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Metallamacrocycle formation through dimerization of metal bioconjugates derived from amino acids and peptides

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Metallamacrocycles of 12, 16, and 22 members are obtained by deprotonation of the carboxylic group of the side chain of iminopyridine complexes derived from the aminoacid β-alanine, and the peptides Gly-Gly and Gly-Gly-Gly. Instead of the expected intramolecular attack to give tridentate (N,N,O) ligands, the deprotonated carboxylate attacks in an intermolecular manner to give dimers in which the ligand acts as a bridge bonded in a κ^2(N,N') chelating fashion to one metal and as κ (O) to the other metal. The formation of the dimers is supported by NMR spectroscopy, mass spectrometry and X-ray crystallography.

Introduction

Bioconjugation has emerged as a convenient tool to insert metal complexes into biomolecules.[1,2] The initial aim has been surpassed by a wide variety of applications ranging from analytical or materials chemistry to nano-chemistry. Additionally, the use of easily available small biomolecules such as amino acids and peptides as ligands in metal complexes has been active for many years.[3] In particular, artificial β-peptides have been used to obtain macrocyclic Ni(II) complexes with internal cavities.[4]

The study of the intramolecular H-bond interactions in proteins is a central field in biochemistry, and organic synthesis has played a very important role in the design of molecules which mimic the different conformations of the proteins.[5] A number of transition metal bioconjugates have been used in recent times to study peptidic H-bonds.[6]

The use of peptides is particularly attractive due to their wide commercial availability and well-established and automated methods for their syntheses.[7] In nature, the function of peptides is determined by their well-defined secondary structures, which lock the side-chain functional groups of their constituent amino acid residues into specific relative conformations. However, free short peptide chains do not spontaneously adopt well-defined conformations, but instead exist in disordered "random-coil" conformations. In order for synthetic peptides to achieve the biological functions or level of chemical specificity of their natural counterparts, it is necessary to create additional structural constraints through covalent or non-covalent interactions.

Cyclization of a peptide by coordination to a metal atom can induce conformational order, either through multidentate coordination of the peptide chain using the metal atom as a "clip" to fix the peptide chain into a specific geometry, or through the formation of a metallacyclic dimer or higher order aggregate.[8] This approach is also advantageous for applications in which the metal atom itself provides biological or catalytic activity. The metal-induced structural order may also be further enhanced through other peptide-peptide non-covalent interactions, such as hydrogen bonding. Naturally-occurring structural motifs such as the α-helix,[9] β-sheet,[10] and γ-turn[11] have been induced in metallocycles. However, the current level of fundamental knowledge of metal-peptide interactions is not yet sufficient to achieve the true rational synthesis of scarce metallacyclopeptide structures, and more fundamental studies are needed.

In the last years, several groups have focused their attention on the use of Schiff base formation as a convenient way to introduce different molecules of biological interest into a variety of organometallic fragments such as $M(CO)_4$ (M= Mo, W)[12] or $M(CO)_3X$ (M = Re, M = ^{99m}Tc, X = Cl, Br)[13], including amino acid esters, dipeptide-esters and nucleosides.

Inspired by the previous work of Alberto et al,[14] we have been interested in the use of complexes containing pyridine-2-carboxaldehyde as k^2(N,O) ligands in metal complexes as convenient precursors for iminopyridine complexes via Schiff condensation,[15] and we have recently shown that these complexes serve also as excellent substrates for hydroxyketone complexes via aldol additions.[16]

In the course of this work we have prepared a family of Mn, Re and Mo complexes containing iminopyridines bearing a side arm derived from amino acids[15b] and peptides.[15d] We anticipated that halide abstraction followed by deprotonation

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with a base would induce the coordination of the carboxylate function, thus affording a tridentate κ^3(N,N',O) iminopyridine

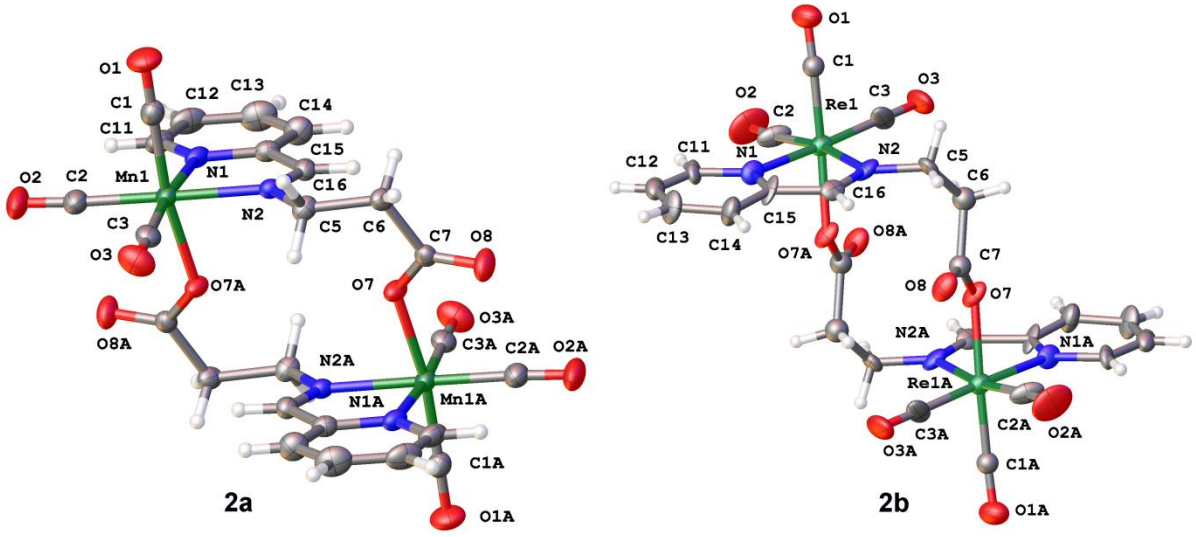


Figure 1. Perspective view of compound **2a** (left) and **2b** (right) showing the atom numbering.

carboxylate. Instead, dimers were formed with the carboxylate function acting as a bridge, thus forming metallamacrocycles of 12, 16 and 22 members. While this work was in progress, Ziegler, Herrick et al reported the preparation of two analogous Re complexes derived from amino acids with short side chains.[17] We present here a general procedure for the preparation of dimers which consist of metallamacrocycles of up to 22 members derived from aminoacids and peptides, which evidence a definite tendency of the ligands to form macrocyclic dimers of Mn, Re and Mo by acting as bridges, thus opening a convenient way to prepare metallamacrocycles including scarce metallacyclopeptides.

Results and Discussion

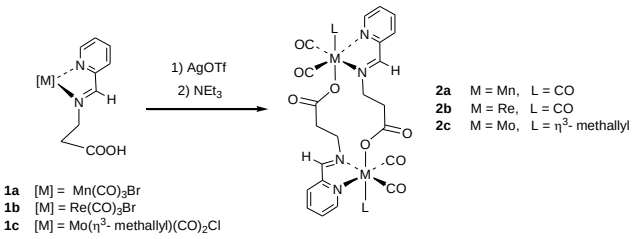
Metallamacrocycles derived from β-alanine.

