Published in final edited form as:

Inorganica Chim Acta. 2013 October 1; 407: . doi:10.1016/j.ica.2013.07.047.

Differences in the CO photolability of *cis*- and *trans*- [RuCl₂(azpy)(CO)₂] complexes: Effect of metal-to-ligand back- bonding

Samantha J. Carrington, Indranil Chakraborty, Josh R. Alvarado, and Pradip K. Mascharak*

Contribution from the Department of Chemistry and Biochemistry, University of California, Santa Cruz, CA 95064, USA

Keywords

2-phenylazopyridine; Ru carbonyl complexes; *cis* and *trans* isomer; CO photolability

1. Introduction

Metal-carbonyl complexes have attracted considerable attention in recent years for their ability to deliver CO in a controlled fashion for several therapeutic applications [1-3]. Although CO was previously considered to be highly toxic, low doses of CO have now been shown to exert significant beneficial effects to oxidatively damaged tissues (such as in strokes or heart attacks) [1]. To date, several metal-carbonyl complexes have been studied under physiologically relevant conditions as CO releasing molecules (CORMs) [4, 5] to achieve such salutary effects. These compounds mostly undergo rapid solvent-assisted CO release, a process hardly amenable for sustained CO delivery under controlled conditions [6]. To circumvent this problem, researchers have sought to design photoCORMs that could deliver CO upon exposure to light [7]. Mn₂(CO)₁₀ and Fe(CO)₅ are the first two compounds proposed as photoCORMs [8]. However, low solubility and significant toxicity associated with such species limit their scope in therapeutic applications.

In recent years, a few research groups have isolated new metal-carbonyl complexes which by virtue of judicious combination of CO and co-ligand, release CO upon photo-activation. For example, Schatzschneider and co-workers have synthesized [Mn(CO)₃(tpm)]⁺ (where tpm = trispyrazolyl methane) and related tris(imidazol-2-yl)- and tris(imidazol-4(5)-yl)phosphine compounds that release CO upon exposure to 365 nm light [9, 10]. Some of these complexes exhibit substantial uptake by human colon cancer cells [9]. Ford and coworkers have recently reported [Re(CO)₃(bpy)(thp)]⁺ (thp = tris(hydroxymethyl)phosphine), a photoCORM with excellent biocompatibility [11]. We

© 2013 Elsevier B.V. All rights reserved.

pradip@ucsc.edu.

Appendix A. Supplementary material: Crystallographic data (excluding structure factors) for the structural analysis have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 940705 and 940706. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The ¹H NMR (Fig. S1), UV-Vis spectral changes for Mb assay (Fig. S2), traces of UV-vis spectral changes (Fig. S3) and the k_{CO} rate plot (Fig. S4) for complex **2** have been provided in the supplementary information.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

have also been engaged in developing photoCORMs based on group 7 and group 8 transition metals [12,13]. Among group 8 metals, the photophysical properties of ruthenium carbonyls are well studied [14,15]. Herein we report the synthesis, molecular structures and properties of *cis*- and *trans*-[RuCl₂(azpy)(CO)₂] (azpy = 2-phenylazopyridine) complexes. The ligand 2-phenylazopyridine is a superior π -acceptor compared to bipyridine or similar conjugated rigid ligand systems because of considerably low-lying π^* orbitals associated with the –N=N– functionality [16]. It is therefore reasonable to expect that the strong metal-to-ligand charge transfer (MLCT) transition(s) will promote labilization of the Ru(II)–CO bonds in carbonyl complexes of this ligand. Indeed, exposure to light results in CO photorelease and more interestingly, these two geometrical isomers exhibit distinctly different rates of CO photorelease under illumination.

2. Experimental

2.1 Materials and Instruments

[Ru(CO)₃Cl₂]₂ was purchased from Strem Chemicals and was used as received. Reagents were of commercial grade and were used without further purification. All the solvents were purified according to the standard procedures [17]. 2-(phenylazo)pyridine (azpy) was synthesized following a reported procedure [16]. The ¹H NMR spectra were recorded at 298 K on a Varian Unity Inova 500 MHz instrument. A Perkin-Elmer Spectrum-One FT-IR was employed to monitor the IR spectra of the reported compounds. UV-vis spectra were obtained with a Varian Cary 5000 UV-Vis-NIR spectrophotometer. Horse heart myoglobin (Mb) was purchased from Aldrich and used as received.

