

## Cis–trans isomerization in the syntheses of ruthenium cyclam complexes with nitric oxide

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### ABSTRACT

The *cis* to *trans* isomerizations during the syntheses of *trans*-[Ru(NO)(OH)(cyclam)](PF<sub>6</sub>)<sub>2</sub>, from *cis*-[RuCl<sub>2</sub>(cyclam)]Cl, and [Ru(NO)Cl(cyclam)](PF<sub>6</sub>)<sub>2</sub>, from *cis*-[RuCl<sub>2</sub>(dmso)<sub>4</sub>], are reported. The novel *trans*-[Ru(NO)(OH)(cyclam)](PF<sub>6</sub>)<sub>2</sub> complex was characterized by X-ray crystallography and vibrational infrared and nuclear magnetic resonance spectroscopies. The Ru–N–O bond angle (176.75°) and  $\nu(\text{NO})$  (1835 cm<sup>−1</sup>) suggest a nitrosonium character for this hydroxo complex. The crystal and molecular structure of *trans*-[Ru(NO)Cl(cyclam)](ClO<sub>4</sub>)<sub>2</sub>·2 H<sub>2</sub>O is also reported. Results presented here support the *cis*–*trans* isomerization observed for the first time with ruthenium cyclam complexes.

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Complexes of cyclam (1,4,8,11-tetraazacyclotetradecane) with several transition metals, such as Cr, Ni, Fe, Cu, Co, Mn, Rh, and Ru, have been reported [1–12]. The interest on these complexes and their analogous relies, at least in part, on the potential applications in fields such as catalysis, photochemistry, and medicine [2,12–21]. In general, metal complexes with cyclam adopt *cis* or *trans* configuration, and *cis* to *trans* isomerization has been reported for the first transition series with known examples for Fe, Cr, Mn, Ni and Co [4,7,22–25]. In solution, pH dependent *cis* to *trans*, as well as *trans* to *cis*, isomerization of [Ni(cyclam)(OH<sub>2</sub>)<sub>2</sub>]<sup>2+</sup> has been reported [22,23]. An increase in the *cis* to *trans* isomerization rate constant value (*k*<sub>obs</sub>) with the increase of pH has been observed for *cis*-[Ni(cyclam)(OH<sub>2</sub>)<sub>2</sub>]<sup>2+</sup> [23]. At pH 7, *cis*-[CrCl<sub>2</sub>(cyclam)]<sup>+</sup> and *cis*-[CoCl<sub>2</sub>(cyclam)]<sup>+</sup> hydrolyze to *cis*-[M(OH)(OH<sub>2</sub>)(cyclam)]<sup>2+</sup> (M = Cr or Co) that undergoes isomerization to the *trans* form [24,26]. For *cis*-[MnCl<sub>2</sub>(cyclam)]Cl, in addition to *cis* to *trans* isomerization, a less common *trans* to *cis* isomerization have been reported upon electrochemical reduction [25]. *cis*-[Ru(NO)X(pyca)<sub>2</sub>]<sup>n+</sup> (pyca = 2-pyridine carboxylate; X = Cl<sup>−</sup>, NO<sub>2</sub><sup>−</sup>, or H<sub>2</sub>O) complexes react with OH<sup>−</sup>, N<sub>3</sub><sup>−</sup>, and OCH<sub>3</sub><sup>−</sup> anions and undergo *cis*–*trans* isomerization upon reduction, without release of NO [27,28].