Complexes **1a-c** were reacted successively with silver triflate to extract the halogen, and then with a base (typically a slight excess of NEt_3 (1.5 equiv) although an excess of K_2CO_3 or NaH can also be employed) to deprotonate the carboxylic group in an attempt to obtain mononuclear complexes with a tridentate N,N,O ligand derived from *β*-alanine. However, dimers **2a-c** (Scheme 1) were obtained instead of the expected mononuclear complexes. The structures of all compounds **2a-c** could be determined by X-ray crystallography, confirming the formation of the corresponding Mn, Re or Mo metallomacrocycle of 12 members instead of the expected mononuclear complex resulting from the intramolecular attack by the COO^- group on the metal atom. The relevant data are collected in Table 1, and the structures are depicted in Figures 1 and 2.

In all three structures of **2a-c** the molecules are centrosymmetric in solid state, and this structure is maintained in solution. Interestingly, the C=O groups of the carboxylate function point outwards from the macrocycle.

When the synthesis of the manganese dimer **2a** was attempted by using $AgClO_4$ (instead of AgOTf) and NEt_3, a different structure **2a'** was obtained which incorporates two two $[NHEt_3]ClO_4$ ion pairs. Each cation is hydrogen bonded to one C=O group on each side of the molecule (see Figure 3). From the distances and angles (see caption to Figure 3), the strength of these H-bonds can be considered as moderate.[18,19] The presence of these ion pairs interacting with the carboxylate oxygen in **2a'** produces an important distortion in the structure; as a result, the symmetry of the macrocycle is lowered and the inversion center is lost. When the same conditions were used with the analogous Re or Mo compounds it was not possible to obtain this type of structure with the ion pairs H-bonded to the macrocycle.

Complexes **2a-2b** were sparingly soluble in most solvents thus preventing a detailed study by NMR. However, despite the low solubility of the complexes, it was possible to obtain their ^1H NMR spectra in acetone-d_6 which suggests that the



Scheme 1. Synthesis of dimers from β-Ala derivatives of Mn, Re and Mo **(2).**

Table 1. Crystal, measurement and refinement data for the compounds studied by X-ray diffraction.

	2a	**2a'**	**2b**	**2c**
Formula	$C_{24}H_{18}Mn_2N_4O_{10}$	$C_{36}H_{50}Cl_2Mn_2N_6O_{18}$	$C_{28}H_{26}N_4O_{11}Re_2$	$C_{16}H_{20}MoN_2O_5$
M_f	632.30	1035.60	966.93	416.28
crystal system	Monoclinic	Orthorhombic	Monoclinic	Triclinic
space group	$P2_1/n$	$Pna2_1$	$P2_1/n$	$P\bar{1}$
a [Å]	8.998(2)	13.104(4)	13.491(4)	8.018(3)
b [Å]	7.703(1)	28.519(9)	15.058(4)	8.590(4)
c [Å]	18.876(3)	13.023(4)	16.017(4)	13.240(6)
α [º]	90.00	90.00	90.00	78.395(7)
β [º]	95.086(4)	90.00	99.703(4)	82.549(8)
γ [º]	90.00	90.00	90.00	74.989(9)
V [Å^3]	1303.1(4)	4867(3)	3207.3(15)	859.9(6)
Z	2	4	4	2
ρ [Mgm^{-3}]	1.611	1.413	2.002	1.608
μ(Mo Kα) [mm^{-1}]	1.033	0.702	7.604	0.790
crystal size [mm]	0.13 x 0.11 x 0.08	0.30 x 0.14 x 0.10	0.07 x 0.06 x 0.02	0.23 x 0.20 x 0.11
F(000)	640	2144	1840	424
θ range [º]	$2.16 \le \theta \le 23.27$	$1.43 \le \theta \le 23.38$	$1.83 \le \theta \le 23.26$	$1.58 \le \theta \le 23.34$
Max./min. transmission	1 / 0.7196	1 / 0.6661	1 / 0.1962	1 / 0.6209
reflns collected	5705	21430	8212	3854
indep. refl. [R(int)]	1887 [0.0441]	5631 [0.0607]	4532 [0.1611]	2447 [0.0487]
reflns with I > 2σ (I)	1303	3553	1848	1899
GOF on F^2	0.865	0.972	0.917	1.120
parameters/restraints	181/0	574/169	377/0	220/0
R_1 (on F, $I > 2\sigma(I)$)	0.0360	0.0698	0.0664	0.0907
wR_2(on F^2, all data)	0.0757	0.2059	0.1739	0.2544
Max/min $\Delta\rho$ [eÅ^{-3}]	0.284/ -0.206	0.817 / -0.307	1.865 / -1.425	2.329/ -0.943
CCDC number	1056951	1056952	1056953	1056954

	4a	**4c_1**	**4c_2**
Formula	$C_{27}H_{24}Mn_2N_6O_{13}$	$C_{34}H_{42}Mo_2N_6O_{12}$	$C_{32}H_{34}Mo_2N_6O_{10}.0.45\ Et_2O$
M_f	750.40	918.62	854.53
crystal system	Monoclinic	Monoclinic	Triclinic
space group	*P2(1)/c*	*P2(1)/c*	$P\bar{1}$
a [Å]	12.307(10)	9.942(3)	14.364(3)
b [Å]	11.341(9)	10.301(3)	15.563(3)
c [Å]	24.874(19)	19.236(5)	21.783(4)
α [º]	90.00	90.00	75.094(4)
β [º]	94.052(15)	91.241(5)	79.901(4)
γ [º]	90.00	90.00	67.876(4)
V [Å^3]	3463(5)	1969.5(9)	4342.2(16)
Z	4	2	4
ρ [Mgm^{-3}]	1.439	1.549	1.044
μ(Mo Kα) [mm^{-1}]	0.798	0.703	0.631
crystal size [mm]	0.16 x 0.11 x 0.06	0.09 x 0.08 x 0.04	0.27 x 0.18 x 0.04
F(000)	1528	936	1776
θ range [º]	$1.64 \le \theta \le 23.35$	$2.05 \le \theta \le 23.27$	$0.97 \le \theta \le 25.43$
Max./min. transmission	1 / 0.1939	1 / 0.7429	1 / 0.7608
reflns collected	14362	8519	35342
indep. refl. [R(int)]	4945 [0.2356]	2827 [0.0434]	15916 [0.1148]
reflns with I > 2σ (I)	1891	1774	5838
GOF on F^2	0.839	0.880	0.734
parameters/restraints	435/0	247/0	905/0
R_1 (on F, $I > 2\sigma(I)$)	0.0775	0.0285	0.0554
wR_2(on F^2, all data)	0.1789	0.0587	0.1269
Max/min $\Delta\rho$ [eÅ^{-3}]	0.374/ -0.378	0.378/ -0.281	0.594/ -0.748
CCDC number	1056955	1056956	1056957

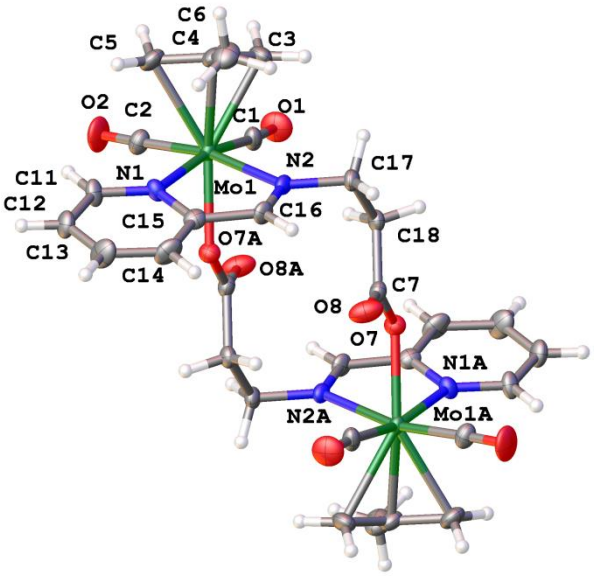


Figure 2. Perspective view of compound **2c** showing the atom numbering.

