions were observed. Thus, the positive charge of the central lanthanide(III) ions is always compensated by the negative charge of the ring and by nitrate or perchlorate anions present in the solution.

Table 1. Negative-ion ESI-MS data for 15-metallacrown-5 complexes derived from (*S*)-(+)-mandelohydroxamic acid, copper(II) ions as the ring metal and with different central cavity metals(M).

Species	$\{M(NO_3)_2[15\text{-}MC\text{-}5]^{2-}\}^-$		$\{M(NO_3)[15\text{-}MC\text{-}5]^{3-}\}^-$	
M	*m*/*z* exp.	*m*/*z* calcd.	*m*/*z* exp.	*m*/*z* calcd.
Y^{III}	1354.6	1354.3	1291.9	1291.3
La^{III}	1404.6	1404.4	1341.9	1341.4
Ce^{III}	1405.6	1405.6	1342.9	1342.5
Nd^{III}	1409.5	1409.6	1346.9	1346.6
Eu^{III}	1417.5	1417.4	1353.9	1354.4
Gd^{III}	1422.6	1422.7	1358.9	1359.7
Dy^{III}	1427.6	1427.9	1363.9	1364.9
Er^{III}	1432.6	1432.7	1369.0	1369.7
Tm^{III}	1434.6	1434.4	1371.7	1371.4
Lu^{III}	1440.6	1440.4	–	–
UO_2^{2+}	–	–	1410.9	1410.5[a]

[a] Value calculated for $\{M[15\text{-}MC\text{-}5]^{3-}\}^-$.

Table 2. Positive-ion mode ESI-MS data for 15-metallacrown-5 complexes derived from (*S*)-(+)-mandelohydroxamic acid, copper(II) ions as the ring metal and with different central cavity metals (M).

Species	$\{M(NO_3)[15\text{-}MC\text{-}5]\}^{2+}$		$\{M(NO_3)[15\text{-}MC\text{-}5]^-\}^+$	
M	*m*/*z* exp.	*m*/*z* calcd.	*m*/*z* exp.	*m*/*z* calcd.
Y^{III}	645.3	645.3	–	–
La^{III}	672.2	672.2	1342.5	1343.4
Ce^{III}	672.7	672.8	1343.9	1344.6
Nd^{III}	674.5	674.8	1347.6	1348.7
Eu^{III}	678.3	678.7	1355.7	1356.4
Gd^{III}	681.8	681.3	1361.7	1361.7
Dy^{III}	683.5	683.9	1366.1	1366.9
Er^{III}	685.7	686.3	1371.5	1371.1
Tm^{III}	686.3	687.2	–	–
Lu^{III}	689.2	690.2	–	–
UO_2^{2+}	706.4	706.8[a]	1412.7	1412.5[a]

[a] Values calculated for $\{M[15\text{-}MC\text{-}5]\}^{2+}$ and $\{M[15\text{-}MC\text{-}5]^-\}^+$.

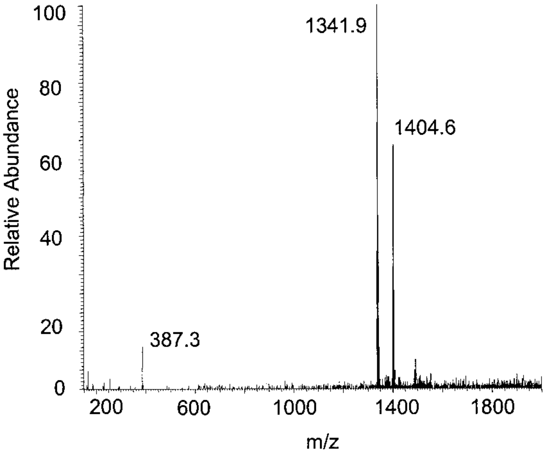


Figure 1. Negative-ion mode ESI-MS spectra of the methanolic solutions containing Cu^{II}/MHA/La^{III} in 5:5:1 ratio.