2.2 Synthesis

2.2.1. Synthesis of *cis*-[RuCl₂(azpy)(CO)₂] (1)—A slurry of 87 mg (0.17 mmol) of [Ru(CO)₃Cl₂]₂ in 13 mL of dry methanol was heated at 45°C for 3 hours resulted in a clear solution. Next, a batch of 63 mg (0.34 mmol) of 2-(phenylazo)pyridine dissolved in 10 mL of methanol was added to it and the mixture was heated for another 3 hours at 45°C when the solution turned bright orange. Evaporation of the solvent under reduced pressure afforded orange powder of *cis*-[RuCl₂(azpy)(CO)₂] which was recrystallized by layering hexanes over a dichloromethane solution. Yield (90 mg, 65%). Anal. Calcd for C₁₃H₉Cl₂N₃O₂Ru, C: 37.97; H, 2.21; N, 10.23. Found: C, 37.89; H, 2.23; N, 10.14. Selected IR (KBr, cm⁻¹) ν_{CO} 2050 and 2000, $\nu_{\text{N=N}}$ 1380. UV-Vis spectrum in CH₂Cl₂ solution, λ_{max} (nm) [ϵ (M⁻¹cm⁻¹)]: 471 (2 500), 363 (13 500). ¹H NMR spectrum (500 MHz) in CDCl₃ solution, δ (ppm): 9.57 (d, 1H, 5Hz), 8.65 (d, 1H, 5Hz), 8.41 (t, 1H, 7.5Hz), 7.92 (t, 1H, 7.5Hz), 7.87 (d, 2H, 10Hz), 7.70 (t, 1H, 7.5Hz), 7.63 (t, 2H, 7.5Hz).

2.2.2. Synthesis of *trans*-[RuCl₂(azpy)(CO)₂] (2)—The *trans* isomer was prepared in an analogous way. However, in this case the slurry of [Ru(CO)₃Cl₂]₂ in dry methanol was heated to reflux (65°C) for 19 hours prior to the ligand addition. After the addition of the ligand, the solution was further refluxed for 3 hours when a deep red solution was obtained. Slow evaporation of this solution afforded dark block-shaped crystals of *trans*-[RuCl₂(azpy)(CO)₂]. Yield (70 mg, 50%). Anal. Calcd for C₁₃H₉Cl₂N₃O₂Ru, C: 37.97; H, 2.21; N, 10.23. Found: C, 38.10; H, 2.23; N, 10.27. Selected IR (KBr, cm⁻¹) ν_{CO} 2070 and 2005, $\nu_{\text{N=N}}$ 1400. UV-Vis spectrum in CH₂Cl₂ solution, λ_{max} (nm) [ϵ (M⁻¹cm⁻¹)]: 482 (14 600), 363 (9 600). ¹H NMR spectrum (500 MHz) in CDCl₃ solution, δ (ppm): 9.21 (d, 1H, 5Hz), 8.68 (d, 1H, 5Hz), 8.37 (t, 1H, 7.5Hz), 8.16 (d, 2H, 5Hz), 7.83 (t, 1H, 5Hz), 7.73 (t, 1H, 5Hz), 7.66 (t, 2H, 5Hz).

2.3 X-ray data collection and structure refinement

Data were collected on a Bruker APEX II single crystal X-ray diffractometer with graphite monochromated Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) by the ω -scan technique in the range 3° to 54° for complex **1** and 3° to 56° for **2**. All data were corrected for Lorentz-polarization and absorption [18]. The metal atoms were located from Patterson maps and the rest of the non-hydrogen atoms emerged from successive Fourier syntheses. The structures were then refined by a full-matrix least squares procedure on F^2 . All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions. The absorption corrections are done using SADABS. Calculations were performed using the SHELXTL V 6.14 program package [19].