iminopyridine systems appear equivalent in solution. However we note that the use of coordinating solvents may compromise the integrity of the dimer. In contrast, molybdenum dimer **2c** was substantially more soluble than its Re and Mn analogues and could be studied by NMR. In this case, the dimer was even soluble in non-coordinating solvents such as CD_2Cl_2 and $CDCl_3$, in which the iminopyridine system is readily observable, with the signals appearing as equivalent in solution, suggesting that an effective centrosymmetric structure is maintained in solution. The unambiguous and correct assignment of the signals was possible with the help of additional 2D NMR experiments (^{1}H-^{1}H COSY and ^{1}H-^{1}H NOESY experiments, see Supporting Information, Fig S1-S2). Remarkably, ^{1}H-^{1}H NOESY shows the proximity of the H^6 proton of the pyridine ring to one of the H^{syn} of the allyl ligand. Additionally a ^{1}H DOSY experiment mixing approximately equimolar amounts of dimer **2c** and its monomeric precursor **1c** was carried out in CD_2Cl_2 (see Supporting Information, Fig S3). The experiment showed the slower diffusion of dimer **2c** with respect to its monomeric precursor **1c**, as would be expected from its greater hydrodynamic radii, thus providing additional evidence of the maintenance of the dimer in solution.

The formation of **2c** was followed by ^{1}H NMR in $CDCl_3$, showing that it was the only soluble product of the reaction (see Supporting Information, Fig S4). Briefly, addition of NEt_3 to **1c** in $CDCl_3$ followed by addition of AgOTf to the resulting purple solution yielded the formation of dimer **2c** as the only iminopyridine-containing reaction product after 3h at room temperature.

Two analogous dimeric complexes containing iminopyridines derived from glycine and L-alanine have been reported previously by Ziegler, Herrick et al.[17] It was claimed that the 10-membered ring rhenium dimers were formed because the geometric restriction on the α-carbon of the amino acid residue does not allow for the intramolecular coordination of the carboxylate oxygen. In contrast, there is not any severe geometric restriction to intramolecular coordination for the four member side-chain of our complexes **2a-c**; as can be concluded by an inspection of molecular models and also the existence of some related structures.[20,21] Nevertheless, the intermolecular attack is preferred to the intramolecular ring - closing affording 12-membered ring dimers. This result is

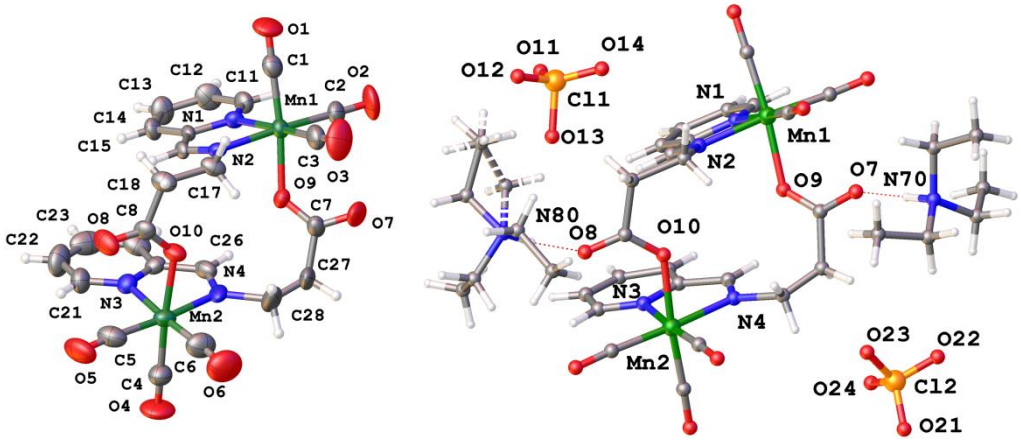


Figure 3. (left) Perspective view of compound **2a'** showing the atom numbering. (right) Perspective view showing the co-crystallizing $[Net_3H\ ClO_4]$ ion pairs. H-bond lengths (Å) and angles (º): N(70)-H(70) 1.03, H(70)...O(7) 1.66(1), N(70)...O(7) 2.662 (12); N(70)-H(70)...O(7) 168.8(8), N(80)-H(80) 1.03, H(80)...O(8) 1.76(8), N(80)...O(8) 2.715(14), N(80)-H(80)...O(8) 163.8(9).

remarkable not only because the dimers contained a longer ring (12-membered versus 10-membered in ref 17) but because the result is extensible to other metal centers allowing the synthesis of metal complexes of Re(I), Mn(I) and

Mo(II). As will be shown below, dimer formation appears to be a definite trend of these complexes independent of the length of the chain.

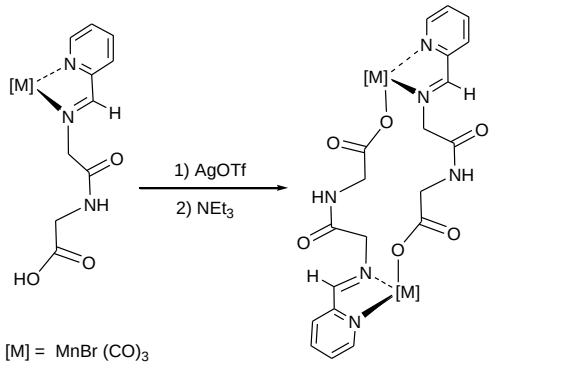
While the very low solubility of **2a** and **2b** and all the dimers derived from Gly-Gly (**4**) and Gly-Gly-Gly (**6**), (see below), could be the driving force for the formation of such dimeric structures, the good solubility observed in the case of the molybdenum dimer **2c** points out that other factors can favor the intermolecular coordination of the carboxylate group versus the expected intramolecular coordination. In a recent communication, we have reported the formation of 10 or 12 membered manganese metallamacrocycles templated by the presence of a proton that is strongly bonded between two oxygen atoms of alkoxo groups.[15d] In a similar vein, the formation of the complexes **2**, **4** and **6** could be facilitated by the formation of H-bonds between carboxylic acids or carboxylic acid-carboxylate groups from the iminopyridine side chain.

Metallamacrocycles derived from Gly-Gly

The study of the chemistry of complexes **3a-c** with a pendant glycylglycine chain is particularly attractive since these compounds include a peptide chain which could interact through H-bonding. Encouraged by the formation of the 12 membered metallacomplexes derived from β-alanine, we decided to test if the formation of such dimers would be extensible to longer chains while keeping the tendency of dimerizing in the three systems: Mn, Re and Mo. We used complexes **3** derived from peptide glycylglycine, Gly-Gly, in order to prepare metallacyclopeptides by using the simple synthetic methodology illustrated above for the synthesis of 12 membered metallacomplexes (see Scheme 2).

