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Heteroleptic complexes *via* solubility control: examples of Cu(II), Co(II), Ni(II) and Mn(II) complexes based on the derivatives of terpyridine and hydroxyquinoline†

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We describe the construction of synthetically challenging heteroleptic complexes by capitalizing on the solubility properties of their corresponding favored homoleptic complexes. We demonstrate that the formation of a heteroleptic Cu^{2+} complex based on 2,2′:6′,2″-terpyridine (Terpy) and 8-hydroxyquinoline (HQ) is not possible due to the insolubility of $(HQ)_2Cu^{2+}$. Replacing HQ with 8-hydroxy-2-quinolinecarbonitrile (HQCN) enabled the solubility of $(HQCN)_2Cu^{2+}$ in acetonitrile, leading to the formation of the heteroleptic complex Terpy(HQCN)Cu^{2+}, **TQCu**. Applying these conditions to the synthesis of the corresponding heteroleptic Co^{2+} complex resulted in TerpyCo^{2+}(acetate)$_2$, which is insoluble in acetonitrile. Upon changing the solvent to methanol, the carbonitrile group of HQCN was converted to carboxyimidate HQOMe yielding a heteroleptic complex Terpy(HQOMe)Co^{2+}, **TQ′Co**. Using this method, we also generated the heteroleptic complex **TQ′Ni** and the polynuclear heteroleptic complex **Q′$_4$Q″$_2$Mn$_4$** (**Q″** = HQO_2Me). Detailed analysis of the complexes included characterization by X-ray diffraction, EPR, UV-Vis, high resolution ESI MS, DFT calculations and electrochemistry. X-ray analysis of **TQCu** revealed distorted square pyramidal geometry, while **TQ′Co** and **TQ′Ni** exhibit distorted octahedral geometry, which includes metal coordination *via* the carboxyimidate nitrogen site. Interestingly, **Q′$_4$Q″$_2$Mn$_4$** was found to contain a $[Mn^{II}_4(\mu_3\text{-}O)_2(\mu_2\text{-}O)_4N_{10}]^{2+}$ core, which adopts a distorted octahedral geometry, and two types of HQ chelators. Thus, **Q′$_4$Q″$_2$Mn$_4$** is also heteroleptic even though it does not contain a Terpy ligand. Solution studies revealed that while **TQCu** is stable in solution, **TQ′Co** and **TQ′Ni** go through ligand exchange and are partially converted to their corresponding homoleptic complexes. Based on these data we could propose a mechanism for the formation of **TQ′Co** and **TQ′Ni** and show that **TQ′Co** can be prepared directly from Terpy and HQOMe.

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Introduction

The ability to control the coordination environment of a metal ion has significant importance in the design and development of metal-based materials including catalysts, selective chelators, sensors and biomimetic models. Typically, a coordination environment comprises metal-binding ligands (MBLs), which can be identical, thus creating homoleptic complexes, or varied, creating heteroleptic complexes. The major advantage of heteroleptic complexes is the possibility of tuning and combining ligand structural and functional properties, thus increasing the versatility of the metallic center.[1] From the metallosupramolecular chemistry point of view, heteroleptic complexes are of particular interest as they represent a promising research platform for the construction of diverse and functional systems.[2] Although such complexes have many advantages, the majority of the known coordination complexes are homoleptic, which are highly uniform and suffer from the lack of chemical and structural diversity.[3] This is mostly because directing the exclusive generation of a heteroleptic product over the two corresponding homoleptic complexes is highly challenging.[4] In order to control the formation of heteroleptic complexes in solution, several strategies can be implied as reported in the literature.[3b,5] One of these strategies is based on maximum site occupancy[6] and the use of sterically hindered MBLs, which cannot form bis-homoleptic complexes due to steric repulsion. Thus, only a 1 : 1 L : M complex is formed, and this further reacts with another ligand, which is less sterically hindered, to form the desired heteroleptic complex. An example of this approach is the HETPHEN strat-

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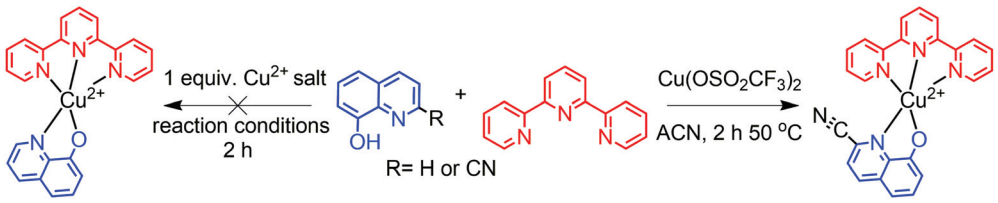
Scheme 1 The helical peptoid **Helix HQT i+3** bearing HQ and Terpy (left) rationally designed for the selective binding of Cu^{2+}, and its intramolecular Cu^{2+} complex (**Helix HQT i+3)Cu** (right).

egy (HETeroleptic PHENanthroline) first applied by Schmittel and coworkers.[7] Another technique is the combination between shape complementary ligands, and this was applied, using isoquinoline/pyridine ligands, to form heteroleptic $[Pd_2L_2L'_2]^{4+}$ coordination cages.[8] A different approach for constructing heteroleptic architectures is based on the properties of the metal ion rather than those of the ligands and exploits the particular penta-coordination geometric preference of copper(II) ions.[9] Using this strategy, we have recently developed a rationally designed helical peptidomimetic oligomer (peptoid) bearing two distinct MBLs, namely derivatives of 2,2′:6′,2″-terpyridine (Terpy) and 8-hydroxyquinoline (HQ). This peptoid enabled the selective recognition of Cu^{2+} and its extraction from a mixture of neighboring metal ions in high concentrations by forming a heteroleptic copper center, as suggested by mass spectrometry and UV-Vis spectroscopy (Scheme 1).[10] Moreover, EPR studies suggested a penta-coordination with a square pyramidal geometry. Hence, we hypothesized that this specific 3D arrangement is the source of the high selectivity to Cu^{2+} over other similar biologically relevant metal ions[11] such as Zn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+} and Mn^{2+} capable of binding these ligands.[12] In order to examine this assumption we set up to synthesize heteroleptic complexes based on Terpy, HQ and some of these metal ions, investigate their properties, and compare their structures.

