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Rebuttal to the article *Pathological crystal structures*

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§ Dr Marilyn Olmstead, a world class X-ray crystallography expert, unfortunately passed away on September 30, 2020.

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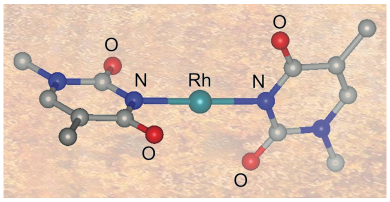
A section in the *Acta Crystallographica Section C* article by Raymond & Girolami [*Acta Cryst*. (2023), C**79**, 445–455] stated that the product of the reaction of $[(Cp^*Rh)_2(\mu\text{-}OH)_3]^+$ (Cp* is 1,2,3,4,5-pentamethylcyclopentadiene) with 1-methylthymine (1-MT) at pH 10 and 60 °C, to synthesize the anionic component $[Rh^I(\eta^1\text{-}N^3\text{-}1\text{-}MT)_2]^-$, was not an Rh^I complex, but rather an Ag^I complex, due to the use of silver triflate (AgOTf) to remove Cl^- from $[Cp^*RhCl_2]_2$ to synthesize $[Cp^*Rh(H_2O)_3](OTf)_2$, a water-soluble crystalline complex. We will clearly show that this premise, as stated, is invalid, while the authors have simply avoided several important facts, including that Cp*OH, a reductive elimination product, at pH 10 and 60 °C, was unequivocally identified, thus leading to the Rh^I anionic component $[Rh^I(\eta^1\text{-}N^3\text{-}1\text{-}MT)_2]^-$. More importantly, AgOH, from the reaction of NaOH at pH 10 with any potentially remaining AgOTf, after the AgCl was filtered off, would be insoluble in water. Furthermore, a control experiment with the inorganic complex $Rh(OH)_3$, reacting with 1-methylthymine at pH 10, provided no product, and this bodes well for a similar fate with AgOTf and 1-methylthymine, *i.e.* at pH 10, AgOTf would again be converted to the water-insoluble AgOH; therefore, no reaction would occur! Finally, a ^1H NMR spectroscopy experiment was carried out with synthesized and crystallized $[Cp^*Rh(H_2O)_3](OTf)_2$ in D_2O at various pD values; at pD 8.65 no reaction took place, while at pD 13.6, and at 60 °C for 2 h, a reductive elimination reaction caused the precipitation of Cp*OH. The subsequent ^1H NMR spectrum clearly demonstrated, in the absence of any Ag^I complexes, that the solution structure and the X-ray crystals in D_2O were similar. A postulated mechanism for this novel anionic component structure, as published previously [Smith *et al.* (2014). *Organometallics*, **33**, 2389–2404], will be presented, along with the experimental data, to insure the credibility of our results. We will also answer the comments in the response of Drs Raymond and Girolami to this rebuttal.



1. Results of our bioorganometallic chemistry reaction with $[Cp^*Rh(H_2O)_3](OTf)_2$ and 1-methylthymine in water at 60 °C and pH 10

Raymond and Girolami (2023) apparently did not fully comprehend that the AgOTf was used to form $[Cp^*Rh(H_2O)_3]$-$(OTf)_2$, *in situ*, in this example, while this aqua complex was used for the reactions with nucleobases, nucleosides, and nucleotides, as a function of pH (Chen *et al.*, 1995; Smith *et al.*, 2014). Moreover, the formed AgCl was not soluble in water; it precipitated out of the aqueous reaction mixture and was filtered off. These authors have also presented no definitive information to justify their premise, since AgOH, a water-insoluble Ag^I complex at pH 10, would be inactive for any reaction with 1-methylthymine, or even a plausible mechanism for Ag^I replacing Rh^I in this bioorganometallic chemistry reaction (Raymond & Girolami, 2023).

Furthermore, the formed $[Cp^*Rh(H_2O)_3](OTf)_2$ (pH 2–5) has been unequivocally shown to have a pH-dependent equilibrium, and provides a μ-OH complex, *i.e.* $[(\mathrm{CpRh})_2(\mu\text{-OH})_2(\mathrm{H_2O})_2](\mathrm{OTf})_2$, at pH 5–7, and $[(\mathrm{CpRh})_2(\mu\text{-OH})_3](\mathrm{OTf/OH})$ at pH 7–10 (Eisen *et al.*, 1995). Thus, the pH was raised to pH 10 and provided $[(\mathrm{CpRh})_2(\mu\text{-OH})_3](\mathrm{OTf/OH})$, which was reacted with 1-methylthymine, and eventually, by raising the temperature to 60 °C, this caused a reductive elimination reaction to occur that gave Cp*OH, identified by GC–MS (gas chromatography–mass spectrometry), after purification. The ironical aspect of this important finding of Cp*OH from a reductive elimination reaction was totally ignored by Raymond & Girolami (2023) and totally negated their supposition of a linear $\mathrm{Ag^I}$ *versus* the linear $\mathrm{Rh^I}$ characterization of this aspect of the X-ray structure (Fig. 1) (Chen *et al.*, 1995; Smith *et al.*, 2014).

