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Structure, chemical and photochemical reactivity and biological activity of some ruthenium amine nitrosyl complexes

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This paper is dedicated to Professor A.B.P. Lever on the occasion of his 65th birthday anniversary. It should be a part of the special issue dedicated to Professor Lever, but, unfortunately, we missed the deadline.

Contents

Abstract

Through spectroscopic (X-ray, Infrared, ^{1}H-NMR, EPR, UV–vis) and electrochemical (cyclic voltammetry, differential pulse polarography) data and quantum mechanical calculations, the formulation [Ru(II)NO$^+$] was attributed to a series of new ruthenium(II) amine compounds. A remarkable stability of the Ru(II) relative to Ru(III) was observed upon coordination to NO. The presence of nitrosyl in the coordination sphere results in dramatic implications in the lability, acidity and redox properties of the ligand *trans* to NO. These effects are higher than expected just on the basis of one unity increment in the metal center charge. Based on molecular orbital (MO) analysis and on reduction product analysis, the site of the reduction $[Ru(NO)]^{3+} + e^- \rightarrow [Ru(NO)]^{2+}$ was assigned to the NO ligand. The dissociation of the coordinated NO^0 is dependent on the *trans* effect and *trans* influence of the *trans* ligand L. Irradiation of the nitrosyl complexes with 300–350 nm light results in NO aquation and formation of the corresponding aquaruthenium(III) complex, i.e.

$$trans\text{-}[Ru(NO)(NH_3)_4L]^{3+} \xrightarrow[H_2O,\ H^+]{h\nu} trans\text{-}[Ru(NH_3)_4(H_2O)L]^{3+} + NO^0$$

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Irradiation in the visible region (400–500 nm) did not result in any observable reaction in solution; however, at low temperature and in the solid state, evidence in favor of the formation of linkage isomers has been obtained. The hypotensive properties of *trans*-$[Ru(NO)(NH_3)_4(P(OC_2H_5)_3)](PF_6)_3$ and *trans*-$[Ru(NO)Cl(cyclam)](ClO_4)_2$ have been demonstrated in mice and rats.

Keywords: Chemical and photochemical reactivity; Biological activity; Ruthenium amine and ruthenium ammine nitrosyl complexes; Nitric oxide donors; Nitric oxide scavengers

1. Introduction

The chemistry [1] of nitric oxide and its relevance to environmental and technological processes [1a,1h] has been recognised and the subject of research for a long time [1]. In the beginning of the last decade, with the discovery of the NO participation in a wide range of physiological processes [2], there was a renewed interest in understanding the fundamental chemistry of NO and of metal nitrosyl complexes [3], and work is still needed to understand better how to control nitric oxide reactivity. In this context, we are also working to gain control over the nitrosyl complexes thermal and photochemical reactivities and therefore to tailor complex ions to a desired target [4].

The hexacoordinate ruthenium amine complexes were chosen due to their outstanding properties [5]. In these complexes, kinetic and thermodynamic reactivities of the axial ligand are sensitive to the ligand in the *trans* position to it in the coordination sphere [5]. Therefore, the judicious choice of the ligand in the *trans* position to the NO in complexes such as *trans*-$[Ru(NO)A_4L]^{n+}$ ($A = NH_3$, A_4 = cyclam) could be used to modulate its reactivity.

The results reported here summarize our efforts in this direction. The tuning of NO is being pursued not only through changes in the axial ligand but also in the equatorial plane of the complex. Ligands as cyclam, hedta, polyamines and polyphosphanes are also under investigation. Biological tests have been carried out with the most promising compounds at biological and medical centers.

2. Synthesis

Since the presence of the NO ligand in the coordination sphere delabilizes the ligand in the *trans* position, the *trans*-$[Ru(NO)(NH_3)_4L]^{3+}$ complexes could not be obtained by reacting *trans*-$[Ru(NO)(NH_3)_4(H_2O)]3+$ with L [4g]. Instead, the compounds *trans*-$[Ru(NO)(NH_3)_4L](X)_3$ where L = triethylphosphite ($P(OEt)_3$), isonicotinamide (isn), nicotinamide (nic), 4-picoline (4-pic), pyridine (py), 4-chloropyridine (4-Clpy), pyrazine (pz), 4-acetylpyridine (4-acpy), N-bound imidazole (imN), C-bound imidazole (imC) and L-histidine (L-hist) have been prepared according to Eq. (1) [4a,4b].

$$trans\text{-}[Ru(NH_3)_4L(H_2O)]^{2+} + NO_2^- + 2H^+ \rightleftharpoons trans\text{-}[Ru(NO)(NH_3)_4L]^{3+} + 2H_2O \quad (1)$$

Except for $L = P(OEt)_3$, the *trans* aqua species were synthesized following the sulfite/sulfate route [4a,4b]. The compound *trans*-$[Ru(NO)(SO_3)(NH_3)_4]Cl$ was isolated by reacting *trans*-$[Ru(SO_3)(NH_3)_4(H_2O)]$ with $NaNO_2$–HCl mixture. The binuclear complex $[(NO)(NH_3)_4RuSSRu(NH_3)_4(NO)]Cl_6 \cdot H_2O$ was obtained [4a] from the reduction of *trans*-$[Ru(NH_3)_4SO_3(NO)]Cl$ with Cd(Hg). This binuclear complex is unstable and decomposes even on standing in the solid state. The main decomposition products of the disulfide complex are H_2S and *trans*-$[Ru(NO)(NH_3)_4(H_2O)]Cl_3$.

The compound *cis*-$[Ru(NO)(NH_3)_4(NO_2)]Br_2$ was prepared [4a] by reacting *cis*-$[Ru(NO)(NH_3)_4(H_2O)](ClO_4)_2$ with $NaNO_2$–HBr.

The cyclam complexes were prepared following two different procedures [4g]. In the first method *trans*-$[Ru(NO)(Cl)(cyclam)](PF_6)_2$ was obtained by reacting *trans*-$[RuCl(CF_3SO_3)(cyclam)](CF_3SO_3)$ with gaseous NO in aqueous medium. The product was isolated as a yellow solid upon $(NH_4)PF_6$ addition at the end of the reaction. In the second method, *trans*-$[Ru(NO)Cl(cyclam)]Cl_2 \cdot 2H_2O$ was prepared refluxing in methanol equimolar amounts of $K_2[Ru(NO)Cl_5]$ and cyclam.

The complex *trans*-$[Ru(NO)Cl(depe)_2](PF_6)_2$ was prepared [4j] by reacting $[Ru(NO)Cl_3] \cdot 5H_2O$ or $[Ru(NO)Cl_5]$ with 1,2-bis(diethylphosphino)ethane (depe) in ethanol.