When lutetium(III) or thulium(III) were used as central cavity ions, additional peaks, that could not be attributed to a 15-metallacrown-5 species with a lanthanide(III) ion in the central cavity, were observed in the ESI-MS spectra. In both cases, a peak at *m*/*z* = 1222 was detected which corresponds to a 15-metallacrown-5 species with copper(II) ion in the central cavity: $\{Cu(OH)[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^{2-}\}^-$. Another peak at *m*/*z* = 993 could be assigned to $\{Cu(OH)[12\text{-}MC\text{-}4]^{2-}\}^-$. As thulium(III) and lutetium(III) are lanthanide ions with a small ionic radius (87 and 85 pm, respectively), this probably leads to less effective encapsulation into the central cavity and thus to a reduced stability of the 15-metallacrown-5 complexes.

The ESI-MS spectra in the positive mode also gave strong evidence for the existence of 15-metallacrown-5 complexes (Table 2). The peak with the highest intensity corresponds to the doubly charged $\{Ln(NO_3)[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]\}^{2+}$ species. Another peak with approx. 10% of the intensity of the former was detected in all the spectra and could be assigned to the $\{Ln(NO_3)[15\text{-}MC_{Cu^{II}N(MHA)}\text{-}5]^-\}^+$ molecular ion.

Only one peak at *m*/*z* = 1410 was observed in the ESI-MS spectra taken in the negative mode for the solution containing the uranyl ion. The mass of this peak could be unambiguously assigned to the intact {UO$_2$[15-MC$_{Cu^{II}N(MHA)}$-5]$^{3-}$}$^-$ molecular ion. The axial coordination of two oxygen atoms in the uranyl ion does not allow for additional binding of counterions, and the first coordination sphere of the uranyl ion is completed by five equatorial oxygen atoms from the metallacrown ring. In the positive mode ESI-MS spectra of the solution containing the uranyl ion, two peaks at *m*/*z* = 706 and 1412 were detected (Figure 2). They correspond to the {UO$_2$[15-MC$_{Cu^{II}N(MHA)}$-5]}$^{2+}$ and {UO$_2$[15-MC$_{Cu^{II}N(MHA-)}$-5]$^-$}$^+$ pentanuclear species, respectively. The peak at *m*/*z* = 1412.7 corresponds to a 15-metallacrown-5 species in which the hydroxyl group in one of the ligands is deprotonated, and the peak at *m*/*z* = 706.4 corresponds to a metallacrown species in which all five hydroxyl groups are protonated.

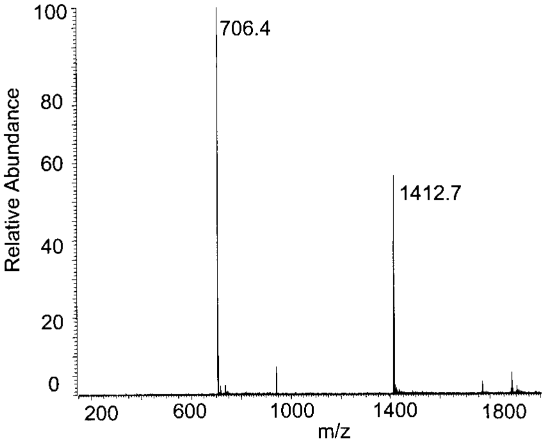


Figure 2. Positive-ion mode ESI-MS spectra of the methanolic solutions containing Cu^{II}/MHA/UO$_2$$^{2+}$ in 5:5:1 ratio.

