Reactivity, photolability, and computational studies of the ruthenium nitrosyl complex with a substituted cyclam *fac*-[Ru(NO)Cl₂(κ³N⁴,N⁸,N¹¹(1-carboxypropyl)cyclam)]Cl·H₂O†

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Received 5th November 2010, Accepted 4th April 2011

DOI: 10.1039/c0dt01541e

Chemical reactivity, photolability, and computational studies of the ruthenium nitrosyl complex with a substituted cyclam, *fac*-[Ru(NO)Cl₂(κ³N⁴,N⁸,N¹¹(1-carboxypropyl)cyclam)]Cl·H₂O ((1-carboxypropyl)cyclam = 3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionic acid), (**I**) are described. Chloride ligands do not undergo aquation reactions (at 25 °C, pH 3). The rate of nitric oxide (NO) dissociation ($k_{\text{obs-NO}}$) upon reduction of **I** is 2.8 s⁻¹ at 25 ± 1 °C (in 0.5 mol L⁻¹ HCl), which is close to the highest value found for related complexes. The uncoordinated carboxyl of **I** has a pK_a of ~3.3, which is close to that of the carboxyl of the non coordinated (1-carboxypropyl)cyclam (pK_a = 3.4). Two additional pK_a values were found for **I** at ~8.0 and ~11.5. Upon electrochemical reduction or under irradiation with light (λ_{irr} = 350 or 520 nm; pH 7.4), **I** releases NO in aqueous solution. The cyclam ring N bound to the carboxypropyl group is not coordinated, resulting in a *fac* configuration that affects the properties and chemical reactivities of **I**, especially as NO donor, compared with analogous *trans* complexes. Among the computational models tested, the B3LYP/ECP28MDF, cc-pVDZ resulted in smaller errors for the geometry of **I**. The computational data helped clarify the experimental acid-base equilibria and indicated the most favourable site for the second deprotonation, which follows that of the carboxyl group. Furthermore, it showed that by changing the pH it is possible to modulate the electron density of **I** with deprotonation. The calculated NO bond length and the Ru/NO charge ratio indicated that the predominant canonical structure is [Ru^{III}NO], but the Ru–NO bond angles and bond index (b.i.) values were less clear; the angles suggested that [Ru^{II}NO⁺] could contribute to the electronic structure of **I** and b.i. values indicated a contribution from [Ru^{IV}NO⁻]. Considering that some experimental data are consistent with a [Ru^{II}NO⁺] description, while others are in agreement with [Ru^{III}NO], the best description for **I** would be a linear combination of the three canonical forms, with a higher weight for [Ru^{II}NO⁺] and [Ru^{III}NO].

Introduction

Efforts from our Laboratory have been directed towards the design and study of ruthenium nitrosyl complexes as nitric oxide

(NO) donors, aiming at biological applications in solution or in matrices.^{1–4} Complexes with the equatorial positions occupied by four amines or aliphatic tetraazamacrocyclic ligands, such as cyclam (1,4,8,11-tetraazacyclotetradecane) and related species have been studied.^{1–13} Compared with the tetraammines, tetraazamacrocyclics impart some differences, such as restriction of substitution reactions to the other ligands because of the inertness of the macrocycle.^{1,5,9,12,14} Significant advances have been achieved in tailoring the NO reactivity for Ru nitrosyl tetraammines, and they have been used as metallopharmaceutical NO pro-drugs^{4,6,11,15–23} In *trans*-[Ru(NO)(NH₃)₄(L)]²⁺ complexes, the judicious choice of the ligand L *trans* to NO may allow for control of the {RuNO}^{6/7} redox potentials, rates of NO release (k_{NO}) after reduction, and electrophilicity of the nitrosyl ligand.^{2,4} For instance, k_{NO} values for L = py (pyridine), P(OEt)₃ (triethylphosphite) or imC (carbon-bound imidazole) are 0.06, 0.98, and 5.1 s⁻¹, respectively. However, when the four ammonias are replaced by cyclam, as in

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† Electronic supplementary information (ESI) available: See DOI: 10.1039/c0dt01541e

trans-[Ru(NO)Cl(cyclam)](PF₆)₂, the rate of NO release has been found to be $6.1 \times 10^{-4} \text{ s}^{-1}$.^{1,2,6} Appending functional groups to N (or C) atoms in the cyclam ring could lead to strategic tuning of the reactivity of tetraazamacrocyclic ruthenium nitrosyl complexes.^{7,8} In addition, these functional groups could provide a linking unit to matrices or molecules of biological importance, which selectively target NO release.

Recently, the synthesis and characterisation of the *fac*-[Ru(NO)Cl₂(κ³N⁴,N⁸,N¹¹(1-carboxypropyl)cyclam)]Cl·H₂O complex ((1-carboxypropyl)cyclam = 3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionic acid) (**I**) has been reported⁷ (Fig. 1). The *fac* configuration was observed in contrast to the expected *trans* arrangement as a result of the κ³ denticity adopted by the mono-N-substituted 1-(carboxypropyl)cyclam ligand.⁷ The cyclam N atom that is bound to the carboxypropyl group remained uncoordinated. In its infrared absorption spectrum, this complex displayed a stretching absorption peak, ν(NO), at 1881 cm⁻¹ and the Ru–N interatomic distance and bond angle for the [RuNO] core of 1.739(2) Å and 167.7(2)°, respectively. Unlike **I**, a majority of cyclam and related complexes generally adopt a *cis* or *trans* configuration with the four cyclam N atoms coordinated to the metal centre.^{1,5,6,8–11,13,14,24–27} These *cis* or *trans* configurations depend on the size of the macrocycle and on the oxidation state of metal,^{1,14,25,27} which can greatly influence their chemical properties.^{1,13,14,25} Besides the influences exerted on the configuration of the complexes, macrocycle size and Ru oxidation state have important roles in the reactivity of the complexes. For instance, while Ru(III) cyclam dichloro complexes are remarkably inert towards ligand substitution, Ru(II) analogous complexes are relatively labile.^{1,14} The inertness of the chloro ligand of Ru(II) cyclam complexes compared with the analogous tetraamine complexes has been attributed to intramolecular Cl⋯H–N interactions.^{1,5,14} Cyclam N-substitution has increased chloride lability by weakening these interactions (mono-N-substitution), as in 1-(3-propylammonium)cyclam,¹⁰ or by eliminating them (tetrasubstitution), as in 1,4,8,11-tetramethylcyclam (14-TMC).¹

Ruthenium nitrosyl ammine and aliphatic tetraazamacrocyclic complexes act as potential NO delivery agents because they release NO upon reduction or under irradiation with light.^{1,2,8,11,28,29} These complexes also have a very rich potential as NO delivery agents

in biological systems.^{4,6,11,15,17–23,28} NO is involved in a remarkably diverse range of physiological and pathophysiological processes.³⁰ NO is known to act as biological messenger responsible for vasodilation, to inhibit platelet aggregation, to play a role in immune response, and to act as a neurotransmitter.^{30–32} Studies have also shown that NO could be involved in cell apoptosis and tumor kills.^{33,34} Thus, compounds that have the ability to release NO are of great interest.

