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Amidino ligands from coupling 1-methylcytosine and nitrile: a new method to incorporate biomolecules to luminescent $Re(CO)_3$ complexes†

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The formation of an amidino chelating ligand from the coupling reaction of 1-methylcytosine and nitrile is the new method herein reported for the incorporation of biologically relevant substrates into rhenium(I) tricarbonyl complexes. The reactions are carried out thermally or microwave assisted.

The use of luminescent rhenium(I) tricarbonyl complexes as labels and probes for biomolecules lies both on their intense and long-lived emission properties, and on the activity and binding selectivity of the biomolecules, which is retained in almost all cases.[1] Therefore, the incorporation of biologically relevant substrates into these complexes is one of the most important challenges for future inorganic medicinal chemistry.[1,2] More recently, IR spectroscopy has been used in these complexes to know the local environment without the need for labels or staining, allowing to combine bimodal IR and luminescent probes. This has been proposed and named as SCoMPIs, for "Single Core Multimodal Probe for Imaging", by Policar's group.[3]

Besides direct coordination of the nucleobase to the *fac*-$Re(CO)_3$ fragment,[4] three main strategies have been developed in order to graft biomolecules to the *fac*-$[ReX(CO)_3(N\text{-}N)]^n$ (N-N = diimine chelating ligand; X = halogen or pseudohalogen, n = 0; X = pyridyl type ligand, n = +1) complexes:[5] the biomolecule may be attached either to the diimine chelating ligand,[6] or to the pyridyl type ligand;[7] whereas the third option is attaching the biomolecule in a tripodal nitrogen-donor ligand on complexes *fac*-$[Re(CO)_3(N\text{-}N\text{-}N)]$ (N-N-N = tripodal nitrogen-donor ligand).[8]

Herein we present a new method to incorporate biomolecules, in this case a nucleobase, to the rhenium(I) tricarbonyl moiety: instead of attaching a biomolecule to a chelating diimine previously coordinated, a new chelating ligand is formed by the reaction of the nucleobase with a coordinated nitrile. This process may be carried out thermally, or microwave assisted.

This reaction is based on the activation of coordinated nitriles by the metal centre, which results in an enhancement of the electrophilicity of the carbon atom, and facilitates the addition of different nucleophiles.[9] For instance, the addition of amines bearing a proton leads to amidines, of particular interest due to their organic, medicinal, or coordination chemistries.[9c] When the amine belongs to a heterocycle containing a donor atom in the appropriate position, the involvement of their electron pair in aromatization makes the resulting chelating amidino ligand significantly interesting. Our previous studies on pyrazole complexes[10] led us to find that the formation of pyrazolylamidino complexes is base-catalysed,[10e] and to study their photochemistry[10f] or their properties as anion receptor.[10b] We envisaged a logical continuation of this previous work by attempting to make a new amidino complex from the reaction of a nucleobase and a rhenium(I) tricarbonyl nitrile precursor, since this reaction has not been previously reported for this metallic moiety, as indicated above. In fact, the field of metal ion-induced modifications to nucleobases is practically unexplored, although the coordination of nucleobases to metals has been profusely reported.[4] The only precedent of metal-mediated transformations coupling reactions with nitriles and nucleobases is the amidino complex $[ReCl_4\{NH{=}C(Me)(Me_2AdH\text{-}\kappa^2N,N\}]$, obtained after reaction of N^6,N^6-dimethyladenine (Me_2AdH) with *cis*-$[ReCl_4(NCMe)_2]$.[11] The rest of processes of this type previously reported included the deprotonation of the nucleobase, affording an anionic chelating amidino ligand in the complexes *cis*-$[L_2Pt\{NH{=}CR(MeAd\text{-}\kappa^2N,N\}]^+$ (MeAdH = 9-methyladenine) or *cis*-$[L_2Pt\{NH{=}CR(MeCy\text{-}\kappa^2N,N\}]^+$ (L = $PMePh_2$, PPh_3; R = Me, Ph; $MeCyH_2$ = 1-methylcytosine).[12]