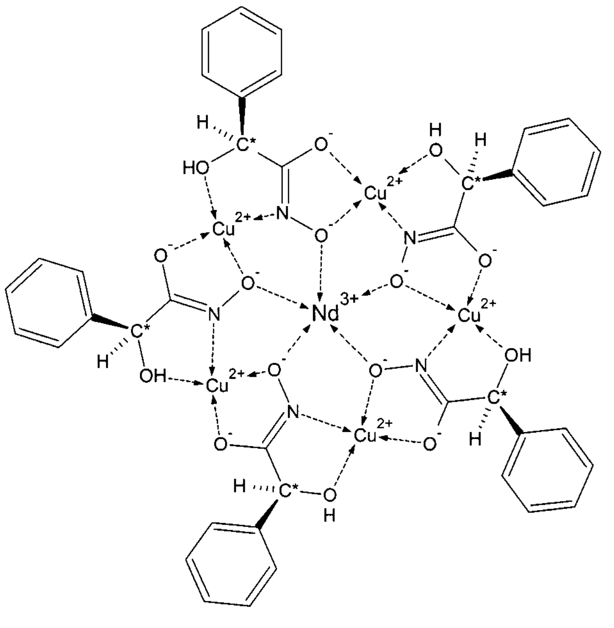


Figure 3. Proposed structure of the pentanuclear Nd[15-MC$_{Cu^{II}N[(S)\text{-}MHA]}$-5] metallacrown complex in solution. The coordination sphere of neodymium(III) ion is completed by nitrate or water ligands.

The spectra of solutions containing racemic DL-mandelohydroxamic acid, copper(II) and neodymium(III) or uranyl were also recorded, and the *m*/*z* values observed in those spectra were identical to the *m*/*z* values observed when (*S*)-mandelohydroxamic acid was used as coordinating ligand.

The presented ESI-MS data indicate that solutions containing copper(II) salt, mandelohydroxamic acid [DL- or (*S*)-] and a central templating ion in methanolic and ethanolic solutions are forming pentanuclear species. The only species detected for the solutions prepared with M = Y, La, Ce, Nd, Eu, Gd, Dy, Er, and UO$_2$ correspond to the intact M[15-MC$_{Cu^{II}N(MHA)}$-5] pentanuclear species. On the basis of the previously mentioned geometric considerations, it is very likely that the structure of the pentanuclear species corresponds to the structure of the planar 15-metallacrown-5 ring, in which lanthanide(III) ions or uranyl ions are encapsulated in the central cavity (Figure 3).

Complexation of Mandelohydroxamic Acid Monitored by UV/Vis Spectroscopy

Titration experiments were performed in order to gain insight into the formation of the metallacrown complexes. Surprisingly, these experiments revealed that the order in which the metal salts are added to the MHA solution is crucial for the formation of metallacrown complexes. Titration of Cu^{II}/DL-MHA solution with neodymium(III) and uranyl in steps of 0.04 equivalents caused a slight decrease in the intensity of the broad shoulder between 300 nm and 450 nm and also the decrease of the d–d transition band at 687 nm. Even after the reaction mixture was let to react for 24 hours, no appearance of new peaks and shifting of the ligand field or d–d bands was observed. The ESI-MS spectra of these solutions were recorded and they did not show any evidence for the existence of pentanuclear species.

On the contrary, the titration of copper(II) to the solutions containing DL-MHA and neodymium(III) in a 5:1 ratio caused significant changes in the UV/Vis spectra. New bands at 330 nm and 638 nm (Figure 4) appeared, and their intensity increased until 5 equivalents of copper(II) were added, and it leveled off upon addition of 6 equivalents of copper(II). The molar absorptivity of the copper(II) ligand field band observed at a Cu/Ln ratio of 5:1 was consistent with the isolated 15-metallacrown-5 sample, dissolved in MeOH. The plot of the ratio of concentrations of neodymium(III) to copper(II) vs. the molar absorptivity at 330 nm and 638 nm is shown in Figure 5. The composition of the sample in which the ratio of Nd/MHA/Cu was 1:5:5 is consistent with the formula Nd[15-MC$_{Cu^{II}N(MHA)}$-5]. With the further increase of lanthanide concentration, no changes in the copper(II) ligand field band were observed, indicating that the presence of excess of lanthanide or uranyl ions does not disturb the metallacrown structures. Indeed, the ESI-MS spectra of the final solution showed exclusively cluster peaks which could be unambiguously assigned to the 15-metallacrown-5 species. The UV/Vis spectrum of Nd[15-MC$_{Cu^{II}N(MHA)}$-5] resembles the UV/Vis spectra of other pentanuclear complexes with lanthanide(III) ions. The band at 330 nm is in agreement with the band at 336 nm observed in the 15-metallacrown-5 complexes with tryptophanhydroxamic acid.[40] This band contains most likely contributions of $N^{-}–O^{-}_{(nitrogen)}$ and $N^{-}–O^{-}_{(oxygen)}$ to copper(II) charge-transfer transitions.