2.4 Photolysis experiment

The rates of CO release upon exposure to UV light were measured with a ($7.66 \times 10^{-5} \text{ M}$ for the *cis* and $7.62 \times 10^{-5} \text{ M}$ for the *trans* isomer) solution of the complexes in $1 \text{ cm} \times 0.4 \text{ cm}$ quartz cuvette. The light sources employed in this study include a UV-Transilluminator (UVP, Inc.) with peak intensity of 5 mW/cm^2 (with a 50%T 325 nm cut off filter) at a distance of 1 cm for no more than 1 min intervals and the electronic spectra were recorded. Prior to recording each spectrum, the cuvette was inverted homogeneously for sufficient mixing. Apparent rates of CO release were followed at an appropriate wavelength for each complex and the logarithm of the complex concentration versus time plot were generated. For quantum yield measurements, a solution in acetonitrile was used to ensure sufficient absorbance ($> 99\%$) at the incident wavelength; no more than 10% photolysis occurred in each measurement. Standard actinometry using ferrioxalate was employed to calibrate the light source (Newport Oriel Apex Illuminator (1 mW power with 1cm distance at 363 nm) [20]. Horse heart myoglobin was dissolved in phosphate buffered saline (PBS, 100 mM, pH 7.4) and reduced by adding sodium dithionite. The concentration of the deoxymyoglobin generated was calculated from the absorbance of the Soret band at 435 nm (extinction coefficient = $121 \text{ mM}^{-1} \text{ cm}^{-1}$). Due to sodium dithionite facilitating the release of CO, an apparatus was constructed using two quartz cuvettes [21]. In the first cuvette under anaerobic condition, the photoactive complex was exposed to UV light (UV-Transilluminator) evolving CO into the headspace. The photoreleased CO was then transferred into the second cuvette containing the reduced Mb solution by a positive pressure of $\text{N}_2(\text{g})$.

3. Results and discussion

3.1 Synthesis

The two complexes were isolated from the reaction of $[\text{RuCl}_2(\text{CO})_3]_2$ with one equivalent of azpy ligand in methanol. However, careful control of the reaction temperature afforded the two different isomers. The *cis*- $[\text{RuCl}_2(\text{azpy})(\text{CO})_2]$ (**1**) complex was isolated when the methanolic solution of $[\text{RuCl}_2(\text{CO})_3]_2$ was first heated for 3 hours at 45°C prior to the addition of azpy to the reaction mixture. Quite in contrast, when the initial methanolic solution of $[\text{RuCl}_2(\text{CO})_3]_2$ was heated to reflux for 19 hours prior to azpy addition, pure *trans*- $[\text{RuCl}_2(\text{azpy})(\text{CO})_2]$ (**2**) was isolated in high yield. Close scrutiny of the reaction conditions revealed that at 45°C , the solvated species in the methanolic solution had the three CO groups in a *facial* disposition (as evident by strong ν_{CO} IR bands at 2148, 2086 and 2065 cm^{-1}) which eventually afforded the *cis*-dichloro isomer upon addition of the ligand. At refluxing temperature (65°C), the solvated species however underwent a *facial-to-meridional* isomerization (as evident by strong ν_{CO} IR bands at 2075 and 2010 cm^{-1}) and led to the *trans* isomer (Scheme 1). Although *facial* disposition of the three CO groups is more likely in terms of better metal-CO back-bonding, the *facial* to *meridional* isomerisation is not unprecedented [22]. Complex **2** has previously been synthesized by Oyama and co-

workers from $[\text{RuCl}_2(\text{CO})_2]_n$ and azpy [23]. The starting material in the present work however affords both the *cis* and *trans* isomer **1** and **2** from the same starting material namely $[\text{RuCl}_2(\text{CO})_3]_2$.

