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Article

Chemical and Photochemical Properties of a Ruthenium Nitrosyl Complex with the *N*-Monosubstituted Cyclam 1-(3-Propylammonium)-1,4,8,11-tetraazacyclotetradecane

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O complexo aminofuncionalizado *trans*-[Ru(NO)Cl(1-pramcyH)](PF$_6$)$_3$ (1-pramcyH = 1-(3-propilamônio)-1,4,8,11-tetraazaciclotetradecano) foi sintetizado através da reação do *trans*-[RuCl(tfms)(1-pramcyH)](tfms)$_2$ (tfms = trifluorometanossulfonato) com óxido nítrico (NO) em solução aquosa ácida. O complexo foi caracterizado por análise elementar, espectroscópica (UV-vis, IV, RMN de ^{1}H e ^{13}C) e eletroquímica. Dois valores de pK$_a$ (7,0 e 8,2) foram determinados para *trans*-[Ru(NO)Cl(1-pramcyH)](PF$_6$)$_3$ e foram atribuídos a um dos prótons do grupo amina do cyclam e ao propilamônio. A redução do *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$ leva à saída rápida de cloreto seguida de saída lenta de NO, enquanto a irradiação do complexo em solução aquosa desaerada resulta na labilização fotoquímica do NO. O rendimento quântico para a fotoaquação do NO diminui com o aumento do comprimento de onda de irradiação e com a diminuição do pH, e é observável apenas a $\lambda_{irr} < 370$ nm. O comportamento do *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$ é semelhante ao do complexo análogo *trans*-[Ru(NO)Cl(cyclam)]$^{2+}$, porém difere daquele do complexo com carboxipropil como substituinte.

The amine-functionalized *trans*-[Ru(NO)Cl(1-pramcyH)](PF$_6$)$_3$ complex (1-pramcyH = 1-(3-propylammonium)-1,4,8,11-tetraazacyclotetradecane) was synthesized from *trans*-[RuCl(tfms)(1-pramcyH)](tfms)$_2$ (tfms = trifluoromethanesulfonate) in acidic aqueous solution in the presence of nitric oxide (NO). The complex was characterized by elemental, spectroscopic (UV-Vis, IR, ^{1}H and ^{13}C NMR) and electrochemical analyses. Two pK$_a$ values (7.0 and 8.2) were estimated for *trans*-[Ru(NO)Cl(1-pramcyH)](PF$_6$)$_3$ and were assigned to one of the cyclam nitrogen protons and to the protonated aminopropyl group. Reduction of *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$ results in rapid loss of chloride followed by slower loss of NO, while irradiation of the complex in aqueous deaerated conditions suggests photochemical labilization of NO. The quantum yields for NO photoaquation decrease as the irradiation wavelength increases, being noticeable only at $\lambda_{irr} < 370$ nm, and increase as pH increases. The behavior of *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$, which contains an aminopropyl substituted cyclam, parallels that reported for the analogous complex with the unsubstituted ligand, but differs from that described for the complex in which carboxypropyl is the substituent.

Keywords: nitrosyl, ruthenium, nitric oxide donor, substituted cylam, mono-*N*-functionalized cyclam

Introduction

The discovery of the participation of nitric oxide (NO) in a wide range of physiological processes and pathologies[1] has launched investigations on NO donors, including metal nitrosyl complexes in solution or immobilized in matrices, aiming at the understanding of both fundamental aspects and biological activity for potential applications.[2-43]

Among the NO donors, ruthenium nitrosyl complexes are particularly attractive because they are stable, can be either water soluble or not, deliver NO at different rates upon activation by reduction at biologically accessible

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potentials and/or by light irradiation, in either solution or matrices.[14-18,34,40-49] These properties can be tuned by the adequate choice of ligands.[14, 18]

It should be pointed out that interesting biological activities for several of these complexes have already been reported.[14,17,21,33,34,37-39] Because NO can be either beneficial or harmful depending on its bioavailability, compounds capable of releasing NO in a specific biological target have potential biological applications and could be useful tools to study the physiological action of NO. Efforts from this laboratory have been directed toward this goal, using several strategies. One of such approaches involves the functionalization of ruthenium nitrosyl complexes, so they can be linked to important entities such as antibodies and to surfaces, in order to obtain selective NO donor drugs or devices.

We have been working with complexes such as *trans*-$[Ru(NO)(NH_3)_4(py\text{-}X)]^{n+}$ (py-X are pyridine, substituted pyridines, pyrazine), *trans*-$[Ru(NO)X(py\text{-}X)_4]^{n+}$ (X = $Cl^–$, $OH^–$, H_2O, $NO_2^–$, etc.), and $[Ru(NO)X(mac)]^{n+}$ (X = $Cl^–$, $OH^–$, H_2O, etc.; mac = tetraazamacrocycle).[14,18,41,45] The tetraazamacrocyclic Ru^{II} and Ru^{III} complexes exhibit some unusual features compared to alicyclic analogues.[18] One of their fundamental properties is the size of the macrocyclic ring. A change in ring size has been shown to markedly affect the electronic spectra, redox potentials, and reactivities of the complexes.[18] Substitution in the ligand may also affect some properties, such as reactivity.

We have reported the syntheses and reactivity of *trans*-$[RuCl(L)(1\text{-pramcyH})]^{n+}$ (1-pramcyH = 1-(3-propylammonium)cyclam), L = $Cl^–$, H_2O, $OH^–$ and tfms (trifluoromethanesulfonate), where cyclam has a pendant ammonium group.[48] The loss of chloride from *trans*-$[RuCl_2(1\text{-pramcyH})]^{2+}$ and *trans*-$[RuCl_2(tmc)]^+$ (tmc = tetramethylcyclam) is faster than that in the corresponding dichloro cyclam complex.[18] However, in very few cases, the substitution in the cyclam ligand imparts a drastic shift from the expected properties of the metal complex.[19,50,51]