Some authors have presented theoretical results for ruthenium nitrosyl complexes. Ford *et al.*,³⁵ in a theoretical and experimental work, performed geometrical and vibrational frequencies calculations for dinitrosyl ruthenium porphyrin complexes. The calculations allowed the most stable conformation to be determined and to solve and verify some ambiguities in the experimental IR spectra. In a series of papers, Sizova and collaborators studied different aspects of the electronic structure of Ru–NO complexes. In a valence bond (VB) analysis, the authors concluded that the complexes in question could be represented by [Ru^{III}NO].³⁶ The electronic structure of some complexes containing the Ru–NO group was investigated by energy decomposition analysis (EDA) and by the analysis of Wiberg and Mayer bond orders. The linear Ru–NO bond was found to be predominantly covalent and Ru–N had a high π character, as suggested by the EDA.³⁷ The analysis of bond orders indicated a significant degree of π electron delocalisation over the Ru–NO group.³⁸ Caramori and Frenking studied some Ru^{II}–NO complexes by EDA and concluded that the orbital term and the Pauli repulsion were responsible for the weakening or strengthening of Ru–NO bond.³⁹ Rose and Mascharak performed DFT and TD-DFT calculations to explain the photosensitisation of the ruthenium nitrosyl group by chromophores. The calculations provided insights into the mechanism of the energy transfer from the dye fragments to the Ru–NO group.⁴⁰ Recently, a theoretical and experimental study was performed on [Ru(trpy)(tmp)(NO)]ⁿ⁺ (trpy = 2,2':6',2''-terpyridine, tmp = 3,4,7,8-tetramethyl-1,10-phenanthroline) in the {RuNO}⁶ and {RuNO}⁷ forms, which included electronic spectra.⁴¹ Among the canonical structures formerly proposed by Enemark and Feltham for {RuNO}ⁿ cores,⁴² the calculations indicated that the main resonance structures of these complexes were [Ru^{II}NO⁺] and [Ru^{III}NO], respectively, with some contribution

Fig. 1 Structures of *fac*-[Ru(NO)Cl₂(κ³N⁴,N⁸,N¹¹(1-carboxypropyl)cyclam)]⁺ (**I**) and of the other six species studied.

of $[\text{Ru}^{\text{I}}\text{NO}^+]$ for $\{\text{RuNO}\}^7$. A sizable $(d_\pi)\text{Ru}(\text{II}) \rightarrow \pi^*(\text{NO}^+)$ back donation was observed for the $\{\text{RuNO}\}^6$ complex.⁴¹ Several other studies also explored the UV-Vis spectra by computational methods. Gorelsky and Lever concluded by TD-DFT calculations that the spectra of some RuNO complexes were dominated by metal to ligand charge transfer bands.⁴³ Lever *et al.* studied the electronic structure and the electronic spectra of some Ru-NO complexes and obtained several correlations for the ground state and spectroscopic parameters.⁴⁴ The photochemistry of some $\{\text{RuNO}\}^6$ complexes was studied and the theoretical calculations helped to explain the unusual photochemical behaviour of *trans*- $[(\text{NC})\text{Ru}(\text{py})_4(\mu\text{-CN})\text{Ru}(\text{py})_4(\text{NO})]^{3+}$.⁴⁵

Herein, the chemical reactivity, photolability, and computational studies of the *fac*- $[\text{Ru}(\text{NO})\text{Cl}_2(\kappa^3\text{N}^4, \text{N}^8, \text{N}^{11}(1\text{-carboxypropyl})\text{cyclam})]\text{Cl}\cdot\text{H}_2\text{O}$ (**I**) are reported. The unusual *fac* configuration influenced its chemical properties compared to analogous complexes with a *trans* configuration. In addition to these substantial differences, complex **I** could also act as a potential NO donor after electrochemical reduction or by irradiation with light. Computational studies were performed to investigate the electronic structure of **I** and to complement experimental data for the acid-base equilibria. Calculations included six deprotonated species (Fig. 1). The theoretical results indicated the preferred site for the second deprotonated species and the changes in the molecular and electronic structure that occur with deprotonation.

Results and discussion

Chemical reactivity

The $\text{p}K_{\text{a}}$ of the carboxyl group of (1-carboxypropyl)cyclam tetrahydrochloride was determined by potentiometric titration as being equal to 3.4 ± 0.1 , which is close to the reported value of 3.6.⁴⁶ Under similar conditions, titrations of **I** were performed (Fig. SI 1†), which allowed one to calculate two $\text{p}K_{\text{a}}$ values, $\text{p}K_{\text{a}1} = 3.3 \pm 0.1$ and $\text{p}K_{\text{a}2} = 8.5 \pm 0.1$. For each inflection point, one acidic hydrogen was titrated according to consumed equivalents of base.

The $\text{p}K_{\text{a}1}$ value of 3.3 is close to the value determined for (1-carboxypropyl)cyclam tetrahydrochloride dihydrate (3.4) under the same conditions and may be attributed to the deprotonation of the carboxyl group. Because the N cyclam atom holding the carboxypropyl pendant group is not coordinated to the Ru atom in **I**, possible inductive effects from the metal centre to the carboxyl group are minimised, thus resulting in similar $\text{p}K_{\text{a}}$ values, as observed. In addition, the first deprotonation being that of the carboxyl group is consistent with theoretical calculations (see ahead). The $\text{p}K_{\text{a}2} = 8.5$ is probably due to the deprotonation of one N-H group of the cyclam ring. This value is consistently lower than those reported for the free ligand (1-carboxypropyl)cyclam⁴⁶ (10.11 and 11.45). The inductive effects of the $\{\text{RuNO}\}^6$ core on the hydrogen of the amine group could have led to the increase in acidity observed. In addition, this result is close to the value obtained for the first N-H deprotonation in the $\text{Ru}(\text{III})$ complex *trans*- $[\text{RuCl}_2(\text{cyclam})]^+$ ($\text{p}K_{\text{a}} \approx 7.9$),²⁶ which is also lower than those reported for the free cyclam ligand (10.6 and 11.6).⁴⁷ The similarity between the $\text{p}K_{\text{a}2}$ of **I** and that of *trans*- $[\text{RuCl}_2(\text{cyclam})]^+$ suggests that, following Enermark and Feltham's⁴² formalism, the canonical structure for the $\{\text{RuNO}\}^6$ core with a higher weight for

this nitrosyl complex is $[\text{Ru}^{\text{III}}\text{NO}]$, while the others are $[\text{Ru}^{\text{II}}\text{NO}^+]$ and $[\text{Ru}^{\text{IV}}\text{NO}^-]$. These findings are consistent with the fact that the $\text{p}K_{\text{a}}$ values of the coordinated water in ruthenium nitrosyls, such as *trans*- $[\text{Ru}(\text{NO})(\text{NH}_3)_4(\text{OH}_2)]^{3+}$ and *trans*- $[\text{Ru}(\text{NO})(\text{salen})(\text{OH}_2)]^+$, are close to those reported for $\text{Ru}(\text{III})$ analogues.^{48,49}

The reactivity of **I** towards OH^- in aqueous solution was investigated at various pH values by means of differential pulse voltammetry (Fig. 2).

Fig. 2 Differential pulse voltammetry of **I** at different pH values. Initial complex concentration: $1 \times 10^{-3} \text{ mol L}^{-1}$ (initial pH ~ 1 , $\mu = 0.5 \text{ mol L}^{-1}$ KCl).

As can be seen in Fig. 2, the cathodic wave shifts to more negative potentials with increasing pH. It was possible to estimate the $\text{p}K_{\text{a}}$ values from Fig. 2 to be ~ 8.0 ($\text{p}K_{\text{a}2}$) and ~ 11.5 ($\text{p}K_{\text{a}3}$). The $\text{p}K_{\text{a}2}$ value is close to the value determined by potentiometric titrations (8.5) and even closer to that observed for the first N-H deprotonation in *trans*- $[\text{RuCl}_2(\text{cyclam})]^+$ ($\text{p}K_{\text{a}} \approx 7.9$).²⁶ The shift of the cathodic peak to more negative potentials, which was detected with rising pH, indicates that $\text{p}K_{\text{a}3}$ (≈ 11.5) might have resulted from the nucleophilic attack of OH^- on **I**. Earlier observations^{2,50,51} demonstrated that ruthenium nitrosyl tetraammine complexes can undergo nucleophilic attack by OH^- , which could result in the respective nitro ($\text{Ru}^{\text{II}}\text{-NO}_2^-$) complex. This behaviour was attributed to the nitrosonium character of the NO ligand in such complexes.^{2,51} The NO infrared stretching frequency, $\nu(\text{NO})$, of **I** (1881 cm^{-1}) was consistent with the $[\text{Ru}^{\text{II}}\text{NO}^+]$ canonical form, but the linearity of the Ru-N-O bond angle was slightly off ($167.7(2)^\circ$),⁷ which suggested some contribution from the $[\text{Ru}^{\text{III}}\text{NO}]$ canonical form.