3. Infrared spectroscopy and electrochemical data

These two techniques proved to be very useful for the characterization of the nitrosyl complexes (see Table 1) and for a preliminary estimation of the NO ligand reactivity towards nucleophiles [1b]. The infrared spectra of the nitrosyl complexes discussed here show NO stretching frequencies between 1871 and 1942 cm^{-1}, compatible with a nitrosonium character for the NO ligand [1b], and Ru–NO bands in the 598–739 cm^{-1} region, which is the same range reported for other ruthenium ammines [1a,1b,1d,1e,1f,1g,1h]. In the voltammetric experiments only one monoelectronic redox process was observed in the range −0.298 to +0.132 V (vs. NHE). This process is reversible at scan rates of 1 V s^{-1} and at 5 °C. The ruthenium centers did not appear

Table 1
Data for $E(NO^+/NO^0)$, ν_{NO} and K_{OH^-} for selected nitrosyl complexes

Complex	K_{OH^-} (l^2 mol^{-2})	$E_{(NO^+/NO^-)}$ (V vs. NHE)	ν_{NO}(cm^{-1})	ΣE_L [c]	Reference
trans-$[Ru(NO)(NH_3)_4(P(Oet)_3)](PF_6)_3$	3.4×10^5	0.132	1909	0.68	[4o]
trans-$[Ru(NO)(NH_3)_4(isn)](BF_4)_3$	2.5×10^8	0.052	1923	0.54	[4b]
trans-$[Ru(NO)(NH_3)_4(nic)](BF_4)_3$	5.9×10^7	0.072	1940	0.56	[4b]
trans-$[Ru(NO)(NH_3)_4(L\text{-hist})](BF_4)$	4.6×10^{13}	−0.108	1921	0.42	[4a]
trans-$[Ru(NO)(NH_3)_4(py)](BF_4)_3)$	2.2×10^5	0.012	1931	0.53	[4b]
trans-$[Ru(NO)(NH_3)_4(4\text{-pic})(BF_4)_3$	7.7×10^5	−0.008	1934	0.51	[13]
trans-$[Ru(NO)(NH_3)_4(imN)](BF_4)_3$	9.7×10^{10}	−0.118	1923	0.40	[4a]
trans-$[Ru(NO)(NH_3)_4(imC)]Cl_3$		−0.298	1913	−0.54	[17]
trans-$[Ru[(NO)(NH_3)_4(pz)](BF_4)_3$	6×10^8	0.112	1942	0.61	[4b]
$[Ru[(NO)(hedta)]$		−0.098	1846		[4k]
trans-$[Ru[(NO)Cl(NH_3)_4](BF_4)_3$	[a]		1888	0.04	[4c]
trans-$[Ru(NO)(NH_3)_4(H_2O)](BF_4)_3$	[b]	−0.148	1912	0.32	[4h]
trans-$[Ru(NO)Cl(cyclam)](PF_6)_2$	[b]	−0.078	1875		[4g,4h]
trans-$[Ru(NO)(NH_3)_4(4\text{-Clpy})](BF_4)_3$	6.0×10^6	0.012	1928	0.54	[13]

trans-$[Ru(NO)(NH_3)_4(L)]^{3+}+20H^- \rightleftharpoons$ *trans*-$[RuNO_2(NH_3)_4(L)]^+ + H_2O$.
[a] Reaction not reversible.
[b] Reaction not observable up to $C_{OH^-} \cong 10^{-3}$ M.
[c] $\Sigma E_L = 4\times E_L$ NH_3 (0.07) + E_LL. Volts vs. NHE.

to be electroactive [4] below +1.1 V. Based on MO analysis using the density functional theory (DFT) and on reduction product analysis, the site of the reduction $[RuNO]^{3+}+e^- \rightarrow [RuNO]^{2+}$ was assigned to be localized in the NO ligand.

For the tetraammines [1f,4] studied, the following electrochemical behavior was observed:

$$\textit{trans}\text{-}[Ru(NO)(NH_3)_4X]^{n+} + e^- \rightarrow \textit{trans}\text{-}[Ru(NH_3)_4(NO)X]^{(n-1)+} \quad (2)$$

$$\textit{trans}\text{-}[Ru(NH_3)_4(NO)X]^{(n-1)+} + H_2O \rightarrow \textit{trans}\text{-}[Ru(NH_3)_4(H_2O)X]^{(n-1)+} + NO \quad (3)$$

If $X = Cl^-$, the halide is aquated first:

$$\textit{trans}\text{-}[RuCl(NH_3)_4(NO)]^{(n-1)+} + H_2O \rightarrow \textit{trans}\text{-}[Ru(NH_3)_4(H_2O)(NO)]^{n+} + Cl^- \quad (4)$$

followed by the NO dissociation.

$$\textit{trans}\text{-}[Ru(NH_3)_4(H_2O)(NO)]^{n+} + H_2O \rightarrow \textit{trans}\text{-}[Ru(NH_3)_4(H_2O)_2]^{n+} + NO \quad (5)$$

Similar behavior was observed [4g,4j] for *trans*-$[Ru(NO)Cl(cyclam)]^{2+}$, and *trans*-$[Ru(NO)Cl(depe)_2]^{2+}$ upon one electron reduction.

A profile close to a straight line was observed from the plot of $E^{\circ\prime}$ (NO^+/NO^0 V vs. NHE) versus $\nu_{(NO)}$ (cm^{-1})(Eq. (6)) (Fig. 1) for the tetraammine complexes of Table 1, suggesting:

$$E^{\circ\prime}(NO^+/NO^0) = (-20\pm4) + (0.010\pm0.002)\nu_{NO} \quad (6)$$

$R = 0.85$; $N = 10$.

Since both ν_{NO} and $E^{\circ\prime}$ (NO^+/NO^0) are dependent on the extent of the $d\pi-p^x_{(NO)}$ donation, the IR data could be useful to estimate the relative oxidizing strength of the coordinated NO.

A correlation [4b,4c] was also observed between ($E^{\circ\prime}$ NO^+/NO^0 V vs. NHE) and ΣE_L [6] which ca. fits the

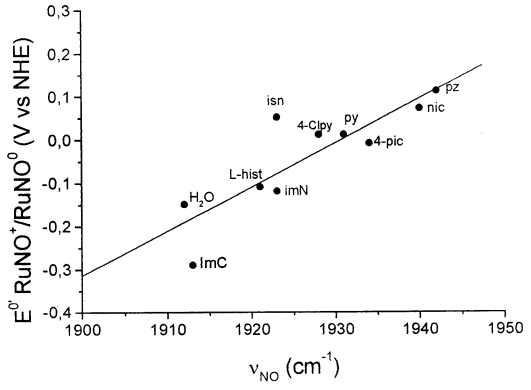

Fig. 1. Plot of ν_{NO} vs. $E^{\circ\prime}$ NO^+/NO^0 in selected nitrosyl ruthenium tetraammine complexes.

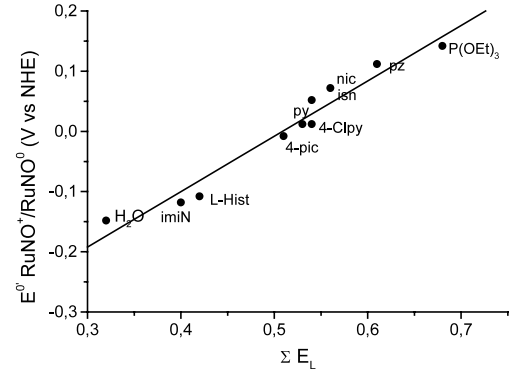

Fig. 2. Plot of ($E^{\circ\prime}$ NO^+/NO^0) vs. Σ of electrochemical ligand parameters (E_L), for selected nitrosyl ruthenium tetraammine complexes.

expression (Eq. (7), Fig. 2)

$$E^{\circ\prime}(NO^+/NO^0) = -(0.47 \pm 0.04) + (0.92 \pm 0.07)\sum E_L \quad (7)$$

$R = 0.92$: $N = 10$.

Only the ligand L in *trans* position to NO is changed along this series. Therefore, the Eq. (6) would correlate the effect of L on the ν_{NO} and $E^{\circ\prime}$ (NO^+/NO^0) in the *trans*-$[Ru(NH_3)_4(NO)]^{3+}$ moiety. A quite nice linear plot is provided by Eq. (7), which correlates E_L[L], through ($4E_L[NH_3]+E_L$[L]), with $E^{\circ\prime}$ (NO^+/NO^0). Since the one electron reduction is the first step on the activation through reduction of a nitrosyl complex to NO release [3c], the Eqs. (6) and (7) are a quite valuable tools to adjust the nitrosyl potential reduction, a key factor in tailoring metallonitrosyl pharmaceuticals as we will see in the following sections.