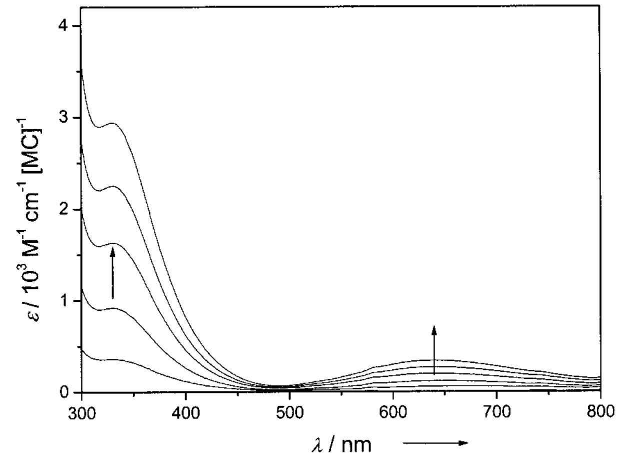


Figure 4. Changes in the UV/Vis absorption spectra of Nd^{III}/MHA solutions in methanol, upon addition of copper(II) ions. Copper(II) ions were added in 0.2 equiv. increments, until the final ratio of Nd^{III}/MHA/Cu^{II} reached 1:5:5 ratio.

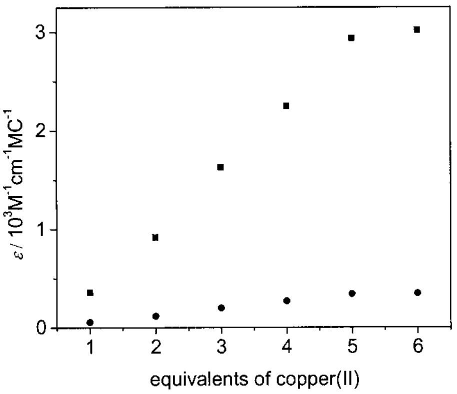


Figure 5. Change of molar absorptivity at 330 nm (squares) and 638 nm (circles) of the Nd^{III}/MHA/Cu^{II} solution as a function of number of copper(II) equivalents.

The complex formation of lanthanide(III) with mandelohydroxamic acid has not been reported before, and no information about the stability of such complexes is available. The X-ray single-crystal structure of the complex formed between europium(III) and analogous α-alaninehydroxamic acid has shown that the hydroxamate group of α-alaninehydroxamate ligands forms a bridge between two europium(III) ions, so that a binuclear complex is formed.[41] However, it has been shown that the addition of copper(II) to solutions of lanthanide(III) and α-aminohydroxamic acid leads to the formation of the 15-metallacrown-5 structure.[37] Obviously, the high lability of the lanthanide(III) ligand bonds may allow for the initially formed products to rearrange into the 15-metallacrown-5 structure upon addition of copper(II) ion.

However, it must be mentioned that factors, such as the acidity of the solution and the different protonation states of the ligand, may be responsible for the fact that the order in which the metal salts are added to the MHA solution is crucial for the formation of the metallacrown complex. The determination of the degree of protonation of the ligand in the presence of copper(II) and lanthanide(III) ions would require thorough potentiometric titrations and evaluation of many possible equilibria involved in the ternary H^+/MHA/Cu^{2+}/Ln^{3+} system.

CD Spectroscopy of 15-Metallacrown-5 Complexes

Because the *R*- and *S*-enantiomeric forms of the MHA are chiral, their copper(II) complexes are expected to be optically active as well. The chirality of the 15-metallacrown-5 complexes formed with *R*- and *S*-enantiomeric forms of the MHA has been studied by circular dichroism (CD) spectroscopy. The ESI-MS spectra of all the solutions used for the spectrophotometric measurements were recorded, and the species observed were consistent with the Ln[15-$MC_{Cu^{II}N(MHA)}$-5] structure as described earlier in the mass spectrometric results. The CD spectrum of methanolic solutions of (*S*)-MHA/Cu^{II}/Nd^{III} (ratio: 1:1:0.2), shows a positive Cotton effect at 342 nm ($\Delta\varepsilon$ = 2.86 mol·L^{-1} cm^{-1}) and two negative Cotton effects at 603 ($\Delta\varepsilon$ = –1.2 mol·L^{-1} cm^{-1}) and 733 nm ($\Delta\varepsilon$ = –1.08 mol·L^{-1} cm^{-1}). If (*R*)-MHA was used as the ligand, the CD spectrum of the resulting complex was the mirror image of the spectrum of the complex of (*S*)-MHA. As expected, the 15-metallacrown-5 complex made from the racemic MHA showed no signal in the CD spectrum (Figure 6).