The synthesis of metallopeptides with the aim of creating specific biological activities has been a topic of interest in the field of bioinorganic chemistry in recent years. The short peptides, which are disorganized as linear chains, can be fixed into specific conformations by the formation of metallacyclic structures through coordination of the peptide residues to a metal center.[22] The ability of these synthetic metallacyclicpeptides to mimic specific structural motifs found in nature, such as the α-helix and β-sheet, has already been demonstrated in several examples.[8, 23] However, in order to rationally design metal-peptide interactions with specific conformations and biological functions, it is necessary to understand the reactivity and coordination behavior between different metal centers, and peptide binding sites, as well as the peptide-peptide non-covalent interactions.

Treatment of complexes **3a-c**, containing iminopyridine derived from the dipeptide Gly-Gly, with $AgOTf/NEt_3$, as described above, led to the formation of dimers **4a-c**. Again, the formation of dimers was preferred over the intramolecular attack to give tricoordinate (N,N',O) to the same metal. In this case the complementary attack of the carboxylate to a neighboring metal produces 16-member metallacycles as seen in Scheme 2. For the molybdenum derivative **4c** it is not necessary to use the silver salt, since treatment of a CH_2Cl_2 suspension of the parent **3c** with a 1.5 equiv of NEt_3 produces immediately a dark violet solution from which the dimer **4c** precipitates slowly as black crystals, while $NHEt_3Cl$ remains in solution. Despite the low solubility of these complexes, it has been possible to obtain crystals suitable for X-ray crystal structure determination of **4a** (Figure 4) and **4c** (Figure 5) by dissolving a small amount of the complex in hot methanol and allowing the solution to cool slowly.



3a [M] = $MnBr(CO)_3$
3b [M] = $ReBr(CO)_3$
3c [M] = $MoCl(\eta^3\text{-methallyl})(CO)_2$

4a [M] = $Mn(CO)_3$
4b [M] = $Re(CO)_3$
4c [M] = $Mo(\eta^3\text{-methallyl})(CO)_2$

Scheme 2. Synthesis of dimers from Gly-Gly derivatives of Mn, Re and Mo (**4**)

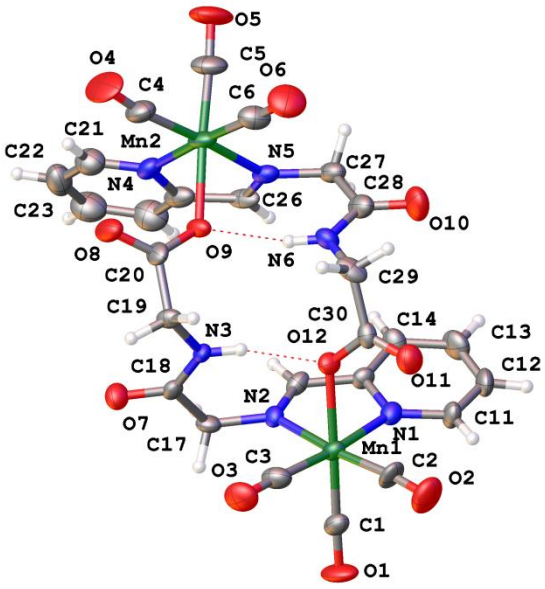


Figure 4. Perspective view of compound **4a** showing the atom numbering. H-bond lengths (Å) and angles (º) $R_2^2(10)$ system: N(3)-H(3) 1.03, H(3)...O(12) 1.844(7), N(3)...O(12) 2.832(8), N(3)-H(3)...O(12) 161.3(5), N(6)-H(6) 1.03, H(6)...O(9) 1.856(8), N(6)...O(9) 2.851(6), N(6)-H(6)...O(9) 162.9(5).

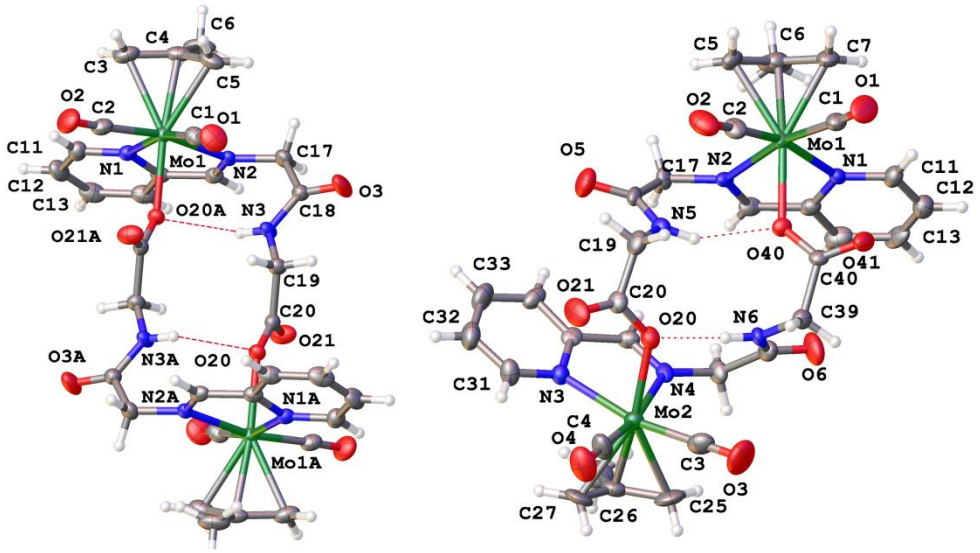


Figure 5. (left) Perspective view of the centrosymmetric structure of compound **4c (4c_1)** in the crystals obtained from hot methanol. H-bond lengths (Å) and angles (º)) $R_2^2(10)$ system: N(3)-H(3) 1.03, H(3)...O(20A) 2.085(2), N(3)...O(20A) 2.957(3), N(3)-H(3)...O(20A) 143.6(7). (right) Perspective view of the noncentrosymmetric structure of compound **4c (4c_2)** obtained by slow crystallisation from the reaction in acetone-d6 at room temperature. H-bond lengths (Å) and angles (º)) $R_2^2(10)$ system, Molecule 1: N(5)-H(5) 1.03, H(5)...O(40) 2.140(8), N(5)...O(40) 2.901(6), N(5)-H(5)...O(40) 147.1(6), N(6)-H(6) 1.03, H(6)...O(20) 1.969(7), N(6)...O(20) 2.827(8), N(6)-H(6)...O(20) 175.9(7). Molecule 2: N(45)-H(45) 1.03, H(45)...O(80) 1.923(8), N(45)...O(80) 2.925(8), N(45)-H(45)...O(80) 164.9(5). N(46)-H(46) 1.03, H(46)...O(60) 1.924(5), N(46)...O(60) 2.746(8), N(46)-H(46)...O(70) 170.6(7).

The ^{1}H NMR spectra of complexes **4a-c** are uninformative due to the low solubility and the broadness of the signals, which can be attributed to the existence of different conformers and probably some dynamic interconversion processes. Lowering of the temperature resulted in the precipitation of the compound. In an attempt to obtain some information the molybdenum derivate was chosen due to its greater solubility in comparison with its Mn and Re analogues in the case of the dimers derived from β-alanine (see above for dimers **2**). The reaction was monitored by ^{1}H NMR by dissolving compound **3c** (15 mg) in acetone-d_6 (0.6 mL) and adding the stoichiometric amount of NEt_3 (5 µL). Successive spectra showed the disappearance of the signal of the carboxylic proton, and the formation of the triethylammonium cation accompanied by the broadening of the signals of the complex. After three days at room temperature, black crystals of **4c** were obtained in the NMR tube (81 % yield). The ^{1}H NMR spectrum of the solution exhibited only the signals of the $[NHEt_3]^+$ cation and a very small amount of some unidentified impurity. The black crystals obtained in the NMR tube were studied by electrospray-ionization time-of-flight high resolution mass spectrometry (ESI-TOF) and X-ray diffraction, confirming the formation of the dimer **4c**. However, as can be seen in figure 5 (left) the dimer adopted a non-centrosymmetric structure (**4c_2**) instead of the centrosymmetric one (**4c_1**) obtained when the compound crystallized from a hot methanol solution.