That equilibrium (see Scheme 1 below) can occur as a two-step process beginning with the OH^- addition to the nitrosyl complex followed by an additional attack by a second OH^- .⁵¹ The presence of three species as products of the equilibrium reactions with OH^- is supported by the observed reversibility. After the solution reached pH ~ 12 , the pH was carefully and slowly decreased by addition of HCl solution. The cathodic waves reappeared at the same potentials. In addition, when **I** was dissolved in solutions with pH previously adjusted to 1.0, 9.5, and 12.0, only one cathodic wave was observed in each case and at the same potentials reported above. Accordingly, the following equilibria can be proposed (Scheme 1).

Scheme 1 Proposed acid-base equilibria for **I**.

The lability of the chloro ligands coordinated to the Ru atom in **I** was investigated by direct potentiometry using a chloride selective electrode. When a freshly prepared 2.5×10^{-4} mol L⁻¹ solution of **I** ($\mu = 0.1$ mol L⁻¹ KNO₃, pH 3) at 25 ± 1 °C was analysed, the chloride concentration was determined to be $2.2 \pm 0.2 \times 10^{-4}$ mol L⁻¹, which was consistent with the presence of one counter-ion, as expected. The measured current remained essentially the same even after 2 h. Furthermore, aqueous solutions of **I** analysed by UV-Vis spectroscopy for 9 h did not present any spectral change that would indicate chloride aquation. Inertness of the ligand in an aqueous solution at room temperature was confirmed by electrospray ionisation mass spectrometry (ESI-MS). When a three-day-old solution of **I** was analysed by ESI-MS, the spectrum showed a cluster of isotopologues in the same m/z range of 468.2 to 480.2 as was observed earlier for freshly prepared solutions,⁷ which characterised a species containing a single Ru and two Cl atoms. The isotopic pattern was therefore consistent with a C₁₃H₂₈O₃N₅RuCl₂ composition⁷ and provided further support to the inertness of the chloro ligands with regards to the substitution.

The substitution inertness of chloro ligands in ruthenium ammine complexes is dependent on their configuration (*cis* or *trans*) and the metal oxidation state (Ru(II) or Ru(III)).¹ Generally, aquation rates increase from Ru(III) to Ru(II) and from *trans* to *cis* complexes.¹ For instance, in tetraammine Ru complexes, such as [RuCl(NH₃)₅]Cl₂ ($k_{\text{Cl}} = 3.1 \times 10^{-6}$ s⁻¹ at 25 °C)⁵² and *trans*-[RuCl₂(NH₃)₄]Cl ($k_{\text{Cl}} = 1.7 \times 10^{-6}$ s⁻¹ at 25 °C), the chloro ligands have been found to be inert towards aquation reactions, while in complexes such as *trans*-[RuCl₂(NH₃)₄] ($k_{\text{obs}} = 0.9$ s⁻¹ at 25 °C) and *cis*-[RuCl₂(NH₃)₄] ($k_{\text{obs}} \sim 32$ s⁻¹ at 25 °C),⁵³ the chloro ligands are labile. However, it has been reported that in ruthenium complexes with aliphatic tetraazamacrocyclic ligands, the same lability is not observed. For example, in *trans*-[RuCl₂(cyclam)]⁺ no aquation reaction was observed within 24 h. For *cis*-[RuCl₂(cyclen)]⁺ (cyclen = 1,4,7,10-tetraazacyclododecane), the observed aquation reaction rate, k_{obs} , was 3.6×10^{-3} s⁻¹ at 25 °C. Ru(II) centers, however, have increased chloro lability, as in *trans*-[RuCl₂(cyclam)] ($k_{\text{obs}} = 0.036$ s⁻¹ at 25 °C),¹ but they are still considered inert compared to analogous ammine complexes. The inertness of the chloro ligands towards substitution in ruthenium cyclam complexes such as *trans*-[RuCl(cyclam)(4-acpy)](BF₄),⁵ *trans*-[Ru(NO)Cl(cyclam)](ClO₄)₂,⁶ and *trans*-[RuCl₂(cyclam)]Br¹⁴ was attributed to interactions between Cl and H–N. These complexes have Cl...H–N interatomic distances of 2.70 Å, 2.43 Å and 2.71 Å, respectively, which are smaller than the sum of the van der Waals radii for H and Cl (3.0–3.3 Å). The intramolecular distances Cl...H–N of 2.652 Å and 3.150 Å in **I**⁷ suggested that similar inertness was expected. Although the distance of 3.150 Å is large,

it is still within the range of the van der Waals radii. The absence of chloro labilization at room temperature in **I** suggests that Cl...H–N intramolecular interatomic distances are short enough to make the chloro ligands inert towards aquation reactions. However, an increase in the temperature to 40 ± 1 °C under the same conditions resulted in one chloro ligand aquation with $k_{\text{obs}} = 5.6 \pm 0.3 \times 10^{-5}$ s⁻¹ and $t_{1/2} = 1.2 \times 10^4$ s⁻¹. It seems reasonable to assume that the aquation reaction more likely proceeds on the Cl⁻ ligand that has the Cl...H–N interatomic distance of 3.150 Å. Although the aquation rate constant was obtained at 40 °C, these results indicated that the inertness of the chloro ligand in **I** is similar to that observed for Ru(III) complexes such as *trans*-[RuCl₂(NH₃)₄]Cl ($k_{\text{obs}} = 1.7 \times 10^{-6}$ s⁻¹ at 25 °C) and *trans*-[RuCl₂(1-(3-propylammonium)cyclam)]⁺ ($k_{\text{obs}} = 8.2 \times 10^{-5}$ s⁻¹ at 25 °C)¹⁰ that also contains a mono-N-substituted cyclam ligand. In the latter complex, the chloro aquation rate is larger than that for *trans*-[RuCl₂(cyclam)]Cl, which is consistent with the weakening of one hydrogen-bonding interaction due to N-substitution.

The chloro aquation was also investigated after one electron reduction by bulk controlled potential electrolysis and chemical reduction with an Eu²⁺ solution. A fast aquation of two chloride ligands was observed in both cases. Because of the experimental conditions used in the reduction, it was not possible to obtain aquation rate constants for these reactions.

Electrochemistry

Redox potentials (*vs.* Ag/AgCl) for **I** and some selected ruthenium nitrosyl tetraazamacrocyclic complexes are displayed in Table 1.

The cyclic voltammogram of **I** in the same medium where the crystals were grown (0.5 mol L⁻¹ HCl) displayed one cathodic peak at -0.39 V (1c) and one anodic peak near -0.16 V (2a) in the range of +0.8 to -0.8 V (*vs.* Ag/AgCl) (Fig. 3). In this medium, this behaviour remained unchanged with scan rates from 0.01 up to 1 V s⁻¹ and in the temperature range of 4 to 25 °C. The E_{pc} for **I** is close to those observed for the analogous complexes, which was attributed to the {RuNO}^{6/7} core reduction (Table 1). The {RuNO}^{6/7} process for *trans*-[Ru(NO)Cl(cyclam)]²⁺ and *trans*-[Ru(NO)Cl(1-(3-propylammonium)cyclam)]³⁺ was reversible in the presence of

Fig. 3 Cyclic voltammogram of **I** in 0.5 mol L⁻¹ HCl at 25 °C and scan rate of 25 mV s⁻¹.

Table 1 {RuNO}^{6/7} reduction potentials of some ruthenium nitrosyl complexes with cyclam and related ligands

Complex	E_{pc} (V) ^a	Ref.
<i>trans</i> -[Ru(NO)Cl(cyclam)] ²⁺ ^b	-0.37	6
<i>trans</i> -[Ru(NO)Cl(1-(3-propylammonium)cyclam)] ³⁺ ^c	-0.34	10
<i>trans</i> -[Ru(NO)Cl(15aneN ₄)] ²⁺ ^d	-0.28	28
<i>fac</i> -[Ru(NO)Cl ₂ (κ ³ N ⁴ ,N ⁸ ,N ¹¹ (1-carboxypropyl)cyclam)] ⁺ ^e	-0.39	this work

^a vs. Ag/AgCl. ^b in 0.1 mol L⁻¹ LiCl solution. ^c in 1.0 mol L⁻¹ HCl solution. ^d in 1.0 mol L⁻¹ CF₃SO₃H solution. ^e in 0.5 mol L⁻¹ HCl solution.

excess chloride, so the cyclic voltammogram (CV) displays both the corresponding cathodic and anodic peaks.^{6,8} The one electron reduction of these two latter complexes was followed by fast chloro aquation in the absence of chloride ions in solution.^{1,6,8} The absence of the corresponding anodic peak (1a) for the reduction wave (1c) in the cyclic voltammograms of **I** (Fig. 3) suggests that NO labilisation is faster compared to the analogous complexes with cyclam and 1-(3-propylammonium)cyclam ligands. The NO release from **I** is supported by *in situ* electrochemical NO detection when its 0.5 mol L⁻¹ HCl solution was submitted to controlled potential electrolysis at -0.5 V.