In a series of related ruthenium ammine complexes, ΣE_L would be related [3c,4b,4c,6] to the *trans*-$[Ru(NH_3)_4L]^{2+}$ moiety's back bond ability to NO. Thus an increase in ΣE_L would be reflected in an increase in the nitrosonium character of the coordinated NO, which as a function of L, will increase as follows:

$$NH_3 \sim H_2O < imN \sim L\text{-hist} < 4\text{-pic} \sim py < isn \sim nic \sim pz < imC < P(OEt)_3$$

These nitrosyl complexes are also electroactive at potentials more negative than −0.6 V, with a second reduction process. Although preliminary, the experiments suggest further reduction at the NO ligand, similar to that reported in the literature for $[Ru(II)(NO^+)(hedta)]^-$ [3g].

4. Electron paramagnetic resonance

The silent EPR spectra of the compounds listed in Table 1 are in agreement with the nitrosonium character suggested by the infrared data [1a,1b]. However, after in situ reduction of the compounds *trans*-$[Ru(NO)Cl(cyclam)]^{2+}$, *trans*-$[Ru(NO)(NH_3)_4(H_2O)]^{3+}$ and *trans*-$[Ru(NO)Cl(depe)_2]^{2+}$ with Eu(II) under strictly anaerobic conditions, and at 77 K, it was possible to detect the appearance of an EPR signal [4g,4h].

The EPR spectrum of *trans*-$[Ru(NO)Cl(cyclam)]^{2+}$ is better resolved [4h] than the other two and has $g_x = 1.995$, $g_y = 2.035$ and $g_z = 1.883$; $A_x = 32.1$ G; $A_y = 17$ G and $A_z = 15$ G. The reduction of the $[Ru(II)NO^+]$ moiety for these three compounds gives an EPR spectrum for which $g_z = 1.9$ and g_x, $g_y = 2.0$. The nearly axial ^{14}N hyperfine matrix has its parallel axis along the x-axis of the g matrix, indicating the unpaired electron is in a p_x-orbital of nitrogen, and therefore, in the π_x-orbital of NO. The observed large anisotropy in the g matrix signifies a large energy difference in the two π-orbitals of the NO bond and is a good indication of the bent character of the NO bound in the $[Ru(II)NO^0]$ moiety.

The observation of the EPR signal for these three complexes is consistent with their smaller specific rate of release of the bonded NO^0 [4h]. The better resolved spectrum of *trans*-$[Ru(NO)Cl(cyclam)]^{2+}$ was obtained due to the smaller specific rate constant of dissociation of NO after reduction of the coordinated NO^+ in this complex. Complexes with larger specific rate constants of dissociation of NO, after reduction at r.t. and then freezed, did not result in good spectra, even at 77 K. Perhaps these spectra could be obtained if reduction could be performed inside the EPR cavity at low temperature.

5. Nuclear magnetic resonance

Table 2 presents proton NMR data for some *trans*-$[Ru(NH_3)_4(NO)L]^{3+}$ complexes. Attempts to detect the proton NMR of NH_3 in the $[Ru(NH_3)_4(NO)L]^{3+}$ complexes in D_2O solutions [4a,4b] were mostly unsuccessful due to rapid exchange with D_2O. The first successful measurements were done in concentrated H_2SO_4 [7]. Earlier ^{14}N and ^{15}N NMR data have also been reported for the NO and NH_3 ligands in a few Ru(II) compounds [8,9], in this work, the NH_3 *cis* to the NO ligand had shifts in the range of 3.6–4.0 ppm relative to TMS and those para to NO had shifts in the range 4.1–4.6 ppm.

Recently [10] with modern FT spectrometers, it has been possible to detect the NH_3-NMR in deuterated dimethylsulfoxide solutions (Table 2) even though the solubility is low. The compounds, in most cases, were not very soluble but a useful spectrum was obtained and the residual water peak in DMSO at 3.34 ppm was visible. This residual water peak was often five to ten times the ammonia peaks in intensity due to the low solubility of the compound being studied. In the cases of $L = H_2O$ and NH_3 no separate residual water peak was found, indicating rapid exchange of the residual water protons and the ammonia protons was taking place. The ammonia peak was easy to identify by its increased line width due to the effects of the ^{14}N quadrupole moment.

A preliminary examination shows, as one might expect, that the proton shift in the equatorial ammonia is influenced only by Ru–NH_3 σ interactions. The Ru–NH_3 bonds are affected by the variation in the electronic density in Ru(II) imposed by the axial ligands, but this variation is sensed by the Ru–NH_3 bonds through their σ interactions. The ammonia molecule is a σ donor and is not considered to play a role in π interactions, and, thus, any transmission of electron density should occur through the Ru–NH_3 σ bonding system. This is confirmed by the data which has the shift of nitrogen

Table 2
^{1}H-NMR chemical shifts for NH_3 in *trans*-$[(Ru(NH_3)_4(NO))_x L]^{n+}$ in DMSO-d_6

x	L	δ (NH_3 per ppm)	Shifts in L per ppm
1	OH^-	4.09	
2	–S–S– bridge	4.10	
1	SO_3^{2-}	4.20	
1	imN	4.47	8.34, 7.57, 7.27
1	$P(OEt)_3$	4.53	4.29(CH_2), 1.32(CH_3)
1	4-pic	4.56	8.36(dbl), 7.76(dbl)
1	py	4.57	8.51(*o*-),8.36(*p*-), 7.91(*m*-)
1	nic	4.61	8.82(s), 8.64(dbl), 8.35(NH_2), 8.00(trpl), 8.03(dbl)
1	pz	4.61	9.27(dbl), 8.62(dbl)
1	isn	4.84	8.89(dbl), 8.61(NH_2), 8.18(dbl)
2	–Cl– bridge	5.88	

bases from L = imN to L = isn changing only from 4.47 to 4.84 ppm. Therefore, we should view the results as a measure of the σ donating ability of L. As a consequence, the NMR data suggest that the –Cl– bridge in $[(NO)(NH_3)_4RuClRu(NH_3)_4(NO)]^{5+}$ is a poor σ donor and the –S–S– bridge in $[(NO)(NH_3)_4RuSSRu(NH_3)_4(NO)]^{4+}$ is better or as good a donor as the nitrogen bases.

6. X-Ray data

Table 3 summarizes the most relevant interatomic distances and bond angles data for selected nitrosyl complexes. In these complexes, the Ru–N distances are in the range 1.71–1.81 Å, and the $[RuNO]^{3+}$ bond angles lie between 172.8 and 180°. The short Ru–NO interatomic distances and nearly linear Ru–N–O bond angles are indicative of multiple bonding between Ru(II) and the nitrosyl, which is indicative of the nitrosonium character in the NO ligand [4b,4f,4g,4j,4p,11–14].

The Ru–NO interatomic distances in *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{3+}$ [4p] and $[Ru(NO)(NH_3)_5]^{3+}$ [12] are, respectively, 0.32 and 0.14 Å shorter than the Ru–NO_2^- interatomic distances in the corresponding nitrite complexes [4q,12b], reflecting the greater extension of the back-bonding $Ru(II) \rightarrow NO^+$ with respect to the Ru–NO_2^-. The Ru–$P(OEt)_3$ bond is 0.20 Å shorter in the nitrite complex than in the nitrosyl analogue. The inverse trend is observed for the *trans* Ru–NH_3

Table 3
Relevant interatomic distances and bond angles for selected nitrosyl and related complexes