Moreover, they stated that Cp*Rh complexes do not, in general, reductively eliminate the Cp* group from Cp*Rh. However, we found a precedent in the literature, in that a $\mathrm{Cp^*RhH_3(SiEt_3)}$ complex in the presence of an excess of $\mathrm{Me_3P}$ gave Cp*H, *i.e.* reductive elimination to provide an $\mathrm{Rh^I}$ complex (Paneque & Maitlis, 1989).

The unique stabilization provided by the π–π interactions of the cationic portion, $[(\mathrm{Cp^*Rh})_2(\mu\text{-OH})_3]_3\mathrm{OH}$, which protected the 12e $\mathrm{Rh^I}$ atom from reactions with $\mathrm{H_2O}$, was to emphasize the special structural aspects of these bioorganometallic complexes. Furthermore, it was our supposition, in this particular case, that the electrostatic interaction between the anionic and cationic components, *i.e.* $[\mathrm{Rh^I}(\eta^1\text{-}N^3\text{-1-MT})_2]^-$ and $[(\mathrm{Cp^*Rh})_2(\mu\text{-OH})_3]^+$, further stabilized adduct formation (Fig. 2).

The putative mechanism for the reductive elimination of Cp*OH is shown in Fig. 3. This mechanism provided a logical pathway for the $\mathrm{Rh^I}$ complex $[\mathrm{Rh^I}(\eta^1\text{-}N^3\text{-1-MT})_2]^-$.

2. Experiments to provide further proof of the structure of the anionic component $[\mathrm{Rh^I}(\eta^1\text{-}N^3\text{-1-MT})_2]^-$

In order to provide more information on the $[\mathrm{Rh^I}(\eta^1\text{-}N^3\text{-1-MT})_2]^-$ structure, in contention with the Raymond and Girolami premise of $\mathrm{Ag^I}$ rather than $\mathrm{Rh^I}$, we had conducted several control experiments, never mentioned by these authors (Smith *et al.*, 2014). The first experiment included the identification of Cp*OH, the reductive elimination product, *via* GC–MS (see *Experimental*, Section 5.3).

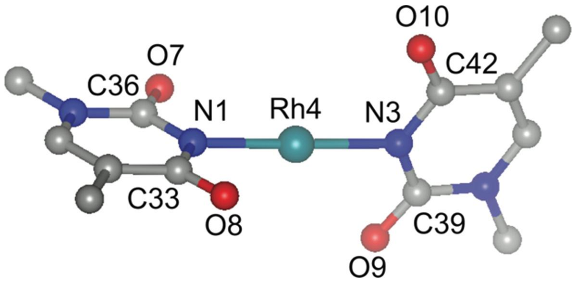


Figure 1
The anionic component $[\mathrm{Rh^I}(\eta^1\text{-}N^3\text{-1-MT})_2]^-$ (Chen *et al.*, 1995; Smith *et al.*, 2014). Reprinted with permission from Smith *et al.* (2014). Copyright (2014) American Chemical Society.

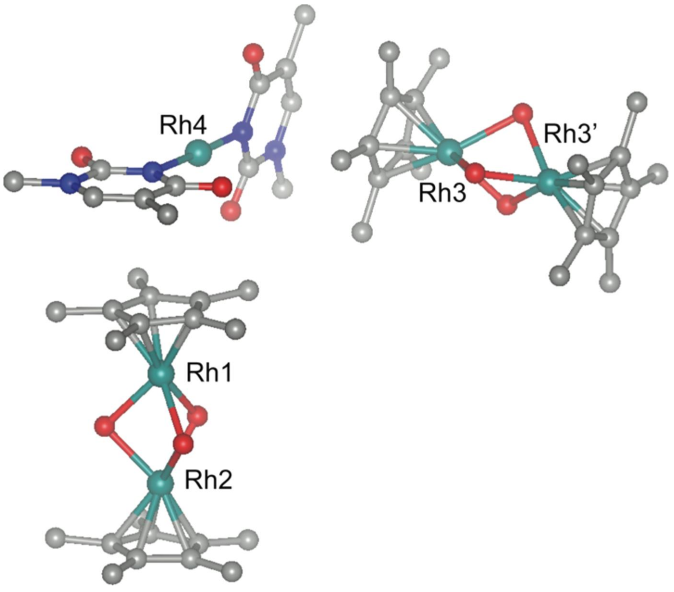


Figure 2
The partial X-ray crystal structure of the anionic and cationic components of $[\mathrm{Rh^I}(\eta^1\text{-}N^3\text{-1-MT})_2]_2[(\mathrm{Cp^*Rh})_2(\mu\text{-OH})_3]_3\mathrm{OH}$, demonstrating the important π–π interactions. Reprinted with permission from Smith *et al.* (2014). Copyright (2014) American Chemical Society.

Secondly, the reaction of pre-synthesized $\mathrm{Rh(OH)_3}$ with 1-methylthymine at pH 10 did not provide any 1-methylthymine complexes, except $\mathrm{Rh(OH)_3}$ had precipitated from the aqueous solution. This result bodes well for a similar result with AgOH, and again, further solidifies the invalid premise of $\mathrm{Ag^I}$ *versus* $\mathrm{Rh^I}$ replacement put forward by Raymond and Girolami (see *Experimental*, Section 5).

