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The one-pot synthesis and the fluorescence and cytotoxicity studies of chlorotricarbonyl(α-diimine)rhenium(I), *fac*-$(CO)_3$(α-diimine)ReCl, complexes

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ABSTRACT

An one-pot reaction of $Re_2(CO)_{10}$ and an α-diimine (1:2 molar ratio) in refluxed 2-chloroethanol afforded the corresponding chlorotricarbonyl(α-diimine)rhenium(I) complexes, *fac*-$(CO)_3$(α-diimine)ReCl, **1**-**4**, in very high yield. The α-diimines in **1**-**4** are 2,2′-bipyridyl, 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, respectively. Alternatively, an one-pot reaction of $Re_2(CO)_{10}$ and an α-diimine (1:2 mole ratio) in refluxed 1-pentanol in the presence of CO_2 and HCl yielded the corresponding chloro complexes, **1**-**4**, in very high yield. **1**-**4** were characterized spectroscopically. Additionally, **3** and **4** were characterized through X-ray crystal structure determinations. The chloro complexes, **1**-**4** exhibit fluorescence both in the solid states and in solutions. Surprisingly, **1**-**4** are cytotoxic against breast, prostate, and lung cancer cell lines.

Rhenium tricarbonyl (α-diimine) complexes of the type, *fac*-$(CO)_3$(α-diimine)ReX, (where, X is an anionic ligand), are of importance because most of these complexes exhibit long-lived metal-to-ligand charge transfer (MLCT) and intra-ligand (IL) excited states in solutions at room temperature [1]. Additionally, similar complexes have been reported to be cytotoxic against numerous cancer cell lines [2]. Among the most frequently studied complexes of this type are *fac*-$(CO)_3$(α-diimine)ReCl because of their unique photochemical and photophysical properties [3]. Generally these complexes are synthesized from the reactions of the corresponding α-diimine ligands with $Re(CO)_5Cl$, which is either available commercially or synthesized from the reaction of $Re_2(CO)_{10}$ with Cl_2. In this communication, we report the one-pot synthesis and the fluorescence and cytotoxicity studies of *fac*-$(CO)_3$(α-diimine)ReCl, **1**-**4**, where, the α-diimines are 2,2′-bipyridyl, 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, respectively.

The reactions of $Re_2(CO)_{10}$ with corresponding α-diimines in refluxed 2-chloroethanol, or 1-pentanol in the presence of CO_2 and HCl, afford **1**-**4** in very high yields according to eqs. (1) and (2) [4]:

$$Re_2(CO)_{10} + 2(\alpha\text{-diimine}) + 2ClCH_2CH_2OH \rightarrow 2fac\text{-}(CO)_3(\alpha\text{-diimine})ReCl, \mathbf{1\text{-}4} + CH_3CH_2OH + ClCH_2CHO(?) + 4CO \quad (1)$$

$$(CO)_{10} + 2(\alpha\text{-diimine}) + CH_3(CH_2)_3CH_2OH + 2HCl \rightarrow 2fac\text{-}(CO)_3(\alpha\text{-diimine})ReCl, \mathbf{1\text{-}4} + CH_3(CH_2)_3CHO(?) + 4CO + 2H_2 \quad (2)$$

We did not explore the mechanism of the reactions. It is, however, possible that ligand substitution reactions yield initially the corresponding dimers, $[Re(CO)_3(\alpha\text{-diimine})]_2$ [5]. The reactions of the dimers with 2-chloroethanol or 1-pentanol/CO_2/HCl in several steps afford the corresponding chloro complexes, **1**-**4**. The IR, ^1H and ^{13}C NMR spectral data of **1**-**4** closely match with the published spectral data of **1**-**4** and similar chloro complexes [6]. Surprisingly, the ^{13}C NMR spectral data of **4** are not available in the literature. The present study reveals that the ^{13}C NMR spectrum of **4** exhibits two characteristic and well-resolved resonances at δ197 and 189 (intensity ratio of 2:1) due to the three terminal carbonyls. The molecular structures of **3** and **4** were established through X-ray crystal structure determinations [7]. The X-ray structures of **1**, **2**, and analogous chloro complexes were reported earlier [8]. The molecular plots of **3** are shown in Fig. 1 and the molecular plots of **4** are shown in Fig. 2. The rhenium atom in **3** or **4** has distorted

