

Ternary rhenium(I) complexes: from fluorescent reporters to interesting scaffolds for dual-imaging heterobimetallic probes

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Abstract: Five ternary tricarbonylrhenium(I) complexes based on a pyridinetriazole moiety, so called pyta, were synthesized and spectroscopically characterized. The photophysical properties of these cationic complexes of general formula, $[\text{Re}(\text{CO})_3(\text{pyta-COOMe})\text{L}]$ (L = substituted pyridine derivatives) have been investigated, as well. Three of them are fluorescent and could be considered as interesting scaffolds for the preparation of dual-imaging heterobimetallic species.

Introduction

Optical imaging is an emerging non-invasive diagnostic modality which offers real-time data acquisition and high spatial resolution. Although its tissue penetration is limited, its excellent sensitivity allows the detection of the fluorescent probe on the cellular level. Therefore, extensive work has been recently devoted to the development of new fluorescent cell imaging reporters.

Among optical reporters, rhenium(I) tricarbonyl complexes of general formula $[\text{Re}(\text{CO})_3(\alpha,\alpha'\text{-diimine})\text{L}]$ (L = halogen or substituted pyridine derivatives) have been widely studied due to their promising photophysical features such as large Stoke shifts allowing easy separation of excitation and emission, long luminescence lifetimes and better resistances to photobleaching compared to those of purely organic fluorescent dyes.[1]

We demonstrated previously, that analogous ternary rhenium(I) complexes based

on a pyridinetriazole framework, so-called pyta, exhibited similar photophysical properties than those based on a bipy moiety.[2] In order to pursue our investigations with this kind of fluorophore, we reported in this paper the synthesis of five new ternary complexes of general formula, $[\text{Re}(\text{CO})_3(\text{pyta-COOMe})\text{L}]$ (L = substituted pyridine derivatives) as well as their optical features. The nature of the ancillary ligand, L, has a direct impact on the electronic properties of the Re-complexes. Moreover, some of fluorescent Re(I) complexes could be also considered as interesting scaffolds for the preparation of dual-imaging heterobimetallic species.[3]

Results and discussion

Recently, we reported the first ^{99m}Tc/Re dinuclear complex as a potential nuclear/optical imaging agent.[3] Bearing this in mind, we anticipated that using substituted pyridines as ancillary ligand could lead to (i) novel ternary

Re(I) complexes as potential optical reporters, (ii) fluorescent scaffold for the further preparation of such heterobimetallic species.

The synthetic strategies are illustrated in Figure 1. The reactive acetonitrile adduct **2** was prepared from the reaction of the corresponding $\{\text{Re}(\text{CO})_3\text{Cl}\}$ complex **1** [2a] with silver triflate salt in acetonitrile. The final ternary Re(I) complexes were obtained after thermally activated substitution reactions with commercially available *meta*- or *para*-substituted pyridine moieties or a pyridine bearing an iminodiacetate chelating site (IDA) *via* a triazolyl unit.[4] The complexes are obtained from modest to good yields (from 38% to 87%), depending on the nature of the pyridine species.

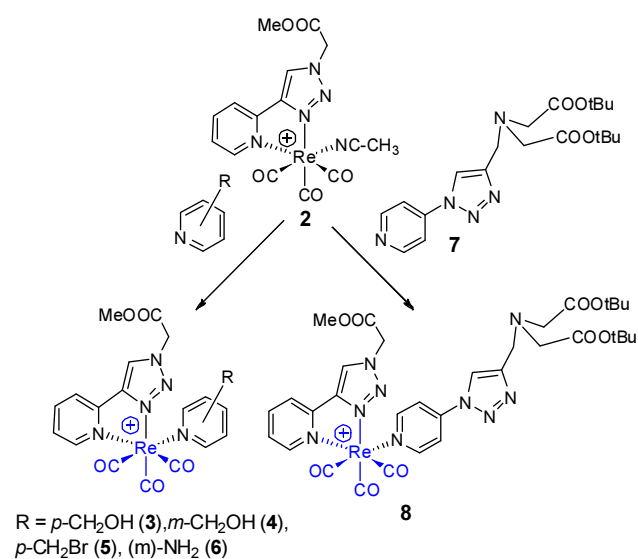


Figure 1. Synthetic pathways

Although not very stable, we succeeded to isolate compound **5** (bromomethyl arm) in modest yield. This interesting result contrasted with previous conclusions of Coogan et al. concerning the formation of similar 3-

