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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

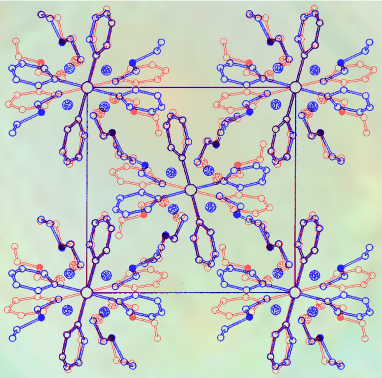
In a recent article (Raymond & Girolami, 2023), we proposed that a compound claimed to contain 'a novel, linear, two-coordinate rhodium(I) anionic amide' (Chen *et al.*, 1995; Smith *et al.*, 2014) actually contained a much more chemically plausible linear two-coordinate silver(I) anion instead. Persuasive 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



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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.

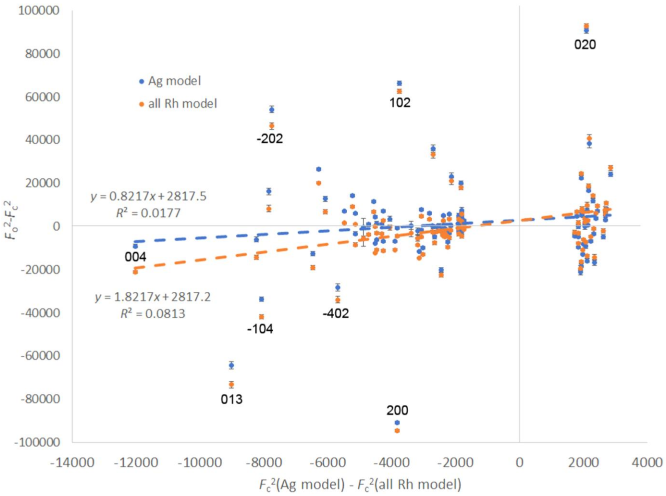

Figure 1
Plot of $F_o^2 - F_c^2$ *versus* F_c^2(Ag model) – F_c^2(all-Rh model) for the 100 reflections with largest absolute values of F_c^2(Ag model) – F_c^2(all-Rh model). The plot includes points for both the Ag model (blue dots) and the all-Rh model (orange dots). Several reflections are very poorly 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**.

References

Chen, H., Olmstead, M. M. & Fish, R. H. (2024). *Acta Cryst.* C**80**, 254–257.

Chen, H., Olmstead, M. M., Maestre, M. F. & Fish, R. H. (1995). *J. Am. Chem. Soc.* **117**, 9097–9098.

Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst.* B**72**, 171–179.

Guay, F. & Beauchamp, A. L. (1979). *J. Am. Chem. Soc.* **101**, 6260–6263.

Raymond, K. N. & Girolami, G. S. (2023). *Acta Cryst.* C**79**, 445–455.

Sheldrick, G. M. (2015). *Acta Cryst.* C**71**, 3–8.

Smith, D. P., Chen, H., Ogo, S., Elduque, A. I., Eisenstein, M., Olmstead, M. M. & Fish, R. H. (2014). *Organometallics*, **33**, 2389–2404.

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

[3] Dr Olmstead died tragically in 2020.