Complex	Ru–N(Ru–NO_x) [a]		Ru–N [b]	Ru–L [c]	Reference
	Distances (Å)	Angles (°)			
trans-$[Ru(NO)(NH_3)_4(H_2O)]Cl$	1.715(5)	178.1(5)	2.10(6)	2.355(3)	[4f]
$(NH_4)_2[Ru(NO)Cl_5]$	1.738(2)	176.7	2.359(5) [d]	2.357(7)	[14a]
$[Ru(NO_2)(NH_3)_5]Cl$	1.906(5)		2.131(6)	2.199(6)	[12]
trans-$[Ru(NO_2)(NH_3)_4(P(OEt)_3)]PF_6$	2.089(5)		2.140(13)	2.218(12)	[4s]
trans-$[Ru(NO)(OH)(NH_3)_4]Cl$	1.735(3)	173.8(3)	2.10(3)	1.961(3)	[12]
$[Ru(NO)(NH_3)_5]Cl_2$	1.770(9)	172.8(9)	2.092(10)	2.017(11)	[12]
trans-$[Ru(NO)Cl(NH_3)_4]Cl_2$	1.81(1)	180	2.109(7)	2.358(3)	[13]
cis-$[Ru(NO)Cl(NH_3)_4]Cl_2$	1.772(5)	175.2(4)	2.102(5)	2.108(5)	[13]
trans-$[Ru(NO)(NH_3)_4(nia)]SiF_6$	1.71(2)	177(1)	2.10(6)	2.14(2)	[4b]
trans-$[Ru(NO)(NH_3)_4(4\text{-pic})]BF_4$	1.725	178.6(4)	2.133(9)	2.094(7)	[13]
trans-$[Ru(NO)(NH_3)_4(P(OEt)_3)](tfa)_3$ [e]	1.766(9)	178.0(8)	2.124(8)	2.420(3)	[4p]
trans-$[Ru(NO)Cl(bpy)_2]ClO_4$	1.751(6)	170.4(5)	2.102(6) [f]	2.306(2)	[14b]
trans-$[Ru(NO)Cl(cyclam)]ClO_4$	1.747(4)	178.0(5)	2.092(4) [f]	2.327(1)	[4g]
[Ru(NO)Cl(salen)]	1.728(6)	173.7(5)	2.013(5) [f]	2.354(2)	[11]
trans-$[Ru(NO)Cl(depe)_2]PF_6$	1.732	177.1		2.367	[4j]
[Ru(NO)(edta)]	1.756(4)	172.8	2.108(4) [f]	2.097(4)	[14c]

[a] $x = 1, 2$.
[b] Ru–NH_3 distance, except where noted; average value.
[c] Ligand in *trans* position to NO.
[d] Equatorial Ru–Cl distances.
[e] tfa = trifluoroacetate.
[f] These Ru–N interatomic distances do not refer to Ru–NH_3 bond.

interatomic distances in $[Ru(NO)(NH_3)_5]^{3+}$ and $[Ru(NO_2)(NH_3)_5]^{+}$ ions. These experimental data are consistent with the σ donor character of the ammine ligand and the biphilic character of the $P(OEt)_3$ ligand (good π acceptor and mild σ donor). The competition between NO^+ and the $P(OEt)_3$ ligands for the π electron density will weaken the Ru–$P(OEt)_3$ bond. The NO_2^- ligand being a weaker π acceptor than NO^+, the Ru(II)–$P(OEt)_3$ π bonding interaction would occur more extensively in the nitrite than in the nitrosyl complexes.

The equatorial Ru–N distances for all complexes in Table 3, except for [Ru(NO)Cl(salen)] [11], are in the range 2.11±0.02 Å. These distances refer to Ru–ammines or Ru–saturated amines, and they are similar to the equatorial Ru–N distance of 2.103 (3) in $[Ru(NH_3)_5Cl]Cl_2$ [14], and in other Ru(III) ammine complexes without nitrosyl [5]. The equatorial Ru–N distance for [Ru(NO)Clsalen] involves an imine nitrogen. Also, the Ru–Cl distances are similar in $[RuCl(NH_3)_5]Cl_2$ (2.346 (1)), *trans*-$[Ru(NO)(Cl)(NH_3)_4]Cl_2$ (2.358 (3)), *trans*[Ru(NO)(Cl)(salen)] (2.354 (2)), and *trans*-$[Ru(NO)Cl(cyclam)](ClO_4)_2$ (2.327 (1)). The above data are consistent with the Ru(II) character of the metal center in the nitrosyl complexes, and are consistent with the infrared and EPR assignments.

As would be expected, the axial ligand is more affected than the equatorial ones by the NO ligand. For $[Ru(NO)(NH_3)_5]^{3+}$, the equatorial Ru–N distance (2.10±0.02) Å is similar to that found in other nitrosylammine ruthenium complexes (see Table 3), which is larger than the axial one (2.017±0.011) Å. These data would suggest that the proton in the axial NH_3 ligand might be more acidic than in the equatorial ones.

7. Thermal reactivity

For the $[Ru(NO)(A_4)L]^{n+}$ complexes the metal center and the other ligands show dramatic alterations in their properties as a consequence of the coordination to NO. For example, the Ru(III)/Ru(II) half cell potentials for $[Ru(NH_3)_6]^{3+/2+}$ and $[Ru(NH_3)_5(H_2O)]^{3+/2+}$ are observed [5] around +0.04 to −0.07 V versus NHE. However, owing to [Ru(II)→NO^+] back bonding, the nitrosyl complexes [4] do not undergo oxidation up to +1.2 V. The lability and the acidity of the ligand in the *trans* position to the NO are drastically altered relatively to other ligand complexes. For example, pyrazine substitutes H_2O in $[Ru(NH_3)_5(H_2O)]^{2+}$ at the specific second order rate constant of 5.6×10^{-2} M^{-1} s^{-1} [5c,5d], and the formation constant for the $[Ru(NH_3)_5pz]^{2+}$ was calculated as 10^{12} M^{-1}. However, *trans*-$[Ru(NO)(NH_3)_4(pz)]^{3+}$ is not formed when excess of pyrazine (1 M) and *trans*-$[Ru(NO)(NH_3)_4(H_2O)]^{3+}$ (1×10^{-3} M) are allowed to react at 40 °C, pH 1.5, for a 48 h period [4a].

The specific rate constant of 4.4 s^{-1} for chloride aquation [15] in $[Ru(NH_3)_5Cl]^{+}$ is indicative of the low affinity of the $[Ru(NH_3)_5]^{2+}$ moiety for Cl^-. However, *trans*-$[Ru(NO)Cl(NH_3)_4]^{2+}$ is a relatively stable complex [1a,1b,4f] and the dimer $\{[(NO)(NH_3)_4Ru]_2Cl\}^{5+}$ remains in aqueous solution ($C_{H^+}\geq10^{-4}$ M) in the presence of oxygen for a week without any sign of decomposition [4f].

The inertness of the water molecule in *trans*-$[Ru(NO)(NH_3)_4(H_2O)]^{3+}$ towards substitution reaction is such that it substitutes slower [4f] than in $[Ru(NH_3)_5(H_2O)]^{3+}$, where the metal center is formally in the (+3) oxidation state. The chloride ion substitutes for the water molecule in $[Ru(NH_3)_5(H_2O)]^{3+}$ with the second order rate constant of 8.7×10^{-5} M^{-1} s^{-1} (40 °C), while for *trans*-$[Ru(NO)(NH_3)_4(H_2O)]^{3+}$ this substitution takes places 30-fold more slowly (3.7×10^{-6} M^{-1} s^{-1}, 40 °C) [4g]. Hence, the effect of NO in the coordination sphere is greater on the substitution lability than increasing the oxidation sate of the metal center by +1.

Another consequence of nitrosyl presence in the metal center coordination sphere can be easily noticed comparing the pK_a's for the Eqs. (8)–(10):

$$t\text{-}[Ru(NO)(NH_3)_4(H_2O)]^{3+} + H_2O \rightleftharpoons t\text{-}[Ru(NO)(OH)(NH_3)_4]^{2+} + H_3O^+, \quad pK_a = 3.1 \tag{8}$$

[4f]

$$[Ru(NH_3)_5(H_2O)]^{3+} + H_2O \rightleftharpoons [Ru(OH)(NH_3)_5]^{2+} + H_3O^+, \quad pK_a = 4.1 \tag{9}$$

[5a]

$$[Ru(NH_3)_5(H_2O)]^{2+} + H_2O \rightleftharpoons [Ru(OH)(NH_3)_5]^{+} + H_3O^+, \quad pK_a = 13.1 \tag{10}$$

[16]

Thus, replacing one NH_3 ligand of $[Ru(NH_3)_5(H_2O)]^{2+}$ by NO^+ increases the acidity of the water molecule by 10 pK_a units.