The reactions of *fac*-$[ReBr(CO)_3(NCMe)_2]$[13] with equimolar amounts of $MeCyH_2$ in refluxing NCR (R = Me, Ph) lead cleanly to *fac*-$[ReBr(CO)_3\{NH{=}C(R)(MeCyH\text{-}\kappa^2N,N\}]$, (R = Me, **1a**; R = Ph, **1b**) as yellow microcrystalline solids (Scheme 1). The formation of the amidino chelating ligand by coupling of 1-methylcytosine and one molecule of acetonitrile is evident in the X-ray crystal structure of **1a**, shown in Figure 1 together with selected distances and angles. Tables with details of the structure determination, and the rest of

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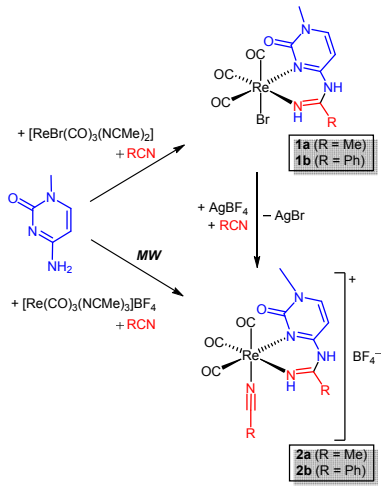
† Electronic Supplementary Information (ESI) available: Synthesis and characterization of the complexes, NBO charges and Wiberg indexes for **1a**, photophysical data, figure of the crystal structure of **2a**, frontier molecular orbital compositions in the ground and excited states, and calculated excited energies and dominant orbital excitations from TD-DFT for **1a** and **2a**. CCDC 1415524-1415525. See DOI: 10.1039/x0xx00000x

spectroscopic data for both complexes in accordance with the geometry deduced by x-ray diffraction can be found in the ESI.



Scheme 1 Syntheses of the amidino complexes from coupling of $MeCyH_2$ and NCR.

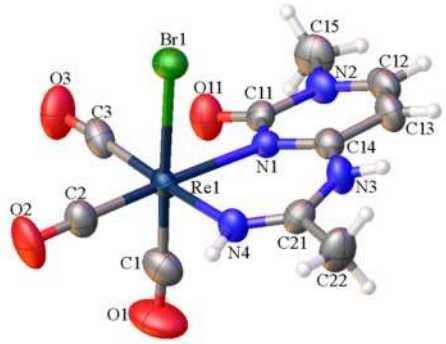


Fig. 1 Perspective view of *fac*-[ReBr(CO)$_3${NH=C(Me)(MeCyH-κ^2*N,N*}], **1a**, showing the atom numbering. Ellipsoids are drawn at 50 % probability. Selected bond lengths (Å) and angles (deg): Re1-N1 2.242(3), N1-C14 1.331(5), N3-C14 1.356(5), N3-C21 1.370(5), N4-C21 1.271(5), Re1-N4 2.132(3), N1-C11 1.409(5), N2-C11 1.400(4), N2-C12 1.346(5), C12-C13 1.322(6), C14-C13 1.417(5); C14-N1-Re1 125.5(2), N1-C14-N3 122.8(3), C14-N3-C21 133.3(3), N4-C21-N3 121.3(4), C21-N4-Re1 132.2(3), N4-Re1-N1 83.28(11).