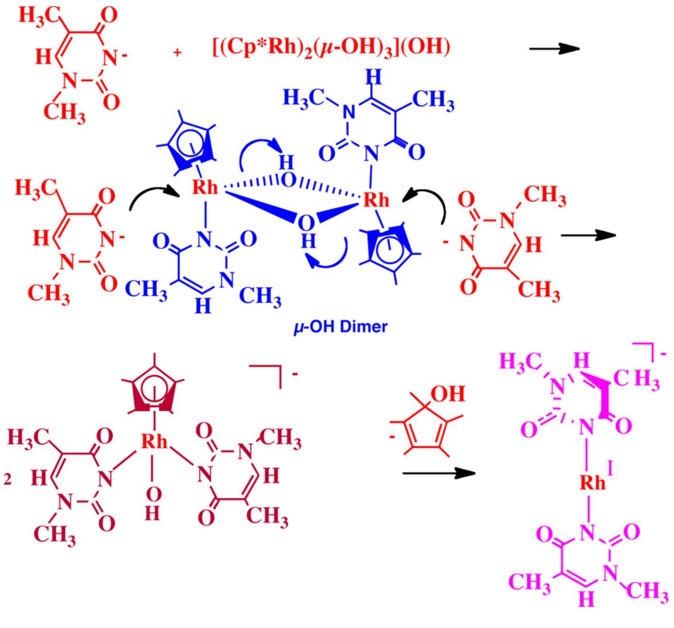


Figure 3
Putative mechanism of the reductive elimination of Cp*Rh-OH to provide the anionic component $[\mathrm{Rh^I}(\eta^1\text{-}N^3\text{-1-MT})_2]^-$. Reprinted with permission from Smith *et al.* (2014). Copyright (2014) American Chemical Society.

The most revealing experiment for the Rh^I anionic component was a ^1H NMR spectroscopy study utilizing the purified and crystalline aqua complex $[Cp^*Rh(H_2O)_3](OTf)_2$, *i.e.* no Ag^I was present. This experiment was conducted in D_2O and at pD 8.65, with no reaction taking place according to ^1H NMR spectroscopy; however, when the pD was raised to 13.6, and the reaction mixture heated to 60 °C for 2 h, Cp*OH again precipitated, and was filtered off. The pronounced upfield shifts were observed for π–π interactions, in concert with the X-ray crystal structure (see *Experimental* for details).

3. Conclusions

It was unfortunate that Marilyn Olmstead could not defend her X-ray structure of $[Rh(\eta^1\text{-}N^3\text{-1-MT})_2]_2[(Cp^*Rh)_2(\mu\text{-OH})_3]_3\text{-OH}$, **12** (Fig. 2); however, we have been able to present data that clearly invalidate the premise of Ag^I instead of Rh^I in the anionic component $[Rh^I(\eta^1\text{-}N^3\text{-1-MT})_2]^-$.

The salient data, not noted in the Raymond and Girolami article, concerning our X-ray structure of the anionic component is as follows: no Ag^I complex, such as AgOH, would be soluble at pH 10 in water to react with 1-methylthymine, as was the case with $Rh(OH)_3$; since the authors stated the similarity of Ag^I with Rh^I, this single fact also eliminates their Ag^I for Rh^I premise.

Further corroborating evidence was the formation and identification of the reductive elimination product, Cp*OH, when the pH and the temperature were raised to 10 and 60 °C, respectively. To reiterate, this seminal fact solidifies the Rh^I thesis and totally discounts the premise of an Ag^I complex for the anionic component $[Rh^I(\eta^1\text{-}N^3\text{-1-MT})_2]^-$ (Chen *et al.*, 1995; Smith *et al.*, 2014).

Finally, the most significant experiment was the ^1H NMR study in D_2O, using the $[Cp^*Rh(H_2O)_3](OTf)_2$ that was purified and crystallized, with no Ag^I contamination. No reaction occurred until the pD was raised to 13.6, and the reaction mixture heated for 2 h at 60 °C. These reaction parameters caused Cp*OH to precipitate out of solution and it was filtered off. The ^1H NMR analysis clearly showed significant upfield shifts of the C6-H signal to 7.10 ppm, or an upfield shift of $\Delta\delta = -0.14$ ppm, while N-Me also moved upfield to 3.10 ($\Delta\delta = -0.05$ ppm) and C5-Me was now at 1.63 ppm ($\Delta\delta = -0.04$ ppm), which was from the 1-MT-Cp* π–π interactions that were shown by the X-ray structure. The $[(Cp^*Rh)_2(\mu\text{-OH})_3]OH$ dimer signal was at 1.38 ppm from 1.41 ppm with a $\Delta\delta = -0.03$ ppm, which further verified that the solid-state and solution structures of complex **12** were very similar (Smith *et al.*, 2014).

In this rebuttal to Rh^I *versus* Ag^I for the anionic component $[Rh^I(\eta^1\text{-}N^3\text{-1-MT})_2]^-$, we have presented a convincing argument that reflected extensive experiments conducted to clearly define Rh^I as the metal for the entire complex. What Raymond and Girolami were focused on was their feelings about the Ag^I structure, without any other viable chemical facts. Furthermore, to reiterate, they apparently did not thoroughly read the Chen *et al.* (1995) and Smith *et al.* (2014) articles, since they totally missed the significance of the reductive elimination product, Cp*OH, clearly to provide an Rh^I anionic component. Moreover, the ^1H NMR study was very revealing in that the pD (pD = pH + 4) and temperature were critical to the Rh^I designation, while totally dismissing the Ag^I scenario. We are confident that the Raymond/Girolami suggestion of Ag^I rather than Rh^I for the anionic component $[Rh^I(\eta^1\text{-}N^3\text{-1-MT})_2]^-$ is clearly incorrect, as our data have demonstrated.