Results and discussion

Attempts towards the synthesis of a heteroleptic copper complex

Our initial efforts to synthesize the heteroleptic Terpy(HQ)Cu^{2+} complex included the reaction between the equimolar mixture of the ligands HQ and Terpy with 1 equiv. of copper acetate in methanol (the mix approach). This reaction resulted in an immediate precipitation of a dark green complex and a bright blue solution. Further investigation of the precipitant and the solution by UV-Vis analysis revealed the formation of the homoleptic complex HQ_2Cu that precipitated and $Terpy_2Cu$ complex that remained in the solution (Fig. S1†). Following this unsuccessful attempt we turned our efforts to the synthesis of this complex *via* the step approach, which included (i) a slow addition of equimolar ligand mixture solution to the Cu^{2+} solution, both in methanol, (ii) addition of 1 equiv. of Terpy to 1 equiv. of Cu^{2+} in methanol followed by slow addition of 1 equiv. of HQ and (iii) addition of 1 equiv. of Cu^{2+} in methanol to the equimolar ligand mixture solution. In addition, we used different copper salts such as copper perchlorate or copper triflate, changed the solvent of the reaction to acetonitrile or increased the temperature of the solution to 50 °C, even for a long period of time of up to 7 days. All these attempts, however, did not afford the heteroleptic complex, but rather yielded the homoleptic complexes as indicated by the precipitation of HQ_2Cu during each reaction. We assume that these unsuccessful attempts were due to the poor solubility of the complex HQ_2Cu both in methanol and acetonitrile and its immediate precipitate, which shifted the reaction equilibrium towards its formation. Thus, we sought to increase the solubility of the homoleptic complexes in order to avoid this problem and chose to use a modified version of the HQ ligand, namely 8-hydroxy-2-quinolinecarbonitrile (HQCN), assuming that the carbonitrile group will facilitate the complex solubility in acetonitrile and enable the formation of the heteroleptic complex (Scheme 2). To verify this assumption, we added 1 equiv. from each ligand to half an equiv. of Cu(II)triflate in 5 mL of acetonitrile. The two solutions were mixed for 2 hours at 50 °C. The precipitate of each solution was separated by centrifugation, washed, dried and weighed, yielding 20.7 mg HQ_2Cu and 1.3 mg $(HQCN)_2Cu$. Thus we have confirmed that $(HQCN)_2Cu$ is more soluble than HQ_2Cu. Indeed, addition of an equimolar mixture of Terpy and HQCN to a solution of Cu^{2+} triflate in acetonitrile and heating the solution at 50 °C for 2 hours resulted in a dark green solution and no precipitate was obtained. After the addition of an aqueous solution of NH_4PF_6 a mustard-brown complex precipitated. It was collected by decantation, washed with water, dried and characterized by electrospray mass spectrometry (ESI MS) and UV-Vis spectroscopy. The molecular weight of the complex as measured by HR-ESI-MS was consistent with the expected mass of the Terpy(HQCN)Cu^{2+} (**TQCu**) complex (Fig. S18 and 19†), providing the first evidence for its formation. UV-Vis analysis of the complex in methanol supported the existence of **TQCu** in solution, showing absorption bands near λ = 266, 325 and 338 nm arising from the coordination of Cu^{2+} to both HQ and Terpy (Fig. S3†). The complex was obtained in a moderate isolated yield of about 60%, and we assume that due to its high solubility in acetonitrile, not all the complex actually precipitated and some of it remained in



Scheme 2 Synthetic routes towards the generation of the heteroleptic complex **TQCu**.

the solution. To support this assumption we have analyzed the filtrate solution, after precipitation, by ESI-MS and the obtained spectra matched the mass of **TQCu** (Fig. S27†). We therefore believe that the actual yield of **TQCu** from this reaction is higher than the isolated yield. Moreover, the ESI-MS spectra did not show any peaks corresponding to the homoleptic complexes $Terpy_2Cu$ and HQ_2Cu (which can result from a ligand exchange), suggesting that **TQCu** is stable under these conditions.

Single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation from acetonitrile/THF solution at room temperature. The complex was crystallized in the monoclinic crystal system (Fig. 1), has an open coordination site and exhibits a slightly distorted square pyramidal geometry with $\tau = 0.188$, which is an index of the degree of trigonality in five coordinate complexes.[13] The crystal structure confirmed the formation of **TQCu**.

EPR measurements conducted in frozen acetonitrile at 150 K indicated the presence of Cu^{2+}, and the Hamiltonian parameters obtained from the simulation were $g_{\|} = 2.21$, $g_{\perp} = 2.063$ and $A_{\|} = 170$ G (Fig. 2). These values are in agreement with a square pyramidal coordination geometry[14] and are similar to the values obtained for the complex (**Helix HQT i+3)Cu** from our previous research (see Scheme 1), which were $g_{\|} = 2.23$, $g_{\perp} = 2.070$ and $A_{\|} = 175$ G, indicating that (**Helix HQT i+3)Cu** has a similar geometric structure, as we previously suggested.[10]

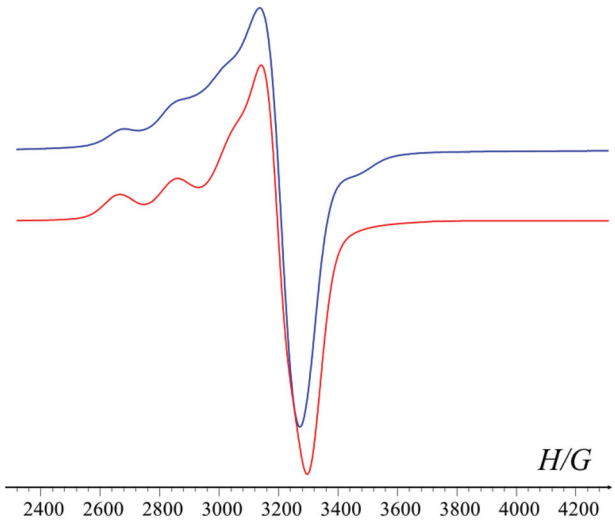


Fig. 2 X-band EPR spectra of the **TQCu** complex (blue line) and its corresponding simulated spectra (red line). The measurements were performed in frozen acetonitrile solution at 150 K, with the (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO) as a reference (g = 2.0058).