This effect was also observed [4g] for the coordinated water molecule in the *trans*-$[Ru(NO)(H_2O)(cyclam)]^{3+/2+}$ complexes. The pK_a values for the H_2O ligand in the oxidized and in the reduced species are 3.0 and 6.4, respectively [4g]. According to MO calculations (DFT) [4a,4b,4f] the strong *trans* NO π-acceptor ability hardening the Ru(II) center would increase the metal π-acceptor ability, thus favoring the H_2O π-donation.

Recently, the increase in the acidity of heterocyclic ligands in *trans*-$[Ru(NO)(NH_3)_4L]^{3+}$ complexes was reported [17]. Particularly, when L = imC (imidazol, bonded through the carbon atom), the pK_a for the coordinated imidazol in the nitrosyl complex (6.3) is five pK_a units lower than in *trans*-$[Ru(NH_3)_5(imC)]^{3+}$ (11.0) [18]. We observed a similar effect for the pyrazine ligand [4a,4b]. The pK_a for the coordinated pz in $[Ru(NH_3)_5(pzH)]^{3+}$ is 2.5 [5a,5c]. However, in *trans*-$[Ru(NO)(NH_3)_4pz]^{3+}$, the pyrazine ligand is not protonated up to $C_{H^+} = 2.0$ M.

The $[M(NO)(NH_3)_5]^{3+}$ species (M = Ru, Os) also yield the corresponding nitrite species by reaction with OH^-, but the products decompose, precluding their isolation as $[M(NO_2)(NH_3)_5]X$ salts. Both reactions, the attack by OH^-, as well as the reactivity of the deprotonated NH_2^- ligand, were reported to occur [1b]**.** This behavior is consistent with the deprotonation of the axial NH_3 ligand, which is more acidic than the equatorial ones, thus generating the quite reactive NH_2^- ligand [1b].

The *trans*-$[Ru(NO)(A_4)L]^{3+}$ complexes do not show NH_2^- reactivity because there are no ammine ligands *trans* to NO, while the equatorial ammines are less acidic. Instead, these complexes react with with OH^- ion [1b,4a,4b]:

$$trans\text{-}[Ru(NO)(NH_3)_4L]^{3+} + 2OH^- \rightleftharpoons trans\text{-}[Ru(NO_2)(NH_3)_4L]^{+} + H_2O \quad (11)$$

The K_{eq} measured for the reaction of *trans*-$[Ru(NO)(NH_3)_4L]^{3+}$ with OH^- are summarized in Table 1. These data have been proposed [1b] as a straightforward way to compare the relative electrophilicity of coordinated nitric oxide in various complexes. According to this, the higher the electron deficiency in the NO fragment, as a consequence of the $[Ru(NH_3)_4L]^{2+}$ core π-acidity, the higher will be the driving force for the reaction of the coordinated NO with OH^-, and also the ν_{NO} stretching frequency. Unfortunately, the observed changes in K_{eq} are in the opposite direction predicted by ν_{NO} and π acidity of L. An unified explanation for the observed trends in K_{eq} has been proposed by Shepherd [3g] which pointed out the relevance of H-bonds between ammonia ligands and the solvent cage for both complexes *trans*-$[Ru(NO)(NH_3)_4L]^{3+}$ and *trans*-$[Ru(NO_2)(NH_3)_4L]^{2+}$. The nitro species thermodynamic stability, which is included in K_{eq} and the specific second order rate constant for the OH^- attack on the NO ligand are very important terms to be considered [1b]. Unfortunately, these data are not yet available to support a more sound discussion in this subject. Probably kinetic data on the OH^- nucleophilic attack on the NO^+ ligand would help clarify this matter.

As mentioned previously a remarkable stability of the Ru(II) regarding the Ru(III) oxidation state was observed upon coordination to NO^+. No less remarkable is the change in the redox properties of the L ligand. The coordinated SO_3^{2-} is easily oxidized to SO_4^{2-} by hydrogen peroxide [4a]. This behavior was the basis of a synthetic procedure developed for cobalt [19] and ruthenium ammines [20] and adapted by us to nitrosyl complexes synthesis [4a,4b]. A quite different behavior is observed for the SO_3^{2-} ligand in *trans*-$[Ru(SO_3)(NH_3)_4L]$ ($L \neq NO$) and in *trans*-$[Ru(NO)(SO_3)(NH_3)_4]^+$. In the first complex, SO_3^{2-} is readily converted to SO_4^{2-} through H_2O_2 addition, whereas in the nitrosyl complex the sulphito ligand is not oxidized even by Ce^{4+} ions. Conversely, by action of Cd(Hg) or Zn(Hg), *trans*-$[Ru(NO)(SO_3)(NH_3)_4)]^+$ easily yields $[(NO)(NH_3)_4Ru{-}S{-}S{-}Ru(NH_3)_4(NO)]^{6+}$ ions [4b].

As can be observed in Table 1, the $E_{1/2}$ values for the reaction $[Ru(II)NO^+] + e \rightarrow [Ru(II)NO^0]$ are sensitive to the nature of the *trans* ligand L. As the π acidity of L increases more nitrosonium character is impressed in the NO ligand and, thus, its reduction is easier. Although no empirical or free energy relationship can be established at this moment, the trend mentioned above is clearly observed.

The specific rate data constants for NO^0 dissociation from the $[Ru^{II}NO^0]^{2+}$ fragment, covering from 5.1 s^{-1} (imC) to 6.1×10^{-4} s^{-1} (cyclam), are summarized in Table 4. Therefore, the *trans* effect and *trans* influence of the L ligand will be quite relevant in determining the NO^0 dissociation in *trans*-$[Ru(NH_3)_4L(NO^0)]^{2+}$. As a matter of fact, the rate for NO^0 dissociation in the ruthenium ammines complexes studied decreases as follows:

$$ImC > P(OEt)_3 > imN > L\text{-}hist > py > H_2O > nic \equiv 4\text{-}pic$$

and for the polydentate ligands as:

$$hedta > cyclam$$

Table 4
Specific rate constants [a] for NO dissociation in $[Ru(II){-}NO^0]$

Complex ion	K_{NO} (s^{-1})	Reference
trans-$[Ru(NO)(NH_3)_4(L\text{-}hist)]^{2+}$ [b]	0.14	[4p]
trans-$[Ru(NO)(NH_3)_4(ImN)]^{2+}$ [b]	0.16	[4p]
trans-$[Ru(NO)(NH_3)_4(nic)]^{2+}$ [b]	0.025	[4p]
trans-$[Ru(NO)(NH_3)_4(py)]^{2+}$ [b]	0.06	[4p]
trans-$[Ru(NO)(NH_3)_4(4\text{-}pic)]^{2+}$ [b]	0.02	[4p]
$[Ru(NO)(hedta)]$ [c]	7.3×10^{-3}	[4k]
trans-$[Ru(H_2O)(NO)(cyclam)]^{2+}$ [c]	6.1×10^{-4}	[4g]
trans-$[Ru(NO)(NH_3)_4((P(OEt)_3)]^{2+}$ [c]	0.98	[4n,4o]
trans-$[Ru(NH_3)_4(imC)(NO)]^{2+}$ [b]	5.1	[17]
trans-$[Ru(NH_3)_4(H_2O)(NO)]^{2+}$ [c]	0.04	[4g]

[a] 25 °C, $\mu = 0.10$ M ($CF_3COOH{-}CF_3COO$, $[H^+] = 10^{-2}$).
[b] Through chronoamperometry.
[c] By spectrophotometry.