The three structures have some common features, presenting a similar pattern of H-bonding which involves the terminal oxygen of the carboxylate which is bonded to the metal and the N-H group of the complementary peptide chain. As seen in figures 4 and 5, it can be described as an $R_2^2(10)$ ring inside the 16 member metallamacrocycle. Another common feature in the solid state structures of compounds **4** is the presence of solvent molecules H-bonded to exocyclic O(21) and its complementary O(31). Only for the centrosymmetric structure **4c_1** are the two molecules of methanol well defined. For **4a** only one molecule of methanol has been successfully refined, while for **4c_2** the electron density found in the proximity of the exocyclic oxygens could not be modeled (see Experimental).

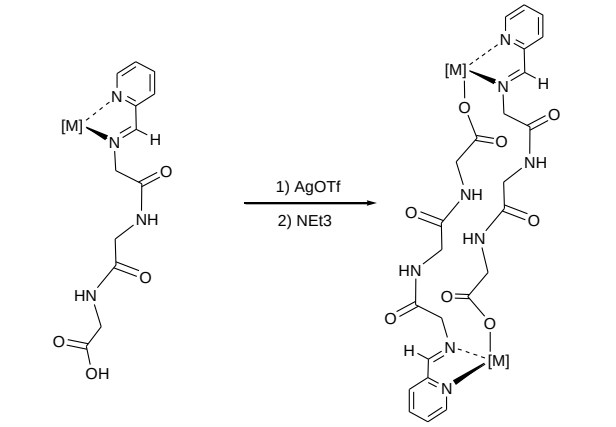
Metallamacrocycles derived from Gly-Gly-Gly

The same procedure as described above for the Gly-Gly derivatives can be applied for those prepared from glycylglycylglycine, Gly-Gly-Gly (See Scheme 3). In this case the resulting dimers are insoluble and therefore, no NMR data could be obtained. The poor solubility of the dimers presented in this work in typical solvents greatly increased as the length of the chain increased (and may be a result of the increase of internal H-bonding). Despite their sparing solubility, metallacyclopeptides **6** were characterized by IR and by electrospray-ionization time-of-flight high resolution mass spectrometry (ESI-TOF), the latter confirming the dimeric structure (See experimental) and evidencing the definitive tendency of the ligands towards the formation of macrocyclic dimers of Mn(I), Re(I) or Mo(II). The tendency of these systems towards dimerization opens a convenient way to the synthesis of metallamacrocycles whose size can be tailored by starting from the appropriate monomeric precursor. While using β-alanine allows the synthesis of Mn(I), Re(I) and Mo(II) metallamacrocycles of 12 members, larger metallamacrocycles of 16 and 22 members can be obtained by starting from the corresponding Gly-Gly or Gly-Gly-Gly monomeric precursor, thus opening a general and easy way to the preparation of

scarce metallacyclopeptides. Finally, these dimers are also interesting since they could serve as cation hosts since they have an effective cavity. Work is underway in our group to validate these assumptions. Particularly promising is dimer **6c** since preliminary tests show that its solubility can be improved by the addition of $Na(B\text{-}3,5\text{-}(CF_3)_2C_6H_3)_4$, thus evidencing a large interaction with the salt.

Conclusions

Deprotonation of the carboxylic group of the side chain of iminopyridine complexes derived from the amino acid β-alanine, dipeptide glycylglycine, or tripeptide glycylglycylglycine, does not lead to intramolecular nucleophilic attack to give tridentate (N,N,O) coordination of the ligand. Instead, the attack is produced in a concerted intermolecular fashion to give dimers in which the ligands act as bridges, didentate (N,N') to one metal and monodentate (O) to the other metal. In previous reports on dimers formed by analogous short-chain complexes derived from alanine, it was concluded that the formation of the dimer was due to geometric restrictions. The generality of this his explanation cannot be maintained since the complexes presented here contain side chains of up to 9 atoms (in the Gly-Gly-Gly residue) which are flexible and would be capable of intramolecular coordination. For derivatives of small amino acids such as β-alanine (**2a**-c) the geometric restrictions pointed out by Herrick et al.. could apply. In the case of derivatives made from gly-gly or gly-gly-gly, the chains would be long and flexible enough to give intramolecular coordination. However it is experimentally observed that the reaction proceeds towards the formation of the head to-tail dimers containing dimetallamacrocycles of 12, 16 and 22 members. It can be concluded therefore that this type of ligands presents a definite tendency towards the formation of dimers. Although, there is not a definite proof to ascertain the factor which drives the process, we tentatively propose that H-bonding could play a significant role in the process. For all the metallacyclopeptides, the H-bonding is established intramolecularly, across the macrocycle, leading to the formation of a ribbon-like arrangement which exhibits an incipient helical twist reminiscent of the α-arrangement found in proteins. Moreover, the peptide side-chains of some of the precursors exhibit in solid state an anti-parallel (head-to-tail) arrangement of the chains, which somewhat anticipates the formation of the head to tail dimers.[15d]



5a [M] = $MnBr(CO)_3$
5b [M] = $ReBr(CO)_3$
5c [M] = $MoCl(h_3\text{-methallyl})(CO)_2$

6a [M] = $Mn(CO)_3$
6b [M] = $Re(CO)_3$
6c [M] = $Mo(\eta^3\text{-methallyl})(CO)_2$

Scheme 3. Formation of dimers from Gly-Gly-Gly derivatives of Mn, Re and Mo.

Experimental

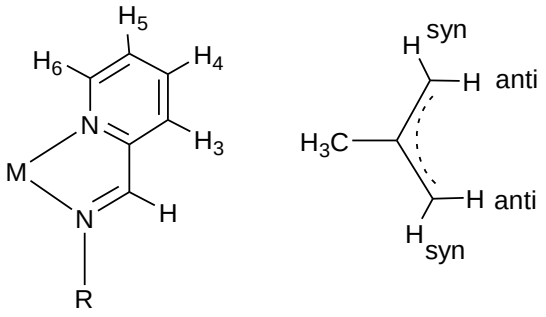
Materials and general methods

All operations were performed under an atmosphere of dry nitrogen using Schlenk and vacuum techniques. Dichloromethane was distilled from CaH_2. THF and diethylether were distilled from Na/benzophenone. Hexane was distilled from Na. Literature procedures for the preparation of starting materials are quoted in each case. Ligands and other reagents were purchased and used without purification unless otherwise stated. Kieselguhr (diatomaceous earth, Merck) was used for filtration. IR spectra in solution were recorded with a Perkin Elmer Spectrum RX I FT-IR instrument, using cells with CaF_2 windows. All mass spectra were collected at the mass spectrometry center at the University of Alcala on a Time-of-flight 6210 LC/MS Agilent Technologies mass spectrometer equipped with electrospray ionization (ESI) and a mass range from 75-11600 u.m.a. The technique used to introduce the sample was Flow injection analysis (FIA). Mobile phase: MeOH(75)/H_2O(25) with 5mM of ammonium formate as an additive. All NMR solvents were stored over molecular sieves and degassed by three freeze-pump-thaw cycles under nitrogen prior to use. NMR experiments were measured on a Bruker AV-400 spectrometer. Chemical shift values are given in ppm. ^1H chemical shifts are referenced to TMS. Complexes **1a-c, 3a-c** and **5a-c** were synthesized as we reported previously.[15b, 15d]

***fac*-[Mn(CO)$_3$κ^3(N,N',O)-pyC(H)=N(CH$_2$)$_2$COO)]$_2$ (2a).**

To a deep-red solution of **1a** (0.198 g, 0.500 mmol) in THF (35 mL) was added AgOTf (0.129 g, 0.500 mmol) and the resulting suspension was stirred for 6 h at room temperature in darkness. The reaction was monitored by IR in solution. The mixture was then filtered through kieselguhr to obtain a yellow solution. To this was added NEt_3 (0.152 g, 1.500 mmol) and the mixture was stirred at room temperature for 2 h and then filtered. Addition of Et_2O gave orange microcrystals of **2a**.