Synthesis and characterization of heteroleptic cobalt and nickel complexes

In order to show that our method can be generalized by applying it to other metal ions, we tried to synthesize the heteroleptic Co complex **TQCo**. Attempts to follow the synthetic procedure used for the generation of **TQCu** were not successful; the obtained complex was the mono(terpyridine)cobalt(II)bis(acetate), **TCo**, as indicated by its single crystal X-ray analysis (Fig. S43†). As this complex was not soluble in acetonitrile and precipitated from the reaction solution, we again assumed that enabling its solubility by modifying the reaction conditions will lead to the formation of the heteroleptic complex as occurred in the case of Cu^{2+}. Indeed, applying the same reaction conditions as in methanol instead of those in acetonitrile yielded a dark red powder, which was further analyzed. This complex exhibits absorption bands near $\lambda = 280$, and 319 nm which corresponds to metal coordination of both HQ and Terpy respectively (Fig. S4†). The molecular weight of the complex as shown by HR-ESI-MS suggested that the complex is bound to methanol (Fig. S20 and 21†). The complex is poorly soluble in MeOH, therefore single crystals suitable for X-ray analysis were obtained by vapor diffusion of diethyl ether into an acetonitrile solution of the complex. According to the X-ray structure, the complex crystallized in the triclinic crystal system, having a distorted octahedral structure with one coordinated oxygen atom and five coordinated nitrogen atoms (Fig. 3A). The X-ray structure revealed that one of the

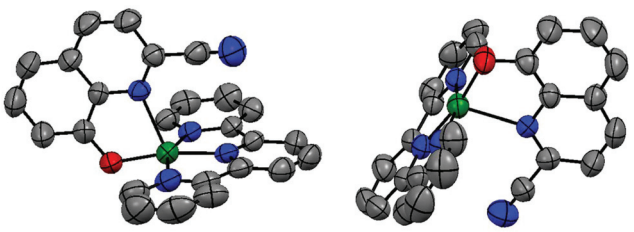


Fig. 1 X-ray structure of the **TQCu** complex. Color code: C, gray; N, blue; O, red; Cu, green. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at the 50% probability level.

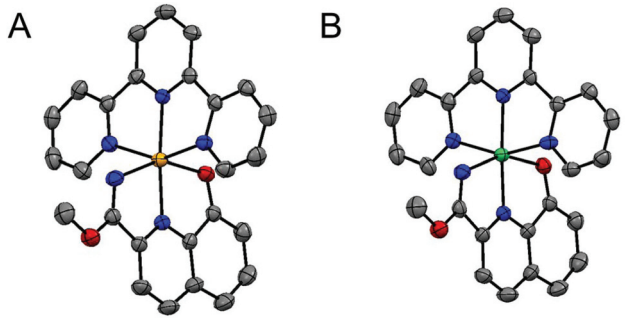


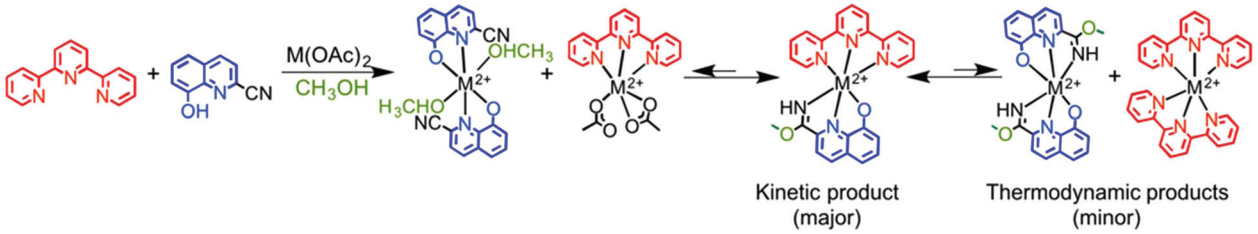
Fig. 3 X-ray structure of (A) **TQ′Co** and (B) **TQ′Ni** complexes. Color code: C, gray; N, blue; O, red; Co, orange; Ni, turquoise. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at the 50% probability level.

coordinated nitrogen atoms is of an imidate group rather than of a carbonitrile group. This observation suggests that the carbonitrile group reacted with methanol in a methanolysis reaction, which was probably promoted by the metal and transformed into a carboxyimidate group.[15] Indeed, the molecular weight of the complex was consistent with this structure, showing an addition of 32 mass units corresponding to the formation of carboxyimidate. This unique example emphasizes the coordination requirements of the cobalt ion to form a hexa-coordinated complex and its inability to produce a stable penta-coordinated complex. Thus, a heteroleptic Co^{2+} complex **TQ′Co** could be only obtained by the use of a solvent that not only coordinates as a sixth (labile) ligand but actually reacts with one of the ligands resulting a modified ligand that is able to strongly coordinate and stabilize this complex. To support this statement, the intramolecular coordination in the Co^{2+} complex was studied using static calculations within DFT. Based on these calculations, the five coordinated Co^{2+} complex is energetically unstable and the addition of methanol to this complex following the coordination of the imine group to the Co^{2+} ion is highly exothermic with **TQ′Co** being 33.43 kcal mol^{-1} lower in enthalpy and 19.48 kcal mol^{-1} lower in free energy than the five-coordinated complex in methanol (see the ESI† for details).