These complexes present interesting configurations by exhibiting a κ^3 denticity for the mono-*N*-substituted 1-(carboxypropyl)cyclam ligand in *fac*-$[Ru(NO)Cl_2(\kappa^3N^4,N^8,N^{11}(1\text{-carboxypropyl)cyclam})]Cl{\cdot}H_2O$,[19] κ^5 for the mono-*N*-substituted *N*-(2-methylpyridyl)cyclam ligand in *cis*-$[Ru(Lpy)NO]^{3+}$ (Lpy = *N*-(2-methylpyridyl)-1,4,8,11-tetraazacyclotetradecane),[50] and κ^6 for the tetra-*N*-substituted 1,4,8,11-tetrakis(2-pyridylmethyl) cyclam in $[Ru(HL)][ClO_4]_3{\cdot}H_2O$ (L = 1,4,8,11-tetrakis(2-pyridylmethyl)cyclam).[51] However, when the substituent is ammoniumpropyl (1-(3-propylammonium)cyclam), the ruthenium complex adopts the expected *trans* configuration in *trans*-$[RuCl(L)(1\text{-pramcyH})]^{n+}$ (L = $Cl^–$, H_2O, $OH^–$) (*trans*-$[Ru(NO)Cl(1\text{-pramcyH})]^{3+}$),[48] instead of the *fac* configuration adopted in *fac*-$[Ru(NO)Cl_2(\kappa^3N^4,N^8,N^{11}(1\text{-carboxypropyl)cyclam})]Cl{\cdot}H_2O$ when the substituent is carboxypropyl.

In order to verify the effect of the ammoniumpropyl substituent on the configuration of the nitrosyl complex, so as to obtain a wider variety of NO donors, in this paper we report the synthesis, characterization, electrochemical and photochemical properties of the *trans*-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$ complex.

Experimental

Chemicals and reagents

Ruthenium trichloride ($RuCl_3{\cdot}nH_2O$) (Strem; 40-45% Ru) was the starting material for the syntheses of the ruthenium complexes. Cyclam was purchased from Aldrich. Acetone, chloroform and ethanol were purified according to literature procedures.[52] Doubly distilled water was used throughout this work. All other materials were reagent grade and were used without further purification.

Syntheses

The *trans*-$[Ru(NO)Cl(cyclam)](PF_6)_2$ complex[25] was synthesized for comparison purposes. ^1H NMR (acetonitrile-d_3) δ 1.59 (m, 4 H, CH_2), 1.94 (d, *J* 6.8 Hz, 2 H, CH_2), 2.16 (d, 2 H, *J* 5.6 Hz, CH_2), 2.61 (m, 4 H, CH_2), 2.86 (q, *J* 5.4 Hz, 2 H, CH_2), 3.09 (d, *J* 7.2 Hz, 2 H, CH_2), 3.32 (m, 4 H, CH_2), 5.12 (s, 2 H, NH), 5.66 (s, 2 H, NH). ^{13}C NMR (acetonitrile-d_3) δ 26.66 (CH_2), 28.83 (CH_2), 49.76 (CH_2), 52.42 (CH_2), 52.93 (CH_2), 55.07 (CH_2)). *Trans*-$[RuCl_2(1\text{-pramcyH})]Cl_2$,[48] *trans*-$[RuCl(tfms)(1\text{-pramcyH})](tfms)_2$,[48] *trans*-$[RuCl(H_2O)(1\text{-pramcyH})](PF_6)_3$[48] and *trans*-$[RuCl(H_2O)(cyclam)](PF_6)_2$[48] complexes were prepared as described elsewhere.

Trans-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$ was prepared by a slight modification of a procedure previously described for the synthesis of *trans*-$[Ru(NO)Cl(cyclam)](PF_6)_2$.[25] An amount of 77 mg (0.10 mmol) of *trans*-$[RuCl(tfms)(1\text{-pramcyH})](tfms)_2$ was dissolved in 10 mL of 0.1 mol L^{-1} HPF_6 solution in a three-necked flask under argon atmosphere and continuous stirring. Nitric oxide, which was generated by dropping 30% nitric acid onto Cu and passing it through a 6 mol L^{-1} solution of NaOH, was bubbled through the solution. After 4 h of bubbling, 1 mL of a saturated aqueous solution of $NH_4(PF_6)$ was added, and the solution was concentrated to *ca*. 2 mL by rotary evaporation under reduced pressure. On cooling, the bright yellow solid, that slowly precipitated, was collected by filtration, washed with acetone, ether, and dried under vacuum. Yield: 45% (0.17 g; 0.046 mmol). Elemental analyses: Found: C, 17.98; H, 3.67; N, 9.65. Calc. for $C_{13}H_{32}ClF_{18}N_6OP_3Ru$: C, 18.16; H, 3.75; N, 9.77%. UV-Vis λ_{max}/nm (water) 272 (ε/(dm^3 mol^{-1} cm^{-1}) 3.1×10^3), 360 (4×10^2) and 455 (90). ^{1}H NMR (acetonitrile-d_3) δ 1.86 (m, 3 H, CH_2), 2.15 (m, 3 H, CH_2), 2.66 (m, 5 H, CH_2), 2.78 (m, 4 H, CH_2), 3.07 (t, *J* 4.5 Hz, 2 H, CH_2), 3.29 (d, *J* 4.8 Hz, 3 H, CH_2), 3.45 (d, *J* 5.2 Hz, 2 H, CH_2), 3.55 (dd, *J* 5.3 Hz, 4 H, CH_2), 5.36 (s, 3 H, NH), 6.06 (s, 1 H, NH), 6.26 (s, 2 H, NH). ^{13}C NMR (acetonitrile-d_3) δ 29.89 (CH_2), 30.05 (CH_2), 30.23 (CH_2), 50.48 (CH_2), 51.20 (CH_2), 53.27 (CH_2), 53.50 (CH_2), 53.82 (CH_2), 54.39 (CH_2), 55.20 (CH_2),55.80 (CH_2), 56.10 (CH_2), 56.54 (CH_2).

Elemental analyses

Analyses were performed at the Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, University of São Paulo, using an Elemental Analyzer CE Instruments, model EA 1110.

Spectra

Electronic absorption spectra were recorded on a Hewlett-Packard model 8452A spectrophotometer using quartz cells. Infrared absorption spectra were obtained in Nujol mulls, in water or in acetonitrile, on a Bomen MB-102 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in 5 mm NMR tubes on a Bruker WH400 spectrometer in acetonitrile-d_3 or D_2O. The EPR experiments were conducted in frozen acetonitrile (77 K) in an ESP-300E Bruker instrument operated with an X-band microwave bridge.