The synthesis of **2a** can be also carried out by substituting an excess of K_2CO_3 or NaH as a base instead of NEt_3. Yield: 0.110g, 70 %. Anal. Calcd. for $C_{24}H_{18}Mn_2N_4O_{10}$: C 45.58, H 2.87, N 8.86. Found C 45.35, H 2.91, N 8.77. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{24}H_{19}Mn_2N_4O_{10}$ $[M+H]^+$ calcd.:632.98567, Found: 632.98716 (2.35 ppm error). IR (THF): ν(CO): 2024 vs, 1935 s, 1911s, cm^{-1}. ^1H NMR (Acetone-d_6): 9.24-8.99 [m (br), 4H, pyC(*H*)=N, pyH^6], 8.33-8.10 [m (br), 4H, pyH^3, pyH^4], 7.47 [s (br), 2H, pyH^5], 4.32-3.98 [m (br), 8H, NCH_2CH_2]. Due to the poor solubility of the compound the NMR assignment should be considered only as tentative. Crystals suitable for X-ray analysis were grown by slow diffusion of Et_2O into a THF solution of the complex at -20 ºC.



Scheme 4. Atom labeling scheme used in the NMR studies for the iminopyridine and allyl ligands

***fac*-[Mn(CO)$_3$$\kappa^3$(N,N',O)-pyC(H)=N(CH$_2$)$_2$COO)]$_2$·$_2$[(NHEt$_3$)(ClO$_4$)] (2a').**

A mixture of compound **1a** (0.198 g, 0.500 mmol) and $AgClO_4$ (0.104 g, 0.500 mmol) was stirred in THF (35 mL) for 6 h in darkness. The reaction was monitored by IR in solution. The mixture was then filtered and NEt_3 (0.152 g, 1.500 mmol) was added. The mixture was stirred for 1 h, and a yellow precipitate of **2a'** began to appear. A layer of Et_2O was deposited on top of the solution and allowed to diffuse at room temperature to produce orange crystals of **2a'**. The supernatant solution was discarded, and the crystals were washed with Et_2O (2 x 15 mL) and dried. Yield 0.155 g, 60%. Anal. Calcd. for $C_{36}H_{50}Cl_2Mn_2N_6O_{18}$: C 41.75, H 4.87, N 8.11. Found C 41.51, H 4.55, N 7.74. IR (THF): ν(CO): 2024 vs, 1935 s, 1912s, cm^{-1}.

***fac*-[Re(CO)$_3$$\kappa^3$(N,N',O)-pyC(H)=N(CH$_2$)$_2$COO)]$_2$ (2b)**

Compound **2b** was prepared as described above for **2a**, by using **1b** (0.100 g, 0.189 mmol), AgOTf (0.049 g, 0.189 mmol) and NEt_3 (0.058 g, 0.567 mmol). The synthesis of **2b** can be also carried out by substituting an excess of K_2CO_3 or NaH as a base instead of NEt_3.Yield 0.060 g, 71%. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{24}H_{19}N_4O_{10}Re_2$ $[M+H]^+$calcd.:897.02107.Found: 897.02280 (1.93 ppm error). IR (THF): ν(CO): 2018 vs, 1917 s, 1895s, cm^{-1}. ^1H NMR (Acetone-d_6): 9.16 [s, 2H, pyC(*H*)=N], 9.03 [d(5), 2H, pyH^6], 8.36-8.30 [m, 4H, pyH^3, pyH^4], 7.81 [m, 1H, pyH^5], 4.22 [m, 4H, NCH_2], 2.25 [m, 4H, CH_2CO]. Due to the poor solubility of the compound the NMR assignment should be considered only as tentative. Crystals suitable for X-ray analysis were grown by slow diffusion of hexane into a THF solution of the complex at -20 ºC.

***cis*-[Mo(κ^3-methallyl)(CO)$_2$ κ^3(N,N',O)-(pyC(H)=N(CH$_2$)$_2$COO)]$_2$ (2c).**

To a solution of **1c** (0.100 g, 0.238 mmol) in CH_2Cl_2 (25 mL) was added NEt_3 (0.036 g, 0.357 mmol) and the mixture was stirred for 20 min. AgOTf (0.061 g, 0.238 mmol) was added and the resulting slurry was stirred in darkness at room temperature for 12 h and then filtered through kieselguhr to obtain a brown solution. Addition of hexane and slow evaporation under vacuum gave compound **2c** as a microcrystalline brown solid. The synthesis of **2c** can be also carried out by substituting an excess of K_2CO_3 instead of NEt_3 Yield 0.075 g, 82 %. Anal. Calcd. for $C_{30}H_{32}Mo_2N_4O_8$: C 46.89, H 4.20, N 7.29. Found C 47.14, H 4.38, N 7.45. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{30}H_{33}Mo_2N_4O_8$ $[M+H]^+$ calcd.:773.04011.Found: 773.04411 (5.17 ppm error). IR (THF): ν(CO): 1947 s, 1857 s, cm^{-1}. ^1H NMR ($CDCl_3$): 8.78 [s, 2H, pyC(*H*)=N], 8.65 [d(5), 2H, pyH^6], 7.93 [td(8, 2), 2H, pyH^4], 7.76 [d(8), 2H, pyH^3], 7.40 [m, 2H, pyH^5], 4.08 [t(11), 2H, NCH_2], 3.75 [m, 2H, NCH_2], 2.77-2.73 [m, 4H, H^{syn}], 2.50 [m, 2H, CH_2COO], 2.16 [m, 2H, CH_2COO], 1.36 [s, 6H, CH_3(methallyl)], 1.23 [s, 2H, H^{anti}], 1.08 [s, 2H, H^{anti}]. Crystals suitable for X-ray analysis were grown by slow cooling of a hot saturated solution of **2c** in methanol.

***fac*-[Mn(CO)$_3$$\kappa^3$(N,N',O)-pyC(H)=NCH$_2$CONHCH$_2$COO)]$_2$ (4a)**

Compound **3b** was synthesized as described above for **2a** by using **3a** (0.150 g, 0.340 mmol), AgOTf (0.087 g, 0.340 mmol) and NEt_3 (0.103 g, 1.020 mmol). Cooling of the solution to -20 ºC produced precipitation of **3a** as orange microcrystals**.** Yield, 0.087 g, 71%. Anal. Calcd. for $C_{26}H_{20}Mn_2N_6O_{12}$: C 43.47, H 2.81, N 11.70. Found C 43.61, H 2.76, N 11.53. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{26}H_{21}Mn_2N_6O_{12}$ $[M+H]^+$ calcd.:718.99730. Found: 718.99903 (2.41 pm error). IR (methanol): ν(CO): 2035 vs, 1945 s, 1932 s, cm^{-1} Crystals suitable for X-ray analysis were grown by slow cooling of a hot saturated solution of **3a** in methanol.