4. Answering the Response of Raymond and Girolami to this rebuttal

The Response of Raymond & Girolami (2024) to this rebuttal included comments that were contradictory to what we stated; for example, '*The rebuttal claims that compound **1** [**12** in Smith et al. (2014)] can be synthesized from the 'purified and crystalline aqua complex [Cp*Rh(H$_2$O)$_3$](OTf)$_2$' and that therefore **1** [**12** in Smith et al. (2014)] could not possibly have contained silver. If this claim were true, it would be significant, but in fact the Experimental section given in the rebuttal (and in the original articles) describes an in situ preparation of this triflate salt, as described in our next point*' (Raymond & Girolami, 2024). The latter statement was patently false, in that the ^1H NMR experiments in D_2O, which incidentally Raymond and Girolami characterized as irrelevant, were conducted with purified crystals of $[Cp^*Rh(H_2O)_3](OTf)_2$ (no Ag^I present) at various pD values (see *Experimental*) and noting the pD values, where no reaction took place until the pD was raised to 13.6 and the temperature was raised to 60 °C to form Cp*OH, that was further purified *via* distillation and the use of a C-18 cartridge, followed by identification by GC–MS (Smith *et al.*, 2014); note that pD = pH + 4.

Drs Girolami and Raymond has further questioned the ^1H NMR spectra results concerning the chemical shifts, but failed to realize that the ^1H NMR spectra of **12** in Chen *et al.* (1995) was conducted in CD_3OD, while the ^1H NMR experiment in Smith *et al.* (2014) with purified $[Cp^*Rh(H_2O)_3](OTf)_2$ was conducted in D_2O, and thus the disparity in chemical shifts he mentioned were solvent driven. The ^1H NMR of the crystals of **12** and the ^1H NMR solution studies were compared in D_2O, and were similar. Thus, his premise that Ag^I must be present in the X-ray results in Chen *et al.* (1995), because of the disparity between the ^1H NMR chemical shift results in Chen *et al.* (1995) and Smith *et al.* (2014), is invalid.

The only relevant statement made by the authors in their Response was a caveat that said the following in their conclusion statement: '*Consequently, we fully acknowledge that the additional evidence we reported above does not prove that **1** [**12** in Smith et al. (2014)] contains silver…*' To reiterate, if Raymond and Girolami read the Smith *et al.* (2014) article, as they stated, they would also see structures not seen previously with inorganic–DNA complexes!

Moreover, I now remember Dr Girolami sending me an email that asked the question, Ag^I *versus* Rh^I, and that led to further experiments published in the Smith *et al.* (2014) article, as described in this rebuttal. One last thought about this scenario of Ag^I *versus* Rh^I is that this type of speculation can cause many colleagues who are interested in our bioorganometallic chemistry with many bioligands to possibly question our published X-ray structural studies in this area of research, even in the written presence of Raymond and Girolami's caveat contending that they were only questioning the X-ray structure of the anionic component $[Rh^I(\eta^1\text{-}N^3\text{-1-MT})_2]^-$. Therefore, we stand firm in that with all their X-ray analysis and caveats, we believe we have shown clearly with the added experiments in Smith *et al.* (2014) that the Ag^I postulate is not valid and that the anionic component $[Rh^I(\eta^1\text{-}N^3\text{-1-MT})_2]^-$ contains an Rh^I metal-ion center!

Furthermore, we will attempt, in the future, to resynthesize complex **12** with pure $[Cp^*Rh(H_2O)_3](OTf)_2$ and obtain an Rh analysis to resolve the Ag^I *versus* Rh^I contention; however, our ^1H NMR experiment in D_2O did show the same chemical shifts, in the absence of any Ag^I contamination, as the ^1H NMR in D_2O for the crystals utilized for an X-ray analysis, which cannot be called irrelevant. To reiterate, the most critical data would be the Rh/Ag elemental analysis to definitively answer the question of Rh^I and not Ag^I for the anionic component of complex **12**.

5. Experimental

5.1. Synthesis of $[Rh^I(\eta^1\text{-}N^3\text{-1-MT})_2]_2[(Cp^*Rh)_2(\mu\text{-OH})_3]_3OH$, 12

To a solution of $[Cp^*RhCl_2]_2$ (0.10 g, 0.16 mmol) in H_2O (15 ml, degassed once) was added AgOTf (0.175 g, 0.68 mmol). The reaction mixture was stirred at ambient temperature for 3 h and was then filtered. The resulting filtrate was treated with 1-MT (0.045 g, 0.32 mmol) and, after all the 1-MT was dissolved, the pH was adjusted to 10 by the addition of 0.1 *N* NaOH. The final reaction mixture was degassed and stirred at 25 °C overnight, and at 60 °C for 2 h to drive the reaction to completion. The solution turned orange, and by reducing the volume of this reaction mixture to ~3 ml, complex **12** was crystallized at 4 °C as orange plates (20% yield). ^1H NMR (400 MHz, CD_3OD): δ 7.24 (*s*, 1H, C6-H), 3.29 (*s*, 3H, N1-Me), 1.85 (*s*, 3H, C5-Me), 1.62 (*s*, 22.5H, Cp*). Elemental analysis calculated (%) for $\mathbf{12}\cdot 10.5H_2O$ ($C_{84}H_{128}N_8O_{18}Rh_8\cdot 10.5H_2O$): C 39.5, H 5.84, N 4.39; found: C 39.3, H 5.65, N 4.55.