Following this synthetic procedure, we next tried to synthesize the corresponding Ni^{2+} complex. Addition of an equimolar amount of the ligands to the solution of nickel acetate in methanol and heating the solution at 50 °C for 2 hours followed by precipitation with aqueous NH_4PF_6 afforded an orange powder. UV-Vis analysis of the complex in methanol revealed absorption bands near λ = 279, 320 and 334 nm, supporting the presence of both Terpy and HQ ligands in the complex (Fig. S6†). HR-ESI-MS analysis of this complex indicated the addition of 32 units to the expected mass, which suggests either coordination to methanol or to a carboxyimidate group similar to the **TQ′Co** complex (Fig. S23 and 24†). The **TQ′Ni** complex is poorly soluble in methanol, thus, it was re-dissolved in acetonitrile and crystalized by vapor diffusion of diethyl ether. The X-ray structure of this complex is indeed very similar to its Co^{2+} analogue; it has a triclinic crystal system with a distorted octahedral geometry and coordinates to the nitrogen of a carboxyimidate that is formed by methanolysis of carbonitrile (Fig. 3B).

Both **TQ′Co** and **TQ′Ni** were obtained in a high isolated yield of about 90%. Here, the low solubility of both complexes in methanol facilitated their precipitation such that their isolated yields resemble their actual yields. The ESI-MS analysis of the complexes was further conducted in acetonitrile due to their high solubility in this solvent. The ESI-MS spectra of both complexes exhibited small peaks that correspond to the half masses of the homoleptic complexes $Terpy_2Co$ and $Terpy_2Ni$, Fig. S20 and S23,† respectively, suggesting that some ligand exchange occurs already at room temperature. In order to further investigate whether **TQ′Co** and **TQ′Ni** are stable in solution or present in equilibrium along with the homoleptic complexes, we performed ESI-MS and UV-Vis analysis after 8 and 24 hours heating of their acetonitrile solutions at 80 °C. Upon heating, the UV-Vis analysis of **TQ′Co** revealed small changes in the spectrum; after 24 hours of heating the peak of the modified HQ ligand was 5 nm blue shifted and the shape of the Terpy peak was changed (Fig. S14†). In the MS spectrum we noted the appearance of two peaks, one at 262, which corresponds to $m/2z$ of $Terpy_2Co$ and one at 461, corresponding to **Q'_2Co**, in which their intensity was increased after 8 and 24 hours (Fig. S32 and 33†). Both MS and UV analysis suggest that the complex **TQ′Co** is not kinetically inert, as heating at 80 °C for several hours led to ligand exchange as evident from the presence of both the homoleptic and heteroleptic complexes. Although the UV-Vis spectrum of the **TQ′Ni** did not exhibit significant changes (Fig. S15†), we could observe the homoleptic complexes in the MS spectra (Fig. S35 and 36†), suggesting that **TQ′Ni** is also not kinetically stable. Therefore, we suggest that the heteroleptic complexes **TQ′Co** and **TQ′Ni** exist in the solution in equilibrium with their corresponding homoleptic Terpy complexes.

On the basis of all the new data we have acquired, we can propose the following mechanism for the formation of the heteronuclear complexes (Scheme 3): first, in methanol, $M(OAc)_2$ (M = Co^{2+} or Ni^{2+}) gets bound either to Terpy, stabilized as a hexa-coordinated complex by coordination to three oxygen atoms from two acetate ligands, or to two HQCN and two methanol ligands, forming $HQCN_2(MeOH)_2M$. Thereafter, the latter complex catalyzes the conversion of HQCN to imidate HQOMe, while becoming unstable. The new imidate ligand replaces the two acetate molecules, resulting in the heteroleptic complex as the kinetic product. The complexes $Terpy_2M$ and $(HQOMe)_2M$ might also be generated but the equilibrium is shifted towards the heteroleptic **TQ′M** product because of its low solubility in methanol, which allows for its rapid precipitation out of the solution. Dissolving **TQ′M** in acetonitrile and heating it for several hours prevents its rapid precipitation thus shifting the equilibrium back towards the formation of the homoleptic complexes $Terpy_2M$ and $(HQOMe)_2M$, leading to their formation as the thermodynamic products that exist in the solution with **TQ′M**.



Scheme 3 Proposed mechanism for the formation of heteroleptic **TQ′M** complexes.

This mechanism emphasizes the role of the solvent in the formation of the heteroleptic complexes. Considering these results, we propose a new approach for the formation of heteronuclear complexes *via* a solvent-based synthetic control. In order to support our suggested approach, we wished to investigate whether we can prepare **TQ′Co** directly from Terpy, HQOMe and cobalt acetate. To this aim, we have synthesized HQOMe, based on a previously reported procedure (see the Experimental section) and it was mixed with equimolar solution of Co(acetate)$_2$ and Terpy, under the same reaction conditions as we have used above. The obtained complex was analyzed by UV-Vis and ESI-MS, exhibiting spectra identical to the ones acquired from the analysis of the complex synthesized from HQCN (Fig. S5 and S22†). The complex was re-dissolved in acetonitrile and crystalized by slow diffusion of diethyl ether to this solution. We could see that the cell parameters obtained from the X-ray analysis of this product were identical to ones obtained for the **TQ′Co** complex. Thus, we demonstrated that this complex could be obtained independently as evidence for the synthetic control we propose in the Introduction.

Finally, we wished to investigate whether a reaction of Cu^{2+} with Terpy and HQCN in methanol will also lead to the formation of the carboxyimidate ligand (HQOMe) and a hexacoordinated copper complex. To this aim, we attempted to synthesize the complex using the same reaction conditions as applied in the synthesis of **TQCu** (see above) but with methanol as a solvent instead of acetonitrile. The product was precipitated after the addition of aqueous solution of NH_4PF_6, and then washed and dried. The MS analysis of the complex showed a peak at 497 corresponding to the calculated mass of the expected complex **TQ′Cu** (Fig. S37†). Due to its poor solubility in methanol, this complex was further re-dissolved in acetonitrile and crystalized by diffusion of diethyl ether into its solution. Interestingly, the X-ray structure of the complex revealed a dinuclear Cu(II) complex **$T_2Q'Cu_2$**, in which one copper ion is hexa-coordinated through a Terpy ligand and a HQCN ligand, which was indeed converted to carboxyimidate forming the HQOMe ligand, and another copper ion is penta-coordinated by the HQOMe ligand through an oxo-bridge to another Terpy ligand and to one acetonitrile molecule (Fig. 4). We therefore suggest that upon re-dissolving the complex in acetonitrile, a solvent molecule coordinates to a tetra-coordinated copper ion leading to a di-copper complex, which crystallizes from the solution. This complex represents