For the ammine complexes the observed trend is the same reported [5a,5c,5d,5e] for ligands *trans* effect and *trans* influence in pseudo-octahedral ruthenium(II) complexes.

Therefore, although substantially more data should be collected in order to define a reliable relationship, it is clear that choosing biphilic ligands as $P(OR)_3$, and taking advantages of polydentate ligands as cyclam or hedta it is possible to design complexes in which $E_{1/2}$ of NO^+/NO^0 couple will lie in the range of many biological reductors (−0.43 to +0.26 V vs. NHE, [1f]) and that will release NO^0 after reduction at a convenient rate.

In our experiments, whenever L is Cl^- it is aquated before NO^0. In all the other cases NO^0 dissociates before L, yielding the corresponding aqua species. The mutual *trans* influence of NO^0 and L would decide the course of the reaction.

The affinity of NO^0 for the $[Ru(NH_3)_4(P(OEt)_3)]^{2+}$ moiety estimated as the equilibrium constant, K_{eq}, of Eq. (12) is equal to $3 \times 10^1\ M^{-1}$, at 25 °C, combining the specific rate data for k_{-NO} ($0.97\ s^{-1}$) [4m,4q] and k_{-NO} ($3 \times 10^1\ M^{-1}\ s^{-1}$) [4p]:

$$t\text{-}[Ru(NH_3)_4(P(OEt)_3)(H_2O)]^{2+} + NO^0 \rightleftharpoons t\text{-}[Ru(NH_3)4(P(OEt)_3)(NO)]^{2+} + H_2O \quad (12)$$

This value of $K_{eq} = 3 \times 10^1\ M^{-1}$ is of the same order magnitude as those reported for the affinity of L = pz, isn, 4-pic, and py [5c,5d] for the $[Ru(NH_3)_4(P(OEt)_3)]^{2+}$ moiety. Therefore, it is likely that the p acceptor ability of NO^0 would be comparable to that of the above-mentioned N-heterocyclic ligands. Thus although to a smaller extent than NO^+, Ru(II) is still able to back bond to the NO^0 ligand formed [3g,3j,4h] to Ru(II).

The equilibrium constant for the reaction (Eq. (13)):

$$t\text{-}[Ru(NH_3)_4(H_2O)(P(OEt)_3)]^{2+} + NO_2^- \rightleftharpoons t\text{-}[Ru(NO_2)(NH_3)_4(P(OEt)_3)]^{+} + H_2O \quad (13)$$

has been recently measured [4q] as $(5 \pm 0.5) \times 10^{-3}\ M^{-1}$ at (25 ± 0.2) °C and $C_{H^+} = 1 \times 10^{-10}\ M^{-1}$. Considering the $Ru–NO_2^-$ and $Ru–NO^+$ interatomic distances of 2.089 and 1.766 Å, respectively, (Table 3), the value of $5 \times 10^3\ M^{-1}$ could be considered as the low limit for the affinity of *trans*-$[Ru(NH_3)_4(H_2O)(P(OEt)_3)]^{2+}$ for NO^+.

8. Spectra, excited states and photochemical behavior

Ruthenium(II) ammines with nitrosyl ligands show UV–vis spectra quite different from those complexes with other unsaturated ligands such as pyridines [4,5a,21–23]. Among the several excited states types that Ru(II) complexes can have, the ligand-field (LF), metal to ligand charge transfer (MLCT), CTTS, and intraligand (IL) excited states are displayed by mononuclear Ru(II) ammine and Ru(II) cyclam $[Ru(II)(A_4)LL']^{n+}$ (A_4 = cyclam or $(NH_3)_4$) species without nitrosyl [5a,21,22,24,25]. The properties of these states depend on the nature of the ligand L, which must have available empty orbitals of appropriate symmetries and energies to combine with the d_π-orbitals of the Ru(II) center. Considering the L–Ru–L′ *z*-axis of *trans* Ru(II) tetraammine cyclam complexes, only one d_π Ru(II)-orbital is involved in π back bonding when L and/or L′ are a pyridine or pyrazine ligand. This implies ligand coplanarity, which, as a matter of fact, is supported by NMR data for several *trans*-$[Ru(NH_3)LL']^{2+}$ complexes (L, L′ = substituted pyridines and pyrazine) [25c,25d]; with nitriles, carbonyl, or nitrosyl two Ru(II) d_π-orbitals are involved. For pyridine type ligands the energies are such that there are strong MLCT absorptions in the visible range of the spectra, normally burying the much less intense LF bands, except in some complexes such as *trans*-$[RuCl(cyclam)L]^+$ (L = isonicotinamide (isn) or 4-acetylpyridine (4-acpy)) [25a] or $[Ru(NH_3)_5(acn)]^{2+}$ (acn = acetonitrile) [26]. For ligands such as phosphites, no MLCT bands are reported to occur in the UV–vis range, and LF bands are the lowest in energy [27].

The presence of the nitrosyl ligand, in the pentaammine and tetraammine complexes, bleaches almost completely the charge transfer absorption in the visible range. The spectra of the nitrosyl complexes display a broad absorption, usually in the 400–500 nm range [1h,4], with a very low absorptivity ($\varepsilon < 1.0 \times 10^2\ M^{-1}\ cm^{-1}$), and another absorption, of higher intensity ($\varepsilon > 1.0 \times 10^2\ M^{-1}\ cm^{-1}$), in the 300–350 nm range, along with other bands in the UV range. Table 5 lists relevant spectral data of some Ru(II) nitrosyl amines.

The first wider attempt to assign the spectra of the nitrosyl complexes of ruthenium(II) ammine complexes was made by Schreiner [1d], based on Manahoran and Gray's assignment for the nitroprusside ion [30,31]. Schreiner [1d] assigned the lower energy bands in the

Table 5
Spectral data of some *trans*-$[Ru(NO)(NH_3)_4L]^{3+}$ complexes in aqueous solution [a]

L	λ_{max} (nm) ε ($mol^{-1}\ L\ cm^{-1}$)	Reference
Im	220(5,300); 234(4,100); 270(830); 324(660); 450(90)	[4a,4i]
L-hist	217(6,600); 232(3,700); 274(590); 320(410); 395(81)	[4a,4i]
4-pic	239(11,200); 262(3,550); 325(220); 460(20)	[4n]
Py	324(160); 474(23)	[4b,4i]
nic	220(9,400); 320(160); 485(23)	[4b,4i]
pz	230(1,000); 276(4,400); 302(660); 468(40)	[4b,4i]
4-acpy	286(3,700); 330(340); 464(40)	[4l,33]
$P(OEt)_3$	260(1,400); 316(216)	[4l]

[a] 10^{-3} M HCl, $\mu = 0.10$ ($NaCF_3COO–CF_3COOH$).