***fac*-[Re(CO)$_3$$\kappa^3$(N,N',O)-pyC(H)=NCH$_2$CONHCH$_2$COO)]$_2$ (4b).**

Compound **4b** was prepared as described above for **2a** by using **2b** (0.200 g, 0.350 mmol), AgOTf (0.90 g, 0.350 mmol), and NEt_3 (0.106 g, 1.05 mmol). Yield: 0.128 g, 75%. Anal. Calcd. for $C_{26}H_{20}N_6O_{12}Re_2$: C 31.84, H 2.06, N 8.57. Found C 32.07, H 2.29, N 8.48. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{26}H_{21}N_6O_{12}Re_2$ $[M+H]^+$ calcd.: 983.03270. Found: 983.03451 (1.84 ppm error). IR (THF): ν(CO): 2022 vs, 1919 s, 1900 s, cm^{-1}.

***cis*-[Mo(κ^3-methallyl)(CO)$_2$ κ^3(N,N',O)-pyC(H)=NCH$_2$CONHCH$_2$ COO)]$_2$ (4c).**

Method A: To a suspension of **3c** (0.150 g, 0.295 mmol) in CH_2Cl_2 was added NEt_3 (0.045 g, 0.442 mmol). The color of the mixture turned to intense violet. Stirring for 48 h produced complete precipitation of **4c** as a violet-black microcrystalline solid. Crystals suitable for X-ray analysis were grown by slow cooling of a hot saturated solution of **4c** in methanol. Under these conditions dimer **4c** adopted a centrosymmetric structure (**4c_1**) (see figure 4). Yield 0.126 g, 87%. Anal. Calcd. for $C_{32}H_{34}$ $Mo_2N_6O_{10}$: C 44.98, H 4.01, N 9.83. Found C 44.74, H 4.10, N 9.63. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{32}H_{35}Mo_2N_6O_{10}$ $[M+H]^+$ calcd.:859.0523. Found: 859.0526 (-

0.38 ppm error). IR (methanol): ν(CO): 1944 vs, 1858 s, cm^{-1}.IR (KBr): ν(CO): 1946 mf, 1856 mf.

Method B: In an NMR tube, 15mg of **3c** in acetone-d_6 were treated with NEt_3 (5μL) and the resulting solution was kept at room temperature. From this solution compound **4c** slowly started to crystalize as black crystals (81% yield, after 3 days). Under these conditions dimer **4c** adopted a non-centrosymmetric structure (**4c_2**) (see figure 4).

***fac*-[Mn(CO)$_3$$\kappa^3$(*N,N',O*)-pyC(H)=N(CH$_2$CONHCH$_2$)$_2$COO)]$_2$, (6a).**

Compound **6a** was prepared as described above for **2a** by using **5a** (0.100 g, 0.201 mmol), AgOTf (0.052 g, 0.201 mmol) and NEt_3 (0.061 g, 0.603 mmol). In this case the reaction mixture was THF (30 mL) and MeOH (10 mL).Yield 0.053 g, 63 %. Anal. Calcd. for $C_{30}H_{26}Mn_2N_8O_{14}$: C 43.28, H 3.15, N 13.46. Found C 43.39, H 3.28, N 13.09. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{30}H_{27}Mn_2N_8O_{14}$ $[M+H]^+$ calcd.:833.0408. Found: 833.0383 (2.96 ppm error). IR (methanol): ν(CO): 2034 vs, 1946 s, 1932 s, cm^{-1}.

***fac*-[Re(CO)$_3$$\kappa^3$(*N,N',O*)-pyC(H)=N(CH$_2$CONHCH$_2$)$_2$COO)]$_2$, (6b)**

Compound **6b** was prepared as described above for **2a** by using **5b** (0.120 g, 0.191 mmol), AgOTf (0.049 g, 0.191 mmol) NEt_3 (0.058 g, 0.573 mmol). In this case the reaction mixture was THF (30 mL) and MeOH (10 mL). Yield 0.080 g, 77 %. Anal. Calcd. for $C_{30}H_{26}N_8O_{14}Re_2$: C 32.91, H 2.39, N 10.23. Found C 33.19, H 2.67, N 10.01. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{30}H_{27}N_8O_{14}Re_2$ $[M+H]^+$ calcd.: 1097.0762. Found: 1097.0738 (2.19 pm error). IR (THF): ν(CO): 2022 vs, 1920 s, 1901 s, cm^{-1}.

***cis*-[Mo(κ^3-methallyl)(CO)$_2$ κ^3(*N,N',O*)-pyC(H)=N(CH$_2$CONHCH$_2$)$_2$ COO)]$_2$ (6c).**

Compound **6c** was prepared as described above for **4c** by using **5c** (0.150 g, 0.288 mmol) and NEt_3 (0.044 g, 0.432 mmol). Yield: 0.118 g, 85%. Anal. Calcd. for $C_{36}H_{40}Mo_2N_8O_{12}$: C 44.64, H, 4.16, N, 11.57. Found C 44.91, H 4.46, N 11.29. Found C 44.74, H 4.10, N 9.63. HR-MS (ESI, positive ion mode ESI-TOF): m/z for $C_{36}H_{41}Mo_2N_8O_{12}$ $[M+H]^+$ calcd.:973.0952. Found: 973.0987 (-3.59 pm error). IR (methanol): ν(CO): 1944 vs, 1858 s, cm^{-1}. IR (KBr): ν(CO): 1948 s, 1861 s, cm^{-1}.

X-Ray diffraction study of 2a, 2a', 2b, 2c, 4a, 4c_1 and 4c_2.

Intensity measurements were made with a Bruker AXS SMART 1000 diffractometer with graphite monochromatized Mo Kα X-radiation and a CCD area detector. Raw frame data were integrated with the SAINT[24] program. A semi-empirical absorption correction was applied with the program SADABS.[25] The structures were solved by direct methods with SIR2002[26], under WINGX,[27] and refined against F^2 with SHELXTL[28] under OLEX2.[29] All non-hydrogen atoms were refined anisotropically unless otherwise stated. Hydrogen atoms were set in calculated positions and refined as riding atoms, with a common thermal parameter. In the structure of 2a' one CH_2 group in one of the triethylammonium cations was found to be disordered in two positions with occupancy 0.7 for C(85A) and 0.3 for C85B. The perchlorate groups were refined with DELU, SIMU and ISOR constraints to keep a reasonable behavior of the anisotropic thermal parameters of the oxygen atoms. For the structures of **4a** and **4c_2** (non-centrosymmetric) some peaks of electron density were found which could correspond to crystallization solvent. Despite repeated attempts it was not possible to get a chemically sensible model, and the residual electron density was treated with the solvent mask technique implemented in OLEX2.[29] Relevant data are included in the cif file. Calculations were made with SHELXTL and PARST,[30] and graphics were made with OLEX2 Crystal data, particular details and CCDC reference numbers are given in Table 1.