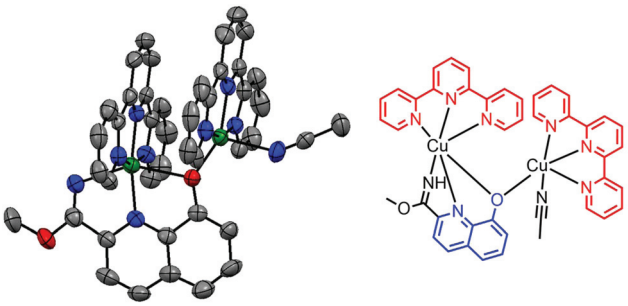


Fig. 4 X-ray and a Chemdraw structure of the **$T_2Q'Cu_2$** complex that was synthesized in MeOH. Color code: C, gray; N, blue; O, red; Cu, green. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at the 50% probability level.

the ability of Cu^{2+} to adopt both a hexa-coordination as well as a penta-coordination, which is not apparent in the case of Co^{2+} and Ni^{2+}.

Overall, the structural data support our previous conclusions regarding the selective binding of the Cu^{2+} ion from the mixture of other metal ions.[10] Both Co^{2+} and Ni^{2+} promote a reaction that will enable them to coordinate to six atoms towards the formation of octahedral geometries, as they are unable to form stable penta-coordinated complexes. The selectivity to Cu^{2+}, which we previously reported[10] can now be rationalized as a consequence of specific intramolecular binding to both HQ and Terpy *via* the formation of a square pyramid geometry, a structure that could be stabilized by Cu^{2+} but not by Co^{2+} or Ni^{2+}.

Formation of $Q'_4Q''_2Mn_4$ cluster

Applying the synthetic procedure that yielded the heteroleptic complexes **TQ′Co** and **TQ′Ni** to a reaction between an equimolar solution of Terpy and HQCN in methanol and Mn (acetate)$_2$, a yellow powder was obtained after being precipitated with an aqueous solution of NH_4PF_6. This was recrystallized by vapor diffusion of diethyl ether into its acetonitrile solution. The X-ray analysis revealed a cluster comprising of four Mn^{2+} ions coordinating six HQ ligands, which was crystallized in the monoclinic crystal system (Fig. 5A). According to the X-ray structure determination, two types of binding environments of the Mn^{2+} ions were observed: four tri-dentate HQOMe ligands with coordinative imidate and two bi-dentate

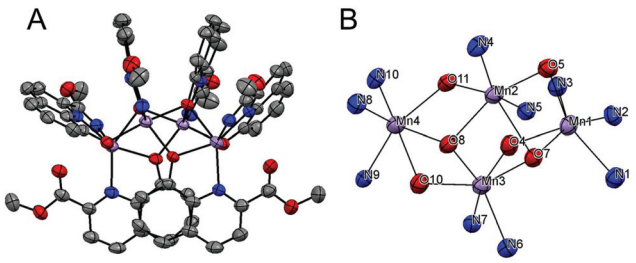


Fig. 5 X-ray structure of the (A) $\mathbf{Q'_4Q''_2Mn_4}$ cluster and (B) its coordination core. Color code: C, gray; N, blue; O, red; Mn, purple. Hydrogen atoms are omitted for clarity. Ellipsoids are drawn at the 50% probability level.

HQO_2Me ligands, in which the carbonitrile groups had converted to form methyl ester groups that do not participate in the metal binding (Fig. 5A). Based on the definition of heteroleptic complexes, which specify them as complexes composed of metal ion(s) coordinating two different types of chelators,[5] $\mathbf{Q'_4Q''_2Mn_4}$ can also be considered a heteroleptic complex. This cluster contains a $[Mn^{II}_4(\mu_3\text{-}O)_2(\mu_2\text{-}O)_4N_{10}]^{2+}$ core and each Mn ion has six coordination arrangements with octahedral geometry displaying Jahn–Teller axial elongation distortion. The metal oxidation state of each Mn atom was established to be +2 based on charge considerations: the inner Mn(2) and Mn(3) ions coordinate two nitrogen atoms and four oxygen atoms, and the outer Mn(1) and Mn(4) ions coordinate three nitrogen and three oxygen atoms with overall four bridging oxygens (O4, O5, O10 and O11) and two triple-bridging oxygens (O7 and O8) (Fig. 5B). The distances between the HQ pairs that coordinate in an alternative manner are in the range of 3.3–3.8 Å, which is in agreement with π–π stacking interactions[16] that the HQ aromatic rings can be involved in. UV-Vis analysis of this complex revealed absorption bands near λ = 257 and 283 nm originating from the two different types of HQ residues (Fig. S11†). The mass of the cluster was confirmed by APCI-MS analysis (Fig. S38†). Attempts to synthesize the heteroleptic complex **TQ′Mn** by addition of a mixture solution of Terpy and HQCN to a solution of $Mn(acetate)_2$ in acetonitrile yielded a yellow precipitate. This was crystallized by vapor diffusion of diethyl ether to its methanolic solution. Similar to the results with cobalt acetate in acetonitrile, the X-ray structure was consistent with the formation of the mono(terpyridine)manganese(II)bis(acetate), **TMn** (Fig. S44†). Other attempts to synthesize the **TQMn** complex including varying the ratio between HQCN and Terpy, changing the order of ligand addition and modifying the ratio between HQCN and Terpy yielded a mixture of products with the major products being **TMn** and $\mathbf{T_2Mn}$; the formation of $\mathbf{T_2Mn}$ was realized from UV-Vis and ESI-MS (Fig. S13 and S25†).