Although [Ru(cyclam)LL']<sup>n+</sup> complexes can be obtained by different synthetic routes, *cis* or *trans* [RuCl<sub>2</sub>(cyclam)]Cl are often used as the starting material [9,29]. The [Ru(mac)LL']<sup>n+</sup> (mac = tetraazamacrocyclic) complexes exhibit different properties that depend on the nature of the L ligands, the size of the macrocycle, and the configuration, *cis* or *trans* [9]. For instance, substitution reactions of the *cis* complexes are usually faster than those of the *trans* ones, especially after reduction of Ru<sup>III</sup> to Ru<sup>II</sup> [9]. For [RuCl<sub>2</sub>(cyclam)]<sup>n+</sup>, chloride aquation rates, in general, increase from Ru(III) to Ru(II) and from *trans* to *cis* complexes [9]. The reduction of the Ru(III) center is followed by fast aquation of both chloro ligands in the *cis* complex while loss of the second chloride in *trans*-[RuCl<sub>2</sub>(cyclam)] is too slow [9,30] to make the synthesis of *trans*-[Ru(cyclam)LL']<sup>n+</sup> feasible. Therefore, such properties have been explored to synthesize a wide variety of [Ru(cyclam)LL']<sup>n+</sup> complexes. For instance, the *cis*-[Ru(cyclam)LL']<sup>2+</sup> (LL' = bpy, phen, or py<sub>2</sub>) (bpy = 2,2'-bipyridine; phen = o-phenantroline; py = pyridine) complexes were prepared following the reduction of *cis*-[RuCl<sub>2</sub>(cyclam)]Cl with amalgamated zinc in neutral aqueous solution [29].

Because nitric oxide plays key roles in several biological processes that depend on its local concentration [31–33], development of controlled NO releasing pro-drugs has been subject of efforts. In this context, our group has been focused on the chemistry, photochemistry, and biological activity of ruthenium nitrosyl complexes [9,11,15–17,34] and also on the synthesis, chemical and photochemical properties of ruthenium complexes with cyclam and related

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ligands,  $[\text{Ru}(\text{mac})\text{LL}']^{n+}$  [9,12,16,19,34–36]. As far as we know, no *cis* to *trans* isomerization has been reported for ruthenium cyclam complexes. The *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})]^{2+}$  complex has been reported to have potential applications as a nitric oxide (NO) donor because it has low toxicity, is stable, water soluble, and releases NO only after reduction ( $k_{\text{NO}} = 6.1 \times 10^{-4} \text{ s}^{-1}$ ) or photochemically [16,34]. Thus, considering the outstanding properties of *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{PF}_6)_2$  and the biological importance of NO, and aiming potential biological applications, we decided to synthesize the analogous *cis*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})]^{2+}$  that is expected to release NO at a larger rate.

In this communication we report the *cis*–*trans* isomerizations observed during the syntheses of *trans*- $[\text{Ru}(\text{NO})(\text{OH})(\text{cyclam})](\text{PF}_6)_2$  (complex **I**) from *cis*- $[\text{RuCl}_2(\text{cyclam})]^+$  and *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{PF}_6)_2$  (complex **II**) from *cis*- $[\text{RuCl}_2(\text{dmsO})_4]$ , and the crystal and molecular structure of the novel complex **I**. Also reported is the crystal and molecular structure of *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{ClO}_4)_2 \cdot 2\text{H}_2\text{O}$  (complex **III**), grown from **II** in perchlorate solution. The orthorhombic complex **III** obtained from this new route, is basically the same as the monoclinic non-hydrated phase previously obtained by the synthesis through reaction of  $\text{K}_2[\text{RuNOCl}_5]$  with cyclam [34].

Complex **I** was prepared by reduction of *cis*- $[\text{RuCl}_2(\text{cyclam})]^+$  with amalgamated zinc in water/ethanol/chloroform (10:5:5 v/v) followed by reaction with nitrite and acidification (see supplementary information). After recrystallization of some amount of the complex, yellow crystals suitable for X-ray analysis were obtained. Complex **II** was prepared by modification of a previously described procedure for the synthesis of  $[\text{Ru}(\text{L}^{\text{py}})\text{NO}](\text{PF}_6)_3$ , ( $\text{L}^{\text{py}} = \text{N}$ -(2-methylpyridyl) cyclam) [37] in an one-pot reaction (see supplementary information). Elemental analysis, % calculated and (% found) for  $\text{C}_{10}\text{H}_{24}\text{N}_5\text{OClRuP}_2$ · $\text{F}_{12}$  (656 g mol<sup>−1</sup>): C = 18.29 (18.16); N = 10.67 (10.35); H = 3.68 (3.56). Crystals suitable for X-ray analysis were obtained when 20 mg of this complex was dissolved in minimum amount of HCl 0.1 mol L<sup>−1</sup> saturated with  $\text{LiClO}_4$ . During crystallization  $\text{PF}_6^-$  counter ions were exchanged by  $\text{ClO}_4^-$  yielding of *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{ClO}_4)_2 \cdot 2\text{H}_2\text{O}$  (**III**).