chloromethylpyridyl bipyridine tricarbonyl-rhenium complex.[5] Indeed, their reaction conditions, close to ours, gave not the desired ternary complex but instead the precursor material $[\text{Re}(\text{CO})_3(\text{bipy})\text{Cl}]$. Our result suggests that ternary Re(I) complexes with a (halogenomethyl)pyridine as ancillary ligand could be synthesized directly, nevertheless, its poor stability renders its isolation difficult. Additionally, it is noteworthy that two major products have been obtained from the reaction of **2** with intermediate **7**. After HPLC purification, compound **8** was obtained in 38% yield. The second product was a structural isomer of **8**, exhibiting the same MS spectrum assignment. We could suggest that this compound resulted from the coupling of **7** to **2** *via* one nitrogen atom of the triazolyl unit of **7**.

All the ternary Re(I) complexes have been fully characterized by ¹H and ¹³C NMR, and ESI-mass spectrometry. As expected, they were cationic and obtained as triflate salts, as confirmed by both, the quadruplet corresponding to the CF₃ part of the triflate ion observed in the ¹³C spectra and the presence of the triflate ion in negative-ion ESI mass spectra. The presence of the *fac*-ReCO₃⁺ core was confirmed by ¹³C NMR, with three peaks at 191-199 ppm region. The electronic spectra of the complexes showed the typical features associated with this kind of ternary complexes, *i.e.* ligand-centered bands at higher energy corresponding to $\pi \rightarrow \pi^*$ transitions and metal-to-ligand charge-transfer (MLCT) bands at

lower energy corresponding to $d\pi(\text{Re}) \rightarrow \pi^*(\text{pyta core})$.

The photo-physical study has been performed with four complexes, compound **5** being not stable enough. The determination of the luminescent features (λ_{exc} , λ_{em} , Φ) of each complex has been performed at room temperature, in acetonitrile solution using $\text{Ru}(\text{bipy})_3\text{Cl}_2$ as reference for the determination of the quantum yield.[5] After irradiation of the MLCT transition of each complex (absorption band at *ca.* 300 nm), complexes **3**, **4** and **8** exhibit a large emission band at 494, 492 and 496 nm, respectively, while **6** is no luminescent (Table 1).

Compound	$\lambda_{\text{exc}}(\text{nm})$	$\lambda_{\text{em}}(\text{nm})$	$\Phi (\%)^{[a]}$
3	294	494	0.64
4	295	492	0.61
6	296	-	-
8	292	496	0.71

[a] Using $[\text{Ru}(\text{bipy})_3]^{2+}$ as the reference [5]

Table 1. Electronic emission spectral data and quantum yields (Φ) in acetonitrile, at 298K

The room temperature quantum yields of the three luminescent complexes have been calculated (Table 1), the values being in agreement with the values measured for other $\text{Re}(\text{I})$ -pyta complexes.[2] Surprisingly, it is noteworthy that the extension of the π -backbone of the pyridine core of the ancillary ligand in **8**, through the direct connection of a triazolyl unit on the pyridine ring, has not a significant impact on the luminescent properties of the corresponding rhenium complex.

Conclusion

Finally, five ternary tricarbonylrhenium(I) complexes based on a pyridinetriazole moiety, were prepared from modest to good yields. Compounds **3**, **4**, and **8** exhibited promising fluorescence properties. They could also be considered as interesting scaffolds for the preparation of optical/nuclear dual-imaging species, by coupling a radiocomplex on the hydroxyl arm of compounds **3** or **4** or by labeling the IDA chelating site of **8** with the $^{99\text{m}}\text{Tc}(\text{CO})_3^+$ core. This work is currently under investigation.