The monoelectronic reduction assigned to the {RuNO}⁶ core in ruthenium ammine nitrosyl complexes results in NO dissociation whose specific rate constants (k_{NO}) depend on the equatorial and axial ligands. For instance, in *trans*-[Ru(NO)(NH₃)₄(L)]ⁿ⁺ (L = nitrogen heterocyclic bases) the k_{NO} values depend on the L-ligand in the *trans* position to NO and span a range of 5.1 s⁻¹ (L = C-bound imidazole) to 0.02 s⁻¹ (L = 4-picoline).² However, for *trans*-[Ru(NO)(OH₂)(cyclam)]³⁺ it was found to be much lower ($k_{NO} = 6.1 \times 10^{-4}$ s⁻¹).^{2,6} The rate of NO dissociation in **I** was investigated by cyclic voltammetry using platinum microelectrode and was estimated to be $k_{obs-NO} = 2.8$ s⁻¹ at 25 ± 1 °C (in 0.5 mol L⁻¹ HCl aqueous solution), which is close to the highest specific rate constant of NO release observed for *trans*-[Ru(NO)(NH₃)₄(L)]ⁿ⁺, and approximately four orders of magnitude larger than that observed for *trans*-[Ru(NO)(H₂O)(cyclam)]³⁺. However, due to the high complexity of the electrode reactions (see below), it is difficult to provide an appropriate parallel with k_{NO} values such as those determined for *trans*-[Ru(NO)(H₂O)(cyclam)]³⁺ and *trans*-[Ru(NO)(NH₃)₄(L)]ⁿ⁺ complexes.

The electrode reactivity for **I** in aqueous solution is more complicated than that observed for analogous complexes, like *trans*-[Ru(NO)Cl(cyclam)]²⁺, because it is possible to assume that both chloro ligands and NO can undergo aquation reactions after {RuNO}⁶ reduction and probably at different rates. The anodic peak (2a) observed in the cyclic voltammograms of **I** is highly dependent on conditions of analysis such as pH, chloride concentration, scan rate, and temperature, while the cathodic peak essentially remains at the same potential (Fig. 4). At pH values of 1.0 (below pK_{a1} (carboxypropyl group)) and 4.7 the CV profile is essentially the same as the one observed in 0.5 mol L⁻¹ HCl (Fig. 3), but with the anodic peak (2a), which appears at -0.16 V at 0.5 mol L⁻¹ HCl, broadened and shifted to around -0.24 V. The cathodic (1c) and anodic (2a) peaks do not seem to correspond to the same redox process, because $\Delta E > \sim 110$ mV and $I_{pa}/I_{pc} \sim 0.5$. Peak 2a is better resolved with scan rates of 20 mV s⁻¹ at pH 4.7 and [Cl⁻] of 0 and 0.1 mol L⁻¹ at 25 °C and in the absence of chloride at 4 °C. At pH 4.7, where the carboxypropyl group is deprotonated and, thus, able to bind to Ru, the influence of

Fig. 4 Cyclic voltammograms in aqueous solution for **I** at 25 °C and scan rate of 20 mV s⁻¹ unless otherwise stated. Curve (A) was obtained at: (i) pH 4.7, [Cl⁻] = 0.1 mol L⁻¹. Profile same as A was also obtained in the following conditions: (ii) pH 4.7, [Cl⁻] = 0 mol L⁻¹, or (iii) pH 4.7, [Cl⁻] = 0 mol L⁻¹, at 4 °C. Curve (B) was obtained at (iv) pH 1, [Cl⁻] = 0.1 mol L⁻¹. Profile same as B was obtained in the following conditions: (v) pH 1, [Cl⁻] = 0 or 4.0 mol L⁻¹, (vi) pH 4.7, [Cl⁻] = 4.0 mol L⁻¹, (vii) pH 4.7, [Cl⁻] = 0.1 mol L⁻¹, scan rates > 100 mV s⁻¹; (viii) pH 4.7, [Cl⁻] = 0.1 mol L⁻¹, at 4 °C.

[Cl⁻], scan rate, and temperature was also investigated. Comparing the conditions (i) and (ii) to (vi) it is possible to infer that [Cl⁻] influences only in large excess. Peak 2a is better resolved at lower scan rates (comparison of conditions (i) and (vii)) and at 25 °C, a borderline situation appears at 4 °C where the better resolved peak in the absence of chloride is broadened with a [Cl⁻] of just 0.1 mol L⁻¹. Among the several possible reactions after labilisation of at least one of the ligands (Cl or NO). In the presence of a large excess of chloride ions, in which the anodic peak (2a) is also broadened and poorly resolved (condition (vi), Fig. 4), the equilibrium of the aquation reaction after NO release should be shifted towards the chloro complex; thus, the proposed carboxyl coordination would be unfavorable. Therefore, the CV would be similar to those obtained at pH 1, as observed. Because the proposed coordination of carboxyl group must be preceded by the labilisation of chloro (or NO) ligand, one would expect that the scan rate and temperature would affect this step. If the cyclic voltammograms are recorded with scan rates of 100 mV s⁻¹ or more (or the temperature is lowered to 4 °C) (conditions (vii) and (viii), respectively, Fig. 4) the anodic wave (2a), which was well resolved at scan rate of 20 mV s⁻¹ and $T = 25$ °C, should become poorly resolved (Fig SI 2 and 3†), as observed. Thus, these findings support the hypothesis of a coupled reaction in

the reduction process, possibly the ligand labilisation followed by carboxylate coordination. This type of coordination has been reported for Ni and Cu complexes with cyclam ligands bearing amino or carboxyl pendant arms, and it depends on pH, resulting in differences in spectroscopic and electrochemical properties.^{54–56} Although the idea of the coordination of the carboxyl substituent seems reasonable, it is still necessary to identify which ligand is being replaced, Cl[−] or NO. A possibility can be drawn from the comparison of cyclic voltammograms at 4 °C in 0.1 mol L^{−1} NaNO₃ and NaCl (pH 4.7, scan rate 20 mV s^{−1}) (Fig SI 4†). At this temperature, the concentration of 0.1 mol L^{−1} chloride ions seems to be sufficient to shift the equilibrium towards the chloro complex, thereby inhibiting the proposed coordination of the carboxyl group. Thus, it was more likely that at least one of the chloro ligands was labilised faster than the nitrosyl ligand after the electrochemical reduction and the vacant position being possibly occupied by the carboxyl group.

Photolability

Ruthenium nitrosyl complexes with macrocyclic ligands (*trans*-[Ru(NO)Cl(mac)]²⁺) (mac = tetraazamacrocyle), such as cyclam and 1,4,8,12-tetraazacyclopentadecane (15aneN4), have been

shown to release NO when irradiated with light of 314, 334, and 355 nm^{1,2,8,11,28,57} like other ruthenium nitrosyl ammine complexes, such as *trans*-[Ru(NO)(NH₃)₄(L)]³⁺ (L = nitrogen heterocyclic bases).^{2,29,49,57} Irradiation of the former complexes led to the corresponding aquo (or hydroxo, depending on the pH) Ru(III) complex and NO (Eqn. 1), without chloride aquation.¹