spectra of *trans*-nitrosyltetraammineruthenium(II) complexes with saturated ligands such as chloro, acetate, hydroxo, to a mixture of a MLCT $t_2 \rightarrow \pi^*(NO)$ transitions of, by then, surprisingly low intensity and a singlet–triplet ($^1A_1 \rightarrow {}^3T_1, {}^3T_2$) transition [1h]. Afterwards, the spectra of some *trans*-$[Ru(NO)(NH_3)_4L]^{3+}$ (L = py, nic, isn, pyr, imN, L-hist, H_2O) were assigned [4a,4b], based on Schreiner's assignment [1h]. Later, a theoretical calculation [4f] of the spectra of *trans*-$[Ru(NO)(NH_3)_4(H_2O)]^{3+}$ was made using ZINDO/S, and more recently, TD-DFT calculations were performed [4i] for the complexes with L = NH_3, OH^-, Cl^-, H_2O, py, and pz. The TD-DFT calculations gave essentially similar results to those obtained with ZINDO/S, but TD-DFT resulted in a better fitting with experimental data. For *trans*-$[Ru(NO)(NH_3)_4(H_2O)]^{3+}$ the TD-DFT calculations gave an energy ordering of the lowest energy transitions inverted from that of the ZINDO/S calculations. The calculations also showed that the number of transitions in the two above mentioned ranges and the contributions from the ligands π and π*-orbital are dependent on L. Noteworthy, for L = py or pz, the HOMO-orbitals are localized on the heterocycle. Also, for the complexes that had their structures calculated, the d_{xy} and $d_{x^2-y^2}$-orbitals of t_{2g} and e_g parentage have an energy ordering inverted from those in the analogous complexes with no nitrosyl. Thus, each absorption band is actually the result of more than one electronic transition, and the composition of the absorption band is dependent on L. As a consequence, there is no a unique description for all complexes and the interpretation of the properties, such as photochemical, that depend on the electronic structure is not straightforward. The expected transitions, according to the TD-DFT calculations, are d–d, MLCT (Ru → NO), MLCT (Ru → L), LMCT (L → Ru), LLCT (L → NO), and IL transitions. The TD-DFT method [4i] confirmed the previous assignments [1d,4a,4b] of the 300–350 nm bands to a d–d transition, but with additional contributions from a MLCT transition. Lastly, the TD-DFT calculations concluded that a singlet–triplet LF transition contribution to the low energy (400–500 nm) absorption was unlikely.

As a result of these electronic differences between the nitrosyl and other ruthenium(II) ammine complexes, the photochemical behavior could be expected to differ. Ammine ruthenium(II) complexes with unsaturated ligands have in general MLCT and LF states as lowest energy excited states (LEES) [5a,21,22,24,25]. Early studies involving pentaammineruthenium(II) complexes resulted in the 'tuning' model [21,24b,32] which also provided an explanation of the photochemistry of some other low-spin d^6 systems with MLCT states. Basically, the complexes that have MLCT as LEES are relatively unreactive, whereas those with a LF as LEES tend to be reactive towards photosubstitution reactions of the ligands or the ammine. For the reactive complexes, initial excitation into the ^{1}MLCT* manifold is followed by relatively efficient interconversion and intersystem crossing to the lowest energy ^{3}LF* from which deactivation pathways lead to photosubstitution or the starting complex. For the *trans*-$[Ru(NH_3)_4LL']^{2+}$ complexes the possible photosusbtitution reactions are:

$$\textit{trans}\text{-}[Ru(NH_3)_4LL']^{2+} \xrightarrow[H_2O]{h\nu} \begin{cases} [Ru(NH_3)_4L(H_2O)]^{2+} + L' \\ [Ru(NH_3)_4(H_2O)L']^{2+} + L \\ [Ru(NH_3)_3LL']^{2+} + NH_3 \end{cases} \quad (14)$$

Ru(II) complexes with saturated ligands showed photooxidation reactions at higher energies, competitive with photosubstitution [21,22,24,26]. This was also the case for some Ru(II) complexes with unsaturated ligands, such as pyridine, although $[Ru(NH_3)_5(py)]^{2+}$ showed only photosubstitution at longer irradiation wavelengths [21,22,24,26]. The photoredox behavior was concluded to result from excitation into charge transfer to solvent (CTTS) states. Complexes such as phosphites, which do not exhibit MLCT or CTTS bands in the UV–vis range showed only photosubstitution reactions [28,29].

There are reports on the photochemical behavior of many nitrosyl metal complexes and related species [1a,3o,4a,4b,4l,11,33,34]. Among such systems, the Ru(II) ammines described here constitute a series of closely related complexes which can be modified systematically, from which generalities can eventually be drawn, despite [4a,4b,4n,33]. The photochemical properties of the ruthenium(II) ammine complexes with nitrosyl have not yet been fully examined. Nonetheless, the results so far obtained indicate that their photochemical behavior is markedly different from the other Ru(II) ammines. Irradiation of the nitrosyl complexes with photons of energies corresponding to the bands in the range of 300–350 nm result in nitric oxide aquation and formation of the corresponding aquaruthenium(III) complex (Eq. (15)).

$$\textit{trans}\text{-}[Ru(NO)(NH_3)_4L]^{3+} \xrightarrow[H_2O,H^+]{h\nu} \textit{trans}\text{-}[Ru(NH_3)_4(H_2O)L]^{3+} + NO^0 \quad (15)$$

The photochemical products have been identified by differential pulse polarography (for NO) and EPR (for Ru(III) complexes). In the analogous Ru(salen)(NO) system [34c], the reaction above was reported to be reversible. However, thus far, this reversibility was not observed for the ruthenium ammines under the experimental conditions used. For the *trans*-$[Ru(NO)(NH_3)_4(L)]^{3+}$ complexes, quantum yields for NO labilization were irradiation wavelength dependent. Tables 5 and 6 display, respectively, spectral data and quantum yields for the release of NO for some nitrosyl complexes of ammineruthenium(II), after irradiation.

Table 6
Quantum yields of NO^0 release for some *trans*-$[Ru(NO)(NH_3)_4L]^{3+}$ complexes in aqueous solutions [a]

L	λ_{max} (nm)	pH	λ_{irr} (nm)	$\phi_{NO}/10^{-3}$
py	225	3.0	330	110±10
	237	4.4	330	130±10
	267			
	324			
	474			
4-pic	239	2.0	330	0.08
	262	3.45	330	0.12
	325	5.0	330	0.26
	460			
pz	230	3.45	313	170±30
	276	4.32	313	230±30
	508			
4-acpy	238	3.45	313	130±30
	286	4.32	313	230±30
	330			
	464			
L-hist	242	3.45	313	67±4
	294	4.32	313	86±4
	336			
	461			

[a] Reference [4l].

Irradiation with longer wavelengths, corresponding to the broad absorption in the 400–500 nm range did not result in any observable photo reaction in solution, under the conditions examined so far [4l,33]. However, some nitrosyl complexes, including those of Ru(II), have been reported to display a reaction, at low temperature, upon irradiation in the 400–500 nm range, monitored by infrared spectra, producing an extremely long-lived metastable state [4d,35]. Although first improperly assigned as 'excited states', these have then been assigned as linkage isomers, either as η^1-oxygen coordinated metal complexes or as η^2-perpendicularly bound NO. Recent results employing photocrystallographic techniques with some Ru(II) nitrosyls provide strong evidence for the formation of such linkage isomers [36], the structures of which were also calculated [36b,37]. This may also be the case when $[Ru(NO)(NH_3)_5]^{3+}$ and *trans*-$[Ru(NO)(OH)(NH_3)_4]^{2+}$ are irradiated in the solid state at low temperature [4d]. These metastable states decay to the original conformation at higher temperatures. Thus, although similar reactions might also be occurring in solution for the Ru(II) ammine nitrosyls when irradiated at wavelengths corresponding to the lower energy absorptions, these possible pathways have not been examined under these conditions.

The above features differ from those of the other Ru(II) ammines in several ways. First of all, remarkably, the observed reaction comes from an upper excited state, not from the LEES. For the nitrosyl complexes, the LEES seems to be unreactive toward photosubstitution, a feature markedly different from other Ru(II) amines with pyridines and azines, which show Ru(II) complexes as photoproducts. At last, for the other Ru(II) ammines, ammonia aquation is a major photochemical pathway, but for the nitrosyl complexes no ammonia photoaquation has yet been detected. However, since formation of the aqua–Ru(III) complex contributes to a change in the pH, and spectral characteristics of the reagents and products are similar, a definite statement on the matter requires further examination of ammonia aquation by other techniques.