Experimental part

All purchased chemicals and analytical grade solvents were used without further purification. $[\text{Re}(\text{CO})_3(\text{pyta-COOMe})\text{Cl}]$, **1** and **7** were prepared according to literature protocols.[2a, 4] ^1H , and ^{13}C NMR spectra were recorded at 300 (75.5) MHz or at 500 (125) MHz (Bruker spectrometers). Chemical shifts are reported in parts per million relative to a residual solvent peak (acetone- d_6). Coupling constants (J) are given in Hertz (Hz) and peak multiplicity is reported as: singlet (s), doublet (d), triplet (t), multiplet (m). ESI Mass spectra were obtained on a Perkin Elmer Sciex API

365 or a Applied Biosystem Q trap mass spectrometers. The fluorescence spectra were obtained with a Cary Eclipse spectrofluorimeter equipped with a Xenon flash lamp source and a Hamamatsu R928 photomultiplier tube.

[Re(CO)₃(pyta-COOMe)(ACN)][OTf], **2**

To a solution of **1** (202 mg, 0.386 mmol) in distilled acetonitrile (40 mL), a solution of silver triflate (119 mg, 0.463 mmol) in distilled THF (4 mL) was added under argon. The mixture was refluxed in the dark overnight. After cooling, the solution was filtered off on sintered glass, then twice on a 0.45 μm-PTFE-Millipore. The solvent was evaporated, giving a white powder which was used with no further purification (250 mg). Yield: 95%. MS: m/z = 528 [M-OTf]⁺.

Ternary rhenium(I) complexes preparation

General procedure: To 0.36 mmol (250 mg) of **2** in 50 mL of distilled THF, 1.8 mmol (5 eq.) of a given ancillary ligand were added, under nitrogen atmosphere. The mixture was refluxed during 5h and then stirred at r.t. during 2 days. The desired complex was precipitated by several additions of pentane (50 mL).

Complex **3**: 200 mg of 4-(hydroxymethyl)pyridine led to 180 mg of **3**. Yield: 67%. ¹H NMR (500 MHz): δ = 3.86 (s, 3H, CH₃), 4.67 (s, 2H, CH₂OH), 5.82 (s, 2H, CH₂), 7.45 (m, 2H, CH_{pyr}), 7.89 (ddd, 1H, J=8.1

Hz, J=5.7 Hz, J=2.4 Hz CH_{pyta}), 8.38 (m, 2H, CH_{pyta}), 8.41 (m, 2H, CH_{pyr}), 9.26 (s, 1H, CH_{pyta}), 9.45 (ddd, 1H, J=5.7Hz, J=1.5 Hz, J=0.9 Hz, CH_{pyta}); ¹³C NMR (125 MHz): δ = 54.4 (CH₂), 54.6 (CH₃), 63.3 (CH₂O), 120.0 (q, CF₃, J=320 Hz), 125.5 (2CH_{pyr} + CH_{pyta}), 129.7, 130.0, 143.7, 156.0 (CH_{pyta}), 151.0, 151.3 (C_{pyta}), 153.5 (2CH_{pyr}), 158.7 (C_{pyr}), 168.2 (COOMe), 191.4-195.7 (3C≡O); MS: m/z= 598 [M⁺], HRMS: m/z calcd (found) 596.0731 (596.0709) [M]⁺.

Complex **4**: 200 mg of 3-(hydroxymethyl)pyridine led to 130 mg of **4**. Yield: 48%. ¹H NMR (500 MHz): δ = 3.87 (s, 3H, CH₃), 4.60 (s, 2H, CH₂OH), 5.82 (s, 2H, CH₂), 7.45 (ddd, 1H, J=7.8 Hz, J=5.4 Hz, J=0.6 Hz, CH_{pyta}), 7.89 (m, 1H, CH_{pyta}), 7.97 (m, 2H, CH_{pyr}), 8.38 (m, 1H, CH_{pyta}), 8.45 (m, 2H, CH_{pyr}), 9.25 (s, 1H, CH_{pyta}), 9.46 (ddd, 1H, J=5.7 Hz, J=1.5 Hz, J=0.9 Hz, CH_{pyta}); ¹³C NMR (125 MHz): δ = 54.4 (CH₂), 54.6 (CH₃), 62.0 (CH₂O), 119.8 (q, CF₃, J=320 Hz), 128.2, 129.7, 130.0, 143.5, 143.7 (CH_{pyta}), 138.3, 139.9, 152.0, 156.0 (CH_{pyr}), 150.9, 151.2 (C_{pyta}), 152.4 (C_{pyr}), 168.3 (COOMe), 193.2-197.4 (3C≡O); MS: m/z = 598 [M⁺]; HRMS: m/z calcd (found) 596.0731 (596.0722) [M]⁺.