5.2. Reductive elimination product Cp*OH

The mechanism for the formation of the anionic component can be tentatively rationalized by the following observations. The distillate of the reaction mixture was analyzed by GC–MS techniques and provided information that Cp*OH was formed (m/z = 151 and 135 for $[M - H]^+$ and $[M - OH]^+$, respectively) during the reaction, which provided clear evidence for the loss of the Cp* ligand from Rh^{III} to Rh^I.

5.3. Identification of Cp*OH *via* GC–MS

The aforementioned orange reaction mixture was distilled at 50 °C *in vacuo*, the distillate was passed through a C-18 cartridge, and finally the Cp*OH was eluted off the cartridge with a small amount of MeOH. The distillate of the reaction mixture was analyzed by GC–MS and provided information that Cp*OH was formed (m/z 151 and 135 for $[M - H]^+$ and $[M - OH]^+$, respectively) during the reaction, which further provided clear evidence for the loss of the Cp* ligand from Rh^{III}.

5.4. ^1H NMR experiments on the reaction of $[Cp^*Rh(H_2O)_3](OTf)_2$ and 1-methylthymine in D_2O, as a function of pD (pD = pH + 4): complex 12

Thus, 18 mg (0.031 mmol) of $[Cp^*Rh(H_2O)_3](OTf)_2$ and 6.1 mg (0.043 mmol) of 1-methylthymine (1-MT) were dissolved in 300 µl of D_2O at pD 10.45. The pD was again measured and found to be 8.65, after the two reactants were dissolved, providing a drop of 1.8 pD units. The ^1H NMR spectrum showed that no reaction had taken place with free 1-MT at 7.24 (C6-H) and 3.15 ppm (N-Me), with the CpRh* signal being at 1.67 ppm. The $[(Cp^*Rh)_2(\mu\text{-OH})_3]^+$ dimer signal was at 1.41 ppm. When the pD was raised to 13.6 with NaOD and the mixture heated for 2 h at 60 °C, as before, Cp*OH precipitated out, and was filtered off, while there was a pronounced upfield shift of the C6-H signal to 7.10 ppm, or an upfield shift of $\Delta\delta = -0.14$ ppm, while N-Me also moved upfield to 3.10 ppm ($\Delta\delta = -0.05$ ppm) and C5-Me was now at 1.63 ppm ($\Delta\delta = -0.04$ ppm), as expected from the 1-MT-Cp* π–π interactions shown by the X-ray structure. The $[(Cp^*Rh)_2(\mu\text{-OH})_3]OH$ dimer signal was at 1.38 ppm (from 1.41 ppm, $\Delta\delta = -0.03$ ppm), which verified that the ^1H NMR in D_2O for the solid-state crystals and solution structures of complex **12** were similar.

5.5. Control experiment: reaction of 1-MT with $[Rh(H_2O)_3](OTf)_3$

$[Rh(H_2O)_3](OTf)_3$ was synthesized by the reaction of $RhCl_3\cdot 3H_2O$ with 3 equivalents of AgOTf in water, while AgCl was filtered from the solution. Reaction of $[Rh(H_2O)_3](OTf)_3$ with 1-MT at pH 10 did not provide complex **12**, as evidenced *via* ^1H NMR spectroscopy, but $Rh(OH)_3$ was formed as a yellow precipitate and was identified *via* elemental analysis. Analysis calculated (%) for $Rh(OH)_3\cdot 1.2H_2O$: Rh 58.6, H 3.08; found: Rh 58.1.

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Response to the rebuttal of the article *Pathological crystal structures*

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We stand fully behind our earlier suggestion [Raymond & Girolami (2023). *Acta Cryst.* C**79**, 445–455] that the claim by Fish and co-workers [Chen *et al.* (1995). *J. Am. Chem. Soc.* **117**, 9097–9098; Smith *et al.* (2014). *Organometallics*, **33**, 2389–2404] of a linear two-coordinate rhodium(I) species is incorrect, and that the putative rhodium atom is in fact silver.

1. Introduction

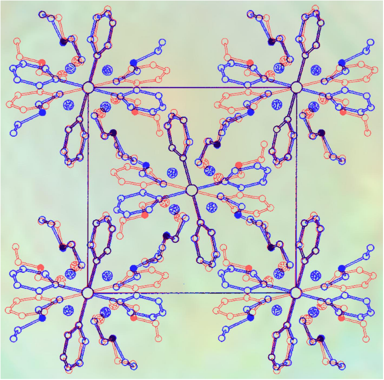
In a recent article (Raymond & Girolami, 2023), we proposed that a compound claimed to contain 'a novel, linear, two-coordinate rhodium(I) anionic amide' (Chen *et al.*, 1995; Smith *et al.*, 2014) actually contained a much more chemically plausible linear two-coordinate silver(I) anion instead. Persuasive evidence that the metal atom in the anion is rhodium and not silver was lacking in the original articles (there was no microanalysis for either Rh or Ag, and no other data that would rule out the presence of silver). In our view, the alternative we proposed is more consistent with both the chemical and the crystallographic data, and therefore should be preferred.