Ligand field excited states are expected to show photosubstitution reactions only. Since for pseudo-octahedral Ru(II) ammines, they would be σ* states. No photoredox processes are expected to occur from these states. For the Ru(II) ammines without nitrosyl ligands, the photosubstitution reactions observed are the only reactions observed, and they come from LF excited states. The MLCT states in these complexes do not lead to any photoreaction. So, LF states in the nitrosyl complexes, in principle, would be expected to result in aquation of the ligands and yield the corresponding Ru(II) aqua species. Our results with nitrosyl species easily show that aquation of nitrosyl or the formation of the corresponding Ru(II) complex are not occurring [4a,4b,4l,33]. The origin of nitric oxide in solution should be from other than a LF state. The aquation of NO^+ would be unlikely since no nitrite has been observed upon irradiation of the complexes [4n]. Similar behavior was reported [38] to occur for $[Ru(NO)(NH_3)_5]^{3+}$ with different counter-ions, for which the authors claim an outer-sphere redox process [38].

Noteworthy, the bands in the 300–350 nm range have a MLCT component, involving Ru(II) to nitrosyl back bonding [4i]. This component was assigned to a $d_{xz,yz} \rightarrow \pi^*(NO)$ transition. Such a transition is consistent with the observed reaction. This (Ru → NO) MLCT would lead to depopulation of Ru(II) d_π-orbital involved in back-bonding to NO^+ and population of a π* NO, with the consequent formation of the formal Ru(III)–NO^0 moiety, as illustrated in Eq. (16).

$$\textit{trans}\text{-}[Ru(II)(NO^+)(NH_3)_4L]^{3+} \xrightarrow{h\nu} [\textit{trans}\text{-}[Ru(III)(NH_3)_4(NO^0)L]^{3+}]^* \quad (16)$$

$$[\textit{trans}\text{-}[Ru(III)(NO^0)(NH_3)_4L]^{3+}]^* \xrightarrow{H_2O,H^+} \textit{trans}\text{-}[Ru(III)(NH_3)_4(H_2O)L]^{3+} + NO^0 \quad (17)$$

Then, from this singlet excited state, relatively efficient interconversion and intersystem crossing to lower energy triplet excited states occur. From the lower energy ^{3}MLCT (Ru → NO; corresponding to the 300–350 nm range), which is not the LEES, a prompt aquation of NO^0 occurs (Eq. (16)), which could be competitive with other deactivation pathways. This requires relatively fast aquation rates and/or long-lived

excited states. The lower energy MLCT transition (corresponding to the 400–500 nm range) involves depopulation of the non-bonding $d_{x^2-y^2}$-orbital, and population of a π* NO-orbital rather than depopulation of the $d_{xz,yz}$-orbitals involved in back-bonding. Thus, this is in principle consistent with a relatively higher difficulty to aquate NO^0.

9. Biological tests

As pointed out in previous sections, all complexes isolated by us are water soluble and thermally robust in solution [4]. The complexes *trans*-$[Ru(NO)(NH_3)_4Y]X_3$, ($X = PF_6^-$ or BF_4^-; Y = nic, isn, L-hist, SO_3^{2-}, imN, $P(OEt)_3$, *cis*-$[Ru(NO)(NO_2)(NH_3)_4]Br_2$ and *trans*-$[Ru(NO)Cl(cyclam)](Z)_2$ ($Z = PF_6^-$, Cl^-, $CF_3SO_3^-$) exhibit low acute toxicity, compared with sodium nitroprusside, as judged from cytotoxicity experiments in cultures of rat hepatocytes ($IC_{50} > 3$ mM) and V79 cells ($IC_{50} \sim 2$ mM) [4o,33,39,40]. *trans*-$[Ru(NO)Cl(cyclam)]Z_2$, *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)](PF_6)_3$, and *trans*-$[Ru(NH_3)_4(P(OEt)_3)(H_2O)](PF_6)_2$, and *trans*-$[RuCl(CF_3SO_3)(cyclam)](CF_3SO_3)_2$, which form some of the decomposition products of the former two complexes, and *trans*-$[RuCl(H_2O)(cyclam)]^+$ and *trans*-$[Ru(NH_3)_4(P(OEt)_3)(H_2O)]^{2+}$, were found [4o,33,39–41] to be at least 20 times less toxic than sodium nitroprusside ($IC_{50} \cong 0.06$ mM) in similar cell culture systems. The approximate lethal dose for *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)](PF_6)_3$ in mice has been calculated to be 257.5 μmol kg^{-1} [39]. For all the complexes studied by us the $E^{\circ}_{(NO+/NO(0))}$ is in the −0.3 to +0.13 V (vs. NHE) [4], and therefore, accessible [2h] to biological reductants.

Among the complexes isolated by us, the *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{3+}$ undergoes thermal release of NO, after nitrosonium reduction by one electron, with the fastest rate [4m] ($k_{-NO} = 0.97\ s^{-1}$), whereas *trans*-$[Ru(NO)(Cl)(cyclam)]^{2+}$ is the slowest [4g] ($k_{-NO} = 6.4 \times 10^{-4}\ s^{-1}$). Taking into account their different rates of release of NO^0 and their capability to be reduced in biological media, the ability of these two compounds to deliver NO via thermal reaction, has been investigated with tests in the evoking mouse neuronal firing in the hippocampus [4m], mitochondria reduction [4o] and vasorelaxation on the blood pressure effects [39–41].

As expected due to the high *trans* effect of the $P(OEt)_3$ ligand [5d] which facilitates the NO release in *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{2+}$, the phosphite complex shows a strong facilitator action on the population evoking neuronal spike (1–2.5 mM increases of 278 ± 46% the normal answer), the EPSP and the spontaneous spike activity [4q]. For the slow NO^0 dissociation in $[Ru(NO)(H_2O)(cyclam)]^{2+}$, this complex did not exhibit such activity in this preparation [4g].

More evidence that the NO release from *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{2+}$ occurs when activated by biological reductants comes from studies with mitochondria. Fluorimetric and electrochemical measurements [4o] show that *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{3+}$ is reduced by mitochondria with a second order specific rate constant of $2 \times 10\ M^{-1}\ s^{-1}$. Since this is about 20 times higher than the rate for NO dissociation in *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{2+}$, this reduction reaction likely proceeds through an outer sphere mechanism.

More extensive have been the studies on blood pressure effects [39,40] with *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{3+}$ and *trans*-$[Ru(NO)Cl(cyclam)]^{+2}$. Endovenous administration in normotensive rats and in different models of hypertensive rats, which were induced with angiotensin II, phenylephrine and L-NAME, shows that the two complexes have different hypotensive properties. The effect was correlated to the rate of release of NO and stability of the reduced $[Ru(II)NO^0]$ compounds, which are dependent on the electron density of the metal centers and on the nature of the ancillary ligands. The phosphite complex, which releases NO in a burst, exhibited a fast and intense effect, comparable to that of equimolar doses of sodium nitroprusside [39,40]. The *trans*-$[Ru(NO)(Cl)(cyclam)]^{2+}$ complex, releasing NO slowly, after reduction, does not show an immediate and intense effect in the normotensive rats, but its effect lasts for about 15 min versus a few seconds in the classical nitrovasodilators [40].

In the presence of methylene blue, a soluble guanylyl cyclase inhibitor [41], the vasodilator effect of both compounds is fully blocked [39,40]. A similar effect is observed when carboxy-PTIO, a well known NO scavenger [42], is administered together with *trans*-$[Ru(NO)(NH_3)_4(P(OEt)_3)]^{2+}$ or *trans*-$[Ru(NO)Cl(cyclam)]^{2+}$, thereby implying an NO release and involvement of NO/cGMP pathway for the observed in vivo vasorelaxation [39,41]. Although preliminary, all these experiments strongly suggest that these two complexes behave as NO deliverers with their effect likely to be primarily dependent on [cGMP] without a metabolic action requisite as sodium nitroprusside does [43].

Chronic toxicity, biodisponibility and studies on the mechanism of NO release for vasorelaxation, using these compounds and their corresponding aqua–Ru(III) species, are in course. Results will be reported soon.

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