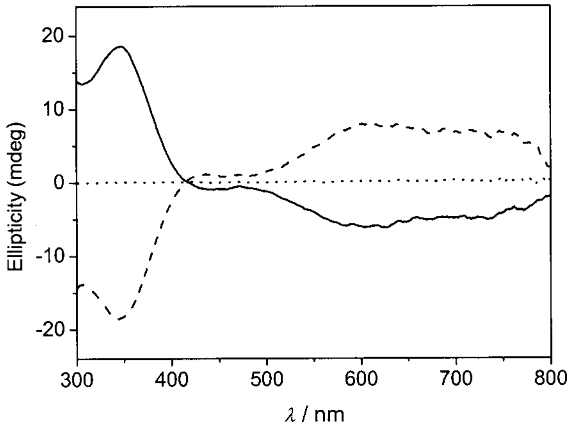


Figure 6. CD absorption spectra of Nd[15-$MC_{Cu^{II}N[(S)\text{-}MHA]}$-5] (full line), Nd[15-$MC_{Cu^{II}N[(R)\text{-}MHA)}$-5] (dotted line) and Nd[15-$MC_{Cu^{II}N(DL\text{-}MHA)}$-5] (dashed line) in methanol.

The chirality of the 15-metallacrown-5 complex implies that all five phenyl groups of the MHA ligand have to be positioned upon the same face of the metallacrown. This side-chain orientation is enforced by the directionality of the metal–nitrogen–oxygen bonds, as it was previously reported in other chiral 15-metallacrown-5 complexes.[22,24]

Proton NMR of of 15-Metallacrown-5 Complexes

Proton NMR signals of nuclei close to paramagnetic metal ions are usually very broad and the extent of paramagnetically induced line broadening depends on the electronic relaxation time of the metal centers.[42] Complexes with paramagnetic copper(II) ions usually exhibit broad NMR signals because of the relatively long electronic relaxation times of copper(II) ($\tau_s = 1{\cdot}10^{-9}$ s to $5{\cdot}10^{-9}$ s). However, a shortening of the electronic relaxation times can occur because of the magnetic coupling between the metal ions.[42] Previous studies have shown that the copper(II) ions in the 15-metallacrown-5 are antiferromagnetically coupled,[22,24] so that the τ_s value of those metallacrowns is shorter than it would be in the absence of magnetic coupling. This could allow the detection of relatively narrow peaks in high-resolution NMR experiments.

The ^{1}H NMR spectrum of the Nd[15-MC$_{\mathrm{Cu^{II}N[(\mathit{R})\text{-}MHA}}$-5] complex in [D$_4$]MeOH showed three peaks at δ = 5.85, 6.58, and 7.75 ppm (Figure 7). The α-proton of the ligand could not be observed, most likely because it was too broad. It has been shown that the protons to the closest proximity to the paramagnetic center are showing the greatest line broadening.[43] The assignment of the peaks was done with the help of two-dimensional proton correlation spectroscopy (COSY). The comparison with the proton NMR spectrum of the previously reported Nd[15-MC$_{\mathrm{Cu^{II}N(L\text{-}tyrha)}}$-5] complex revealed that the aromatic protons of the mandelohydroxamate ligand appear in the same region as the signals of the aromatic protons of the tyrosinehydroxamate ligand. The simplicity of the spectra, i.e. the presence of only one set of resonances indicates the fivefold pseudosymmetry of the molecule. The NMR results are consistent with those of the previously studied lanthanide(III) containing 15-metallacrown-5 copper(II) complexes, which also showed only one set of ligand resonances.[24]

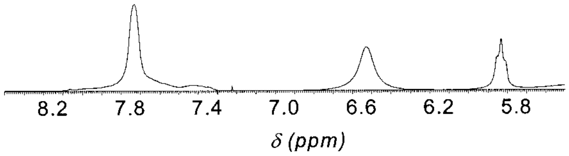


Figure 7. Proton NMR spectrum of Nd[15-MC$_{\mathrm{Cu^{II}N[(\mathit{R})\text{-}MHA]}}$-5] complex in [D$_4$]MeOH solution.