As indicated above, there are not previous reports of crystal structures containing amidino ligands derived from the coupling of nitriles and $MeCyH_2$. The chelate six-membered ring containing the rhenium atom is almost planar, with a very slight distortion towards a boat conformation, where Re1 and N3 are 0.245(6) and 0.065(6) Å above the mean plane formed by N1, C14, C21 and N4. The latter mean plane forms an angle of 6.36(15)° with the cytosine ring, resulting in a twisted nucleobase ligand. Moreover, the mean plane of the whole nucleobase forms an angle of 12.79(12)° with the coordination plane defined by the C2, C3, N1, and N4 atoms. All these distorsions seem to be intended to move away the carbonyl group in the methylcytosine fragment from the carbonyl ligand in *cis* to the nitrogen donor atom of the nucleobase fragment. In fact, the O11-O3 and O11-C3 distances (2.948(4) and 2.591(6) Å) are well below the sum of the respective van der Waals radii, 3.04 and 3.22 Å, respectively). Obviously, the high steric crowding in this side of the molecule brings these two carbonyls apart from each other, and any chemical interaction between them should be discarded. The Re-N distances (2.242(3) and 2.132(3) Å) are similar to those previously found in pyrazolylamidino complexes,[10] whereas two different C-N distances are found in the chelate six membered ring: those where C=N bonds may be proposed (N1-C14 1.331(5) and N4-C21 1.271(5) Å) are in the expected range for double C(sp^2)=N(sp^2) bonds,[14] but the other CN distances (N3-C14 1.356(5) and N3-C21 1.370(5) Å) are shorter than those expected for a single C(sp^2)–N(sp^2) bond.[14] The tricoordinate N3 atom should be labelled as sp^2 since it is planar, what implies that its electron pair should be delocalized. In order to support this, an NBO study was performed on the minimum geometry to calculate the Wiberg indexes of the bonds in the coordinated chelating ligand. The results, collected in Figure S1, support that the bond distances found in the crystal structure have an electronic origin and they are not due to packing effects. Therefore, the best description for this ligand is that depicted in Scheme 1, although resonance forms where the C-N3 bonds have a double character also contribute to the resonance hybrid, as expected for the planar geometry of N3. Concerning this point, it should be pointed out that determining the energy of the possible tautomers is essential in biological processes, since those energetically less stable may be active intermediates for many transformations, what affects the mechanism of the processes where the biomolecule is involved.[15] In fact, both the monodeprotonated cytosine anion, and the involvement of cytosine in hydrogen bonds or in coordination to metals have been theoretically evaluated.[16]

The *N*-bound hydrogen atom of the amidino ligand is involved in a hydrogen bond with the oxygen atom of a Me_2CO molecule present in the crystal. The distances and angles detected (H(3)···O(91), 2.015(3) Å; N(3)···O(91) 2.874(4) Å, N(3)–H(3)···O(91) 176.6(3)°) leads to consider this hydrogen bond as "moderate".[17]

The new chelating ligands are robust enough so they remain unchanged when the complexes undergo further reactivity. Thus, the reactions of complexes **1** with $AgBF_4$ in NCR afford the cationic complexes *fac*-[Re(CO)$_3$(NCR){NH=C(R)(MeCyH-κ^2*N,N*}]BF_4, (R = Me, **2a**; R = Ph, **2b**) after substituting the bromido ligand by NCR (Scheme 1). The crystallographic data for **2a** may be found in the ESI, as well as their spectroscopic data. The distances and angles found in the crystal structure of **2a** are very similar to those found for the structure of **1a**, discussed above.

These cationic complexes can also be obtained in a one-pot process from *fac*-[Re(CO)$_3$(NCMe)$_3$]BF_4,[18] 1-methylcytosine, and the nitrile by a microwave assisted reaction, in 10 min at 180°C. The yields are slightly lower than those obtained when the reaction is carried out by traditional methods (76% *vs*. 92% for **2a**, 60% *vs*. 83% for **2b**). However, they are clearly higher than those once the yields of the necessary previous steps of **1a** and **1b** are considered (global yields 53% and 46% respectively, considering that the yield of both parent complexes *fac*-[ReBr(CO)$_3$(NCMe)$_2$] and *fac*-[Re(CO)$_3$(NCMe)$_3$]BF_4 from *fac*-[ReBr(CO)$_5$] are higher than 90% and therefore are almost quantitative). Therefore the microwave assisted reaction is a better synthetic method considering the whole atomic economy, since the microwave assisted processes

start from *fac*-$[Re(CO)_3(NCMe)_3]BF_4$. We are not aware of previous reports on the use of microwave to form amidines from nitriles and amines. However, microwave is not a suitable way to obtain the neutral bromido complexes **1**, as the yields in this case are much lower than those obtained by refluxing the nitriles.