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Notes and references

1. G. Jaouen. "Bioorganometallics", ed., Wiley-VCH,Weinheim, 2006
2. N. Metzler-Nolte, *Angew. Chem., Int. Ed.*, 2001, 40, 1040-1043.
3. Laurie, S. H. in Comprehensive Coordination Chemistry, Wilkinson, G.; Gillard, R. D.; Mc Cleverty, J. A.; Eds. Pergamon, Oxford, UK. 1987. Vol 2, Chapter 20.2
4. R. Miyake, S. Tashiro, M. Shiro, K. Tanaka and M. Shionoya, *J. Am. Chem. Soc.*, 2008, 130, 5646-5647.
5. (a) D. Wang, W. Liao and P. S. Arora, *Angew. Chem., Int. Ed.*, 2005, 44, 6525-6529; (b) D. L. Holmes, E. M. Smith and J. S. Nowick, *J. Am. Chem. Soc.*, 1997, 119, 7665-7669.
6. (a) J. N. Smith, Z. Shirin and C. J. Carrano, *J. Am. Chem. Soc.*, 2003, 125, 868-869; (b) J. N. Smith, J. T. Hoffman, Z. Shirin and C. J. Carrano, *Inorg. Chem.*, 2005, 44, 2012-2017.
7. G. Roelfes, *ChemCatChem*, 2011, 3, 647-648.
8. M. Albrecht and P. Stortz, *Chem. Soc. Rev.*, 2005, 34, 496-506.
9. (a) M. J. Kelso, H. N. Hoang, W. Oliver, N. Sokolenko, D. R. March, T. G. Appleton and D. P. Fairlie, *Angew. Chem., Int. Ed.*, 2003, 42, 421-424; (b) M. R. Ghadiri and A. K. Fernholz, *J. Am. Chem. Soc.*, 1990, 112, 9633-9635; (c) M. J. Kelso, R. L. Beyer, H. N. Hoang, A. S. Lakdawala, J. P. Snyder, W. V. Oliver, T. A. Robertson, T. G. Appleton and D. P. Fairlie, *J. Am. Chem. Soc.*, 2004, 126, 4828-4842.
10. G. Platt, M. S. Searle and C.-W. Chung, *Chem. Commun.*, 2001, 1162-1163.
11. J. P. Snyder, A. S. Lakdawala and M. J. Kelso, *J. Am. Chem. Soc.*, 2003, 125, 632-633.
12. (a) R. S. Herrick, K. L. Houde, J. S. McDowell, L. P. Kiczek and G. Bonavia, *J. Organomet. Chem.*, 1999, 589, 29-37; (b) R. Garcia-Rodriguez and D. Miguel, *Dalton Trans.*, 2006, 1218-1225; (c) R. S. Herrick, J. Dupont, I. Wrona, J. Pilloni, M. Beaver, M. Benotti, F. Powers and C. J. Ziegler, *J. Organomet. Chem.*, 2007, 692, 1226-1233.
13. (a) R. Alberto, R. Schibli, A. P. Schubiger, U. Abram, H. J. Pietzsch and B. Johannsen, *J. Am. Chem. Soc.*, 1999, 121, 6076-6077; (b) P. Wang, J. E. Miller, L. M. Henling, C. L. Stern, N. L. Frank, A. L. Eckermann and T. J. Meade, *Inorganic Chemistry*, 2007, 46, 9853-9862; (c) R. S. Herrick, I. Wrona, N.

McMicken, G. Jones, C. J. Ziegler and J. Shaw, *J. Organomet. Chem.*, 2004, 689, 4848-4855.
14. W. Wang, B. Spingler and R. Alberto, *Inorg. Chim. Acta*, 2003, 355, 386-393.
15. (a) C. M. Alvarez, R. Garcia-Rodriguez and D. Miguel, *Dalton Trans.*, 2007, 3546-3554; (b) C. M. Alvarez, R. Garcia-Rodriguez and D. Miguel, *J. Organomet. Chem.*, 2007, 692, 5717-5726; (c) C. M. Alvarez, R. Garcia-Rodriguez, J. M. Martin-Alvarez and D. Miguel, *Dalton Trans.*, 2010, 39, 1201-1203; (d) C. M. Alvarez, R. Garcia-Rodriguez and D. Miguel, *Inorg. Chem.,* 2012, 51, 2984-2996; (e) C. M. Alvarez, L. A. Garcia-Escudero, R. Garcia-Rodriguez and D. Miguel, *Chem. Commun.*, 2012, 48, 7209-7211.
16. (a) C. M. Alvarez, R. Carrillo, R. Garcia-Rodriguez and D. Miguel, *Chem. Eur. J.*, 2013, 19, 8285-8293; (b) C. M. Alvarez, R. Carrillo, R. Garcia-Rodriguez and D. Miguel, *Chem. Commun.*, 2011, 47, 12765-12767; (c) C. M. Alvarez, R. Carrillo, R. Garcia-Rodriguez and D. Miguel, *Chem. Commun.*, 2012, 48, 7705-7707.
17. H. Qayyum, R. S. Herrick and C. J. Ziegler, *Dalton Trans.*, 2011, 40, 7442-7445.
18. T. Steiner, *Angew. Chem., Int. Ed.*, 2002, 41, 48-76.
19. Jeffrey, G. A., An introduction to Hydrogen bonding, Oxford University Press, New York, 1997. Ch. 2.
20. I. G. Santos, U. Abram, R. Alberto, E. V. Lopez and A. Sanchez, *Inorganic Chemistry*, 2004, 43, 1834-1836.
21. Coordination of the $NHCH_3$ group to the metal center in Mn and Re iminopyridines with a $(CH_2)_3NHMe$ side chain produced the expected monomeric complex. Unpublished result
22. D. P. Fairlie, M. L. West and A. K. Wong, *Curr. Med. Chem.*, 1998, 5, 29-62.
23. M. Albrecht, P. Stortz, J. Runsink and P. Weis, *Chem. - Eur. J.*, 2004, 10, 3657-3666.
24. SAINT+. *SAX area detector integration program. Version 6.02. Bruker AXS, Inc. Madison, WI*, 1999.
25. G. M. Sheldrick, *SADABS, Empirical Absorption Correction Program. University of Göttingen: Göttingen, Germany*, 1997.
26. (a) M. C. C. Burla, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Polidory, G.; Spagna, R. , *SIR2002, A program for automatic solution and refinement of crystal structures*; (b) M. C. C. Burla, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R., *J. Appl. Cryst*, 1999, 32, 115-119.
27. L. J. Farrugia, *J. Appl. Cryst.*, 1999, 32, 837-838.
28. (a) G. M. Sheldrick, *Acta Cryst.*, 2008, A64, 112-122; (b) G. M. Sheldrick, *SHELXTL, An integrated system for solving, refining, and displaying crystal structures from diffraction data. Version 5.1. Bruker AXS, Inc. Madison, WI*, 1998.
29. O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, OLEX2: *A complete structure solution, refinement and analysis program*. *J. Appl. Cryst.*, 2009, 42, 339-341.
30. (a) M. Nardelli, *Comput. Chem.*, 1983, 7, 95-97; (b) M. Nardelli, *J. Appl. Crystallogr.*, 1995, 28.
31. (a) I. J. C. Bruno, J. C; Edgington, P.R; Kessler, M. K.; Macrae, C. F.; McCabe, P.; Pearson, J.; Taylor, R., *Acta Cryst.*, 2002, B58, 389-397; (b) C. F. E. Macrae, P. R; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J., *J. Appl. Cryst*, 2006, 39, 453-457.