It is noteworthy to emphasize the fact that whereas the NMR signals were observable for the 15-metallacrown-5 complex in which several highly paramagnetic ions are present, no NMR spectrum could be obtained for the complexes formed in the absence of lanthanide(III) ions. Obviously, there are significant differences in the relaxation times of copper(II) ions in these two types of complexes. The absence of any protons in the NMR spectrum recorded in the absence of lanthanide(III) is consistent with the presence of mononuclear copper(II) complexes.

Conclusions

In this paper we explore the strategy that leads to the formation of pentanuclear copper(II) complexes with the mandelohydroxamic ligand. The results of ESI-MS, UV/Vis, CD, and NMR studies are consistent with the formation of 15-metallacrown-5 complexes. The mandelohydroxamic ligand as novel scaffold for the 15-metallacrown-5 complex fulfils the geometric requirements which bring five metal ions into a plane, enforcing an angle of 108° between adjacent metal ions, and thus enforcing the formation of a planar, pentagonal ring. Our study shows that for the self-assembly of the 15-metallacrown-5, the presence of lanthanide(III) or uranyl ions is essential, as it has been demonstrated before. As it has been suggested before that lanthanide(III) ions are being recognized and encapsulated by 15-metallacrown-5 complexes, this study shows that lanthanide(III) ions may have a templating effect and could play a crucial role in the early stages of 15-metallacrown-5 formation.

Experimental Section

Synthesis of the Ligands: The ligands, (*R*)-(–)-mandelohydroxamic acid, (*S*)-(+)-mandelohydroxamic acid and DL-mandelohydroxamic acid were synthesized from the corresponding ethyl ester. The preparation method for (*S*)-(+)-mandelohydroxamic acid and DL-mandelohydroxamic acid is identical to that of the synthesis of (*R*)-(–)-mandelohydroxamic acid that is described below.

Synthesis of Ethyl (*R*)-(–)-Mandelate: To a solution of (*R*)-(–)-mandelic acid (100 mmol, 15.2 g) in ethanol (170 mL) was added H_2SO_4 (5 mL) as the catalyst. The reaction mixture was heated at reflux temperature for 4 h. After the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure. Then, after addition of dichloromethane, the organic layer was neutralized by a saturated $NaHCO_3$ solution and dried with $MgSO_4$. Dichloromethane was removed under reduced pressure. Yield: 91% (16.41 g). ^{1}H NMR ([D$_6$]DMSO, 300 MHz, ppm): δ = 1.13 (t, 3 H, CH_3), 4.07 (t, 2 H, OCH_2), 5.11 (d, 1 H, CH), 6.04 (d, 1 H, OH), 7.40 (m, 5 H, H-aromatic).

Synthesis of (*R*)-(–)-Mandelohydroxamic Acid: To a solution of $NH_2OH{\cdot}HCl$ (2 equiv., 182 mmol, 12.65 g) in methanol (110 mL), potassium hydroxide (3 equiv., 273 mmol, 15.29 g) dissolved in methanol (42 mL) was added under nitrogen. The hydroxylamine solution was cooled to 0 °C and KCl was removed by filtration. The solution was added to (*R*)-(–)-mandelic ethyl ester (1 equiv., 91 mmol, 16.41 g) and stirred at room temperature during 12 h. The white precipitate of the potassium salt was filtered off and dried (10.53 g, 51 mmol, 56% yield). To a suspension of the potassium salt in methanol was added 12 M HCl (51 mmol, 4.25 mL). Potassium chloride precipitated and was filtered off. The solvent of the filtrate was partially removed under reduced pressure and water was added to the solution. The solution was left to stand at 4 °C to allow the final product to crystallize. Yield: 51% (4.35 g). ^{1}H NMR ([D$_6$]DMSO, 300 MHz, ppm): δ = 4.89 (d, 1 H, CH), 5.95 (d, 1 H, OH), 7.40 (m, 5 H, H-aromatic), 8.77 (s, 1 H, NH), 10.72 (s, 1 H, $OH_{\mathrm{hydr.}}$). $C_8H_9NO_3$ (167 g/mol): calcd. C 57.48, H 5.43, N 8.38; found C 57.16, H 5.49, N 8.32.