Moreover, aiming to synthesize $\mathbf{Q'_4Q''_2Mn_4}$ independently, we have used the commercially available 8-hydroxy-2-quinolinecarboxylic acid in order to prepare HQO_2Me by a simple esterification reaction (see the Experimental section). This was further reacted in a mixture with HQOMe and $Mn(acetate)_2$ using an appropriate ratio between all the reactants under the same reaction conditions in which this cluster was previously obtained. The product was analyzed by UV-Vis exhibiting a spectrum, which was different from the UV-Vis spectrum of $\mathbf{Q'_4Q''_2Mn_4}$ (Fig. S12†) suggesting that the complex that was obtained in this method is different from the $\mathbf{Q'_4Q''_2Mn_4}$ cluster. The new complex was crystallized by diffusion of diethyl ether to a complex dissolved in acetonitrile but to date, high-resolution structure by X-ray analysis could not be obtained, however the analysis exhibits cell parameters different from the $\mathbf{Q'_4Q''_2Mn_4}$ parameters, supporting the assumption that different complexes were obtained. Attempts to change the ratio of the reactants and the reaction time yielded the same UV-Vis spectrum, which is different from that of $\mathbf{Q'_4Q''_2Mn_4}$. Nevertheless, we believe that the mechanism for the formation of $\mathbf{Q'_4Q''_2Mn_4}$, which probably involves self-assembly in solution, is more complicated than the formation mechanism of the **TQ′M** complexes. Therefore, even though we cannot obtain this cluster directly from the two HQOMe and HQO_2Me ligands, we cannot exclude in this case the synthetic solvent control we proposed in the Introduction.

Cyclic voltammetry (CV) of the complexes

The heteroleptic complexes obtained in this study were analyzed by cyclic voltammetry and their redox properties were realized (Fig. 6). The heteroleptic copper complex **TQCu** undergoes a quasi-reversible oxidation of $Cu^{2+/3+}$ at E_p = 0.76 V *vs.* $Ag/AgNO_3$ and an irreversible reduction peak of $Cu^{2+/+}$ at E_p = −0.2 V. The oxidation peak at 1.04 V may be attributed to the ligand-centered irreversible oxidation processes (Fig. 6A). Differential Pulse Voltammetry (DPV) analysis revealed an oxidation process of $Cu^{2+/3+}$ centered at 0.8 V followed by the oxidation of the ligand at 1.0 V (Fig. S46†). The heteroleptic cobalt complex **TQ′Co** exhibits reversible oxidation of $Co^{2+/3+}$ coupled at E^{ox}_p of 0.04 V (Fig. 6B). The cyclic voltammogram (CV) of the heteroleptic **TQ′Ni** complex exhibits a quasi-reversible peak centered at E_p = 0.58 V, which corresponds to the $Ni^{2+/3+}$ oxidation potential followed by irreversible reduction of the $Ni^{2+/+}$ couple at E_p = −0.82 V (Fig. 6C). The DPV analysis of this complex shows one oxidation peak at 0.48 V associated with the $Ni^{2+/3+}$ oxidation process (Fig. S47†). The CV of $\mathbf{Q'_4Q''_2Mn_4}$ suggests irreversible two oxidation processes of the Mn ions from the oxidation states +2 to +4. According to the X-ray analysis there are two types of Mn atoms, the inner atoms coordinate to four oxygen atoms and two nitrogen atoms while the outer Mn ions coordinate to three oxygen and three nitrogen atoms. Therefore, we would expect to see distinct oxidation potentials of each type of Mn ion, with the Mn ions connected to four oxygen atoms displaying a higher oxidation potential due to larger electronegativity of the oxygen atoms withdrawing electron density from the metal center. Indeed, the CV of the complex displays one oxidation peak around 0.76 V, which may be attributed to $Mn^{2+/3+}$ oxidation processes of two different types of Mn ions that overlap, followed by further two oxidation processes of $Mn^{3+/4+}$ at 1.08 V

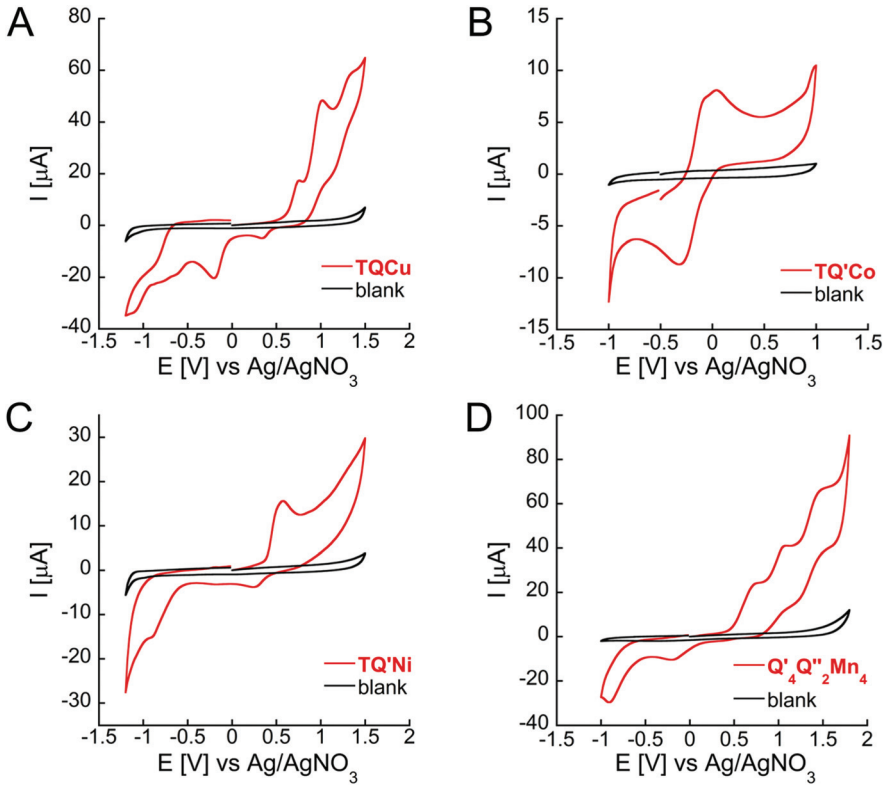


Fig. 6 Cyclic voltammograms of metal complexes (A) **TQCu** (1 mM), (B) **TQ'Co** (1 mM), (C) **TQ'Ni** (1 mM) and (D) $\mathbf{Q'_4Q''_2Mn_4}$ (0.5 mM) that were recorded in acetonitrile at rt. with 0.1 M TBA-PF_6 as the supporting electrolyte using a glassy carbon working electrode, platinum counter electrode, and $Ag/AgNO_3$ reference electrode. Scan rate: 100 mV s^{-1}.