Investigations on the photolabilisation of NO from **I** in phosphate buffer solution (pH 7.4) were performed under irradiation with light at 350 and 520 nm in the presence of the NO scavenger myoglobin⁵⁸ Mb(III) (Fig. 5). Direct reactions of NO with iron metalloproteins, such as Mb(III) and the related haemoglobin and cytochrome C, are among the most important reactions in which NO participates.⁵⁹ *In vitro*, Mb(III) reacts with NO forming Mb(III)NO that reacts with OH[−] leading to nitrite and Mb(II); then, Mb(II) reacts with NO forming Mb(II)NO.⁶⁰ In phosphate buffer solution at pH 7.4, Mb(III) displays a Soret absorption maximum at 408 nm (1.5 × 10⁵ mol L^{−1} cm^{−1}) and a band at 500 nm (1 × 10⁴ mol L^{−1} cm^{−1}) in the Q-band region,^{60,61} whereas Mb(II)NO presents a band at 420 nm (1.29 × 10⁵ mol L^{−1} cm^{−1}) and two bands at 545 and 578 nm in the Q-band region. For comparison

Fig. 5 Spectral changes during photolysis of **I** (A) and *trans*-[Ru(NO)(NH₃)₄(py)]³⁺ (B) with light of 350 nm in phosphate buffer solution (pH 7.4) in the presence of Mb(III). (C) Irradiation with light of 520 nm of **I** in phosphate buffer solution (pH 7.4) in the presence of Mb(III).

purposes, photolyses of *trans*-[Ru(NO)(NH₃)₄(py)](PF₆)₃ (pyNO) were performed using irradiation with $\lambda_{\text{irr}} = 350$ nm under the same conditions. This complex releases NO with $\phi_{\text{Ru}} = 0.18 \pm 0.01$ ($\lambda_{\text{irr}} = 330$ nm, pH 6.4)²⁹ Irradiation with $\lambda_{\text{irr}} \geq 380$ nm (at 25 °C) did not result in any observable photoreaction in solution for *trans*-[Ru(NO)(NH₃)₄(L)]ⁿ⁺ or *trans*-[Ru(NO)Cl(mac)]ⁿ⁺ (mac = cyclam, 15aneN4, or 1-(3-aminopropyl)cyclam).^{1,2,8,28,29}

Fig. 5 shows that upon light irradiation the Mb(III) Soret band at 408 nm decreases, with the appearance of three new bands, one at 420 nm and two at 542 and 578 nm in the Q-band region. An additional band also appears at 330 nm. As judged from photolysis experiments of **I** in the absence of Mb(III) under the same conditions, this band is probably due to the presence of a Ru(III) complex as photoproduct. The appearance of a band in the same region was also observed during light irradiation of *trans*-[Ru(NO)(NH₃)₄(py)]³⁺, which has been attributed to the formation of *trans*-[Ru(OH)(NH₃)₄(py)]²⁺ at this pH.²⁹ These spectral changes can be interpreted as the result of NO being released from **I** (or pyNO) with the consequential reductive nitrosylation of Mb(III), which led to Mb(II)NO as the final product. The spectrum of authentic Mb(II)NO formed by the direct reaction of Mb(II) and NO also displayed a high intensity absorption band at 420 nm (1.29×10^5 mol L⁻¹ cm⁻¹) and lower intensity bands at 545 and 578 nm.^{60,61} In addition, the photolysis of the *trans*-[Ru(NH₃)₄(NO₂)(P(OEt₃))₃]³⁺ solution, which led to NO production by a radical mechanism,⁵⁸ also resulted in a very similar spectral pattern due to the reductive nitrosylation of Mb(III). These results suggest that irradiation at 520 nm is able to promote NO photolabilization. Complex **I** showed a low intensity (log $\epsilon = 1.88$) broad band with an absorption maximum centered at 532 nm⁷; a Ru_{dn}- π^* (NO) transition could have contributed to this because irradiation of light in bands with such origin have shown to be responsible for NO photoaquation^{1,2,29} from other Ru nitrosyls. As far as we know, this is the first example of a ruthenium nitrosyl complex with a saturated cyclic amine that is able to release NO with irradiation of light in the visible range. To understand the origin of such a behaviour, further studies will be necessary.

Computational studies

Among the several computational models tested (see ESI, Table SI 1†) for the bond lengths of the fully protonated *fac*-[Ru(NO)Cl₂(κ^3 N⁴,N⁸,N¹¹(1-carboxypropyl)cyclam)]⁺, (**I**), the B3LYP/ECP28MDF, cc-pVDZ model was determined to be the most adequate. The geometry of **I** was compared with species already observed, or conceivably possible, in solution at different pHs, as follows: deprotonated at the carboxyl, (**II**); deprotonated at N3, (**III**); deprotonated at the carboxyl group and in N1, (**IV**), or at N2, (**V**), or at N3 (**VI**); and *fac*-[Ru(NO₂)Cl₂(κ^3 N⁴,N⁸,N¹¹(1-C₂H₄-COO)cyclam)]⁻ deprotonated at the carboxyl and at N2 (**VII**) (see Fig. 1). The atom numbering is the same as that used in the crystallographic study of **I**,⁷ and is represented in Fig. 6. **III** was studied because **II** has a very short O12–H[N3] hydrogen bond and long N3–H, indicating the possibility of spontaneous migration of this hydrogen to O12. **IV**, **V**, and **VI** were studied because it was not possible to determine the most favourable site for the second deprotonation experimentally. Finally, **VII** was studied because **V** is the most stable di-deprotonated form.

Fig. 6 Structure and numbering of **I**.

From **I** to **II**, the carboxyl group moves towards N1 and N3 by the loss of the O11 proton and the oxygen atoms of this group rotate by 90°. Both movements can be explained by strengthening of the O12–H[N3] and O11–H[N1] hydrogen bonds (Fig. 7a). The changes from **I** to **III** are less noticeable, and only the rotation of the carboxyl group is observed (Fig. 7a). After the second deprotonation, the carboxyl group approached the cyclam ring, and there is also a rotation of the C12–C11 bond due to the strengthening of O12–H[N1] and/or O(12)–H[N(3)] hydrogen bonds. It is also possible to observe changes in the cyclam ring, particularly in the neighborhood of N4 and at the NO group. These results indicate that the second deprotonation changes almost all of the electronic structure of **I** (Fig. 7b). The superposition of **V** and **VII** indicates a rotation of the carboxyl group and the movement of this group towards the cyclam ring (Fig. 7c).

A comparison of the bond lengths of **I** and the deprotonated species **II** and **III** indicates that the largest changes in bond length are observed around the deprotonation site (Table 2). Not only does the Ru–N3 distance shorten in **III**, but the Ru–Cl1 also lengthen due to the *trans* effect from the deprotonated N3. Deprotonation at the carboxyl group produces a very strong hydrogen bond, O12–H[N3], which in turn results in a significantly increased N3–H distance. This hydrogen bond can be classified as a double charge-assisted hydrogen bond, ($\pm$)CAHB, which is a strong hydrogen bond.⁶² The shortening of the N3–O11 distance with respect to the sum of van der Waals radii is 26% which is a significant contraction compared with results presented by Gilli *et al.* for crystallographic data of organic compounds.⁶³ Another hydrogen bond is formed between O12 and H[N1]. In addition, O11–H[N1] is strengthened at the expense of the increase in the O11–H[N3] distance. In contrast, **III** does not present any strong hydrogen bonds. These findings partially explain the larger stability of **II** compared with **III**. The changes in the bond lengths for the second deprotonation of **II** are similar to those observed for the deprotonation of N3: the Ru–N_{cyclam} shortens for the N that was deprotonated. Also, one Ru–Cl bond and all O12–H[N] were lengthened. The Cl2–H–N2 distance increases, for **III**, **IV**, and **VI** compared to **I**. A comparison between **V** and the Ru–NO₂

Fig. 7 Superposition of the deprotonated species of **I**: (a) **I**, white; **II**, red; **III**, blue. (b) **II**, white; **IV**, red; **V**, blue; **VI**, green. (c) **V**, white; **VII**, red. The molecules were superposed by Ru1, Cl1, and Cl2. The orientation is the same as in Fig. 6: chlorines are in the upper left and NO in the upper right. The hydrogen atoms have been omitted for clarity.

dianion, **VII**, indicates an enlargement of the Ru–N and of the N–O bonds, and an increase in Ru–N1 and Ru–N3 bond lengths, as expected. Also, all hydrogen bond distances increase.