Because *cis*- $[\text{RuCl}_2(\text{cyclam})]\text{Cl}$  was synthesized from *cis*- $[\text{RuCl}_2(\text{dmsO})_4]$  that may undergo *cis*–*trans* isomerization, *trans*- $[\text{RuCl}_2(\text{cyclam})]\text{Cl}$  was also synthesized in order to check for the identity and purity of the *cis* complex. The UV–vis spectra and redox potentials of *cis*- $[\text{RuCl}_2(\text{cyclam})]\text{Cl}$ , as determined by cyclic voltammetry and differential pulse voltammetry match with reported values (see supplementary information, Figure S17), eliminating any possibility of contamination of the *cis* complex with some *trans*.

Fig. 1 is an ORTEP plot of **I**. Listing of atomic coordinates and equivalent isotropic displacement parameters, full intramolecular bond distances and angles, hydrogen coordinates, and anisotropic thermal parameters are available from the authors and were deposited at the Cambridge Crystallographic Data Centre, reference number CCDC 843698.

Bond distances and angles show that the molecular structure of **I** is similar to those of the closely related tetraazamacrocyclic complexes *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{ClO}_4)_2$  [34] and *trans*- $[\text{Ru}(\text{NO})(\text{OH})(\text{tmc})](\text{ClO}_4)_2$  ( $\text{tmc} = 1,5,9,13$ -tetramethyltetraazacyclohexadecane) [38]. The Ru atom is coordinated to the four N atoms of the cyclic amine and is placed essentially on the best least squares plane through them [at 0.092(2) Å]; one hydroxo and one nitrosyl groups complete the six coordination sites. The average Ru–N<sub>cyclam</sub> interatomic distance of the coordinated nitrogens in **I** (see table S12 in supplementary information) of 2.086 Å is close to the average interatomic distance exhibited by the closely related *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{ClO}_4)_2$  and *trans*- $[\text{RuCl}(\text{cyclam})(4\text{-acpy})](\text{BF}_4)$  (4-acpy = 4-acetylpyridine) that show average Ru–N<sub>cyclam</sub> interatomic distances of 2.092(4) Å and 2.097(2) Å, respectively, which are shorter than those shown by Ru(II) amines and close to those of Ru(III) complexes [9,34,35]. However, in *trans*- $[\text{RuCl}(\text{cyclam})(4\text{-acpy})](\text{BF}_4)$ , the shortening of