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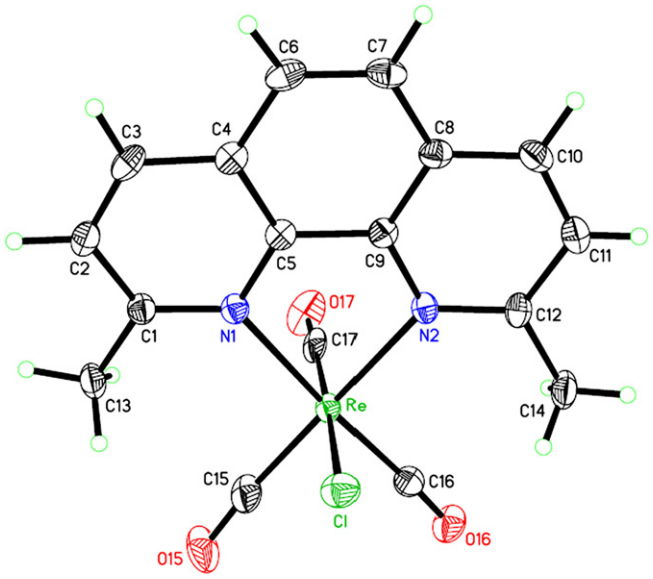

Fig. 1. The X-ray crystal structure of **3**. Selected bond lengths (Å): Re–C(15), 1.905(4); Re–C(16), 1.916(3); Re–C(17), 1.933(4); Re–N(1), 2.224(3); Re–N(2), 2.211(3); O(15)–C(15), 1.160(5); O(16)–C(16), 1.155(4); O(17)–C(17), 1.128(4); Re–Cl, 2.4765(9). Selected bond angles (°): C(17)–Re–Cl, 175.56(9); C(16)–Re–Cl, 97.24(11); C(15)–Re–Cl, 91.02(13).

octahedron with three terminal CO's in a facial arrangement, an α-diimine, and a chloride ligand. There may be a small amount of trans CO/Cl disorder in **3** as indicated by the shortened C17-O17 bond distance and the more linear Re-C17-O17 bond angle relative to the other carbonyl groups. This type of disorder is typical for these complexes [9]. The axial CO and Cl ligands in **4** are disordered across the equatorial plane.

The UV-visible spectra of **1**-**4** are very similar to the UV-visible spectra of **1**-**4** published earlier by several research groups [6,10]. The fluorescence spectra [11] of **1**-**4** in DMSO are shown in Fig. 3. The quantum yields (ϕ) of **1**-**4** were determined from the following equation [12] using the solution of equal absorbance (≈0.089) with crystal violet in methanol as reference standard (ϕ = 0.54 [13])

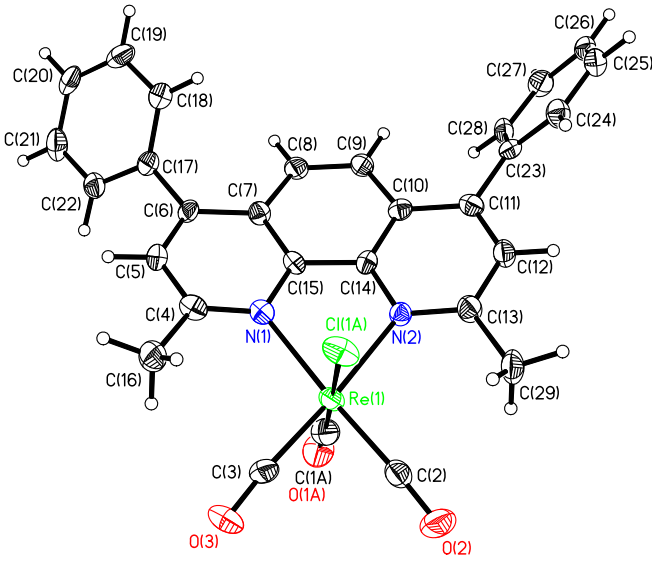

Fig. 2. The X-ray crystal structure of the major component of **4**. Selected bond lengths (Å): Re(1)–C(1A), 1.902(18); Re(1)–C(2), 1.898(7); Re(1)–C(3), 1.911(6); Re(1)–Cl(1A), 2.421(3). Selected bond angles (°): C(2)–Re(1)–Cl(1A), 91.9(2); C(1A)–Re(1)–Cl(!A), 179.6(6); C(3)–Re(1)–Cl(1A), 91.0(2).