Electrochemical measurements

Cyclic voltammetry and controlled potential electrolysis were performed with a PARC 273 potentiostat/galvanostat. All tests were carried out using a conventional three-electrode cell. Glassy carbon and platinum gauze were used as working electrodes for cyclic voltammetry and coulometry, respectively. Ag/AgCl and platinum wire were used as the reference and auxiliary electrodes respectively. Electrochemical data were obtained in different media, as follows: pH 1 (CF_3SO_3H/CF_3SO_3Na, μ = 0.1 mol L^{-1}); pH 4.32 (CF_3COOH/CF_3COONa, μ = 0.1 mol L^{-1}); pH 1 (HCl/KCl, μ = 0.1 mol L^{-1}); pH 7.9 ($NaH_2PO_4{\cdot}H_2O/Na_2HPO_4$, μ = 0.1 mol L^{-1}); pH 6 (LiCl, μ = 0.2 mol L^{-1}); and acetonitrile, μ = 0.1 mol L^{-1}, containing tetrabutylammonium hexafluorophosphate [tba(PF_6)]. All solutions were deaerated by bubbling high purity argon, and thermostated using a Haake FK ultracryostat. The reported $E_{1/2}$' values are the arithmetic means of the E_{pa} and E_{pc} values.

The spectroelectrochemical measurements in the UV-Vis region were carried out in a quartz cell with 0.030 cm optical path, using gold mini-grid, Ag/AgCl and platinum wire as working, reference and auxiliary electrodes respectively. Analogous measurements in the infrared region were carried out using gold mini-grid, Ag wire and gold wire as working, reference and auxiliary electrodes respectively, mounted in a CaF_2 window with 0.020 cm optical path. Successive UV-Vis or IR spectra for *trans*-[Ru(NO)Cl(cyclam)]$(PF_6)_2$ and *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ were recorded during the reduction process of the complexes at 25 °C, with applied potentials of –500 mV *vs*. Ag/AgCl in acetonitrile solutions. The pH measurements were performed using a 430 Analion or a Corning pH meters.

Photolyses

Monochromatic irradiations at 313, 334 and 370 nm were carried out using a 150 W Xenon lamp in an Oriel Universal Arc Lamp Source (model 6253). For photolysis at the appropriate wavelengths, the irradiation wavelength was selected with Oriel interference filters, with an average band path of 10 nm.

The progress of the photoreactions was monitored spectrophotometrically on a MB Bomem 102 FTIR spectrophotometer, using a ZnSe ATR crystal, or on an HP8452A diode array spectrophotometer for *in-situ* vibrational and electronic spectroscopy respectively. For most runs, the initial concentration of the complex was *ca.* 10^{-2} (infrared experiments) to 10^{-3} mol L^{-1} (UV-Vis experiments) in the following buffers: CF_3SO_3H/CF_3SO_3Na (μ = 0.1 mol L^{-1}; pH 1), CH_3COOH/CH_3COONa (μ = 0.1 mol L^{-1}; pH 4.75); CH_3COOH/CH_3COONa (μ = 0.1 mol L^{-1}; pH 4.90), or Na_2HPO_4/NaH_2PO_4 (μ = 0.1 mol L^{-1}; pH 7.4). The collimated beam intensities ranged from 1×10^{-9} to 4×10^{-8} einstein^{-1} cm^{-2} as determined by ferrioxalate actinometry. The chemical actinometer potassium tris(oxalato)ferrate(III) was prepared according to Calvert and Pitts.[53] After the equilibration of the cell holder temperature, photolysis begun by irradiating the sample for a period of time ranging from 0 to 7200 s, with increments of 1200 s.

Considering that the coordinated water of *trans*-[RuCl(1-pramcyH)(OH_2)]$^{3+}$ has a pK_a of 3.1,[48] the calculated NO quantum yield was based on the concentrations of the photoproduct *trans*-[RuCl(1-pramcyH)(L)]$^{n+}$ (L = H_2O,

OH^-), obtained by spectroscopic determination with absorbance readings at λ = 356 nm for the photolysis at pH = 1. At this pH, *trans*-$[RuCl(1\text{-}pramcyH)(OH_2)]^{3+}$ (λ_{max}/nm = 356, ε/(dm^3 mol^{-1} cm^{-1}) = 2900) is formed. At pHs 4.75 and 4.90, a mixture of *trans*-$[RuCl(1\text{-}pramcyH)(OH_2)]^{3+}$ and *trans*-$[RuCl(1\text{-}pramcyH)(OH)]^{2+}$ (λ_{max} = 315, ε = 830) is obtained. At pH 7.4, only *trans*-$[RuCl(1\text{-}pramcyH)(OH)]^{2+}$ (λ_{max} = 310, ε = 1.0 x 10^3) is produced.

The calculated ϕ_{NO} values were plotted *versus* % of the reaction (ϕ x % R). The extrapolated spectroscopic quantum yield at R = 0% was taken as ϕ_{NO} for the photoaquation of NO from *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)]^{3+}$. Evaluation of ϕ_{NO} at R = 0 % eliminates possible complications resulting from secondary photolysis of primary reaction products and inner filter effects.

Results and Discussion

Syntheses

The synthesis of the 1-pramcyH complex uses *trans*-$[Ru(tfms)Cl(1\text{-}pramcyH)](tfms)_2$ as precursor, which, in acidic aqueous solution, aquates with a specific rate constant, k_1, of 6.5×10^{-2} s^{-1} at pH 1, forming *trans*-$[RuCl(OH_2)(1\text{-}pramcyH)]^{3+}$.[48] As for the cyclam complex, *trans*-$[Ru(NO)Cl(cyclam)](PF_6)_2$, *trans*-$[RuCl(H_2O)(1\text{-}pramcyH)]^{3+}$ generates *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)]^{3+}$ in the presence of NO. The nitrosyl complex was obtained as its hexafluorophosphate salt, *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)](PF6)_3$, which is soluble in water, acetonitrile, methanol and dimethylsulfoxide, and in a lesser extent in acetone.

Because the complex was isolated in acidic medium (0.1 mol L^{-1} HPF_6), the aminopropyl group is protonated. Potentiometric titration allowed estimation of two pK$_a$ values (7.0 and 8.2) for *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)](PF_6)_3$, which should be ascribed to one of the cyclam nitrogen protons and to the protonated propylammonium. Considering that the cyclam nitrogen of the related complexes *trans*-$[RuCl(cyclam)(NHC(O)4\text{-}py)]^+$ (py = pyridine), *trans*-$[RuCl_2(1\text{-}pramcyH)]^{2+}$, and *trans*-$[RuCl(OH)(1\text{-}pramcyH)]^{2+}$ have pK$_a$ values of 7.9, 8.0, and 7.8, respectively,[48,54] and free propylammonium has a pK$_a$ of 9.8,[55,56] it is difficult to undoubtedly assign the pK$_a$ values. However, it is more likely that the pK$_a$ of 7.0 refers to the cyclam nitrogen and that of 8.2 to propylammonium, value that is lower than 9.8 due to the charge effect of the Ru metal center, as expected.