Some of the authors of the original articles, however, disagree with our suggested reformulation and have written a rebuttal (Chen *et al.*, 2024). Here we will respond to that rebuttal and provide additional crystallographic evidence that lends further support to our conclusion that the two-coordinate rhodium atom in the crystal is actually silver. Let us be clear: in writing our previous article, we did not intend to question any of Dr Fish's other work on rhodium–DNA chemistry. We intended merely to point out what we strongly believe is an error, as a lesson to others of the importance of combining both chemical and crystallographic expertise.

2. Chemical evidence

Contrary to the claims in the rebuttal, before writing our 2023 article we had thoroughly read the relevant articles; in fact, we were led to our suggested reformulation only after thinking in detail about both the chemical and crystallographic evidence provided in them. We have now carefully considered all of the new arguments in the current rebuttal, and here detail why we find them unconvincing. We will refer to the compound at issue, $[Rh^{I}(C_6H_7N_2O_2)_2]_2[Cp^*Rh(\mu\text{-}OH)_3RhCp^*]_3(OH)\cdot 46.5H_2O$,[1] as compound **1**, where $C_6H_7N_2O_2$ is a deprotonated 1-methylthymine anion.

(1) The rebuttal claims that compound **1** can be synthesized from the 'purified and crystalline aqua complex, $[Cp^*Rh(H_2O)_3](OTf)_2$' and that therefore **1** could not possibly have



contained silver. If this claim were true, it would be significant, but in fact the *Experimental* section given in the rebuttal (and in the original articles) describes an *in situ* preparation of this triflate salt, as described in our next point.

(2) Compound **1** was prepared by adding AgOTf (0.68 mmol) to $[Cp^*RhCl_2]_2$ (0.16 mmol) in water, followed by filtration of the solution (away from the precipitated AgCl) and addition of 1-methylthymine; finally NaOH was added to adjust the pH to 10 and compound **1** was isolated after the resulting solution was heated to 60 °C for 2 h and then concentrated (Smith *et al.*, 2014). Because the AgOTf was added in slight stoichiometric excess, this procedure would have afforded a filtrate that contained about (0.68 mmol) − 4(0.16 mmol) = 0.04 mmol of silver ions. Compound **1**, which was isolated in 20% yield, contains eight metal atoms per formula unit (*versus* two metal atoms per formula unit for $[Cp^*RhCl_2]_2$); therefore, the molar yield of **1** was (0.16 mmol)(0.2)(2)/(8) = 0.008 mmol. Two of the eight metal atoms per formula unit are in the supposed two-coordinate anion, which would therefore require 0.016 mmol of metal atoms. Because over two times this quantity of silver was likely present in the filtrate, more than enough silver would have been available for the two-coordinate anion in **1** to be an argentate species.

(3) The rebuttal states correctly that most of the silver would have been filtered away as AgCl, but also claims that adding NaOH to the filtrate would precipitate any remaining silver by forming AgOH. The rebuttal argues that no silver would remain to be incorporated into the ultimate reaction product, compound **1**, because AgOH is insoluble in water at pH 10. It is true that AgOH has a very low solubility in pure water at this pH, but it is a well-known phenomenon that strongly-coordinating groups can solubilize what are otherwise insoluble metal salts; addition of ammonia, for example, to aqueous suspensions of AgCl causes this salt to dissolve owing to the formation of the $[Ag(NH_3)_2]^+$ ion. In the present case, 1-methylthymine was added before the solution was treated with hydroxide, and the 1-methylthymine anion is known to be a strongly-coordinating group for the silver(I) ion (Guay & Beauchamp, 1979).

(4) Although GC–MS data (gas chromatography–mass spectrometry) were presented in support of the formation of the molecule 'Cp*OH' as a by-product of the synthesis, in our view, a low-resolution MS spectrum (without any other spectroscopic or analytical data) is simply not sufficient to establish the identity of this by-product unambiguously, and we disagree with the rebuttal's contention that this product was 'unequivocally identified.' But even if Cp*OH had been produced in the reaction, this fact would not prove that compound **1** contains the claimed two-coordinate rhodium species, because the amount of 'Cp*OH' formed was not quantified and the yield of **1** is relatively small. Similarly, we point out that the one cited literature precedent, in which Cp*H is reductively eliminated from a rhodium(V) Cp* hydride complex, is chemically rather different from the proposed loss of Cp*OH from a rhodium(III) Cp* species by hydroxide attack: the oxidation states involved are different, and different C—*X* bonds are formed. But even granting that Cp* can occasionally be lost from a rhodium complex, this fact also does not prove that compound **1** contains the claimed two-coordinate rhodium species. It is important to keep in mind that facts consistent with a hypothesis do not necessarily prove that the hypothesis is true.

(5) The discussion in the rebuttal (and in the original articles) of the stabilizing effect of π–π interactions is an *ex post facto* argument to try to rationalize why **1** could possibly contain a two-coordinate rhodium(I) species – an outcome that the text of the original articles acknowledged was in need of explanation. Of course these π–π interactions would equally well stabilize **1** if the two-coordinate anion contained silver instead of rhodium.