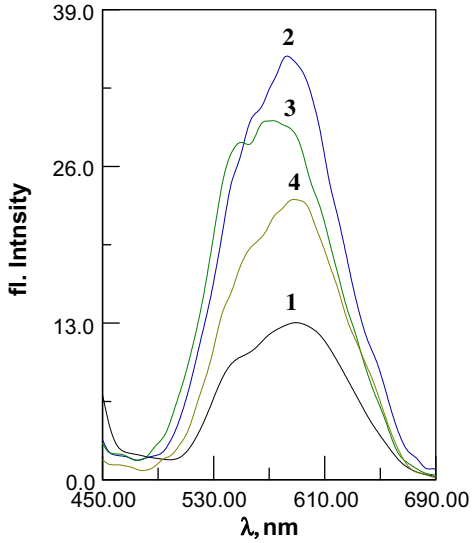

Fig. 3. Fluorescence spectra of the *fac*-chlorotricarbonyl(α-diimine)rhenium(I) complexes in DMSO (**1**: 1.9486 x 10^{-4} M *fac*-$(CO)_3$(bipy)ReCl; **2:** 2.0590 × 10^{-4} *fac*-$(CO)_3$(phen)ReCl; **3**: 2.1403 × 10^{-4} M *fac*-$(CO)_3$(2,9-Me_2–phen)ReCl; **4**: 1.6513 × 10^{-4} M *fac*-$(CO)_3$(2,9-Me_2–4,7-Ph_2–phen)ReCl).

$$\phi_u = \left(\frac{1-10^{-A_s}}{1-10^{-A_s}}\right)\left(\frac{F_u}{F_s}\right)\left(\frac{n_u^2}{n_s^2}\right)\phi_s$$

The subscripts u and s refers to the unknown and the standard, respectively, n is the refractive index, and *F* is the integrated area of the fluorescence band. Strichler method was used to determine the fluorescence lifetime [14]:

$$1/\tau_0 = 2.88 \times 10^{-9} n^2 \overline{\nu_f^3} \phi^{-1} \int_{\bar{\nu}}^{\varepsilon} -d\bar{\nu}$$

Table 1
Photophysical parameters of **1**-**4**

Compound	λ_{ex} (nm)	λ_{em} (nm)	ε (× 10^3/M-cm)	ϕ	τ_0 (ns)
1	319	576.47	2.897	0.261	21.0
2	319	577.19	4.375	0.603	32.0
3	319	577.98	3.259	0.483	38.0
4	319	578.31	5.036	0.459	29.0
Ref. Sample	319	630.21	–	0.56	–

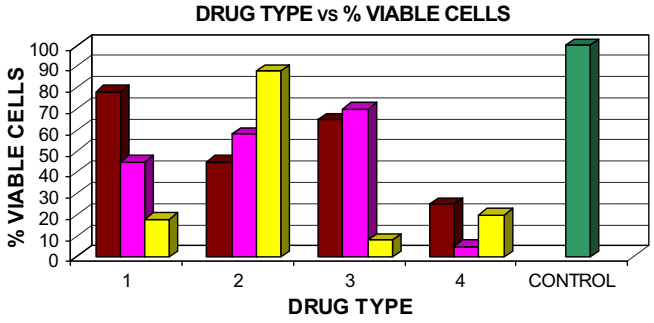

Fig. 4. Plot of drug type vs. % viable cells. Brown, pink, and yellow represent breast, prostate, and lung cancer cell lines, respectively. Green represents control – cells exposed to DMSO only. (1) Cancer cells treated with 1 μg/mL of **1**. (2) Cancer cells treated with 1 μg/mL of **2**. (3) Cancer cells treated with 1 μg/mL of **3**. (4) Cancer cells treated with 4 μg/mL of **4**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1 summarizes the photophysical parameters of the chloro complexes, **1**-**4**. Most importantly, the chloro complexes, **1**-**4** are cytotoxic against human breast (MCF 7), prostate (PC3), and lung (H522) cancer cell lines. The cytotoxicities were studied [15] in the concentration range of 0.5–4.0 μg/mL. **1**-**4** are barely active in 0.5 μg/mL concentration (not shown). However, **1** or **3** are very active against lung cancer cell lines in an optimum concentration of 1 μg/mL (Fig. 4). Although **4** is not active in 1 μg/mL concentration (not shown), it is extremely active against all cancer cell lines in an optimum concentration of 4 μg/mL (Fig. 4). Detailed cytotoxicity studies using a wide range of concentrations of **1**-**4** and the mechanism of actions of **1-4** are in progress.

Acknowledgement

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Appendix A. Supplementary material

CCDC 683150 and CCDC 682962 contain the supplementary crystallographic data for **3** and **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2008.05.033.