IR, EPR, NMR and electronic spectra

In nitrosyl complexes, an IR absorption band assigned to NO stretching in the 1950-1800 cm^{-1} region is associated with a linear structure for Ru–N–O and a nitrosonium character (NO^+).[57] Ruthenium complexes of this type are often represented by the resonance form $Ru^{II}(NO^+)$. As pointed out earlier, this formulation is one of several resonance forms (others being $Ru^{III}(NO)$ and $Ru^{IV}(NO^-)$), and, following Enemark and Feltham's[58] notation, the $\{Ru\text{-}NO\}^6$ complexes are highly delocalized. The IR spectrum of nujol mulls of *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)](PF_6)_3$ displays three peaks at 1880 cm^{-1}, 1865 cm^{-1} and 1842 cm^{-1} (Figure 1). In the IR spectra of ruthenium nitrosyl complexes recorded from Nujol mulls or KBr pellets, the NO stretching band sometimes appears as two or more peaks or as one peak with one or two shoulders. This feature has been assigned to solid state effects.[18] However, only one peak at 1875 cm^{-1} appears in the spectrum of the aqueous solution of *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)](PF_6)_3$; it is shifted to 1864 cm^{-1} in acetonitrile (Figure 2), indicating a solvent dependence for the ν(NO). These peaks support the nitrosonium character of NO in this complex. An attempt to obtain an EPR spectrum for *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)](PF_6)_3$ showed no signal, giving further support to the IR assignment.

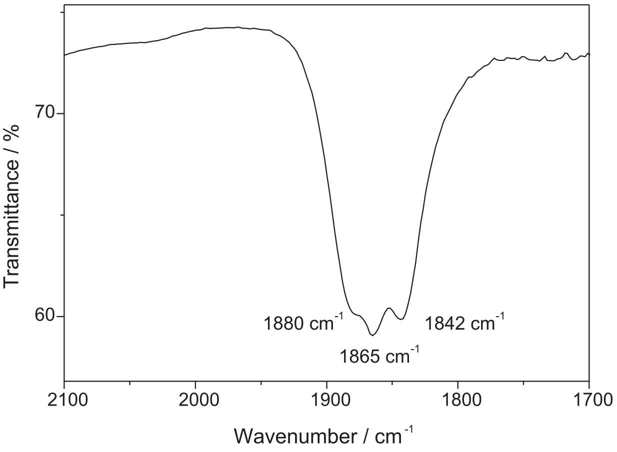

Figure 1. Infrared spectrum of *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)](PF_6)_3$ in nujol mull.

The ^1H and ^{13}C NMR spectra of *trans*-$[Ru(NO)Cl(1\text{-}pramcyH)](PF_6)_3$ are consistent with the presence of the 3-propylammonium group ($-(CH_2)_3NH_3^+$) bound to a cyclam nitrogen. The ^1H NMR chemical shifts in the 5-7.5 ppm range can be assigned to the hydrogen atoms linked to the nitrogens of cyclam and those of the 3-propylammonium group (Figure S1 in Supplementary Information).

In the already described ^1H NMR spectrum of *trans*-$[Ru(NO)Cl(cyclam)](PF_6)_2$ obtained in D_2O,[25] the NH's hydrogen signals are absent because of fast H-D exchange.[18,60] Hence, the ^1H NMR spectrum of *trans*-$[Ru(NO)Cl(cyclam)](PF_6)_2$ was obtained in acetonitrile-*d*$_3$

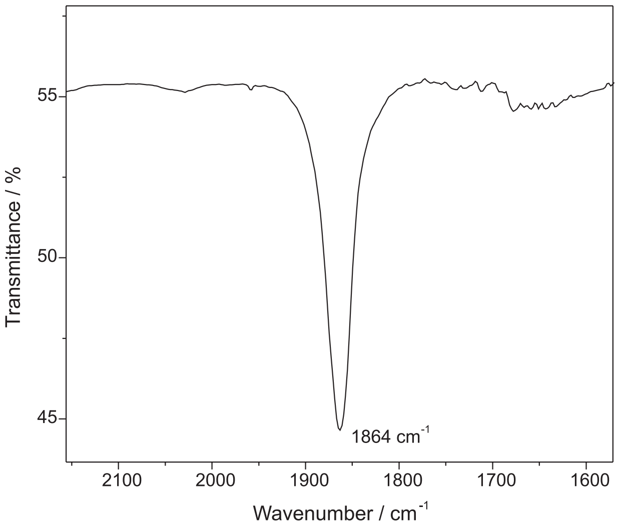

Figure 2. Infrared spectrum of a 10^{-2} mol L^{-1} acetonitrile solution of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$.

for comparison, and it has a relatively simple resonance pattern regarding the NH-cyclam hydrogens, as a result of the higher symmetry of the cyclam moiety in this geometry.[25] There are two signals in the 5-7.5 ppm range (δ = 5.12 and 5.66 ppm) (see Experimental section), with 2:2 intensities, assigned to four NH hydrogens of cyclam. In its turn, the ^{1}H NMR spectrum of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ in acetonitrile-d_3 shows three signals of NH hydrogens with 3:1:2 intensities (Figure S1). The signal with δ 5.36 ppm was assigned to the hydrogen atoms linked to the nitrogen of 3-propylammonium group, while the signals with δ 6.06 and δ 6.26 ppm were assigned to hydrogen atoms linked to the cyclam nitrogens. These signals were absent in the ^{1}H NMR in D_2O because of fast H-D exchange. The integral of the signals assigned to the carbon chain hydrogens of the 1-(3-propylammonium) cyclam ligand is consistent with 26 hydrogens in this molecule (see Experimental section).