(6) The lack of formation of **1** from the reaction of *in-situ*-generated $[Rh(H_2O)_x][OTf]_3$ with 1-methylthymine at high pH is irrelevant to the question whether **1** contains silver. With reference to the ^{1}H NMR experiments on the reaction of $[Cp^*Rh(H_2O)_3](OTf)_2$ and 1-methylthymine in D_2O as a function of pD, the rebuttal claims that '*our ^{1}H NMR experiment in D_2O did show the same chemical shifts, in the absence of any Ag^I contamination, as those for the crystals utilized for an X-ray analysis*.' But the ^{1}H NMR spectrum of **1** gave 1-methylthymine shifts of δ 7.24, 3.29, and 1.85, whereas the Ag-free experiment gave shifts of δ 7.10, 3.10, and 1.63. It is evident that these shifts are far from being the same. An addition to the rebuttal was the claim that '*The ^{1}H NMR of the crystals of [the compound at issue] and the ^{1}H NMR solution studies [of the addition of **1-MT** to purified $[Cp^*Rh(H_2O)_3](OTf)_2$] were compared in D_2O, and were similar.*' But this claim is unsupported by any documentation; furthermore, 'similar' is very different from 'the same'. As a side note, the rebuttal claims that Cp*OH precipitates out of an aqueous solution at pH 13.6. This claim is highly unlikely because Cp*OH would certainly be deprotonated to form a sodium salt under these conditions (if it did not undergo some other reaction, such as dehydration to tetramethylfulvene).

(7) Finally, we point out that there are many examples of crystal structures that contain elements that were absent in the supposed starting materials, and we gave several examples of this phenomenon in our previous article. Atoms from the solvent, the reaction vessel, the atmosphere, minor impurities in reagents, and other sources can and sometimes do find their way into a crystal. In addition, it is possible to mislabel or confuse samples, so that a crystal used for a single-crystal diffraction analysis may consist of a substance generated by a completely different procedure than the one thought to have been employed. In our previous article, we also gave several examples of this phenomenon. For these reasons, there is no such thing as an ironclad guarantee that silver absolutely cannot be present in a crystal, simply owing to the way the crystal was prepared (or was thought to be prepared). The same is true of most elements in the periodic table.

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[1] Note the large number of water molecules per formula unit, some of which were disordered and modeled with partial occupancies in the published crystal structure.

3. Crystallographic evidence

Here we provide some crystallographic evidence in support of our suggestion that the two-coordinate species in **1** is a complex of silver instead of rhodium. As we pointed out in our earlier article, the atomic numbers of Ag and Rh differ by 4% and are difficult but not impossible to distinguish by X-ray crystallography.

(1) The crystal structure of **1** was reported by Fish and coworkers twice, once in 1995 as ZEKYET in the Cambridge Structural Database (CSD; Groom *et al.*, 2016), and again in 2014 as ZOLFOX (Chen *et al.*, 1995; Smith *et al.*, 2014). It is important to point out that ZEKYET was rerefined and reentered into the CSD as ZOLFOX but using the original data from 1995. Therefore, the new experimental work reported by Fish and co-workers in 2014 is actually not relevant to the reported crystal structure.

(2) From the ZOLFOX CIF file we created .ins and .hkl files which we then examined with *SHELX* (Sheldrick, 2015). When Ag is substituted for either Rh1 or Rh2 (which are attached to Cp* groups and thus really are Rh atoms), the $wR2$ factor *increases* slightly in both cases from 0.197 to 0.204. Rh3 is also attached to Cp*, but this molecule is badly disordered, so we did not investigate what happens when that atom is replaced with silver. But when the two-coordinate 'Rh4' atom is replaced with Ag, the $wR2$ factor *decreases* slightly, from 0.197 to 0.195 if the weighting parameters are left unchanged, and from 0.197 to 0.193 if the WGHT card is allowed to refine. Substitution of Ag for any of the atoms assigned as Rh causes the displacement parameters for that atom to increase slightly (as would be expected no matter whether the atom really is Rh or Ag), but the change still leaves the displacement parameters at reasonable values.

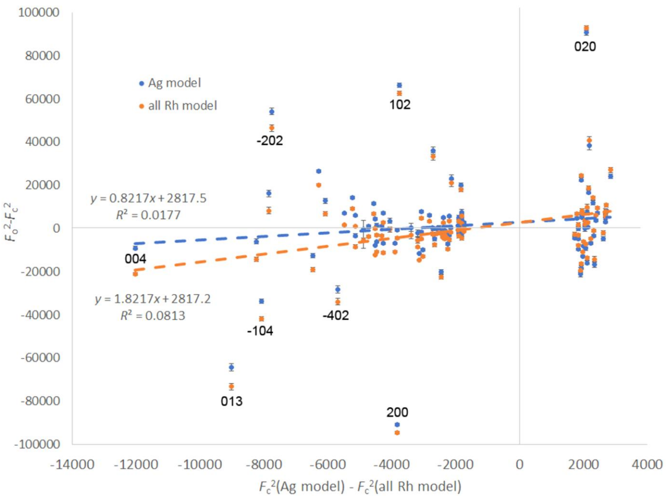

Figure 1
Plot of $F_o^2 - F_c^2$ *versus* F_c^2(Ag model) – F_c^2(all-Rh model) for the 100 reflections with largest absolute values of F_c^2(Ag model) – F_c^2(all-Rh model). The plot includes points for both the Ag model (blue dots) and the all-Rh model (orange dots). Several reflections are very poorly modeled, no matter whether the two-coordinate atom is Ag or Rh (*hkl* indices are shown for some of them). These poorly-modeled reflections have small indices and scattering angles (and are among the most intense) in the entire data set. Instead of omitting them as statistical outliers, we chose to retain them even though they will add noise to the analysis.