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[4] Synthesis of **1**-**4**: Method A: In a typical experiment a mixture of about 1.5 mmol of $Re_2(CO)_{10}$ and 3.0 mmol of an α-diimine was refluxed in 35 mL of 2-chloro ethanol for about 24 h. The mixture was then allowed to cool to room temperature and finally cooled to −5 °C. Orange solid of the corresponding chlorotricarbonyl(α-diimine) rhenium(I) were separated by filtration. The filtrate was discarded. The solid was recrystallized in CH_2Cl_2–hexane at −5 °C. Microcrystals of **1**-**4** were collected by filtration. Yields, 86–93%. Method B: In a typical experiment a mixture of about 1.5 mmol of $Re_2(CO)_{10}$, 3.0 mmol of an α-diimine, and 3 mmol of HCl was refluxed in 35 mL of 1-pentanol for about 24 h while CO_2 was bubbled through the solution. The mixture was cooled to room temperature and −5 °C. Microcrystals of **1**-**4** were collected through filtration. Yields, 78–86%. ^{1}H NMR data for **4** ($CDCl_3$, δ): 7.89(s, 2H, phen), 7.69(s, 2H, C_6H_5), 7.56(m, 6H, C_6H_5), 7.52(m, 4H, phen), 3.00(m, 6H, CH_3). ^{13}C NMR data for **4** ($CDCl_3$,δ): 196.8 (CO), 189.1 (CO), 162.6 (phen), 150.9 (phen), 149.0 (phen), 135.9 (C_6H_5, 129.6 (C_6H_5), 129.5 (C_6H_5), 129.0 (C_6H_5), 127.3 (phen), 126.4 (phen), 124.3 (phen), 31.3 (CH_3).
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[7] X-ray intensity data for **3** were collected on a D8 goniostat equipped with a Bruker APEXII CCD detector using synchrotron radiation tuned to $\lambda = 0.7749$ Å. The data were corrected for absorption and beam corrections. The structure was solved by a combination of direct methods in SHELXTL v6.14 and the difference Fourier technique and refined by full-matrix least squares on F^2. Non-hydrogen atoms were refined with anisotropic displacement parameters. All H-atoms positions were located directly from the difference map and the coordinates refined. Crystal data for **3**: $C_{17}H_{12}N_2O_3ClRe$, $M = 513.94$, yellow crystals, $0.06 \times 0.03 \times 0.02$ mm^3, monoclinic, space group $P2_{1/c}$, $a = 7.8696(9)$ Å, $b = 21.597(3)$ Å, $c = 9.5771(12)$ Å, $\alpha = 90°$, $\beta = 104.516(4)°$, $\gamma = 90°$, $V = 1575.8(3)$ Å^3, $Z = 4$, $\mu = 9.800$ mm^{-1}, θ range = 2.06–31.11°, 22561 reflections collected, 3905 ($R_{int} = 0.0654$) independent reflections, number of variables = 253, $R = 0.0236$, $R_w = 0.0579$, and goodness-of-fit = 1.035. X-ray intensity data for **4** were collected on a Bruker SMART APEXII defractometer equipped with an Oxford Cryosystems 700 Series Cryostream Cooler and Mo Kα radiation ($\lambda = 0.71073$ Å). Unit cell refinement on all observed reflections, and data reduction with corrections for Lp and decay were performed using SAINT. Scaling and a numerical absorption correction were done using SADABS. The structure was solved by direct methods and refined by full-matrix least squares on F^2. Non-hydrogen atoms were refined wit anisotropic displacement coefficients. The H-atoms were assigned isotopic displacement coefficients and their coordinates were allowed to ride on their respective carbons. Crystal data for **4**: $C_{29}H_{20}N_2O_3ClRe$, $M = 666.12$, yellow prisms, $0.015 \times 0.050 \times 0.088$ mm^3, monoclinic, space group $P2_{1/c}$ (No. 14), $a = 9.8109(1)$ Å, $b = 7.7000(1)$ Å, $c = 31.9033(5)$ Å, $\alpha = 90°$, $\beta = 95.317(1)°$, $\gamma = 90°$, $V = 2399.73(5)$ Å^3, $Z = 4$, $\mu = 5.211$ mm^{-1}, θ range = 2.08–27.50°, 40855 reflections collected, 5511 ($R_{int} = 0.0737$) independent reflections, number of variables = 355, $R = 0.0448$, $R_w = 0.0713$, and goodness-of-fit = 1.284.
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