3.2 Crystal structure of the complexes

Orange needles of *cis*- $[\text{RuCl}_2(\text{azpy})(\text{CO})_2]$ (**1**) were obtained by layering hexanes over its solution in dichloromethane while dark block-shaped crystals of *trans*- $[\text{RuCl}_2(\text{azpy})(\text{CO})_2]$ (**2**) were obtained through slow evaporation of its methanolic solution. The crystallographic data are listed in Table 1 and the two structures are shown in Figures 1 and 2 respectively. The coordination geometry of the Ru(II) center in both complexes is distorted octahedral and the two CO ligands are *cis* to each other. Also in both the molecules, the N–N distances of the azo group are uniformly longer (1.279(14) Å for **1** and 1.261(2) Å for **2**) than that of azpy (1.25 Å) [24] which can be rationalized in terms of significant Ru(II) π -back-bonding. The five-membered chelate ring in both complexes are satisfactorily planar (mean deviations of 0.0125 Å in **1** and 0.0144 Å in **2**) and the dihedral angles between the pyridine ring and the phenyl ring are 40 and 35° for **1** and **2** respectively. Close inspection of the metric parameters of the two isomers however reveals certain differences. To begin with the two Cl^- ligands are in *cis*- and *trans*- disposition in **1** and **2** respectively. Next, out of the two CO ligands, one CO is uniformly *trans* to the N(1) (N_{py}) atom of the ligand while the other CO is *trans* to a Cl^- in **1** and to N(3) (N_{azo}) atom in **2**. Such disposition makes the Ru–N(1) distances very similar for the two complexes whereas there is a significant increase of 0.051 Å in Ru–N(3) distance for the *trans* isomer **2**. Also, a relatively weaker π -back-donation to the azo group is evident from the noticeable lengthening of N(2)–N(3) distances (0.018 Å) going from the *trans* to the *cis* isomer. The weaker π -back-donation to the azo group in **2** arises from the sheer competition in back-bonding between the azo(π) and the CO for the same metal orbital. In case of the structurally similar *cis*- and *trans*- $[\text{RuCl}_2(\text{bpy})(\text{CO})_2]$, this differentiation in π -back-bonding does not arise due to the symmetric nature of the bpy ligand compared to azpy [24]. The structure of **2** described in this account matches very well with that reported by Oyama and co-workers [23].

3.3 Spectroscopic properties

The two CO ligands in **1** and **2** give rise to ν_{CO} bands in the expected region (2050 and 2000 cm^{-1} for **1**, 2070 and 2005 cm^{-1} for **2**). In addition, The $\nu_{\text{N}=\text{N}}$ stretch in **1** is observed at 1380 cm^{-1} whereas the same in **2** appears at 1400 cm^{-1} (N–N bond shorter). Both complexes display well-resolved ^1H NMR spectrum (Figure 3 and Figure S1) consistent with the diamagnetic ground state of the Ru(II) center. Both isomers are stable in solvents such as methanol, chloroform, and dichloromethane. Once isolated, the two isomers are stable and do not interconvert in solution even upon heating. The electronic absorption spectra of the two complexes consist of two strong bands around 500 and 360 nm. Although the absorption spectra of the two isomers are quite similar, the extinction coefficients of both bands of **1** (the *cis* isomer) is higher than those of **2**. The absorption near 500 nm is most likely to arise from MLCT ($\text{Ru}(\text{d}) \rightarrow \text{azo}(\pi)$) transition much like that observed in $[\text{RuCl}_2(\text{bpy})(\text{CO})_2]$ [26].

3.4 Photo release rate studies

Previous studies on similar carbonyl complexes of Ru(II) have shown that illumination resulted in CO release without any loss of halides [26]. Irradiation of **1** and **2** with low-power (5 mW, 325 nm) UV light also results in CO photorelease as evident by reduced myoglobin assay (Figure 4 and Figure S2). Upon illumination, solutions of **1** and **2** in dichloromethane exhibit distinct isosbestic points, indicating clean conversions to the corresponding photo products (Figure 5 and Figure S3). Kinetic studies on the rates of CO

photorelease (k_{CO}) in dichloromethane indicates that the k_{CO} value of **2** ($0.55 \pm 0.01 \text{ min}^{-1}$, Figure S4) is considerably faster than that of **1** ($0.19 \pm 0.01 \text{ min}^{-1}$, Figure 6). Additionally, the quantum yield values at 363 nm (ϕ_{363}) for **1** and **2** are 0.018 ± 0.001 and 0.023 ± 0.001 respectively. We attribute the faster CO release in case of **2** to the superior pK_{a} -acidity of the azo group which leads to preferential labilization of CO *trans* to it. For the same reason, despite lower molar absorptivity **2** exhibits faster CO photorelease compared to the *cis*-isomer **1**.