It was possible to see that the NO bond length of NO agreed with those calculated for **I**–**IV** from calculations of NO interatomic distances using the B3LYP, cc-pVDZ model for the isolated NO⁺, NO, and NO[−], which were 1.068, 1.154, 1.241 Å, respectively (Table 2). These results indicate that the canonical form [Ru^{III}NO] may have contributed significantly to complex **I**, as reported for some other Ru–NO compounds,³⁷ and are in

agreement with the p*K*_a values of the coordinated water for *trans*-[Ru(NO)(NH₃)₄(OH₂)]³⁺ and *trans*-[Ru(NO)(salen)(OH₂)]⁺.^{48,49}

The Ru–NO bond angle for **I** is approximately 10° off the linearity (Table SI 2†), while Caramori and Frenking reported calculated Ru–N–O bond angles of 179.1°, 179.9° and 180.0° for *trans*-[Ru(NO)(NH₃)₄(L)]ⁿ⁺ (L = NH₃, Cl[−], H₂O),³⁹ and Ford and collaborators reported 176.9° as the Ru–N–O bond angle for [Ru(NO)(NH₃)₅]³⁺, using the B3LYP density functional and the 3-21G basis set, for an experimental value of 172.8°.³⁵ The data for **I** suggests that the electronic structure of this molecule may be a contribution from two canonical forms: the linear [Ru^{II}NO⁺] and the bent [Ru^{III}NO]. However it is important to remember that the use of the structure/oxidation state correlations is sometimes problematic, as recently discussed.⁶⁴ The first and second deprotonation steps do not cause any significant changes in bond angles. The same is observed for the loss of the second proton. The only exception is **V**, which presents several significant changes not only in the bond angles in which N2 is involved. These findings indicate that the structure of **V** presents the largest changes around ruthenium compared with all the other deprotonated forms studied in this work.

The calculated vibrational wavenumbers of **I** compare very well with the experimental values obtained, and the deviations are less than 6% (Table 3). The deprotonated and dideprotonated species, **II**–**VII**, present smaller N5–O5 stretching wavenumbers, compared to **I**. In contrast, *v*(Ru–N5) hardly changes with deprotonation. The largest changes in the stretching frequencies are observed in **V**, compared to **II**, and this is consistent with the larger geometric changes. With the carboxyl deprotonation of **I**, it is possible to observe a very large decrease in the N3–H stretching wavenumber in **II**, reinforcing the observation that the N3–H–C=O hydrogen bond is a very strong bond. Compared to **I**, that vibrational energy decreases for all the other deprotonated and di-deprotonated complexes, but not very strongly; these results indicate that a hydrogen bond is present in **III**–**VI**, but it is not as strong as in **II**. The *v*(Ru–Cl) values decrease for all the deprotonated complexes, indicating that there is a redistribution of electronic density after the proton loss, which affects the ruthenium and the atoms linked to it.

Table 4 presents the NPA atomic charges. For **I**, the Ru charge is three times larger than that for NO, suggesting that the oxidation state of the metal is III. With the first deprotonation, the ruthenium charge becomes slightly more positive, the NO becomes less positive, and the chloro ligands are more negative compared to **I**, which is consistent with the IR data. As a result, the electron density of the RuNO group is almost constant and RuNOCl₂ positive charge decreases from **I** to **II** or from **I** to **III**. With the second deprotonation, the largest changes in Ru charge take place in **VI**, which loses 0.568 electron, probably because the N3–H–O12 very strong hydrogen bond, present in **II** is lost in **VI**. Additionally, there is a strong repulsion between the negative carboxylate group with N3, also negative. In contrast, there is a strong decrease in the NO charge with the deprotonation of N3 (**VI**) and an increase in the NO charge in **VII**. As a consequence, the RuNO charge is only 0.500 electron for **VI**. Changes in the Cl1 and Cl2 summed up charges are much less accentuated. The electron density of the RuNOCl₂ group increases with the second deprotonation; the largest effect is detected for **VI** and the smallest for **IV**. In addition, the electron density of cyclam and the 1-carboxypropyl

Table 2 Bond lengths for (I)–(VII), Å, for the geometry optimization in vacuum

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
	(Exp.) ^a	(Calc.)					
Ru–N5	1.739(2)	1.737	1.733	1.725	1.723	1.761	1.723
Ru–N2	2.111(2)	2.170	2.163	2.181	2.175	1.979	2.179
Ru–N1	2.133(2)	2.190	2.172	2.187	2.095	2.171	2.167
Ru–N3	2.146(2)	2.211	2.187	2.098	2.194	2.226	2.086
Ru–Cl1	2.3789(7)	2.391	2.416	2.485	2.433	2.459	2.509
Ru–Cl2	2.3798(7)	2.389	2.412	2.413	2.512	2.460	2.445
O5–N5	1.149(3)	1.145	1.149	1.156	1.162	1.170	1.161
O11–H[N1]		2.488	2.249	2.701	—	2.337	2.794
O11–H[N3]		2.057	3.375	—	3.415	—	—
Cl1–H–N2		2.498	2.511	2.482	2.516	—	2.500
Cl2–H–N2		3.200	3.213	3.252	3.333	—	3.303
O12–H[N1]		4.202	2.353	3.768	—	2.406	2.701
O12–H[N3]		4.260	1.722	—	1.779	1.835	—
N3–H		1.031	1.054	—	1.051	1.045	—

^a From ref. ⁷ ^b There are two equivalent N–O bond lengths for VII.**Table 3** Vibrations of I–VII, cm^{−1}, calculated in vacuum

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
ν	(Exp.) ^a	(Calc.)					
N5–O5	1881	1984	1962	1931	1907	1854	1912
N1–H[N1]	3200	3339	3399	3313	—	3427	3415
N2–H[N2]	3200	3405	3415	3408	3417	—	3233
N3–H[N3]	3200	3364	2938	—	3040	3117	—
C–H		3165–2965	3194–2918	3162–2902	3144–2829	3176–2871	3130–2852
Ru–N5		625	630	624	— ^b	604	629
Ru–Cl		326	311, 326	309, 265	292	272	296, 257

^a From ref. ⁷ ^b Not observed due to coupling of several vibrational modes.**Table 4** NPA charges, calculated in vacuum

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
Ru	0.770	0.813	0.819	0.866	0.839	0.245	0.781
NO	0.241	0.201	0.121	0.142	0.008	0.256	−0.702
RuNO	1.011	1.014	0.940	1.008	0.848	0.500	0.079
Cl1+Cl2	−0.896	−0.989	−1.075	−1.154	−1.107	−0.888	−1.238
RuNOCl ₂	0.115	0.025	−0.135	−0.147	−0.260	−0.387	−1.159
Cyclam	0.629	0.597	−0.083	−0.161	−0.062	0.102	0.874
N1H	−0.270	−0.259	—	—	−0.253	−0.209	−0.281
N2H	−0.263	−0.255	−0.256	−0.273	—	−0.202	—
N3H	−0.255	−0.255	−0.268	−0.248	−0.252	—	−0.286
N4	−0.617	−0.618	−0.615	−0.605	−0.612	−0.612	−0.605
prop ^a	0.256	−0.622	0.218	−0.693	−0.678	−0.715	−0.715

^a Carboxypropyl

groups decreases with the first and second deprotonation steps. The charges of the NH groups are almost constant with changes in the protonation states of I. The Ru and cyclam positive charge increases from VI to VII, which is similar to I; NO and both Cl ligands present high electron density. All of these observations reinforce the conclusion that changes in the protonation state and at the site of deprotonation affect the electron distribution of all atoms of I. These results indicate that varying the pH of the solution make it possible to modulate the electron distribution in I. Interestingly, the charge decrease shown by the NPA charge calculations for the RuNO groups of V and VI is in agreement

with the expected negative shifts observed in the redox potentials assigned to {RuNO}⁶ with pH increase. This observation rules out the formation of IV because the RuNO charge becomes constant.