(3) Also illuminating is that, for the original all-Rh structure, two of the tallest peaks in the final difference map, Q2 and Q3, were very close to the two-coordinate 'Rh4' position and had peak electron densities of just over 1 e Å^{-3}, but when the Rh4 atom is replaced with Ag, the two peaks nearest to Ag4 were Q13 and Q39, with much smaller heights of 0.75 and 0.51 e Å^{-3}. Thus, silver provides a better fit to the electron-density distribution at the two-coordinate metal site than does rhodium.

(4) The substitution of silver for rhodium in the two-coordinate sites necessarily changes all of the calculated structure factors (and also the overall scale factor), in part owing to anomalous scattering: both Rh and Ag have absorption edges close to the Mo $K\alpha$ energy. Certain reflections will be more sensitive to this change than others, and we can determine this sensitivity simply by comparing the lists of calculated squared structure factors, F_c^2, for the two models. To do so, we placed the two models on the same absolute scale (which involved dividing the F_o^2, σF_o^2, and F_c^2 values for the Ag model by 1.03182), calculated the difference F_c^2(Ag model) – F_c^2(all-Rh model) for all 12700 reflections in ZOLFOX, and then sorted the list to identity the 100 reflections for which this difference has the largest absolute value. For these 100 reflections, we created an xy plot (Fig. 1) in which the x value is the difference F_c^2(Ag model) – F_c^2(all-Rh model) and the y value is $F_o^2 - F_c^2$. In this plot, each reflection appears twice: once with a y value for the Ag model (blue dots) and a second time with a y value for the all-Rh model (orange dots). Reflections that are most sensitive to the identity of the metal in the two-coordinate site will have large x values (*i.e.* those to the far left and far right), and the better of the two models will be indicated by having more reflections with y values values closer to zero.

Reflections that appear in the upper right (+ +) or lower left (– –) quadrants are those for which the Ag model gives F_c^2 values that better agree with experiment (F_o^2); reflections that appear in the lower right (+ –) or upper left (– +) quadrants are those for which the all-Rh model gives better agreement. About two-thirds of the 100 reflections are in the (+ +) or (– –) quadrants, and this observation provides additional evidence in favor of the Ag model. Also consistent with this conclusion are the two least-squares lines, which are a measure of the agreement of F_c^2 and F_o^2: the Ag model is better than the all-Rh model because the slope is closer to zero. In addition, because the intensities of these 100 reflections are the most sensitive to the substitution of Ag for Rh, the $wR2$ factors calculated from this subset should be more indicative of the identity of the two-coordinate atom than the $wR2$ factors calculated for all 12700 reflections. Indeed, we find that, with unit weights, $wR2 = 0.180$ for the Ag model *versus* 0.188 for the all-Rh model.

4. Conclusions

We said above that facts consistent with a hypothesis do not necessarily prove that the hypothesis is true. Consequently, we fully acknowledge that the additional evidence we reported above does not prove that **1** contains silver (nor does it prove that all the metal atoms are rhodium). The differences among the various crystallographic models we studied are small, as one might expect from the similarity of the atomic numbers of Rh and Ag. But it is also clear to us that the crystallographic data are *more consistent* with the conclusion that **1** contains a two-coordinate silver(I) complex than a two-coordinate rhodium(I) complex. Also relevant is that this conclusion is chemically more plausible, owing to the large number of known two-coordinate silver(I) complexes *versus* the absence of any other two-coordinate rhodium(I) complex in the entire chemical literature.

We should add that in July 2004 one of us (GSG) wrote by email to both Dr Fish and Dr Olmstead suggesting that the two-coordinate rhodium atom in this crystal was silver.[2] Dr Fish, the corresponding author, replied but did not reply to a follow-up email. Dr Olmstead, the crystallographer, responded that she had not been told that the presence of silver in the crystal was a possibility; she offered to reinvestigate the structure, but as far as we are aware this was never done.[3]

Scientists who reach a conclusion that has ample literature precedent still have the obligation to consider and discuss alternative hypotheses that may also be consistent with the data. Authors who reach any surprising or unprecedented conclusion, however, bear a much greater burden: they must not only consider and discuss alternative and less-exciting hypotheses, they must also provide convincing proof that these alternatives are false. In the present case, for example, such proof could entail remaking **1**, verifying by crystallography that its structure is identical to that determined previously, showing (perhaps by powder X-ray diffraction) that the bulk sample is homogeneous and consists of the same material as that examined by single-crystal diffraction, and carrying out a microanalysis that shows that no silver is present. We are convinced, however, that such a protocol would show that about 6.3% by weight of silver is in fact present in crystals of **1**.

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[2] Copies of the correspondence may be requested from GSG.

[3] Dr Olmstead died tragically in 2020.