The ^{13}C NMR spectrum of *trans*-[Ru(NO)Cl(cyclam)]$(PF_6)_2$ in acetonitrile-d_3 displays six signals in the 26-56 ppm range assigned to the CH_2 aliphatic carbons present in the macrocyclic ligand, and is consistent with that of *trans*-[RuCl(cyclam)(4-acpy)]$(BF_4)_2$.[59] In its turn, the ^{13}C NMR spectrum of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ in acetonitrile-d_3 shows thirteen peaks (Figure S2), assigned to the CH_2 aliphatic carbons present in the 1-(3-propylammonium)cyclam ligand. The structure of this complex in solution is shown in Figure 3, and is similar to those of *trans*-[Ru(NO)Cl(cyclam)]$(PF_6)_2$,[25] *trans*-[RuCl(cyclam)(4-acpy)]$(BF_4)_2$,[59] and *trans*-[$RuCl_2$(cyclam)]Br.[61] This *trans* configuration is the thermodinamically expected one, unlike that of *fac*-[Ru(NO)Cl_2(κ^3N^4,N^8,N^{11}(1-carboxypropyl)cyclam)]$^+$, a very closely related cyclam monosubstituted complex, where the cyclam ring N (with the carboxypropyl pendant arm instead of an aminopropyl) is not coordinated to the ruthenium, resulting in κ^3 denticity.[19]

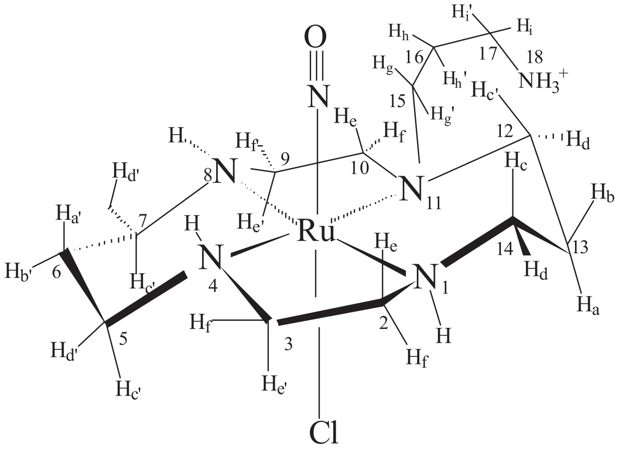

Figure 3. Structure of *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$.

The electronic spectrum of *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$ (Figures S3 and S4) is similar to those of other ruthenium nitrosyl complexes,[17,18,25] especially that of the related cyclam complex, *trans*-[Ru(NO)Cl(cyclam)]$^{3+}$, as expected. This is due to the similarity of the ligands and, therefore, the bands were assigned by analogy. The spectrum of a pH 1 aqueous solution of *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$ displays one band at 272 nm (ε/(dm^3 mol^{-1} cm^{-1}) = 3.1×10^3), ascribed to a ligand to metal charge transfer (LMCT) [$p_\pi(Cl) \rightarrow e_g(Ru)$], and another band at 360 nm ($\varepsilon = 4\times10^2$) assigned to at least a spin-allowed d-d transition plus an additional contribution from a metal to ligand charge transfer (MLCT) due to a $d_\pi(Ru)\rightarrow\pi^*(NO)$ transition. The band at 455 nm (ε = 90) was assigned to a ligand field transition with a possible contribution from another $d_\pi(Ru)\rightarrow\pi^*(NO)$ MLCT transition.

Redox potentials

The cyclic voltammetry study of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ in acetonitrile [25º C; 100 mV s^{-1}; μ = 0.1 mol L^{-1} tba(PF_6)] reveals three electrochemical processes in the –1.6 V to + 1 V range (*vs*. Ag/AgCl): Ep_{2c} = –1350 mV, Ep_{1c} = –320 mV and Ep_{1a} = –220 mV (Figure S5). The ratio of the Ep_{1c} and Ep_{1a} current peak heights approaches unity as the scan rate increases, consistent with a coupled chemical reaction, assigned to the slow loss of NO following reduction to *trans*-[Ru(NO)Cl(1-pramcyH)]$^{2+}$, similarly to *trans*-[Ru(NO)Cl(cyclam)]$^+$.[25] If the [Ru^{II}-NO^+] formalism is considered, the Ep_{1c} and Ep_{1a} processes can be attributed to the NO^+/NO^0 (or $\{RuNO\}^{6/7}$)

$$\textit{trans}\text{-[RuCl(NO)(1-pramcyH)]}^{3+} \underset{-e\ \ 1a}{\overset{+e\ \ 1c}{\rightleftharpoons}} \textit{trans}\text{-[RuCl(NO)(1-pramcyH)]}^{2+} \tag{1}$$

$$\textit{trans}\text{-[RuCl(NO)(1-pramcyH)]}^{2+} \underset{-e}{\overset{+e\ \ 3c}{\rightleftharpoons}} \textit{trans}\text{-[RuCl(NO)(1-pramcyH)]}^{+} \tag{2}$$

couple by analogy with *trans*-$[Ru(NO)Cl(cyclam)]^{2+}$, for which $Ep_{1c} = –210$ mV and $Ep_{1a} = –150$ mV (*vs*. Ag/AgCl) were obtained (equation 1). The previously reported values of Ep_{1c} = –262 mV and Ep_{1a} = –82 mV (*vs*. Ag/AgCl)[25] were probably due to an ohmic drop. The Ep_{2c} process at –1.35 V can be assigned to the $\{RuNO\}^{7/8}$ process, similarly to *trans*-$[Ru(NO)Cl(cyclam)]^{n+}$ (equation 2).[25]

The cyclic voltammetric behavior of *trans*-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$ in 0.1 mol L^{-1} CF_3SO_3H/CF_3SO_3Na at pH 1 and 25 ºC is very similar to that of *trans*-$[Ru(NO)Cl(cyclam)]^{3+}$.[25] At a 100 mV s^{-1} scan rate, there are three electrochemical processes, namely Ep_{1c} = –390 mV, Ep_{2c} = –530 mV, and Ep_{2a} = –400 mV *vs*. Ag/AgCl (Figure 4). At these conditions, peak 1a (see ahead) is enveloped by peak 2a; peaks 2c and 2a are pH dependent in the 1-9 pH range, while the others are pH independent. When the cyclic voltammogram is run in 0.2 mol L^{-1} LiCl at pH 6 or in 0.1 mol L^{-1} HCl/KCl at pH 1, only two peaks are detected, Ep_{1c} at –370 mV and Ep_{1a} at –290 mV *vs*. Ag/AgCl; peaks 2a and 2c are no longer observed (Figure S6). These results are consistent with suppression of the chloride dissociation, and the observed redox process is assigned to the $\{RuNO\}^{6/7}$ couple for *trans*-$[Ru(NO)Cl(1\text{-pramcyH})]^{3+}$ (equation 1).