4. Conclusions

In summary, results of the present study demonstrate that even simple geometric isomers of carbonyl complexes such as **1** and **2** can exhibit different rates of CO photorelease (k_{CO}). Interesting is to note that in both isomers, the two CO ligands are *cis* to each other. It is only the disposition of the two chloride ligands (*cis* and *trans*) that brings one CO ligand *trans* to the azo-N donor of the asymmetric azpy ligand. The *trans*-labilizing effect of this donor center causes the observed faster CO photorelease by **2**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support from National Science Foundation Grants CHE-957251 and DMR-1105296 is gratefully acknowledged.

References

1. Motterlini R, Otterbein LE. Nat Rev Drug Discovery. 2010; 9:728–743. and references therein.
2. Mann BE, Motterlini R. Chem Commun. 2007:4197–4208.
3. Johnson TR, Mann BE, Clark JE, Foresti R, Green CJ, Motterlini R. Angew Chem Int Ed. 2003; 42:3722–3729.
4. Romao CC, Blattler WA, Seixas JD, Bernardes GJL. Chem Soc Rev. 2012; 41:3571–3583. [PubMed: 22349541]
5. Alberto R, Motterlini R. Dalton Trans. 2007:1651–1660. [PubMed: 17443255]
6. Johnson TR, Mann BE, Teasdale IP, Adam H, Foresti R, Green CJ, Motterlini R. Dalton Trans. 2007:1500–1508. [PubMed: 17404651]
7. Schatzschneider U. Inorg Chim Acta. 2011; 374:19–23.
8. Motterlini R, Clark JE, Foresti R, Sarathchandra P, Mann BE, Green CJ. Circ Res. 2002; 90:e17–e24. [PubMed: 11834719]
9. Niesel J, Pinto A, N'Dongo HWP, Merz K, Ott I, Gust R, Schatzschneider U. Chem Commun. 2008:1798–1800.
10. Kunz PC, Huber W, Rojas A, Schatzschneider U, Spingler B. Eur J Inorg Chem. 2009:5358–5366.
11. Pirri AE, Pallaoro A, Wu G, Ford PC. J Am Chem Soc. 2012; 134:18197–18200. [PubMed: 23077984]
12. Gonzalez MA, Carrington SJ, Fry NL, Martinez J, Mascharak PK. Inorg Chem. 2012; 51:11930–11940. [PubMed: 23088740]
13. Gonzalez MA, Yim MA, Cheng S, Moyes A, Hobbs AJ, Mascharak PK. Inorg Chem. 2012; 51:601–608. [PubMed: 22148670]
14. Hartl F, Aarnts MP, Nieuwenhuis HA, Van Slageren J. Coord Chem Rev. 2002; 230:107–125.
15. Stufkens DJ, Vl ek A Jr. Coord Chem Rev. 1998; 177:127–179.
16. Dougan SJ, Melchart M, Habtemariam A, Parsons S, Sadler PJ. Inorg Chem. 2006; 45:10882–10894. [PubMed: 17173447]

17. Perrin, DD.; Armarego, WLF. Purification of Laboratory Chemicals. Pergamon Press; 1988.
18. North ACT, Philips DC, Mathews FS. Acta Crystallogr. 1968; 24:351–359.
19. Sheldrick, GM. SHELXTL V 6.14, Bruker Analytical X-ray systems. Madison, WI: 2000.
20. Montalti, M.; Credi, A.; Prodi, L.; Gandolfi, MT. Handbook of Photochemistry. Taylor and Francis; 2006.
21. McLean S, Mann BE, Poole RK. Anal Biochem. 2012; 427:36–40. [PubMed: 22561917]
22. Hsu SCN, Yeh WY. J Chem Soc Dalton Trans. 1998:125–132.
23. Oyama D, Asuma A, Hamada T, Takase T. Inorg Chim Acta. 2009; 362:2581–2588.
24. Mostad A, Romming C. Acta Chem Scand. 1971; 25:3561–3568.
25. Haukka M, Kiviaho J, Ahlgrh M, Pakkanen TA. Organometallics. 1995; 14:825–833.