and at 1.48 V. DPV analysis (Fig. S48†) reveals three oxidation peaks centered at 0.7 V, 1.02 V and 1.34 V with the first peak being relatively wide, supporting our assumption of two overlapping signals assigned to the $Mn^{2+/3+}$ oxidation of two different types of Mn atoms.

Conclusions

In this work we describe the synthesis of unique heteroleptic complexes based on 8-hydroxy-2-quinolinecarbonitrile and terpyridine ligands with the metal ions Cu^{2+}, Co^{2+}, Ni^{2+} and Mn^{2+}. This includes full characterization by X-ray diffraction, EPR, UV-Vis, HR-ESI-MS, paramagnetic NMR, elemental analysis, DFT calculations and cyclic voltammetry. Our results demonstrate the effect of the solvent used during the synthesis on the nature of the complexes formed. In acetonitrile we could only obtain the heteroleptic complex **TQCu** that has a pseudo square pyramidal geometry. Using similar reaction conditions in methanol we could generate heteroleptic complexes of Co^{2+}, Ni^{2+} and Mn^{2+} due to methanolysis of carbonitrile to carboxyimidate, which resulted in an additional coordination site to form octahedral complexes. These findings support our previous hypothesis regarding the association between the high affinity and selectivity of a Terpy(HQ)peptidomimetic oligomer to Cu^{2+} over Co^{2+}, Ni^{2+}, and Mn^{2+} and provide insights into the coordination geometry of the formed metallopeptoid complexes. Importantly, this study emphasizes the challenges in the synthesis of heteroleptic complexes suggesting an additional path for their production, which considers the solubility properties of the homoleptic products. Moreover, our results suggest that the use of different solvents, especially ones that can coordinate metal ions and/or react with the other ligand(s), can assist in obtaining heteroleptic complexes not only as a result of solubility changes but also due to ligand(s) modification. This observation should be applicable for numerous ligand systems towards the construction of various heteroleptic complexes, clusters and biomimetic chelators.

Experimental section

Materials

Ammonium hexafluorophosphate, 2,2′:6′,2″-terpyridine, sodium methoxide and nickel acetate tetrahydrate were purchased from Alfa Aesar; 8-hydroxy-2-quinolinecarbonitrile, and manganese acetate tetrahydrate were purchased from Acros; cobalt acetate tetrahydrate and copper acetate monohydrate were purchased from MERCK; tetrabutylammonium hexa-

fluorophosphate (TBAP) was purchased from Fluka; copper(II) trifluoromethanesulfonate, acetonitrile (ACN) and 8-hydroxyquinoline were purchased from Sigma-Aldrich; methanol (MeOH) was purchased from Macron, and 8-hydroxy-2-quinolinecarboxylic acid was purchased from Maybridge. These reagents and solvents were used without additional purification.

Methods

Mass spectrometry measurements were performed on an Advion expression CMS mass spectrometer under electrospray ionization (ESI), direct probe with ACN (0.1% formic acid), flow rate 0.2 ml min^{-1}, on a Brucker maxis II mass spectrometer under atomic pressure chemical ionization (APCI) or under electrospray ionization (ESI) and on a Waters LCT Premier mass spectrometer under electrospray ionization (ESI), direct probe ACN : H_2O (70 : 30), flow rate 0.3 ml min^{-1}. UV-Vis measurements were performed using an Agilent Cary 60 UV-Vis spectrophotometer. Electrochemistry was carried out on an Iviumstat XRe potentiostat. EPR spectra were recorded on a Bruker EMX-10/12 X-band (ν = 9.4 GHz) digital EPR spectrometer, in frozen ACN solution at 150 K temperature with (2,2,6,6-tetramethyl-1-piperidinyl)oxidanyl (TEMPO, g = 2.0059) in an inner tube for determination of the g-factor. Spectra processing and simulation were performed using Bruker WIN-EPR and SimFonia Software. For the X-ray crystallographic measurements single crystals were covered with Paratone-N oil and mounted on a Kappa CCD diffractometer under a flow of liquid nitrogen, except of **TQCu**, which was measured at 293 K. Data collection was performed using monochromated Mo Kα radiation (λ = 0.71073 Å) using φ and ω scans to cover the Ewald sphere.[17] The structures were solved by SHELXS-97 direct methods and refined by the SHELXL-97 program package.[18] The atoms were refined anisotropically and hydrogen atoms were included using the riding model. Mercury 3.5 Software was used for the graphic representations.[19] The calculations were performed using the Gaussian 09′ software, using the PBE1PBE functional with the 6-31+G(d,p) basis set. Stable=opt utility was employed to ensure the conversion of the wave function to the lowest state. All geometries were optimized ensuring a local minimum configuration with all positive frequencies. Elemental analyses were performed on a Flash 2000 Thermo Scientific Organic Elemental Analyzer. ^{1}H-NMR and ^{13}C-NMR measurements were performed on Bruker spectrometers AVIII400 and AVIII500.

Synthesis of the heteroleptic complexes

General. To a solution of metal ions (0.215 mmol, 43 mM) in 5 mL ACN or MeOH an equimolar amount of the ligands Terpy and HQCN (50 mg and 36.5 mg respectively, 0.215 mmol, 43 mM each) in 5 mL ACN or MeOH was added dropwise. After stirring for 2 hours at 50 °C the complexes were precipitated by addition of a 10-fold excess of NH_4PF_6 in 10–20 ml of water. The precipitates were separated from the solution by centrifugation, washed twice with water and lyophilized overnight. To obtain single crystals for X-ray analysis the complex **TQCu** was crystalized by slow evaporation from an ACN/THF solution. Other complexes were crystalized by vapor diffusion of diethyl ether to their ACN solution.