As indicated above, the interest on these complexes lies on the incorporation of the nucleobase into a luminescent complex. It is well known that the $Re(CO)_3$ complexes with chelate N-donor ligands are likely to be phosphorescent.[19] In this way, we have recently described some similar complexes with pirazolylamidino ligands, and discussed which changes occur in the emission features when structural modifications are made.[10f] Nonetheless, we have measured some photophysical properties of compounds **1a** and **2a**, in order to check the luminescent behaviour of these nucleobase complexes. Their absorption spectra (see Figure S2 and Table S1 in the ESI) are very similar to those of pyrazolylamidino $Re(CO)_3$ complexes.[10f] Thus, the intense bands observed in the UV region at high energy (250-320 nm) have an intraligand (IL) origin, while the lowest energy absorption bands are assigned to a mixture of MLCT Re→π*(L), ligand-to-ligand charge-transfer (LLCT), and halide-to-ligand charge-transfer (XLCT) transitions. As expected, the substitution of the anionic σ-donor/π-donor bromido ligand by a neutral σ-donor acetonitrile ligand led to an hypsochromic shift, in this case of *ca*. 60 nm in the low energy absorptions. Emission spectra showed bands in the range 500-580 nm, with quantum yields from 0.009 to 0.013 %, values that are in accordance with those found for the pirazolylamidino complexes.

In order to support the assignment of the low-lying absorption transitions as MLCT, theoretical calculations at the same level of theory as for the pirazolylamidino complexes discussed above have been carried out for complexes **1a** and **2a**. These calculations showed that the highest occupied molecular orbitals (HOMOs) have a mixed Re/CO/Br character with different contributions in the case of the neutral complex **1a**, while the HOMOs of the cationic complex **2a** have a Re/CO character. In both cases the LUMO is mainly centred in the nucleobase ligand, confirming the metal to ligand charge transfer nature of the optical transitions (full details can be found in the ESI).

In summary, new luminescent rhenium(I) tricarbonyl complexes containing amidino chelating ligands are obtained by coupling nitriles and 1-methylcytosine. The formation of new amidino chelating ligands in this system by extending this reaction to couple different nitriles and new nucleobases (besides cytosine, adenine and guanine contain donor atoms in the appropriate position to form new amidino ligands) is to be expected. Neutral and cationic complexes have been synthesized, the latter may also be obtained in a microwave reactor, which opens the door to the coordination of a wide range of substrates to the system.

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Table of Contents Text

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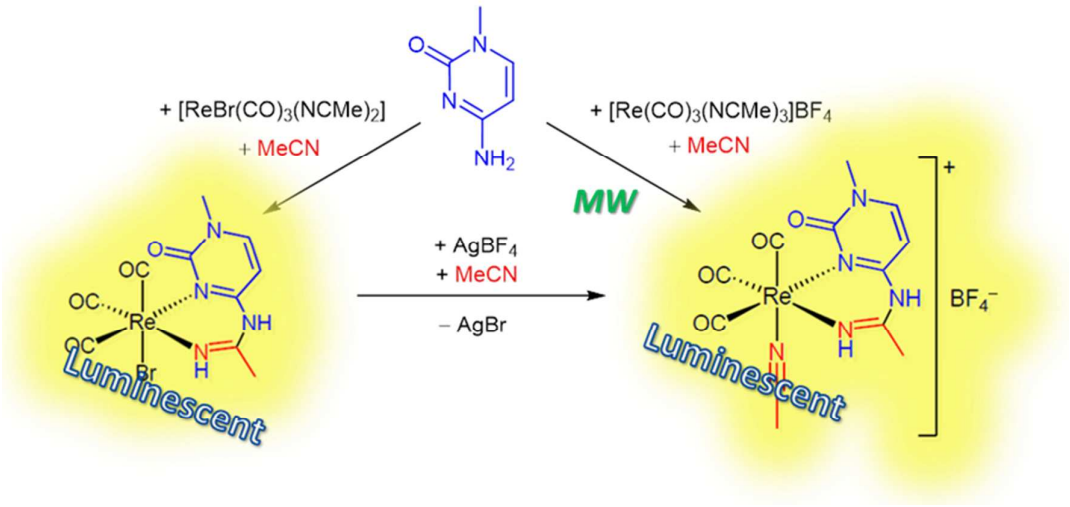

Graphical Abstract

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