Wiberg bond indexes, (b.i.), which are related to bond order, are listed in Table 5. It is not possible to conclude whether the most important canonical structure for I is [Ru^{III}NO] or [Ru^{IV}NO[−]] by comparing the b.i. for NO in I (1.916) with this index for the isolated NO[−], NO, and NO⁺ (2.005, 2.100 and 2.802, respectively) due to the close b.i. of NO[−] and NO. As stated in the discussion of bond angles, two canonical structures, [Ru^{III}NO] or [Ru^{II}NO⁺], probably contribute largely to I in contrast with the conclusions

Table 5 Wiberg bond indexes for **I–VII**, calculated in vacuum

	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
Ru–N5	1.425	1.455	1.495	1.522	1.352	1.657	0.425
Ru–N2	0.347	0.351	0.324	0.322	0.581	0.450	0.659
Ru–N1	0.355	0.390	0.565	0.566	0.386	0.516	0.335
Ru–N3	0.354	0.390	0.359	0.384	0.360	0.714	0.317
Ru–Cl1	0.561	0.518	0.397	0.494	0.502	0.633	0.494
Ru–Cl2	0.567	0.524	0.532	0.383	0.481	0.733	0.455
O(5)–N5	1.916	1.880	1.821	1.818	1.770	1.836	1.492
O(11)–H[N1]	0.009	0.018	0.008	—	0.695	0.004	0.000
O(11)–H[N3]	0.034	0.000	—	0.002	0.014	—	0.056
Cl(1)–H–[N2]	0.005	0.009	0.000	—	0.005	0.008	0.000
Cl(2)–H–[N2]	0.002	0.000	—	0.078	0.071	—	0.003
N3–H	0.712	0.616	—	0.614	0.655	—	0.678

about b.i.; this finding is consistent with Pauling's electroneutrality principle from which the $[\text{Ru}^{\text{IV}}\text{NO}^-]$ is less likely. This result shows that further studies will be necessary to clarify the weight of the different canonical structures, $[\text{Ru}^{\text{II}}\text{NO}^+]$, $[\text{Ru}^{\text{III}}\text{NO}]$, and $[\text{Ru}^{\text{IV}}\text{NO}^-]$ in the Ru–NO core. All changes in those indexes are consistent with changes in bond lengths. The Ru–N5 b.i. increases with the first protonation and the N5–O5 bond length decreases. For **III**, it is also possible to observe a decrease in the Ru–Cl b.i., indicating a redistribution of the electronic density after the deprotonation in N3. Similar to the loss of the first proton, the second deprotonation causes changes in distinct parts of the molecule, which is sometimes far from the deprotonation site. For example, in **VI** it is possible to observe changes in the b.i. of the carboxylate bonds, which can be attributed to modifications in the hydrogen bonds that involve O11 and O12. **VI** is the compound where the b.i. changes the most with the second deprotonation, and this can be ascribed to the loss of N–H–OC hydrogen bond. Bond indexes for all bonds involving ruthenium increase, and the N5–O5 b.i. decreases. This decrease is also observed for all the other deprotonated species. In contrast, the Ru–N5 b.i. increases for **IV**, decreases for **V**, and the other Ru–N and Ru–Cl b.i. change or remain constant depending on the deprotonation site. Large decreases in Ru–N5 and in O5–N5 are observed from **VI** to **VII**, which is consistent with the change from NO to NO_2 . Also, it is possible to observe changes in the b.i. for the hydrogen bonds, which is consistent with the bond length and conformational changes.

The analysis of the energies in vacuum or in water (Table 6) indicates that the first deprotonation occurs in the carboxyl group, **II**. The deprotonation at N3, **III**, is approximately $10 \text{ kcal}\cdot\text{mol}^{-1}$ less stable compared to the COOH group, and it is too unstable

to be observed in standard conditions. After the second deprotonation, the only species observed in vacuum or in aqueous solution is **V** because **IV** and **VI** have very high relative Gibbs energies.

Conclusions

The chemical reactivity and the photolability of the coordinated NO of the *fac*- $[\text{Ru}(\text{NO})\text{Cl}_2(\kappa^3\text{N}^4, \text{N}^8, \text{N}^{11}(1\text{-carboxypropyl})\text{cyclam})]\text{Cl}\cdot\text{H}_2\text{O}$ (**I**) complex were investigated. Although this complex has a very different architecture compared to analogous complexes, such as *trans*- $[\text{Ru}(\text{NO})\text{Cl}(\text{cyclam})](\text{PF}_6)_2$, due to the κ^3 coordination mode of the substituted cyclic amine which results in *fac* configuration, the chloride inertness in **I** is similar to that observed in the *trans* analogous complexes. The two chloride ligands do not undergo aquation reactions at room temperature possibly due to $\text{Cl}\cdots\text{H}-\text{N}$ interatomic distances, which are in the range of van der Waals radii for H and Cl. Complex **I** also undergoes OH^- reversible reactions and 3 pKa values were determined.

The presence of the coordinated NO in the *fac*- $[\text{Ru}(\text{NO})\text{Cl}_2(\kappa^3\text{N}^4, \text{N}^8, \text{N}^{11}(1\text{-carboxypropyl})\text{cyclam})]\text{Cl}\cdot\text{H}_2\text{O}$ makes this complex a potential nitric oxide donor because under chemical and electrochemical reductions it is able to release NO at a rate similar to that of the fastest ruthenium tetraammine analogue reported thus far. Under irradiation with light of 350 or 520 nm, **I** is also able to release NO and promote reductive nitrosylation of myoglobin.

Molecular quantum mechanical calculations were made to clarify the structural changes that **I** undergoes in each step of the observed acid-base equilibria, and to determine what is

Table 6 Enthalpies, Gibbs energies (Hartree), and relative enthalpies and Gibbs energies (kcal/mol) for **I–VII**, calculated without or with a cavity of water

	Vacuum				Water	
	<i>H</i>	ΔH	<i>G</i>	ΔG	<i>G</i>	ΔG
(I)	–2026.32055		–2026.39964		–2026.78464	
(II)	–2025.92750	0.00	–2026.00498	0.00	–2026.39611	0.00
(III)	–2025.90993	11.02	–2025.98979	9.54	–2026.37777	11.51
(IV)	–2025.39213	9.73	–2025.46984	8.83	–2025.90317	7.55
(V)	–2025.40763	0.00	–2025.48391	0.00	–2025.91521	0.00
(VI)	–2025.39374	8.71	–2025.47197	7.49	–2025.90668	5.35
(VII)	–2100.58350		–2100.66669		–2026.78464	

the most favourable site for the second deprotonation. Among the computational models tested in the theoretical calculations, B3LYP/ECP28MDF,cc-pVDZ resulted in the smallest errors for the experimental geometry of **I**. Calculations of energies in vacuum and in water indicated that the first deprotonation should occur at the carboxypropyl group and the second deprotonation at N2. A superposition of structures of different species and the comparison of geometric parameters indicate that complex changes occur after the first and second deprotonation steps, which affects the whole molecule. The carboxypropyl deprotonated species, **II**, presents a very strong N–H–O resonance assisted hydrogen bond, which stabilises this compound. The calculated NO bond length and the Ru/NO charge ratio indicate that the predominant canonical structure is $[\text{Ru}^{\text{III}}\text{NO}]$, but Ru–NO bond angles and b.i. provide a less clear picture; bond angles suggest that $[\text{Ru}^{\text{II}}\text{NO}^+]$ can contribute to the electronic structure of **I** and b.i. indicate a contribution from $[\text{Ru}^{\text{IV}}\text{NO}^-]$. Taking into consideration that some experimental data are consistent with a $[\text{Ru}^{\text{II}}\text{NO}^+]$ description and others are in agreement with $[\text{Ru}^{\text{III}}\text{NO}]$, the best description for **I** would be a linear combination of the three canonical forms, with a higher weight for $[\text{Ru}^{\text{II}}\text{NO}^+]$ and $[\text{Ru}^{\text{III}}\text{NO}]$. It is clear that further studies with smaller and simpler $\{\text{RuNO}\}^6$ complexes will be necessary. All of these data combined with the calculated NPA charges and vibrational frequencies indicate that the first and the second deprotonation steps produce complex changes in the electronic structure of **I**, not only in the neighborhood of the metal, but also at further regions of the molecule. These findings suggest that the properties of this and other Ru–NO complexes can be modified by changing the protonation state.