TQCu: To a solution of 1 equiv. of Cu(II) triflate (77.7 mg, 0.215 mmol, 43 mM) in 5 mL ACN an equimolar amount of the ligands Terpy and HQCN was added. Final product weight and yield: 78 mg, 60%. HR-ESI-MS: calculated $[M]^+$: 465.0645; found: 465.0645. UV-Vis: λ = 266, 325 and 338 nm. Elemental analysis of the precipitate: ($C_{25}H_{16}N_5OCuPF_6$) calculated: C: 49.15%, H: 2.64%, N: 11.46%; found: C: 49.94%, H: 2.92%, N: 11.46%.

TQ′Co: To a solution of 1 equiv. of Co(II) acetate (53.5 mg, 0.215 mmol, 43 mM) in 5 mL MeOH an equimolar amount of the ligands Terpy and HQCN was added. Final product weight and yield: 113 mg, 83%. HR-ESI-MS: calculated $[M]^+$: 493.0949; found: 493.0991. UV-Vis: λ = 280 and 319 nm. Elemental analysis of the precipitate: ($C_{26}H_{20}N_5O_2CoPF_6$) calculated: C: 48.92%, H: 3.16%, N: 10.97%; found:[20] C: 45.70%, H: 2.95%, N: 9.85%. ^{1}H NMR (500 MHz, CD_3CN) sharp peaks that span over almost 120 ppm.

TQ′Ni: To a solution of 1 equiv. of Ni(II) acetate (53.3 mg, 0.215 mmol, 43 mM) in 5 mL MeOH an equimolar amount of the ligands Terpy and HQCN was added. Final product weight and yield: 127 mg, 93%. HR-ESI-MS: calculated $[M]^+$: 492.0970; found: 492.0943. UV-Vis: λ = 279, 320 and 334 nm. Elemental analysis of the precipitate: ($C_{26}H_{20}N_5O_2NiPF_6$) calculated: C: 48.94%, H: 3.16%, N: 10.97%; found:[20] C: 45.37%, H: 3.11%, N: 9.96%. ^{1}H NMR (500 MHz, CD_3CN) sharp peaks that span over almost 100 ppm.

Q′$_4$Q″$_2$Mn$_4$: To a solution of 1 equiv. of Mn(II) acetate (52.5 mg, 0.215 mmol, 43 mM) in 5 mL MeOH an equimolar amount of the ligands Terpy and HQCN was added. After precipitation, the complex was recrystallized from the ACN/ether solution. Final product weight and yield: 82 mg, 66%. APCI-MS: calculated $[M]^+$: 1424.09; found: 1423. 43. UV-Vis: λ = 257 and 283 nm. Elemental analysis of the precipitate: ($C_{66}H_{48}N_{10}O_{14}Mn_4P_2F_{12}$) calculated: C: 46.32%, H: 2.82%, N: 8.17%; found:[20] C: 42.71%, H: 2.93%, N: 9.37%.

T$_2$Q′Cu: To a solution of 1 equiv. of Ni(II) acetate (42.8 mg, 0.215 mmol, 43 mM) in 5 mL MeOH an equimolar amount of the ligands Terpy and HQCN was added. Final product weight and yield: 115 mg, 84%. UV-Vis: λ = 273, 326 and 339 nm.

Synthesis of methyl 8-hydroxyquinoline-2-carboxyimidate (HQOMe)

Methyl 8-hydroxyquinoline-2-carboxyimidate was synthesized similarly to a previously published procedure.[21] To a solution of 8-hydroxy-2-quinolinecarbonitrile (0.5 g, 2.94 mmol) in methanol (20 ml) MeONa was added (50 mg, 0.926 mmol) and the mixture was stirred for 24 hours at 40 °C. The solution was dried by vacuum and the product was dissolved in ethyl acetate (30 ml), washed with water and brine, dried over $MgSO_4$ and the solvent was evaporated to obtain a final product as a pale-yellow solid (0.52 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H), 7.16 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.44 (t, 1H), 7.91 (d, J = 8.5 Hz, 1H), 8.2 (d,

J = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.26, 111.04, 117.89, 119.03, 129.25, 137.44, 137.88, 145.51, 152.47, 166.61. ESI-MS: calculated $[M + H]^+$: 203.22; found: 203.11.

Synthesis of methyl 8-hydroxyquinoline-2-carboxylate (HQO_2Me)

Methyl 8-hydroxyquinoline-2-carboxylate was synthesized similarly to a previously published procedure.[22] To a solution of 8-hydroxy-2-quinolinecarboxylic acid (0.3 g, 1.59 mmol) in MeOH (10 ml) four drops of concentrated sulfuric acid were added and the mixture was refluxed for 24 hours. The solution was concentrated in a vacuum and saturated aqueous $NaHCO_3$ was added to the residue. The product was extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent was evaporated to obtain a final product as a yellow solid (0.24 g, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.16 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.49 (t, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.2 (d, J = 8.6 Hz, 1H), 8.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.96, 111.07, 117.69, 121.65, 129.75, 130.29, 137.28, 137.77, 145.40, 153.26, 165.53. ESI-MS: calculated: 203.06; found: 226.18 $[M + Na]^+$.

Conflicts of interest

There are no conflicts to declare.

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($C_{26}H_{20}N_5O_2NiPF_6 \cdot 2H_2O$) calculated: C: 46.32%, H: 3.59%, N: 10.39%; found: C: 45.37%, H: 3.11%, N: 9.96%. ($C_{66}H_{48}N_{10}O_{14}Mn_4P_2F_{12} \cdot 2H_2O$) calculated: C: 45.28%, H: 2.99%, N: 8.00%; found:[16] C: 42.71%, H: 2.93%, N: 9.37%.

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