Synthesis of the Metallacrowns

(1) Nd[15-MC-5]·3(HCOO)·3(H_2O): $Nd(NO_3)_3{\cdot}6H_2O$ (109 mg, 0.25 mmol) was dissolved into methanol (50 mL) and (*R*)-MHA (167 mg, 1 mmol) was added. The solution was stirred for 10 min, then sodium methoxide (108 mg, 2 mmol) was added to the reaction mixture. After another 10 min, anhydrous copper(II) chloride

(170 mg, 1 mmol) was added. The mixture was stirred for 2 h until the solution became green. Finally sodium formate (68 mg, 1 mmol) was added, and the blue-green precipitate was filtered, washed with water to remove sodium chloride and dried under vacuum. $C_{43}H_{44}Cu_5N_5NdO_{24}$ (1476.8 g/mol): calcd. C 34.97, H 3.00, N 4.74; found C 35.15, H 3.57, N 4.81.

(2) Nd[15-MC-5]·3(CH_3COO)·(H_2O): $Nd(NO_3)_3·6H_2O$ (109 mg, 0.25 mmol) was dissolved into methanol (50 mL) and (*R*)-MHA (167 mg, 1 mmol) was added. The solution was stirred for 10 min, then sodium methoxide (108 mg, 2 mmol) was added to the reaction mixture. After another 10 min, anhydrous copper(II) chloride (170 mg, 1 mmol) was added. The mixture was stirred for 2 h until the solution became green. Finally the sodium acetate (82 mg, 1 mmol) was added, and the blue-green precipitate was filtered, washed with water to remove sodium chloride and dried under vacuum. $C_{46}H_{46}Cu_5N_5NdO_{22}$ (1518.9 g/mol): calcd. C 37.26, H 3.13, N 4.72; found C 37.41, H 3.13, N 4.69.

UV/Vis and CD Spectrophotometry: UV/Vis absorption spectra were recorded with a Shimadzu UV-1601PC spectrophotometer using quartz cells of 1-cm path length. Circular dichroism spectra were recorded with a JASCO J-810 spectropolarimeter using quartz cells of 2-cm path length. The spectra were measured between 200 nm and 900 nm. The concentration of the copper(II) and mandelohydroxamic acid in methanol was always 0.5 mM. A neodymium(III) nitrate stock solution (0.25 mM). was prepared in methanol for the UV/Vis titration experiment. Different amounts of this solution were added to the copper(II)/mandelohydroxamic solution in order to obtain different ratios of Nd^{III}/Cu^{II}. The solutions were left to stir overnight before measurement. The Nd^{III}/Cu^{II} ratio was varied in steps of 0.04 from 0 to 0.28.

ESI-MS Method: Electrospray ionization mass spectra were recorded with a Q-TOF 2 mass spectrometer (Micromass, Manchester, UK). Some of a ethanolic metallacrown solution, prepared with 1 mmol of the copper(II) and mandelohydroxamic acid and 0.2 mmol of the central metal ion, was injected in the apparatus at a flow rate of 5 μL/min.

Proton NMR: Proton nuclear magnetic resonance spectra were recorded in deuterated methanol solutions with a Bruker Avance 300 spectrometer operating at 300 MHz. A 500 μL solution of [D_4]MeOH containing equimolar amounts of $Cu(OAc)_2$ and (*R*)-(–)-mandelohydroxamic acid (0.1 M) was added 1.0 equiv. of $Nd(NO_3)_3$. This was achieved by adding 60 μL of a neodymium(III) nitrate [D_4]MeOH solution (0.166 M).

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