Experimental

Materials

NaCl (99.99% purity, Merck) was dried and stored under vacuum prior to use. The oxidised form of myoglobin (horse heart) was obtained from Sigma. All other solvents and reagents were of analytical grade and used as supplied or purified when necessary, according to standard methods.⁶⁵ Commercially available argon (Air Liquide) was passed through a MnO_2 column for deoxygenation prior to use in degassing aqueous solutions for photolability studies. All manipulations with air sensitive compounds were conducted following conventional techniques.⁶⁶ Deionised water was used throughout the work.

Preparations

The free ligand (1-carboxypropyl)cyclam was synthesised and characterised as reported previously.⁷ The (1-carboxypropyl)cyclam tetrahydrochloride dihydrate was obtained by dissolving ~0.2 g of the colourless oil, (1-carboxypropyl)cyclam ligand, in 10 mL of absolute ethanol followed by the slow addition of 2 mL of a 6 mol L^{-1} HCl aqueous solution. The mixture was cooled for 2 h. The white solid was collected by filtration, washed with ethanol, diethylether, and then dried under vacuum. Elemental analysis: C, 33.00; N, 7.48; H, 11.97. Calcd for $\text{C}_{13}\text{H}_{36}\text{O}_4\text{N}_4\text{Cl}_4$: C, 33.34; N, 7.91; H, 11.21. ^1H NMR (400 MHz; D_2O) δ_{H} /ppm: 1.99–2.11 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.78 (2H, t, CH_2CO), 3.22–3.33 (10 H, m), 3.46–3.51 (8H, m). ^{13}C NMR

(100 MHz; D_2O) δ_{C} /ppm: 21.90 and 22.35 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 32.17 (CH_2CO), 40.99, 41.57, 44.59, 44.82, 45.24, 48.89, 48.90, 51.82, 53.10 (CH_2N), 177.69 (CO). IR ν_{max} /cm $^{-1}$ 1735 (COOH).

The *fac*- $[\text{Ru}(\text{NO})\text{Cl}_2(\kappa^3\text{N}^4, \text{N}^8, \text{N}^{11}(1\text{-carboxypropyl})\text{cyclam})]\text{Cl} \cdot \text{H}_2\text{O}^7$ and *trans*- $[\text{Ru}(\text{NO})(\text{NH}_3)_4(\text{py})](\text{PF}_6)_3$ ⁶⁷ complexes were synthesised and characterised as reported.

Physical measurements

IR spectra were obtained in a Bomem MB 102 FTIR spectrophotometer using KBr pellets. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DRX400 spectrometer. UV-Vis spectra were acquired in a Hewlett–Packard 8452A or a UV-Vis NIR Varian-Cary 500 spectrophotometers. Elemental analyses were conducted at the Analytic Central of Chemistry Institute of University of Sao Paulo.

Cyclic voltammetry and differential pulse voltammetry measurements were performed on a Princeton Applied Research (PAR) 273A model potentiostat/galvanostat. All experiments were performed using a conventional three-electrode system. Glassy carbon and platinum gauze were used as working electrodes for cyclic and differential pulse voltammetry, as well as potential controlled electrolysis, respectively. Platinum wire and Ag/AgCl electrodes were used as a counter-electrode and reference electrode, respectively. All measurements were conducted in a previously argon degassed aqueous solution. Solution temperatures were maintained using a Haake FK model ultracryostat. The reported $E'_{1/2}$ values were reported the arithmetic mean of E_{pa} and E_{pc} values.

NO detection was performed using an NO meter from Innova-Instruments Inc. This apparatus detects NO directly by means of an amperometric technique.

The rate of NO release ($k_{\text{obs-NO}}$) after electrochemical reduction was estimated with an Autolab PGSTAT 30 (Eco Chemie) bipotentiostat using a platinum microelectrode⁶⁸ (effective radii $15.4 \pm 0.3 \mu\text{m}$) as working electrode and Ag/AgCl and platinum wire as the reference and counter-electrode, respectively, at $25 \pm 1^\circ\text{C}$. Scan rates from 0.5 to 40 V s^{-1} were used, and $k_{\text{obs-NO}}$ was determined from plots of $(E_{\text{pc}} - E_{1/2})$ vs. $\log 1/v$, obtained by combination of the equations below.

$$E_{\text{pc}} = E_{1/2} - (RT/nF) 0.780 + (RT/2nF) \ln \lambda$$

$$\lambda = kRT/nFv$$

pK_a values

pK_a values for (1-carboxypropyl)cyclam tetrahydrochloride and **I** were determined by potentiometric titrations. The ionic strength of $2.0 \times 10^{-3} \text{ mol L}^{-1}$ (ligand or complex) solutions was adjusted with 0.1 mol L^{-1} NaCl aqueous solution. Aliquots of a 0.025 mol L^{-1} NaOH aqueous solution were added using a Metrohm E72 burette at 60 s time intervals. The increase in pH was monitored using a digital Analion PM 600 model pHmeter/conductivitymeter. All experiments were performed in the dark. Estimations on pK_a were also performed by running a differential pulse voltammogram experiment after each addition of NaOH aliquots to a $1.0 \times 10^{-3} \text{ mol L}^{-1}$ solution of **I** in 0.5 mol L^{-1} HCl.

Chloride lability

The chloride ligand aquation from **I** was investigated by potentiometric measurements. A digital Analion PM 600 model pH meter/conductivimeter equipped with an Analion Cl651 model chloride selective and Ag/AgCl reference electrode was used. The calibration of selective electrode was performed before each experiment using aqueous NaCl stock solutions with concentrations in the 5.0×10^{-5} to 5.0×10^{-3} mol L⁻¹ range and an ionic strength of 0.1 mol L⁻¹ NaNO₃ and at pH 3. The temperature of solutions of **I** (using the same ionic strength and pH) was maintained at 25 or 40 ± 0.2 °C using a Haake FK model ultracryostat. The pseudo-first-order rate constant (k_{obs}) for Cl⁻ ligand dissociation was determined from the slope of ln[Cl⁻] vs. time at 40 °C. All experiments were performed in the dark.

Photolability of the nitrosyl ligand

Photolysis experiments for **I** and *trans*-[Ru(NO)(NH₃)₄(py)](PF₆)₃ (pyNO) ($\sim 1.0 \times 10^{-3}$ mol L⁻¹) were performed at pH 7.4 phosphate buffer aqueous solution in a 1.0 cm⁻¹ path length quartz cell capped with a glass reservoir containing ~ 1 mg of myoglobin (Mb(III)). After degassing for 20 min with argon, Mb(III) was mixed and dissolved in the solution. Solutions of **I** (or pyNO) with Mb(III) were photolysed at 350 nm in a Rayonet Photochemical Reactor at 25 °C with constant magnetic stirring, and were monitored spectrophotometrically. For photolysis at 520 nm, a Light Emitting Diode (LED) system with a power of 92 W/m² was used. Solutions were photolysed below 5% of reaction to minimise inner filter effects. No spectral changes were observed for Mb(III) solutions without **I** (or pyNO) using the same procedures. Dark reactions were performed simultaneously by using solutions of identical composition. As inferred from their UV-Vis spectra, solutions of ruthenium nitrosyls (**I** or pyNO), Mb(III), and Mb(III) + ruthenium nitrosyls (**I** or pyNO) were stable at room temperature for at least 1 day.

Computational Methods

Some computational models were tested for *fac*-[Ru(NO)-Cl₂(κ³N⁴,N⁸,N¹¹(1-carboxypropyl)cyclam)]Cl·H₂O, as described in ESI†; the B3LYP/ECP28MDF, cc-pVDZ model was able to satisfactorily reproduce the experimental geometries. This model was used to calculate the optimisation and vibrational frequencies for all other species. A single point calculation was accomplished by B3LYP/ECP28MDF, aug-cc-pVDZ. The atomic charges were calculated by the NPA method^{69,70} and the bond indexes by the Wiberg method.⁷¹ All calculations were made in vacuum, except the for the determination of Gibbs energies in water that were conducted by the IEFPCM method.⁷² The superposition of the different structures was conducted by VEGA ZZ 2.3.1 software.⁷³ The structure in Fig. 6 was illustrated with the aid of the CYLview software.

Acknowledgements

The authors thank the Brazilian Agencies CAPES, CNPq, FAPESB and Fapesp for grants and fellowships as well as Professor Alzir A. Batista for use of his laboratory and Cynthia M. C. Prado Manso for revision of the English language.

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