Complex **5**: 460 mg of 4-(bromomethyl)pyridine led to 143 mg of **5**. Yield: 42%. ¹H NMR (300 MHz): δ = 3.84 (s, 3H, CH₃), 4.98 (s, 2H, CH₂), 5.71 (s, 2H, CH₂), 7.68 (m, 1H, CH_{pyta}), 8.25 (m, 1H, CH_{pyta}), 8.35 (m, 3H, 2CH_{pyr} + CH_{pyta}), 9.07 (m, 3H, 2CH_{pyr} +

CH_{pyta}), 9.16 (s, 1H, CH_{pyta}); ¹³C NMR (75 MHz): δ = 30.7 (CH₂Br), 53.9 (CH₂), 54.5 (CH₃), 120.5 (q, CF₃, J=320 Hz), 124.6, 128.1, 128.5, 142.1, 155.1 (CH_{pyta}), 129.6, 144.0 (2x2CH_{pyr}), 150.7, 151.1 (C_{pyta}), 161.0 (C_{pyr}), 168.3 (COOMe), 197.8-199.3 (3C≡O); MS: m/z = 742 [M + HBr]⁺.

Complex **6**: 170 mg of 3-aminopyridine led to 230 mg of **6**. Yield: 87%. ¹H NMR (500 MHz): δ = 3.79 (s, 3H, CH₃), 5.85 (2d, 2H, J=10Hz, CH₂), 7.03 (m, 2H, H_{pyr}), 7.37 (m, 1H, H_{pyr}), 7.69 (m, 1H, H_{pyr}), 7.83 (m, 1H, H_{pyta}), 8.39 (m, 2H, H_{pyta}), 9.24 (m, 1H, H_{pyta}), 9.25 (s, 1H, H_{pyta}); ¹³C NMR (125 MHz): δ = 53.0 (CH₂), 53.6 (CH₃), 119.9 (q, CF₃, J=320 Hz), 122.4, 127.1, 137.9, 138.9 (CH_{pyr}), 123.3, 128.3, 128.7, 141.3, 154.5 (CH_{pyta}), 147.8 (C_{pyr}), 148.6, 149.1 (C_{pyta}), 167.1 (COOMe), 192.3-196.3 (3C≡O); MS: m/z = 582 [M]⁺.

Complex **8**: 650 mg of **7** led to 128 mg of **8** after HPLC purification (XBridge C18 column, 150x19 mm, flow: 20 mL/min., solvent: H₂O-0.1%TFA/CH₃CN-0.1%TFA, gradient: 0-2 min., 90/10 to 45/55; 2-11 min., 35/65. λ=240 nm. Yield: 38%. ¹H NMR (500 MHz): δ = 1.44 (s, 18H, CH₃), 3.75 (s, 4H, CH₂), 3.88 (s, 3H, CH₃), 4.40 (s, 2H, CH₂), 5.62 (s, 2H, CH₂), 7.90 (m, 1H, CH_{pyta}), 8.10 (m, 2H, CH_{pyr}), 8.40 (m, 2H, CH_{pyta}), 8.70 (m, 2H, CH_{pyr}), 8.85 (s, 1H, CH), 9.35 (s, 1H, CH_{pyta}), 9.50 (m, 1H, CH_{pyta});

¹³C NMR (125 MHz): δ = 27.3 (CH₃tBu), 48.6 (CH₂), 52.6 (CH₂), 52.8 (CH₃OMe), 54.4 (2CH₂), 81.5 (C_tBu), 116.0 (q, CF₃, J=320 Hz), 116.2 (2CH_{pyr}), 123.2 (CH), 123.7 (CH_{pyta}), 127.9 (2CH_{pyta}), 141.9 (CH_{pyta}), 144.6 (C_{pyr}), 144.9 (C), 149.2 (C_{pyta}), 149.6 (C_{pyta}), 154.3 (2CH_{pyr} + CH_{pyta}), 166.4 (COOMe), 168.3 (COOtBu), 194.0-198.3 (3C≡O); MS: m/z = 893 [M⁺]; HRMS: m/z calcd (found) 890.2387 (890.2400) [M]⁺; HPLC: t_r = 4.41 min.

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