Reduction of *trans*-$[Ru(NO)Cl(1\text{-pramcyH})]^{3+}$ at –400 mV should be followed by a fast chloride release, as verified by a test with silver nitrate, to form *trans*-$[Ru(NO)(OH_2)(1\text{-pramcyH})]^{3+}$ (equation 3), which then loses NO at a smaller rate, to form *trans*-$[Ru(OH_2)_2(1\text{-pramcyH})]^{3+}$ (equation 4). The pH dependent 2c/2a pair of peaks was attributed to the $\{RuNO\}^{6/7}$ couple in *trans*-$[Ru(NO)(OH_2)(1\text{-pramcyH})]^{4+}$ (equation 5), after loss of chloride.

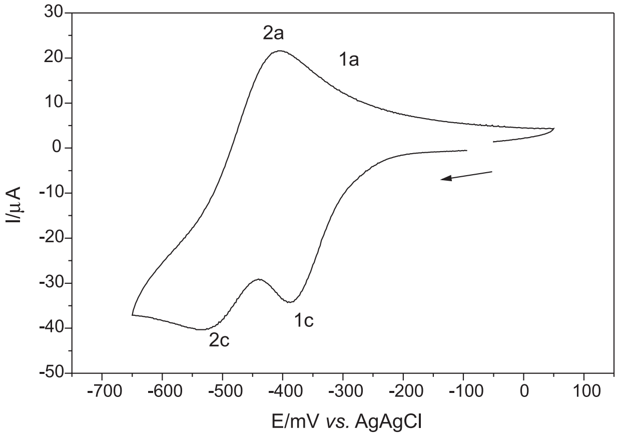

Figure 4. Cyclic voltammogram of a 7×10^{-3} mol L^{-1} solution of *trans*-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$. Conditions: 0.1 mol L^{-1} CF_3SO_3H/CF_3SO_3Na at pH 1; 100 mV s^{-1}; glassy carbon, Ag/AgCl and platinum wire as the working, reference and auxiliary electrodes, respectively; T = 25 ºC.

Only when the scan range is extended further to –1.5 V (*vs*. Ag/AgCl) in 0.1 mol L^{-1} CF_3SO_3H/CF_3SO_3Na at pH 1, and the coordinated NO^0 undergoes a further reduction process $\{RuNO\}^{7/8}$ (equation 6), or at smaller scan rates, is it possible to observe the presence of the *trans*-$[Ru(H_2O)_2(1\text{-pramcyH})]^{3+}$ species (equation 7) in the repetitive scan mode. The *trans*-$[Ru(H_2O)_2(1\text{-pramcyH})]^{3+}$ species exhibits a reversible, pH dependent, one electron electrochemical process at $E_{1/2}$ = –50 mV close to the

$$\textit{trans}\text{-[RuCl(NO)(1-pramcyH)]}^{2+} + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \textit{trans}\text{-[Ru(OH}_2\text{)(NO)(1-pramcyH)]}^{3+} + Cl^{-} \tag{3}$$

$$\textit{trans}\text{-[Ru(OH}_2\text{)(NO)(1-pramcyH)]}^{3+} + H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \textit{trans}\text{-[Ru(OH}_2\text{)}_2\text{(1-pramcyH)]}^{3+} + NO \tag{4}$$

$$\textit{trans}\text{-[Ru(OH}_2\text{)(NO)(1-pramcyH)]}^{4+} \underset{-e\ \ 2a}{\overset{+e\ \ 2c}{\rightleftharpoons}} \textit{trans}\text{-[Ru(OH}_2\text{)(NO)(1-pramcyH)]}^{3+} \tag{5}$$

$$\textit{trans}\text{-[Ru(OH}_2\text{)(NO)(1-pramcyH)]}^{3+} \underset{-e}{\overset{+e\ \ 3c}{\rightleftharpoons}} \textit{trans}\text{-[Ru(H}_2\text{O)(NO)(1-pramcyH)]}^{2+} \tag{6}$$

$$\textit{trans}\text{-[Ru(H}_2\text{O)}_2\text{(1-pramcyH)]}^{4+} \underset{-e\ \ 4a}{\overset{+e\ \ 4c}{\rightleftharpoons}} \textit{trans}\text{-[Ru(H}_2\text{O)}_2\text{(1-pramcyH)]}^{3+} \tag{7}$$

$$trans\text{-}[Ru(OH_2)(NO)(1\text{-pramcyH})]^{3+} + H_2O \rightleftharpoons trans\text{-}[Ru(OH)(NO)(1\text{-pramcyH})]^{2+} + H_3O^+ \qquad pKa\ ca.\ 7 \tag{8}$$

$$trans\text{-}[Ru(OH_2)(NO)(1\text{-pramcyH})]^{4+} + H_2O \rightleftharpoons trans\text{-}[Ru(OH)(NO)(1\text{-pramcyH})]^{3+} + H_3O^+ \qquad pKa\ ca.\ 2 \tag{9}$$

reported value, at pH 1, of –100 mV[48] and of –155 mV for *trans*-$[Ru(H_2O)_2(cyclam)]^{2+}$.[61] The possibility that the Ep_{3c} process may involve five electrons and result in reduction of NO to amine, as reported for some cases,[62-64] is under investigation in our laboratories.

From plots of Ep_{2c} *versus* pH it was possible to estimate the equilibrium constants for the reactions represented in equations 8 and 9.

The estimated pK_a value of 2 for the *trans*-$[Ru(NO)(OH_2)(1\text{-pramcyH})]^{4+}$ species is close to those of *trans*-$[Ru(NO)(OH_2)(cyclam)]^{3+}$ and *trans*-$[Ru(NO)(OH_2)(NH_3)_4]^{3+}$ species, pK_a = 3.1.[25,42] As in the case of the latter two complexes and others, such as *trans*-$[Ru(salen)(NO)(OH_2)]^+$ with a pK_a of 4,[40] it indicates a strong Ru^{III} character.