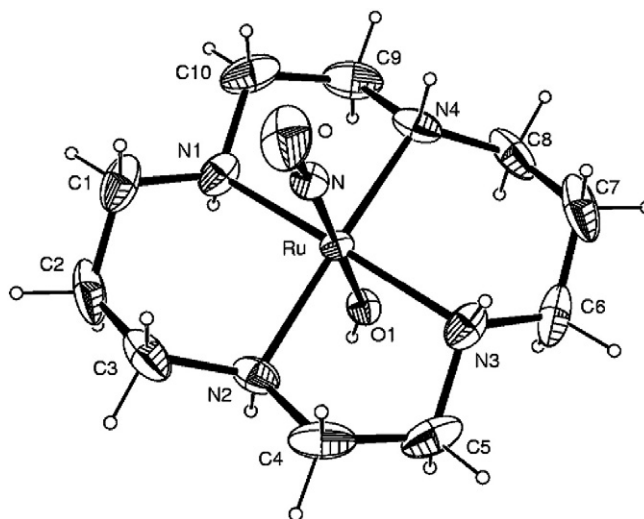


Fig. 1. ORTEP plot of the complex with anisotropic displacement ellipsoids shown to 20% probability. The two  $\text{PF}_6^-$  anions were not included for clarity. Selected bond lengths [Å] and angles [°] are as follows: Ru–N, 1.771(5); Ru–O, 1.935(4); O–N, 1.081(7); O(1)–H, 0.887(4); Ru–N(1), 2.080(5); Ru–N(2), 2.069(5); Ru–N(3), 2.094(5); Ru–N(4), 2.099(5); O–N–Ru, 176.7(5); Ru–O(1)–H, 158.3(4); N–Ru–O(1), 179.67(18); N–Ru–N(2), 91.5(2); O(1)–Ru–N(2), 88.8(2); N–Ru–N(1), 90.9(2); O(1)–Ru–N(1), 88.8(2); N(2)–Ru–N(1), 96.3(3); N–Ru–N(3), 94.1(2); O(1)–Ru–N(3), 86.1(2); N(2)–Ru–N(3), 83.8(3); N(1)–Ru–N(3), 174.9(2); N–Ru–N(4), 93.6(2); O(1)–Ru–N(4), 86.2(2); N(2)–Ru–N(4), 174.96(19); N(1)–Ru–N(4), 83.4(3); N(3)–Ru–N(4), 96.1(3).

Ru–N<sub>cyclam</sub> bond was attributed to annular constraint imparted by the rigidity of the macrocycle what would also be expected to occur for *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{ClO}_4)_2$  (average Ru–N<sub>cyclam</sub> interatomic distance of 2.092 Å), and, similarly, for *trans*- $[\text{Ru}(\text{NO})(\text{OH})(\text{cyclam})](\text{PF}_6)_2$ . The Ru–OH distance (1.935 Å) of **I** is very close to that of *trans*- $[\text{Ru}(\text{NO})(\text{OH})(\text{NH}_3)_4]\text{Cl}_2$  (1.961 Å) [39], while the Ru–NO distance (1.771 Å) falls in the range of other ruthenium nitrosyl amines [9,40]. The OH and NO ligands are in the same axis; the N–Ru–OH angle is 179.67° and the O–N–Ru angle is 176.75°. This last angle suggests a nitrosonium character for NO.

At variance with the monoclinic non-hydrated phase previously obtained by the synthesis through reaction of  $\text{K}_2[\text{RuNOCl}_5]$  with cyclam [34], complex **III** crystallizes in the orthorhombic space group, Pnma, with the complex sited on a crystallographic symmetry plane which contains the Cl–Ru–NO line (see Figure S11, Table S13 and Table S14, supplementary information). Also, there are two  $\text{H}_2\text{O}$  molecules in the crystal lattice, whereas crystals of *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{ClO}_4)_2$  are monoclinic, space group, P21/c, and the complex is located on a general position. Crystallographic data for complex **III** have been deposited at the Cambridge Crystallographic Data Centre, reference number CCDC 843636.

The infrared absorption spectrum of mono crystals of **I** (see Fig. S12, supplementary information) shows band characteristic of the macrocycle, the  $\text{PF}_6^-$  stretching band at 839 cm<sup>−1</sup>, and the  $\nu_{\text{NO}}$  band at 1830 cm<sup>−1</sup>, in the range generally associated with nitrosyl metal complexes and consistent with a nitrosonium character and the linearity of the RuNO moiety [9,40,41]. For *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{ClO}_4)_2$ , the  $\nu_{\text{NO}}$  band appears at 1875 cm<sup>−1</sup>, [9,34] so, there is a consistent shift of this frequency to lower energy for the hydroxo complex. This is similar to what occurs for *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{NH}_3)_4]\text{Cl}_2$  and *trans*- $[\text{Ru}(\text{NO})(\text{OH})(\text{NH}_3)_4]\text{X}_2$ ; for the chloro complex the  $\nu_{\text{NO}}$  band appear at 1878 cm<sup>−1</sup> [42] and for the OH complexes, it appears at 1855, 1850, and 1845 cm<sup>−1</sup>, for X = Cl, Br, and I, respectively [42].

The assignment of the NMR spectra was done by comparing the <sup>1</sup>H and <sup>13</sup>C chemical shift ( $\delta$ ) values of the spectra of complex **I** to those of related species [34,35] and mainly on the correlations observed in the 2D spectra (<sup>1</sup>H–<sup>1</sup>H COSY, <sup>1</sup>H–<sup>13</sup>C HMQC –  $J^1$ – $J^1$  coupling,

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