Highlights

- Both cis and trans isomer of $[\text{RuCl}_2(\text{azpy})(\text{CO})_2]$ have been synthesized from $[\text{RuCl}_2(\text{CO})_3]_2$
- Both isomers release CO upon exposure to UV light
- The trans isomer releases CO faster

Fig. 1. Molecular structure of *cis*-[RuCl₂(azpy)(CO)₂] (**1**) (thermal ellipsoids are shown at 50% probability level and the hydrogen atoms are omitted for clarity) and selected bond distances (Å): Ru(1)-C(1) 1.885(15), Ru(1)-C(2) 1.977(16), Ru(1)-N(3) 2.060(10), Ru(1)-N(1) 2.069(11), Ru(1)-Cl(1) 2.386(4), Ru(1)-Cl(2) 2.415, N(3)-N(2) 1.279(14).

Fig. 2.

Molecular structure of *trans*-[RuCl₂(azpy)(CO)₂] (**2**) (thermal ellipsoids are shown at 50% probability level and the hydrogen atoms are omitted for clarity) and selected bond distances (Å): Ru(1)-C(1) 1.893(2), Ru(1)-C(2) 1.946(2), Ru(1)-N(1) 2.0953(15), Ru(1)-N(3) 2.1110(14), Ru(1)-Cl(2) 2.3683(6), Ru(1)-Cl(1) 2.3969(5), N(3)-N(2) 1.261(2).

Fig. 3. Partial ^1H NMR spectrum of *cis*-[RuCl₂(azpy)(CO)₂] (1) in CDCl₃ solution at 298 K

Fig. 4. UV-Vis traces from the Mb assay for **1**. Formation of the Mb-CO adduct (blue trace) from reduced Mb (red trace) is evident by the shift in the Soret band from 435 nm to 424 nm.

Fig. 5. Changes in the electronic absorption spectrum of 1 in CH_2Cl_2 solution upon exposure to light (325 nm)

Fig. 6. Plot of $\ln[1]$ vs. time in CH_2Cl_2 solution at 298 K upon exposure to 325 nm (concentration of $1 = 7.66 \times 10^{-5} \text{ M}$)

Scheme 1.

Table 1Crystal data and structure refinement parameters for **1** and **2**.

	1	2
Empirical formula	C ₁₃ H ₉ Cl ₂ N ₃ O ₂ Ru	C ₁₃ H ₉ Cl ₂ N ₃ O ₂ Ru
F _w	411.20	411.20
Temp(K)	296	296
Wavelength (Å)	0.71073	0.71073
Crystal system	monoclinic	triclinic
Space group	P2(1)/c	P-1
<i>a</i> (Å)	8.706(2)	7.1975(4)
<i>b</i> (Å)	24.831(6)	8.9619(5)
<i>c</i> (Å)	7.0675(17)	12.3854(7)
(deg)	90	86.4330(10)
(deg)	107.282(3)	80.1640(10)
(deg)	90	70.1660(10)
<i>V</i> (Å ³)	1459.0(6)	740.45(7)
<i>Z</i>	4	2
Density (calcd) (Mg m ⁻³)	1.872	1.844
Abs coeff (mm ⁻¹)	1.446	1.425
No. of unique reflns	3354	3597
<i>b</i> <i>R</i> ₁	0.0918	0.0204
<i>c</i> _w <i>R</i> ₂	0.2389	0.0544
<i>a</i> GOF on F ²	1.070	1.066

$$^a\text{GOF} = [\sum w(F_o^2 - F_c^2)^2 / (N_o - N_v)]^{1/2} \quad (N_o = \text{number of observations, } N_v = \text{number of variables}).$$

$$^bR_1 = \sum ||F_o| - F_c| / \sum |F_o|.$$

$$^c\text{w}R_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum |F_o|^2]^{1/2}$$