Spectroelectrochemistry

The infrared and UV-Vis spectral changes observed for *trans*-$[RuCl(NO)(1\text{-pramcyH})](PF_6)_3$ when it is submitted to a controlled potential electrolysis at –500 mV *vs.* Ag/AgCl in acetonitrile (μ = 0.1 mol L^{-1} tba(PF_6)) are shown in Figures 5 and 6. We were unable to avoid some solvent evaporation during the experiments, which may explain the absence of clean isosbestic points. The intensity of the ν(NO) band at 1864 cm^{-1} decreases, while a new peak appears at 1810 cm^{-1}, the intensity of which increases. These changes are consistent with the reduction of the nitrosyl ligand, forming *trans*-$[Ru(NO)Cl(1\text{-pramcyH})]^{2+}$, and are similar to results previously described in the literature.[18,25]

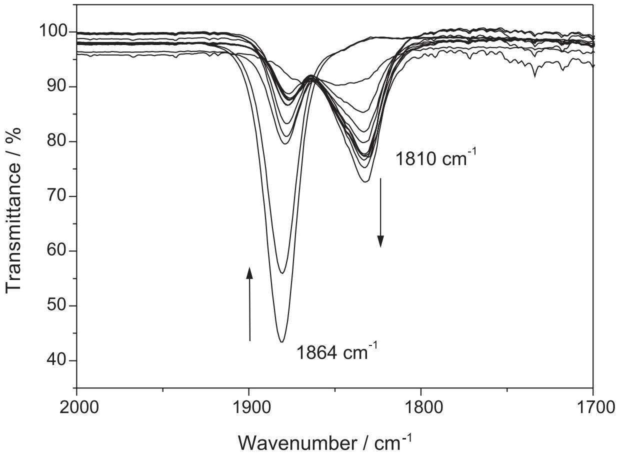

Figure 5. Infrared spectral changes during controlled potential electrolysis at –500 mV (*vs*. Ag/AgCl) of *trans*-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$ in a 2.1×10^{-2} mol L^{-1} acetonitrile solution containing 0.1 mol L^{-1} tba(PF_6) at 25 °C. Time intervals between spectra: 10 min.

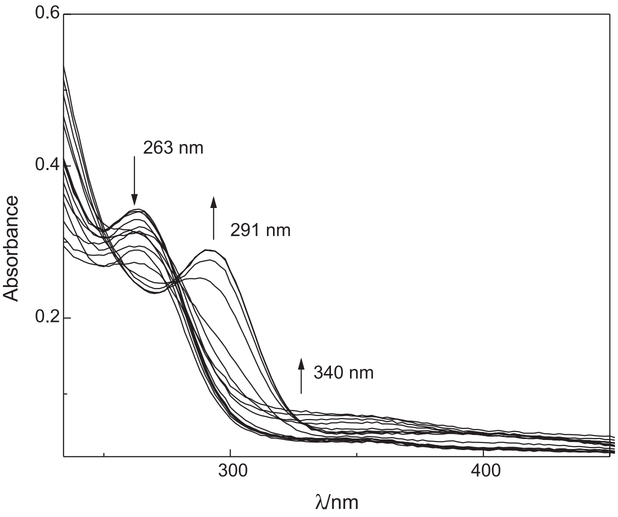

Figure 6. UV-Vis spectral changes during controlled potential electrolysis at –500 mV (*vs*. Ag/AgCl) of a 2.1×10^{-2} mol L^{-1} acetonitrile solution of *trans*-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$ containing 0.1 mol L^{-1} tba(PF_6) at 25 °C. Time intervals between spectra: 10 min.

However, it has been reported that the spectra of reduced froms of nitrosyl complexes show the ν(NO) peak at much lower wavenumbers.[65,66]

The electronic absorption spectral changes observed for *trans*-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$ consist of an absorbance decrease at 263 nm with a concomitant increase at 291 nm. The final electronic absorption spectrum is assigned to the *trans*-$[Ru(NO)Cl(1\text{-pramcyH})]^{2+}$ complex. Likewise, the UV-Vis monitoring of the non-exhaustively controlled potential electrolysis of *trans*-$[RuCl(cyclam)(NO)](PF_6)_2$, carried out in the same conditions to promote reduction of NO^+ to NO, shows absorbance decrease at 254 nm with concomitant increase at 298 nm, which in acetonitrile and under a reductive potential should denote coordinated NO^0.

Photochemical studies

Irradiation of *trans*-$[Ru(NO)Cl(1\text{-pramcyH})](PF_6)_3$ in a deaerated 0.1 mol L^{-1} HPF_6 solution with light of λ = 334 nm results in the decrease in intensity of the ν(NO) band at 1875 cm^{-1} (Figure 7). This decrease undoubtedly suggests the photochemical labilization of NO (equation 10). Similar changes in the infrared spectrum had already been observed with 10^{-2} mol L^{-1} *trans*-$[RuCl(NO)(cyclam)]^{2+}$ and *trans*-$[RuCl([15]aneN_4)NO]^{2+}$ solutions at pH 7,[17] and with *trans*-$[RuCl(NO)(cyclam)]^{2+}$ in a xerogel matrix.[16] Addition of silver nitrate solution to the photolyzed solution did not

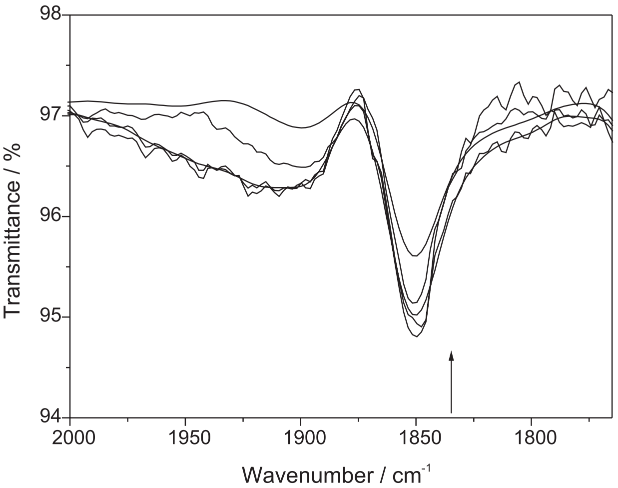

Figure 7. Infrared spectral changes during photolysis (λ = 334 nm) of a 1×10^{-2} mol L^{-1} solution of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ in 0.1 mol L^{-1} HPF_6 at 25 °C. Total photolysis time: 3 h.

evidence formation of AgCl, indicating that chloride is not labilized as far as this assay is considered.

The UV-Vis spectral changes during photolysis of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ with 334 nm light at pH 1 are shown in Figure 8. There is a broad absorption increase in the 300-390 nm region, which is consistent with the formation of the Ru^{III} aquo complex photoproduct, *trans*-[Ru(OH_2)Cl(1-pramcyH)]$^{3+}$ (equation 10), as observed for *trans*-[RuCl(NO)(cyclam)]$(PF_6)_2$[27] and other ruthenium ammine nitrosyl complexes.[16,17] At this pH, *trans*-[Ru(OH_2)Cl(1-pramcyH)]$^{3+}$ has an absorption band at λ_{max}/nm = 356 (ε/(dm^3 mol^{-1} cm^{-1}) = 2900). At pH 4.75 or 4.90, the photoproduct is mainly *trans*-[Ru(OH)Cl(1-pramcyH)]$^{2+}$, which absorbs at λ_{max} = 356 (ε = 830). At pH 7.4, *trans*-[Ru^{III}(OH)Cl(1-pramcy)]$^{+}$ absorbs at λ_{max} = 356 (ε = 2900).

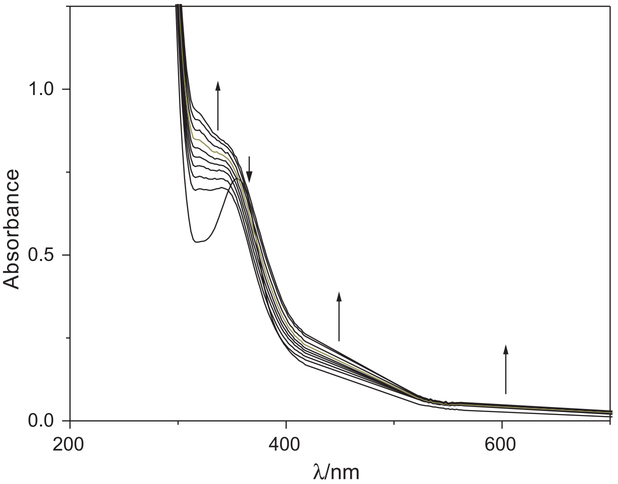

Figure 8. UV-Vis spectral changes during photolysis (λ = 334 nm) of a 2.6×10^{-2} mol L^{-1} solution of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ in CF_3SO_3H/CF_3SO_3Na (μ = 0.1 mol L^{-1}, pH 1) at 25 °C. Total photolysis time: 3h.

The photoproducts quantum yields for the photolysis of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ are shown in Table 1.

Table 1. Quantum yield values for NO photoaquation from *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ at different pH values and irradiation wavelengths

pH	λ_{irr}/nm	ϕ_{NO}^{a}
1.00	313	0.009 (± 0.001)
1.00	334	0.008 (± 0.001)
1.00	370	< 0.0010
4.75	313	0.010 (± 0.002)
4.75	334	0.009 (± 0.001)
4.75	370	< 0.001
4.90	313	0.030 (± 0.002)
4.90	334	0.011 (± 0.001)
4.90	370	< 0.002
7.40	313	0.10 (± 0.002)
7.40	334	0.09 (± 0.01)
7.40	370	< 0.003

[a]Average values of three determinations. pH 1 in a CF_3SO_3H/CF_3SO_3Na (μ = 0.1 mol L^{-1}; pH 1); pH 4.75 and 4.90 (0.01 mol L^{-1} acetate buffer); pH 7.4 in 0.1 mol L^{-1} phosphate buffer.

The quantum yields pattern for the photolysis of *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ is similar to those of other nitrosyl ruthenium(am(m)ine) complexes.[14,17,18,46,67] The quantum yields decrease as pH decreases and as the irradiation wavelength increases, being noticeable only at λ_{irr} < 370 nm. The larger quantum yields achieved at larger pH values can be explained, as in the case of the analogous *trans*-[Ru(NO)$(NH_3)_4$(py-X)]$^{3+}$ complexes,[46] as follows. The *trans*-[Ru(NO)Cl(1-pramcyH)]$(PF_6)_3$ complex has 3 pK_a values, and as the pH increases, in addition to other species a larger fraction of the product is in the hydroxo form. Different species are not necessarily expected to have the same quantum yields. Also, the hydroxo complex is likely to be much less reactive toward the back reaction with NO than the corresponding aquo product, and, thus, has larger quantum yields. As a matter of fact, the increase in quantum yield with larger pH is also consistent with the synthesis of *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$ (see Experimental).

$$\textit{trans}\text{-[RuCl(NO)(1-pramcyH)]}^{3+} \xrightarrow[\text{H}_2\text{O, H}^+]{h\nu} \textit{trans}\text{-[RuCl(OH}_2\text{)(1-pramcyH)]}^{3+} + \text{NO} \qquad (10)$$

Conclusions

The procedures described here result in the successful synthesis of a ruthenium nitrosyl complex with the substituted 1-(3-propylammonium)cyclam, *trans*-[Ru(NO)Cl(1-pramcyH)](PF$_6$)$_3$. Unlike 1-carboxypropyl, which results in a *fac* configuration for the nitrosyl complex, the aminopropyl results in the thermodynamically expected *trans* arrangement. This amine functionalized complex can be linked to a peptide, or an antibody, for selective biological activity. It can also be bound to a support in a device, such as a stent, to form a drug eluting stent. The behavior of *trans*-[Ru(NO)Cl(1-pramcyH)]$^{3+}$, which contains a substituted cyclam, parallels that of the cyclam analog, suggesting that these complexes could maintain their properties when linked to a biomolecule. Electrochemical and photochemical experiments suggest the labilization of NO. Like other ruthenium am(m)mine nitrosyl complexes, such as *trans*-[Ru(NO)(NH$_3$)$_4$(py-X)]$^{n+}$ and *trans*-[RuCl(NO)(cyclam)](PF$_6$)$_2$, *trans*-[Ru(NO)Cl(1-pramcyH)](PF$_6$)$_3$ is attractive for potential biological applications because it is stable, water-soluble, and can deliver NO upon activation by reduction at a biologically accessible potential and/or by irradiation with light. Current research in this lab is directed toward these goals for potential applications of the complexes as NO donors.

Supplementary Information

^{1}H NMR, ^{13}C NMR and electronic absorption spectra, as well as cyclic voltammograms recorded for *trans*-[Ru(NO)Cl(1-pramcyH)](PF$_6$)$_3$, are available free of charge at http://jbcs.sbq.org.br, as a pdf file.

Acknowledgments

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